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ARTICLES

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nature chemistry

Catalytic, stereospecific *syn*-dichlorination of alkenes

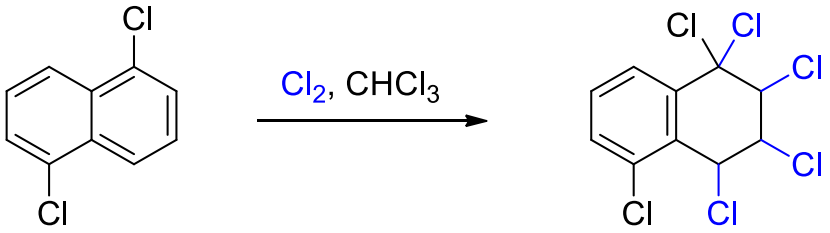
Alexander J. Cresswell†, Stanley T.-C. Eey† and Scott E. Denmark*

Vivek S. Raut

RCC meeting

04 June 2015

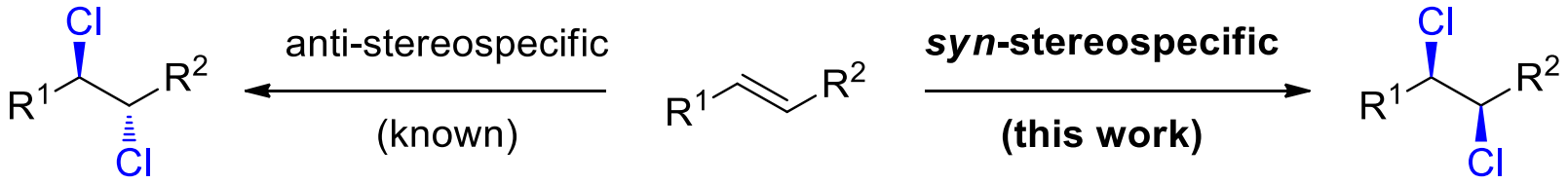
Back ground



1,5-dichloronaphthalene

A . Atterberg and O. Widman *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1841–1844.

- Cl_2 generated in situ such as H_2O_2–HCl, $KMnO_4$–Me_3SiCl–$BnEt_3NCl$ (Markó–Maguire reagent) and Oxone-NaCl
- Some milder and more practical electrophilic chlorinating agents like SO_2Cl_2, $PhICl_2$, Et_4NCl_3 (Mioskowski's reagent), NCS-PPh_3 (Yoshimitsu's reagent)



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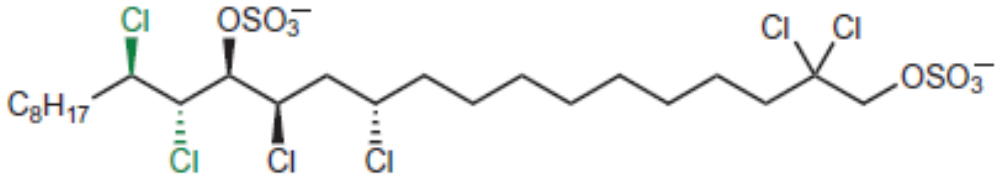
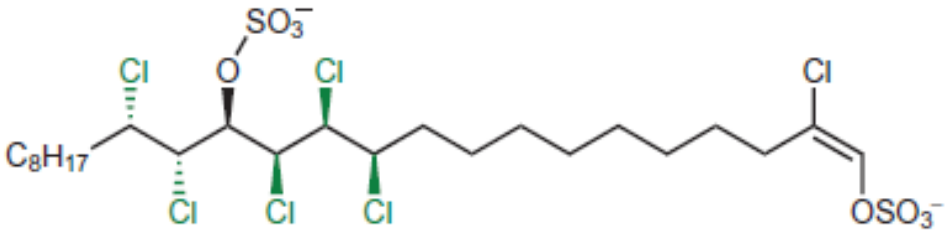
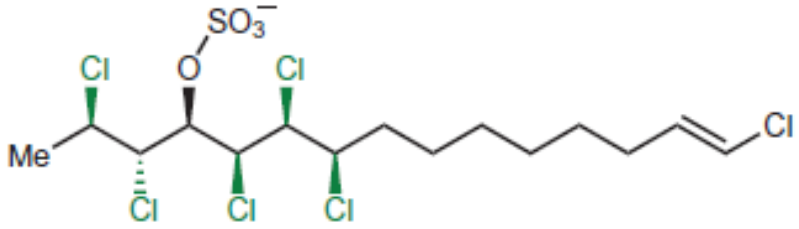


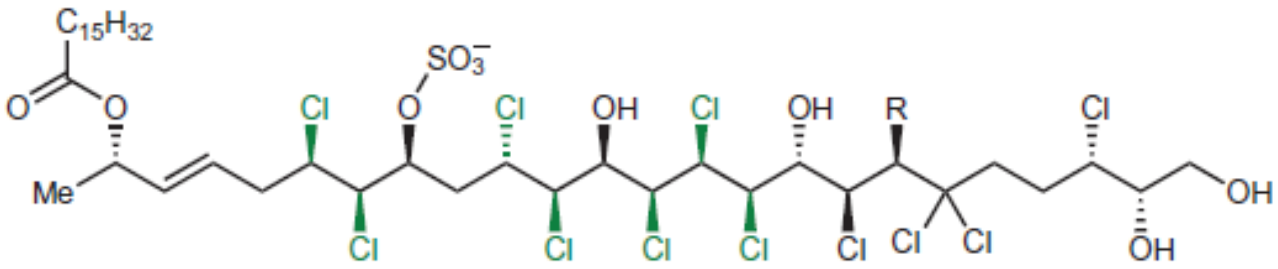
Danicalipin A (**1**)



Malhamensilipin A (**2**)



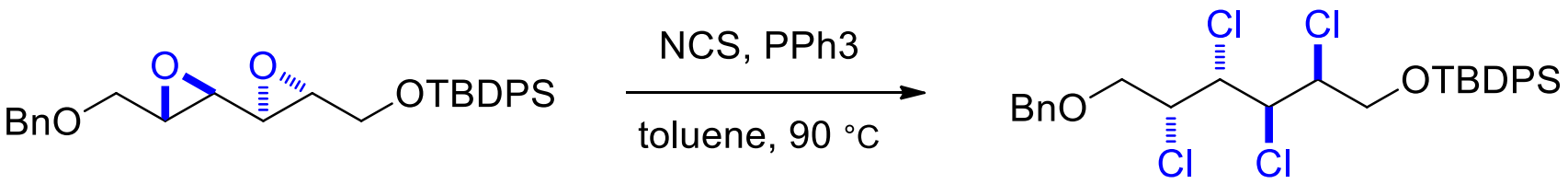
Mytilipin A (**3**)



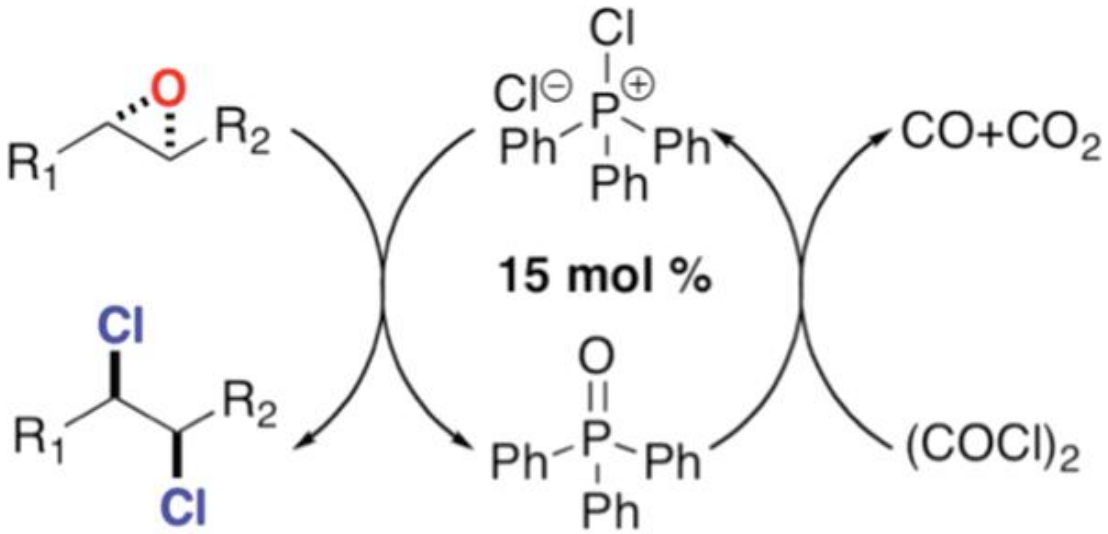
Mytilipin B (R = OH) (**4**)
Mytilipin C (R = H) (**5**)

Chlorosulfolipids: a class of stereochemically complex, polychlorinated natural products isolated from marine sources

Back ground



T. Yoshimitsu, N. Fukumoto and T. Tanaka *J. Org. Chem.* **2009**, *74*, 696–702.



R. Denton, X. Tang and A. Przeslak *Org. Lett.* **2010**, *12*, 4678–4681.

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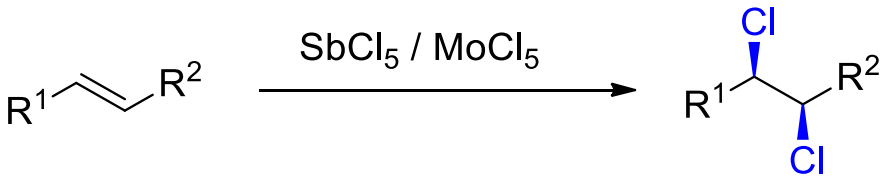
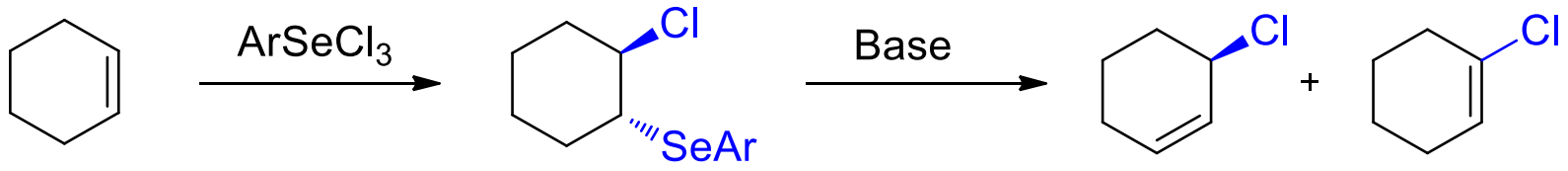
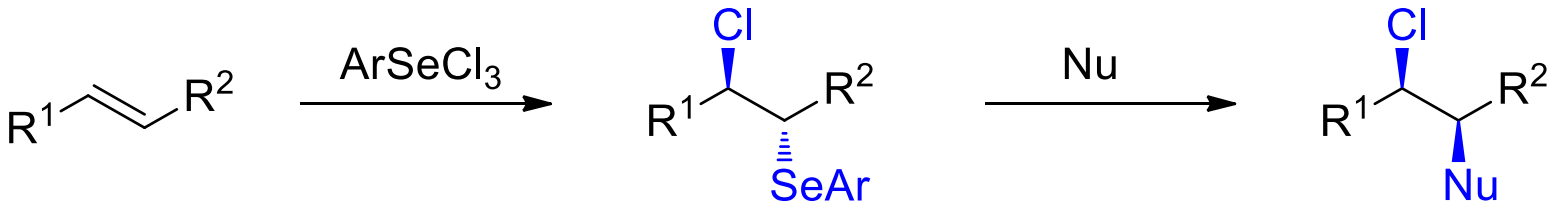


S. Uemura, A. Onoe and M. Okano *Bull. Chem. Soc. Jpn* **1974**, 47, 692–697, J. S. Jr San Filippo, A. F. Sowinski and L. J. Romano, *J. Am. Chem. Soc.* **1975**, *97*, 1599–1600, W. A. Nugent, *Tetrahedron Lett.* **1978**,*19*, 3427–3430.

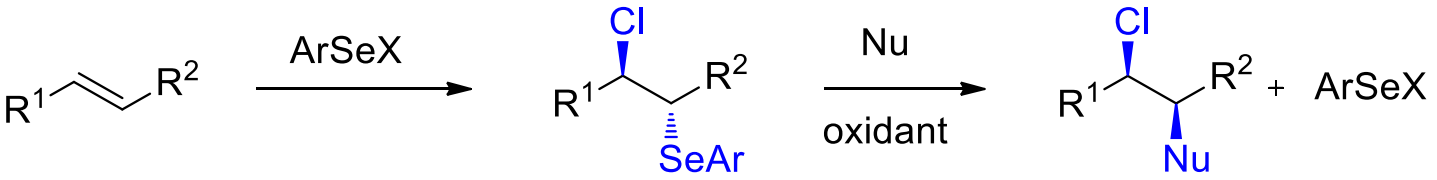


D. G. Garratt, and G. H. Schmid, *Can. J. Chem.* **1974**, *52*, 3599–3606, L. Engman, *J. Org. Chem.* **1987**, 52, 4086–4094.



T. Hori and K. B. Sharpless, J. Org. Chem. **1979**, *44*, 4204–4208, A. M Morella and D. A. Ward, Tetrahedron Lett. **1984**, *25*, 1197–1200, A. M Morella and D. A. Ward Tetrahedron Lett. **1985** 26, 2899–2900, C. Paulmier, *Phosphorus Sulfur Silicon Relat. Elem.* **2001**, *172*, 25–54.

Back ground



Oxidant

- it must not react (or must react only very slowly) with the alkene substrate
- it must not oxidize chloride ions to molecular Cl_2 or any other active 'Cl+' equivalent over the timescale of the reaction
- it must not contain or release nucleophiles that might outcompete chloride in the reaction
- it must not lead to the formation of selenoxide intermediates that are capable of rapid *syn*-elimination

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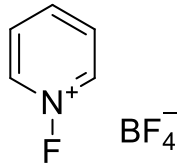
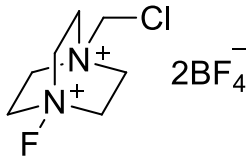


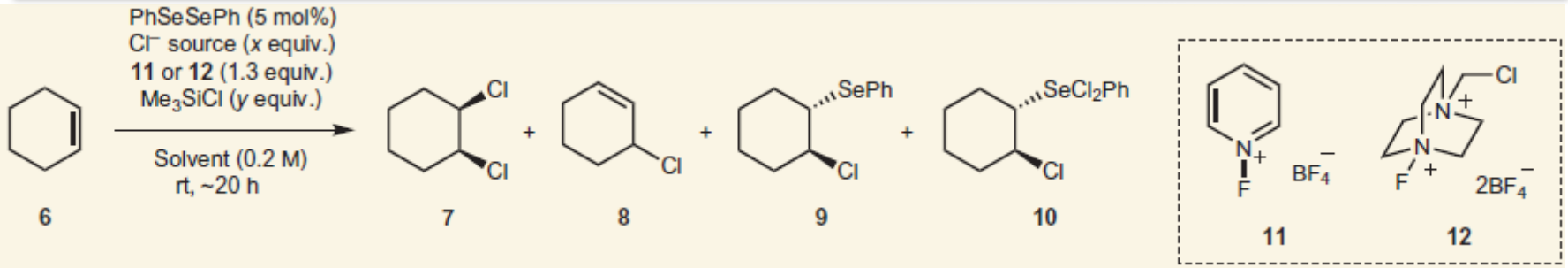
N-fluoropyridinium
tetrafluoroborate
CAS# 107264-09-5



Selectfluor
CAS# 140681-55-6

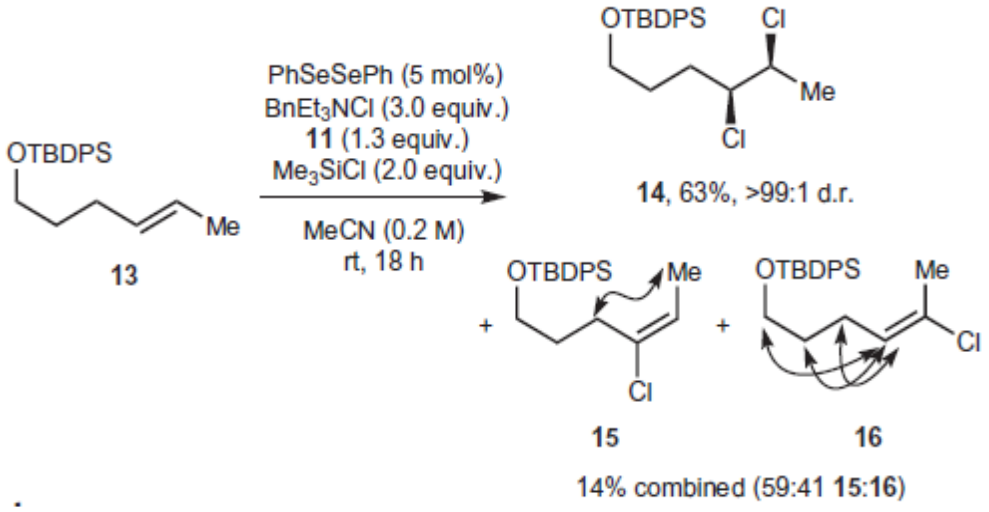
K. M. Engle, T-S. Mei, X. Wang, and J-Q. Yu *Angew. Chem. Int. Ed.* **2011**, *50*, 1478–1491.

Reaction development with cyclohexene

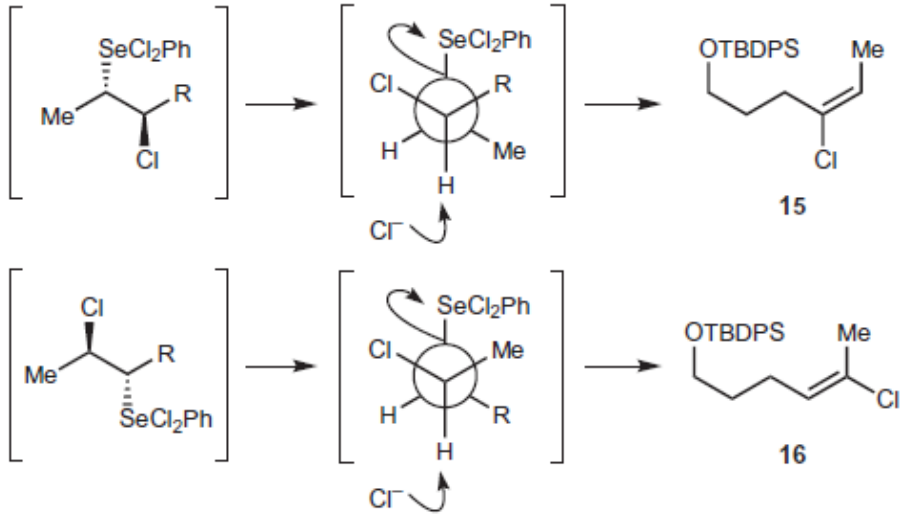


Sr.	Cl⁻ source (equiv.)	Oxidant	Me_3SiCl (equiv.)	Solvent	NMR yield (%)				
					6	7	8	9	10
1	*n*-Bu_4NCl (3.0)	11	0.0	MeCN-d_3	50	19	3	9	0
2	*n*-Bu_4NCl (3.0)	11	1.0	MeCN-d_3	12	61	10	10	0
3	***n*-Bu_4NCl (3.0)**	**11**	**2.0**	**MeCN-d_3**	**0**	**81**	**10**	**0**	**0**
4	*n*-Bu_4NCl (3.0)	11	3.0	MeCN-d_3	0	81	8	0	0
5	*n*-Bu_4NCl (2.5)	11	2.0	MeCN-d_3	0	74	10	0	0
6	*n*-Bu_4NCl (0.0)	11	2.0	MeCN-d_3	54	0	2	0	8
7	*n*-Bu_4NCl (3.0)	11	2.0	CD_2Cl_2	0	73	12	4	0
8	*n*-Bu_4NCl (3.0)	11	2.0	THF-d_8	55	17	2	0	0
9	*n*-Bu_4NCl (3.0)	12	2.0	MeCN-d_3	0	71	10	0	0
10	**$BnEt_3NCl$ (3.0)**	**11**	**2.0**	**MeCN-d_3**	**0**	**83**	**10**	**0**	**0**

E2 elimination by-products

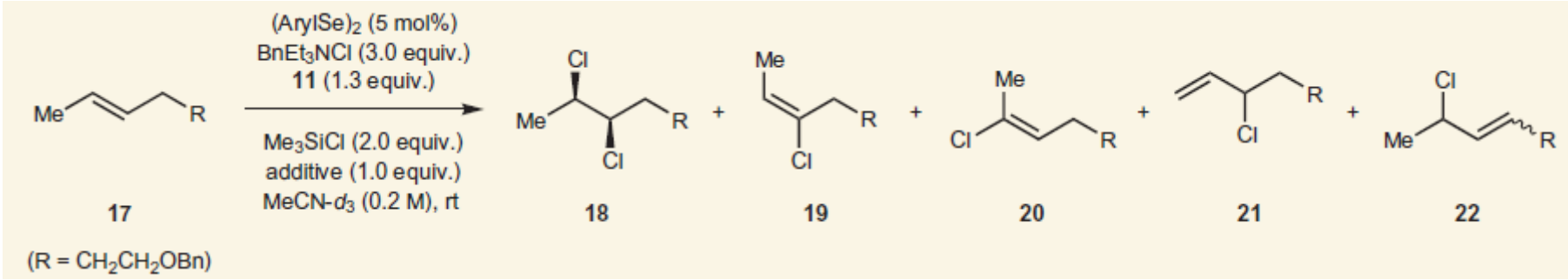


Formation of vinylic chloride by-products 15 and 16 from the dichlorination of alkene 13 and determination of their configurations



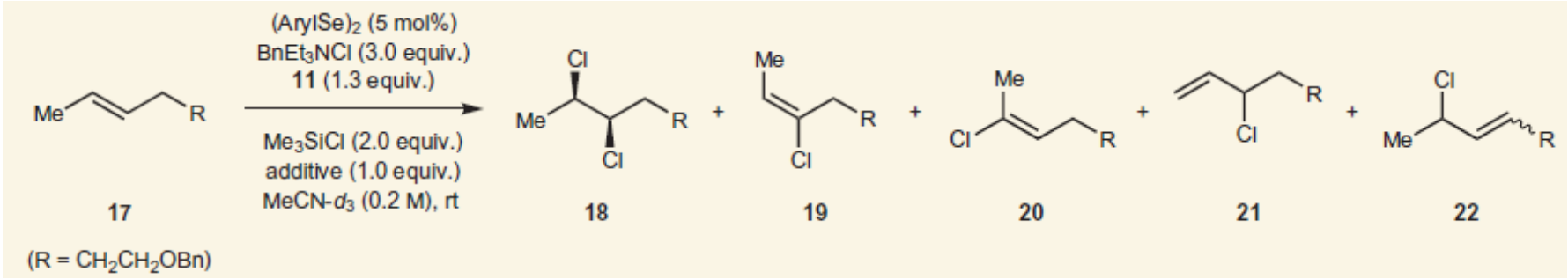
Mechanistic rationale for the formation of vinyl chlorides 15 and 16 from constitutionally isomeric anti-chloroselenylated intermediates via antiperiplanar elimination.

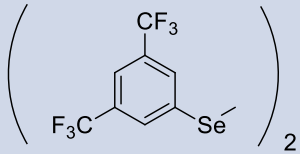
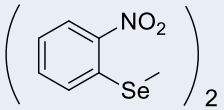
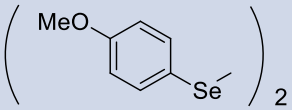
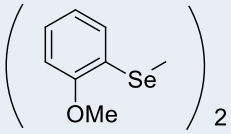
Reaction development with (E)-1-benzyloxy-4-hexene



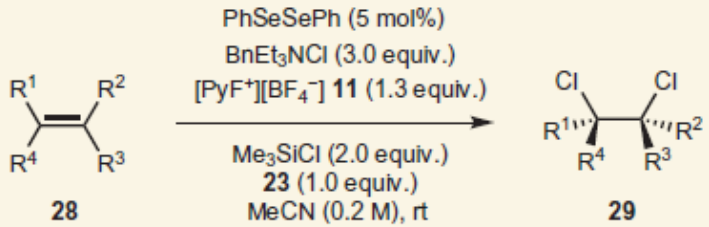
Sr. No.	$(ArylSe)_2$	Additive	Time (h)	**18**:(**19** + **20** + **21** + **22**)	**18** d.r.
1	PhSeSePh	--	6	80:20	99:1
2	PhSeSePh	Sulfolane	2	80:20	99:1
3	PhSeSePh	HMPA	3	82:18	98:2
4	PhSeSePh	DMPU	3.5	80:20	98:2
5	PhSeSePh	DMI	2.5	80:20	99:1
6	PhSeSePh	Ph3P=O	3.5	80:20	98:2
7	PhSeSePh	Pyridine N-oxide	2.5	80:20	98:2
8	**PhSeSePh**	**2,6-Lutidine N-oxide 23**	**2**	**80:20**	**99:1**

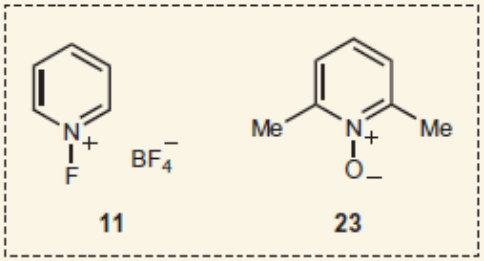
Reaction development with (E)-1-benzyloxy-4-hexene

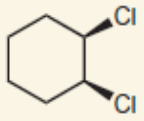


Sr. No.	$(ArylSe)_2$	Additive	Time (h)	**18**:(**19** + **20** + **21** + **22**)	**18** d.r.
9		--	10	58:42	88:18
10		--	18	59:41	55:451
11		--	3.5	90:10	99:1
12		--	8	83:17	98:2

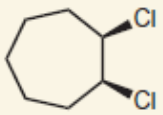
Reaction generality



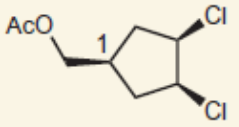




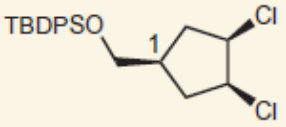
7, 51% (80%*), >99:1 d.r. (10 h) [83%*, >99:1 d.r.]



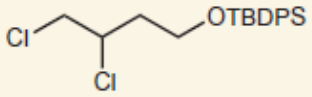
29a, 77% (96%*) d.r. 99:1 d.r. (4 h)



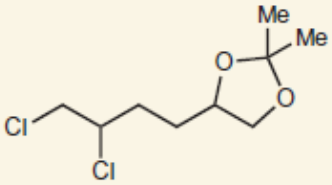
29b, 73%, >99:1 d.r., 89:11 d.r. at C(1)† (24 h), [76%, >99:1 d.r., 90:10 d.r. at C(1)†]



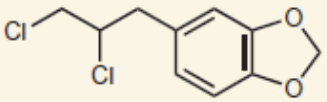
29c, 71%, >99:1 d.r., 91:9 d.r. at C(1) (16 h)



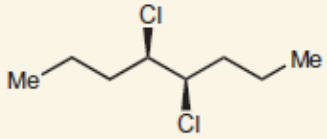
29d, 91% (6 h) [91%]



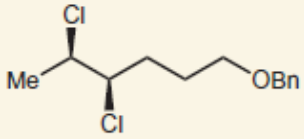
29e, 85% (4.5 h)



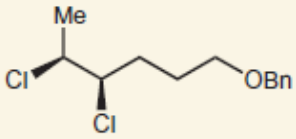
29f, 77% (3.5 h)



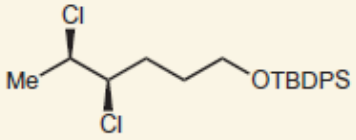
29g, 40% (66%*) d.r. 99:1 d.r. (4 h)



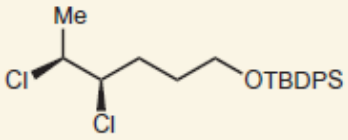
18, 71%, 99:1 d.r. (3.5 h) [64%, >99:1 d.r.]



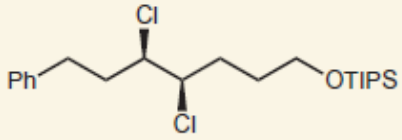
29h, 67%, >99:1 d.r. (4 h) [67%, >99:1 d.r.]



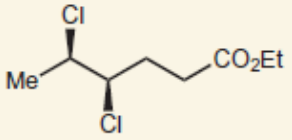
14, 64%, >99:1 d.r. (4 h) [63%, >99:1 d.r.]



29i, 67%, >99:1 d.r. (6 h) [63%, >99:1 d.r.]

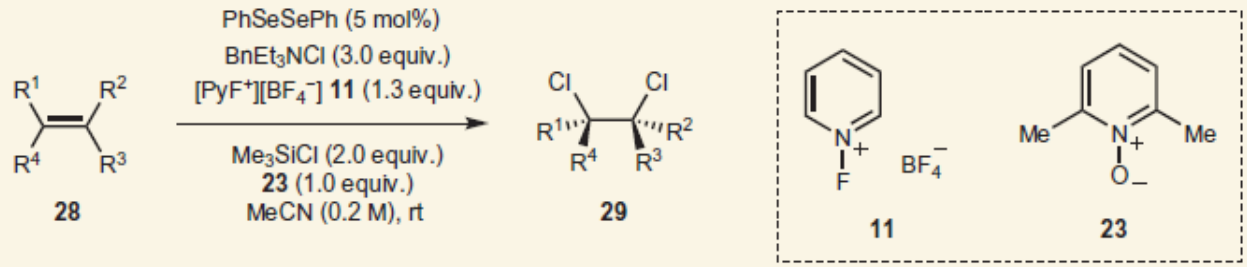


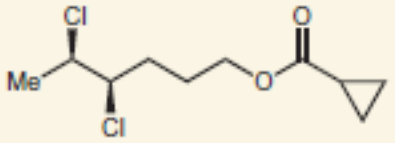
29j, 37%‡, 97:3 d.r. (5 h)



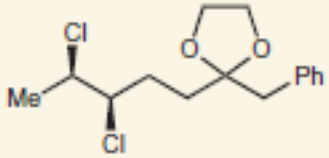
29k, 70%, >99:1 d.r. (3.5 h)

Reaction generality

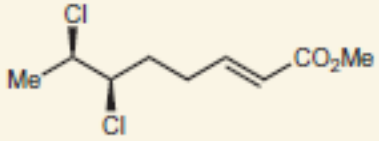




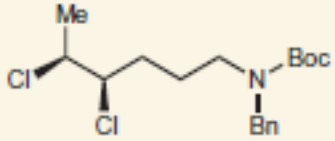
29l, 69%, >99:1 d.r.
(3.5 h)



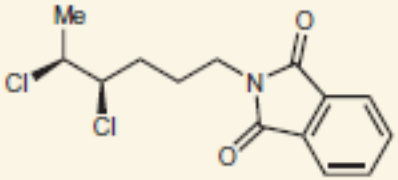
29m, 73%, >99:1 d.r.
(3.5 h)



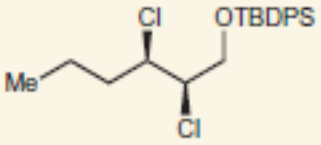
29n, 70%, 99:1 d.r.
(4.5 h)



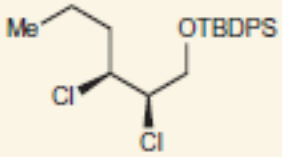
29o, 72%, 99:1 d.r.
(5 h)



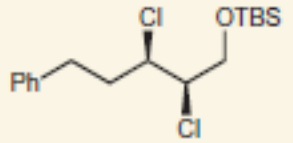
29p, 72%, 97:3 d.r.
(3.5 h)



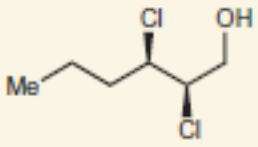
29q, 71%, >99:1 d.r.
(7 h)



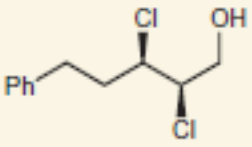
29r, 67%, 99:1 d.r.
(9 h)



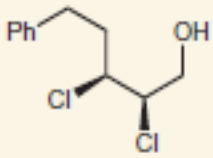
29s, 47%§, >98:2 d.r.‖
(6 h)



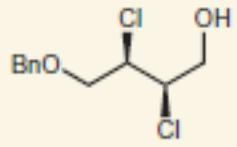
29t, 66%¶, 99:1 d.r.
(14 h)



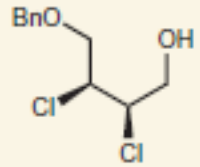
29u, 76%¶, 98:2 d.r.
(9 h)



29v, 71%¶, 98:2 d.r.
(9 h)

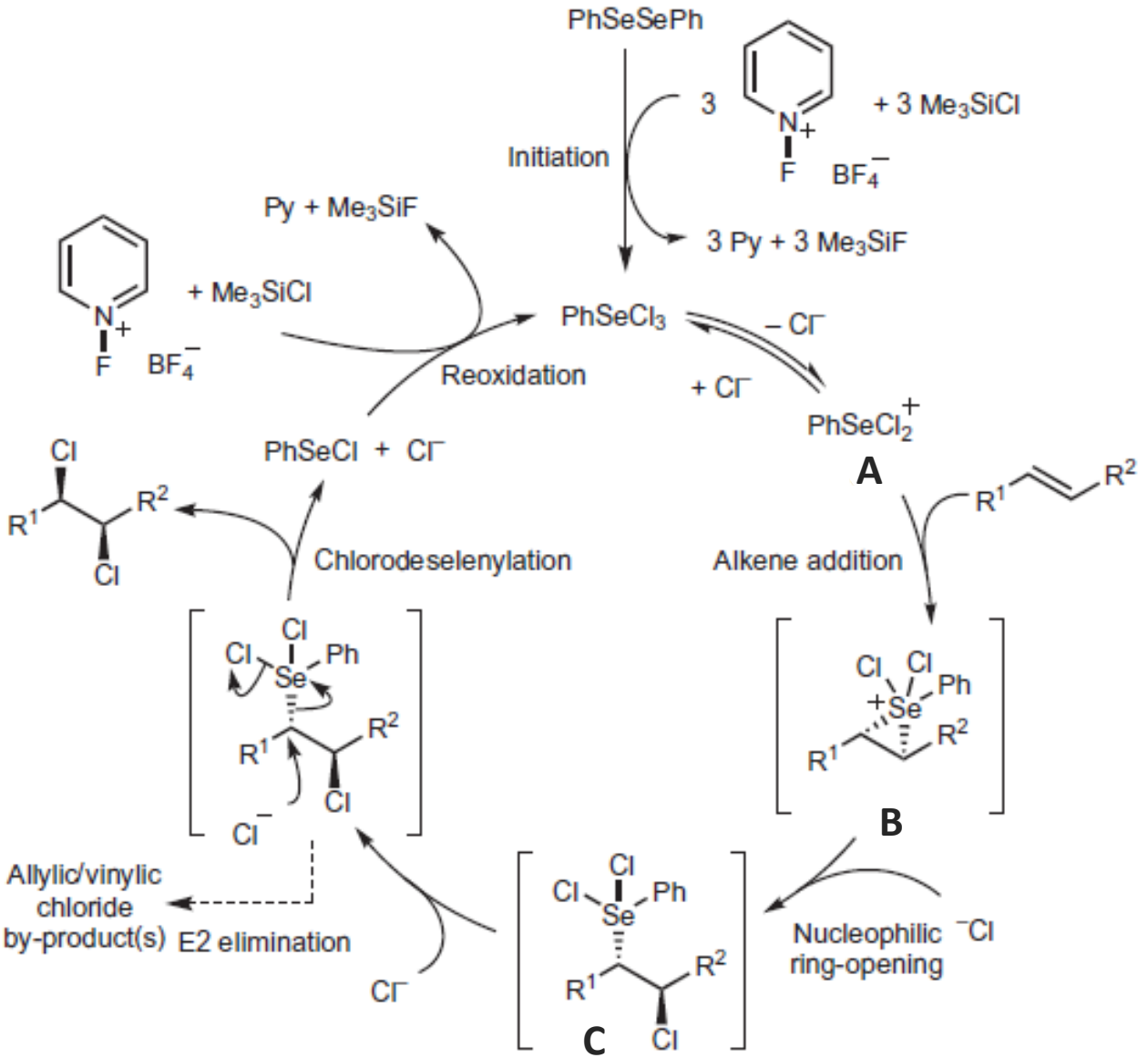


29w, 67%¶, 56:44 d.r.
(47 h)



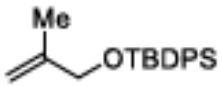
29x, 73%¶, 93:7 d.r.#
(15 h)

Proposed mechanism

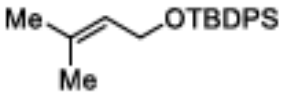


Problematic Substrates

1,1-Disubstituted and trisubstituted alkenes

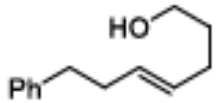


S31

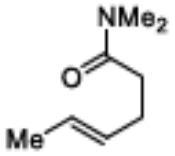


S32 (allylic chloride as major product)

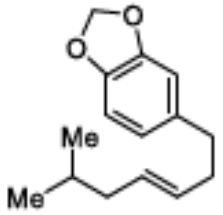
Alkenes bearing pendant nucleophiles



S43

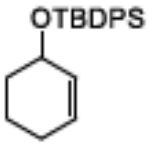


S44

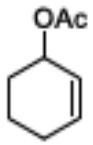


S45

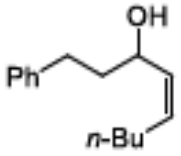
Secondary allylic alcohols and derivatives



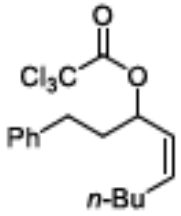
S33, 51% conv. to complex mixture, including an allylic chloride (21%) (tentatively assigned)



S34, 35% conv. to ~1:1 mixture of dichloride: allylic chloride (tentatively assigned)

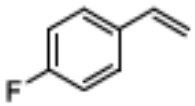


S35

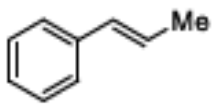


S36, mainly SM and *anti*-dichloride from background dichlorination

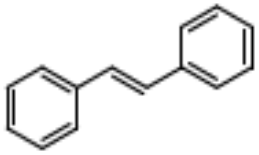
Conjugated alkenes



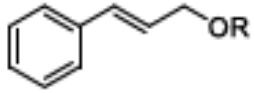
S37



S38 (50:50 *syn*:*anti*)



S39 (58:42 *syn*:*anti*)



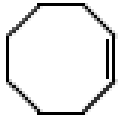
S40, R = TBDPS (50:50 *syn*:*anti*)
S41, R = H (75:25 *syn*:*anti*)

S42

Problematic Substrates

Alkenes giving *anti*-dichlorination

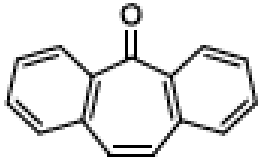
Medium-Ring Cycloalkenes



S46 (98:2 *anti*:*syn*)

Electron-Poor Alkenes

S49 (<99:1 *anti*:*syn*)

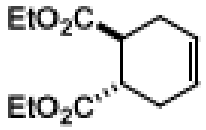


S50 (<99:1 *anti*:*syn*)

Miscellaneous Functionalized Alkenes

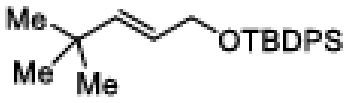
S51, R = Cbz (>98:2 *anti*:*syn*)
S52, R = Boc (>98:2 *anti*:*syn*)

S53 (<99:1 *anti*:*syn*)



S54 (<99:1 *anti*:*syn*)

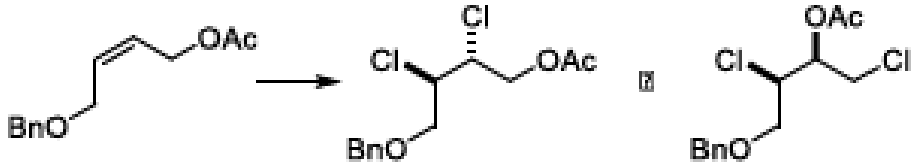
Alkenes with branching at the allylic position



S47, 50% conv.,
80:20 *anti*:*syn*

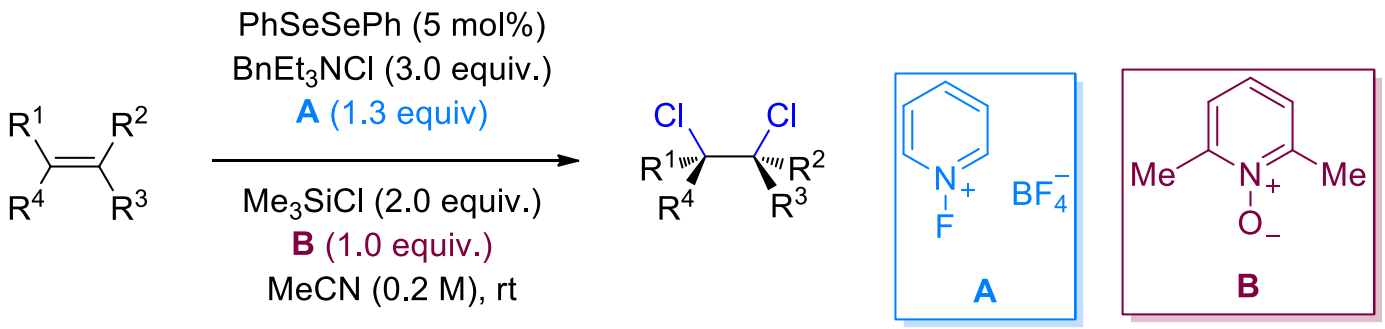
S48, 74% conv.,
86:14 *anti*:*syn*

Allylic Acetates



S55 **S56**, 38% **S57** 10%

Summary



- Developed selenium catalysed *syn*-stereospecific dichlorination of alkenes
- *Direct alkene syn-dichlorination*
- *The method is applicable to a wide variety of functionalized cyclic and acyclic 1,2-disubstituted alkenes*
- *Some problematic substrate*

Thank You