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Lewis Acid Catalyzed Diels-Alder Cycloadditions of Chiral Butenolides to Cyclopentadiene: *endo/exo* Stereoselectivity.

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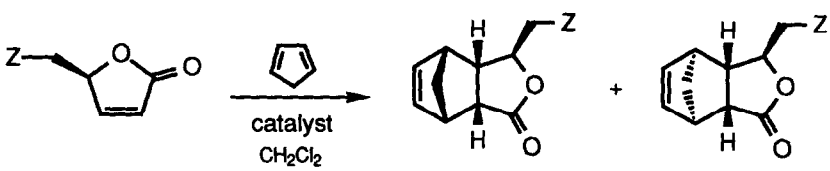
Abstract. *The influence of several Lewis acids as catalysts in the Diels-Alder cycloadditions of cyclopentadiene to (R)-β-angelica lactone, **1**, and (S)-5-hydroxymethyl-2(5H)-furanone, **2**, respectively, have been investigated. The best results have been provided by the pair $ZnCl_2/EtAlCl_2$ for **1** and by ZnI_2 for dienophile **2**, enhancing significantly the rate and the stereoselectivity of these reactions and affording the corresponding endo adducts in 80-90% yields.*

INTRODUCTION

Chiral butenolides (2(5*H*)-furanones) have been used as dienophiles in Diels-Alder cycloadditions to generate adducts in a stereoselective manner. These molecules are important building blocks in the synthesis of a variety of products,[1] and in particular the addition to cyclopentadiene affords polyfunctional norbornene derivatives which can be employed to prepare santalene,[1c] thromboxane antagonists,[1e,f] and carbocyclic nucleosides[1g] among other interesting compounds.

In our laboratory we have studied the reactions between cyclopentadiene and several chiral butenolides, such as **1** and **2**. We reported a few years ago that these dienophiles react with cyclopentadiene at 100-110 °C for 20 hours to afford mixtures of *endo/exo* adducts in 50-80% yields.[2] *endo* Adducts were always the major products and we showed that the ratio of the stereoisomers produced in each case is temperature dependent, not as a result of a thermodynamic equilibrium but due to a kinetically controlled process. On the other hand, facial diastereoselectivity is excellent since only *anti* adducts were detected. (Scheme 1).



anti-endo *anti-exo*

1	Z = H	**4a**	**4b**
2	OH	**5a**	**5b**
3	$OSiPh_2t$-Bu		

Scheme 1

Obtaining single stereoisomers in high yields is a crucial feature for synthetic purposes. We later investigated, therefore, the use of Lewis acids as catalysts in such cycloadditions in order to improve the *endo/exo* stereoselectivity and also to find milder conditions to avoid the formation of by-products induced by the high temperatures required to achieve the uncatalyzed reactions.

In this paper we report the results obtained from the study on the catalyzed Diels-Alder reactions between cyclopentadiene and (*R*)-β–angelica lactone, **1**,[3] and (*S*)-5-hydroxymethyl-2(5*H*)-furanone, **2**,[4] respectively, as different examples of chiral butenolides. Dienophile **2** is a very useful synthon[1] but pyrolytic elimination of water in the thermal reaction conditions leads to the formation of 5-methylen-2(5*H*)-furanone which in turn evolves towards other compounds, thus lowering the yield in the expected adducts.[5] The catalytic activity of aluminum and zinc has been explored as well as the influence exerted by the nature of the accompanying halide in the later case.

RESULTS AND DISCUSSION

A selection of the performed experiments and the results obtained are listed in Table 1. Reactions were carried out on (10-15):1 mixtures of the diene and butenolide **1** or **2** in dichloromethane and were monitored by GLC for dienophile **1** and by HPLC for dienophile **2**.

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

Entry	Butenolide	Catalyst	Equiv	Temp °C	Time h	Adducts	Yield %	*endo/exo* Ratio[b]	*endo* % Yield
1	**1**	----	----	110	20	**4a/4b**	90[c]	3	67
2	**1**	$EtAlCl_2$	0.8	-23	85	**4a/4b**	75[d]	10	71
3	**1**	$ZnCl_2/EtAlCl_2$	0.1/0.3	20	8	**4a/4b**	95[d]	6	82
4	**2**	----	----	100	22	**5a/5b**	60[c]	4	48
5	**2**	$ZnCl_2/EtAlCl_2$	0.4/0.2	20	21	**5a/5b**	72[d]	11	66
6	**2**	ZnF_2	0.5	35	118	**5a/5b**	78[e]	6	67
7	**2**	$ZnCl_2$	0.5	35	8	**5a/5b**	55[e]	15	51
8	**2**	$ZnBr_2$	0.5	35	7	**5a/5b**	72[e]	10	66
9	**2**	ZnI_2	0.5	15	21	**5a/5b**	95[c]	10	87

[a] 10-15 Mol of diene per mol of dienophile was used. [b] Determined by GLC for **4a/4b** and by HPLC for **5a/5b**. [c] Isolated yield. [d] Determined by GLC. [e] Determined by HPLC

$EtAlCl_2$ and zinc halides were used as catalysts. The ratio of isomers and total yields were determined through calibration curves made from the pure isolated isomers; 4-chloroacetophenone was used as internal standard in GLC determinations, and the external method was used in HPLC. In all cases, the uniformity of the ratios of *endo/exo* adducts was verified throughout the process, proving that interconversion between the

isomers does not occur under the reaction conditions. Optical purity of adducts was verified by comparison with the same compounds obtained through uncatalyzed processes, which had previously been characterized.[2]

There are scarce precedents on the use of Lewis acids to catalyze the Diels-Alder cycloadditions of chiral butenolides. One instance is the earlier described reaction between butenolide **3** (Scheme 1) and butadiene catalyzed by $AlCl_3$ and carried out at 55 °C for one week, to afford the expected *anti* adduct in good yield.[6]

We have recently published that $EtAlCl_2$ is a good catalyst which enhances highly both facial and *endo/exo* stereoselectivity in the Diels-Alder reactions of cyclopentadiene to some chiral pentenoates, being achieved at -23 °C for 1.5 hours.[7] For this reason we tried first the cycloaddition of butenolide **1** to cyclopentadiene in similar conditions (entry 2). *endo/exo* Stereoselectivity was improved more than three-fold with respect to that observed in the uncatalyzed reaction (entry 1). However, butenolides are dienophiles less active than the related open-chain esters and need longer reaction times to produce adducts in good yields. Moreover, the instability of the catalyst used at the rather high concentration necessitates low temperatures and in these conditions the reaction was very slow.

The use of the combined couple $ZnCl_2/EtAlCl_2$ has afforded good results in several rections.[8] In our case, the use of 0.1 eq of $ZnCl_2$ and 0.3 eq of $EtAlCl_2$ at 20 °C for 8 hours led to the production of the *endo* adduct **4a** in 82% yield. This yield is significantly higher than in the uncatalyzed process, and was obtained at lower temperatures for shorter reaction time (compare entries 1 and 3). Fig. 1 shows the kinetic curves for this reaction.

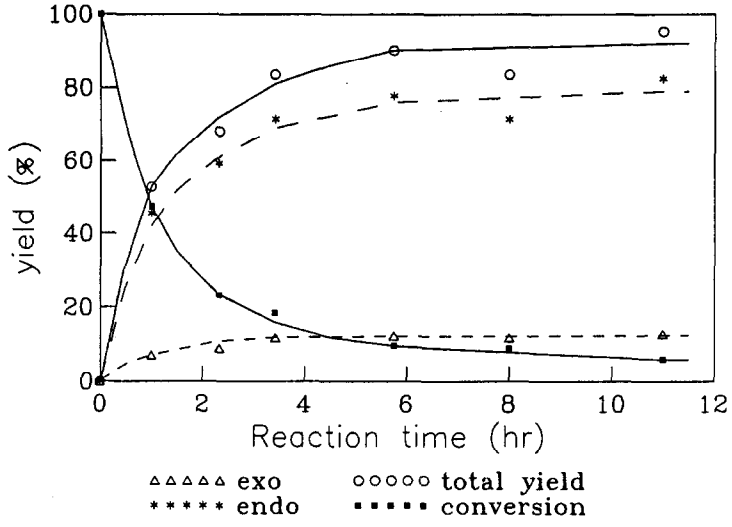


*Fig 1. Reaction of (R)-β-angelica lactone, **1**, with excess of cyclopentadiene in CH_2Cl_2 under the catalysis of 0.1/0.3 eq of $ZnCl_2/EtAlCl_2$, at 20 °C.*

In the case of butenolide **2**, the use of $ZnCl_2/EtAlCl_2$ allows the yield of the *endo* isomer **5a** to be improved with respect to the uncatalyzed cycloaddition (compare entries 4 and 5) but the results obtained in this case were less satisfactory than for butenolide **1**, owing to the competition with the above mentioned side-reaction.

Zinc halides have been shown to be good catalysts in Diels-Alder reactions,[9] and we have explored, therefore, the activity of these Lewis acids by studying the influence exerted on the rate and the selectivity of

these processes by the number of equivalents of the catalyst, the nature of the halide, and the temperature. The best conditions are summarized in Table 1, entries 6-9. ZnF_2 was the less active Lewis acid, the process requiring about five days to afford adducts in 78% yield with only a slightly enhanced stereoselectivity with respect to the uncatalayzed reaction. Better and comparable results were obtained when the other three halides were used. Although enhancement of the *endo/exo* stereoselectivity follows the order $ZnCl_2 > ZnBr_2 > ZnI_2$ (compare entries 7,8 in Table 1 and entry 1 in Table 2), ZnI_2 exhibited the greatest activity on the reaction rate, as shown in Fig 2, giving the best results when 0.5 equivalents of catalyst were used (Fig 3).

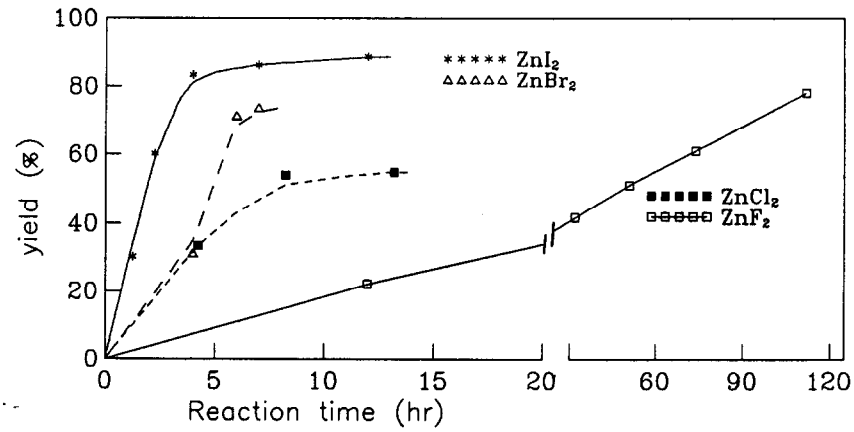


Fig 2. Reaction of (S)-5-hydroxymethylbutenolide, 2, with 15 eq of cyclopentadiene in CH_2Cl_2 in the presence of 0.5 eq of ZnX_2 (X= F, Cl, Br, I) at 35 °C

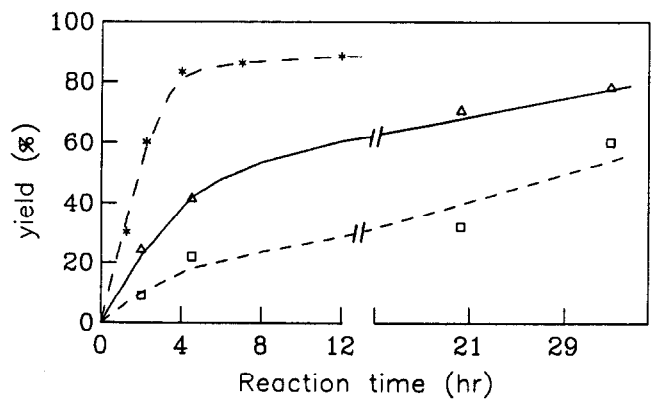


Fig 3. Influence of the number of equivalents of ZnI_2 on the reaction of butenolide 2, with excess cyclopentadiene in CH_2Cl_2 at 35 °C.

The influence of the temperature on the stereoselectivity was verified by means of the experiments listed in Table 2. *endo/exo* Ratio was higher at low temperatures, even though the reaction was much faster at 35 °C than at 15-20 °C, as expected. Moreover, the absence of interconversion of the *endo-exo* adducts was verified throughout the process as shown in Fig 4.

Table 2. Influence of the temperature on the *endo/exo* stereoselectivity and on the product yield in the ZnI_2 catalyzed reaction between **2** and cyclopentadiene.[a]

Entry	Temperature (°C)	Time (h)	% Yield[b]	*endo/ exo* Ratio[b]
1	35	4	83	7
2	20	21	84	11
3	15	21	93	10

[a] All reactions were performed by using 0.5 mol of catalyst and 15 mol of diene per mol of dienophile. [b] Determined by HPLC.

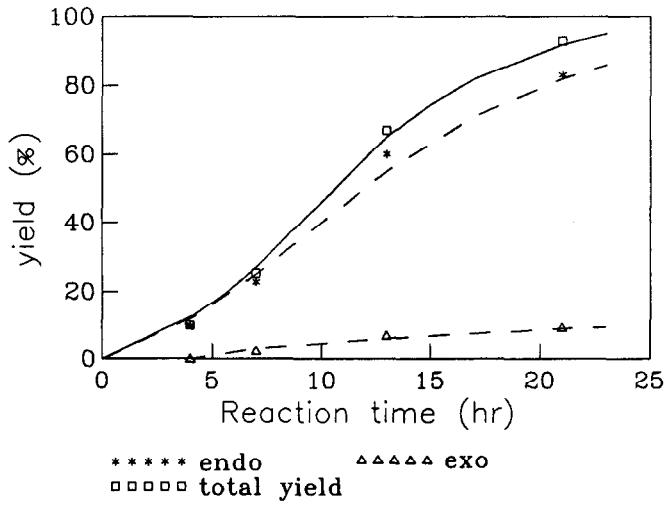


Fig. 4 Reaction of butenolide 2 with 15 eq of cyclopentadiene in CH_2Cl_2 in the presence of 0.5 eq of ZnI_2 at 15 °C.

As a consequence of this study, the greatest of conversion into adducts was achieved in a reasonable time period, whereas the formation of by-products was prevented.

In conclusion, the use of catalysts such as $EtAlCl_2$ and zinc halides in the Diels-Alder cycloadditions of cyclopentadiene to chiral butenolides presents noteworthy advantages with respect to the uncatalyzed reactions, in order to obtain *endo* adducts in high yields (80-90%) under mild reaction conditions.

EXPERIMENTAL SECTION

General Procedures for Uncatalyzed Diels-Alder Cycloadditions. The reactions and their workup followed a previous description,[2] and the conditions are detailed in Table 1.

Full characterization of the adducts obtained has been reported in a previous work.[2]

General Procedures for Catalyzed Diels-Alder Cycloadditions. All manipulations of air-sensitive compounds were carried out by standard Schlenk techniques. Dichloromethane was used as a solvent, previously distilled over calcium hydride and treated under argon. 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. Tables 1 and 2 show the catalyst-dienophile ratio, reaction temperature and time conditions, ratio of isomeric adducts, and yield for each experiment.

A typical experiment (Table 1, entry 9) was run as follows: ZnI_2 (0.32 mg, 1.0 mmol) was added to a solution of lactone **2** (0.23 mg, 2 mmol) in 3 mL of dichloromethane. The mixture was stirred at 15 °C for 30 min. Then cyclopentadiene (15 mmol, 2.5 mL) was added and the resulting solution was stirred at 15 °C for 21 h. For analysis, an aliquot of the reaction mixture (at different times) was poured into ice-10% aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined extracts were dried and the solvent was evaporated. The residue was filtered through a 240-400 mesh silica gel column (8 x 120 mm) by using a 4:1 hexane-ethyl acetate mixture as an eluent, affording samples ready to be injected into the HPLC chromatograph. After 21 h the reaction mixture was treated as described above but the residue was flash-chromatographed on a 20 x 300 mm column to afford the pure isolated products.

GLC 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 pure isolated adducts. *p*-Chloroacetophenone was used as internal standard. The external method was used in HPLC determinations.

GLC chromatography: Capillary column (crosslinked methyl silicon gum, 12 m x 0.2 mm x 0.3 μm). Conditions: 120 °C initial temp.; 190 °C injector temp.; 240 °C detector temp. HPLC chromatography: Column NUCLEOSYL 100 C2 (25 cm x 4 mm x 7 μm). 20:80 H_2O-MeCN as eluent at 1.0 ml/min flow. Diode-array detector.

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