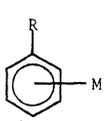
Iron-Stabilized Carbocations as Intermediates for Organic Synthesis

Anthony J. Pearson

Summary. Attachment of a transition metal moiety to an olefinic ligand presents the organic chemist with unequaled opportunities to control the regio- and stereospecificities of bond formation. Applications of cationic dienyliron-carbonyl complexes to a range of natural product syntheses have been developed. These applications show how the iron-carbonyl unit directs the regio- and stereochemistry of nucleophile addition. They also show that the iron-carbonyl unit can be used to stabilize otherwise inaccessible carbocations, thereby making them readily available as synthetic intermediates.

The synthetic organic chemist is faced with an ever-increasing number of methods for accomplishing carbon-carbon bond formation, methods for protection of sensitive functional groups in a molecule, and methods for the interconversion of certain functional groups, together with the means of overcoming problems of stereocontrol. It is not surprising, therefore, that many synthetic chemists cannot pay close attention to the developments made in transition metal organometallic chemistry; there is enough to do in keeping up with the more traditional elements of organic chemistry. However, the attachment of a transition metal moiety of some kind to an organic ligand offers diverse possibilities for the selective activation or protection of, for example, olefinic groups. Within recent years these methods have been applied to organic synthesis. Often a total synthesis of some complex natural product or analog that is achieved via a transition metal complex is no better (or no worse) in number of steps and overall yield than the more conventional methods of synthesizing the same molecule. However, at an early developmental stage, it is more important to demonstrate that such applications are possible. In fact, the statement that target-oriented organic synthesis makes a contribution to fundamental organometallic chemistry is probably truer than the converse statement. This will become clearer as the discussion proceeds.

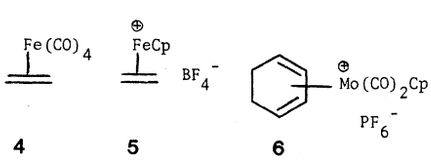
In this article, I present some new applications of organoiron complexes to organic synthesis, but first it is pertinent to make a few comments concerning organometallic chemistry in general. Many features of transition metal complexes make them potentially significant, but for such complexes to be useful, we need to effect transformations that on the uncomplexed organic ligand are either impossible or extremely difficult, or else we must be able to prepare useful intermediates that are not readily accessible by standard methods. As an example of the former requirement, reaction of aromatic molecules with nucleophiles occurs only in a few cases where the aromatic ring is strongly activated by the attachment of, for example, a nitro group, and even then the type of nucleophile that may be employed is severely limited. However, attachment of a $Cr(CO)_3$, $Mn(CO)_3^+$, or $FeCp^+$ (Cp = cyclopentadienyl) group to the aromatic molecule, as in complexes **1**, **2**, and **3**, results in considerable activation, leading to ready addition of a wide range of nucleophiles to the aromatic ligand (*1–3*). Isolated alkenes and dienes are also inert to nucleophilic attack. However, ethylene complexes such as **4** (*4*) and **5** (*5*) and diene complexes such as **6** (*6*) all undergo facile addition of nucleophiles. There are, of course, some problems associated with the removal of metal from the products of nucleophile addition in certain cases but with proper focus these problems will eventually be solved.



1 M = $Cr(CO)_3$

2 M = $[Mn(CO)_3]^+$ BF_4^- or PF_6^-

3 M = $[FeCp]^+$ BF_4^- or PF_6^-



4 **5** **6**

Examples of organic intermediates that are readily available with organometallic chemistry but either unobtainable or difficult to prepare by standard methods are given below.

All of the above discussion refers to transition metal complexes behaving as stoichiometric reagents. The other useful attribute of organometallic systems, which is well known, is their capacity to act as catalysts for various conversions. Many industrial processes, including polymerization, hydroformylation, and related reactions, utilize catalysis in one form or another and, in this respect, organometallic chemistry is well established. However, this article presents only stoichiometric reactions and how to utilize the chemistry of complexed ligands for purposes of multistage synthesis.

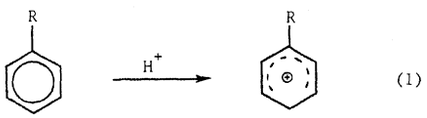
Cyclohexadienyl Cations in Synthesis

My research, performed in collaboration with my co-workers, has, for the past 6 years, been directed at the synthetic application of dienyl cations that are stabilized by their attachment to an iron (0) moiety, usually of the type $Fe(CO)_2L$ (L = CO, triarylphosphine, or triarylphosphite). We have been guided by the philosophy that deeper understanding of basic chemical phenomena often evolves from the challenges that arise through the discipline of a well-defined target, and in this article I have selected highlights from our work illustrating the interplay of target synthesis and fundamental discovery. We have aimed at both the synthesis of natural products and the construction of molecules that might be useful for studying certain organic reactivity phenomena.

As a starting example, let us consider the simple cyclohexadienyl cation. Organic chemistry textbooks tell us that this type of cation is an intermediate during reactions of benzene with electrophiles, and indeed, treatment of benzene with strong acid gives solutions of the cation that may be characterized spectroscopically (*7*). However, the dienyl cation is far too unstable to allow isolation or even generation in situ and further use as a synthetic intermediate. It is

The author is in the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106.

worth noting at this point that similar protonation of anisole occurs *para* to the methoxy group to give the 3-methoxy-substituted cation, again stable only in strong acid solution (summarized in Eq. 1) (*8*).

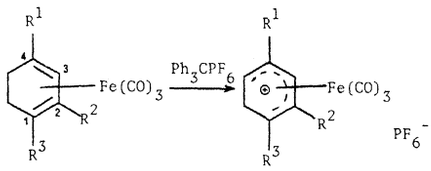


(1)

R = H, OMe

On the other hand, tricarbonylcyclohexadienyliron hexafluorophosphate or tetrafluoroborate **8a** is readily prepared, as shown in Fig. 1, as a stable yellow solid that can be stored in a reagent bottle indefinitely at room temperature (*9*). Of particular interest is the formation of substituted complexes **8b** and **8c**, since these do not contain a 3-methoxy-substituted (or 1-methoxy-substituted) cyclohexadienyl cation, which might have been expected to be the more stable species on the basis of organic chemistry. The metal-stabilized cations obtained by hydride abstraction thus appear to be largely complementary to those produced by protonation of aromatic rings in the absence of a metal (see below).

Despite the stability of these iron-bound carbocations, they are highly reactive toward nucleophiles. For example, the complex **8a** reacts instantaneously at room temperature with the dimethyl malonate anion to give a quantitative yield of the cyclohexadiene complex **9a**. The reaction is regiospecific, occurring only at the dienyl terminus, and stereospecific, occurring *trans* to the metal, as shown in Fig. 2. The stereospecificity of this reaction ultimately will be useful for generating optically active organic molecules, since a number of substituted dienyl complexes can now be prepared in optically active form (*10*). In order to be useful for organic synthesis, the product diene-$Fe(CO)_3$ complexes, for example, **9a**, must fulfill a number of requirements. First, we should be able to remove the metal selectively and in high yield without affecting sensitive functional groups in the complex or resulting organic molecules. Second, in order to take advantage of the potential of the metal in masking the diene part of the molecules, we should be able to carry out a range of transformations on functional groups in an attached substituent without affecting the metal moiety. Third, we should be able to prepare useful organic intermediates not easily obtained by standard methods.

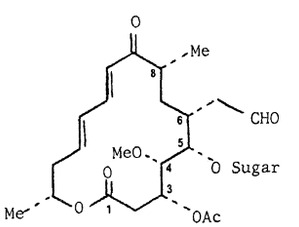


7 8

a) $R^1 = R^2 = R^3 = H$
b) $R^1 = R^3 = H$, $R^2 = OMe$
c) $R^1 = OMe$, $R^2 = H$, $R^3 = Me$
d) $R^1 = OMe$, $R^2 = H$, $R^3 = Et$
e) $R^1 = OPr^i$, $R^2 = H$, $R^3 = Et$
f) $R^1 = OMe$, $R^2 = H$, $R^3 = CH_2CH_2OMe$
g) $R^1 = OPr^i$, $R^2 = H$, $R^3 = CH_2CH_2OMe$

Fig. 1.

I now describe a series of transformations that illustrate the first and third requirements above. The dimethyl malonate adduct **9a** may be decomplexed to give the cyclohexadiene derivative **10** in 90 percent yield by treatment with trimethylamine-*N*-oxide (*11*). This particular type of functionally substituted diene is not readily available by standard methods of organic synthesis. It turns out to be a fairly useful compound, being readily converted to the dienylacetic acid **11**. We were able to use this to explore a novel lactonization promoted by selenium-based electrophiles, followed by allylic selenoxide [2,3]sigmatropic rearrangement (Fig. 3), to give the hydroxy lactone **12** in a stereospecific and regiospecific manner (*12*). The hydroxy lactone and its derived acetate thus obtained can be ozonolized to give molecules **13** and **14**, which might be useful as building blocks for synthesis of the macrolide antibiotic Magnamycin B (**15**),



15 Magnamycin B

since they have the correct relative stereochemistry corresponding to C-4, C-5, and C-6. Thus, we are able to prepare in a very simple way a dienoic acid that is not easily made by other methods and on it explore new reactions that can be used for the purposes of total synthesis. Actually, stereochemical outcome of the selenolactonization process turned out to be very interesting from the mechanistic angle but we will refrain from discussing it here.

Gamma Alkylation of α,β-Unsaturated Ketones

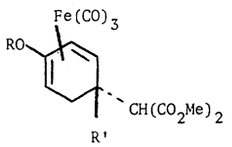
Other iron-stabilized cyclohexadienyl cations are well known by chemists, and these also turn out to be useful for synthesis. Let us examine the reactivity of the methoxy-substituted complex **8b**. When treated with a range of carbon nucleophiles, for example, stable enolates and their equivalents or allylsilanes and other alkylating agents, reaction occurs entirely at the dienyl terminus remote from the methoxy group to give the diene complexes, for example, **9b** (Fig. 2). These may be converted to 4-substituted cyclohexenones **17** in high yield (*13*). In terms of synthetic equivalents, then, the complex **8b** may be regarded as the equivalent of the cyclohexenone γ-cation **18**, the overall process **8b** → **17** corresponding to γ-alkylation of cyclohexenone. When compared with efforts directed at the same γ-alkylation of cyclohexenone through the reaction of its silyl dienol ether **19** with electrophiles (*14*), the γ-cation approach offers considerable advantage in selectivity, yield, and variety of substituents that can be introduced. What is more, the silicon-directed method appears to be suitable only for cyclohexenones that do not already carry a substituent at position 4.

On the other hand, the organoiron method gives excellent "γ-alkylation" results for a range of substituted derivatives. In particular, reaction of the methyl-substituted complex **8c** with stable enolate anions, for example, from dimethyl malonate and various β-keto esters, gives almost exclusively the products (**20**) of γ-alkylation. Although this is more limited than the reaction for the complex **8b**, we have been able to utilize the behavior of **8c** for synthesis of a range of natural products and related compounds. Of some interest is our ability to effect short synthesis (*15*), of trichothecene analogs such as **21** (Fig. 4). This synthesis utilized a novel, regiospecific C–C bond-forming reaction in which the cyclopentane and cyclohexane rings were joined at their points of highest substitution in a single, simple step. The natural products related to this compound are mycotoxins, some of which are suspected as being present in chemical warfare agents such as "yellow rain"; mycotoxins are also a serious agricultural problem and have been investigated as potential antitumor agents. Synthetic analogs are of interest in developing antitoxins and also as potential nontoxic therapeutic agents. The synthesis of **21** also illustrates the diversity of

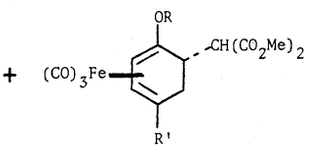
transformations possible in the presence of the diene-$Fe(CO)_3$ unit and the selective removal of metal at a later stage.

When we switch from the methyl-substituted complex **8c** to complexes bearing substituents larger than methyl, there arises a problem with regioselectivity due to fairly obvious steric effects. For example, the ethyl-substituted complex **8d**, on reaction with the sodium enolate of dimethyl malonate, gives a 3.6:1 mixture of complexes **22a** and **23a**. We were

8d to **8g** ⟶



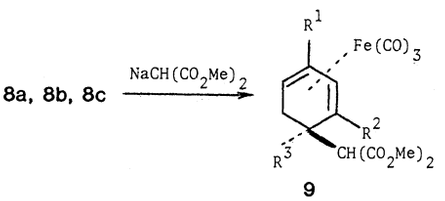
22



23

a) R = Me, R' = Et
b) R = i-Pr, R' = Et
c) R = Me, R' = CH_2CH_2OMe
d) R = i-Pr, R' = CH_2CH_2OMe

concerned with improving this ratio, since mixtures always bring with them a separation problem as well as a lower yield of the desired product. We found that the regioselectivity during addition of malonate anion to **8d** is dependent on the nature of the metal cation associated with the enolate (*16*). For example, the ratios of **22a** and **23a** obtained with $LiCH(CO_2Me)_2$ (3:1), $NaCH(CO_2Me)_2$ (4.6:1), and $KCH(CO_2Me)_2$ (5.6:1) increase as the degree of association between enolate and cation decreases. These results give us some information regarding the factors that control the regioselectivity of nucleophile addition and indicate that probably the major determining factor is a strong interaction between the highest occupied molecular orbital (HOMO) of the nucleophile and the lowest unoccupied molecular orbital (LUMO) of the dienyl complex, as might be expected. The issue is complicated by steric effects from substituents on the dienyl ligand and coulombic effects arising from the difference in positive charge shared by the two ends of the dienyl group. A major problem is that unambiguous results are not available from molecular orbital calculations on the dienyl complex; this is an area where further advances in theoretical chemistry are required.

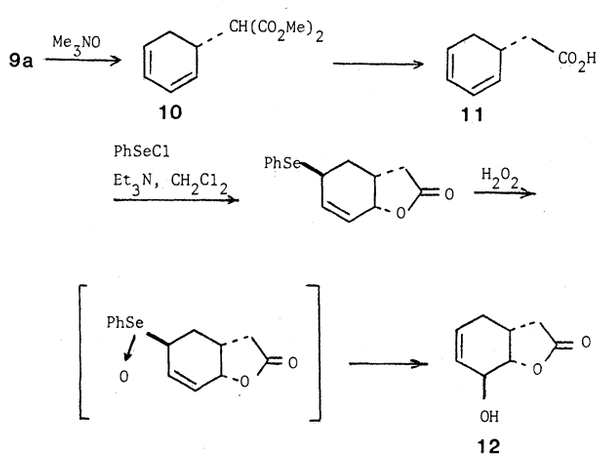


9

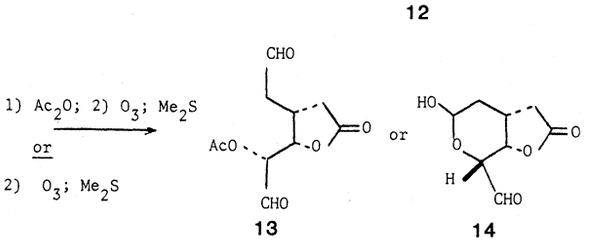
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = OMe$, $R^2 = R^3 = H$
c) $R^1 = OMe$, $R^2 = H$, $R^3 = Me$

Fig. 2.

Even though a marked improvement in the regioselectivity of enolate addition is achieved by altering the countercation, it would be even better if a single product could be obtained ideally in quantitative yield so that separation would not be needed. This might be accomplished by taking advantage of steric versus electronic effects. Thus, we could increase the size of the alkoxy group by changing from methoxy- to isopropoxy, as in dienyl complex **8e**. However, this requires that we effect hydride abstraction regiospecifically from precursor diene complex **7e** (see Fig. 1), and although this occurs for the methoxy-substituted complex **7d** and gives dienyl complex **8d**, it was not known whether the larger isopropoxy group would lead to detrimental steric effects during this reaction, by interaction with the incoming bulky triphenylmethyl cation. Fortunately, nature is on the chemist's side, since there appears to be an electronic effect favoring hydride loss from C-5 in the diene complexes.

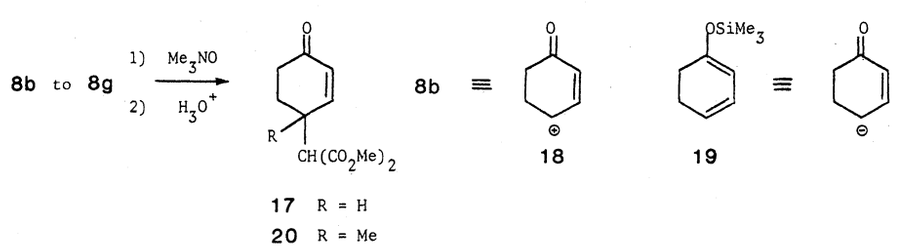


10 **11** **12**

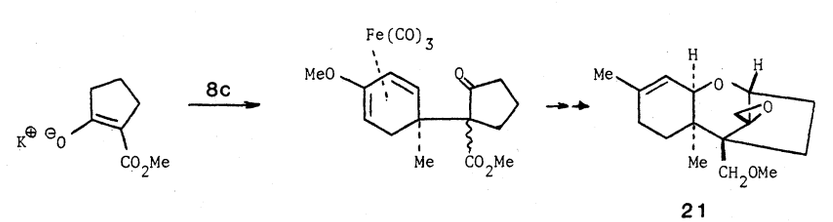


13 **14**

Fig. 3.



17 R = H
20 R = Me



21

Fig. 4.

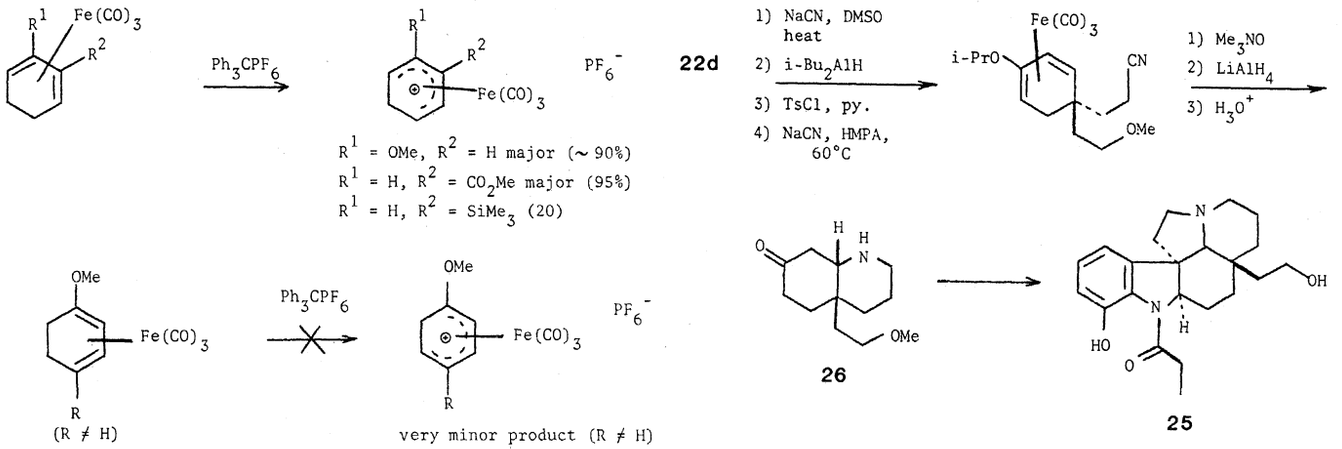


Fig. 5 (left) and Fig. 6 (right).

Treatment of the isopropoxy-substituted derivative **7e** with $Ph_3C^+PF_6^-$ gives the desired dienyl complex **8e** in 98 percent yield (*17*). Reaction of this complex with $KCH(CO_2Me)_2$ gives the single product **22b** in essentially quantitative yield.

Factors Controlling Hydride Abstraction

Let us now examine more carefully the outcome of the above hydride abstraction process. The conversion of the diene complex **7e** to dienyl derivative **8e** appears to be highly favored despite the presence of a sterically demanding, but electron donating, alkoxy group. Moreover, the dienyl cation obtained, namely, a 2-alkoxy–substituted derivative, is the one we would least have expected on the basis of a knowledge of the relative stabilization of uncomplexed dienyl cations (see above; compare with the well-known *ortho-para* directing effects of alkoxy groups during electrophilic aromatic substituents). Instead, we might have expected to obtain a 1-alkoxy–substituted dienyl cation, for example, **24**. The directing effect of electron-withdrawing (cation-destabilizing) substituents on the process of hydride abstraction is also shown in the examples given in Fig. 5. In all cases where steric effects at the two CH_2 groups are balanced, we obtain the dienyl complex least expected from a knowledge of (ground-state) organic chemistry. We have interpreted this as follows (*18*): given a choice of two product dienyl complexes, the one that is favored corresponds to the free dienyl cation with the higher-energy HOMO and lower-energy LUMO. The reason is that this combination leads to a better energy match and therefore a better synergic interaction with filled (interacting with LUMO) and unfilled (interacting with HOMO) iron *d* orbitals. Consequently, a stronger bonding situation is realized in the product as well as in the transition state, since this is most likely product-like. This means that the activation energy is lower for formation of the 2-alkoxy–substituted derivative, but it must be stressed that this is only when steric effects are balanced. An alternative explanation is based on the observation that C-2 (and C-4) are the most positive positions in the dienyl complexes (*19*). Thus, electron-releasing substituents at these positions stabilize, whereas electron acceptors destabilize the complexes (*20*).

Application of Regiocontrol

We were now in a position to take advantage of these interesting discoveries, and for this purpose we set ourselves the target of synthesizing the *Aspidosperma* alkaloid limaspermine (**25**) in racemic form (*21*). We had earlier discovered that the methoxyethyl-substituted complex **8f** reacted with dimethyl sodiomalonate [$NaCH(CO_2Me)_2$] to give a 2.5:1 mixture of diene complexes **22c** and **23c**. We did not consider this to be good enough for a reaction to be incorporated as a key C–C bond-forming process in a multistep total synthesis. However, using the isopropoxy-substituted complex **8g** in conjunction with the potassium enolate of dimethyl malonate gave a 10:1 mixture of complexes **22d** and **23d**, from which pure **22d** was obtained in high yield by simple recrystallization. This material was transformed as shown in Fig. 6 to the decahydroquinoline intermediate **26**, again illustrating the remarkable stability of the diene-$Fe(CO)_3$ unit toward a wide range of chemical transformations, such as decarboxylation and homologation. It is noteworthy that the tricarbonyl (2-alkoxycyclohexadiene)-iron grouping is effectively a protected cyclohexenone, allowing functional group interconversions on the side chain that would be troublesome in its absence. The decahydroquinoline **26** was then converted to (±)-limaspermine (**25**) by standard organic chemical transformations. This represented the first total synthesis of a complex natural product (five rings; four chiral centers) from such organoiron precursors.

Other Approaches to Regiocontrolled Nucleophile Addition

Two other possible methods for controlling the regiochemistry of nucleophile addition to dienyl complexes relied upon the formation of a ring to tie down the newly introduced substituent. The first method, which is fairly obvious, is to perform the nucleophile addition intramolecularly. To test this we required dienyl complexes containing latent nucleophiles in the side chain, and we chose to study the preparation and reactions of complexes bearing enolizable groups, namely, β-keto ester, gem-diester, cyano ester, and gem-dinitrile, as shown in Fig. 7. The requisite complexes were readily prepared, again illustrating the stability of the metal moiety during a range of organic transformations. Cyclization of all of these compounds except the gem-diesters occurred on treatment with mild base, affording the spirocyclic compounds (*22*). Although this study was limited to the formation of spirocyclic systems, we anticipate that further development will ultimately lead to more general ring-forming reactions. However, a spirocenter is an important focal point in a number of fairly important natural products (*23*).

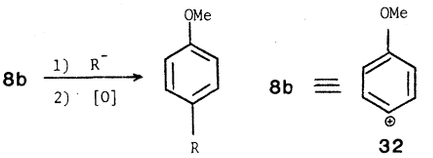
The second method involving ring for-

mation relied on the ability of primary amine nucleophiles to add reversibly to dienyl complexes. This allowed a series of equilibria to be obtained, ultimately giving high yield of a single product.

Thus treatment of the *p*-toluenesulfonyloxy–substituted dienyl complexes **27a** and **27b** with benzylamine resulted in excellent yields of the azaspirocyclic compounds **28a** and **28b**, which could be converted to the enones **29a** and **29b** (Fig. 8). The latter compound proved to be an effective intermediate for synthetic approaches to the important arrow poison histrionicotoxin (**30**). We have already converted **29b** to the biologically active compound (±)-dependentylperhydrohistrionicotoxin (**31**) and anticipate that modifications of the sequence of organic transformations will ultimately lead to a synthesis of histrionicotoxin itself (*24*).

Aryl Cation Equivalents

The addition of carbon nucleophiles to simple cyclohexadienyl-$Fe(CO)_3$ cations also provided an opportunity to examine the potential of these complexes as aryl cation equivalents suitable for application to total synthesis. For example, the known complex **8b**, readily prepared from anisole, reacts with a range of nucleophiles to give diene complexes of general structure **9b**, with groups other than $CH(CO_2Me)_2$ attached. Removal of the metal followed by oxidation of the dienol ether to aromatic ring gives *p*-substituted anisole derivatives. Thus, the complex **8b** may be regarded as the synthetic equivalent of the *p*-anisyl cation **32**. There are now a number of



32

variously substituted cyclohexadienyl-$Fe(CO)_3$ complexes in the literature, so that we have access to a large number of specific aryl cation equivalents. Addition of nucleophilic entities onto an aromatic ring can also be accomplished with the use of arene-$Cr(CO)_3$ complexes and arene-$Mn(CO)_3$ cations (see above); the directing capacity of substituents, for example, OMe, on the arene ligand of these systems is often different from that encountered in the organoiron series. Also, the overall reactivity of these complexes towards nucleophiles is different. Consequently, these three organometallic species offer a complementary array of aryl cation equivalents. We illustrate below the potential applicability of complex **8b** to natural products synthesis with our approach to *O*-methyljoubertiamine (**33**), a Sceletium alkaloid related to the pharmacologically active ingredients of the drug Channa, which is used as a narcotic by the bushmen of Namaqualand.

Our synthesis (*25*) of this alkaloid is summarized in Fig. 9; we produced the enone **35**, which had earlier been converted to *O*-methyljoubertiamine by Sanchez (*26*). The complex **8b** was readily converted to the *p*-anisyl-substituted cyclohexenone derivative **34** by the sequence shown, and this was homologated to the Sanchez intermediate. Although this method is no better than more conventional syntheses, it illustrates the potential use of aryl cation equivalents in synthetic design.

Stereochemical Control in Awkward Ring Sizes

While five- and six-membered carbocycles are widely used for the stereocontrolled construction of complex molecules, there are few comparable applications of cycloheptane derivatives. This stems from the absence of methodology suitable for stereocontrolled introduction of functionalized and other substituents onto the seven-membered ring and is also attributable to the lack of general understanding of conformation-reactivity relationships in this ring size. In the belief that the use of an attached transition metal moiety would introduce conformational bias, impose stereochemical features on the ring, and possibly transmit its effect across distances, we investigated the basic chemistry of iron-stabilized cycloheptadienyl cations. Although the tricarbonyliron complex **36a** and the dicarbonyl-triphenylphosphine iron complex **36b** have been reported, only superficial studies of their reactivity toward

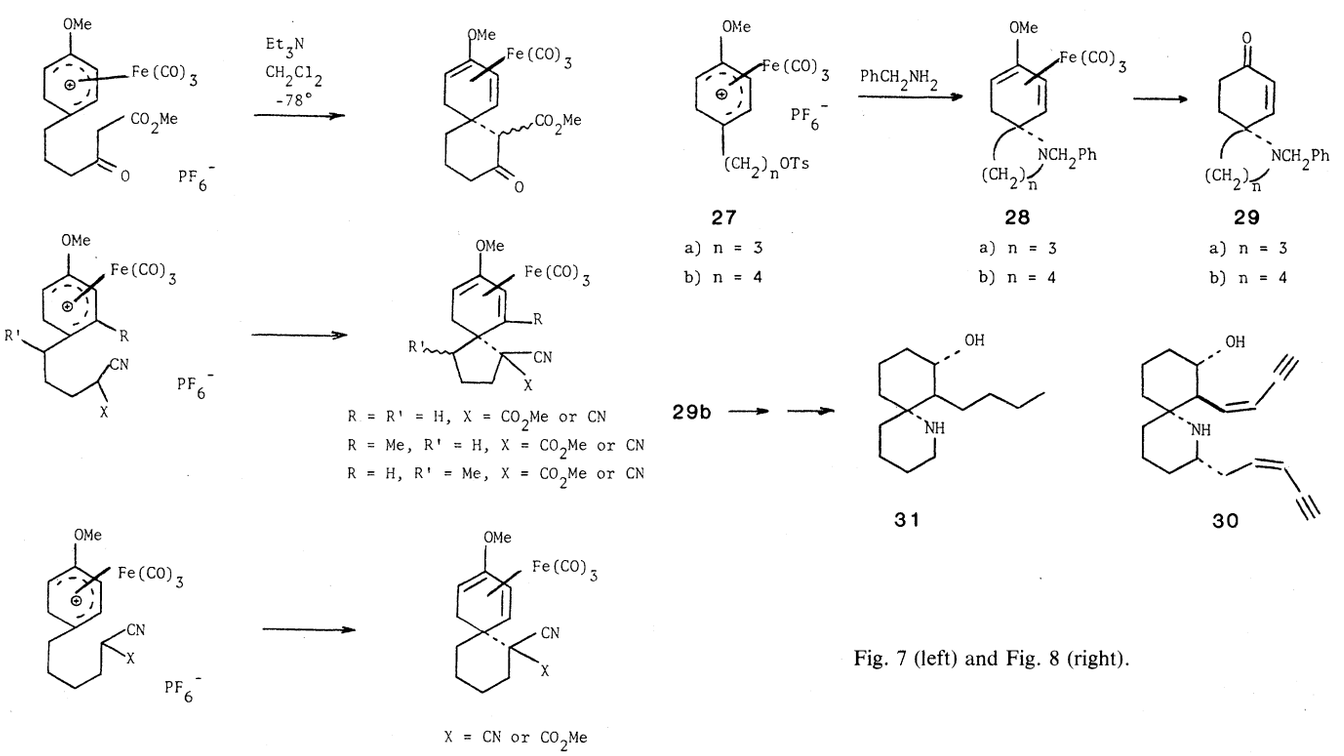


Fig. 7 (left) and Fig. 8 (right).

carbon nucleophiles had been undertaken (*27*). Indeed, the results obtained in those studies are discouraging, since it was shown that the $Fe(CO)_3$ derivative **36a** underwent addition of nucleophiles such as CN^- with poor selectivity and in low yield to give mixtures of the diene complex **37a** and the unusual σ, π-allyl product **38a**. When the triphenylphosphine derivative **36b** was treated with cyanide (or sodium borohydride), only products of type **38b** were obtained. These results led to the proposal that nucleophilic attack at C-2 in **36b** is largely due to the *trans* effect of the phosphine ligand, leaving us with the impression that this would occur for any nucleophile (*28*). The results of our work, now outlined, demonstrate that this is not the case, but that regioselectivity of the reaction is sensitive also to the nature of the nucleophile.

First, we undertook a study of reactions of the tricarbonyl complex **36a** with a broader range of nucleophiles than had been previously examined. As expected, the yields were very low in comparison to the yields from the same reactions on the analogous cyclohexadienyl complex **8a**. Thus, while stable enolates [for example, $NaCH(CO_2Me)_2$] were found to react at C-1, giving diene complexes of type **37a** [R = $CH(CO_2Me)_2$], moderate yields were obtained (40 to 50 percent). Similarly organocuprates gave C-1 adducts **37a** (R = Me), but again in low yield (5 to 20 percent), there being many side products. We decided to alter the ligand environment of the metal, but in order to produce large quantities of complex to allow a systematic investigation of nucleophile addition, as well as an investigation of potential synthetic applications, we required a preparation suitable for large-scale work. None of the published methods for synthesizing the triphenylphosphine derivative **35b** were suitable, nor were we able at that stage in our investigation to improve the yield of this compound. However, treatment of tricarbonylcycloheptadieneiron **39a** with triphenylphosphite in refluxing di-*n*-butyl ether gave the complex **39c** in 85 to 90 percent yield. Hydride abstraction from **39c**, with triphenylmethyl hexafluorophosphate in dichloromethane, gave the required dienyl complex **36c** in yields greater than 95 percent. We were able to perform this sequence on a large scale, giving the complex **36c** in 150- to 200-gram batches, and we were now in a position to make a proper study of nucleophile additions (Fig. 10) (*29*).

The reaction of **36c** with lithium dimethyl-cuprate gave only the methyl-substituted diene complex **37c** (R = Me) in almost quantitative yield. Reaction of **36c** with methyllithium gave only the C-2 adduct **38c** (R = Me), also in very high yield. Thus, there is a pronounced dependence of regioselectivity on the nature of the nucleophile. Attack by dimethyl sodiomalonate as nucleophile gave the diene complex **37c** [R = $CH(CO_2Me)_2$], in quantitative yield, whereas reaction with thiophenoxide (PhS^-) gave **37c** (R = SPh), and reaction with cyanide gave the C-2 adduct **38c** (R = CN). The latter two nucleophiles are typical examples of nucleophiles that show different "softness" (*30*), PhS^- being softer than CN^-, and it appears from our work that the complexes **36** may be regarded as ambident electrophiles, C-1 being the soft center and C-2 the hard center. This is particularly true for **36b** and may be an extremely useful observation with regard to classification of nucleophiles. We must, however, defer any discussion as to why this phenomenon is observed until we have access to accurate and extensive molecular orbital calculations on the dienyl complexes. It should also be remembered that at no time have we observed nucleophile attack at C-2 in the analogous cyclohexadienyl complexes, and it is not yet clear whether this is due to severe ring strain in a product from this mode of addition, or whether the size of the ring alters the pattern of molecular orbitals for the dienyl-metal grouping.

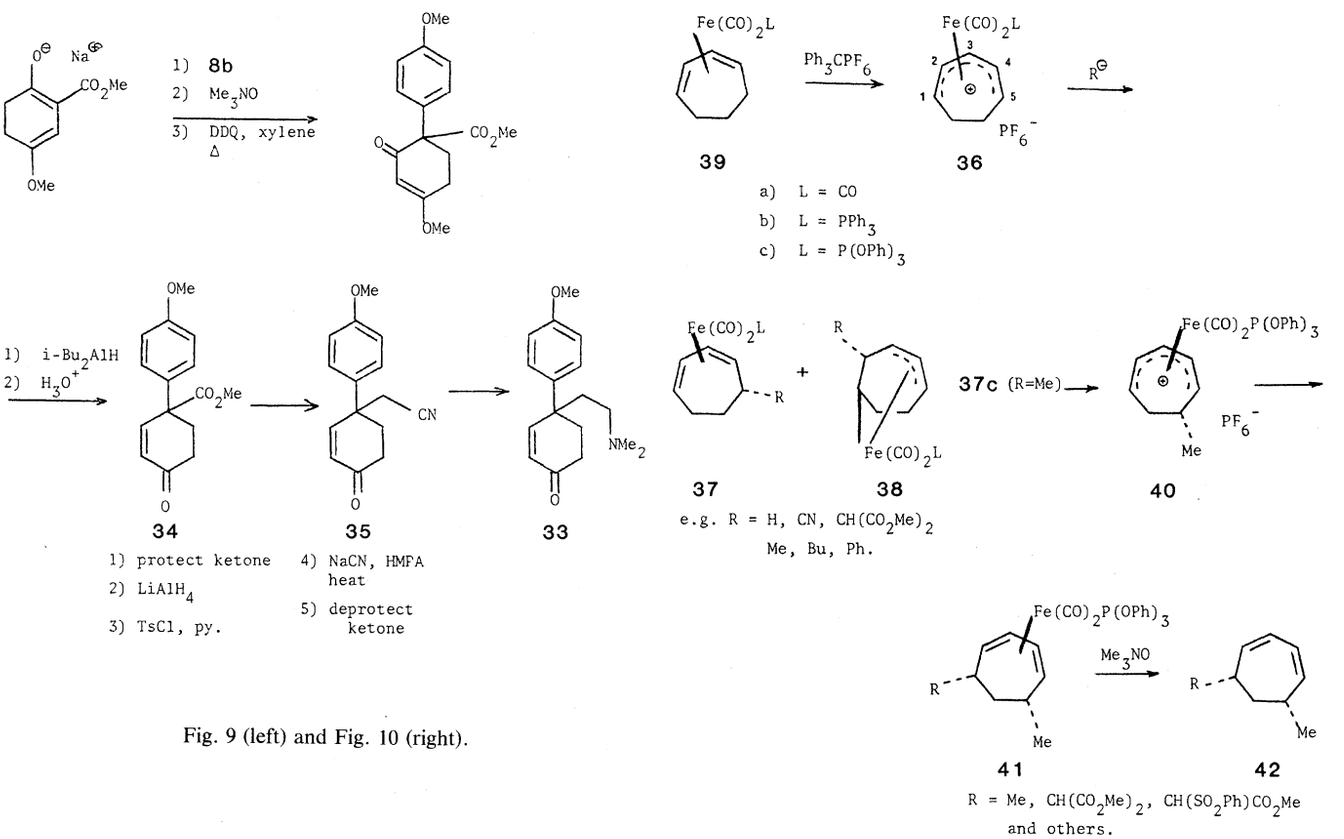
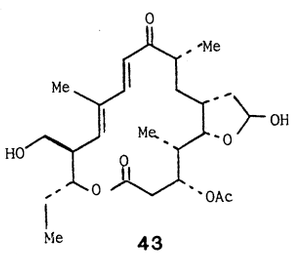


Fig. 9 (left) and Fig. 10 (right).

What is most interesting is that the methyl-substituted diene complex **37c** (R = Me) can now be subjected to a second hydride abstraction sequence, which occurs readily to give the methyl-substituted dienyl complex **40** in about 95 percent yield, and this reacts with a second nucleophile in a sterospecific manner and in very high yield. Chemical evidence in favor of the stereospecific addition of nucleophile *trans* to the metal comes from the reaction of the *n*-butyl-substituted complex **37c** (R = *n*-Bu) with triphenylmethylhexafluorophosphate, a reaction that occurs much more sluggishly than that with the methylated derivative **37c** (R = Me). Since the trityl cation removes only the hydride *trans* to metal, we might expect that a larger (*trans*) substituent would cause steric retardation of this reaction, as is observed. Both the hydride abstraction and the nucleophile addition processes appear to be subject to stereoelectronic control, although this remains to be established. Removal of the metal from the products of second nucleophile addition gives stereochemically defined disubstituted cycloheptadiene derivatives. Some of our results are summarized in Fig. 10.

Having produced the disubstituted cycloheptadienes, for example, **42** [R = $CH(CO_2Me)_2$], we are in a position to examine further functionalization of the diene with a view to accomplishing syntheses of complex natural products. To this end we have set ourselves the targets Magnamycin B (**15**) and tylonolide (**43**) the aglycone of tylosin, both of



43

which are important macrolide antibiotics. While aiming for those targets, we have developed new approaches to organic synthesis, both conceptually and technically, and we have made progress in understanding reactivity of the dienyliron complexes being utilized. Through this research, we have accumulated data on the factors governing nucleophile addition to alkoxy-substituted cyclohexadienyliron complexes. At present we are not only concerned with how organic synthesis will benefit from organometallic chemistry, but also with how much organometallic chemistry will benefit from its attempted application.

References and Notes

1. Chromium complexes: G. Jaouen, in *Transition Metal Organometallics in Organic Synthesis*, H. Alper, Ed. (Academic Press, New York, 1978), vol. 2, pp. 65–120; M. F. Semmelhack, *Tetrahedron* **37**, 3956 (1981), *Ann. N.Y. Acad. Sci.* **295**, 36 (1977).
2. Manganese complexes: G. Winkaus, L. Pratt, G. Wilkinson, *J. Chem. Soc.* (1961), p. 3807; A. Mawby, P. J. C. Walker, R. J. Mawby, *J. Organomet. Chem.* **55**, C39 (1973); P. J. C. Walker and R. J. Mawby, *Inorg. Chem.* **10**, 404 (1971); *Inorg. Chim. Acta* **7**, 621 (1973); *J. Chem. Soc. Dalton Trans.* (1973), p. 622; R. J. Angelici and L. J. Blacik, *Inorg. Chem.* **11**, 1754 (1972); P. L. Pauson, and J. L. Segal, *J. Chem. Soc. Dalton Trans.* (1975), p. 1677; *ibid.*, p. 1683; G. A. M. Munro and P. L. Pauson, *Isr. J. Chem.* **15**, 258 (1976/77); *J. Organomet. Chem.* **160**, 177 (1978); P. Bachmann, K.-R. Repp, H. Singer, *Z. Naturforsch.* **326**, 471 (1977); K. K. Bhasin, W. S. Balkeen, P. L. Pauson, *J. Organomet. Chem.* **204**, C25 (1981); A. J. Pearson and I. C. Richards, *ibid.*, **258**, C41 (1983).
3. A. J. Deeming, in *Comprehensive Organometallic Chemistry*, G. Wilkinson *et al.*, Eds. (Pergamon, New York, 1982), vol. 4, p. 499.
4. B. W. Roberts and J. Wong, *J. Chem. Soc. Chem. Commun.* (1977), p. 20; B. W. Roberts, M. Ross, J. Wong, *ibid.* (1980), p. 428.
5. M. Rosenblum, *Acc. Chem. Res.* **7**, 122 (1974).
6. J. W. Faller, H. H. Murray, D. L. White, K. H. Chao, *Organometallics* **2**, 400 (1983).
7. G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, G. D. Mateescu, *J. Am. Chem. Soc.* **94**, 2034 (1982).
8. G. A. Olah and Y. Mo, *J. Org. Chem.* **38**, 353 (1973).
9. E. O. Fischer and R. D. Fischer, *Angew. Chem.* **72**, 919 (1960).
10. A. J. Birch and B. M. R. Bandara, *Tetrahedron Lett.* **21**, 2981 (1980); A. J. Birch, W. D. Raverty, G. R. Stephenson, *ibid.*, p. 197; A. J. Birch and G. R. Stephenson, *ibid.* **22**, 779 (1981); B. M. R. Bandara, A. J. Birch, L. F. Kelly, T. C. Khor, *ibid.* **24**, 2491 (1983); A. J. Birch, W. D. Raverty, G. R. Stephenson, *J. Chem. Soc. Chem. Commun.* (1980), p. 857.
11. Y. Shvo and E. Hazum, *J. Chem Soc. Chem. Commun.* (1974), p. 336.
12. A. J. Pearson, T. Ray, I. C. Richards, J. Clardy, L. Silveira, *Tetrahedron Lett.* **24**, 5781 (1983).
13. A. J. Pearson, *Acc. Chem. Res.* **13**, 463 (1980); in *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone, E. W. Abel, Eds. (Pergamon, New York, 1982), vol. 8, pp. 939–1011.
14. E. Colvin, *Silicon in Organic Synthesis* (Butterworths, London, 1981), p. 230.
15. A. J. Pearson and C. W. Ong, *J. Am. Chem. Soc.* **103**, 6686 (1981).
16. A. J. Pearson, T. R. Perrior, D. C. Rees, *J. Organomet. Chem.* **226**, C39 (1982).
17. A. J. Pearson, P. Ham, C. W. Ong, T. R. Perrior, D. C. Rees, *J. Chem. Soc. Perkin Trans. 1* (1982), p. 1527.
18. A. J. Pearson, *Transition Met. Chem.* **6**, 67 (1981).
19. A. J. Birch, P. W. Westerman, A. J. Pearson, *Aust. J. Chem.* **29**, 1671 (1976); D. W. Clack, M. Monshi, L. A. P. Kane-Maguire, *J. Organomet. Chem.* **107**, C40 (1976); R. Hoffmann and P. Hofman, *J. Am. Chem. Soc.* **98**, 598 (1976).
20. L. A. Paquette and R. G. Daniels, *Organometallics* **1**, 757 (1982).
21. A. J. Pearson, D. C. Rees, C. W. Thornber, *J. Chem. Soc. Perkin Trans. 1* (1983), p. 619, and references cited therein.
22. A. J. Pearson, *ibid.* (1980), p. 400; _____, P. Ham, D. C. Rees, *ibid.* (1982), p. 489; A. J. Pearson, T. R. Perrior, D. A. Griffin, *ibid.* (1983), p. 625.
23. J. A. Marshall, S. F. Brady, N. H. Andersen, *Fortschr. Chem. Org. Naturst.* **31**, 283 (1974).
24. A. J. Pearson, P. Ham, D. C. Rees, *Tetrahedron Lett.* **21**, 4637 (1980); A. J. Pearson and P. Ham, *J. Chem. Soc. Perkin Trans. 1* (1983), p. 1421.
25. A. J. Pearson, I. C. Richards, D. V. Gardner, *J. Chem. Soc. Chem. Commun.* (1982), p. 807.
26. I. H. Sanchez, and F. R. Tallabs, *Chem. Lett.* (1981), p. 891.
27. R. Aumann, *J. Organomet. Chem.* **47**, C28 (1983); R. Burton, M. L. H. Green, E. W. Abel, G. Wilkinson, *Chem. Ind. (London)* (1958), p. 1952; R. Burton, L. Pratt, G. Wilkinson, *J. Chem. Soc.* (1961), p. 594; H. J. Dauben and D. J. Bertelli, *J. Am. Chem. Soc.* **83**, 497 (1961); M. A. Hashmi, J. D. Munro, P. L. Pauson, J. M. Williamson, *J. Chem. Soc. A* (1967), p. 240; J. Evans, D. V. Howe, B. F. G. Johnson, J. Lewis, *J. Organomet. Chem.* **61**, C48 (1973); D. A. Brown, S. K. Chawla, W. K. Glass, *Inorg. Chim. Acta* **19**, L31 (1976); L. A. P. Kane-Maguire, T. I. Odiaka, P. A. Williams, *J. Chem. Soc. Dalton Trans.* (1981), p. 200; P. Hackett, B. F. G. Johnson, J. Lewis, G. Jaouen, *ibid.* (1982), p. 1247.
28. R. Edwards, J. A. S. Howell, B. F. G. Johnson, J. Lewis, *J. Chem. Soc. Dalton Trans.* (1974), p. 2105.
29. A. J. Pearson, S. L. Kole, B. Chen, *J. Am. Chem. Soc.* **105**, 4483 (1983).
30. G. Klopman, *ibid.* **90**, 223 (1968).

31. Supported by the Science and Engineering Research Council, the Cancer Research Campaign, Imperial Chemical Industries, and Beecham Pharmaceuticals Ltd. (Great Britain) and by the National Institutes of Health and National Science Foundation (United States). I am extremely grateful to all those co-workers, most of whose names appear in the references, who have contributed to this work.