

# Diastereoselective Diels-Alder reactions. The role of the catalyst. 2<sup>1</sup>

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**To Rudy Abramovitch on the occasion of his 70<sup>th</sup> birthday**  
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## Abstract

The Diels-Alder reaction between (*R*)-(-)-methyl (*Z*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-2-propenoate **1** and cyclopentadiene in the presence of one equivalent of Et<sub>2</sub>AlCl or BF<sub>3</sub> gave stereochemical results opposite to those obtained with one equivalent of EtAlCl<sub>2</sub>, SnCl<sub>4</sub>, or TiCl<sub>4</sub>. Energy minimizations of proposed complexes of these Lewis acids with the chiral dienophile at the RHF/3-21G level suggest that whereas the former coordinate singly to the nitrogen, the latter complex to both the nitrogen and the carbonyl oxygen of the substrate. These different complexes expose diastereotopic faces of the dienophile to reaction with the diene.

**Keywords:** Catalysis, complexation, diastereoselection, Diels-Alder reactions

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## Introduction

The importance of the asymmetric Lewis acid-catalyzed Diels-Alder and hetero-Diels Alder reactions in organic synthesis has been emphasized in a number of recent reviews.<sup>2</sup> Moreover, Lewis acids are frequently effective in promoting selectivity in other processes, such as the ene,<sup>3</sup> imino ene,<sup>4</sup> Claisen,<sup>5</sup> Friedel-Crafts,<sup>6</sup> and the aldol and related<sup>7</sup> reactions. In these processes the stereochemical outcome is often linked to the intermediacy of a chiral reactant coordinated to a Lewis acid catalyst or an achiral reactant coordinated to a chiral Lewis acid catalyst. The nature of the Lewis acid and of the coordination site(s) is often unclear and no unifying conceptual model has been developed that offers predictive value for synthesis.

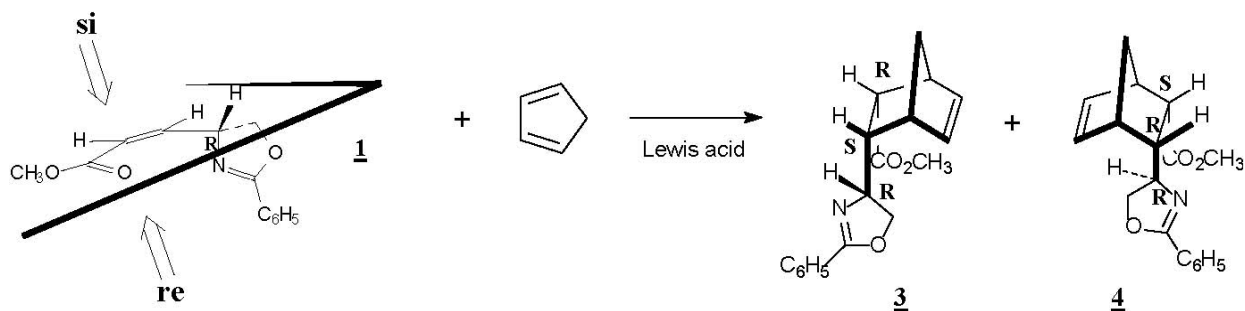
## Results and Discussion

We have been studying Lewis acid catalyzed Diels-Alder reactions of cyclopentadiene with the readily available chiral oxazoline (*R*)-(-)-methyl (*Z*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-2-

propenoate (**1**) that is prepared from (*S*)-serine<sup>8</sup> and has been employed in reaction sequences leading to polyhydroxylated pyrrolidines (azasugars).<sup>9</sup>



Configurationaly pure substances such as **1** and the related Garner aldehyde **2**<sup>10</sup> exemplify the utility of natural  $\alpha$ -aminoacids for generating stereochemically defined structures suitable for incorporation into the design of synthetic targets or as agents by which asymmetry may be induced into intermediates. In this vein, we recently reported<sup>1</sup> that Et<sub>2</sub>AlCl-catalyzed reaction of **1** with cyclopentadiene led to a mixture of *endo* diastomeric adducts **3** and **4** in which the former, the product of  $\alpha$ -*re*-face addition, predominated (88:12). Strikingly, catalysis of the same reaction by EtAlCl<sub>2</sub> resulted in the product of  $\alpha$ -*si*-face addition preferentially leading to **4** (98:2). We now report a more comprehensive evaluation of this reaction with a number of common Lewis acids and computations which allow us to suggest that the diastereoselectivity may be predicted.



## Equation

Reactions of **1** with 1.0 equivalent of Lewis acid (Table 1) were conducted in dichloromethane with excess cyclopentadiene over a 24 h period (-78 °C to rt). The ratios of **3:4** were determined by HPLC and an X-ray crystal structure was obtained for **4**.<sup>1</sup>

**Table 1.** Reactions of Cyclopentadiene with **1** and Lewis Acid Catalysts

Lewis acid Catalyst	Equiv.	3:4	Yield (%) [3+4]
Et <sub>2</sub> AlCl	1.0	88:12	58
BF <sub>3</sub> .Et <sub>2</sub> O	1.0	78:22	54
Cu(OTf) <sub>2</sub>	1.0	60:40	46
SnCl <sub>2</sub>	1.0	30:70	32
SnCl <sub>4</sub>	1.0	12:88	58
EtAlCl <sub>2</sub>	1.0	2:98	50
EtAlCl <sub>2</sub>	1.4	53:47	50
TiCl <sub>4</sub>	1.0	2:98	69

Calculations (at the RHF/3-21G level) to optimize the geometry of the presumed complexes of the Lewis acids evidencing a strong preference for one or the other diastereomer, *viz.* Et<sub>2</sub>AlCl, BF<sub>3</sub>, SnCl<sub>4</sub>, EtAlCl<sub>2</sub> (1 equiv.) and TiCl<sub>4</sub> were carried out.<sup>11</sup> Chelates of **1** with the Lewis acid at **each** of its three potential complexation sites, *i.e.*, (1) the carbonyl oxygen and the (2) nitrogen and (3) oxygen of the oxazoline ring, singly and the carbonyl oxygen and either the nitrogen or the oxygen of the oxazoline ring, simultaneously, were evaluated. Representative results are given in **Table II**.

The results suggest that singly associated complexes involve only nitrogen (free carbonyl *s-trans*) as shown in the **Equation** and reaction at the  $\alpha$ -*re*-face yielding **3**. A chelated structure incorporating nitrogen and carbonyl oxygen, markedly encumbers the  $\alpha$ -*re*-face and leads to preferential reaction at the  $\alpha$ -*si*-face, producing **4**.

**Table 2.** A portion of the computational data for the coordination of Lewis acids with dienophile **1**

Lewis Acid	Ligand	RHF/3-21G* Energy (hartrees)	Relative energy (kcal/mol)
BF <sub>3</sub>	Oxazoline Nitrogen	<b>-1096.0841832</b>	
	Carbonyl Oxygen	-1096.0576942	
Et <sub>2</sub> AlCl	Carbonyl Oxygen	-1629.0180563	+4.0
	Oxazoline Nitrogen	<b>-1629.0243769</b>	0.0
	Both <sup>a</sup>	-1629.0190743	+3.3
EtAlCl <sub>2</sub>	Carbonyl Oxygen	-2008.1896094	+6.9
	Oxazoline Nitrogen	-2008.1779852	+14.2
	Both <sup>a</sup>	<b>-2008.2005357</b>	0.0
TiCl <sub>4</sub> <sup>b</sup>	Both <sup>a</sup>	<b>-3448.3851464</b>	

**Table 2.** Continued

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SnCl <sub>4</sub> <sup>c</sup>	Both <sup>a</sup>	<b>-8601.2114019</b>
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<sup>a</sup> The initial PM3 construction began with coordination to the carbonyl oxygen and the oxazoline nitrogen. <sup>b</sup> PM3 structures for single associations to give pentacoordinated Ti species ranged from -547 to -560 kcal/mol; the hexacoordinated structure was -562 kcal/mol. <sup>c</sup> PM3 energies for SnCl<sub>2</sub> were -132.3 kcal/mol (square planar) and -131.4 kcal/mol (tetrahedral).

It is of particular note that the basic imine nitrogen of **I** renders this dienophile unique. We attempted to evaluate possible involvement of a pentacoordinate aluminum species in order to rationalize the dramatically opposite diastereoselectivity of Et<sub>2</sub>AlCl versus EtAlCl<sub>2</sub>. Hexa- and pentacoordinate species have been identified by x-ray crystallography in some systems,<sup>12</sup> and reasonably invoked in others.<sup>13</sup> Importantly, additional EtAlCl<sub>2</sub> in this reaction produced a lowered diastereoselectivity. If the observed *si*-face preference had been due to a tetrahedral aluminum chelate (a positively charged species) with a second equivalent of Lewis acid employed to accept a chloride and act as a counterion, then additional Lewis acid would have been expected to increase the diastereoselectivity.<sup>14</sup> The decrease in diastereoselection that is observed when excess EtAlCl<sub>2</sub> is used is consistent with the intermediacy of a chelate in which the aluminum is pentacoordinate and the excess Lewis acid complexes to produce a species with essentially the same facial selectivity as that formed from Et<sub>2</sub>AlCl.

**Table 3.** Reactions of cyclopentadiene with dienophiles having two or more basic sites to coordinate with EtAlCl<sub>2</sub>

Entry	Dienophile	Lewis Acid	7:8	Ref.
1	 R=H	TiCl <sub>4</sub> EtAlCl <sub>2</sub>	93:7 33:67	15a
2	 R=H	TiCl <sub>4</sub> EtAlCl <sub>2</sub> BF <sub>3</sub>	5:95 90:10 84:16	15b
3	 R=H	EtAlCl <sub>2</sub>	96:4	15c
4	 R=	Et <sub>2</sub> AlCl EtAlCl <sub>2</sub> none	1:19 1:27 1:14	15d

<sup>a</sup>Indicates calculated position of coordination for EtAlCl<sub>2</sub>

A number of examples of asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by EtAlCl<sub>2</sub> that involve dienophiles bearing more than a single Lewis base site have been reported (**Table III**). The results indicated that EtAlCl<sub>2</sub>, Et<sub>2</sub>AlCl, and BF<sub>3</sub> coordinate to a single Lewis base site in the relevant dienophiles, while TiCl<sub>4</sub> probably coordinates as a chelate and produces opposite diastereoselection. Geometry optimizations at the RHF/3-21G level were performed by us for various possible coordinations of EtAlCl<sub>2</sub> with the dienophiles listed in entries 1-3; extensive computations had already been reported for entry 4.<sup>15e</sup> The lowest energy complexes

with EtAlCl<sub>2</sub> for each dienophile involved a single association with a carbonyl as indicated in **Table III**. Although these complexes are flexible and suggest only modest diastereoselectivity, chelated structures would have favored formation of the other diastereomers as in the case of TiCl<sub>4</sub>; the computations are consistent with experiment. Therefore, the profound reversal of stereoselectivity observed with EtAlCl<sub>2</sub> versus Et<sub>2</sub>AlCl and dienophile **1**, we ascribe to the previously unobserved effect of a coordinating nitrogen atom that may favor formation of a pentacoordinated structure in the case of EtAlCl<sub>2</sub>.

The results presented here suggest that: (1) diastereoselectivity of Lewis acid catalyzed reactions can hinge critically upon the nature of the coordinating sites present in the reactant, (2) diastereoselectivity can be altered not only by using different Lewis acid catalysts but also by changing the achiral ligands present on the metal atom, and (3) the profound reversal of the stereoselectivity observed with a change of Lewis acid from Et<sub>2</sub>AlCl to EtAlCl<sub>2</sub> in the reaction of butadiene with **1** may be attributed to the previously unobserved effect of a coordinating nitrogen atom that favors a pentacoordinated structure for EtAlCl<sub>2</sub>.

## References and Notes

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