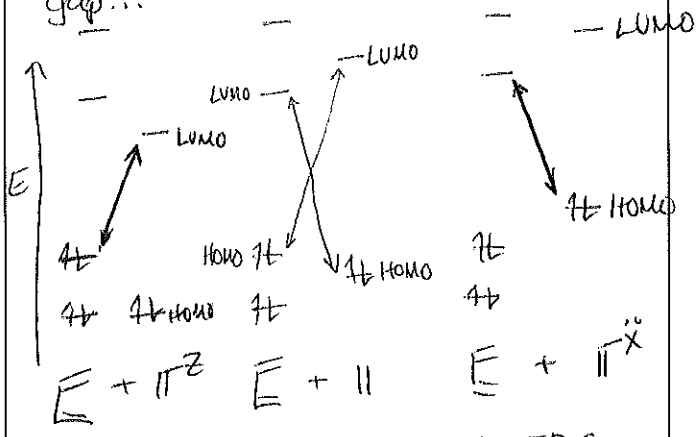
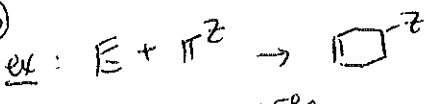
① Lecture 20 (continued)

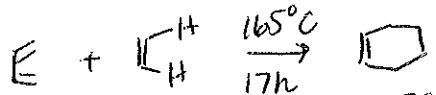
Rates & Regiochemistry of Cycloadditions.

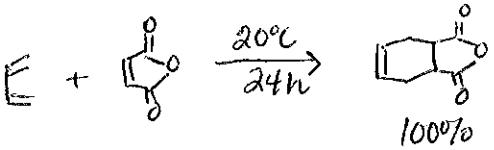
→ Substituent Effects

② Rates are determined by HOMO/LUMO gap...

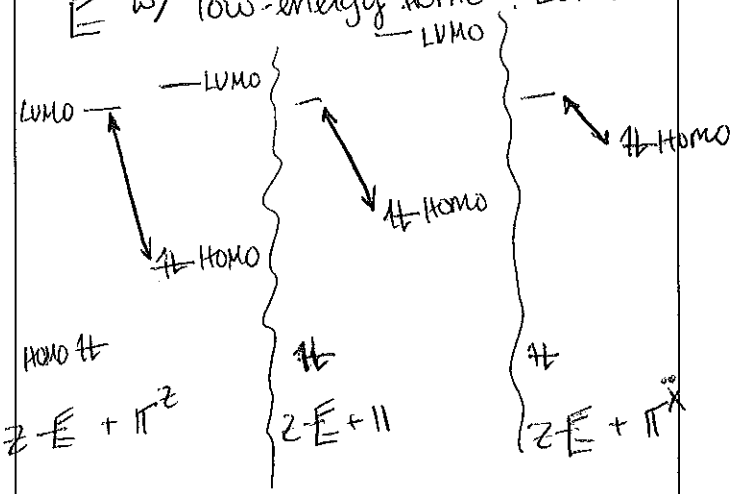


③ ex: $E + \pi^{Z} \rightarrow$ 

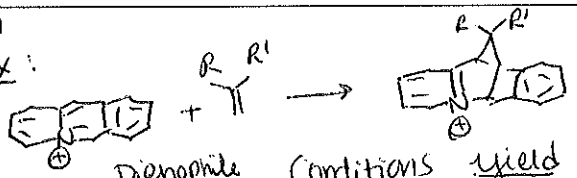




④ Inverse Electron Demand

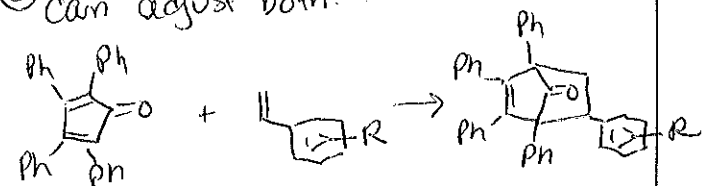


⑤ ex:



	Dienophile	Conditions	Yield
High Homo	EtO, OEt	4 min @ 25°C	75%
Medium Homo	OH	275 min @ 100°C	75%
Low Homo	CN	1080 min @ 100°C	75%

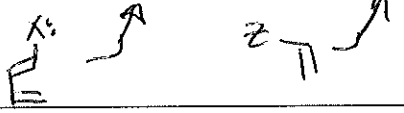
⑥ Can adjust both.



R	p-NMe2	p-OMe	H	p-Cl	m-NO2PH
k (×10⁶ M⁻¹ s⁻¹)	338	102	73	78	88

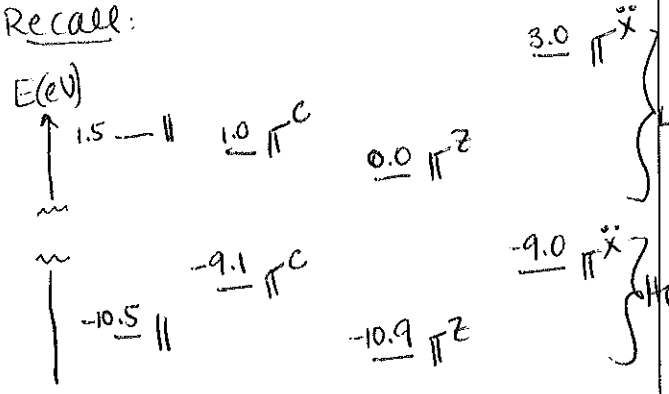
EDG ← | → EWG

Fastest rxns w/ high HOMO + low LUMO



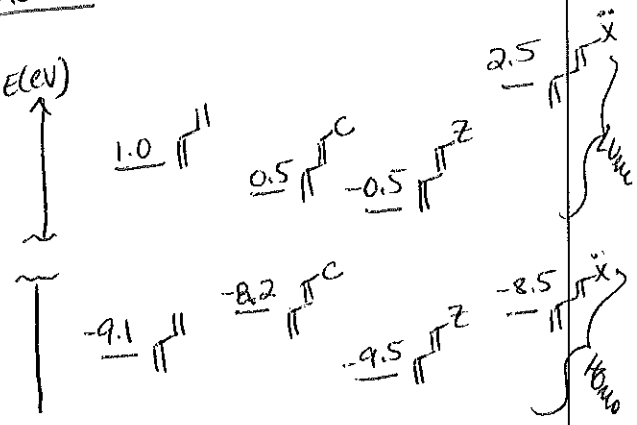
(7) Estimating Energies of Dienophiles:

Recall:



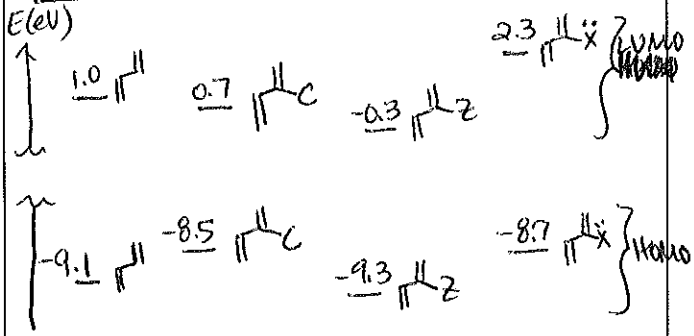
C = extra conjugation Z = EWG X = EDG

(8) Dienes: C-1 Substituents



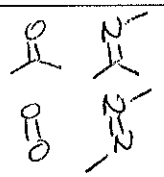
*Same effect of substituents as on olefins.

(9) Dienes: C-2 Substitution

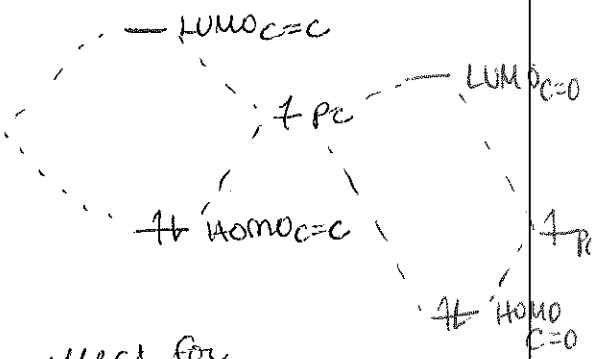


Same as for C-1 substitution, but not as large.

(10) Hetero-dienophiles
↳ low LUMO.

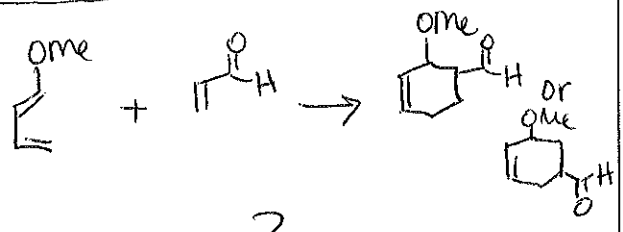


Recall:



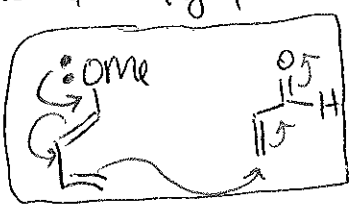
(similar effect for heterodienes.)

(11) REGIOSELECTIVITY



?

(12) Fast & dirty prediction:

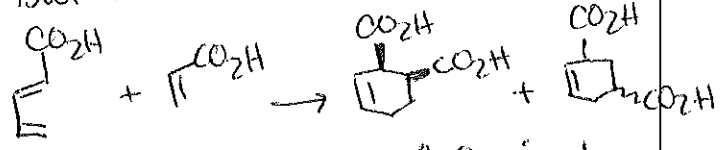


vs.

Push arrows to get maximum effect out of substituents.

(13)

But what about



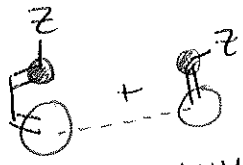
8.8 : 1

→ Hard to explain w/ arrow pushing.

(14)

Only "top" of p-orbital shown.

Coeffient Controlled



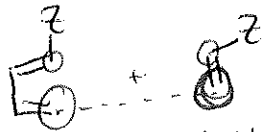
HOMO −9.5eV

LUMO 0 eV

Big/Big small/small

Only important p-orbitals shown.

gap = 9.5 eV



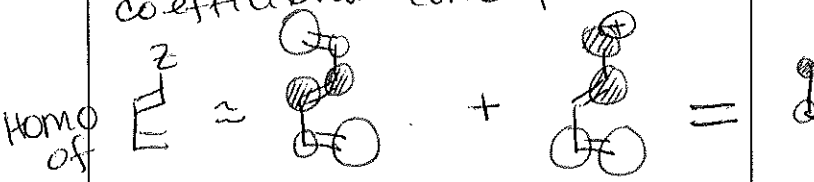
LUMO −0.5eV

HOMO −10.9eV

gap = 11.4 eV

(15)

Where did these coefficients come from?



HOMO of hexatriene

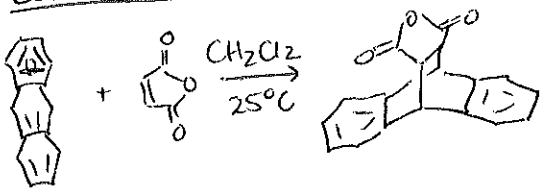
↑ More similar to this, so weighted more heavily.

HOMO of pentadienyl cation.

(16)

(See handouts).

(17) Lewis acid acceleration

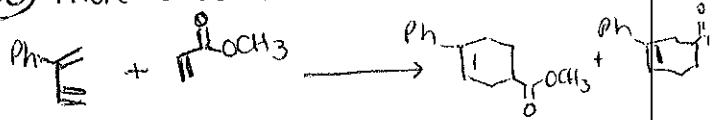


Additive	$t_{1/2}$
none	2400h
$AlCl_3$ (1 equiv)	<1 min

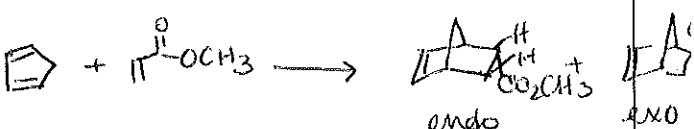
Yates & Eaton JACS 1960, 82, 4436.

* One of the 1st LA-accelerated organic transformations!

(18) more observations:



no catalyst	80 : 20
w/ $AlCl_3$	97 : 3



endo exo

no catalyst	82 : 18
w/ $AlCl_3 \cdot OEt_2$	99 : 1

(19)

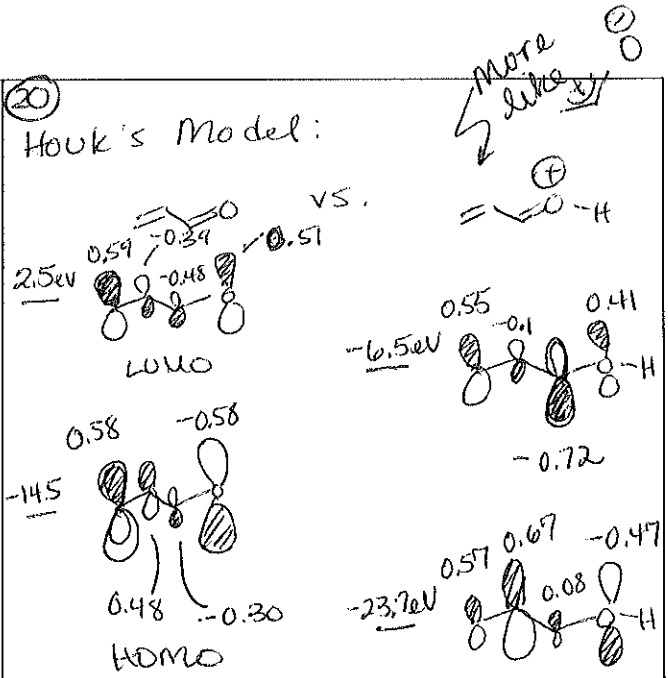
LA increases rate, regiosel & stereo endo/exo selectivity.

Why?

MO perturbation
(Houk JACS 1973, 95, 4094)

(20)

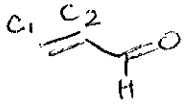
Houk's Model:



(21)

Rates: Lower LUMO

Regiochem: Bigger Difference in coefficients @ C1 & C2



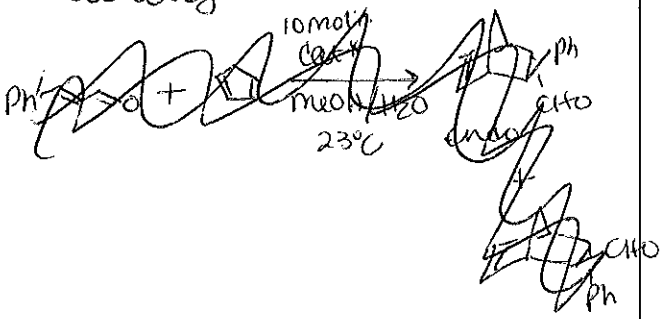
Endo/Exo: Bigger 2° Orbital interactions.

(Bigger coefficients on carbonyl oxygen).

(22)

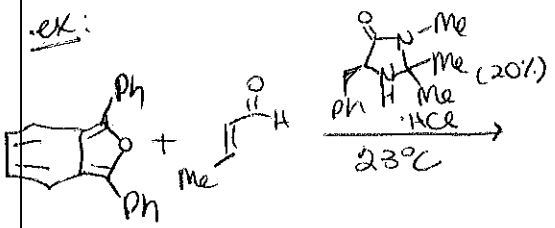
Many.

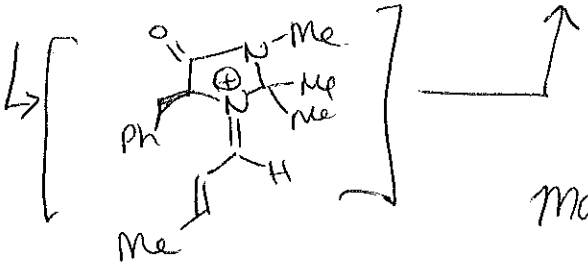
Now: Chiral LA catalysts & other "LUMO lowering" catalysts...



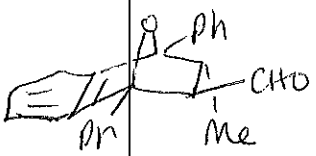
(23)

ex:





(24)



75% yield
35:1 (exo:endo)
96% ee

MacMillan JACS 2000, 122, 4243.