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Diastereoselective Diels–Alder reactions. The role of the catalyst

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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_2AlCl gave stereochemical results opposite to those obtained with one equivalent of $EtAlCl_2$. Energy minimizations of proposed complexes of these Lewis acids with the chiral dienophile at the RHF/3–21G level suggest that the aluminum is tetrahedrally complexed with Et_2AlCl, but bound in a trigonal bipyramid with $EtAlCl_2$. These complexes expose the diastereotopic faces of the dienophile to reaction with diene. © 2000 Elsevier Science Ltd. All rights reserved.

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The utility of Lewis acid catalyzed Diels–Alder reactions for the synthesis of natural products, many of which are chiral, has been repeatedly demonstrated.[1] The clear value of this synthetic tool has prompted studies of asymmetric induction using chiral dienes[2] as well as Lewis acids complexed with chiral auxiliaries[3] or with chiral dienophiles.[4] However it does not appear to have been explicitly recognized that the role of the *achiral* Lewis acid may specifically dictate the stereochemical outcome of the reaction in which it is employed.

The chiral oxazoline (*R*)-(−)-methyl (*Z*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-2-propenoate (**1**) is readily prepared from (*S*)-serine[5] and has been employed in reaction sequences leading to polyhydroxylated pyrrolidines (azasugars).[6] We examined the reaction of **1** as a chiral dienophile with cyclopentadiene using both diethylaluminum chloride (Et_2AlCl) and ethylaluminum dichloride ($EtAlCl_2$); these Lewis acids produced dramatically different and opposite diastereomeric ratios of the *endo*-adducts **2** and **3** (Scheme 1).

Reaction of **1** with one equivalent of diethylaluminum chloride in dichloromethane and an excess of cyclopentadiene over a 24 h period (−78°C→room temperature) produced a 88:12 mixture of **2**:**3** in 58% yield (77% conversion) while, under the same conditions, the use of ethylaluminum dichloride

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[†] Details of the X-ray crystal structure may be obtained from this author. Refined coordinates and bond distances have been deposited at the Cambridge Crystallographic Data Center.

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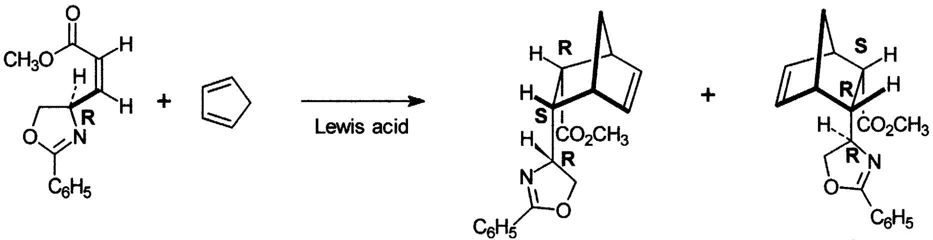

1 **2** **3**

Scheme 1.

yielded a 2:98 mixture in 50% yield (63% conversion).[7] Compounds **2** and **3** were the only detectable Diels–Alder products of these reactions; *exo*-products were not observed. Compound **2** was an oil, but **3** was crystalline and its structure was determined as shown below (Fig. 1).

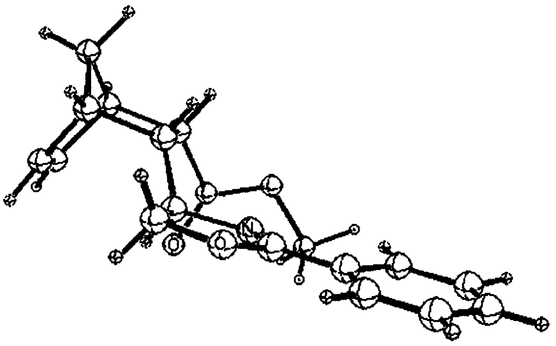

Fig. 1. A representation of the X-ray structure determined for the crystalline diastereomer **3**

Although there are some cases in which pentacoordinate aluminum species, bound as trigonal bipyramids, have been used to account for observed diastereoselectivity[1,8] the sense of asymmetric induction in Diels–Alder reactions involving aluminum complexes of carbonyl containing dienophiles has generally been consistent with the view that the aluminum is bound (in a complex which is tetrahedral at aluminum) to the carbonyl oxygen. This view appears to have been accepted both for cases (a) where there is only a single site at which complexation might occur[9] as well as (b) those where the association with Lewis acid resulting in additional bonding to the metal, e.g. pentacoordinate aluminum, might have been invoked.[4,10]

The experimental observations reported above are inconsistent with the different Lewis acids forming similar complexes. Therefore, sets of tetrahedral and trigonal bipyramidal complexes of **1** with diethylaluminum chloride and ethylaluminum dichloride formed by ligating (a) to the carbonyl oxygen, (b) the carbonyl oxygen and the oxazoline nitrogen, and (c) the oxazoline nitrogen were all evaluated at the RHF/3–21G level.[11] The results of these minimizations have provided a conceptual basis for the very different diastereoselections obtained experimentally. As shown below for the evaluated sets, the lowest energy structure obtained for a complex of diethylaluminum chloride with **1** was tetrahedral at aluminum and involved a single association of the aluminum with the nitrogen of the oxazoline ring (Fig. 2). However, the lowest energy complex of **1** with ethylaluminum dichloride was a trigonal bipyramid in which the oxazoline nitrogen and the carbonyl oxygen were associated with aluminum equatorially and the two chlorines were axial (Fig. 3). The structures shown below were obtained from the calculations, and have been oriented to indicate that the upper face of the alkene is more exposed to reaction with cyclopentadiene.

Lewis Acid	Ligand	RHF/3-21G* Energy (hartrees)	Relative energy (kcal/mol)
Et_2AlCl	Carbonyl Oxygen	-1629.0116445	+8.0
	Oxazoline Nitrogen	-1629.0243769	0.0
	Both	-1629.0190743	+3.3
$EtAlCl_2$	Carbonyl Oxygen	-2008.1788406	+13.6
	Oxazoline Nitrogen	-2008.1779852	+14.2
	Both	-2008.2005357	0.0

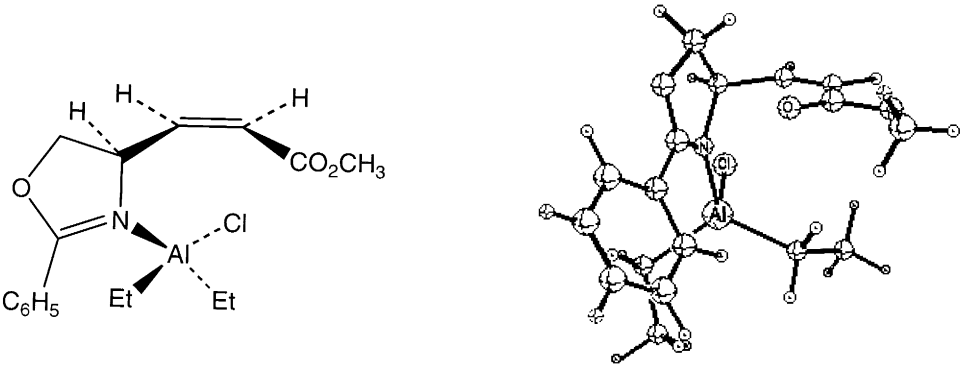

Fig. 2. The RHF/3–21 minimized structure of **1** complexed with diethylaluminum chloride

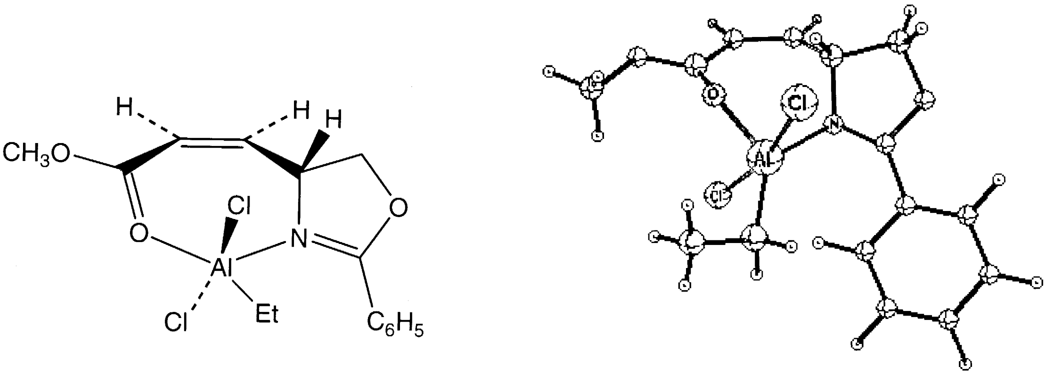

Fig. 3. The RHF/3–21 minimized structure of **1** complexed with ethylaluminum dichloride

While *sp*^{2} hybridized nitrogen is expected to be more basic than *sp*^{2} oxygen and (at least in the gas phase) *sp*^{3} hybridized oxygen,[12] steric effects at the less encumbered carbonyl group might have led to an assumption of preferential oxygen complexation for both Lewis acids at that site. Nonetheless, it is clear that the minimum energy complex of **1** (at the level of computation examined) with diethylaluminum chloride (shown above) should lead to the noncrystalline diastereomer **2** while the different minimum energy complex with ethylaluminum dichloride preferentially produces the crystalline isomer **3**.

Although pentacoordinate complexes of aluminum have been considered in order to explain experimental observations[1,13] and crystallographic studies have identified penta- and hexacoordinated aluminum species,[14,15] the evidence for pentacoordination of aluminum during reactions is limited and the application of calculations that support such extended coordination for aluminum in the Diels–Alder reaction are without precedent.

It is therefore intriguing to speculate, as suggested by the calculations reported here, that coordination number may shift solely as a result of (apparently innocuous) substitution and that this might be utilized in planning more elaborate syntheses.

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