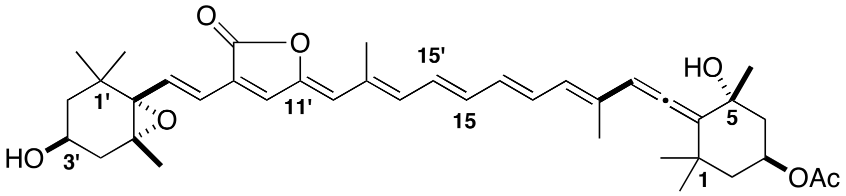
Stereoretentive Suzuki-Muyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (–)-Peridinin



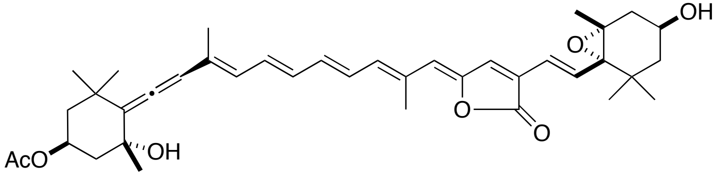
Eric M. Woerly, Alan H. Cherney, Erin K. Davis and Martin D. Burke

***J. Am. Chem. Soc.* (ASAP)**

Current Literature
May, 2010

Isolation and Structural Features:

- Isolated in 1890 by Schütt from fresh-water dinoflagelletes (causing red-tide, > 10^6 cells/mL).
- Later isolated from corals, clams and sea anemones.
- Dinoflagelletes - red pigment important for photosynthesis.

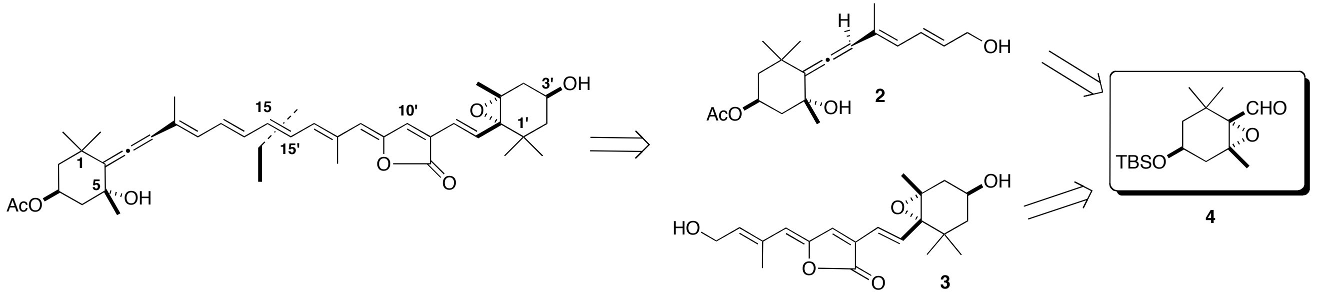


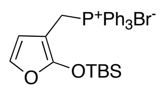
(+)-Peridinin

- Full structure and assignment of Peridinin wasn't achieved till 1971.
- Interesting features:
  - (*Z*)-γ-ylidenebutenolide moiety (anticancer activity?)
  - C37 nor-carotnoide
  - Stereogenic allene.
- More recently, Peridinin suggested as $^1O_2$ quencher; associated with atherosclerosis rheumatoid arthritis and cancer, contributing to the aging process.
- 1st Total synthesis of (±)-Perdinin was completed over 100 years later by Ito (1993), confirmed the structure.

Schütt, F. *Ber. Deut. Bot. Ges.* **1890**, 8, 9.
Lieean-Jensen, S. *at al J. Am. Chem. Soc.* **1971**, 93, 1823
Johansen, J. E.; Borch, G.; Liaaen-Jensen, S. *Phytochemistry* **1980**, 19, 441
Yamano, Y.; Tode, C.; Ito, M. *J. Chem. Soc. Perkin. Trans. 1* **1993**, 1599.

Katsumra's Total Synthesis:





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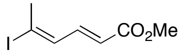
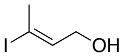
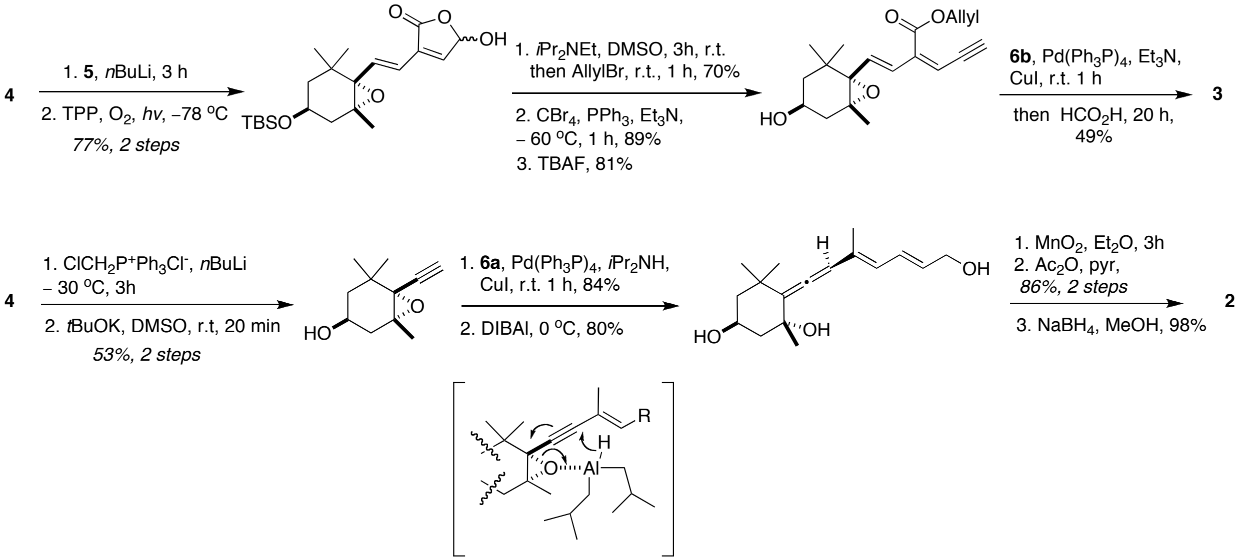


6a



6b



1. **5**, nBuLi, 3 h
2. TPP, O_2, $h\nu$, –78 ^oC

77%, 2 steps

1. $i$$Pr_2NEt$, DMSO, 3h, r.t. then AllylBr, r.t., 1 h, 70%
2. CBr_4, PPh_3, Et_3N, – 60 ^oC, 1 h, 89%
3. TBAF, 81%

6b, $Pd(Ph_3P)_4$, Et_3N, CuI, r.t. 1 h

then HCO_2H, 20 h, 49%

1. $ClCH_2P^+Ph_3Cl^-$, nBuLi – 30 ^oC, 3h
2. tBuOK, DMSO, r.t, 20 min

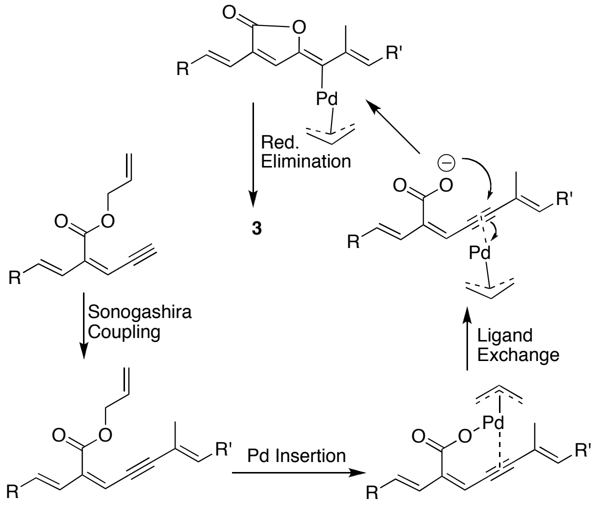
53%, 2 steps

1. **6a**, $Pd(Ph_3P)_4$, $i$$Pr_2NH$, CuI, r.t. 1 h, 84%
2. DIBAl, 0 ^oC, 80%

1. MnO_2, Et_2O, 3h
2. Ac_2O, pyr,

86%, 2 steps

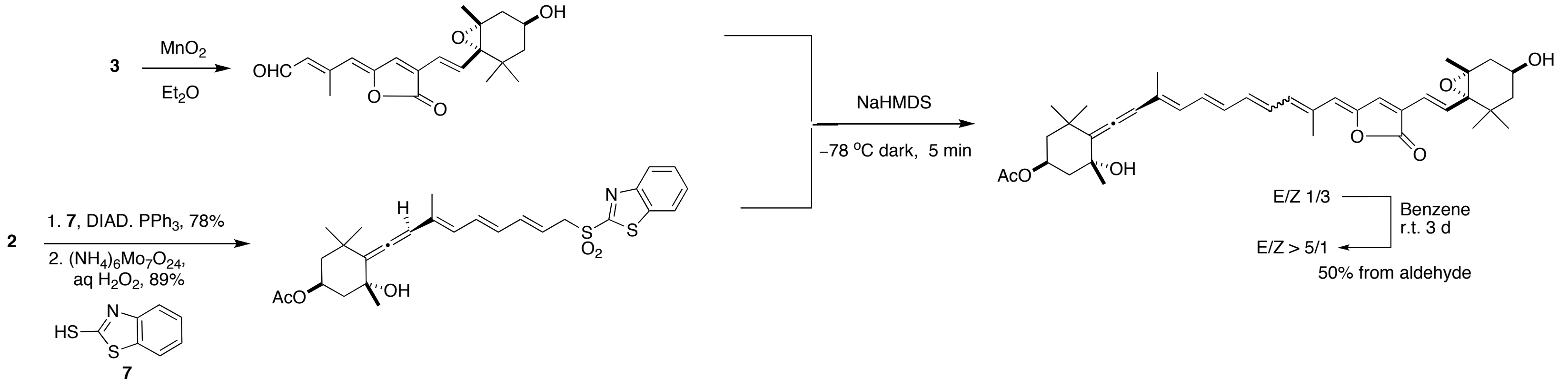
3. $NaBH_4$, MeOH, 98%

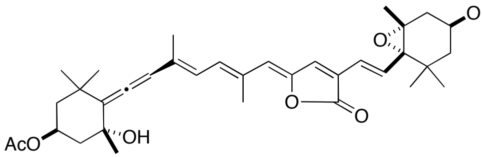


"Domino Reaction"

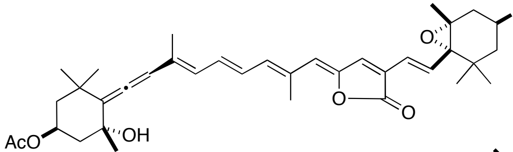
Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949.
Yamano, Y.; Tode, C.; Ito, M. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1599.

Katsumra's Total Synthesis cont.

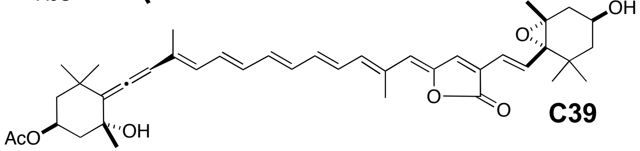




C33



C35



C39

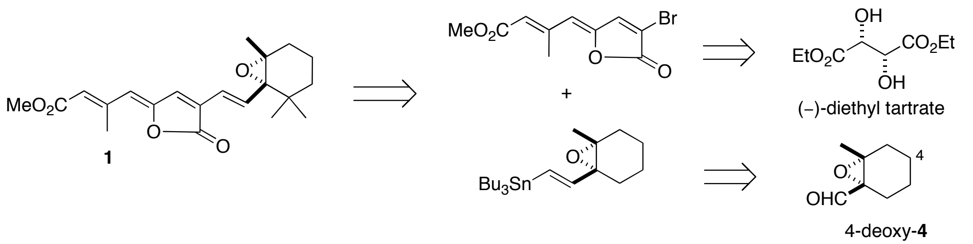
Table 2. λ_{max} and Stark Spectral Data of Peridinin and Derivatives

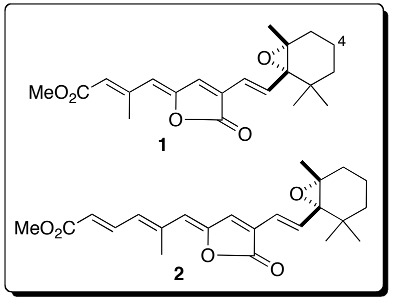
	λ_{max} (nm)		
	hexane	methanol	$\lvert \Delta\mu \rvert$ ($\times 10^{-29}$ C·m)
C33-peridinin **2**	416.0	429.5	
C35-peridinin **3**	436.5	455.0	4.25
peridinin **1**	454.0	472.0	5.42
C39-peridinin **4**	469.0	488.5	5.29

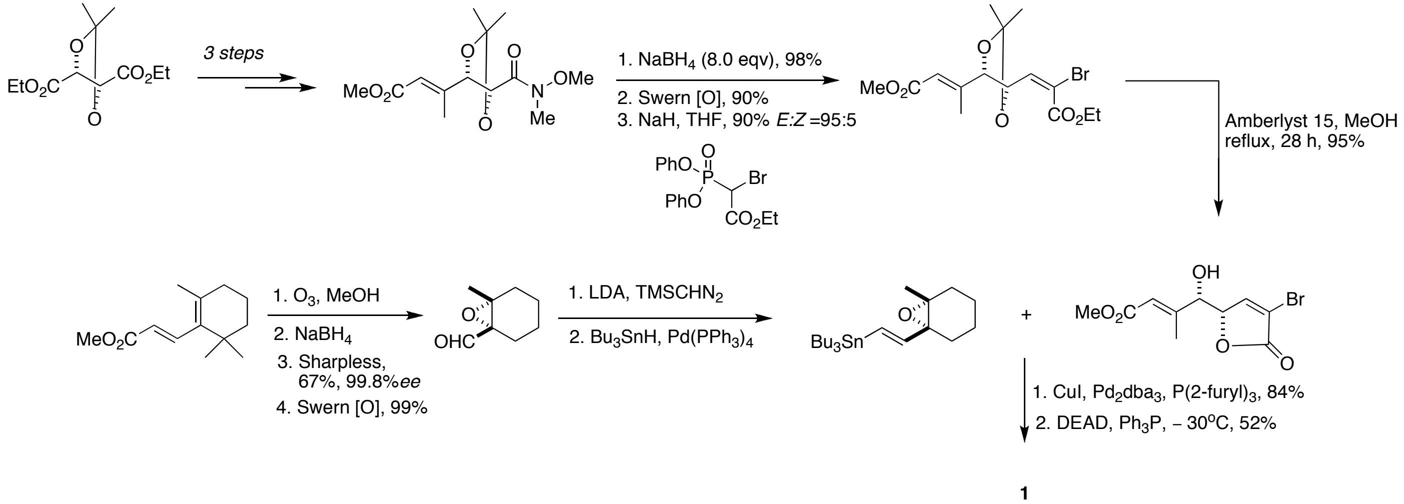
- Peridinin posses large static dipole moment facilitating energy transfer.

Katsumura *at el Org. Lett*. **2009**, 11, 5006.

Brückner's Approach to the Butenolide Moeity:



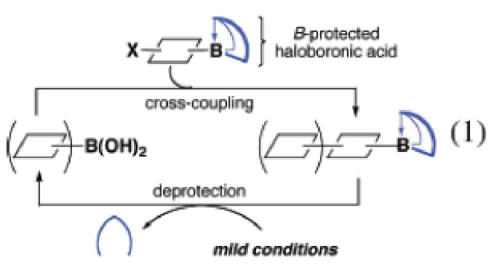


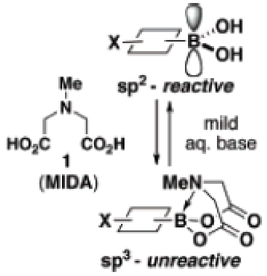


- **2** was also prepared in the same fashion.
- Later in 2006, used the same methodology to complete the synthesis of Peridinin.

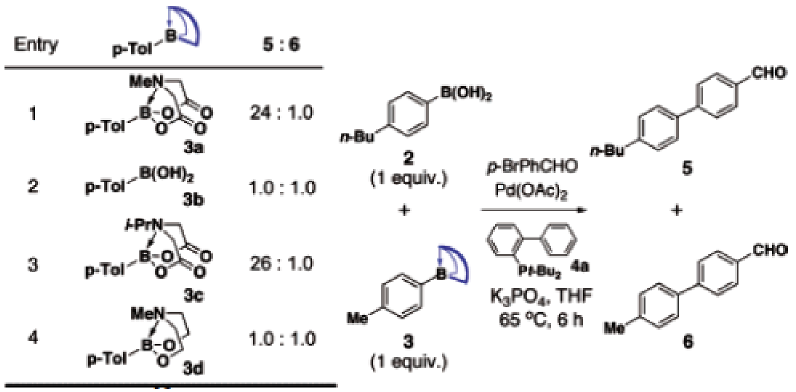
Olpp, T.; Brückner, R. *Angew. Chem., Int. Ed.* **2005**, 44, 15533.
Olpp, T.; Brückner, R. *Angew. Chem., Int. Ed.* **2006**, 45, 4023.

Burke's Work: MIDA Mask

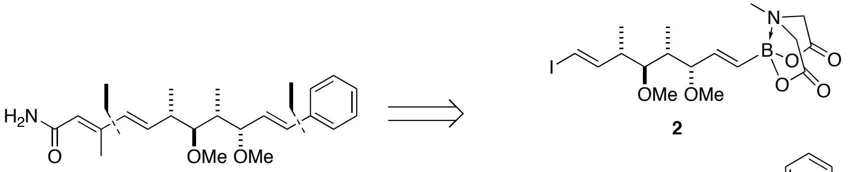




- Highly unreactive.
- Very stable to most C-C conditions.
- Easily removable under mild conditions.
- Stable to silica chromatography and storage.



Entry	p-Tol–B	5 : 6
1	3a	24 : 1.0
2	3b	1.0 : 1.0
3	3c	26 : 1.0
4	3d	1.0 : 1.0

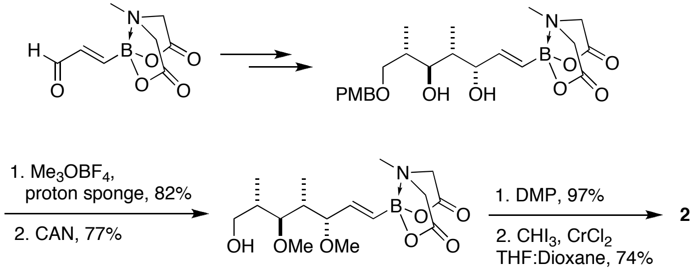


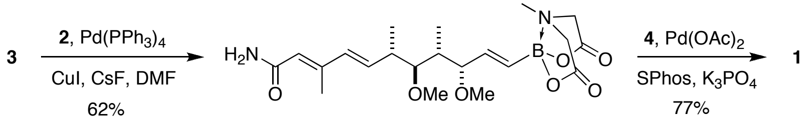
1 Crocacin C

2

3

4

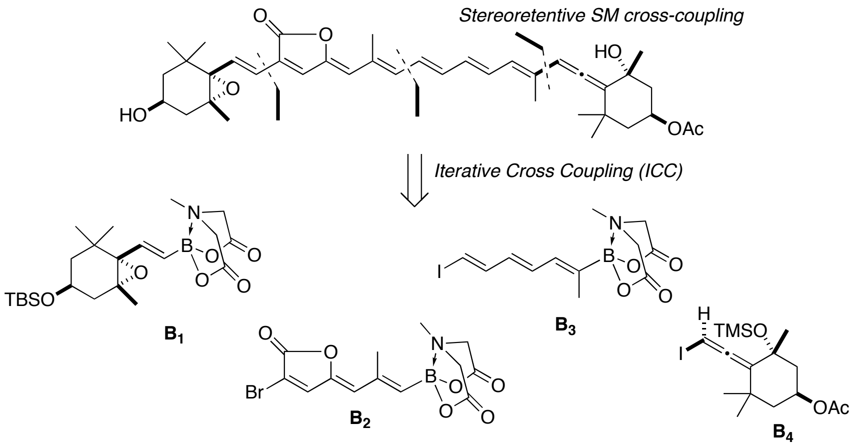




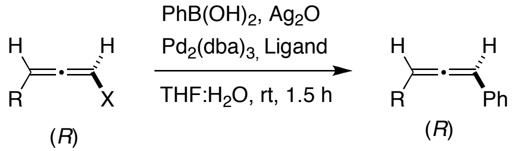
- Nine linear steps synthesis of crocacin C

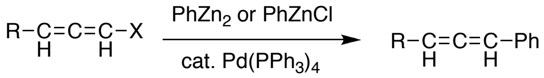
Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, 129, 6716.
Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, 130, 14084.

Title Paper - Key Reaction:

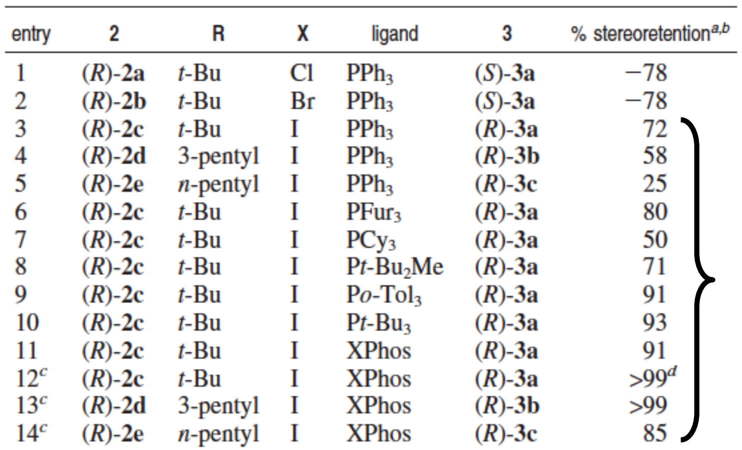


Key Reaction:





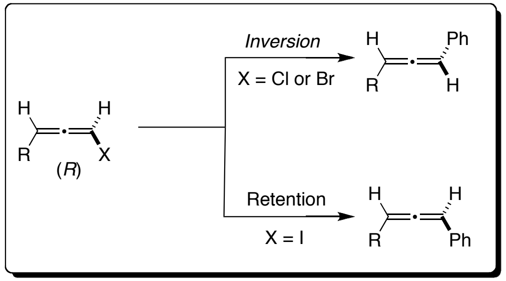
$$\mathrm{R{-}\underset{H}{C}{=}C{=}\underset{H}{C}{-}X} \xrightarrow[\text{cat. Pd(PPh}_3)_4]{\text{PhZn}_2\text{ or PhZnCl}} \mathrm{R{-}\underset{H}{C}{=}C{=}\underset{H}{C}{-}Ph}$$



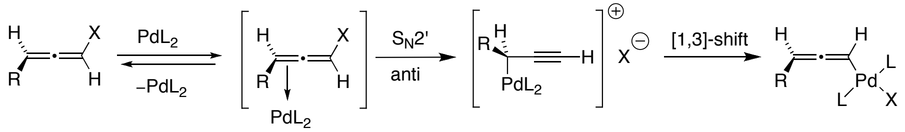
entry	2	R	X	ligand	3	% stereoretention[a,b]
1	(*R*)-**2a**	*t*-Bu	Cl	PPh_3	(*S*)-**3a**	−78
2	(*R*)-**2b**	*t*-Bu	Br	PPh_3	(*S*)-**3a**	−78
3	(*R*)-**2c**	*t*-Bu	I	PPh_3	(*R*)-**3a**	72
4	(*R*)-**2d**	3-pentyl	I	PPh_3	(*R*)-**3b**	58
5	(*R*)-**2e**	*n*-pentyl	I	PPh_3	(*R*)-**3c**	25
6	(*R*)-**2c**	*t*-Bu	I	$PFur_3$	(*R*)-**3a**	80
7	(*R*)-**2c**	*t*-Bu	I	PCy_3	(*R*)-**3a**	50
8	(*R*)-**2c**	*t*-Bu	I	P*t*-Bu_2Me	(*R*)-**3a**	71
9	(*R*)-**2c**	*t*-Bu	I	P*o*-Tol_3	(*R*)-**3a**	91
10	(*R*)-**2c**	*t*-Bu	I	P*t*-Bu_3	(*R*)-**3a**	93
11	(*R*)-**2c**	*t*-Bu	I	XPhos	(*R*)-**3a**	91
12[c]	(*R*)-**2c**	*t*-Bu	I	XPhos	(*R*)-**3a**	>99[d]
13[c]	(*R*)-**2d**	3-pentyl	I	XPhos	(*R*)-**3b**	>99
14[c]	(*R*)-**2e**	*n*-pentyl	I	XPhos	(*R*)-**3c**	85

Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* (ASAP)
Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, 50, 3042.

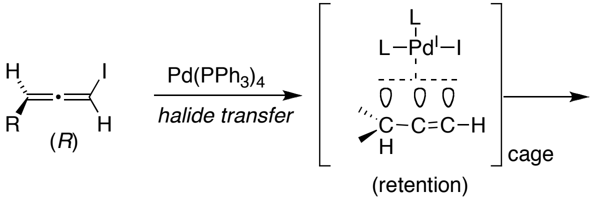
Pd(0)-Catalysed Phenylation of 1-Haloallenes:



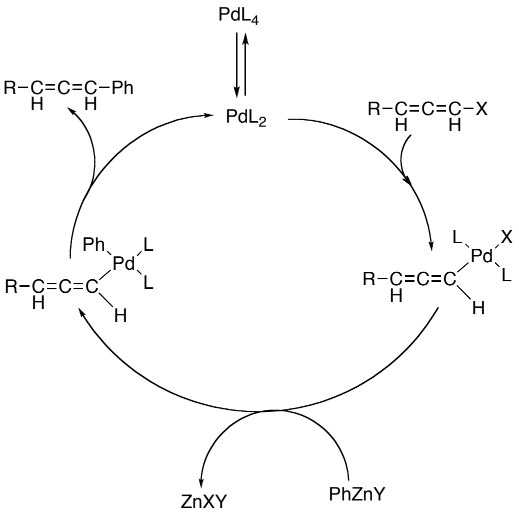
Inversion:



Retention:



- Oxidative addition to Pd decreases I > Br > Cl, as in vinyl halides.
- Heavier metals, group VIII show affinity to heavy halogens.
- Possible radical intermediate in which recombination rate is faster.

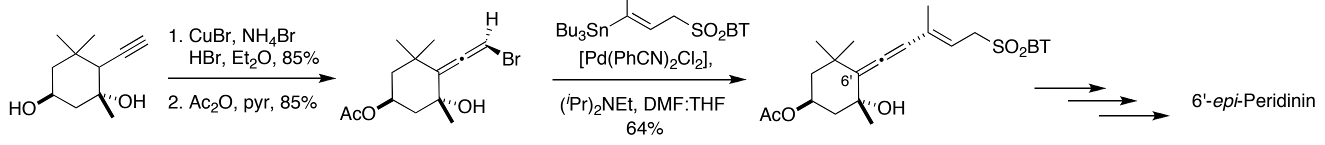


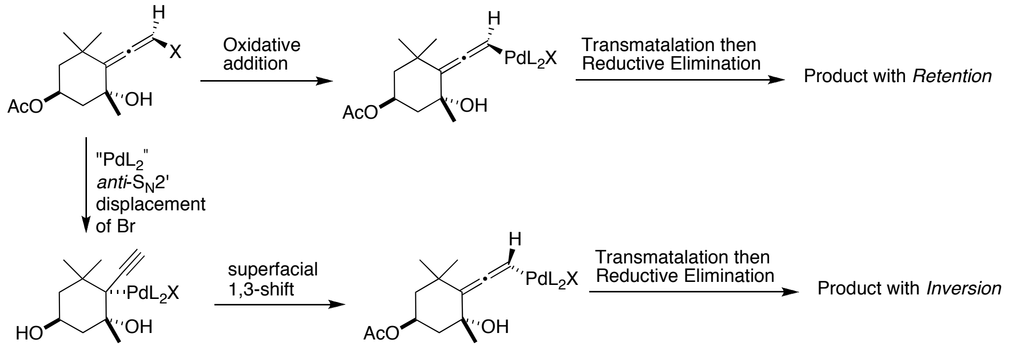
Proposed catalytic cycle

Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, 50, 3042.

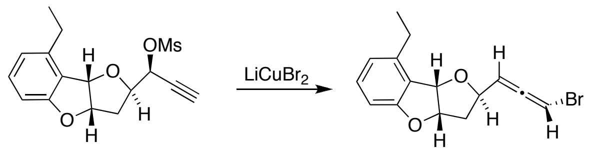
Application in Synthesis:

Lera's Synthesis of Peridinin:

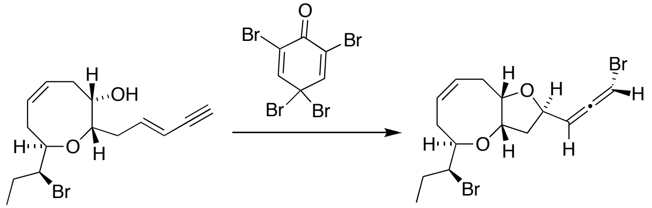




Haloallene Natural Products:



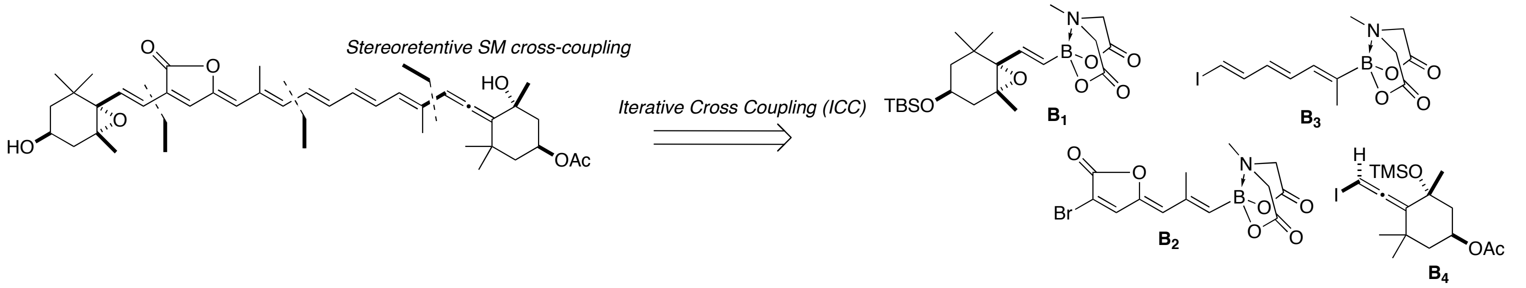
Panacene

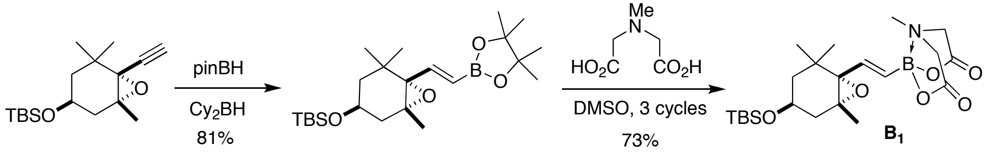


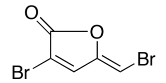
Laurellene

Vaz, B.; Domínguez, M.; Alvarez, R.; de Lera, A. R. *Chem.-Eur. J.* **2007**, 13, 1273.
K. S. Feldman, C. C. Mechem, L. Nader, *J. Am. Chem. Soc.* **1982**, 104, 4011.
M. T. Crimmins, E. A. Tabot, *J. Am. Chem. Soc.* **2000**, 122, 5473.

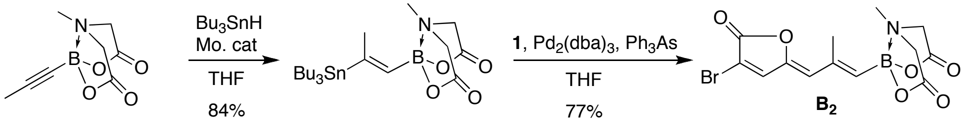
Title Paper: Forward Synthesis







1

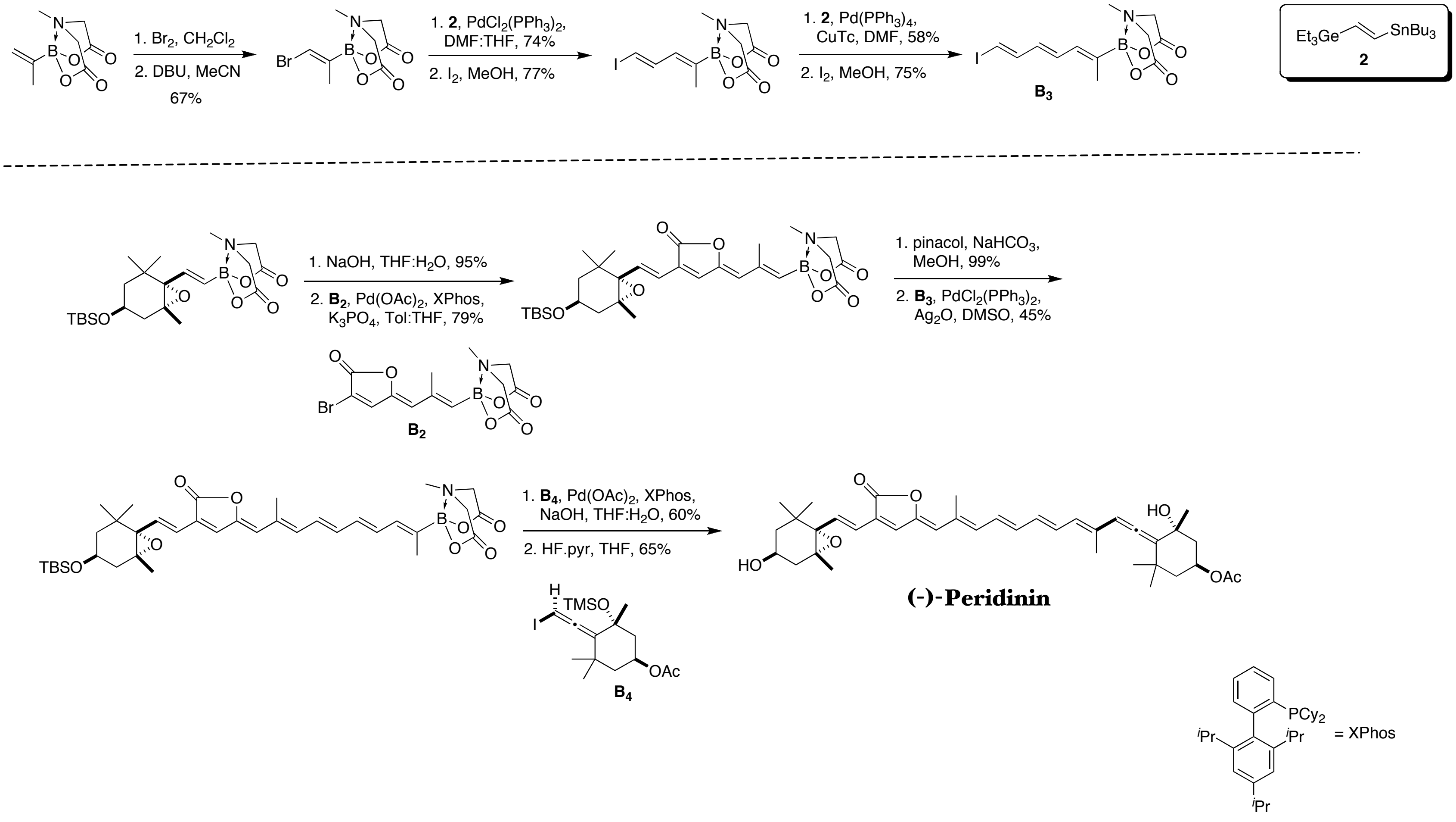


Mo cat = $[Mo(allyl)Br(CO)_2(CH_3CN)_2]$

Structure confirmed by X-ray

Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* (ASAP)
Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949.
Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

Total Synthesis of (-)-Peridinin: Final Steps



Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* (ASAP)

Conclusion:

- Synthesis of (+)-Peridinin focused on a late stage construction of olefins, which proved problematic due to the E/Z isomerization.
- Burke's strategy proved successful in avoiding the isomerization using a different approach, SM cross coupling, in his synthesis of (-)-Peridinin.
- Combination of bulky substituent and ligand promoted stereoretention in SM cross coupling of Iodo-allenes.
- Using a more stable MIDA boronates which has a lot of advantageous in the modern synthetic chemistry.
- Achieved 1st Stereoselective total synthesis of (–)-Peridinin.