DIENE-TRANSMISSIVE HETERO DIELS-ALDER REACTION OF 1,5-DIPHENYL-1,4-PENTADIEN-3-ONE

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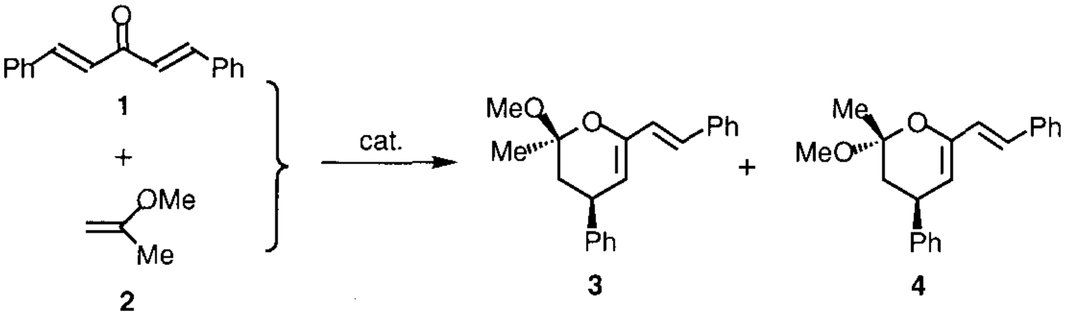
Abstract - The diene-transmissive hetero Diels-Alder reaction of 1,5-diphenyl-1,4-pentadien-3-one is described. Stereoselectivity of the inverse electron-demand Diels-Alder reaction of electron-rich vinyl ethers at the first stage was greately affected by the nature of Lewis acid-catalysts: The ZnX_2 (X=Cl, I)-, $MgBr_2$- and $Eu(fod)_3$-catalyzed reactions gave the corresponding *endo*-adducts, whereas *exo*-adducts were formed in the $GaBr_3$-, $AlCl_3$-, and Et_2AlCl-catalyzed reactions. In the sequential Diels-Alder reaction initial cycloadducts readily reacted with electron-deficient dienophiles such as 1,2,4-triazolinedions, tetracyanoethene, and maleimides to give the corresponding cross-bis-cycloadducts.

The diene-transmissive Diels-Alder reaction of cross-conjugated trienes[1,2] and heterotrienes[3-5] offers a versatile synthetic route to hydronaphthalene- and heteroatom-containing hydronaphthalene-skeletons. Recentely, we have reported[5] the first example for the diene-transmissive Diels-Alder reaction of a 2-vinyl-1-oxabutadiene system, 1,5-diphenyl-1,4-pentadien-3-one (**1**), in which electron-rich enamines were used as the first dienophiles and then electron-deficient dienophiles as the second. As it is known that 1-oxabutadiene systems such as α,β-unsaturated aldehydes and ketones undergo the hetero Diels-Alder reactions with electron-rich vinyl ethers offering a convenient route to 2-alkoxy-3,4-dihydro-2*H*-pyrans,[6] we have investigated the diene-transmissive Diels-Alder reaction of **1** using vinyl ethers at the first stage and then electron-deficient dienophiles at the second.

The Diels-Alder Reaction of 1 with Vinyl Ethers. In the hetero Diels-Alder reactions of simple 1-oxabutadiene systems high reaction temperature and long reaction time are usually required. Use of Lewis acid catalyst is effective to increase the rate of cycloadditions and high pressure works as well.[7] We have previously found[8] that remarkable rate enhancement and high *endo*-selectivity were achieved by use of

$ZnCl_2$ in the hetero Diels-Alder reactions of 1-oxabutadienes, 2-oxa-3-alkenylphosphonates, with vinyl ethers. Also, the $ZnCl_2$-catalyzed reaction of **1** with enamines proceeded in an *endo*-addition manner to give the single cycloadduct in moderate to good yield.[5] Thus, the reaction of **1** with 2-methoxypropene (**2**) was first investigated under the influence of $ZnCl_2$. In the reaction at 20 °C **1** was recovered unchanged quantitatively, but at increased reaction temperature two stereoisomeric cycloadducts (**3**), mp 82-83 °C, and

Table 1. Diels-Alder Reactions of **1** with **2**.[a]



Entry	Solvent[b]	Catalyst	Molar ratio[c]	Temp. (°C)	Time (h)	Product (%)[d] 3	4	3/4
1	B	$ZnCl_2$	1/0.1/20	20	6	no reaction		
2	B	$ZnCl_2$	1/0.1/20	45	6	21	3	88/12
3	B	$ZnCl_2$	1/0.1/20	55	6	45	8	85/15
4	B	$ZnCl_2$	1/0.1/20	65	6	53	7	88/12
5	B	ZnI_2	1/0.1/20	45	6	30	2	94/6
6	B	ZnI_2	1/0.1/20	55	6	82	7	92/8
7	B	ZnI_2	1/0.1/20	65	6	86	11	89/11
8	B	$MgBr_2$	1/1/20	55	6	26	6	81/19
9	B	$Eu(fod)_3$[e]	1/0.1/40	55	6	19	2	90/10
10	B	$Eu(fod)_3$[e]	1/1/40	55	6	63	7	90/10
11	B	$FeCl_3$	1/0.1/20	10	0.5	46	47	50/50
12	B	$FeCl_3$	1/0.05/5	10	0.5	49	48	50/50
13	B	$GaBr_3$	1/0.1/5	25	1	9	61	13/87
14	B	$AlCl_3$	1/0.1/20	10	6	5	44	10/90
15	DM	Et_2AlCl	1/0.5/10	0	6	20	65	24/76
16	T	Et_2AlCl	1/0.5/5	- 5	3	7	73	9/91
17	T	Et_2AlCl	1/0.5/5	20	3	8	73	10/90

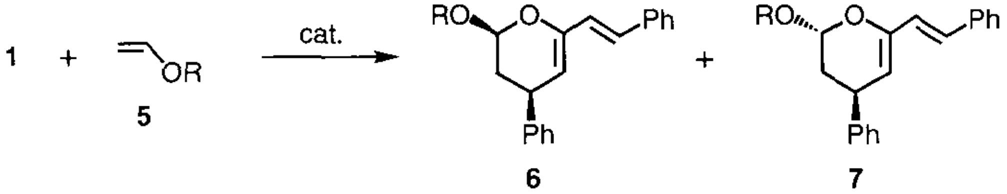
a) All the reactions were carried out in a dry solvent under argon. b) B: benzene, DM: dichloromethane; T: toluene. c) Molar ratio of **1**/catalyst/**2**. d) Yields and ratios are for chromatographically purified products.e) $Eu(fod)_3$: europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate).

(**4**), mp 88-89 °C, were isolated in low to moderate yield with a ratio of 85-88/15-12 together with the recovery of **1** (Entries 2-4 in Table 1). On the basis of spectral data[9] as well as of X-Ray crystallographic analysis of cross-cycloadduct of **3** to 4-methyl-1,2,4-triazoline-3,5-dione described below, the major product (**3**) and minor one (**4**) were assigned to *r*-2-methyl-2-methoxy-*t*-4-phenyl-6-styryl- and *r*-2-methyl-2-methoxy-*c*-4-phenyl-6-styryl-3,4-dihydro-2*H*-pyran, respectively. This implies that the reaction proceeded in a high regio- and stereoselective manner, although the yields of adducts were low. Since **3** and **4** correspond to the *endo*- and *exo*-addition products regarding the methoxy group in **2**, the former type adduct is hereinafter abbreviated as *endo*-adduct and the latter type one as *exo*-adduct, respectively.

Since the yields of adducts in the above $ZnCl_2$-catalyzed reactions were not so high, the reactions in the presence of various Lewis acids other than $ZnCl_2$ were investigated. The selected data are listed in Table 1. The reactions in the presence of ZnI_2, $MgBr_2$, and $Eu(fod)_3$, as well as the above $ZnCl_2$-catalyzed one, gave the *endo*-adduct (**3**) as major product (Entries 5-10). From the standpoint of both the yield and selective formation for the *endo*-adduct (**3**), however, ZnI_2 was superior to other catalysts.

In contrast to the above catalyzed-reactions, it has been found that the reactions under the influence of $GaBr_3$, $AlCl_3$, and Et_2AlCl gave the *exo*-adduct (**4**) as major product (Entries 13-17); particularly Et_2AlCl is an excellent catalyst for the formation of **4**. Although $FeCl_3$-catalyst exhibited a remarkable rate acceleration, the stereoselectivity was not observed (Entreis 11 and 12).

Table 2. Diels-Alder Reactions of **1** with **5a**-**5c**.[a)]



a : R=Et ; **b** : R=*n*-Bu ; **c** : R=*i*-Bu

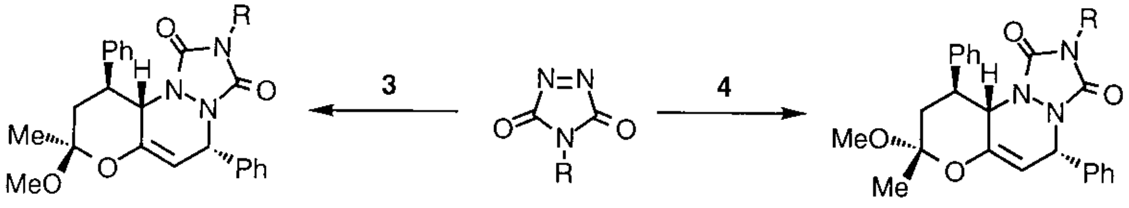
Entry	Vinyl ether	Solvent	Catalyst	Molar ratio[b)]	Temp. (°C)	Time (h)	Product (%)[c)] 6	7	6/7
1	**5a**	benzene	ZnI_2	1/0.1/20	55	6	62 (**6a**)	3 (**7a**)	95/5
2	**5b**	benzene	ZnI_2	1/0.1/20	55	6	84 (**6b**+**7b**)		99/1[d)]
3	**5c**	benzene	ZnI_2	1/0.1/20	55	6	62 (**6c**+**7c**)		99/1[d)]
4	**5a**	toluene	Et_2AlCl	1/0.1/10	20	1	5 (**6a**)	41 (**7a**)	10/90
5	**5b**	toluene	Et_2AlCl	1/0.1/10	20	1	50 (**6b**+**7b**)		10/90[d)]
6	**5c**	toluene	Et_2AlCl	1/0.1/10	20	1	43 (**6c**+**7c**)		10/90[d)]

a) All the reactions were carried out in a dry solvent under argon. b) Molar ratio of **1**/catalyst/**5**.
c) In Entries 1 and 4 yields and ratios are for chromatographically purified products. d) Determined by ^1H NMR.

Next, the reaction of **1** with mono-substituted vinyl ethers such as ethoxy- (**5a**), *n*-butoxy- (**5b**) and *i*-butoxyethene (**5c**) was investigated under the influence of ZnI_2 and Et_2AlCl. Although the reactivity of **5** to **1** was somewhat lower than that of **2**, the major products in the ZnI_2-catalyzed reaction were *endo*-cycloadducts (**6**), whereas those in the Et_2AlCl-catalyzed one were *exo*-cycloadducts (**7**) (Table 2).[10]

It is noteworthy that a dramatic change of stereoselectivity depending on the nature of Lewis acids was observed in the reaction of **1** with vinyl ethers. To the best of our knowledge, such examples have not so far been reported.[11]

Sequential Diels-Alder Reaction of Initial Adducts. Both initial *endo*- (**3**) and *exo*-cycloadduct (**4**) readily reacted with electron-deficient cyclic azo-compounds such as 4-methyl- (**8a**) or 4-phenyl-1,2,4-triazoline-4,5-dione (**8b**) (in benzene, rt., 2 h) to give the corresponding bis-adducts (**9a**), mp 195-196 °C (decomp), and (**10a**), mp 204-205 °C (decomp), or (**9b**), mp 188-189 °C (decomp), and (**10b**), mp 185-186 °C (decomp), in good yields, respectively (Scheme 1).[12]



9a (85%)
9b (95%)

8

a : R=Me ; **b** : R=Ph

10a (72%)
10b (93%)

Scheme 1

The structure of **9a** in which 8-methoxy and 10-phenyl groups are *cis* was unambiguously established by its X-Ray crystallographic analysis (Figure 1).[13]

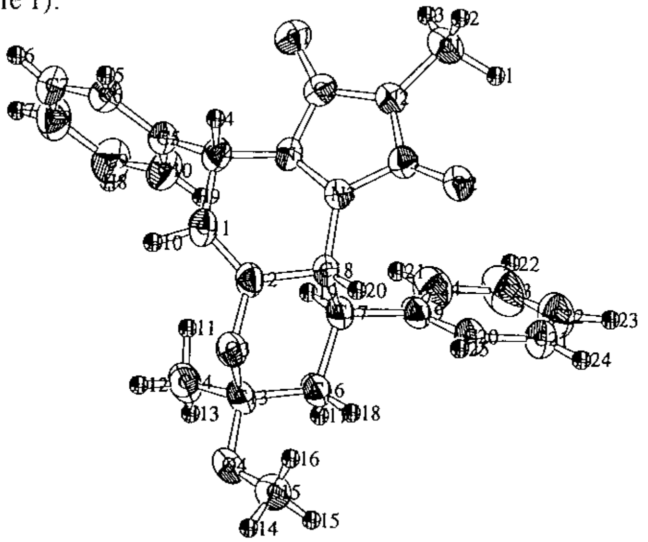


Figure 1. An ORTEP drawing of **9a**.

Based on the structure of **9a**, it is evident that the initial cycloadduct (**3**) is an *endo*-adduct in which 2-methoxy and 4-phenyl groups are *cis*. It was thus assumed that the isomer (**4**) is an *exo*-adduct in which 2-methoxy- and 4-phenyl groups are *trans*.

Sequential Diels-Alder reaction using electron-deficient alkenes was next investigated.

The reaction of initial adducts (**3**), (**4**) and (**6a**) with tetracyanoethene proceeded smoothly (in benzene, rt, 2 h) to give the corresponding bis-adducts, (**11**), mp 203-205 °C (decomp), (**12**), mp 199-200 °C (decomp), and (**13**), mp 200-201 °C (decomp), in good yields.[14] Although the reaction of **3**, **4** and **6a** toward *N*-methyl- or *N*-phenylmaleimide was somewhat sluggish, the reactions in benzene under reflux for 20 h afforded the corresponding adducts (**14a**), mp 189-190 °C, (**14b**), mp 208-209 °C, (**15b**), mp 212-214 °C, and (**16**), mp 153-155 °C (decomp), respectively (Scheme 2).[15]

11 : R=OMe, R'=Me (90%)
12 : R=Me, R'=OMe (71%)
13 : R=OEt, R'=H (79%)

14a : R=Me, R'=OMe, R''=Me (52%)
14b : R=Ph, R'=OMe, R''=Me (72%)
15b : R=Ph, R'=Me, R''=OMe (34%)
16 : R=Me, R'=OEt, R''=H (53%)

Scheme 2

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8. E. Wada, S. Kanemasa, and O. Tsuge, *Chem. Lett.*, **1989**, 675.
9. All the new compounds reported herein were characterized by spectroscopy and microanalysis. All the NMR spectra in this paper were measured in $CDCl_3$. **3**: colorless prisms; ^1H NMR δ 1.53 (3H, s), 2.06 (2H, d, *J*=7.8 Hz), 3.38 (3H, s), 3.64 (1H, dt, *J*=3.1, 7.8 Hz), 5.04 (1H, d, *J*=3.1 Hz), 6.52, 6.99 (each 1H, d, *J*=16.0 Hz), 7.10-7.60 (10H, m); ^{13}C NMR δ 22.15, 38.11, 39.56, 49.06,

100.77, 106.17, 123.96, 126.46, 126.58, 127.32, 127.53, 127.68, 128.43, 128.59, 131.02, 144.83, 149.61; MS *m/z* 306 (M$^+$). **4**: colorless prisms; ^{1}H NMR δ 1.57 (3H, s), 1.74 (1H, dd, *J*=12.2, 13.4 Hz), 2.23 (1H, ddd, *J*=1.7, 6.3, 13.4 Hz), 3.37 (3H, s), 3.81 (1H, ddd, *J*=2.1, 6.3, 12.2 Hz), 5.11 (1H, br s), 6.51, 6.95 (each 1H, d, *J*=15.6 Hz), 7.20-7.50 (10H, m); ^{13}C NMR δ 22.97, 36.15, 41.83, 49.08, 98.69, 108.66, 124.01, 126.47, 126.55, 127.46, 127.62, 128.34, 128.57, 137.12, 144.94, 147.91; MS *m/z* 306 (M$^+$).

10. On the basis of the reaction of **1** with **2**, it was assumed that major adducts (**6**) in the ZnI$_2$-catalyzed reaction are *endo*, while those (**7**) in the Et$_2$AlCl-catalyzed reaction are *exo*. **6a**: colorless prisms; mp 59-60 °C; ^{1}H NMR δ 1.31 (3H, t, *J*=7.0 Hz), 1.70-2.51 (2H, m), 3.50-4.42 (3H, m), 4.98 (1H, d, *J*=2.2 Hz), 5.16 (1H, dd, *J*=2.3, 8.6 Hz), 6.48, 6.95 (each 1H, d, *J*=16.0 Hz), 7.10-7.60 (10H, m); MS *m/z* 306 (M$^+$). **7a**; colorless prisms; mp 63-64 °C; ^{1}H NMR δ 1.30 (3H, t, *J*=7.1 Hz), 1.80-2.02 (1H, m), 2.20-2.40 (1H, m), 3.60-3.80 (2H, m), 4.02-4.20 (1H, m), 4.98 (1H, d, *J*=2.0 Hz), 5.16 (1H, dd, *J*=2.0, 8.9 Hz), 6.50, 6.94 (each 1H, d, *J*=16.1 Hz), 7.10-7.39 (10H, m); MS *m/z* 306 (M$^+$).

11. Stereoselectivity in the thermal, pressure-promoted, and Lewis acid catalyzed [4+2] cycloaddition reactions of β,γ-unsaturated α-keto esters with vinyl ethers was discussed (D. L. Boger and K. D. Robarge, *J. Org. Chem.*, 1988, **53**, 3373).

12. **9a**: colorless prisms; IR (KBr) 1775, 1717 cm^{-1}; ^{1}H NMR δ 1.50 (3H, s), 2.40 (2H, d, *J*=8.0 Hz), 2.78 (3H, s), 3.10-3.60 (1H, m), 3.46 (3H, s), 4.90-5.25 (3H, m), 7.10-7.60 (10H, m); ^{13}C NMR δ 22.38, 24.85, 41.01, 44.93, 49.20, 55.30, 60.37, 103.59, 104.05, 127.43, 127.68, 128.45, 128.86, 139.33, 141,02, 148.10, 150.59, 155.93; MS *m/z* 419 (M$^+$).

13. Crystal data for **9a**: C$_{24}$H$_{25}$N$_3$O$_4$, M=419.48, monoclinic, space group P2$_{1/c}$ (#14), a=11.023 (2) Å, b=8.8011 (9) Å, c=21.937 (2) Å, β=90.830 (3)°, V=2128.0 (4) Å^3, Z=4, Dcalc=1.309 g/cm^3, μ(CuKα)=7.36 cm^{-1}, Rigaku AFC7R diffractometer, 6770 reflections with I>3.00σ(I), R=0.072, Rw=0.086.

14. **13**: colorless needles, IR (KBr) 2254 cm^{-1}; ^{1}H NMR δ 1.31 (3H, t, *J*=7.2 Hz), 2.08-2.70 (2H, m), 3.22-4.20 (4H, m), 4.45 (1H, dd, *J*=1.9, 4.5 Hz), 5.06 (1H, dd, *J*=3.8, 5.7 Hz), 5.57 (1H, dd, *J*=1.9, 4.5 Hz), 7.18-7.75 (10H, m); ^{13}C NMR δ 15.16, 38.44, 41.11, 41.41, 43.68, 44.89, 46.50, 65.07, 100.23, 103.36, 108.50, 110.08, 111.63, 128.54, 129.33, 129.59, 130.23, 131.17, 132.04, 137.93, 147.79; MS *m/z* 434 (M$^+$).

15. The structure of **14-16** was assumed on the basis of spectral data and inspection of molecular modeles. **14a**: IR (KBr) 1750, 1698 cm^{-1}; ^{1}H NMR δ 1.57 (3H, s), 1.70-2.30 (2H, m), 2.30-2.75 (1H, m), 2.85 (3H, s), 2.86-3.25 (2H, m), 3.34 (3H, s), 3.40-4.15 (2H, m), 5.52 (1H, m), 7.05-7.65 (10H, m); ^{13}C NMR δ 23.45, 24.74, 35.35, 41.83, 41.96, 43.54, 44.29, 47.56, 48.97, 102.89, 104.58, 127.04, 127.17, 127.94, 128.23, 128.70, 128.77, 139.21, 141.85, 152.99, 175.67, 176.83; MS *m/z* 417 (M$^+$).

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