

Review

Ferrocenyl Migrations and Molecular Rearrangements: The Significance of Electronic Charge Delocalization

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Abstract: The enhanced stabilization of a carbocationic site adjacent to a ferrocenyl moiety was recognized within a few years of the discovery of sandwich compounds. While a detailed understanding of the phenomenon was the subject of some early debate, researchers soon took advantage of it to control the ease and direction of a wide range of molecular rearrangements. We, here, discuss the progress in this area from the pioneering studies of the 1960s, to more recent applications in chromatography and analytical detection techniques, and currently in the realm of bioactive organometallic complexes. Several classic reactions involving ferrocenyl migrations, such as the pinacol, Wolff, Beckmann, and Curtius, are discussed, as well as the influence of the ferrocenyl substituent on the mechanisms of the Nazarov, Meyer-Schuster, benzoin, and Stevens rearrangements. The preparation and isomerizations of ferrocenyl-stabilized vinyl cations and vinylcyclopropenes, together with the specific cyclization of acetylcyclopentadienyl-metal derivatives to form 1,3,5-substituted benzenes, demonstrate the versatility and generality of this approach.

Keywords: metal-stabilized carbocations; reaction mechanisms; NMR; bioorganometallics

1. Introduction

The ability of the ferrocenyl moiety to stabilize an adjacent carbocationic center has long been attributed to delocalization of the electron deficiency onto the iron atom [1]. The X-ray crystallographically established [2,3] tendency of the cationic α -carbon atom to lean towards the metal as in **1**, was originally interpreted in terms of an overlap of the vacant $2p$ orbital on carbon with a filled $3d$ orbital of suitable symmetry on iron [4]. Taking a more extreme view, one could regard the system as a neutral fulvene ligand coordinated to a $[(C_5H_5)Fe]^+$ unit, as depicted in **2** (Figure 1), but this has been criticized based on the low barrier to rotation about the exocyclic bond in some cases [5,6].

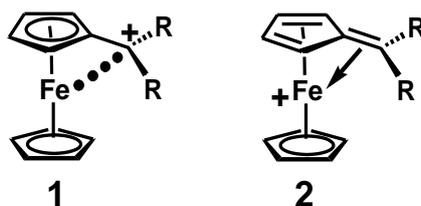


Figure 1. Delocalization of charge from the cationic α carbon onto the iron atom.

Fortunately, a comprehensive overview of this, sometimes controversial, phenomenon has been presented by Gleiter, Bleiholder, and Rominger [7]. Nevertheless, it is this character of charge

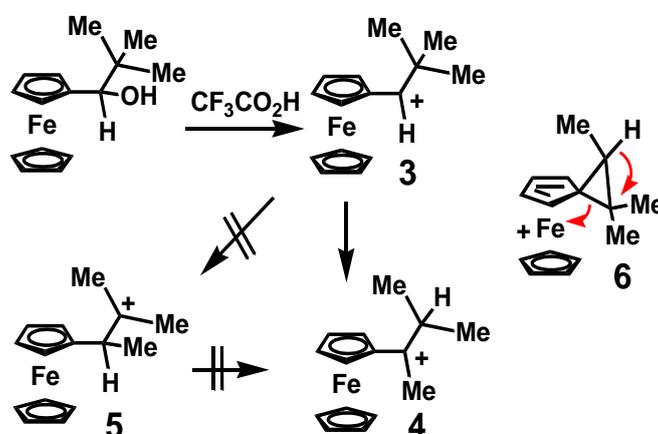
delocalization that facilitates a number of molecular rearrangements or ferrocenyl migrations, as we shall attempt to demonstrate.

2. Ferrocenyl-Mediated Carbocationic Rearrangements

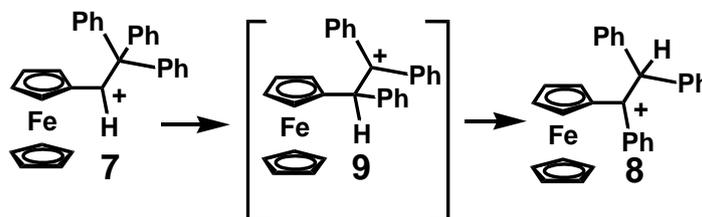
2.1. Isomerizations of Secondary to Tertiary Carbocations

Following pioneering studies by Cais [8], dissolution of ferrocenyl-substituted alcohols in trifluoroacetic acid allowed the acquisition of well-resolved ^1H NMR spectra by several other groups [9–11], and revealed the unusual stability of the carbocations so generated. Subsequently, in a series of ground-breaking papers, Watts and his group reported the rearrangement behavior of a number of alkylferrocenyl carbocations upon protonation of their precursor alcohols [12].

Typically, the quantitative conversion of the ferrocenyl-stabilized secondary carbocation **3** into its tertiary isomer **4**, is in accord with the accepted hierarchy of stable carbocations. At first sight, this appears to be a double shift rearrangement whereby an alkyl migration to form the β -ferrocenyl cation **5** is followed by a [1,2]-hydrogen shift to yield the observed product. However, the authors did not prefer this mechanism since the intermediate rearrangement product, **5**, would undoubtedly be thermodynamically disfavored relative to the ferrocenyl-stabilized starting cation **3**. Instead, they proposed that the initial methyl migration might proceed synchronously with the formation of a short-lived *spiro*-diene species **6** (depicted in Scheme 1) which could reopen with concomitant hydrogen migration, thus generating the observed final product [13]. In such a scenario, the cationic charge would be delocalized onto the metal in the transition state. The analogous rearrangement of $[\text{Fc}-\text{CH}-\text{CPh}_3]^+$, **7**, into $[\text{Fc}-\text{CPh}-\text{CHPh}_2]^+$, **8**, was also observed (Scheme 2), but in this case the doubly-benzylic cation $[\text{Fc}-\text{CHPh}-\text{CPh}_2]^+$, **9**, might be a viable intermediate [14].



Scheme 1. Rearrangement of 2° to 3° ferrocenyl trimethyl-carbocations.

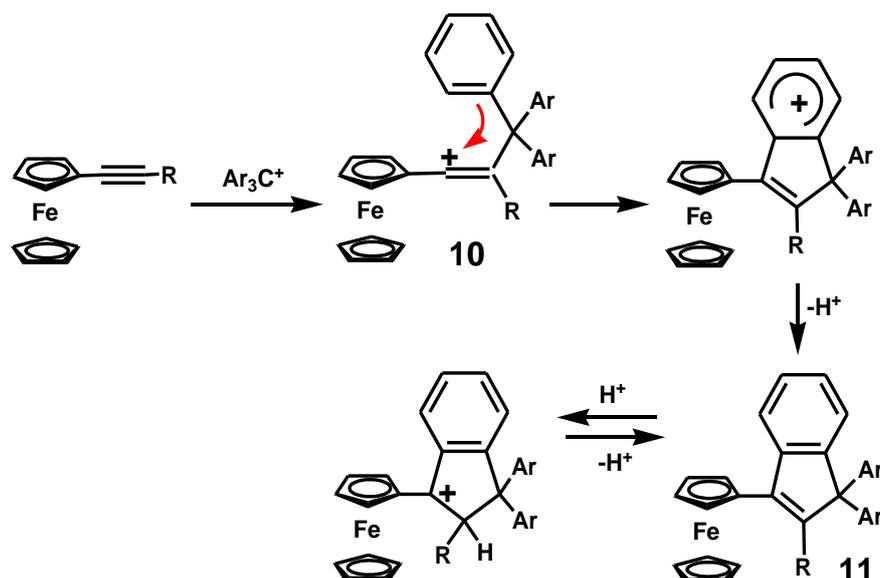


Scheme 2. Rearrangement of 2° to 3° ferrocenyl triphenyl-carbocations.

2.2. Rearrangements of Vinyl and Allyl Cations

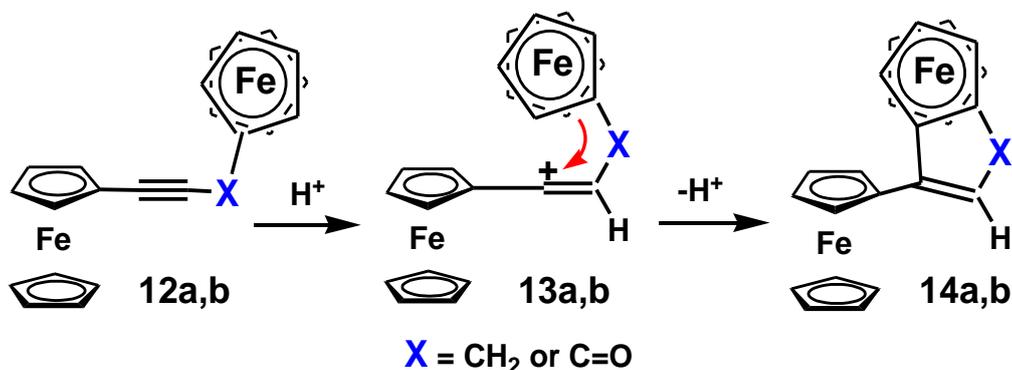
This work was elegantly extended to include the addition reactions of trityl cations to alkynylferrocenes to generate ferrocenyl-stabilized vinyl carbocations, **10**, that underwent cyclization

to form indenenes, **11** [15]. The thermodynamic driving force in each case is the positioning of a carbocationic site adjacent to the ferrocenyl moiety, as shown in Scheme 3.



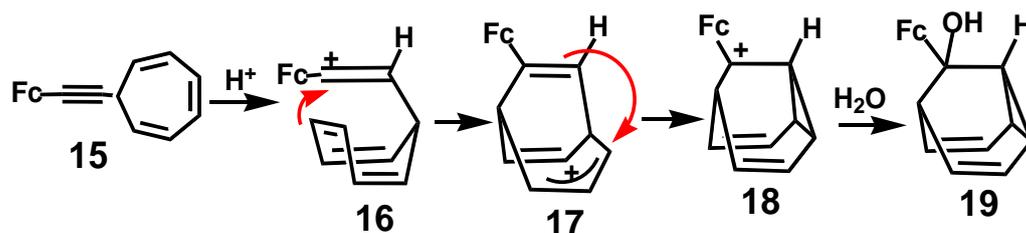
Scheme 3. Indene formation by cyclization of a ferrocenyl-vinyl carbocation.

In a variant of this concept, the diferrocenyl-alkynes $\text{Fc}-\text{C}\equiv\text{C}-\text{CH}_2-\text{Fc}$, **12a**, and $\text{Fc}-\text{C}\equiv\text{C}-\text{C}(=\text{O})-\text{Fc}$, **12b**, were treated with trifluoroacetic acid to form the ferrocenyl-stabilized vinyl cations, **13a,b** [15]. In these systems, cyclization occurred by electrophilic attack on the alkyl- or acyl-linked ferrocenyl substituent to form $(\eta^5\text{-cyclopentadienyl})(3\text{-ferrocenylpentalenyl})\text{iron}$, **14a**, or $(\eta^5\text{-cyclopentadienyl})(3\text{-ferrocenyl-1-oxo-pentalenyl})\text{iron}$, **14b**, respectively, as depicted in Scheme 4.



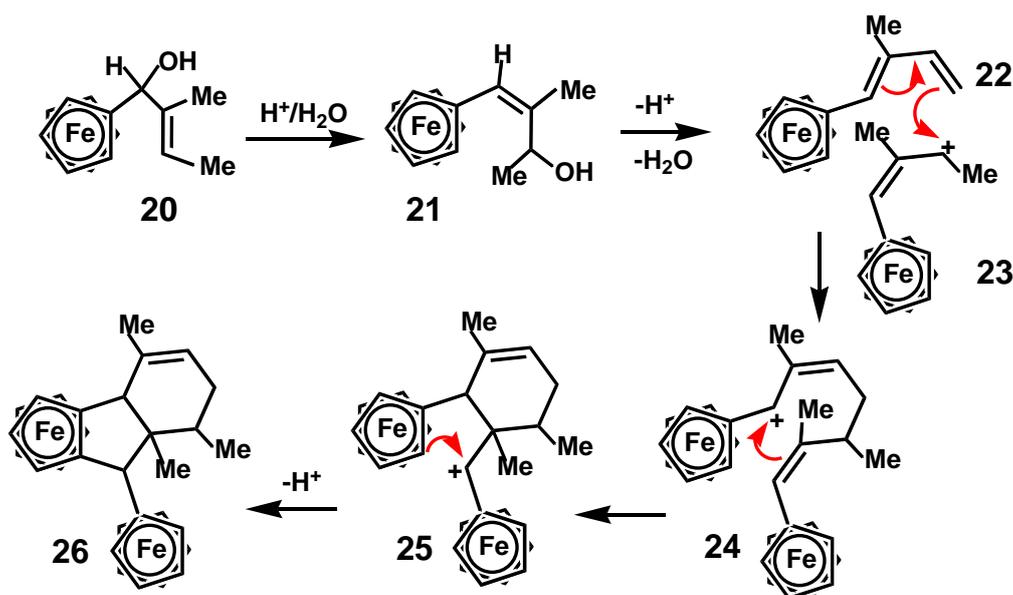
Scheme 4. Ferrocenopentalene formation by cyclization of a ferrocenyl-vinyl carbocation.

In another remarkable example, protonation of the alkynylcycloheptatriene derivative, **15**, yielded a ferrocenyl-stabilized vinyl cation, **16**, that eventually yielded a tricyclic alcohol. The proposed mechanism (Scheme 5) involves attack by a double bond of the trienyl unit at the vinylic cation to generate the 6-ferrocenylbicyclo [3.2.2]nona-3,6,8-trien-2-yl cation, **17**; subsequent cyclopropyl ring closure yields the ferrocenyl-stabilized cation **18**, and ultimately the alcohol **19** [15].



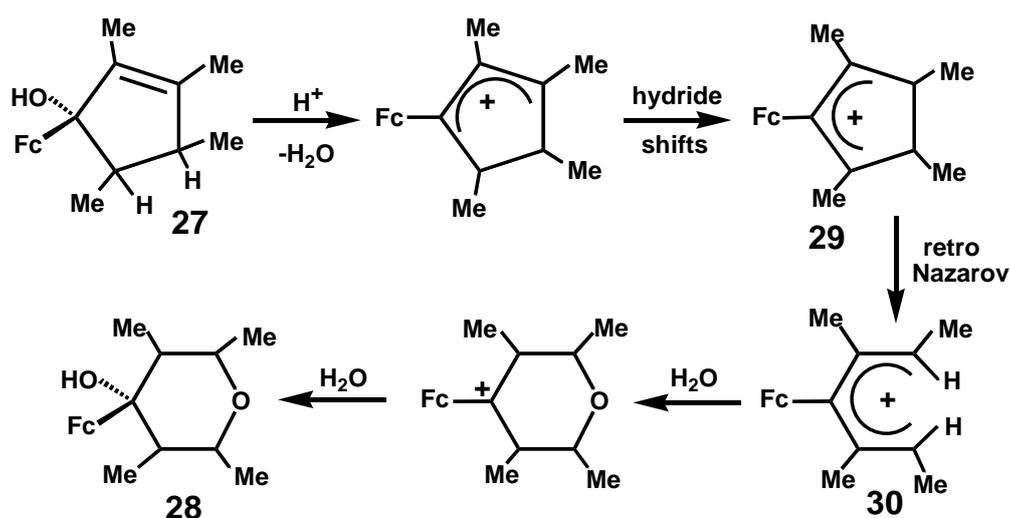
Scheme 5. Cyclization of a cycloheptatrienyl unit onto a ferrocenyl-vinyl carbocation.

Another unexpected cyclization leading to formation of a polycyclic system was reported by the Schottenberger group who prepared the ferrocenyl allyl alcohol **20** that underwent an allyl rearrangement thus forming a vinylferrocene, **21**, thereby positioning the hydroxy substituent near the chain terminus. Treatment with concentrated sulfuric acid yielded as one of the products a dimer whose structure, shown in Scheme 6, was established by X-ray crystallography [16]. The authors advanced a mechanism whereby elimination of water formed the diene **22**, which then participated in a [4 + 2] Diels-Alder cycloaddition with the ferrocenyl allyl cation **23** prior to eventual indene formation. One might perhaps more realistically envisage a stepwise process involving electrophilic attack by the allyl cation on the diene to form the ferrocenyl-stabilized intermediate **24**, closure of the six-membered ring to generate a different cationic site adjacent to the other ferrocenyl moiety, as in **25**, and finally ring closure onto ferrocene, thus yielding the observed final product **26**.



Scheme 6. Dimerization of a ferrocenyl-allyl cation.

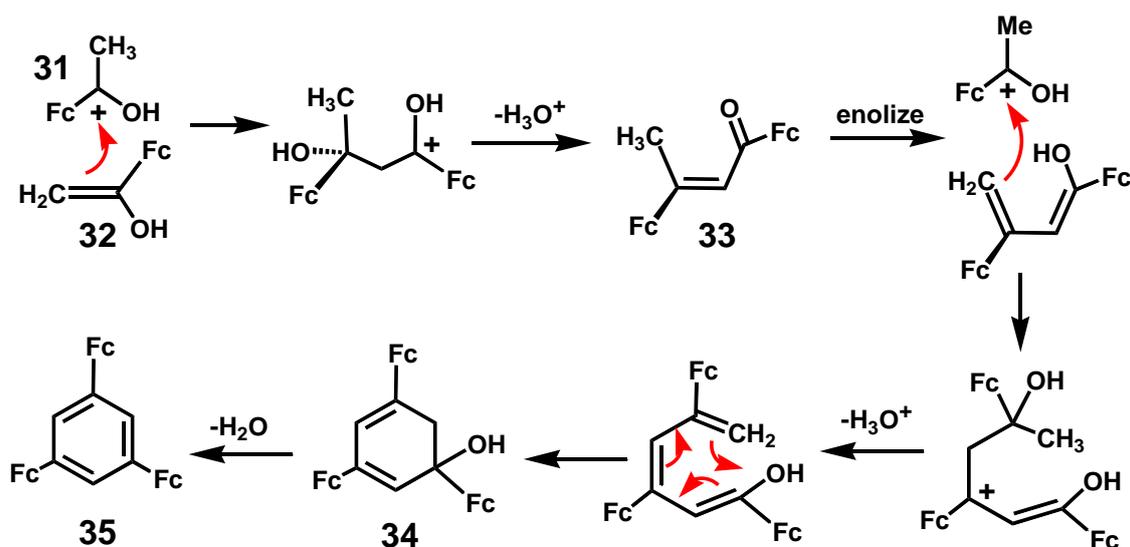
A second fascinating observation from the same laboratory resulted from the protonation of 1-ferrocenyl-2,3,4,5-tetramethylcyclopent-2-en-1-ol, **27**, to form 4-ferrocenyl-4-hydroxy-2,3,5,6-tetramethyltetrahydropyran, **28** [16]. The proposed mechanism involves initial elimination of water together with a series of hydride shifts to form the ferrocenyl-allyl cation **29** that can ring-open, in a reversal of the normal Nazarov cyclization, to generate the divinylferrocenyl cation **30**. Now, aqueous hydrolysis to form the tetrahydropyran framework is followed by addition of a second molecule of water to furnish the final product, **28**, as illustrated in Scheme 7.



Scheme 7. Ferrocenyl-mediated retro-Nazarov ring-opening to form a hydroxytetramethyl-tetrahydropyran.

2.3. Ferrocene-Mediated Cyclization to form Trisubstituted Aromatics, 1,3,5- $C_6H_3(ML_n)_3$

Treatment of acetylferrocene with $SiCl_4$ /ethanol provides a convenient route to the specific formation of 1,3,5-triferrocenylbenzene [17]. This contrasts with the transition metal-catalyzed trimerizations of ethynylferrocene which yield a mixture of 1,2,4 and 1,3,5 isomers [18,19]. The proposed mechanism shown in Scheme 8 involves initial reaction of the cation $[FcC(OH)CH_3]^+$, **31**, with the enol form of the ketone, **32**; this process continues in a stepwise manner as the chain gradually grows, via intermediates **33** and **34**, prior to the final dehydration leading to **35**. This is a general reaction and has also been exploited in the case of (acetylcyclopentadienyl)-manganesetricarbonyl which, likewise, yields the 1,3,5-trisubstituted aromatic [17]. Moreover, mixed species are also accessible, as typified by the Fe_2Mn example, **36**, shown in Figure 2; indeed, the bimetallic Fe–Mn precursor, **37**, corresponding to **33** in Scheme 7 has also been characterized by X-ray crystallography [20]. This approach has also been used to prepare C_{3h} -symmetric polycyclic systems [17].



Scheme 8. Proposed mechanism for the cyclization of $(CH_3C(=O)C_5H_4)ML_n$ precursors, where $ML_n = Fe(C_5H_5)$ or $Mn(CO)_3$, to form 1,3,5-trisubstituted benzenes.

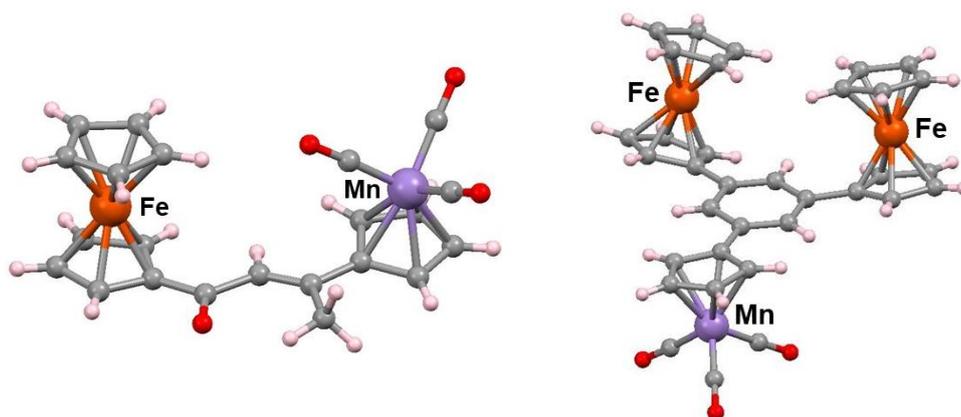
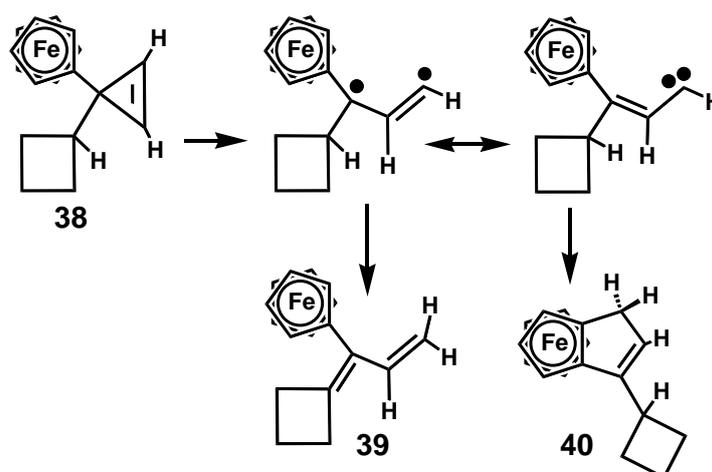


Figure 2. Molecular structures of the mixed iron-manganese complexes **36** and **37**.

In some ways, the ferrocenyl group behavior may be compared to that of apparently related molecular fragments, such as $(\eta^5\text{-C}_5\text{H}_4)\text{Mn}(\text{CO})_3$ or $(\eta^6\text{-C}_6\text{H}_5)\text{Cr}(\text{CO})_3$, which can also accommodate the build-up of positive charge on an adjacent atom [21] as, for example, in the above-mentioned preparation of $1,3,5\text{-C}_6\text{H}_3[(\text{C}_5\text{H}_4)\text{Mn}(\text{CO})_3]_3$ analogous to 1,3,5-triferrocenylbenzene [17]. However, this is not necessarily a true comparison since the metal tricarbonyl complexes can also stabilize an α -carbanion through delocalization of the negative charge onto the carbonyl ligands by enhanced back-donation of electron density into the π^* manifold [22]. This is most evident in metal carbonyl infrared stretching frequencies, ν_{CO} , that decrease dramatically in the anions relative to their values in the corresponding cations.

3. Rearrangements of Vinylcyclopropenes

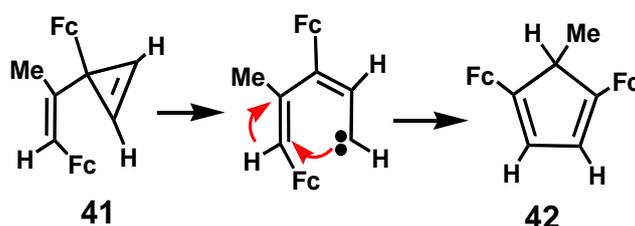
The thermal instability of vinylcyclopropenes is markedly enhanced when they also bear ferrocenyl substituents. Thus, decomposition of 3-cyclobutyl-3-ferrocenylcyclopropene, **38**, brought about rearrangement even at 0 °C to give 3-cyclobutyliden-3-ferrocenylpropene, **39**, and 3-cyclobutyl-1H-cyclopentaferrocene, **40** [23]. Mechanistically, one can invoke a ferrocenyl-stabilized diradical species or a vinyl carbene, as in Scheme 9. The products can therefore arise either by hydrogen migration, or by attack on the ferrocenyl unit to form **39** or **40**, respectively.



Scheme 9. Thermal rearrangement of 3-cyclobutyl-3-ferrocenylcyclopropene.

In the closely related system, 3-ferrocenyl-3-(2-ferrocenyl-1-methylvinyl)cyclopropene, **41**, which bears two ferrocenyl substituents, rearrangement occurs at 20 °C in benzene solution to yield 1,4-diferrocenyl-5-

methylcyclopentadiene, **42** (Scheme 10). Once again, the intermediacy of a vinyl carbene or a diradical species has been suggested [24].

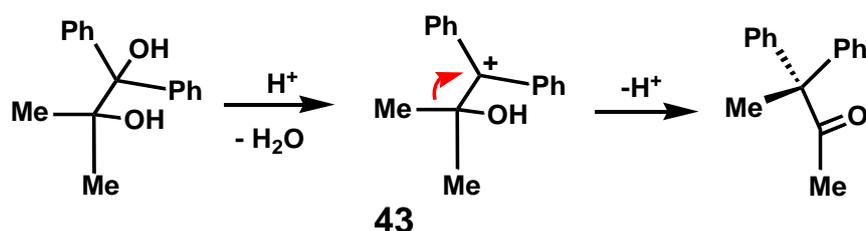


Scheme 10. Thermal rearrangement of 3-ferrocenyl-3-(2-ferrocenyl-1-methylvinyl)cyclopropene.

4. Ferrocenyl Migration onto an Electron-Deficient Carbon Center

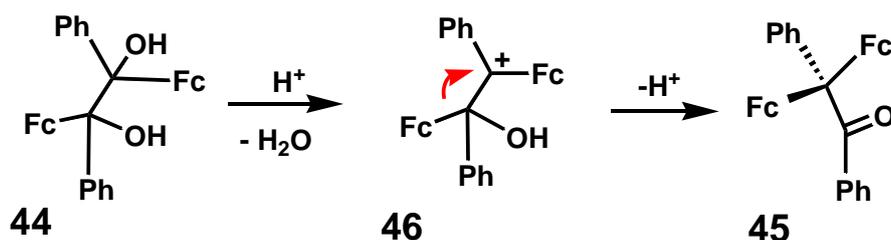
4.1. Pinacol Rearrangements

Migratory aptitude is a widely invoked parameter to account for the selectivity and ease of molecular rearrangements [25]. Typically, in cationic species, it is commonly assumed that a phenyl migration is favored over that of its methyl counterpart because of charge delocalization in the phenonium ion transition state. However, such generalizations must be treated with caution. For example, upon protonation of the pinacol $\text{Ph}_2\text{C}(\text{OH})\text{-CMe}_2\text{OH}$, it is a methyl that preferentially migrates (Scheme 11), not because the alkyl group has a better migratory aptitude than the aryl substituent, but rather that the more favored carbocation, **43**, is doubly benzylic [26].



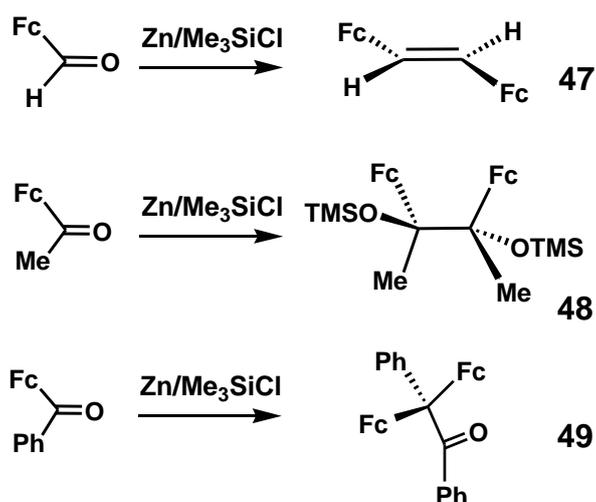
Scheme 11. Pinacol rearrangement showing methyl rather than phenyl migration.

To make a fair comparison, for example between phenyl and ferrocenyl, one must eliminate such extraneous factors. This was first discussed by Weliky and Gould [27] in 1956 who prepared 1,2-diferrocenyl-1,2-diphenyl-ethanediol, **44**, by treatment of benzoylferrocene with cobalt dichloride in the presence of a Grignard reagent. They noted that this pinacol “rearranged with remarkable ease (merely upon passing gaseous HCl over its solution in benzene) to the pinacolone **45**.” Clearly, ferrocenyl was favored over phenyl migration, as in Scheme 12. Later work by several groups [28–30] revealed, not surprisingly, that ferrocenyl migration was also favored over an alkyl shift ($\text{R} = \text{Me}, \text{Et}, \text{Pr}, \text{Bu}$). Subsequently, however, it was found that phenyl migration in cation **46** is indeed observable, but that the ferrocenyl shift was preferred by a factor of ~ 8 . Interestingly, it was noted that the rearrangement behavior of the *threo* and *erythro* isomers of **44** was identical [31].



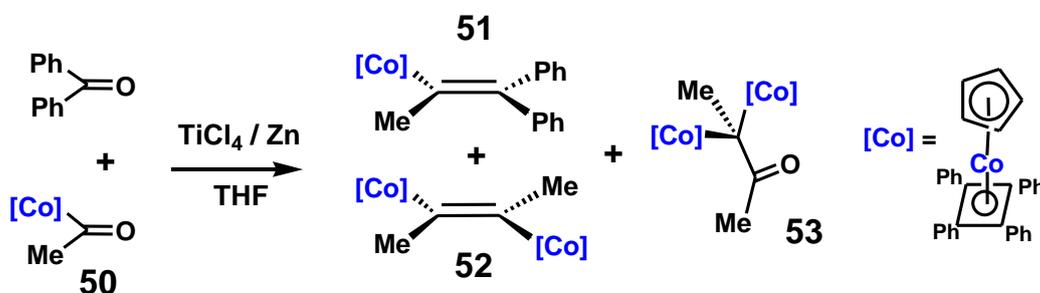
Scheme 12. Pinacol rearrangement showing favored migration of ferrocenyl over phenyl.

Much more recently, a comprehensive study of the modified Clemmensen reduction of formylferrocene, acetylferrocene, and benzoylferrocene was reported by Bildstein [32]. In this case, the normal reagents, Zn/HCl, were replaced by Zn/Me₃SiCl in the expectation that deoxygenation to obtain the corresponding alkenes, R(Fc)C=C(Fc)R, would be enhanced by formation of Me₃Si–O–SiMe₃ with its energetically favorable silicon-oxygen linkages. Experimentally, however, as shown in Scheme 13, the isolated products were *trans*-diferrocenylethene, **47**, 2,3-diferrocenyl-2,3-bis(trimethylsiloxy)butane, **48**, and 2,2-diferrocenyl-1,2-diphenyl-ethan-1-one, **49**, respectively. These three products were each unambiguously characterized by X-ray crystallography. It is reasonable to assume that the pinacolone, **49**, must have been derived from the diphenyl analogue of the disiloxy-pinacol **48**. Related work in this area, including synthetic routes to ferrocenyl cumulenes, has been fully reviewed elsewhere [33].



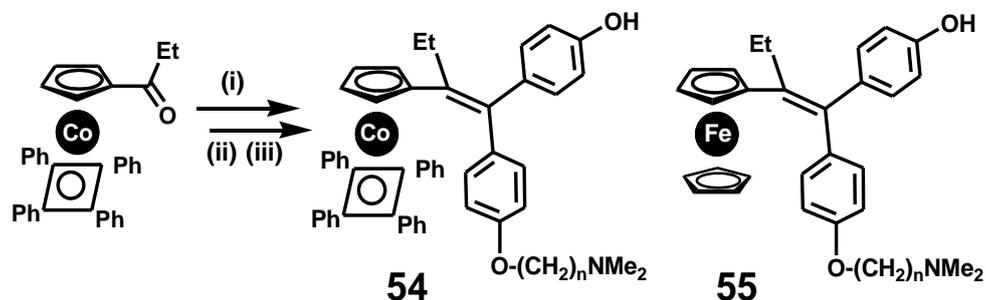
Scheme 13. Experimentally observed products derived from Clemmensen reduction of formylferrocene, acetylferrocene, and benzoylferrocene.

These results may be compared with those found in the course of the closely analogous McMurry reaction of (η^5 -acetylcyclopentadienyl)(η^4 -tetraphenylcyclobutadiene)cobalt, **50**, with benzophenone [34]. The products observed in addition to the desired hetero-coupled alkene, **51**, were *trans*-2,3-bis[(η^5 -cyclopentadienyl)(η^4 -tetraphenylcyclobutadiene)cobalt]-2-butene, **52**, and 3,3-bis-[(η^5 -cyclopentadienyl)(η^4 -tetraphenylcyclobutadiene)cobalt]butan-2-one, **53**, which parallel the structures of Bildstein's iron complexes, **47** and **49**. Once again, the homo-coupled alkene adopts the *trans* structure, and it is the cobalt sandwich moiety that has migrated to form the pinacolone, as shown in Scheme 14.



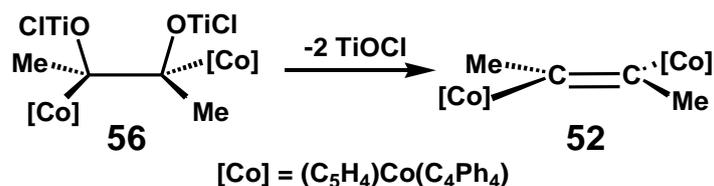
Scheme 14. Experimentally observed products derived from the McMurry reaction of [(η^5 -MeC(=O)C₅H₄)Co(η^4 -C₄Ph₄)] with benzophenone.

This reaction was important for the development of a synthetic route to cobaltifens, **54**, (Scheme 15) [35], the cobalt analogues of ferrocifens, **55**, that are now under intensive investigation for their activity against breast cancers and other related diseases [36] (see Section 7).

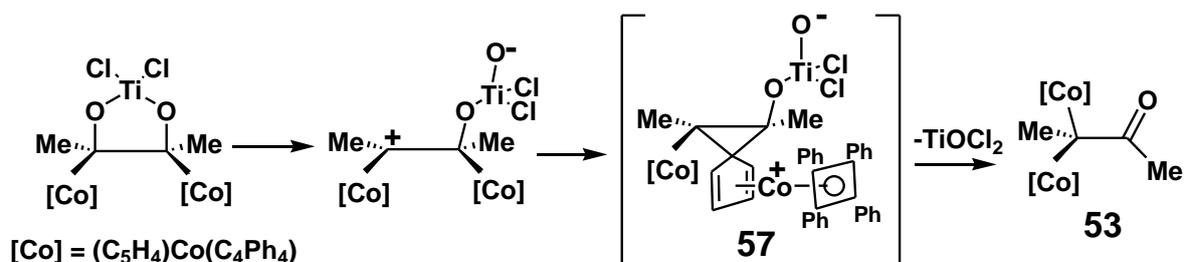


Scheme 15. Synthetic route to cobaltifens: reagents (i) (*p*-HOC₆H₄)₂C=O, Zn, TiCl₄, THF; (ii) NaH, DMF, (iii) Cl(CH₂)_{*n*}NMe₂, NEt₃, THF.

Following the mechanistic proposals of Bogdanović [37] and of Geise [38], it was suggested that one could visualize formation of the *trans*-alkene **52** from the C₂-symmetric intermediate **56** (Scheme 16). In contrast, when the bulky metallocenyl groups are positioned in a *cis* fashion, alkene formation may be sterically hindered and instead a pinacol-to-pinacolone rearrangement via a metal-stabilized cationic structure, **57**, is the preferred option (Scheme 17).



Scheme 16. McMurry coupling of (C₄Ph₄)Co[C₅H₄C(=O)Me] to form the *trans*-alkene, **52**.



Scheme 17. Pinacolone formation in a McMurry reaction of (C₄Ph₄)Co[C₅H₄C(=O)Me].

The corresponding bridging structure, **58**, that facilitates a ferrocenyl migration would serve the same purpose (but markedly more efficiently) as the phenonium ion, **59**, that allows delocalization of positive charge in the transition state for phenyl migrations (Figure 3).

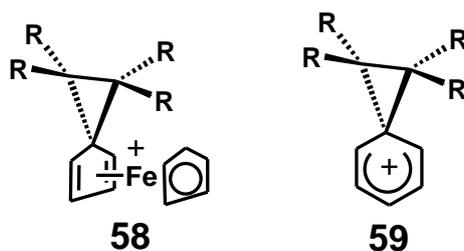
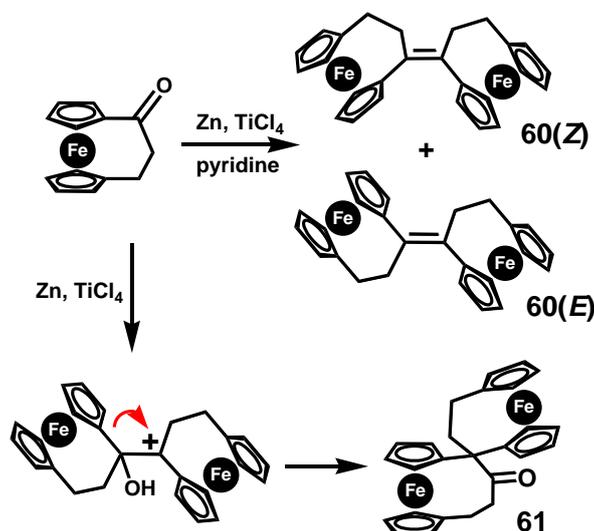


Figure 3. Transition states for ferrocenyl and phenyl rearrangements whereby positive charge is delocalized onto the migrating group.

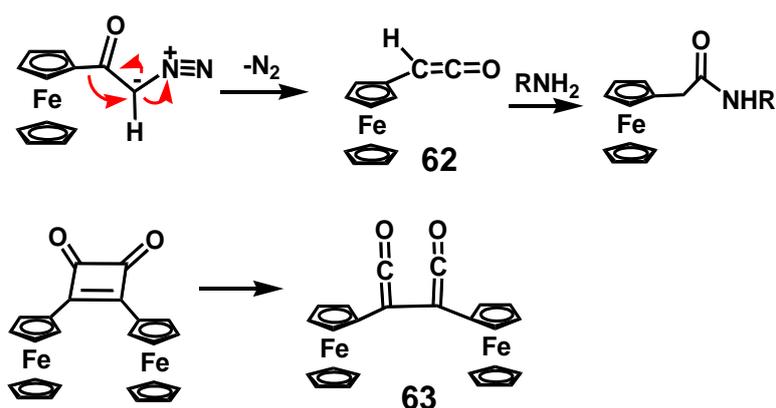
A particularly fascinating pinacol-to-pinacolone rearrangement was reported by Härter and colleagues who studied the McMurry reaction of [3]ferrocenophanone under different conditions [39]. When the standard reagent system (TiCl_4/Zn) was augmented with pyridine, the homo-coupled product bis-[3]ferrocenophane-1-ylidene, **60**, (as an *E/Z* mixture) was obtained in 70% yield (Scheme 18). In contrast, in the absence of pyridine, the major product was the spiro-linked pinacolone **61**, which was unequivocally characterized by X-ray crystallography.



Scheme 18. McMurry coupling and pinacol rearrangement of [3]ferrocenophanone.

4.2. Wolff Rearrangements

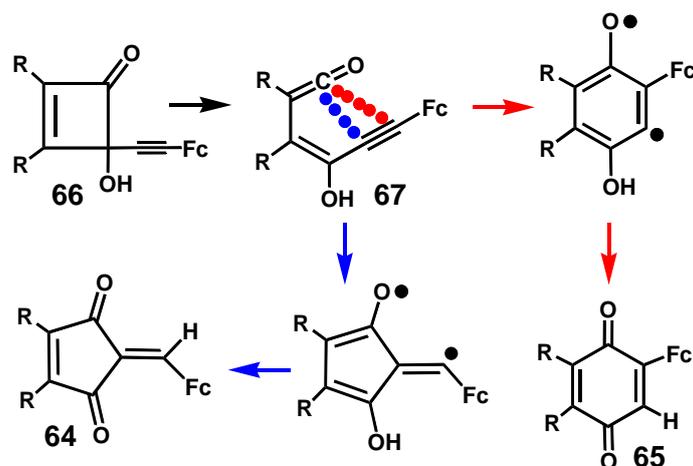
Thermal or photochemical dissociation of α -diazoketones liberates nitrogen to form the corresponding ketene. Whether the reaction involves formation of free carbenes, or proceeds via a concerted process is still the subject of discussion. Nevertheless, the ketenes produced by migration of the alkyl group onto the electron-deficient carbon are versatile species that react with nucleophiles, such as water, alcohols or amines, to form carboxylic acids, esters, or amides, but are also routinely used as partners in [2 + 2] cycloadditions [40]. Diphenylketene is a stable solid but the existence of ferrocenylketene, **62**, has only been verified spectroscopically by laser flash photolysis, and was then trapped by reaction with *n*-butylamine [41]. Similarly, the bis-ketene **63** is detectable in the photolysis of 1,2-diferrocenyl-1-cyclobuten-3,4-dione (Scheme 19).



Scheme 19. Generation of ferrocenylketene, 62, and bis-ferrocenylketene, 63.

4.3. Rearrangements of Alkynyl-4-hydroxy-2-cyclobutenones

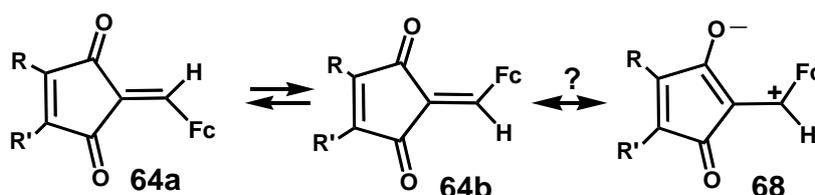
In the continuing search for novel anti-cancer agents, the 2-alkylidene-4-cyclopentene-1,3-dione framework [42] has attracted considerable recent attention. The remarkable bioactivity of ferrocenyl-containing molecules, in particular the ferrocifens [36], prompted the preparation of a series of 2-ferrocenylidene-4,5-dialkyl-4-cyclopenten-1,3-diones, 64. As shown in Scheme 20, these molecules are formed, along with their isomeric benzoquinones, 65, when 4-ferrocenyl-ethynyl-4-hydroxy-2-cyclobutenones, 66, undergo thermal rearrangement when heated at reflux in dioxane [43].



Scheme 20. Rearrangement of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones into 2-ferrocenylidene-4-cyclopenten-1,3-diones and 5-ferrocenyl-1,4-benzoquinones.

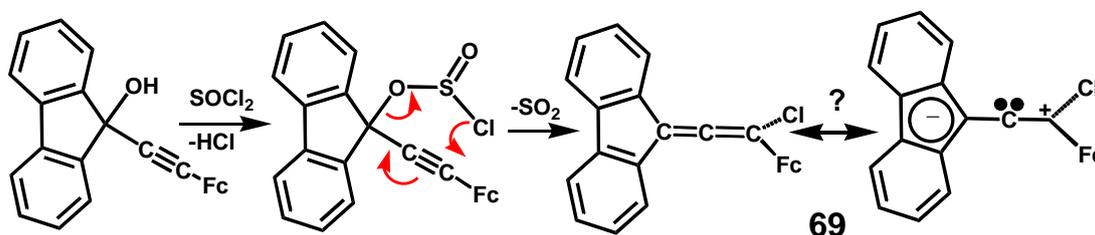
Although this reaction does not start from a diazoketone, the intermediacy of a ketene, and the role of the ferrocenyl unit in stabilizing adjacent cations or radicals, reveal some parallels to the Wolff rearrangement. Upon heating, 66 undergoes electrocyclic ring opening to form the conjugated ketene 67 that can ring-close in two different ways. In each case, the diradical so-formed then proceeds by hydrogen migration to yield the observed products.

Interestingly, when $R \neq R'$, the two geometric isomers 64a and 64b interconvert when heated at 125 °C, and it has been suggested that a zwitterionic contribution, 68, to the structure would facilitate rotation about the $\text{C}=\text{CHFc}$ linkage (Scheme 21).



Scheme 21. Proposed mechanism for the interconversion of 42a and 42b via a zwitterionic structure.

In a somewhat comparable situation, the potential push-pull ferrocenylidene-fluorenyl allene, **69**, that was synthesized by Meyer-Schuster rearrangement of the precursor alkynol with thionyl chloride (Scheme 22), was investigated to test the possibility that the terminal groups might stabilize the separate charges thus generating carbene character at the allene central carbon. Although the ^{13}C NMR spectrum of **69** revealed a peak at 198 ppm, in the normal range for the central carbon in an allene, the molecule was stable only below $-20\text{ }^\circ\text{C}$ and readily dimerized [44].

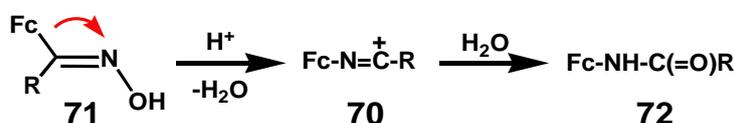


Scheme 22. Meyer-Schuster rearrangement of an alkynol to form the potential push-pull allene, **69**.

5. Ferrocenyl Migration onto an Electron-Deficient Nitrogen Center

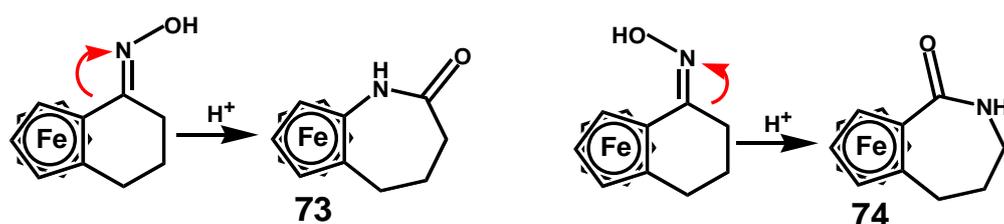
5.1. Beckmann Rearrangements

Oximes are readily preparable by reaction of the precursor aldehyde or ketone with hydroxylamine hydrochloride [45]. When treated with reagents (e.g., H_2SO_4 , PCl_5 , or SOCl_2) that convert the hydroxyl into a leaving group, it brings about migration of the *anti* substituent to form a nitrilium ion, **70**; typically, Beckmann rearrangement of the ferrocenyl oxime **71** and subsequent hydrolysis yielded the secondary amide **72** (Scheme 23) [46]. This specific geometric requirement contrasts with the situation in the pinacol rearrangement whereby the identity of the migrating group is controlled primarily by its migratory aptitude rather than its geometric alignment. Interestingly, several carbamate derivatives of ferrocenyl ketoximes have demonstrated acetylcholin-esterase activity [47].



Scheme 23. Beckmann rearrangement of a ferrocenyl oxime.

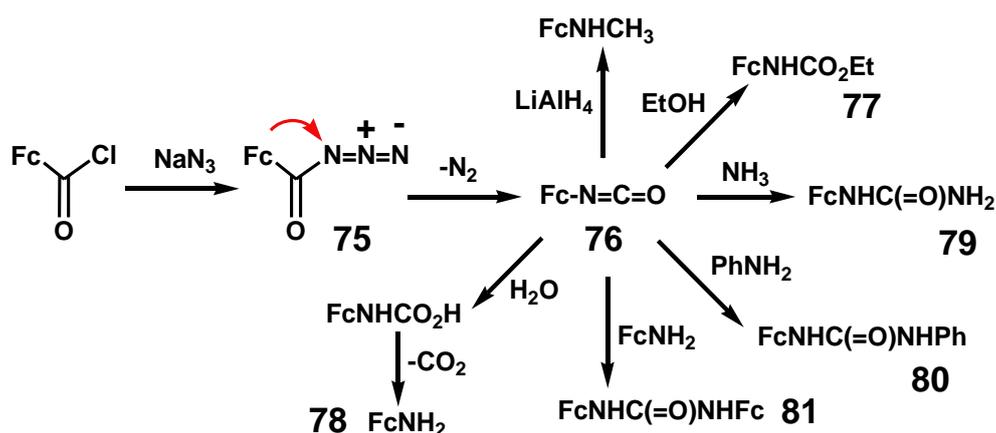
While the Beckmann reaction was extensively explored in pioneering investigations by Schlögl involving a range of alkyl- or aryl-substituted ferrocenyl oximes, probably the most explicit examples are those derived from ferrocenocyclohexanones, as in Scheme 24. In these cases, the structures of the resulting ferrocenocaprolactams, **73** and **74**, are clearly controlled by the *syn* or *anti* orientation of their precursor oximes [46].



Scheme 24. Beckmann rearrangement of *anti* and *syn* ferrocenocyclohexanone oximes.

5.2. Curtius Rearrangements

Thermolysis of acyl azides proceeds with loss of nitrogen to form isocyanates. Although they can be isolated, the reaction is often carried out in the presence of a nucleophilic solvent such as an alcohol or amine to form esters or ureas. In contrast to the Wolff rearrangement that can proceed via a carbene intermediate, the Curtius rearrangement is almost certainly a concerted process that does not involve a discrete nitrene [25]. Rearrangement of ferrocenoyl azide, **75**, by thermolysis in refluxing dry toluene furnished ferrocenyl isocyanate, **76**. As shown in Scheme 25, reaction with ethanol or water produces ethyl ferrocenylcarbamate, **77**, or ferrocenylcarbamic acid, prior to loss of CO₂ and formation of ferrocenylamine, **78**. In addition, ammonia, aniline, and ferrocenylamine react with ferrocenoyl isocyanate to yield *N*-ferrocenylurea, **79**, *N*-ferrocenyl-*N'*-phenylurea, **80**, and *N,N'*-diferrocenylurea, **81**, respectively [48].



Scheme 25. Curtius rearrangement of ferrocenoyl azide to ferrocenyl isocyanate.

Several practical applications of this procedure have since been reported. Curtius rearrangement of ferrocenoyl azide in the presence of a number of hydroxysteroids to form carbamates, such as **82** (Figure 4), has been used in high performance liquid chromatography using electrochemical detection. Maximum sensitivity was achieved by using a silver–silver chloride reference electrode with a detection limit of 0.5 pmol. This derivatization procedure has allowed the facile characterization of the products of the bioconversion of digoxigenin [49]. Moreover, in a more recent study, it has been shown that molecules in which the ferrocenyl carbamate unit is linked to a boronic acid ester, as in **83**, provide a very sensitive and rapid electrochemical detection technique for hydrogen peroxide and glucose; this can be used to follow enzyme activity and cell signaling pathways [50].

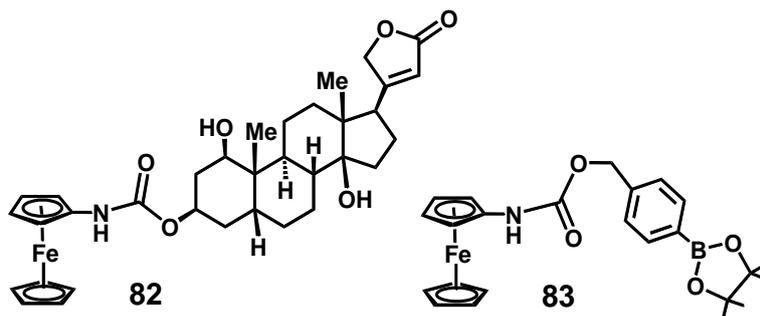
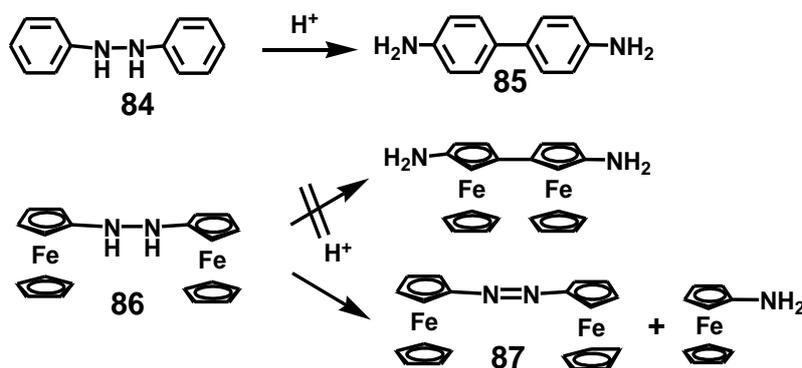


Figure 4. Steroidal and boronic acid ester carbamates derived by reaction of alcohols with ferrocenyl isocyanate.

5.3. Benzidine Rearrangement

Protonation of hydrazobenzene, **84**, brings about cleavage of the HN–NH linkage and coupling of the phenyl substituents, normally in the *para*-positions to form 4,4'-diaminobiphenyl (benzidine), **85**. In the course of their pioneering studies of derivatives of ferrocene, the Nesmeyanov group attempted the benzidine rearrangement of hydrazoferrocene, **86**, but to no avail (Scheme 26). The major products arose from disproportionation to form azoferrocene, **87**, and ferrocenylamine [51]. When the ferrocenyl unit was instead incorporated as a substituent in hydrazobenzene, the major products upon treatment with HCl were ferrocenylazobenzene, ferrocenylaniline, and aniline, again resulting from disproportionation rather than rearrangement [52].

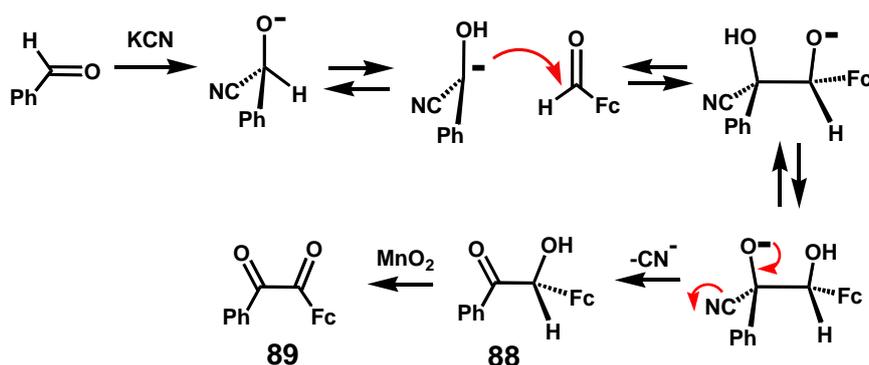


Scheme 26. Attempted benzidine rearrangement of hydrazoferrocene.

6. Anionic Rearrangements of Ferrocenyl Compounds

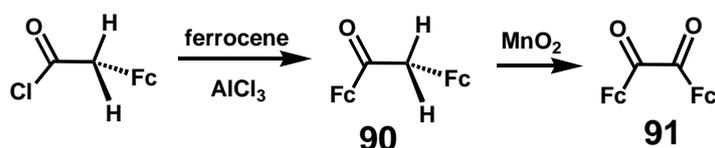
6.1. Benzoin and Benzils

The cyanide-catalyzed condensation of aromatic aldehydes, with subsequent oxidation of the benzoin so-formed, provides a convenient route to benzils [53]. However, when starting from formylferrocene, this procedure failed. Moreover, the mixed benzoin condensation of benzaldehyde and formylferrocene yields only a single product, Ph(C=O)–CH(OH)Fc, **88** [54]. As is evident from the mechanism shown in Scheme 27, this situation arises because nucleophilic attack by cyanide at the ferrocenyl carbonyl, followed by tautomerization, would generate a carbanionic site adjacent to the sandwich moiety—evidently an unfavorable and unlikely circumstance. Instead, the cyanide undergoes addition to the benzaldehyde carbonyl group. Oxidation with MnO₂ yields the mixed benzil Fc(C=O)(C=O)Ph, **89** [54].



Scheme 27. Benzoin condensation of benzaldehyde with ferrocenylaldehyde.

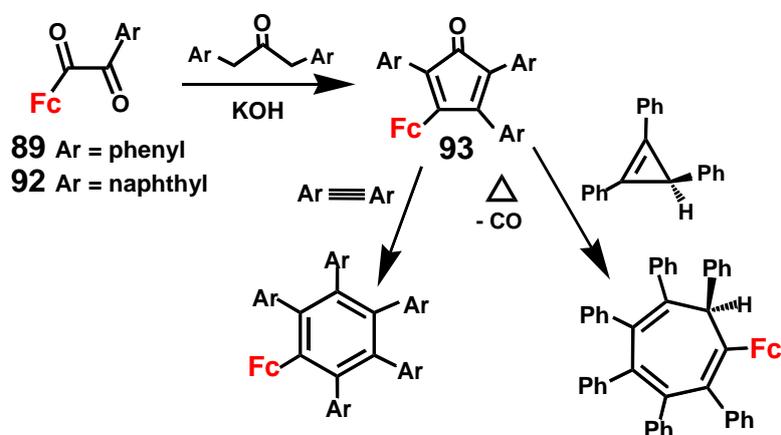
However, an indirect route to ferrocil (Scheme 28) was successfully achieved by Rinehart who found that the Friedel–Crafts acylation of ferrocene with the acid chloride of ferrocenylacetic acid yielded ferrocenylacetylferrocene (desoxyferrocil), **90** [55]; subsequent oxidation with freshly prepared MnO₂ furnished ferrocil, **91**, in 86% yield [56].



Scheme 28. Synthetic route to ferrocil.

In a modification of this approach, the Nesmeyanov group showed that the MnO₂-mediated oxidation of 1,2-diferrocenylethane furnished *trans*-diferrocenylethene, **47**, and small quantities of ferrocil. Satisfyingly, further oxidation of the alkene gave **91** in 40% yield [57]. Unsurprisingly, ferrocil does not undergo the benzil-to-benzilic acid rearrangement; once again, such a process would have required the migration of a ferrocenyl unit under electronically unfavorable anionic conditions.

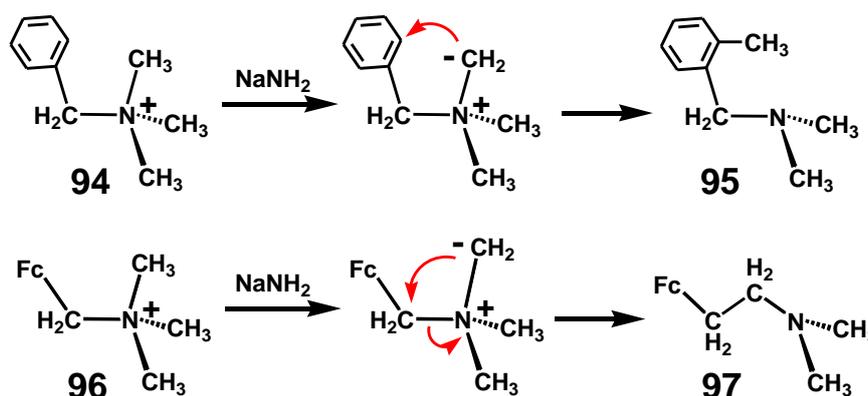
The ready availability of the mixed benzils 1-ferrocenyl-2-aryl-1,2-dioxoethane, **89** and **92**, has been shown to provide a convenient route to ferrocenyl-triaryl-cyclopentadienones, **93** that are versatile precursors to the sterically hindered arenes C₆R₅Fc, where R = phenyl or β-naphthyl, and the cycloheptatriene C₇Ph₆HFc (Scheme 29) [54,58,59].



Scheme 29. Synthetic routes to poly-arylated benzenes and cycloheptatrienes.

6.2. Stevens Rearrangement

In a conventional Stevens rearrangement, deprotonation of a quaternary ammonium salt generates an ylid whereby one of the substituents undergoes migration from nitrogen. Typically, as shown in Scheme 30, under these conditions the benzyltrimethylammonium salt, **94**, is converted to 2-methylbenzyltrimethylammonium salt, **95**. In contrast, upon methylation to form **96**, *N,N*-dimethyl-aminomethylferrocene undergoes a quite different isomerization process to generate *N,N*-dimethylaminoethylferrocene, **97** [60]. This may be rationalized on the basis that, as noted in Section 6.1, the ferrocenyl moiety is less willing than phenyl to tolerate negative charge. We note, however, that more recently, it has been suggested that the mechanism of the Stevens rearrangement may actually involve radical coupling within a solvent cage [61].



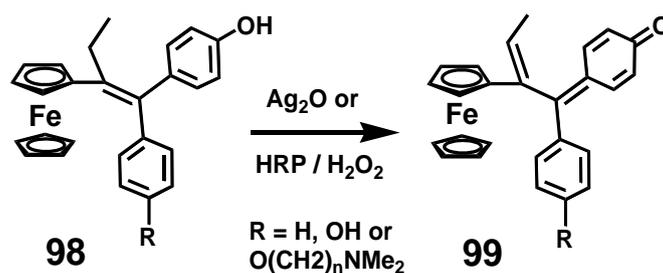
Scheme 30. Different Stevens rearrangements for analogous phenyl and ferrocenyl structures.

7. Ferrocenes in Bioorganometallic Chemistry

7.1. Quinone Methides

Bioorganometallic chemistry, a neologism introduced by a small group of us in the mid-1980s [62, 63], focuses on the bioactivity of complexes possessing at least one metal-carbon bond. It was developed to extend the range and efficacy of metal-based systems beyond that of the widely-used platinum drugs. Although many transition-metal complexes have been studied, *ferrocifens*, the ferrocenyl analogues of *tamoxifen*, the current first-line treatment of hormone-dependent breast cancers, whereby a phenyl has been replaced by ferrocenyl, have proved particularly successful against both hormone-dependent and hormone-independent tumors [64].

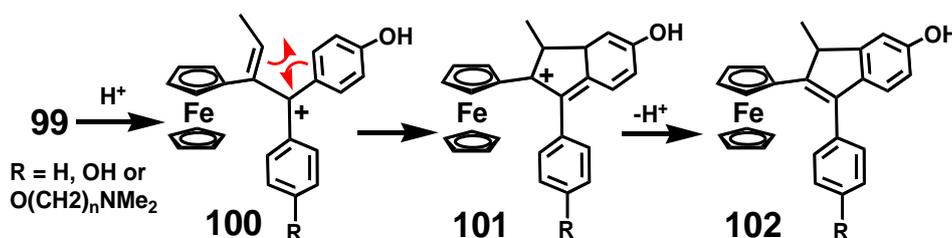
Their activity is predicated on the reversible redox activity of the ferrocenyl moiety that mediates conversion of ferrociphenols, **98**, into the corresponding quinone methides, **99**, that undergo Michael additions with thiols or selenols of key proteins crucial to maintaining redox balance in the cell [65–67]. The net result is to inhibit the regeneration of thioredoxin that defends the cell from attack by reactive oxygen species (ROS), such as hydroxyl radicals. The mode of action of thioredoxin is to trap the ROS by abstraction of hydrogen from its vicinal cysteine thiols, which then form disulfides, a process reversible only by thioredoxin reductase in conjunction with NADPH [67]. Generation of these quinone methides can also be accomplished in vitro by chemical oxidation of ferrociphenols with silver oxide, or enzymatically by using horseradish peroxidase (HRP/ H_2O_2), as depicted in Scheme 31.



Scheme 31. Chemical or enzymatic conversion of ferrociphenols into quinone methides.

7.2. Formation of Indenes

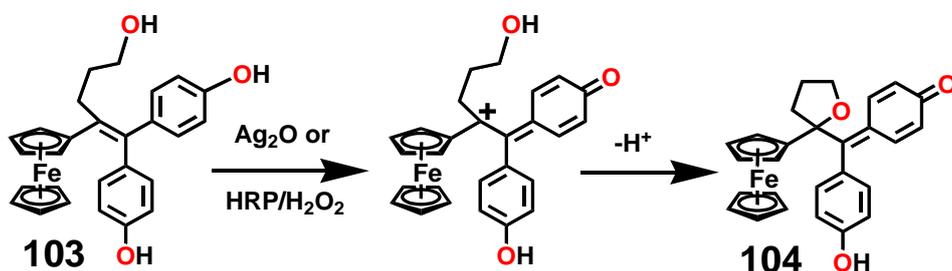
The rearrangement behavior of these bioactive ferrocenyl-containing molecules parallels that of the more conventional systems discussed already. Protonation of ferrocenyl quinone methides brings about rearomatization of the quinone ring and initially generates a doubly-benzylic carbocation, **100**, that readily cyclizes so as to place the electron deficiency adjacent to the ferrocenyl substituent, as in **101**, leading ultimately to formation of indene **102** (Scheme 32) [68], entirely analogous to the reactions described in Section 2.2.



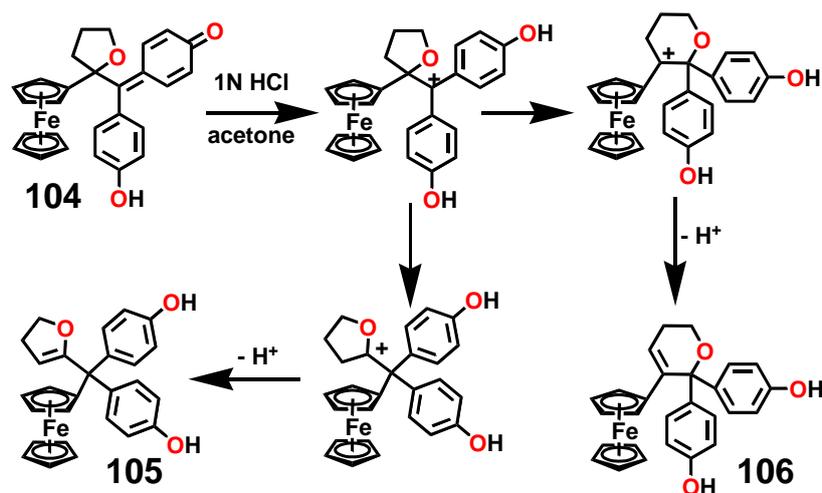
Scheme 32. Protonation of a ferrocenyl quinone methide leads to formation of indenenes.

7.3. Formation and Rearrangement of a Ferrocenyl-Tetrahydrofuranyl Quinone Methide

A particularly interesting transformation occurs in the enzymatic or chemical oxidation of the hydroxypropyl-ferrociphenol, **103**, that yields, among other products, a spiro-bonded tetrahydrofuran derivative, **104** (Scheme 33). When protonated, this molecule undergoes both ferrocenyl migration and ring expansion to yield the dihydrofuran, **105**, and the dihydropyran, **106**, respectively (Scheme 34) [65]. Their X-ray crystal structures are shown as Figure 5.



Scheme 33. Chemical or enzymatic oxidation of the hydroxypropyl-ferrociphenol, **103**, yields the tetrahydrofurananyl-quinone methide, **104**.



Scheme 34. Ferrocenyl migration and ring expansion upon protonation of the tetrahydrofuranyl-quinone methide, 104.

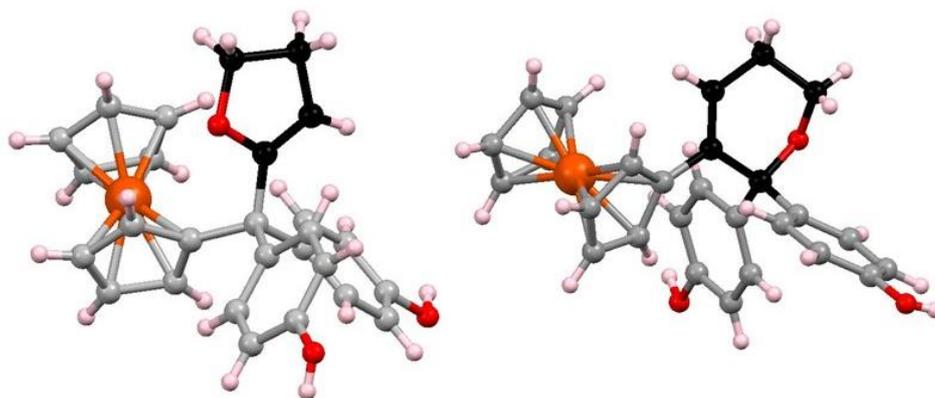
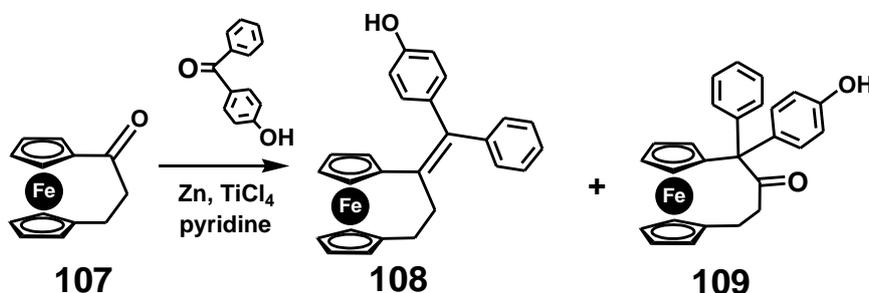


Figure 5. Molecular structures of (left) dihydrofuran, 105, and (right) dihydropyran, 106.

7.4. Pinacol-to-Pinacolone Rearrangement of Ansa-Ferrociphenols

In yet another example in the bioorganometallic arena, the synthesis of an *ansa*-ferrociphenol from [3]ferrocenophanone, 107, by McMurry coupling yields not only the desired alkene, 108, but also the corresponding pinacolone, 109, (Scheme 35) both of whose X-ray crystal structures are shown as Figure 6.



Scheme 35. Pinacol rearrangement of a [3]ferrocenophanone.

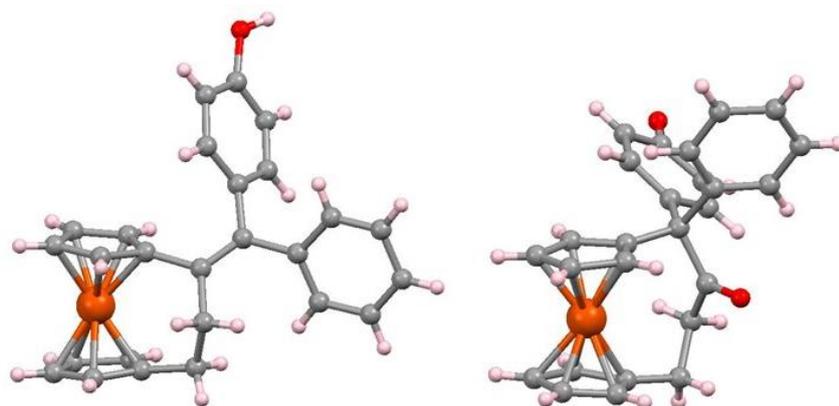
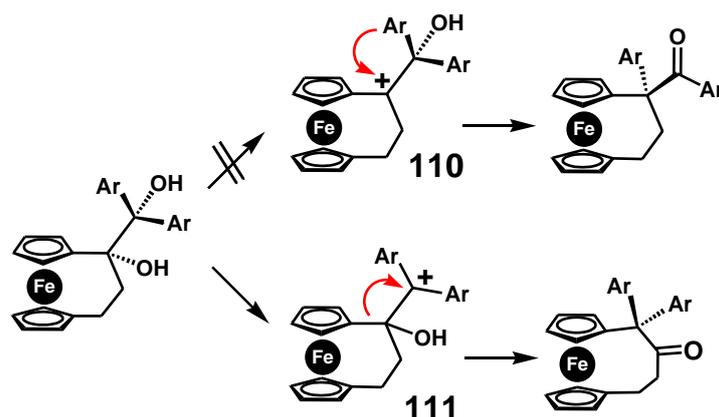


Figure 6. Molecular structures of the *ansa*-ferrocenyl pinacolone, **108**, and the pinacolone, **109**.

In this case, there are two possible pinacolones: one derived by cation formation adjacent to the ferrocenyl group, as in **110**, the other at the doubly-benzylic position, **111**, as illustrated in Scheme 36. In the event it is the latter that succeeds, it is presumably to relieve the ring strain in the three-carbon bridge thereby forming the pinacolone possessing a four-carbon link between the cyclopentadienyl rings [69]. Moreover, in this strained system, the potential carbocation, **110**, adjacent to ferrocene, is unable to enhance its stability by bending towards the metal.



Scheme 36. Carbocation formation at a doubly-benzylic site, rather than adjacent to *ansa*-ferrocenyl.

8. Concluding Comments

The remarkable ability of the ferrocenyl moiety to stabilize a neighboring carbocationic site manifests itself in a number of ways. In some cases, such as $[(C_5H_5)Fe(C_5H_4-CPh_2)][BF_4]$, the species is sufficiently stable to be isolated and structurally characterized by X-ray crystallography. In others, it directs the course of an isomerization or migration by stabilizing a transition state or intermediate by alleviating the electron deficiency and tolerating any excess positive charge on the iron atom.

It is particularly gratifying that the incorporation of ferrocenyl units into bioactive materials has been so successful. We have already discussed its role in enhancing the efficacy and range of applicability of *tamoxifen* by replacing a phenyl substituent by ferrocenyl in the *ferrocifens* for the treatment of a broad range of cancers [63]. Another spectacular advance has been the adoption of *ferroquine* as a replacement for *chloroquine* in the world-wide fight against malaria [70]. It is evident that the electronic control exerted by the ferrocenyl group continues to attract attention, and will undoubtedly lead to additional practical applications.

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