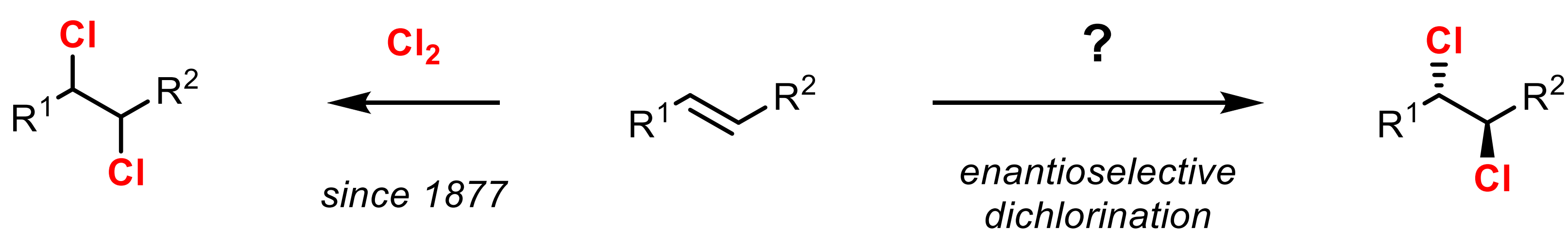
Current Literature 5/21/2016
Keita Takubo (Wipf group)

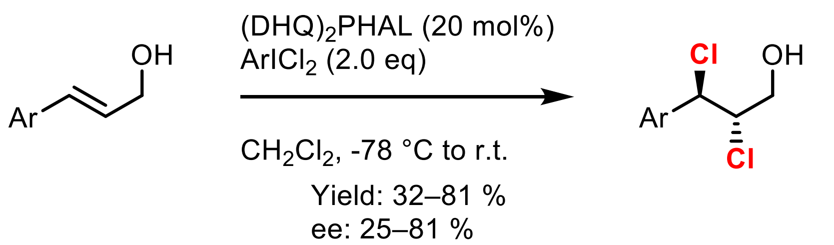
Catalytic Enantioselective Dihalogenation and the Selective Synthesis of (−)-Deschloromytilipin A and (−)-Danicalipin A

Matthew L. Landry, Dennis X. Hu, Grace M. McKenna, and Noah Z. Burns*

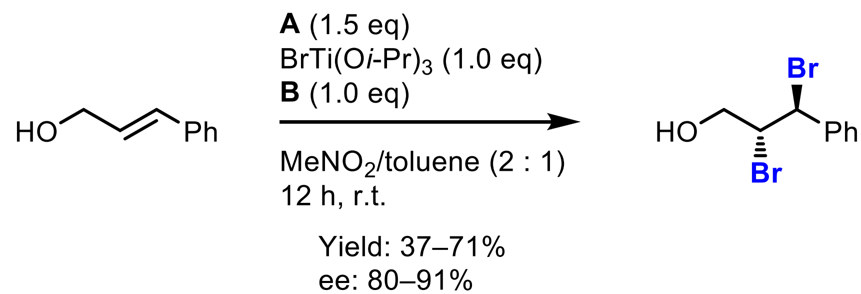
J. Am. Chem. Soc., **2016**, *138* (15), 5150–5158.



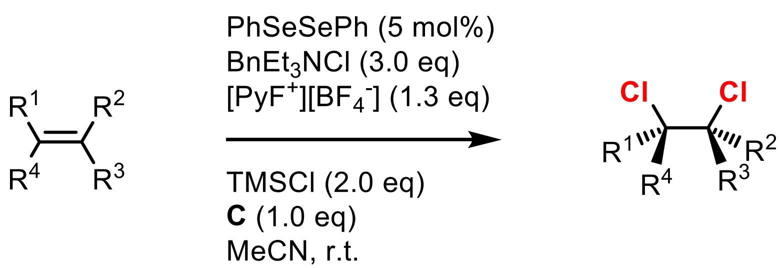
Stereoselective dihalogenation of alkenes



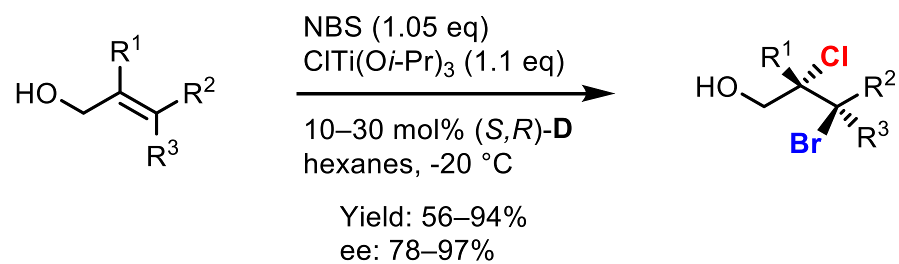
K. C. Nicolaou *et al*., *J. Am. Chem. Soc.* **2011**, *133*, 8134–8137.



N. Z. Burns et al., *J. Am. Chem. Soc.*, **2013**, *135*, 12960.

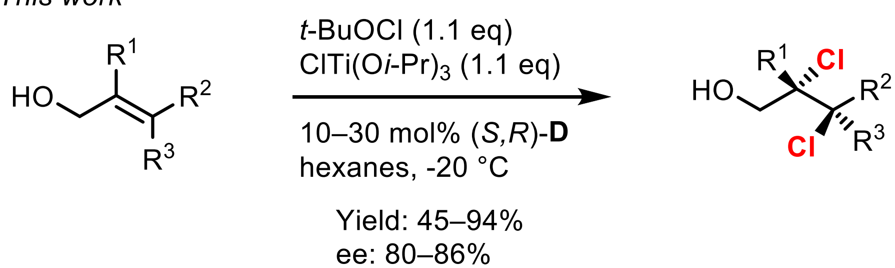


S. E. Denmark et al, *Nature Chem*., **2015**, *7*, 146–152.

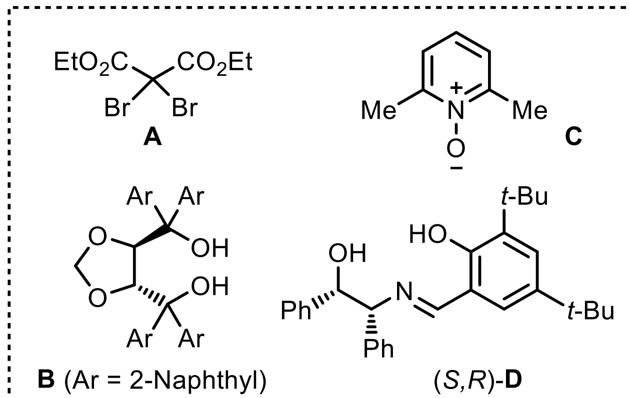


N. Z. Burns et al., *J. Am. Chem. Soc.*, **2015**, *137*, 3795.

This work

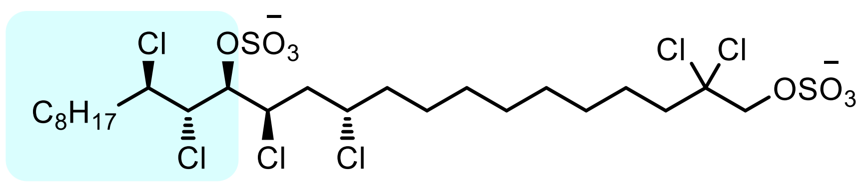


N. Z. Burns et al., *J. Am. Chem. Soc.*, **2016**, *138*, 5150.

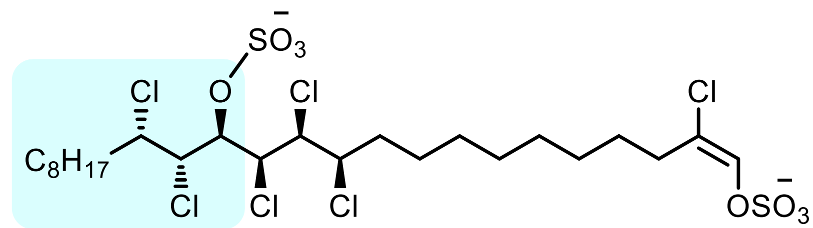


Chlorosulfolipids (CSLs)

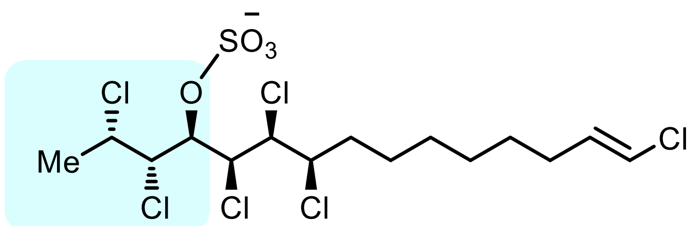
- Isolation: *Ochromonas danica* and *Poterioochromonas malhamensis* in 1962



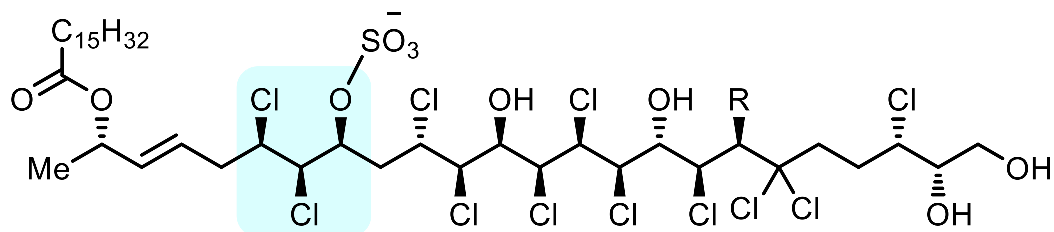
Danicalipin A



Malhamensilipin A
(IC_{50} = 35 μM against pp60$^{v\text{-}src}$ protein tyrosin kinase)



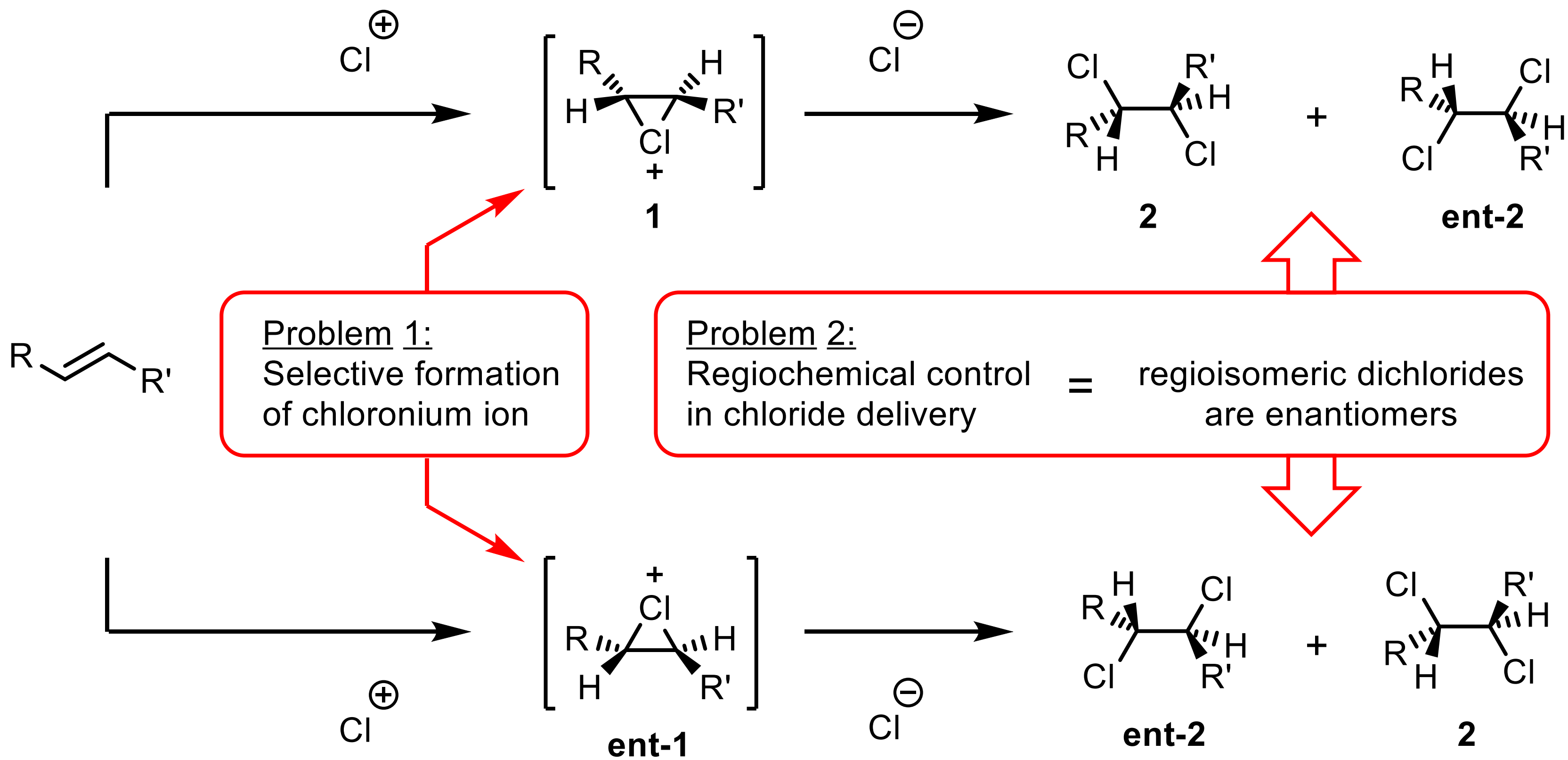
Mytilipin A



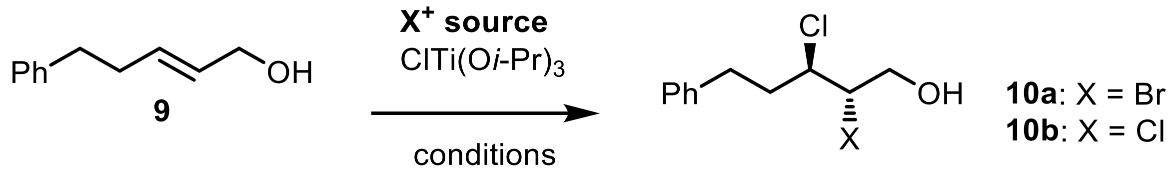
Mytilipin B (R = OH)
Mytilipin C (R = H)

Research on CSLs are difficult owing to the lack of availability of CSLs from natural resources and chemical access to CSLs.

A challenge in Enantioselective Dichlorination

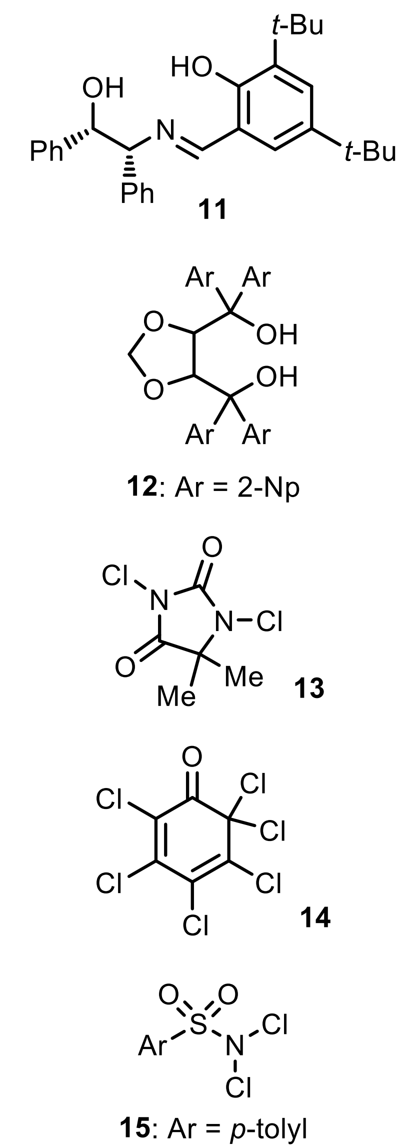


Development of an Enantioselective Dechlorination

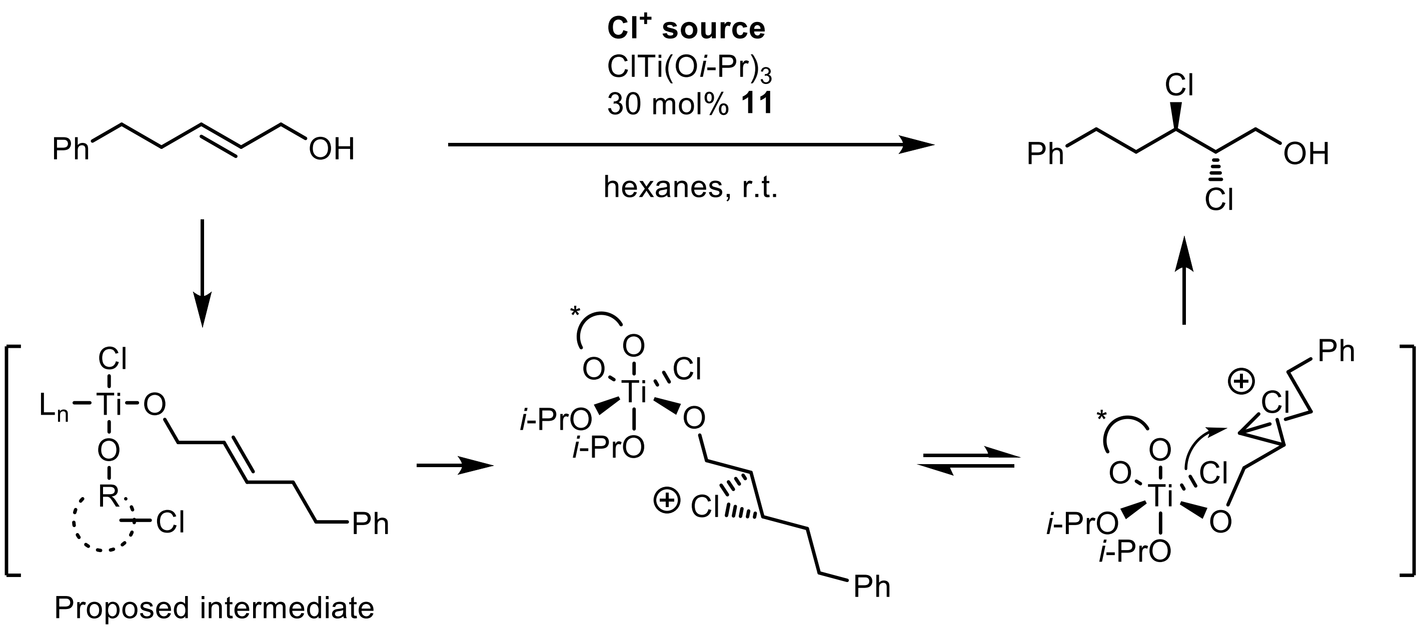


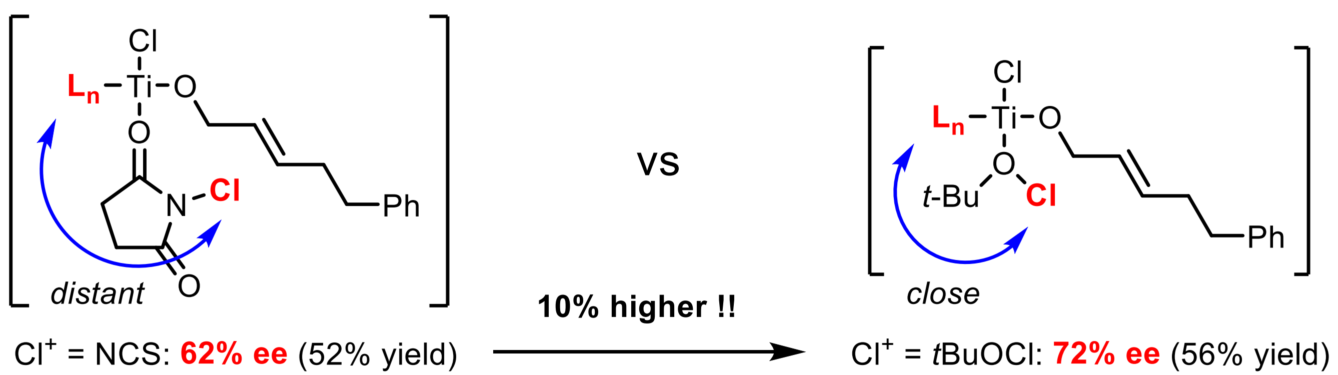
entry	X^+ source	conditions	yield (%)	ee (%)
1	NBS	30 mol% **11**, hexanes, r.t.	90	66 (1.7 : 1.0)[a]
2	NBS	30 mol% **11**, hexanes, -20 °C	81	90 (3.0 : 1.0)[a]
3	NCS	30 mol% **11**, hexanes, r.t.	52	62
4	**13**	30 mol% **11**, hexanes, r.t.	70	65
5	$PhICl_2$	30 mol% **11**, hexanes, r.t.	12	6
6	**14**	30 mol% **11**, hexanes, r.t.	trace	–
7	**15**	30 mol% **11**, hexanes, r.t.	66	58
8	*t*-BuOCl	30 mol% **11**, hexanes, r.t.	56	72
9	*t*-BuOCl	30 mol% **12**, hexanes, r.t.	73	5
10	*t*-BuOCl	30 mol% **11**, CH_2Cl_2, r.t.	62	20
11	*t*-BuOCl	30 mol% **11**, Et_2O, r.t.	75	67
12	*t*-BuOCl	30 mol% **11**, hexanes, -20 °C	77	78
13	***t*-BuOCl**	**10 mol% 11, hexanes, -20 °C**	**82**	**76**

a) Ratio of bromochloride constitutional isomers.

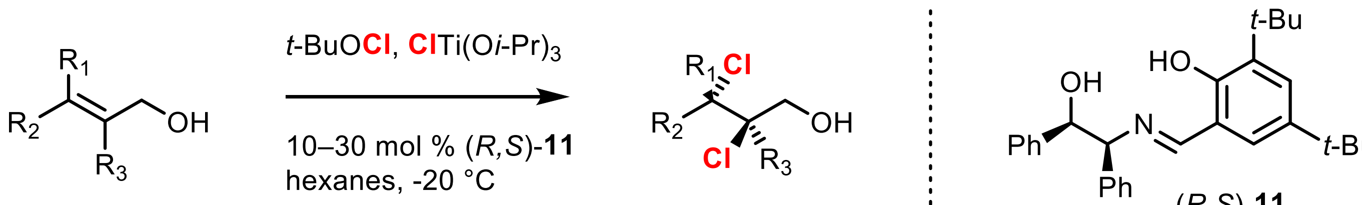


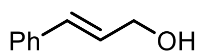
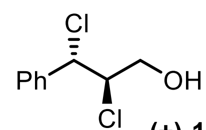
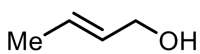
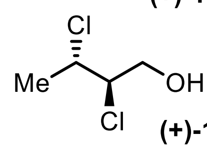
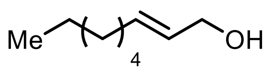
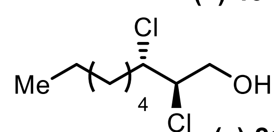
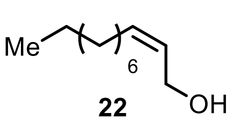
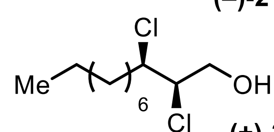
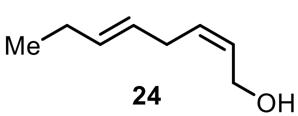
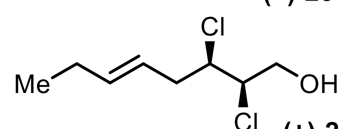
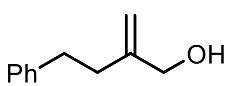
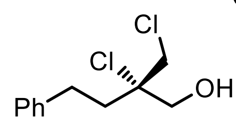
Proposed Mechanism



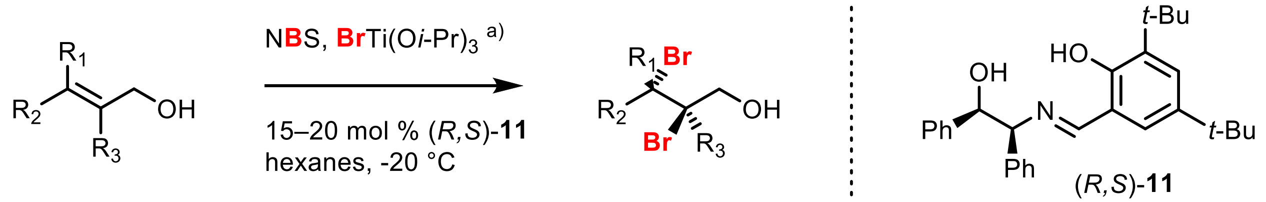


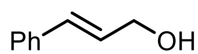
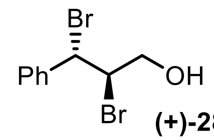
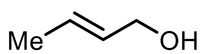
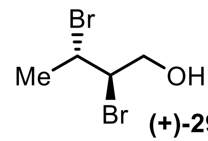
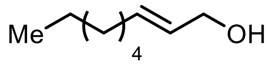
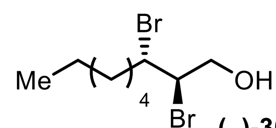
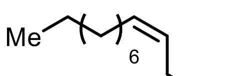
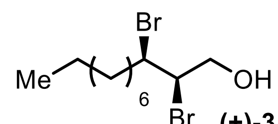
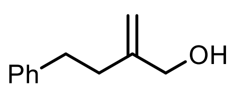
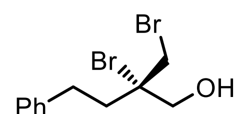
Dichlorination Substrate Scope



entry	*substrate*	yield (%)	ee (%)	mol (%) **11**	*product*	prior art or use in synthesis
1	 **16**	83	91	10	 **(+)-17**	Nicolaou (2011): 58%, 61% ee $ArICl_2$, 20 mol% $(DHQD)_2PHAL$
2	 **18**	64	80	15	 **(+)-19**	**(deschloro)mytilipin A** Vanderwal (2013): (⍰)-19 *Burns* (this work): (+)-19
3	 **20**	86	83	15	 **(–)-21**	**danicalipin A** Yoshimitsu (2011): (+)-21 Vanderwal (2014): (⍰)-21 *Burns* (this work): (–)-19
4	 **22**	64	81	20	 **(+)-23**	**malhamensilipin A** Vanderwal (2014): (⍰)-23
5	 **24**	45	85	30	 **(+)-25**	**nominal undecachlorosulfolipid** (yet to be utilized)
6	 **26**	61	90	30	 **(+)-27**	*Burns* (2015)

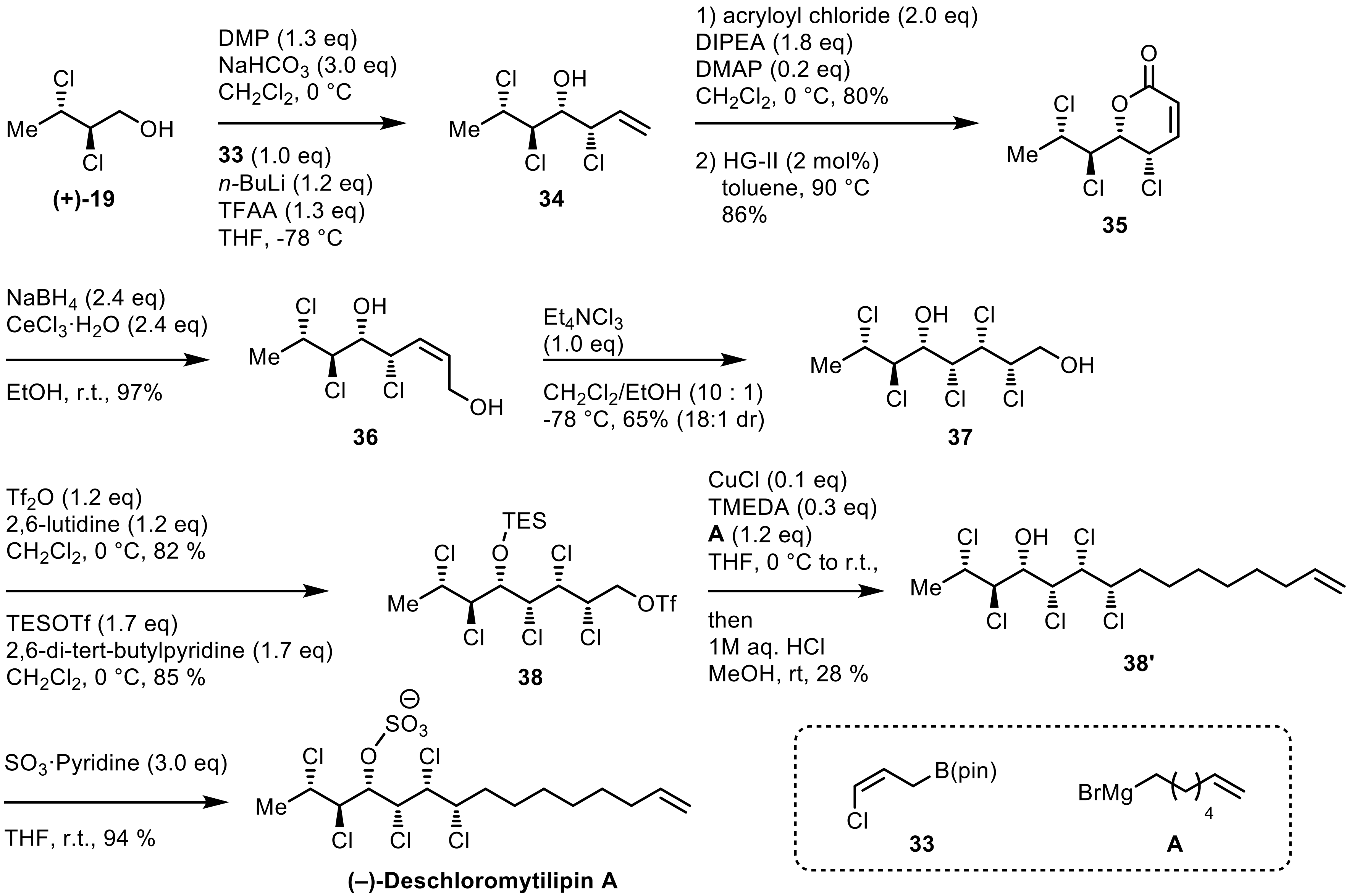
Dibromination Substrate Scope



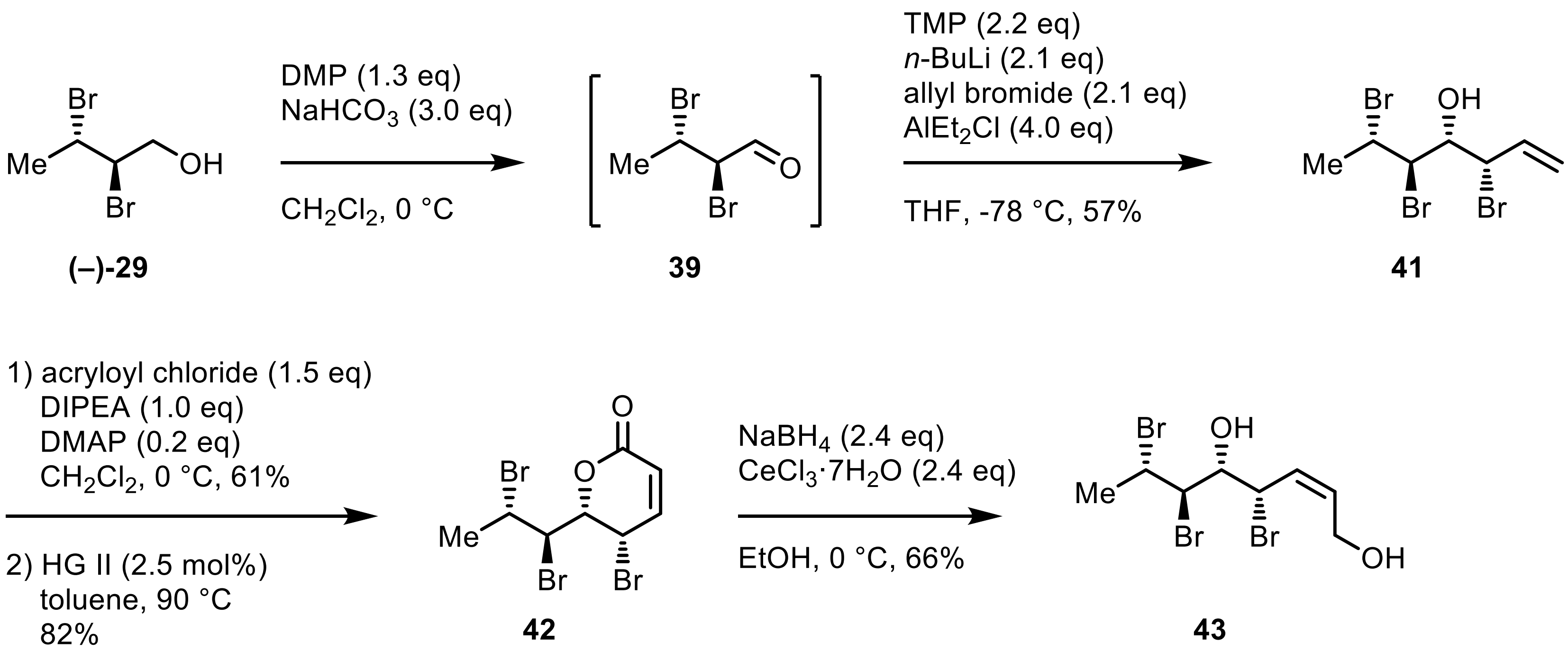
entry	*substrate*	yield (%)	ee (%)	mol (%) **11**	*product*
1 [b)]	 **16**	75	87	15	 **(+)-28**
2	 **18**	82	80	20	 **(+)-29**
3 [c)]	 **20**	86	80	15	 **(–)-30**
4 [c)]	 **22**	79	86	20	 **(+)-31**
5 [c)]	 **26**	84	81	20	 **(+)-27**

a) Conditions unless otherwise noted: 1.1–1.2 equiv NBS, 1.1–1.3 equiv BrTi(O*i*-Pr)$_3$, 15–20 mol % (*R,S*)-**11**, hexanes, . 20 °C, 4–12 h. b) 3:1 hexanes/CCl_4. c) absolute configuration unconfirmed.

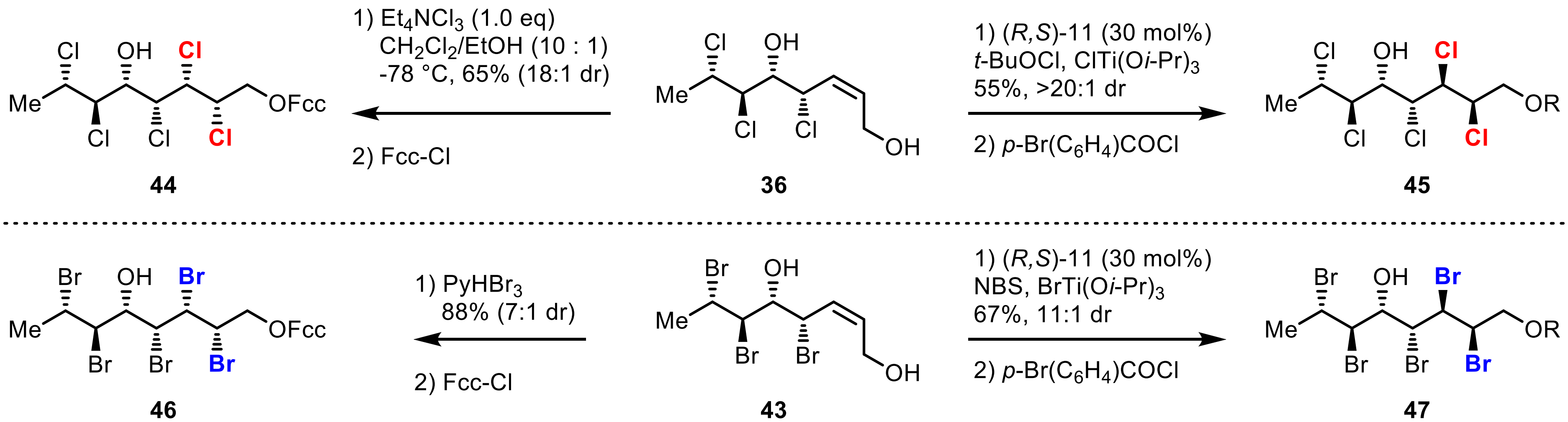
Synthesis of (–)-Deschloromytilipin A



Synthesis of Stereotetrad

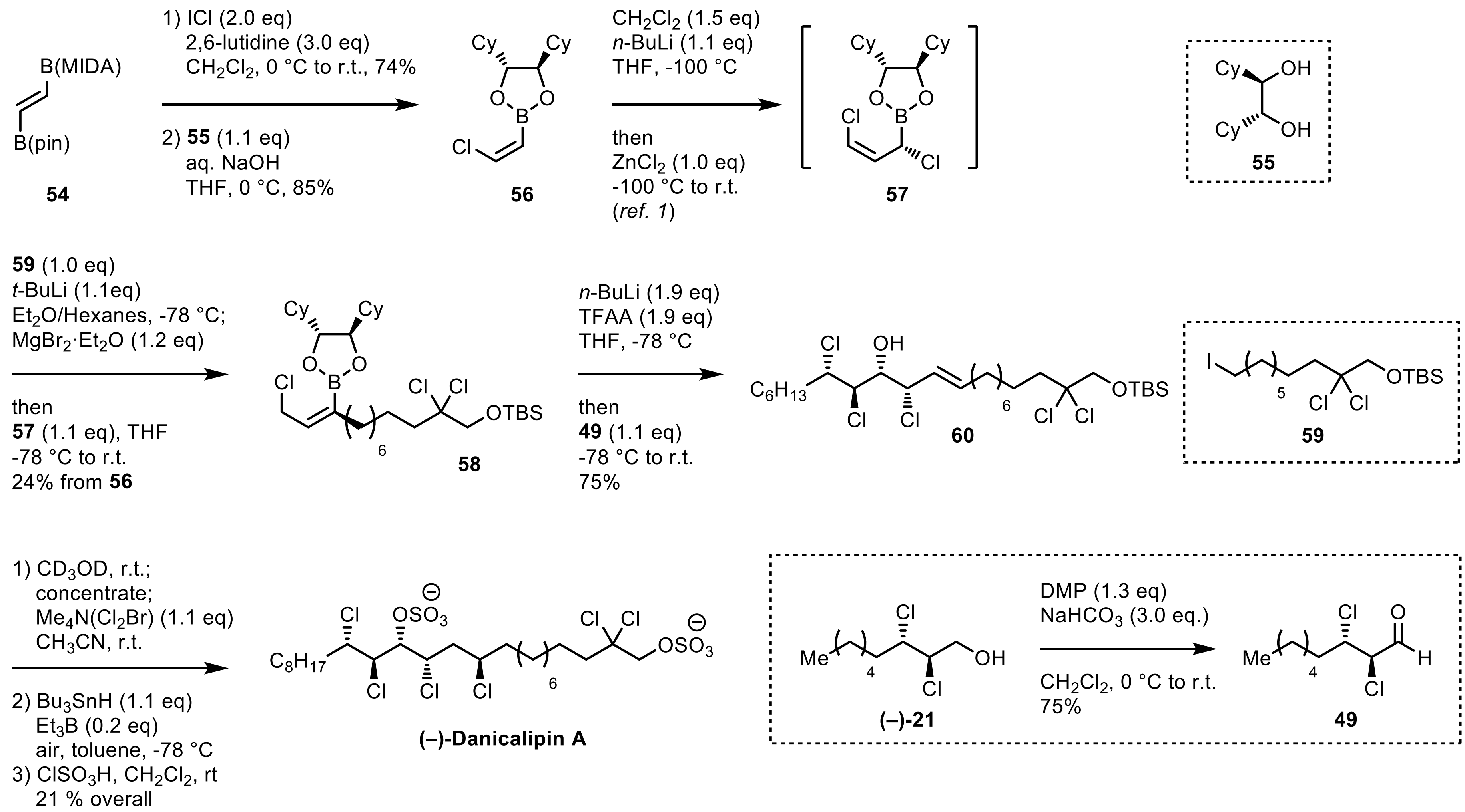


Synthesis of Stereohexads



1. Synthesis and characterization of polybromide stereohexads would help confirm the existence of putative bromosulfolipids.
2. Conformational data on stereohexads could provide insight in to the manner in which these molecules assemble in a lipid membrane.
3. Investigation of unnatural stereohexads would expand the repertoire of characterization data for complex polyhalostereoarrays.

Concise Synthesis of (–)-Danicalipin A



Reference

1) Matteson, D. S., *J. Org. Chem*. **2013**, *78*, 10009.

Rationale for the Effect of *O*-Deuteration