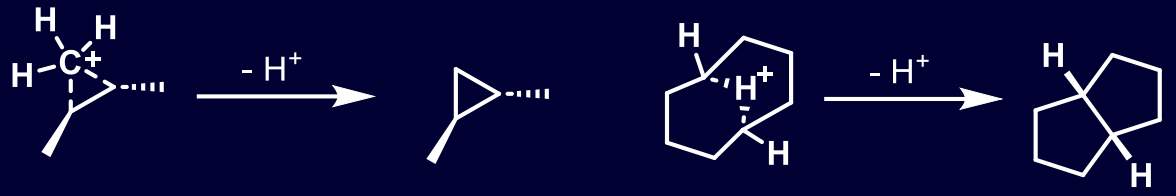


Protonated Cyclopropane, Hydrido-Bridged Cycloalkyl Cation and Remote Elimination

Weijie Mao,

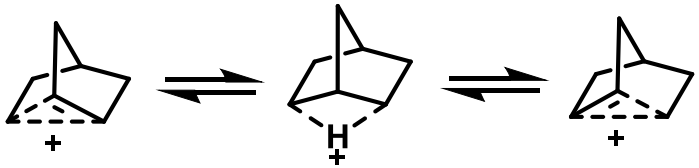
College of Chemistry and Molecular Engineering,

March, 1st, 2025

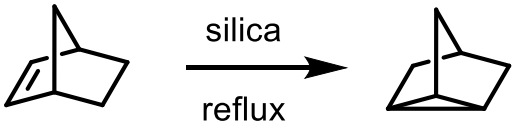
Outline

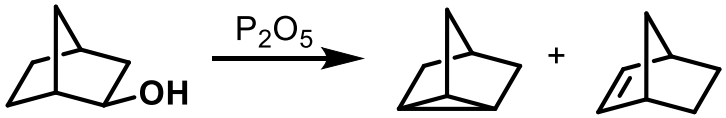
- Protonated Cyclopropane and Cationic Cyclopropanation
  - Proposal and Determination of PCP^+
  - Structure and Bonding Pattern of PCP^+
  - Cationic Cyclopropanation
- Hydrido-Bridged Cycloalkyl Cation and Remote Elimination
  - Structure of Hydrido-Bridged Cycloalkyl Cation
  - Remote Elimination
- Summary and Perspective

Proposal of Protonated Cyclopropane

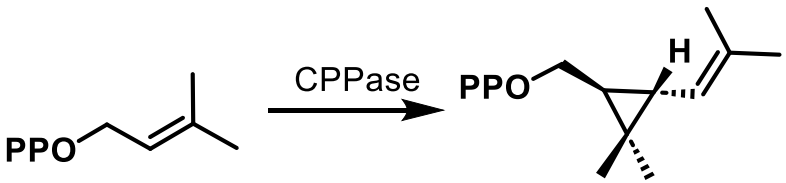


Winstein, S. et. al. *J. Am. Chem. Soc.* **1952**, *74*, 5, 1154.

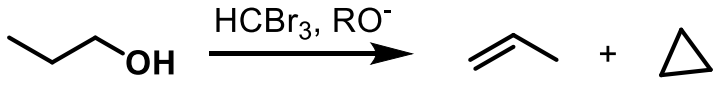


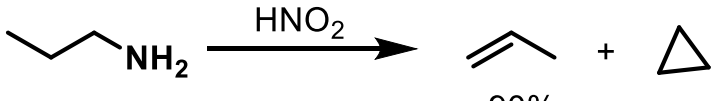


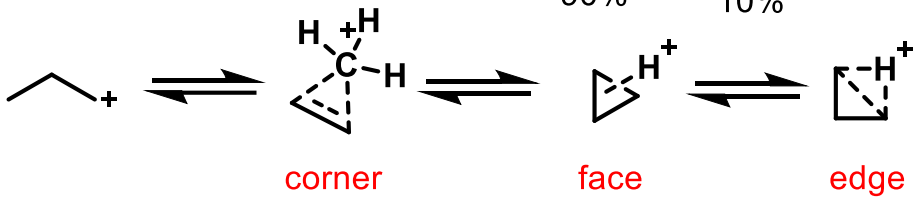
von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1958**, *80*, 1700.



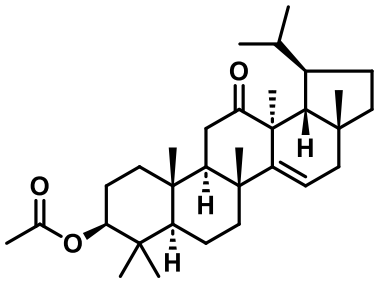
Godin, P. J.; Thain, E. M. *Proc. Chem. Soc.* **1961**, *9*, 452.
Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70.



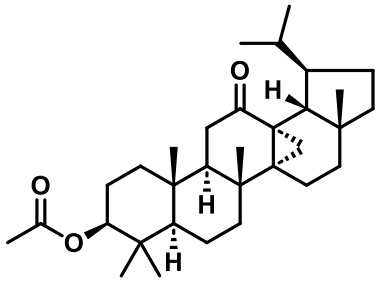




Skell, P. S. *J. Am. Chem. Soc.* **1960**, *82*, 2971.



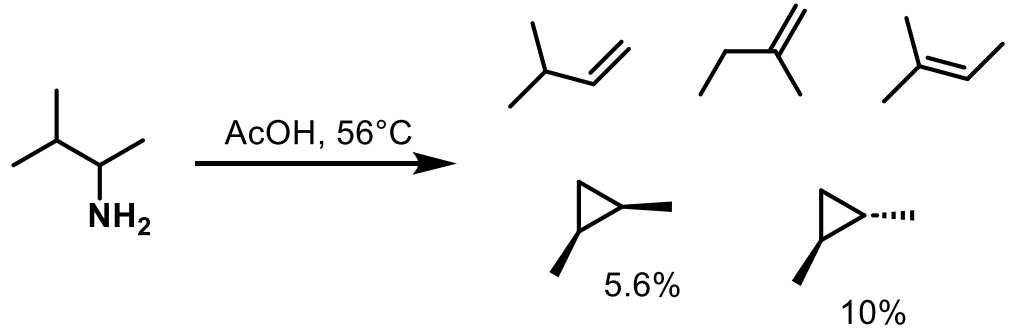
(Questioned structure?)

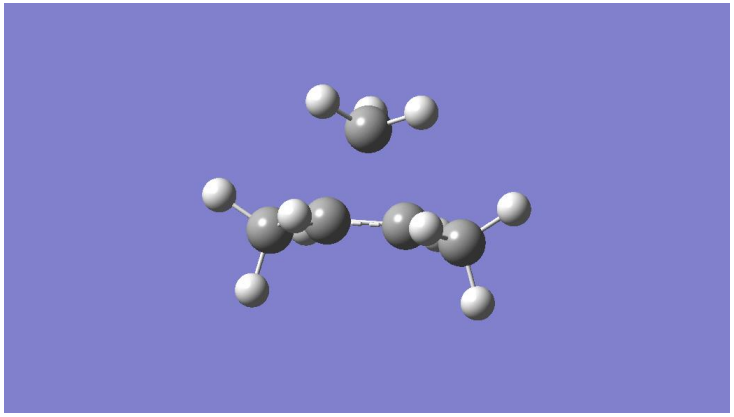


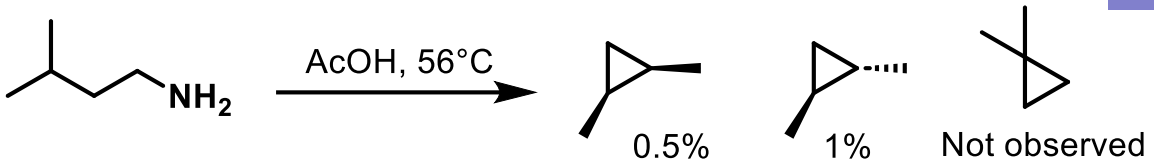
Colorless in $CHCl_3/C(NO_2)_4$
UV at 200–214 nm

Beaton, J. M. et. al. *J. Chem. Soc.* **1955**, 3992.

Intermediate as Carbenium 1,2 Migration?



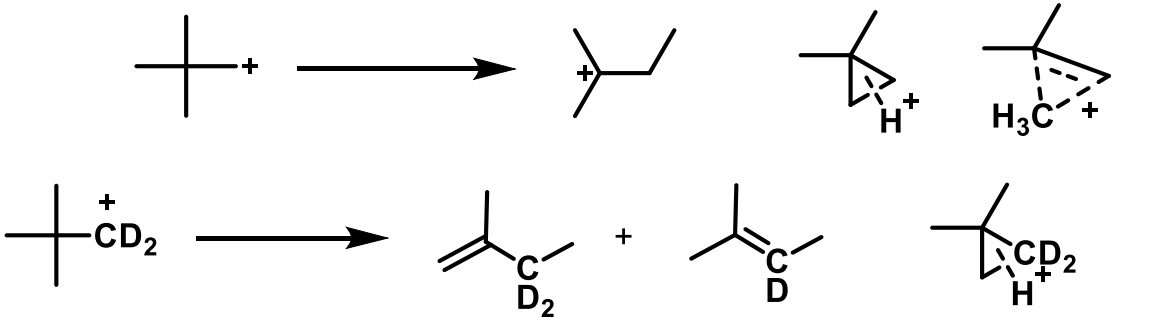


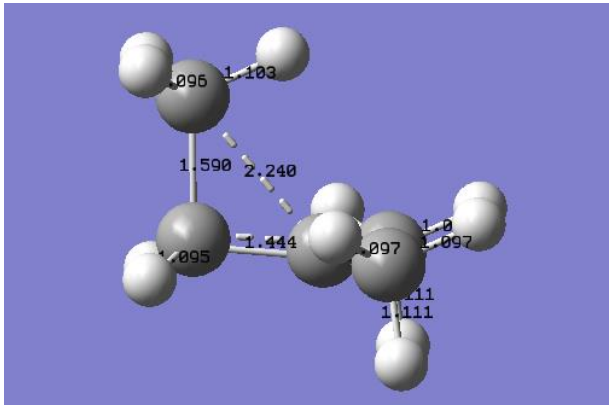


	Mode #	Frequency	Infrared
1	1	78.96	11.2958
2	2	207.43	25.8000

Silver, M. S. *J. Am. Chem. Soc.* **1960**, *82*, 2971.

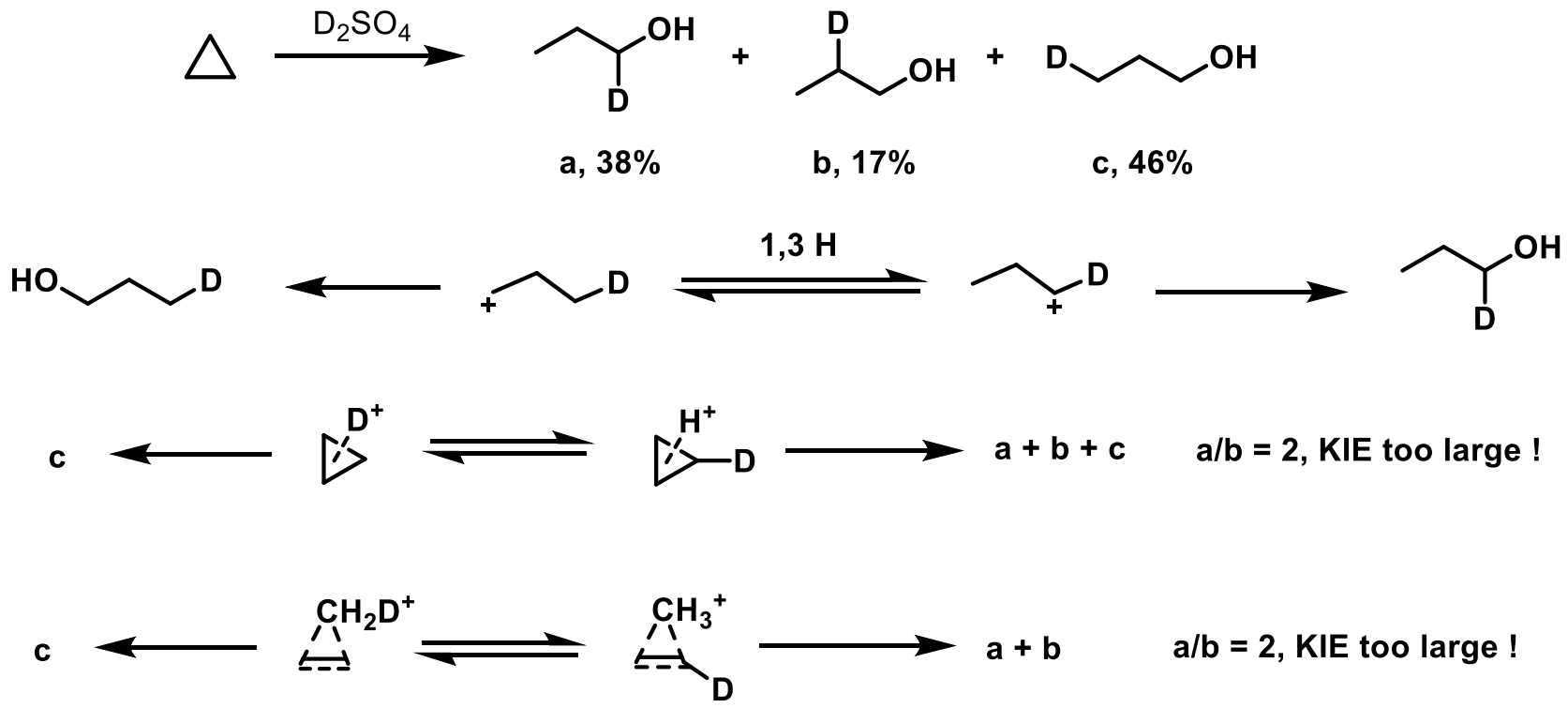
M06-2X(D3)/def2TZVP





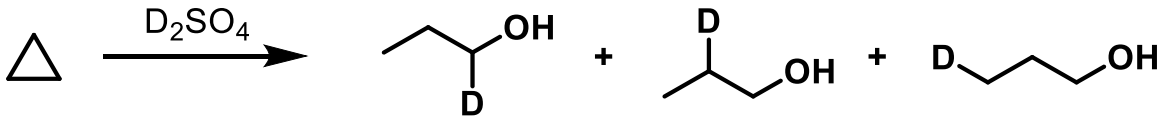
Skell, P. S. et. al. *J. Am. Chem. Soc.* **1960**, *82*, 5257.

Clues from Protonation of Cyclopropane

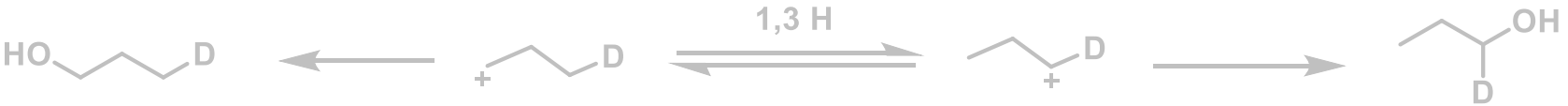


Collins C. J. *Chem. Rev.* **1969**, *69*, 4, 543–550.

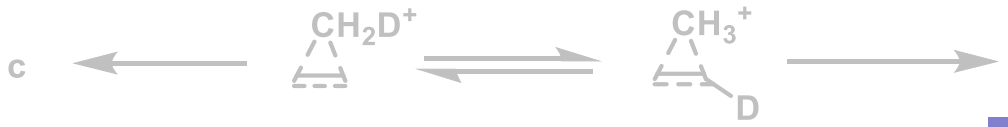
Clues from Protonation of Cyclopropane



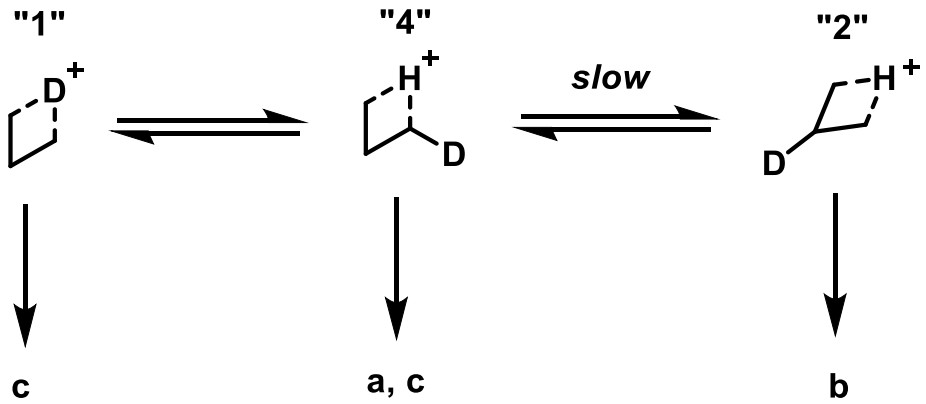
a, 38% **b, 17%** **c, 46%**

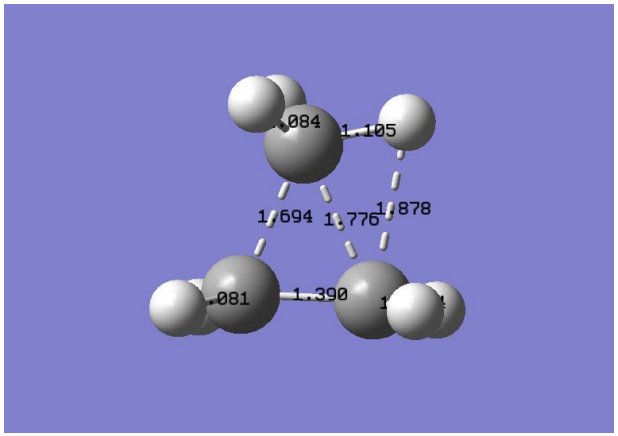


a + b + c a/b = 2, KIE too large !



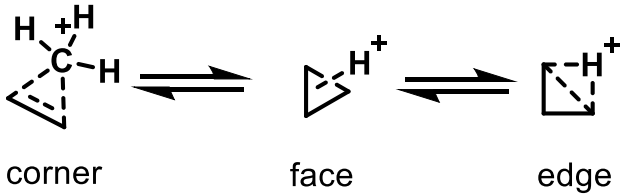
a + b a/b = 2, KIE too large !



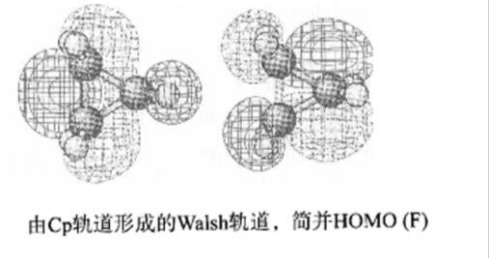


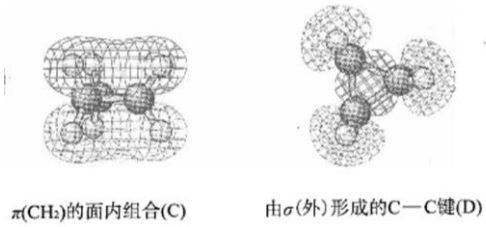
Collins C. J. *Chem. Rev.* **1969**, *69*, 4, 543–550.

Understanding PCP+ Structure

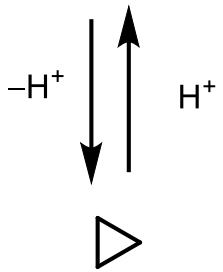


a. PCP+ = Cyclopropane + H+

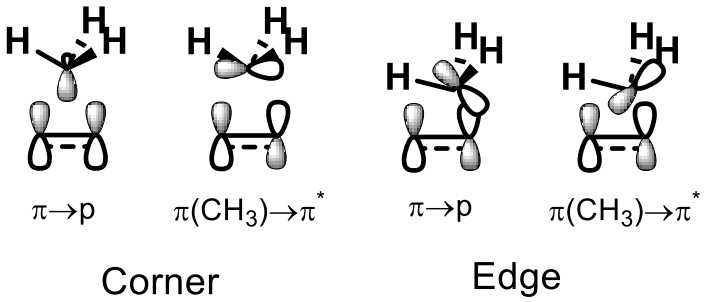




Face PCP+ is disfavored.



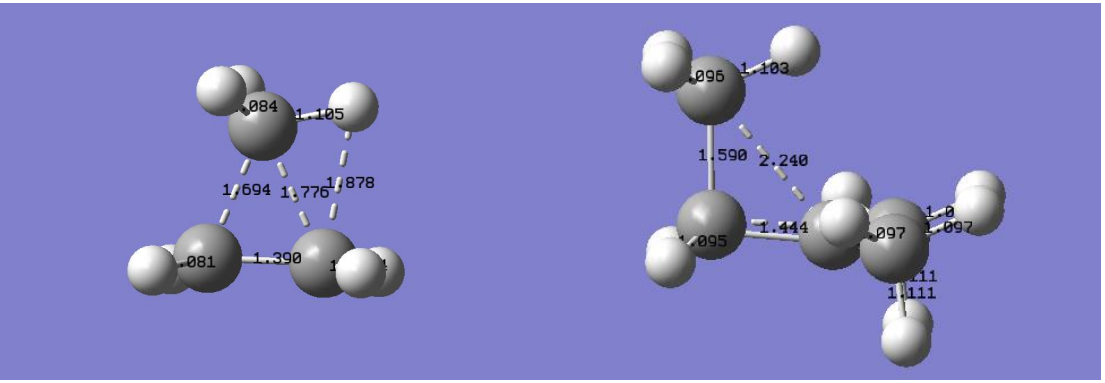
b. PCP+ = Alkene + CH_3^+

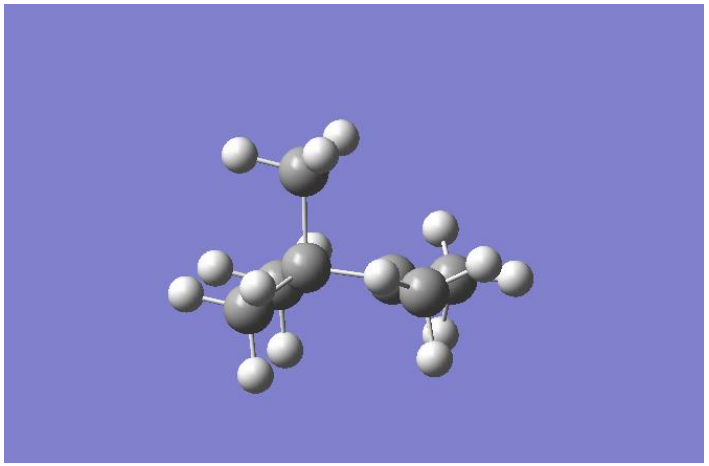


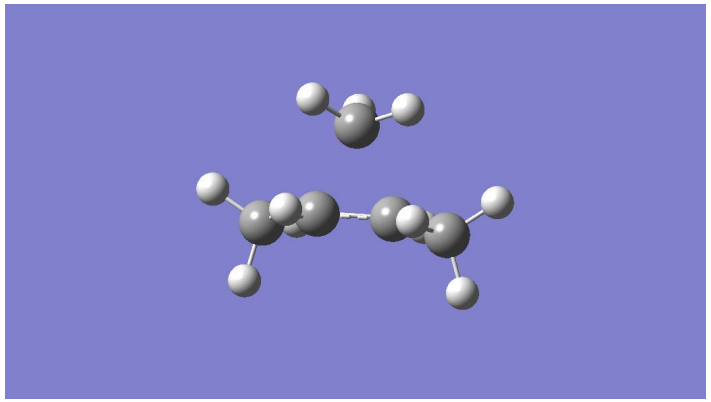
Corner PCP+ has a C-C-C 3c-2e bond.
Edge PCP+ has a C-H-C 3c-2e bond.

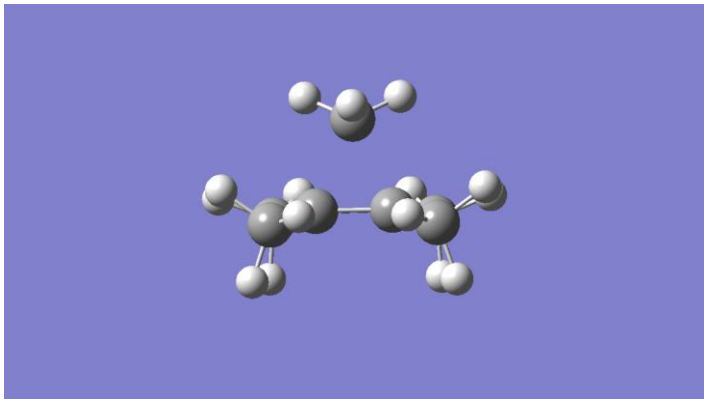
Electron sufficient alkenes prefer corner structure.
Symmetric alkenes prefer corner structure.

Understanding PCP^+ Structure







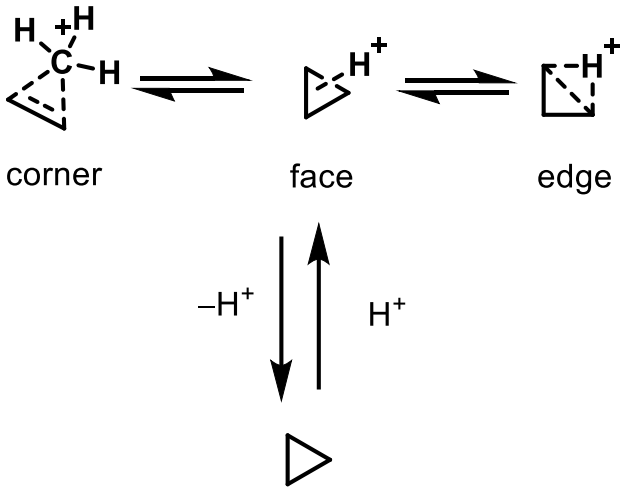


Electron sufficient alkenes prefer corner structure.
Symmetric alkenes prefer corner structure.
Avoid tertiary carbocation.

	Mode #	Frequency	Infrared
1	1	-147.76	88.6669
2	2	91.52	3.1919

+ 2.89 kcal by M06-2X(D3)/def2TZVP

PCP^+ Elimination Problem



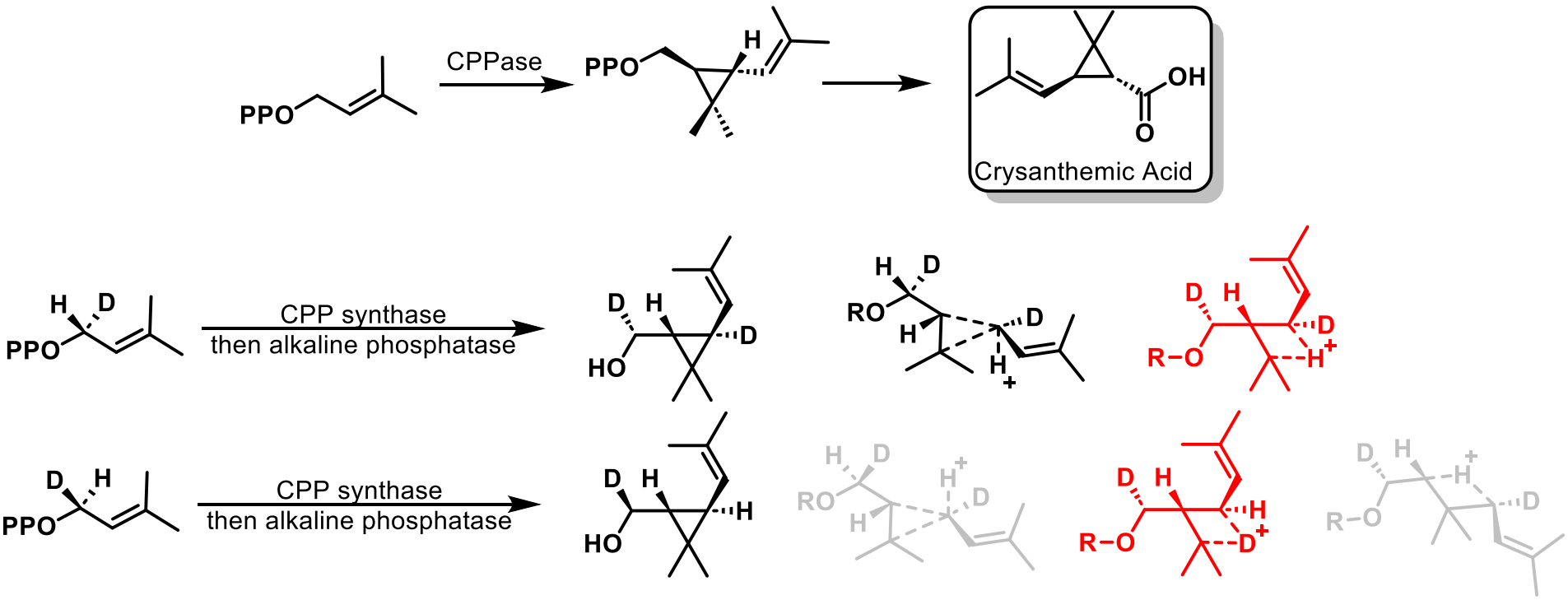
Edge PCP^+ or corner PCP^+ as TS of cyclopropane protonation?
Could one of the PCP^+ become an ambimodal transition state?

A plausible tendency:

Symmetric alkenes prefer corner structure.

“Protonation” of “Cyclopropane” prefer edge structure.

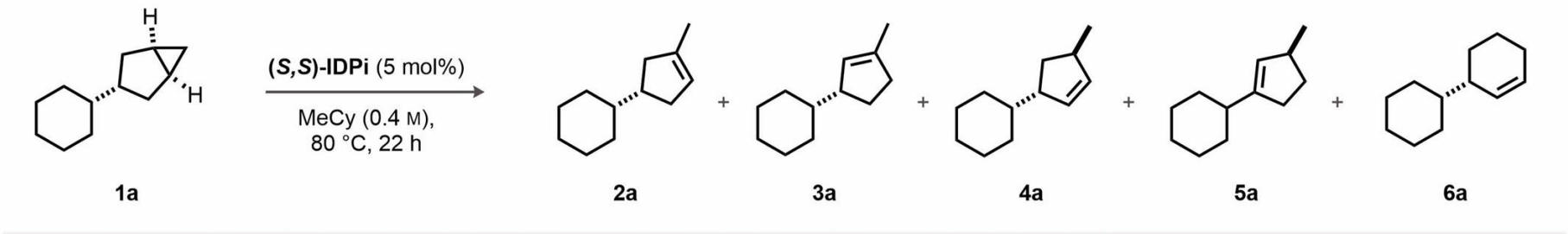
Learning from Nature…

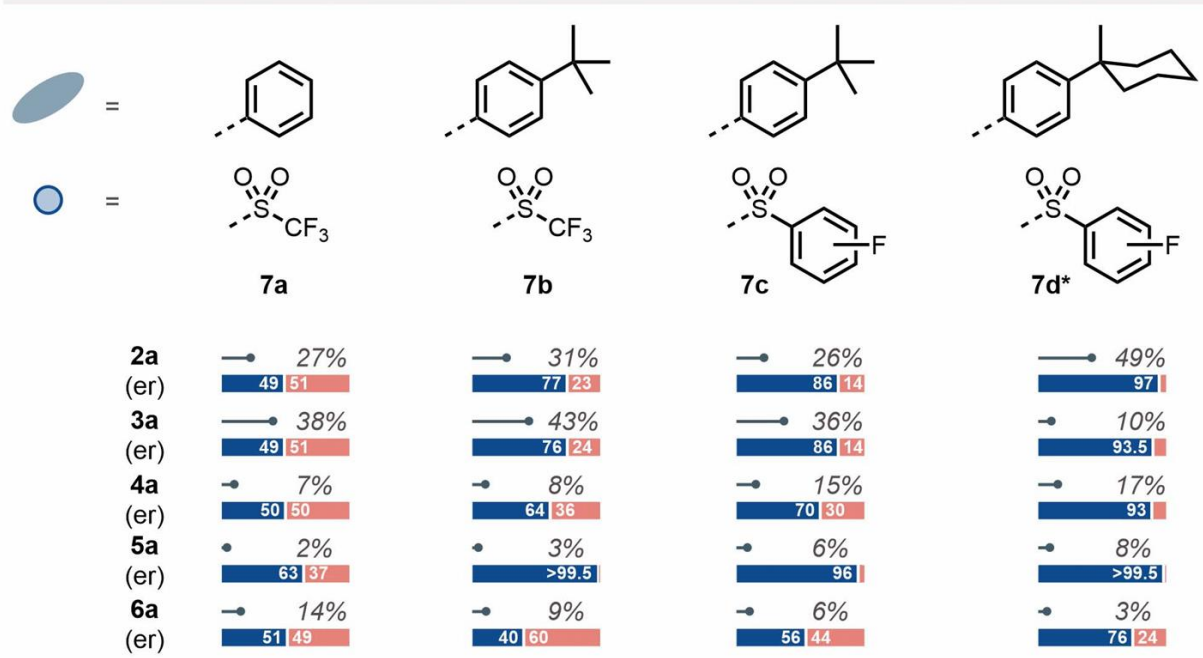


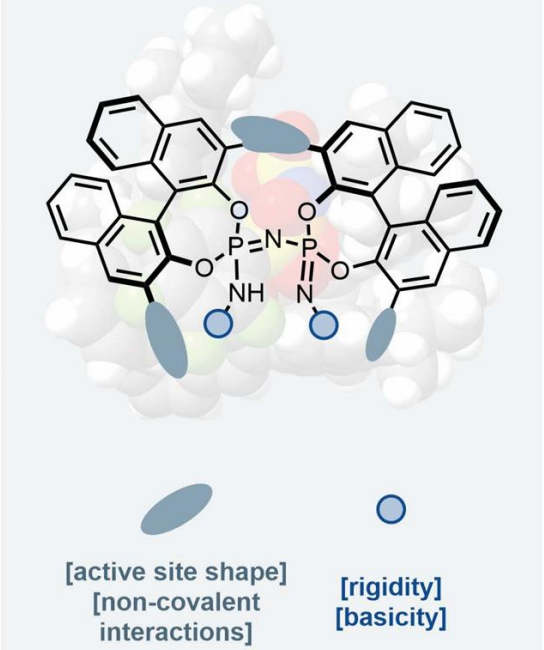
Deprotonation probably via an **edge protonated cyclopropane**!
However, in an enzyme, the orientation of base is fixed.
Thus Corner PCP⁺ as TS could not be excluded.

Godin, P. J.; Thain, E. M. *Proc. Chem. Soc.* **1961**, *9*, 452.
Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70.
Thulasiram, H. V.; Erickson, H. K.; Poulter, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 1966.

Learning from *Science…*

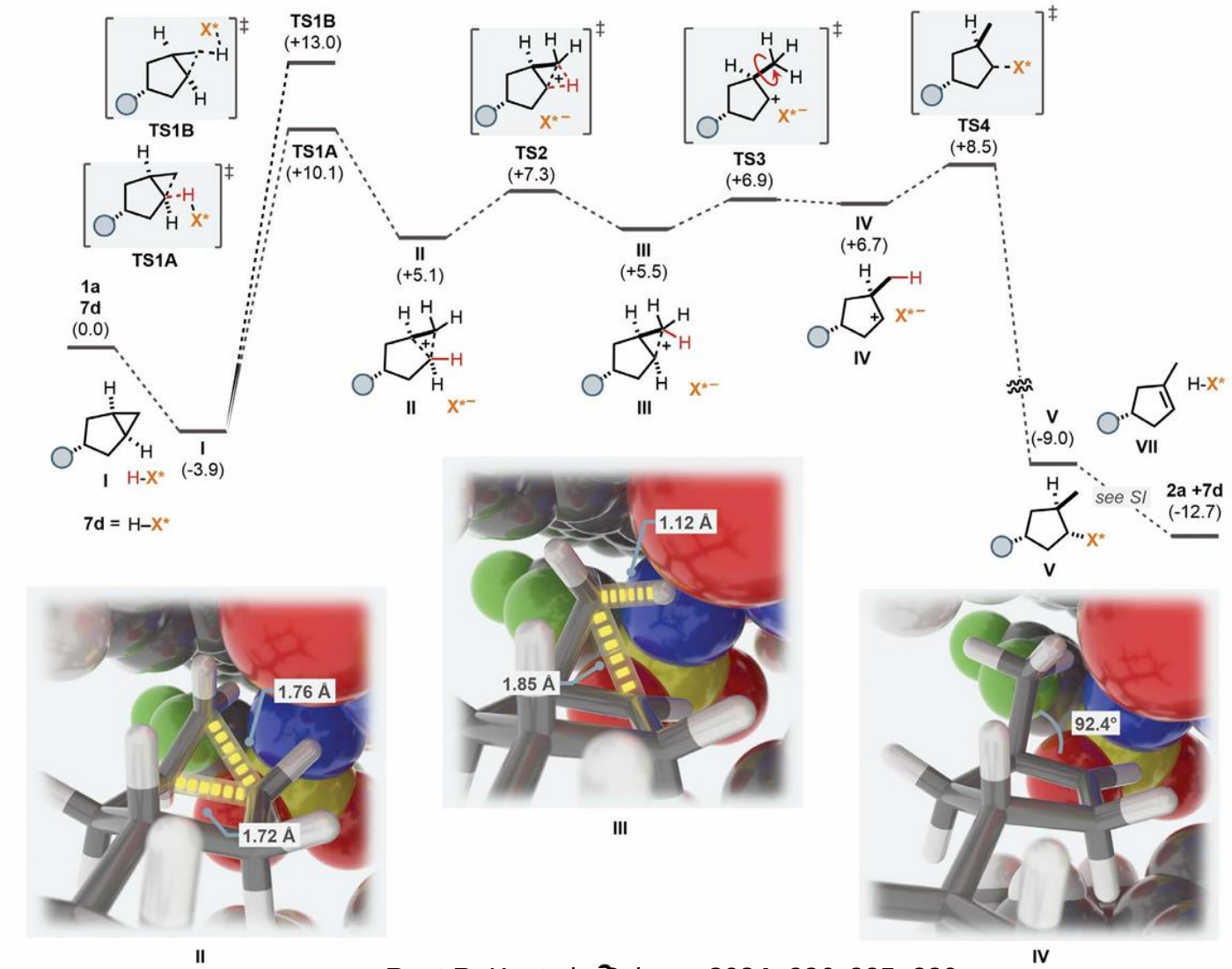






Raut R. K. et al., *Science* **2024**, *386*, 225–230.

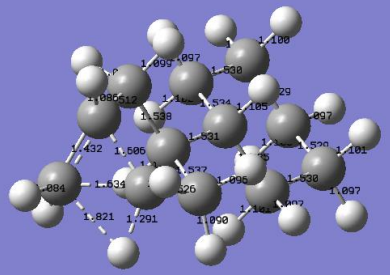
Learning from *Science…*



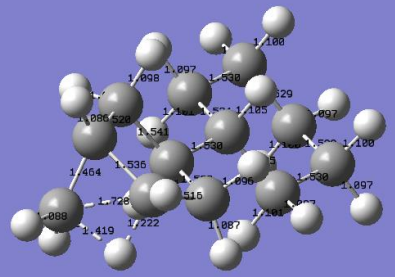
Raut R. K. et al., *Science* **2024**, *386*, 225–230.

Learning from *Science…*

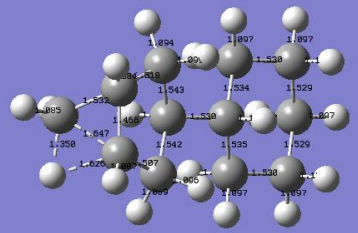
TS1A

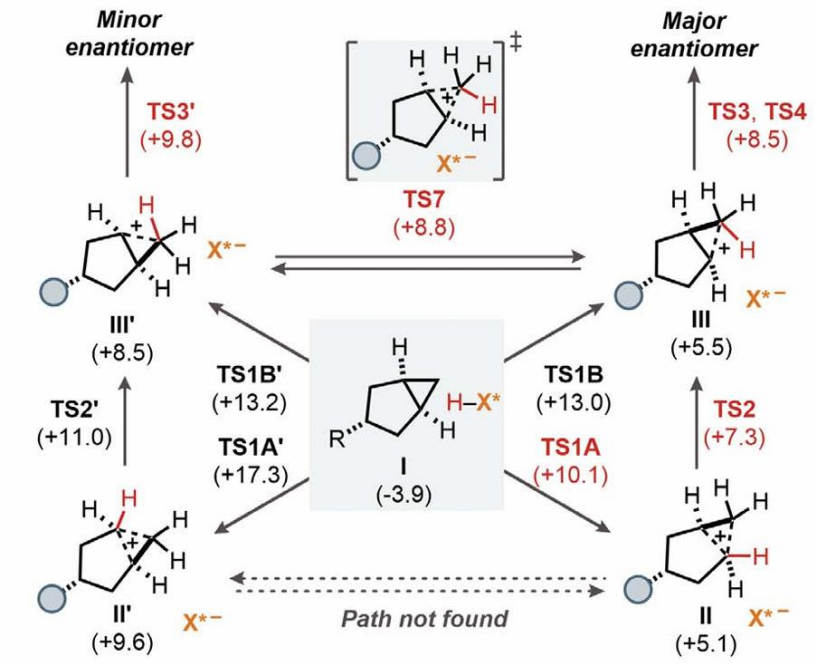


TS2



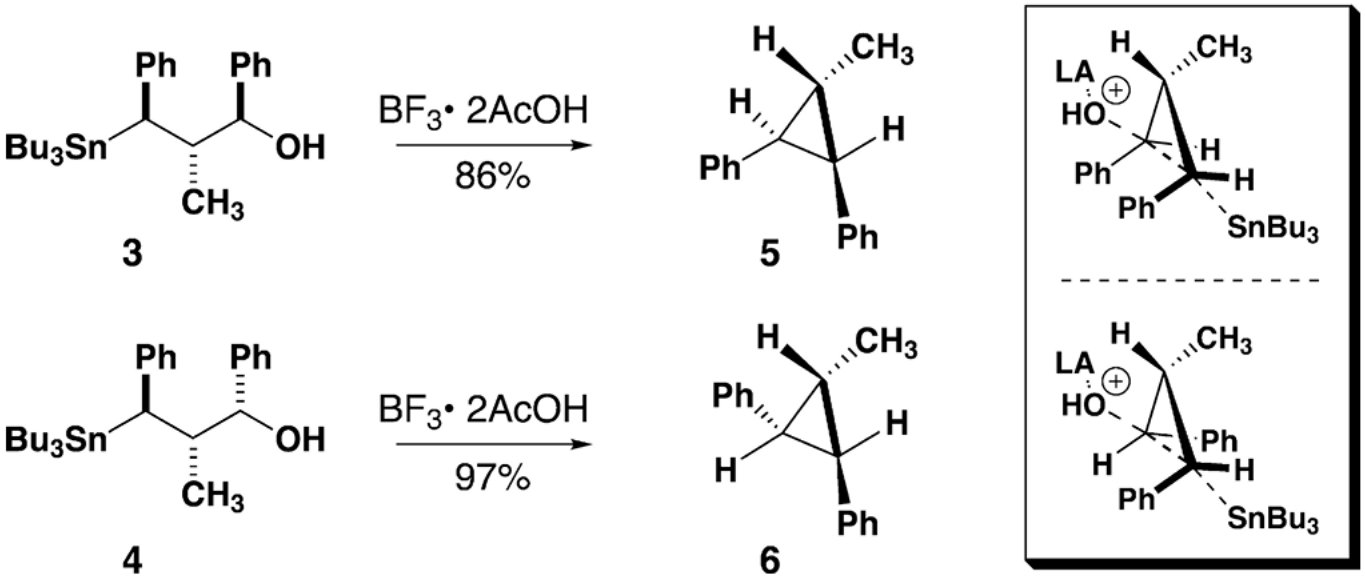
TS1B





Raut R. K. et al., *Science* **2024**, *386*, 225–230.

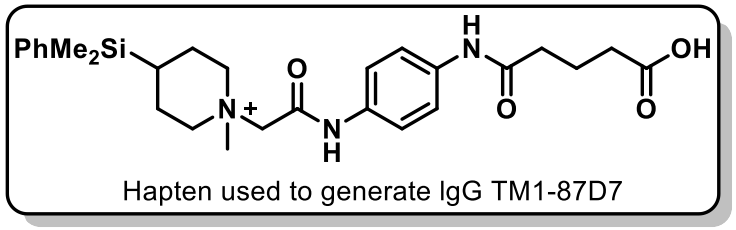
Comparison with Sn Elimination

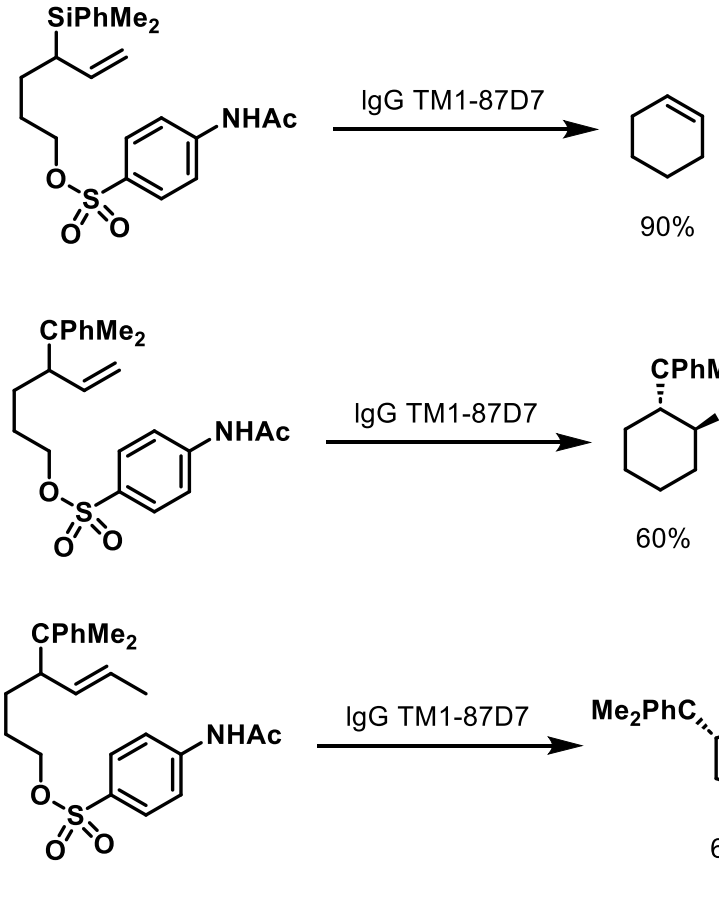


"Concerted" formation of carbenium ion and leaving of $SnBu_3$.
"$SnCP^+$" not formed, orbital instead of charge control?

Taylor, R. E. et al. *Tetrahedron* **2003**, *59*, 5623.

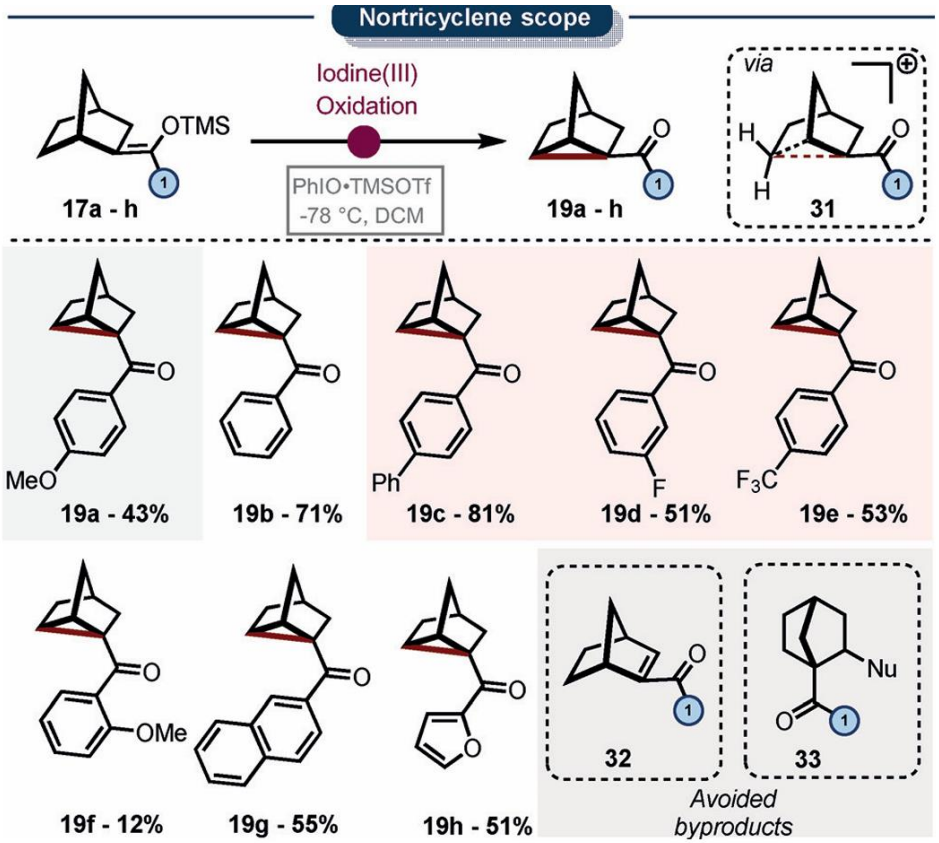
Cationic Cyclopropanation by Antibody Catalysis

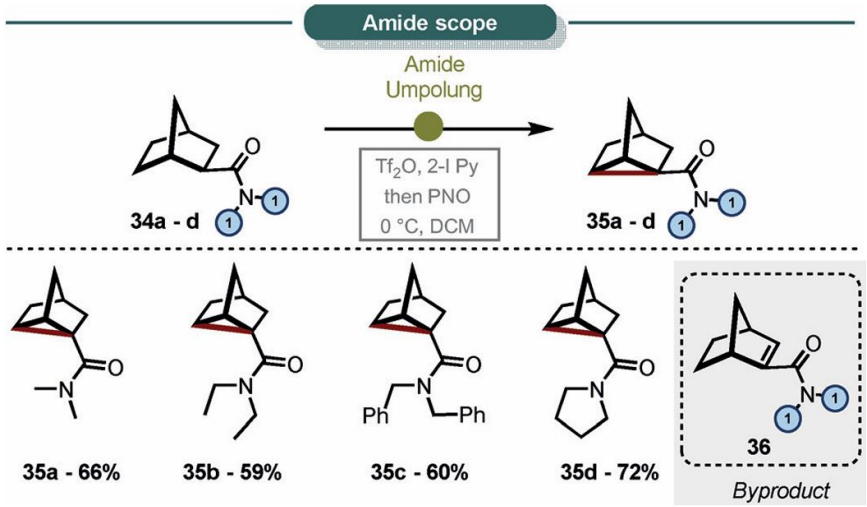




Li, T.; Janda, K. D.; Lerner, R. A. *Nature* **1996**, *379*, 326.
Lee, J. K.; Houk, K. N. *Angew. Chem., Int. Ed.* **1997**, *36*, 1003.

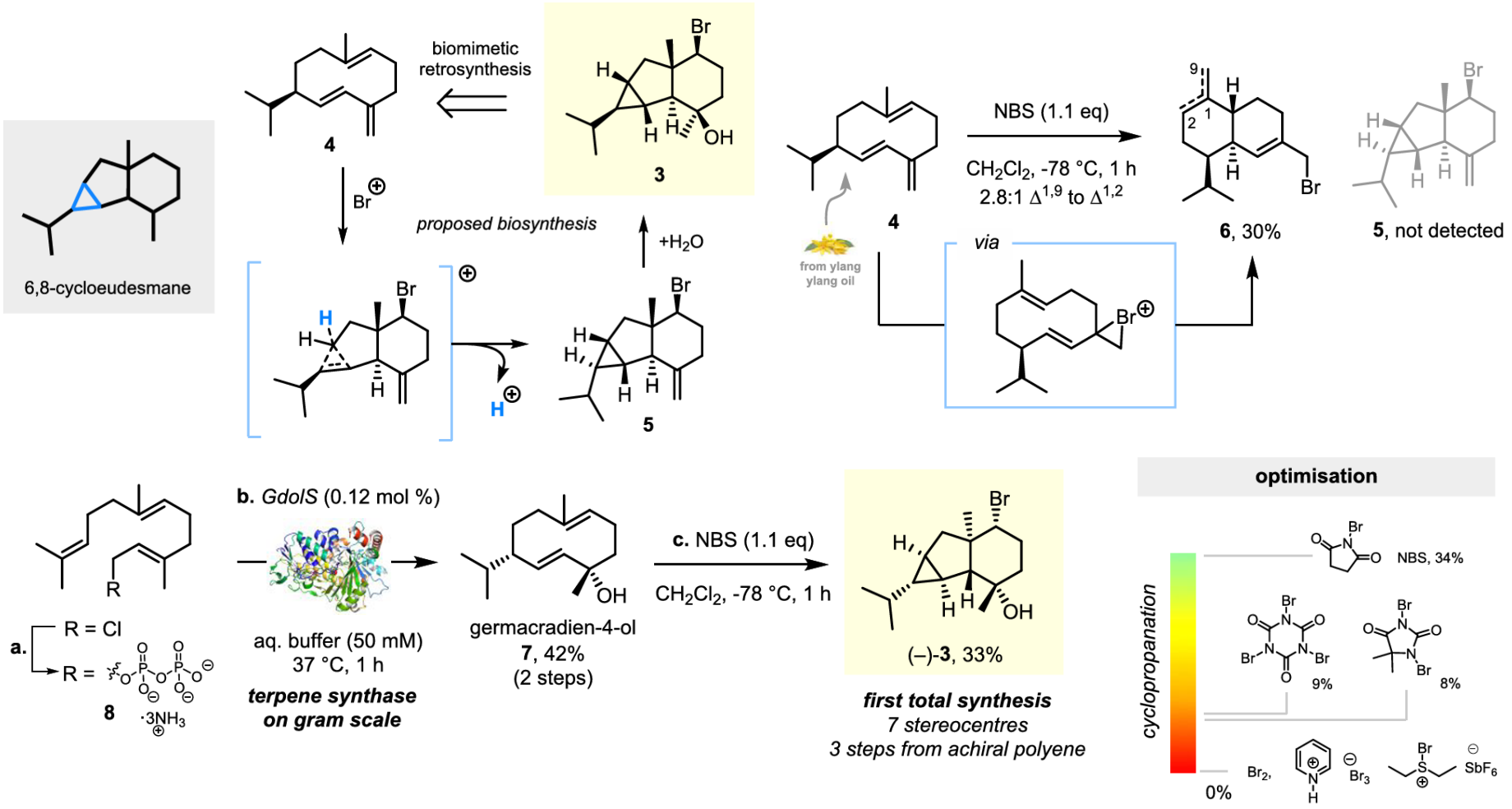
Cyclopropanation by Oxidative Umpolung





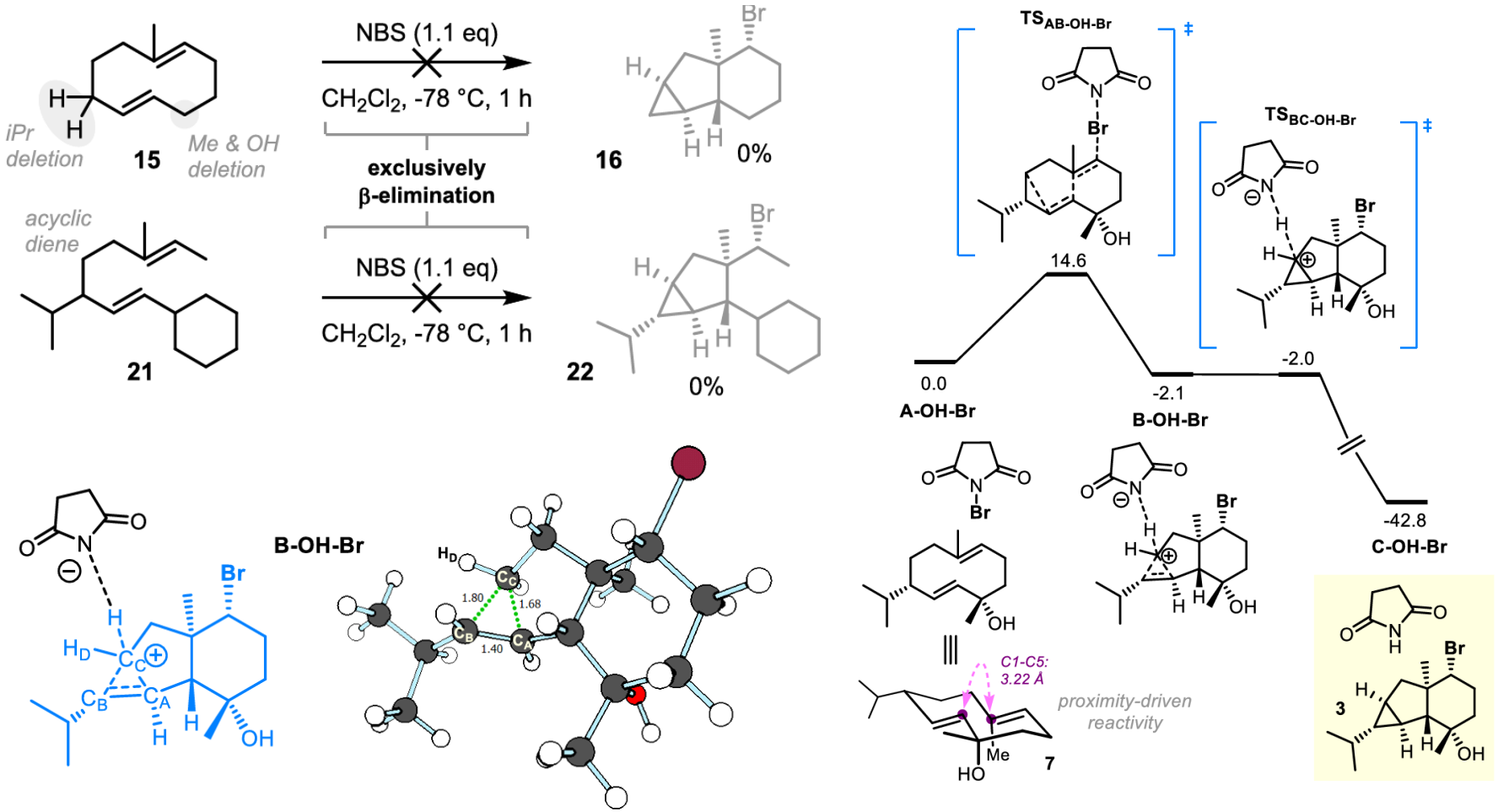
Bauer, A.; ... Maulide, N. *Angew. Chem., Int. Ed.* **2020**, *59*, 18208.

Biomimetic Cationic Cyclopropanation



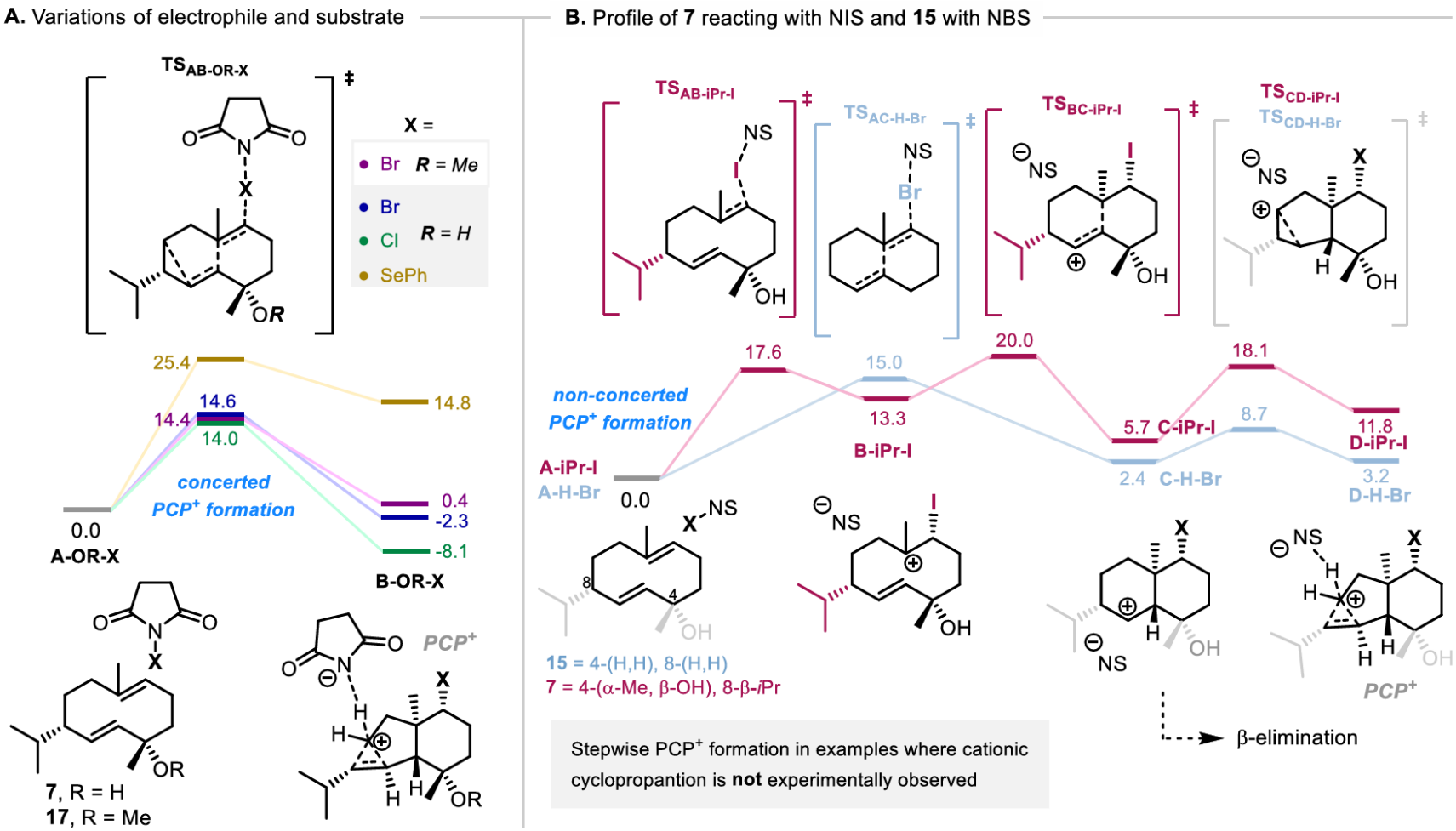
Grant, P. S.; … Maulide, N. *J. Am. Chem. Soc*. **2023**, *145*, 5855.

Mechanistic Insight



Grant, P. S.; … Maulide, N. *J. Am. Chem. Soc*. **2023**, *145*, 5855.

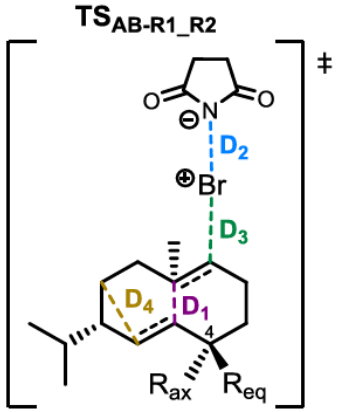
Concerted Formation of PCP⁺ is Essential



Grant, P. S.; … Maulide, N. *J. Am. Chem. Soc*. **2023**, *145*, 5855.

Early TS is Beneficial?

A. Transition states for cationic cyclopropanation of hypothetical substrates



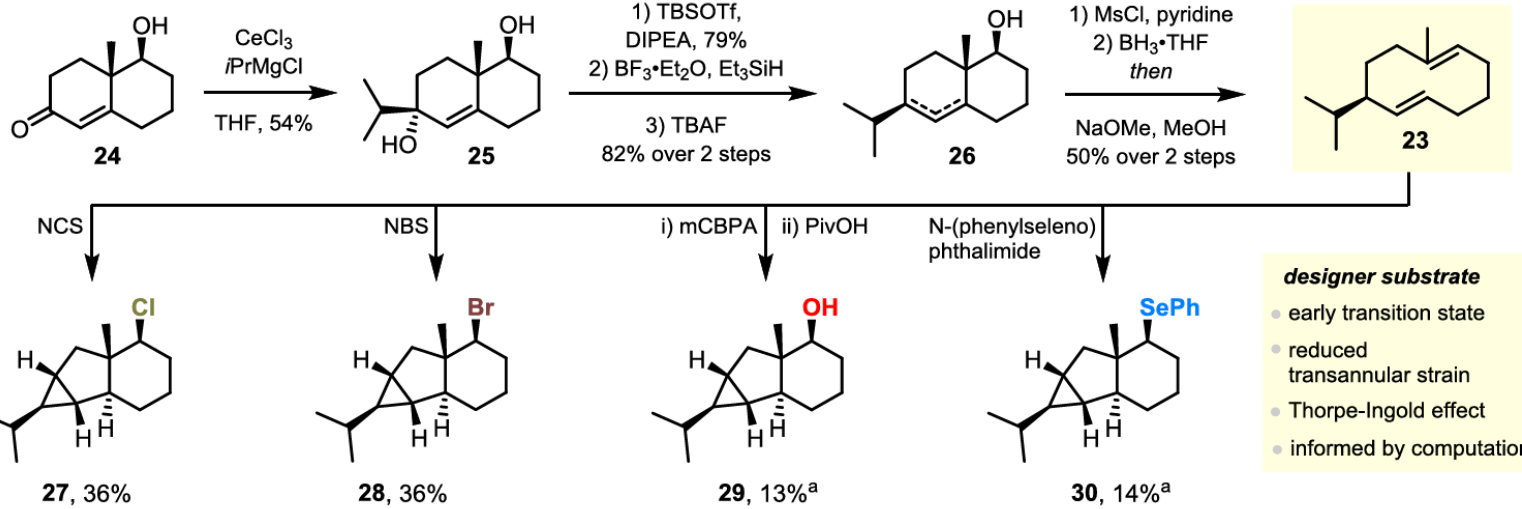
Bond Length (Å)

	#	R_{ax}	D_1	D_2	D_3	D_4
R_{eq} = H	1	H	2.22	2.50	2.04	2.42
	2	OH	2.09	2.58	2.02	2.42
	3	Ph	2.07	2.63	2.00	2.42
	4	OMe	2.14	2.57	2.02	2.43
	5	Me	-	-	-	-
R_{eq} = Me	6	H	2.25	2.47	2.06	2.42
	7	OH	2.12	2.56	2.02	2.43
	8	Ph	-	-	-	-
	9	OMe	2.10	2.59	2.02	2.43
	10	Me	-	-	-	-

early TS — *late TS*

#	R_1	$\Delta G^{\ddagger}$ (kcal/mol)	ΔG (kcal/mol)
1	H	14.6	-0.5
2	OH	14.0	-1.9
3	Ph	16.0	4.4
4	OMe	14.8	-2.9
5	H	13.8	-5.3
6	OH	14.6	-2.3
7	Ph	18.0*	7.5
8	OMe	14.4	0.4

PBE0-D3BJ/def2-TZVP-SMD/ SVP

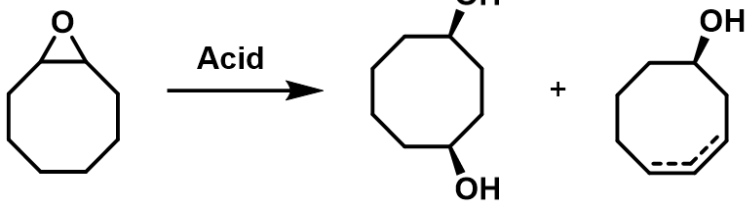


Grant, P. S.; … Maulide, N. *J. Am. Chem. Soc*. **2023**, *145*, 5855.

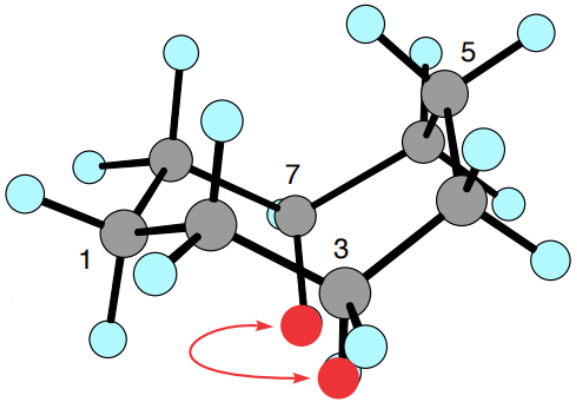
Outline

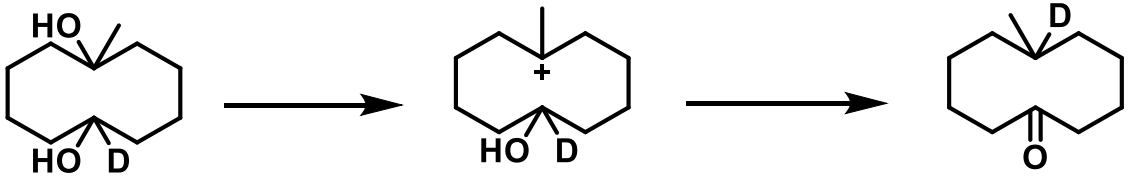
- Protonated Cyclopropane and Cationic Cyclopropanation
  - Proposal and Determination of PCP^+
  - Structure and Bonding Pattern of PCP^+
  - Cationic Cyclopropanation
- Hydrido-Bridged Cycloalkyl Cation and Remote Elimination
  - Structure of Hydrido-Bridged Cycloalkyl Cation
  - Remote Elimination
- Summary and Perspective

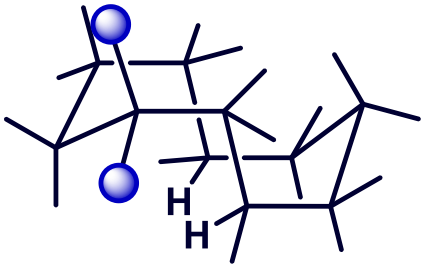
Intramolecular Hydride Shift



Cope, A. C.; Johnson, H. E. *J. Am. Chem. Soc*, **1957**, *79*, 3889.

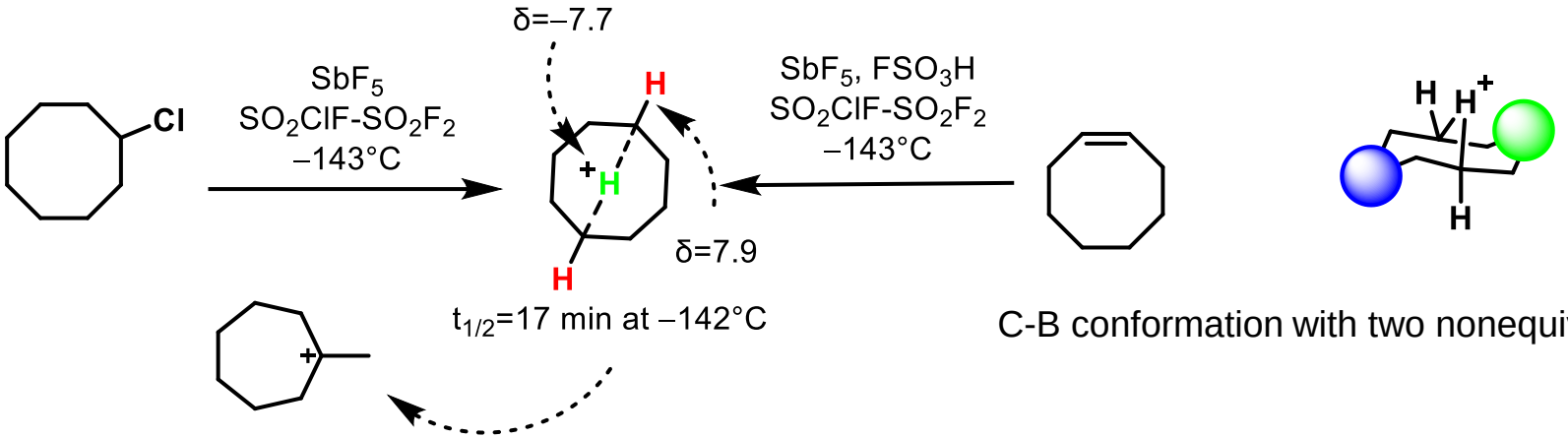




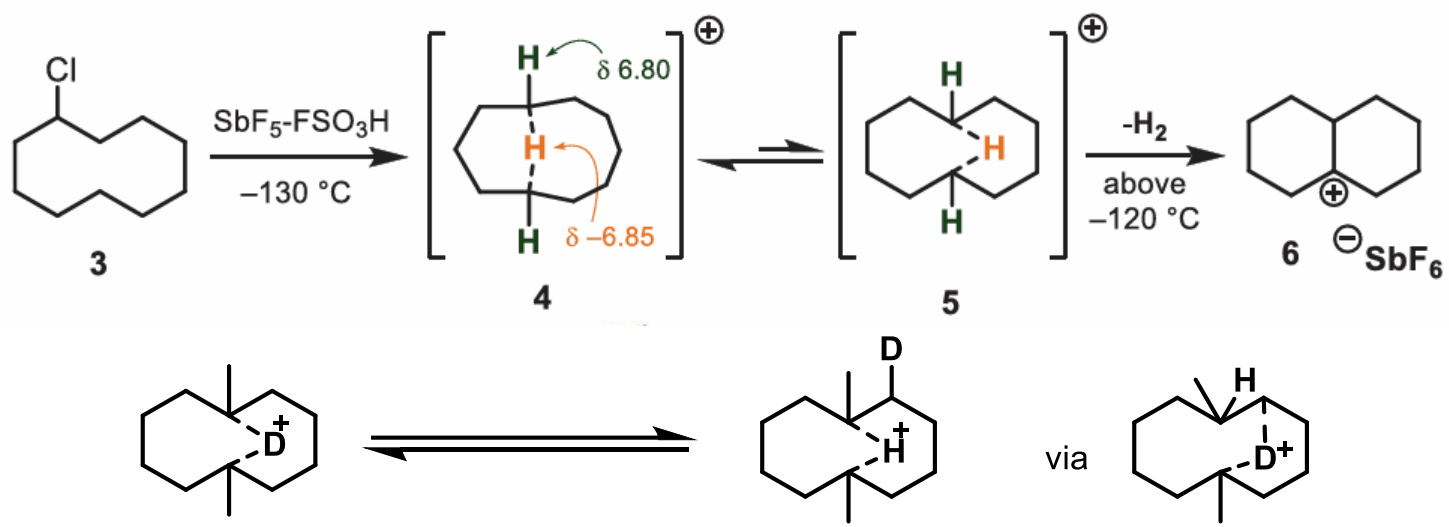


Prelog, V.; Küng, W. *Helv. Chim. Acta,* **1956**, *39*, 1394.

Hydrido-Bridged Cycloalkyl Cations

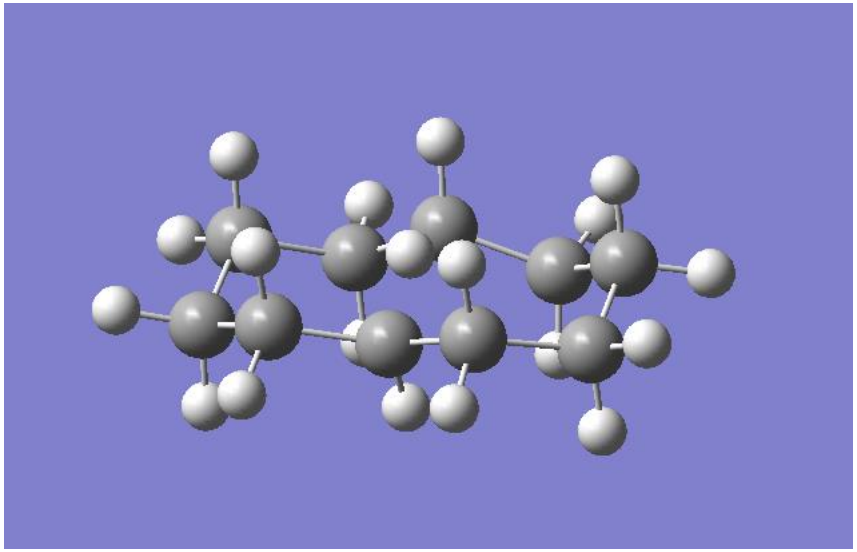


C-B conformation with two nonequivalent CH_2

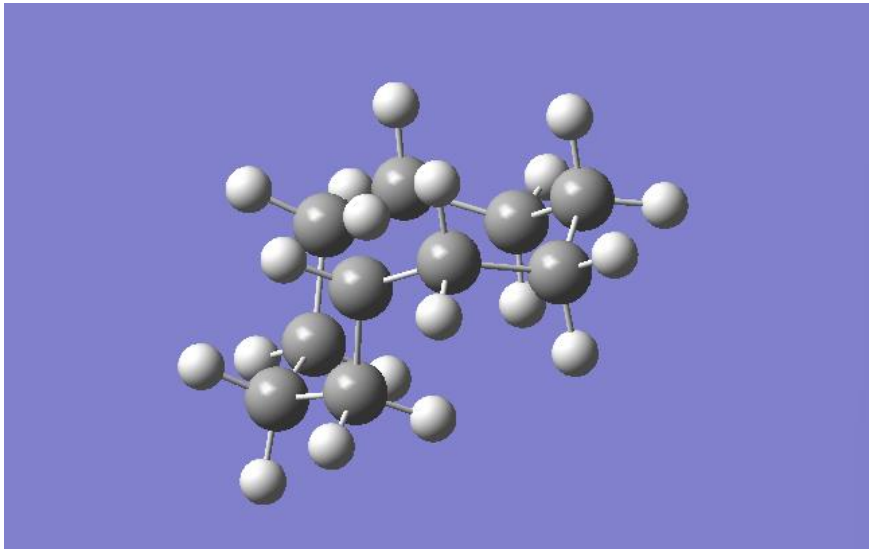


Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1979**, *101*, 3240.
Kirchen, R. P.; Sorensen, T. S. et. al. *J. Am. Chem. Soc.* **1981**, *103*, 588.
Grant, P. S. et al., *Science* **2024**, *384*, 815.

cis- or *trans*-Fused?



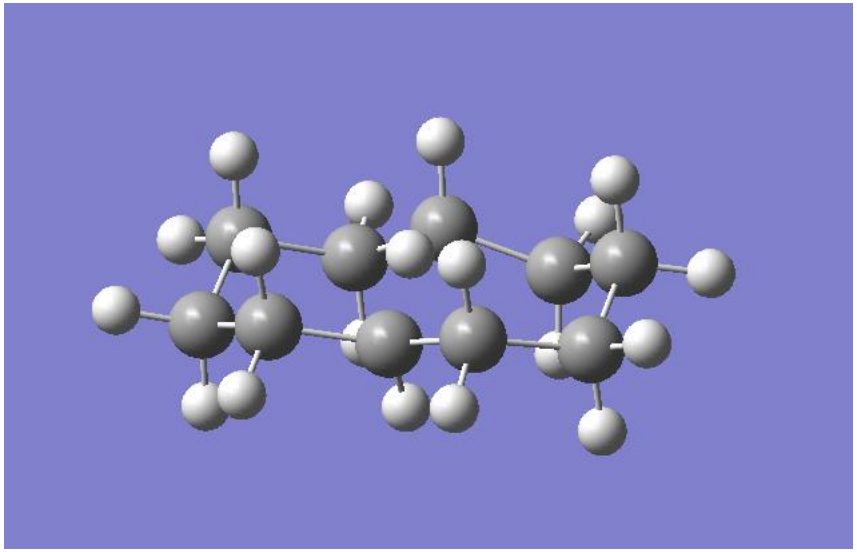
d(C-H)=124.0 pm
∠C-H-C = 133°
Mulliken Charge on H: +0.158



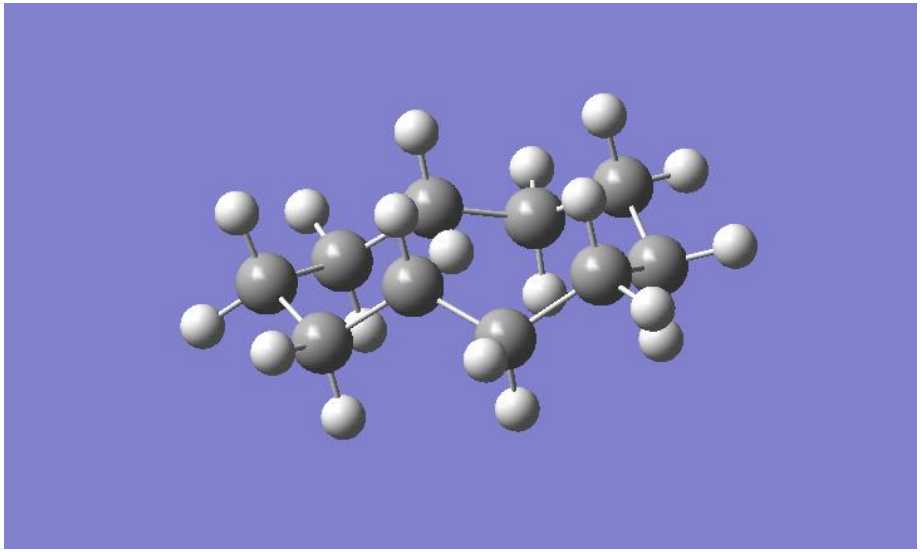
d(C-H)=125.0 pm
∠C-H-C = 147°
Mulliken Charge on H: +0.145

ΔE < 0.2 kcal by M06-2X(D3)/def2TZVP

6+6 or 5+7?



d(C-H)=124.0 pm
∠C-H-C = 133˚
Mulliken Charge on H: +0.158

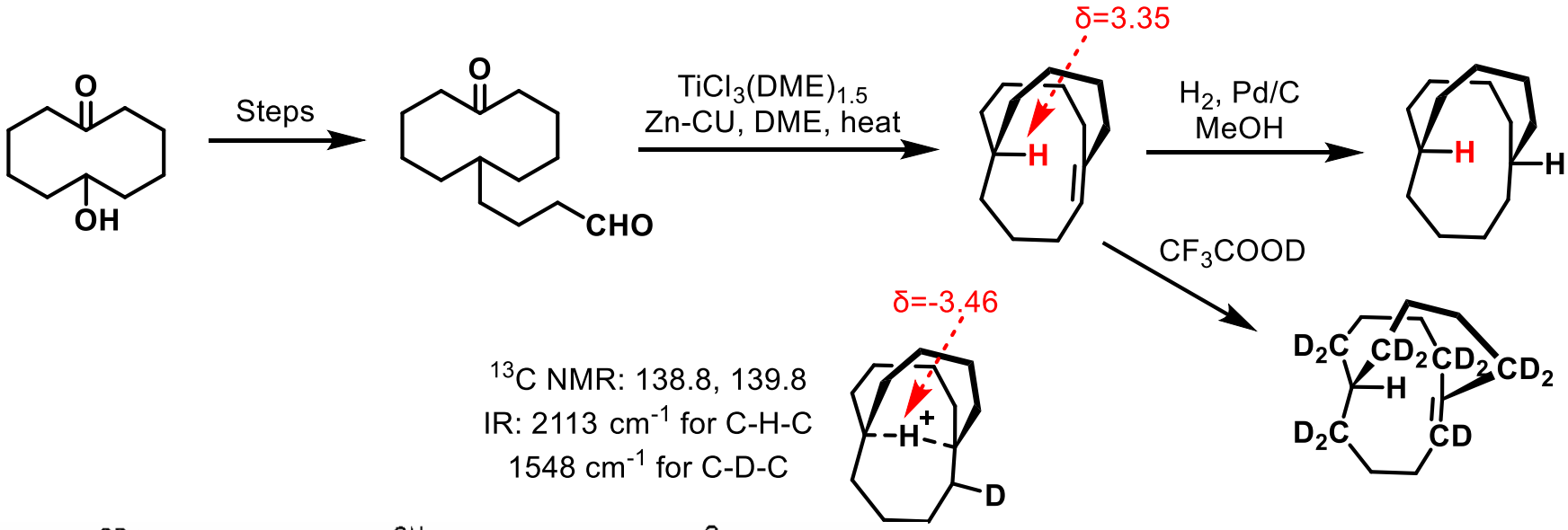


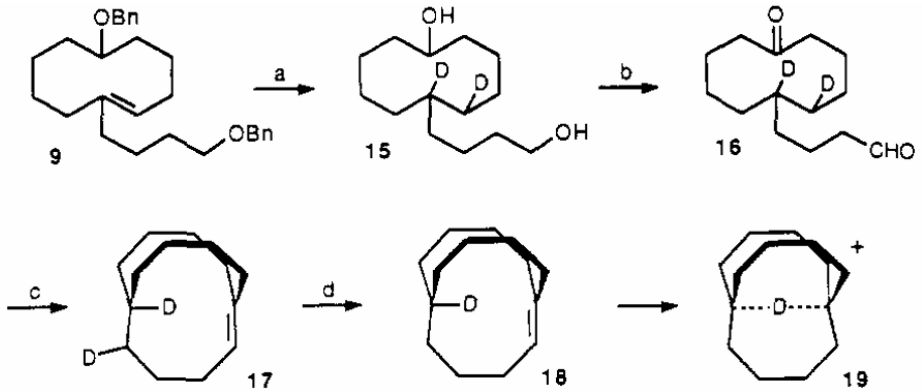
d(C-H)=125.0 pm
∠C-H-C = 144˚
Mulliken Charge on H: +0.033

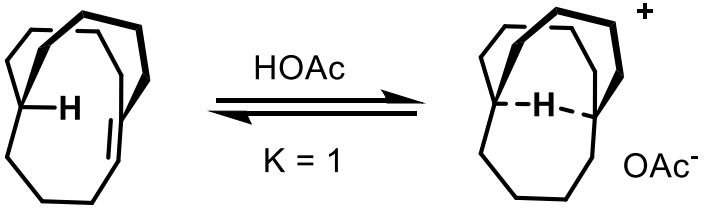
The latter is more stable for 1.5 kcal by M06-2X(D3)/def2TZVP

The result is in agreement with Grant, P. S. et al. *Science* **2024**, *384*, 815.

A Stable Hydrido-Bridged Cycloalkyl Cation







(a) D_2, Pd/C, CH_3OH, EtOAc, HOAc; (b) PCC, CH_2Cl_2, NaOAc; (c) $TiCl_3 \cdot (DME)_{1.5}$, Zn-Cu, DME, Δ; (d) HCl, H_2O.

McMurry, J. E. et. al. *J. Am. Chem. Soc.* **1989**, *111*, 8867.

Remote Proton Elimination

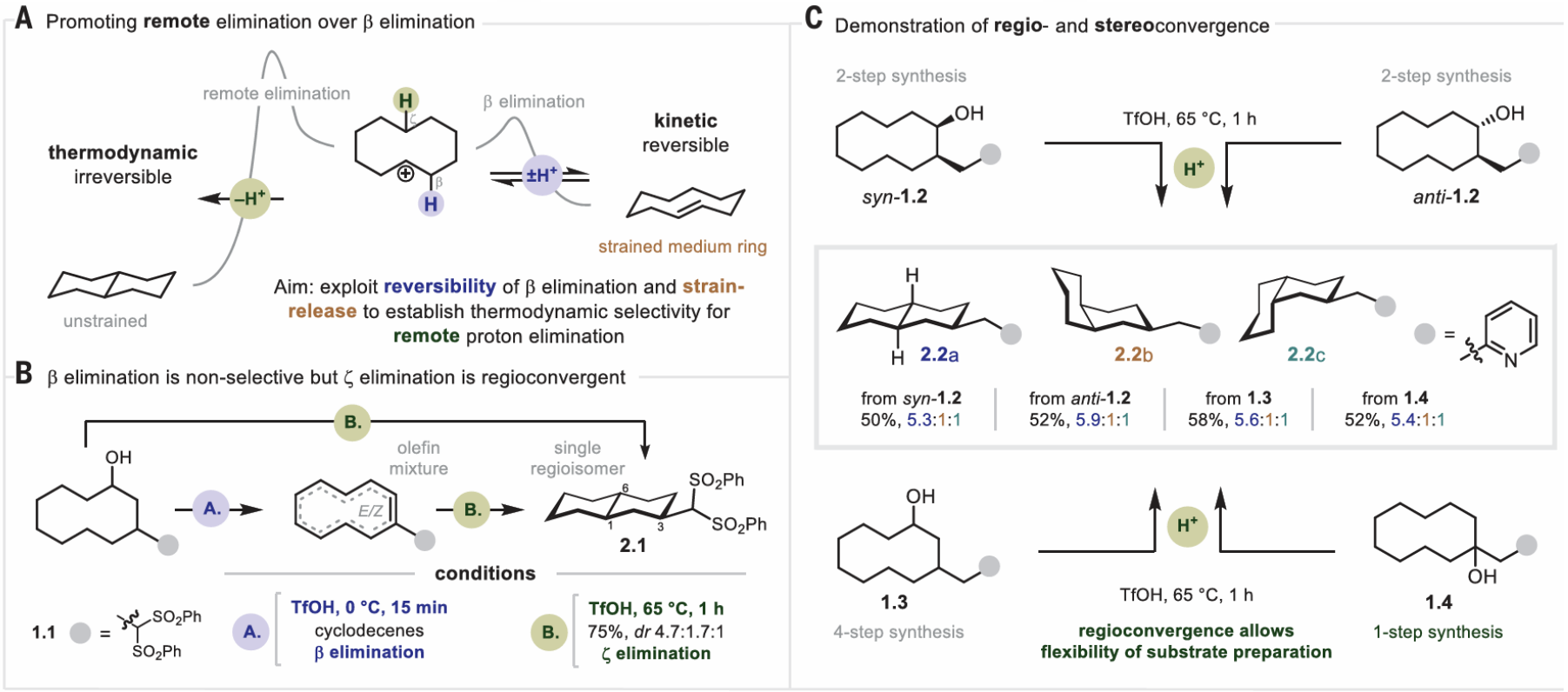
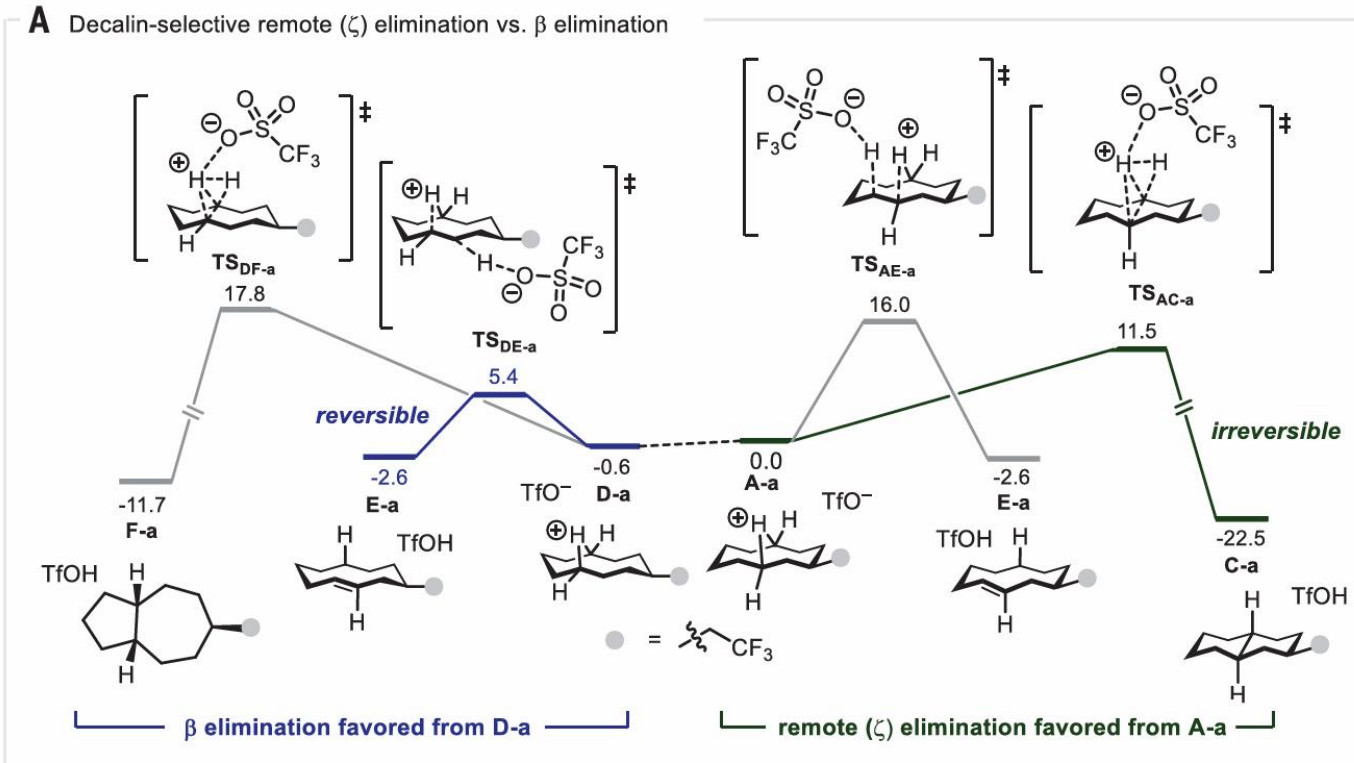
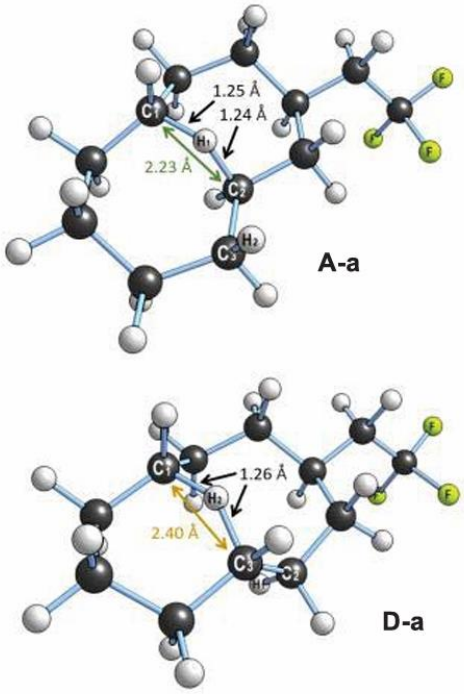


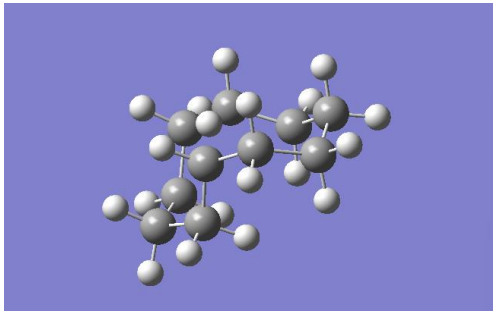
Fig. 2. Reaction development. (**A**) Mechanistic underpinning of thermodynamic ζ-elimination selectivity. (**B**) Contrasting β elimination from the intermediate carbocation (reversible and nonselective) with regioconvergent ζ elimination; yield and *dr* of **2.1** are given from **1.1**. (**C**) Experimental demonstration of regioconvergence. Conditions were as described in Fig. 3.

Grant, P. S.; … Maulide, N. *Science* **2024**, *384*, 815.

Key Problems: 6+6 or 5+7, Cis or Trans?

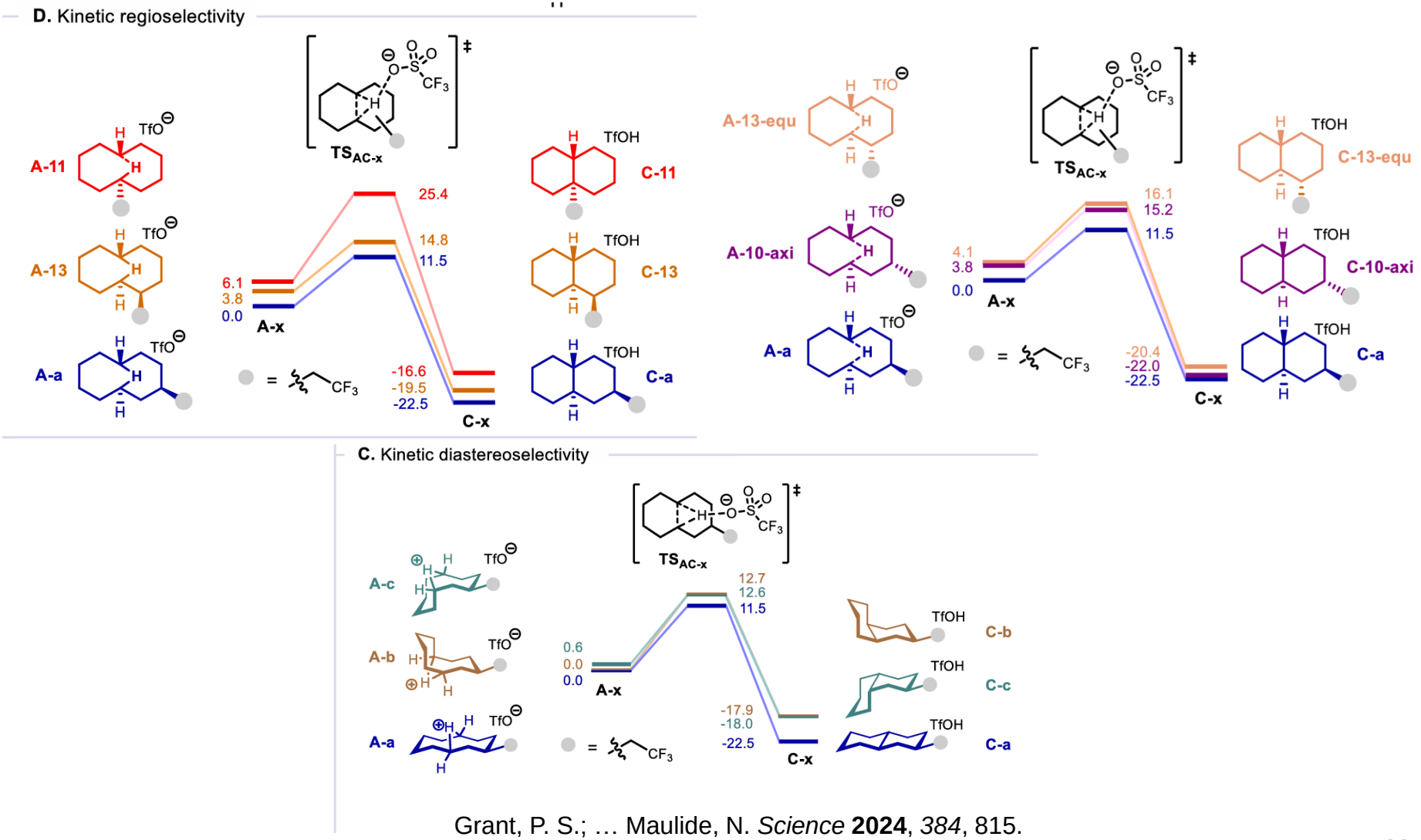






Grant, P. S.; … Maulide, N. *Science* **2024**, *384*, 815.

Regioselectivity?



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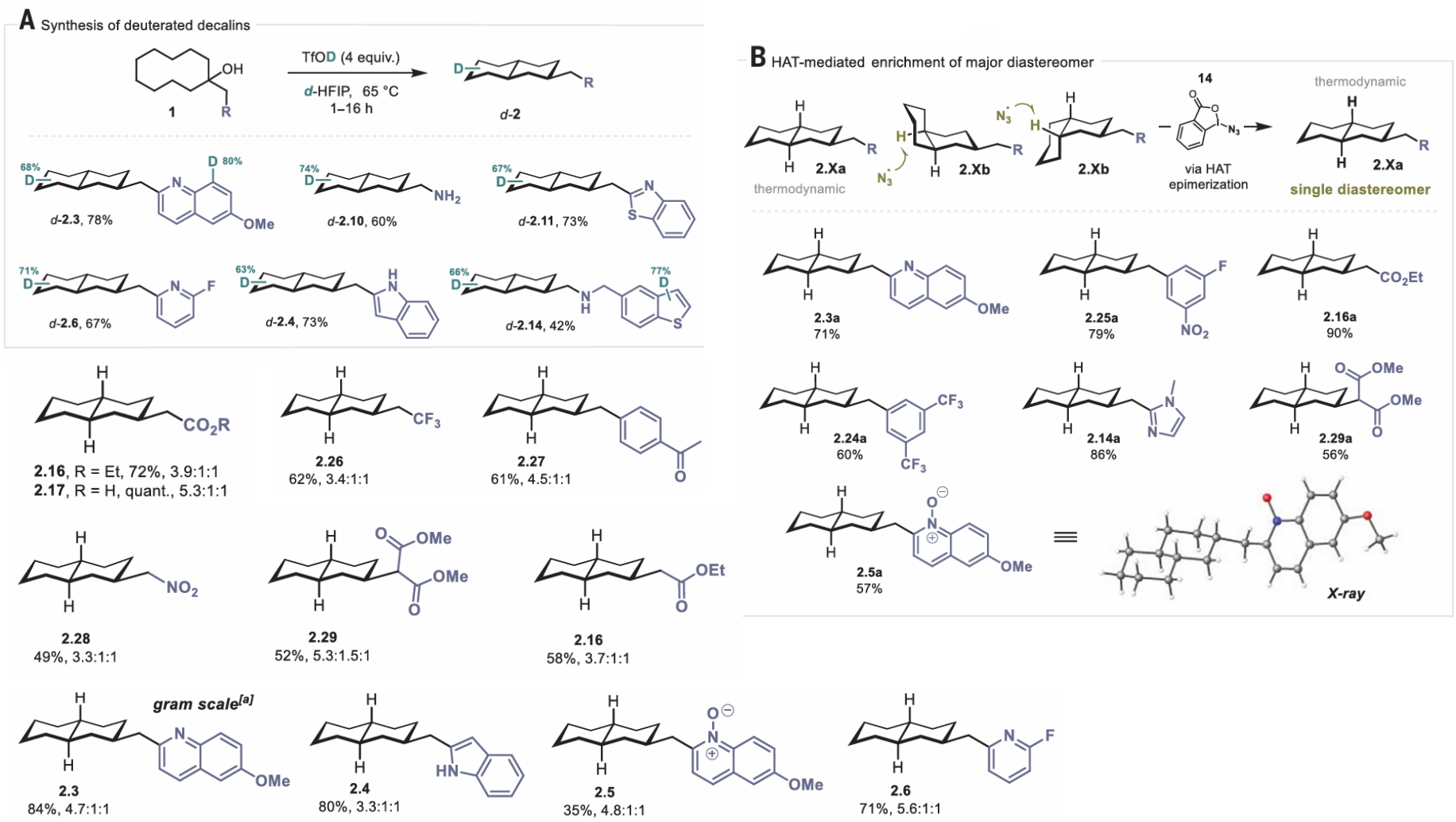
Substrate Scope and Epimerization



Grant, P. S.; … Maulide, N. *Science* **2024**, *384*, 815.

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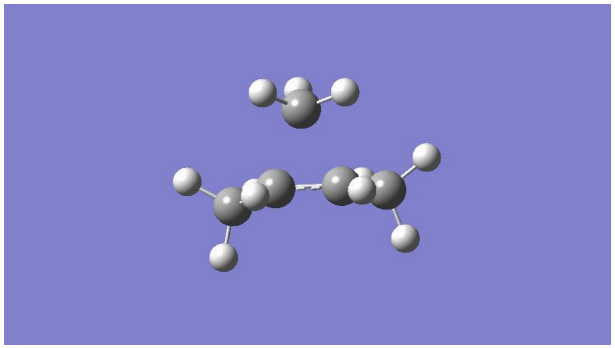
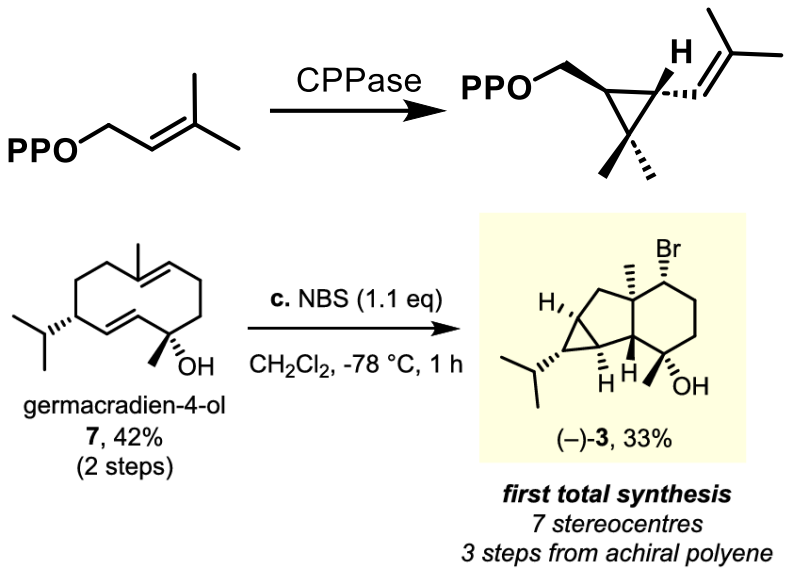
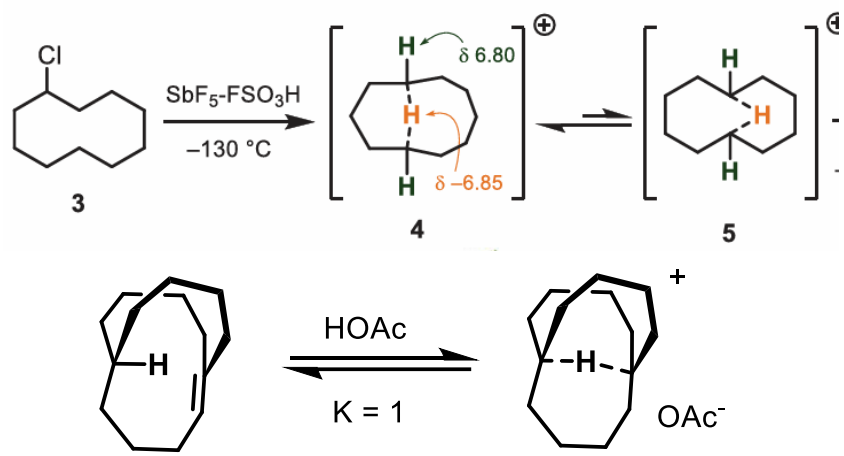
Conclusion

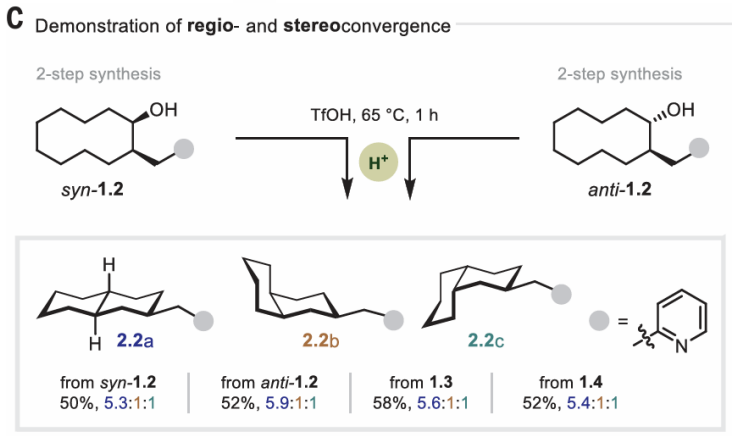
Protonated Cyclopropane and Cationic Cyclopropanation





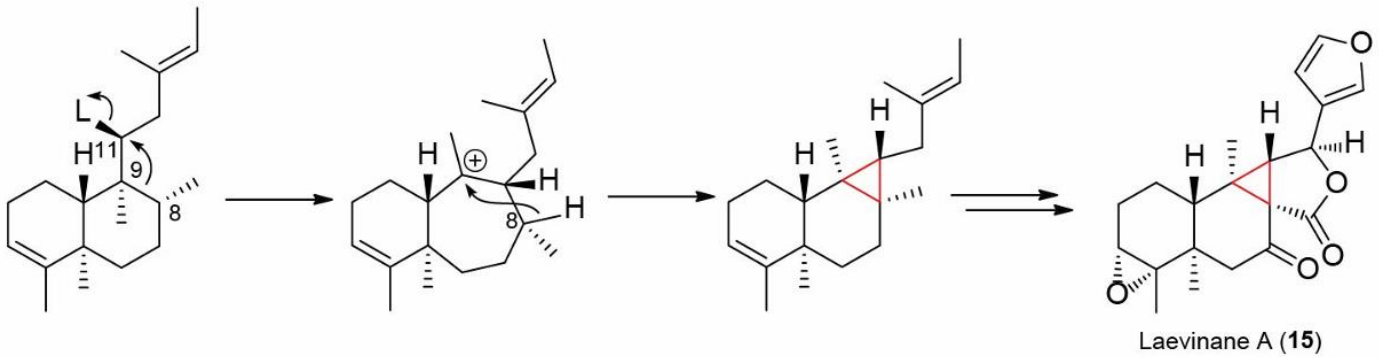
Hydrido-Bridged Cycloalkyl Cation and Remote Elimination



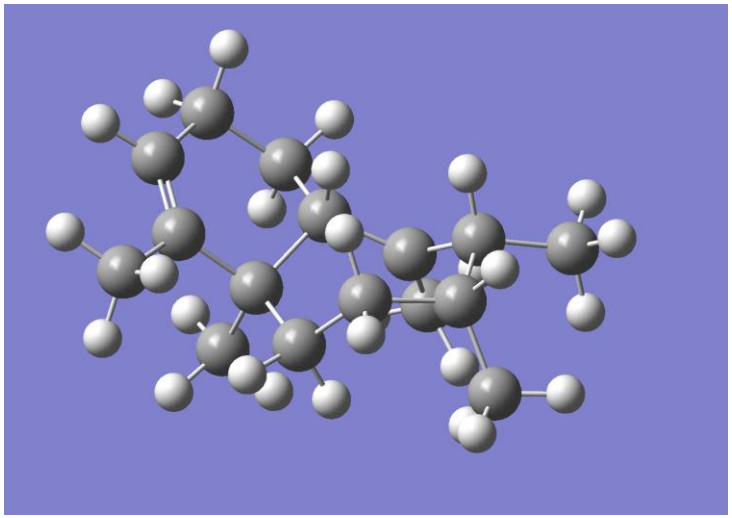


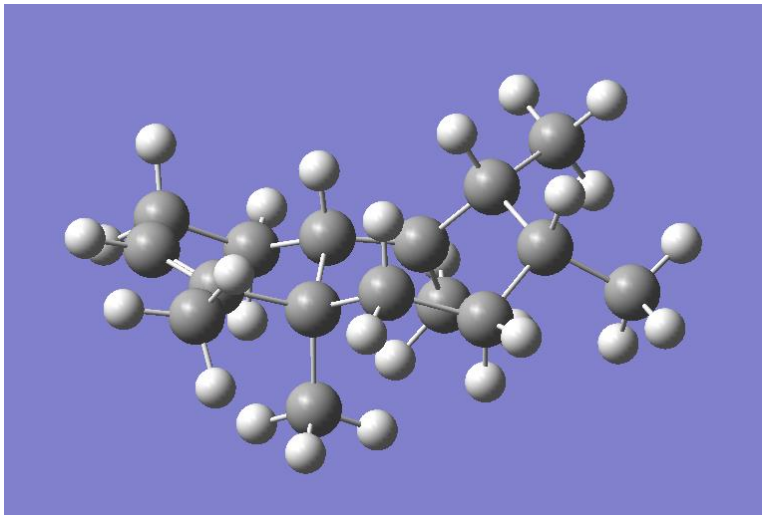
PCP$^+$ Elimination for 6 fused 3?

Proposed Biosynthesis of Laevinane A

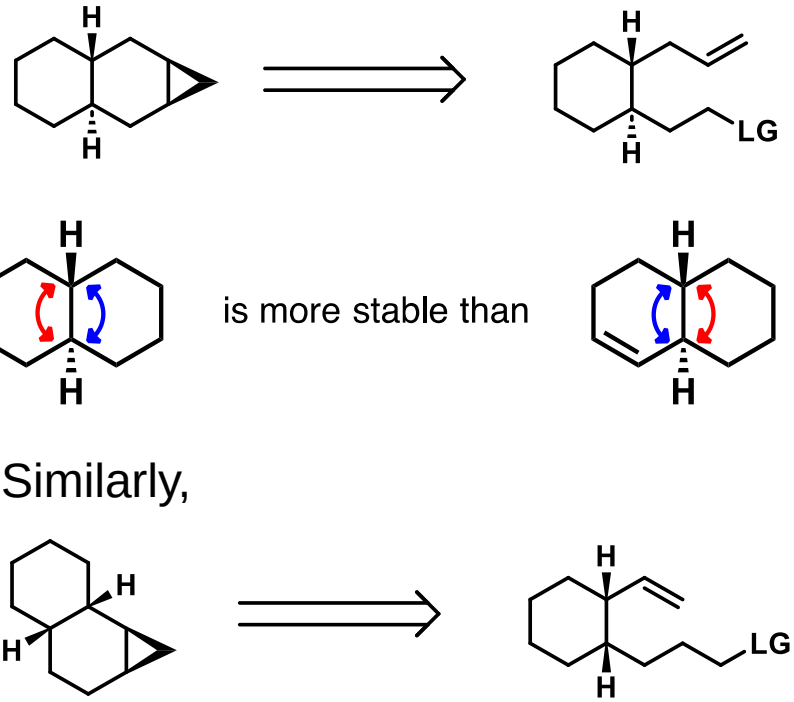


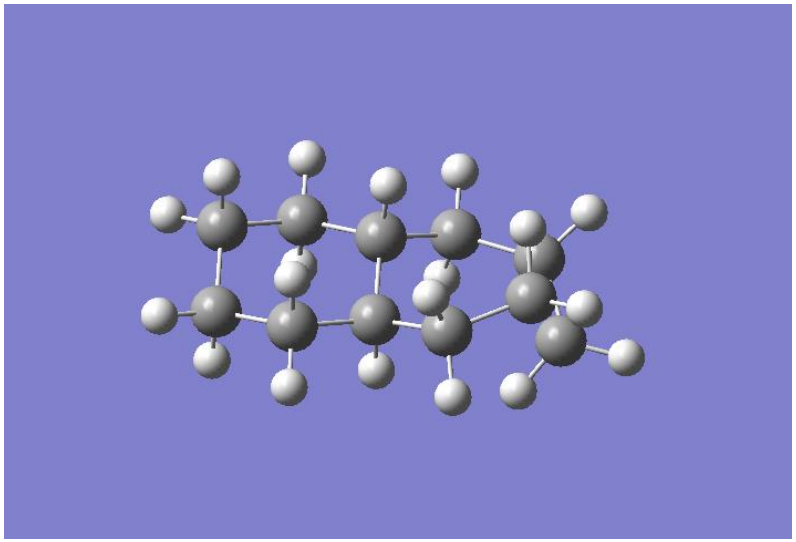
Laevinane A (**15**)





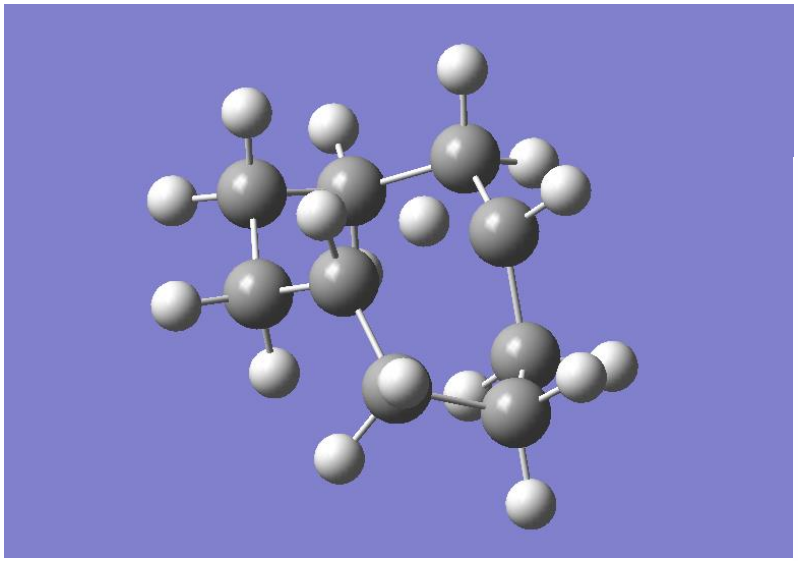
Construction of 6 fused 3?

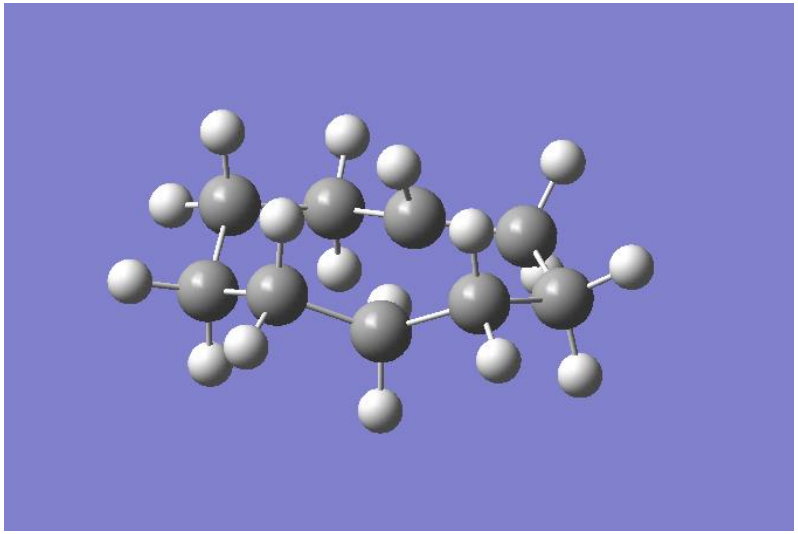




Moreover: Utilizing biomacromolecule to limit the structure of SM for a better cyclopropanation configuration? Molecular evolution to obtain those desired biomacromolecules?

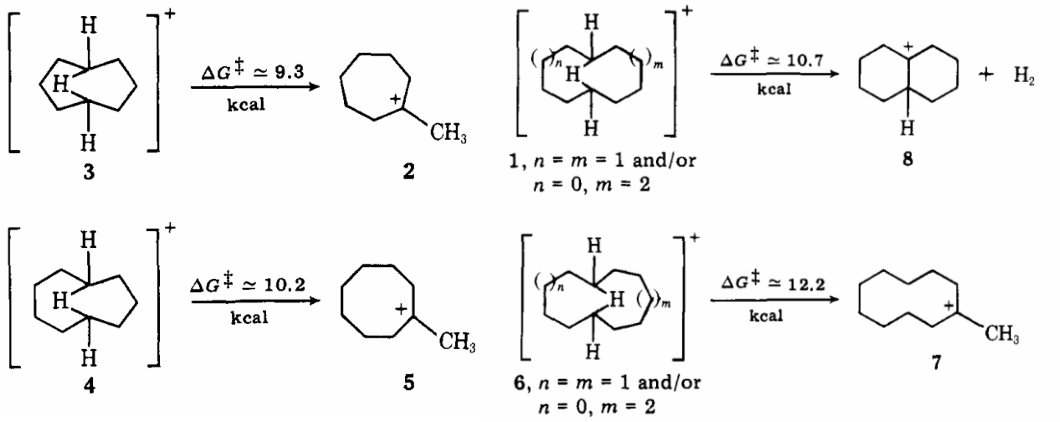
Remote Elimination for 6 fused 5?

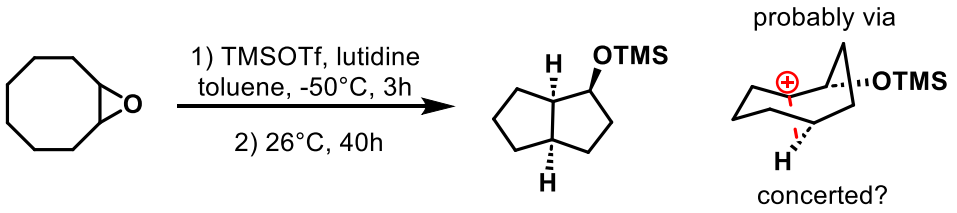




cis structure is more stable by 6.4 kcal/mol

Concern:





Murata S. et. al. *J. Am. Chem. Soc.* **1979**, *101*, 2738–2739.