Complementary Regioselection in Nucleophile Additions to Cationic η^5-Cyclohexadienyl Iron Complexes

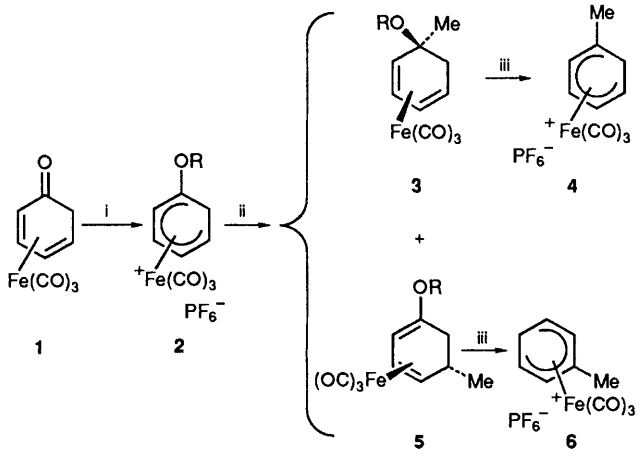
G. Richard Stephenson,* Philip W. Howard, David A. Owen and Andrew J. Whitehead

School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, UK

1-Alkoxy and 1-acetoxy substituted tricarbonyl(η^5-cyclohexadienyl)iron(1+) complexes undergo reactions with nucleophiles at opposite ends of the π-system in a reversal of regiocontrol that offers novel possibilities for complementary control strategies in applications in asymmetric synthesis, since the two series of complexes can be obtained from the same precursor.

Regioselective alkylation reactions are an essential requirement for the efficient application of chiral electrophilic π-complexes in asymmetric synthesis.[1] Suitable directing groups on the metal-bound π-system are required to ensure regioselectivity is maintained. Good regiocontrol, however, inevitably precludes access to the alternative regioisomer series, so restricting the range of structural types accessible from a particular compound. This can be a limitation in synthetic applications, if compounds from the inaccessible regioisomer series are required. In order to improve the synthetic versatility of tricarbonyl(η^5-cyclohexadienyl)-iron(1+) complexes,[2] we have begun an examination of methods that reverse the normal regiocontrol of directing groups on the dienyl system by use of similar replacement groups that have different control properties in the alkylation step.

This paper describes the first example of a reversal of regiocontrol based on this strategy. The results arise from an investigation that compares the regiodirecting influence of OEt and OAc substituents at C-1, in reactions that add a methyl group to the dienyl ligand. We have recently described[3] the addition of PhLi at C-1 of the η^5-1-ethoxycyclohexadienyl complex **2a**; to confirm the regioselectivity of methyl group addition, a similar reaction has been examined employing MeLi as the nucleophile. This produced the expected C-1 adduct **3a** in 83% yield,† a result consistent with the now well established[4] *ipso* directing effect of C-1 alkoxy substituents (Scheme 1). For comparison, the 1-acetoxy substituted cyclohexadienyl cation **2b** was prepared, by reaction of the cyclohexadienone complex **1**[5] with HPF_6 in acetic anhydride at 0 °C. The product **2b** was precipitated as a yellow powder in 88% yield by addition of diethyl ether. Alkylation of the 1-acetoxy cation with methyllithium proved to be well regiocontrolled, but, in contrast to the *ipso* directing effect of 1-alkoxy substituents, the alkylation of **2b** now favoured only addition at the far end of the π-system, producing the adduct **5b** in 54% yield. These results, summarized in Table 1 (entries 1 and 3), indicate that alkoxy and acetoxy groups provide opposite regiocontrol effects.



Scheme 1 *Reagents and conditions*: **a**; R = Et **b**; R = Ac; i, Et_3OPF_6 (see ref. 3) for R = Et, Ac_2O, HPF_6 for R = Ac; ii, see Table 1; iii, HBF_4 then NH_4PF_6

† All new complexes have been characterised by NMR, IR and mass spectroscopy, and by microanalysis or high resolution mass spectrometry.

The use of dimethylcuprate to introduce the methyl substituent was examined next. Reaction between the 1-ethoxy complex **2a** and dimethylcuprate (Table 1, entry 2) produced a 2 : 3 mixture of **3a** and **5a**. Comparison of the yields listed in Table 1 shows that the use of the cuprate reagent was less efficient, as well as less regioselective, than the corresponding reaction using methyllithium. When the 1-acetoxy complex **2b** was used, however, better results were obtained (Table 1, entry 4). Addition proceeded only at the far end of the π-system to form the regioisomer **5b** in 50% yield.

Comparison of ^1H NMR spectra of **3a, 5a** and **5b** allowed convenient regiochemical assignments to be made. Conclusions were based on the integration values for the diene hydrogens and the multiplicity of the methyl signals, which appeared as a singlet in **3a**, but as doublets in **5a** and **5b**. Confirmation of the regiochemical assignment was obtained by the conversion of the products into two different cyclohexadienyl complexes, by removal of the OEt or OAc groups in acid. Reaction of **3a** with CF_3CO_2H at 0 °C afforded the 1-methyl substituted salt **4** which was precipitated in 85% yield by addition of ammonium hexafluorophosphate. The corresponding reaction of the acetoxy substituted complex **5b** proceeded in accord with findings recently reported for similar alkoxy substituted complexes, which are known to rearrange extensively before loss of the alkoxy group. The favoured pathway involves substituted η^3-allyl intermediates that retain the best stabilization of positive charge.[6] As expected, in the case of **5b**, only the 3-substituted salt **6** was formed. The product was isolated by precipitation as before in 62% yield. These experiments demonstrate that the complementary regioselectivity arising through the use of 1-alkoxy and 1-acetoxy substituents can give practical access to two separate series of regioisomers.

These studies have thus identified a fundamental difference between the regiodirecting effects of alkoxy and acyl substituents, a distinction that may reflect the differences in the electron donation by these groups to the π-system. To make use of the reversed regiodirecting effect of the 1-acetoxy substituent, organolithium reagents appear at present to be the best nucleophiles to employ, since early experiments with

Table 1 Effect of substituents and nucleophile on regioselectivity

Entry	Substituents R	Nu	Reagent	Product ratio 3 : 5		Combined yield (%)
1	Et	Me	MeLi[b]	100	—[a]	83
2	Et	Me	Me_2CuLi[c]	40	60	36
3	Ac	Me	MeLi[b]	—[a]	100	62
4	Ac	Me	Me_2CuLi[c]	—[a]	100	50

[a] None was isolated. [b] In CH_2Cl_2–diethyl ether at −78 °C. [c] In tetrahydrofuran–diethyl ether at 0 °C.

other nucleophiles such as hydride donors suggested that competing nucleophile addition could occur at the acetoxy group to re-form the dienone **1**. However, since this product could also arise through hydrolysis of **2b**, further work is needed to define the scope of the reaction. We are examining other nucleophiles and acetoxy substituted cyclohexadienyl complexes having already demonstrated in the present case of methyl group addition, the first example of a reversal of regioselectivity by the use of complementary directing groups on electrophilic transition metal π-complexes.

G. R. S. thanks The Royal Society for a 1983 University Research Fellowship. P. W. H. thanks the SERC for a postdoctoral fellowship, D. A. O. thanks Glaxo Group Research for financial support for a Ph.D. studentship, and A. J. W. thanks Roche Products for the purchase of chemicals for use in an undergraduate research project. We thank Drs H. Finch, S. Swanson (Glaxo) and M. R. Attwood (Roche) for assistance.

Received, 15th January 1991; Com. 1/00220A

References

1 G. R. Stephenson, R. P. Alexander, C. Morley and P. W. Howard, *Phil. Trans. R. Soc. Lond. A*, 1988, **326**, 545.
2 For recent examples of the use of tricarbonyliron complexes in organic synthesis, see: A. J. Pearson and B. A. Boden, *J. Chem. Soc., Perkin Trans. 1*, 1990, 723; A. J. Pearson and M. K. O'Brian, *J. Org. Chem.*, 1989, **54**, 4663; H.-J. Knolker, M. Bauermeister, D. Bläser, R. Boese and J. B. Pannek, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 223; A. J. Birch, L. F. Kelly and D. V. Weerusria, *J. Org. Chem.*, 1988, **53**, 278; R. P. Alexander, C. Morley and G. R. Stephenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2069; G. R. Stephenson, R. D. Thomas, and F. Cassidy, *J. Organomet. Chem.*, 1991, **402**, C59.
3 D. A. Owen, G. R. Stephenson, H. Finch and S. Swanson, *Tetrahedron Lett.*, 1990, **31**, 3401.
4 For an example establishing the directing effect of a C-1 OMe group, see: I. M. Palotai, G. R. Stephenson, W. J. Ross and D. E. Tupper, *J. Organomet. Chem.*, 1989, **364**, C11.
5 A. J. Birch, P. E. Cross, J. Lewis, D. A. White and S. B. Wild, *J. Chem. Soc. (A)*, 1968, 332.
6 D. A. Owen, G. R. Stephenson, H. Finch and S. Swanson, *J. Organomet. Chem.*, 1990, **395**, C5.