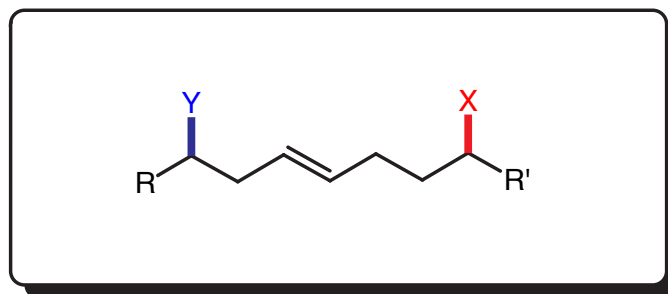


Diastereoselective Construction of Remote Stereocenters: The use of Chiral Allylstannanes & Claisen Rearrangements



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

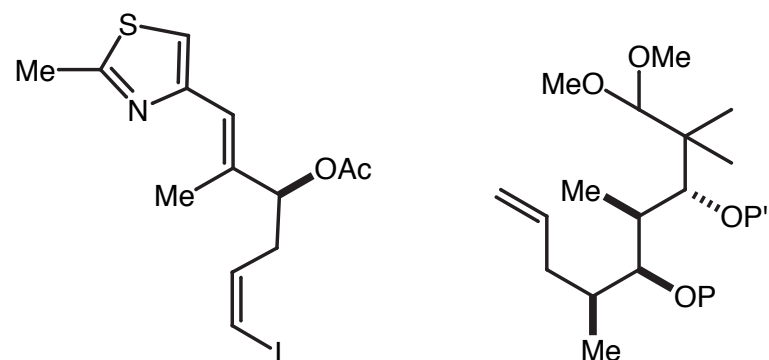
Useful references:

- 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

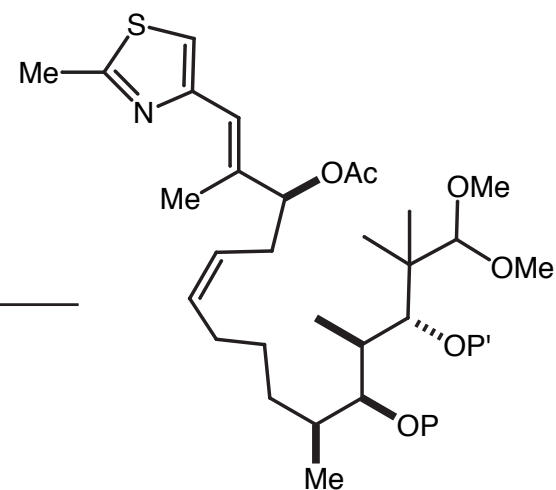
- Coupling of Chiral Fragments**

- Asymmetric Induction by Reagent Control
- Asymmetric Induction by Substrate Control
- Chirality Transfer Methodology



i) 9-BBN
ii) PdCl₂(dppf)₂,
Cs₂CO₃, Ph₃As

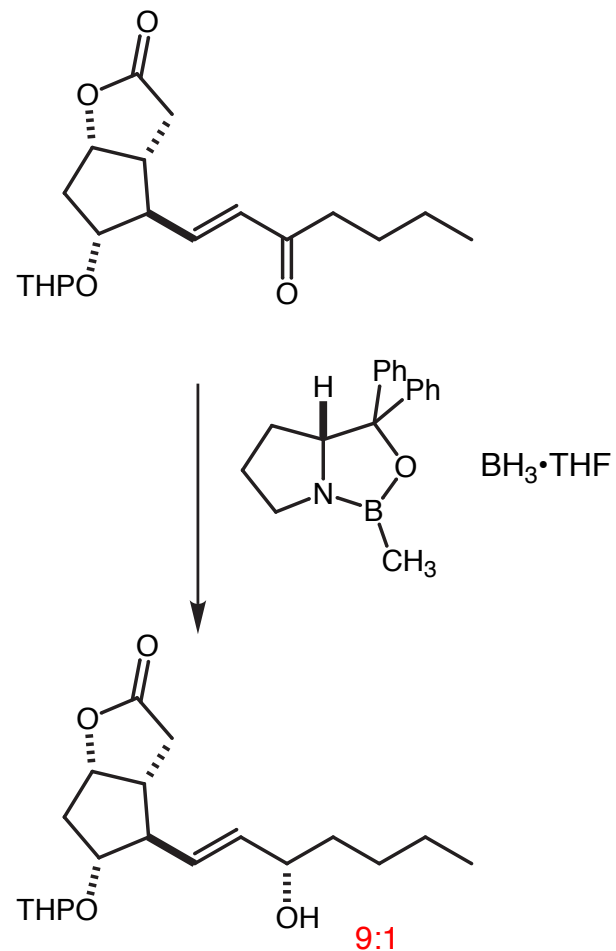
Epothilone A



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

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

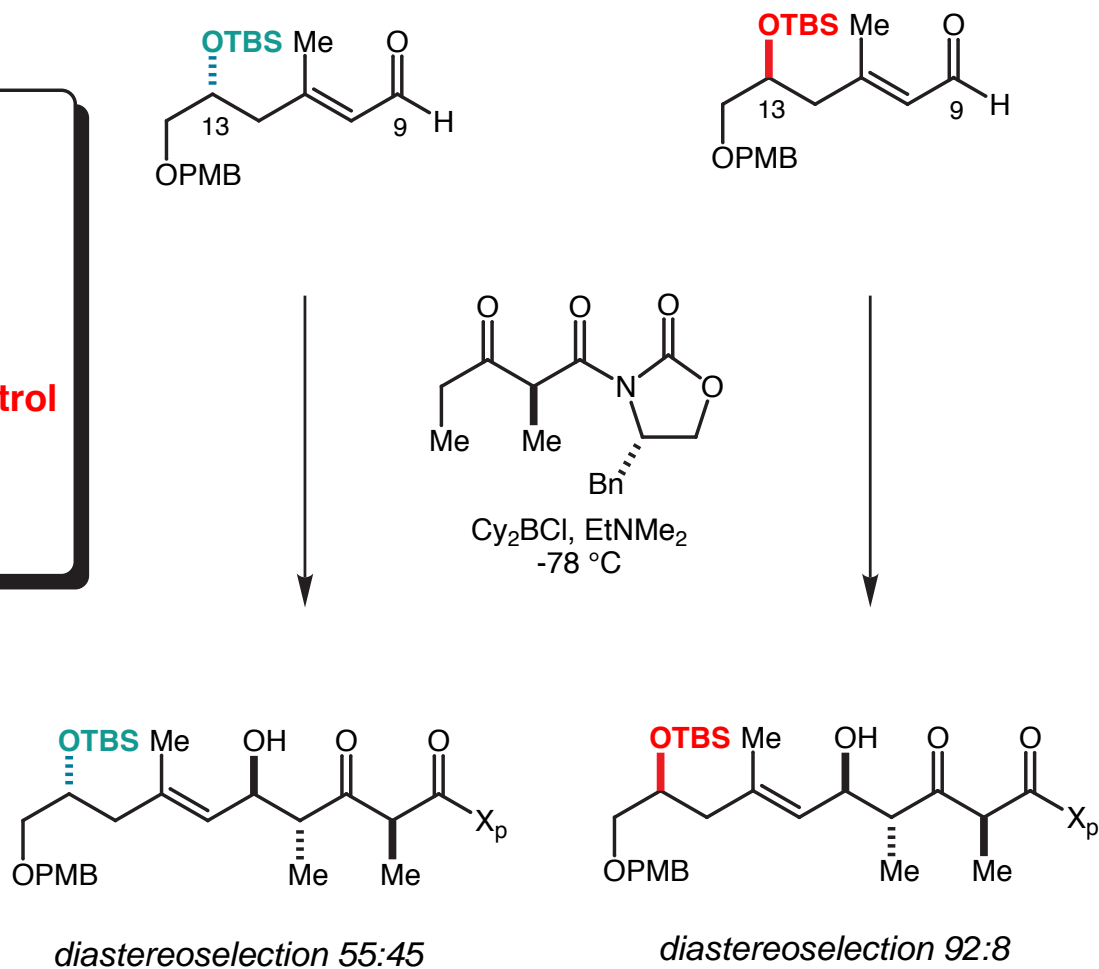
- Coupling of Chiral Fragments
- **Asymmetric Induction by Reagent Control**
- Asymmetric Induction by Substrate Control
- Chirality Transfer Methodology



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

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

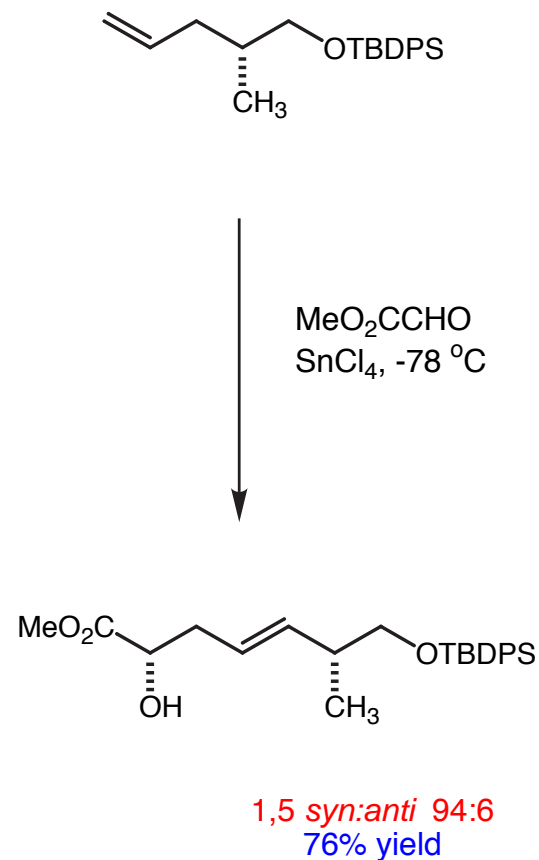
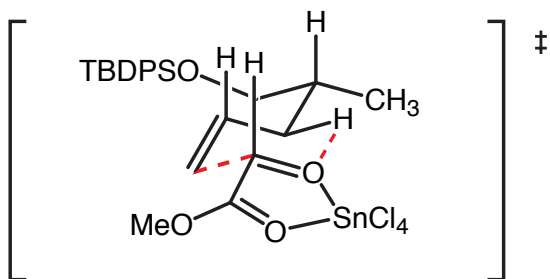
- Coupling of Chiral Fragments
- Asymmetric Induction by Reagent Control
- **Asymmetric Induction by Substrate Control**
- Chirality Transfer Methodology



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

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

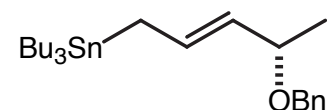
- Coupling of Chiral Fragments
- Asymmetric Induction by Reagent Control
- **Asymmetric Induction by Substrate Control**
- Chirality Transfer Methodology



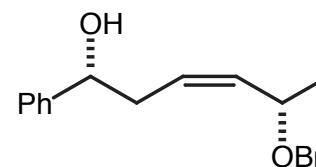
Mikami, K. *J. Org. Chem.* **1992**, *57*, 6105

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

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



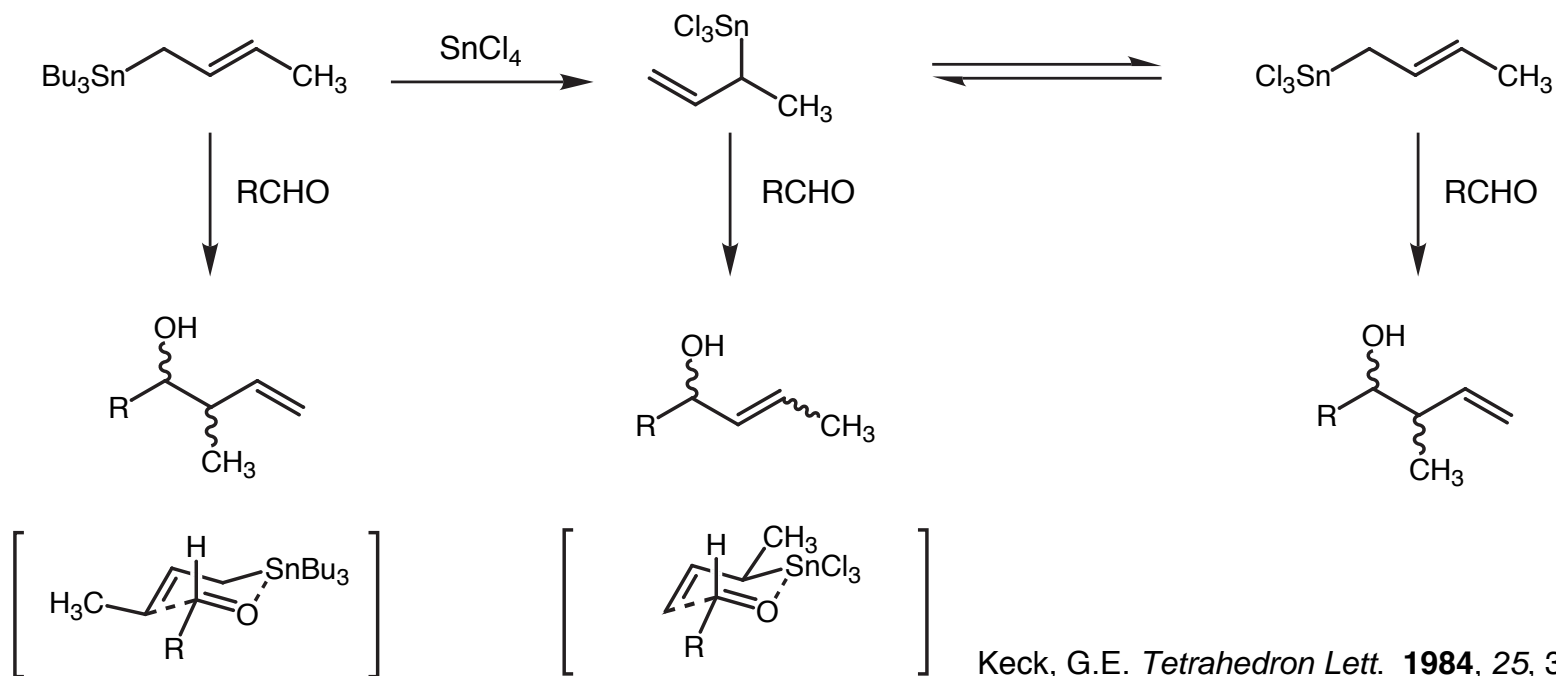
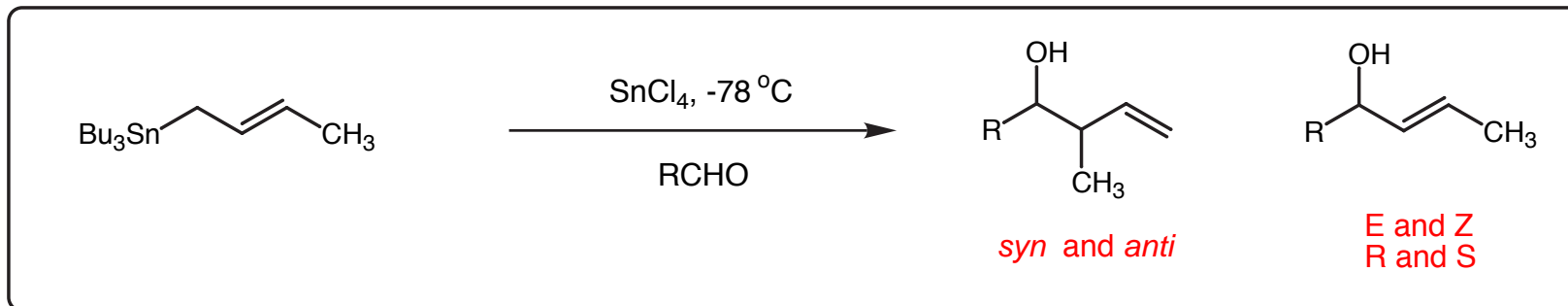
i.) SnCl₄, 5 min, -78 °C
ii.) PhCHO, 1 hour



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

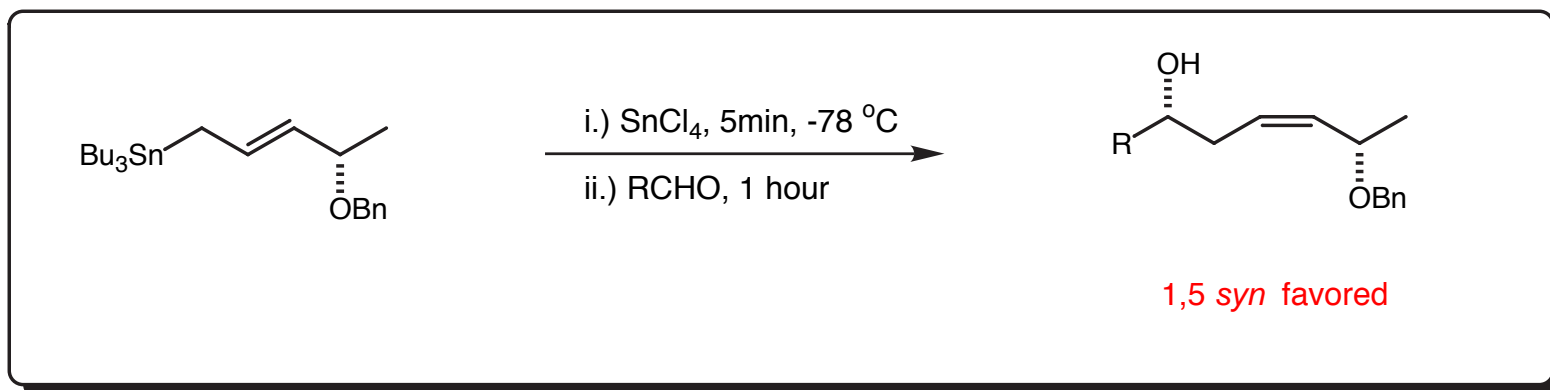
Thomas, E.J. *Tetrahedron Lett.* **1990**, 31, 6239

SnCl₄ 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

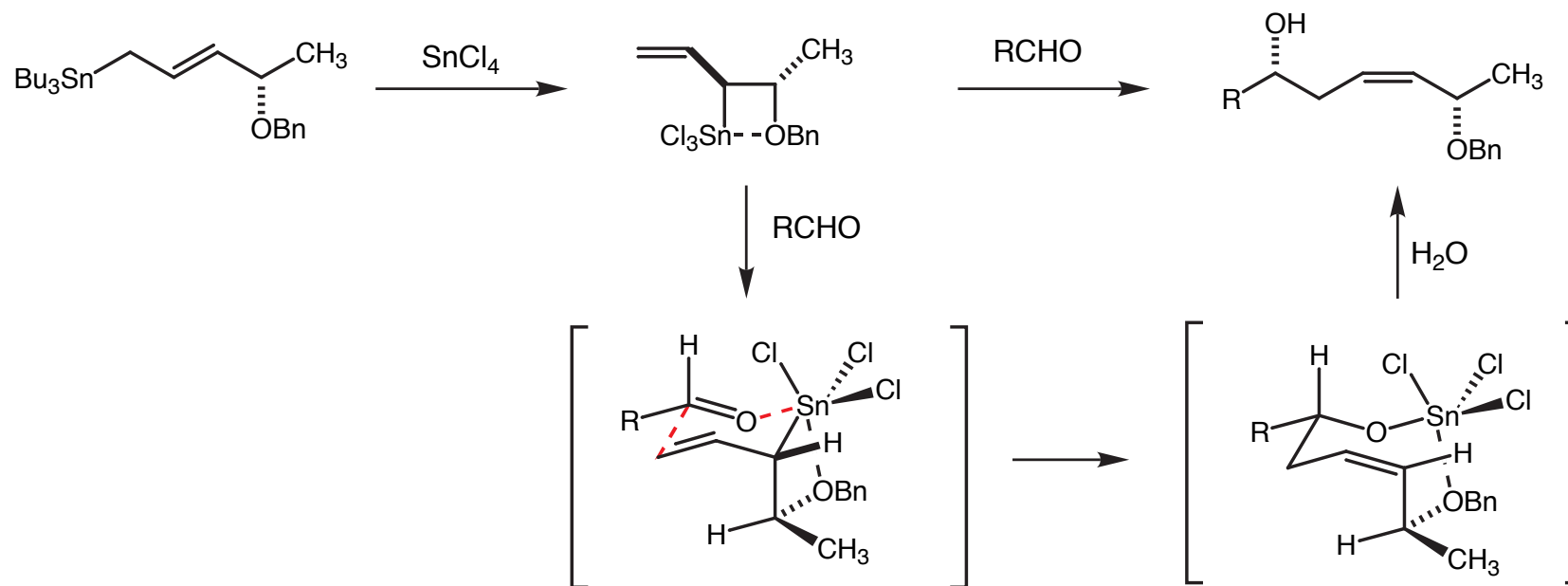
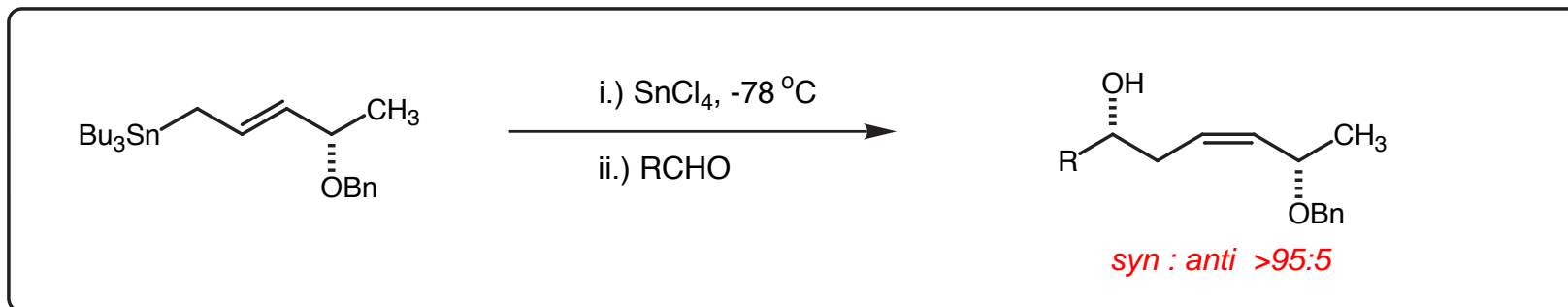
1,5-Asymmetric Induction Using 4-Alkoxy-allylstannanes



Aldehydes	Yield	1,5 <i>syn</i> : <i>anti</i>
PhCHO	90	98 : 2
p-ClC ₆ H ₄ CHO	77	94 : 6
p-NO ₂ C ₆ H ₄ CHO	77	95 : 5
p-MeOC ₆ H ₄ CHO	77	97 : 3
furfural	72	95 : 5
CH ₃ CH ₂ CH ₂ CHO	84	95 : 5
(CH ₃) ₂ CHCHO	84	93 : 7
(CH ₂) ₅ CHCHO	78	92 : 8
PhCH=CHCHO	64	95 : 5
MeO ₂ CCHO	68	95 : 5

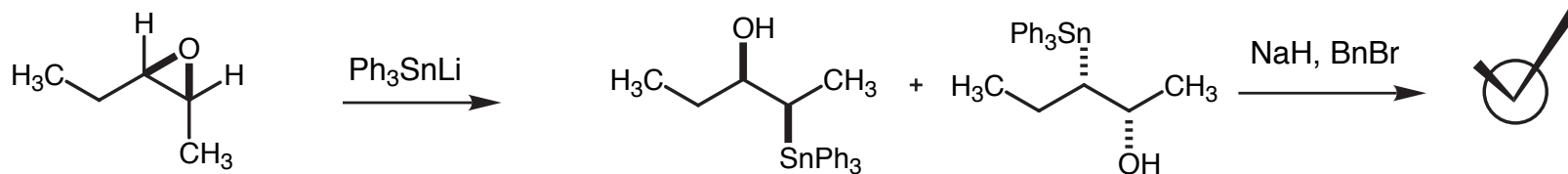
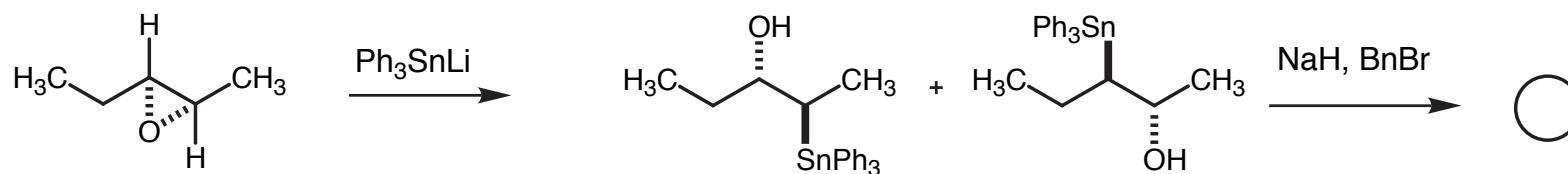
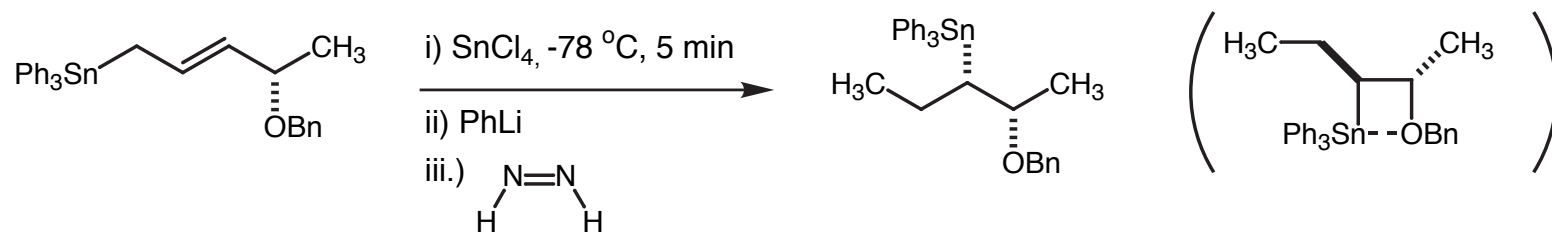
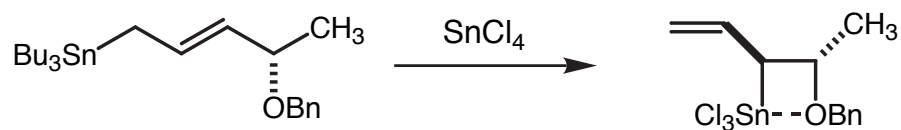
Thomas, E.J. *Tetrahedron Lett.* **1990**, 31, 6239
 Thomas, E.J. *Chemtracts* **1994**, 7, 207

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



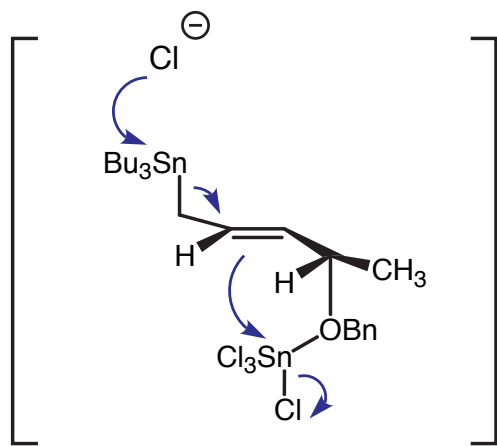
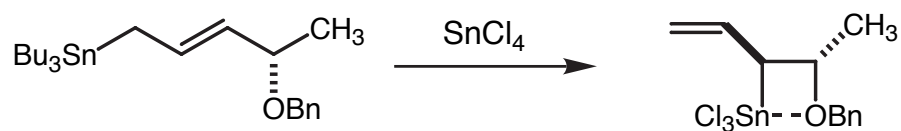
Thomas, E.J. *Tetrahedron Lett.* **1990**, 31, 6239

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

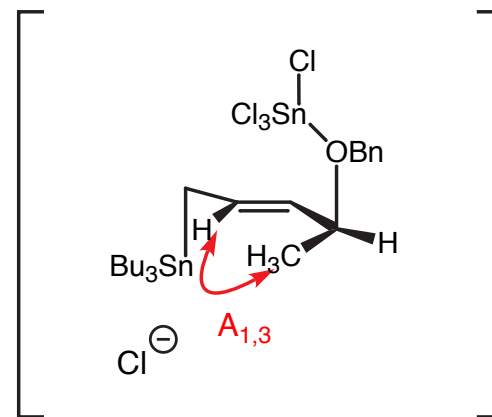


Thomas, E.J. *Chem. Commun.* **1998**, 8, 899

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

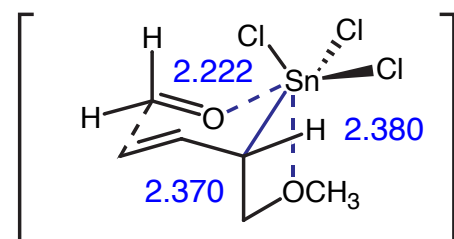
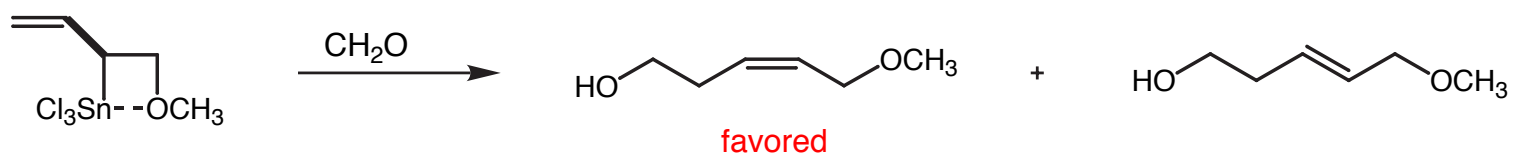
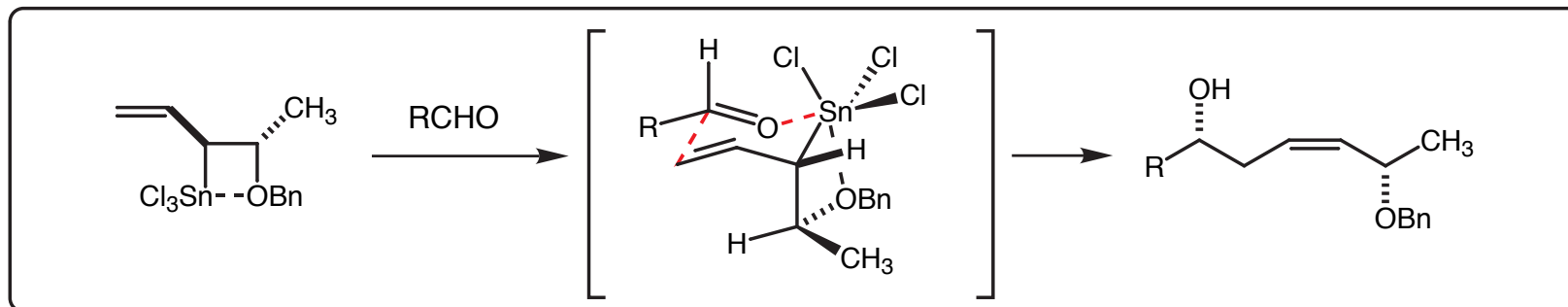


Favored: $A_{1,3}$ minimized

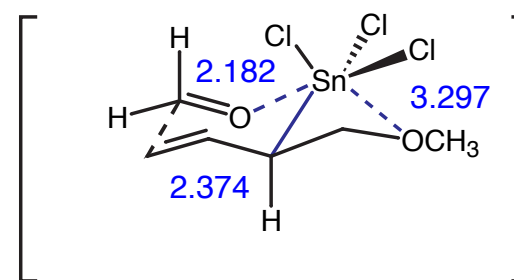


Disfavored

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



$$\Delta E = 1.9 \text{ kcal}\cdot\text{mol}^{-1}$$

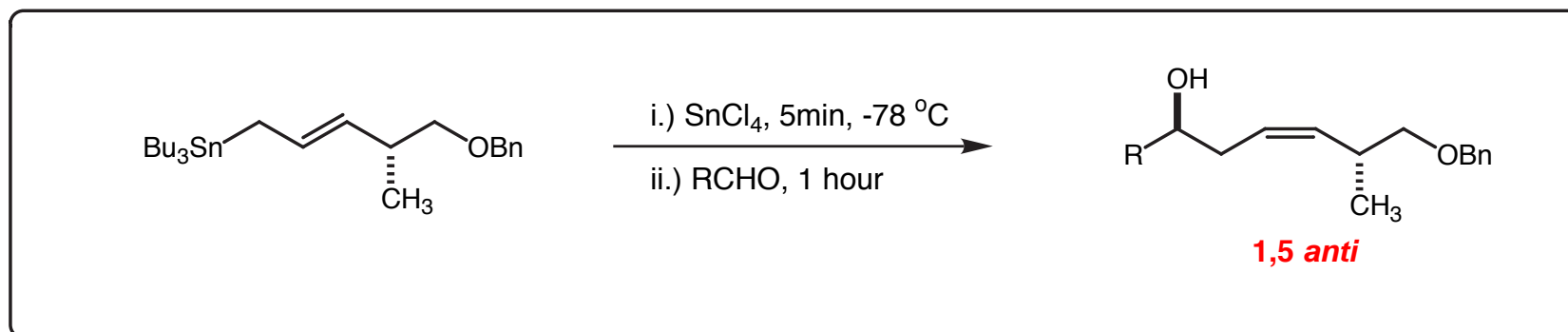


$$\Delta E = 12.0 \text{ kcal}\cdot\text{mol}^{-1}$$

(GAUSSIAN94 Calculation, split valence basis)

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

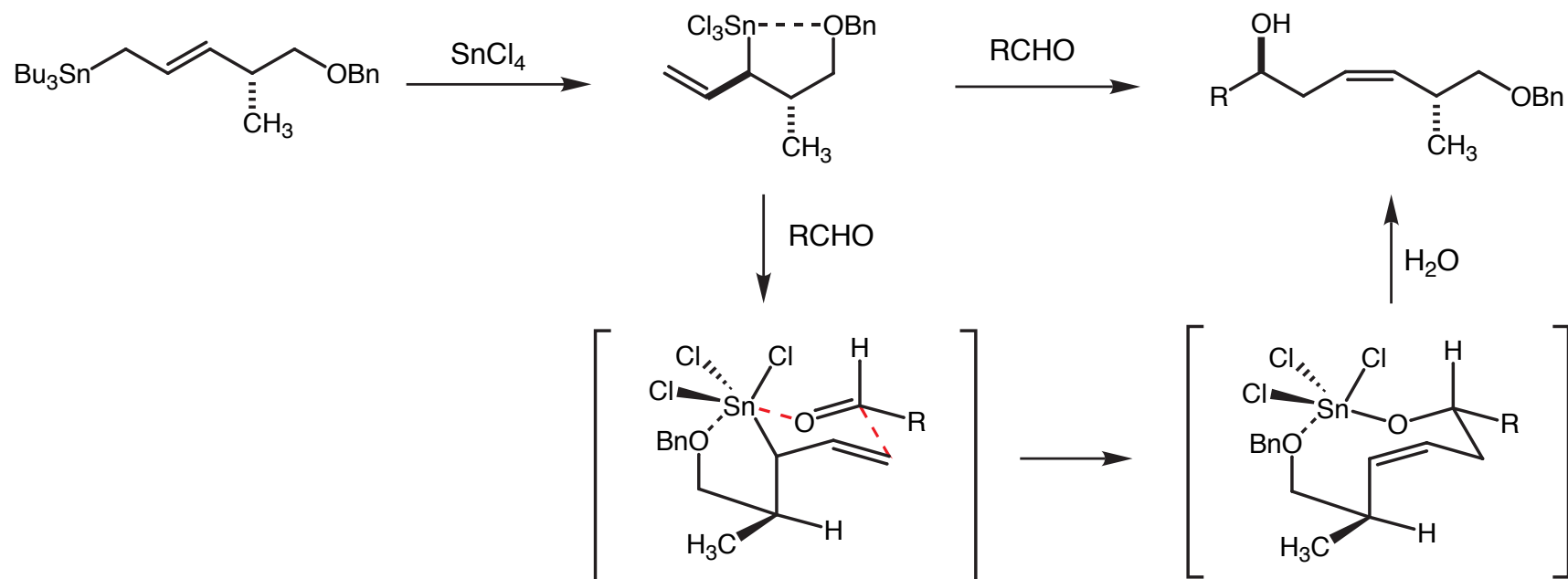
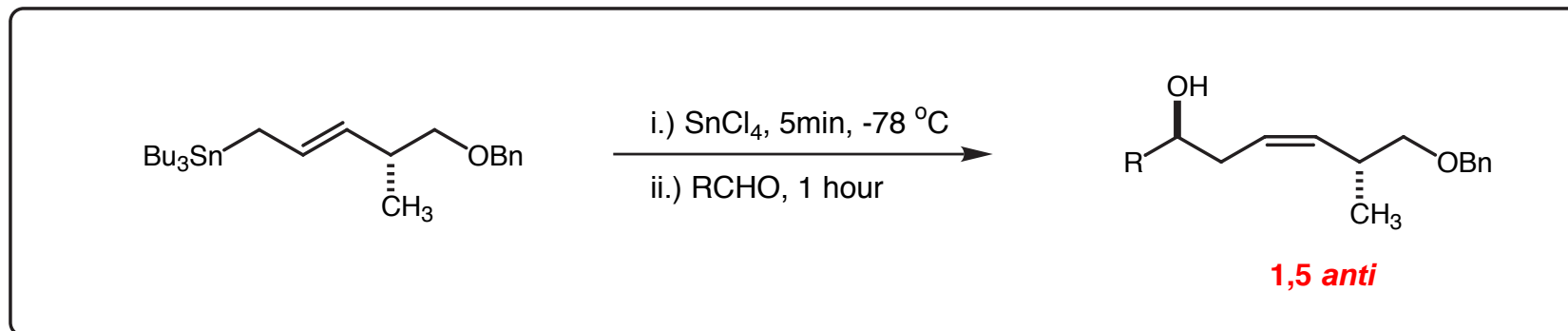
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes



Aldehydes	Yield	1,5- <i>anti</i> : 1,5 <i>syn</i>
PhCHO	86	96 : 4
<i>p</i> -ClC ₆ H ₄ CHO	67	96 : 4
<i>p</i> -MeOC ₆ H ₄ CHO	65	96 : 4
CH ₃ CH ₂ CHO	70	95 : 5
(CH ₃) ₂ CHCHO	81	95 : 5

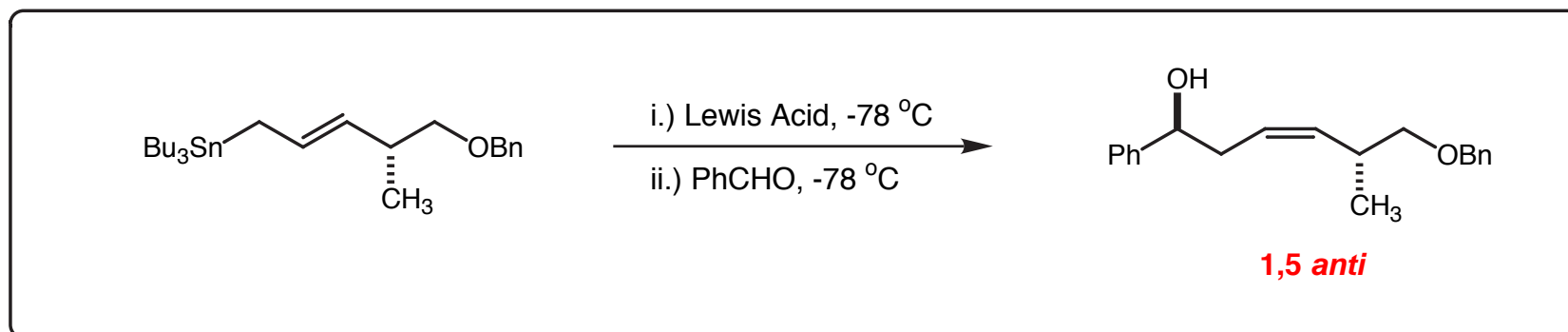
Thomas, E.J. *Synlett* **1992**, 585

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



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

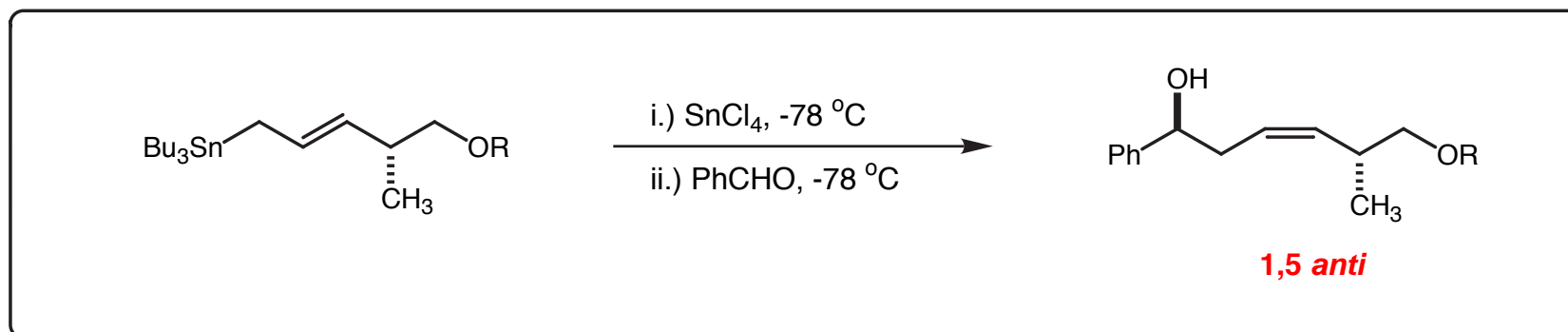
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes



Lewis Acids	Yield	1,5- <i>anti</i> : 1,5 <i>syn</i>
SnCl_4	86	96 : 4
BuSnCl_3	40	95 : 5
SnBr_4	75	99 : 1
Bu_2SnCl_2	low	--
TiCl_4	low	--
$\text{BF}_3 \cdot \text{OEt}_2$	low	--
$\text{AlCl}_3 \cdot i\text{-PrOH}$	low	--

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

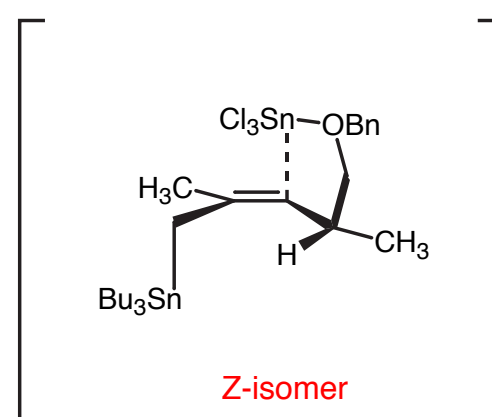
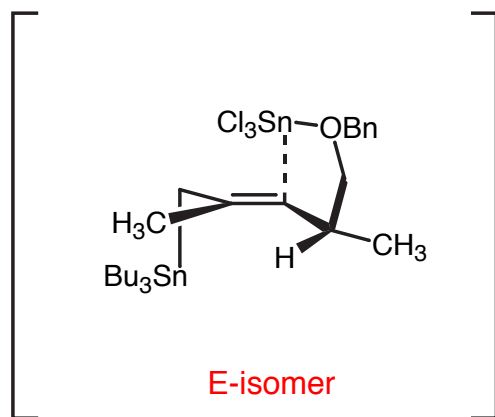
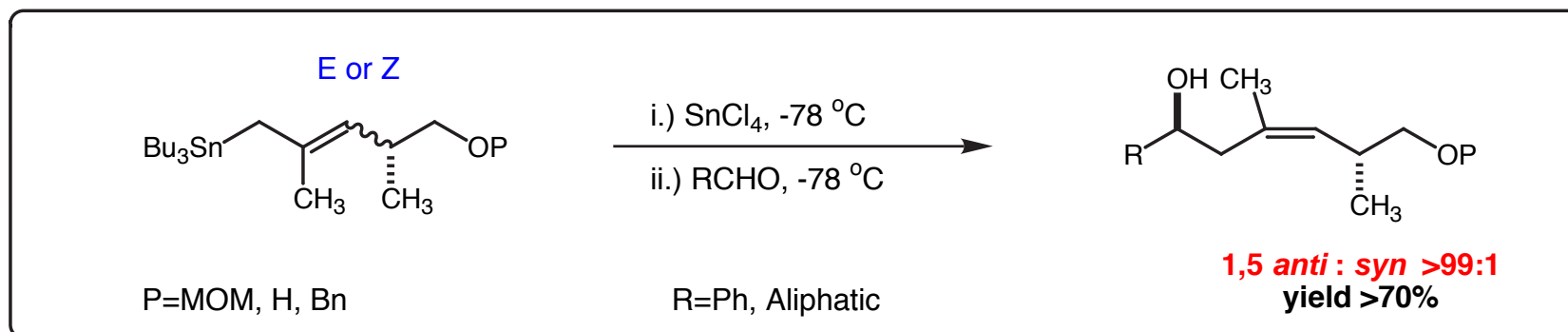
1,5-Asymmetric Induction Using 5-Alkoxy-allylstannanes



R	Yield	1,5- <i>anti</i> : 1,5- <i>syn</i>
<i>p</i> -MeOC ₆ H ₄ CH ₂	80	95 : 5
MOM	66	93 : 7
SEM	71	80 : 20
SiMe ₂ ^t Bu	60	81 : 19
SiPh ₂ ^t Bu	61	80 : 20

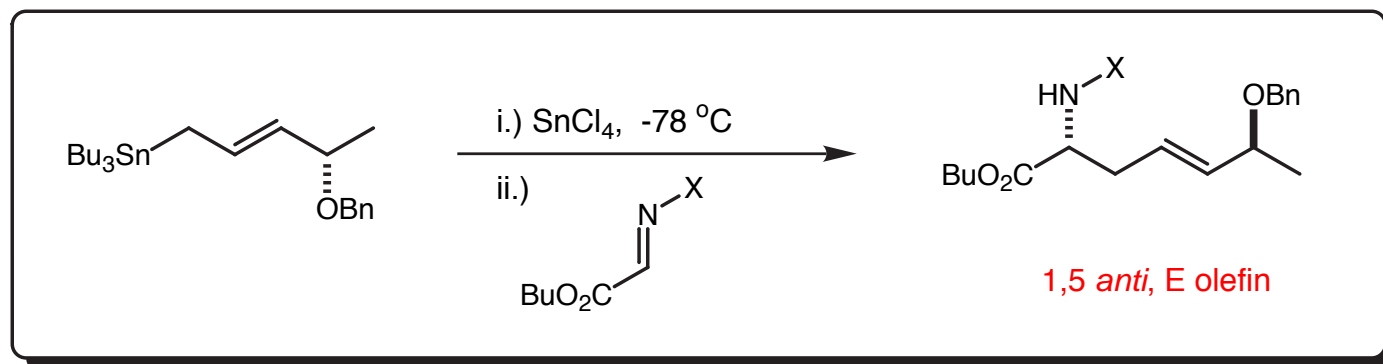
Thomas, E.J. *Tetrahedron Lett.* **1993**, 34, 3933

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

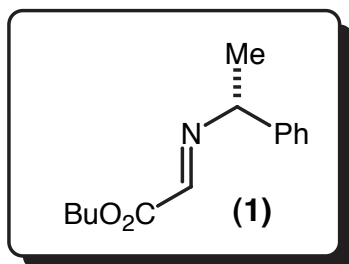


Thomas, E.J. *Perkin Trans. I*, **1993**, 2863

1,5-Asymmetric Induction with Imines

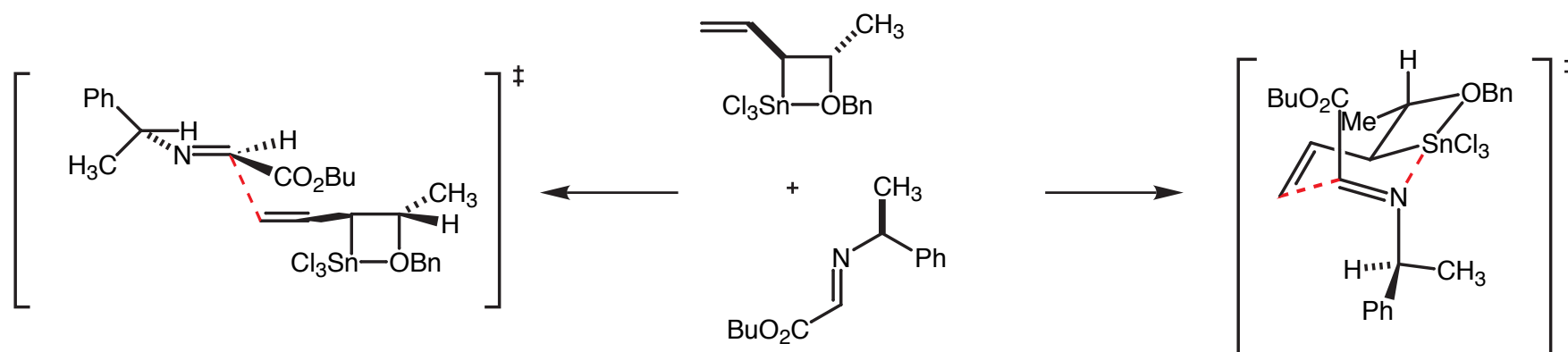
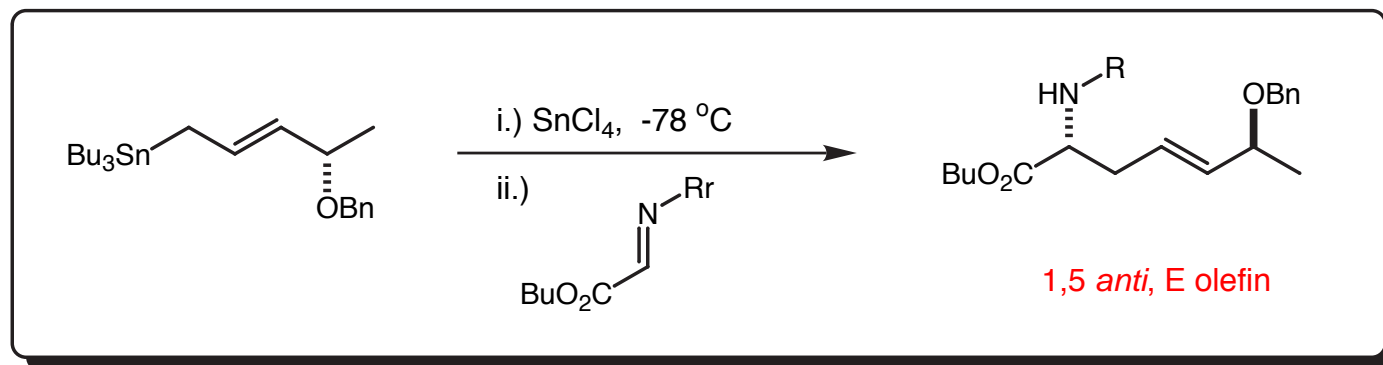


X	Yield	<i>anti</i> : <i>syn</i>
CHPh_2	79	90 : 10
CMe_2Ph	75	90 : 10
OBn	67	90 : 10
(1)	72	90 : 10 Mismatched
ent - (1)	73	96 : 4 Matched



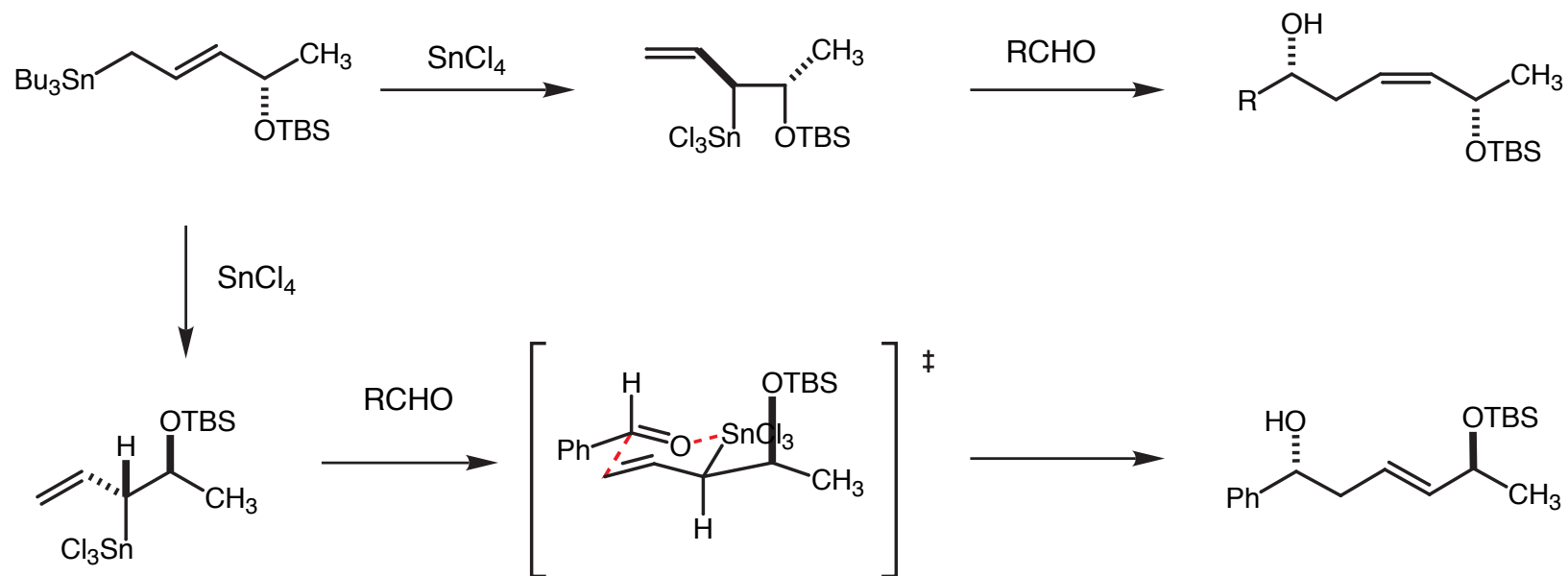
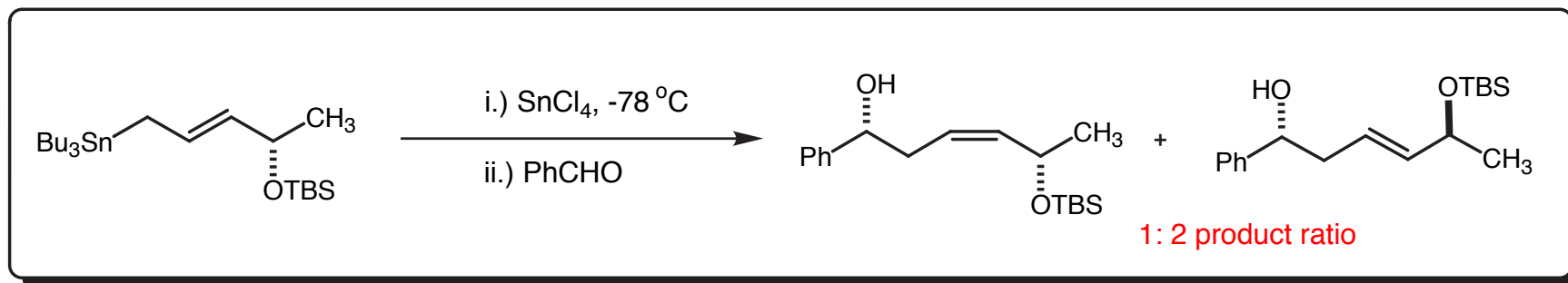
Thomas, E.J. *Chem. Commun.* **1995**, 6, 657
 Thomas, E.J. *Tetrahedron. Assym.* **1995**, 4, 2575

1,5-Asymmetric Induction with Imines



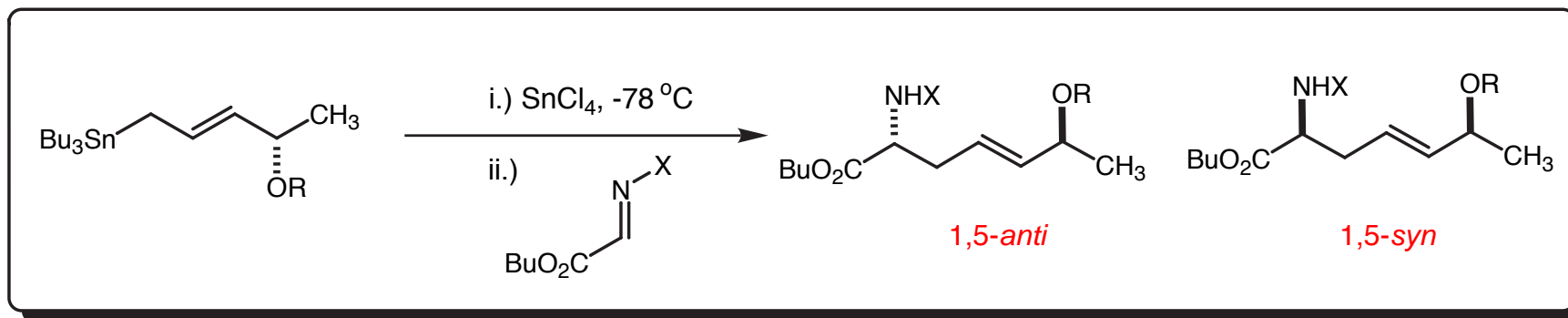
Thomas, E.J. *Chem. Commun.* **1995**, 6, 657

Limitations of the Allylstannane Chemistry



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

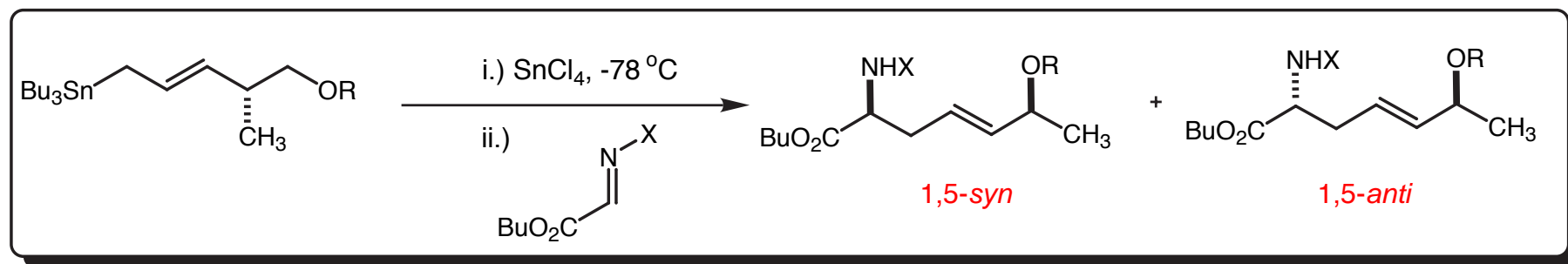
Limitations of the Allylstannane Chemistry



Stannane (R)	Imine (X)	Yield	1,5- <i>anti</i> : 1,5 <i>syn</i>
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. *Tetrahedron Asym.* **1995**, 6, 2579

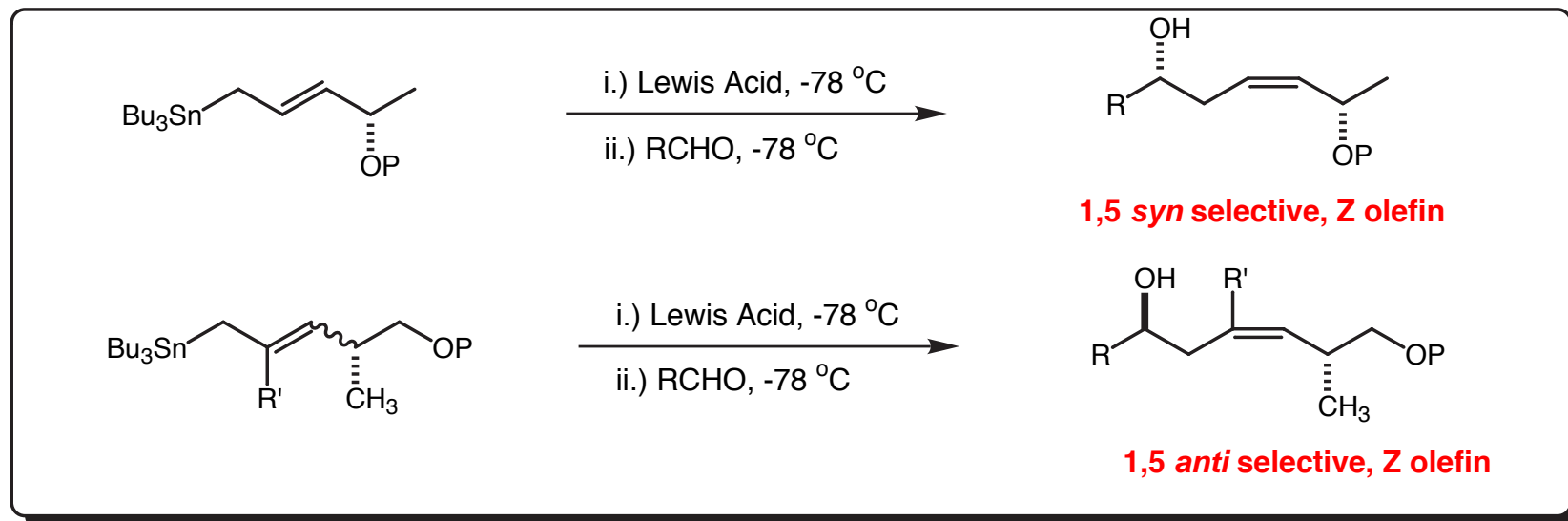
Limitations of the Allylstannane Chemistry



Stannane (R)	Imine (X)	Yield	1,5 <i>syn</i> : 1,5- <i>anti</i>
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

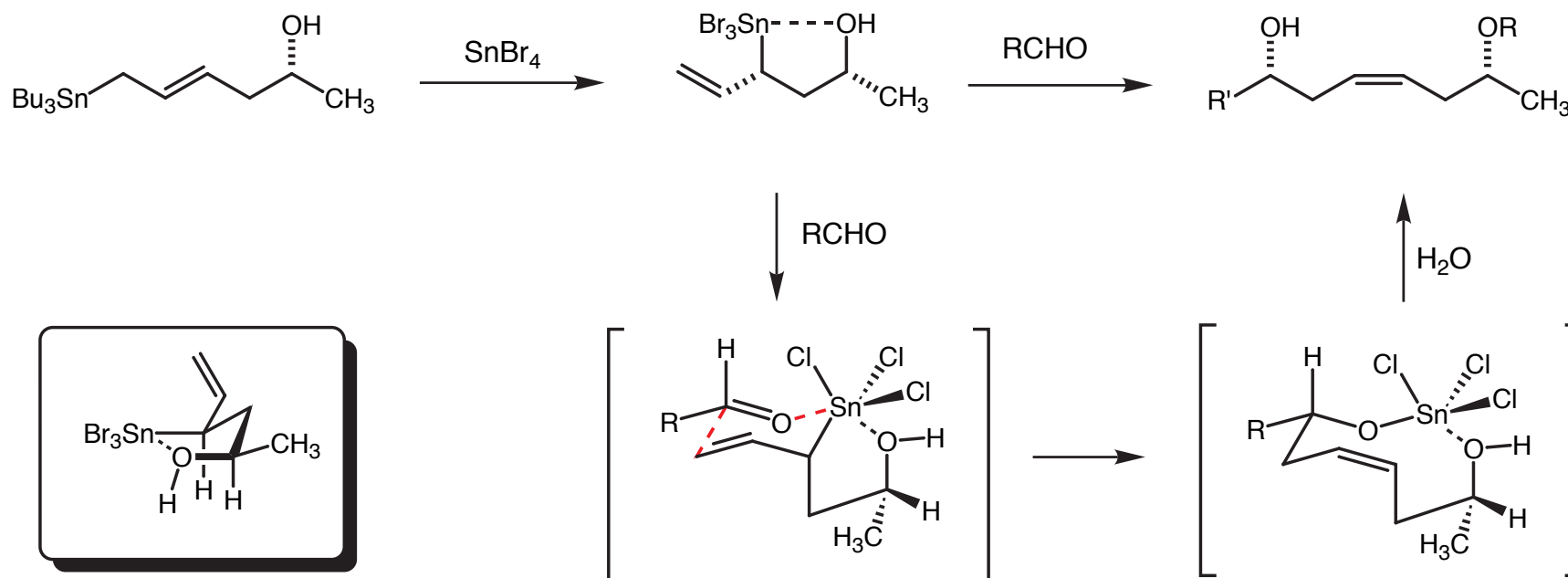
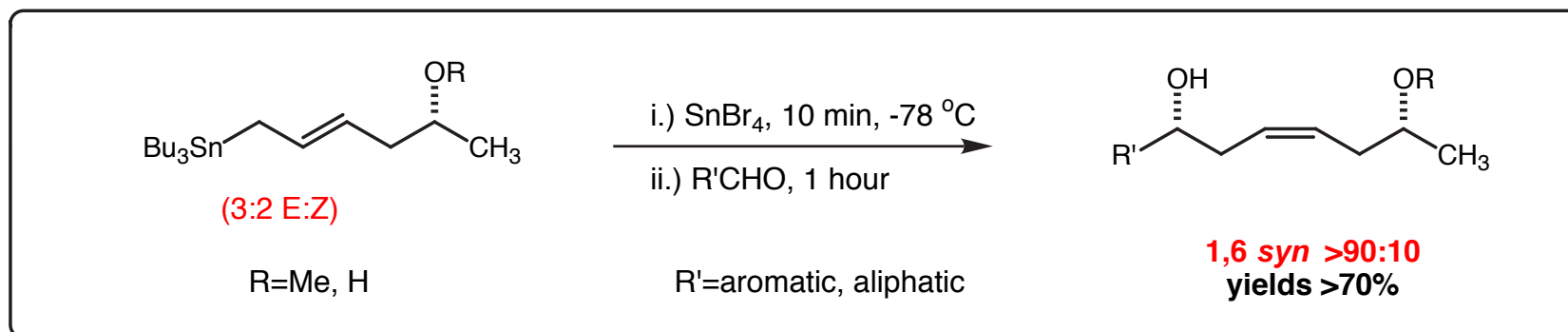
Thomas, E.J. *Tetrahedron Assym.* **1995**, 6, 2579

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



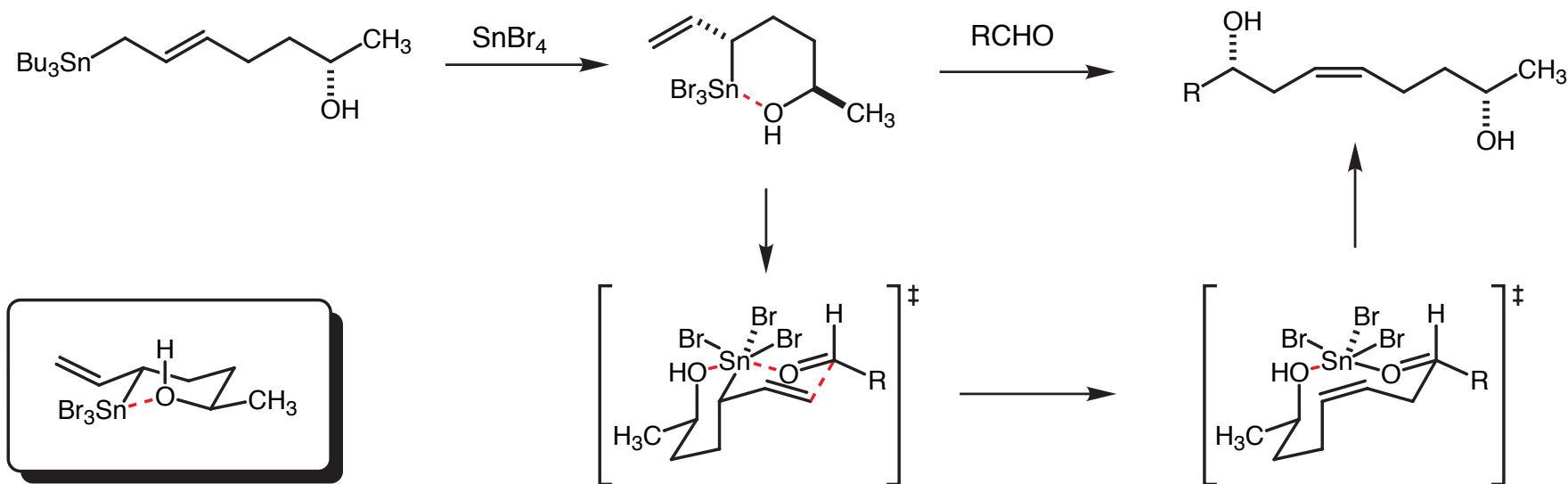
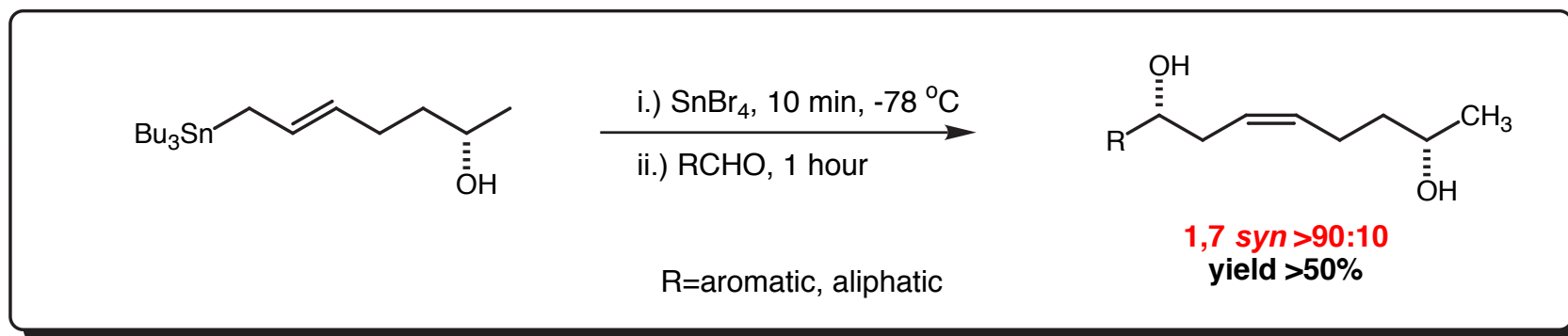
- SnCl_4 or SnBr_4
- Chelating protecting group on oxygen is necessary
Other heteroatoms are also effective (N, S)
- 2-Substitution on the olefin is acceptable
SM olefin geometry is not important
- High selectivities for a range of aldehydes and imines
Generally >95:5 diastereoselectivity

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



Thomas, E.J. *Tetrahedron Lett.* **1993**, 24, 3935

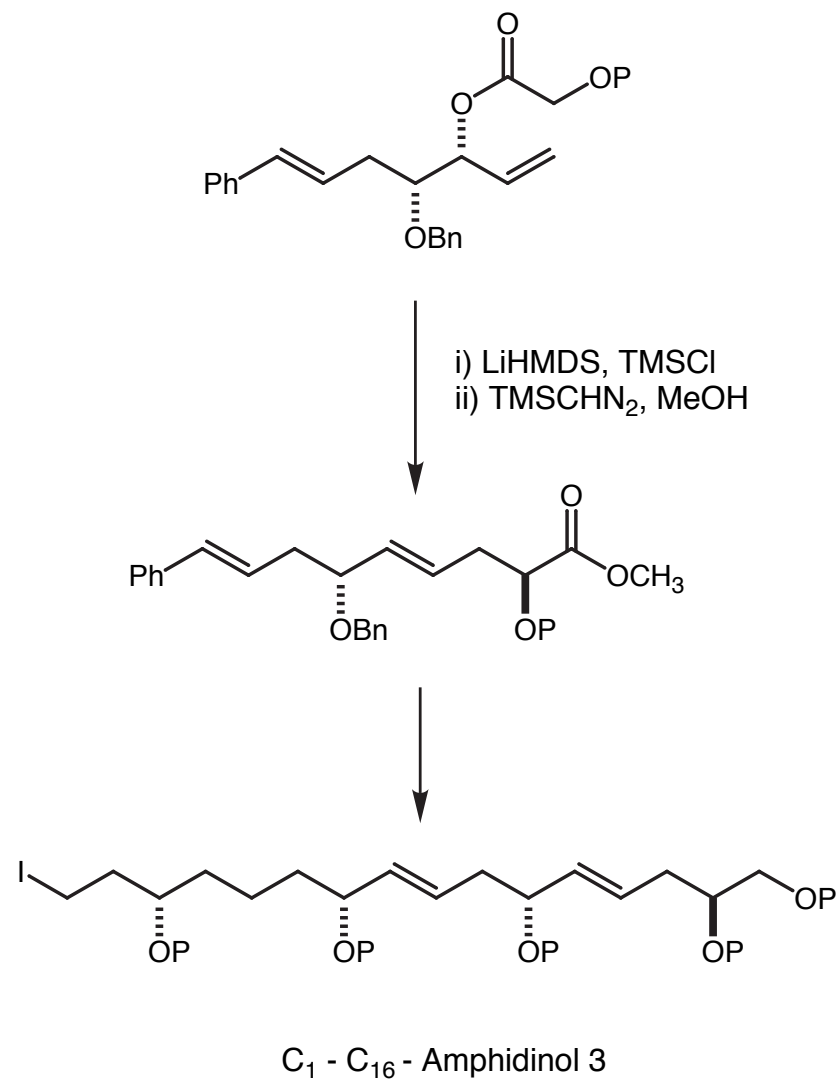
1,7-Asymmetric Induction Using 6-Alkoxy-allylstannanes



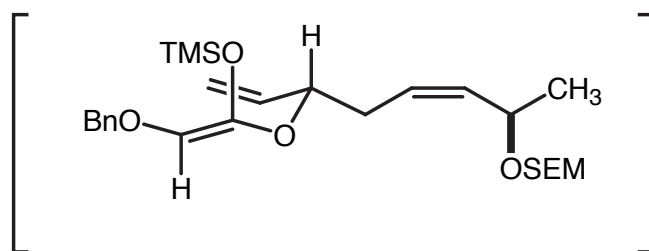
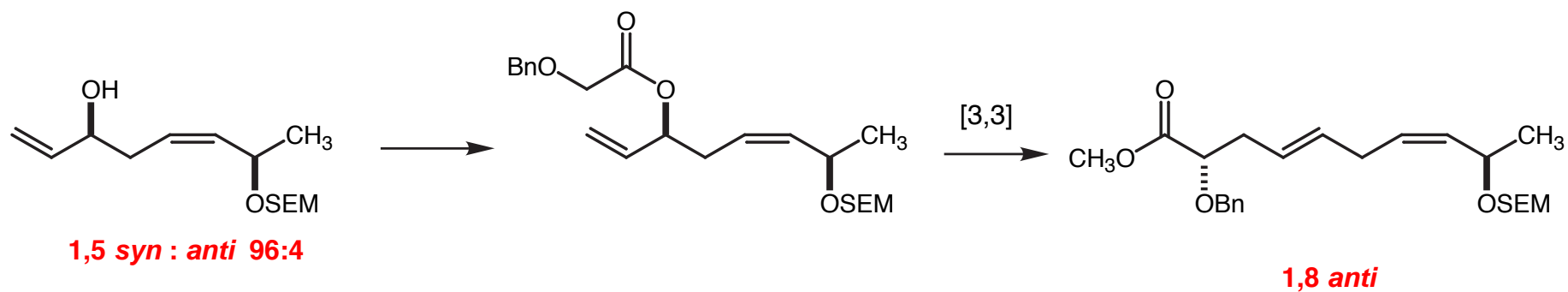
Thomas, E.J. *Chem. Commun.* **1994**, 3, 283

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

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- Asymmetric Induction by Substrate Control
- **Chirality Transfer Methodology**

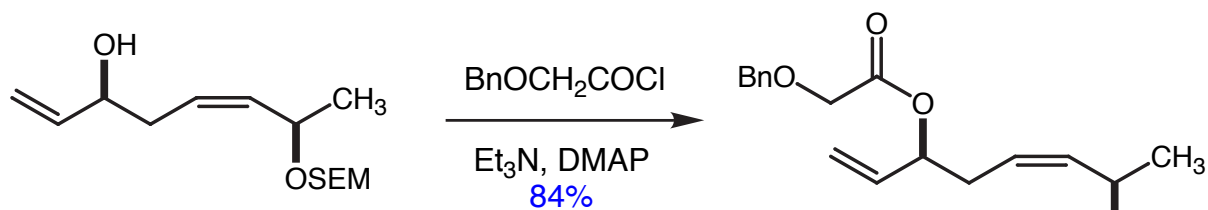
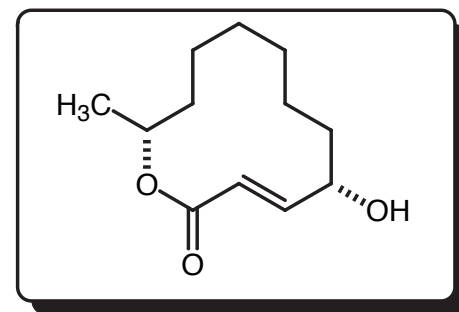


2-Step 1,8-Asymmetric Induction via Chirality Transfer (Ireland-Claisen Rearrangement)



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

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

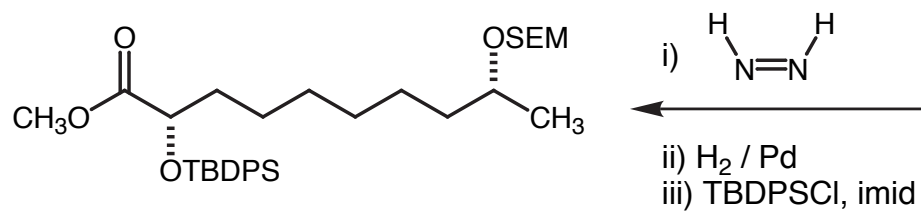


1,5 syn : anti 96:4
77% from (±)-stannane

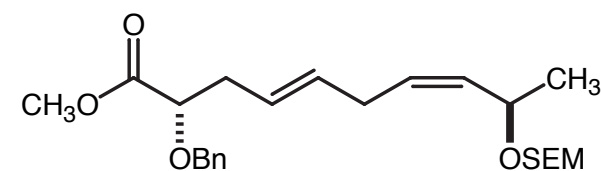
i) LiHMDS, -78 °C

ii) TMSCl, -78 to RT
iii) TMSCHN₂

80%



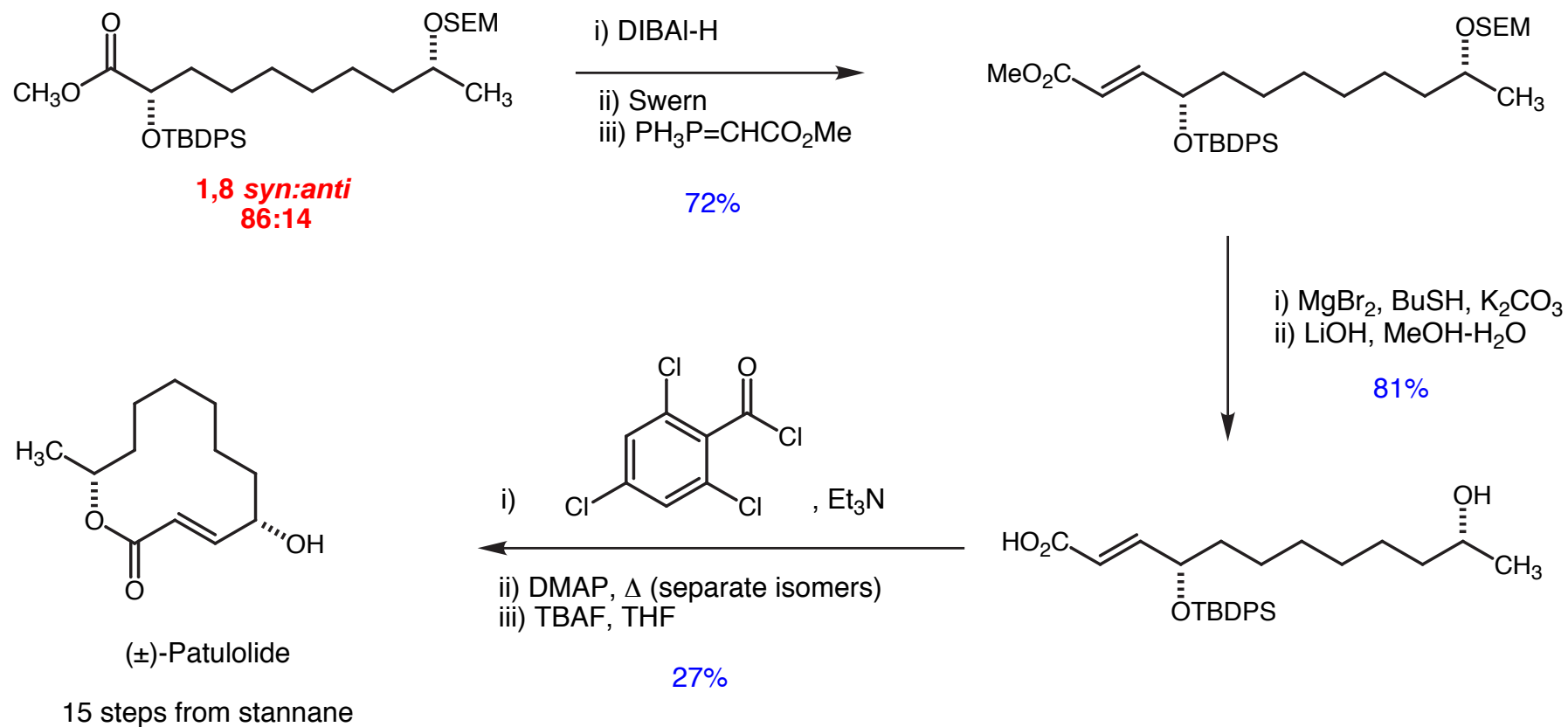
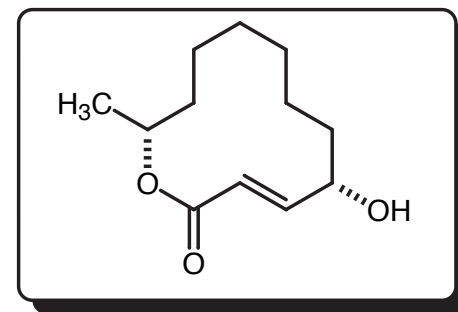
71%



1,8 anti : syn
86:14

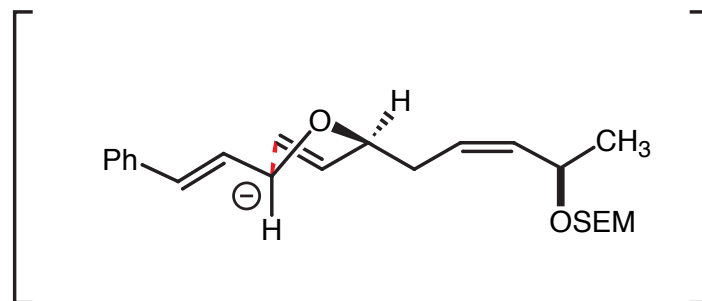
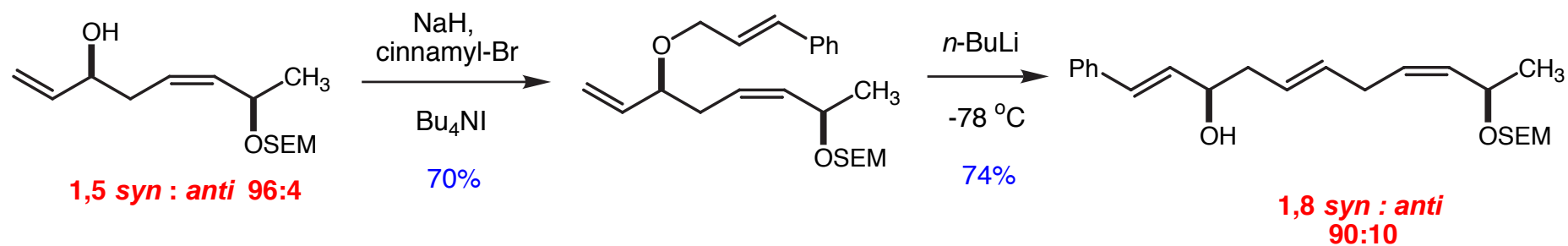
Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 471

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



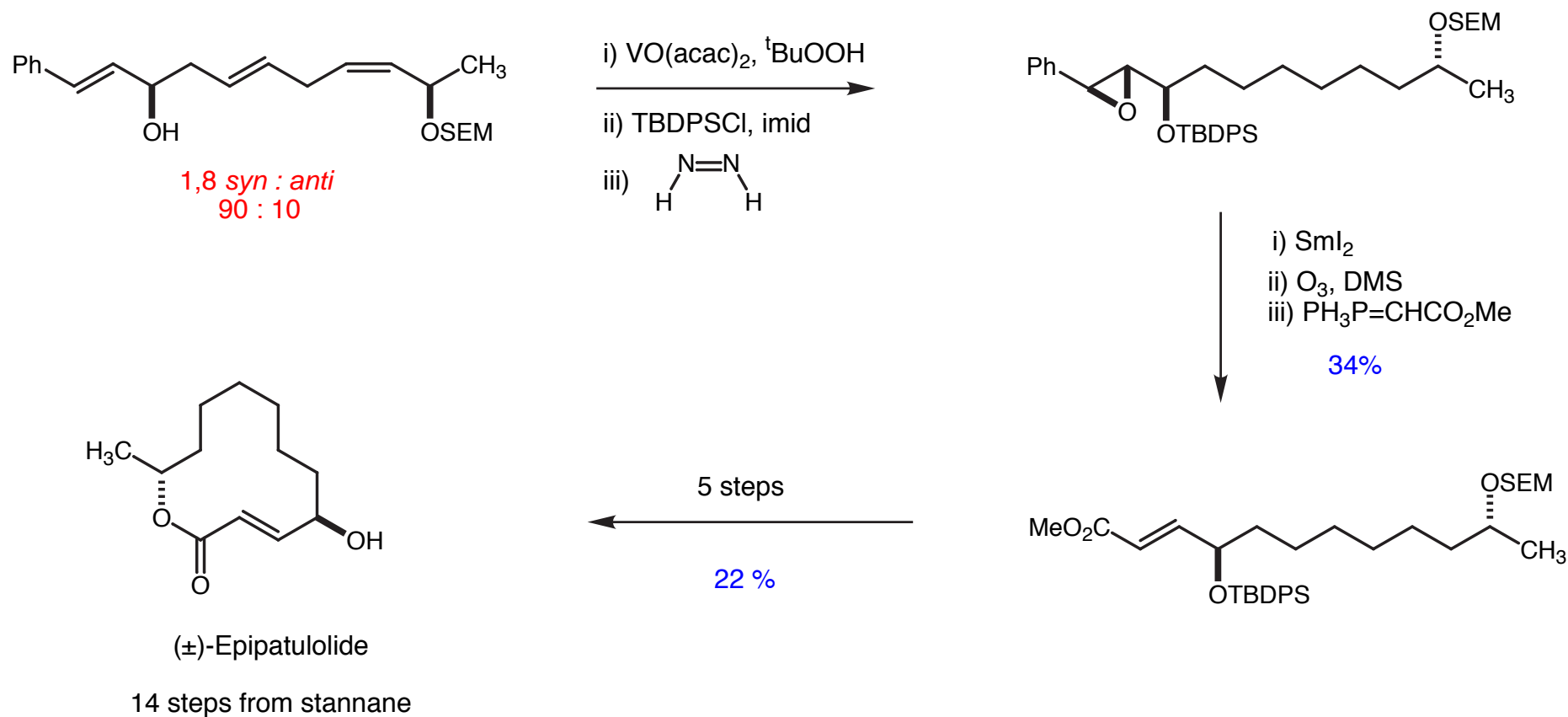
Thomas, E.J. *Tetrahedron Lett.* **1999**, *40*, 471

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



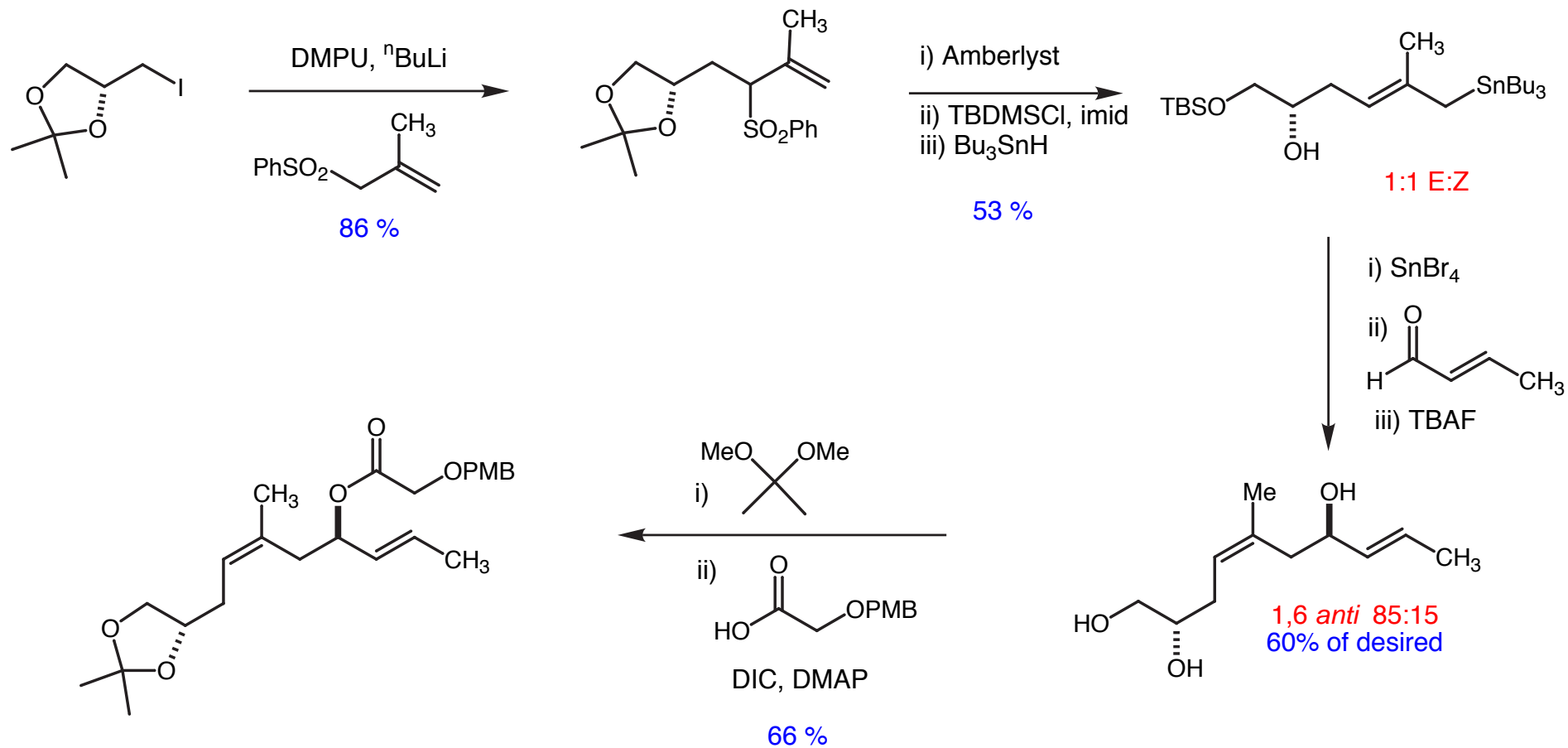
Thomas, E.J. *Tetrahedron Lett.* **1999**, 40, 475

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



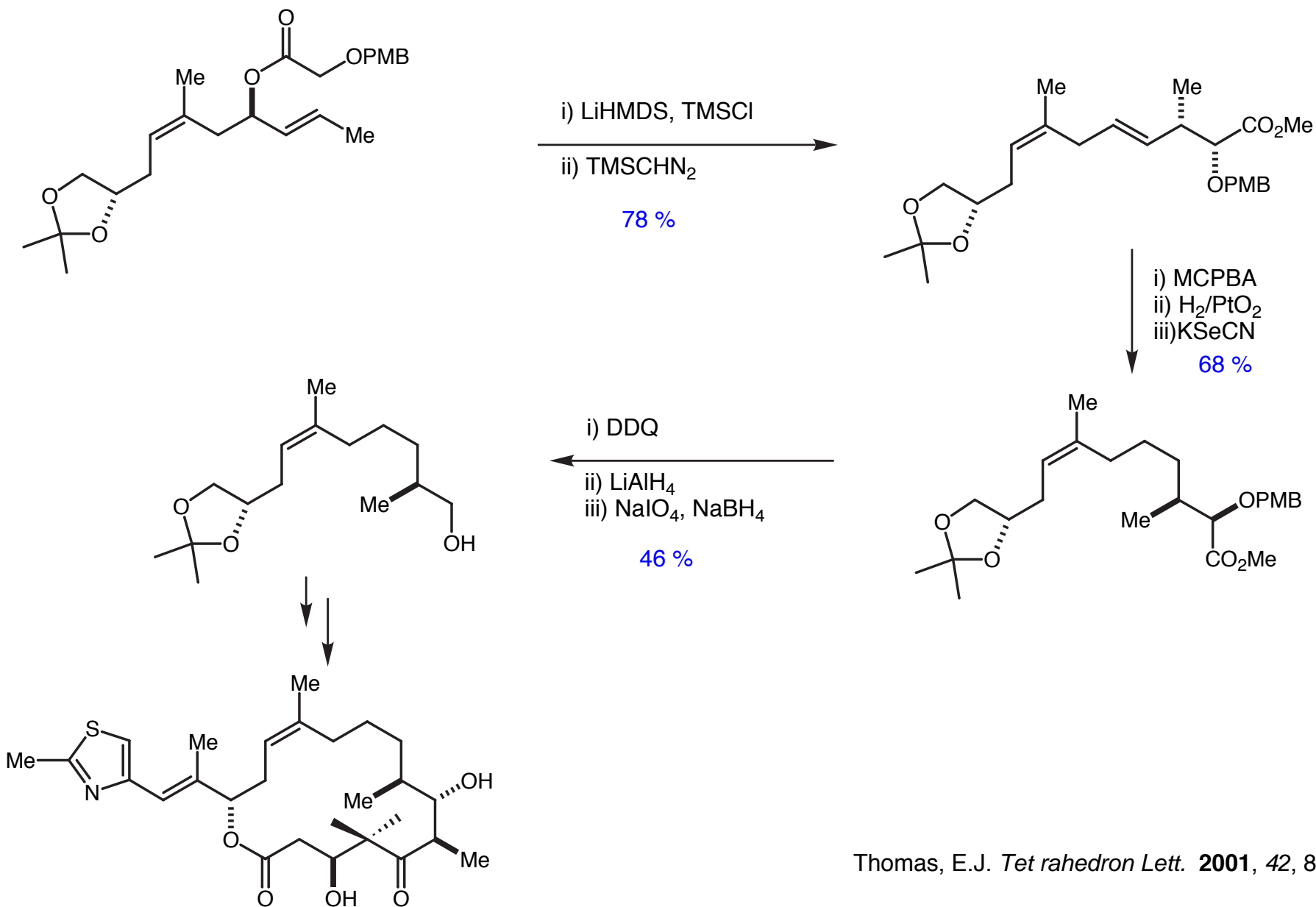
Thomas, E.J. *Tetrahedron Lett.* **1999**, 40, 475

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

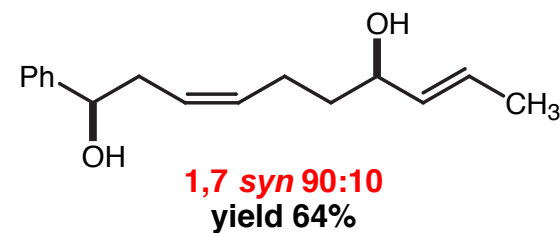
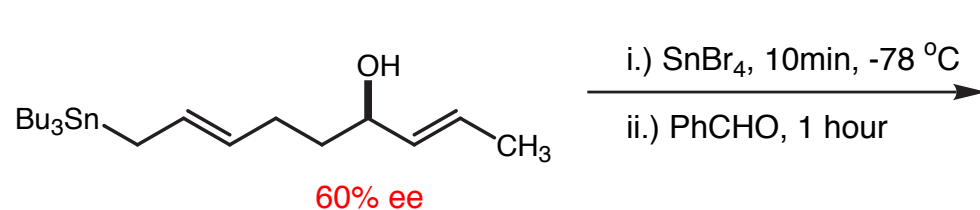


Thomas, E.J. *Tetrahedron Lett.* **2001**, 42, 8373

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

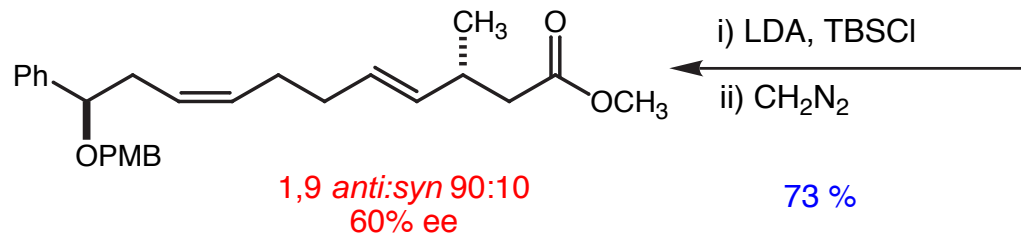
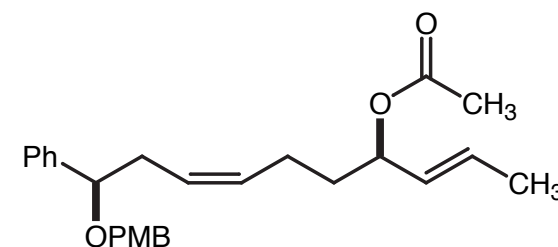


1,9-Relationship Constructed by 1,7 Induction Followed by a Claisen Rearrangement



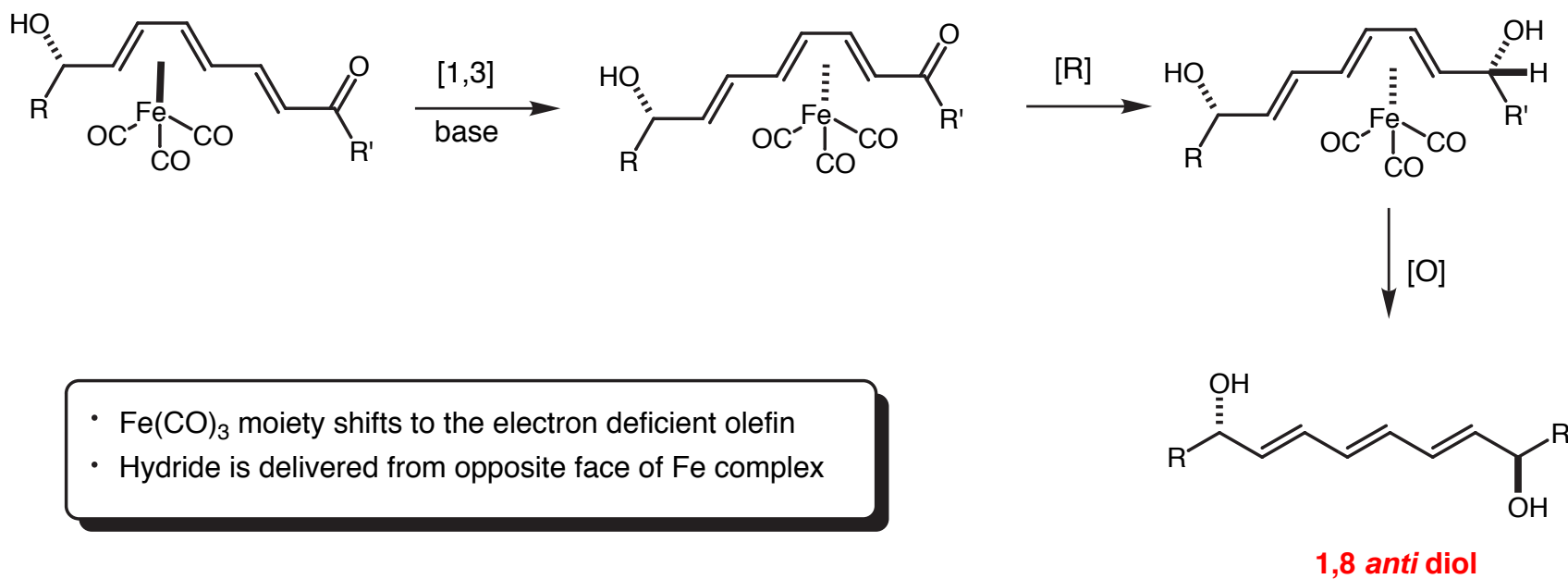
i) TBDPSCI, imid
ii) NaH, PMBCl
iii) TBAF
iiii) Ac₂O, NEt₃

49 %



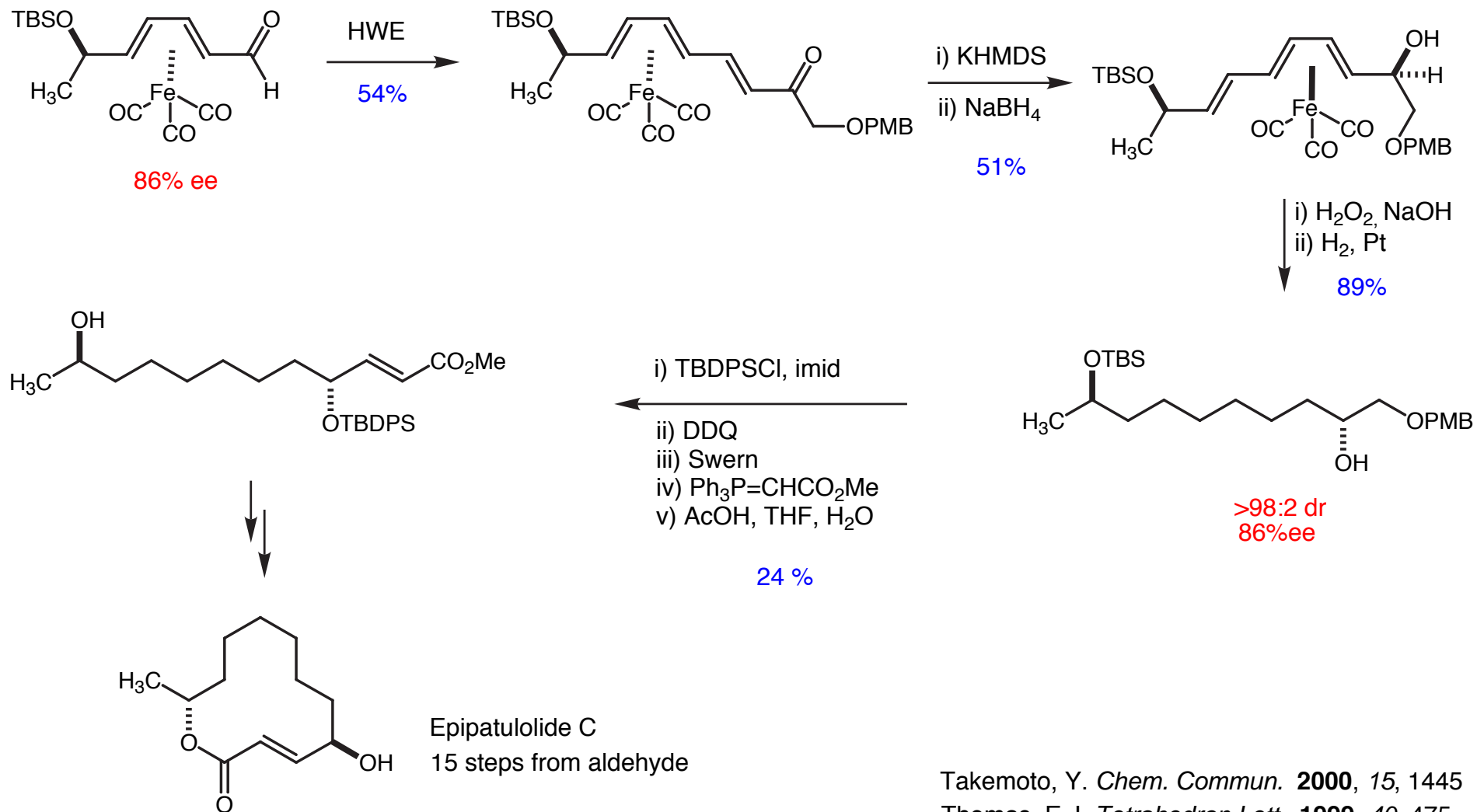
Thomas, E.J. *Tetrahedron*. **1999**, 55, 3723

Fe(CO)₃ Complexes as Chiral Transfer Groups



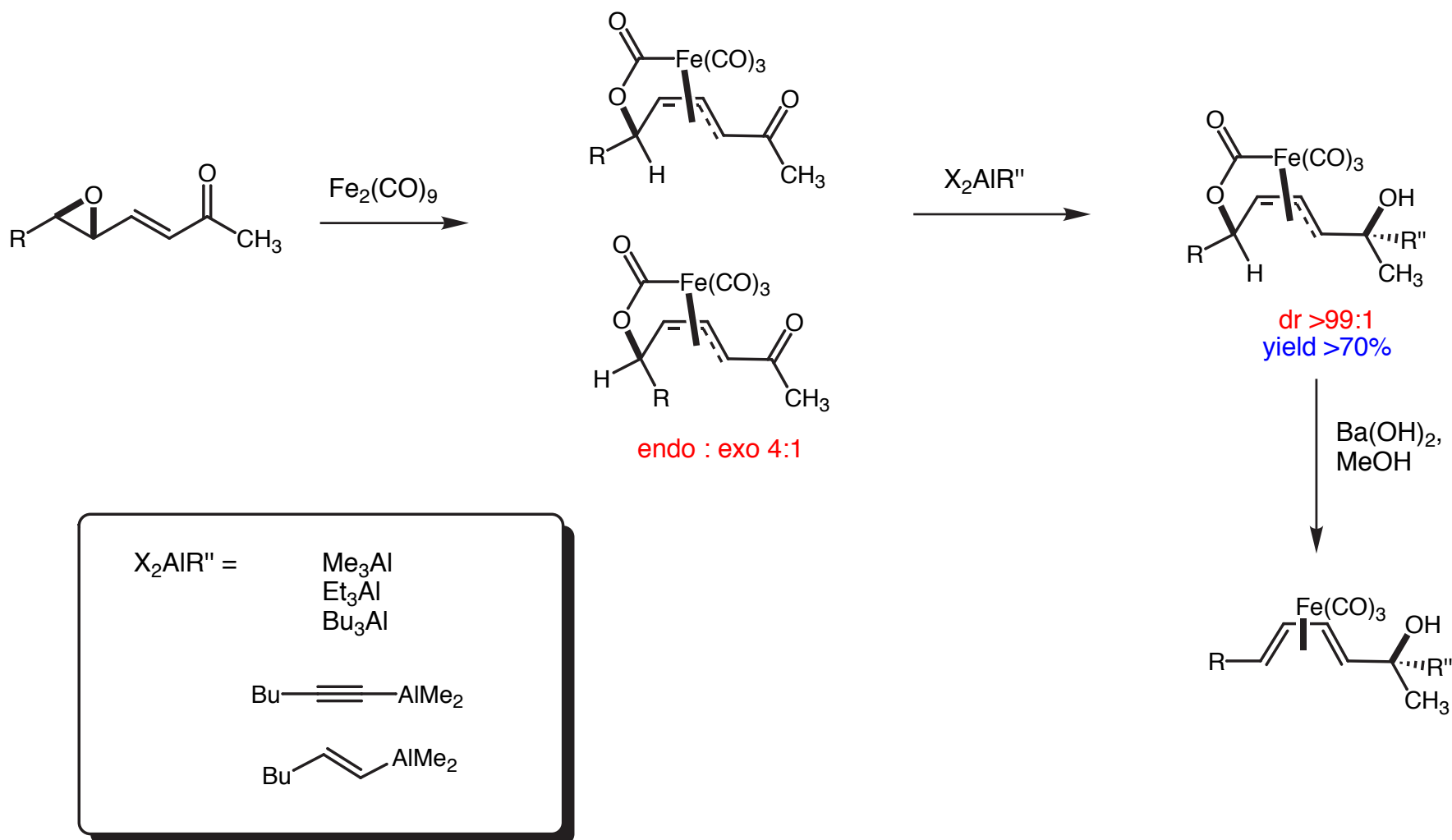
Takemoto, Y. *Chem. Commun.* **2000**, 15, 1445

Fe(CO)₃ Complexes as Chiral Transfer Groups: Formal Synthesis of Epipatulolide



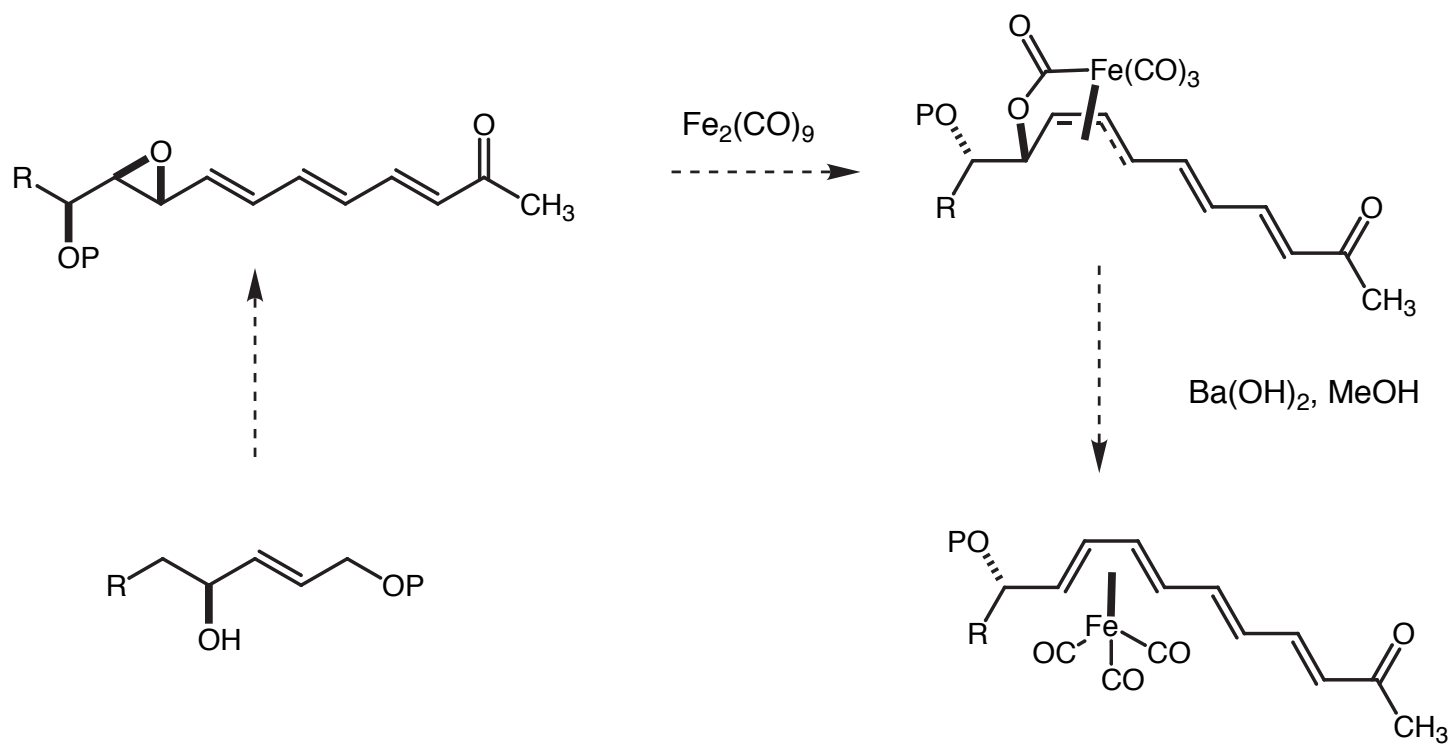
Takemoto, Y. *Chem. Commun.* **2000**, 15, 1445
 Thomas, E.J. *Tetrahedron Lett.* **1999**, 40, 475

Fe(CO)₃ Complexes as Chiral Transfer Groups

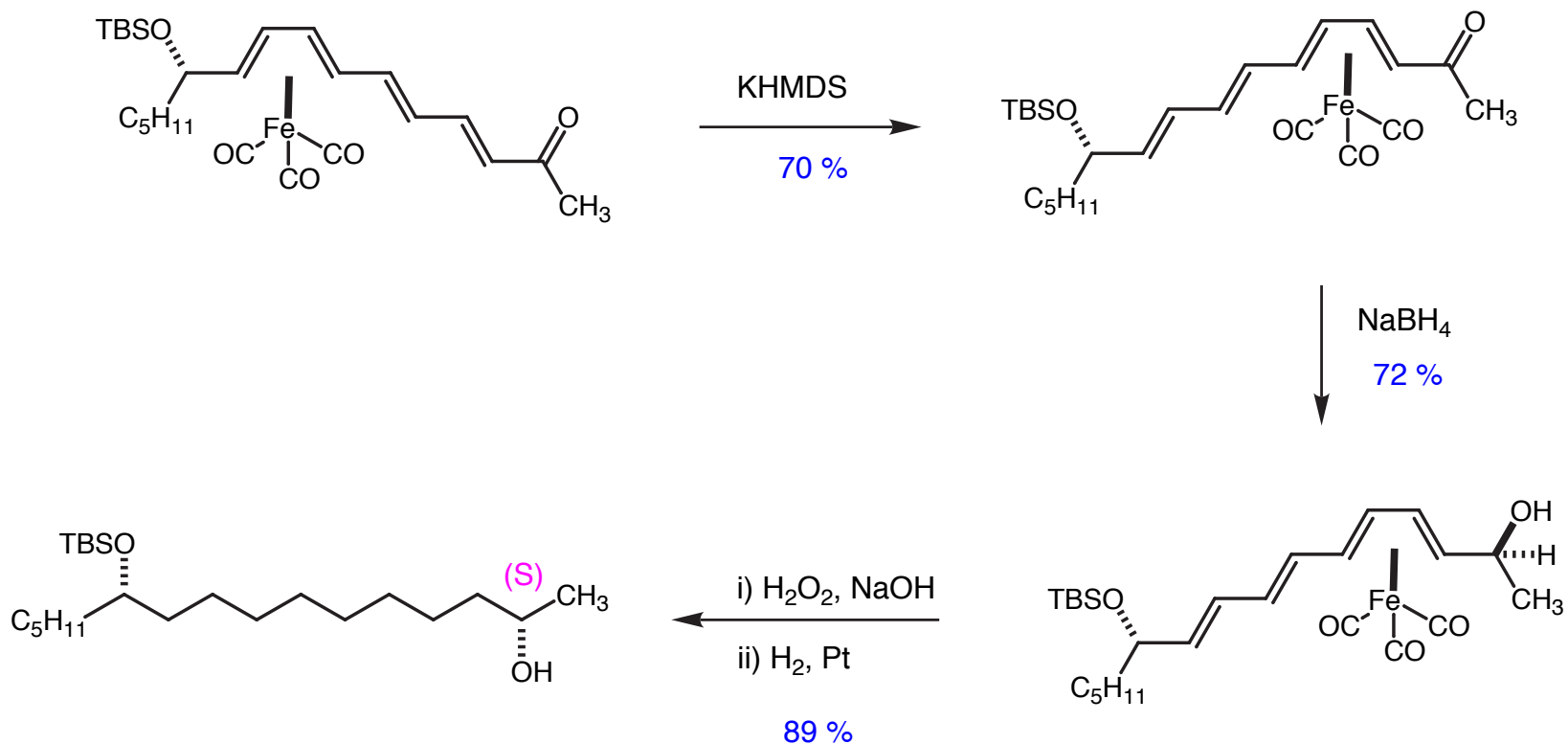


Ley, S.V. *Perkin Trans. I* **1997**, 3299

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



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



Stereochemistry determined by
Mosher Ester Analysis

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

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

