Synthesis of and Asymmetric Cycloaddition with Chiral Diiron Acyl Complexes

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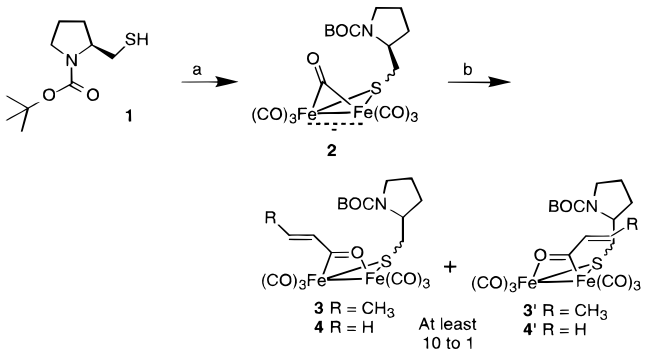
Received December 5, 1996

The use of stoichiometric transition metal reagents in organic synthesis has seen a considerable amount of growth in the last 20 years. These reagents bring a number of useful and unique characteristics to organic synthesis.[1,2] Such reagents often allow access to reaction manifolds that are not available to standard organic reagents. There are also examples of transition metal compounds exhibiting increased reactivity due to their electronic nature. In other cases, stoichiometric organometallic reagents bring structures to organic synthesis that have potential in directing the stereochemical outcome of reactions. Of these unique structure types, there are few asymmetric transition metal complexes where the chirality resides at the metal.[3−5] The synthesis of these complexes is often complicated, involving resolution of diastereomers. This paper reports the first synthesis of asymmetric diiron acyl complexes[6−9] in an optically active form. These complexes exhibit enhanced reactivity *and* unique selectivity in the dipolar cycloaddition of nitrones, giving optically active 4-substituted isoxazolidenes. The cycloaddition of nitrones with α,β-unsaturated ester analogs,[10−15] and other carbonyl compounds,[16−20] in high diastereoselectivity has been an ongoing problem. The chiral diiron reagents reported in this paper perform this reaction with high selectivity providing access to optically active 4-isoxazolidenes of either enantiomer.

Our inital approach to the synthesis of asymmetric diiron complexes was to take a thiol containing a chiral center and carry out the standard procedure developed by Seyferth.[6−9] The hope was that the chirality in the thiol would induce selective addition of the acid chloride to one of the two diastereotopic iron atoms in the anionic diiron intermediate (**2**, Figure 1). Given the distance the thiol-based chiral center was from the two iron atoms it must discriminate between, we felt this was an ambitious goal. The acid chloride could also add to the complex from the side away from the bridging thiol. It was difficult to see how such an addition could be controlled by a chiral thiol attached to the opposite side of the complex. Despite these potential problems, this approach was taken. If reaction of the acid chloride and the diiron anion failed to be selective, we would still have diastereomeric complexes and the potential to separate them. The first thiol used was the thiol from *N*-Boc-protected prolinol (**1**).[21] This thiol was chosen because of the rigid structure of the five-membered ring and the large steric volume of the Boc group attached to the nitrogen. Reaction of triiron dodecacarbonyl with this thiol and triethylamine in THF gave the characteristic yellow solution (**2**). Addition of crotonyl or acryloyl chloride to this solution, followed by overnight stirring, gave the desired acyl complexes; crotonyl in 65% yield and acrylate in 45% yield.



(a) $Fe_3(CO)_{12}$, Et_3N, THF; (b) crotonyl chloride or acryloyl chloride

Figure 1.

Because of hindered rotation of the Boc-protected proline, the NMR line shape of the product complexes was broad, making it difficult to assess the ratio of diastereomers. On the basis of analysis of the ^{13}C NMR resonances for the *tert*-butyl of the Boc group, the ratio of the major product to the sum of the two minor products was approximately 10:1. Along with the potential for different complexes due to rotational isomers, there are two other types of diastereomers possible with these diiron complexes. The acid chloride could have added to either of the two iron atoms, giving diastereomers that differ in the sense of chirality between the iron atoms and the chiral carbon from the thiol. This was the selectivity we set out to control. The other type of diastereomeric relationship possible is between the sulfur atom and the other chiral centers in the molecule. We have seen this type of isomer with these complexes before and have shown that this relationship does not have a profound effect on the reactivity of these complexes.[15,22]

With all of these diastereomers possible, we were both surprised and pleased with the results obtained upon reaction with a selection of nitrones (Table 1).[23−26] We found that reaction of the mixture of diastereomeric complexes with nitrones gave the expected cycloadducts with high selectivity. After cycloaddition, the cycloadduct was liberated from the iron

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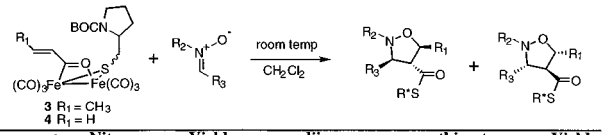
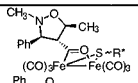
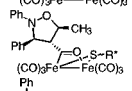
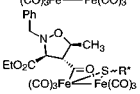
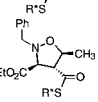
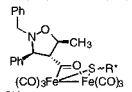
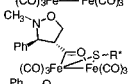
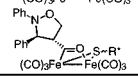
S0002-7863(96)04195-9 CCC: $14.00

Table 1. Nitrone Additions to Chiral Diiron Acyl Complexes



3 $R_1 = CH_3$
4 $R_1 = H$

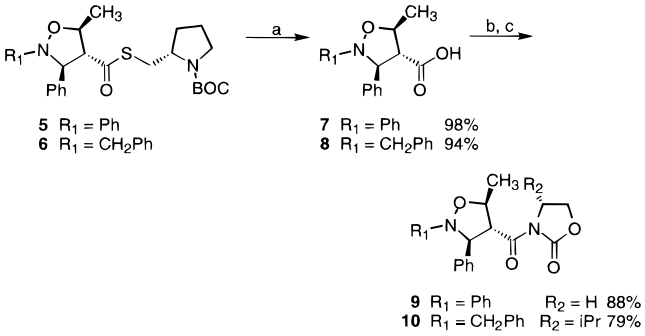
Rnx No.	Cpd [a]	Nitrone	Yield Cyclo-adduct	diiron product	thioester product	Yield thioester ratio [b]
1	3		80% 18hrs			95% 10:1
2	3		83% 24hrs			91% >25:1
3	3		75% 96hrs			89% >25:1
4	3		70% 24hrs			96% >25:1
5	4		60% 6hrs			70% 20:1
6	4		59% 3hrs			60% 15:1

[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.

by oxidation with Ce(IV).[15,22] Oxidative removal of the metal not only converts the organometallic species to the synthetically useful thioester moiety but also removes one of the potential centers of chirality. This reduces the number of possible diastereomers to 2 and allows for accurate determination of the product ratio.

In each case, the cycloaddition of nitrones was run on the mixture of complexes (Table 1). In every case, oxidative removal of the transition metal showed the cycloaddition to proceed with high selectivity and in good yield. Reaction with either the crotonyl (**3**) or acrylate (**4**) derived complex gave useful results, with the crotonyl-derived complexes reacting with higher selectivity. A variety of nitrones were examined. The reaction proceeded in good yield and high selectivity with nitrones that have *N*-aryl or -alkyl groups. The reaction of *C*-carbethoxy-*N*-benzyl nitrone with the crotonyl complex also proceeded in good yield and with high selectivity.

While it was quickly clear that the cycloadditions of nitrones with these complexes proceeded with good selectivity, the absolute sense of this selectivity remained to be determined. This was accomplished by correlation of the products of two different cycloadditions with known compounds (Figure 2). Thioesters **5** and **6** were converted to know isoxazolidines **9** and **10**, respectively.[10−12] Hydrolysis of thioesters **5** and **6** gave the respective acids (**7** and **8**) which were then converted to the isoxazolidines by standard chemistry. These molecules were found to have the same optical rotations as those reported for **9** and **10**.[11] The transformation of **6** to **10** was also used as a check that our determination of the ratio of diastereomers formed in the reaction sequence was correct. The ratios in Table 1 were determined by analysis of ^1H and ^{13}C NMR spectra for diastereomeric thioesters. This approach left the possibility that if two different diastereomers had similar NMR spectra their



5 $R_1 = Ph$
6 $R_1 = CH_2Ph$

7 $R_1 = Ph$ 98%
8 $R_1 = CH_2Ph$ 94%

9 $R_1 = Ph$ $R_2 = H$ 88%
10 $R_1 = CH_2Ph$ $R_2 = iPr$ 79%

(a) LiOH, H_2O, 3 hrs, 0°C; (b) $(CH_3)_3CCOCl$, THF, -78°C; (c) oxazolidin-2-one, nBuLi, THF, -78°C

Figure 2.

ratio may have been incorrectly determined.[27] For this reason we chose to introduce the chiral center of an asymmetric oxazolidinone. This places a well-defined chiral group closer to the other chiral centers in the molecule and gives us further evidence that the reported product ratios are correct and not due to an inability to resolve diastereomeric compounds in the NMR.

This correlation now makes it possible to know the correct enantiomer of proline to use to obtain the desired configuration of the three chiral centers formed in this reaction. We are currently attempting to determine the absolute configuration of the starting diiron complex. This knowledge will allow us to determine whether the diiron complexes react in an s-cis or an s-trans configuration. While this information will increase our understanding of these reagents, it is not critical for the use of this reaction, since we know which absolute configuration of the starting proline provides a given absolute configuration of the product. As a final proof, we synthesized the diiron complex using the thiol from D-proline. Reaction with *N*-methyl-*C*-phenyl nitrone gave, after oxidaton, the opposite enantiomer in good yield and high selectivity.

We are currently working on the development of this chemistry as a route to β-amino acids and β-lactams. Along with that, work is being done to determine the structure of the diiron anion as well as the diiron acyl complexes. Through this information, it may be possible to determine the origin of both the selectivity observed in the synthesis of the acyl complexes and their selectivity in 1,3-dipolar cycloadditions.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE-9316821) and Washington University. We also gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: Experimental details and spectroscopic data (9 pages). See any current masthead page for ordering and Internet access instructions.

JA964195F

(27) The ratio of greater than 25:1 represents none of the minor isomer observed in the proton NMR of the crude reaction mixture.