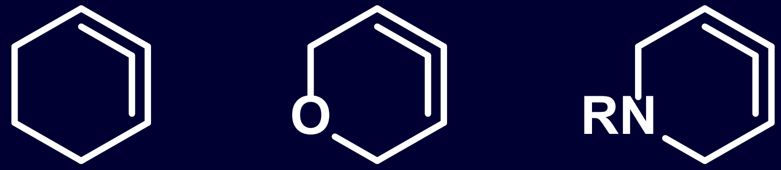
Strained Cyclic Allenes



Jiaqi Liu
College of Chemistry and Molecular Engineering
Center for Life Sciences

March 25, 2023

Outline

- Introduction
- Reactions and selectivity of strained cyclic allenes
  - Cycloaddition reactions
  - Metal catalyzed reactions
- Summary

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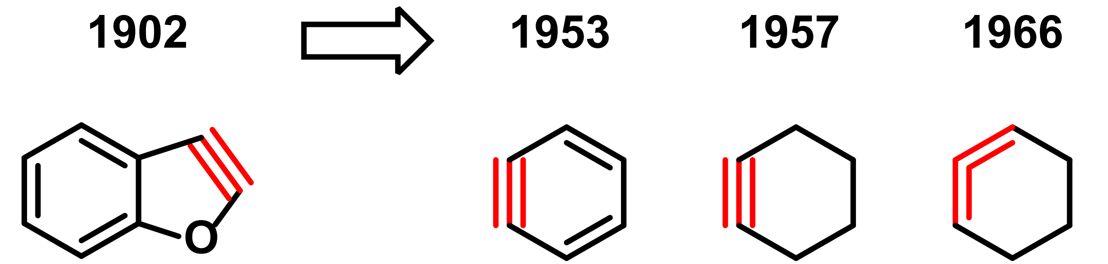
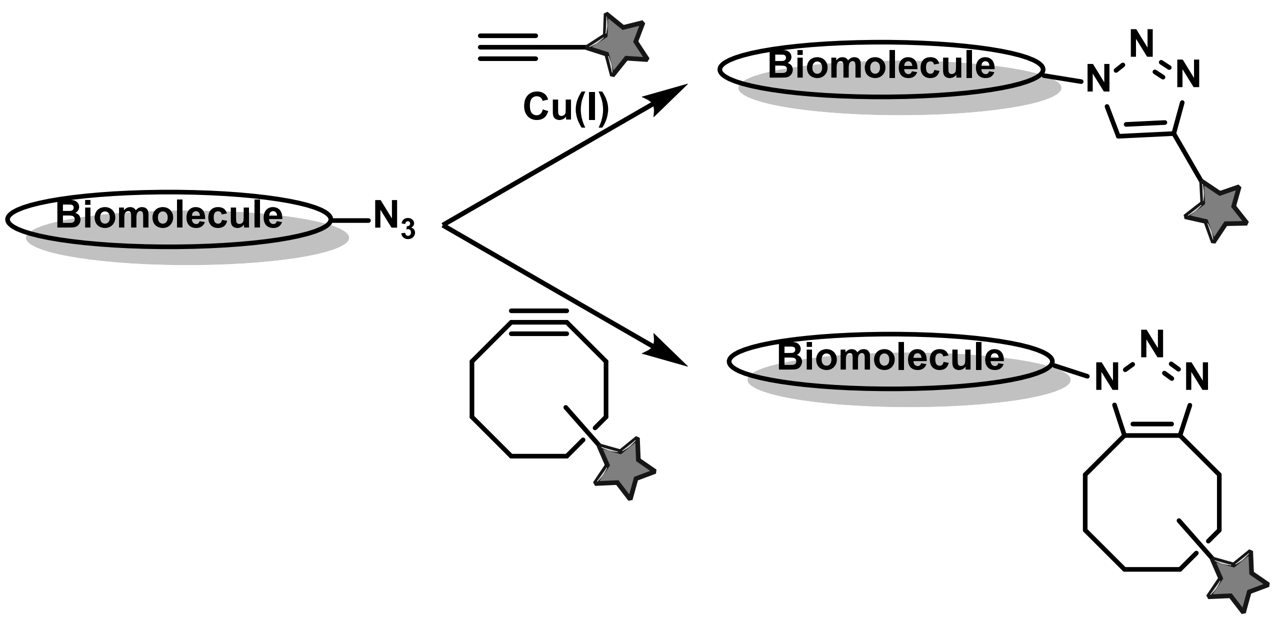
Strained Cyclic Intermediates



Controversial proposal

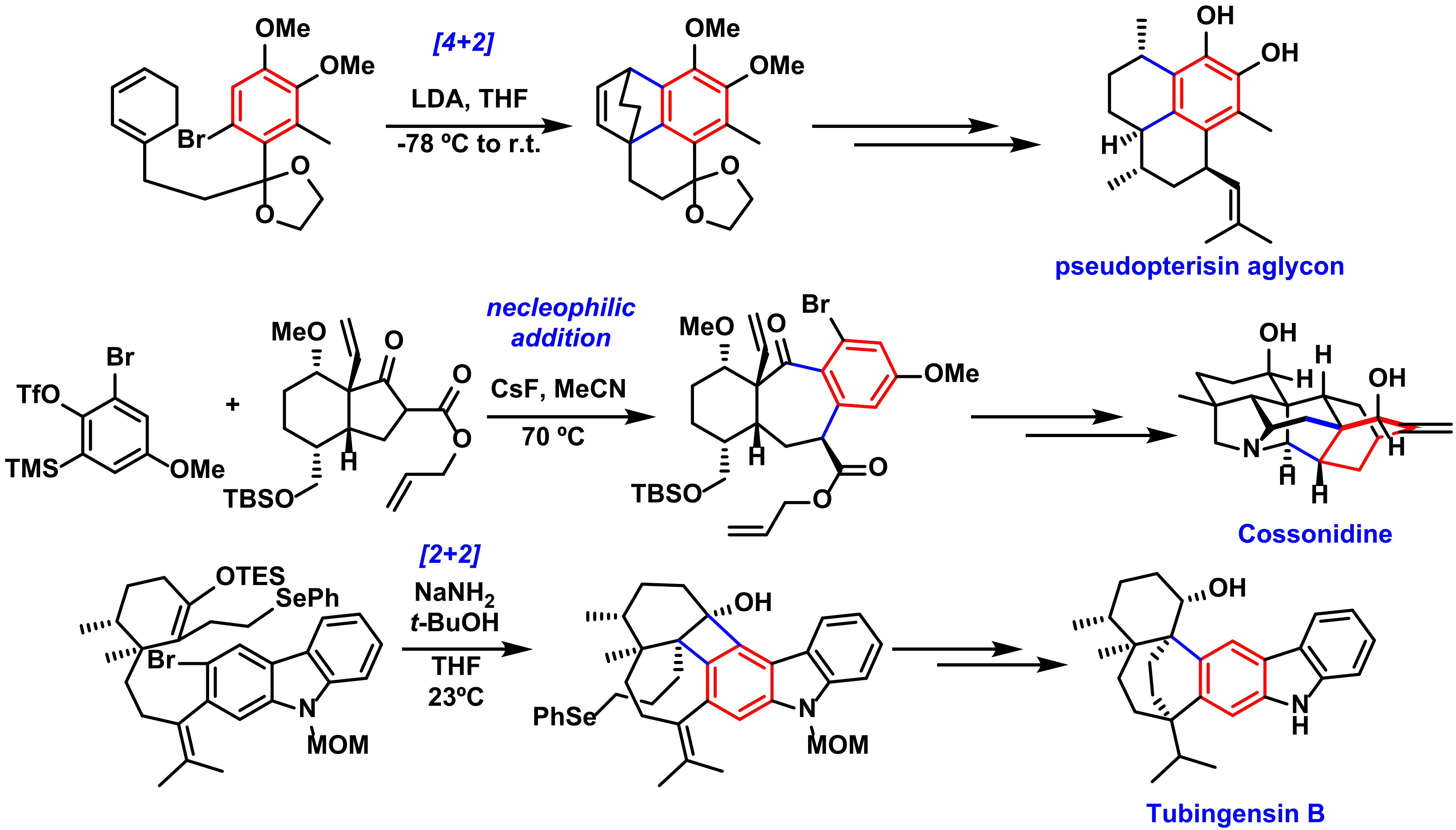
Validation



Anthony, S. M.; Wonilowicz, L. G.; McVeigh, M. S.; Garg N. K. *JACS Au.* **2021**, *1*, 897−912.

Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998.

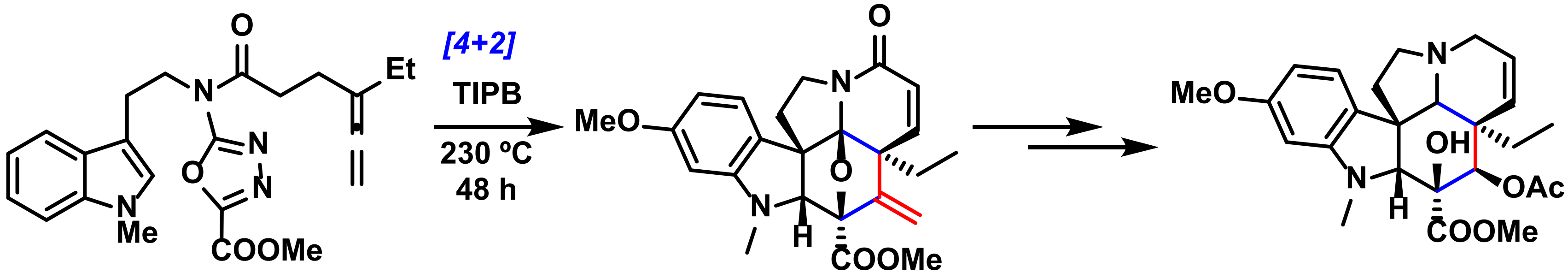
Applications of the Intermediates



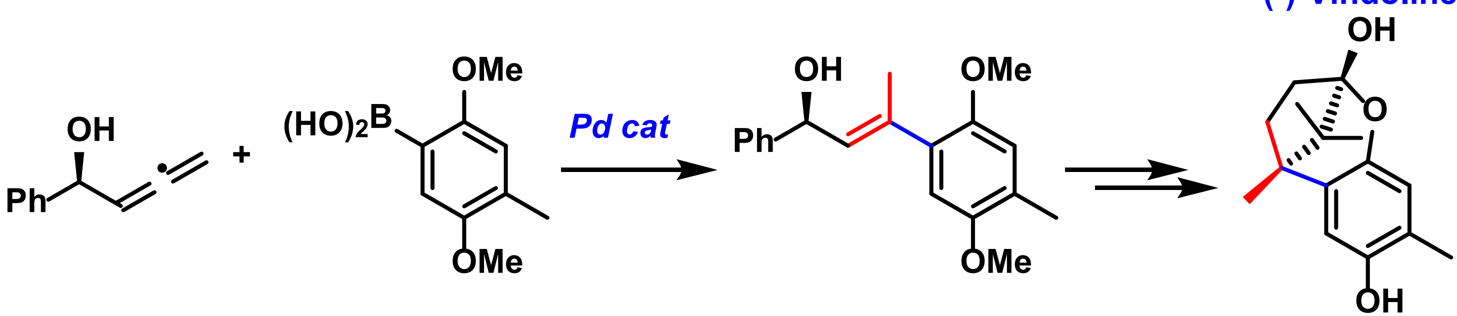
Takikawa, H.; Nishii, A.; Sakaib, T.; Suzuki, K. *Chem. Soc. Rev.*, **2018**, *47,* 8030−8056.

Allenes

1887	1924-1952	Until now
First synthesis Misidentified	Natural product discovery Finally identified	Development in cycloaddition and coupling



(-)-Vindoline

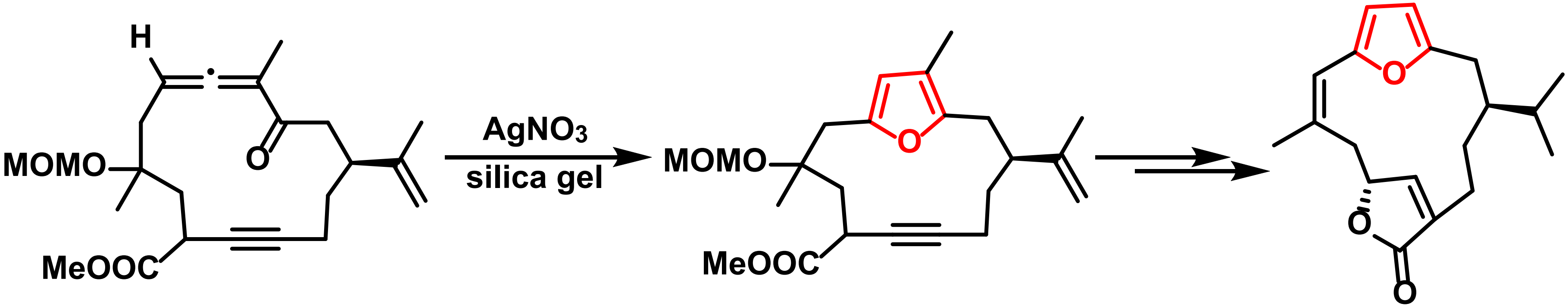


Enokipodin A

Sears, J. E.; Barker, T. J.; Boger, D. L. *Org. Lett.* **2015**, *17*, 5460−5463.

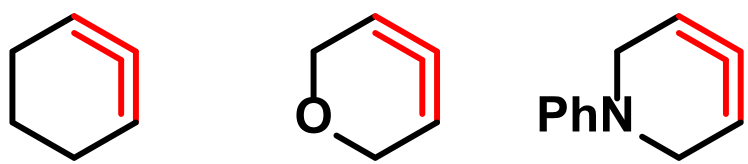
Yoshida, M.; Shoji, Y.; Shishido. K. *Org. Lett.* **2009**, *11*, 1441−1443.

Strained Cyclic Allenes



Enantiomer of Rubifolide

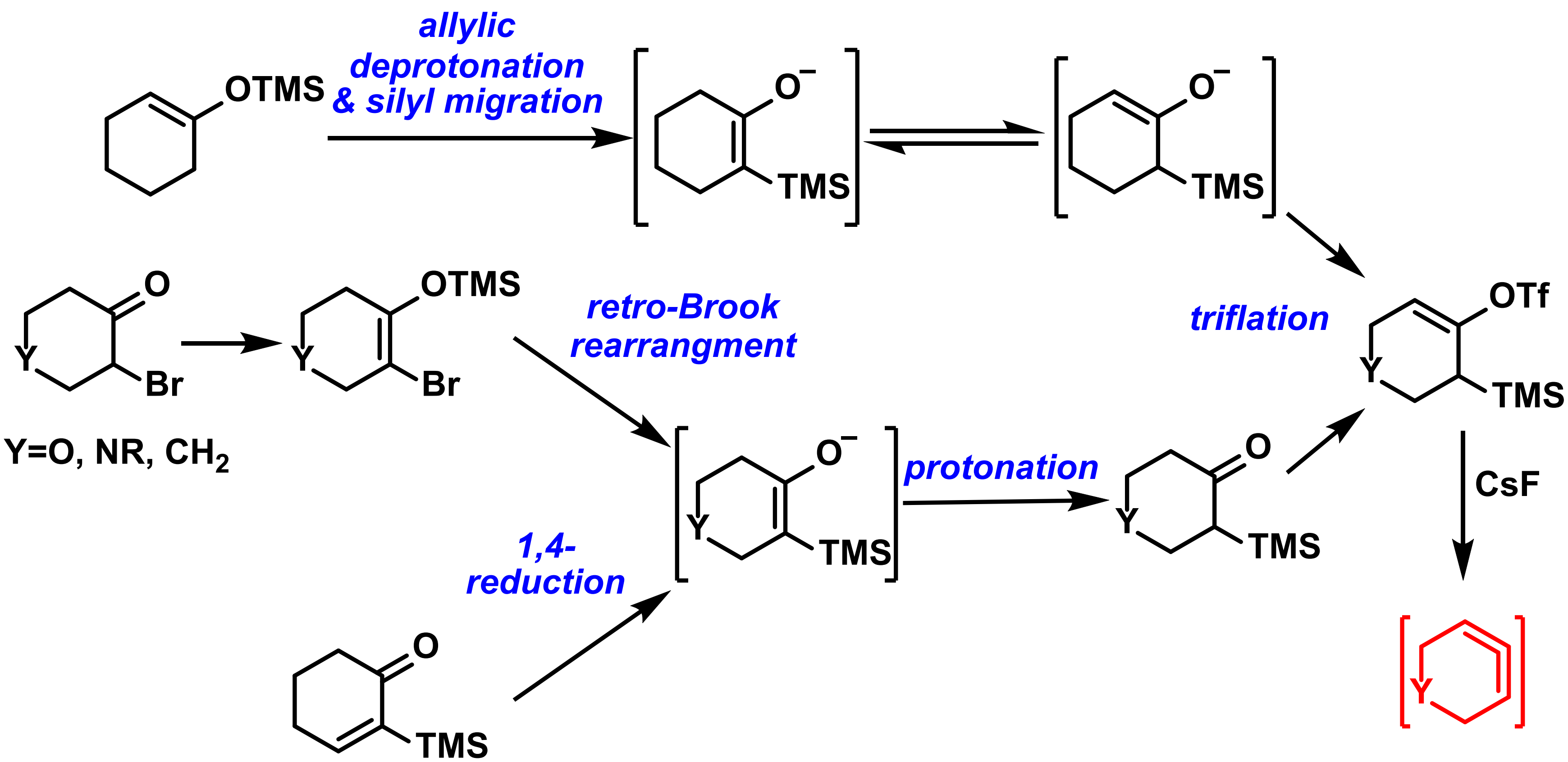
1966 **1987** **1994**



Marshall, J. A.; Sehon, C. A.; *J. Org. Chem*. **1997**, *62,* 4313–4320.

Barber, J. S. et. al. *Nat. Chem.* **2018**, *10,* 953–960.

Preparation of Strained Cyclic Allenes



Chari, J. V.; Ippoliti, F. M.; Garg N. K. *J. Org. Chem*. **2019**, *84*, 3652−3655.

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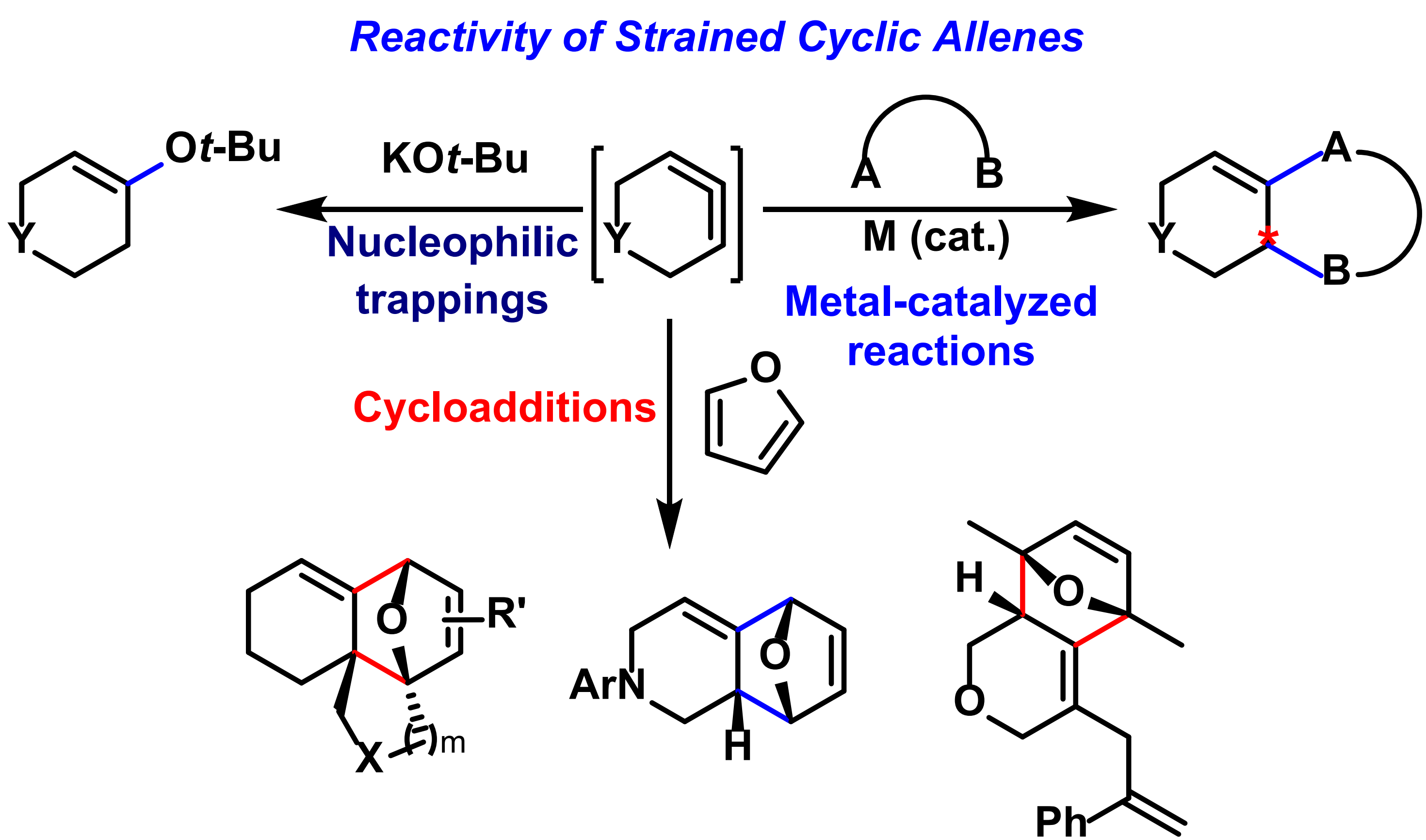
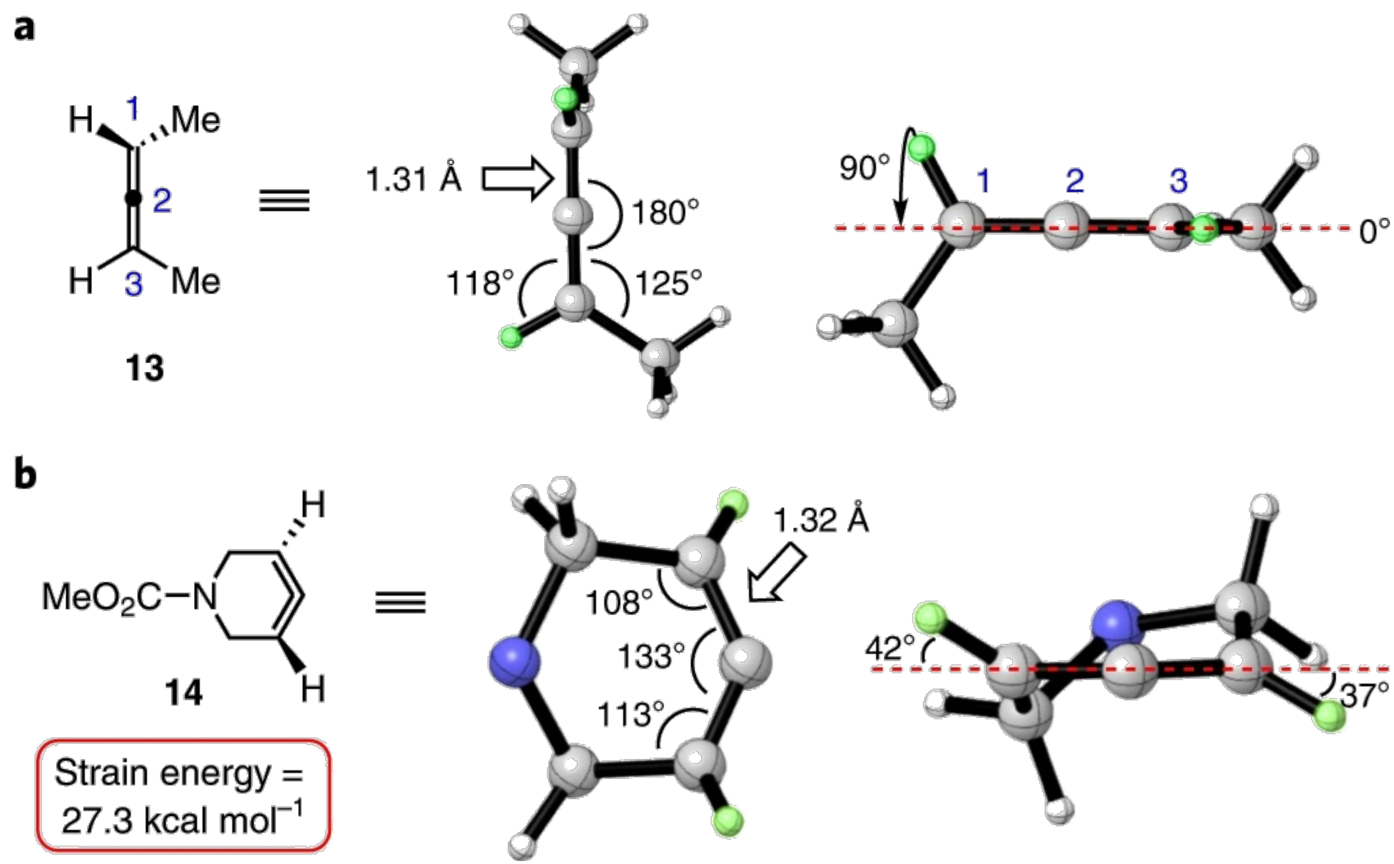
Reactivity of Strained Cyclic Allenes



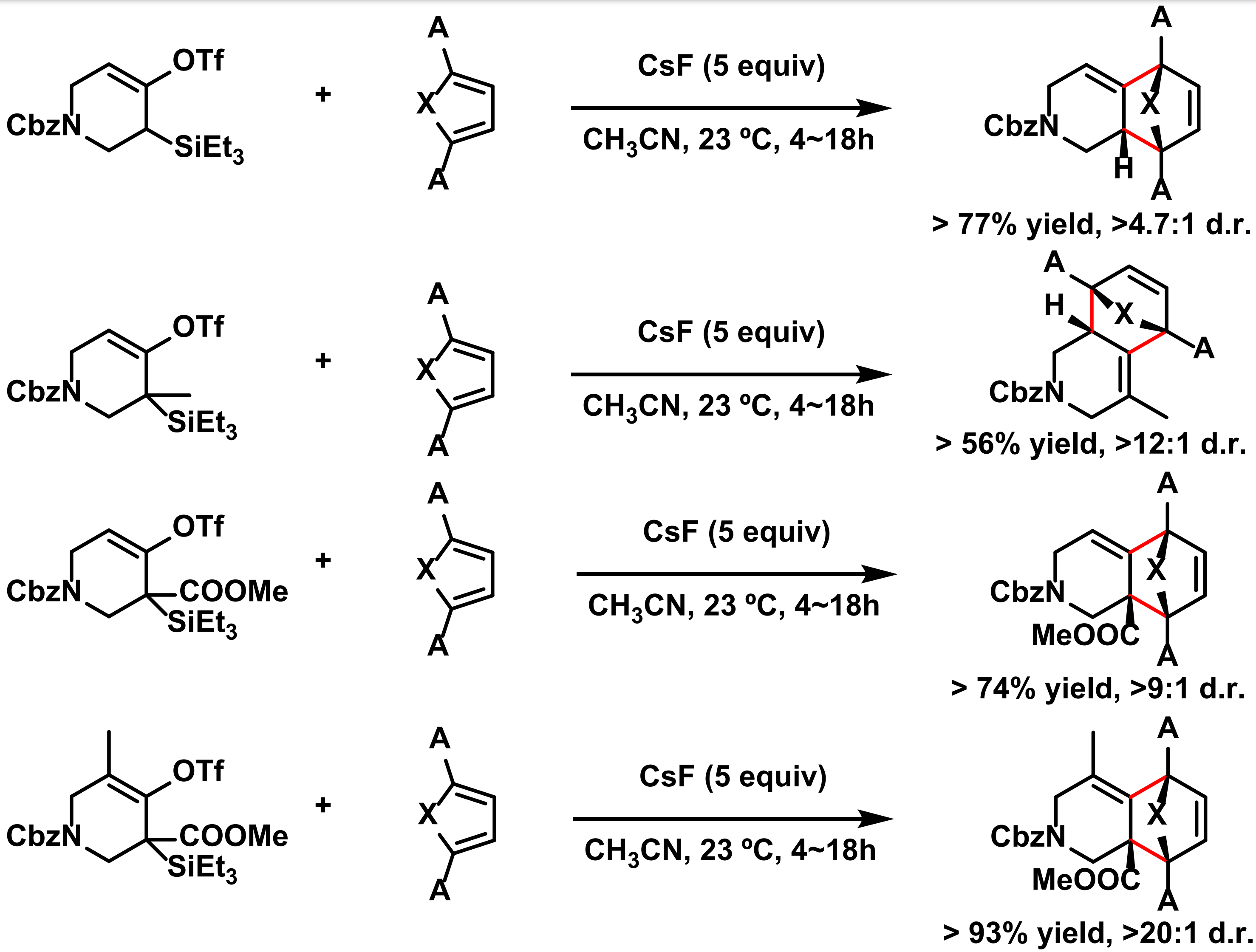
Kelleghan, A. V. et. al. *J. Am. Chem. Soc*. **2021**, *143,* 9338−9342.

Structure of Azacyclic Allenes



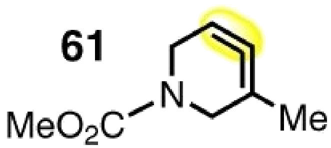
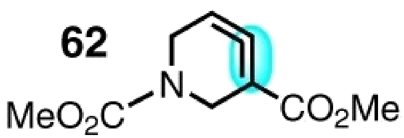
Barber, J. S. et. al. *Nat. Chem.* **2018**, *10,* 953–960.

D-A Reaction of Strained Cyclic Allenes



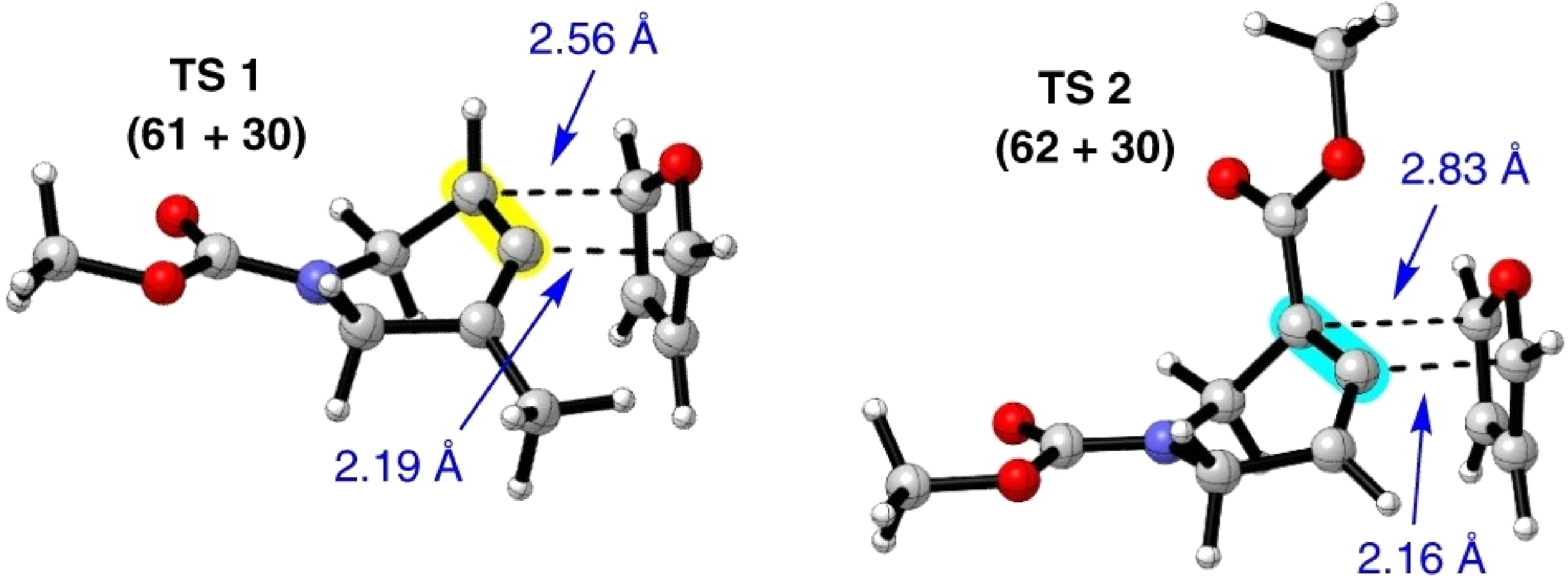
Barber, J. S. et. al. *Nat. Chem.* **2018**, *10,* 953–960.

Theoretical Study of Regioselectivity

Diels–Alder partners	ΔG and ΔE (major regioisomer)	ΔG and ΔE (minor regioisomer)	$\Delta\Delta G$ and $\Delta\Delta E$
61  +  **30**	TS1 $\Delta G^{\ddagger} = 19.1$ $\Delta E^{\ddagger} = 4.6$ $\Delta E_{dist}^{\ddagger} = 10.9$ $\Delta E_{int}^{\ddagger} = -6.3$	$\Delta G^{\ddagger} = 20.6$ $\Delta E^{\ddagger} = 6.2$ $\Delta E_{dist}^{\ddagger} = 11.2$ $\Delta E_{int}^{\ddagger} = -5.0$	$\Delta\Delta G^{\ddagger} = -1.5$ $\Delta\Delta E^{\ddagger} = -1.6$ $\Delta\Delta E_{dist}^{\ddagger} = -0.3$ $\Delta\Delta E_{int}^{\ddagger} = -1.3$
62  +  **30**	TS2 $\Delta G^{\ddagger} = 12.8$ $\Delta E^{\ddagger} = -1.6$ $\Delta E_{dist}^{\ddagger} = 8.2$ $\Delta E_{int}^{\ddagger} = -9.8$	$\Delta G^{\ddagger} = 17.7$ $\Delta E^{\ddagger} = 3.1$ $\Delta E_{dist}^{\ddagger} = 7.5$ $\Delta E_{int}^{\ddagger} = -4.4$	$\Delta\Delta G^{\ddagger} = -4.9$ $\Delta\Delta E^{\ddagger} = -4.7$ $\Delta\Delta E_{dist}^{\ddagger} = 0.7$ $\Delta\Delta E_{int}^{\ddagger} = -5.4$

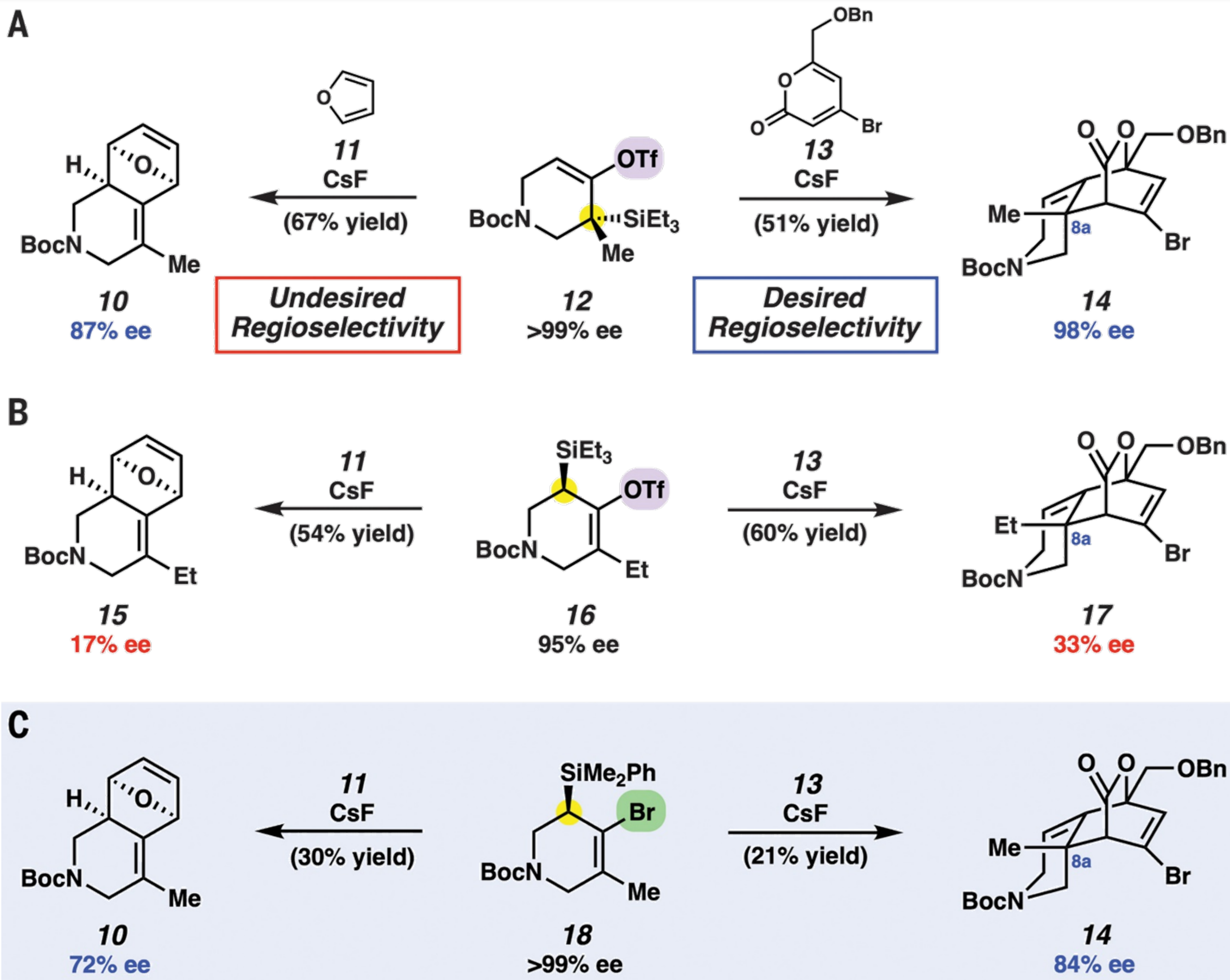
Barber, J. S. et. al. *Nat. Chem.* **2018**, *10,* 953–960.

Transition State of D-A



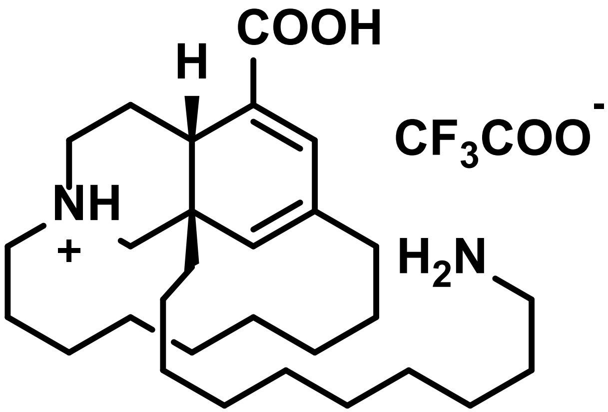
Barber, J. S. et. al. *Nat. Chem.* **2018**, *10,* 953–960.

Dienes Changes Regioselectivity

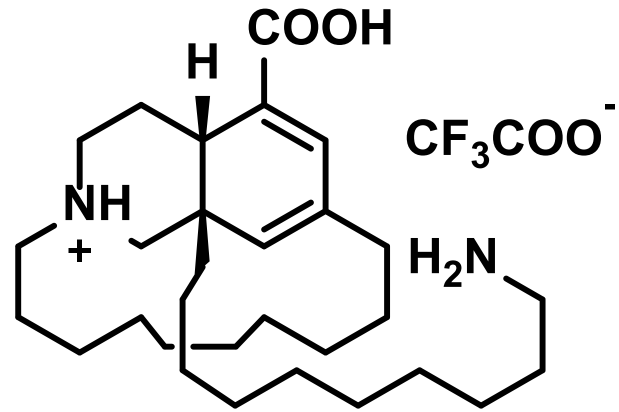


Ippoliti, F. M. et. al. *Science* **2023,** *379,* 261–265.

Lissodendoric Acid Family



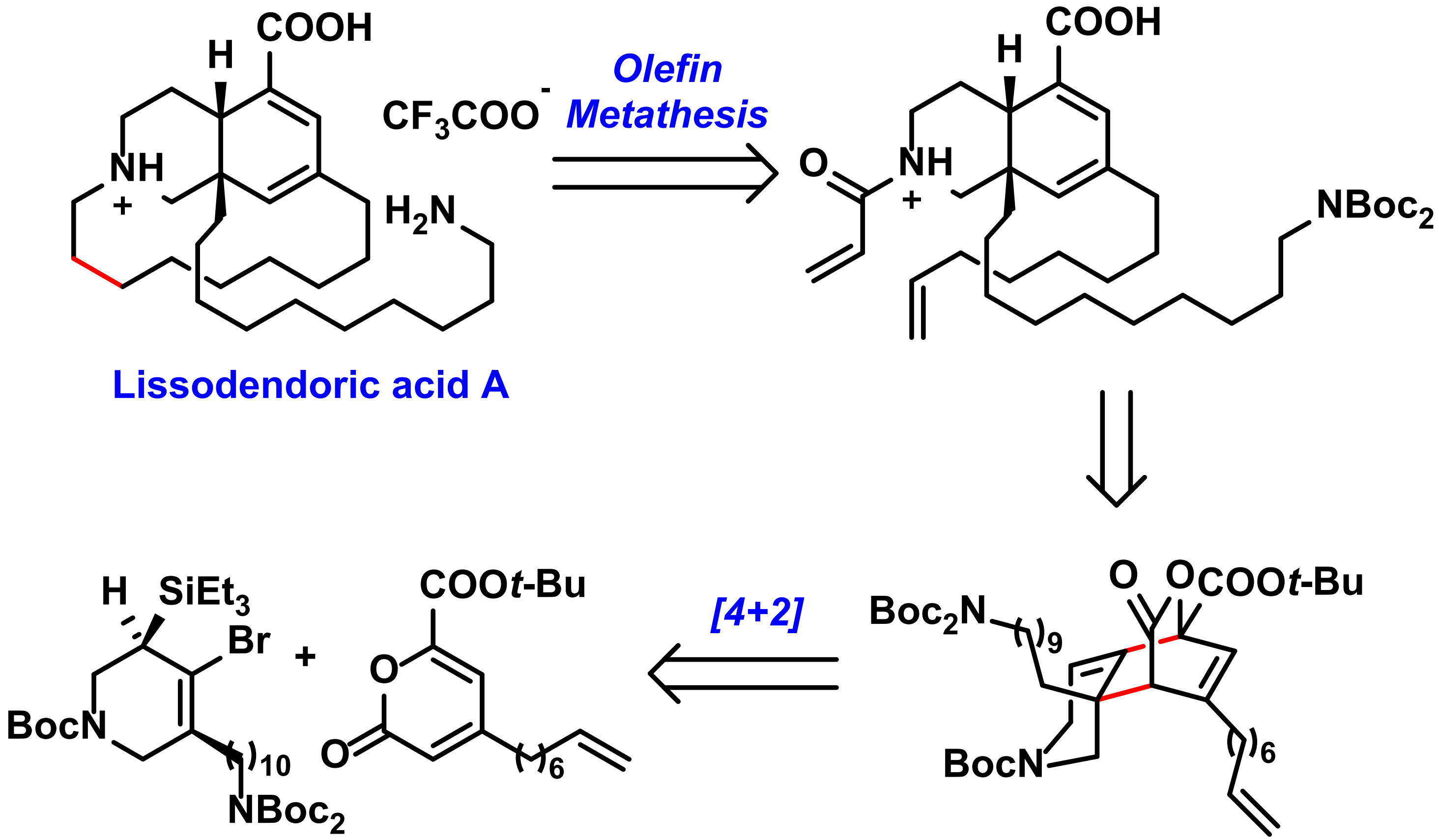
Lissodendoric acid A



Lissodendoric acid B

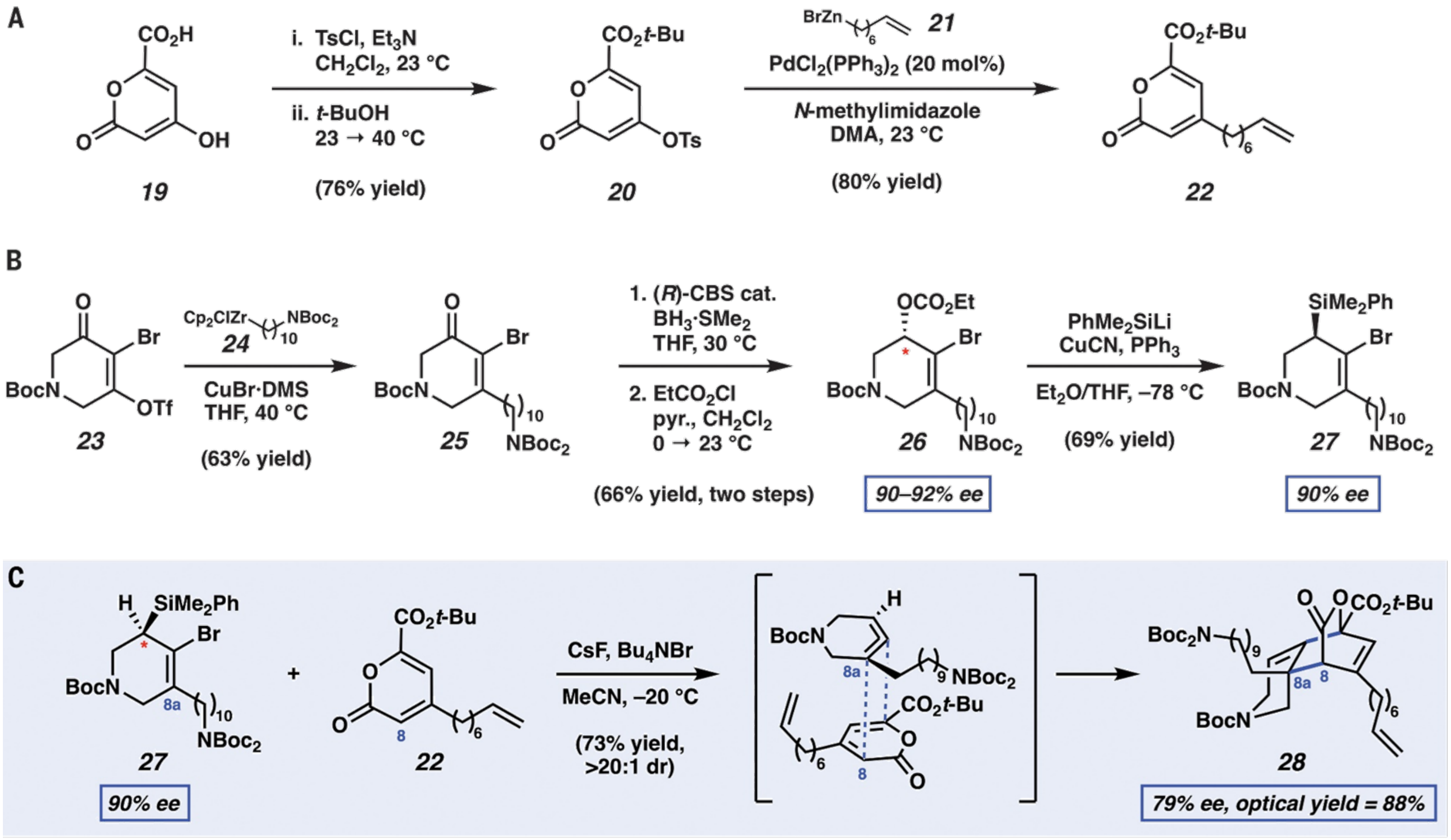
Lyakhova, E. G. et. al. *Org. Lett.* **2017**, *19,* 5320−5323.

Retrosynthesis



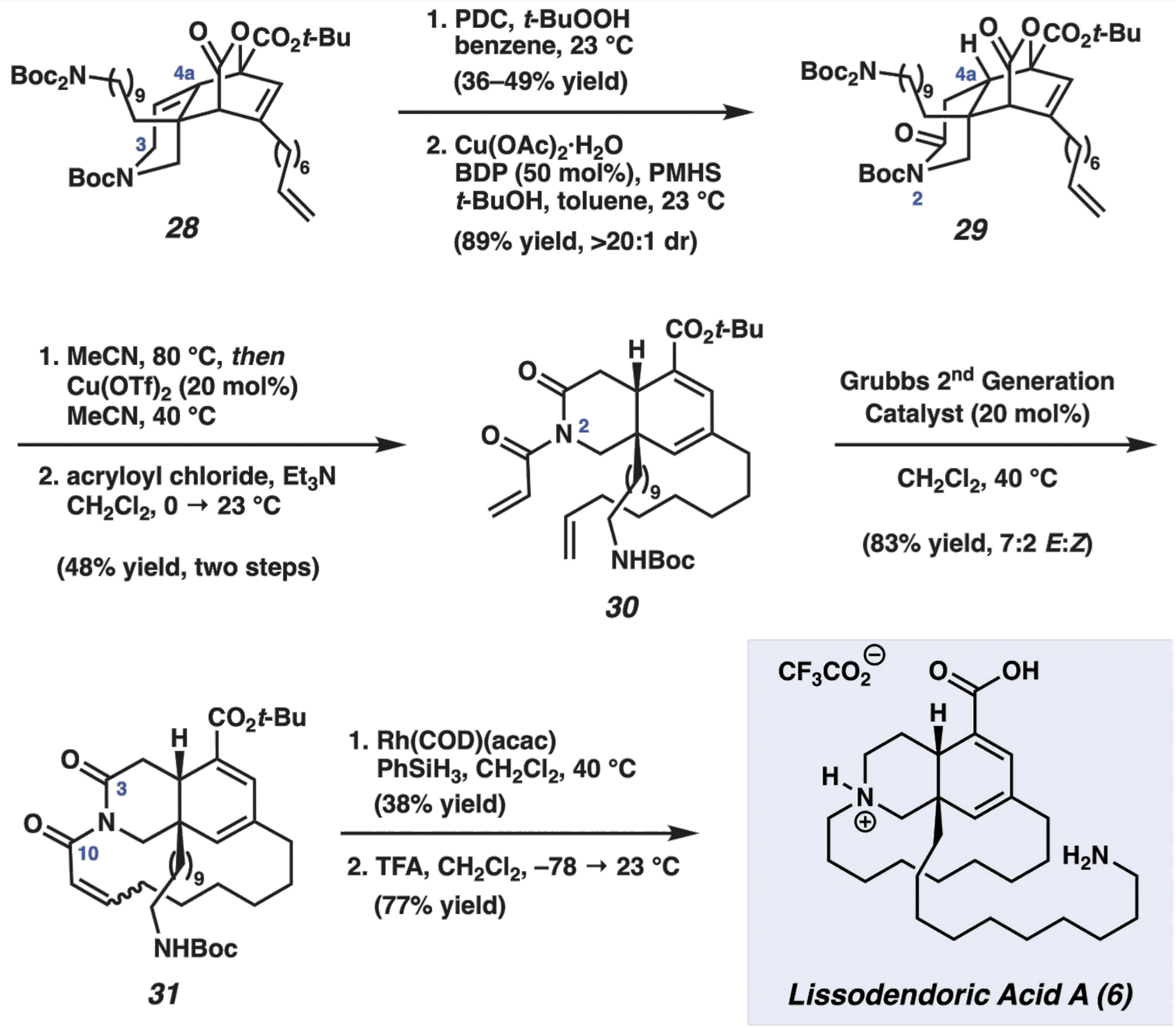
Ippoliti, F. M. et. al. *Science* **2023,** *379,* 261–265.

Key Reaction through Strained Cyclic Allenes



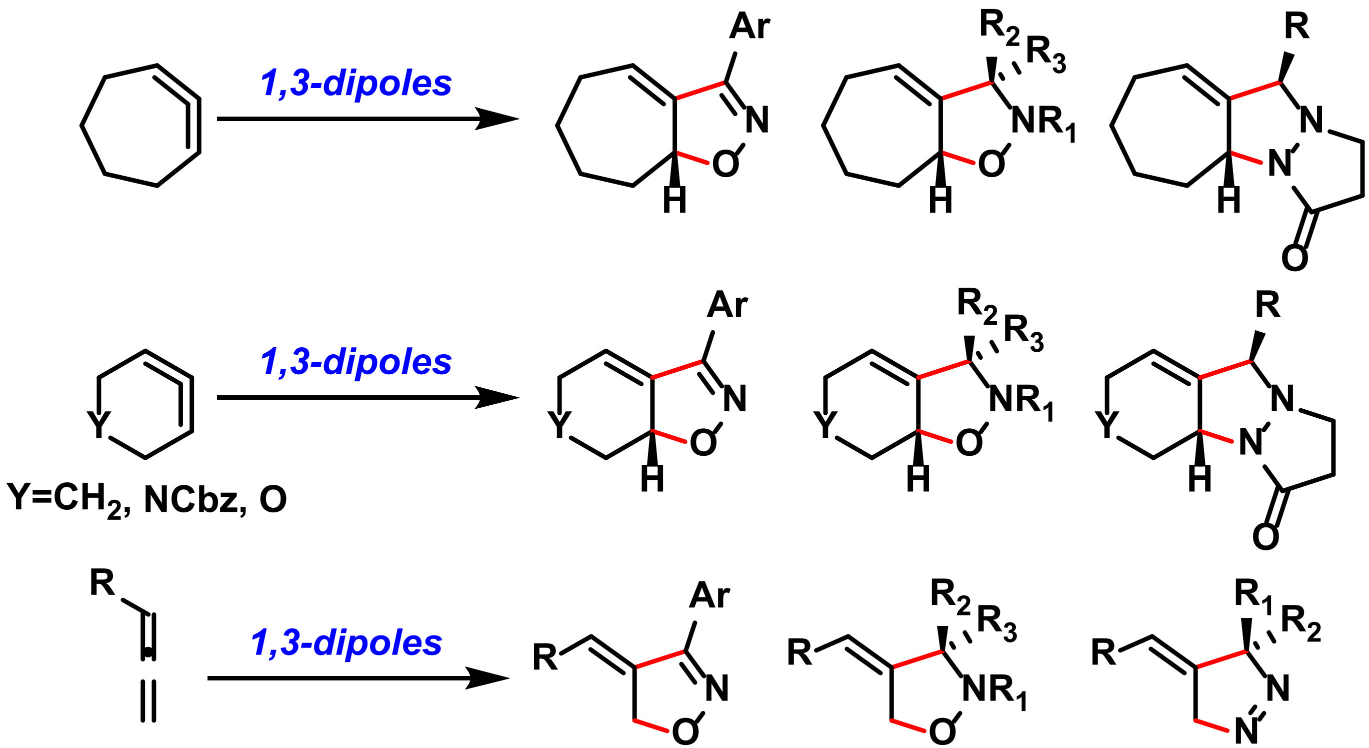
Ippoliti, F. M. et. al. *Science* **2023,** *379,* 261–265.

Total Synthesis



Ippoliti, F. M. et. al. *Science* **2023,** *379,* 261–265.

1,3-Dipole Cycloaddition Reaction



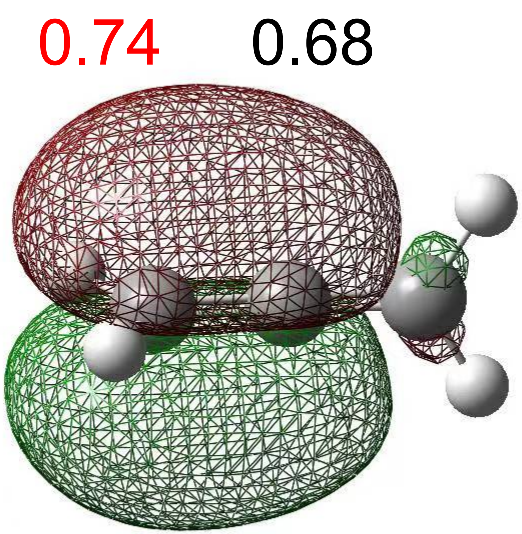
Barber, J. S. et. al. *Nat. Chem.* **2018***, 10,* 953–960.

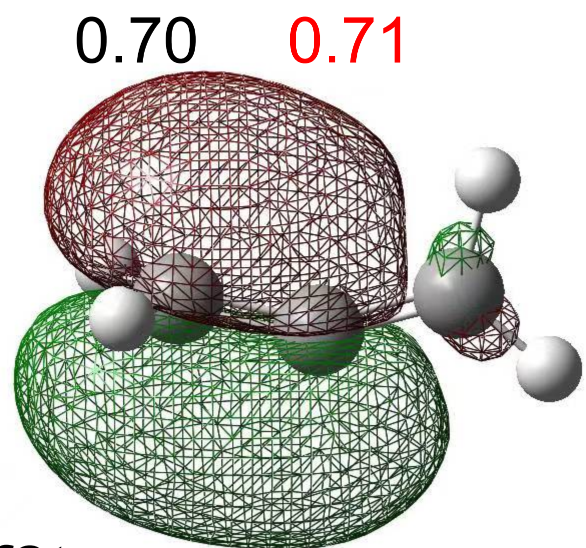
Yamano, M. M. et. al. *Angew. Chem. Int. Ed.* **2019,** *58,* 5653–5657.

Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry,* **2004**.

MOs of the Strained Cyclic Allenes

	HOMO/eV	LUMO/eV
Strained Cyclic Allenes a	-6.60	-0.12
Strained Cyclic Allenes b	-6.45	-0.29
Strained Cyclic Allenes c	-6.62	-0.14
Strained Cyclic Allenes d	-6.76	-0.49
Dipole 1	-6.98	-2.59
Dipole 2	-6.22	-2.55

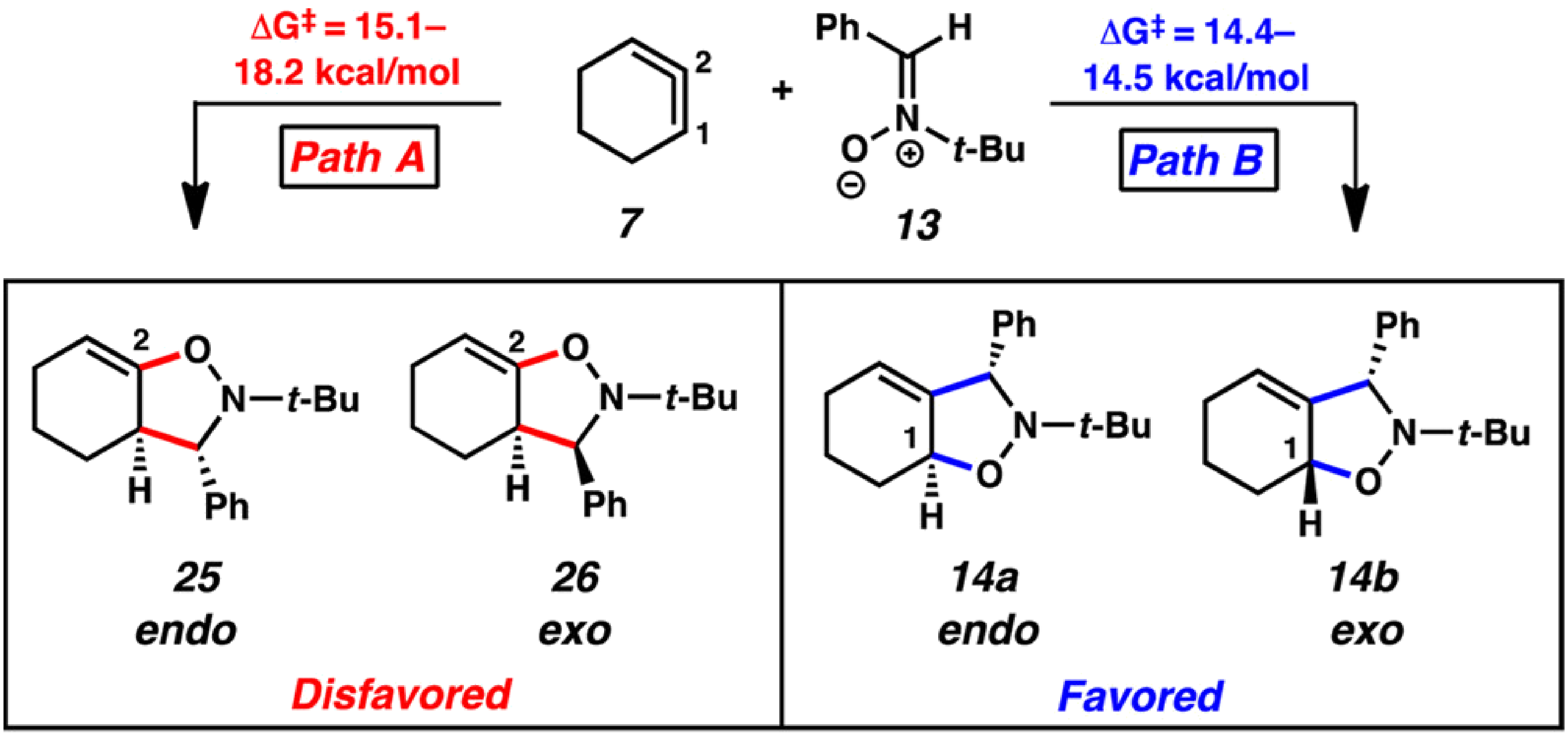




B3LYP-D3/def2tzvp

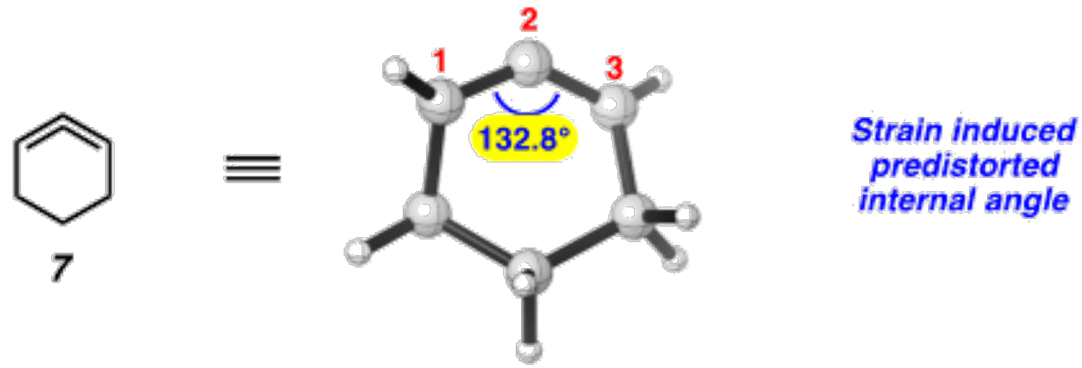
Efrimova, M. M. et. al. *Org. Biomol. Chem.* **2021**, *19,* 9773–9784.

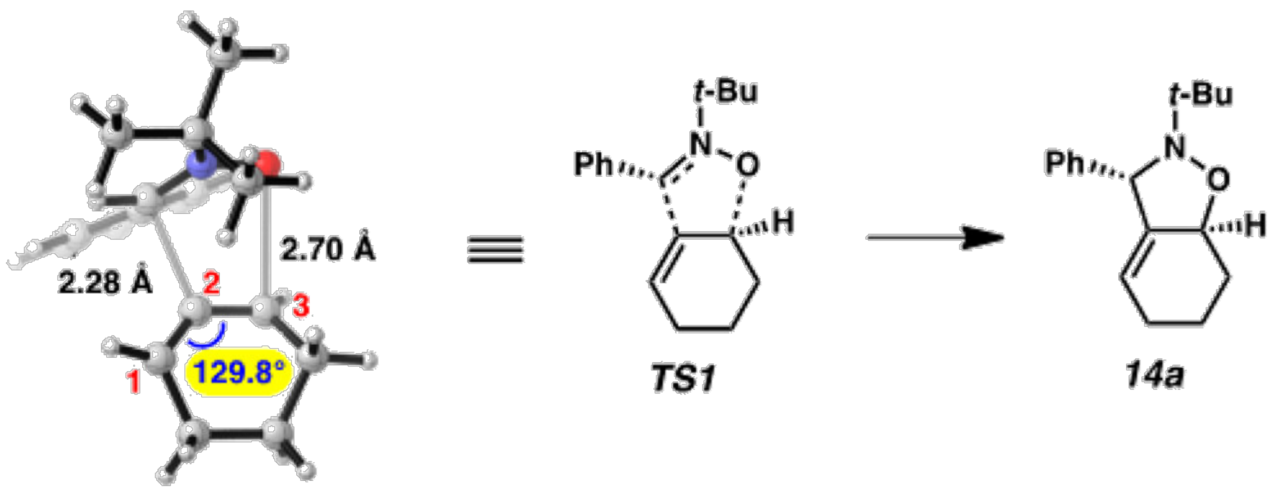
Theoretical Study of 1,3-Dipole Cycloaddition



Barber, J. S. et. al. *J. Am. Chem. Soc.* **2016**, *138,* 2512−2515.

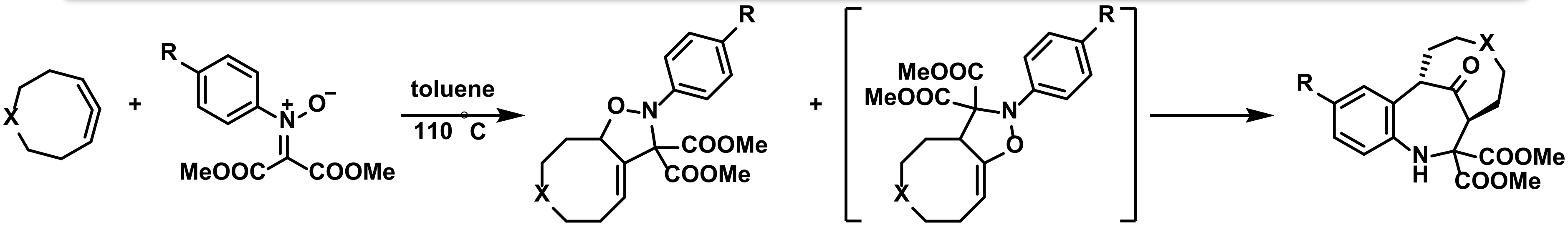
TS of 1,3-Dipole Cycloaddition



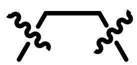
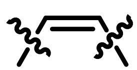


Barber, J. S. et. al. *J. Am. Chem. Soc.* **2016**, *138,* 2512−2515.

Selectivity of 1,3-Dipole Cycloaddition

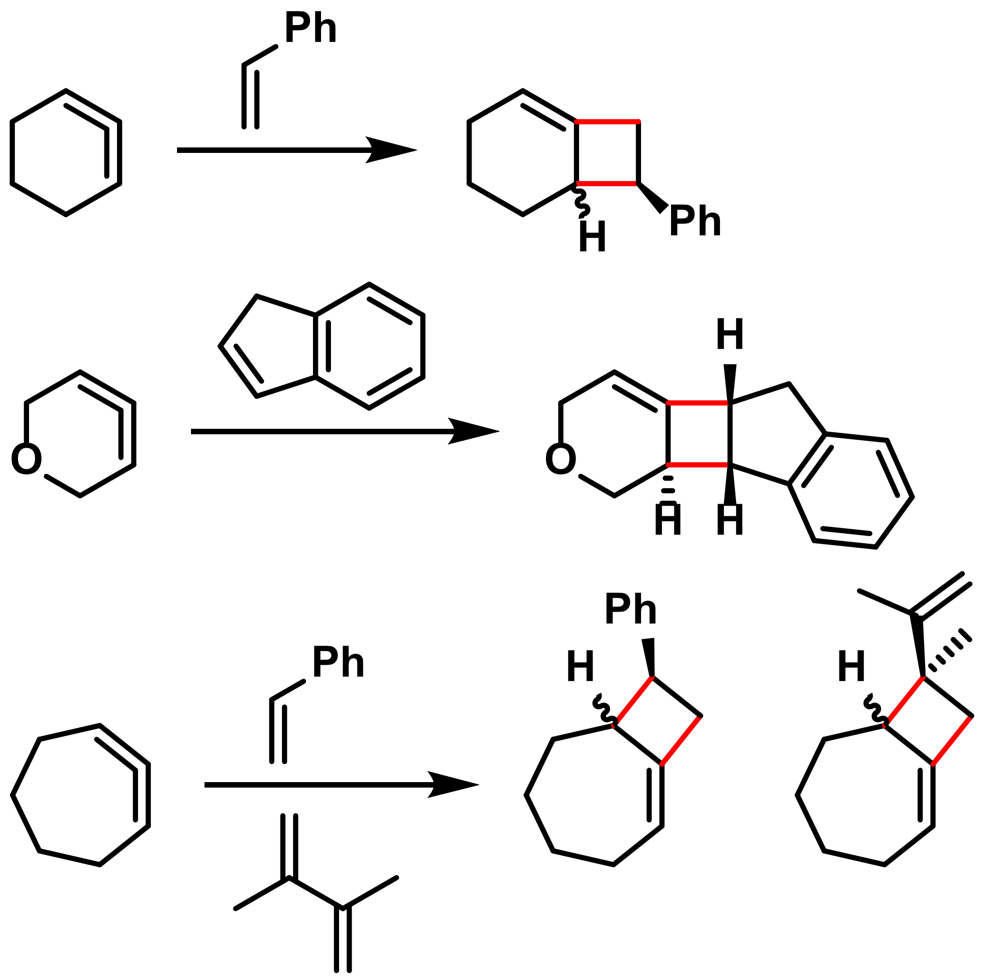


P1 P2

X	R	Ratio P1:P2	Isolated yield, %	
			P1	P2
	H	3.0:1	68	14
	Br	3.6:1	70	17
	Me	3.7:1	67	16
	OMe	4.5:1	75	17
	H	2.0:1	60	24
	Br	2.0:1	57	27
	Me	2.0:1	59	27
	OMe	2.0:1	65	21

Efrimova, M. M. et. al. *Org. Biomol. Chem.* **2021**, *19,* 9773–9784.

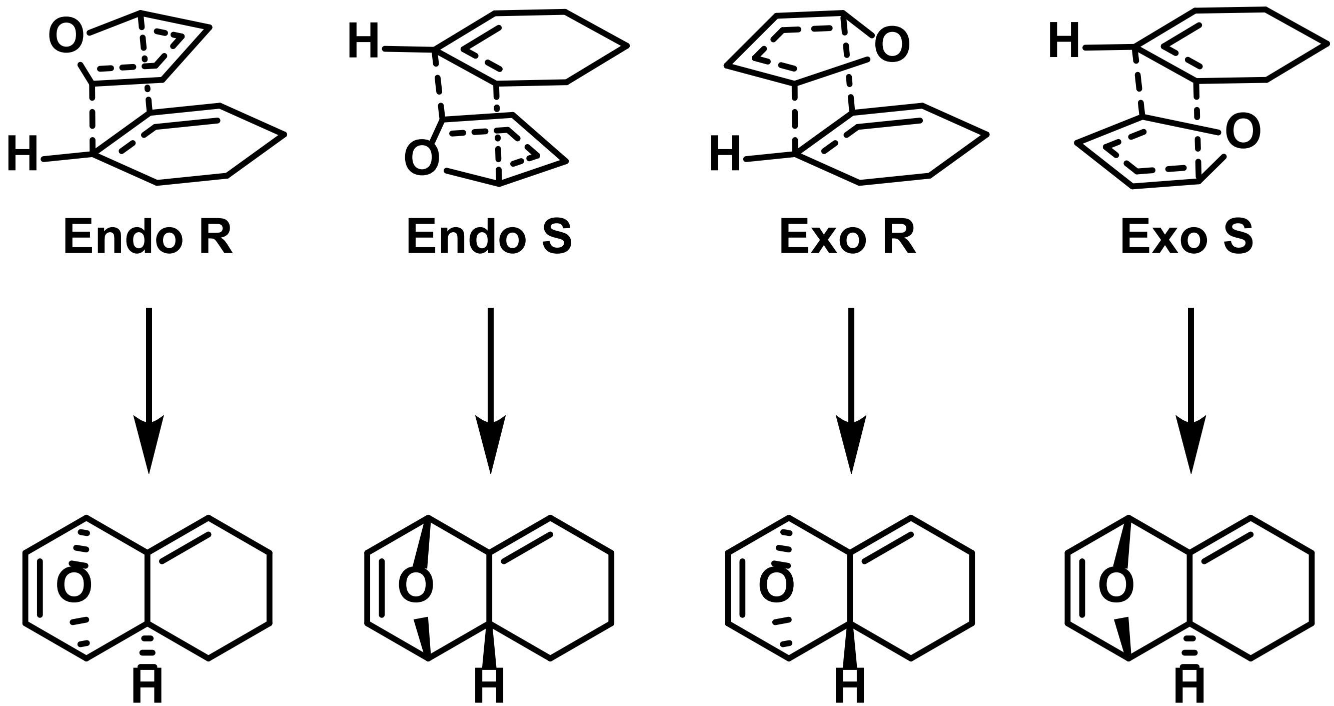
[2+2] Cycloaddition



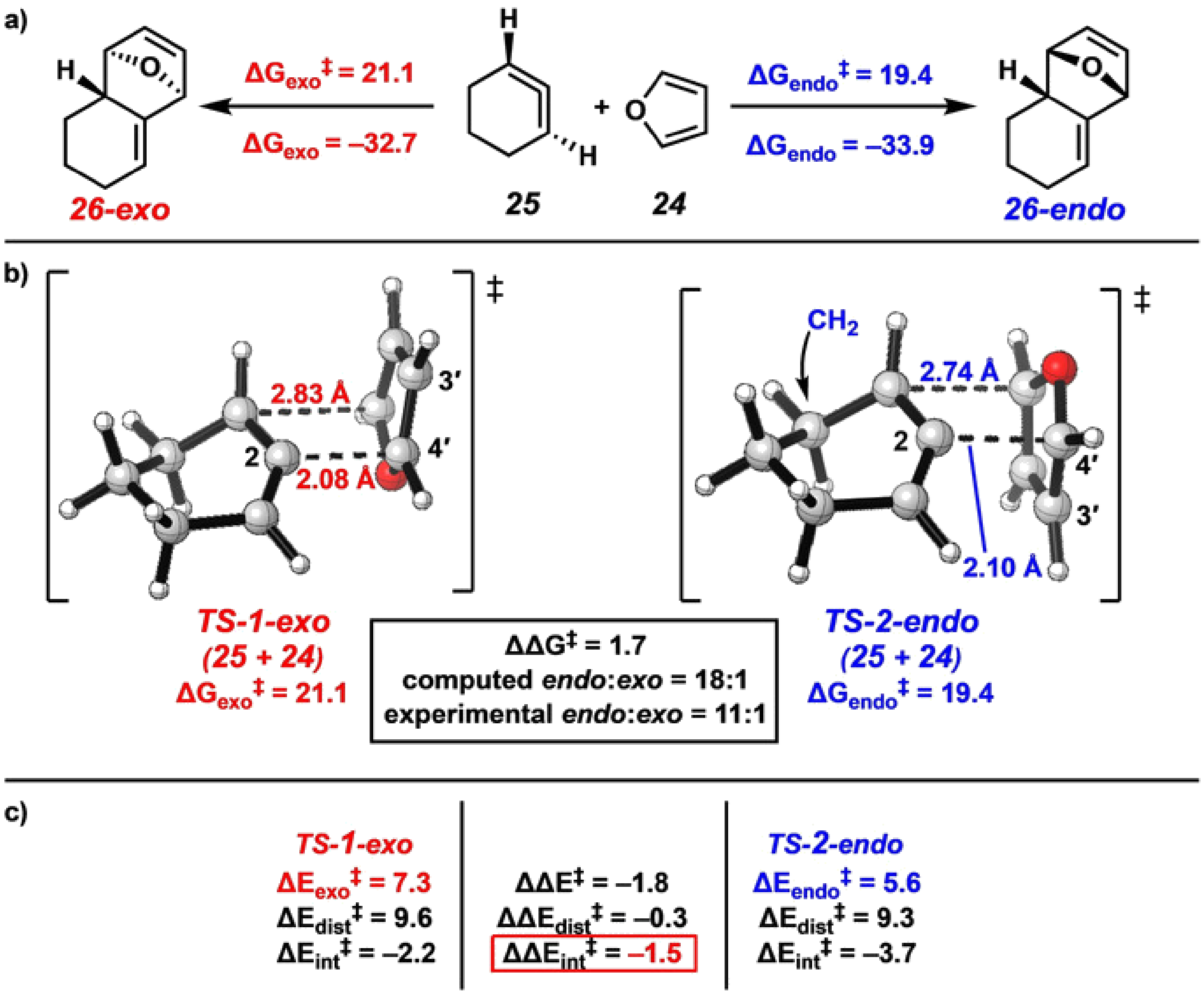
Yamano, M. M. et. al. *Angew. Chem. Int. Ed.* **2019,** *58,* 5653–5657.

Almehmadi, Y. A.; West, F. G.; *Org. Lett.* **2020**, *22,* 6091−6095.

Stereoselectivity

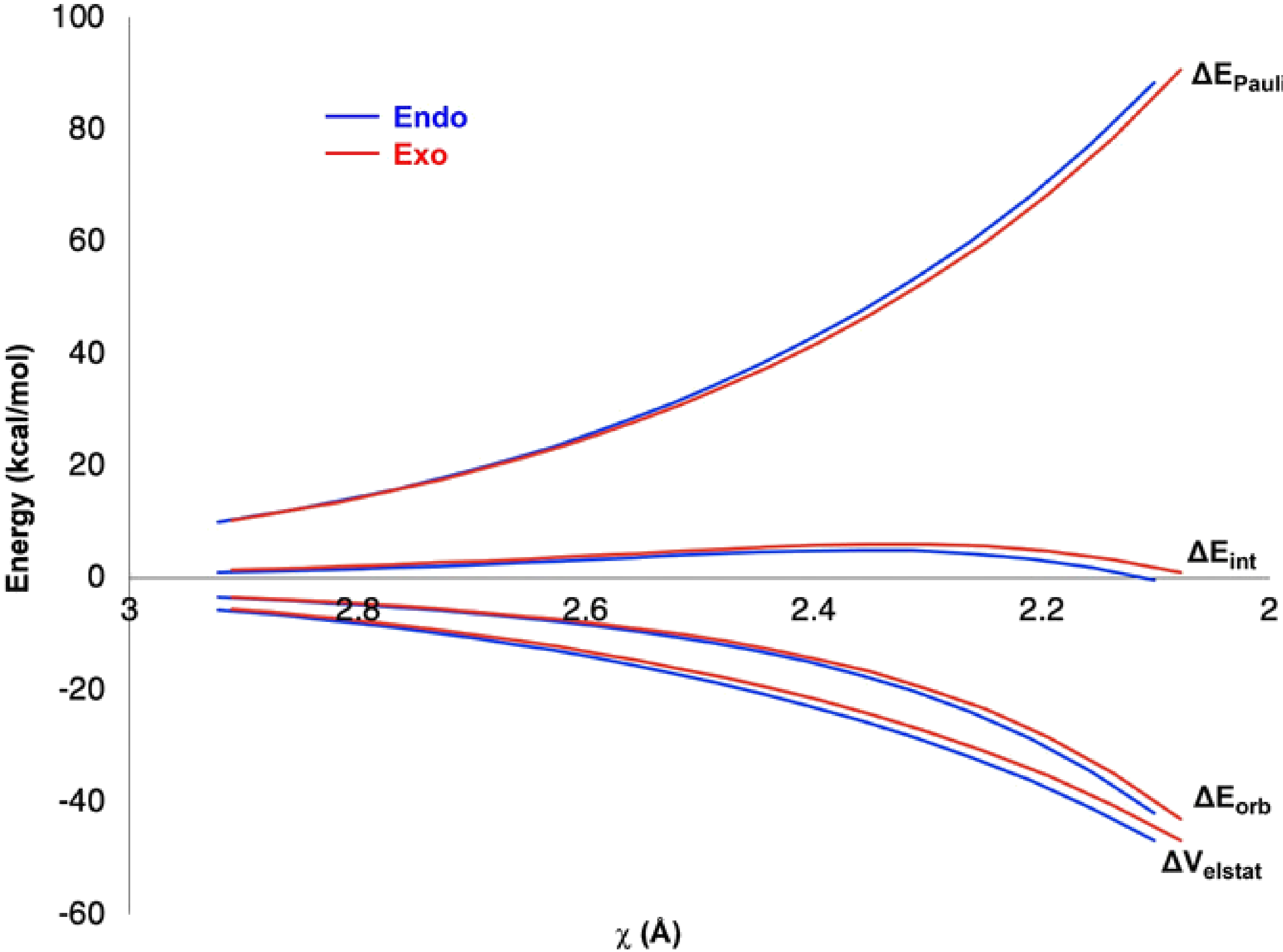


Theoretical Study of Stereoselectivity



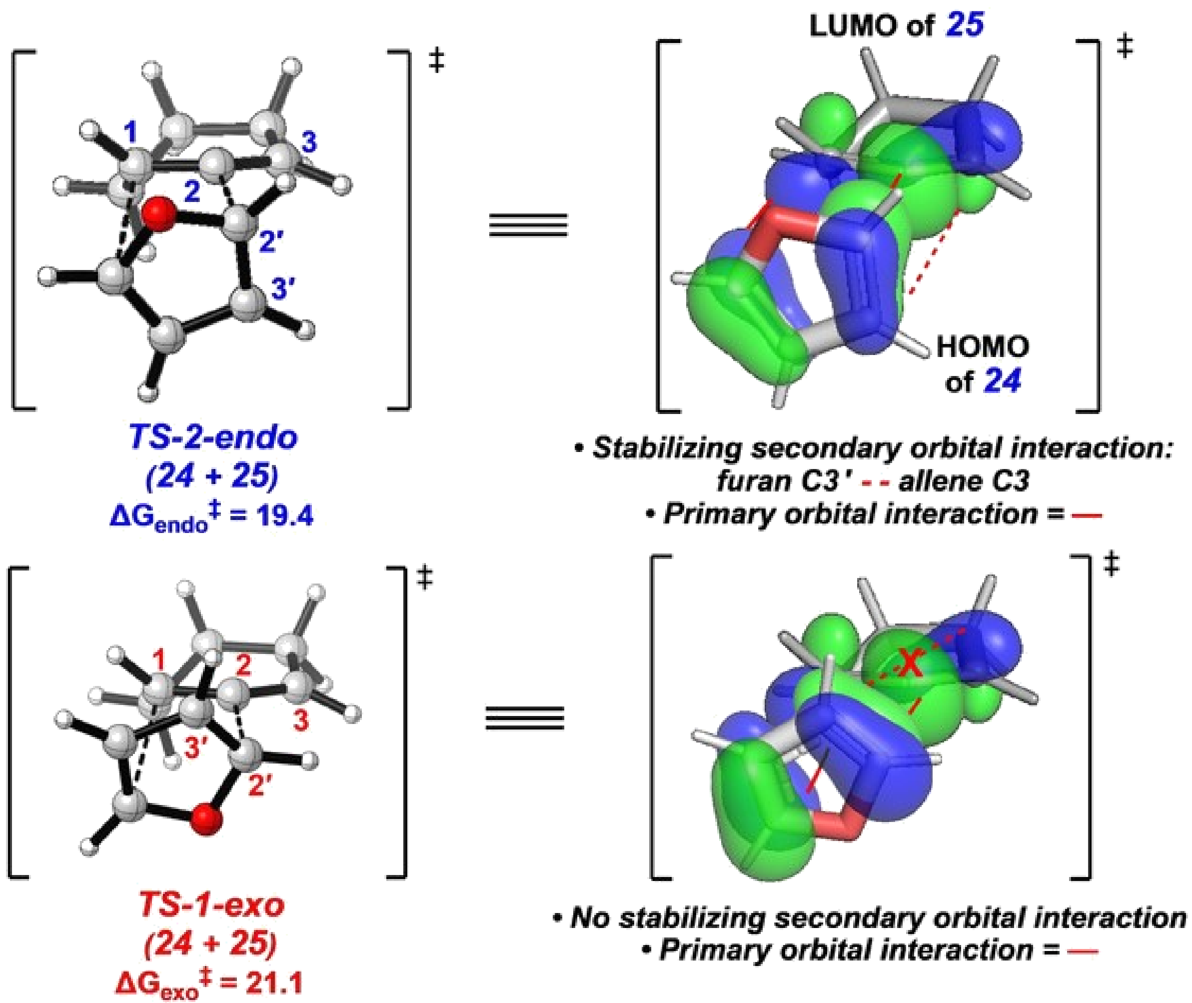
Ramirez. M. et. al. *Angew. Chem. Int. Ed.* **2021**, *60,* 14989–14997.

EDA Analysis



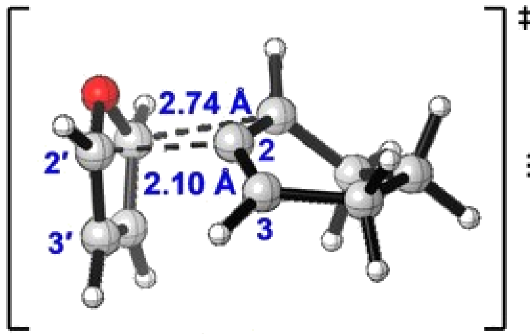
Ramirez. M. et. al. *Angew. Chem. Int. Ed.* **2021**, *60,* 14989–14997.

TS and MO Models

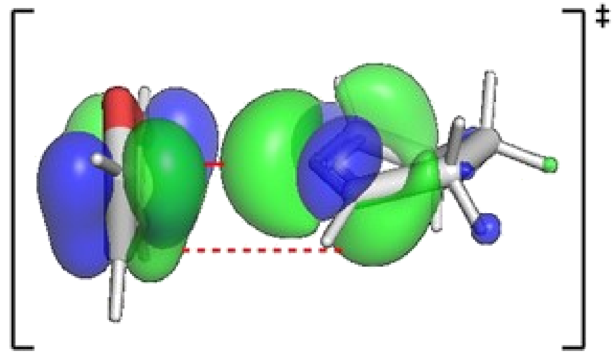


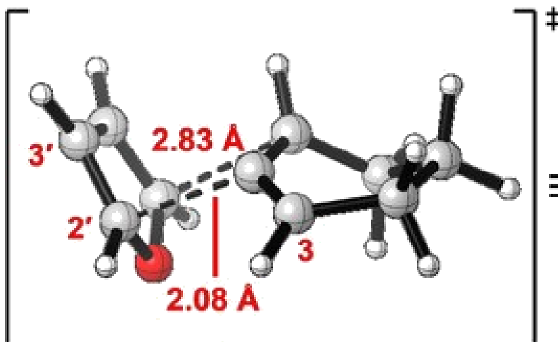
Ramirez. M. et. al. *Angew. Chem. Int. Ed.* **2021**, *60,* 14989–14997.

TS and MO Models

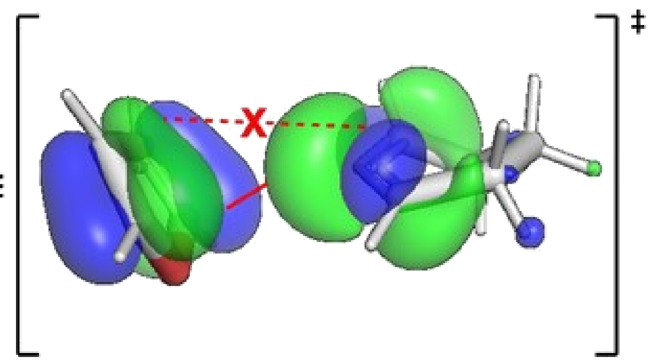


TS-2-endo
(24 + 25)
$\Delta G_{endo}^{\ddagger} = 19.4$



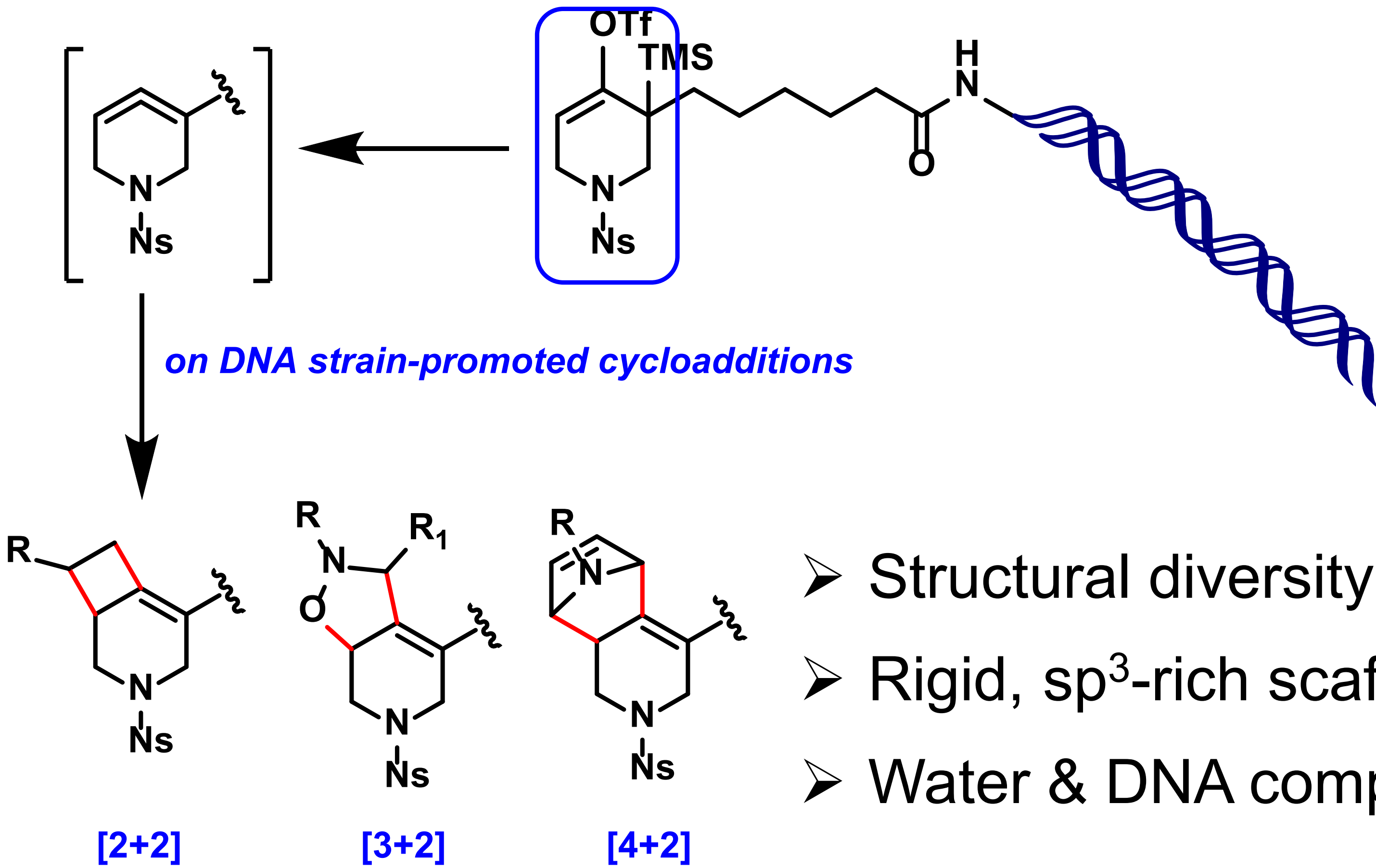


TS-1-exo
(24 + 25)
$\Delta G_{exo}^{\ddagger} = 21.1$



Ramirez. M. et. al. *Angew. Chem. Int. Ed.* **2021**, *60,* 14989–14997.

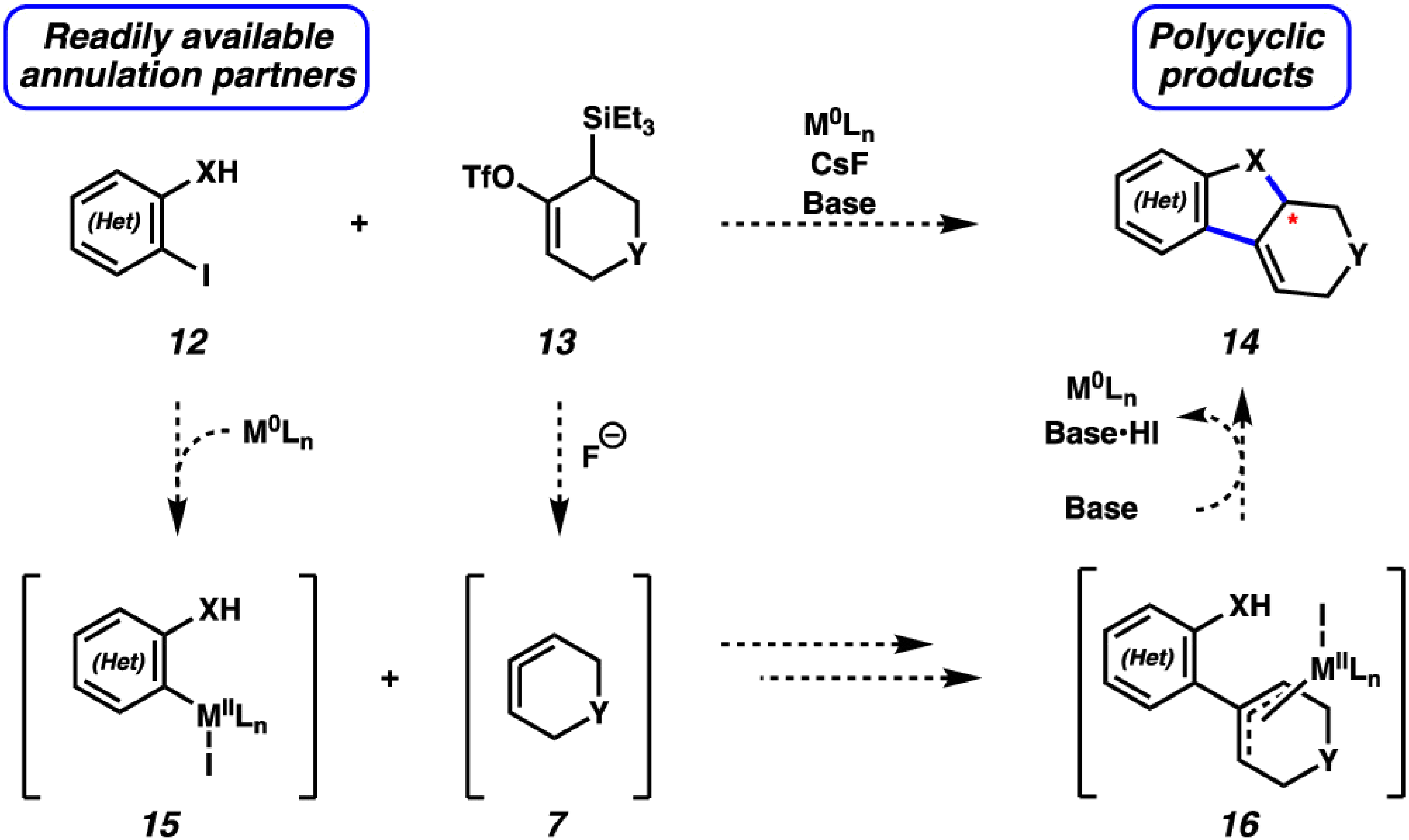
DNA-Encoded Library Synthesis



- Structural diversity
- Rigid, sp^3-rich scaffolds
- Water & DNA compatible

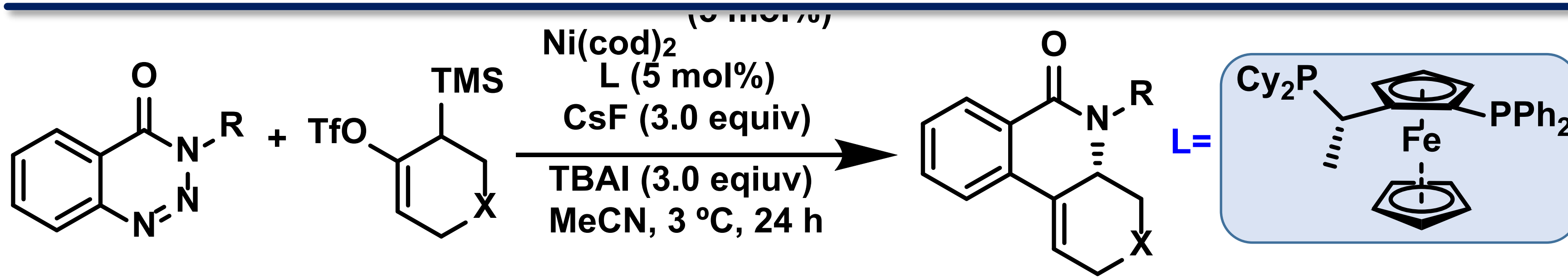
Westphal, M. V. et. al. *J. Am. Chem. Soc.* **2020**, *142*, 7776−7782.

Metal Catalyzed Reaction



Kelleghan, A. V. et. al. *J. Am. Chem. Soc*. **2021**, *143,* 9338−9342.

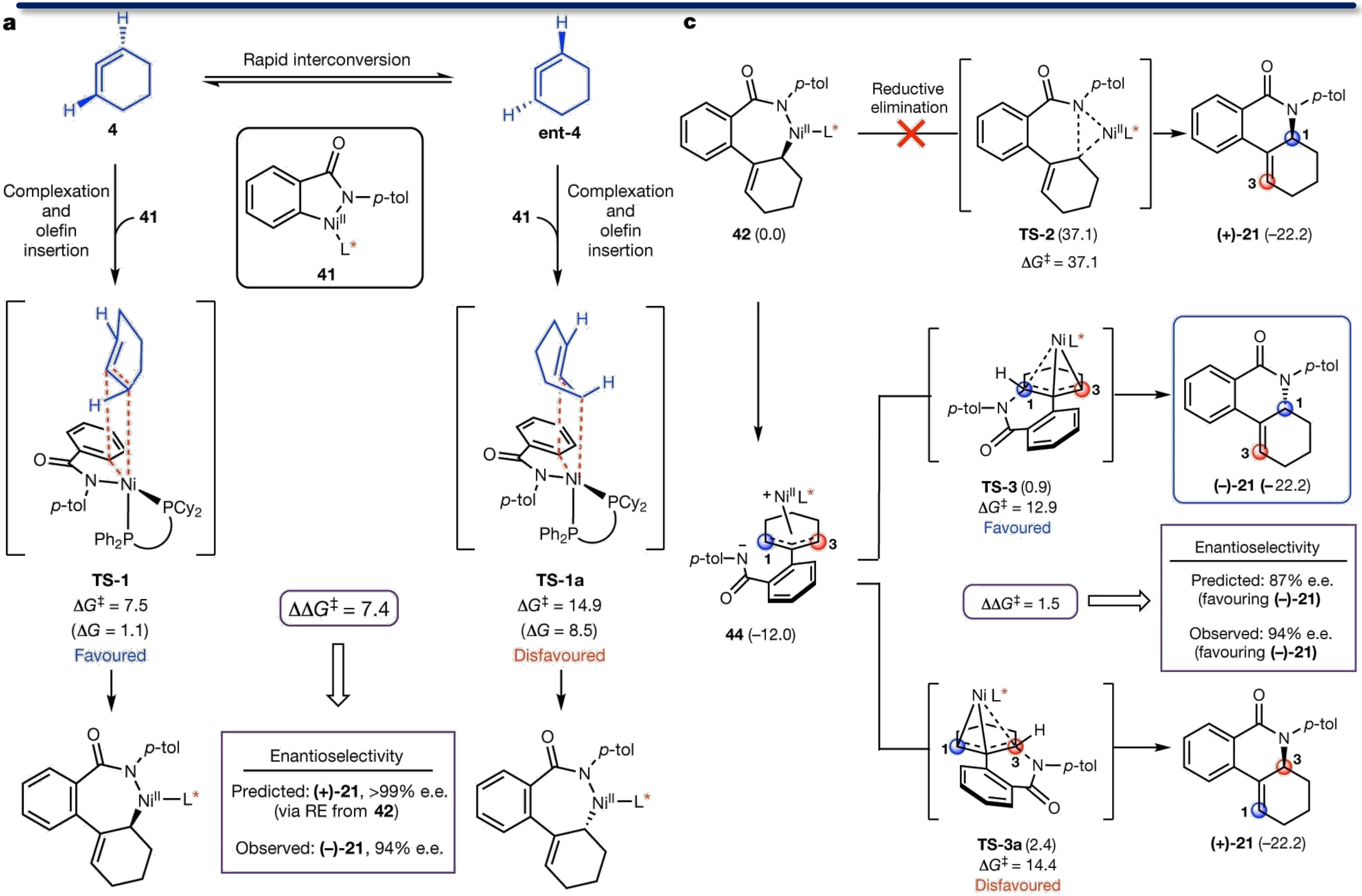
Ni Catalyzed Reaction



Entry	R	X	Yield (%)	e.e. (%)
1	*p*-tol	CH_2	85	94
2	Ph	CH_2	81	92
3	4-F-C_6H_4	CH_2	71	91
4	Me	CH_2	78	88
5	PMP	CH_2	72	94
6	Bn	CH_2	73	81
7	*p*-tol	NBoc	70	81
8	*p*-tol	NCbz	63	81
9	*p*-tol	O	84	81
10	Bn	NBoc	66	84

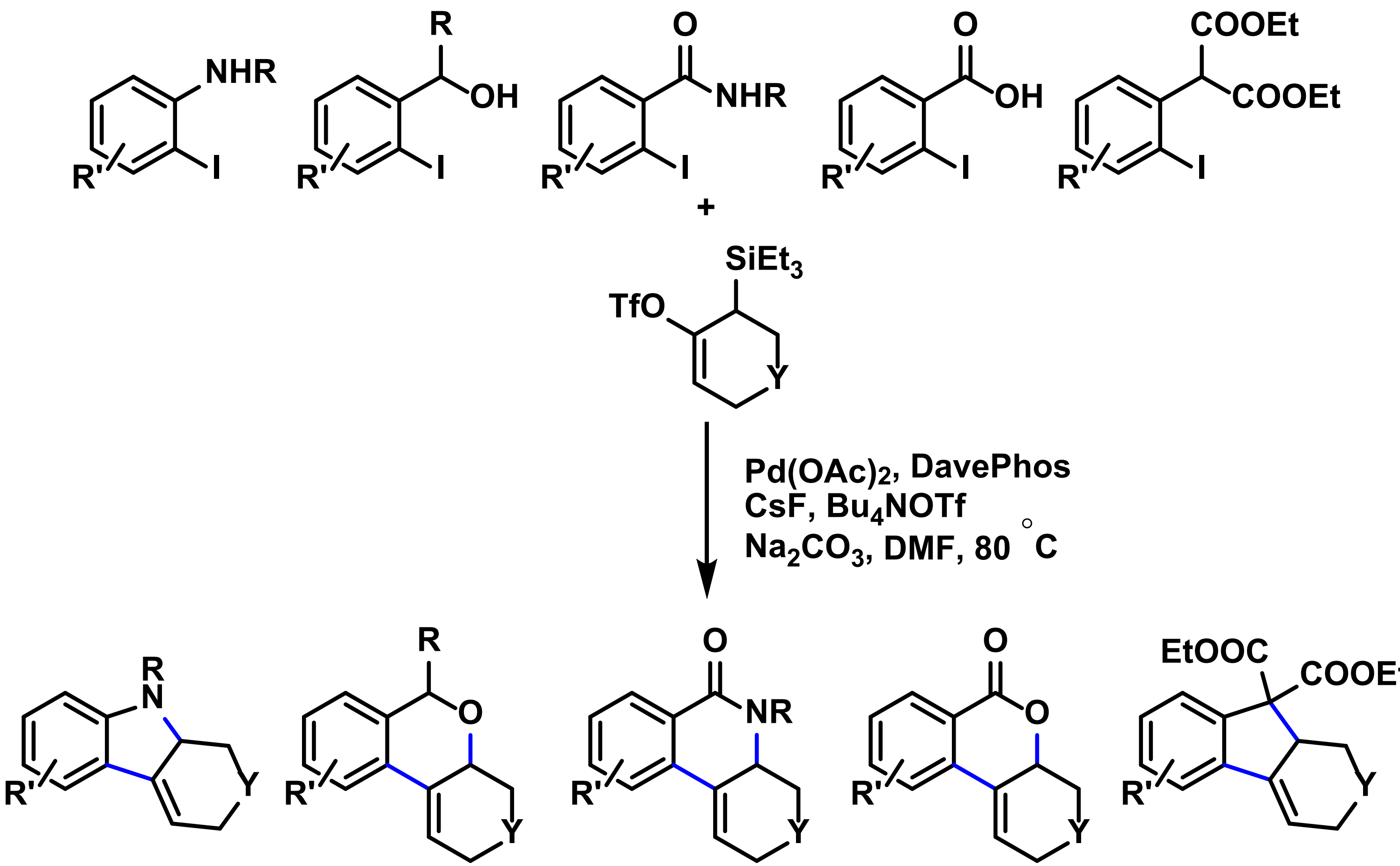
Yamano, M. M. et. al. *Nature* **2020,** *586,* 242−247.

Ni Catalyzed Mechanism



Yamano, M. M. et. al. *Nature* **2020,** *586,* 242−247.

Pd Catalyzed Reaction



Kelleghan, A. V. et. al. *J. Am. Chem. Soc*. **2021***, 143,* 9338−9342.

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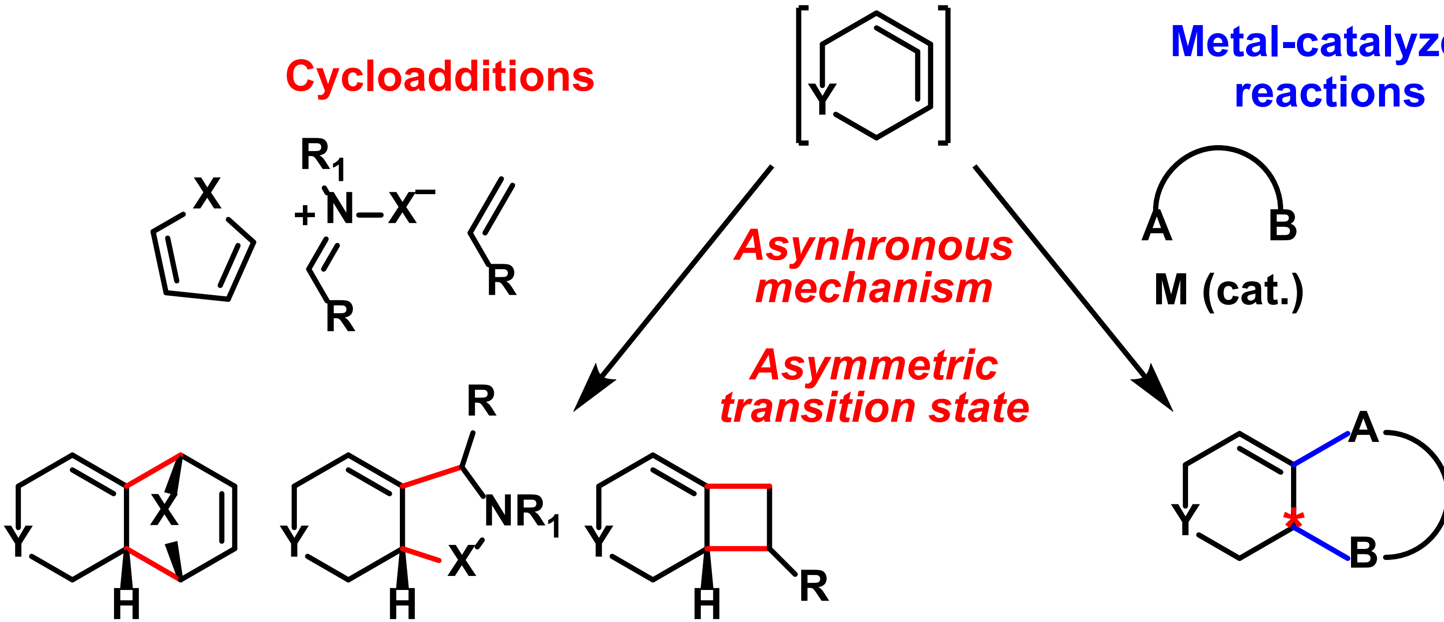

Regioselective
Stereoselective

Enantioriched
Polycyclic scaffolds