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LETTERS

Stereocontrolled Cyclization of Unactivated Alkene Onto Cationic Dienyl Iron Tricarbonyl Systems

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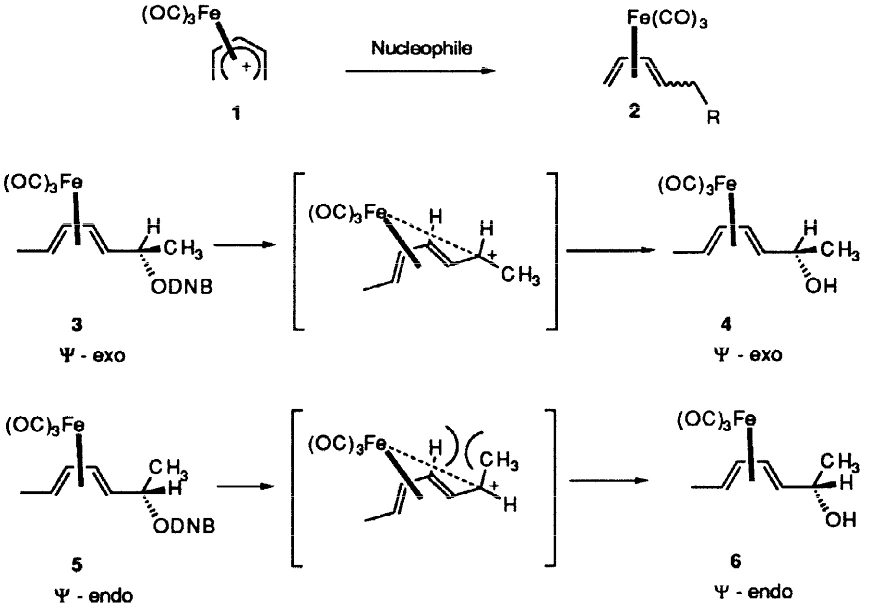
Abstract: Treatment of pentadienol-Fe(CO)$_3$ complexes, having alkene functionality in the side chain, with boron trifluoride, results in a stereospecific cyclization by reaction of the alkene with a stabilized carbocation intermediate; the stereochemical outcome was confirmed by X-ray structure determination of one of the products.

Acyclic pentadienyl iron tricarbonyl cations, of general structure **1** (Scheme 1), are known to undergo reactions with a wide variety of nucleophiles, and methodology for carbon-carbon bond formation has been developed utilizing this chemistry.[1] More recently, it has also been demonstrated that the diene-Fe(CO)$_3$ moiety can provide anchimeric assistance during Lewis acid-promoted reactions of pentadienol-iron complexes with nucleophilic species, a process that can be summarized mechanistically as outlined in Scheme 1.[2] Consistent with this mechanism is the observation that the Ψ-exo complex **3** (DNB = dinitrobenzoate) reacts more rapidly than the Ψ-endo complex **5**, since the latter must proceed through a sterically more congested transition state during the iron-assisted ionization.

Scheme 1



This reactivity has been utilized for stereospecific carbon-carbon bond formation by using activated alkenes, such as allylsilanes as nucleophiles,[3] and it has also been shown to allow cyclization by intramolecular reactions with oxygen- and sulfur-based nucleophiles.[4] We reasoned that the latter intramolecular version might

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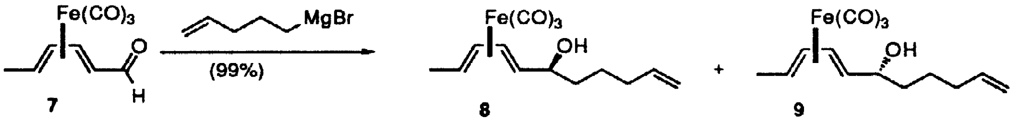
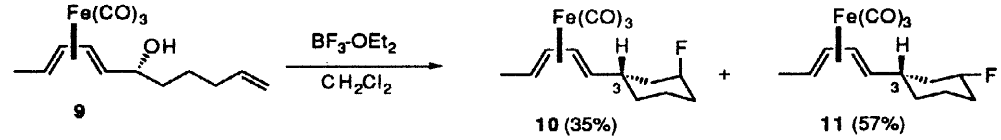
be useful for carbon-carbon bond construction, thereby allowing a useful approach for annulation, by using an alkene in place of the heteroatom nucleophile. This Letter describes our initial findings that indicate the potential of this protocol with simple unactivated alkene side chains. We also observe some unusual behavior that appears to be the result of tight ion pair formation.

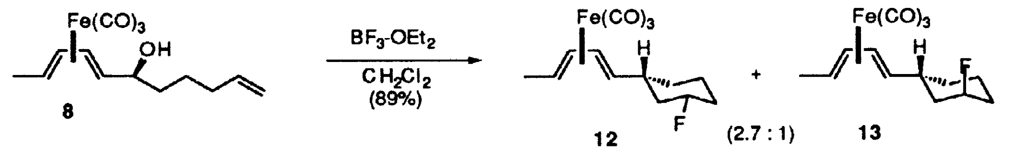
Diastereomeric (1,7,9-undecatrienol)iron tricarbonyl complexes were prepared by Grignard addition to (2,4-hexadienal)iron tricarbonyl (**7**), a known complex. The diastereomers have strikingly different R_f values on silica gel, as previously observed for simpler analogs **4** and **6**.[5] Flash chromatography separation gave pure **8** and **9** in 61% and 38% yields, respectively. In its preferred conformation, the exposed hydroxy group of the Ψ-exo diastereomer would account for its polar behavior, while the unusual non-polar character of Ψ-endo diastereomer is in agreement with its stereochemistry with a sterically shielded hydroxy group. The assignment of Ψ-exo stereochemistry to the more polar diastereomer for the simple dienol complex **4** has been confirmed by X-ray crystallography.[6] Therefore, the relative stereochemistry of the major product **8** of Grignard addition was assigned as 6S,7R (Ψ-endo), and that of the minor product **9** as 6R,7R (Ψ-exo). The formation of the Ψ-endo diastereomer as the major product is in agreement with results of Howell and Grée for MeMgI addition to aldehyde **7**.[7] It should be noted that, for the simpler case of (3,5-heptadienol)iron tricarbonyl, it has been shown that the major (Ψ-endo) diastereomer can be converted to the minor one (Ψ-exo) by treatment with alumina.[8]



Treatment of alcohol **9** with 3 equiv. of BF_3-OEt_2 in CH_2Cl_2 at -78 °C with subsequent warming to rt resulted in the formation of two chromatographically separable fluorides, **10** and **11**, in 35% and 57% yields, respectively. The structures of **10** and **11** as six-membered carbocycles were assigned on the basis of APT ^{13}C NMR spectra, which clearly exhibited signals of CHF fragments (doublets at 89.07 and 91.52 ppm, respectively). Due to the steric bulk of the dieneiron tricarbonyl moiety, both epimeric fluorides should exist in a locked chair conformation with the (diene)$Fe(CO)_3$ being in an equatorial orientation. The ^1H NMR spectrum of **11** shows the CHF resonance as a dtt with J_{HH} = 10.6 (t), 4.5 Hz (t), characteristic of an axial hydrogen.



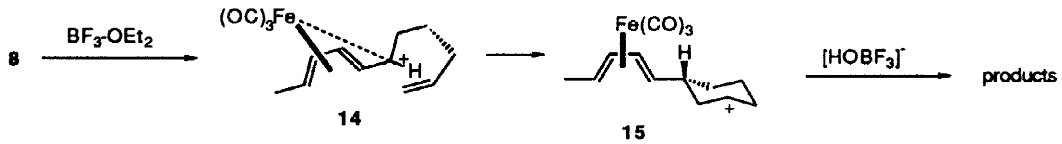
The ^{19}F NMR spectrum of **11** exhibits a doublet at -168.61 ppm, characteristic of an equatorial fluoride,[9] while the corresponding spectral data for **10** are characteristic of a cyclohexane derivative with an axial fluorine substituent (4.84 ppm, dtt, J_{HH} = 4, 2 Hz in ^1H NMR, and -182.6 ppm, dt in ^{19}F NMR). It should be noted that *only one diastereomer* of each fluoride was formed during this reaction. The stereochemistry at C3 was therefore assumed to correspond to that of C6 of the starting alcohol (i.e., the result of net retention of configuration, as is usual with these systems). This was confirmed by X-ray crystal structure determination on the product **11** (Figure 1).[10]



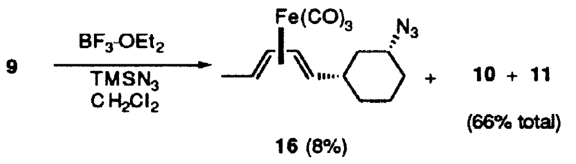
Cyclization of Ψ-endo alcohol **8** under the same conditions (BF_3-OEt_2, CH_2Cl_2, -78 °C to rt) resulted in the formation of cyclohexyl fluoride complexes **12** and **13** in 89% yield, as an inseparable mixture (2.7:1 ratio).

Formation of the cyclohexyl fluoride derivatives can be explained by Lewis acid (BF_3-OEt_2) induced ionization of alcohol with anchimeric assistance from the iron atom, leading to the formation of a stabilized transoid (pentadienyl)Fe(CO)$_3$ cation **14** (Scheme 2). Attack of the pendant olefin with accompanying carbon-carbon bond formation would then proceed from the face opposite to iron tricarbonyl, resulting in the product of formal nucleophilic substitution with net retention of configuration at the position α- to the dieneiron tricarbonyl. Reaction of the resulting cyclohexyl cation **15** with $[BF_3OH]^-$ (or BF_3) as a source of external nucleophile results in the formation of fluorides. To our knowledge, this is the first example of intramolecular cationic carbocyclization of pentadienyliron tricarbonyl complexes with a pendant olefin. Formation of a six-, rather than a five-membered ring can be rationalized in terms of greater stability of secondary *vs*. primary cation.

Scheme 2



In an attempt to introduce nucleophiles other than fluoride, a reaction of **9** in the presence of azidotrimethylsilane was performed. When a 1:1 ratio of BF_3-OEt_2 and $TMSN_3$ was used, only fluorides were produced. Use of a large excess of azidotrimethylsilane (10 equiv. $TMSN_3$, 3 equiv. BF_3-OEt_2) yielded azide **16** in only 8% yield, with fluorides **10** and **11** still being the major products. This result can be attributed to the formation of tight ion pairs during the ionization and cyclization process, followed by rapid return of the fluoride from $[HOBF_3]^-$ to the product cation, which requires ion pair separation before interception by azide can occur.



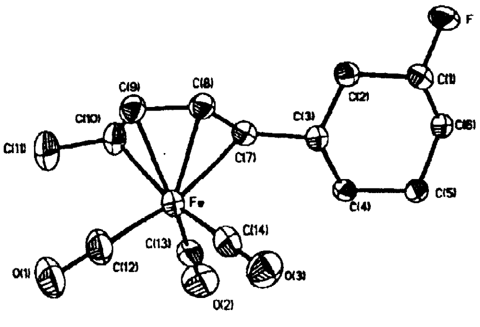
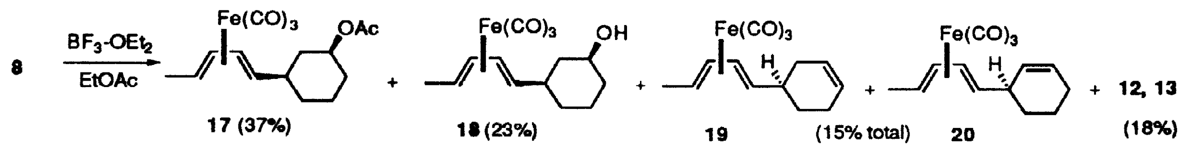


Figure 1. X-Ray structure of **11**
(hydrogens omitted for clarity)

Treatment of alcohol **8** with BF_3-OEt_2 in *anhydrous* EtOAc (-78 °C, then rt, 10 min) resulted in the formation of acetate **17** (37%), alcohol **18** (23%), a mixture of triene complexes **19** and **20** (15%, *ca*. 4:1 ratio) and fluorides **12** and **13** (18%). Both acetate **17** and alcohol **18** were obtained as single diastereomers, with equatorial functional groups (J_{HH} = 11, 4.3 Hz for H-1 of **17** and 10.5, 4 Hz for H-1 of **18**). Thus, the presence of iron tricarbonyl controls stereochemistry at both C3 and C1 of the resulting cyclohexanol derivatives. In this case ion pair separation is facilitated by solvent (EtOAc) which then adds to the product cyclohexyl cation to give an orthoester derivative, eventually leading to both **17** and **18**. (A control experiment, in which 10 equiv. of water was added to the reaction mixture, led to complete suppression of the cyclization, indicating that orthoester derivative breakdown most likely leads to both the acetate and alcohol products).



In summary, a novel stereocontrolled, achimerically assisted cation cyclization of diene-Fe(CO)3 complexes, having alkene side chains, has been developed. Future investigations will explore the scope of this process, and its potential applications in synthesis.

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[10] Crystals of **11** were grown by slow evaporation (5 days) of solvent from a solution in pentane; m.p. 57-58 °C. All inquiries regarding the crystal structure of **11** should be directed to Professor A. Alan Pinkerton at the University of Toledo. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.. Selected bond lengths (Å) are: Fe-C(7), 2.140(4); Fe-C(8), 2.062(4); Fe-C(9), 2.062(4); Fe-C(10), 2.155(4); C(7)-C(8), 1.421(5); C(8)-C(9), 1.418(5); C(9)-C(10), 1.419(6); C(3)-C(7), 1.505(5); C(2)-C(3), 1.535(5); C(1)-F, 1.411(4).