Endo-Selective Reactions of α,β-Unsaturated Hexacarbonyldiiron Bridging Acyl Complexes with Nitrones

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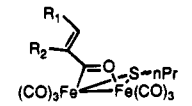
The [3 + 2] dipolar cycloaddition of nitrones with electron-deficient olefins is a reaction that has seen considerable use in organic synthesis.[1,2] A wide variety of natural products have been synthesized using this reaction; amino sugars,[3,4] β-amino acids,[5] alkaloids[6−8] and β-lactams[9−13] are just four examples. Despite the considerable use of this reaction there are limitations on its utility. Unlike the Diels−Alder reaction, the [3 + 2] dipolar cycloaddition often suffers from a lack of regio- and stereoselectivity. Electron-deficient monosubstituted olefins give mixtures of 5- and 4-substituted isoxazolidines, the ratio of which depends on steric effects and the electron-withdrawing ability of the substituent.[14−16] The reactions of acyclic nitrones with dipolarophiles give mixtures of endo and exo type products which not only decrease the yield of useful product but are often difficult to predict.[17,18] A significant advance in the synthetic utility of this reaction would be the development of a dipolarophile that gives high stereo- and regioselectivity in its reaction with nitrones. This paper reports that diiron acyl complexes (Figure 1) undergo stereo- and regioselective [3 + 2] cycloaddition with a variety of nitrones. These complexes are then oxidatively converted to synthetically useful thioesters.

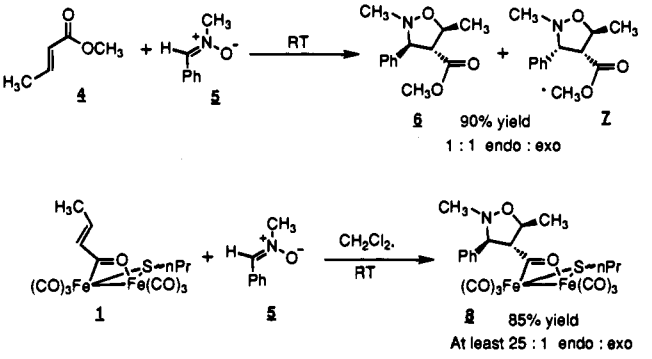
The air-stable, chromatographable, α,β-unsaturated complexes are synthesized by the method of Seyferth in routinely good yield (Figure 1).[19−22] The reactivity of the complexes has been probed with a number of nitrones. We have found these reactions to be high yielding, regiospecific, and stereoselective. *C*-Phenyl-*N*-methylnitrone (**5**) has been reported to give a 1:1



1 $R_1 = CH_3$ $R_2 = H$ 80%
2 $R_1 = H$ $R_2 = H$ 40%
3 $R_1 = H$ $R_2 = CH_3$ 67%

Figure 1.

Scheme 1



endo:exo ratio of products in its reaction with methyl crotonate (**4**)[17] (Scheme 1). This nitrone reacts with diiron acyl complex **1** to give a 25:1 endo:exo ratio.[23,24] In general the reactions of α,β-unsaturated complexes **1**−**3** with nitrones are endo selective. We have looked at methyl, benzyl, *tert*-butyl, and phenyl substituents on the nitrone nitrogen. We have also examined aromatic, aliphatic, and carboxyl substituents on the sp^2 carbon of the nitrone. In all but one case the reaction with the crotonyl complex **1** gives high yields and high diastereoselectivity. The reaction with *C*-methyl-*N*-benzylnitrone gives a 1:1 mixture of diastereomers (reaction 3, Table 1). At this time, the origin of the stereoselectivity is not known. It is interesting to note that *C*-carboxy-*N*-benzylnitrone isomerizes at room temperature.[25] Despite this, the reaction is highly diasteroselective for the endo product (reaction 4, Table 1). The stereoselective formation of one product in this reaction can be explained by the selective addition of one isomer of the nitrone, by isomerization of the initial adduct to the product or by the addition being reversible and ultimately giving the selectivity we observe. At this time we do not know which of these possible pathways are operating.

The regioselectivity of the reaction of nitrones with dipolarophiles is controlled by a combination of electronic and steric factors. The reaction of nitrones with monosubstituted dipolarophiles often gives mixtures of regioisomers. The reaction of *C*-phenyl-*N*-methylnitrone (**5**) with methyl acrylate (**9**) is reported to give an 8:2 ratio of regioisomers, favoring the 5-substituted isoxazolidine **10**, where the less sterically demanding oxygen has added to the substituted carbon[26] (Scheme 2). If the diiron acyl complexes are more electron deficient than the corresponding esters, one would anticipate that the regiochemistry of the reaction of an acrylate type complex with nitrones might be controlled by electronic factors and favor the 4-substituted isoxazolidine product. This turns out to be the case: the reaction of acyl complex **2** with *C*-phenyl-*N*-methylnitrone gives the 4-substituted isoxazolidine product **12**,

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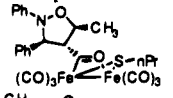
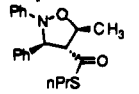
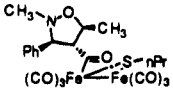
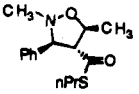
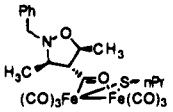
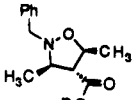
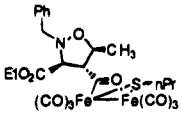
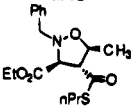
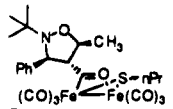
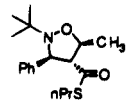
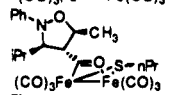
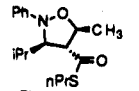
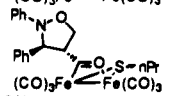
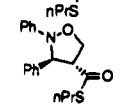
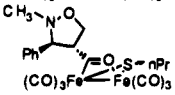
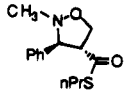
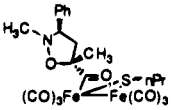
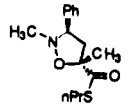
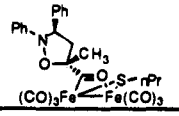
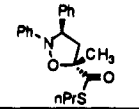
Table 1. Nitrone Additions to Diiron Acyl Complexes

Rnx No.	Complex[a]	Nitrone	Yield Cycloadduct	endo/exo[b]	diiron product	thioester product	Yield thioester
1	1		88% 18hs	25:1			81%
2	1		83% 24hs	30:1			81%
3	1		88% 16hs	1:1			91%
4	1		75% 65hs	20:1			88%
5	1		78% 96hs	25:1			88%
6	1		87% 30hs	20:1			60%
7	2		73% 2.5hs	20:1			77%
8	2		71% 6hs	23:1			62%
9	3		47% 48hs	30:1			71%
10	3		30% 60hs	>25:1			86%

[a] The α,β-unsaturated complexes exist as two isomers at sulfur. The cycloaddition reactions are run in the mixture of isomers. [b] The endo:exo ratios were determined by NMR after conversion to the thioester.

exclusively. This reaction is also highly stereoselective, giving a 20:1 endo:exo ratio. Ultimately electronic control is overwhelmed by steric effects. The reaction of the 1,1-disubstituted acyl complex **3** gives 5-substituted isoxazolidines (reactions 9 and 10, Table 1).

In order for these complexes to be of utility in organic chemistry it is necessary to be able to remove the metal in a productive manner. We have found that the metal can be removed from these diiron acyl complexes with ceric ammonium nitrate to yield thioester products.[27] In the case of the isoxazolidines the metal can be removed, at low temperature, in good yield to give the corresponding thioesters.

In conclusion, we have shown that the diiron acyl complexes are useful dipolarophiles reacting with nitrones in a regio- and stereoselective manner. We are currently developing methods to obtain the acyl complexes in optically pure form in order to perform asymmetric cycloaddition reactions.

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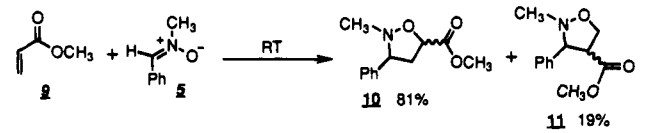
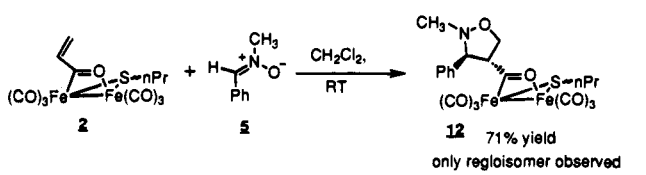
Scheme 2





Supplementary Material Available: Experimental details and spectral and analytical data for various isoxazolidines (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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