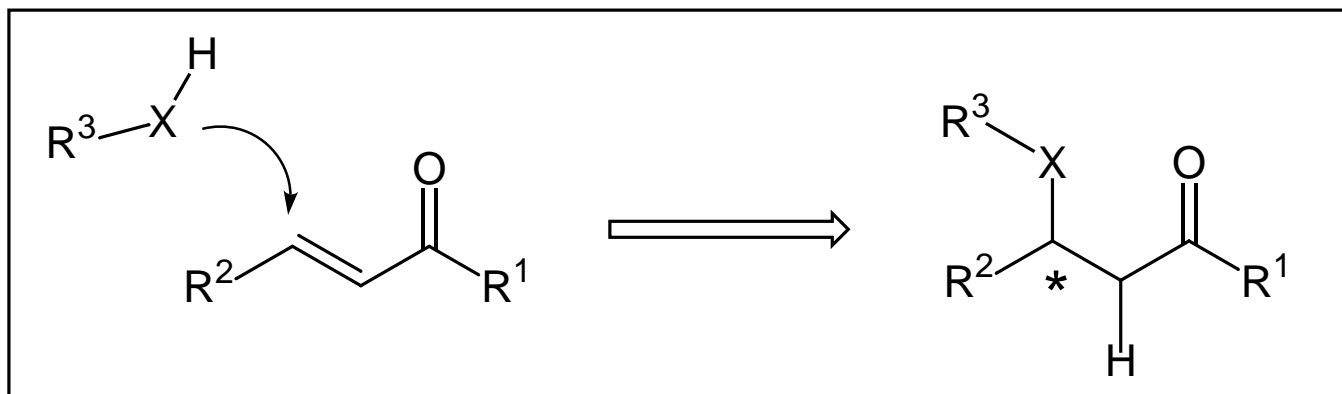


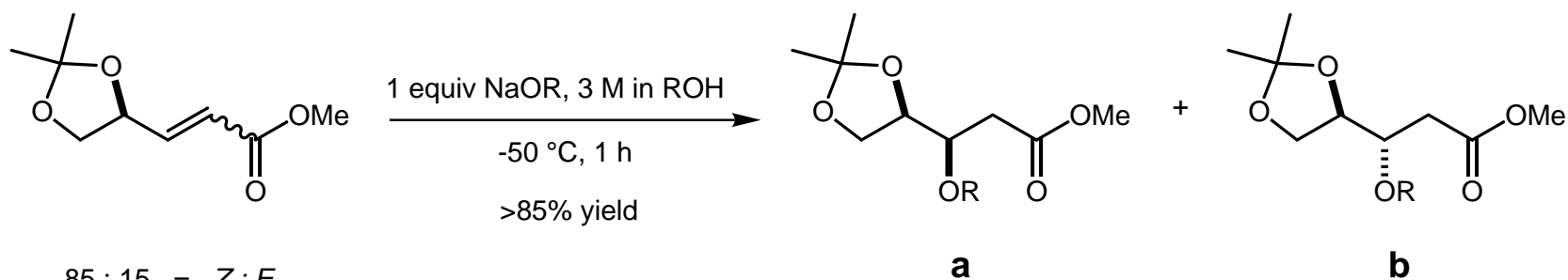
# Asymmetric Heteroatom Conjugate Additions

David Favor  
Evans Group Seminar  
3/10/00

- I. a) Diastereoselective Oxygen Nucleophiles  
b) Enantioselective Oxygen Nucleophiles
- II. a) Diastereoselective Nitrogen Nucleophiles  
b) Enantioselective Nitrogen Nucleophiles
- III. a) Diastereoselective Sulfur Nucleophiles  
b) Enantioselective Sulfur Nucleophiles
- IV. a) Diastereoselective Chlorine Additions

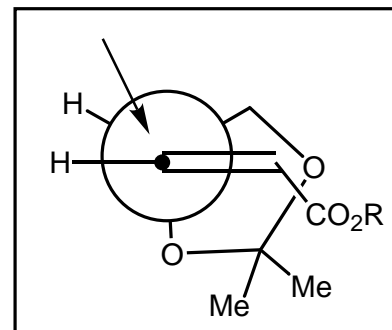


## Asymmetric Alkoxide Addition to a $\gamma$ -Chiral Enone



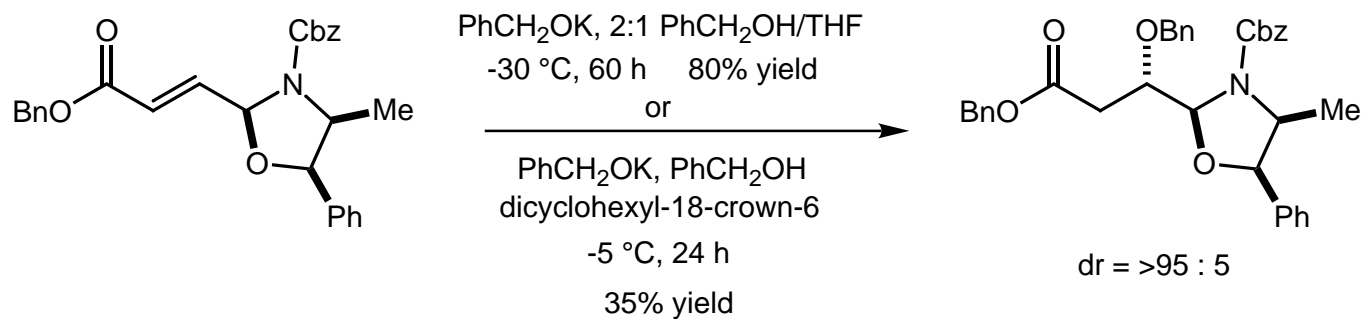
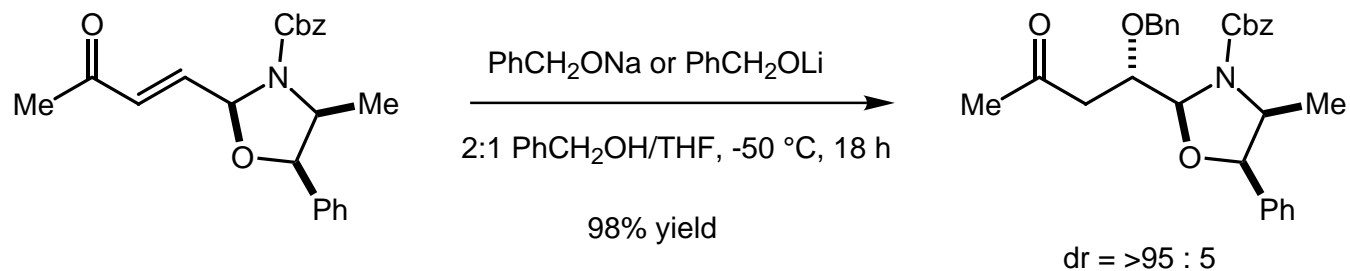
85 : 15 = *Z* : *E*

<u>Alcohol</u>	<u>T</u> (°C)	<u>dr</u> (a:b)	<u>time</u> (min)
MeOH	25	60:40	6
MeOH	-50	91:9	6
MeOH	-78	95:5	60
EtOH	-50	86:14	60
BnOH	-10	76:24	120



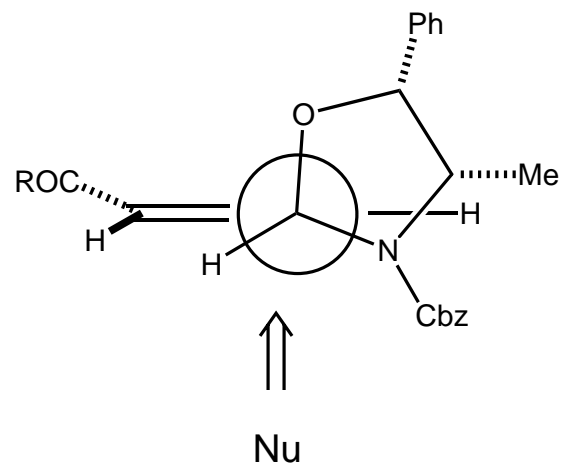
Mulzer, J.; Kappert, M.; Gottfried, H.; Jibril, I. *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 704.

## Diastereoselective Benzylalcohol Additions to $\delta$ -Substituted- $\alpha,\beta$ -unsaturated Esters

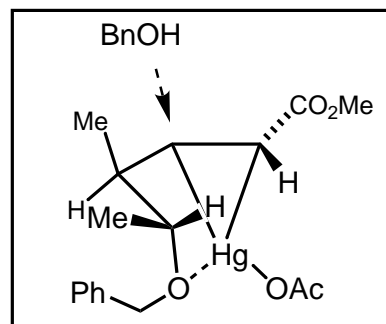
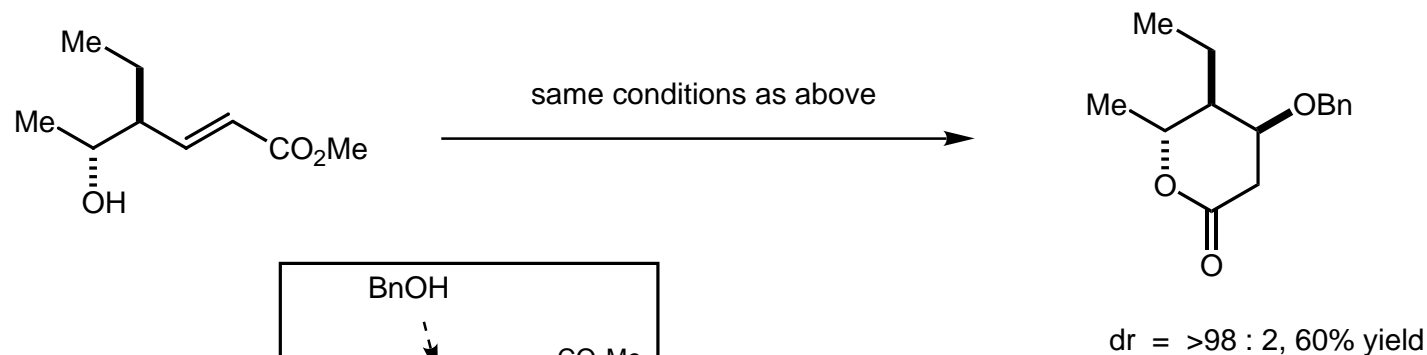
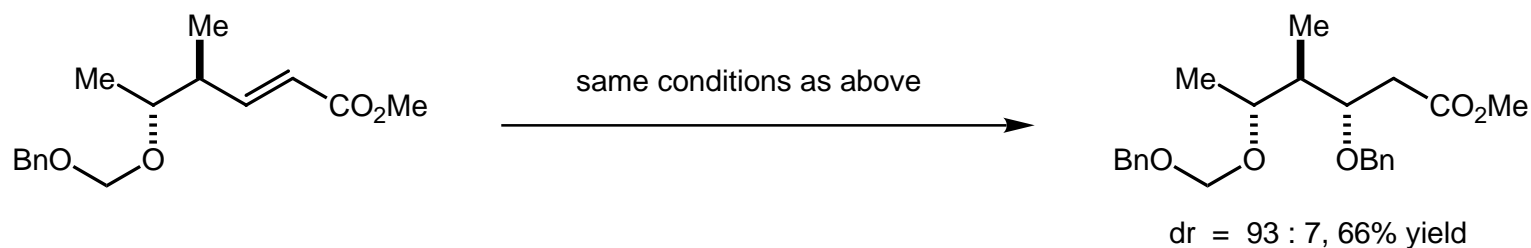
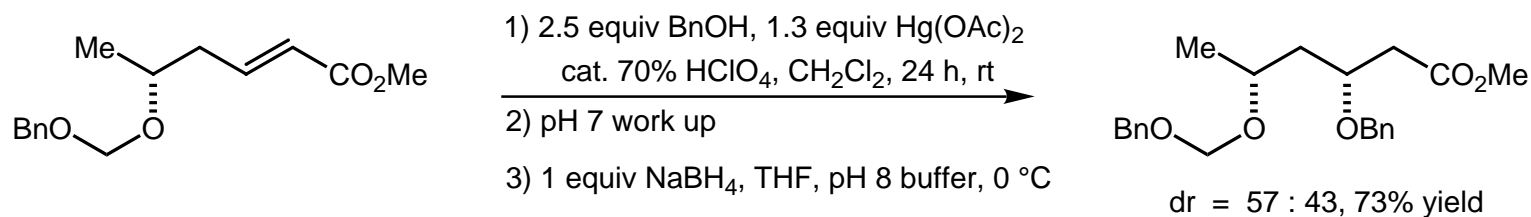


Insensitivity to counterion implies a non-chelated mechanism.

Bernardi, A.; Cardani, S.; Scolastico, C.;  
 Villa, R. *Tetrahedron* **1990**, *46*, 1987.

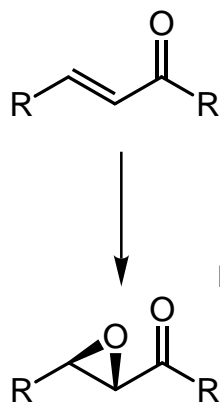


## Diastereoselective Benzyloxymercuration of $\gamma$ -Alkyl- $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated Esters



Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407.

# Enantioselective Epoxidation of $\alpha,\beta$ -Enones Utilizing Polyamino Acids Catalysts



Reaction conditions:  
cross-linked polystyrene with  
grafted with polylysine (n = 32)  
 $\text{H}_2\text{O}_2$ -NaOH,  $\text{PhCH}_3$

First example of the use of polyamino acid for enantioselective epoxidation:  
Julia, S.; Masana, J.; Vega, J. C.  
*Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929.

For a review of polyamino acid mediated epoxidations see:

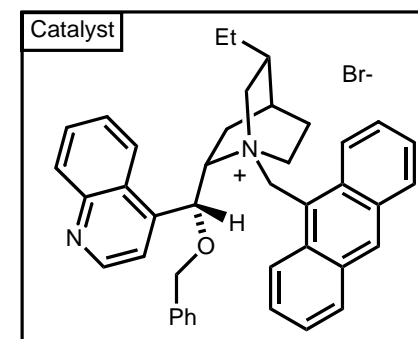
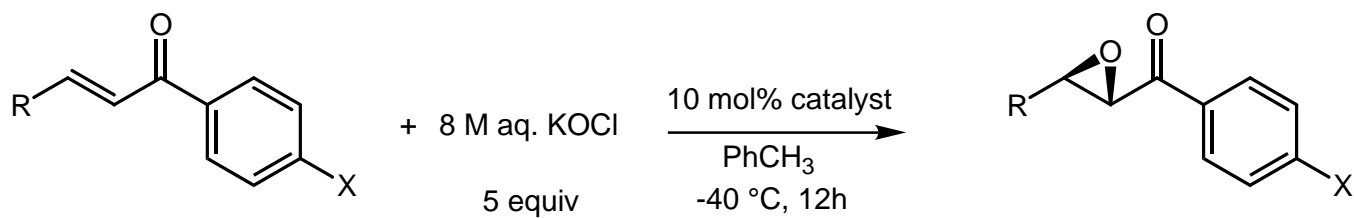
Ebrahim, S.; Wills, M. *Tetrahedron: Asymm* **1997**, *8*, 3163.

Pu, L. *Tetrahedron: Asymm* **1998**, *9*, 1457.

	<u>%ee</u>	<u>%yield</u>
	99	98
	90	89
	76	56
	90	89
	83	56
	99	98
	87	83

Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047.

## Enantioselective Epoxidation of $\alpha,\beta$ -Enones



<u>R</u>	<u>X</u>	<u>%ee</u>	<u>% yield</u>
Ph	H	93	96
Ph	F	98	93
<i>p</i> -NO <sub>2</sub> Ph	H	94	90
pentyl	F	91	90
C <sub>6</sub> H <sub>11</sub>	H	94	85
<i>p</i> -MeOPh	H	95	70
$\beta$ -Napht	H	93	87

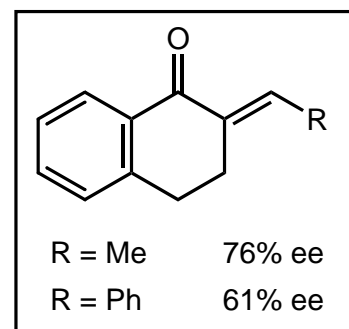
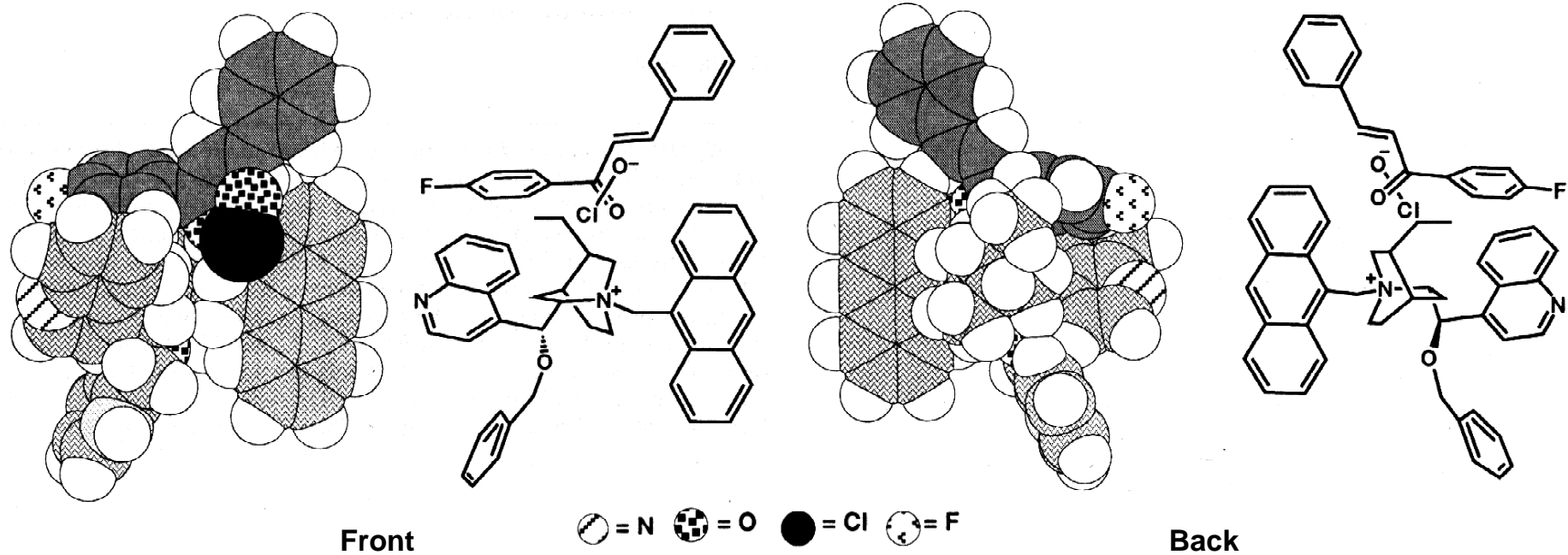
8 more substrates reported

Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

First example: Helder, R.; Hummel, J. C.; Laane, R. W.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831.

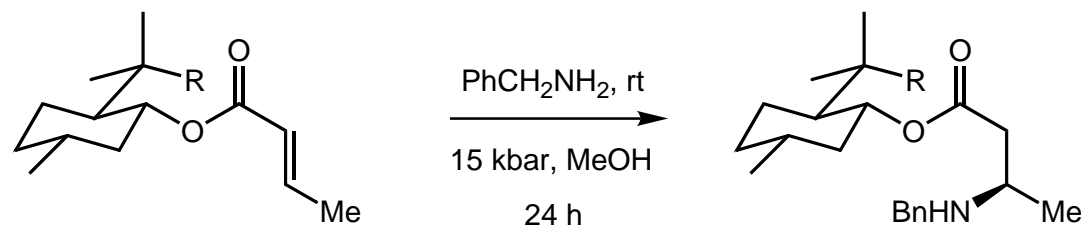
# Enantioselective Epoxidation of $\alpha,\beta$ -Enones

## Stereochemical Rational



Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

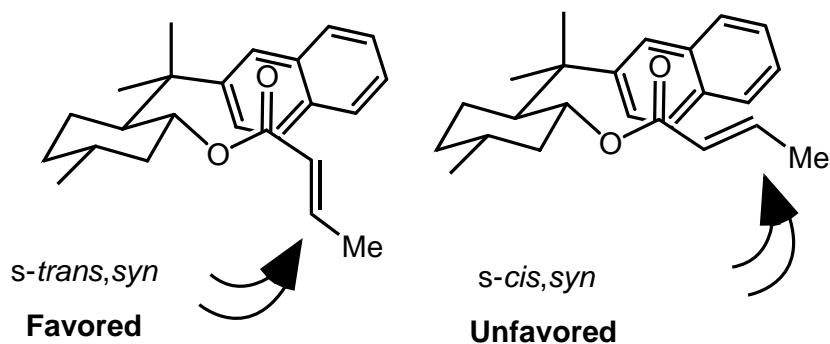
## Asymmetric Addition of Benzylamine to Menthylcrotonate Derivatives



R=	%de	% yield
Ph	60	85
<i>p</i> -PhOPh	95	90
$\beta$ -Napht	99	50

Polar, protic solvents are required.  
Reactions fail in THF and CH<sub>2</sub>Cl<sub>2</sub>.

d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.  
Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500.

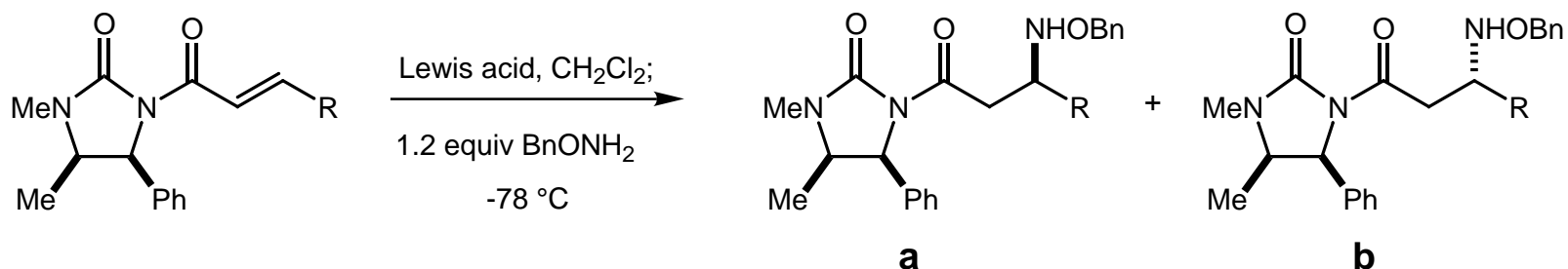


Gas phase calculations indicated that methyl acrylate prefers the *s-cis,syn* conformation. (Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.)

The dipole moment of the *s-trans,syn* and the *s-cis,syn* crotonates are 2.55 and 1.65 D respectively. (George, W. O.; Hassid, D. V. *J. Chem. Soc., Perkin Trans. 2* **1972**, *4*, 400.)



## Diastereoselective Additions of *O*-Benzylhydroxylamine to Unsaturated Amides

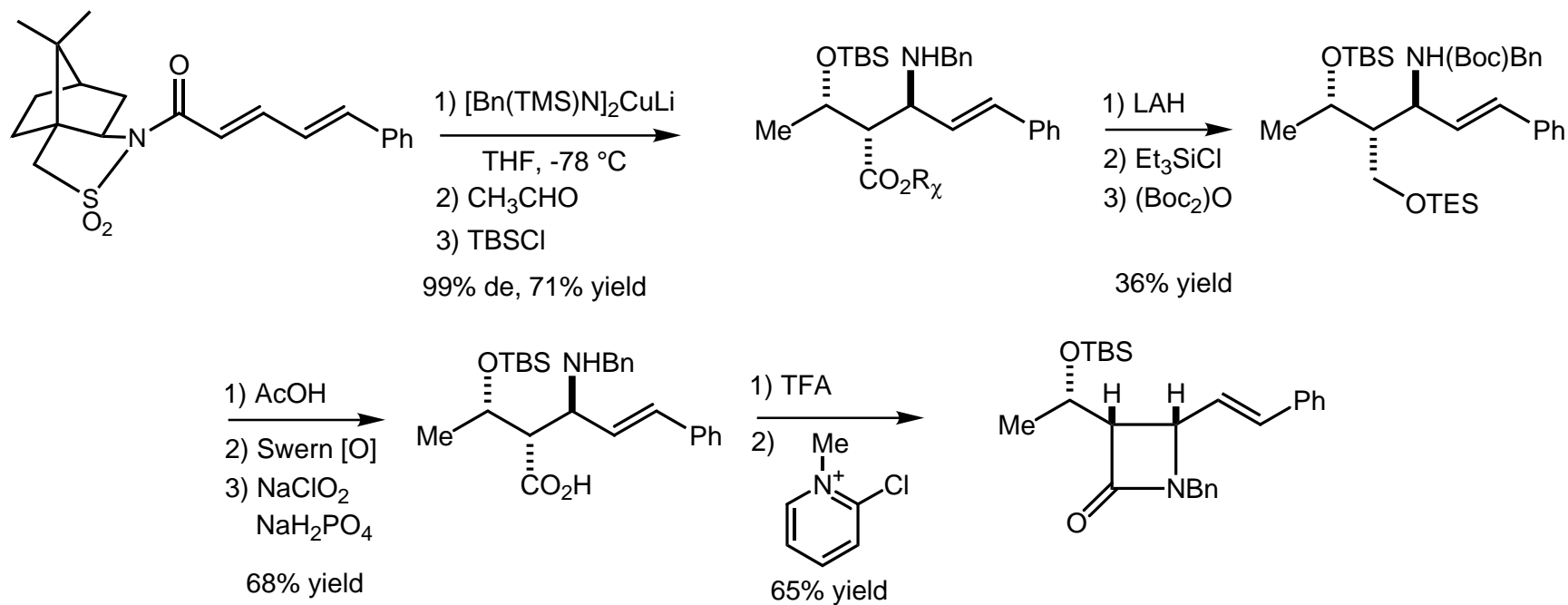
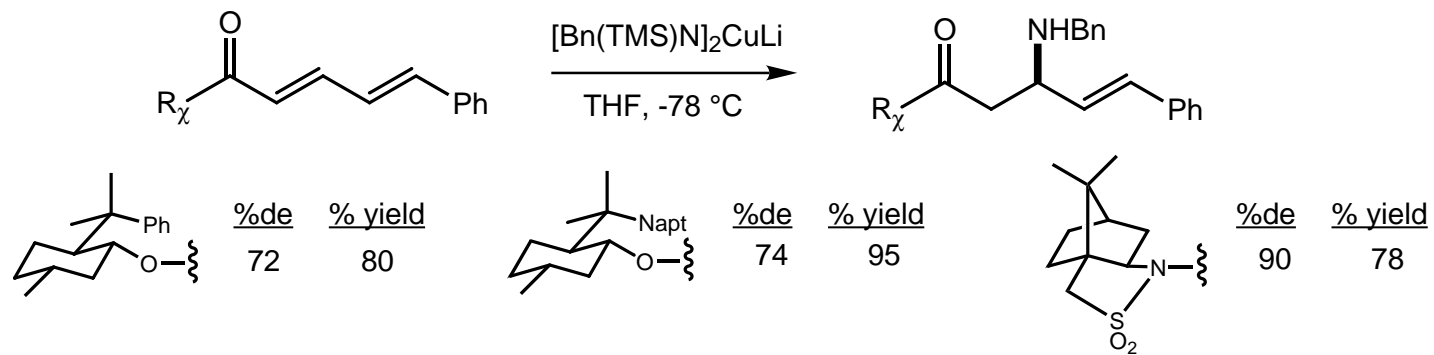


<u>Lewis acid</u>		<u>R</u>	<u>dr (a:b)</u>	<u>% yield</u>	
TiCl <sub>4</sub>	1.0 eq	Me	80:20	80	 Nonchelate product
TiCl <sub>4</sub>	1.0 eq	Pr	77:23	90	
AlCl(Me) <sub>2</sub>	1.4 eq	Me	19:81	65	 Chelate product
AlCl(Me) <sub>2</sub>	2.0 eq	Me	20:80	70	
AlCl(Me) <sub>2</sub>	1.4 eq	Pr	13:87	81	
AlCl(Me) <sub>2</sub>	2.0 eq	Pr	11:89	83	

Evans Diels-Alder Conditions  
*J. Am. Chem. Soc.* **1988**, *110*, 1238.

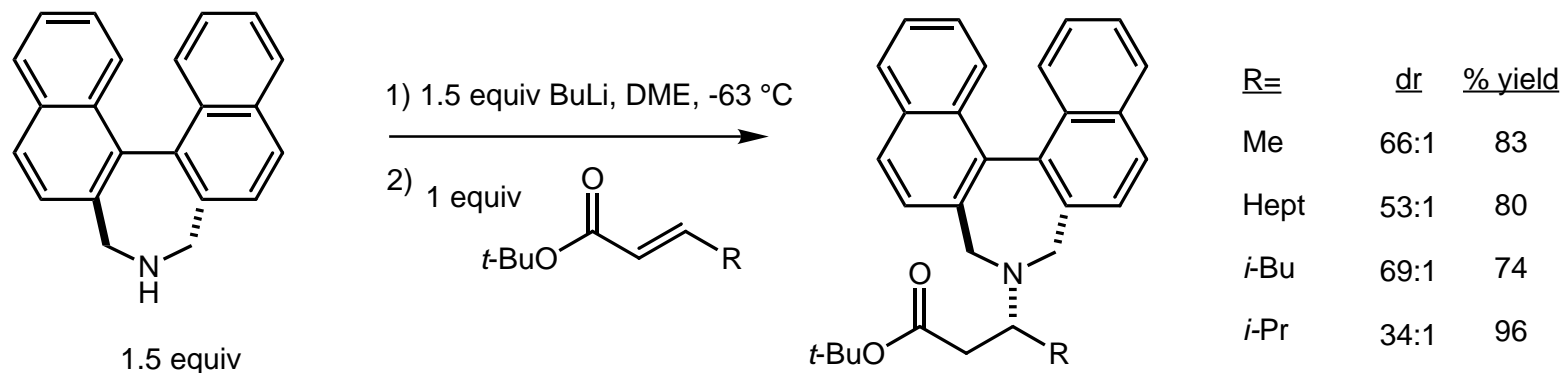
Amoroso, R.; Cardillo, G.; Sabitino, P.; Tomasini, C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615.

# Asymmetric Addition of Amines to Crotonate Derivatives: Three Component $\beta$ -Lactam Synthesis



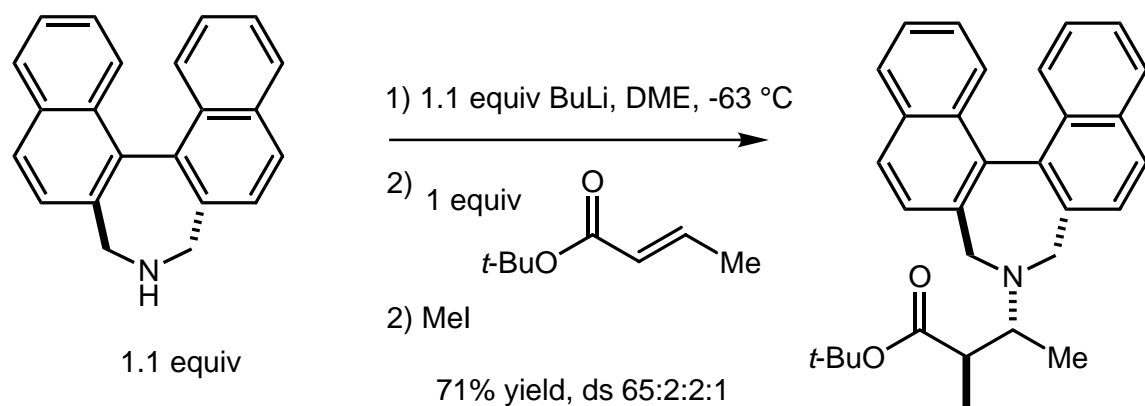
Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427.

# Asymmetric Addition of 1,1'-Binaphthylamine to Crotonates

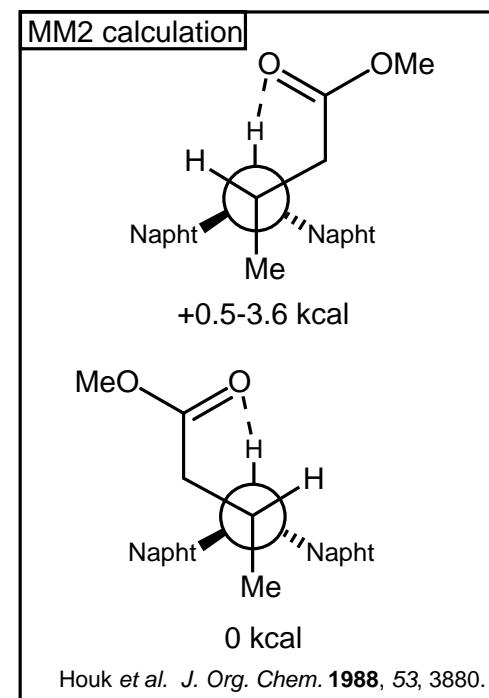


Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.

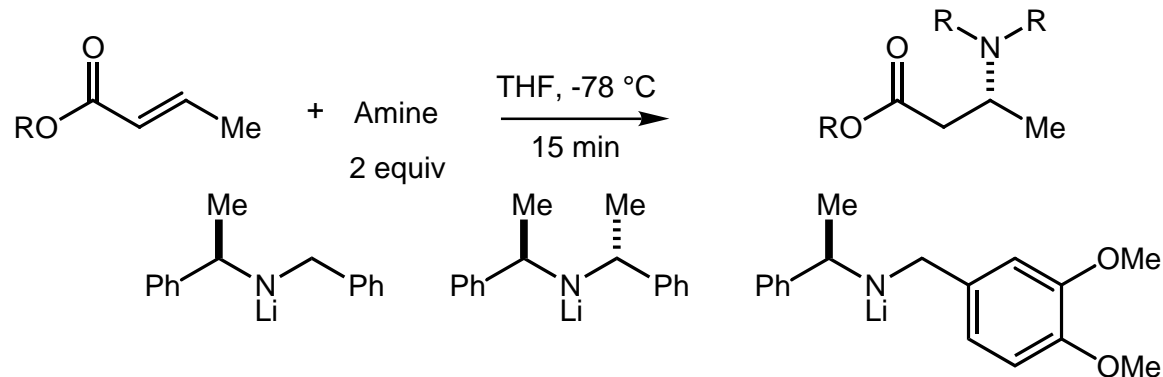
Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114.



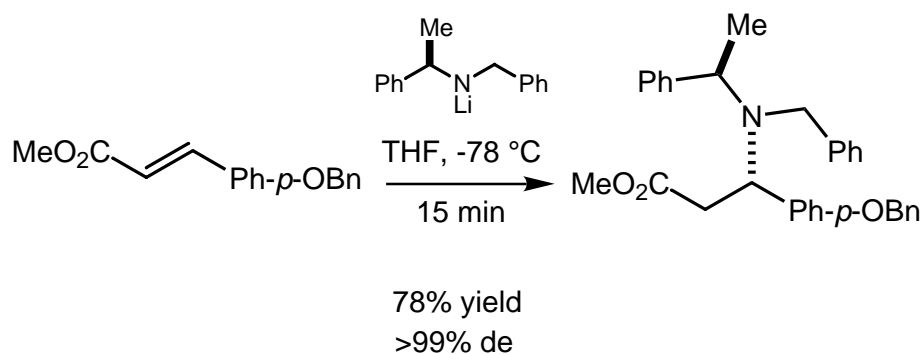
Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1994**, *59*, 649.



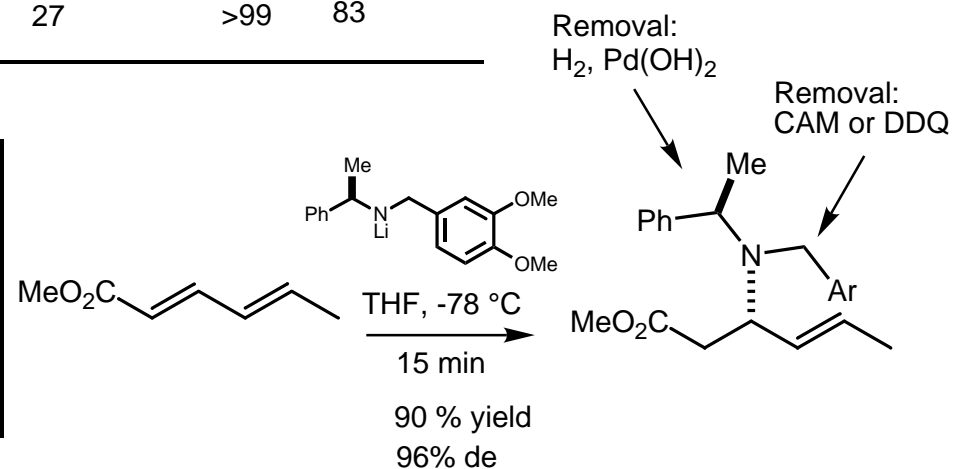
# Asymmetric Addition of Lithiated $\alpha$ -Methylbenzamide Derivates to Crotonates



R	%de	% yield	%de	% yield	%de	% yield
Me	95	85	>99	57	95	68
Bn	95	88	98	23 (at 0 °C)	96	74
<i>t</i> -Bu	>99	82	>99	27	>99	83

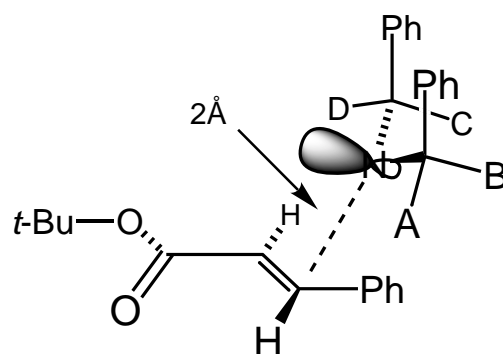


Davies, S. G.; Ichihara, O. *Tetrahedron: Asymm.* **1991**, 3, 183.

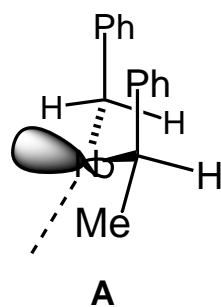


Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1998**, 3, 6045.

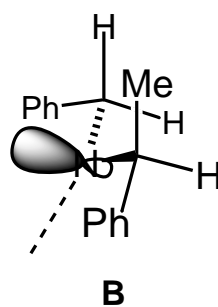
## Calculated Stereochemical Model for Addition of Lithiated $\alpha$ -Methylbenzylamide Derivates to Crotonates



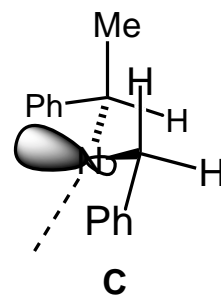
"The conformational reorganization which occurs as the amide approaches the ester bears striking resemblance to the wings of a butterfly in flight which, as it alights on a leaf, assumes a parallel orientation."



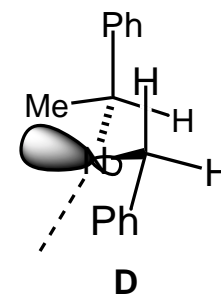
Energy: 0 kJ mol<sup>-1</sup>



+11 kJ mol<sup>-1</sup>



+12 kJ mol<sup>-1</sup>

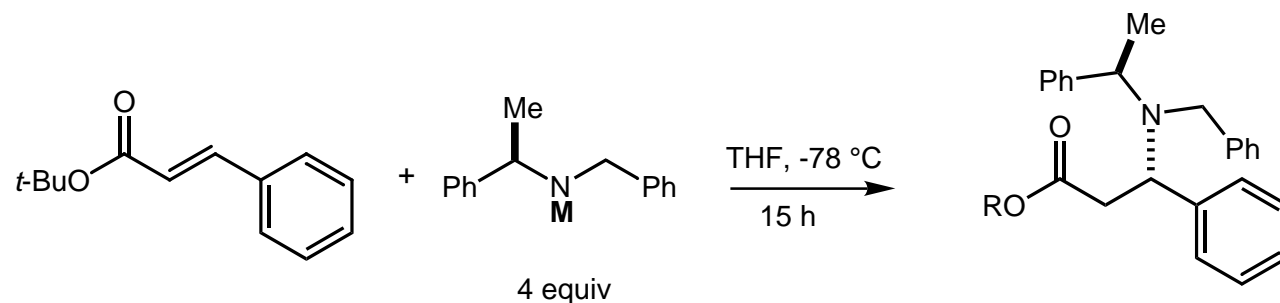


+17 kJ mol<sup>-1</sup>

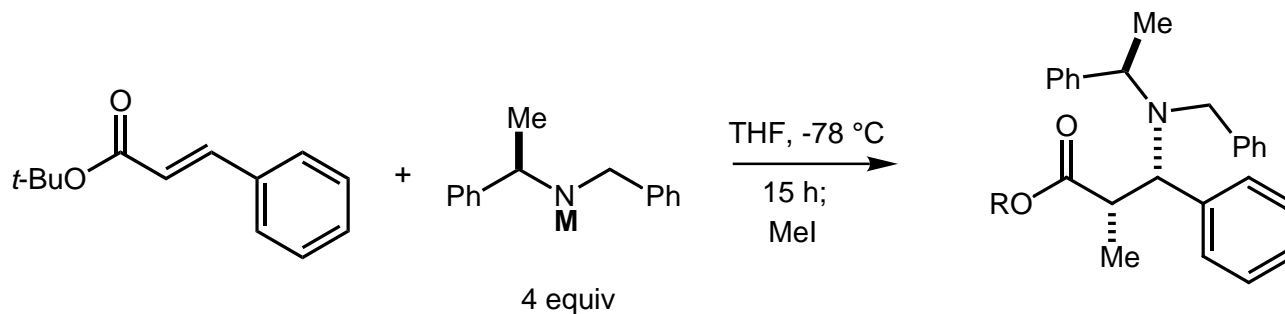
CHEM-X modelling package was used (Chemical Design Limited, Chepping Norton, UK).

Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymm.* **1994**, 5, 1999.

## Tandem Asymmetric Addition of $\alpha$ -Methylbenzylamide/Alkylation to Crotonates



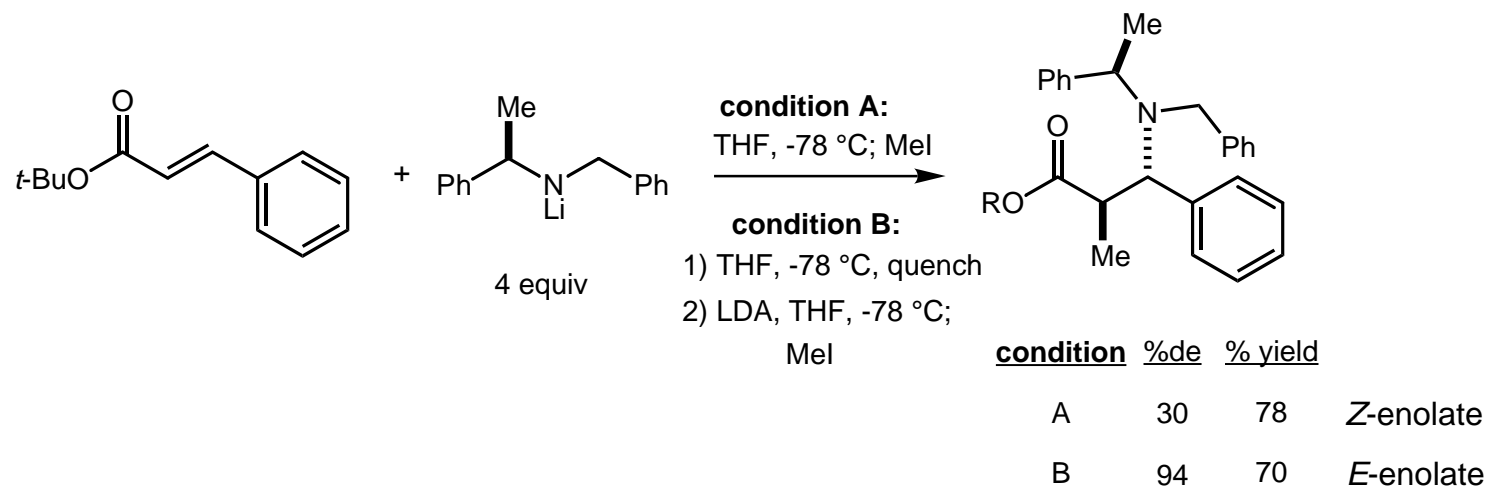
<b>M</b>	<u>%de</u>	<u>% yield</u>	<u>t (h)</u>
Li	95	92	1
Mg	$\geq 95$	78	15



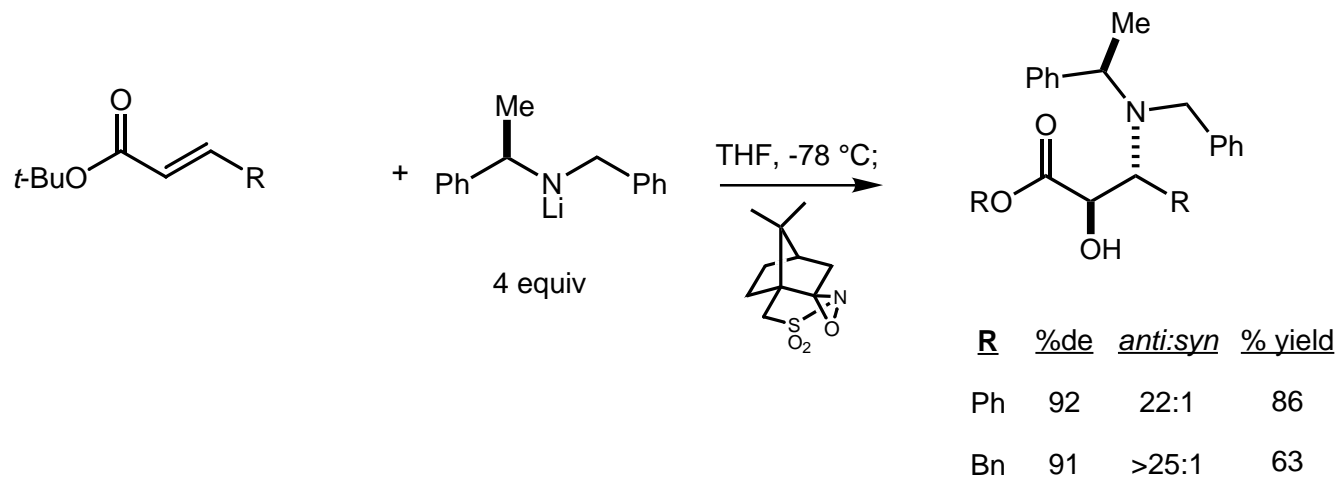
<b>M</b>	<u>%de</u>	<u>% yield</u>	
Li	30	78	
Mg	90	73	← 19 : 1 <i>syn</i> : <i>anti</i>

Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Walters, I. A. S. *Tetrahedron Asymm.* **1994**, 5, 35.

## Tandem Asymmetric Addition of $\alpha$ -Methylbenzylamide to Crotonates



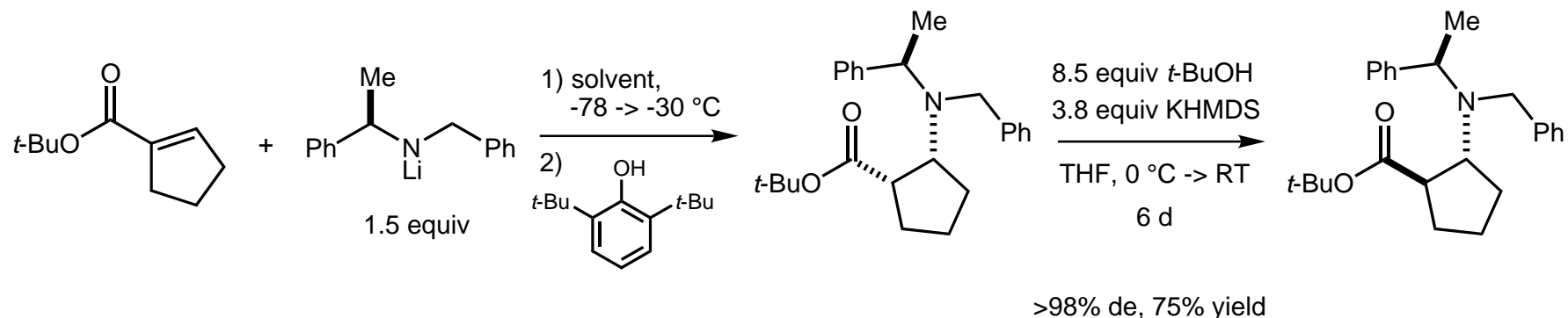
Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *Chem. Comm* **1993**, 1153.



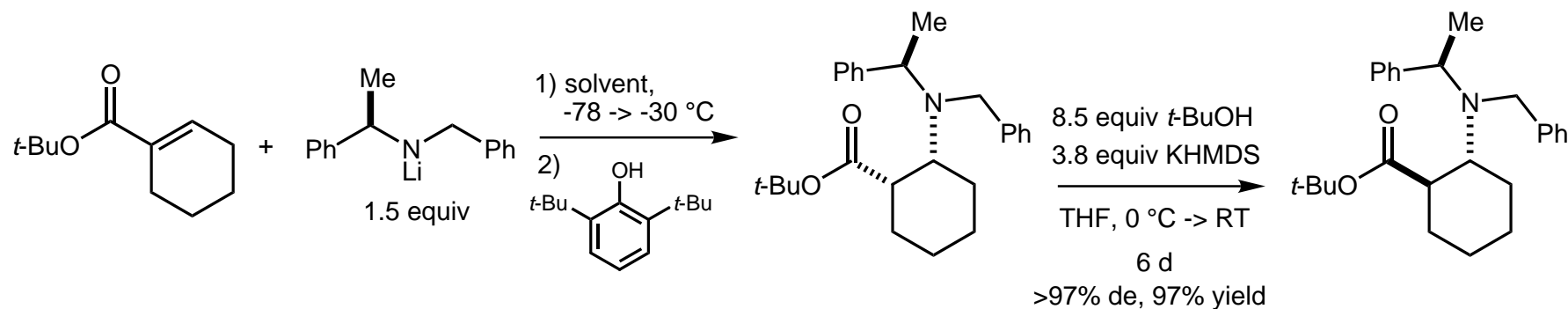
Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Synlett* **1993**, 731.

Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Perkin Trans. 1* **1993**, 1375.

## Asymmetric Addition of Lithiated $\alpha$ -Methylbenzylamide Derivates to Crotonates



solvent	T( $^{\circ}\text{C}$ )	%de	% yield
THF/PhCH <sub>3</sub>	-78	71	85
THF	-95	>98	65

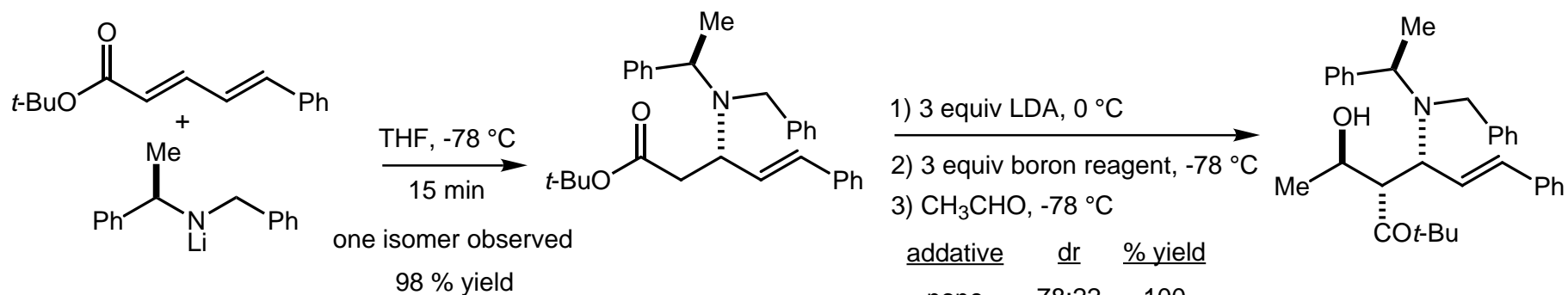


solvent	T( $^{\circ}\text{C}$ )	%de	% yield
THF/PhCH <sub>3</sub>	-78	>95	70
THF	-95	>95	70

Davies, S. G.; Ichihara, O.; Lenior, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411.

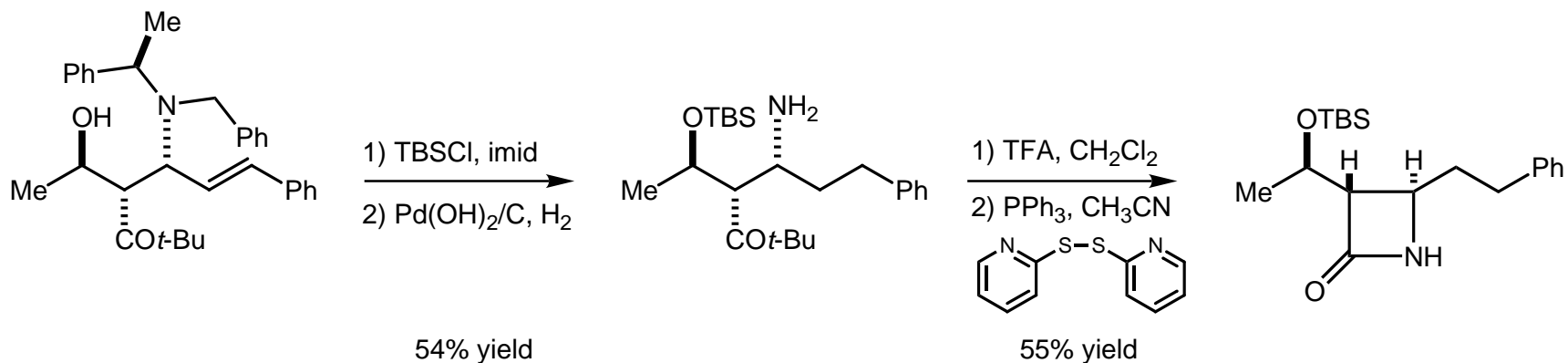


# Asymmetric Addition of Amines to Crotonate Derivatives: Three Component $\beta$ -Lactam Synthesis



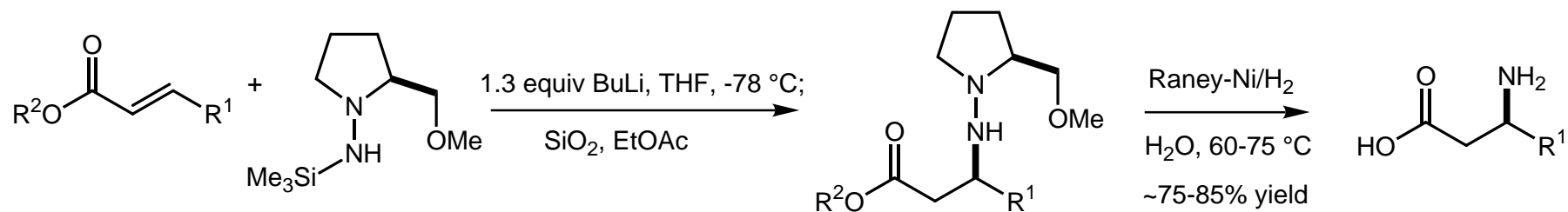
- 1) 3 equiv LDA, 0 °C  
 2) 3 equiv boron reagent, -78 °C  
 3) CH<sub>3</sub>CHO, -78 °C

additive	dr	% yield
none	78:22	100
Bu <sub>3</sub> B	81:19	72
Et <sub>3</sub> B	86:14	82
(BuO) <sub>3</sub> B	75:25	82
(MeO) <sub>3</sub> B	91:9	89



Asao, N.; Tsukada, N.; Yamamoto, Y. *Chem. Comm.* **1993**, 1660.

## Asymmetric Addition of TMS-SAMP to Unsaturated Esters

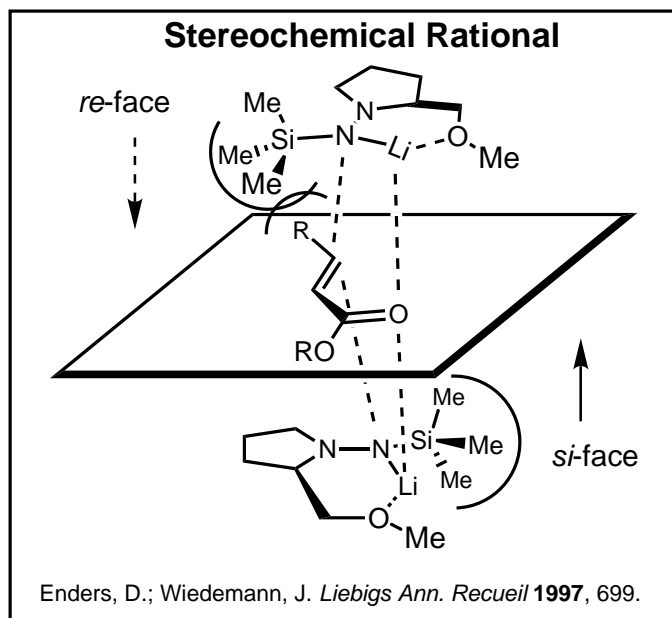


1.3 equiv

**TMS-SAMP**

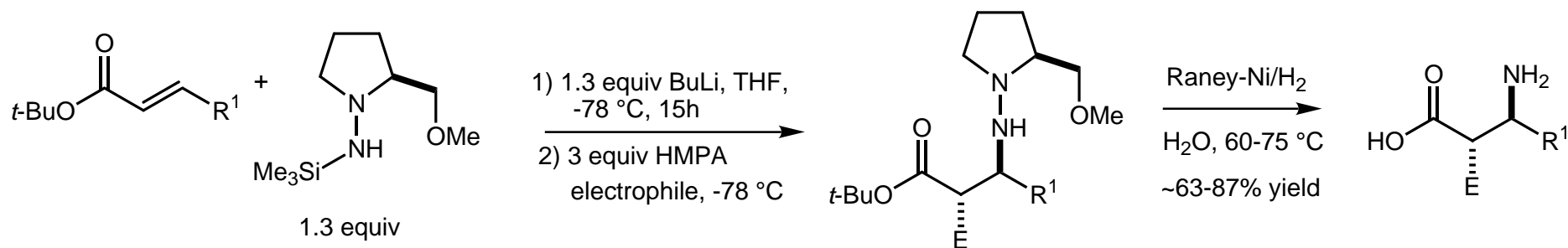
(S)-2-methoxymethyl-1-trimethylsilylpyrrolidine

$R^1$	$R^2$	%de	% yield
Me	Me	95	48
Pr	Me	95	40
<i>i</i> -Pr	<i>t</i> -Bu	98	32
$C_{11}H_{23}$	<i>t</i> -Bu	97	67



Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 455.

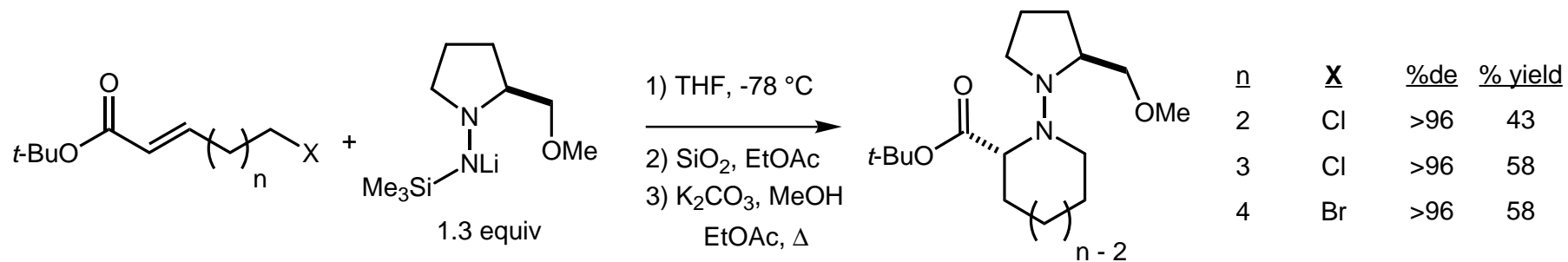
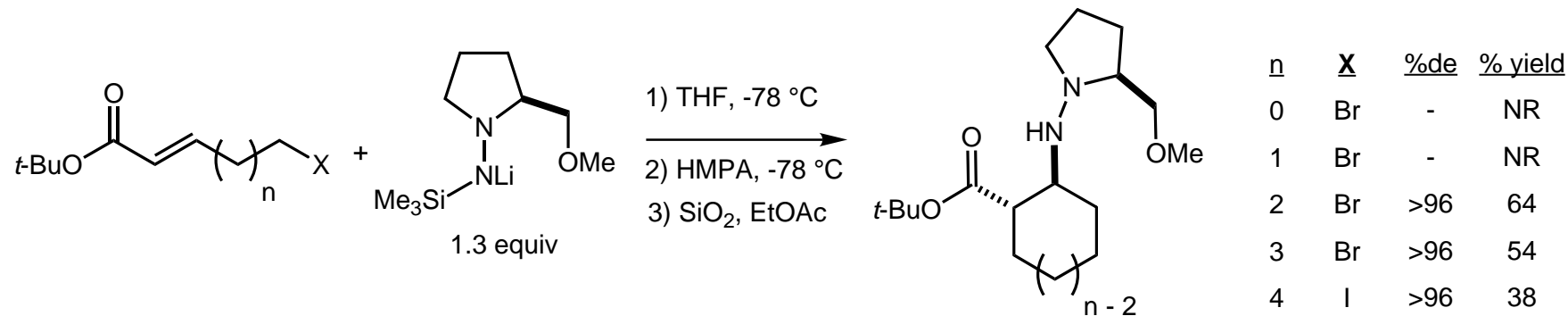
## Tandem Asymmetric Addition of TMS-SAMP/Alkylation of Unsaturated Esters



<u>R</u>	<u>Electrophile</u>	<u>%yield</u>	<u>%de</u>
Et	MeI	56	77
Et	PhCH <sub>2</sub> Br	26	76
Et		51	>96
Ph	EtI	34	>96
Ph	C <sub>4</sub> H <sub>9</sub> I	64	>96
Ph		52	>96
Ph	PhCH <sub>2</sub> Br	67	>96

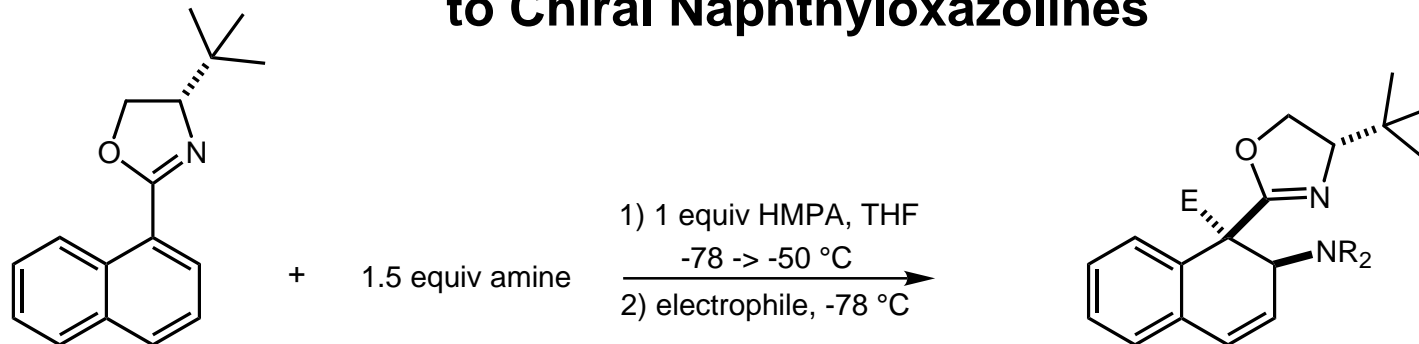
Enders, D.; Bettray, W.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 1322.

## Tandem Asymmetric Addition of TMS-SAMP/Cyclization of Unsaturated Esters

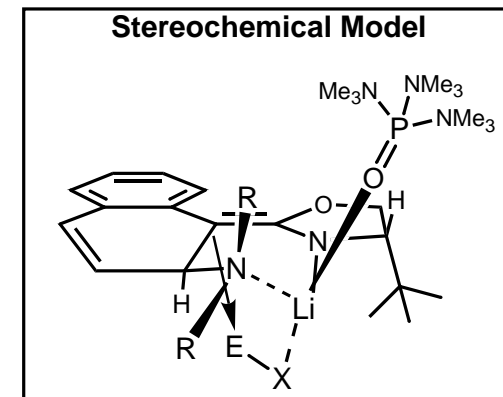


Enders, D.; Wiedemann, J. *Liebigs Ann. Recueil* **1997**, 699.

# Asymmetric Addition of Lithiated Amines to Chiral Naphthyloxazolines

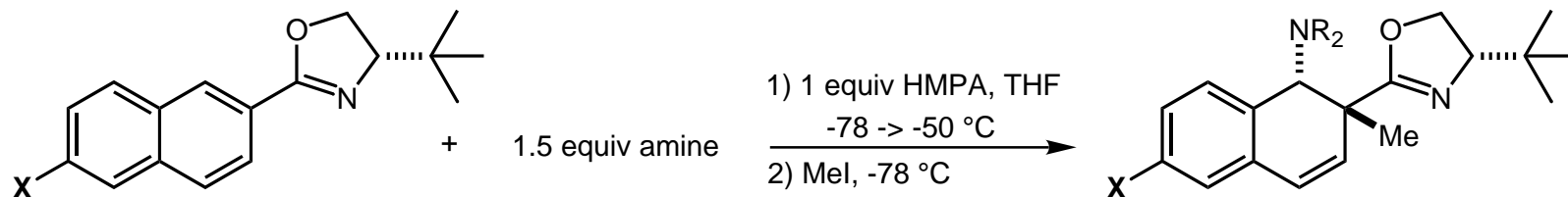


	Electrophile	%yield	dr
	Mel	94	98.5 : 1.5
	Mel	93	>99 : 1
	Mel	NR	NR
	Mel	NR	NR
	Mel	NR	NR
	Mel	95	>99 : 1
		92	>99 : 1
		67	>99 : 1
	Mel	96	>99 : 1



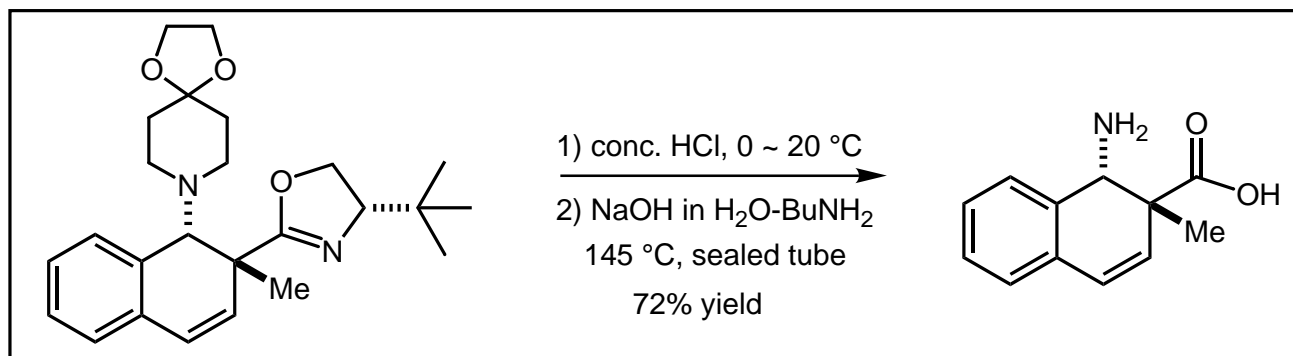
Shimano, S.; Meyers, A., I. *J. Am. Chem. Soc.* **1994**, *116*, 6437.  
Shimano, S.; Meyers, A., I. *J. Org. Chem.* **1995**, *60*, 7445.

## Asymmetric Addition of Lithiated Amines to Chiral Naphthyloxazolines

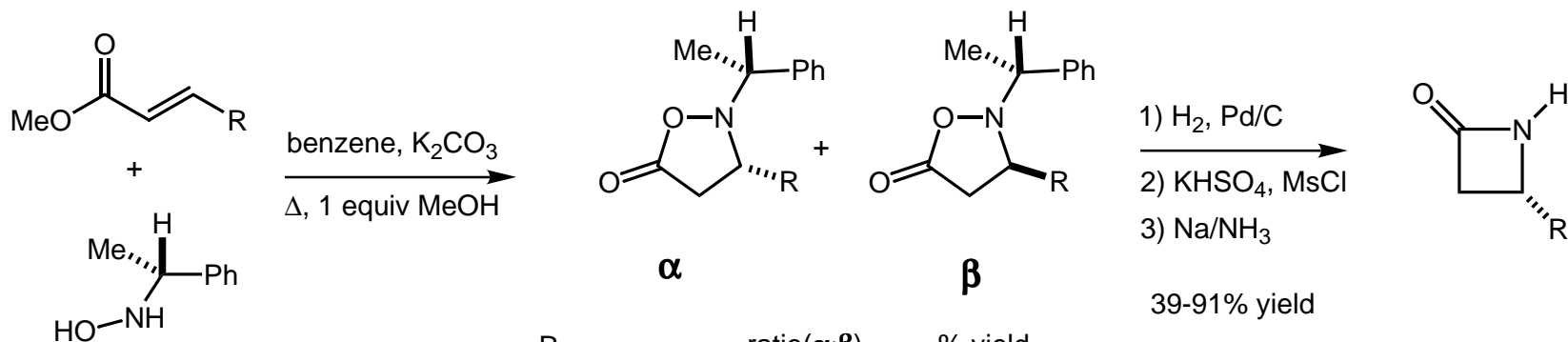


X	%yield	dr	
	H	91	97.5 : 2.5
	MeO	90	>99 : 1
	H	NR	NR
	H	94	>99 : 1
	H	94	>99 : 1
	H	94	>99 : 1

Shimano, S.; Meyers, A., I. *J. Am. Chem. Soc.* **1994**, *116*, 6437.  
Shimano, S.; Meyers, A., I. *J. Org. Chem.* **1995**, *60*, 7445.

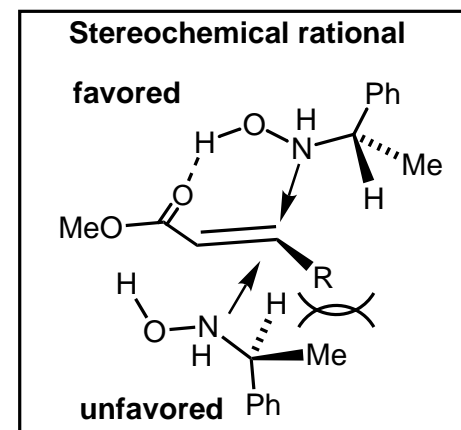


# Asymmetric Additions of $\alpha$ -Methylbenzyl Hydroxylamine to Unsaturated Esters



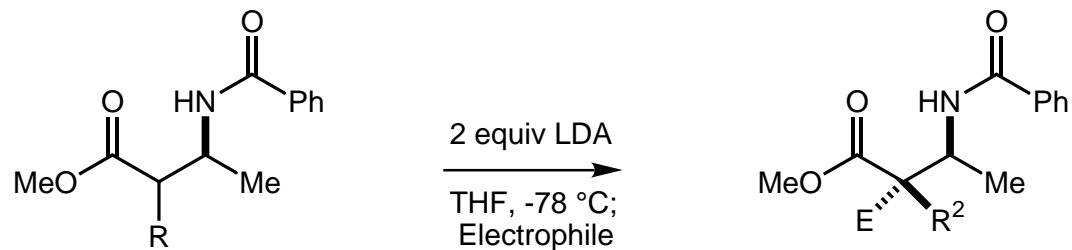
<u>R</u>	<u>ratio(<math>\alpha</math>:<math>\beta</math>)</u>	<u>% yield</u>
Me*	80:20	91
Me ( <i>cis</i> )	86:14	22
Pr	82:18	80
<i>i</i> -Pr	80:20	74
Ph	69:31	54
CH <sub>2</sub> CO <sub>2</sub> Me	70:30	65

\* $\alpha$ : $\beta$  ratios of other solvents:  
hexanes (90:10)  
ether (70:30)  
diglyme (65:35)

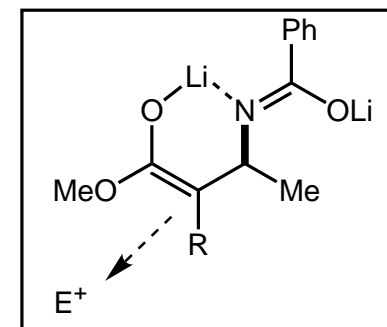


Baldwin, S. W.; Aube, J. *Tetrahedron Lett.* **1987**, 28, 179.

## Diastereoselective Alkylations of $\beta$ -Aminoesters



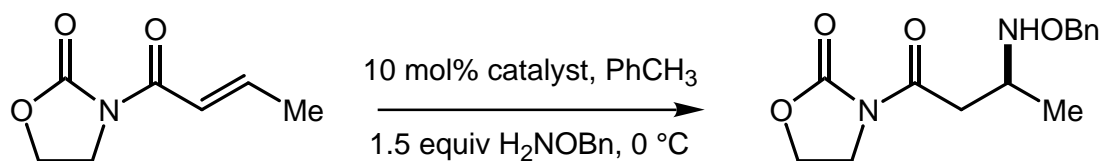
<u>R=</u>	<u>Electrophile</u>	<u>dr</u>	<u>% yield</u>
H	CH <sub>3</sub> I	4:1	50
H	CH <sub>3</sub> CH <sub>2</sub> I	16:1	73
H	CH <sub>2</sub> =CHCH <sub>2</sub> Br	31:1	70-90
H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br	36:1	70-90
Me	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br	99:1	80



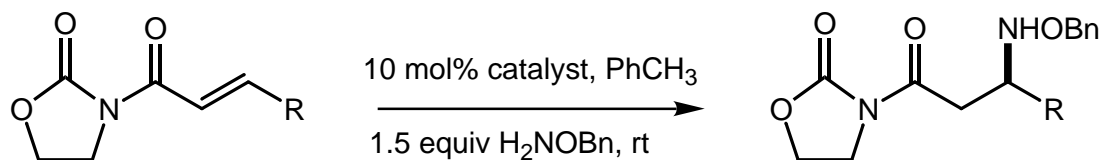
Seebach, D.; Estermann, H. *Tet. Lett.* **1987**, 28, 3103.



## Enantioselective O-Benzylhydroxylamine Additions to Unsaturated Imides

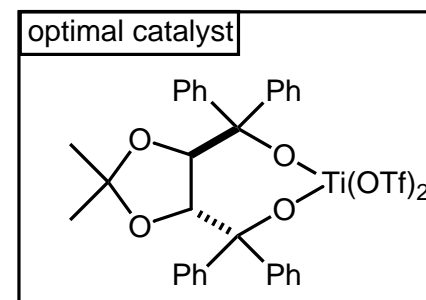


28% ee, 100% conversion



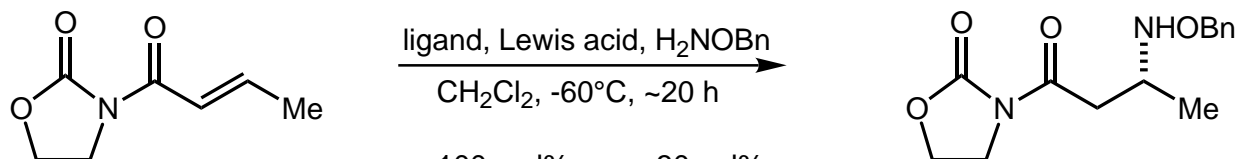
R= Pr 35% ee, 94% conversion

R= Ph 42% ee, 69% conversion

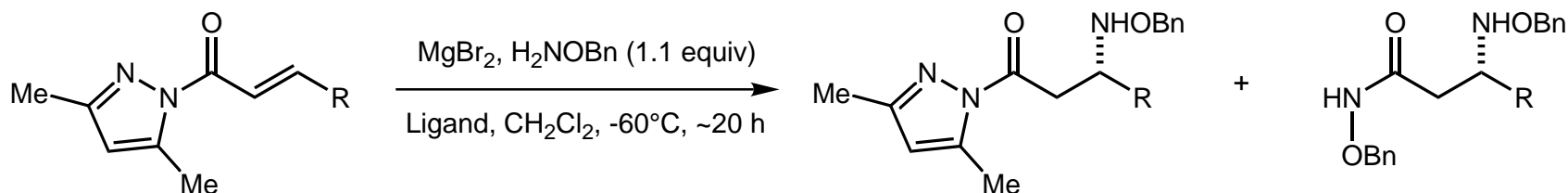


Falborg, L.; Jorgensen, K. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823.

# Enantioselective *O*-Benzylhydroxylamine Additions to Enones

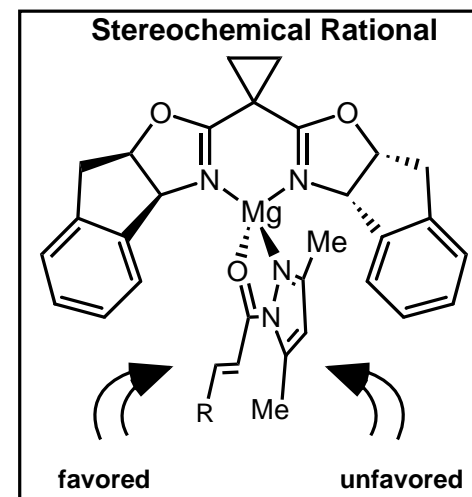


Lewis acid	100 mol%		30 mol%	
	% ee	% yield	% ee	% yield
MgBr <sub>2</sub>	28	81	65	98
MgI <sub>2</sub>	41	74	42	94



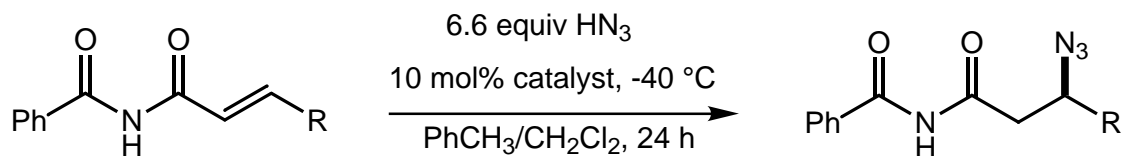
R	100 mol%		30 mol%		10 mol%	
	% ee	% yield	% ee	% yield	% ee	% yield
Me	96	62	92	80	88	87
Et	92	56	92	74	88	84
C <sub>6</sub> H <sub>11</sub>	90	39	90	53	70	57
Bn	96	62	95	80	90	85
<i>i</i> -Pr	83	41	87	76	67	56
Ph	78	21	83	24	NR	NR

MgI<sub>2</sub>, Zn(OTf)<sub>2</sub>, Mg(OTf)<sub>2</sub>, ZnBr<sub>2</sub>, and Sn(OTf)<sub>2</sub> all gave lower yields and/or selectivity.



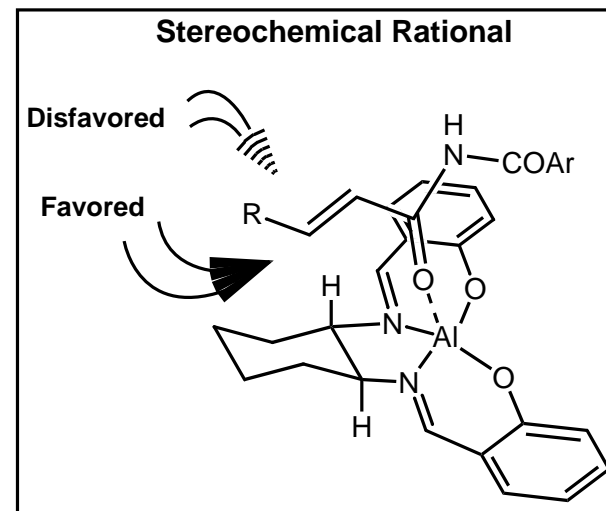
Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615.

# Enantioselective Hydrazoic Acid Additions to Unsaturated Amides

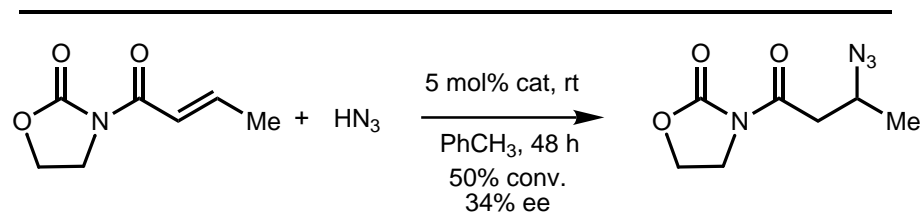


R=	% ee	% yield
	96	96
	97	97
	95	97
	95	98
	58	60
	95	97
	96	93
	97	99

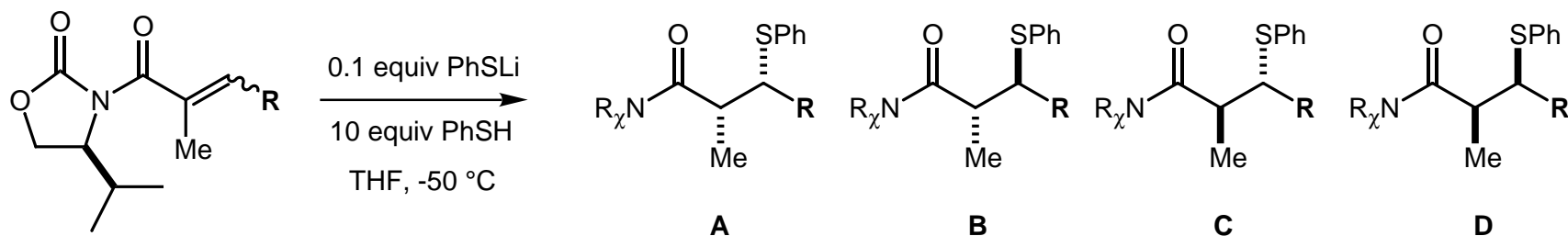
**Catalyst:**



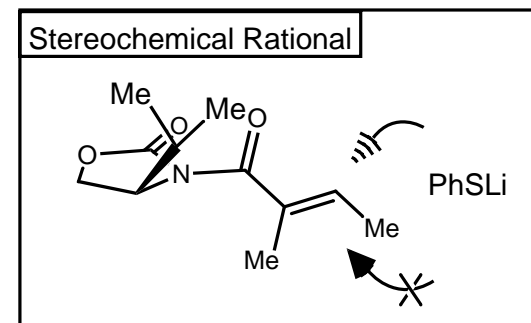
Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.



## Diastereoselective Thiophenol Additions to Unsaturated Imides



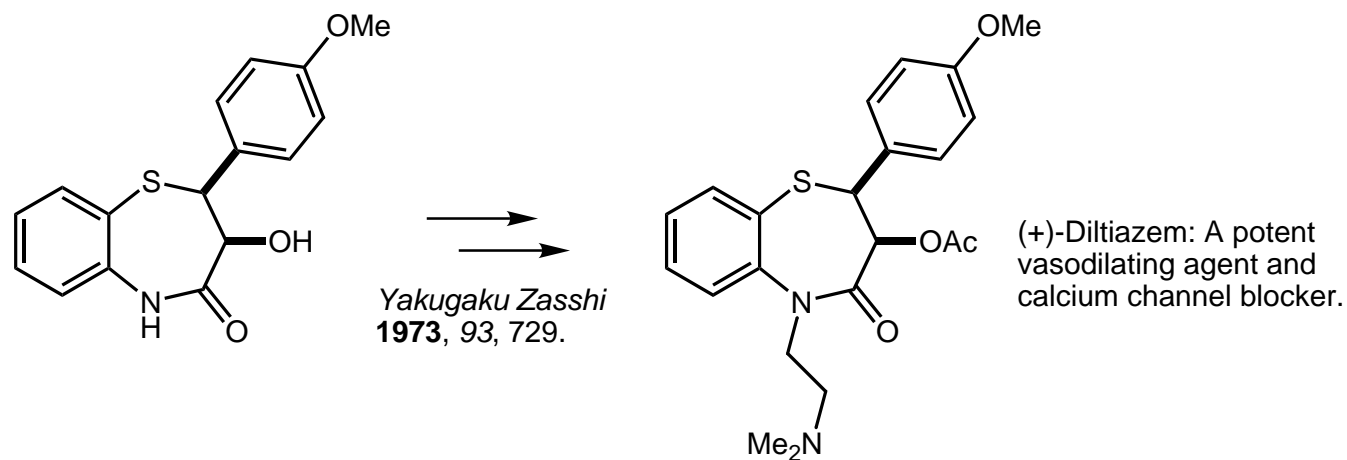
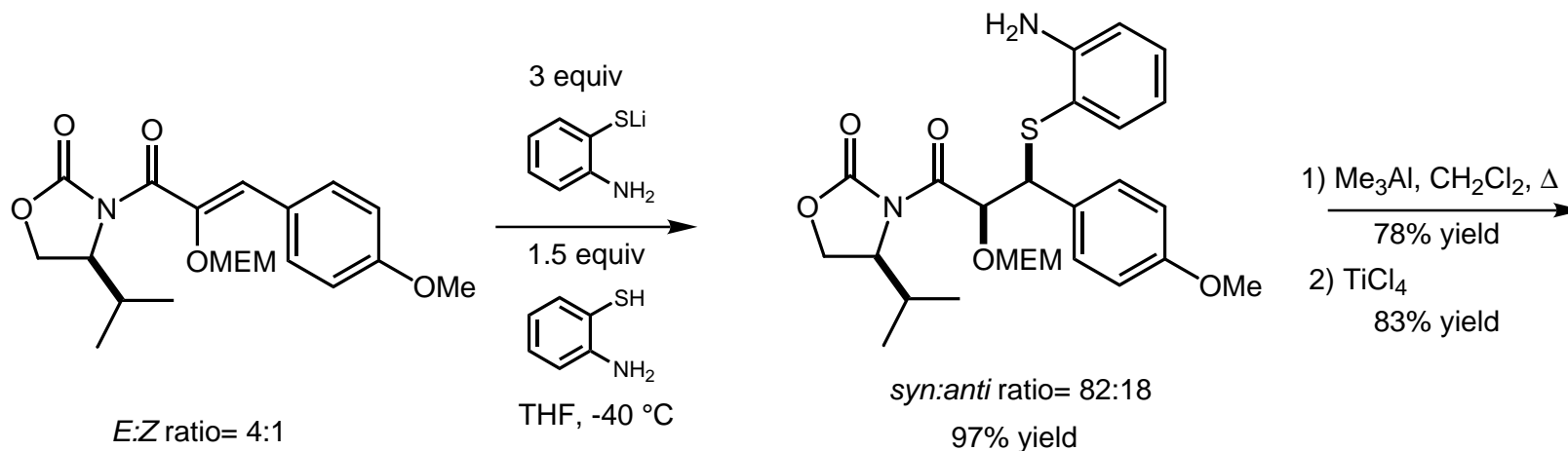
<u>R=</u>	<u>T(°C)</u>	<u>%_yield</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
<i>E</i> -Me	-50	98	>89	<1	4	6
<i>Z</i> -Me	-30	95	3	4	<1	>92
<i>E</i> -Ph	0	91	8	2	45	45
<i>Z</i> -Ph	0	96	8	1	22	69



Miyata, O.; Shinada, T.; Nimomiya, I.; Naito, T. *Tetrahedron Lett.* **1991**, 32, 3519.

Miyata, O.; Shinada, T.; Nimomiya, I.; Naito, T. *Tetrahedron* **1997**, 53, 2421.

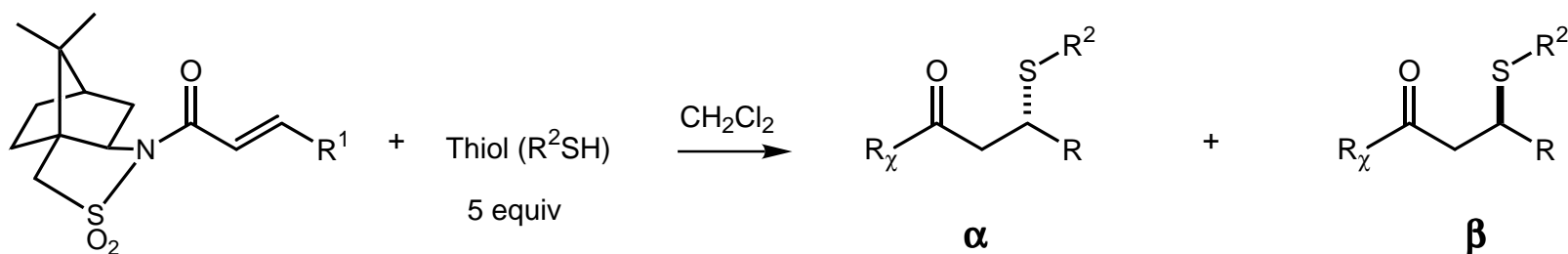
# Diastereoselective Thiophenol Additions to Unsaturated Amides: Formal Synthesis of (+)-Diltiazem



Miyata, O.; Shinada, T.; Nimomiya, I.; Naito, T. *Tetrahedron Lett.* **1991**, 32, 3519.

Miyata, O.; Shinada, T.; Nimomiya, I.; Naito, T. *Tetrahedron* **1997**, 53, 2421.

## Asymmetric Addition of Thiols to *N*-Enoylsultams



R = Me  
Thiol =  $HSCH_2CO_2Me$

1.5 equiv  $TiCl_4$

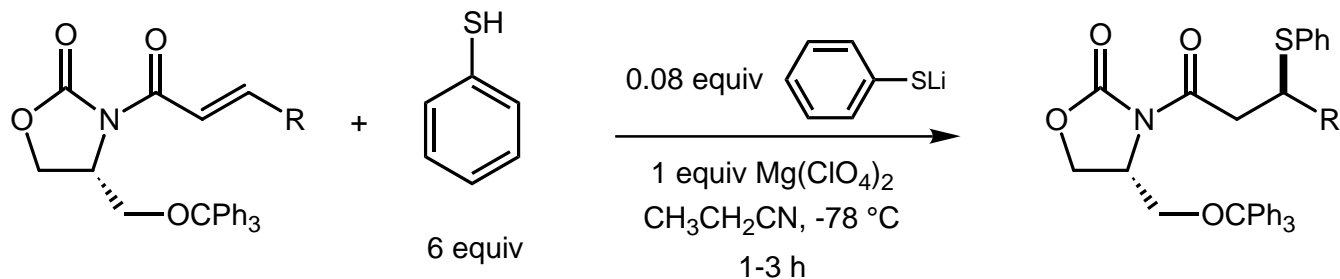
Catalyst	T(°C)	t(h)	ratio( $\alpha$ : $\beta$ )	% yield
$Et_3N$	-78	2	50:50	65
$Et_2AlCl$	25	5	70:30	51
$BF_3 \cdot Et_2O$	25	75	-	NR
$TiCl_4$	-78	3	80:20	96
10 mol% $LiSCH_2CO_2Me$	-50*	5	50:50	86

\*THF used

$R^1$	Thiol ( $R^2$ )	T(°C)	t(h)	ratio( $\alpha$ : $\beta$ )	% yield
Me	$CH_3COSH$	25	24	86:14	56
Me	$HSCH_2CH_2CO_2Me$	-78	6	89:11	89
Me	$PhCH_2SH$	-78	48	65:35	79
Me	$PhSH$	25	24	60:40	98
Me	<i>o</i> - $(CO_2Me)PhSH$	-78	3	99:1	67
Ph	$HSCH_2CO_2Me$	-78	24	87:13	72

Wu, M.-J.; Wu, C.-C.; Tseng, T.-C. *J. Org. Chem.* **1994**, *59*, 7188.

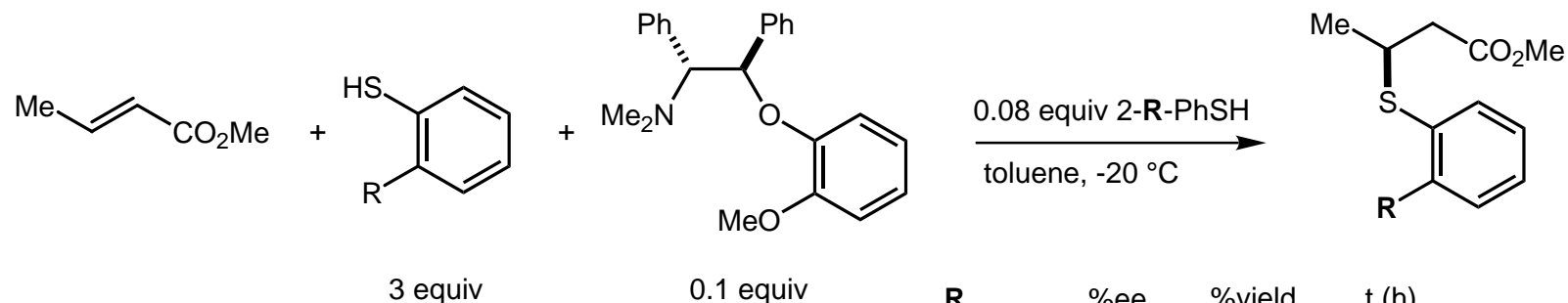
## Diastereoselective Thiophenol Additions to Unsaturated Amides



<u>R</u>	<u>% de</u>	<u>% yield</u>
Me	86	90
<i>i</i> -Pr	96	91
Bu	89	71
Ph	98	90
$\text{CO}_2\text{Me}$	70	64

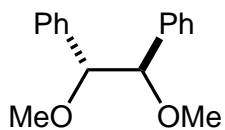
Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1995**, *60*, 6188.

# Enantioselective Arylthiolate Additions to $\alpha,\beta$ -Unsaturated Esters

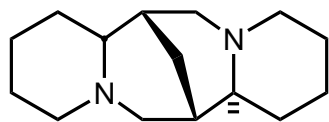


<u>R</u>	<u>%ee</u>	<u>%yield</u>	<u>t</u> (h)
H	71	99	3
Me	79	93	2
<i>i</i> -Pr	85	99	2
<i>t</i> -Bu	90	99	1
TMS	88	97	1

Other attempted ligands:

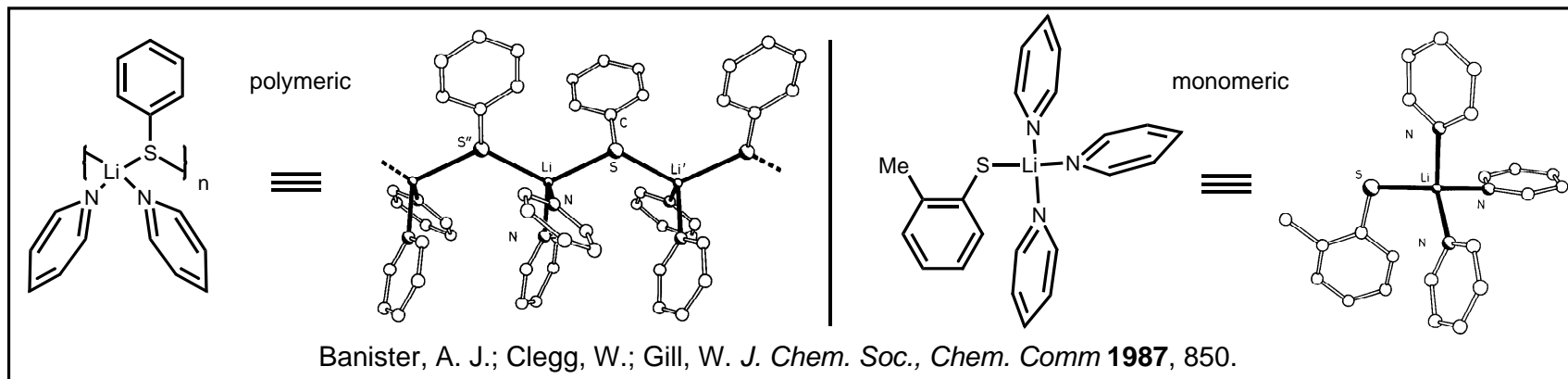


6% ee, 92% yield



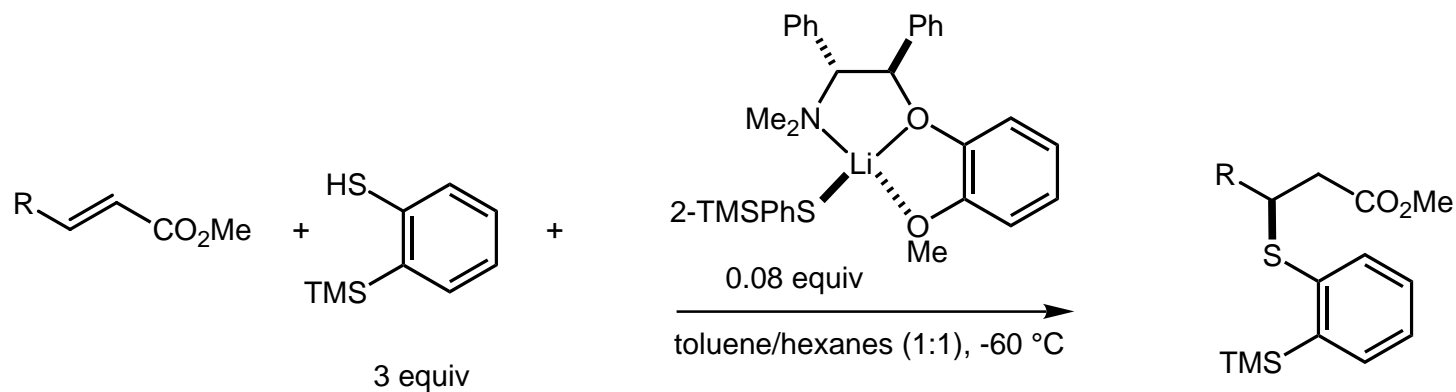
15% ee, 86% yield

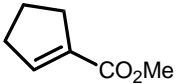
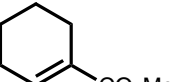
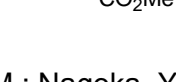
Nishimura, K.; Ono, M.; Nagoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974.





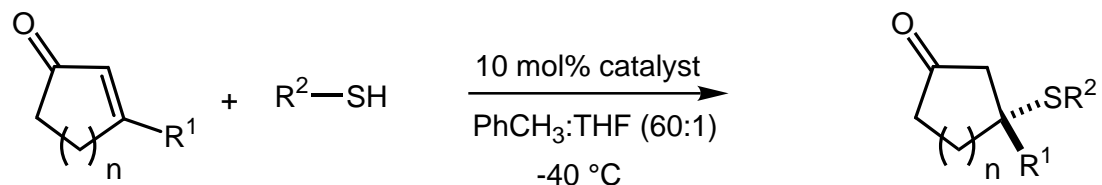
# Enantioselective Arylthiolate Additions to $\alpha,\beta$ -Unsaturated Esters



R	%ee	%yield	t (min)
Me	97	99	120 (at -78 °C)
Et	93	99	18
<i>i</i> -Bu	94	93	30
Ph	70	78	72 (at -40 °C)
Bn	95	98	30
	96 <i>cis</i>	82	33
	92 <i>trans</i>	10	33
	83	84	60 (at -20 °C)

Nishimura, K.; Ono, M.; Nagoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974.

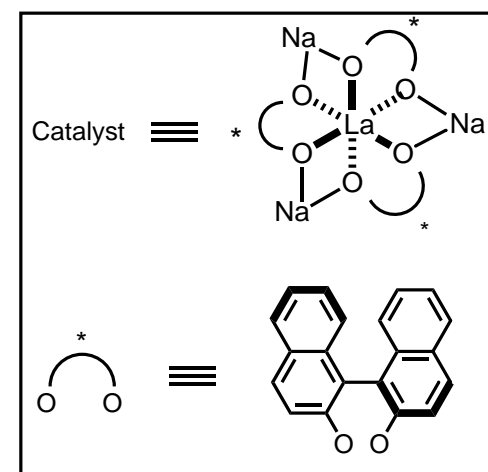
## Enantioselective Thiol Additions to Cyclic Enones



Enone	Thiol ( $R^2SH$ )	% ee	% yield	time (h)
$n = 2, R_1 = H$		84	93	0.3
$n = 2, R_1 = H$		68 <sup>1,2</sup>	87	0.3
$n = 2, R_1 = H$		90	86	14
$n = 1, R_1 = H$		56	94	4
$n = 3, R_1 = H$		83	87	41 (20 mol% cat)
$n = 2, R_1 = Me$		85	56	43 (20 mol% cat, $-20\text{ }^\circ\text{C}$ )
		56	41	NA

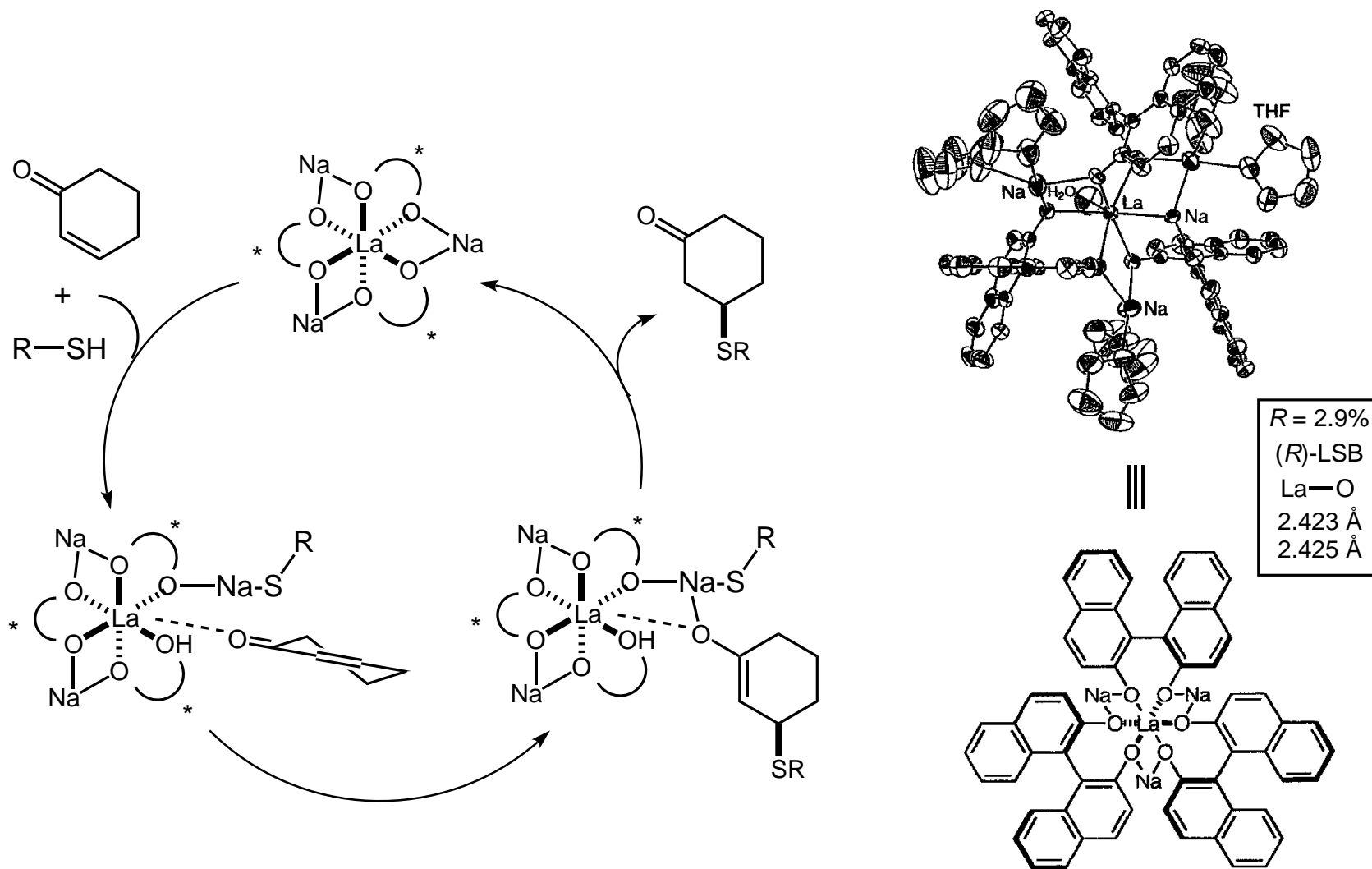
<sup>1</sup> 2% ee was observed in THF

<sup>2</sup>  $AlLi(binapht)_2$ , 29% ee  
 $GaNa(binapht)_2$ , 3% ee  
 $LaLi_3(binapht)_3$ , 10% ee  
 $LaK_3(binapht)_3$ , 39% ee  
 $Labinapht$ , 22% ee



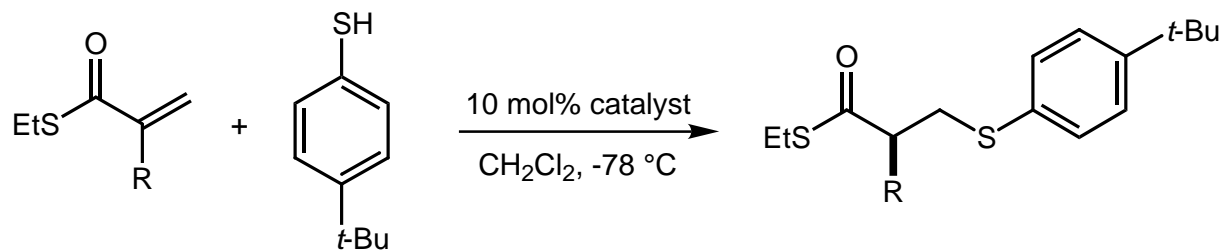
Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

# Enantioselective Thiol Additions to Enones



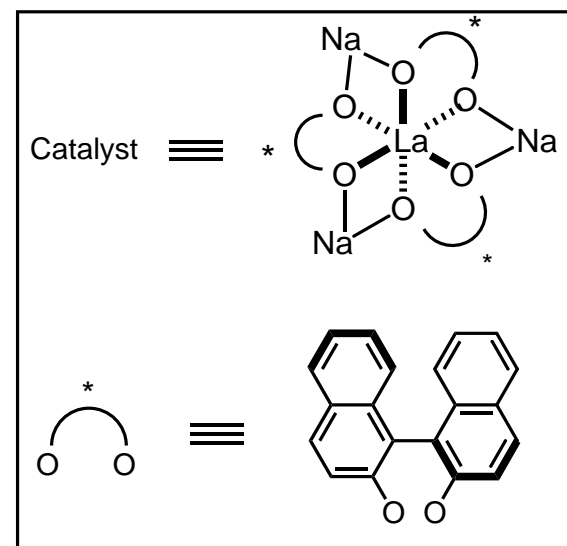
Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

## Catalytic Asymmetric Protonations in Michael Additions of Thiols to Enones



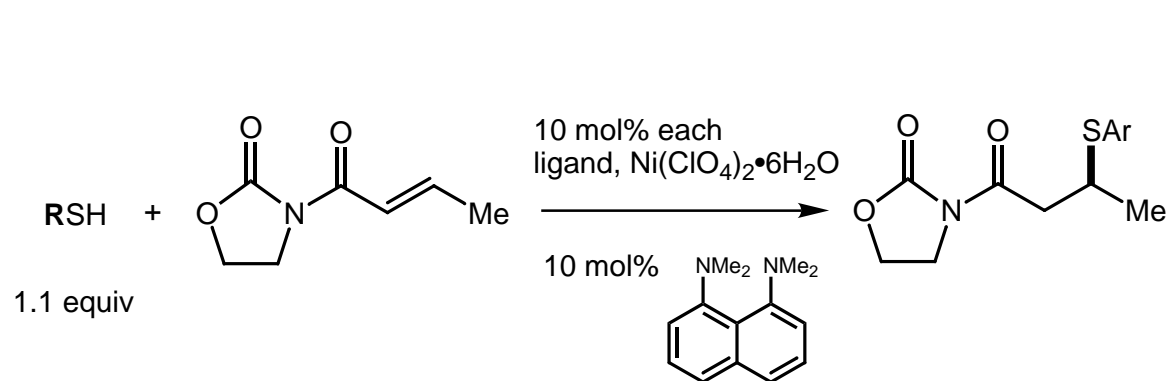
2 mol% cat, 10 mmol scale →

<u>Metal</u>	<u>R</u>	<u>%ee</u>	<u>% yield</u>
La	Me	88	90
Sm	Me	93	86
Sm	Me	88	89
Sm	<i>i</i> -Pr	90	78
Sm	Bn	87	89
Sm	Ph	84	98



Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

## Enantioselective Thiol Additions to Unsaturated Imides



<b>R</b>	CH <sub>2</sub> Cl <sub>2</sub> /THF (10:1), 96 h, 0 °C		THF, no proton sponge, 24 h, rt	
	<u>%ee</u>	<u>% yield</u>	<u>%ee</u>	<u>% yield</u>
Ph*	94	84	80	quant
<i>o</i> -Tolyl	95	99	89	82
Mesityl	96	36	95	84
<i>β</i> -Naphth	91	88	87	94
<i>α</i> -Naphth	55	92	87	73

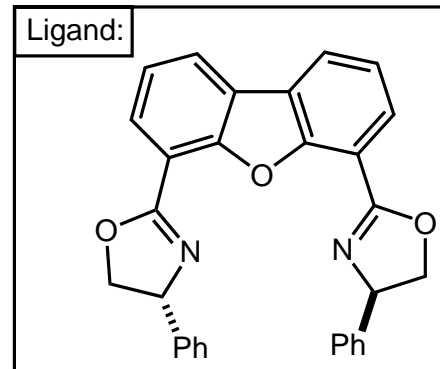
Anhydrous catalyst gave no ee.

ZnI<sub>2</sub>, Zn(OTf)<sub>2</sub>, Mg(ClO<sub>4</sub>)<sub>2</sub>, and Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, and Sn(OTf)<sub>2</sub> all gave satisfactory catalytic activity with poor enantioselectivity.

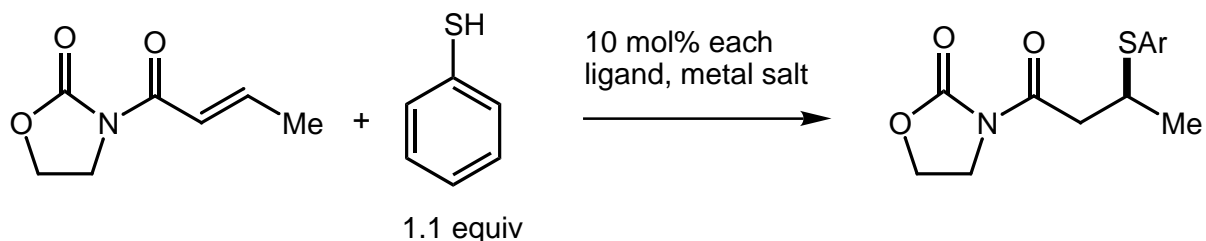
Perchlorates of Cu(II), Fe(II), and Mn(II) showed only low catalytic activity.

\*in CH<sub>2</sub>Cl<sub>2</sub> only afforded 79% ee, 81% yield

Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8112.

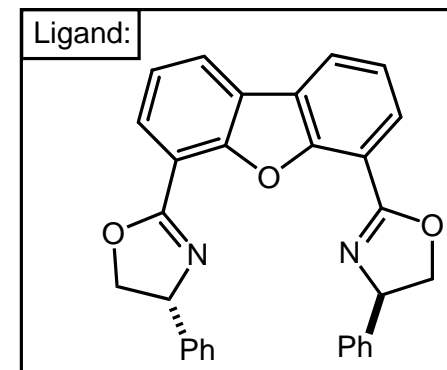


## Enantioselective Thiol Additions to Unsaturated Imides



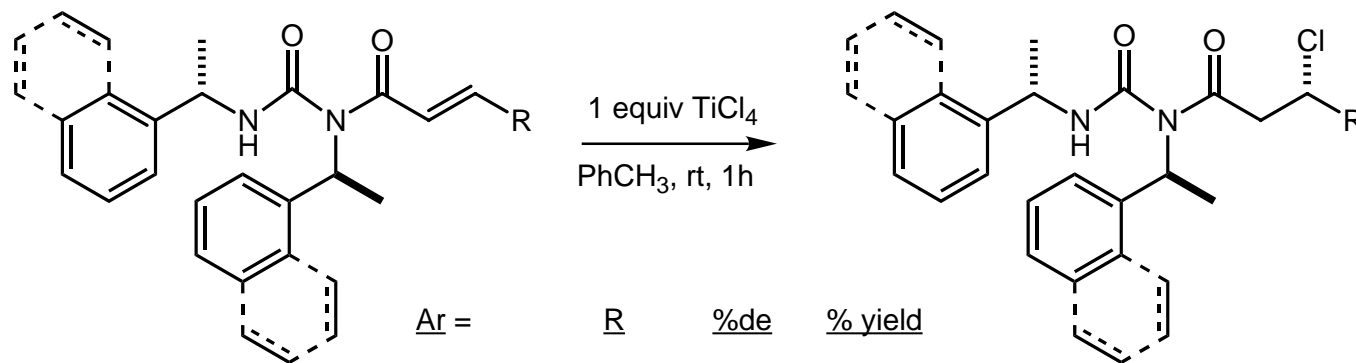
entry	metal salt <sup>a</sup>	solvent	temp (°C)	time (h)	yield (%) <sup>b</sup>	ee (%)
1	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	rt	48	81	79
2	NiBr <sub>2</sub> + AgClO <sub>4</sub> (2 equiv)	CH <sub>2</sub> Cl <sub>2</sub>	rt	72	50	0
3	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	rt	24	91	20
4	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	-78	48	33	-17
5	NiBr <sub>2</sub> + AgClO <sub>4</sub> (2 equiv)	Et <sub>2</sub> O	rt	48	50	-10
6	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	Et <sub>2</sub> O	rt	24	42	73
7	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	THF	rt	24	quant	80
8	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	THF	0	72	62	7
9	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub> /MeOH (1:1 v/v)	rt	24	quant	82
10	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub> /AcOH (10:1 v/v)	rt	48	99	0
11	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub> /sat'd aq NH <sub>4</sub> Cl (10:1 v/v)	rt	48	99	-27

<sup>a</sup> Catalyst was prepared in situ from equimolar amounts of DBFOX/Ph and metal salt in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Isolated yield.



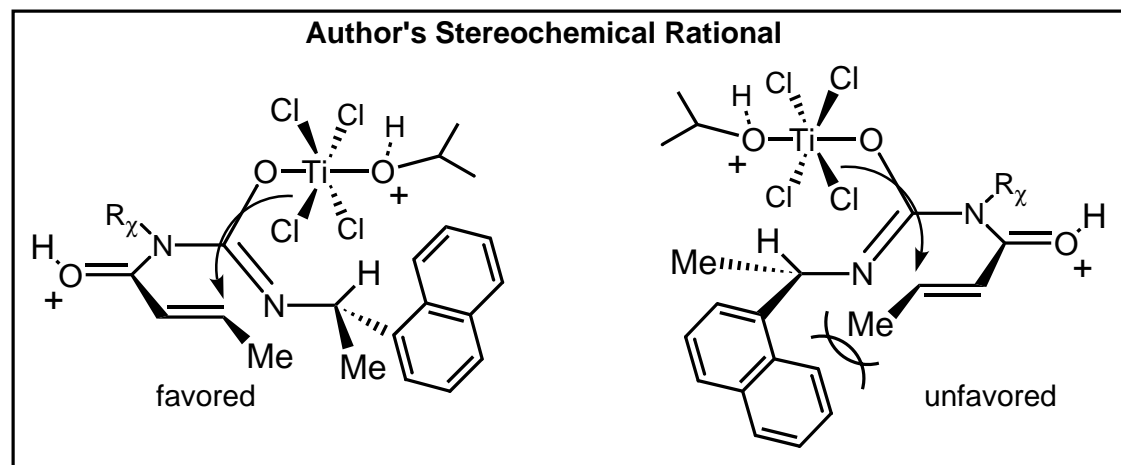
Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8112.

# Conjugate Addition of Chlorine to $\alpha,\beta$ -Unsaturated Chiral Amides

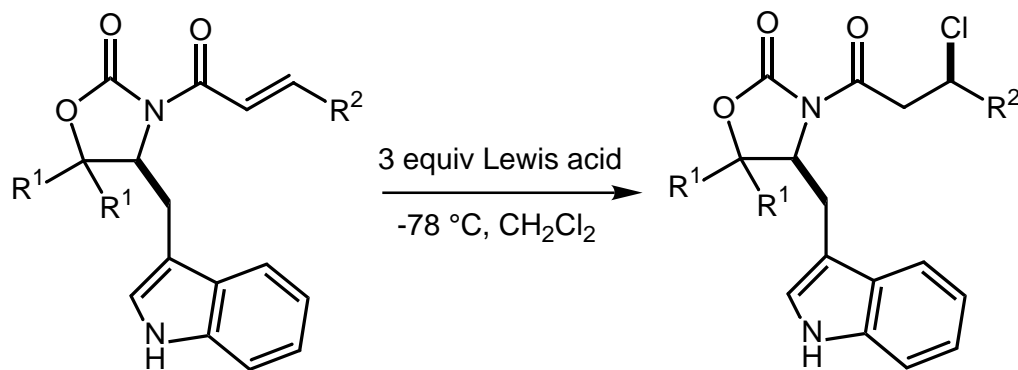


Ar =	R	%de	% yield
Ph	Me	32	50
Ph	Et	66	86
Ph	Pr	10	72
1-Napht	Me	78	54
1-Napht	Et	60	50
1-Napht	Pr	48	29

Kishikawa, K.; Furusawa, A.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *J. Org. Chem.* **1993**, *58*, 7296.

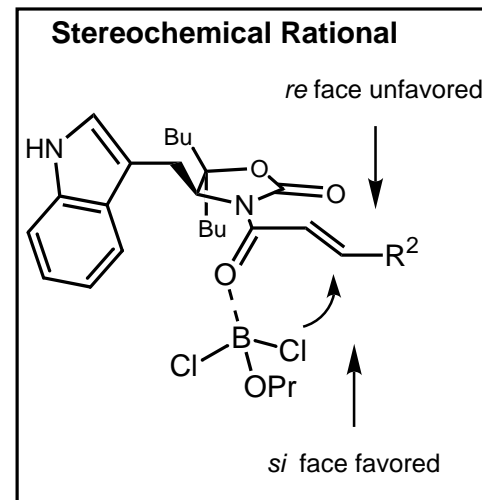


# Conjugate Addition of Chlorine to $\alpha,\beta$ -Unsaturated Chiral Imides



<u>Lewis acid</u>	<u>R<sup>1</sup></u>	<u>R<sup>2</sup></u>	<u>dr</u>	<u>% yield</u>
BCl <sub>2</sub> - <i>i</i> -OPr	H	Me	50:50	30
BCl <sub>2</sub> - <i>i</i> -OPr	Me	Me	75:25	98
BCl <sub>2</sub> - <i>i</i> -OPr	<i>n</i> -Pr	Me	83:17	80
BCl <sub>2</sub> - <i>i</i> -OPr	<i>n</i> -Bu	Me	86:14	90
BCl <sub>2</sub> -OMe	<i>n</i> -Bu	Me	92:8	98
BCl <sub>2</sub> - <i>i</i> -OPr	<i>n</i> -Bu	<i>n</i> -Pr	>99:1	80
BCl <sub>2</sub> -OMe	<i>n</i> -Bu	<i>n</i> -Pr	>99:1	80

Lower yields (20-30%) were obtained with 1 equiv of Lewis acid with the same diastereoselectivity.



← imide hydrolysis: LiOH/H<sub>2</sub>O<sub>2</sub> 80% yield

Cardillo, G.; Di Martino, E.; Gentilucci, L.; Tamasini, C.; Tomasoni, L. *Tetrahedron: Asymm.* **1995**, 6, 1957.