Stoichiometric Applications of Acyclic π-Organoiron Complexes to Organic Synthesis

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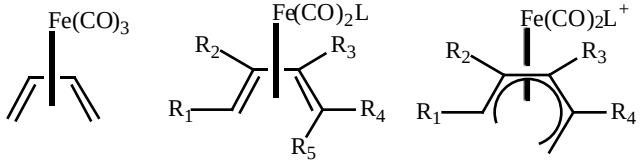
Abstract: The application of acyclic (diene)iron complexes and (pentadienyl)iron cations in organic synthesis has steadily increased over the past 20 years. This is due to their ease of preparation, their stability toward a wide variety of reaction conditions, the manifold method for removal of the $Fe(CO)_3$ 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 ot 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-organometallic 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 $(C_4H_6)Fe(CO)_3$ [2a]. Considerably later, after the elucidation of the structure of ferrocene, Pauson and Hallam proposed a π-complex (**1**) for $(C_4H_6)Fe(CO)_3$ 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, PPh_3) to the synthesis of polyene natural products.



1 **2** **3**

Fig. (1). $(Diene)Fe(CO)_2L$ and $(pentadienyl)Fe(CO)_2L^+$ complexes.

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 $Fe(CO)_5$,

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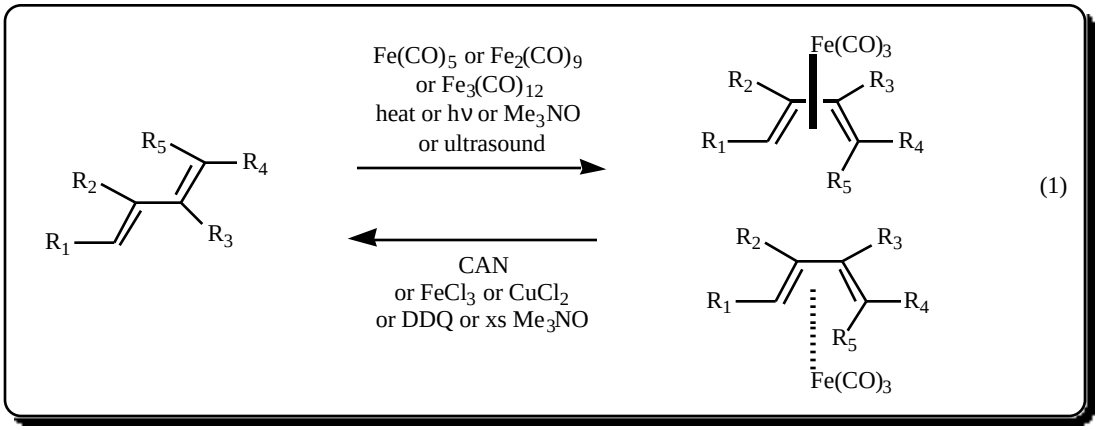


$Fe_2(CO)_9$, or $Fe_3(CO)_{12}$, either thermally, photochemically, or with the influence of ultrasonic stirring, or by dry state-adsorption techniques (eqn. 1) [4]. Room temperature complexation using $Fe(CO)_5$ may be accomplished by decarbonylation with trimethylamine N-oxide [5]. Complexation of non-conjugated dienes under thermal conditions usually leads to isomerization to afford the conjugated (1-4-η^4-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(η^2-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 10^4 @ 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 $Fe_2(CO)_9$ affords pentadiene complexes **11a** [13]. The intermediacy of a (pentenediyl)iron species **12** has been proposed. Reaction of methylenecyclopropanes **13** with $Fe_2(CO)_9$ yields diene complexes **11b** [14]. Ring opening of vinyloxiranes **14** with $Fe(CO)_5$ produces the corresponding π-allyl iron lactone

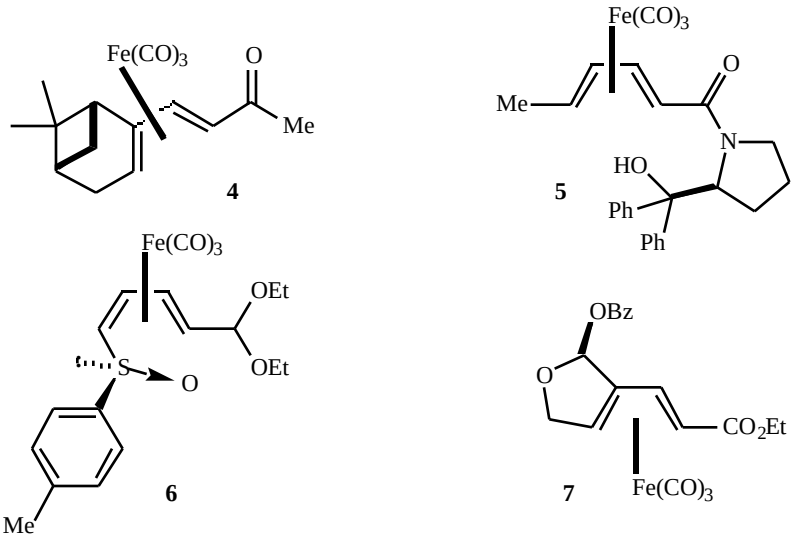
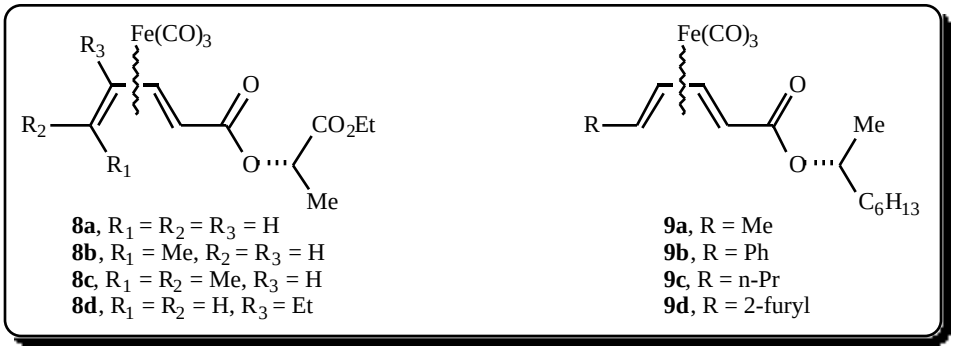


Fig. (2). Optically active acyclic (diene)iron complexes prepared by diastereoselective complexation.



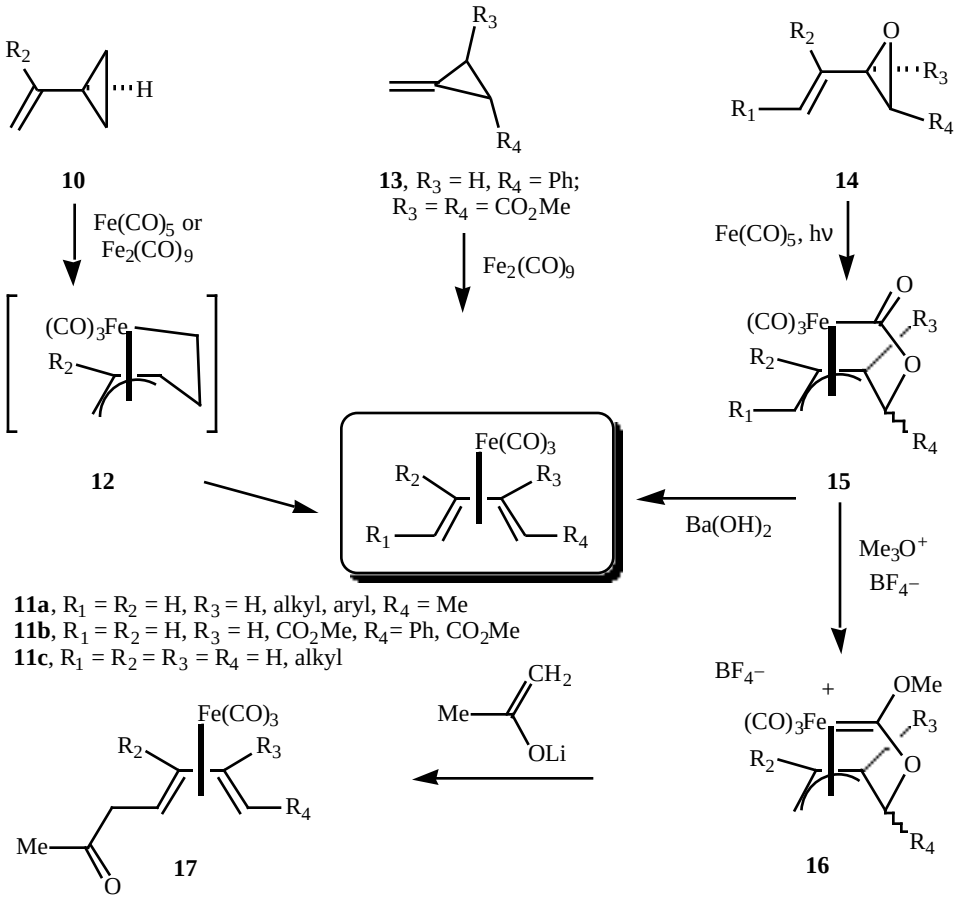
8a, $R_1 = R_2 = R_3 = H$
8b, $R_1 = Me$, $R_2 = R_3 = H$
8c, $R_1 = R_2 = Me$, $R_3 = H$
8d, $R_1 = R_2 = H$, $R_3 = Et$

9a, R = Me
9b, R = Ph
9c, R = n-Pr
9d, R = 2-furyl

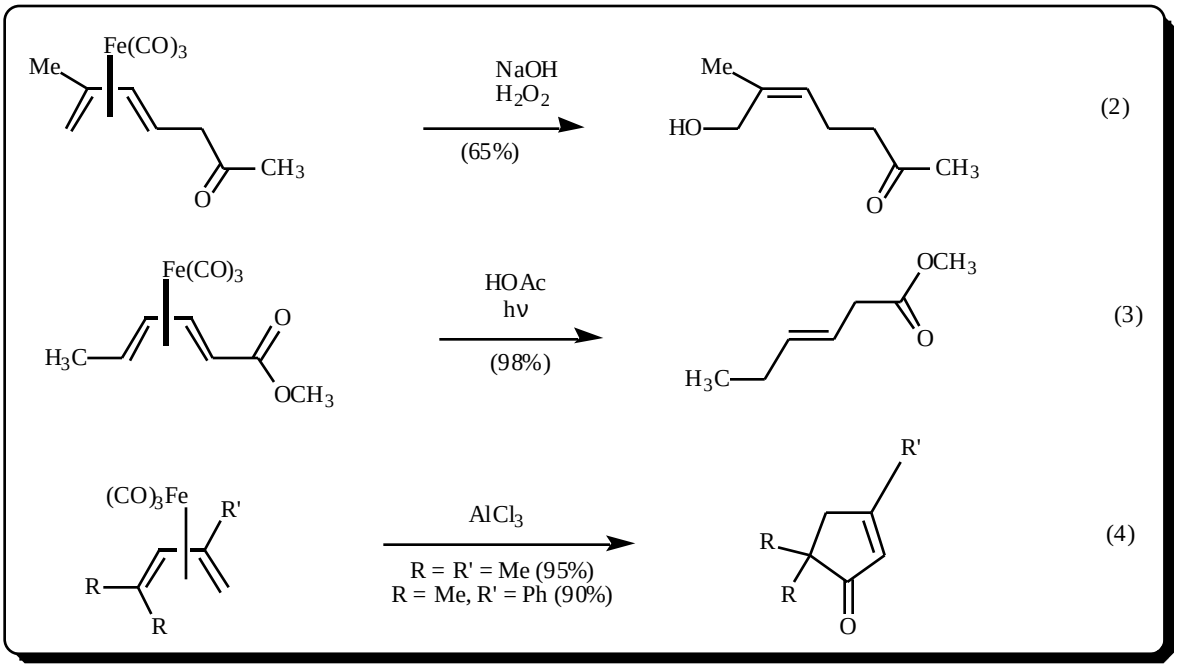
complexes **15**. Treatment of **15** with barium hydroxide leads to diene complexes **11c** via decarboxylation [15]. Alternatively, alkylation of the π-allyl iron lactone complexes **15** with Meerwein's salt yields the chelated π-allyl carbene cations **16** [16]. Reaction of cations **16** with enolate 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 $FeCl_3$, $CuCl_2$, $(NH_4)_2Ce(NO_2)_6$ [CAN], Me_3NO or DDQ (eqn. 1) [17]. Normally, oxidation of (diene)$Fe(CO)_3$ complexes with H_2O_2 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 $AlCl_3$ yields 2-cyclopentenones, however the yields are



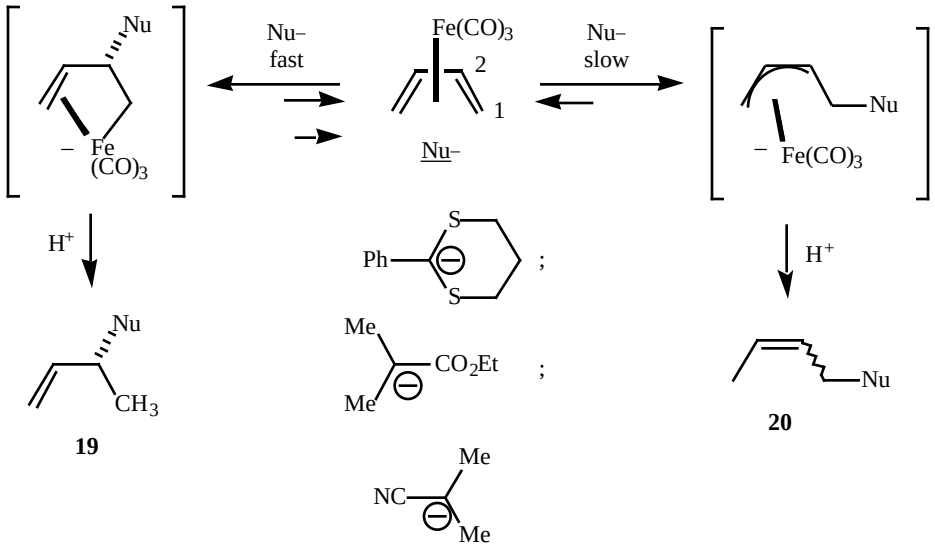
Scheme 1.



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

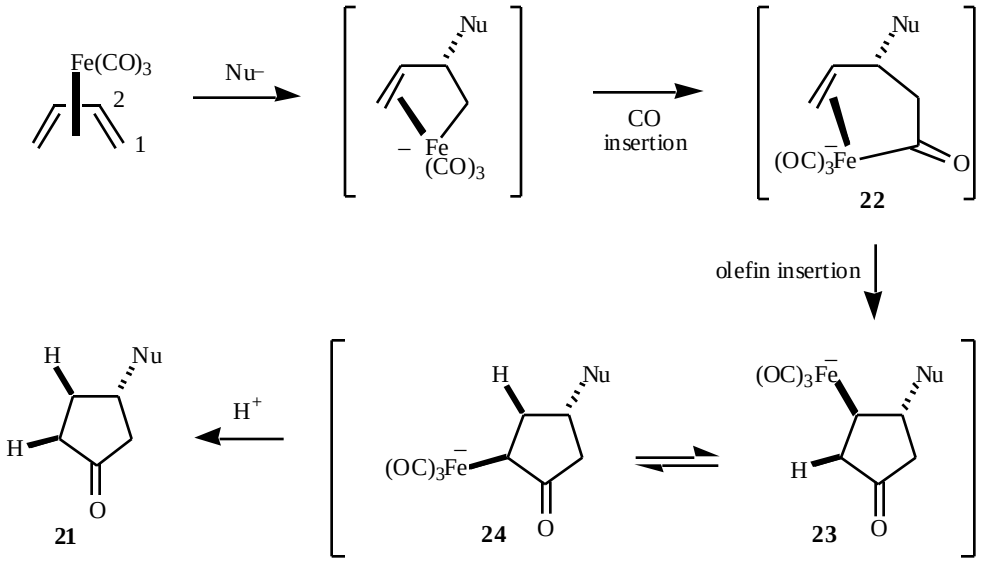
Zerovalent transition metal carbonyl moieties may act as electron acceptors and thus activate coordinated polyene ligands toward nucleophile attack. For example, reaction of $(C_4H_6)Fe(CO)_3$ with strong carbon nucleophiles, followed by protonation, gives olefinic products **19** and **20** (Scheme 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 $(C_4H_6)Fe(CO)_3$ 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 varients of this reaction have been

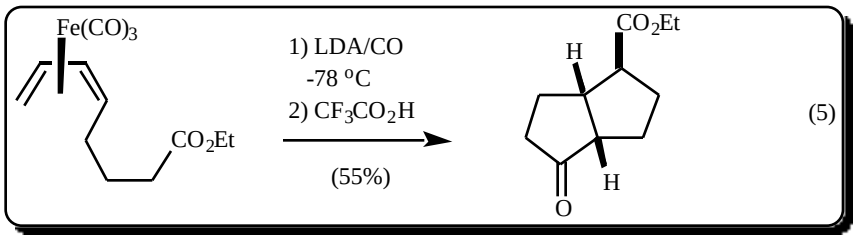


Scheme 2.

reported for the preparation of bicyclo[n.3.0]-alkanones (eqn. 5) [23].

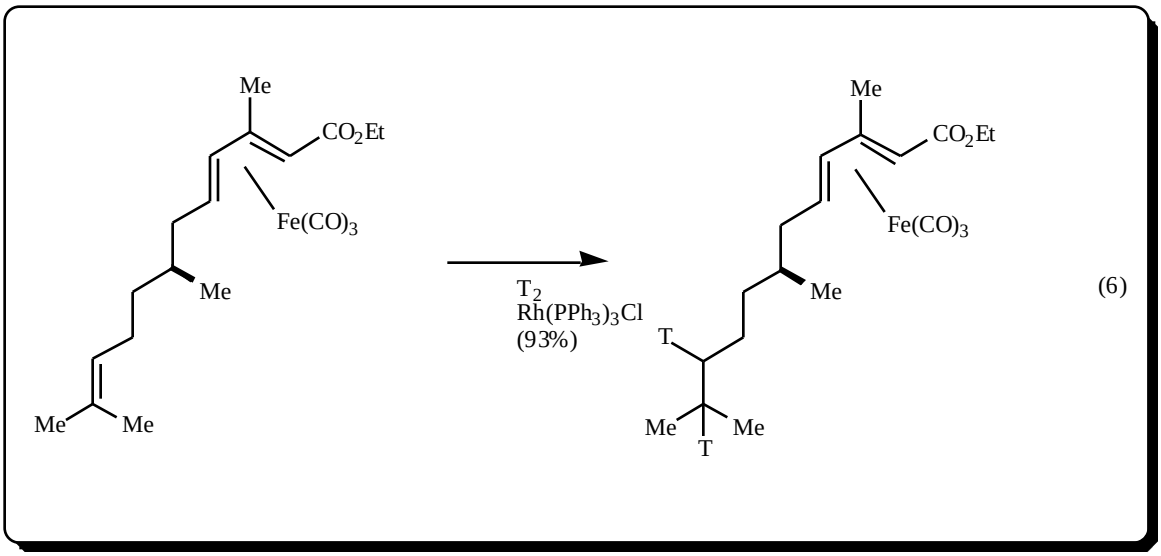


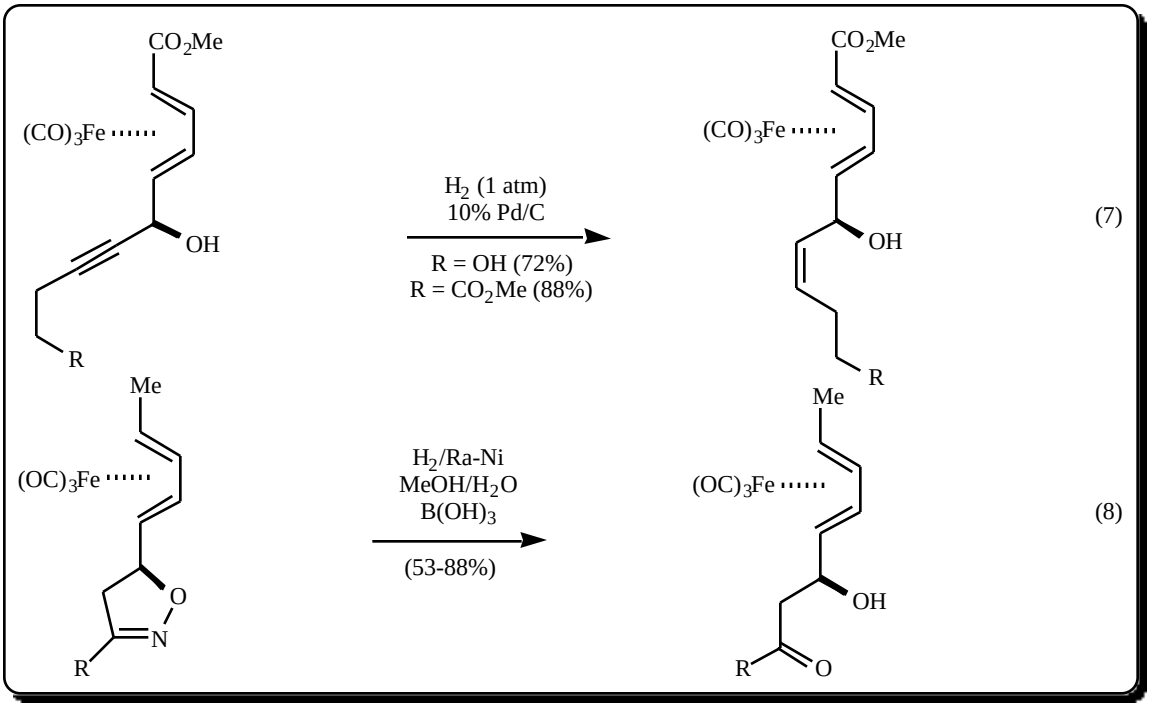
Scheme 3



USE OF THE TRICARBONYL-IRON FUNCTIONALITY AS A PROTECTING GROUP

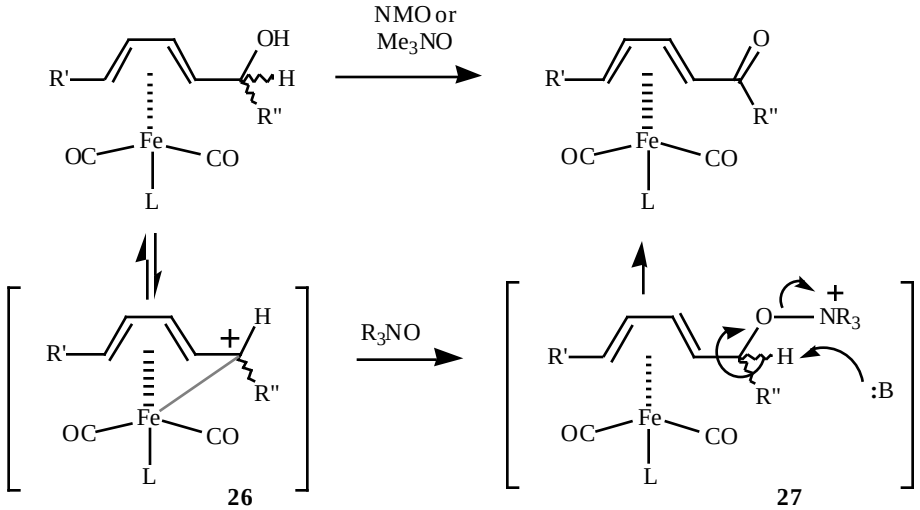
Complexation of an $Fe(CO)_3$ group to a conjugated diene efficiently protects the diene toward a variety of reduction, oxidation and cycloaddition reactions. For example, the $Fe(CO)_3$ group has been used as a protecting group for the C2-C5 diene segment in the preparation of a tritium labeled insect growth regulator via catalytic reduction ($T_2/Rh(PPh_3)_3Cl$) (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 (diene)$Fe(CO)_3$ group is stable to conditions which effect reductive hydrolysis of an adjacent isoxazoline (eqn. 8) [25].

While (diene)$Fe(CO)_3$ complexes are susceptible to decomplexation by strong oxidizing agents, this functionalty is stable to a wide variety of milder oxidation conditions. Alcohol oxidation, in the presence of a (diene)$Fe(CO)_3$ moiety has been successfully accomplished with PDC/4Å sieves (60%) [26], MnO_2 (60-80%) [27], DMSO/$(COCl)_2$/NEt_3 (67-71%) [28], SO_3-pyr (54-65%) [29], nPrMgBr/1,1'-(azodicarbonyl)dipiperidine (78-89%) [29,30], or Ag_2CO_3 (56%) [31]. A novel chemoselective, metal-mediated, oxidation of 1˚ or 2˚ alcohols adjacent to a (diene)$Fe(CO)_3$ 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. PPh_3) increases the yield.

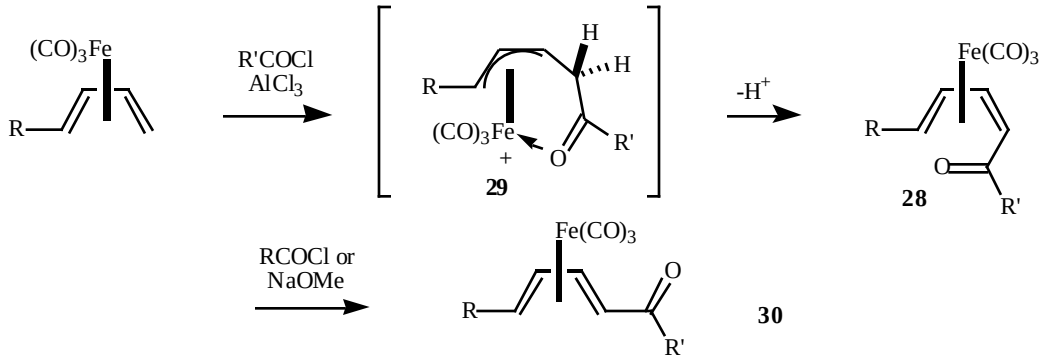


(R' = alkyl, CO_2Me, H; R" = H, alkyl; L = CO, PPh_3)

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 (η^3-allyl) complex **29** is subsequently deprotonated 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 LTA$_4$ [35b], and the C8-C15 segment of protomycinolide IV [36].



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 **30** proceeds with high diastereoselectivity (>90% de) to afford predominantly the ψ-*endo* alcohol [38]. In comparison, nucleophilic addition to (2*E*,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], LTB$_4$ [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 LTA$_4$ [35b].

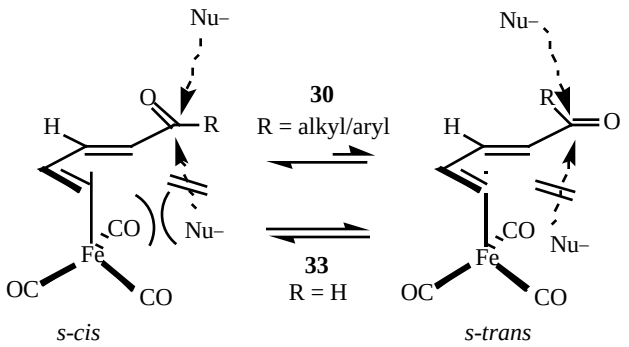
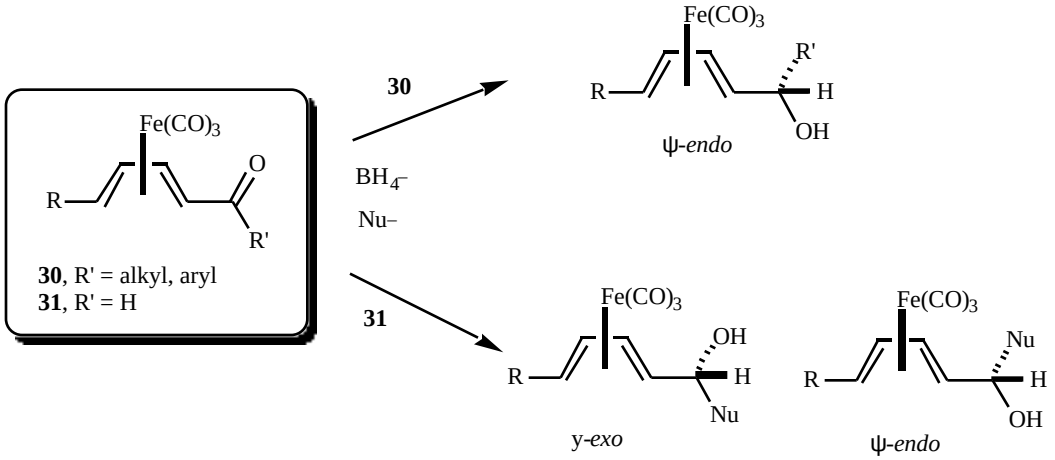
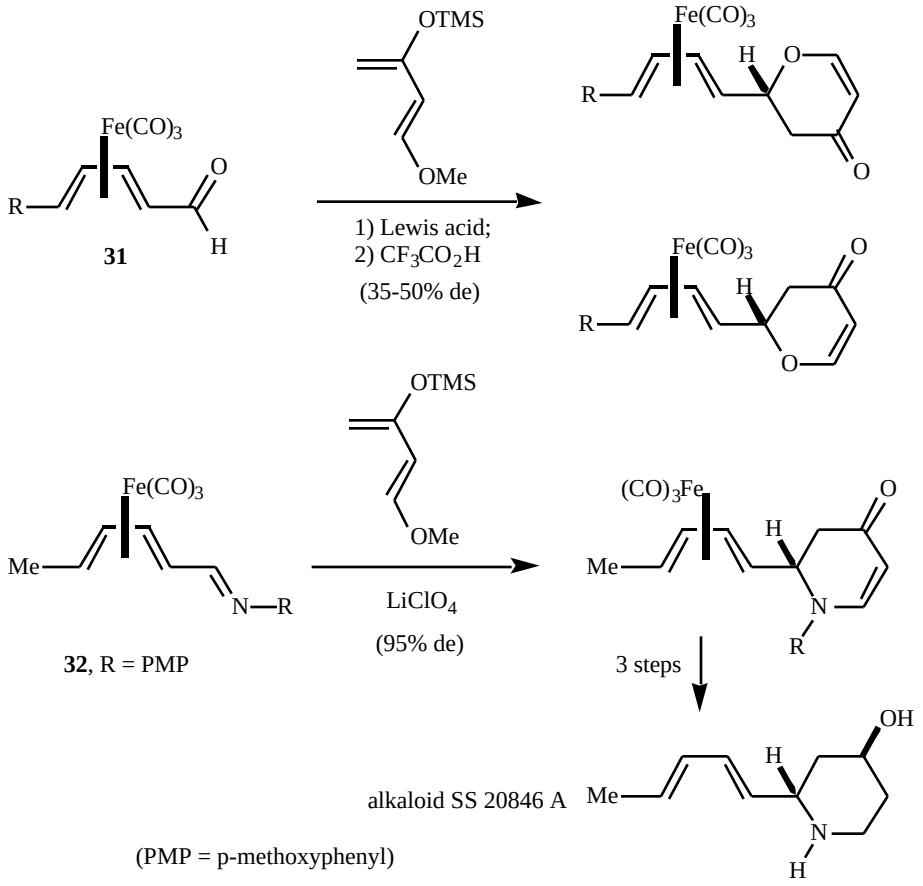


Fig. (3). Diastereoselective addition to (Dienal)- and (dienone)iron complexes.



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 diastereoselectivity is indicative of a greater bias toward the *s*-trans conformer about the diene-to-imine bond, due to unfavorable steric interactions in the *s*-cis conformer. For example, cyclocondensation of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene with (dienylimine) complex **32** in the presence of a catalytic amount of $LiClO_4$ gives the corresponding dehydropiperidone with excellent diastereoselectivity (>95% de, Scheme 7) [47]. The product has been utilized in the asymmetric



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**).

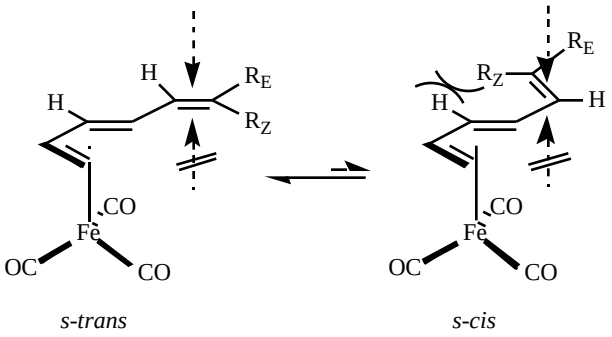
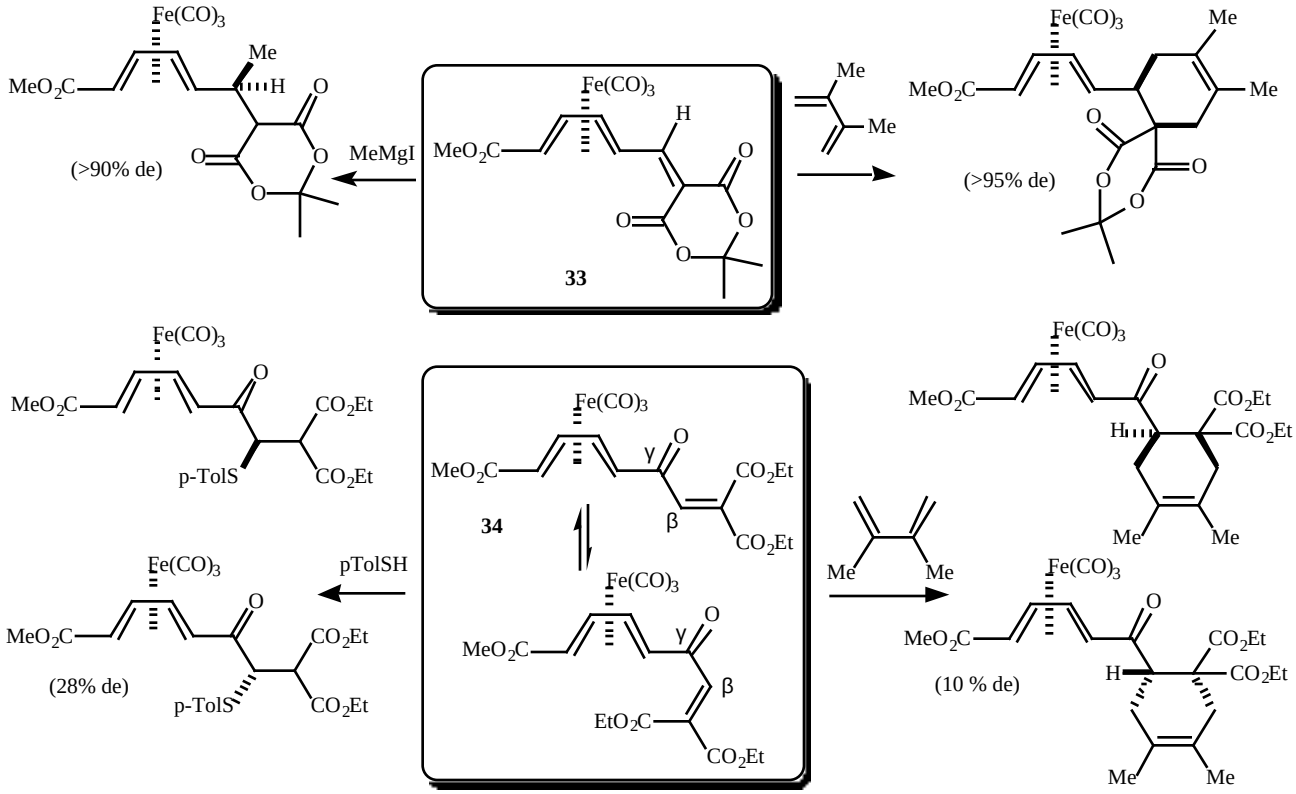


Fig. (4). Diastereoselective addition to conjugated (triene)iron complexes.

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.

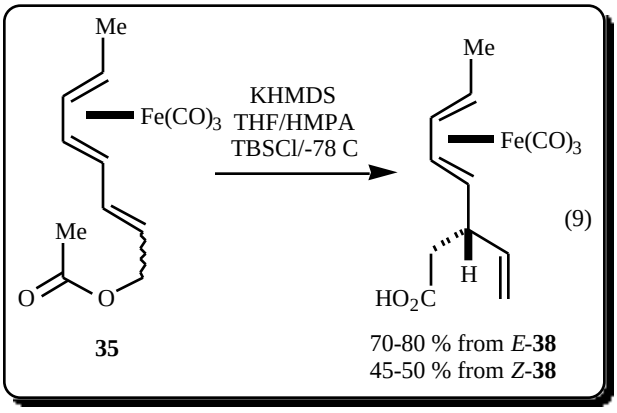
The cycloadditions of olefins appended to a (diene)Fe(CO)$_3$ complex have been examined. Diels-Alder cycloaddition of the activated (triene)Fe(CO)$_3$ complex (**33**) is reported to afford a single product (Scheme 8) [50]. In comparison, Diels-Alder cycloaddition of dienyl vinyl ketone complex **34**, 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



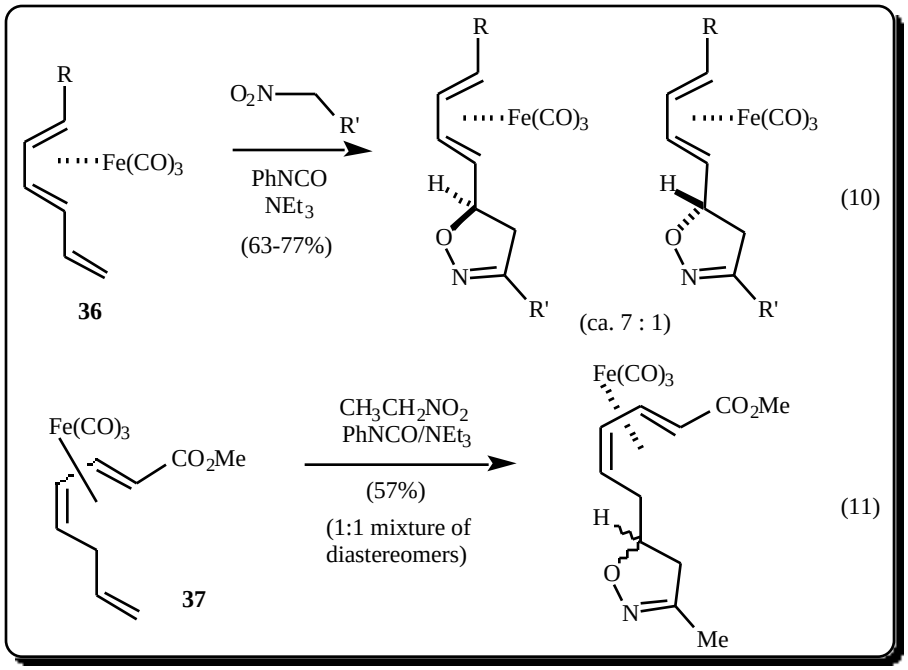
Scheme 8.

bond is formed anti to the sterically bulky $Fe(CO)_3$ group.



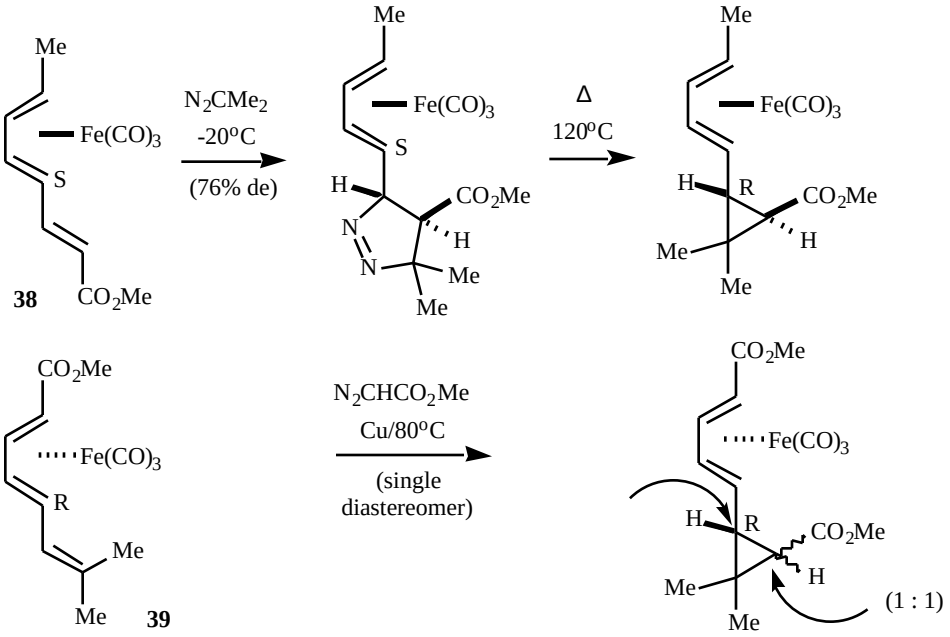
the C11-C24 fragment of macrolactin A [29]. In contrast to the reactivity of **36**, intramolecular nitrile oxide-olefin cyclo-addition for "skipped" triene complex **37** gave an equimolar mixture of diastereomers (eqn. 11) [54]. In this case, the lack of diastereoselectivity may indicate that the steric bulk of the $Fe(CO)_3$ group is too far distant from the pendent olefin and/or that there is not a preferred reactive conformers about the C-C single bonds.

(Triene)$Fe(CO)_3$ complexes bearing a pendant electron deficient alkene (e.g. **38**) undergo dipolar cycloaddition with diazomethane or diazopropane to give the corresponding Δ^2-pyrazolines with good diastereoselectivity (Scheme 9) [55]. The Δ^2-pyrazolines can be thermalized to the corres-



While *intramolecular* nitrile oxide-olefin cyclo-condensations occur with good diastereo-selectivity, *intermolecular* cyclocondensations of nitrile oxides with 3-substituted-1-alkenes are generally less diastereoselective (ca. 0-54% de) [52]. In comparison, *intermolecular* addition of nitrile oxides to conjugated triene complexes **36** results in the formation of the corresponding isoxazolines in good yield and with good diastereoselecticity (ca. 80% de) (eqn. 10) [25, 53]. Thus the combination of the steric bulk of the $Fe(CO)_3$ group and the conformational preference for the s-*trans* isomer results in uncommonly high diastereoselectivity for this intermolecular cyclo-condensation. This methodology has been used in an enantioselective synthesis of (+)-gingerol [53b], the carbon skeleton of (+)-streptenol D [25b] and ponding cyclopropyl diene complex. Similar cyclopropyl diene complexes have been obtained by cyclopropanation of a (triene)$Fe(CO)_3$ complex (**39**) with methyl diazoacetate [56]. While in both cases the cyclopropanation reagent approaches the face opposite to the $Fe(CO)_3$, in order to obtain the (R) stereochemistry at the dienylcyclopropane carbon the absolute stereochemistry of the precursor (diene)iron precursor must be the opposite [(S)-**38** vs. (R)-**39**] since different groups are added in the two examples. These cyclopropyl diene products were used for the preparation of intermediates for pyrethroid synthesis.

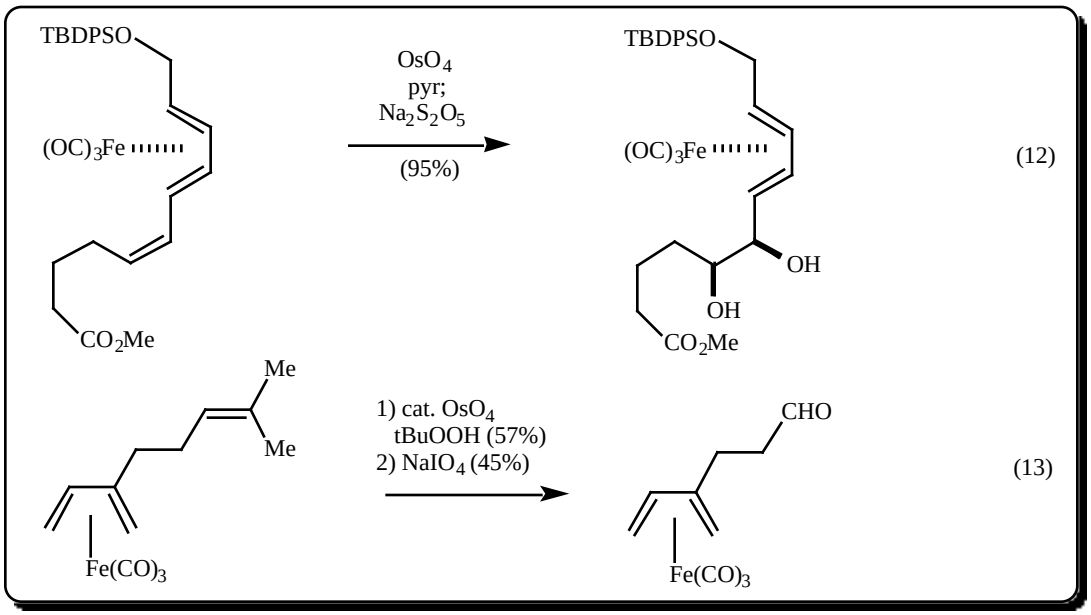
Osmylation of conjugated (triene)$Fe(CO)_3$ complexes (**40**) proceeds with excellent diastereo-selectivity, with dihydroxylation occurring via the

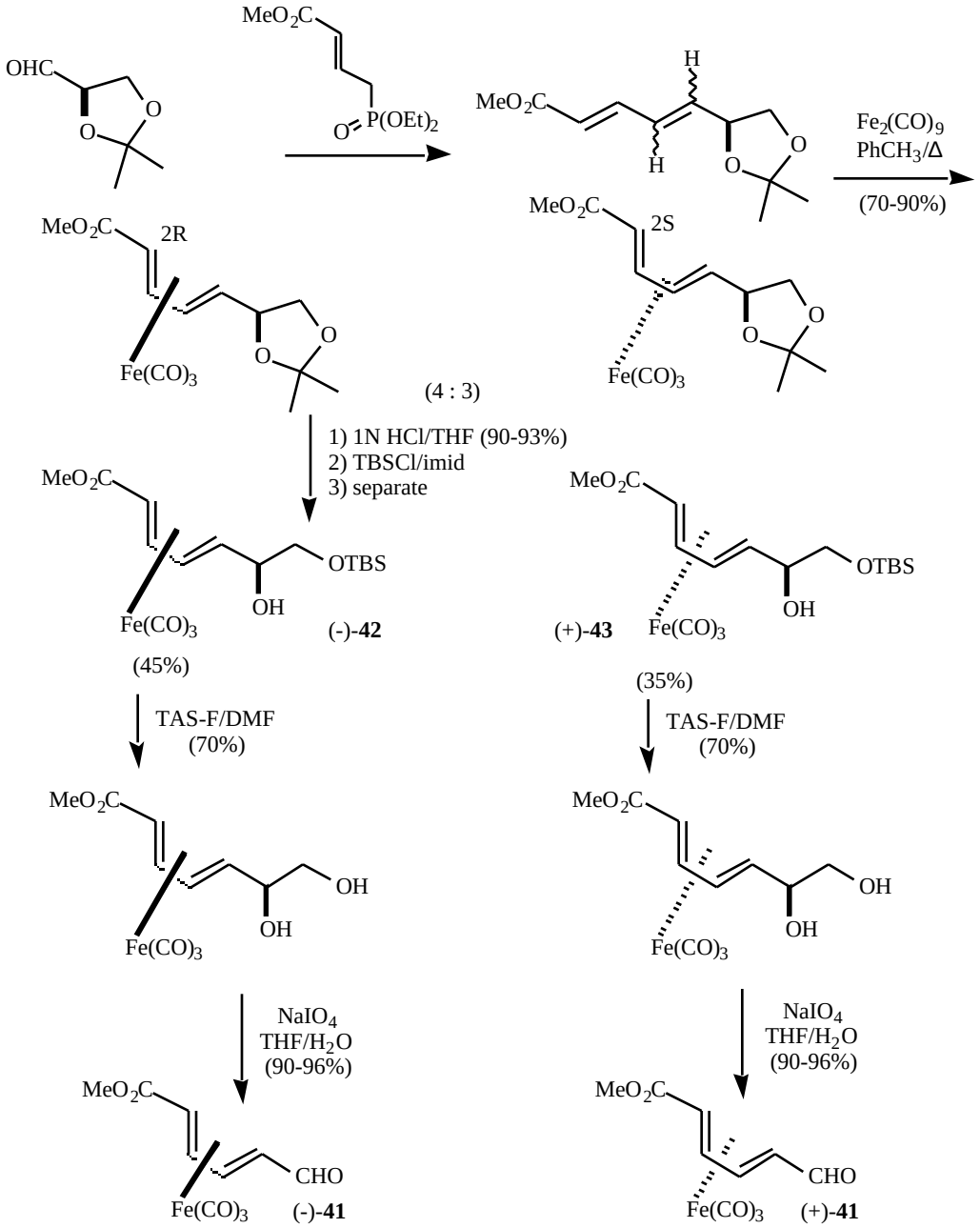


Scheme 9.

s-trans conformer 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 $NaIO_4$. 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 $NaIO_4$ 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 $Fe_2(CO)_9$ 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 $NaIO_4$ gave the enantiomers (-)-**41** and (+)-**41** in excellent yield.





Scheme 10.

ALKYLATION AND ALDOL CONDENSATIONS OF (DIENOATE)- AND (DIENONE)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**).

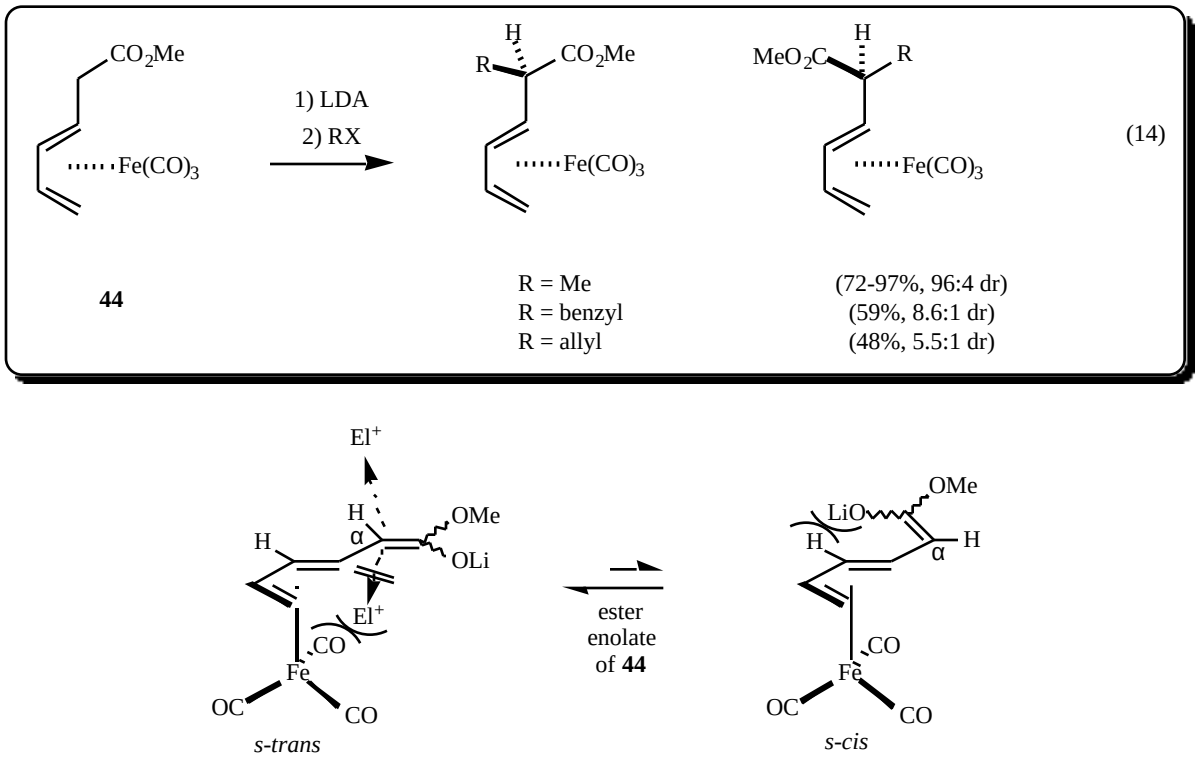
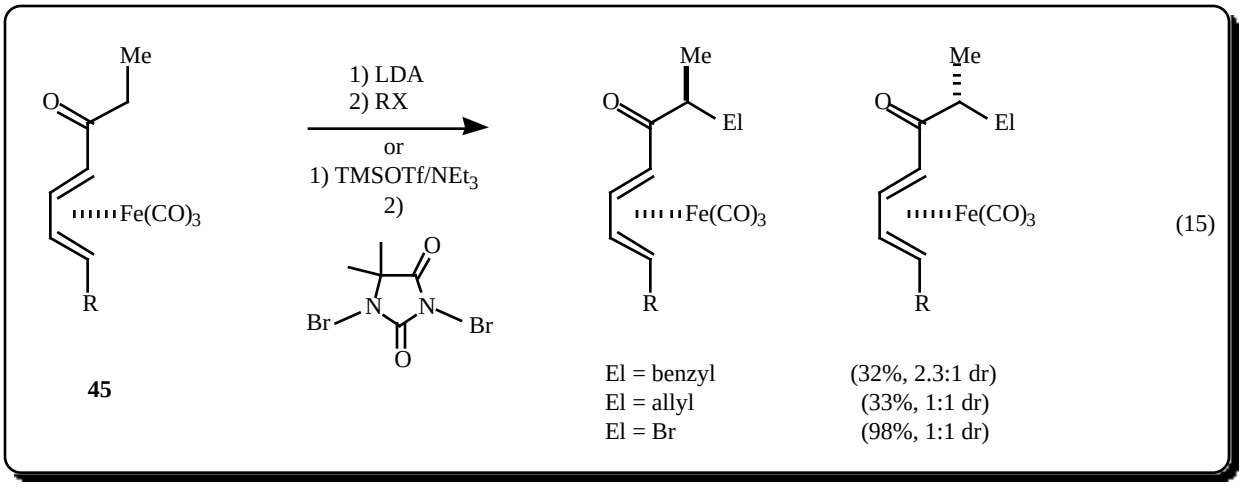


Fig. (5). Diastereoselective alkylation of ester enolate anion of (methyl 3,5-hexadienoate)$Fe(CO)_3$.



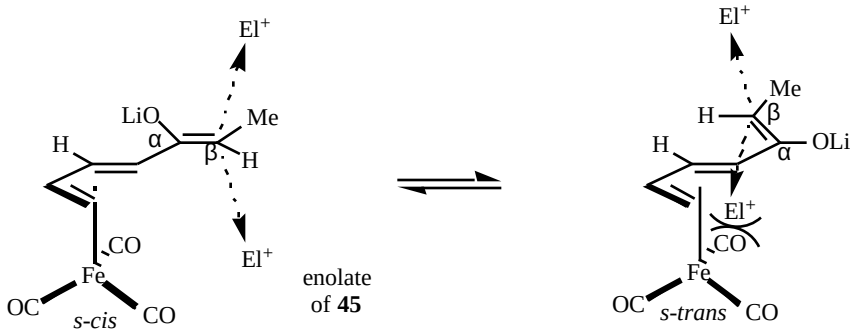


Fig. (6). Diastereoselective alkylation of enolate anion of (*E*,*E*-dienone)$Fe(CO)_3$ complexes.

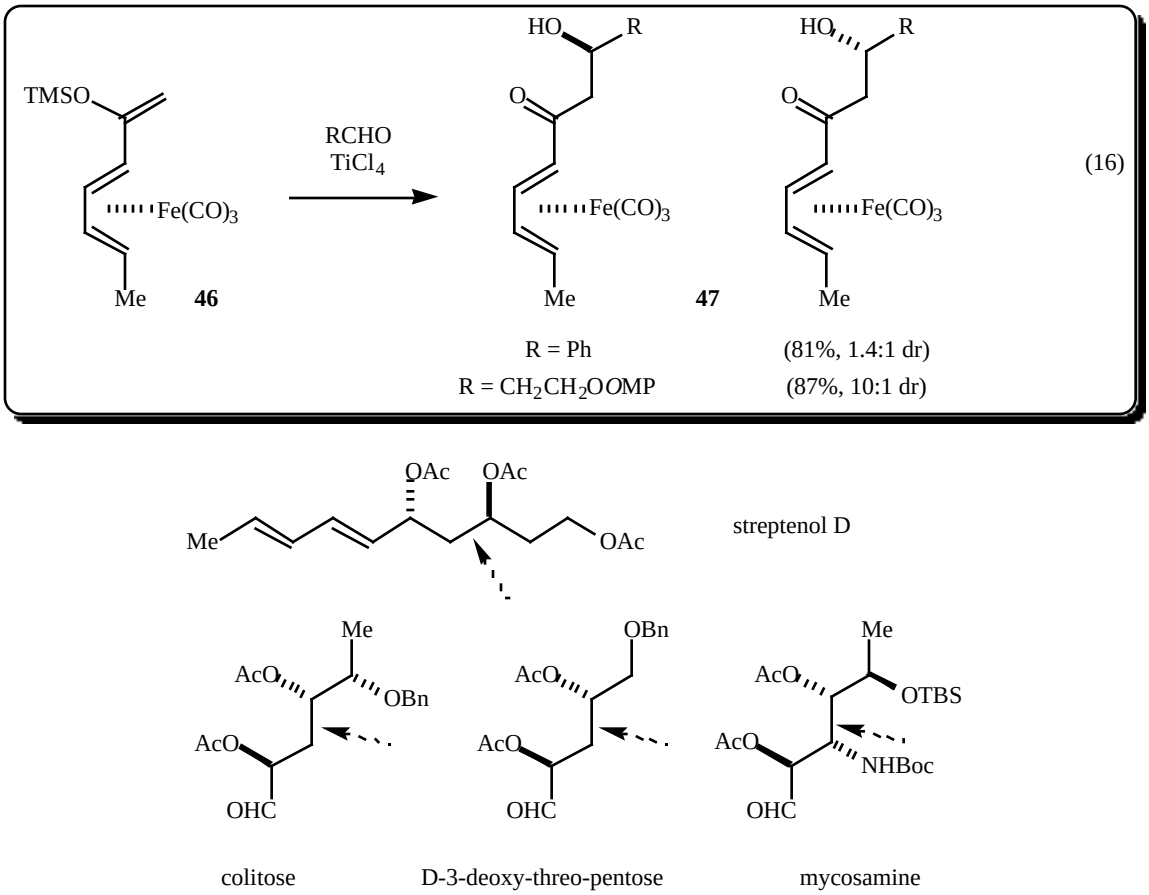


Fig. (7). Natural products prepared by aldol condensation of (dienone)$Fe(CO)_3$ with aldehydes (arrow indicates bond formed).

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

In 1960, Fischer demonstrated that hydride abstraction from (cyclohexadiene)$Fe(CO)_3$ (**48**) gave the stable (cyclohexadienyl)$Fe(CO)_3^+$ cation (**49**) [62]. Nucleophilic attack at the terminal carbon of **49** gives substituted (cyclohexadiene)$Fe(CO)_3$ 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-joubertiamine (**52**) [63b], carbazole (**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 (pentadienyl)$Fe(CO)_3^+$ cations (**56**) via protonation of (pentadienol)$Fe(CO)_3$ 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

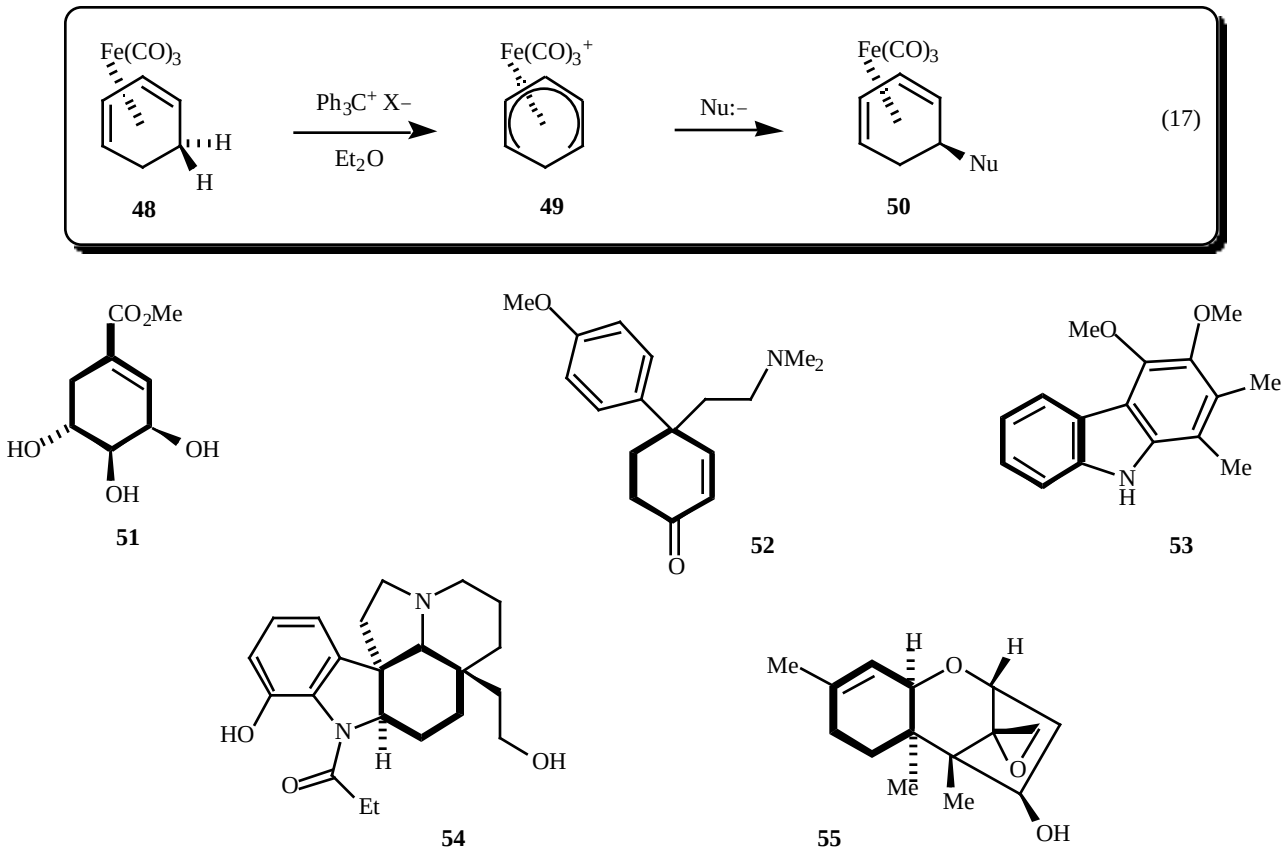
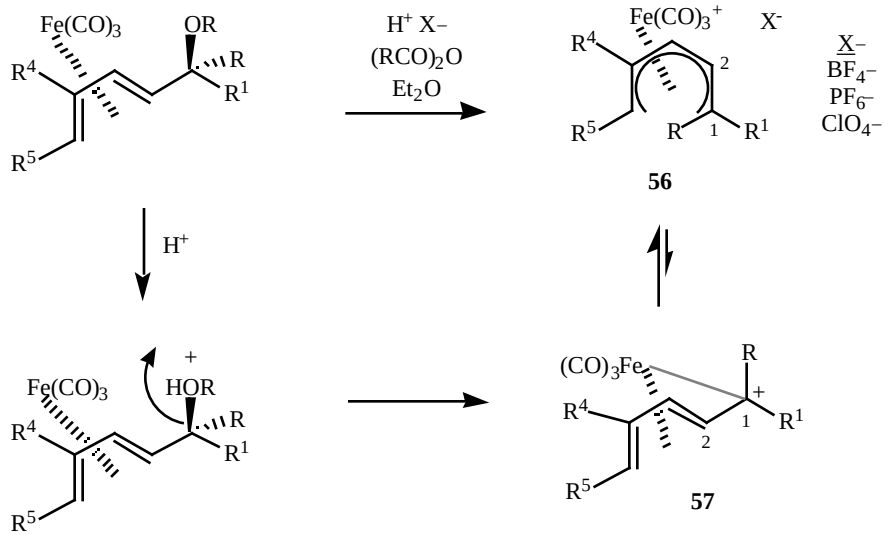


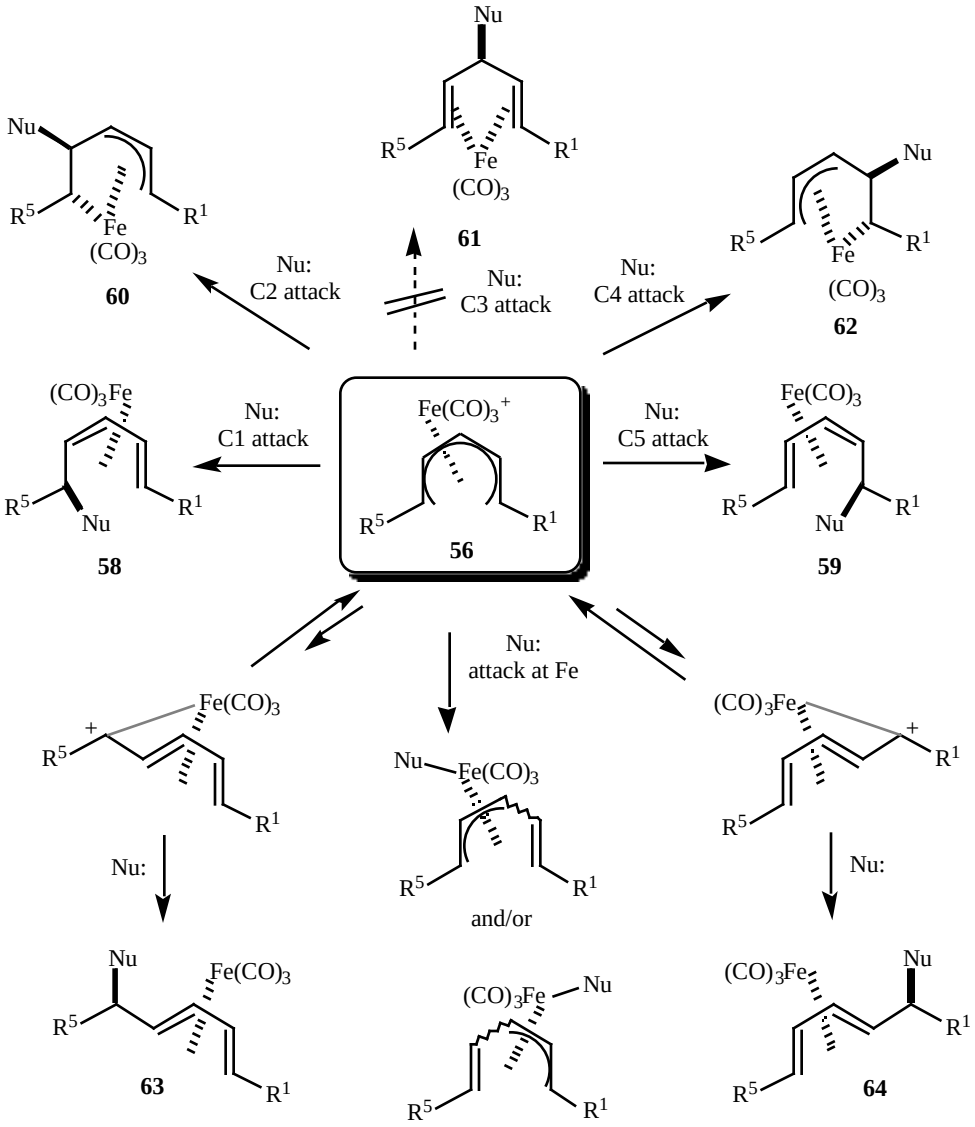
Fig. (8). Natural products prepared via nucleophilic addition to (cyclohexadienyl)$Fe(CO)_3$+ cations.

retention of configuration about the C1-C2 bond [65]. Recent DFT calculations on the parent cation (R = R^1 = R^4 = R^5 = H) predict that the cisoid structure (**56**) is 9.2 kcal mol^{-1} more stable than the transoid structure (**57**) [66]. Concordant with this energy difference, the NMR spectra of nearly all (pentadienyl)$Fe(CO)_3^+$ cations reveal only the cisoid geometry. While **56** is more stable than **57**, 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; $E_a \approx 13$ kcal mol^{-1}) [67].

(Pentadienyl)iron(1+) cations **56** are excellent organometallic electrophiles toward a wide variety



Scheme 11.

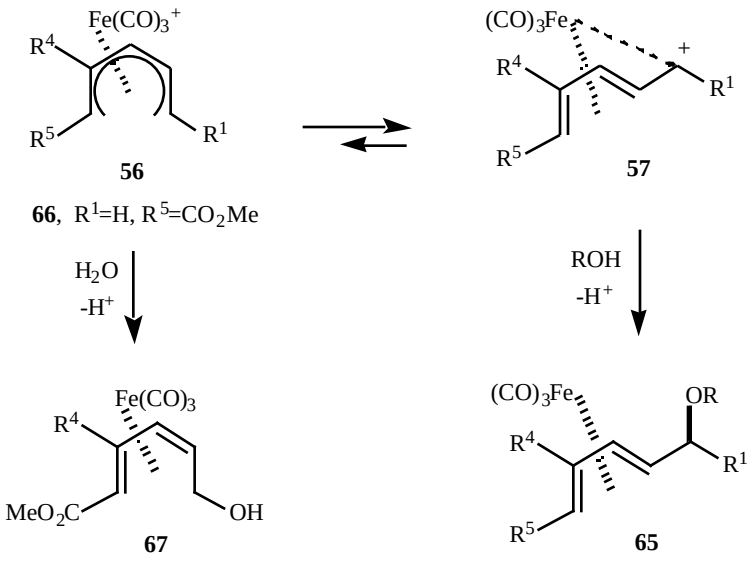


Scheme 12.

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

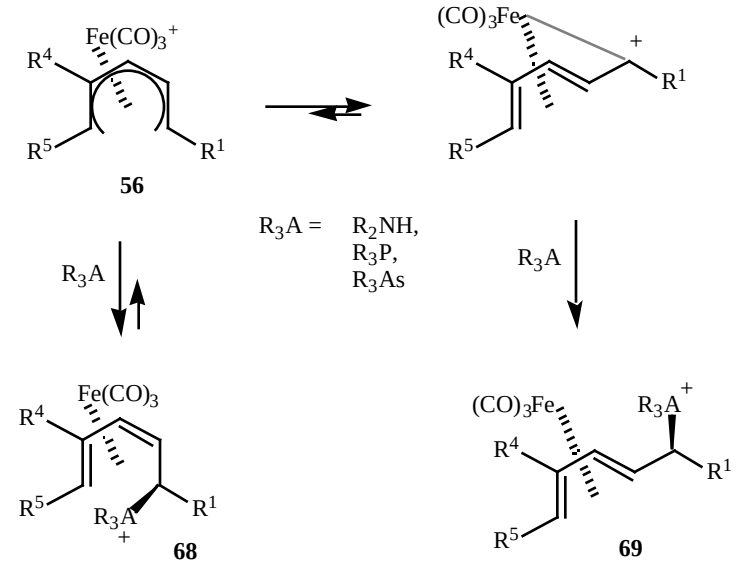
In general, the reaction of water or alcohol with cations **56** yields (*E,E*-dienol)- or (*E,E*-dienyl ether)$Fe(CO)_3$ complexes **65** (Scheme 13) [7a, 64, 65, 68, 69]. The ψ-*exo*-*E,E*-dienol products are the result of attack by the weak oxygen nucleophile on the less stable, but more reactive, 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 reversiblity 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** (R_3A = PPh_3) 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.

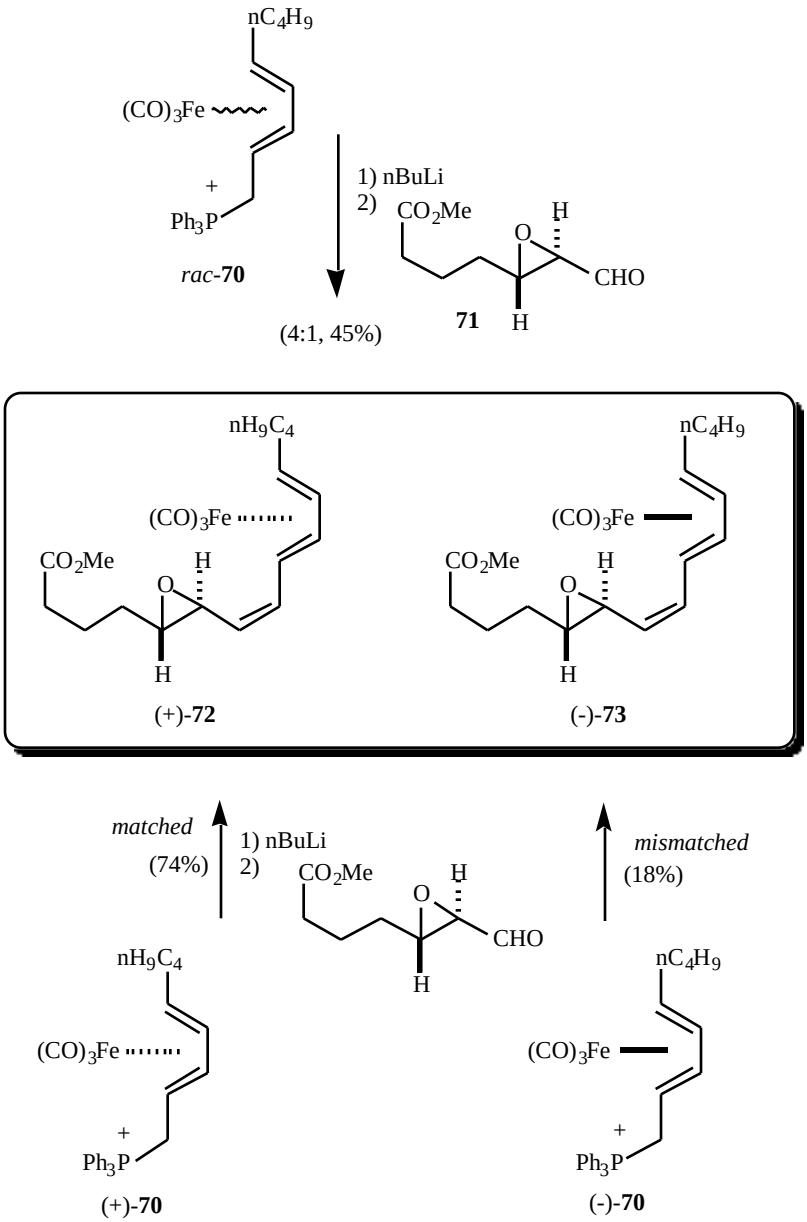
fashion to produce the trienyl epoxides (+)-**72** and (-)-**73** (4:1 dr, Scheme 15) [76c]. These results represent matched and mismatched combinations respectively. Separate reaction of the ylide derived from (+)-**70** with **71** gave (+)-**72** in considerably greater yield (74%) than the reaction 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 regio-selectivity for these reductions. In contrast, reaction of (1-methoxycarbonylpentadienyl)-$Fe(CO)_2PPh_3^+$ with $NaBH_3CN$ proceeds via attack at an internal carbon to afford the σ,π-allyl complex **74** in excellent yield (eqn. 18) [78].

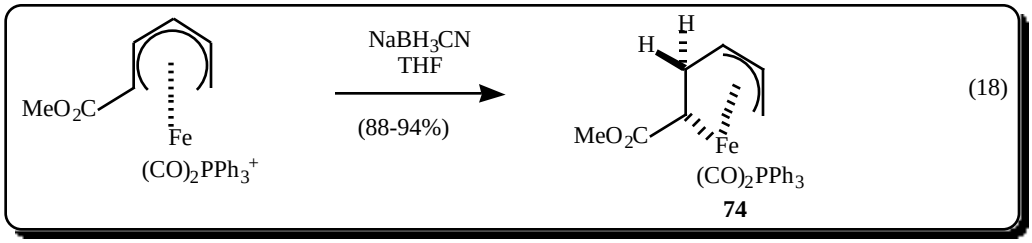
2. Reaction with Carbon Nucleophiles

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

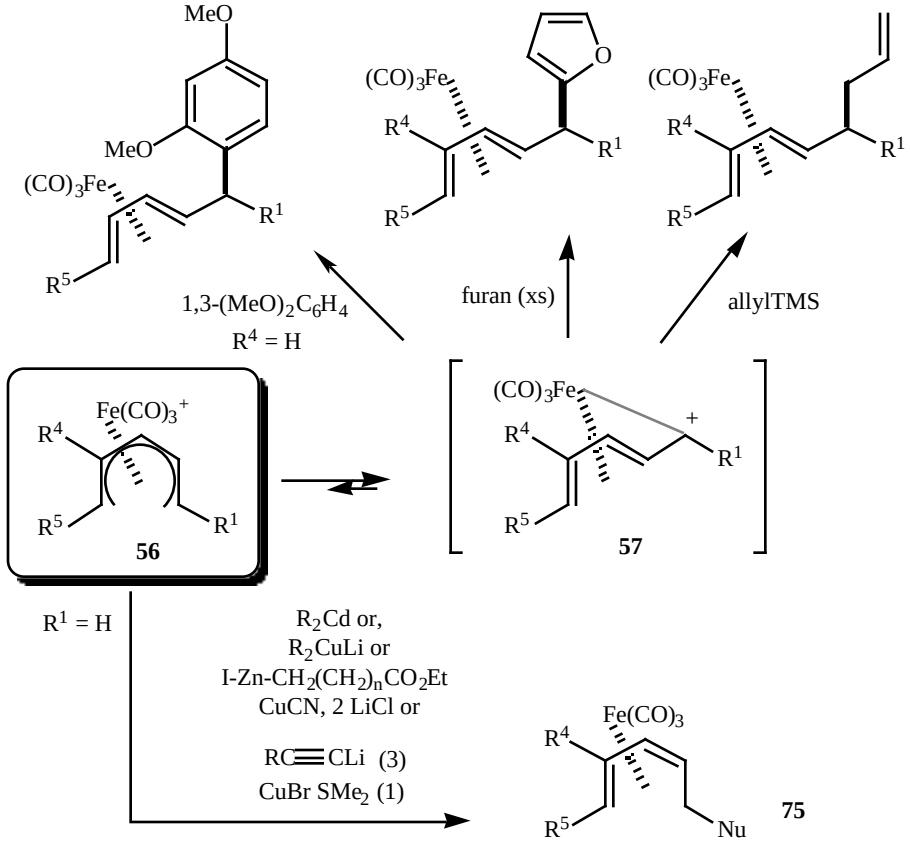


Scheme 15.

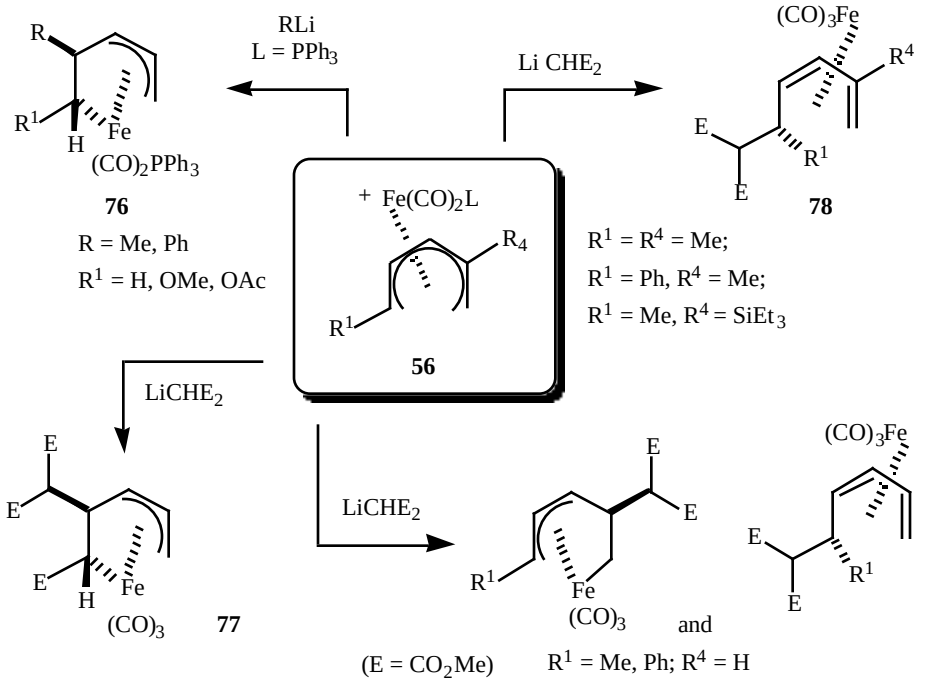


cations **56** with gives *E,E*-diene complexes (Scheme 16). These products presumably arise via attack on the less stable, but more reactive, transoid pentadienyl form of the cations. In contrast, the reaction of simple organocadmium reagents [82], organocuprates [27, 68a,b, 83] or functionalized organozinc 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 lithiums with (pentadienyl)$Fe(CO)_2PPh_3^+$ cations gives pentenediyl complexes **76** via nucleophilic attack at C2 (Scheme 17) [84]. Similarly, the reaction of stabilized carbon nucleophiles such dimethylmalonate anions with (1-methoxycarbonyl-pentadienyl)$Fe(CO)_3^+$ 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 $Fe(CO)_3$ 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 C4 has a pronounced directing



Scheme 16.



Scheme 17.

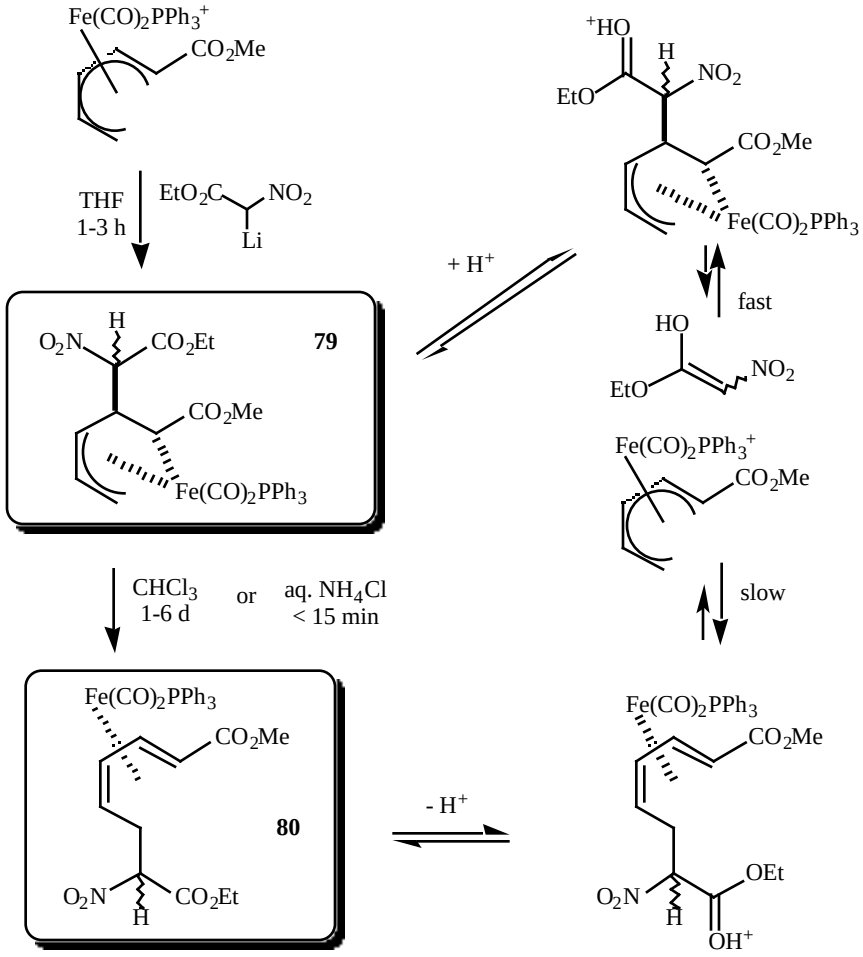
effect for malonate attack at C1. Regioselectivity of nucleophilic attack on $Fe(CO)_2PPh_3$ complexed pentadienyl cations is generally improved over that of the corresponding $Fe(CO)_3$ complexed cations due to the increased stability/decreased reactivity of the $Fe(CO)_2PPh_3$ cations [85, 86].

Recent evidence suggests that nucleophilic attack at the internal dienyl carbon is the result of kinetic control. Thus, reaction of (1-methoxycarbonylpentadienyl)$Fe(CO)_2PPh_3^+$ with the anion of ethyl nitroacetate, followed by *aqueous* workup, gave the (pentenediyl)-$Fe(CO)_2PPh_3$ 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_6D_6 solution. In addition, treatment of an ethyl acetate solution of **79** with saturated aqueous NH_4Cl 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 substitutent 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, (pentenediyl)-$Fe(CO)_3$ 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

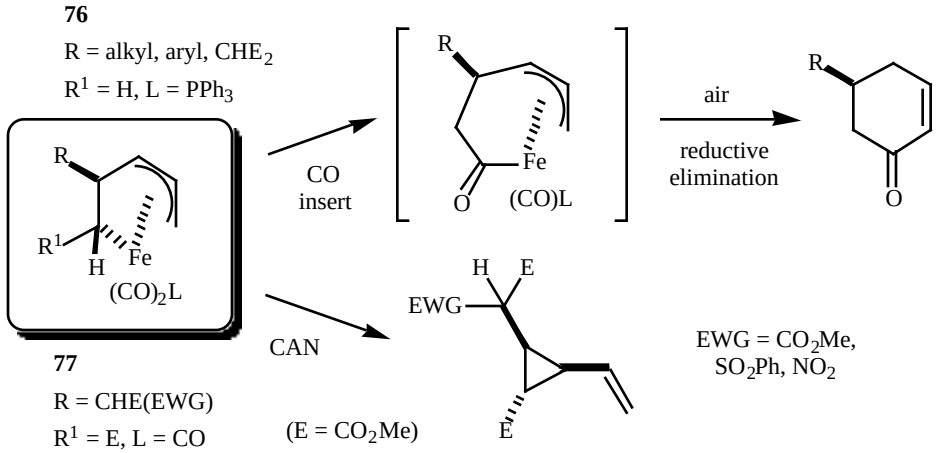
Lillya and coworkers demonstrated that solvolysis of ψ-*exo* dienyl dinitrobenzoates **81** (acetone/H_2O) occurs ca. 10-60 times faster than for the free ligand while the corresponding ψ-*endo* dienyl dinitrobenzoates **82** undergo solvolysis slower than the free ligands [88]. The solvolyses occur 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



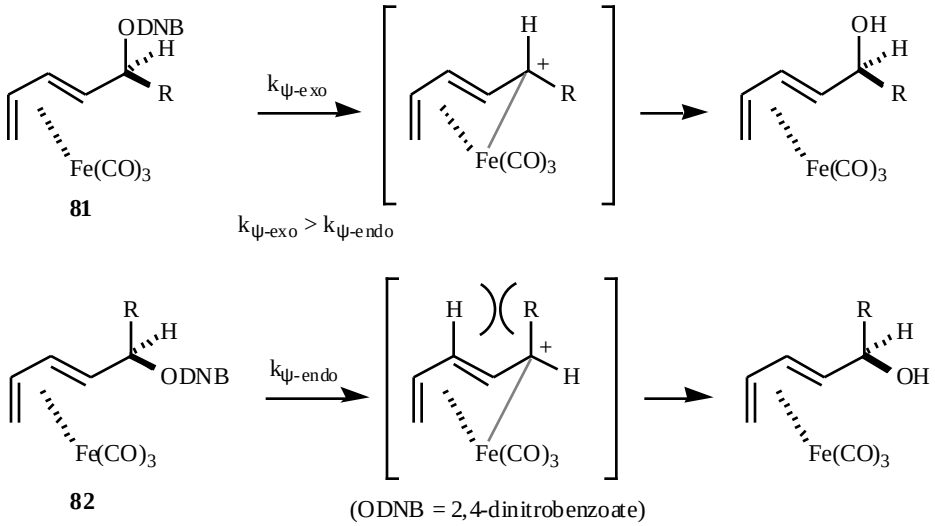
Scheme 18.

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 nucleophilies [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



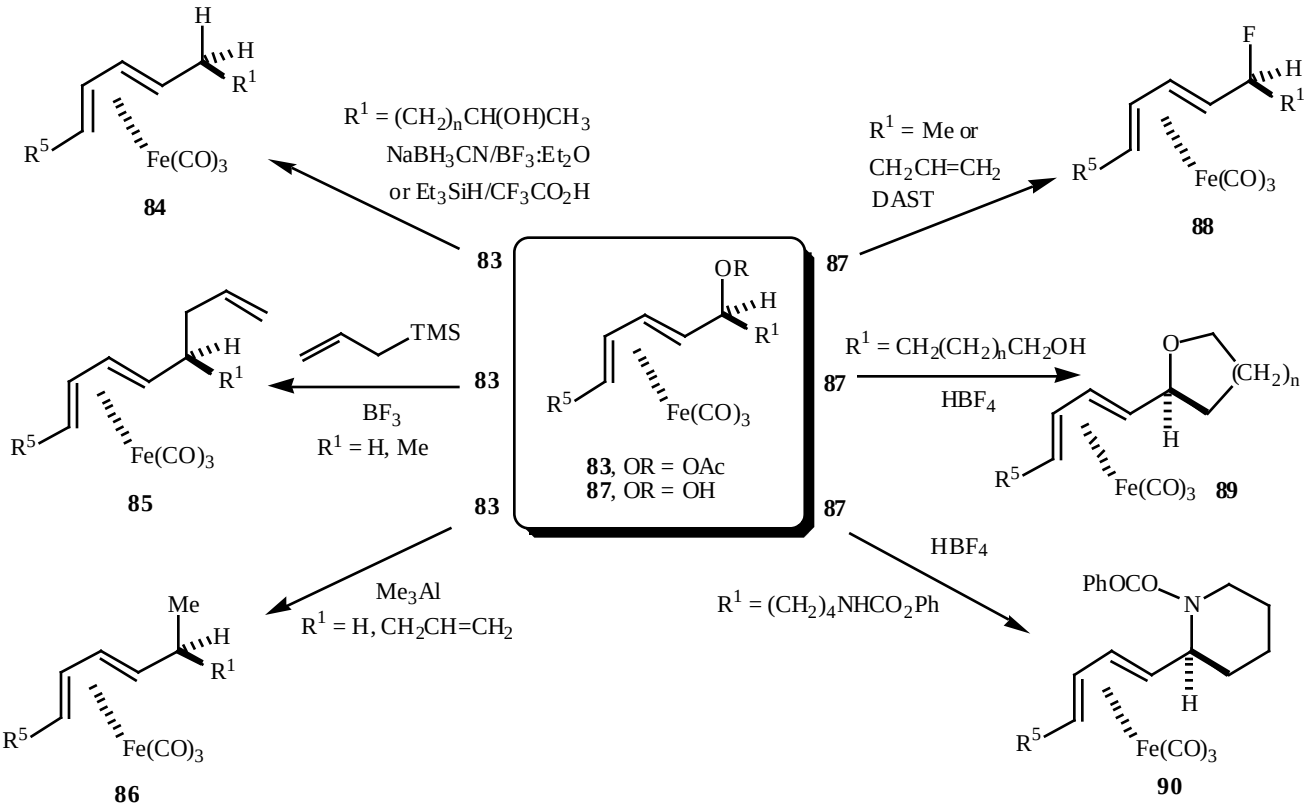
Scheme 19.



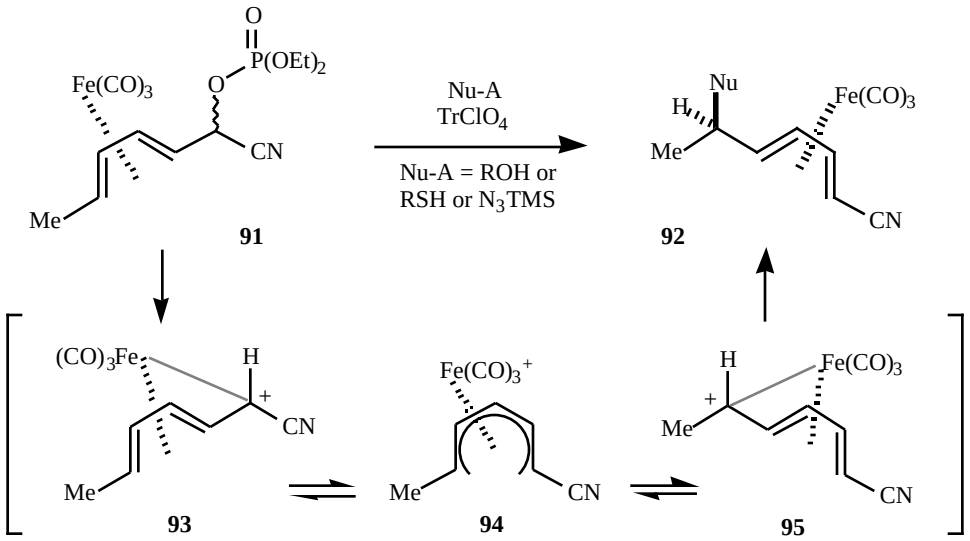
Scheme 20.

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 goup should



Scheme 21.



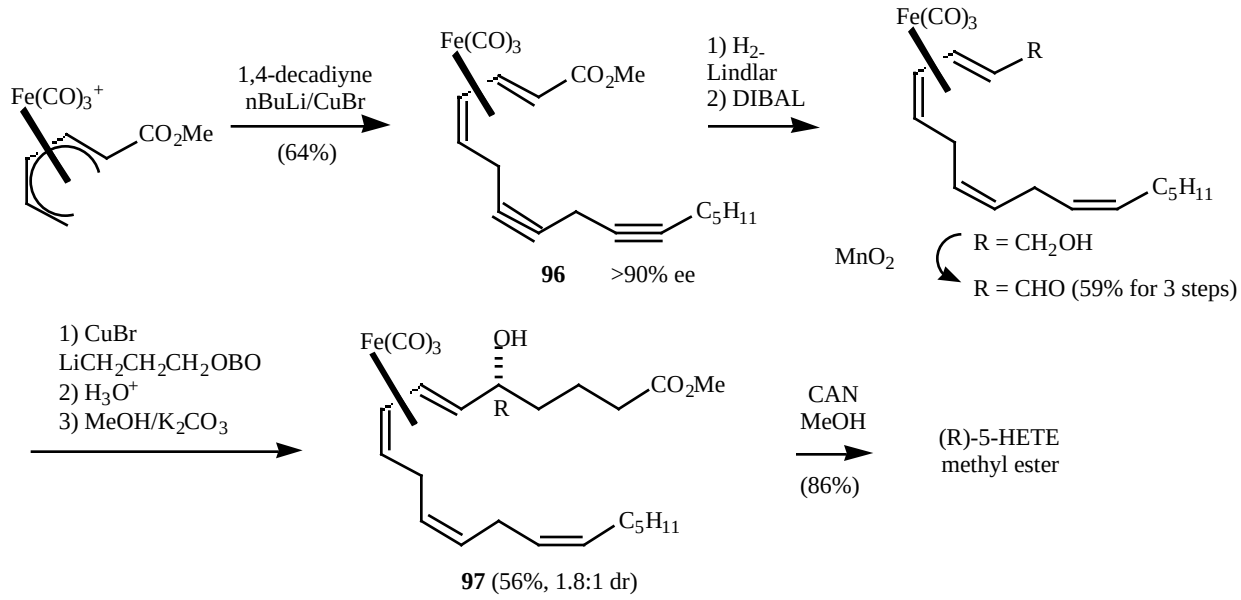
Scheme 22.

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.

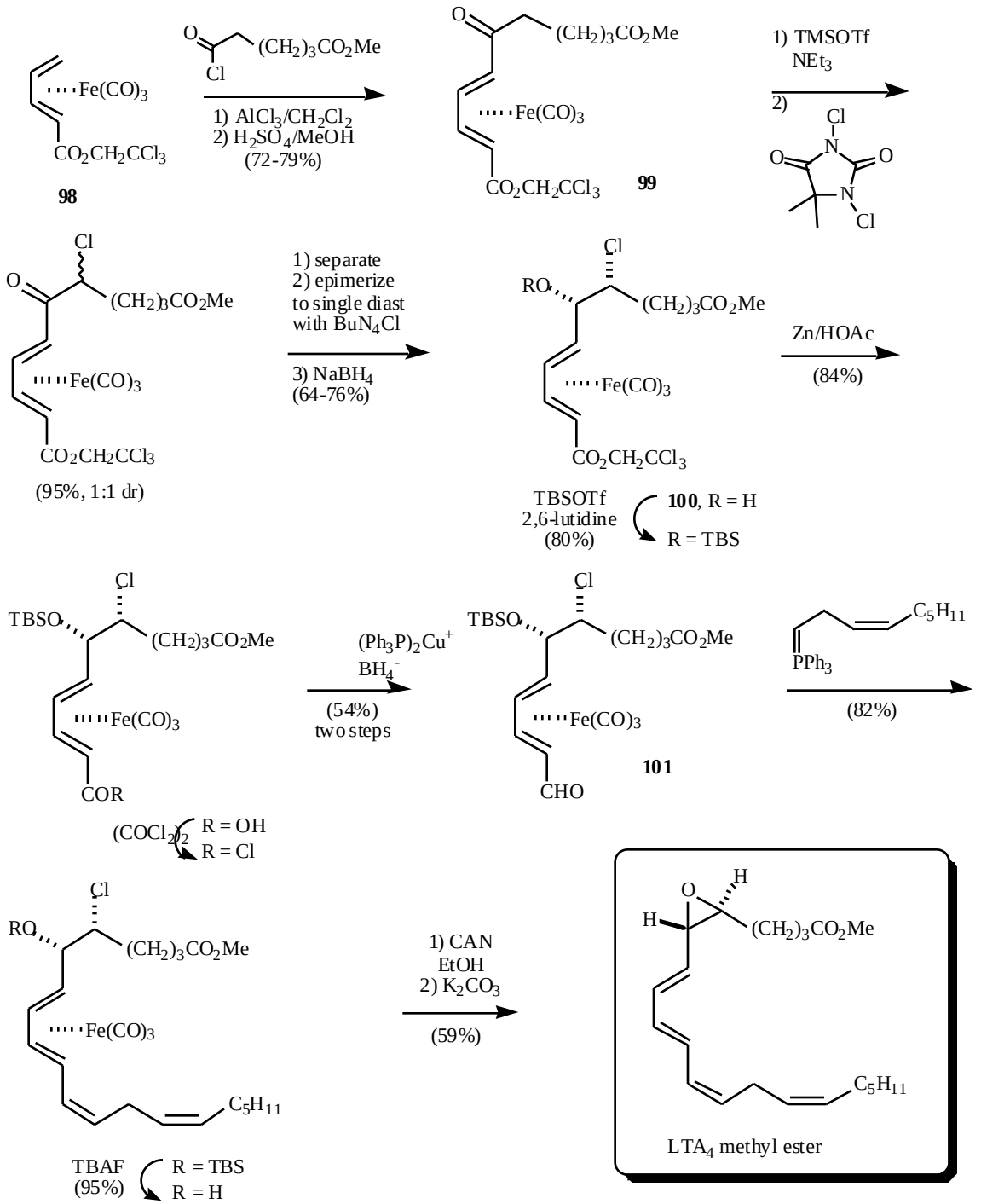
5-Hydroxyeicosatetraenoic acid (5-HETE) is an oxygenated metabolite of arachadonic acid. It has been proposed that 5-HETE may have the ability to regulate renal function and that it may play a role in B cell activation [94]. Tao and Donaldson have reported a synthesis of (R)-5-HETE methyl ester which utilizes organoiron methodology (Scheme 23) [27]. Addition of the cuprate derived from 1,4-decadiyne to optically active (1-methoxycarbonylpentdienyl) $Fe(CO)_3^+$ 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



Scheme 23. The Tao and Donaldson synthesis of 5-HETE methyl ester (OBO = oxabicyclo[2.2.2]octane).

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 6*E*,8*Z*-diene segment and for introduction of the C5 stereocenter 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

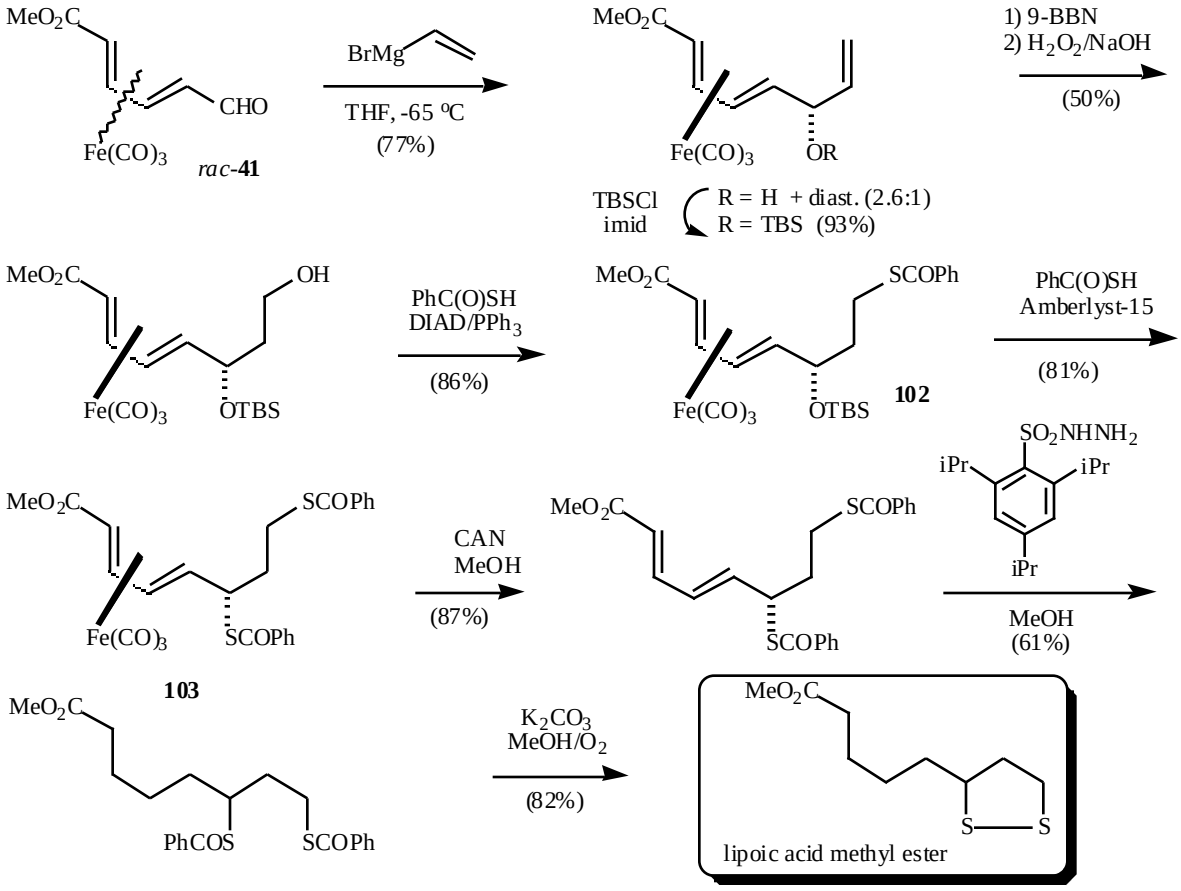


Scheme 24. The Franck-Neumann and Colson synthesis of (-)-LTA_4 methyl ester.

the acid chloride of adipic methyl hemiester, followed by isomerization gave the 6-oxo-2*E*,4*E*-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 tetraene chlorohydrin which upon treatment with potassium carbonate gave LTB_4. 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 *diastereospecific* fashion.

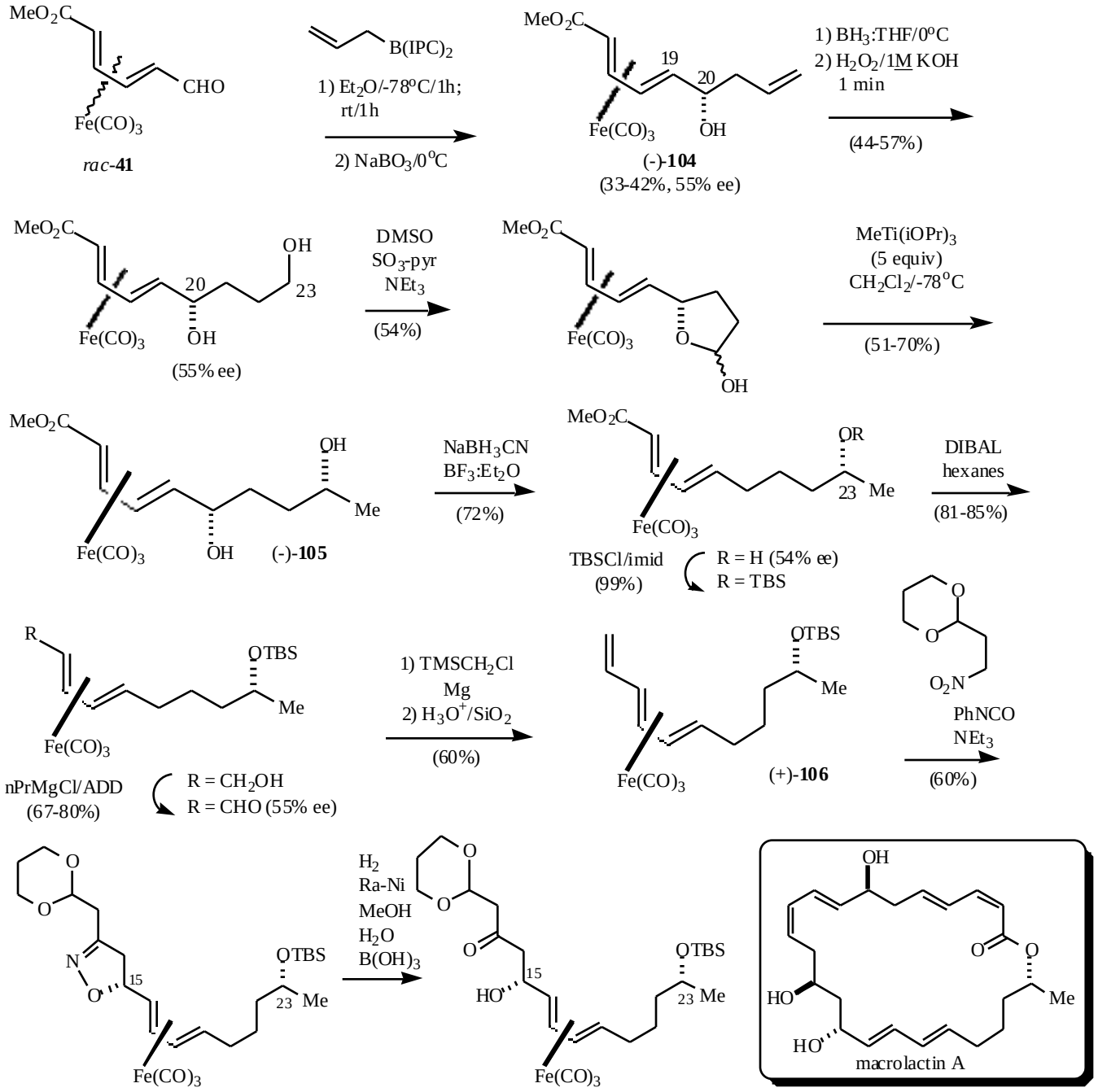
The biologically widespread antioxidant lipoic acid has demonstrated theraputic activity in diabetes as well as other diseases and medical conditions [96]. Grée, *et al.*, have reported a synthesis of racemic lipoic methyl ester which utilizes organoiron methodology (Scheme 25) [44]. Diastereoselective addition of vinyl mag-nesium bromide to *rac*-**41** gave a mixture of separable allylic alcohols (2.6:1 dr). Hydroxyl group protection, followed by hydroboration-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. Decomplexation 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 hydroboration-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

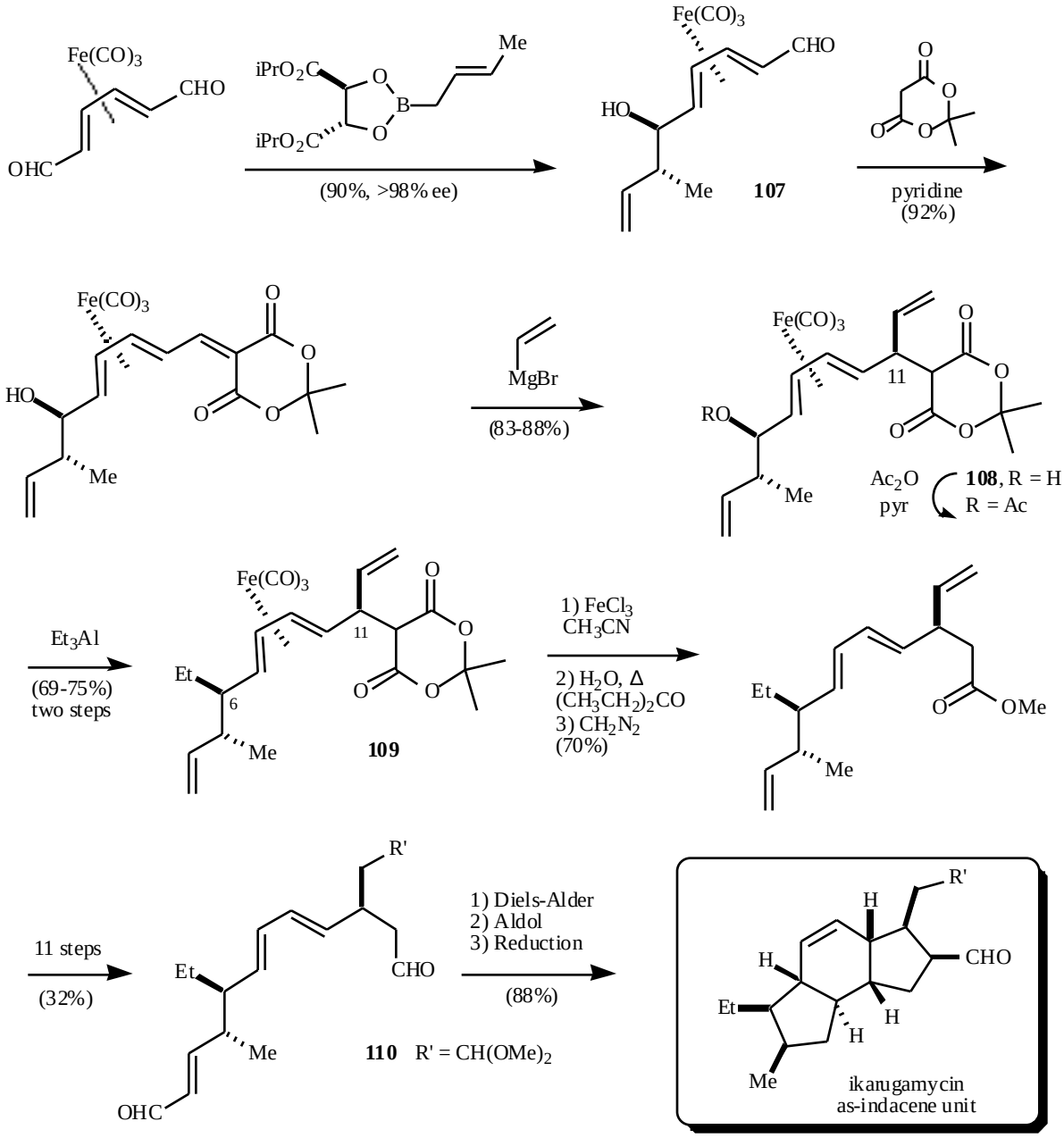


Scheme 25. The Gree, et al., synthesis of lipoic acid methyl ester.

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.



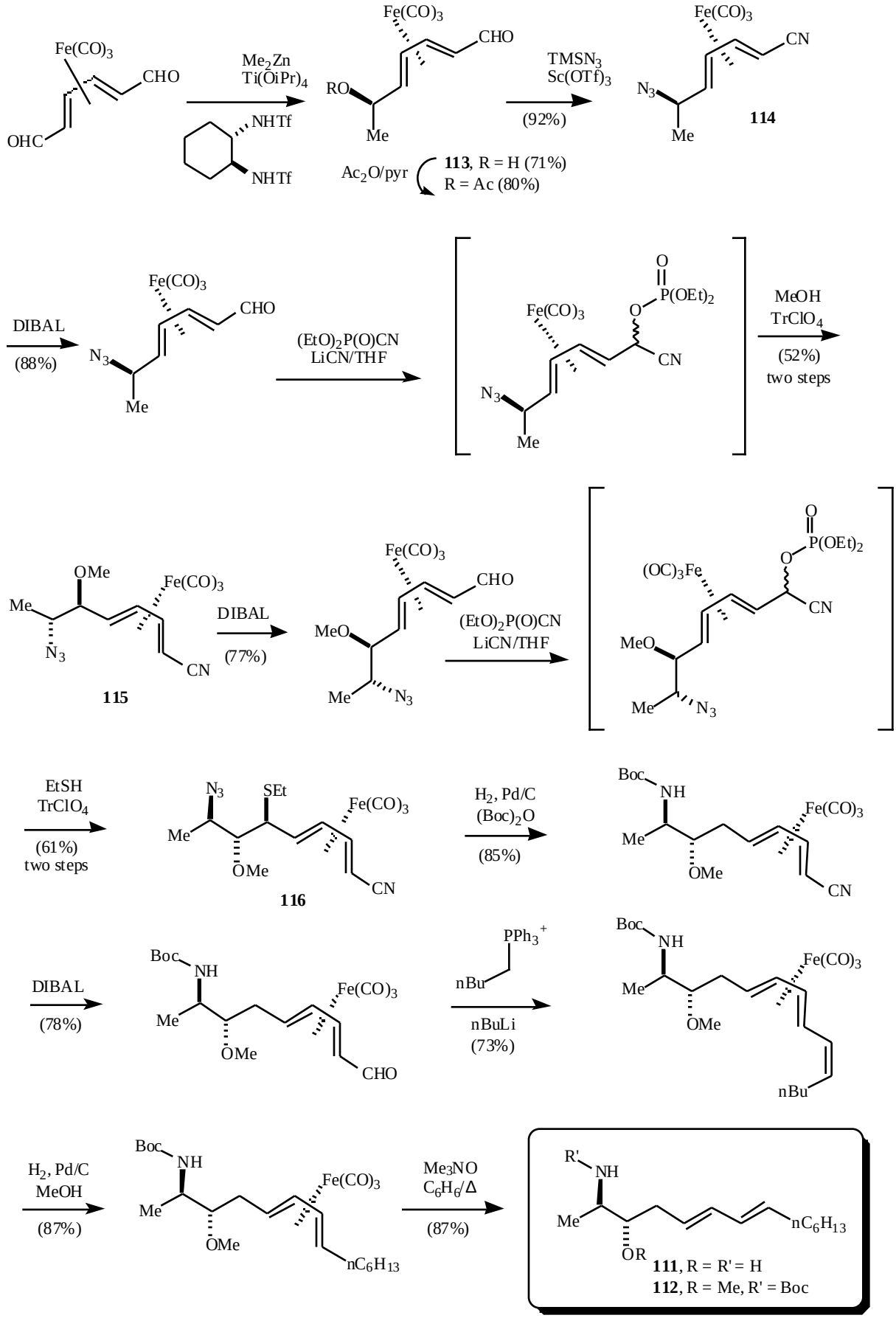
Scheme 26. The Prahlad and Donaldson synthesis of the C11-C24 segment of macrolactin A.



Scheme 27. The Roush and Wada synthesis of the as-indacene segment of ikarugamycin.

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]. De-symmetrization of meso (2,4-hexadiedial)$Fe(CO)_3$ 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



Scheme 28. The Takemoto, et al., synthesis of an amino alcohol polyene natural product.

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)$Fe(CO)_3$. 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 dienyl 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 thioethyl substitutent and transformation of the azide 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 decomp-lexation gave **112**.

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 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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