

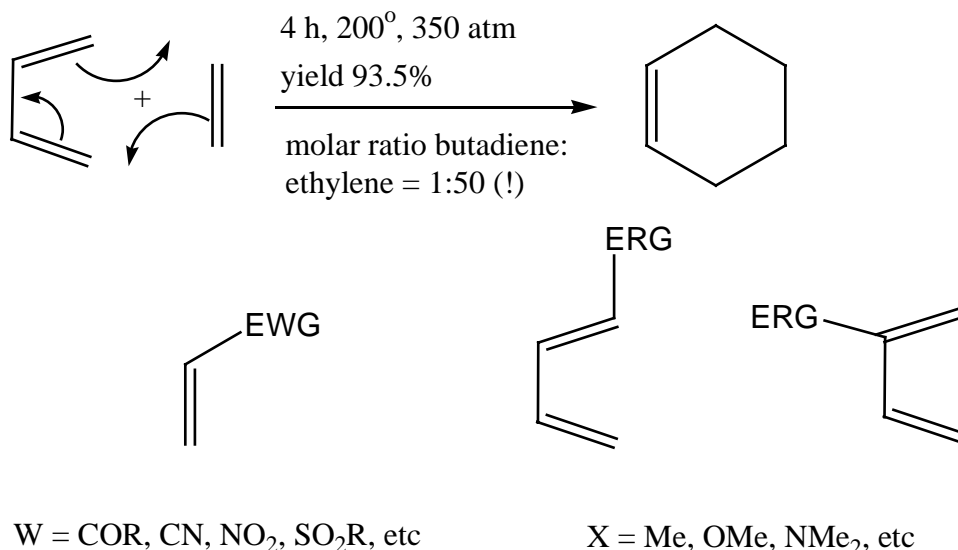
## Appendix.

### *Diels-Alder Reactions*

#### A. BACKGROUND INFORMATION.

One of the most efficient method (high yield, controlled stereochemistry, diverse functionality) to construct rings from smaller fragments is via *cycloaddition reactions*. The reverse reaction, namely splitting of a ring into smaller fragments is termed *cycloreversion reaction* is also an important synthetic tool. (For example, in the present experiment it is the cracking of cyclopentadiene dimer to cyclopentadiene monomer.) Six-membered ring built from fragments of four atoms linked together by two conjugated double bonds (diene) and a fragment containing two atoms linked by a double bond or triple bond (dienophile) is known as Diels-Alder<sup>1</sup> (**D-A**) reaction. It is often shorthand as a [4+2]- $\pi$ -electron cycloaddition. During the **retro-D-A**, a six-membered ring is split into a diene (often an aromatic compound) and a homonuclear (alkene, alkyne) or heteronuclear (CO)  $\pi$  bond.

The simplest example of a **D-A** reaction is the reaction between butadiene and ethylene to form cyclohexene. Both the diene and the dienophile display a very low reactivity. Please note the very sluggish reaction conditions: high pressure and unusual high butadiene: ethylene molar ratio (Swiss patent, *Chem. Abstract* **89**, 59709).

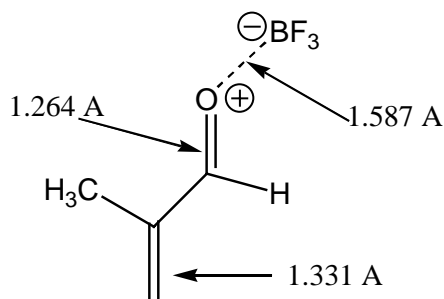


Nevertheless, dienophile substituted with electron withdrawing group(s) and/or diene substituted with electron donor group(s) reacts at lower temperature, at atmospheric pressure while the cyclohexene derivatives result with medium to very high yield. An alternative version is the **inverse electron demand D-A** reaction when an *electron-rich alkene* reacts with an *electron-poor diene*.

The diene must be able to assume *s-cis* conformation. If the conjugated double bonds are rigidly fixed in the *s-trans* configuration, the respective diene do not undergo **D-A** reaction.

<sup>1</sup> Otto Diels and his student Kurt Alder received the Nobel Prize in 1950 “for their discovery and development of the diene synthesis.” The first paper, in a series that linked forever their names, is: Diels, O.; Alder, K. *Ann.* **1928**, 460, 98.

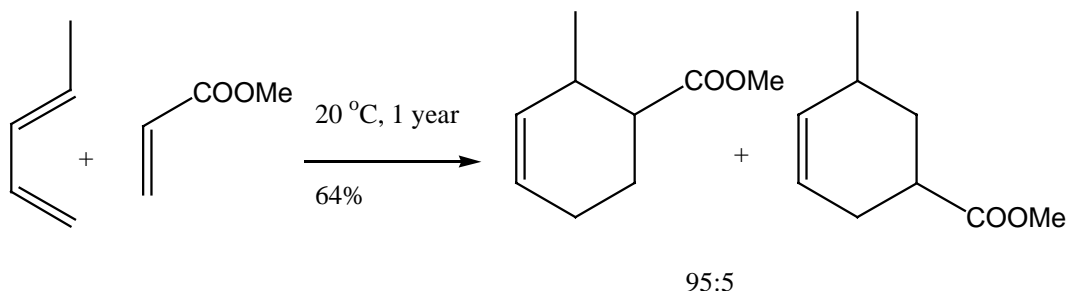
Larger rate acceleration (shorter reaction time, room or lower temperature, often with an increase in the regioselectivity) can be achieved using Lewis acid catalysts like  $\text{AlCl}_3$ ,  $\text{Et}_2\text{AlCl}$ ,  $\text{BF}_3$ ,  $\text{B}(\text{OAc})_3$ ,  $\text{ZnCl}_2$ ,  $\text{SnCl}_4$ ,  $\text{TiCl}_4$ . Because the Lewis acid coordinates at the Lewis base side of the dienophile, for example, at the carbonyl oxygen of methacrolein makes the CO group even more electron-withdrawing and, therefore, more reactive. The crystalline phase (X-ray, see figure below) and in solution structure (Nuclear Overhauser Effect) of the methacrolein boron trifluoride are both displaying an *s-trans* frame of the  $\alpha,\beta$ -enal and the Lewis acid coordinated *syn* to the lone pair to the formyl proton.<sup>2</sup>



### Stereochemistry of the D-A reaction.

1. Regioselectivity.
2. Stereoselectivity:
  - a. Diastereoselective (*endo*, *exo*).
  - b. Enantioselective (R, S).

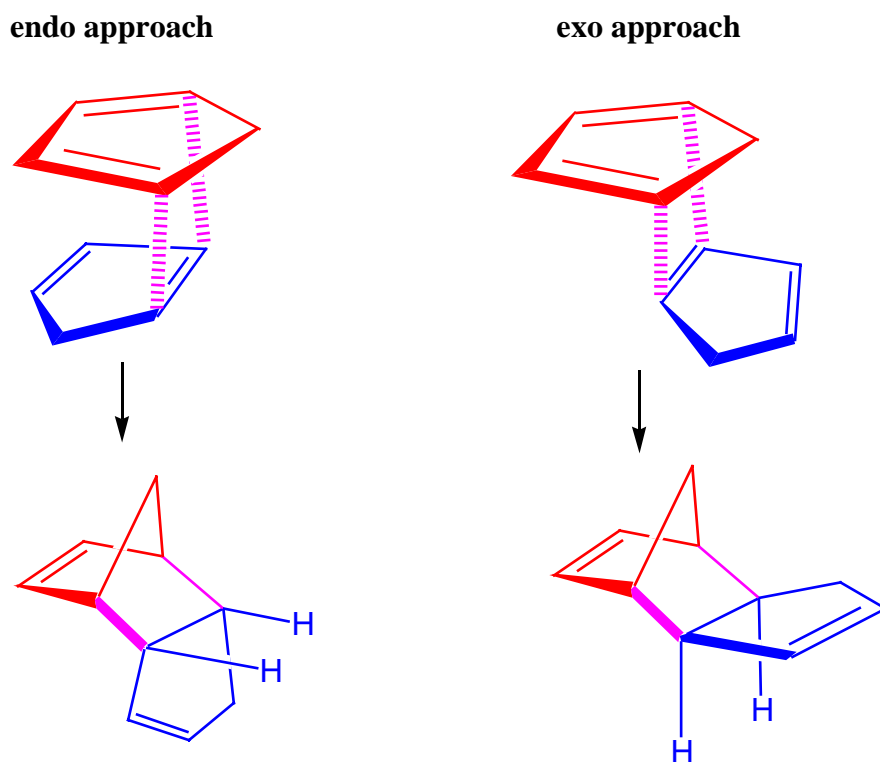
1. Unsymmetrical diene like piperylene reacts with methyl acrylate to yield two isomeric adducts (two regioisomers), that differ only by the relative orientation of the two substituents, methyl and carbomethoxy, respectively.



2a. In absence of a catalyst, *endo* product is preferentially formed (*Alder endo rule*). Cycloaddition of methacrolein to cyclopentadiene (see Table 1) yields a mixture of **exo-CHO-3** and **endo-CHO-3** diastereoisomers in a ratio that is dramatically dependent on reaction conditions. For example, at relative high temperature and longer reaction time the aldehyde group shows a preference for *endo* position, (see entry 1-3). At lower temperature and in presence of a Lewis catalyst (see entry 4) *exo* diastereoisomer is preponderantly formed. For example, cyclopentadiene, the diene employed in the

<sup>2</sup> Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Letters* **1992**, 33, 6945.

present experiment, has a limited shelf lifetime at room temperature (8% is converted into its dimer in 4 h and 50% in 24 h) because it reacts with itself to form the *endo* diastereoisomer:



2b. **D-A** reactions make simultaneously two carbon-carbon bonds, and if the product lacks plane of symmetry, create four stereocenters in the process. Thus, a synthesis of a molecule containing several stereocenters via a Diels-Alder reaction may be particularly efficient, provided that the relative and absolute stereochemistry of the Diels-Alder reaction can be controlled. There is no general way of accomplishing this objective for all types of Diels-Alder reactions, but the catalyst developed recently (1989) in Hisashi Yamamoto's group. (Nagoya University) provide good stereocontrol with a number of useful combinations of substrates.<sup>3</sup>

<sup>3</sup> For a comprehensive review of the effective catalysts inducing *ee* in the range of 87-99% in the cycloaddition of cyclopentadiene to methacrolein see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, 37, 388.

Table 1. Selected literature example of non-catalyzed (entries 1–3, NA means not available), Lewis acid catalyzed (entry 4) and Lewis acid and Bronsted and Lewis acid catalyzed (entries 5-7) cycloaddition of methacrolein to cyclopentadiene.

Entry	Molar ratio Cyclopentadiene/ methacrolein	Time (h)	solvent	Temperature (°C)	catalyst	<b>Exo- CHO-3 /endo- CHO-3</b>	Yield %	ee% (absolute config.)	Lit .
1	1:0.8	2-3	-	100	-	Mostly <i>endo</i>	74	-	<sup>4</sup>
2a	1 : 1.19	11	-	150	-	Mostly <i>endo</i>	84	-	<sup>5</sup>
2b	1 : 0.8	10	-	170	-		7(!)		
3a	NA	NA	NA	NA	NA	70:30	NA	NA	<sup>6</sup>
3b	1 : 0.5	10	-	120	-	58:42	74	-	<sup>7</sup>
4	1 : 0.8	?	toluene	-50	AlCl <sub>3</sub>	94:6	78	-	<sup>8</sup>
5	1 : 0.88	3	toluene	-78	Chiral* ROAlCl <sub>2</sub>	98:2	69	72	<sup>9</sup>
6	4 : 1	1.5	CH <sub>2</sub> Cl <sub>2</sub>	-78	(RO) <sub>4</sub> B**	>99:1	99	99 (R)	<sup>10</sup>
7	3 : 1	3	CH <sub>2</sub> Cl <sub>2</sub>	-78	(Acyloxy) borane***	90:10	85	96 (R)	<sup>11</sup>

\* From menthol and EtAlCl<sub>2</sub>

\*\* R is a binaphthol derivative (for more details see the paper)

\*\*\* The catalyst is the one prepared in the present experiment. The catalyst derived from natural tartaric acid yield the R isomer.

<sup>4</sup> **Chemically assigned:** Beckmann, S.; Bamberger, R. *Liebigs Ann. Chem.* **1953**, 580, 198.

<sup>5</sup> **Chemically assigned:** Meek, J. S.; Trapp, W. B. *J. Am. Chem. Soc.* **1957**, 79, 3909.

<sup>6</sup> **First <sup>1</sup>H NMR assignment,** *exo* CHO absorbs with 0.31 ppm downfield from *endo* CHO: Moen, R. V.; Makowski, H. S. *Analytical Chem.* **1971**, 43, 1629.

<sup>7</sup> Griesbeck, A. G. *Synthesis.* **1990**, 144.

<sup>8</sup> Bloch, R.; Gilbert, L. *Tetrahedron* **1988**, 44, 2523.

<sup>9</sup> Hashimoto, S.-I.; Komeshima, N.; Koga, K. *J.C.S. Chem. Comm.* **1979**, 437.

<sup>10</sup> Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, 120, 6920.

<sup>11</sup> Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, 54, 1481.

## B. An Electronic Insight into Diels-Alder Reactions.

The regio- and stereoselectivities of Diels-Alder cycloaddition are easily rationalized by examining only the frontier molecular orbitals (**F.M.O.**)<sup>12</sup> of diene and dienophiles. Frontier orbitals are the highest occupied molecular orbital (**HOMO**) and lowest unoccupied molecular orbital (**LUMO**). Woodward and Hoffmann<sup>13</sup> pointed out in 1965 that if the cycloaddition is concerted, during the D.-A. reaction the **HOMO** of the diene interacts in phase (constructive overlap) with **LUMO** of the dienophile:

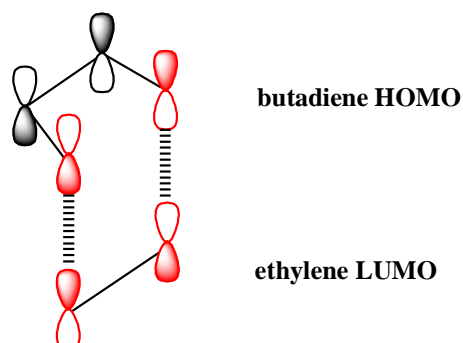


Fig. A1. In phase interaction of HOMO of butadiene with LUMO of ethylene.

Based on perturbation theory, Klopman<sup>14</sup> and Salem<sup>15</sup> have derived an expression for energy gain when the orbitals of one reactant interacts with those of another. There are three terms that contribute to energy changes: the first is a closed shell repulsion (occupied orbitals of diene repel the occupied orbitals of dienophile), the second term is Coulombic repulsion and attraction (important for ionic reactions) and the third is the interaction of all filled orbitals with all the unfilled of correct symmetry (especially the HOMO of diene interact with LUMO of dienophile that makes the largest contribution to equation 1). For a cycloaddition reaction the third term is defined as:

$$\Delta E = \sum_r^{\text{occ.}} \sum_s^{\text{unocc.}} - \sum_r^{\text{unocc.}} \sum_s^{\text{occ.}} \frac{2(\sum_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s} \quad (1)$$

where:

$c_{ra}$  is the coefficient of atomic orbital  $a$  in molecular orbital  $r$ , where  $r$  refers to molecular orbitals of one molecule and  $s$  refers to those on the other.

$E_r$  is the energy of molecular orbital  $r$ .

$\beta_{ab}$  is the resonance integral; it is assumed to be proportional with the overlap integral  $S$ .

2 is the occupancy number (interaction involves two electrons).

<sup>12</sup> Review: Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57.

<sup>13</sup> Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 4388; see also the review: Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim, 1970.

<sup>14</sup> Klopman, G. *J. Am. Chem. Soc.* **1968**, 90, 223.

<sup>15</sup> Salem, L. *J. Am. Chem. Soc.* **1968**, 90, 543 and 553.

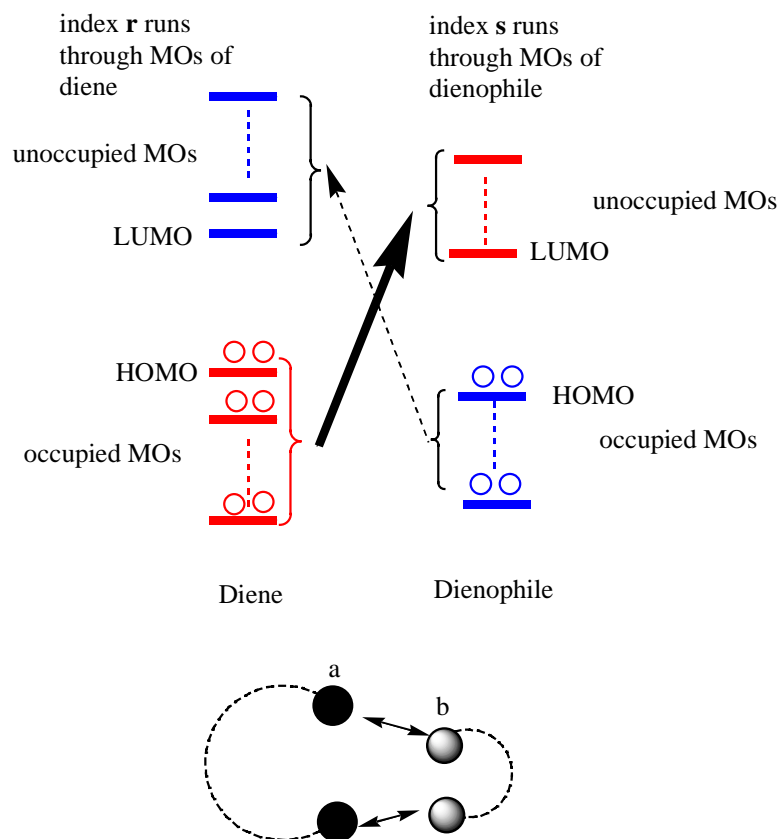


Fig. A2. Orbitals interaction in a Diels-Alder reactions.

According to **F.M.O.** the reactivity is correlated with the properties of highest filled and lowest vacant orbitals of the reacting molecules. The interaction energy described in equation (1) now is simplified to equation (2).

$$\Delta E = \frac{2(c_{HOMO1}^{diene} c_{LUMO1}^{dienophile} \beta_{11} + c_{HOMO4}^{diene} c_{LUMO2}^{dienophile} \beta_{24})^2}{E_{HOMO}^{diene} - E_{LUMO}^{dienophile}} + \frac{2(c_{HOMO1}^{dienophile} c_{LUMO1}^{diene} \beta_{11} + c_{HOMO2}^{dienophile} c_{LUMO4}^{diene} \beta_{24})^2}{E_{HOMO}^{dienophile} - E_{LUMO}^{diene}} \quad (2)$$

In practice it was noted that for numerous diene-dienophile  $E_{HOMO}^{diene} - E_{LUMO}^{dienophile} \gg E_{HOMO}^{dienophile} - E_{LUMO}^{diene}$ , therefore  $\Delta E$  becomes:

$$\Delta E = \frac{2(c_{HOMO1}^{diene} c_{LUMO1}^{dienophile} \beta_{11} + c_{HOMO4}^{diene} c_{LUMO2}^{dienophile} \beta_{24})^2}{E_{HOMO}^{diene} - E_{LUMO}^{dienophile}} \quad (3)$$

Thus, the larger are the coefficients and the smaller is the **HOMO-LUMO** energy gap, the lower is the activation energy for the respective **D.-A.** reaction.

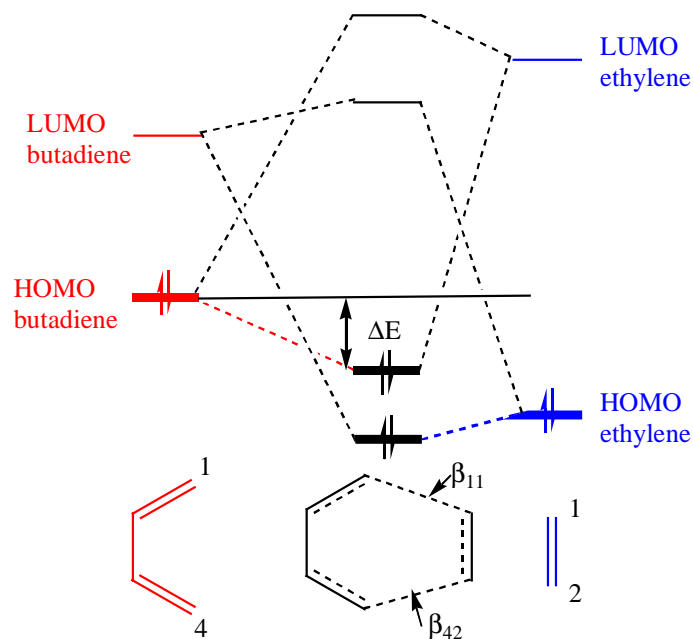


Fig. A3. F.M.O. interaction in a Diels-Alder reactions.

1. **Substituents effect.** Why an **electron-releasing group (ERG)** on the butadiene skeleton and **electron withdrawing-group(s) (EWG)** on ethylene make the **D.-A.** reaction efficient and rapid?

**ERG** are “pushing” up the diene’s **HOMO** (see Fig. A5). **EWG** are “pushing” down the dienophile’s **LUMO** (see Fig. A6). Because the energy gap is becoming smaller,  $\Delta E$  is becoming larger (equation 3). The consequence of this effect is a dramatic increase in the rate of the cycloaddition.

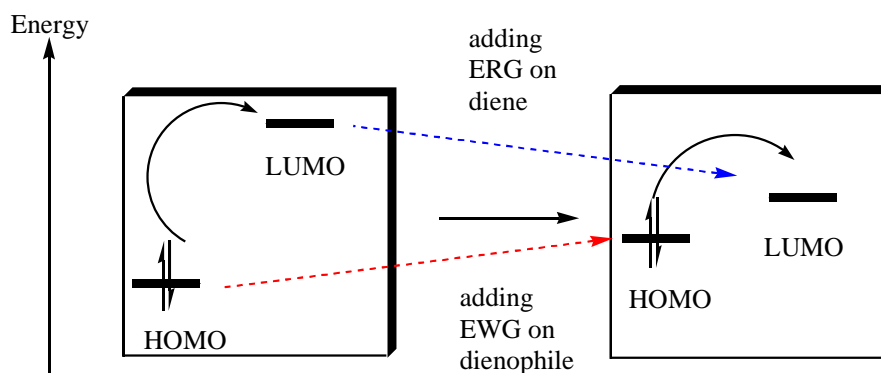


Fig. A4. Substituents effect on the HOMO-LUMO gap.

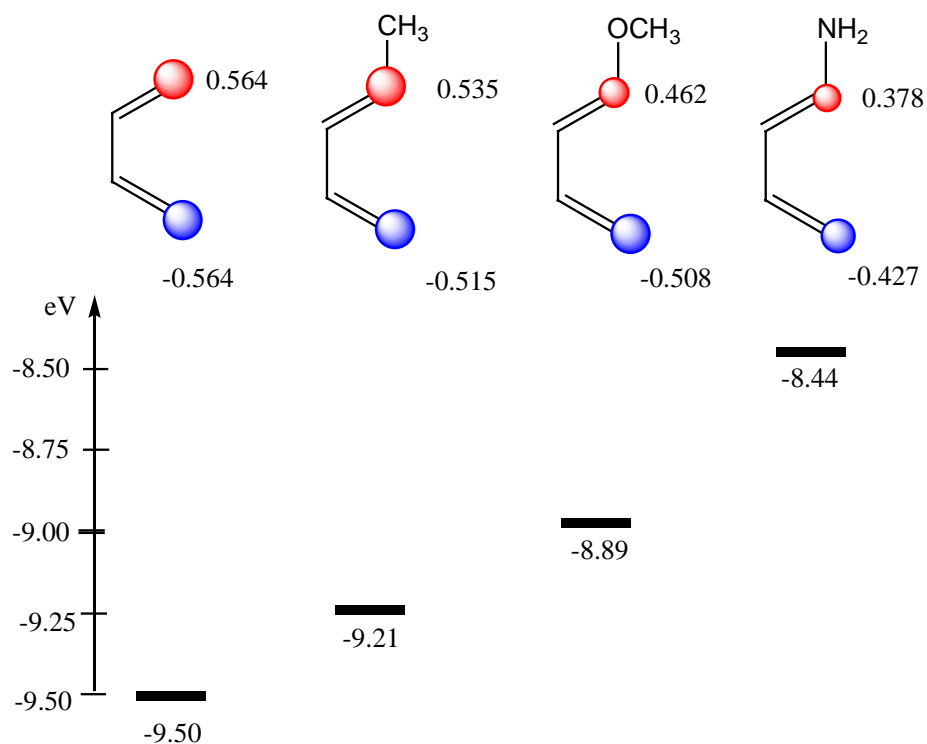


Fig. A5. Calculated (PM3-ProSpartan) HOMO energy (in eV) for some 1-substituted butadiene. The magnitude of the coefficients in the HOMO wave function at the terminal carbons is also provided. Circles with different colors means that the coefficient are of opposite signs.

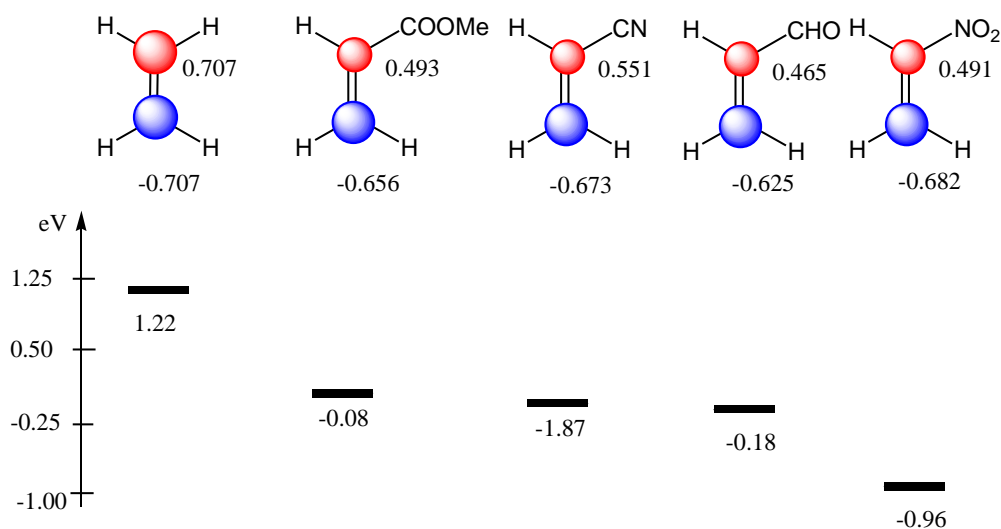
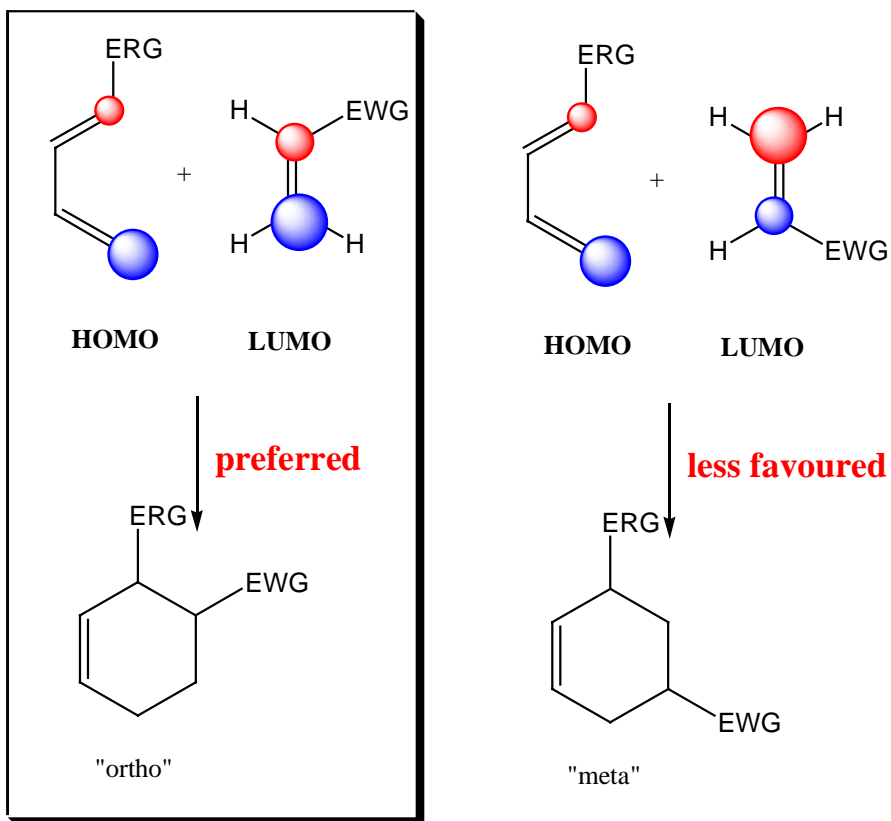


Fig. A6. Calculated (PM3-ProSpartan) LUMO energy (in eV) for some substituted Ethylene. The magnitude of the coefficients in the LUMO wave function is also provided. Circles with different colors means that the coefficient are of opposite signs.



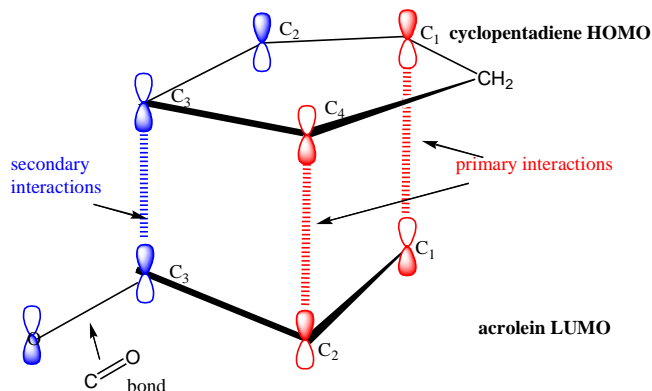
2. **Regioselectivity.** An acceptable explanation for regioselectivity can be provided by examining the F.O. of dienophile and diene. If the reaction is uncatalyzed and there is a lack of strong solvent effect, a key role in orienting the direction of the cycloaddition represents the size of the coefficient on the individual atoms that are forming the new bonds. The new bonds are formed preferentially when “large-large” and “small-small” (Houk rule<sup>16</sup>) overlap:



### 3. Diastereoselectivity.

*Endo* addition is favored as result of secondary interaction(s) (colored in blue) among the F.M.O. of diene at C<sub>2</sub>, C<sub>3</sub> and dienophile at C<sub>3</sub>. Secondary interaction will

<sup>16</sup> Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

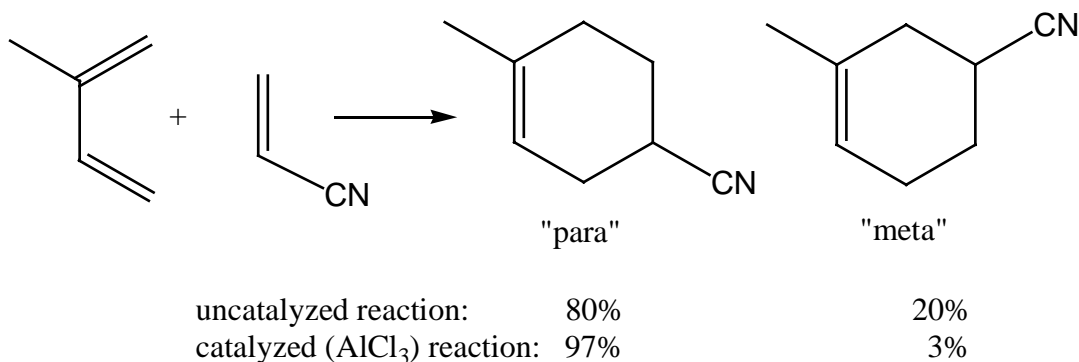


lower the height of the transition state. However, the endo diastereoisomer is less stable (because of steric repulsions) thermodynamically than the exo isomer. Exo isomer, although requires higher energy of activation is more stable thermodynamically. Endo isomer is said to be formed under *kinetic control*. Exo isomer is formed under *thermodynamic control*.

### 3. Lewis acid catalysis.

#### a. Non-chiral catalysts.<sup>17</sup>

As result of complexation of the Lewis acid with carbonyl group a large increase in the effective electronegativity of the substituent with a lowering of the dienophile LUMO. This effect contributes to reducing the energy gap in equation (3) and hence an increase in the rate of cycloaddition. For example, in the cycloaddition of isoprene to acrylonitrile<sup>18</sup>, AlCl<sub>3</sub> produces an acceleration of 10<sup>5</sup>(!) at 20 °C. Additionally, note the increase in the regioselectivity.

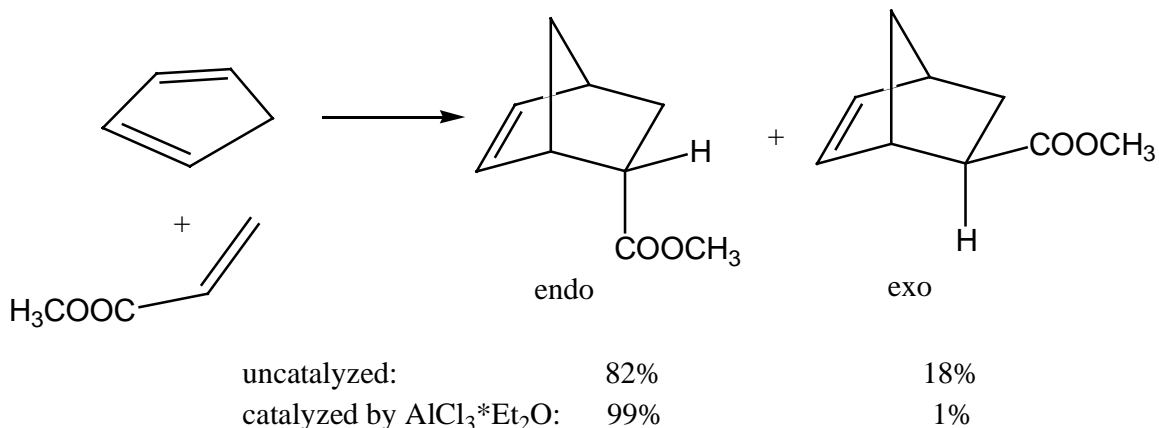


Also, the stereoselectivity, *exo:endo* ratios, increases if Lewis catalyst is employed. For example, the uncatalyzed cycloaddition of cyclopentadiene to methyl acrylate yields a

<sup>17</sup> For the **first example** of a Lewis acid catalyzed Diels-Alder reaction see: Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, 82, 4436.

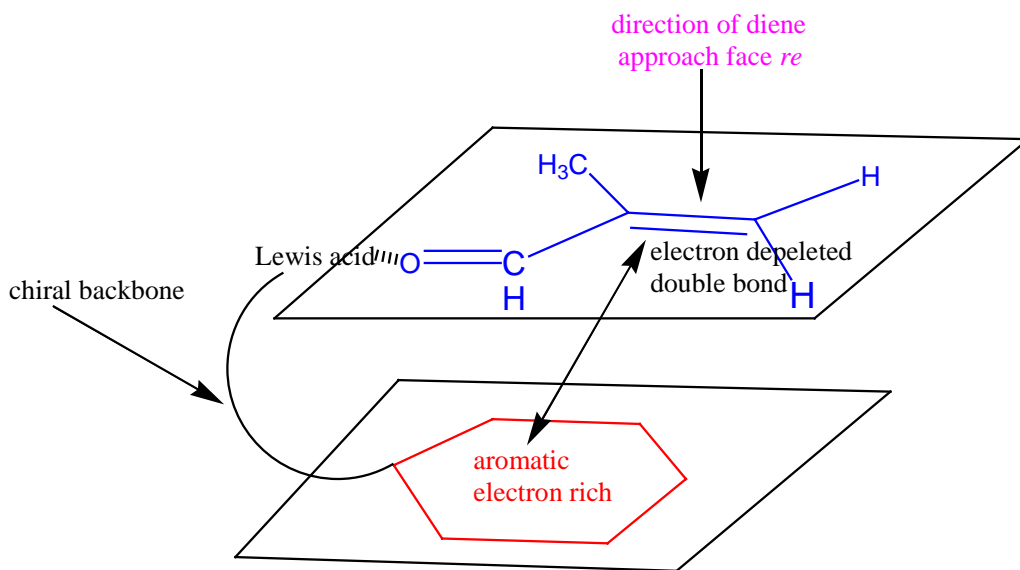
<sup>18</sup> Inukai, T.; Kojima, T. *J. Org. Chem.*, **1966**, 31, 1121.

mixture of *endo:exo* diastereoisomer of ratio 82:18; the catalyzed cycloaddition in presence of  $\text{AlCl}_3 \cdot \text{Et}_2\text{O}$  give a 99:1 mixture of *endo:exo* isomers.<sup>19</sup>



### b. Chiral Lewis acid catalysts.

Additional to the kinetic effect (low reaction temperature) that is described above, chiral Lewis catalyst induces enantioselectivity, that could reach >99% *ee*. The chiral tether could bring the aromatic ring only in one out of the two relevant conformation: either above the *re* or *si* face of the double bond.



Attractive intramolecular interactions<sup>20</sup> in the transition state among the electron depleted double bond (*acceptor*) and the electron rich aromatic ring (*donor*) will consolidate the conformation. The electron deprivation of CC bond is the effect of the

<sup>19</sup> Inukai, T.; Kojima, T. *J. Org. Chem.*, **1967**, 32, 869, 872.

<sup>20</sup> Corey, I. J.; Loh, T.-P. *J. Am. Chem. Soc.*, **1991**, 113, 8966.

conjugation with CO bond, which is further augmented by Lewis acid coordination to the oxygen.