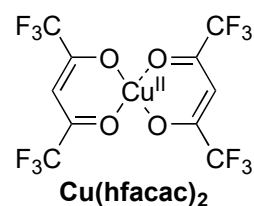
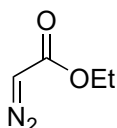
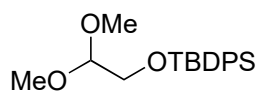
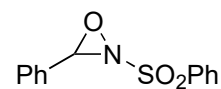
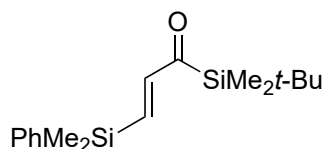
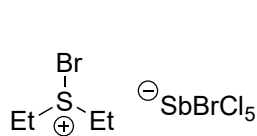
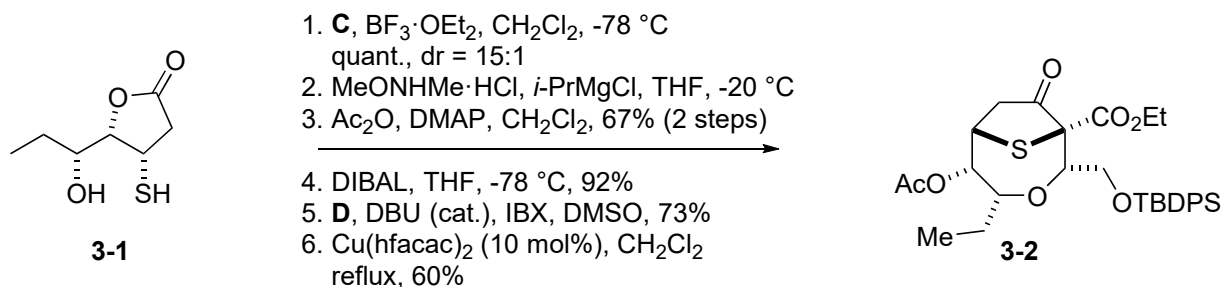
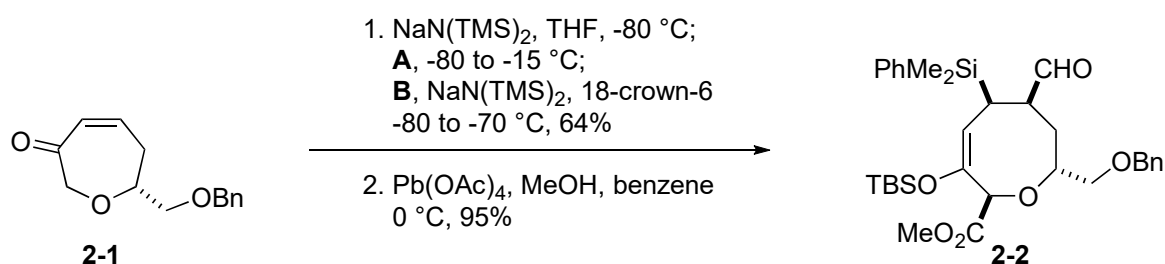
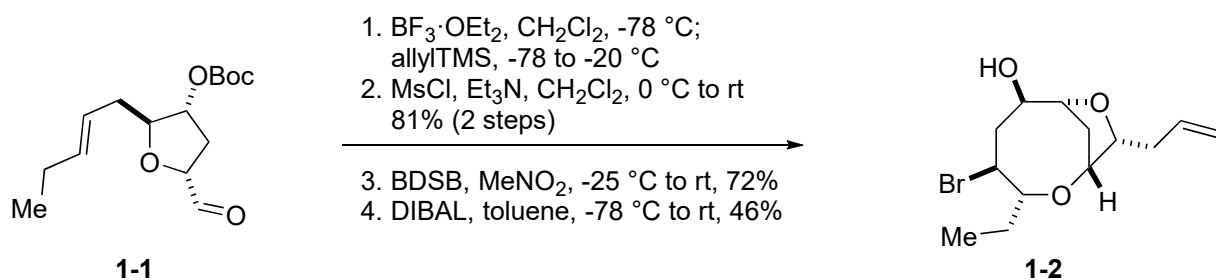


Problem Session (5)

2017.10.28. Hiroaki Matoba

Please provide each reaction mechanisms and explain the stereoselectivities.



Problem Session (5)

2017.10.28. Hiroaki Matoba

Topics: Synthetic studies of Lauroxocanes

Introduction

Laurencia C15 acetogenins

Isolated from *Laurencia* sp. (red algae)
cyclic bromoether core (4-12 membered ring)

Laroxocanes

8-membered ring ether
the largest subset of the *Laurencia* C15 acetogenins family

Laurencin

Isolation

Laurencia glandulifera (Irie et al. *TL*, **1965**, *16*, 1091.) etc...

Total syntheses (method for construction of oxecene core)

Masamune et al. *TL*, **1977**, *18*, 2507. (ring expansion: from bicyclo [3.3.1] nonane)
Murai and Tsushima *TL*, **1992**, *33*, 4345. (ring expansion: from bicyclo [4.2.0] octane)
Overman et al. *JACS*, **1995**, *117*, 5958. (acetal-vinylsulfide cyclization)
Holmes et al. *JACS*, **1997**, *119*, 7483. (Baeyer-Villiger oxidation: from cycloheptenone)
Crimmins and Emmitte *OL*, **1999**, *1*, 2029. (RCM)
Fujiwara et al. *TL*, **2005**, *46*, 6819. (RCM)
Kim et al. *OL*, **2005**, *7*, 75. (intramolecular amide enolate alkylation)

Formal syntheses

Palenzuela et al. *Synlett*, **1996**, 983. (SN2 reaction of α -sulfonyl anion to epoxide)
Hofmann and Krüger *JACS*, **1997**, *119*, 7499. (intramolecular allylboration)
Crimmins and Choy *JACS*, **1999**, *121*, 5653. (RCM)
Pansare and Adsool *OBC*, **2008**, *6*, 2011. (RCM)
Martin et al. *JOC*, **2010**, *75*, 6660. (RCM)
West et al. *OL*, **2017**, *19*, 552. (Stevens rearrangement: from bicyclo [4.3.0] nonane)

Laurefucin

Isolation

Laurencia subopposita (Wratten and Faulkner *JOC*, **1977**, *42*, 3343.) etc...

Total synthesis

Kim et al. *JACS*, **2008**, *130*, 16807. (intramolecular amide enolate alkylation)

Formal synthesis

Snyder et al. *JACS*, **2012**, *134*, 17714. (ring expansion: from bicyclo [3.3.0] octane)

Laurallene

Isolation

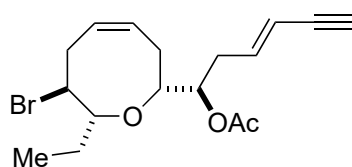
Laurencia nipponica (Fukuzawa and Kurosawa *TL*, **1979**, *20*, 2797.) etc...

Total syntheses

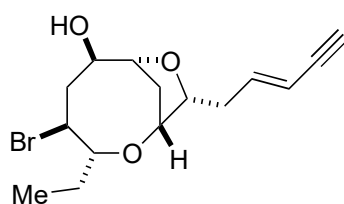
Crimmins and Tabet *JACS*, **2000**, *122*, 5473. (RCM)
Suzuki et al. *TL*, **2003**, *44*, 3175. (cyclization of hydroxy epoxide)
Kim et al. *JACS*, **2012**, *134*, 20178. (RCM)

Formal syntheses

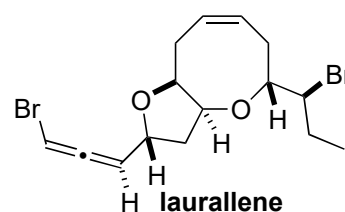
Takeda et al. *OL*, **2008**, *10*, 1803. ([3+4] annulation)
Takeda et al. *JOC*, **2010**, *75*, 3941. ([3+4] annulation)



laurencin



laurefucin

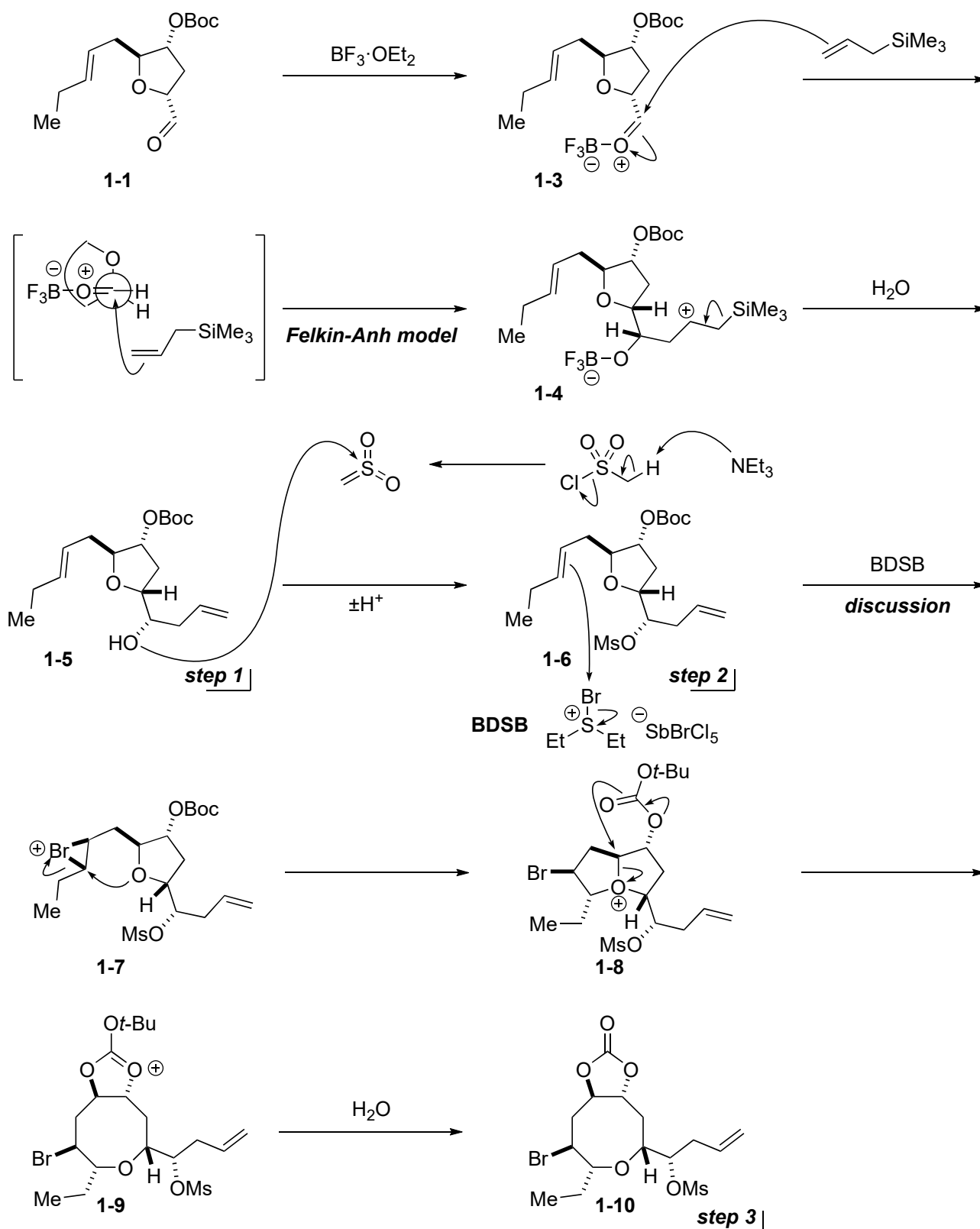
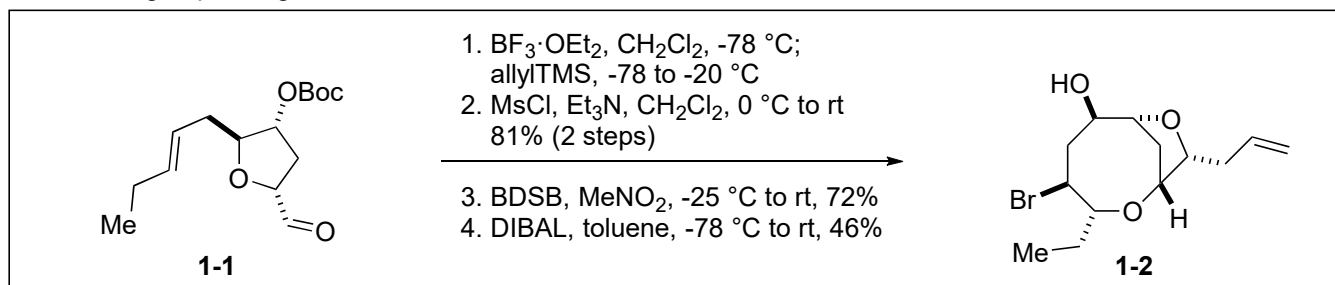


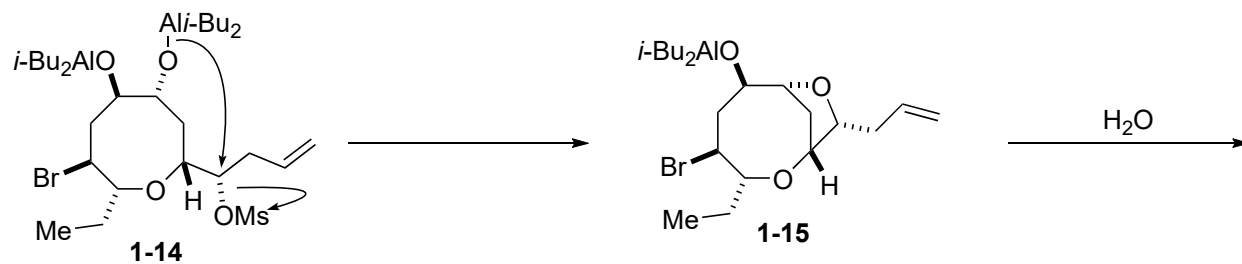
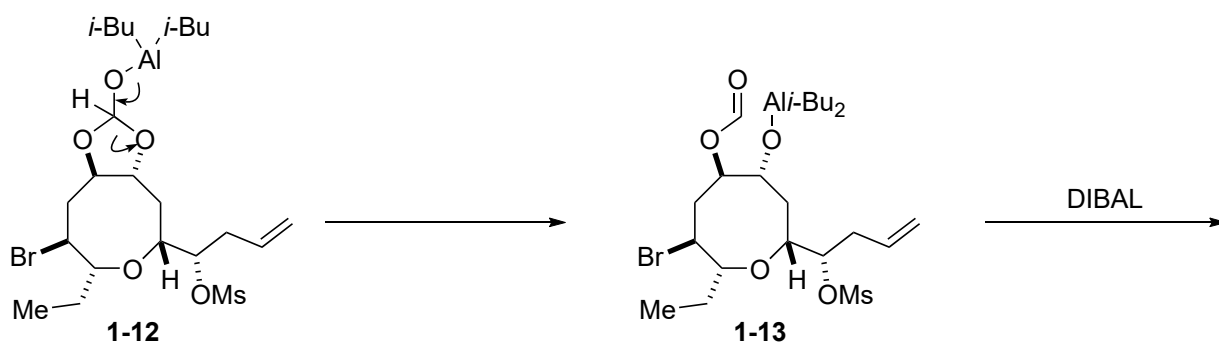
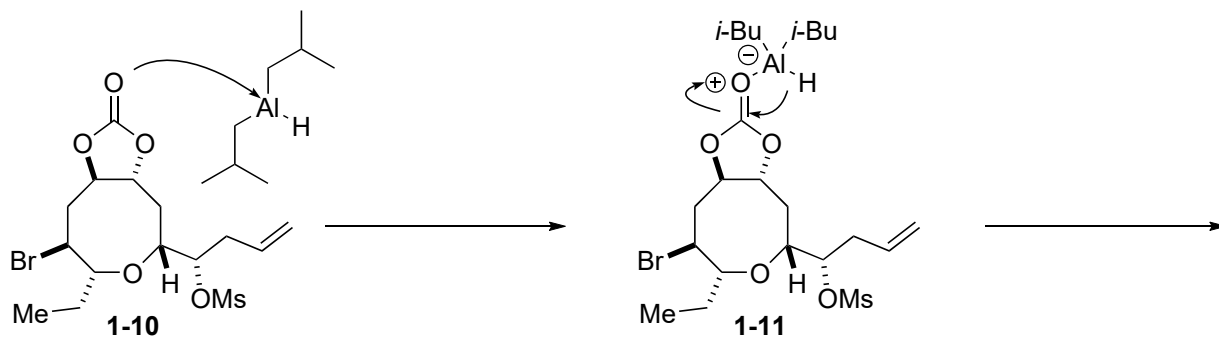
laurallene

Answer

1. Formal synthesis of (±)-Laurefucin Snyder et al. *JACS*, **2012**, *134*, 17714

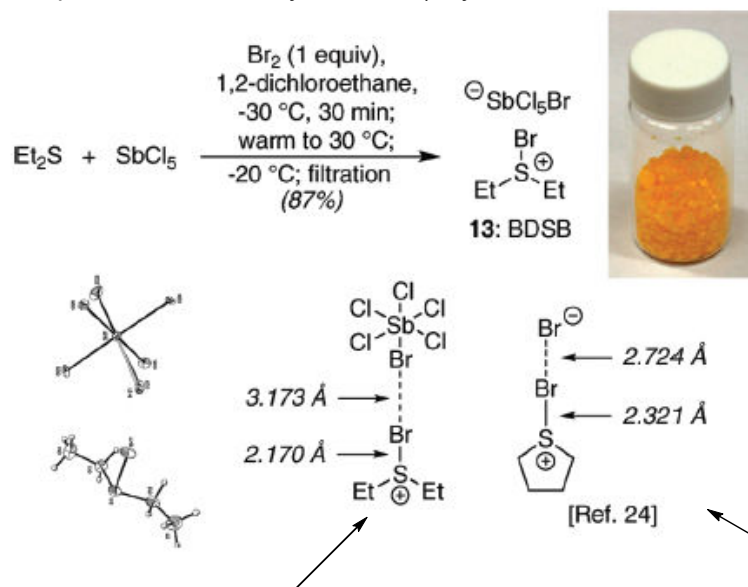
key: Ring-expanding bromoetherification





Discussion: BDSB mediated cyclization

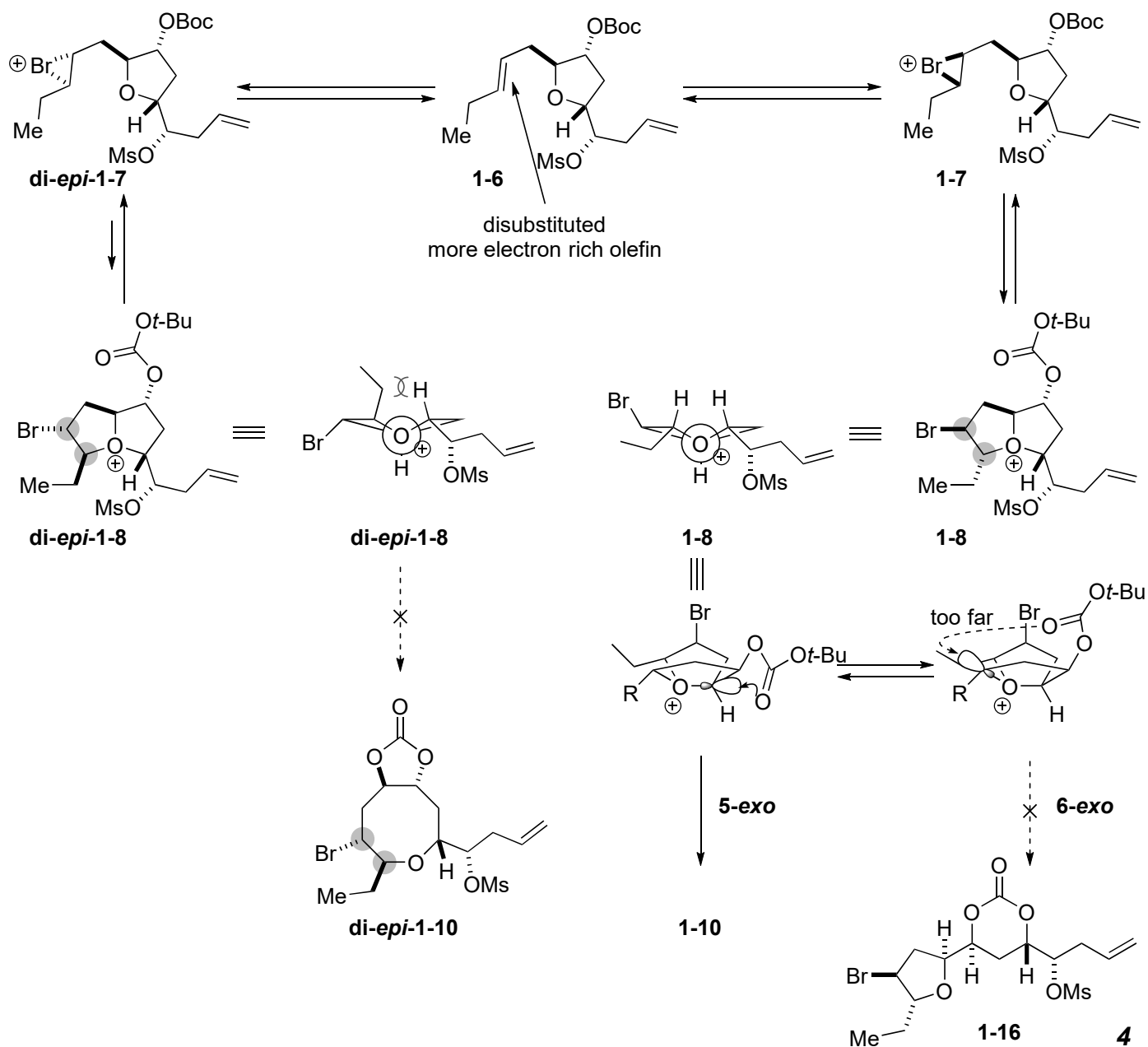
1. Properties and reactivity of BDSB (Snyder et al. *ACIE*, **2009**, *48*, 7899. *JACS*, **2010**, *132*, 14303.)



very effective reagent for cation- π cyclization

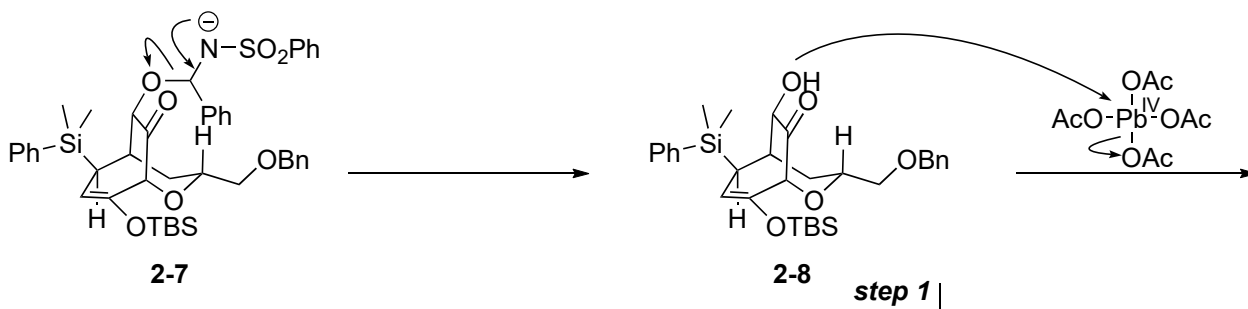
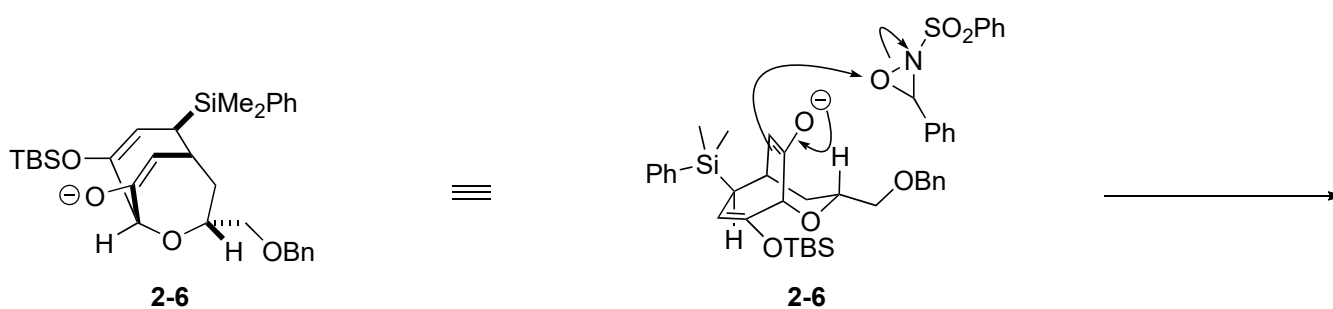
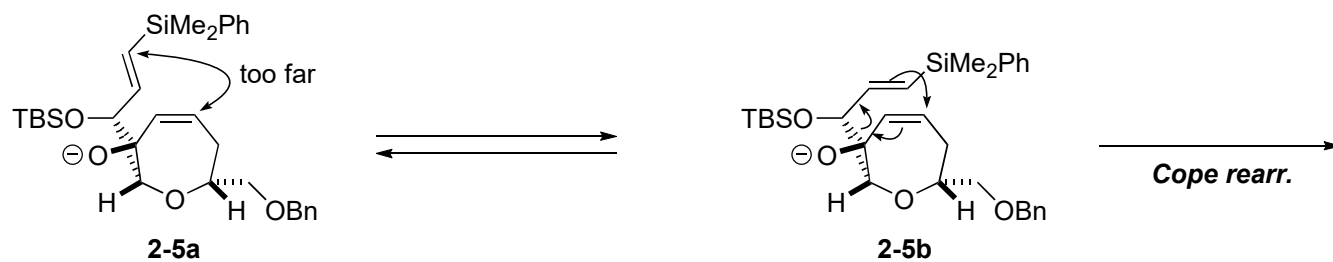
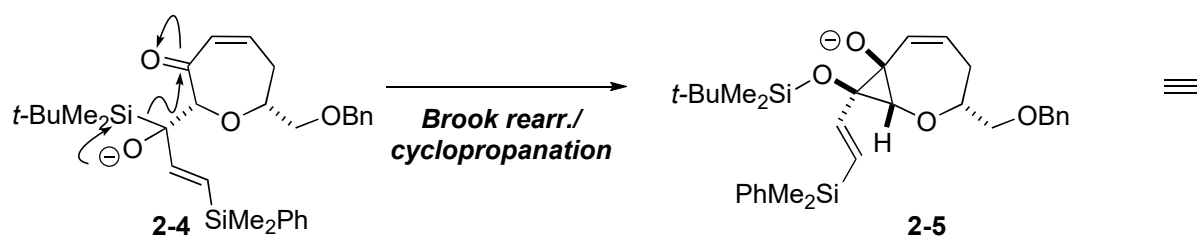
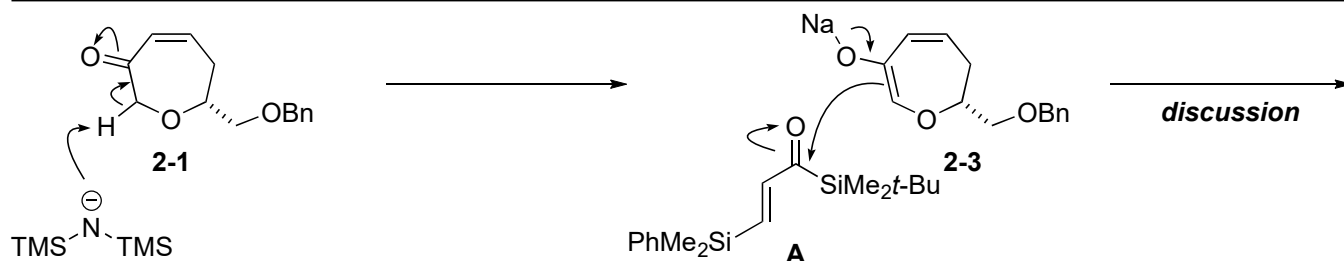
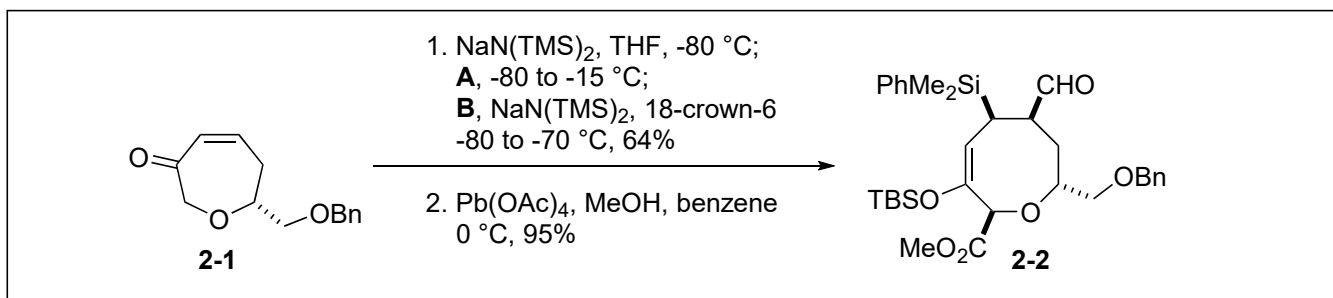
ineffective reagent for cation- π cyclization

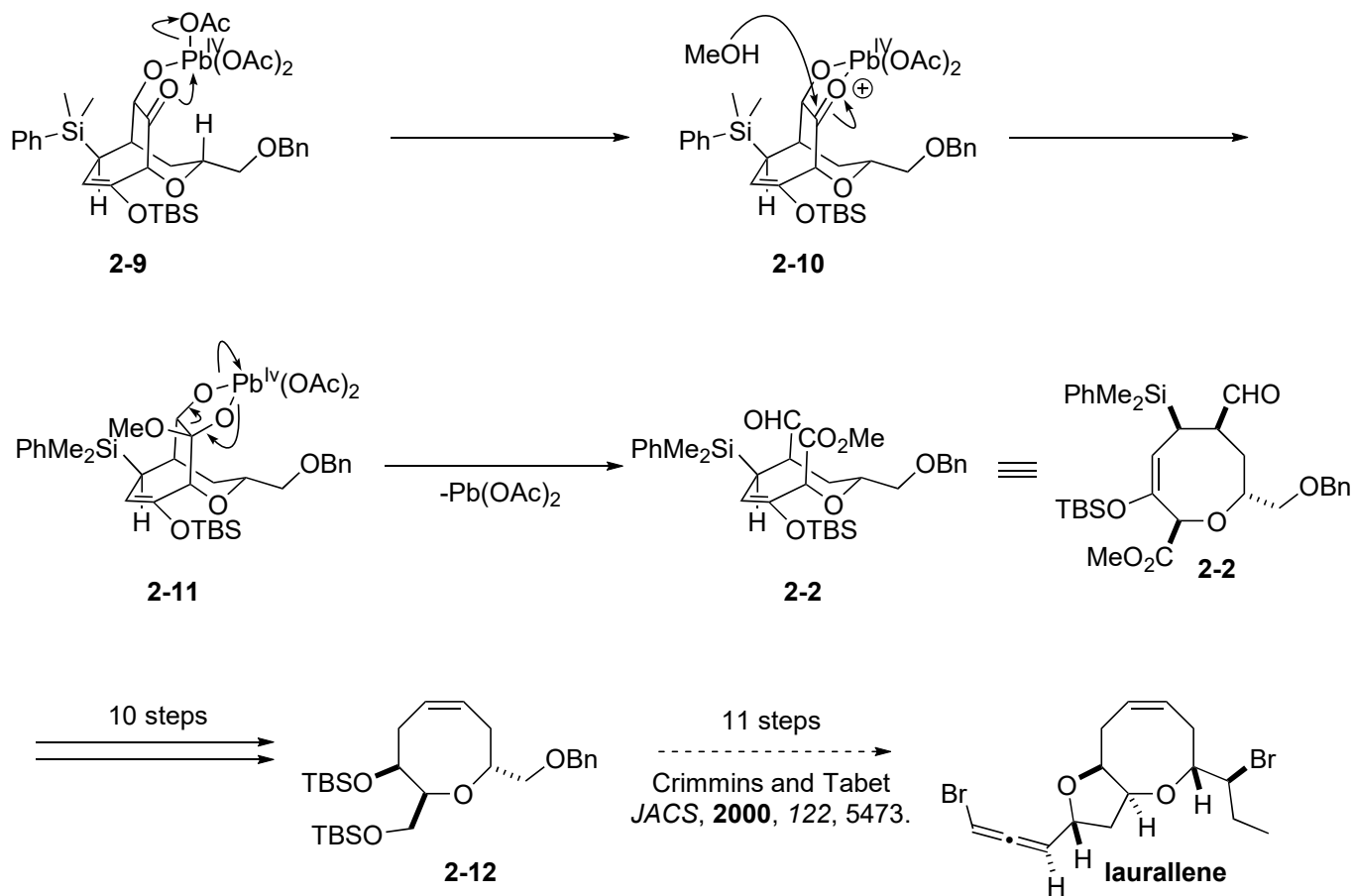
2. Regio and stereoselectivity



2. Formal synthesis of (+)-Laurallene Takeda et al. *OL*, **2008**, *10*, 1803.

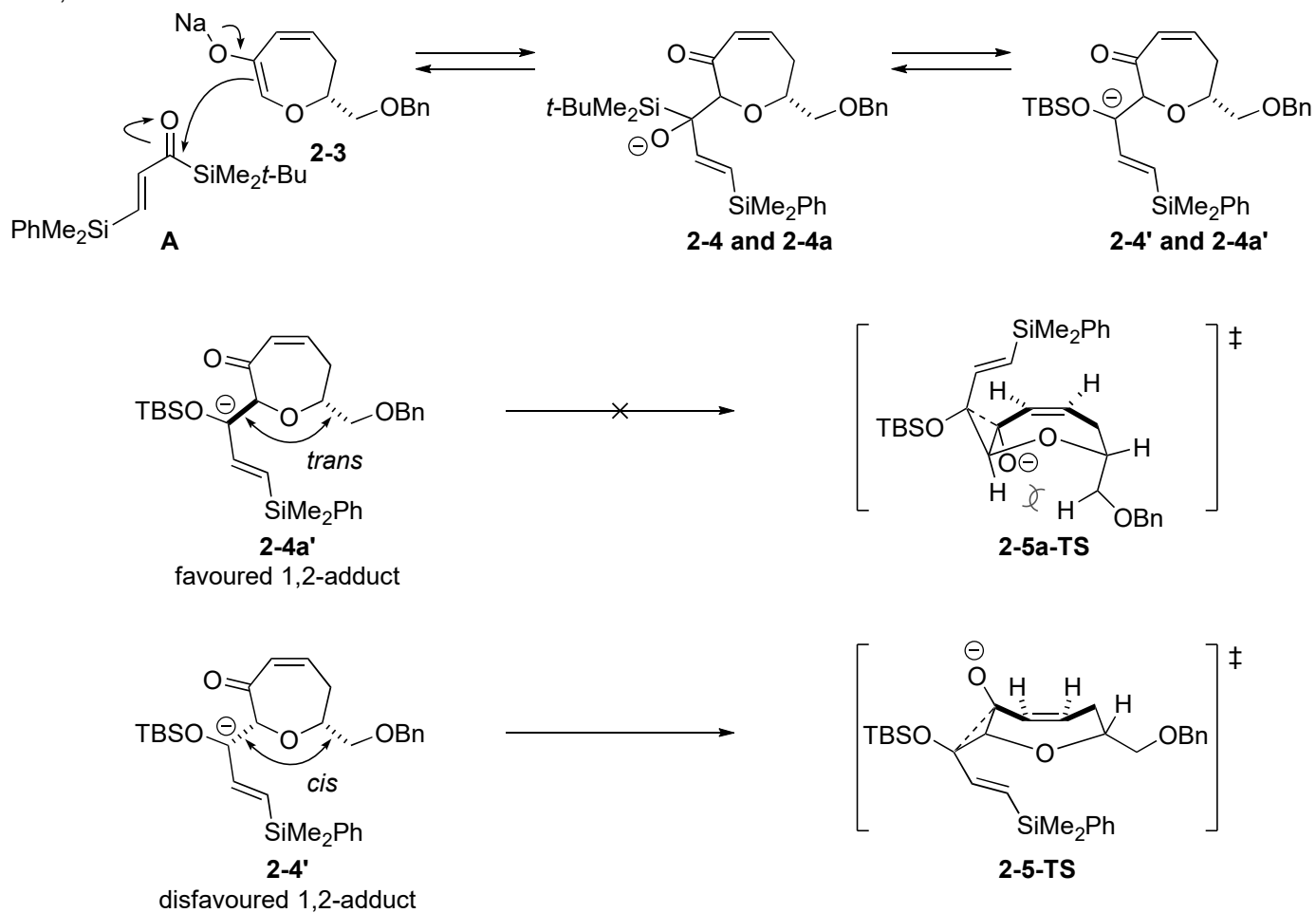
key: Brook rearrangement mediated [3+4] annulation



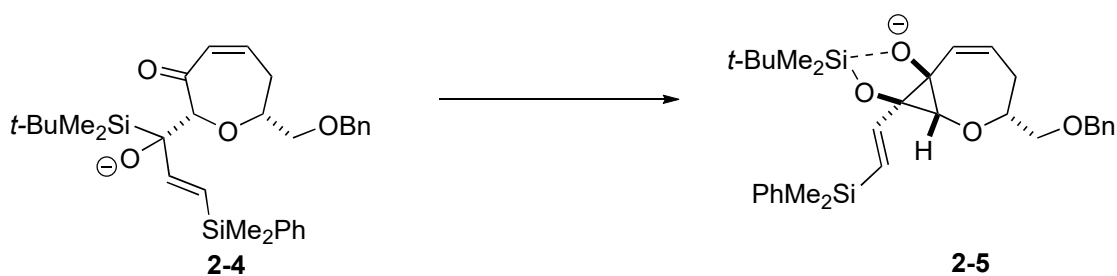


Discussion: [3+4] annulation

1. 1,2-addition

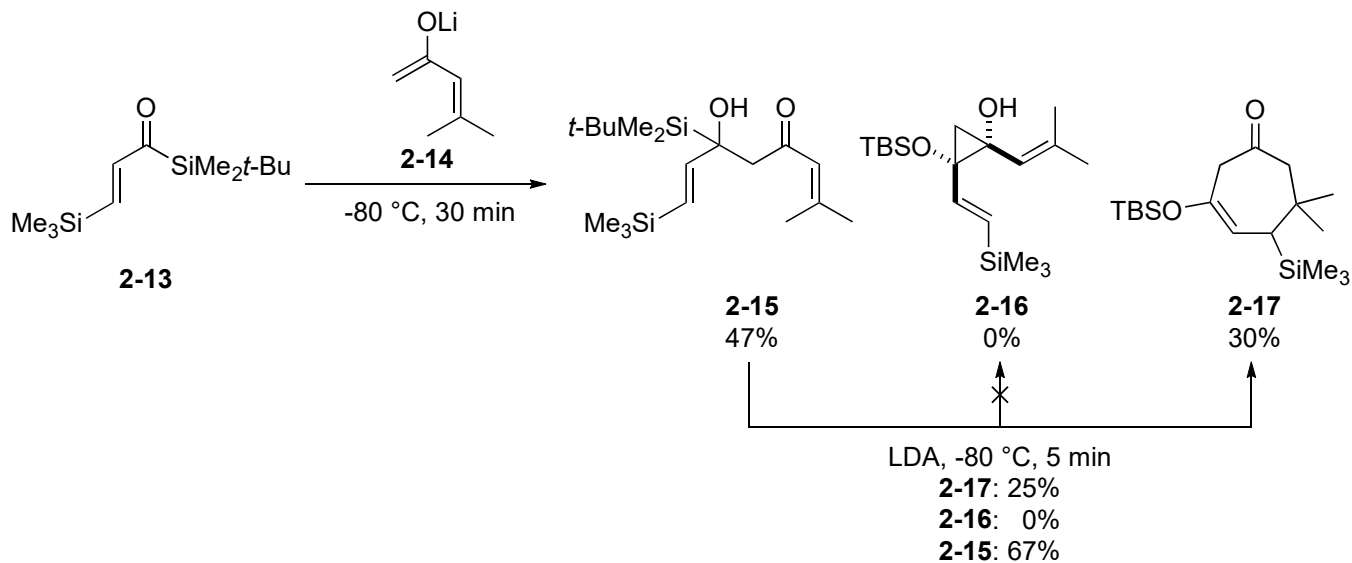


2. Brook rearrangement -> 1,2-addition

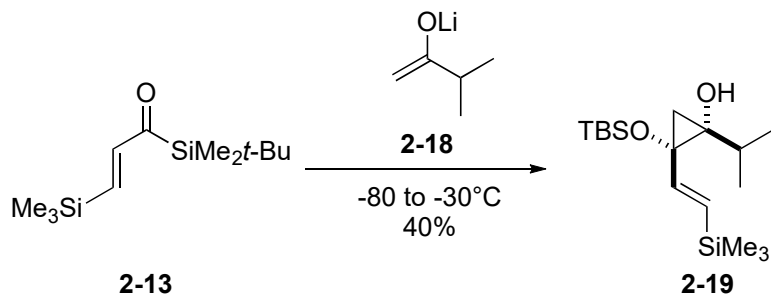


Internal O-Si coordinated structure invokes the stereoselectivity.

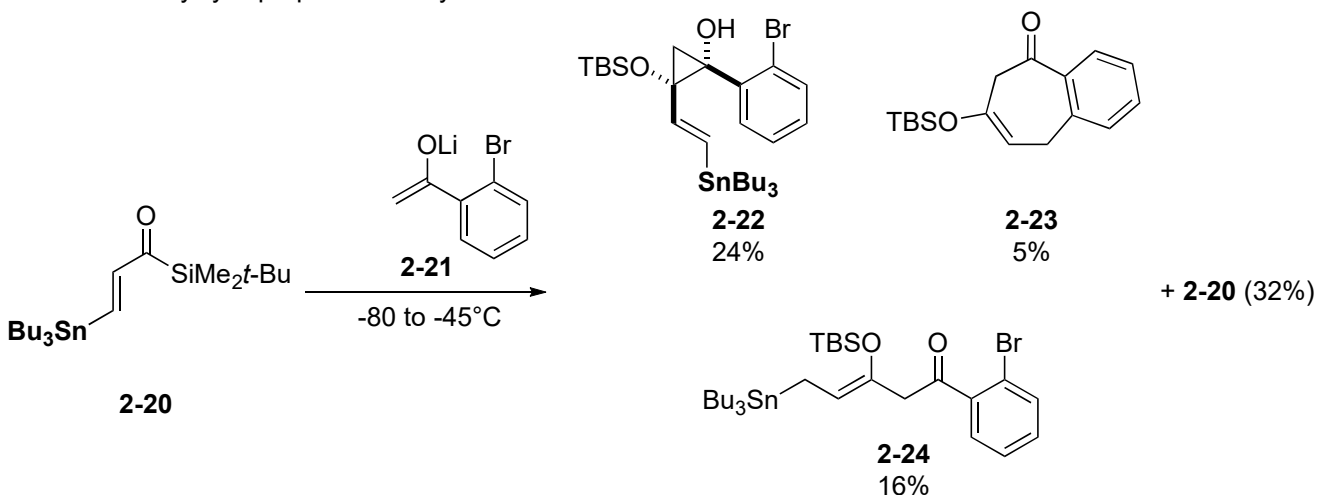
Experiments to trap the intermediate (Takeda et al. *JACS*, **1995**, *117*, 6400. *JACS*, **1998**, *120*, 4947.)
 Attempt to isolate divinylcyclopropane for vinyl silane



Isolation of related cyclopropane intermediate

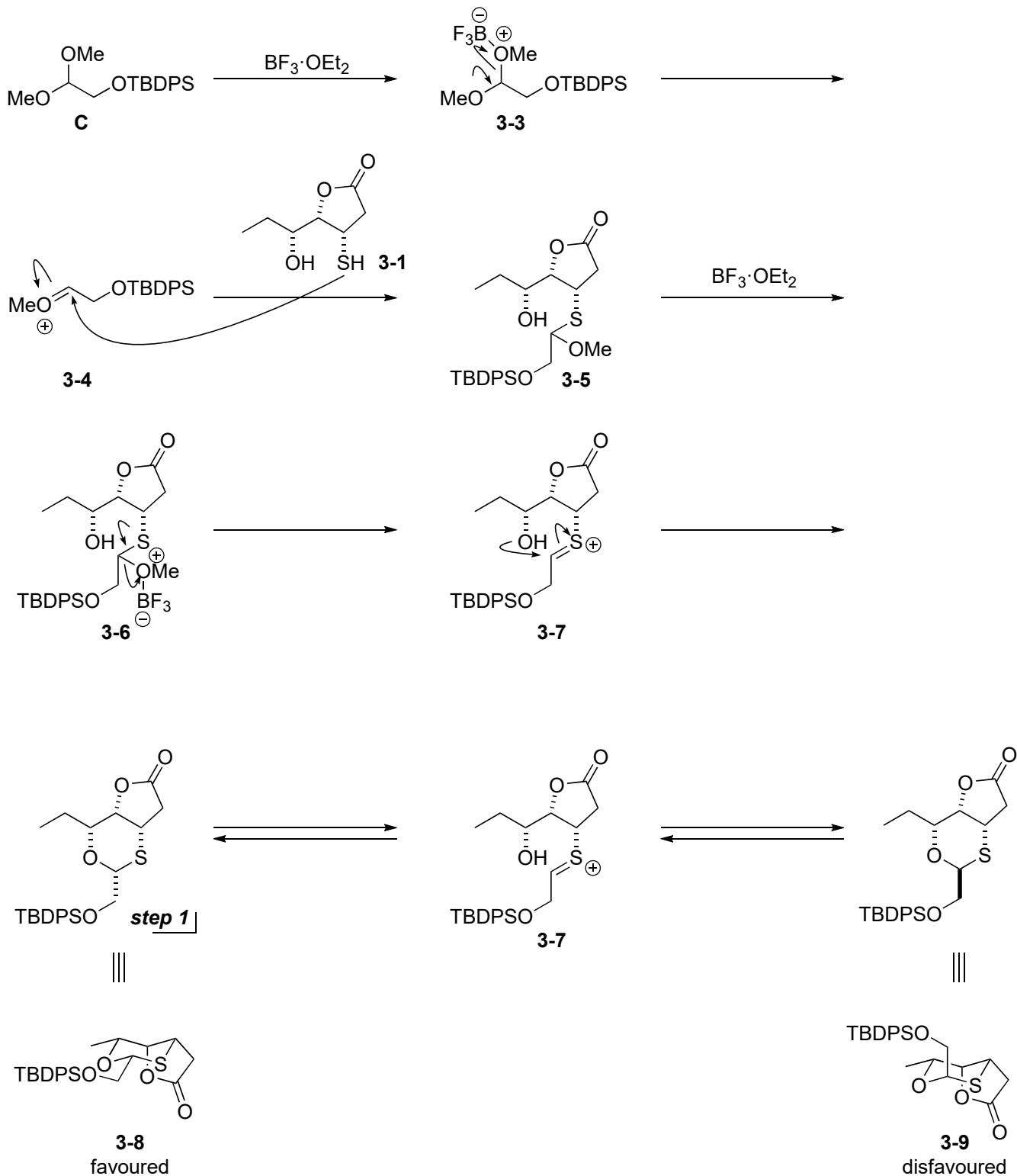
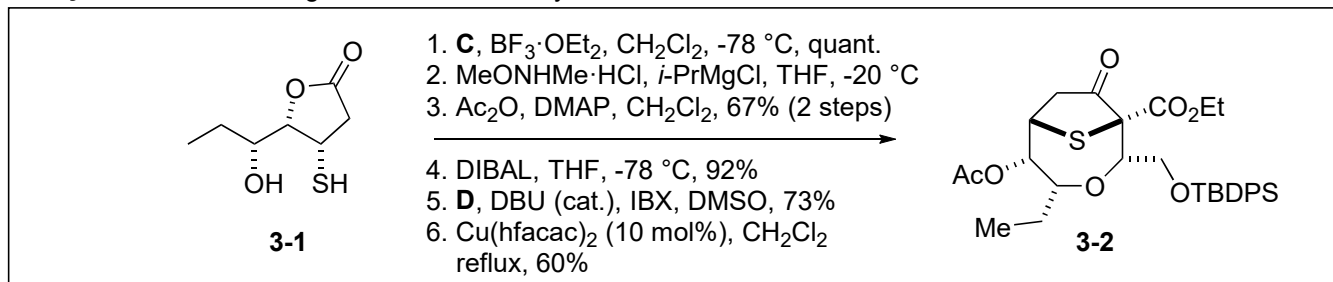


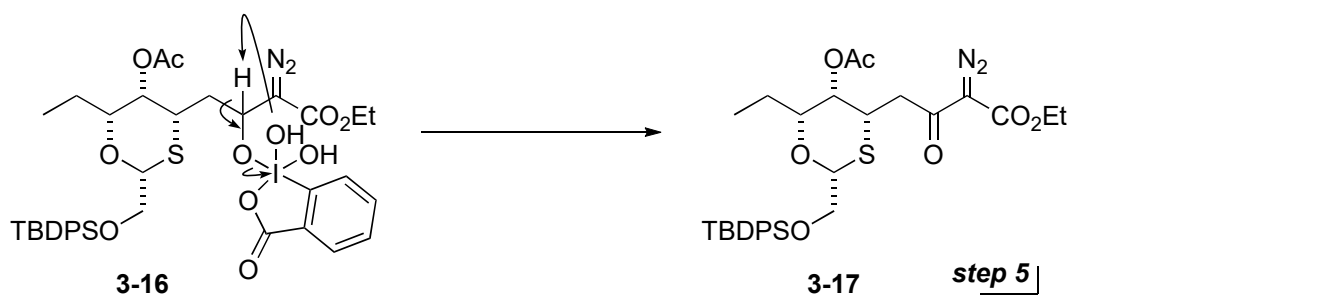
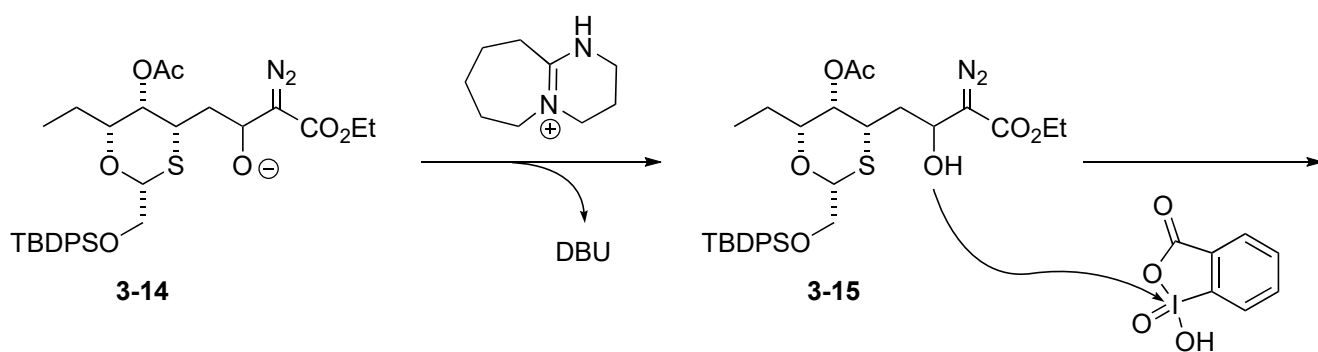
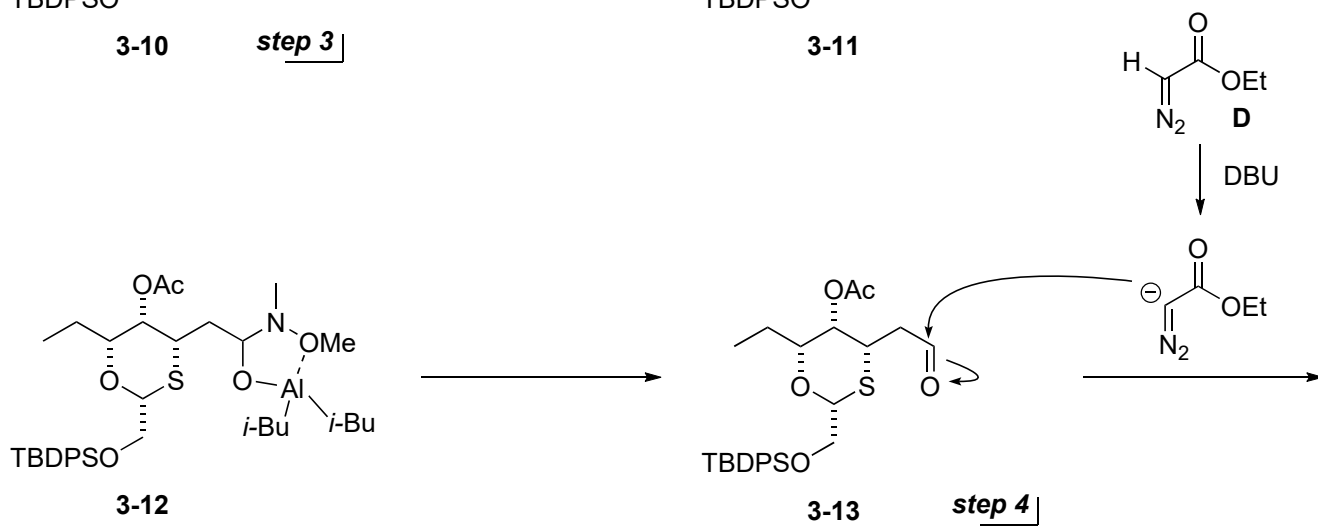
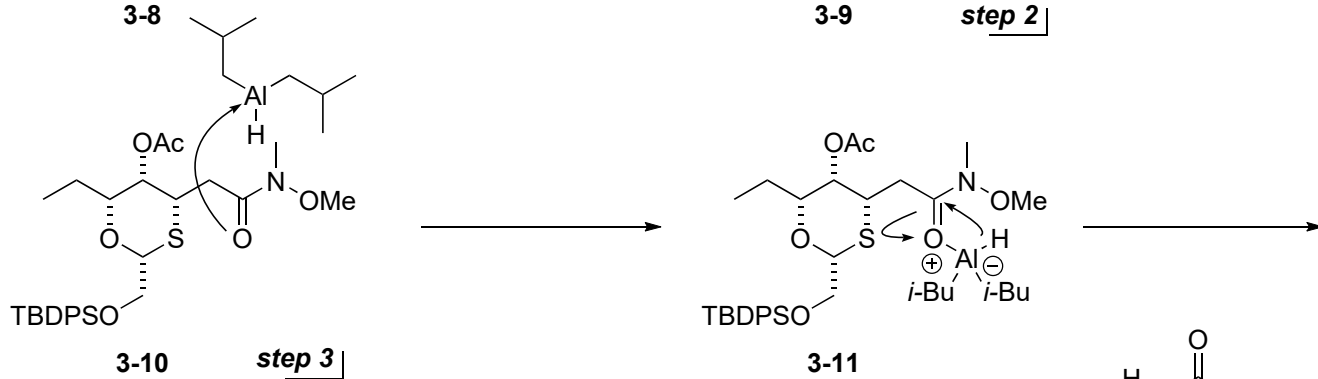
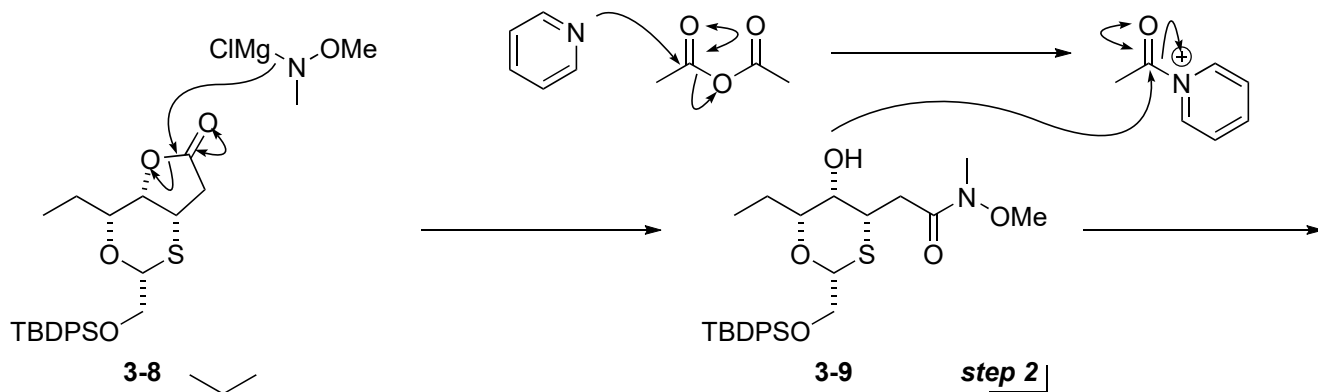
Isolation of divinylcyclopropane for vinyl stannane

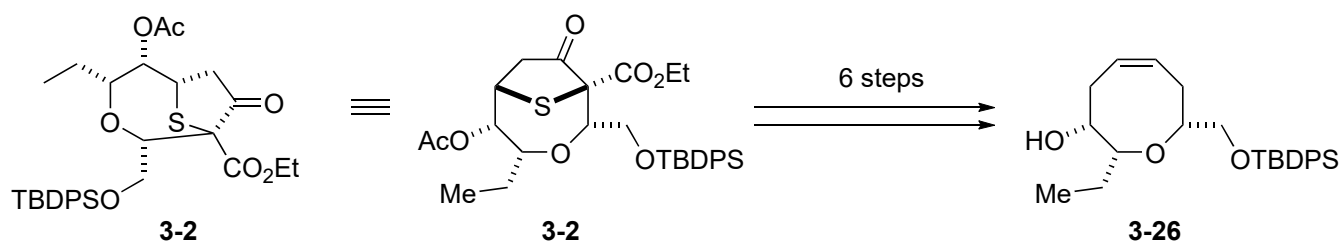
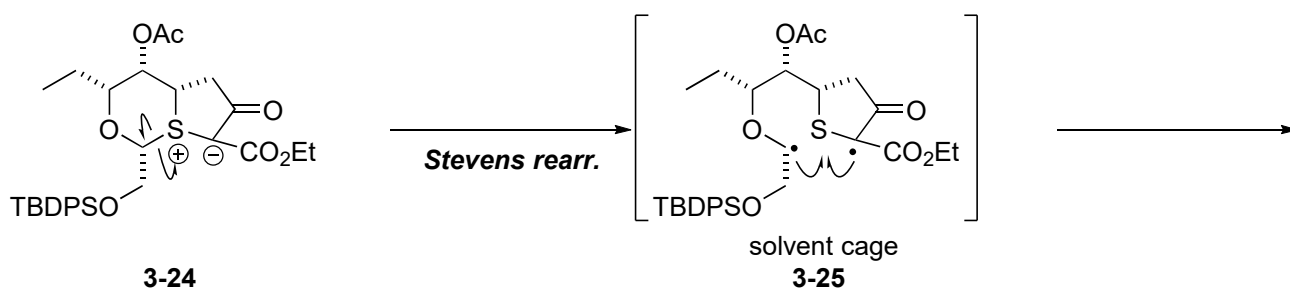
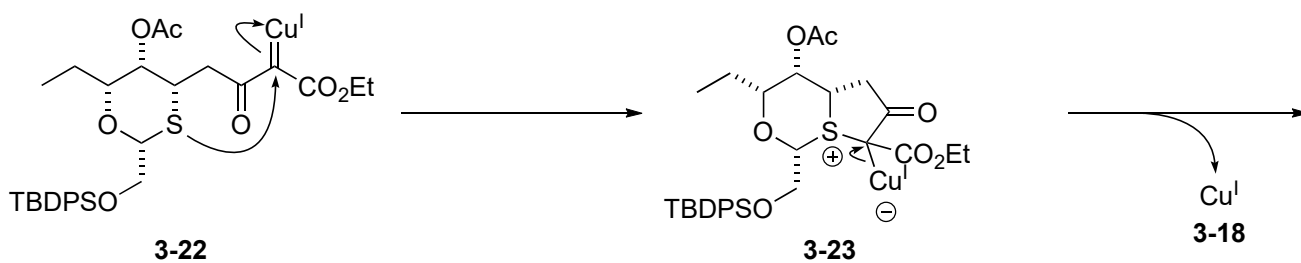
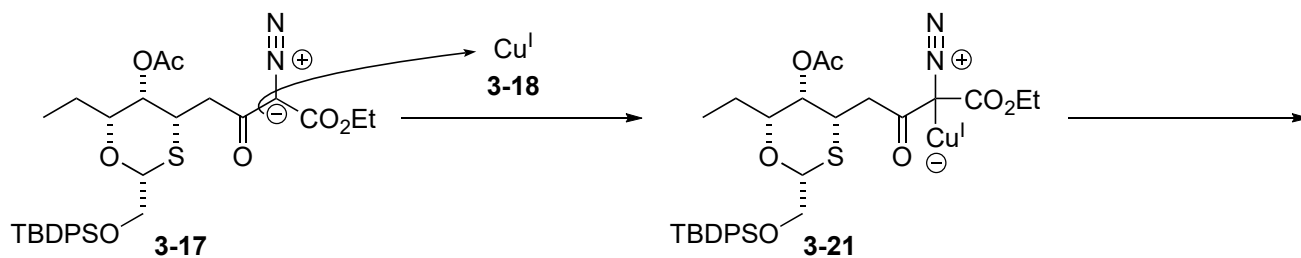
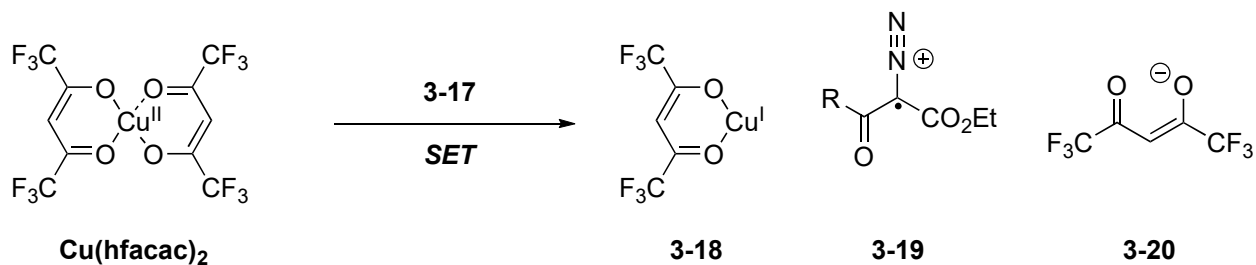


3. Formal synthesis of (+)-Laurencin West et al. *OL*, **2017**, *19*, 552.

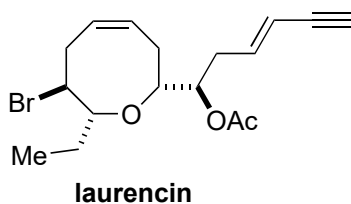
key: Stevens rearrangement of sulfonium ylide







8 steps
 Holmes et al.
 JACS, 1997, 119, 7483.



Discussion:

1. Cu(I) mediated decomposition of diazo compound

1-1. Cu(II) catalyzed cyclopropanation (Kochi et al. *JACS*, **1973**, *95*, 3300)

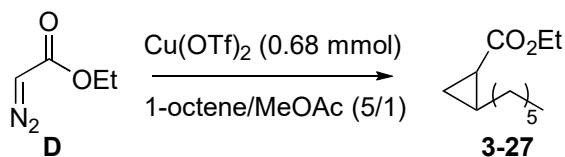


Figure 4 indicated...

After addition of 1 eq. of **D** to Cu(II), the yield of **3-27** was less than 20%. (**1**)

As the addition of **D** was continued, the yield of **3-27** eventually approached quantitative (based on the incremental amount of **D** added.) (**2**)

The addition of more Cu(II) caused a sharp drop in the relative yield of **3-27** (**3**)

Cu(II) reacts with diazo compound firstly and generate Cu(I), which is true active species in this reaction.

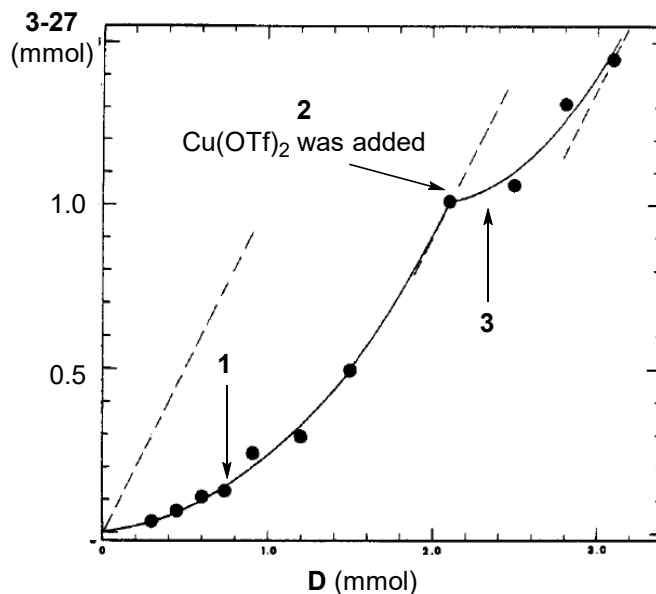
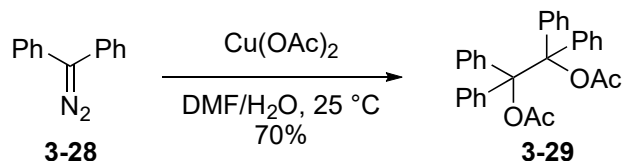
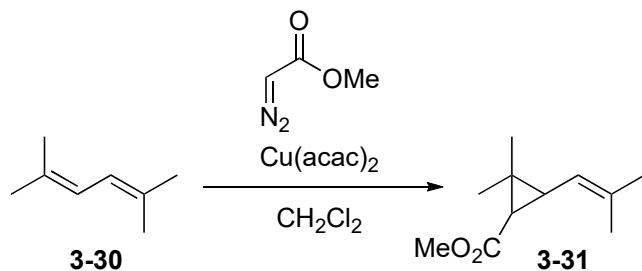


Figure 4. Homogeneous cyclopropanation of octene-1 with incremental amounts of ethyl diazoacetate in the presence of copper(II) triflate (0.68 mmol) in methyl acetate solutions. Dashed lines represent theoretical slopes for quantitative yield of adduct from diazo compound. Additional copper(II) triflate (0.40 mmol) was added after a total of 2.1 mmol of diazoacetate was added.

1-2. Reaction of Cu(II) salt and diazo compound (Nozaki et al. *Tetrahedron*, **1971**, *27*, 5353.)



1-3. UV-VIS spectroscopy of Cu(acac)₂ catalyzed cyclopropanation (Safiullin et al. *Kinetics and Catalysis*, **2008**, *49*, 43.)



As reaction proceeding, absorbance at 630 nm (derived from Cu(II)) of the reaction mixtures were decreasing.

If, after the reaction, the reaction mixture is exposed to air, the absorbance of the solution will increase nearly to its initial value. This is evidence that Cu(I) is oxidized with oxygen to Cu(II).

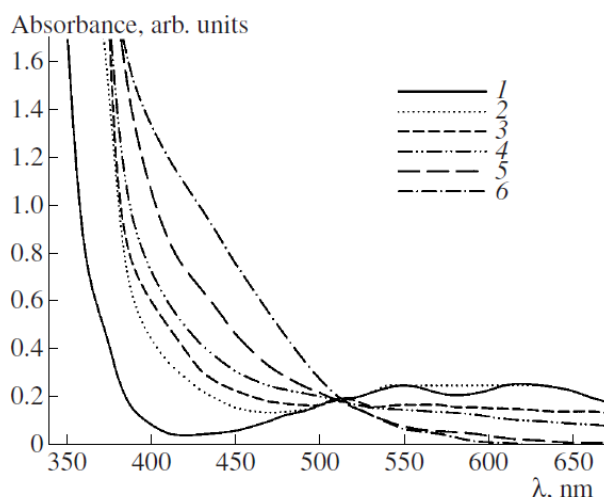
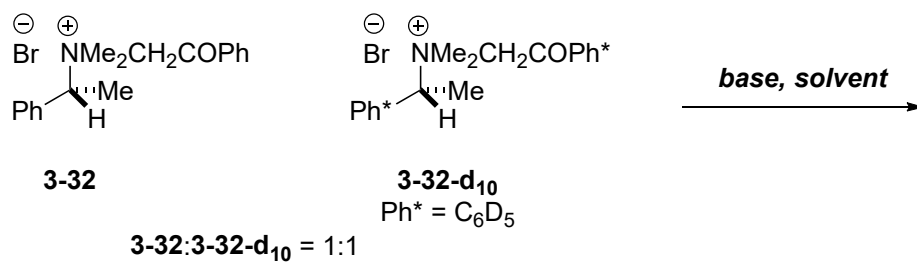
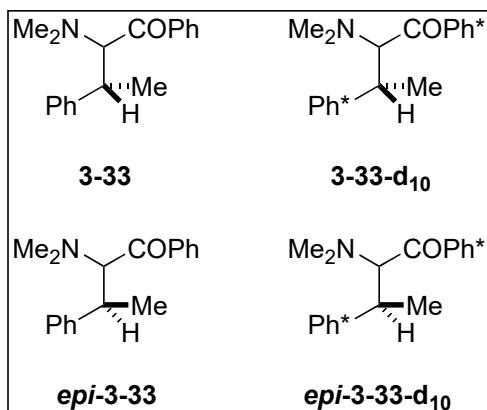


Fig. 5. Optical absorption spectra of a reacting mixture of 2,5-dimethylhexa-2,4-diene and copper acetylacetonate in dichloroethane (**1**) in the absence of methyl diazoacetate, (**2**) immediately after the addition of methyl diazoacetate, and (**3-6**) some time after the addition of methyl diazoacetate: (**3**) 34, (**4**) 41, (**5**) 61, and (**6**) 76 min. $[\text{Cu(acac)}_2] = 5.4 \times 10^{-3}$ mol/l, $[\text{CH}_3\text{OC(O)CHN}_2] = 0.7$ mol/l, $[(\text{CH}_3)_2\text{C}=\text{CHCH}=\text{C}(\text{CH}_3)_2] = 1.2$ mol/l, $[\text{H}_2\text{O}] = 0.2$ mol/l, and $T = 296$ K.

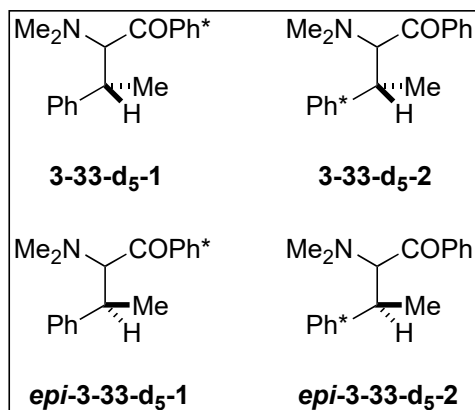
2. Solvent effect of Stevens rearrangement (Ollis et al. *J. Chem. Soc., Perkin Trans 1*, **1983**, 1009.)



intra- or intermolecular product



crossover (intermolecular) product



Solvent	Base	Temp. (±2 °C)	Solvent viscosity ^a (cP)	Intermolecularity ^b (%)	Intramolecular stereoselectivity ^c (%)	<i>k_o</i> / <i>k_{r+t}</i>	<i>k_o</i> / <i>k_d</i>
Methanol	NaOMe	0	0.8	6.9	76	6.3	6.7
Methanol	NaOMe	40	0.5	16.7	70	4.7	2.5
Methanol	NaOMe	60	0.3	22.9	—	—	1.7
t-Butyl alcohol	NaOMe	50	1.4	10.5	75	6.0	4.3
Cyclohexanol	NaOMe	50	13	5.5	81	8.5	8.6
Glycerol	NaOH	50	142	2.5	92	23.0	19.5
Water	NaOH	0	1.8	0.1	99	198	>100
Water	NaOH	50	0.6	4.3	82	9.1	11.1

In more viscous solvent, the reaction exhibits lower intermolecularity and higher stereoselectivity.