Stoichiometric Applications of Acyclic π-Organoiron Complexes to Organic Synthesis

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Abstract: The application of acyclic (diene)iron complexes and (pentadienyl)iron cations in organic synthesis has steadily increased over the past 20 years. This is due to their ease of preparation, their stability toward a wide variety of reaction conditions, the manifold method for removal of the Fe(CO)₃ group, and the low cost of iron carbonyls. The (tricarbonyl)iron adjunct may serve in three capacities: i) as a protecting group for conjugated dienes, ii) to direct the formation of chiral centers adjacent to the complexed dient, and iii) to stabilize the formation of positive charge adjacent to the complexed diene (i.e. pentadienyl cations). Specific examples of these attributes will be presented in this review. One of the advantages of stoichiometric organometallic reagents is the ability to repeatedly utilize the same metal center to control a number of different bond forming reactions. Six examples will be presented which demonstrate this potential for acyclic (diene)iron complexes and (pentadienyl) iron cations.

INTRODUCTION

Since the synthesis and structural characterization of ferrocene in 1951, the catalytic and stoichiometric use of organometallic complexes in organic synthesis has grown tremendously [1]. In order to be effective, transition metal catalysts depend upon the lability of the ligand-to-metal coordination to ensure high turn-over numbers. In contrast, the stoichiometric use of π-organo-metallic complexes depends on the inherent stability of certain ligand-to-metal combinations. Due to the ease of preparation of (diene)Fe(CO)₃ complexes, their stability toward a wide variety of reaction conditions, the manifold methods for removal of the Fe(CO)₃ group, and the low cost of iron carbonyls, these complexes have become useful reagents in organic synthesis.

The first complex of a conjugated diene was reported in 1930 by Reihlen and coworkers. Reaction of butadiene with Fe(CO)₅ gave a yellow-brown oil with the molecular formula (C₄H₆)Fe(CO)₃ [2a]. Considerably later, after the elucidation of the structure of ferrocene, Pauson and Hallam proposed a π-complex (1) for (C₄H₆)Fe(CO)₃ which was eventually confirmed by crystal structure analysis at low temperature [2b,c]. Since that time interest in diene-metal complexes as starting materials for organic synthesis has led to the preparation and/or characterization of (conjugated diene)metal complexes of nearly all of the transition metals. Because there are numerous reviews devoted to the reactivity (cyclohexadienyl)Fe(CO)₃⁺ cations [3], this article will focus on applications of acyclic (diene)Fe(CO)₂L complexes (2) and (pentadienyl)Fe(CO)₂L⁺ cations (3) (L = CO, PPh₃) to the synthesis of polyene natural products.

PREPARATION OF NEUTRAL DIENE-IRON COMPLEXES

The most common method for preparation of (diene)Fe(CO)₃ complexes is by direct coordination of the free ligand using either Fe(CO)₅,
Fe₂(CO)₉, or Fe₃(CO)₁₂, either thermally, photochemically, or with the influence of ultrasonic stirring, or by dry state-adsorption techniques (eqn. 1) [4]. Room temperature complexation using Fe(CO)₅ may be accomplished by decarbonylation with trimethylamine N-oxide [5]. Complexation of non-conjugated dienes under thermal conditions usually leads to isomerization to afford the conjugated (1-4-η⁴-diene) complex [4b], except in cases where the non-conjugated diene is constrained in a bicyclic or polycyclic ring system. Complexation under mild reaction conditions can be achieved by using (α, β-enone)-Fe(CO)₃ complexes, (1-aza-1,3-diene)Fe(CO)₃ complexes, or bis(η²-cyclooctene)Fe(CO)₃ as metal transfer species [6].

Complexation of a prochiral diene ligand results in the formation of a racemic mixture. There are only a few examples of the preparation of optically active acyclic (diene)Fe(CO)₃ complexes via highly diastereoselective complexation of optically active ligands (4-7, Fig. 2) [7]. Alternatively, optically pure dienoate complexes may be prepared by chromatographic separation of the optically active diastereomeric complexes, in which one of the centers of chirality resides in the ester functionality (e.g. 8 and 9) [8]. Other methods for the preparation of optically active acyclic (diene)Fe(CO)₃ complexes include classical resolution [9], chromatographic separation using chiral supports [10], kinetic resolution [11], or desymmetrization of meso complexes [12]. While racemization of acyclic (diene)Fe(CO)₃ complexes does not occur at ambient temperatures, it is observed at elevated temperatures (ca. 2.3-2.7 x 10⁴ @ 119 °C) [9b].

(Diene)Fe(CO)₃ complexes may also be formed by ring opening of strained cyclic compounds (Scheme 1). The thermal reaction of vinylcyclopropanes 10 with Fe(CO)₅ or Fe₂(CO)₉ affords pentadiene complexes 11a [13]. The intermediacy of a (pentenediy) iron species 12 has been proposed. Reaction of methylenecyclopropanes 13 with Fe₂(CO)₉ yields diene complexes 11b [14]. Ring opening of vinylxiranes 14 with Fe(CO)₅ produces the corresponding π-allyl iron lactone

![Fig. (2). Optically active acyclic (diene)iron complexes prepared by diastereoselective complexation.](image-url)
complexes 15. Treatment of 15 with barium hydroxide leads to diene complexes 11c via decarboxylation [15]. Alternatively, alkylation of the π-allyl iron lactone complexes 15 with Meerwein’s salt yields the chelated π-allyl carbene cations 16 [16]. Reaction of cations 16 with enolate anions produces the diene complexes 17 in which a new C-C bond has been formed.

METHODS FOR LIBERATION OF DIENE LIGAND

Oxidation of (diene)iron complexes leads to destruction of the complex with concomitant liberation of the organic ligand. Reagents useful for this transformation are FeCl₃, CuCl₂, (NH₄)₂Ce(NO₃)₆ [CAN], Me₃NO or DDQ (eqn. 1) [17]. Normally, oxidation of (diene)Fe(CO)₃ complexes with H₂O₂ simply liberates the ligand, however reaction of certain (6-oxo-1,3-diene)Fe(CO)₃ complexes (18) with hydrogen peroxide gives allylic alcohols (eqn. 2) [18]. Photochemical reduction of (diene)iron complexes in acetic acid gives the corresponding alkene (eqn. 3) [19]. This reduction is regioselective only for dienes bearing a terminal electron withdrawing group. Cyclocarbonylation of (diene)Fe(CO)₃ complexes mediated by AlCl₃ yields 2-cyclopentenones, however the yields are

Scheme 1.
acceptable only for 1,1,3-trisubstituted diene complexes (eqn. 4) [20].

Zerovalent transition metal carbonyl moieties may act as electron acceptors and thus activate coordinated polyene ligands toward nucleophile attack. For example, reaction of \((\mathrm{C}_4\mathrm{H}_8)\mathrm{Fe}\,(\mathrm{CO})_3\) with strong carbon nucleophiles, followed by protonation, gives olefinic products 19 and 20 (Scheme 2) [21]. The ratio of 19 to 20 depends upon the reaction temperature and time. At low temperature and for short reaction times (-78 °C, 30 min) the major product is 19, while at higher temperature and longer reaction time (0 °C, 2 h) the major product is 20. This selectivity is rationalized by kinetically controlled attack at the more electron-poor carbon (C2) at low temperature. Nucleophilic attack is reversible and under conditions where an equilibrium is established the thermodynamically more stable (allyl)Fe(CO)$_3^-$ is favored.

The reaction of \((\mathrm{C}_4\mathrm{H}_8)\mathrm{Fe}\,(\mathrm{CO})_3\) with carbon nucleophiles under CO pressure (2 atm, -78° → 0 °C) gives cyclopentanone products (21, Scheme 3) [22]. Nucleophilic attack on the (diene)Fe(CO)$_3$ complex is followed by CO insertion to give the acyl anion species 22. Olefin insertion into the Fe-acyl bond generates the Fe-alkyl complex 23 which is in equilibrium with the Fe-enolate species 24 via β-hydride elimination/reinsertion steps. Intramolecular variants of this reaction have been

Scheme 2.
reported for the preparation of bicyclo[2.3.0]-
alkanones (eqn. 5) [23].

\[
\begin{align*}
\text{Fe(CO)}_3 & \quad \text{Nu}^- \\
\text{C} & \quad \text{Nu}^- \\
\text{H} & \quad \text{H} \\
\text{Nu} & \quad \text{Nu} \\
\end{align*}
\]

Scheme 3

USE OF THE TRICARBONYL-IRON FUNCTIONALITY AS A PROTECTING GROUP

Complexation of an Fe(CO)₃ group to a conjugated diene efficiently protects the diene toward a variety of reduction, oxidation and
cycloaddition reactions. For example, the Fe(CO)₃
group has been used as a protecting group for the

\[
\begin{align*}
\text{Fe(CO)}_3 & \quad \text{Nu}^- \\
\text{C} & \quad \text{Nu}^- \\
\text{H} & \quad \text{H} \\
\text{Nu} & \quad \text{Nu} \\
\end{align*}
\]

C2-C5 diene segment in the preparation of a tritium labeled insect growth regulator via catalytic reduction (T₂/Rh(PPh₃)_3Cl) (eqn. 6) [24a]. Notably, addition of hydrogen to an uncomplexed C=C double bond in a (triene)-Fe(CO)₃ complexes mediated by Pd or Pt catalysts is sometimes problematic [24b]; the attempted
reduction of (dienyne)Fe(CO)₃ complexes (25) with Pd/C proceeds only to the (triene)Fe(CO)₃ complex (eqn. 7) [24c]. The (dien)Fe(CO)₃ group is stable to conditions which effect reductive hydrolysis of an adjacent isoxazoline (eqn. 8) [25].

While (dien)Fe(CO)₃ complexes are susceptible to decomplexation by strong oxidizing agents, this functionality is stable to a wide variety of milder oxidation conditions. Alcohol oxidation, in the presence of a (dien)Fe(CO)₃ moiety has been successfully accomplished with PDC/4Å sieves (60%) [26], MnO₂ (60-80%) [27], DMSO/(COCl)₂/NEt₃ (67-71%) [28], SO₃-pyr (54-65%) [29], nPrMgBr/1,1’-(azodicarbonyl)dipiperiti-
dine (78-89%) [29,30], or Ag₂CO₃ (56%) [31]. A novel chemoselective, metal-mediated, oxidation of 1° or 2° alcohols adjacent to a (dien)Fe(CO)₃ group uses amine N-oxides (Scheme 4) [32]. The following mechanism is proposed to account for these results. Ionization of a hydroxyl group adjacent to the complexed diene results in the intermediacy of a transoid pentadienyl cation 26 (vide infra). Addition of the amine oxide generates species 27, which undergoes elimination of the amine. Notably, the presence of electron withdrawing groups on the diene ligand decreases the yield of oxidation, while the presence of good Lewis basic ligands (e.g. PPh₃) increases the yield.

Scheme 4.
C-C BOND FORMATION VIA FRIEDEL-CRAFTS ACYLATION OF (DIENE)Fe(CO)₃ COMPLEXES

The Freidel-Crafts acylation of 1 was first reported in 1969, well after the acylation of ferrocene. Normally, attempted acylation of 1,3-dienes leads to polymerization. In contrast, electrophilic acylation of (diene)Fe(CO)₃ complexes gives the corresponding cis-dienone complexes 28 (Scheme 5) [33]. Electrophilic attack occurs on the face of the ligand which is bound to the metal. The initially generated cationic (η³-allyl) complex 29 is subsequently deproto- nated to afford 28. Isomerization of 28 to the thermodynamically more stable trans-dienone complex 30 may be effected by additional acylhalide or base. This methodology for C-C bond formation has been utilized in the synthesis of a series of conjugated diene pheromones [34], the leukotriene LTA₄ [35b], and the C8-C15 segment of protomycinolide IV [36].

\[
\begin{align*}
(CO)_3Fe & \quad \rightarrow \\
R' & \quad + \\
(CO)_3Fe \quad \rightarrow \\
\text{R'COCl or NaOMe} & \quad \rightarrow \\
\end{align*}
\]

Scheme 5.

DIASTEREOSELECTIVE ADDITION TO (DIENAL)-, (DIENONE)-, OR (DIENYL-IMINE)Fe(CO)₃ COMPLEXES

Diastereoselective nucleophilic addition to chiral ketones or aldehydes depends upon facial selectivity. Due to the steric bulk of the (tricarbonyl)iron group, approach of nucleophiles to (dienal)- and (dienone)Fe(CO)₃ complexes (31 and 30 respectively) occurs on the face opposite to the metal. If there is a predominance of one of the rotomers about the diene-to-carbonyl bond, then nucleophilic addition may occur in a diastereoselective fashion. Complexes 31 and 30 may exist in an equilibrium between two conformers, s-cis and s-trans (Fig. 3). For (sorbaldehyde)Fe(CO)₃, low temperature NMR studies indicate that the proportion of s-cis:s-trans conformers is nearly 1:1 [37]. In comparison, solution IR spectral data for complexes 30 indicate that these exist predominantly as one conformer [38]. Since X-ray crystal structures of complexes 30 generally exhibit the s-cis geometry, then this conformer is also proposed to be the predominant species in solution. This analysis is consistent with the experimental results. Reduction of (E,E-dienone)Fe(CO)₃ complexes proceeds with high diastereoselectivity (>90% de) to afford predominantly the ψ-endo alcohol [38]. In comparison, nucleophilic addition to (2E,4-dienal)Fe(CO)₃ complexes (31) proceeds with variable diastereoselectivity, depending on both the complex and the nucleophile (Scheme 6) [39].

In general, the diastereomeric secondary alcohol products are easily separable by chromatography, with the ψ-exo isomer being less mobile than the ψ-endo isomer [40]. As might be anticipated, nucleophilic addition to a ketone or aldehyde functionality remote to the (diene)Fe(CO)₃ group occurs in a non-diastereoselectivity fashion [41].

Nucleophilic addition to complexed dienals has been utilized in the enantioselective syntheses of 5-HETE methyl ester [27], AF toxin IIc [42], LTB₄ [43], lipoic acid methyl ester [44], and model compounds for the C7-C19 segment of macrolactin A [45], while reduction of a complexed dienone was utilized in an enantiospecific synthesis of LTA₄ [35b].

Fig. (3). Diastereoselective addition to (Dienal)- and (dienone)iron complexes.
Scheme 6.

Lewis acid catalysed aldehyde-diene cyclocondensation (LACDAC) of (dienal)Fe(CO)$_3$ complexes 31 with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, followed by acidic work-up, gives the corresponding dihydropyrone complexes with modest diastereoselectivity (Scheme 7) [46]. In comparison to the modest diastereoselectivity observed for addition to aldehydes, addition to dienylimine complexes occurs with considerably greater diastereoselectivity. The greater diastereo-

Scheme 7.
synthesis of dienyl piperidine natural products SS 20846 A.

**DIASTEREOSELECTIVE ADDITIONS TO (TRIENE)Fe(CO)₃ COMPLEXES**

Similar to (dienylimine)iron complexes, addition to (triene)iron complexes generally occurs with excellent diastereoselectivity. This high level of diastereoselectivity reflects a greater bias for the s-trans conformer over the s-cis conformer, due to unfavorable steric interactions in the s-cis conformer (Fig. 4).

Michael additions to α,β-unsaturated complexes 33, in which nucleophilic attack occurs adjacent to the (diene)Fe(CO)₃ moiety, proceed in a highly stereoselective fashion (Scheme 8) [48]. This reactivity has been utilized in the synthesis of (-)-verbenalol and (-)-epiverbenalol and the as-indacene unit of ikarugamycin. In comparison, Michael addition to α,β-unsaturated complex 34, in which the attack occurs more remote to the (diene)Fe(CO)₃ moiety proceeds with only 28% de [49]. This more modest diastereoselectivity may be due to reaction of both conformers about the β-γ bond.

The cycloadditions of olefins appended to a (dienyliccarbonyl)Fe(CO)₃ complex have been examined. Diels-Alder cycloaddition of the activated (triene)Fe(CO)₃ complex (33) is reported to afford a single product (Scheme 8) [50]. In comparison, Diels-Alder cycloaddition of dienyl vinyl ketone complex 34, in which the dienophile is separated from the stereodirecting (diene)Fe(CO)₃ group by the intervention of a carbonyl group, proceeds with only modest diastereoselectivity [49].

The Ireland ester enolate Claisen rearrangement of trienylacetates 35 (either E or Z) gave the carboxylic acid as a single diastereomer upon workup (eqn. 9) [51]. The product appears to arise from the cyclic transition state in which the C-C
bond is formed anti to the sterically bulky Fe(CO)\textsubscript{3} group.

\begin{align*}
\text{Me} & \quad \text{KHMD} & \quad \text{THF/HMPA} \\
\text{Fe(CO)\textsubscript{3}} & \quad \text{TBS} & \quad \text{Cl/78 C} \\
\text{Me} & \quad \text{Me} & \\
\text{O} & \quad \text{O} & \\
\text{35} & & \\
\text{70-80\% from \textit{E}-38} \\
\text{45-50\% from \textit{Z}-38}
\end{align*}

\begin{align*}
\text{Me} & \quad \text{Fe(CO)\textsubscript{3}} & \quad \text{Me} \\
\text{O} & \quad \text{O} & \\
\text{35} & & \\
\text{70-80\% from \textit{E}-38} \\
\text{45-50\% from \textit{Z}-38}
\end{align*}

While \textit{intramolecular} nitrile oxide-olefin cyclocondensations occur with good diastereoselectivity, \textit{intermolecular} cyclocondensations of nitrile oxides with 3-substituted-1-alkenes are generally less diastereoselective (ca. 0-54\% de) [52]. In comparison, \textit{intermolecular} addition of nitrile oxides to conjugated triene complexes 36 results in the formation of the corresponding isoxazolines in good yield and with good diastereoselectivity (ca. 80\% de) (eqn. 10) [25, 53]. Thus the combination of the steric bulk of the Fe(CO)\textsubscript{3} group and the conformational preference for the \textit{s-trans} isomer results in uncommonly high diastereoselectivity for this intermolecular cyclocondensation. This methodology has been used in an enantioselective synthesis of (+)-gingerol [53b], the carbon skeleton of (+)-streptenol D [25b] and the C11-C24 fragment of macrolactin A [29]. In contrast to the reactivity of 36, \textit{intramolecular} nitrile oxide-olefin cyclo-addition for "skipped" triene complex 37 gave an equimolar mixture of diastereomers (eqn. 11) [54]. In this case, the lack of diastereoselectivity may indicate that the steric bulk of the Fe(CO)\textsubscript{3} group is too far distant from the pendent olefin and/or that there is not a preferred reactive conformation about the C-C single bonds.

(Triene)Fe(CO)\textsubscript{3} complexes bearing a pendant electron deficient alkene (e.g. 38) undergo dipolar cycloaddition with diazomethane or diazopropene to give the corresponding \(\Delta^2\)-pyrazolines with good diastereoselectivity (Scheme 9) [55]. The \(\Delta^2\)-pyrazolines can be thermalized to the corres-
s-trans conformation on the olefin face anti to the Fe(CO)₃ group (eqn. 12) [57]. This methodology has been used in the enantiospecific synthesis of 5, 6- and 11,12-diHETEs. Exposure of (diene)-Fe(CO)₃ complexes to ozone [58a] or to Pb(OAc)₄ [58b] leads to their destruction, however this functionality is stable to NaIO₄. Thus, pendent C=C bonds may be cleaved by sequential dihydroxylation and glycol cleavage (eqn. 13) [58b].

The stability of the (diene)Fe(CO)₃ functionality to NaIO₄ glycol cleavage has been put to use in an efficient preparation of the enantiomers of (methyl 6-oxo-2,4-hexadienoate)Fe(CO)₃ (41), a complex which has found use in the synthesis of a wide variety of polyene natural products (Scheme 10) [59]. Beginning with glyceraldehyde acetonide, Horner-Emmons olefination gives the corresponding dienoate. Thermal complexation with Fe₂(CO)₉ gave a nearly equimolar mixture of diastereomeric complexes. While these diastereomers were difficult to separate, the corresponding 2° alcohol complexes, ψ-endo (-)-42 and ψ-exo (+)-43, prepared by acetonide hydrolysis and protection of the 1° alcohol group, are readily separate by column chromatography. Separate, regeneration of the vicinal diols followed by NaIO₄ gave the enantiomers (-)-41 and (+)-41 in excellent yield.
ALKYLATION AND ALDOL CONDENSATIONS OF (DIENOATE)- AND (DIENO-NE)Fe(CO)$_3$ COMPLEXES

Alkylation of (methyl 3,5-hexadienoate)-Fe(CO)$_3$ (44) α to the diene occurs with good to excellent diastereoselectivity (eqn. 14) [36]. In contrast, alkylation of (dienone)Fe(CO)$_3$ complexes 45 at the carbon β to the diene, or halogenation of the silyl enol ether derived from 45, proceeds with minimal selectivity (eqn. 15) [35, 36]. In all of these cases the diastereoselectivity has been shown to be the result of kinetic control. The relative diastereoselectivity for the reactions of 44 and 45 may be rationalized in the following fashion. The ester enolate of 44 may exist in an equilibrium between two conformers, s-trans and s-cis (Fig. 5). The s-cis conformer should be considerably less stable due to steric interactions present between the enolate and the diene, and thus alkylation should proceed predominantly on the s-trans ester enolate. The lower energy transition state for alkylation of the s-trans enolate requires approach of the electrophile on the face opposite to the bulky Fe(CO)$_3$ group. For 45 the situation is less clear. The TMS enol ethers of (dienone)Fe(CO)$_3$ complexes are almost entirely in the Z-configuration [60a]. The Z-enolate of 45...
may exist in an equilibrium between two conformers, s-trans and s-cis (Fig. 6). Inspection of molecular models indicates that there should not be a large energy difference between these two conformers. In addition, for the s-cis conformer, approach of the electrophile at the β carbon on either face of the enolate does not involve significant steric interactions. Thus, the lower diastereoselectivity for alkylation of 45, compared to alkylation of 44, may be due to reaction of both the s-trans and s-cis conformers and to a decrease in the steric influence of the Fe(CO)₃ group due to its greater distance from the reactive center.

Condensation of silyl enol ether complexes 46 with aldehydes, under Mukaiyama conditions, gives the corresponding crossed aldol products 47 (eqn. 16) [60]. A broad range of diastereoselectivities is observed which appear to depend on the nature of the aldehyde, the Lewis acid used, and the order of addition of the reactants. While many results have been generated, a unifying rationale for the selectivity has not yet been proposed. This methodology has been utilized for the preparation of streptenol D [60b], colitose [60c], D-3-deoxy-threo-pentose [60d], and mycosamine [60e] (Fig. 7).

Fig. (5). Diastereoselective alkylation of ester enolate anion of (methyl 3,5-hexadienoate)Fe(CO)₃.
Fig. (6). Diastereoselective alkylation of enolate anion of \((E, E\)-dienone)\(\text{Fe(CO)}_3\) complexes.

Fig. (7). Natural products prepared by aldol condensation of \((\text{dienone})\text{Fe(CO)}_3\) with aldehydes (arrow indicates bond formed).

**PREPARATION AND REACTIVITY OF (PENTADIENYL)IRON(1+) CATIONS [61]**

In 1960, Fischer demonstrated that hydride abstraction from \((\text{cyclohexadiene})\text{Fe(CO)}_3\) (48) gave the stable \((\text{cyclohexadienyl})\text{Fe(CO)}_3^+\) cation (49) [62]. Nucleophilic attack at the terminal carbon of 49 gives substituted \((\text{cyclohexadiene})\text{Fe(CO)}_3\) complexes 50 (eqn. 17). Since that time Birch, Pearson, Stephenson, Knölker and others have utilized this reactivity for the synthesis of natural products such as methyl shikimate (51) [63a], \(O\)-methyl-joubertamine (52) [63b], car-bazole (53) [63c], and limaspermine alkaloids (54) [63d] and trichothecenes (55) [63e] (Fig. 8).

Shortly after the preparation of 49, Pettit and coworkers reported the preparation of the corresponding acyclic \((\text{pentadienyl})\text{Fe(CO)}_3^+\) cations (56) via protonation of \((\text{pentadienol})\text{Fe(CO)}_3\) complexes (Scheme 11) [64]. Subsequently, Lillya, et al., demonstrated that ionization of the hydroxyl substituent occurs with anchimeric assistance from iron and that isomerization of the initially generated transoid pentadienyl cation (57) to the more stable cisoid cation occurs with...
Fig. (8). Natural products prepared via nucleophilic addition to (cyclohexadienyl)Fe(CO)$_3^+$ cations.

It is generally believed that the two species exist in equilibrium, in solution. Spectroscopic evidence for this equilibrium has been obtained for only a single sterically biased case (R = R$^1$ = R$^5$ = Me, R$^4$ = H; E$_a$ ≈ 13 kcal mol$^{-1}$) [67].

(Pentadienyl)iron(1+) cations 56 are excellent organometallic electrophiles toward a wide variety of nucleophiles.
of nucleophiles. *A priori*, the reactivity of cations 56 might be anticipated to be similar to that of the corresponding (cyclohexadienyl)iron cation 49 (eqn. 17). While this is true for a number of cases, there exist significant differences between the reactivity of cyclic cations 49 and that of the acyclic cations 56. Nucleophilic attack can take place on the cisoid form of the pentadienyl cation at either termini to afford the *E,Z*-diene complexes 58 or 59, or on the internal atoms of the ligand (C2/C3/C4) to afford complexes 60, 61 or 62 (Scheme 12). Alternatively, since the transoid form exists in equilibrium with the cisoid form, nucleophilic attack on the transoid pentadienyl cation to generates *E,E*-diene complexes 63 or 64. Nucleophilic attack at the metal, with concomitant loss of a ligand, is a final possibility. Except for attack at C3, all of these possibilities have been observed.

1. Reaction with Heteroatom Nucleophiles or Hydride Nucleophiles

In general, the reaction of water or alcohol with cations 56 yields (*E,E*-dienol)- or (*E,E*-dienyl ether)Fe(CO)3 complexes 65 (Scheme 13) [7a, 64, 65, 68, 69]. The ψ-exo-*E,E*-dienol products are the result of attack by the weak oxygen nucleophile on the less stable, but more reactive, transoid pentadienyl form of the cations on the face opposite to iron. In contrast, the reaction of water with pentadienyl cations bearing an electron withdrawing substituent (e.g. 66) gives the corresponding *Z,E*-dienol complex 67 [70, 71]. This difference in product formation may be due to the decreased overall stability, and therefore increased reactivity, of the cations 66 compared to cations 56.
Scheme 13.

Reaction of cations 56 with 1°/2° amines [72], phosphines [68, 73-75], and arsines [75] affords the cationic complexes 68/69 (Scheme 14). Deprotonation of the ammonium salts generates the correspondingly substituted amine complexes. Where significant steric interactions between the ammonium or phosphonium group and other substituents are present, nucleophilic attack may be reversible [68c, 72d, 73]. Kinetic nucleophilic attack occurs on the more abundant cisoid form of the cation to generate E,Z-diene complexes 68. At higher temperatures and longer reaction times, the thermodynamically more stable E,E-diene complex 69 is formed via nucleophilic attack on the much less abundant transoid form of the pentadienyl cation. This reversibility has been utilized for the preparation of an optically active dienyl phosphonium salt from the meso cation (2,4-dimethylpentadienyl)Fe(CO)₃⁺ cations [73a] and for the kinetic resolution of racemic α-methylbenzylamine by reaction with an optically pure cation (38% de) [72d].

Deprotonation of either the E,Z- or the E,E-dienyltriphenylphosphonium salts 68 or 69 (R₃A = PPh₃) generates the corresponding E,E-dienyl ylides [76]. Reaction of these ylides with aldehydes gives the complexed trienes. The Z-selectivity of the complexed ylides (≥ 4:1, Z:E) is superior to that for uncomplexed dienyl ylides (ca. 1:1, Z:E). Chiral discrimination has been observed for these olefinations. Thus, the chiral ylide derived from rac-70 reacts with the optically active epoxy-aldehyde 71 in a diastereoselective

Scheme 14.
fashion to produce the trienyl epoxides (+)-72 and (-)-73 (4:1 dr, Scheme 15) [76c]. These results represent matched and mismatched combinations respectively. Separate reaction of the ylide derived from (+)-70 with 71 gave (+)-72 in considerably greater yield (74%) than the reaction of the ylide derived from (-)-70 with 71 to give (-)-73 (18%).

Reaction of cations 56 with anionic metal-hydrides predominantly yields the corresponding E,Z-diene complexes, however minor amounts of E,E-diene complexes are also observed [68, 77]. There are only a few examples of good regioselectivity for these reductions. In contrast, reaction of (1-methoxycarbonylpentadienyl)Fe(CO)₂PPh₃⁺ with NaBH₃CN proceeds via attack at an internal carbon to afford the σ,π-allyl complex 74 in excellent yield (eqn. 18) [78].

2. Reaction with Carbon Nucleophiles

The reaction of (pentadienyl)iron(1+) cations (56) with carbon nucleophiles has been examined. Depending on the nucleophile, substituents present on the pentadienyl ligand, and on the nature of spectator ligands, E,Z-diene complexes (58/59), E,E-diene complexes (63/64), and/or pentenediyl complexes (60/62) are formed as products.

The reaction of weak carbon nucleophiles, such as electron-rich aromatics [79], furan [80], or allyltrimethylsilane [68, 81] with (pentadienyl)iron

Scheme 15.
cations \(56\) with gives \(E,E\)-diene complexes (Scheme 16). These products presumably arise via attack on the less stable, but more reactive, transoid pentadienyl form of the cations. In contrast, the reaction of simple organocadmium reagents [82], organocuprates [27, 68a,b, 83] or functionalized organozinc reagents in the presence of CuCN [23] with cations \(56\) occurs via attack at the sterically least hindered terminus to afford \(E,Z\)-diene complexes \(75\). For mono-substituted or 1,2-disubstituted pentadienyl cations nucleophilic attack occurs at the less sterically hindered terminus of the pentadienyl ligand with excellent regioselectivity, however for 1,4-disubstituted pentadienyl cations mixtures of regioisomeric products are formed.

The reaction of alkyl or aryl lithiurns with (pentadienyl)\(\text{Fe(CO)}_2\text{PPh}_3^+\) cations gives pentenediyl complexes \(76\) via nucleophilic attack at \(C_2\) (Scheme 17) [84]. Similarly, the reaction of stabilized carbon nucleophiles such dimethylmalonate anions with (1-methoxycarbonyl-pentadienyl)\(\text{Fe(CO)}_3^+\) yields pentenediyl complexes \(77\) [85]. In comparison, the reaction of dimethylmalonate anion with 1-alkyl- or 1-arylsubstituted cations \(56\) gives mixtures of pentenediyl and diene complexes [84], while reaction of dimethylmalonate anion with 1,4-disubstituted cations \(56\) yields \(Z\)-1,3-diene complexes \(78\) [68b, 83]. The general trends can be summarized as follows: nucleophilic attack by malonate anions on \(\text{Fe(CO)}_3\) complexed 1-substituted pentadienyl cations occurs with little regioselectivity unless there is either a strongly electron withdrawing or strongly electron donating substituent present at the terminal position of the ligand. The presence of a substituent at \(C_4\) has a pronounced directing
effect for malonate attack at C1. Regioselectivity of nucleophilic attack on Fe(CO)$_2$PPh$_3$ complexed pentadienyl cations is generally improved over that of the corresponding Fe(CO)$_3$ complexed cations due to the increased stability/decreased reactivity of the Fe(CO)$_2$PPh$_3$ cations [85, 86].

Recent evidence suggests that nucleophilic attack at the internal dienyl carbon is the result of kinetic control. Thus, reaction of (1-methoxy-carbonylpentadienyl)Fe(CO)$_2$PPh$_3$+ with the anion of ethyl nitroacetate, followed by aqueous workup, gave the (pentenediyli)-Fe(CO)$_2$PPh$_3$ complex 79 as an equimolar mixture of diastereomers (Scheme 18) [54]. In contrast to (pentenediyl)iron complex 77, which is constitutionally stable in solution, (pentenediyl)-iron complex 79 rearranges to (E,Z-diene)iron complex 80 upon standing in CDCl$_3$ for 1-2 days. The interconversion of 79 to 80 occurs slower in C$_6$D$_6$ solution. In addition, treatment of an ethyl acetate solution of 79 with saturated aqueous NH$_4$Cl effected rapid rearrangement (<15 min) to 80. It has been proposed that interconversion of the kinetically controlled product 79 into the thermodynamically more stable diene complex 80 occurs via protonation at the carbonyl oxygen followed by dissociation into the pentadienyl cation and the ketene hemiacetal (Scheme 18). Recombination at C5 and deprotonation gives 80.

The pentenediyl complexes 76 which do not possess an electron withdrawing substituent at the σ-bound carbon are unstable. Air oxidation proceeds by way of carbonyl insertion followed by reductive elimination to give cyclohexenones (Scheme 19) [84a, 85a]. In contrast, (pentenediyli)-Fe(CO)$_3$ complexes 77, bearing an electron withdrawing substituent at the σ-bound carbon, are considerably more stable [85a]. Oxidative decomplexation utilizing CAN affords vinylcyclopropanecarboxylates in good yields (Scheme 19) [85b, 87]. The difference in stability of 76 and 77, and their divergent paths for the loss of the iron atom, may be attributed to the retarding effect of an electron withdrawing substituent on the rate of carbonyl insertion.

SUBSTITUTION OF (DIENOL)- AND (DIENYL ACTATE)Fe(CO)$_3$ COMPLEXES

Lillya and coworkers demonstrated that solvolysis of ψ-exo dienyl dinitrobenzoates 81 (acetone/H$_2$O) occurs ca. 10-60 times faster than for the free ligand while the corresponding ψ-endo dienyl dinitrobenzoates 82 undergo solvolysis slower than the free ligands [88]. The solvolyses occur with net retention of configuration (Scheme 20). These results are rationalized on the basis of ionization of the leaving group with anchimeric assistance from the iron atom, followed by attack of water on the face of the cation opposite to iron (i.e. double inversion). The ψ-exo dinitrobenzoates have the leaving group oriented favorably for this ionization, while the ψ-endo dinitrobenzoates must
undergo rotation about the diene-to-Cα bond which would bring the remaining substituent at the α-carbon into steric congestion with the dienyl portion of the molecule.

The reaction of transoid (pentadienyl)iron cations, generated via ionization of (dienyl acetate)iron complexes (83) in the presence of protic or Lewis acids, with weak hydride nucleophiles [25b, 29, 89] or weak carbon nucleophiles [81, 90] gives (E,E-diene)Fe(CO)₃ products 84, 85, and 86 (Scheme 21). The stereoselective substitution of dienol complexes 87 using (diethylamino)sulfur trifluoride [DAST], proceeding via

Scheme 18.

Scheme 19.
the intermediacy of transoid pentadienyl cations has been reported to afford dienyl-fluorides 88 in a stereoselective fashion [91]. Cyclization of dienols 87, bearing a pendant heteroatom nucleophile, under acidic conditions affords 5, 6, or 8-membered ring dienyl hetero-cycles 89 and 90 [92].

The reaction of dienyl cyanophosphonate complexes 91 with heteroatom nucleophiles in the presence of silver or trityl perchlorate gave the product from a 1,2-transposition of the Fe(CO)₃ group (Scheme 22) [93]. This transformation is proposed to involve generation of the transoid pentadienyl cation 93 followed by rearrangement to the cisoid pentadienyl cation 94. The cisoid pentadienyl cation 94 is in equilibrium with the two transoid pentadienyl cations 93 and 95; however 93 should be less stable than 95 since the electron withdrawing cyano group should

Scheme 20.

Scheme 21.
destabilize the adjacent cationic charge. Thus, weak nucleophiles react with the transoid pentadienyl cation \(95\) to generate the products \(92\).

**SYNTHETIC APPLICATIONS WHICH MAKE MULTIPLE USE OF (DIENE)IRON COMPLEXES**

The previous discussions has emphasized the stability of (diene)iron complexes. One of the advantages of stoichiometric organometallic reagents is the ability to repeatedly utilize the same metal center to control a number of different bond forming reactions. The following six syntheses, taken from a number of laboratories, creatively demonstrate this potential for acyclic (diene)iron complexes and (pentadienyl)iron cations.

5-Hydroxyeicosatetraenoic acid (5-HETE) is an oxygenated metabolite of arachadonic acid. It has been proposed that 5-HETE may have the ability to regulate renal function and that it may play a role in B cell activation [94]. Tao and Donaldson have reported a synthesis of (R)-5-HETE methyl ester which utilizes organoiron methodology (Scheme 23) [27]. Addition of the cuprate derived from 1,4-decadiyne to optically active (1-methoxycarbonylpentadienyl) Fe(CO)\(_3\)\(^+\) cation afforded the \(E,Z\)-diene complex \(96\). Reduction of \(96\) in the presence of Lindlar catalyst gave the corresponding tetraenoate. Functional group manipulation gave the aldehyde complex, which

\[ \text{Fe(CO)}_3 \text{CO}_2\text{Me} \xrightarrow{1,4\text{-decadiyne} \text{ nBuLi/CuBr}} (64\%) \xrightarrow{1) \text{H}_2\text{-Lindlar} \ 2) \text{DIBAL}} \text{Fe(CO)}_3\text{CO}_2\text{Me} < 90\% \text{ ee} \xrightarrow{\text{MnO}_2} \text{R} = \text{CHO \ (59\% \ for \ 3 \ steps)} \]

\[ \text{Fe(CO)}_3\text{OH} \xrightarrow{1) \text{CuBr} \ LiCH_2\text{CH}_2\text{CO}_2\text{OBO} \ 2) \text{H}_2\text{O}^+ \ 3) \text{MeOH/K}_2\text{CO}_3} \text{Fe(CO)}_3\text{OH} \xrightarrow{\text{CAN} \ \text{MeOH}} (\text{R})-5\text{-HETE methyl ester} \]

\[ \text{Fe(CO)}_3 \text{CO}_2\text{Me} \xrightarrow{1,4\text{-decadiyne} \text{ nBuLi/CuBr}} (64\%) \xrightarrow{1) \text{H}_2\text{-Lindlar} \ 2) \text{DIBAL}} \text{Fe(CO)}_3\text{CO}_2\text{Me} \xrightarrow{\text{MnO}_2} \text{R} = \text{CHO \ (59\% \ for \ 3 \ steps)} \]

\[ \text{Fe(CO)}_3\text{OH} \xrightarrow{1) \text{CuBr} \ LiCH_2\text{CH}_2\text{CO}_2\text{OBO} \ 2) \text{H}_2\text{O}^+ \ 3) \text{MeOH/K}_2\text{CO}_3} \text{Fe(CO)}_3\text{OH} \xrightarrow{\text{CAN} \ \text{MeOH}} (\text{R})-5\text{-HETE methyl ester} \]

**Scheme 22.**

**Scheme 23.** The Tao and Donaldson synthesis of 5-HETE methyl ester (OBO = oxabicyclo[2.2.2]octane).
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underwent diastereoselective nucleophilic addition followed by unmasking the oxabicyclo[2.2.2]octane protecting group to give 97 and its (5S) diastereomer (1.8:1 dr). Oxidative removal of the Fe(CO)$_3$ group gave 5-HETE methyl ester (>90% ee). In this synthesis, the Fe(CO)$_3$ adjunct served to control the formation of the 6E,8Z-diene segment and for introduction of the C5 stereo-center in a diastereoselective fashion.

A second arachadonic acid metabolite, LTA$_4$ is a highly reactive species centrally related to the formation of the physiologically active leukotrienes LTB$_4$, -C$_4$, -D$_4$, and -E$_4$. These are known to be mediators of inflammatory response [95]. Franck-Neumann and Colson have reported a synthesis of (5S,6S)-LTA$_4$ methyl ester which exploits organoiron methodology (Scheme 24) [35b]. Friedel-Crafts acylation of the optically active (pentadienoate)Fe(CO)$_3$ complex 98 with

Scheme 24. The Franck-Neumann and Colson synthesis of (-)-LTA$_4$ methyl ester.
the acid chloride of adipic methyl hemiester, followed by isomerization gave the 6-oxo-2E,4E-dienoate 99. Generation of the silyl enol ether, followed by halogenation gave the α-chloroketone as an equimolar mixture of separable diastereomers. Reduction of the 5R-diastereomer gave exclusively the 6S,5R-chlorohydrin 100; the diastereoselectivity of the reduction was controlled due to the steric bulk of the (tricarbonyl)iron adjunct. Protection of the hydroxyl group, followed by functional group manipulation led to the aldehyde 101. Wittig olefination, removal of the TBS protecting group, and decomplexation gave the tetracene chlorohydrin which upon treatment with potassium carbonate gave LTB₄. In this synthesis, the Fe(CO)₃ adjunct served to control the formation of the C6-C7 bond and for introduction of the C6 stereocenter in a diastereoselective fashion.

The biologically widespread antioxidant lipoic acid has demonstrated therapeutic activity in diabetes as well as other diseases and medical conditions [96]. Grée, et al., have reported a synthesis of racemic lipoic methyl ester which utilizes organoiron methodology (Scheme 25) [44]. Diastereoselective addition of vinyl magnesium bromide to rac-41 gave a mixture of separable allylic alcohols (2.6:1 dr). Hydroxyl group protection, followed by hydoroboration-oxidation gave the 1° alcohol which was converted into the thioester 102 via a Mitsunobu reaction. Reaction of 102 with excess thiobenzoic acid in the presence of Amberlyst-15 resin gave the bis-thiobenzoate 103 with retention of configuration. This reaction occurs via in situ generation of the transoid pentadienyl cation. Deprotivation of 103 followed by hydrazine mediated reduction and hydrolysis/oxidation gave racemic lipoic acid methyl ester. Use of this methodology with optically active 41 should give the optically active lipoic acid. In this synthesis, the Fe(CO)₃ adjunct served to control the formation of the C6-C7 bond in a diastereoselective fashion and for protection of the diene under the hydoroboration-oxidation conditions.

Macrolactin A is a 24-membered polyene macrolide isolated from a taxonomically undefined deep sea bacterium which exhibits antiviral activity against Herpes Simplex I and II and against HIV[97]. Prahlad and Donaldson have reported an enantioenriched synthesis of the C11-C24 segment which utilizes organoiron methodology (Scheme 26) [29, 54]. This synthesis also begins with racemic 41, however reaction with

![Scheme 25](image-url)
allylbis(isopinocampheyl)borane [98], followed by oxidative workup gave the optically active homoallylic alcohol complex (-)-104 (55% ee) which is separable from the accompanying diastereomeric alcohol. Hydroboration-oxidation and Parikh-Doering oxidation of the resultant 1° alcohol gave the corresponding lactol complex. Methylation of the lactol exploited conditions pioneered by Tsuchihashi, et al., [99] to afford the syn-1,4-diol (-)-105 as a single diastereomer. Selective ionic reduction of (-)-105 occurs via the intermediacy of the transoid pentadienyl cation. Protection and functional group transformation of the resultant hydroxy dienoate eventually afforded the triene complex (+)-106. Intermolecular nitrile oxide-olefin cycloaddition produced the isoxazoline which was subjected to reductive hydrolysis to give the β-hydroxyketone. In this synthesis, the Fe(CO)₃ i) participated in the allylation/resolution of rac-41, ii) mediated the removal of the C20 hydroxyl group via ionic reduction, iii) controlled the formation of the C15 stereocenter in a diastereospecific fashion via nitrile oxide-olefin cyclocondensation, and finally iv) acted as a protecting group for the diene during the isoxazoline reductive hydrolysis conditions.

Scheme 26. The Prahlad and Donaldson synthesis of the C11-C24 segment of macrolactin A.
Ikarugamycin is a polycyclic lactam which exhibits antibiotic activity [100]. Roush and Wada have reported a synthesis of the as-indacene unit of this target which utilizes organoiron methodology (Scheme 27) [48b]. Desymmetrization of meso (2,4-hexadienedial)Fe(CO)$_3$, via chiral crotylboration gave the homoallylic alcohol complex 107 with excellent enantiomeric excess. Condensation of 107 with Meldrum's acid produced the Knovenagel product. Conjugate addition of vinyl magnesium bromide to the activated olefin gave 108 in which the C11 stereocenter was introduced in a diastereospecific fashion. Acylation afforded a dienyl acetate, which upon treatment with triethylaluminum underwent substitution to yield 109, via the intermediacy of an in situ generated transoid pentadienyl cation. Oxidative decomplexation gave the free ligand, which was eventually transformed into the triene 110. Intramolecular Diels-Alder cyclization followed by intramolecular aldol condensation and reduction gave the tricyclic segment of ikarugamycin. In this synthesis, the Fe(CO)$_3$ adjunct served to control the diastereospecific formation of both the C6 and C11 stereocenters.

The amino alcohol 111, structurally related to the sphingosines, was isolated from the sponge.
Xestospongia sp. This E,E-diene was found to inhibit the growth of Candida albicans [101]. Takemoto, et al., have reported a synthesis of the N-Boc-O-methyl derivative of this target (112) which prominently features, in a reiterative fashion, their novel 1,2-iron transposition methodology (cf. Scheme 22). As in the previous example, this synthesis begins with meso (2,4-hexadiendial)Fe(CO)₅. Addition of dimethylzinc in the presence of Ti(iPrO)₄ and a catalytic amount of the chiral cyclohexyldiamine ligand gave the mono-alcohol 113 in 71% yield, 96% ee (Scheme 28) [93c]. Acylation, followed by substitution with trimethylsilyl azide proceeded via the intermediacy of the in situ generated transoid pentadienyl cation to furnish 114. Under these conditions the aldehyde functionality was simultaneously converted into a nitrile group. Regeneration of the aldehyde was accomplished by DIBAL reduction. Reaction of the aldehyde with diethyl phosphorocyanidate in presence of LiCN, followed by reaction of the resultant O-phosphoryl cyanohydrin with methanol and trityl perchlorate effected the 1,2-transposition strategy to yield the dieny ether complex 115. With the stage set for repetition of this strategy, reduction of 115 followed by phosphocyanation and treatment with thioethanol/trityl perchlorate gave 116. Catalytic reduction of 116 in the presence of (Boc)₂O effected cleavage of the thioethanol substituent and transformation of the azido into a protected amino functionality. The synthesis was completed by conversion of the cyano group to an aldehyde functionality, and Wittig olefination. Catalytic reduction and decmplexation gave 117.

SUMMARY

The above discussion illustrates the ability of a (tricarbonyl)iron adjunct to serve in three capacities: i) as a protecting group for conjugated dienes, ii) to direct the formation of chiral centers adjacent to the complexed diene, and iii) to stabilize the formation of a positive charge adjacent to the complexed diene (i.e. pentadienyl cations). Due to the stability of these complexes to a wide variety of reaction conditions these attributes may be repetitively applied while maintaining the (diene)iron functionality.

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Stoichiometric Applications of Acyclic π-Organoiron Complexes


