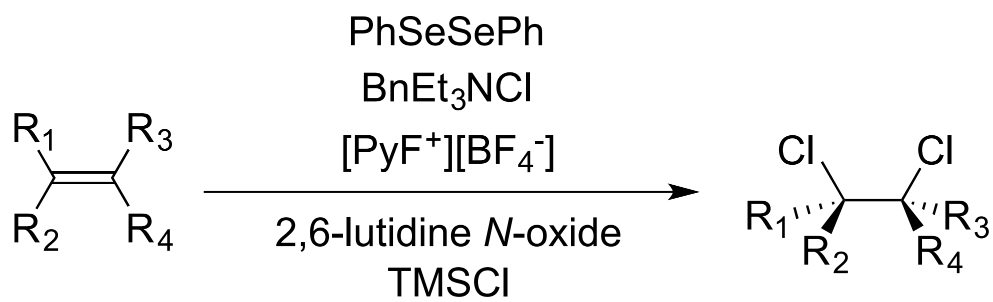


Catalytic, stereospecific syn-dichlorination of alkenes

A.J. Cresswell, S.T.-C. Eey and S. E. Denmark. Nature Chemistry 2015, vol 7, 146-152

Current literature
Yongzhao Yan
Jan 31st 2015

Chlorosulfolipids

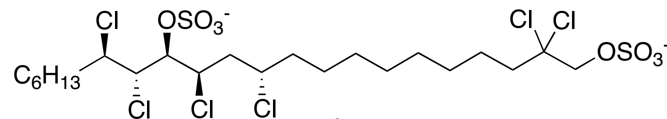
Chlorosulfolipids was first reported in 1969 and ignored by synthetic chemists for the ensuing 40 years.

Danicalipin A (**1**) was isolated by Haines and Block from *Ochromaonas danica*. It is a key component of **algal membranes**.[1]

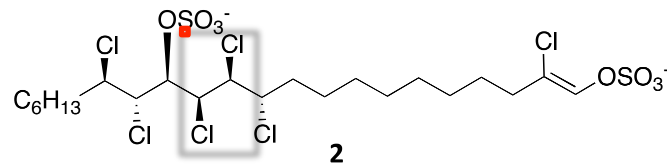
Malhamensilipin A (**2**) is isolated in 1994 from alga *O. malhamensis*. It displays activity in **kinase assay**.[2]

Ciminiello and Fattorusso reported isolation of 3-5 from Adriatic mussels. These lipids were deemed to be the causative agents in **seafood poisoning**.[3]

-Heavily chlorinated linear hydrocarbon motifs
-Complicated stereochemical structures
-Toxicity mechanism



1



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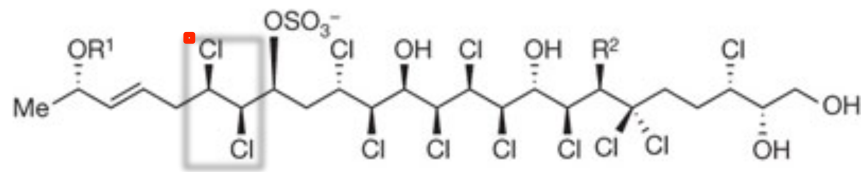
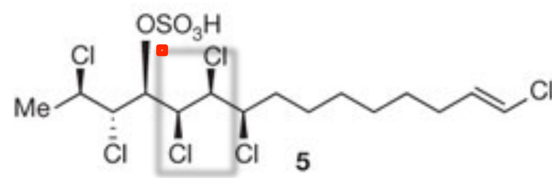


$R^1 = C(O)C_{15}H_{31}$, $R^2 = OH$ (**3**) $R^1 = C(O)C_{15}H_{31}$, $R^2 = H$ (**4**)

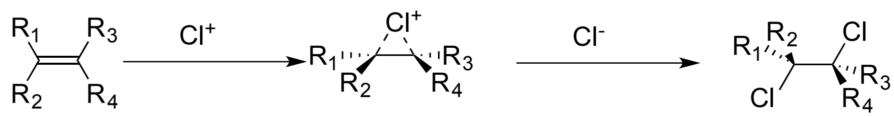


5

1. T. H. Haines, M. Pousada, B. Stern and G. L. Mayers, *Biochem. J.*,1969, 113, 565–566.
2. J. L. Chen, P. J. Proteau, M. A. Roberts, W. H. Gerwick, D. L. Slateand R. H. Lee, *J. Nat. Prod.*, 1994, 57, 524–527.
3. P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno,M. Di Rosa, A. Ianaro and R. Poletti, *J. Am. Chem. Soc.*, 2002, 124,13114–13120.

Alkene dichlorination: *syn* vs. *anti*

anti:



Cl^+ source: Cl_2, SO_2Cl_2, $PhICl_2$, Et_3NCl_3, NCS-PPh_3

in situ Cl^+ source: H_2O_2-HCl, $KMnO_4$-TMSCl-$BnEt_3NCl$, Oxone-NaCl

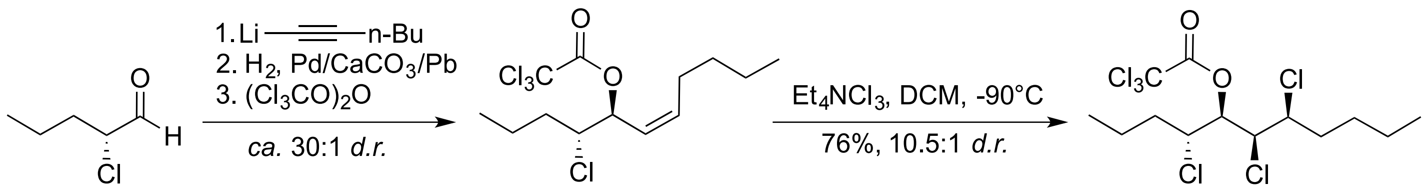
syn?:

1. Kharasch, M. S. & Brown, H. C. *J. Am. Chem. Soc*. **61**, 3432–3434 (1939).
2. Tanner, D. T. & Gidley, G. C. *J. Org. Chem.* **33**, 38–43 (1968).
3. Schlama, T., Gabriel, K., Gouverneur, V. & Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **36**, 2342–2344 (1997).
4. Kamada, Y., Kitamura, Y., Tanaka, T. & Yoshimitsu, T. *Org. Biomol. Chem*. **11**, 1598–1601 (2013).
5. Ho, T-L., Gupta, B. G. B. & Olah, G. A. *Synthesis* 676–677 (1977).
6. Markó, I. E., Richardson, P. R., Bailey, M., Maguire, A. R. & Coughlan, N. *Tetrahedron Lett.* **38**, 2339–2342 (1997).
7. Ren, J. & Tong, R. *Org. Biomol. Chem*. **11**, 4312–4315 (2013).

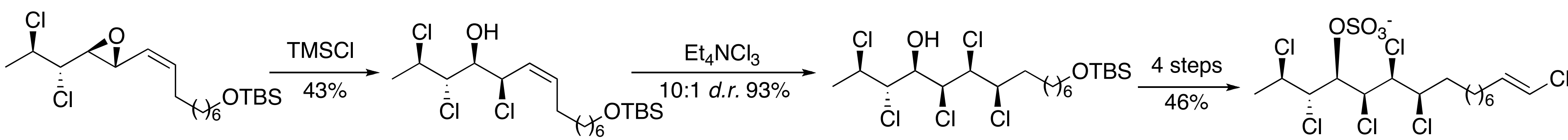
Alkene *syn* dichlorination

-

Vanderwal's diastereoselective dichlorination of (*Z*)-allylic trichloroacetates



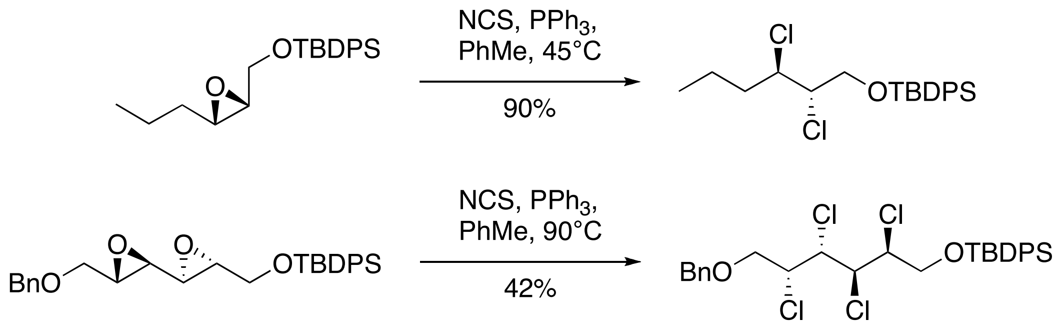
Applied in total synthesis of chlorosulfolipid



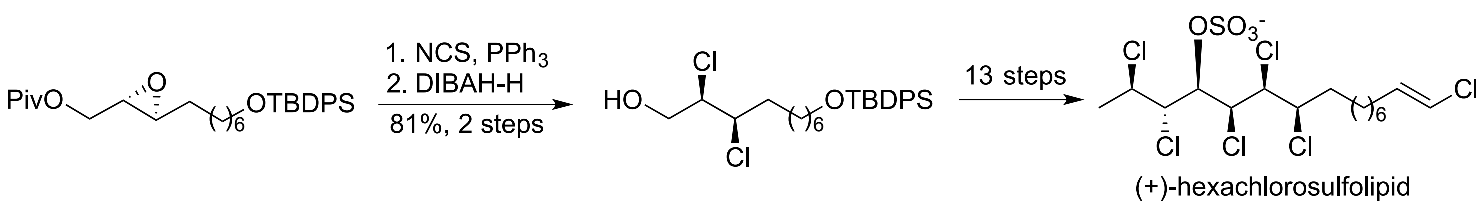
1. G. M. Shibuya, J. S. Kanady and C. D. Vanderwal, *J. Am. Chem.Soc.*, 2008, **130**, 12514–12518.
2. Nilewski, C., Geisser, R. W. & Carreira, E. M. *Nature* **547**, 573–576 (2009).

Alkene *syn* dichlorination

Yoshimitsu's deoxydichlorination of epoxide



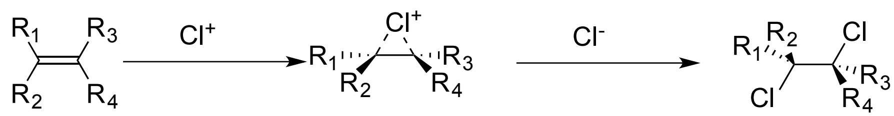
Sharpless enantioselective epoxidation



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

Alkene dichlorination: *syn* vs. *anti*

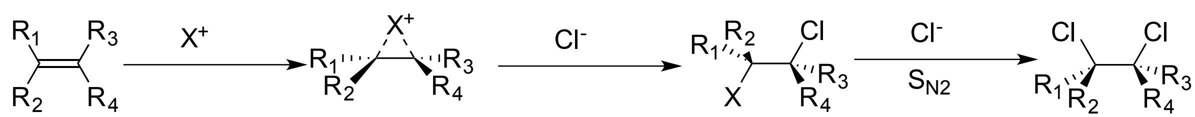
anti:



Cl^+ source: Cl_2, SO_2Cl_2, $PhICl_2$, Et_3NCl_3, NCS-PPh_3

in situ Cl^+ source: H_2O_2-HCl, $KMnO_4$-TMSCl-$BnEt_3NCl$, Oxone-NaCl

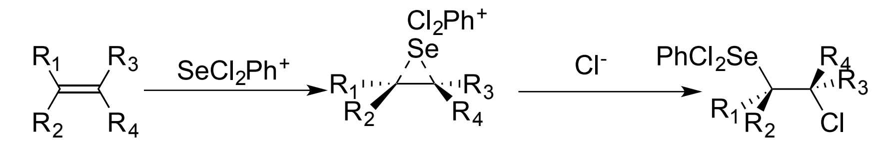
syn?:



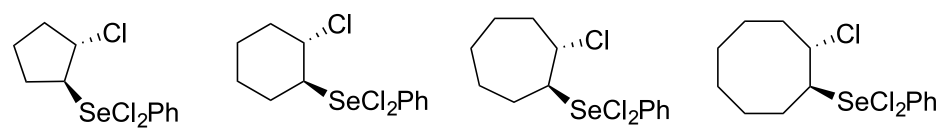
1. Kharasch, M. S. & Brown, H. C. *J. Am. Chem. Soc*. **61**, 3432–3434 (1939).
2. Tanner, D. T. & Gidley, G. C. *J. Org. Chem.* **33**, 38–43 (1968).
3. Schlama, T., Gabriel, K., Gouverneur, V. & Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **36**, 2342–2344 (1997).
4. Kamada, Y., Kitamura, Y., Tanaka, T. & Yoshimitsu, T. *Org. Biomol. Chem*. **11**, 1598–1601 (2013).
5. Ho, T-L., Gupta, B. G. B. & Olah, G. A. *Synthesis* 676–677 (1977).
6. Markó, I. E., Richardson, P. R., Bailey, M., Maguire, A. R. & Coughlan, N. *Tetrahedron Lett.* **38**, 2339–2342 (1997).
7. Ren, J. & Tong, R. *Org. Biomol. Chem*. **11**, 4312–4315 (2013).

Phenylselenium trichloride *anti* addition

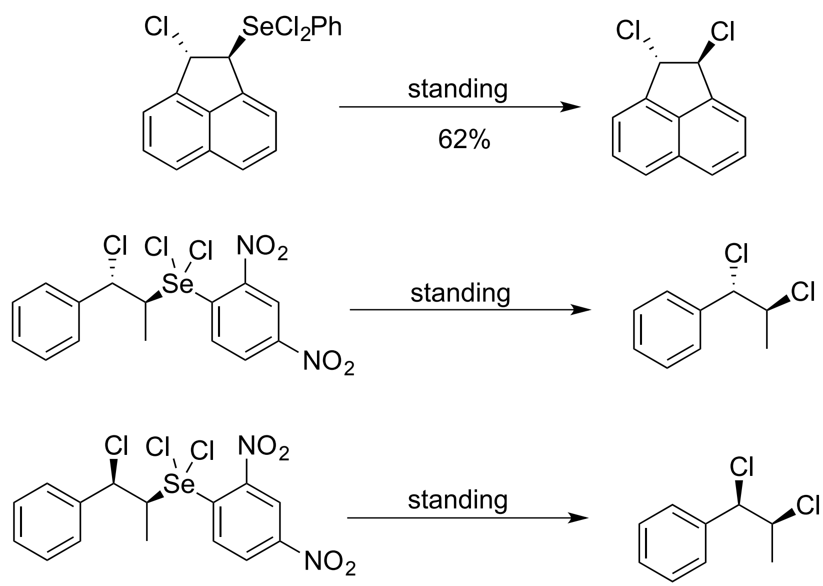
anti:



Quantitative:



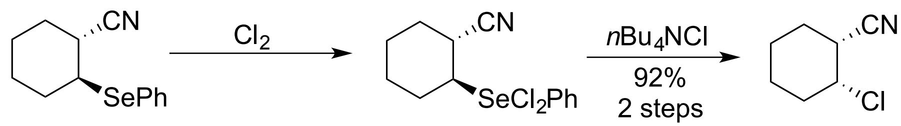
1,3 chloro-shift:



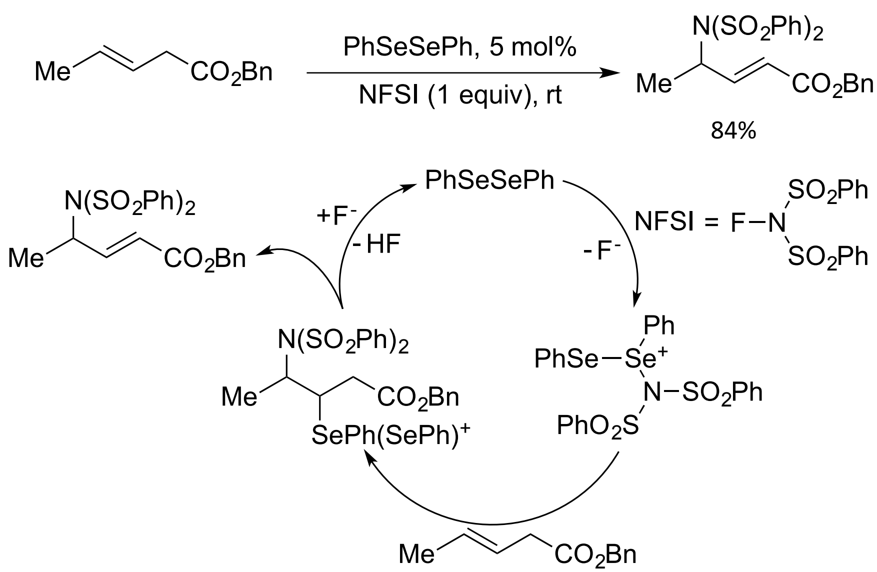
1. Engman, L. J. Org. Chem. 52, 4086–4094 (1987).

Nucleophilic substitution phenylselanyl group

Nucleophilic substitution and Se(II) to Se(IV) oxidation:



Catalytic phenylselanyl group:

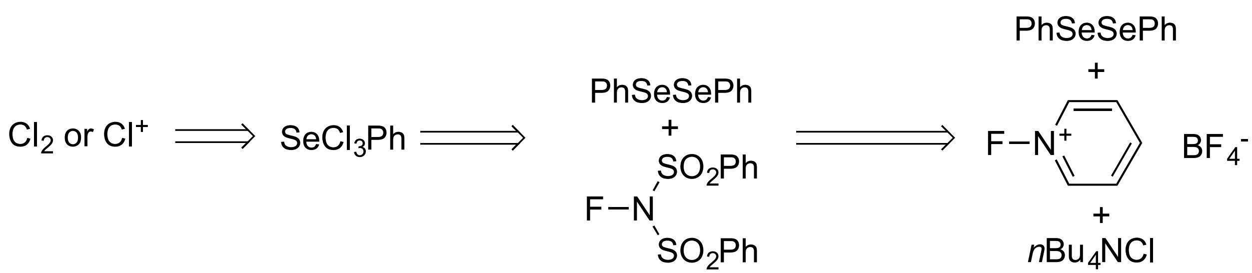


1. Morella, A. M. & Ward, D. A. Tetrahedron Lett. 26, 2899–2900 (1985).
2. Trenner, J., Depken, C., Weber, T. & Breder, A. Angew. Chem. Int. Ed. 52, 8952–8956 (2013).

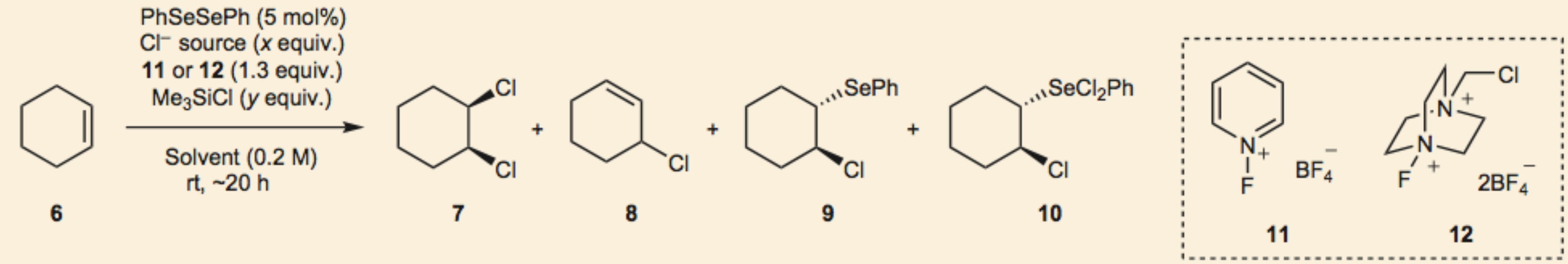
Catalytic cycle design

Oxidant choice :

1. no reaction with alkene by itself
2. no or minimum Cl^+ formation
3. weak nucleophlicity



Reaction Development

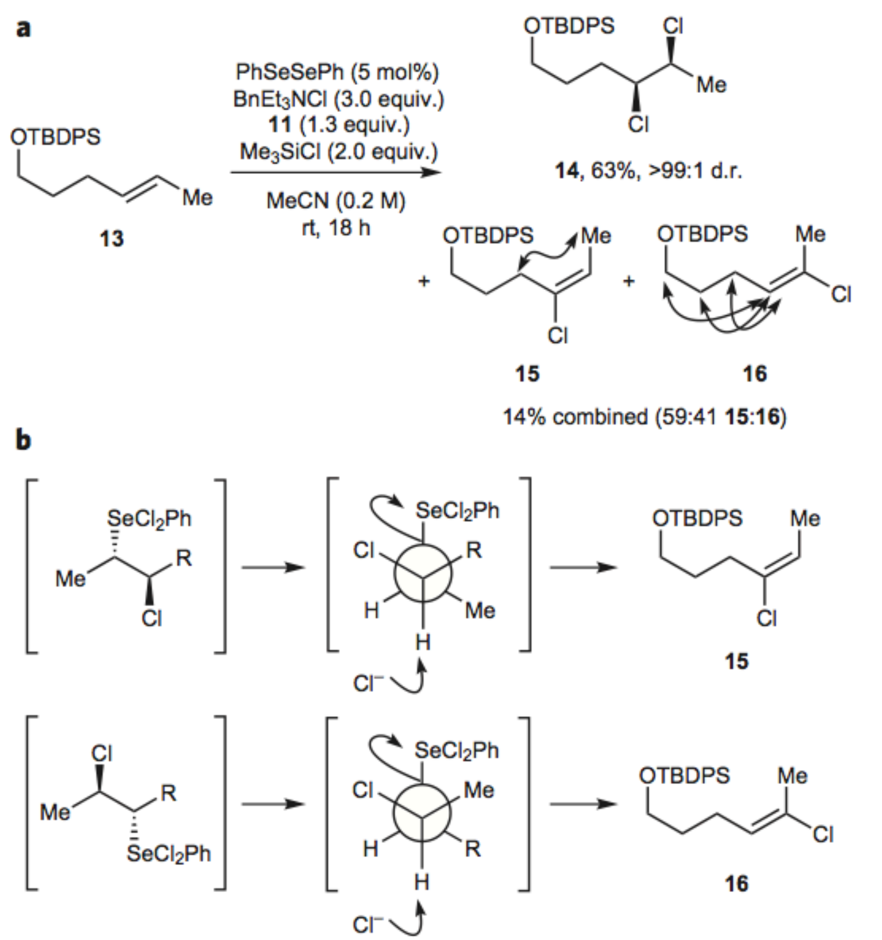


Entry	Cl^- source (equiv.)	Oxidant	Me_3SiCl (equiv.)	Solvent	NMR yield (%)*				
					6	7	8	9	10
1	n-Bu_4NCl (3.0)	11	0.0	MeCN-d_3	50	19	3	9	0
2	n-Bu_4NCl (3.0)	11	1.0	MeCN-d_3	12	61	10	10	0
3	n-Bu_4NCl (3.0)	11	2.0	MeCN-d_3	0	81	10	0	0
4	n-Bu_4NCl (3.0)	11	3.0	MeCN-d_3	0	81	8	0	0
5	n-Bu_4NCl (2.5)	11	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

*Measured by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane (1.0 equiv.) as an internal standard; †11% of an unidentified species was also observed by ^1H NMR spectroscopy.

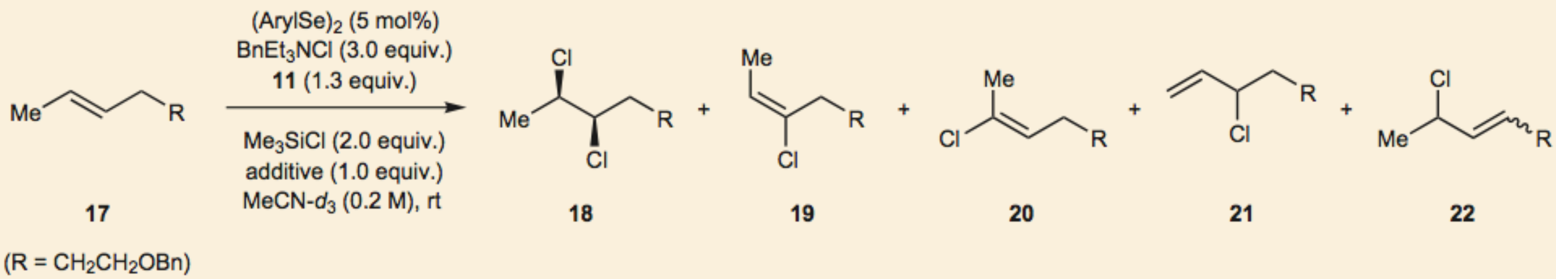
TMSCl acts as a F^- trapper.

E2 elimination or selenoxide *syn*-elimination



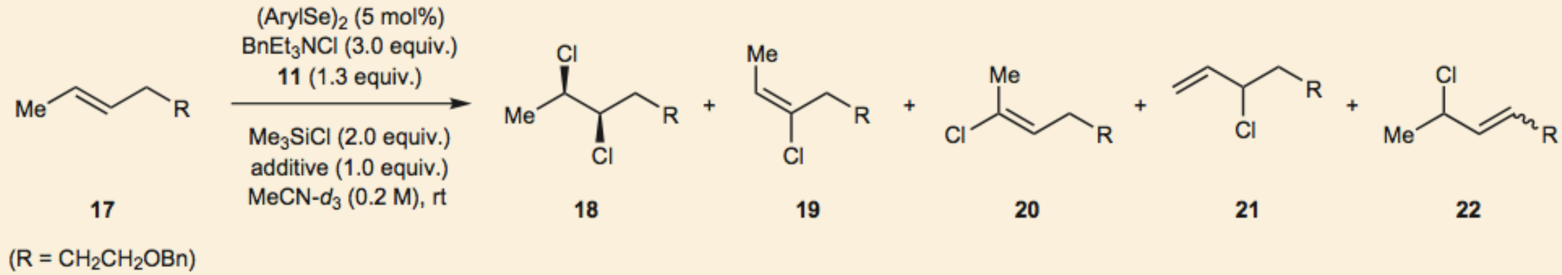
Reaction Development

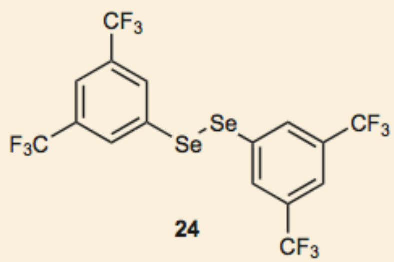
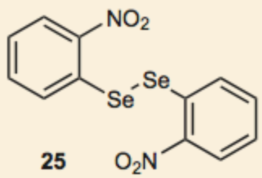
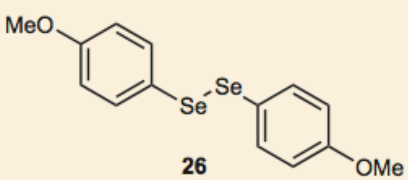
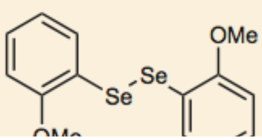
-



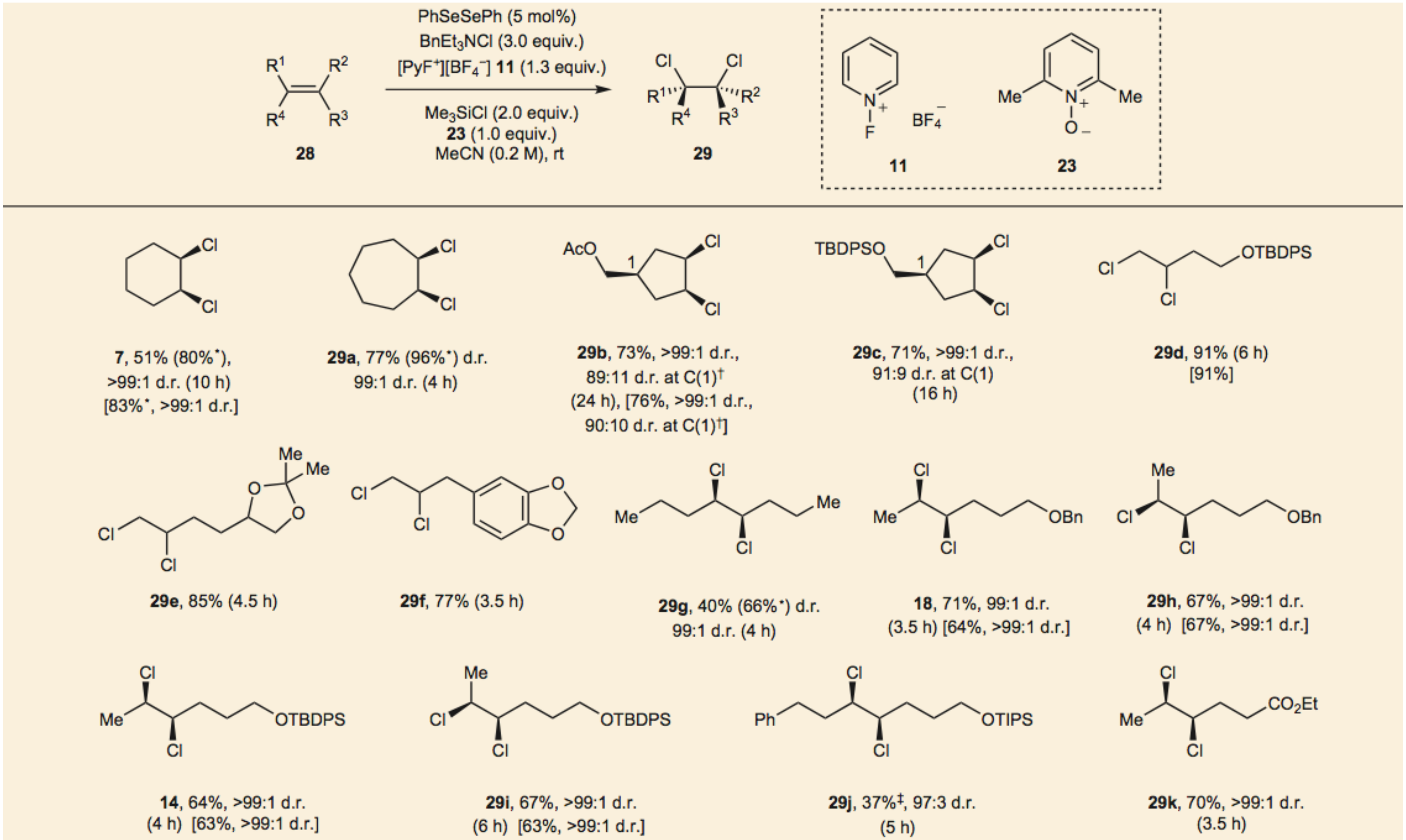
Entry	$(ArylSe)_2$	Additive	Time (h)	18:(19 + 20 + 21 + 22)*	18 d.r.*
1	PhSePh	–	6	80:20	99:1
2	PhSeSePh	Sulfolane[†]	2	80:20	99:1
3	PhSeSePh	HMPA	3	82:18	98:2
4	PhSeSePh	DMPU	3.5	80:20	98:2
5	PhSeSePh	DMI	2.5	80:20	99:1
6	PhSeSePh	$Ph_3P=O$	3.5	80:20	98:2
7	PhSeSePh	Pyridine *N*-oxide	2.5	80:20	98:2
8	PhSeSePh	2,6-Lutidine *N*-oxide 23	2	80:20	99:1

Reaction Development

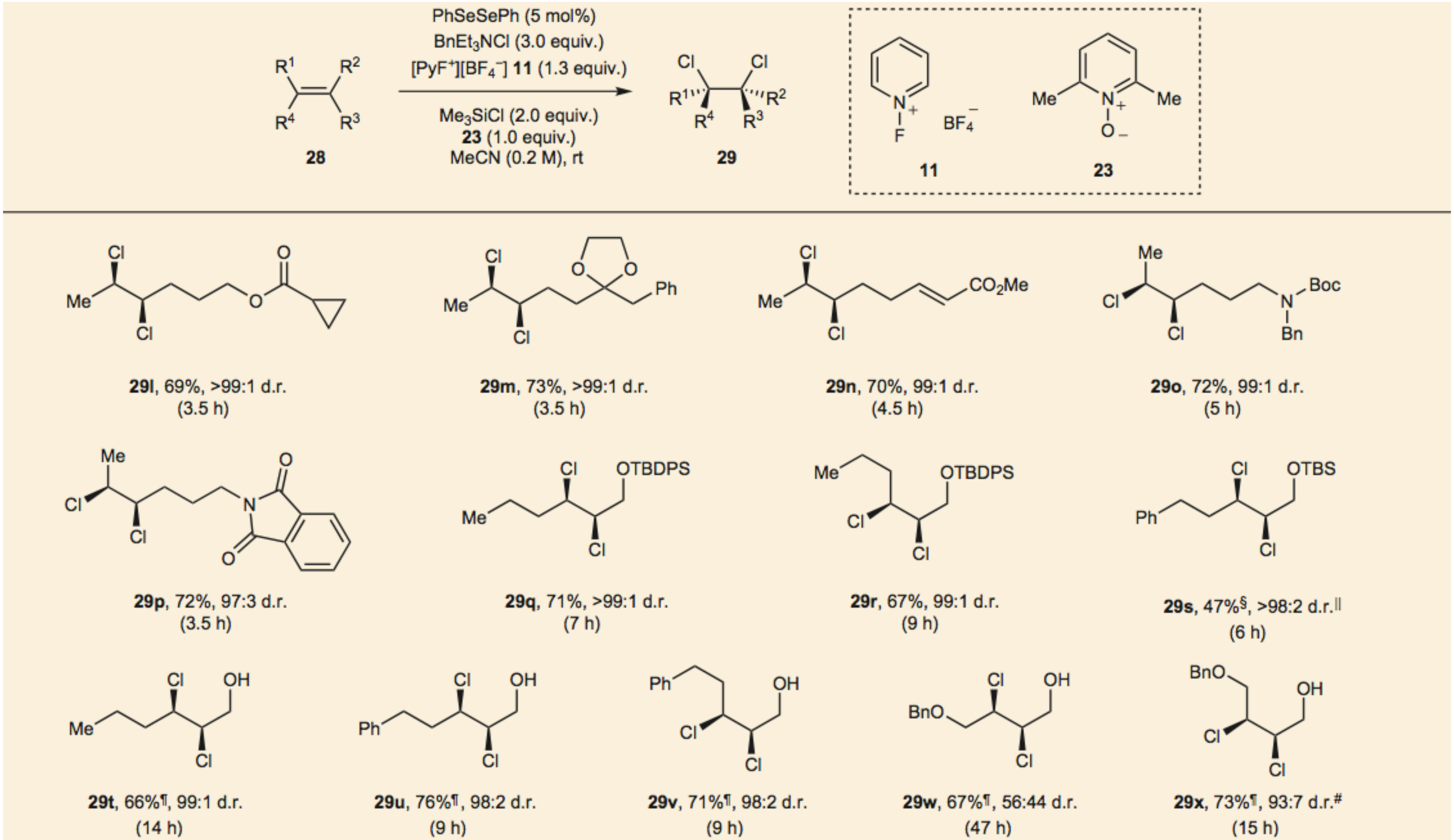


Entry	(ArylSe)$_2$	Additive	Time (h)	18:(19 + 20 + 21 + 22)*	18 d.r.*
9	 24	–	10	58:42	88:18
10	 25	–	18	59:41	55:45
11	 26	–	3.5	90:10	99:1
12		–	8	83:17	98:2

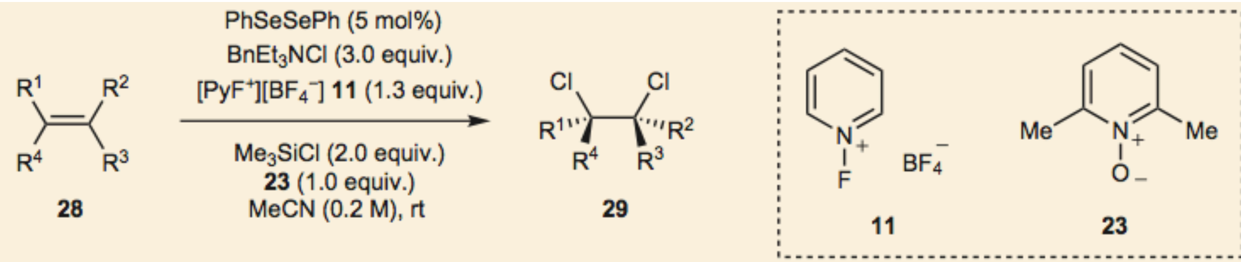
Reaction Scope



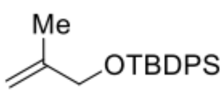
Reaction Scope



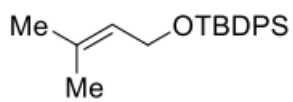
Reaction Scope



1,1-Disubstituted and trisubstituted alkenes

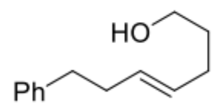


S31

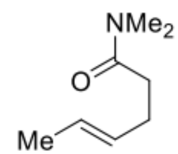


S32 (allylic chloride as major product)

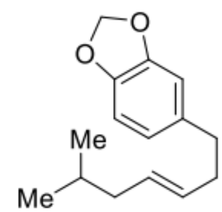
Alkenes bearing pendant nucleophiles



S43

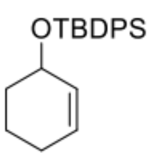


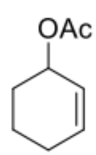
S44

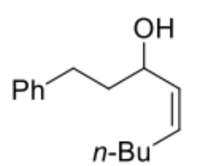


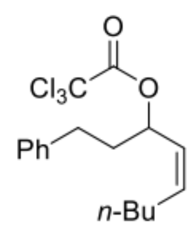
S45

Secondary allylic alcohols and derivatives

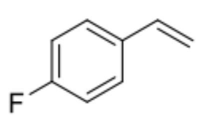




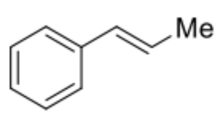




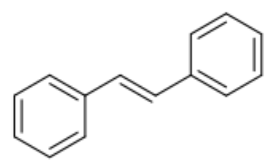
Conjugated alkenes



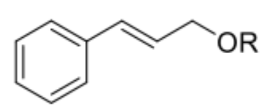
S37



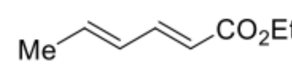
S38 (50:50 *syn*:*anti*)



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

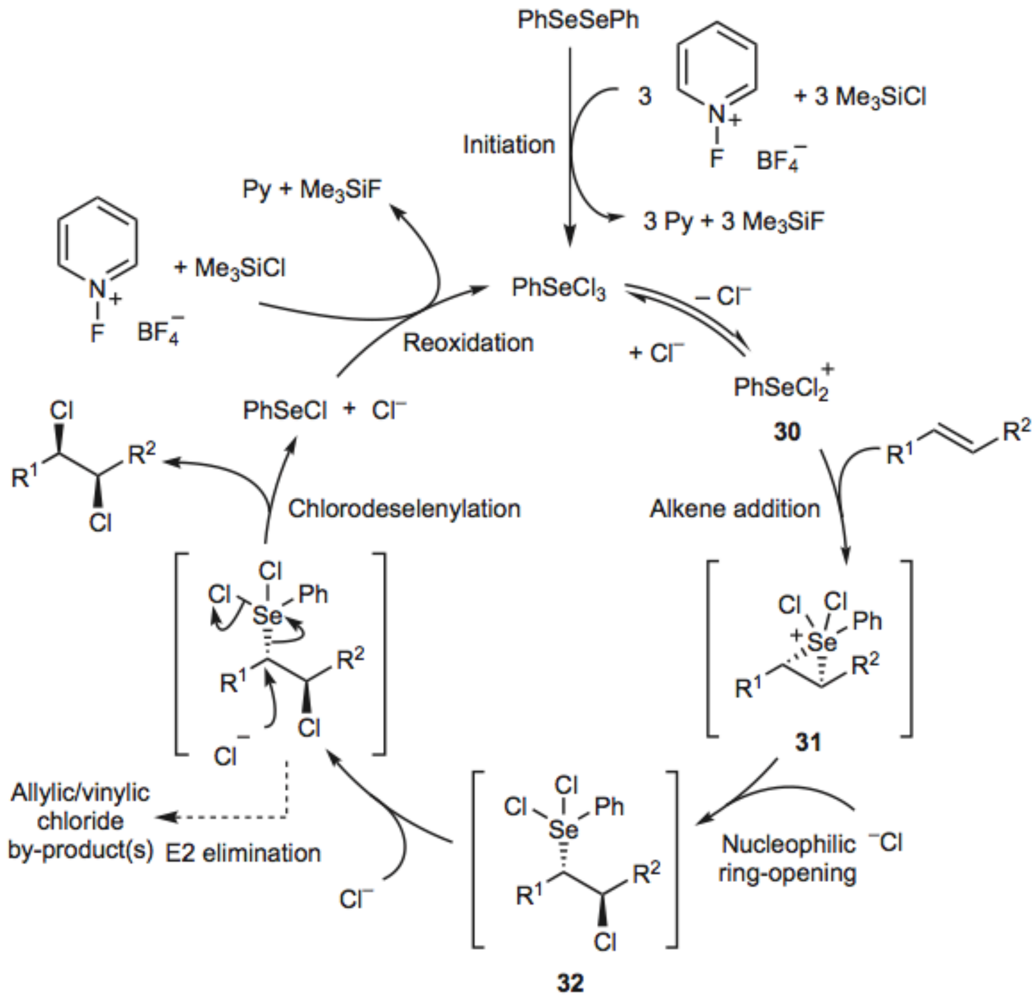


S40, R = TBDPS (50:50 *syn*:*anti*)
S41, R = H (75:25 *syn*:*anti*)



S42

Mechanism


PhSeSePh
Initiation
3
+ 3 Me3SiCl
BF4
3 Py + 3 Me3SiF
Py + Me3SiF
+ Me3SiCl
PhSeCl3
– Cl–
+ Cl–
Reoxidation
PhSeCl2+
30
PhSeCl + Cl–
Chlorodeselenylation
Alkene addition
31
Allylic/vinylic chloride by-product(s)
E2 elimination
Nucleophilic ring-opening
32

Conclusion

1. Catalytic stereospecific *syn*-dichlorination of alkene.
2. Reaction design and oxidant choice.
3. Chlorination without Cl^+
4. Enantioselective version.
5. Reaction scope & chlorosulfolipid synthesis

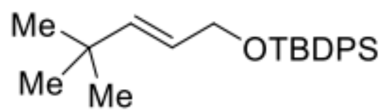
Reaction Scope

Alkenes giving *anti*-dichlorination

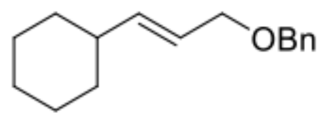
Medium-Ring Cycloalkenes

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

Alkenes with branching at the allylic position

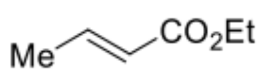


S47, 50% conv., 80:20 *anti*:*syn*

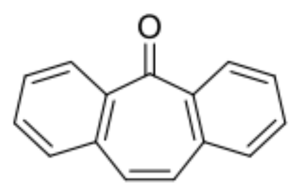


S48, 74% conv., 86:14 *anti*:*syn*

Electron-Poor Alkenes



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



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