

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

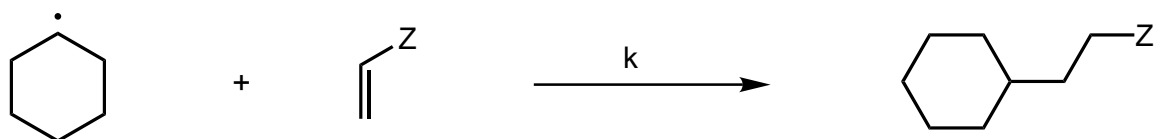
Renaud and Gerster *ACIEE* **1998**, 37, 2562

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

Zachary Sweeney
Evans Group Seminar
February 23, 2001

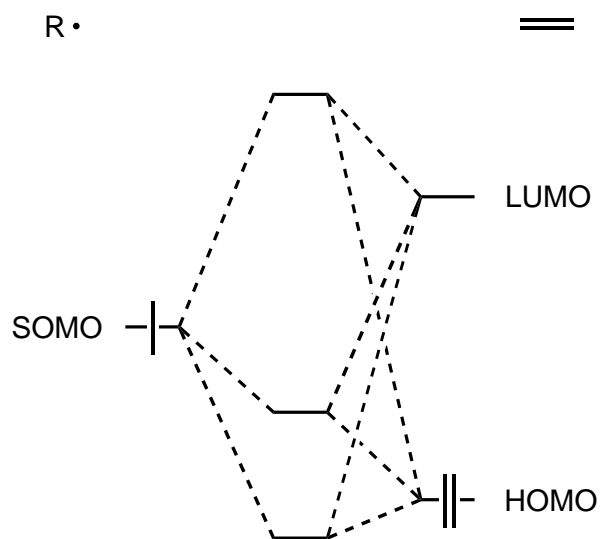
Formation of CC Bonds By Addition of Radicals to Alkenes

- Simple alkyl radicals are nucleophilic



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

Z	k_{rel}
CHO	34
CO ₂ CH ₃	6.7
C ₆ H ₆	1.0
ⁿ C ₄ H ₉	0.0004

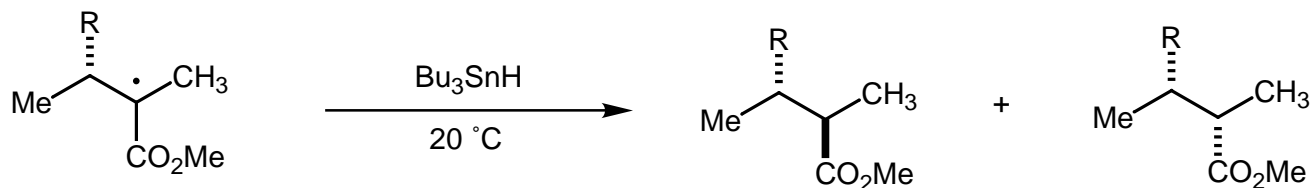


- Reactions are strongly exothermic since a σ -bond is formed and a π -bond is broken.
- According to FMO theory, raising the energy of the SOMO (increasing SOMO-LUMO interactions) will increase the rate of reactions.
- Electrophilic radicals react with electron-rich alkenes. In this case the SOMO-HOMO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

Giese, ACIEE, 1983, 753.

Allylic Strain Effects in Radical Reactions

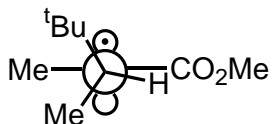
- Enolate Radical Chemistry



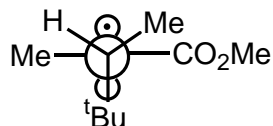
- Calculations and EPR studies suggest planar enolate conformation arising from conjugation of the radical with the ester functionality.

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

Ground States

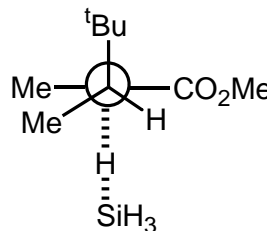


A-strain conformation
E = 0.0 kcal/mol

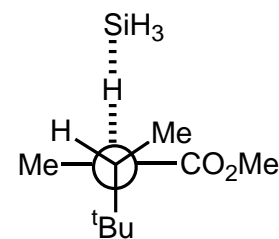


Felkin-Anh conformation
E = 1.5 kcal/mol

Transition States



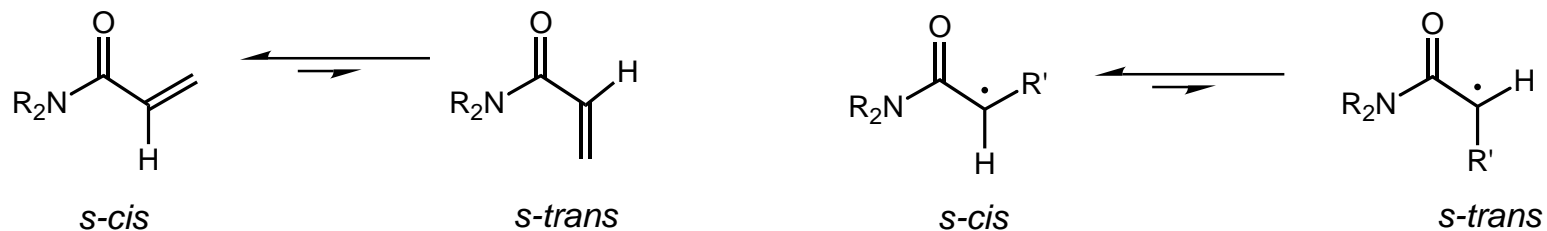
E = 0.0 kcal/mol
(*anti* product)



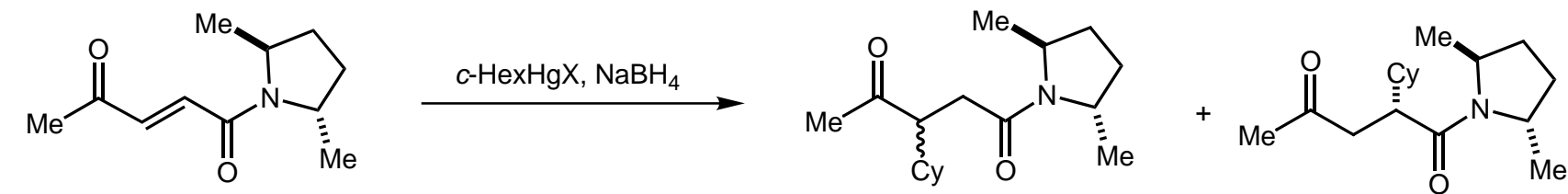
E = 2.7 kcal/mol
(*syn* product)

Early Efforts Toward Acyclic Stereochemical Control

- Amide groups were used to provide conformational control.



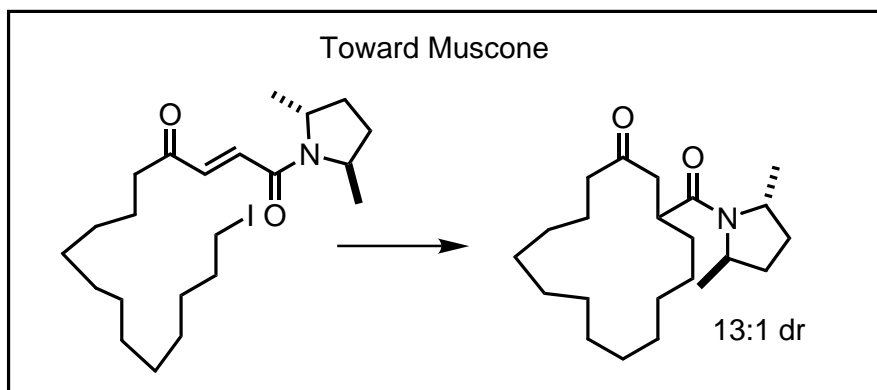
- C_2 -symmetric auxiliaries or dipole-dipole effects were used to fix the orientation of the auxiliary.



A : B = 1:1

A
dr: 60:40

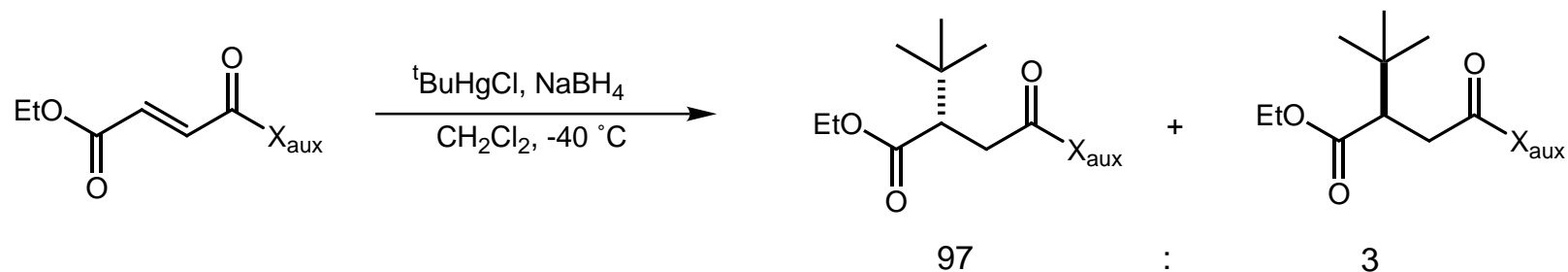
B
dr: 93:7



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

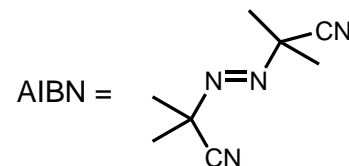
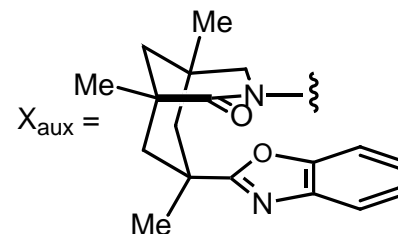
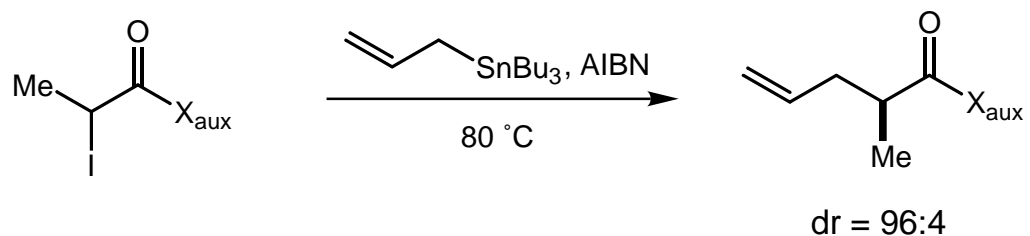
Early Efforts Toward Auxiliary-Based Control

- Curran, Rebek- auxiliary that can control β -stereoselectivity

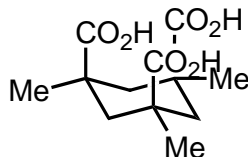


- No α -addition was observed under these conditions

- The auxiliary was also effective for radical allylation reactions.



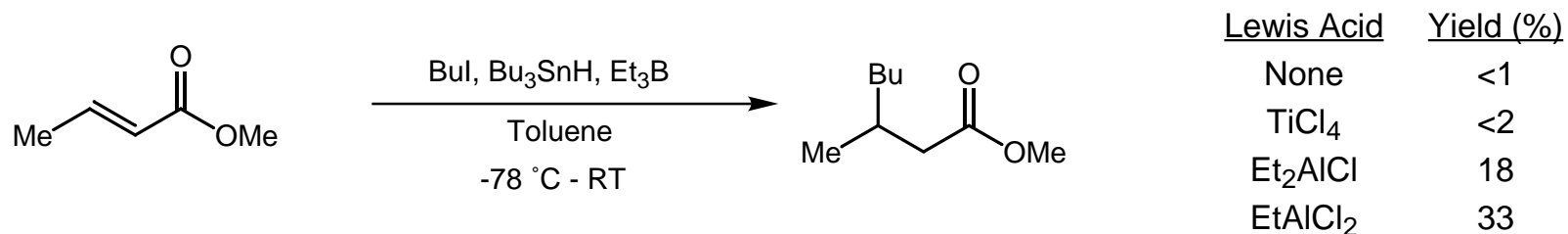
- Auxiliary Synthesized in 7 steps from



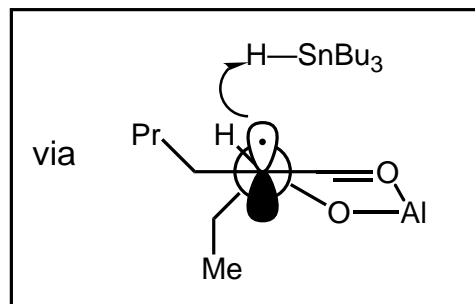
Curran, Rebek, JACS, 1992, 114, 7007.

Lewis Acid-Enhanced Reactivity of Unsaturated Esters and Amides

- Lewis acids increase yields of conjugate additions



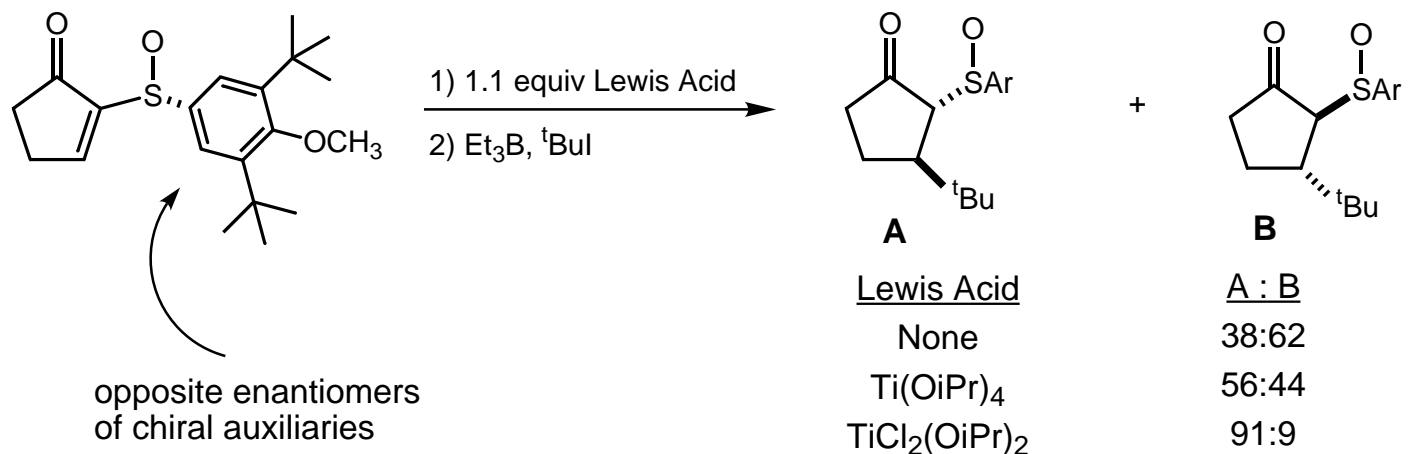
- Chelate control



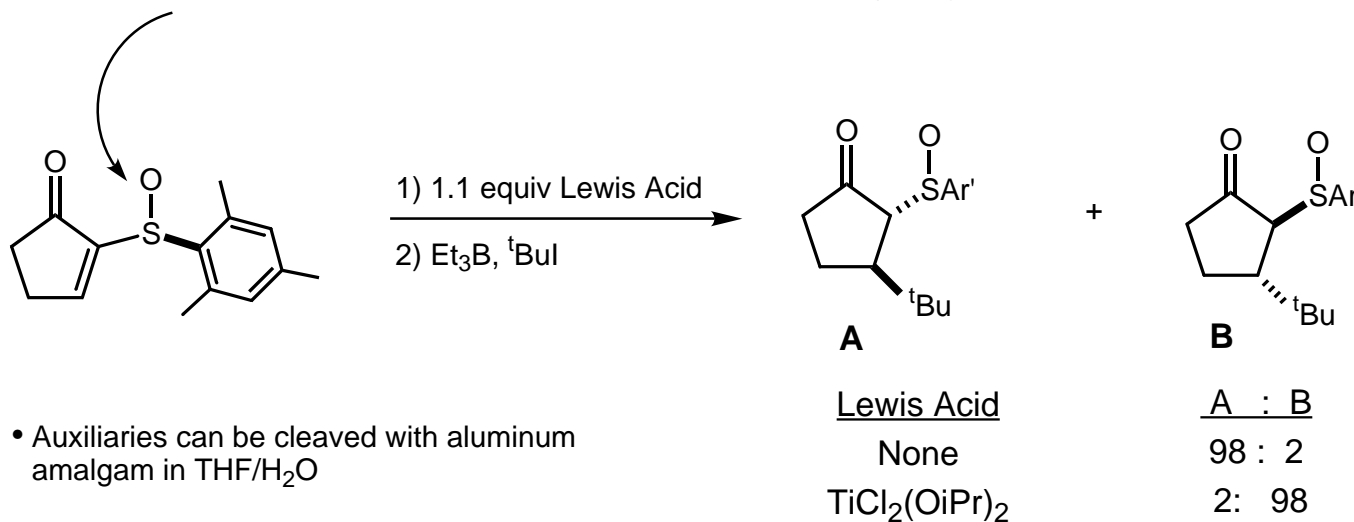
<u>Lewis Acid</u>	<u>Yield</u>	<u>syn:anti</u>
None	34	65:35
Et ₂ AlCl	76	87:13

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

Asymmetric Radical Addition to α -Sulfinylcyclopentenones



opposite enantiomers
of chiral auxiliaries

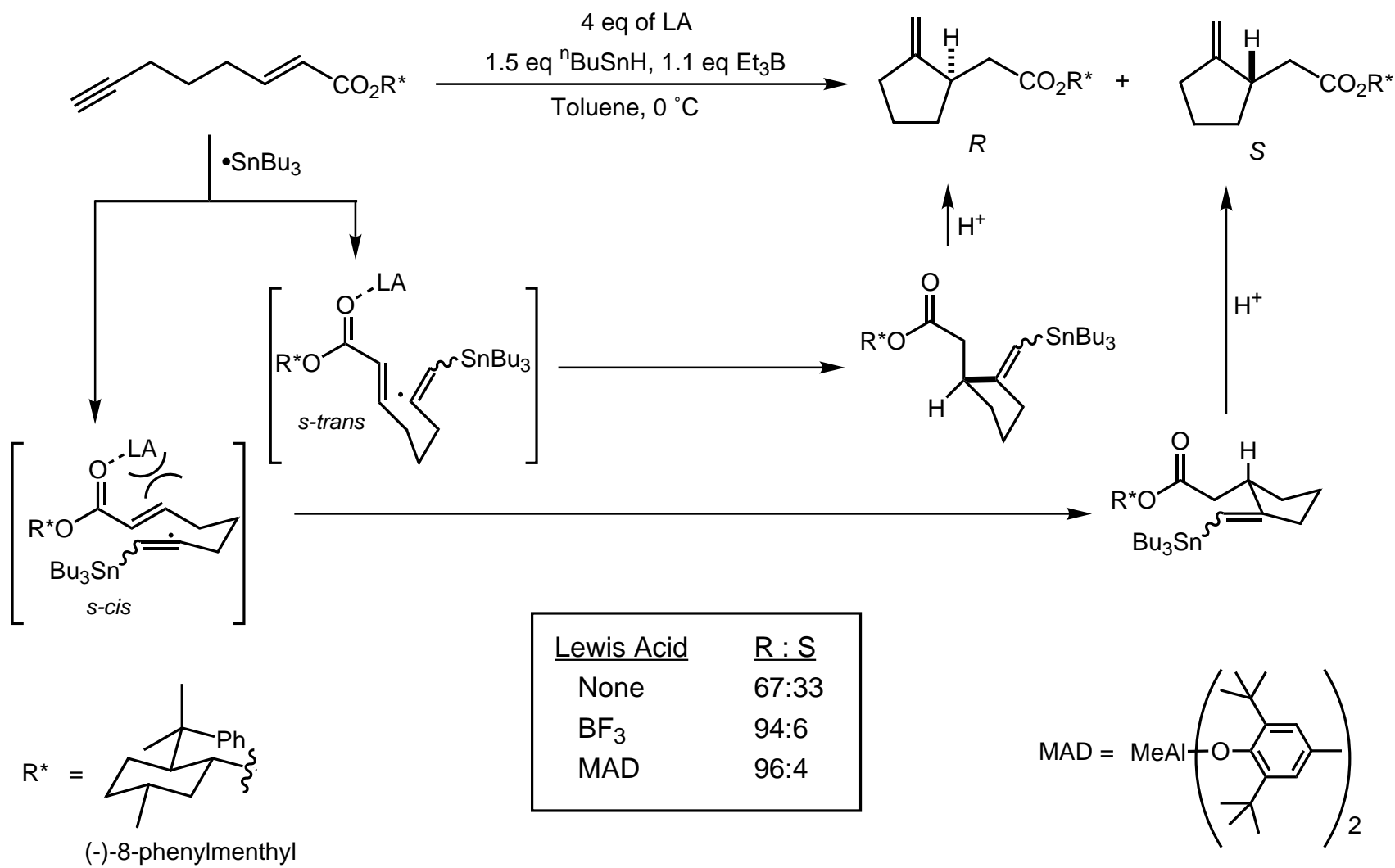


• Auxiliaries can be cleaved with aluminum amalgam in THF/ H_2O

Toru, JACS, 1993, 10464.
Toru, JOC, 1997, 7794

Lewis Acid Promoted Diastereoselective Radical Cyclization

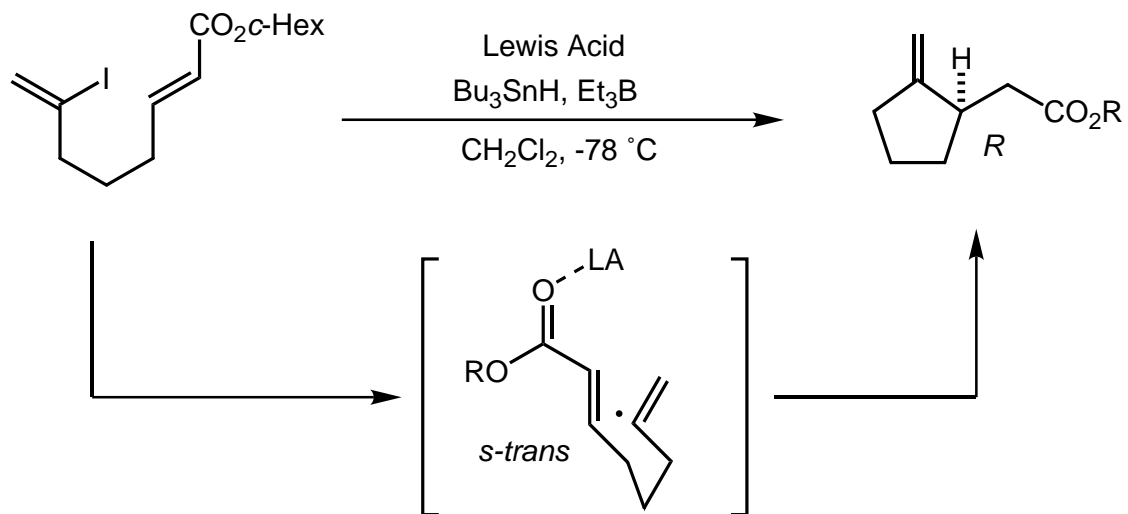
- Coordination of the Lewis acid controls *s-cis/s-trans* conformation of ester



Nishida, JACS, 1994, 6455.

Enantioselective Lewis Acid Promoted Radical Cyclization

- First report of chiral Lewis Acid mediated radical cyclization

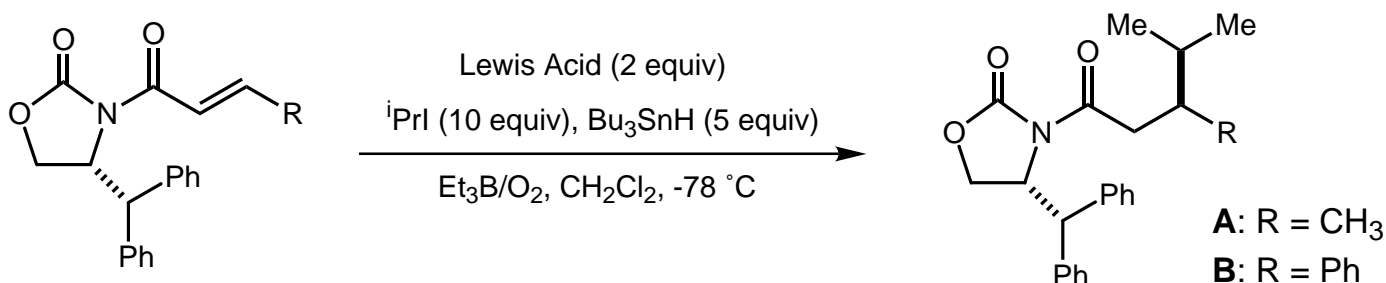


<u>Lewis Acid</u>	<u>equiv</u>	<u>ee (%)</u>
(Binol)AlMe	1	2
	1	12
	4	36

- 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

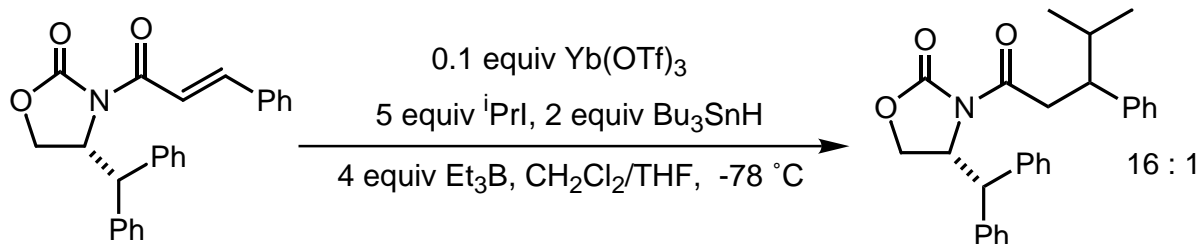


Substrate	Lewis Acid	Yield (%)	dr
A	None	60	1.3:1
A	BF ₃ •OEt ₂	80	1.3:1
A	Et ₂ AlCl	70	4:1
A	Sc(OTf) ₃	90	15:1
A	Yb(OTf) ₃	93	25:1
B	Yb(OTf) ₃	89	45:1

- Very strong Lewis Acids (i.e. TiCl₄) gave products of hydride reduction.

- Reactions using TMS₃SiH failed.

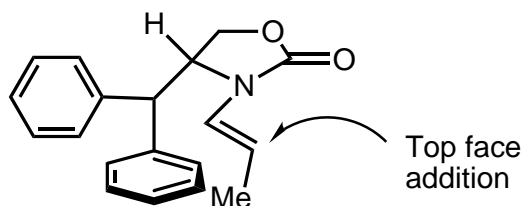
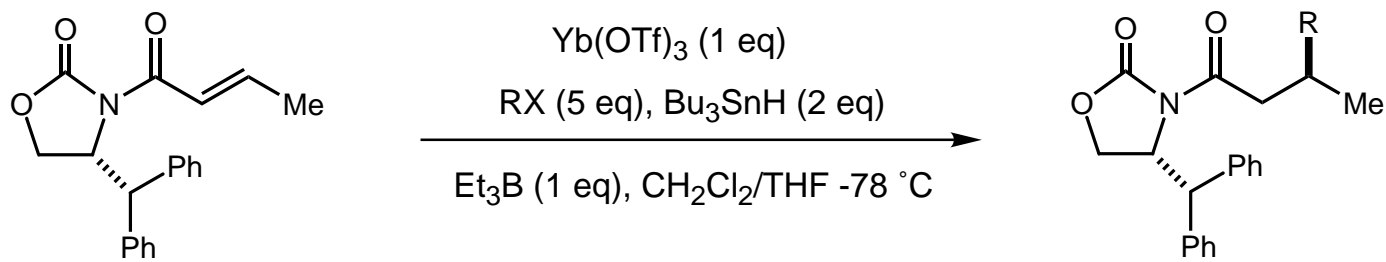
Optimized Reaction Employing Catalytic Lewis Acid



- 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

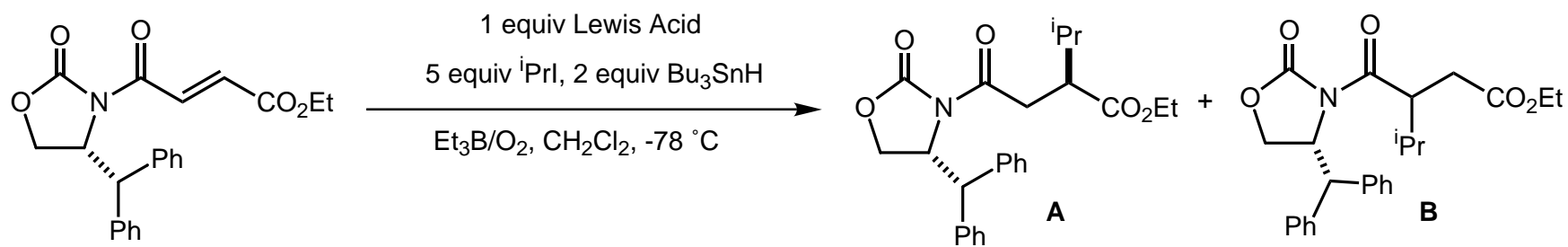


<u>RX</u>	<u>Yield (%)</u>	<u>dr</u>
ⁱ PrI	90	25:1
ⁱ PrBr	90	25:1
EtI	84	12:1
^c HexI	92	16:1
^t BuI	82	14:1
MeOCH ₂ Br	84	14:1
MeC(O)Br	85	7:1

- Low yields were observed with PhI, MeI, PhCH₂I, AllylI, AcOCH₂Br, and BrCH₂CO₂Bn.

Sibi, JACS, 1999, 7517

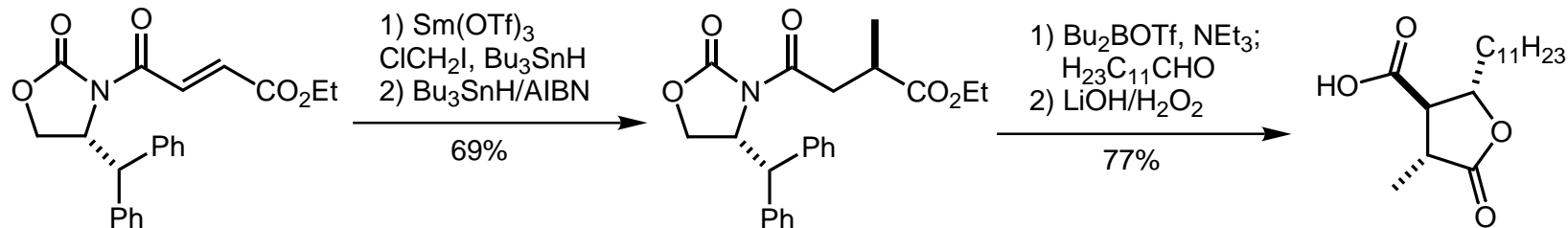
Intermolecular Additions to Fumarate Derivatives



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

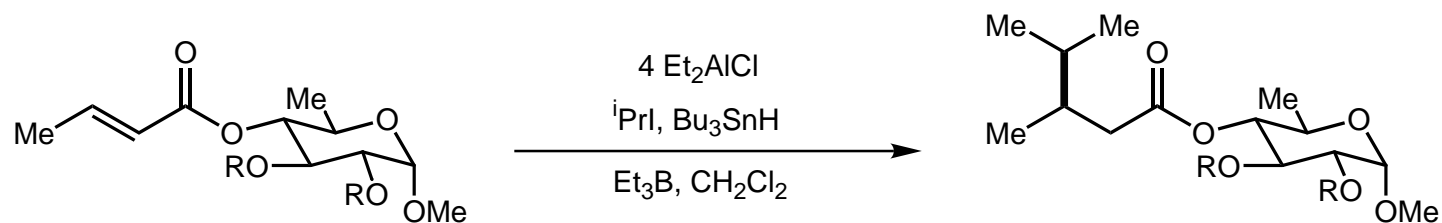
<u>LA</u>	<u>A : B</u>	<u>dr A</u>
None	1.6 : 1	11 : 1
$\text{BF}_3 \cdot \text{OEt}_2$	1.2 : 1	9 : 1
$\text{Er}(\text{OTf})_3$	71 : 1	>100 : 1

Synthesis of Nephosteranic Acid:



Sibi, ACIEE, 1997, 274

α -D-Glucopyranoside Derivatives as Auxiliaries

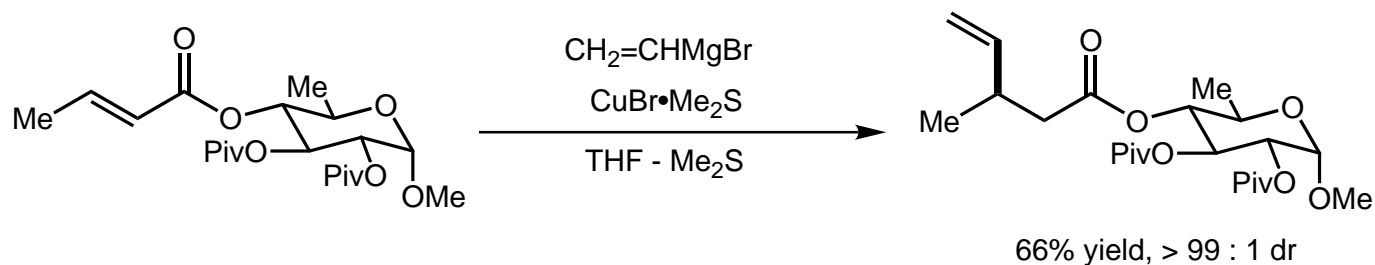


- When no LA was used, the product was racemic.
- Lower selectivity was observed with 1 equiv of Et_2AlCl .

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

Tadano, Synlett, 2000, 979

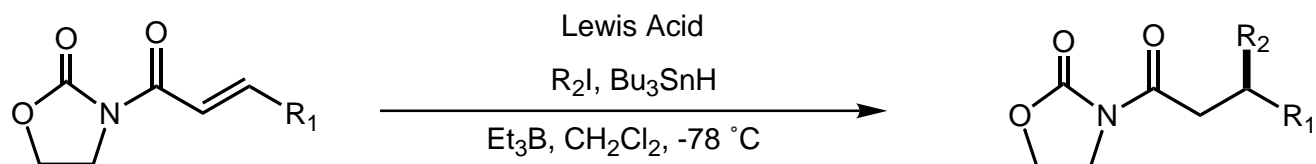
Analogous Cuprate Additions:



Tadano, Org. Lett., 1999, 1447.

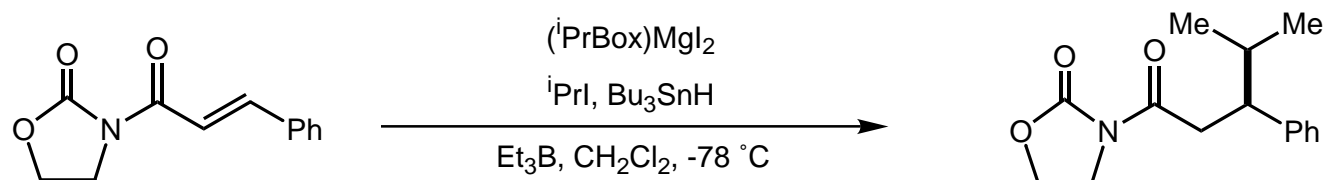
Enantioselective Lewis Acid Catalysis in Radical Conjugate Additions

- Experiments with stoichiometric Lewis Acid



R ₁	R ₂	Lewis Acid	Yield (%)	ee (%)
Ph	ⁱ Pr	(ⁱ PrBox)MgI ₂	88	82
Me	^t Bu	(PhBox)Zn(OTf) ₂	90	82

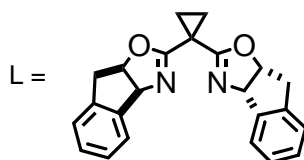
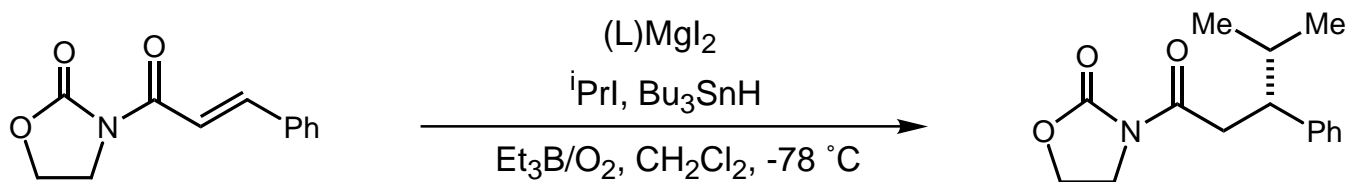
- Experiments with catalytic Lewis Acid



eq Mg	Yield (%)	ee (%)
0.2	86	67
0.05	57	40

Sibi, Porter, JACS, 1996, 9200

Improved Selectivity using (Indabox)MgI₂ Complexes

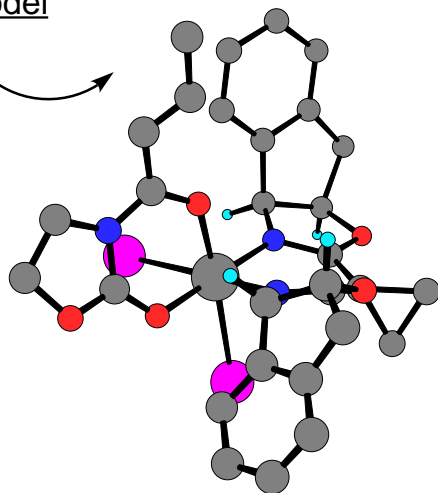


<u>Eq LA</u>	<u>Yield</u>	<u>ee</u>
1	88	93
0.2	95	96
0.05	92	90

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

Model

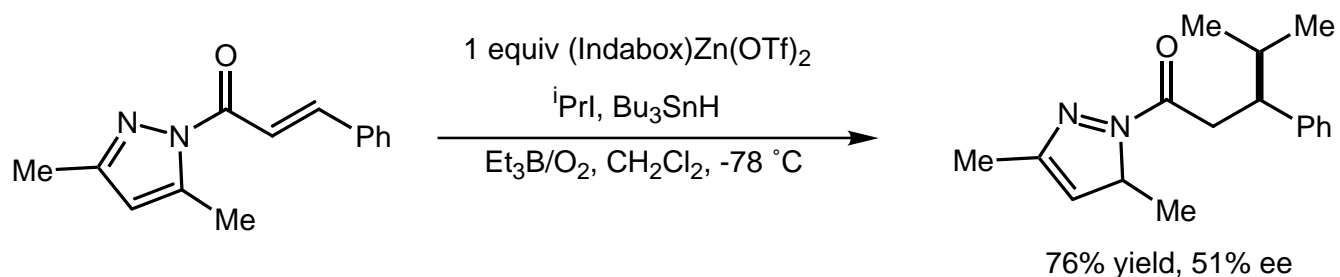
Attack from front face



- 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.

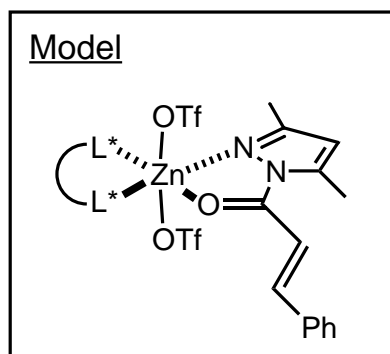
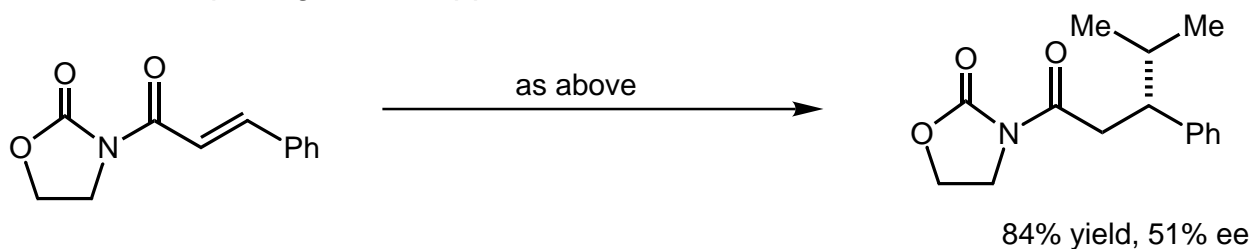
Sibi, JOC, 1997, 3800

The Pyrazole Template in Radical Conjugate Additions



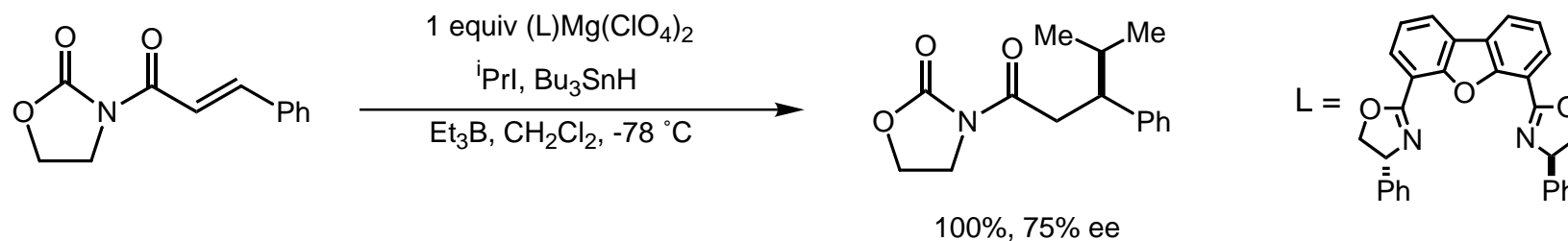
- Reactions with other Mg(II), Zn(II) salts were unselective.
- Unsubstituted pyrazoles gave low yields

An oxazolidinone template gave the opposite enantiomer



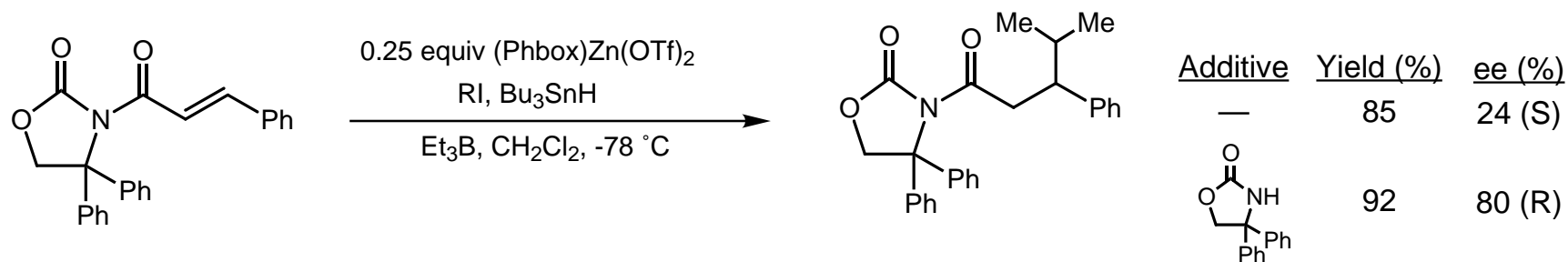
Sibi, Tett. Lett., 1997, 5955

Other Conjugate Radical Addition Reactions



- Almost 30 Lewis Acids were screened.

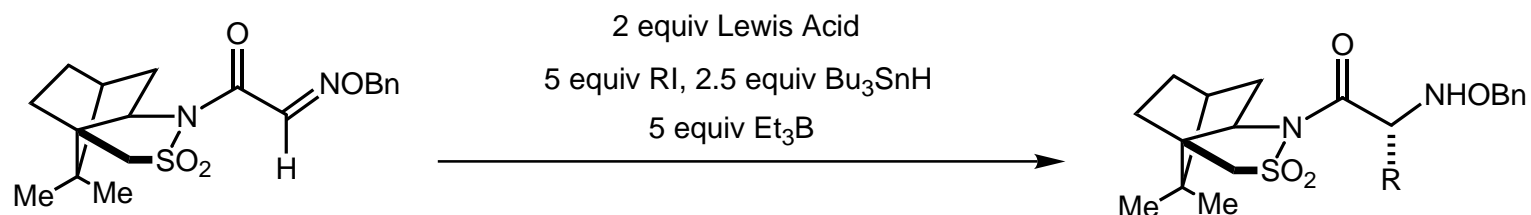
Kanemasa, Curran, Tetrahedron: Asym., 1999, 2417



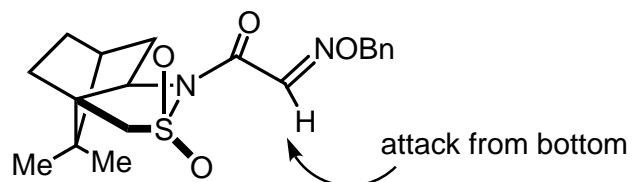
- Additive was shown to compete with substrate for coordination to the zinc center.

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

Carbon Radical Addition to Glyoxylic Oxime Ethers

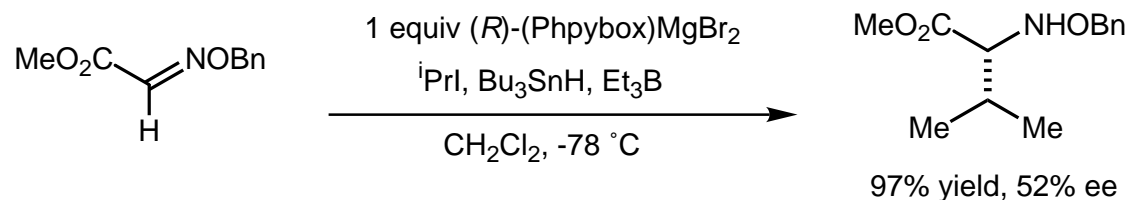


- configuration of substrate is controlled by dipole and steric interactions
- reaction was also run without Bu₃SnH



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

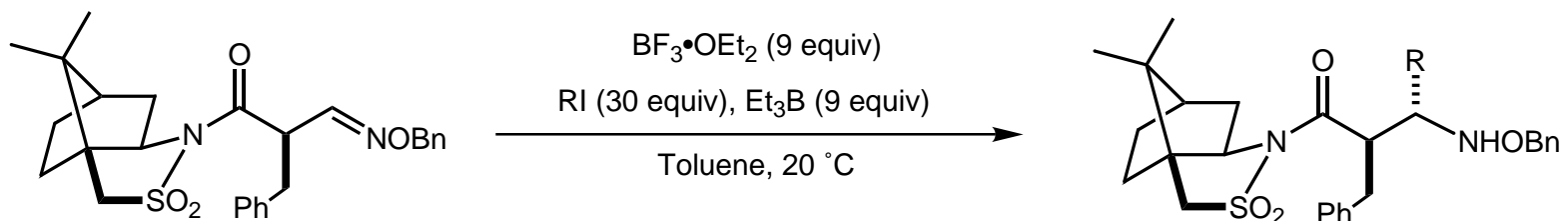
Chiral Lewis Acid promoted additions



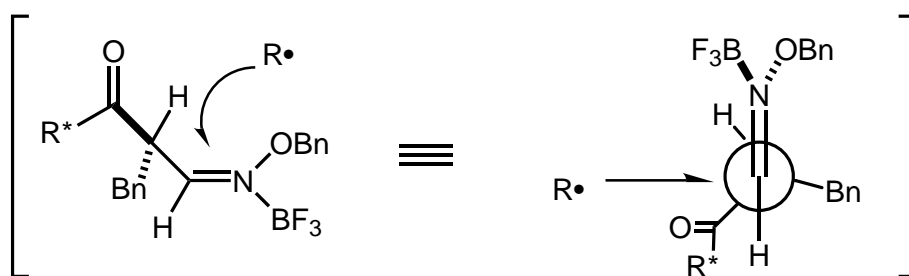
- For reactions on solid phase see Naito, Org. Lett., 2000, 1443

Naito, JOC, 2000, 176

Radical Addition to Oxime Ethers: β -Amino Acids

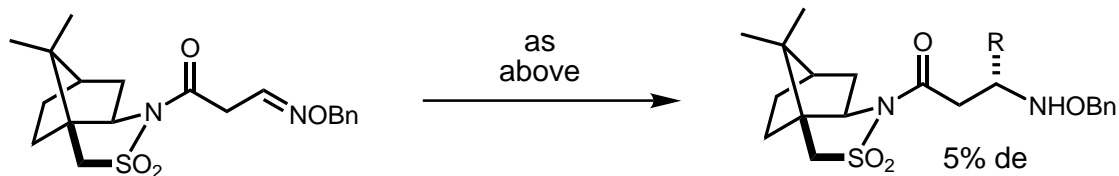


• no reaction occurred in the absence of $\text{BF}_3 \cdot \text{OEt}_2$



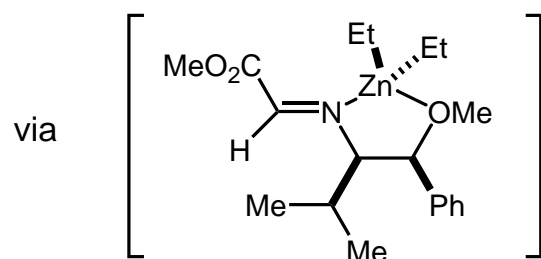
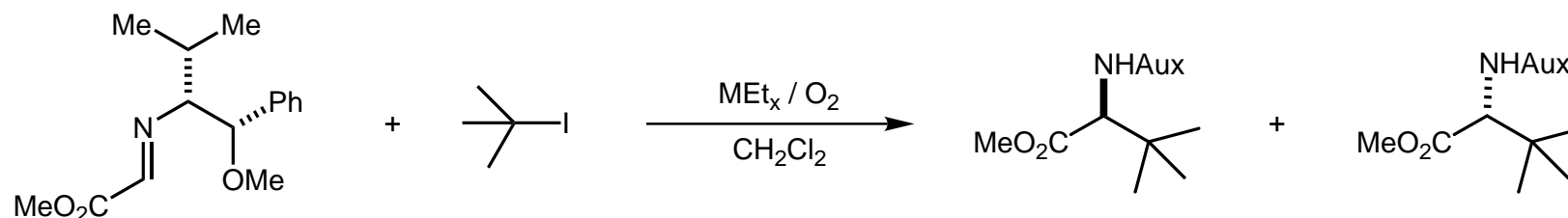
R	Yield (%)	dr
ⁱ Pr	70	>95 : 5
^c Hexyl	57	>95 : 5
^c Pentyl	59	>95 : 5
^s Bu	50	>95 : 5
ⁱ Bu	20	>95 : 5

α -Substituent required for good selectivity



Naito, Org. Lett., 1999, 569

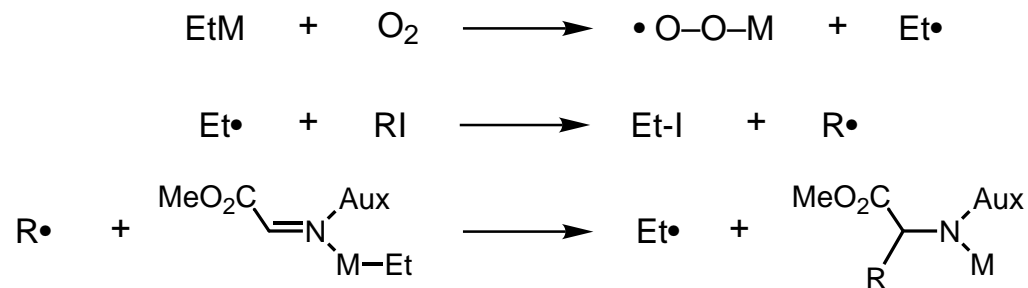
Radical Additions to Glyoxylate Imines



MEt_x	T ($^{\circ}\text{C}$)	dr
BEt_3	20	55 : 45
ZnEt_2	-40	8 : 92

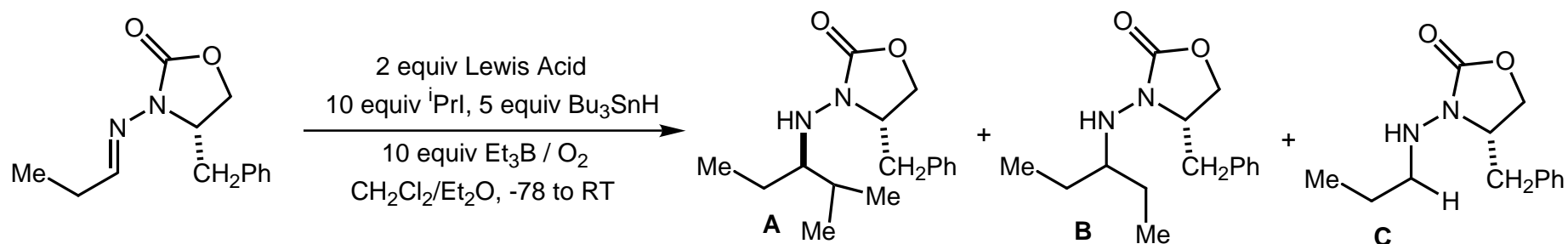
- MEt_x acts as initiator, chain transfer agent, and activating Lewis acid.
- No Sn is required, however a large excess of MEt_x and alkyl iodide is used in these reactions

Sn-Free Radical Reactions



Bertrand, Tetrahedron, 2000, 3951.

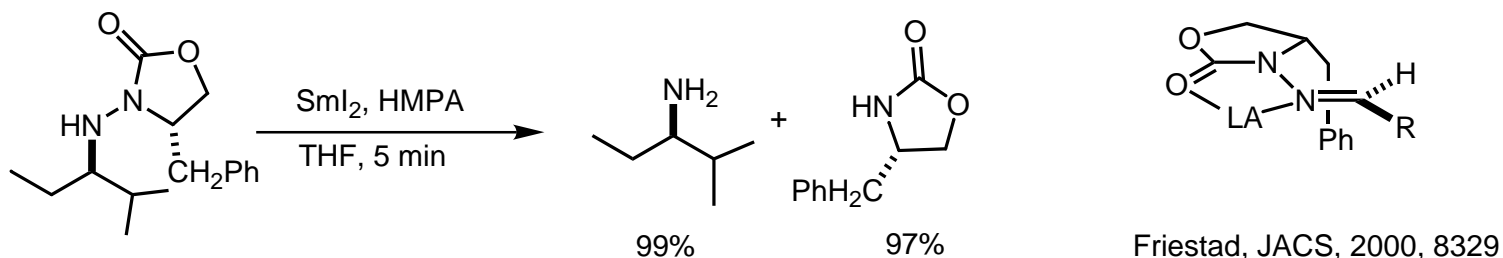
Intermolecular Radical Addition to Hydrazones



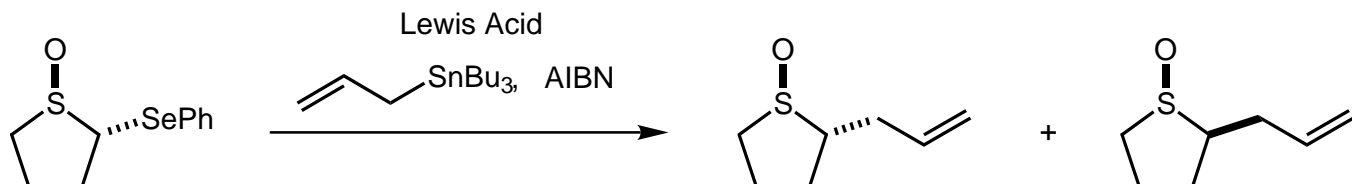
- In all reactions A was formed as a single diastereomer.
- Several alkyl radicals gave 42-60% yields of addition products in >96:4 dr.
- Benzaldimine also provided good selectivities.

<u>Lewis Acid</u>	<u>A : B : C</u>	<u>Yield A (%)</u>
None	-	0
$\text{BF}_3 \cdot \text{OEt}_2$	0 : 0 : 100	0
$\text{Yb}(\text{OTf})_3$	96 : 4 : 0	32
$\text{Zn}(\text{OTf})_2$	91 : 9 : 0	60

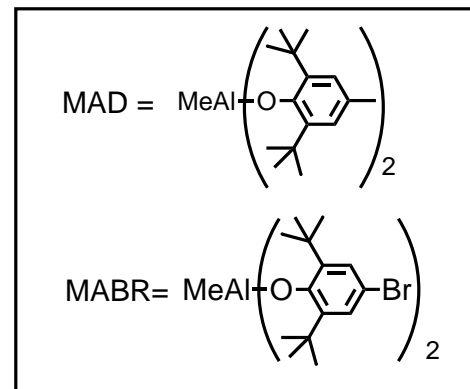
Auxiliary Removal:



Allylation of α -Sulfinyl Radicals



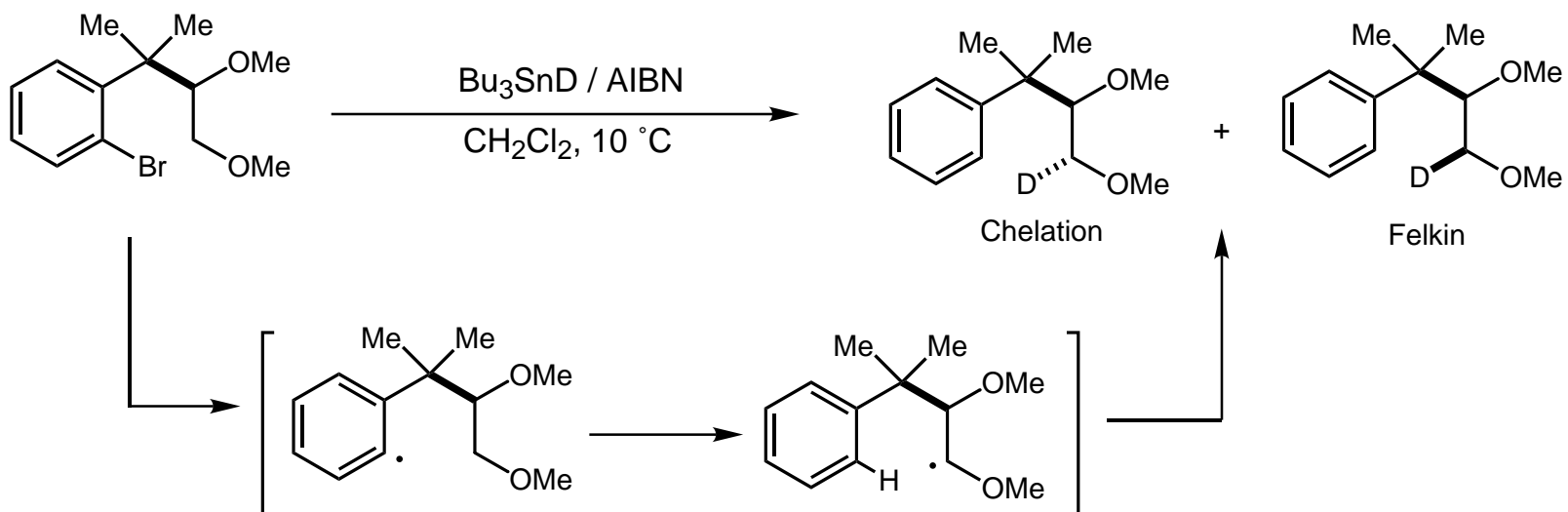
<u>Solvent</u>	<u>Lewis Acid</u>	<u>trans : cis</u>
propionitrile	—	77:23
propionitrile	LiClO ₄	90:10
CH ₂ Cl ₂	—	82:18
CH ₂ Cl ₂	MAD (1)	98:2
CH ₂ Cl ₂	MABR (1)	98:2
CH ₂ Cl ₂	MABR (0.1)	90:10



- 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

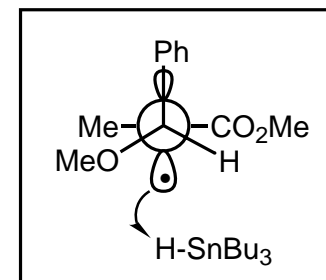
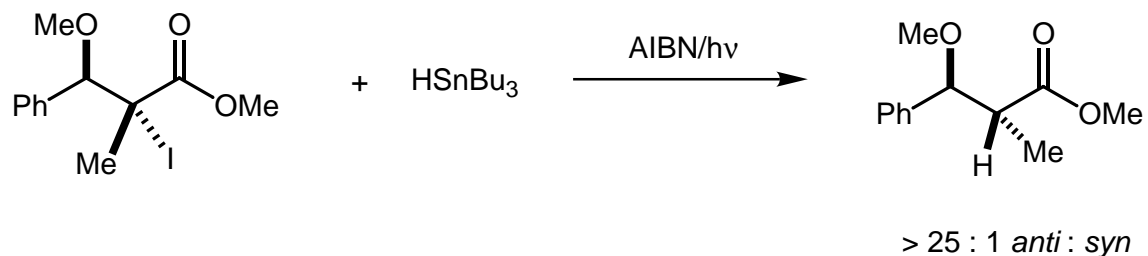


<u>Felkin-Anh</u>	<u>Chelation Control</u>	<u>Lewis Acid</u>	<u>Chelation/Felkin</u>
		—	1 : 2.5
		$\text{ZnCl}_2 \cdot \text{OEt}_2$	1 : 1.4
		$\text{Ti}(\text{OiPr})_3\text{Cl}$	1 : 3
		$\text{MgI}_2 \cdot \text{OEt}_2$	17 : 1

Renaud, JACS, 1995, 6607

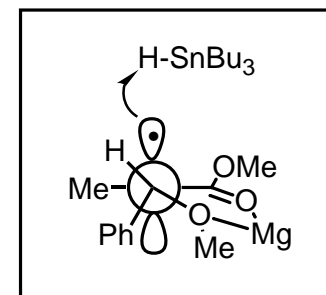
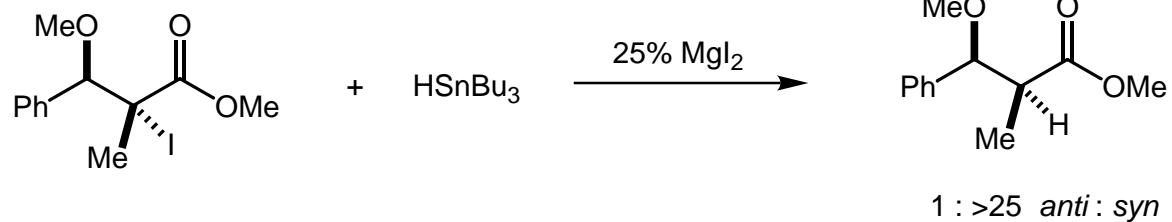
Stereoselective Chelation Controlled Reductions

- Reduction in the Absence of Lewis Acid

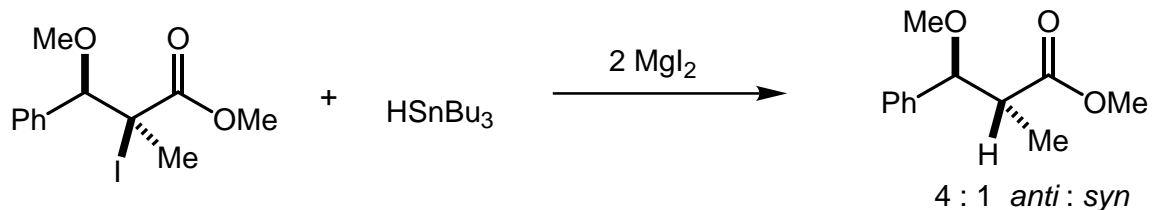


- Reduction under Chelation Control

Anti:



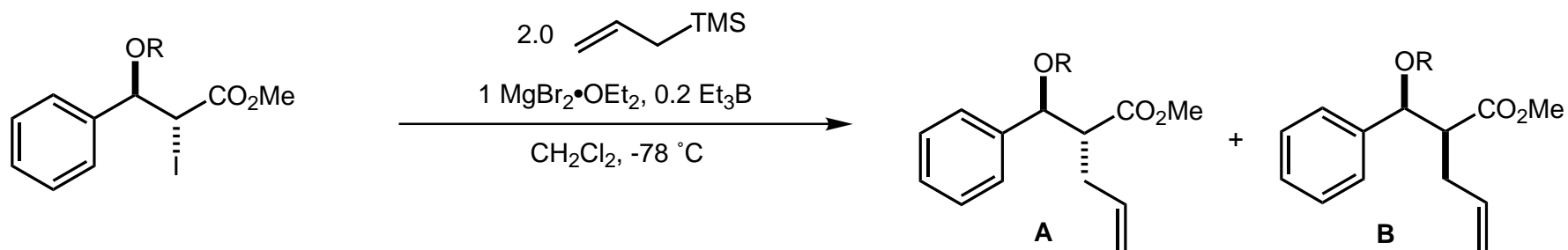
Syn:



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

Guindon, JACS, 1991, 9701

Stereoselective Allylations

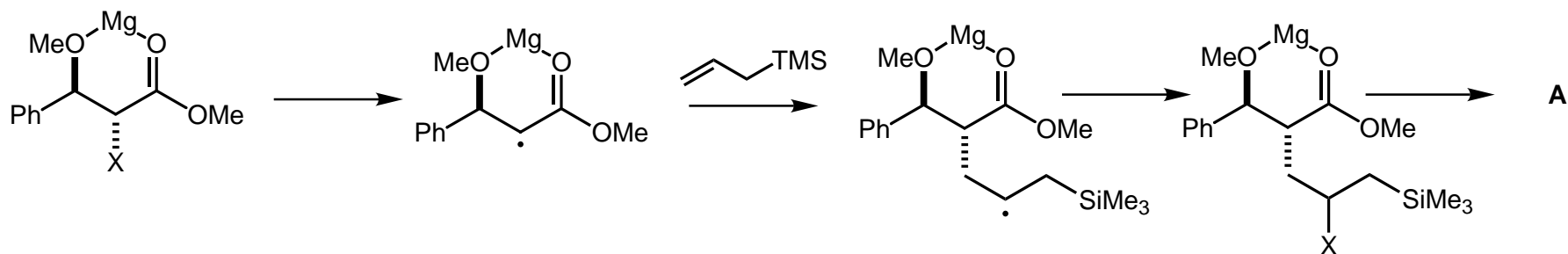


- Reactions with added Lewis acid proceed more readily.

- increased rate of atom transfer?
- increased rate of allyl addition?

<u>OR</u>	<u>A : B</u>
OTBS	1 : 10
OMe	42 : 1

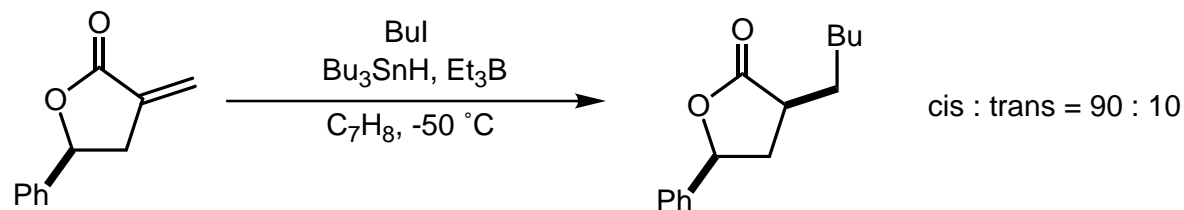
Group Transfer Mechanism



Guindon, JACS, 1996, 12528

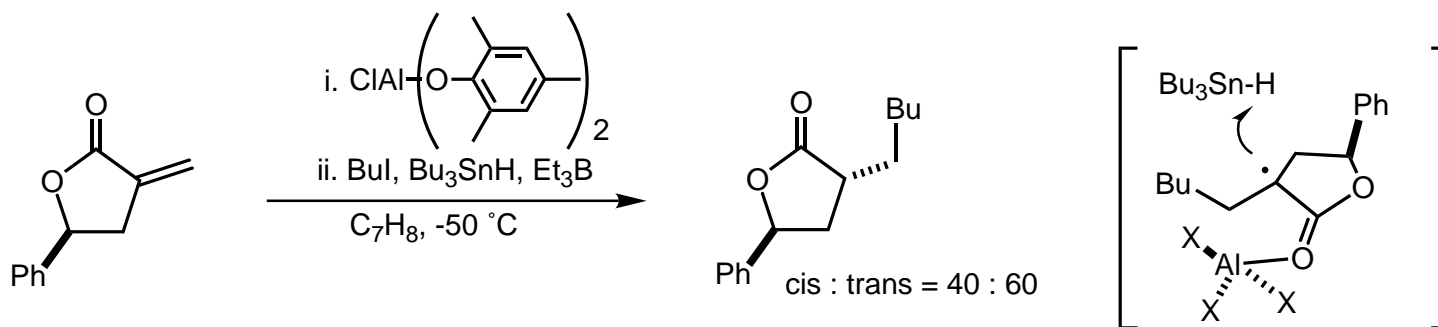
Stereoselective Addition to α -Methylenebutyrolactones

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



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

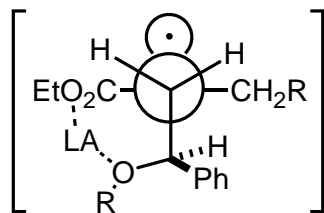
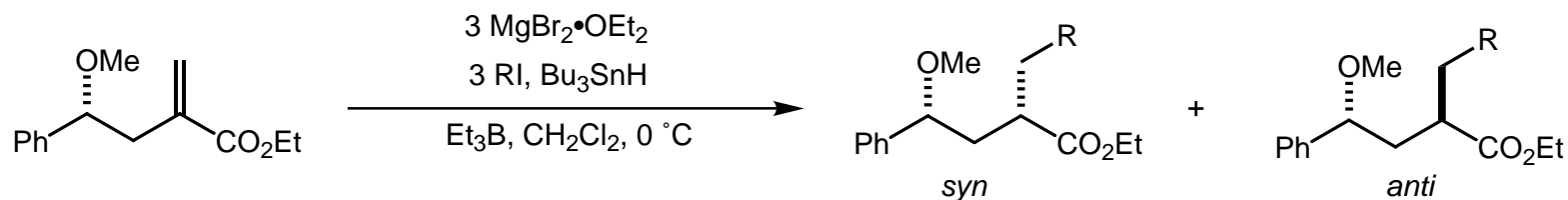
- Reversal of diastereoselectivity using bulky Lewis Acids



Sato, Chem. Commun., 1995, 1043

Chelation Controlled 1,3-Asymmetric Induction

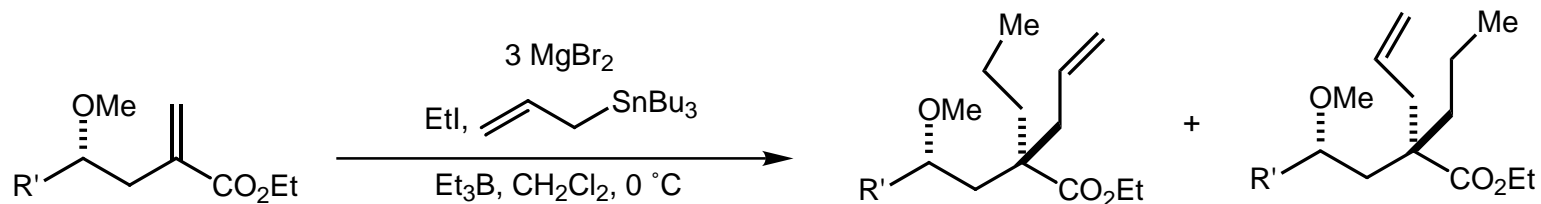
Reduction Reactions



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 MgBr₂

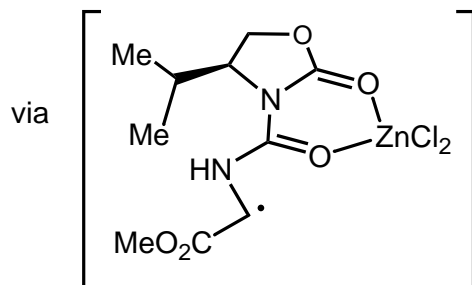
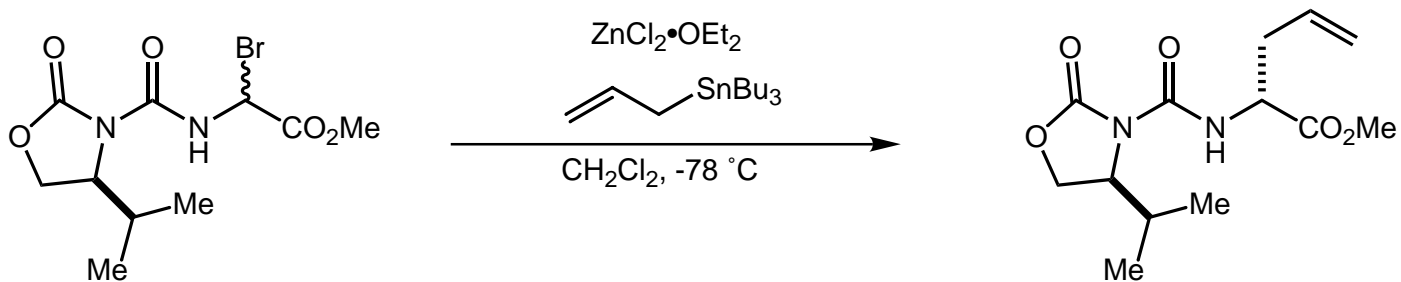
Allylation Reactions



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

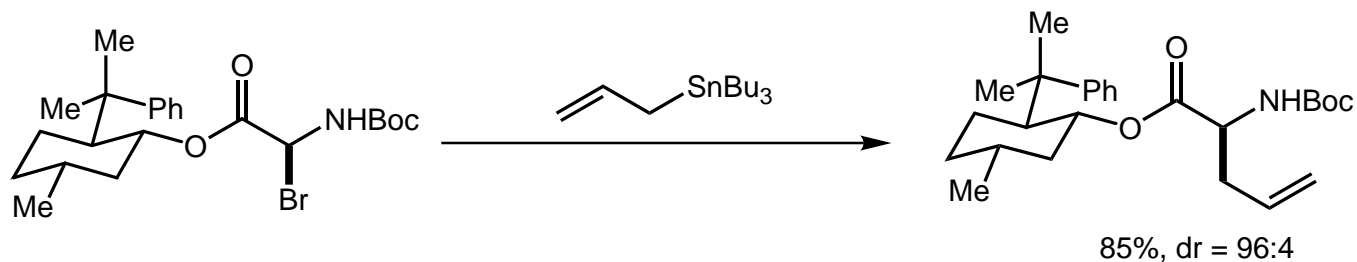


Equiv ZnCl_2	Yield (%)	dr
2	85	87:13
0.1	65	67:33

- The reaction did not occur in the absence of ZnCl_2 .

Yamamoto, JACS, 1994, 421

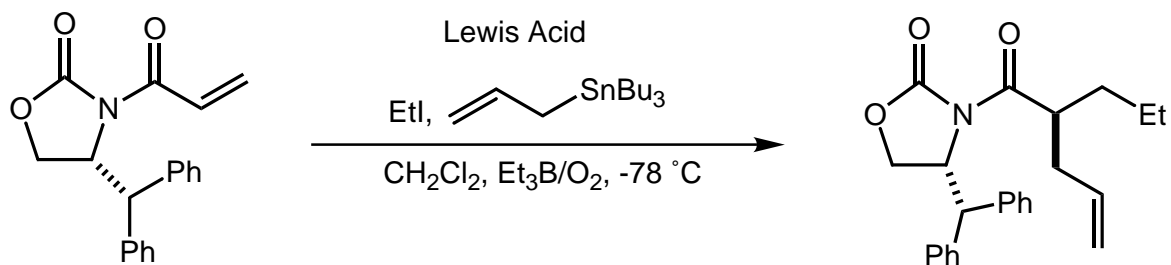
Initial report:



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

Hamon, Chem. Commun., 1991, 722

Diastereoselective Radical Allylation

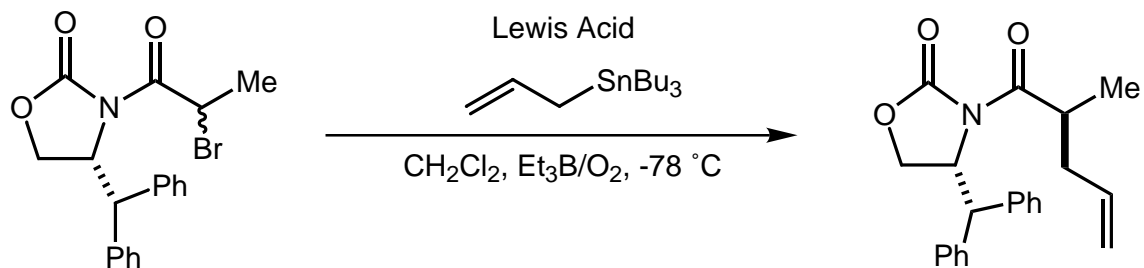


<u>Lewis Acid</u>	<u>Yield</u>	<u>dr</u>
—	90	1:1
BF ₃ •OEt ₂	90	1.0 : 1.8
MgBr ₂ •OEt ₂	93	>100 : 1
Yb(OTf) ₃	90	>100 : 1

- 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, ⁱPrI, ^tBuI, ^cHexI, MeOCH₂Br, MeC(O)Br, and PhC(O)Br.

Sibi, JOC, 1996, 6090

Study of ρ Selectivity with Chiral Oxazolidinones

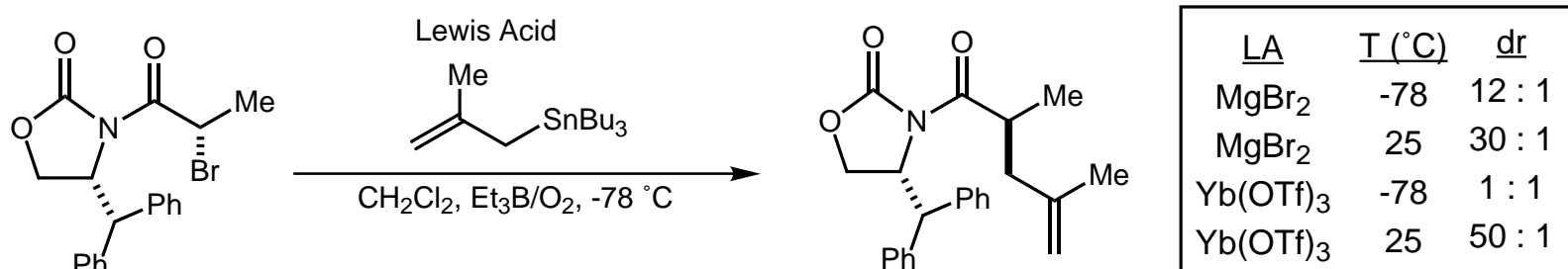
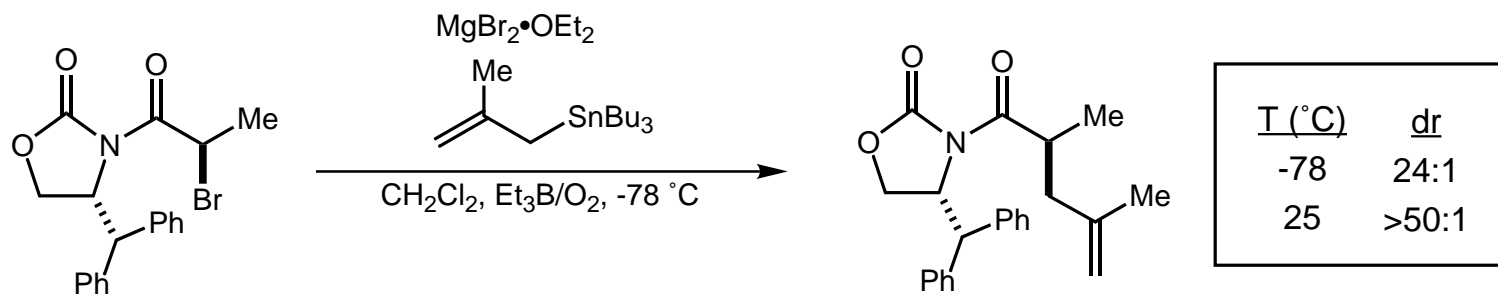


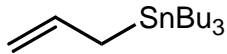
<u>Lewis Acid</u>	<u>Yield</u>	<u>dr</u>
—	93	1:1
$\text{MgBr}_2 \cdot \text{OEt}_2$	90	>100 : 1
$\text{Sc}(\text{OTf})_3$	94	>100 : 1
$\text{Yb}(\text{OTf})_3$	64	5 : 1

- 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

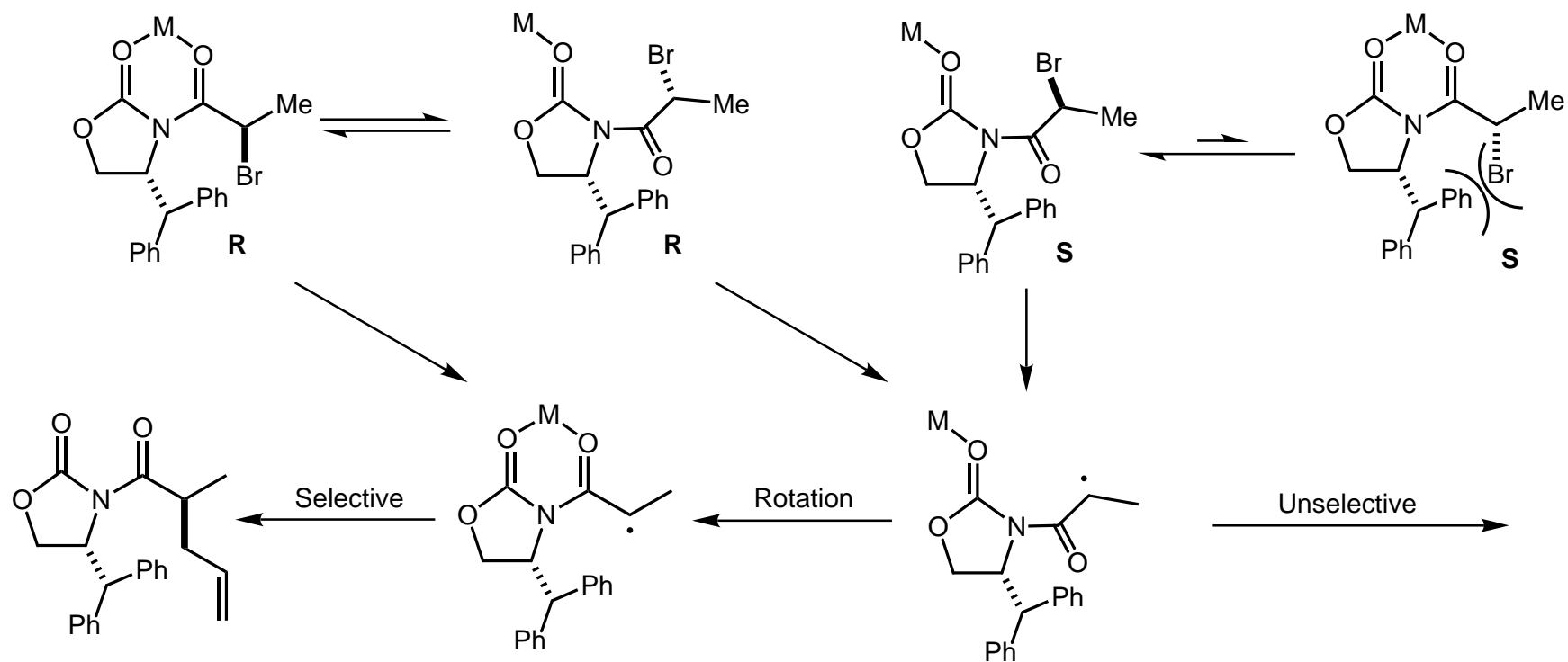
Mechanistic Study Revealed that the Mechanism Was Complex



- The Mg-mediated reaction with  provided 40:1 dr for both starting diastereomers at $-78\text{ }^\circ\text{C}$, 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

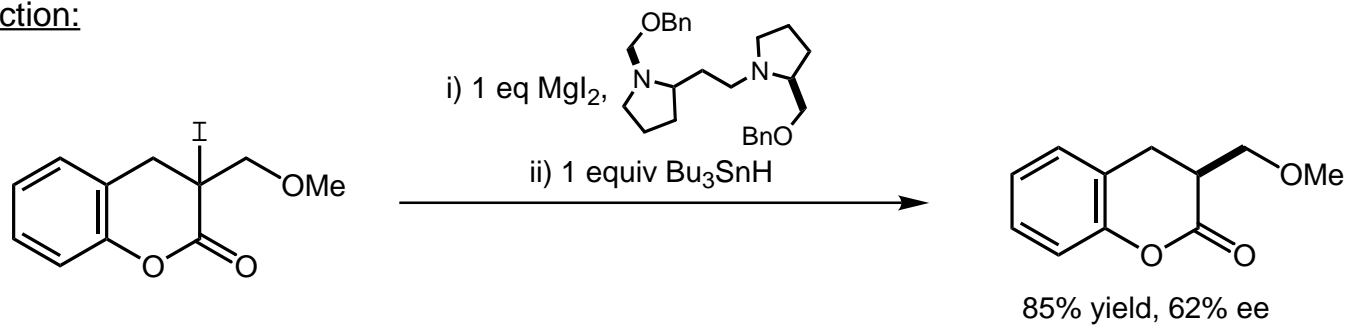


- Rate of rotation must increase with temperature faster than the rate of trapping with allyl stannane.
- The relative rates of rotation vs. allyl trapping explain why slower reacting allyl reagents show higher selectivity.

Sibi, JACS, 2000, 8873

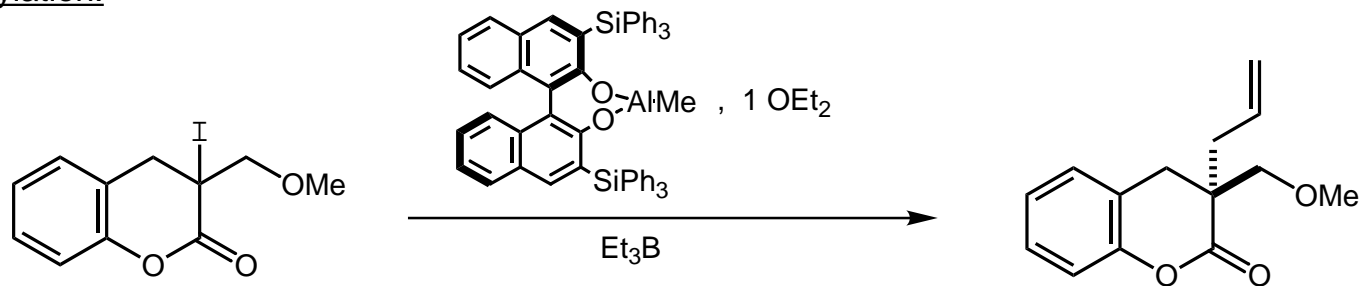
Enantioselective Reduction/Allylation of an α -Iodolactone

Reduction:



Hoshino, Chem. Commun., 1995, 481

Allylation:

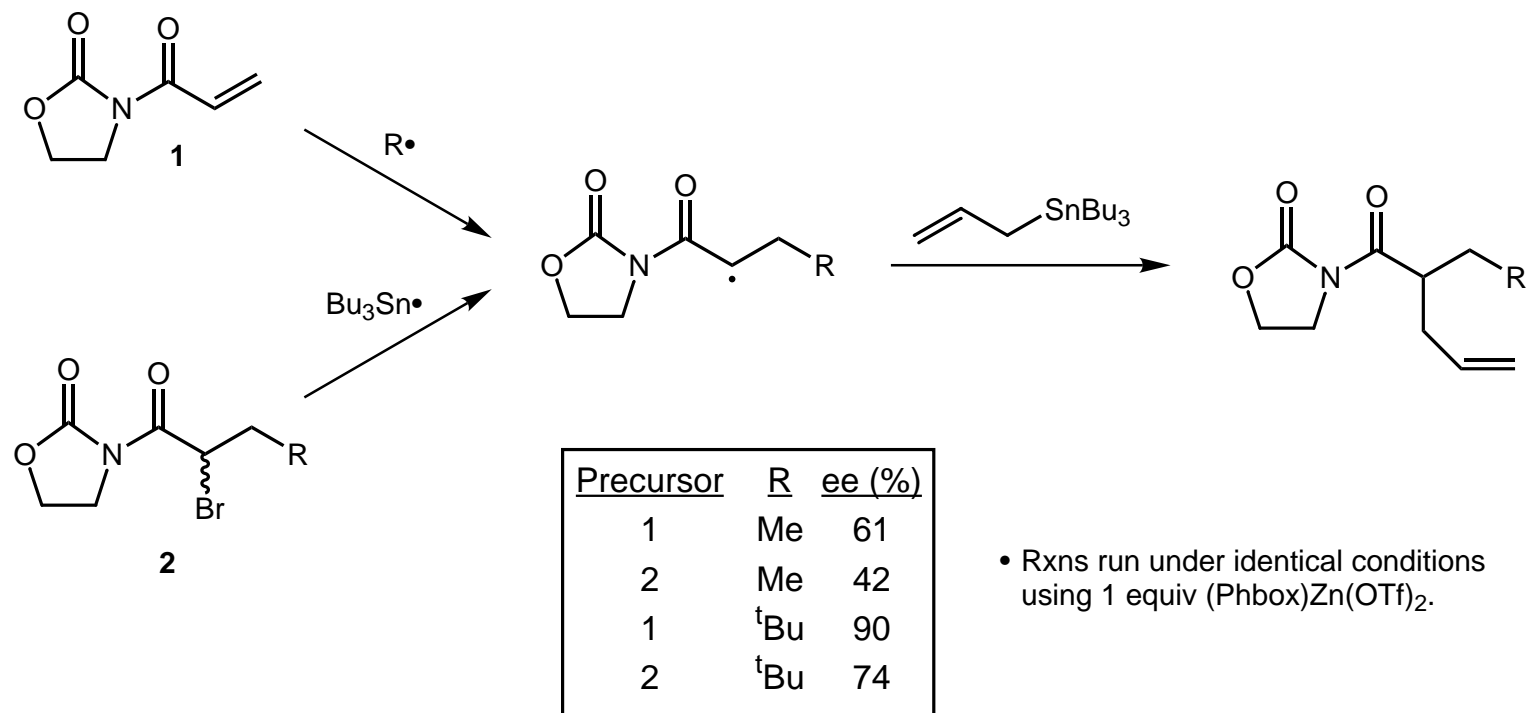


- More than 1 equiv of Et_2O was detrimental to ee.

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

Hoshino, JACS, 1997, 11713

Study of ρ Selectivity with Chiral Lewis Acids

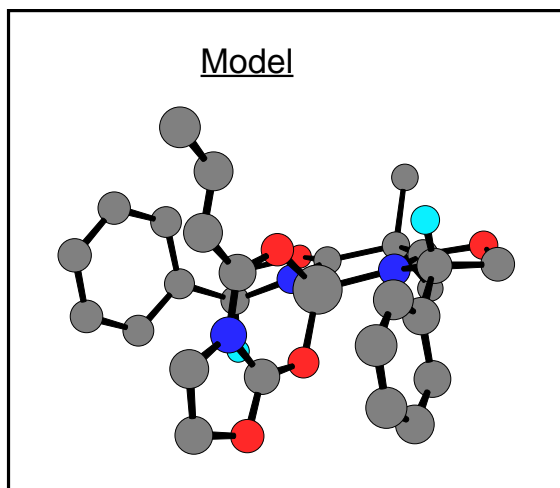
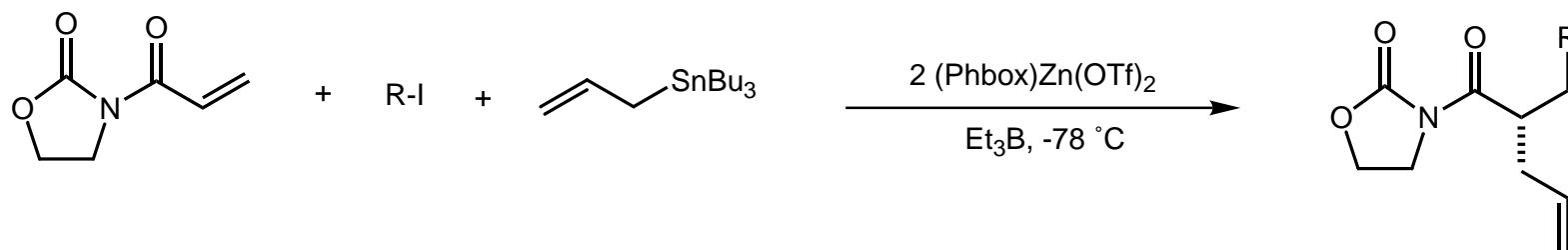


- Rxns run under identical conditions using 1 equiv (Phbox)Zn(OTf)₂.

- 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 XSnBu₃ byproduct negatively effected ee.

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

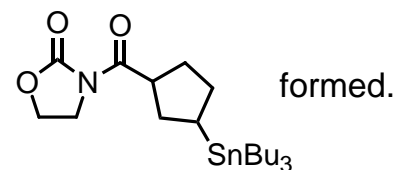
Enantioselective Allylation Using Chiral Lewis Acids



- Reaction proceeds well with only 1.5 equiv RI,
1.5 equiv Bu_3SnH

R	Yield (%)	ee (%)
^cHex	92	72
^tBu	85	88

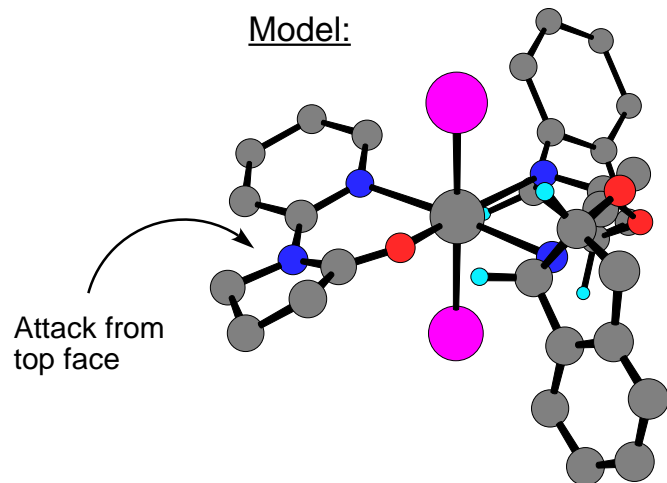
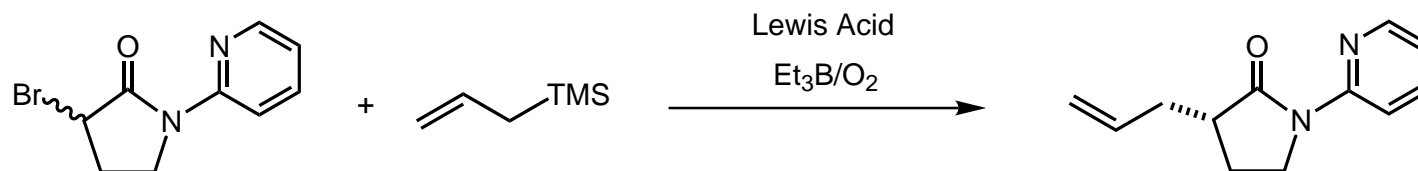
- At higher T, significant amounts of



formed.

Porter, JACS, 1995, 11029

Enantioselective Reactions of Radicals Generated from γ -Lactams

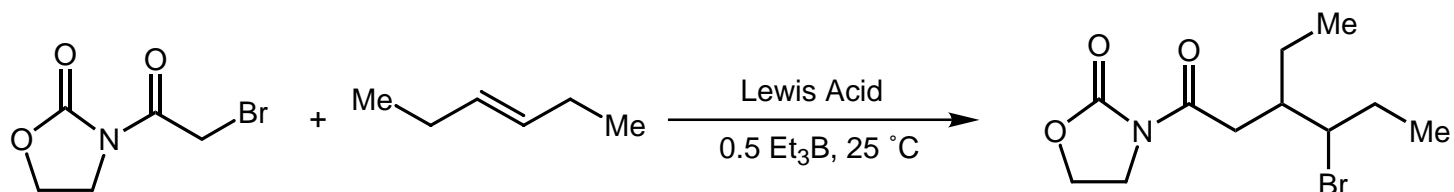


<u>Lewis Acid (eq)</u>	<u>T (°C)</u>	<u>ee (%)</u>	<u>Yield (%)</u>
(Phbox)Zn(OTf) ₂ (1)	-78	59	70
(Indabox)Zn(OTf) ₂ (1)	-78	96	75
(Indabox)Zn(OTf) ₂ (1)	-20	80	91
(Indabox)Zn(OTf) ₂ (0.2)	-20	81	69

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

Porter, Tetrahedron Lett., 1999, 6713

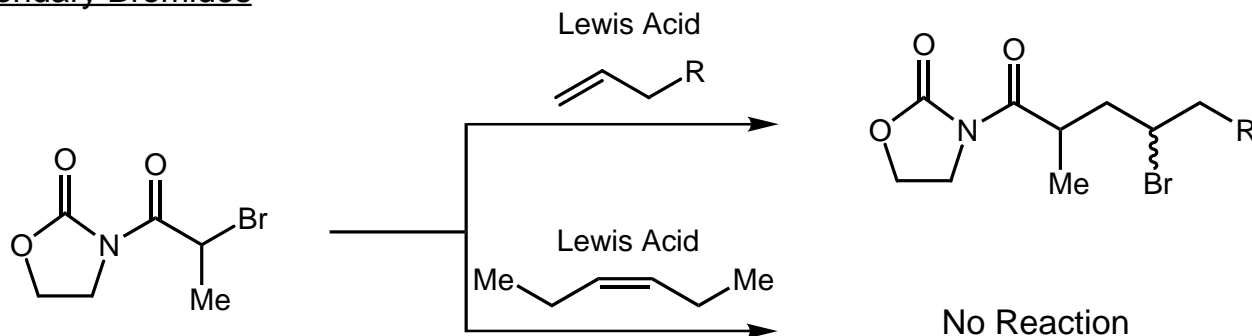
Lewis Acid Promoted Atom-Transfer Radical Additions



- 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) ₂	16
Sc(OTf) ₃	47
Yb(OTf) ₃	100

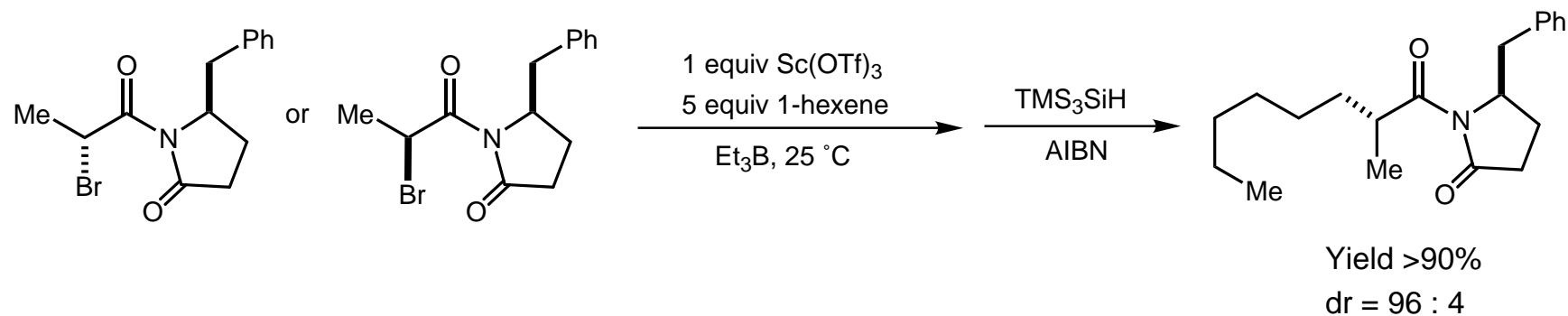
Secondary Bromides



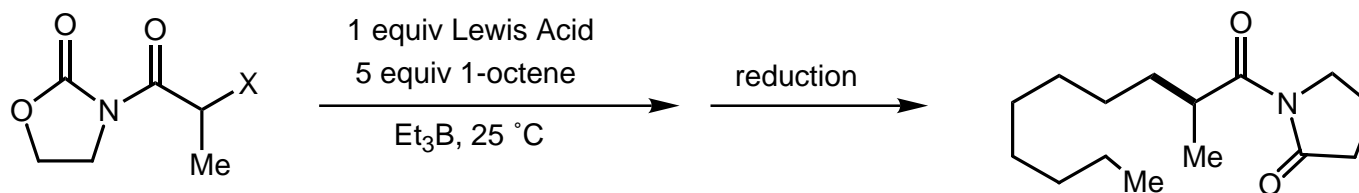
Porter, JACS, 1999, 5155

Diastereoselective and Enantioselective Atom Transfer

Diastereoselective Reactions



Enantioselective Reactions

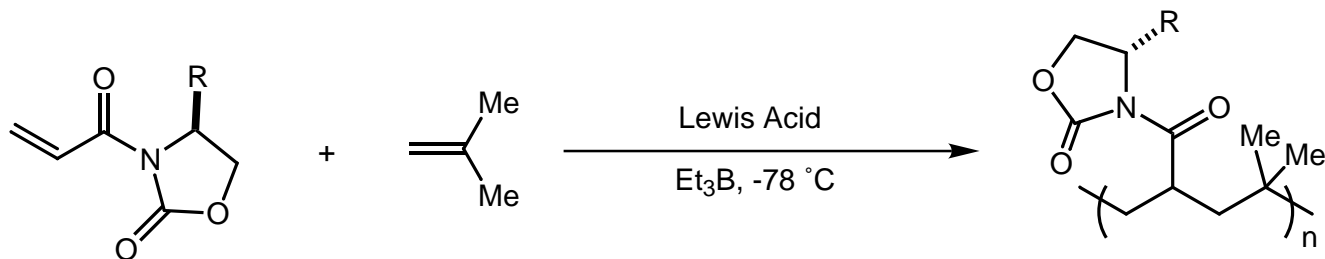


X	Lewis Acid	Yield (%)	ee (%)
Br	(Phbox)Sc(OTf) ₃	64	0
Br	(Phbox)Zn(OTf) ₂	0	—
I	(Phbox)Zn(OTf) ₂	<15	40

Porter, JACS, 1999, 5155

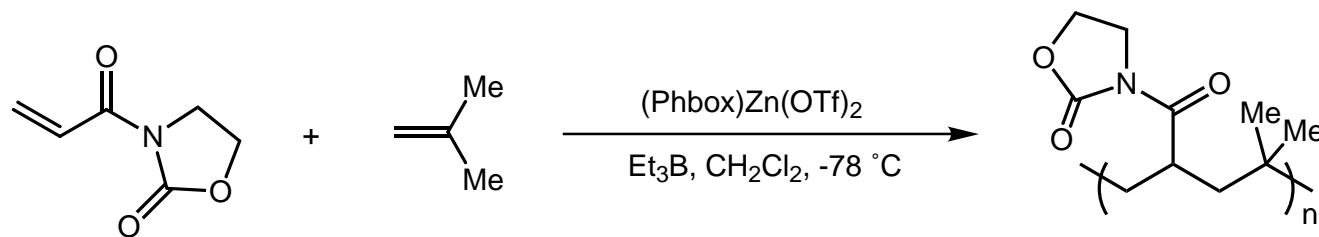
Free-Radical Polymerization of Acrylimides

Diastereoselective Copolymerization



- Degree of copolymerization depended on Lewis Acid. $\text{Sc}(\text{OTf})_3$ in Et_2O gave best results (1:1).
- R = Bn provided > 95:5 diastereoselectivity.

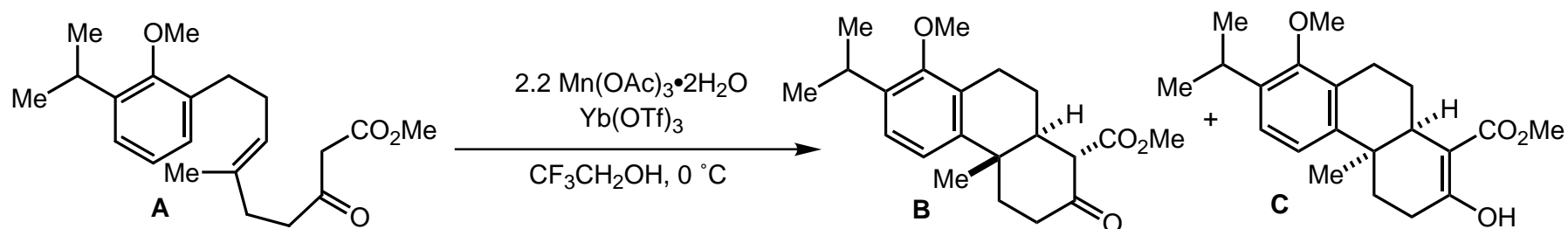
Enantioselective Copolymerization



- 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) ₃ (1.0)	3	69/10
Yb(OTf) ₃ (0.3)	3.5	59/8

Effect of Yb(OTf)₃ on Ketone-Enol Equilibrium:

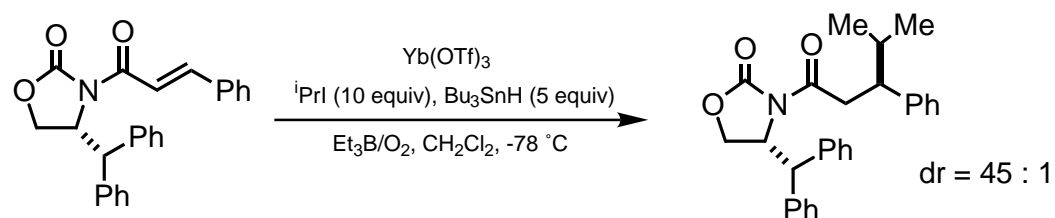
substrate	% in enol form (in MeOH)		
	0 equiv Yb	0.5 equiv Yb	1.0 equiv Yb
	18.1	66.9	72.0

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.