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New Zinc(II)-Based Catalyst for Asymmetric Azomethine Ylide Cycloaddition Reactions

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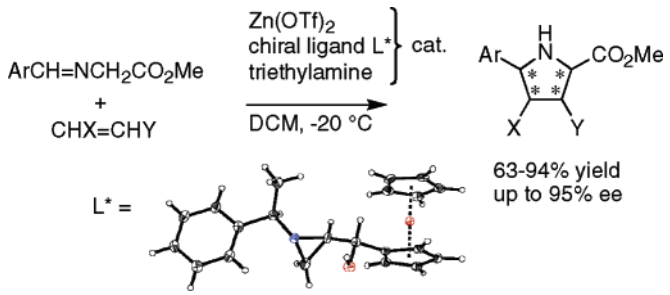
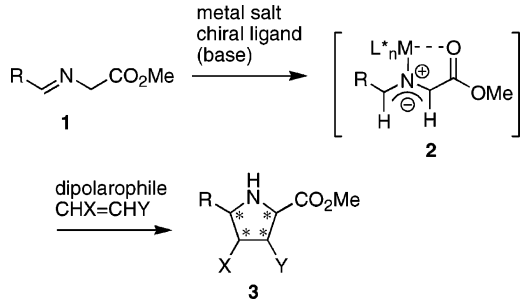
ABSTRACT



A new chiral aziridino alcohol ligand for zinc(II)-catalyzed azomethine ylide cycloadditions is described. In the presence of this catalyst, *N*-arylidene glycine methyl esters react with a variety of dipolarophiles to give substituted pyrrolidines in very good to excellent chemical yields and up to 95% ee. The absolute sense of asymmetric induction appears to be dipolarophile-dependent.

Azomethine ylides[1] and related species[2] are important reactive intermediates that have considerable synthetic potential because they undergo [3+2] cycloadditions with alkenes to give substituted pyrrolidines. Because the pyrrolidine ring system is found in many bioactive substances, the development of more effective procedures for the asymmetric syntheses of substituted pyrrolidines is of great importance. The seminal discovery that N-metalated azomethine ylides undergo facile [3+2] cycloadditions[3] has led to the development of catalytic asymmetric versions of this important reaction (Scheme 1). This possibility could be divined from Grigg's seminal work using stoichiometric quantities of metal salts and chiral ligands.[4] A number of

Scheme 1. Catalytic Asymmetric Azomethine Ylide Cycloaddition



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|| University of Akron.

(1) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, Chapter 1.
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(3) (a) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, p 161. (b) Kanemasa, S. *Synlett* **2002**, *9*, 1371.

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laboratories have now reported catalytic asymmetric [3+2] azomethine ylide cycloadditions employing a variety of chiral ligand−metal combinations (Figure 1).[5,6] Despite these

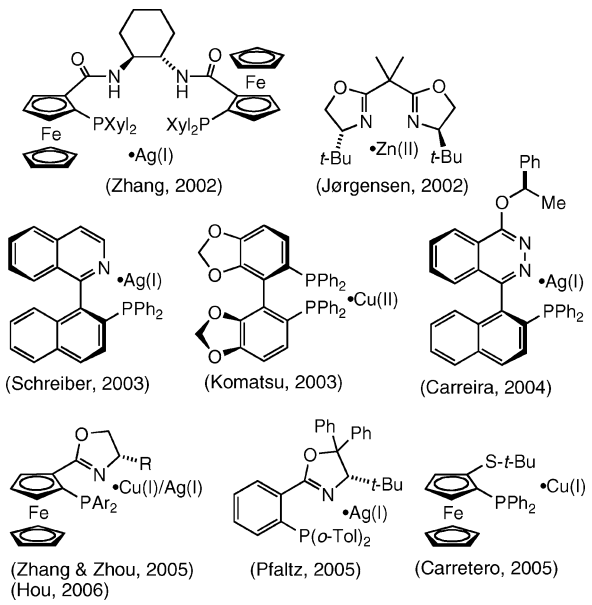


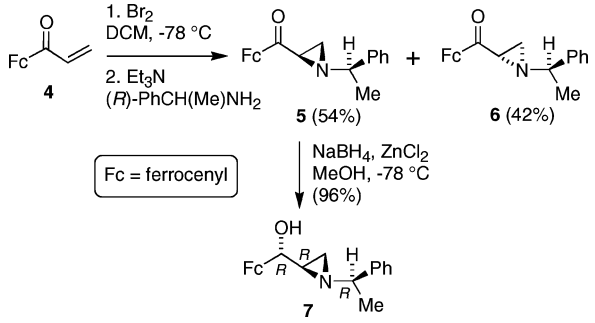
Figure 1. Known chiral ligand−metal combinations for catalytic asymmetric azomethine ylide cycloadditions.

impressive advances, there remains a need for new catalysts that are easily prepared and can tolerate variation of both the dipole and the dipolarophile components.

We now report a novel zinc(II) catalyst for the [3+2] cycloaddition between three glycine methyl ester aldimine-derived azomethine ylides and a representative set of dipolarophile types (acrylate, fumarate, maleate, and maleimide). This procedure utilizes a novel ferrocenyl-substituted aziridino alcohol as the chiral ligand. The ease of ligand preparation is a particularly attractive feature of this new catalyst system. Under optimized reaction conditions, substituted pyrrolidine products are formed in generally high yields and with ee's ranging from 68 to 95%. Interestingly, the absolute sense of asymmetric induction is found to be consistently reversed in the case of dimethyl maleate. Of the catalytic asymmetric azomethine ylide cycloadditions reported to date, only Jørgensen's original study (see ref 6a) employed a zinc-based catalyst system. In that work, only two types of dipolarophiles were examined (acrylates and dimethyl fumarate).

Our chiral ligand design was based on the known attributes of ferrocene-derived ligands[7] and an improved route to acryloylferrocene (**4**).[8] We were also cognizant that aziridinyl alcohols serve as effective chiral ligands for dialkylzinc additions to aldehydes.[9] These considerations prompted us to survey a series of chiral aziridino alcohols that could be prepared from **4** and led to the crystalline aziridinyl alcohol **7** as the most promising chiral ligand candidate.[10] The synthesis of **7** commenced with Gabriel−Cromwell aziridination[11,12] of enone **4** using (*R*)-methylbenzylamine (Scheme 2). This reaction gave a mixture of diastereomeric aziridinyl

Scheme 2. Synthesis of Chiral Ligand **7**



ketones **5** (54%) and **6** (42%) that were easily separated by flash chromatography on silica gel.[13] Stereocontrolled reduction of aziridinyl ketones **5** with $NaBH_4 + ZnCl_2$ (chelation control)[14] according to Lee and co-workers afforded the *syn*-aziridinyl alcohol **7** in high yield. Compound **7** is a stable yellow crystalline solid (mp 83−85 °C) that is soluble in typical organic solvents. Its (*R*,*R*,*R*)-configuration was confirmed by X-ray crystallography (Figure 2).[15]

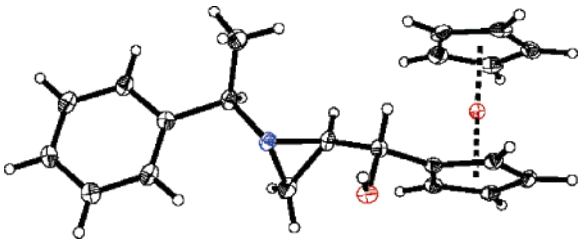


Figure 2. ORTEP diagram from the X-ray crystallographic analysis of ligand **7**.

The combination of ligand **7** with $Zn(OTf)_2$ produced a very effective catalyst for the asymmetric cascade imine → azomethine ylide → [3+2] cycloaddition reaction (Table 1). Three known aldimines, $ArCH{=}NCH_2CO_2Me$ (Ar = phenyl,

(4) (a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

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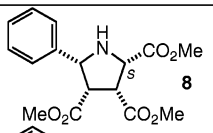
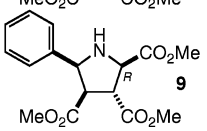
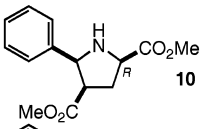
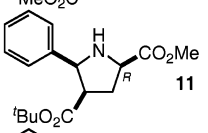
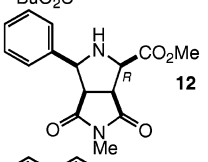
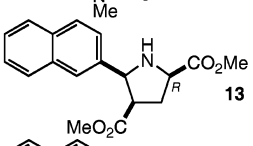
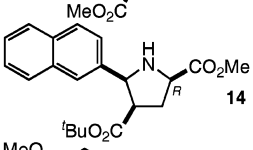
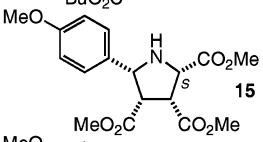
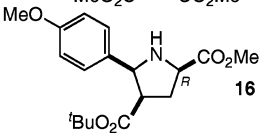
Table 1. Catalytic Asymmetric Azomethine Ylide Cycloadditions with Ligand **7**[a]

entry	aldimine	dipolarophile	catalyst loading (mol% $Zn(OTf)_2$)	yield (%)	ee (%)	product
1a	PhCH=NCH$_2$CO$_2$Me	dimethyl maleate	10.0	88	90	
1b	PhCH=NCH$_2$CO$_2$Me	dimethyl maleate	5.0	88	82	 **8**
2	PhCH=NCH$_2$CO$_2$Me	dimethyl fumarate	10 .0	85	68	 **9**
3	PhCH=NCH$_2$CO$_2$Me	methyl acrylate	10.0	83	46	 **10**
4a	PhCH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	10.0	93	88	
4b	PhCH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	5.0	94	88	 **11**
5	PhCH=NCH$_2$CO$_2$Me	N-methyl maleimide	10.0	92	70	 **12**
6a	2-NpCH=NCH$_2$CO$_2$Me	methyl acrylate	10.0	92	37	
6b	2-NpCH=NCH$_2$CO$_2$Me	methyl acrylate	5.0	85	36	 **13**
7a	2-NpCH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	10.0	85	78	
7b	2-NpCH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	5.0	63	76	 **14**
8a	*p*-MeOC$_6$H$_4$CH=NCH$_2$CO$_2$Me	dimethyl maleate	10.0	70	95	
8b	*p*-MeOC$_6$H$_4$CH=NCH$_2$CO$_2$Me	dimethyl maleate	5.0	67	90	 **15**
9a	*p*-MeOC$_6$H$_4$CH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	10.0	79	84	
9b	*p*-MeOC$_6$H$_4$CH=NCH$_2$CO$_2$Me	*t*-butyl acrylate	5.0	63	80	 **16**

[a] Procedure: (Rigorously dry conditions were employed; see Supporting Information for details.) To $Zn(OTf)_2$ (10.0 or 5.0 mol %) was added ligand **7** (11.5 or 5.8 mol %) in DCM (1.8 mL per mmol of imine) under Ar at room temperature. The homogeneous mixture was stirred at this temperature for about 1 h and then cooled to −20 °C when the imine (1 equiv), Et_3N (10.0 mol %, distilled and stored over NaOH), and the dipolarophile (1.1 equiv) were added sequentially. The reaction was stirred at −20 °C until judged complete by TLC (~6 h for the higher and 14 h for the lower catalyst loadings), at which point the solvent was removed under reduced pressure and the product was isolated by flash column chromatography on silica gel.

2-naphthyl, and 4-methoxyphenyl; prepared as described in ref 6a), were employed as azomethine ylide precursors. Cycloadditions with a standard set of electron-deficient dipolarophiles (dimethyl maleate, dimethyl fumarate, methyl acrylate, *tert*-butyl acrylate, and *N*-methylmaleimide) were investigated, and the products' enantiomeric excesses (ee's) were determined by chiral HPLC analysis. In each case, a very clean cycloaddition occurred in DCM solution at −20

(7) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659.

(8) Dogan, Ö.; Senol, V.; Zeytinci, S.; Koyuncu, H.; Bulut, A. *J. Organomet. Chem.* **2005**, *690*, 430.

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(10) All four possible stereoisomeric aziridinyl alcohols were synthesized and tested. The crystalline chiral ligand **7** was clearly superior to the other three oily aziridinyl alcohol diastereomers. (See Supporting Information for details.)

(11) Cromwell, N. H.; Babson, R. D.; Harris, C. E. *J. Am. Chem. Soc.* **1943**, *65*, 312.

(12) Dogan, Ö.; Zeytinci, S.; Bulut, A. *Synth. Commun.* **2005**, *35*, 1067.

(13) Because the ferrocene group imparts a red color to these compounds, the purification of **5** and **6** could be conveniently monitored visually.

(14) Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K. *J. Org. Chem.* **2003**, *68*, 7675.

°C,[16] providing pyrrolidines in high yield after flash chromatography. Qualitatively similar results in terms of yield and enantiomeric excess were obtained with 10 and 5 mol % catalyst loadings, though the latter reactions were slower. The relative stereochemistry of the cycloadducts was consistent with endo addition of the dipolarophile to an (*E*,*E*)-configured metalated azomethine ylide. When acrylate dipolarophiles were employed, the cycloaddition reaction was regioselective for the 2,4,5-trisubstituted pyrrolidine.

The observed ee's with ligand **7** at 10 mol % catalyst loading ranged from 90 to 95% with dimethyl maleate (entries 1a and 8a) and from 78 to 88% with *tert*-butyl acrylate (entries 4a, 7a, and 9a) and were 68% for dimethyl fumarate and 70% for *N*-methylmaleimide (entries 2 and 5). Cycloadditions with methyl acrylate gave the lowest ee's (entries 3 and 6a). Except for the reactions with dimethyl maleate, all of the Zn^{II}-catalyzed [3+2] cycloadditions using ligand **7** gave (2*R*)-configured pyrrolidines preferentially. The absolute configurations shown for the cycloadducts **8**−**16** derive from comparison of their optical rotation and chiral HPLC data with values reported in the literature (see Supporting Information). In the case of cycloadduct **8**, the absolute configuration was unambiguously confirmed by chemical correlation with a compound that had been previously characterized by X-ray crystallography.[17] Literature assignments for all cycloadducts except **12** were based on analogy with structurally related compounds that had been characterized by X-ray crystallography.

The experimentally observed *re* facial selectivity with acrylate, fumarate, and maleimide dipolarophiles can be rationalized by the pre-transition state (TS) shown in Figure 3. According to this working model, the Zn^{II} atom is four coordinate and the stereocenter at C2 of the aziridine determines the chirality of the complex. The (*E*,*E*)-dipole is oriented such that the phenyl group is positioned on the convex face of the bicyclic ring system formed by zinc(II) chelation to aziridino alcohol. In such a complex, the N-substituent of ligand **7** effectively blocks the dipolarophile approach from the bottom (*si*) face of the ylide, resulting in *re* attack. Although the observed endo selectivity can be ascribed to a stereoelectronic effect, a five-coordinate Zn^{II} complex with the ester dipolarophiles acting as ligands is also possible (see ref 6a). Such an ensemble may be preferred over *si*-favoring alternatives with a bulky *tert*-butyl ester. At present, we do not have an adequate explanation for the endo-*si* selectivity that is observed with dimethyl maleate.

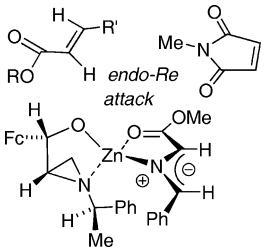

Figure 3. Proposed endo-*re* pre-TS leading to cycloadducts **9**−**14** and **16**.

In summary, a novel chiral ligand for Zn^{II}-catalyzed [3+2] cycloadditions of azomethine ylides is described. A key feature of this ligand system is its ease of preparation, which is facilitated by the judicious incorporation of a ferrocenyl group into its structure. This catalytic asymmetric 1,3-dipolar cycloaddition procedure is applicable to a variety of standard dipolarophiles, providing substituted pyrrolidines in high yields and up to 95% ee. These preliminary results warrant further development of ferrocenyl-substituted aziridino alcohols as chiral ligands for catalytic asymmetric transformations.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) CCDC−619170 (chiral ligand **7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

(16) We initially employed Jørgensen's original reaction conditions (ref 6a). However, the use of THF gave inferior results in our case, presumably due to the heterogeneous nature of the reaction in this solvent.

(17) The previously prepared pyrrolidine acylsultam **17** (Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71) was saponified and then Fisher-esterified to give the *levorotary* C2-epimerized pyrrolidine triester **18**. On the other hand, treatment of cycloadduct **8** with methoxide gave the *dextrorotary* C2-epimerized pyrrolidine triester **ent-18**.