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OPTICALLY ACTIVE TRICARBONYL(CYCLOHEXADIENYL)IRON(1+) SALTS: SYNTHETIC EQUIVALENTS TO SPATIALLY DIRECTED ORGANIC CATIONS

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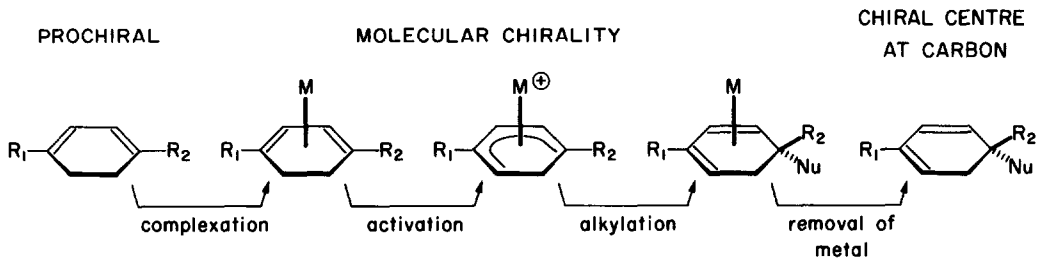
Summary: *Optically active tricarbonyl(cyclohexadienyl)iron(1+) salts I, II and III are examples of olefin complexes with molecular asymmetry due to coordination with a transition metal. Their reactions serve to direct the eventual specific formation of a new chiral centre of known absolute configuration. The absolute configuration of the 2-methoxy-5-methyl salt I is defined and its application to the asymmetric synthesis of γ-disubstituted cyclohexenones is described.*

Transition metal π-complexes can be employed in organic synthesis to provide both activation and stereo-control. Complexed intermediates derived from prochiral substrates possess a molecular centre of chirality which may be utilised through stereospecific reactions to direct the formation of a new chiral centre at carbon. The molecular centre of chirality is destroyed when the metal is detached to leave a modified carbon skeleton. This strategy for asymmetric synthesis by means of tricarbonyliron complexes comprises the four processes indicated in Scheme 1.

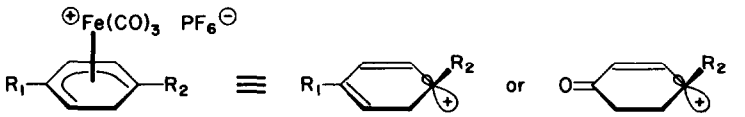


Scheme 1

While this paper concerns the use of $Fe(CO)_3$ complexes, the principles are general to many transition metal π-complexes; $Cr(CO)_3$ complexes of arenes have been utilised[1] in asymmetric synthesis and we, and other authors, have indicated the potential extension of synthetic processes employing racemic mixtures of complexes of iron,[2,3,4] cobalt[5] and palladium.[6]

Partially resolved $Fe(CO)_3$ complexes of simple 1,3-dienes are available by asymmetric induction during complexation. We have recently described[7] the preparation of optically active 2-substituted tricarbonyl(cyclohexadienyl)iron(1+) salts and their conversion[8] into the terpenes (R)-(-)-cryptone and (S)-(+)-"α"-phellandrene. This stereospecific alkylation demonstrates the ability of the $Fe(CO)_3$ group to direct the formation of chiral centres of known configuration. Tricarbonyl(cyclohexadienyl)iron(1+) salts can be regarded[9] as the synthetic equivalents of cyclohexenone cations and the optically active salts I, II and III

may thus be designated equivalents of the specific spatially directed sp^3 cations shown in Scheme 2.



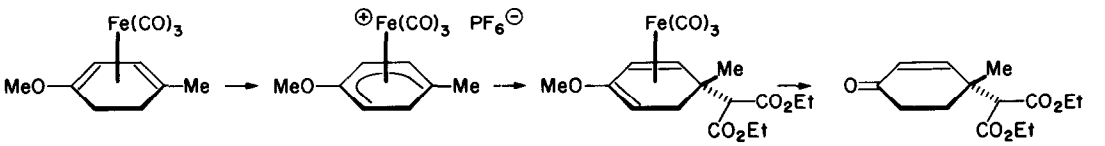
I: (-) R_1 = OMe, R_2 = Me
II: (-) R_1 = OMe, R_2 = H
III: (-) R_1 = Me, R_2 = H

(R_1 = OMe)

Scheme 2

The syntheses of cryptone and phellandrene by this method present some practical difficulties. In the case of cryptone the chiral centre is produced at an enolisable position and the optical yield is reduced by partial racemisation of the enone, while with "α"-phellandrene, removal of the metal from the complex could not so far be achieved without concomitant formation of "α"-terpinene and p-cymene. It was desirable to examine a process where none of these problems occur, in order to determine whether, apart from such effects, the sequence can be accomplished without racemisation. Tricarbonyl[(1,2,3,4,5-η)-2-methoxy-5-methyl-2,4-cyclohexadien-1-yl]iron(1+) PF_6(1-) (I) was selected for this purpose since removal of the coordinated metal group after alkylation of I with the sodium enolates of malonate esters is known[2,10] to proceed without difficulty, and racemisation of the ketonic product is blocked by the C-4 methyl substituent.

The (-) isomer of the salt I ($[\alpha]_D$ = -73°, c = 11, MeCN: ca. 40% e.e.) was obtained by unambiguous hydride abstraction[11] from the neutral diene complex IV ($[\alpha]_D$ = -54°, c = 5, $CHCl_3$). The known[8] configuration of IV leads to the definition of the absolute configuration of I as drawn in Scheme 3.



IV I V VI

Scheme 3

Alkylation by a standard procedure[10] gave V ($[\alpha]_D$ = +42°, c = 7, $CHCl_3$) which was converted in 70% yield[12] into the (-) isomer of VI ($[\alpha]_D$ + -11°, c = 2, $CHCl_3$) by treatment with pyridinium chlorochromate[13] in CH_2Cl_2 for 3.5 h at 23°. Investigation of the optical purity of VI by examination of its PMR spectrum in the presence of europium-(D-3-TFA-camphorate)$_3$ in $CDCl_3$ at both 28° and -30° failed to give a quantitative value for the enantiomeric excess. Other means were needed to assess the optical efficiency of the process. The formation of VI was incomplete after 3.5 h and some V was recovered (37%).

This sample had the same rotation as the starting material. Furthermore, when the product VI was treated again under the same conditions it was recovered without racemisation. While neither product nor starting material is racemised in this final step, the possibility of partial racemisation of the free methoxy-diene intermediate could not yet be eliminated. However, this too seems unlikely, since protonation at C-4 would be expected to be more favourable for the complex than for the free ligand, due to the ability of the $Fe(CO)_3$ group to stabilise the allyl cation thus formed. Partial racemisation during decomplexation was observed when $FeCl_3 \cdot 6H_2O$ (1 gm $FeCl_3 \cdot 6H_2O$, 10 ml EtOH, 1 ml conc.HCl:pH 1) was used. The process was slow, requiring 14 h at 50-60° for partial conversion into VI. Recovered starting material had a slightly reduced rotation. When V ($[\alpha]_D$ = +42°) was dissolved in EtOH/HCl at pH 1 (5:1, v/v) for 70 h, the $[\alpha]_D$ of the recovered V was reduced to +36°, presumably by slow protonation at C-4 to produce a symmetrical η^3-allyl intermediate. Though 2-methoxydiene complexes have been found[14] to protonate specifically at C-1 in conc. H_2SO_4, in the reversible conditions used here the occurrence of the required occasional protonation at C-4 is acceptable. Acidic conditions in this step are therefore to be avoided.

The compound IV was obtained by asymmetric complexation[7] using (-)-3β-acetoxypregna-5,16-diene-20-one. By performing the transfer reaction in benzene at 65° for 90 h, an improved enantiomeric excess of about 40%[15] was achieved. While still too low for true synthetic applications, this suffices to define the configurations of key complexes and to determine whether the conditions or reagents lead to partial racemisation of the products or intermediates in Scheme 1. Fully resolved diene complexes have been prepared, either by complexation[3] of optically active substrates, e.g. (-)-carvone, or by classical resolution of racemic mixtures of complexes.[16] Extension of these methods, or improvement in efficiency of the asymmetric complexation procedure would make available a wide range of potential intermediates to fully resolved chiral centres at carbon.

In order to employ this type of synthetic approach it is in general necessary to use stoichiometric compounds in a series of discrete reaction steps. The $Fe(CO)_3$ is one of a class of superimposed lateral control groups, which in this instance confers on the organic portion the possibility of asymmetry and the unique reactivity characteristics, notably the unusual cation stability and the steric specificity due to complete distinction between the two sides of the ring. Ready attachment and removal of the group renders it analogous to external structural scaffolding, rather than to the nuclear organic activating groups normally used for synthetic control, which may or may not be readily removed or altered.

Further synthetic capabilities result from the fact that the $Fe(CO)_3$ is resistant to a wide range of classical reagents, and it can serve as a protecting group for the methoxy-diene (that is, for the equivalent 2-cyclohexenone) until this structure is unmasked by removal of the metal portion.

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