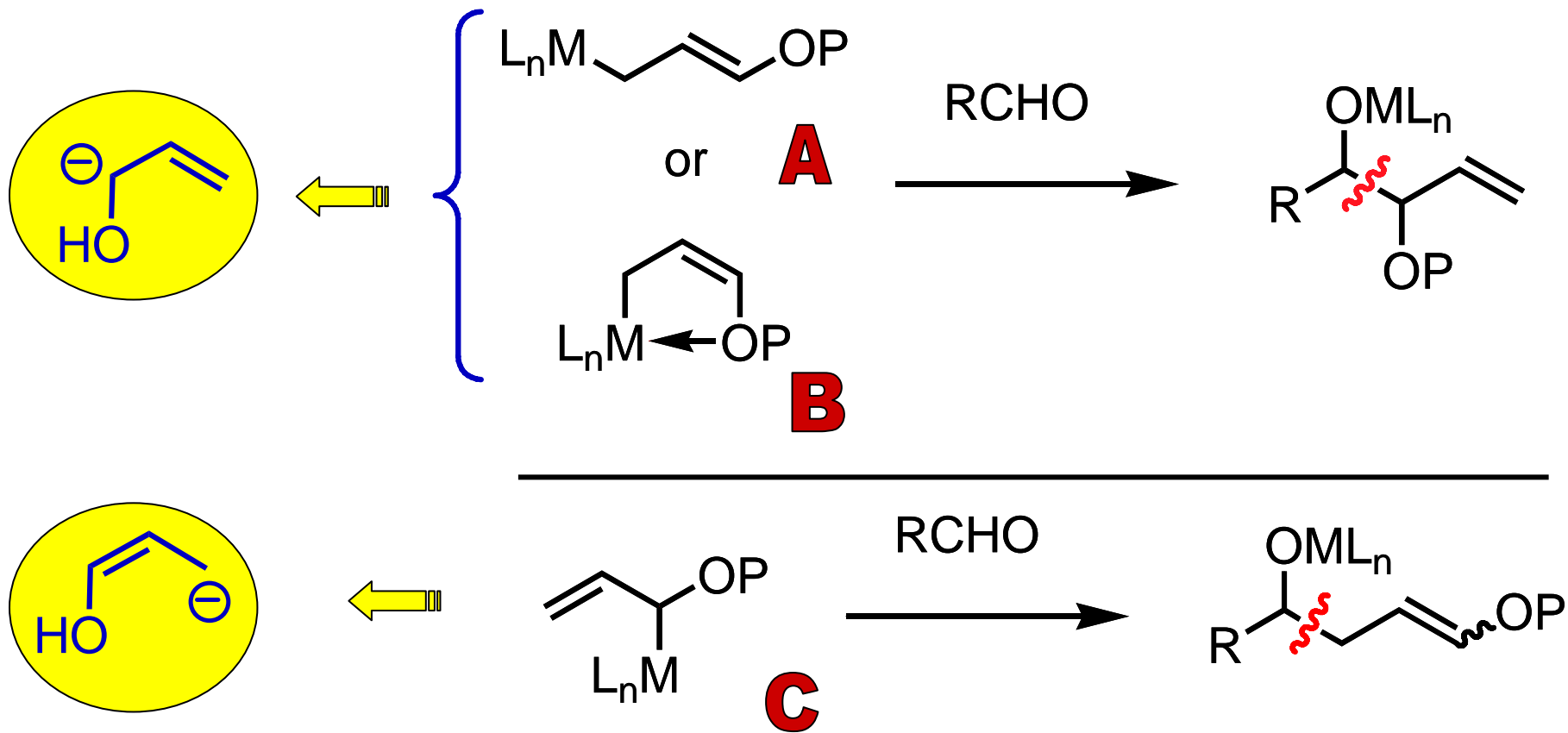


**Claudio Trombini**

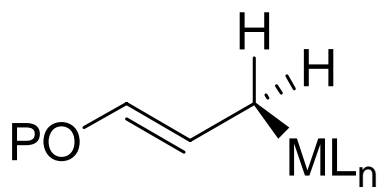
*UNIVERSITÀ DI BOLOGNA  
DIPARTIMENTO DI CHIMICA "G. CIAMICIAN"*

# **Recent Developments in the Chemistry of Functionalized Allylic Organometallics**

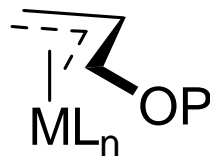
*Ischia Advanced School in Organic Synthesis  
Sep. 16-22, 2006*



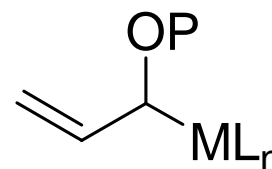
# Oxy-substituted Allylic Organometallic Compounds: Metallotropic Equilibria



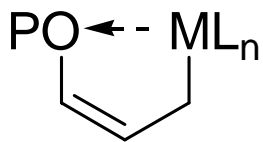
**A**  $\eta^1 E \gamma$



$\eta^3$  *syn*



**C**  $\eta^1 \alpha$

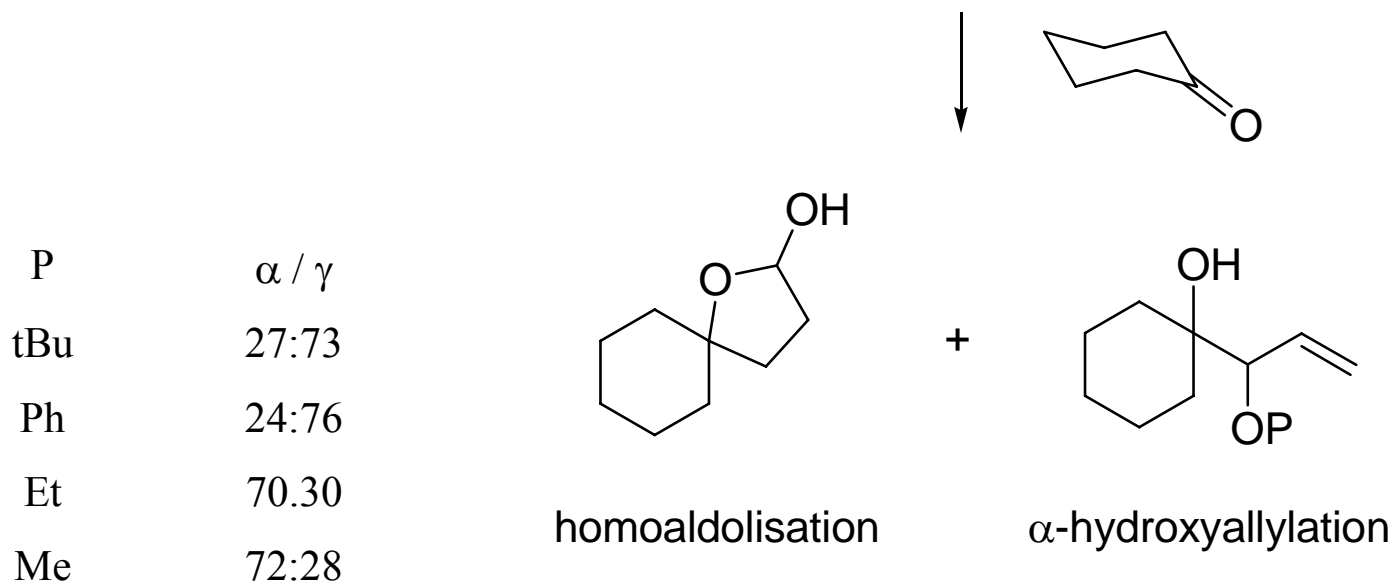
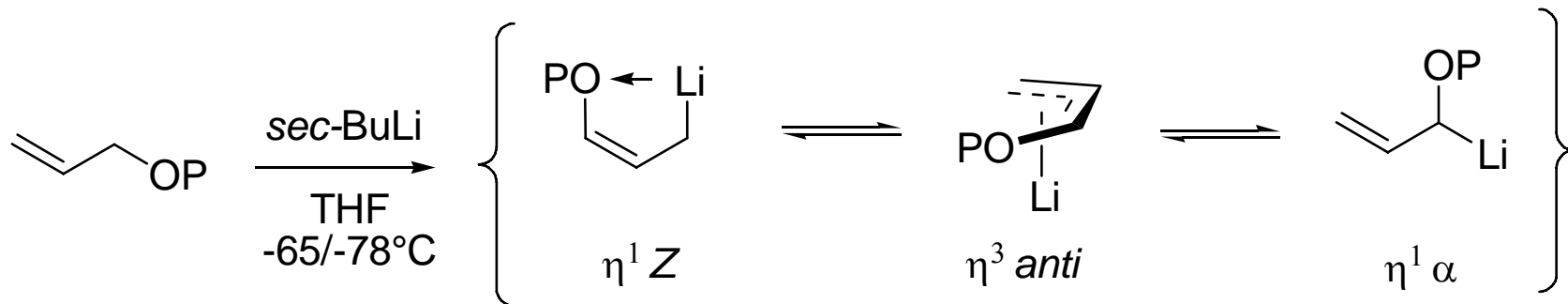


**B**  $\eta^1 Z \gamma$

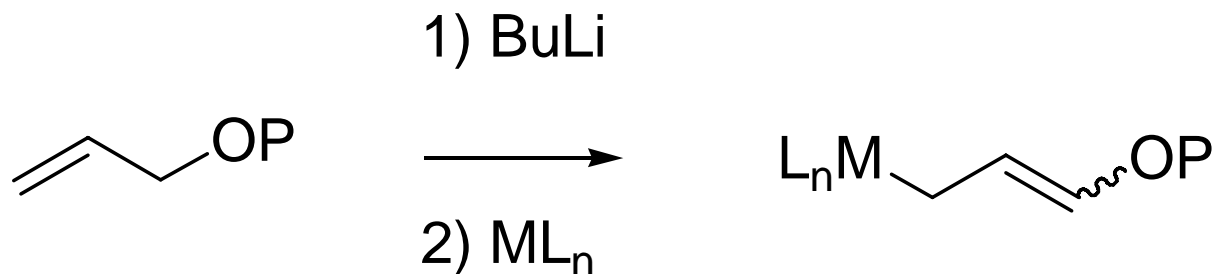


$\eta^3$  *anti*

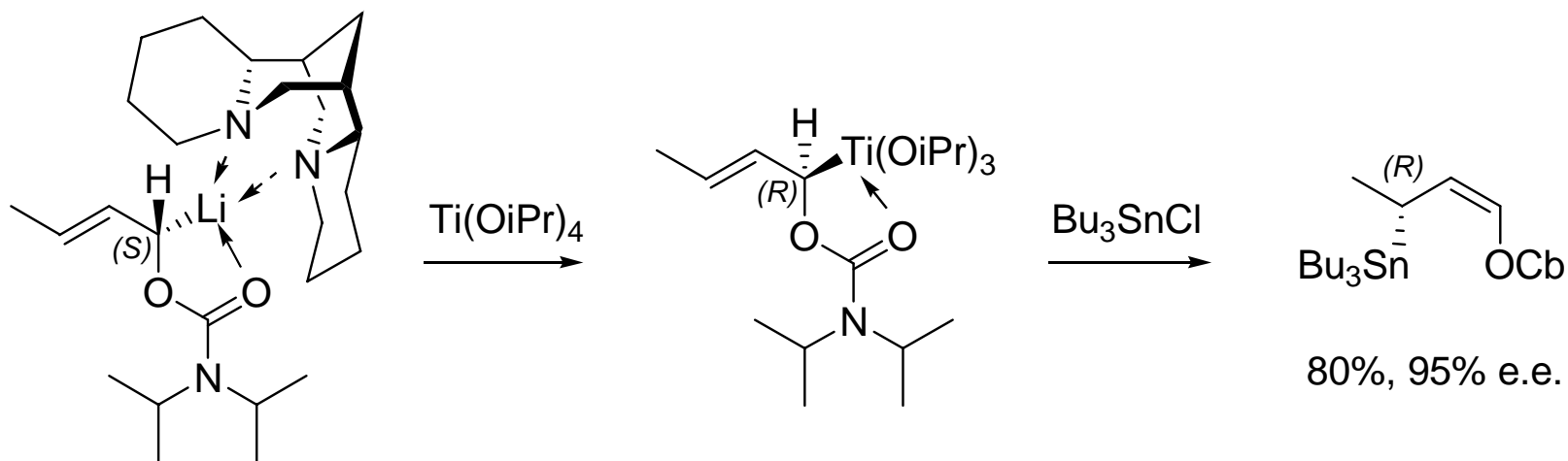
# Lithiated Allyl Ethers



# Lithiated Allyl Ethers as Precursors of 3-Alkoxyallyl Organometals



**Examples:**  $M = InCl_3, ZnBr_2, Et_3Al, L_3TiCl, L_2BX, L_3SnCl$ , etc.

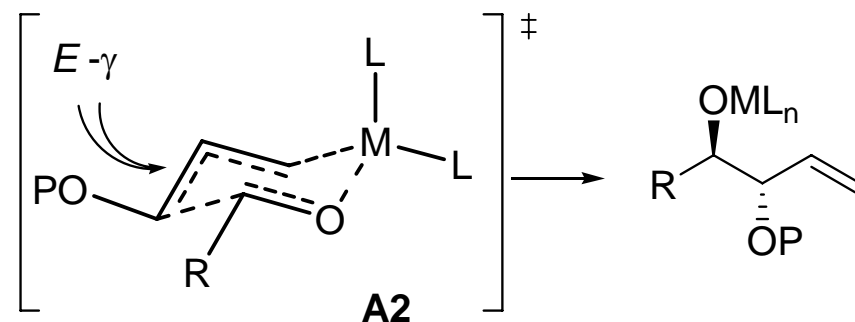
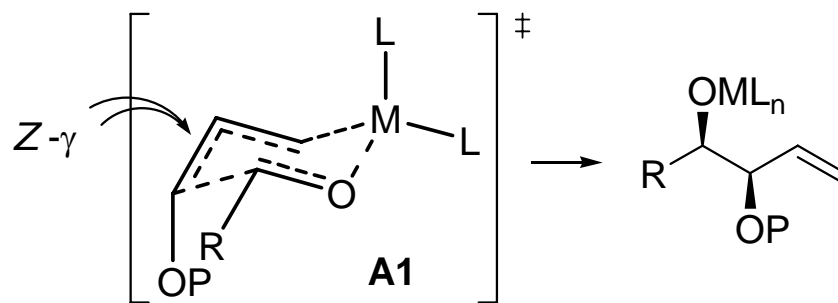


# Alkoxyallylation of carbonyl compounds with RO-CH=CH-CH<sub>2</sub>M Complexes: Simple Diastereoselection

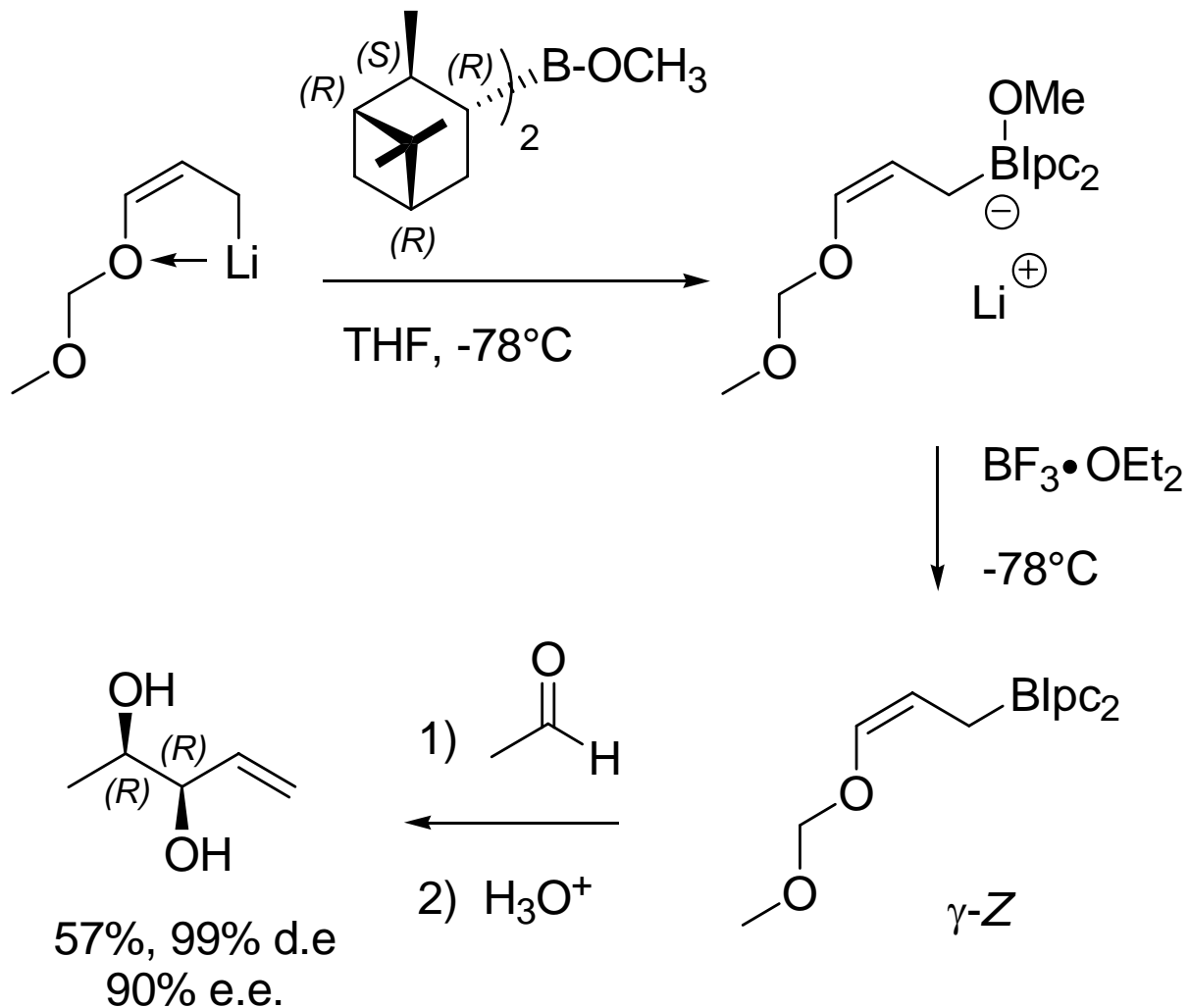
- Diastereoselective complexes (e.g., M = B)

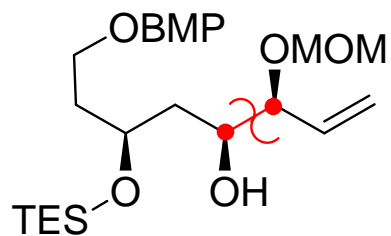
- *metallotropic shift much slower than the nucleophilic addition reaction*

-  *$\eta^1$ -E- $\gamma$  and  $\eta^1$ -Z- $\gamma$  display a stereodivergent reactivity (e.g. Zimmermann-Traxler rationale)*



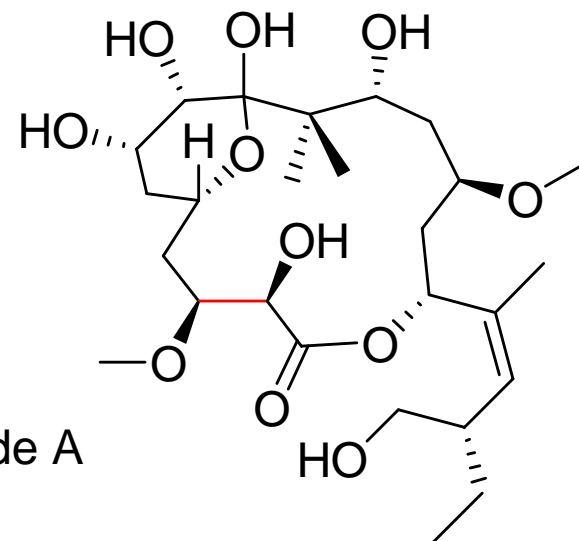
# Z-3-Alkoxyallyl Boranes



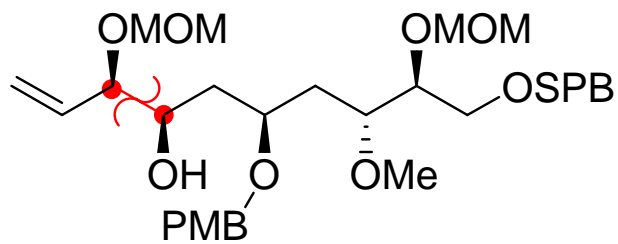


>90% d.e.

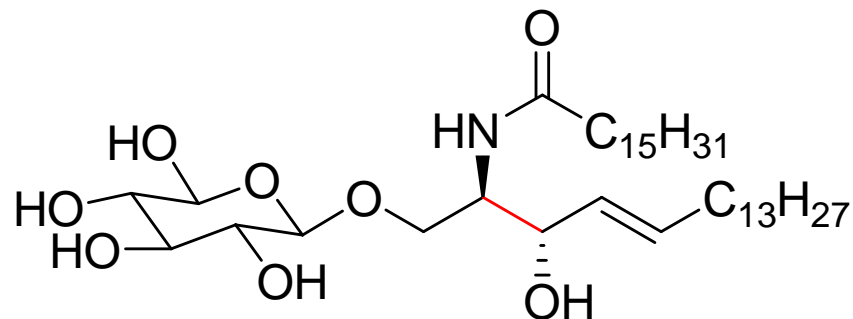
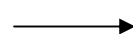
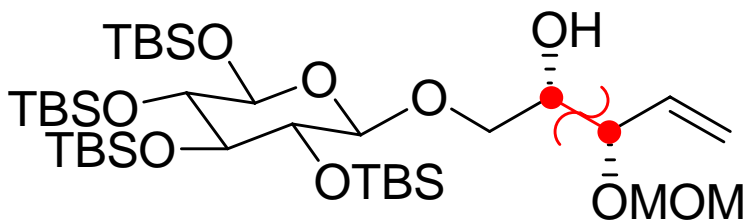
Liao, X.; Wu, Y.; De Brabander, J. K.  
*Angew. Chem. Int. Ed. Eng.* **2003**, 42, 1648.



Peloruside A



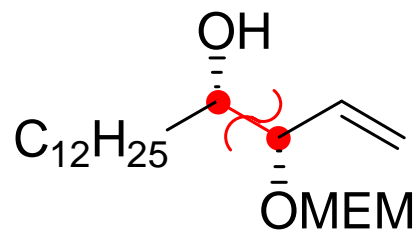
Liu, B.; Zhou, W. -S.  
*Org. Lett.* **2004**, 6, 71.



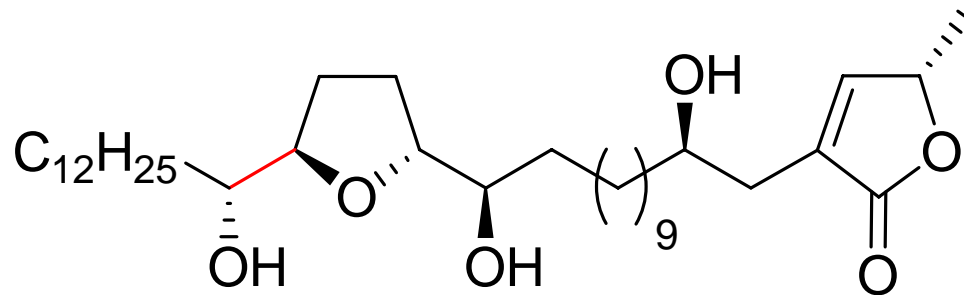
Glucosylceramide

Barrett, A. G. M. et al, *J. Org. Chem.* **2000**, 65, 6508.



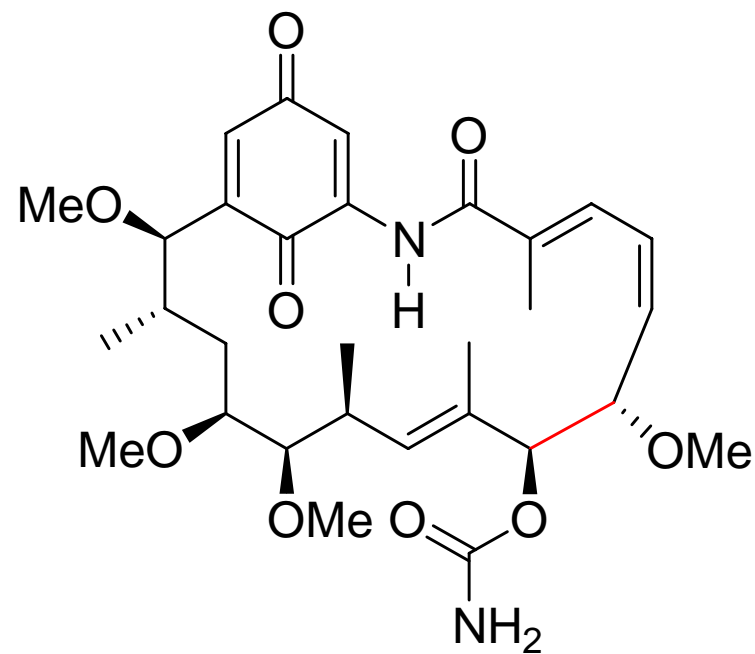
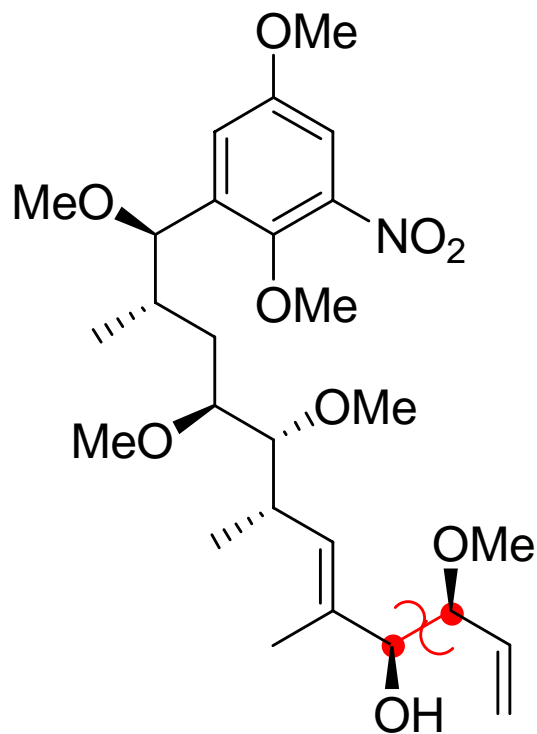


95% e.e.



Murisolin

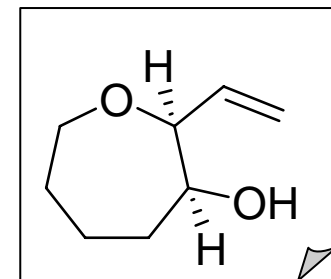
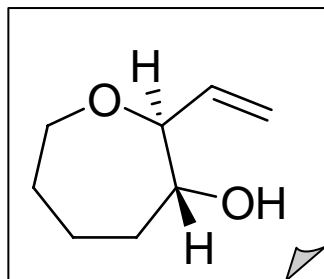
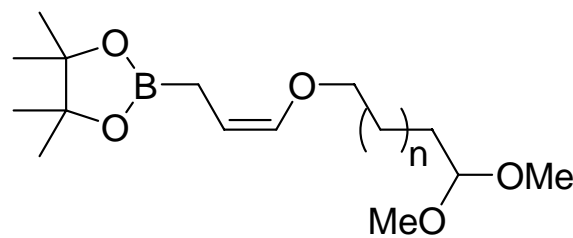
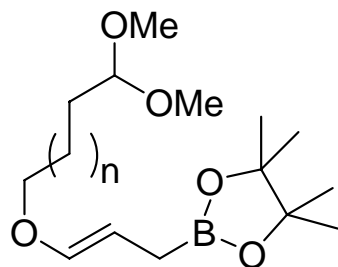
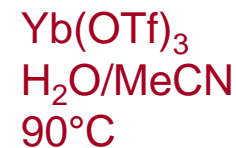
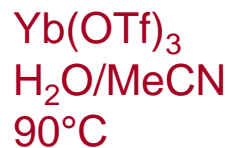
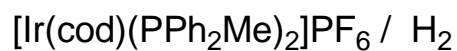
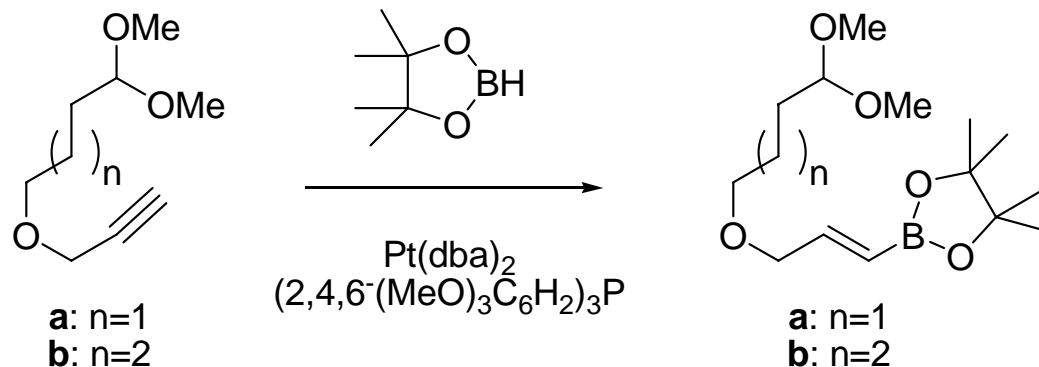
Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, 126, 36.



Carter, K. D.; Panek, J. S. *Org. Lett.* **2004**, 6, 55.

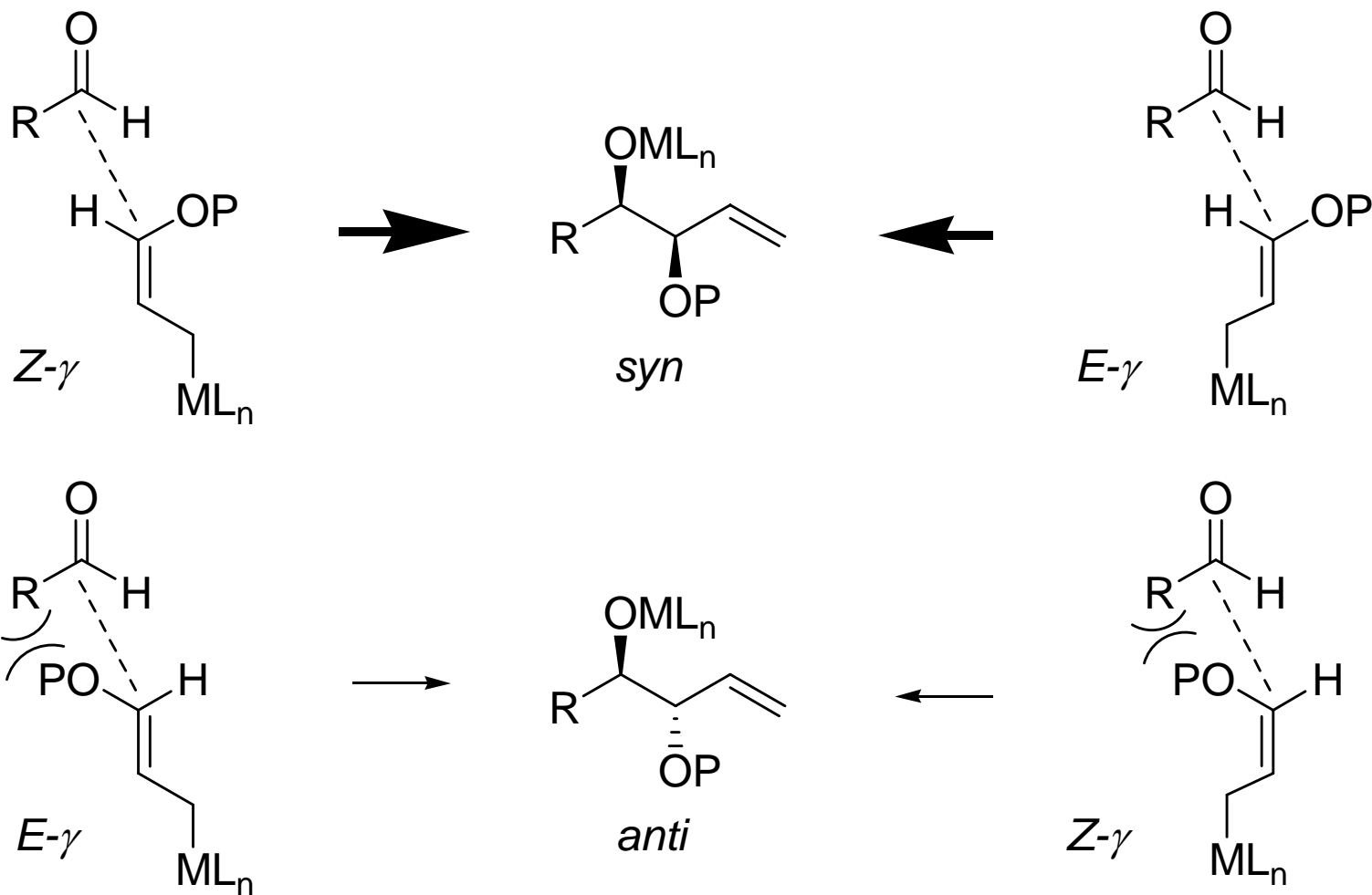
Herbimycin A

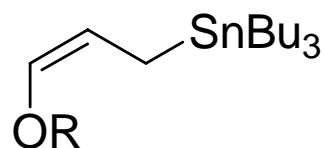
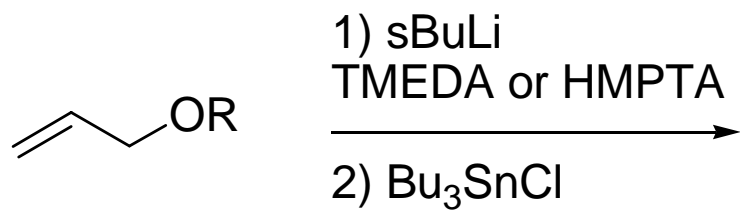
# Stereoselective approaches to *E* and *Z*-3-Alkoxyallyl Boronates



Yamamoto, Y. et al *Tetrahedron*, **2003**, 59, 537

Alkoxyallylation of carbonyl compounds with  
 $\text{RO-CH=CH-CH}_2\text{M}$  Complexes:  
 Diastereoconvergent complexes (e.g.,  $\text{M} = \text{Sn}$ )  
 - *Open-chain (e.g. anti periplanar) TS's involved*





**a-d**

**a:** R = Me

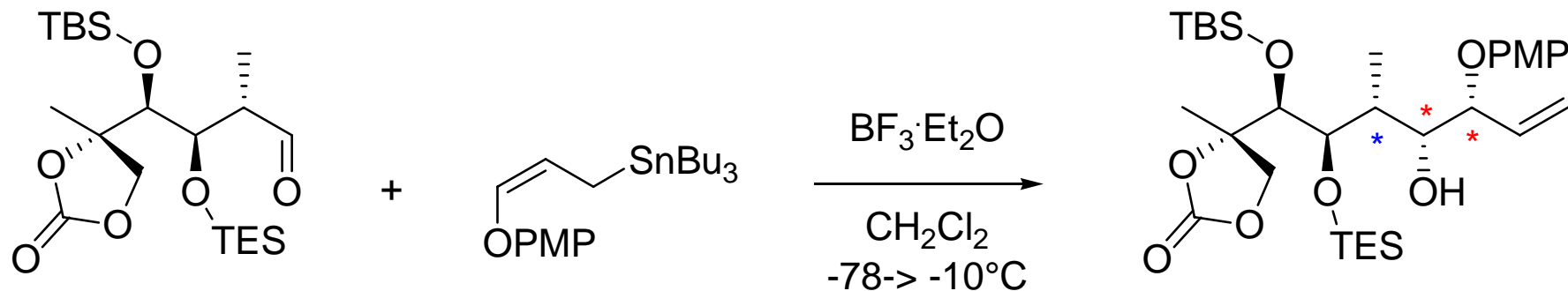
**b:** R = TBS

**c:** R = PMP

**d:** R = MOM

Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, 28, 139.

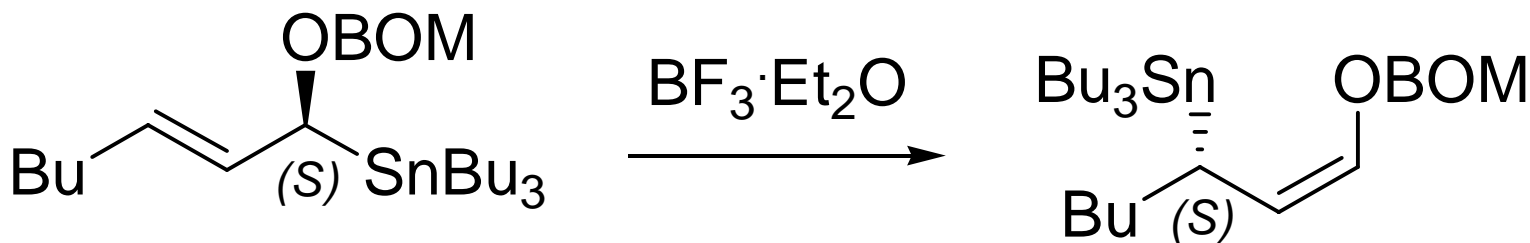
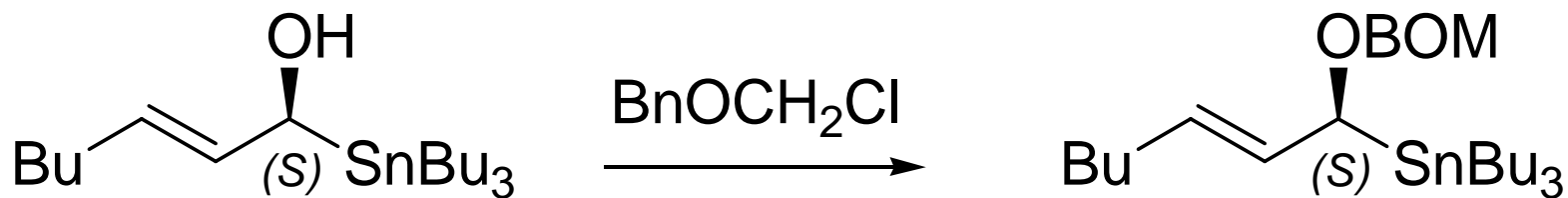
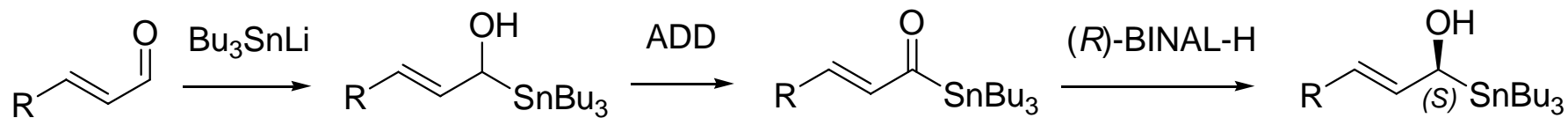
Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, 28, 143.



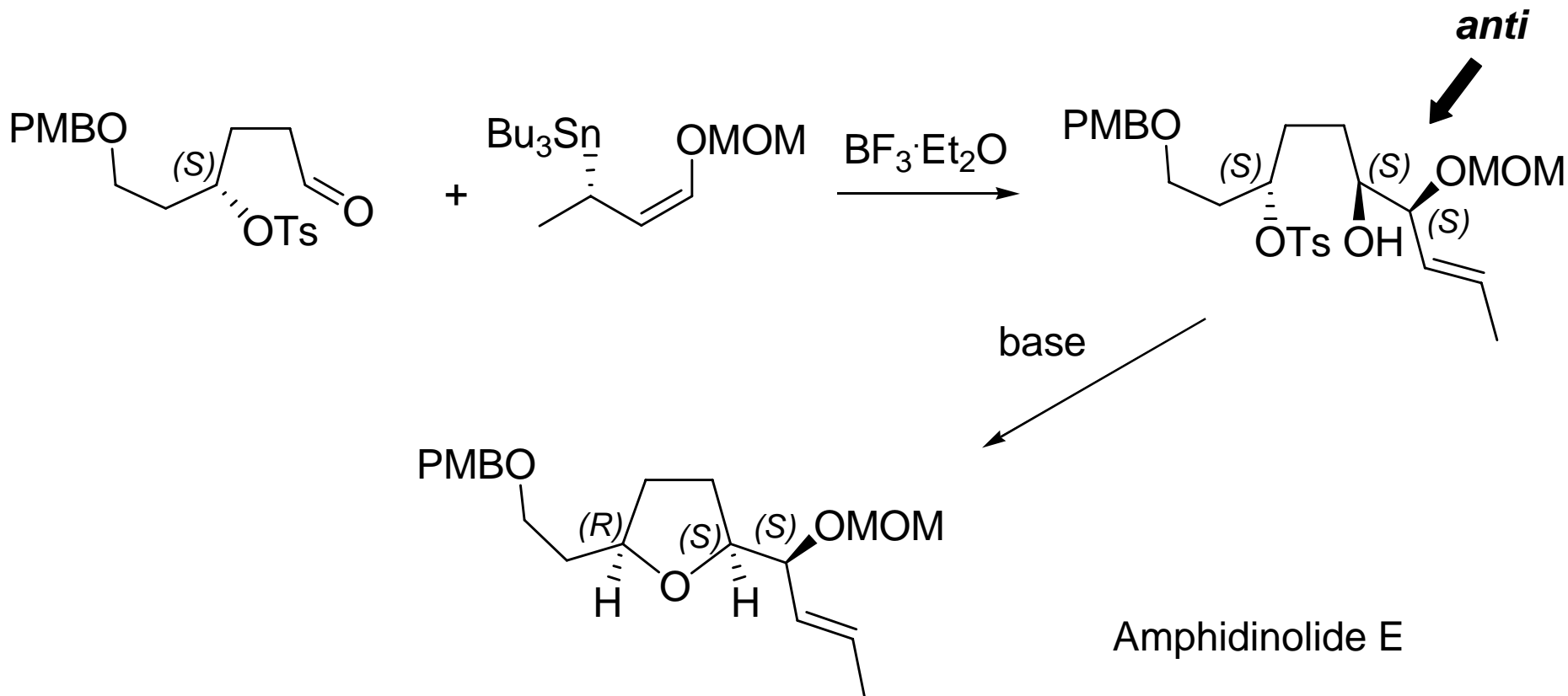
93%

non-chelation model

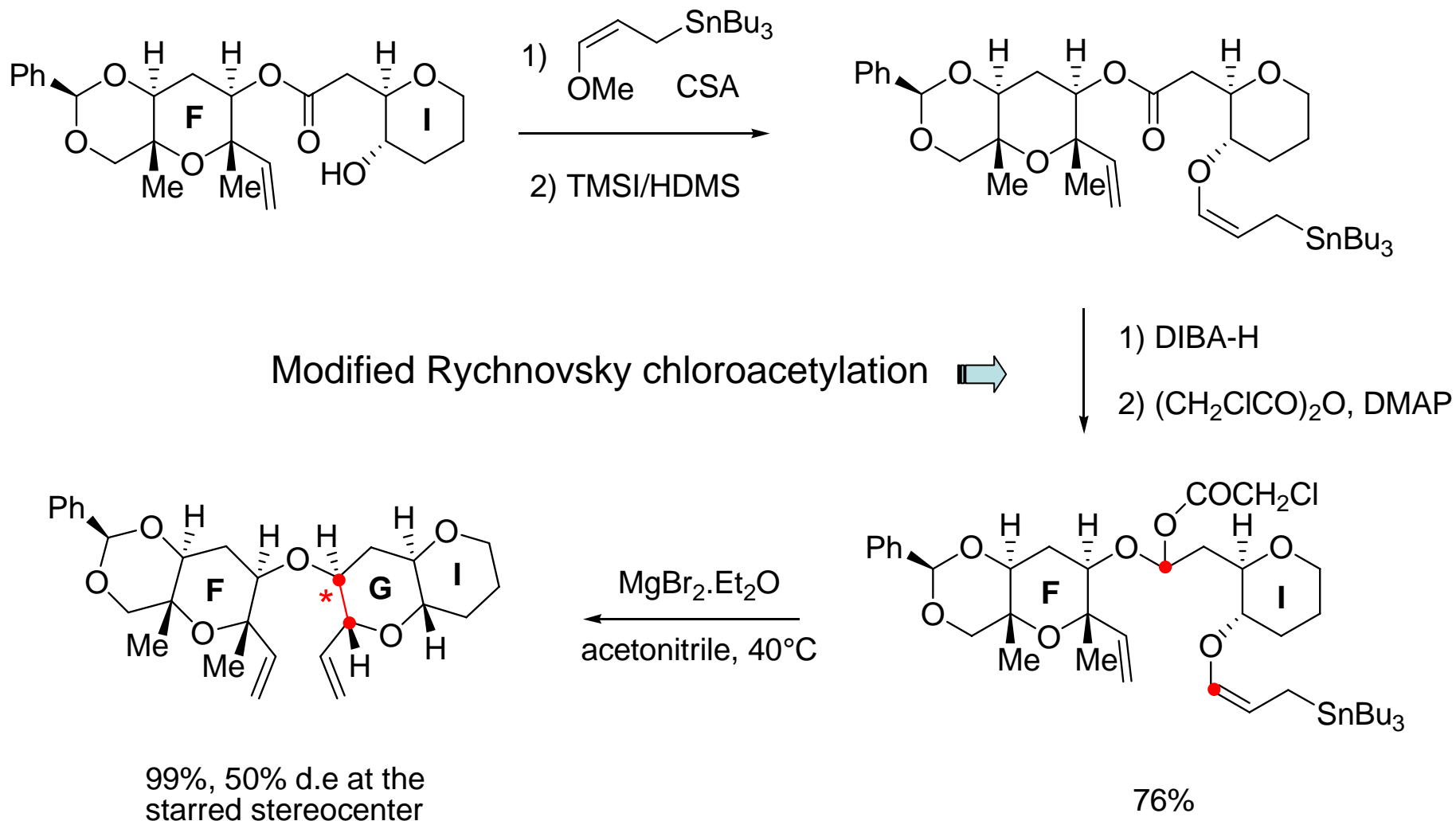
Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, 65, 8730.



# Synthetic applications of Z 3-alkoxyallyl stannanes

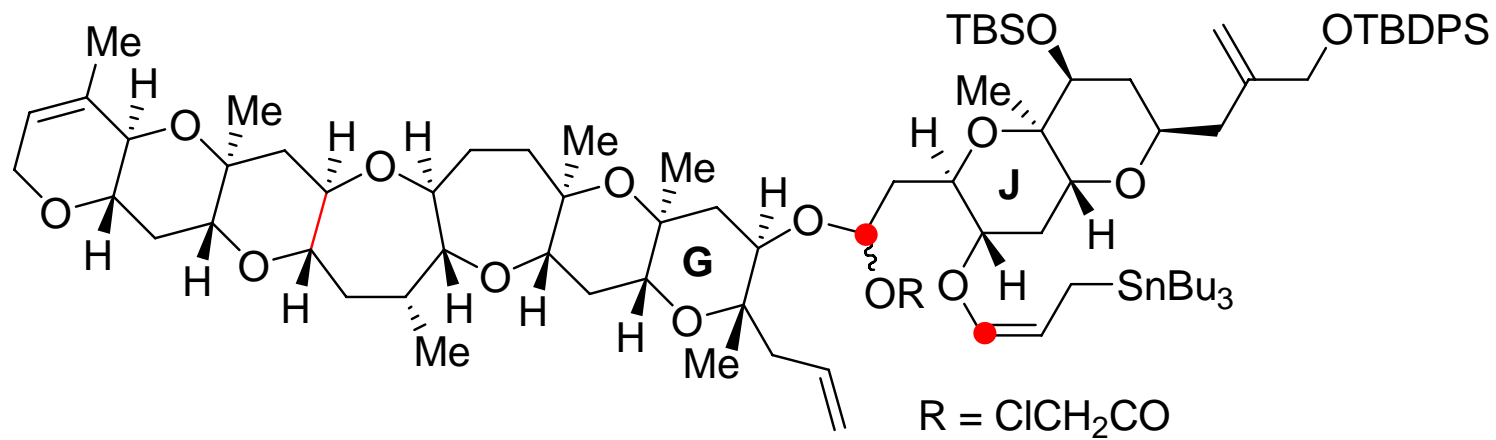


# 3-Alkoxyallyl stannane route to marine polycyclic ethers: intramolecular allylation

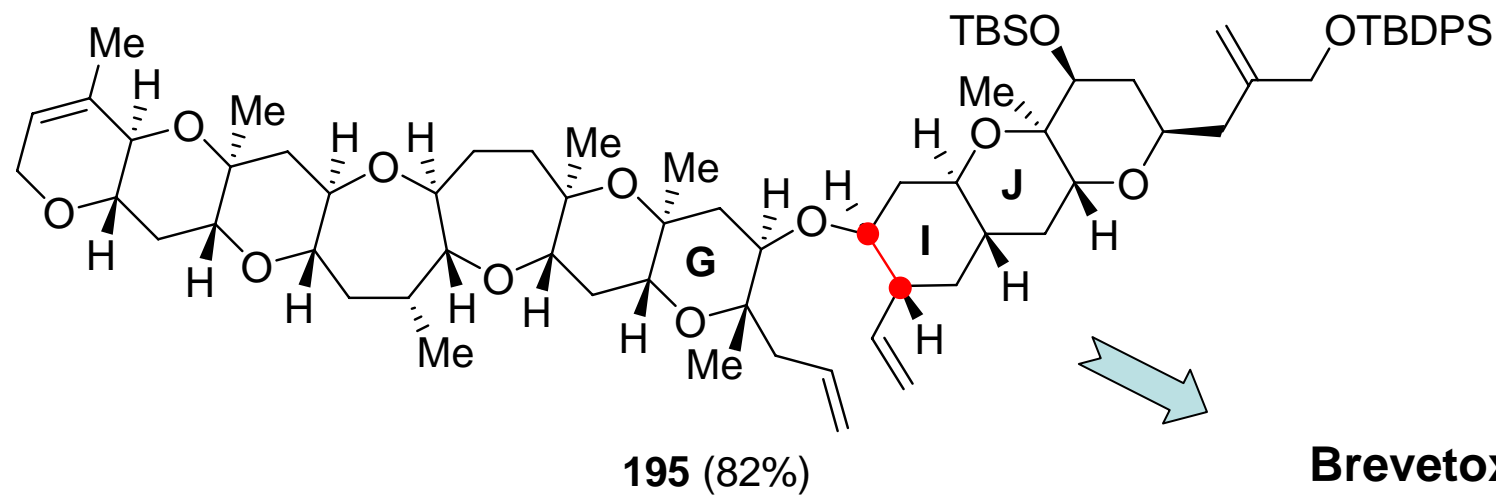


Kadota, I.; Ueno, H.; Sato, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, 47, 89.

Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, 38, 423.

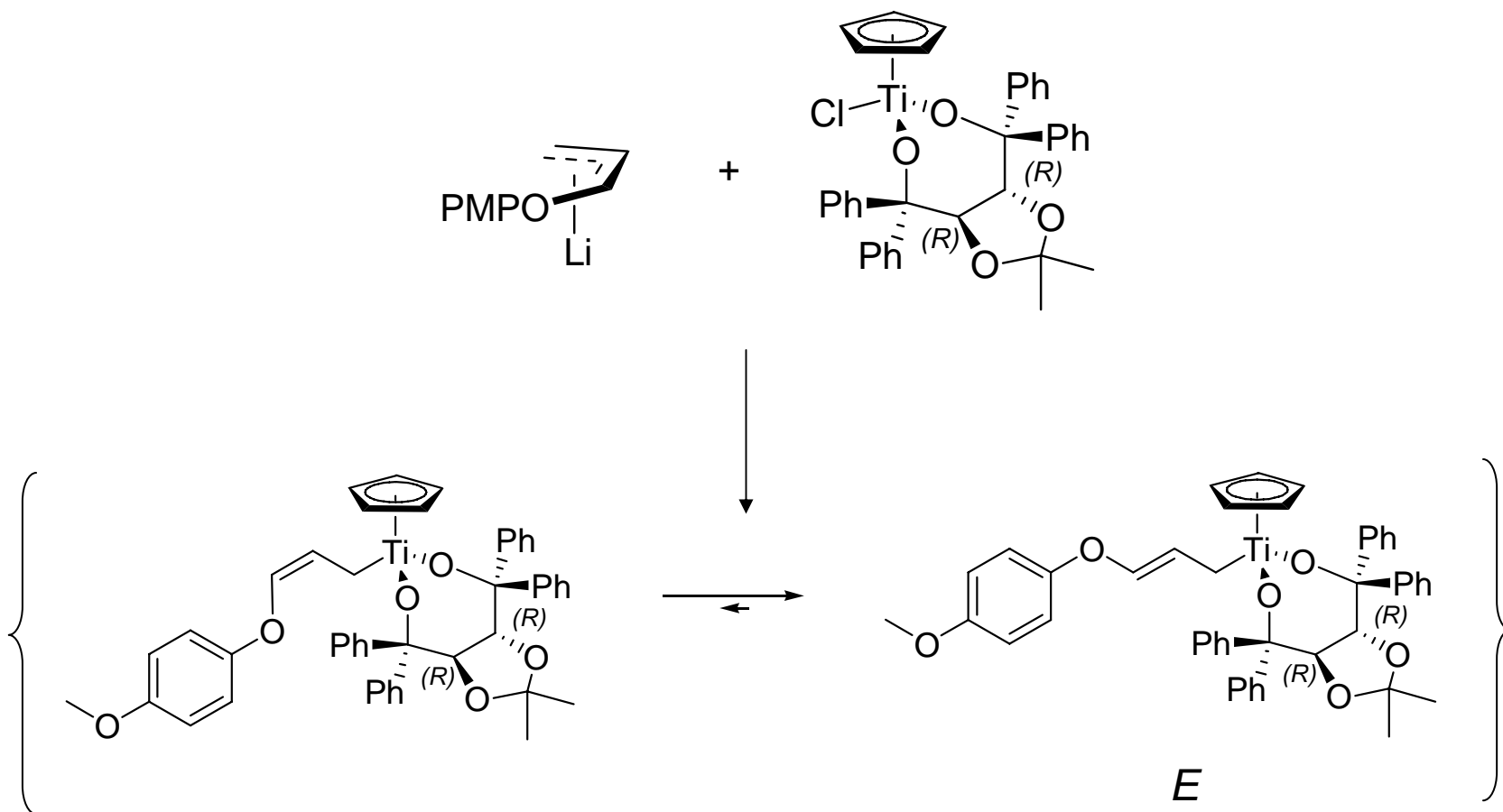


$\text{MgBr}_2 \cdot \text{Et}_2\text{O}$   
 acetonitrile,  $40^\circ\text{C}$

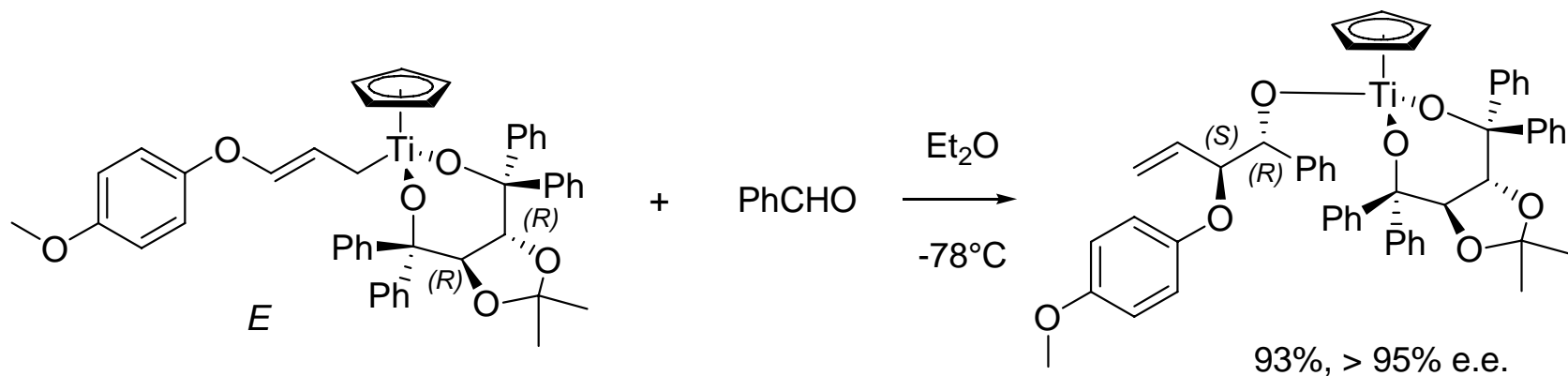




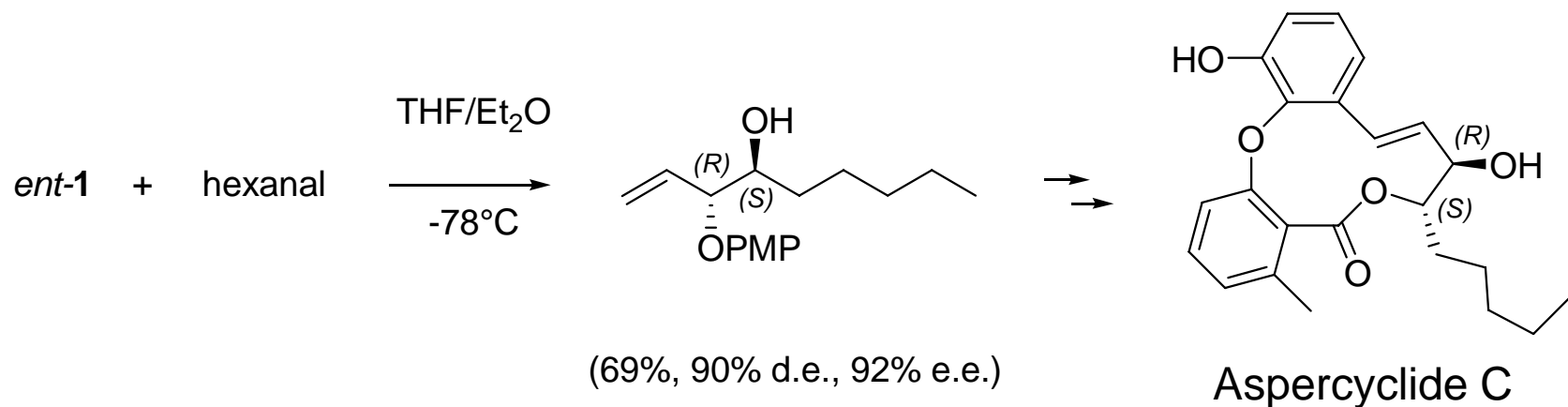
# Alkoxyallylation of carbonyl compounds with $\text{RO-CH=CH-CH}_2\text{M}$ Complexes: Diastereoconvergent complexes (e.g., $\text{M} = \text{Ti}$ ) - *fast metallotropic fluxionality, cyclic TS's*



# Chiral 3-Aryloxyallyl Titanium Complexes

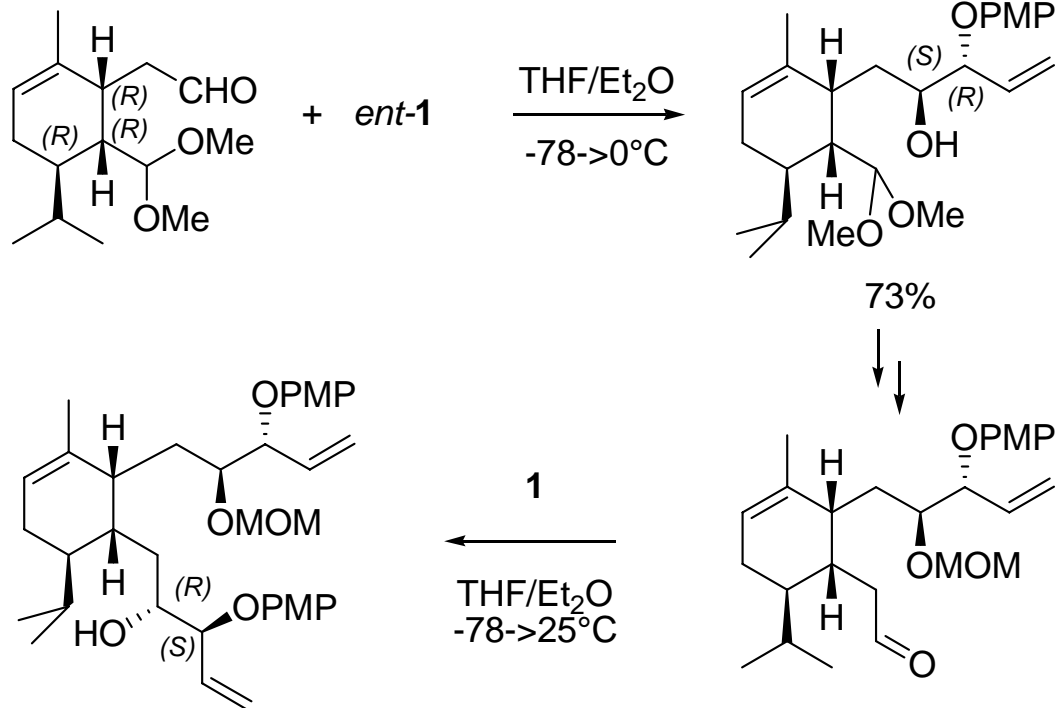
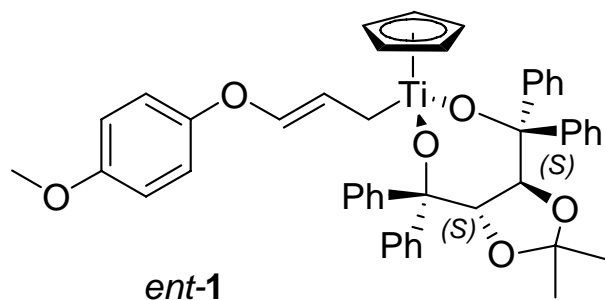


Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F.  
*J. Am. Chem. Soc.* **1992**, *114*, 2321.



Fürstner, A.; Müller, C. *Chem. Commun.* **2005**, 5583.

# Chiral 3-Aryloxyallyl Titanium Complexes

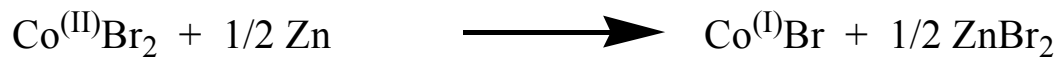
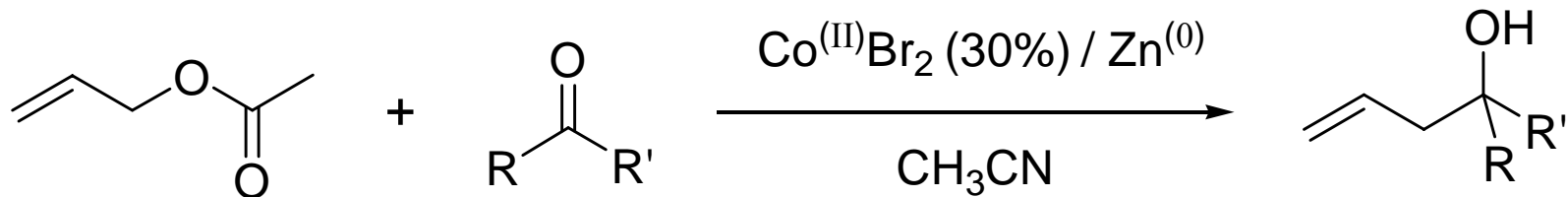


# New methodologies for the hydroxyallylation reaction, under Barbier/Grignard conditions

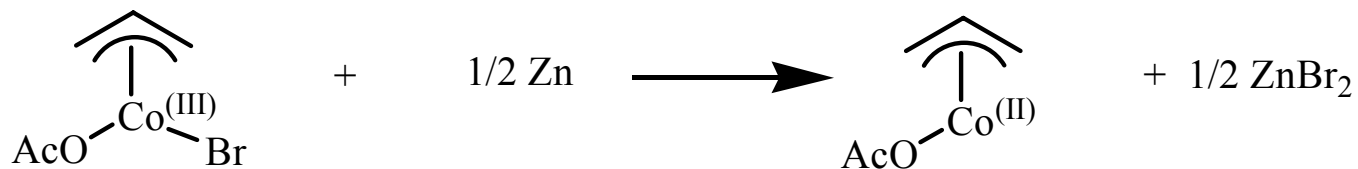
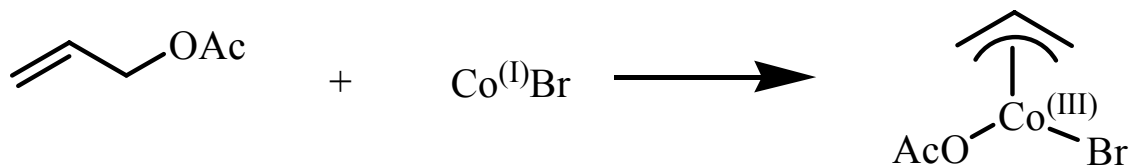
- Searching for substrates, suitable for the oxidative addition to low valent metals

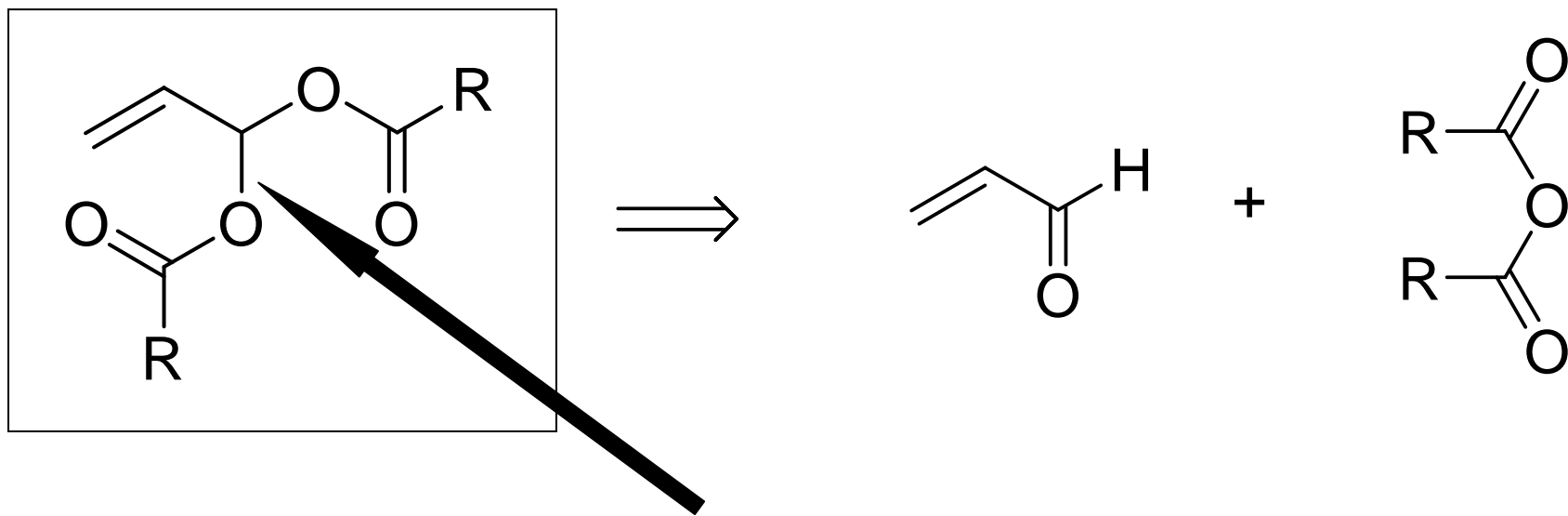
**Co(I)**

# Cobalt(I) Oxidative Addition to Allyl Acetate



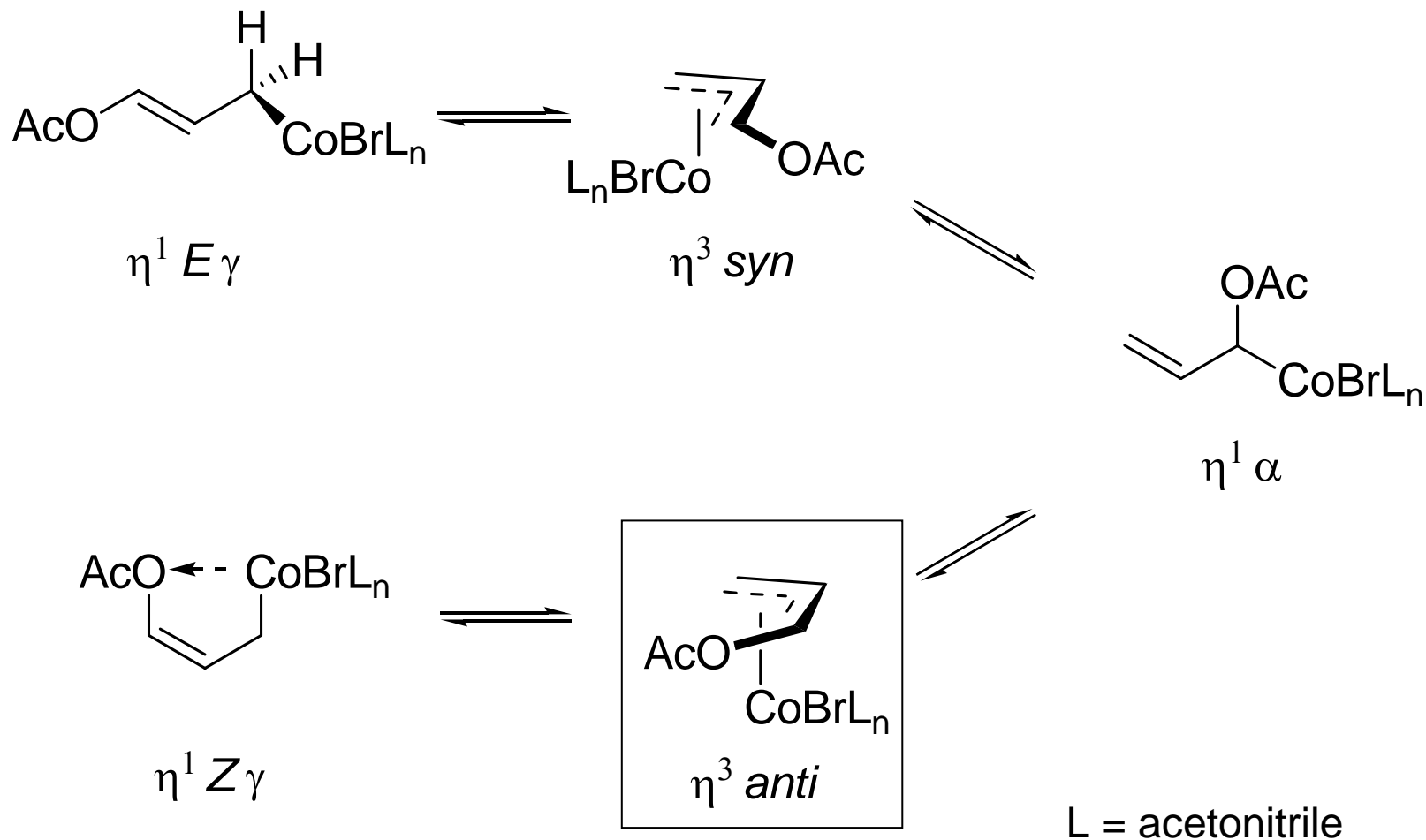
50-95%



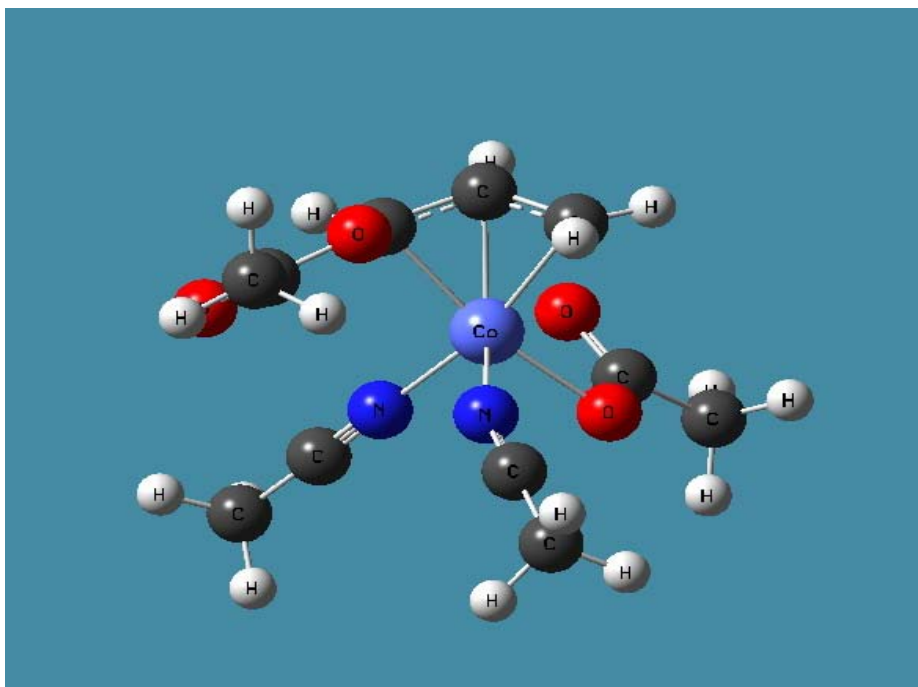
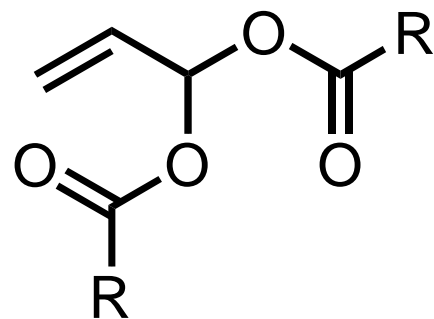


**Does Co(I) insert here, as in the case of allyl acetate?**

# The metallotropic shift

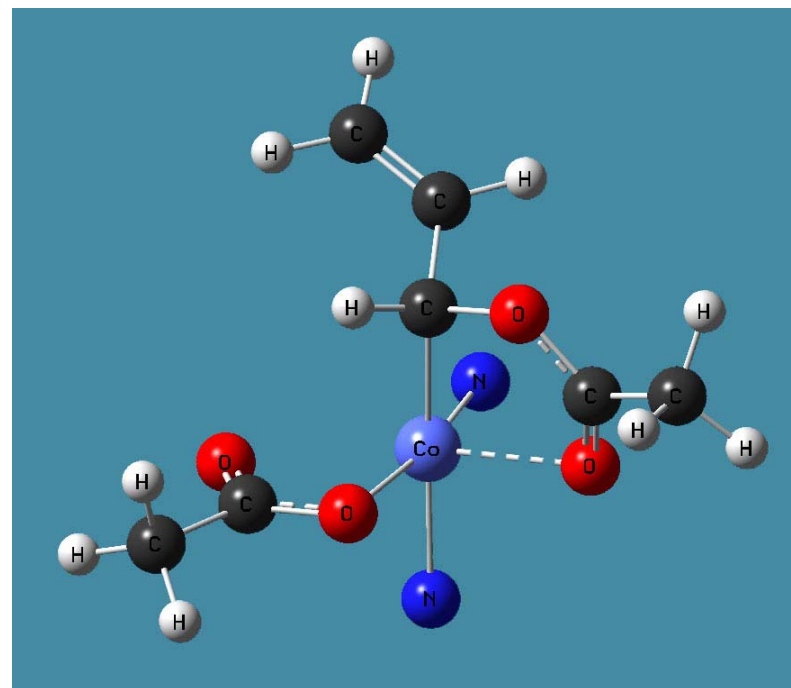


The insertion of Co(I) into the lowest minima



$\eta^3 - \text{anti}$

$\Delta E = 0 \text{ Kcal/mol}$

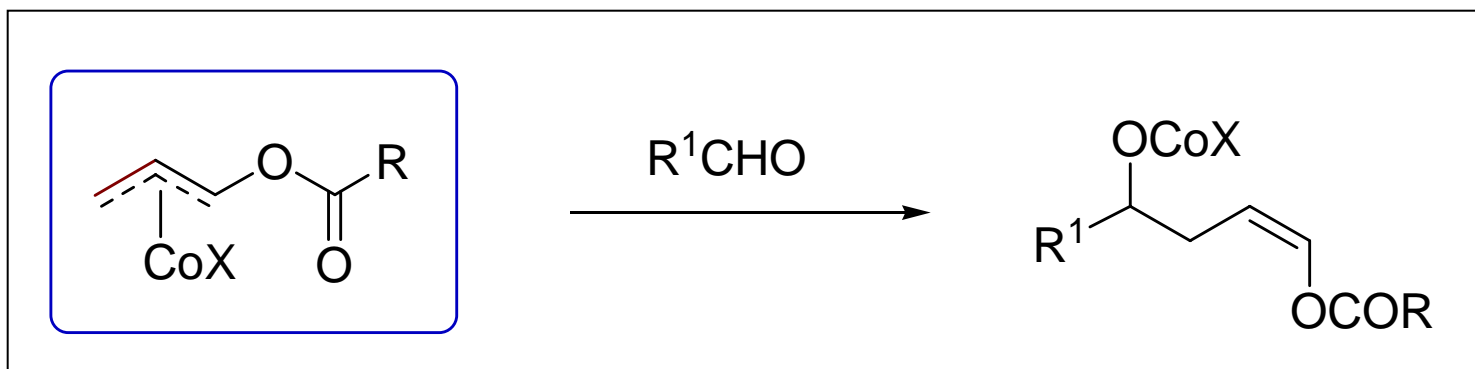


$\eta^1 - \alpha$

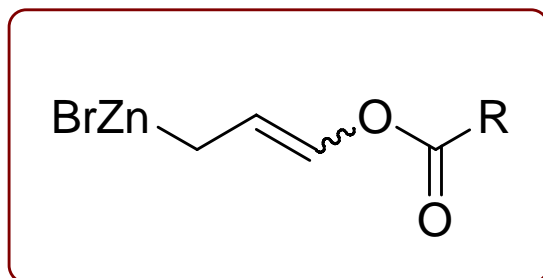
$\Delta E = 1,3 \text{ Kcal/mol}$



# Possible Fates of Allylic Cobalt(II) Complexes: Addition to Aldehydes *vs* Transmetalation

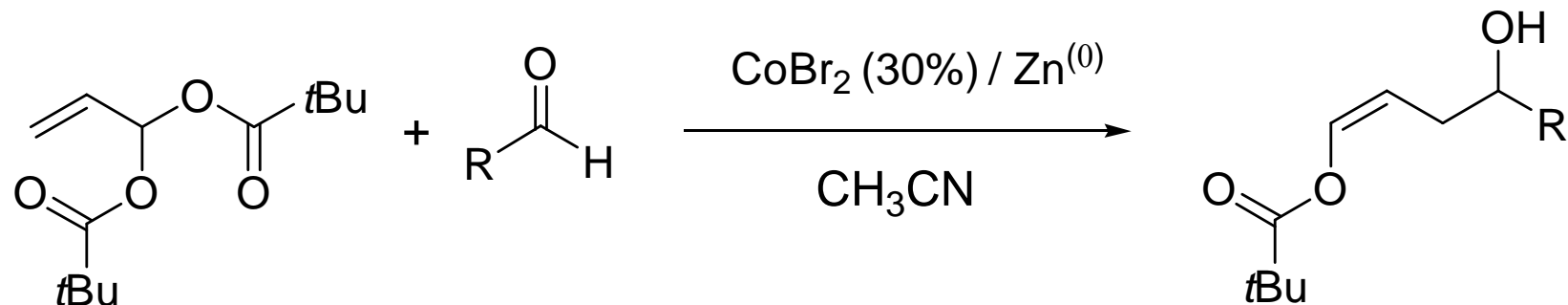


$\text{ZnBr}_2$



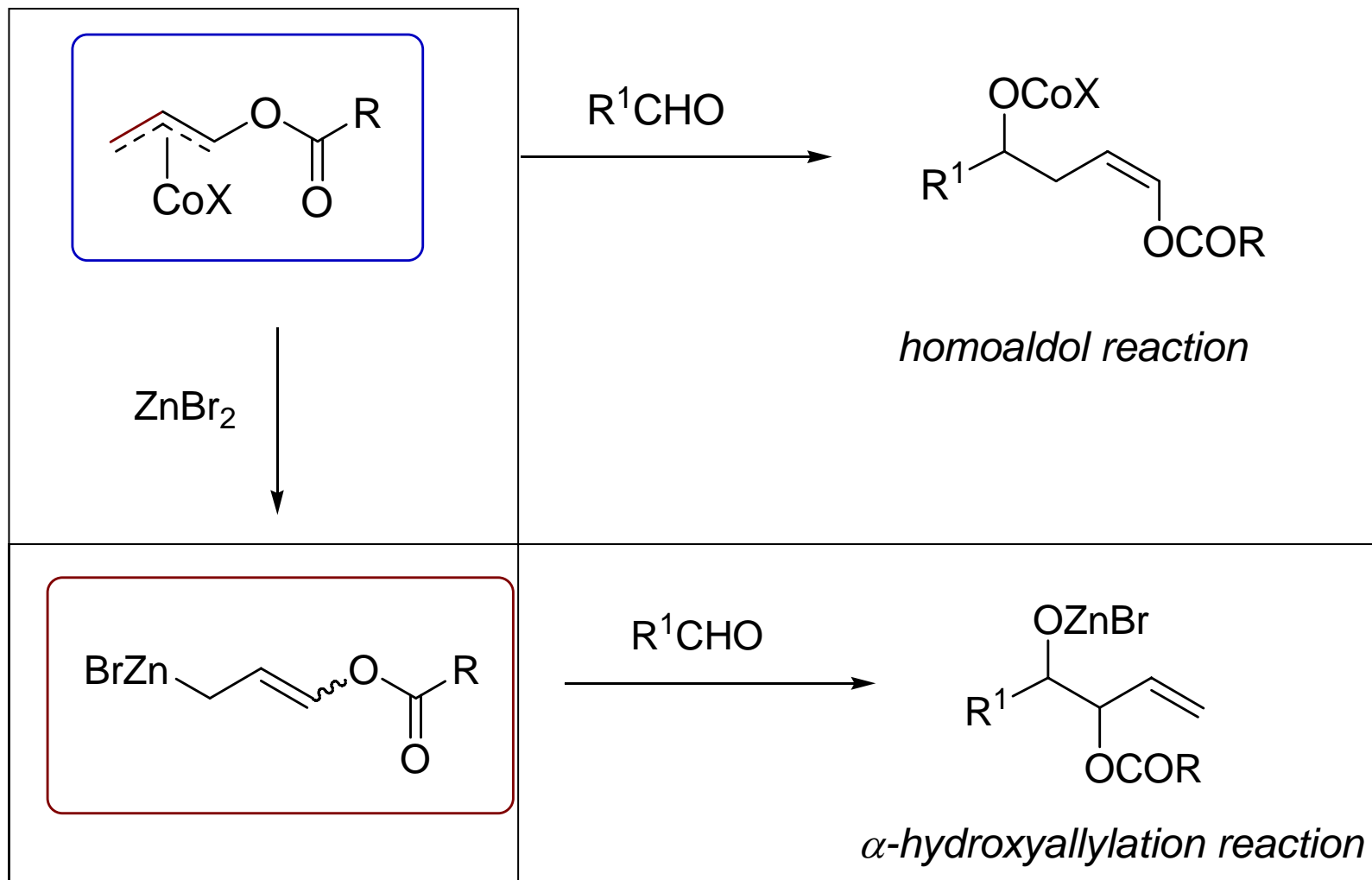
*α-hydroxyallylation reaction*

# Homoaldol Reaction with Allylidene dipivalate



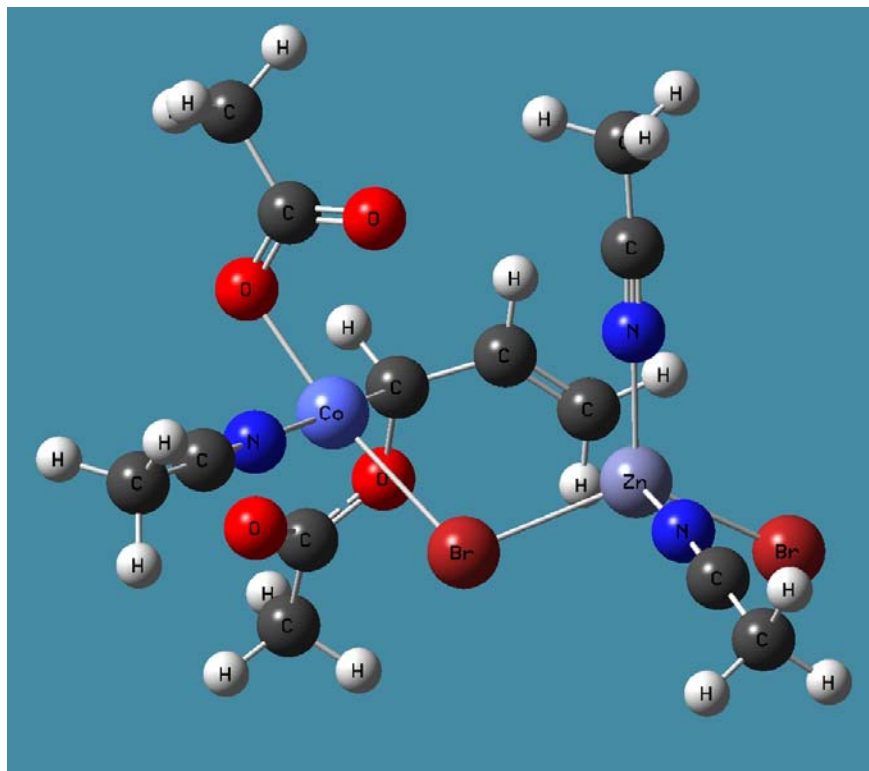
RCHO	T (°C)	Y (%)
<b>Benzaldehyde</b>	<b>20</b>	<b>90</b>
<b>2-Furaldehyde</b>	<b>20</b>	<b>68</b>
<b>Anisaldehyde</b>	<b>20</b>	<b>83</b>
<b>Tolualdehyde</b>	<b>20</b>	<b>83</b>
<b><i>n</i>-C<sub>7</sub>H<sub>15</sub>CHO</b>	<b>0</b>	<b>62</b>
<b>PhCH<sub>2</sub>CH<sub>2</sub>CHO</b>	<b>0</b>	<b>70</b>
<b>(CH<sub>3</sub>)<sub>2</sub>CHCHO</b>	<b>0</b>	<b>82</b>
<b><i>c</i>-C<sub>6</sub>H<sub>11</sub>CHO</b>	<b>0</b>	<b>73</b>

# Possible Fates of Allylic Cobalt(II) Complexes: Addition to Aldehydes *vs* Transmetalation

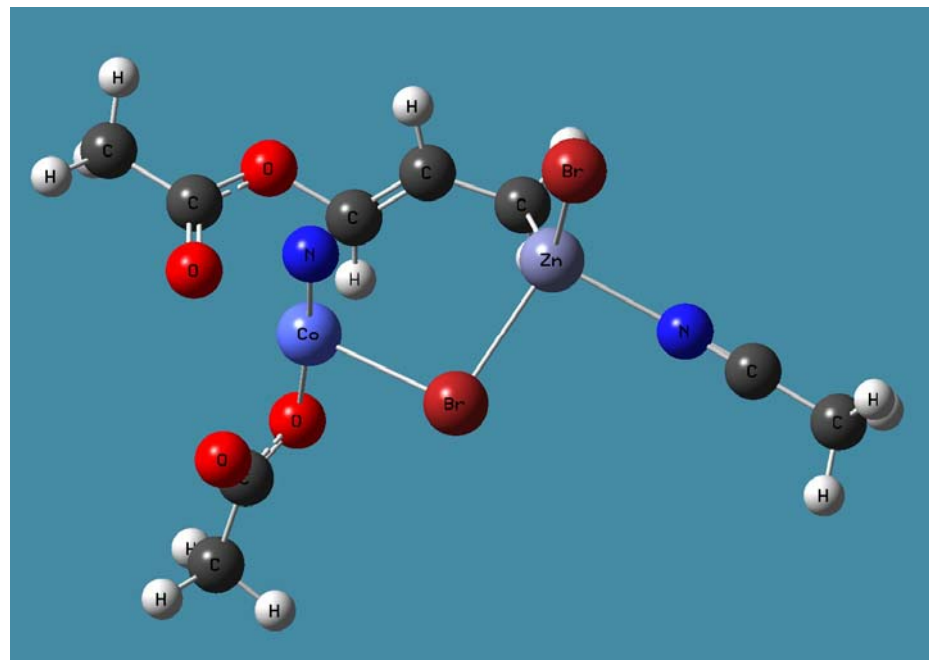
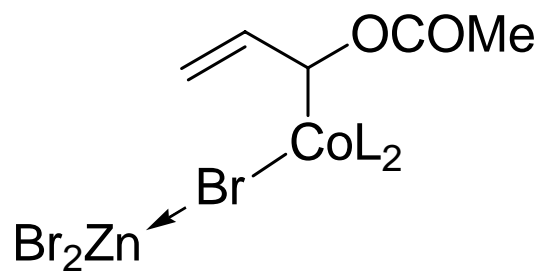


# $\alpha$ -Hydroxyallylation Reaction with Allylidene diacetate

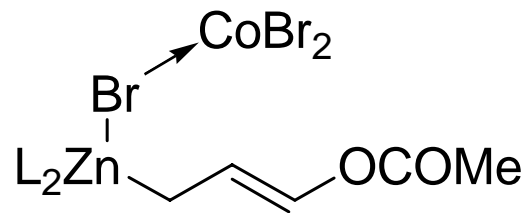
## Modeling the allyl Co / ZnBr<sub>2</sub> transmetalation step



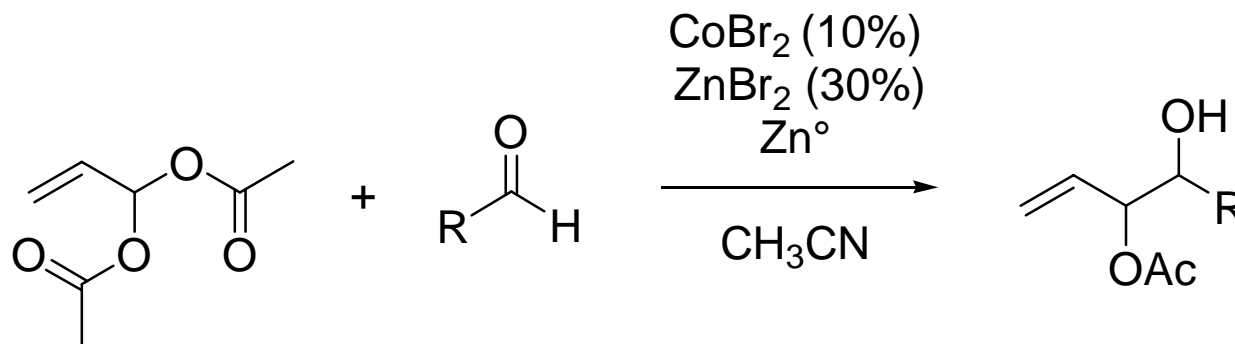
*The early stage*



*The late stage*



# $\alpha$ -Hydroxyallylation Reaction with Allylidene diacetate Allyl Co / ZnBr<sub>2</sub> transmetalation



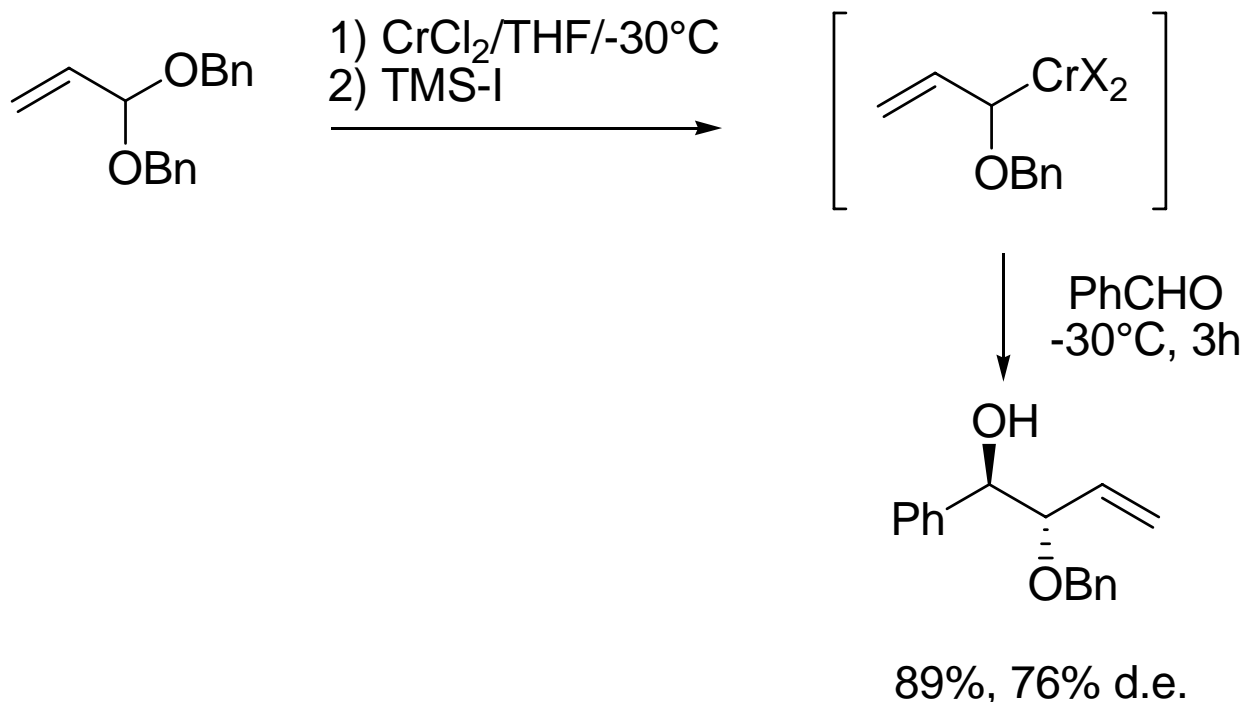
RCHO	Y (%)	<i>syn</i> : <i>anti</i>
Benzaldehyde	80	70 : 30
<i>p</i> -Chloro-benzaldehyde	75	75 : 25
Anisaldehyde	71	70 : 30
Cinnamaldehyde	55	70 : 30
<i>n</i> -C <sub>7</sub> H <sub>15</sub> CHO	60	20 : 80
(CH <sub>3</sub> ) <sub>2</sub> CHCHO	60	2 : 98
(CH <sub>3</sub> ) <sub>3</sub> CHO	55	1 : 99
<i>c</i> -C <sub>6</sub> H <sub>11</sub> CHO	61	2 : 98

# New methodologies for the hydroxyallylation reaction, under Barbier/Grignard conditions

- Searching for substrates, suitable for the oxidative addition to low valent metals

**Cr(II)**

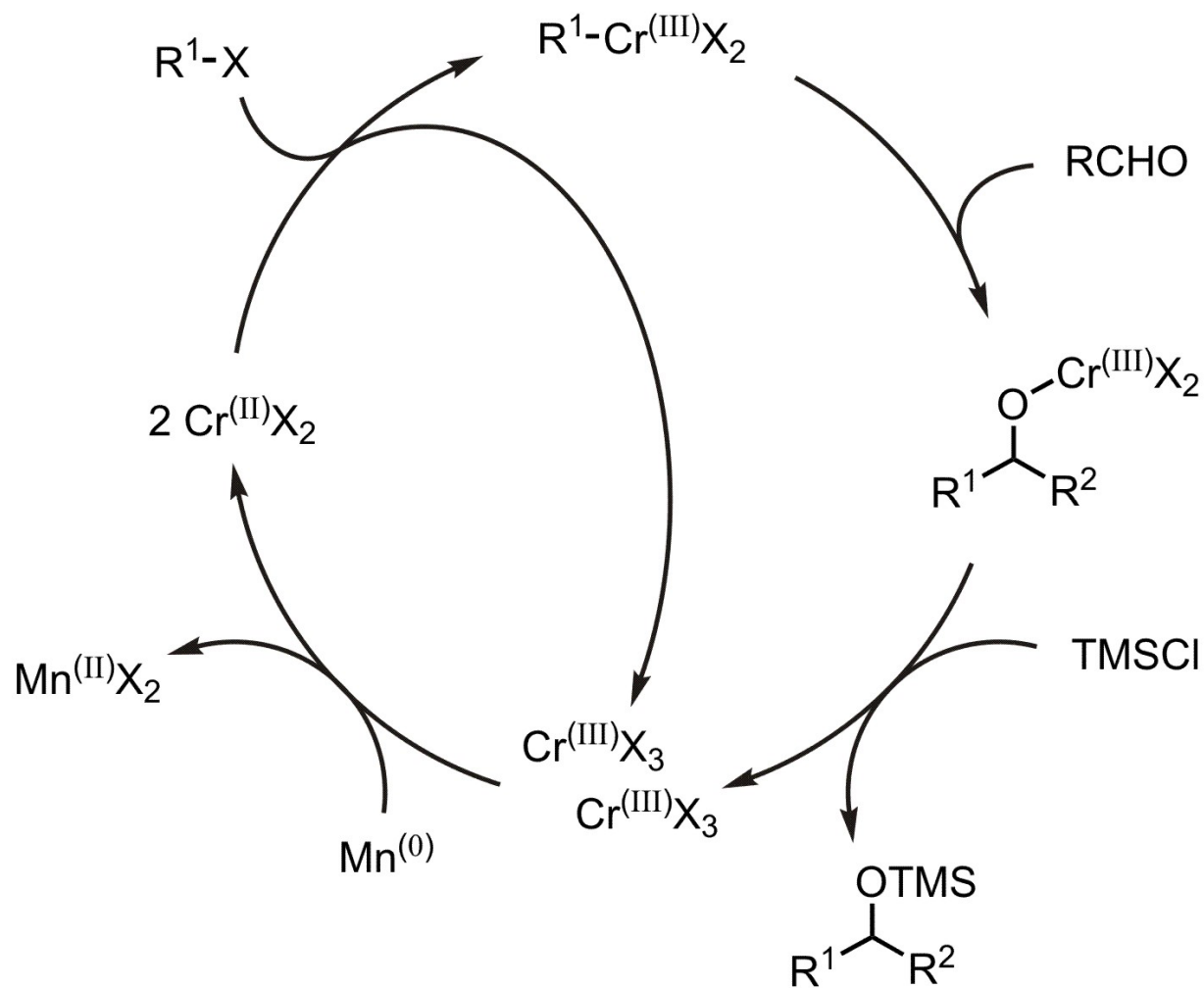
# The Nozaki-Hiyama-Kishi coupling of organic halides and carbonyl compounds, mediated by Cr(II), applied to acrolein acetals



Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, 29, 5263

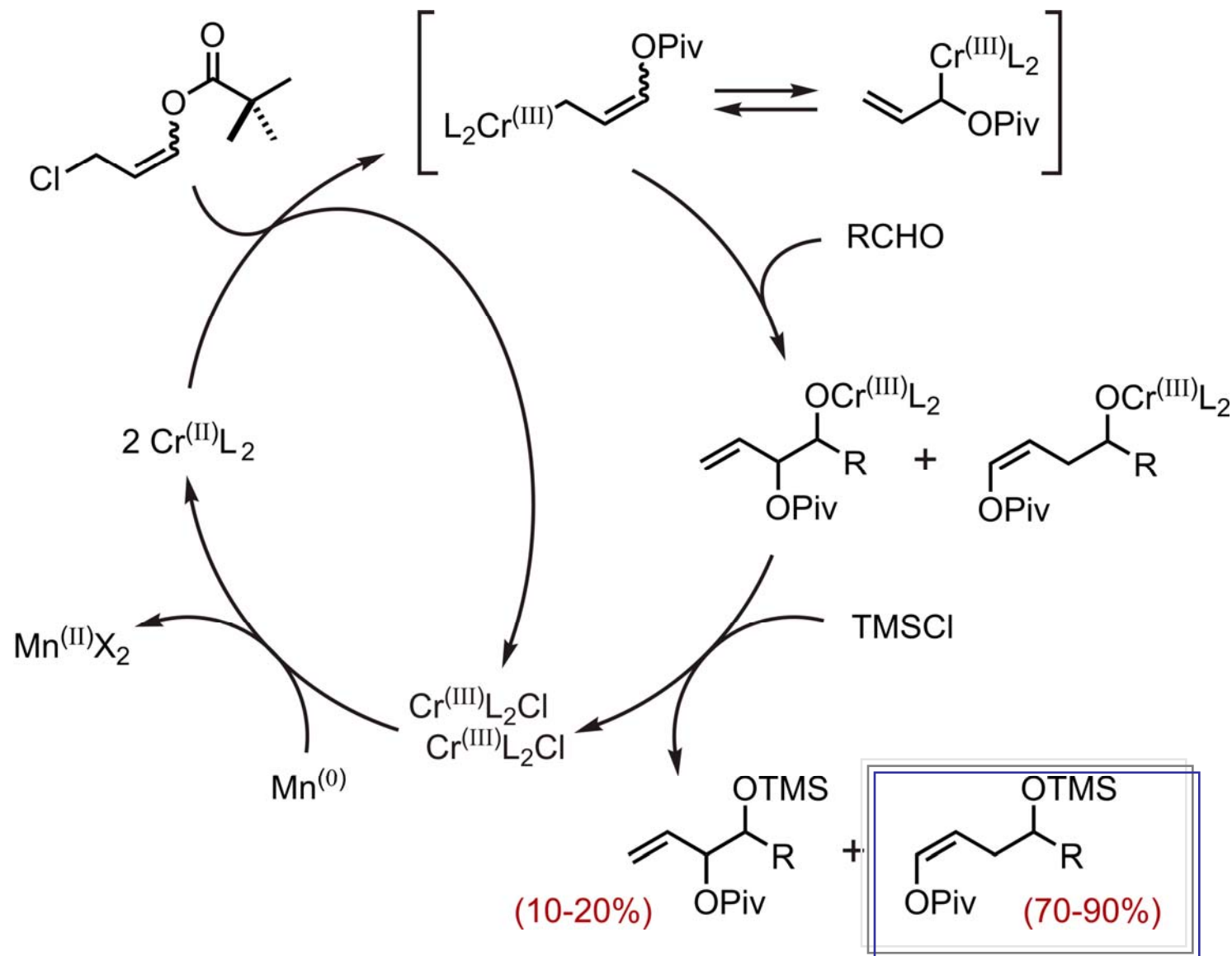
Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem. Int. Ed. Eng.* **2001**, 40, 1116

# Fürstner catalytic version of the Nozaki-Hiyama-Kishi reaction

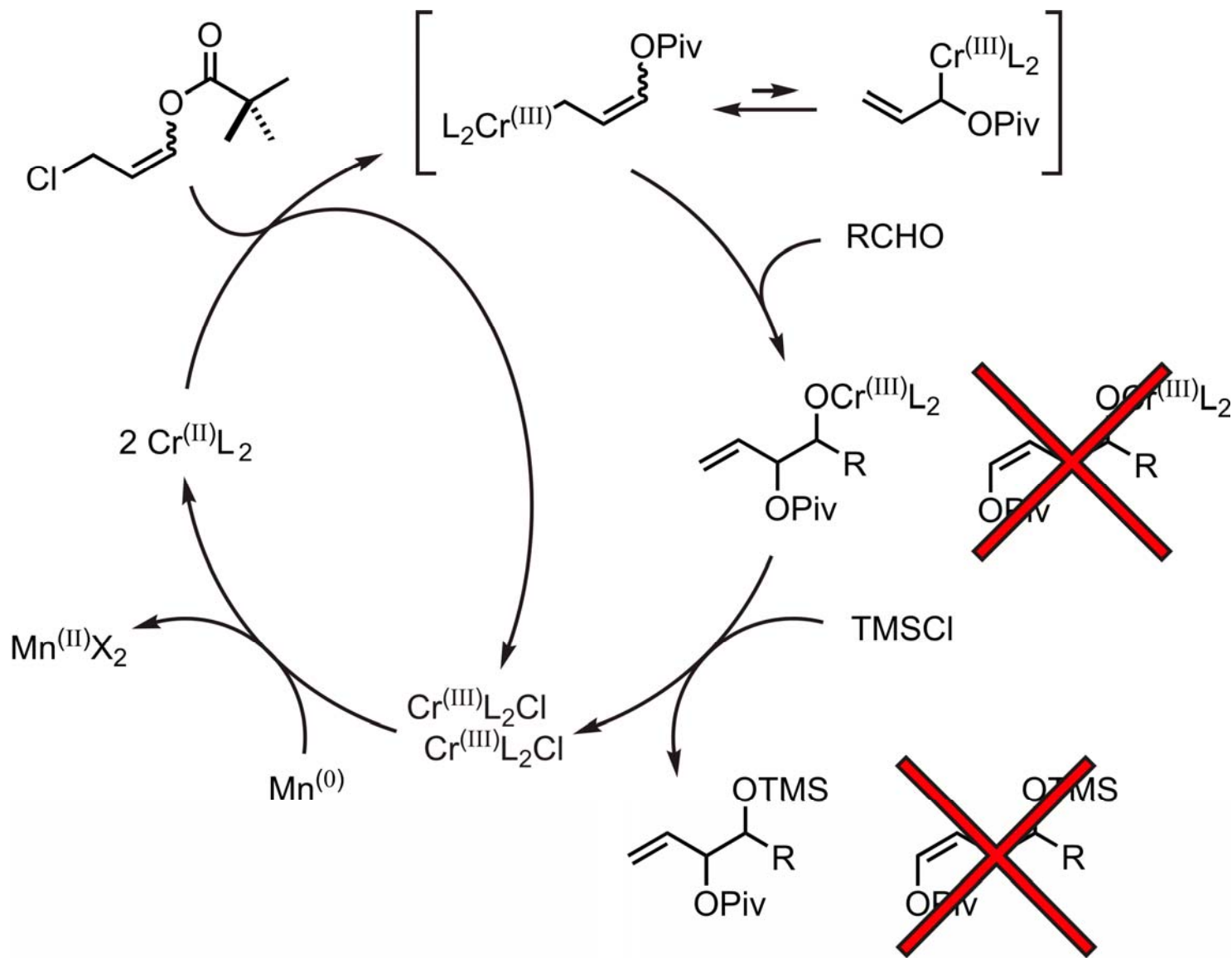


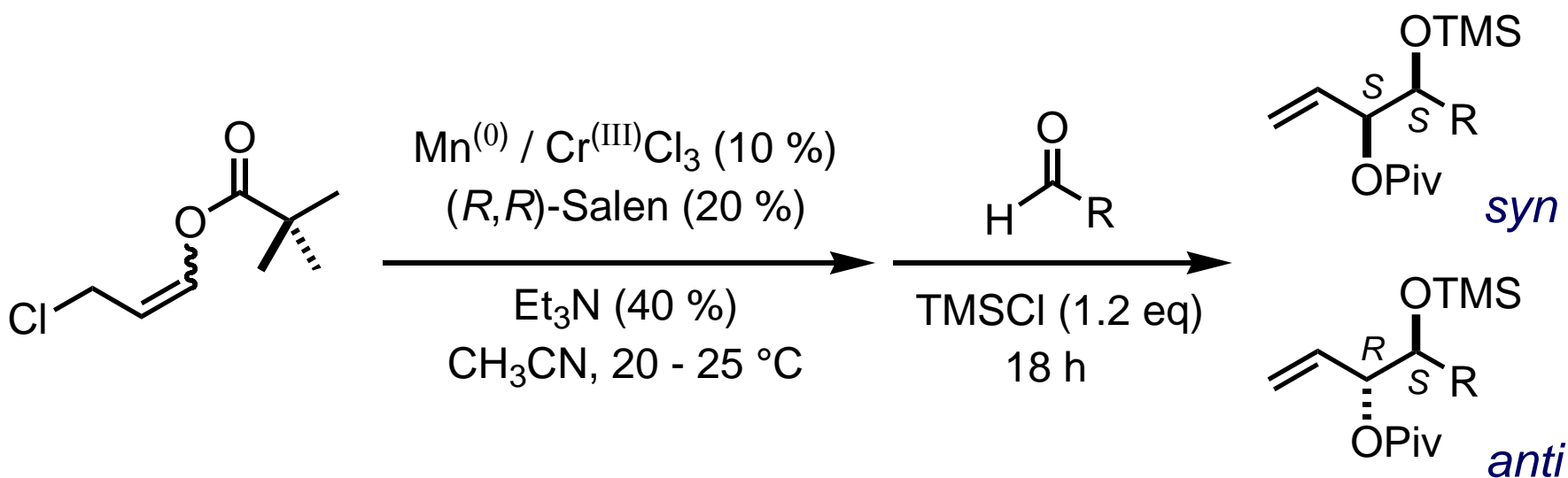


Conditions: Mn(0), CrCl<sub>3</sub> (30%), Bu<sub>4</sub>NI (20%), TMSCl, AN, 60°C



# A chiral ligand in action: Jacobsen Salen



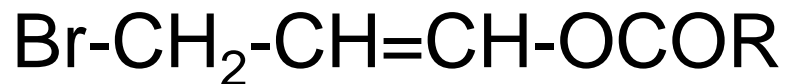


R of RCHO	Y (%)	Syn : Anti	Syn e.e. (%)	Anti e.e. (%)
Cyclohexyl	68	83 : 17	94	67
<i>n</i> -Pentyl	50	83 : 17	93	65
2-Phenylethyl	78	85 : 15	99	85
<i>i</i> -Propyl	45	72 : 28	92	77
2-Methylpropyl	55	80 : 20	92	60
Phenyl	77	71 : 29	64	43
2-Naphthyl	60	78 : 22	73	23

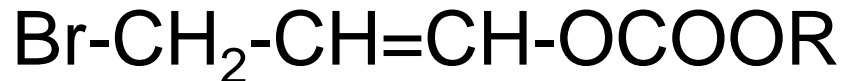
# New methodologies for the hydroxyallylation reaction, under Barbier/Grignard conditions

- Searching for substrates, suitable for the oxidative addition to low valent metals

**Zn, In**

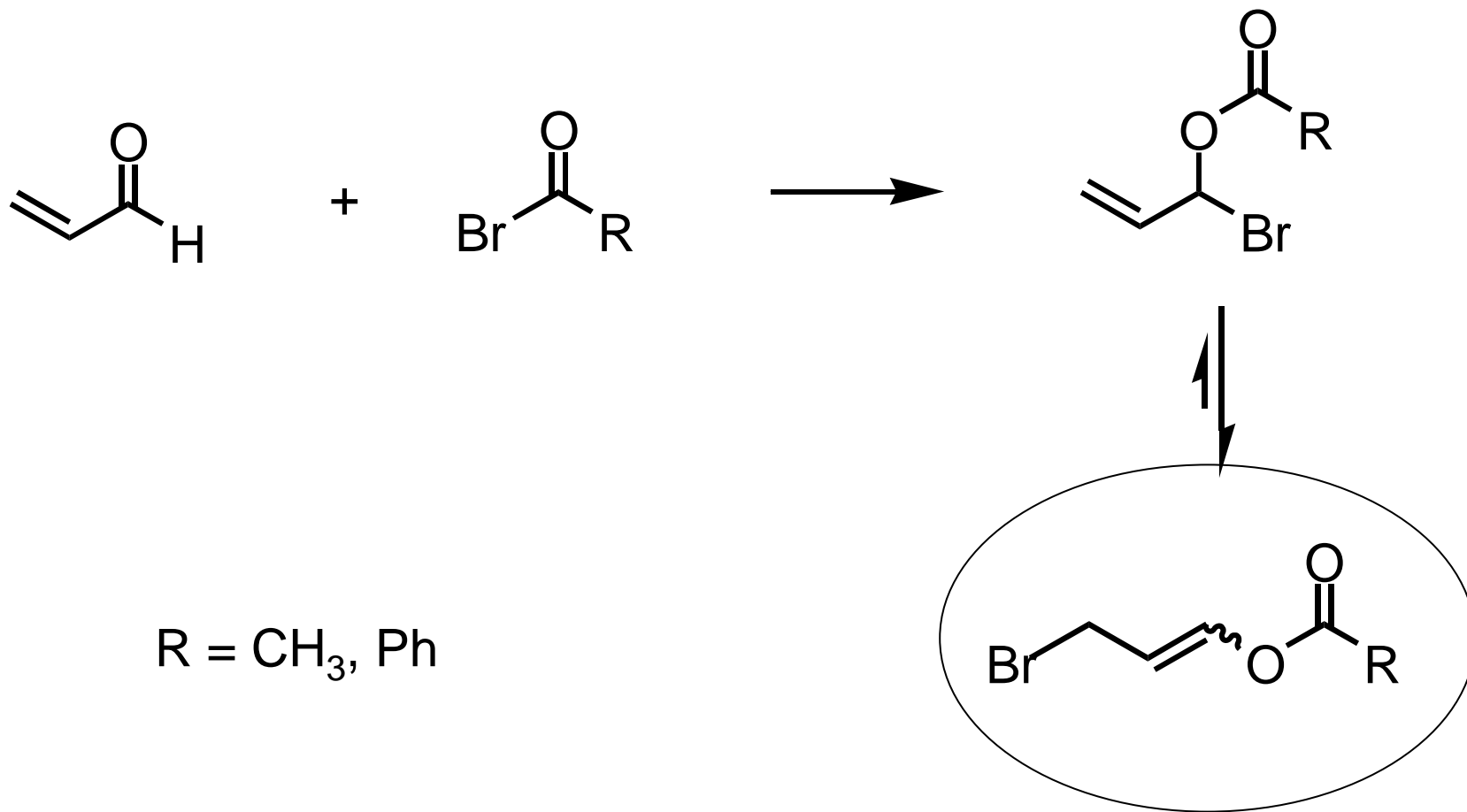


and



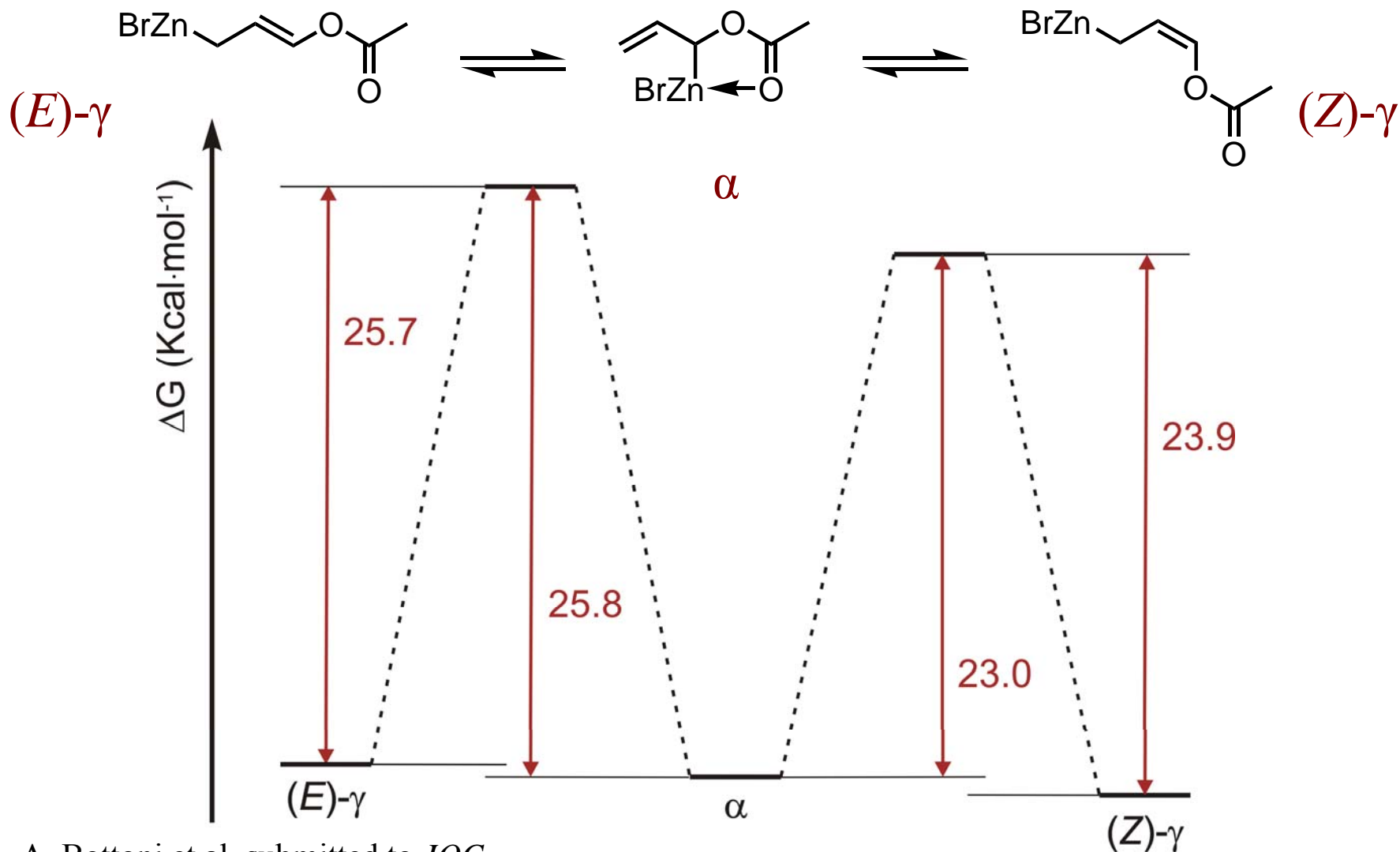
# 3-Halo-propenyl Esters

## Haloacylation of Acrolein

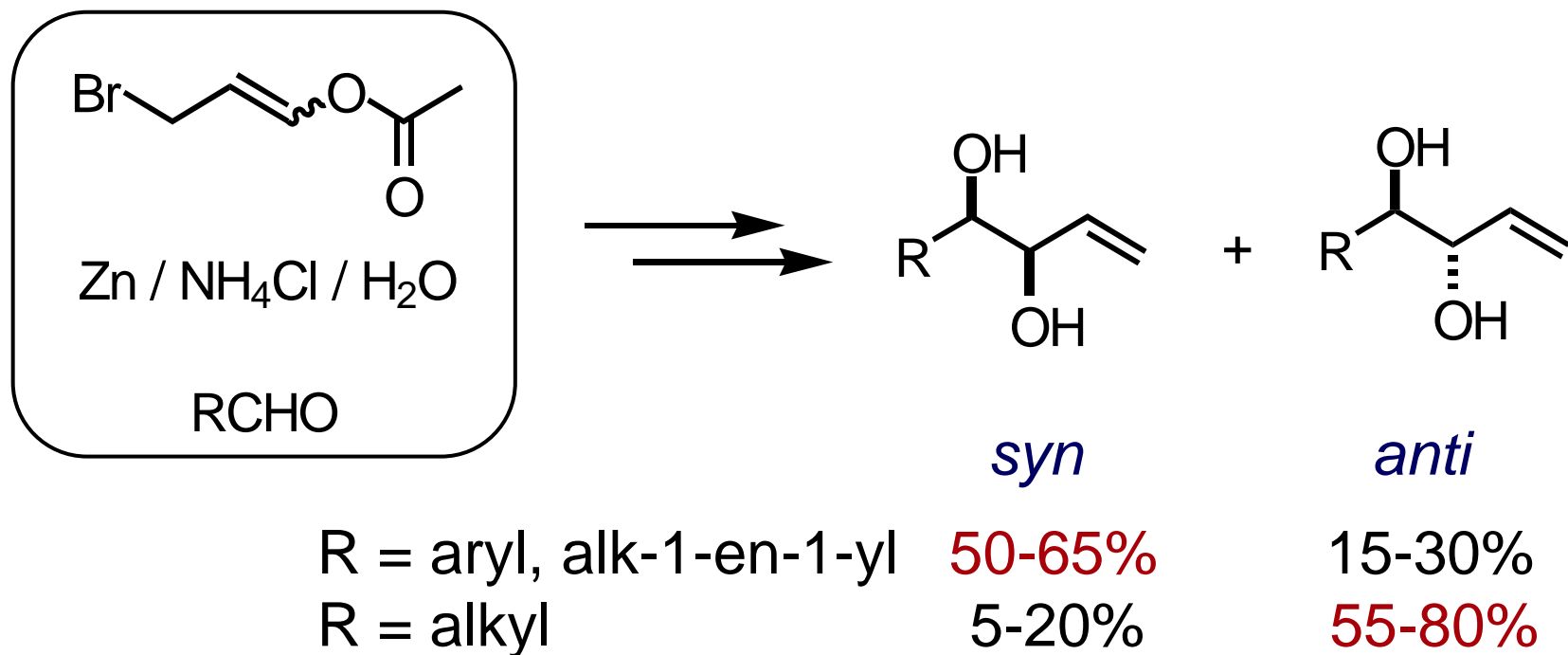


# The 1,3-Metallotropic Shift. Theoretical Investigation

(DFT-B3LYP and MP2: 3-21G\* , DZVP , 6-311G\* basis sets)

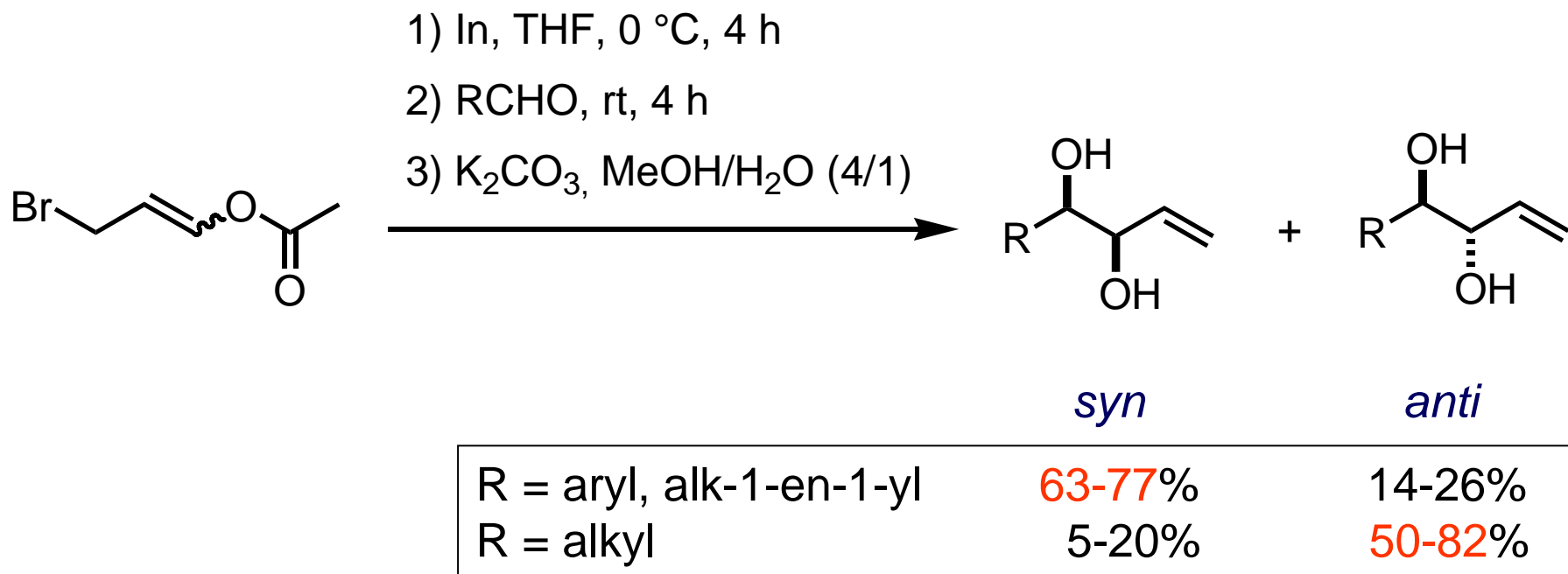


# Zinc-promoted Barbier-type Acetoxyallylation of Aldehydes in *aq* NH<sub>4</sub>Cl. An Efficient, Environmentally Friendly Protocol



**This protocol works with ketones, too, in the presence of 20% of THF; yields up to 98% and same stereocrossover with aromatic or fully aliphatic ketones**

# Indium-promoted Grignard-type $\alpha$ -Hydroxyallylation of Aldehydes in Organic Solvents (THF, MeCN, DMF,...)

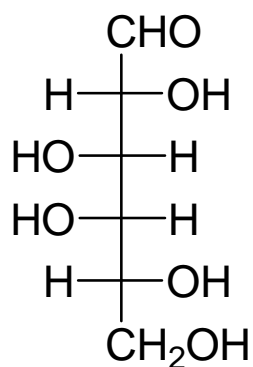


M. Lombardo et al. *Org. Lett.* **2001**, 2981-2983

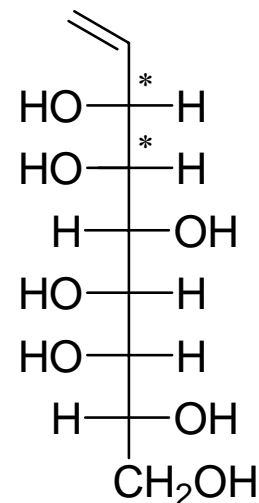
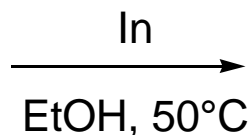
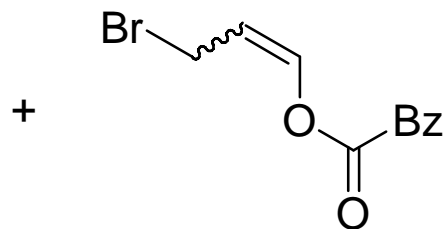
M. Lombardo et al. *J. Org. Chem.* **2003**, 68, 997-1006



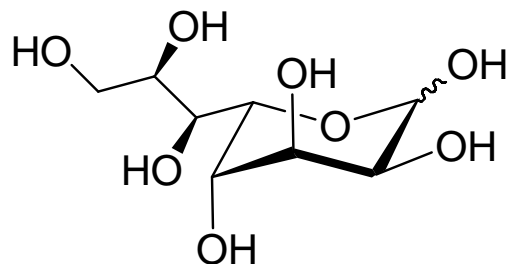
# Two-carbon homologation of aldoses via three-carbon chain elongation



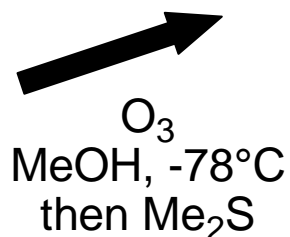
D-galactose



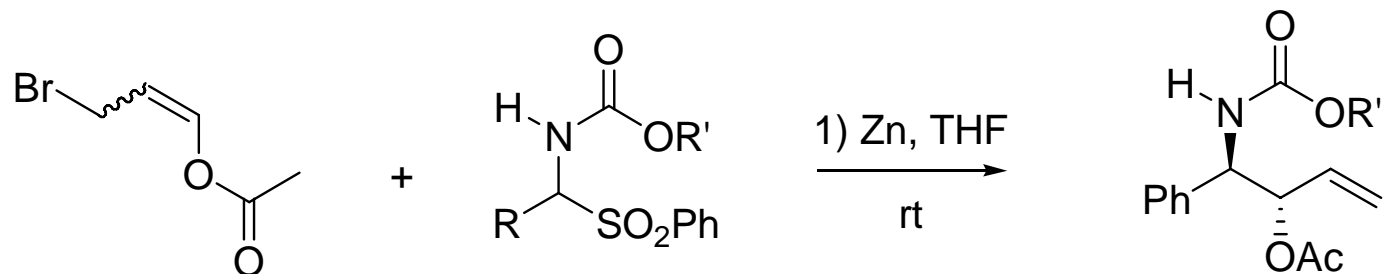
90%, 3.5:1 d.r.



D-threo-L-gulo-octose



# $\alpha$ -Hydroxyallylation of $\alpha$ -amidoalkyl phenylsulfones *anti*-diastereoselective synthesis of 1,2-amino-alcohols

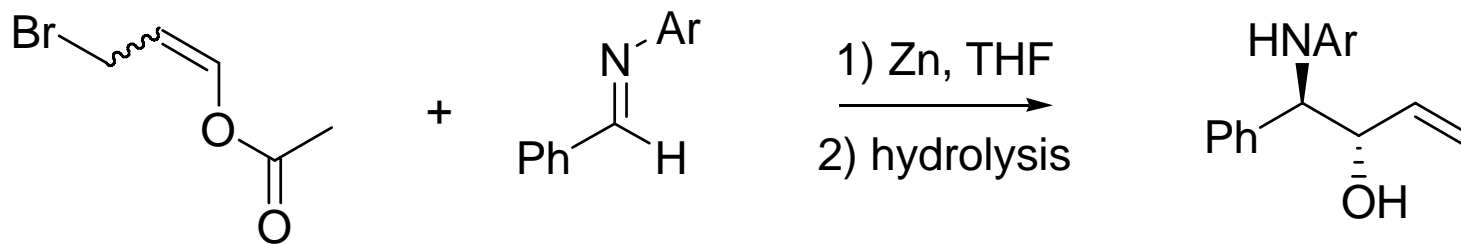


50-88%

*anti*/*syn* = 80-20 - 95.5

Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530

Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303



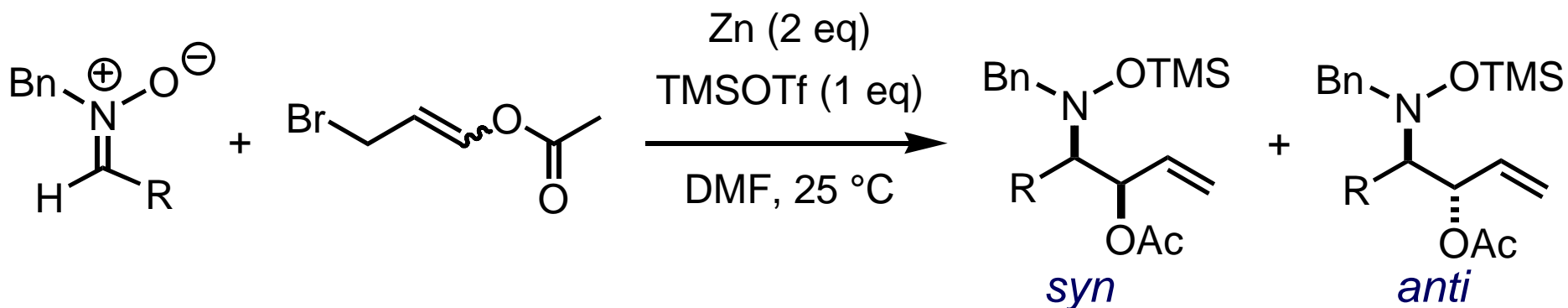
70-86%,

*anti*/*syn* = 85:15 - 95.5

Kenicke, L.; Fristrup, P.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2005**, *127*, 15756

# $\alpha$ -Hydroxyallylation of Nitrones

*Syn*-diaseteroselective synthesis of 1,2-amino alcohols



$\text{R} = \text{alkyl, phenyl}$       $\text{Y} = 70\text{-}87\%$ , *syn/anti* = 60/40 ÷ 80/20

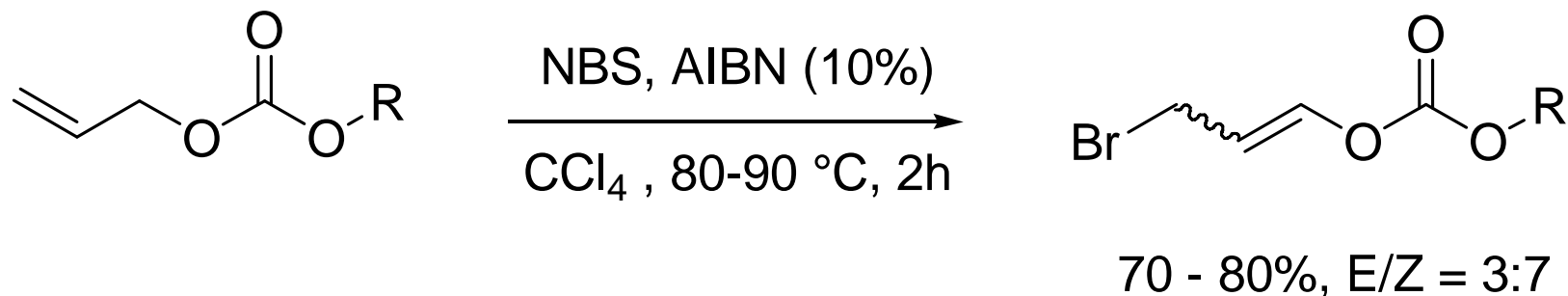
M. Lombardo et al. *Tetrahedron Letters* **2005**, 46, 3789

Nucleophilic addition of organometallics to nitrones, see:

M. Lombardo & C. Trombini *Curr. Org. Chem.* **2002**, 6, 695-713

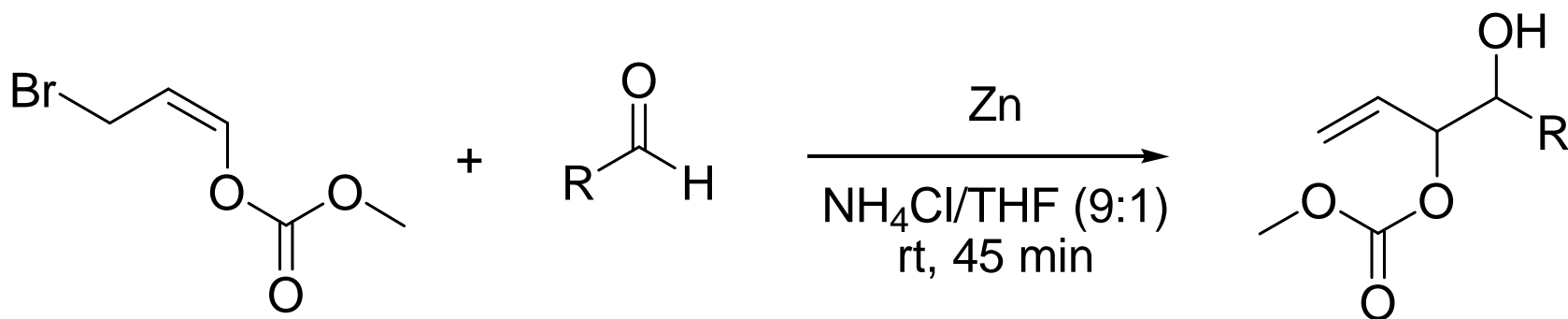
M. Lombardo & C. Trombini *Synthesis* **2000**, 759-774

# 3-Halo-propenyl Carbonates: Free-radical Bromination of Allyl Carbonates



R = Me, Ph, tBu

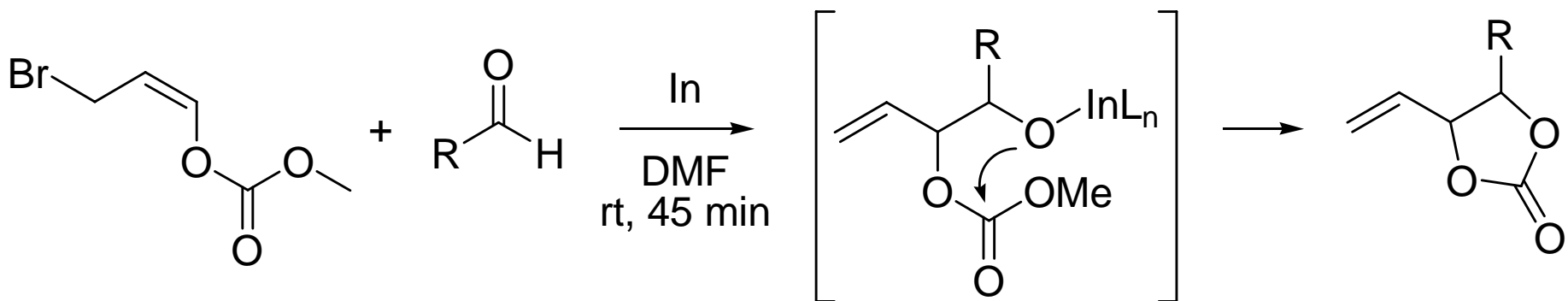
# 3-Halo-propenyl Carbonates: $\alpha$ -Hydroxyallylation of Carbonyl Compounds in Water (Barbier conditions)



Aromatic and conjugated aldehydes: Y = 88-98%, *syn* = 70-88% /*anti* 12-30%

Saturated aldehydes: Y = 85-95%, *syn* = 5-30% /*anti* 70-95%

# 3-Halo-propenyl Carbonates: $\alpha$ -Hydroxyallylation of Carbonyl Compounds in DMF (*Barbier or Grignard conditions*)

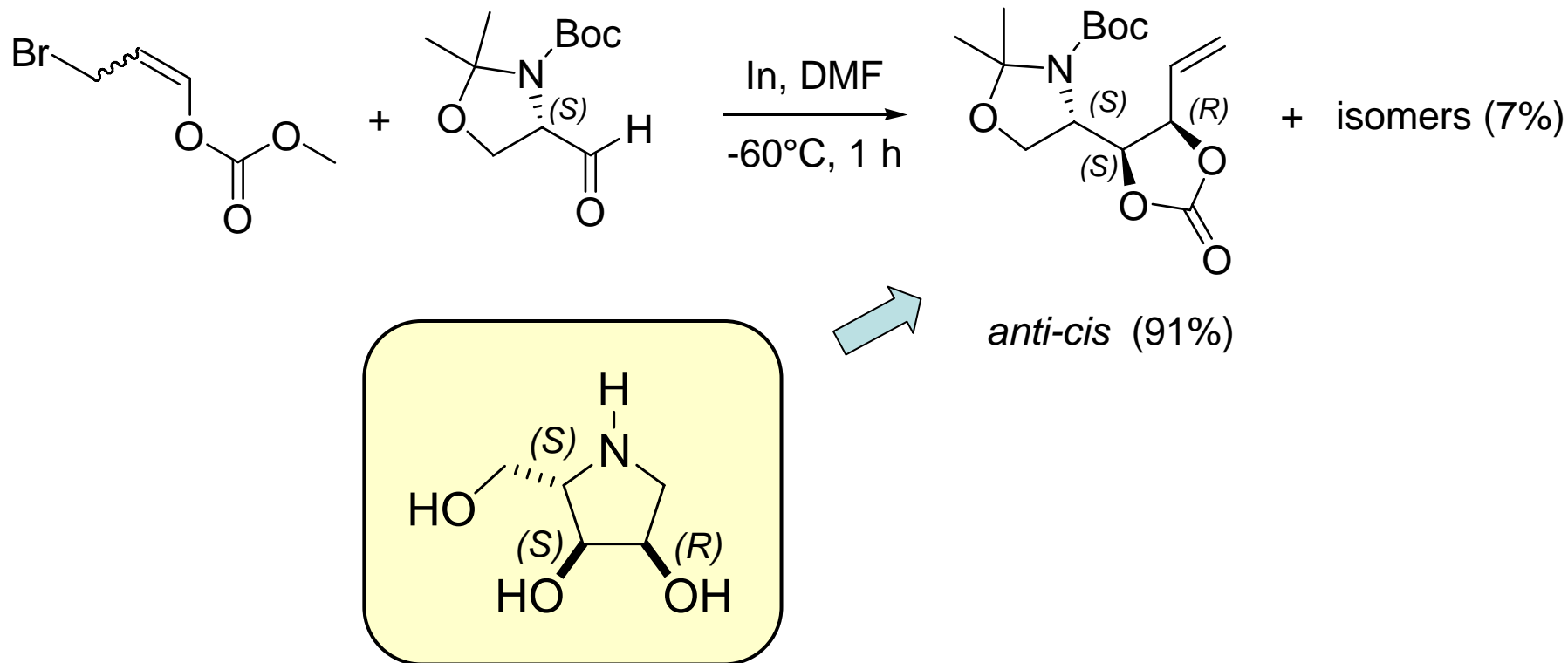


Aromatic and conjugated aldehydes: Y = 91-98%, *trans* 77-95% *cis* = 5:23%

Saturated aldehydes: Y = 88-98%, *trans* 7-28% *cis* = 72-93%  
*trans/cis* = 28:72 - 7:93

Usual diastereoselectivity, almost invariant in the temperature range  $-50^{\circ}\text{C} \div +20^{\circ}\text{C}$  (p-nitrophenylbenzaldehyde reacts quantitatively, but under Grignard conditions, only).

# 3-Halo-propenyl Carbonates: $\alpha$ -Hydroxyallylation of the Garner aldehyde in DMF

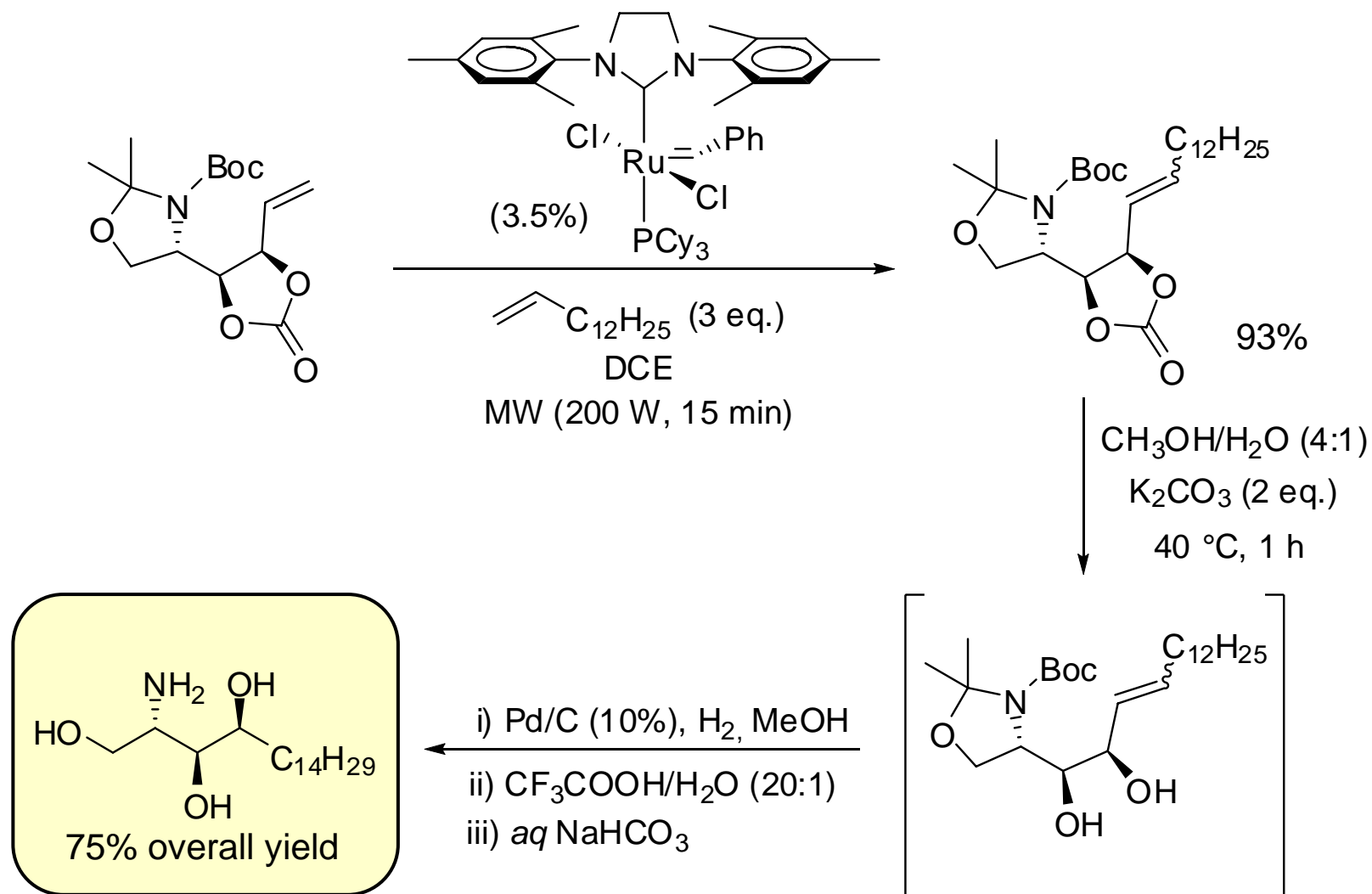


M. Lombardo et al. *Org. Lett.* **2006**, 8, 3303

M. Lombardo et al. *Tetrahedron* **2004**, 60, 11725

M. Lombardo et al. *Tetrahedron Lett.* **2003**, 44, 9147-9149

# Synthesis of D-ribo-phytosphingosine





# 3-Halo-propenyl Carbonates: $\alpha$ -Hydroxyallylation of imines and of $\alpha$ -amido-alkyl phenylsulfones.

The most efficient routes to *anti*-1,2 aminoalcohols.

