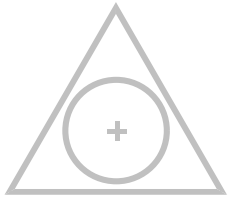
Cyclopropenium Ions in Catalysis

2024.4.13 Literature Seminar

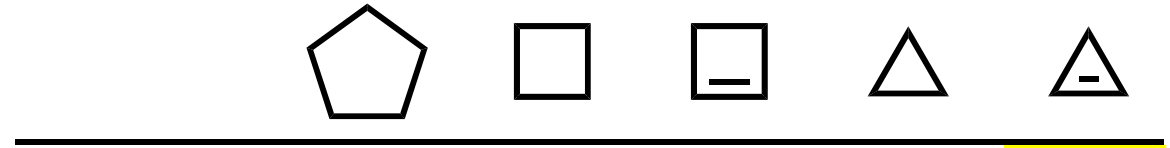
M2 Shuji Toyama

Contents

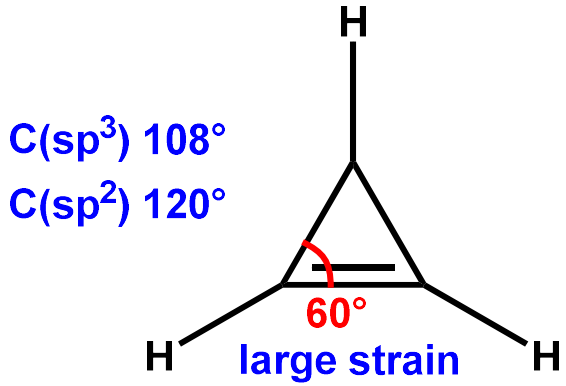


Characteristic of Cyclopropenium Ions

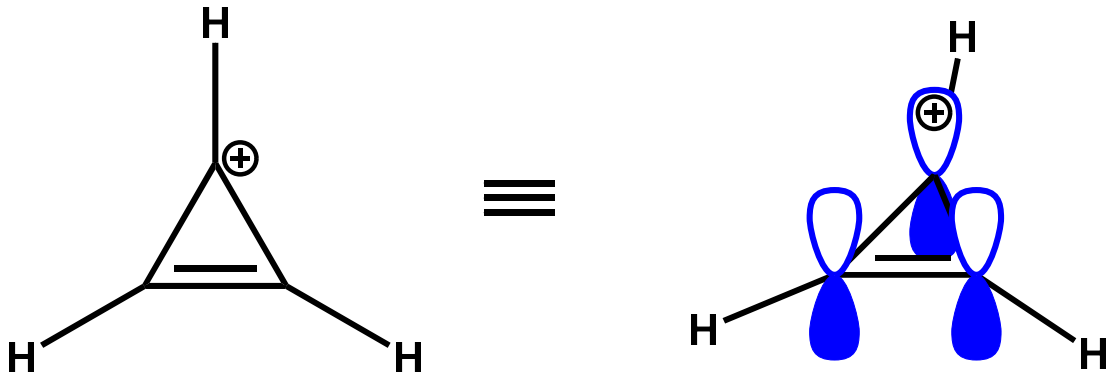
■ Ring strain of cyclopropene



strain energy[1] (kcal/mol)	6.2	26.5	28.7	27.5	55.2



■ Aromaticity of cyclopropenium ion



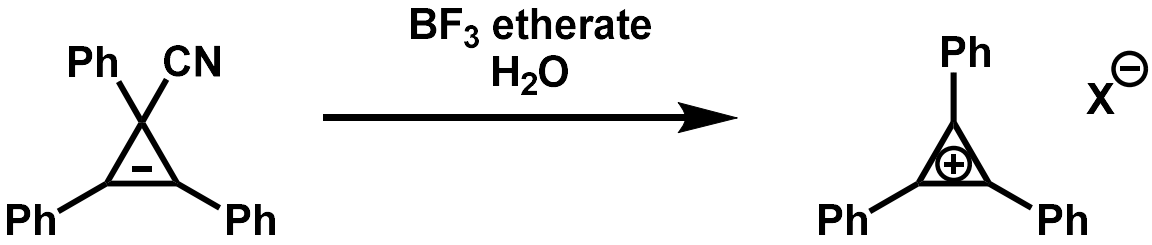
2 π electrons

Cyclopropenium ion satisfies Hükel's rules of aromaticity.
$(4n + 2)\pi$, n = 0, 1, 2, …

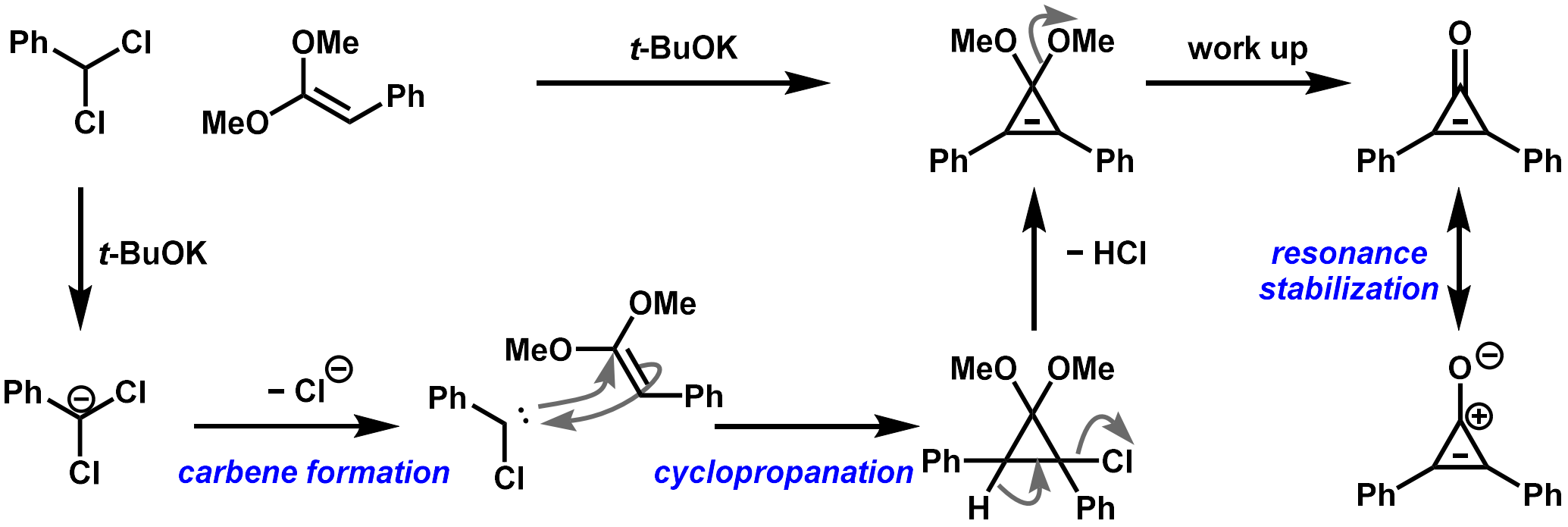
1) Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312.

Discovery of Cyclopropenium Ions

- The first synthesis of cyclopropenium ion was achieved by Breslow (1957).



- Cyclopropenone was also synthesized by Breslow (1959).



1) Breslow, R. *J. Am. Chem. Soc.* **1957**, 79, 5318.
2) Breslow, R.; Haynie, R.; Mirra J. *J. Am. Chem. Soc.* **1959**, *81*, 247.

Introduction of Authors

Prof. Tristan H. Lambert

1998 B.S., @ The University of Wisconsin
2004 Ph.D., @ California Institute of Technology (Prof. MacMillan, D.)
2004- Postdoctoral fellow @ Memorial Sloan-Kettering Cancer Center (Prof. Danishefsky, S.)
2006- Postdoctoral fellow @ Columbia University
2011- Associate Professor @ Columbia University
2016- Professor @ Columbia University
2018- Professor @ Cornell University

Research topic: Intriguing chemical building blocks such as aromatic ions and their application to problems in the areas of catalysis, reaction design, and polymers

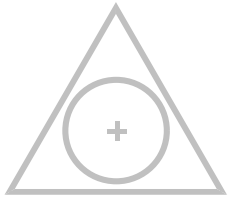
Prof. Ying-Yeung Yeung

2001 B.S., @ The Chinese University of Hong Kong (Prof. Chow, H.-F.)
2005 Ph.D., @ The Chinese University of Hong Kong (Prof. Chow, H.-F.)
2005- Postdoctoral fellow @ Harvard University (Prof. Corey, E. J.)
2008- Assistant Professor @ National University of Singapore
2014- Associate Professor @ National University of Singapore
2015- Assistant Professor @ The Chinese University of Hong Kong
2019- Professor @ The Chinese University of Hong Kong

Research topic: Organocatalysis, Asymmetric halogenation reactions, Multi-component synthesis and Novel functional molecules synthesis for biological studies

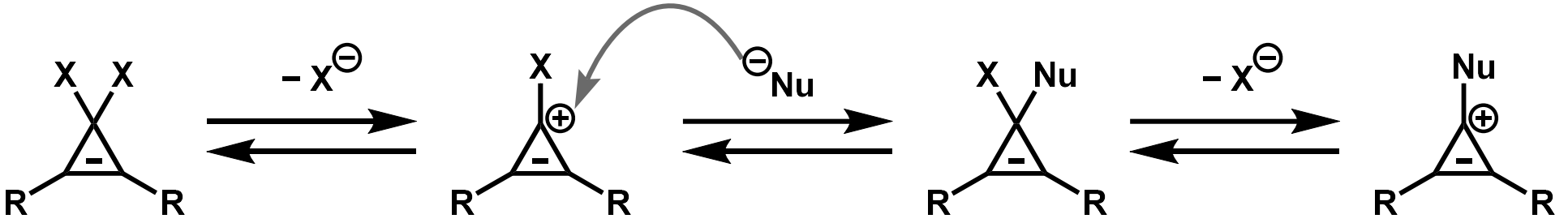
1) https://www.cyclopropenium.com/about-tristan
2) https://chem.cuhk.edu.hk/people/academic-staff/yyy/
3) https://academictree.org/chemistry/publications.php?pid=504805

Contents

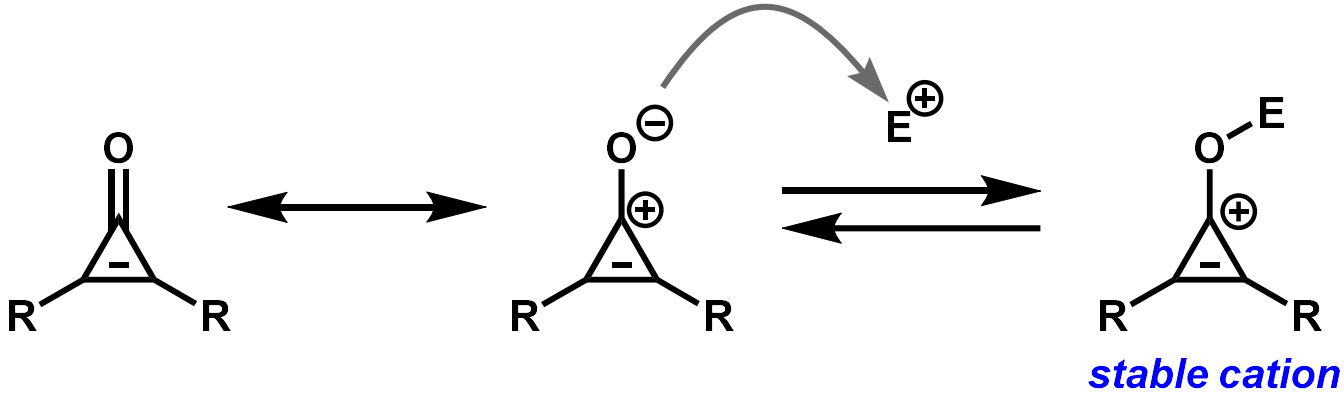


Design of Catalyst (1)

■ Nucleophilic substitution reaction promoted by stable cation

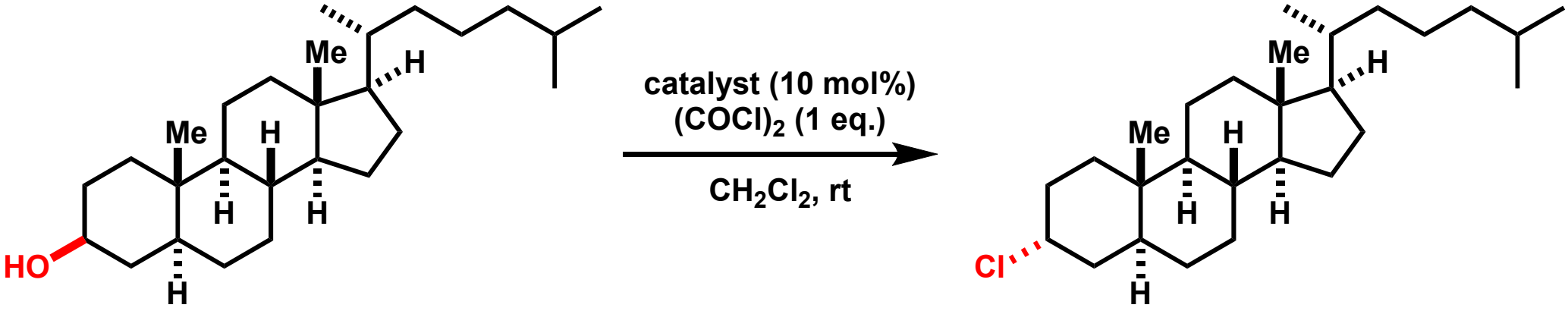


■ High nucleophilicity of carbonyl-*O* of cyclopropenone



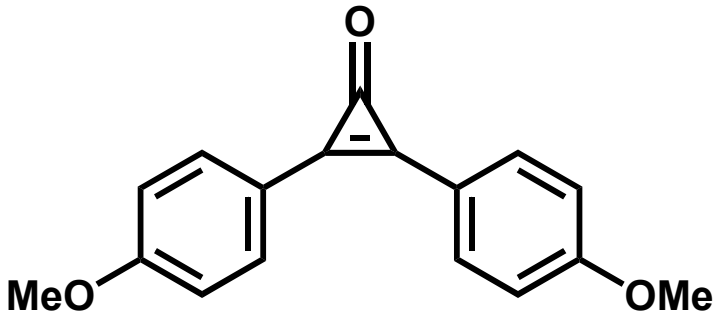
1) Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 12222.
2) Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, *55*, 3057.

Appel Type Chlorination



cholestanol

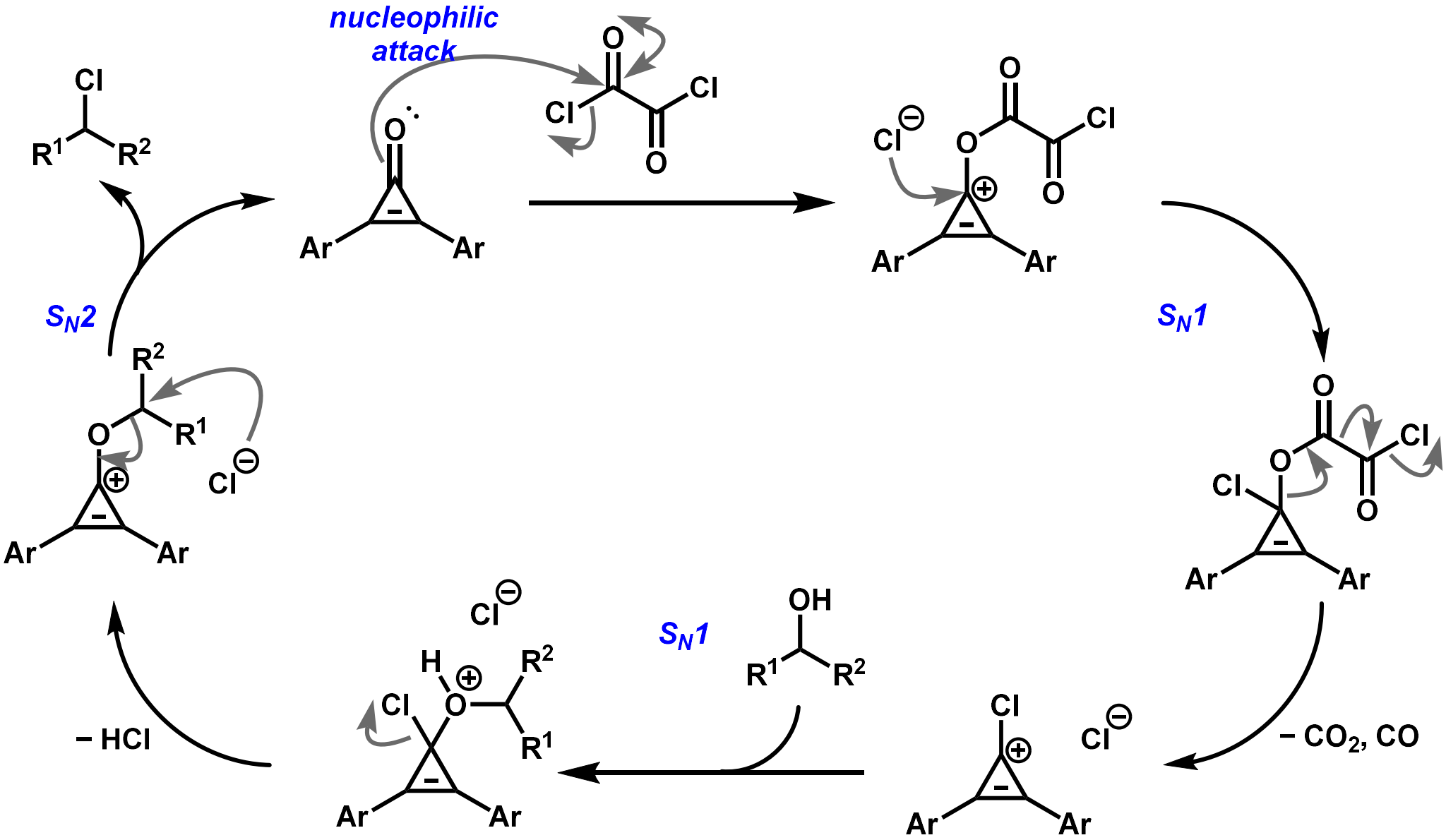
68%, dr > 98:2



catalyst

1) Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 12222.
2) Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, *55*, 3057.

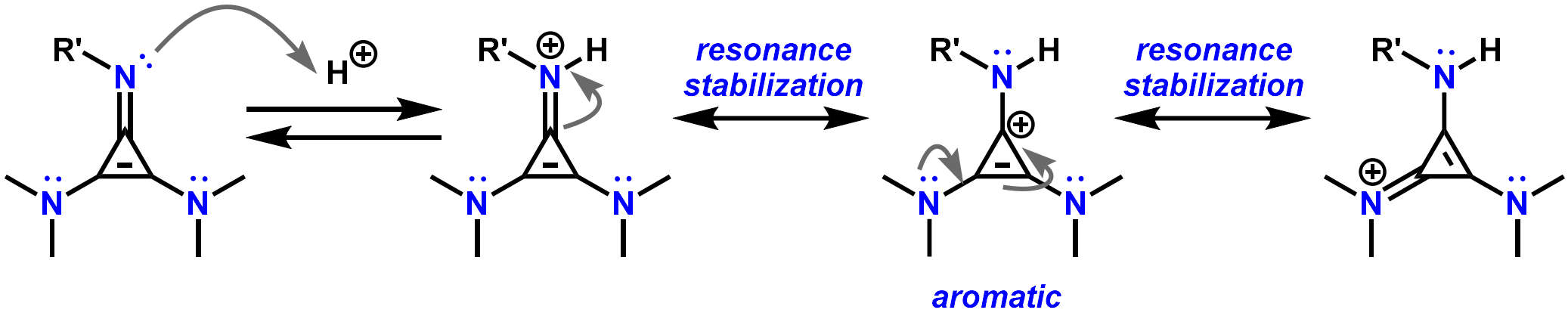
Proposed Reaction Mechanism

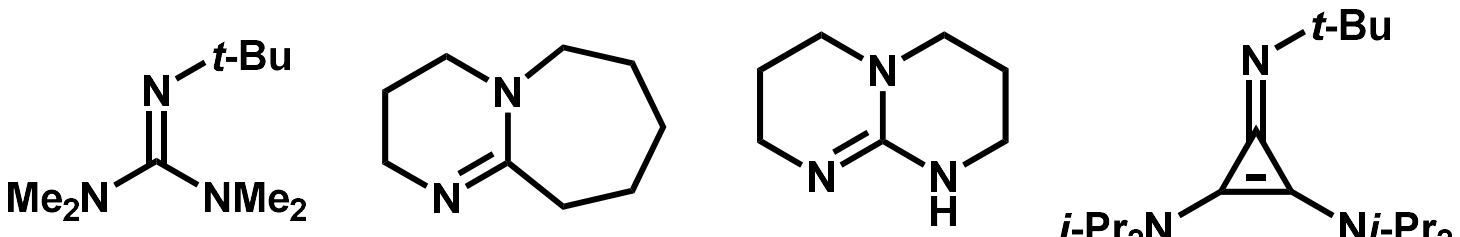


1) Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 12222.
2) Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, *55*, 3057.

Design of Catalyst (2)

■ **Stable cation of conjugate acid → Strong basicity**

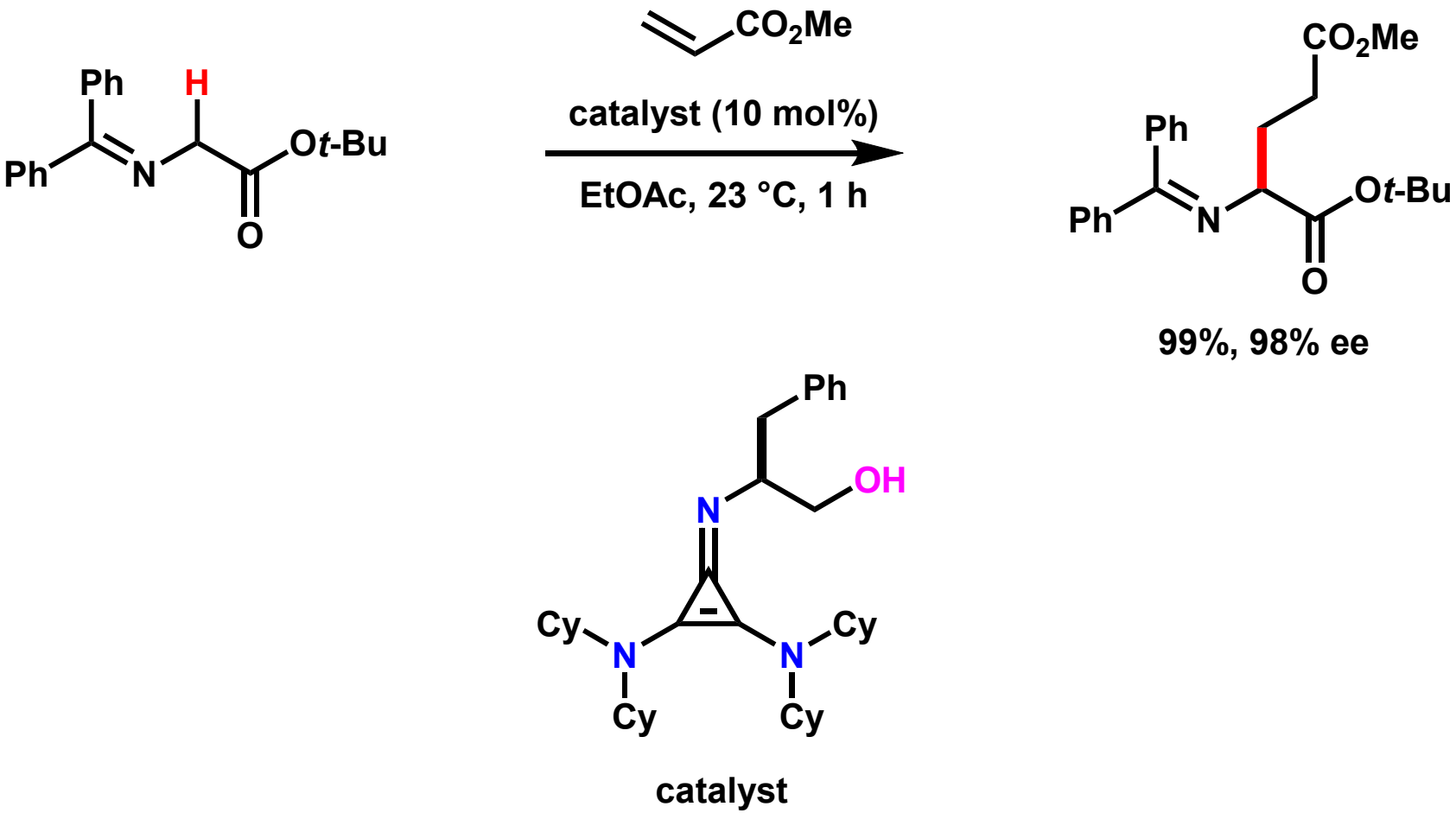




	BTMG	DBU	TBD	
pK_{BH+}	23.6	24.3	26.0	27.5

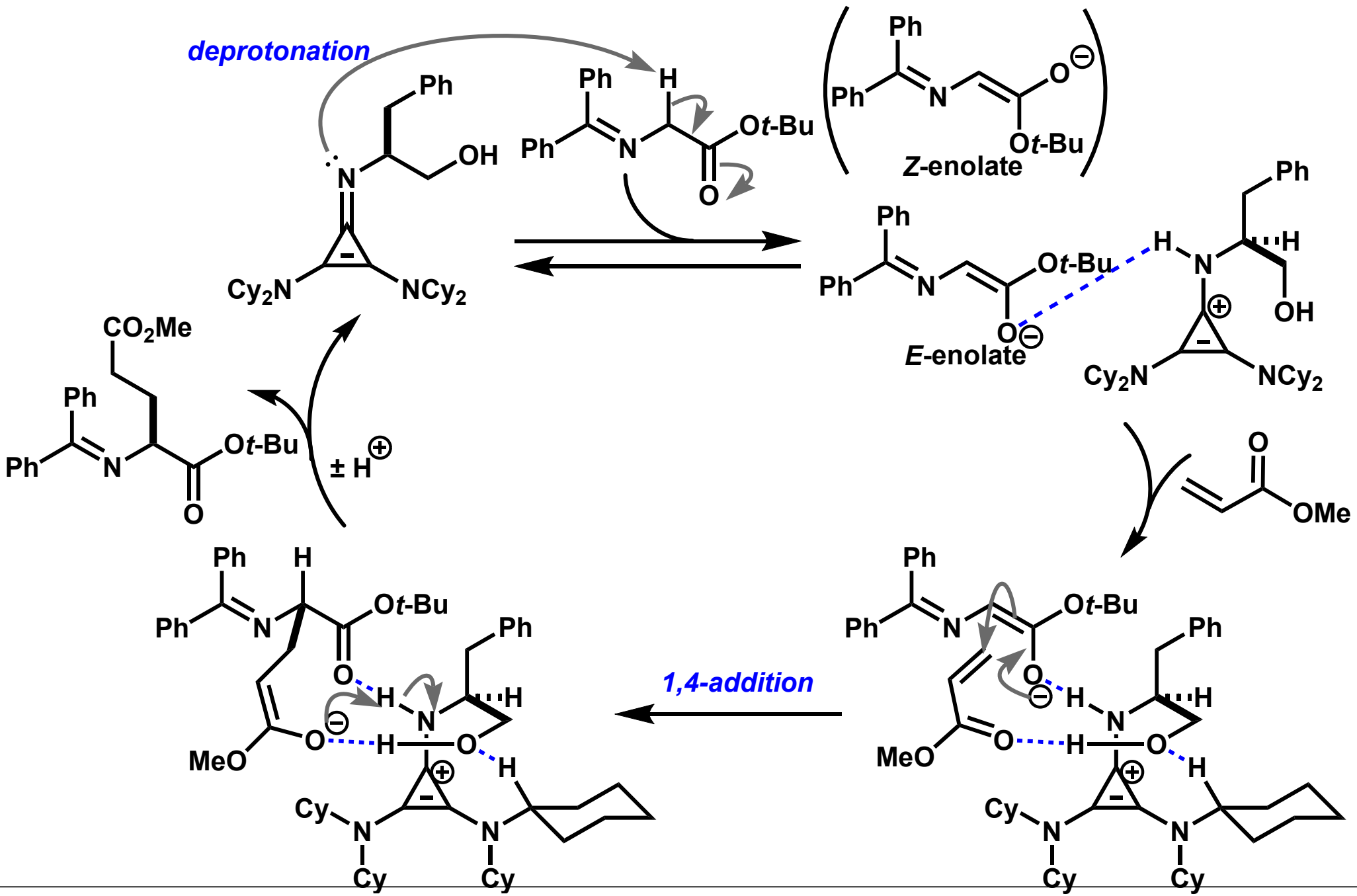
1) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
2) Bandar, J. S.; Barthelme, A.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537.

Asymmetric 1,4-Addition



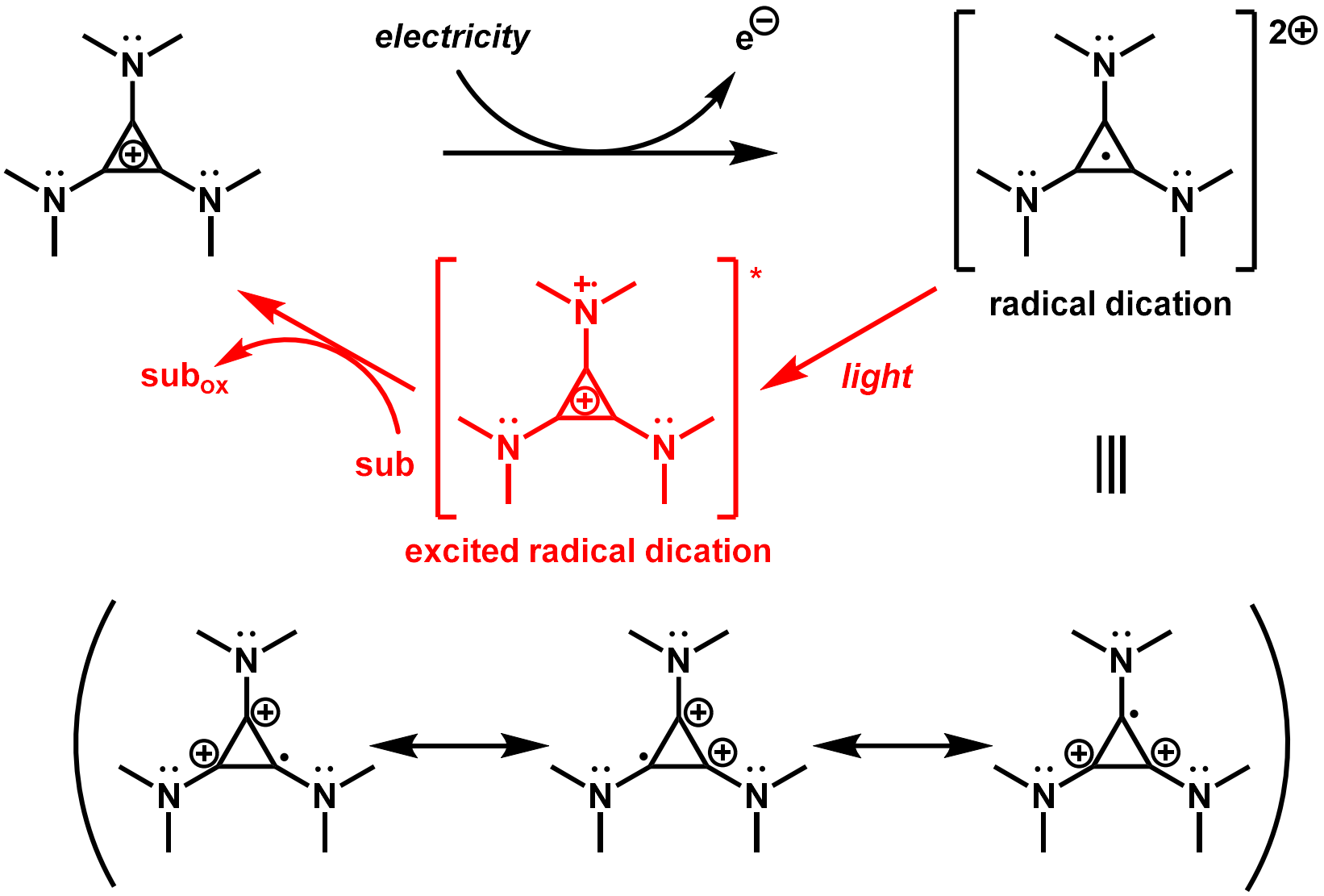
1) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
2) Bandar, J. S.; Barthelme, A.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537.

Proposed Reaction Mechanism



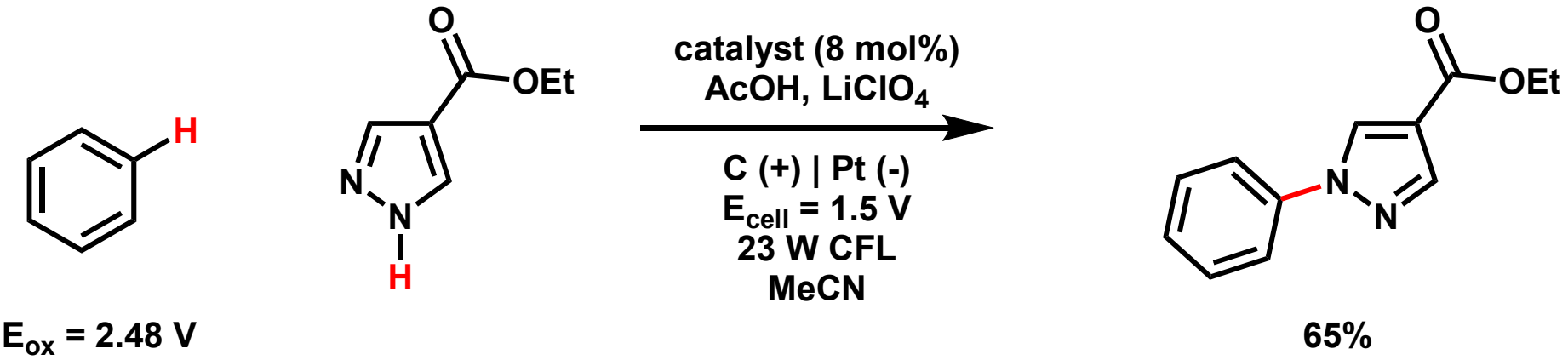
1) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
2) Bandar, J. S.; Barthelme, A.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537.

Design of Catalyst (3)



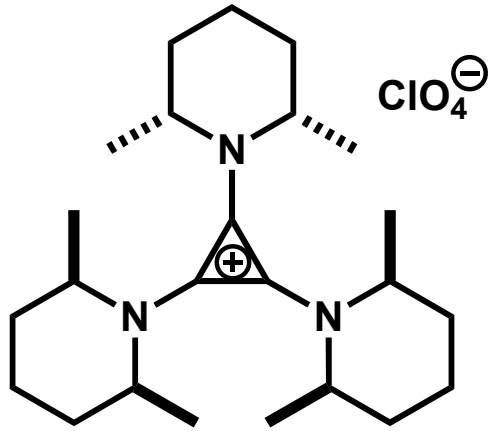
1) Weiss, R.; Klaus Sohloter, K. *Tetrahed. Lett.* **1975**, *40,* 3491.
2) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

Electrophotocatalytic Coupling



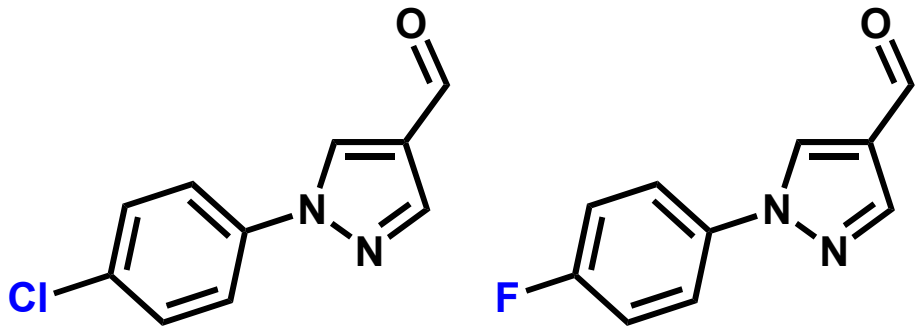
E_{ox} = 2.48 V

65%



catalyst

CFL: Compact Fluorescent Lamp

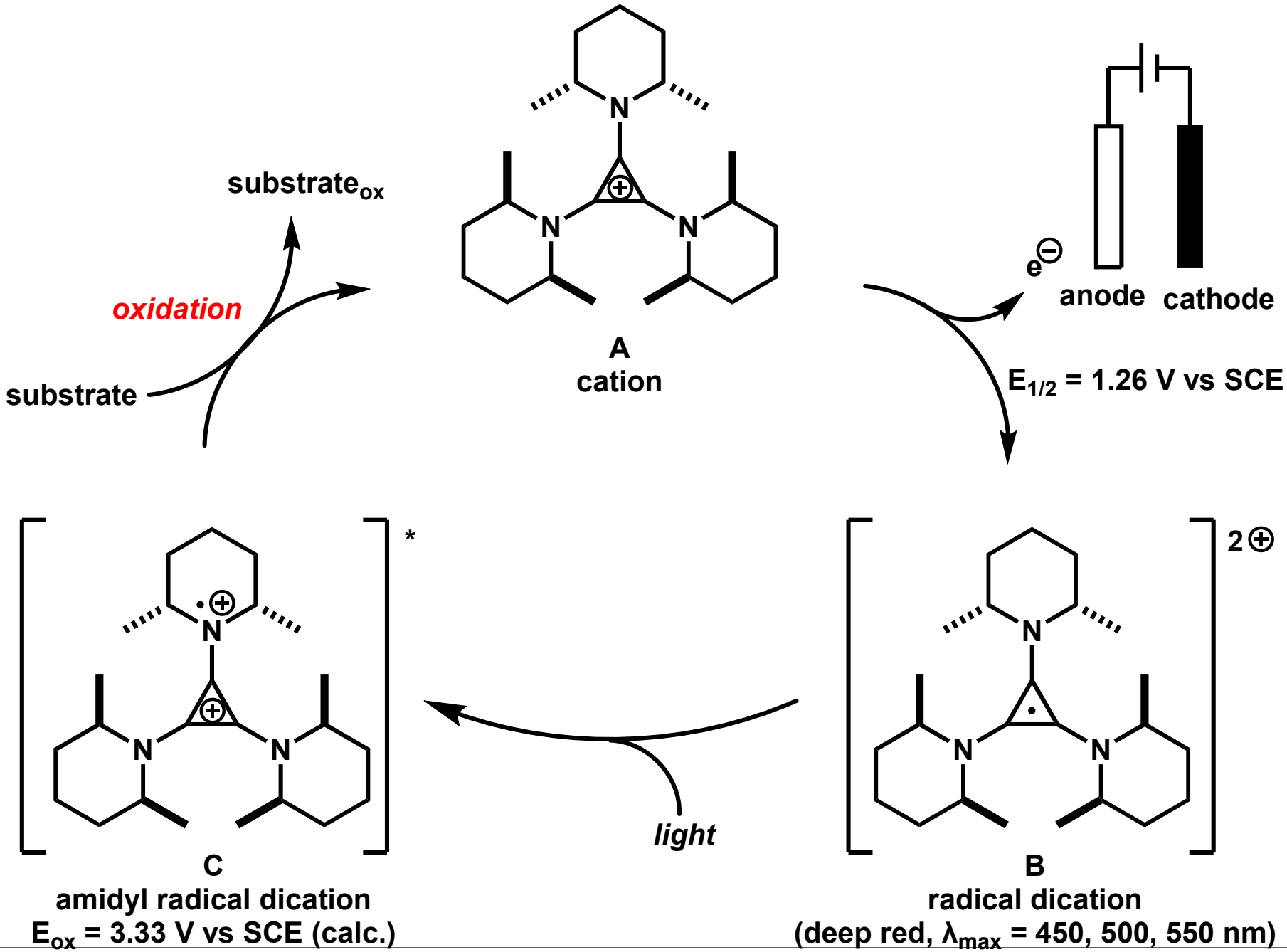


56%
p:*o*:*m* = 4:1:1

36%
p:*o*:*m* = 5:1:1

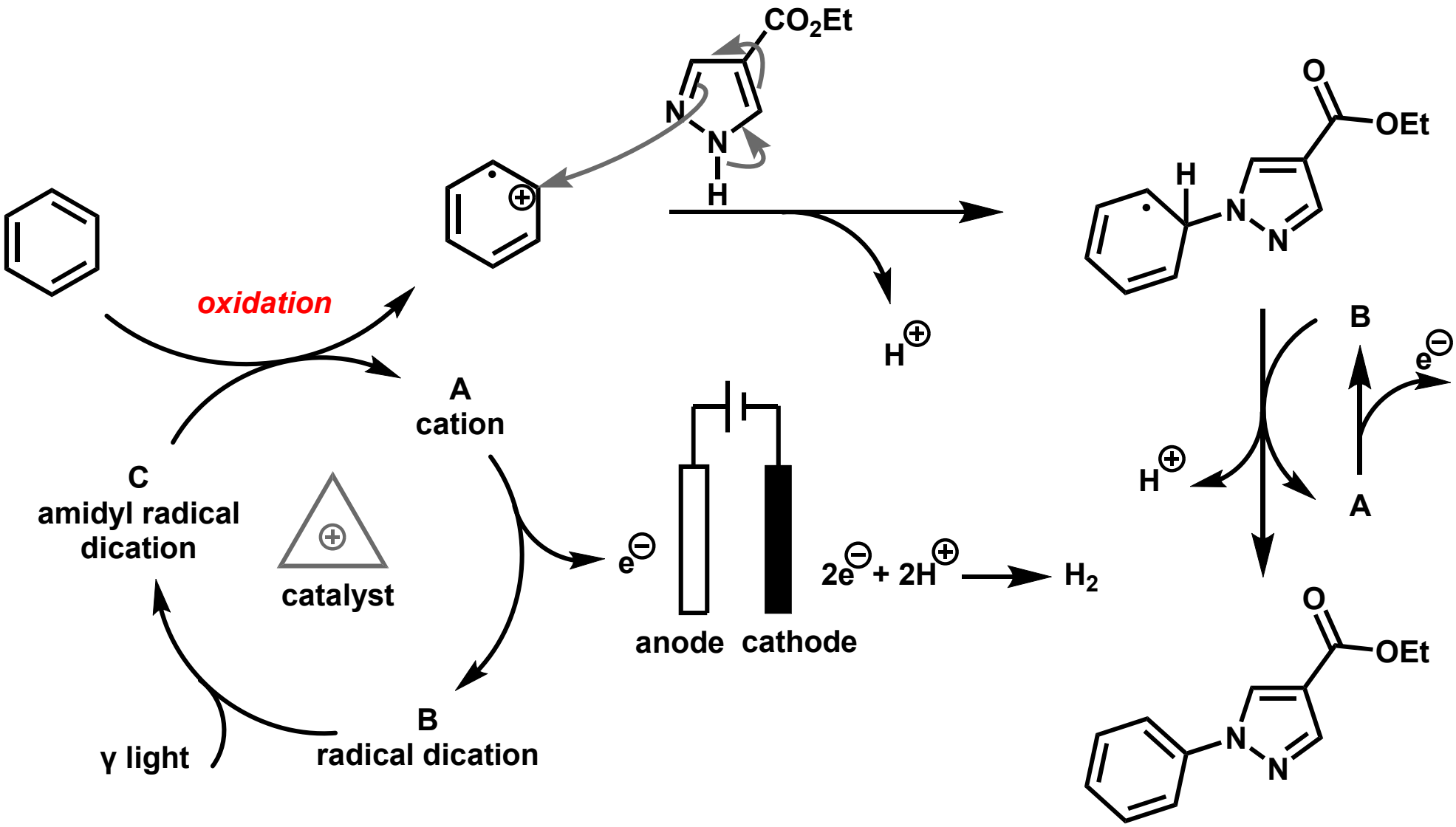
1) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

Proposed Reaction Mechanism (1)



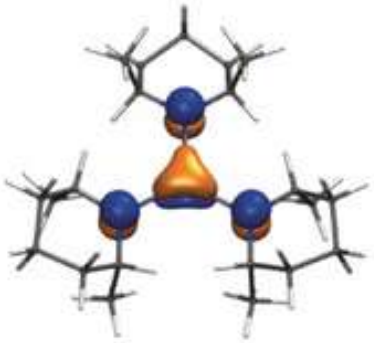
1) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

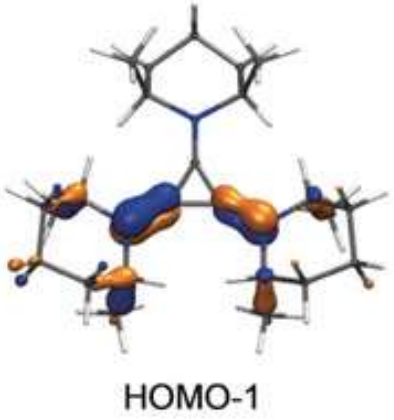
Proposed Reaction Mechanism (2)

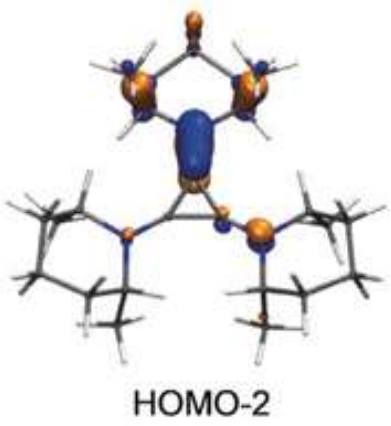


1) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

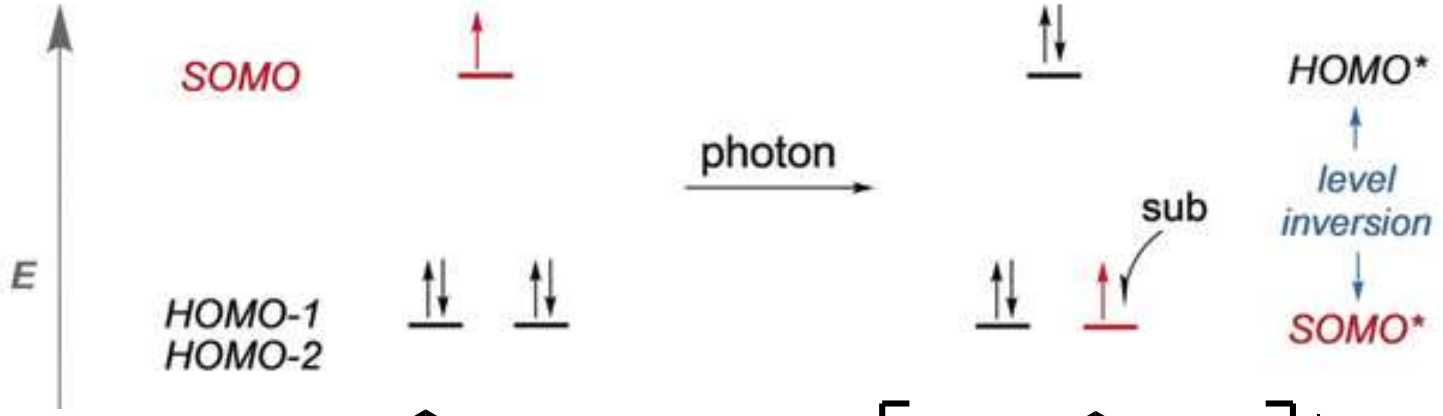
HOMO-SOMO Level Inversion

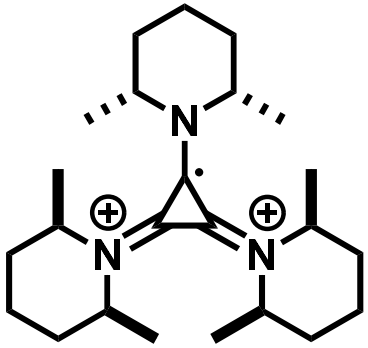




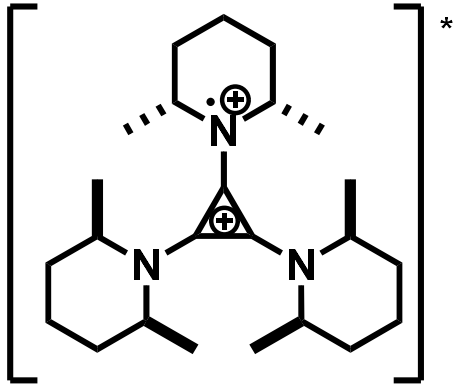


■ **The energy level of SOMO and HOMO**



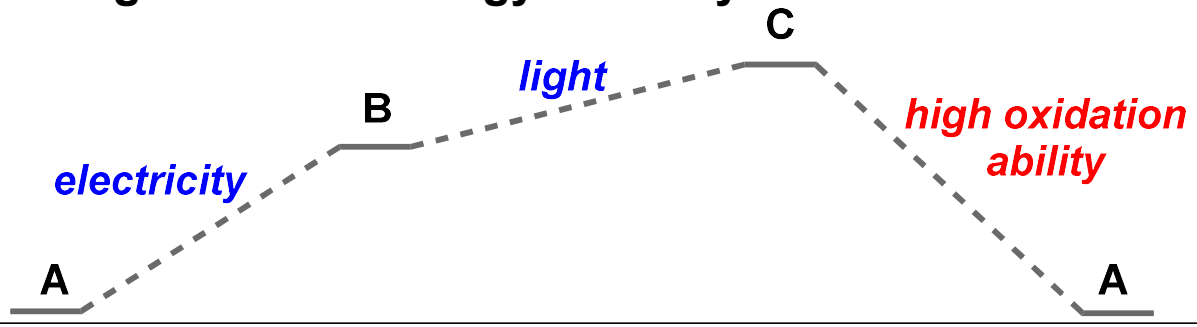


B
radical dication



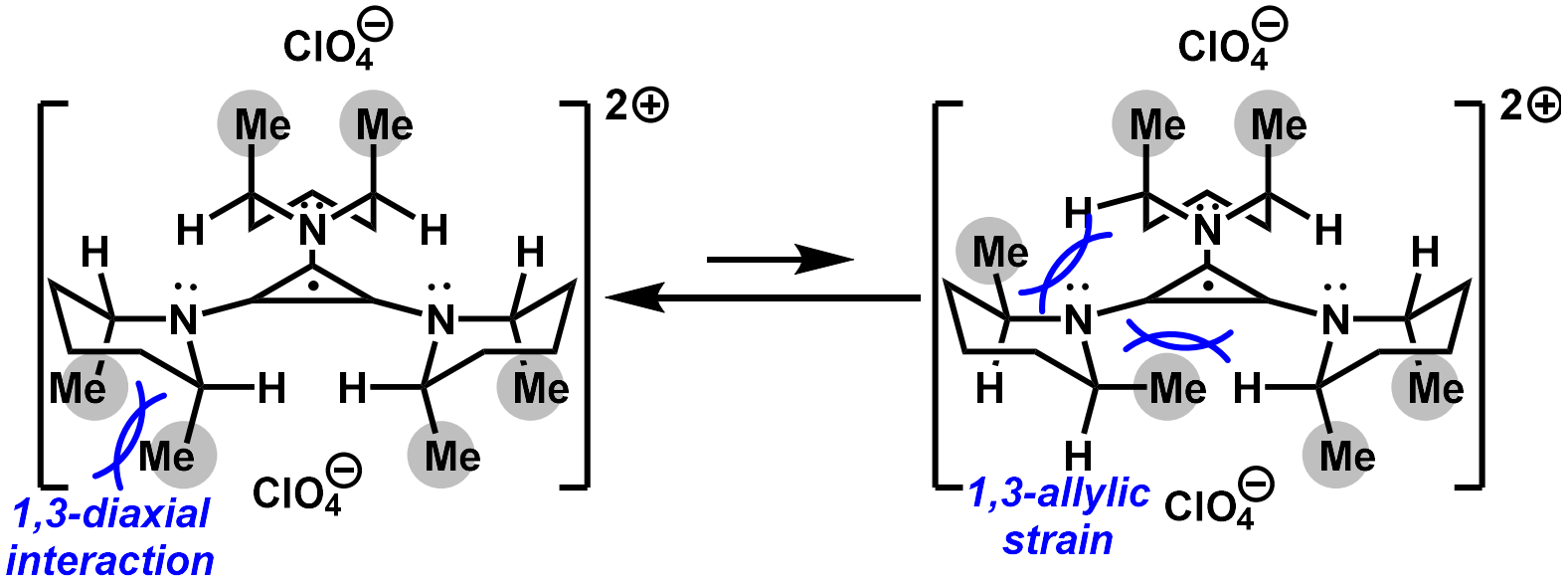
C
photoexcited radical dication

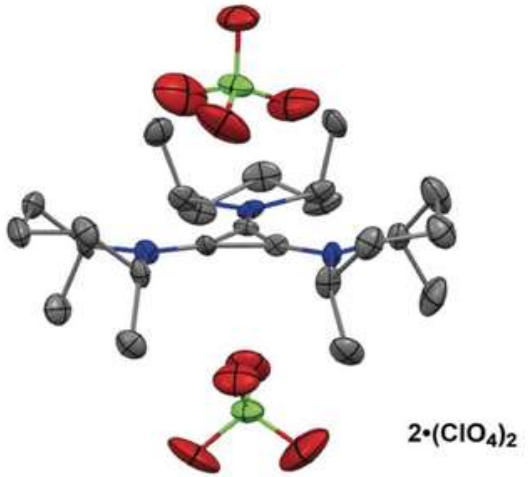
■ **Concise diagram of the energy of catalyst**



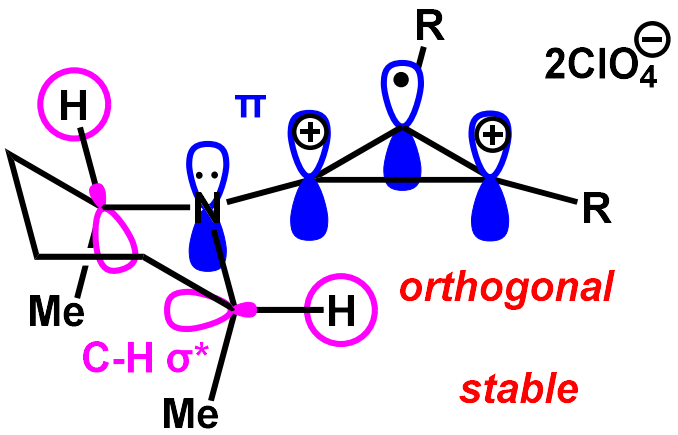
1) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

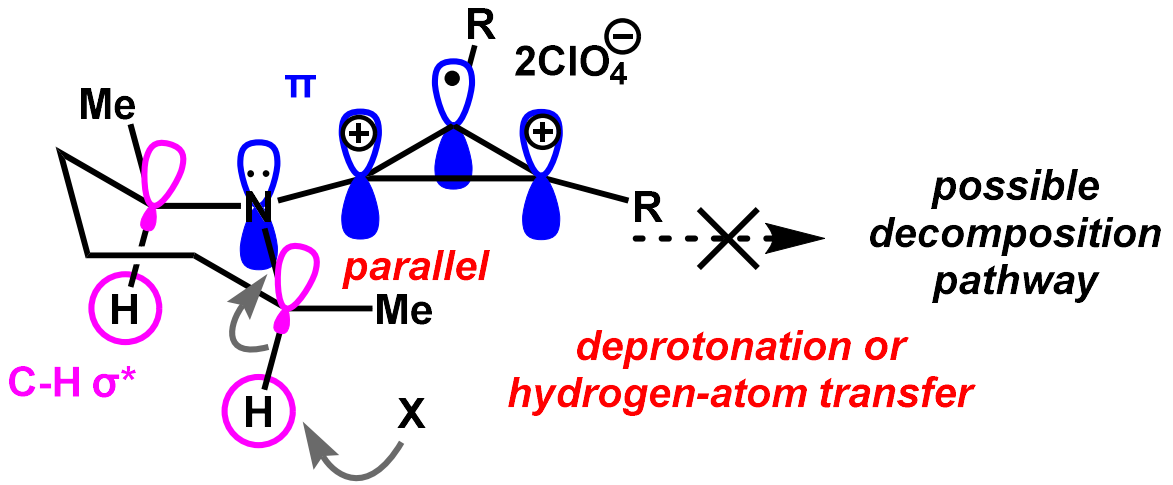
Stable Radical Dication B





X-ray structure of radical dication B





1) Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318.

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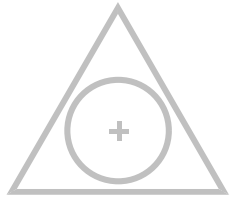
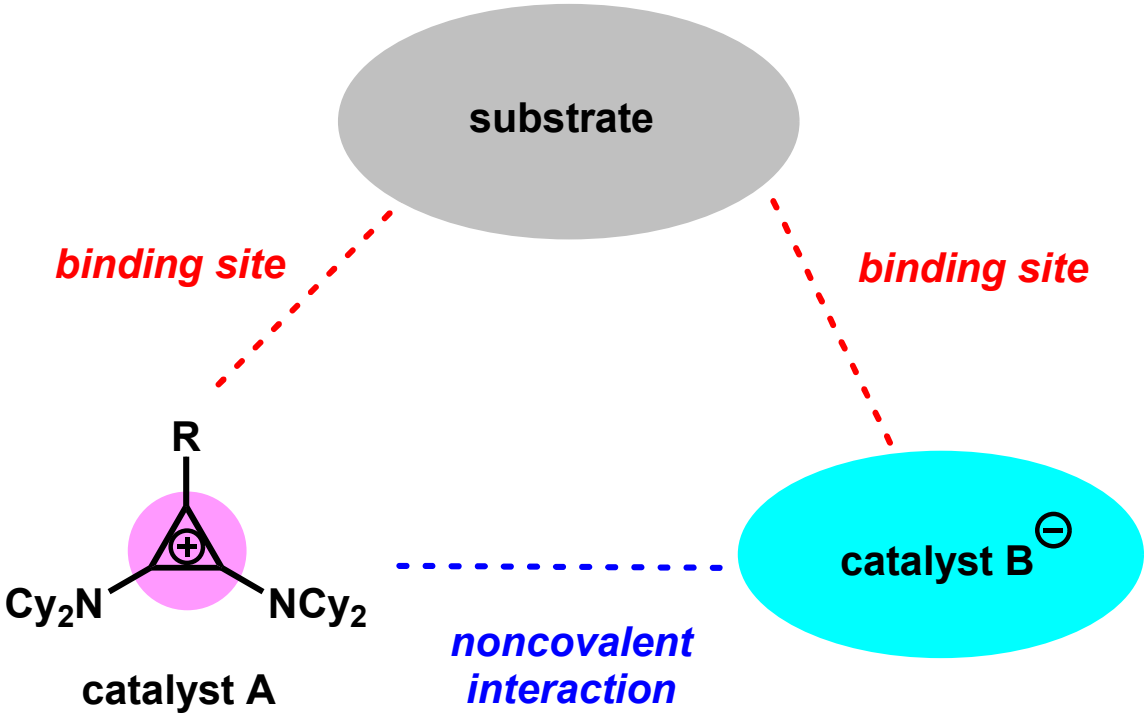


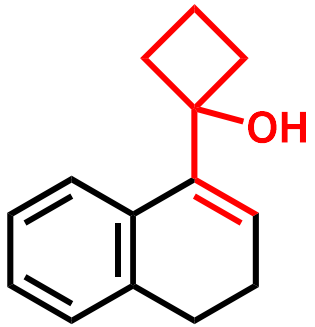
Design of Catalyst (4)

- **Co-catalyst enabled by electrostatic interaction between cyclopropenium catalyst A and anionic catalyst B**



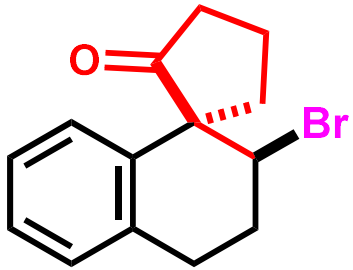
1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

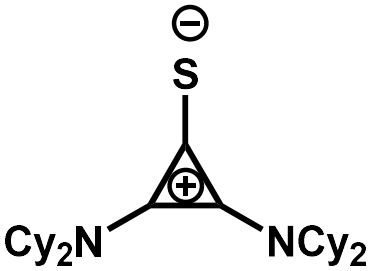
Asymmetric Bromination and Ring Expansion



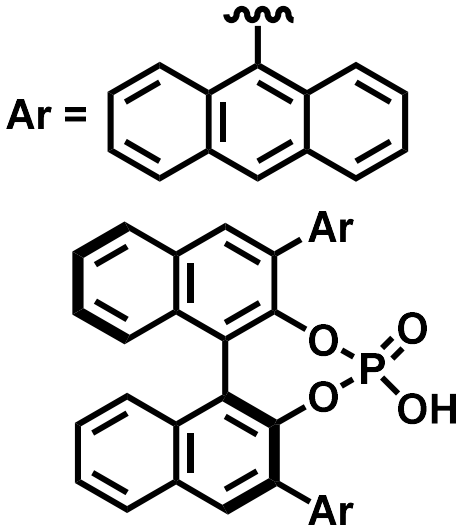
catalyst A (5 mol%)
phosphine B (5 mol%)
NBS (1.5 eq.)

toluene, −40 °C, 9 h

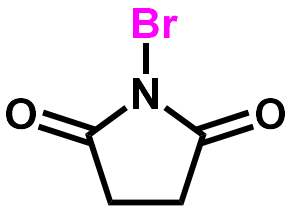




catalyst A



phosphine B

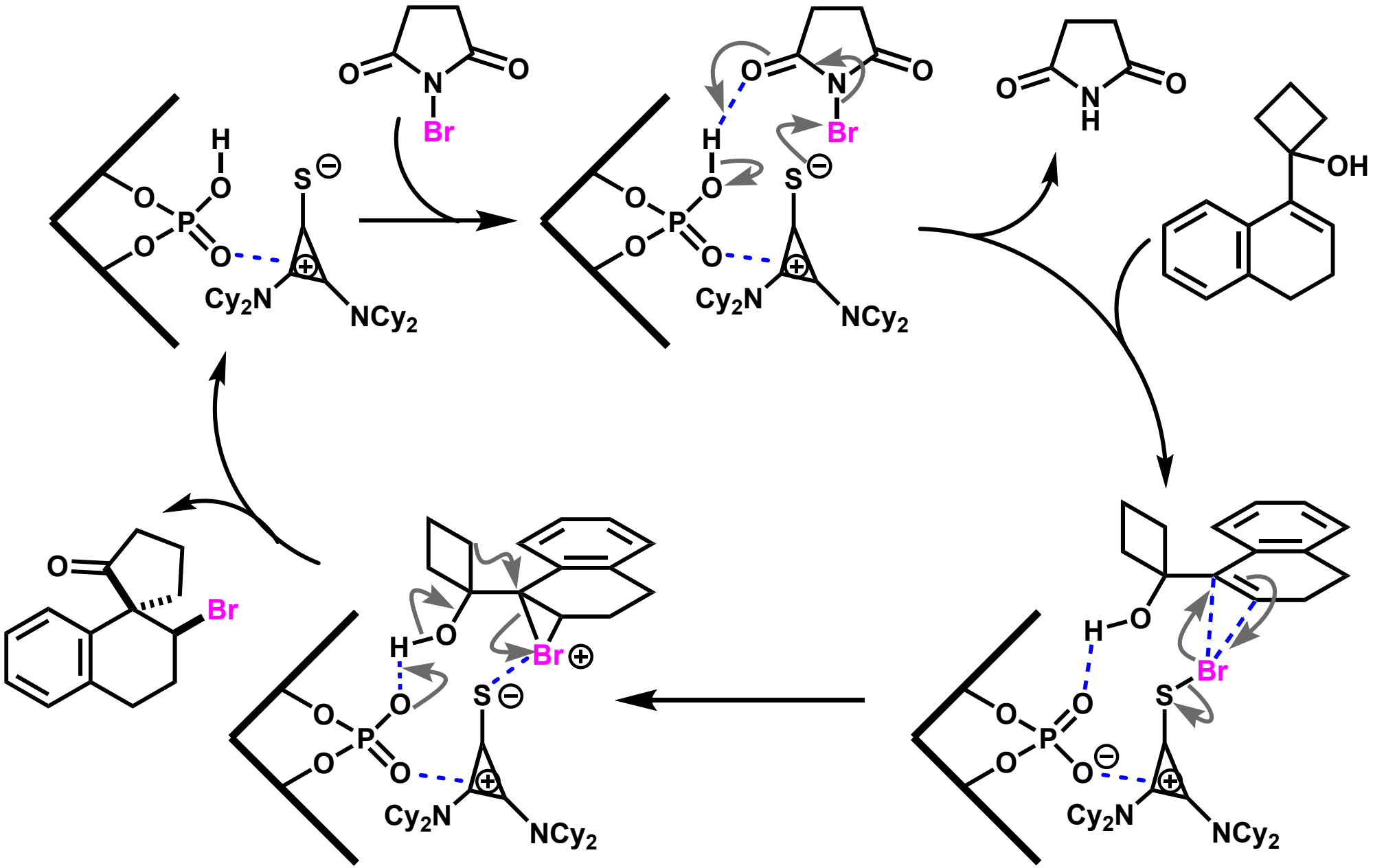


NBS

A	B	result
none	none	0%
none	5 mol%	1% (15% ee)
5 mol%	none	2% (0% ee)
5 mol%	5 mol%	80% (76% ee)

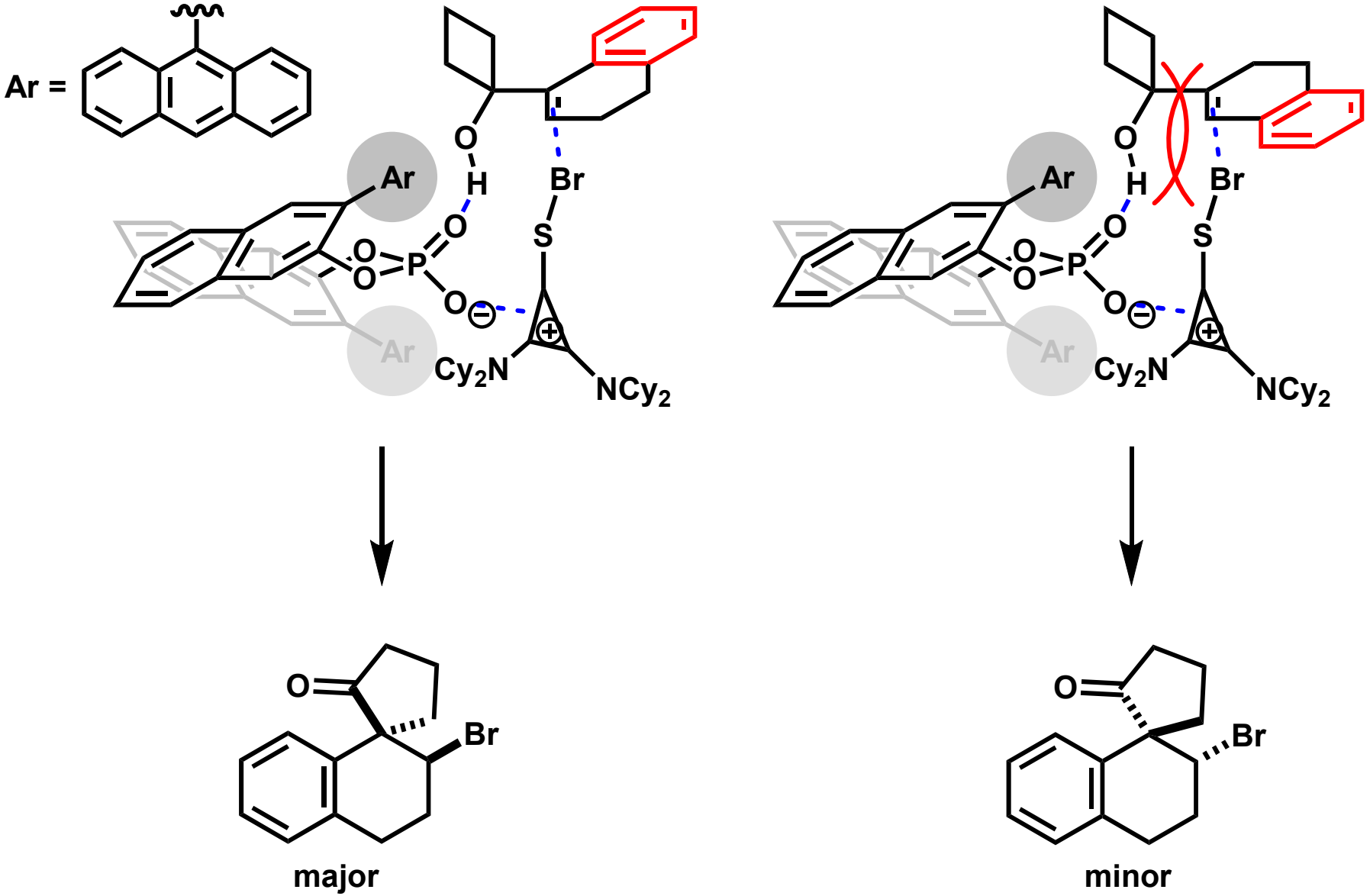
1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

Proposed Reaction Mechanism



1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

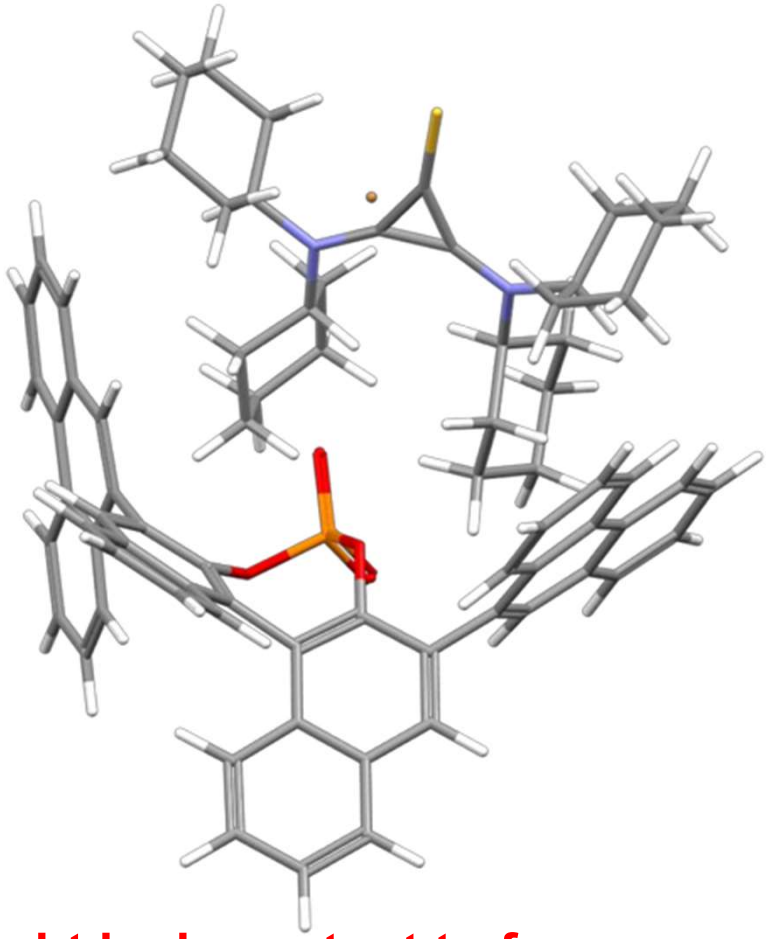
Enantioselectivity

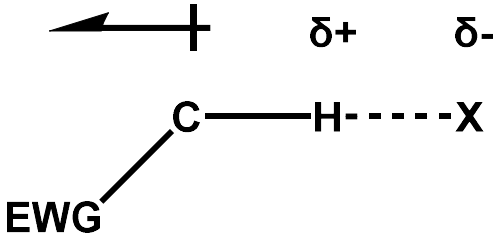


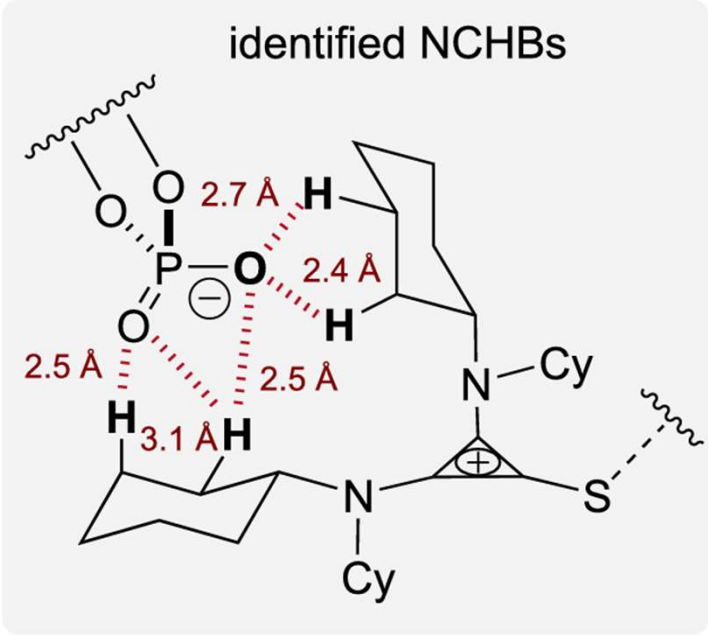
1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

Nonclassical Hydrogen Bonds (NCHBs)

- **There seemed to be C−H···X hydrogen bonds induced by the inductive effect of cyclopropenium ion.**





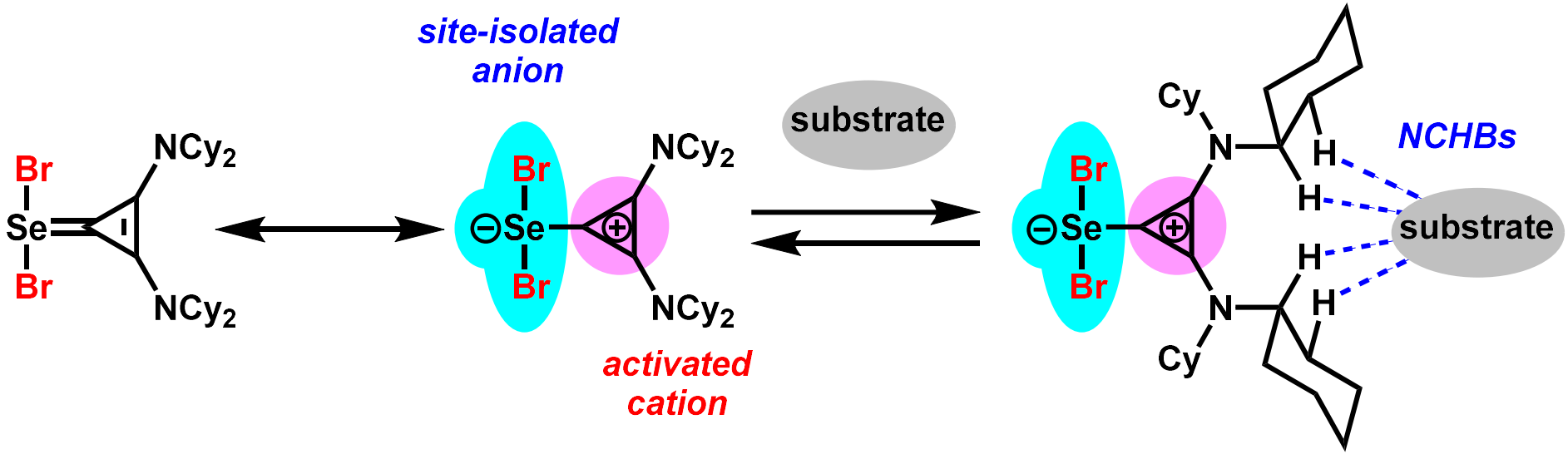


→ **It might be important to form several hydrogen bonds although each one is small interaction.**

1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

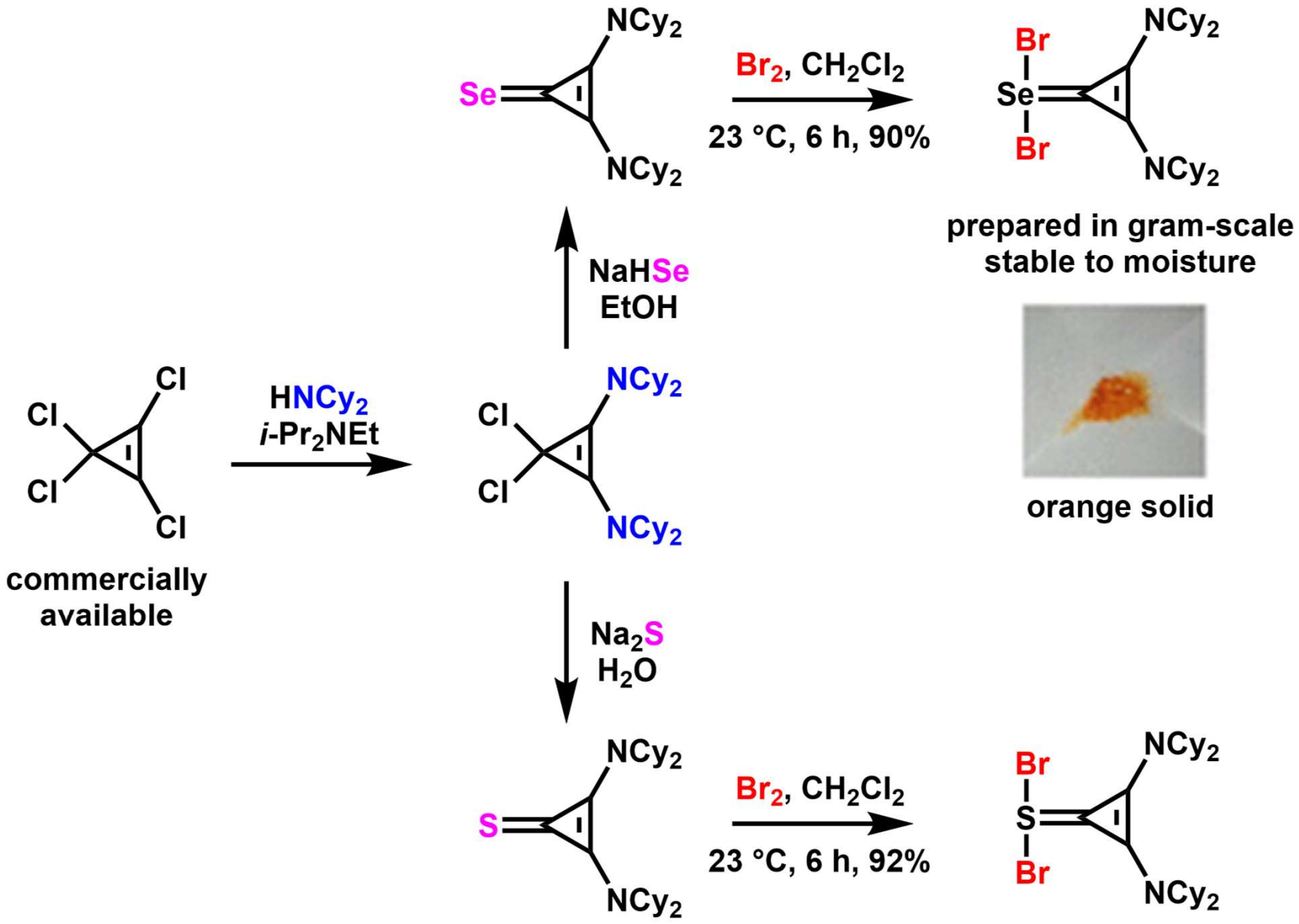
Design of Catalyst (5)

- **By introducing Br atom, the catalyst would be more polarized and thus be better for NHCBs donor.**



1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

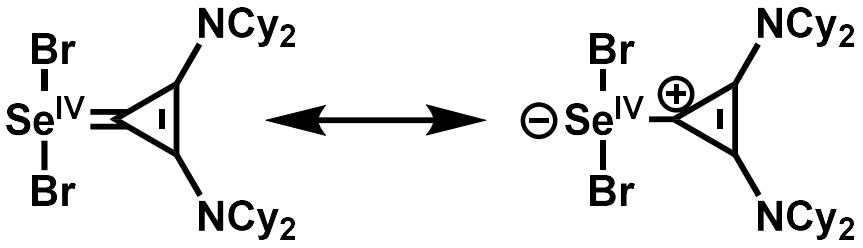
Synthesis of Catalyst

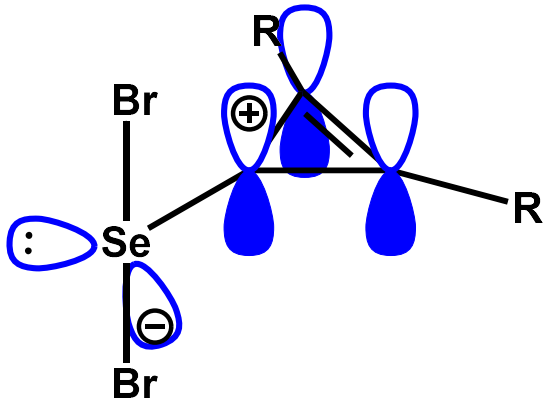


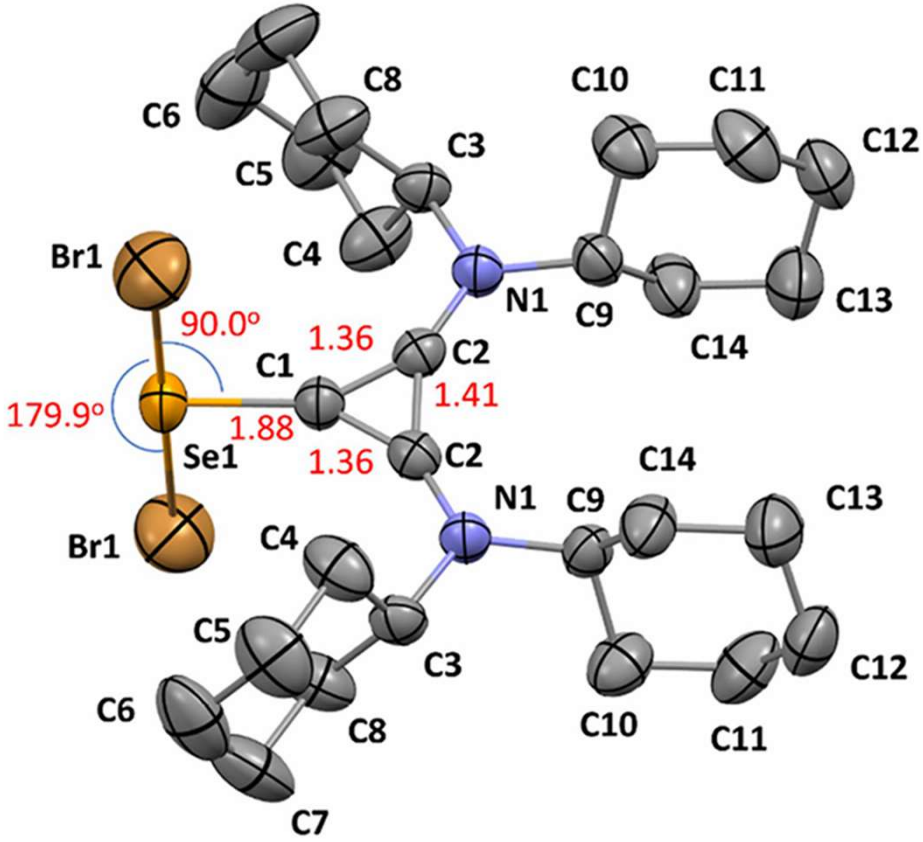
1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

Structure of Catalyst

^{34}Se: $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 3d^{10}\ 4s^2\ 4p^4$



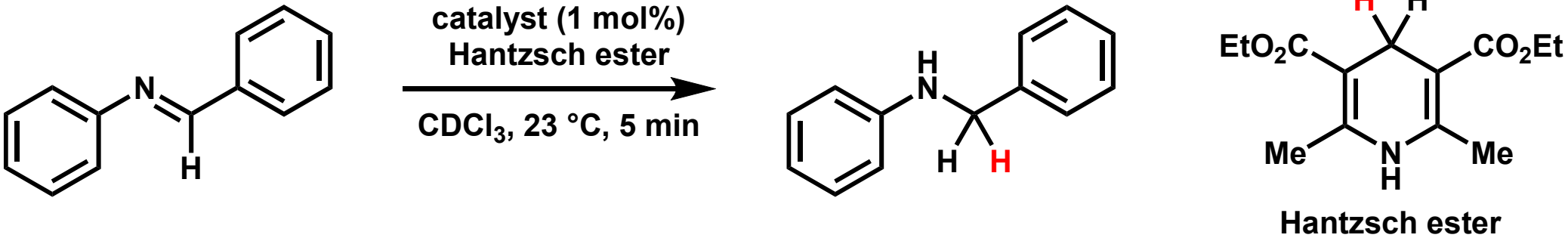




X-ray crystal structure

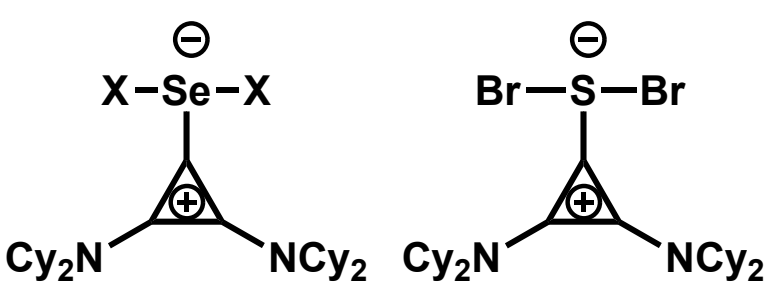
1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

Hydrogenation of Imine



Hantzsch ester

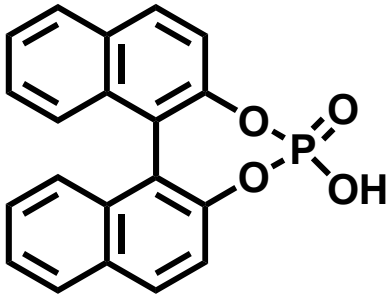
catalyst:



X = Br : 82%
X = Cl : 92%

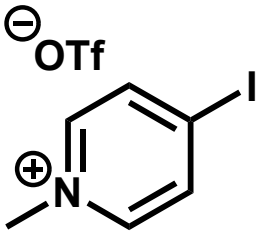
95%

Cyclopropenium ion catalysts



81%

Hydrogen-bond catalyst

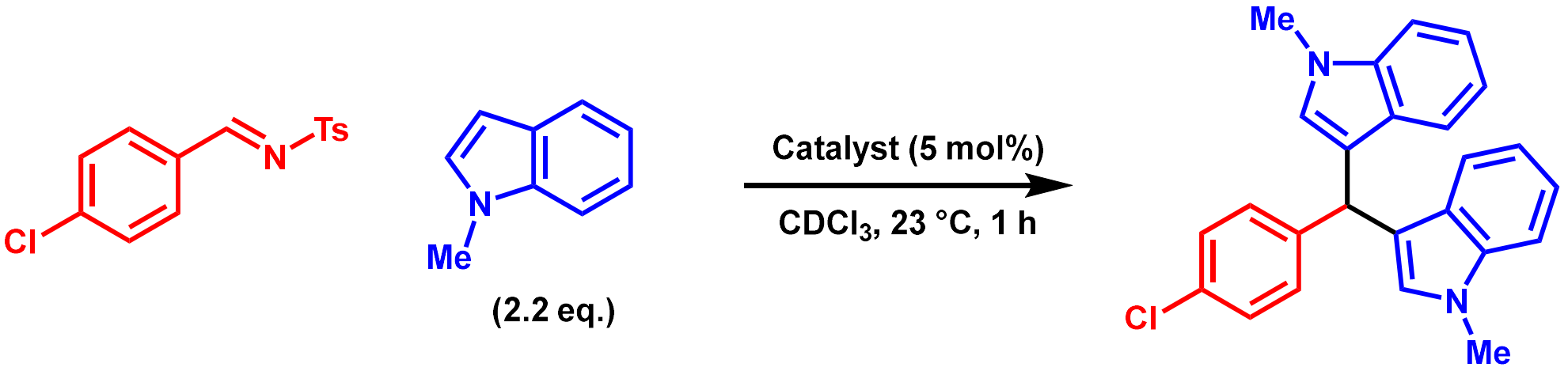


54%

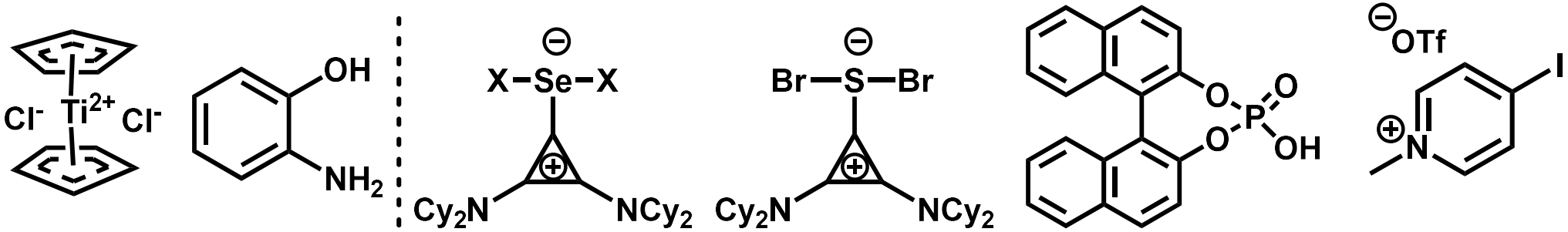
Halogen-bond catalyst

1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

Friedel-Crafts Reaction



Catalyst:



3 mol% 6 mol%
MeCN, 97%[2)]
Lewis acid

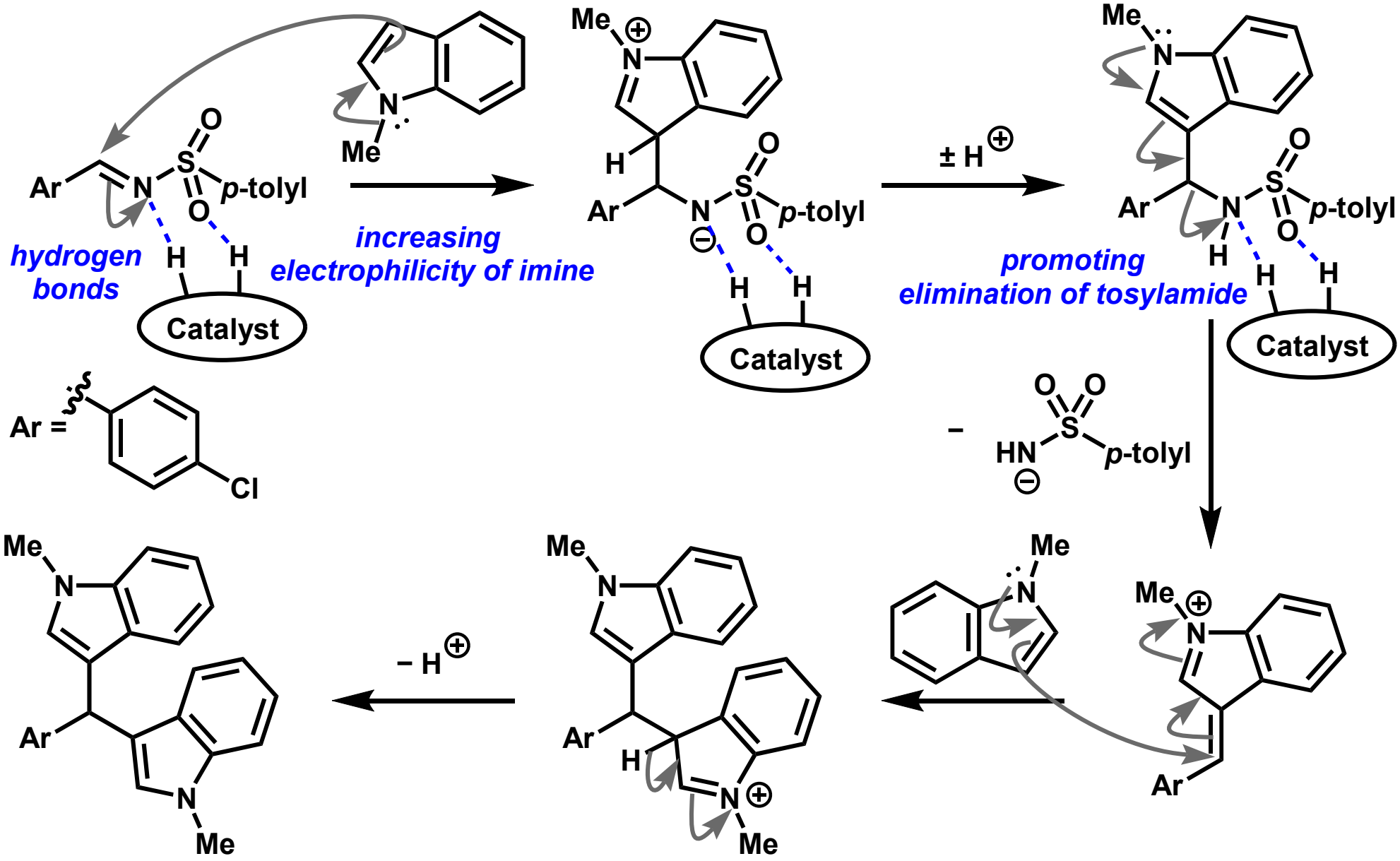
X = Br : 99%
X = Cl : 96%
95%
Cyclopropenium ion catalysts

29% (3 h)
Hydrogen-bond catalyst

0%
Halogen-bond catalyst

1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.
2) Xiu Wang, X.; Wang, Z.; Zhang, G.; Zhang, W.; Wu, Y.; Gao, Z. *Eur. J. Org. Chem.* **2016**, 502.

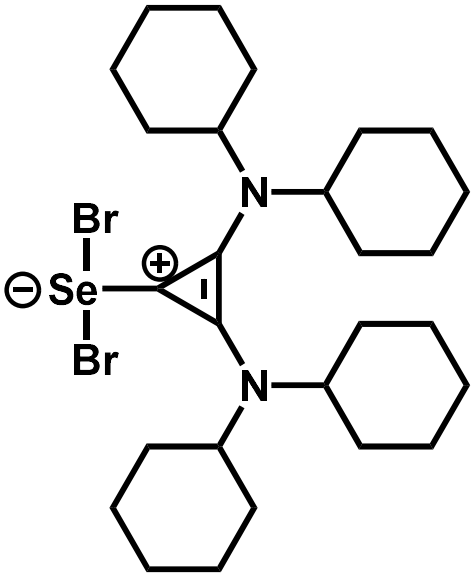
Proposed Reaction Mechanism*

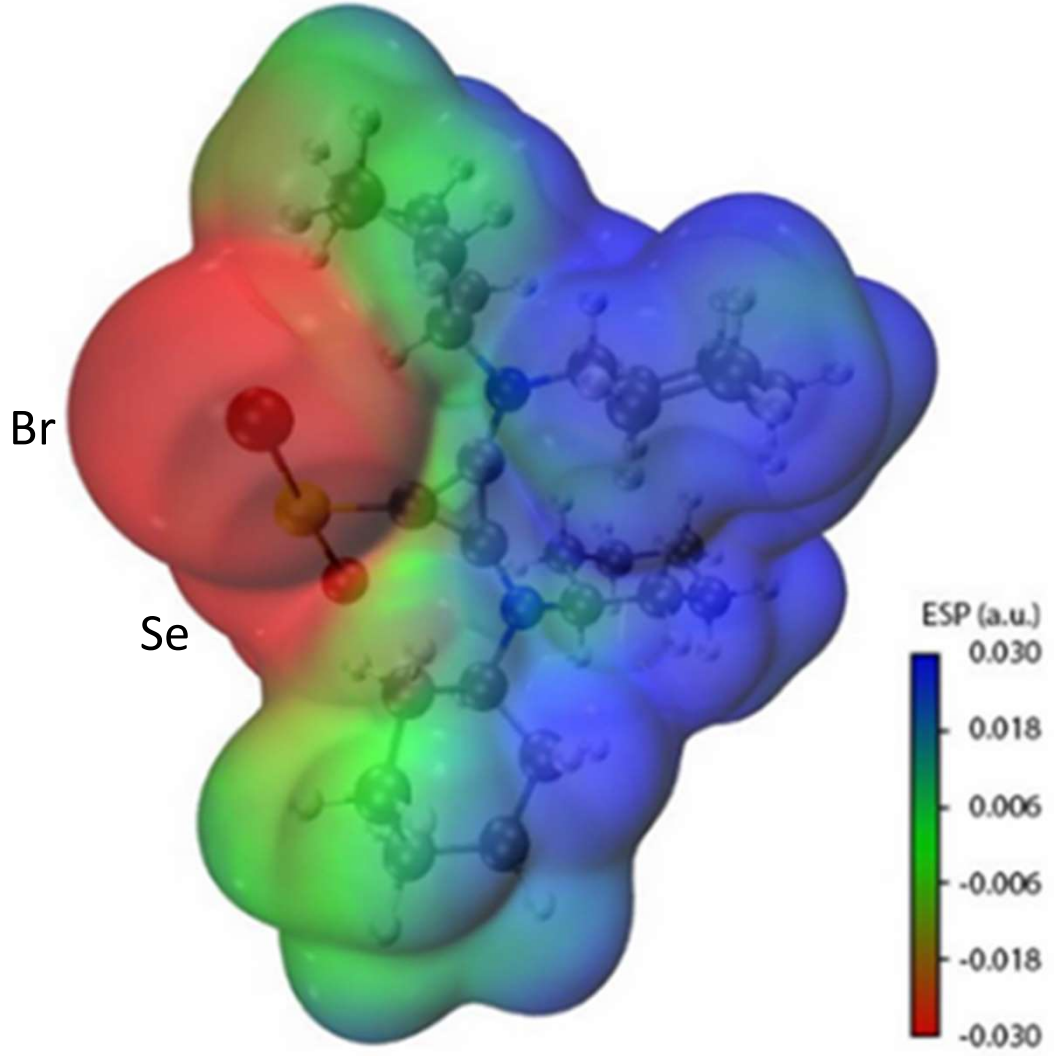


* Reaction mechanism was not mentioned in the literature.

1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

Site Isolation of Anion and Cation



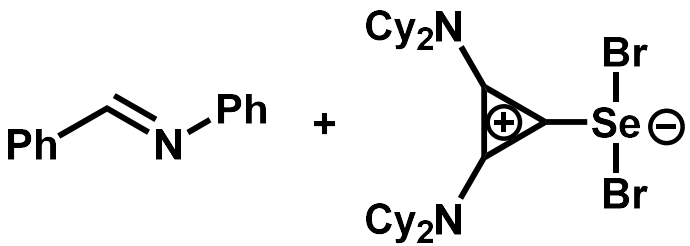


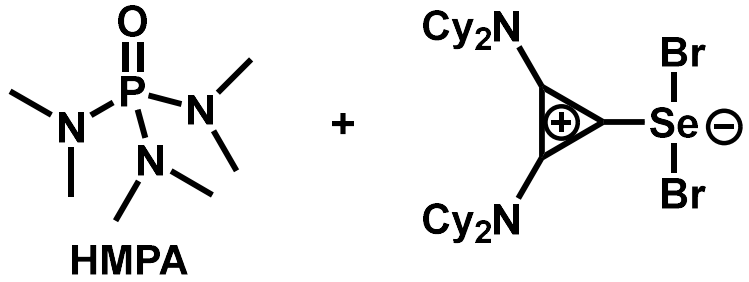
Electrostatic potential (ESP) map

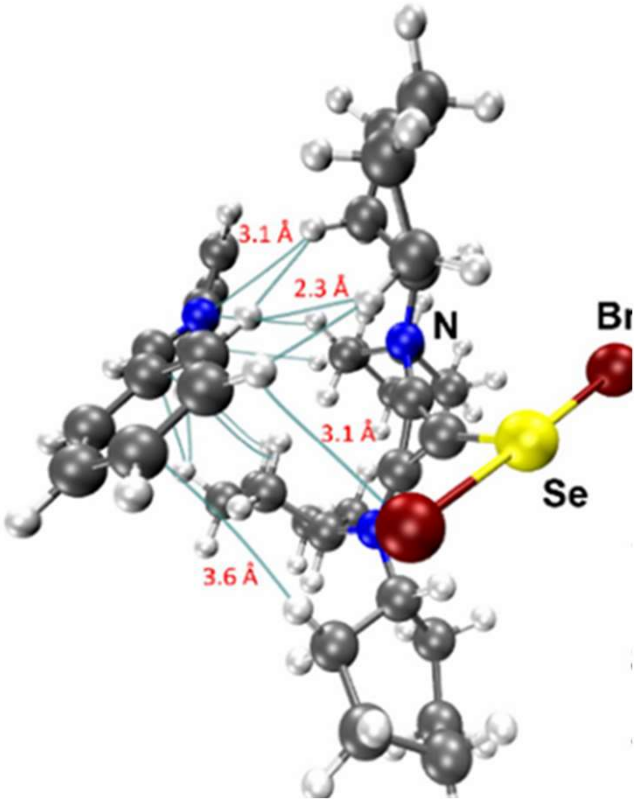
Negative charge is mainly localized at Br atom.
In contrast, positive regions are found on the cyclohexyl hydrogens.

1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

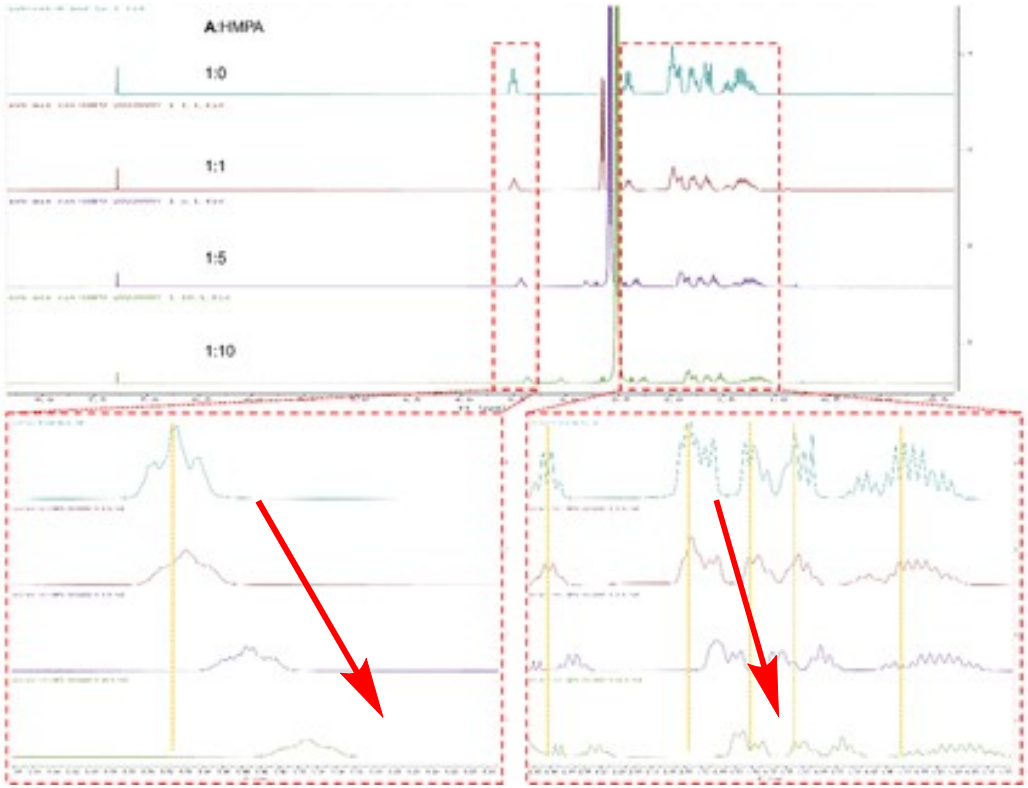
The Catalyst Activated Imine by NCHBs







Bonding energy = −13.4 kcal/mol



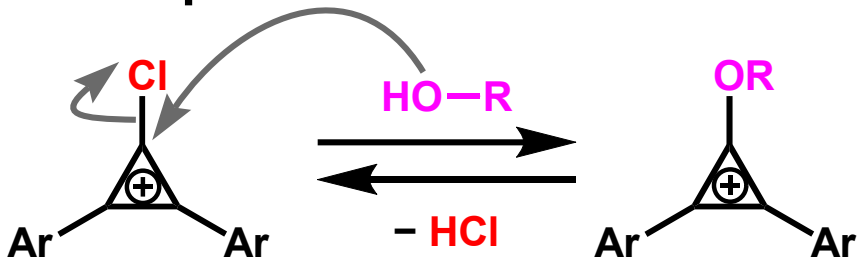
The NMR shift of cyclohexyl C-Hs got up-field as the ratio of HMPA was increased.
→ NCHBs are likely to exist.

→ Several hydrogen bonds are formed to activate the substrate although each one is small interaction.

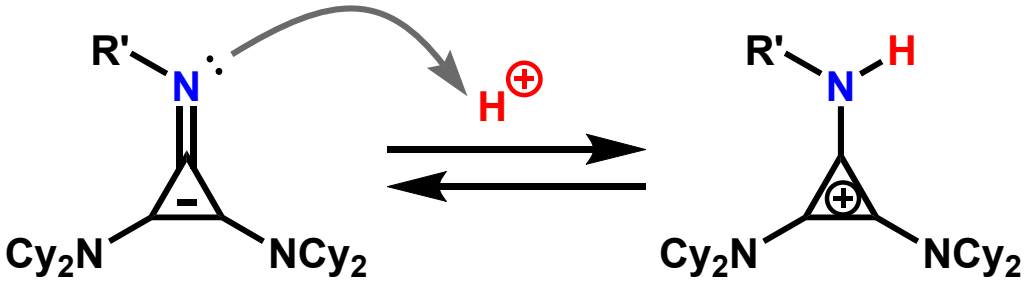
1) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

Summary

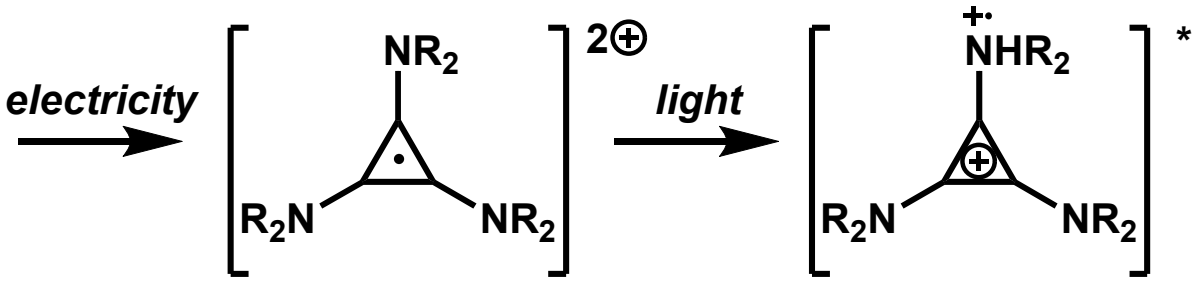
Nucleophilic substitution



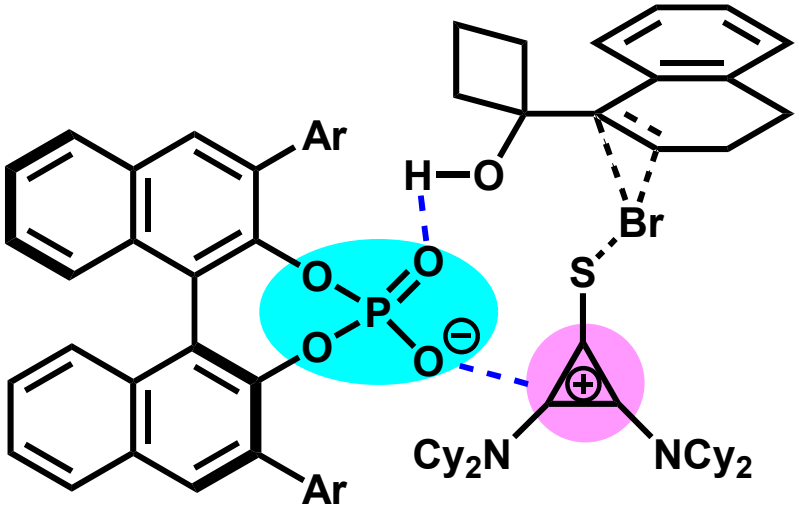
Brønsted base



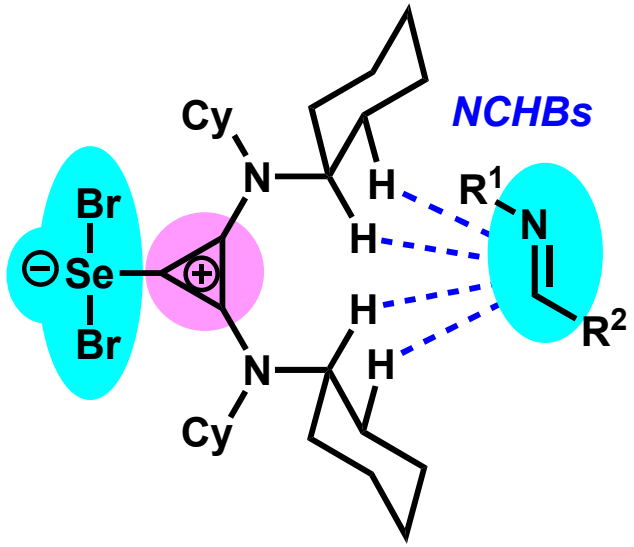
Electrophoto-excited radical dication



Co-catalyst



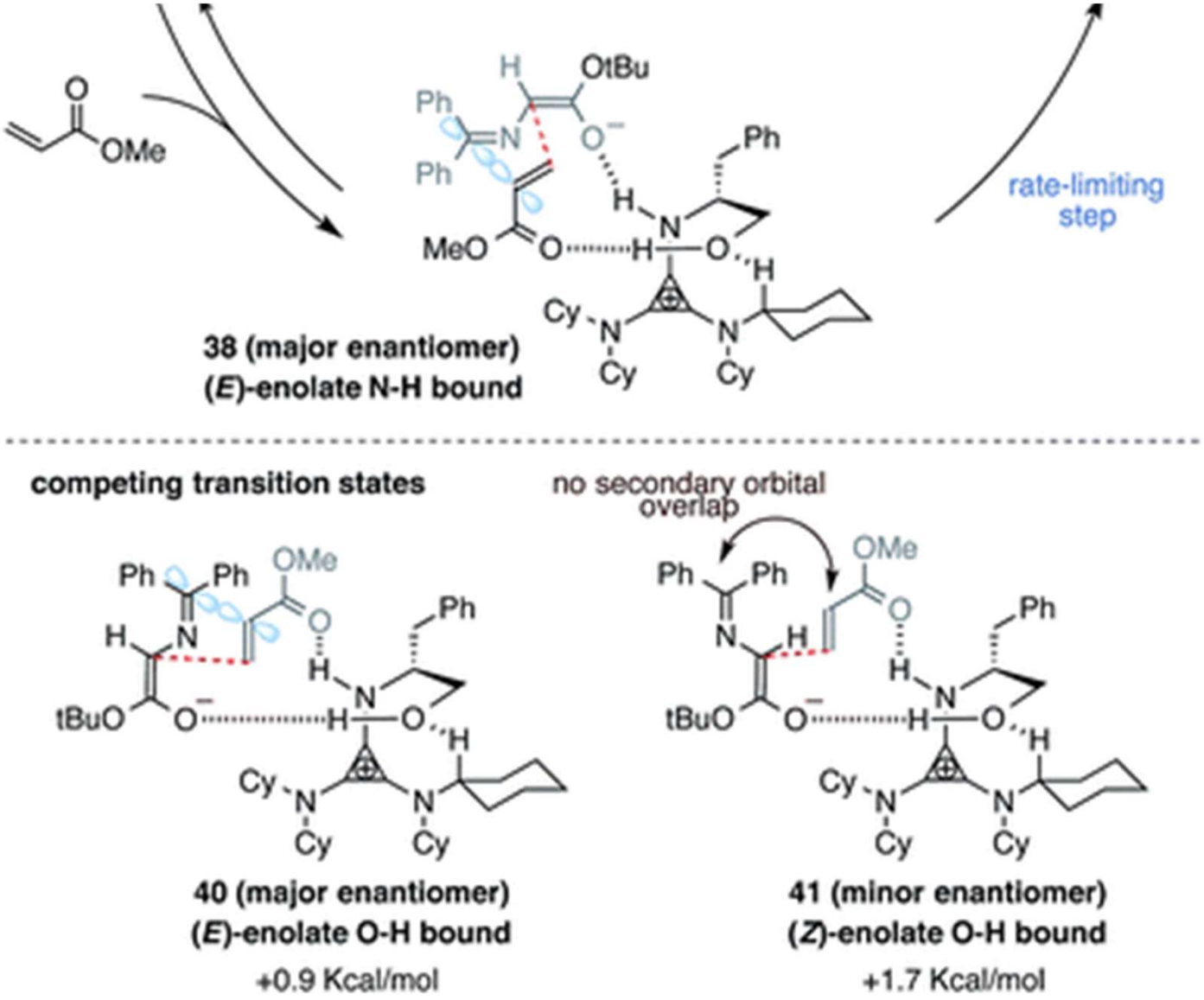
Nonclassical hydrogen bonds



1) Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, *55*, 3057.
2) Yang, J.; Zhang, Y.; Wang, H.-C. F.; Huang, J.; Tse, Y.-L. S.; Yeung, Y.-Y. *ACS. Catal.* **2024**, *14*, 3018.

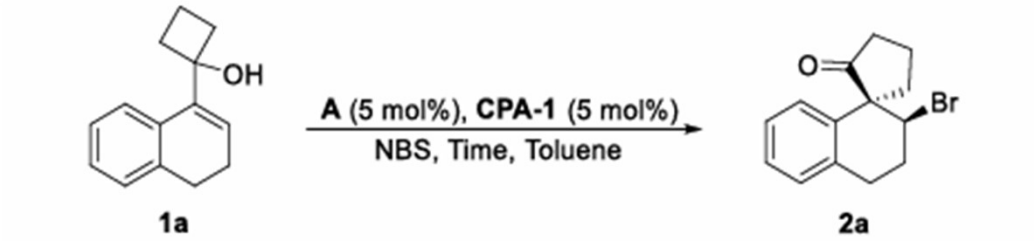
Appendix

Explanation of Asymmetric 1,4-Addition

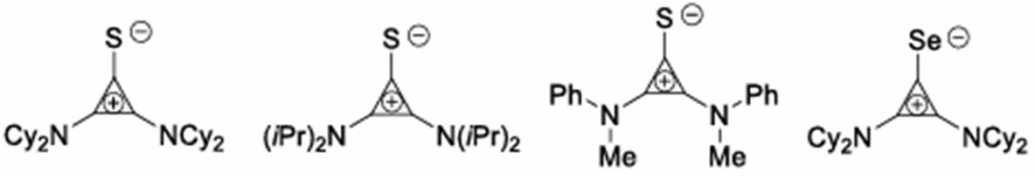


1) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
2) Bandar, J. S.; Barthelme, A.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537.

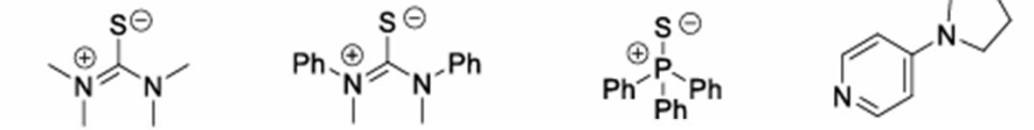
Catalyst Investigation of Bromination



1a **2a**



A1 **A2** **A3** **A4**

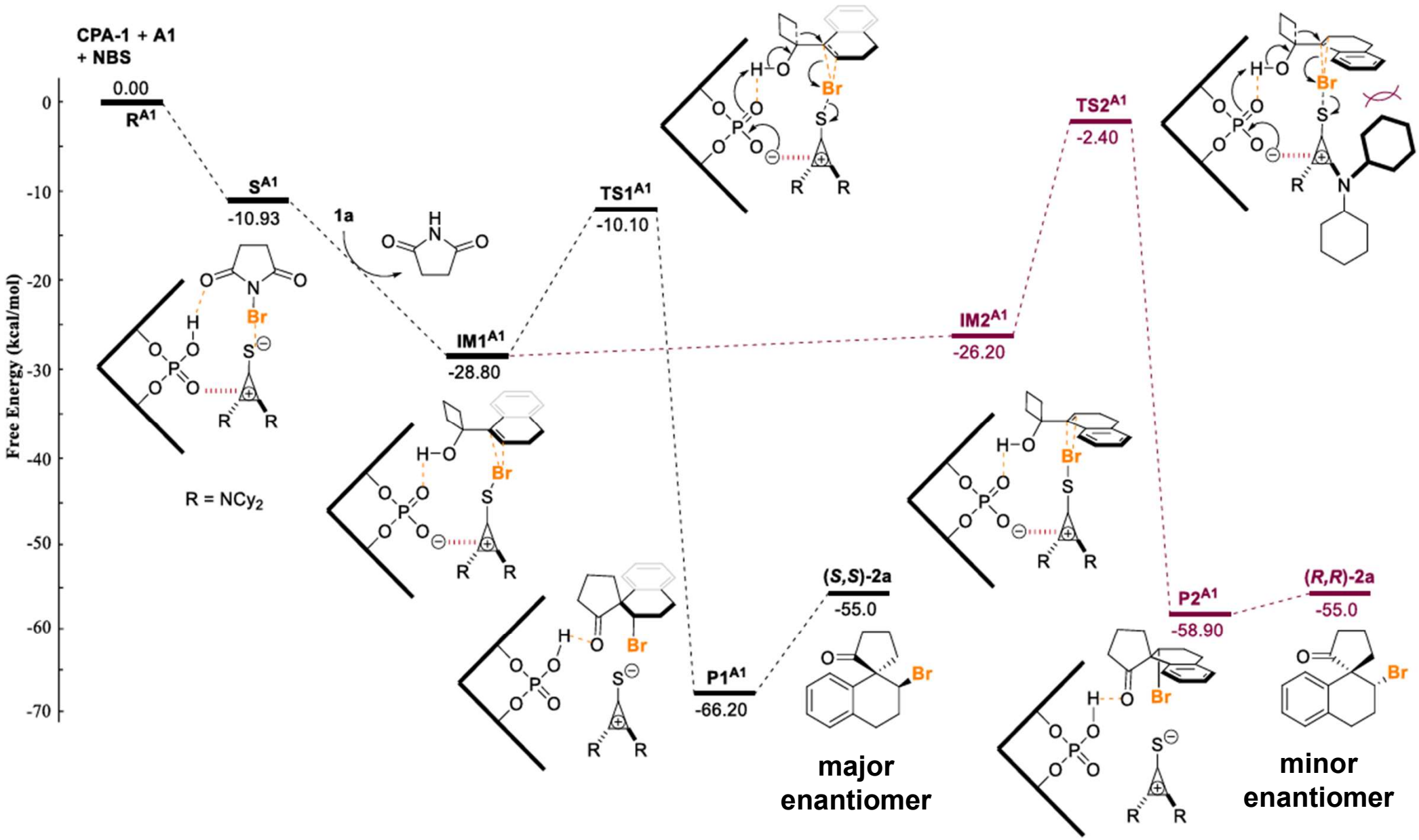


A5 **A6** **A7** **B2**

Entry	A	Temp (°C)	Time (h)	e.r.
1	-	-40	36	57.5: 42.5
2	**A1**	-40	36	91.0: 9.0
3	**A2**	-40	36	75.5: 24.5
4	**A3**	-40	36	84.0: 16.0
5	**A4**	-40	36	88.5: 11.5
6	**A5**	-40	36	70.0: 30.0
7	**A6**	-40	36	70.0: 30.0
8	**A7**	-40	36	61.5: 38.5
9	**B2**	-40	36	72.0: 28.0
10	**A1**	-60	120	93.5: 6.5
11	**A1**	-70	120	87.5: 12.5
12	**A4**	-60	120	95.0: 5.0
13	**A4**	-70	120	98.5: 1.5

1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

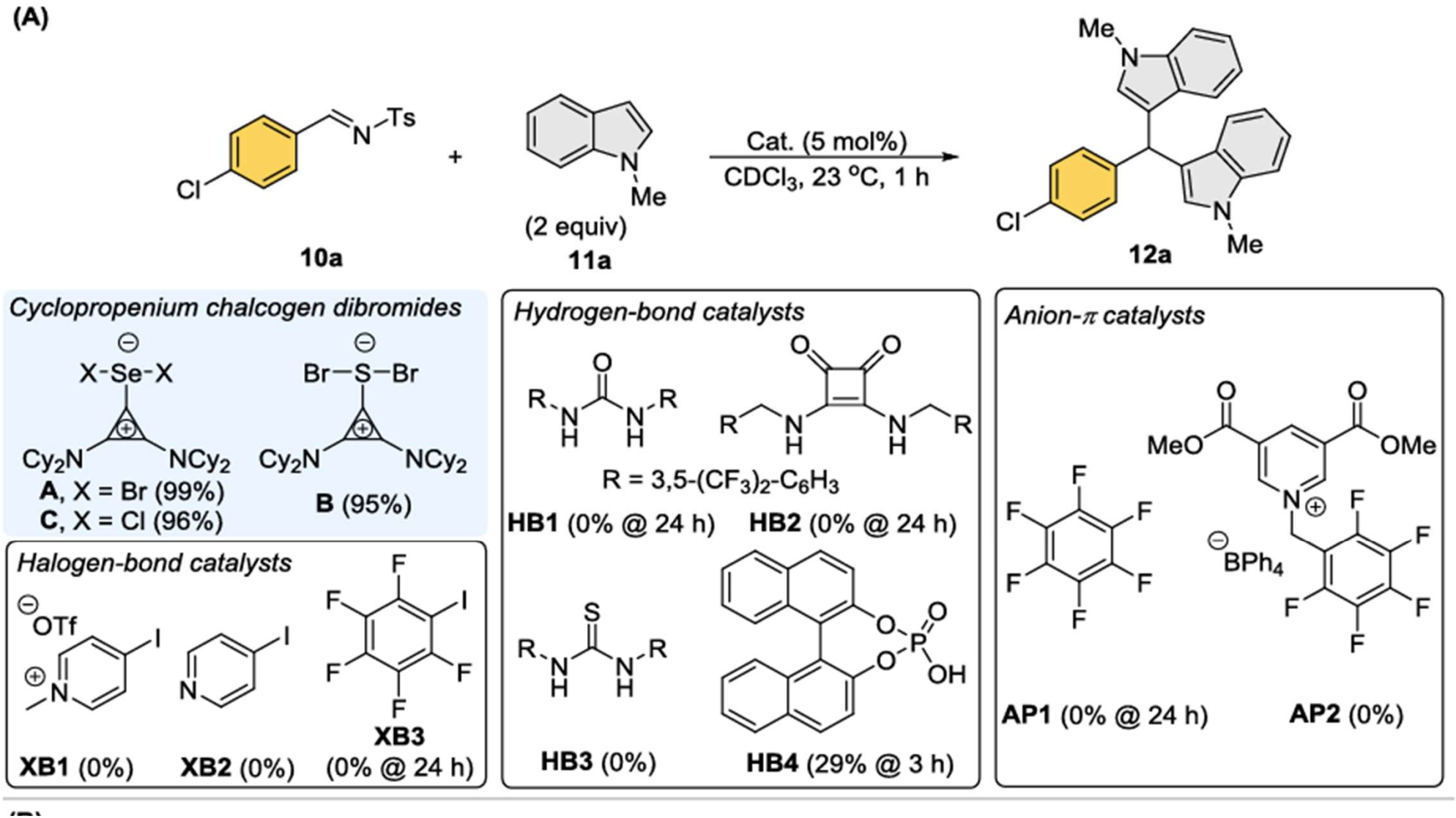
DFT calculation of Bromination



DFT calculation (wB97X-D/def2-TZVP(toluene))

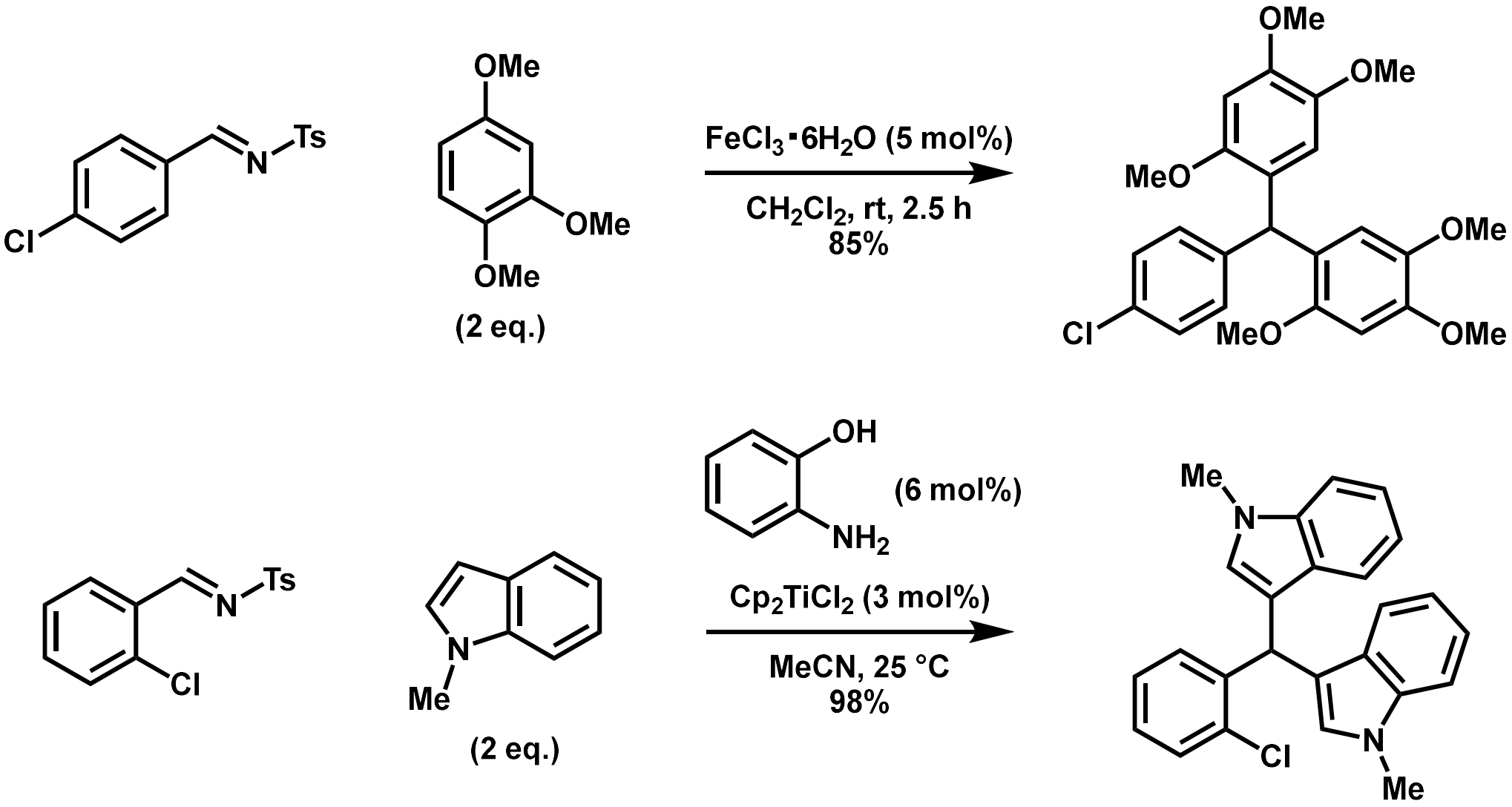
1) Zheng, T.; Chen, R.; Huang, J.: Gonçalves, T. B.; Huang, K.-W.; Yeung, Y.-Y. *Chem.* **2023**, *9*, 1255.

Friedel-Crafts Reaction



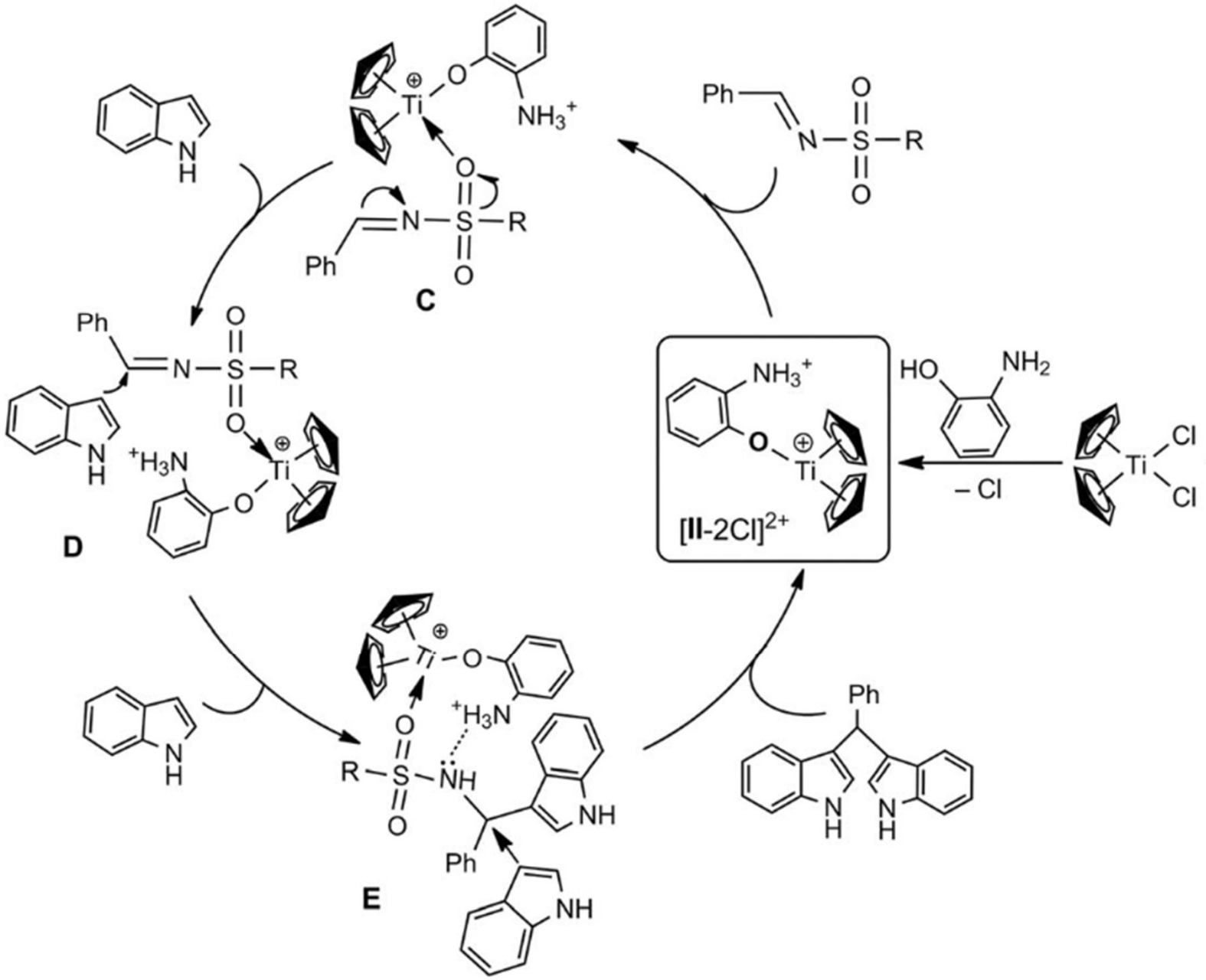
1) Xiu Wang, X.; Wang, Z.; Zhang, G.; Zhang, W.; Wu, Y.; Gao, Z. *Eur. J. Org. Chem.* **2016**, 502.

Friedel-Crafts Reaction with Lewis Acid (1)



1) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2010**, *75*, 5240.
2) Xiu Wang, X.; Wang, Z.; Zhang, G.; Zhang, W.; Wu, Y.; Gao, Z. *Eur. J. Org. Chem.* **2016**, 502.

Friedel-Crafts Reaction with Lewis Acid (2)



1) Xiu Wang, X.; Wang, Z.; Zhang, G.; Zhang, W.; Wu, Y.; Gao, Z. *Eur. J. Org. Chem.* **2016**, 502.