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# Application of FAM ligands in the metal-promoted catalytic enantioselective synthesis of organic compounds

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Novel ferrocenyl substituted aziridinyl methanol (FAM) ligands were synthesized and successfully used in metal-promoted catalytic enantioselective azomethine ylide cycloadditions, diethylzinc additions to enones, alkynylzinc additions to aldehydes, diethylzinc additions to aldehydes, and Henry reactions. These reactions are summarized in this report.

## Introduction

The asymmetric synthesis of organic compounds is an important area of research. Asymmetric synthesis can be accomplished (1) starting from a chiral substrate, (2) using a chiral reagent, (3) by resolution of a racemic mixture, (4) using enzymes, (5) using asymmetric catalysts, and (6) using organocatalysts.

During the last 2 decades asymmetric synthesis using chiral catalysts has received considerable attention. In 2001, the Nobel Prize was given to Sharpless, Noyori, and Knowles due to their contributions in the field of catalytic asymmetric synthesis. The method promises to produce large quantities of chiral compounds using a chiral catalyst. In most cases the catalyst can be recovered and reused; therefore, it is potentially an environmentally friendly method. Recently, the use of organocatalysts (small chiral organic compounds) has become popular. Although it has not yet reached the level of metal-based catalysis, this area is developing rapidly.

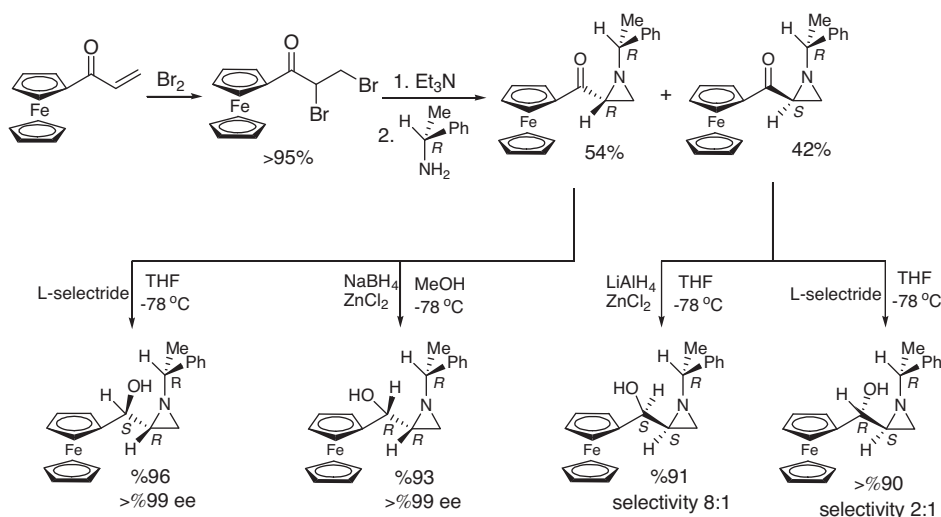
This short review is a summary of our contributions to the field of asymmetric catalysis using a new ligand system that we developed. These chiral ligands—ferrocenyl substituted aziridinyl methanols (FAMs)—can be used with a metal salt to catalyze a variety of C-C bond-forming reactions.

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## Ligand synthesis

FAM ligands were synthesized on a gram scale via a concise, easily applicable efficient method. This synthesis is summarized in Scheme 1 and the experimental details have been described.<sup>1</sup>

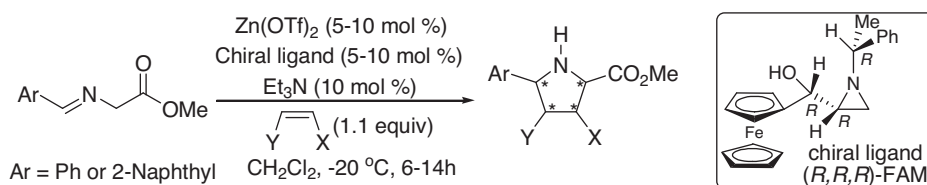


Scheme 1. Synthesis of FAM ligands.

All 4 diastereomers of the FAM ligands derived from (*R*)-methylbenzylamine can be synthesized starting from readily available acryloyl ferrocene. Gabriel-Cromwell reaction of this starting material leads to the diastereomeric aziridino ketones in high yields. This is followed by the stereocontrolled reduction of the ketone group (Felkin-Anh control → syn, chelation control → anti) to complete the synthesis. To date, these compounds have served as chiral ligands in 5 different catalytic asymmetric reactions.

## Azomethine ylide cycloadditions

The first reaction examined (Scheme 2) was the catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-deficient dipolarophiles.<sup>1,2</sup> This is an important and atom-economical reaction for the synthesis of pyrrolidines in which 2 C-C bonds and up to 4 stereogenic centers are formed in a single step. Pyrrolidine structures are found in the structure of many natural compounds and drugs; therefore, the efficient asymmetric synthesis of pyrrolidines is highly desirable.



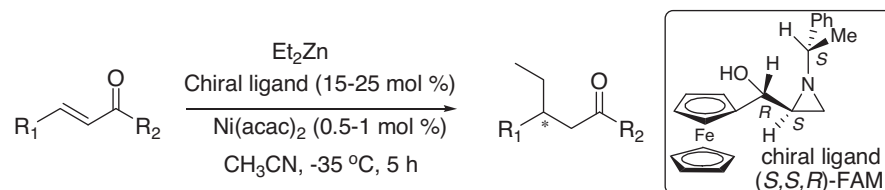
Scheme 2. Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides.

For the synthesis of pyrrolidines the starting imine was obtained by condensation of glycine methyl ester with benzaldehyde or 2-naphthaldehyde. (*R,R,R*)-FAM-Zn served as a good chiral catalyst for this reaction

(Scheme 2). Using 5-10 mol % of this catalyst with different dipolarophiles (dimethyl maleate, methyl acrylate, tert-butyl acrylate, and N-methylmaleimide) and imines, pyrrolidines were obtained in 63%-94% yield and in 36%-95% ee.

### Additions of diethylzinc to enones

The second reaction examined was the diethylzinc addition to enones (Scheme 3).<sup>3,4</sup> This is a commonly studied C-C bond formation reaction.

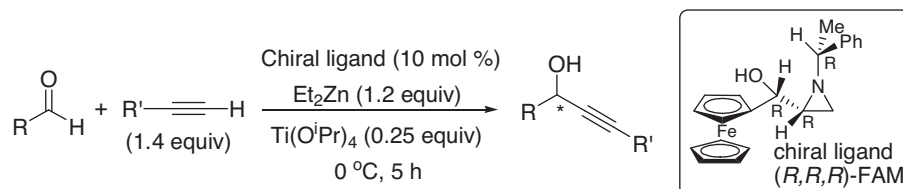


**Scheme 3.** Catalytic enantioselective diethylzinc addition to enones.

Enones having mainly aryl groups at  $R_1$  and  $R_2$  were used as the starting materials. The (*S,S,R*)-FAM ligand + Ni(II) salt served as an effective catalyst for this reaction. As can be seen, the chiral ligand was used in 15–25 mol % with 0.5–1.0 mol % Ni(acac)<sub>2</sub> in acetonitrile at 35 °C. From this reaction,  $\beta$ -ethylated ketones were isolated in 55%–96% yield and in 16%–80% ee.

### Additions of alkynylzinc reagents to aldehydes

Another reaction in which one of the FAM ligands was used was alkynylzinc addition to aldehydes (Scheme 4).<sup>5,6</sup> The product propargylic alcohols are versatile building blocks for many chiral organic compounds. Among the FAM ligands used, (*R,R,R*)-FAM was optimal.

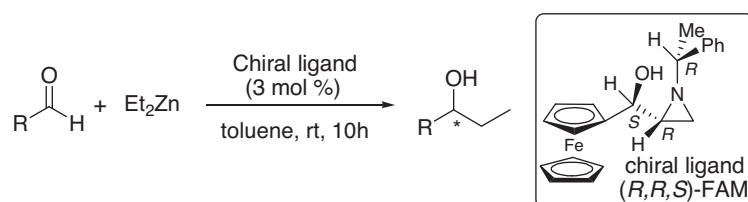


**Scheme 4.** Catalytic enantioselective alkynylzinc addition to aldehydes.

This reaction was applied to a wide spectrum of aldehydes, including aliphatic, aromatic, hetero-aromatic, and  $\alpha,\beta$ -unsaturated aldehydes. Phenylacetylene, 1-hexyne, and 1-heptyne were employed as the alkynes in these reactions. Propargylic alcohols were thus obtained in 80%–96% yield and 86%–98% ee.

### Additions of diethylzinc to aldehydes

FAM ligands also served as excellent catalyst components for diethylzinc addition to aldehydes (Scheme 5).<sup>7,8</sup> This is also an important C-C bond formation reaction, providing a general method for the enantioselective synthesis of secondary alcohols. Additionally, it is considered a test reaction for understanding the catalytic potential of new chiral catalysts.

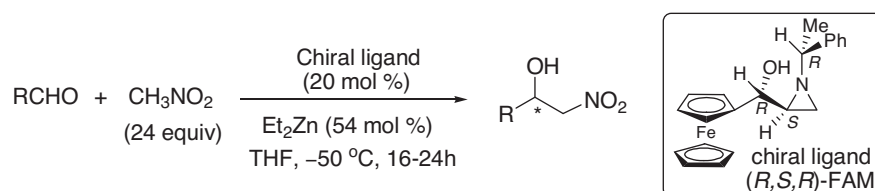


**Scheme 5.** Catalytic enantioselective diethylzinc addition to aldehydes.

Using 3 mol % of (*R,R,S*)-FAM ligand, secondary alcohols were obtained in 52%–99% yield and 80%–99% ee. The reaction worked efficiently with aromatic, aliphatic, and  $\alpha,\beta$ -unsaturated aldehydes.

## Henry reactions

Chiral FAM ligands were also tested in the asymmetric nitroaldol or Henry reaction (Scheme 6).<sup>9,10</sup> The products of this reaction are highly valuable as the starting materials for 1,2-amino alcohols and  $\beta$ -hydroxy acids.



**Scheme 6.** Catalytic enantioselective nitroaldol or Henry reaction.

The (*R,S,R*)-FAM ligand was the most effective for this asymmetric nitroaldol reaction. Using 20 mol % of this ligand with diethylzinc, nitroaldol products were isolated in 71%–97% yield and 71%–91% ee. The catalyst worked with a variety of aldehydes (aromatic, aliphatic,  $\alpha,\beta$ -unsaturated, and heteroaromatic) and  $\alpha$ -ketoesters.

## Summary

In summary, FAM ligands were effective catalyst components when used with metals (Zn, Ni, and Ti) for the asymmetric synthesis of useful organic compounds (pyrrolidines, secondary alcohols, propargylic alcohols,  $\beta$ -ethylated ketones, and  $\beta$ -nitro alcohols). A key feature of these ligand systems is their ease of preparation, which is facilitated by the judicious incorporation of a ferrocenyl group into their structures. They can be synthesized on a gram scale in 3 easy steps and are purified easily by flash column chromatography on silica gel. Due to their dark yellow color, one can follow the progress of the chromatography with the naked eye. In most cases, FAM ligands can be recovered in high yields and reused without losing their activity. Another advantage of these ligands is that their antipodes can be prepared easily starting from (*S*)-methylbenzylamine at the aziridine formation step. The catalytic effect of these ligands on other asymmetric reactions is under investigation in our laboratory and will be reported in due course.

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