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Preliminary communication

Transition metal mediated asymmetric synthesis XII *. Tricarbonyliron complexes as intermediates to isoquinuclidines

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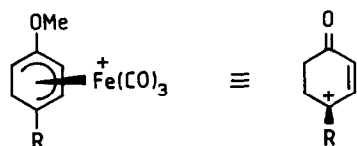
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Abstract

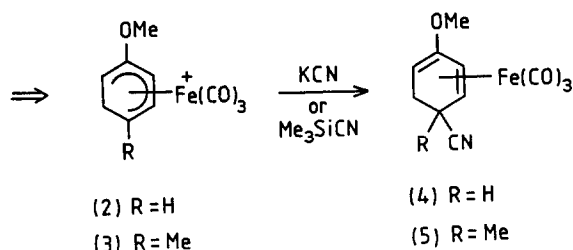
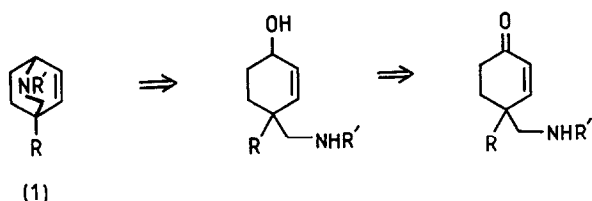
Tricarbonyl(η^5 -2-methoxy-5-methylcyclohexadienyl)iron(1+) hexafluorophosphate(1-) has been converted into a dehydroisoquinuclidine. Although the scope of the process is limited by competing aromatisation during removal of the tricarbonyliron group from the organic ligand, it is appropriate in situations where substituents block aromatisation. Cyclisation to the dehydroisoquinuclidine is facilitated by the use of an intermediate bearing a secondary amine.

Since the presence of an isoquinuclidine ring system in a molecule is frequently associated with significant pharmacological properties [1], enantioselective routes to compounds of this type are of increasing importance. In efforts to develop new applications of chiral electrophilic π -complexes in asymmetric synthesis, we have explored an approach to the dehydroisoquinuclidine structure **1** based on the equivalence [2] of tricarbonyl(η^5 -methoxycyclohexadienyl)iron(1+) complexes to stereocontrolled enone cation synthons of the type shown in Scheme 1. In this



Scheme 1.

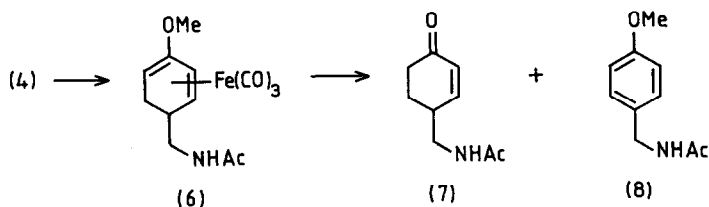
* For Part XI see D.A. Owen, G.R. Stephenson, H. Finch and S. Swanson, *Tetrahedron Lett.*, 30 (1989) 2607.

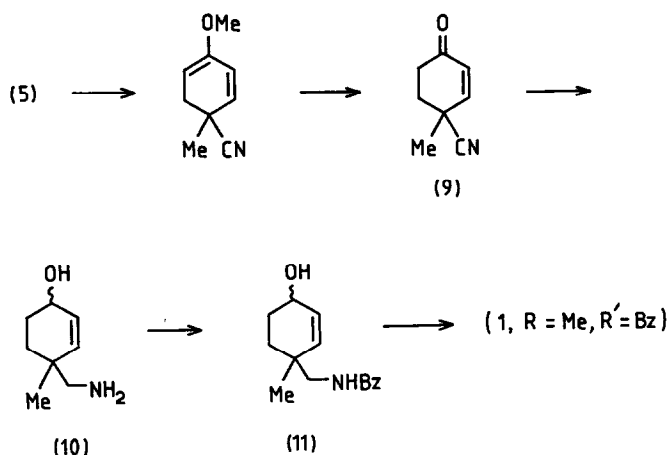


Scheme 2.

approach (Scheme 2), the chirality of attachment of the metal ensures control of the configuration of the chiral centre formed in the nucleophile addition step. This paper describes the results of two model studies that establish the possibility and scope of this route.

The nitrile starting material **4** which was needed for the first of these studies was easily obtained by reaction [3] of the 2-methoxycyclohexadienyl cation **2** with potassium cyanide (Scheme 2). Attempted removal of the metal with ceric ammonium nitrate, however, gave only aromatic products. In order to obtain an alternative substrate for metal removal, hydrogenation of **4** was undertaken using Raney nickel in acetic anhydride. This afforded the acetamide **6** in 98% yield. Once again, attempts to remove the metal to yield the enone **7** were hindered by aromatisation, affording mostly the known [4] arene **8**, which was identified by comparison with authentic material produced by acetylation of 4-methoxybenzylamine. Of the decomplexation conditions examined, oxidation with ferric chloride gave encouraging results and traces of the required compound were identified in the crude product. Trimethylamine *N*-oxide, pyridinium chlorochromate, and sodium peroxide either failed to remove the metal entirely, or else caused extensive aromatisation. Only with ceric ammonium nitrate could any of the enone **7** be obtained. This compound was separated from a mixture of products by the formation of its 2,4-dinitrophenylhydrazone derivative, which was formed in 35% yield. In this case, too, competing aromatisation during the decomplexation step had proved a severe problem





In the hope of obtaining sufficient material to allow examination of the cyclisation step leading to the dehydroisoquinuclidine, attention switched to the dienyl complex **3**, which would yield products in which aromatisation would be blocked by the methyl substituent. Reaction of **3** with trimethylsilyl cyanide gave the known adduct [5] **5** from which the metal was successfully removed by reaction with trimethylamine *N*-oxide. Hydrolysis of the enol ether afforded the enone **9** [6*] (65% from **5**) which was converted into the amine **10**, with concomitant 1,2-reduction of the ketone, by reaction with lithium aluminium hydride. The product **10** was obtained in 93% yield as a 3:1 mixture of diastereoisomers.

Conditions for cyclisation to form the isoquinuclidine were then investigated. Reactions of **10** with *p*-toluenesulphonic acid, with PPh₃ · Br₂, and with thionyl chloride (followed by treatment with base), were all unsuccessful, but, by application of the latter procedure with a derivatised substrate, a sample of the cyclisation product was at last obtained. Experience with related cyclisations had suggested that secondary amines often give superior results [7]. Accordingly, we elected to prepare the benzyl derivative **11**, using conditions [8] which were known to be successful with similar compounds. Condensation of **10** with benzaldehyde, followed by reduction of the resulting imine with sodium borohydride, afforded **11** in 86% yield. Chlorination of **11** was examined. This provided the expected mixture of regioisomeric allyl chlorides which were used directly in the cyclisation step without separation. Heating with potassium carbonate in isopropanol effected the required cyclisation. The isoquinuclidine product (**1**, R = Me, R' = Bz) was isolated by column chromatography in 28% yield based on **11**. This product (**1**, R = Me, R' = Bz) showed the expected alkene C–H resonances at 6.14 and 6.23 ppm for the unsaturation in the isoquinuclidine ring, a feature that was absent in spectra of crude products from the attempted cyclisations using other conditions that were discussed above.

* Reference number with asterisk indicates a note in the list of references.

The identity of the cyclisation product was confirmed by examination of its fragmentation in the mass spectrometer. In addition to the molecular ion at 213 (M^+ , 10%), significant fragment ions at 185 ($M^+ - C_2H_4$, 37%) and 184 ($M^+ - C_2H_4 - H$, 47%) which were absent in mass spectra of uncyclised compounds, confirmed the presence of the heterocyclic bridge in **1** ($R = Me$, $R' = Bz$), since fragmentation by retro-Diels-Alder loss of ethene [9] from the carbocyclic ring would be followed by loss of H^+ to give the *N*-benzyl-3-methylpyridinium ion observed at mass 184.

The reaction sequence from **3** to **1** ($R = Me$, $R' = Bz$) provides the first example of the preparation of an isoquinuclidine from tricarbonyl(η^5 -cyclohexadienyl)iron-(1+) cations, electrophilic reagents of a type which are finding increasing use in stereocontrolled organic synthesis [10].

In this preliminary investigation we have demonstrated that, in cases where aromatisation does not intervene, it is possible to form the isoquinuclidine ring system by a reaction sequence that starts with cationic cyclohexadienyl iron π -complexes of a type which are available in homochiral form [11]. Since the stereochemistry of attachment of the CH_2NHBz bridge is determined by the complete diastereoselectivity of nucleophile addition to the cationic dienyl complex, relay of chirality from the metal complex to the heterocyclic product should be possible. Further studies that seek to establish more practical procedures for the cyclisation step, and for metal removal without the limitations presently imposed by aromatisation side-reactions, are currently under investigation in work that will apply this approach to the enantioselective synthesis of isoquinuclidine natural products.

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