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Internally Lewis Acid-Catalyzed Diels-Alder Cycloadditions

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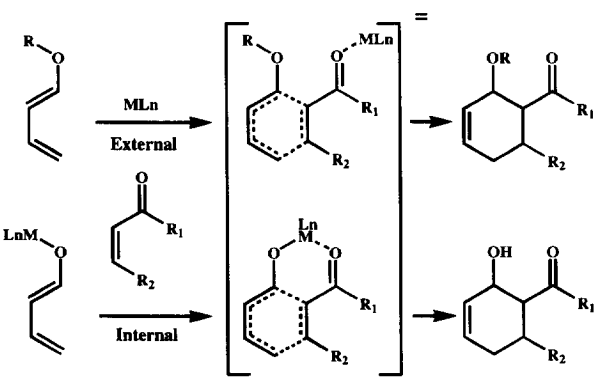
Abstract: Suitable dienes, covalently connected to a Lewis acid, such as 1-dimethylaluminum dienolates, undergo very rapid and selective Diels-Alder cycloadditions with various dienophiles. For these processes, a cooperativity between enthalpic (dienophile activation) and entropic (reactants pre-association) factors is thought to be responsible for the high reactivities and regio/stereo-selectivities observed. © 1997 Elsevier Science Ltd.

Introduction: Over the past 70 years, the Diels-Alder cycloaddition has undoubtedly emerged as the most powerful and versatile six-member ring formation process[1]. Lewis acid catalysis has proven here to be an extremely fertile concept[2], allowing reactions to be carried out under mild conditions, and in most cases with high regio- and stereocontrol. For these Lewis acid-catalyzed processes, activation is essentially of enthalpic origin: coordination of a basic carbonyl group on the dienophile is responsible for its increased polarization and electrophilicity (LUMO energy lowering effect).

The other main way to improve both rate and/or regio/stereoselectivity of these reactions is to perform them in an intramolecular fashion[1c,3]. Of course, the bridging tether must be either part of the desired product or removed in some subsequent step(s). To date, with very few exceptions, covalent bonds have been used to link the diene and the dienophile[4]. In that latter case, the activation origin is mainly entropic.

Being confronted with the cycloaddition of 1-alkoxy-substituted butadienes with various dienophiles, including maleimides, we felt that more was to be gained if we could take advantage of both activation modes. Covalently connecting the Lewis acid to the diene, as depicted in scheme 1, was thought to be the best solution: both enthalpic activation upon dienophile coordination, and entropic activation with the pre-association of the reacting entities, could be expected to act in synergy.



Scheme 1

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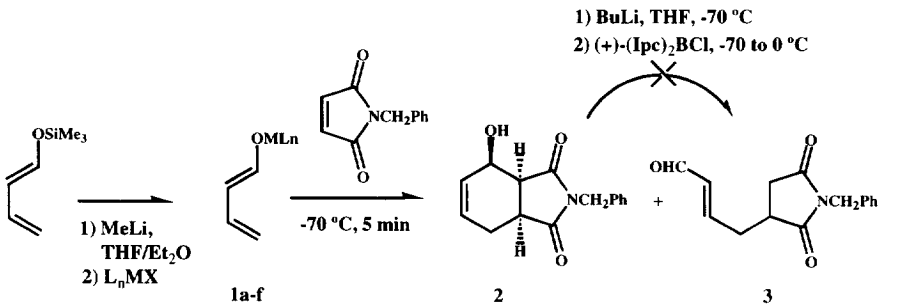
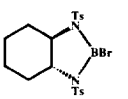
Of course, the reactivity outcome was only part of the picture, and we were even more concerned about the regio- and stereochemical profiles of these "internally catalyzed" cycloadditions. We felt this new coordination mode could offer new opportunities for both issues[5]. For instance, internal Lewis acid complexation could tune or change the regio- or stereoselectivity obtained with a basic carbonyl-containing dienophile (*vide infra*).

The absolute stereochemistry issue is also another important feature: owing to its putative rigidified bicyclic [6-6] transition state, we speculated the system depicted in scheme 1 to be specially well suited to provide high levels of enantiocontrol and a good scope in asymmetric Diels-Alder cycloadditions[6].

Results: The method employed for the preparation of dienes **1a-f** (metallic dienolates) is outlined in scheme 2. Starting from the (substituted) trimethylsiloxy-butadiene, a silicon-lithium exchange reaction, according to Stork[7], followed by transmetallation gave the expected dienes. Cycloadditions were performed with N-benzyl maleimide (NBM) as a model Lewis-basic dienophile. With this protocol in hand, metal scrutiny could be easily performed.



Diene	L_nMX	Yield (%)[a]	Yield (%)
1a	none	21	-
1b	Me_2AlCl	65	-
1c	$(iPrO)_3TiCl$	53	-
1d	$La(OTf)_3$	12	-
1e [b]	$(+)\text{-}(Ipc)_2BCl$	46	13
1f [c]		47	14

a) Yields based on the starting silyl enol ether. b) Low enantionmer ratio (e.r.) for **2** (<55/45). c) Enantiopure (R,R) isomer, prepared according to ref. 16 (e.r. for **2**= 65/35).

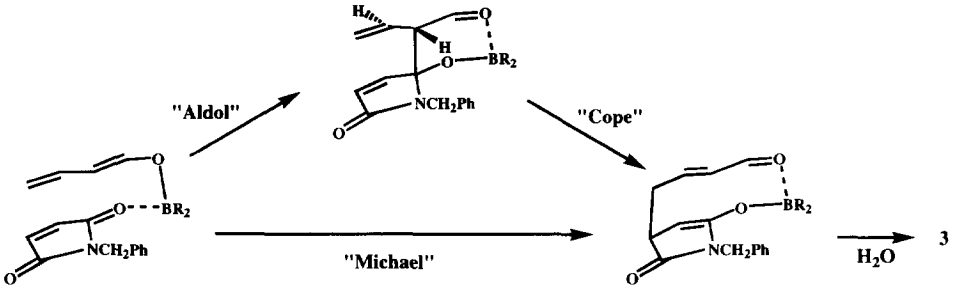
Scheme 2

Noteworthy, every reaction came to completion within 5 min at -70 °C. The very high reactivities of dienes **1a-f** could be compared to the corresponding 1-alkyloxy- or 1-acyloxybutadienes under "externally catalyzed" or thermal conditions, which require between 6 hours and several days at 25-70 °C[8]. Equally important, exclusive endo stereochemistry was observed for cycloadduct **2**.

Among various metals tested, aluminum and titanium were shown to be the best and the former was thus selected for the following study. Interestingly, a Michael addition-type by-product **3**, was obtained with boron Lewis acids (dienes **1e,f**). This (E)-α-β unsaturated aldehyde was most likely formed competitively:

deprotonation of adduct **2** at low temperature, followed by transmetallation with (+)-$(Ipc)_2BCl$ and warming at 0 °C for several hours, left **2** unchanged.

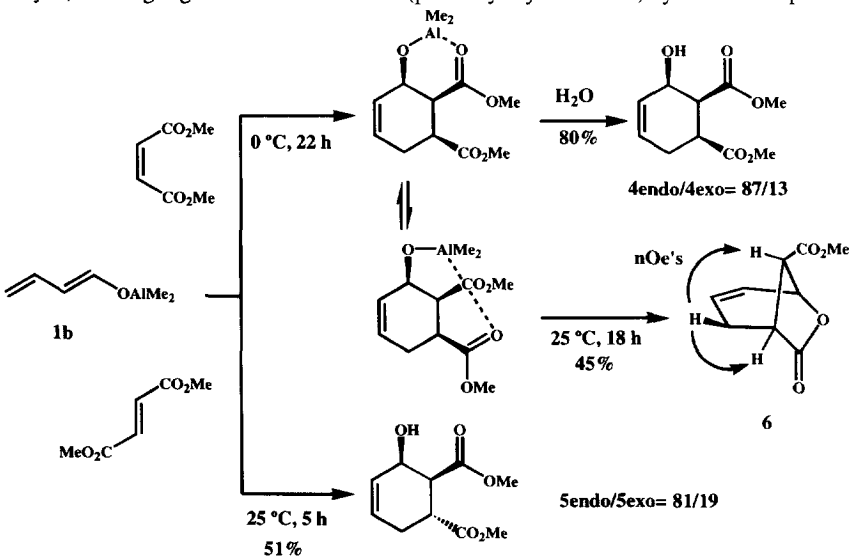
Actually two distinct mechanisms are conceivable for the production of **3**: either a direct γ-1,4 addition of the boron dienolate reagent on the maleimide, or a tandem syn-selective aldol addition/anionic oxy-Cope rearrangement (scheme 3)[9]. As boron enolates are well-known partners in aldol reactions with aldehydes and ketones (imide and ketone carbonyls electrophilicities are expected to be similar) and the oxy-Cope rearrangement is expected to be facilitated by chelate rigidification and double bond reconjugation, we prefer this latter mechanism.



Scheme 3

Nevertheless, the presence of this Michael addition by-product might argue for a general anionic stepwise mechanism in these cycloadditions, even when **3** is not observed[10]. Although we cannot rule out such tandem mechanisms in the maleimide case, the highly endo preference of these cycloadditions is strongly reminiscent of the maleimide behaviour in Diels-Alder processes.

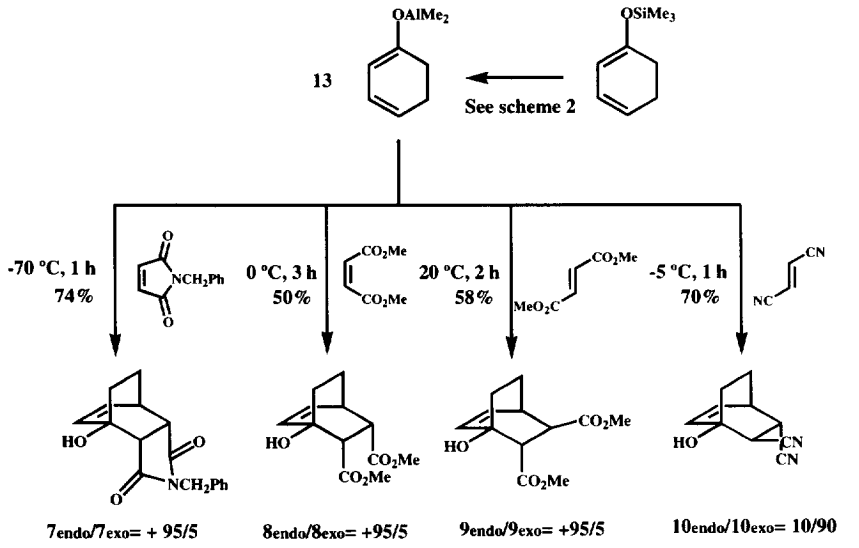
To test the anionic mechanism hypothesis, methyl fumarate and methyl maleate were reacted with **1b** (scheme 4). With methyl maleate at 0 °C, cycloadduct **4** was obtained as a chromatographically separable endo/exo mixture in high yield. Upon warming at room temperature, the major endo aluminum alkoxide intermediate underwent an intramolecular transesterification reaction to give the bicyclic [3.2.1] lactone **6**. Cycloadduct **5** was produced as an inseparable mixture of trans stereoisomers (assigments made upon inspection of NMR and IR spectra). Thus both cycloadducts, **4** and **5**, retained their dienophile stereochemistry[11], a strong argument for a concerted (probably asynchronous) cycloaddition process.



Scheme 4

1-Dimethylaluminumoxy-1,3-cyclohexadiene **13**[12] was also evaluated with an array of disubstituted dienophiles, to give access to the interesting bicyclo[2.2.2]octane skeleton (scheme 5). In each case, very low temperatures and/or short reaction times were applicable. Consequently, reaction mixtures were often much cleaner and the yields higher (compared to their uncatalyzed or "externally-catalyzed" counterparts).

For instance, the methyl fumarate cycloaddition ran to completion within 2 hours at 20 °C (yield 58%), whereas under thermal conditions 1-trimethylsiloxy-1,3-cyclohexadiene required the same time, but at xylene reflux (140 °C, 59% after desilylation). With 1 equivalent of added Me_2AlCl, 6 hours at 70 °C were still needed (40% after desilylation). Similarly, **10** was cleanly formed in 1 hour at -5 °C against 12 hours at 70 °C for the uncatalyzed reaction (toluene, 48% after desilylation).

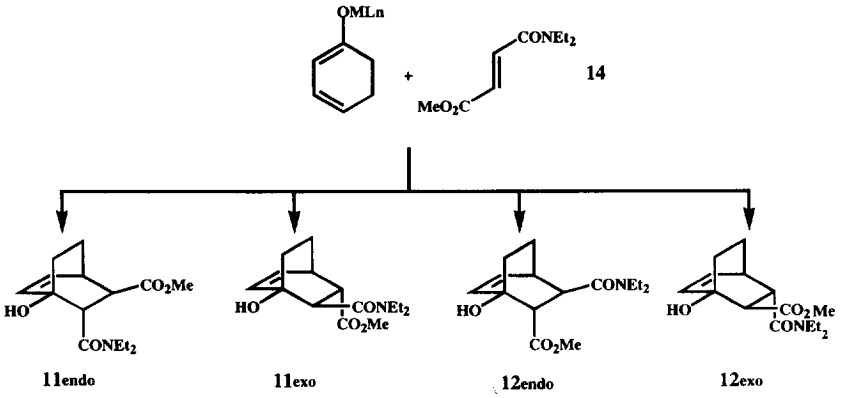


Scheme 5

Very high endo selectivity was again observed with NBM, methyl fumarate and methyl maleate. A good exo selectivity was also obtained with fumaronitrile. These results deserve some comments, especially in the light of the "thermal" results: in our hands, cycloadditions between 1-trimethylsiloxy-1,3-cyclohexadiene and methyl fumarate or fumaronitrile gave endo/exo ratios in the range 30/70-35/65. Similar values have been published for the cycloaddition of fumaroyl chloride and fumaronitrile with 1-methoxy-1,3-cyclohexadiene[12,13]. This apparently weak exo selectivity was either completely reversed (endo/exo≥95/5 for methyl fumarate) or increased (endo/exo=10/90 for fumaronitrile) with diene **13**. This spectacular result is consistent with the intuitive picture of a transition state in which internal diene coordination effectively occurs with methyl fumarate but not with fumaronitrile.

At this point, two crucial (but related) questions were raised: are dienes, such as **1b** or **13**, able to promote true bicyclic [6,6] transition states with Lewis basic dienophiles, or their high reactivity/selectivity a reflection of their high HOMO energy (electron-rich dienes)? Is a real combination of enthalpic and entropic factors operating here?

To prove the existence of a bicyclic [6,6] transition state, two sets of experiments were carried out. One using a unsymmetrical dienophile (scheme 6) and one with a unsymmetrical diene (scheme 7). When mixed fumaro ester-amide **14** (prepared from fumaroyl chloride) was reacted with **13**, exquisite regiocontrol was observed and, as expected, the more Lewis basic amide function directed the formation of regioisomers **11endo/exo** vs. **12endo/exo** (scheme 6).

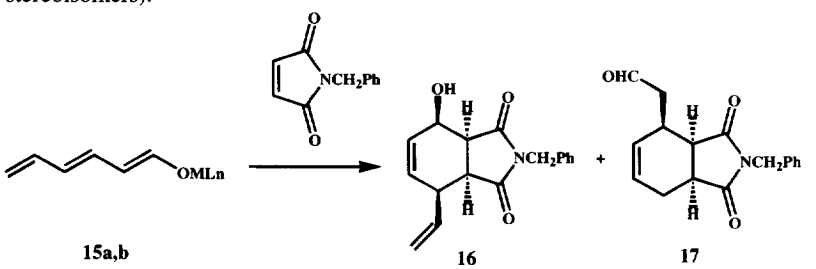


MLn= $AlMe_2$ **50** [THF, 0 °C, 3 h, 58%]	**50**	-	-
MLn= $SiMe_3$ **17** [Xylene, 140 °C, 11 h, 58%]	**3**	**31**	**49**
MLn= $SiMe_3$ **59** [THF, Me_2AlCl (1.2 eq.), 70 °C, 7 h, 40%]	**41**	-	-

Scheme 6

Under thermal conditions, **14** gave a mixture of the four possible regio/diastereoisomers. Owing to its greater electron withdrawing nature, the ester group directed the regioselectivity and **12endo/exo** were formed predominantly (**12/11**=80/20). If the same reaction was carried out in the presence of 1.2 equiv. of "external" Me_2AlCl, the coordinated amide function then became more electron-withdrawing and the regioselectivity was again reversed.

At this point, although Lewis acid catalysis was demonstrated (under these conditions), we had still no definitive evidence for an intramolecular bicyclic transition state. Thus, triene **15a**, prepared from sorbaldehyde[14], was found to react thermally with NBM exclusively at its less substituted terminal position to give **17** as a single endo isomer (THF, 70 °C, 47% after treatment with Bu_4NF, scheme 7). Switching from silicon to aluminum, gave a completely different result: **16** was isolated as the sole product in high yield (both are pure endo stereoisomers).

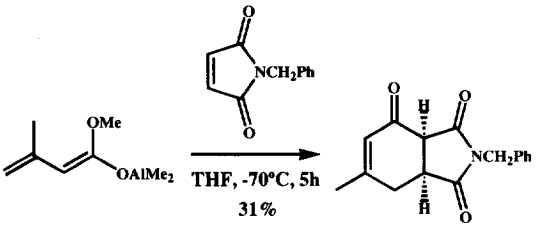


15a, MLn= $SiMe_3$ [THF, 70 °C, 3 h]	-	47%
15b, MLn= $AlMe_2$ [THF, -70 °C, 2 h]	93%	-
15b +Et_3N (2 equiv.) [THF, -70 °C, 3 h]	32%	4%

Scheme 7

Importantly, this test-reaction could be carried out in ether or in THF (two solvents of very different complexing properties) without noticeable change. Even the presence of added triethylamine (2 equiv.) could not revert this regioselectivity. This result clearly establishes that diene **15b** is able to react with basic dienophiles through a bicyclic transition state.

Finally, a Lewis acid-containing ketene acetal could be used as well, although the cycloaddition is not as general and the (unoptimized) yield lower (scheme 8)[15].



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Scheme 8

From the above results, we have clearly shown that Lewis-acid functionalized dienes, such as dimethylaluminum dienolate, are able to undergo extremely rapid and regio- and stereoselective Diels-Alder cycloadditions with various dienophiles. We believe these concerted processes, which benefit from the cooperativity of enthalpic (dienophile activation) and entropic (reactants pre-association) factors, are likely to find new interesting applications: for instance in catalyst- or substrate-controlled asymmetric cycloadditions, or in total synthesis (where mild reaction conditions are sought after). Further work in this area (asymmetric cycloadditions) is still in progress, and will be reported in due course.

Acknowledgments: We thank our colleagues at the analytical department (M.Lanson, L.Godde, J.L.Dumoulin and J.Guillaud-Saumur) for their accurate and dedicated contribution, and Rhône-Poulenc Ind. for permission to publish these results.

EXPERIMENTAL PART

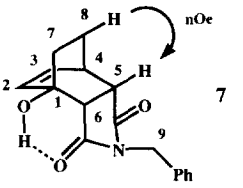
General Remarks: Enantiomer ratio measurements were done by chiral HPLC using a Daicel Chiralpack AD column (4.6 x 250 mm) coupled with a UV detector (230 nm). Mixtures of heptane/isopropanol (70/30⇒ 80/20) were used as eluents (1 mL/min). TLC was carried out on precoated silica gel $60F_{254}$ plates (Merck) visualized by UV light (254 nm) and a $KMnO_4/K_2CO_3$ dip. ^1H and ^{13}C-NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^1H) or a AM 300 (300 MHz for ^1H; 75 MHz for ^{13}C) instrument at 295 K. DMSO-d_6 was used as solvent (unless otherwise specified) with HMDS as internal standard. For IR spectra, a Perkin-Elmer 1750 FTIR, and for MS/HRMS a Fisons ZAB-3F instrument were used.

All reactions were carried out under argon, with Fluka absolute puriss. grade solvents (used without further purification). Preparative flash-chromatographies were performed with 20-45 µm Amicon silica gel. 1-Acetoxydienes were either purchased or obtained from industrial source (1-acetoxyisoprene, Rhône-Poulenc Animal Nutrition), and distilled under reduced pressure prior to use. All other reagents were commercially available and used without further purification.

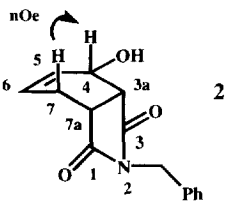
General procedure for the cycloaddition of dienes 1b, 13 or 15b with dienophiles (exemplified for the synthesis of cycloadduct 7endo). 1-Trimethylsiloxy-1,3-cyclohexadiene (0.355 g, 2.10 mmol) was dissolved in dry THF (5 mL) and cooled to -40/-35°C. A methyllithium solution (1.6M-ether, 1.40 mL, 2.24 mmol) was then slowly added and the reaction mixture was left at this temperature for 30 min. (disappearance of the silyl enol ether could be followed by TLC). After cooling at -70 °C, a solution of dimethylaluminumchloride (1M-hexane, 2.24 mL, 2.24 mmol) was added drop-to-drop and stirring was continued for 15 min. N-Benzylmaleimide (0.560 g, 3.11 mmol) was then added and the cycloaddition followed by TLC (eluent:

ether/pentane=3/1). The reaction was usually very fast (here <1 h). After an ethanol quench (1.5 mL), the reaction mixture was diluted with 10 mL of ether, warmed to room temperature, and filtered through a silica bed (≈2 cm) to remove the aluminum salts. The organic phase was washed with a saturated sodium bicarbonate solution then with brine, dried over magnesium sulphate and concentrated *in-vacuo*. ^{1}H NMR of the crude product indicated the only presence of adduct **7** and excess NBM. Cycloadduct **7** was recrystallized from a methylene chloride/ether mixture to give 0.440 g of white crystals (74% yield, based on the starting silyl enol ether).

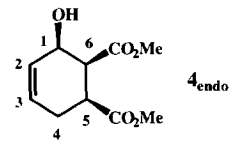
1-Hydroxy-5,6-(N-benzylsuccinimido)bicyclo[2.2.2]oct-2-ene (cycloadduct**7**); $C_{17}H_{17}NO_3$; *^{1}H-NMR (ppm)*: 1.19-1.56 (m, 2H); 1.27-1.64 (m, 2H); 2.81 (d, J=8.0 Hz, H_6); 3.02 (dd, J=8.0, 3.0 Hz, H_5); 2.85 (m, H_4); 4.39 (s, $2H_9$); 5.25 (s, OH); 5.89 (dd, J=8.5, 6.0 Hz, H_3); 5.95 (d, J=8.5 Hz, H_2), 7.10-7.22 (m, $5H_{arom.}$). *IR (cm^{-1})*: 3532, 1765, 1686, 1647, 1629, 1583, 1497, 1455, 1396, 702. *MS (EI+) m/e*= 283, 255, 96. *HRMS*: calc: 283.1208; found: 283.1213. *An (%)* calc: C=72.07; H=6.05; N=4.94; found: C=71.6; H=6.1; N=5.3.



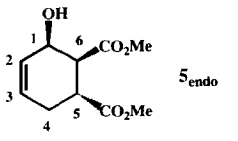
2-Benzyl-4-hydroxy-1,3,3a,4,7,7a-hexahydro-1H-isoindole-1,3-dione (cycloadduct **2**) $C_{15}H_{15}NO_3$; *^{1}H-NMR (ppm)*: 2.12 (m, H_7^{ax}); 2.59 (ddd, J=16.0, 6.0, 2.0 Hz, H_7^{eq}); 3.07 (ddd, J=9.0, 2.0 Hz, H_{7a}); 3.23 (dd, J=9.0, 6.5 Hz, H_{3a}); 3.90 (d, J=9.5 Hz, OH); 4.37 (m, H_4); 4.57 (s, CH_2Ph), 5.72 (m, H_6); 5.93 (ddd, J=10.0, 3.0, 2.0 Hz, H_5); 7.20-7.30 (m, $5H_{arom.}$). *IR (cm^{-1})*: 3620, 3506, 1765, 1691, 1605, 1497, 1457, 748, 735, 697. *MS (EI+) m/e*= 257, 239. *HRMS*: calc: 257.1052; found: 257.1043. *An (%)* calc: C=70.02; H=5.88; N=5.44; found: C=69.8; H=5.9; N=5.7.



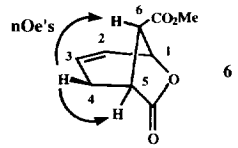
5,6-Bis(methoxycarbonyl)-1-hydroxycyclohex-2-ene (cycloadduct **4endo**) $C_{10}H_{14}O_5$; *^{1}H-NMR (ppm)*: 2.14 (m, H_4^{ax}); 2.36 (m, H_4^{eq}); 2.94 (m, H_5); 3.14 (m, H_6); 3.48 (s, OCH_3); 3.54 (s, OCH_3); 4.34 (m, H_1), 5.00 (s, OH); 5.47 (m, H_2); 5.60 (m, H_3). *IR (cm^{-1})*: 3540, 3449, 3032, 2954, 1738, 1659, 1439, 1200. *MS (EI+) m/e*= 214, 196, 182, 154. *HRMS*: calc: 214.0841; found: 214.0834. *An (%)* calc: C=56.10; H=6.59; O=37.34; found: C=55.80; H=6.45; O=37.90.



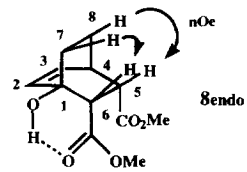
5,6-Bis(methoxycarbonyl)-1-hydroxycyclohex-2-ene (cycloadduct **5endo**) $C_{10}H_{14}O_5$; *^{1}H-NMR (ppm)*: 1.91 (m, H_4^{ax}); 2.29 (m, H_4^{eq}); 2.67 (dd, J=12.0, 4.0 Hz, H_6); 2.85 (m, H_5); 3.54 (2 s, OCH_3); 4.20 (m, H_1), 4.97 (s, OH); 5.72 (m, H_2-H_3). *IR (cm^{-1})*: 3610, 2954, 1738, 1657, 1439. *MS (EI+) m/e*= 182, 154. *HRMS*: calc: 182.0579; found: 182.0579. *An (%)* calc: C=56.10; H=6.59; O=37.34; found: C=55.65; H=6.60; O=38.0.



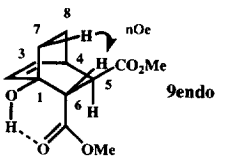
Lactone **6** $C_9H_{10}O_4$; *^{1}H-NMR (ppm)*: 2.29 (m, H_4); 2.57 (m, H_4'); 3.05 (m, H_5); 3.22 (s, H_6); 3.63 (s, OCH_3); 4.92 (bd, J=5.5 Hz, H_1), 5.86 (bd, J=9.5 Hz, H_3); 6.21 (ddt, J=9.5, 5.5, 2.0 Hz, H_2). *IR (cm^{-1})*: 2955, 2914, 2847, 1791, 1737, 1634, 1437, 1200. *MS (EI+) m/e*= 182 (w), 151, 138, 123, 79. *HRMS*: calc: 151.0395; found: 151.0408.



1-Hydroxy-5,6-bis(methoxycarbonyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **8endo**) $C_{12}H_{16}O_5$; *^{1}H-NMR (ppm)*: 1.16-1.52 (m, $2H_7$+$2H_8$); 2.65 (m, H_4); 3.01 (d, J=11.0 Hz, H_6); 3.10 (dd, J=11.0, 2.5 Hz, H_5); 3.36 (s, OCH_3); 3.41 (s, OCH_3); 5.23 (s, OH); 5.90 (d, J=8.5 Hz, H_2); 6.08 (dd, J=8.5, 6.5 Hz, H_3). *IR (cm^{-1})*: 3590, 3548, 3060, 3011, 1742, 1621, 1435, 1200. *MS (EI+) m/e*= 240, 209, 181, 96. *HRMS*: calc: 240.0998; found: 240.0999.

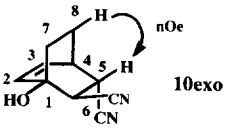


1-Hydroxy-5,6-bis(methoxycarbonyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **9endo**) $C_{12}H_{16}O_5$; *^{1}H-NMR (ppm)*: 1.15-1.48 (m, $2H_7$+$2H_8$); 2.55 (dd, H_5); 2.72 (m, H_4); 2.93 (d, J=5.0 Hz, H_6); 3.49 (s, OCH_3); 3.57 (s, OCH_3); 5.26 (s, OH); 5.97 (m, H_2); 6.13 (m, H_3). *IR (cm^{-1})*: 3580, 3528, 1734, 1620, 1437, 1200. *MS (EI+) m/e*= 240, 209, 181, 96. *HRMS*: calc: 240.0998; found: 240.0999.



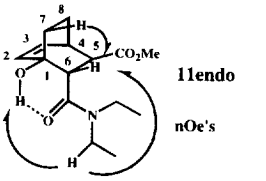
9endo

1-Hydroxy-5,6-dicyanobicyclo[2.2.2]oct-2-ene (cycloadduct **10exo**) $C_{10}H_{10}N_2O$; *^{1}H-NMR (pyridine d_5, ppm)*: 1.36-1.76 (m, $2H_8$); 1.57-2.32 (m, $2H_7$); 2.91 (m, H_4); 3.46 (dd, J=5.5, 2.5 Hz, H_6); 3.64 (dd, J=5.5, 2.0 Hz, H_5); 6.28 (dd, J=8.5, 6.0 Hz, H_3); 6.62 (d, J=8.5 Hz, H_2). *IR (cm^{-1})*: 3593, 3068, 3053, 2253, 2243, 1617, 1455. *MS (EI+) m/e*= 174, 146, 96. *HRMS*: calc: 174.0793; found: 174.0791.



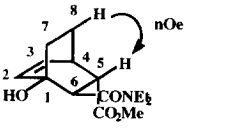
10exo

1-Hydroxy-5-methoxycarbonyl-6-(N,N-diethylcarbamoyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **11endo**) $C_{15}H_{23}NO_4$; *^{1}H-NMR (ppm)*: 1.14 (m, H_8); 1.17 (m, H_7); 1.49 (m, H_7+$H_{8'}$); 2.69 (m, H_4+H_5); 3.16 (bd, J=6 Hz, H_6); 3.50 (s, OCH_3); 5.10 (s, OH); 5.93 (d, J=8.5 Hz, H_2); 6.03 (dd, J=8.5, 6.5 Hz, H_3). *IR (cm^{-1})*: 3523, 1735, 1631, 1450, 1200. *MS (EI+) m/e*= 281, 186, 96. *HRMS*: calc: 281.1627; found: 281.1624.



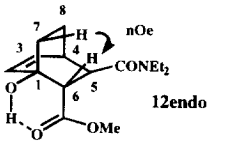
11endo

1-Hydroxy-5-methoxycarbonyl-6-(N,N-diethylcarbamoyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **11exo**) $C_{15}H_{23}NO_4$; *^{1}H-NMR (ppm)*: 0.89 (m, H_7); 1.20 (ddt, J=12.0, 11.0, 3.0 Hz, H_8); 1.62 (m, $H_{8'}$); 1.90 (ddd, J=11.0, 10.0, 3.0 Hz, $H_{7'}$); 2.77 (m, H_4); 2.95 (m, H_5+H_6); 3.40 (s, OCH_3); 5.18 (s, OH); 5.96 (dd, J=8.5, 6.5 Hz, H_3); 6.16 (bd, J=8.5 Hz, H_2).
^{13}C-NMR (ppm): 13.15, 13.98, 25.14, 27.25, 32.04, 41.66, 46.95, 47.57, 51.53, 73.38, 129.43, 140.97, 170.02, 174.03. *IR (cm^{-1})*: 3610, 1733, 1615, 1450, 1200. *MS (EI+) m/e*= 281, 186, 96. *HRMS*: calc: 281.1627; found: 281.1616.



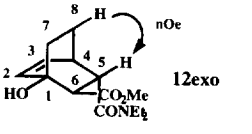
11exo

1-Hydroxy-6-methoxycarbonyl-5-(N,N-diethylcarbamoyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **12endo**) $C_{15}H_{23}NO_4$; *^{1}H-NMR (ppm)*: 1.03 (m, H_8); 1.15 (m, H_7); 1.54 (m, $H_{7'}$); 1.63 (m, $H_{8'}$); 2.41 (m, H_4); 2.68 (ddd, J=5.5, 2.0, 1.5 Hz, H_5); 3.11 (d, J=5.5 Hz, H_6); 3.46 (s, OCH_3); 5.15 (s, OH); 5.99 (bd, J=8.5 Hz, H_2); 6.17 (dd, J=8.5, 6.5 Hz, H_3). *IR (cm^{-1})*: 3584, 3532, 1729, 1646, 1450, 1200. *MS (EI+) m/e*= 281, 186, 96.



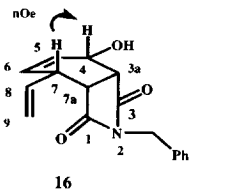
12endo

1-Hydroxy-6-methoxycarbonyl-5-(N,N-diethylcarbamoyl)bicyclo[2.2.2]oct-2-ene (cycloadduct **12exo**) $C_{15}H_{23}NO_4$; *^{1}H-NMR (ppm)*: 1.01 (m, H_7); 1.21 (m, H_8); 1.66 (m, $H_{8'}$); 1.89 (m, H_7); 2.44 (m, H_4); 2.81 (bd, J=6.0 Hz, H_6); 2.94 (m, H_5); 3.53 (s, OCH_3); 5.30 (s, OH); 5.87 (dd, J=8.5, 6.5 Hz, H_3); 6.05 (bd, J=8.5 Hz, H_2). *IR (cm^{-1})*: 3597, 3529, 1736, 1719, 1647, 1450, 1200. *MS (EI+) m/e*= 281, 186, 96.



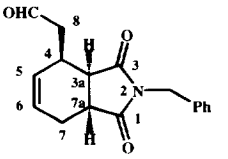
12exo

2-Benzyl-4-hydroxy-7-vinyl-1,3,3a,4,7,7a-hexahydro-1H-isoindole-1,3-dione (cycloadduct **16endo**) $C_{17}H_{17}NO_3$; *^{1}H-NMR (ppm)*: 3.07 (m, H_7); 3.21 (dd, J=8.5, 6.5 Hz, H_{3a}); 3.25 (dd, J=8.5, 7.0 Hz, H_{7a}); 4.39 (m, H_4); 4.45 (s, CH_2Ph); 4.96 (bd, J=16.0 Hz, H_9); 5.06 (bd, J=10.5 Hz, $H_{9'}$); 5.24 (s, OH); 5.75 (dt, J=9.5, 3.0 Hz, H_6); 5.88 (dd, J=9.5, 2.5 Hz, H_5); 6.08 (ddd, J=16.0, 10.5, 8.0 Hz, H_8); 7.15 (m, $5H_{arom}$). *IR (cm^{-1})*: 3501, 1770, 1697, 1642, 1630, 1401, 898, 699, 737. *MS (EI+) m/e*= 283, 265, 188, 96, 91. *HRMS*: calc: 283.1210; found: 283.1208.



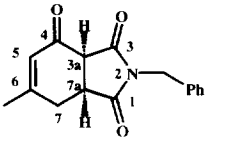
16

2-Benzyl-4-(2-oxoethyl)-1,3,3a,4,7,7a-hexahydro-1H-isoindole-1,3-dione (cycloadduct **17endo**) $C_{17}H_{17}NO_3$; *^{1}H-NMR (ppm)*: 2.13 (m, H_{7ax}); 2.45 (bdd, J=15.0, 7.0 Hz, H_{7eq}); 2.75 (m, H_4); 2.85 (m, H_8); 3.02 (m, $H_{8'}$); 3.21 (m, H_{7a}); 3.28 (m, H_{3a}); 4.43 (s, CH_2Ph); 5.59 (bdd, J=9.0, 3.0 Hz, H_5); 5.81 (m, H_6); 7.08-7.21 (m, $5H_{arom}$); 9.69 (s, CHO). *IR (cm^{-1})*: 2730, 1772, 1723, 1698, 1606, 1401, 734, 699. *MS (EI+) m/e*= 283, 255, 188, 91. *HRMS*: calc: 283.1210; found: 283.1208.



17

2-Benzyl-6-methyl-1,3,3a,4,7,7a-hexahydro-1H-isoindole-1,3,4-trione (cycloadduct **18**) $C_{16}H_{15}NO_3$; *1H-NMR (ppm)*: 1.89 (s, CH_3); 2.66 (bdd, J=18.0, 8.0 Hz, H_{7eq}); 2.95 (bd, J=18.0 Hz, H_{7ax}); 3.62 (ddd, J=8.5, 8.0, 2.0 Hz, H_{7a}); 3.73 (d, J=8.5 Hz, H_{3a}); 4.49 (s, CH_2Ph); 5.85 (bs, H_5); 7.08-7.22 (m, $5H_{arom}$). *IR (cm^{-1})*: 1703, 1654, 1634, 1605, 1584, 1495, 1455, 701. *MS (EI+) m/e*= 269, 91, 42. *HRMS*: calc: 269.1052; found: 269.1053.



18

REFERENCES AND NOTES

1. a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 28-; b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, **1990**; c) Trost, B.M.; Fleming, I.; Paquette, L.A. *Comprehensive Organic Synthesis* **1991**, *Vol. 5*, 315-399; d) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876-889.

2. a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436-4437; b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741-761.

3. Graig, D. *Chem. Soc. Rev.* **1987**, *16*, 187-238 and references cited therein.

4. Some exemples of "temporary covalent tethers" in Diels-Alder cycloadditions are available. Boron: a) Nicolaou, K.C.; Liu, J.J.; Hwang, C.K.; Dai, W.M.; Guy, R.K. *J. Chem. Soc. Chem. Commun.* **1992**, 1118-1120; b) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171-1172. Mg/Al: c) Stork, G.; Chan, T.Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595-6596. Silicon: ref. 3c) and d) Stork, G.; Chan, T.Y.; Breault, G. *J. Am. Chem. Soc.* **1992**, *114*, 7578-7579; e) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478-6480. Hydrogen bonds have sometimes been used as putative "transient tethers". An early exemple could be found in Woodward's reserpine synthesis: f) Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; .Kierstead, R.W; *Tetrahedron* **1958**, *2*, 1-57; g) Okamura, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Chem. Lett.* **1996**, 193-194; h) Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1991**, *113*, 7630-7640; i) Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1990**, *112*, 6743-6744; j) Trost, B.M.; Lee, D.C. *J. Org. Chem.* **1989**, *54*, 2274-2275; k) Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S.; Siret, P.; Keck, G.E.;Gras, J.L. *J. Am. Chem. Soc.* **1978**, *100*, 8031-8034.

5. A similar effect of regio- and stereocontrol in 1,3 dipolar cycloadditions by internal Lewis acid coordination was recently published: Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49-50; Kanemasa, S.; Tsuruoka, T.; Yamamoto, H. *Tetrahedron Lett.* **1995**, *36*, 5019-5022; Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324-2339; Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87-90.

6. Will be published separately.

7. Stork, G.; Hurdlik, P.F. *J. Am. Chem. Soc.* **1968**, *90*, 4462-4464.

8. Ref. 4h) and a) Suckling, C.J.; Tedford, M.C.; Bence, L.M.; Irvine, J.I.; Stimson, W.H. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1925-1929; b) Baldwin, S.W.; Greenspan, P.; Alaimo, C.; McPhail, A.T. *Tetrahedron Lett.* **1991**, *32*, 5877-5880; c) Larsen, D.S.; Stoodley, R.J. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1841-1852.

9. Such tandem reaction sequences are known to give γ-substitution products: Ballester, P.; Costa, A.; Raso, A.G.; Gomez-Solivellas, A.; Mestres, R. *J. Chem. Soc. Perkin Trans. I* **1988**, 1711-1717; Ballester, P.; Garcia-Raso, A.; Gomez-Solivellas, A.; Mestres, R. *Tetrahedron Lett.* **1985**, *26*, 2485-2488.

10. Cascade Michael-Michael or "anionic" stepwise Diels-Alder cycloadditions are known: a) Ihara, M.; Makita, K.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 6008-6013 and references cited therein. b) Riant, O.; Kagan, H.B. *Tetrahedron* **1994**, *50*, 4543-4554; c) Koerner, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 2662-2672; and **1989**, *54*, 6-9; d) Marchand, A.P.; Annarpurna, P.; Watson, W.H.; Nagl, A. *J. Chem. Soc. Chem. Commun.* **1989**, 281-282; e) Nagaoka, H.; Kobayashi, K.; Okamura, T.; Yamada, Y.; *Tetrahedron Lett.* **1987**, *28*, 6641-6644 and **1987**, *28*, 2021-2024; f) Ihara, M.; Katagi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Chem. Commun.* **1987**, 721-722; g) Ihara, M.; Takahashi, T.; Shimizu, N.; Ishida, Y.; Sudow, I.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Chem. Commun.* **1987**, 1467-1468; h) Cory, R.M.; Renneboorg, R.M. *J. Org. Chem.* **1984**, *49*, 3898-3904; i) Gibbons, E.G. *J. Am. Chem. Soc.* **1982**, *104*, 1767-1769; j) Roberts, M.R.; Schlessinger, R.H. *J. Am. Chem. Soc.* **1981**, *103*, 724-725; k) Gibbons, E.G. *J. Org. Chem.* **1980**, *45*, 1540-1541; White, K.B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439-2443; l) Spitzer, D. *Tetrahedron Lett.* **1978**, *34*, 3349-3350; m) Kraus, G.A.; Roth, B. *Tetrahedron Lett.* **1977**, 3129-3132; n) Kraus, G.A.; Sugimoto, H. *Tetrahedron Lett.* **1977**, 3929-3930; o) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jp.* **1975**, *48*, 3769-3770; p) Ohnuma, T.; Oishi, T.; Ban, Y. *J. Chem. Soc. Chem. Commun.* **1973**, 301-302.

11. For a stepwise mechanism, rapid rotation around the C5-C6 bond in the Michael addition intermediate would yield a mixture of cis/trans products, irrespective of the dienophile stereochemistry.

12. Prepared from 1-trimethylsiloxy-1,3-cyclohexadiene: Clarke, C.; Fleming, I.; Fortunak, J.D.M.; Gallagher, P.T. *Tetrahedron* **1988**, *44*, 3931-3944.

13. a) Cruse, W.B.T.; Fleming, I.; Gallagher, P.T.; Kennard, O. *J. Chem. Res.* **1979**, 372-373; b) Fleming, I.; Michael, J.P.; Overman, L.E.; Taylor, G.F. *Tetrahedron Lett.* **1978**, 1313-1314.

14. 1-Trimethylsiloxy-1,3,5-hexatriene is a mixture of E,E,E (roughly 75%) and Z,E,E isomers. Traces of other stereoisomers are also present. A slight excess was used (1.5 equiv.).

15. Both acidic (protic) and ketone/aldehyde-containing dienophiles did not give the cycloaddition reaction with diene **13**, setting the major limitations of this methodology.

16. Corey, E.J.; Soo Kim, S. *Tetrahedron Lett.* **1990**, *31*, 3715-3719; Corey, E.J.; Yu, C-M.; Soo Kim, S. *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.

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