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On the Use of Ferrocenyl Cations as Chiral Lewis Acids: Evidence for Protic Acid Catalysis

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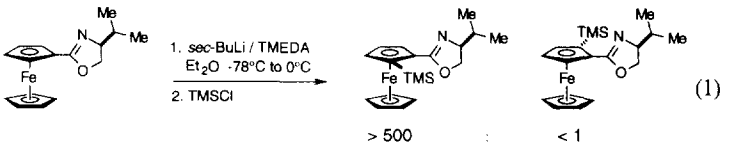
Abstract: The preparation of cation **1** is described, as is the use of this material as a catalyst in the Diels-Alder reaction. While the addition of **1** does promote the Diels-Alder reaction, it is not the catalytic species. Rather, it acts as a source of protic acid which is the true catalyst.

We recently described a method for the asymmetric synthesis of ferrocene complexes possessing planar chirality which relies on the diastereotopic group selective deprotonation of chiral ferrocenyl oxazolines (eq 1).[1] The goal of this study is to prepare asymmetric catalysts which take advantage of the properties of the



(1)

ferrocene nucleus, as well as chiral ligands for transition metals which rely on the planar chirality of substituted ferrocenes. We describe in this communication our work on the synthesis of a chiral Lewis acid in which a ferrocenyl cation is the Lewis acidic component. This system is based on the observation of Mukaiyama and co-workers that trityl salts are capable of catalyzing numerous reactions, including the aldol reaction between electron-rich olefins and aldehydes or acetals, the 1,4-addition of silyl nucleophiles to α,β-unsaturated ketones and ester equivalents, and the reduction of ketones and aldehydes with trialkyl silanes.[2] We chose to examine chiral ferrocenyl cations rather than simply designing a chiral trityl molecule because of the advantages offered by the ferrocene template. First, the ferrocene nucleus is known to greatly stabilize cations α to the cyclopentadienyl ring.[3] This allows for the preparation of stable cationic salts for use as catalysts in a similar fashion to trityl. Second, the ferrocene molecule is rendered chiral by differential substitution of one of the cyclopentadienyl rings. Third, our work and the work of others on the mechanism of Lewis acid-mediated additions to chiral acetals[4] suggests that chiral, acyclic oxocarbenium ions can undergo addition reactions with excellent levels of asymmetric induction in which the sense of asymmetric induction is readily predicted. In this communication, we describe the preparation of cation **1** and our mechanistic studies on its use as a catalyst for the Diels-Alder reaction (Figure 1).[5] A recent report by Kagan[6] describing a similar approach prompts us to disclose our results at this time.

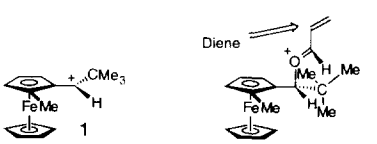
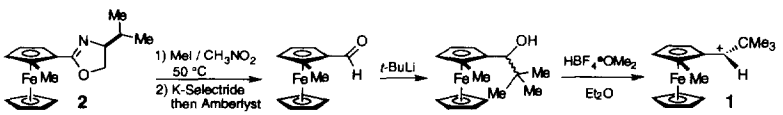


Figure 1

Cation **1** was prepared from the previously described substituted ferrocenyl oxazoline **2**[1a] as shown in Scheme 1. The oxazoline was alkylated with methyl iodide in nitromethane and then reduced to the aminal with K-Selectride. The aminal was then hydrolyzed to the aldehyde by stirring with Amberlyst in wet THF. Addition of *tert*-BuLi to the aldehyde provided a 1:1 mixture of diastereomeric alcohols. Treatment of this mixture with HBF_4•OMe_2 in ether resulted in the precipitation of a solid which was washed with ether to remove the remaining HBF_4. A 400 MHz ^1H NMR spectrum of this cation in $CDCl_3$ is shown in Figure 2.

Scheme 1



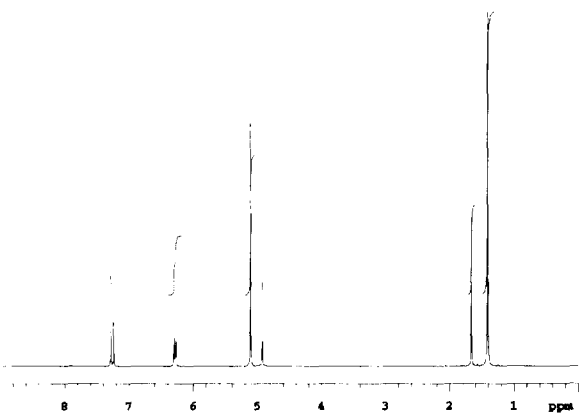
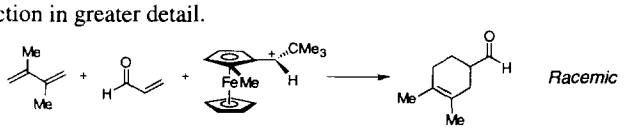


Figure 2 400 MHz ^1H NMR spectrum of **1**.

We examined the use of this cation as a catalyst in the Diels-Alder reaction of acrolein with 2,3-dimethylbutadiene and with isoprene. Reactions were conducted at room temperature in various solvents containing 10% catalyst and 2% 2,6-di-*tert*-butylpyridine, which was added to scavenge any trace acid that may be present. Although we observed catalysis,[7] in every case the enantiomeric excess of the product was 0% within experimental error (Scheme 2).[8] Similar results were obtained using methacrolein as the dienophile. Our experience with the Diels-Alder reaction of other vinyl oxocarbenium ions[9] led us to expect that some asymmetric induction should be observed if we were accessing the desired reactive intermediate. We therefore suspected that traces of acid were responsible for the catalysis we observed and examined the mechanism of the reaction in greater detail.

Scheme 2



We first wished to ascertain if aldehydes bind to the ferrocenyl cation. We therefore examined the ^1H and ^{13}C spectra of a mixture of the cation and methacrolein, but saw no significant changes in the chemical shifts of either species. We did observe a broadening of the carbonyl carbon and the β-carbon of the aldehyde, suggesting that there is a reversible interaction between the cation and the aldehyde that is at the intermediate exchange rate on the NMR time-scale (Figure 3).

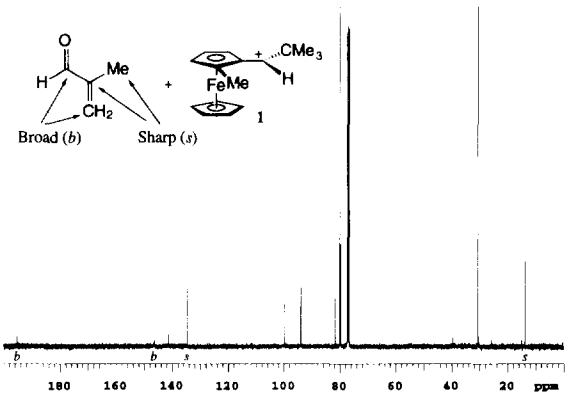


Figure 3 ^{13}C NMR spectrum of **1** in the presence of methacrolein. Resonances due to methacrolein are indicated by *b* for broad resonances and *s* for sharp resonances.

We then decided to follow the progress of the reaction by NMR. A $CDCl_3$ solution containing approximately stoichiometric amounts of aldehyde, cation, and diene, and 16 mol% of 2,6-di-*tert*-butylpyridine was monitored by NMR every half hour for 10 hours and at 12 hours. Representative spectra are shown in Figure 4. We found that approximately half of the 2,6-di-*tert*-butylpyridine is protonated immediately after preparing the solution, and that the 2,6-di-*tert*-butylpyridine is slowly consumed while the amount of protonated 2,6-di-*tert*-butylpyridine increases. Little Diels-Alder product is observed until all of the 2,6-di-*tert*-butylpyridine is consumed (9 hours), at which time the rate of product formation increases drastically. This is illustrated in the graph shown in Figure 5. It appears that a background reaction liberates protic acid, and that once all of the base is consumed, the protic acid catalyzes the Diels-Ader reaction. The protic acid may be derived from nucleophilic attack of the diene on the cation followed by loss of H^+, or from the hydrolysis of the cation due to moisture slowly permeating the septum of the NMR tube.

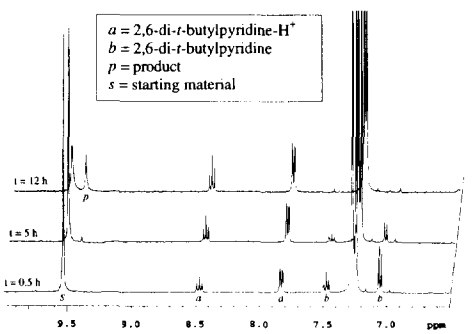


Figure 4 400 MHz ^1H NMR spectrum of reaction mixture.

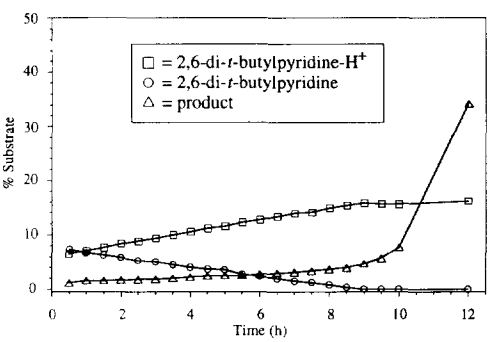
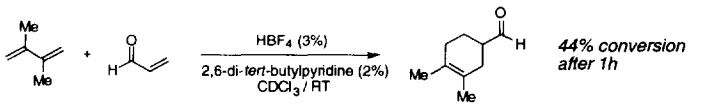


Figure 5 Plot of % substrate vs time.

This hypothesis requires that HBF_4, in the presence of 2,6-di-*tert*-butylpyridinium tetrafluoroborate, be a competent catalyst for the Diels-Alder reaction. In order to test this, an equimolar mixture of 2,3-dimethylbutadiene and acrolein in $CDCl_3$ was treated with 3 mol% HBF_4•OMe_2 and 2 mol% 2,6-di-*tert*-butylpyridine, and the reaction was monitored by NMR at room temperature (Scheme 3). After 1 hour the Diels-Alder reaction had proceeded to 44% conversion, and after 2.3 hrs, to 54% conversion, indicating that HBF_4 is in fact a competent catalyst for this reaction.



Scheme 3

In conclusion, we have demonstrated that ferrocenyl cation **1** is readily prepared in non-racemic form. However, it only weakly binds aldehydes and is not an effective catalyst for the Diels-Alder reaction. It can serve as a precursor to protic acid which is the true catalyst for the reaction. Any effort to design chiral ferrocenyl cations as chiral Lewis acids must take this into account.

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3 The pK_R+ of trityl cation is -6.6, while that of α-hydroxymethylferrocene is -1.5. See: Arnett, E. M.; Hofelich, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2889; Cerichelli, G.; Floris, B.; Ortagi, G. *J. Organomet. Chem.* **1974**, *78*, 241.

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7 Under these conditions, no reaction is observed in the absence of the cation.

8 Enantiomeric excess was determined by converting the product to the acetal derived from (*R,R*)-2,4-pentanediol by the method of Noyori (Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357) followed by ^1H NMR analysis of the resulting diastereomeric acetals.

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