



# Enantioselective, Lewis Base-Catalyzed, Functionalization of Alkenes

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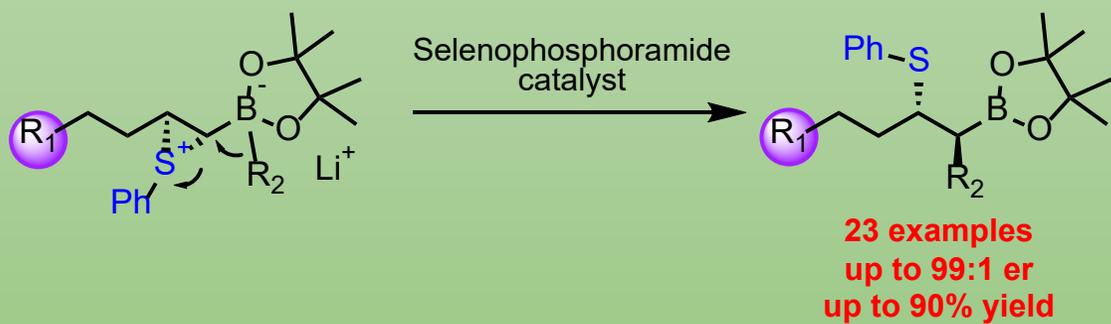
JESSE PANGER

Research Summary

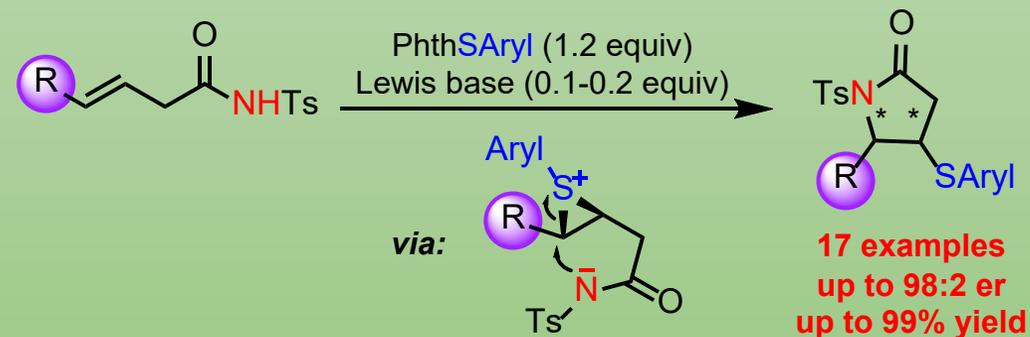
19 JUL 2022

# Projects: Variable Success Along the Way

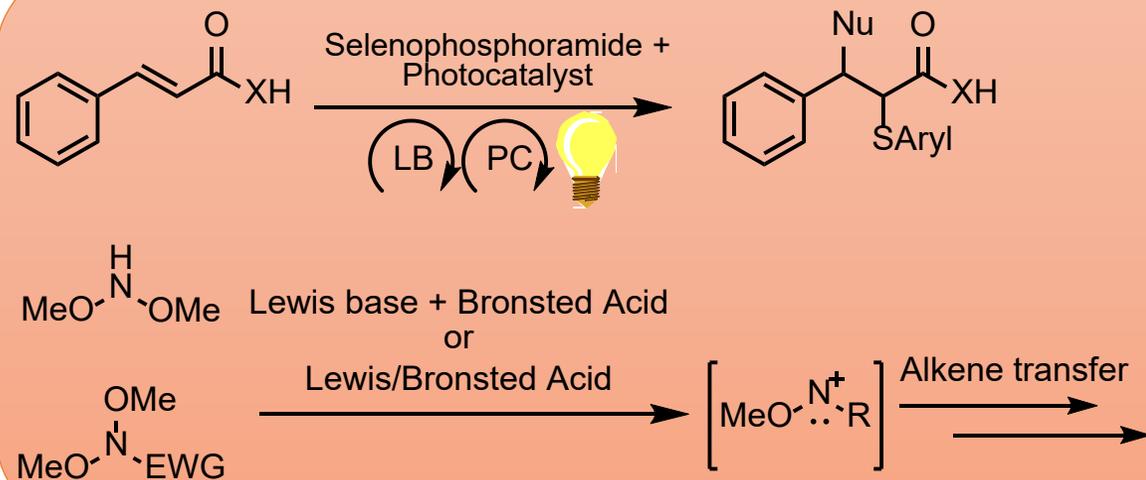
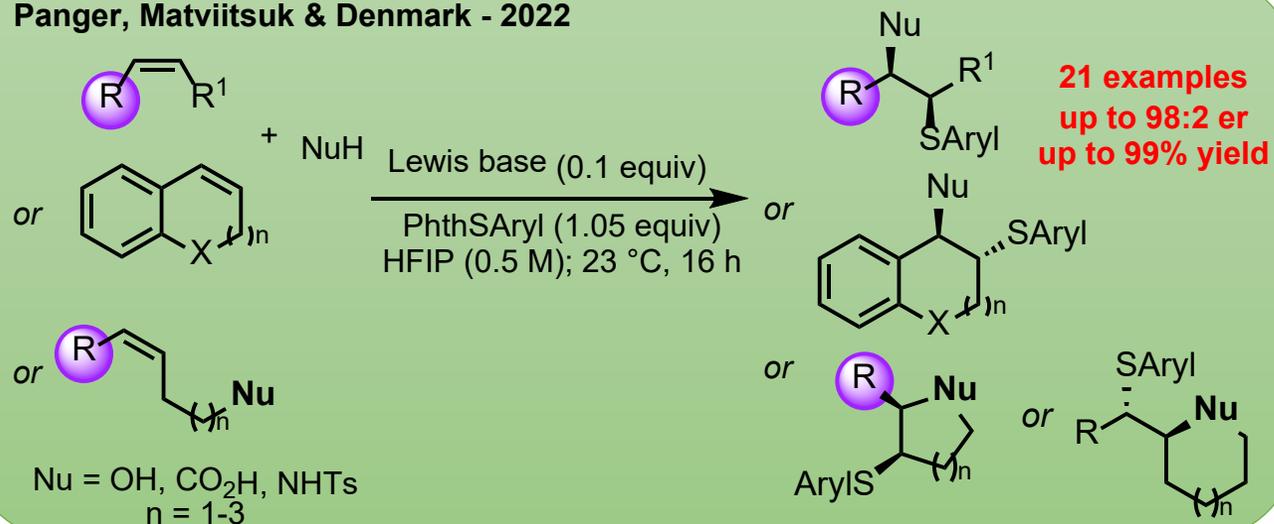
Tao, Robb, Panger, & Denmark - 2018



Panger & Denmark - 2020

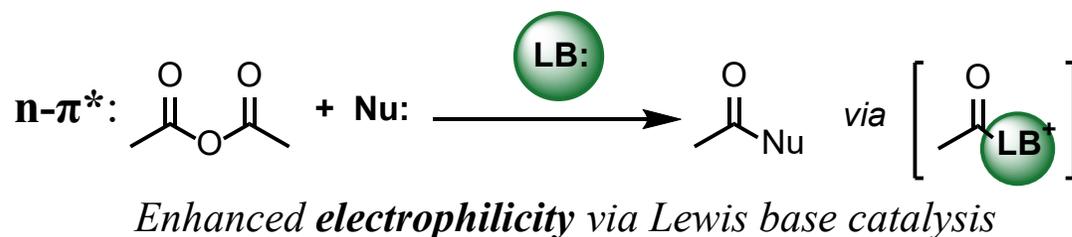
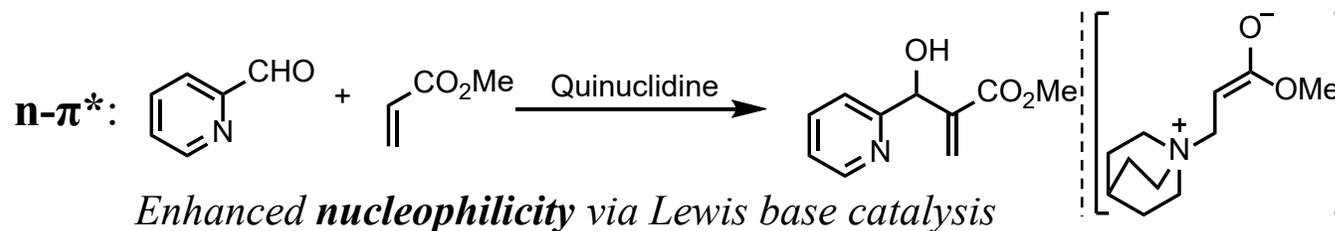
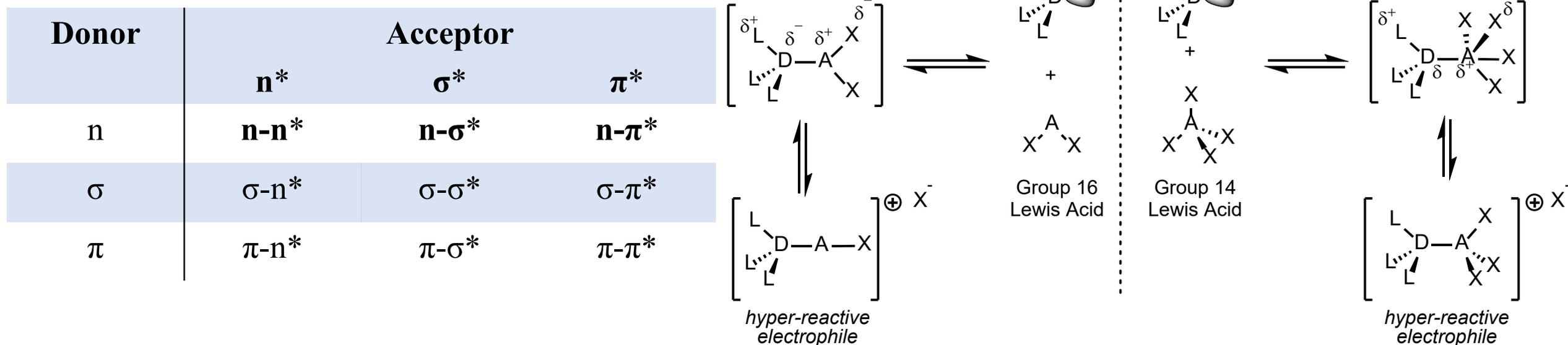


Panger, Matviitsuk & Denmark - 2022



# Lewis Base Catalysis: n-σ\*

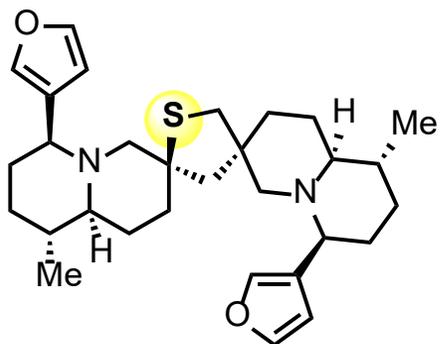
## Jensen's Orbital Analysis



# Incorporation of Sulfur into Organic Molecules

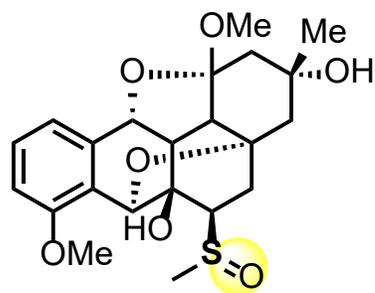
## Sulfur-containing natural products

Thioethers



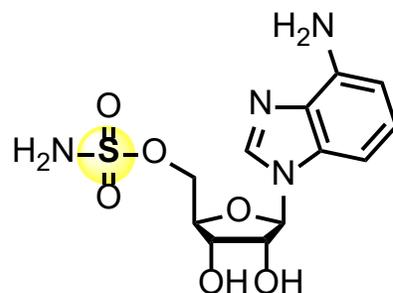
Neothiobinupharidine

Sulfoxides



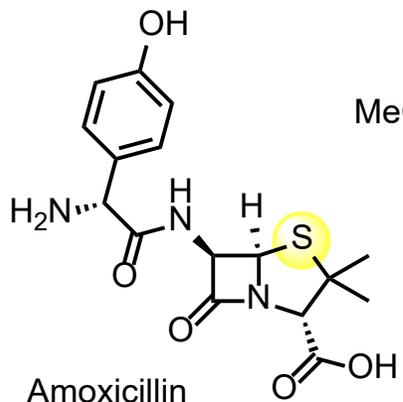
Grisemycin

Sulfamate

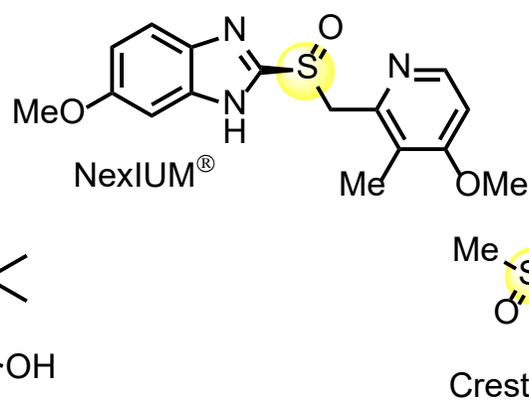


Nucleocidin

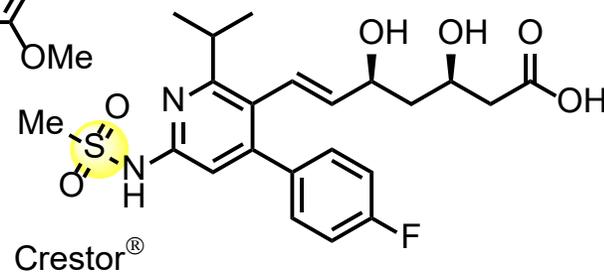
## Sulfur-containing pharmaceutical agents



Amoxicillin

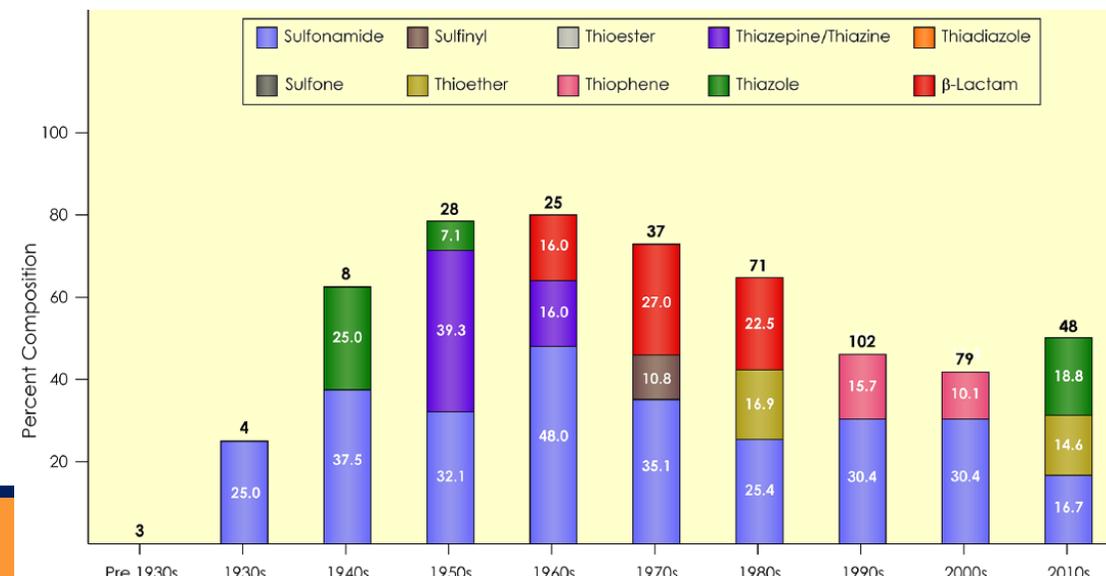
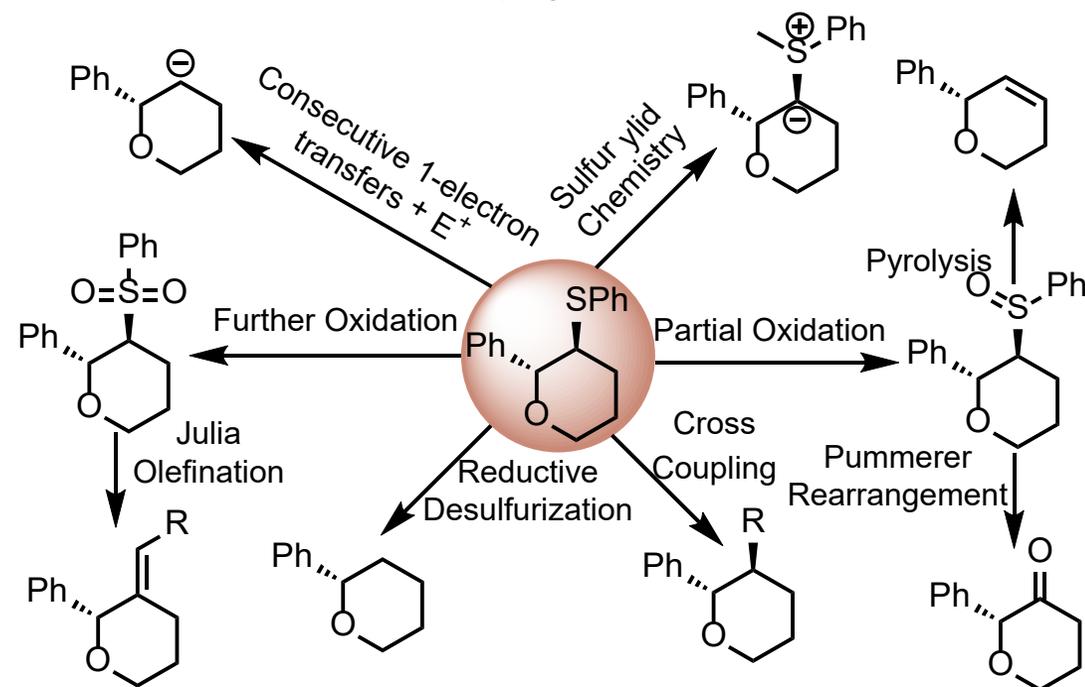


NexIUM®

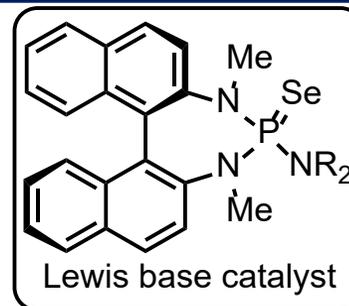
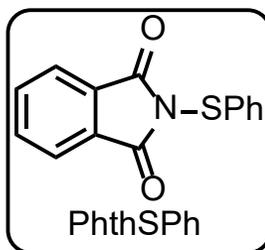
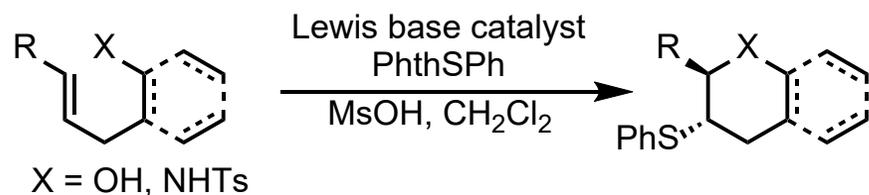


Crestor®

## Common reactions that employ sulfur:

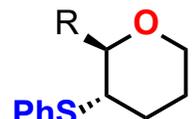


# Sulfenofunctionalization in the Denmark Lab: 2011–2017



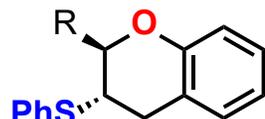
- ✓ Generates vicinal stereocenters
- ✓ Clean reaction profiles
- ❖ Sub-ambient conditions
- ❖ Strong acid present

## Thioetherification - 2011



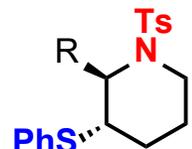
via alcohols

## Thioetherification - 2017



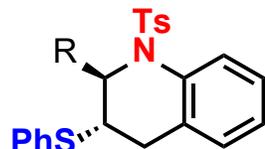
via phenols

## Sulfenoamination - 2014



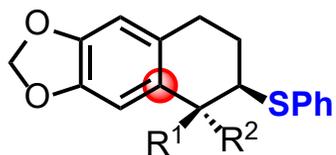
via amines

## Sulfenoamination - 2017



via anilines

## Carbosulfenylation - 2013

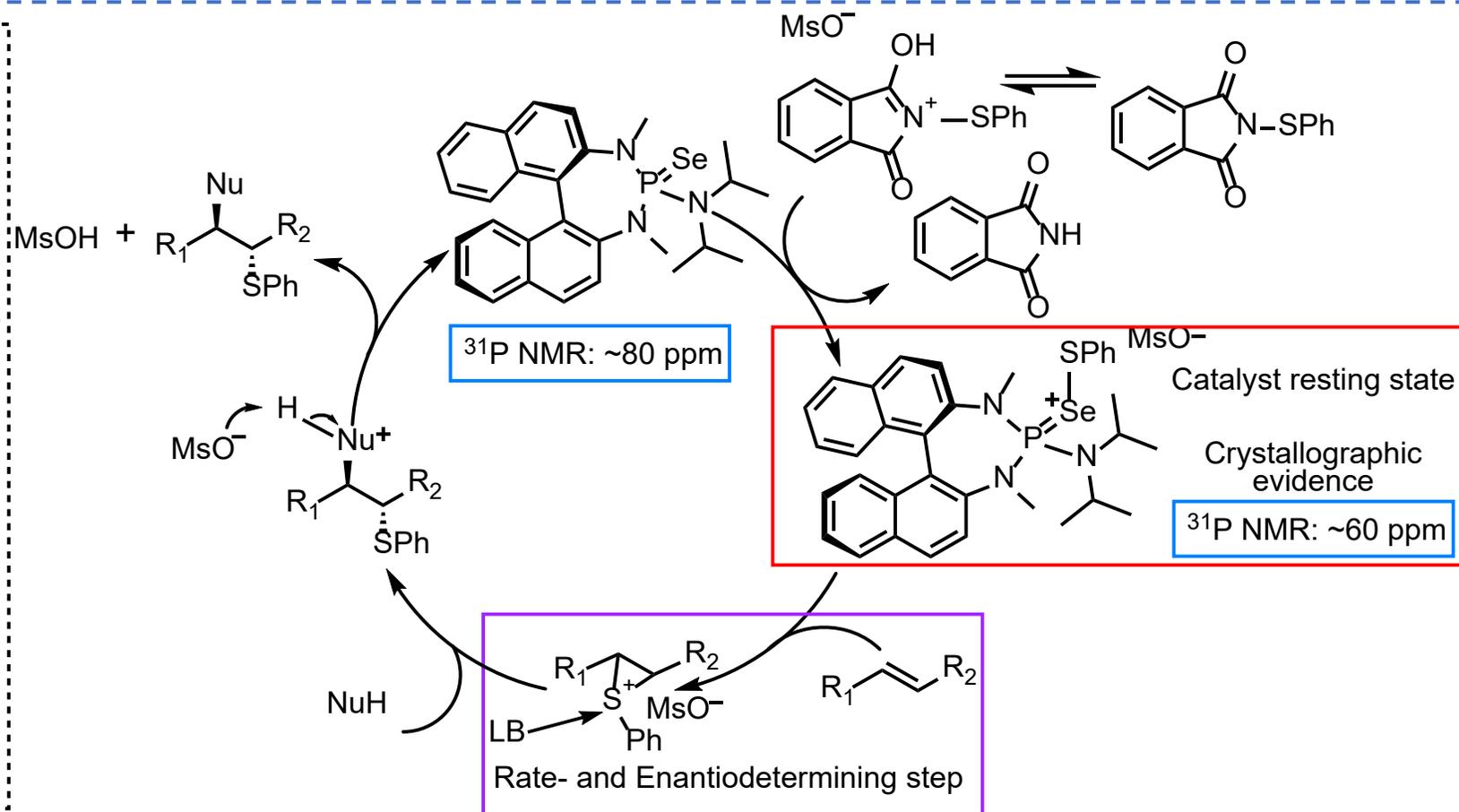


electron-rich arenes

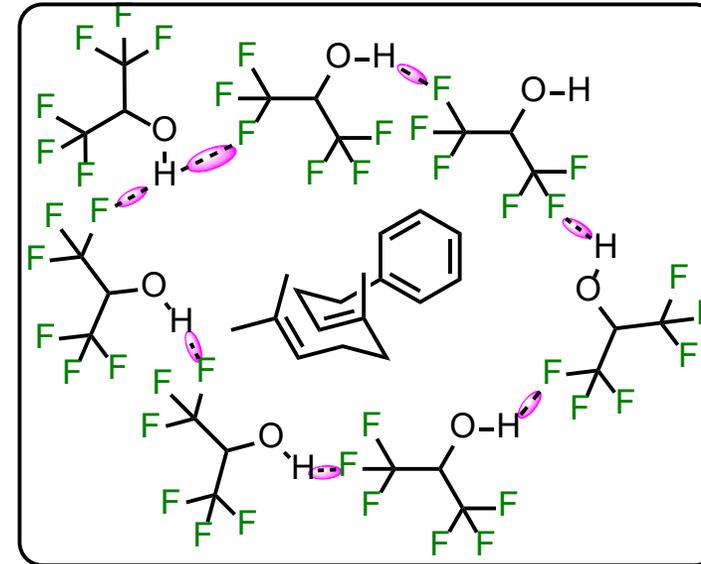
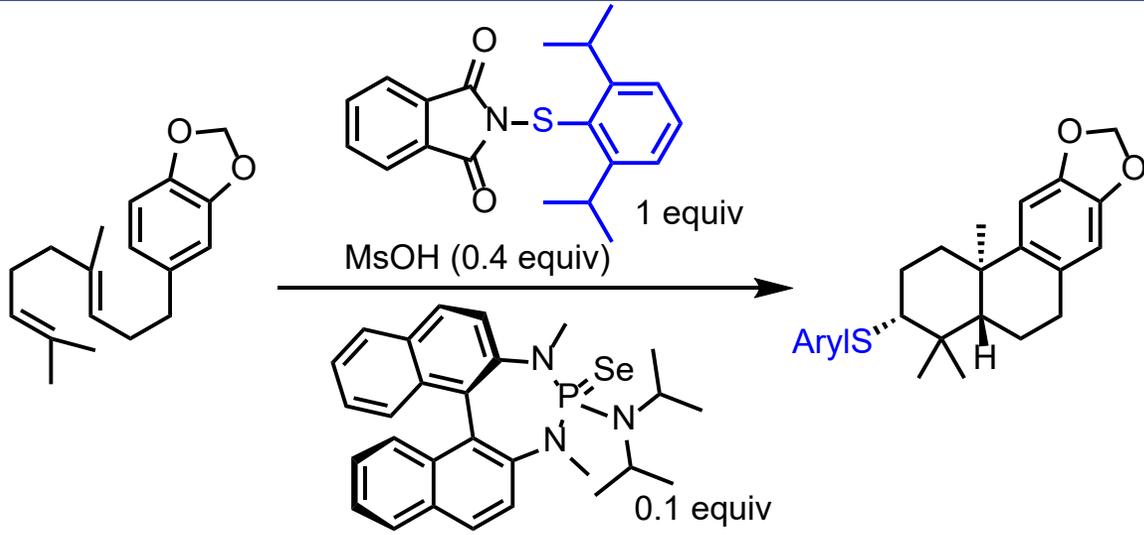
## $\alpha$ -Sulfenylation - 2014



via enoxy silanes



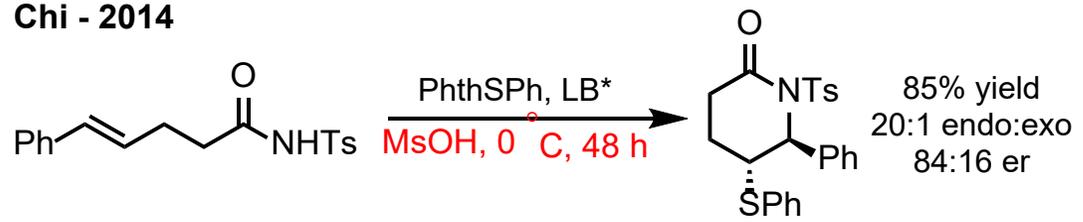
# Advances in Lewis Base Catalysis: HFIP as an Enabling Solvent



- ✓ Suppressed sulfenylation of internal alkene
- ✓ Obviates need for strong acid

Solvents used: CH<sub>2</sub>Cl<sub>2</sub>, PhMe, MeNO<sub>2</sub>, PhCl, TFT, MeCN: complex mixture  
 HFIP (no acid additive): clean conversion

Chi - 2014

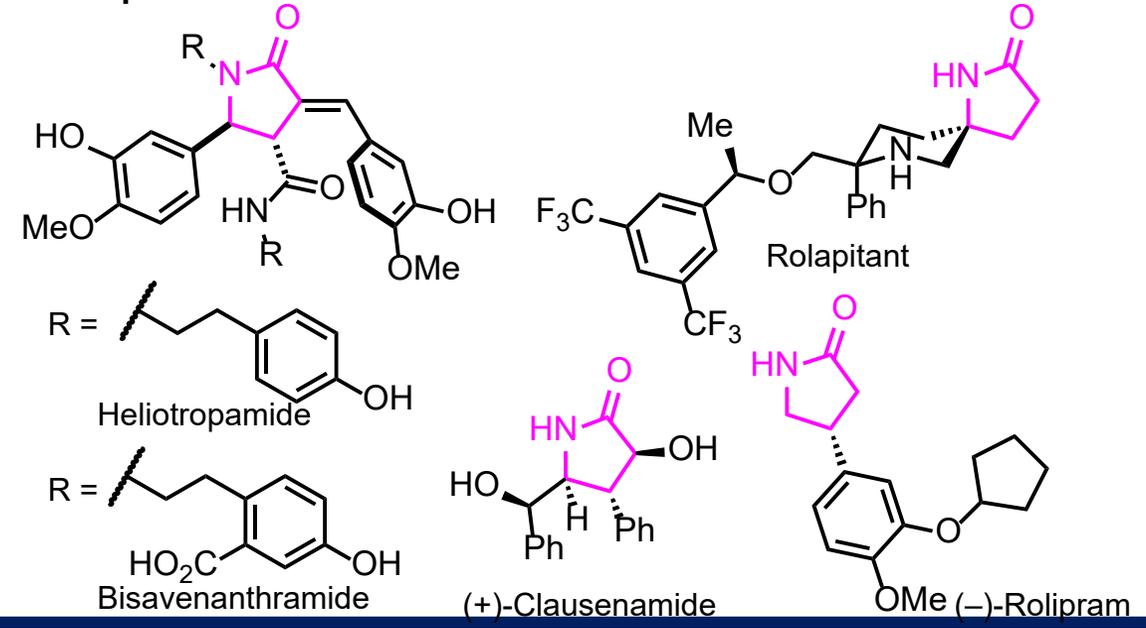


Strong acid, long reaction time, moderate er, good yield

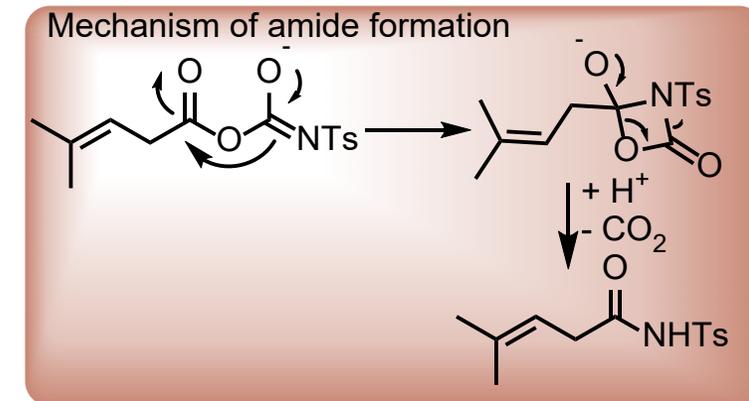
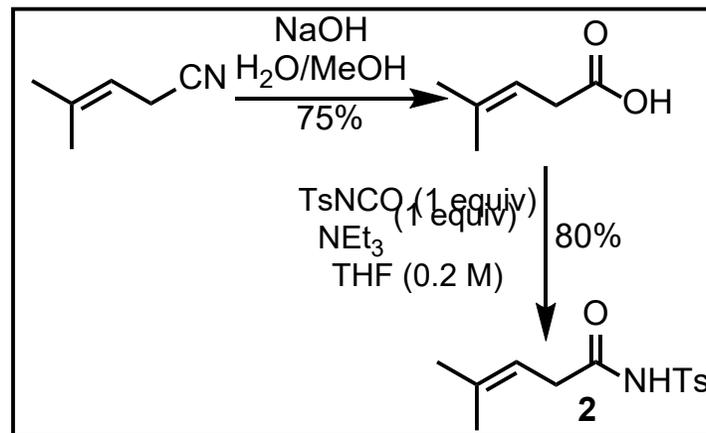
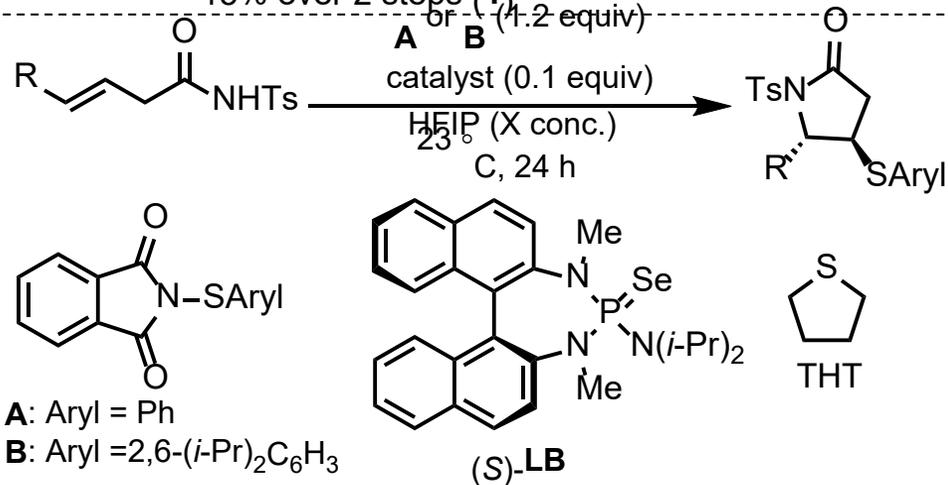
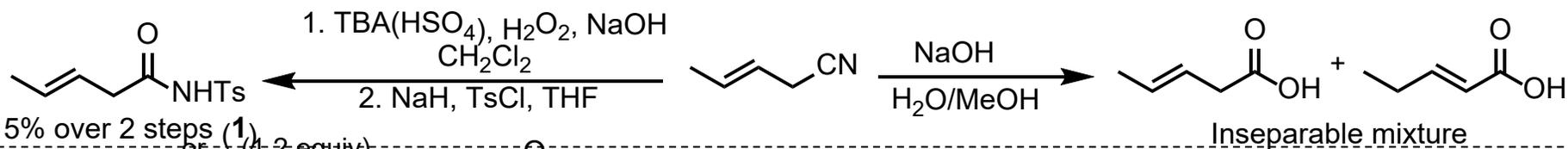
Can this be optimized for a superior reaction profile?



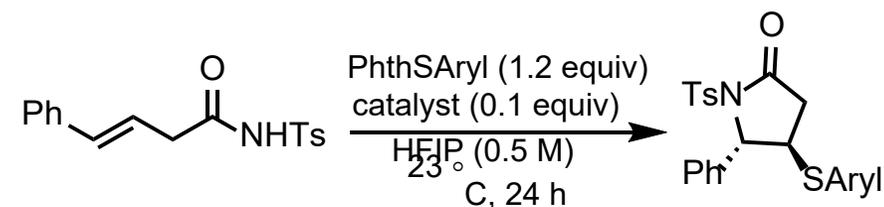
Examples of  $\gamma$ -lactams in natural products and pharmaceuticals



# Initial Investigations and Substrate Synthesis



entry	substrate	sulfonylating agent	catalyst	conc. (M)	yield (%)	er
1	1	B	-	0.2	0	-
2	1	B	THT	0.2	85 (93)	-
3	1	B	(S)-LB	0.2	(12)	nd
4	1	A	THT	0.5	(87)	-
5	1	A	(S)-LB	0.3	(82)	nd
6	2	A	THT	0.2	62 (87)	-
7	2	A	(S)-LB	0.2	83 (82)	65:35



PhthSPh, THT: 85% yield

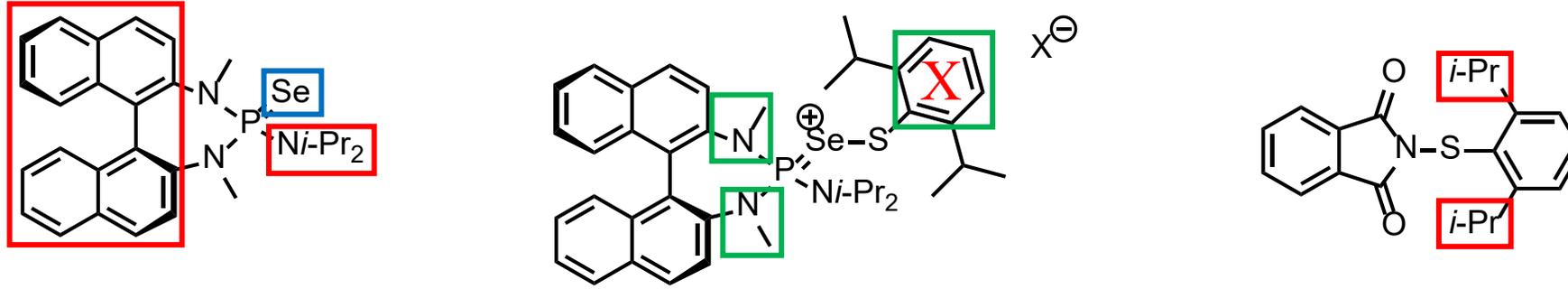
PhthSPh, LB\*: 83% yield, 84:16 er

PhthSAryl, LB\*: 76% yield, 98:2 er

Numbers in parentheses are NMR yields



# Development of a Highly Reactive Lewis Base Catalyst

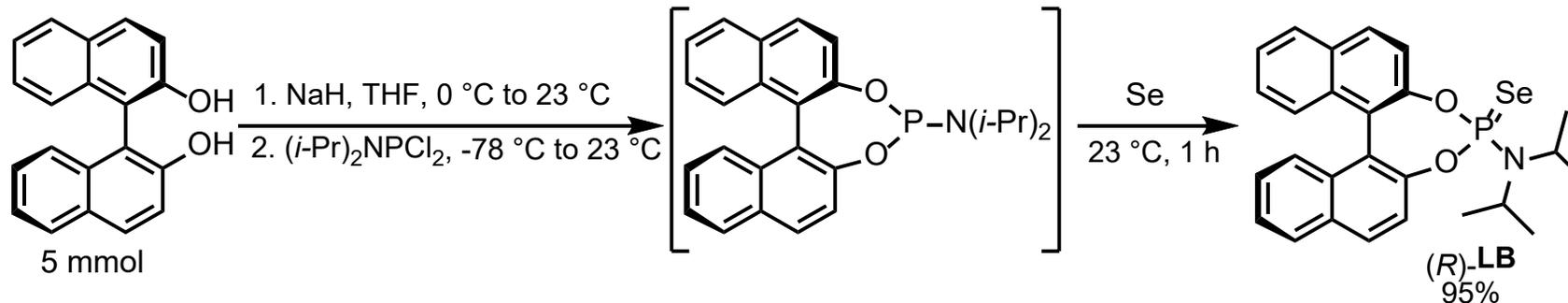


Necessary for enantioselectivity

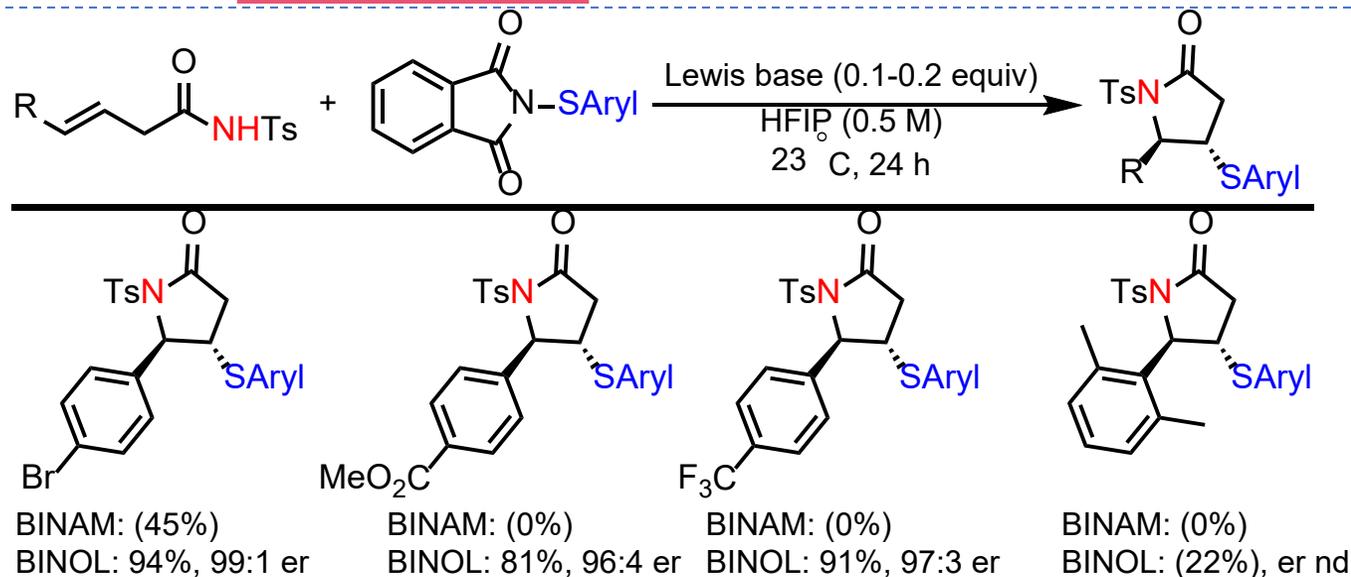
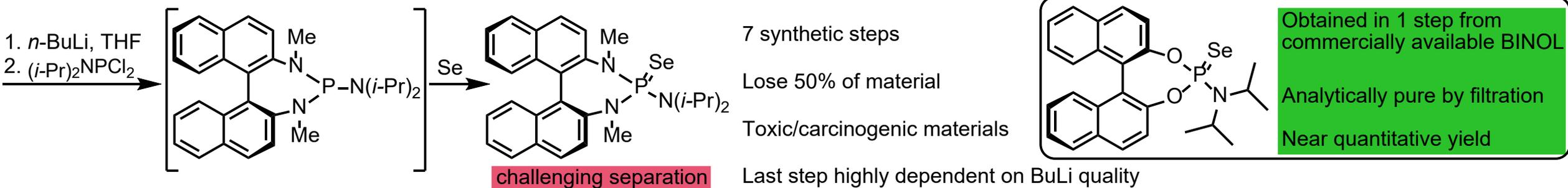
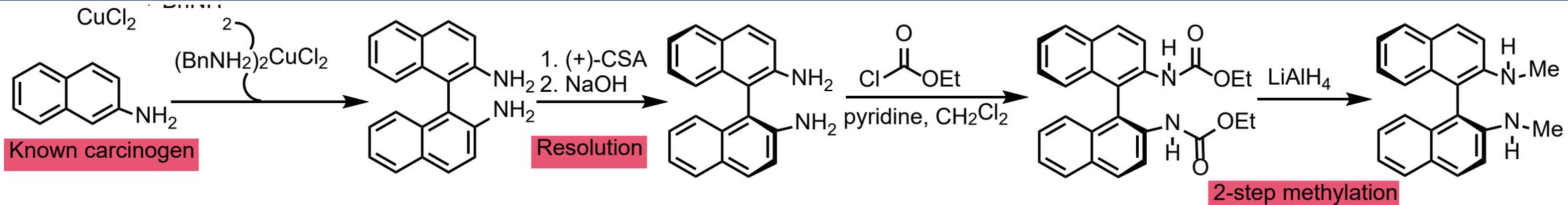
Necessary for catalysis

Potential handles to increase reactivity

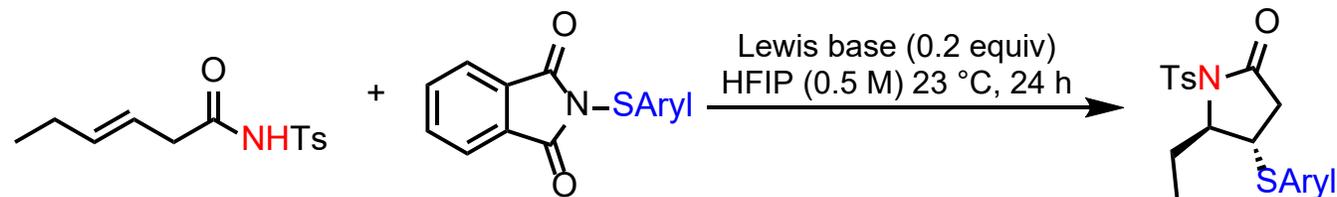
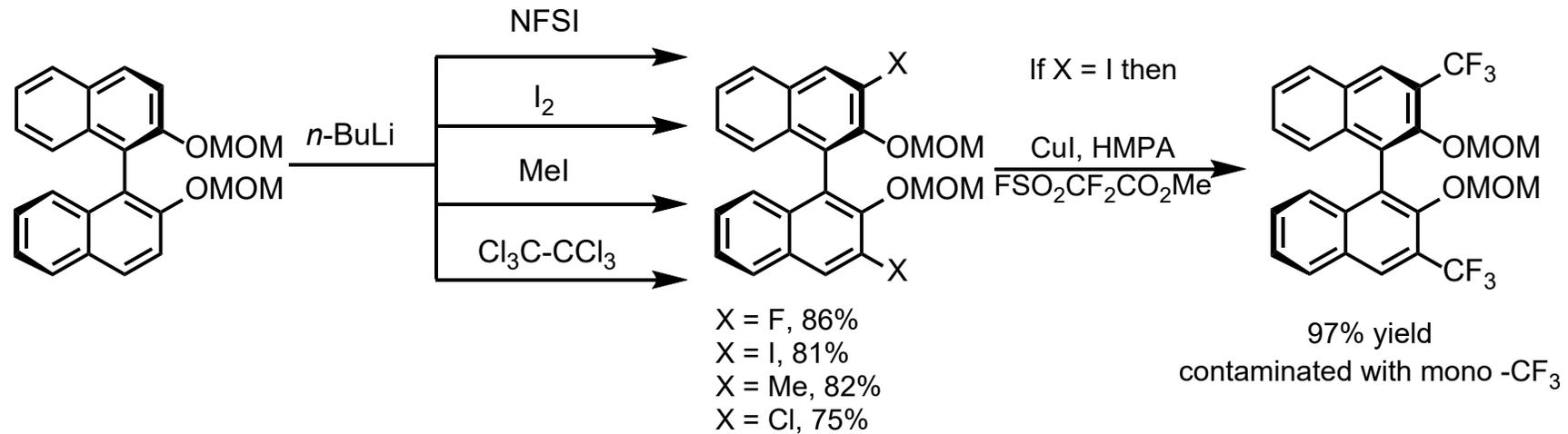
1. Sulfenium ion transfer insensitive to electronics on arene
2. Catalyst modification to render *decreased* Lewis basicity



# Comparing Lewis Bases: BINOL vs. BINAM

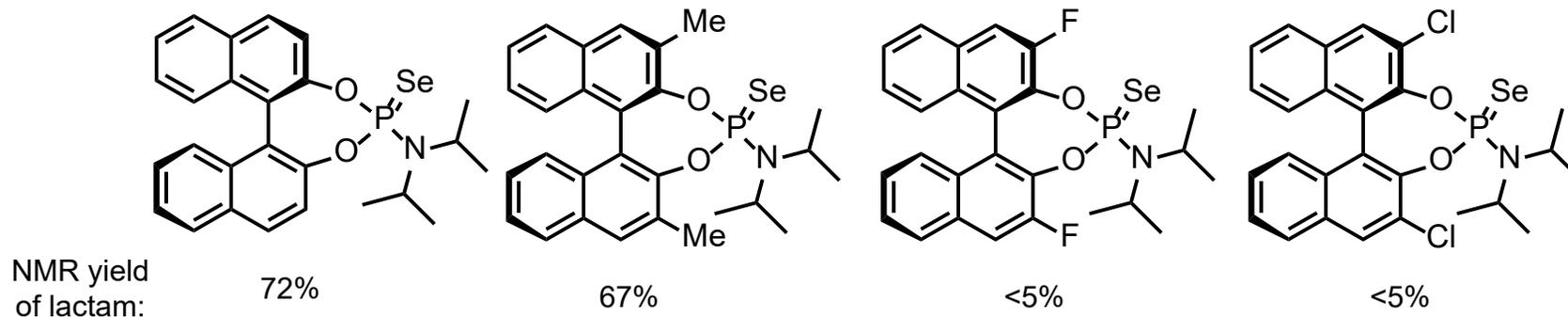


# Development of a Novel Selenophosphoramidate Catalyst

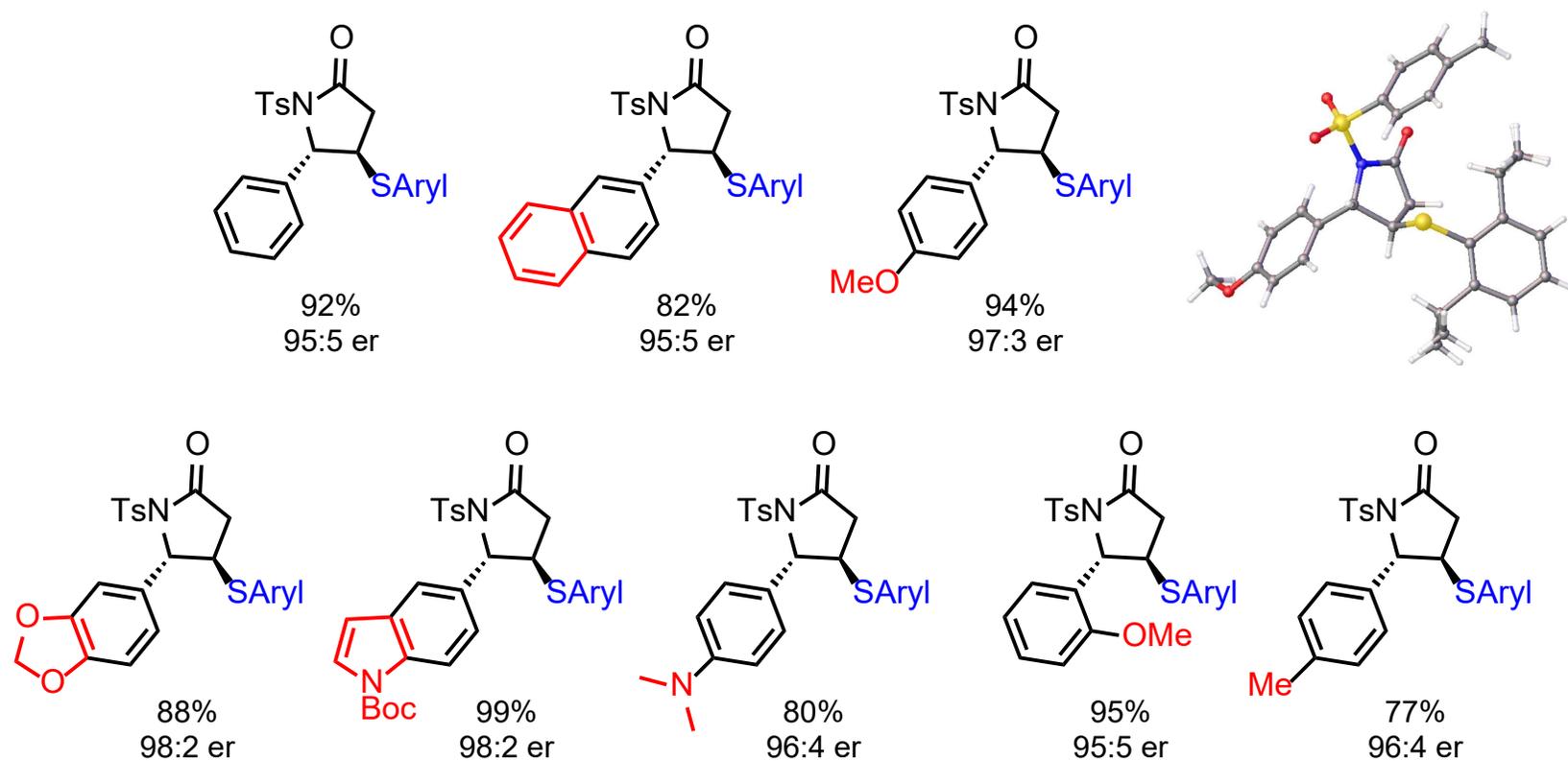
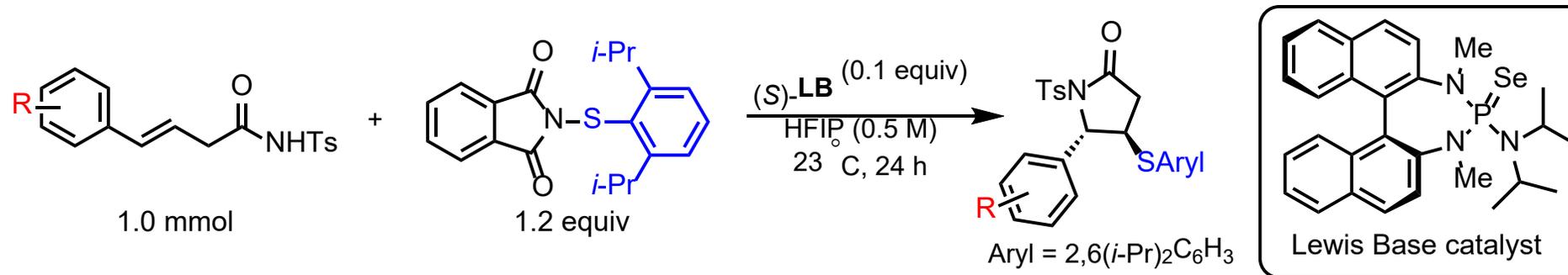


## Summary of Work

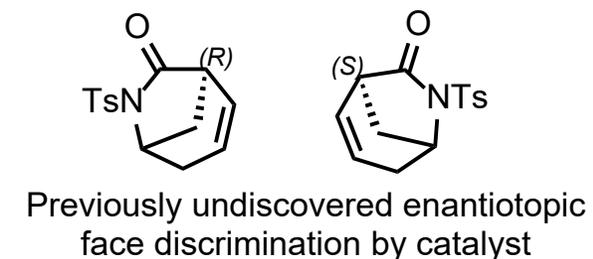
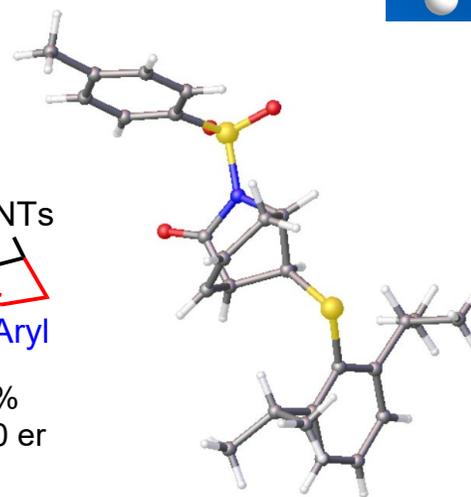
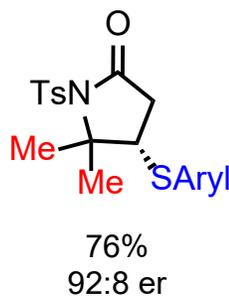
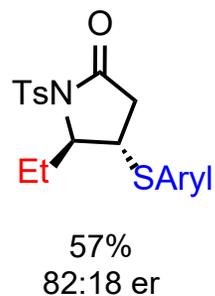
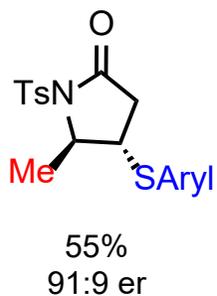
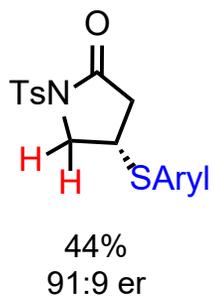
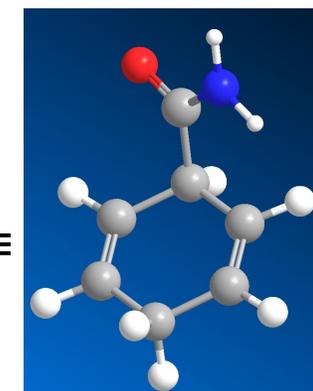
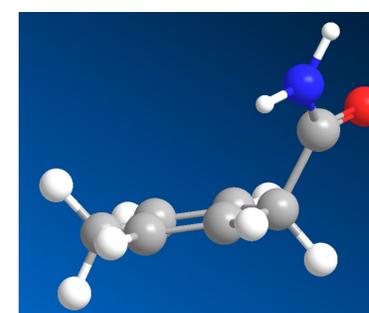
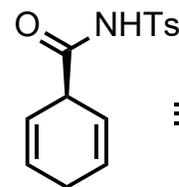
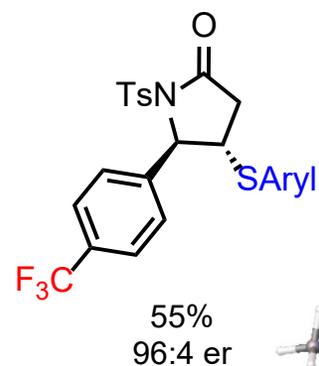
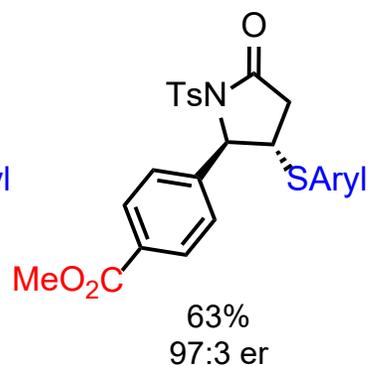
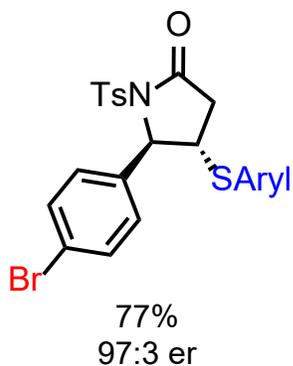
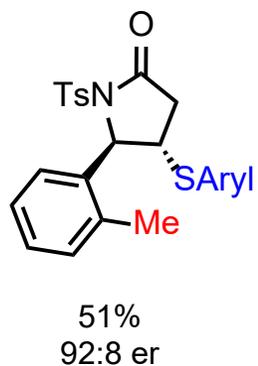
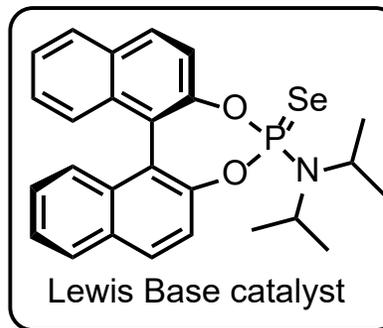
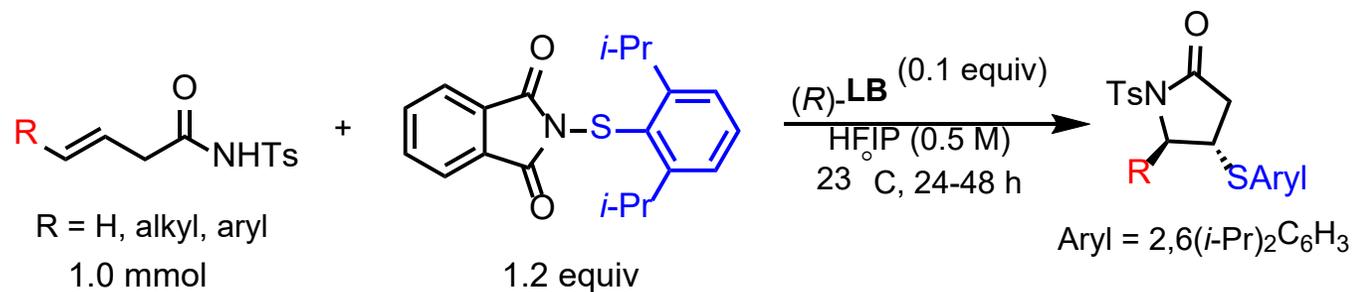
- Diverse substrates tested including electron-rich, electron-poor, and sterically encumbered.
- New Lewis base catalysts have been tested for rate/selectivity.
- Alkene geometries assessed for conversion/selectivity.



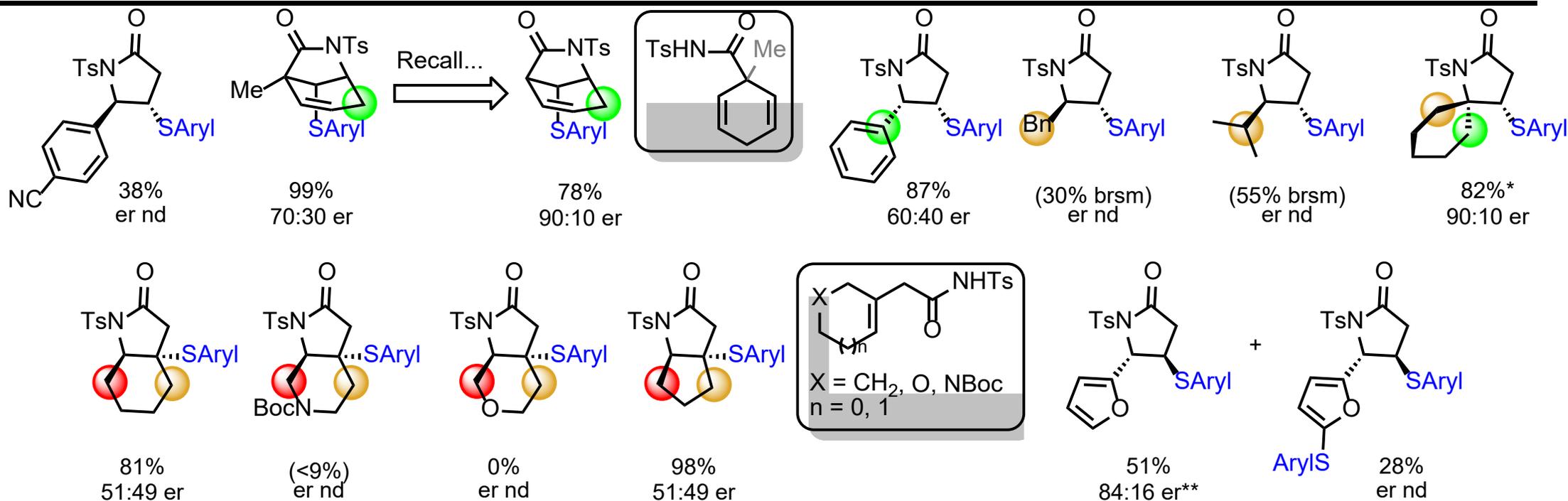
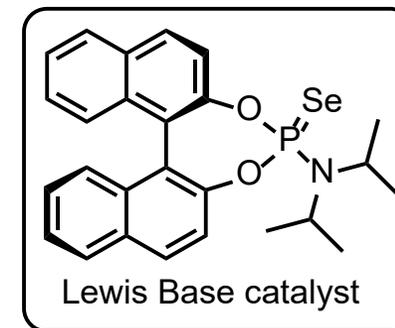
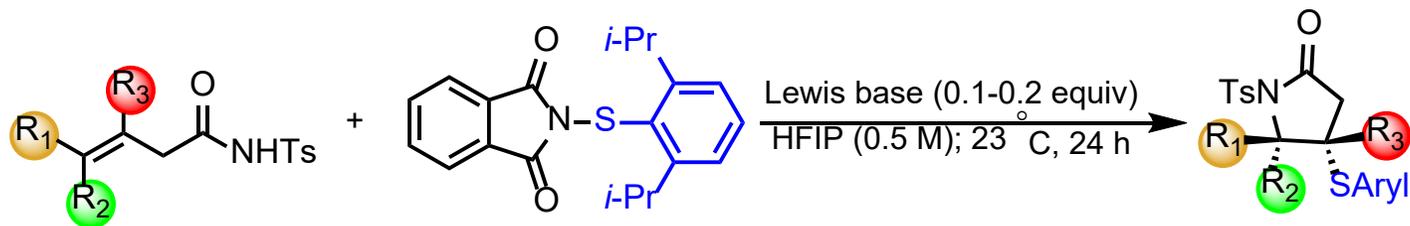
# Scope with BINAM-Derived Lewis Base Catalyst



# Scope with BINOL-Derived Lewis Base Catalyst



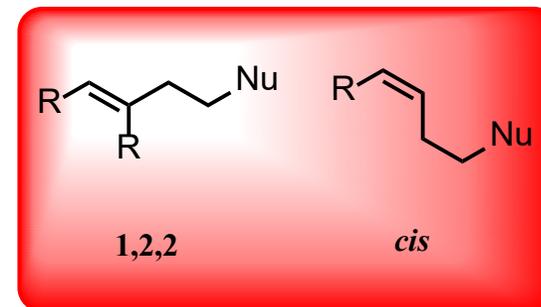
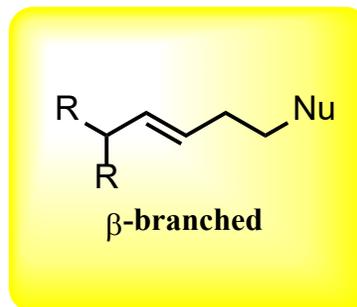
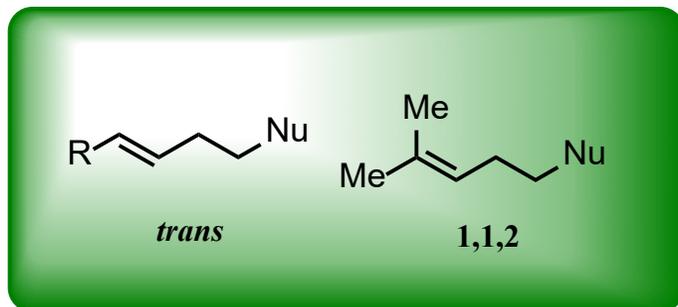
# Poorly Performing Substrates



\* Yield of impure mixture (HFIP adduct)

\*\* Yield and er using 2,6-dimethylphenyl-substituted sulfenylating agent

# Assessment of Alkene Geometries



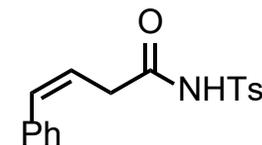
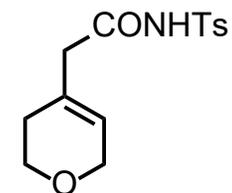
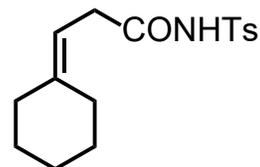
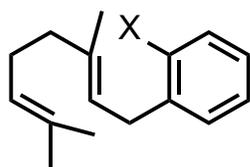
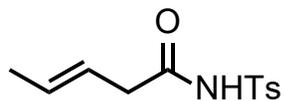
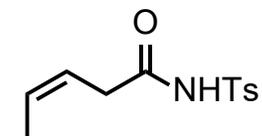
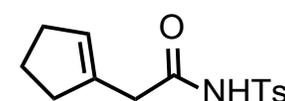
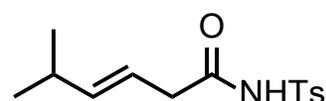
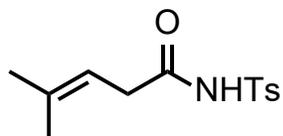
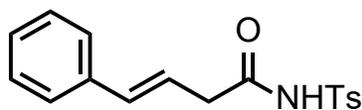
*Trans*

1,1,2

$\beta$ -branched

1,2,2

*Cis*



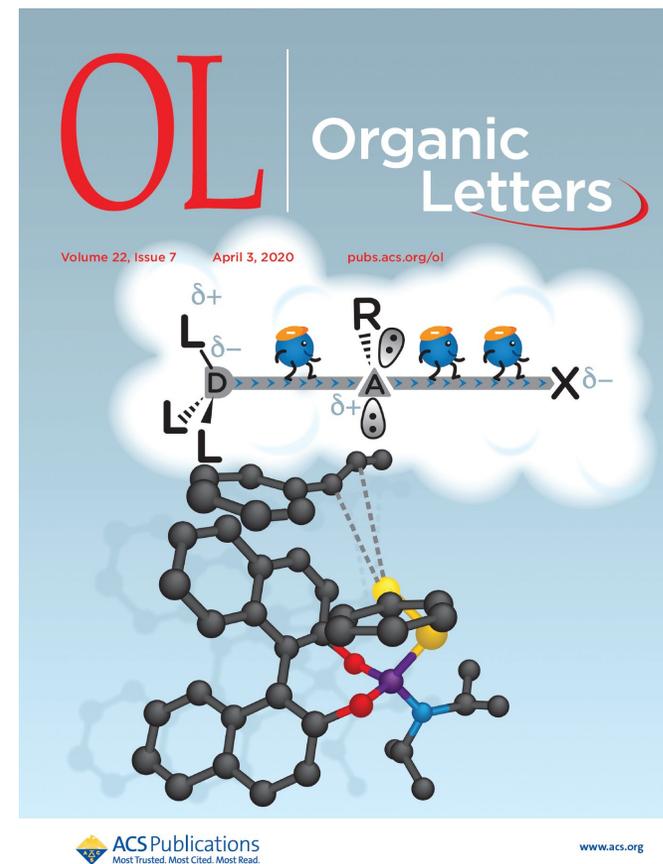
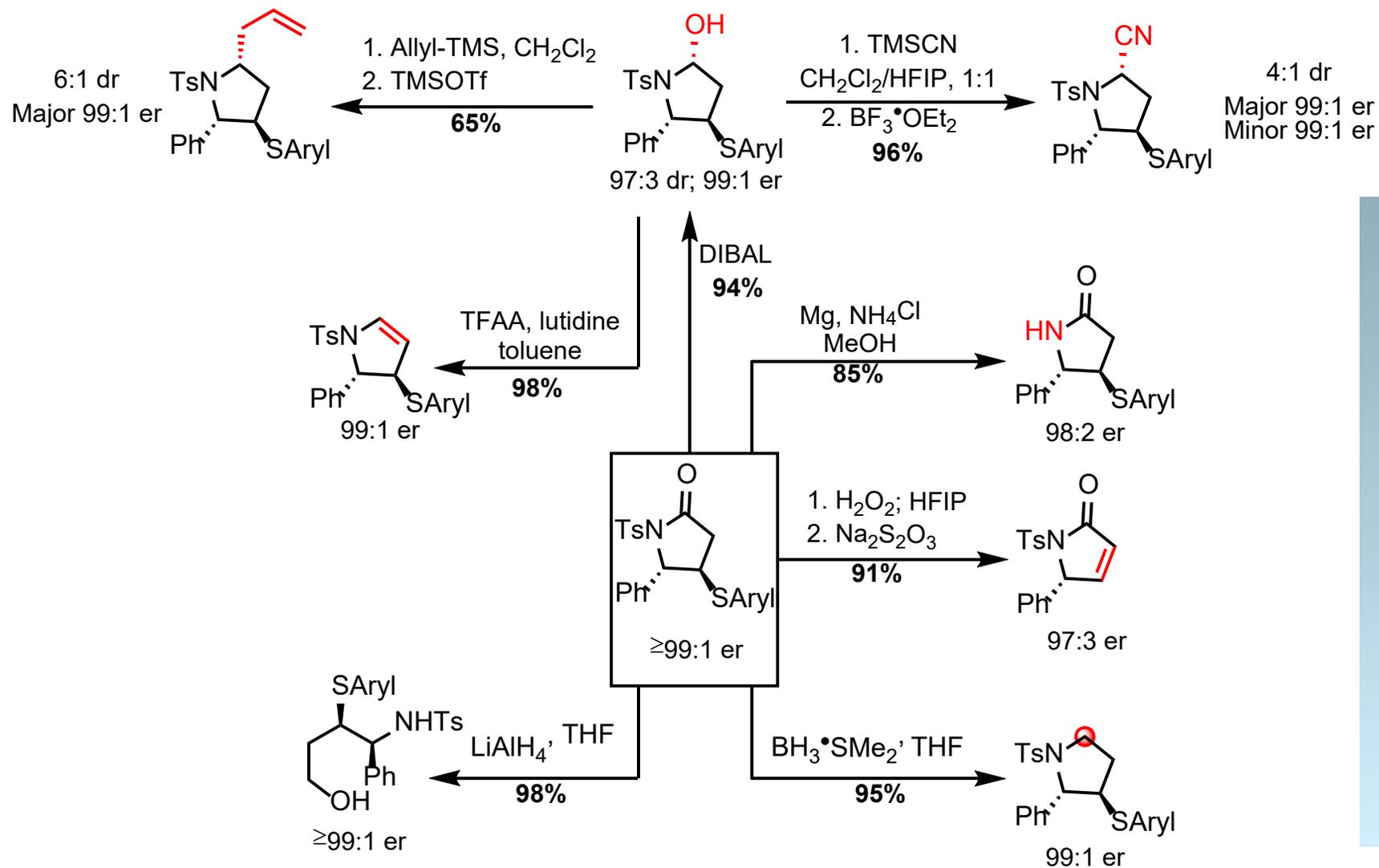
**High yield**  
**High er**

**Moderate yield**  
**Variable er**

**Variable yield**  
**Poor er**

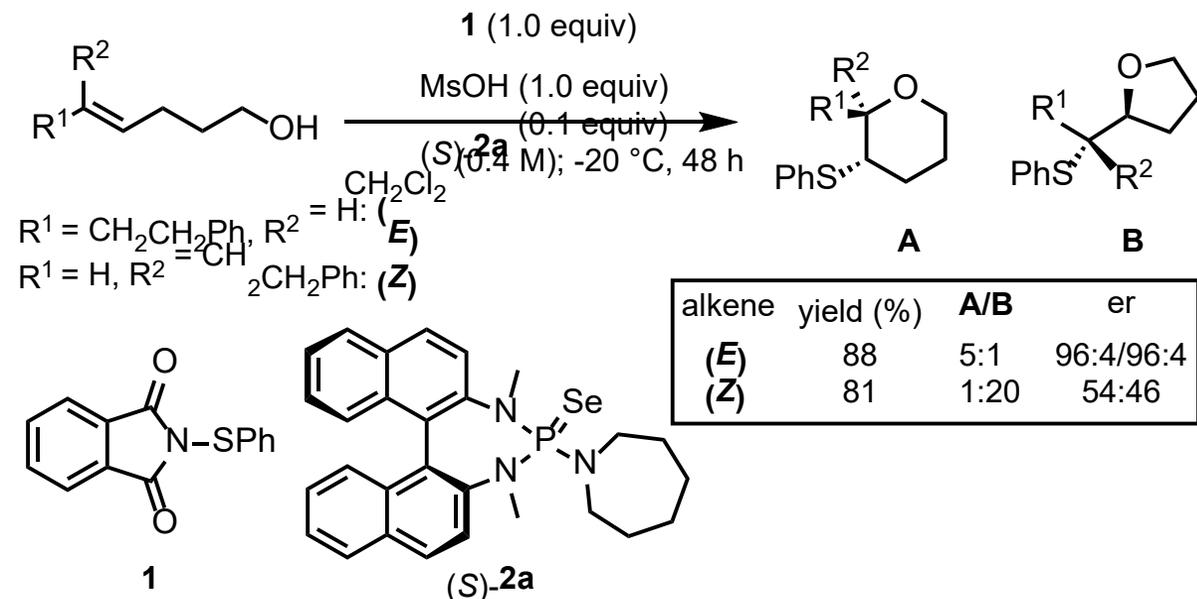
**High yield**  
**Poor er**

# Derivatizations

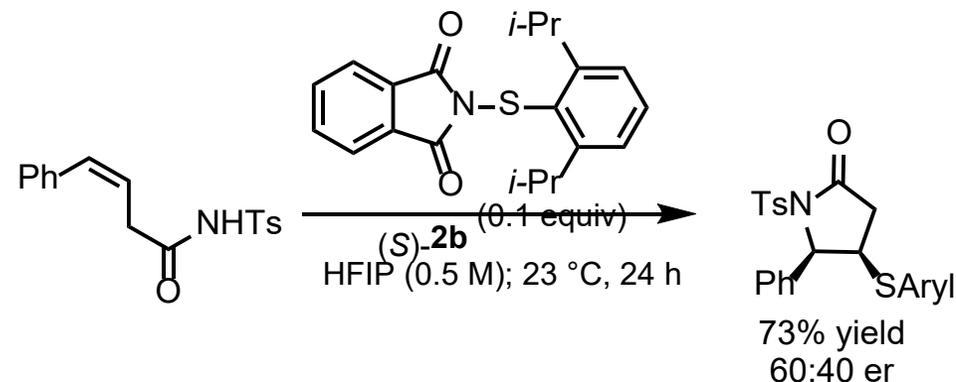
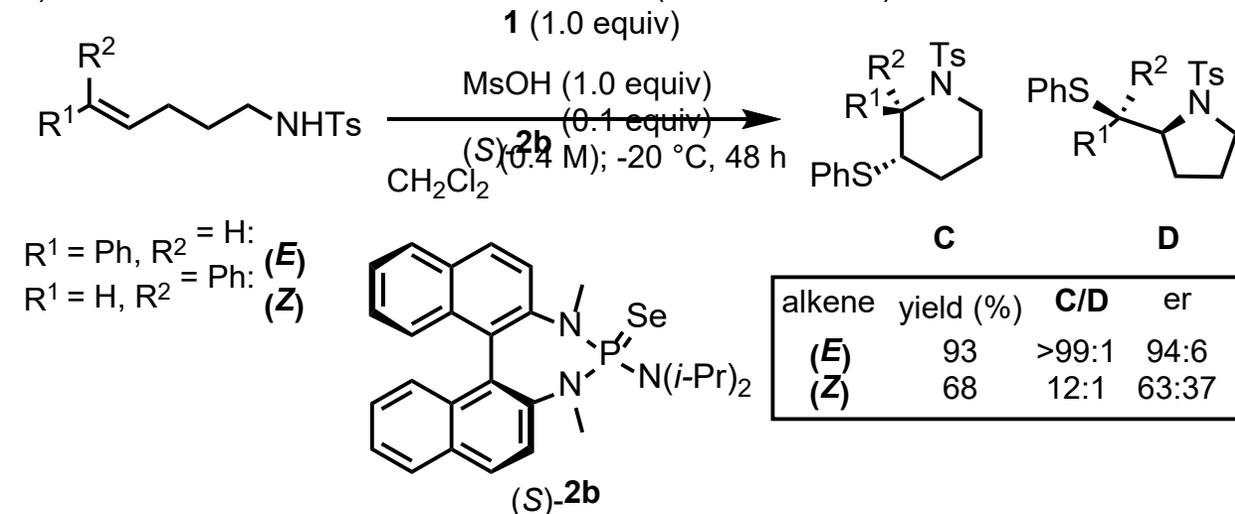


# Unsuccessful Sulfenofunctionalizations of Z-Alkenes

A) First catalytic, enantioselective sulfenofunctionalization (Denmark, 2011):

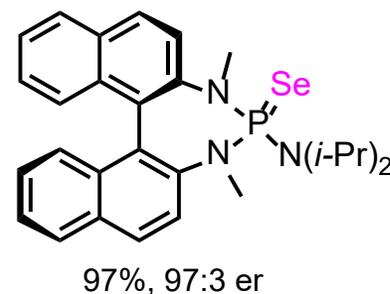
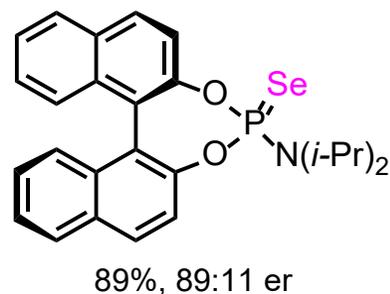
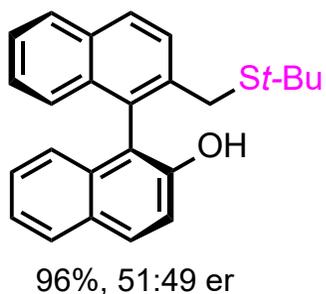
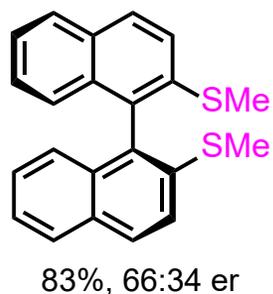
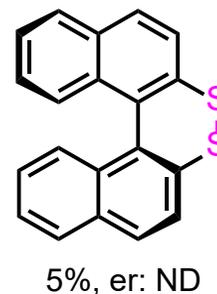
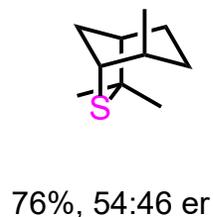
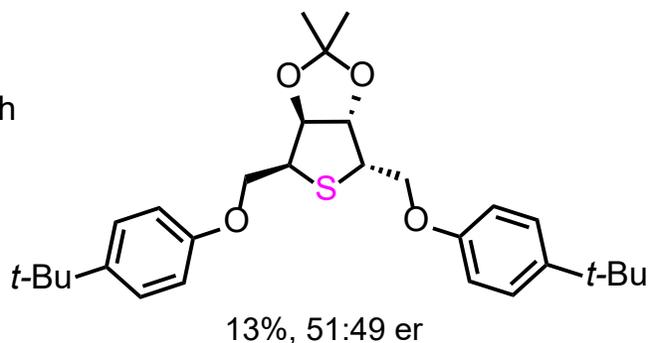
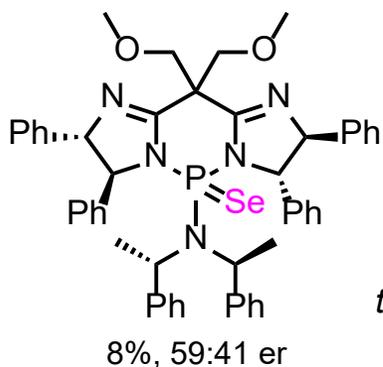
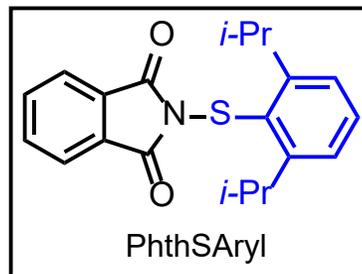
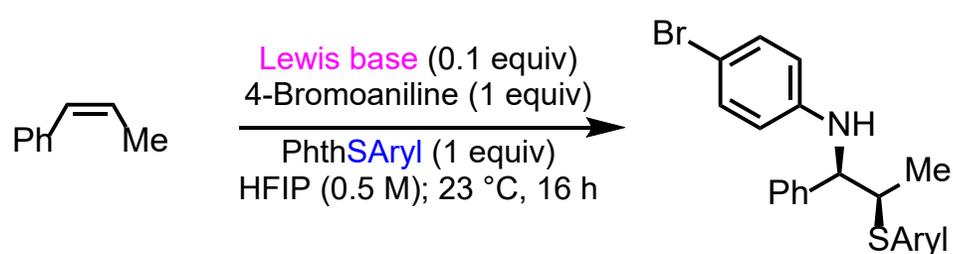


B) Intramolecular sulfenoamination of olefins (Denmark, 2014):

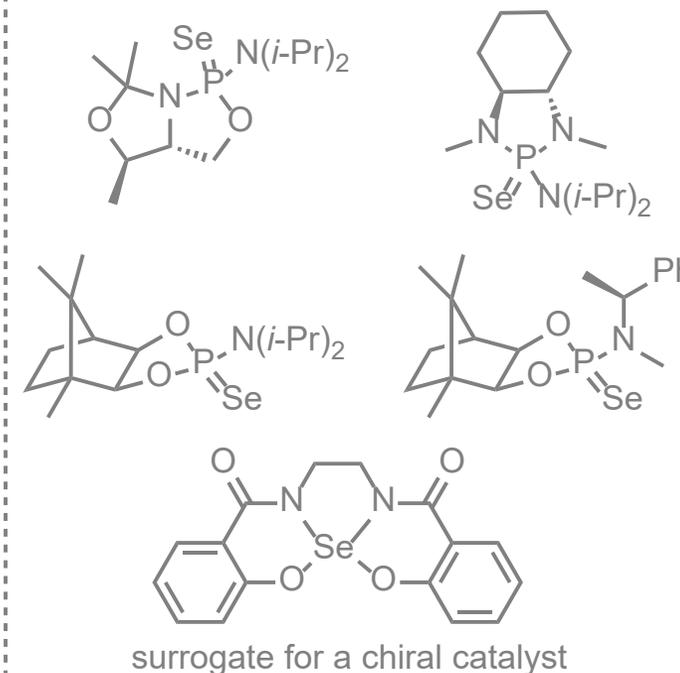


- Which effects lead to poor recognition of *Z*-configured alkenes?
- Are there catalyst scaffolds that can better accommodate different alkenes geometries?
- What reactivity differences between *E* and *Z*-alkenes exist?

# Z-Alkene-Selective Catalyst Screen



Catalysts screened with other substrates

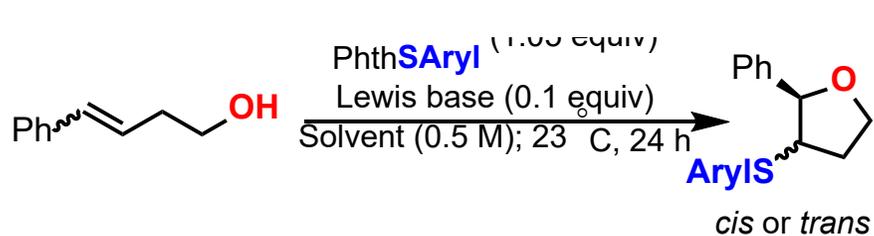


**How could this result go unnoticed for 10 years?**

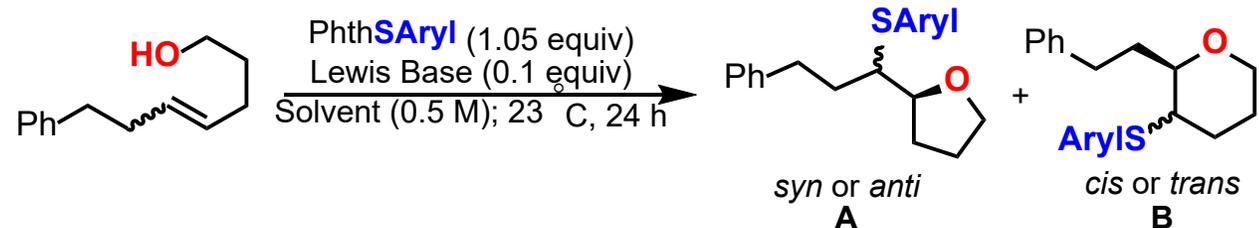
with A. Matviitsuk  
& A. Roth



# Investigating the Origin of Enantioselectivity: Solvent Effects



Entry	Substrate	Conditions	Product	e.r.
1		HFIP	<i>trans</i>	97:3
2		CH <sub>2</sub> Cl <sub>2</sub> MsOH (0.4 equiv)	<i>trans</i>	97:3
3		HFIP	<i>cis</i>	98:2
4		CH <sub>2</sub> Cl <sub>2</sub> MsOH (0.4 equiv)	<i>cis</i>	97:3

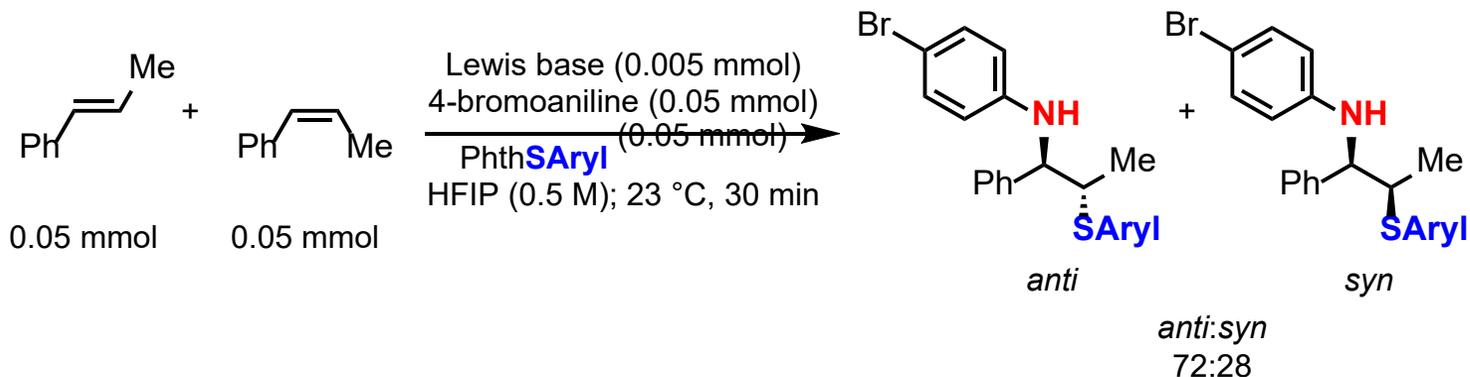


Entry	Substrate	Conditions	Selectivity (A:B)	e.r.
1		HFIP	1.3:1	<i>anti</i> -A = 98:2 <i>trans</i> -B* = 98:2
2		CH <sub>2</sub> Cl <sub>2</sub> MsOH (0.4 equiv)	1:2	<i>anti</i> -A = 98:2 <i>trans</i> -B* = 98:2
3		HFIP	>20:1	<i>syn</i> -A = 71:29
4		CH <sub>2</sub> Cl <sub>2</sub> MsOH (0.4 equiv)	>20:1	<i>syn</i> -B = 67:33

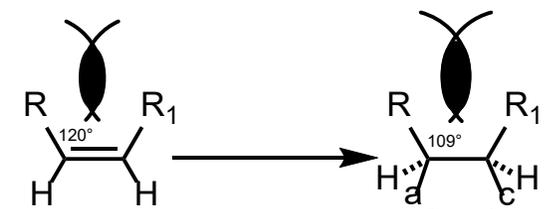
1. There is negligible effect on enantioselectivity by the solvent.
2. (*Z*)-Styryl alkenes are recognized well by the catalyst but (*Z*)-alkyl-substituted alkenes are not.
3. Insights into relative rates and kinetic selectivity of differently substituted alkenes.

# Further Studies and Analysis of *E* vs. *Z*-Alkenes

## Competition experiment between *trans* and *cis*- $\beta$ -methylstyrene

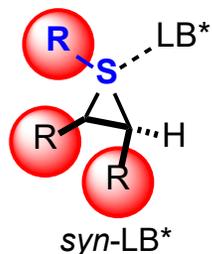
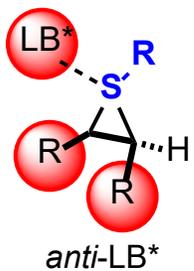


## Steric changes during 1,3-dipolar cycloaddition



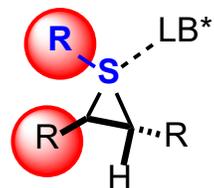
Bond angle compression increases eclipsing interactions leading to higher EA

## *Cis*-alkene-derived thiiranium ions

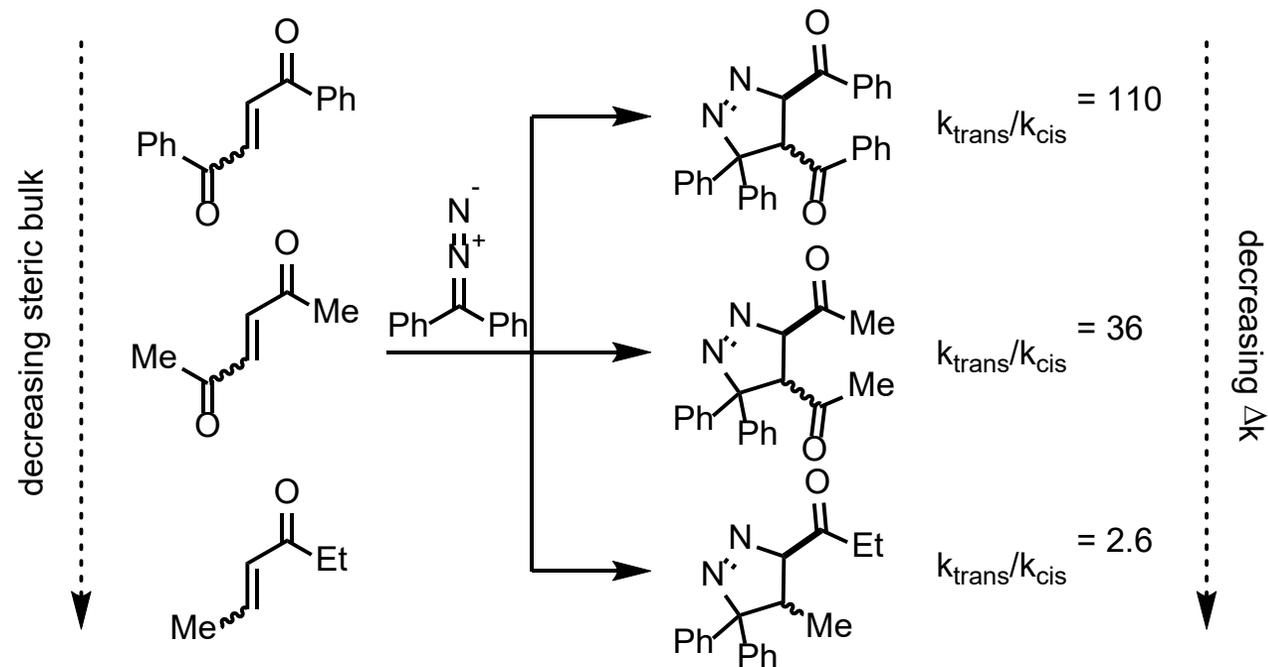


unavoidable steric interactions raise barrier to sulfenium ion transfer

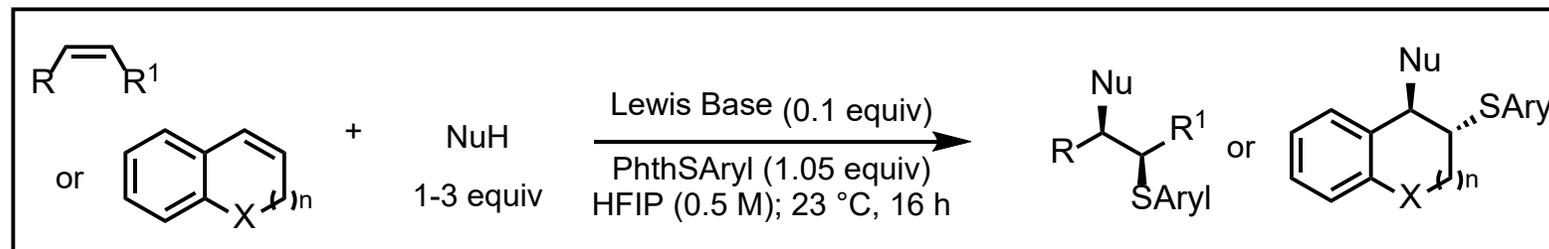
## *Trans*-alkene-derived thiiranium ion



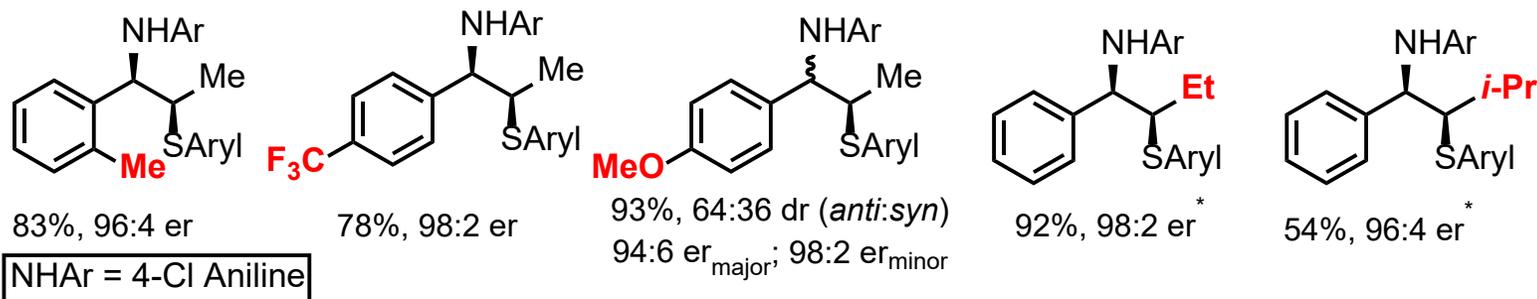
reduced steric interactions lead to lower barrier of sulfenium ion transfer



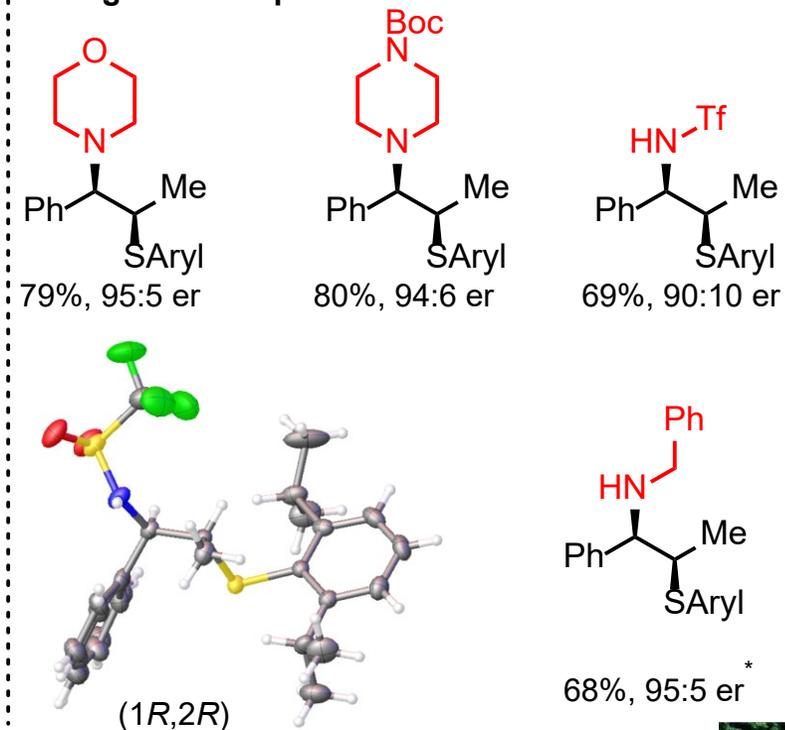
# Substrate Scope for *Intermolecular* Sulfenofunctionalizations



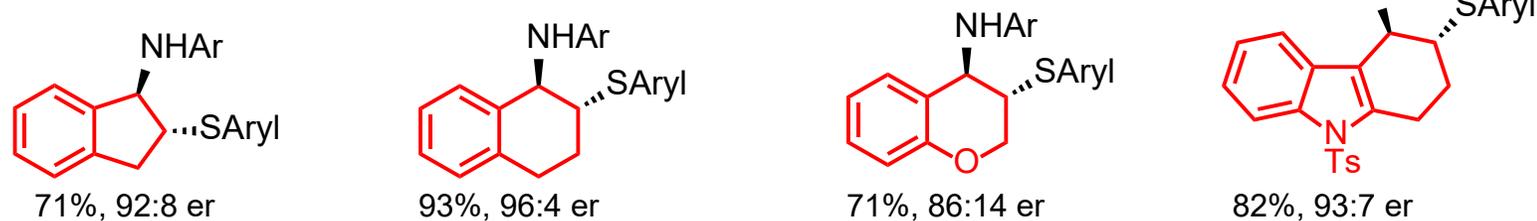
## Acyclic Alkenes



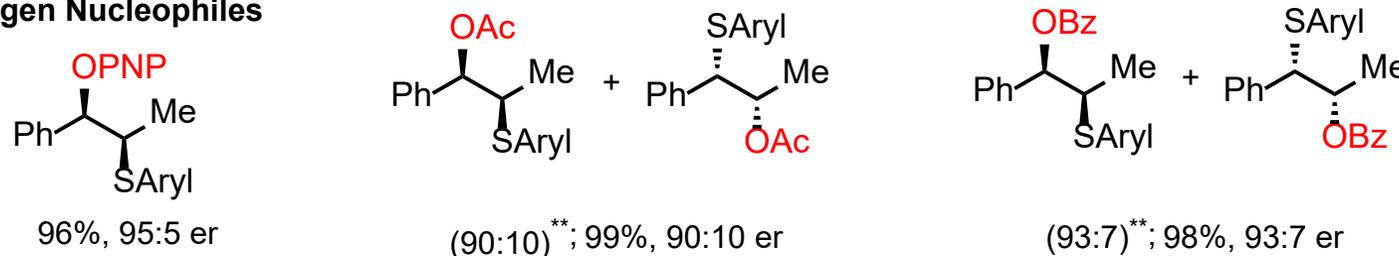
## Nitrogen Nucleophiles



## Cyclic Alkenes



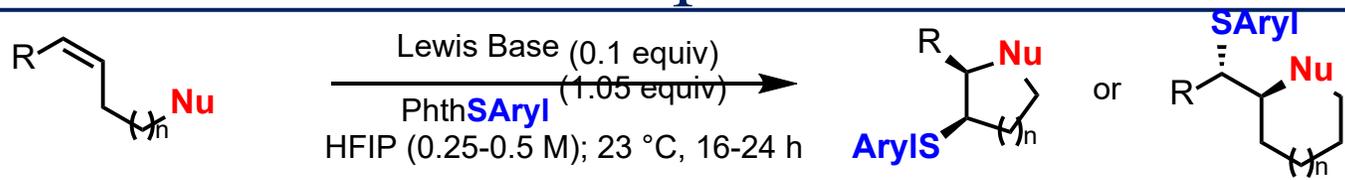
## Oxygen Nucleophiles



with A. Matviitsuk



# Substrate Scope for *Intramolecular* Sulfenofunctionalizations



substrate	product	yield (%)	er
		63	98:2
		88	97:3
		86	97:3 87:13 dr
		92	98:2
		84	95:5*
		64	96:4

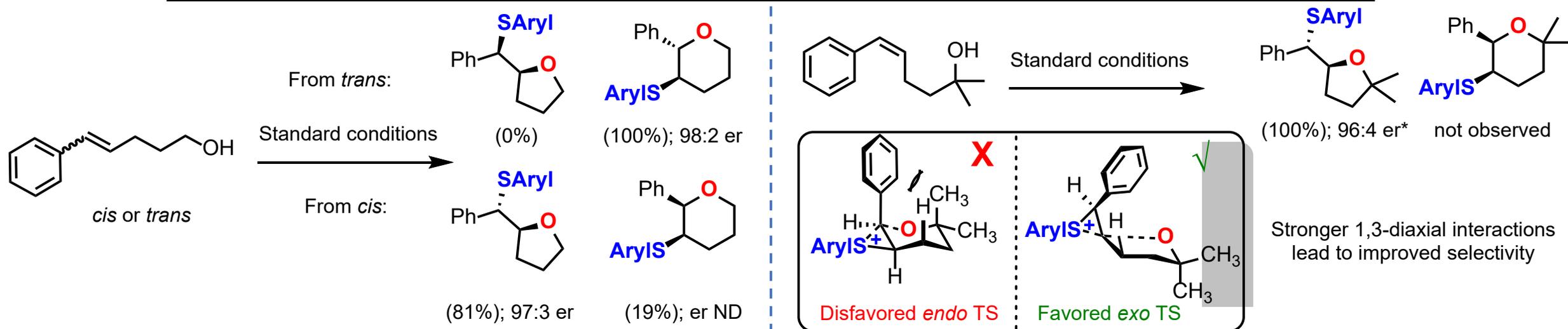
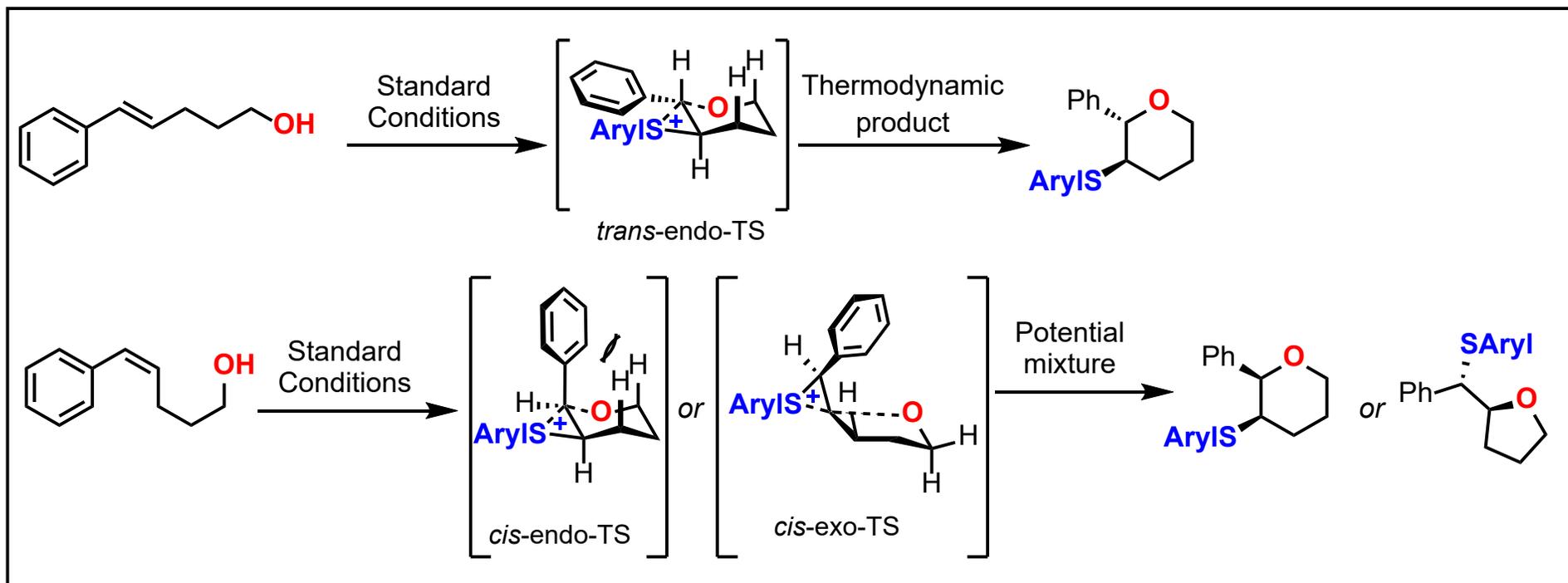
Observations on cyclizations of variable tether length and nucleophile present:

- (1) Heterocycles include: furan, pyrrolidine, lactone, pyran, and oxazoline.
- (2) Kinetic *exo* product observed as major unless the product would be a 4-membered ring
- (3) Degree of stereo-erosion (4-OMe) not equal to intermolecular capture (64:36 dr)

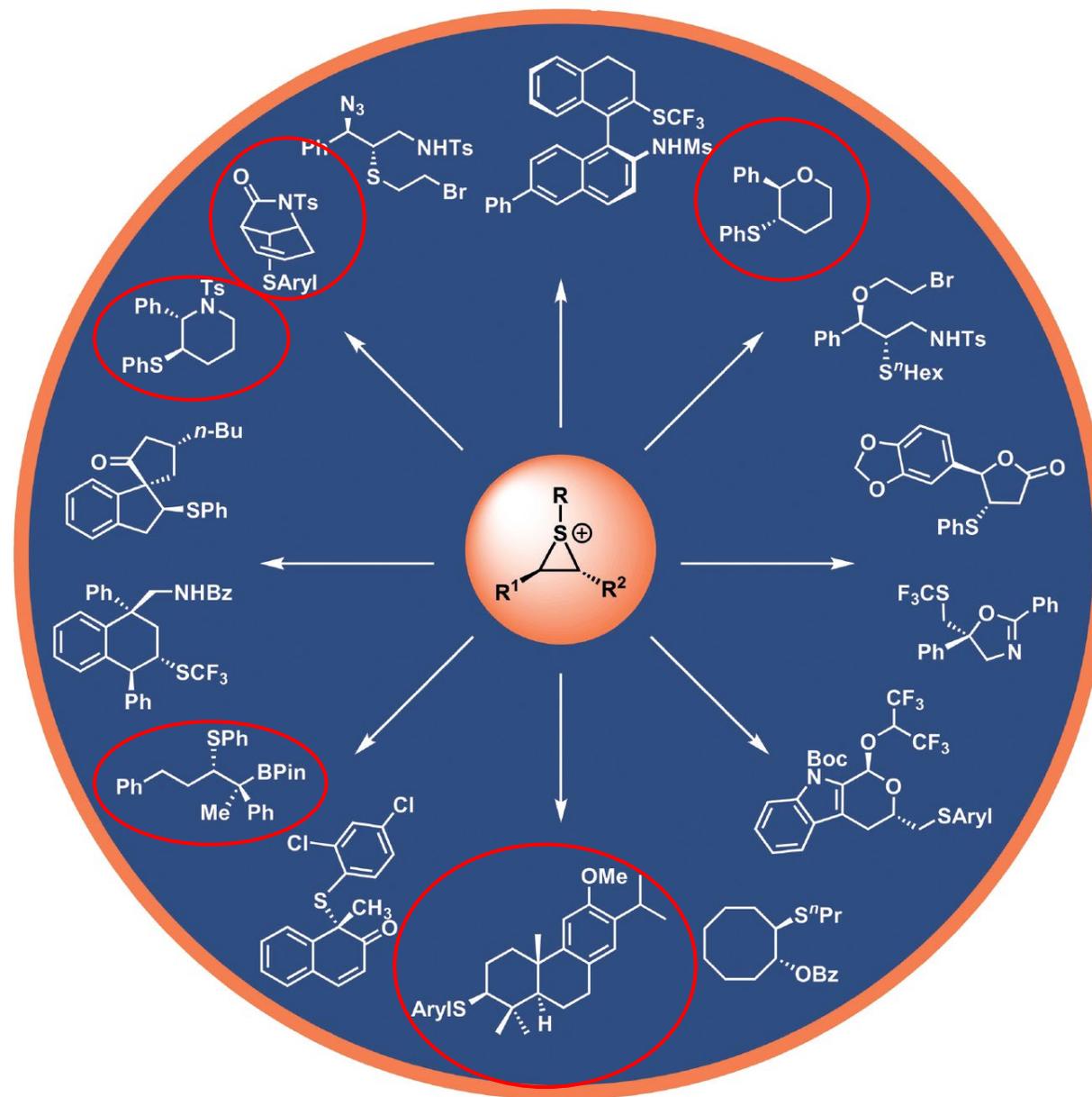
with A. Matviitsuk



# Rationalization for *Exo/Endo* Selectivity



# Summary of Sulfenofunctionalization Reactions



# Shifting Perspectives on Selenium



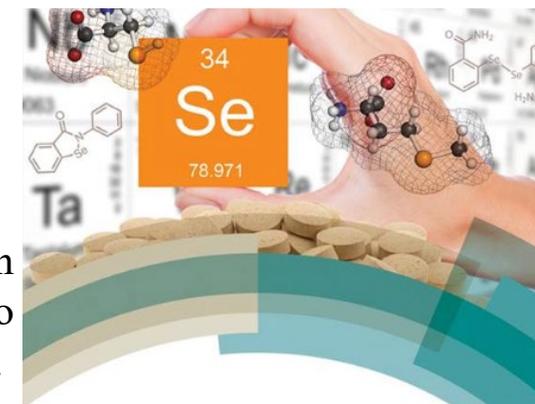
*The gas has the odor of sulphuretted hydrogen gas, when it is diluted with air; but if it is breathed less diluted, it produces a painful sensation in the nose and a violent inflammation, ending in a catarrh, which continues for a considerable length of time. I am still suffering from having breathed, some days ago, a bubble of selenuretted hydrogeous gas, no larger than a small pea. Scarcely had I perceived the hepatic taste in the fauces, when I experienced another acute sensation: I was seized with a giddiness, which, however, soon left me, and the sensibility of the schneiderian membrane was so far destroyed that the strongest ammonia produced scarcely any effect upon the nose.*

Jacob Berzelius (1779-1848)

Catarrh: excessive discharge or buildup of mucus in the nose or throat

Fauces: arched opening at the back of the mouth

Schneiderian: 'nasal'



In 200+ years of selenium research, academic opinion shifted from avoidance (toxicity concerns) to acceptance by way of its malleable chemical properties.

The recommended daily dietary allowance of selenium can be obtained by one Brazil-nut

Bust of Berzelius in selenium

## Organoselenium Compounds in Biology and Medicine

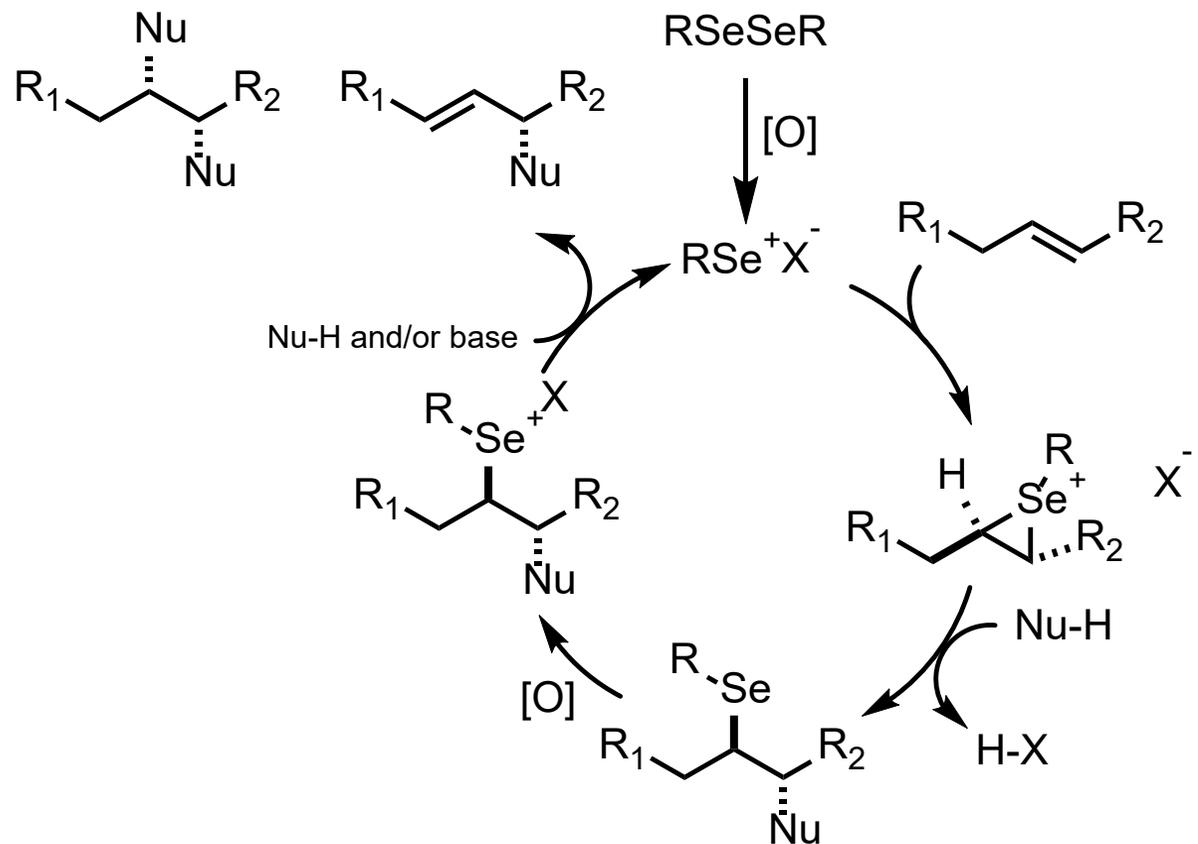
Synthesis, Biological and Therapeutic Treatments

Edited by Vimal Kumar Jain and K. Indira Priyadarsini





# General Mechanism of Selenium-Catalyzed Difunctionalization of Alkenes



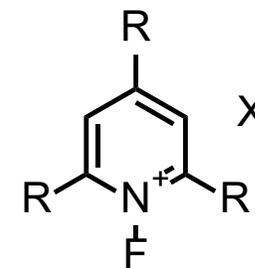
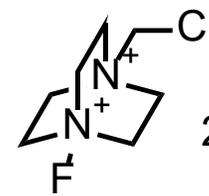
Classes of oxidants:

1. Peroxo/Persulfate

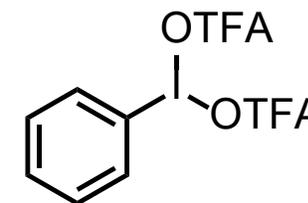
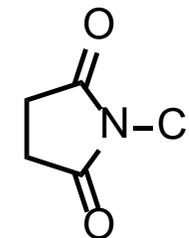
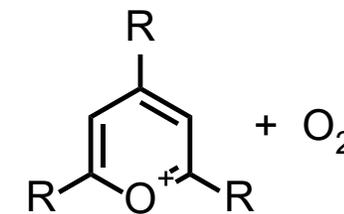
2. N-F Reagents

3.  $O_2$  + pyrylium

4.  $Cl^+$  or  $I^{(III)}$  reagents

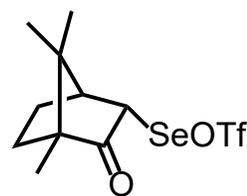
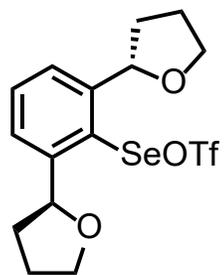
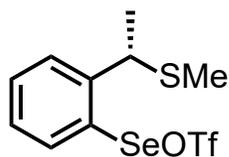
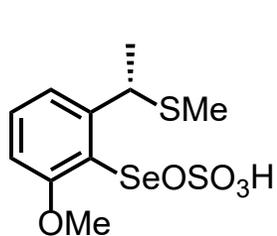
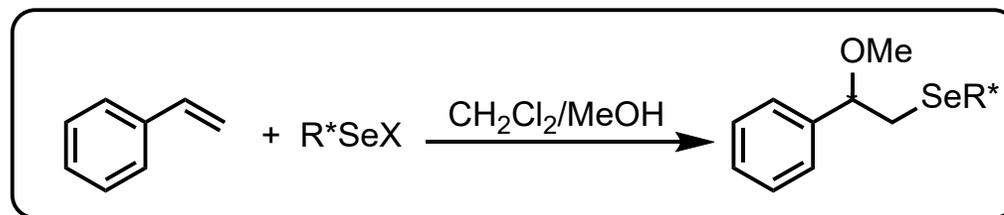


$R = H, Me$   
 $X = BF_4^-, OTf^-$

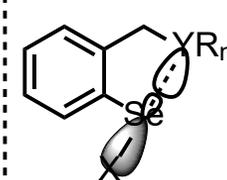


1. There are 2 distinct oxidation events with different oxidation potentials
2. Second displacement occurs on highly hindered carbon
  - a) Competition between nucleophilic attack and elimination

# Chiral, Electrophilic Organoselenium Reagents: Stoichiometric Se<sup>II</sup>

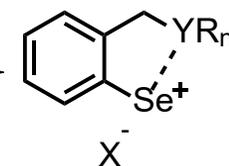


## Lewis base activation of Group 16



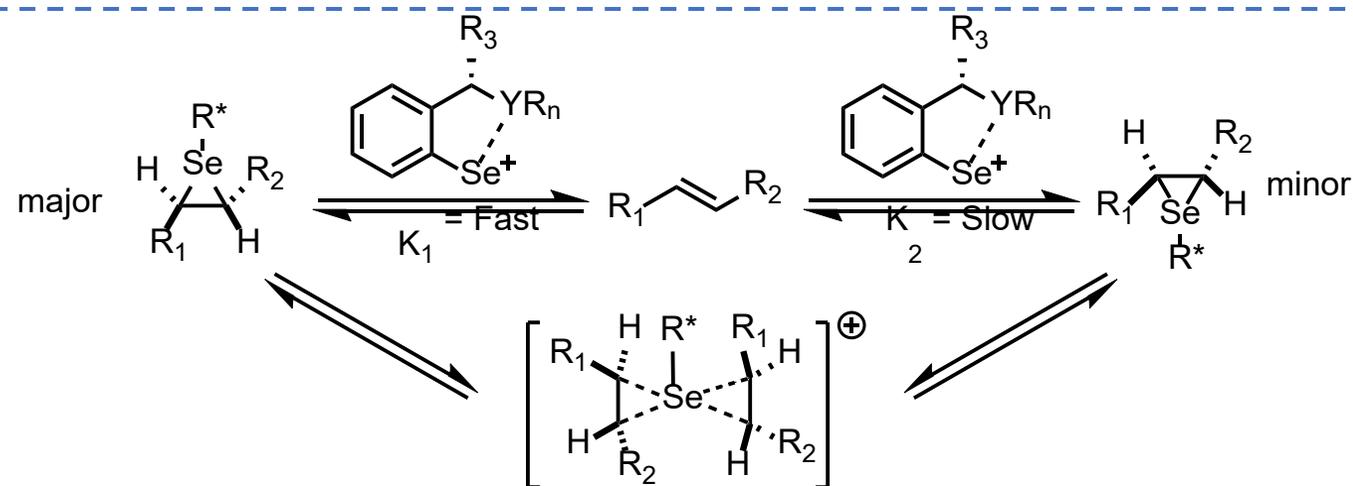
$n \rightarrow \sigma^*$

effect of chalcogen bonding on electrophilic organoselenides



Increased conformational rigidity from chalcogen bond

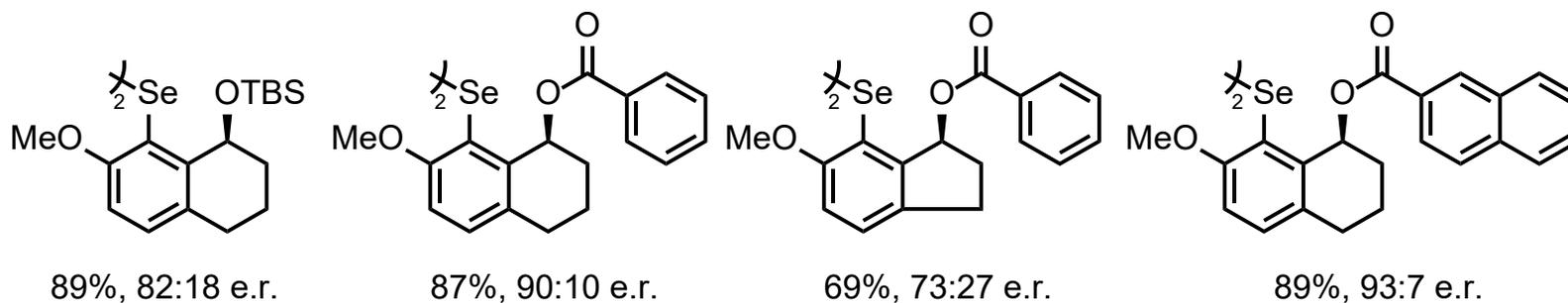
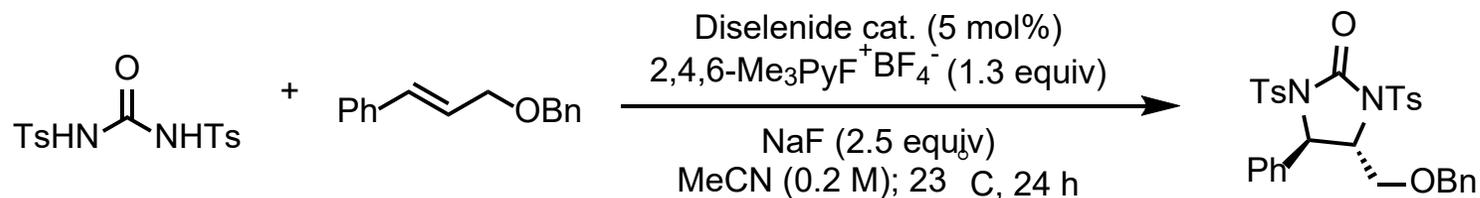
Temp (°C):	-30	-30	-78	-78	25
Yield (%):	72	90	73	77	95
d.r.:	98:2	90:10	97:3	74:26	88:12



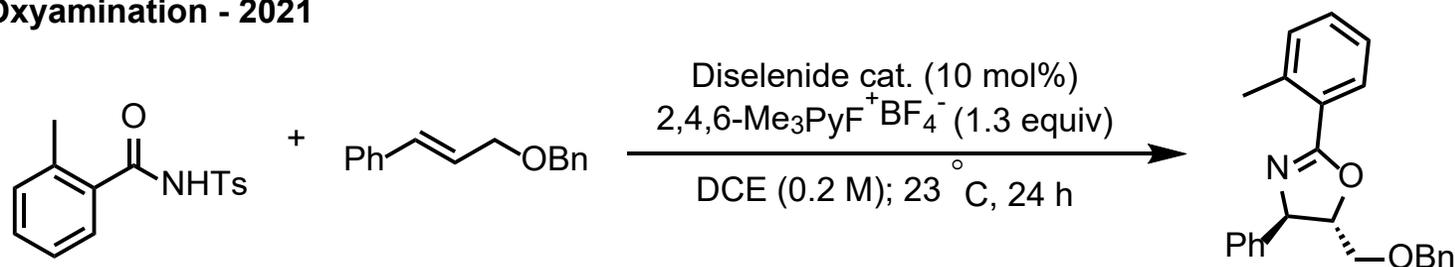
## Evidence of DKR mechanism by olefin-to-olefin transfer

# Recent Advances in Selenium Redox Catalysis

## Diamination - 2019



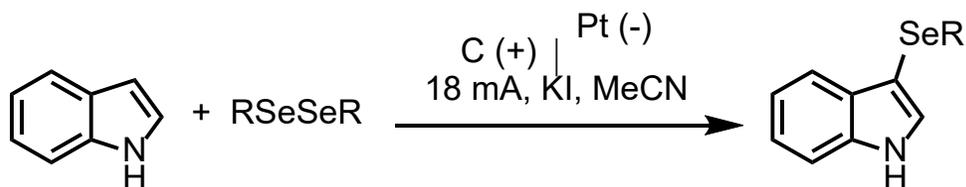
## Oxyamination - 2021



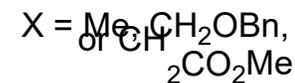
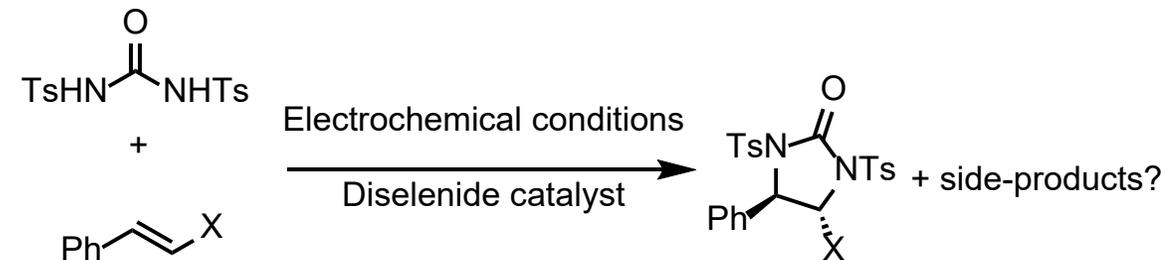
**Use of N-Fluorocollidinium limits substrate scope, is atom-inefficient, and requires special handling procedures**

# Transition to Electrochemical Oxidation

Many reports of achiral, stoichiometric selenofunctionalizations

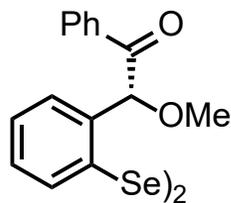
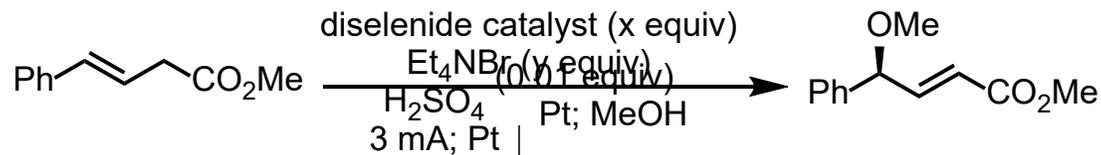


Model Reaction

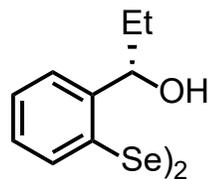


Optimization performed on IKA Electrasyn

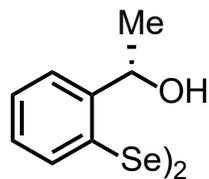
Asymmetric, intermolecular oxyselenenylation-deselenenylation (Wirth - 2006)



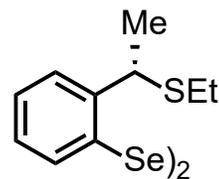
0.1 equiv Se cat.  
0.2 equiv Et<sub>4</sub>NBr  
56% yield, 59:41 er



0.1 equiv Se cat.  
0.2 equiv Et<sub>4</sub>NBr  
29% yield, 72:28 er



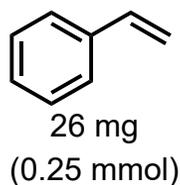
0.1 equiv Se cat.  
0.1 equiv Et<sub>4</sub>NBr  
55% yield, 53:47 er



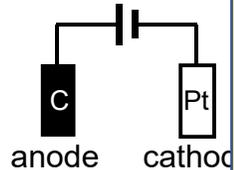
0.05 equiv Se cat.  
0.5 equiv Et<sub>4</sub>NBr  
38% yield, 83:17 er

# Orienting Experiments & Preliminary Findings

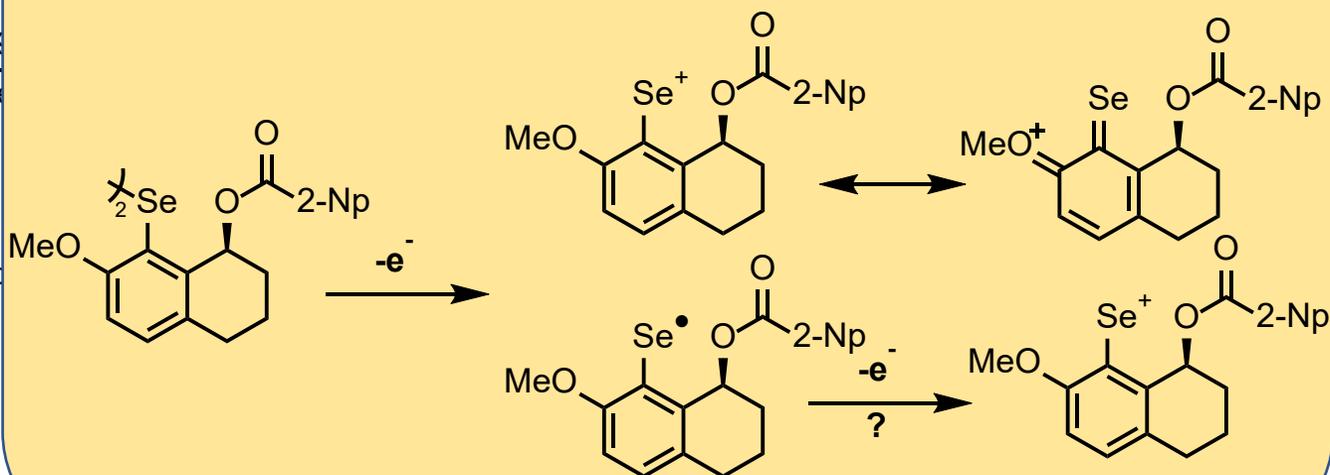
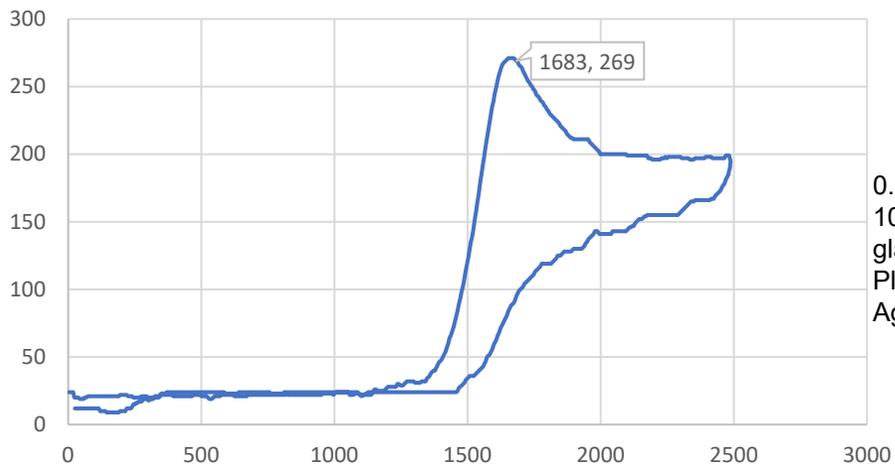
## Electrochemical Cell Verification



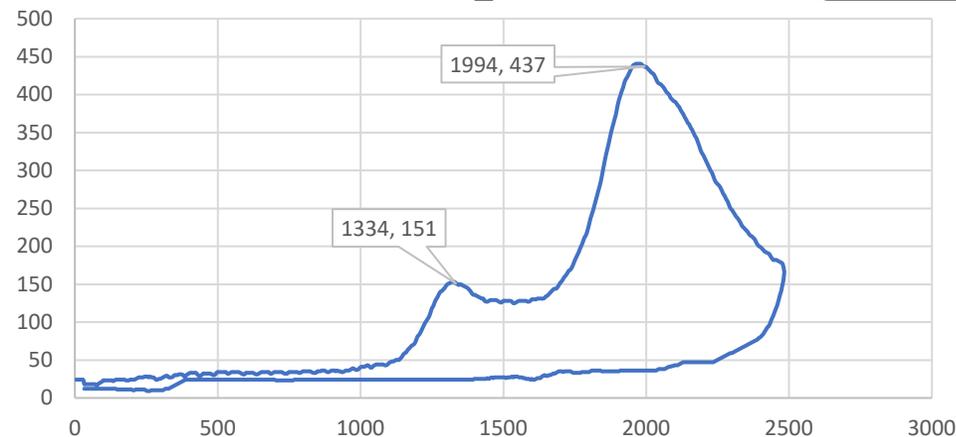
PhSeSePh (0.5 equiv)  
KI (0.25 equiv); 23 mg  
MeCN:H<sub>2</sub>O (10:1, 10 mL)  
I = 6.0 mA, undivided



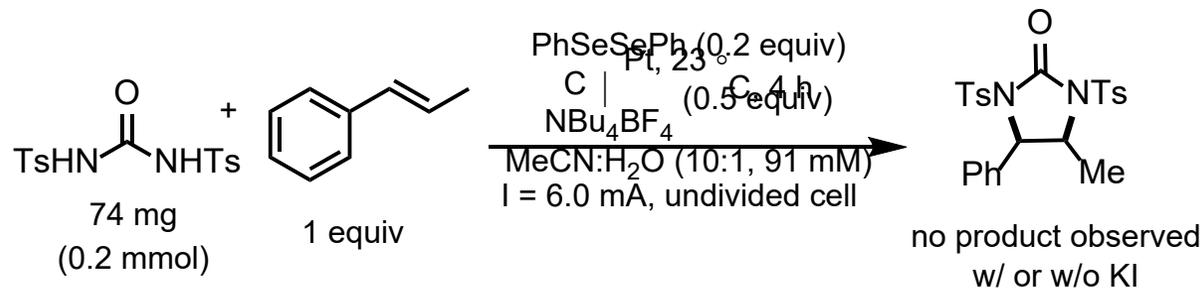
PhSeSePh\_50mV/s



Se\* Cat\_100mV

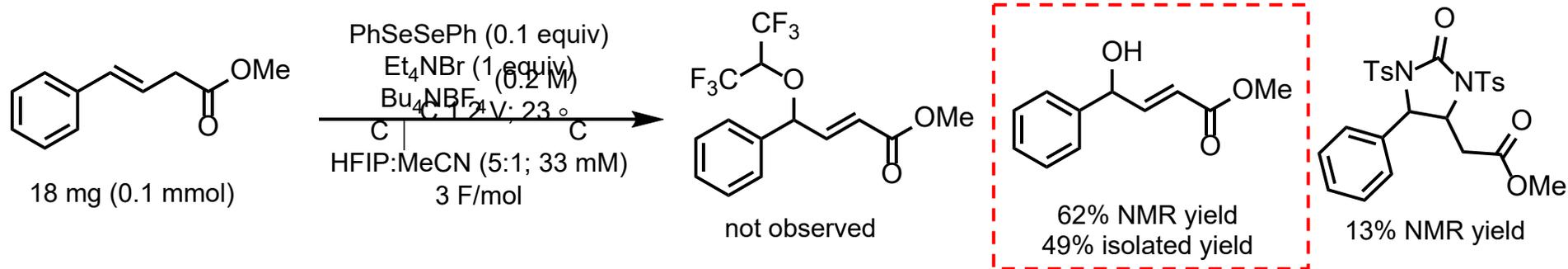


# Optimization of Enantioselective Diamination of Alkenes



Other optimization experiments performed however a substrate change was employed to leverage known reactivity

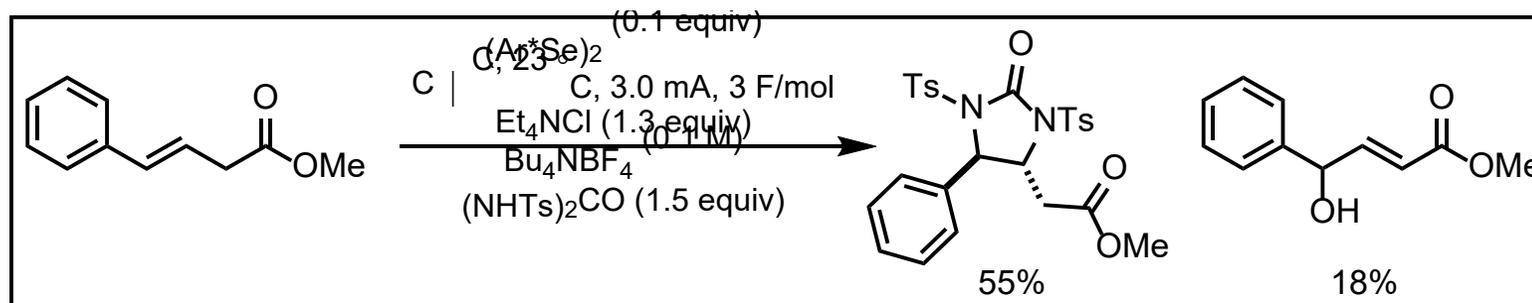
## First real hit...



Rigorous drying of electrolytes required to remove water

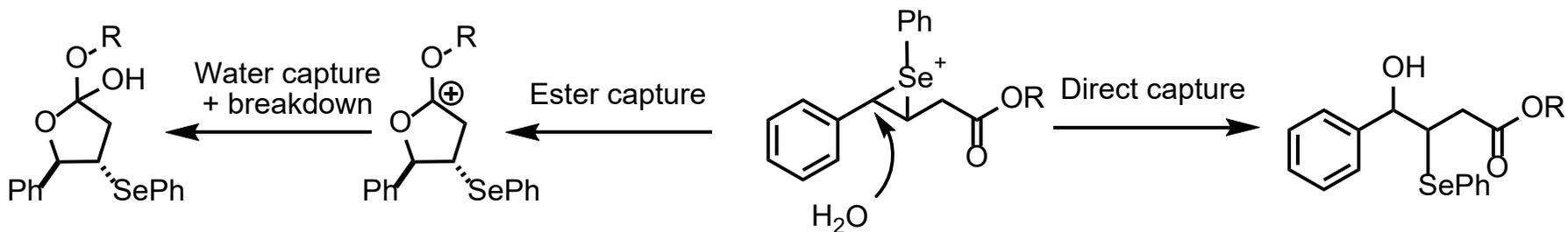
Result prompted a search into reaction parameters including...

- Electrolytic mediators
- Supporting electrolytes
- Constant voltage of amperage?
- Electrode choice
- Solvent blend
- Faradaic efficiency

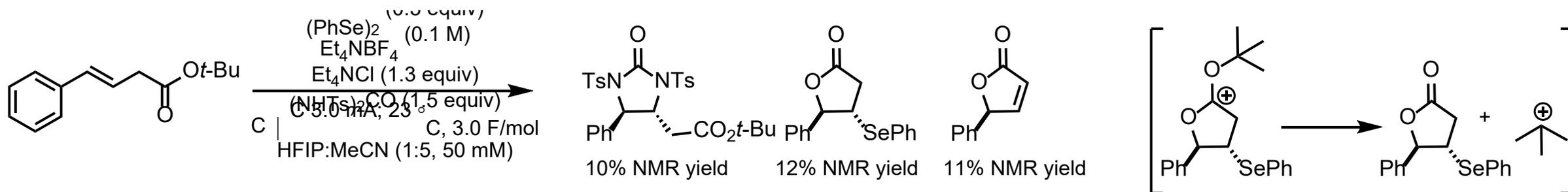


# Unexpected Source of Oxygen Capture in Electrochemical System

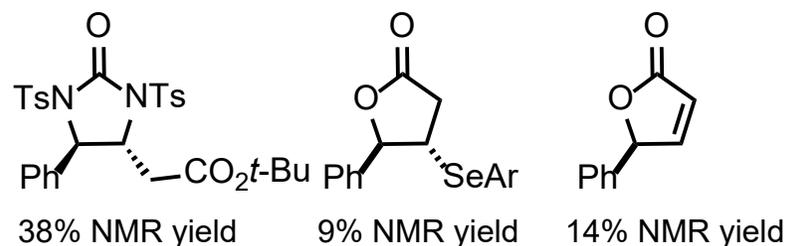
## Chemoselectivity of water capture



## *t*-Bu ester provides evidence for indirect 'water' capture

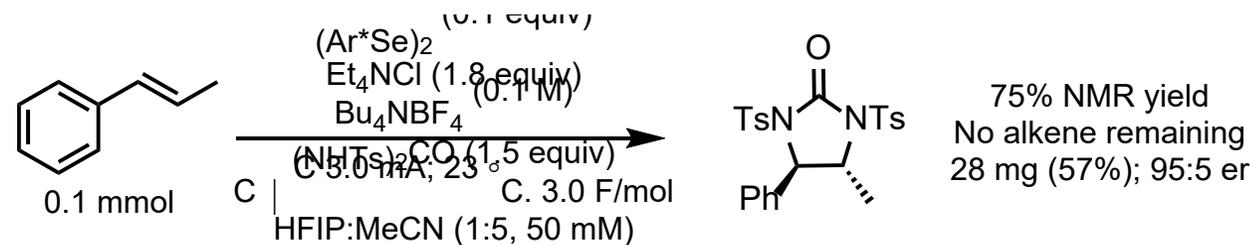
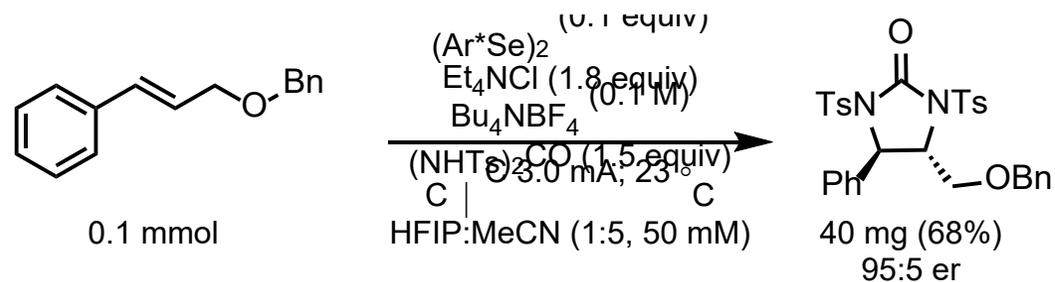


when using the chiral catalyst...

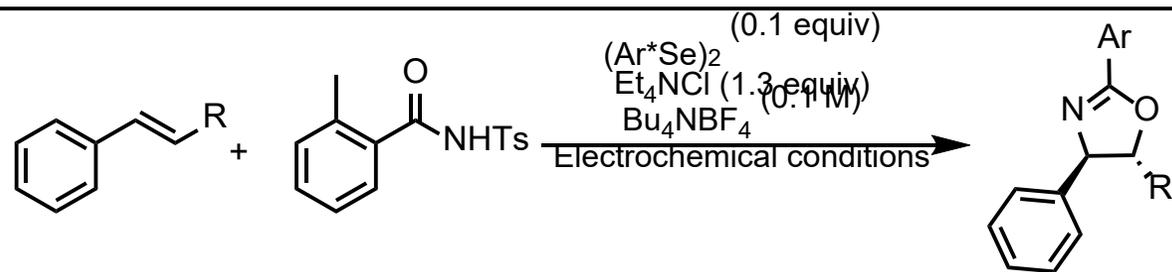
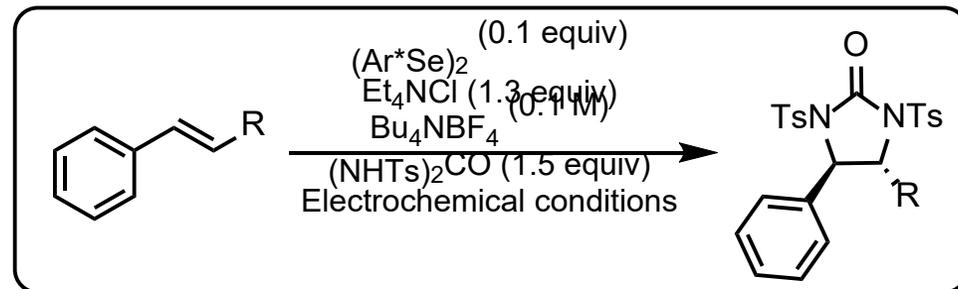


# Preliminary Experiments and Outlook

## Another substrate?



## Goal 1: Obtain comparable yields for enantioselective diamination:



## Goal 2: Obtain comparable yields for enantioselective oxyamination:

## Goal 3: Expand the scope for enantioselective alkene difunctionalizations:

