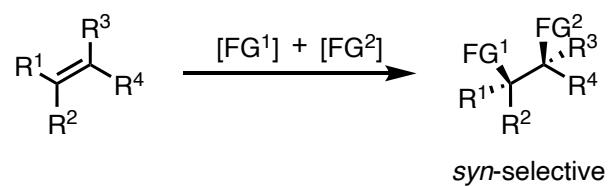


Strategy for the *syn*-selective functionalization of alkenes



2023/11/2 (Thu)
Keigo Nagami

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4. Carbofunctionalization

- 4-1) Carboamination**
- 4-2) Carboboration/Carbosilylation**

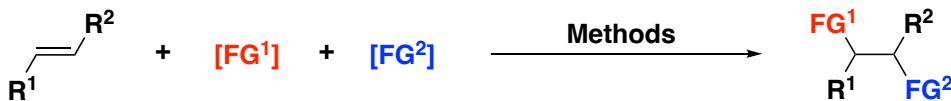
5. Halofunctionalization

- 5-1) Mono-halofunctionalization**
- 5-2) Dihalogenation**

6. Proposal

1. Introduction

1-1. Difunctionalization of alkenes



Methods

Organocatalyzed

Electrochemistry

Radical functionalization

Photocatalyzed

Transition metal catalyzed

1-2. Selectivities

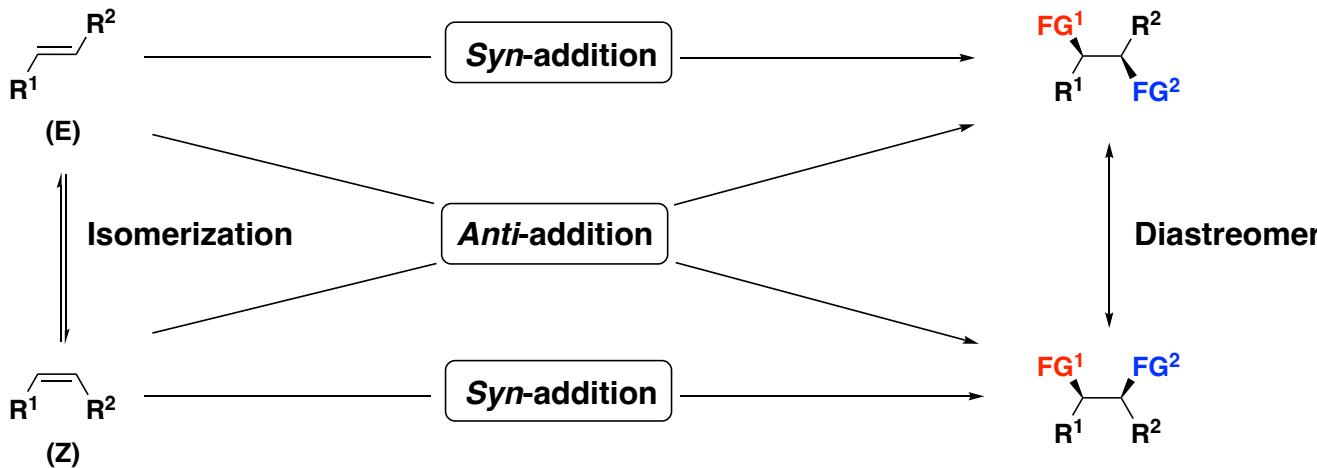
Regioselectivity



Diastereoselectivity



Enantioselectivity



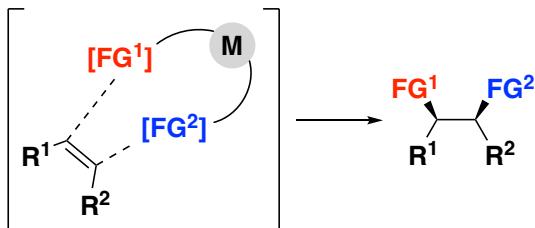
- Pre-isomerization is needed.

- Cyclic alkenes are not tolerated.

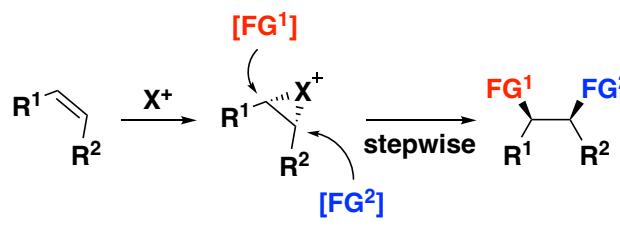
→ **Syn selective addition are desired.**

1-3. Methods for syn-addition

Type I



Type II

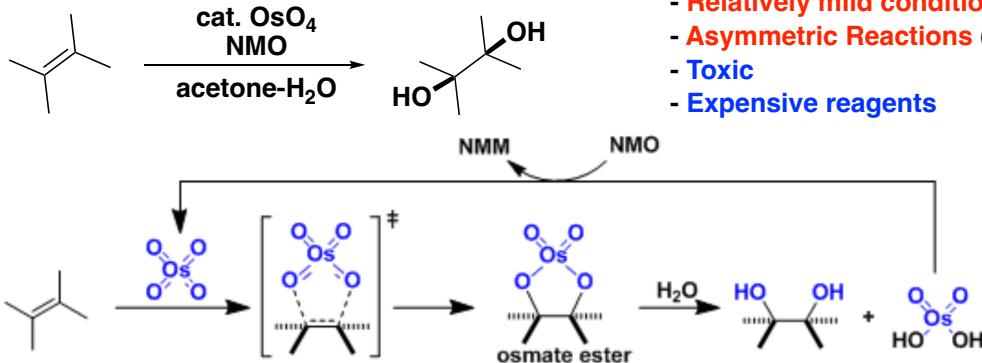


Etc...

2. Dihydroxylation

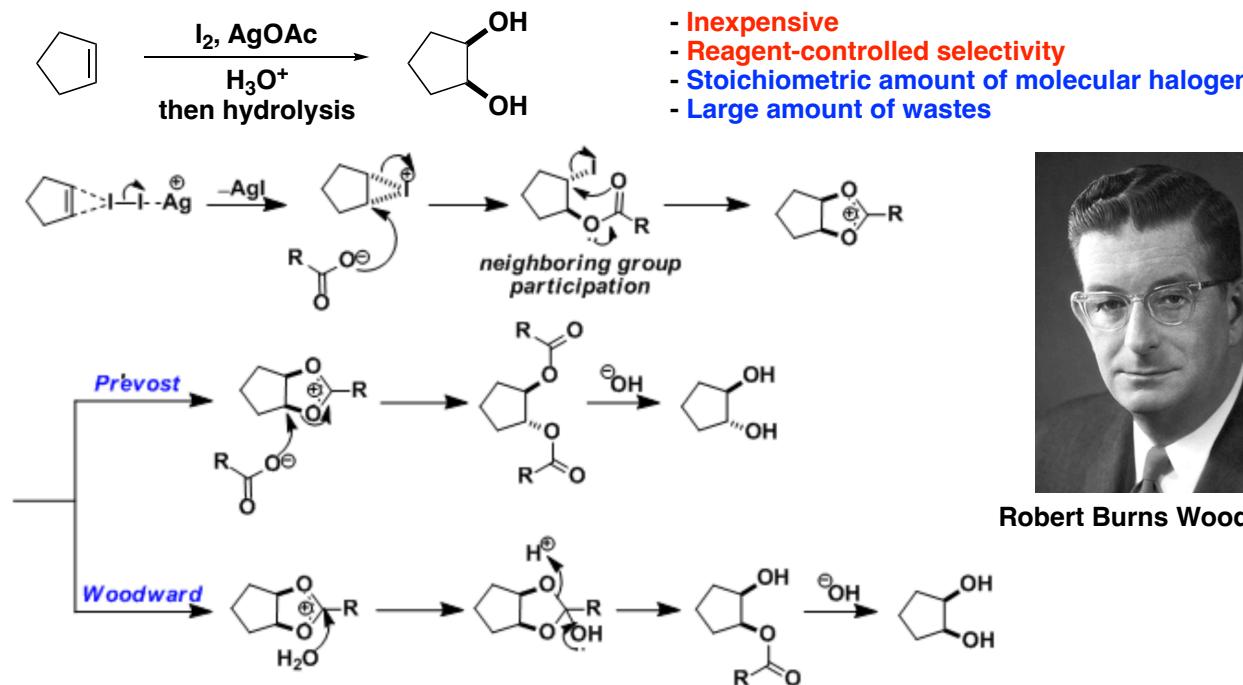
2-1. Background

Osmium-Catalyzed Reaction (1936~¹)



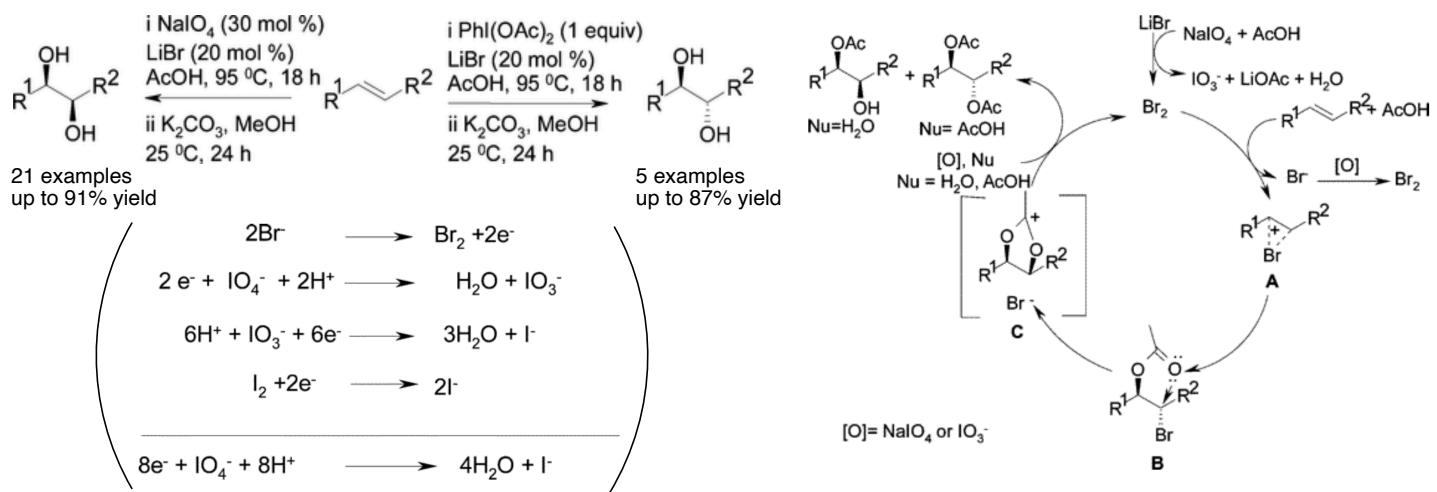
- Highly versatile
- Relatively mild conditions
- Asymmetric Reactions (ex. 1980 Sharpless²)
- Toxic
- Expensive reagents

Woodward Reaction (1958³)



Robert Burns Woodward

2-2. Transition-metal-free Reaction⁴



1) Milas, N. A. et. al. *J. Am. Chem. Soc.* **1936**, *58*, 1302.

2) Sharpless, K. B. et. al. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

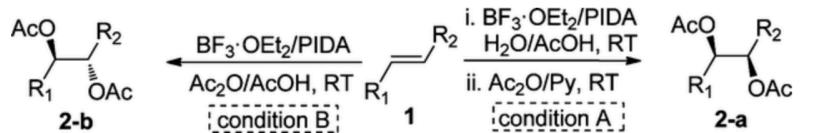
3) Woodward, R. B. et. al. *J. Am. Chem. Soc.* **1958**, *80*, 209.

4) Sudalai, A. et. al. *Org. Lett.* **2005**, *7*, 5071.

2. Dihydroxylation

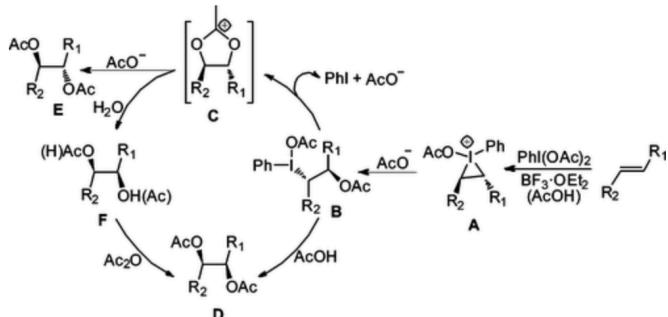
2-3. Metal-free Reaction

2-3-1 $\text{PhI(OAc)}_2 / \text{BF}_3\cdot\text{OEt}_2^1$

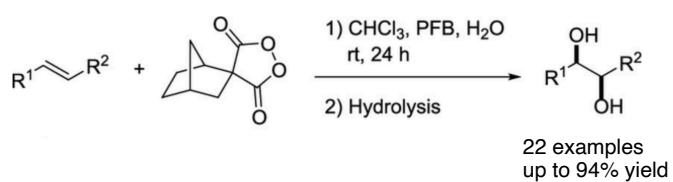


12 examples up to 97% yield

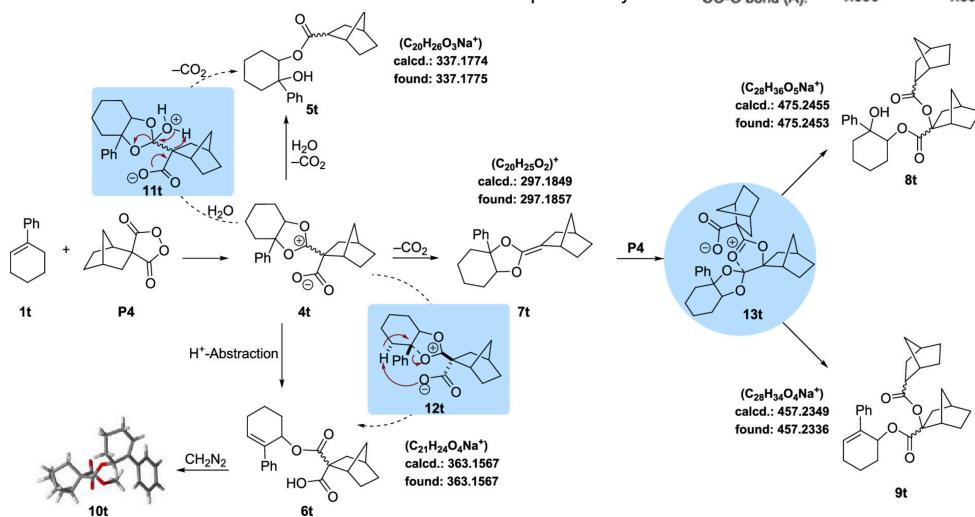
12 examples up to 100% yield



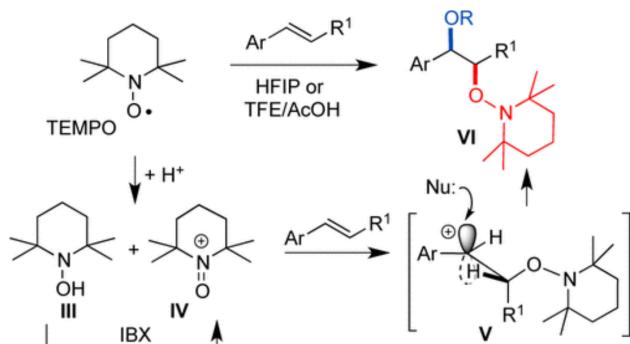
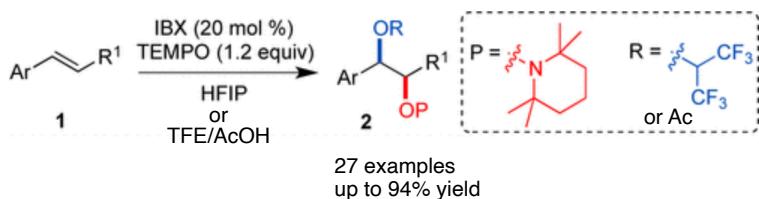
2-3-2 Cyclic Acyl Peroxides²



P1	P2	P3	P4	P5
O-O bond (\AA): 1.476	1.476	1.471	1.467	1.466
C(CO_2) angle: 107.56	104.01	102.34	102.02	102.51
CO-O bond (\AA): 1.390	1.392	1.377	1.382	1.375



2-3-3 IBX-TEMPO³



1) Li, Z. et. al. *J. Org. Chem.* **2011**, *76*, 9997.

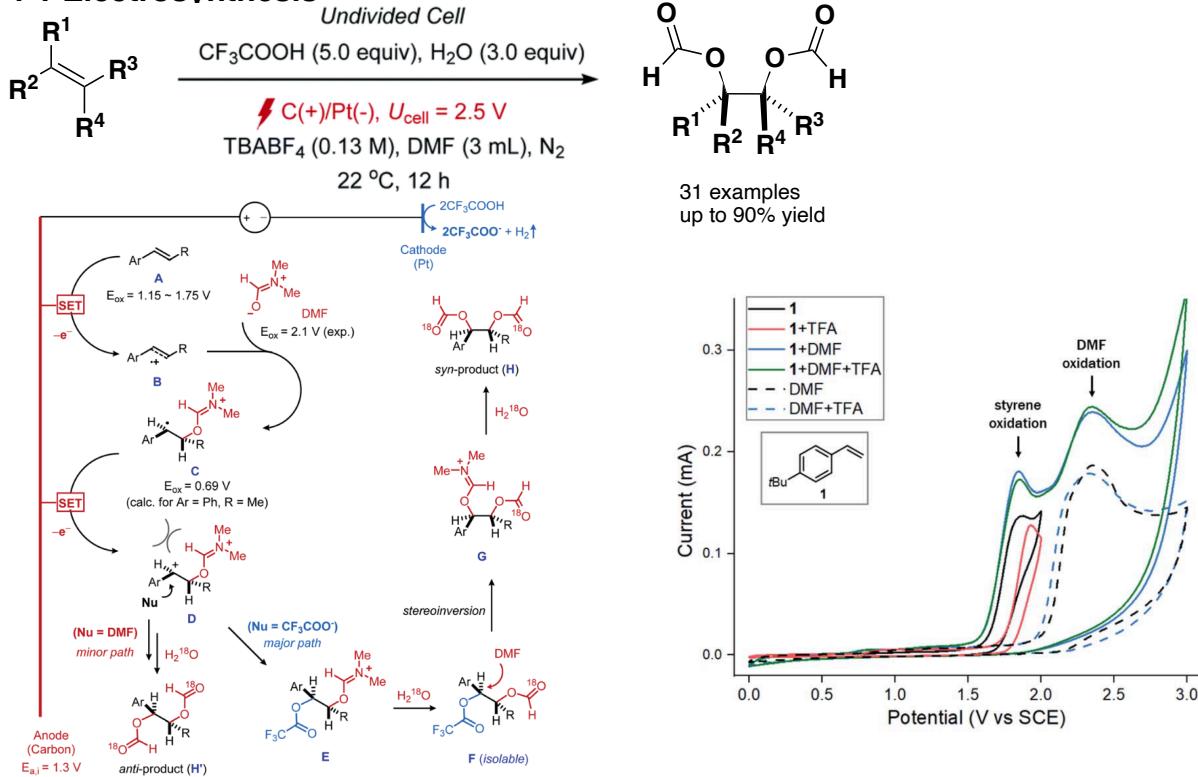
2) Schreiner, P. et. al. *J. Org. Chem.* **2019**, *84*, 12377.

3) Donohoe, T. J. et. al. *Org. Lett.* **2016**, *18*, 5880.

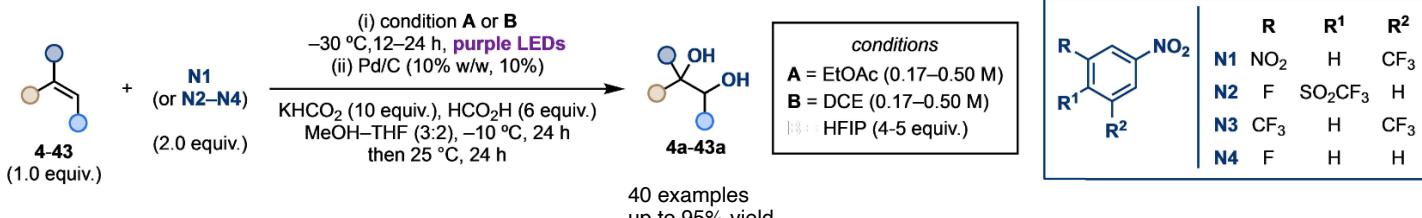
2. Dihydroxylation

2-4. Recent Reports

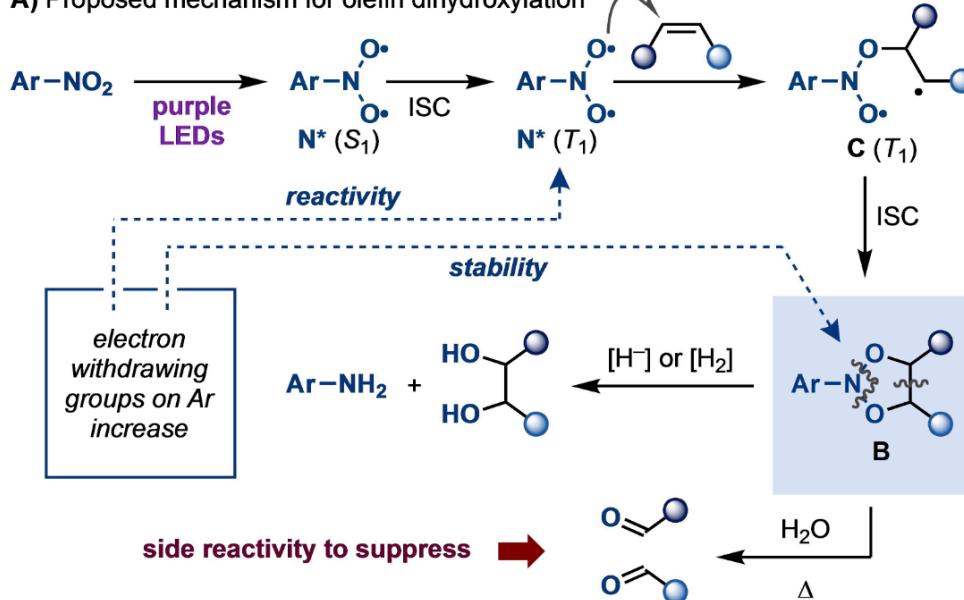
2-4-1 Electrosynthesis¹



2-4-1 Nitroarenes²



A) Proposed mechanism for olefin dihydroxylation

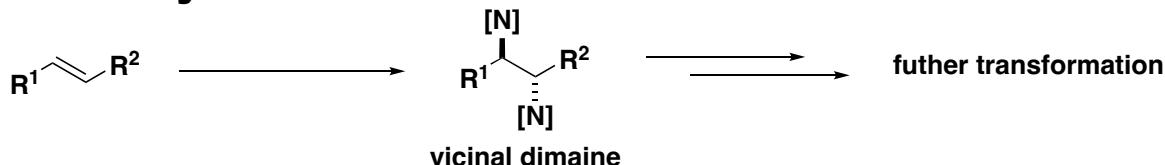


1) Kim.H. et. al. *Chem. Sci.* **2021**, *12*, 5892.

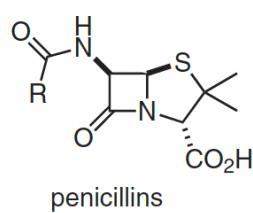
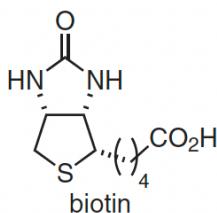
2) Leonori. D. et. al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202214508.

3. Diamination

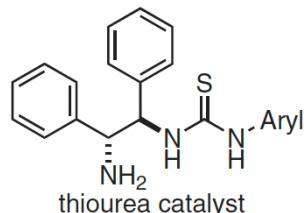
3-1. Utility of diamination¹



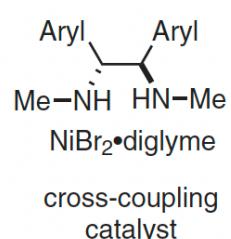
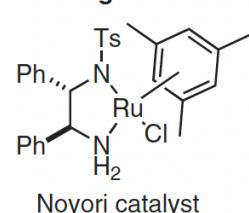
natural products



organocatalysts

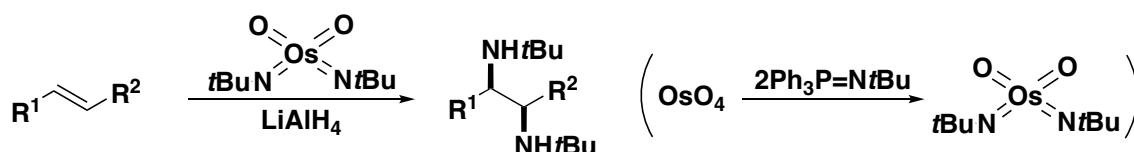


chiral ligands



3-2. Background of *Syn*-selective Diamination

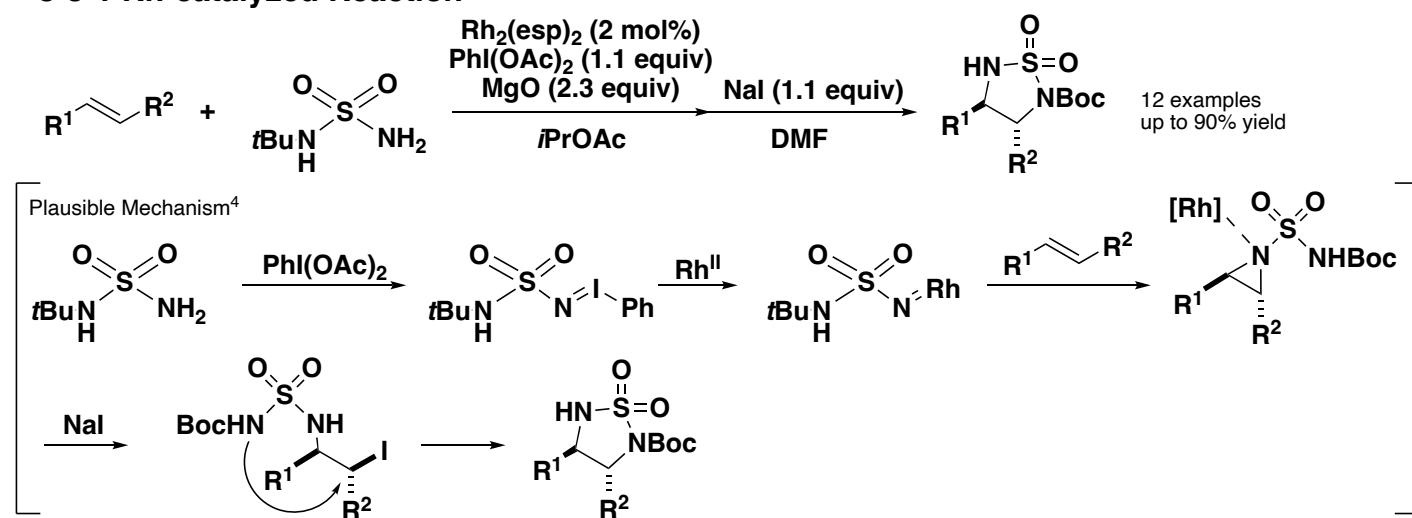
Sharpless 1977²



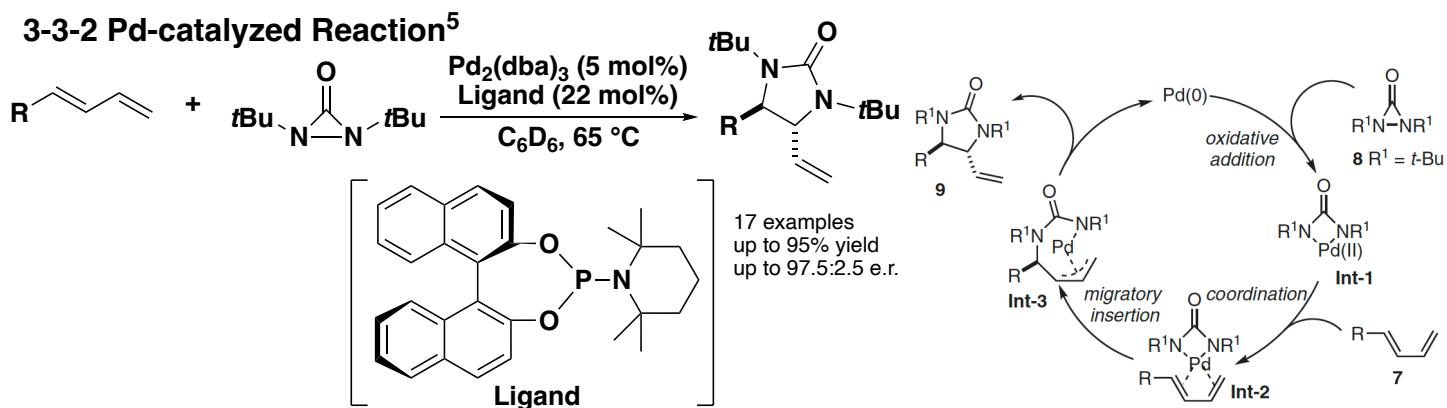
Karl Barry Sharpless

3-3. Metal-catalyzed Diamination

3-3-1 Rh-catalyzed Reaction³



3-3-2 Pd-catalyzed Reaction⁵



1) Denmark, S. E. et al. *Synthesis*. **2021**, 53, 3951.

2) Sharpless, K. B. et al. *J. Am. Chem. Soc.* **1977**, 99, 3203.

3) Bois, J. D. et al. *J. Am. Chem. Soc.* **2014**, 136, 13506.

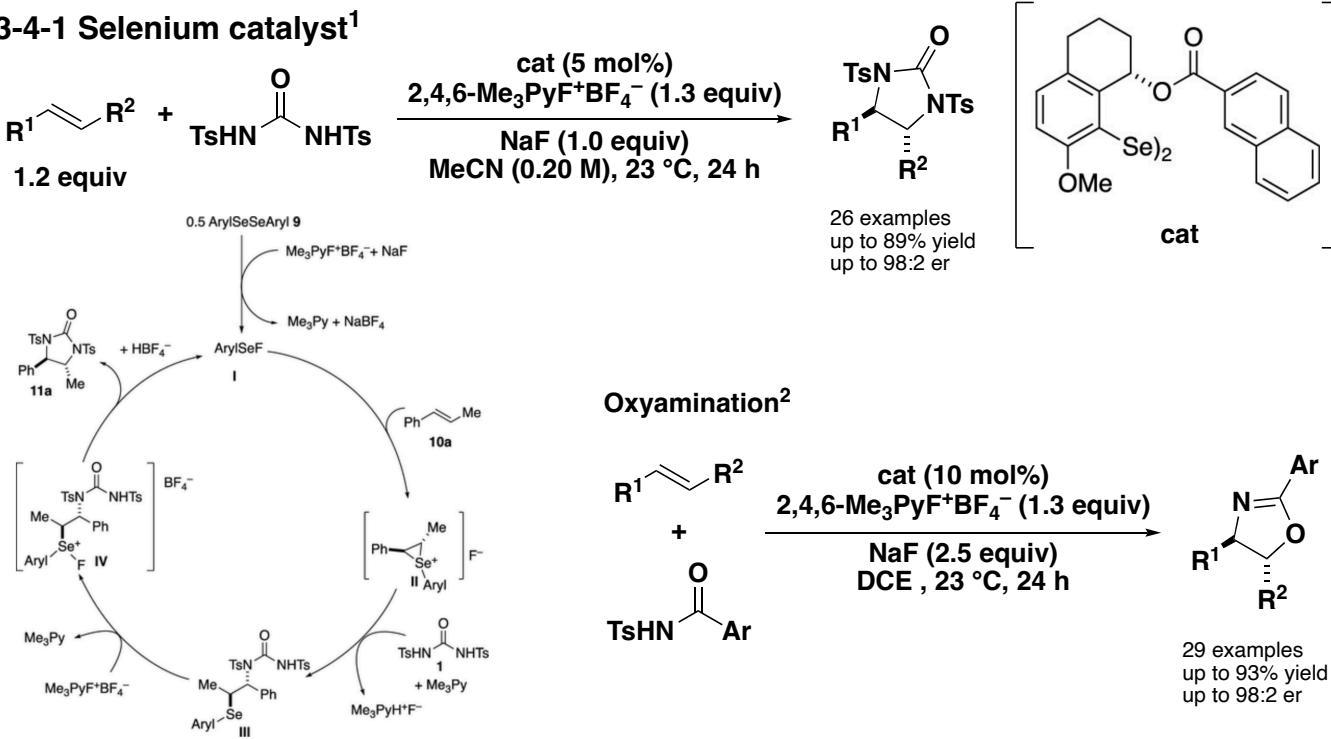
4) Dauban, P. et al. *Angew. Chem.* **2010**, 122, 1678.

5) Shi, Y. et al. *J. Am. Chem. Soc.* **2007**, 129, 762.

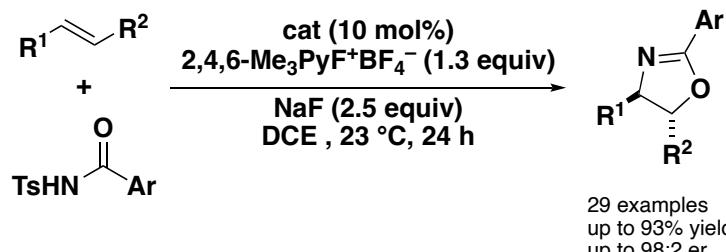
3. Diamination

3-4. Recent Reports

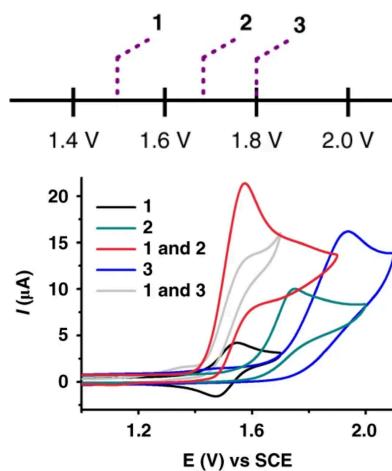
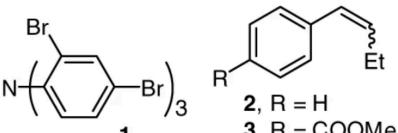
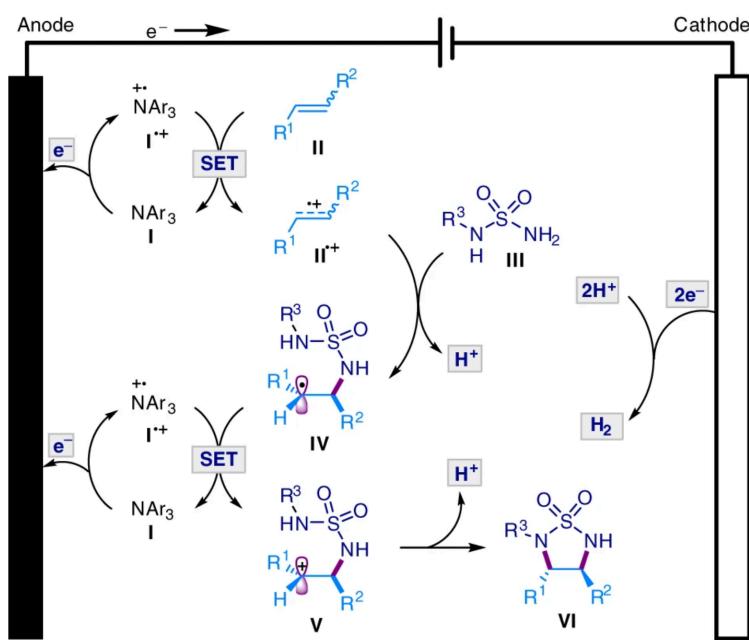
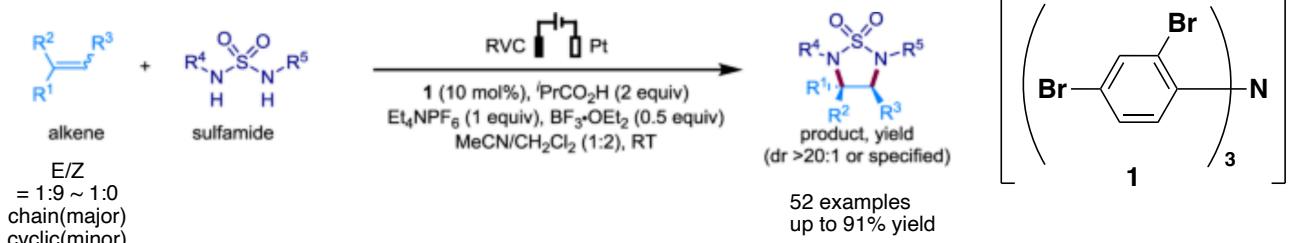
3-4-1 Selenium catalyst¹



Oxyamination²



3-4-2 Stereoselective Electrocatalytic Diamination³



1) Denmark, S. E. et al. *J. Am. Chem. Soc.* **2019**, *141*, 19161.

2) Denmark, S. E. et al. *J. Am. Chem. Soc.* **2021**, *143*, 13408.

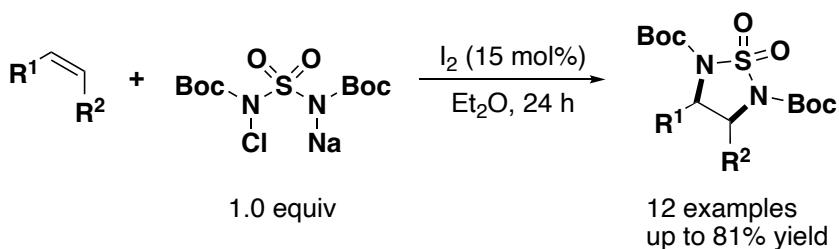
3) Xu, H.-C. et al. *Nat. Commun.* **2019**, *10*, 4953.

3. Diamination

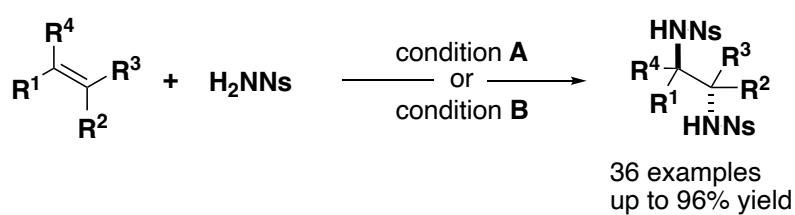
3-4. Recent Reports

3-4-3 Diasterodivergent Diamination by Iodine catalyst¹

syn-addition



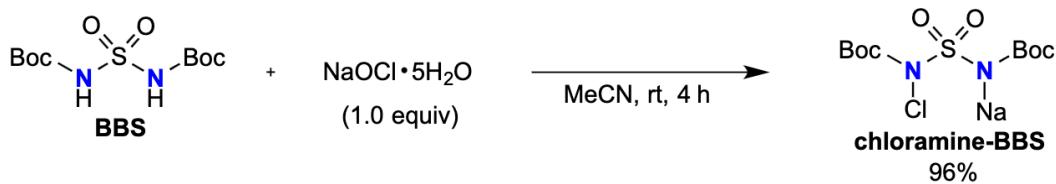
anti-addition



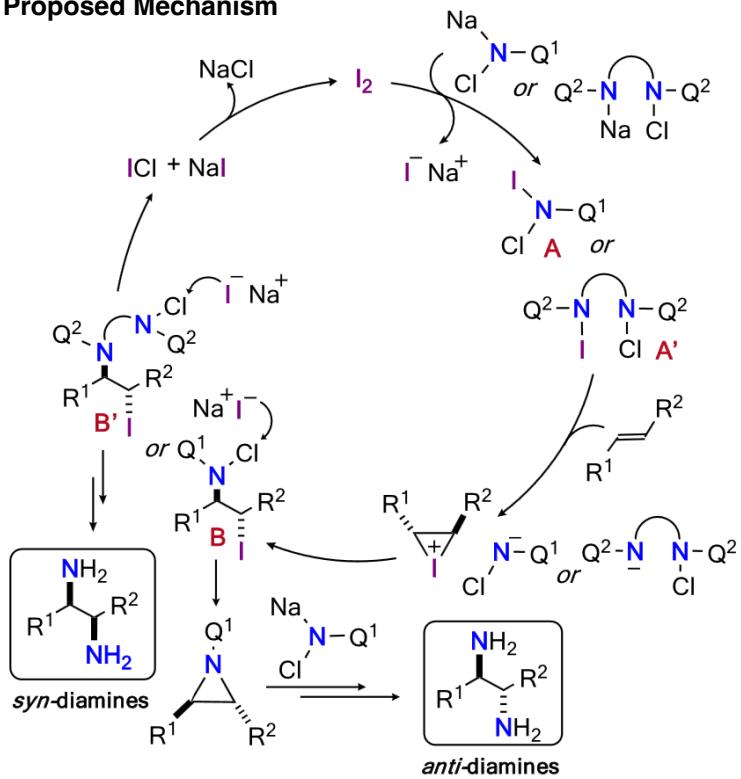
condition A : H_2NNs (2.0 equiv), I_2 (10 mol%)
 $\text{NaOCl}\cdot 5\text{H}_2\text{O}$ (2.0 equiv)
 MeCN , 40°C , 12 h

condition B : H_2NNs (2.2 equiv), I_2 (10 mol%)
 $\text{NaOCl}\cdot 5\text{H}_2\text{O}$ (2.0 equiv)
 MeCN , rt, 12 h to 80°C , 12 h

Synthesis of Diaminating Reagent



Proposed Mechanism

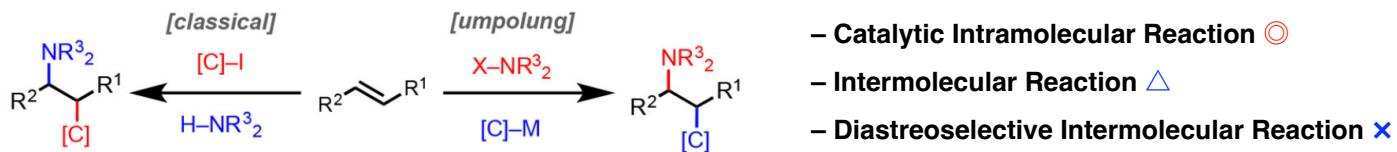


1) Minakata S. et. al. *J. Am. Chem. Soc.* 2021, 143, 4112.

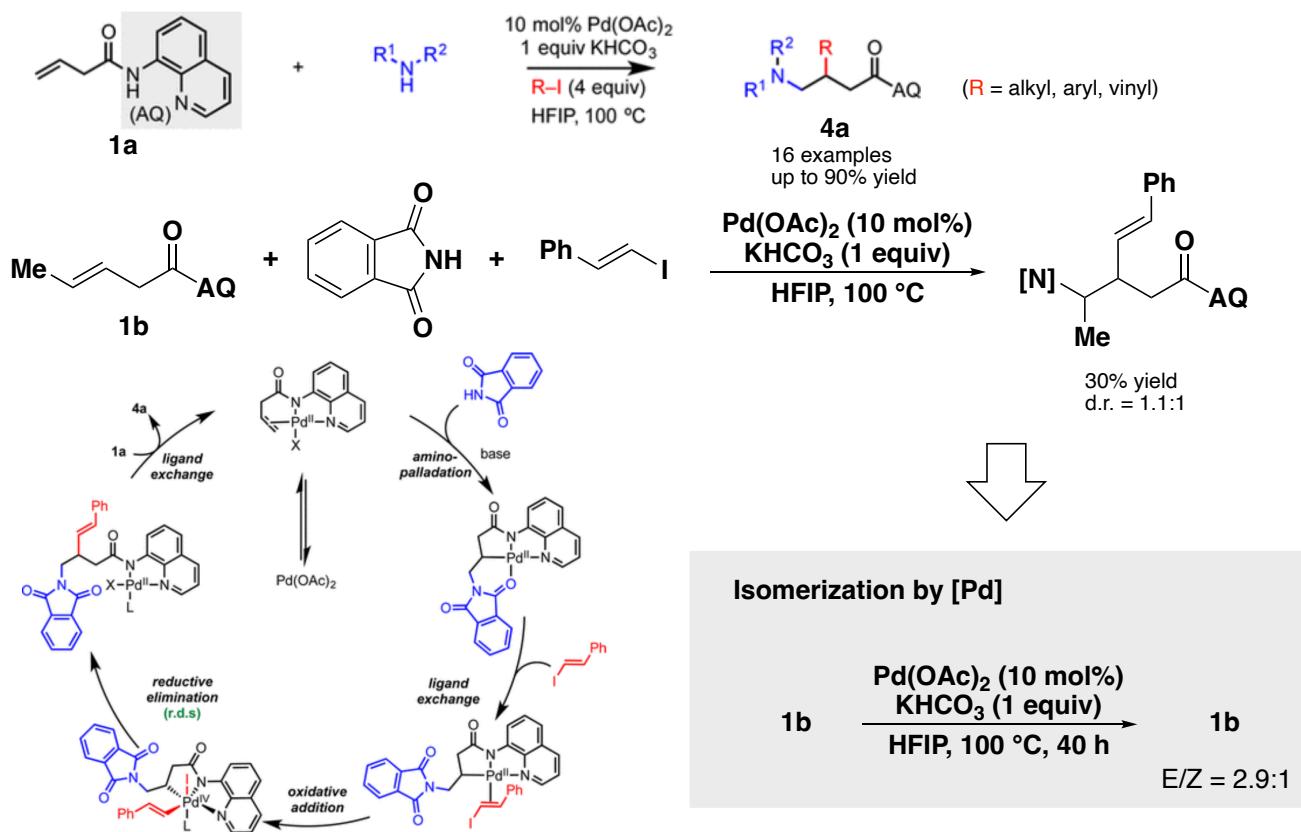
4. Carbofunctionalization

4-1. Carboamination

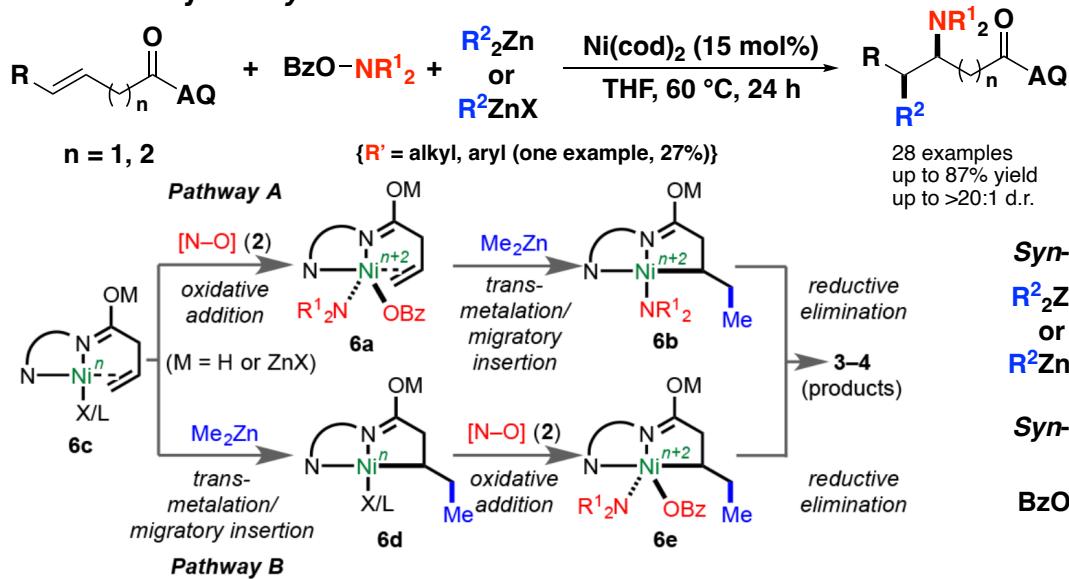
Background¹



Catalytic Intermolecular Carboamination of Unactivated Alkenes¹



Nickel-Catalyzed *Syn*-Carboamination²



1) Engle, K. M. et al. *J. Am. Chem. Soc.* **2017**, *139*, 11261.

2) Engle, K. M. et al. *ACS Catal.* **2019**, *9*, 224.

3) Engle, K. M. et al. *Nature Commun.* **2021**, *12*, 6280.

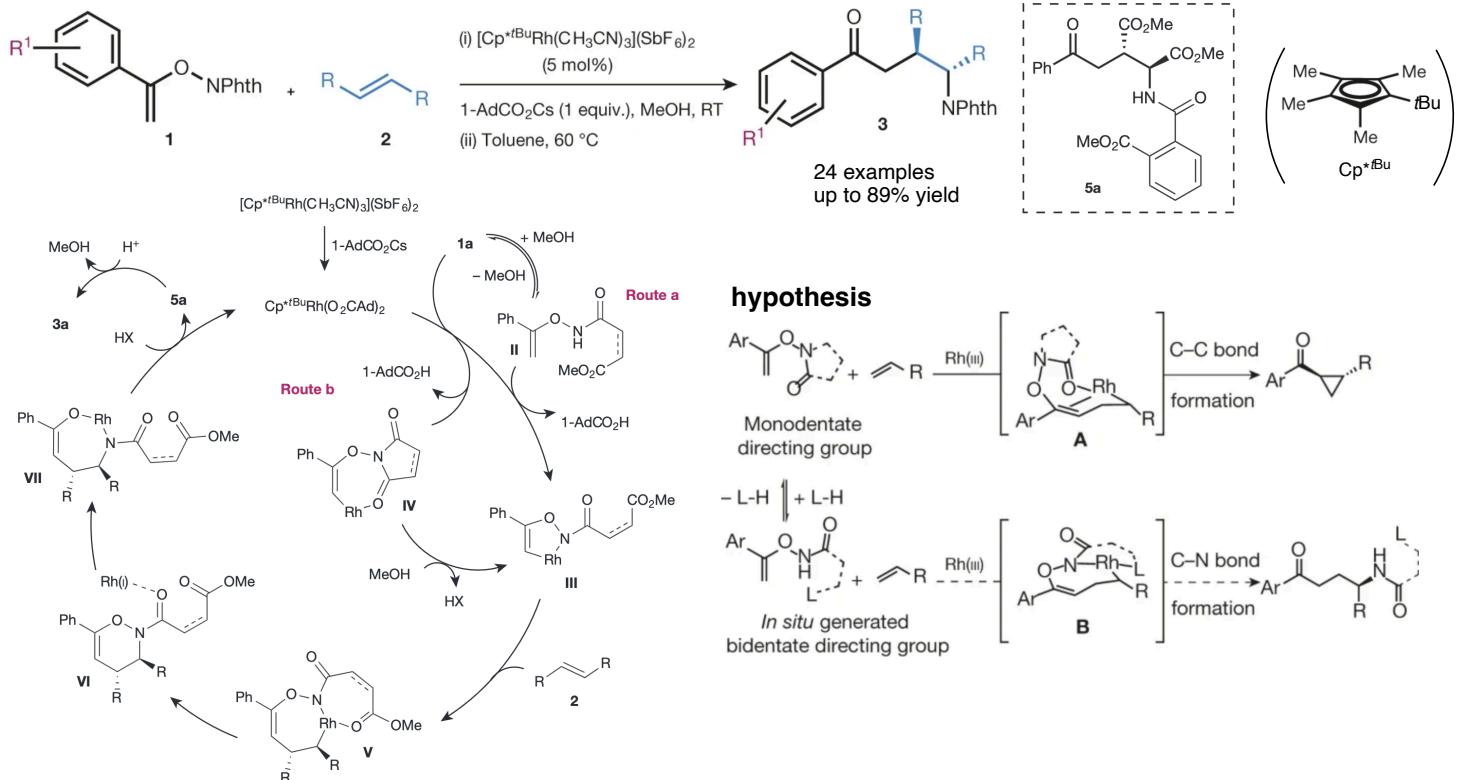
4) Engle, K. M. et al. *J. Am. Chem. Soc.* **2017**, *139*, 10657.

4. Carbofunctionalization

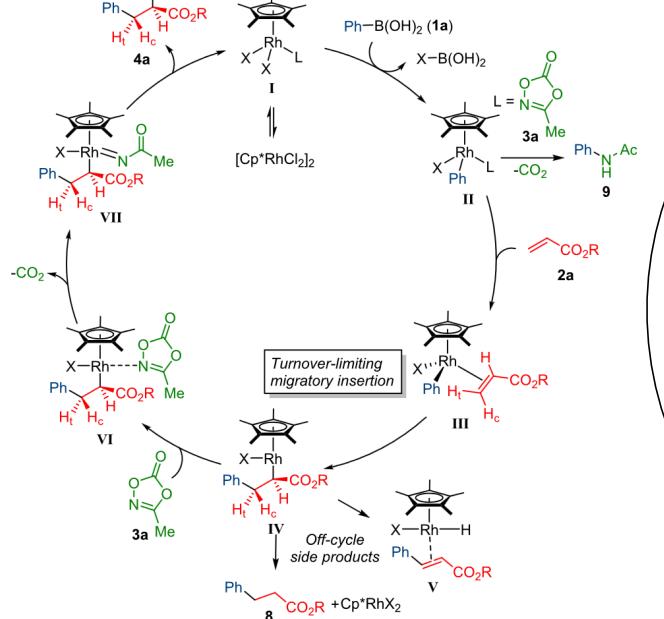
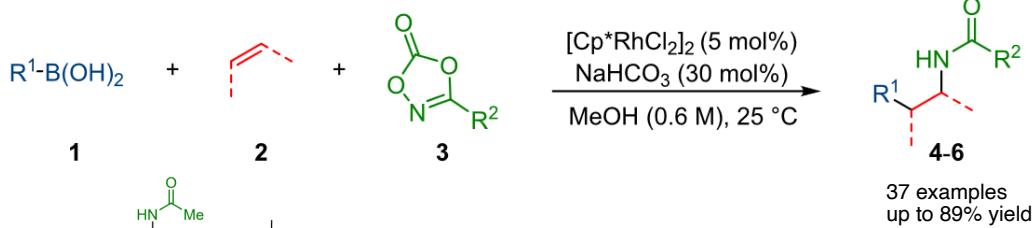
4-1. Carboamination

Rhodium-Catalyzed *Syn*-Carboamination

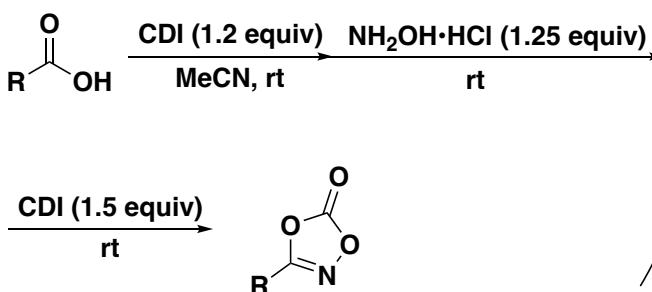
Carboamination via Rhodacycle Intermediate¹



Intermolecular Carboamination²



Synthesis of aminating reagents³



1) Rovis.T. et. al. *Nature* 2015, 527, 86.

2) Rovis.T. et. al. *ACS Catal* 2021, 11, 8585.

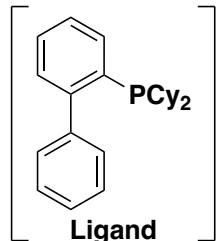
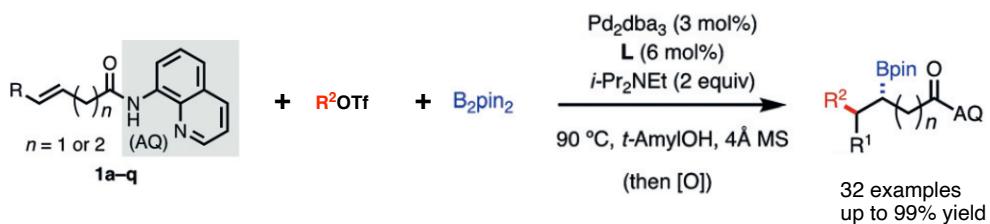
3) Blakey.S. B. et. al. *ACS Catal* 2019, 6, 5474.

4. Carbofunctionalization

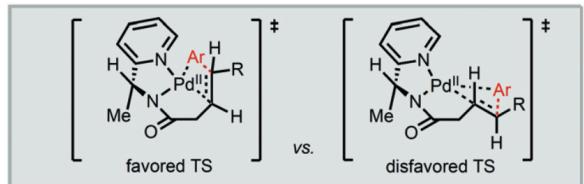
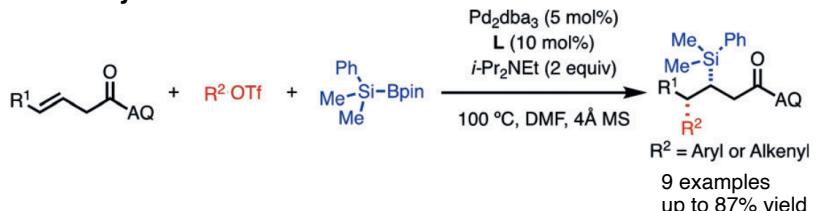
4-2. Carboboration/Carbosilylation

Palladium Catalyzed Carboboration and Carbosilylation¹

Carboboration

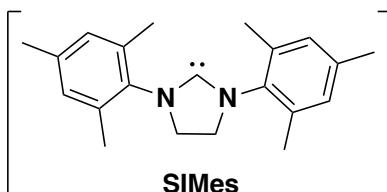
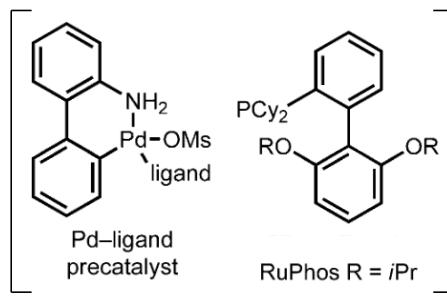
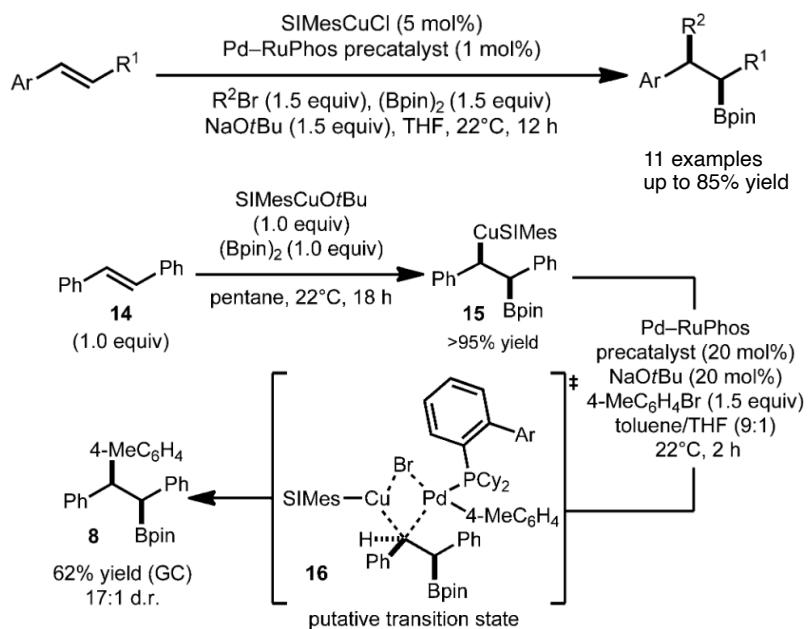


Carbosilylation

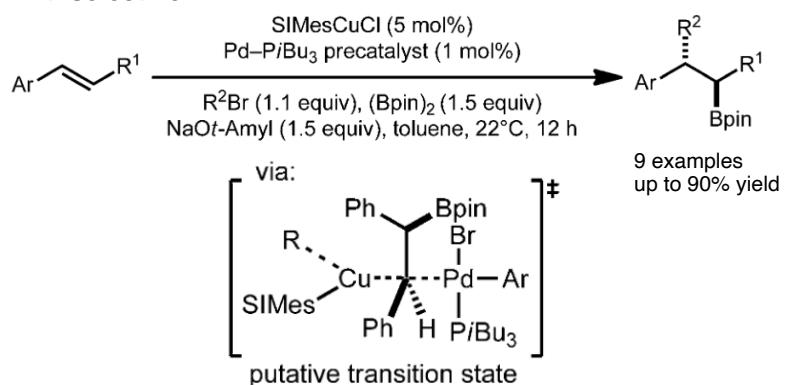


[Cu]/[Pd] Catalysis for Diastereoselective Carboboration²

Syn-selective



Anti-selective



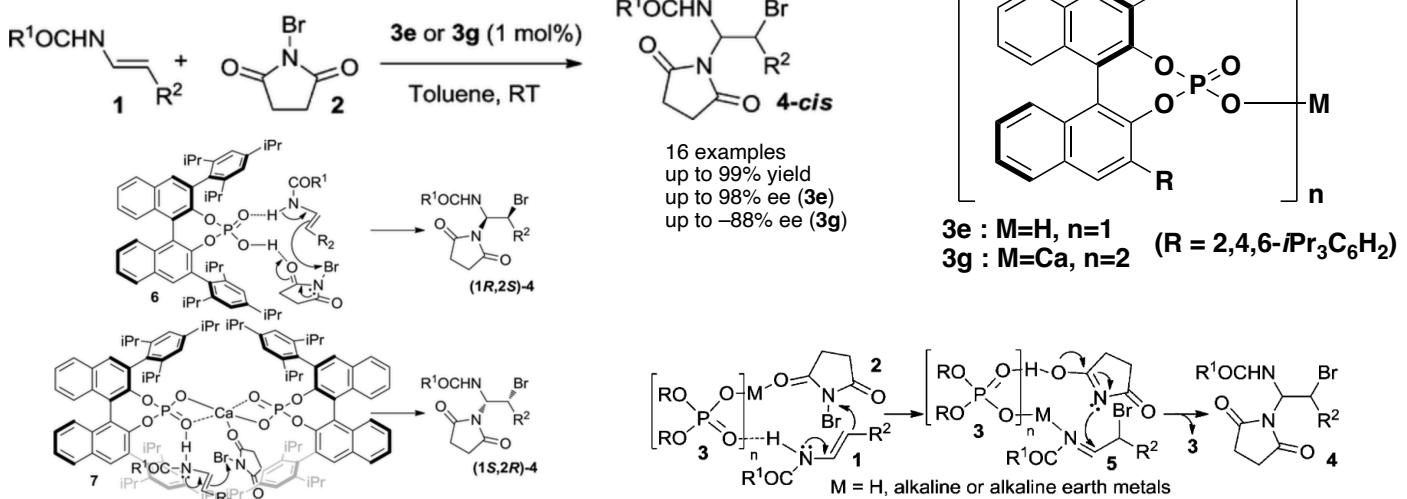
1) Engle.K. M. et. al. Angew. Chem. Int. Ed. 2019, 58, 17068.

2) Brown.M. K. et. al. Angew. Chem. Int. Ed. 2015, 54, 5228.

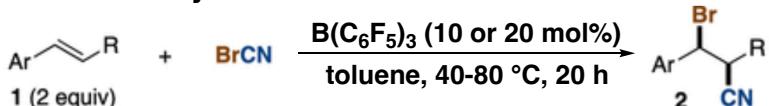
5. Halofunctionalization

5-1. Monohalo-functionalization

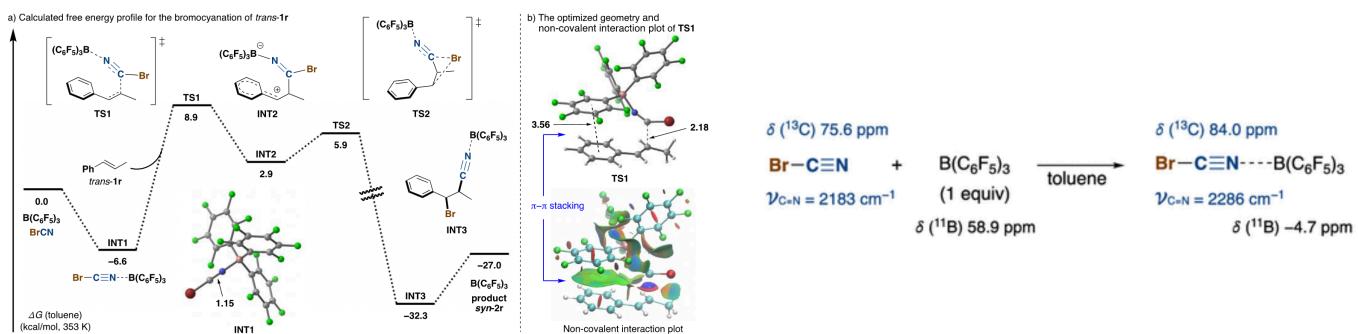
5-1-1 Bromoamination¹



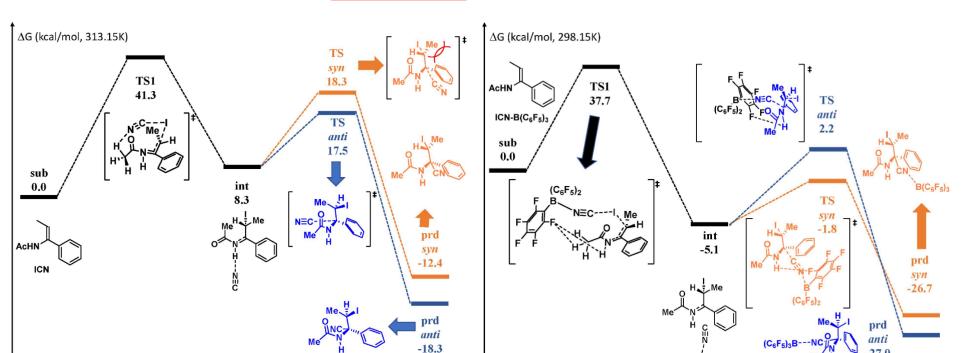
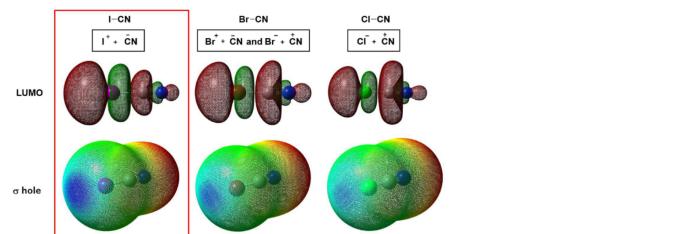
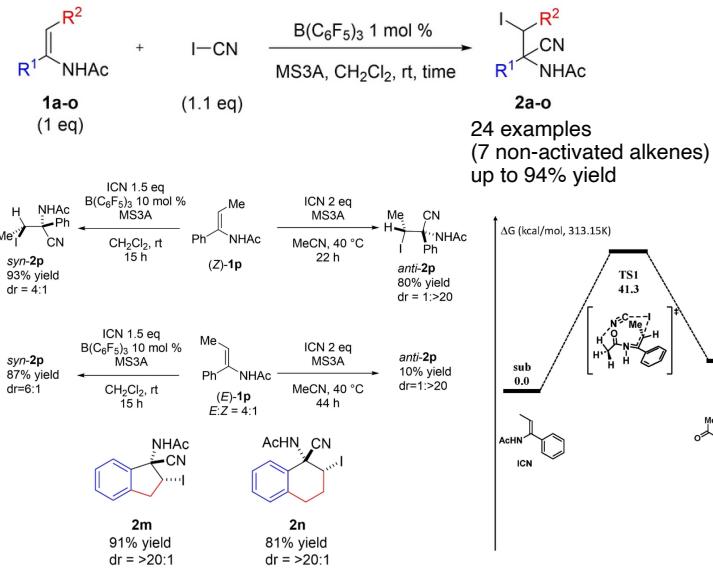
5-1-2 Bromocyanation²



27 examples
up to 81% yield



cf. Iodocyanation³



1) Masson, G. et. al. *J. Am. Chem. Soc.* **2012**, 134, 10389.

2) Minakata, S. et. al. *Org. Lett.* **2023**, 25, 2537.

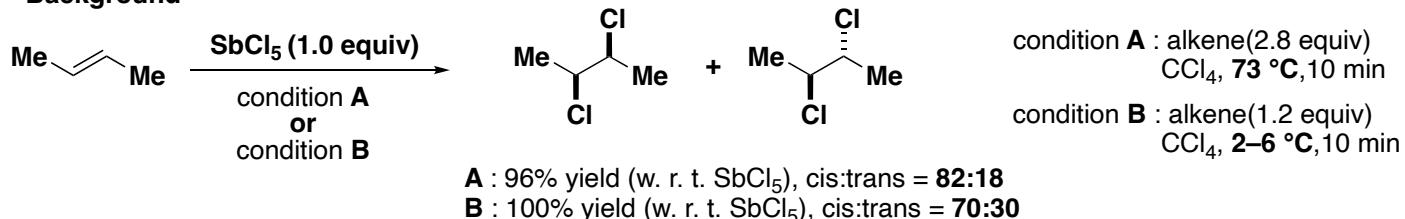
3) Arai, T. et. al. *Adv. Synth. Catal.* **2023**, 365, 3247.

5. Halofunctionalization

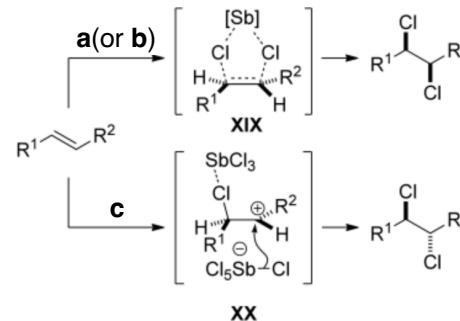
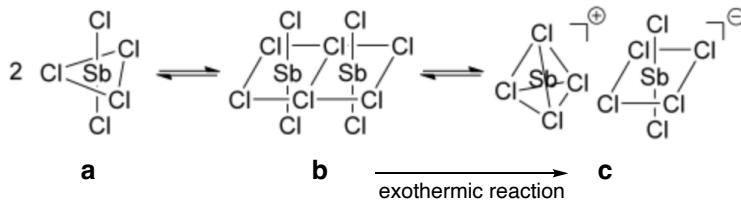
5-2. Dihalogenation

5-2-1 *Syn*-Dichlorination

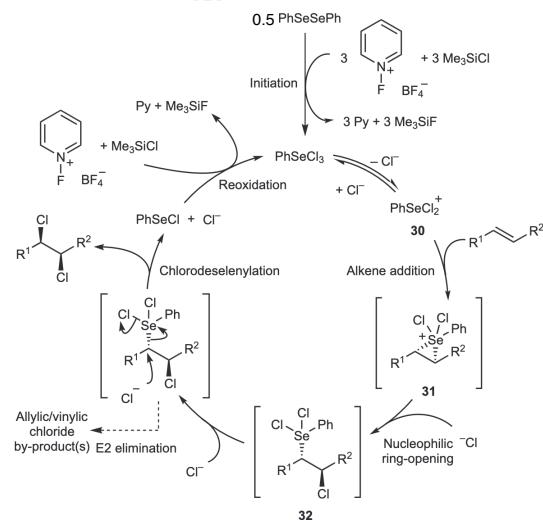
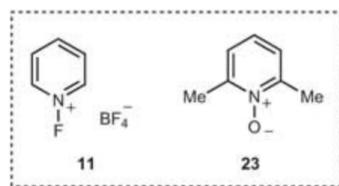
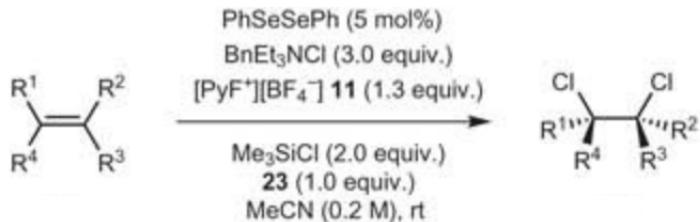
Background¹



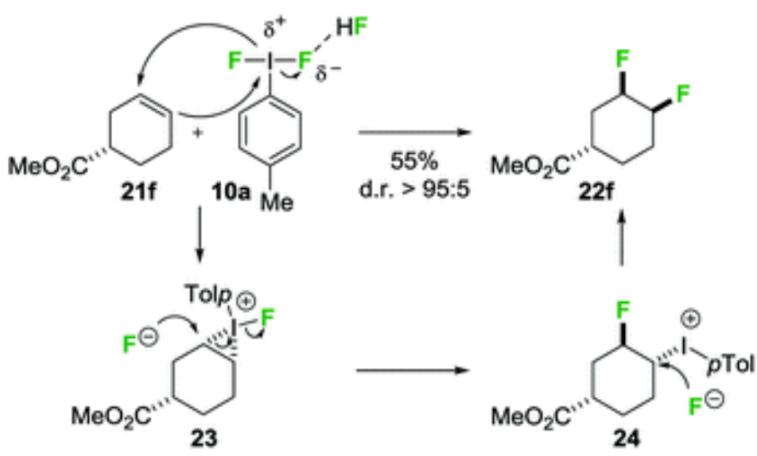
Mechanism of selectivity



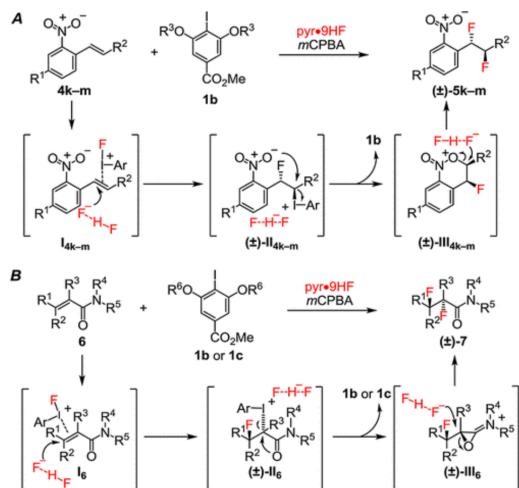
Se-Catalyzed *Syn*-Dichlorination²



5-2-2 *Syn*-Difluorination³



Anti-Difluorination⁴



1) Uemura, S. et. al. *Bull. Chem. Soc. Jpn.* **1974**, 47, 692.

2) Denmark, S. E. et. al. *Nat. Chem.* **2015**, 7, 146.

3) Hara, S. et. al. *Synlett.* **1998**, 495.

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