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Lewis Acid-Catalyzed Hetero Diels-Alder Reactions of Readily Enolizable 1-Oxa-1,3-dienes, 2-Oxo-3-alkenylphosphonates, with Vinyl Ethers

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Remarkable rate enhancement is achieved by use of a weak Lewis acid catalyst such as zinc chloride or bromide in the hetero Diels-Alder reactions of 2-oxo-3-alkenylphosphonates as readily enolizable 1-oxa-1,3-dienes with vinyl ethers. Highly endo-selective cycloadducts, 2,4-cis-3,4-dihydro-2H-pyrans, are produced in good yields.

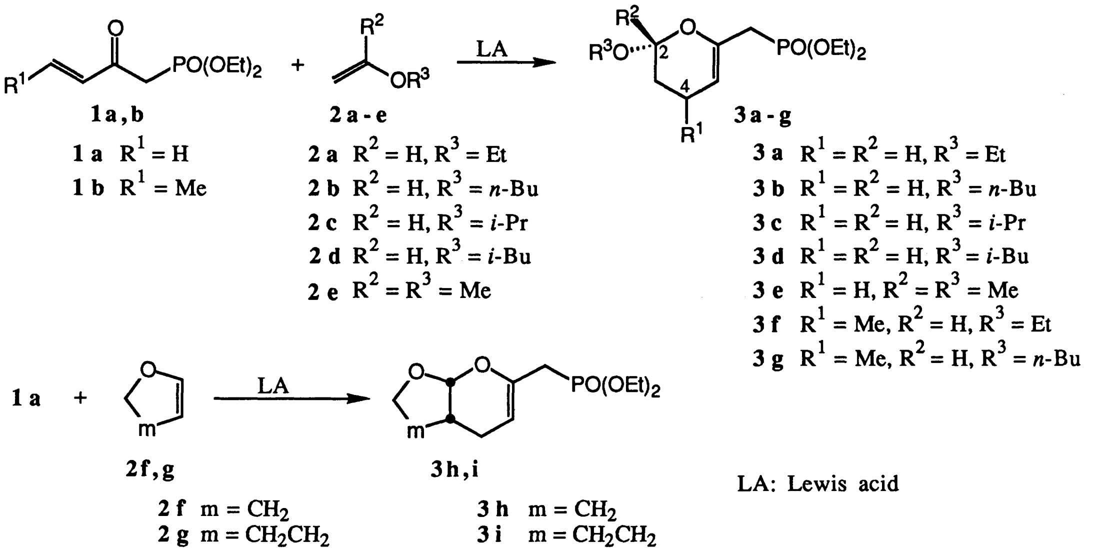
α,β-Unsaturated aldehydes and ketones undergo hetero Diels-Alder reactions, as electron-deficient dienes, with vinyl ethers offering a convenient route to 2-alkoxy-3,4-dihydro-2H-pyrans.1) High reaction temperature and long reaction time are usually required. Use of Lewis acid catalyst2) is effective to increase the rate of cycloadditions and high pressure3) works as well.

In Lewis acid-catalyzed cycloadditions, selection of an appropriate catalyst is important since a strong acid accelerates not only Diels-Alder reactions but also cationic polymerization of vinyl ethers. A lantanide catalyst, known as the most effective catalyst, has achieved a sufficient degree of enhancement of reactivity and exclusive formation of endo cycloadducts in the Diels-Alder reactions of 2-alkenals,2d,4) while the zinc chloride-catalyzed reactions of α,β-unsaturated aldehydes and ketones have remained poor in activation of the dienes.2a,5) The undesired polymerization of vinyl ethers would be suppressed if a weak Lewis acid is employed in less than one equivalent to α,β-unsaturated carbonyl compounds which are capable of forming a stable chelation.

We have reported that diethyl 2-oxo-3-alkenylphosphonates as readily enolizable α,β-unsaturated ketones successfully undergo hetero Diels-Alder reactions with vinyl ethers,6,7) where rather severe reaction conditions were needed (18 - 96 h at 85 - 185 °C in a sealed tube) and poor stereoselectivities resulted (exo:endo = 70:30 to 60:40). Catalysis by Lewis acid is expected in the Diels-Alder reactions of 2-oxo-3-alkenylphosphonates if no Lewis acid-mediated enolization of the hetero 1,3-dienes takes place. To the best of our knowledge, there is no example reported so far on the action of a Lewis acid with readily enolizable α,β-unsaturated carbonyl compounds.

The present communication describes an effective catalysis by zinc chloride or bromide in the Diels-Alder reactions of diethyl 2-oxo-3-alkenylphosphonates with vinyl ethers. These weak Lewis acids led to neither enolization of the enones nor polymerization of the vinyl ethers. Remarkable acceleration of the rate of Diels-Alder reactions produced highly endo-selective cycloadducts.

To examine the catalysis of Lewis acid in Diels-Alder reactions of readily enolizable α,β-unsaturated carbonyl compounds, diethyl 2-oxo-3-butenylphosphonate (1a) was allowed to react with several vinyl ethers 2a-g in the presence of zinc chloride to give cycloadducts 3a-e and 3h,i in good yields (Scheme 1 and Table 1).



Scheme 1.

In the absence of catalyst, cycloadditions needed nearly 20 h at 85 °C in a sealed tube (Entries 1 and 5). However, it took only 3 h at room temperature for cycloadditions to be completed when a little less than one equivalent of catalyst was used (Entries 2, 3, and 6-9), while cyclic vinyl ethers 2f,g were less reactive (Entries 10 and 11). Use of more than one equivalent of catalyst should be avoided

Table 1. Diels-Alder Reactions of Enone **1a** with Vinyl Ethers

Entry	Vinyl ether		Reaction conditions				Product (yield/%)[a]
	2	equiv.	solvent	catalyst (equiv.)	temp/°C	time/h	
1	**2a**	20	benzene	none	85[b]	18	**3a** (83)
2	**2a**	20	benzene	$ZnCl_2$ (0.7)	rt	3	**3a** (92)
3	**2a**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	3	**3a** (91)
4	**2a**	2	CH_2Cl_2	$ZnCl_2$ (0.43)	rt	24	**3a** (87)[c] **1a** (4)[c]
5	**2b**	20	benzene	none	85[b]	20	**3b** (88)
6	**2b**	20	benzene	$ZnCl_2$ (0.75)	rt	3	**3b** (91)
7	**2c**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	3	**3c** (87)
8	**2d**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	3	**3d** (90)
9	**2e**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	3	**3e** (87)
10	**2f**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	12	**3h** (89)
11	**2g**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	24	**3i** (56)

a) Yield of isolated products. b) Carried out in a sealed tube. c) Determined by ^1H NMR spectrum of the unpurified mixture.

because the excess catalyst causes ready polymerization of vinyl ethers, and rate acceleration was insufficient in the presence of a catalytic amount (Entry 4). In these catalyzed reactions, vinyl ethers were employed in excess since partial polymerization took place under the reaction conditions. No significant difference was observed in the reaction in benzene and dichloromethane.

To see the stereoselectivity of Lewis acid-catalyzed Diels-Alder reactions of 2-oxo-3-alkenylphosphonates with vinyl ethers, one alkyl moiety was introduced at the 4-position of enone 1a.

Reaction of diethyl (E)-2-oxo-3-pentenylphosphonate (1b) with twenty equivalents of vinyl ether 2b without any catalyst required 48 h at 130 - 135 °C to give a 34:66 mixture of endo- and exo-isomers of cycloadduct 3g (Scheme 1 and Entry 6 in Table 2). Although this reaction was accelerated by zinc chloride, some of the starting enone 1b was recovered unchanged (Entries 1 and 5). A lower reaction temperature was favored for endo selectivities (Entries 1, 5, and 6).

Table 2. Diels-Alder Reactions of Enone **1b** with Vinyl Ethers

Entry	Vinyl ether 2	equiv.	Reaction conditions solvent	catalyst (equiv.)	temp/°C	time/h	Product (yield/%)[a]	cis:trans[b]
1	**2a**	2	CH_2Cl_2	$ZnCl_2$ (0.82)	rt	48	**3f** (72)[c) **1b** (27)[c]	93:7
2	**2a**	3	CH_2Cl_2	$ZnBr_2$ (0.9)	-10	36	**3f** (79) **1b** (9)	95:5
3	**2a**	2	CH_2Cl_2	$ZnBr_2$ (1)	-20	48	**3f** (74)[c] **1b** (24)[c]	96:4
4	**2a**	3	CH_2Cl_2	$ZnBr_2$ (1)	-20	48	**3f** (92)[c] **1b** (7)[c]	96:4
5	**2b**	20	benzene	$ZnCl_2$ (0.9)	45	6	**3g** (90) **1b** (4)	86:14
6	**2b**	20	benzene	none	130-135[d]	48	**3g** (88)	34:66

a) Yield of isolated products. b) Determined by GLC. c) Determined by ^{1}H NMR spectrum of the isolated mixture. d) Carried out in a sealed tube.

In the presence of a little stronger Lewis acid, zinc bromide, cycloadditions were sufficiently accelerated. Thus, the zinc bromide-catalyzed reaction of enone 1b with three equivalents of vinyl ether 2a at -20 °C for 48 h gave 92% yield of cycloadduct 3f in a 96:4 stereoisomeric ratio along with a small amount of unchanged 1b (7%, Entry 4).

It was our great surprise that diethyl 2-oxo-3-alkenylphosphonates 1 as readily enolizable α,β-unsaturated ketones did not suffer from serious enolization by the action of a Lewis acid but instead were satisfactorily activated in their hetero Diels-Alder reactions. Formation of a stable chelation was indicated on the basis of the following observations: 1) Although both zinc chloride and bromide are only

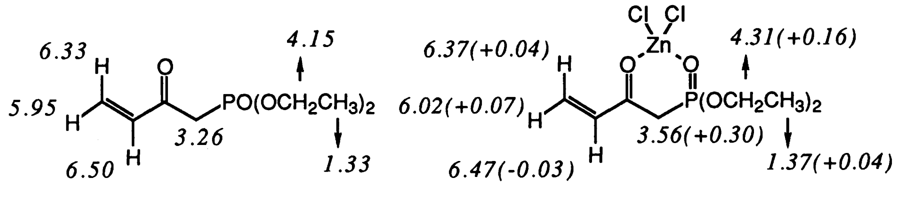


Fig. 1. ^{1}H NMR Spectra of **1a** in deuteriochloroform in the absence (left) or presence (right) of zinc chloride (0.8 equiv.).

sparingly soluble in such nonpolar solvents as benzene and dichloromethane, they become very soluble in the presence of enones 1; 2) In the absence of enones 1, vinyl ethers undergo a rapid cationic polymerization upon treatment with zinc chloride or bromide.

As shown by the ^{1}H NMR spectrum of a mixture of diethyl 2-oxo-3-butenylphosphonate (1a) and zinc chloride (0.8 equiv.) in deuteriochloroform, no sign of enolization was observed (Fig. 1). Almost all hydrogens of 1a shifted downfield due to a tight six-membered zinc chelation.

These results indicate that in hetero Diels-Alder reactions of α,β-unsaturated carbonyl compounds with vinyl ethers a sufficient degree of rate acceleration as well as high endo selection would be achieved by the action of an ordinary Lewis acid catalyst if the hetero dienes can make a stable chelation. Use of stronger Lewis acids such as aluminum chloride and titanium chlorides in these reactions is now under investigation.

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4) In the presence of a lantanide catalyst, Yb(fod)$_3$, crotonaldehyde and cinnamaldehyde react with ethyl vinyl ether at room temperature to give exclusively endo-selective cycloadducts in 60 - 80% yields (Ref. 2d).

5) Only 35% yield of the cycloadduct was obtained in the zinc chloride-catalyzed reaction of 3-buten-2-one with methyl vinyl ether (2 equiv.) which was carried out at 90 °C for 30 min. Even with α,β-unsaturated aldehydes instead of the corresponding ketones, the rate enhancement remained unsatisfactory (Ref 2a).

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