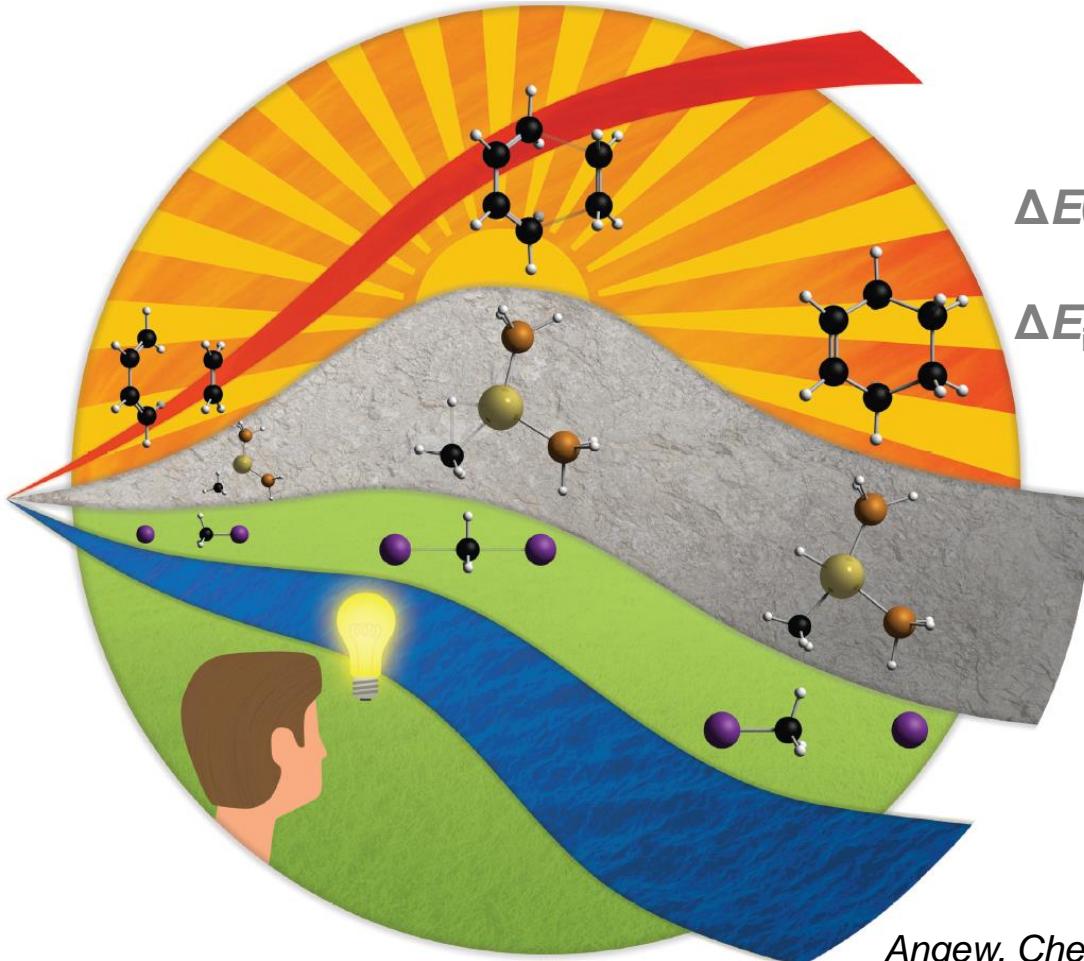


In-Depth Understanding of Chemical Reactivity



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

$$\Delta E_{\text{int}}(\zeta) = \Delta E_{\text{elstat}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{orb}}(\zeta)$$

2022. 1. 8

Haruka Fujino

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- 1. Introduction of Activation Strain Model (ASM) and
and Energy Decomposition Analysis (EDA)**

- 2. Recent Example of ASM-EDA Using Automated Program
“PyFrag 2019”-Assisted ASM-EDA
(*ACS Catal.* 2021, 11, 7489)**

- 3. Application of ASM-EDA to Intramolecular Reactions
(*J. Org. Chem.* 2020, 85, 9272)**

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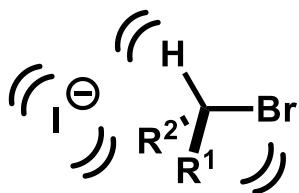
- 3. Application of ASM-EDA to Intramolecular Reactions
(*J. Org. Chem.* 2020, 85, 9272)**

Understanding chemical reactivity thorough computational techniques is demanded.

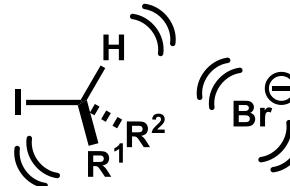
Question: How can we integrate these factors? What is the predominant element in each reaction?

Routine Protocols in Computational Chemistry

1. Calculate equilibrium geometry for reactant(s)

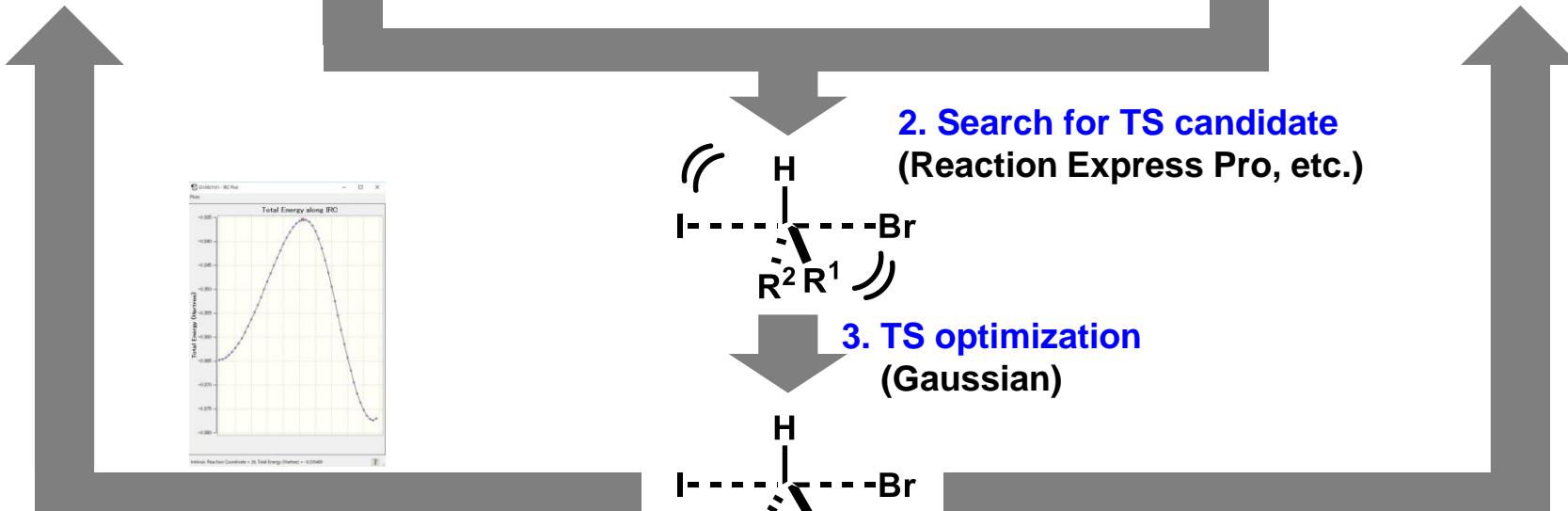


1'. Calculate equilibrium geometry for product(s)



local minimum: the optimize structure of reactant(s)
(zero imaginary frequencies)

local minimum: the optimize structure of product(s)
(zero imaginary frequencies)



4. Compute IRC
(Gaussian)

saddle point: the optimize structure of TS
(one imaginary frequency)

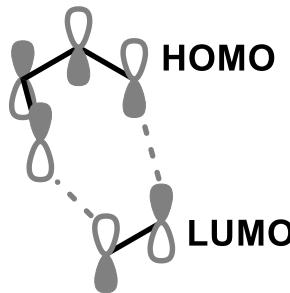
4. Compute IRC
(Gaussian)

IRC: intrinsic reaction coordinate

Classics of Reactivity Models

■ electronic theory of organic chemistry (1910's -)

■ frontier molecular orbital (FMO) theory (1952)



Prof. Fukui



Prof. Woodward



Prof. Hoffmann

MO theory describing HOMO-LUMO interactions

→ This model usually **neglected the “distortion” of molecules** that occurs upon reaction.

Woodward-Hoffmann rules
(1965)

For details, see:
150509_PS_Shunichiro_Katoh

■ Marcus theory (1956)



Prof. Marcus

In Marcus theory, activation barriers are expressed in terms of the intrinsic reactivity of a thermoneutral reference reaction system and the influence of the thermodynamics of the reaction.

This intrinsic barrier is described in terms of reorganization energy in solution upon vertical electron transfer.

→ This model does **not have answer the question of why a particular thermoneutral reference system has the intrinsic reactivity.**

$$E_{\text{[TS]}^{\ddagger}} = E_{\text{intrinsic}} + c E_{\text{rxn}}$$

Activation Strain (Distortion-Interaction) Model

■ Activation strain model (ASM), a.k.a. distortion-interaction model is a fragment-based approach to insight into physical factors controlling reactivity and selectivity.

Potential energy surface $\Delta E(\zeta)$ is decomposed as follows:

$$\Delta E(\zeta) = \Delta E_{\text{strain},R1}(\zeta) + \Delta E_{\text{strain},R2}(\zeta) + \Delta E_{\text{int}}(\zeta)$$
$$\Leftrightarrow \Delta E_{\text{int}}(\zeta) = \Delta E(\zeta) - (\Delta E_{\text{strain},R1}(\zeta) + \Delta E_{\text{strain},R2}(\zeta))$$

$\Delta E_{\text{strain}}(\zeta)$: the strain energy of each fragment
(a.k.a. distortion energy $\Delta E_{\text{dist}}(\zeta)$)
usually positive value, destabilizing

$\Delta E_{\text{int}}(\zeta)$: interaction energy between two fragments
usually negative value, stabilizing



Prof. Bickelhaupt



Prof. Houk

In the TS,

$$d\Delta E_{\text{strain},R1+R2}(\zeta^{\text{TS}})/d\zeta = - d\Delta E_{\text{int}}(\zeta^{\text{TS}})/d\zeta$$

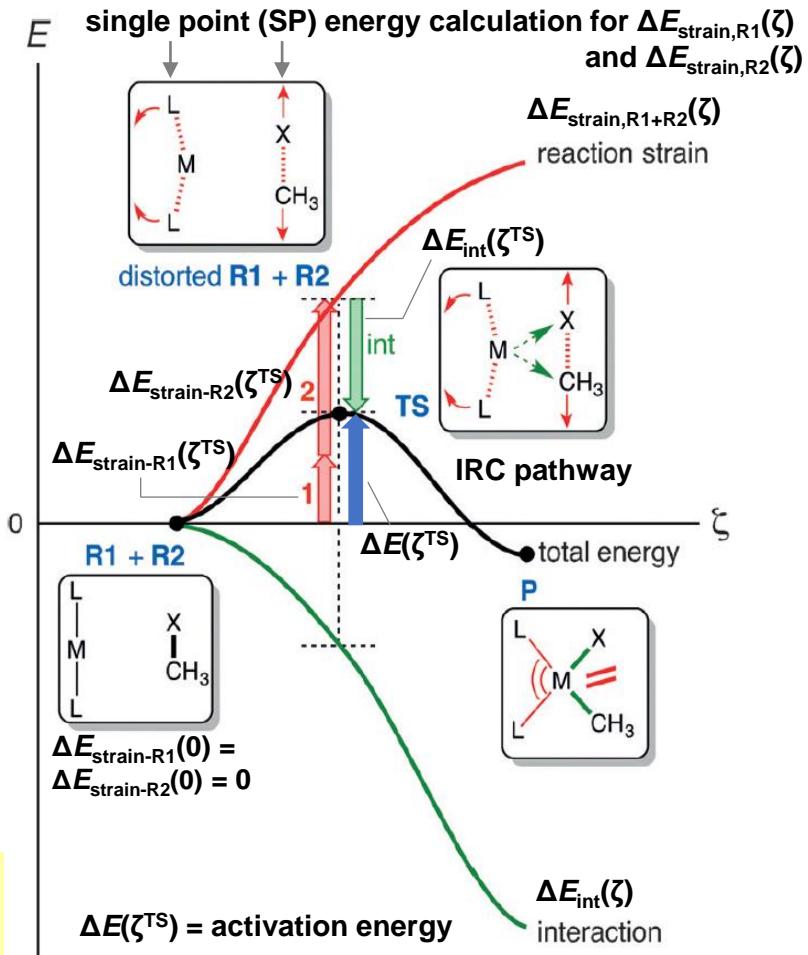
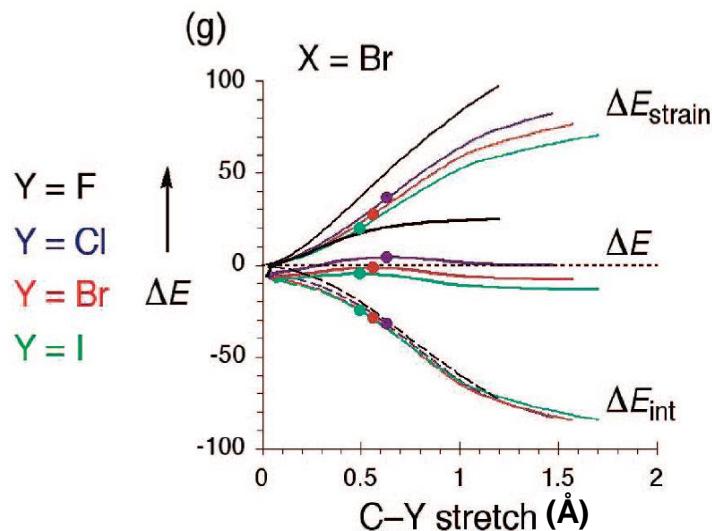


Figure 1. The activation-strain model exemplified using a metal-mediated C–X bond activation: $\Delta E^+ = \Delta E_{\text{strain}}^+[\text{reactant } 1] + \Delta E_{\text{strain}}^+[\text{reactant } 2] + \Delta E_{\text{int}}^+$.

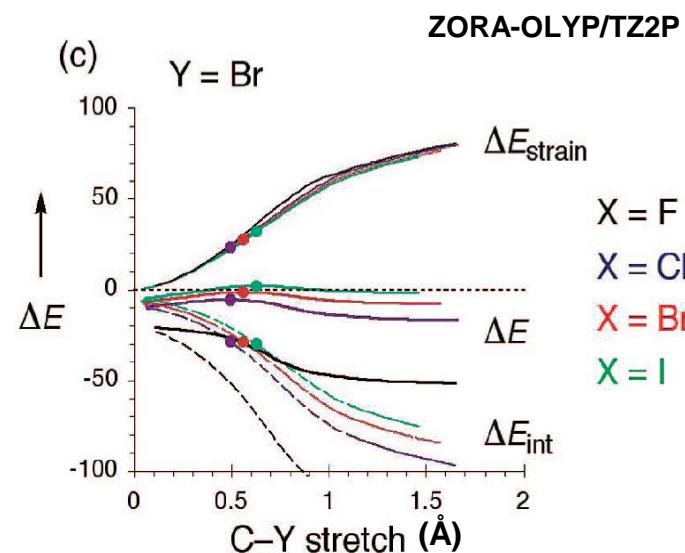
For representative reviews on ASM model, see: (a) Fernández, I.; Bickelhaupt, F. M. *Chem. Soc. Rev.* **2014**, *43*, 4953. (b) Wolters, L. P.; Bickelhaupt, F. M. *WIREs Comput. Mol. Sci.* **2015**, *5*, 324. (c) Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070.

An Example of ASM: S_N2 Reaction



strain control

- Leaving group ability derives from **the carbon-leaving group (C-Y) bond strength.**
(Stronger C-Y bond carries higher energy penalty.)



interaction control

- Nucleophilicity is determined by the **electron-donor capability of the nucleophile.**
- Question: What causes the *better interaction?*

Morokuma-Kitaura Model

- a quantitative analysis scheme of **equilibrium structure**
- energy decomposition within Hartree-Fock approximation
- successfully applied to hydrogen-bonded complexes (see Fig 1.) and electron donor-acceptor complex

$$\Delta E = E_{\text{elstat}} + E_{\text{pl}} + E_{\text{ex}} + E_{\text{ct}}$$

ΔE : total stabilization energy of two molecules (A and B)

E_{elstat} : electrostatic component, E_{pl} : polarization component

E_{ex} : exchange component (Pauli repulsion), E_{ct} : charge transfer component



Prof. Morokuma Prof. Kitaura

If molecular functions are A^0 and B^0 and the sum of their energies are E_0 :

(i) a Hartree product of isolated molecular wave-functions:

$$\Psi_1 = A^0 \cdot B^0$$

$$E_1 = E_0 - E_{\text{elstat}}$$

(ii) a Hartree wave-function for the complex in which intermolecular electron exchange is not allowed:

$$\Psi_2 = A \cdot B$$

$$E_2 = E_0 - (E_{\text{elstat}} + E_{\text{pl}})$$

(iii) a Hartree-Fock product of isolated molecular wave-functions:

$$\Psi_3 = \alpha(A^0 \cdot B^0) [\alpha: \text{antisymmetrizer}]$$

$$E_3 = E_0 - (E_{\text{elstat}} + E_{\text{ex}})$$

(iv) a Hartree-Fock wave-function for the complex:

$$\Psi_4 = \alpha(A \cdot B)$$

$$E_4 = E_0 - \Delta E = E_0 - (E_{\text{elstat}} + E_{\text{pl}} + E_{\text{ex}} + E_{\text{ct}})$$

In case of $\text{H}_2\text{CO} \cdots \text{OH}_2$, $\Delta E = 3.45 \text{ kcal/mol}$

($R_{\text{O-H}}$: 1.89 Å, $\theta = -63.9^\circ$);

E_{elstat} : 4.64, E_{pl} : 0.18, E_{ex} : -6.71, E_{ct} : 5.34

(kcal/mol)

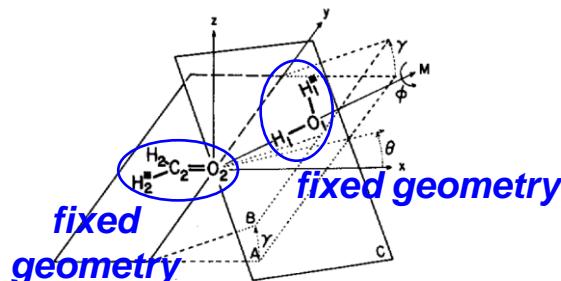
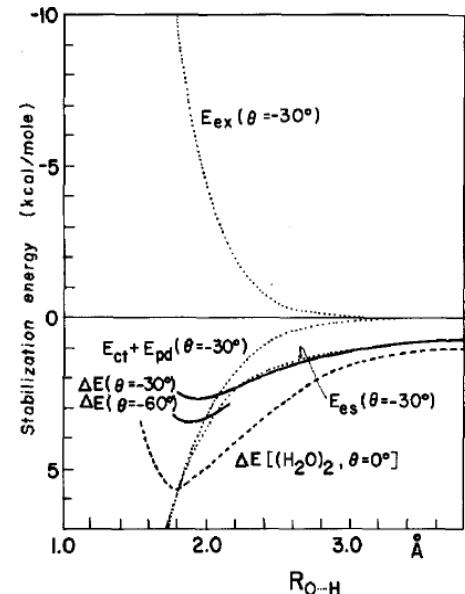


FIG. 1. Linear hydrogen bond model of $\text{H}_2\text{CO} \cdots \text{H}_2\text{O}$. The atoms O_2 , H_1 , and O_1 are collinear. See text on how to generate $R_{\text{O-H}}$, $\gamma=\phi=0$. All curves are for $\text{H}_2\text{CO} \cdots \text{H}_2\text{O}$, unless specified for $(\text{H}_2\text{O})_2$.



- Because each molecular structure is fixed in this model, this model can not be applied to TS and reaction pathway analysis.

(a) Morokuma, K. *J. Chem. Phys.* 1971, 55, 1236.

(b) Kitaura, K.; Morokuma, K. *Int. J. Quantum. Chem.* 1976, 10, 325.

Energy Decomposition Analysis (EDA)

■ Energy decomposition analysis (EDA) methods bridge the gap between electronic structure calculations and conceptual interpretations of molecular interaction energy (*i.e.* $\Delta E_{\text{int}}(\zeta)$).

(NOTE: Theoretically, Morokuma-Kitaura model and ASM can be regarded as a kind of EDA. However, in this presentation, the term of EDA is used only for the decomposition of $\Delta E_{\text{int}}(\zeta)$.)

■ EDA is the Kohn-Sham molecular orbital (KS-MO) theory-based approach, enabling to further analyze $\Delta E_{\text{int}}(\zeta)$ as follows:

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

ΔE_{elstat} : electrostatic energy (the Classic Coulomb interaction between the unperturbed charge distributions of the deformed reactants, usually attractive)

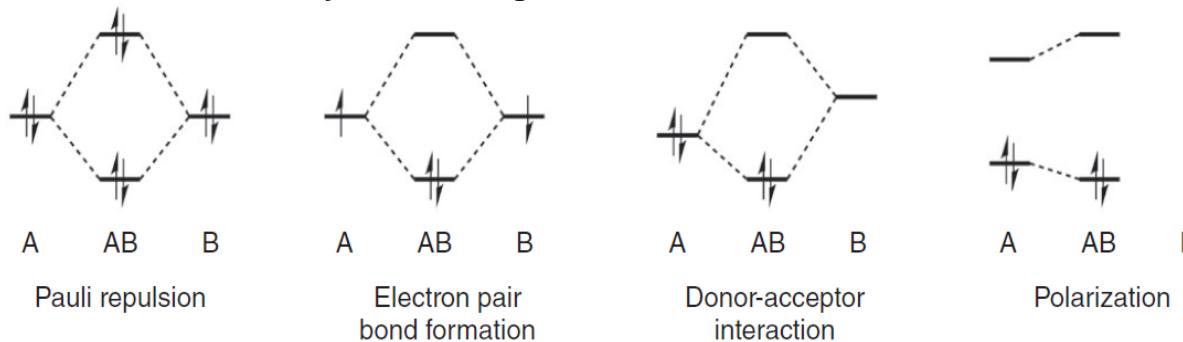
→ further analyzed by Hirshfeld surface analysis, molecular electrostatic potential (MEP) etc.

ΔE_{Pauli} : Pauli repulsion (destabilizing interaction between occupied orbitals; *i.e.* steric repulsion)

ΔE_{oi} : polarization (empty-occupied orbital) and charge transfer (donor-acceptor interactions including HOMO-LUMO interaction)

$$\Delta E_{\text{oi}}(\zeta) = \sum_{\Gamma} E_{\text{oi}(\Gamma)}^{\text{F}}$$

→ further decomposed into contributions from each irreducible representations Γ of the point group to which the molecular system belongs.



Orbital interaction diagrams for the most commonly appearing interactions.

■ In EDA, not only equilibrium structures but transition states (TS) and nonstationary points along intrinsic reaction coordinate (IRC) can be analyzed.

ADF Software and PyFrag 2019 Automated Program

■ **Amsterdam Density Functional (ADF)¹⁾: the only software package available to EDA.**

ASM can be carried with any other quantum chemical software package including Gaussian.



routine work (equilibrium geometry, IRC, etc.)

✓

✓

ASM

✓

✓

EDA

✗*

✓

* Unlike EDA, Morokuma-Kitaura analysis is available in Gaussian 16.

■ **PyFrag 2019^{2a)}: the free-of-charge open-source automated program for ASM-EDA approach**

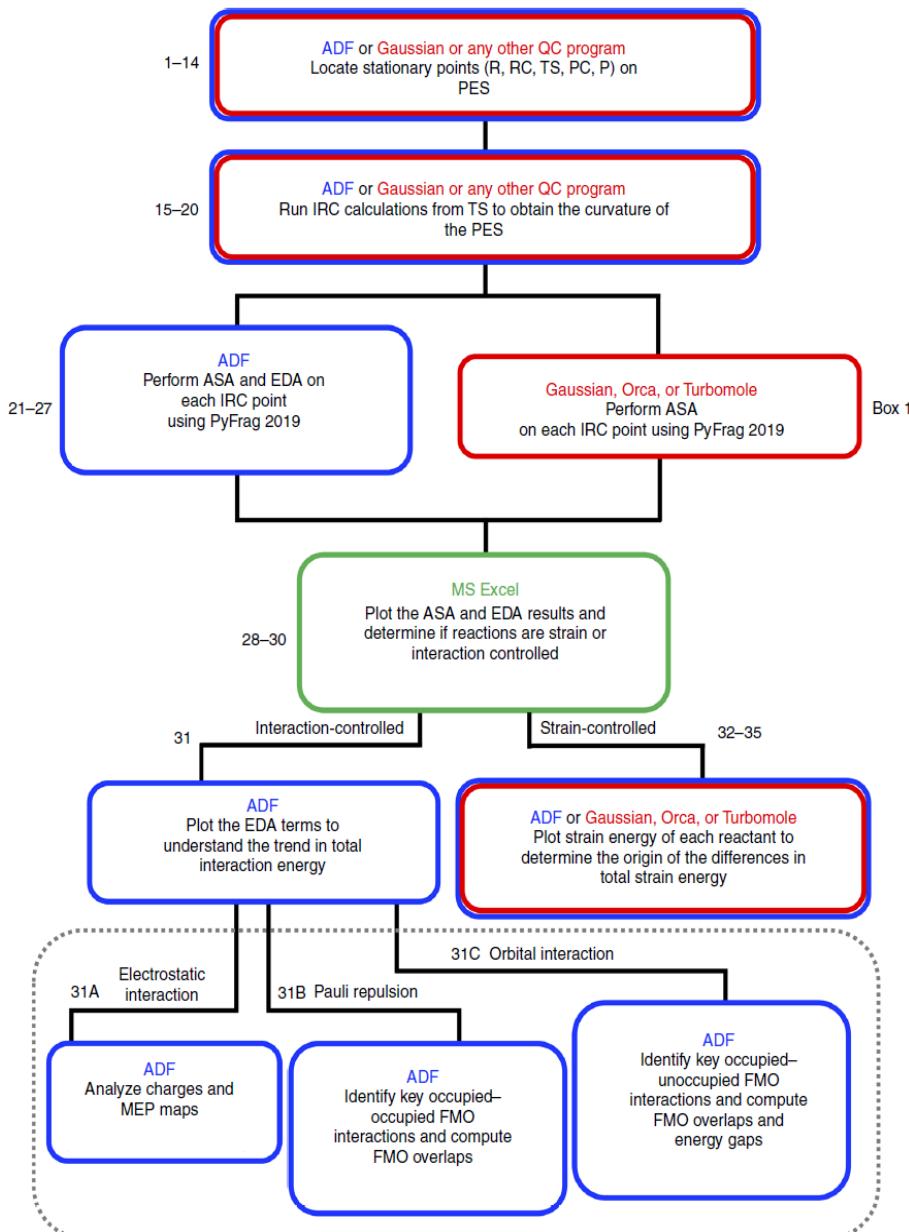
- updated version of PyFrag 2008^{2b)}
- compatible with ADF, Gaussian, and some other software (EDA is unavailable when using Gaussian.)
- Users are required to simply supply approximate geometries of the stationary points (reactants, TS, products).
- The computational progress and the convergence of the required geometry and TS optimization can be monitored at runtime.
- After completing the computations, PyFrag 2019 visualizes the results in a automated way.

1. te Velde, G. et al. *J. Comput. Chem.* **2001**, 22, 931.

2. (a) Halmin, T. A.; Bickelhaupt, F. M. et al. *J. Comput. Chem.* **2019**, 40, 2227.

(b) Bickelhaupt, F. M. et al. *J. Comput. Chem.* **2008**, 29, 312.

Schematic Workflow of ASM-EDA Approach



ADF: Amsterdam Density Functional
R: reactant(s)
RC: reactant complex
TS: transition state
P: product(s)
PC: product complex
IRC: intrinsic reaction coordinate
PES: potential energy surface
ASM: activation strain model
EDA: energy decomposition analysis
QC: quantum chemical
MEP: molecular electrostatic potential
FMO: fragment molecular orbital

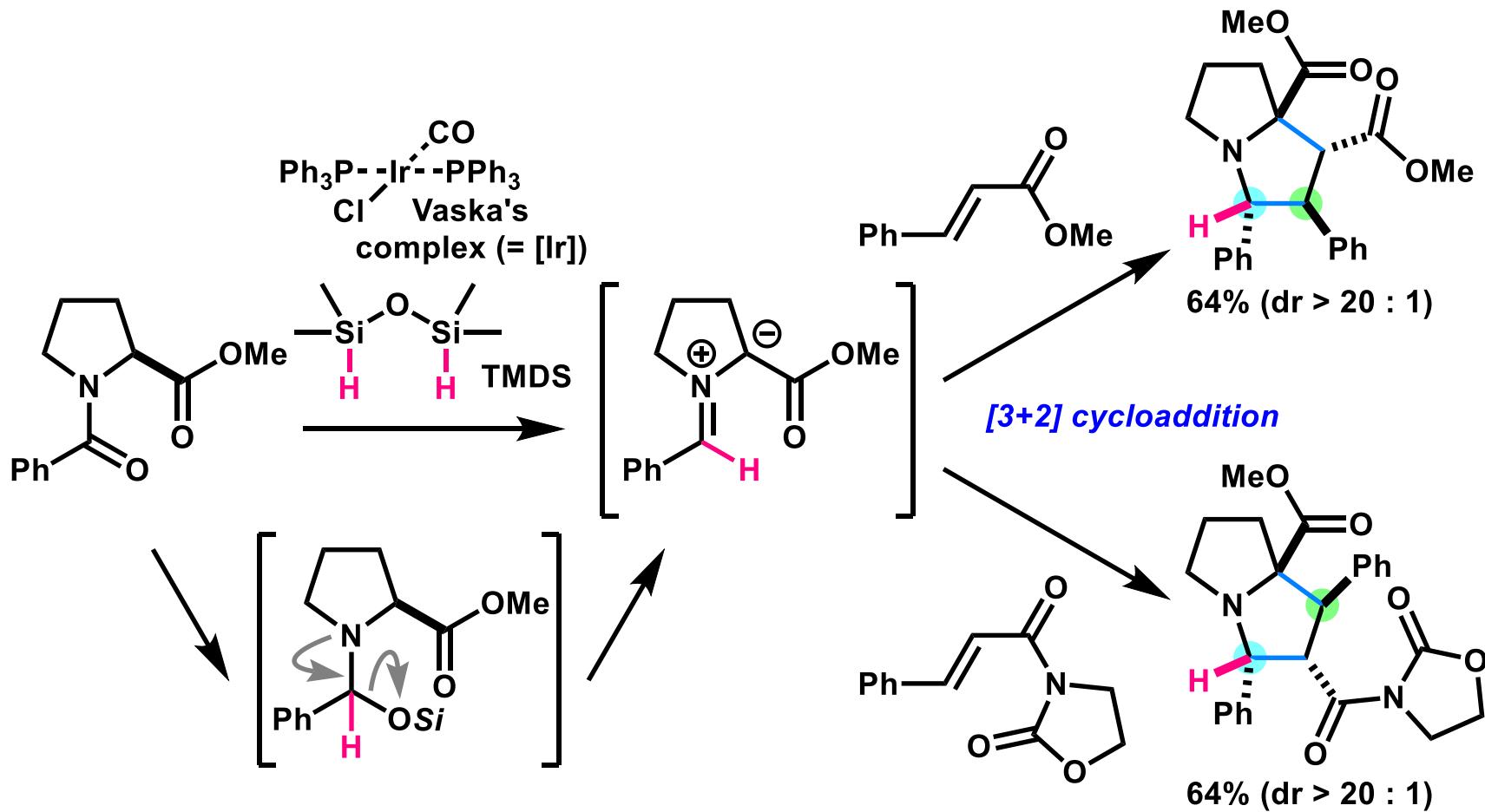
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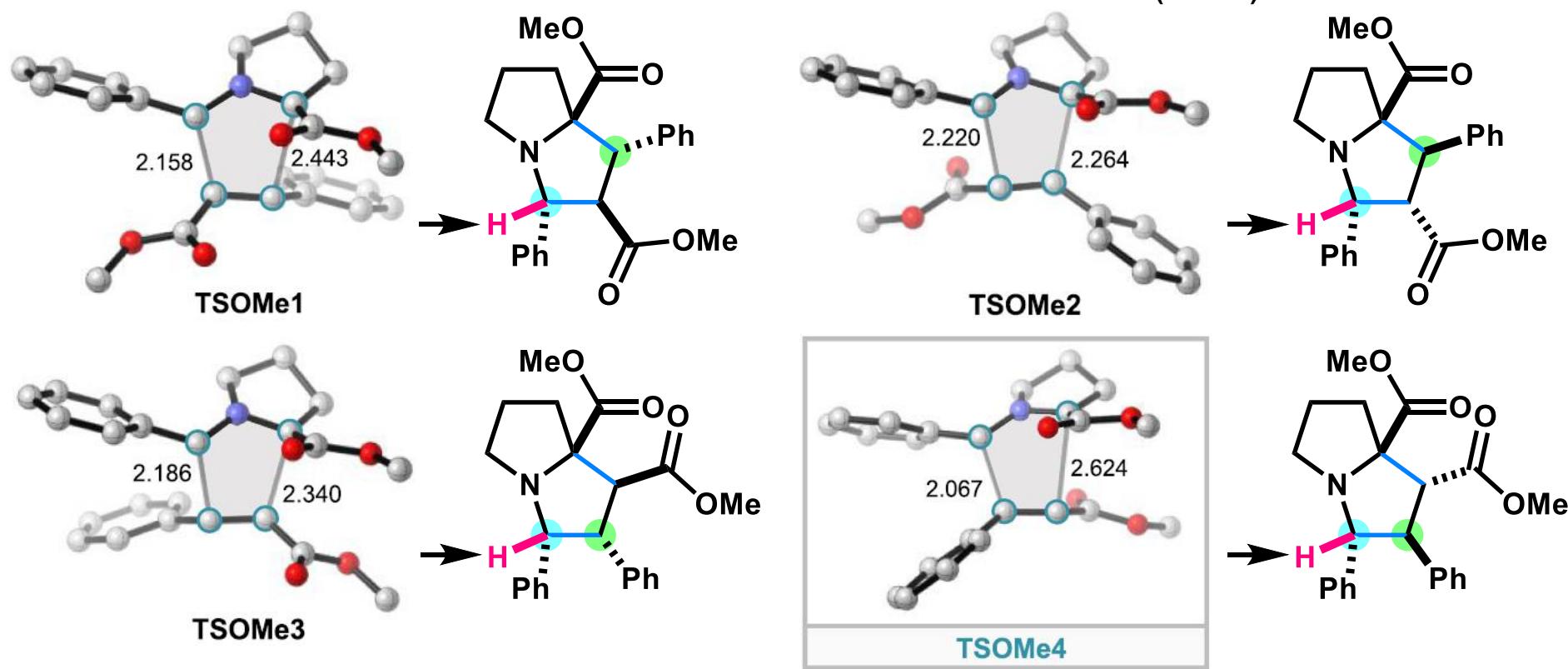
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[3+2] Cycloaddition of Azomethine Ylide



ASM Analysis of [3+2] Cycloaddition (1)



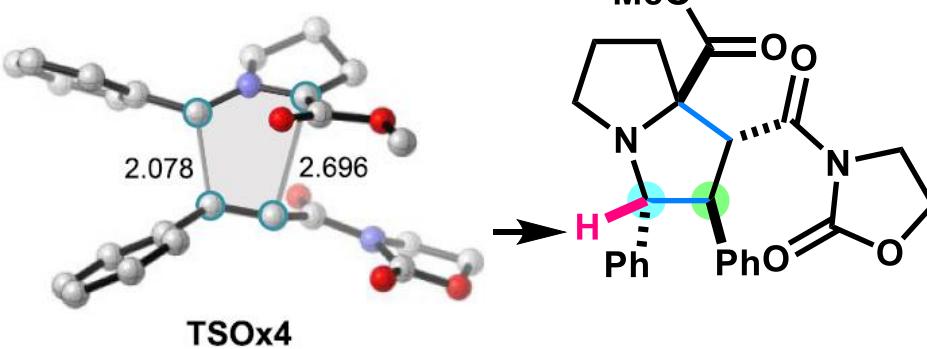
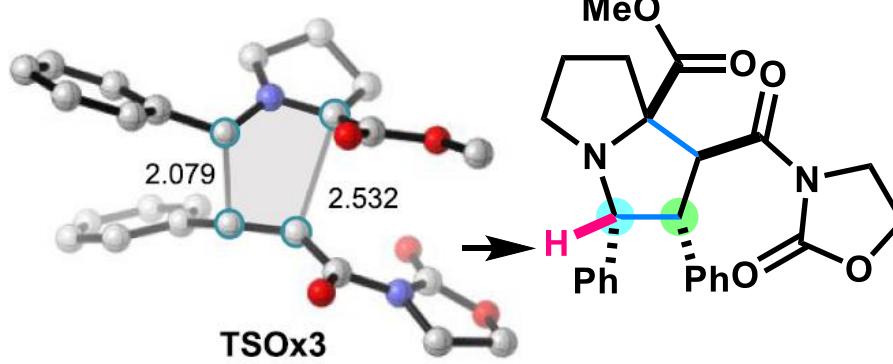
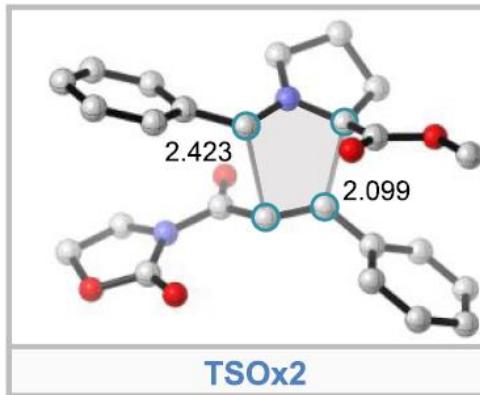
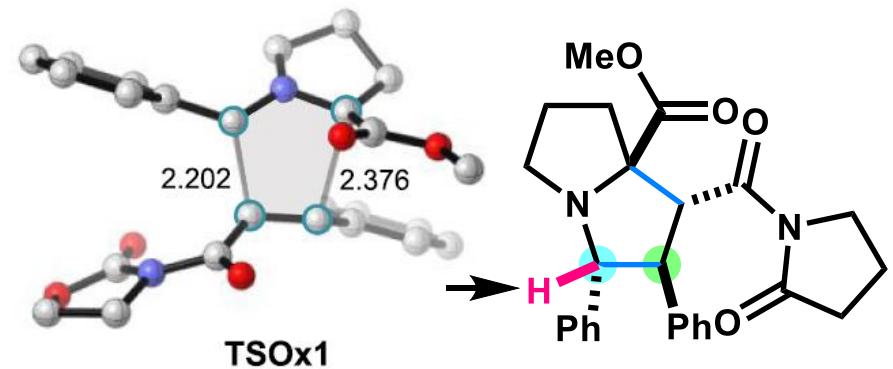
(kcal mol ⁻¹)	ΔG^\ddagger	ΔE^\ddagger	$\Delta E^\ddagger_{\text{strain}}$	$\Delta E^\ddagger_{\text{int}}$	$\Delta E^\ddagger_{\text{strain,dipole}}$	$\Delta E^\ddagger_{\text{strain,alkene}}$
TSOMe1	16.8	1.2	27.2	-26.0	14.0	13.2
TSOMe2	13.9	-2.7	30.6	-33.2	14.7	15.9
TSOMe3	18.0	1.7	31.5	-29.8	15.7	15.8
TSOMe4	13.5	-2.7	25.7	-28.3	11.5	14.1

→ strain control

Energies (kcal/mol) and bond lengths (Å) of TS geometries are provided here.

ASM Analysis of [3+2] Cycloaddition (2)

COSMO(toluene)-M06-2X/TZ2P//BP86/TZ2P



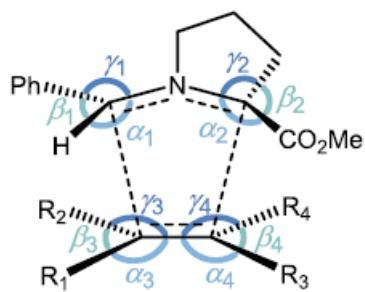
→ interaction control

(kcal mol ⁻¹)	ΔG^\ddagger	ΔE^\ddagger	$\Delta E^\ddagger_{\text{strain}}$	$\Delta E^\ddagger_{\text{int}}$	$\Delta E^\ddagger_{\text{int,gas}}$	$\Delta E^\ddagger_{\text{Pauli}}$	$\Delta V^\ddagger_{\text{elstat}}$	$\Delta E^\ddagger_{\text{oi}}$
TSOx1	14.4	-1.3	28.8	-30.1	-31.7	79.4	-51.1	-60.0
TSOx2	11.4	-5.0	30.2	-35.2	-37.5	97.7	-64.6	-70.6
TSOx3	16.8	0.6	30.8	-30.2	-31.4	85.3	-52.2	-64.5
TSOx4	11.6	-4.9	24.1	-29.1	-31.5	82.2	-54.4	-59.2

Energies (kcal/mol) and bond lengths (Å) of TS geometries are provided here.

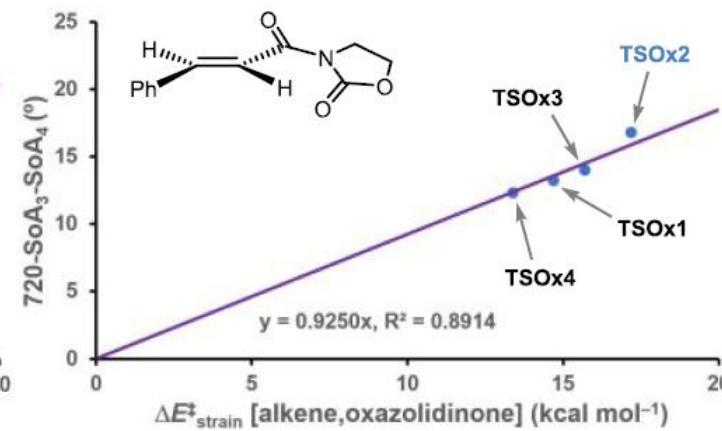
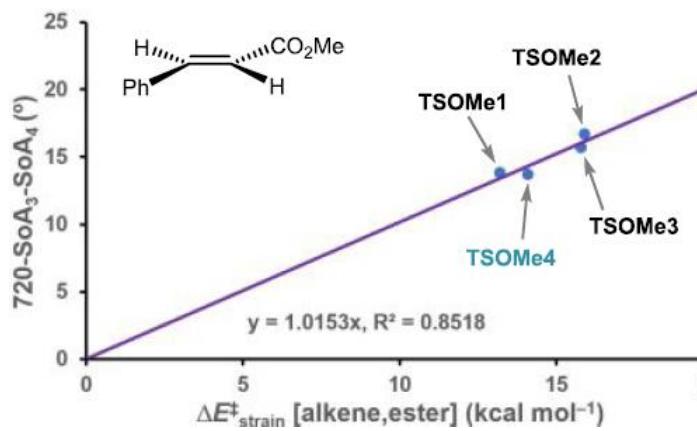
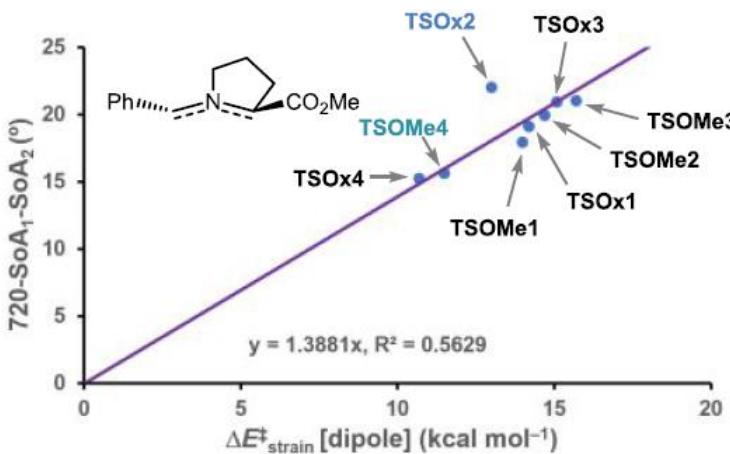
Strain Energy and Sum of Angles (SoA) Analysis

COSMO(toluene)-M06-2X/TZ2P//BP86/TZ2P



$$SoA_n = \alpha_n + \beta_n + \gamma_n \quad (\text{°})$$

$SoA = 360^\circ \rightarrow \text{planar}$
 $SoA < 360^\circ \rightarrow \text{distorted}$

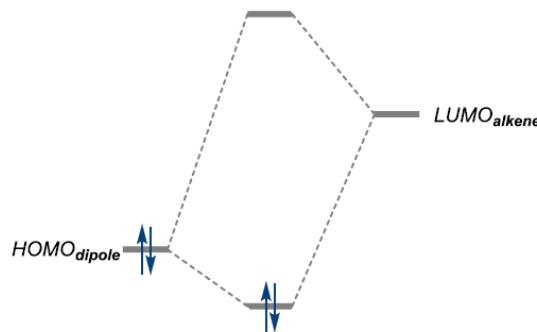


$720-\text{SoA}_1-\text{SoA}_2 \approx 0$ and $720-\text{SoA}_3-\text{SoA}_4 \approx 0 \rightarrow \text{"more asynchronous"} \rightarrow \text{less destabilizing } \Delta E^\ddagger_{\text{strain}}$

- good linear relationship between the normalized sum of angles (SoA) of pyramidization at two reacting carbon atoms and the strain energies of each fragment.

Frontier MO Analysis and MEP Analysis

B | Frontier molecular orbital (FMO) analysis

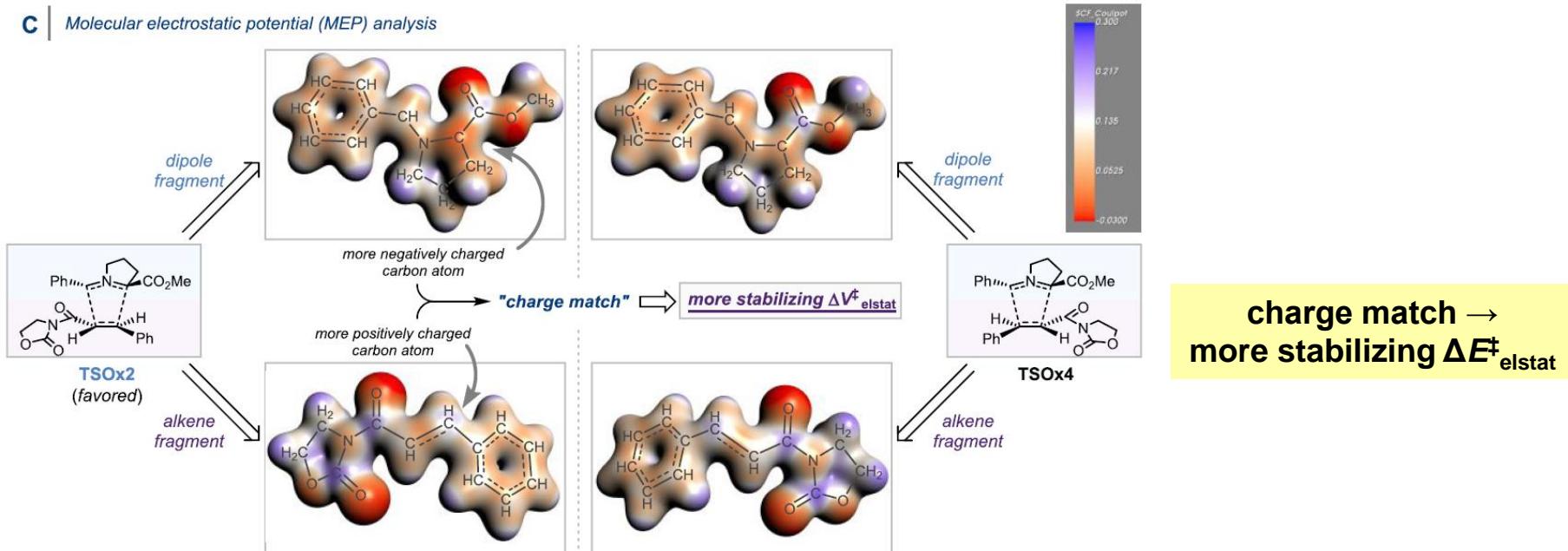


COSMO(toluene)-M06-2X/TZ2P//BP86/TZ2P

higher $S^2/\Delta\epsilon \rightarrow$ more stabilizing ΔE^\ddagger_{oi}

TS	$\Delta\epsilon$ $HOMO_{dipole}$ - $LUMO_{alkene}$ (eV)	Orbital Overlap S	$S^2/\Delta\epsilon \times 10^3$
TSOx1	4.1	0.17	7.4
TSOx2	3.9	0.19	9.0
TSOx3	4.0	0.17	7.4
TSOx4	4.1	0.16	6.5

C | Molecular electrostatic potential (MEP) analysis



charge match \rightarrow more stabilizing $\Delta E^\ddagger_{elstat}$

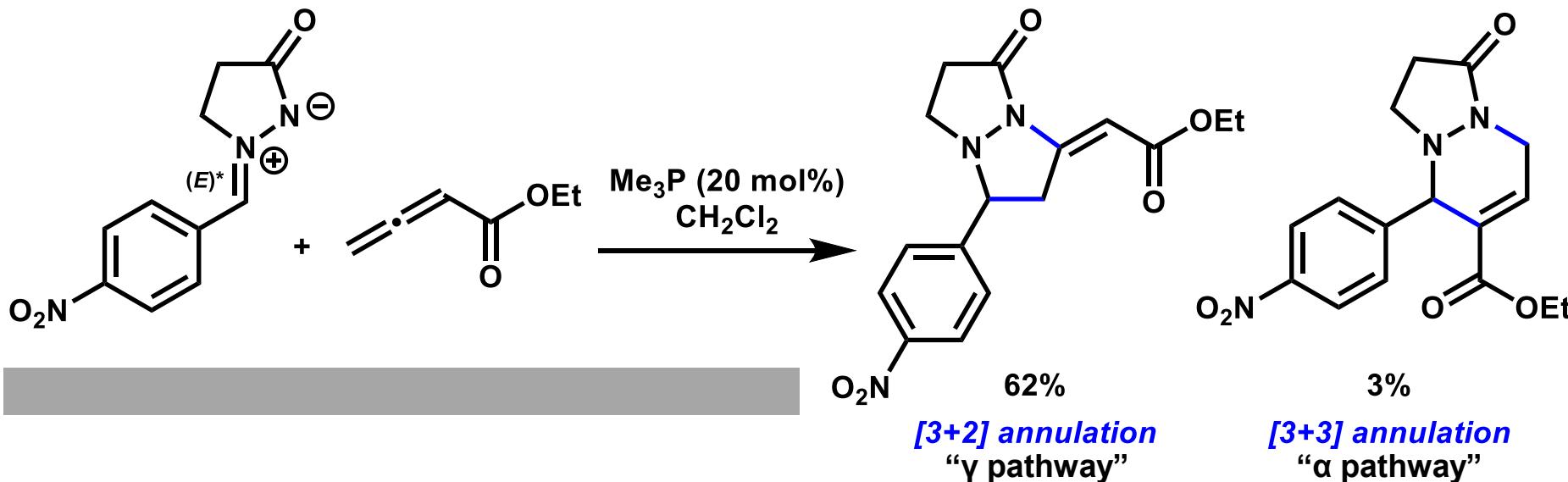
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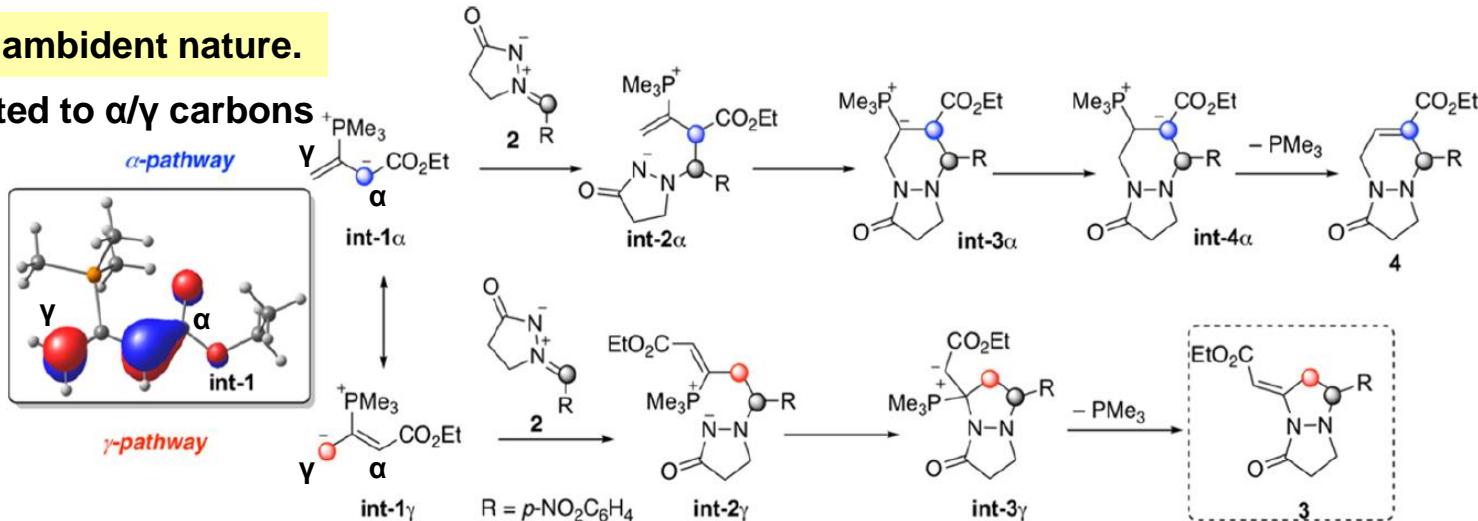
Phosphine-Catalyzed [3+3] Annulation



■ plausible reaction mechanism for the competitive [3+2]/[3+3] phosphine-catalyzed annulation

HOMO exhibits ambident nature.

equally distributed to α/γ carbons

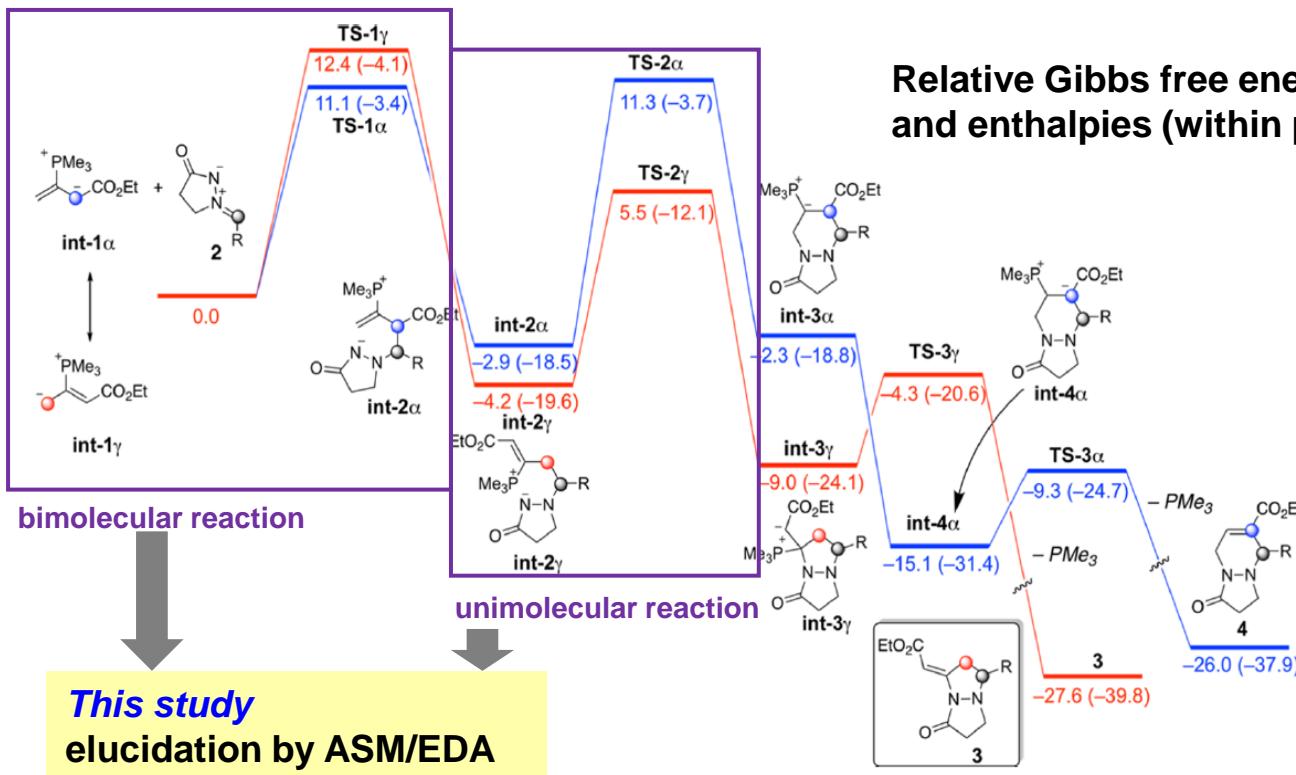


(a) Kwon, O. et al. *J. Am. Chem. Soc.* **2011**, 133, 13337.

(b) Gallardo-Fuentes, S.; Ormazábal-Toledo, R.; Fernández, I. *J. Org. Chem.* **2020**, 85, 9272.

Computed Reaction Profile

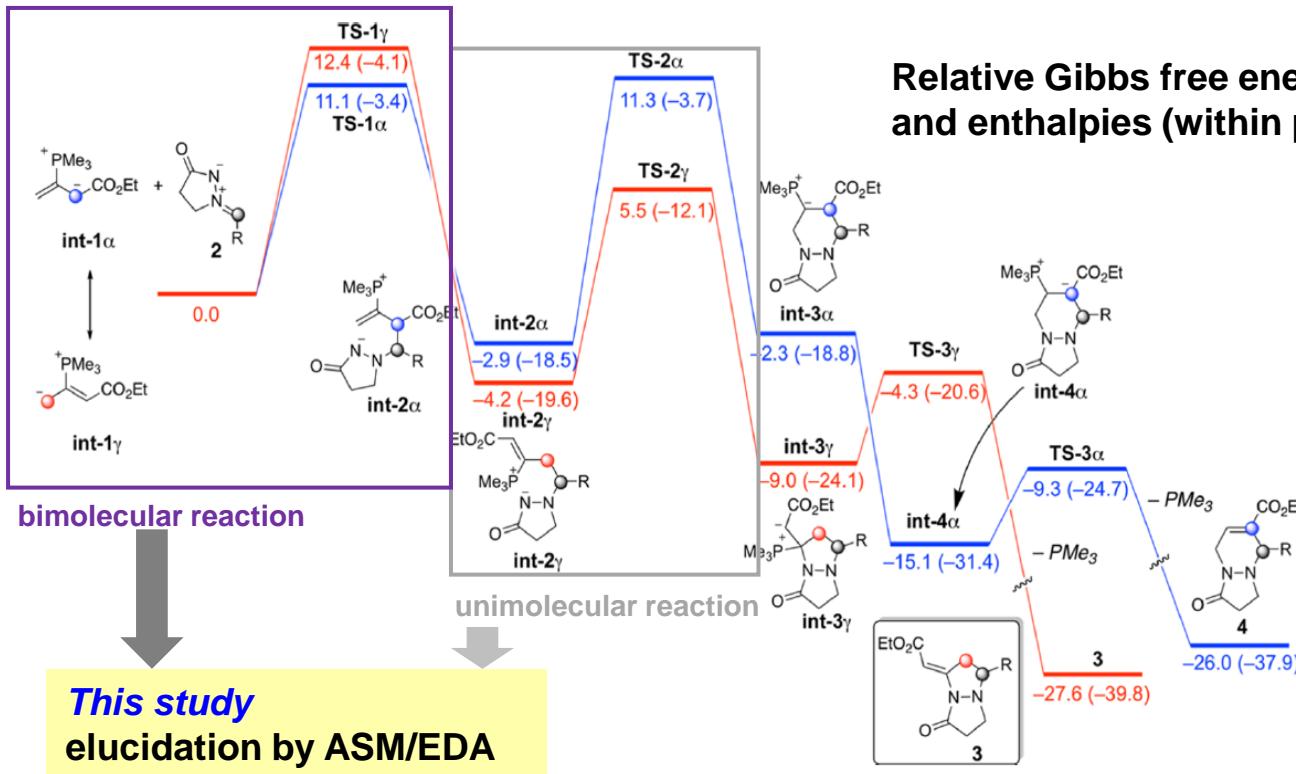
SMD(CH_2Cl_2)-M06-2X/6-31+G(d,p)



- α -Pathway (blue) is disfavored due to the high activation energy from $\text{int-2}\alpha$ to $\text{TS-2}\alpha$ ($\Delta\Delta G_{\text{TS-2}\alpha} = 14.2$ kcal/mol). (vs $\Delta\Delta G_{\text{TS-2}\gamma} = 9.7$ kcal/mol)
→ kinetically controlled
- On the other hand, the difference of the activation energy in the first phase (bimolecular reaction) is trivial ($\Delta\Delta G_{\text{TS-1}\alpha} = 11.1$ kcal/mol vs $\Delta\Delta G_{\text{TS-1}\gamma} = 12.4$ kcal/mol)

Computed Reaction Profile

SMD(CH_2Cl_2)-M06-2X/6-31+G(d,p)



- α -Pathway (blue) is disfavored due to the high activation energy from int-2 α to TS-2 α ($\Delta\Delta G_{\text{TS-2}\alpha} = 14.2$ kcal/mol). (vs $\Delta\Delta G_{\text{TS-2}\gamma} = 9.7$ kcal/mol)
→ kinetically controlled
- On the other hand, the difference of the activation energy in the first phase (bimolecular reaction) is trivial ($\Delta\Delta G_{\text{TS-1}\alpha} = 11.1$ kcal/mol vs $\Delta\Delta G_{\text{TS-1}\gamma} = 12.4$ kcal/mol)

ASM/EDA in Bimolecular Reaction (γ -Pathway)

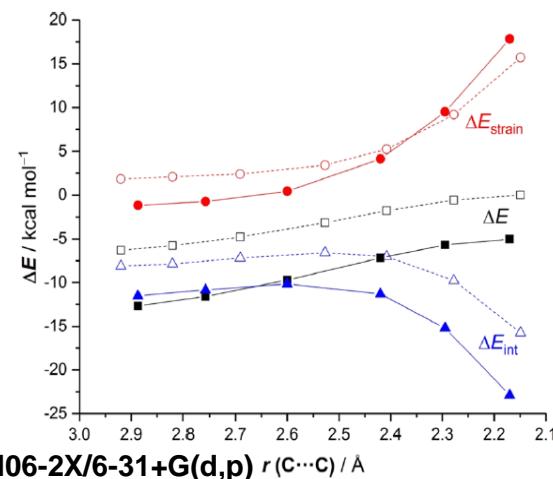
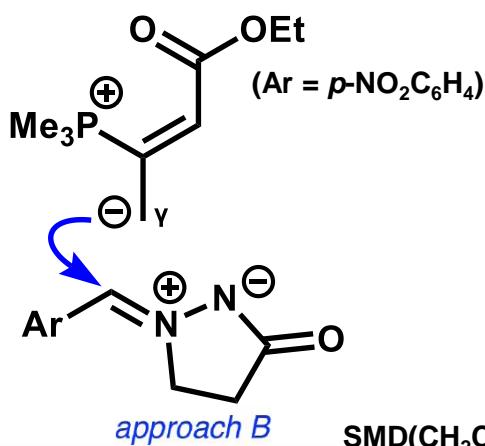
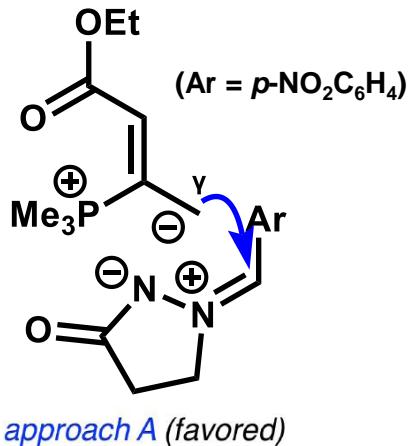
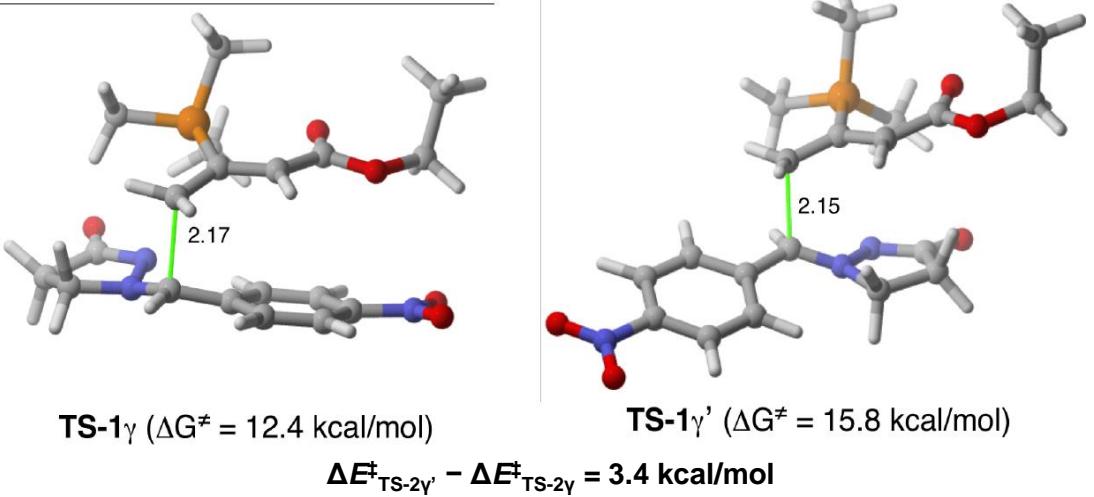


Figure 5. Comparative ASDs for the competitive approaches A (solid lines) and B (dotted lines) associated with the initial nucleophilic addition involving int-1 and 2 (γ -pathway). All data have been computed at the SMD(dichloromethane)-M062X/6-31+G(d,p) level.



→ interaction control

→ Both ΔE_{elstat} and ΔE_{orb} are decisive.

(* $\Delta E_{oi} = \Delta E_{\text{orb}}$: orbital interaction)

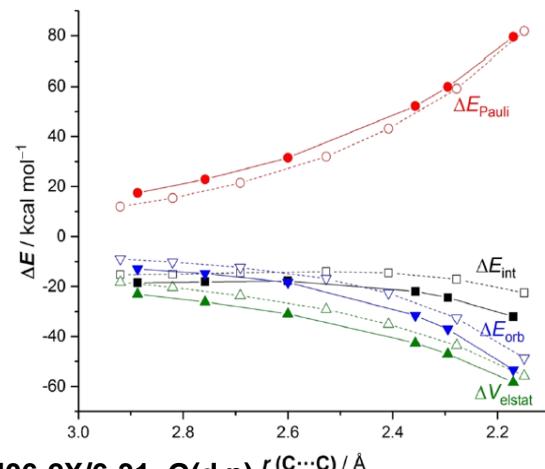


Figure 6. Decomposition of the interaction energy along the reaction pathway for approaches A (solid lines) and B (dotted lines) associated with the initial nucleophilic addition involving int-1 and 2 (γ -pathway). All data have been computed at the M06-2X/TZ2P//SMD(dichloromethane)-M062X/6-31+G(d,p) level.

ASM/EDA in Bimolecular Reaction (γ - vs α -Pathways)

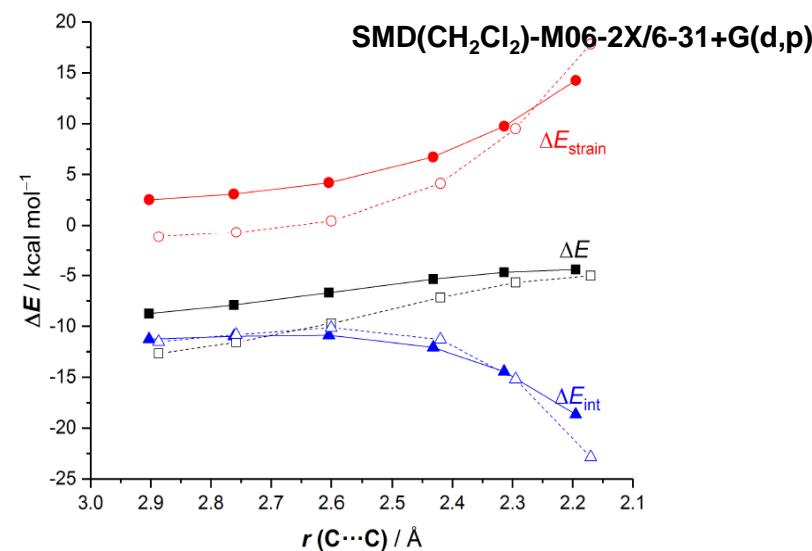
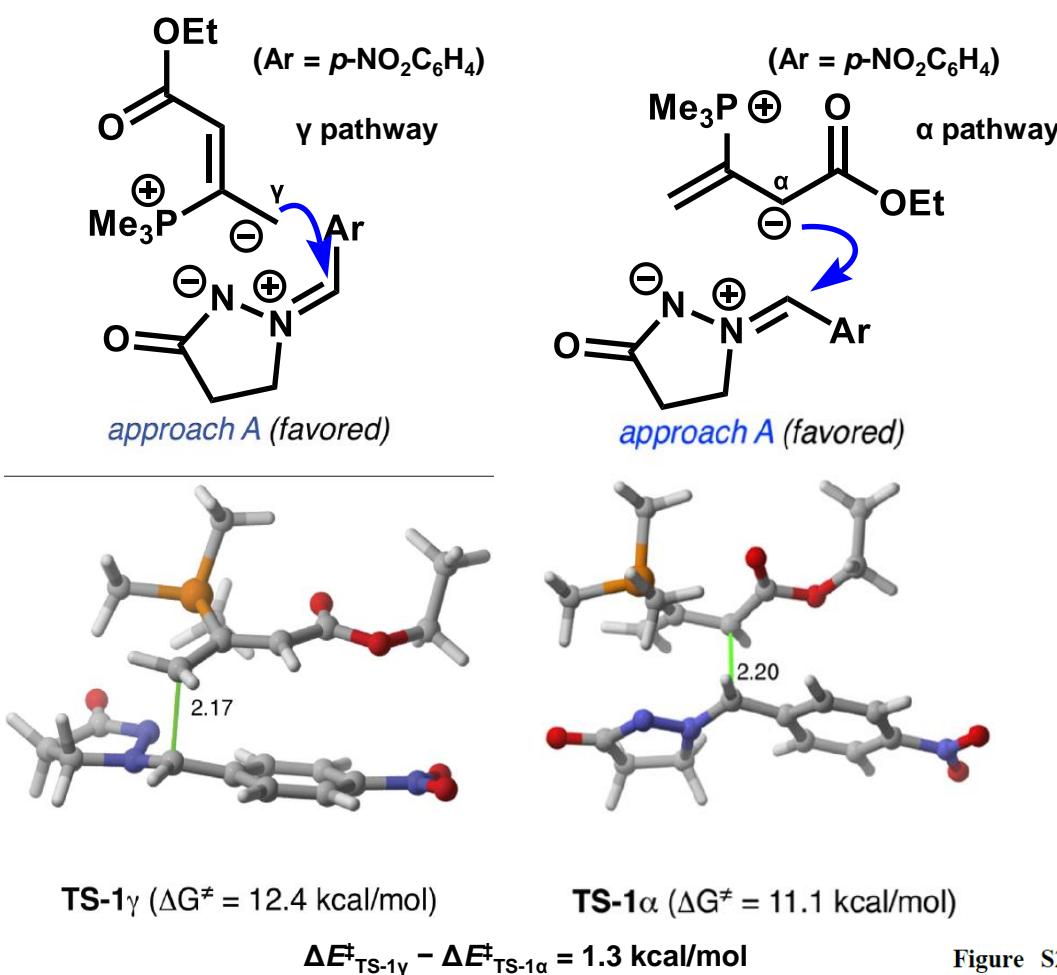
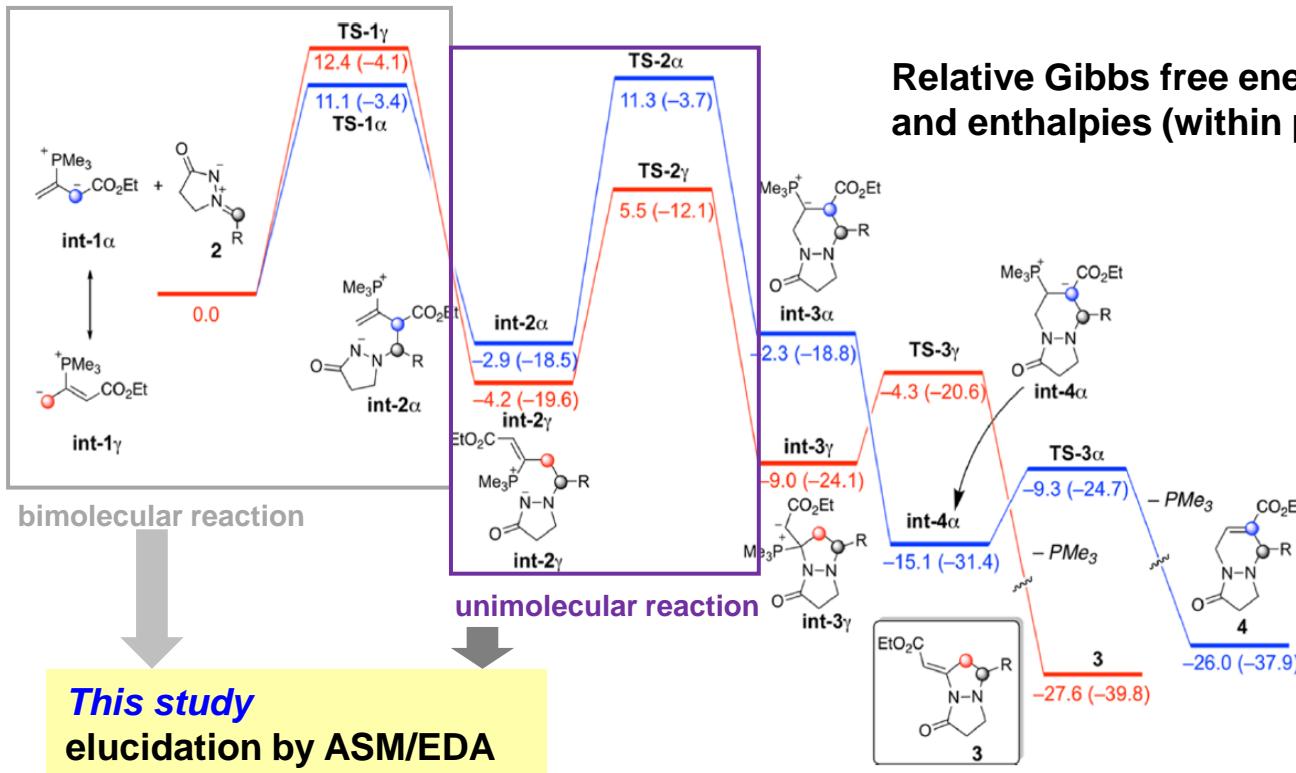


Figure S2. Comparative activation strain diagrams for the competitive nucleophilic addition involving **int-1** and **2**, namely α -pathway (solid lines) and γ -pathway (dotted lines). All data have been computed at the SMD(dichloromethane)-M062X/6-31+G(d,p) level.

The predominant factor (strain energy or interaction energy) in the difference of $\Delta E^\ddagger_{TS-1\alpha}$ and $\Delta E^\ddagger_{TS-1\gamma}$ is ambiguous. However, it does not matter because the decisive step for the observed γ -selectivity is not here.

Computed Reaction Profile

SMD(CH_2Cl_2)-M06-2X/6-31+G(d,p)

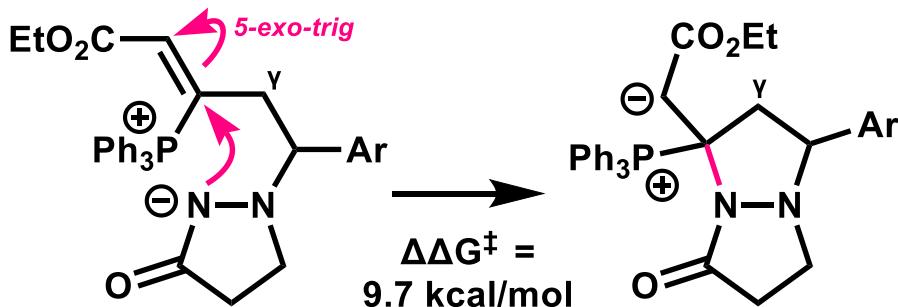


- α -Pathway (blue) is disfavored due to the high activation energy from int-2 α to TS-2 α ($\Delta\Delta G_{\text{TS-2}\alpha} = 14.2$ kcal/mol). (vs $\Delta\Delta G_{\text{TS-2}\gamma} = 9.7$ kcal/mol)
→ kinetically controlled
- On the other hand, the difference of the activation energy in the first phase (bimolecular reaction) is trivial ($\Delta\Delta G_{\text{TS-1}\alpha} = 11.1$ kcal/mol vs $\Delta\Delta G_{\text{TS-1}\gamma} = 12.4$ kcal/mol)

Free Barrier Energies of Cyclization Modes

■ from γ -pathway intermediate

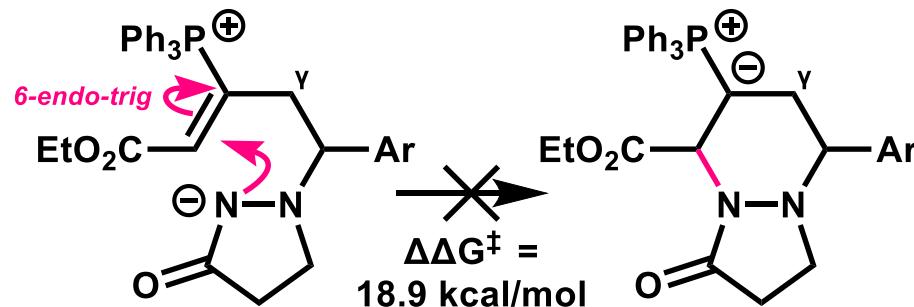
- 5-exo-trig cyclization



(* $\Delta\Delta G^\ddagger$: free barrier energies of cyclization)

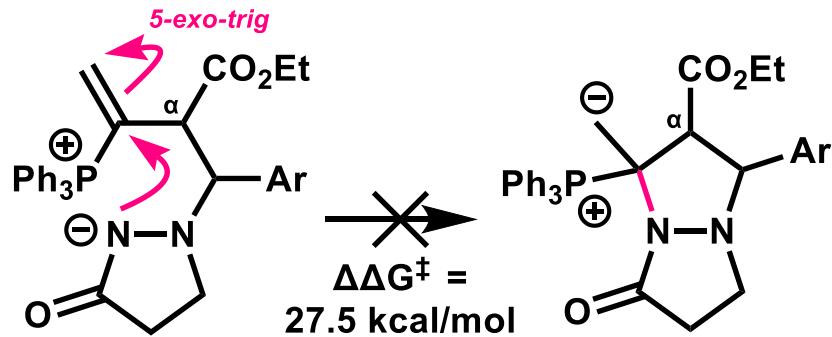
SMD(CH₂Cl₂)-M06-2X/6-31+G(d,p)

- 6-endo-trig cyclization

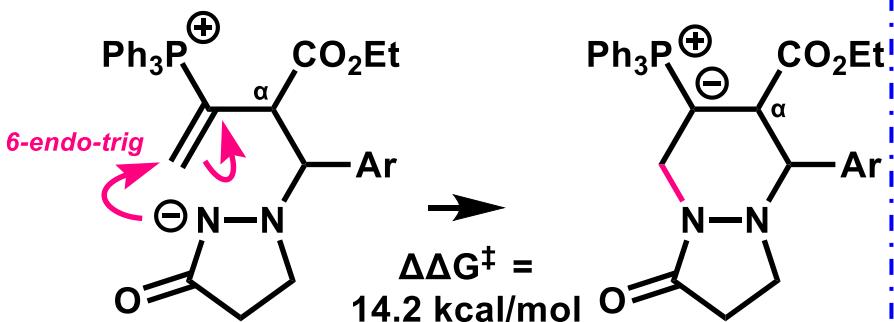


■ from α -pathway intermediate

- 5-exo-trig cyclization



- 6-endo-trig cyclization



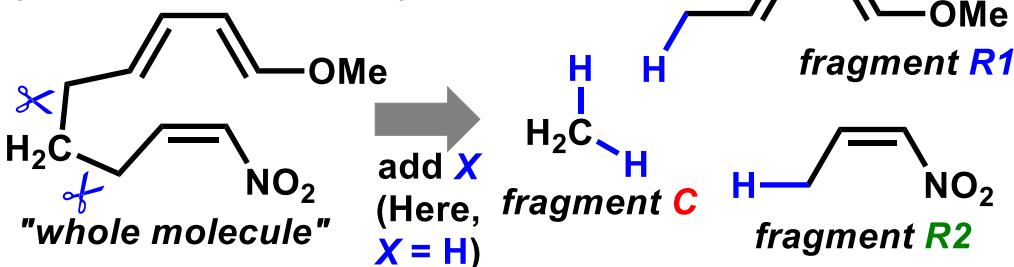
Question: What is the dominant factor for 5-exo-trig cyclization in the γ -pathway?

Application of ASM to Unimolecular Reaction (1)

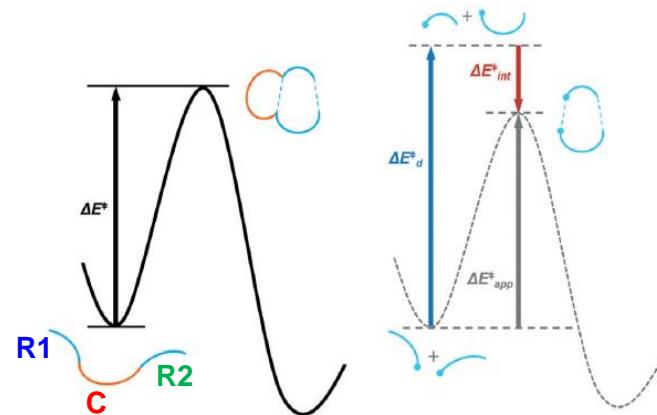
– Houk's Three-Fragment Approach^{1,2} –

ASM analysis of unimolecular reactions can be conducted by fragment-based approaches.

(Diels-Alder substrate)



R1/R2: first/second reaction centers, C: connector



$$\begin{aligned} * \Delta E_d &= \Delta E_{\text{strain}} \\ \Delta E_{\text{app}}^{\ddagger} &= (\Delta E^{\ddagger}_{\text{strain},R1} + \Delta E^{\ddagger}_{\text{strain},R2}) - \Delta E^{\ddagger}_{\text{int},R1-R2} \\ &= \Delta E^{\ddagger}_{\text{whole}} + \Delta E^{\ddagger}_{\text{strain},C} \end{aligned}$$

- detach each component of the whole molecule into C, R₁, and R₂.
- replace the loose ends with a chemically similar functional group X (X = H in the above example)

hypothesis:

- Strain energy ($\Delta E_{\text{strain}} = \Delta E_d$) is additive.
(i.e. $\Delta E_{\text{strain,whole}} = \Delta E_{\text{strain},R1} + \Delta E_{\text{strain},R2} + \Delta E_{\text{strain},C}$)
- $\Delta E_{\text{int},R1-C} = \Delta E_{\text{int},R2-C} = 0$

$$\rightarrow \Delta E = \Delta E_{\text{strain},R1} + \Delta E_{\text{strain},R2} + \Delta E_{\text{strain},C} + \Delta E_{\text{int},R1-R2}$$

caution:

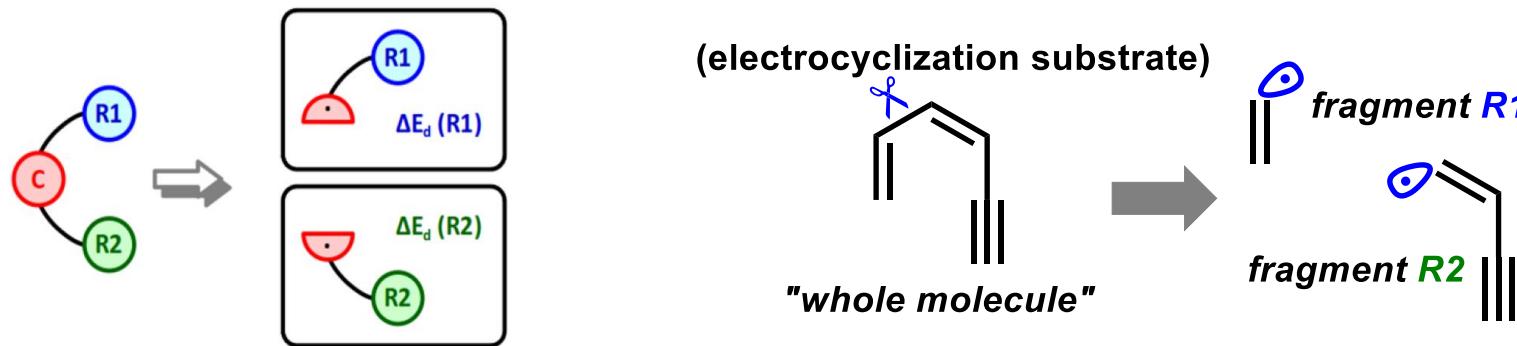
- Fragment design should be carefully conducted because it may induce errors in the calculation of $\Delta E_{\text{strain},C}$ in the case existing a new X-X interaction not included in the original *whole molecule*.
- Newly added C-X bond can affect strain energy of each fragment.

1. For a review, see: Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070.
 2. (a) Krenske, E. H.; Houk, K. N.; Holmes, A. B.; Thompson, J. *Tetrahedron Lett.* **2011**, *52*, 2181.
 (b) Velasco-Juárez, E.; Arpa, E. M. *Theor. Chem. Acc.* **2021**, *140*, 107.

Application of ASM to Unimolecular Reaction (2)

– Bickelhaupt's Two-Fragment Approach^{1,2} –

ASM analysis of unimolecular reactions can be conducted by fragment-based approaches.



- homolytic bond cleavage in the connector
- $\Delta E_{\text{strain},R1}$ and $\Delta E_{\text{strain},R2}$ can be calculated by single-point energy calculations considering the independent fragments as open-shell doublets

hypothesis:

- Strain energy ($\Delta E_{\text{strain}} = \Delta E_d$) is additive.
(i.e. $\Delta E_{\text{strain,whole}} = \Delta E_{\text{strain},R1} + \Delta E_{\text{strain},R2}$)

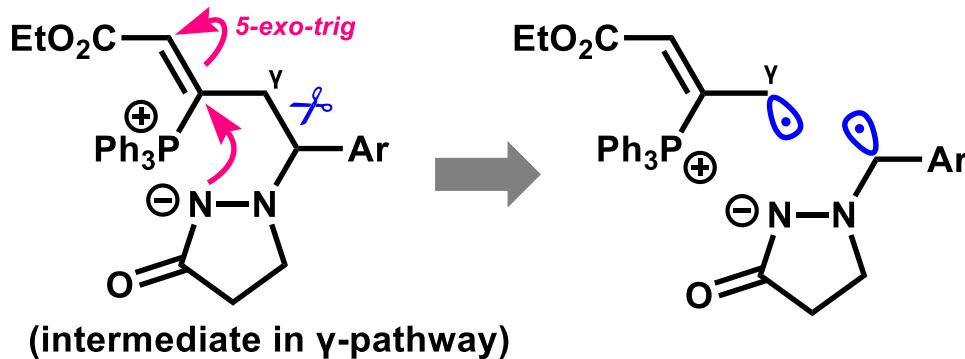
$$\rightarrow \Delta E = \Delta E_{\text{strain},R1} + \Delta E_{\text{strain},R2} + \Delta E_{\text{int},R1-R2}$$

■ This Bickelhaupt's approach was implemented in the present study described in the main literature.

1. For a review, see: Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070.
2. (a) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem. Eur. J.* **2012**, *18*, 12395.
(b) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem. Eur. J.* **2014**, *20*, 10791.

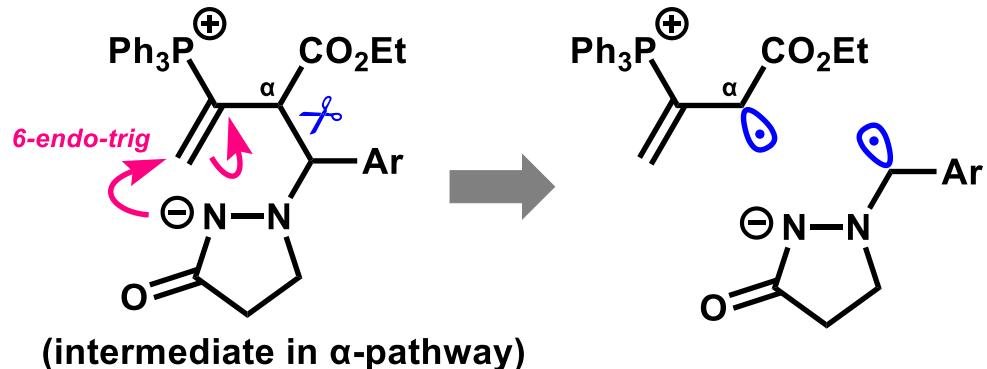
ASM Comparison for 5-exo-trig and 6-endo-trig

■ major pathway (5-exo-trig cyclization from γ -pathway intermediate)



(intermediate in γ -pathway)

■ minor pathway (6-endo-trig cyclization from α -pathway intermediate)



(intermediate in α -pathway)

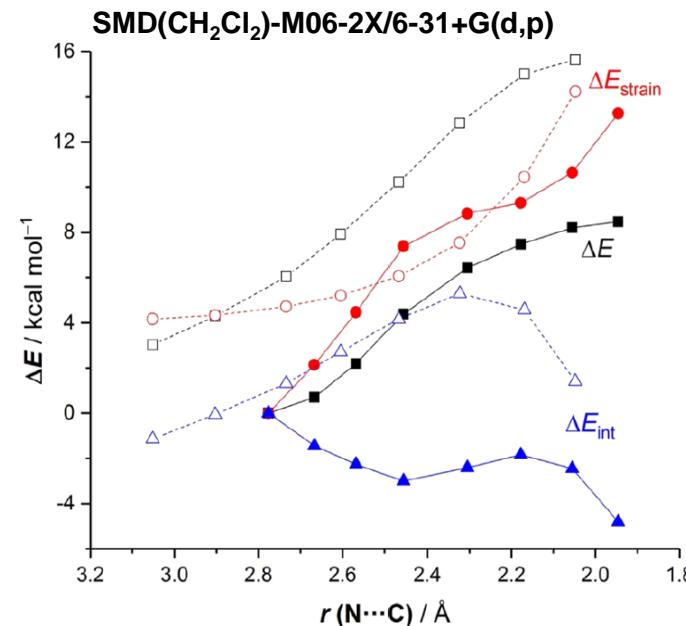


Figure 9. Comparative ASDs for 5-exo-trig (γ -pathway, solid lines) and 6-endo-trig (α -pathway, dotted lines) cyclization reactions. All data have been computed at the SMD(dichloromethane)-M062X/6-31+G(d,p) level.

- Both pathway exhibit similar ΔE_{strain} values especially at the transition state region.
→ Change of ΔE_{int} is responsible for the selectivity.

EDA Comparison for 5-exo-trig and 6-endo-trig

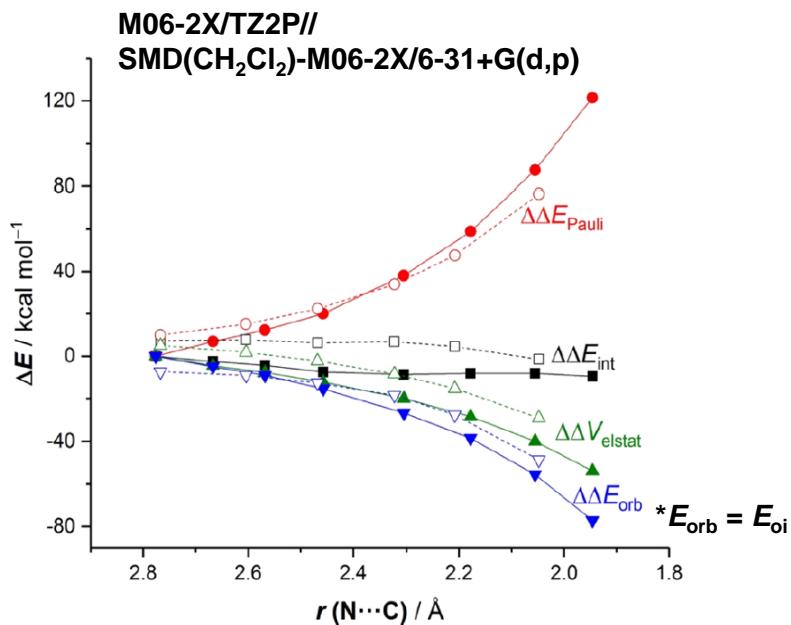


Figure 10. Decomposition of the interaction energy along the reaction pathway for 5-exo-trig (γ -pathway, solid lines) and 6-endo-trig (α -pathway, dotted lines) cyclization reactions. All data have been computed at the M06-2X/TZ2P//SMD(dichloromethane)-M062X/6-31+G(d,p) level.

The sum of $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$ is decisive for $\Delta\Delta E_{\text{int}}$.

$\Delta E(\rho)$: stabilization energy by the charge flow from $\text{LP}(\text{N}^-) \rightarrow \pi^*(\text{C}=\text{C})$ at the same consistent N...C bond forming a distance of 2.1 Å.

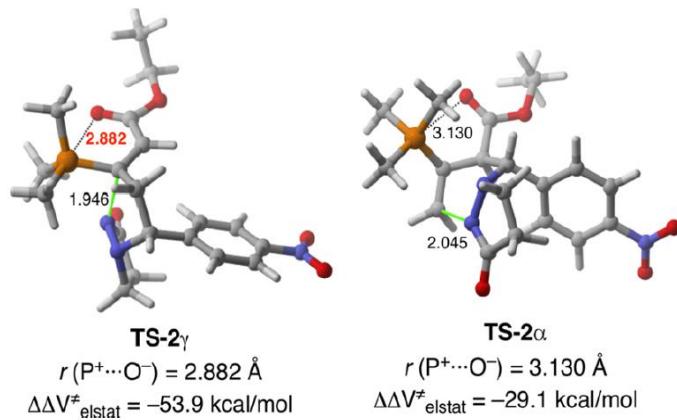


Figure 11. $\text{P}^+\cdots\text{O}^-$ interactions and $\Delta\Delta V_{\text{elstat}}^\ddagger$ values in TS-2 γ (left) and TS-2 α (right).

■ EDA-NOCV (a.k.a. ETS-NOCV) analysis (NOCV: the natural orbital for chemical valence)

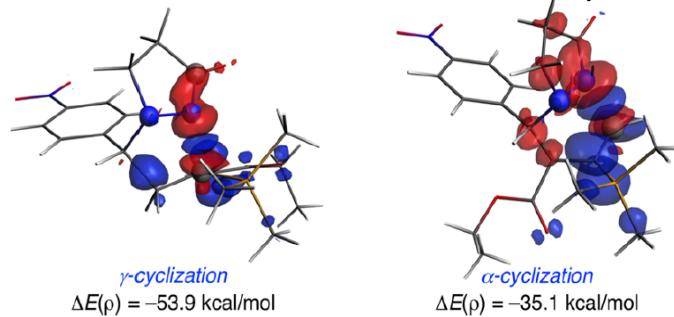
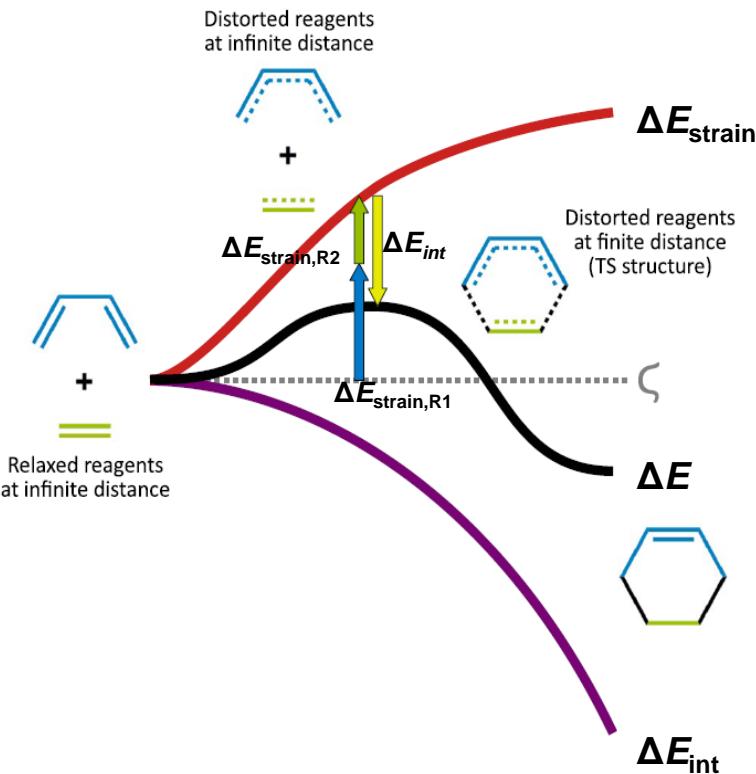


Figure 12. Plot of the deformation densities $\Delta\rho$ of the pairwise orbital interactions between the interacting fragments and the corresponding stabilization energies $\Delta E(\rho)$ computed for the cyclization reactions of the γ - (left) and α -pathways (right). The color code of the charge flow is red → blue.

Summary



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

$$\Delta E_{\text{int}} = \Delta E_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{orb}}$$

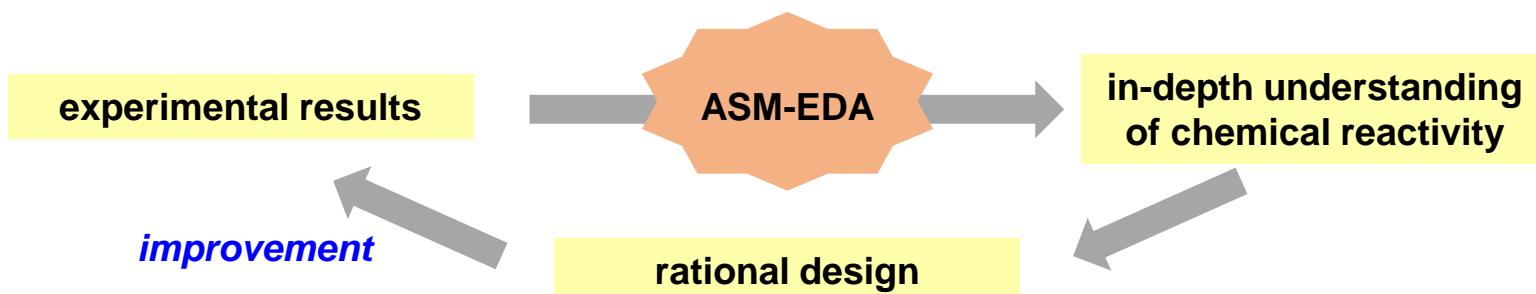
ΔE_{strain} : strain energy of deformed reagent(s)
 ΔE_{int} : interaction energy between deformed reagents

ΔE_{elstat} : electrostatic energy

ΔE_{Pauli} : Pauli repulsion

ΔE_{oi} : polarization and charge transfer

- Activation strain model (ASM) establishes a causal relationship between trends in reactivity and underlying physical factors that are rooted in the molecular and electronic structures of reactants.
- Energy decomposition analysis (EDA) can further analyze ΔE_{int} which is decomposed into the electrostatic interaction (ΔE_{elstat}), Pauli repulsion (ΔE_{Pauli}) and orbital interaction (ΔE_{oi}).



Appendix

Theoretical Background of EDA

$$\Delta E_{\text{int}} = \Delta E_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}}$$

The distorted fragments with frozen charge densities A and B are brought from infinite separation to the position in the molecule. This state is the promolecule with the product wavefunction $\Psi_A \Psi_B$ and the energy E_{AB}^0 . The interaction between frozen charge densities of A and B at the equilibrium geometry of B gives the quassical Coulomb interaction ΔE_{elstat} .

$$\Delta E_{\text{elstat}} = \sum_{\alpha \in A} \sum_{\beta \in B} \frac{Z_\alpha Z_\beta}{R_{\alpha\beta}} + \int d\mathbf{r} V_B(\mathbf{r}) \rho_A(\mathbf{r}) + \int d\mathbf{r} V_A(\mathbf{r}) \rho_B(\mathbf{r}) + \iint d\mathbf{r}_1 \mathbf{r}_2 \frac{\rho_A(\mathbf{r}_1) \rho_B(\mathbf{r}_2)}{r_{12}}$$

Then, the product wavefunction $\Psi_A \Psi_B$, which is normalized but violates the Pauli principle, is antisymmetrized and renormalized to give an intermediate state ψ^0 with the corresponding energy E^0 . The energy difference between E_{AB}^0 and E^0 is termed as exchange (Pauli) repulsion ΔE_{Pauli} .

$$\begin{aligned}\psi^0 &= N\alpha\{\Psi_A \Psi_B\} \\ \Delta E_{\text{Pauli}} &= E_{AB}^0 - E^0\end{aligned}$$

Finally, ψ^0 is relaxed to yield the final state Ψ_{AB} of the molecule A–B with the energy E_{AB} . The associated energy lowering comes from the orbital mixing, and thus, it can be identified as covalent contribution to the chemical bond. It is termed orbital interaction ΔE_{oi} .

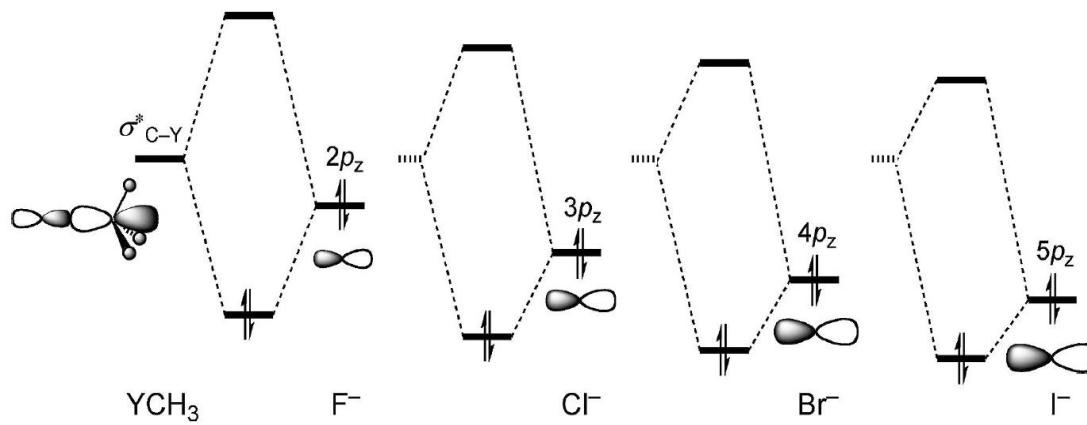
$$\Delta E_{\text{oi}} = E_{AB} - E_{AB}^0$$

$$\Delta E_{\text{oi}} = \sum_{\Gamma} E_{\text{oi}(\Gamma)}^{\Gamma}$$

-
1. von Hopffgarten, M.; Frenking, G. *WIREs Comput. Mol. Sci.* **2012**, 2, 43.
 2. Su, P.; Tang, Z.; Wu, W. *WIREs Comput. Mol. Sci.* **2020**, 10, e1460.

An Example of ASM: S_N2 Reaction

SCHEME 3. HOMO–LUMO Interaction of X[−] = F[−], Cl[−], Br[−], and I[−] with a Halomethane CH₃Y



An Example of Single-Point ASM

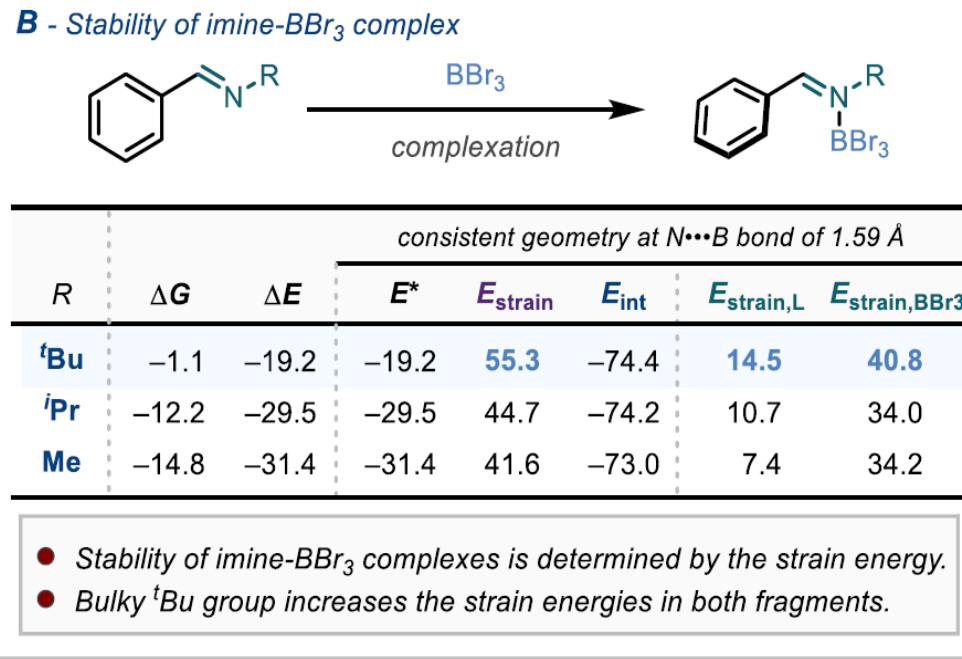


Figure 3. (A) Energy profiles with various imines and the geometries of imine-BBr₃ complexes, and (B) relative stabilities of imine–BBr₃ complexes. The activation strain analysis was performed at consistent geometry with a B–N bond distance of 1.59 Å. Energies (kcal mol⁻¹) and bond lengths (Å) of computed geometries are provided in the inset.

Houk's Three-Fragment Approach

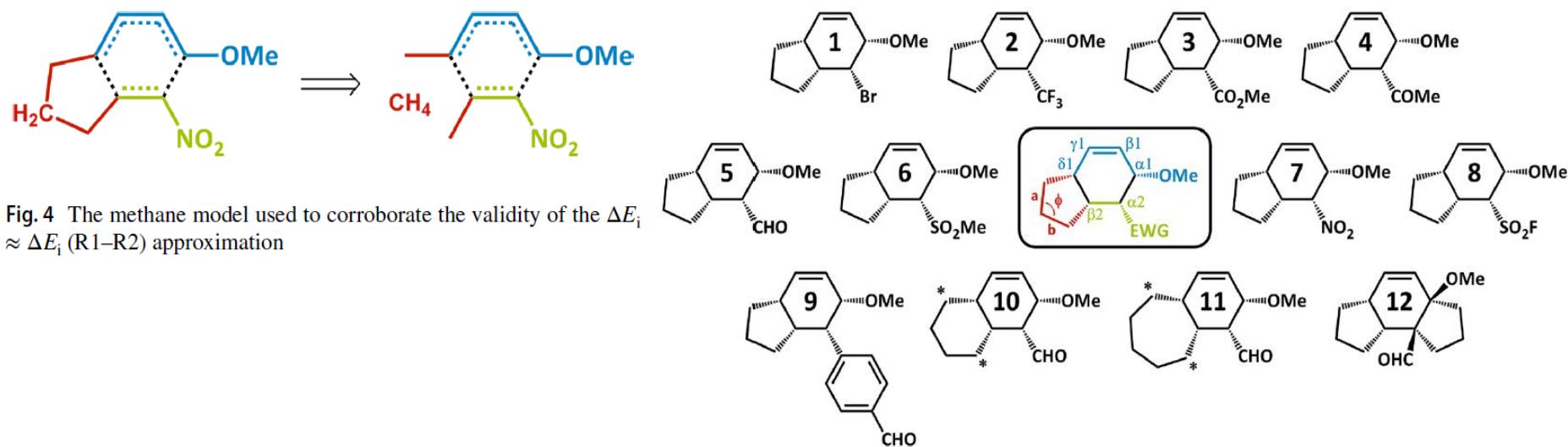
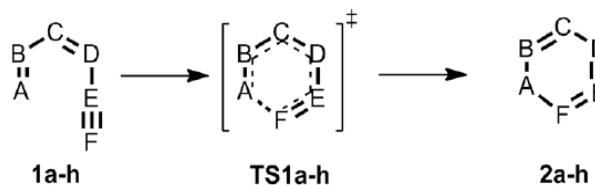


Fig. 4 The methane model used to corroborate the validity of the $\Delta E_i \approx \Delta E_i(R1-R2)$ approximation

Entry	ΔE^\ddagger	ΔE_{reac}	$\Delta E_d(R1)$	$\Delta E_d(R2)$	$\Delta E_d(C)$	ΔE_d	ΔE_i	σ^-
1	22.95	-31.42	19.62	13.53	2.91	36.06	-13.11	0.25
2	18.97	-32.89	17.76	11.82	2.91	32.48	-13.52	0.65
3	19.98	-27.28	18.68	13.07	1.46	33.20	-13.22	0.75
4	19.57	-26.72	17.65	14.18	1.69	33.52	-13.95	0.84
5	17.89	-26.53	17.36	14.67	1.27	33.29	-15.40	1.03
6	17.91	-32.95	17.41	14.61	1.30	33.31	-15.40	1.13
7	15.55	-31.79	15.54	14.30	1.23	31.07	-15.52	1.27
8	15.58	-29.65	16.26	14.10	2.03	32.39	-16.81	1.54
9	19.92	-26.56	19.01	11.97	-0.36	30.63	-10.71	-
10	19.52	-28.91	16.70	13.33	0.86	30.89	-11.37	-
11	21.22	-29.05	14.75	13.66	4.15	32.56	-11.34	-
12	16.43	-37.19	13.62	9.53	3.00	25.97	-9.54	-

Bickelhaupt's Two-Fragment Approach



	A	B	C	D	E	F
a	CH ₂	CH	CH	CH	C	CH
b	CHMe	CH	CH	CH	C	CH
c	NH	CH	CH	CH	C	CH
d	O	CH	CH	CH	C	CH
e	CH ₂	N	CH	CH	C	CH
f	CH ₂	CH	N	CH	C	CH
g	CH ₂	CH	CH	N	C	CH
h	CH ₂	CH	CH	CH	C	N

Table 1. Activation strain analysis of ene-ene-yne cyclization reactions **1a-h**→**2a-h**.^[a]

Entry	Reaction	ΔE^\ddagger	ΔE_R	$\Delta\Delta E_{int}^{[b]}$	$\Delta\Delta E_{strain}^\ddagger$ [c] (fragment 1)	$\Delta\Delta E_{strain}^\ddagger$ [c] (fragment 2)	$\Delta\Delta E_{strain}^\ddagger$ (total)	NICS (R _p) ^[d]
1	a	37.1 (36.8)	12.8 (14.0)	-5.6	16.2	26.5	42.7	-12.0
2	b	38.4 (37.9)	14.8 (15.8)	-7.0	18.1	27.2	45.3	-11.8
3	c	23.9 (23.8)	-6.1 (-3.4)	-3.4	2.2	25.1	27.3	-1.3
4	d	30.2 (30.3)	17.4 (19.4)	-8.4	5.3	33.3	38.6	-1.5
5	e	31.5 (31.2)	11.1 (12.6)	-9.0	11.9	28.6	40.5	-13.2
6	f	37.3 (37.1)	11.3 (15.3)	-9.5	14.2	32.7	46.8	-9.7
7	g	33.7 (33.1)	3.8 (5.1)	-7.8	17.0	24.3	41.5	-9.9
8	h	54.4 (53.6)	44.0 (44.3)	-2.6	31.2	25.8	57.0	-9.0

[a] Energy in kcal mol^{-1} (in parentheses with ZPE correction) computed at M06-2X/def2-TZVPP. [b] $\Delta\Delta E_{int} = [E - (\text{TS1}) - E(\text{frag1 in geom of TS1}) - E(\text{frag2 in geom of TS1})] - [E(1) - E(\text{frag1 in geom of 1}) - E(\text{frag2 in geom of 1})]$.

[c] $\Delta\Delta E_{strain} = [E(\text{frag1 in geom of TS1}) + E(\text{frag2 in geom of TS1})] - [E(\text{frag1 in geom of 1}) - E(\text{frag2 in geom of 1})]$.

[d] NICS values computed at the (3,+1) ring critical point of the electron density.

Marcus Theory vs ASM

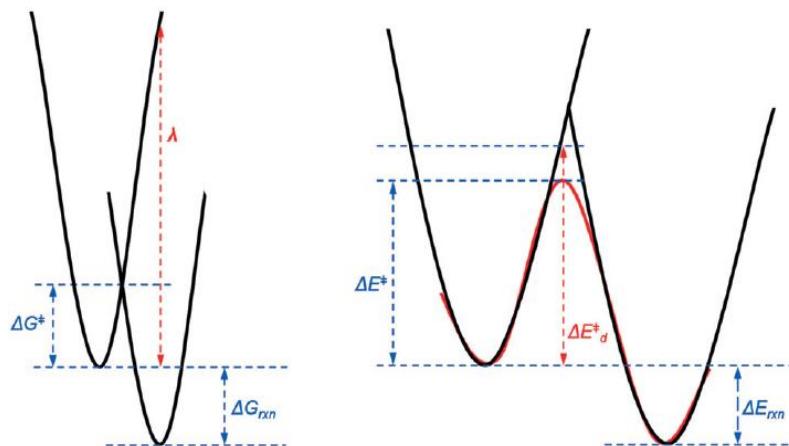


Figure 17. Energy terms involved in Marcus theory (left) in comparison to the D/I model (right).