Stereoselective Allylation of Imines

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Research Topic Seminar

10-30-04

Topic Overview:

- Introduction

- Imines: Why is C=N different?

- Synthesis of Allylating Reagents

- Applications to Natural Product Synthesis

- Previous Wipf Group Methodology

- Current Work

Why is allylation a useful process?

- High degree of stereoselectivity

- Great variety of reactivity depending on the allylmetal species used

- New methods for synthesis of allylating species have allowed for highly functionalized product formation

- Products of allylation reactions are useful buliding blocks for natural product synthesis
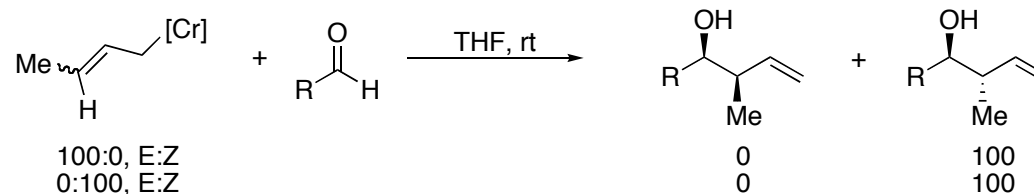
Classification of Allylating Reagents

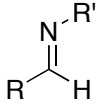•Type I: reactions wherein the *syn*/*anti* ratio reflects the *Z*/*E* ratio of the starting allylmetal

93:9, E:Z
5:95, E:Z

6
96

94
4
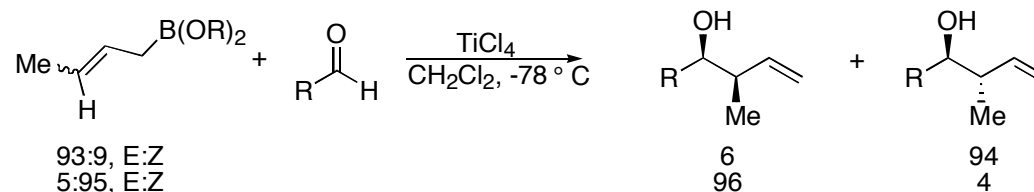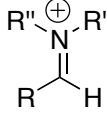
•Type II: reactions wherein the product is predominately *syn* independent of the allylmetal geometry

100:0, E:Z
0:100, E:Z

98
99

2
1
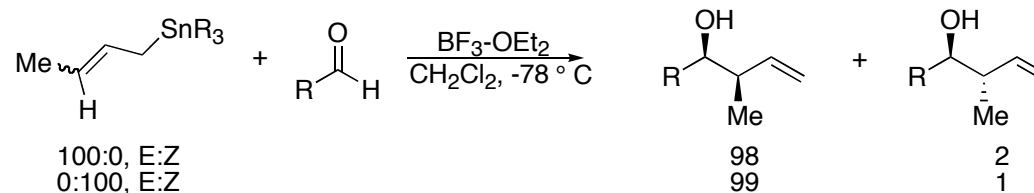
•Type III: reactions wherein the product is predominately *anti* independent of the allylmetal geometry

100:0, E:Z
0:100, E:Z

0
0

100
100

Comparison between C=O and C=N

C=X bond E:	173-181	143	XXX	kcal.mol^{-1}
Polarization (δ):	+ 0.51	+ 0.33	+ 0.54	

Reduced electrophilicity of the C=N double bond

Often unstable and difficult to synthesize - most methodology has only been directed to aromatic imines

Side reactions observed with organometallics

*E-Z* geometery problem associated with C=N double bonds

Allyllithium Reagents:

Very basic: Restricted to aromatic or α-substituted aldimines

Cannot be synthesized via halogen-metal exchange reaction due to the competing substitution process

Most commonly formed by the trasnmetalation of the corresponding allyltin species
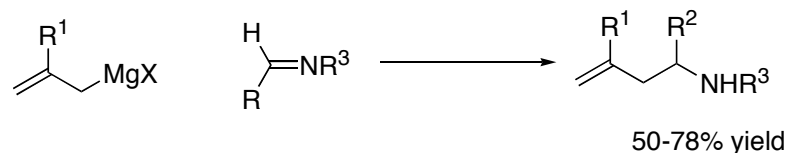
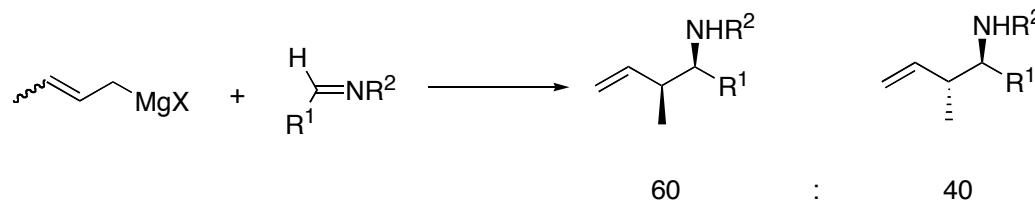Chloroallyllithium useful species for the synthesis of 2-vinyl aziridines:
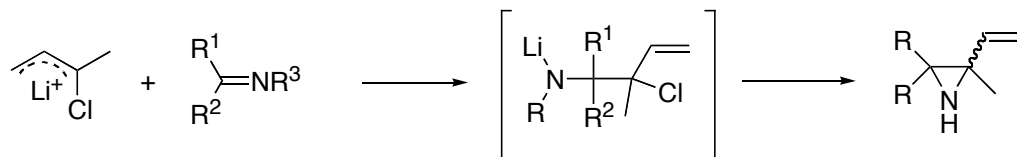
J. Organomet. Chem. **1980**, *202*, 233.

Allylmagnesium Reagents

Higher yields seen that with allyllithium reagents; sometimes α-protons are tolerated in alaphatic aldimines (lower yield)
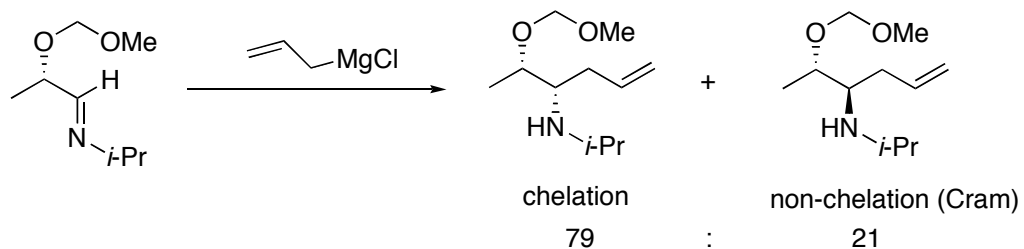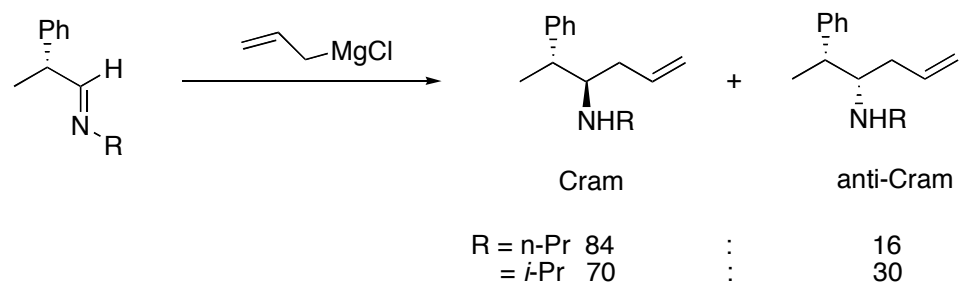
50-78% yield

Very low diastereoselectivity seen with crotylmagnesium bromide:
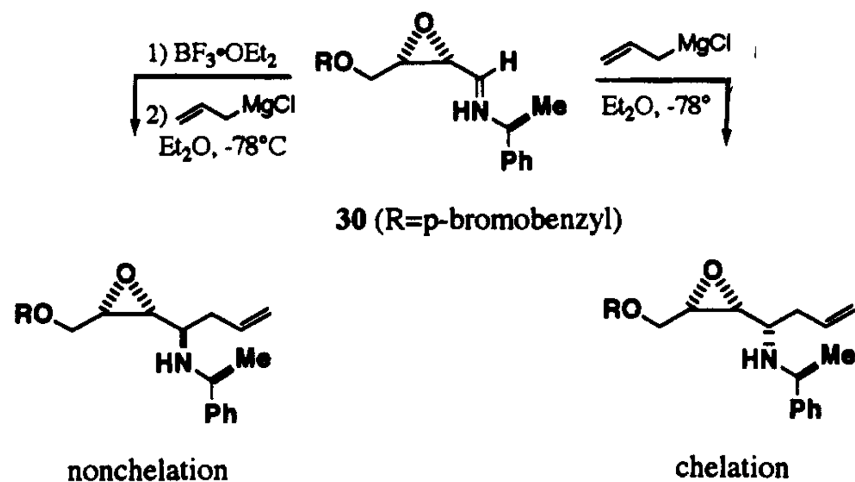
60 : 40

Review: Kleinmann, E. F.; Volkmann, R. A. In *Compreh. Org. Synth.*, Heathcock, C. H., Ed.; Pergamon: Oxford, **1990;** Vol. 2, p 975.

Selectivity of Allylmagnesium

R = n-Pr 84   :   16
  = i-Pr   70   :   30

chelation   non-chelation (Cram)
    79   :   21

J. Am. Chem. Soc. **1986**, *108*, 7778.

Addition of External Lewis Acid Reverses Selectivity

30 (R=p-bromobenzyl)

nonchelation

chelation

Tetrahedron Lett. **1992**, *33*, 3355.

Allylzinc Reagents

Usually prepared from the treatment of an allylhalide with zinc dust or zinc salts under Barbier condiditons - often chosen due to ease of preparation and compatibility with other organic functional groups

Diastereoselectivity of crotylzinc reagents low as with magnesium and lithium

Much more tolerant of alaphatic aldimines - High diastereoselectivity seen when chiral auxiliary is used in allylations:
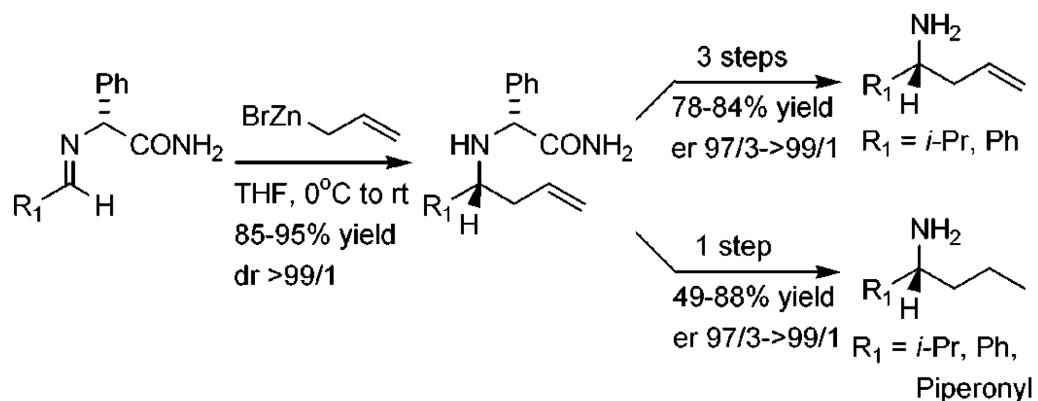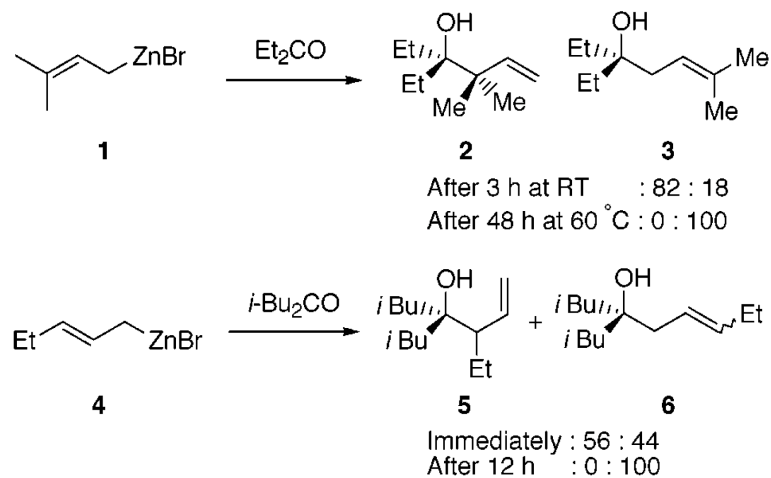

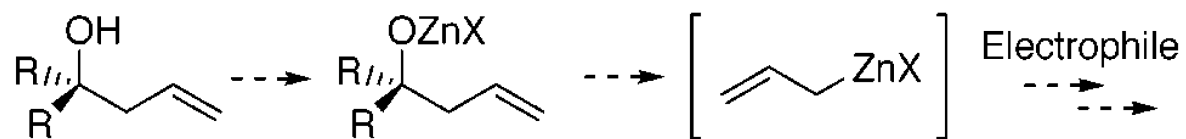*Org. Lett* **2001**, *3*, 3943.

Masked Allylzincs

Synthesis of allylmetals has traditionally been plauged by Wurtz homocoupling products

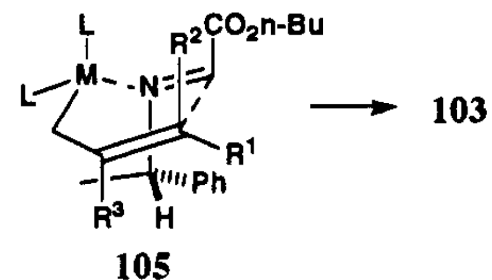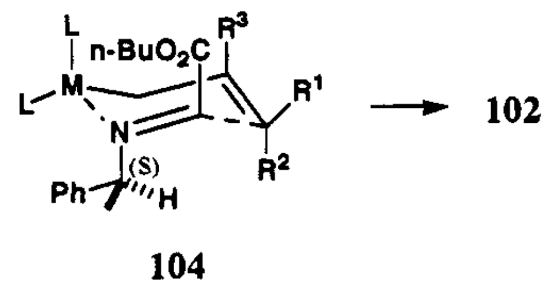Creative Solution:

Zinc allylations are reversible!

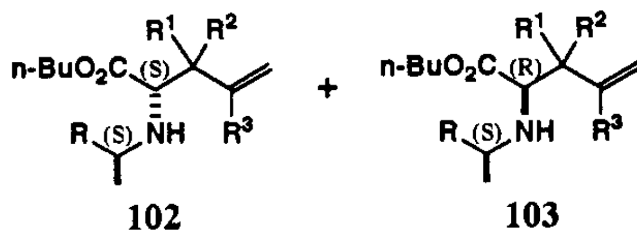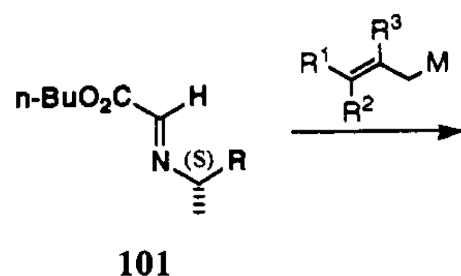After 3 h at RT   : 82 : 18
After 48 h at 60 °C : 0 : 100

Immediately : 56 : 44
After 12 h   : 0 : 100

J. Org. Chem. **1999**, *64*, 186.

Entry	Imine	Product	Yield (%)[a]
1	28	29	90
2	30	31	63
3	32	33	63
4	34	35	67

J. Org. Chem. **1999**, *64*, 186.
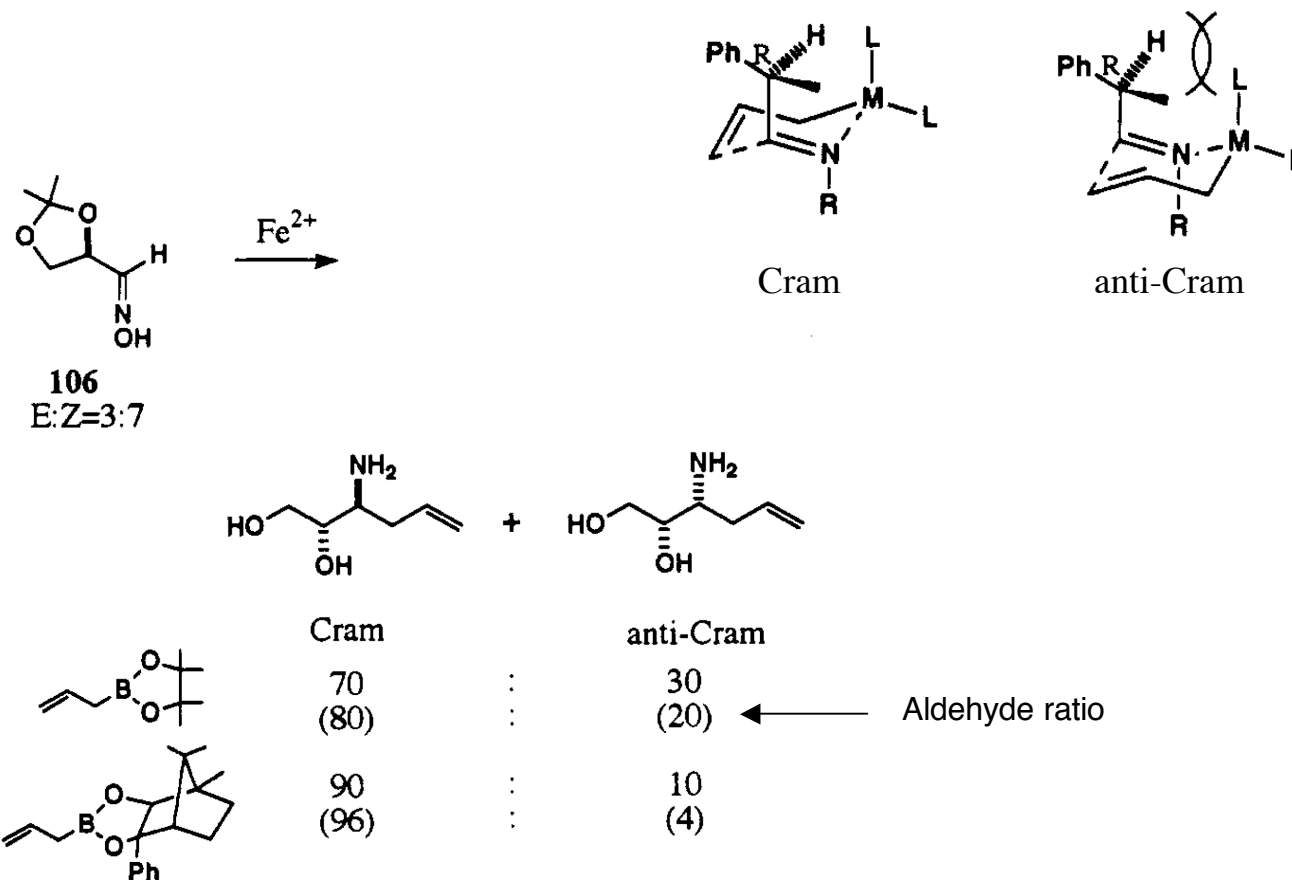
Allylic Boron Reagents

Allylzinc reagents give low yield and almost no diastereoselectivity in the above reaction

The use of allyl 9-BBN increased the selectivity to 98:2! (102 major)

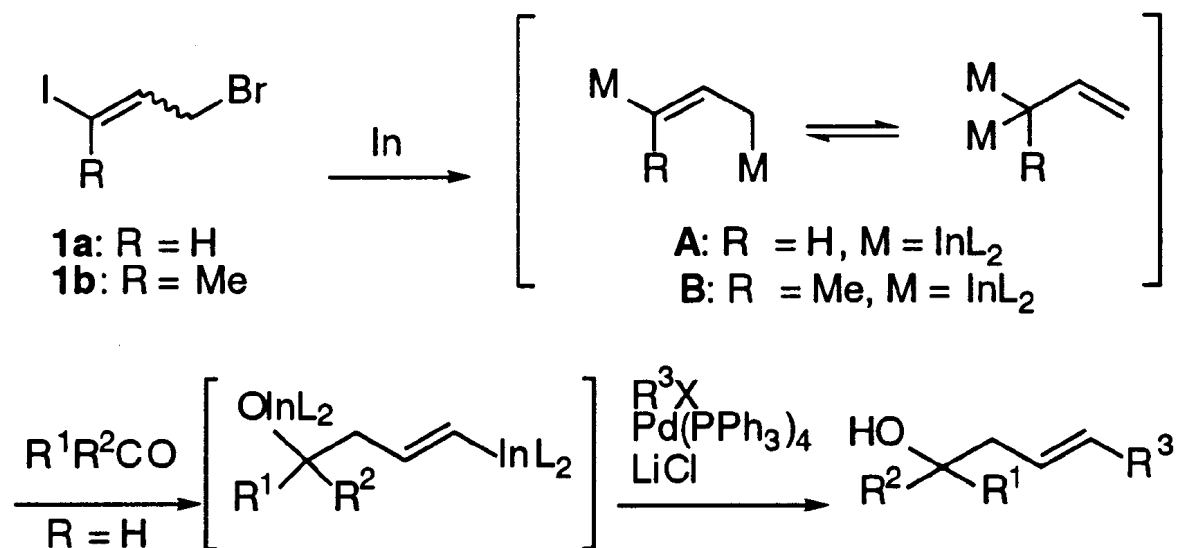Reversal of selectivity seen with methylallyl 9-BBN used (103 major)

Reagent of Choice for Cram Selectivity

106
E:Z=3:7

Fe^{2+}

Cram   anti-Cram

	Cram		anti-Cram
(pinacol boronate)	70 (80)	:	30 (20)	← Aldehyde ratio
(Ph boronate)	90 (96)	:	10 (4)

Dimetallic Allylating Reagents: Indium

1a: R = H
1b: R = Me

A: R = H, M = InL_2
B: R = Me, M = InL_2

J. Org. Chem. **2003**, *68*, 1309.

$$\textbf{1} \quad \xrightarrow[\text{2) R}^4\text{X, Pd(PPh}_3)_4\text{, LiCl}]{\text{1) In, R}^2\text{CH=NR}^3} \quad \underset{\underset{\textbf{6a-h}}{\text{NHR}^3}}{R^2 \overset{R^1}{\diagup}\!\!\! R^4}$$
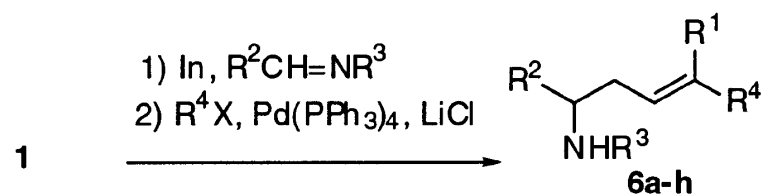
| Entry	1	R^2	R^3	R^4X		Yield (%)
1^b	**1a**	Ph	Ph	PhI	**6a**	57
2	"	Ph	SO_2Ph	PhI	**6b**	77
3	"	Ph	SO_2Ph	∕∕∕Cl	**6c**	43
4	"	Ph	SO_2Ph	Ph∕∕∕Br (E:Z=86:14)	**6d**	31
5	"	n-Bu	SO_2(Tol-p)	PhI	**6e**	47
6	"	i-Pr	SO_2(Tol-p)	PhI	**6f**	51
7^c	**1b**	Ph	SO_2Ph	PhI	**6g**	22
8^d	"	Ph	SO_2Ph	PhI	"	52
9^d	"	Ph	SO_2Ph	Ph∕∕∕Br (E:Z=86:14)	**6h**	44

Allylic Zirconium

Methods of formation were limited to reaction of Cp_2ZrCl_2 with ethers or hydrozirconation of allenes
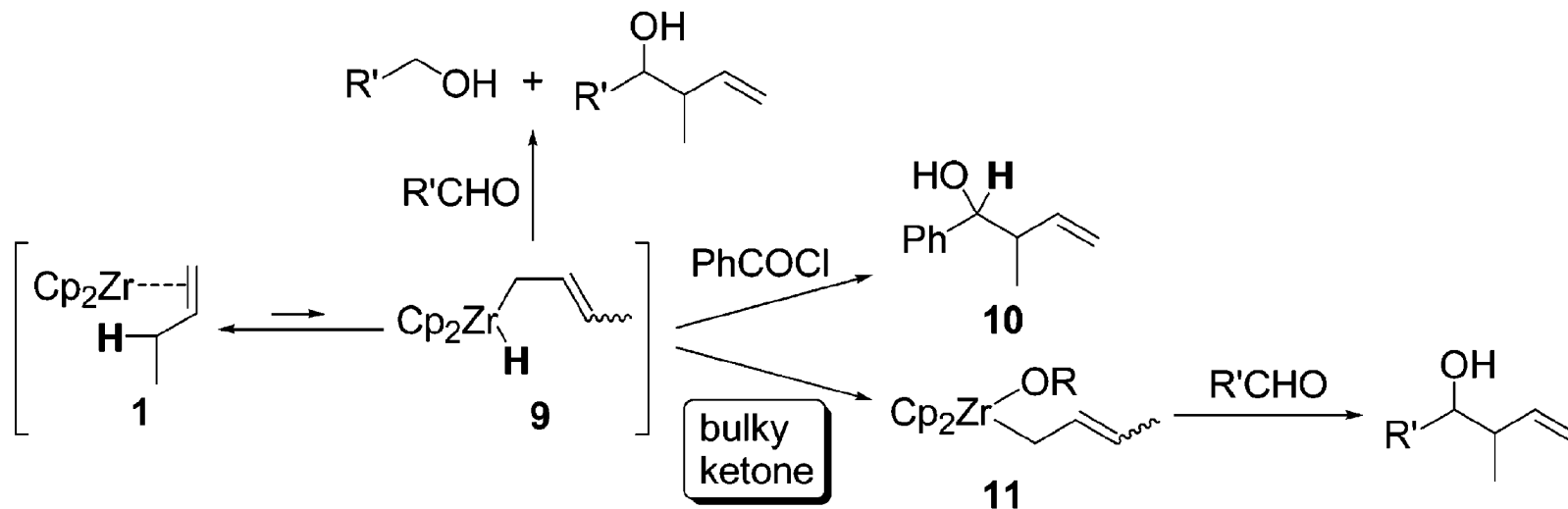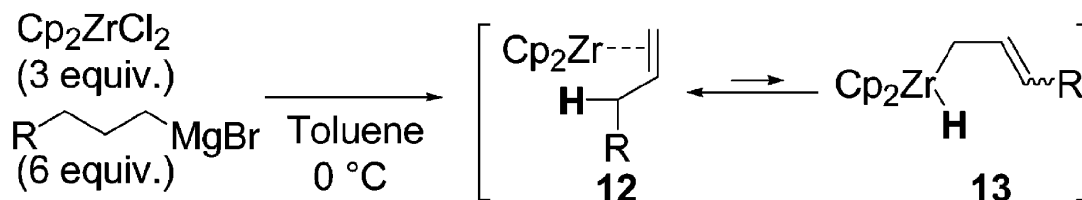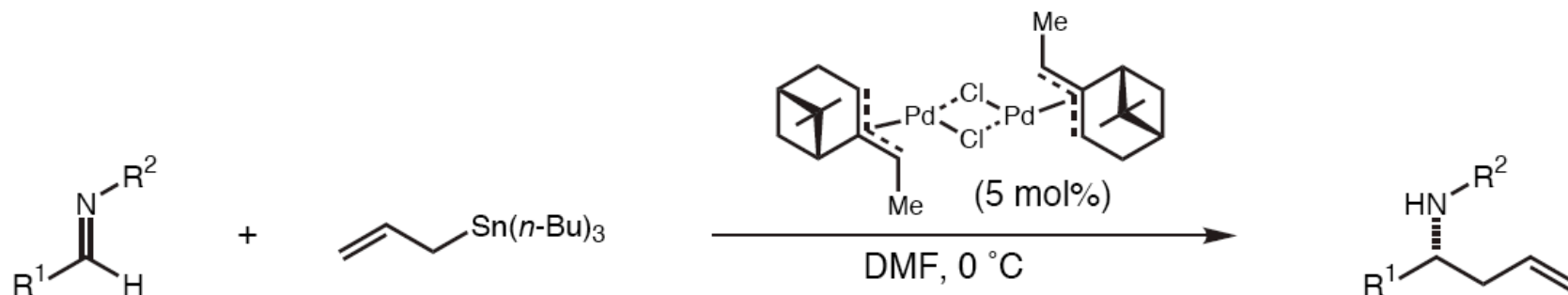

J. Org. Chem. **2004**, *69*, 3302.

Addition to Imines
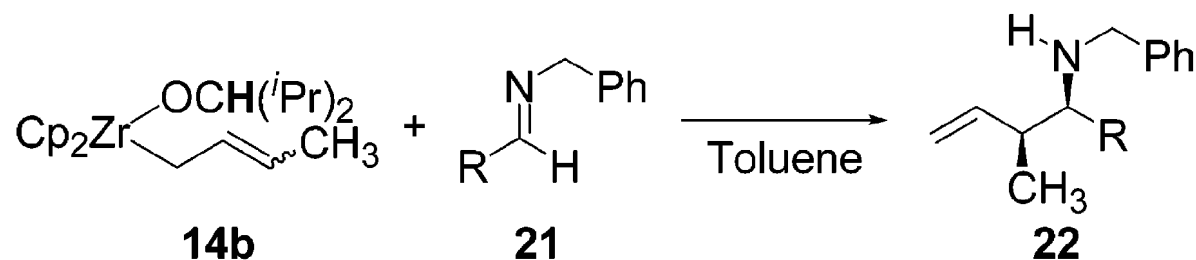
entry	method[a]	R	product	yield (%)	*anti*/*syn*
1	**A**	Ph	**22a**	67	11/89
2	**A**	$i\text{-}C_3H_7$	**22b**	73	17/83
3	**A**	$c\text{-}C_6H_{11}$	**22c**	69	18/82
4	**B**	Ph	**22a**	87	25/75
5	**B**	$i\text{-}C_3H_7$	**22b**	87	22/78
6	**B**	$c\text{-}C_6H_{11}$	**22c**	74	22/78

J. Org. Chem. **2004**, *69,* 3302

Catalytic Asymmetric Allylation of Imines: Palladium

R[1]	R[2]	yield (%)	ee (%)
Ph	Bn	62	81
	PMB	50	80
	Ph	74	0
	n-Pr	30	70
4-(MeO)C$_6$H$_4$	Bn	48	78
(E)-PhCH=CH	Bn	68	61

Running the reaction with *allylsilane* also possible under the following conditions: 5 mol% cat., allyltrimethylsilane (2 equiv.), TBAF (0.5 equiv.), n-hexane/THF, 0 ˚C (similar yields and ee)
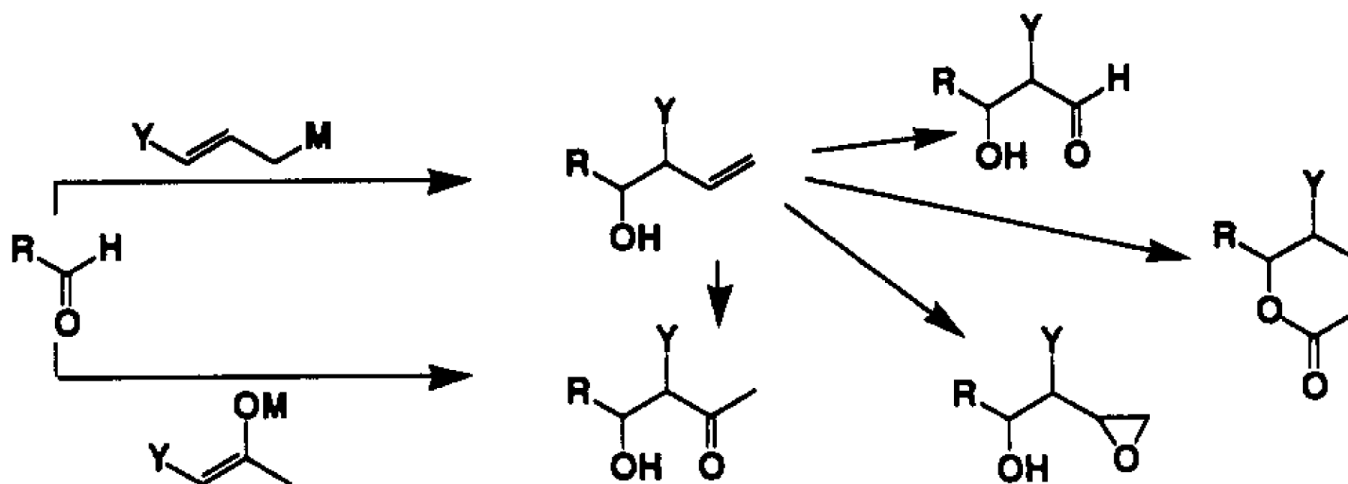
J. Am. Chem. Soc. **1998**, *120*, 4242.

Proposed Catalytic Cycle
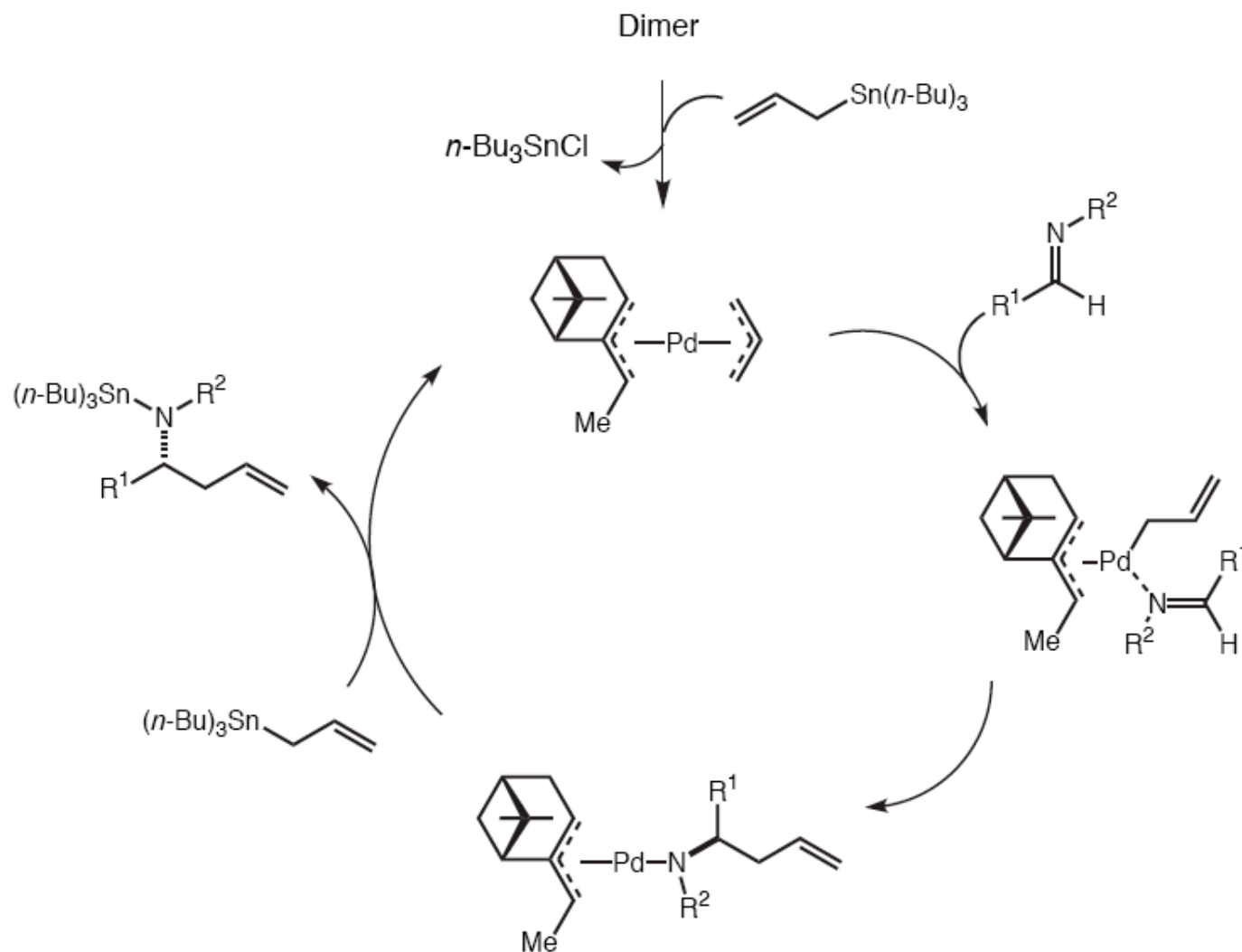

J. Am. Chem. Soc. **1998**, *120*, 4242.

Why so much interest?

Allylation reactions can be used to form similar intermediatesas the aldol reaction, one of the most used synthetic reactions.


The products of allylation reactions can be much more versatile - this has been exploited for decades with aldehydes and ketones but due to lack of good methodology, the application of this to imine chemistry has fallen behind but is constantly growing due to the large amount of nitrogen containing natural products and investigation into stereoselective imine chemistry.

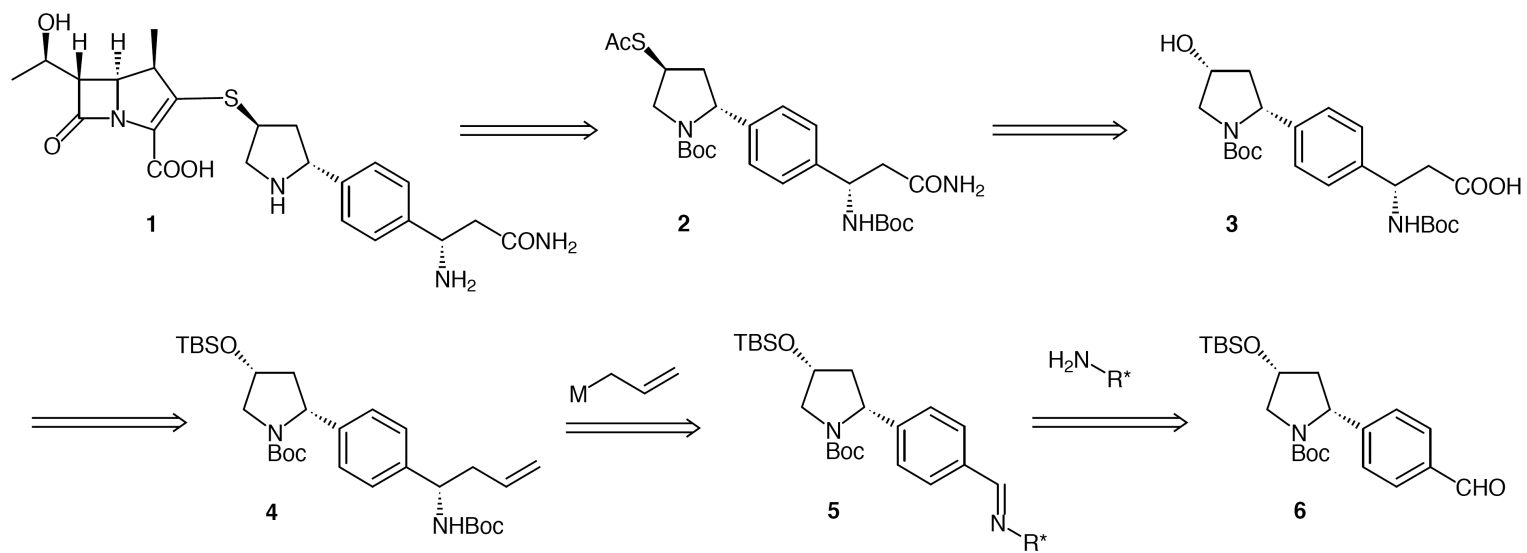# Application to Natural Product Synthesis

(+)-Negamycin (1)

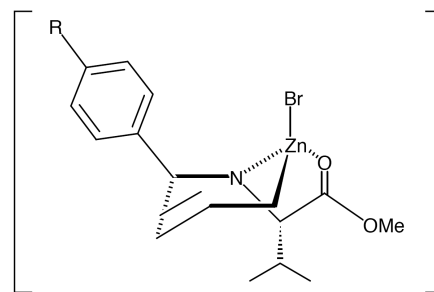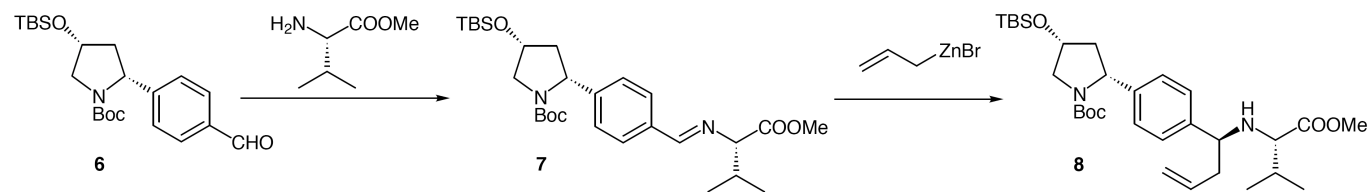

7

CeCl$_3$, THF, -40 ^{o}C

BrZnCH$_2$CH=CH$_2$

B
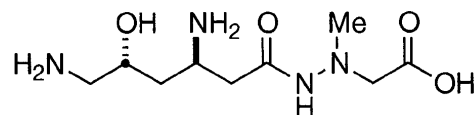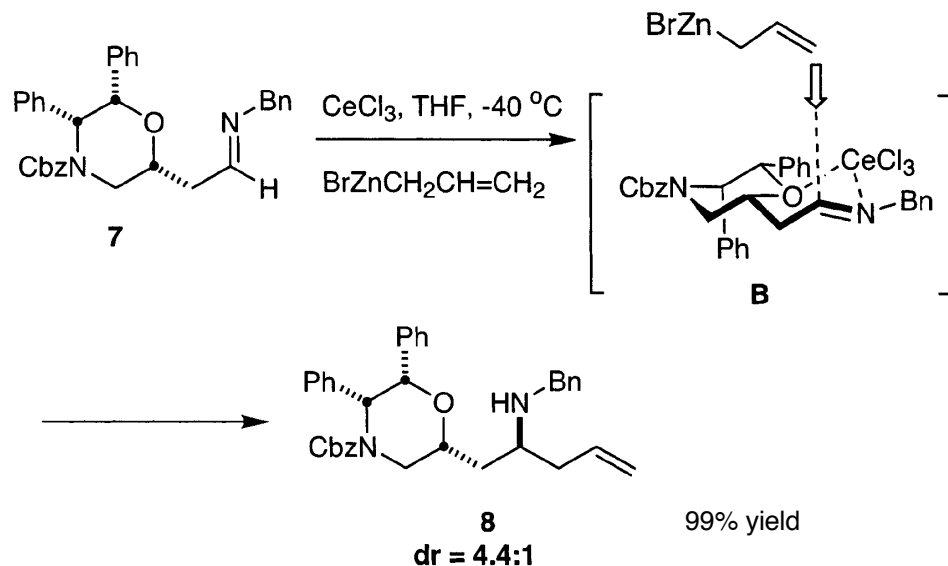
Allylation first attempted with allylsilane and allylstannes with various lewis acids, but low yields and diastereoselectivities were obtained.

8
dr = 4.4:1

99% yield

J. Org. Chem. **2002**, 67, 6361

Practically and Scalability

R*: chiral auxiliary group

77% yield
Multi-gram scale

Narrow Range of Conditions
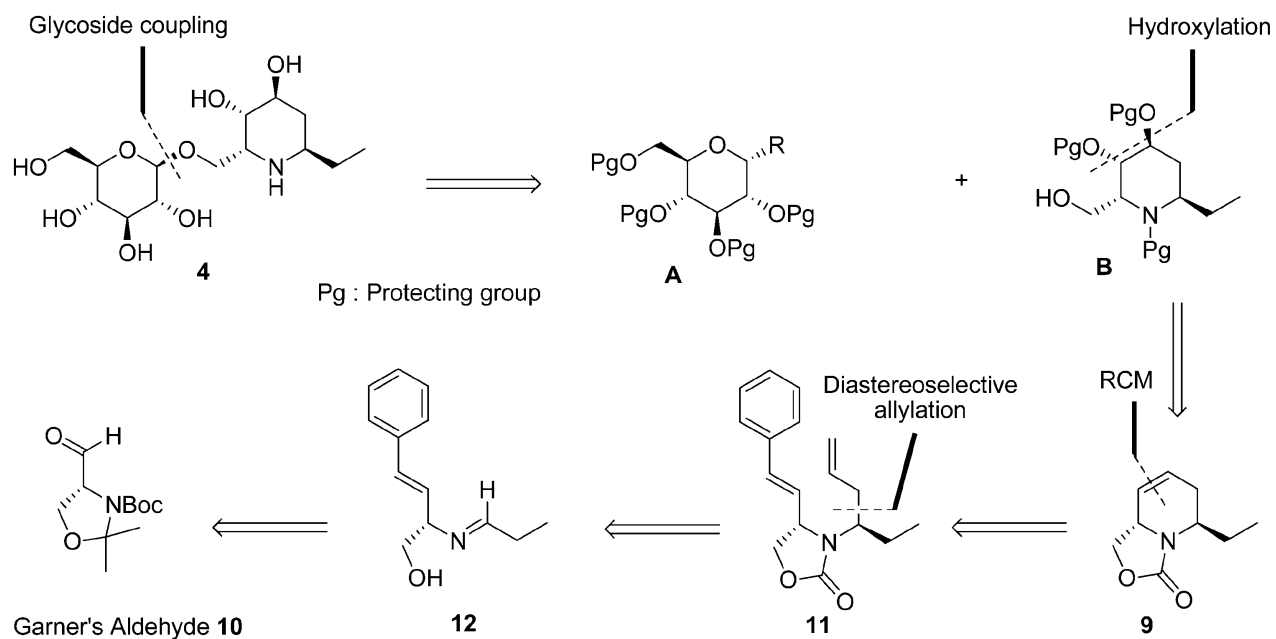
$$7 \xrightarrow[\substack{\text{Solvent Additive} \\ \text{Temp.}}]{\diagup\!\!\!\diagup\!\!\!\diagdown\text{ZnBr}} 8$$
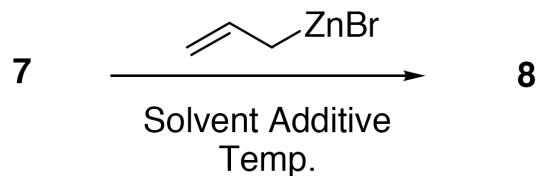
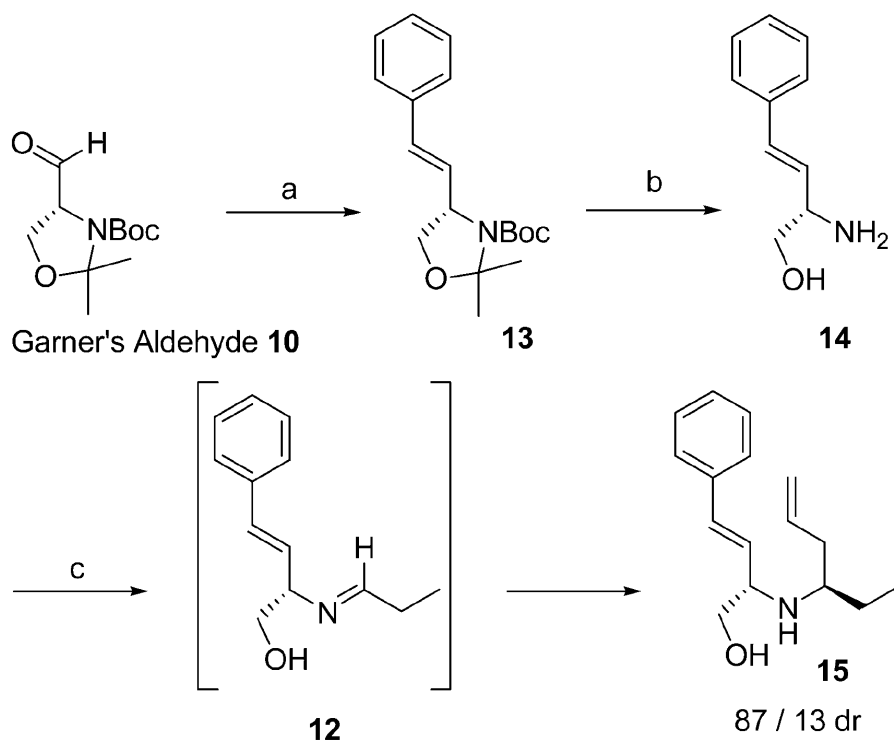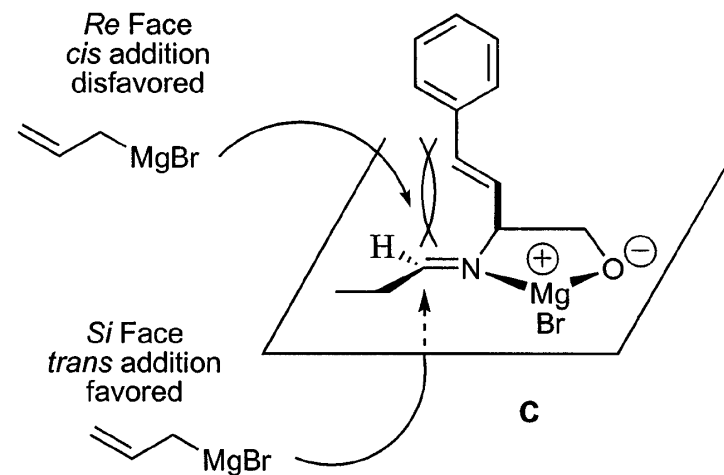| Entry	Solvent	Additive	Temp.	Yield[c]
1	THF	none	$0\,°C \rightarrow$ r.t.	n.r.[d]
2	THF	$CeCl_3 \cdot 7\,H_2O$ (x 0.1)	$0\,°C \rightarrow$ r.t.	n.r.[d]
3	THF	none	60 °C	~ 40%
4	THF	$CeCl_3$[b] (x 0.8)	60 °C	20%
5	THF	$CeCl_3 \cdot 7\,H_2O$ (x 0.8)	60 °C	39%
6	Et_2O	none	reflux	n.r.[d]
7	CH_2Cl_2	none	reflux	trace
8	Benzene	none	60 °C	n.r.[d]
9	Dioxane	none	60 °C	n.r.[d]
10	MeCN	none	60 °C	n.r.[d]
11	DMF	none	60 °C	69%
12	DMSO	none	60 °C	n.r.[d]

1-*O*-*β*-D-Glucopyranosyl-5-deoxyadenophorine

Retrosynthetic Analysis:

*J. Org. Chem.* **2004**, *69*, 1497.

Proposed Allylation TS:

Re Face
cis addition
disfavored

Si Face
trans addition
favored

c

Garner's Aldehyde **10**   a→   **13**   b→   **14**

c→   **12**   →   **15**

87 / 13 dr

Allylation preformed with allylmagnesium bromide in 87% yield

Synthesis of Cyclohexenylamines

Barbier allylation conditions have generally been restricted to simple allylating reagents, mainly allyl bromide. Also, most methodology has been accomplished with aromatic aldimines
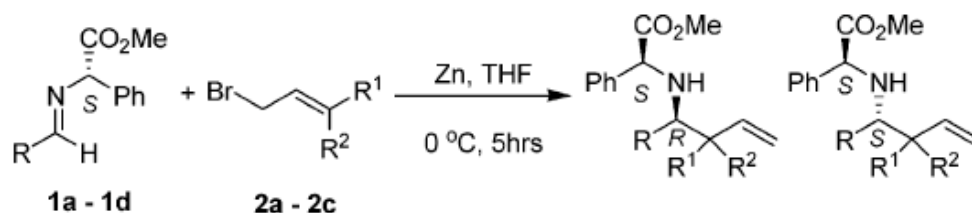
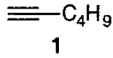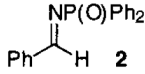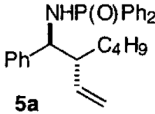| entry	imine	R	homoallylic amine	R^1	R^2	yield (%)	dr $(S,R:S,S)^c$	syn:anti^d
1	1a	c-C$_6$H$_5$	3a	Me	H	94	80:20	75:25^e
2	1a	c-C$_6$H$_5$	3b	Me	Me	92	89:11	
3	1a	c-C$_6$H$_5$	3c	Ph	H	65	88:12	82:18^f
4	1b	Ph(CH$_2$)$_2$	4a	Me	H	39	78:22	79:21^e
5	1b	Ph(CH$_2$)$_2$	4b	Me	Me	72	89:11	
6	1b	Ph(CH$_2$)$_2$	4c	Ph	H	58	88:12	90:10^f
7	1c	CH$_2$=CH(CH$_2$)$_2$	5a	Me	H	59	75:25	86:14^e
8	1c	CH$_2$=CH(CH$_2$)$_2$	5b	Me	Me	72	89:11	
9	1c	CH$_2$=CH(CH$_2$)$_2$	5c	Ph	H	62	90:10	95:5^e
10	1d	CH$_3$CH$_2$CH=CH(CH$_2$)$_2$	6a	Me	H	53	80:20	81:19^e
11	1d	CH$_3$CH$_2$CH=CH(CH$_2$)$_2$	6b	Me	Me	92	90:10	
12	1d	CH$_3$CH$_2$CH=CH(CH$_2$)$_2$	6c	Ph	H	67	90:10	88:12^e

J. Org. Chem. ASAP

Ring-Closing Methathesis
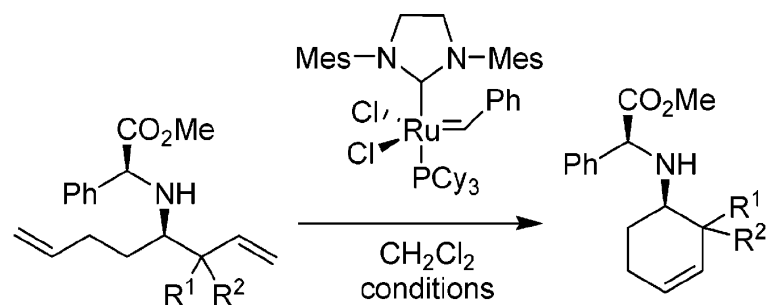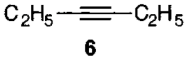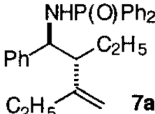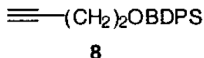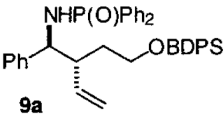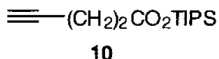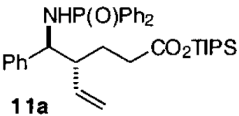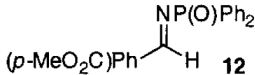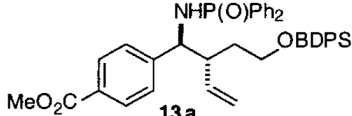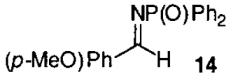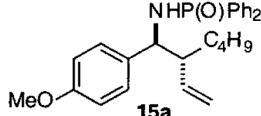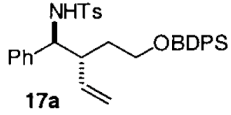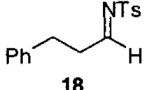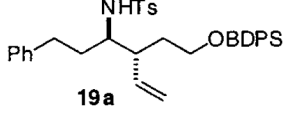
entry	homoallylic amine	R^1	R^2	T (°C)	time (h)	product	yield (%)
1	**5a**	Me	H	40^b	6	**7a**	84
2	**5b**	Me	Me	25	12	**7b**	92
3	**5c**	Ph	H	40^b	6	**7c**	86

J. Org. Chem. ASAP

Previous Work in the Wipf Group
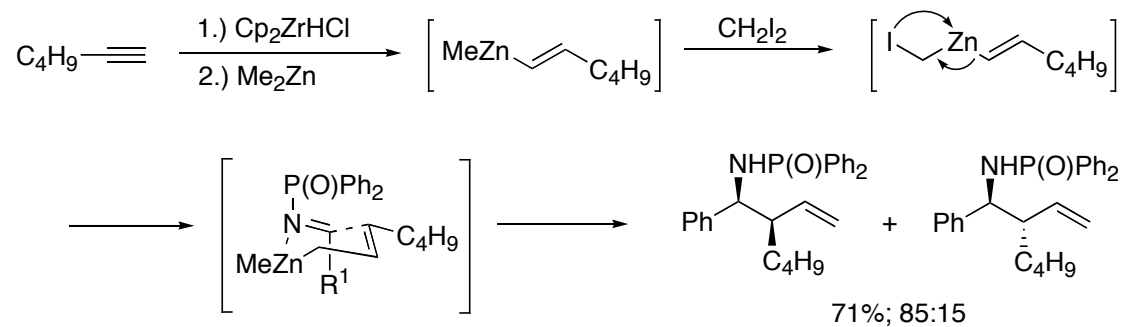
Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.

71%; 85:15

entry	alkyne	aldimine	homoallylic amide[a]	yield[b]	diastereoselectivity[c]
1	≡—C$_4$H$_9$ **1**	Ph—CH=NP(O)Ph$_2$ **2**	**5a** Ph, C$_4$H$_9$, NHP(O)Ph$_2$	71%	85:15
2	C$_2$H$_5$—≡—C$_2$H$_5$ **6**	**2**	**7a** Ph, C$_2$H$_5$, C$_2$H$_5$, NHP(O)Ph$_2$	49%	75:25
3	≡—(CH$_2$)$_2$OBDPS **8**	**2**	**9a** Ph, OBDPS, NHP(O)Ph$_2$	72%	85:15
4	≡—(CH$_2$)$_2$CO$_2$TIPS **10**	**2**	**11a** Ph, CO$_2$TIPS, NHP(O)Ph$_2$	48%	62:38
5	**8**	(p-MeO$_2$C)Ph—CH=NP(O)Ph$_2$ **12**	**13a** MeO$_2$C, OBDPS, NHP(O)Ph$_2$	69%	85:15
6	**1**	(p-MeO)Ph—CH=NP(O)Ph$_2$ **14**	**15a** MeO, C$_4$H$_9$, NHP(O)Ph$_2$	79%	83:17
7	**8**	Ph—CH=NTs **16**	**17a** Ph, OBDPS, NHTs	81%	60:40
8	**8**	Ph—CH$_2$CH$_2$—C=NTs(H) **18**	**19a** Ph, OBDPS, NHTs	87%	>95:5