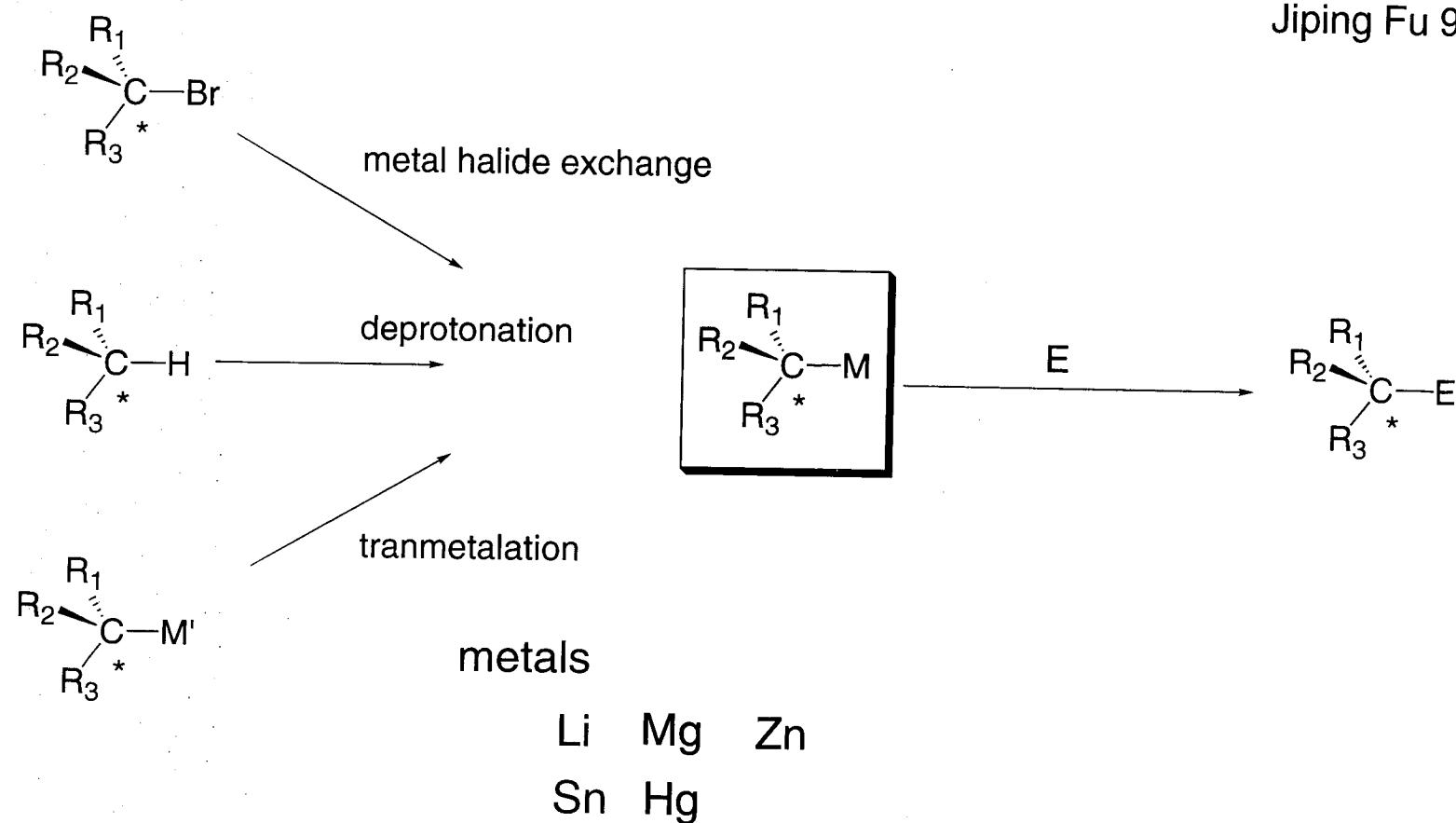


# *Configuration Stable Organometallic Reagents*

Jiping Fu 9/25/01

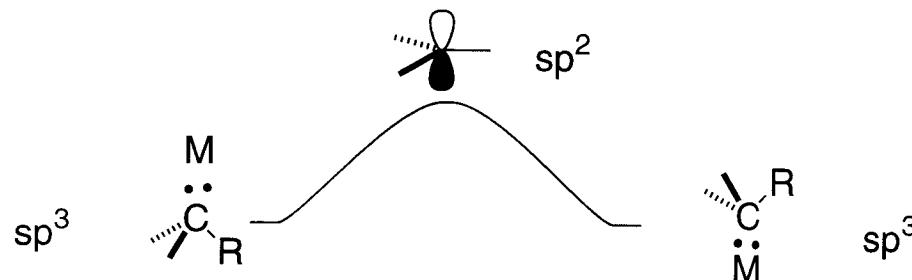


configurational stabilities

generation in enantiopure form

applications in synthesis

# Configuration Stabilities



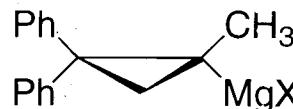
covalet bonded compound are more configurationally stable

Sn      Hg      Zn      Mg      Li

$\pi$ -accept groups decrease the energy of inversion barrier

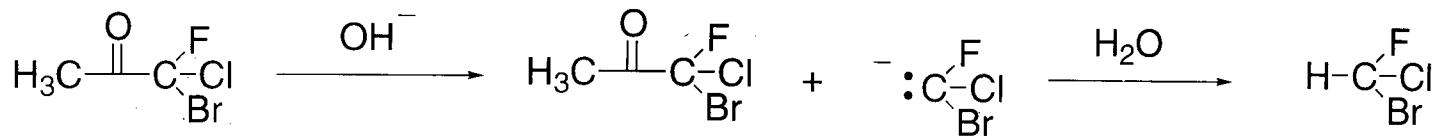


the ring strain



Walborsky, H. M. et al. *J. Am. Chem. Soc.* **1964**, *86*, 3288.

electron withdrawing groups such as halides, OR, S, Se raise the energy of inversion barrier

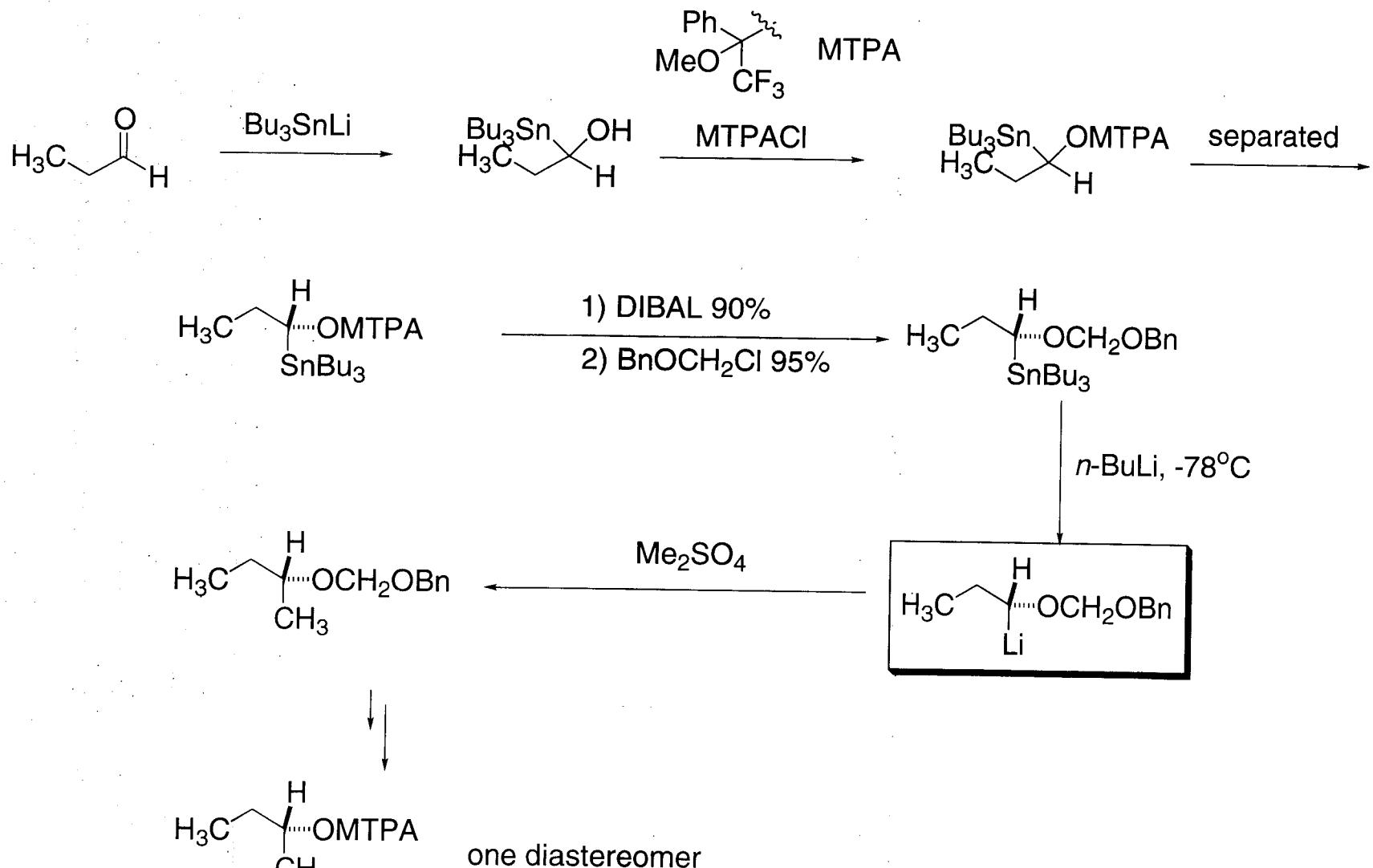


$[\alpha]_D$ : +0.39

$[\alpha]_D$ : +0.25

Hargreaves, M. K. et al. *J. Chem. Soc. C*, **1971**, 1013.

# Tin-Lithium Exchange

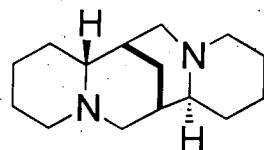
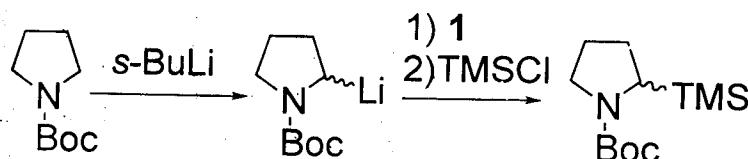
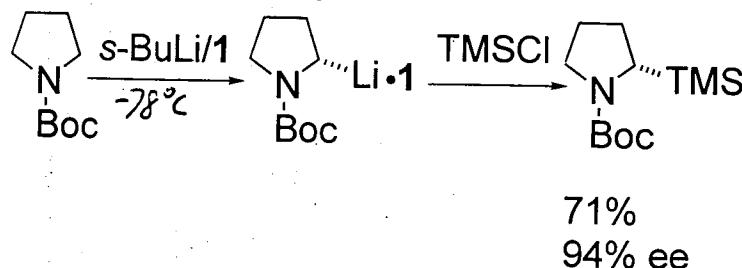


Overall retention of configuration. The Anion once formed is configuration stable.

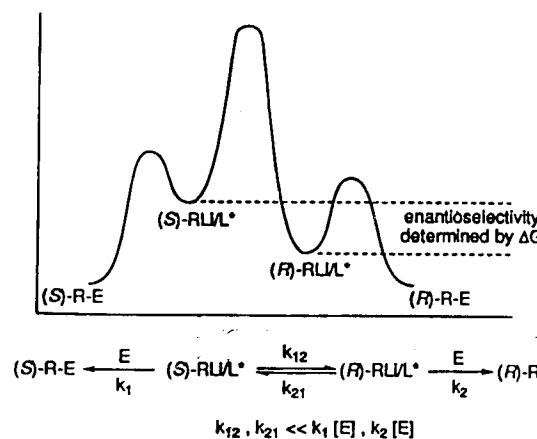
Still, W. C. et al. *J. Am. Chem. Soc.* **1980**, 102, 1201.

## *Chiral Lithium-Sparteine Complex*

### asymmetric deprotonation



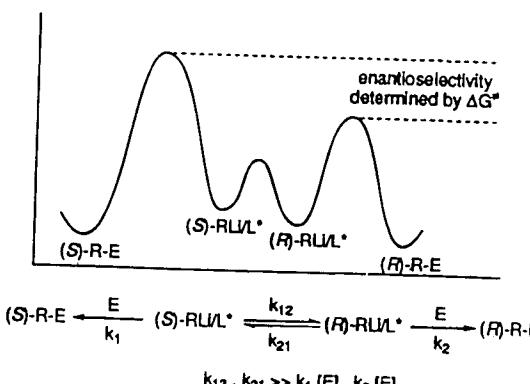
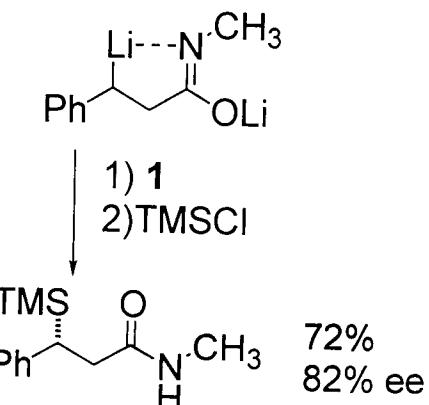
## racemic



**Figure 1.** Energy diagram and kinetic definition for dynamic thermodynamic resolution.

Stereochemistry determining step:  
deprotonation.

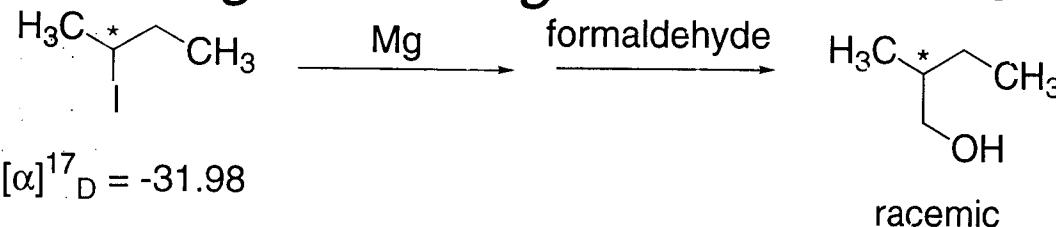
## Stereochemistry determining step: substitution.



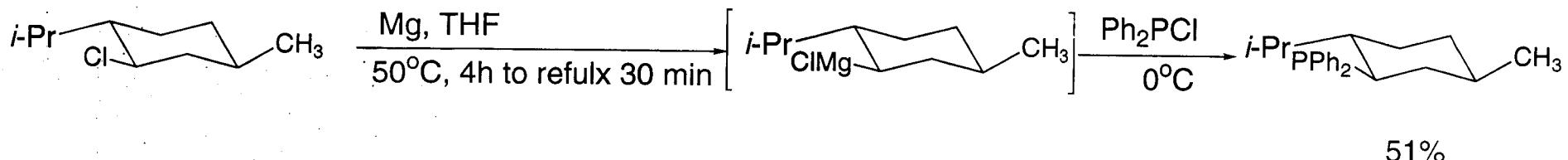
**Figure 2.** Energy diagram and kinetic definition for dynamic kinetic resolution.

Beak, P. et al. *Acc. Chem. Res.* **1996**, *29*, 552; Beak, P. et al. *Acc. Chem. Res.* **2000**, *33*, 715; Hoppe, D. et al. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 2282.

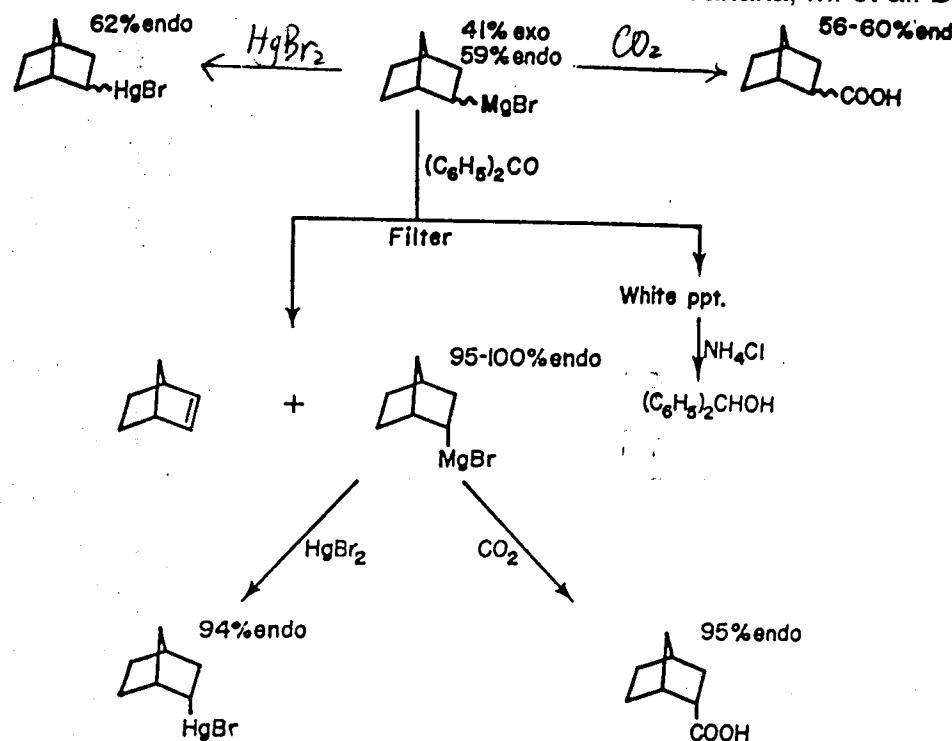
# Grignard Reagents from Halide



Pickard, et al. *J. Chem. Soc.* 1911, 99, 45.

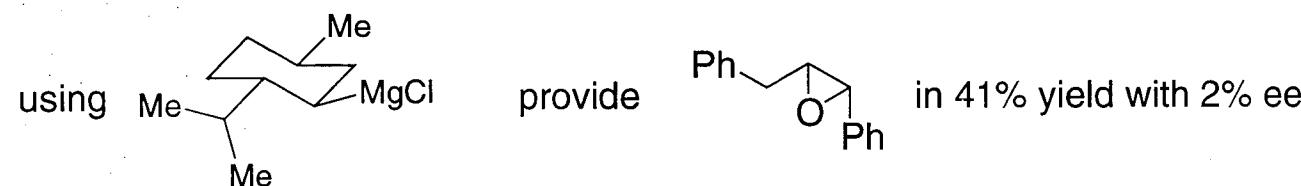
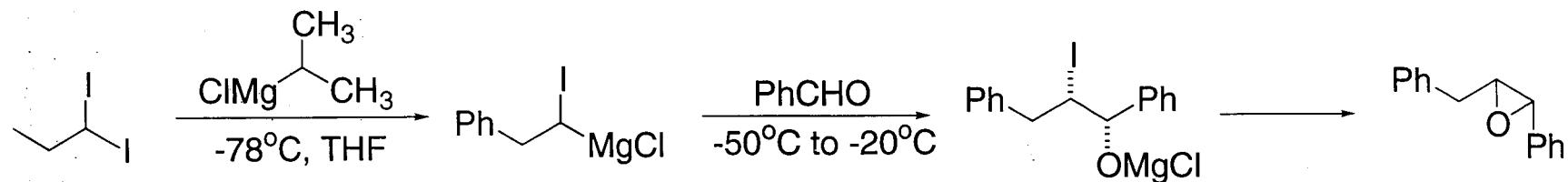


Tanaka, M. et al. *Bull. Chem. Soc. Jpn.* 1975, 48, 1094.

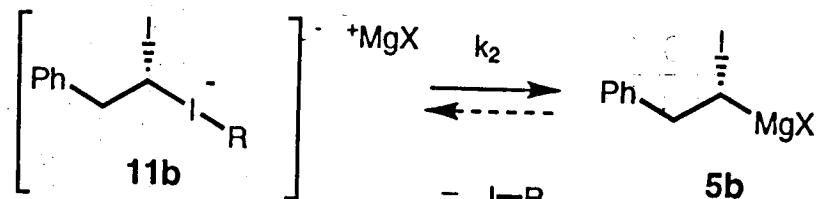
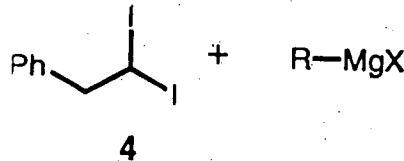
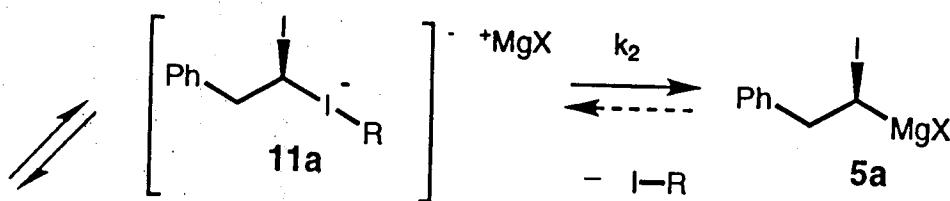


Jesen, F. R. et al. *J. Am. Chem. Soc.* 1966, 88, 3437

## Desymmetrization of Diiiodide



stereochemistry determining step?

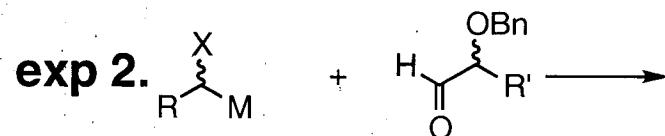
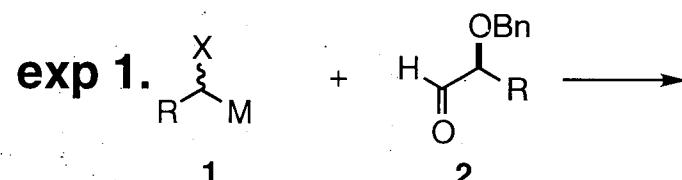
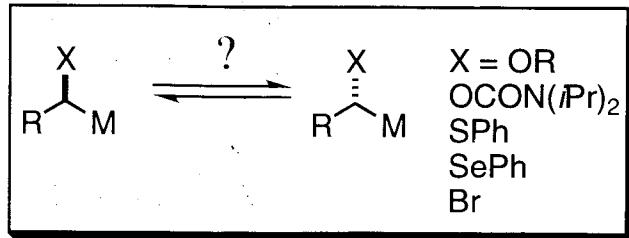


suggest the use of chiral  
magnesium cation

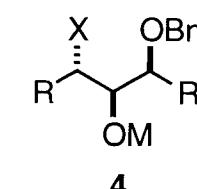
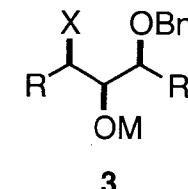
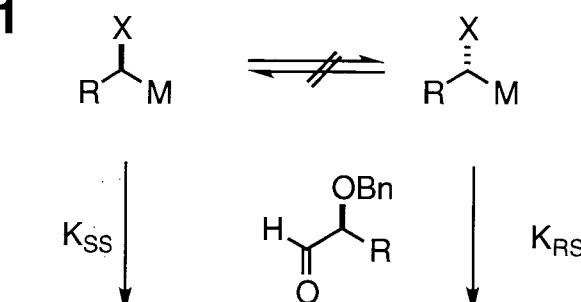
Scheme 3. Course of the reaction of **4** to give **5** via the ate complexes **11**.

Hoffmann, R. W. et al. *Chem. Eur. J.* 1999, 5, 337.

# Hoffmann Configurational Stability Test



**exp 1**



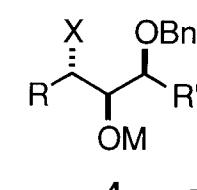
= 50 : 50

**exp 2.**

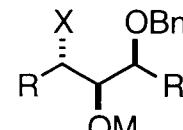
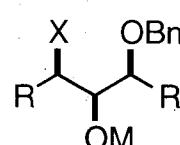
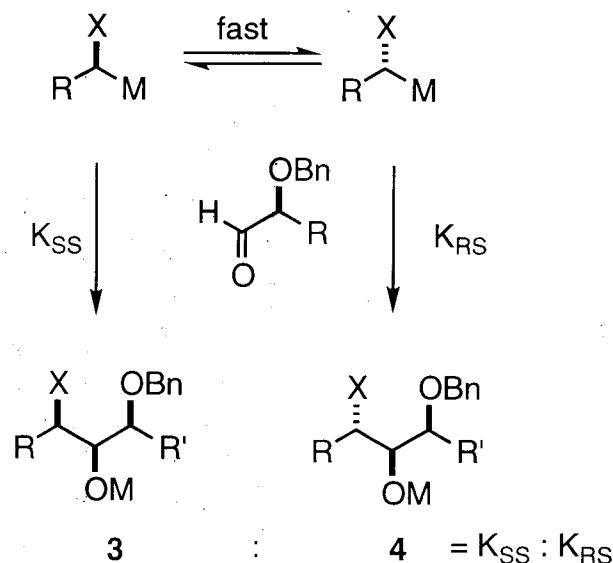


$K_{\text{SS}} = K_{\text{RR}}$

$K_{\text{RS}} = K_{\text{SR}}$

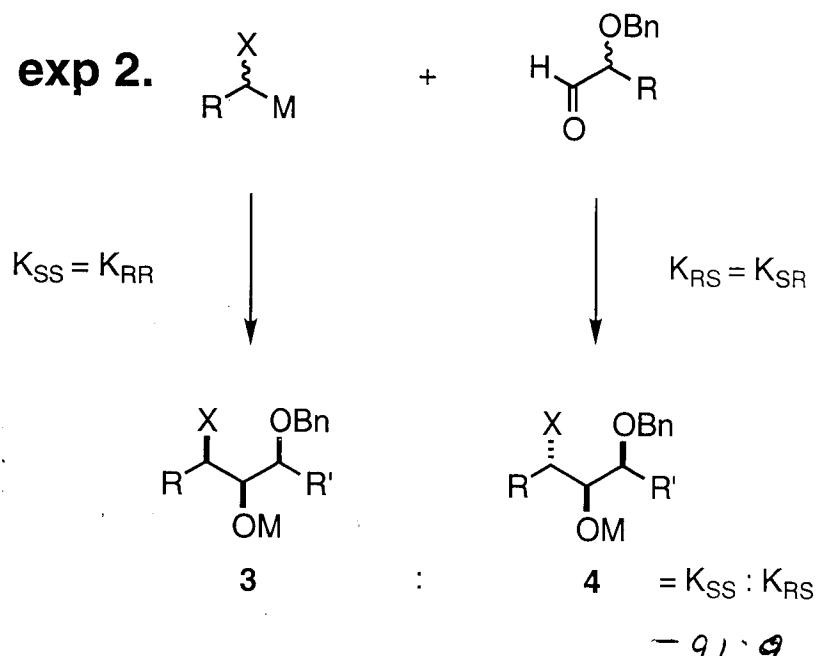
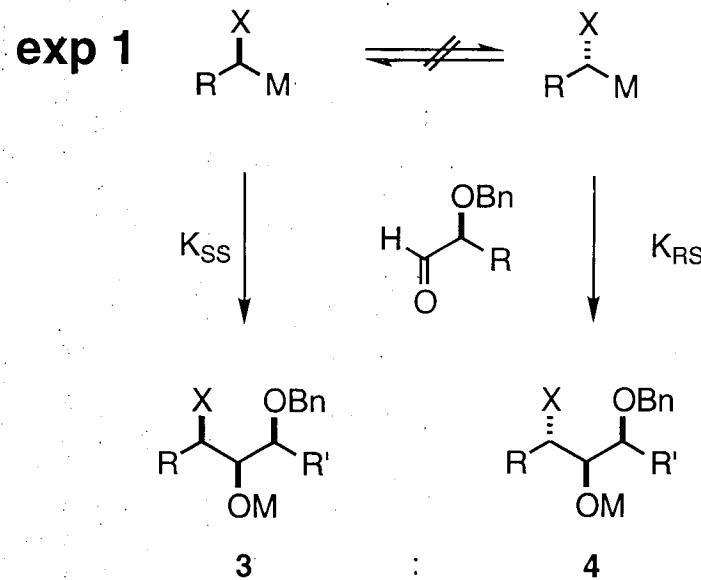
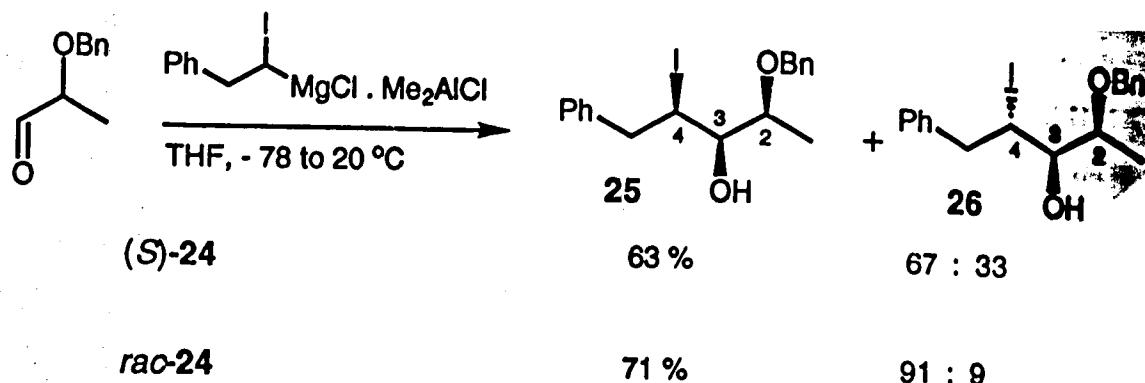


$= K_{\text{SS}} : K_{\text{RS}}$

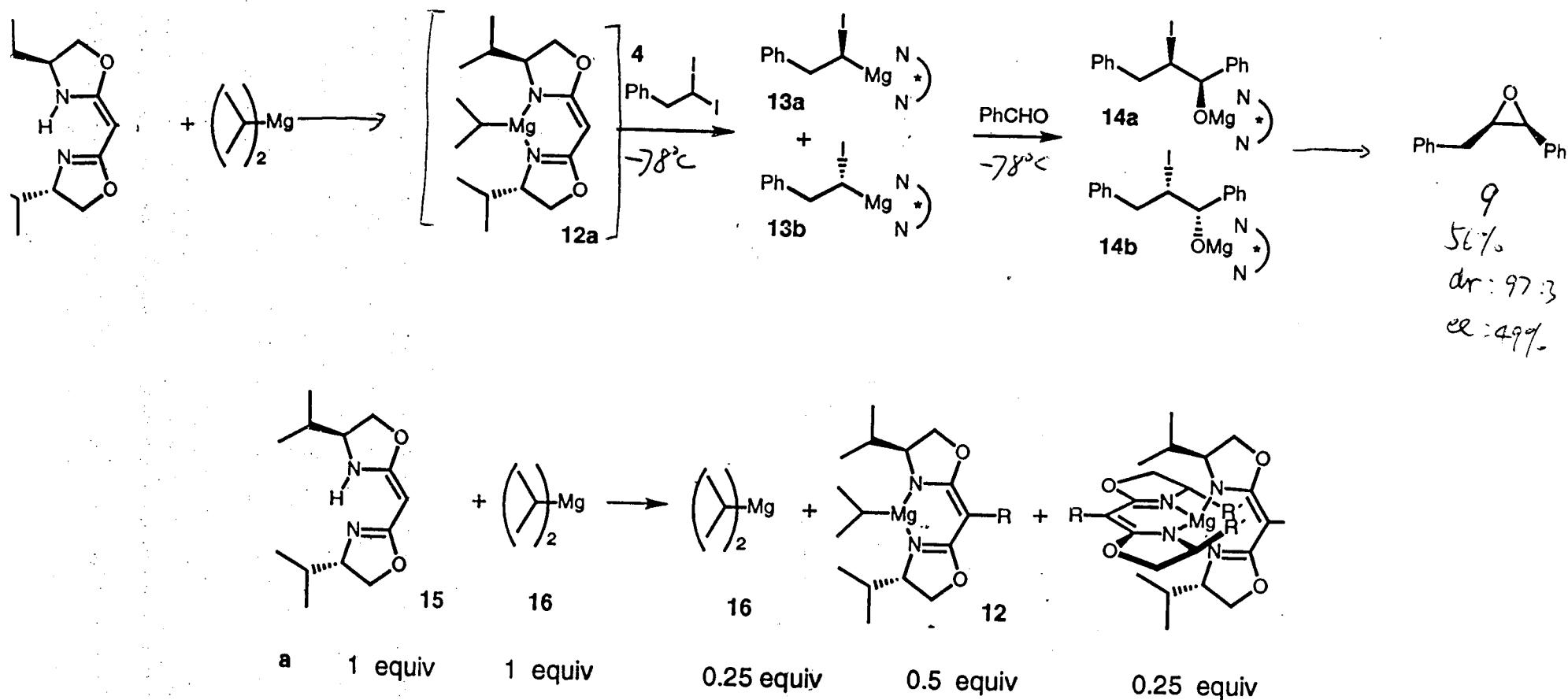


$= K_{\text{SS}} : K_{\text{RS}}$

## *Result of Test*

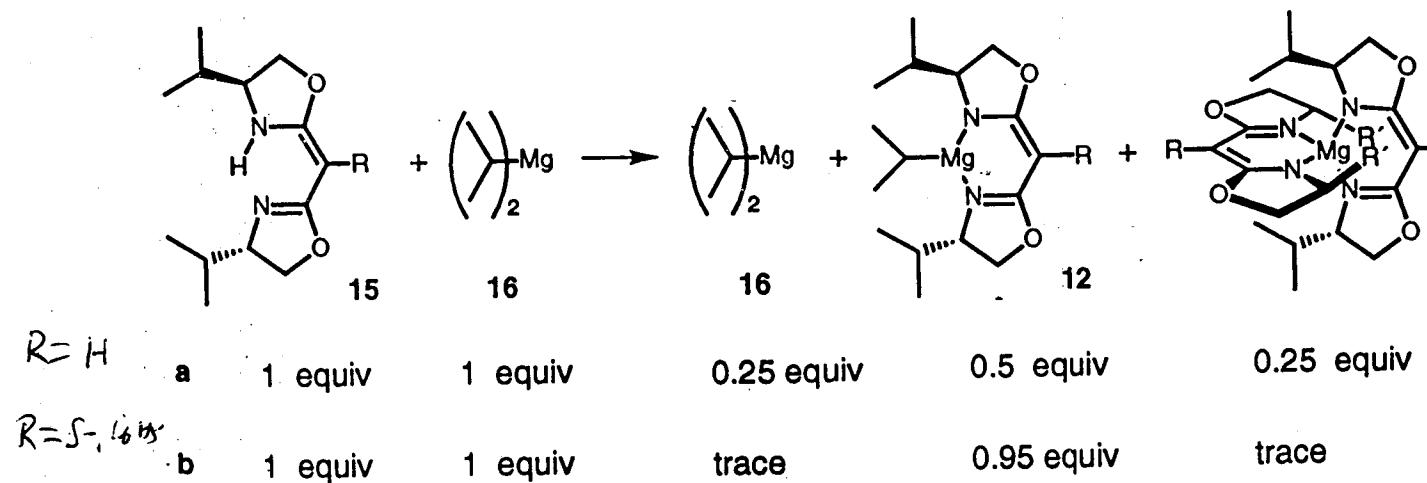


# Chiral Magnesium Cation Complex

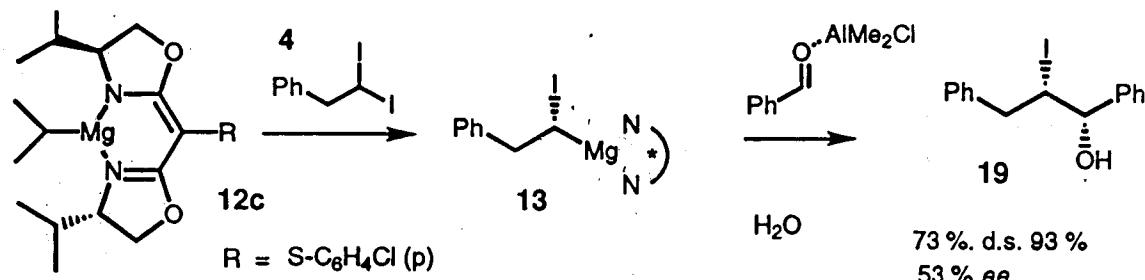


Formation of **16** could compromise the ee of product.  
**15** is too basic.

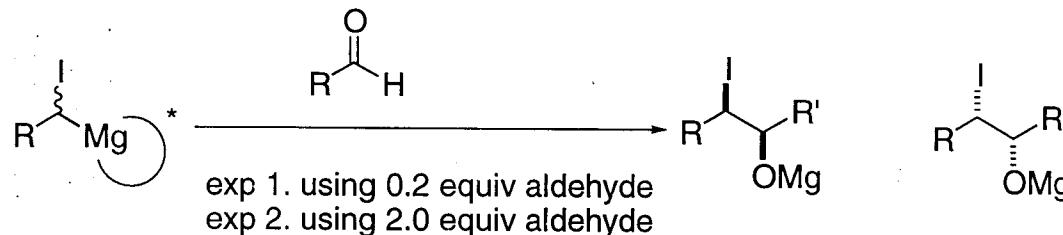
## Chiral Magnesium Cation Complex (II)



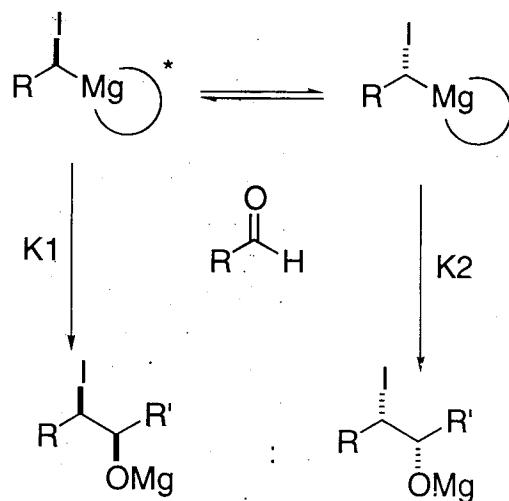
Slightly improvement of ee



## Hoffmann Configuration Stability Test (II)

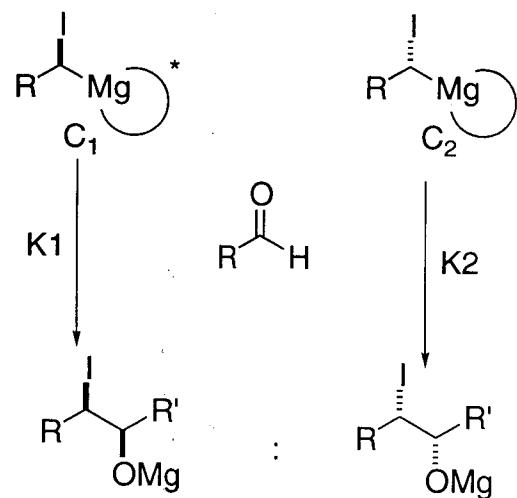


If chiral center is labile

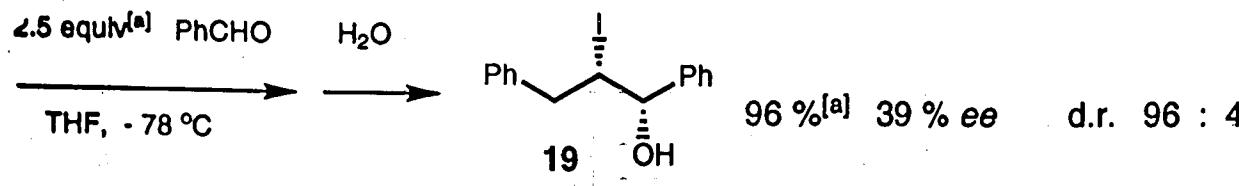


exp1 and exp2 will provide same result  
 $er = K_1 / K_2$

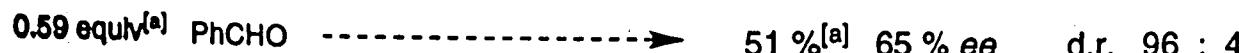
If chiral center is stable



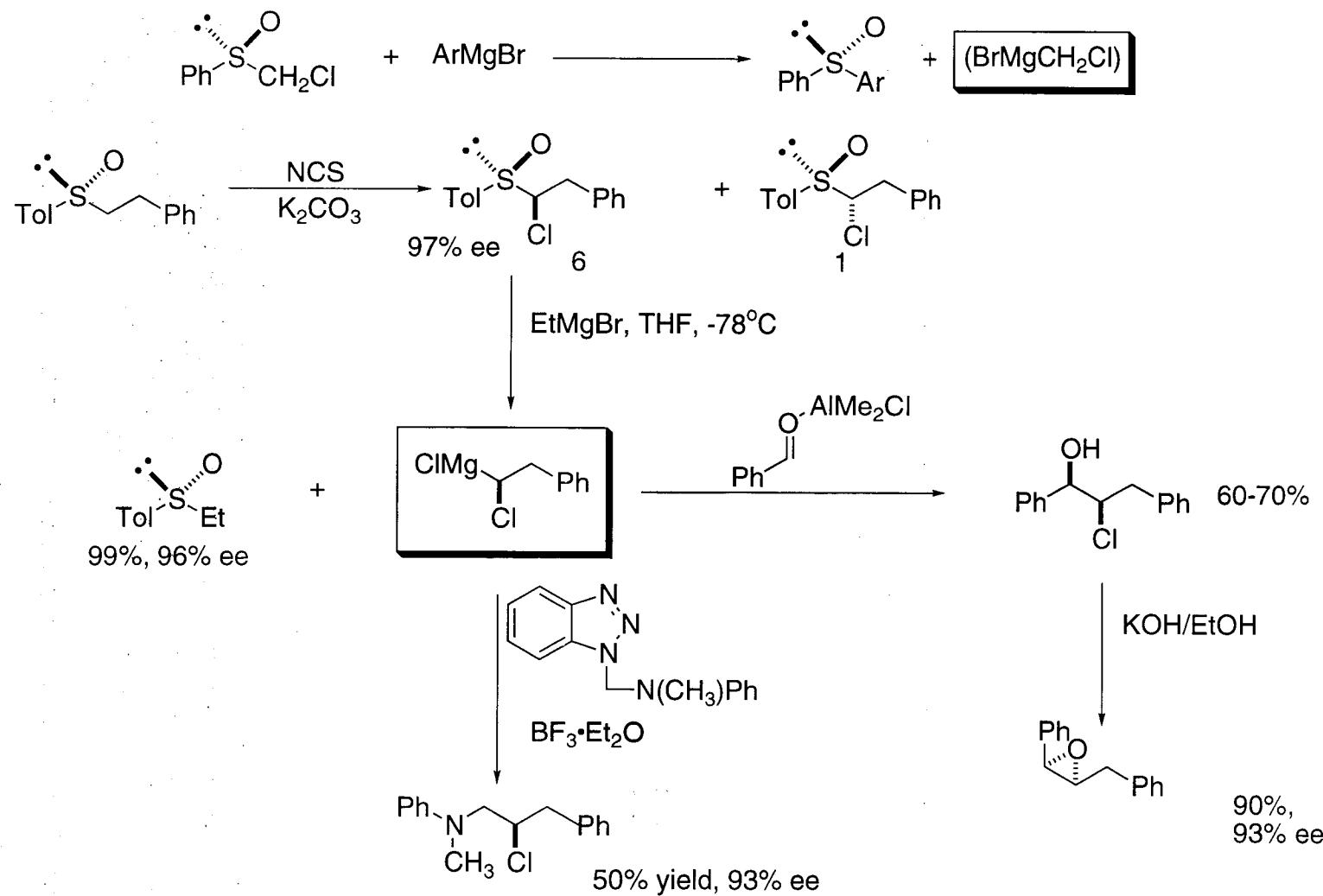
exp1 er =  $C_1 K_1 / C_2 K_2$   
 exp2 er =  $C_1 / C_2$



96 %<sup>[a]</sup> 39 % ee d.r. 96 : 4

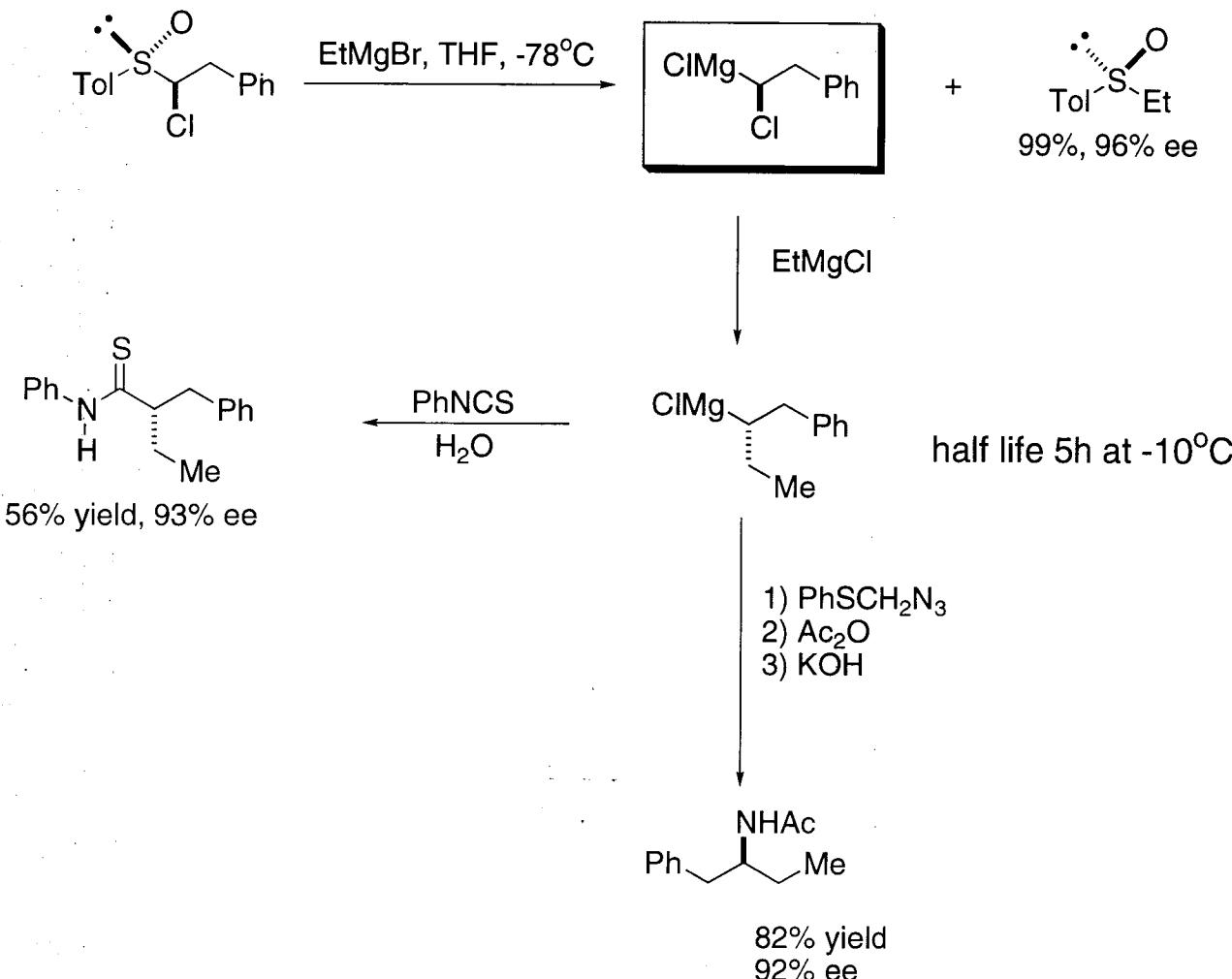


# Sulfoxide-Magnesium Exchange

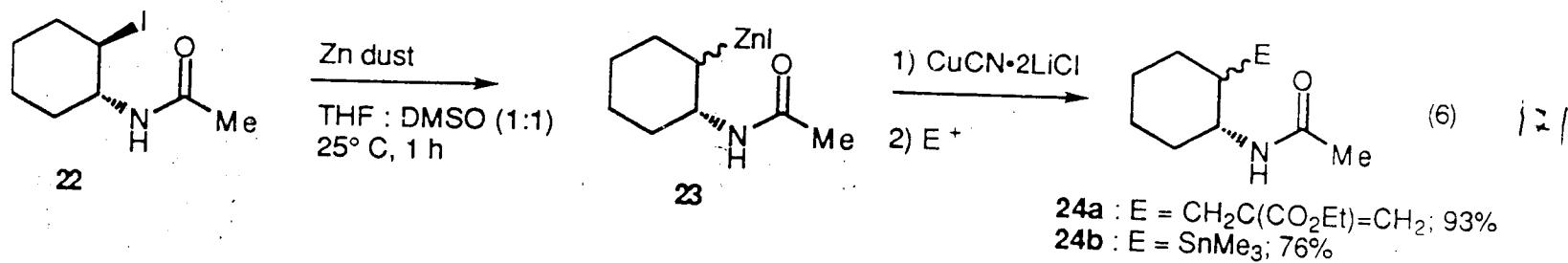
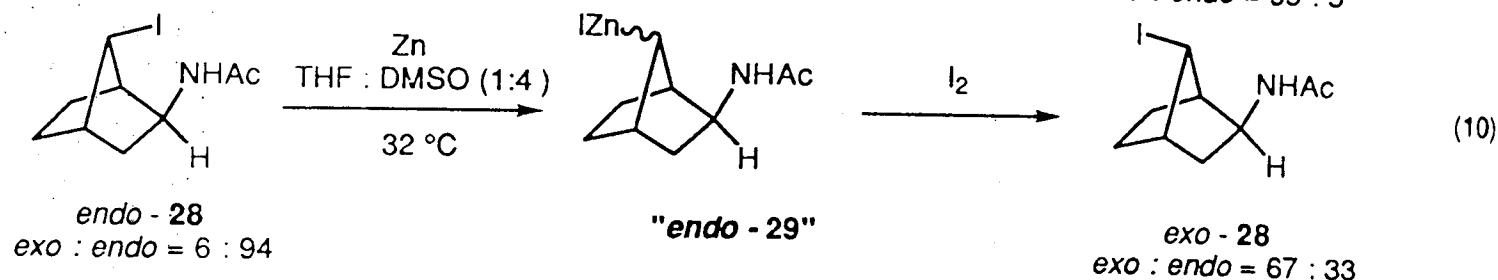
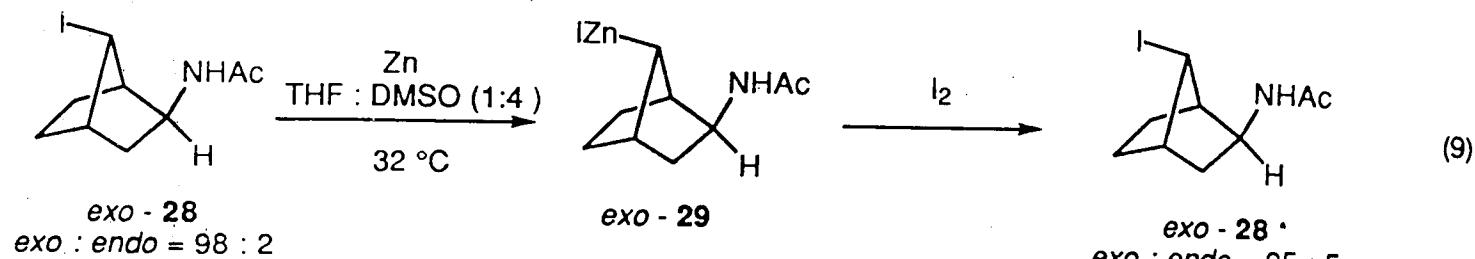


Hoffmann, R. W. et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 338.

# Chiral Secondary Grignard Reagents

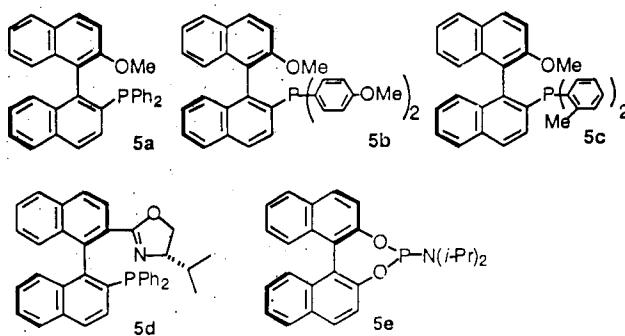
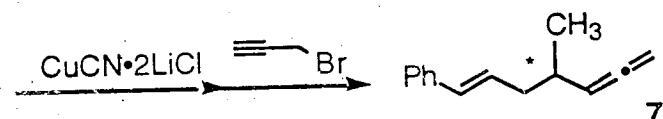
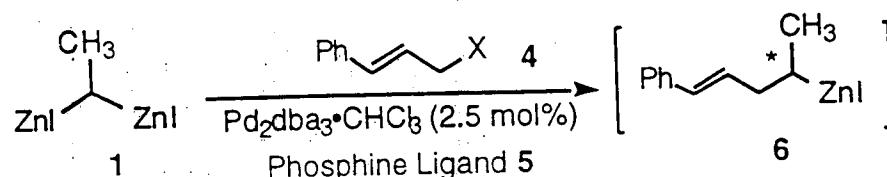
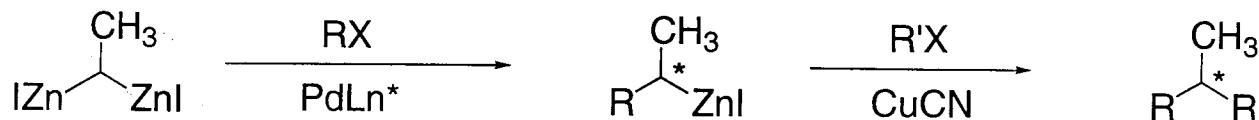


# Configuration Stable Zinc Reagents by Iodide Exchange



The iodide exchange method is certainly not general and fails for more flexible molecules.

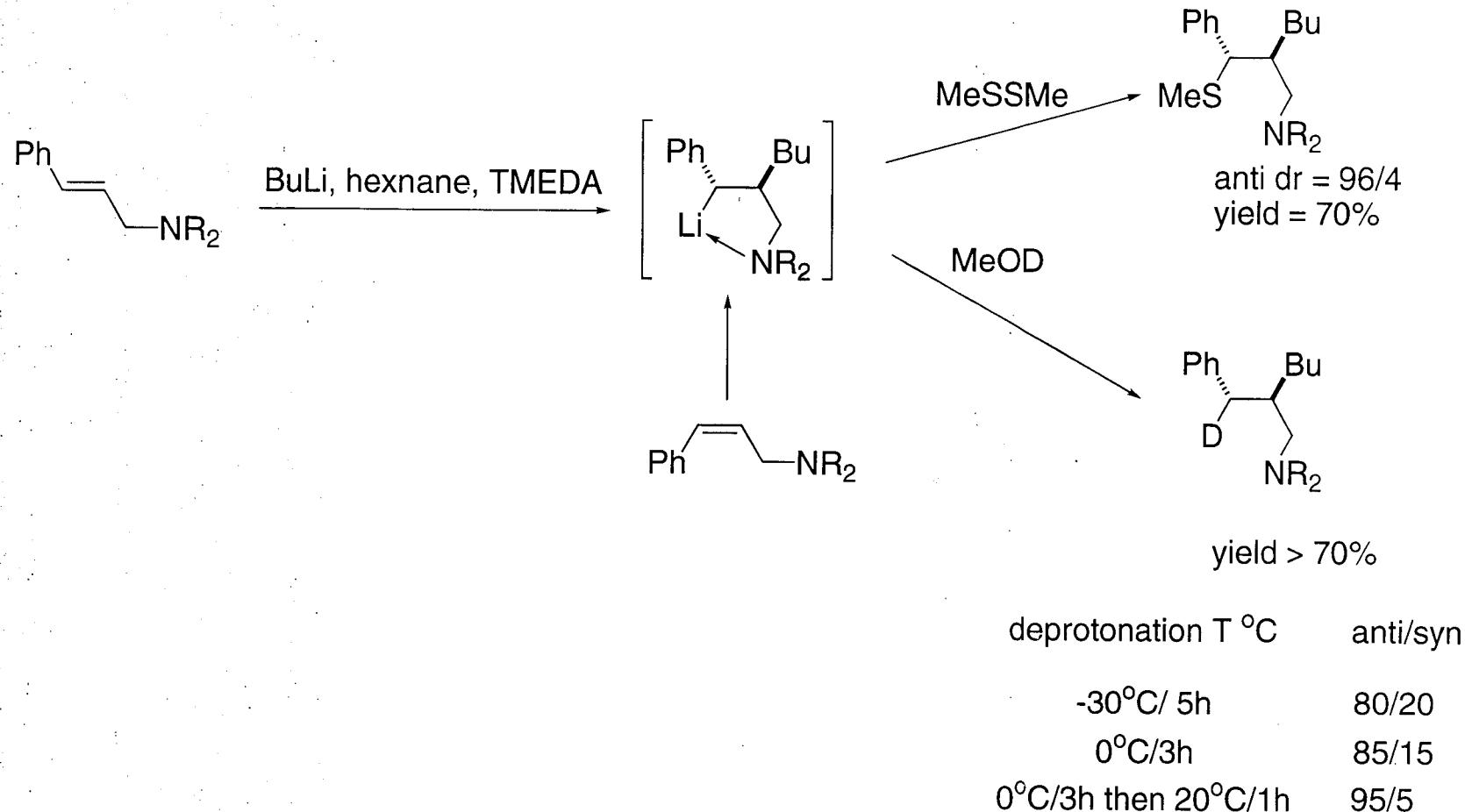
# Desymmetrization of Dizincioethane



Entry	X in 4	Ligand	Yield of 7	% ee <sup>b</sup>	R, S
1	Cl	5a <sup>9a</sup>	81 %	10	R
2	OAc	5a	78 %	22	R
3	OBz	5a	68 %	31	R
4	OCO <sub>2</sub> Me	5a	69 %	32	R
5	OCO <sub>2</sub> i-Bu	5a	70 %	33	R
6	OCO <sub>2</sub> i-Bu	5b <sup>9b</sup>	73 %	32	R
7	OCO <sub>2</sub> i-Bu	5c <sup>9c</sup>	<1 %	—	—
8	OCO <sub>2</sub> i-Bu	5d <sup>9c</sup>	<1 %	—	—
9	OCO <sub>2</sub> i-Bu	5e <sup>9d</sup>	40 %	13	S

(a) For the preparation of **6**, **1** (1.0 mmol), **Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub>** (0.25 mmol), **5** (0.1 mmol), and **4** (1.0 mmol) were used. Resulting **6** was treated with **CuCN·2LiCl** (1.2 mmol) at -30 °C and reacted with propargyl bromide to give **7**. (b) Enantiomeric purity was determined by GPC (Chrompack CP-Chiralsil-Dex CB, 25 m × 0.25 mm, 40 °C, 60min; 2 °C/min to 130 °C; 130 °C, 130 min for (*S*)-**7**, 140 min for (*R*) -**7**.

## Lithium Anion



The observation is consistent with thermodynamic control of the benzylic organolithium.

# Zn anion

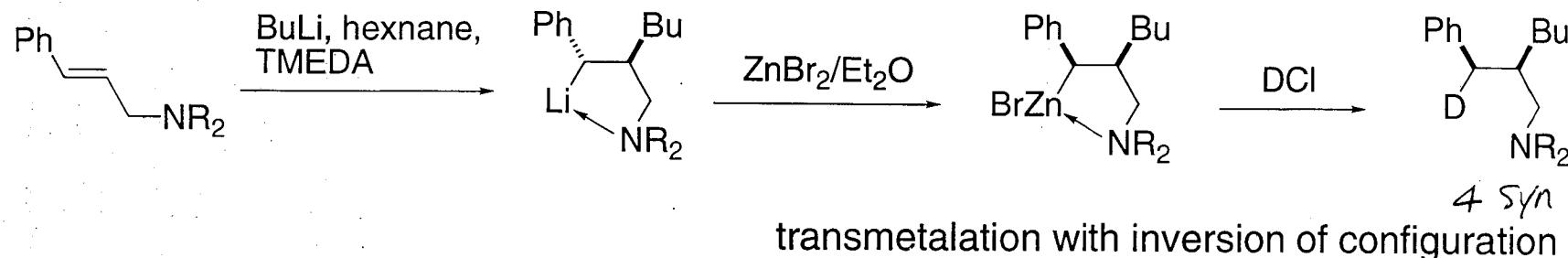
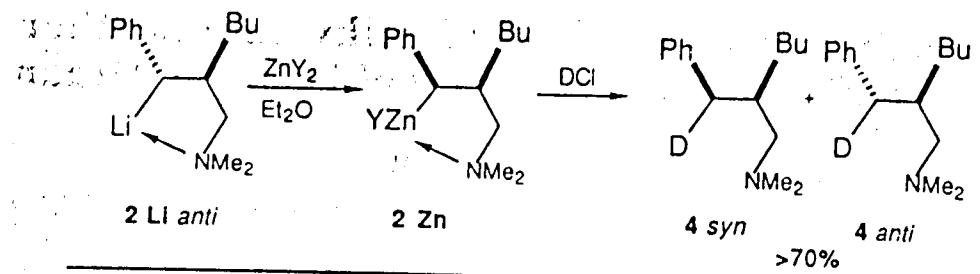


Table 1

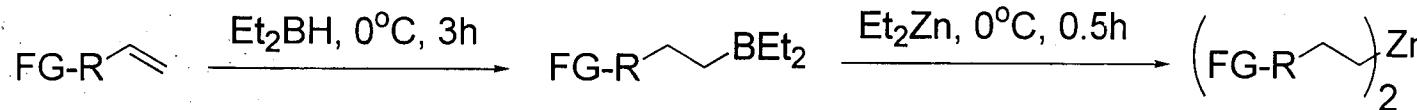


entry	zinc addns <sup>a</sup>	T (°C)/time before quench with DCl <sup>b</sup>	4 syn/4 anti <sup>c</sup>
1	none	20/30 min	8/92
2	ZnBr <sub>2</sub>	-30/30 min	95/5
3	<b>ZnBr<sub>2</sub></b>	<b>-30/4 h</b>	<b>95/5</b>
4	ZnBr <sub>2</sub>	-30 to 0/15 min	70/30
5	ZnBr <sub>2</sub>	0/1 h	50/50
6	ZnBr <sub>2</sub>	50/2 h	≈5/95
7	ZnCl <sub>2</sub>	-30 to 0/15 min	70/30
8	BuZnBr	-30 to 0/30 min	30/70
9	Et <sub>2</sub> Zn	0/1 h	≈20/80
10	Et <sub>2</sub> Zn	-50/30 min	≈20/80

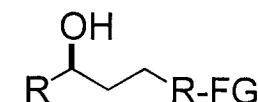
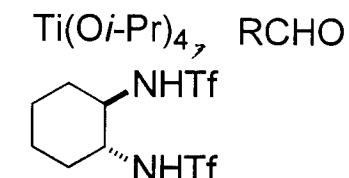
<sup>a</sup> The zinc derivative is slowly added at -60 °C in Et<sub>2</sub>O solution.

<sup>b</sup> DCl is introduced at -60 °C. <sup>c</sup> A value of 95/5 indicates that only one stereoisomer was detected by <sup>1</sup>H NMR (400 MHz) with approximately 70–90% deuteration.

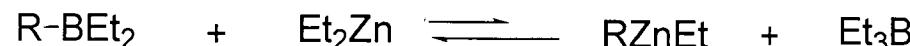
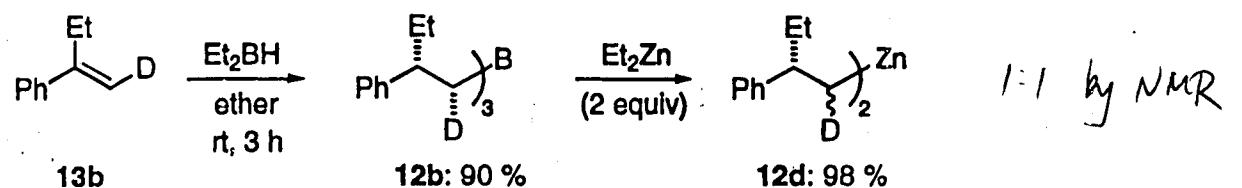
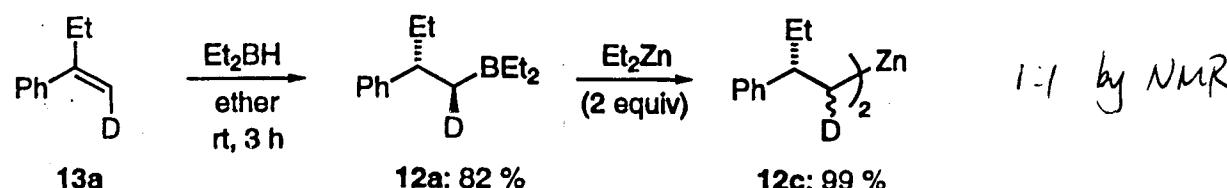
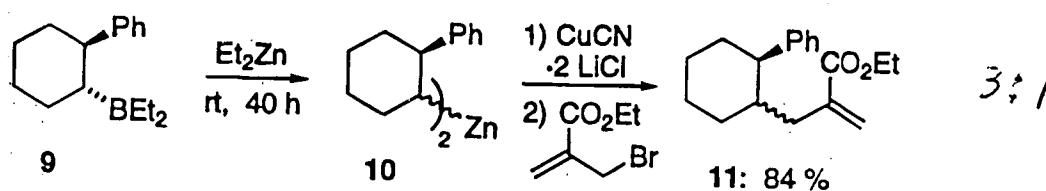
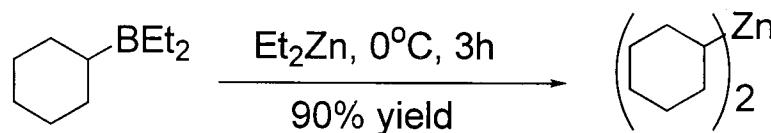
# Dialkylzincs via Boron-Zinc Exchange



entry	FG-R in 3	R in RCHO 57	product 56	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	C <sub>8</sub> H <sub>17</sub>	Ph		56a 87	92
2.	C <sub>8</sub> H <sub>17</sub>			56b 75	78 (96) <sup>c</sup>
3	C <sub>8</sub> H <sub>17</sub>			56c 62	> 96
4.	C <sub>10</sub> H <sub>21</sub>	Ph		56d 57 (88)	64 (>96) <sup>d</sup>
5	C <sub>10</sub> H <sub>21</sub>			56e 73	> 96
6		Ph		56f 17	> 96 <sup>e</sup>
7	c-Hex	Ph		56g 67	80
8	PivO(CH <sub>2</sub> ) <sub>3</sub>	Ph		56h 70	93
9	PivO(CH <sub>2</sub> ) <sub>3</sub>	c-Hex		56i 22	78
10	PivO(CH <sub>2</sub> ) <sub>4</sub>			56j 52	95
11	PivO(CH <sub>2</sub> ) <sub>5</sub>			56k 41	85 <sup>c</sup>
12	PivO(CH <sub>2</sub> ) <sub>6</sub>	iPrCH <sub>2</sub>		56l 60	90
13				56m 69	80

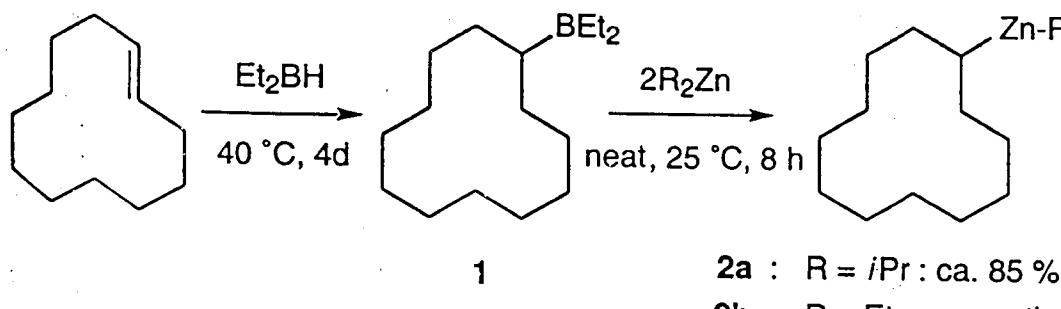


# Initial Attempts on Configuration Stable Zinc Reagents



The failure is probably due to the slow and equilibrated reaction.

# Exchange Using *i*-Pr<sub>2</sub>Zn



exchange using *i*-Pr<sub>2</sub>Zn is much more fast than using Et<sub>2</sub>B

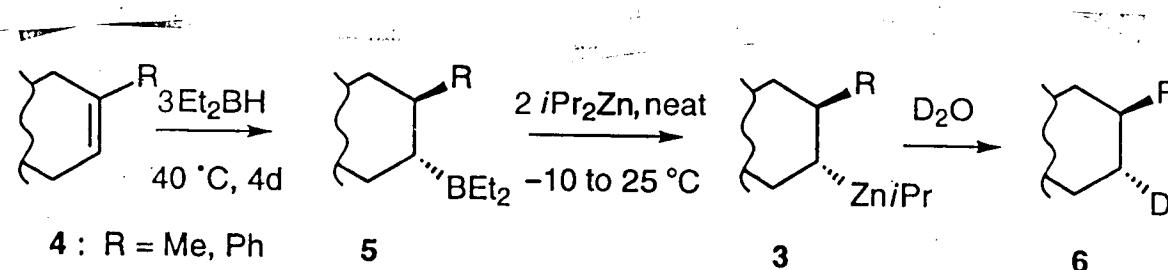
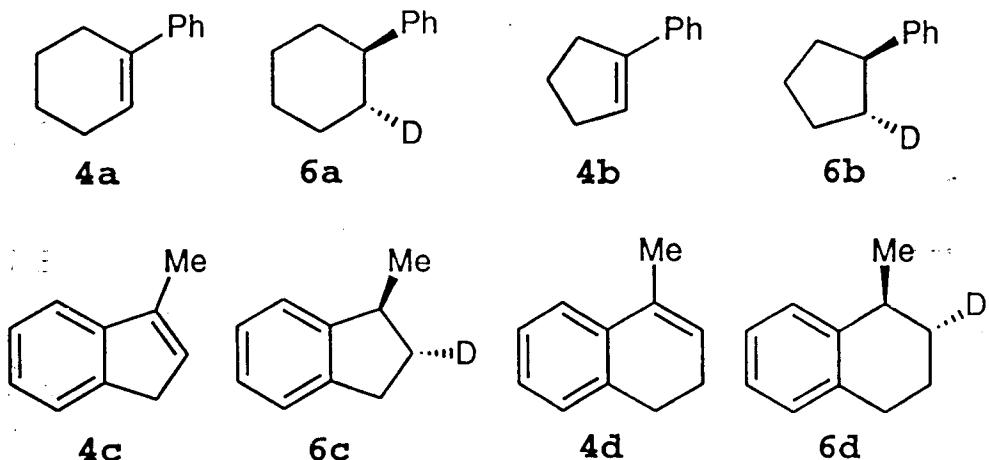


Table 1. Yields of 6 as well as conditions of the boron–zinc exchange.

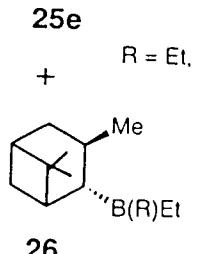
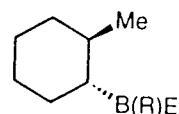
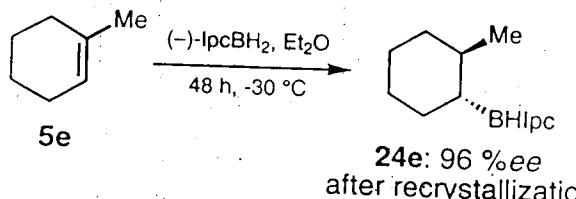
entry	4	6	T [°C]	t [h] [a]	trans:cis [b]	Yield [%] [c]
a	b	4a	25	7	100:0	56
b	b	6a	25	7	87:13	54
b	b	4b	-10	10	98:2	56
c	c	6b	25	7	88:12	47
c	c	4c	-10	10	99:1	61
d	d	6c	-10	10	97:3	60



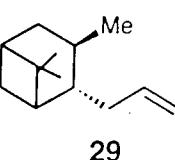
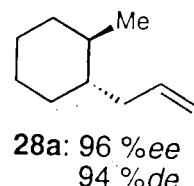
[a] Temperature and time required for the boron–zinc exchange reaction. [b] The trans:cis ratio was determined by <sup>2</sup>H NMR spectroscopy. [c] Overall yield (based on the olefin 4) of analytically pure products.

# Enantioselective Sequence

20



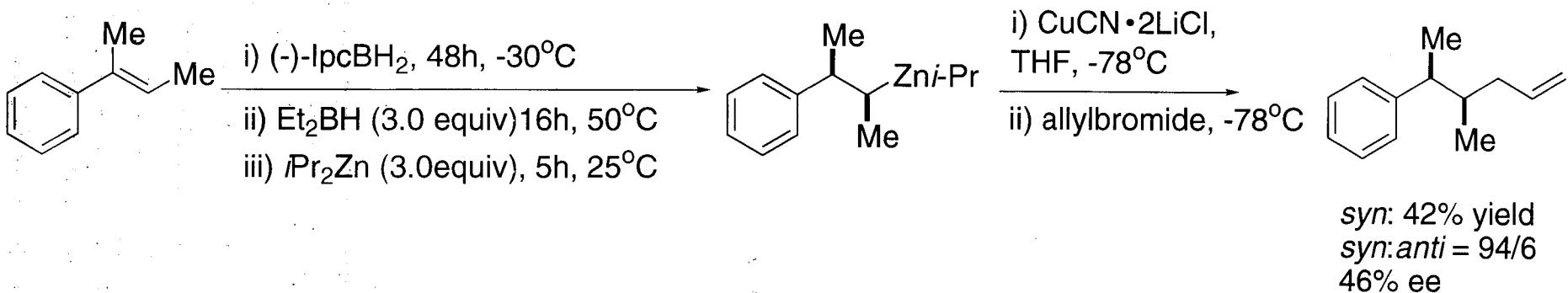
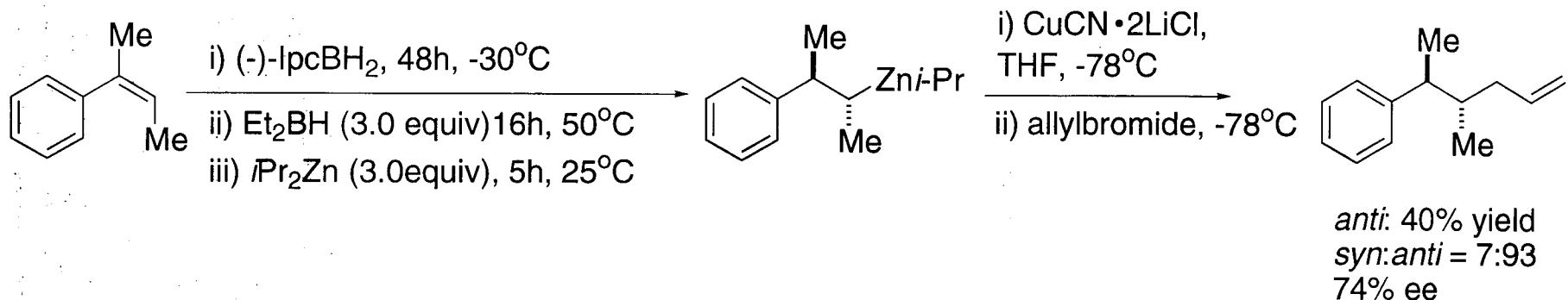
i)  $iPr_2Zn$ , 25 °C  
ii)  $CuCN \cdot 2LiCl$ ,  
-78 °C  
iii) allyl bromide



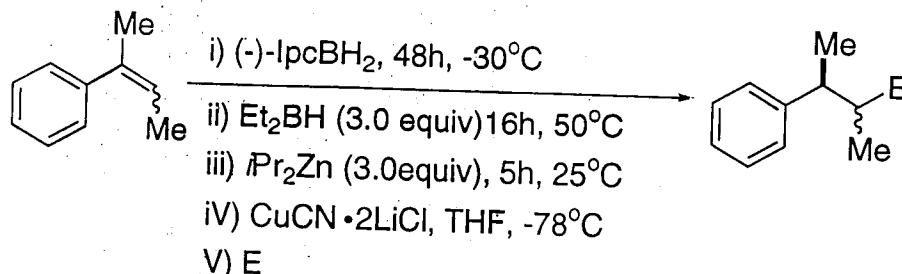
Entry	27	Product	28	trans:cis ratio	ee <sup>[a]</sup>	Yield [%] <sup>[b]</sup>
1	e	<chem>C1CCCCC1[C@H](C=C1)C=C</chem>	<b>28a</b>	98:2	94	[c]
2	e	<chem>C1CCCCC1[C@H](C=C1)C(=O)OC(=O)C</chem>	<b>28b</b>	93:7	96	[c]
3	e	<chem>C1CCCCC1[C@H](C=C1)C#CTMS</chem>	<b>28c</b>	94:6	96	[c]
4	a	<chem>C1CCCCC1[C@H](C=C1)C2=CC=CC=C2</chem>	<b>28d</b>	97:3	20	45
5	b	<chem>C1CCCCC1[C@H](C=C1)C2=CC=CC=C2</chem>	<b>28e</b>	97:3	94	47
6	f	<chem>C1CCCCC1[C@H](C=C1)C2=CC=C(C=C2)c3ccccc3</chem>	<b>28f</b>	98:2	84	77
7	c	<chem>C1=CC=C(C=C1)C2=CC=C(C=C2)c3ccccc3</chem>	<b>28g</b>	97:3	66	40
8	c	<chem>C1=CC=C(C=C1)C2=CC=C(C=C2)C(=O)C3=CC=CC=C3</chem>	<b>28h</b>	99:1	64	43
9	d	<chem>C1=CC=C(C=C1)C2=CC=C(C=C2)c3ccccc3</chem>	<b>28i</b>	98:2	42	40

[a] Enantiomeric ratio of the major diastereomer determined by GC analysis on a chiral  $\beta$ -cyclodextrin column. [b] Yield of analytically pure product based on the starting olefin. [c] Desired products are contaminated by pinene-derived products with electrophiles.

# Acyclic Organo Zinc



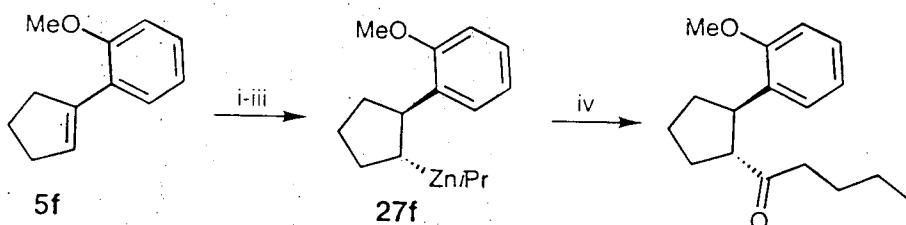
# Acyclic Organo Zinc (II)



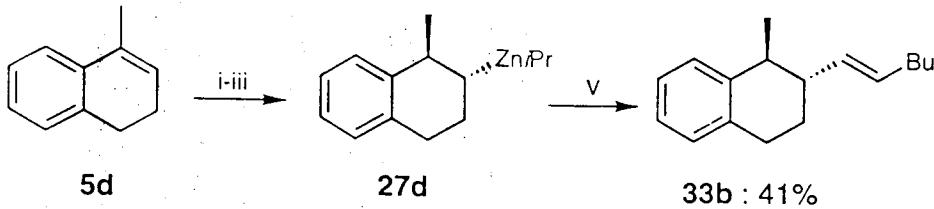
Entry	31	Product	32	anti:syn ratio	ee <sup>[a]</sup>	Yield [%] <sup>[b]</sup>
1	anti		anti-32a	92:8	74	40
2	anti		anti-32b	90:10	74	38
3	anti		anti-32c	94:6	82	41
4	anti		anti-32d	97:3	56	41
5	syn		syn-32a	6:94	46	42
6	syn		syn-32b	2:98	44	35
7	syn		syn-32c	11:89	46	35
8	syn		syn-32d	5:95	56	38

[a] Enantiomeric ratio of the major diastereomer determined by GC analysis on a chiral  $\beta$ -cyclodextrin column. [b] Yield of analytically pure products based on the olefin.

# Pd Catalyzed Coupling



33f : 58%  
*trans:cis* = 99 : 1  
81 %ee



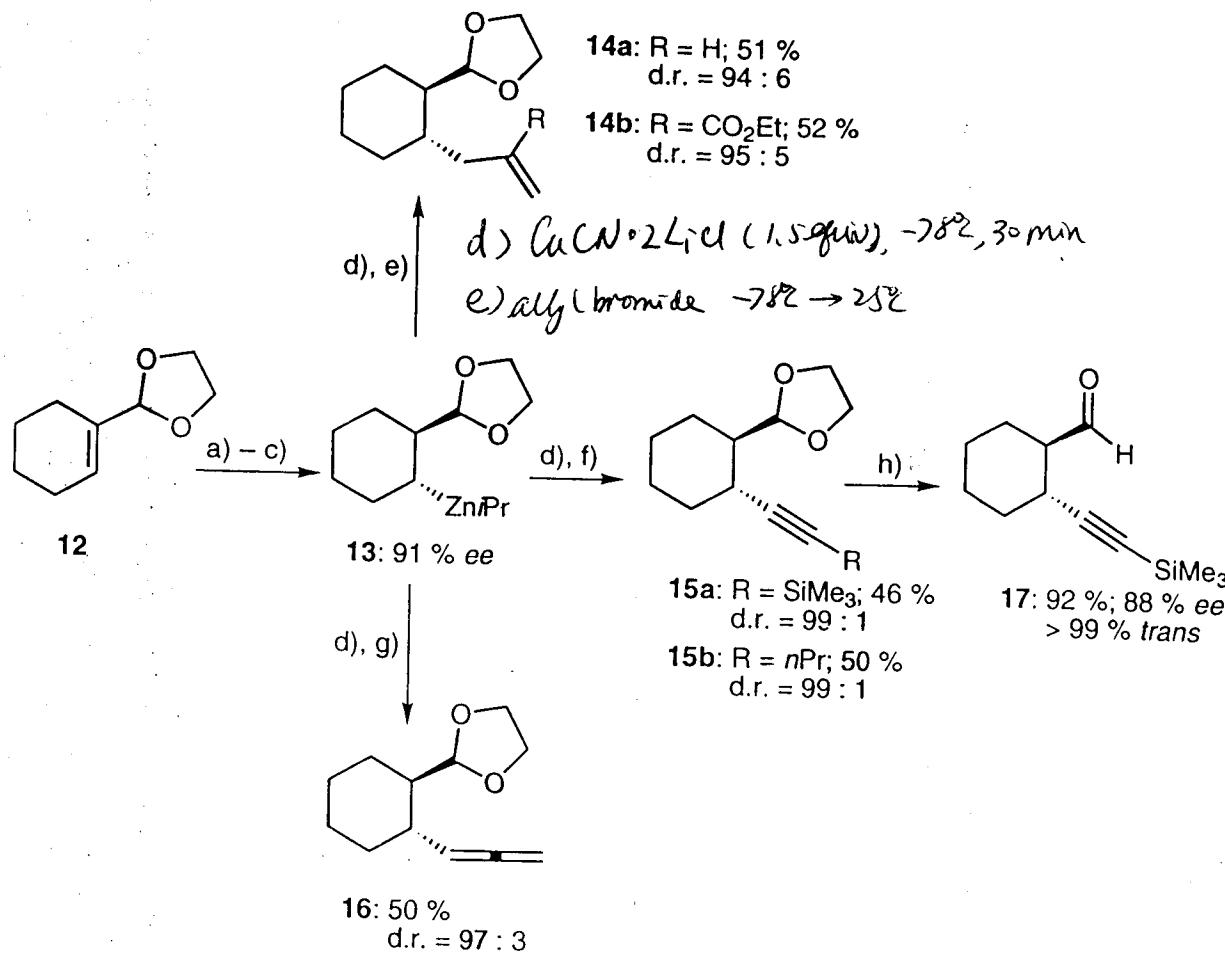
33b : 41%  
*trans:cis* = 99 : 1  
56 %ee

heme 14. i) (-)-IpcBH<sub>2</sub>, 48 h, -30 °C; ii) Et<sub>2</sub>BH, 16 h, 50 °C then vacuo;  
) *i*Pr<sub>2</sub>Zn, 5 h, 25 °C then vacuo; iv) [Pd(dba)<sub>2</sub>] (2 mol %), P(*o*-tolyl)<sub>3</sub> (1 mol %), pentanoyl chloride, dioxane, 0 °C to 25 °C, 16 h; v) [Pd(dba)<sub>2</sub>] (2 mol %), P(*o*-tolyl)<sub>3</sub> (4 mol %), *E*-1-iodohexene, THF, 0 °C then 25 °C, 1 h.

Entry	27	Product	33	<i>trans:cis</i> ratio	ee <sup>[a]</sup>	Yield [%] <sup>[b]</sup>
1	c		33a	99:1	56	35
2	d		33b	99:1	52	41
3	f		33c	98:2	83	40
4	c		33d	92:8	64	39
5	d		33e	92:8	60	43
6	f		33f	99:1	81	58
7	anti-31		33g	90:10	88	45
8	c		33h	95:5	60	41

[a] Enantiomeric ratio of major diastereomer determined by GC analysis on a chiral  $\beta$ -cyclodextrin column. [b] Yield of analytically pure products based on the starting olefin.

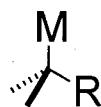
# Formal Enantioselective Michael Addition



Scheme 4. Enantioselective conjugate functionalization of the unsaturated acetal **12** by an asymmetric hydroboration and boron–zinc exchange sequence. a) (-)-IpcBH<sub>2</sub> (1.1 equiv, –25 °C, 48 h); b) Et<sub>2</sub>BH (5 equiv, 50 °C, 16 h); c) iPr<sub>2</sub>Zn (5 equiv, 25 °C, 5 h); d) CuCN·2LiCl (1.5 equiv, –78 °C, 30 min); e) allylic bromide (5 equiv, –78 °C to 25 °C, 10 h for **14a** or 5 equiv, –40 °C, 48 h for **14b**); f) alkynyl bromide (5 equiv, –40 °C, 16 h); g) propargyl bromide (5 equiv, –40 °C, 16 h); h) 5% HCl, 35 °C, 16 h.

# *Summary*

## Configuration stability



- R electron withdrawing group configurationally more stable
- R  $\pi$ -donating group configurational less stable
- M Mg stable at low T, Zn stable at room temperature

## Hoffmann configuration stability test

racemic organometallic reagents are used

## Preparation

### Organolithium

tin-lithium exchange

asymmetric deprotonation/ formation of chiral lithium anion •sparteine complex

### Grignard reagent

Iodine-Magnesium exchange using chiral magnesium cationic complex

sulfoxide-magnesium exchange: chiral secondary Grignard regeants

### Organozinc reagent

desymmetriczation of dizincioethane catalyzed by chiral Pd complex

transmetalation from lithium: inversion of configuration

transmetalation from boron: retension of configuration