Double-σ-Hole XB-Donor Catalysts

2025.4.26 Literature Seminar

M2 Yo Matsumoto

Contents

Prof. Benjamin List & Prof. Stefan M. Huber

Prof. Benjamin List

1993: B.S. @ Free University of Berlin
1997: Ph.D @ University of Frankfurt (Prof. J. Mulzer)
1997~1998: postdoctoral research @ Scripps Research Institute
1999~2003: Assistant Professor @ Scripps Research Institute (Tenure Track)
2003~2005: Group Leader @ Max-Planck-Institut für Kohlenforschung
2004~: Honorary Professor @ University of Cologne
2005~: Director @ Max-Planck-Institut für Kohlenforschung
2012~2014: Managing Director @ Max-Planck-Institut für Kohlenforschung
2018~: Specially Appointed Professor@ Hokkaido University Institute for Chemical Reaction Design and Discovery
Topic: Aminocatalysis, Brønsted-Acid-Catalysis, Organic Lewis Acid Catalysis

Prof. Stefan M. Huber

2003: B.S. @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Robert Weiss)
2007: Ph.D @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Robert Weiss)
2007~2008: postdoctoral research @the University of Minnesota (Prof. Christopher J. Cramer, Prof. William B. Tolman)
2008: postdoctoral research @ the Université de Genève (Prof. LAura Gagliardi)
2009: postdoctoral research @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Harald Gröger)
2009~2013: independent research @ Technische Universität München
2014~2021: Associate Professor @ Ruhr-Universität Bochum
2022~ Full Professor @ Ruhr-Universität Bochum
Topic: Biomolecule, Organocatalysis (Hydrogen bond, Halogen bond, Chalcogen bond)

1. https://www.kofo.mpg.de/en/research/homogeneous-catalysis 2. https://www.huberlab.ruhr-uni-bochum.de/hlab/team/index.html.en

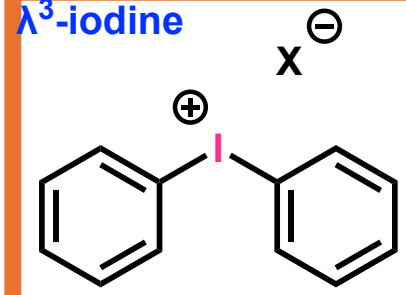
Hypervalent Iodine

127
53 I

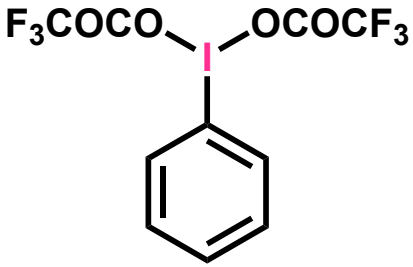
Electron configration: $[Kr]4d^{10}5s^25p^5$
van der Waals radius: 2.2 Å

Role in total synthesis: Radical precusor, Metal coupling precusor
Oxidation (hypervalent iodine) … etc.

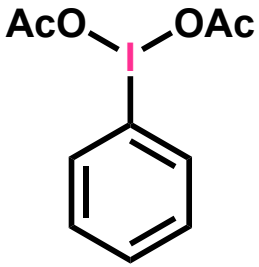
λ^3-iodine



Diaryliodonium Salts

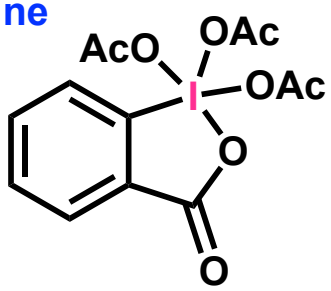


PIFA



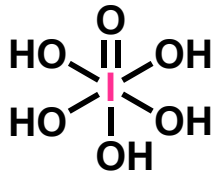
PIDA

λ^5-iodine

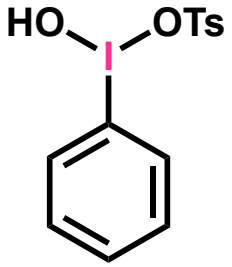


Dess-Martin periodinane

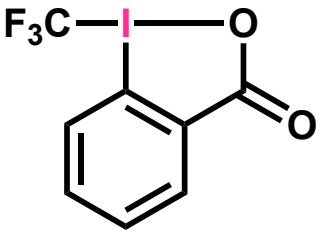
I(VII) type



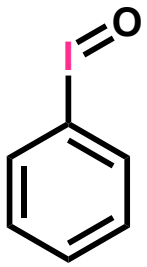
Orthoperiodic Acid



Koser's reagent



Togni II reagent



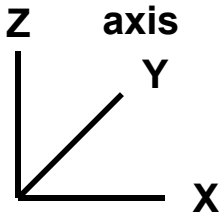
Iodosylbenzene

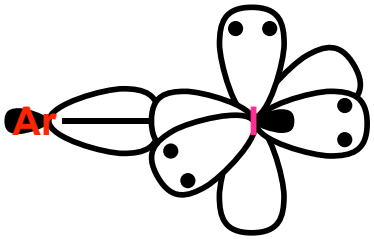
https://fiu-iodine.org/studies/ (2025/4/25. ヨウ素学会)

σ Hole: Halogen Halogen Interaction

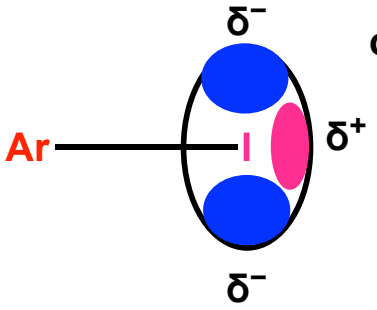
See 241122_LS_Hibiki_Asai_Halogen_Halogen_Interaction

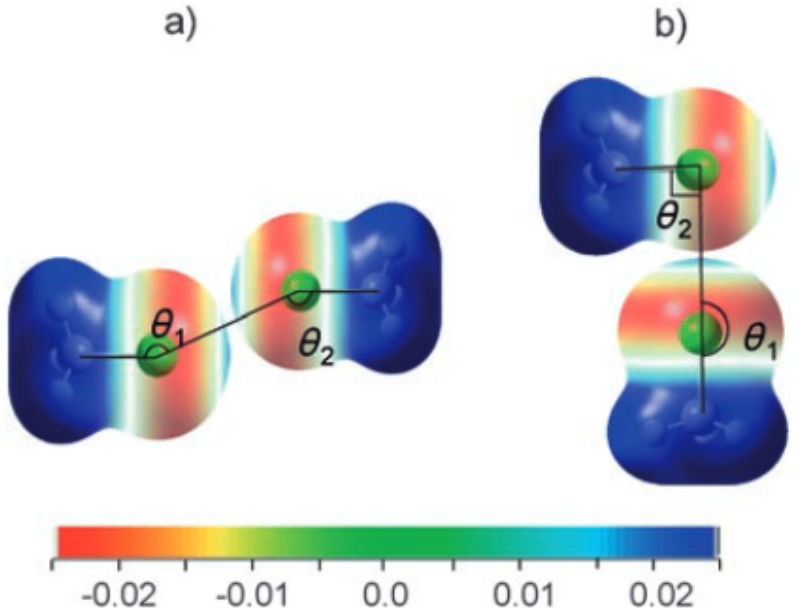
σ-Hole of Halogen





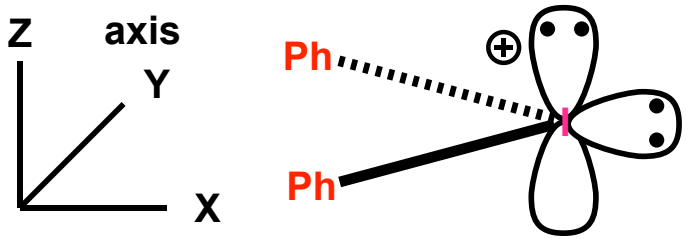
σ-hole:
C-I σ* > lone pair of p_x orbital





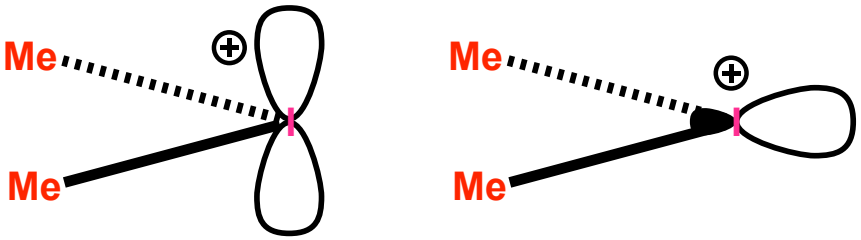
Two Types of Halogen-Halogen Interaction

Double σ-Hole: Iodine(III) (Ph_2I^+ Species) I



2 lone pairs in p_x orbital and p_z orbital

Model Compound $\{I(CH_3)_2^+\}$

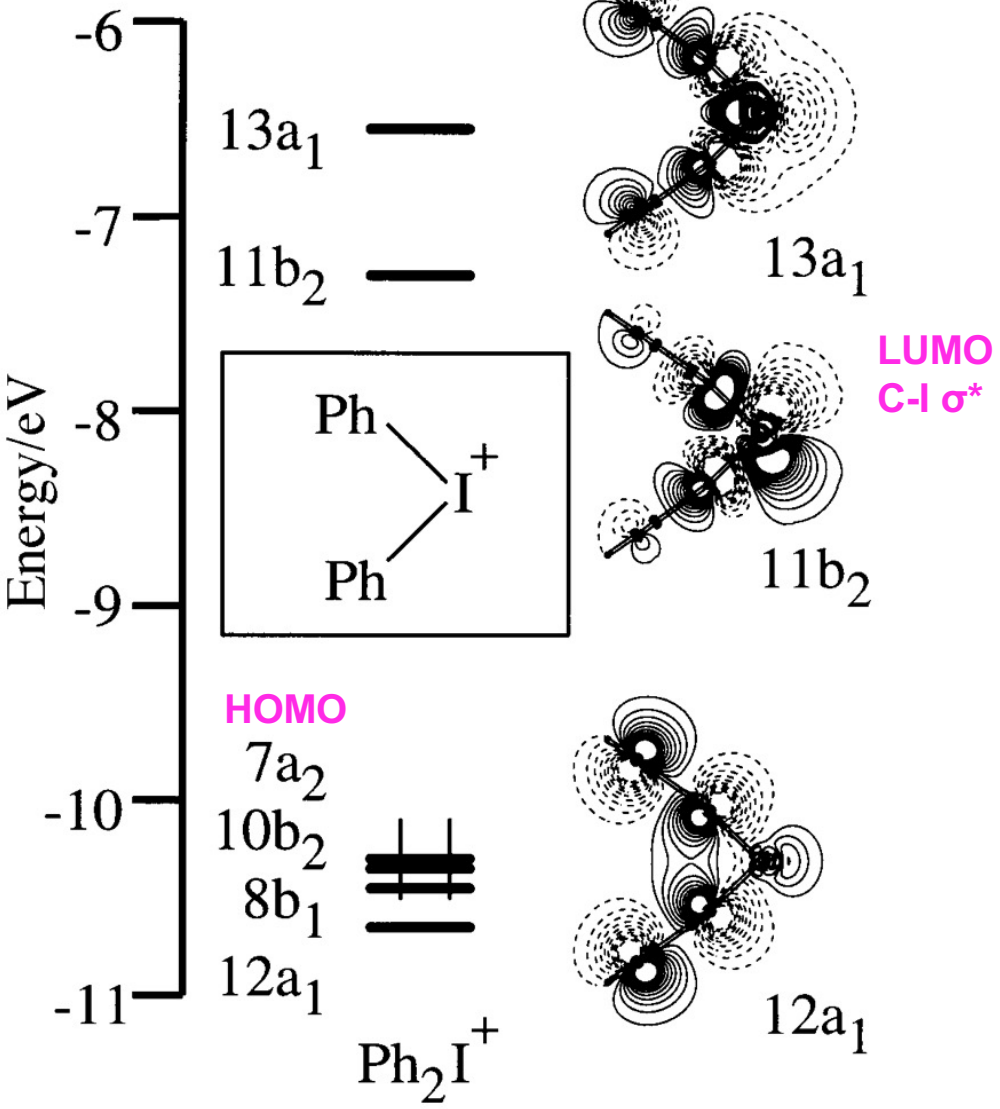


HOMO **Second HOMO**

Valence electron population:

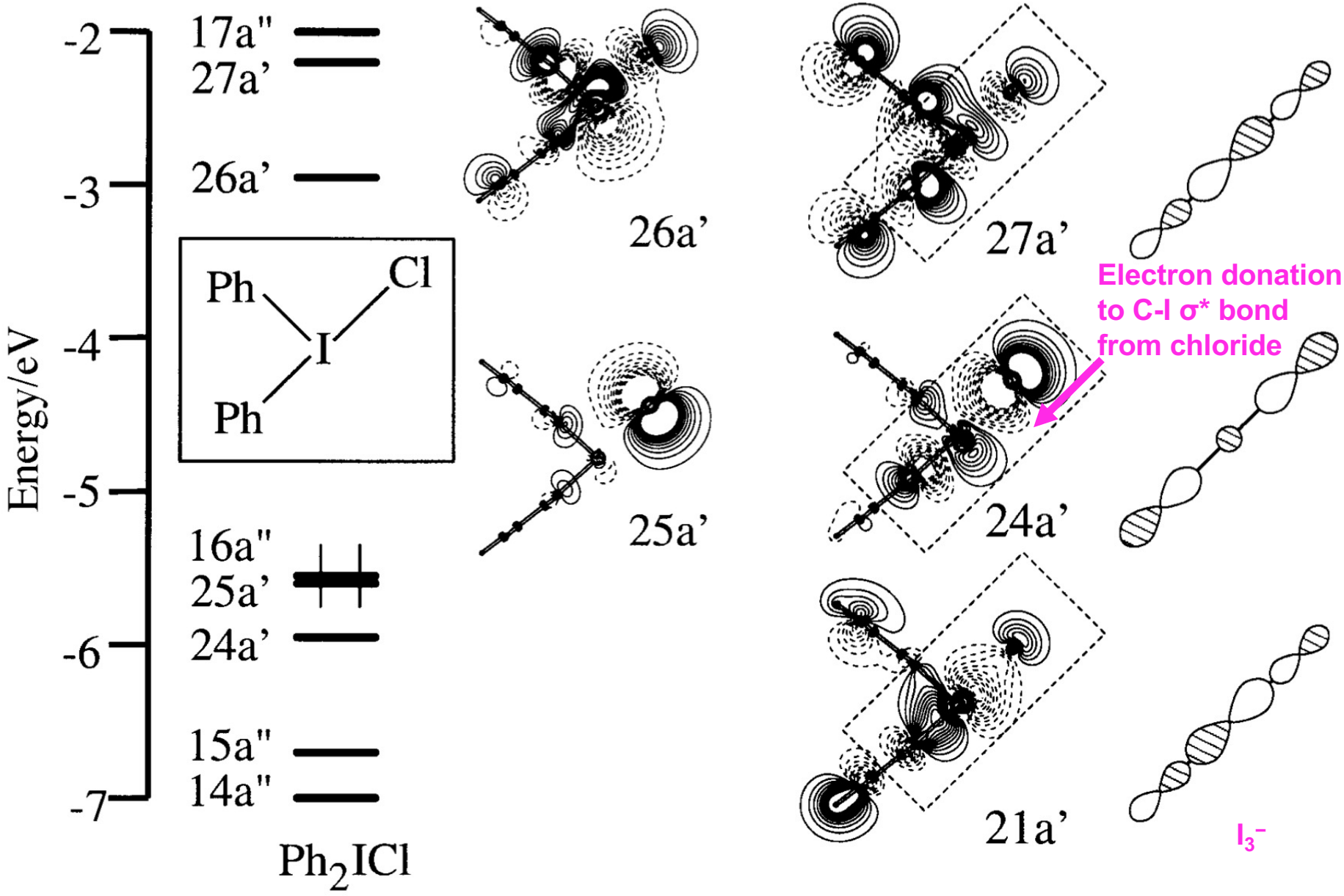
$5s^{1.77}$, $5p_x^{1.46}$, $5p_y^{1.13}$, $5p_z^{1.99}$

Iodine electron configuration: $[Kr]4d^{10}5s^25p^5$



1. Ikezawa,H.; Takahashi, M.; Takeda, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1959.
2. Landrum, G. A.; Goldberg, N.; Hoffmann, R.; Minyaev, R. M. *New. J. Chem.* **1998**, *22*, 883.

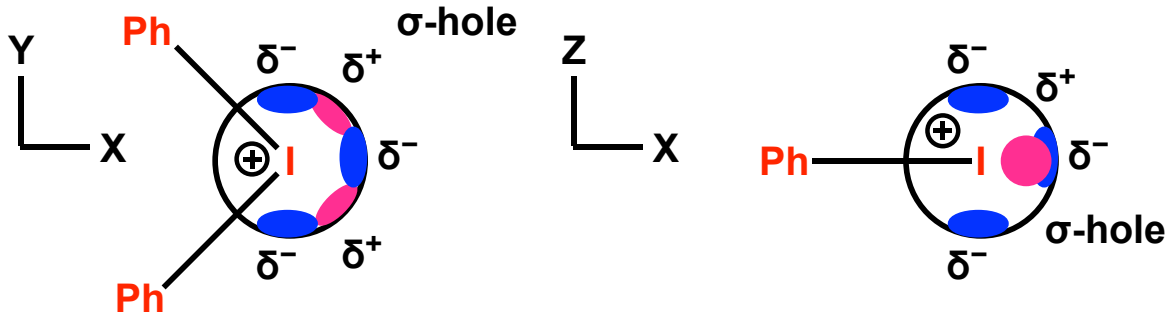
Double σ-Hole: Iodine(III) (Ph_2I^+ Species) II



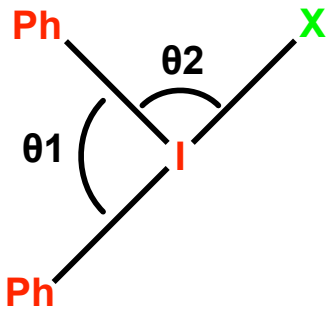
Landrum, G. A.; Goldberg, N.; Hoffmann, R.; Minyaev, R. M. *New. J. Chem.* **1998**, *22*, 883.

Double σ-Hole: Iodine(III) (Ph_2I^+ Species) III

Double σ-Hole of Iodonium (III) Salts



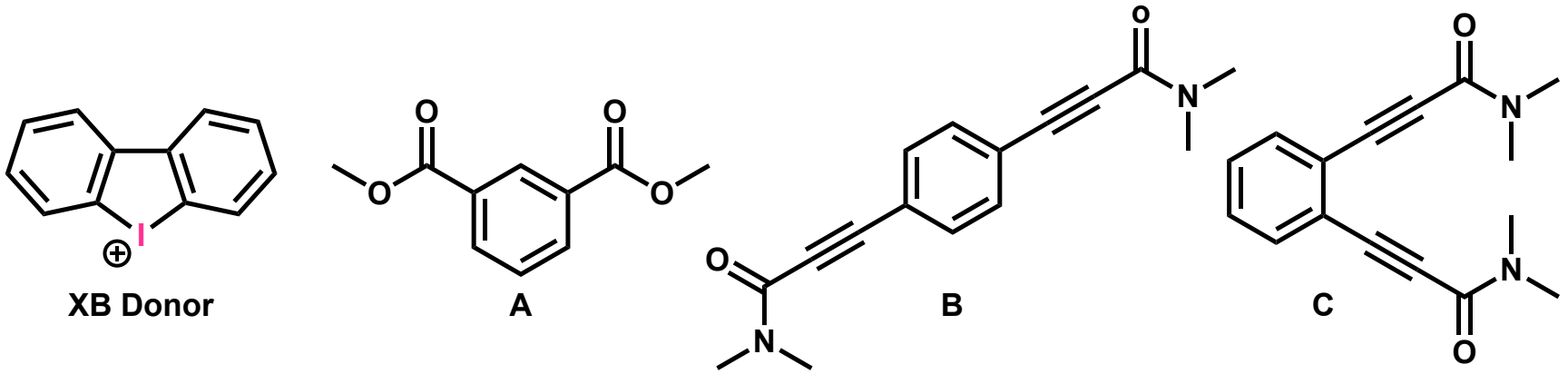
Angle of Ph_2IX species

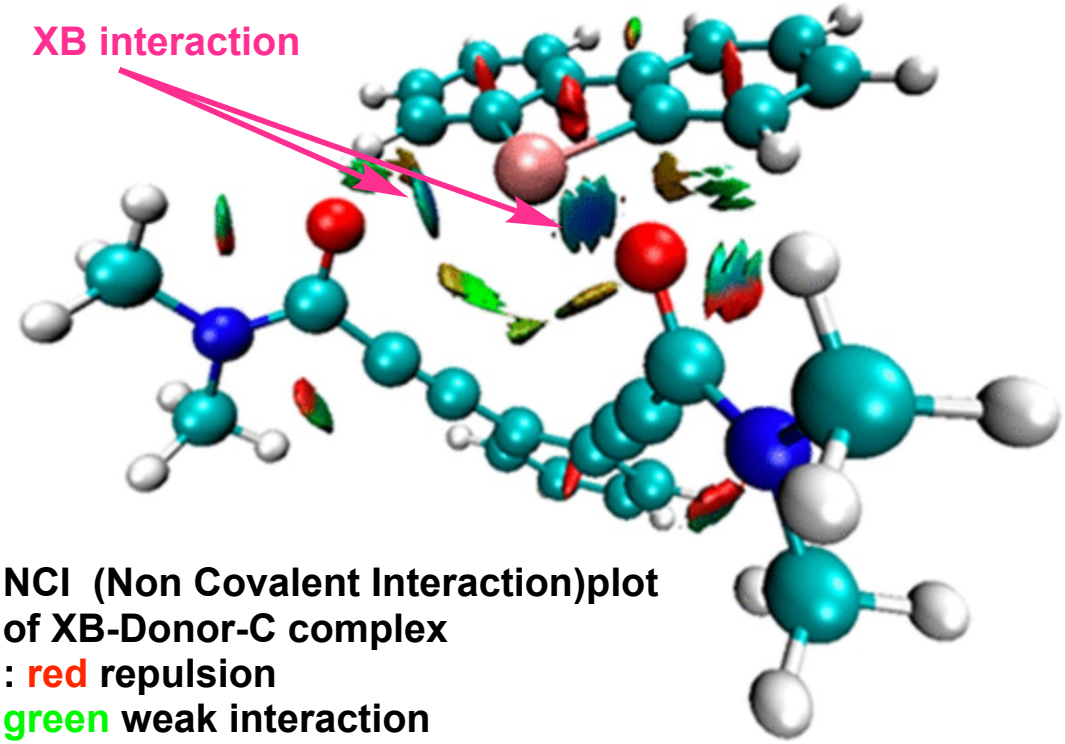


X	Cl	Br	I
θ1/º	80	82	82
θ2/º	87	86	88

Landrum, G. A.; Goldberg, N.; Hoffmann, R.; Minyaev, R. M. *New. J. Chem.* **1998**, *22*, 883.

Double σ-Hole Donor as Lewis Acid





NCI (Non Covalent Interaction)plot of XB-Donor-C complex
: red repulsion
green weak interaction
blue strong interaction

Binding Energy of XB Donor's Adduct Formation

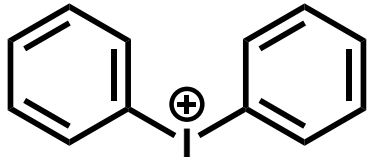
	A	B	C
Binding constants (M^{-1})	$1.6 * 10^1$	$1.5 * 10^3$	$8.3 * 10^4$
Experimental ΔG	−1.7	−4.4	−6.3
Calculated ΔG (SMD, PCM)	0.0, 0.4	−1.3, −2.8	−9.1, −6.6

Heinen, F.; Engelage, E.; Cramer, C. J.; Huber, S. M. *J. Am. Chem. Soc,* **2020**, *142*, 8633.

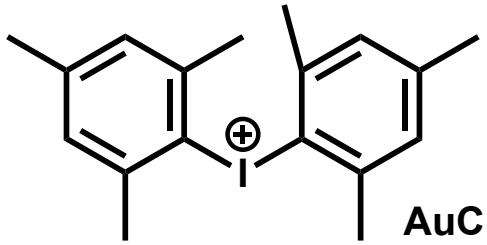
Double σ-Hole: Diaryliodonium (III) Salt

Hirshfeld surfaces:
a method that reveals the hydrophilic nature of intermolecular interactions in a molecular system.

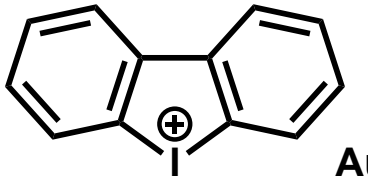
Top 2



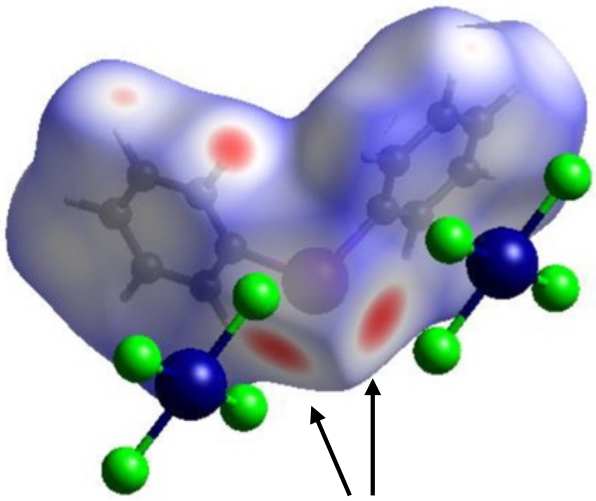
Bottom left $AuCl_4^{\ominus}$

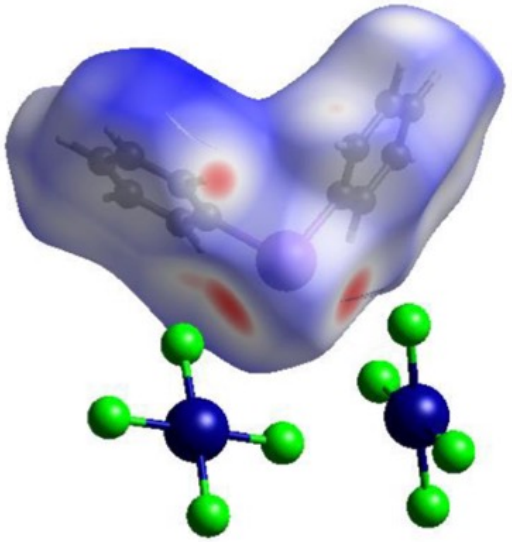


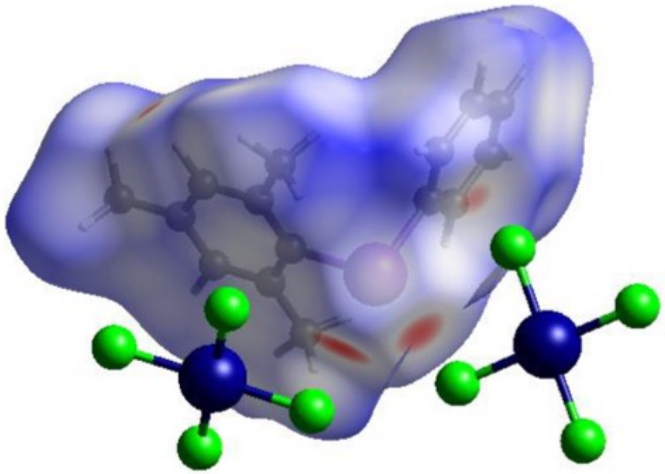
Bottom right $AuCl_4^{\ominus}$

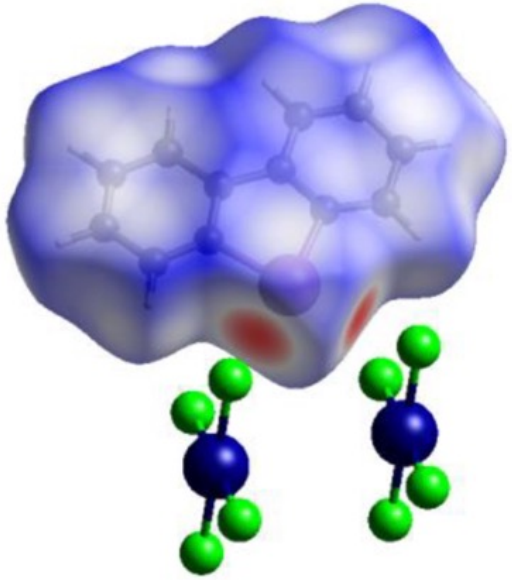


$AuCl_4^{\ominus}$



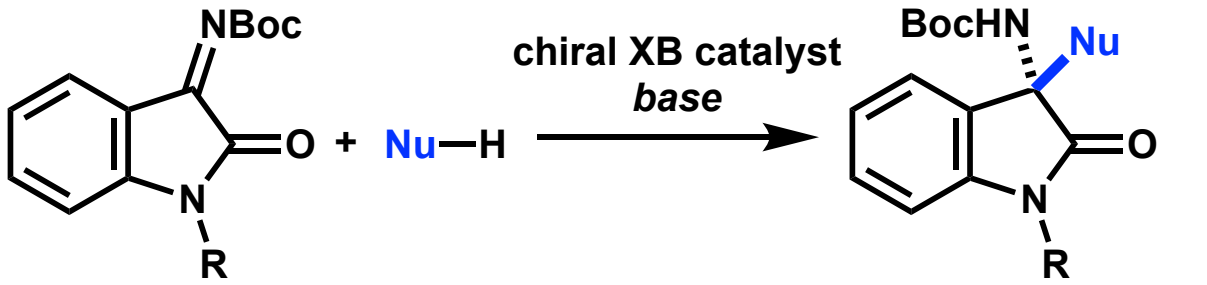




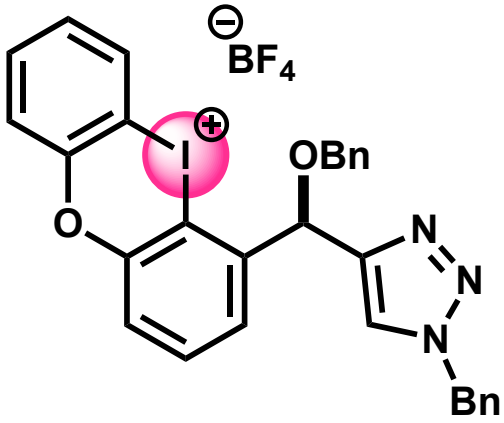


Aliyarova, I. S.; Ivanov, D. M.; Soldatova, N. S.; Novikov, A. S.; Postnikov, P. S.; Yusubov, M. S.; Kukushkin, V. Y. *Cryst. Growth Des.* **2021**, *21*, 1136.

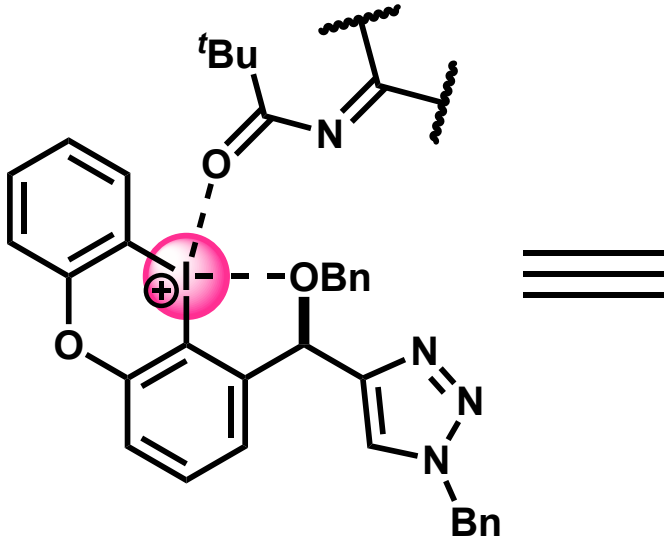
Previous Work: Chiral Iodonium (III) Salts Catalyst



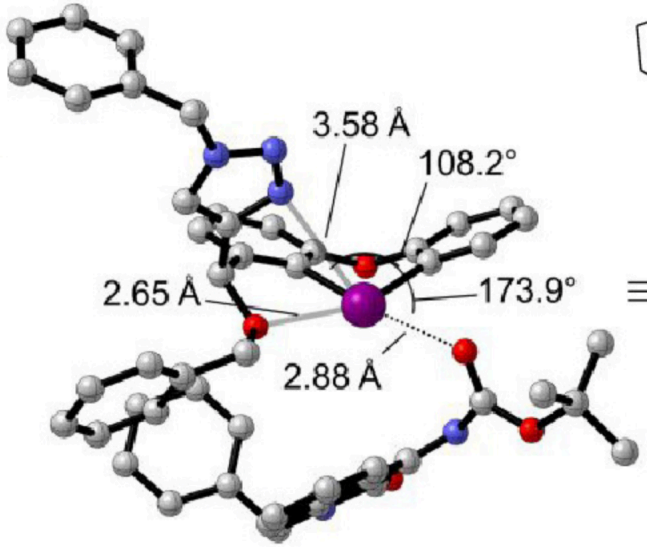
up to 99%, 99% ee

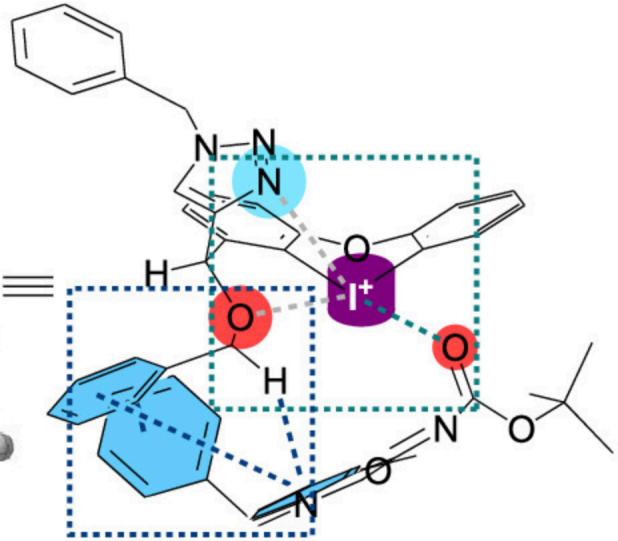


chiral XB catalysis



Activation formation

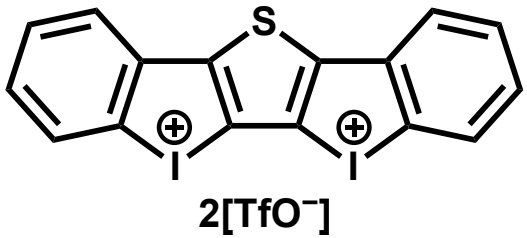




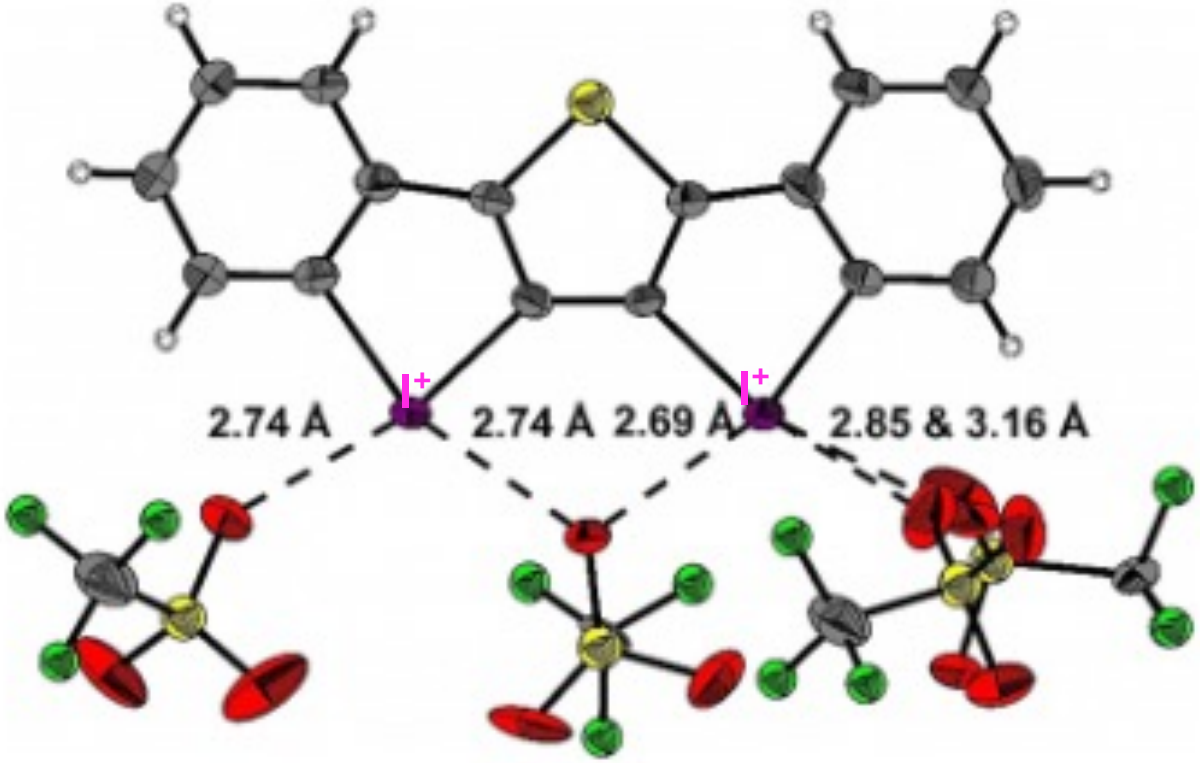
DFT Calculation: B3LYP-D3/def2-TZVP

Damrath, M.; Scheele, T.; Duvinage, D.; Neudecker, T.; Nachtscheim, B. J. *ACS Catalysis* **2025**, *1*, 422.

Bidentate XB (Halogen Bonding) Donor I



Bidentate XB Donor

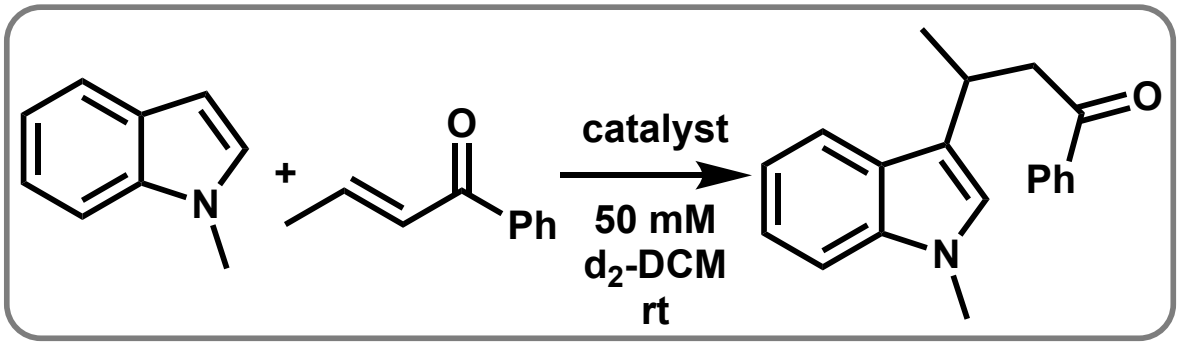


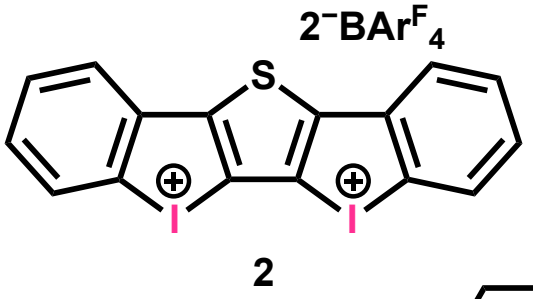
X-ray structural analysis

Angle of C-I···O: 159~160 °
I···O distances: 2.69-2.73 Å
(van der Waals radii: 3.50 Å)

Heinen, F.; Reinhard, D. L.; Engelage, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 5069.

Bidentate XB (Halogen Bonding) Donor II





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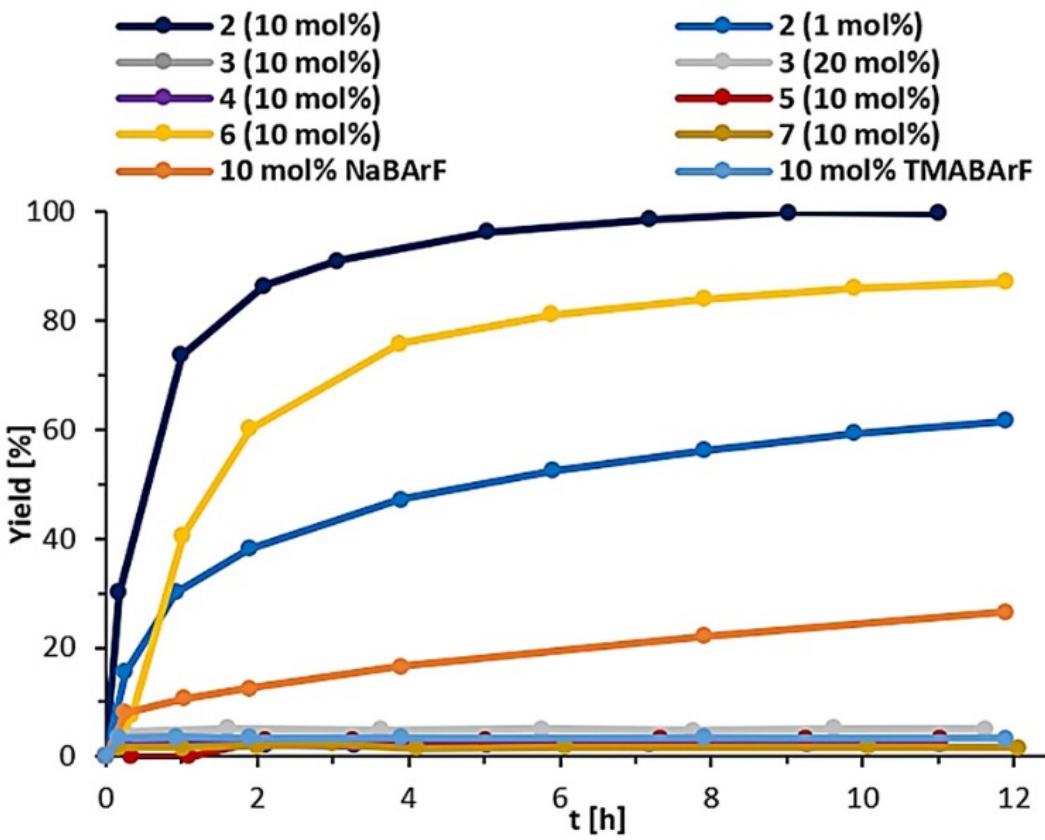
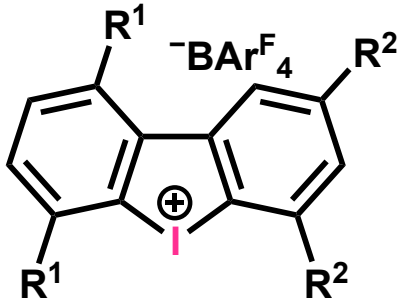
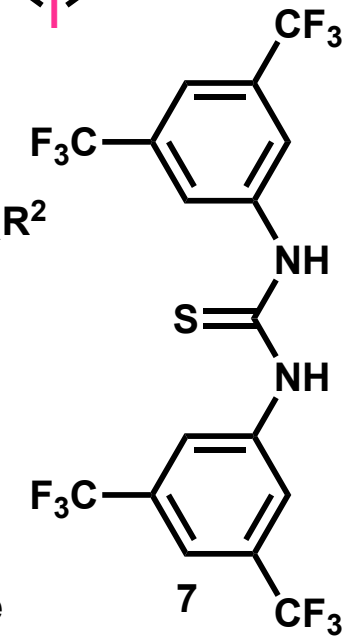




3: R^1 = H, R^2 = H
4: R^1 = Me, R^2 = H
5: R^1 = Me, R^2 = Me



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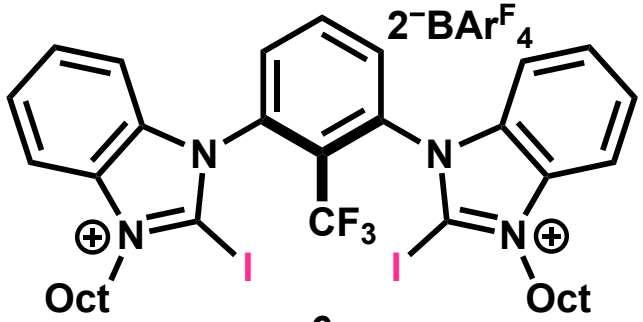
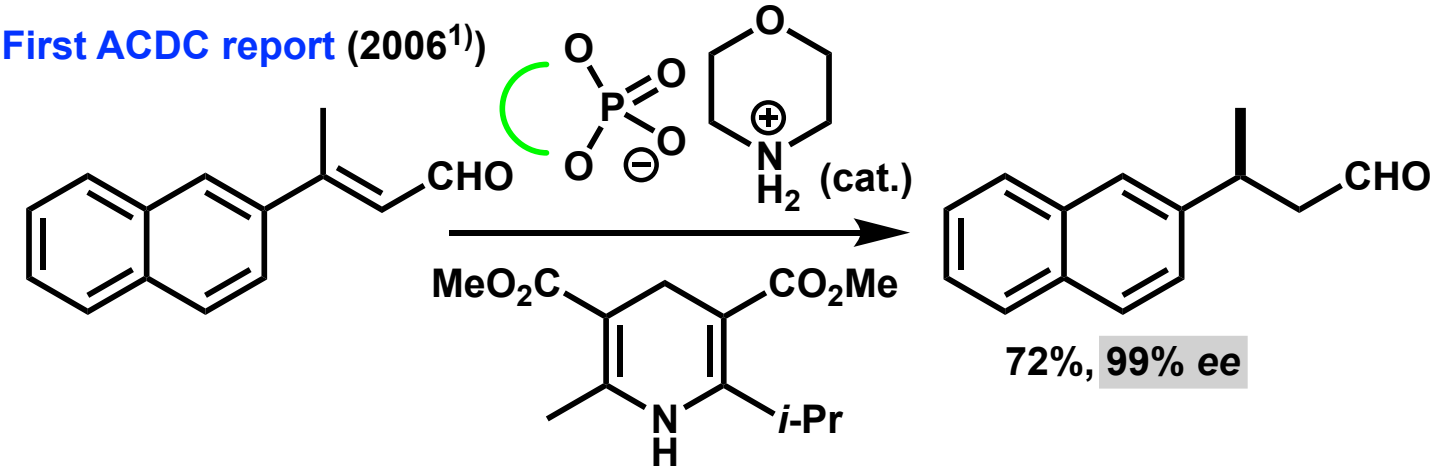


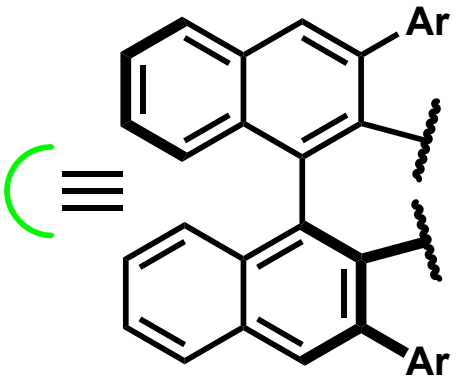
6

Heinen, F.; Reinhard, D. L.; Engelage, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 5069.

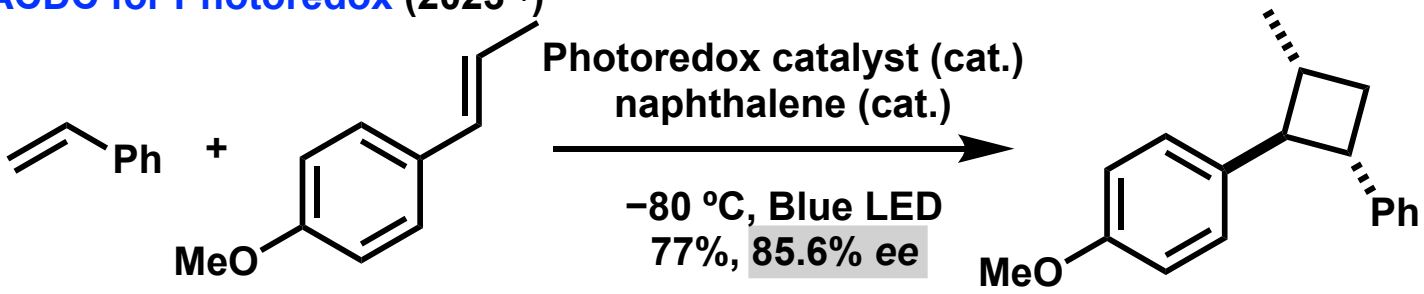
ACDC: Asymmetric Counteranion Directed Catalysis

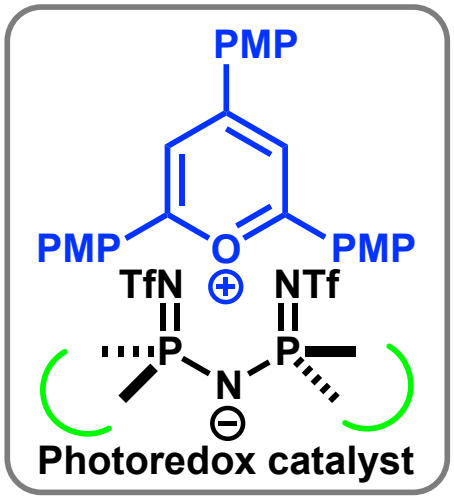
First ACDC report (2006[1])



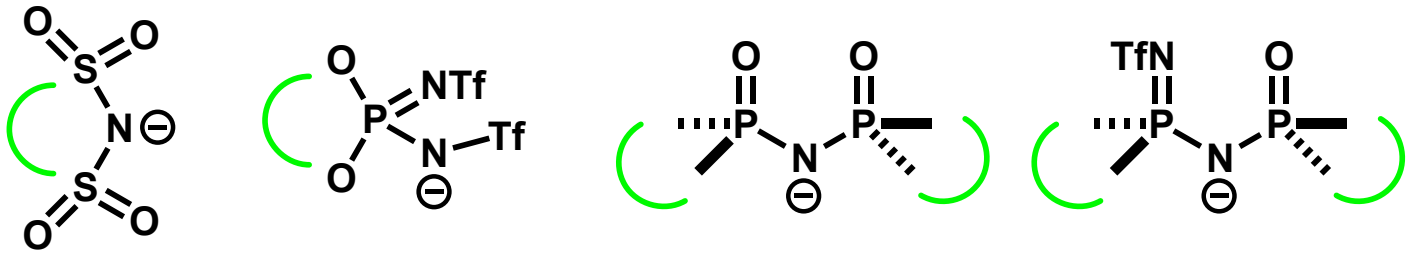


ACDC for Photoredox (2023[2])





Other ACDC (aryl group has a wide variety, so does pKa)

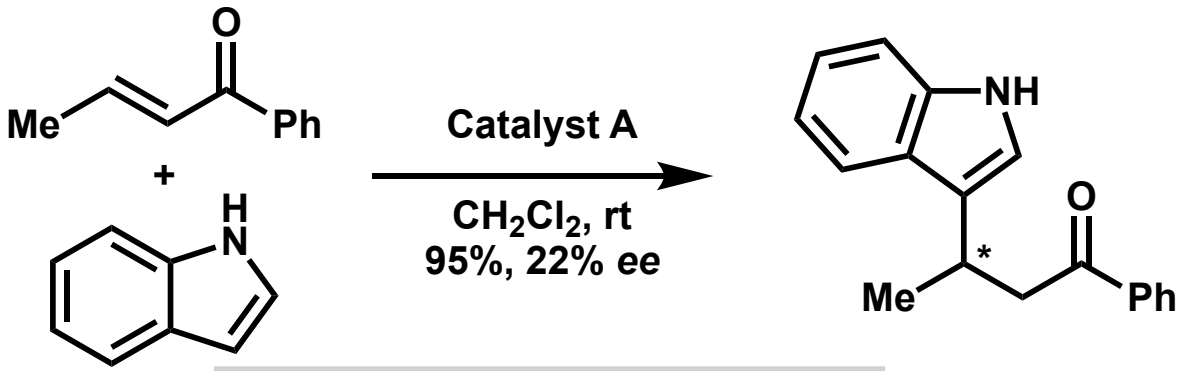


See 180630_LS_Tsukasa_Shimakawa_Asymmetric_Brøsted_Acid_Catalysis_Developed_By_Benjamin_List's Group. 1. Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, 45, 4193. 2. Das, S.; Zhu, C.; Demirbas, D.; Bill, E.; De, C. K.; List, B. *Science* **2023**, *379*, 494.

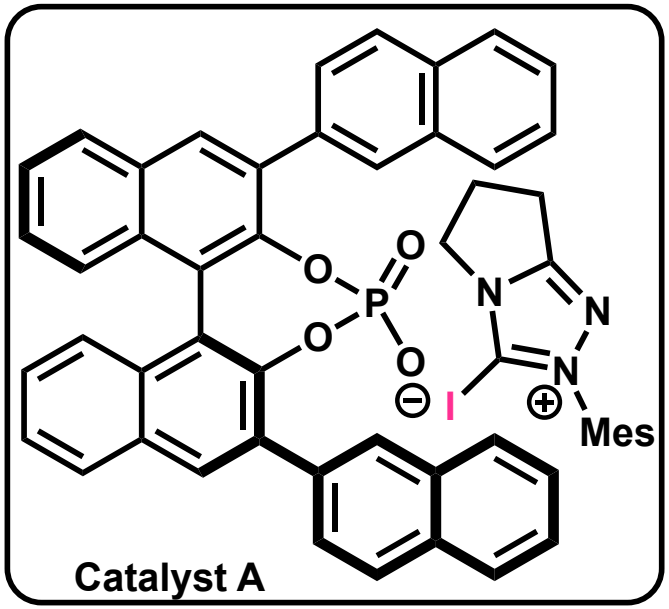
Previous Work: Asymmetric Reaction by XB & ACDC

ACDC: Asymmetric Couteranion Directed Catalysis

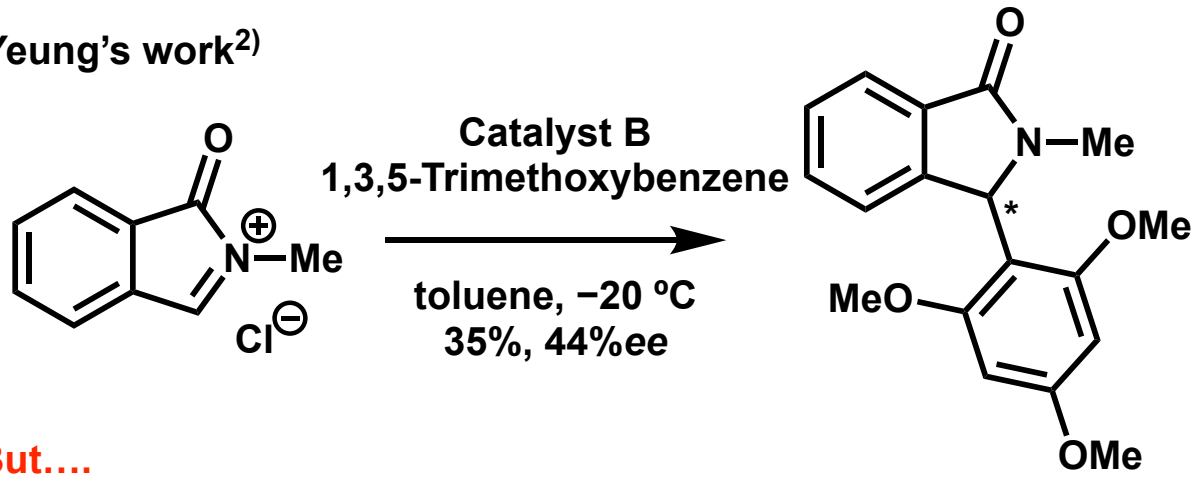
Scheidt's work[1)]

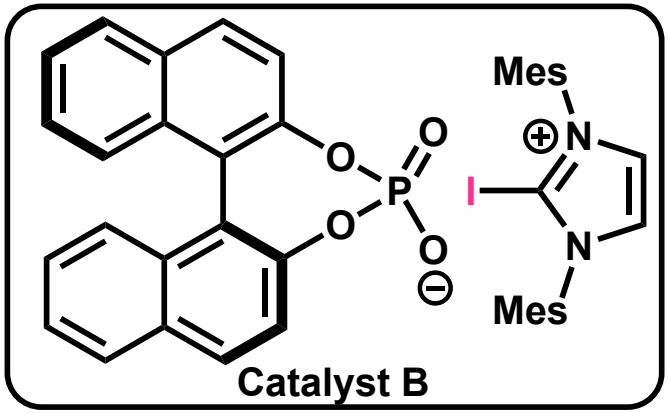


Catalyst A →Chiral phsphoric acid
95%, 8% *ee*



Yeung's work[2)]





But….

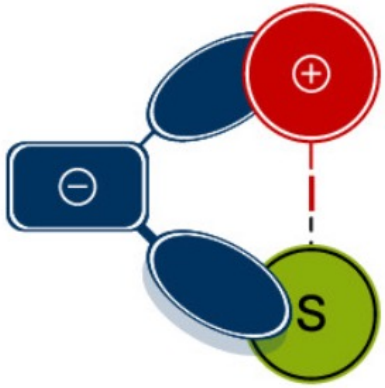
No control experiment was conducted to eliminate the possibility of steric control by 「hidden」 Brønsted acid.

1. Squitieri, R. A.; Fitzpatrick, K. P.; Jaworski, A. A.; Scheidt, K. A. *Chem. Eur. J.* **2019**, *25*, 10069.
2. Chan, Y.-C.; Yeung, Y.-Y. *Org. Lett.* **2019**, *21*, 5665.

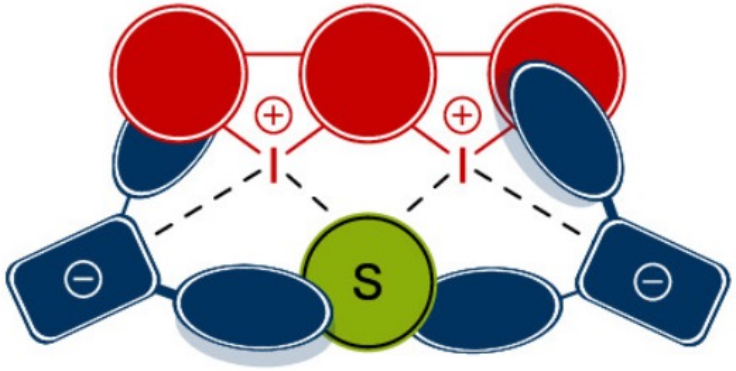
Contents

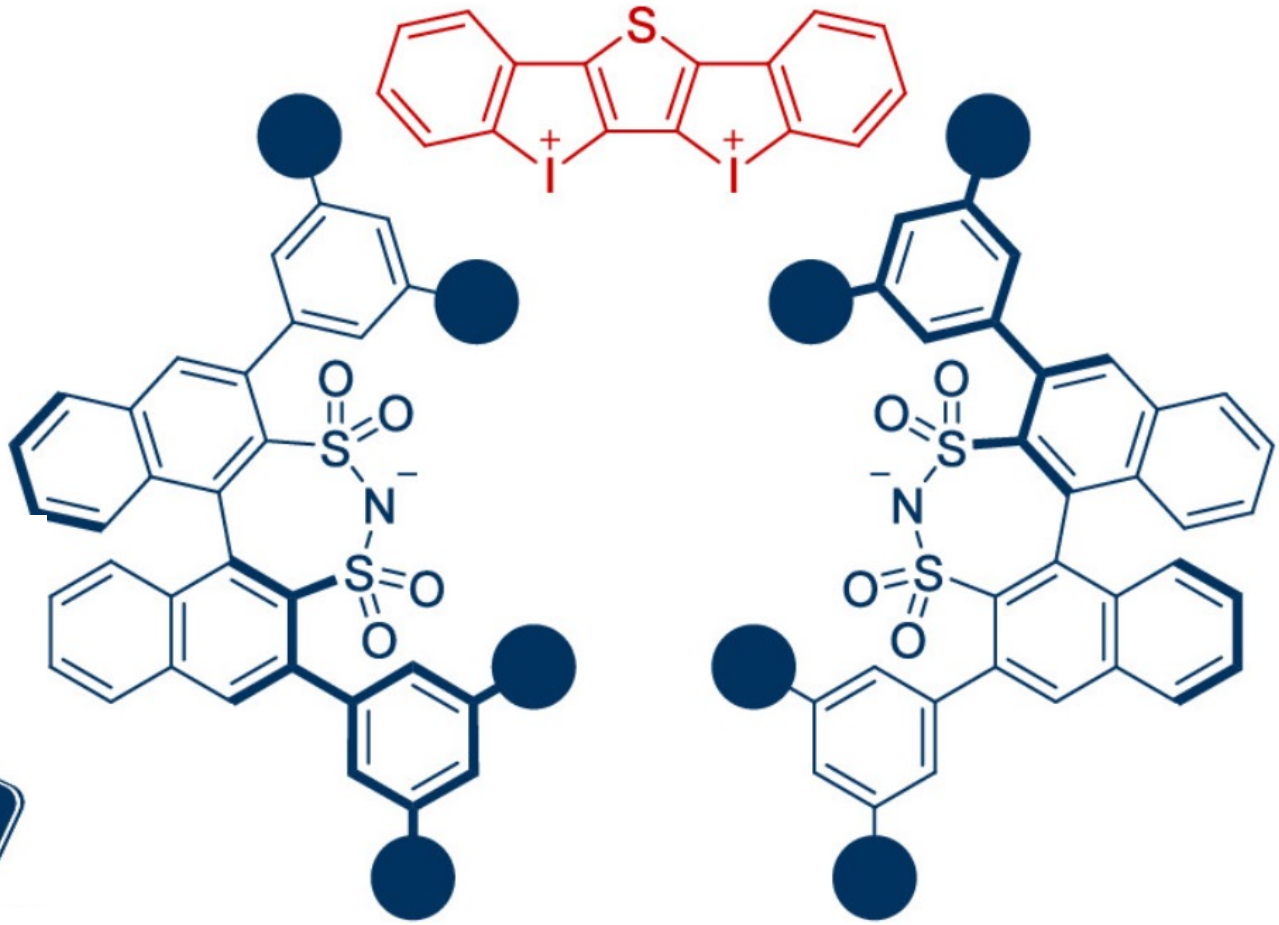
Catalyst Concept

Previous type



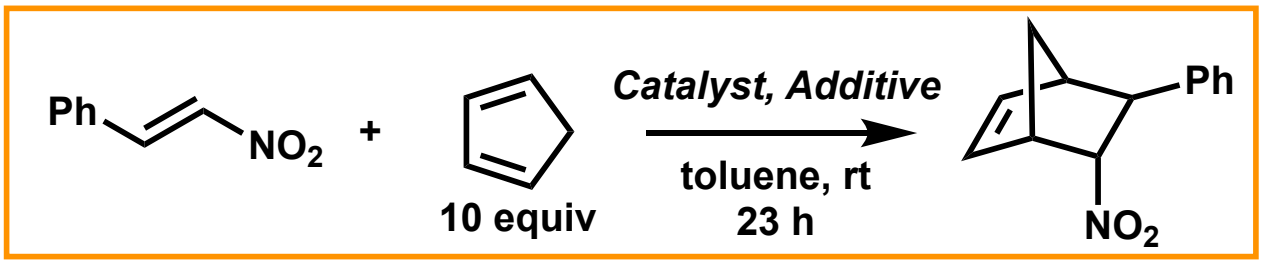
This work

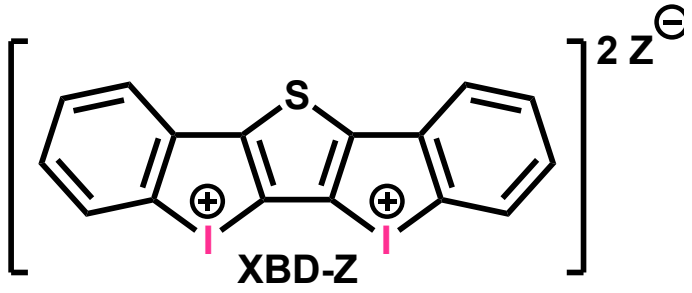




Reinhard, D. L.; Iniutina, A.; Reese, S.; Shaw, T.; Merten, C.; List, B.; Huber, S. M. *J. Am. Chem. Soc.* **2025**, *147*, 8107.

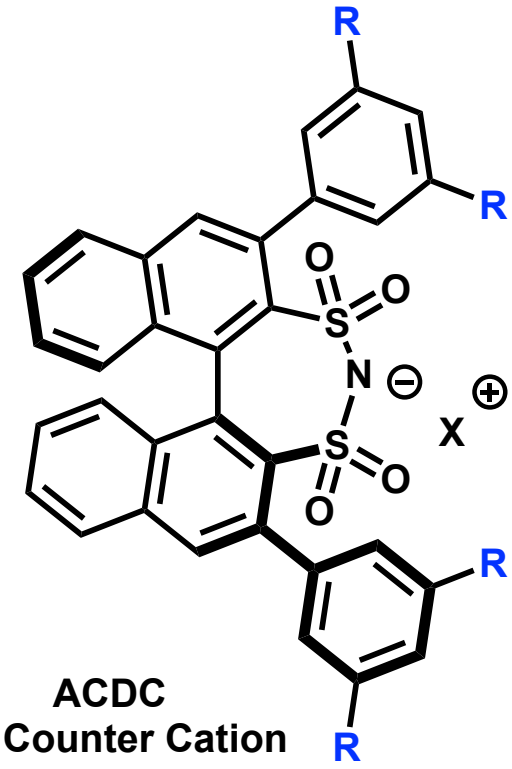
Optimization I



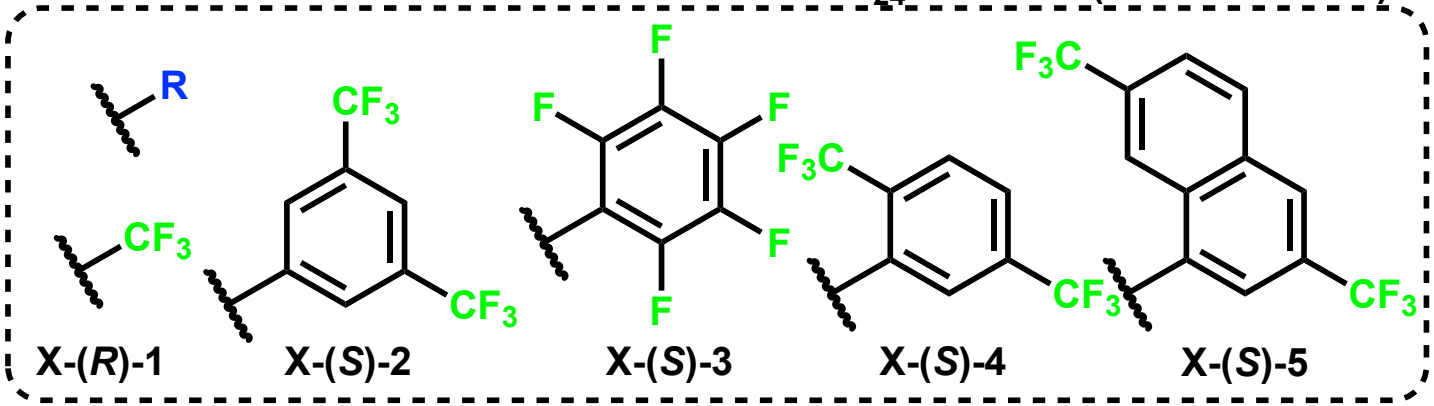


XBD-Z

Z = $BArF_{24}$ or ACDC (Counter Anion)



ACDC
X = Counter Cation



X-(*R*)-1 X-(*S*)-2 X-(*S*)-3 X-(*S*)-4 X-(*S*)-5

Entry	*Catalyst (mol%)*	*Additive(mol%)*	*Yield(%)*	*ee(%)*
0	-	-	12	-
1	XBD-$BArF_{24}$(10)	-	60	-
2	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*R*)-1 (20)	37	50
3	-	N(*n*Bu)$_4$-(*R*)-1 (20)	8	2
4	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-2 (20)	23	38
5	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-3 (20)	35	52
6	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-4 (20)	46	72
7	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-5 (20)	69	70

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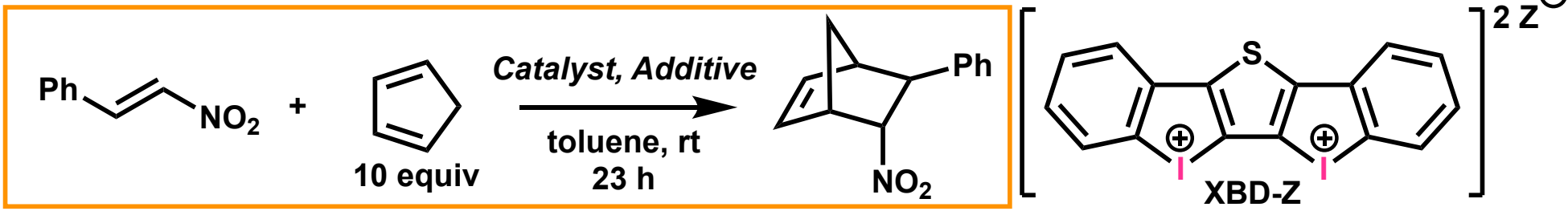
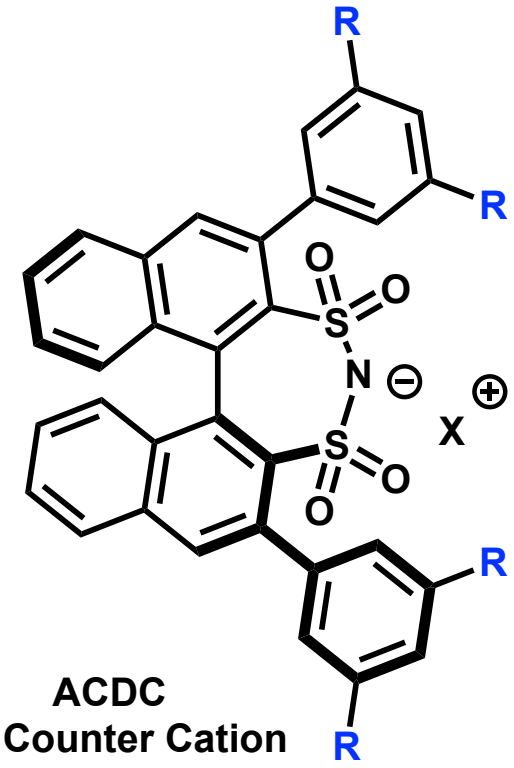
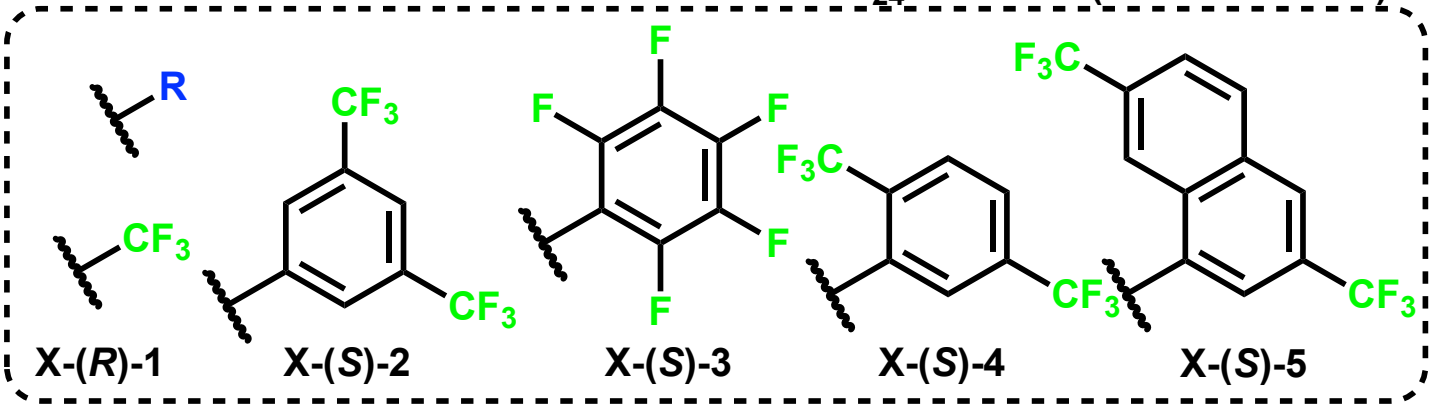
Optimization II



Z = $BArF_{24}$ or ACDC (Counter Anion)



ACDC
X = Counter Cation



X-(*R*)-1 X-(*S*)-2 X-(*S*)-3 X-(*S*)-4 X-(*S*)-5

Entry	*Catalyst (mol%)*	*Additive (mol%)*	*Yield(%)*	*ee(%)*
0	-	-	12	-
6	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-4 (20)	46	72
7	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-5 (20)	69	70
8	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-5 (10)	34	4*
9	XBD-$BArF_{24}$(10)	N(*n*Bu)$_4$-(*S*)-5 (30)	54	64
10	XBD-(*S*)-4 (10)	-	94	86
11	XBD-(*S*)-5 (10)	-	>95	76

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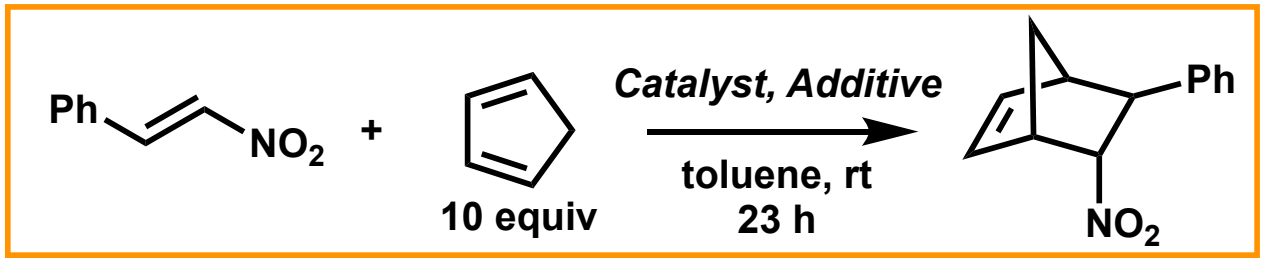
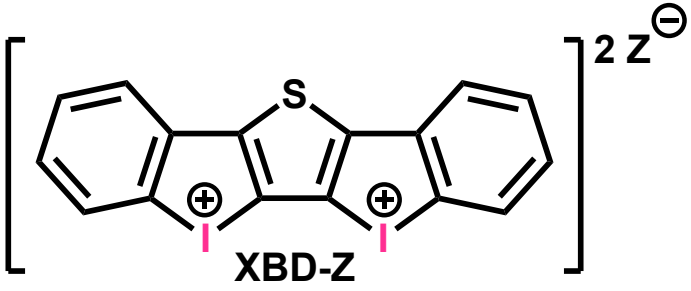
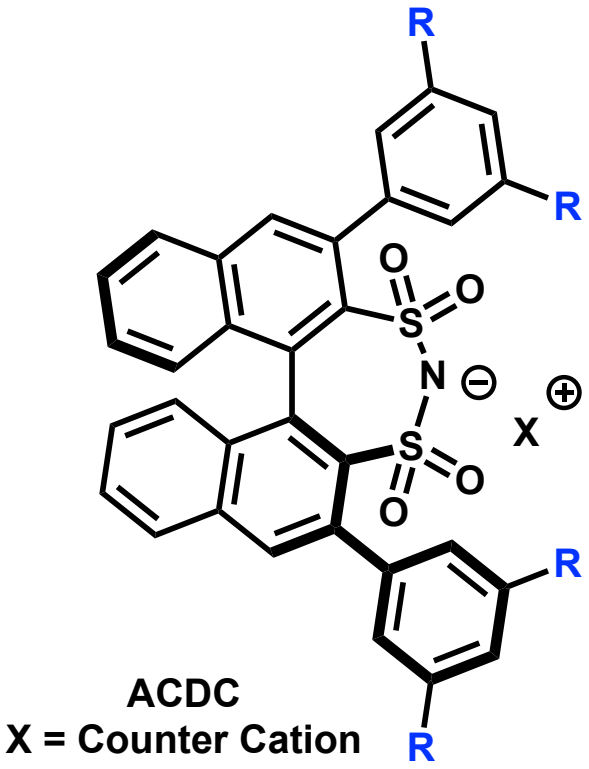
Optimization III

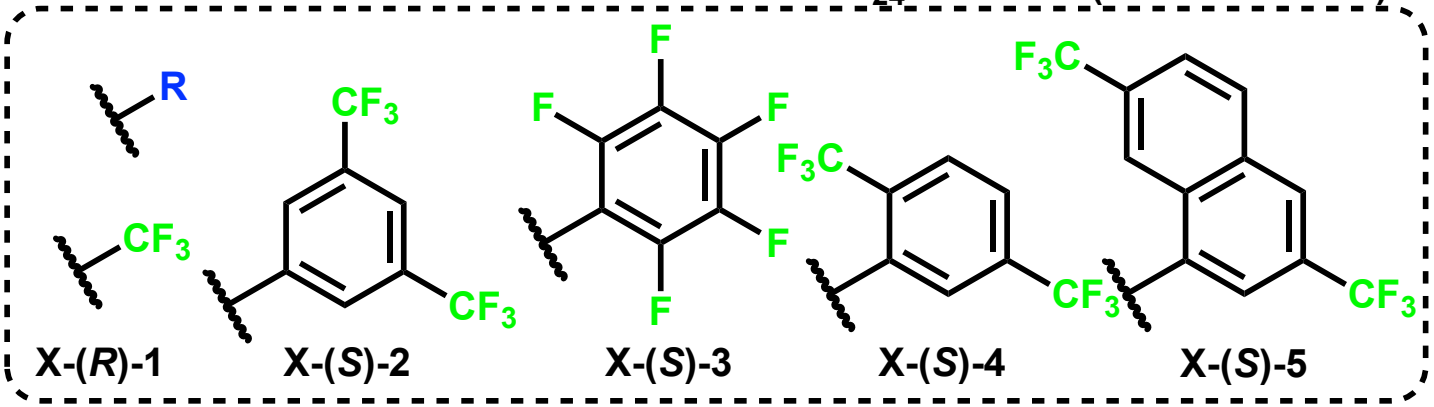




Z = $BArF_{24}$ or ACDC (Counter Anion)



ACDC
X = Counter Cation



Entry	Catalyst (mol%)	Concentration (mM)	Yield(%)	ee(%)
0	-	100	12	-
10	XBD-(*S*)-4 (10)	50	94	86
11	XBD-(*S*)-4 (10)	12.5	56	89
12	XBD-(*S*)-4 (5)	12.5	32	86
13	XBD-(*S*)-4 (2)	12.5	10	74
14	H-(*S*)-4 (20)	50	9	2

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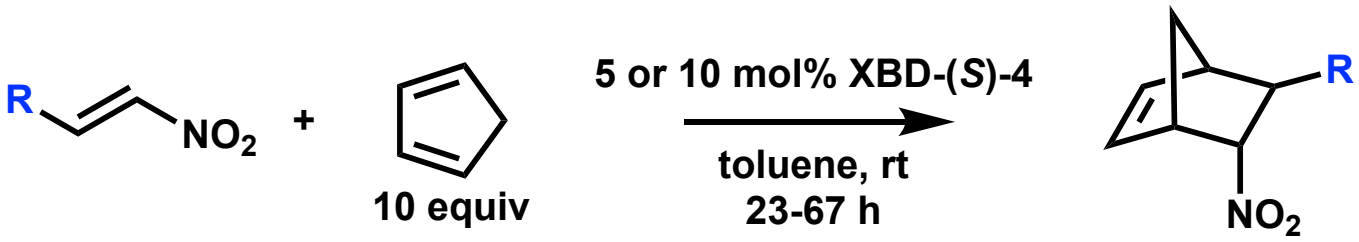
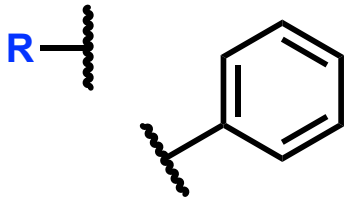
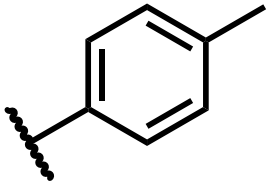
Substrate Scope

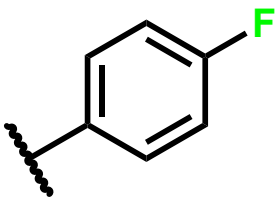




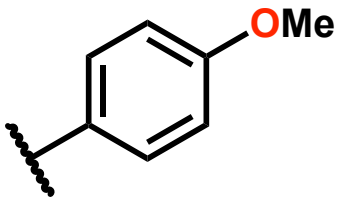
10 mol%, 23 h
56%, 89% *ee*



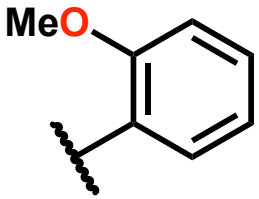
5 mol%, 67 h
91%, 90% *ee*



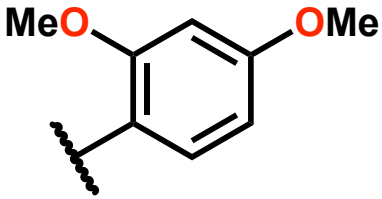
10 mol%, 23 h
75%, 86% *ee*



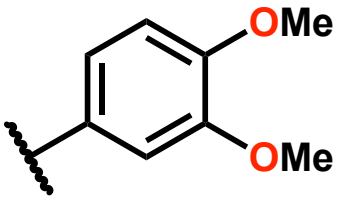
5 mol%, 67 h
95%, 93% *ee*



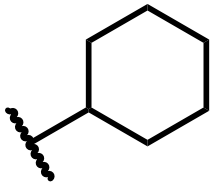
5 mol%, 67 h
96%, 94% *ee*



5 mol%, 67 h
86%, 96% *ee*



5 mol%, 67 h
66%, 95% *ee*



10 mol%, 65 h
8%, 58% *ee*

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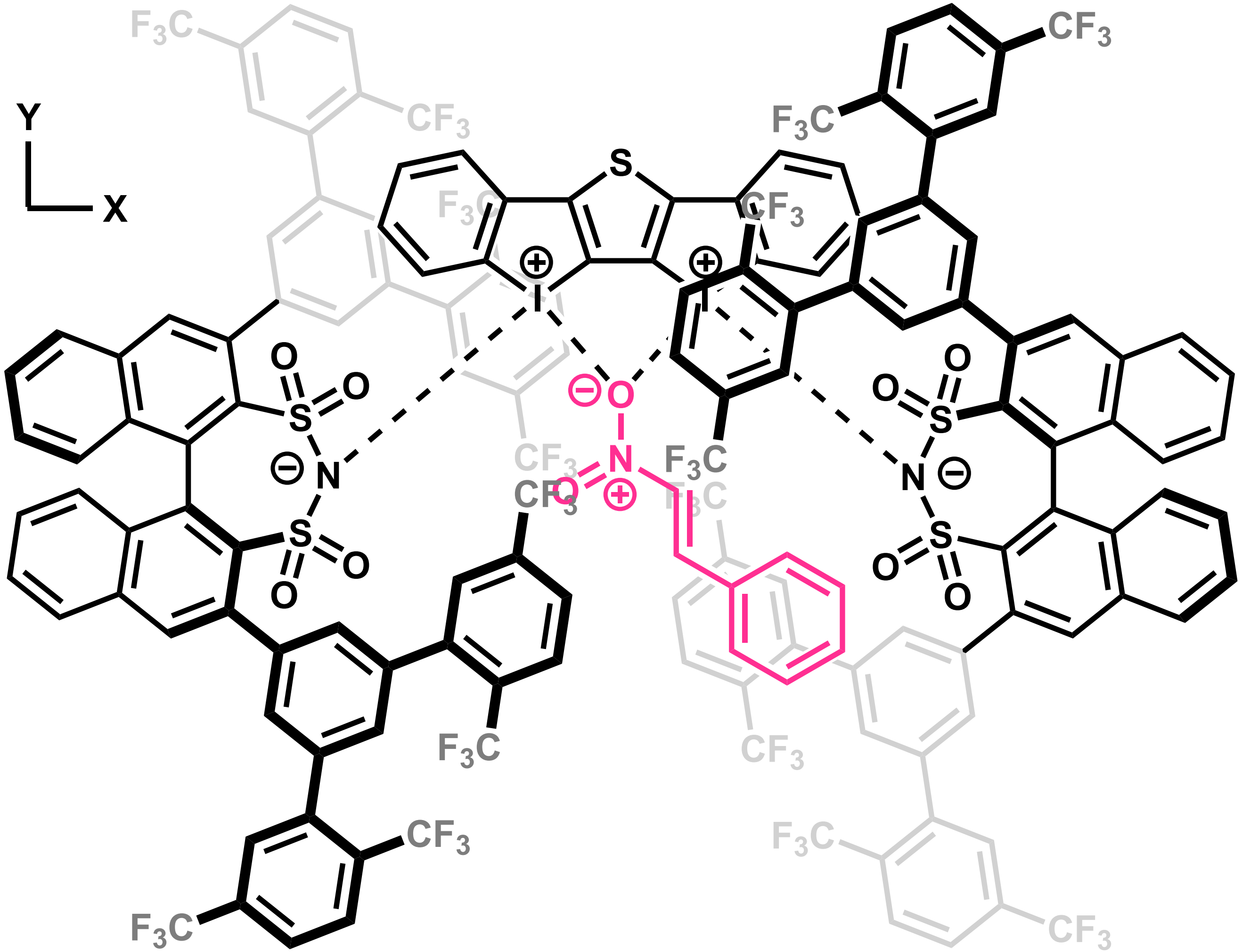
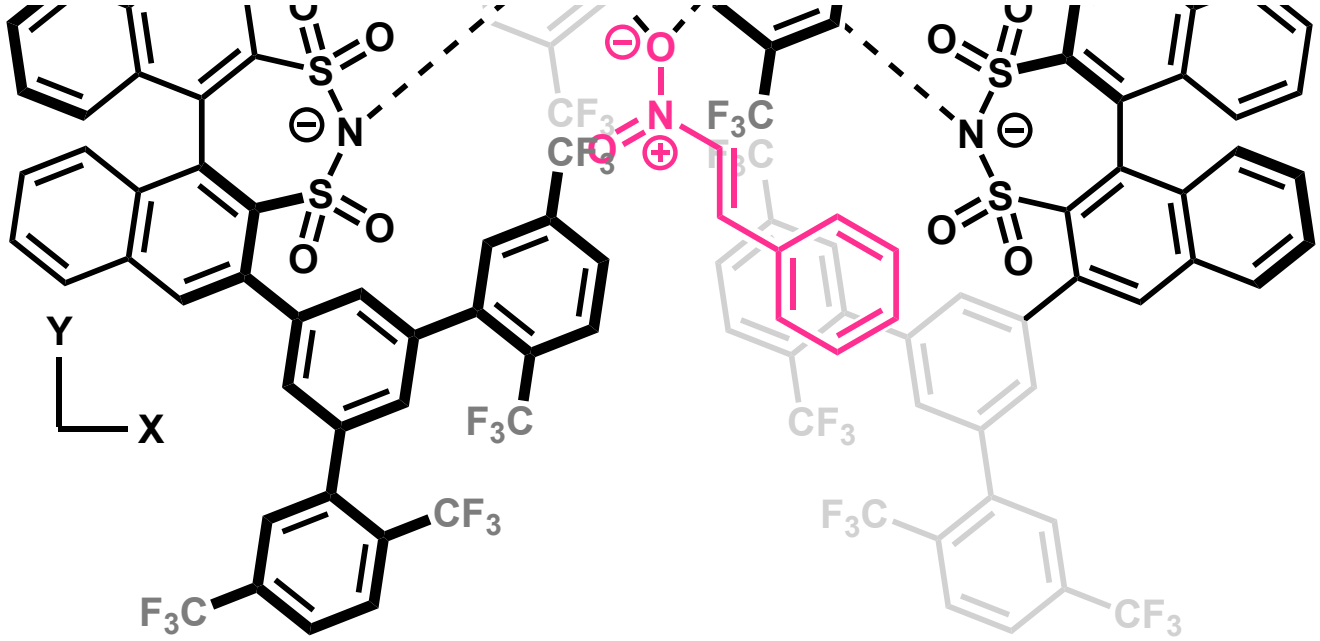
Enantio-Selectivity: My Proposal I

If catalyst concept worked well

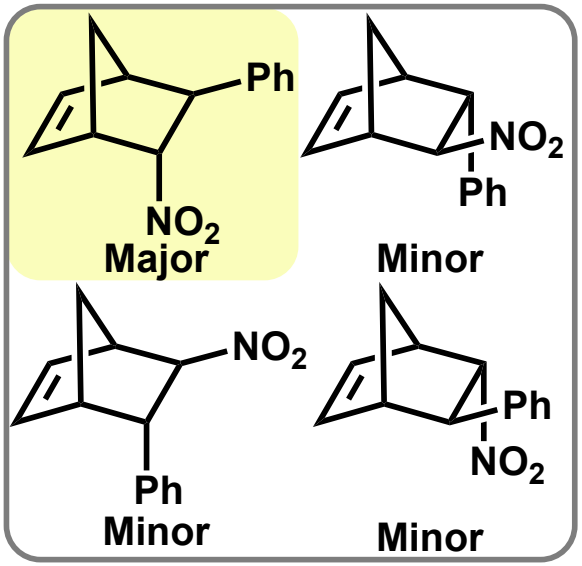


Reinhard, D. L.; Iniutina, A.; Reese, S.; Shaw, T.; Merten, C.; List, B.; Huber, S. M. *J. Am. Chem. Soc.* **2025**, *147*, 8107.

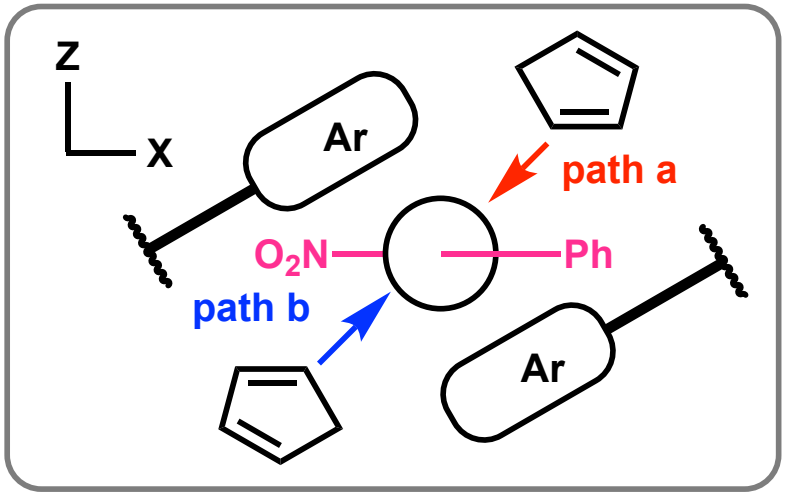
Enantio-Selectivity: My Proposal II



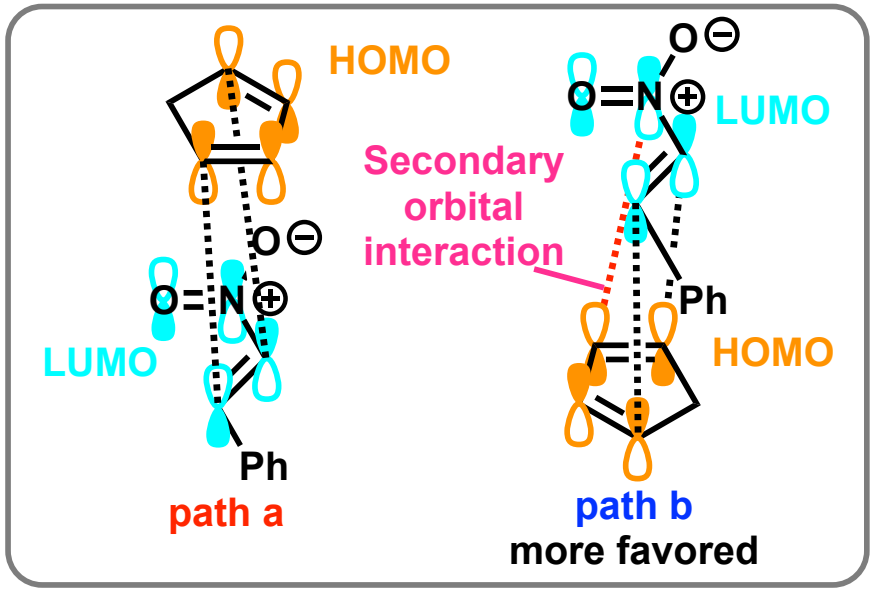
Products



See along the direction of the Y axis

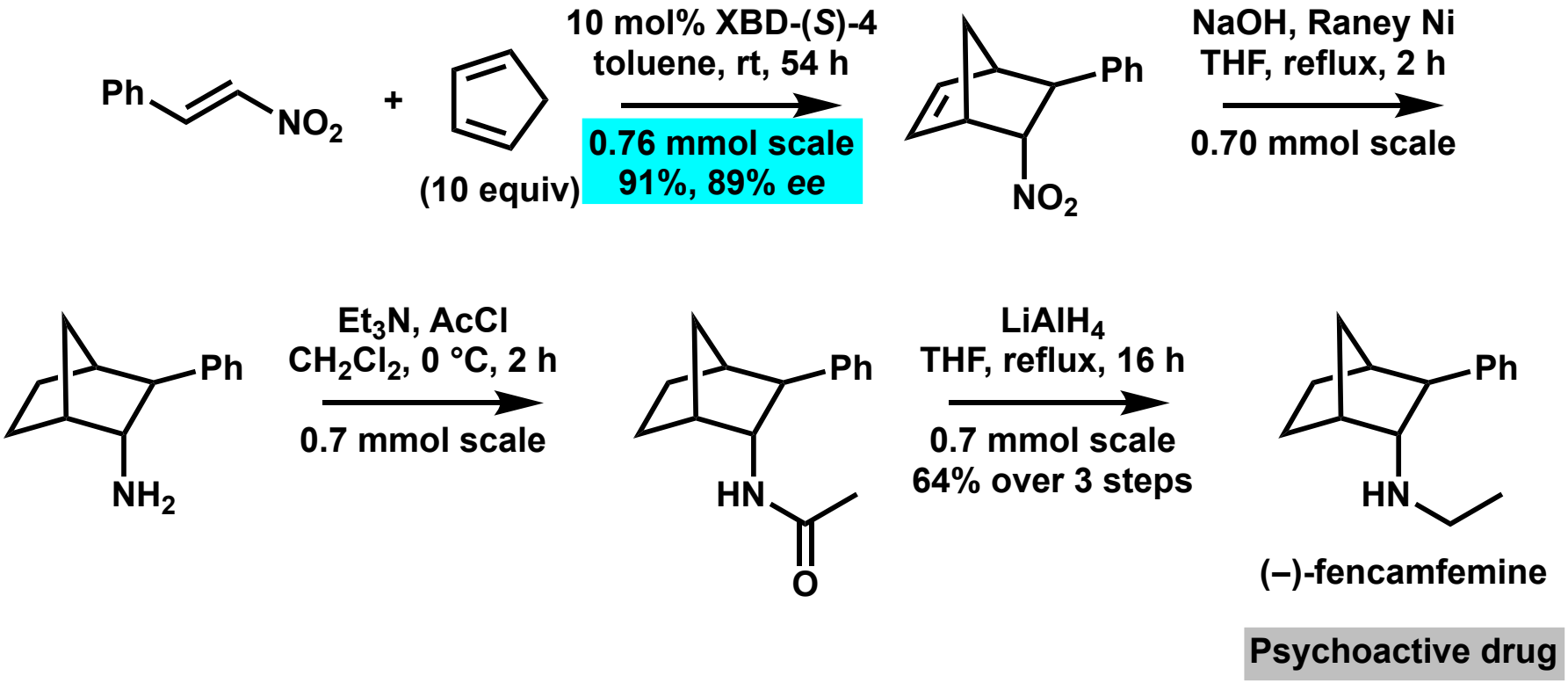


Transition state of Diels-Alder reaction



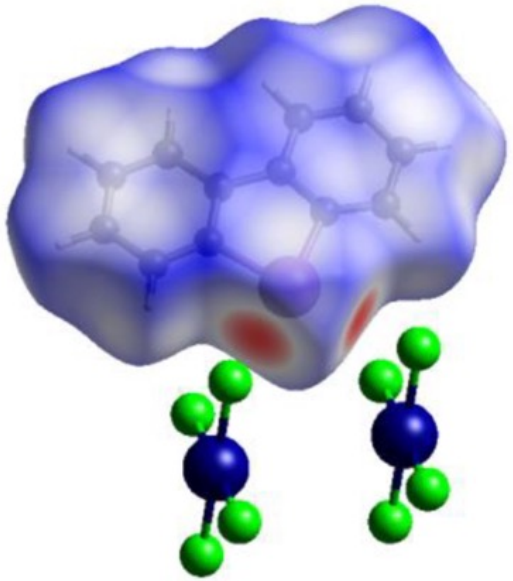
Reinhard, D. L.; Iniutina, A.; Reese, S.; Shaw, T.; Merten, C.; List, B.; Huber, S. M. *J. Am. Chem. Soc.* **2025**, *147*, 8107.

Application to Synthesis of (−)-fencamfamine



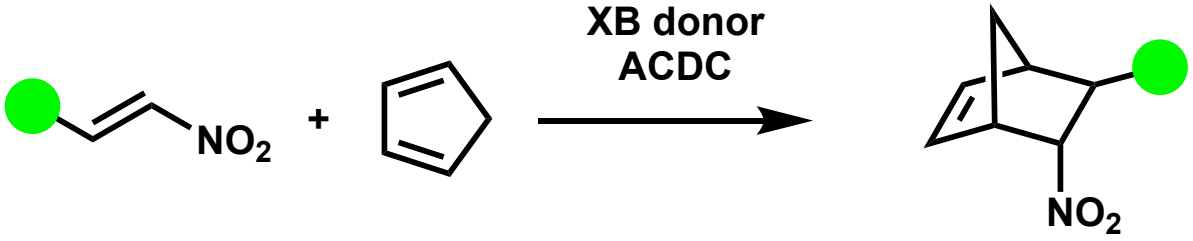
Reinhard, D. L.; Iniutina, A.; Reese, S.; Shaw, T.; Merten, C.; List, B.; Huber, S. M. *J. Am. Chem. Soc.* **2025**, *147*, 8107.

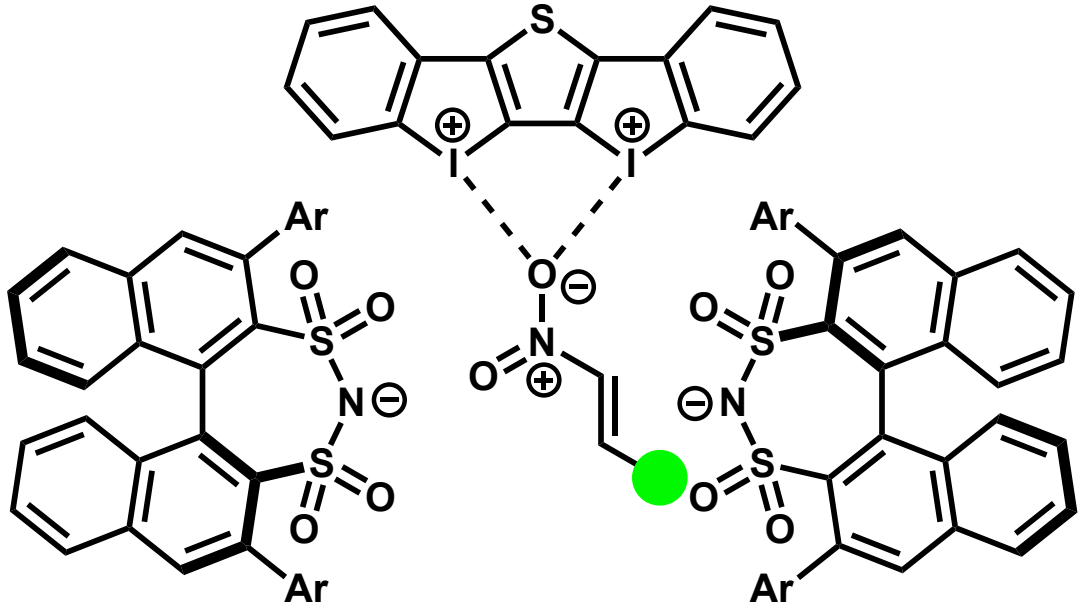
Summary



Double σ-hole of iodine (III)

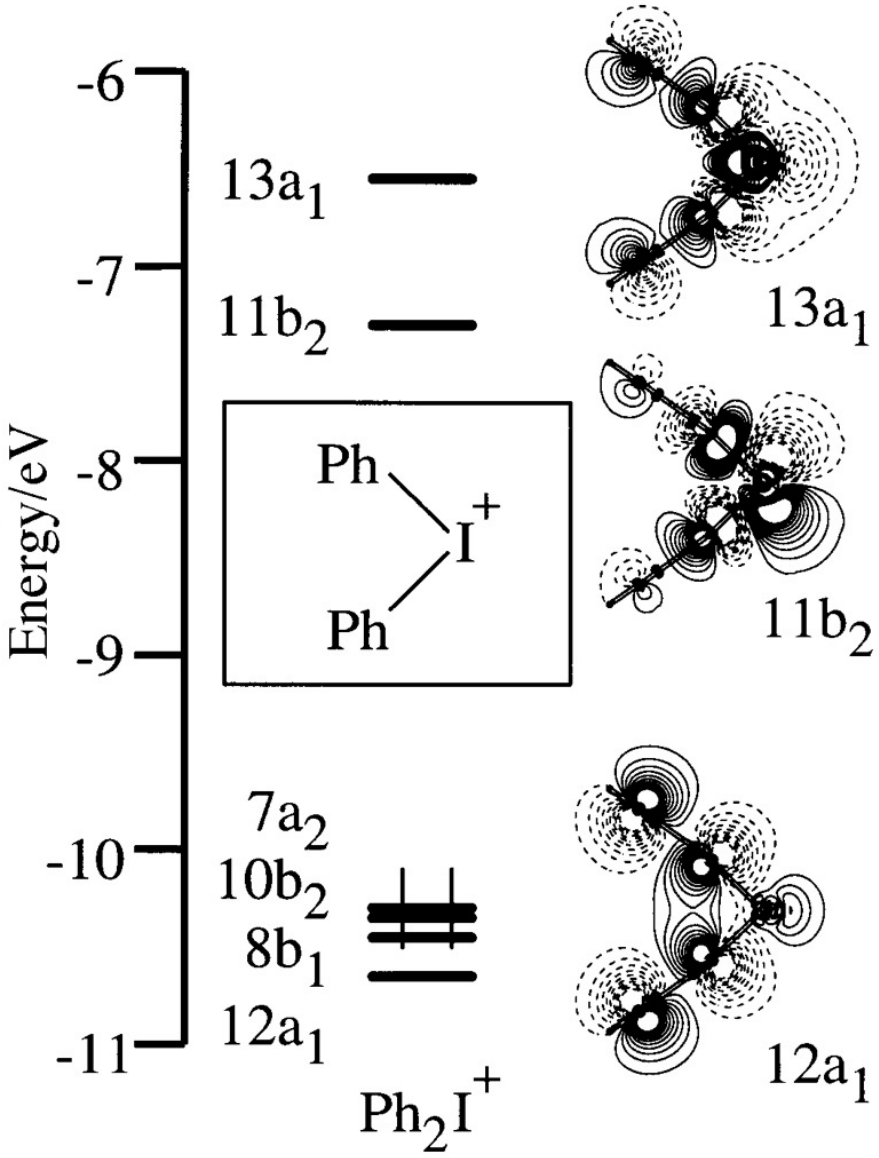
Highly enantioselective Diels-Alder reaction

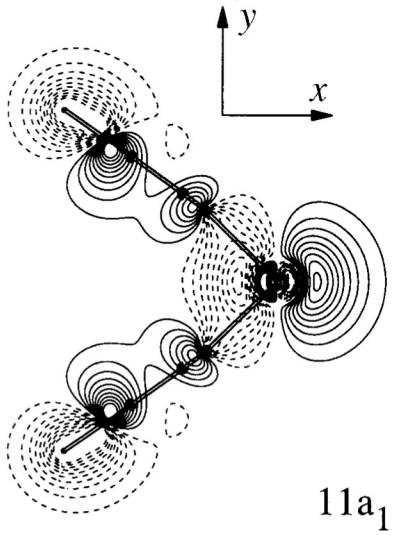




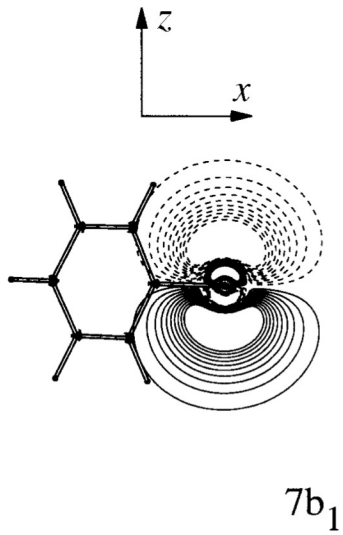
Appendix

Lone-Pair Orbital of Diphenyl Iodonium Salt





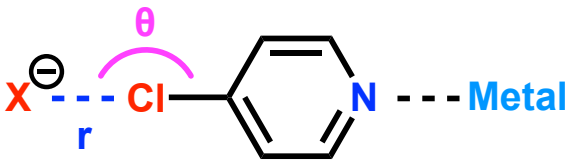
−12.34 eV



−11.78 eV

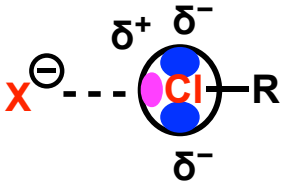
Landrum, G. A.; Goldberg, N.; Hoffmann, R.; Minyaev, R. M. *New. J. Chem.* **1998**, *22*, 883.

Halogen Halide Interaction



		r	θ	ΔE
no metal	F^-	2.344 Å	179.7 º	−14.28 kcal/mol
	Cl^-	3.093 Å	179.8 º	−6.28 kcal/mol
	Br^-	3.309 Å	175.6 º	−5.22 kcal/mol
Cu^+	F^-	2.243 Å	180.0 º	−27.99 kcal/mol
	Cl^-	2.930 Å	180.0 º	−16.87 kcal/mol
	Br^-	3.119 Å	180.0 º	−15.12 kcal/mol

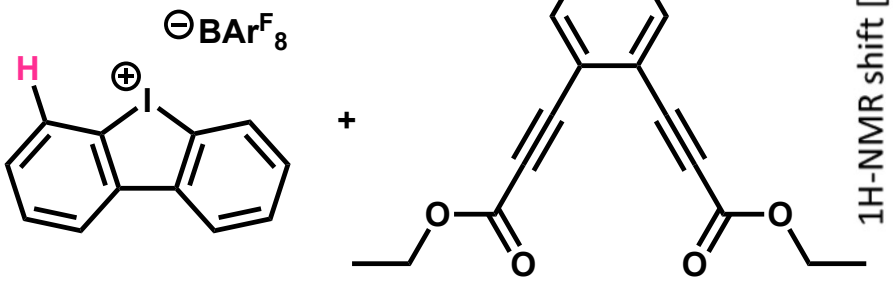
b97-1/lanl2dz(pp) (for Cu)
b97-1/aug-cc-pvdz (for others)

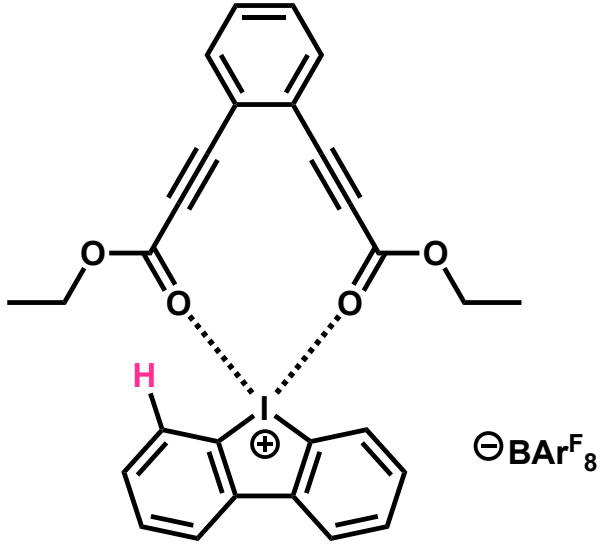


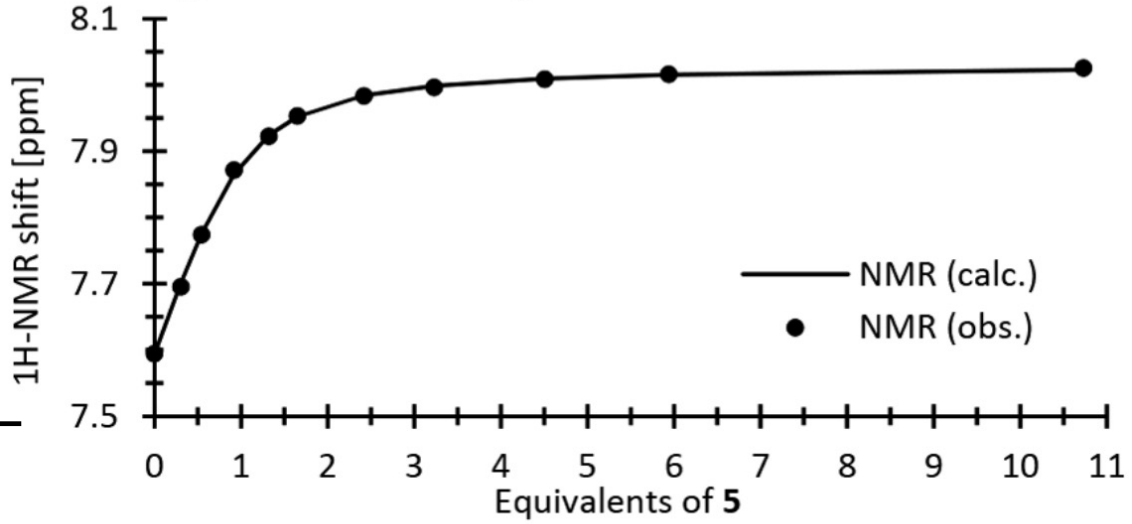
Halide intracts with σ-hole of halogen.

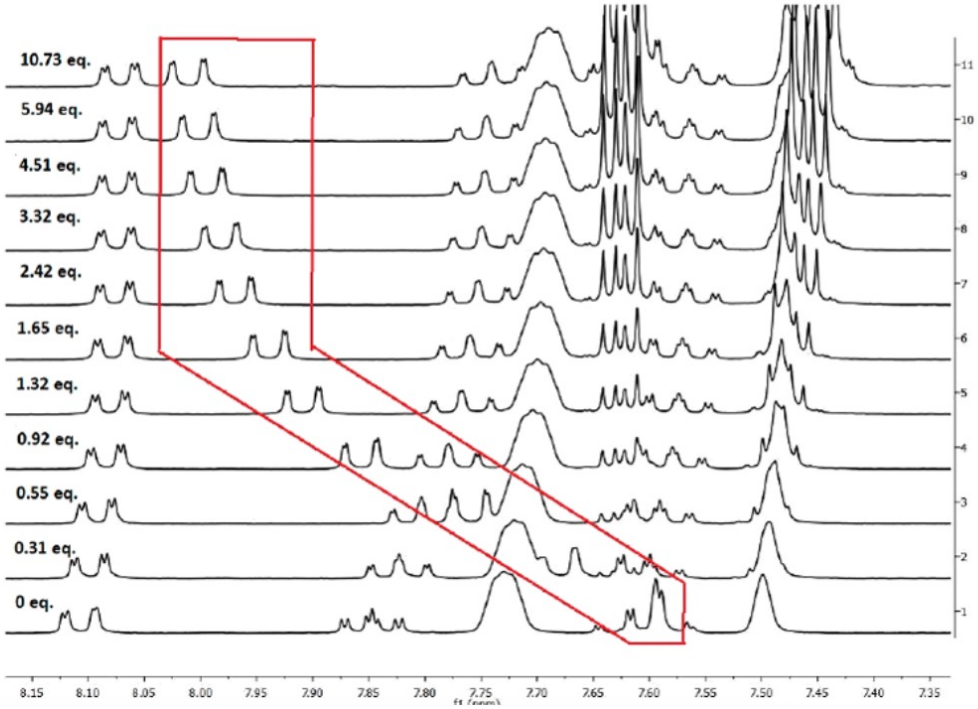
Xu, L.; Lv, J.; Sang, P.; Zou, J.-W.; Yu, Q.-S.; Xu, M.-B. *Chem. Phys.* **2011**, *379*, 66.
Slide 17 page of 241122_LS_Asai_Hibiki_Halogen_Halogen_Interaction

^{1}H NMR & ITC Experiment



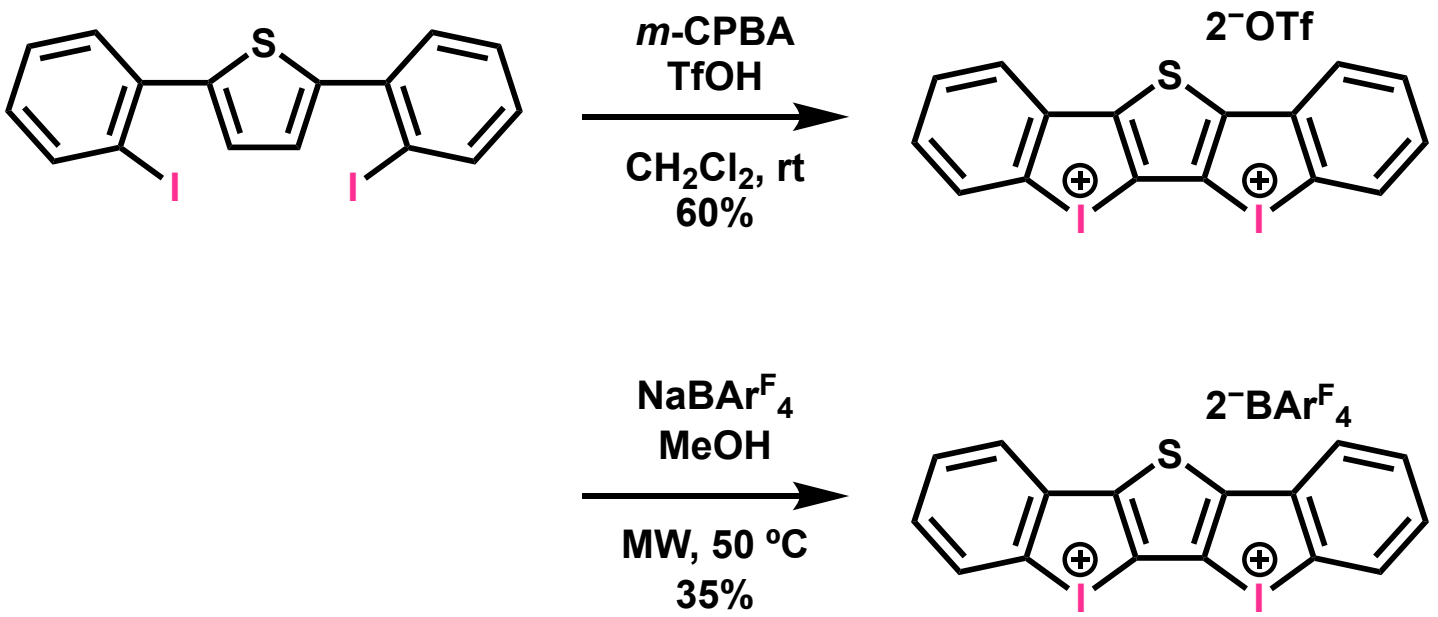






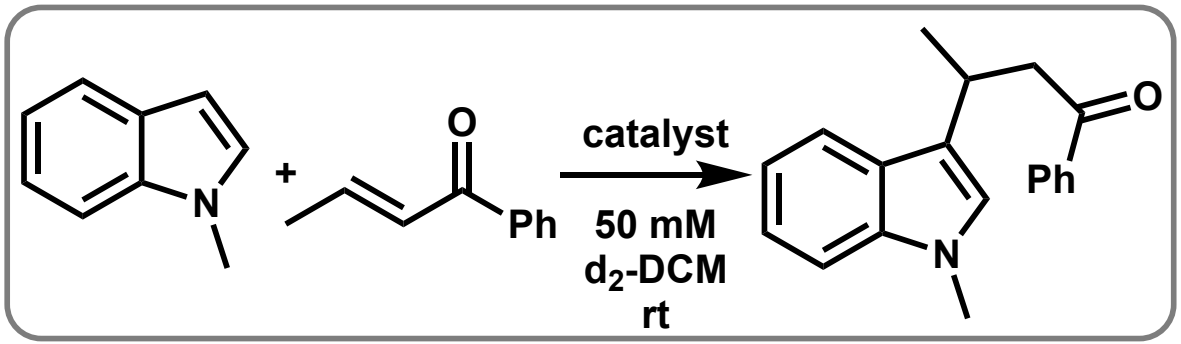
Heinen, F.; Engelage, E.; Cramer, C. J.; Huber, S. M. *J. Am. Chem. Soc,* **2020**, *142*, 8633.

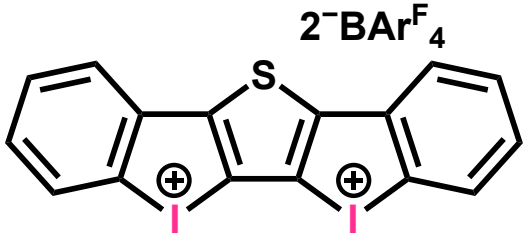
Synthesis of XB Donor

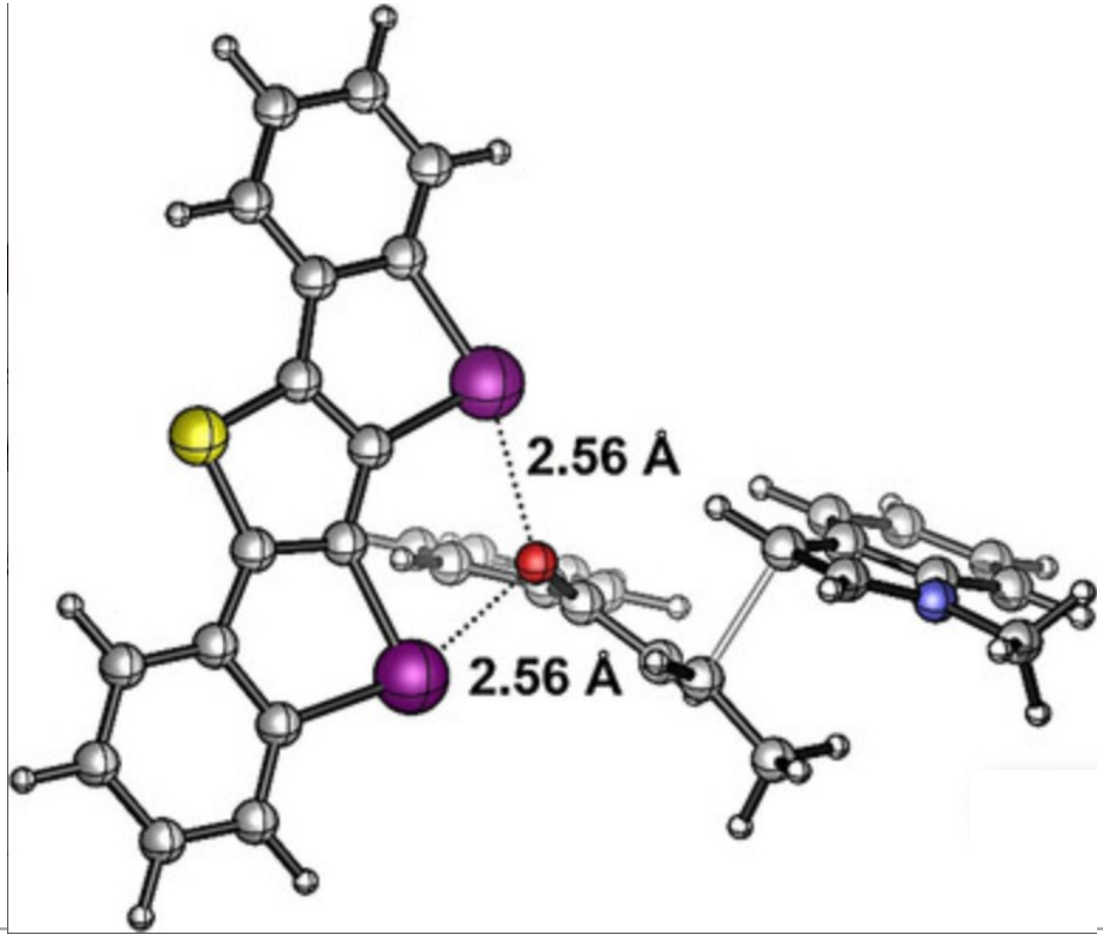


Wu, B.; Yoshikai, N. *Angew. Chem.* **2015**, *127*, 8860.
Heinen, F.; Reinhard, D. L.; Engelage, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 5069.

DFT Calcucation: Michael Addition







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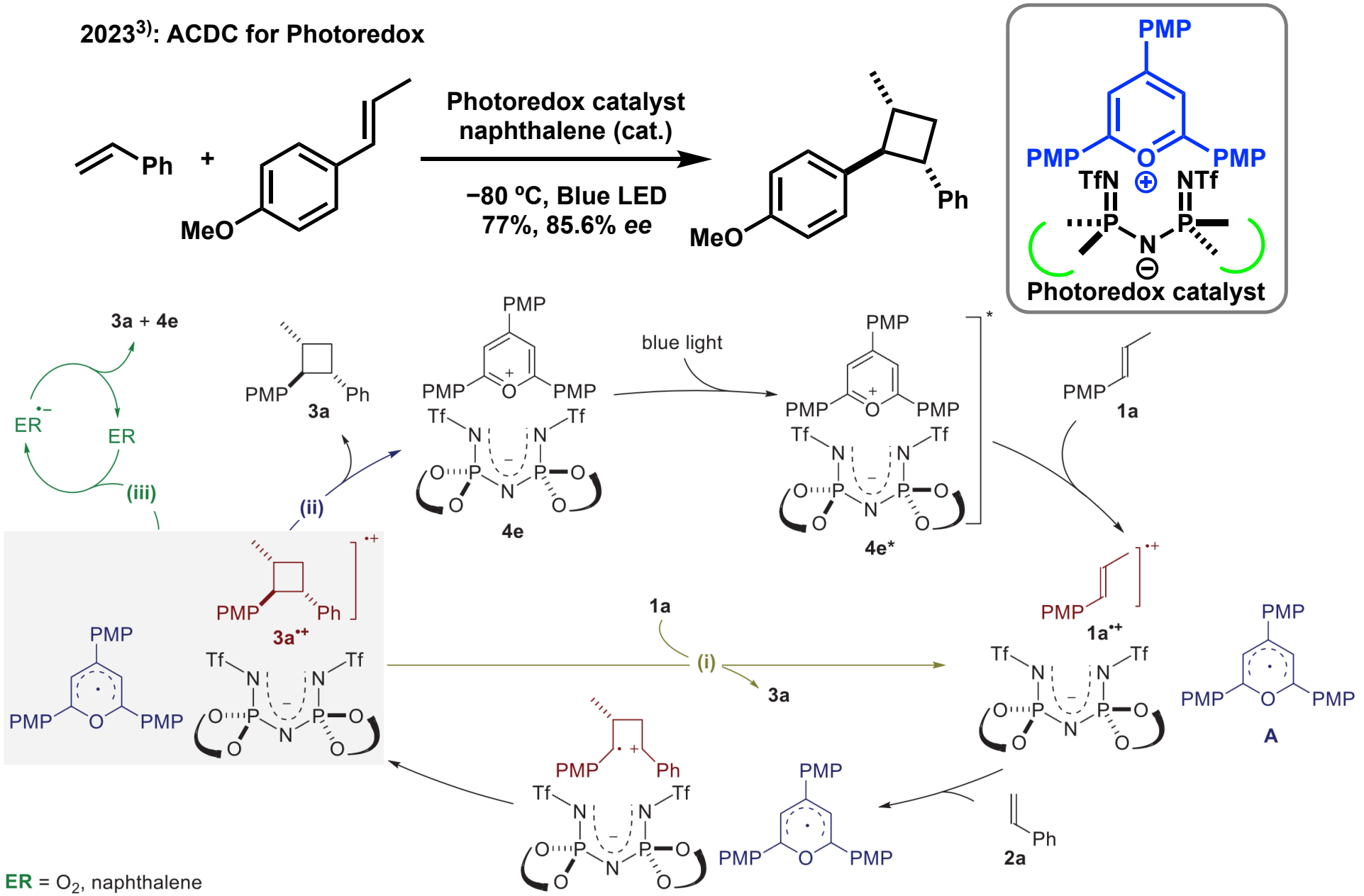
Proposed Catalytic Cycle: Photoredox ACDC



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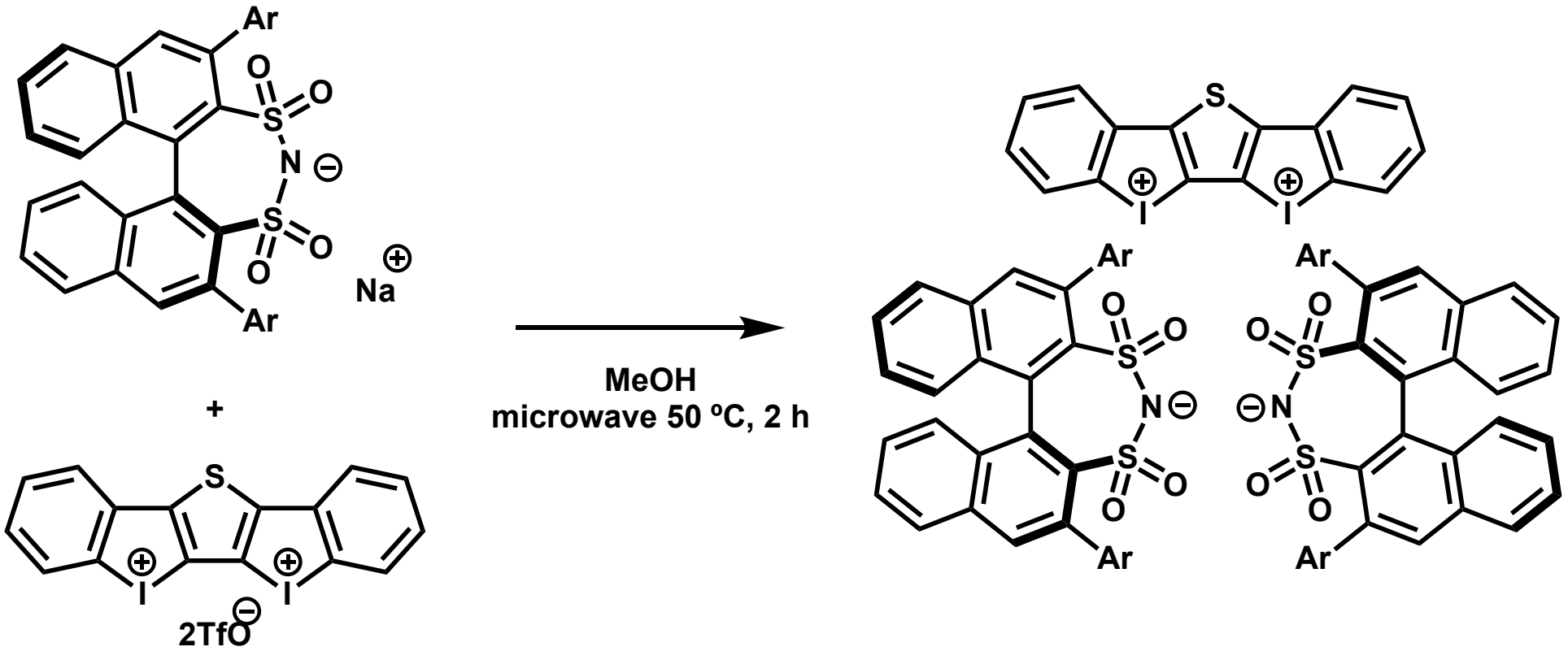
Catalyst Synthesis



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