

# Lewis Acids In Free Radical Reactions

## Outline

- I. Early efforts to control stereochemistry in acyclic radical reactions
- II. Nucleophilic Radical Reactions
  - a. Conjugate addition reactions.
  - b. Reactions of oximes, imines, and hydrazones.
- III. Electrophilic Radical Reactions
  - a. Allylation and Reduction
  - b. Atom-Transfer Reactions
  - c. Mn(III)-Initiated Cyclizations

## Reviews

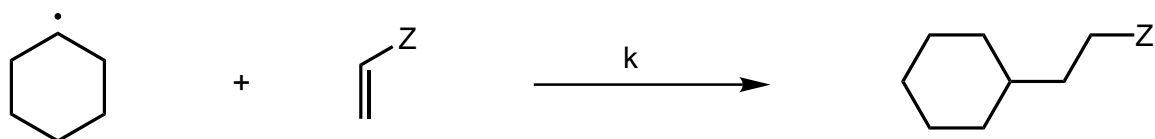
Renaud and Gerster *ACIEE* **1998**, 37, 2562

Sibi and Porter *Acc. Chem. Res.* **1999**, 32, 163

Zachary Sweeney  
Evans Group Seminar  
February 23, 2001

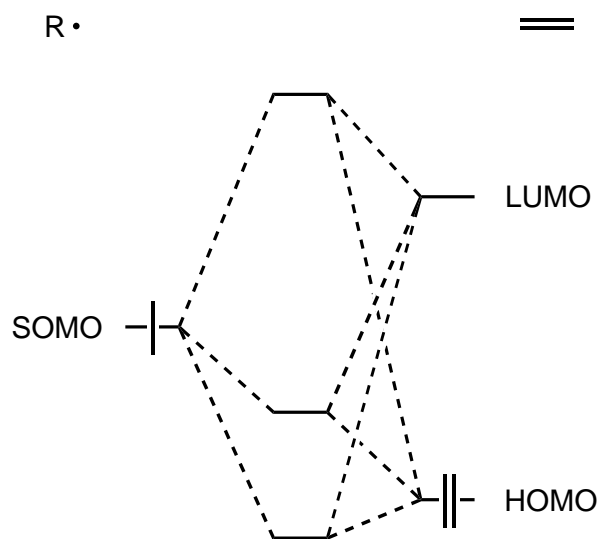
# Formation of CC Bonds By Addition of Radicals to Alkenes

- Simple alkyl radicals are nucleophilic



- Alkenes are attacked almost exclusively at the terminal position of the alkene.

Z	$k_{rel}$
CHO	34
CO <sub>2</sub> CH <sub>3</sub>	6.7
C <sub>6</sub> H <sub>6</sub>	1.0
<sup>n</sup> C <sub>4</sub> H <sub>9</sub>	0.0004

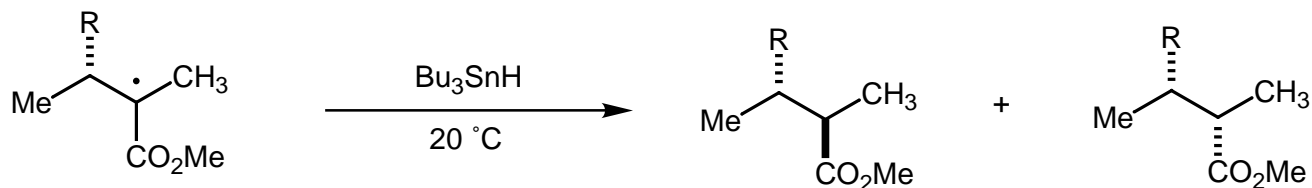


- Reactions are strongly exothermic since a  $\sigma$ -bond is formed and a  $\pi$ -bond is broken.
- According to FMO theory, raising the energy of the SOMO (increasing SOMO-LUMO interactions) will increase the rate of reactions.
- Electrophilic radicals react with electron-rich alkenes. In this case the SOMO-HOMO interaction is dominant.

Giese, ACIEE, 1983, 753.

# Allylic Strain Effects in Radical Reactions

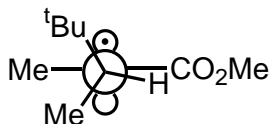
- Enolate Radical Chemistry



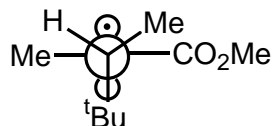
- Calculations and EPR studies suggest planar enolate conformation arising from conjugation of the radical with the ester functionality.

R	<i>anti</i> : <i>syn</i>
<sup>t</sup> Bu	25 : 1
TMS <sub>3</sub> Si	16 : 1
Ph	2 : 1

## Ground States

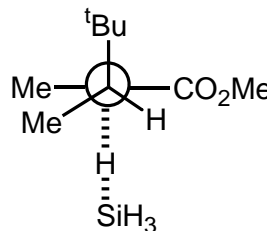


A-strain conformation  
E = 0.0 kcal/mol

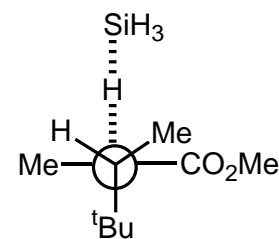


Felkin-Anh conformation  
E = 1.5 kcal/mol

## Transition States



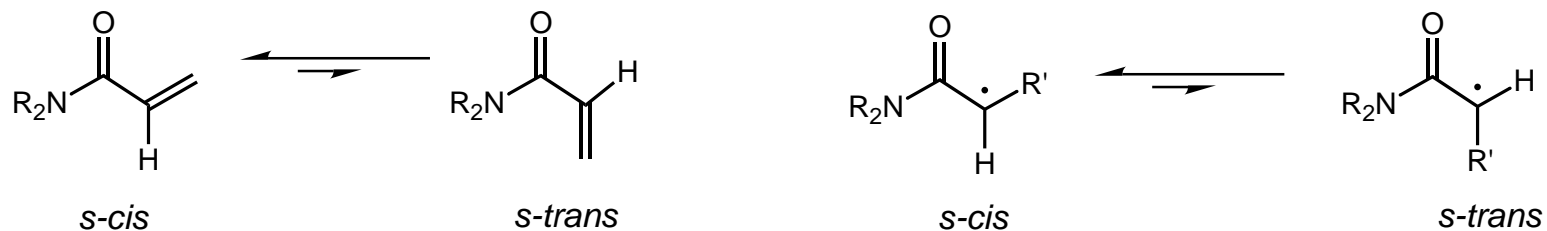
E = 0.0 kcal/mol  
(*anti* product)



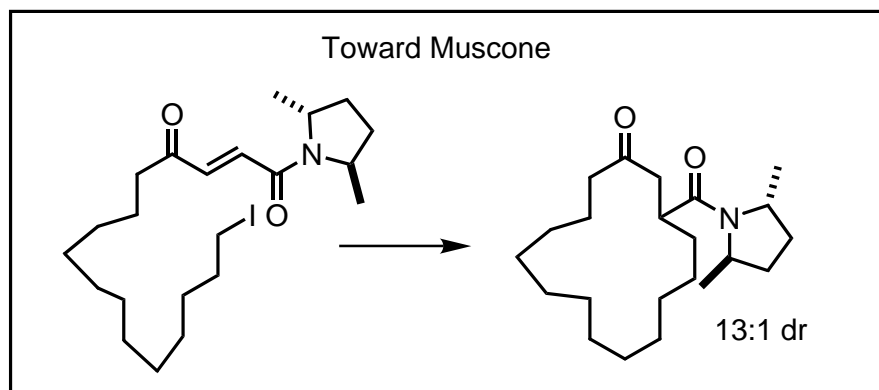
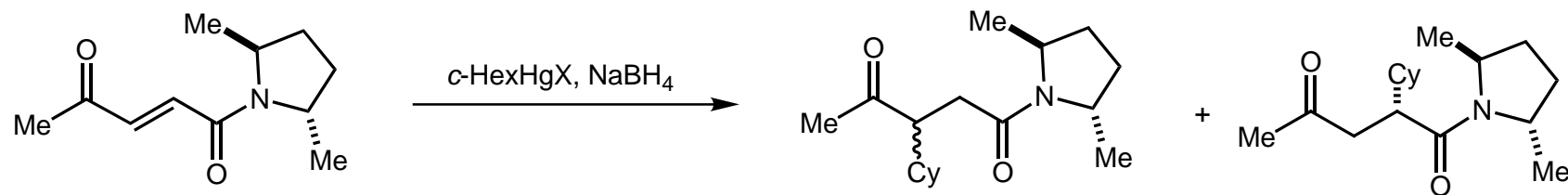
E = 2.7 kcal/mol  
(*syn* product)

## Early Efforts Toward Acyclic Stereochemical Control

- Amide groups were used to provide conformational control.



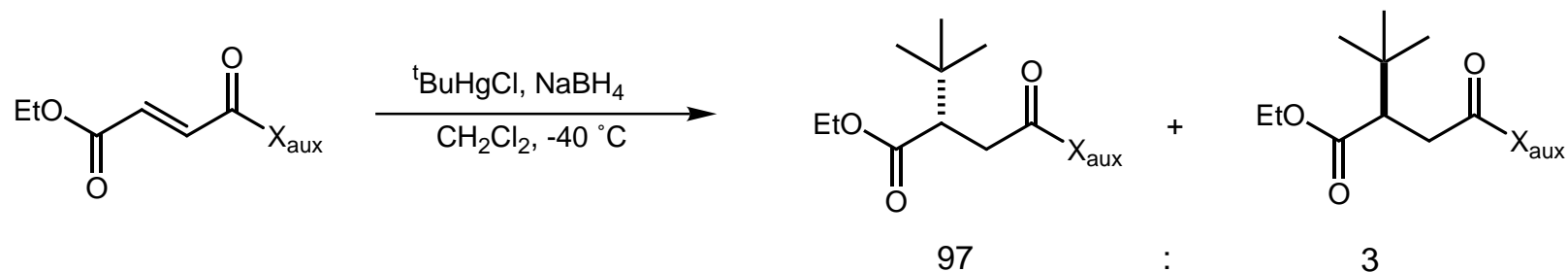
- $\text{C}_2$ -symmetric auxiliaries or dipole-dipole effects were used to fix the orientation of the auxiliary.



Porter, JACS, 1989, 111, 8309, 8311.

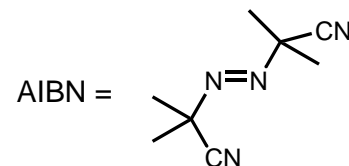
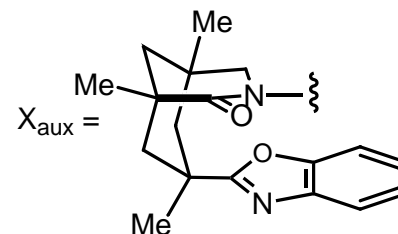
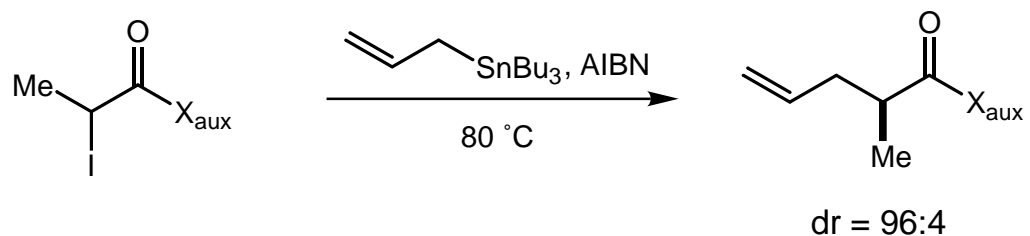
## Early Efforts Toward Auxiliary-Based Control

- Curran, Rebek- auxiliary that can control  $\beta$ -stereoselectivity

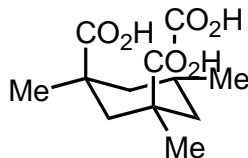


- No  $\alpha$ -addition was observed under these conditions

- The auxiliary was also effective for radical allylation reactions.



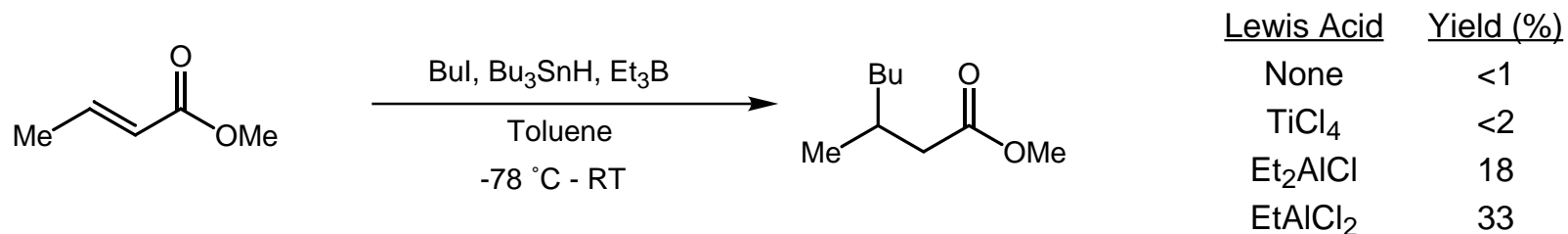
- Auxiliary Synthesized in 7 steps from



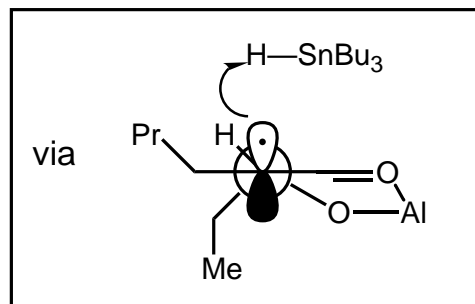
Curran, Rebek, JACS, 1992, 114, 7007.

# Lewis Acid-Enhanced Reactivity of Unsaturated Esters and Amides

- Lewis acids increase yields of conjugate additions



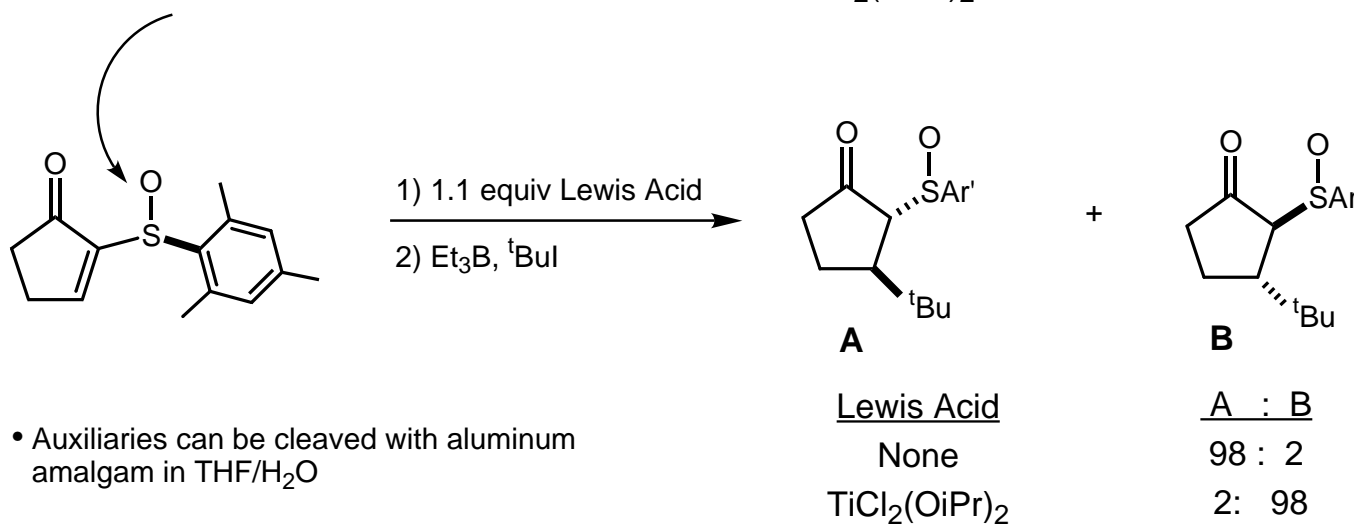
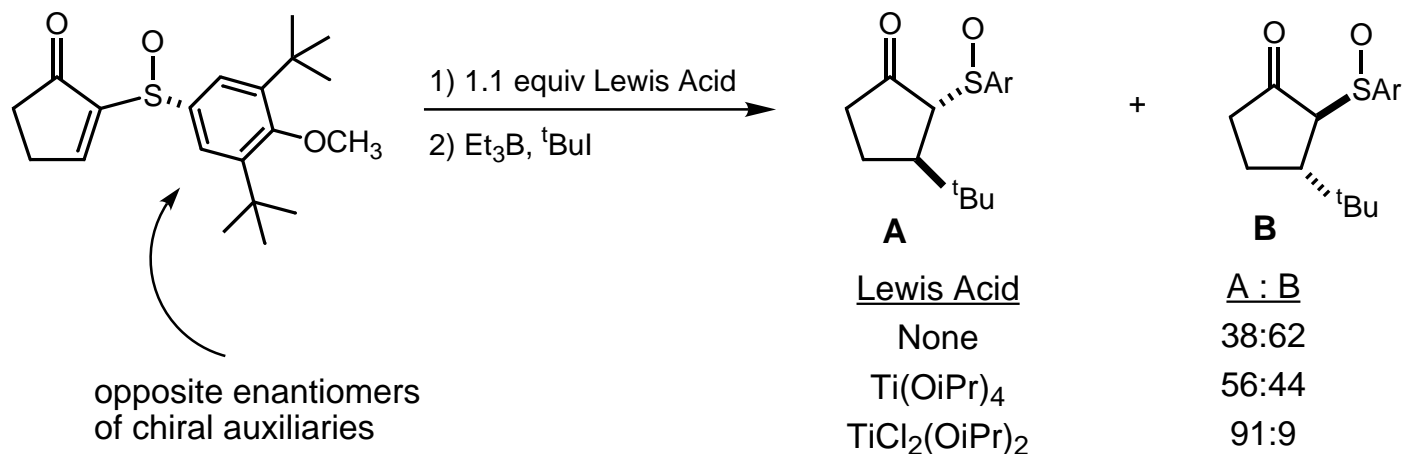
- Chelate control



<u>Lewis Acid</u>	<u>Yield</u>	<u>syn:anti</u>
None	34	65:35
Et <sub>2</sub> AlCl	76	87:13

Sato, F. J. Org. Chem., 1995, 60, 3576.

# Asymmetric Radical Addition to $\alpha$ -Sulfinylcyclopentenones

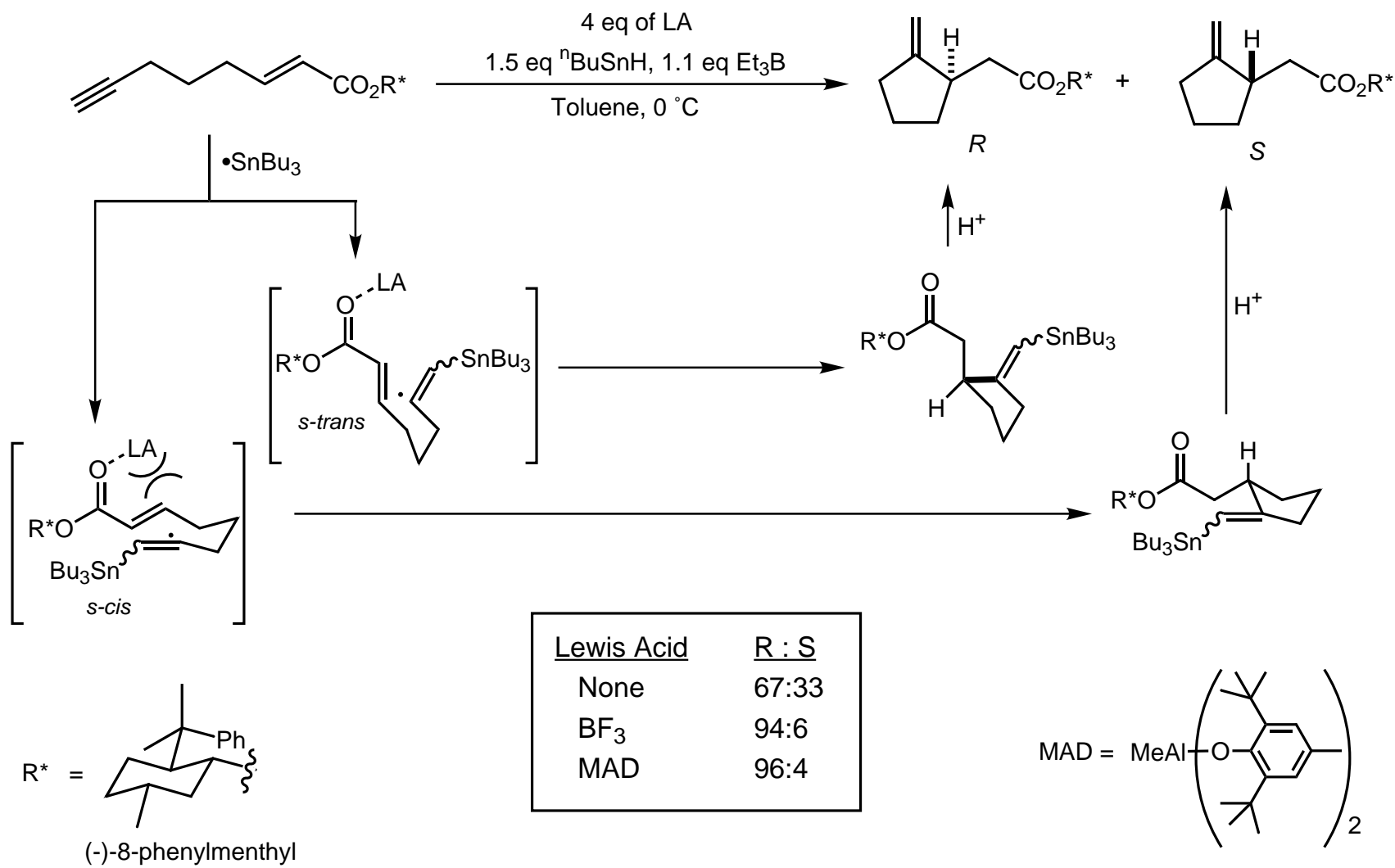


Toru, JACS, 1993, 10464.

Toru, JOC, 1997, 7794

# Lewis Acid Promoted Diastereoselective Radical Cyclization

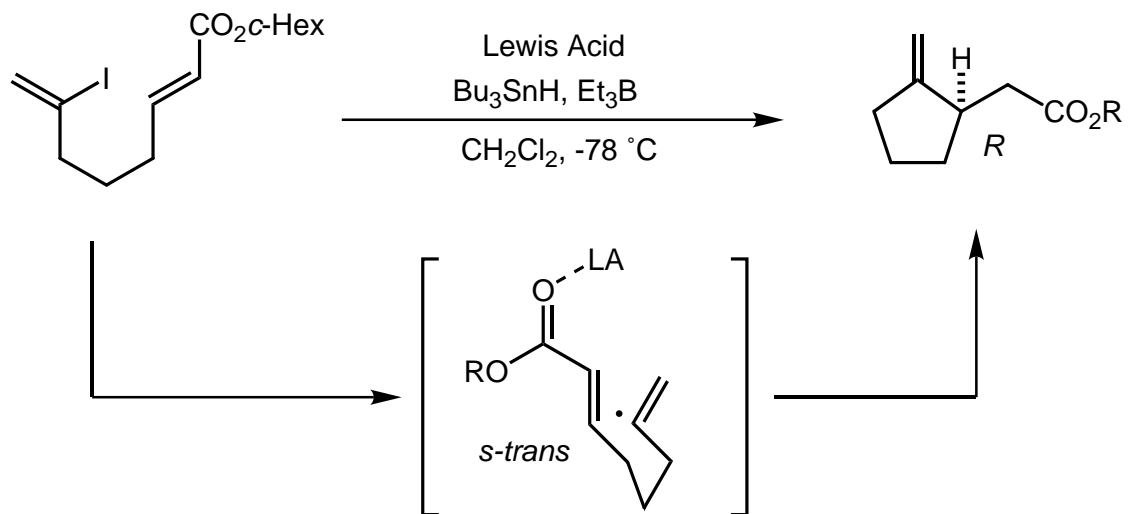
- Coordination of the Lewis acid controls *s-cis/s-trans* conformation of ester



Nishida, JACS, 1994, 6455.

# Enantioselective Lewis Acid Promoted Radical Cyclization

- First report of chiral Lewis Acid mediated radical cyclization

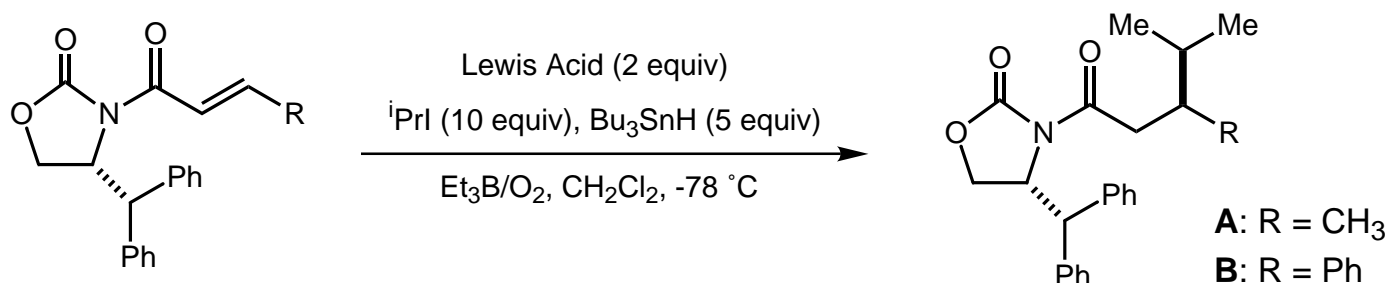


<u>Lewis Acid</u>	<u>equiv</u>	<u>ee (%)</u>
(Binol)AlMe	1	2
	1	12
	4	36

- Reactions using the same Lewis Acid and the Weinreb amide provide the *S*-product in 26% ee.

Nishida, Chem. Commun., 1996, 579.

## Lewis Acid Catalyzed Intermolecular Radical Additions

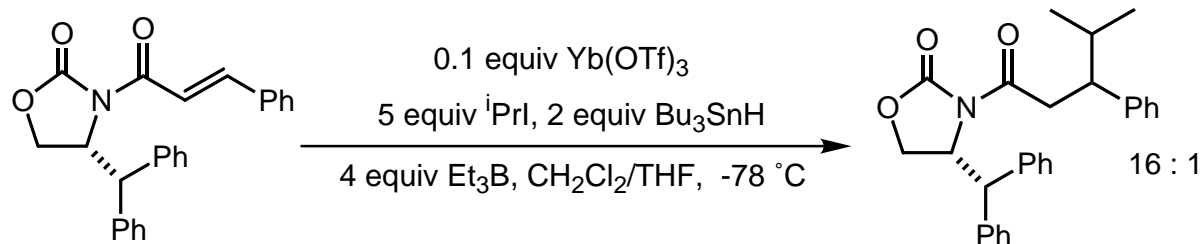


Substrate	Lewis Acid	Yield (%)	dr
<b>A</b>	None	60	1.3:1
<b>A</b>	BF <sub>3</sub> •OEt <sub>2</sub>	80	1.3:1
<b>A</b>	Et <sub>2</sub> AlCl	70	4:1
<b>A</b>	Sc(OTf) <sub>3</sub>	90	15:1
<b>A</b>	Yb(OTf) <sub>3</sub>	93	25:1
<b>B</b>	Yb(OTf) <sub>3</sub>	89	45:1

- Very strong Lewis Acids (i.e. TiCl<sub>4</sub>) gave products of hydride reduction.

- Reactions using TMS<sub>3</sub>SiH failed.

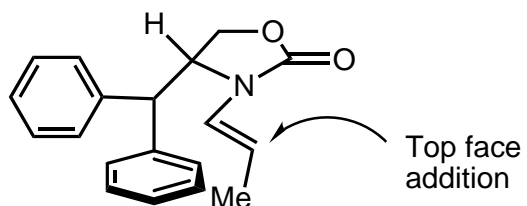
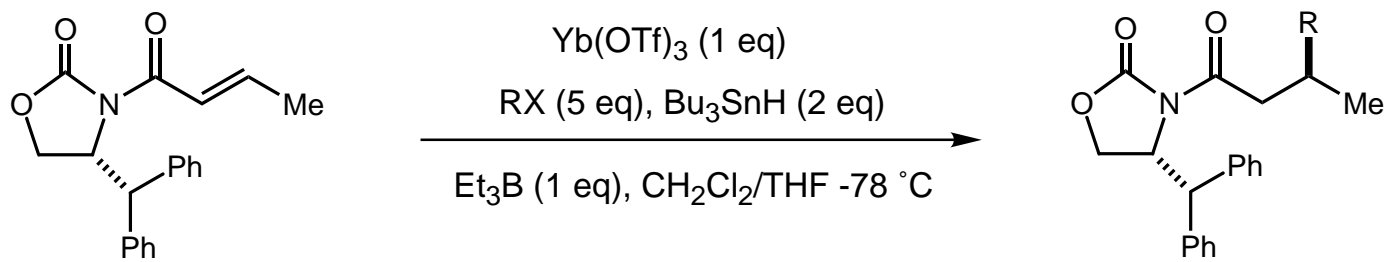
### Optimized Reaction Employing Catalytic Lewis Acid



- dr increased to 23:1 with 0.1 equiv ethylene glycol

Sibi, JACS, 1995, 10779.  
 Sibi, JACS, 1999, 7517.

## Diastereoselective Radical Addition: Effect of the Nucleophile

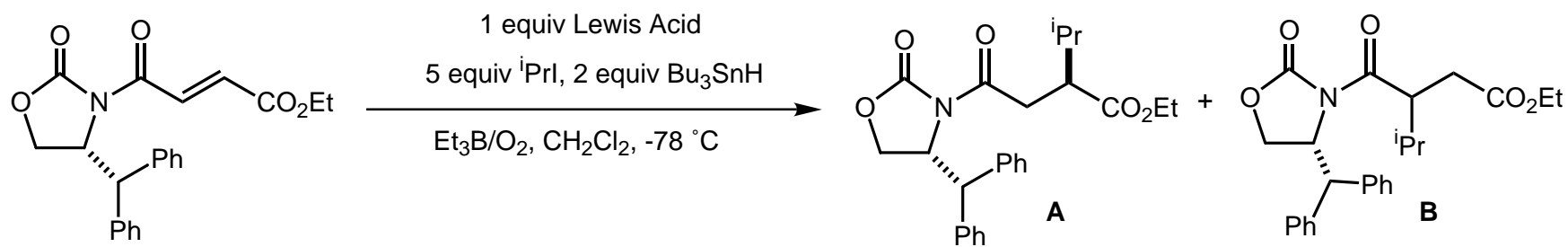


<u>RX</u>	<u>Yield (%)</u>	<u>dr</u>
<sup>i</sup> PrI	90	25:1
<sup>i</sup> PrBr	90	25:1
EtI	84	12:1
<sup>c</sup> HexI	92	16:1
<sup>t</sup> Bul	82	14:1
MeOCH <sub>2</sub> Br	84	14:1
MeC(O)Br	85	7:1

- Low yields were observed with PhI, MeI, PhCH<sub>2</sub>I, AllylI, AcOCH<sub>2</sub>Br, and BrCH<sub>2</sub>CO<sub>2</sub>Bn.

Sibi, JACS, 1999, 7517

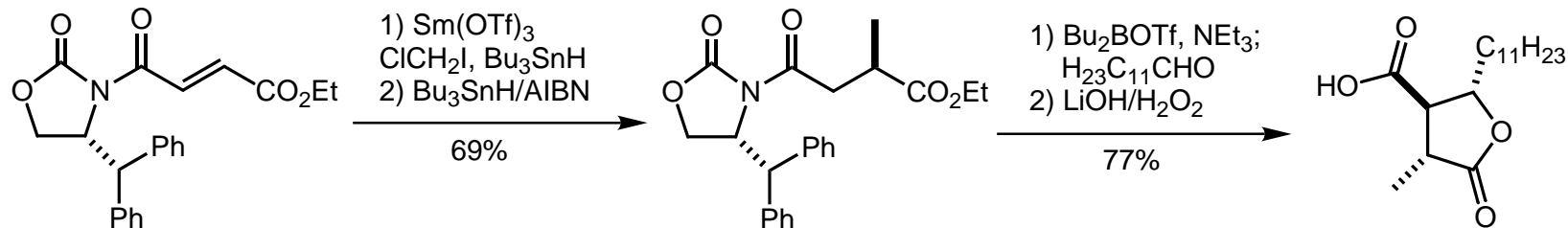
## Intermolecular Additions to Fumarate Derivatives



- All yields > 90%, many lanthanides function well.
- Stoichiometric LA required for high dr, although regioselectivity is still high.

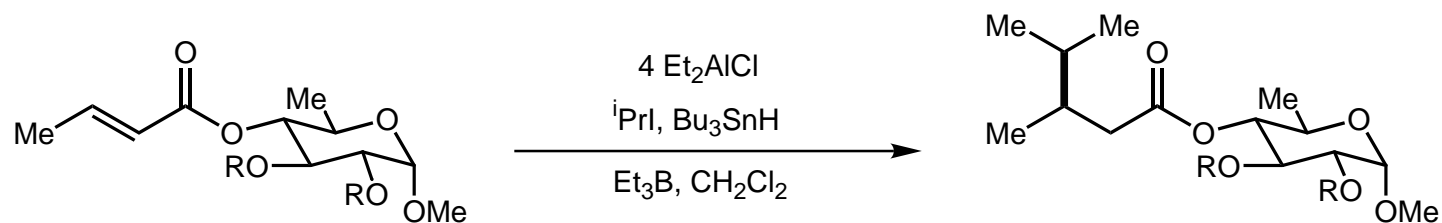
<u>LA</u>	<u>A : B</u>	<u>dr A</u>
None	1.6 : 1	11 : 1
$\text{BF}_3 \cdot \text{OEt}_2$	1.2 : 1	9 : 1
$\text{Er}(\text{OTf})_3$	71 : 1	>100 : 1

### Synthesis of Nephosteranic Acid:



Sibi, ACIEE, 1997, 274

## $\alpha$ -D-Glucopyranoside Derivatives as Auxiliaries

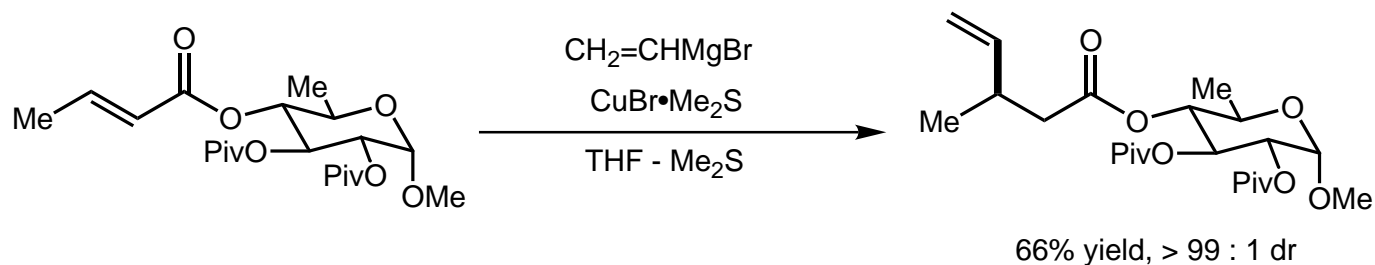


- When no LA was used, the product was racemic.
- Lower selectivity was observed with 1 equiv of  $\text{Et}_2\text{AlCl}$ .

R	Yield (%)	dr
Piv	84	92:8
MesC(O)	100	95:5
TBS	98	90:10

Tadano, Synlett, 2000, 979

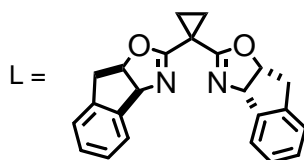
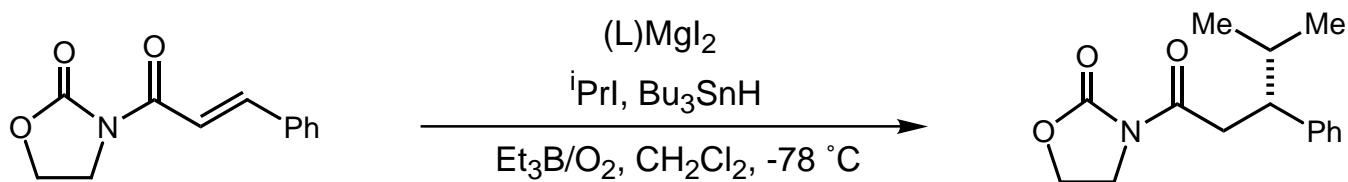
### Analogous Cuprate Additions:



Tadano, Org. Lett., 1999, 1447.



## Improved Selectivity using (Indabox)MgI<sub>2</sub> Complexes

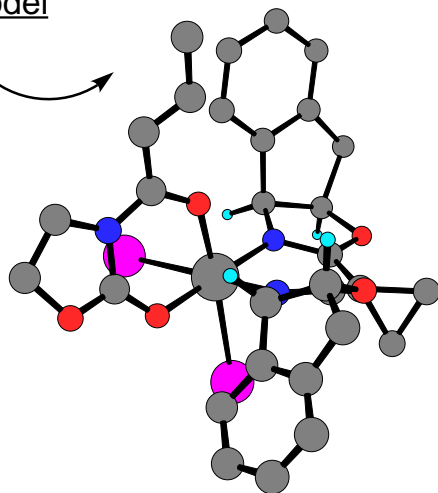


<u>Eq LA</u>	<u>Yield</u>	<u>ee</u>
1	88	93
0.2	95	96
0.05	92	90

- Other ligand backbone rings gave lower enantioselectivities (Bu = 82% ee, Pent = 82% ee).
- No other reactions were reported.

### Model

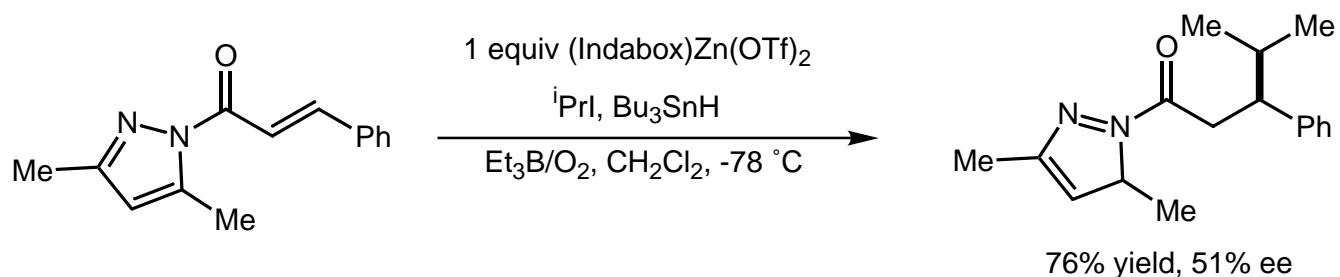
Attack from front face



- Authors suggest an octahedral model with *cis*-iodine ligands.
- This model provides the same selectivity that is predicted from a four-coordinate tetrahedral metal-substrate complex.

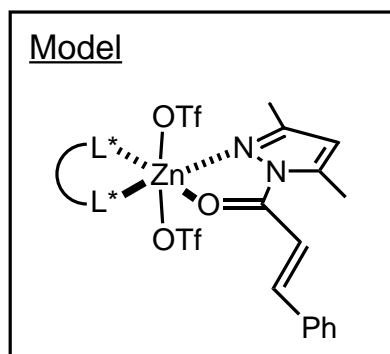
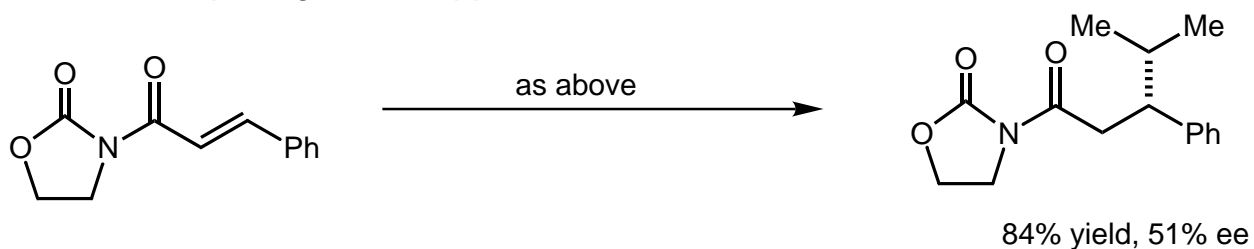
Sibi, JOC, 1997, 3800

## The Pyrazole Template in Radical Conjugate Additions



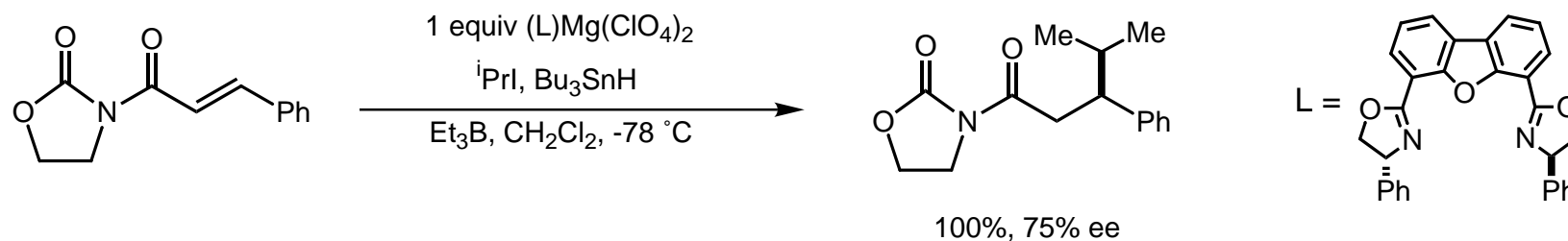
- Reactions with other Mg(II), Zn(II) salts were unselective.
- Unsubstituted pyrazoles gave low yields

An oxazolidinone template gave the opposite enantiomer



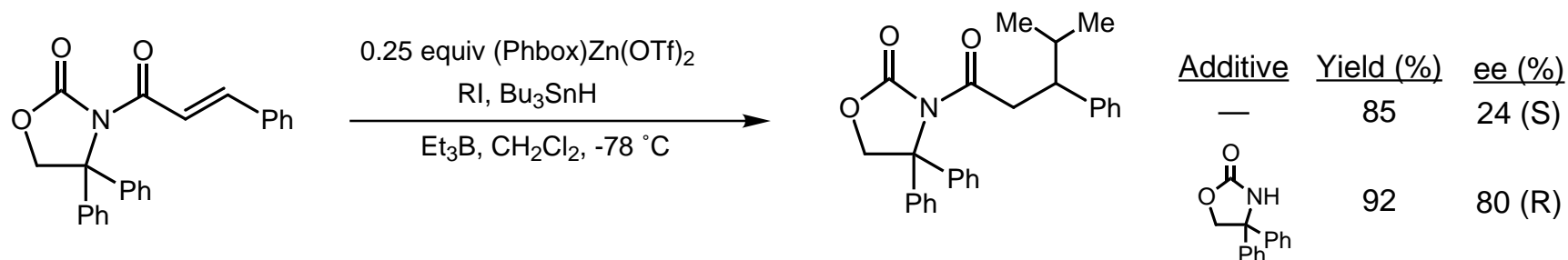
Sibi, Tett. Lett., 1997, 5955

## Other Conjugate Radical Addition Reactions



- Almost 30 Lewis Acids were screened.

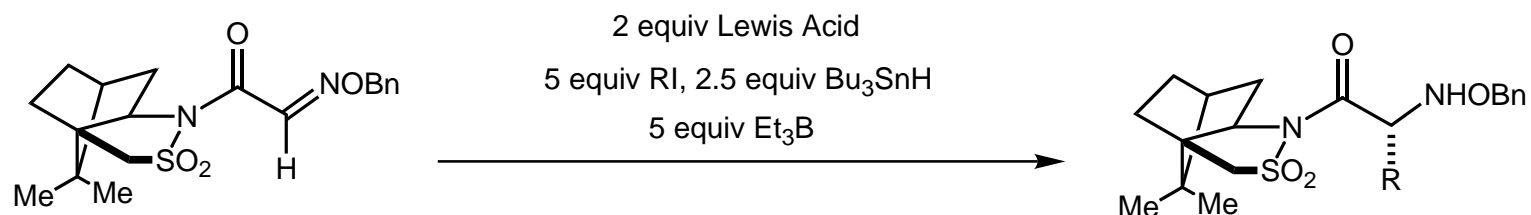
Kanemasa, Curran, *Tetrahedron: Asym.*, 1999, 2417



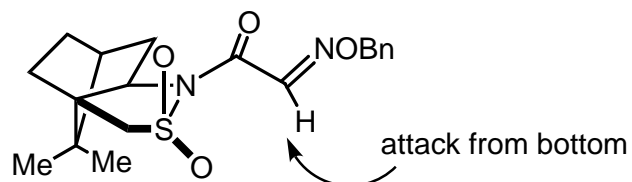
- Additive was shown to compete with substrate for coordination to the zinc center.

Murakata, Hoshino, *Org. Lett.*, 2001, 299

## Carbon Radical Addition to Glyoxylic Oxime Ethers

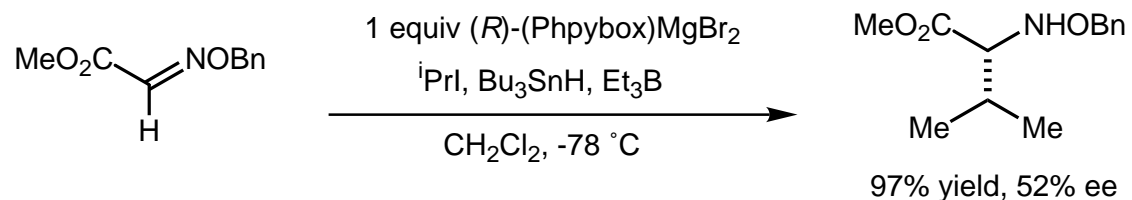


- configuration of substrate is controlled by dipole and steric interactions
- reaction was also run without Bu<sub>3</sub>SnH



Lewis Acid	Yield (%)	dr
—	73	96 : 4
BF <sub>3</sub> •OEt <sub>2</sub>	80	96 : 4
Et <sub>2</sub> AlCl	57	90 : 10
Zn(OTf) <sub>2</sub>	73	94 : 6
Yb(OTf) <sub>3</sub>	72	92 : 8

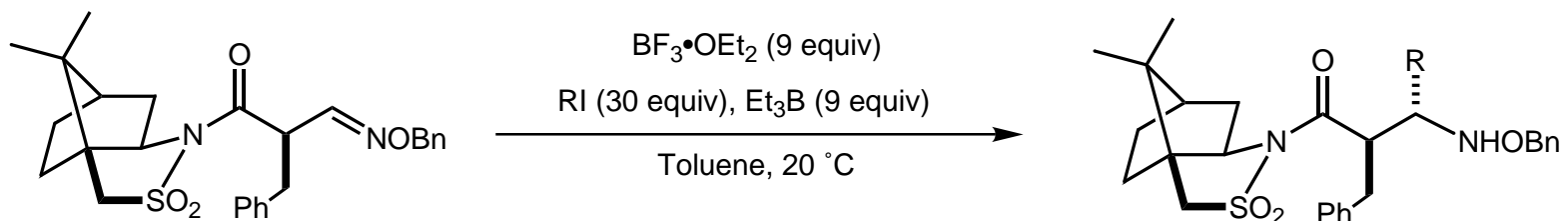
### Chiral Lewis Acid promoted additions



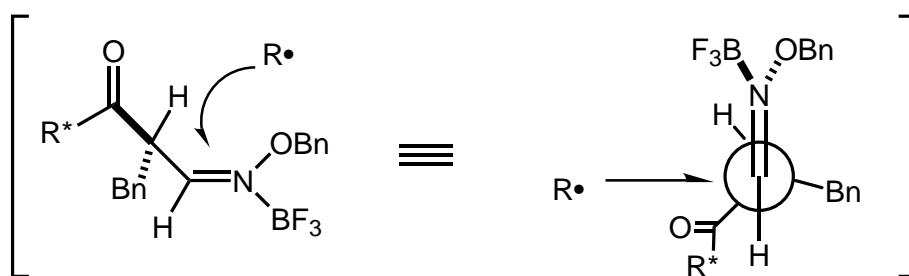
- For reactions on solid phase see Naito, Org. Lett., 2000, 1443

Naito, JOC, 2000, 176

## Radical Addition to Oxime Ethers: $\beta$ -Amino Acids

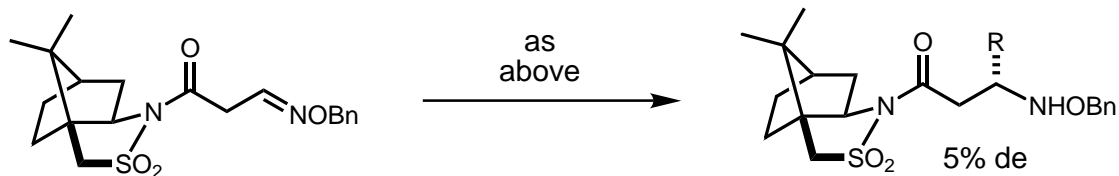


• no reaction occurred in the absence of  $\text{BF}_3 \cdot \text{OEt}_2$



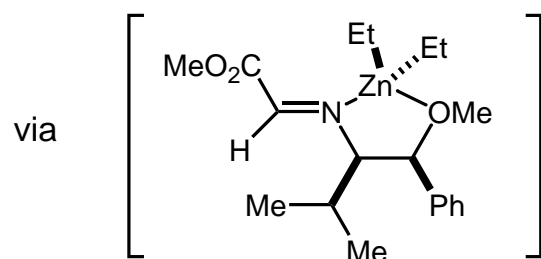
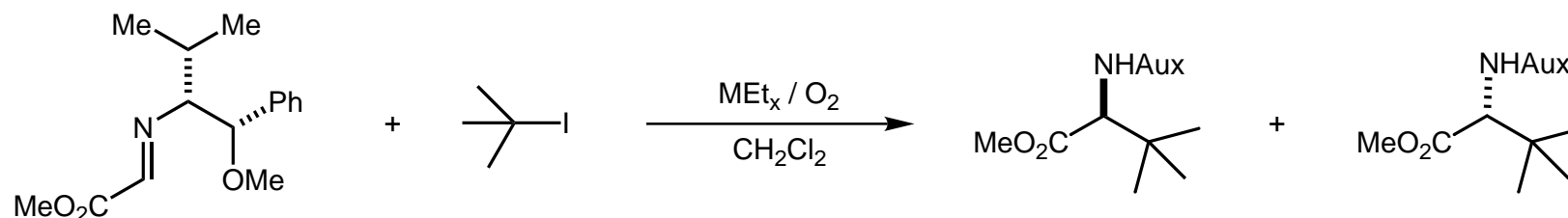
R	Yield (%)	dr
<sup>i</sup> Pr	70	>95 : 5
<sup>c</sup> Hexyl	57	>95 : 5
<sup>c</sup> Pentyl	59	>95 : 5
<sup>s</sup> Bu	50	>95 : 5
<sup>i</sup> Bu	20	>95 : 5

$\alpha$ -Substituent required for good selectivity



Naito, Org. Lett., 1999, 569

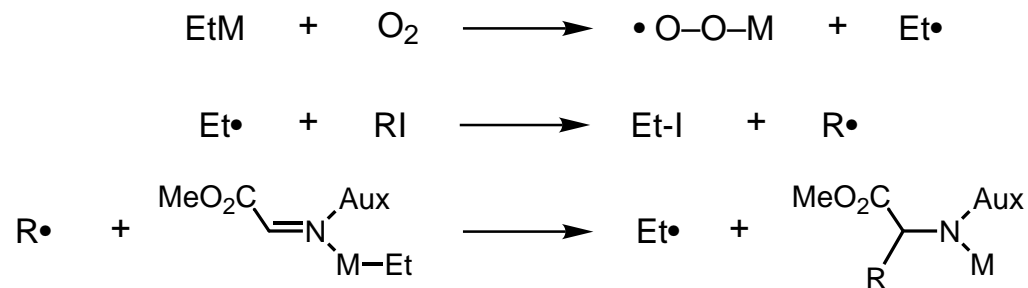
## Radical Additions to Glyoxylate Imines



$\text{MEt}_x$	$T$ ( $^{\circ}\text{C}$ )	$\text{dr}$
$\text{BEt}_3$	20	55 : 45
$\text{ZnEt}_2$	-40	8 : 92

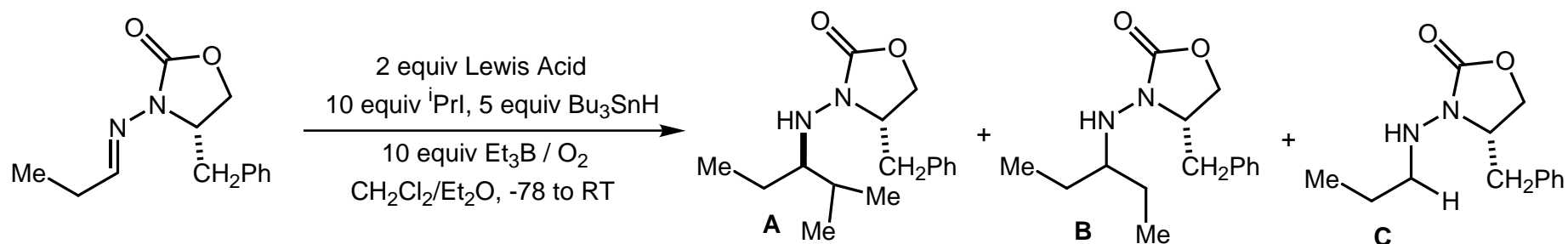
- $\text{MEt}_x$  acts as initiator, chain transfer agent, and activating Lewis acid.
- No Sn is required, however a large excess of  $\text{MEt}_x$  and alkyl iodide is used in these reactions

### Sn-Free Radical Reactions



Bertrand, Tetrahedron, 2000, 3951.

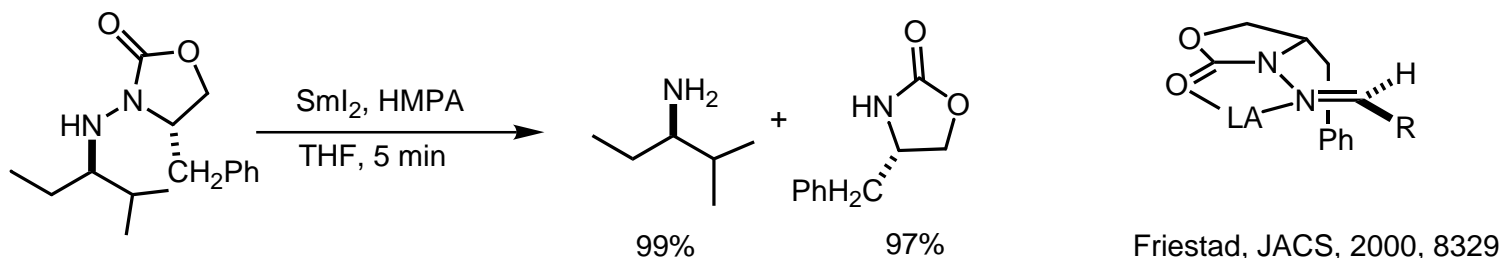
## Intermolecular Radical Addition to Hydrazones



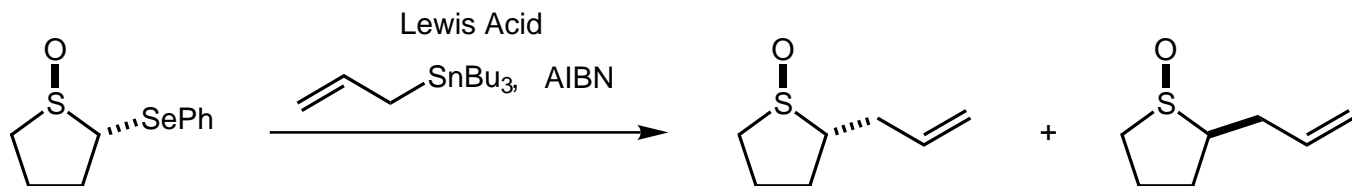
- In all reactions A was formed as a single diastereomer.
- Several alkyl radicals gave 42-60% yields of addition products in >96:4 dr.
- Benzaldimine also provided good selectivities.

<u>Lewis Acid</u>	<u>A : B : C</u>	<u>Yield A (%)</u>
None	-	0
BF <sub>3</sub> •OEt <sub>2</sub>	0: 0 : 100	0
Yb(OTf) <sub>3</sub>	96: 4 : 0	32
Zn(OTf) <sub>2</sub>	91 : 9 : 0	60

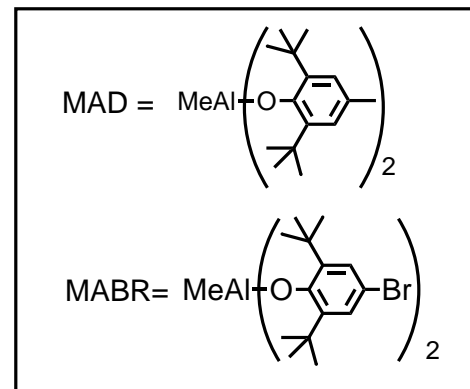
### Auxiliary Removal:



## Allylation of $\alpha$ -Sulfinyl Radicals



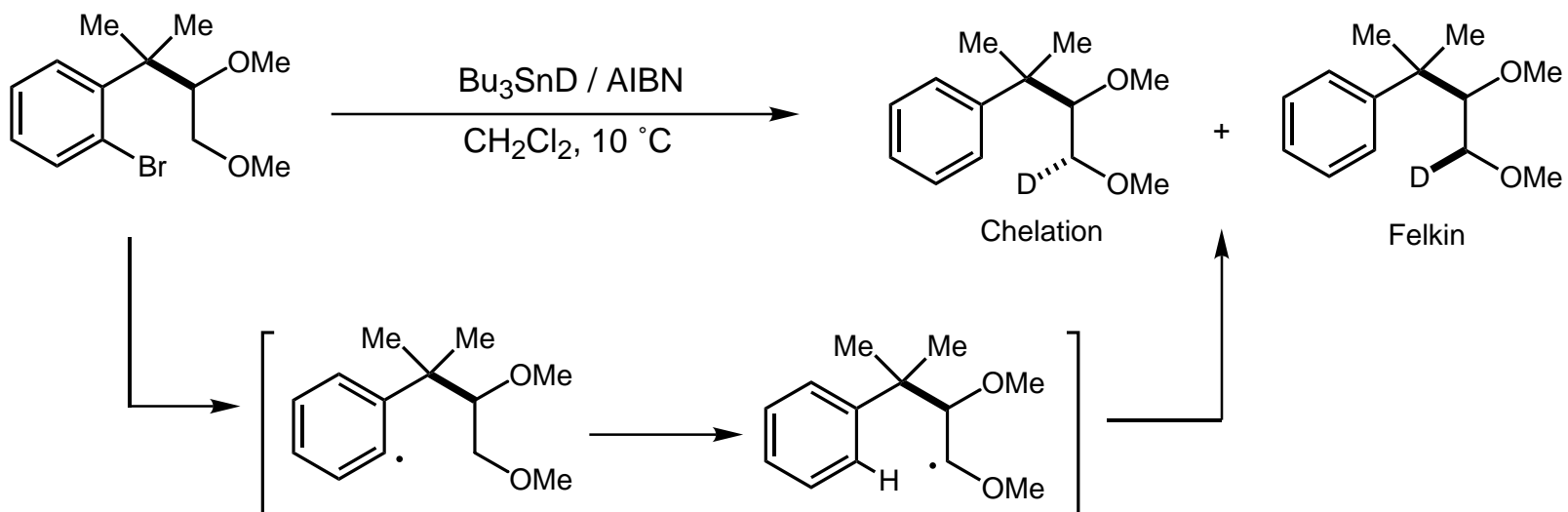
<u>Solvent</u>	<u>Lewis Acid</u>	<u>trans : cis</u>
propionitrile	—	77:23
propionitrile	$\text{LiClO}_4$	90:10
$\text{CH}_2\text{Cl}_2$	—	82:18
$\text{CH}_2\text{Cl}_2$	MAD (1)	98:2
$\text{CH}_2\text{Cl}_2$	MABR (1)	98:2
$\text{CH}_2\text{Cl}_2$	MABR (0.1)	90:10



- Selectivities were increased with the use of catalytic amounts of Lewis acid.

Renaud, JACS, 1991, 7803  
 Renaue, Curran, JACS, 1994, 3547

## Stereoselective Reactions of 1,2-Dioxysubstituted Radicals

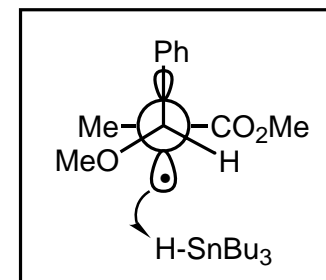
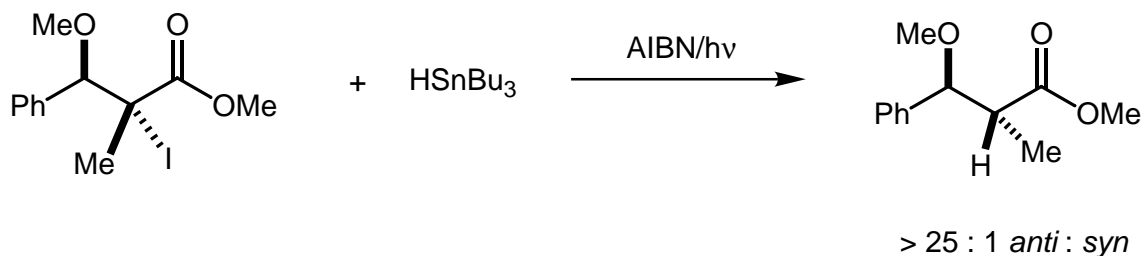


<u>Felkin-Anh</u>	<u>Chelation Control</u>	<u>Lewis Acid</u>	<u>Chelation/Felkin</u>
		—	1 : 2.5
		$\text{ZnCl}_2 \cdot \text{OEt}_2$	1 : 1.4
		$\text{Ti}(\text{OiPr})_3\text{Cl}$	1 : 3
		$\text{MgI}_2 \cdot \text{OEt}_2$	17 : 1

Renaud, JACS, 1995, 6607

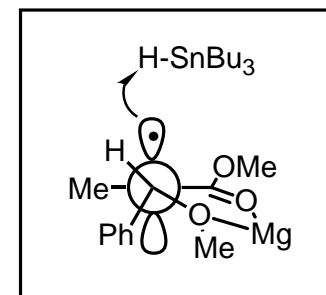
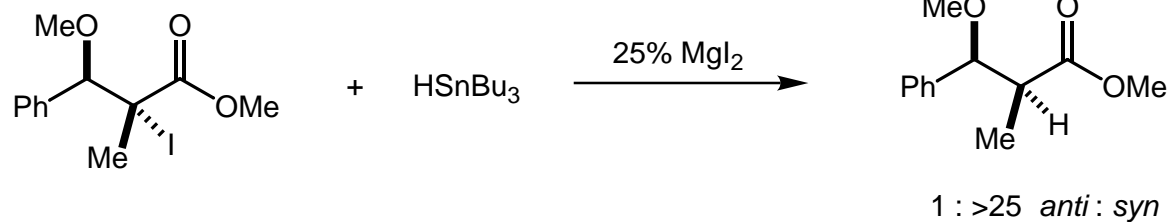
# Stereoselective Chelation Controlled Reductions

- Reduction in the Absence of Lewis Acid

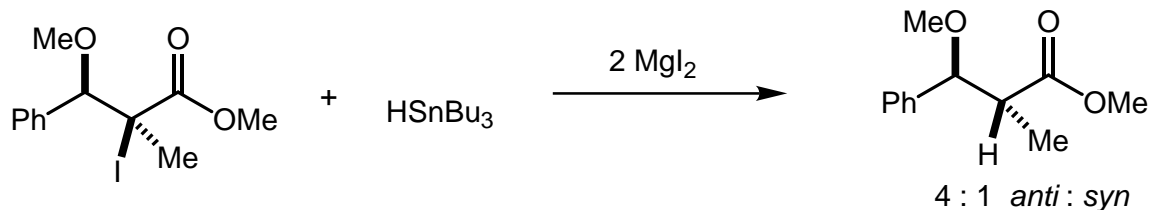


- Reduction under Chelation Control

Anti:



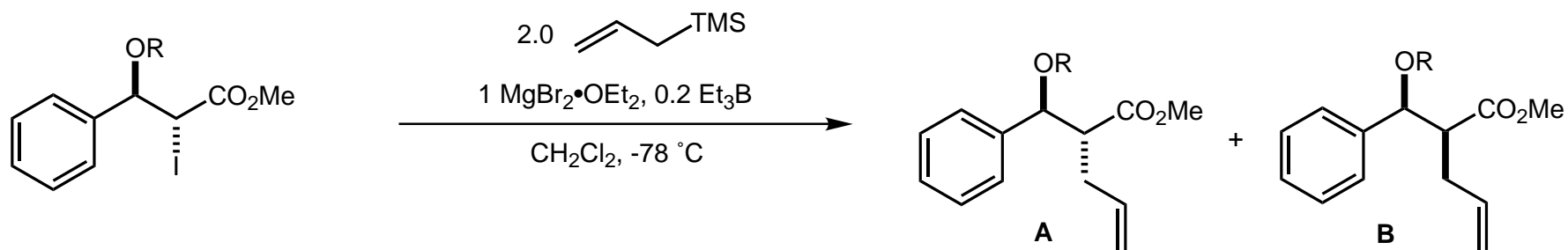
Syn:



Attributed to unfavorable  $A_{1,2}$  interactions in C-I bond-breaking step under chelation control.

Guindon, JACS, 1991, 9701

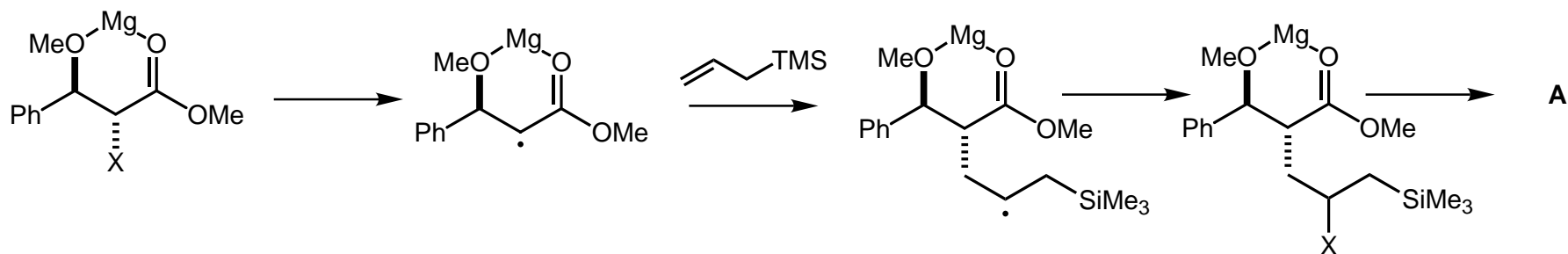
## Stereoselective Allylations



- Reactions with added Lewis acid proceed more readily.
  - increased rate of atom transfer?
  - increased rate of allyl addition?

OR	A : B
OTBS	1 : 10
OMe	42 : 1

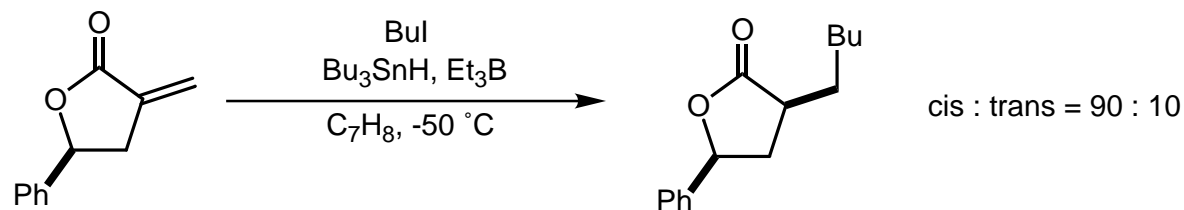
### Group Transfer Mechanism



Guindon, JACS, 1996, 12528

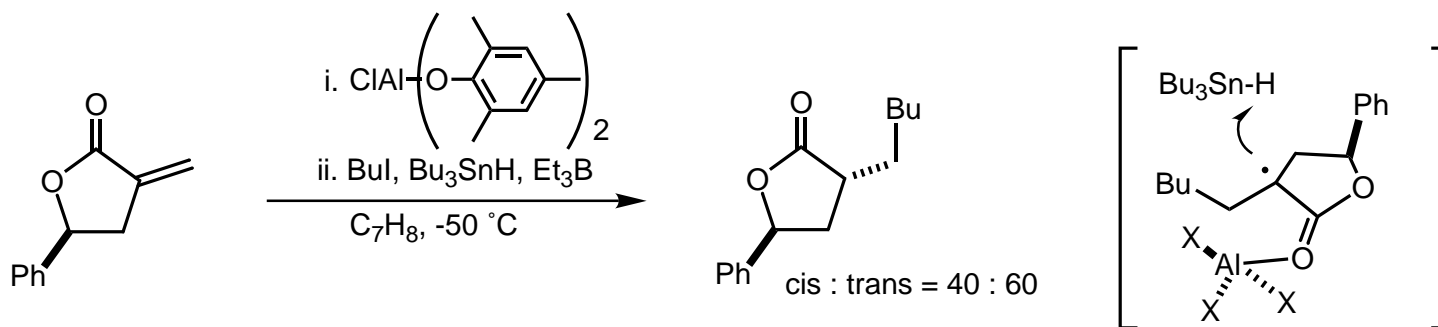
## Stereoselective Addition to $\alpha$ -Methylenebutyrolactones

- Reactions in the absence of Lewis Acid are highly diastereoselective.



- $\rho$  radical is generated by addition of alkyl radical to  $\alpha,\beta$ -unsaturated ester.
- Major product formed by  $\text{H}\cdot$  delivery from face opposite phenyl group.

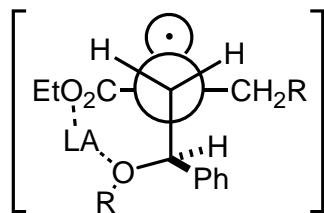
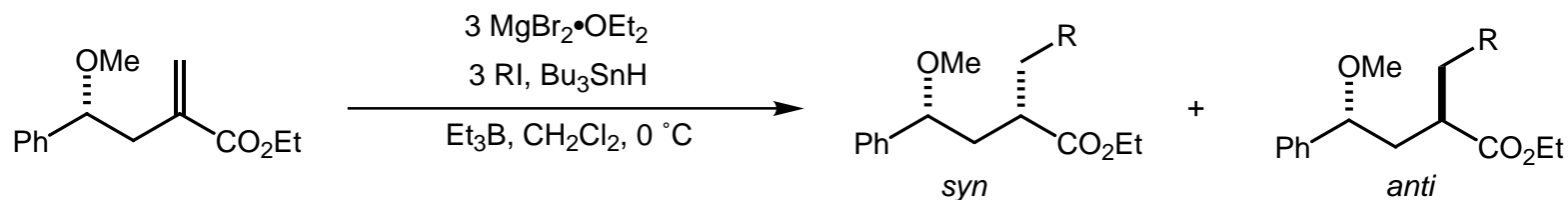
- Reversal of diastereoselectivity using bulky Lewis Acids



Sato, Chem. Commun., 1995, 1043

# Chelation Controlled 1,3-Asymmetric Induction

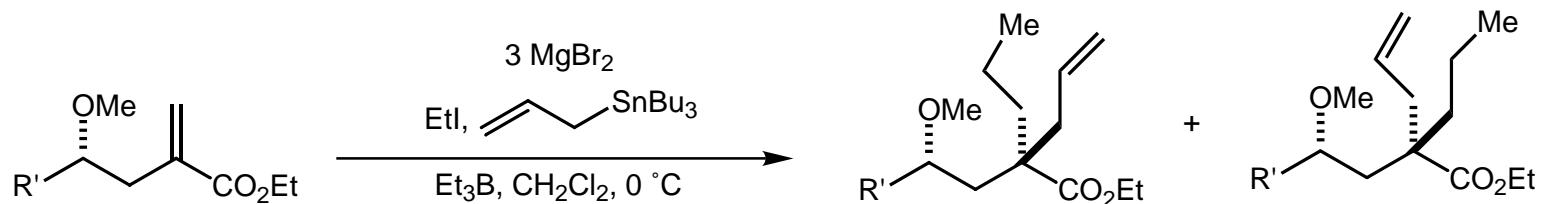
## Reduction Reactions



R	Yield (%)	syn : anti
<i>i</i> -Pr	86	1 : 1.4
<i>i</i> -Pr	96	4.3 : 1
<i>c</i> -Hex	70	3.7 : 1
<i>t</i> -Bu	91	1 : 3.8

← no MgBr<sub>2</sub>

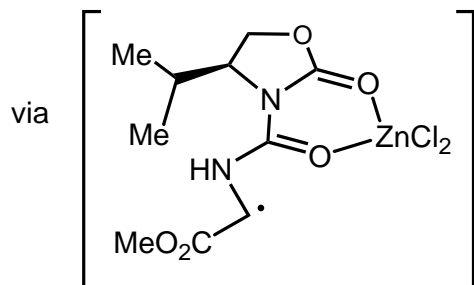
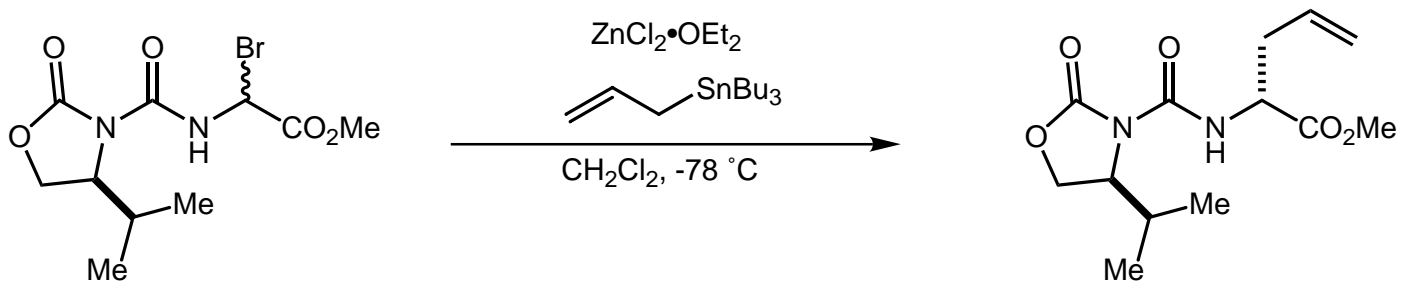
## Allylation Reactions



R'	Yield	"syn" : "anti"
Ph	48	5.5 : 1
<i>i</i> -Pr	63	>50 : 1
<i>t</i> -Bu	56	>50 : 1

- The allylation reaction did not proceed without Lewis Acid.

## Zinc Accelerated Allylation of Bromoglycinate Derivatives

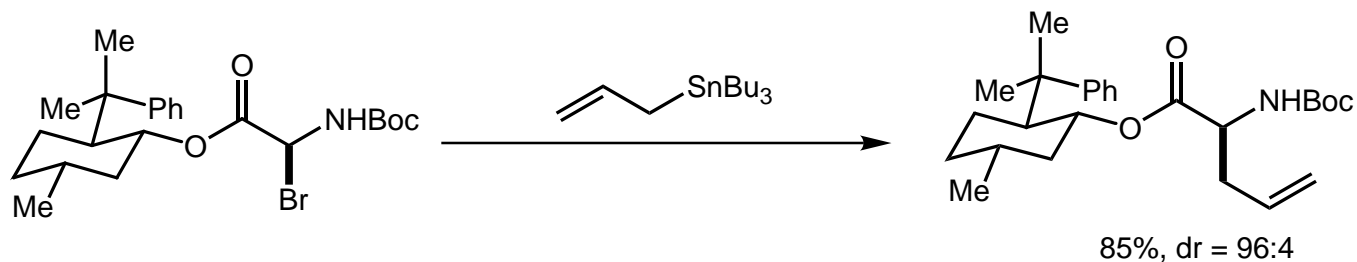


Equiv ZnCl <sub>2</sub>	Yield (%)	dr
2	85	87:13
0.1	65	67:33

- The reaction did not occur in the absence of ZnCl<sub>2</sub>.

Yamamoto, JACS, 1994, 421

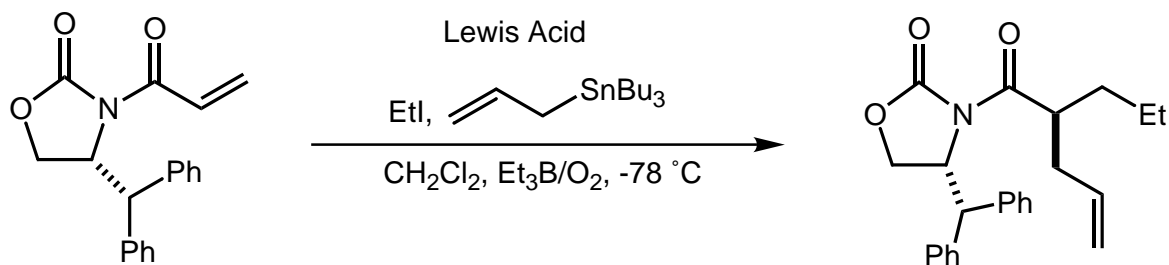
### Initial report:



- Both reactions could occur by nucleophilic attack on the corresponding imine.

Hamon, Chem. Commun., 1991, 722

## Diastereoselective Radical Allylation

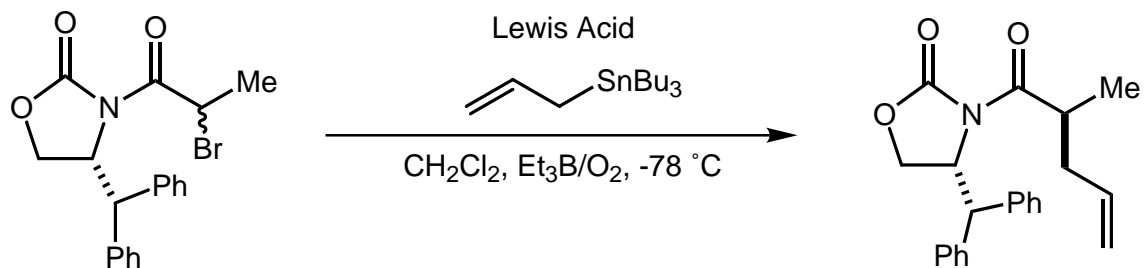


<u>Lewis Acid</u>	<u>Yield</u>	<u>dr</u>
—	90	1:1
BF <sub>3</sub> •OEt <sub>2</sub>	90	1.0 : 1.8
MgBr <sub>2</sub> •OEt <sub>2</sub>	93	>100 : 1
Yb(OTf) <sub>3</sub>	90	>100 : 1

- Two equivalents of Lewis Acid were used in most cases.
- Several lanthanide triflates also provide high selectivities.
- High (>50:1) selectivities were observed using MeI, <sup>i</sup>PrI, <sup>t</sup>BuI, <sup>c</sup>HexI, MeOCH<sub>2</sub>Br, MeC(O)Br, and PhC(O)Br.

Sibi, JOC, 1996, 6090

## Study of $\rho$ Selectivity with Chiral Oxazolidinones

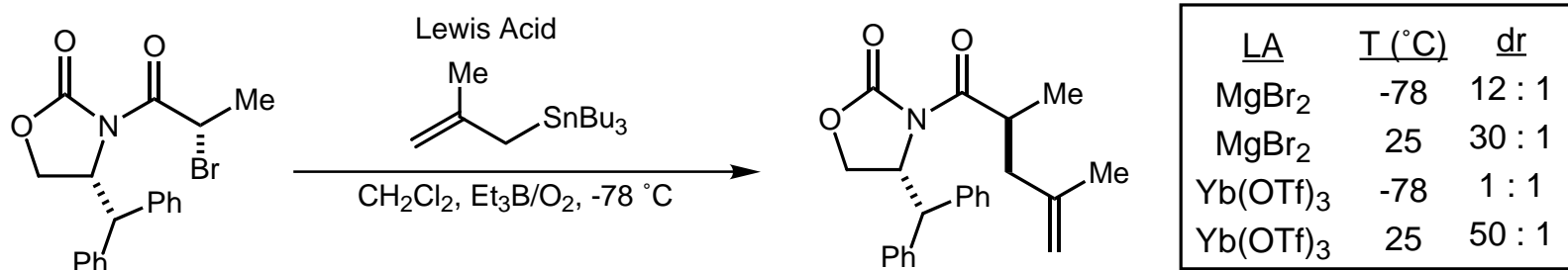
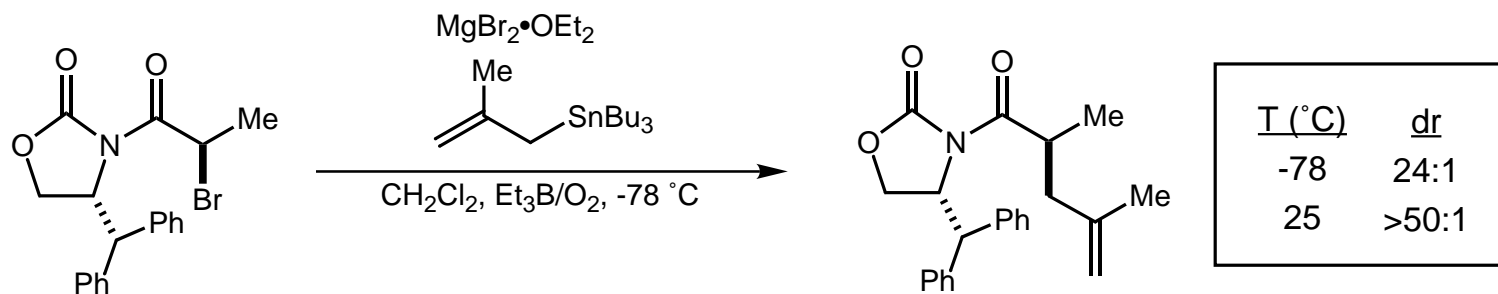


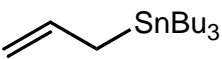
<u>Lewis Acid</u>	<u>Yield</u>	<u>dr</u>
—	93	1:1
$\text{MgBr}_2 \cdot \text{OEt}_2$	90	>100 : 1
$\text{Sc}(\text{OTf})_3$	94	>100 : 1
$\text{Yb}(\text{OTf})_3$	64	5 : 1

- Low dr observed using  $\text{Yb}(\text{OTf})_3$  could not be explained since this Lewis Acid gave good selectivities when similar radicals were generated by addition.

Sibi, ACIEE, 1996, 190

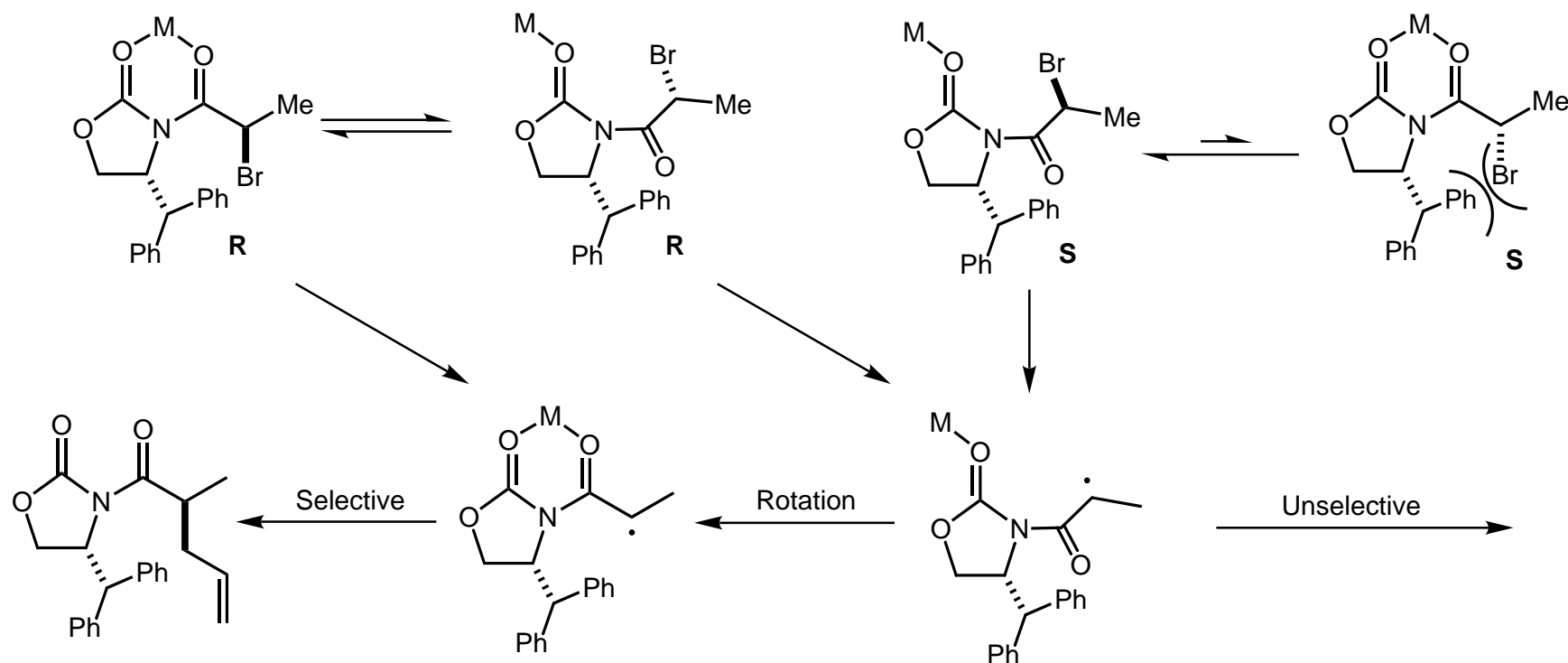
## Mechanistic Study Revealed that the Mechanism Was Complex



- The Mg-mediated reaction with  provided 40:1 dr for both starting diastereomers at -78 °C, increasing to >50:1 at RT.
- Conclusion: reaction selectivity is dependent on the configuration of starting diastereomer, the reactivity of allyl stannane, and the identity of the Lewis Acid.

Sibi, JACS, 2000, 8873

## Explanation for the Reaction Selectivity

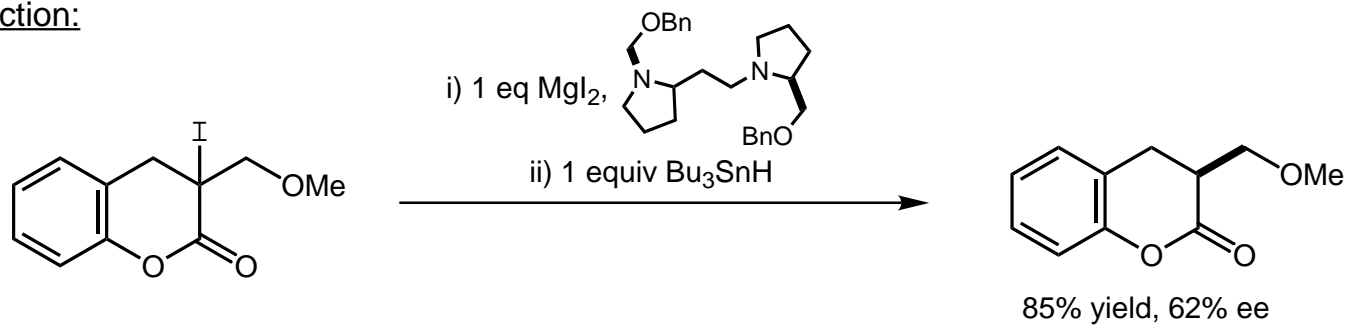


- Rate of rotation must increase with temperature faster than the rate of trapping with allyl stannane.
- The relative rates of rotation vs. allyl trapping explain why slower reacting allyl reagents show higher selectivity.

Sibi, JACS, 2000, 8873

# Enantioselective Reduction/Allylation of an $\alpha$ -Iodolactone

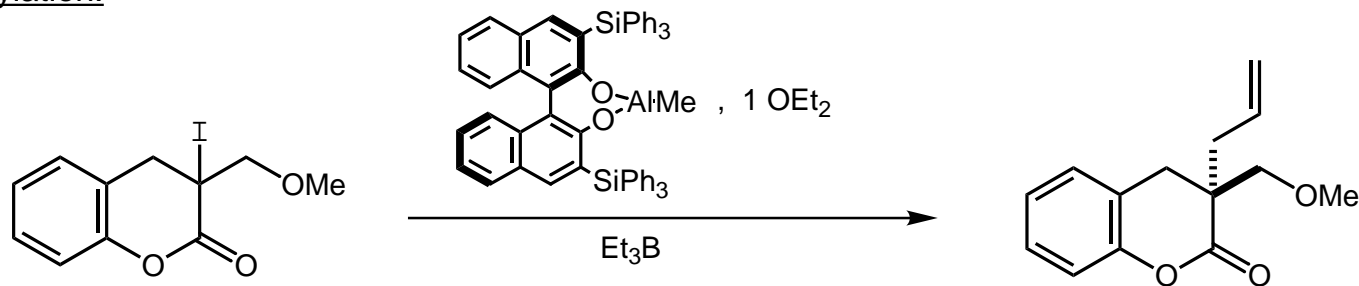
## Reduction:



85% yield, 62% ee

Hoshino, Chem. Commun., 1995, 481

## Allylation:

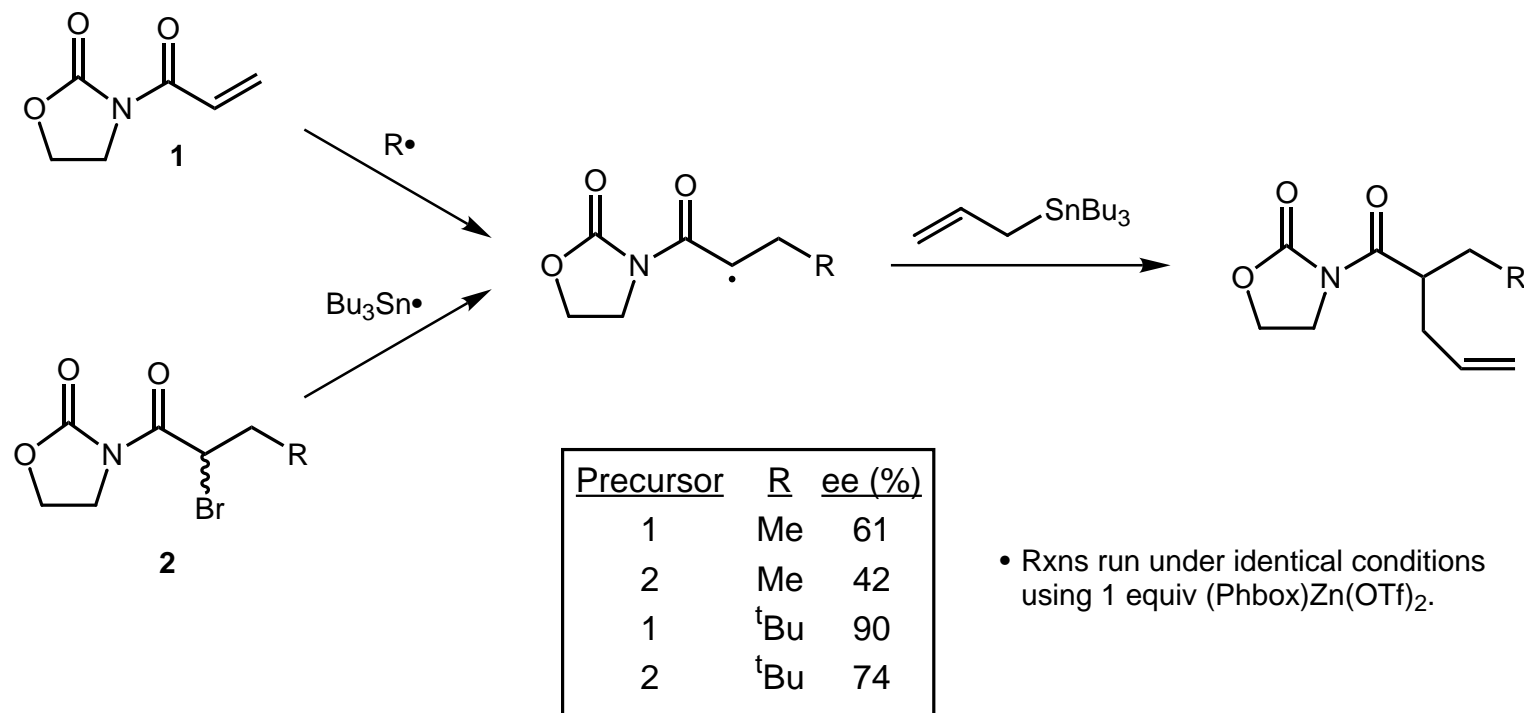


- More than 1 equiv of  $Et_2O$  was detrimental to ee.

Equiv Al	Yield (%)	ee (%)
1.0	84	81
0.2	81	80
0.1	83	72

Hoshino, JACS, 1997, 11713

## Study of $\rho$ Selectivity with Chiral Lewis Acids

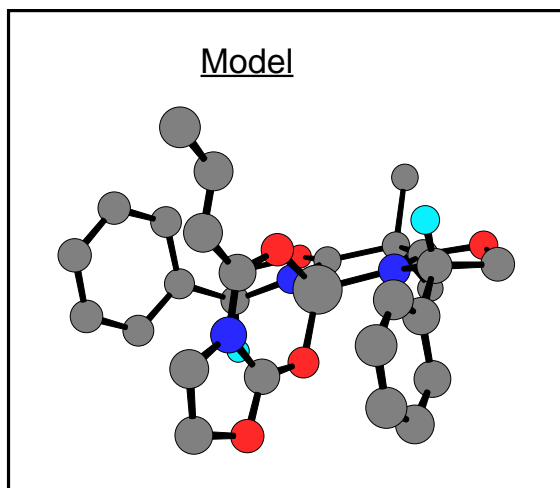
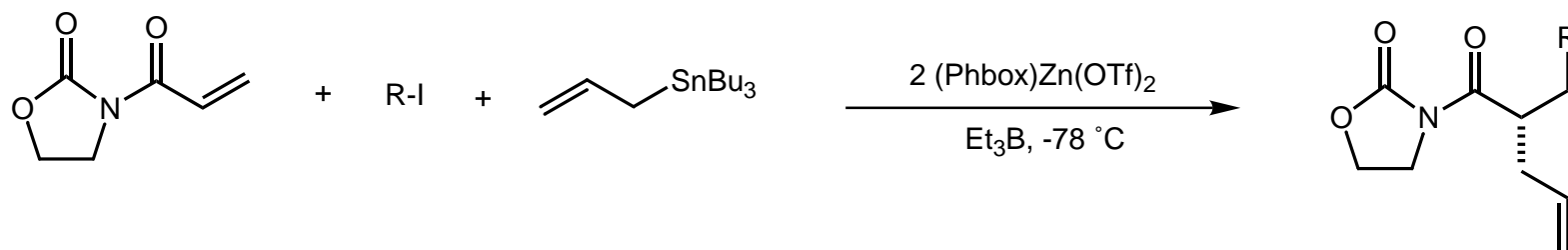


- Rxns run under identical conditions using 1 equiv (Phbox)Zn(OTf)<sub>2</sub>.

- Reactions are clearly not proceeding through a common intermediate.
- Possible that equilibria of diastereomers of complex of **2** with chiral Lewis Acid are responsible for lower enantioselectivities observed in reactions starting with **2**.
- Later investigations discovered that XSnBu<sub>3</sub> byproduct negatively effected ee.

Porter, Tetrahedron Lett., 1997, 2067  
Porter, JOC, 1997, 6702

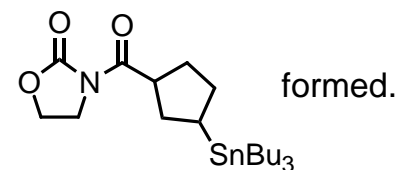
## Enantioselective Allylation Using Chiral Lewis Acids



- Reaction proceeds well with only 1.5 equiv RI,  
1.5 equiv  $\text{Bu}_3\text{SnH}$

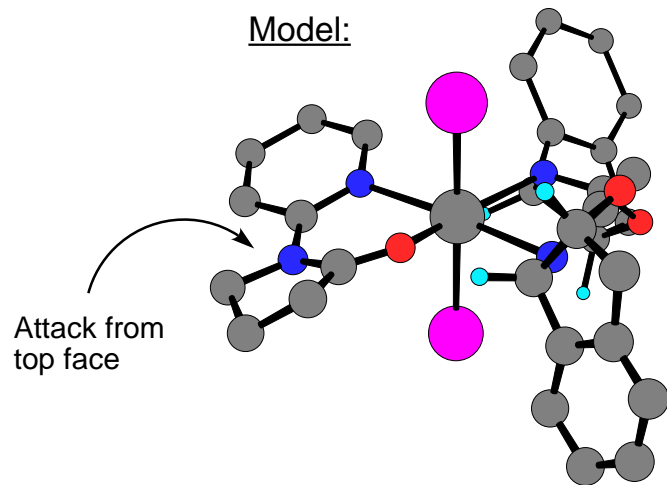
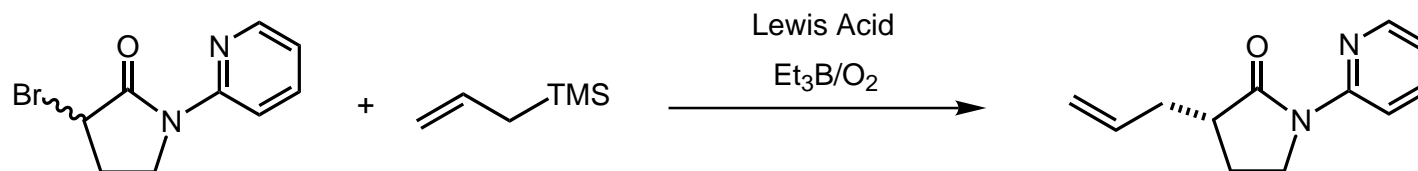
R	Yield (%)	ee (%)
<sup>c</sup> Hex	92	72
<sup>t</sup> Bu	85	88

- At higher T, significant amounts of



Porter, JACS, 1995, 11029

# Enantioselective Reactions of Radicals Generated from $\gamma$ -Lactams

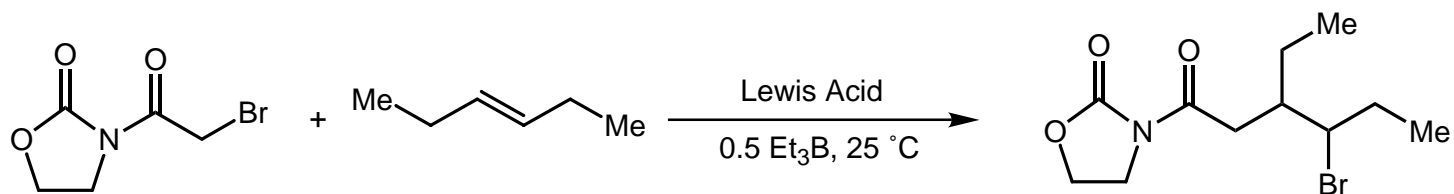


<u>Lewis Acid (eq)</u>	<u>T (°C)</u>	<u>ee (%)</u>	<u>Yield (%)</u>
(Phbox)Zn(OTf) <sub>2</sub> (1)	-78	59	70
(Indabox)Zn(OTf) <sub>2</sub> (1)	-78	96	75
(Indabox)Zn(OTf) <sub>2</sub> (1)	-20	80	91
(Indabox)Zn(OTf) <sub>2</sub> (0.2)	-20	81	69

- Yield was increased with additional Lewis Acid, while ee was unaffected.

Porter, Tetrahedron Lett., 1999, 6713

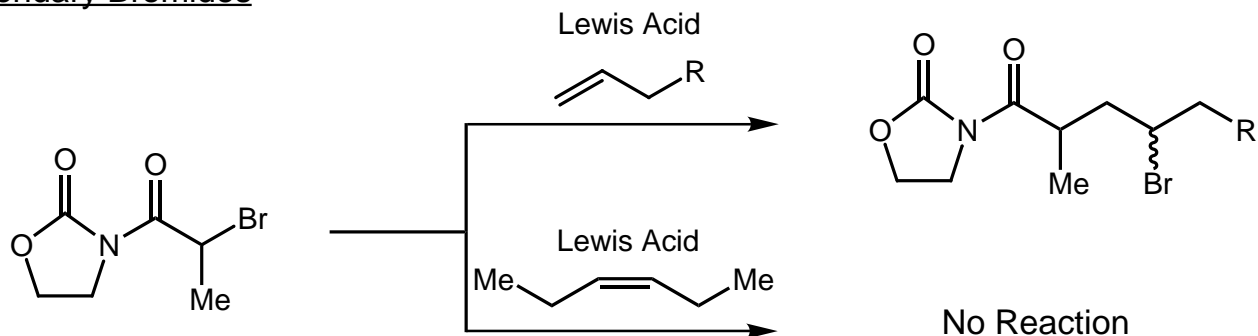
## Lewis Acid Promoted Atom-Transfer Radical Additions



- With Lewis Acid activation, alkenes are nucleophilic enough to react with the radical intermediate.
- Atom transfer products can be isolated if alkenes, rather than allyl-metal reagents, are used as nucleophiles

<u>Lewis Acid (1 equiv)</u>	<u>Conversion (%)</u>
None	<10
Mg(OTf) <sub>2</sub>	16
Sc(OTf) <sub>3</sub>	47
Yb(OTf) <sub>3</sub>	100

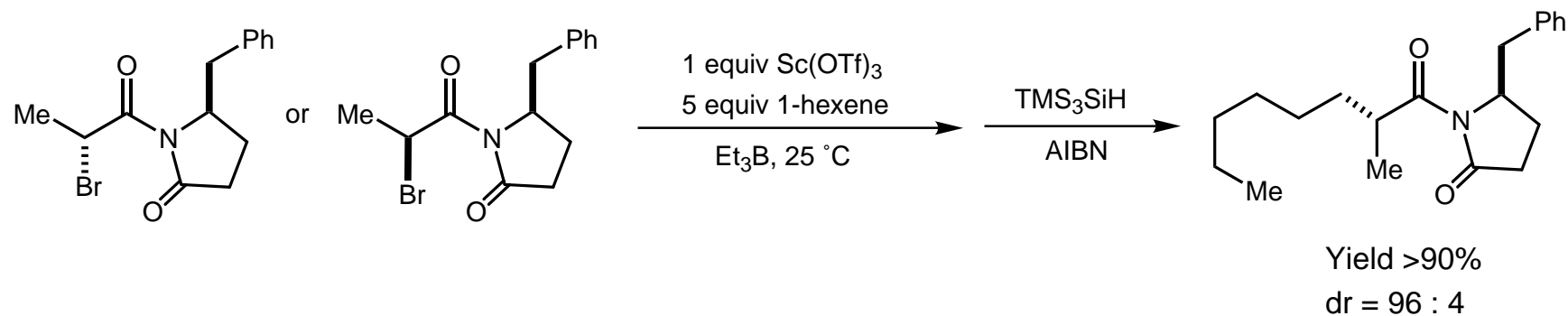
### Secondary Bromides



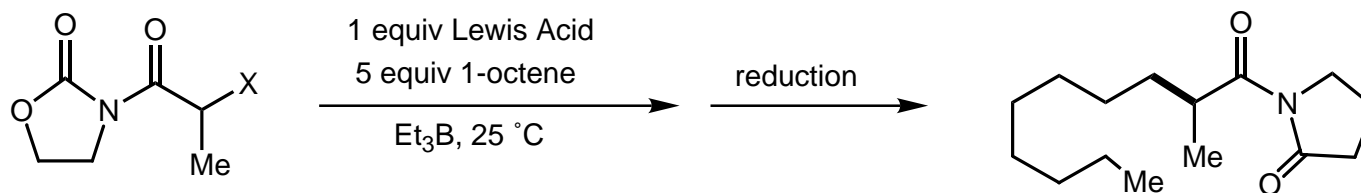
Porter, JACS, 1999, 5155

# Diastereoselective and Enantioselective Atom Transfer

## Diastereoselective Reactions



## Enantioselective Reactions

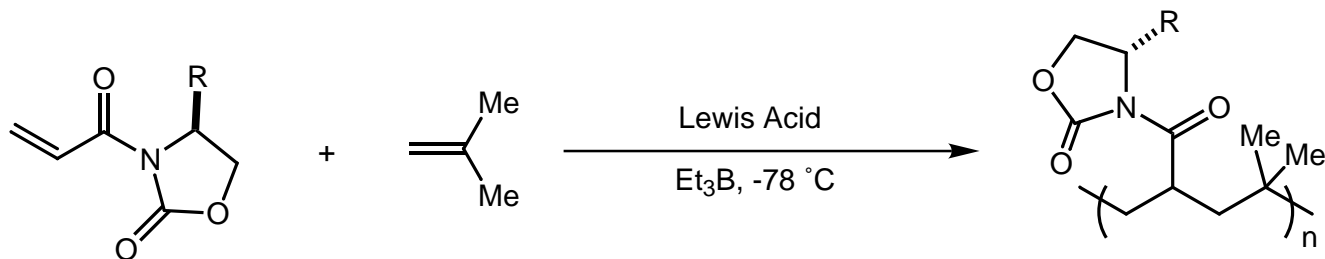


X	Lewis Acid	Yield (%)	ee (%)
Br	(Phbox)Sc(OTf) <sub>3</sub>	64	0
Br	(Phbox)Zn(OTf) <sub>2</sub>	0	—
I	(Phbox)Zn(OTf) <sub>2</sub>	<15	40

Porter, JACS, 1999, 5155

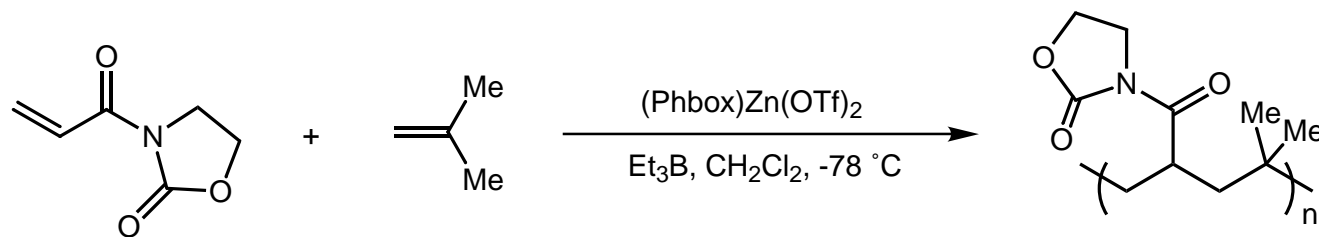
# Free-Radical Polymerization of Acrylimides

## Diastereoselective Copolymerization



- Degree of copolymerization depended on Lewis Acid.  $\text{Sc}(\text{OTf})_3$  in  $\text{Et}_2\text{O}$  gave best results (1:1).
- R = Bn provided > 95:5 diastereoselectivity.

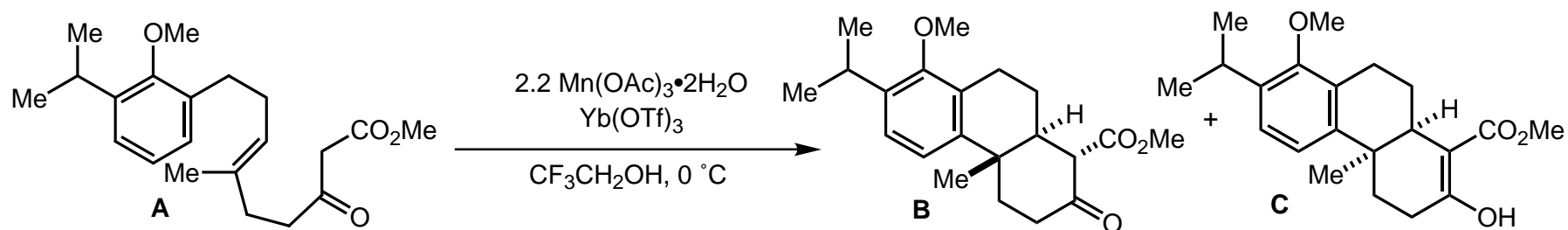
## Enantioselective Copolymerization



- To get good copolymerization, 3.7 equiv of Zn were required.
- Polymer was formed in approximately 60% ee.

Porter, JOC, 2000, 775.

# Lanthanide Triflates Catalyze Mn(III)-Based Radical Cyclization



- Lewis Acid increases % of A and also increases electrophilicity of radical intermediate.

Lewis Acid	Time (h)	Yield (B/C)
—	24	36/7
Yb(OTf) <sub>3</sub> (1.0)	3	69/10
Yb(OTf) <sub>3</sub> (0.3)	3.5	59/8

## Effect of Yb(OTf)<sub>3</sub> on Ketone-Enol Equilibrium:

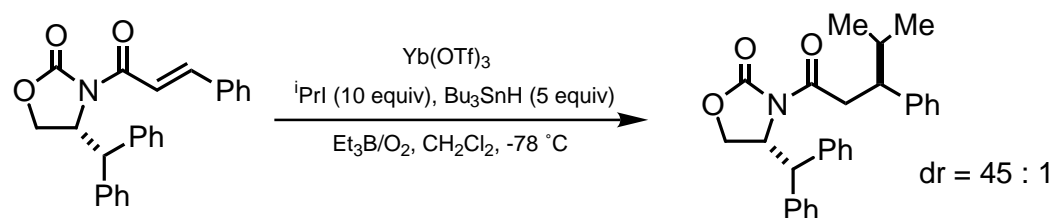
substrate	% in enol form (in MeOH)		
	0 equiv Yb	0.5 equiv Yb	1.0 equiv Yb
	18.1	66.9	72.0

See V. Cee, Evening Seminar, 4/27/99

Yang, JACS, 2000, 1658

## Lewis Acids In Free Radical Reactions - Reflections

- Lewis acids can increase the rate of radical reactions either by activating the radical acceptor or by increasing the reactivity of electrophilic radicals.
- Lewis acids can control the stereochemistry of radical reactions by changing the conformation of the radical intermediate or the radical acceptor.
- Several auxiliary-controlled reactions proceed with high diastereoselectivity in the presence of Lewis acids.



- A few enantioselective Lewis acid-catalyzed reactions have been developed.
- The stereoselective reactions that have been developed usually require large amounts of alkyl halide and/or tin reagents.