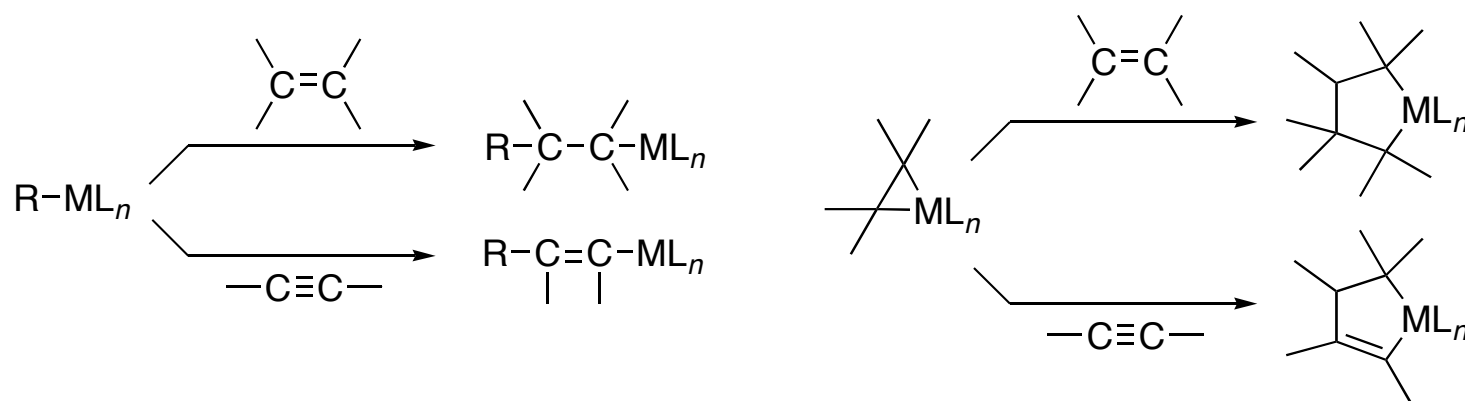


# Zr-Catalyzed Carbometallation



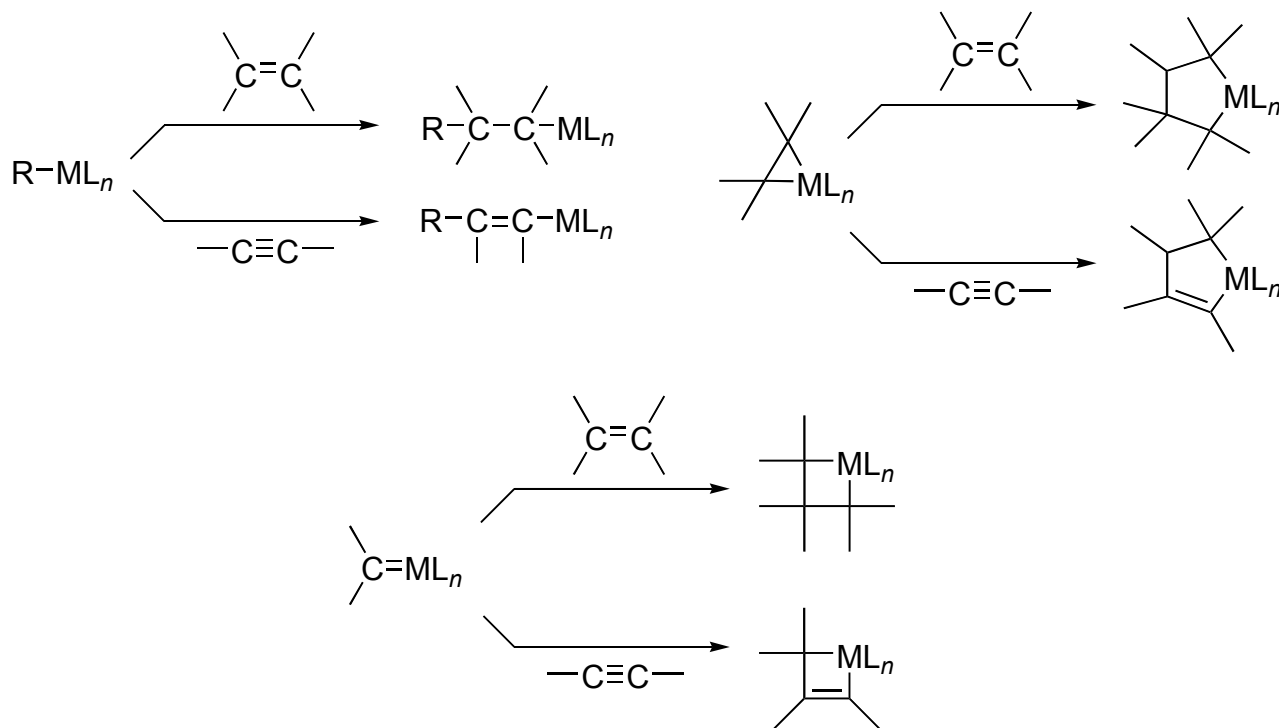
*Wipf Group Research Topic Seminar*

*Juan Arredondo*

*November 13, 2004*

# Carbometallation

- Term coined for describing chemical processes involving net addition of carbon-metal bonds to carbon-carbon  $\pi$ -bonds.
- One of the several patterns for C-C bond formation observable with organotransition-metal complexes along with *reductive elimination*, *migratory insertion*, etc.

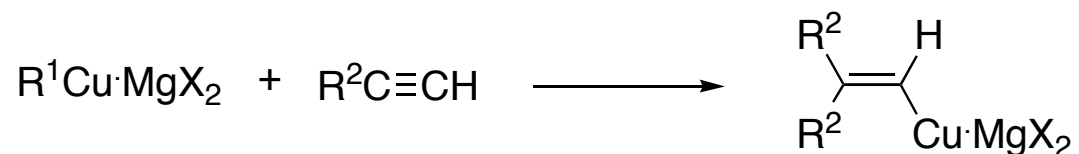


# Timeline

- In 1959, Natta first reported the polymerization of propylene with  $\text{TiCl}_4/\text{AlEt}_3$ . Reaction proceeds with relative asymmetric induction with polymer sections of the same absolute configuration (isotactic). Subsequent work was focused on finding a soluble of group IV metallocene catalyst (Ti, Zr, Hf).

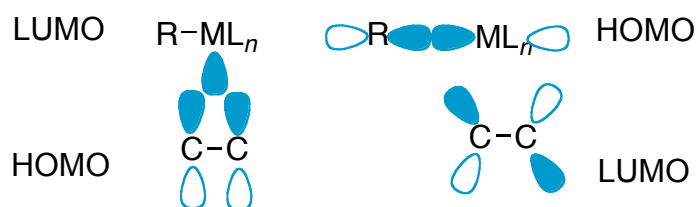
## Controlled Monocarbometallation of Alkenes and Alkynes

- Stereo- and regioselective single-state addition of organometallics species can be a valuable synthetic tool.
- Normant's carbocupration (1976) was the first example with high selectivity and reasonable generality. Limitations arose from the thermal instability of the alkylcopper reagents and capricious effects of proximal heteroatoms.



- Schwartz's systematic investigation (1974) of hydrozirconation of alkenes and alkynes with  $\text{Cp}_2\text{ZrHCl}$  and observations of its addition to alkenes and alkynes by Wales and coworkers.
- Kaminsky's use of  $\text{Cp}_2\text{ZrCl}_2$  and methylaluminumoxanes as catalyst for alkene polymerization (1976).
- Negishi's catalyzed carboalumination with Ti and Zr (1978).

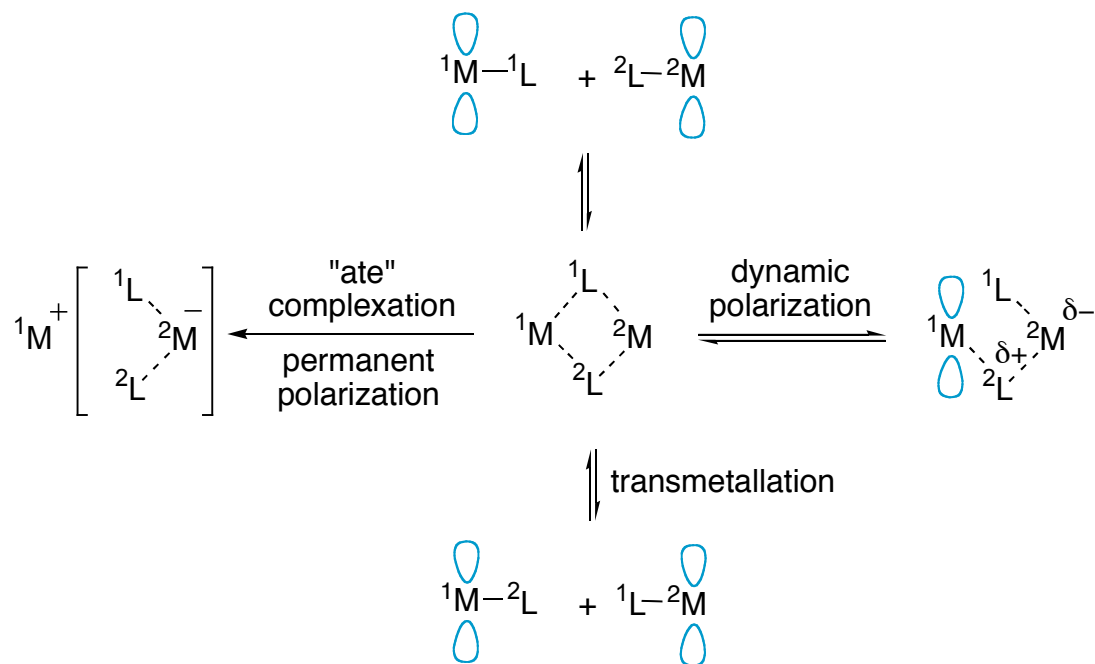
## Carbometallation: FMO Analysis



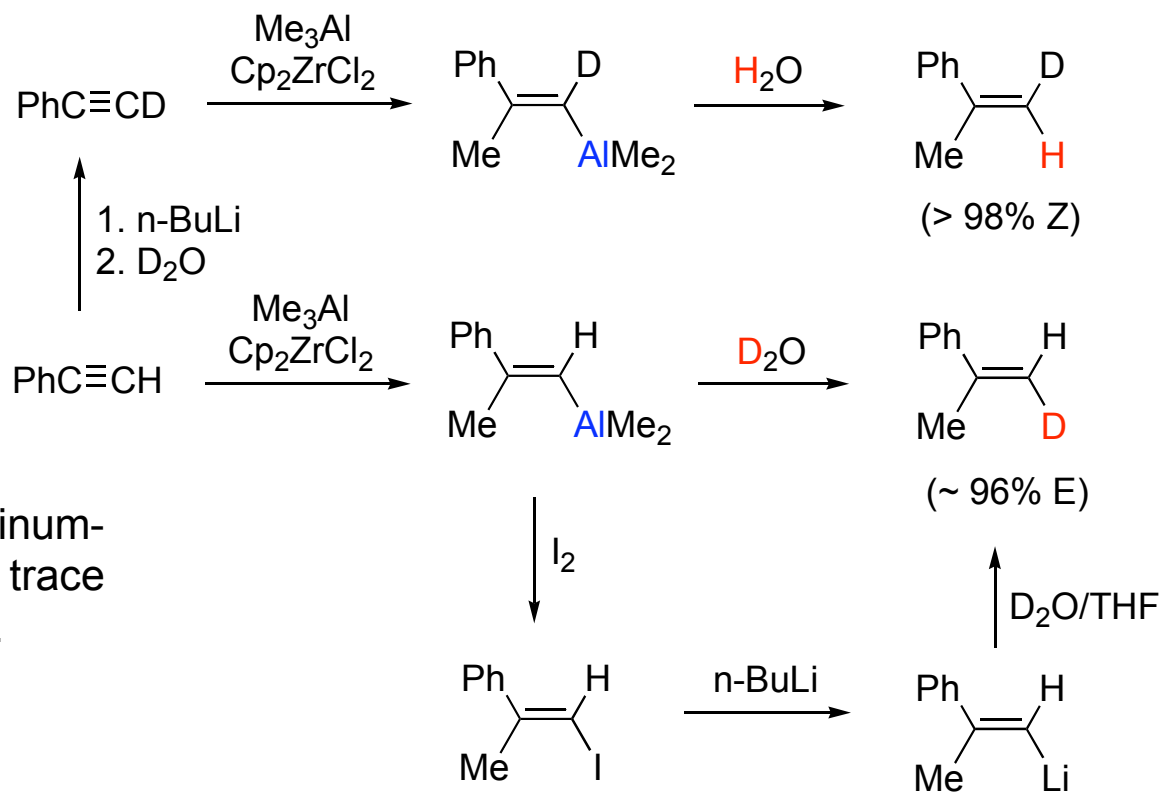
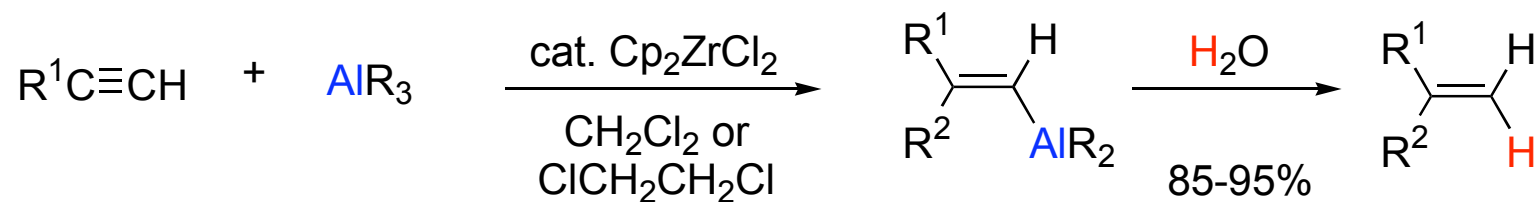
- Structural requirement for organometallic reagent is the availability of a low-lying metal empty orbital.
- Carbometallations that proceed *via* pericyclic reactions can be facile and highly stereoselective.
- Energy of activation for carbometallation would be higher than that of hydrometallation due greater steric requirements of C groups than H.

## Dynamic Polarization

- Two Lewis acids (or electrophiles) which make one of them more acidic (or electrophilic), while making the other more basic (or nucleophilic).

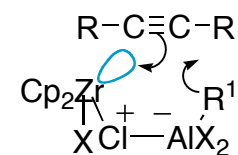
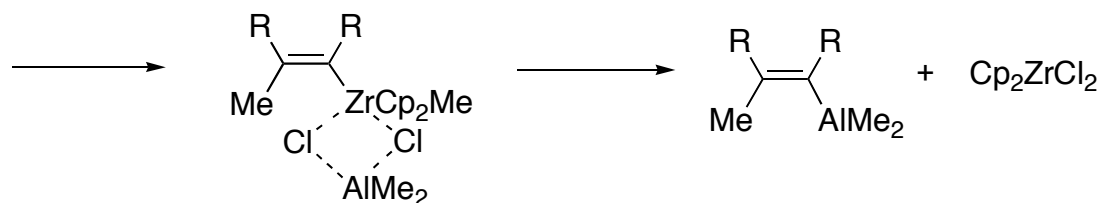
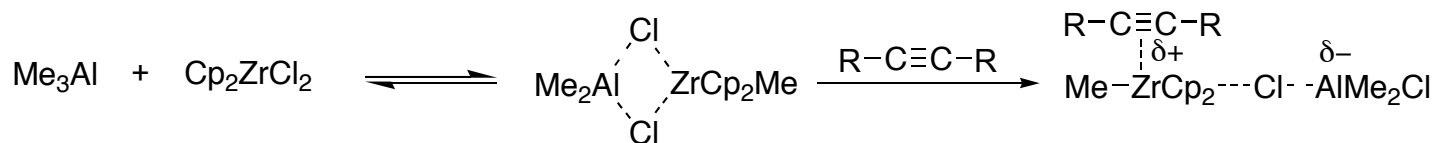


# Zirconium-Catalyzed Carboalumination of Alkynes

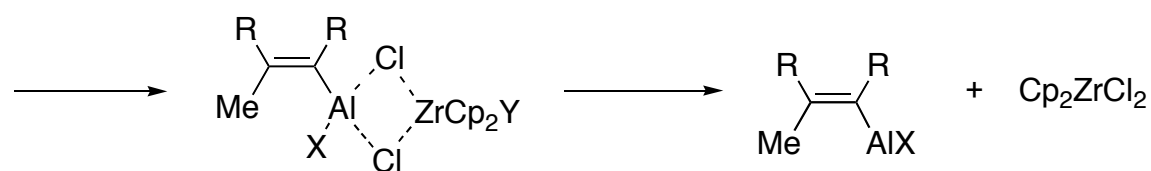
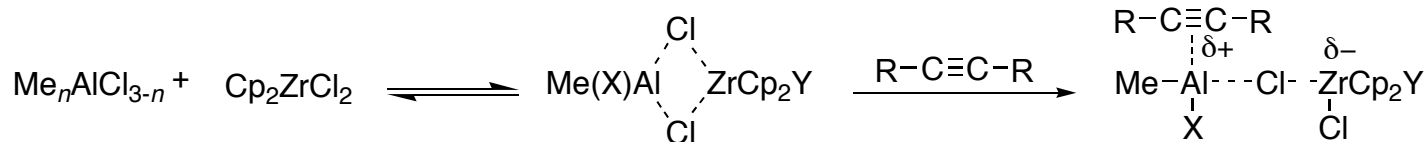


- If  $\text{Cp}_2\text{ZrCl}_2$  is omitted or aluminum-free  $\text{Cp}_2\text{ZrMeCl}$  is used, only trace amount of the alkene is obtained.

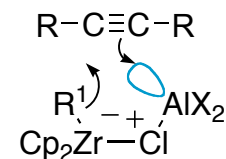
# Mechanistic Studies



X = Cl and/or R<sup>1</sup>  
R<sup>1</sup> = Me, Et and higher alkyl



n = 3 or 2  
X and Y = Me or Cl



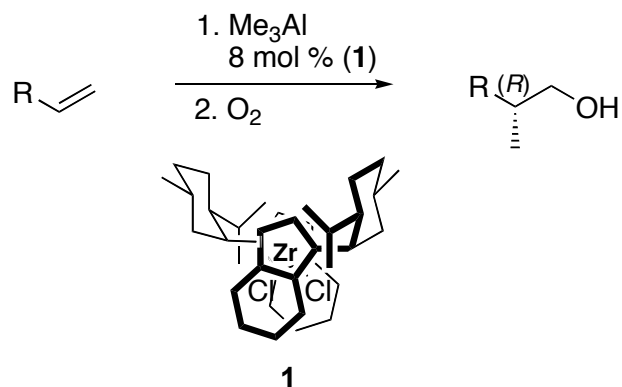
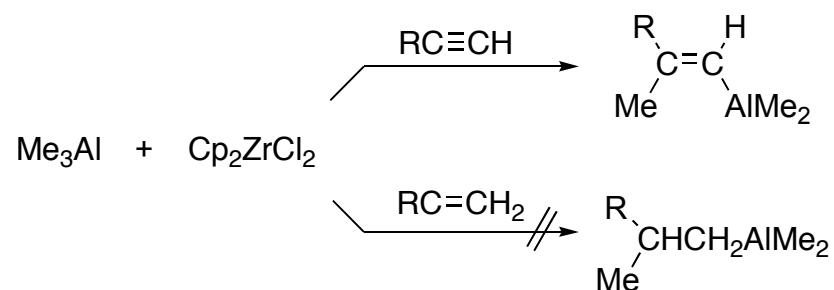
X = Cl and/or R<sup>1</sup>  
R<sup>1</sup> = Me, Et and higher alkyl

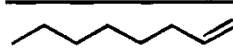
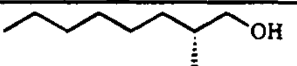
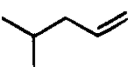
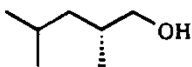
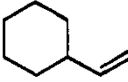
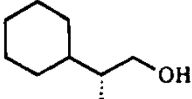
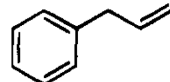
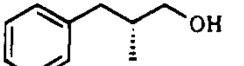
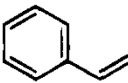
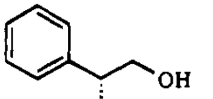
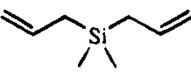
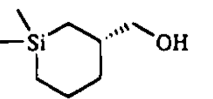
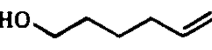
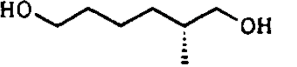
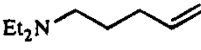
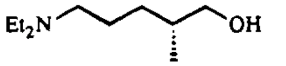
- Me<sub>2</sub>AlCl-Cl<sub>2</sub>ZrCp<sub>2</sub> induced carbometallation
- Cp<sub>2</sub>Zr(CD<sub>3</sub>)Cl deuterium incorporation (< 4%)

Negishi, E. et al. *J. Am. Chem. Soc.* **1978**, 100, 2252, *J. Am. Chem. Soc.* **1981**, 103, 4985, *J. Am. Chem. Soc.* **1985**, 107, 6639



# Zirconium-Catalyzed Enantioselective Methylalumination of Unactivated Alkenes

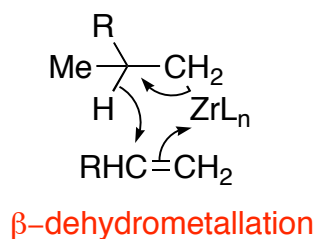
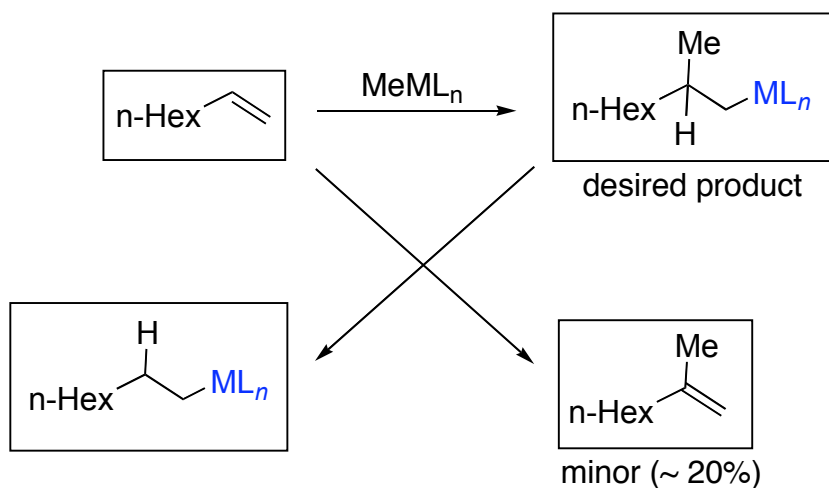


substrate	time, h	product	yield, <sup>b</sup> %	ee, %
	12		88	72
	12		92	74
	12		80	65
	24		77	70
	528		30	85
	12		81	74
	12 <sup>c</sup>		79	75
	96 <sup>d</sup>		68	71

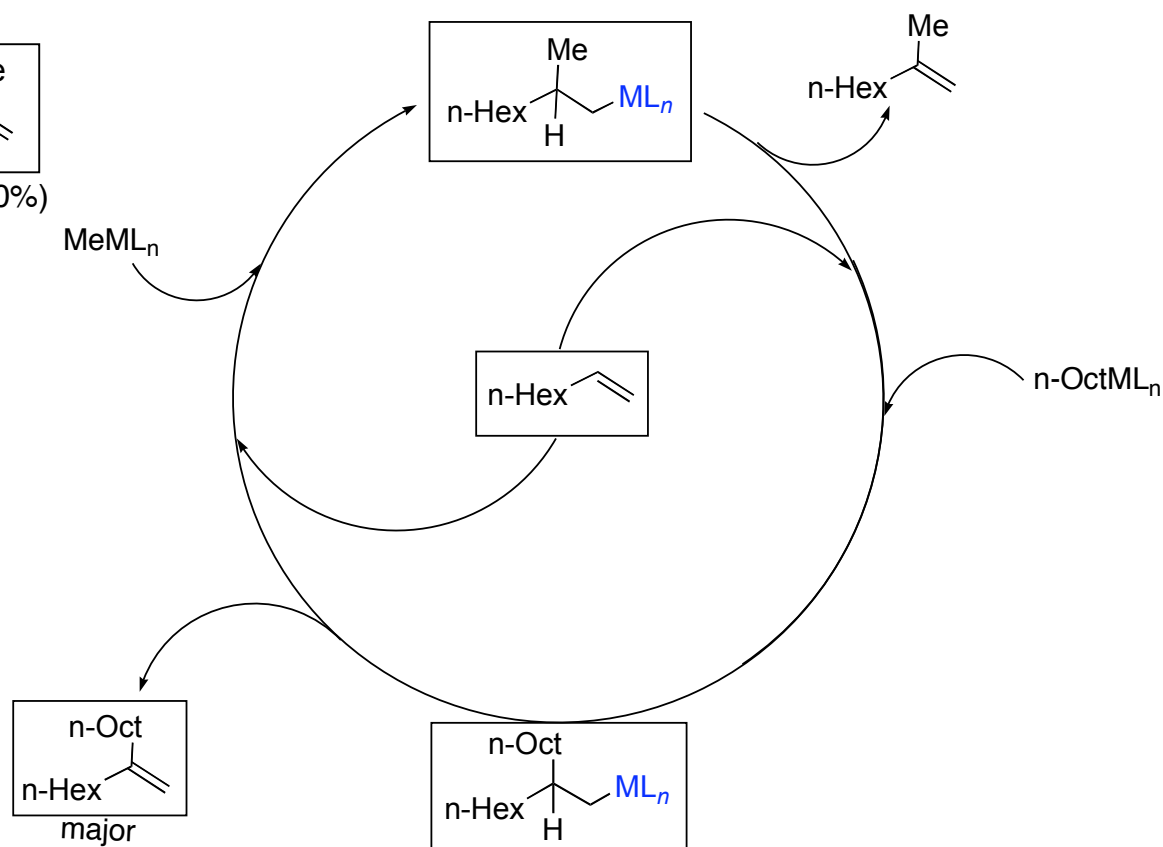


# Stoichiometric vs. Catalytic Carbometallation

## Stoichiometric Process

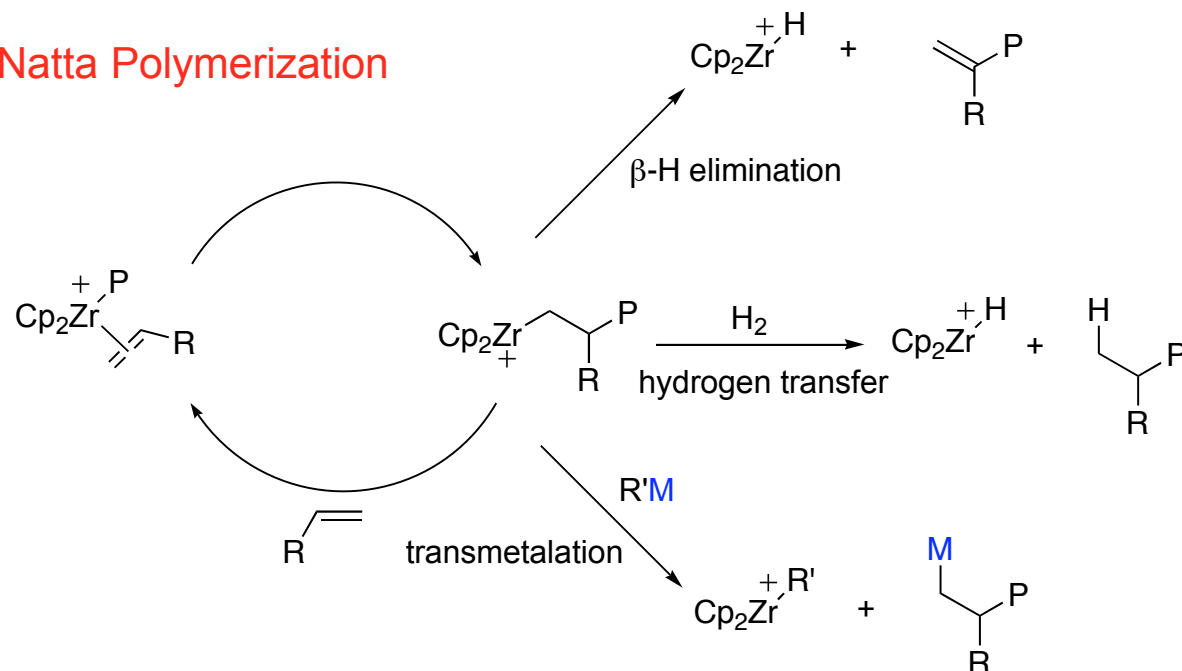


## Catalytic Cycle



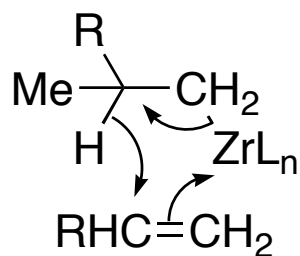
# Competing Reactions

## Ziegler-Natta Polymerization

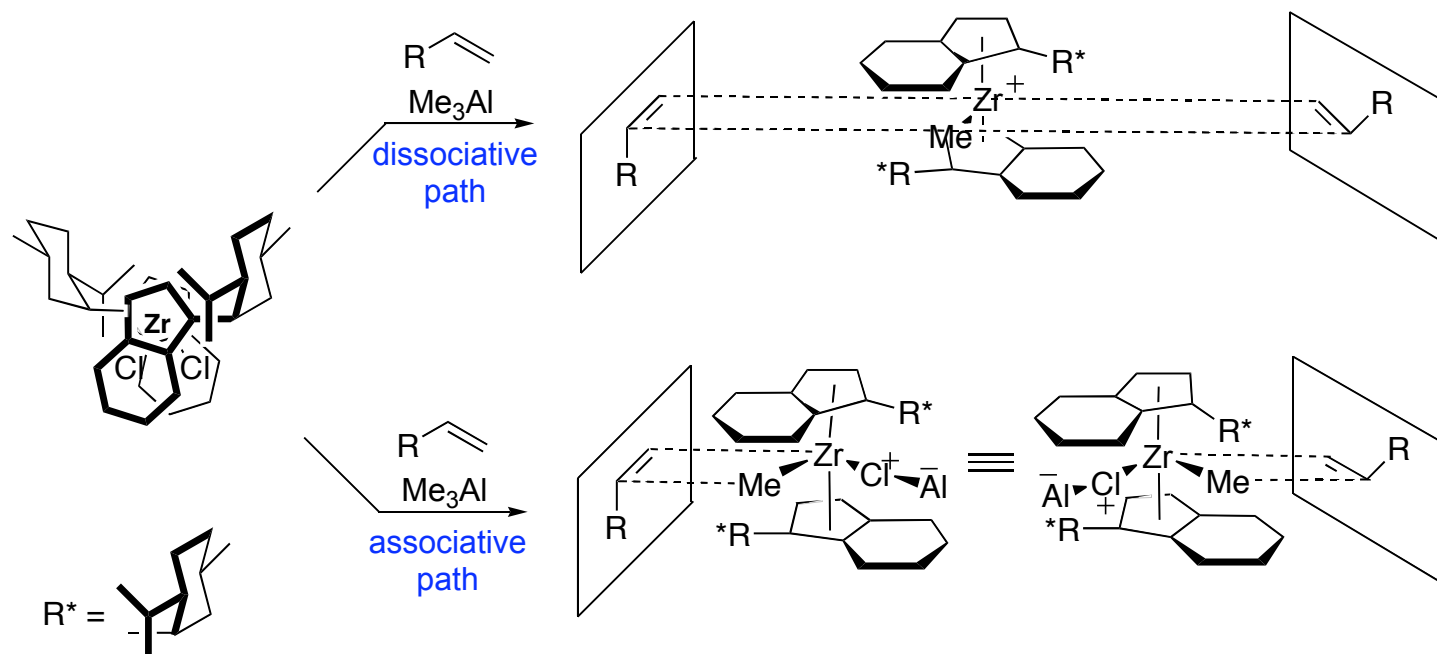


- Polymerization and oligomerization
- $\beta$ -Dehydrometallation leading to Zr-catalyzed hydrometallation
- Zr-catalyzed cyclic carbometallation of alkenes
- Zr-centered carbometallation *vs.* Al- or other metal-centered carbometallation

# Mechanism



- The use of bulky ligands in  $(\text{NM})_2\text{ZrCl}_2$  or NMI is responsible for suppressing  $\beta$ -H transfer hydroalumination.
- Polymerization is minimized with the use of one equiv. or less of alkene relative to the alkylalane reagent.

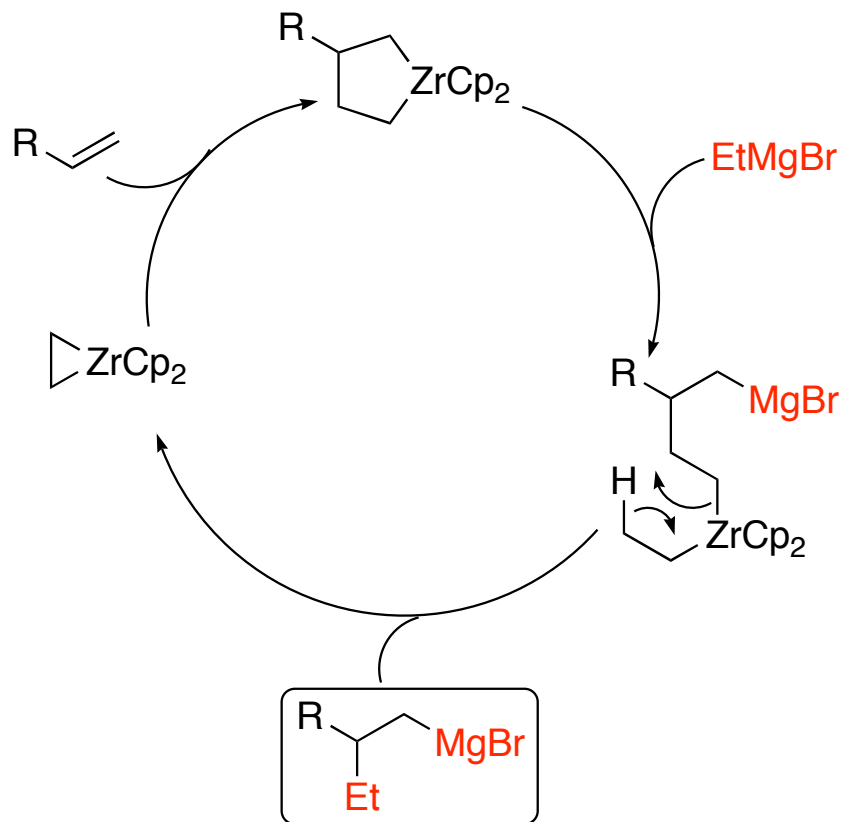


Negishi, E. In *Catalytic Asymmetric Synthesis*, Ojima (Ed), **2000**, p.165

# Mechanisms of Carboalumination and related reactions

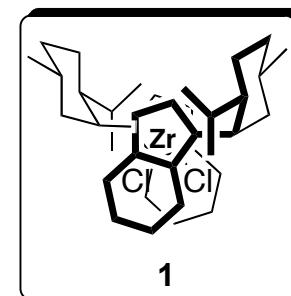
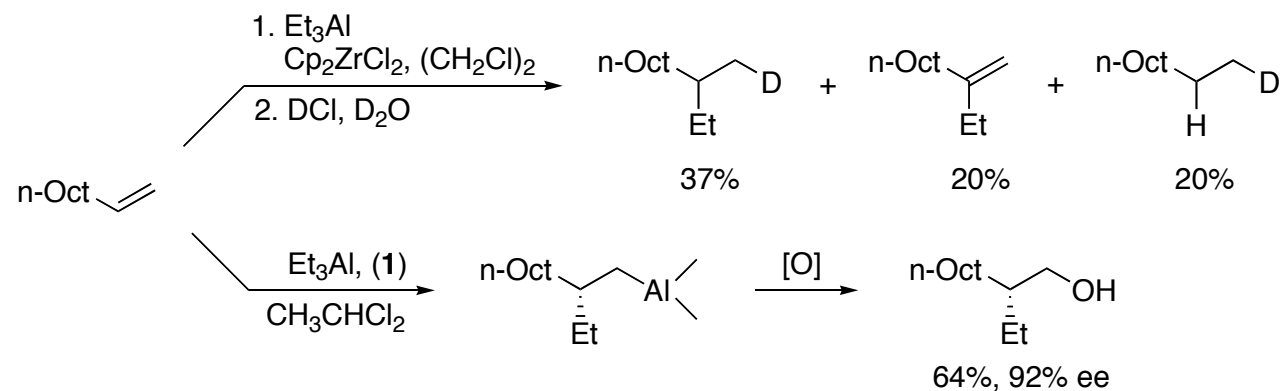
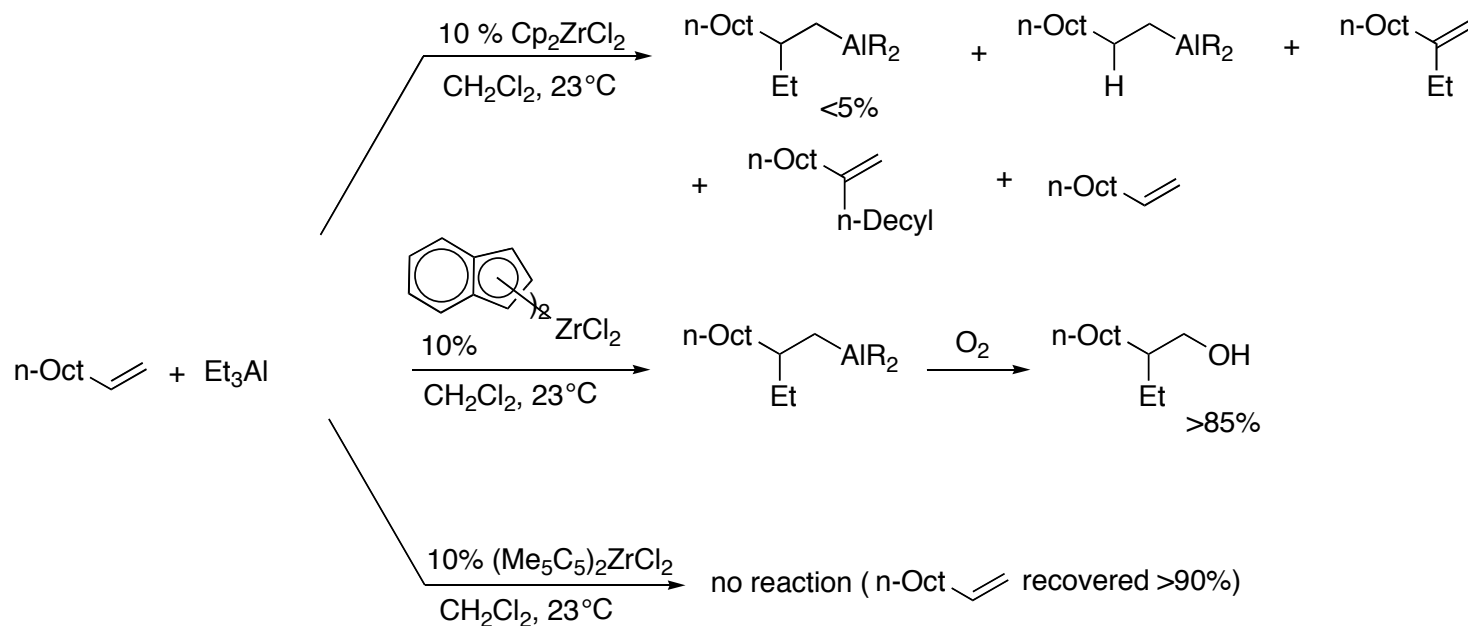
Mode	Monometallic	Bimetallic
Acyclic	Not known with alkylzirconiums (with possible exceptions, e.g., allylzirconation)	$\text{R}^1\text{C}\equiv\text{CH} \xrightarrow[\text{(Negishi, 1978)}]{\text{R}^2\text{AlX}_2/\text{Cl}_2\text{ZrCp}_2} \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^2 \end{array} \begin{array}{c} \text{H} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{AlX}_2 \end{array}$
Cyclic	<ul style="list-style-type: none"> <li>• Dzhemilev ethylmagnesiumation (1983)</li> <li>• Mechanism clarified by Negishi-Takahashi (1991)</li> </ul> $\text{R}-\text{CH}=\text{CH}_2 \xrightarrow[\text{cat. Cl}_2\text{ZrCp}_2]{\text{EtMgBr}} \text{R}-\text{CH}(\text{Et})-\text{CH}_2\text{MgBr}$	<ul style="list-style-type: none"> <li>• Negishi Zr-Catalyzed Ethyl- and higher alkylaluminumation (1978)</li> <li>• Mechanism clarified by Negishi (1996)</li> </ul> $\text{RC}\equiv\text{CR} \xrightarrow[\text{cat. Cl}_2\text{ZrCp}_2]{\text{Et}_3\text{Al}} \begin{array}{c} \text{R} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{Et} \end{array} \begin{array}{c} \text{R} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{AlX}_2 \end{array}$
Competitive Hydrometallation	<ul style="list-style-type: none"> <li>• Hydroalumination (Negishi, 1980) and Hydrozirconation (Negishi, 1984)</li> </ul>	<ul style="list-style-type: none"> <li>• Catalyzed by a large number of Lewis-acidic metal complexes (Negishi, 1999)</li> </ul>

# Dzhemilev Ethylmagnesiumation of Alkenes (monometallic cyclic)



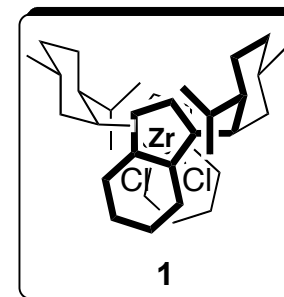
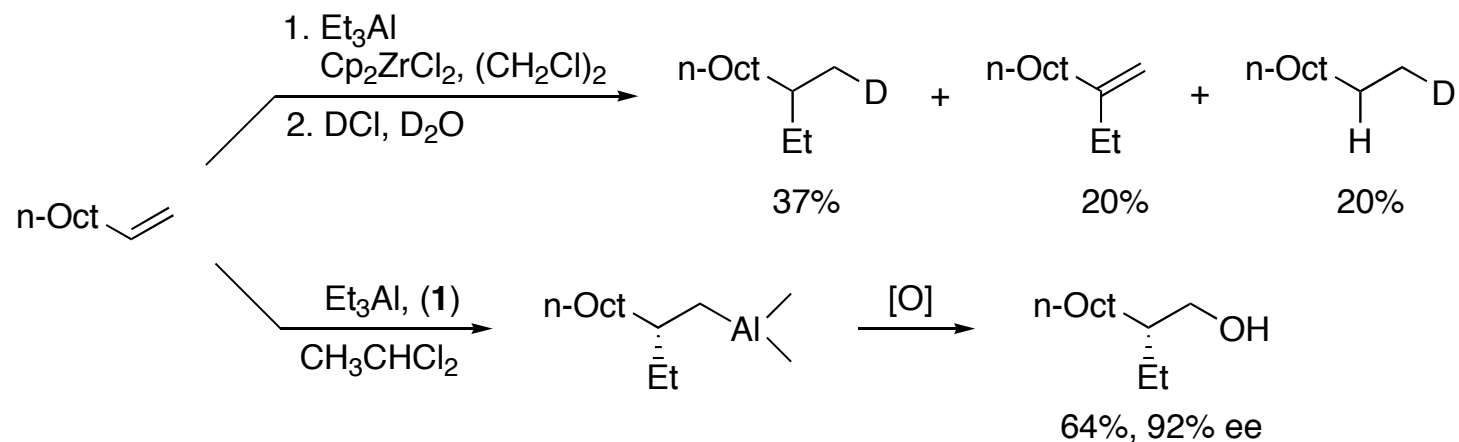
- Reaction failed with methylmagnesium derivatives

# Zr-Catalyzed Enantioselective Ethylaluminumation



Negishi, E., et al. *J. Am. Chem. Soc.* **1996**, *118*, 1577

# Ethyl-alumination of Monosubstituted Alkenes

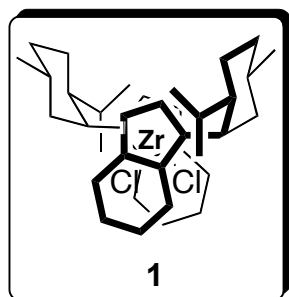
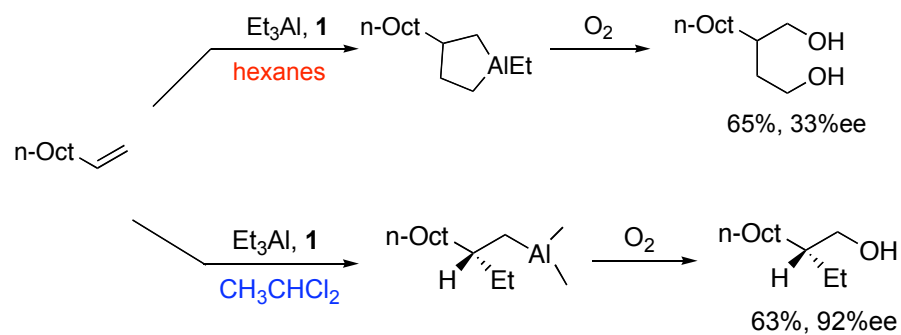


## Enantioselectivity (Methyl vs. Ethyl)

Substrate	Me <sub>3</sub> Al		Et <sub>3</sub> Al	
	Yield, %	% ee	Yield, %	% ee
RCH=CH <sub>2</sub> (R = <i>n</i> -C <sub>4</sub> H <sub>9</sub> , <i>n</i> -C <sub>6</sub> H <sub>13</sub> , <i>n</i> -C <sub>8</sub> H <sub>17</sub> )	88	72	63–75	90–93
<i>i</i> -BuCH=CH <sub>2</sub>	92	74	77	90
PhCH <sub>2</sub> CH=CH <sub>2</sub>	77	70	69	93
<i>c</i> -HexCH=CH <sub>2</sub>	80	65		
HO(CH <sub>2</sub> ) <sub>4</sub> CH=CH <sub>2</sub>	79	75	88	90
Et <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub> CH=CH <sub>2</sub>	68	71	56	95

Negishi, E., et al. *J. Am. Chem. Soc.* **1996**, *118*, 1577; *Pure Appl. Chem.*, **2001**, *73*, 239

## Solvent & Temperature Effect



substrate	R of $\text{R}_3\text{Al}$	solvent	temp °C	time h	quenching agent	product	yield <sup>b</sup> %	%ee
<i>n</i> -Bu-1-ene	Et	$(\text{CH}_2\text{Cl})_2$	25	4	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	65	68
<i>n</i> -Bu-1-ene	Et	$\text{C}_6\text{H}_4\text{-Cl}$	25	4	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	70	68
<i>n</i> -Bu-1-ene	Et	$\text{C}_6\text{H}_3\text{-Cl}_2$	25	4	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	72	67
<i>n</i> -Bu-1-ene	Et	$\text{CH}_2\text{Cl}_2$	25	6	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	57	81
<i>n</i> -Bu-1-ene	Et	$\text{CH}_2\text{Cl}_2$	0	6	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	63	92
<i>n</i> -Bu-1-ene	Et	$\text{CH}_2\text{Cl}_2$	-25	6	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	60	94
<i>n</i> -Bu-1-ene	Et	$\text{CH}_3\text{CHCl}_2$	25	6	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	70	86
<i>n</i> -Bu-1-ene	Et	$\text{CH}_3\text{CHCl}_2$	0	24	$\text{O}_2$	<i>n</i> -Bu-1,2-diol	74	93
<i>n</i> -Oct-1-ene	Et	$\text{CH}_3\text{CHCl}_2$	0	12	$\text{O}_2$	<i>n</i> -Oct-1,2-diol	64	92
<i>i</i> -Bu-1-ene	Et	$\text{CH}_3\text{CHCl}_2$	0	24	$\text{O}_2$	<i>i</i> -Bu-1,2-diol	77	90
Ph-1-ene	Et	$\text{CH}_3\text{CHCl}_2$	0	24	$\text{O}_2$	Ph-1,2-diol	69	93
$\text{HO}(\text{CH}_2)_4$ -1-ene	Et <sup>c</sup>	$\text{CH}_3\text{CHCl}_2$	10	24	HCl	$\text{HO}(\text{CH}_2)_4$ -1,2-diol	88	90
$\text{Et}_2\text{N}(\text{CH}_2)_3$ -1-ene	Et <sup>d</sup>	$\text{CH}_3\text{CHCl}_2$	25	72	$\text{O}_2$	$\text{Et}_2\text{N}(\text{CH}_2)_3$ -1,2-diol	56	95
$\text{Me}_2\text{Si}(\text{Me})_2$ -1-ene	Et	$\text{CH}_3\text{CHCl}_2$	0	24	$\text{O}_2$	$\text{Me}_2\text{Si}(\text{Me})_2$ -1,2-diol	66	96
$\text{HO}(\text{CH}_2)_4$ -1-ene	<i>n</i> -Pr <sup>f</sup>	$\text{CH}_3\text{CHCl}_2$	10	24	HCl	$\text{HO}(\text{CH}_2)_4$ -1,2-diol	90	91
<i>n</i> -Oct-1-ene	<i>n</i> -Pr	$\text{CH}_3\text{CHCl}_2$	0	12	$\text{O}_2$	<i>n</i> -Oct-1,2-diol	62	91
<i>n</i> -Pr-1-ene	<i>n</i> -Oct	$\text{CH}_3\text{CHCl}_2$	0	12	$\text{O}_2$	<i>n</i> -Pr-1,2-diol	59	85

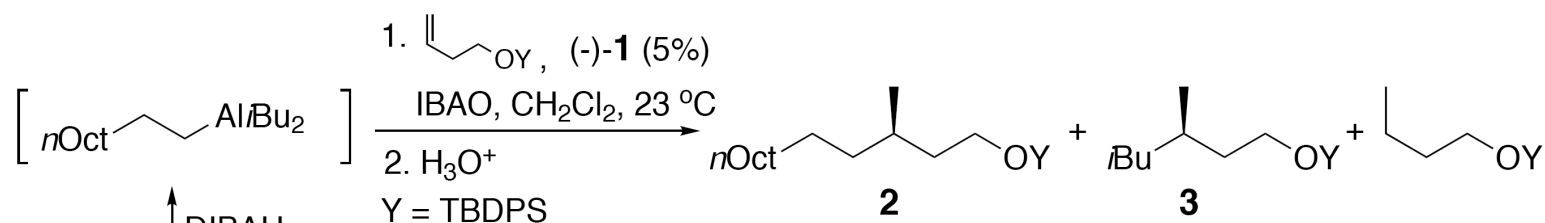
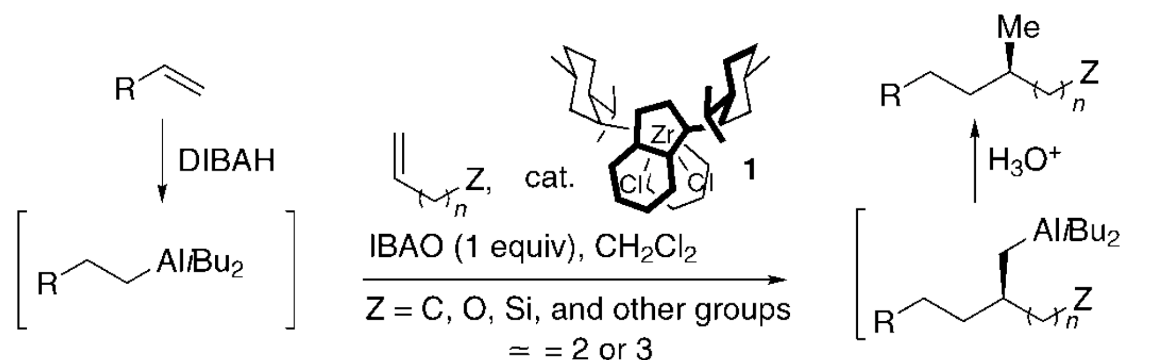
Negishi, E., et al. *J. Am. Chem. Soc.* **1996**, *118*, 1577

Juan Arredondo @ Wipf Group



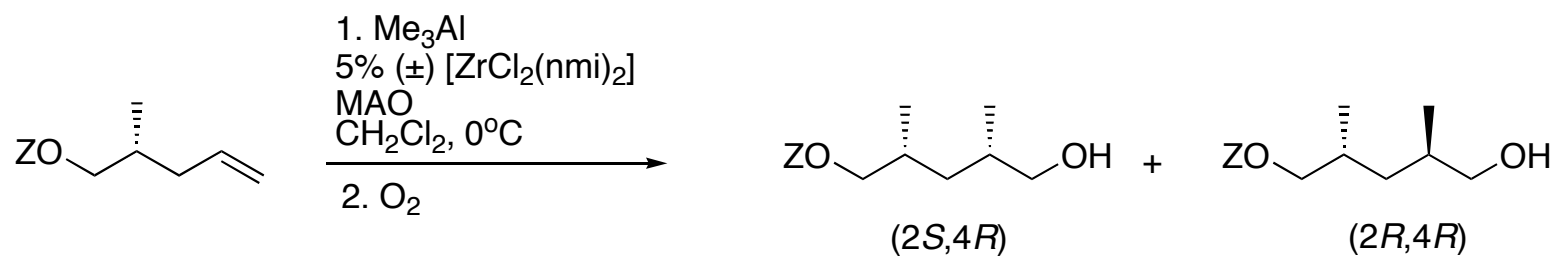
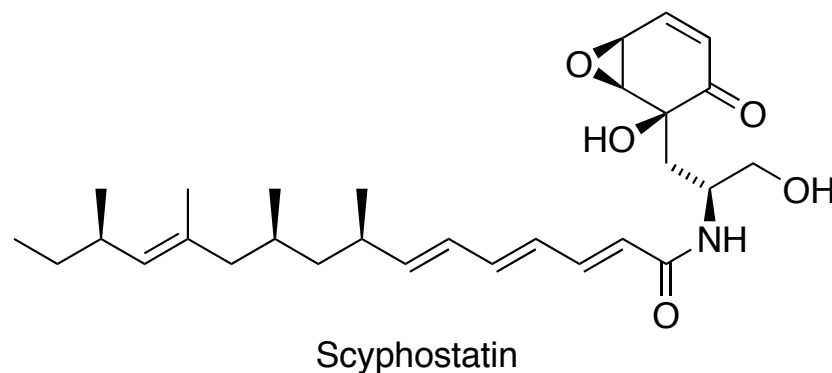
# Synthetic Applications

## Hydrometallation/Alkylaluminumation Tandem Process



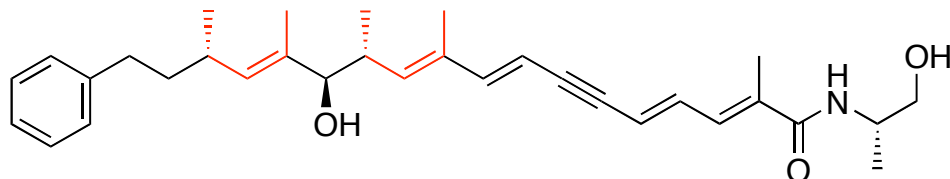
IBAO [equiv]	t [h]	<b>2</b> [%] (ee [%])	<b>3</b> [%]	nBuOY [%]
1.0	3	84 (91)	trace	16
0	48	80 (90)	trace	15

# Synthetic Applications



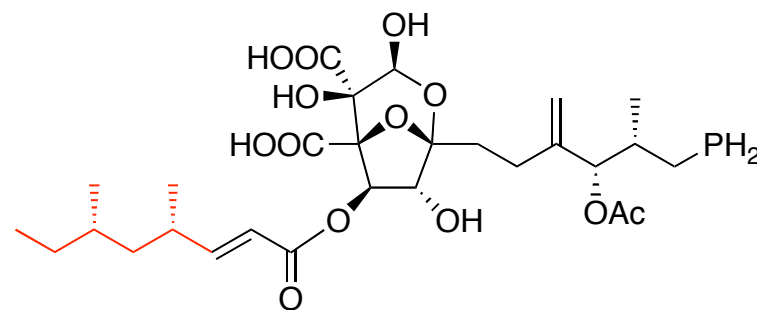
Z	[ZrCl <sub>2</sub> (nmi) <sub>2</sub> ]	Combined yield [%] <sup>[a]</sup>	2 <i>S</i> ,4 <i>R</i> /2 <i>R</i> ,4 <i>R</i> before chromatography <sup>[b]</sup>
TBS	(+)	75	13/1
TBS	(-)	72	1/8
TBDPS	(+)	82	10/1
TBDPS	(-)	81	1/10

# Synthetic Applications

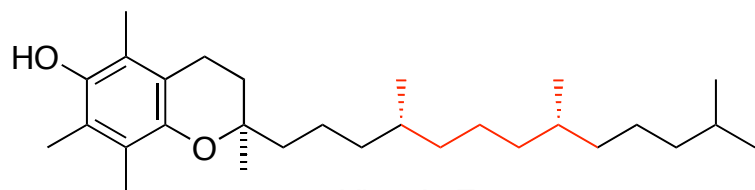


6,7-dehydrostipiamide

Negishi, E. *et al. Org. Lett.* **2004**, 6, 1425

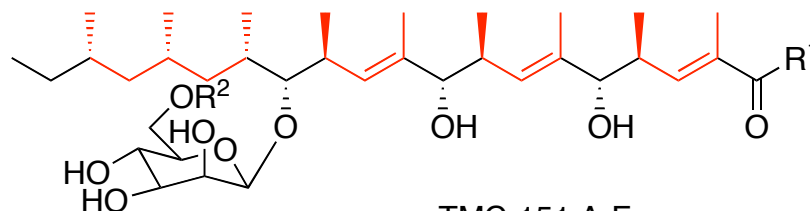


Zaragozic Acid A



Vitamin E

Negishi, E. *et al. Org. Lett.* **2001**, 3, 3253

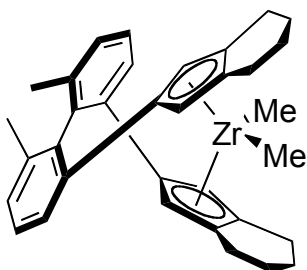
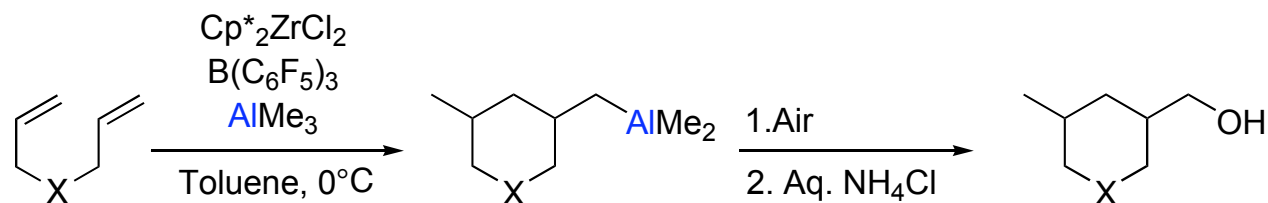


TMC-151 A-F

$R^1 = C_6H_8(OH)_5$   
or  
 $C_5H_7O(OH)_4$   
 $R^2 = H$  or  $Ac$

Negishi, E. *et al. PNAS*, **2004**, 43, 5782

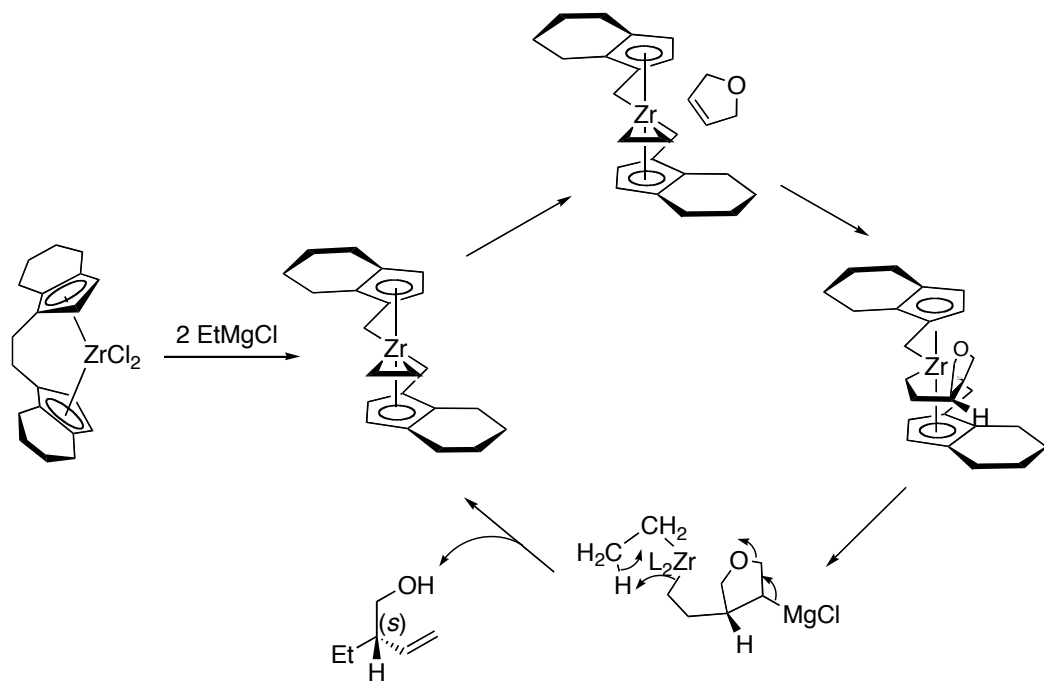
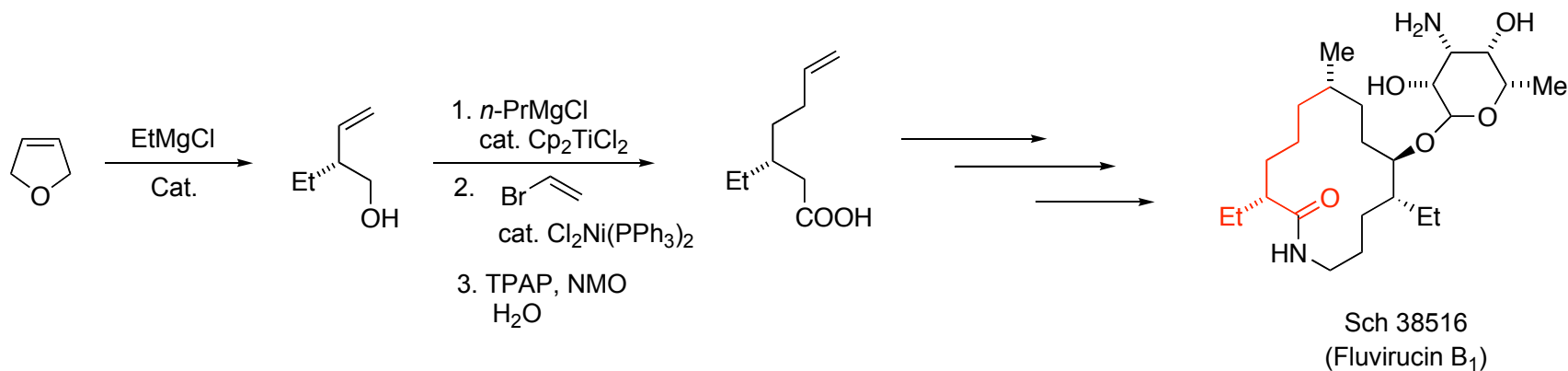
# Carbometallation of $\alpha,\omega$ -Dienes



- Chlorinated solvents (DCM, DCE) Improved reaction rates.
- Mechanism not fully understood, perhaps a cationic process.

Olefin	Product	% Yield	Selectivity
		62	66 % trans
		67	68% trans
		78	70% cis
		63	55 %ee
		78	66 %ee
		58	63 % ee
		53	53 % ee

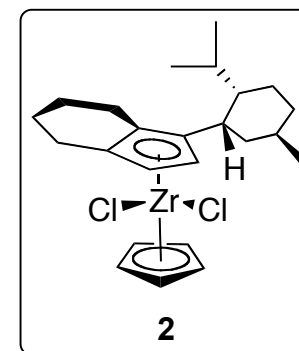
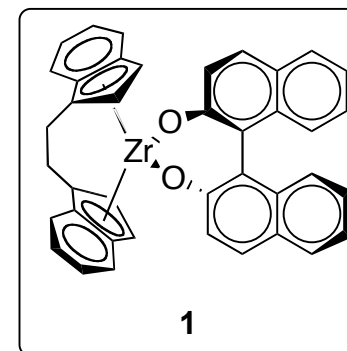
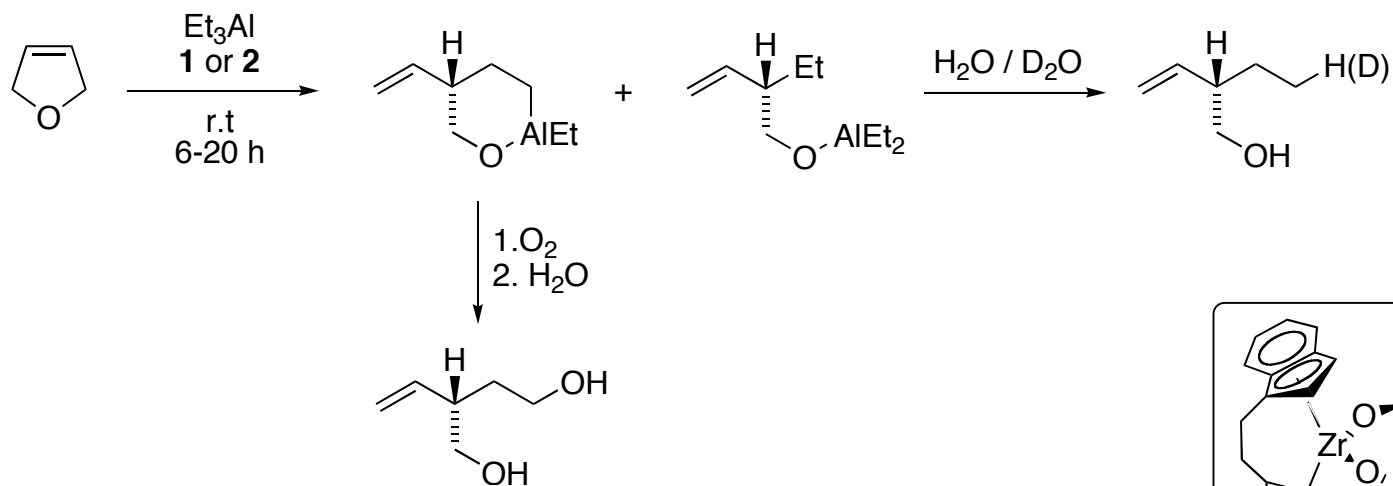
# Carbomagnesation-Elimination Of Cyclic Alkenes



Substrate	R of RMgCl	Product	Yield, %	% ee
	Et		65	>97
	Et		75	>95
	Et		73	95
	Et		75	92
	<i>n</i> -Pr, <i>n</i> -Bu		35-40	>95

Hoveyda A. et al. *J. Am. Chem. Soc.* **1993**, *115*, 6997  
*J. Am. Chem. Soc.* **1995**, *117*, 2943

# Carboalumination-Elimination Tandem Reaction of Allylic Derivatives

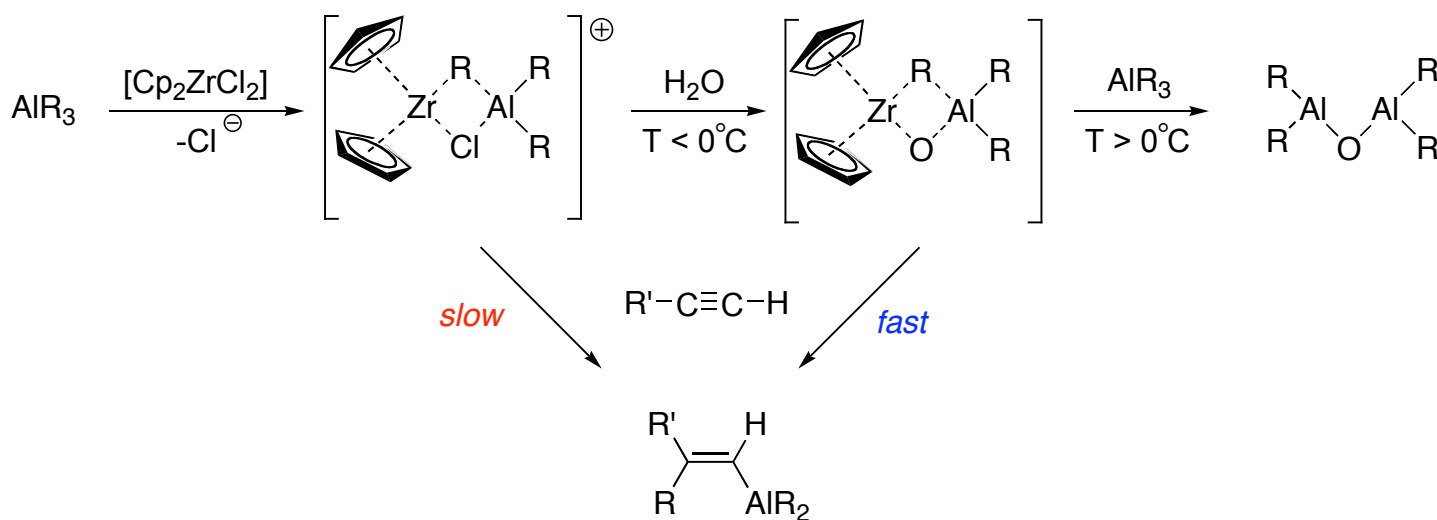
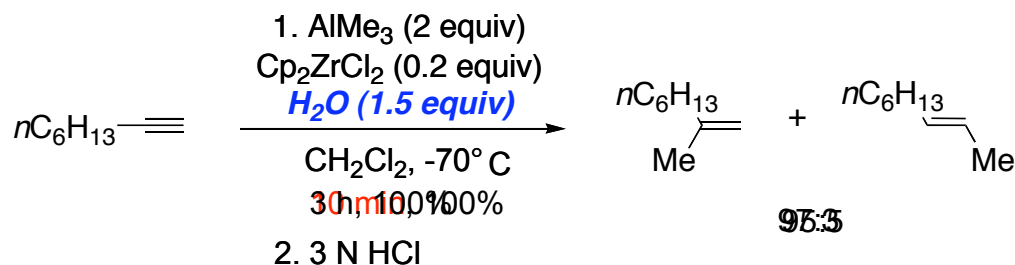


R	EtM	Cat.	$\text{E}^+$	Solvent	% Yield	% ee
NHPh	EtMgCl	<b>2</b>	MeSSMe	$\text{Et}_2\text{O}$	90	81
NHPh	$\text{Et}_2\text{Mg}$	<b>2</b>	MeSSMe	THF	95	75
NHPh	$\text{Et}_2\text{Mg}$	<b>1</b>	MeSSMe	THF	39	26
NHCy	EtMgCl	<b>2</b>	MeSSMe	$\text{Et}_2\text{O}$	87	83
SPh	$\text{Et}_3\text{Al}$	<b>2</b>	$\text{H}_2\text{O}$	hexane	76	64
OH	$\text{Et}_2\text{Mg}$	<b>2</b>	$\text{H}_2\text{O}$	THF	75	56
OH	$\text{Et}_2\text{Mg}$	<b>1</b>	$\text{H}_2\text{O}$	THF	27	27

Whitby, R., *et al. Tetrahedron Lett.* **1997**, *38*, 2335; *Tetrahedron Lett.* **1998**, *54*, 14617

# Wipf Group Contributions

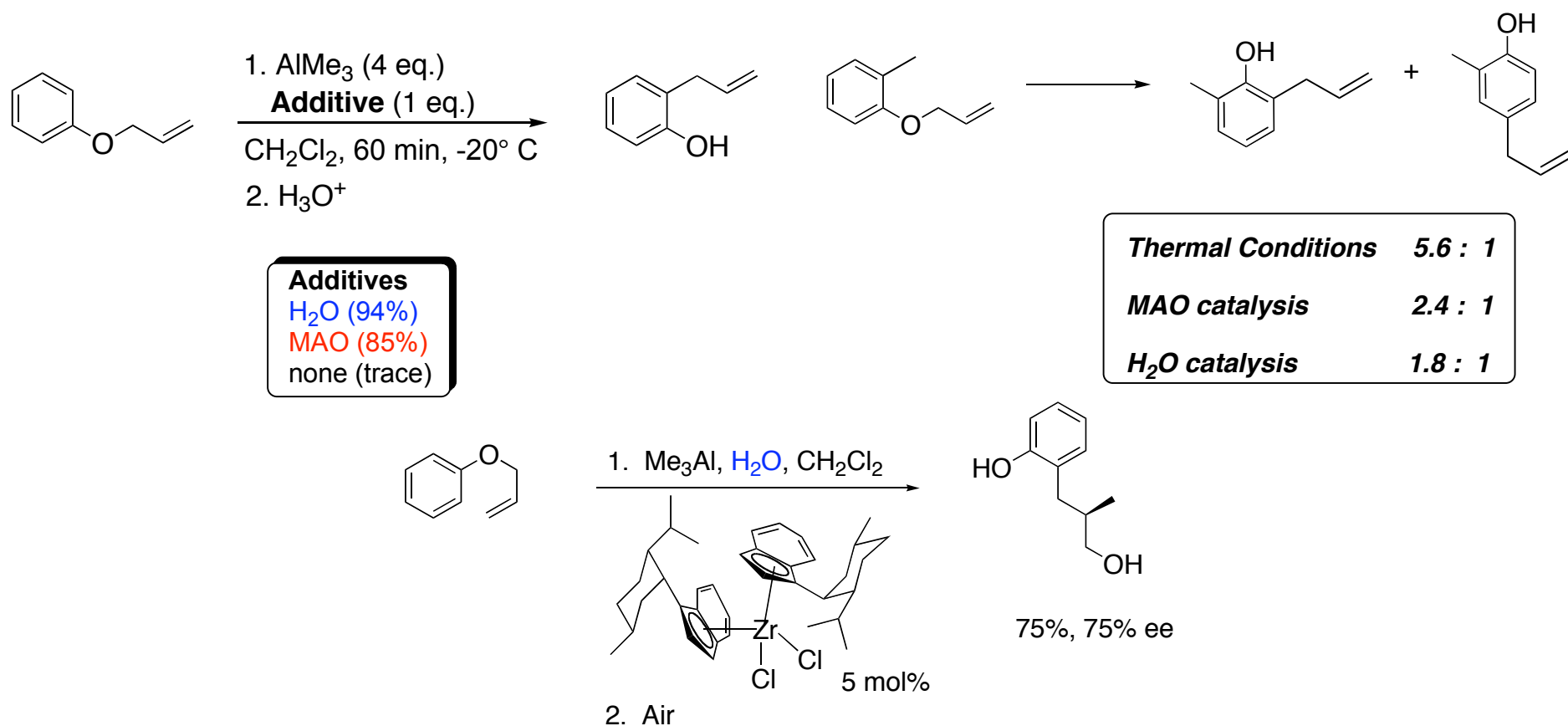
## Water-Accelerated Carboalumination





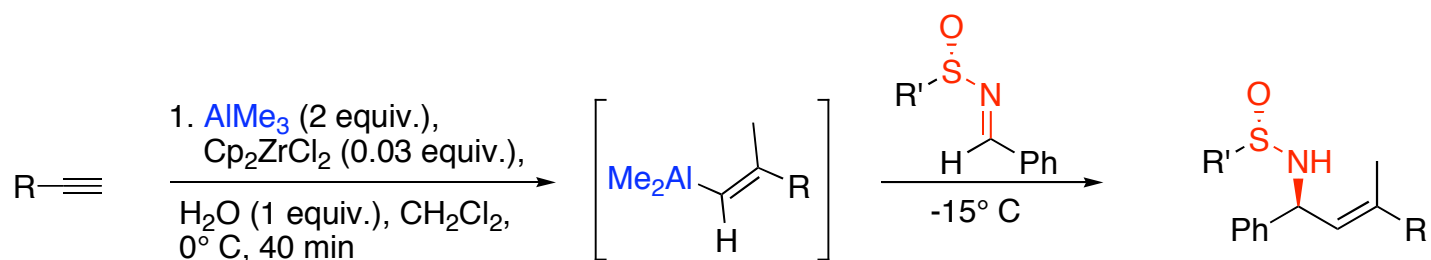


## Tandem Claisen Rearrangement-Asymmetric Carboalumination



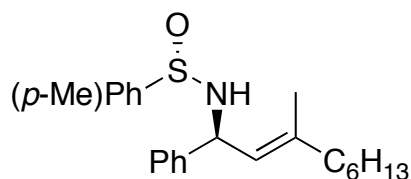
- Significant improvement in regioselectivity in favor of the *para*-Claisen product was observed.
- Mechanism origin is attributed to a transient strong Lewis acid related, but not identical to MAO. Structure of active species remains to be elucidated.

## ■ Sulfinimine Addition and Asymmetric Synthesis of Allylic Amines

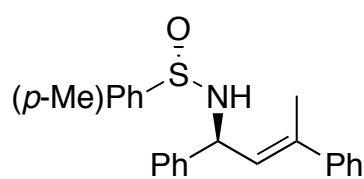


R = C<sub>6</sub>H<sub>13</sub>, Ph, *t*-Bu, Bu  
TIPSO(CH<sub>2</sub>)<sub>3</sub>

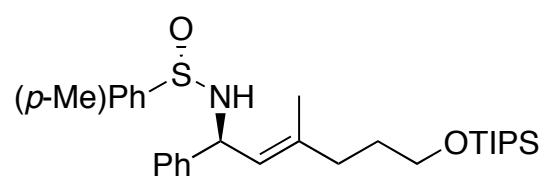
R' = (*R*) OR (*S*)(*p*-Me)Ph,  
(*t*-Bu)Ph



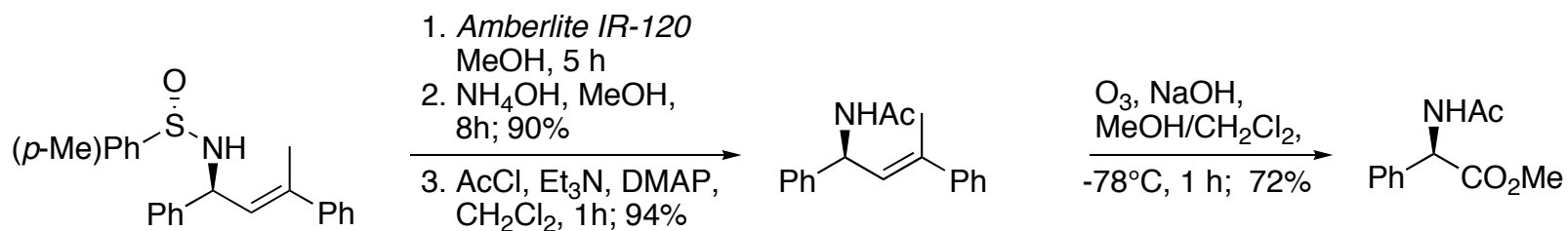
80%, 90% de



76%, 90% de



75%, 78% de



“...further optimization, especially with respect to chiral zirconocene catalyst, is desirable, ...”

Negishi, E. In *Catalytic Asymmetric Synthesis*, Ojima (Ed), **2000**, p. 170, Wiley, New York

“Further improvements in % ee will depend on the development of more effective zirconocene catalyst”

Wipf et al. *Org. Lett.* **2001**, 3, 1503

