En Route to the Enantioselective *syn*-Dichlorination of Olefins

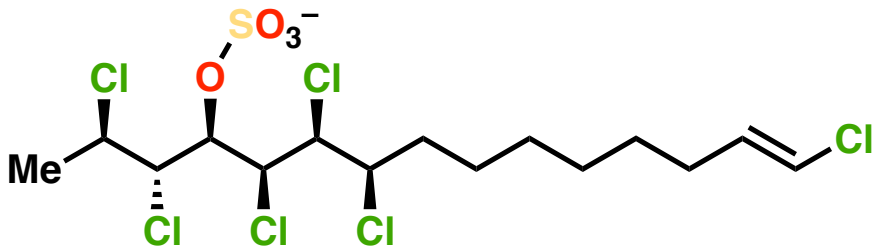
BRAD GILBERT

DENMARK GROUP MEETING, SEPTEMBER 25, 2018

Outline

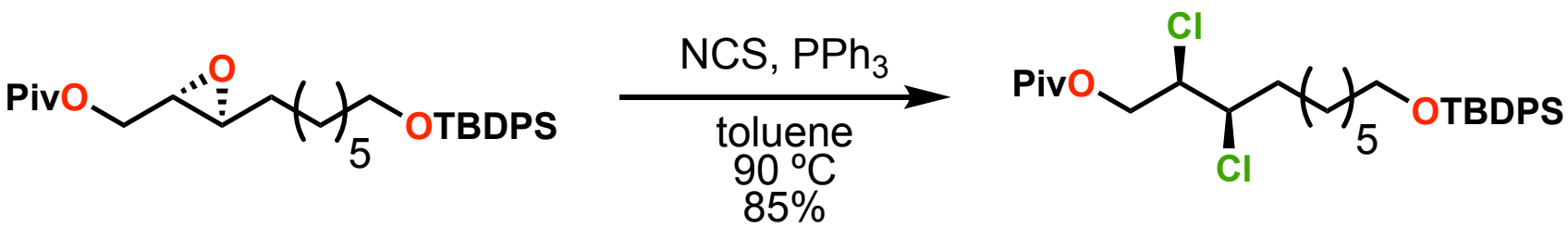
1. **Introduction**
    1. Why do we care about selective dihalogenation?
    2. What are the current best approaches to the selective dihalogenation of olefins?
        1. Diastereoselective methods
        2. Enantioselective methods
2. **Background**
3. **Early catalyst design and synthesis**
4. **Later catalyst designs**
5. **Chlorolactonization**

Vicinal Dihalides in Natural Products



Mytilipin A:

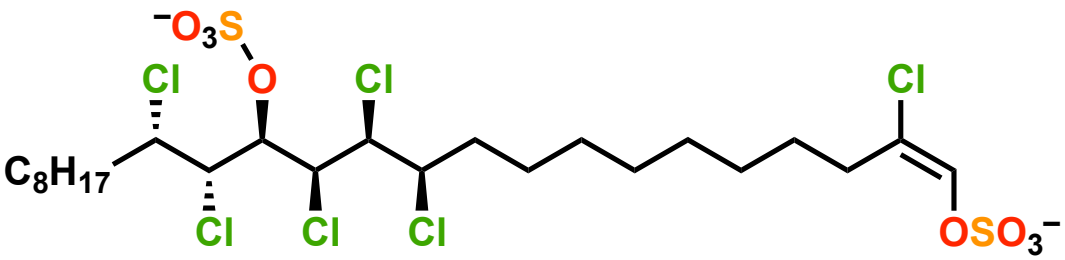
- One of the constituent toxins in toxic mussels
- First (racemic) synthesis by E. M. Carreira and coworkers
- First enantioselective synthesis by T. Yoshimitsu and coworkers *via* stereospecific epoxide opening



- Alternative enantioselective approach by C. D. Vanderwal followed a ring-opening kinetic resolution of a dichloro vinyl epoxide with the Denmark bisphosphoramide catalyst

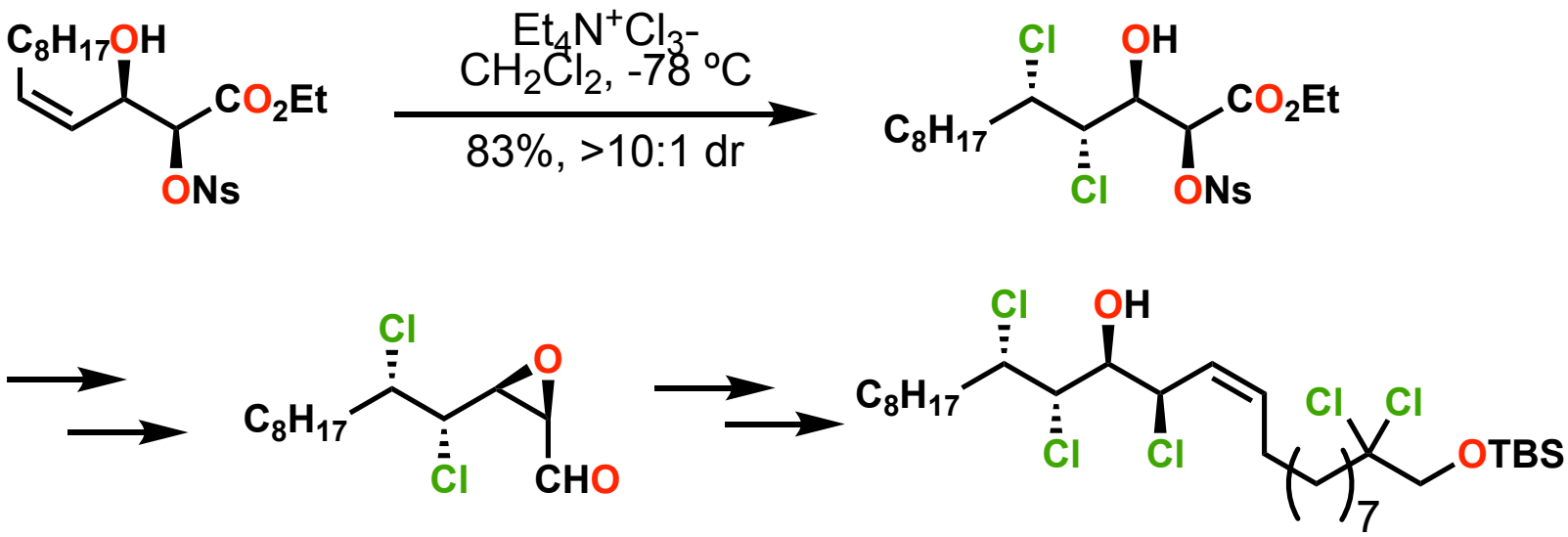
C. Nilewski, R. W. Geisser, E. M. Carreira, *Nature* **2009**, *457*, 573 – 576.
T. Yoshimitsu, N. Fujumoto, R. Nakatani, N. Kojima, T. Tanaka, *J. Org. Chem.* **2010**, *75*, 5425 – 5437.
W.-J. Chung, J. S. Carlson, D. K. Bedke, C. D. Vanderwal. *Angew. Chem. Int. Ed.* **2013**, *52*, 10052-10055.

Vicinal Dihalides in Natural Products



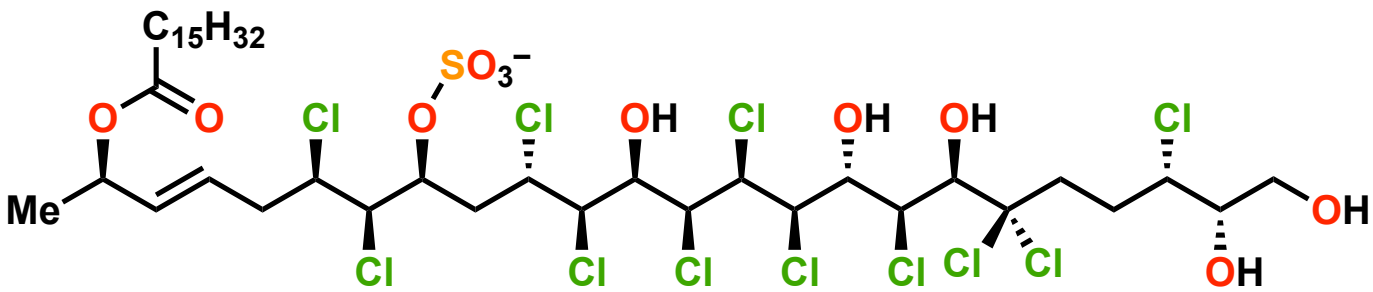
Malhamensilipin A

- Antimicrobial and inhibitor of protein tyrosine kinase
- First enantioselective synthesis by C. D. Vanderwal

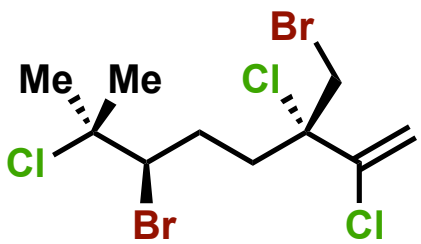


J. L. Chen, P. J. Proteau, M. A. Roberts, W. H. Gerwick, D. L. Slate, R. H. Lee, *J. Nat. Prod.*, **1994**, *57*, 524–527.
D. K. Bedke, G. M. Shibuya, A. R. Pereira, W. H. Gerwick, C. D. Vanderwal, *J. Am. Chem. Soc.*, **2010**, *132*, 2542–2543.

Vicinal Dihalides in Natural Products

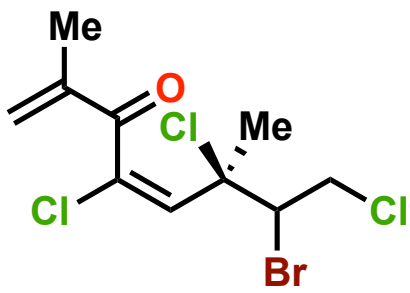


Mytilipin B

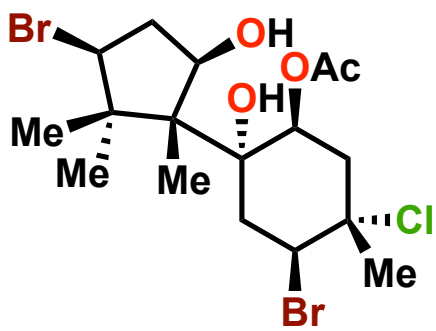


(+)-Halomon

- Cytotoxic
- Potential antitumor agent

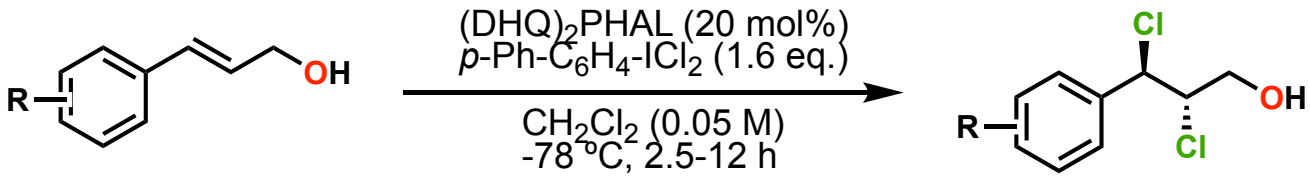


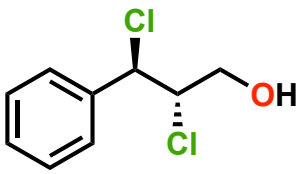
(–)-Plocamenone



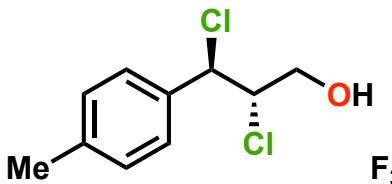
Algoane

Enantioselective Methods: Nicolaou

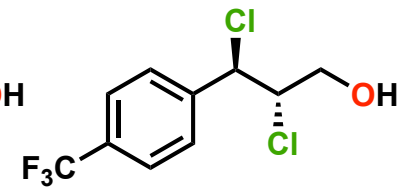




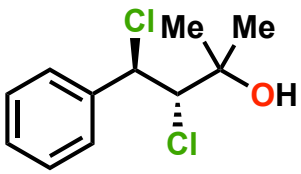
63%
90:10 e.r.



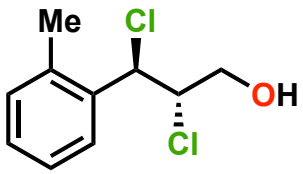
65%
72:28 e.r.



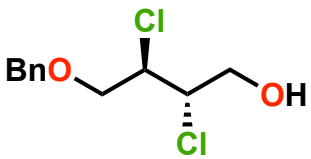
75%
74:26 e.r.



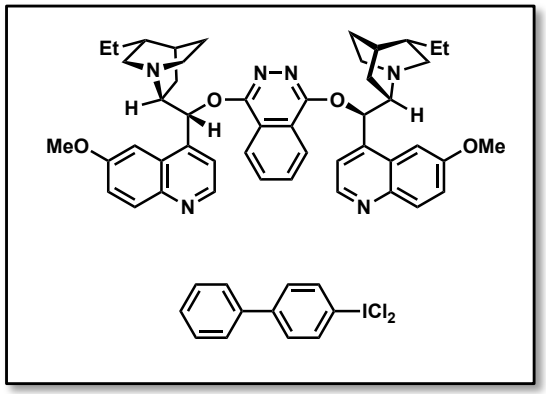
90%
72:28 e.r.



63%
84:16 e.r.



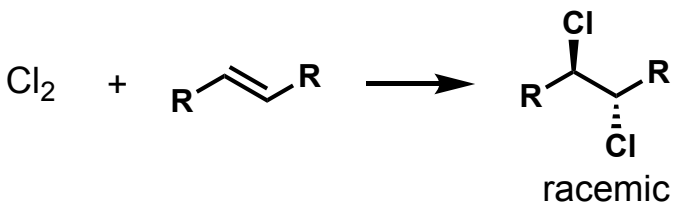
48%
72:28 e.r.



Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. Enantioselective Dichlorination of Allylic Alcohols. *J. Am. Chem. Soc.* **2011**, *133*, 8134-8137.

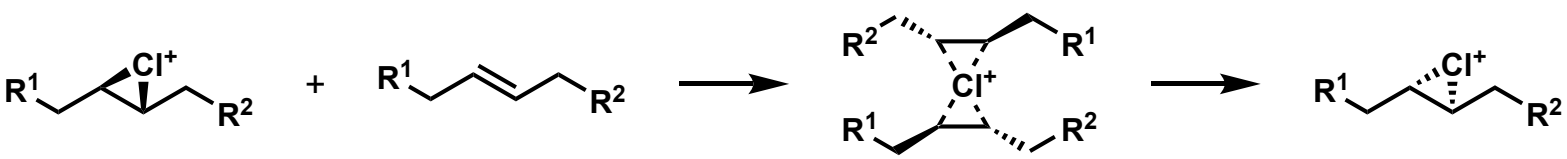
Enantioerosion Can Follow Many Paths

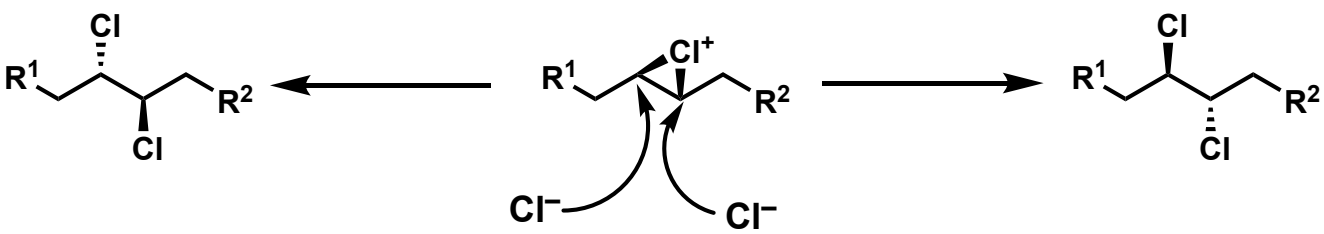
$ArICl_2 \longrightarrow ArI + Cl_2$



More generally:

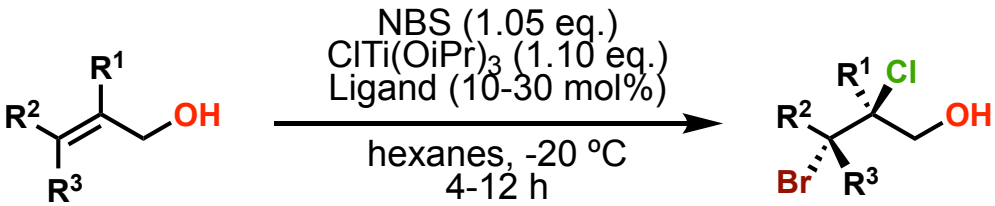
$\text{“}Cl^{+}\text{”} + Cl^{-} \longrightarrow Cl_2$

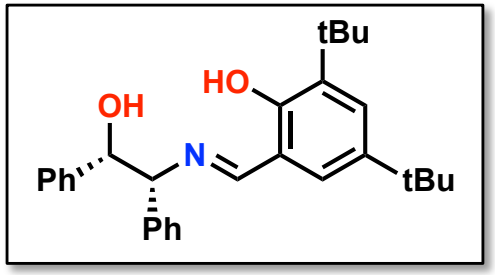


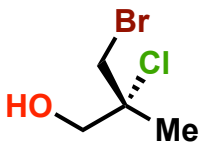


Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. Catalytic, Stereoselective Dihalogenation of Alkenes: Challenges and Opportunities. *Angew. Chem. Int. Ed.* **2015**, *54*, 15642-15682.

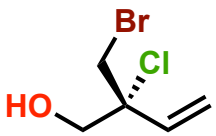
Enantioselective Methods: Burns



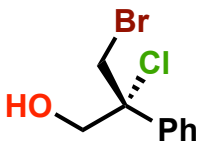




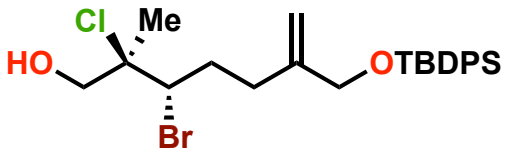
59%, 95:5 e.r.
>20:1 r.r. (20 mol%)



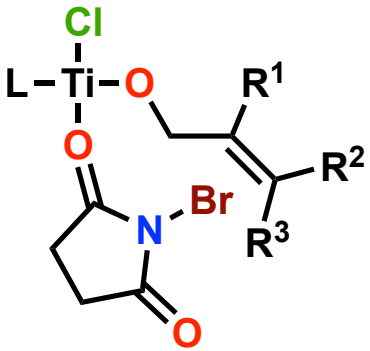
74%, 94:6 e.r.
>20:1 r.r. (10 mol%)

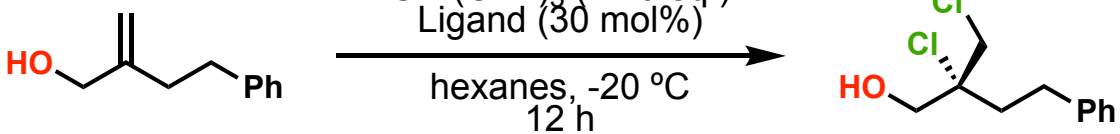


57%, 91:9 e.r.
>20:1 r.r. (20 mol%)



64%,89:11 e.r.
>20:1 r.r. (10 mol%)



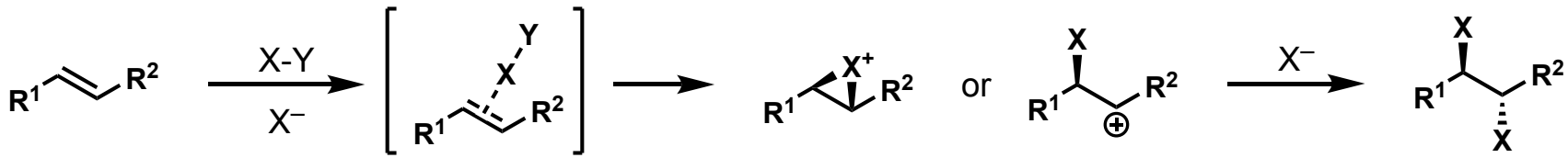


61%, 95:5 e.r.

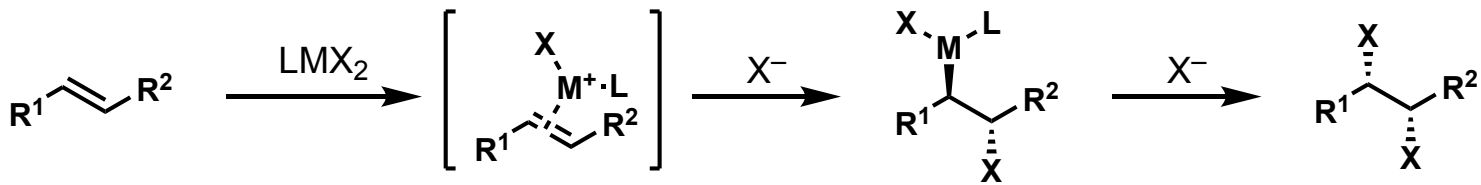
Hu, D. X.; Seidl, F. J.; Bucher, C.; Burns, N. Z. Catalytic Chemo–, Regio–, and Enantioselective Bromochlorination of Allylic Alcohols. *J. Am. Chem. Soc.* **2015**, *137*, 3795-3798.

Dihalogenation Classification

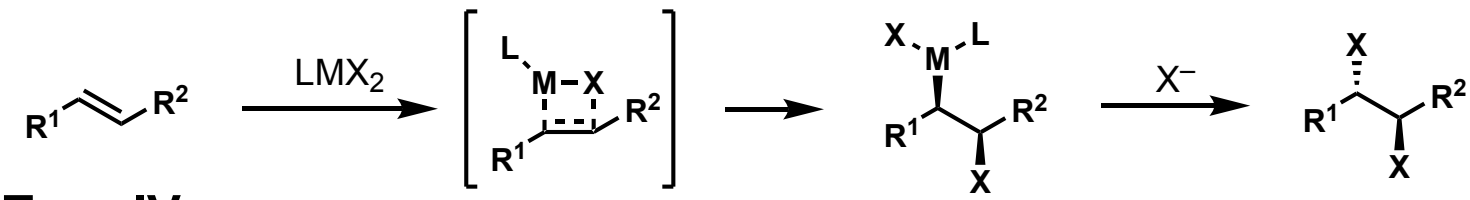
Type I Dihalogenation:



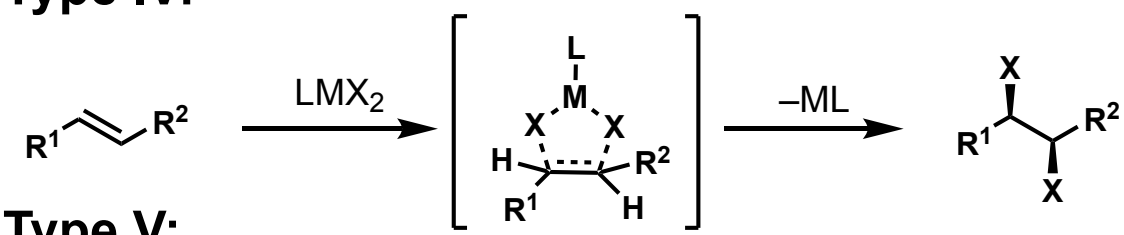
Type II:



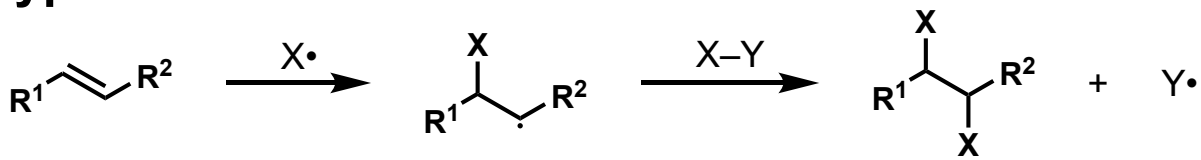
Type III:



Type IV:



Type V:



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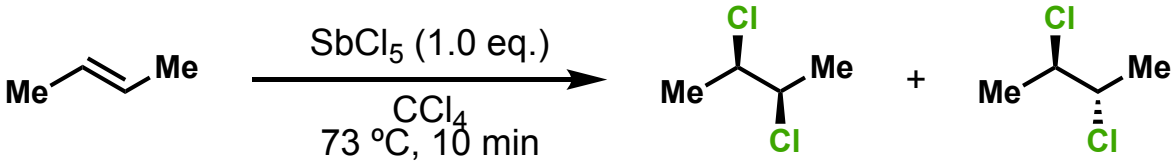
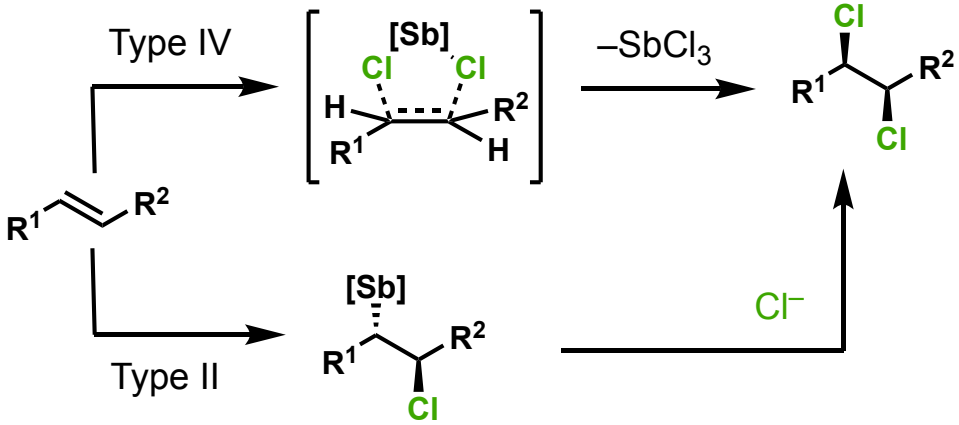
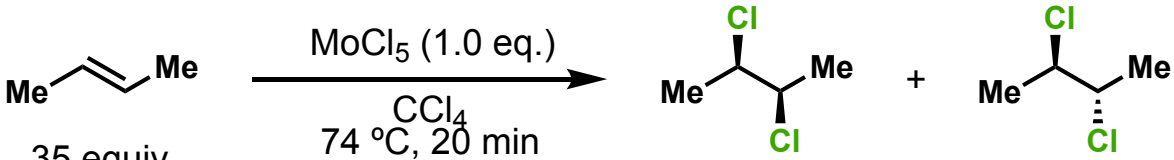
Alternative Approaches to Dihalogenation



82:18
96% combined yield





92:8
85% combined yield

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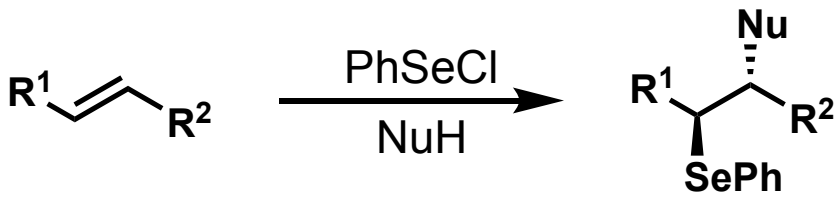
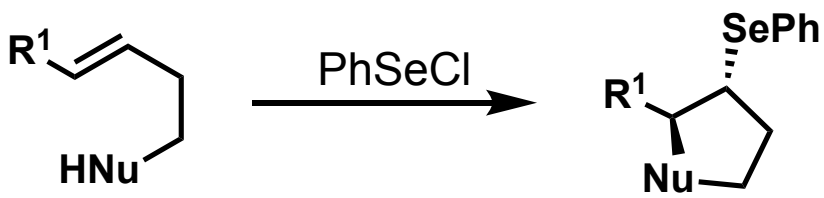
Outline

1. **Introduction**
2. **Background**
    1. Electrophilic selenofunctionalization
    2. Chiral electrophilic selenium reagents
    3. $PhSe^{II-IV}$ catalysis
    4. $PhSe^{II-IV}$-catalyzed syn-dichlorination of olefins
        1. Reaction optimization
        2. Substrate scope
        3. Mechanistic investigations
3. **Early catalyst design and synthesis**
4. **Later catalyst designs**
5. **Chlorolactonization**

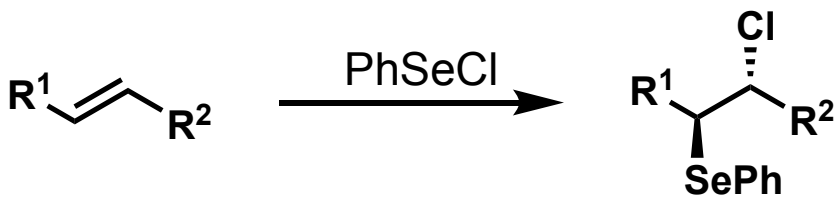
Electrophilic Selenium Reagents



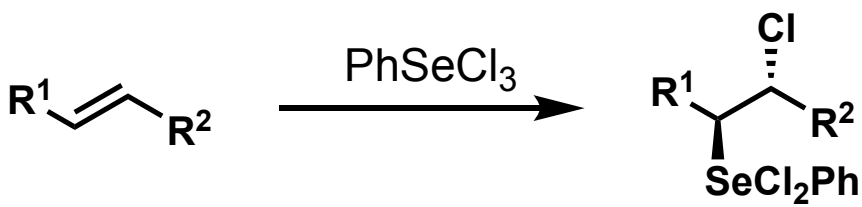
Selenofunctionalization



Selenocyclization

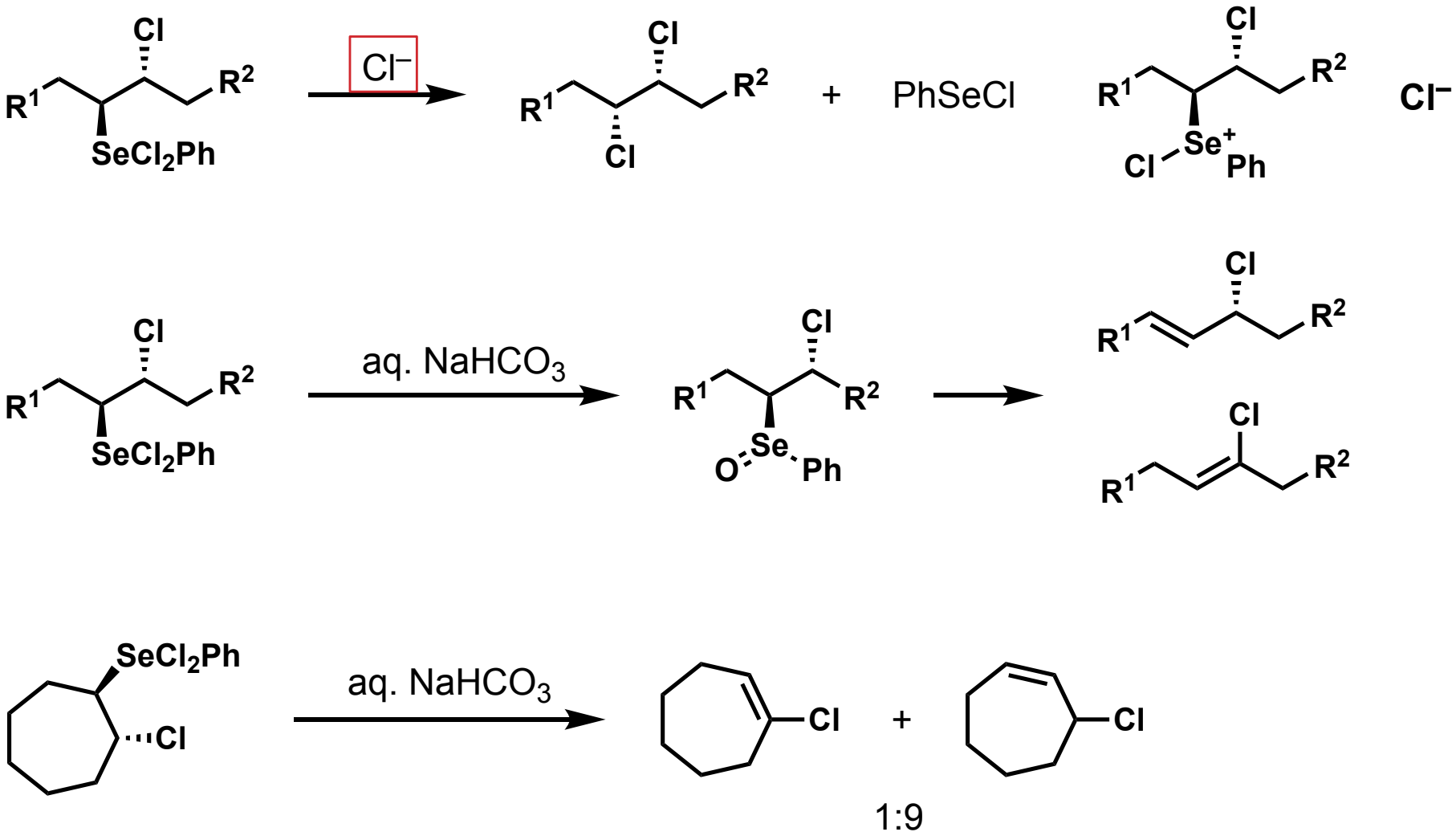


Selenohalogenation



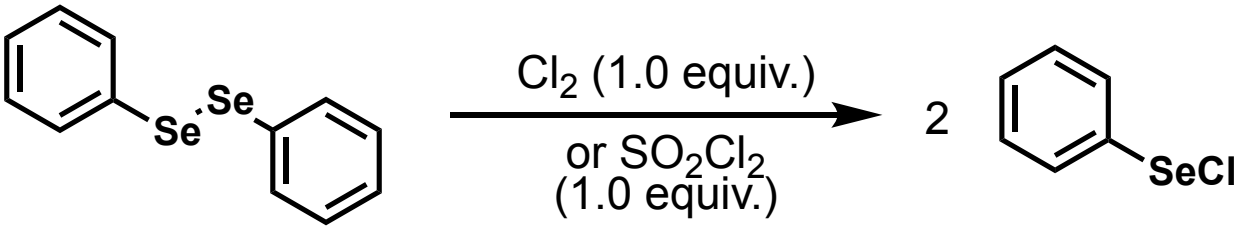
Santi, C.; Santoro, S. Electrophilic Selenium; In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2012; pp 1-53.
Engman, L. Phenylselenium Trichloride in Organic Synthesis. *J. Org. Chem.* **1987**, *52*, 4086-4094.

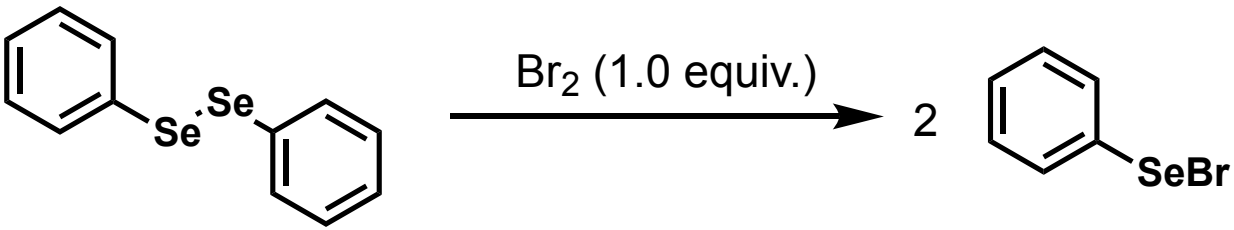
Arylalkylselenium(IV) Dichlorides

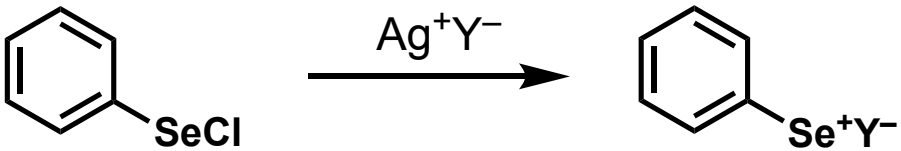


Engman, L. Phenylselenium Trichloride in Organic Synthesis. *J. Org. Chem.* **1987**, *52*, 4086-4094.

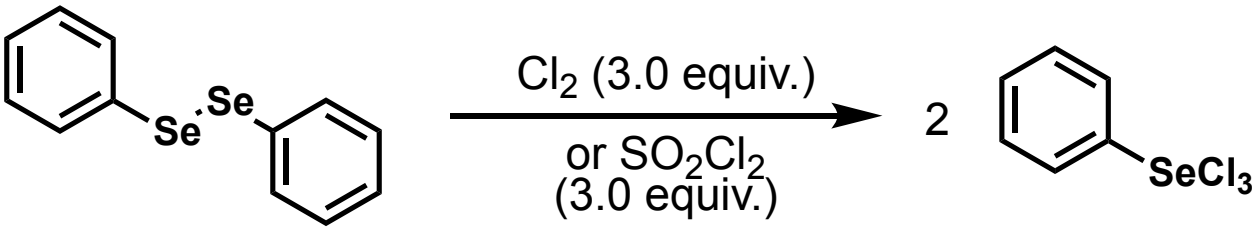
Electrophilic Selenium Reagents: Preparation





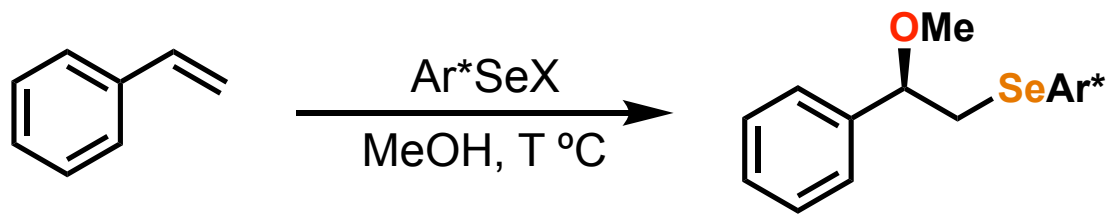


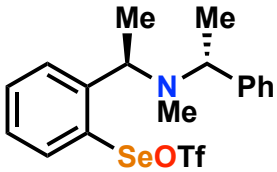
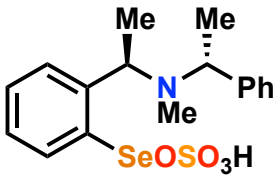
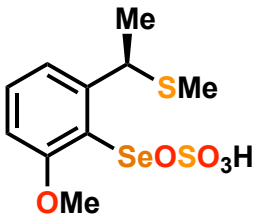
Y = PF_6, SbF_6, OTs, OTf, Saccharin



Santi, C.; Santoro, S. Electrophilic Selenium; In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2012; pp 1-53.

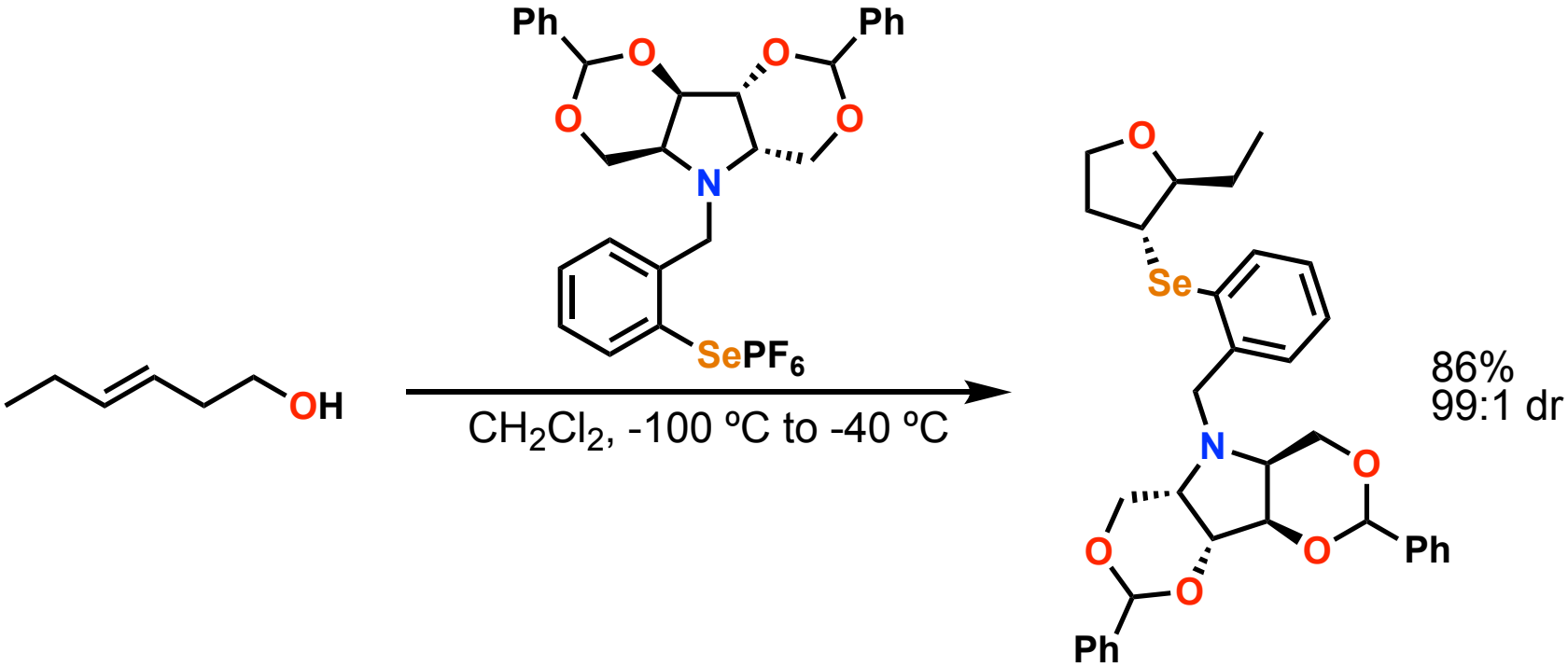
Chiral Electrophilic Selenium Reagents

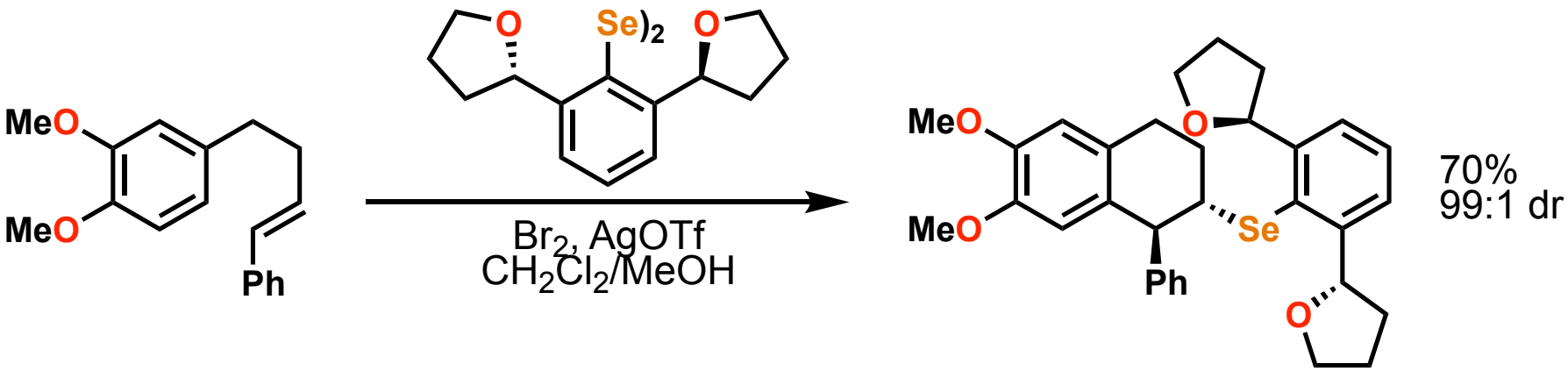


Reagent	Temperature	Yield	d.r.
	-78 ºC	40%	95:5
	25 ºC	70%	97:3
	-30 ºC	72%	98:2

Santi, C.; Santoro, S. Electrophilic Selenium; In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2012; pp 1-53.

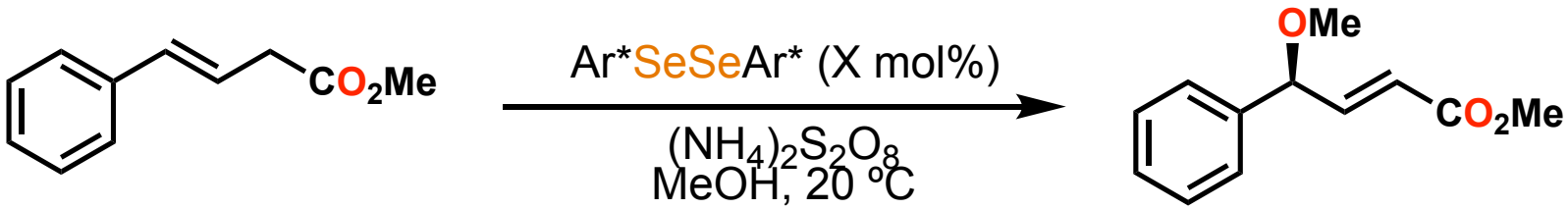
Chiral Electrophilic Selenium Reagents

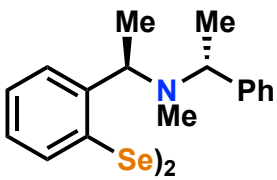
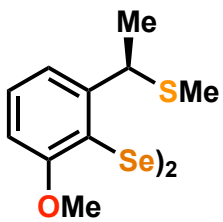




Santi, C.; Santoro, S. Electrophilic Selenium; In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2012; pp 1-53.
Fujita, K.-I.; Murata, K.; Iwaoka, M.; Tomoda, S. Design of Optically Active Selenium Reagents Having a Chiral *Tertiary* Amino Group and Their Application to Asymmetric Inter- and Intramolecular Oxyselenylations. *Tetrahedron*, **1997**, *53*, 2029-2048.

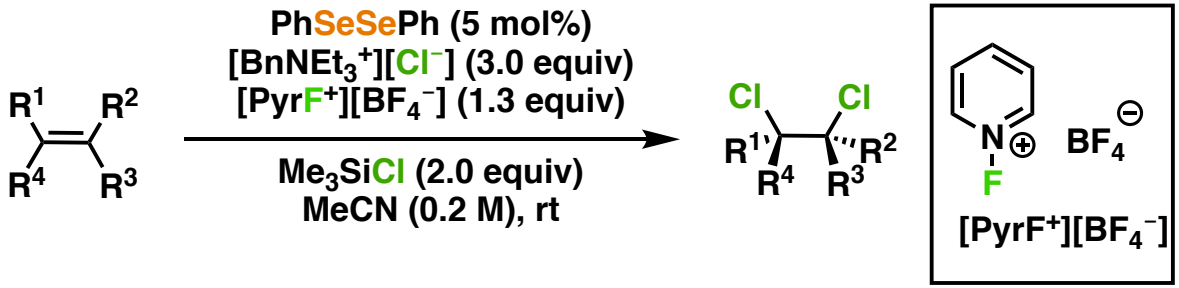
Asymmetric Se^{II-IV} Catalysis

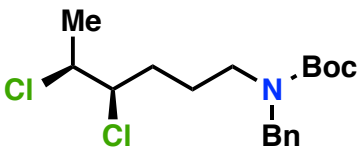


Precatalyst	X mol%	Yield	e.r.
	100	50%	97:3
	10	12%	97:3
	5	98%	89:11

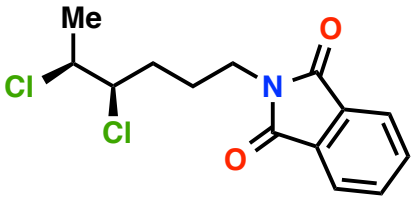
Santi, C.; Santoro, S. Electrophilic Selenium; In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2012; pp 1-53.

Catalytic *syn*-Dichlorination of Olefins

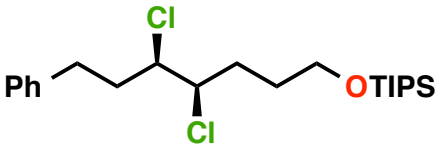




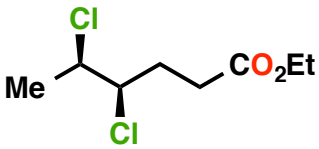
72%, 99:1 dr
(5 h)



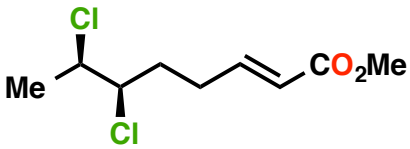
72%, 97:3 dr
(3.5 h)



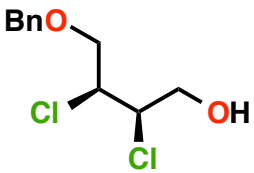
37%, 97:3 dr
(5 h)



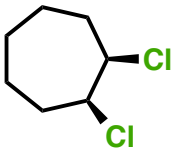
70%, >99:1 dr
(3.5 h)



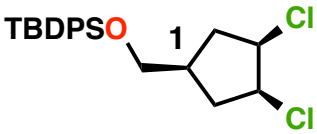
70%, 99:1 dr
(4.5 h)



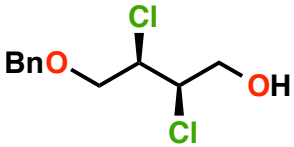
73%, 93:7 dr
(15 h)



77%, 99:1 dr
(4 h)



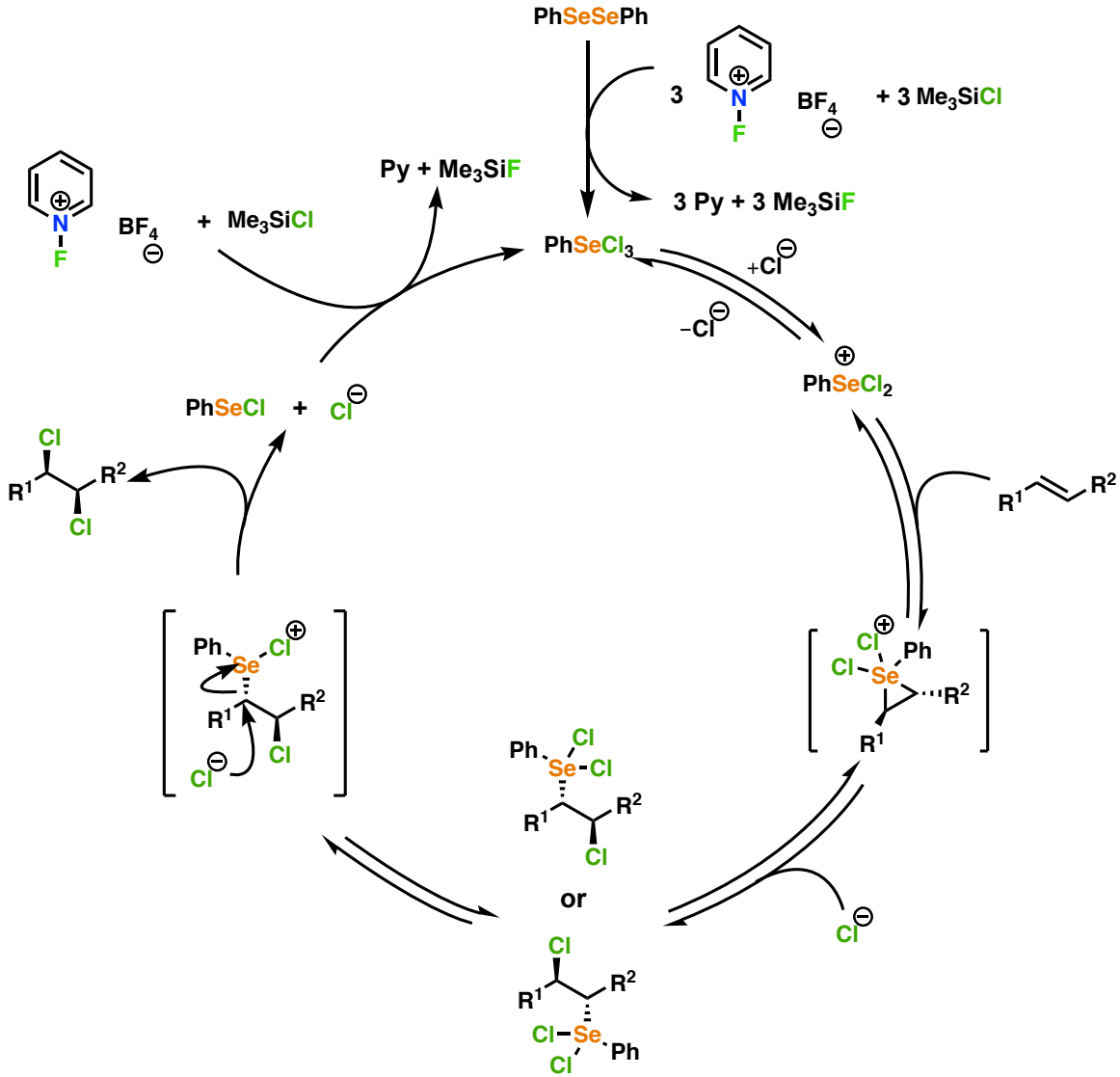
71%, >99:1 dr
91:9 at C(1) (16 h)



67%, 56:44 dr
(47 h)

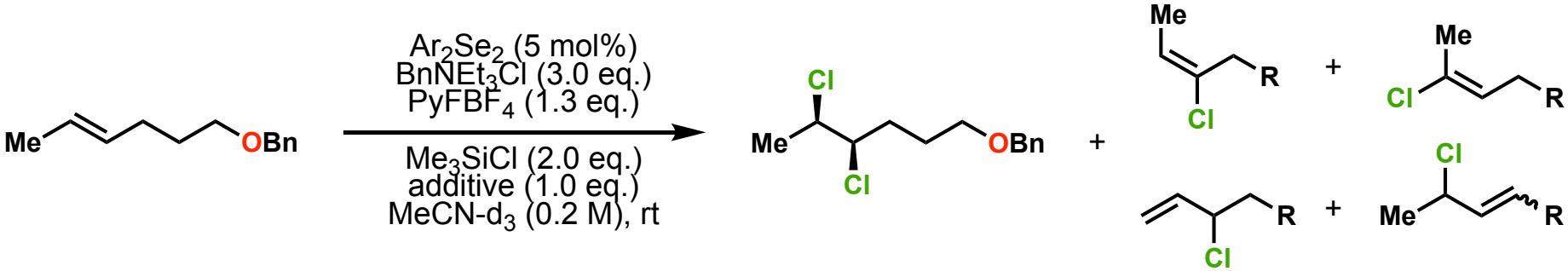
Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. Catalytic, stereospecific *syn*-dichlorination of alkenes. *Nature Chem.* **2015**, *7*, 146-152.

Catalytic Cycle



- Displacement by chloride is the most likely RDS
- Each step up to displacement by chloride to the product is potentially reversible
- Could also undergo $PhSe^{II}Cl$ addition to the olefin

Optimization

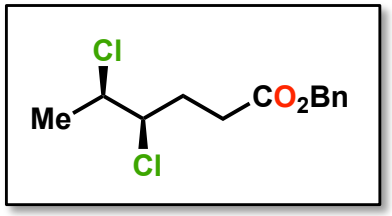


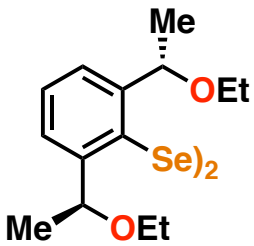
Ar_2Se_2	Additive	Time (h)	Dichlor.:Elim.	d.r.
Ph_2Se_2	–	6	80:20	99:1
Ph_2Se_2	Sulfolane	2	80:20	99:1
Ph_2Se_2	2,6-lutidine-N-oxide	2	80:20	99:1
$[3,5\text{-}(CF_3)_2C_6H_3]_2Se_2$	–	10	58:42	88:18
$[2\text{-}NO_2C_6H_4]_2Se_2$	–	18	59:41	55:45
$[4\text{-}MeOC_6H_4]_2Se_2$	–	3.5	90:10	99:1
$[2\text{-}MeOC_6H_4]_2Se_2$	–	8	83:17	98:2

Outline

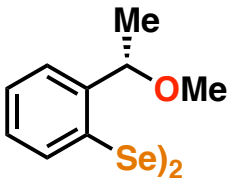
1. **Introduction**
2. **Background**
3. **Early catalyst design and synthesis**
    1. Ether coordinating groups
    2. Oxazoline coordinating groups
    3. Amide, amine and urea coordinating groups
4. **Later catalyst designs**
5. **Chlorolactonization**

Ether Coordinating Groups

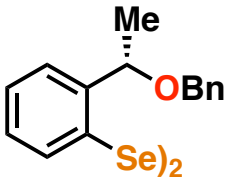




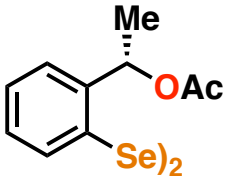
dr 30:70
er 60:40



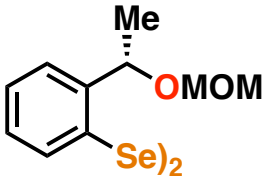
er 55:45



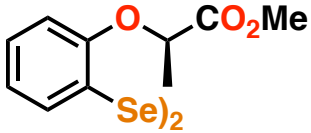
er 60:40



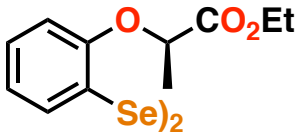
dr 70:30
er 60:40



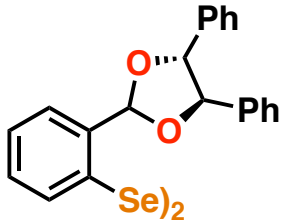
er 65:35



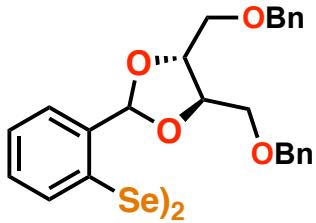
er 53:47



er 50:50



er 51:49



er 52:48

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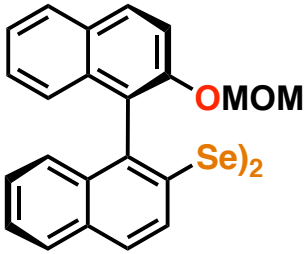

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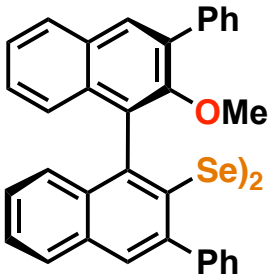
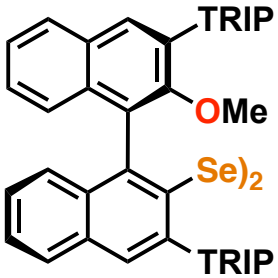


er 50:50

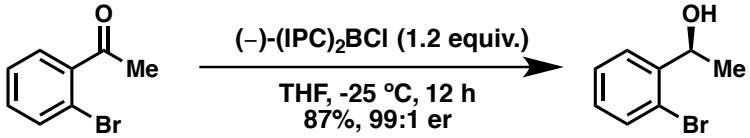


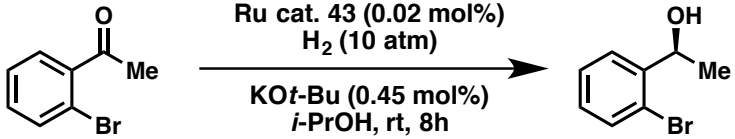
no conversion

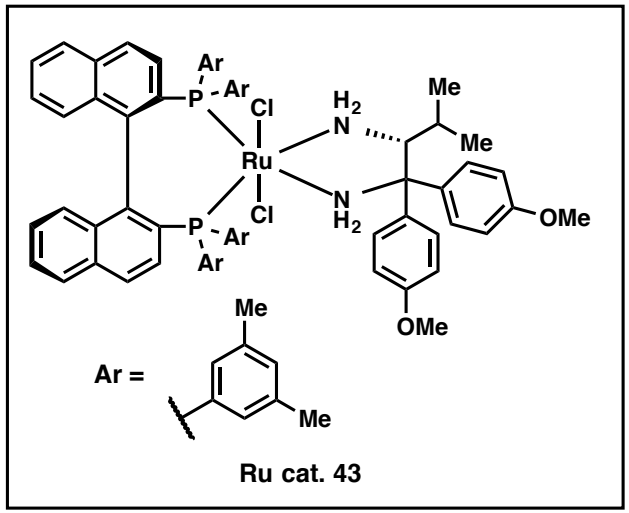
**

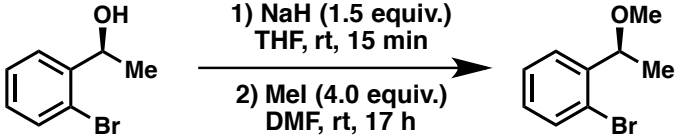
*With S. T.-C. Eey. **With G. R. Zhang

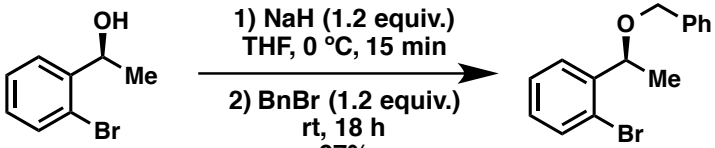
Example Synthetic Route

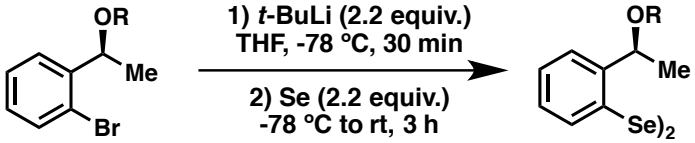




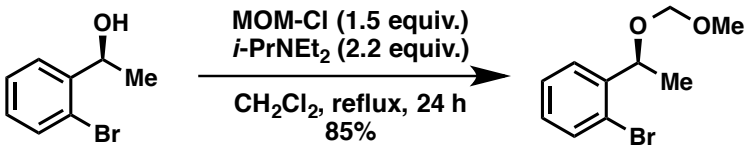






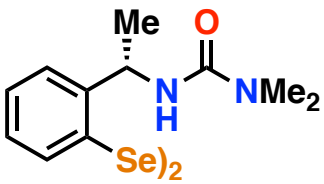


R = Me 48%
R = Bn 49%
R = MOM 64%

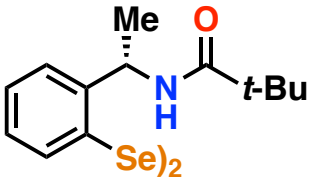


Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Ktatayama, E.; England, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703-1707.

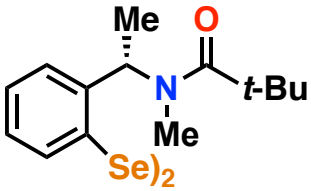
Amide, Amine and Urea Coordinating Groups



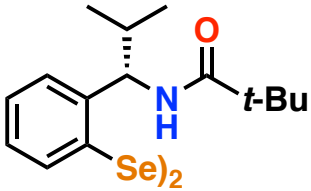
dr 70:30
er 50:50



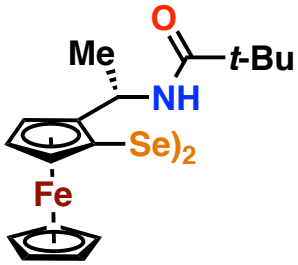
er 70:30



er 55:45



dr 83:17
er 60:40



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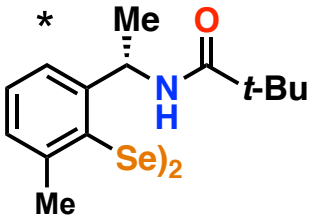

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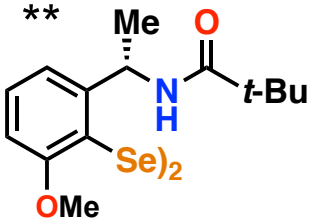
er 74:26



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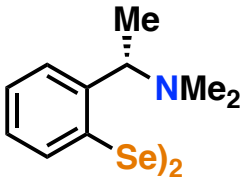

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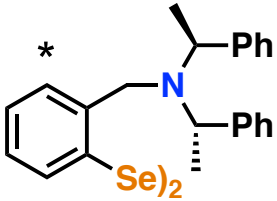
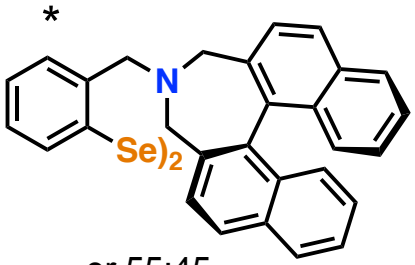
er 70:30



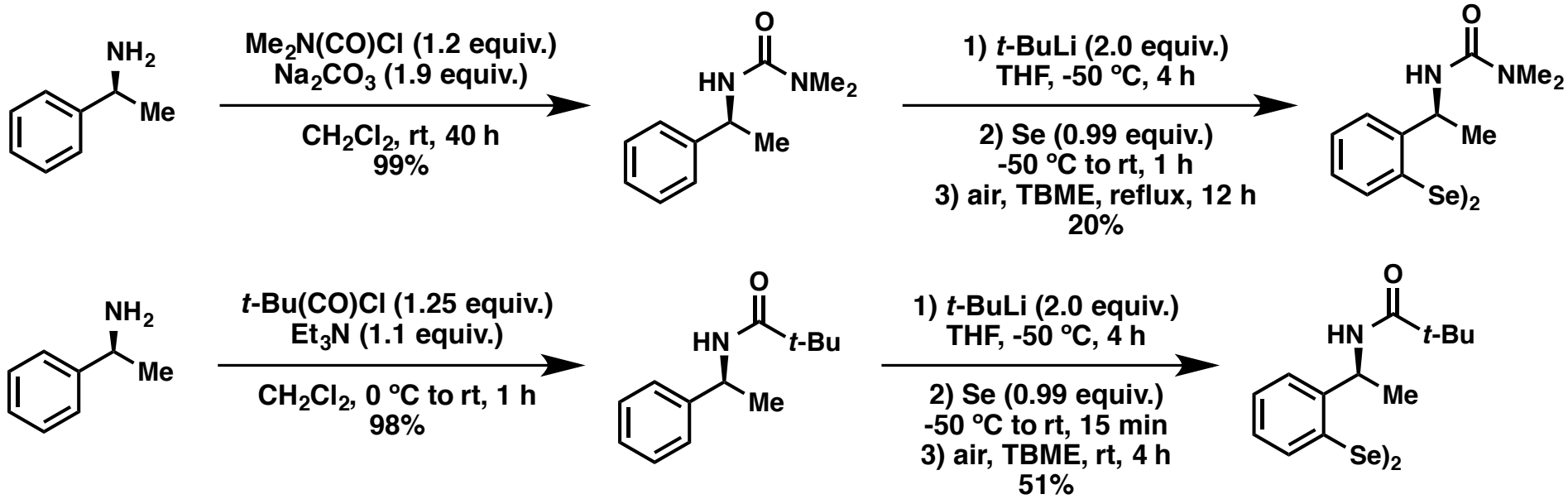
er 53:47



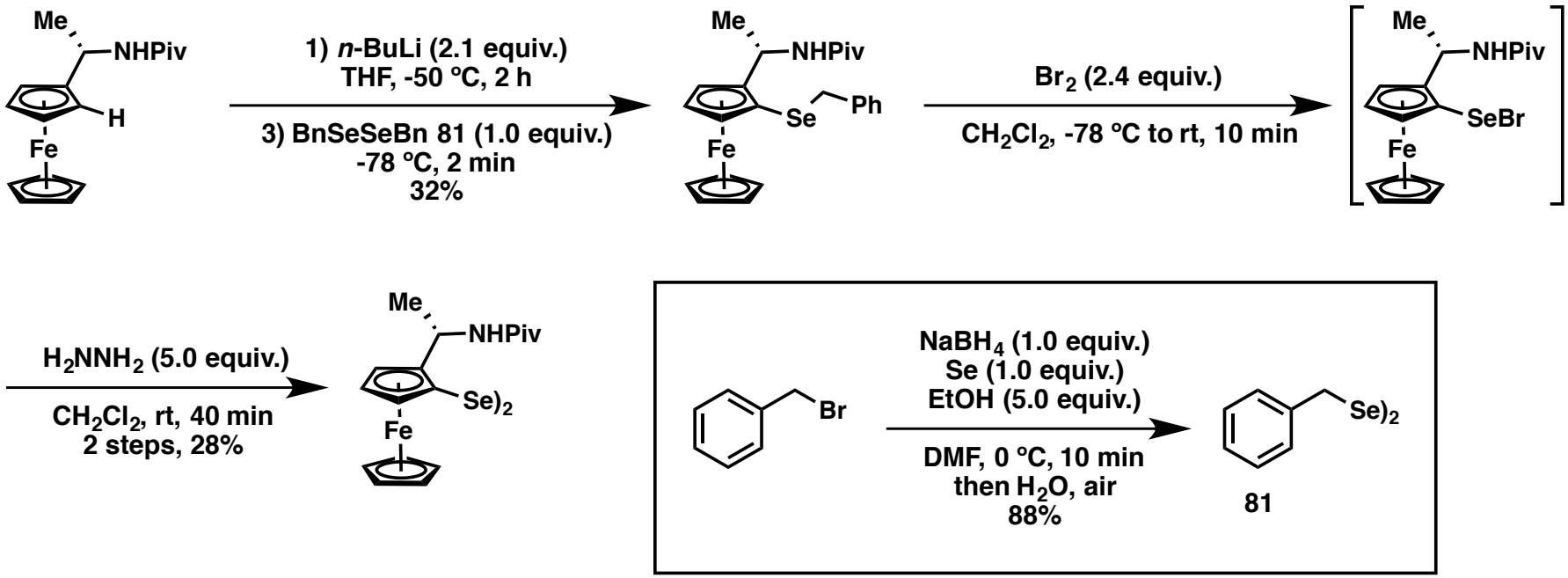
er 55:45

*With P. Ryabchuk. **With O. Garry

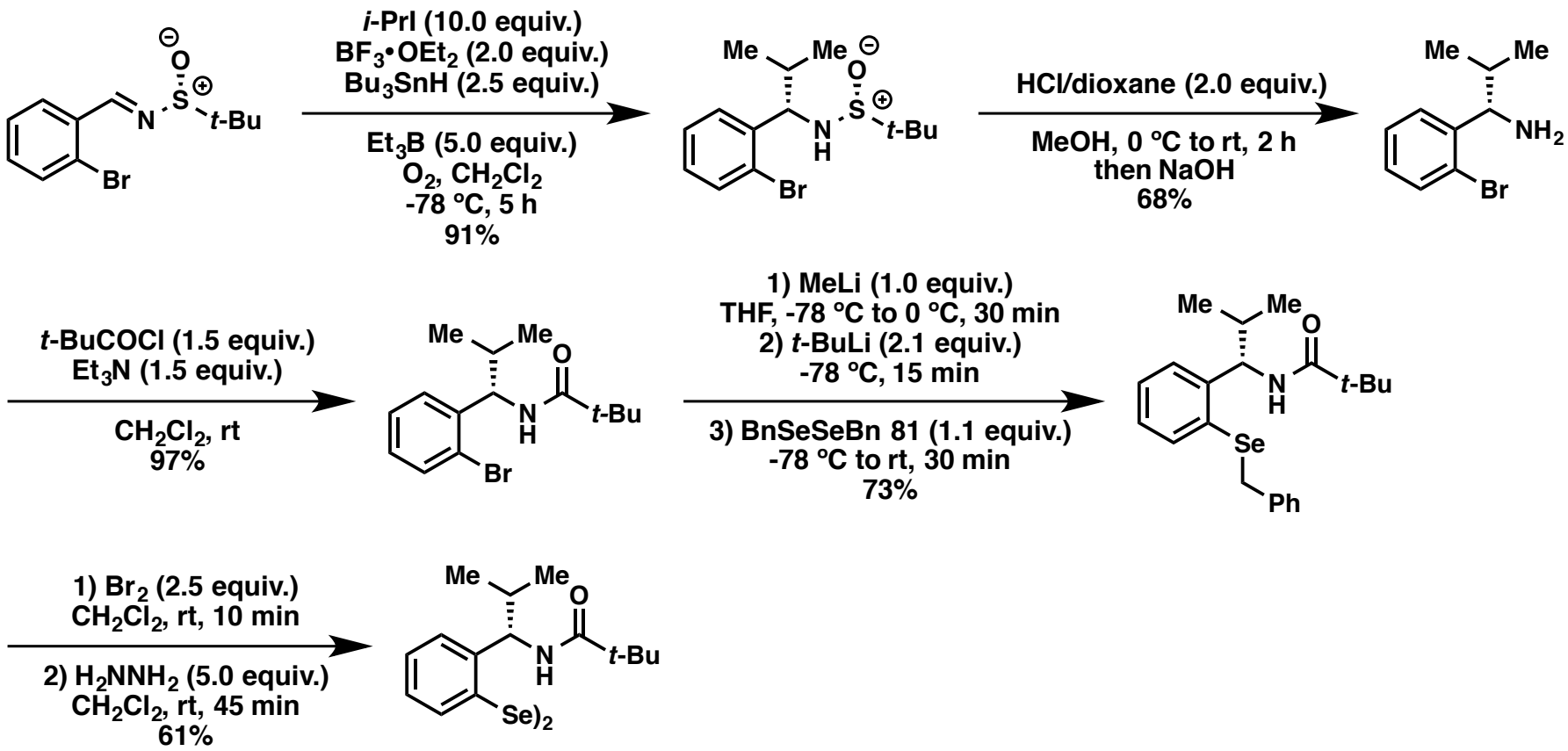
Example Synthetic Route



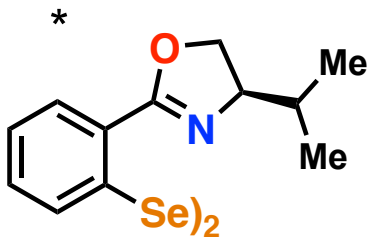
Example Synthetic Route



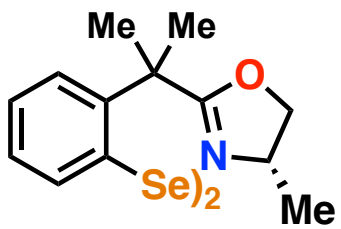
Example Synthetic Route



Oxazoline Coordinating Groups



er 54:46



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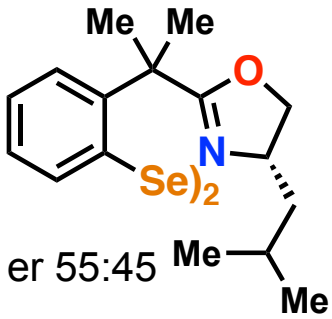

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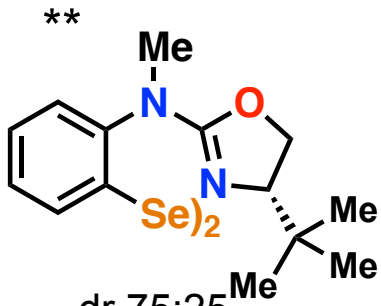
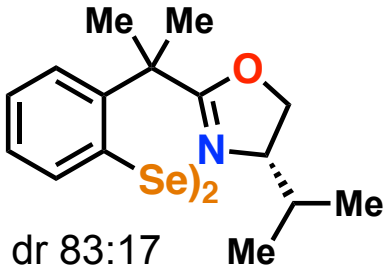
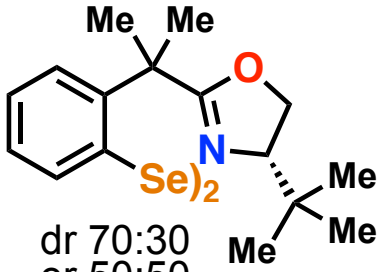


dr 75:25
er 51:49



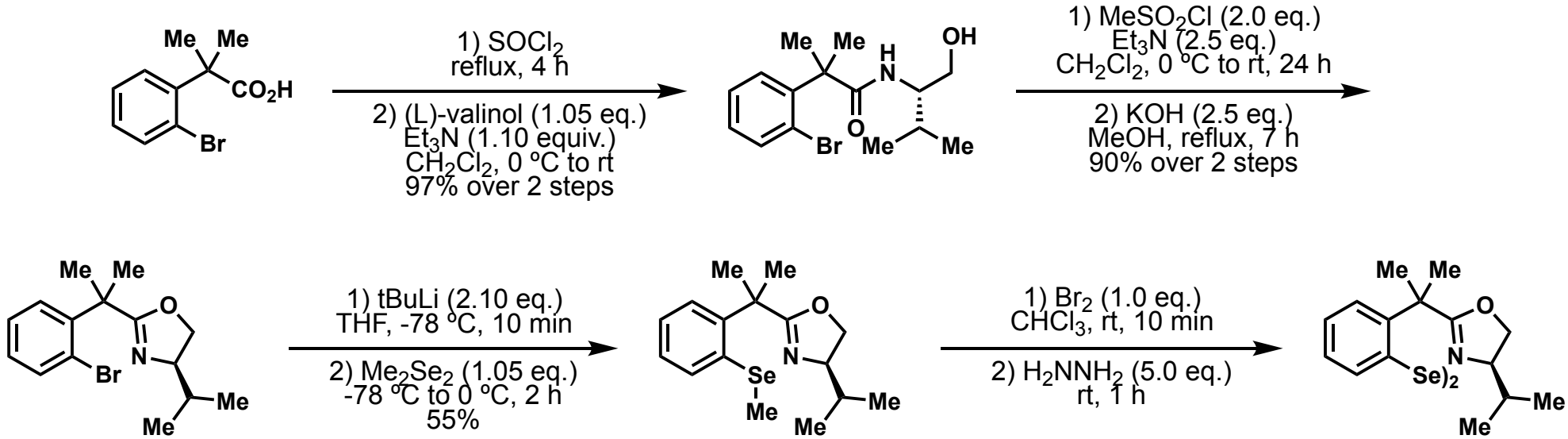
dr 83:17
er 60:40



dr 70:30
er 50:50

*With S. T.-C. Eey. **With G. R. Zhang.

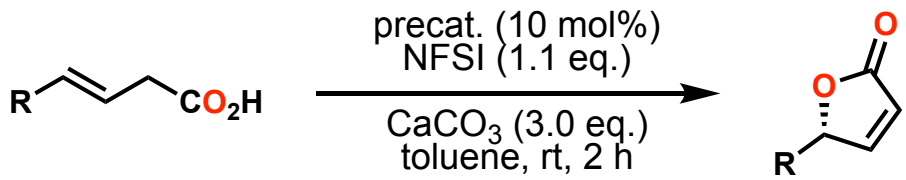
Example Synthetic Route

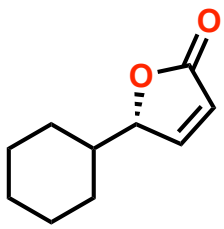


Outline

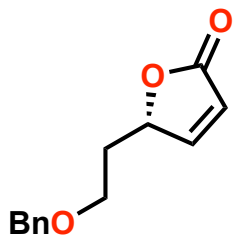
1. **Introduction**
2. **Background**
3. **Early catalyst design and synthesis**
4. **Later catalyst designs**
    1. Rigid catalyst backbones in room-temperature Se-redox catalysis
    2. Catalyst synthesis and evaluation
5. **Chlorolactonization**

Rigid Electrophilic Arylselenium Catalysts

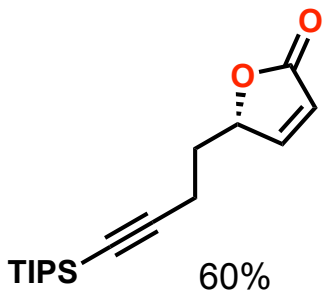




99%
e.r. 98:2



98%
e.r. 98:2



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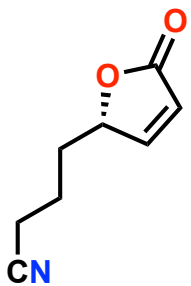

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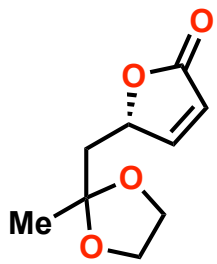
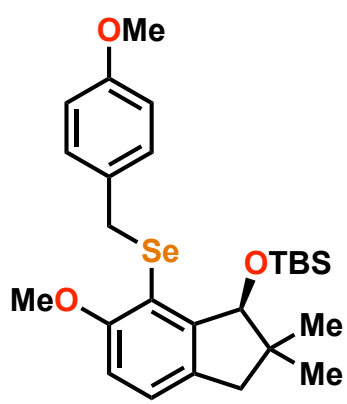
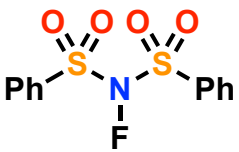
e.r. 97:3



93%
e.r. 97:3



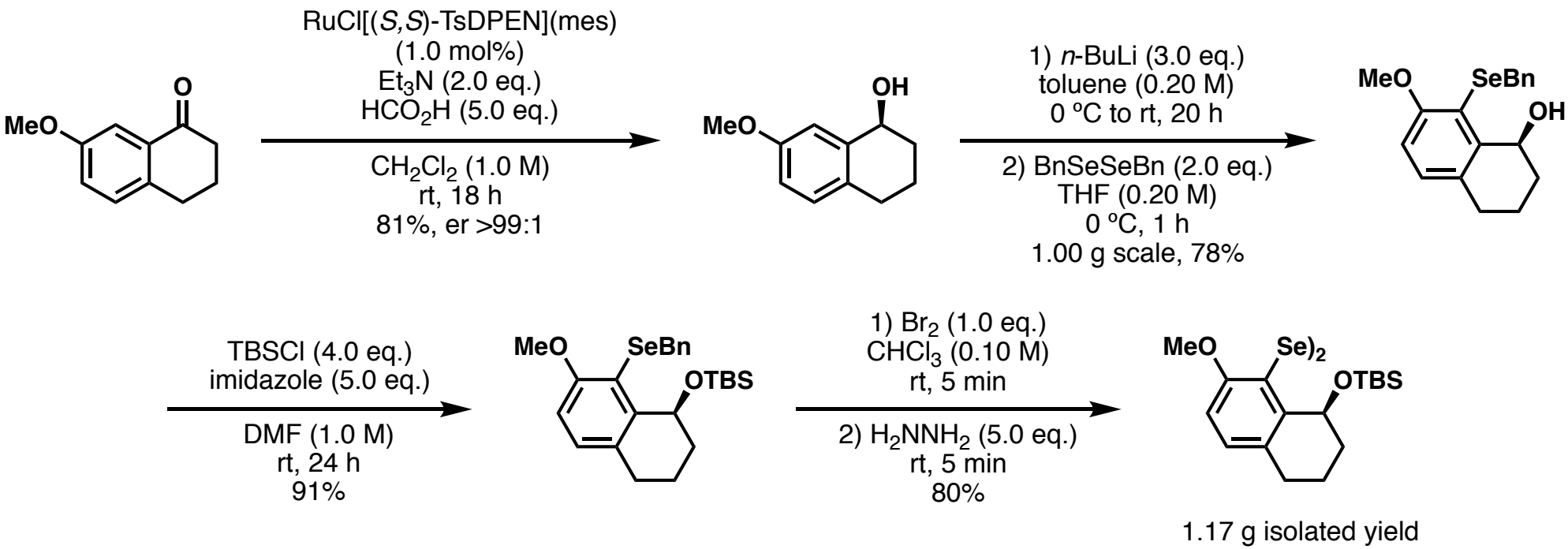
precatalyst



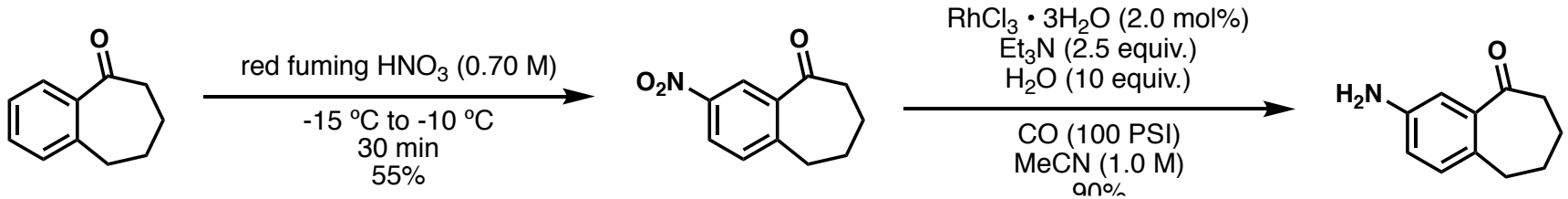
NFSI

Kawamata, Y.; Hashimoto, T.; Maruoka, K. A Chiral Electrophilic Selenium Catalyst for Highly Enantioselective Oxidative Cyclization. *J. Am. Chem. Soc.* **2016**, *138*, 5206-5209.

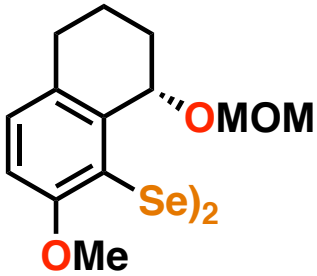
Catalyst Synthesis



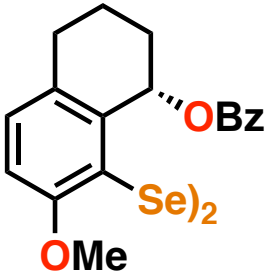
Catalyst Synthesis



Bicyclic, Rigid Catalysts



er 70:30



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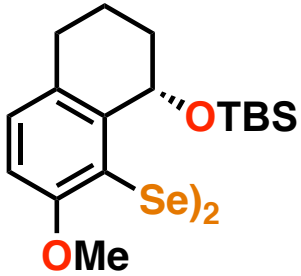

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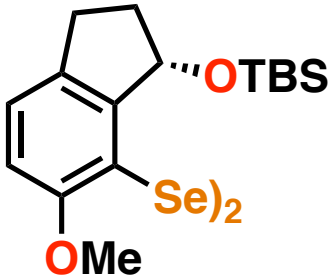

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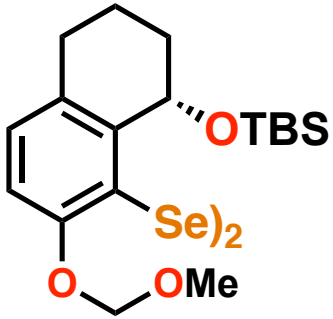

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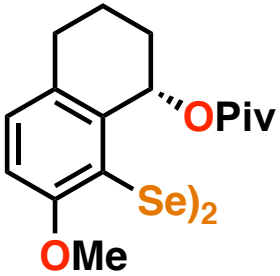

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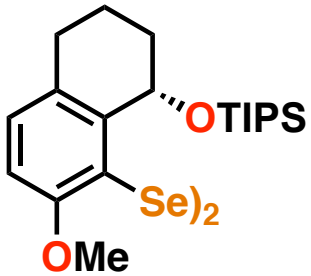

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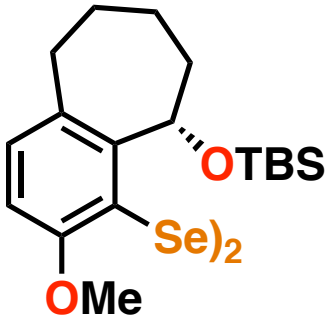

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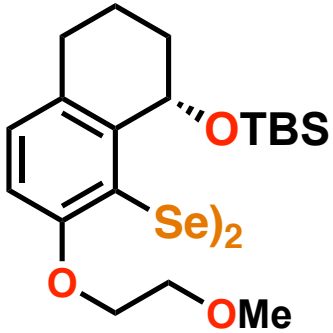
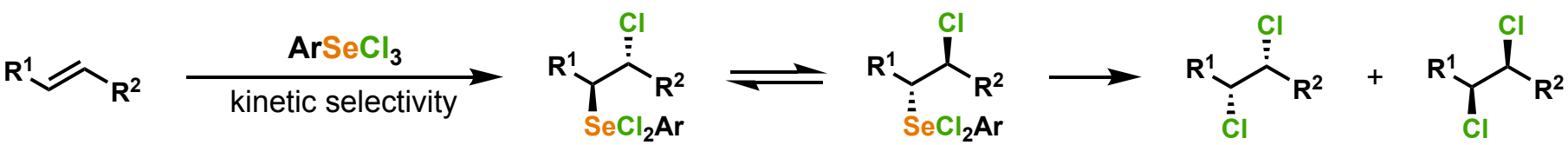


er 70:30

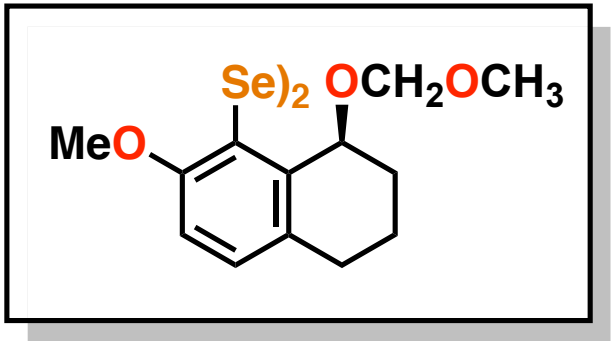
Potential Issues Limiting Selectivity

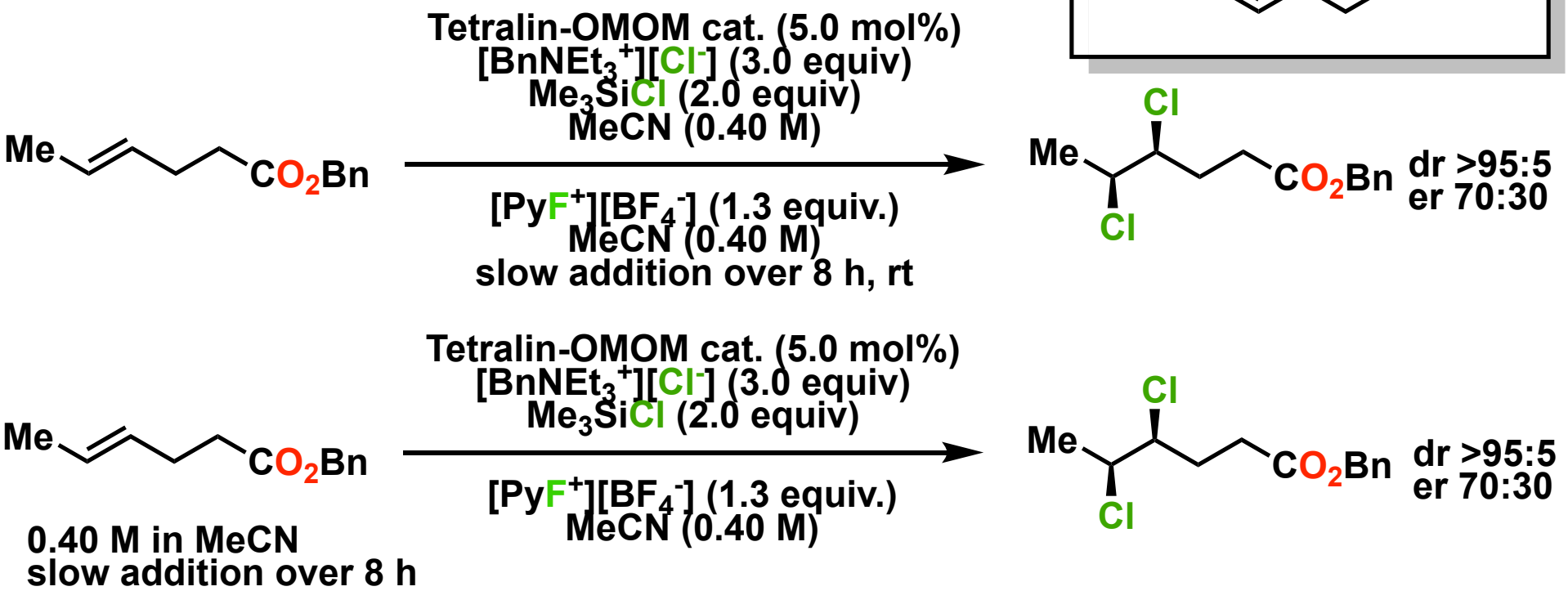
- **Low intrinsic selectivity**
  - Potentially solved by better-informed catalyst design
- **Competing pathways**
  - $ArSe^{II}Cl$ and $ArSe^{IV}Cl_3$ could undergo olefin addition with different geometries and different selectivities
  - Potentially solved by slowly adding either substrate or oxidant to limit the reaction to the more selective pathway
- **Epimerization of catalytic intermediates before turnover**
  - Displacement by chloride is likely the turnover-limiting step
  - Can be viewed as kinetic versus thermodynamic selectivity



thermodynamic mixture

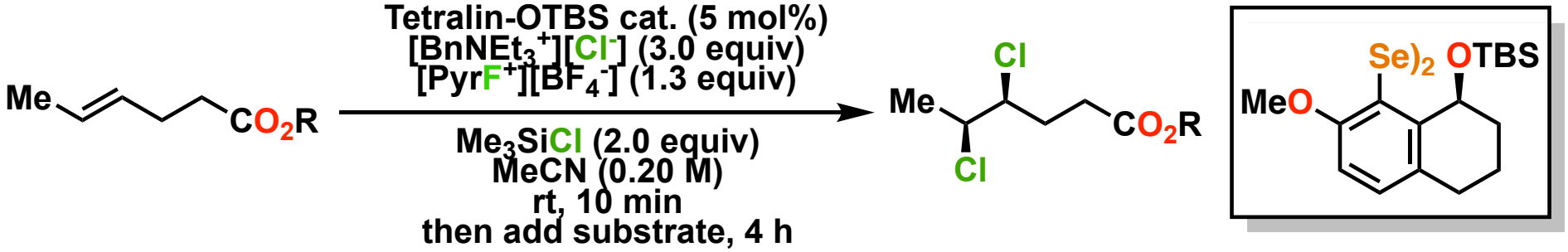
Experimental Determination of Se Oxidation State





- Slow addition of oxidant was intended to ensure that $ArSe^{II}Cl$ had time to react with the olefin prior to oxidation and displacement

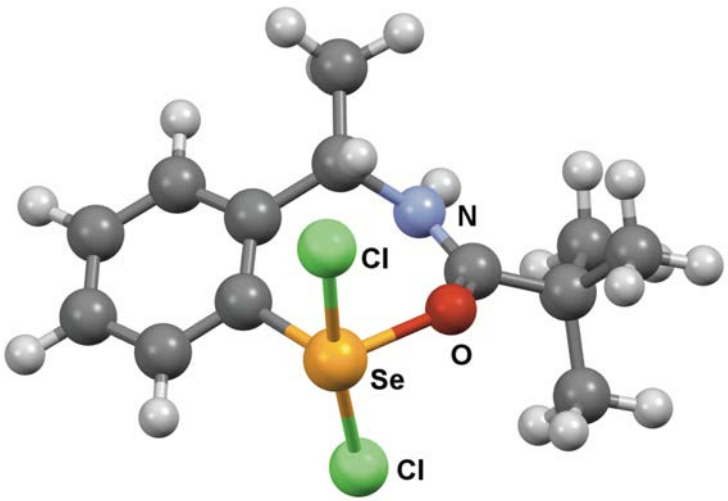
Experimental Determination of Se Oxidation State

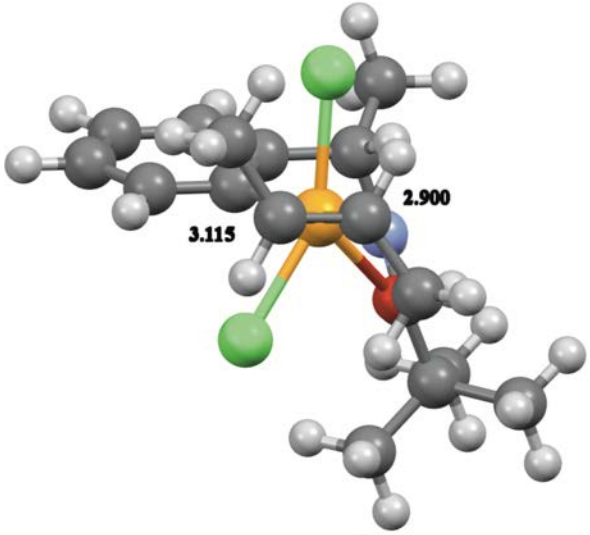


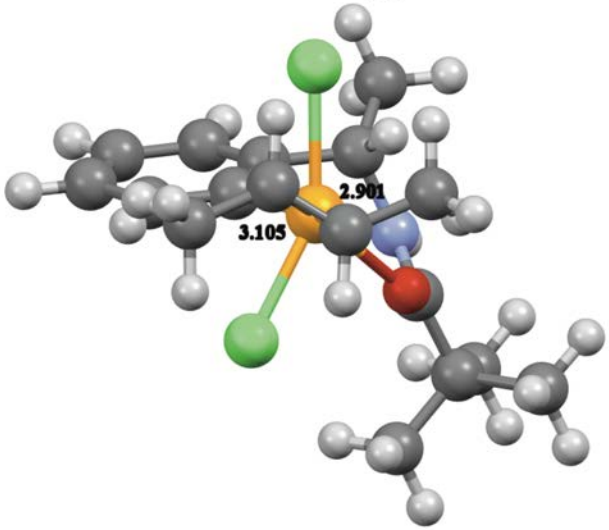
R =	er at 10% conversion	er at 100% conversion
–Bn	76:24	75:25
–CH_2-1-naphthyl	74:26	66:34
–CH_2-2-naphthyl	79:21	61:39
–CH_2-4-C_6H_4-OMe	79:21	76:24
–$CH_2CH_2CH_2$-4-C_6H_4OMe	77:23	75:25

- There appears to be no dependence of er on conversion for simple benzylic esters
- Larger π-sytems appear to lead to worse er at later conversion

Modeling Se^{IV} Catalytic Intermediates



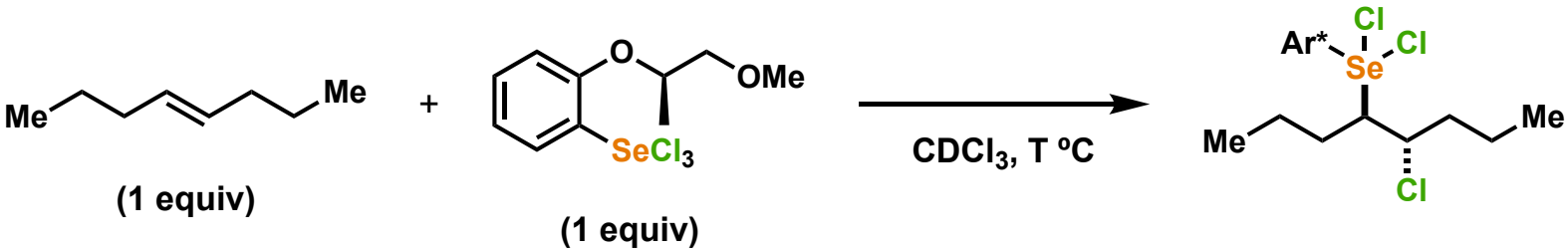




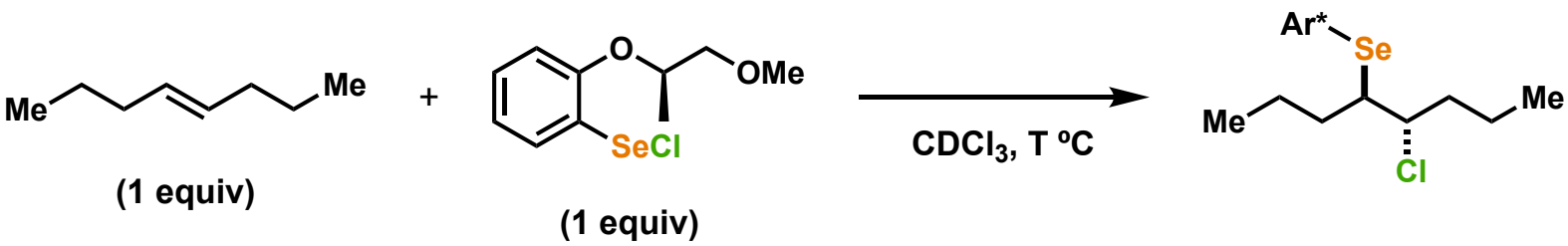
- $[ArSe^{IV}Cl_2]^+$ was modeled to undergo side-on approach by the olefin with the $\Delta\Delta G^{\ddagger}$ calculated to be 2.3 kcal/mol (~90:10 er at room temp.)

With Hao Wang

Intrinsic Diastereoselectivity



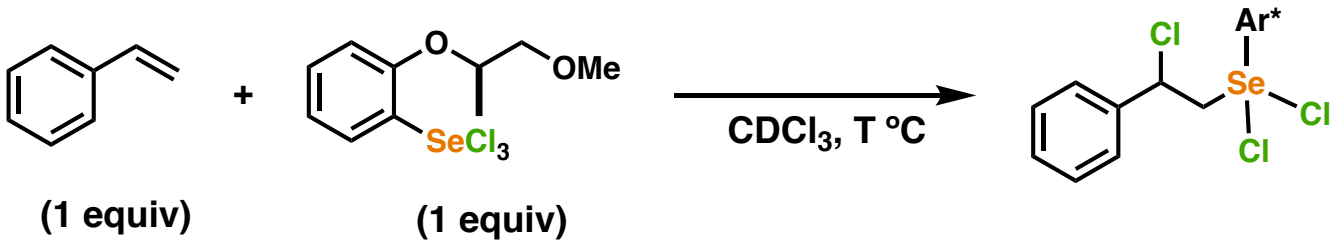
Temperature	-65 ºC	0 ºC	25 ºC
d.r.	57:43	58:42	54:46



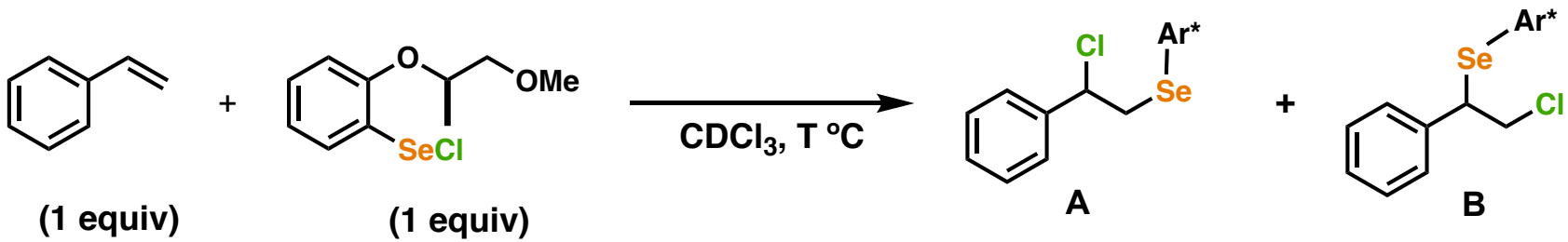
Temperature	-65 ºC	0 ºC	25 ºC
d.r.	50:50	50:50	50:50

Eey, S. Catalytic, Stereospecific *Syn*-Dichlorination of Alkenes – Development of a Catalytic, Enantioselective Reaction. Postdoctoral Report, University of Illinois, 2015.

Intrinsic Diastereoselectivity



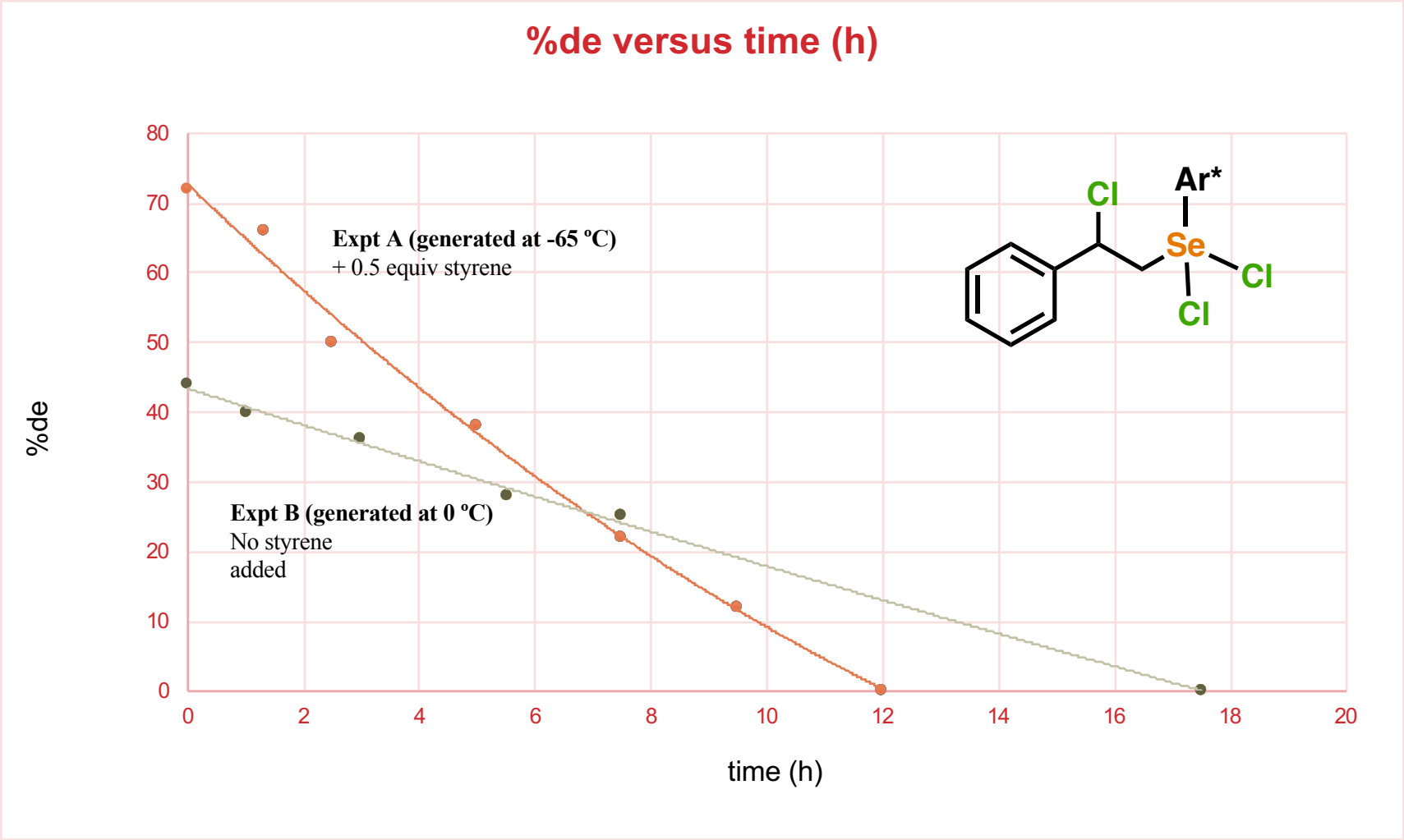
Temperature	-65 °C	0 °C	25 °C
d.r.	86:14	72:28	65:35



Temperature	-65 °C	0 °C	25 °C
A:B (r.r.)	85:15	65:35	53:47
A d.r.	97:3	85:15	74:26
B d.r.	96:4	88:12	75:25

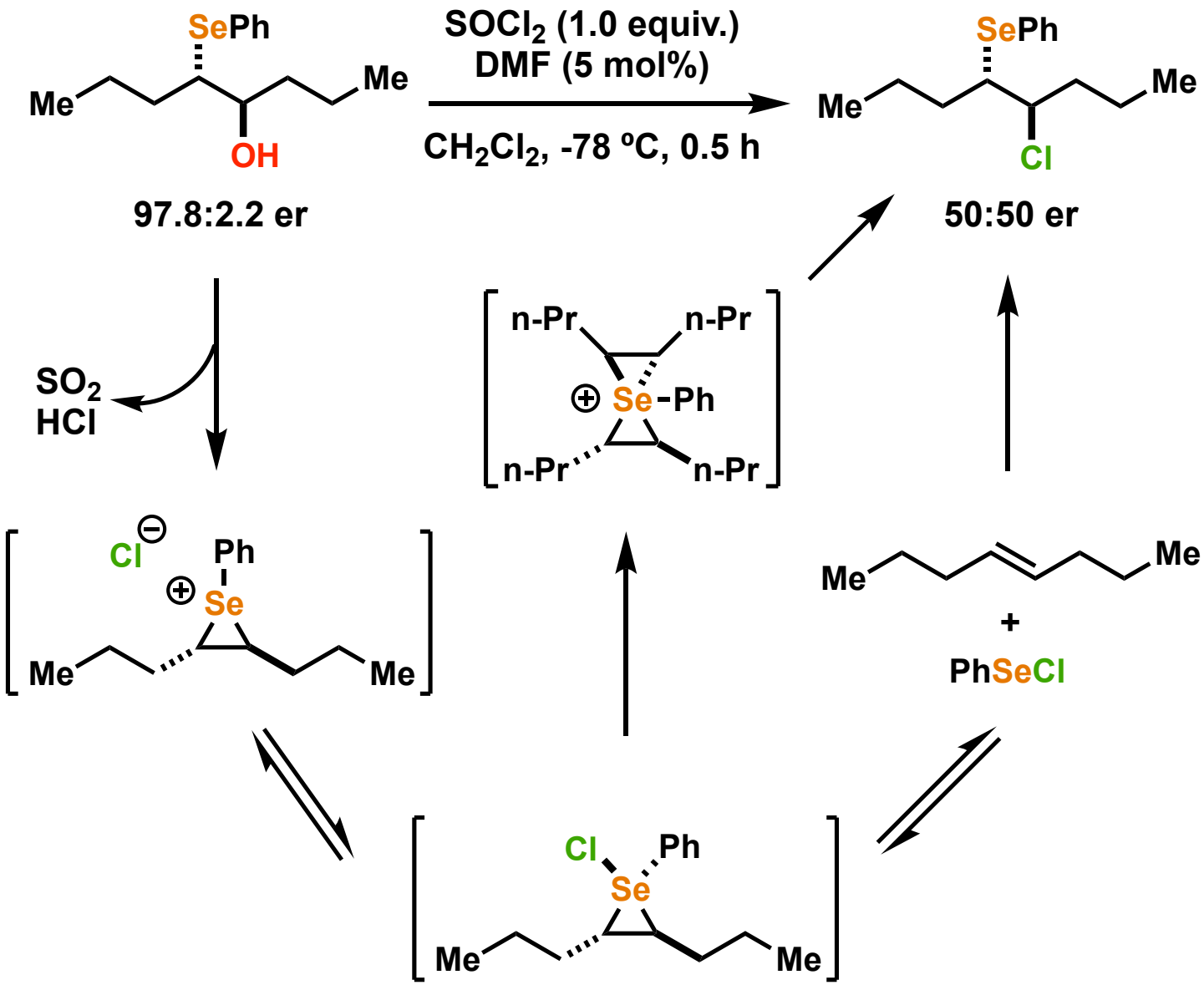
Eey, S. Catalytic, Stereospecific *Syn*-Dichlorination of Alkenes – Development of a Catalytic, Enantioselective Reaction. Postdoctoral Report, University of Illinois, 2015.

Enantioerosion of Chloralkyl Intermediate



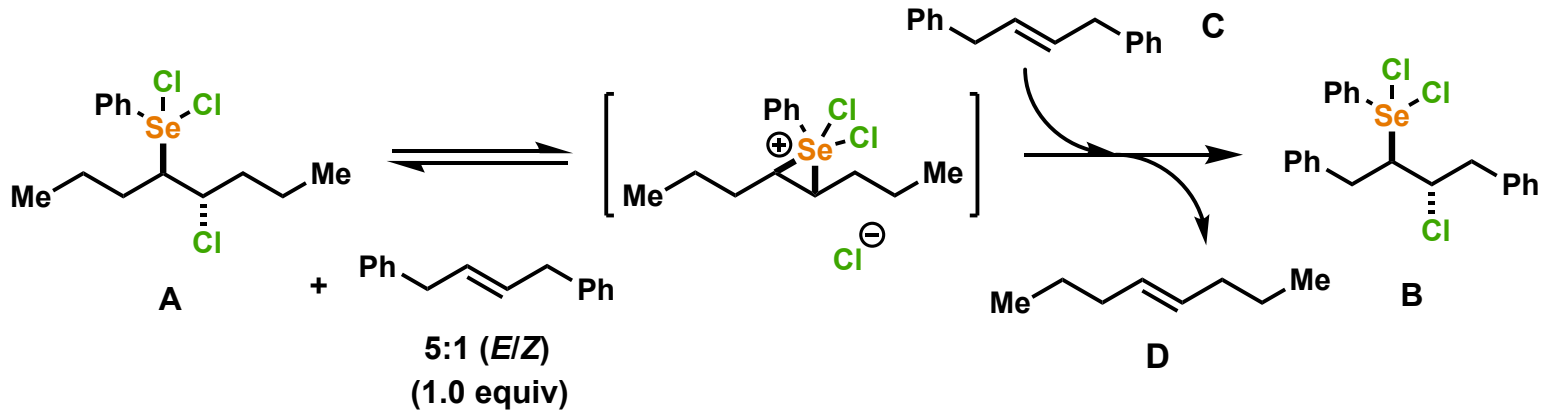
Eey, S. Catalytic, Stereospecific *Syn*-Dichlorination of Alkenes – Development of a Catalytic, Enantioselective Reaction. Postdoctoral Report, University of Illinois, 2015.

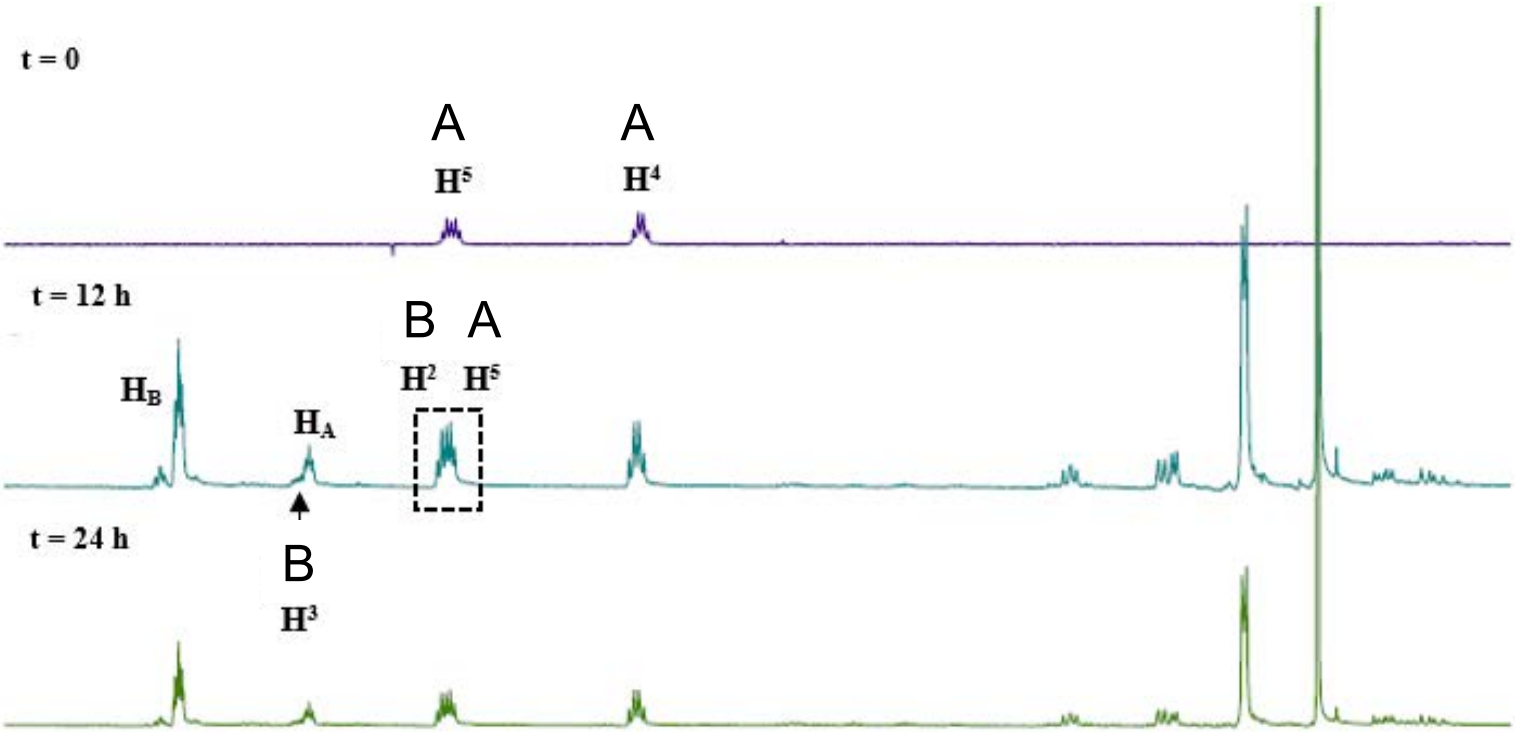
Seleniranium Crossover (Se^{II})

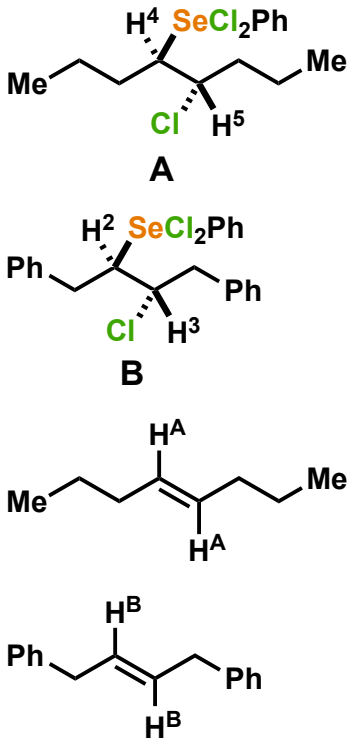


Eey, S. Catalytic, Stereospecific *Syn*-Dichlorination of Alkenes – Development of a Catalytic, Enantioselective Reaction. Postdoctoral Report, University of Illinois, 2015.

Seleniranium Crossover (Se^{IV})







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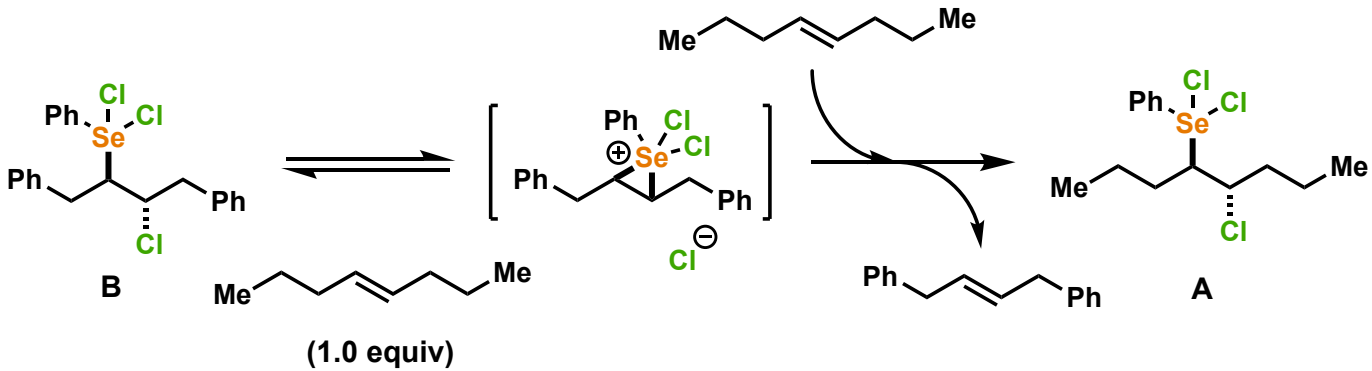
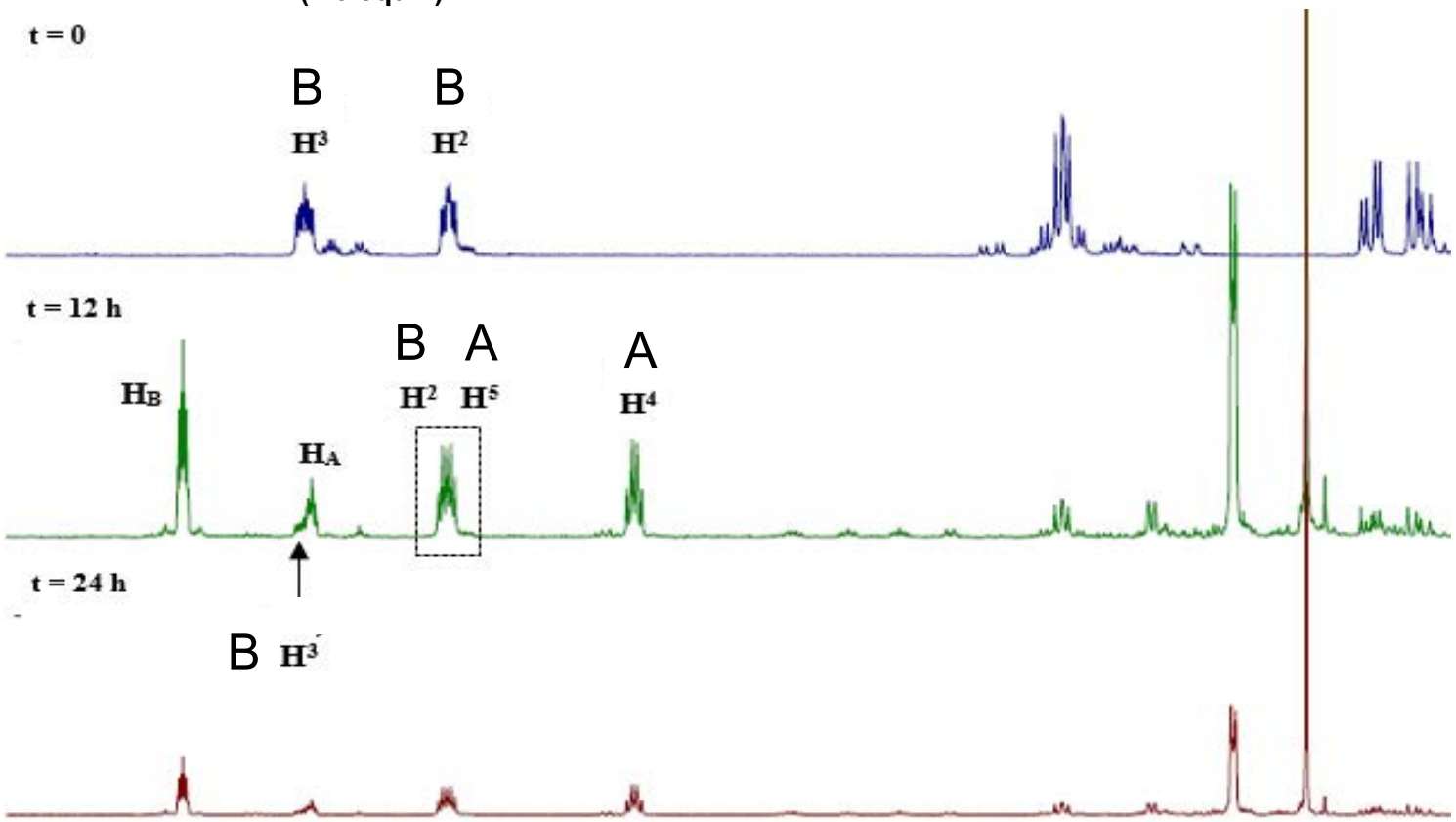
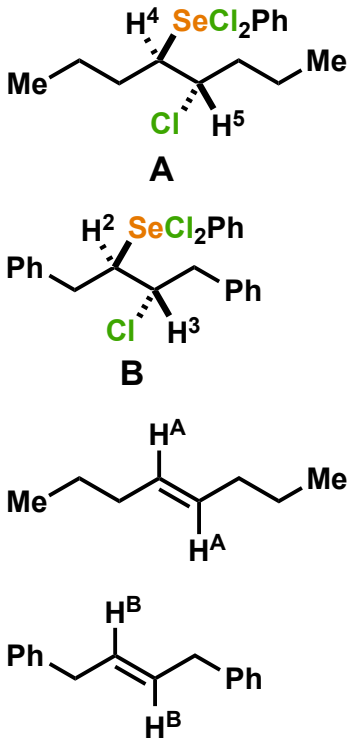
Seleniranium Crossover (Se^{IV})





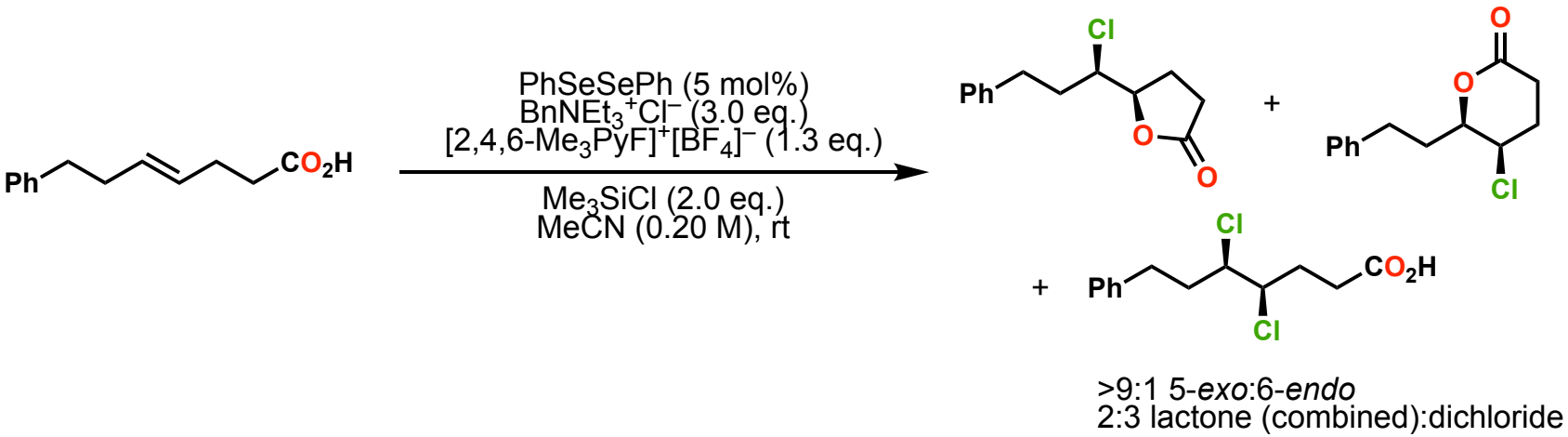


Eey, S. Catalytic, Stereospecific *Syn*-Dichlorination of Alkenes – Development of a Catalytic, Enantioselective Reaction. Postdoctoral Report, University of Illinois, 2015.

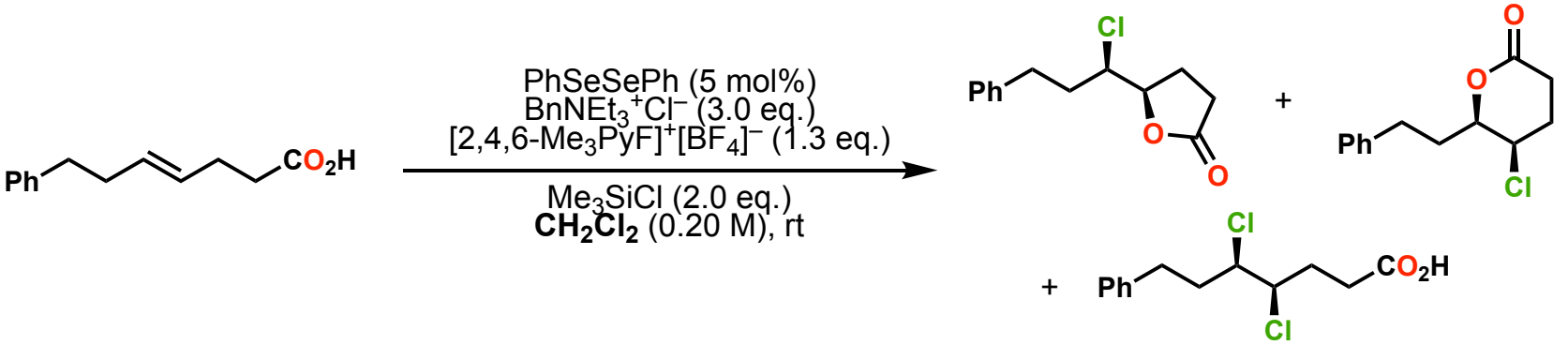
Outline

1. **Introduction**
2. **Background**
3. **Early catalysts synthesis**
4. **Later catalyst designs**
5. **Chlorolactonization**
    1. Initial hits
    2. Condition screening
    3. Final two catalysts
    4. Chloroetherification and -amination

Chlorolactonization

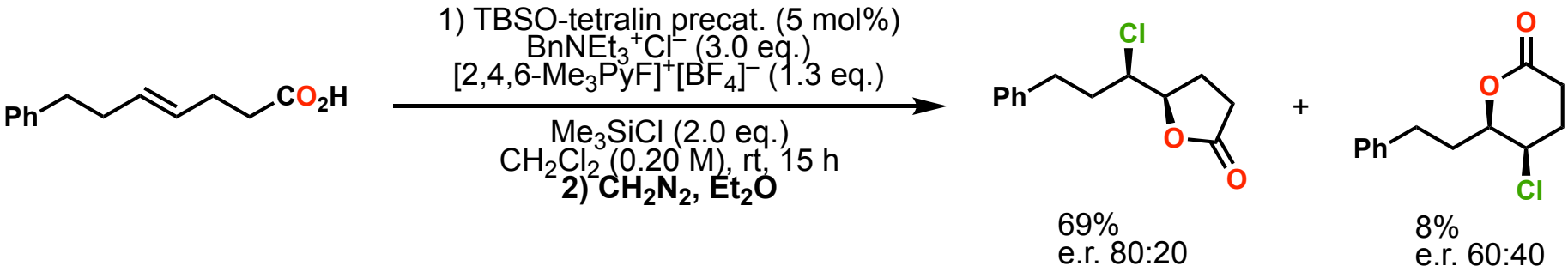


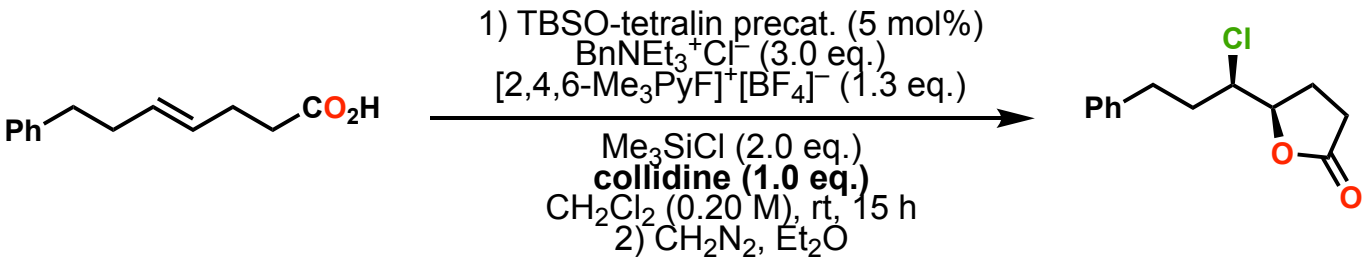
>9:1 5-*exo*:6-*endo*
2:3 lactone (combined):dichloride



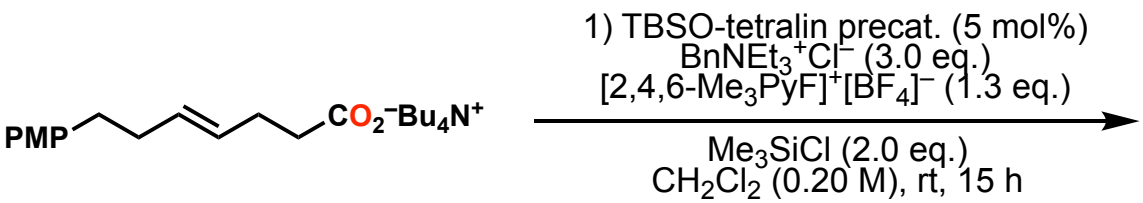
5:1 5-*exo*:6-*endo*
3:2 lactone (combined):dichloride

Chlorolactonization



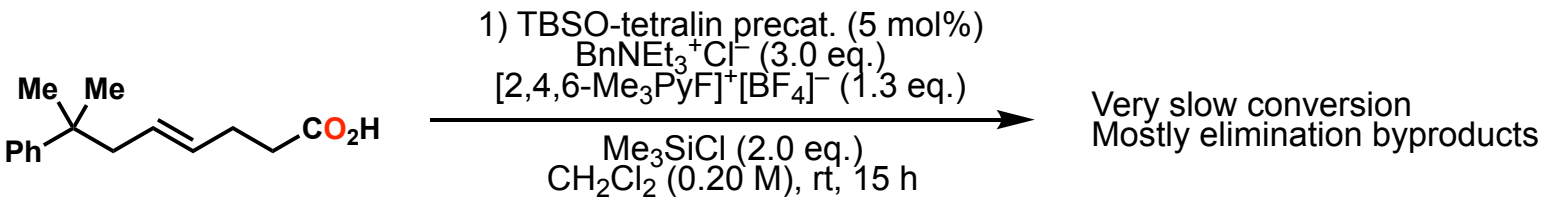


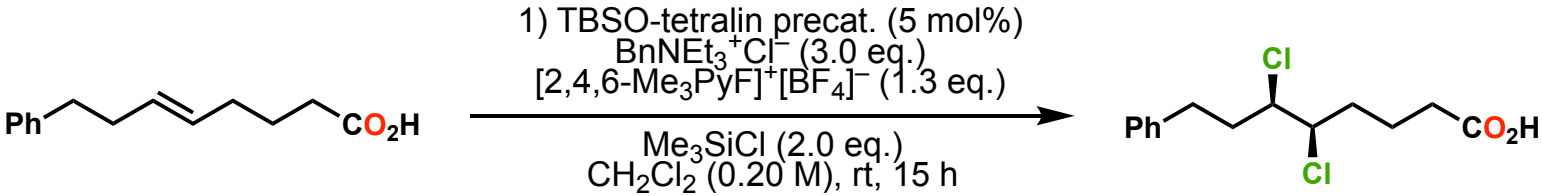
5-*exo*:6-*endo*:dichloride
75:15:10
elimination greatly increased
42% isolated
e.r. 80:20

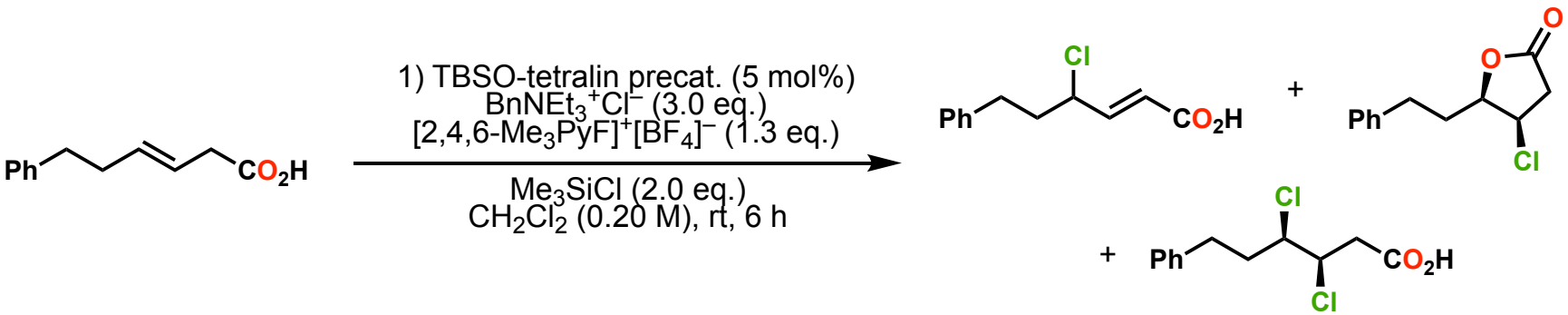


Predominately elimination byproducts

Chlorolactonization

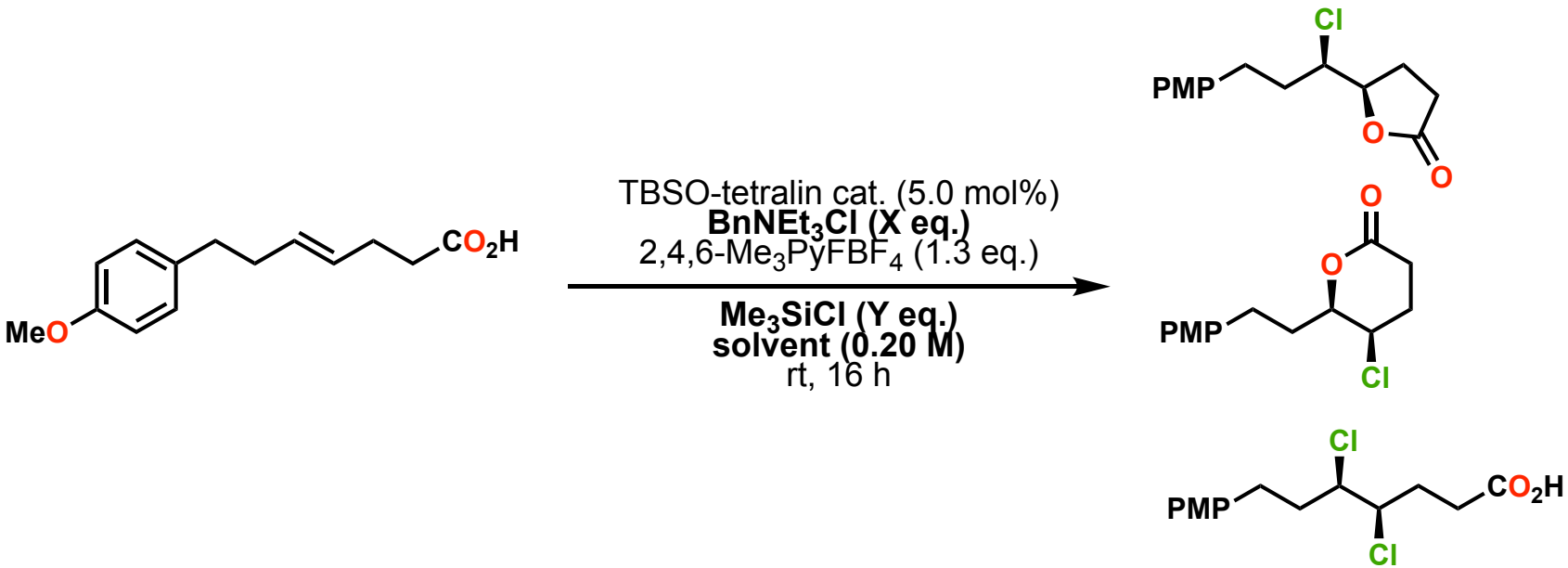






7:3:1 allylic:lactone:dichloride

DOE for Condition Screening



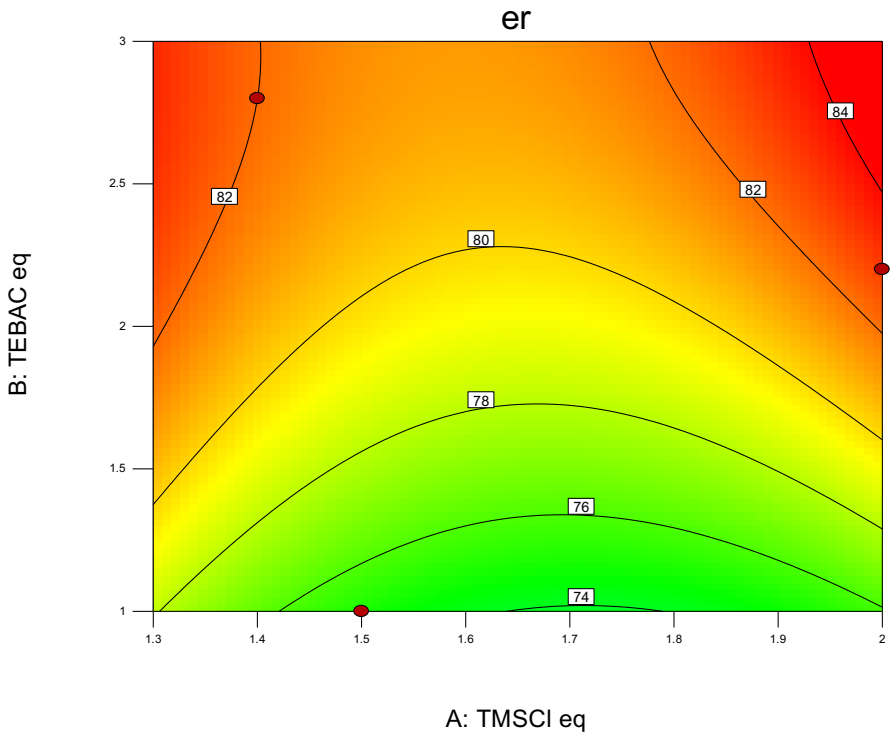
- **Selected 20 solvents**
- **Varied equivalents of $BnNEt_3Cl$ (from 1.0 to 3.0) and Me_3SiCl (from 1.3 to 2.0) in increments of 0.2**
- **73 reactions total**
- **Measured ratio of 5-*exo* to 6-*endo*, total lactone to *syn*-dichloride and enantiomeric ratio of the 5-*exo* (major) lactone product.**

DOE Results

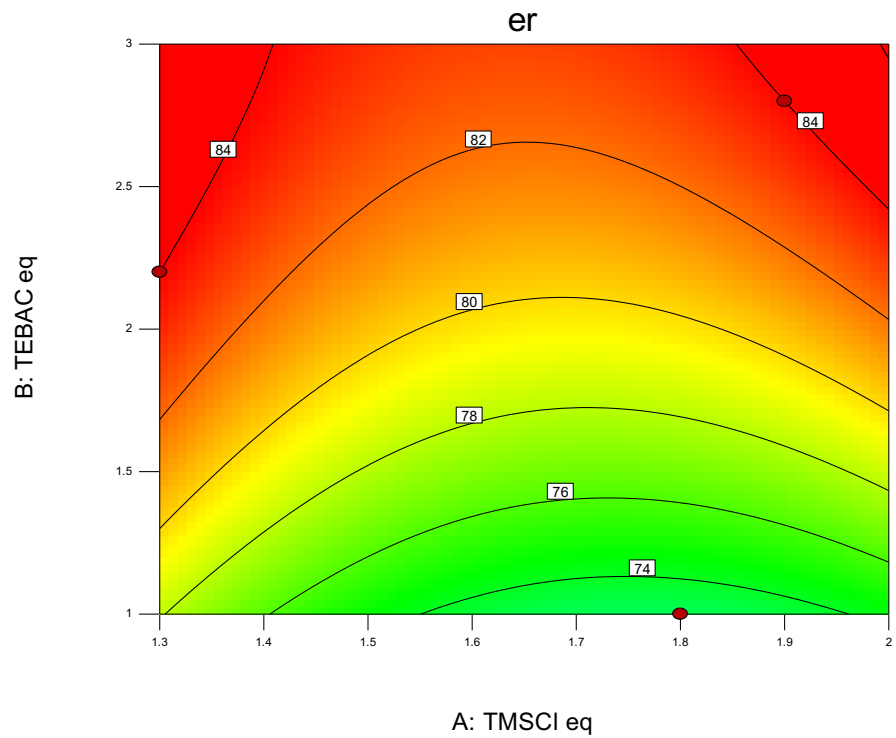
Several solvents gave no productive reaction:

- **Et_2O, DME, THF, NMP, and DMPU gave little or no conversion**
- **TFE and HFIP fully consumed the starting material but gave a complex mixture with none of the expected products**

$MeNO_2$

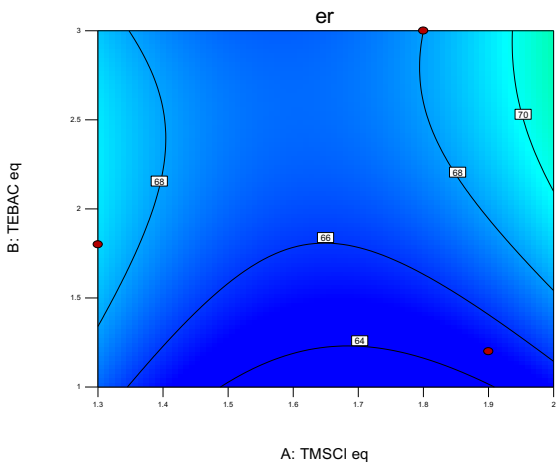


DCE

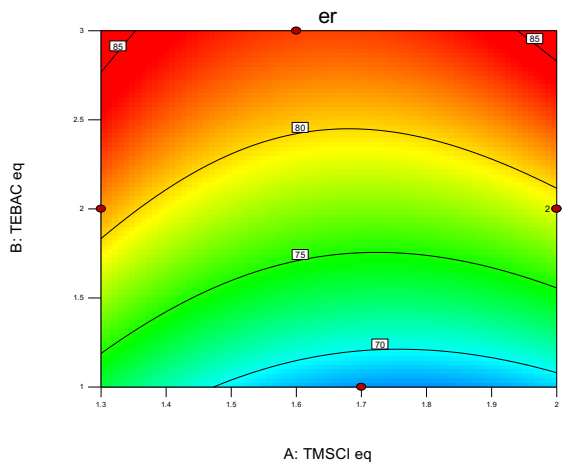


DOE Results

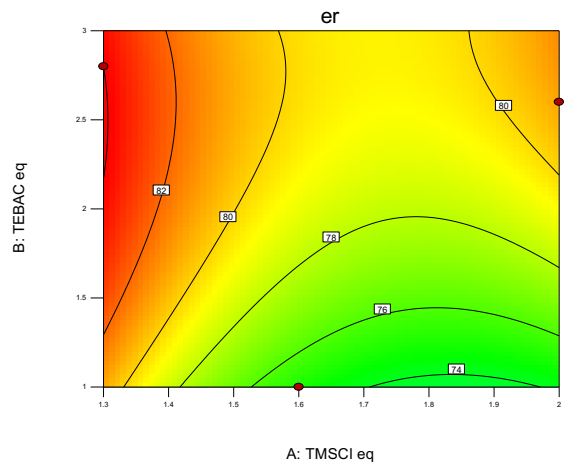
$CHCl_3$



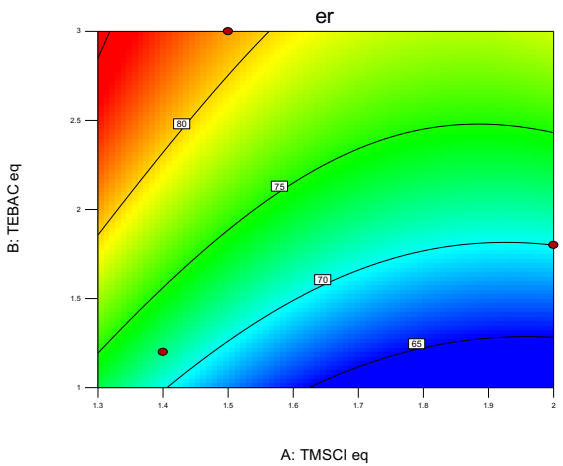
CH_2Cl_2



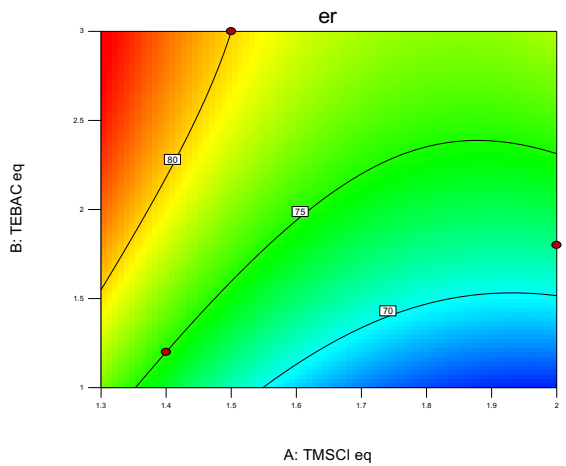
MeCN



$ClHC{=}CCl_2$

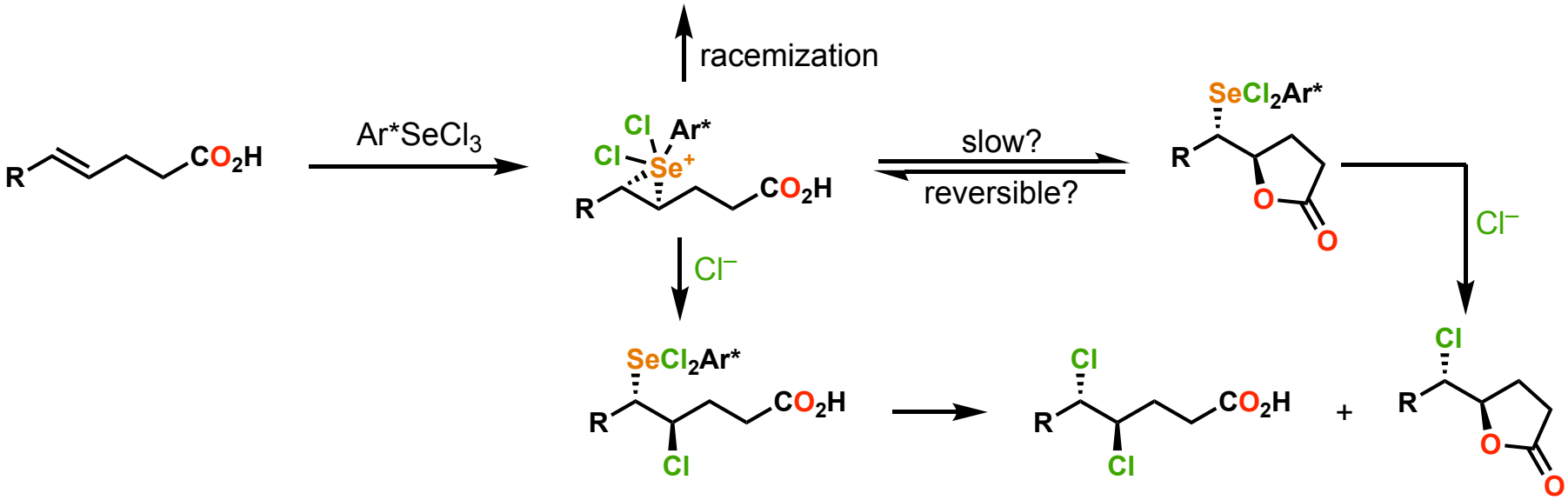


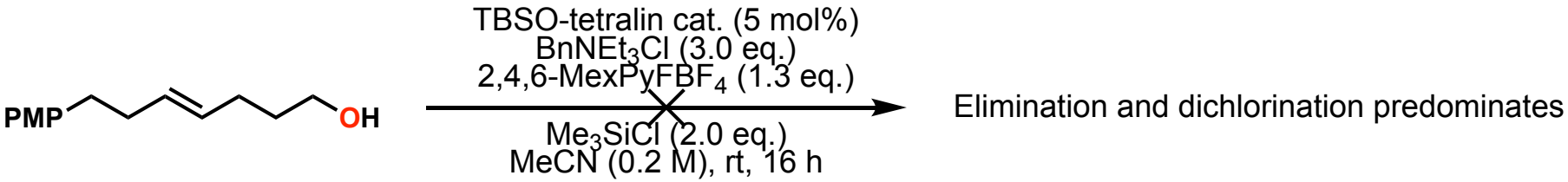
$(CH_3)_2CHCN$

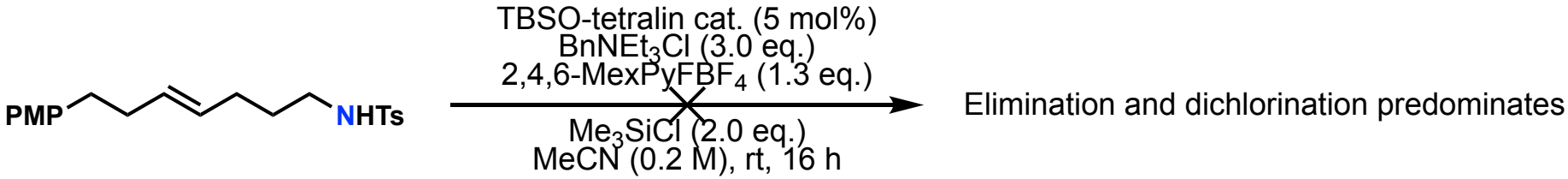


- In general, higher Cl^- loading led to higher e.r., but also greater proportion of dichloride
- Certain solvents led to better selectivities

Chloroetherification and -amination







Conclusions

- **Many of the catalysts evaluated are likely to have high intrinsic diastereoselectivity, perhaps even at room temperature, although this still needs to be tested**

- **The observed low product e.r.s (dichloride and chlorolactone) are likely the consequence of racemization by seleniranium exchange with unreacted alkene**

- **Displacement of $ArSe^{IV}Cl_2$ by Cl^- is most likely the turnover limiting step, and may also be the enantiodetermining step**

- **Future work should aim to accelerate the turnover limiting step to avoid seleniranium exchange, or to stabilize the seleniranium against exchange**