Stereocontrolled Multiple Functionalization of Cycloheptadienoneiron Complexes *via* Enolate Alkylation

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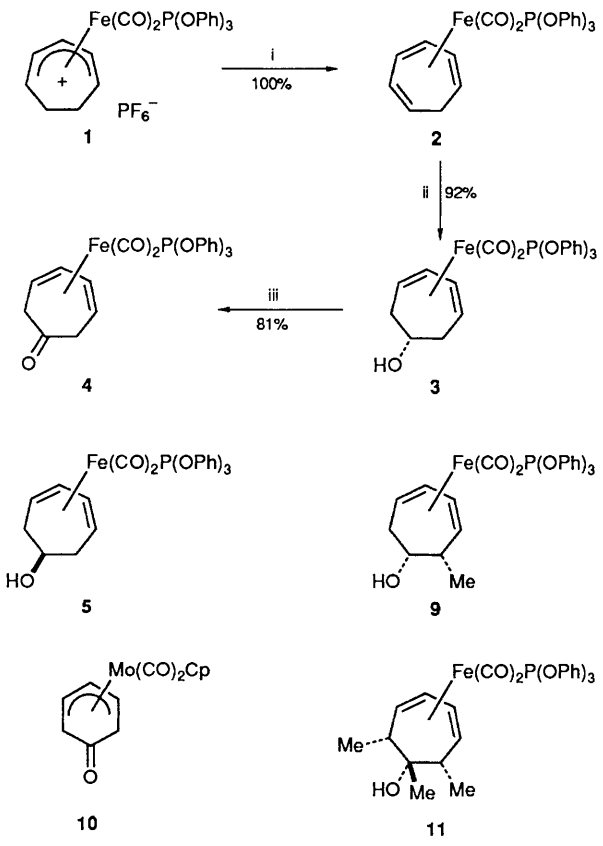
Alkylation of enolates from tricarbonyl(6-oxocycloheptadiene)iron occurs with complete stereoselectivity *trans* to the metal, while reduction of the ketone occurs with stereochemistry dictated by the boat conformation adopted by these molecules.

We have previously described methods for stereocontrolled multiple alkylation of six- and seven-membered carbocycles *via* nucleophile additions to cationic diene–molybdenum and dienyl–iron complexes,[1] methodology which has now also been successfully applied to heterocyclic ring systems.[2] More recently, it was shown that oxocyclohexenyl–molybdenum π-allyl complexes are readily converted to enolates, and their alkylation can be effected in a stereocontrolled manner to give more densely substituted molecules.[3] The major drawback with the π-allyl–molybdenum system as a stereodirecting moiety is that ligand disengagement remains a vexing problem in all but a few cases. Accordingly, we have turned our attention towards cycloheptadieneiron systems, since these are now well understood in terms of conformation, reactivity and decomplexation.

Deprotonation of the readily prepared[1a] complex **1** afforded the η^4-triene complex **2** in quantitative yield (Scheme 1).† Hydroboration of **2** gave a single alcohol **3** in 92% yield, assigned the stereochemistry shown based on subsequent

† All new compounds were purified by flash chromatography or preparative TLC, and were fully characterized by 200 MHz ^{1}H NMR, IR and mass spectrometry.



Scheme 1. *Reagents and conditions*: i, Et_3N, CH_2Cl_2, room temp.; ii, BH_3, tetrahydrofuran (THF); H_2O_2, NaOH; iii, Swern oxidation

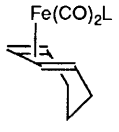


Fig. 1 Boat conformation of cycloheptadiene–$Fe(CO)_3$ complex

experiments (*vide infra*). The regiochemistry of the hydroboration is consistent with the well known ability of diene–$Fe(CO)_2L$ systems to stabilize neighbouring positive charge, as required in the transition state for borane addition. Swern oxidation[4] of **3** gave the ketone **4** in 81% yield.

Previous NMR assignments from our laboratory,[1a] and X-ray crystallographic work by Williams' group[5] have shown that substituted cycloheptadiene–$Fe(CO)_3$ complexes exist predominantly in a boat conformation (Fig. 1). Not only does this relieve 1,3-diaxial interactions between *exo* substituents, but it also relieves the eclipsing interaction between C–Fe and C–CH_2 bounds (Fig. 2). This distinguishes these complexes from cyclohexenyl–$Mo(CO)_2(C_5H_5)$ systems which adopt a chair conformation,[3,6] and we accordingly expect differences in the stereochemical outcome of reactions that might be sensitive to conformational effects. Reduction of **4** with sodium borohydride gave a 3:5 mixture of **3** and the stereoisomeric alcohol **5**, while reduction with L-selectride gave exclusively **3**. This is strongly suggestive that **4** prefers the boat conformation.

Alkylation of the enolate from **4** proceeded with complete stereoselectivity. Treatment of **4** with lithium diisopropylamide (LDA) at −100 °C, followed by excess of MeI, gave an 86% isolated yield of a single monoalkylated compound **6**, together with 8% of dialkylated compound **7** (Scheme 2). Variation of stoichiometry and reaction temperature gave no improvement in the mono- to di-alkylation ratio. Treatment of the mixture of **6** and **7** with LDA–MeI under the same

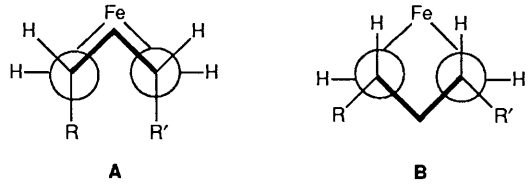
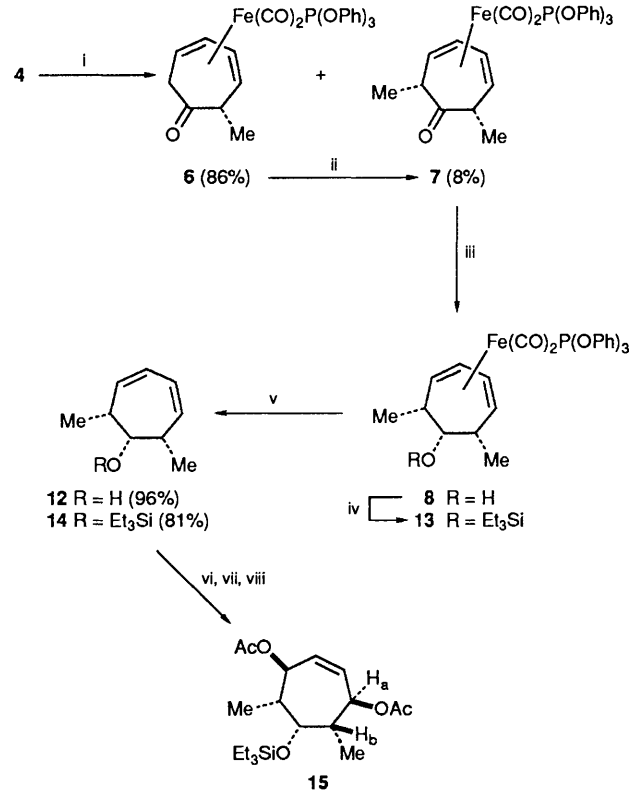


Fig. 2 Newmann projections for cycloheptadiene–$Fe(CO)_3$, showing relief of non-bonded interaction between substituents (R and R′) and between Fe and 6-CH_2, on going from chair (**A**) to boat (**B**) conformation of the diene ligand



Scheme 2. *Reagents and conditions*: i, LDA, THF, −100 °C, then MeI; ii, LDA, MeI (see text); iii, $NaBH_4$ MeOH, Et_2O, 0 °C, 2 h; iv, $Et_3SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C; v, for **8**, $CuCl_2$, EtOH; for **13**, CrO_3·2pyridine, CH_2Cl_2, reflux; vi, $^1O_2$, tetraphenylporphyrin, CH_2Cl_2; vii, $LiAlH_4$; viii, Ac_2O, Et_3N, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2

conditions gave exclusively complex **7** in 84% overall yield from **4**. No products of *gem*-dialkylation or over-alkylation were obtained.

Reduction of **7** with sodium borohydride proceeded with >99% stereoselectivity (by NMR) to give the alcohol **8** in 95% yield. The stereochemistry of **8** was confirmed by single crystal X-ray structure determination,‡ which showed **8** to adopt the boat conformation and which also supports the stereochemical assignment made for complex **3**. Similarly, reduction of the monoalkylated complex **6** gave **9** stereoselectively (4:1 mixture). The stereochemical outcome during the reduction of **4**, **6** and **7** is opposite to that observed for analogous molybdenum complexes (see structure **10**), thus emphasising the importance of conformational effects.§ Treatment of **7**

‡ We thank R. J. Shively and E. A. Zarate of this department for X-ray crystallography. Details will be published in the full paper describing this work.

§ Functionalization of the uncomplexed alkene in η^4-cycloheptatriene–$Fe(CO)_3$ complexes always occurs stereoselectively *trans* to the metal. Here, the complex cannot adopt a boat conformation, the ligand remains relatively flat, and the steric effects of the $Fe(CO)_3$ group dominate.

with methylmagnesium bromide gave a single tertiary alcohol **11**, the stereochemistry of which was assigned by analogy with the borohydride reduction results.

Decomplexation of **8** to give the cycloheptadiene **12** was readily accomplished using $CuCl_2$–EtOH.[7] Alternatively, protection of **8**, followed by treatment of the silyl ether **13** with Collins' reagent,[8] gave **14** in 81% overall yield. Further manipulation of the diene using previously reported procedures requires that the known[9] directing effect of the silyl ether group is outweighed by the opposite directing effect of the methyl groups.[8,10] This is not unreasonable based on the relative proximity of these groups to the diene. In the event, singlet oxygen addition, followed by reduction of the endoperoxide and acetylation of the so-formed diol, afforded **15**, the stereochemistry of which was readily assigned using ^1H NMR spectroscopy (diaxial couplings are observed between H_a and H_b).

In summary, it is possible to generate and alkylate enolates on the cycloheptadieneiron system without haptotropic rearrangement,[11] and to convert the products into cycloheptenes having densely packed stereocentres. The applications of this chemistry in the area of ionophore and macrolide antibiotic synthesis will form the basis of future work in our laboratory.

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