Lewis Acid Catalyzed Diels-Alder Additions of Cyclopentadiene to Methyl *(E)*- and *(Z)*-*(S)*-4,5-di-*O*-isopropylidenepent-2-enoates: Rate and Stereoselectivity.

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Abstract. Rate, and endo/exo and facial diastereostereoselectivity of the title reactions have been highly enhanced under the action of aluminum, among other metals used as catalysts, compared to the thermal processes. EtAlCl$_2$ and Et$_2$AlCl were the reagents that afforded the best results.
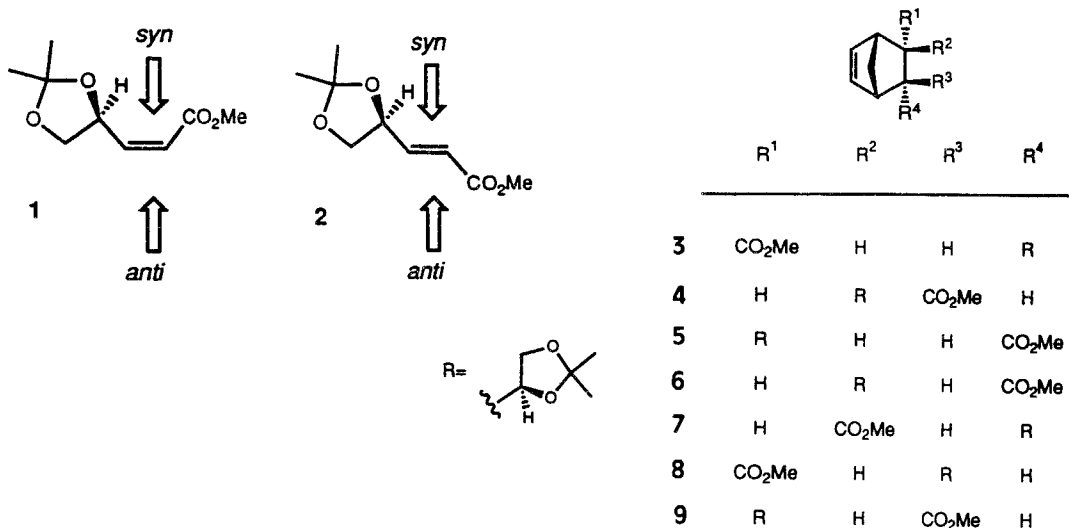
INTRODUCTION

The great influence of Lewis acid catalysts on the rates and both regiochemical and stereochemical selectivities of Diels-Alder reactions[1] has been largely exploited in asymmetric synthesis.[2] Recent studies on the reactions of optically active dienophiles,[2] dienes,[2] and catalysts[3] highlight its importance.

We have recently reported that methyl (S)-(Z)-4,5-di-O-isopropylidene-pent-2-enoate 1[4] reacts with excess cyclopentadiene at 80 °C for 8 hours to afford a mixture of the stereoisomeric adducts 3-5 in 94% yield, in which 3 was the major product. In a similar manner, the (E)-enoate 2[4] was reacted with excess cyclopentadiene affording a mixture of the four possible diastereoisomers with predominance of the (syn-exo)-adduct (60% relative ratio). (See Chart I, and entries 1 and 9 in Table 1). These compounds result from a preferred (syn)-face orientation of the dienophile towards cyclopentadiene.[5] Furthermore, a theoretical study was made to rationalize the observed facial selectivity, showing the influence that electronic and steric factors exert over the geometry of the transition states leading to the major isomers in each case.

In an extension of this work, and bearing in mind the valuable synthe-tic potential of polyfunctional chiral norbornene derivatives, we present our results on these reactions carried out under the catalysis of several Lewis— acid complexes. The influence of the catalysts, both on the rate and

on the diastereoselection of the additions, was studied with respect to the
nature of the utilized metal and the accompanying ligands.

Chart I

	R^1	R^2	R^3	R^4
3	CO$_2$Me	H	H	R
4	H	R	CO$_2$Me	H
5	R	H	H	CO$_2$Me
6	H	R	H	CO$_2$Me
7	H	CO$_2$Me	H	R
8	CO$_2$Me	H	R	H
9	R	H	CO$_2$Me	H

RESULTS AND DISCUSSION

The experiments were performed on (5-10):1 mixtures of cyclopentadiene
and pentenoate **1** or **2** in an appropriate solvent which was dichloromethane
in most of cases. Concentration of the dienophile was in the range 0.2-0.4
M. Table 1 shows the reaction conditions and the results of selected
experiments. Reactions were monitored by G.L.C.; the ratio of isomers and
total yields were determined through calibration curves made from the pure
isolated isomers and with 4-chloroacetophenone as internal standard.
Several commonly used catalysts, listed in Table 1, were chosen to carry
out this study.

No reaction was observed when insoluble ZnCl$_2$ was used, and yields
were very poor when the cycloadditions were carried out in the presence of
t-BuMe$_2$SiOTf or TiCl$_4$. In these two last cases most of the starting
dienophile was recovered, while the diene polymerized. Higher
concentrations of catalyst impeded the dienophile-catalyst complex
formation, with the solutions becoming very viscous, resulting in much
polymerization and small amounts of adducts being obtained. Moreover, the
solution boiled and the reactants carbonized when 0.3 eq of t-

Table 1. Lewis acid catalyzed reactions between enoates **1** and **2**, and cyclopentadiene.[a]

Entry	Ester[b]	Catalyst	Equiv.[c]	Temp.[d]	Time[e]	Ratio[f] endo/exo 3+5/4	Ratio[f] syn/anti 3+4/5	% Yield[f]
1	1	----	--	80	8	6	14	94
2	1	$ZnCl_2$	0.06	50	16	---	---	--
3	1	$t\text{-}BuMe_2SiOTf$	0.02	r.t.	53	--[g]	--[g]	8
4	1	$TiCl_4$	0.2	-23	9.5	---	---	traces
5	1	Cp_2TiCl_2	0.4	60	23	9	14	92
6	1	Et_3Al	1.1	-23	10	37	17	69
7	1	Et_2AlCl	1.1	-23	2.7	38	19	91
8	1	$EtAlCl_2$	0.8	-23	1.5	37	27	84
9	2	----	--	80	8	0.5	6	95
10	2	Et_2AlCl	1.1	-23	2.5	3	--[h]	95

[a] 5-10 Mol of diene per mol of dienophile was used. [b] 0.2 M Solution in dichloromethane but in toluene in entry 5. [c] Respect to the dienophile. [d] °C. [e] Hours. [f] Determined by GLC. [g] Only **3** was detected. [h] Only syn-adducts were detected.

$BuMe_2SiOTf$ was used.

In contrast, the organometallic compounds Cp_2TiCl_2 and particularly Et_2AlCl afforded better results, giving adducts in good yields, with enhanced diastereoselection with respect to the uncatalyzed cycloaddition (Table 1, entry 7). Et_2AlCl is a mild catalyst with a moderate Lewis acid strength, which has been widely used in Diels-Alder reactions.[6,7b,8,9]

In these two cases, the uniformity of the ratios of the endo/exo adducts **3+5/4**, as well as the syn/anti diastereoisomers, **3+4/5**, was verified throughout the process, proving that interconversion between these isomers does not occur under the reaction conditions. The kinetic curves show that the addition catalyzed by Cp_2TiCl_2 proceeds smoothly and slowly, while Et_2AlCl displays higher catalytic activities (Fig. 1). Indeed the latter catalyst resulted in the reaction going effectively to completion in only 3.5 hours at -23 °C. Longer reaction

times and higher temperatures were needed to obtain similar results when using Cp_2TiCl_2. On the other hand, part of this reagent remained insoluble when increasing the number of equivalents. Toluene was better solvent than dichloromethane in this case.
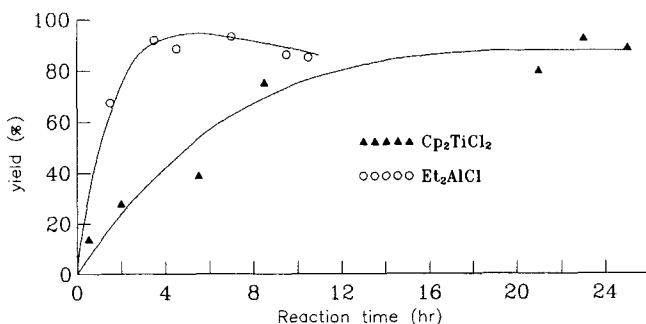

Fig. 1 . Reaction of methyl $(S)-(Z)-4,5-di-O-$isopropylidenepent-2-enoate with 10 equiv. of cyclopentadiene in the presence of the shown catalysts (experimental conditions listed in Table 1).

In a second step, we realized a comparative study of the Diels-Alder reaction of cyclopentadiene and ester **2** catalyzed by the soluble organoaluminum complexes Et_3Al, Et_2AlCl and $EtAlCl_2$, respectively. The use of $AlCl_3$ was avoided owing to its insolubility in the organic reaction medium and to its strong acidity which promotes much polymerization.

The results obtained are summarized in Table 1 and in Fig. 2, and show that catalytic activity follows the order $EtAlCl_2$ > Et_2AlCl > $AlEt_3$, which agrees with other aluminum mediated Diels-Alder reactions. This is also the
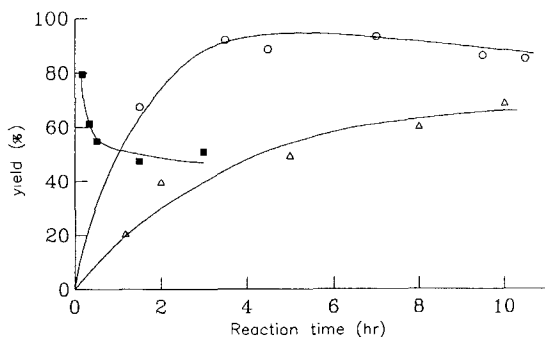

Fig. **2**. Reaction of methyl $(S)-(Z)-4,5-di-O-$isopropylidene-pent-2-enoate with excess of cylopentadiene in the presence of organoaluminum catalysts, 1.1 equiv. ; -23 °C ; CH_2Cl_2.

▵▵▵▵▵ : **Et₃Al**;   ○○○○○ : **Et₂AlCl**;   ■■■■■ : **EtAlCl₂** ;
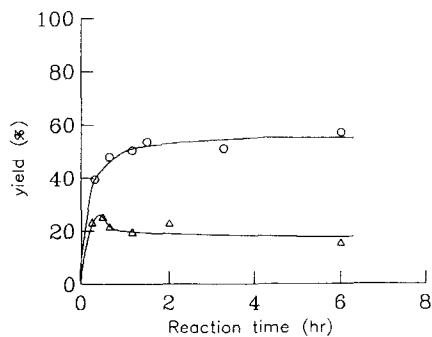

Fig. **3**. Reaction of methyl $(S)-(Z)-4,5-di-O-$isopropylidenepent-2-enoate with 1 equivalent of cyclopentadiene in the presence of $EtAlCl_2$, 0.2 M in CH_2Cl_2, at -23 °C

○○○○○ : [dienoph.] = [diene] = 0.1 M

▵▵▵▵▵ : [dienoph.] = [diene] = 0.7 M

same order as that assumed for the relative Lewis acidity of these complexes.[5]

Effectively, $EtAlCl_2$ produces the highest enhancement of rate and diastereoselection of the studied reaction. Nevertheless, Fig. 2 shows that this cycloaddition proceeds very quickly in the presence of 1.1 eq of $EtAlCl_2$ but concentration of the cycloadducts produced decreases rapidly before completion. The following experiments were made to verify the influence of the quantity of diene and of catalyst on the optimal reaction conditions. The diene and the dienophile were reacted at the same molar ratio in 0.1 and 0.7 M solutions, respectively, concentration of catalyst being 0.2 M in both cases. Fig. 3 shows that higher reactant concentration (deficiency of catalyst) induces a lot of competing polymerization, a better result being obtained working in a more diluted solution (excess of catalyst), although the total yield did not reach 55% (Fig. 3). Therefore, it seemd that excess diene was necessary to achieve good yields. Consequently, the reaction was actually realized by using a 1:5 molar ratio of dienophile-diene in the presence of deficiency of catalyst. Fig. 4 shows that the use of 0.8 eq of $EtAlCl_2$ provides the best extent of conversion into adducts, which remain unaltered for several hours under these reaction conditions.
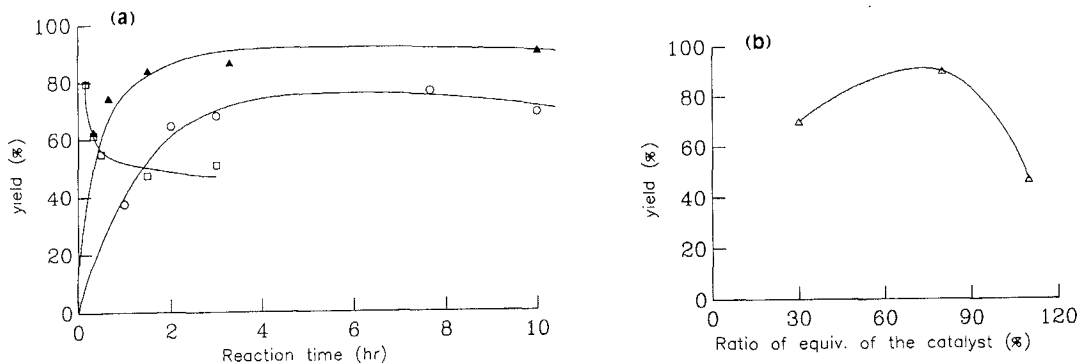

Fig. **4**. Reaction of methyl–(S)–(Z)–4,5–di–O–isopropylidene–pent–2–enoate with excess of cyclopentadiene in the presence of different ratio of $EtAlCl_2$, −23 °C, CH_2Cl_2.

(a) ooooo : 0.3 equiv.   (b) △△△△△ · % Yield vs nª equiv. of the catalytst
    ▲▲▲▲▲ : 0.8 equiv.   after 3 h. reaction time.
    ooooo : 1.1 equiv.

Endo-stereoselectivity has been highly enhanced in the aluminum promoted reactions studied herein, with the ratio ef endo/exo adducts being very insensitive to the nature of the different ligands (Compare entries 6–

8 in Table 1). However, although augmentation of endo-selectivity under Lewis acid catalysis is well known,[1a,1d-e,7] much less atention has been paid to improvement of face-diastereoselection in catalyzed Diels-Alder cycloadditions.[8]

In our case, despite the fact that the observed syn-specifity has been increased to a lesser extent than endo-selection, an important improvement was observed with respect to the thermal process, when using Et_2AlCl and $EtAlCl_2$, but it was found to be the same under the action of Cp_2TiCl_2 (Compare entry 1 with entries 7, 8 and 5 in Table 1). These results show than neither titanium nor aluminum act as chelating agents[9] by coordination to both the carbonyl and a dioxolane oxygen atom, giving cyclic complexes which should favour the anti-face orientation (Fig. 5 (a)). Instead, the active conformer must correspond to a non-chelated complex such as described in Fig. 5 (b), in which 1 is attacked at the less shielded face, leading preferentially to syn-adducts. Theoretical investigations on the nature and on the geometry of the catalyst-dienophile complexes in the ground and in the transition state are being carried out in our laboratory in order to explain these experimental findings.
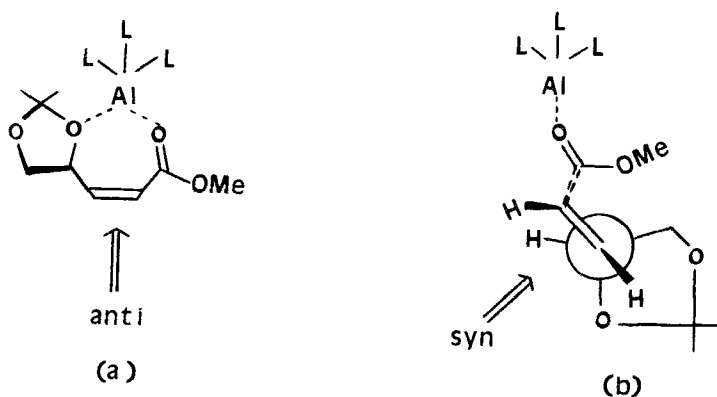

Fig. 5. Chelated (a) and non-chelated (b) models for the aluminum-ester 1 complex, showing in each case the most favourable face orientation to the diene.

In summary, both $EtAlCl_2$ and Et_2AlCl have proved to be good catalysts to achieve the Diels-Alder cycloaddition of chiral enoate 1 and cyclopentadiene. On the other hand, the catalytic activity of these aluminum reagents is not very different and, although the former induces better syn-diastereoselection, the easier manipulation of Et_2AlCl makes it more convenient for practical synthetic purposes when working on a large scale.

The Diels-Alder cycloaddition of the (E)-enoate 2 and cyclopentadiene

performed in the presence of Et_2AlCl was also studied.   Takano et al.[10] have reported the Et_2AlCl-catalyzed reaction of cyclopentadiene and the ethyl ester–derivative of the same (E)-pentenoic acid as ester 2, giving a 3:1 mixture of 6 and 7, with complete face-diastereoselection. A similar result has been obtained in our case, as expected, when 2 was reacted with 5 mol of cyclopentadiene and 1.1 mol of Et_2AlCl at -23 °C for 2.5 h. (Table 1, entry 10). Fig. 6 shows the kinetic curves for this reaction. It is noteworthy that in this case, facial selectivity has been enhanced, and endo/exo selectivity has been not only improved but reversed, since the endo isomer 6 is actually the major product in contrast with the result of thermal reaction, from which the exo-adduct 7 was predominant.
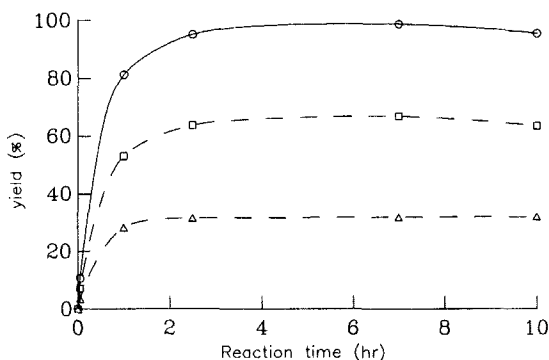

Fig. 6. Reaction of methyl–(S)–(E)–4,5–di–O–isopropylidene–pent–2–enoate with 5 equiv. of cyclopentadiene in the presence of 1.1 equiv. of Et_2AlCl,–23 °C, CH_2Cl_2.

ᴑᴑᴑᴑᴑ total yield;   ᴐᴐᴐᴐᴐ endo 6;   ᴧᴧᴧᴧᴧ exo 7.

Detailed kinetics as well as a theoretical study on these reactions are being carried out, and results will be published in a near future.

EXPERIMENTAL SECTION

General Procedures for Thermal Diels–Alder Cycloadditions. The reactions and their workup followed a previous description,[5] and the conditions are detailed in Table 1.
    Full characterization of the adducts obtained has been reported in previous works.[5]

General Procedures for Catalyzed Diels–Alder Cycloadditions. All manipulations of air-sensitive compounds were carried out by use of standard Schlenk techniques. All solvents were treated under nitrogen. Dichloromethane was distilled from calcium hydride, and toluene was

distilled from sodium. Cyclopentadiene was cracked from the dimer and used
freshly distilled. Catalysts were obtained from commercial sources.

Reactions were performed in glass reactors fitted with septum
containing teflon-stoppers. Table 1 shows the ratio catalyst-dienophile,
solvent, reaction temperature and time conditions, ratio of isomeric
adducts, and yield for each experiment.

A typical experiment (Table 1, entry 7) was run as follows: Et_2AlCl in
hexane (1.1 mL of a 1M solution) was added to a solution of ester 1 (1
mmol) in 5 ml of dichloromethane. The mixture was stirred at -23 $^{\circ}$C for 0.5
h. Then cyclopentadiene (5 mmol) was added and the resulting solution was
stirred at -23 $^{\circ}$C for 2.7 h. For analysis a standard hexane solution of
internal standard p-chloroacetophenone was poured into ice-10% aqueous
sodium bicarbonate and an aliquot of the reaction mixture (at different
times) added. The layers were separated and the aqueous phase was extracted
with dichloromethane. The combined extracts were dried and evaporated. The
residue was injected into the gas chromatograph, furnished with a capillary
column (crosslinked methyl silicone gum, 12 m x 0.2 mm x 0.3 μm). Condi-
tions: 130 $^{\circ}$C initial temp.; 190 $^{\circ}$C injector temp.; 240 $^{\circ}$C detector temp.

Quantitative determination of stereoisomer-ratios, and yields of
conversion were realized by using correction factors which were calculated
from calibration curves. These were made from the starting dienophiles and
from the pure isolated adducts.

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