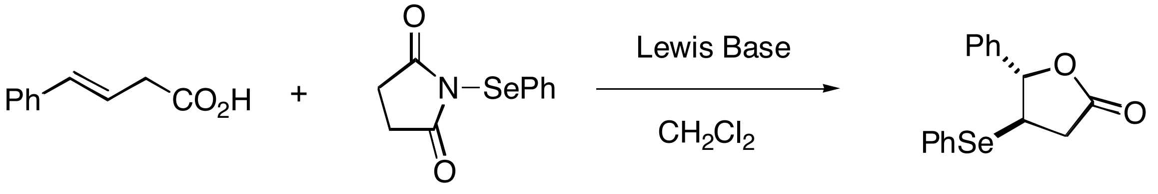
Lewis Base Activation of Lewis Acids: Development of a Lewis Base Catalyzed Selenolactonization

Denmark, S.E. and Collins, W.R. *Org. Lett.* **2007**, *9*, 3801-3804.



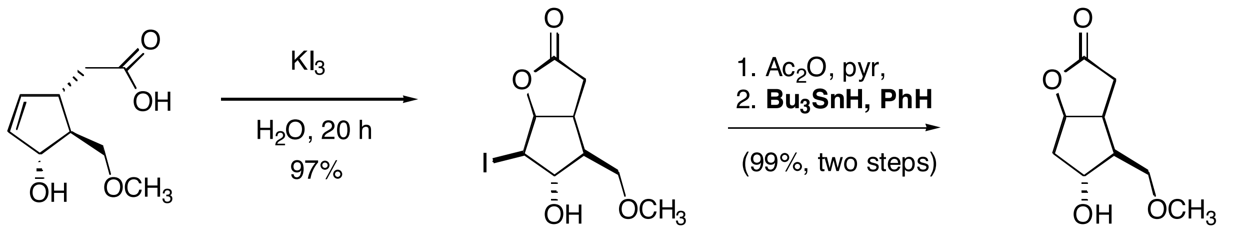
Presented by:
Melissa Sprachman
October 27, 2007

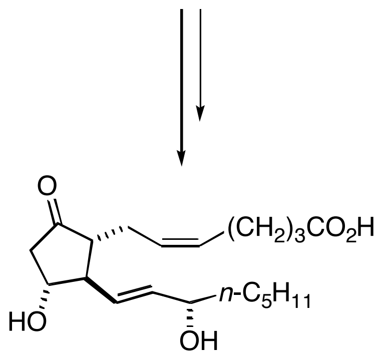
Lactonization Reactions

Halolactonization:

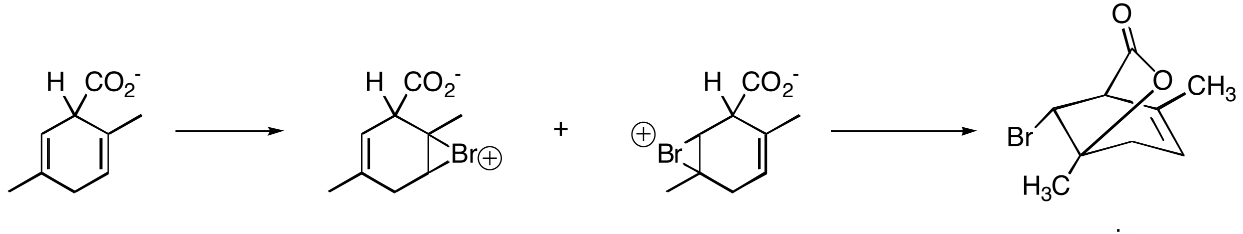
Corey's Prostaglandin Synthesis

J. Am. Chem. Soc. **1970**, *92, 397.*





Mechanism-- Markovnikov Addn:

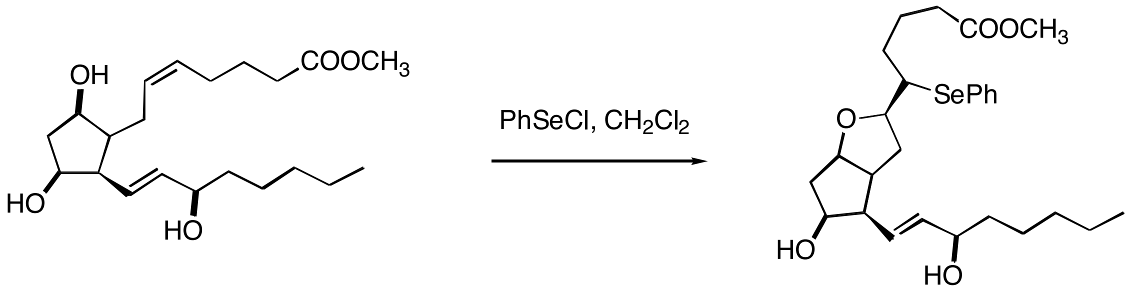


J. Org. Chem. **1975**, *40*, 2843.

Selenolactonization:

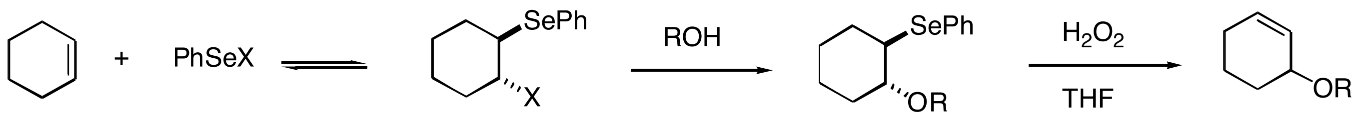
Nicolaou's Prostaglandin Synthesis

J. Am. Chem. Soc. **1981**, *103*, 3480.



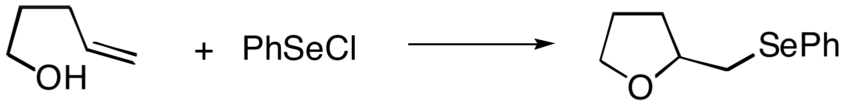
Development of Organoselenium Chemistry

Sharpless: Preparation of Allylic Alcohols:



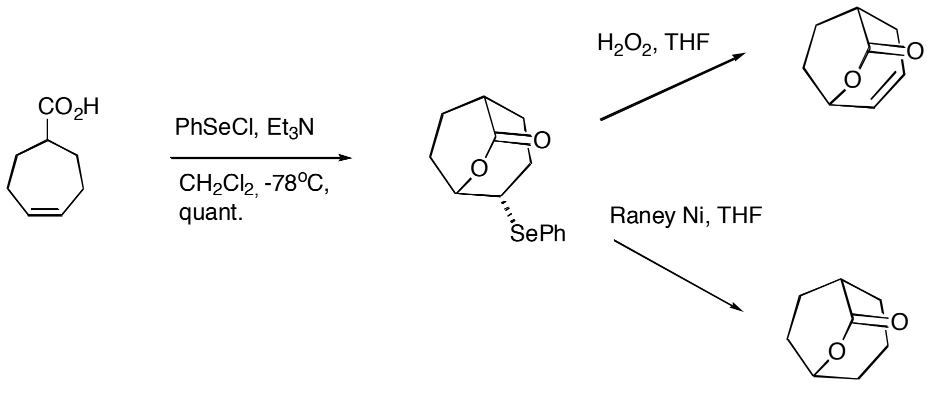
J. Org. Chem. **1974**, *39*, 429.

Campos, Clive: Cyclofunctionalization:



J. Chem. Soc. Chem. Commun. **1977**, 725.

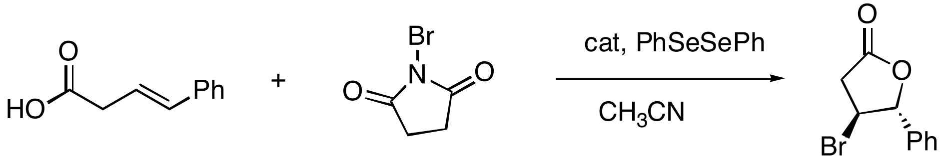
Clive, Nicolaou: Selenolactonization:

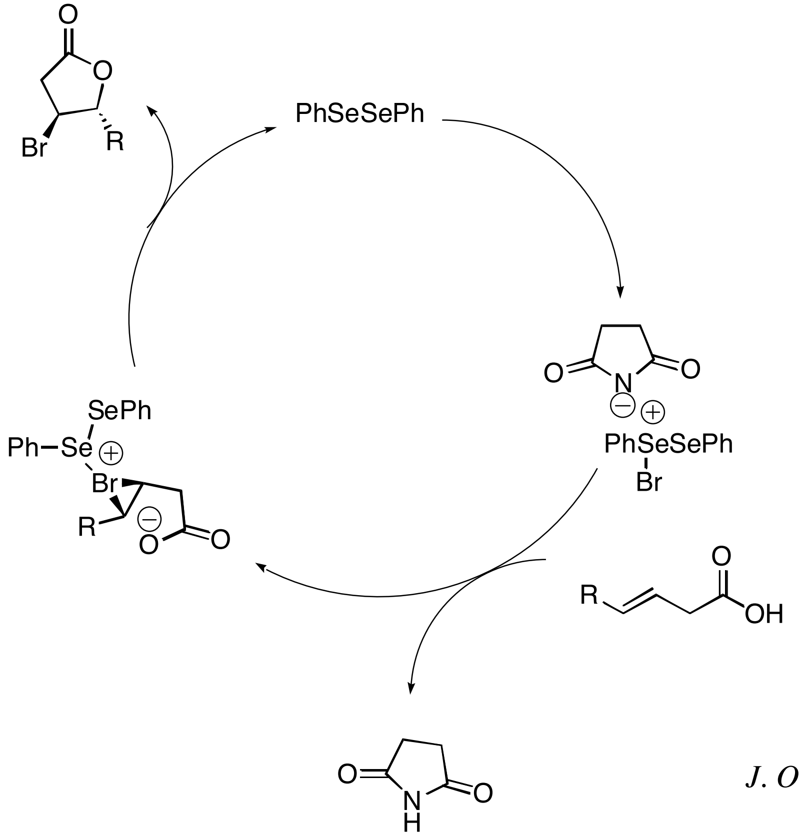


J. Am. Chem. **1977,** *99*, 3185.

Recent Developments in Selenium Chemistry

Selenium catalyzed halolactonization:

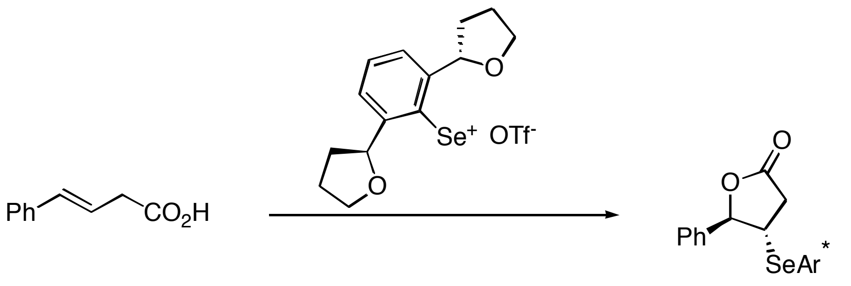




J. Org. Chem. **2004**, *69*, 8979.

Developments in Selenium Chemistry

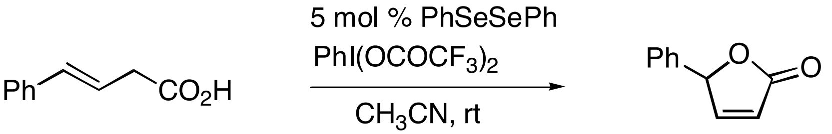
Use of Enantiopure Selenium Reagents:

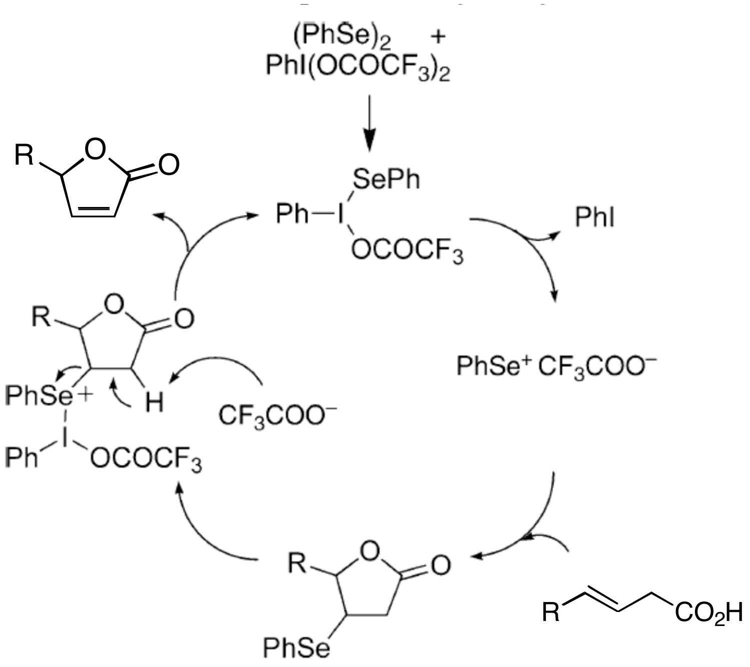


99 % *de*, 62% yield

Tetrahedron Lett. **1997**, *38*, 4753.

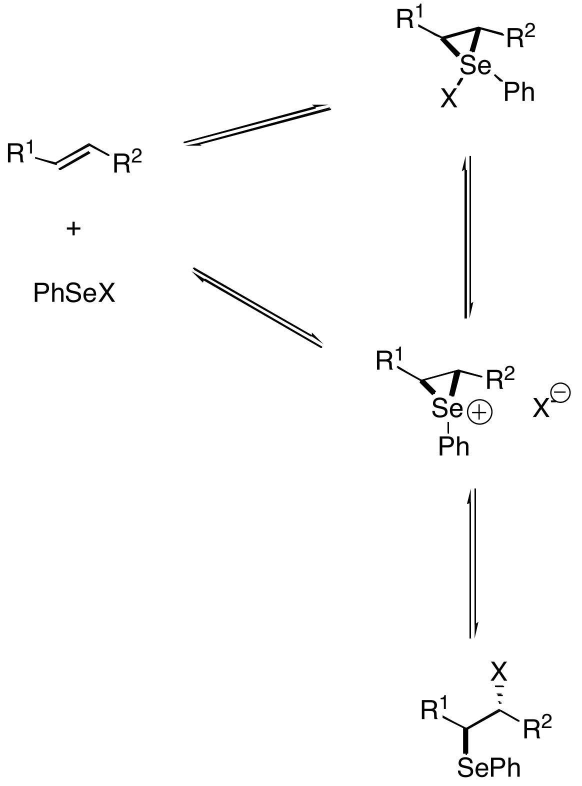
Catalytic Use of Selenium Electrophiles:





Org. *Lett*. **2007**, *9*, 3169.

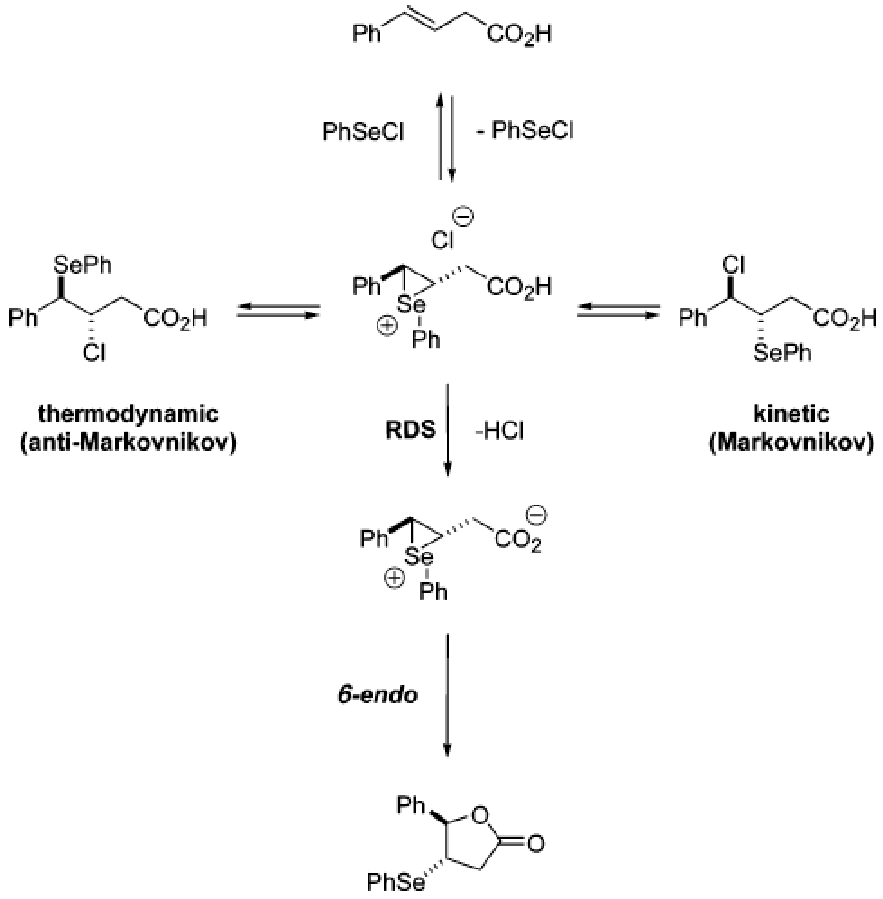
Initial Studies on the Mechanism of Selenolactonization



--Based on initial observation of stereospecific anti-addition of benzenesleneyl halides to alkenes

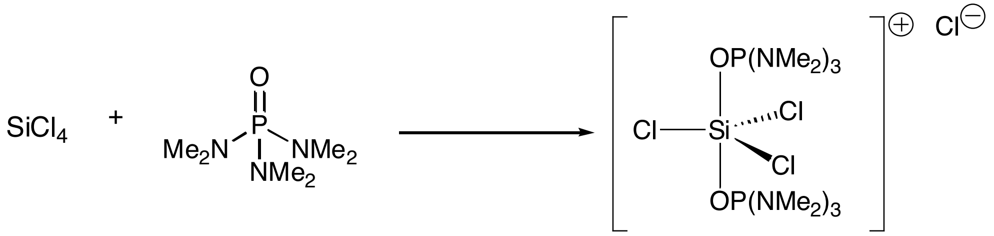
--Both the episelenurane and the seleniranium ion have been isolated and characterized

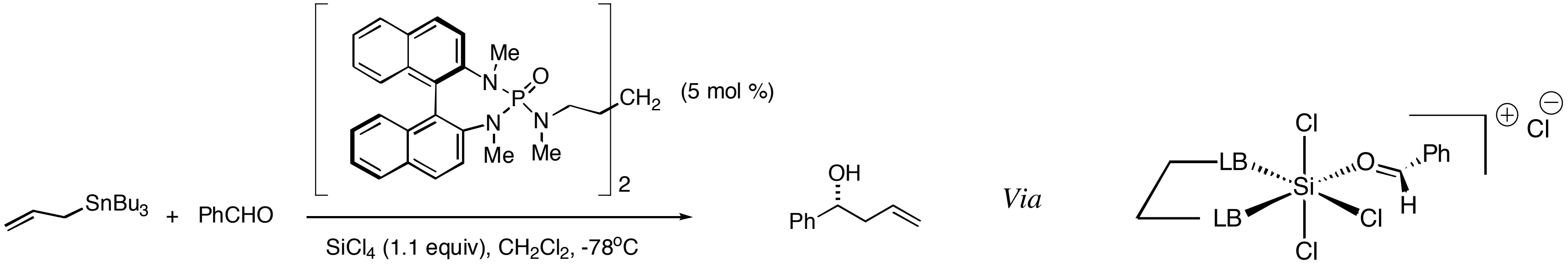
Proposed Mechanism of Selenocyclization:



Denmark et al. *J*. *Org*. *Chem*. **2006**, *71*, 7293

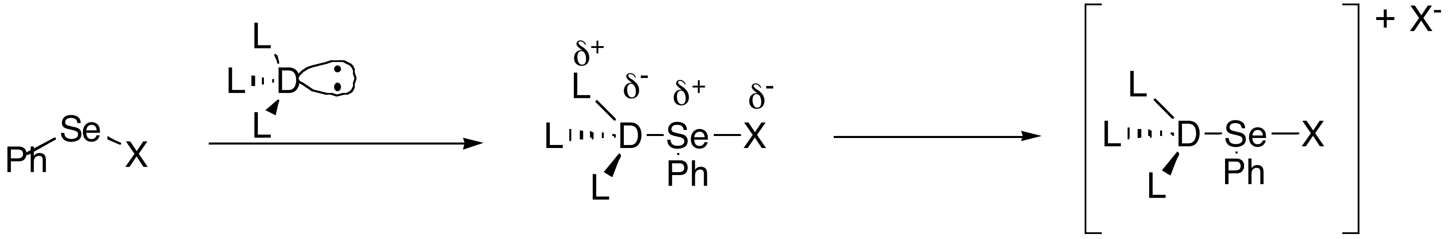
Lewis Base Activation of Lewis Acids





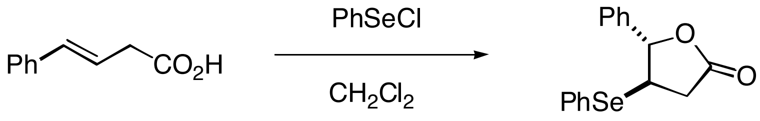
Denmark, S. E. in *Modern Aldol Reactions;* Marhwalk, R., Ed.: Wiley-VCH: Weinheim, 2004

Activation of a Selenium Electrophile?



Development of a Lewis Base Promoted Selenolactonization

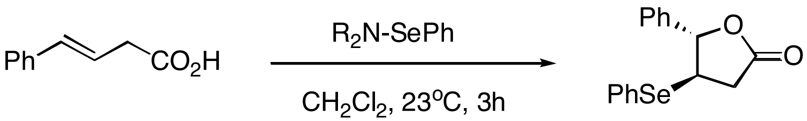
Initially studied reaction:

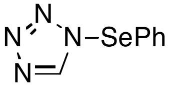
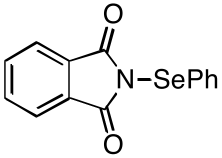
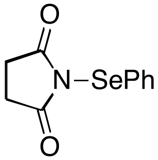


--Benzeneselenyl chloride reacts with olefins spontaneously at cryogenic temperatures

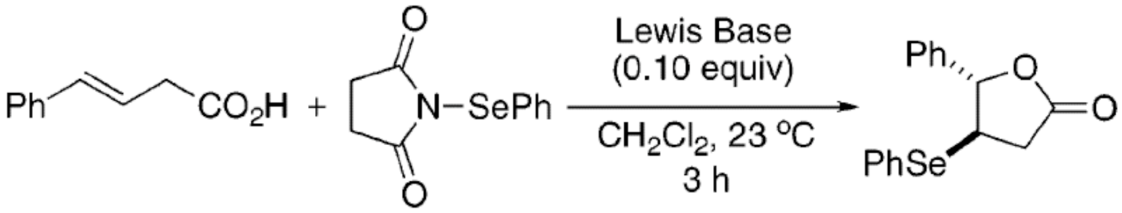
--Competitive pathways of seleniranium ion trapping and reversible formation of seleniranium ion exist

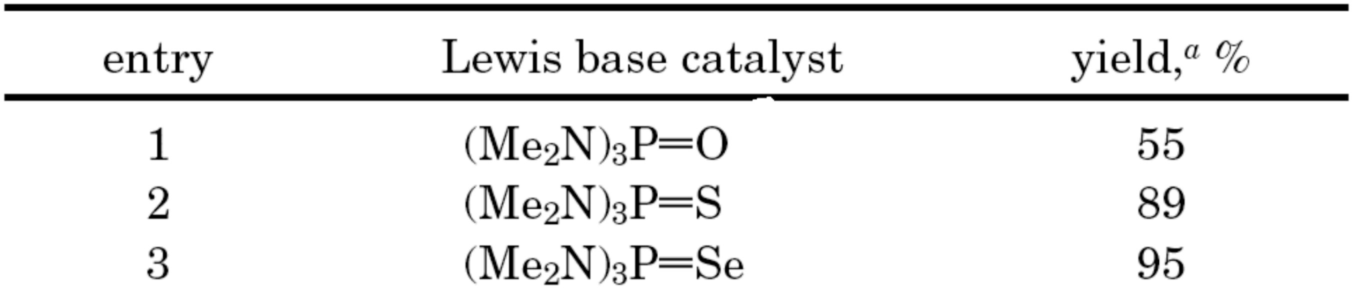
---> Choice of Leaving Group is Critical



Selenamide	Yield of Selenolactone (%)
	87
	79
	18
	8

Finding a Feasible Lewis Base Activator

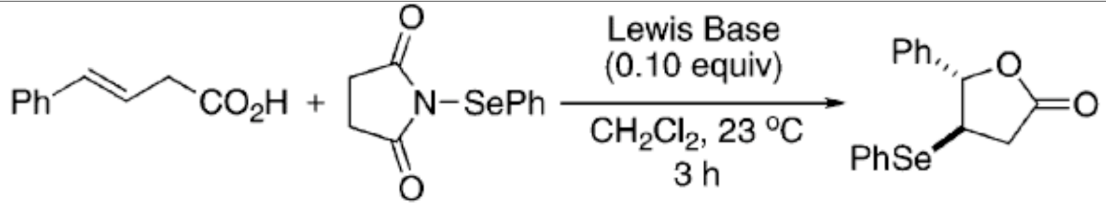


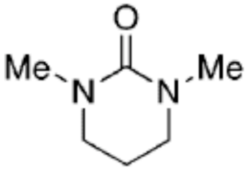
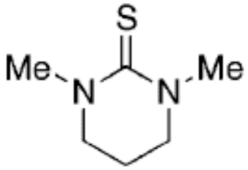


entry	Lewis base catalyst	yield,[a] %
1	$(Me_2N)_3P{=}O$	55
2	$(Me_2N)_3P{=}S$	89
3	$(Me_2N)_3P{=}Se$	95

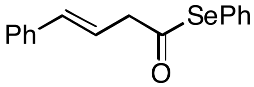
**Use of softer chalcogens enhanced reaction efficiency: Reaction times ranged from 3 h with HMPA to 10 min with thiophosphoramide to < 5 min with selenophosphoramide!

Survey of Lewis Bases

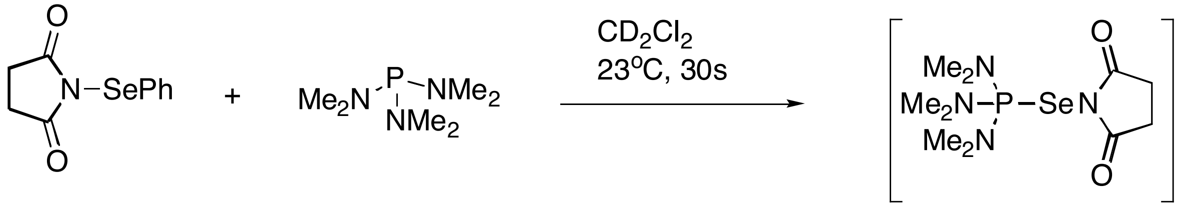


entry	Lewis Base	yield %
1	$Ph_3P{=}O$	6
2	$(Cy)_3P{=}O$	20
3		51
4	$Ph_3P{=}S$	93
5	$(Cy)_3P{=}S$	88
6		87
7	$(Me_2N)_3P$	92
8	$(PhO)_2(Me_2N)P$	0
9	$(PhO)_3P$	0

--> Isolated ~10% Selenol ester



Mechanistic Insight: Observation of an HMPT-Selenium Adduct

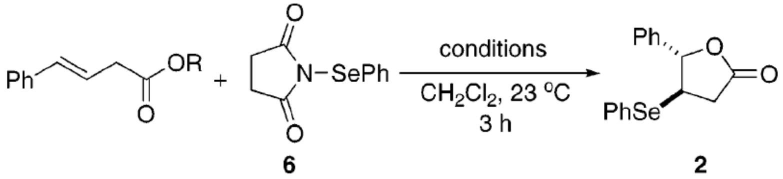


Prior to Olefin Coordination Either…

1.) Ionization of the N-Se bond to form a contact ion pair or

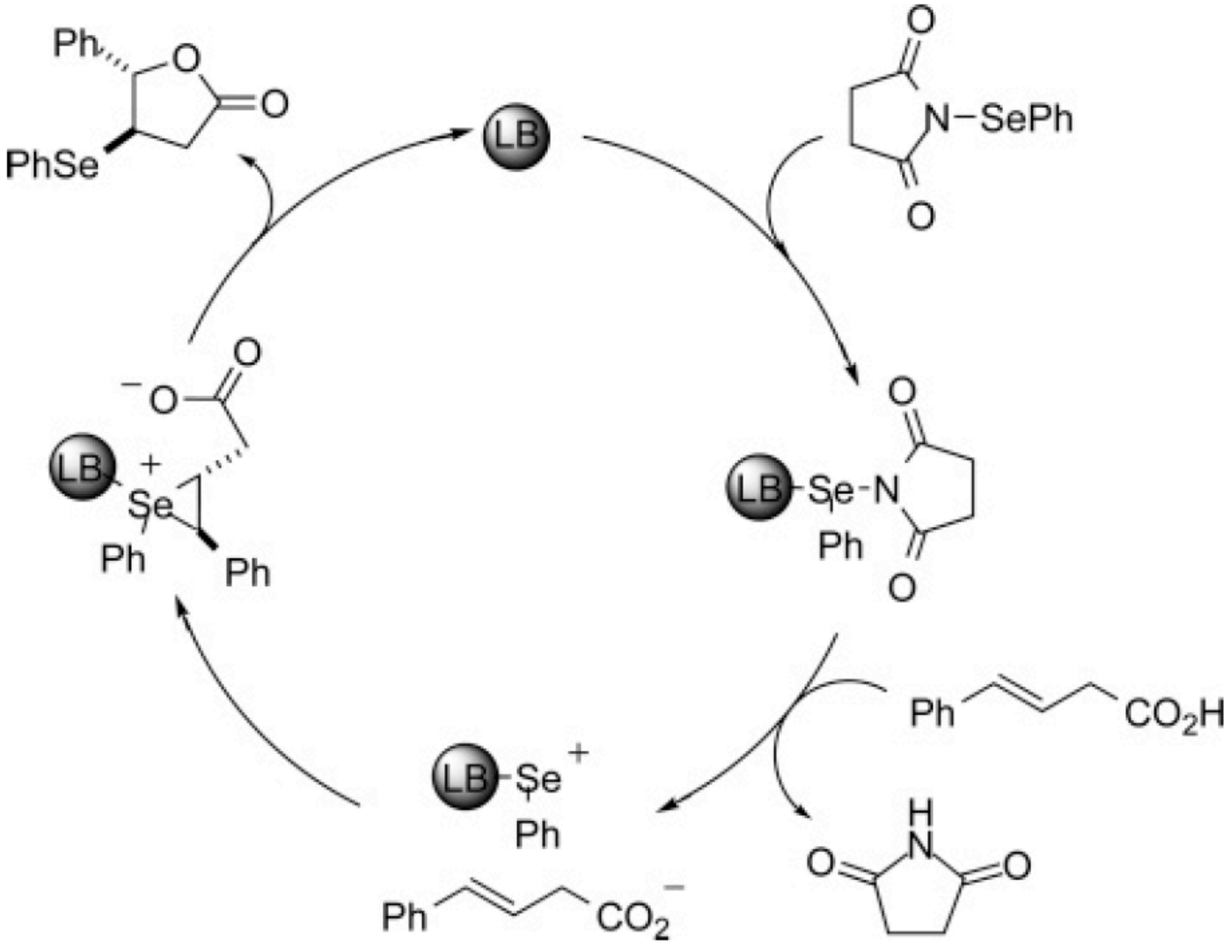
2) Activation of the succinimide LG to form a selenium cation

Role of the Carboxylate Proton:

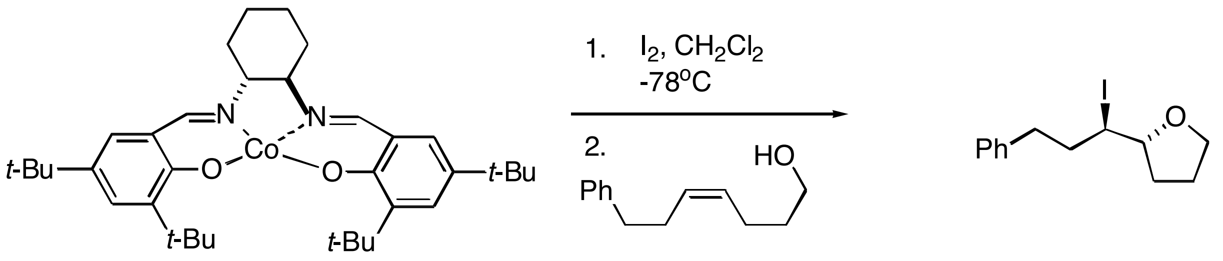


entry	R	conditions	yield,[a] %
1	H (**1**)	1.0 equiv of DTBMP, 0.1 equiv of $(Me_2N)_3P{=}Se$	0
2	$SiMe_3$ (**15**)	0.1 equiv of $(Me_2N)_3P{=}Se$	0
3	$SiMe_3$ (**15**)	1.0 equiv of AcOH	13
4	$SiMe_3$ (**15**)	1.0 equiv of AcOH, 0.1 equiv of $(Me_2N)_3P{=}Se$	91

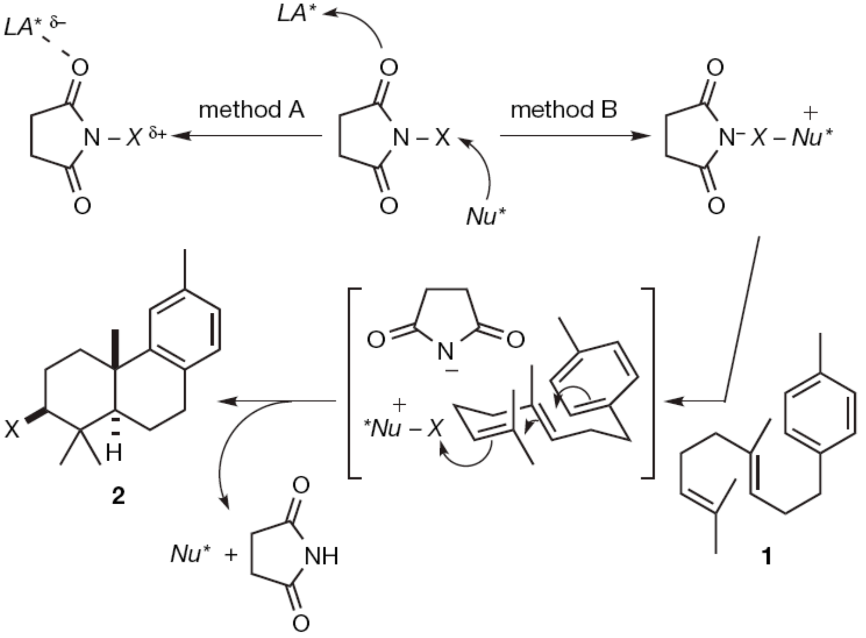
Postulated Catalytic Cycle Based on Collective Data



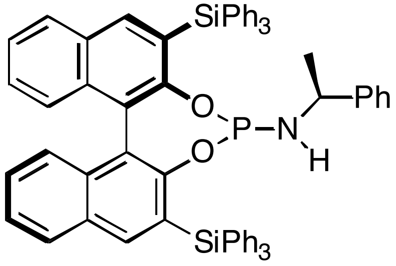
Recent Developments in Electrophile-Promoted Cyclizations



J. Am. Chem. Soc. **2003**, *125*, 15748.



Nu* =



Nature, **2007**, *445*, 900.

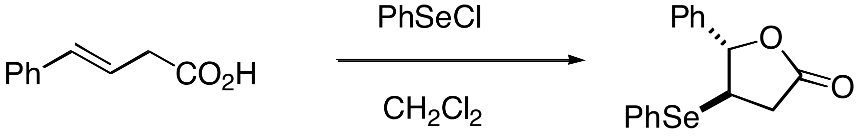
Summary and Outlook

-- Lewis base catalyzed selenolactonization was performed, and viable proof for reaction intermediates was established.

--The successful suppression of the background reaction and rapid turnover rate make asymmetric modifications a possibility.

-- The inherent toxicity of selenium may prove a barrier in the overall utility of these transformations; however, the concept of Lewis base activation of electrophiles is worthwhile.

Development of a Lewis Base Promoted Selenolactonization



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