

The Activation Strain Model : Understanding Reactivity and Selectivity of Chemical Reactions

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September 4th, 2014

Introduction

- “Chemistry is the science of substances: their structure, their properties, the reactions that change them into other substances”.

-- Linus Pauling

Useful Theories:

Woodward–Hoffmann rules

Frontier molecular orbital (FMO) theory

valence-bond theory

Marcus theory

Activation strain model

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Contents

- **Activation strain model**
- **Applications in chemical reactions**
 - Reactivity study
 - Selectivity study
- **Summary**

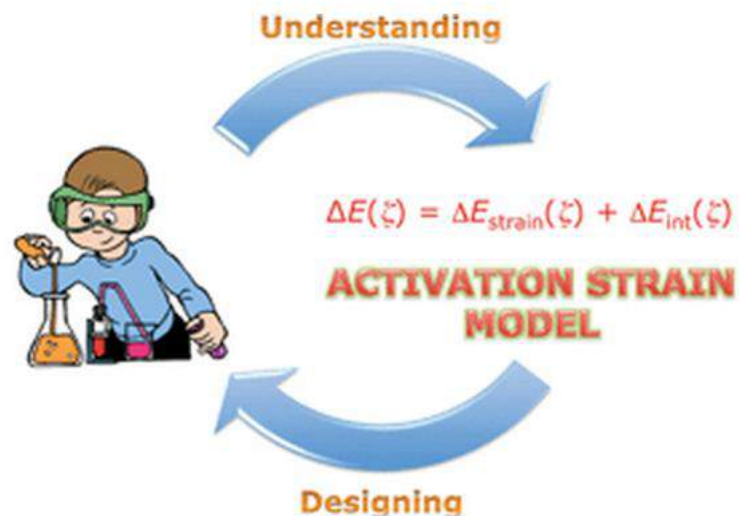
Activation Strain Model

The activation strain model (ASM), also known as the distortion/interaction model, is a fragment-based approach to understanding chemical reactions and the associated barriers.

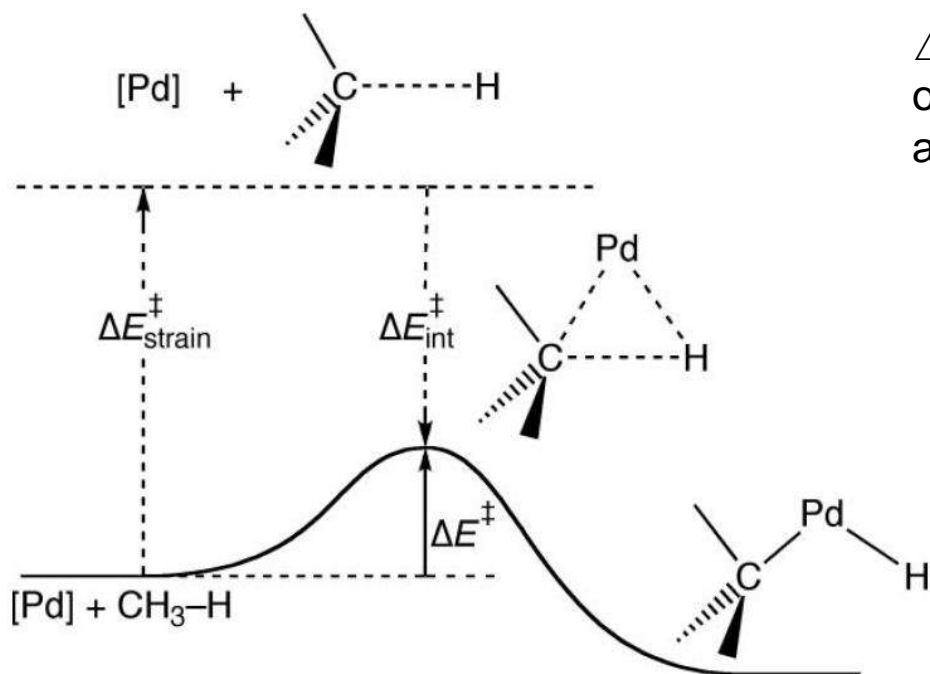
$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta)$$

$\Delta E_{\text{strain}}(\zeta)$: Strain (or distortion) energy, which is associated with the structural deformation that the reactants undergo

$\Delta E_{\text{int}}(\zeta)$: The interaction between these increasingly deformed reactants



Activation Strain Model



$\Delta E_{\text{int}}(\zeta)$ depends on their electronic structure, on how they are mutually oriented as they approach each other, negative (stabilizing)

$$\Delta E_{\text{int}}(\zeta) = \Delta V_{\text{elst}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{oi}}(\zeta)$$

- ✓ classical electrostatic interaction
- ✓ interactions between occupied orbitals, the steric repulsion
- ✓ orbital interaction accounts for charge transfer, polarization

$\Delta E_{\text{strain}}(\zeta)$ is determined by the rigidity of the reactants, the extent to which groups must reorganize in a particular reaction mechanism, positive (destabilizing), a factor that gives rise to the occurrence of a reaction barrier

Activation Strain Model

- The ASM establishes a causal relationship between reaction barriers and the properties of reactants and characteristics of reaction mechanisms.
- Reactivity trends depend on the capability of reactants to interact, the distortivity (extent of deformation) associated with a reaction mechanism, and the reactants' flexibility
- Activation Strain Analyses yield design principles for chemical reactions.



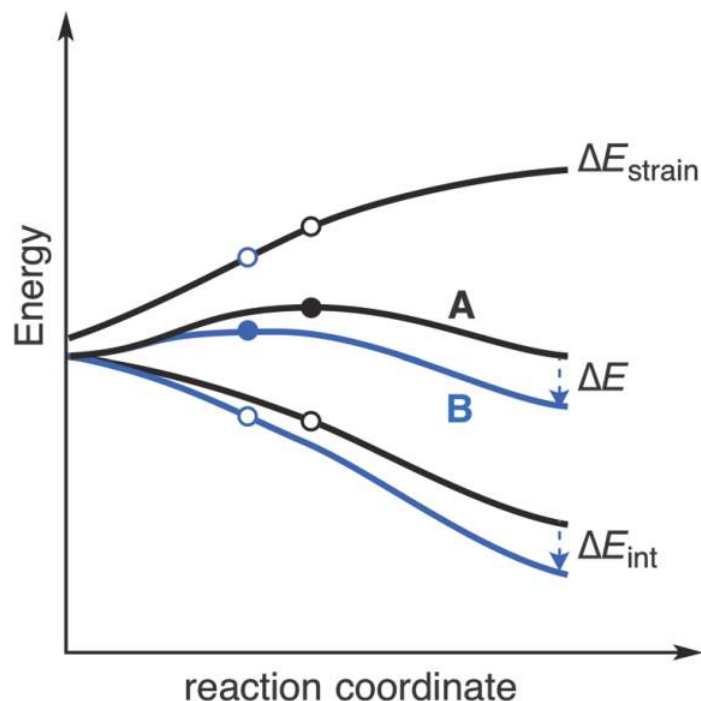
F. M. Bickelhaupt



K. N. Houk

Activation Strain Model

- *A single-point analysis at the TS, only, yields values that can be misleading!*



TS point:

a lower activation barrier in **B** is due to a lower activation strain for reaction **B**, rather than a more stabilizing TS interaction

Reaction coordinate:

The interaction of reaction **B** is clearly more stabilizing at any given point along the reaction coordinate than that of reaction **A**

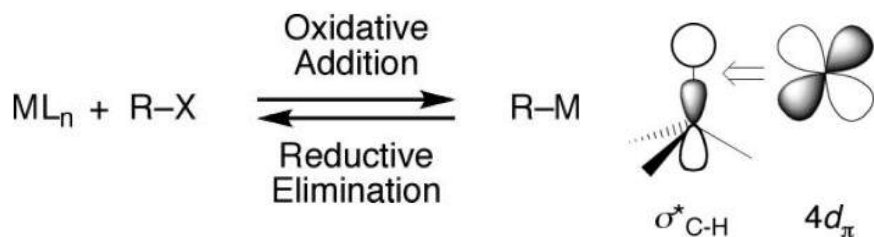
Be cautious when comparing the single-point energies of TSs occurring at different points along the reaction coordinate!

Contents

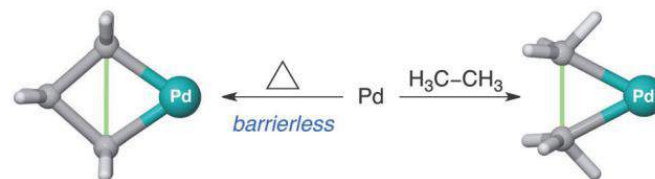
- Activation strain model
- **Applications in chemical reactions**
 - Reactivity study
 - Selectivity study
- Summary

Bond Activation

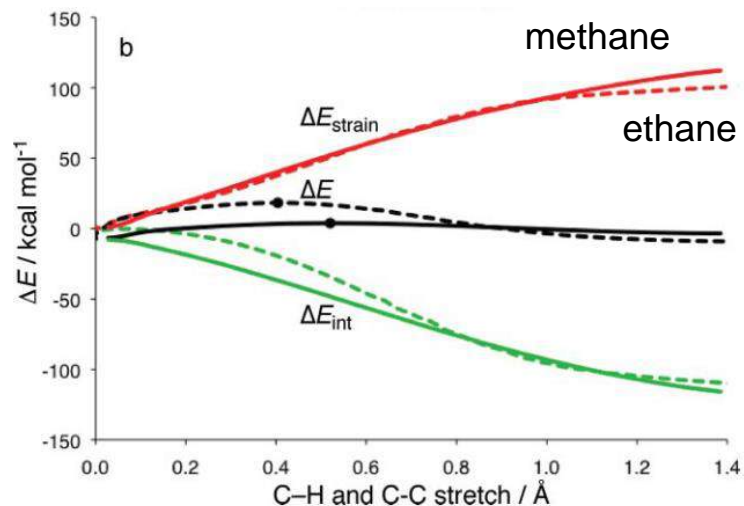
Substrate effect



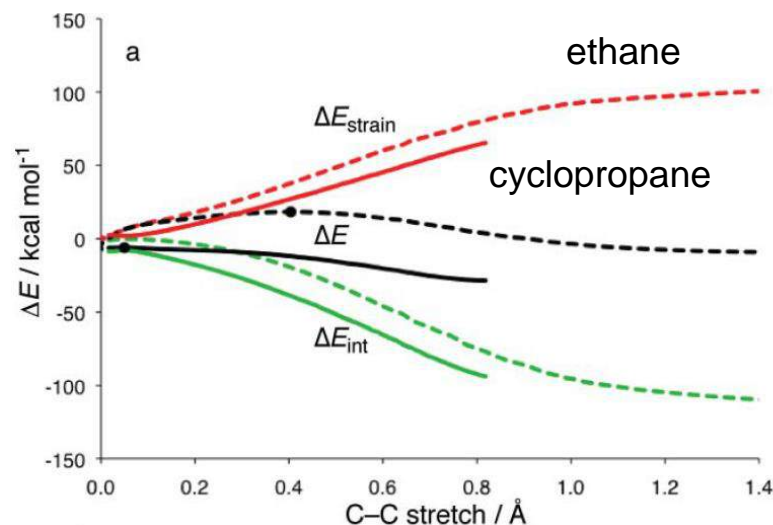
- C-C vs. C-C(cyclo) bond



- C-H vs. C-C bond



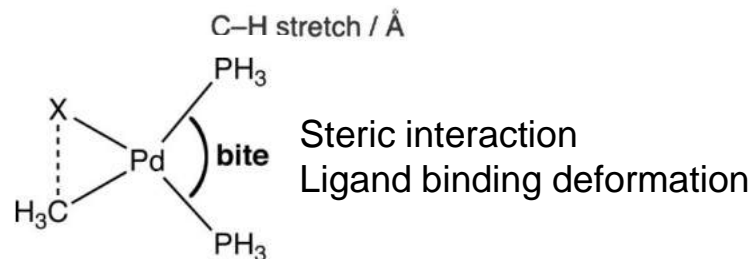
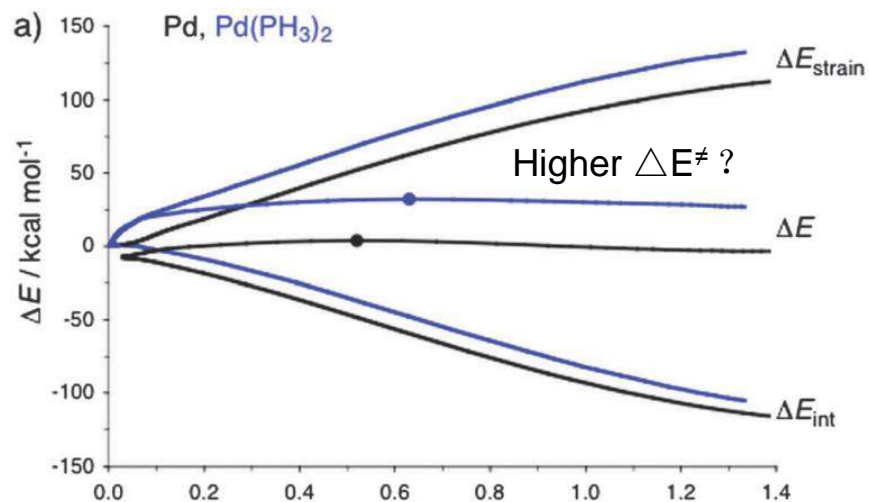
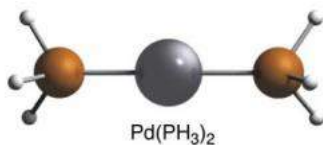
there is very little steric shielding on the side of the hydrogen, interaction with the C-H bond proceeds easily



both the strain, interaction terms are stabilized for oxidative insertion into cyclopropane

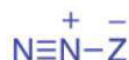
Bond Activation

- Ligand effect



1,3-Dipolar Cycloadditions

Diazonium Betaines



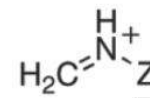
- 1 Z = O, Nitrous Oxide
- 2 Z = NH, Hydrazoic Acid
- 3 Z = CH₂, Diazomethane

Nitrilium Betaines

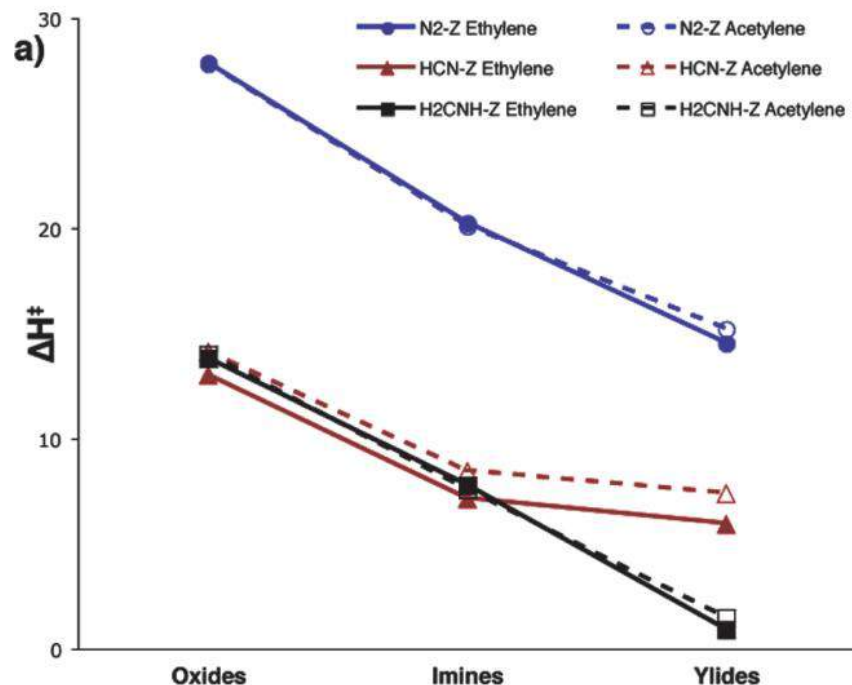


- 4 Z = O, Fulminic Acid
- 5 Z = NH, Formonitrile Imine
- 6 Z = CH₂, Formonitrile Ylide

Azomethine Betaines



- 7 Z = O, Methylene Nitrene
- 8 Z = NH, Formoazomethine Imine
- 9 Z = CH₂, Formoazomethine Ylide



There is a smooth decrease in barrier height from oxides to imines to ylides

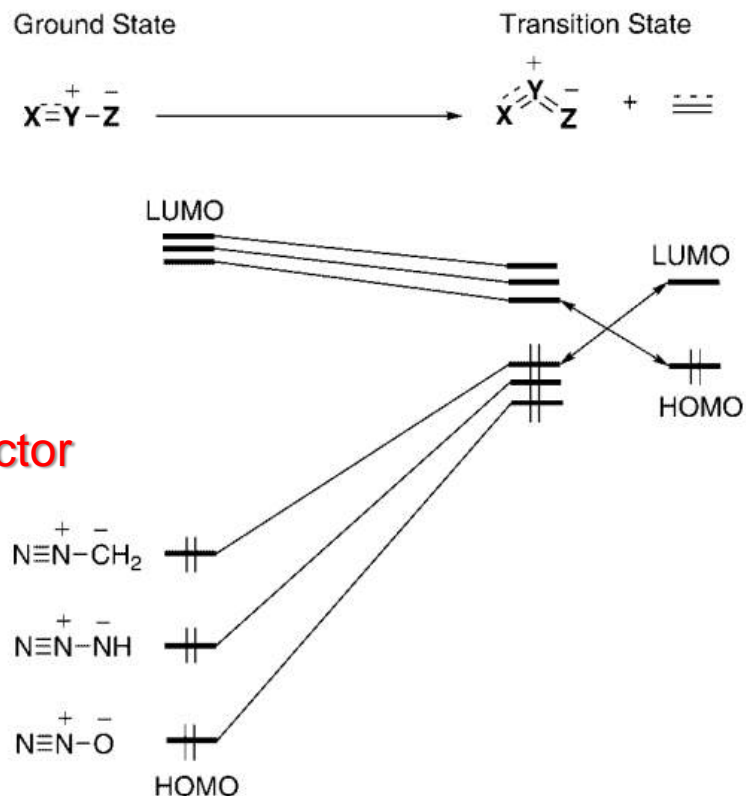
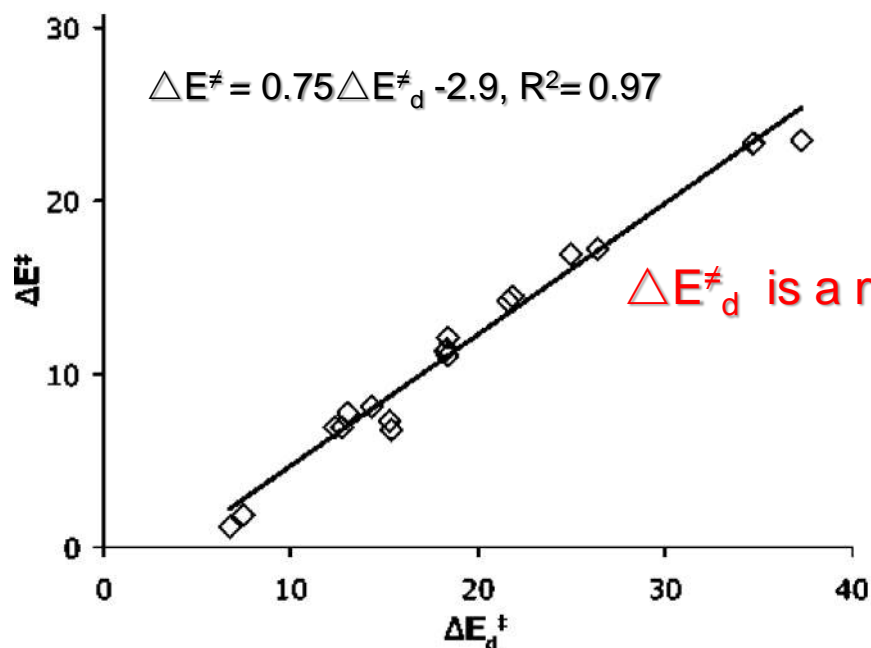
The NB, AB classes have almost identical barrier heights

Ethylene, acetylene barriers are nearly identical for a given type of 1,3 dipole

D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.*, 2007, **129**,10646

1,3-Dipolar Cycloadditions

The energy of distortion is related to the dipole stability.

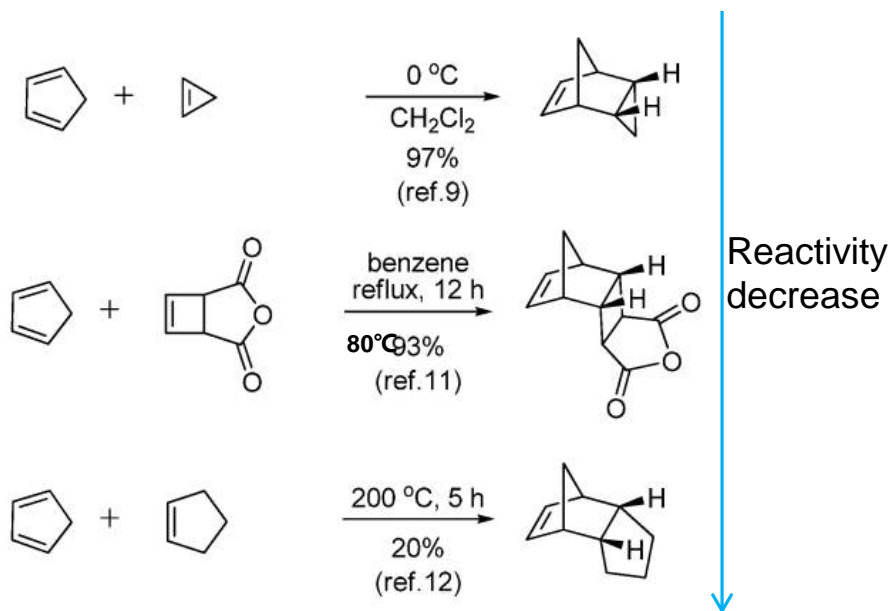


$\text{X}=\text{Y}^+-\text{Z}^-$ is stabilized by electronegative Z atoms, so the stability order of the dipoles: oxide > imine > ylide.

The narrow HOMO-LUMO gap of the ylides results in a very low ΔE_d^\ddagger .
When X=N, the dipole is stabilized compared to those with X=C

Diels–Alder Reaction

• Reactivity



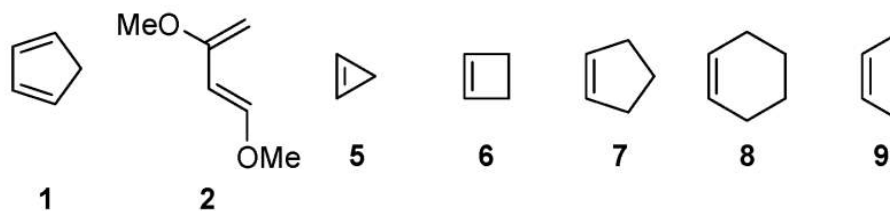
Ring-strain accounts for the reactivity of cycloalkenes ?

Table 1. Strain Energies (*SE*, in kcal/mol) of Cycloalkenes and Cycloalkanes

	<i>SE</i>		ΔSE	
cyclopropene	55.2	cyclopropane	27.5	27.7
cyclobutene	28.4	cyclobutane	26.5	1.9
cyclopentene	4.1	cyclopentane	6.2	-2.1
cyclohexene	-0.3	cyclohexane	0	-0.3

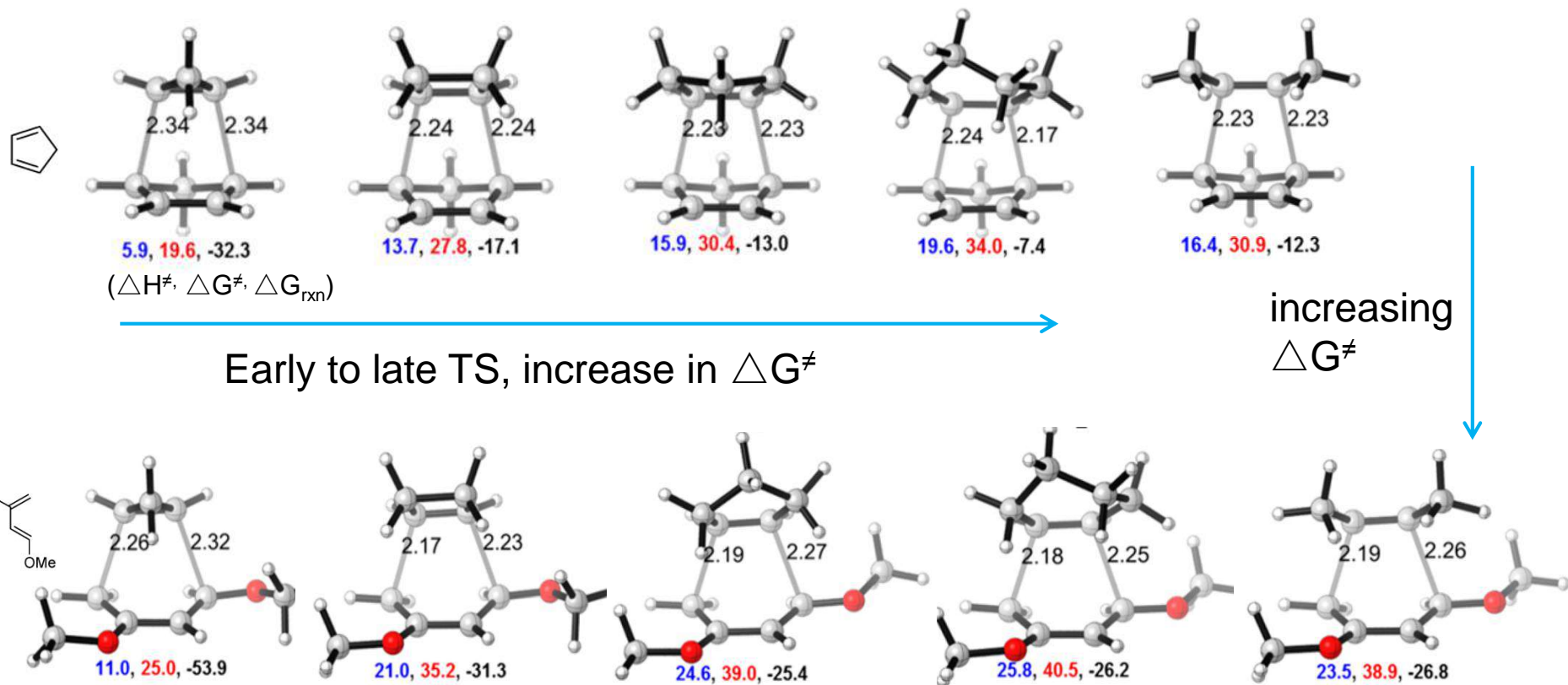
Strain-release only influences the reactivity of cyclopropene and is not a general descriptor of reactivity.

Distortion/interaction model



Diels–Alder Reaction

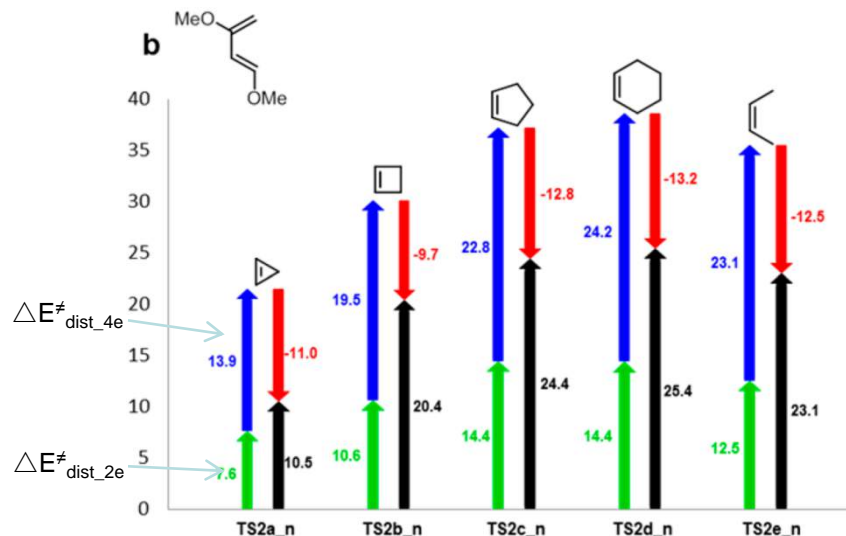
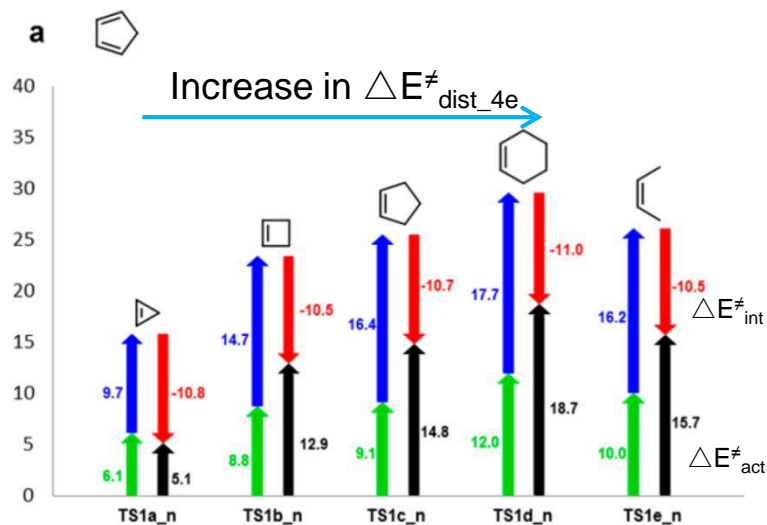
- Transition structures



Diels-Alder Reaction

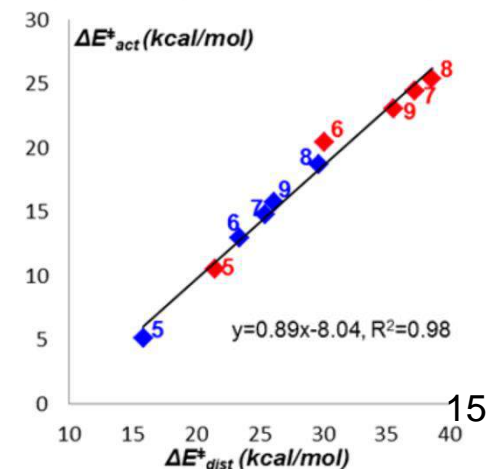
• Distortion/Interaction analysis

$\Delta E^{\ddagger}_{\text{dist}}$ determine reactivities

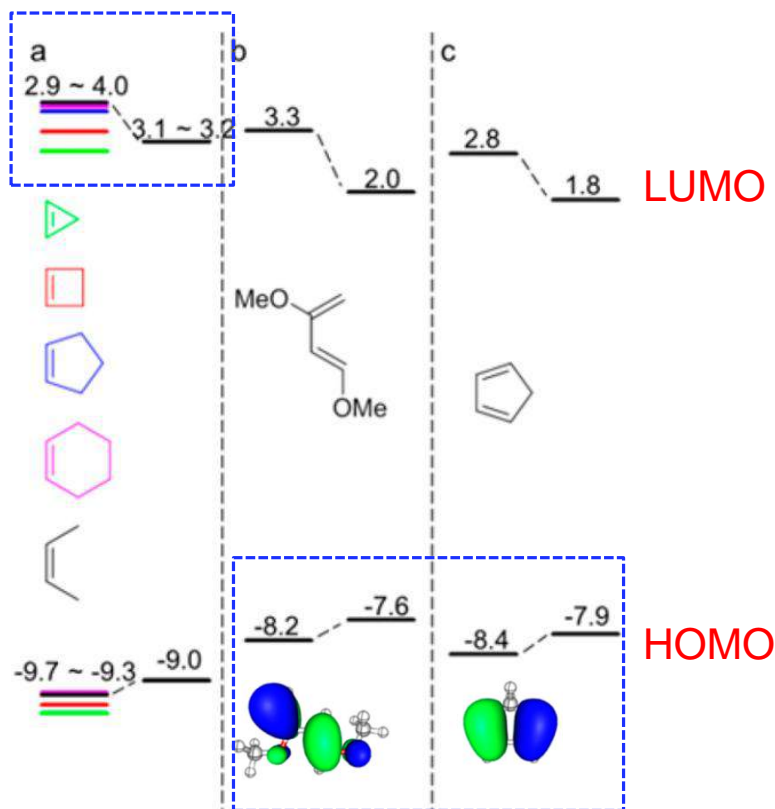


- The increase in $\Delta E^{\ddagger}_{\text{dist_4e}}$ as the dienophile changes from cyclopropene to cyclohexene, consistent with the trend of early/late TS
- The interaction energies remain essentially constant
- Larger $\Delta E^{\ddagger}_{\text{int}}$ in **b** due to the smaller HOMO – LUMO gap
- Larger $\Delta E^{\ddagger}_{\text{dist_4e}}$ in **b**, due to the trans/cis conformational change and steric repulsion

F. Liu, R. S. Paton, S. Kim, Y. Liang, K. N. Houk,
J. Am. Chem. Soc., 2013, **135**, 15642

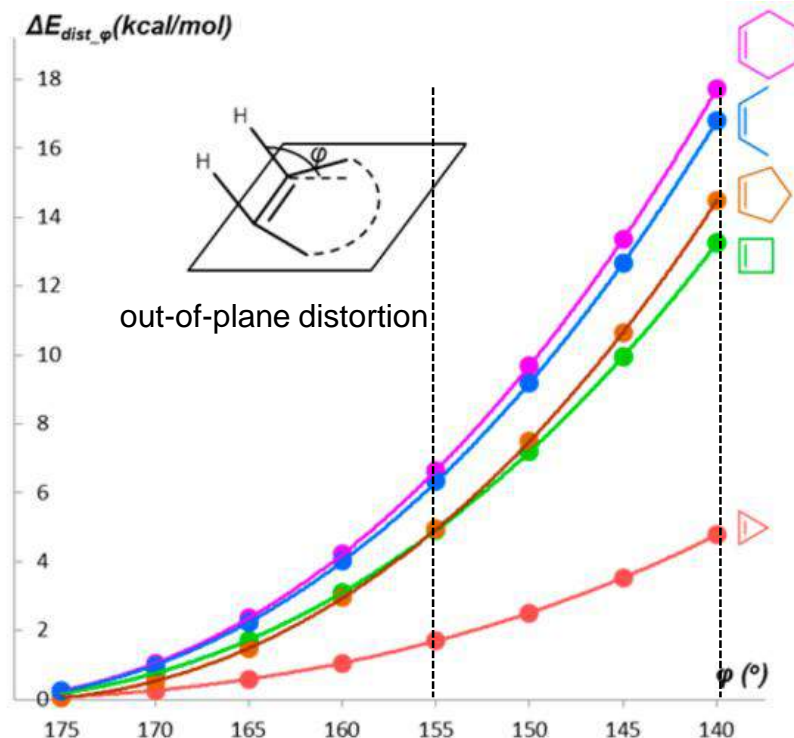


Diels–Alder Reaction



Smaller HOMO–LUMO gap gives better interaction
The distortion of reactants facilitates the interaction between molecular orbitals

- The reactivities of different alkenes originate from the distortion energies.



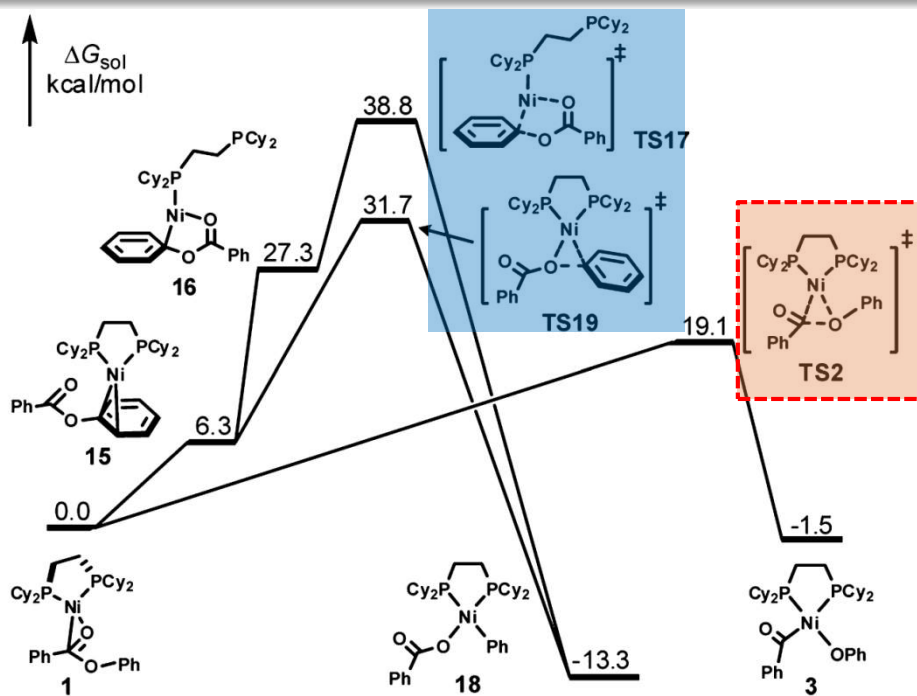
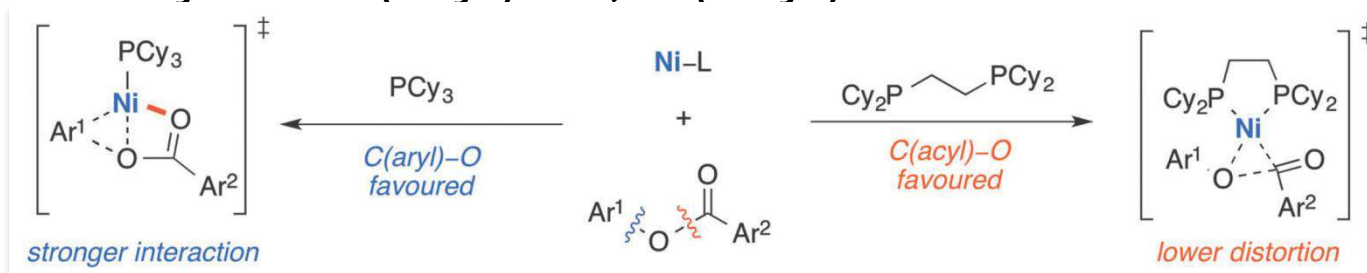
In TS zone, the distortion energy of cyclopropene is significantly lower than other dienophiles, and as size increases, the distortion energy increases

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Ligand Effects on Chemoselectivity

- Ni-Catalyzed C(aryl)-O, C(acyl)-O activation

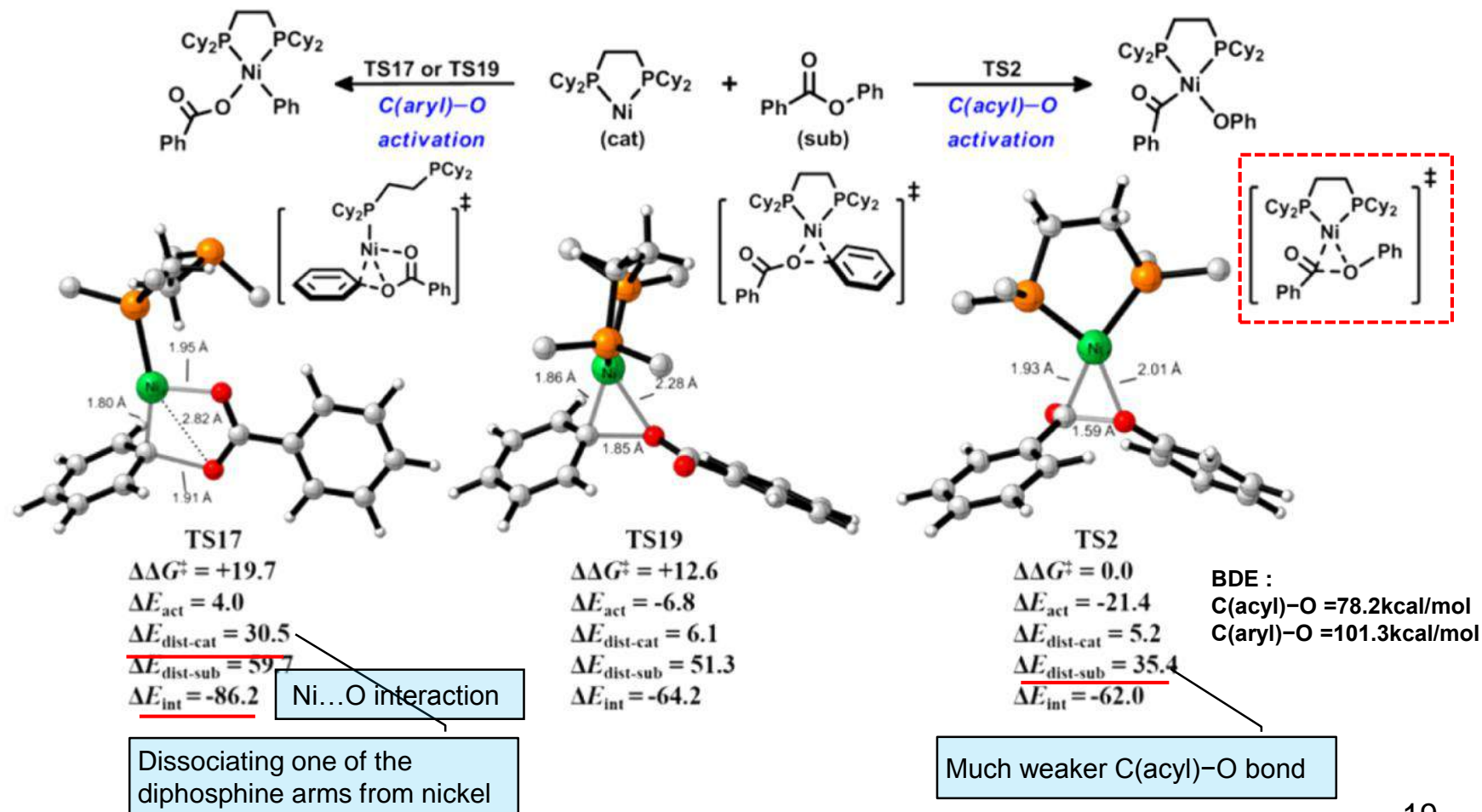


bidentate phosphine ligands favors C(acyl)-O activation

Ni/dcype catalyzed activation pathways

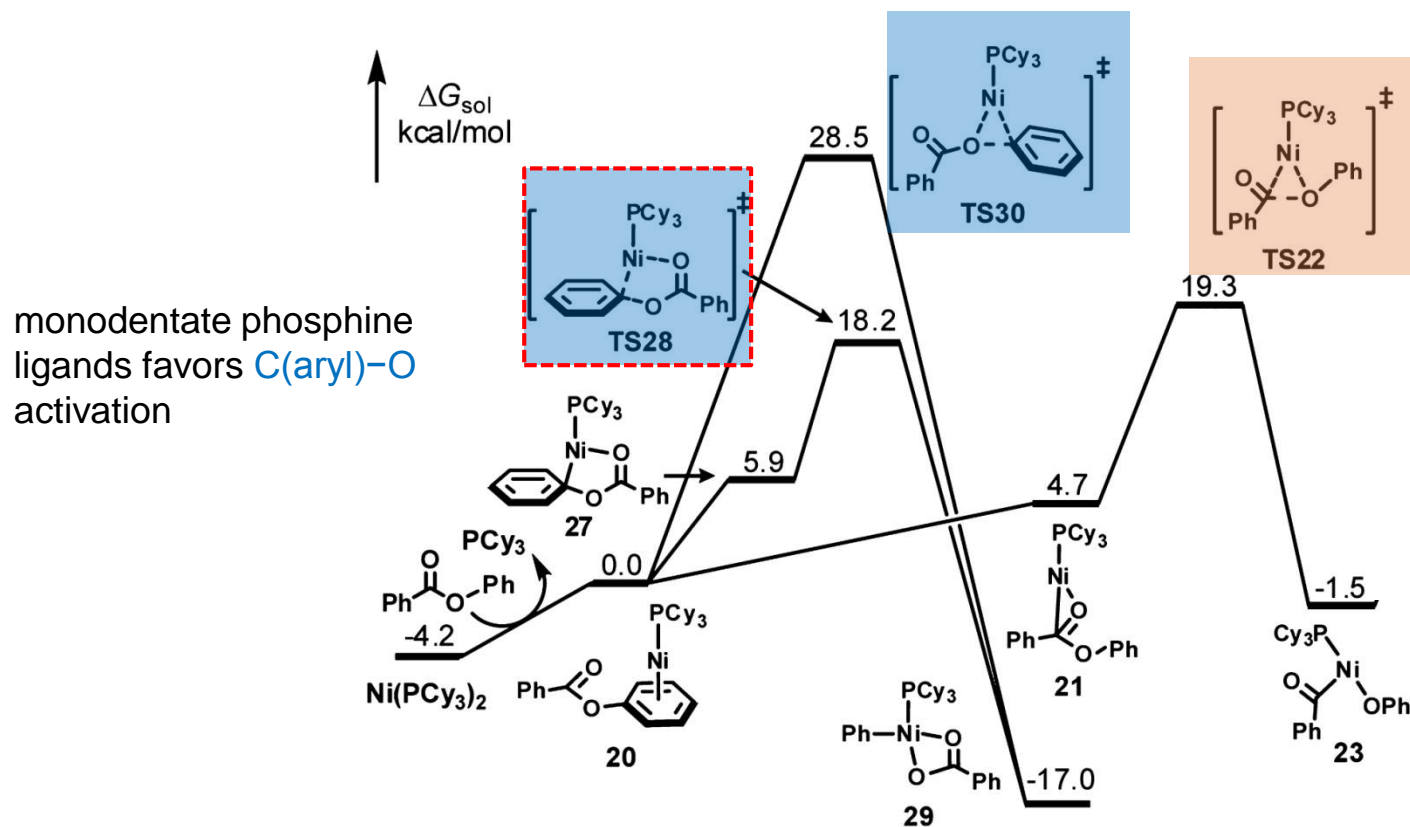
Ligand Effects on Chemoselectivity

- Distortion/Interaction analysis



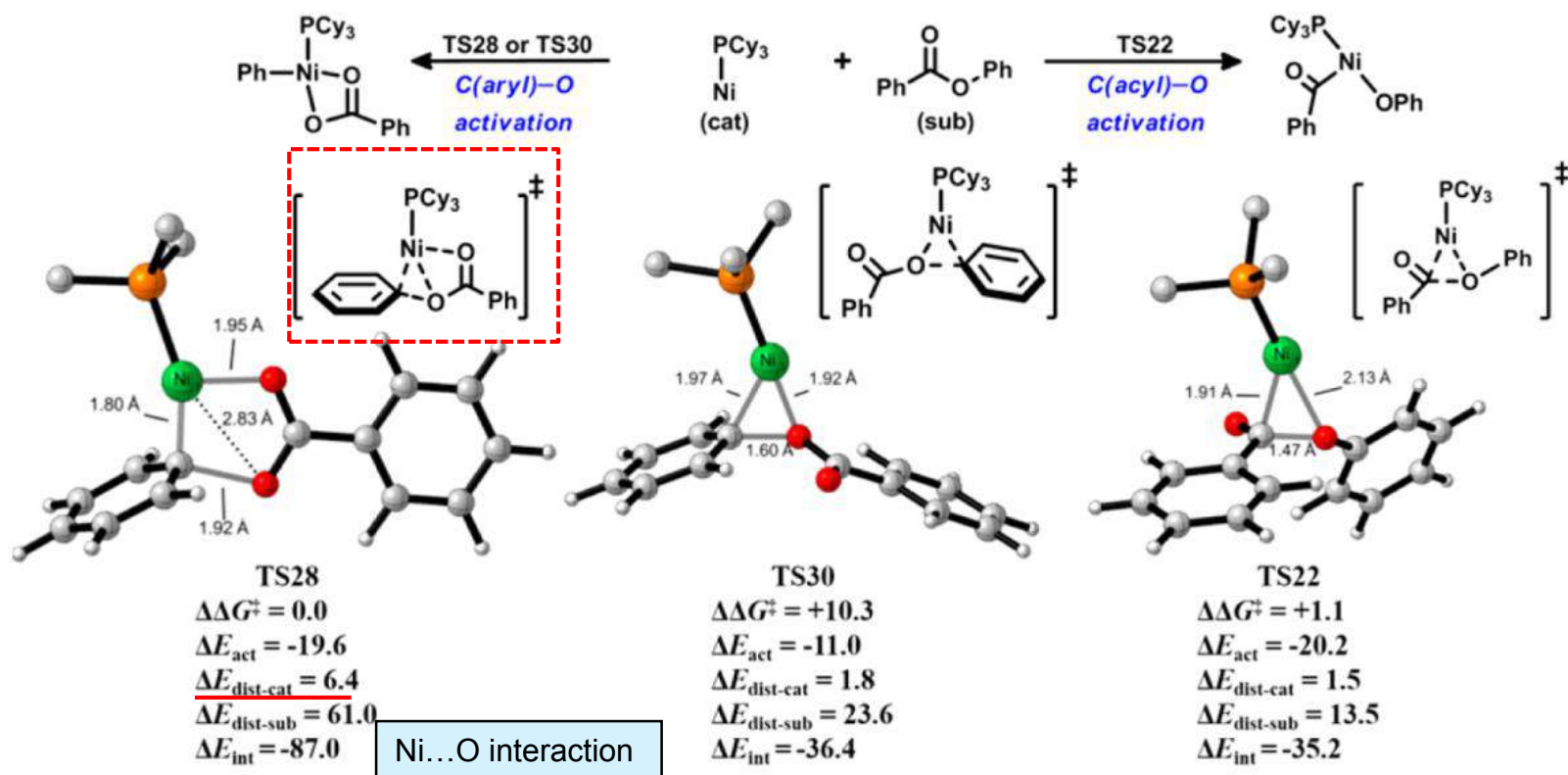
Ligand Effects on Chemoselectivity

- Ni/PCy₃ -catalyzed activation pathways

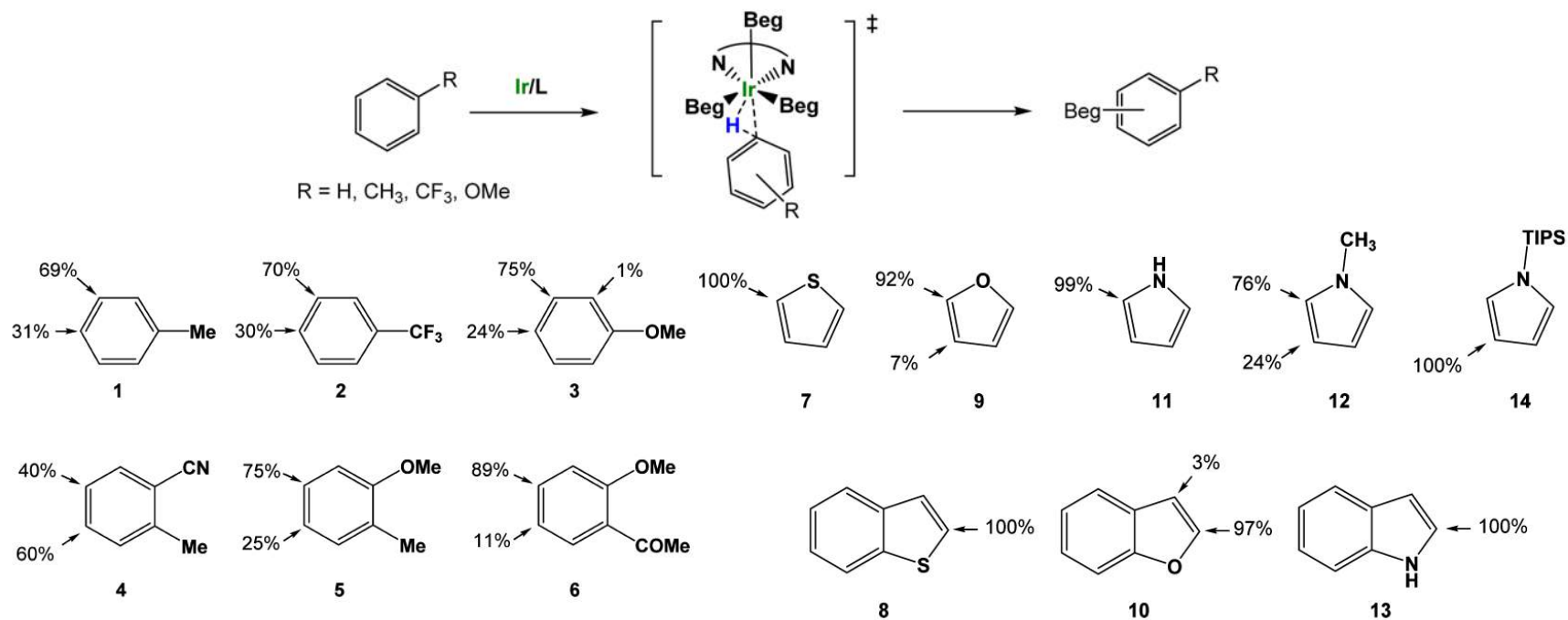


Ligand Effects on Chemoselectivity

- Distortion/Interaction analysis



Origins of Selectivities in C–H Borylation



Origin of region selectivity are not well understood

Factors: steric effects

the homolytic or heterolytic dissociation energies of C–H bond

the stability of the forming Ir–C bond

pKa of the C–H bond

Origins of Selectivities in C–H Borylation

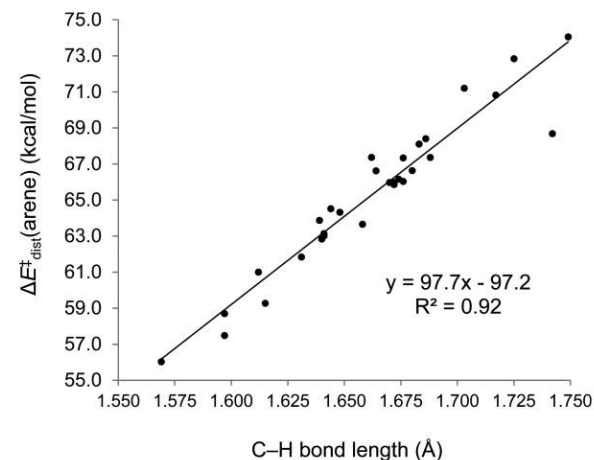
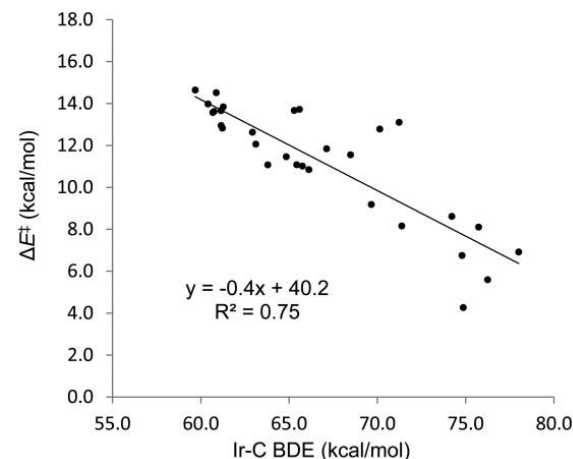
- Distortion/interaction analysis

substrate	borylation position	ΔE^\ddagger	$\Delta E_{\text{dist}}^\ddagger$ (Ir cat.)	$\Delta E_{\text{dist}}^\ddagger$ (arene)	$\Delta E_{\text{int}}^\ddagger$	TS C–H length (Å)
7	2	6.8	10.9	59.3	-63.5	1.615
	3	11.8	10.2	70.8	-69.2	1.717
8	2	5.6	10.8	57.5	-62.6	1.597
	3	9.2	10.6	64.3	-65.7	1.648
9	2	8.1	10.9	58.7	-61.5	1.597
	3	12.8	9.9	71.2	-68.3	1.703
10	2	6.9	10.8	56.0	-59.9	1.569
	3	8.6	10.6	61.0	-63.0	1.612

Substrate distortion is not the major factor that controls regioselectivities:

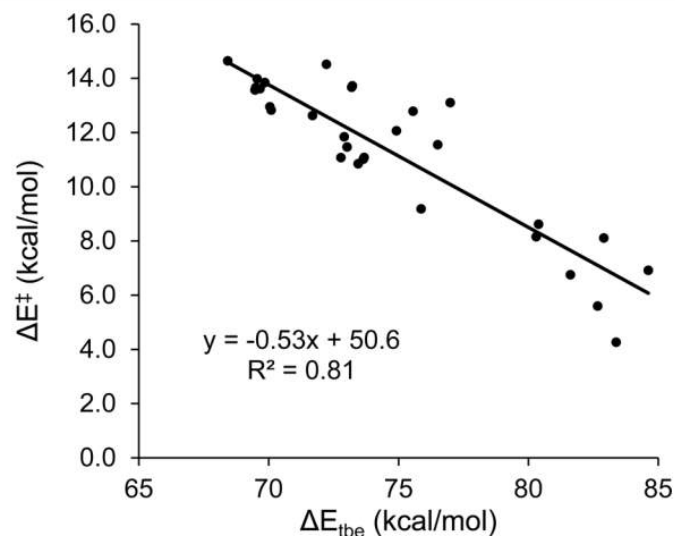
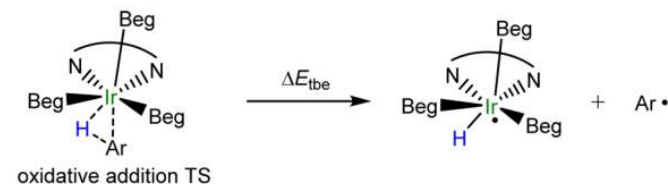
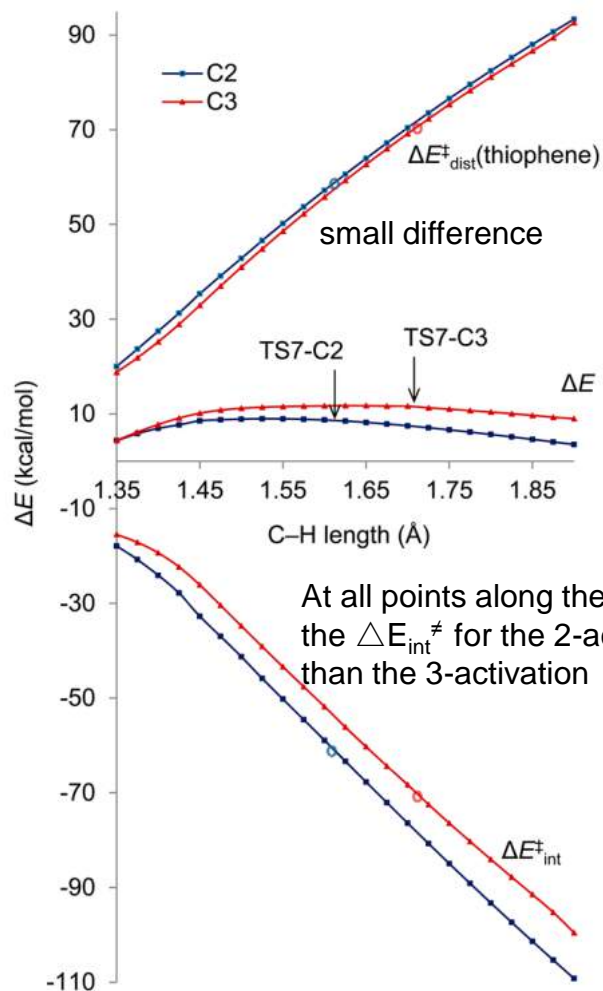
$\Delta E_{\text{dist}}^\ddagger$ is mainly controlled by the position of the transition state on the reaction coordinate, does not correlate well with the ΔE^\ddagger or the strength of the C–H bond

No obvious correlation between $\Delta E_{\text{int}}^\ddagger$, ΔE^\ddagger



early TS \longrightarrow late TS

Origins of Selectivities in C–H Borylation



Ir–C bonding interaction contributes significantly to stabilize the TS, determines regioselectivity

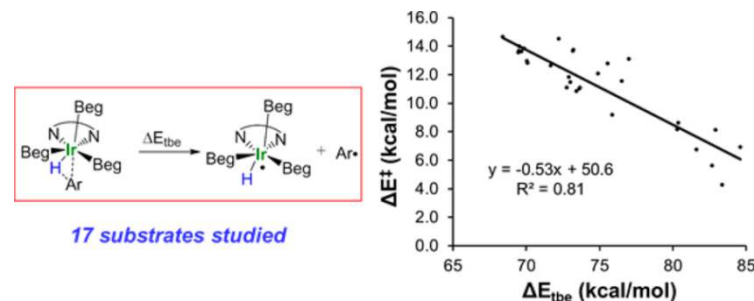
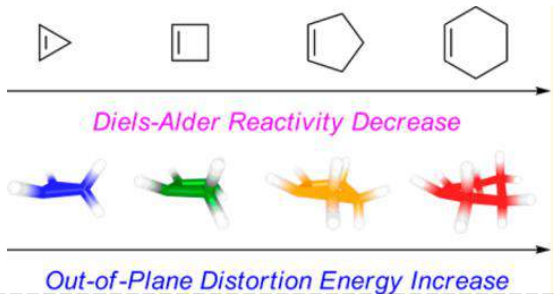
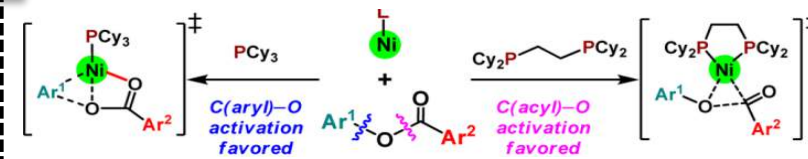
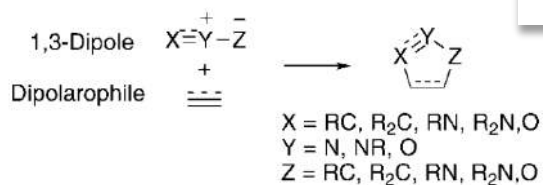
Summary

Activation Strain Model

$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta)$$

Reactivity

Selectivity



Design new reactions with high reactivity and selectivity

Thank You!