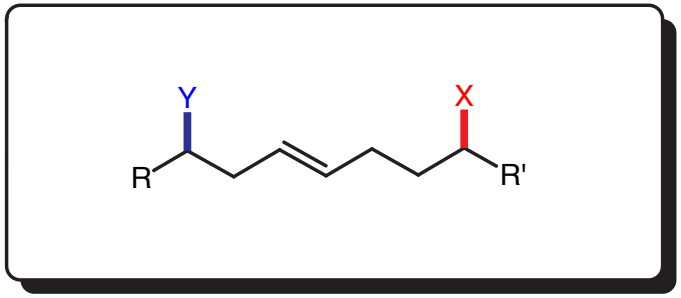
Diastereoselective Construction of Remote Stereocenters: The use of Chiral Allylstannes & Claisen Rearrangements



Scott Peterson
Evans' Group Friday Seminar

May 24, 2002

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

- Coupling of Chiral Fragments
- Asymmetric Induction by Reagent Control
- Asymmetric Induction by Substrate Control
- Chirality Transfer Methodology

Useful references:

- Warren, S. *Perkin I*. **1999**, 1899
- Thomas, E.J. *Chemtracts*. **1994**, *7*, 207

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

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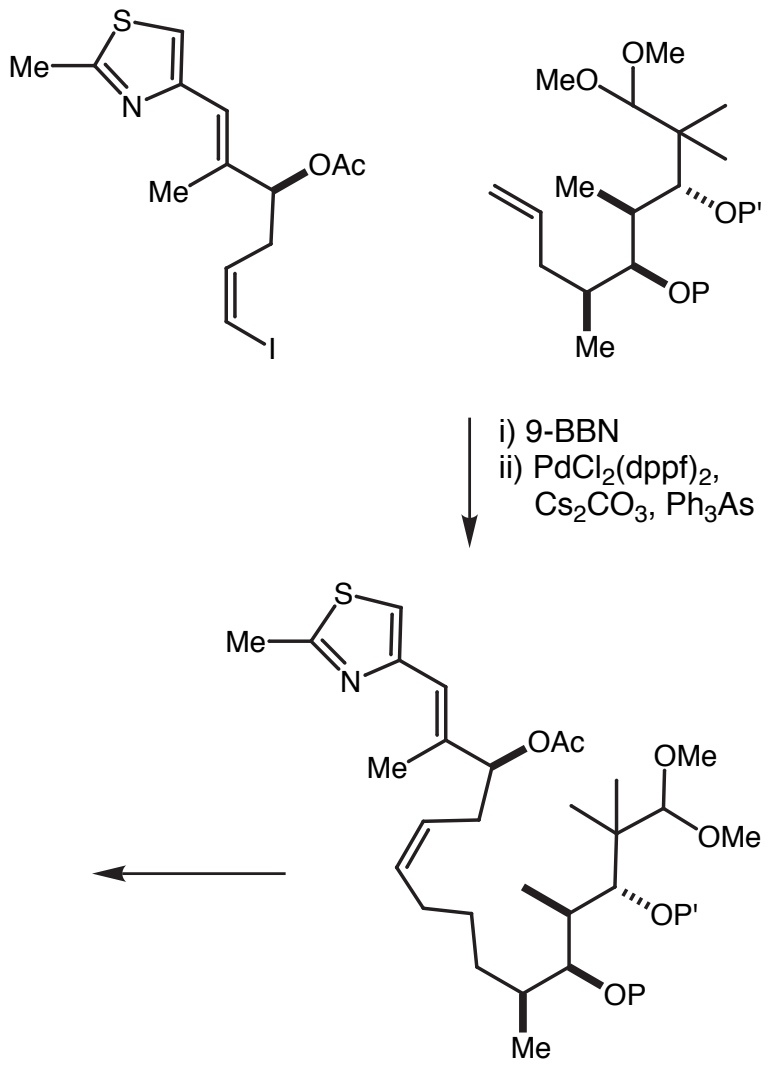

Danishefsky, S.J. *ACIEE* **1996**, *35*, 2801

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

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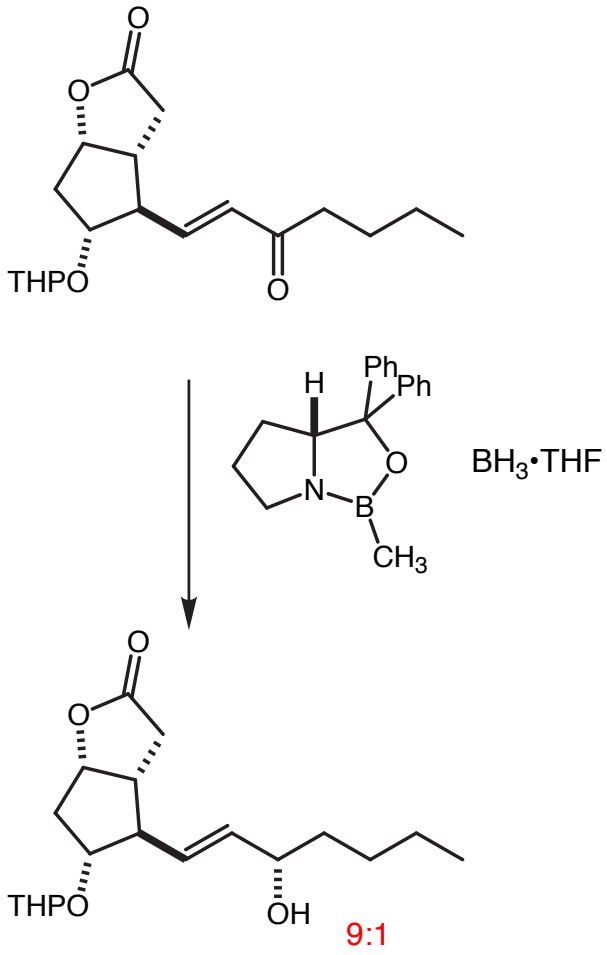

Corey, E.J. *J. Am. Chem Soc.* **1987**, *109*, 7925

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

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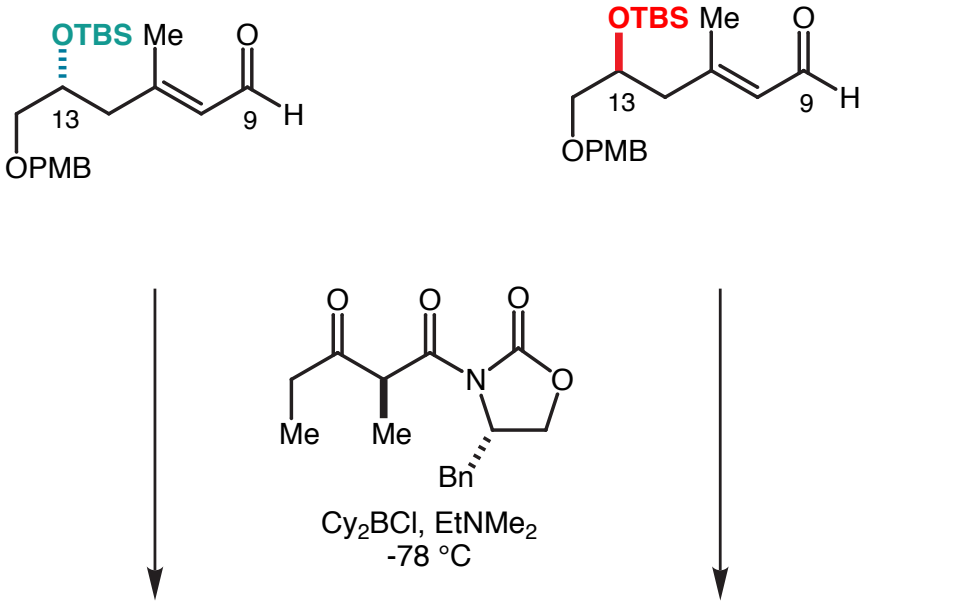

diastereoselection 55:45

diastereoselection 92:8

Evans, D.A. *J. Am. Chem. Soc.* **2002**, *124*, 5654

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

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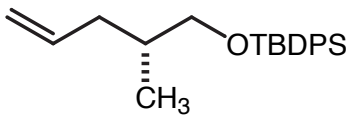
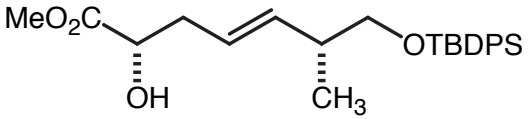
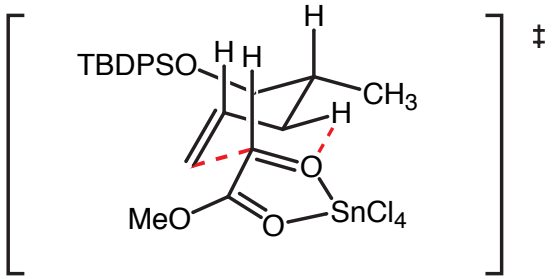


MeO_2CCHO
$SnCl_4$, -78 °C



1,5 *syn:anti* 94:6
76% yield



Mikami, K. *J. Org. Chem.* **1992**, *57*, 6105

Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

- Coupling of Chiral Fragments
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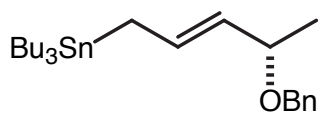
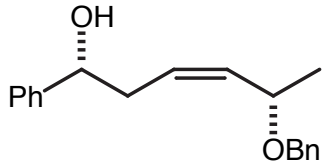


i.) $SnCl_4$, 5 min, -78 °C

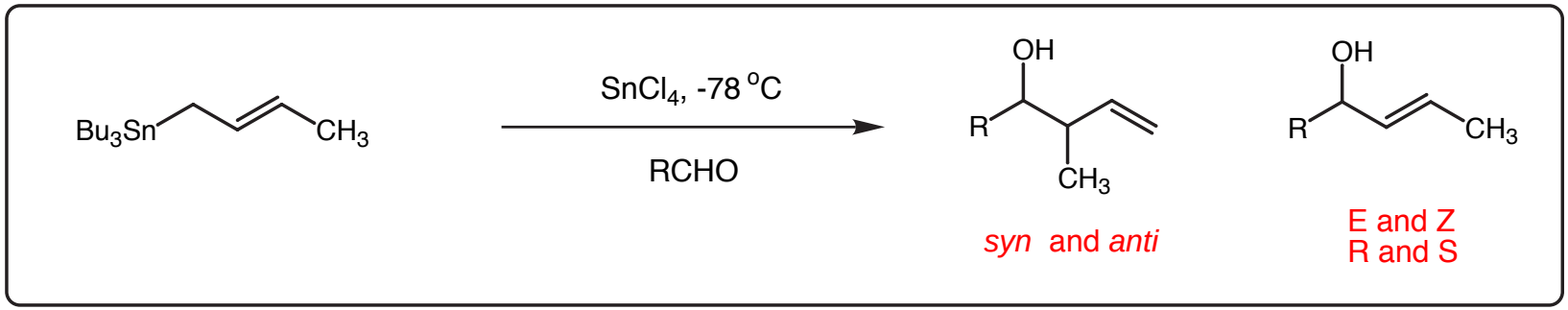
ii.) PhCHO, 1 hour

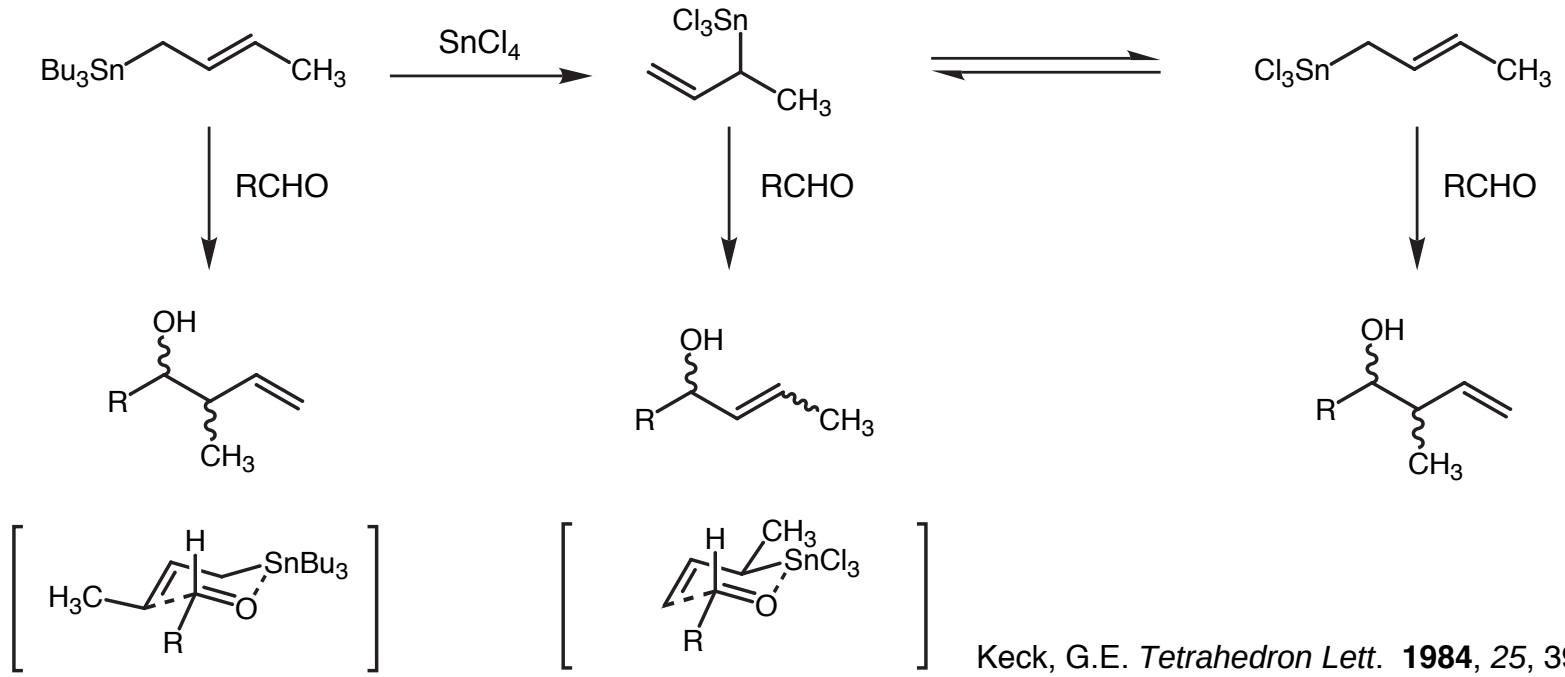


1,5 *syn*:*anti* >98:2
Z olefin formed exclusively
90% yield

Thomas, E.J. *Tetrahedron Lett.* **1990**, *31*, 6239

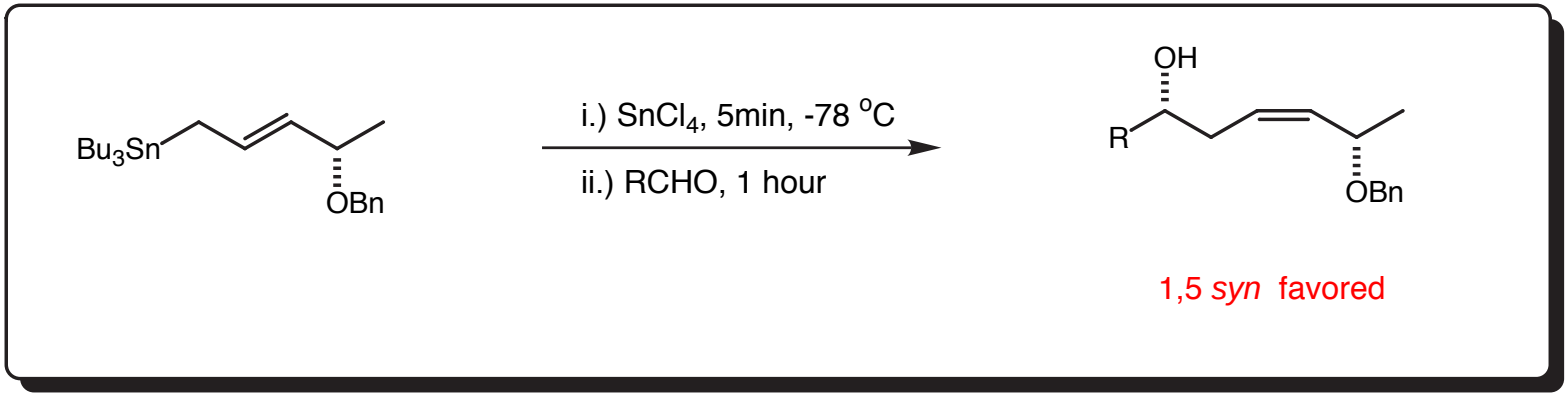
$SnCl_4$ Catalyzed Allylstannane Reactions





Keck, G.E. *Tetrahedron Lett*. **1984**, *25*, 3927
Keck, G.E. *J. Am. Chem. Soc.* **1989**, *111*, 8136
Denmark, S.E. *J. Am. Chem Soc.* **1988**, *110*, 984

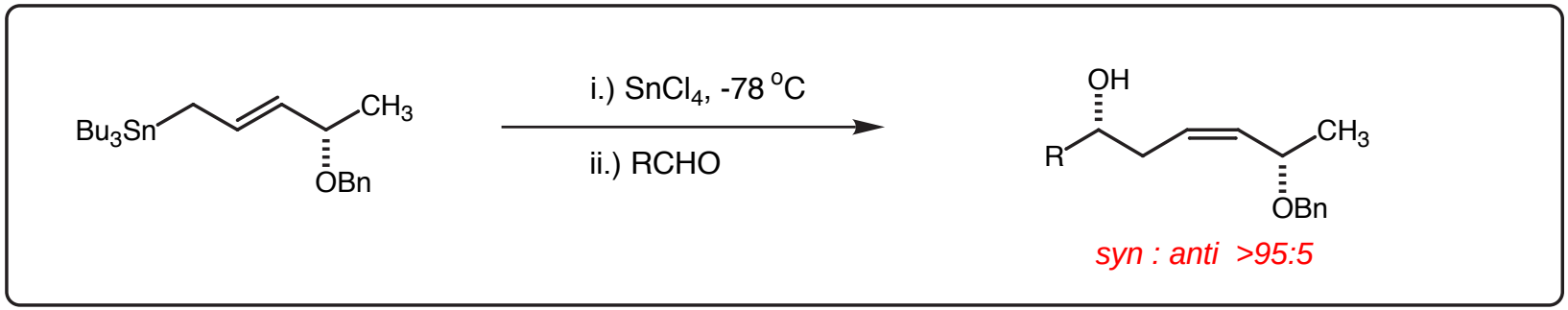
1,5-Asymmetric Induction Using 4-Alkoxy-allylstannanes

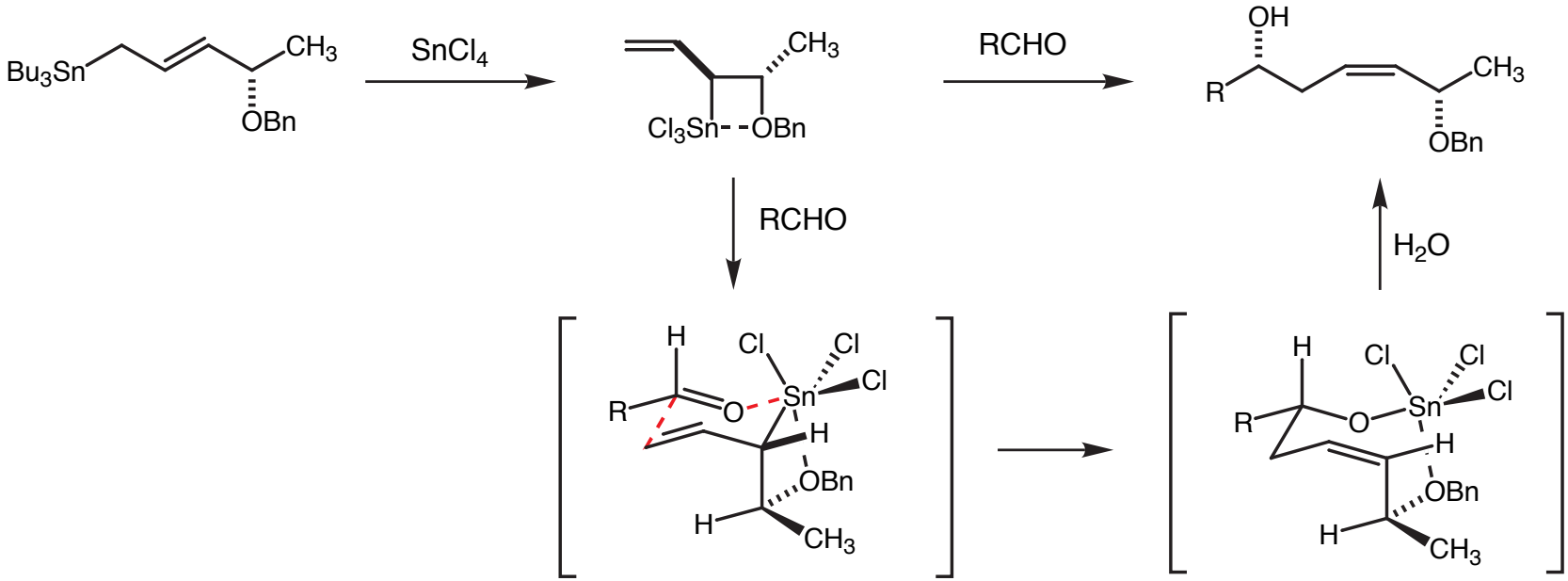


Aldehydes	Yield	*1,5 syn* : *anti*
PhCHO	90	98 : 2
p-ClC_6H_4CHO	77	94 : 6
p-$NO_2C_6H_4CHO$	77	95 : 5
p-$MeOC_6H_4CHO$	77	97 : 3
furfural	72	95 : 5
$CH_3CH_2CH_2CHO$	84	95 : 5
$(CH_3)_2CHCHO$	84	93 : 7
$(CH_2)_5CHCHO$	78	92 : 8
PhCH=CHCHO	64	95 : 5
MeO_2CCHO	68	95 : 5

Thomas, E.J. *Tetrahedron Lett.* **1990**, *31*, 6239
Thomas, E.J. *Chemtracts* **1994**, *7*, 207

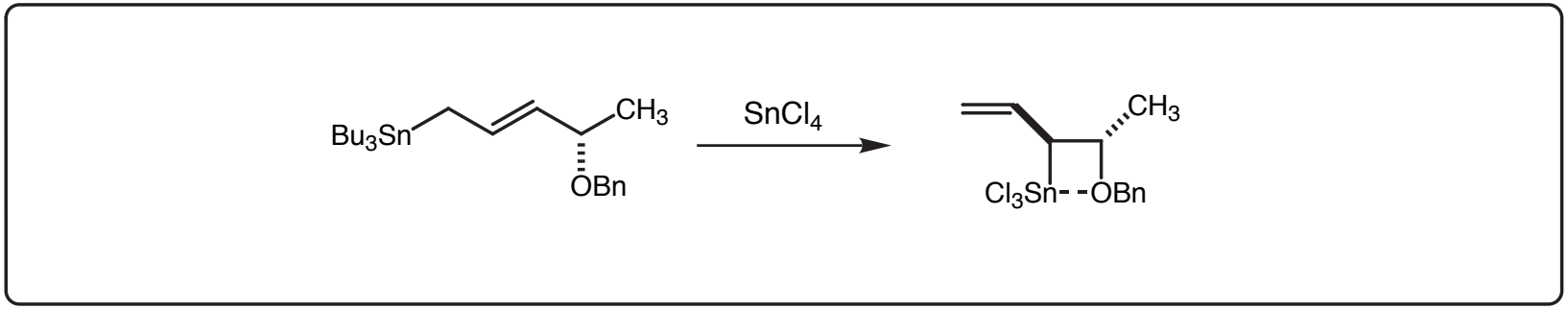
Mechanism for 1,5 Induction with 4-Alkoxy-allylstannanes

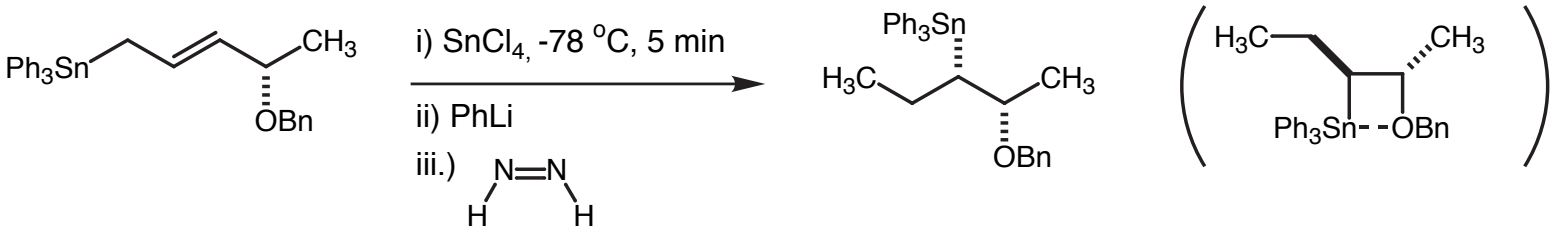


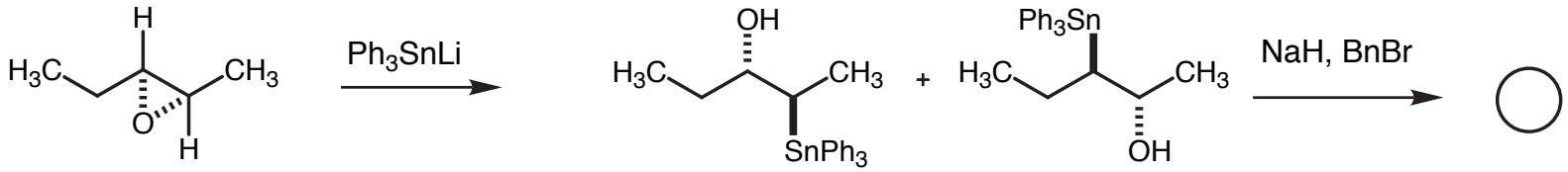


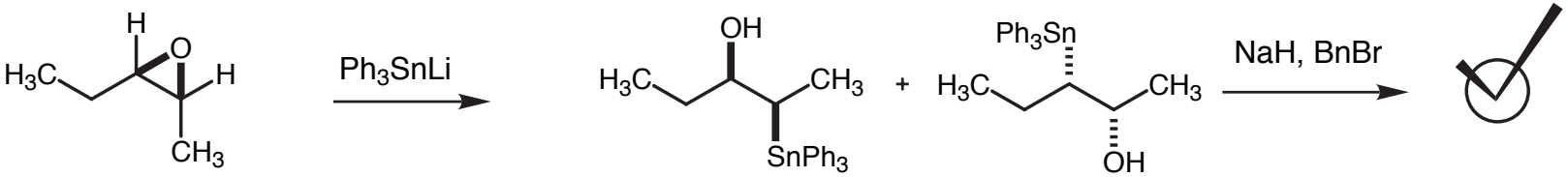
Thomas, E.J. *Tetrahedron Lett.* **1990**, *31*, 6239

Mechanism for 1,5 Induction with 4-Alkoxy-allylstannanes



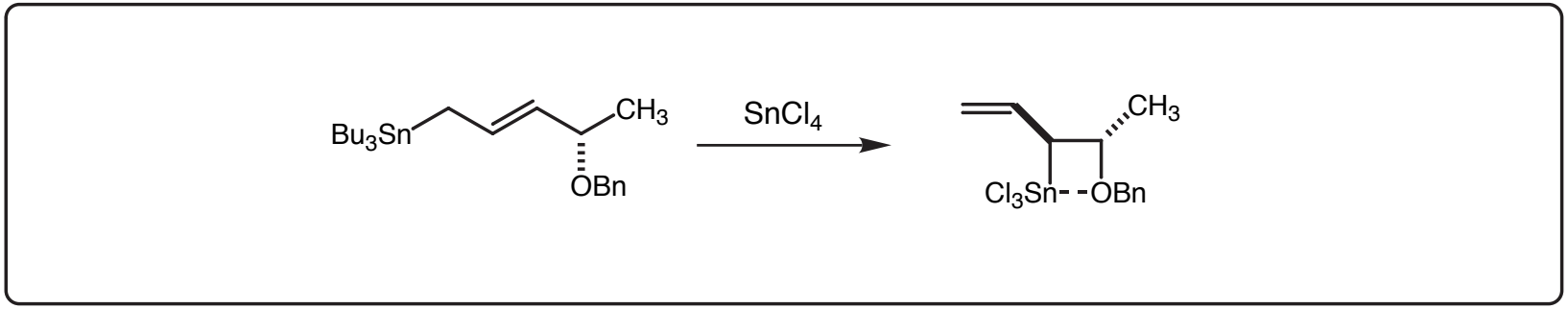


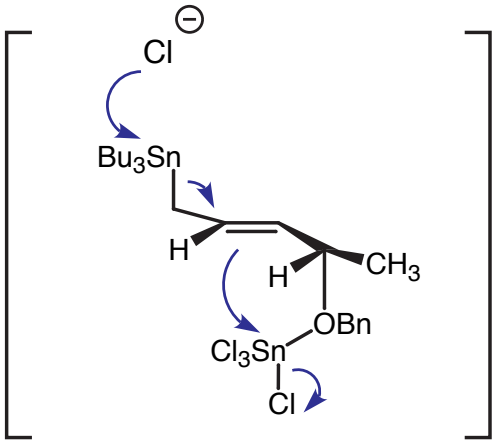




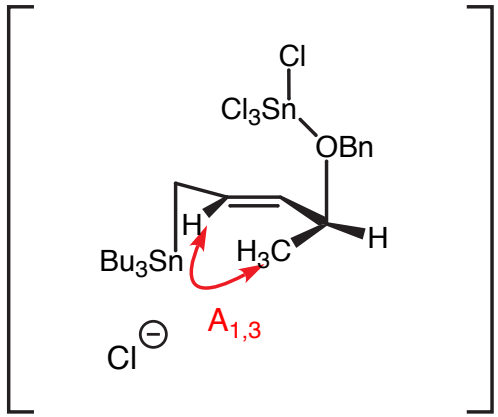
Thomas, E.J. *Chem. Commun*. **1998**, *8*, 899

Mechanism for 1,5 Induction with 4-Alkoxy-allylstannanes





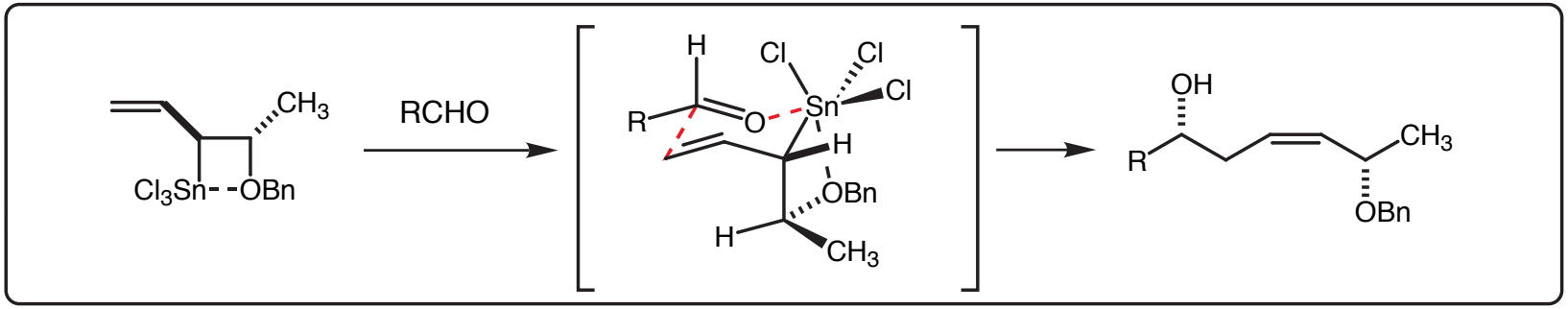
Favored: $A_{1,3}$ minimized

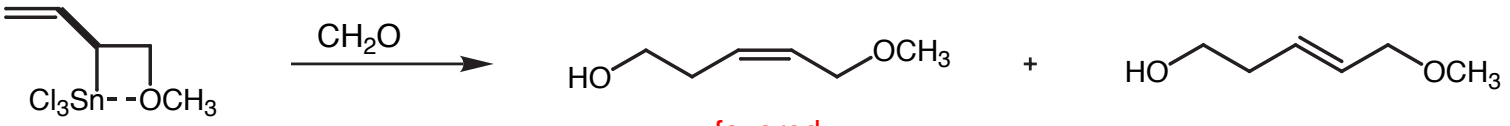


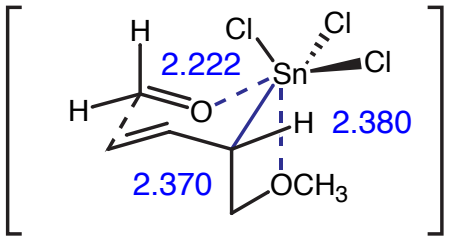
Disfavored

Thomas, E.J. *Chem. Commun*. **1998**, *8*, 899

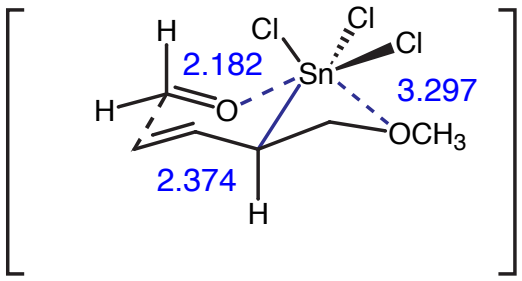
Mechanism for 1,5 Induction with 4-Alkoxy-allylstannanes







ΔE = 1.9 kcal•mol^{-1}

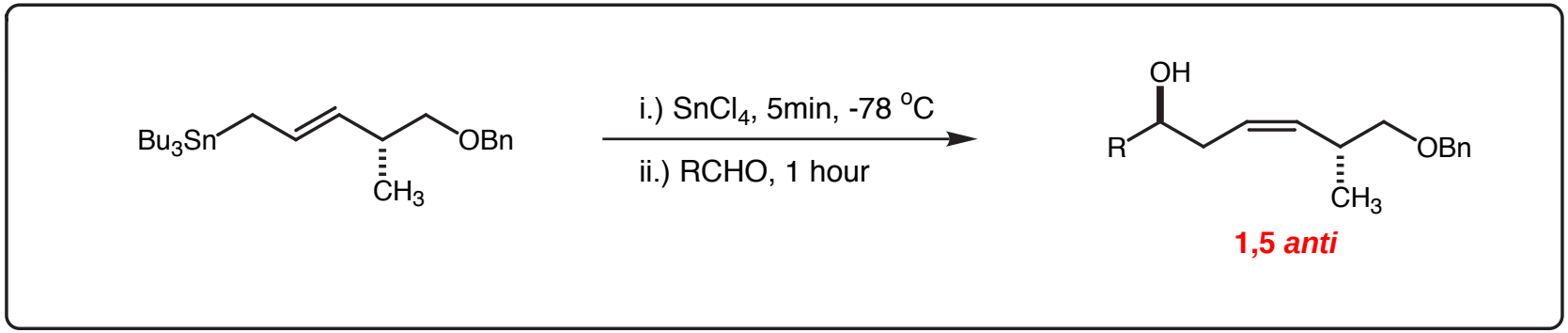


ΔE = 12.0 kcal•mol^{-1}

(GAUSSIAN94 Calculation, split valence basis)

Thomas, E.J. *Chem. Commun*. **1998**, *8*, 899

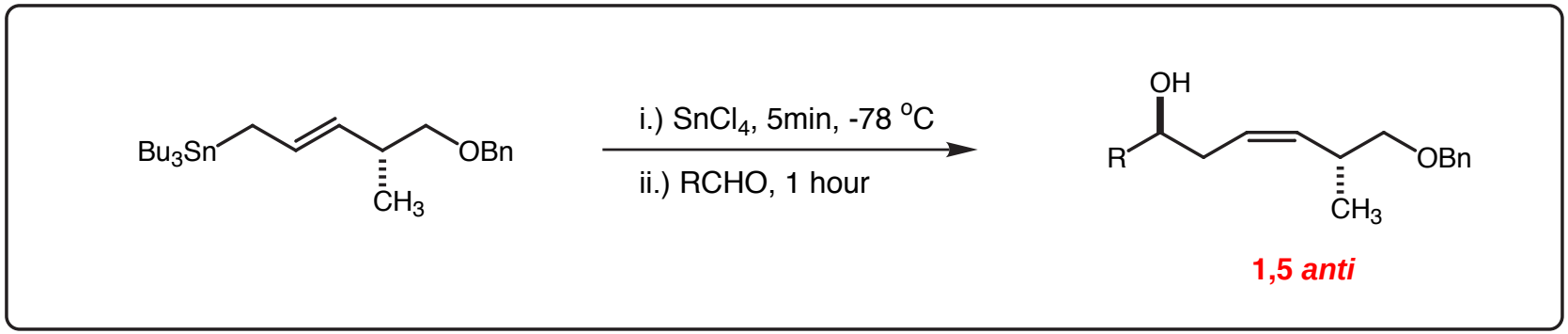
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes

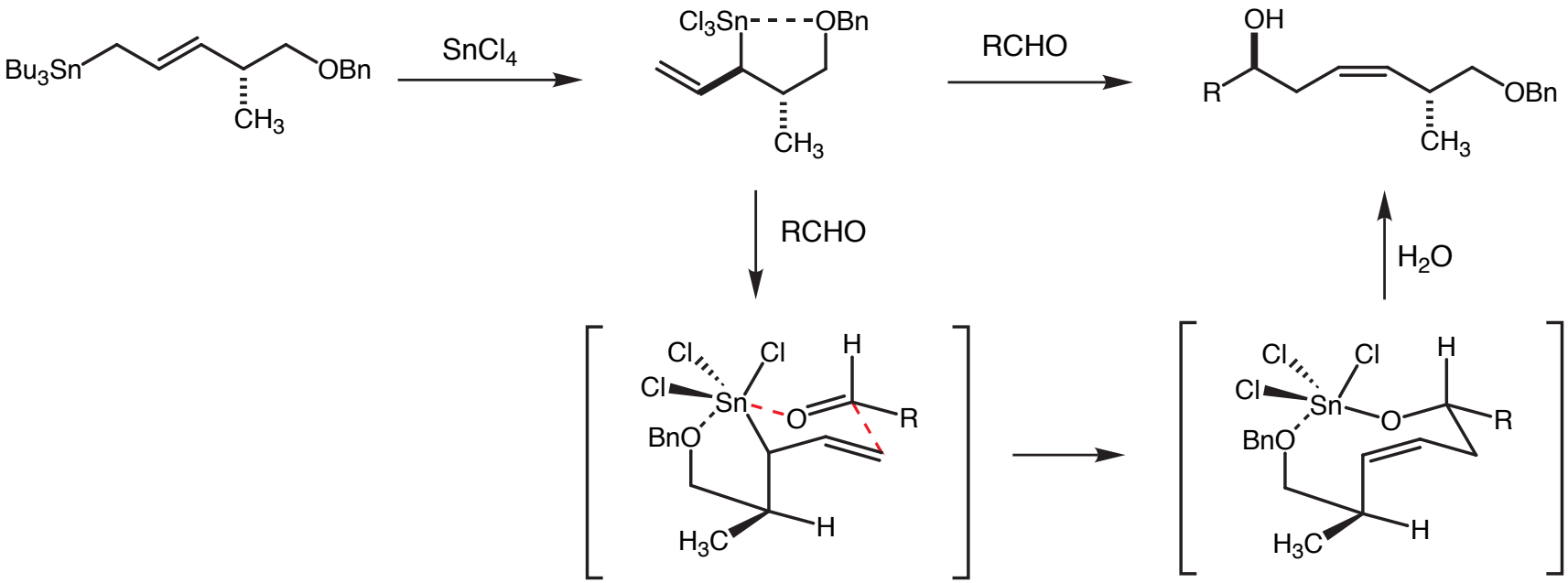


Aldehydes	Yield	1,5-*anti* : 1,5 *syn*
PhCHO	86	96 : 4
p-ClC_6H_4CHO	67	96 : 4
p-$MeOC_6H_4CHO$	65	96 : 4
CH_3CH_2CHO	70	95 : 5
$(CH_3)_2CHCHO$	81	95 : 5

Thomas, E.J. *Synlett* **1992**, 585

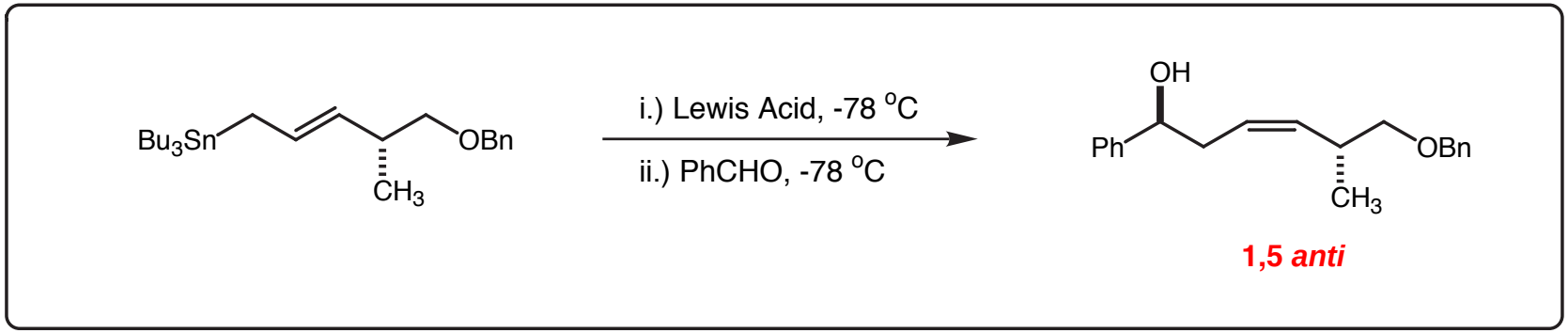
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes





Thomas, E.J. *Synlett* **1992**, 585

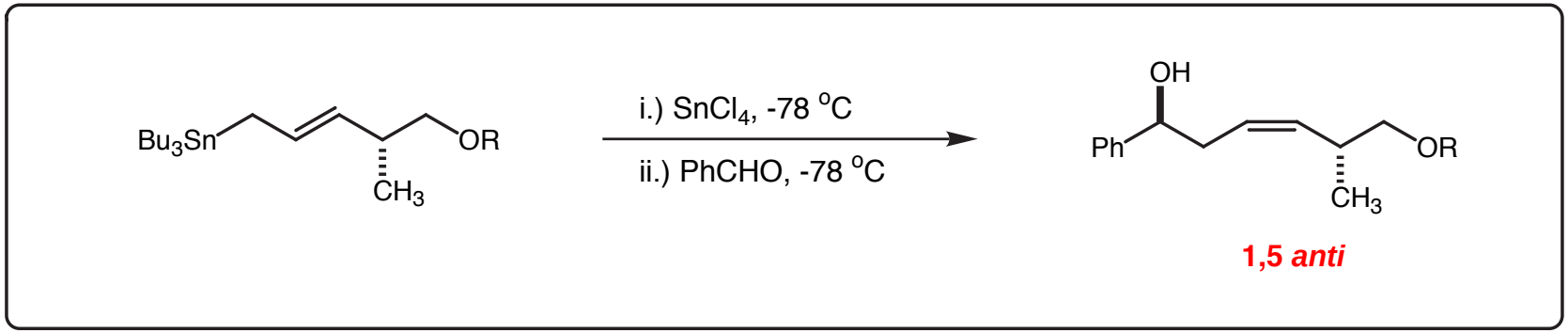
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes



Lewis Acids	Yield	1,5-*anti* : 1,5 *syn*
$SnCl_4$	86	96 : 4
$BuSnCl_3$	40	95 : 5
$SnBr_4$	75	99 : 1
Bu_2SnCl_2	low	--
$TiCl_4$	low	--
$BF_3 \bullet OEt_2$	low	--
$AlCl_3 \bullet {}^{i}PrOH$	low	--

Thomas, E.J. *Synlett* **1992**, 585

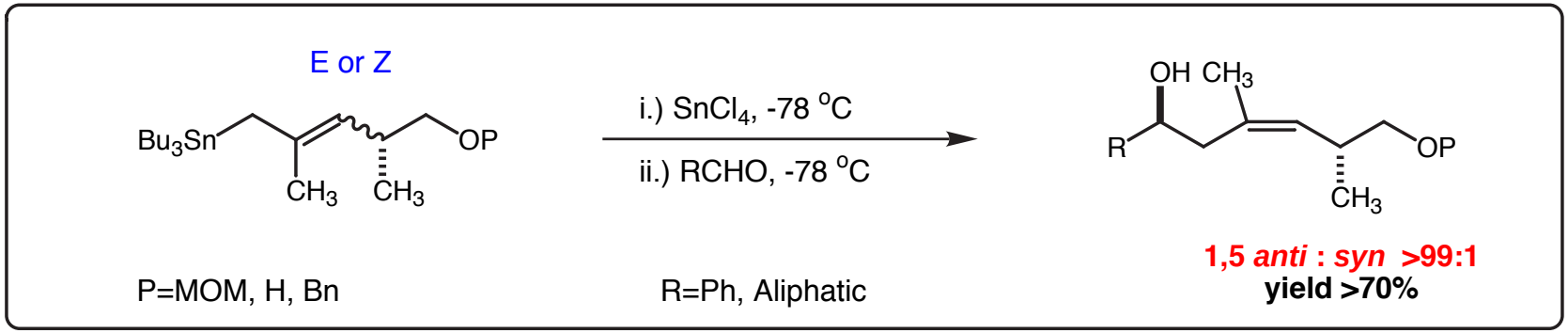
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes

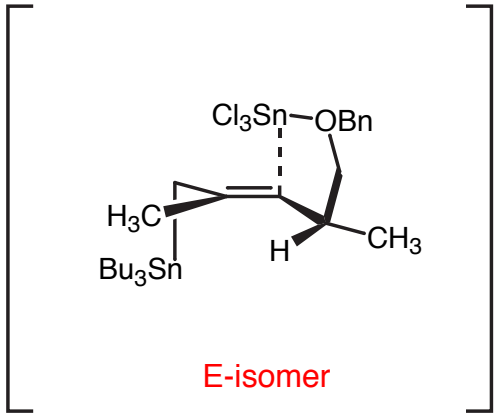


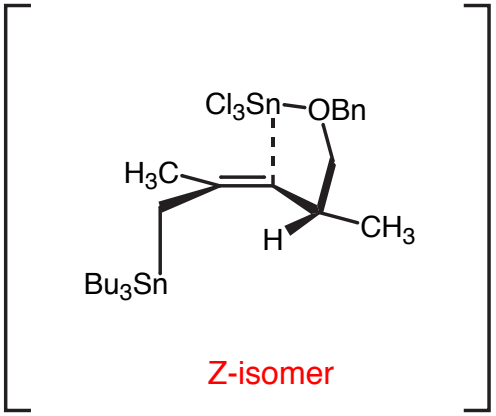
R	Yield	1,5-*anti* : 1,5 *syn*
p-$MeOC_6H_4CH_2$	80	95 : 5
MOM	66	93 : 7
SEM	71	80 : 20
$SiMe_2{}^tBu$	60	81 : 19
$SiPh_2{}^tBu$	61	80 : 20

Thomas, E.J. *Tetrahedron Lett.* **1993**, *34*, 3933

1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes

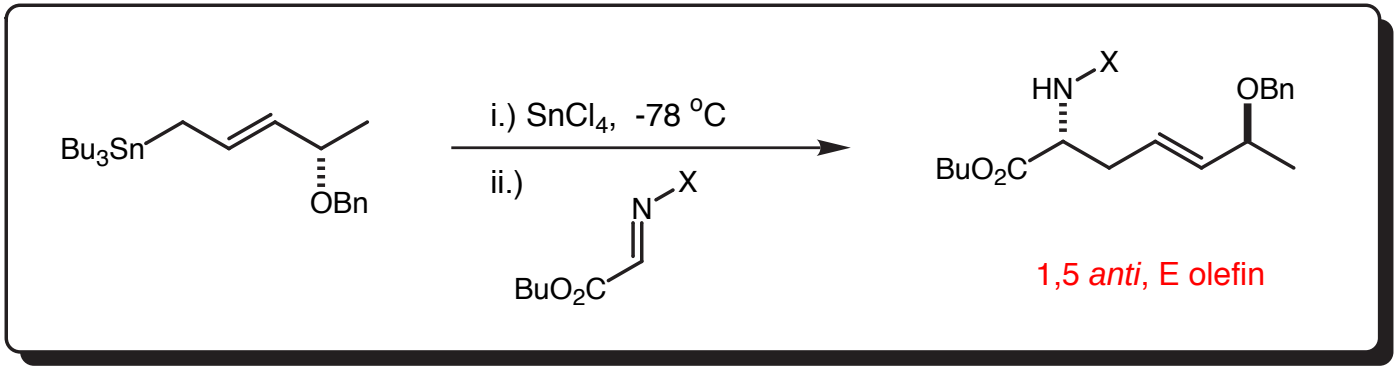




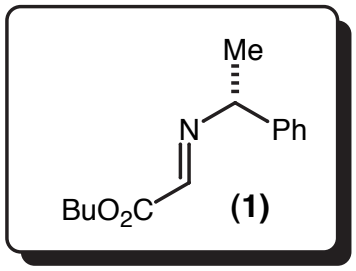


Thomas, E.J. *Perkin Trans. I* ,**1993**, 2863

1,5-Asymmetric Induction with Imines

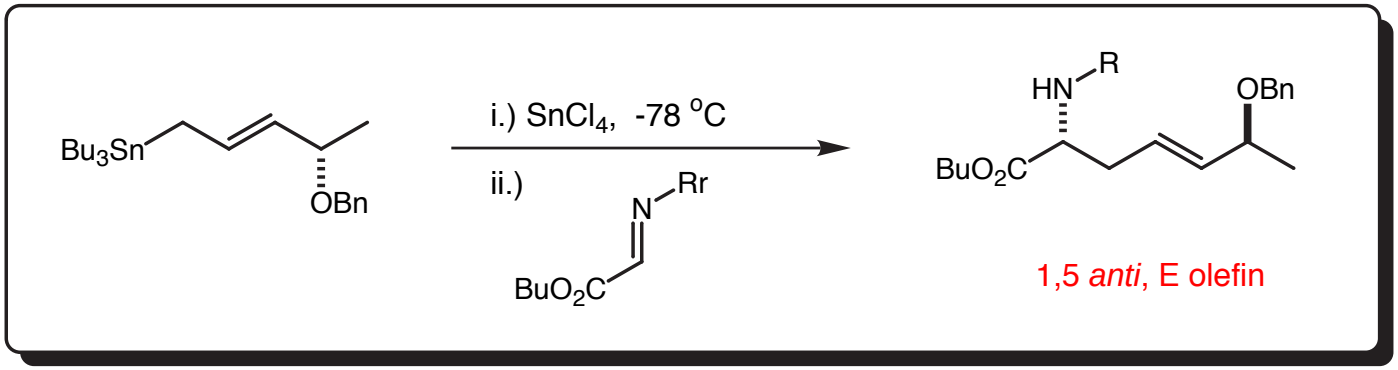


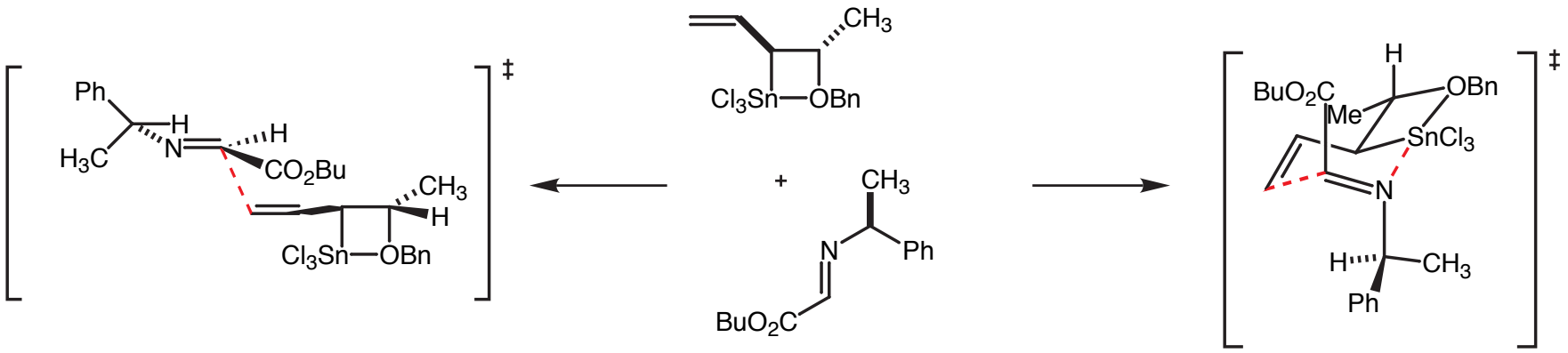
X	Yield	*anti* : *syn*	
$CHPh_2$	79	90 : 10	
CMe_2Ph	75	90 : 10	
OBn	67	90 : 10	
(1)	72	90 : 10	Mismatched
ent - (1)	73	96 : 4	Matched



Thomas, E.J. *Chem. Commun.* **1995**, *6*, 657
Thomas, E.J. *Tetrahedron. Assym*. **1995**, *4*, 2575

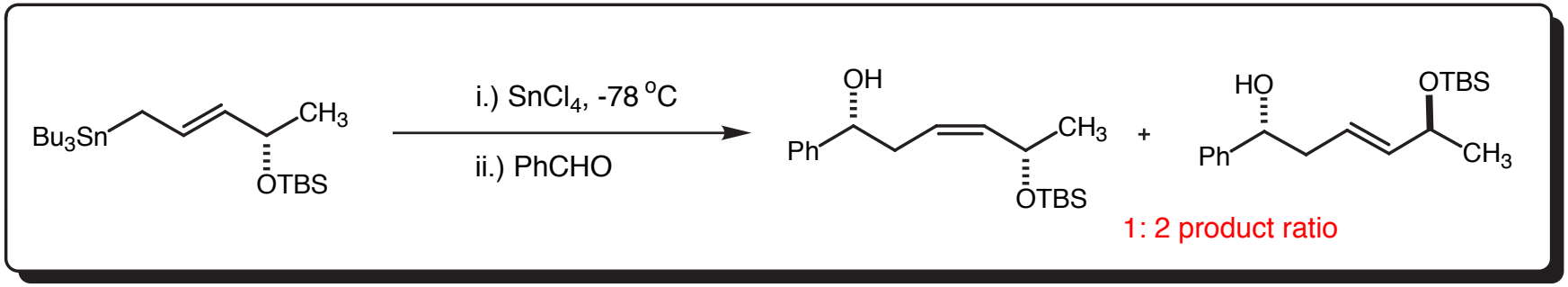
1,5-Asymmetric Induction with Imines

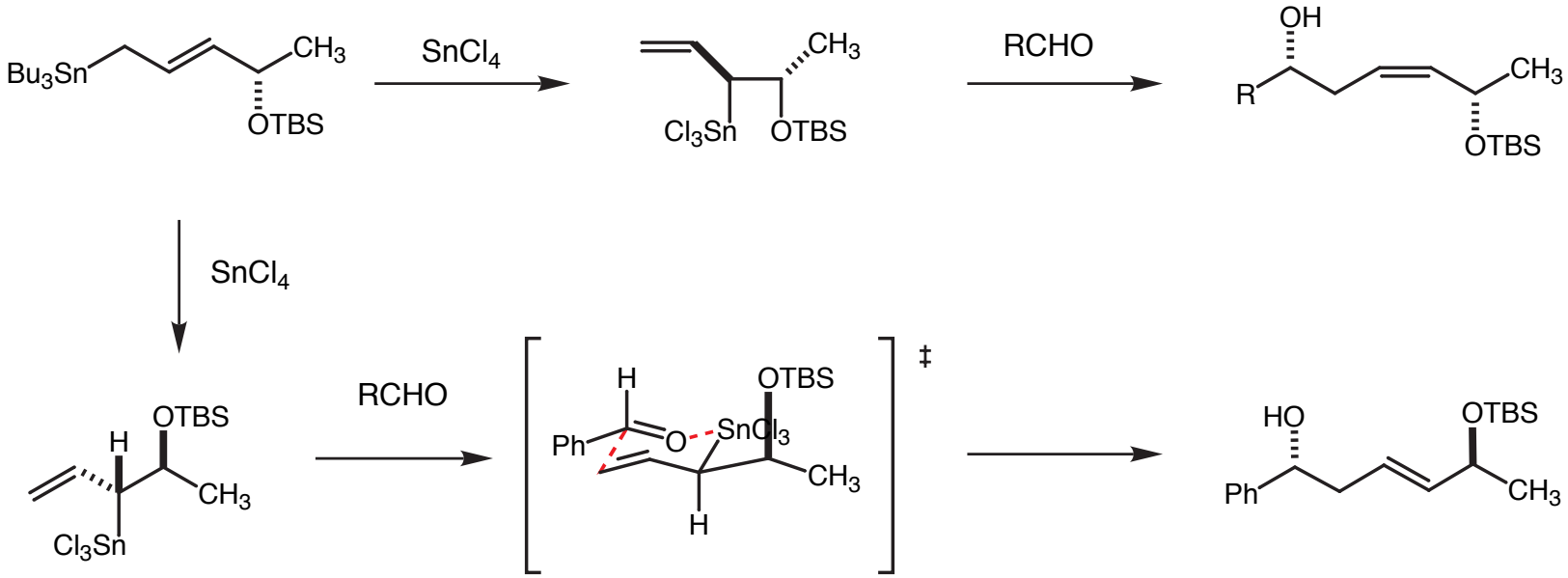




Thomas, E.J. *Chem .Commun.* **1995**, *6*, 657

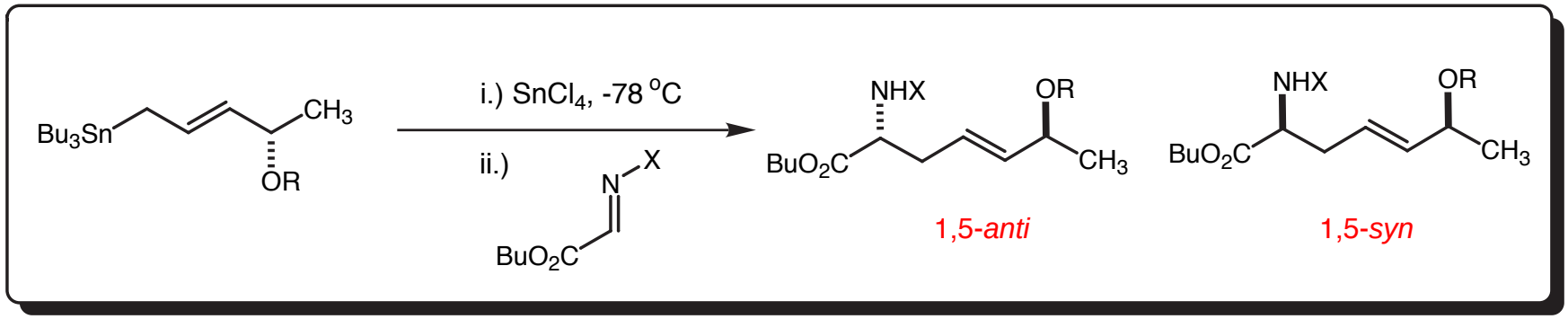
Limitations of the Allylstannane Chemistry





Thomas, E.J. *Tet rahedron Assym*. **1995**, *6*, 2579

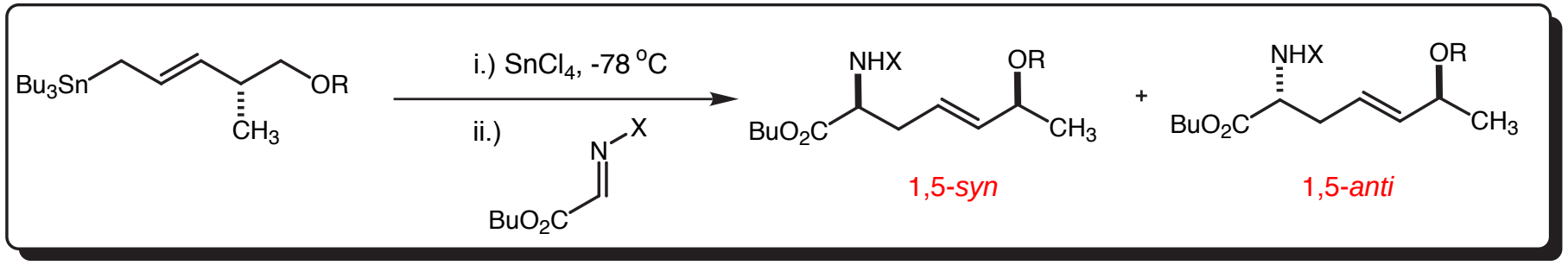
Limitations of the Allylstannane Chemistry



Stannane (R)	Imine (X)	Yield	1,5-*anti* : 1,5 *syn*
Bn	$CHPh_2$	79	90 : 10
Bn	(S)-CHMePh	73	96 : 4
Bn	(R)-CHMePh	72	90 : 10
TBS	$CHPh_2$	74	25 : 75
TBS	(S)-CHMePh	76	25 : 75
TBS	(R)-CHMePh	93	33 : 67

Thomas, E.J. *Tet rahedron Assym*. **1995**, *6*, 2579

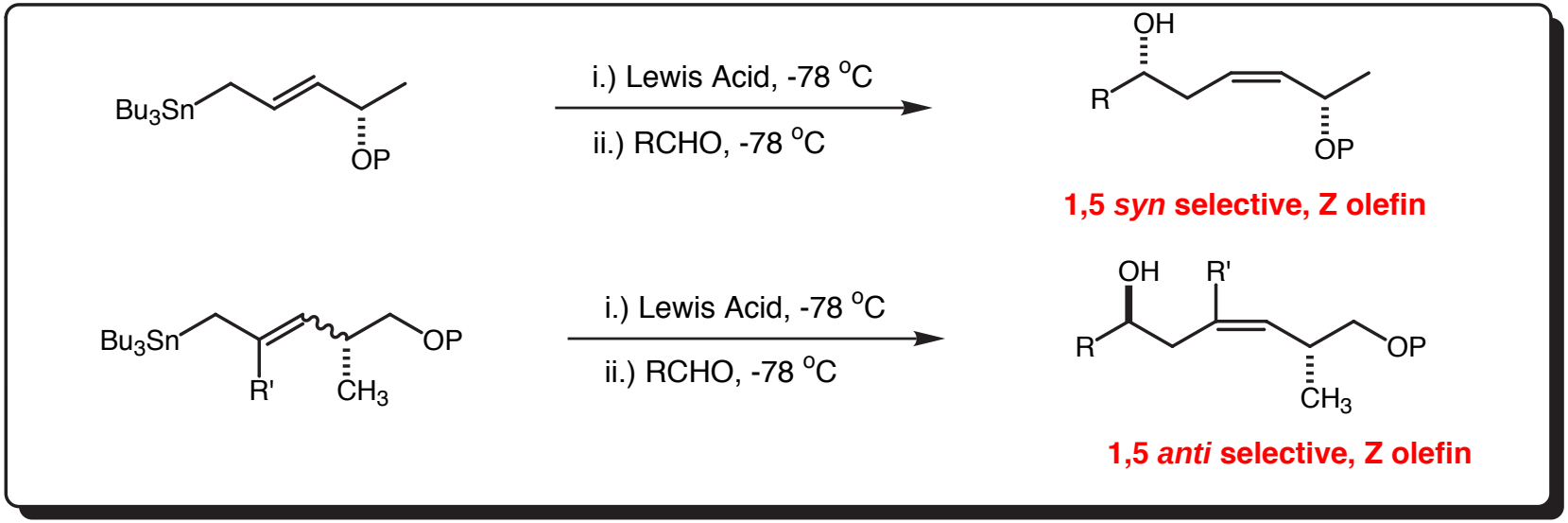
Limitations of the Allylstannane Chemistry



Stannane (R)	Imine (X)	Yield	1,5 *syn* : 1,5-*anti*
Bn	$CHPh_2$	78	95 : 5
Bn	(S)-CHMePh	82	98 : 2
Bn	(R)-CHMePh	73	90 : 10
$SiMe_2{}^tBu$	$CHPh_2$	77	80 : 20
$SiMe_2{}^tBu$	(S)-CHMePh	80	67 : 33
$SiMe_2{}^tBu$	(R)-CHMePh	74	75 : 25

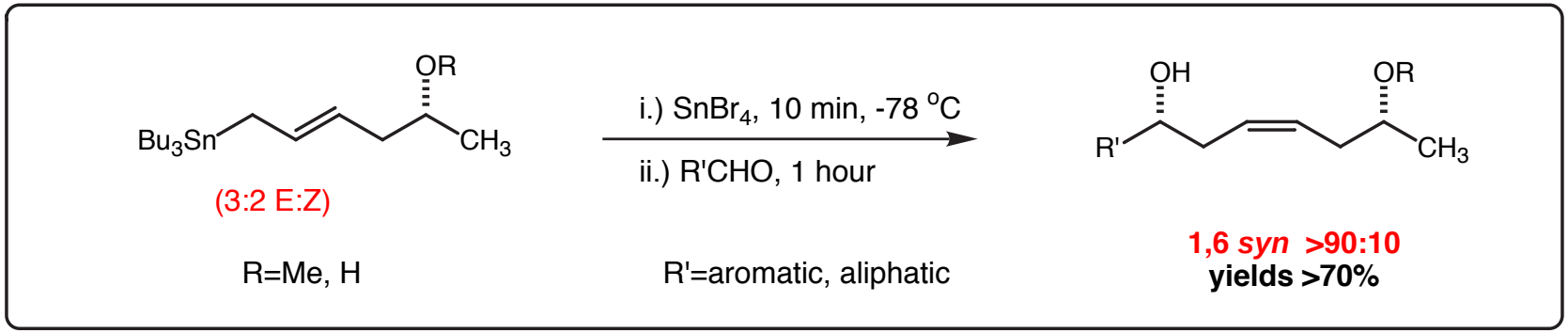
Thomas, E.J. *Tetrahedron Assym*. **1995**, *6*, 2579

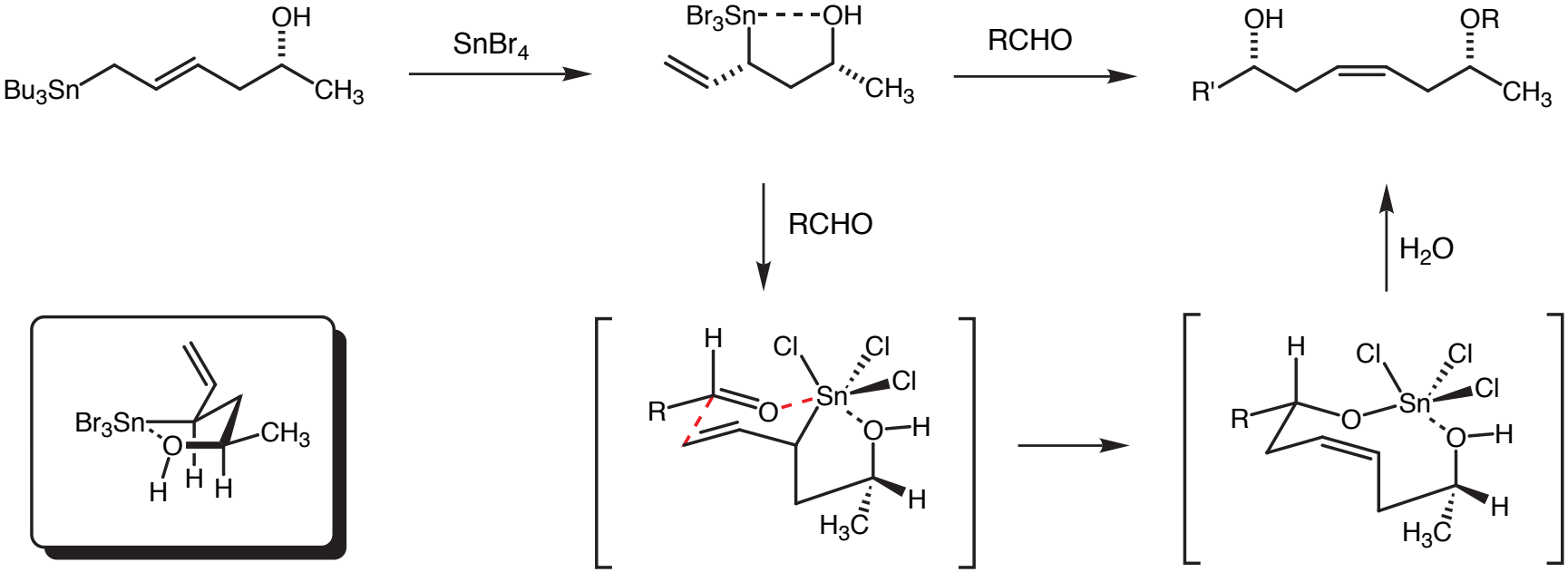
1,5-Asymmetric Induction with 4/5-Alkoxy-allylstannanes



- $SnCl_4$ or $SnBr_4$
- Chelating protecting group on oxygen is necessary
  Other heteroatoms are also effective (N, S)
- 2-Substitution on the olefin is acceptable
  SM olefin geometry is not important
- High selectivities for a range of aldehydes and imines
  Generally >95:5 diastereoselctivity

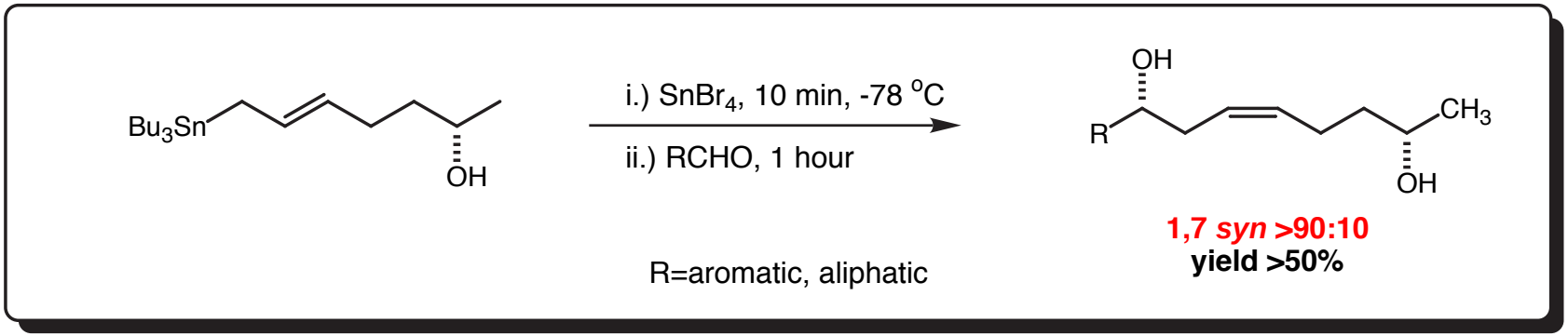
1,6-Asymmetric Induction Using 5-Alkoxy-allylstannanes

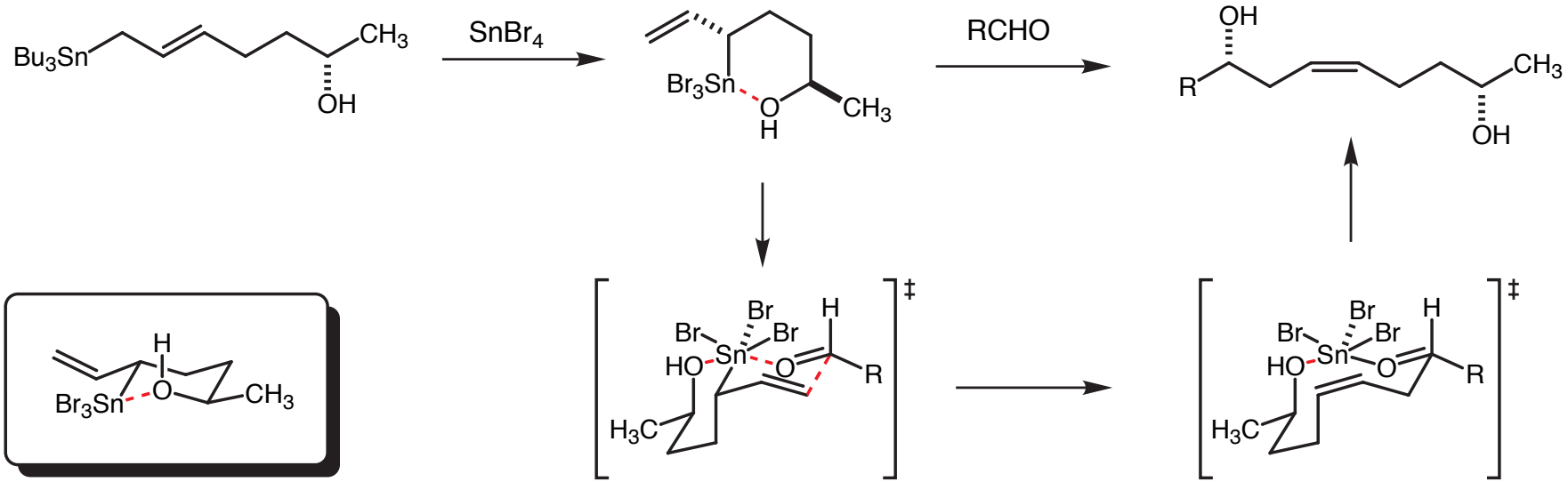




Thomas, E.J. *Tet rahedron Lett.* **1993**, *24*, 3935

1,7-Asymmetric Induction Using 6-Alkoxy-allylstannanes

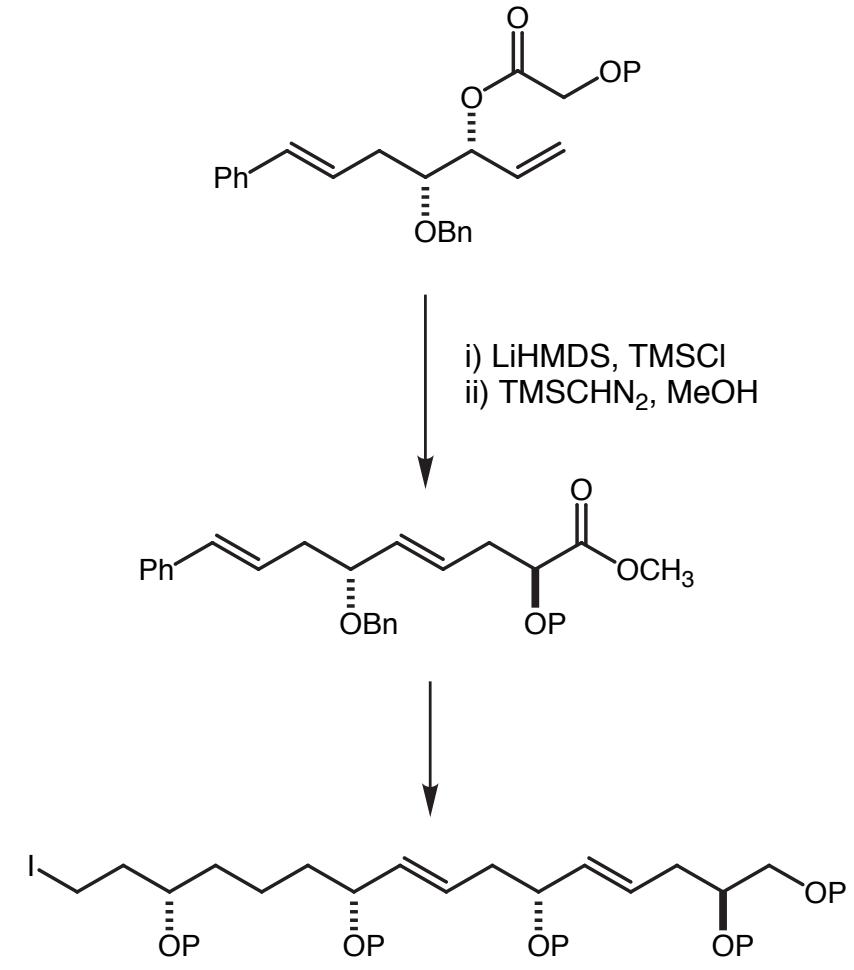




Thomas, E.J. *Chem. Commun.* **1994**, *3*, 283

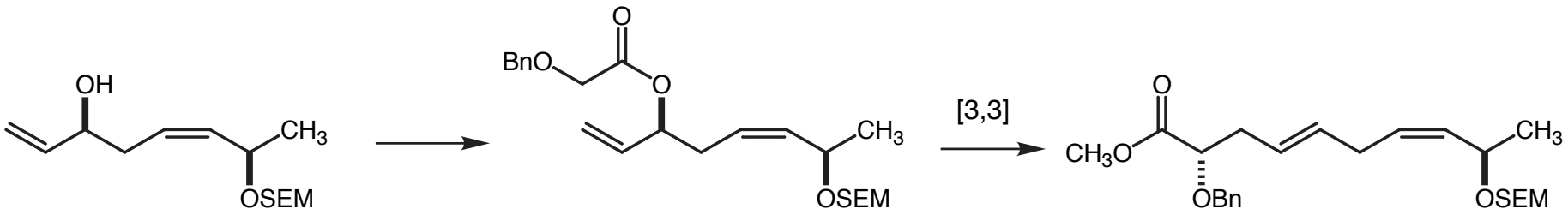
Synthetic Strategies for the Construction of Remote Stereogenic Centers Across a Double Bond

- Coupling of Chiral Fragments
- Asymmetric Induction by Reagent Control
- Asymmetric Induction by Substrate Control
- **Chirality Transfer Methodology**



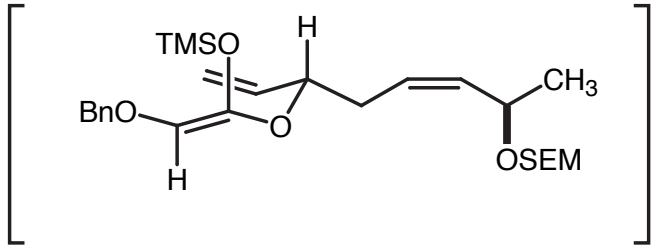
C_1 - C_{16} - Amphidinol 3

2-Step 1,8-Asymmetric Induction via Chirality Transfer (Ireland-Claisen Rearrangement)



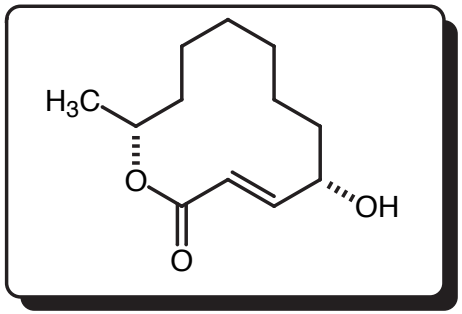
1,5 *syn* : *anti* 96:4

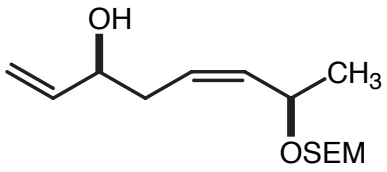
1,8 *anti*



Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 471

2-Step 1,8-Asymmetric Induction
Synthesis of (±)-Patulolide

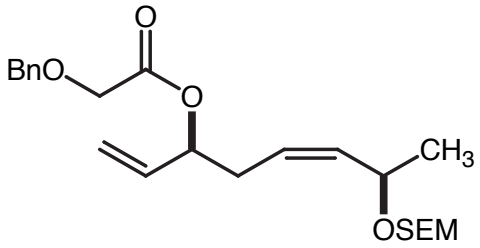




1,5 *syn* : *anti* 96:4
77% from (±)-stannane

$BnOCH_2COCl$

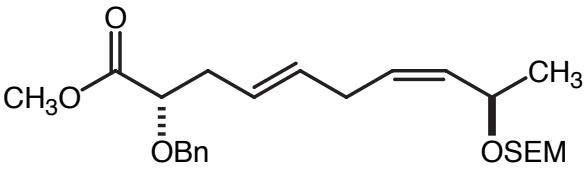
Et_3N, DMAP
84%



i) LiHMDS, -78 °C

ii) TMSCl, -78 to RT
iii)$TMSCHN_2$

80%

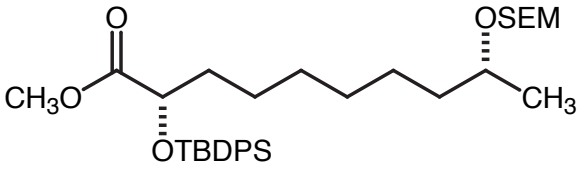


1,8 *anti* : *syn*
86:14

i) 

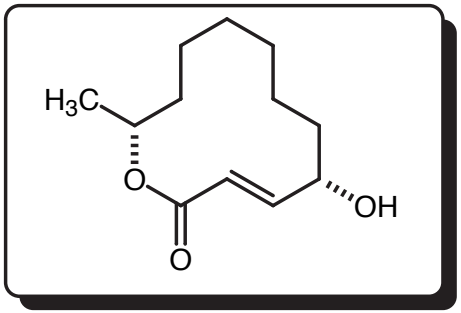
ii) H_2 / Pd
iii) TBDPSCl, imid

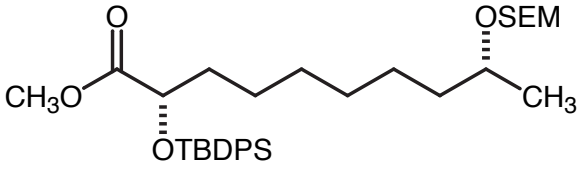
71%



Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 471

2-Step 1,8-Asymmetric Induction Synthesis of (±)-Patulolide



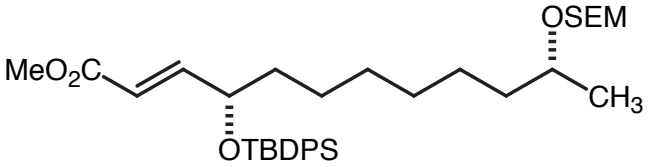


1,8 *syn:anti*
86:14

i) DIBAl-H

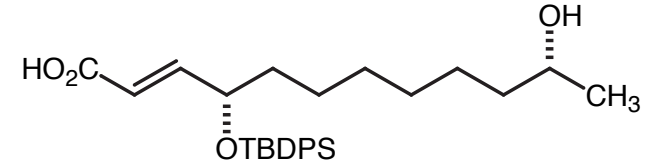
ii) Swern
iii) $PH_3P{=}CHCO_2Me$

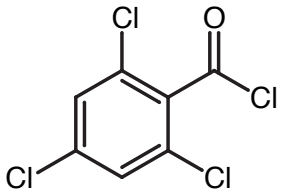
72%



i) $MgBr_2$, BuSH, K_2CO_3
ii) LiOH, $MeOH\text{-}H_2O$

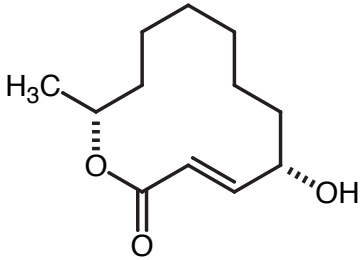
81%



i)  , Et_3N

ii) DMAP, Δ (separate isomers)
iii) TBAF, THF

27%

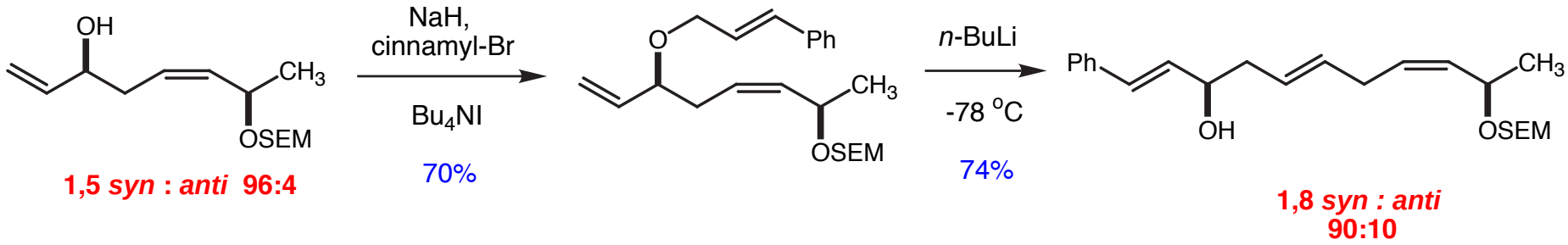


(±)-Patulolide

15 steps from stannane

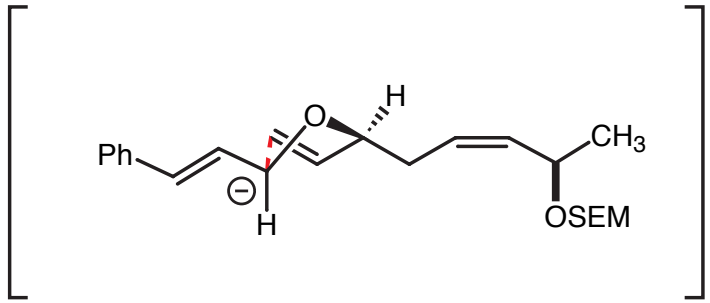
Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 471

2-Step 1,8-Asymmetric Induction via Chirality Transfer (2,3 Wittig Rearrangement)



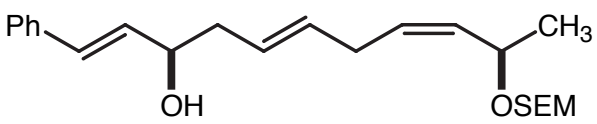
1,5 *syn* : *anti* 96:4

1,8 *syn* : *anti* 90:10



Thomas, E.J. *Tet rahedron Lett.* **1999**, *40*, 475

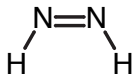
2-Step 1,8-Asymmetric Induction
Synthesis of (±)-Epipatulolide

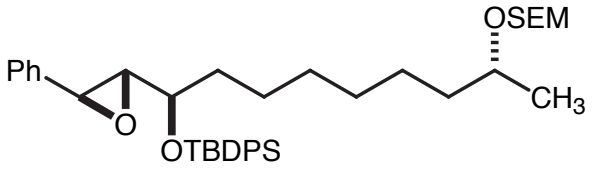


1,8 *syn : anti*
90 : 10

i) $VO(acac)_2$, ^tBuOOH

ii) TBDPSCl, imid

iii) 

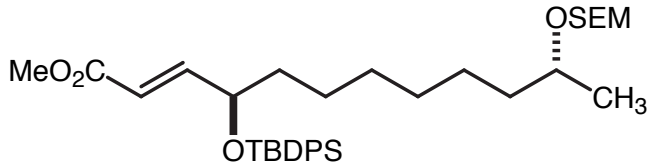


i) SmI_2

ii) O_3, DMS

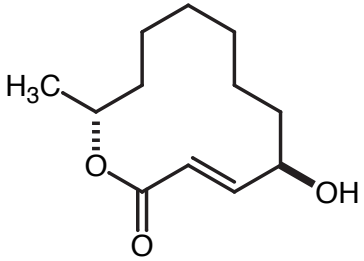
iii) $PH_3P{=}CHCO_2Me$

34%



5 steps

22 %

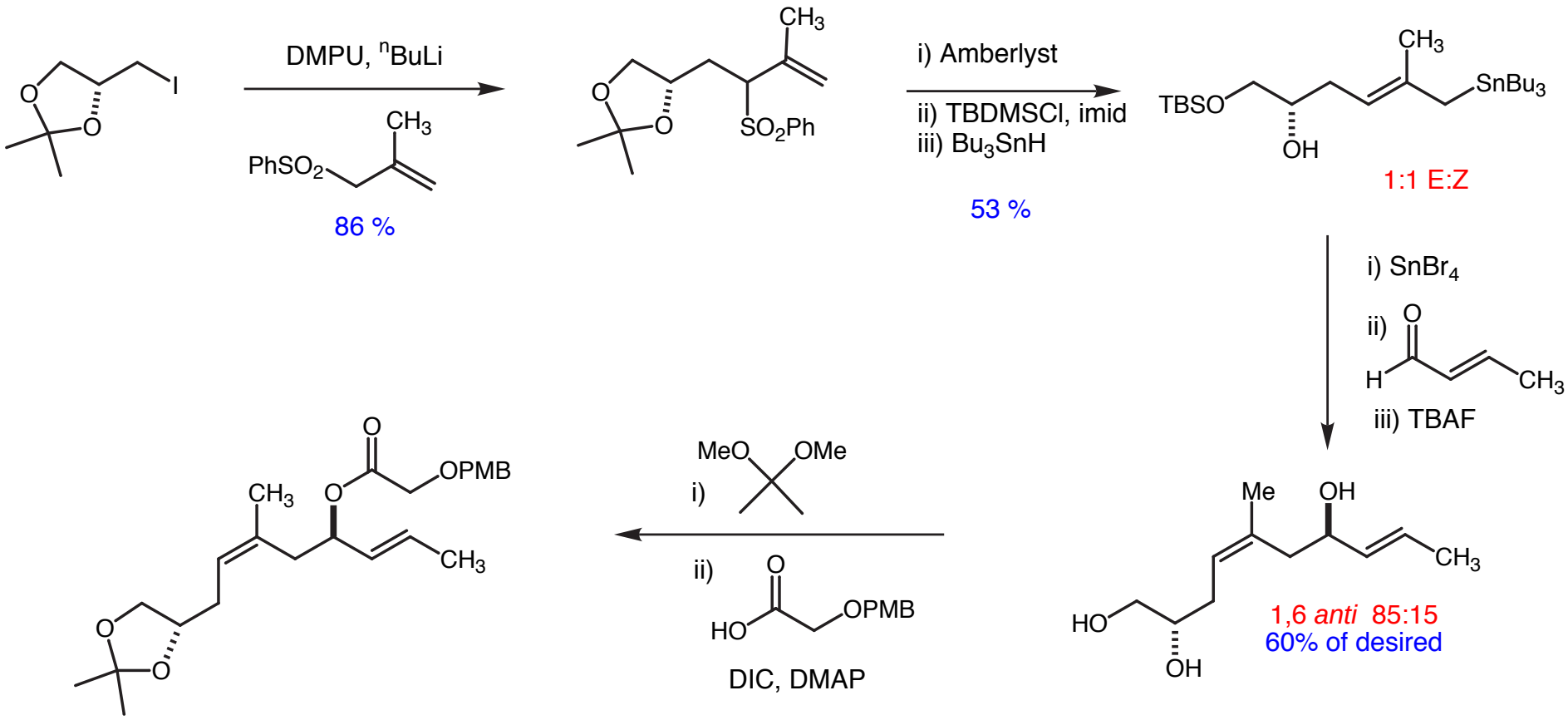


(±)-Epipatulolide

14 steps from stannane

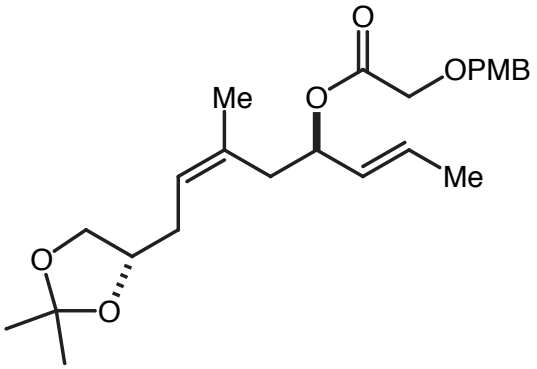
Thomas, E.J. *Tet rahedron Lett.* **1999**, *40*, 475

2-Step 1,8-Asymmetric Induction
Syntheses of Epothilones B and D



Thomas, E.J. *Tetrahedron Lett.* **2001**, *42*, 8373

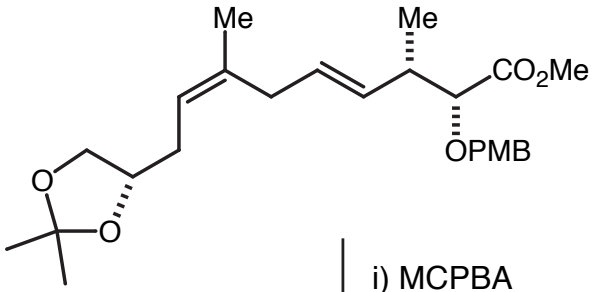
2-Step 1,8-Asymmetric Induction
Syntheses of Epothilones B and D



i) LiHMDS, TMSCl

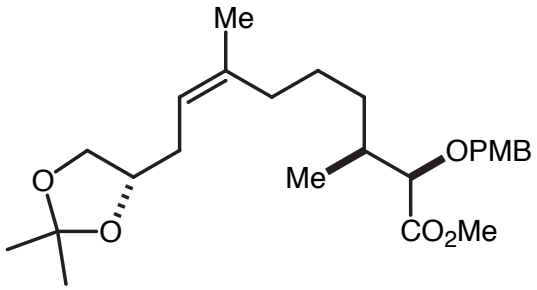
ii) $TMSCHN_2$

78 %



i) MCPBA
ii) H_2/PtO_2
iii)KSeCN

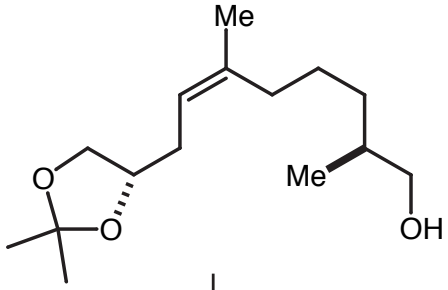
68 %

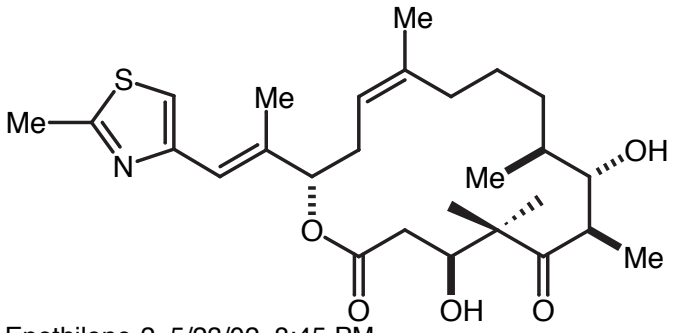


i) DDQ

ii) $LiAlH_4$
iii) $NaIO_4$, $NaBH_4$

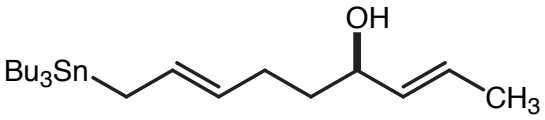
46 %





Thomas, E.J. *Tet rahedron Lett.* **2001**, *42*, 8373

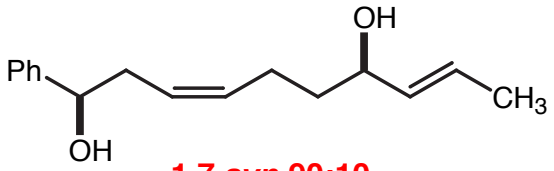
1,9-Relationship Constructed by 1,7 Induction Followed by a Claisen Rearrangement



60% ee

i.) $SnBr_4$, 10min, -78 °C

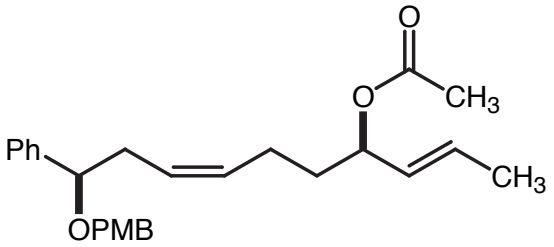
ii.) PhCHO, 1 hour



1,7 *syn* 90:10
yield 64%

i) TBDPSCl, imid
ii) NaH, PMBCl
iii) TBAF
iiii) Ac_2O, NEt_3

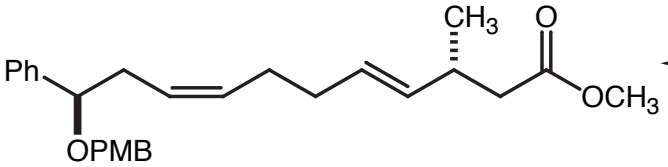
49 %



i) LDA, TBSCl

ii) CH_2N_2

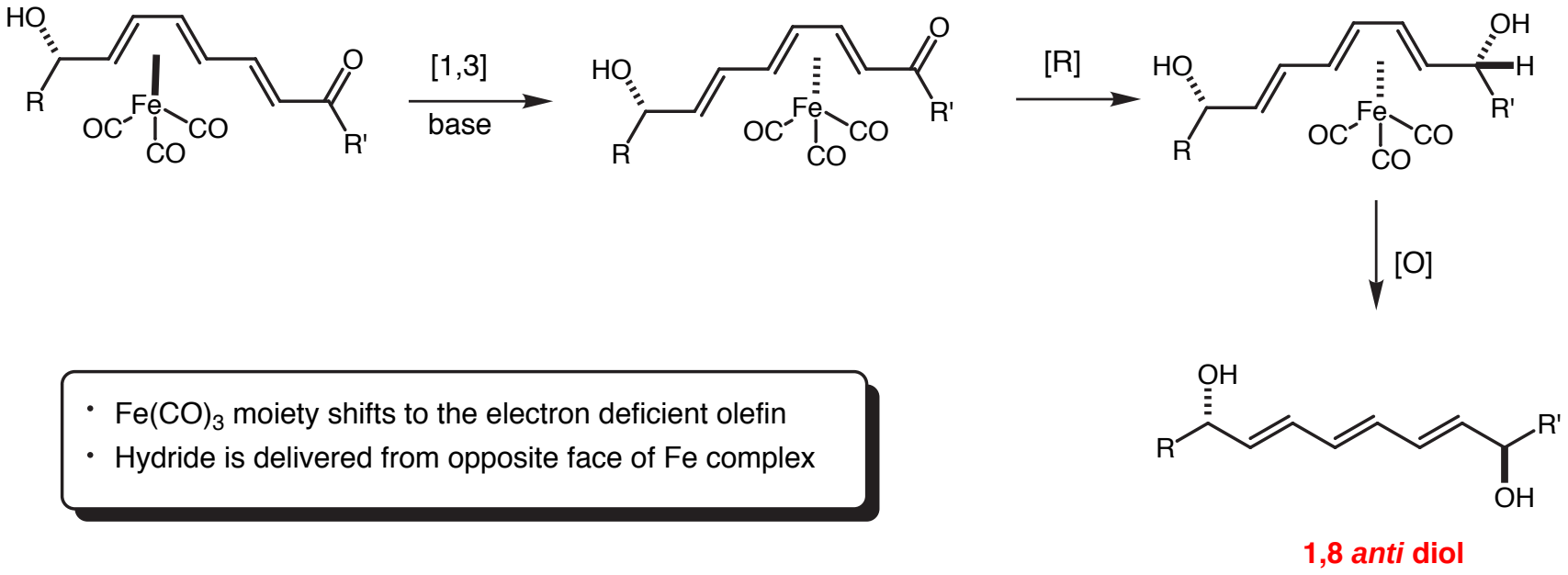
73 %



1,9 *anti:syn* 90:10
60% ee

Thomas, E.J. *Tetrahedron.* **1999**, *55*, 3723

$Fe(CO)_3$ Complexes as Chiral Transfer Groups

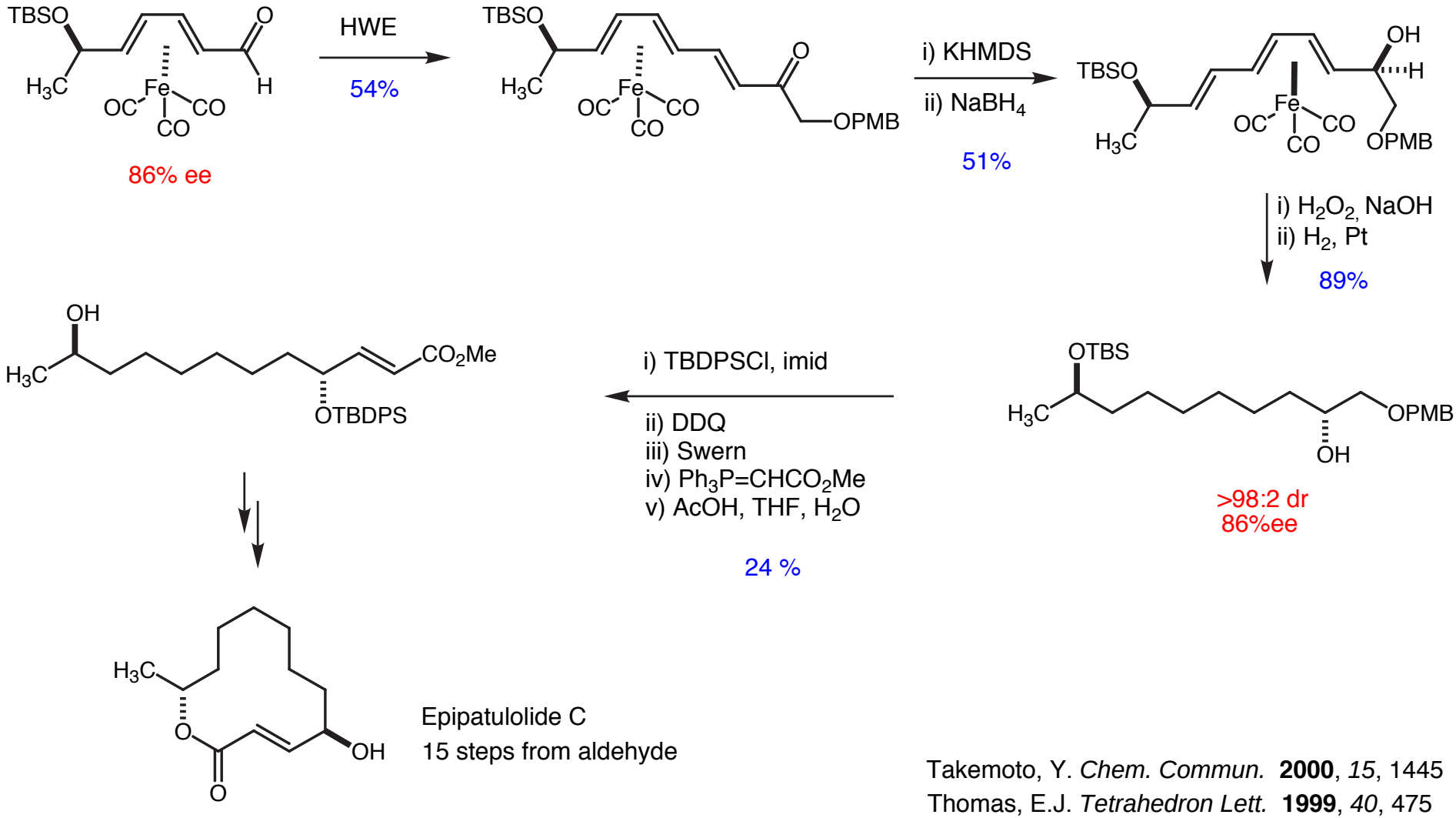


- $Fe(CO)_3$ moiety shifts to the electron deficient olefin
- Hydride is delivered from opposite face of Fe complex

1,8 *anti* diol

Takemoto, Y. *Chem. Commun.* **2000**, *15*, 1445

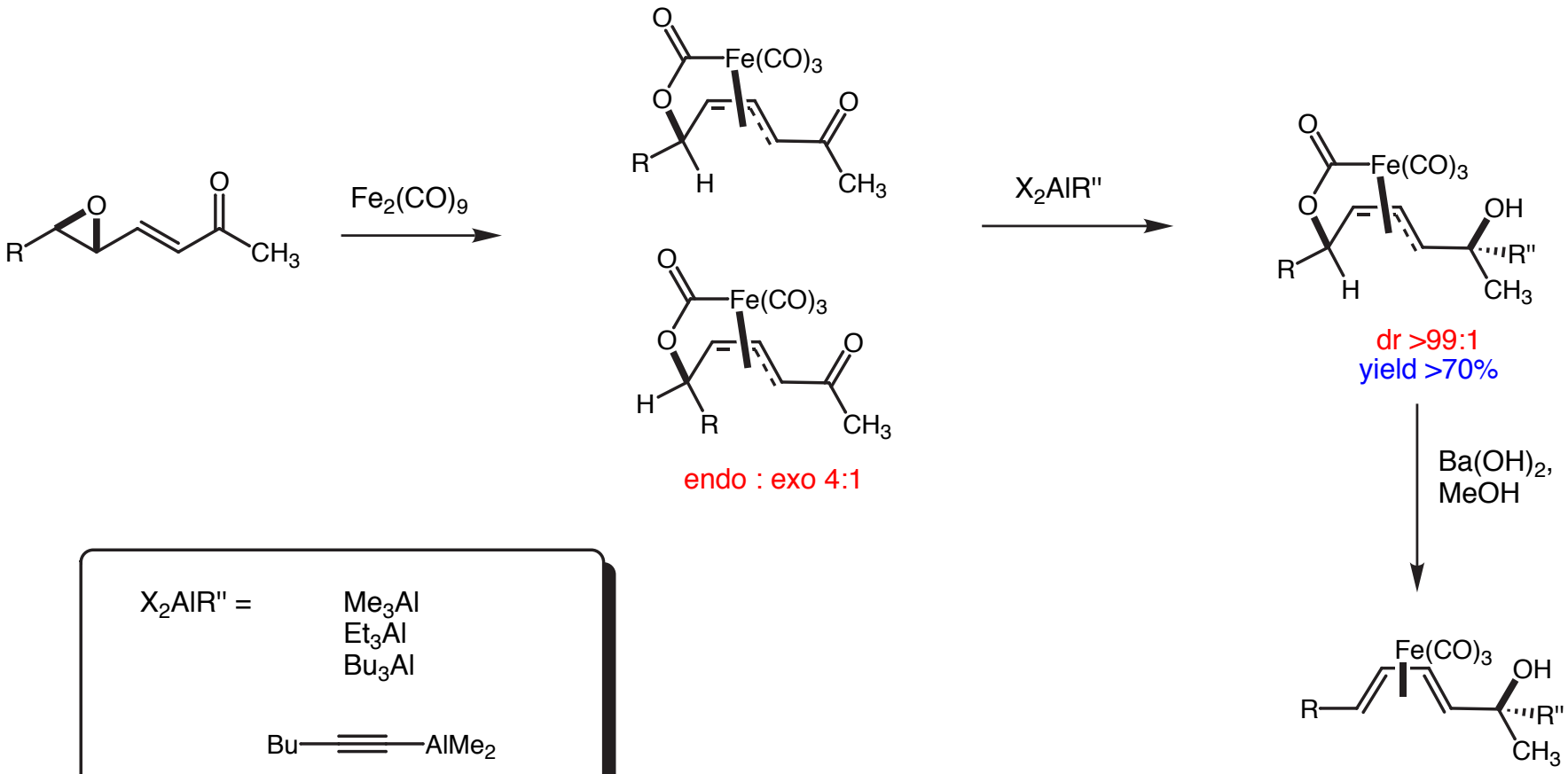
$Fe(CO)_3$ Complexes as Chiral Transfer Groups: Formal Synthesis of Epipatulolide



Takemoto, Y. *Chem. Commun.* **2000**, *15*, 1445
Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 475

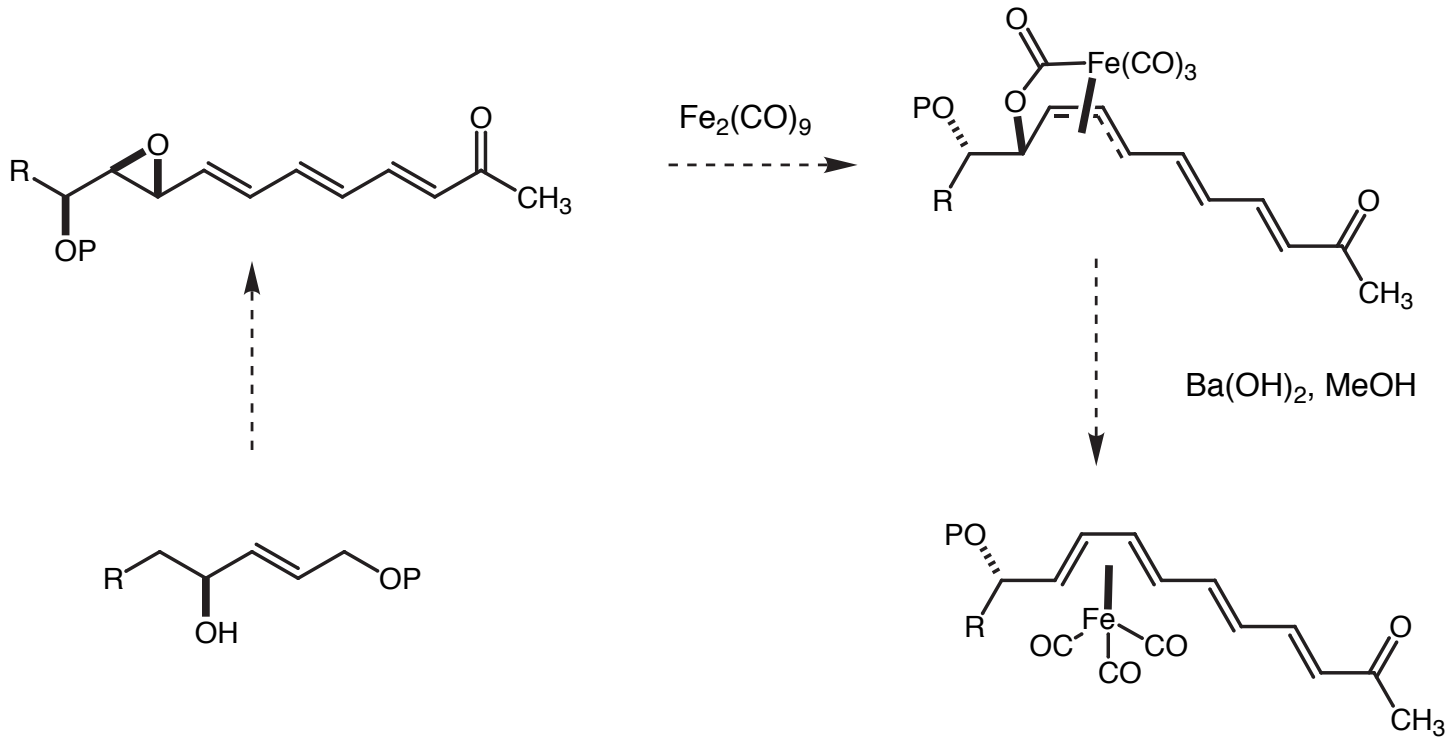
37-FeCO3 1,3 shift epipat 5/23/02 9:01 PM

$Fe(CO)_3$ Complexes as Chiral Transfer Groups

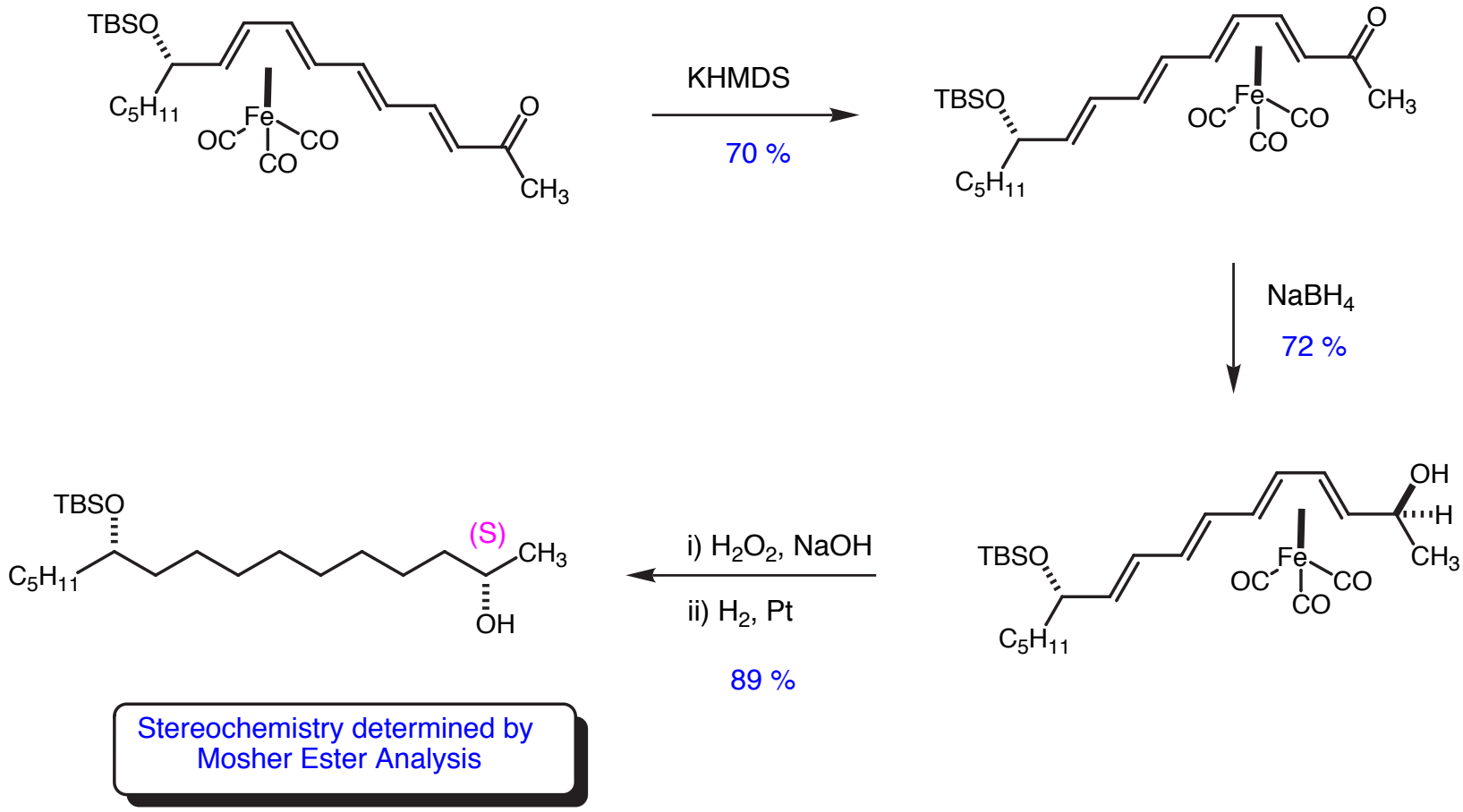


Ley, S.V. *Perkin Trans. I* **1997**, 3299

Possibility for 1,10-Asymmetric
Combining the Work of Ley and Takemoto



Possibility for 1,10-Asymmetric Induction Using $Fe(CO)_3$ Complexes



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