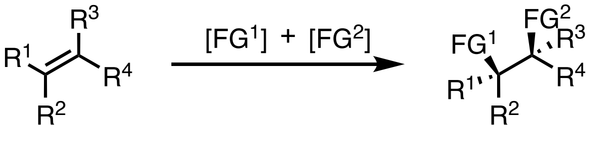
Strategy for the *syn*-selective functionalization of alkenes



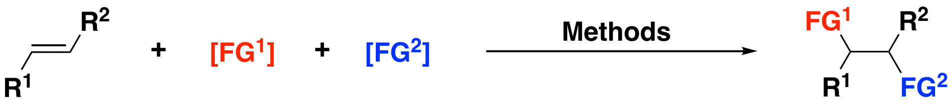
syn-selective

2023/ 11/ 2 (Thu)
Keigo Nagami

Contents

1. Introduction

1-1. Difunctionalization of alkenes



Methods

Organocatalyzed

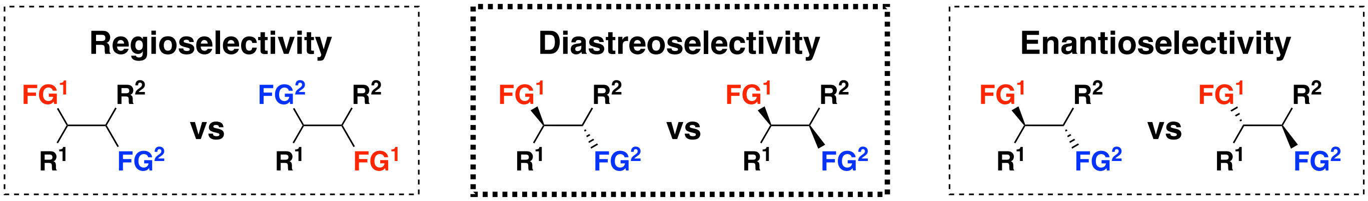
Electrochemisty

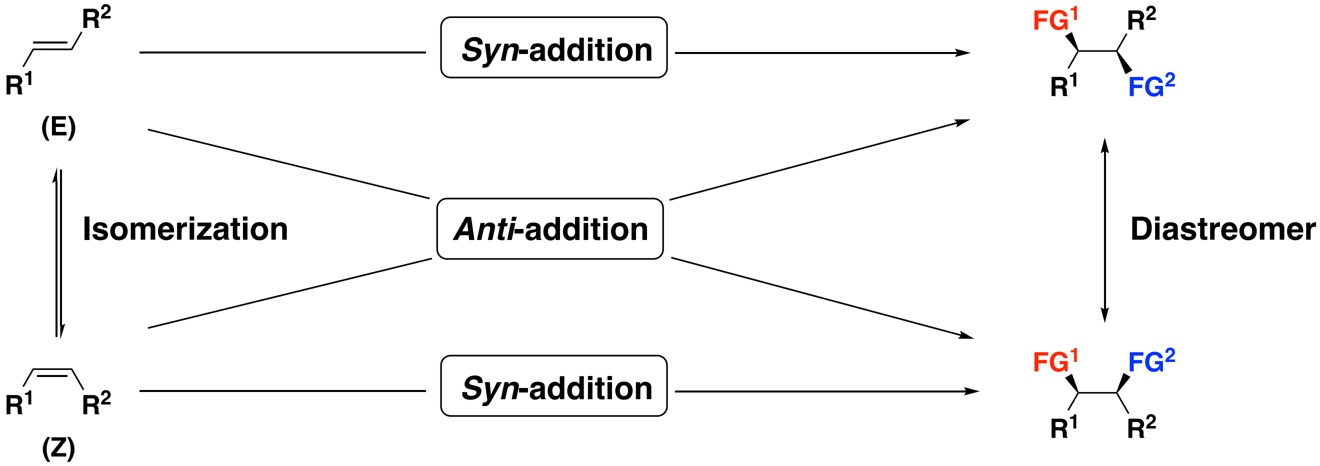
Radical functionalization

Photocatalzed

Transition metal catalyzed

1-2. Selectivities

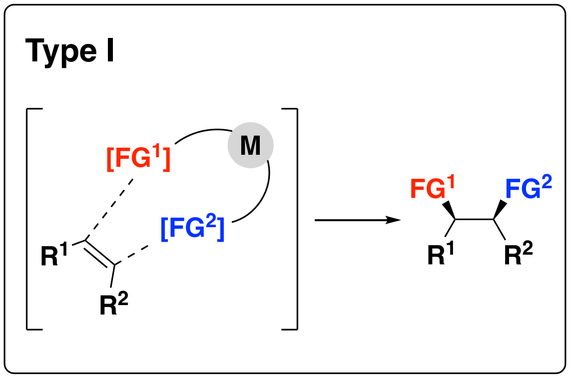


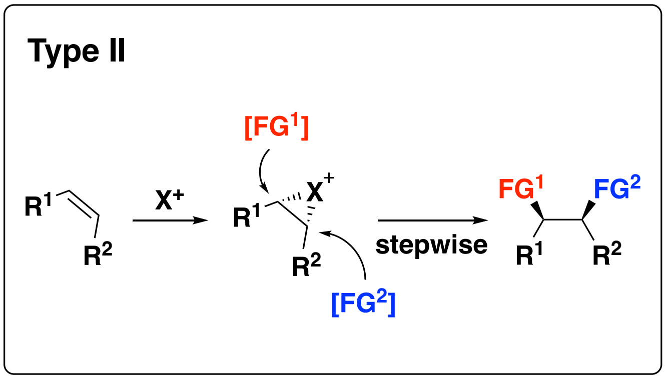


- Pre-isomerization is needed.
- Cyclic alkenes are not tolerated.

⇒ ***Syn* selective addition are desired.**

1-3. Methods for *syn*-addition



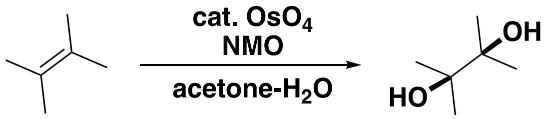


Etc…

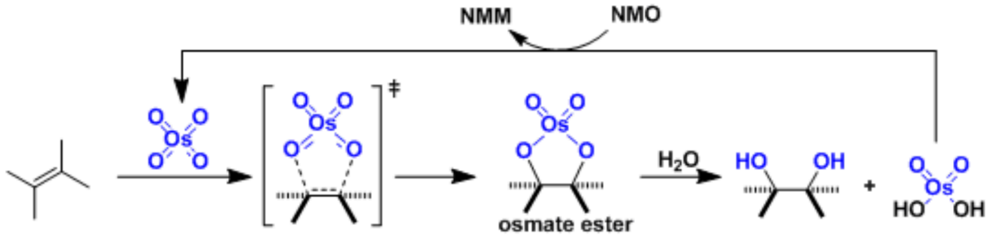
2. Dihydroxylation

2-1. Background

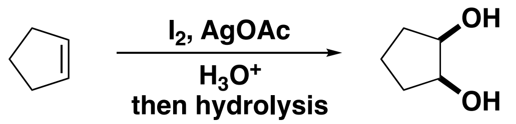
Osmium-Catalzed Reaction (1936～[1])



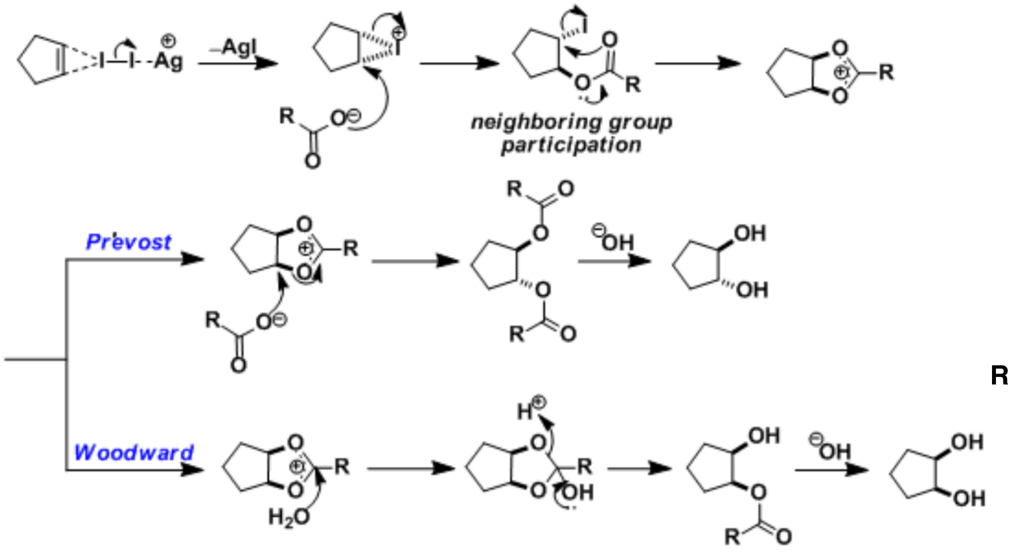
- **Highly versatile**
- **Relatively mild conditions**
- **Asymmetric Reactions** **(ex. 1980 Sharpless[2])**
- **Toxic**
- **Expensive reagents**



Woodward Reaction (1958[3])

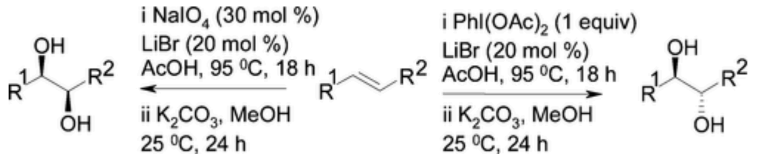


- **Inexpensive**
- **Reagent-controlled selectivity**
- **Stoichiometric amount of molecular halogen**
- **Large amount of wastes**



Robert Burns Woodward

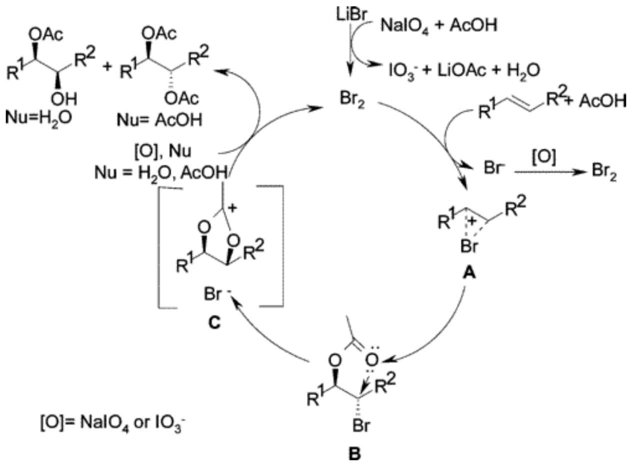
2-2. Transition-metal-free Reaction[4]



21 examples
up to 91% yield

5 examples
up to 87% yield

$$\left(\begin{array}{lcl}
2Br^- & \longrightarrow & Br_2 + 2e^- \\
2\,e^- + IO_4^- + 2H^+ & \longrightarrow & H_2O + IO_3^- \\
6H^+ + IO_3^- + 6e^- & \longrightarrow & 3H_2O + I^- \\
I_2 + 2e^- & \longrightarrow & 2I^- \\
\hline
8e^- + IO_4^- + 8H^+ & \longrightarrow & 4H_2O + I^-
\end{array}\right)$$



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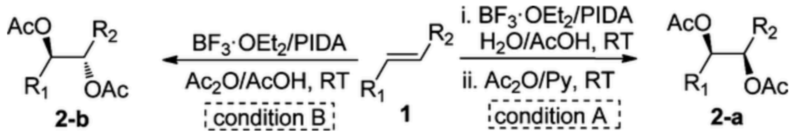
1) Milas. N. A. *et. al. J. Am. Chem. Soc.* **1936**, *58*, 1302.
2) Sharpless. K. B. *et. al. J. Am. Chem. Soc.* **1980**, *102*, 4263.
3) Woodward. R. B. *et. al. J. Am. Chem. Soc.* **1958**, *80*, 209.
4) Sudalai. A. *et. al. Org. Lett.* **2005**, *7*, 5071.

2. Dihydroxylation

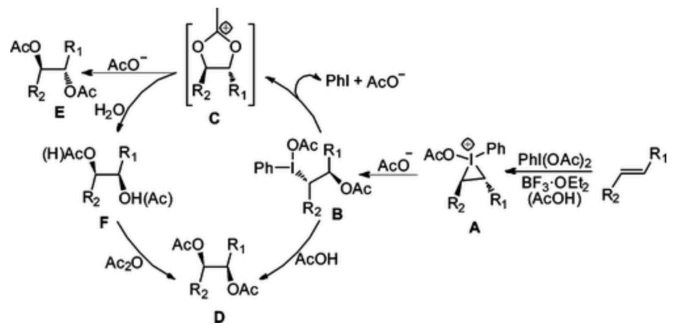
2-3. Metal-free Reaction

2-3-1 $PhI(OAc)_2$ / $BF_3·OEt_2$[1]

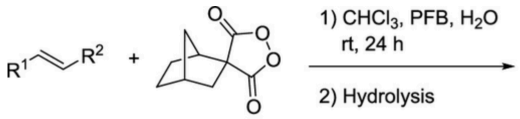


12 examples
up to 97% yield

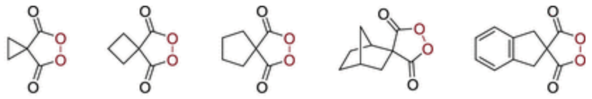
12 examples
up to 100% yield



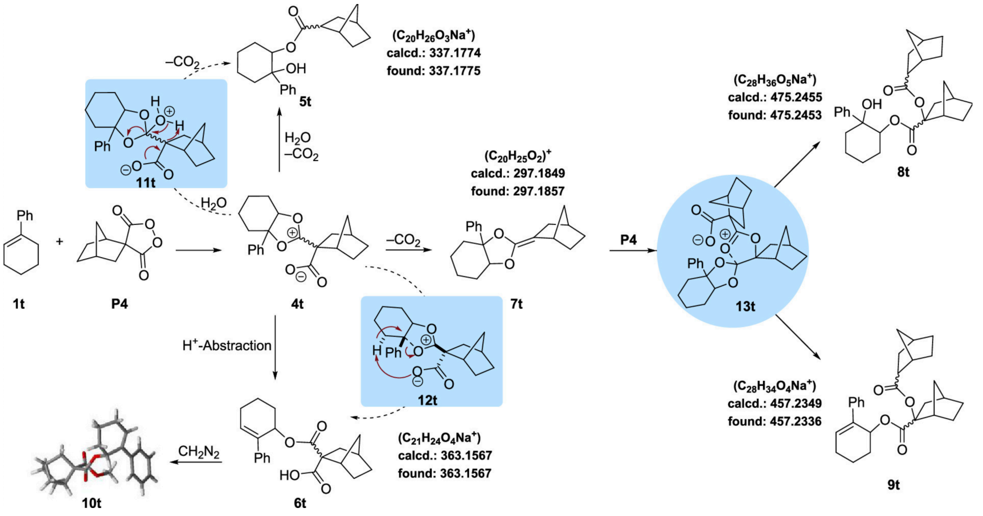
2-3-2 Cyclic Acyl Peroxides[2]



22 examples
up to 94% yield

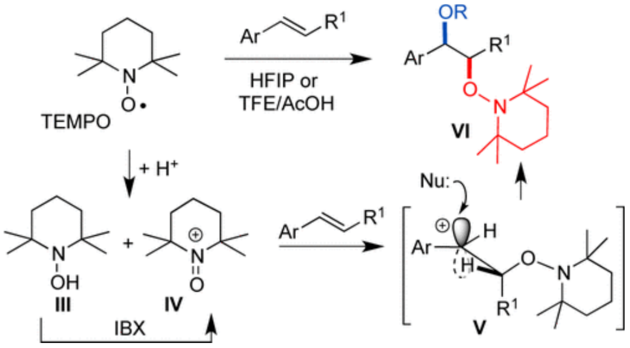


	P1	P2	P3	P4	P5
O-O bond (Å):	1.476	1.476	1.471	1.467	1.466
$C(CO)_2$ angle:	107.56	104.01	102.34	102.02	102.51
CO-O bond (Å):	1.390	1.392	1.377	1.382	1.375



2-3-3 IBX-TEMPO[3]

27 examples
up to 94% yield



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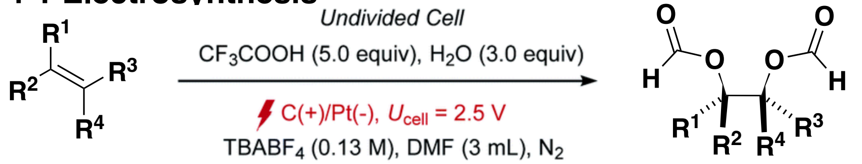
1) Li. Z. *et. al. J. Org. Chem.* **2011**, *76*, 9997.
2) Schreiner. P. *et. al. J. Org. Chem.* **2019**, *84*, 12377.
3) Donohoe. T. J. *et. al. Org. Lett.* **2016**, *18*, 5880.

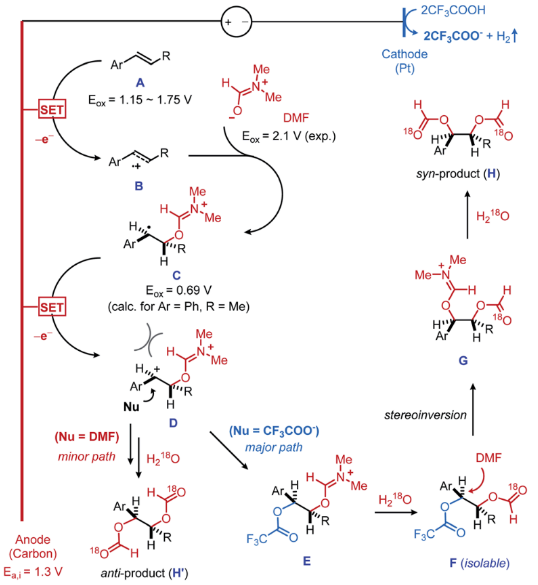
2. Dihydroxylation

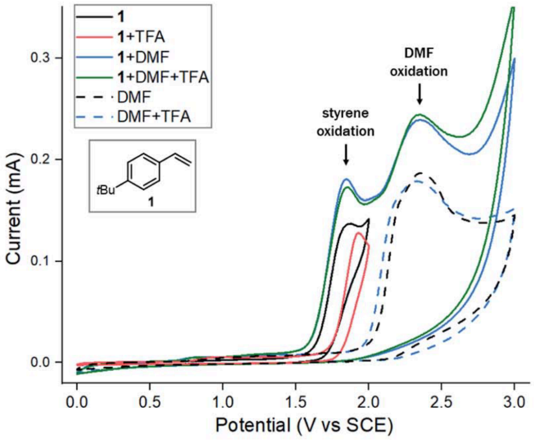
2-4. Recent Reports

2-4-1 Electrosynthesis[1]

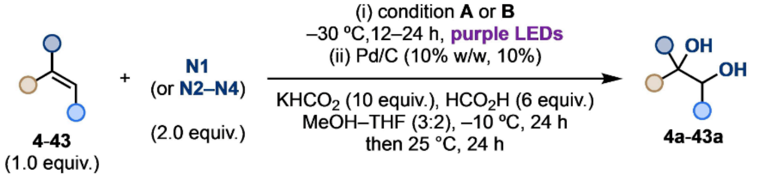


31 examples
up to 90% yield





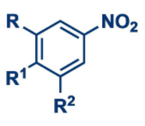
2-4-1 Nitroarenes[2]



4-43
(1.0 equiv.)

4a-43a

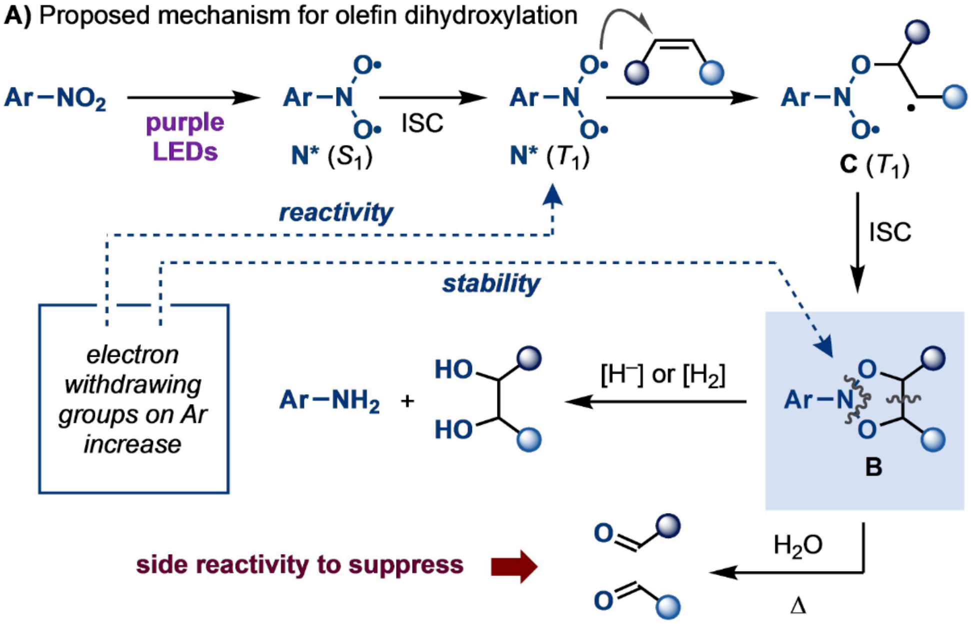
conditions
A = EtOAc (0.17–0.50 M)
B = DCE (0.17–0.50 M)
HFIP (4-5 equiv.)



	R	R¹	R²
N1	NO_2	H	CF_3
N2	F	SO_2CF_3	H
N3	CF_3	H	CF_3
N4	F	H	H

40 examples
up to 95% yield

A) Proposed mechanism for olefin dihydroxylation



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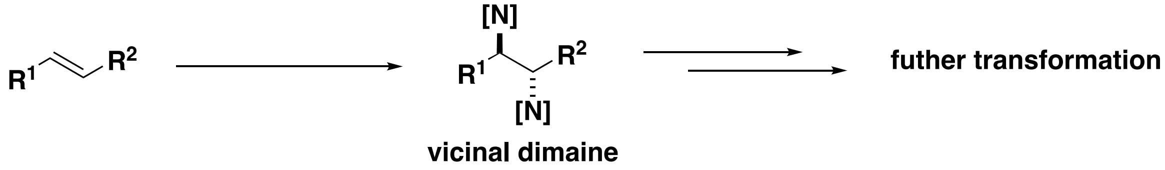
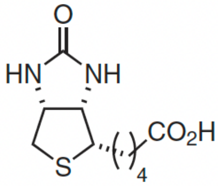
1) Kim.H. *et. al. Chem. Sci.* **2021**, *12*, 5892.
2) Leonori. D. *et. al. Angew. Chem. Int. Ed.* **2023**, *62*, e202214508.

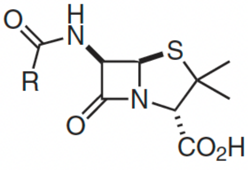
3. Diamination

3-1. Utility of diamination[1]

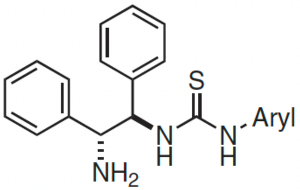


natural products

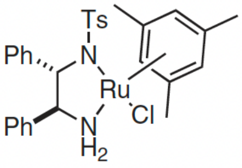

biotin

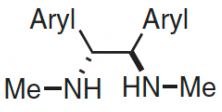

penicillins

organocatalysts


thiourea catalyst

chiral ligands

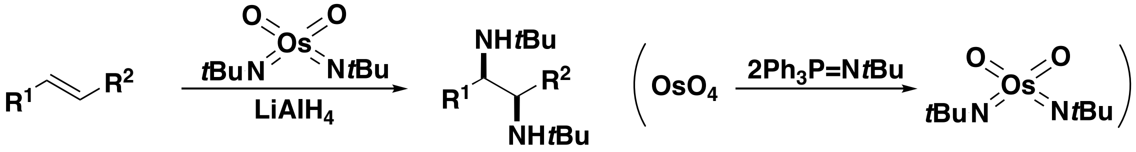

Noyori catalyst

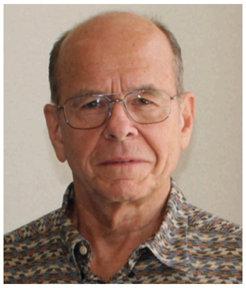

$NiBr_2$•diglyme

cross-coupling catalyst

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

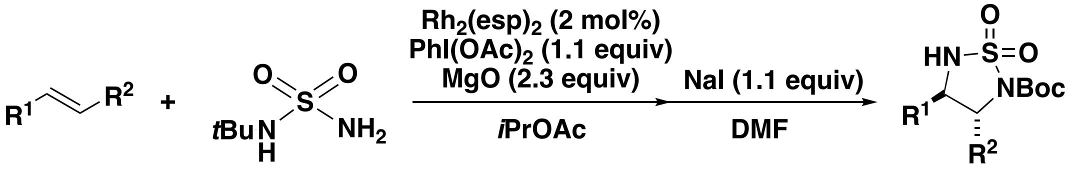
Sharpless 1977[2]



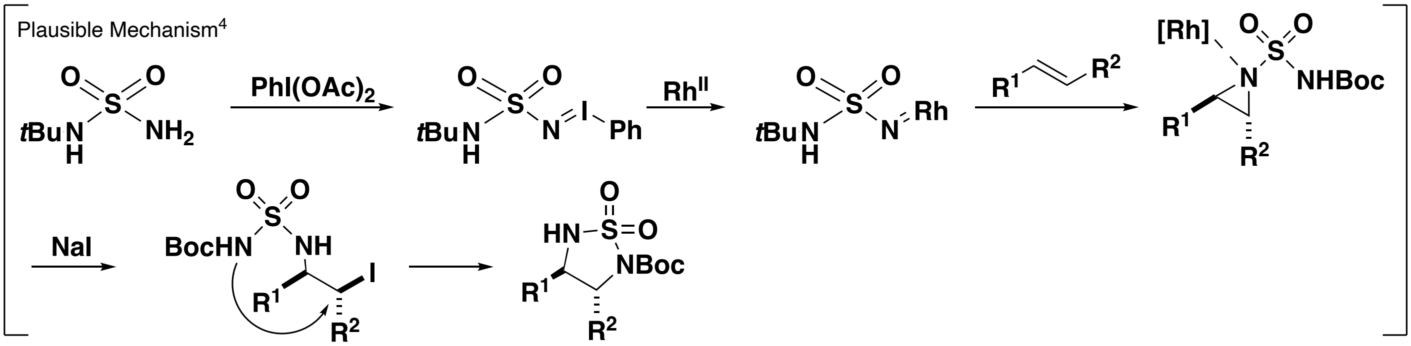

Karl Barry Sharpless

3-3. Metal-catalyzed Diamination

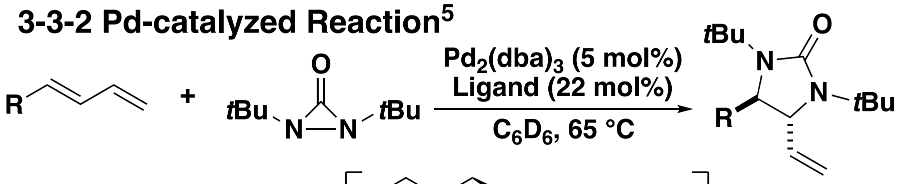
3-3-1 Rh-catalyzed Reaction[3]

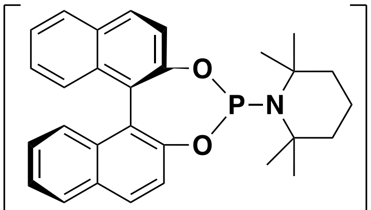


12 examples
up to 90% yield

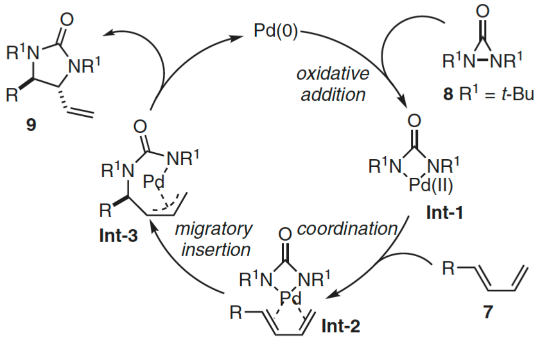

Plausible Mechanism[4]

3-3-2 Pd-catalyzed Reaction[5]




Ligand

17 examples
up to 95% yield
up to 97.5:2.5 e.r.



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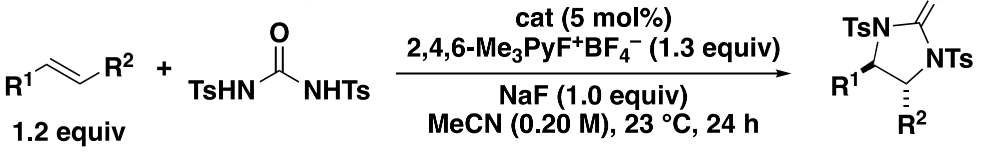
1) Denmark. S. E. *et. al. Synthesis.* **2021**, *53*, 3951.
2) Sharpless. K. B. *et. al. J. Am. Chem. Soc.* **1977**, *99*, 3203.
3) Bois. J. D. *et. al. J. Am. Chem. Soc.* **2014**, *136*, 13506.
4) Dauban. P. *et. al. Angew. Chem.* **2010**, *122*, 1678.
5) Shi. Y. *et. al. J. Am. Chem. Soc.* **2007**, *129*, 762.

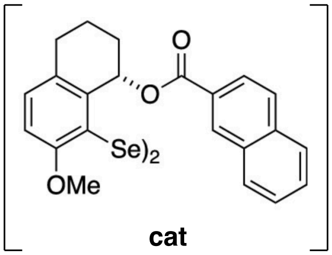
3. Diamination

3-4. Recent Reports

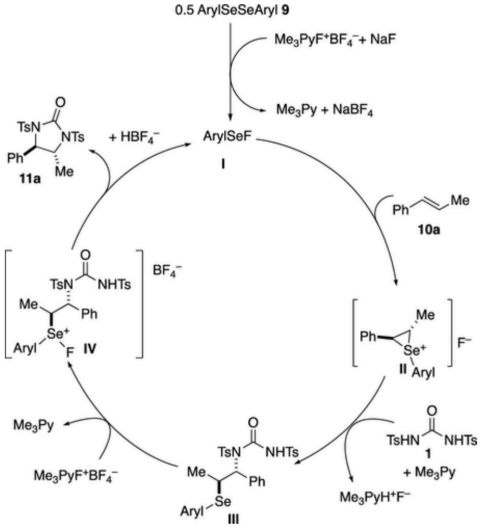
3-4-1 Selenium catalyst[1]



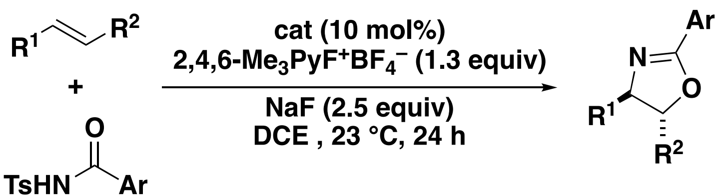
26 examples
up to 89% yield
up to 98:2 er



cat

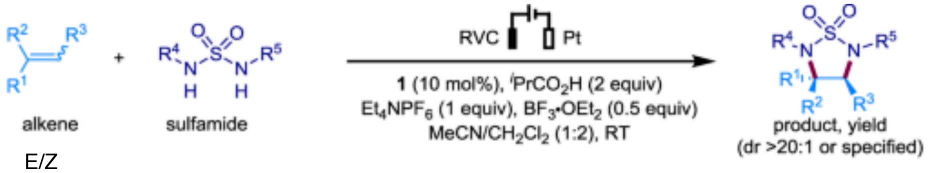


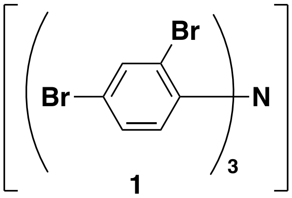
Oxyamination[2]



29 examples
up to 93% yield
up to 98:2 er

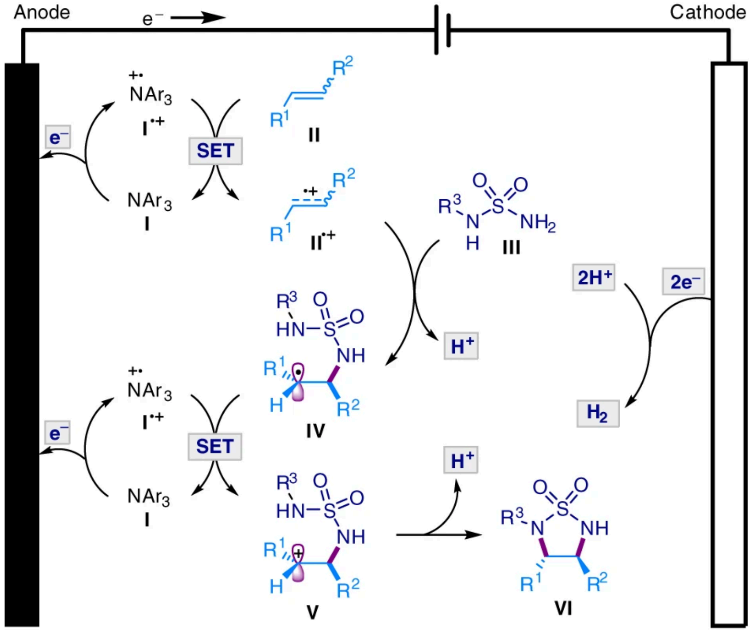
3-4-2 Stereoselective Electrocatalytic Diamination[3]

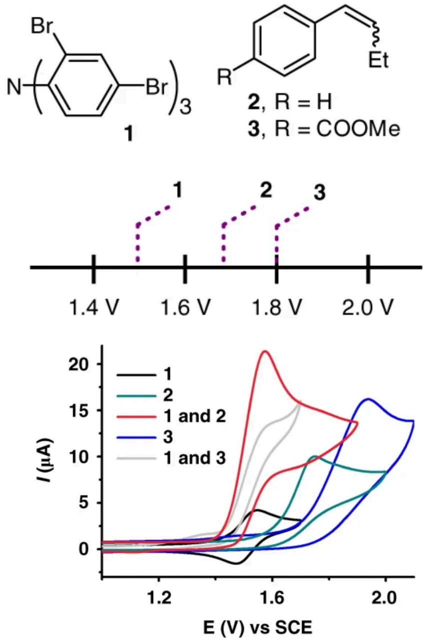




E/Z
= 1:9 ~ 1:0
chain(major)
cyclic(minor)

52 examples
up to 91% yield





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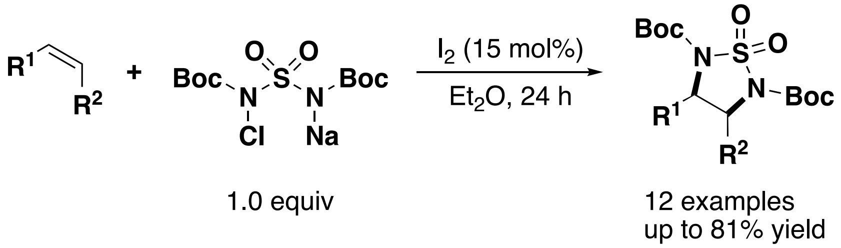
1) Denmark. S. E. *et. al. J. Am. Chem. Soc.* **2019**, *141*, 19161.
2) Denmark. S. E. *et. al. J. Am. Chem. Soc.* **2021**, *143*, 13408.
3) Xu. H.-C. *et. al. Nat. Commun.* **2019**, *10*, 4953.

3. Diamination

3-4. Recent Reports

3-4-3 Diasterodivergent Diamination by Iodine catalyst[1]

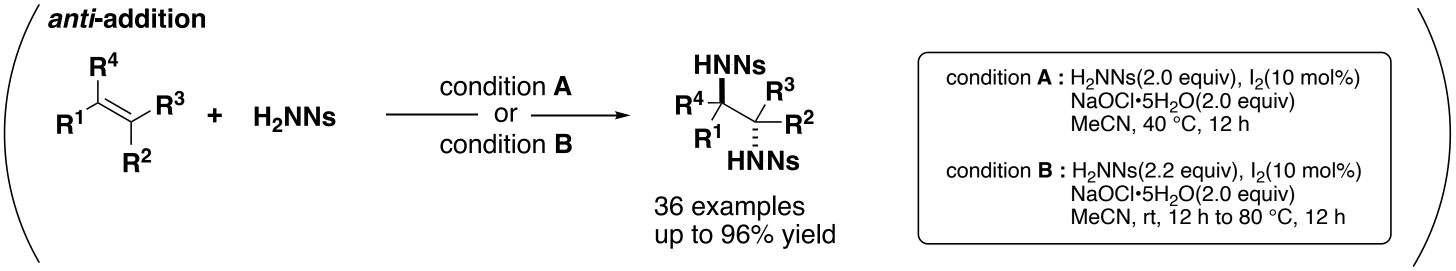
***syn*-addition**



1.0 equiv

12 examples
up to 81% yield

***anti*-addition**



36 examples
up to 96% yield

condition **A** : H_2NNs(2.0 equiv), I_2(10 mol%)
$NaOCl•5H_2O$(2.0 equiv)
MeCN, 40 °C, 12 h

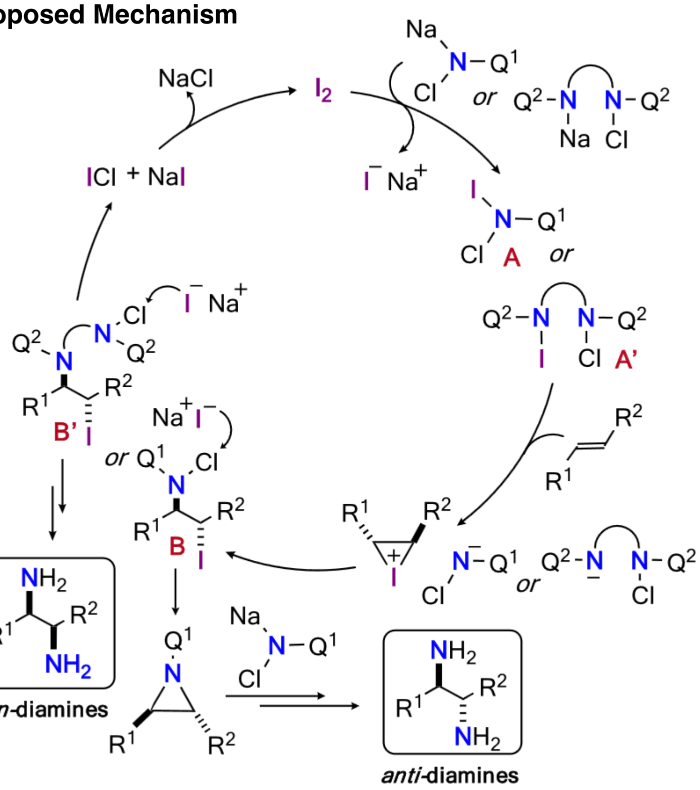
condition **B** : H_2NNs(2.2 equiv), I_2(10 mol%)
$NaOCl•5H_2O$(2.0 equiv)
MeCN, rt, 12 h to 80 °C, 12 h

Synthesis of Diaminating Reagent

BBS

chloramine-BBS
96%

Proposed Mechanism



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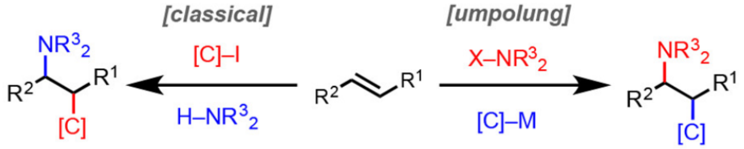
1) Minakata S. *et. al. J. Am. Chem. Soc.* **2021**, *143*, 4112.

4. Carbofunctionalization

4-1. Carboamination

Background[1]

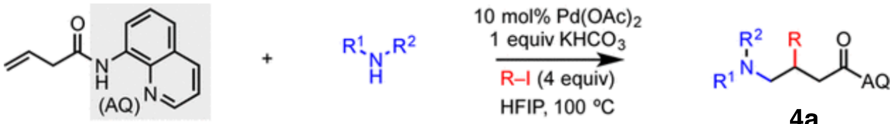


– **Catalytic Intramolecular Reaction** ◎

– **Intermolecular Reaction** △

– **Diastreoselective Intermolecular Reaction** ×

Catalytic Intermolecular Carboamination of Unactivated Alkenes[1]

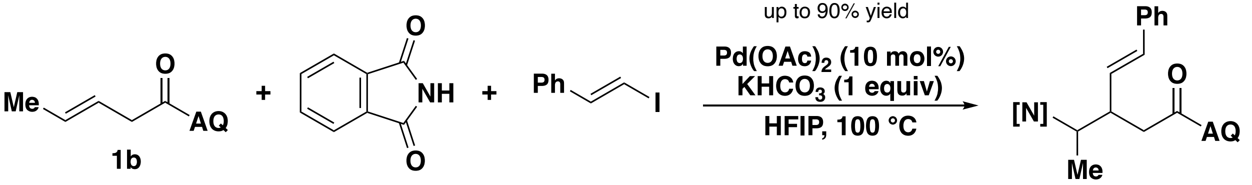


1a

(R = alkyl, aryl, vinyl)

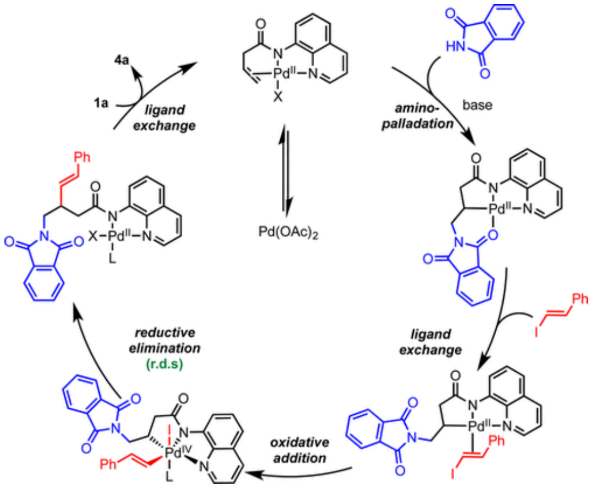
4a

16 examples
up to 90% yield



1b

30% yield
d.r. = 1.1:1

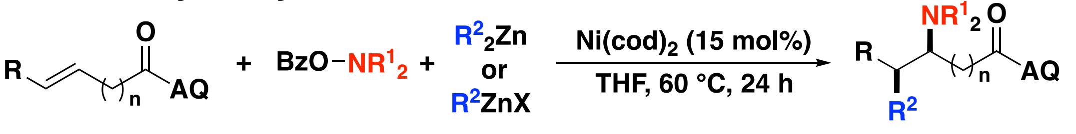


Isomerization by [Pd]

$$1b \xrightarrow[\text{HFIP, 100 °C, 40 h}]{Pd(OAc)_2\ (10\ mol\%)\ KHCO_3\ (1\ equiv)} 1b$$

E/Z = 2.9:1

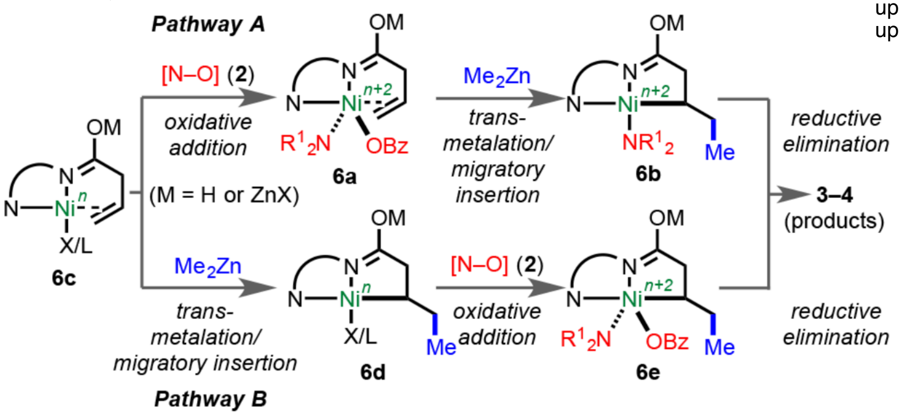
Nickel-Catalyzed *Syn*-Carboamination[2]



n = 1, 2

{R' = alkyl, aryl (one example, 27%)}

28 examples
up to 87% yield
up to >20:1 d.r.



***Syn*-Arylamination[3]**

R^2_2Zn or R^2ZnX ⇨ $ArB(OH)_2$

46 examples
up to 82% yield
up to >20:1 d.r.

***Syn*-Dicarbofunctionalization[4]**

BzO–NR$^1_2$ ⇨ ArI

26 examples
up to 88% yield
up to >20:1 d.r.

---

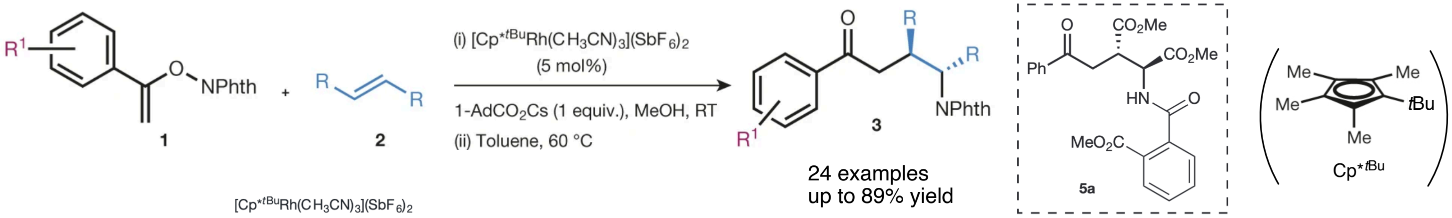
1) Engle. K. M. *et. al. J. Am. Chem. Soc.* **2017**, *139*, 11261.
2) Engle. K. M. *et. al. ACS. Catal.* **2019**, *9*, 224.
3) Engle. K. M. *et. al. Nature. Commun.* **2021**, *12*, 6280.
4) Engle. K. M. *et. al. J. Am. Chem. Soc.* **2017**, *139*, 10657.

4. Carbofunctionalization

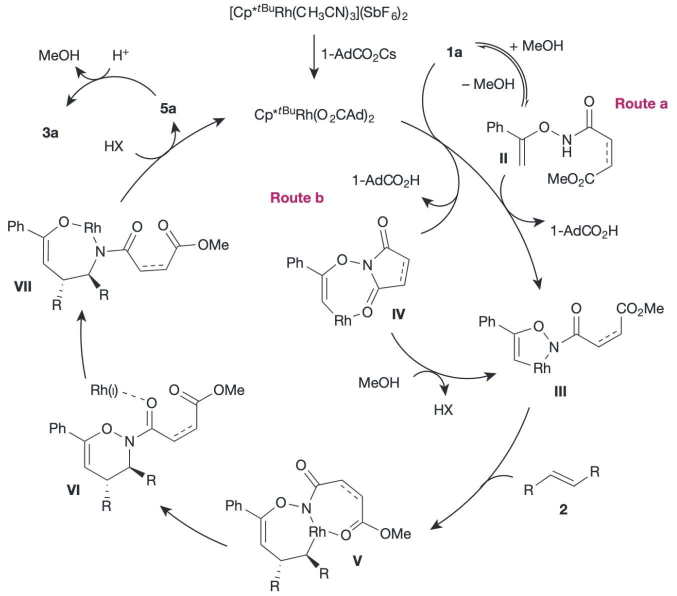
4-1. Carboamination

Rhodium-Catalyzed *Syn*-Carboamination

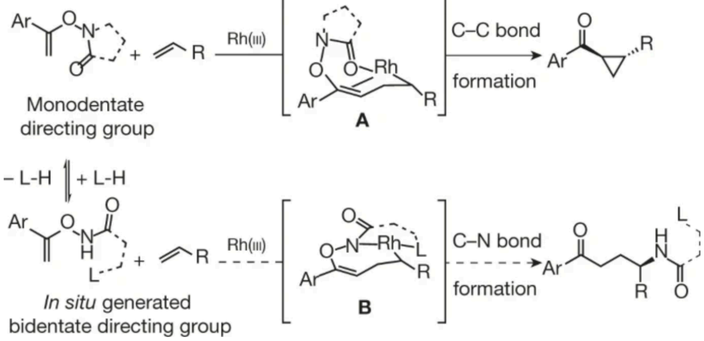
Carboamination via Rhodacycle Intermediate[1]



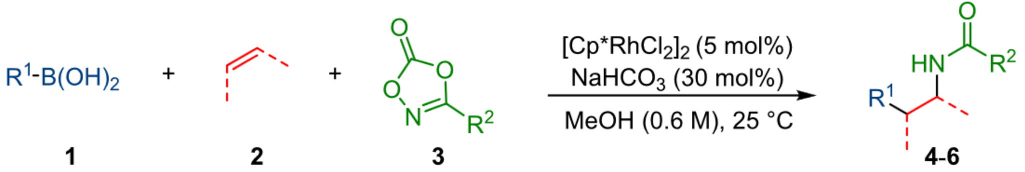
24 examples
up to 89% yield



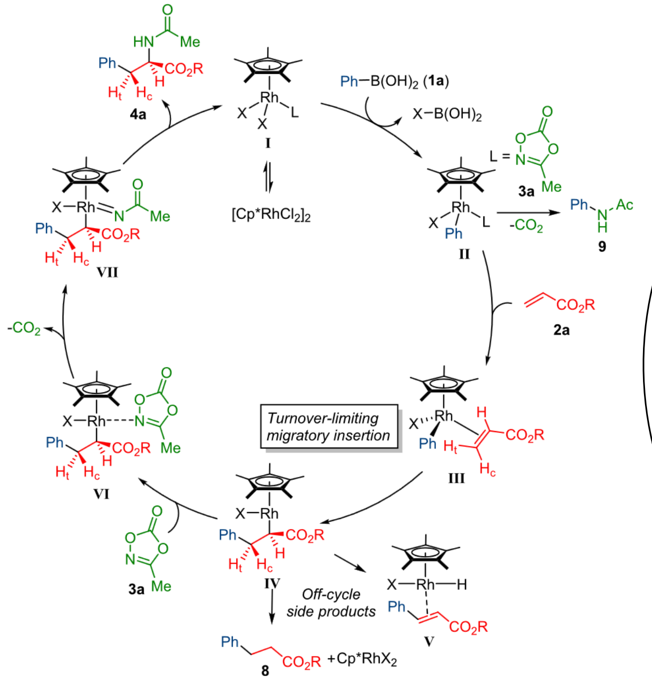
hypothesis



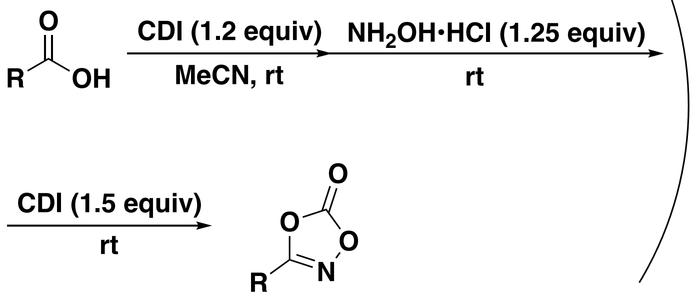
Intermolecular Carboamination[2]



37 examples
up to 89% yield



Synthesis of aminating reagents[3]



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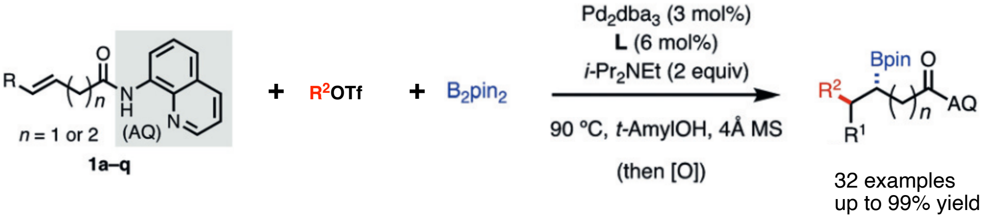
1) Rovis.T. *et. al. Nature* **2015**, *527*, 86.
2) Rovis.T. *et. al. ACS Catal* **2021**, *11*, 8585.
3) Blakey.S. B. *et. al. ACS Catal* **2019**, *6*, 5474.

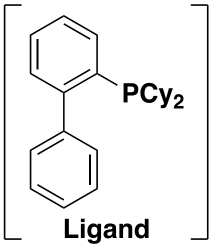
4. Carbofunctionalization

4-2. Carboboration/Carbosilylation

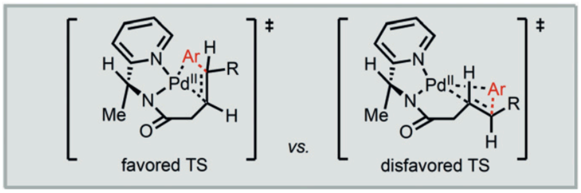
Palladium Catalyzed Carboboration and Carbosilylation[1]

Carboboration



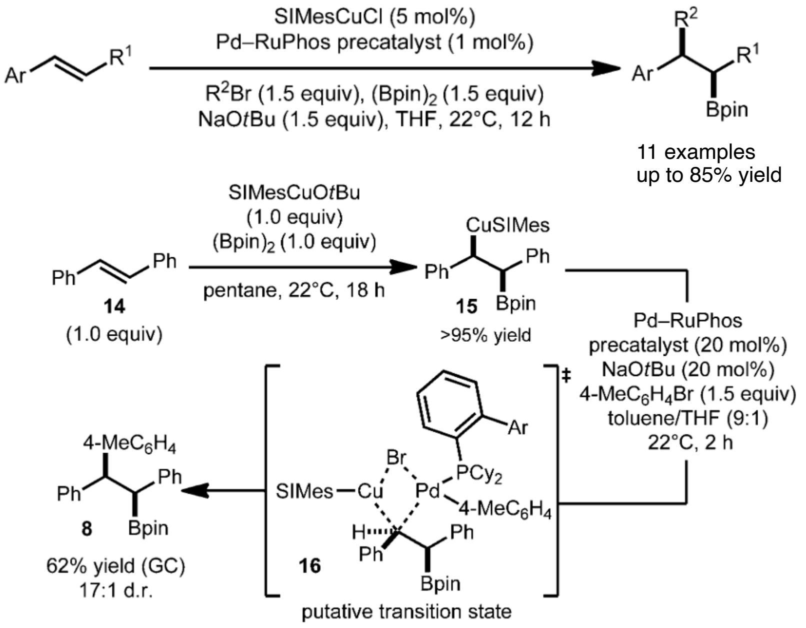


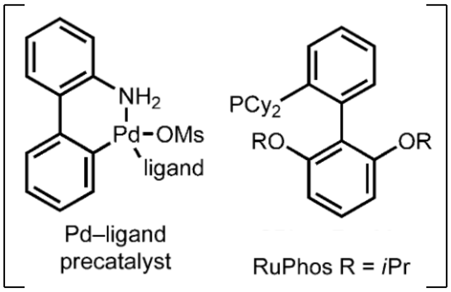
Carbosilylation

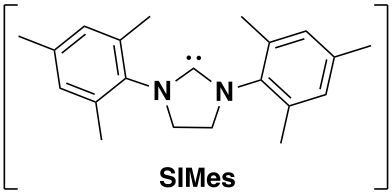


[Cu]/[Pd] Catalysis for Diastreoselective Carboboration[2]

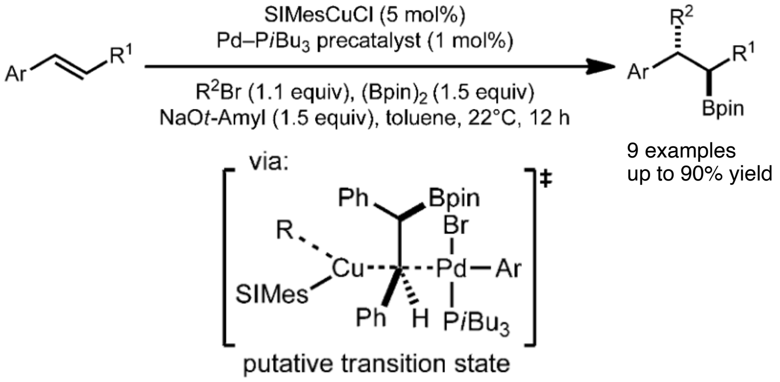
***Syn*-selective**







***Anti*-selective**



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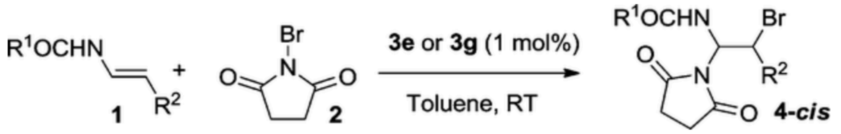
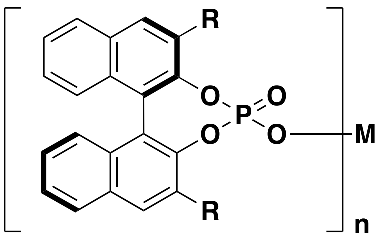
1) Engle.K. M. *et. al. Angew. Chem. Int. Ed.* **2019**, *58*, 17068.
2) Brown.M. K. *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 5228.

5. Halofunctionalization

5-1. Monohalo-functionalization

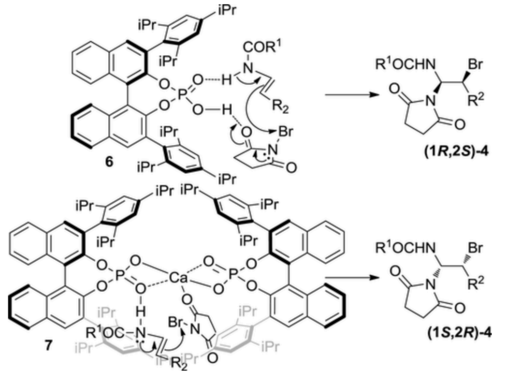
5-1-1 Bromoamination[1]

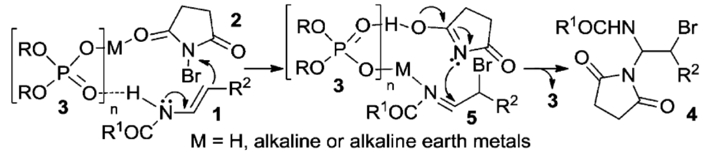




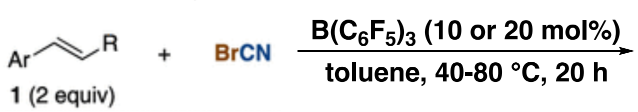
3e : M=H, n=1
3g : M=Ca, n=2
(R = 2,4,6-*i*$Pr_3C_6H_2$)

16 examples
up to 99% yield
up to 98% ee (**3e**)
up to –88% ee (**3g**)

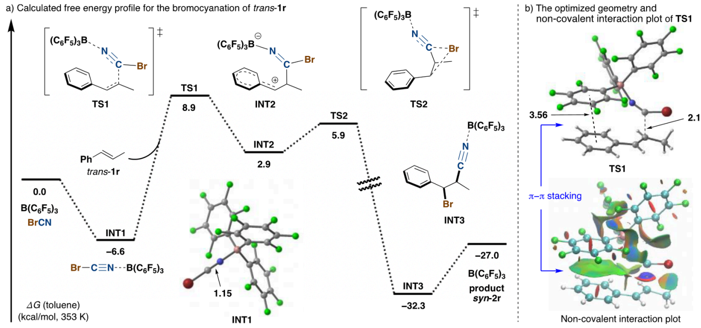


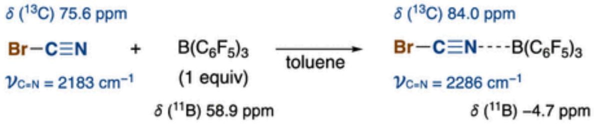


5-1-2 Bromocyanation[2]

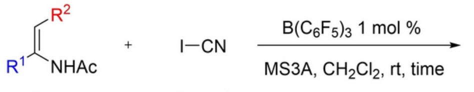


27 examples
up to 81% yield



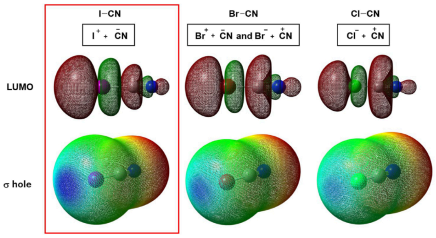


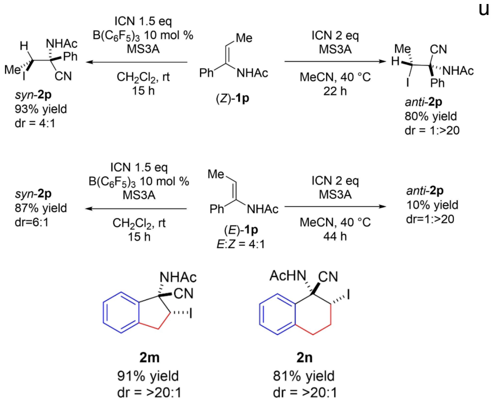
cf. Iodocyanation[3]

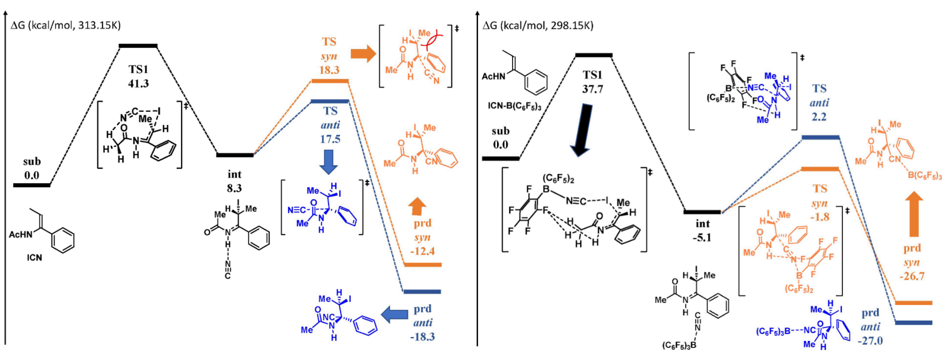


1a-o (1 eq)
(1.1 eq)
2a-o

24 examples
(7 non-activated alkenes)
up to 94% yield







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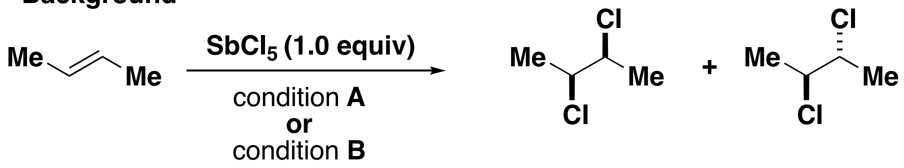
1) Masson. G. *et. al. J. Am. Chem. Soc.* **2012**, *134*, 10389.
2) Minakata. S. *et. al. Org. Lett.* **2023**, *25*, 2537.
3) Arai. T. *et. al. Adv. Synth. Catal.* **2023**, *365*, 3247.

5. Halofunctionalization

5-2. Dihalogenation

5-2-1 *Syn*-Dichlorination

Background[1]

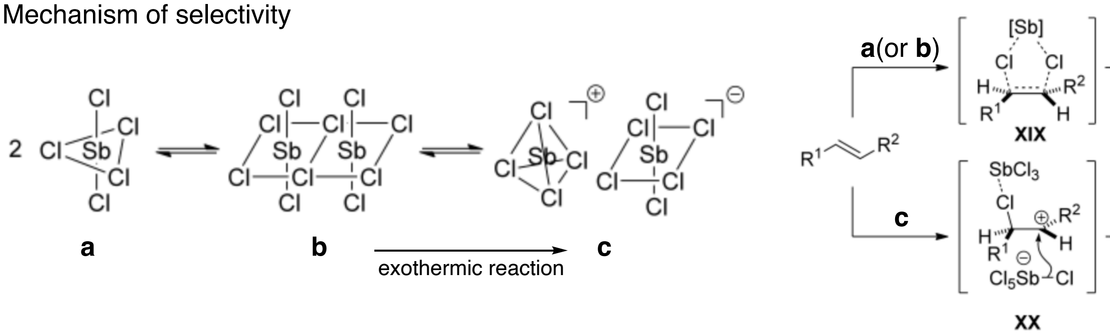


condition **A** : alkene(2.8 equiv)
CCl$_4$, **73 °C**,10 min

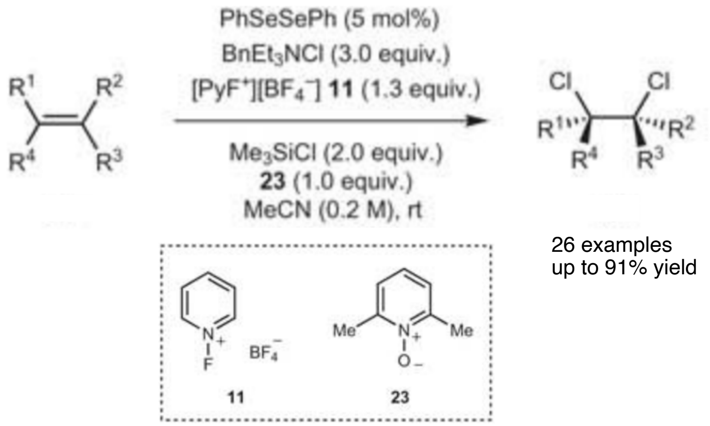
condition **B** : alkene(1.2 equiv)
CCl$_4$, **2–6 °C**,10 min

A : 96% yield (w. r. t. SbCl$_5$), cis:trans = **82:18**
B : 100% yield (w. r. t. SbCl$_5$), cis:trans = **70:30**

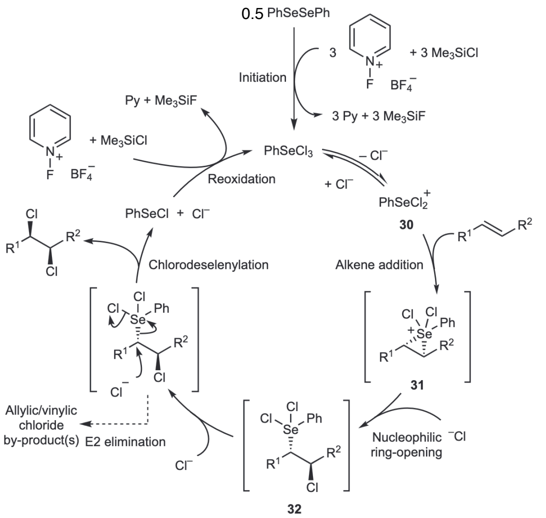
Mechanism of selectivity



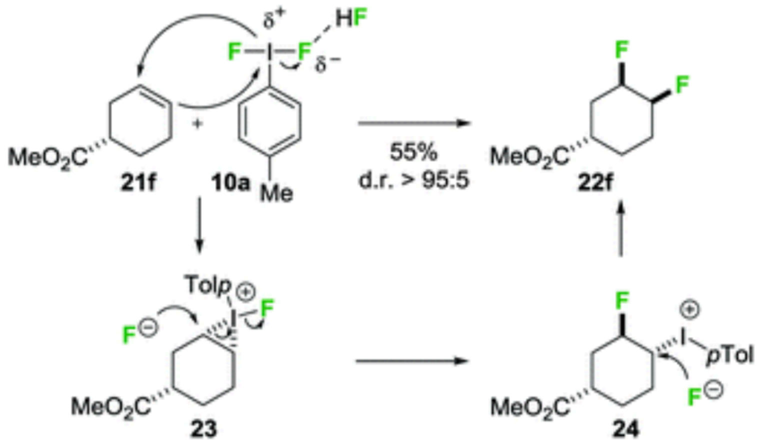
Se-Catalyzed *Syn*-Dichlorination[2]



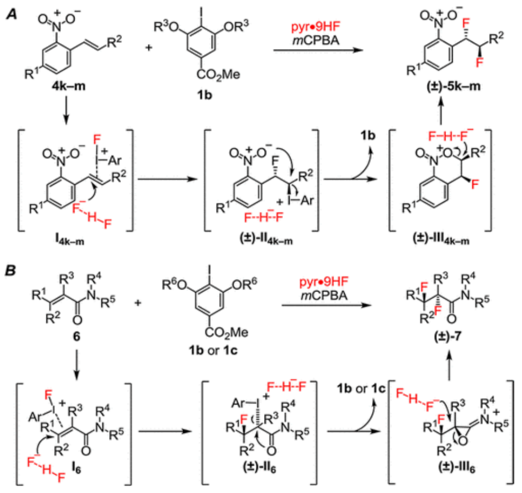
26 examples
up to 91% yield



5-2-2 *Syn*-Difluorination[3]



***Anti*-Difluorination**[4]



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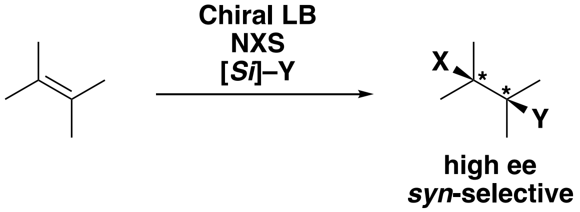
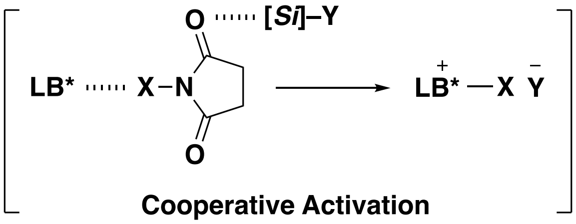
1) Uemura. S. *et. al. Bull. Chem. Soc. Jpn.* **1974**, *47*, 692.
2) Denmark. S. E. *et. al. Nat. Chem.* **2015**, *7*, 146.
3) Hara. S. *et. al. Synlett.* **1998**, 495.
4) Jacobsen. E. N. *et. al. J. Am. Chem. Soc.* **2016**, *138*, 5000.

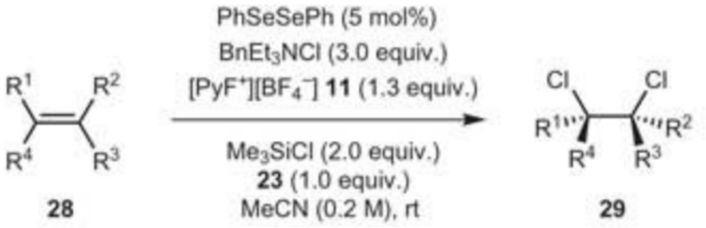
6. Proposal

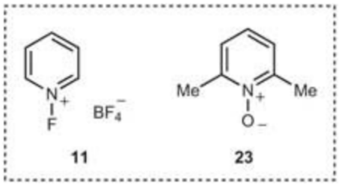
Proposal : Enantio– and *Syn*-Selective Homo/Hetrohalogenation of Alkenes

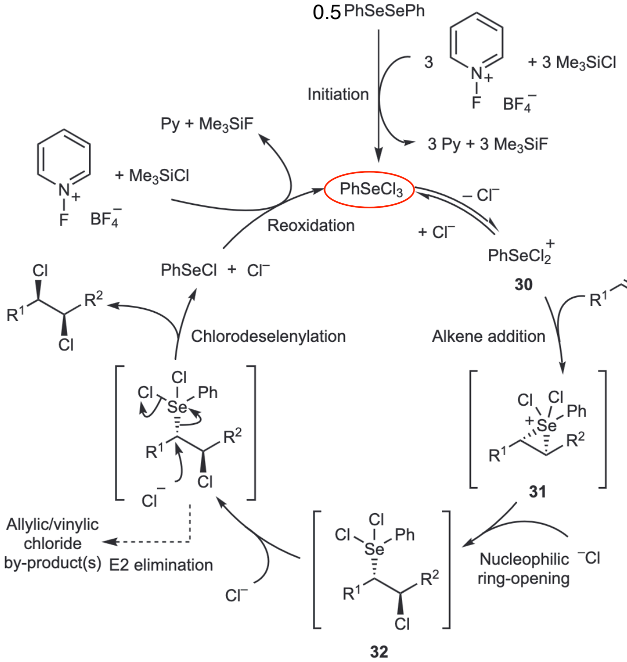




Previous Methods for Dichlorination







Problem

1. **$PhSeX_3$ are unstable compound.**

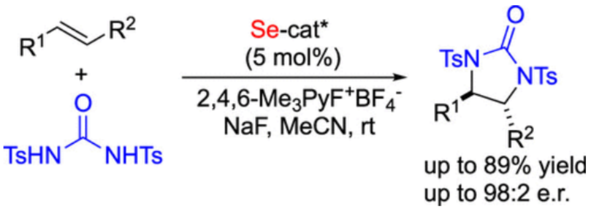
ex.[1]

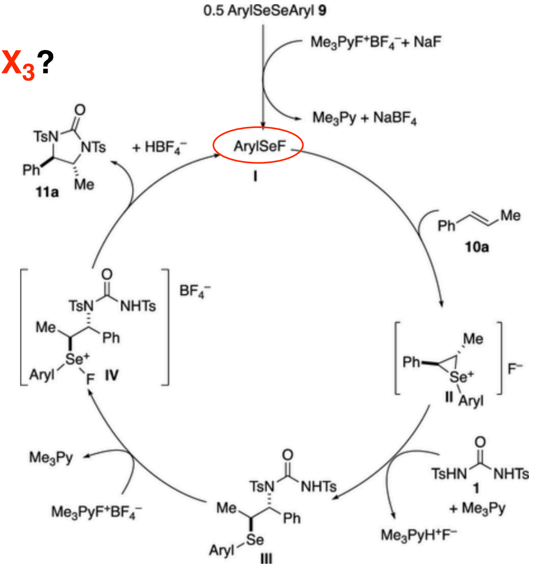
$$PhSeBr_3 \underset{rt}{\rightleftharpoons} PhSeBr + Br_2$$ **(*Anti*-reaction occur.)**

2. **$PhSeX_3$ cannot be applied to hetrohalogenation.**

dichlorination ◎ dibromination △ iodochlorination × bromochlorination ×

3. **Enantioselective reaction are difficult by using $PhSeX_3$?**





Ease of asymmetric induction

Ar*SeF > Ar^*SeCl_3 ??

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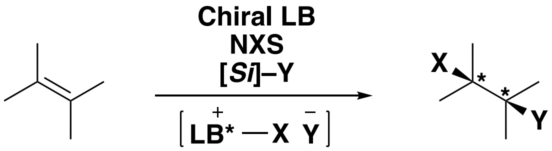
[1] Engman. L. *et. al. J. Org. Chem.* **1987**, *52*, 4086.

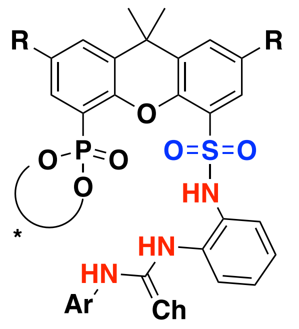
6. Proposal

Proposal : Enantio– and *Syn*-Selective Homo/Hetrohalogenation of Alkenes

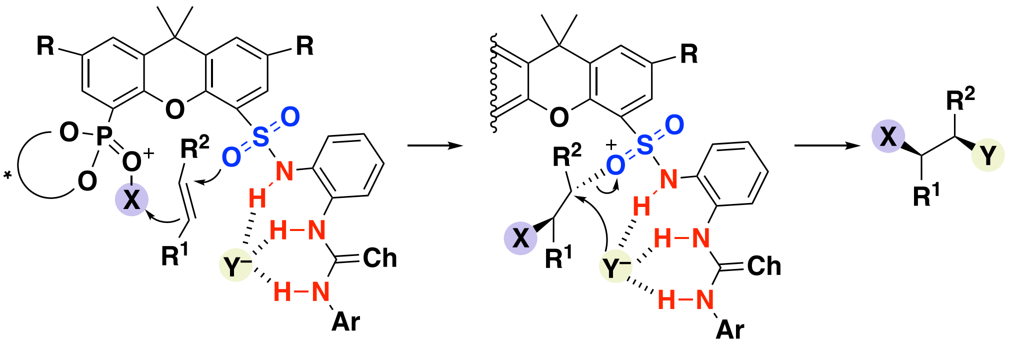


- achievement of homo and heterohalogenation
- highly enantio- and *syn*-selective reaction
- no need for DG group of substrate

Chiral Lewis Base Catalyst

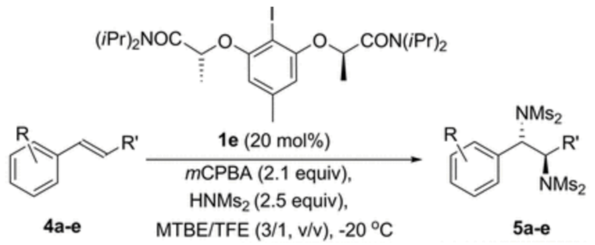


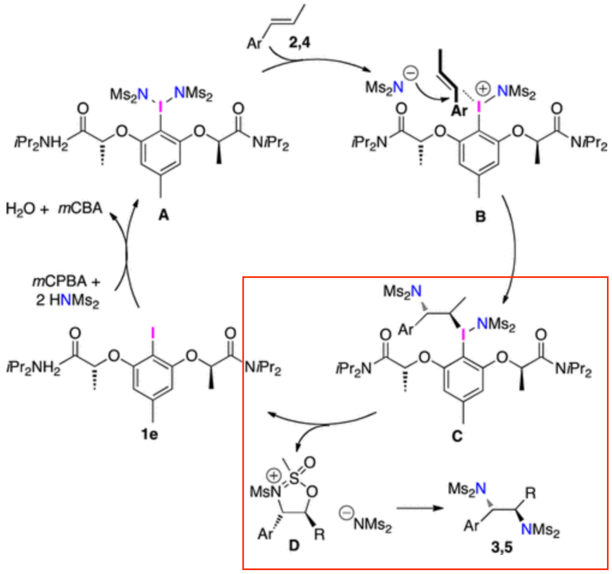
Mechanism



Reference

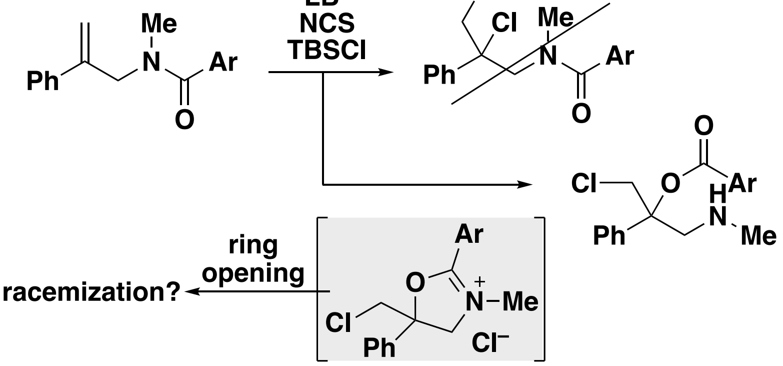
Nucleophile(RSO_2R) of catalyst[1]

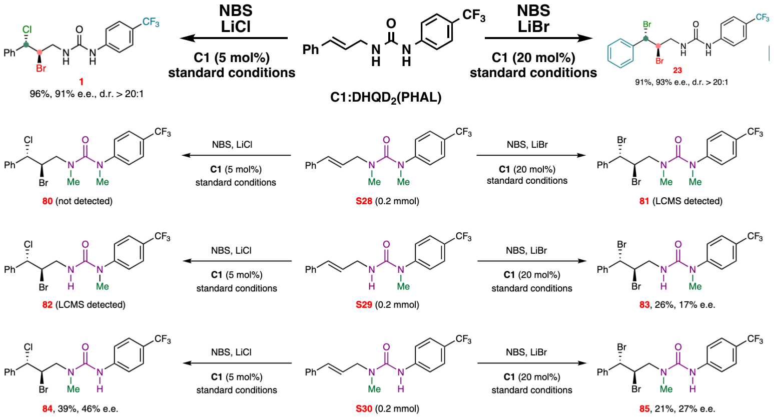




Effect of urea group[2]

Previous Work





Urea secure the halide in the promixity to reactive site.
→Improve the nucleophilicity of halide.

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1) Martínez. C. *et. al. J. Am. Chem. Soc.* **2017**, *139*, 4354.
2) Tan. B. *et. al. Nat. Catal.* **2021**, *4*, 692.