Journal of Organometallic Chemistry, 319 (1987) C5–C10
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Preliminary communication

PLANAR CHIRALITY IN ORGANOMETALLIC COMPLEXES: APPLICATIONS IN ORGANIC ENANTIOMER SYNTHESIS

IAN M. PALOTAI, G. RICHARD STEPHENSON*
School of Chemical Sciences, University of East Anglia, Norwich, Norfolk, NR4 7TJ (Great Britain)

and LEON A.P. KANE-MAGUIRE
Department of Chemistry, University of Wollongong, Wollongong, New South Wales 2500 (Australia)

(Received September 15th, 1986)

Summary

Tricarbonyl(η^5-2-methyl-3-methoxycyclohexadienyl)iron(1 +) PF_6(1 −) (**2**) undergoes regioselective alkylation by (−)-1-phenylethylamine and by phosphoramide derivatives of carboxylic acid esters. The diastereomeric 1-phenylethylamine adducts were separated and reconverted into (+)-**2** and (−)-**2** by treatment with TFA. Resolved complexes such as **2** have stereochemical properties, arising from the presence of a planar chiral element, which preclude racemisation during their use in organic enantiomer synthesis.

Compounds which contain planar chiral elements [1] have found little application in asymmetric synthesis until work began on the alkylation of transition metal π-complexes. Unlike conventional organic examples such as 'strapped' arenes, metal π-complexes formed from prochiral ligands comprise a planar chiral element which is capable of demonstrating very high chemical differentiation between the two faces of the plane in the ligand. We have recently reported [2] several instances in which iron complexes with planar chirality have been utilized with complete stereocontrol as equivalents of cyclohexenone cation synthons. This note concerns the uses of resolved complexes as chiral intermediates to 5-substituted 2-methylcyclohexenones (Scheme 1) in terpene synthesis and draws attention to the advantages inherent in this general approach when applied in organic enantiomer synthesis.

Consideration of the mechanism proposed [3] for the racemisation of organoiron complexes such as **3a**, shown in Scheme 2, indicated that the addition of a further substituent to the planar chiral element would transform this process from a racemisation reaction into a regioisomerisation reaction. This arises because, when

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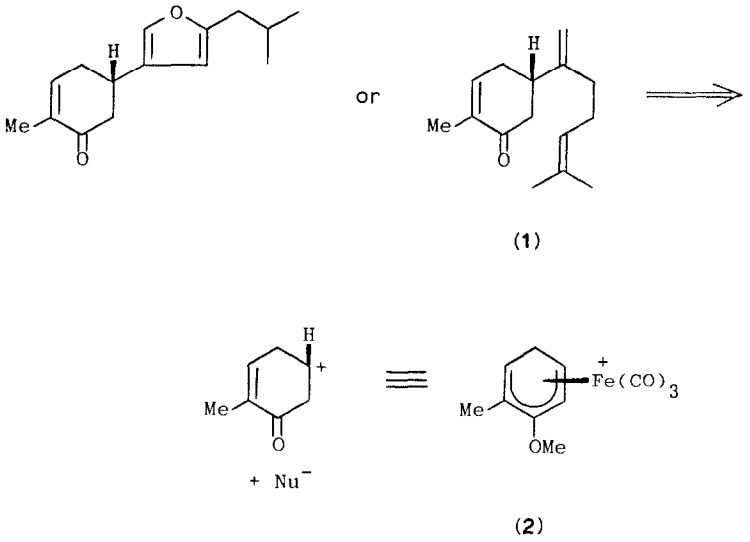


SCHEME 1.

suitably substituted, tricarbonyliron * complexes cannnot form a symmetrical intermediate, whatever changes might occur to the position and extent of bonding to the metal. Such a planar chiral element, once introduced in fully resolved form, will render synthetic intermediates immune to racemisation until the stage at which the metal is removed to afford an organic product. If the final metal complex can be obtained as a single regioisomer, it follows that it must also be optically pure.

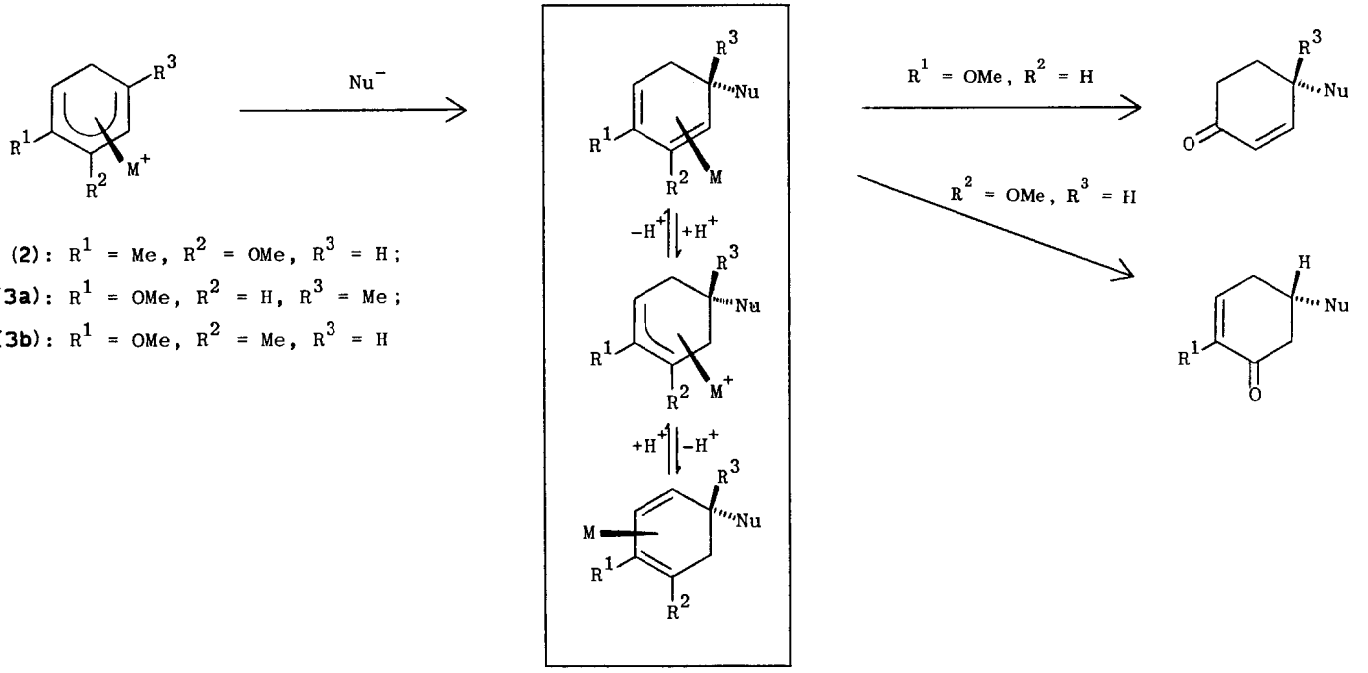
As a first step towards the exploitation of these unusual properties, we have examined the resolution and alkylation of doubly substituted π-complexes of type **2**. Our initial investigation [4] of organoiron complexes with these properties, however, was troubled by the poor regioselectivity of alkylation reactions of **2**. We now describe the regiocontrolled alkylation procedures for the introduction of an alkyl side-chain suitable for the synthesis of cryptomerione (**1**), and for the addition of chiral auxiliaries for use in the resolution of **2** so making these complexes available in optically active form for application in enantiomer synthesis.

The alkylating agents **4b** and **4c**, in which the stabilized enolate functionality was expected to encourage regioselective alkylation of **2**, were prepared from **4a** in 91 and 76% yields respectively, by reaction with potassium hydride followed by the appropriate alkyl halides, iodomethane and 5-bromo-2-methyl-2-pentene (**5**). Unlike

(*continued on p. C9*)

* In principle, this property is common to all transition metal π-complexes with suitably substituted prochiral ligands, provided no mechanism is available for the metal to exchange between the faces of the ligand. For tricarbonyliron complexes such isomerisation reactions, which would be revealed by the formation of mixtures of diastereoisomers from products such as **6** and **7** or by the racemisation of optically active complexes previously studied (ref. 8), can be ruled out except in special circumstances (ref. 9). The situation with other synthetically useful metal complexes requires separate investigation in each case; the extensively studied chromium arene complexes appear not to equilibrate in this way (ref. 10). Some palladium allyl complexes can undergo reactions of this type (ref. 11), but here, too, racemisation can be precluded by the correct positioning of substituents (ref. 12).

SCHEME 2.

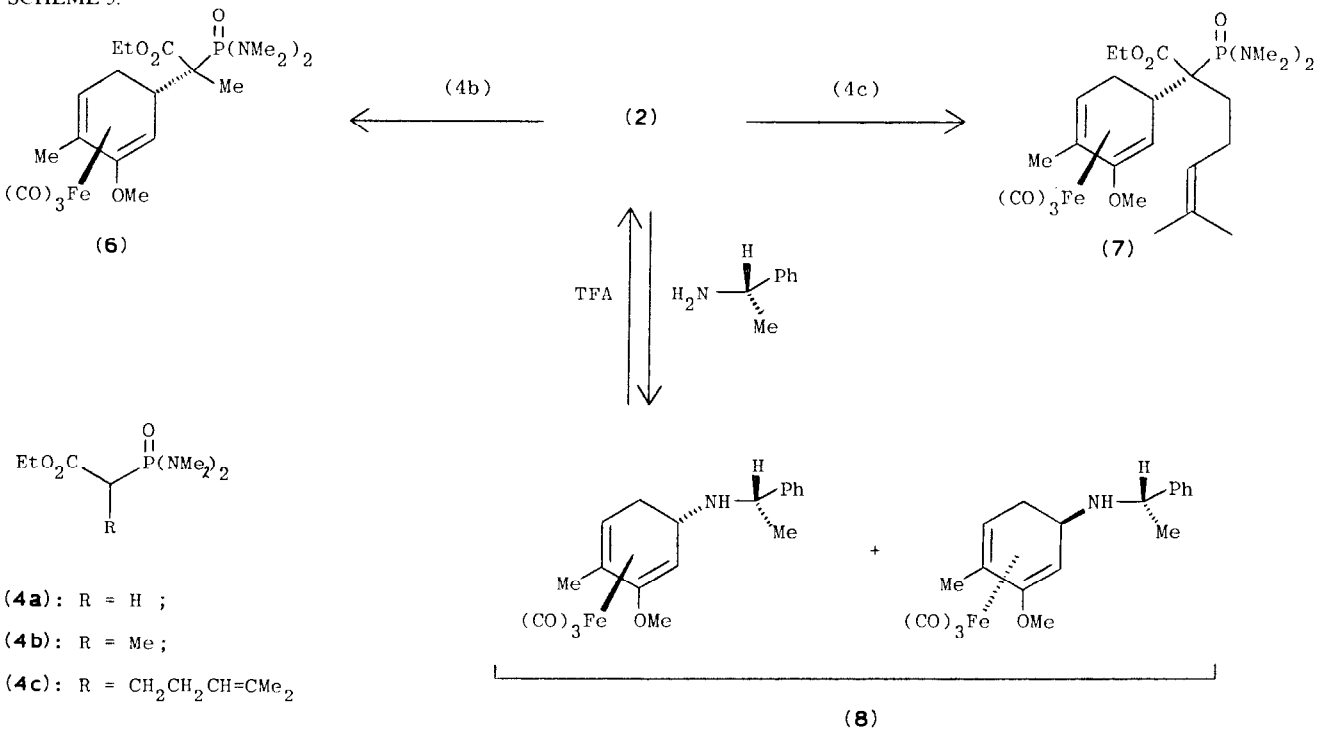


(2): R^1 = Me, R^2 = OMe, R^3 = H ;

(3a): R^1 = OMe, R^2 = H, R^3 = Me ;

(3b): R^1 = OMe, R^2 = Me, R^3 = H

SCHEME 3.


EtO2C
P(NMe2)2
O
Me
(CO)3Fe
OMe
(6)
(4b)
(2)
(4c)
(7)
TFA
H2N
H
Ph
Me
NH
(8)
(4a): R = H ;
(4b): R = Me ;
(4c): R = CH2CH2CH=CMe2

the related alkylation [5] of phosphonate esters, no problems with elimination were encountered in the use of **5**. Reaction of the sodium enolate of **4b** with the salt (±)-**2** gave a low yield of alkylation product. Use of potassium hydride to form the enolates proved somewhat more effective. In both cases, alkylation products **6** and **7** were obtained as single regioisomers. Stereocontrol at the new chiral centre in the cyclohexadiene ring, destined to become C(5) of the enone product, was complete, demonstrating once again the powerful influence of the metal as a control centre. Both **6** and **7** were shown by NMR to be mixtures of diastereoisomers at the position α to the ring, but since this centre will subsequently be removed, control at this position is not required.

Addition of (−)-1-phenylethylamine ($[\alpha]_D - 37°$) to (±)-**2** was also regiocontrolled, affording, in 80% yield, the expected [6,7] mixture of diastereoisomers **8** which both arise from addition of the nucleophile *trans* to the metal. In view of our earlier successful resolution [6] of the salt **3b** on an analytical scale by HPLC, separation of **8a** and **8b** was examined by preparative HPLC on a Dynamax 21.4 mm I.D. silica column eluted with petrol/isopropanol/triethylamine (90/3/1). Samples of **8a** ($[\alpha]_D - 275°$) and **8b** ($[\alpha]_D + 116°$), obtained in this way, were shown to be pure by NMR and HPLC. It is notable, however, that the recovery of the complexes from the column was poor. Losses at this stage could arise by dissociation of phenylethylamine, but, unlike an example reported [7] for *N*-methylphenylethylamine, alcohol byproducts were not produced. Removal of the chiral auxiliary from **8a** by treatment with TFA afforded (−)-**2** ($[\alpha]_D - 179°$) in 74% yield. The enantiomer, (+)-**2** ($[\alpha]_D + 155°$), was similarly obtained from **8b**. The optical purity of these products is under investigation. The ability to effect the resolution and controlled alkylation of doubly substituted complexes such as **2** completes the necessary prerequisites for the demonstration of their use in the organic synthesis of natural products.

Stoichiometric metal π-complexes with planar chirality offer a number of advantages over catalytic systems when employed in enantiomer synthesis. The metal is not displaced from the product during alkylation, and so can be retained through a series of reactions to block racemisation and to serve as a control centre at subsequent steps. In addition, activation arises from the metal, not from the substituents that are destined to become functional groups in the product. This leads to considerable flexibility in synthesis design. This paper describes our initial results in a program of work that aims at first to demonstrate these advantages by the synthesis of simple natural products in which the absolute configuration and optical purity of a single chiral centre arises as a consequence of the stereochemical properties of complexes comprising a resolved planar chiral element, a first step towards the ultimate practical realization of the full potential of metal π-complexes as chiral synthetic equivalents.

Acknowledgements. GRS thanks The Royal Society for a 1983 University Research Fellowship.

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