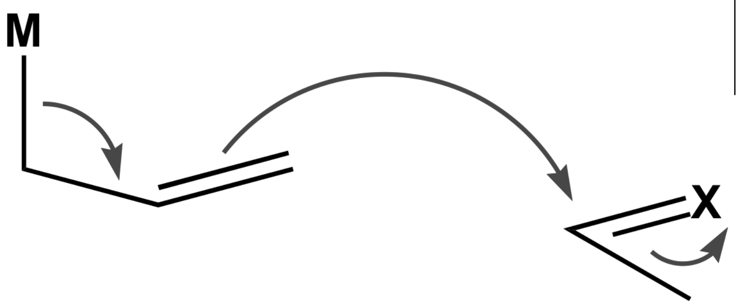
I. Basic Principles

ID. Allylations & Crotylations

What other alternatives to the aldol reaction do you know?

- halolactonization of enones (erythronolide)
- α-deoxigenation of α,β-epoxy ketones (erythronolide)
- hetero-Diels-Alder synthesis of pyranones (epothilone)



Reviews:

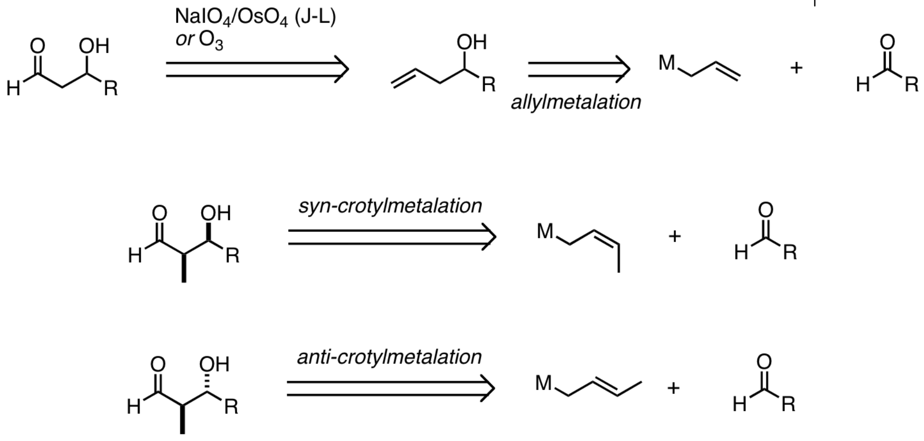
Merino, P.; Tejero, T.; Delso, J. I.; Mannucci, V. "Stereoselective allylation reactions of imines and related compounds." *Curr. Org. Synth.* **2005**, *2*, 479-498.

Kennedy, J. W. J.; Hall, D. G. "Recent advances in the activation of boron and silicon reagents for stereocontrolled allylation reactions." *Angew. Chem., Int. Ed.* **2003**, *42*, 4732-4739.

Denmark, S. E.; Fu, J. P. "Catalytic enantioslelective addition of allylic organometallic reagents to aldehydes and ketones." *Chem. Rev.* **2003**, *103*, 2763-2793.

Roush, W. R. *Comprehensive Organic Synthesis* **1991**, vol. 2, p. 1.

Retrosynthetic Scheme



M = B, Al, Si, Ti, Cr, Zr, Zn, Sn, In, Ba,.....

Early Work

Pioneering papers on the stereocontrolled use of allylic organometallics were reported by

- Buse and Heathcock, *THL* **1978**, 1865.
- Hoffmann and Zeiss, *Angew. Chem. Int. Ed. Engl.* **1982**, *18*, 306.
- Yamamoto et al., *JACS* **1980**, *102*, 306.

Regioselectivity of Allylation

Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H., "Allylbarium reagents: Unprecedented regio- and stereoselective allylation reactions of carbonyl compounds." *J. Am. Chem. Soc.* **1994**, *116*, 6130-6141.

The stereochemical outcome of allyl-metal additions can be classified into three groups:

- I. the syn/anti ratio of the products reflects the Z/E geometry of the crotyl moiety (B, Al, Sn, Si (Δ-reactions)).

- **II. syn-selective irrespective of olefin geometry (Sn, Si, Ti).**

- III. anti-selective irrespective of olefin geometry (Ti, Cr, Zr, In, Zn).

Caveat:

→ transmetalation, and allyl-Ti is type I reagent! (THL **1984**, *25*, 3927):

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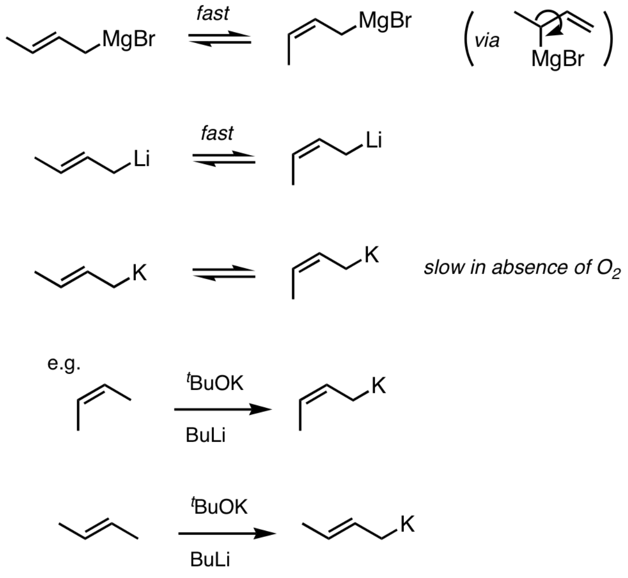
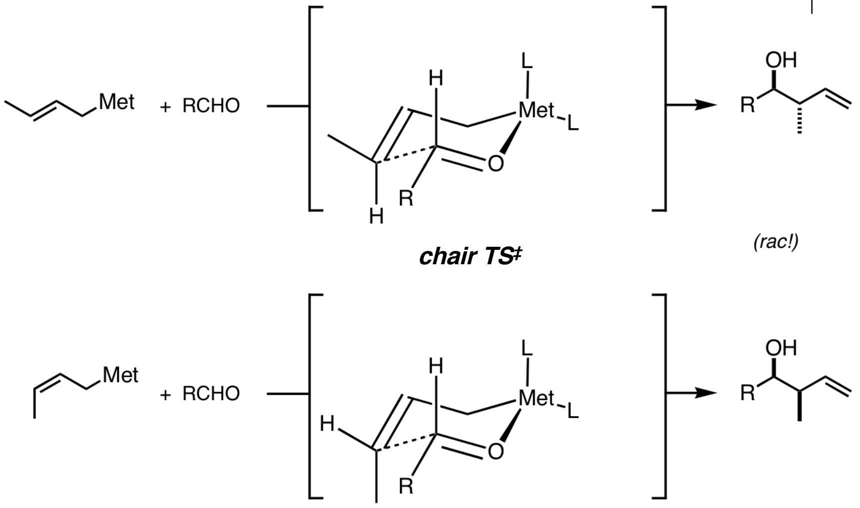
configurational stability: important for synthesis of type I organometallics

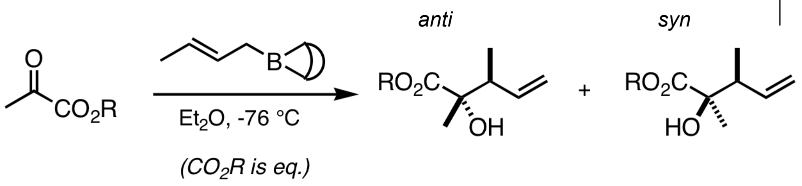


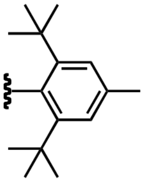
slow in absence of O_2

I. the syn/anti ratio of the products reflects the Z/E geometry of the crotyl moiety (B, Al, Sn, Si (Δ-reactions)).

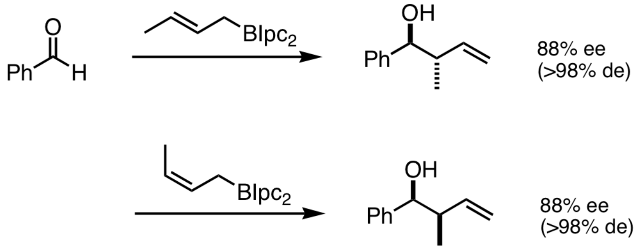


The dialkylcrotylboranes are the most reactive but also the least configurationally stable of the allylborane reagents (borderline type III).



R = Me	73	:	27
R = Ph	80	:	20
	100	:	0

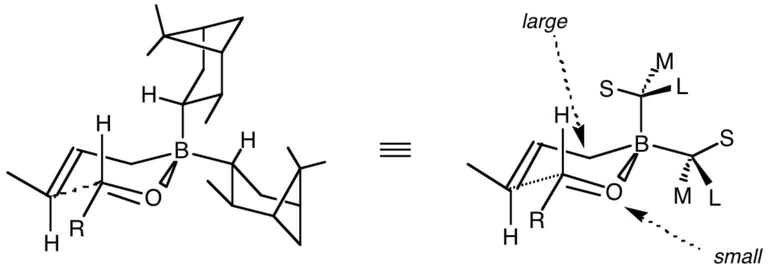
Brown's Allylboranes:



88% ee
(>98% de)

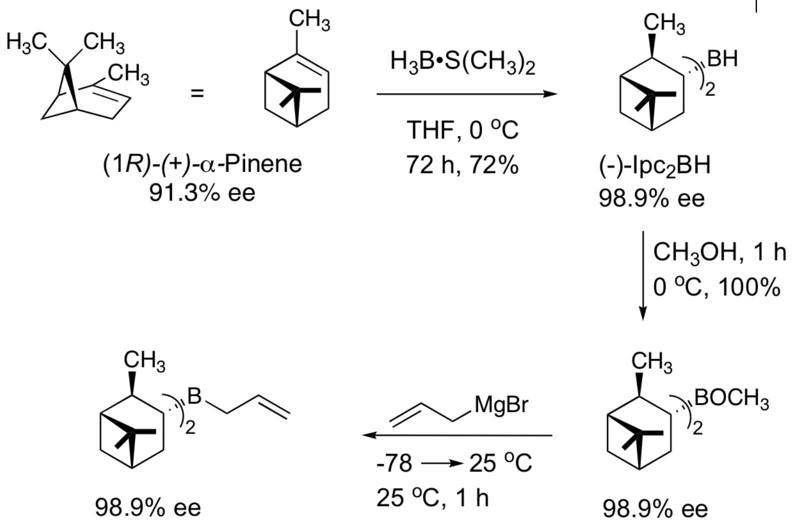
88% ee
(>98% de)

JOC **1986**, *51*, 432
JACS **1986**, *108*, 5919



minimizes steric interactions

Prolonged incubation at 0 °C affords enantiomerically enriched Ipc_2BH, due to the equilibration of $Ipc_4B_2H_2$ with α-pinene and $Ipc_3B_2H_3$; the symmetrical dimer crystallizes preferentially.



(1*R*)-(+)-α-Pinene
91.3% ee

$H_3B•S(CH_3)_2$

THF, 0 °C
72 h, 72%

(-)-Ipc_2BH
98.9% ee

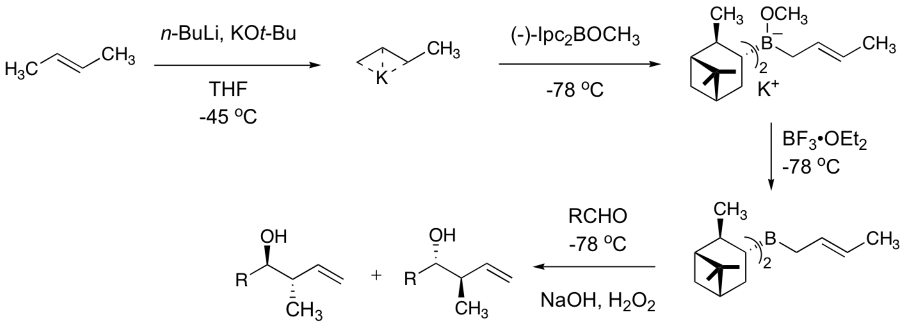
CH_3OH, 1 h
0 °C, 100%

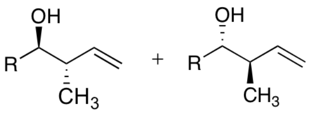
-78 ⟶ 25 °C
25 °C, 1 h

98.9% ee

98.9% ee

The crotylboranes are used immediately after methoxide decomplexation from the ate complex by boron trifluoride at -78 °C to avoid crotyl isomerization.

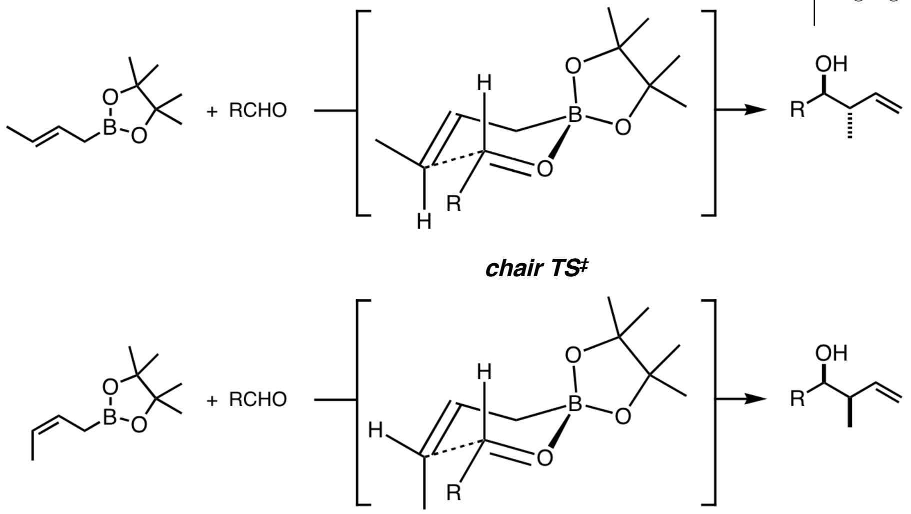




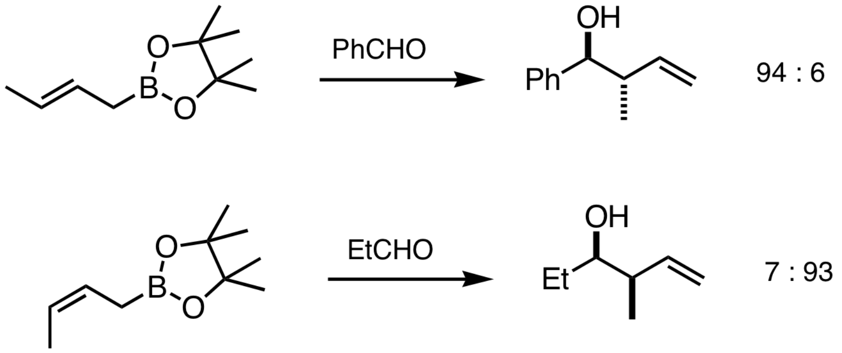
A **B**

α-pinene	aldehyde	yield (%)	**A:B**	ee (%)
+	CH_3CHO	78	95:5	90
-	CH_3CHO	76	4:96	92
+	C_2H_5CHO	70	95:5	90
-	C_2H_5CHO	69	4:96	92
+	CH_2=CHCHO	65	95:5	90
+	C_6H_5CHO	79	94:6	88

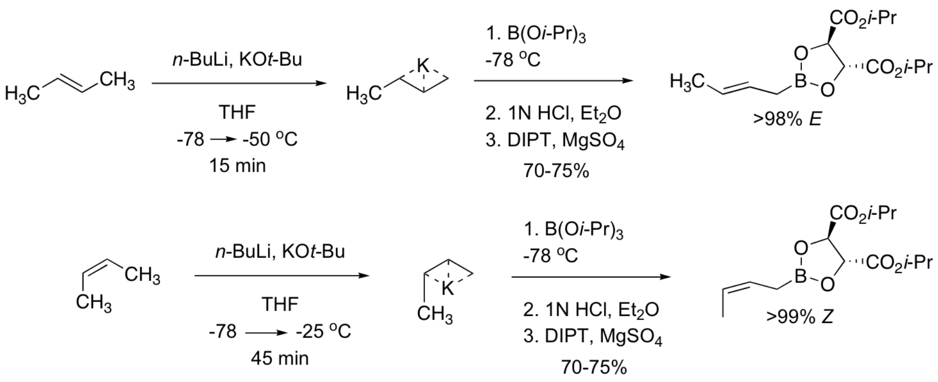
Hoffmann, 1979: Boronates are more configurationally stable

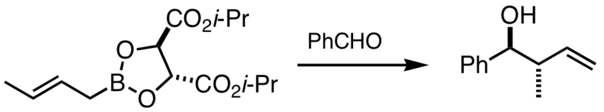


chair TS‡

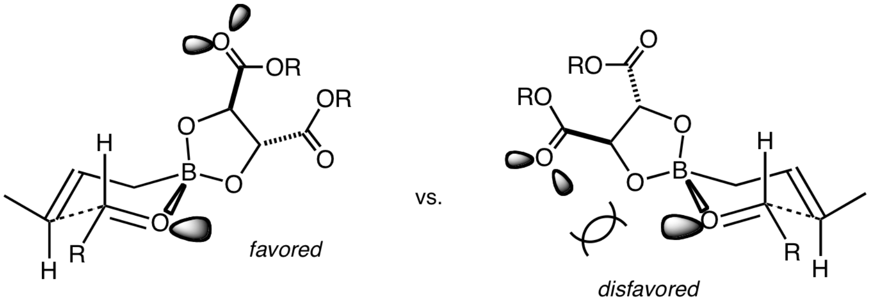


Roush: Tartrate-derived allyl boronates:





67% ee



sterics and lone-pair repulsion

JOC **1992**, *57*, 2047

Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 192.

Silacyclobutanes - Effect of strain-release on reactivity

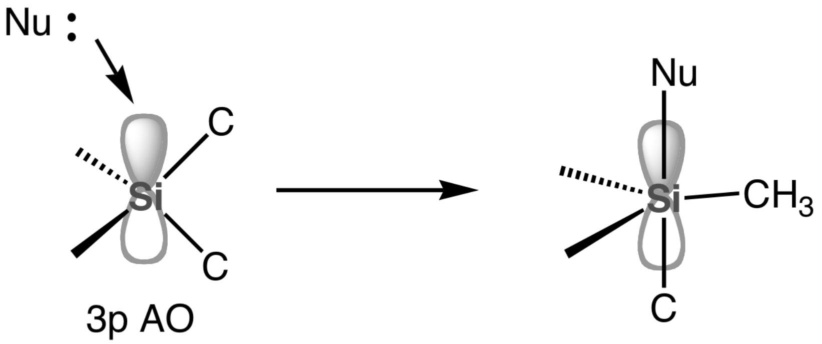
Zhang, X.; Houk, K. N.; Leighton, J. L. "Origins of stereoselectivity in strain-release allylations." *Angew. Chem., Int. Ed.* **2005**, *44*, 938-941.

Myers, Denmark, Utimoto:

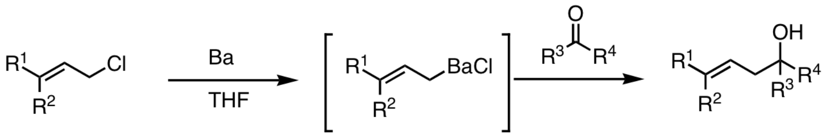
Silacyclobutanes

Denmark and co-workers proposed that the silicon atom constrained in a four-membered ring (a silacyclobutane) should behave like a coordinatively unsaturated group III element (*J. Am. Chem. Soc.* **1994**, *116*, 7026). Oshima et al. showed that 1-phenyl-3-buten-1-ol was obtained in 85% yield by heating a mixture of a silacyclobutane and benzaldehyde for 12 h at 130 °C (*J. Org. Chem.* **1994**, *59*, 7152):

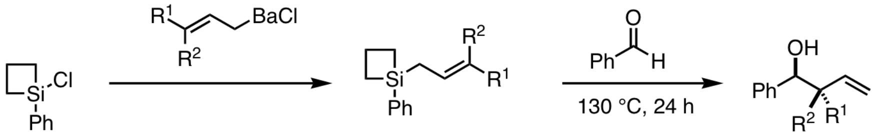
Due to the compression of the C-Si-C angle, silacyclobutanes are much stronger Lewis acids than methyl-substituted silanes. The reaction of allylsilanes takes place via pentacoordinate trigonal bipyramidal transition states. The strong ability of tetravalent silicon to expand its valency and the strong ability of silicon constrained in a four-membered ring to attract electrons are the most important factors that make silacyclobutanes very reactive (Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 5366-72).



Preparation of silacyclobutane:



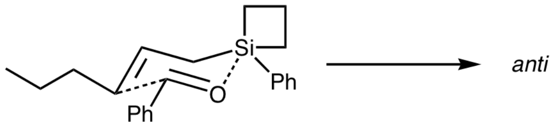
J. Am. Chem. Soc. **1991**, *113*, 8955



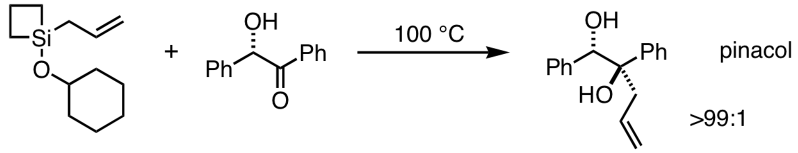
R^1 = H, R^2 = *n*-Pr *anti:syn* = 5:95

R^1 = *n*-Pr, R^2 = H *anti:syn* = 95:5

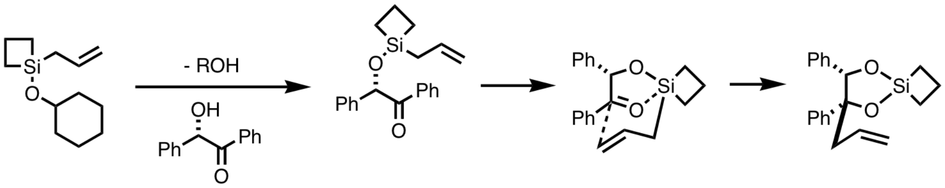
Transition state:



Also:

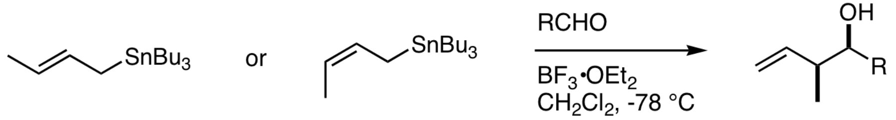


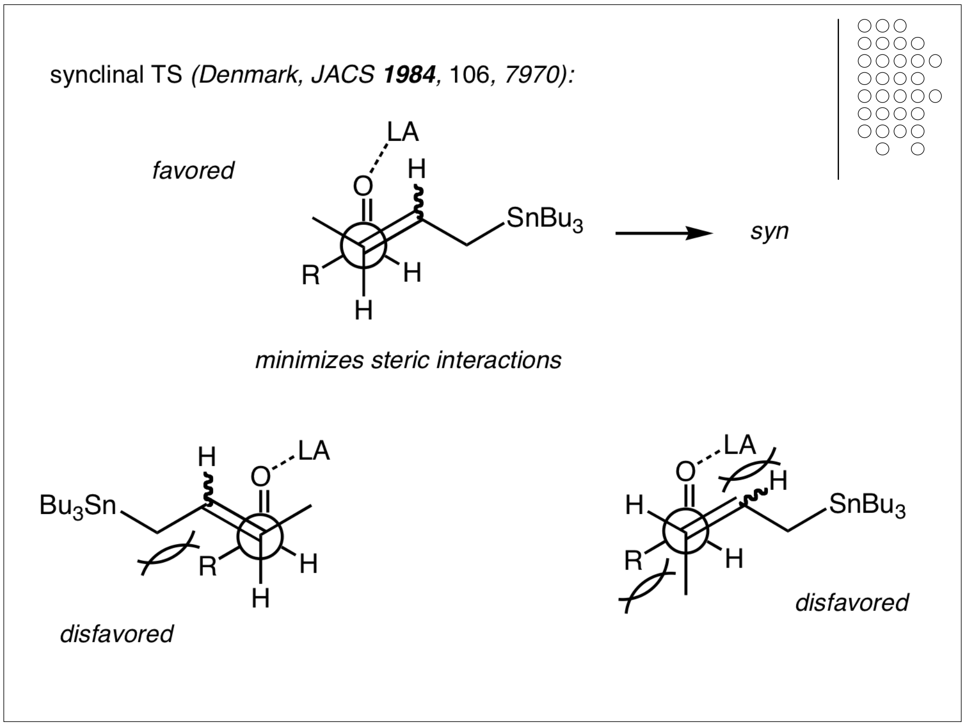
Transition state:



II. syn-selective irrespective of olefin geometry (Sn, Si, Ti).

Y. Yamamoto:





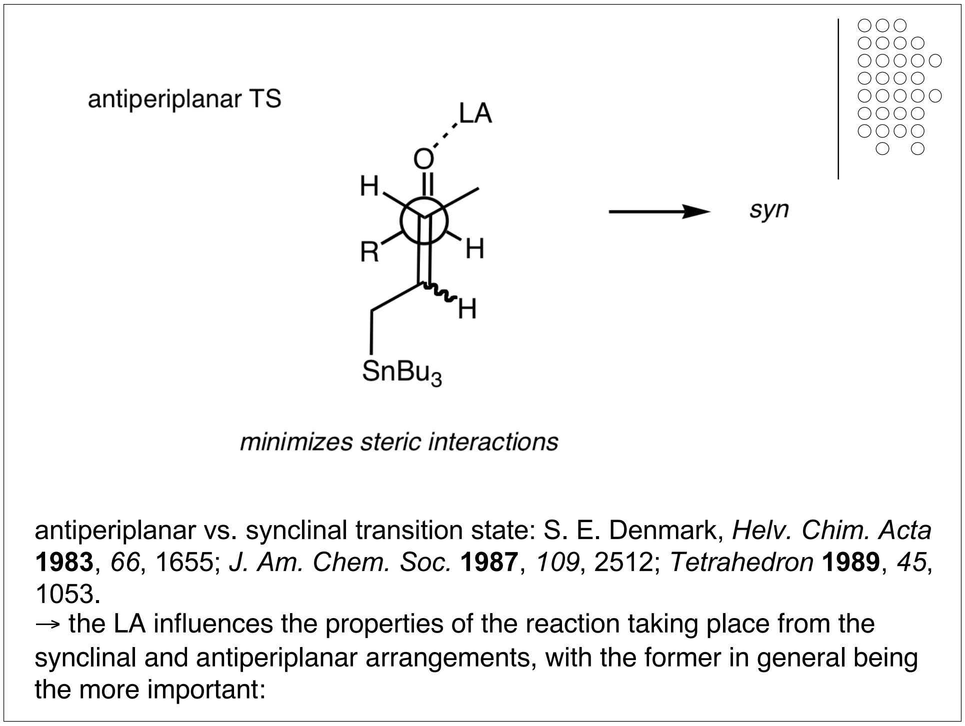
synclinal TS *(Denmark, JACS **1984**,* 106*, 7970):*

favored → *syn*

minimizes steric interactions

disfavored

disfavored



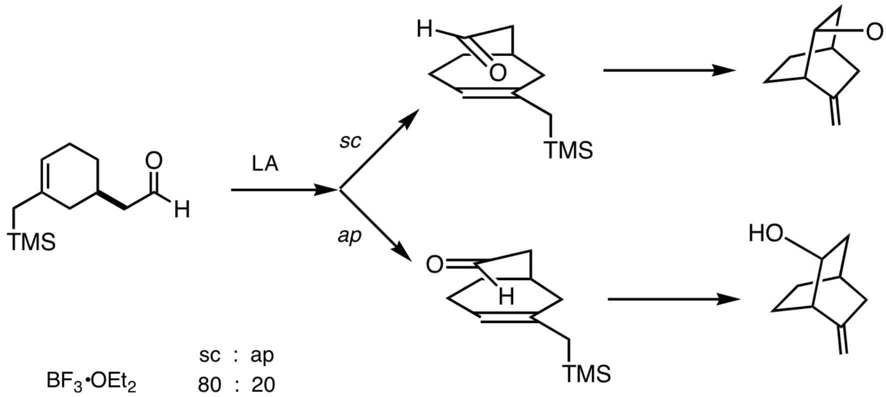
antiperiplanar TS

→ *syn*

minimizes steric interactions

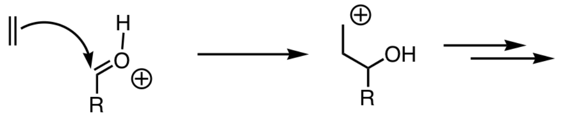
antiperiplanar vs. synclinal transition state: S. E. Denmark, *Helv. Chim. Acta* **1983**, *66*, 1655; *J. Am. Chem. Soc.* **1987**, *109*, 2512; *Tetrahedron* **1989**, *45*, 1053.

→ the LA influences the properties of the reaction taking place from the synclinal and antiperiplanar arrangements, with the former in general being the more important:



	sc : ap
$BF_3 \cdot OEt_2$	80 : 20
$FeCl_3$	70 : 30
Et_2AlCl	66 : 34
$SnCl_4$	49 : 51

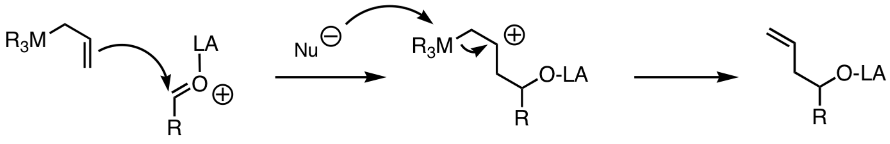
Related: Prins reaction



many products

mechanistic continuum between aldol and FC reactions

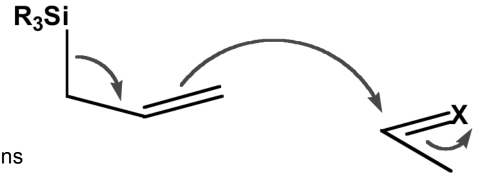
e.g.



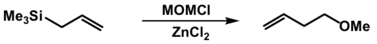
M = Si, Sn

LA = H^+ is inappropriate. Why?

- ***Reactions of Allyl- and Crotylsilanes***
- Tetraorganosilanes
- Electrophiles
- Regiochemistry
- Selected synthetic applications

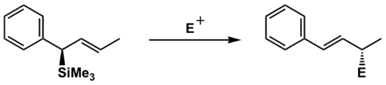


1970 **Chain Extension of Organosilanes**



(1970)

1980 **Golden Age of Allylsilanes / Propargylsilanes / Vinylsilanes**



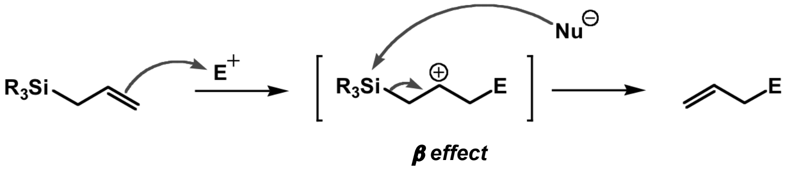
(1982)

1990 **Asymmetric Applications**

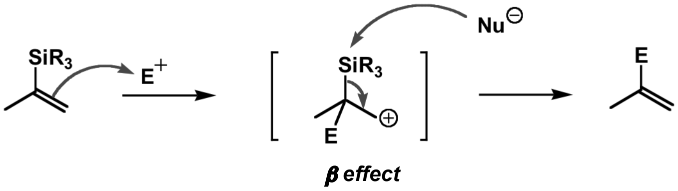
2000 **Activation/Generalization of Scope**

Mechanisms

Allylsilanes

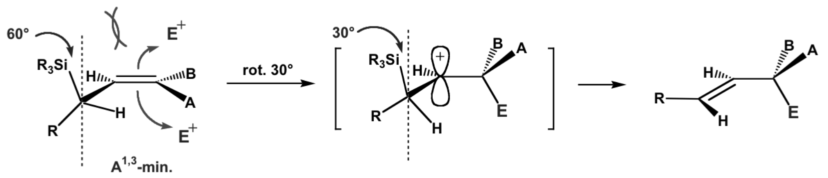


Vinylsilanes



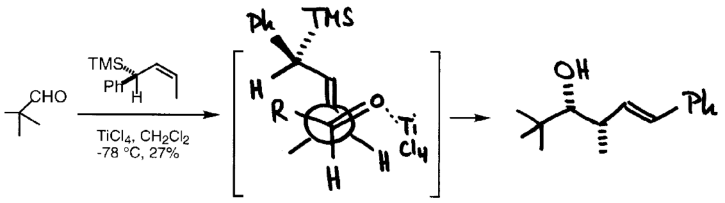
Stereochemistry

anti-S_E' : Ground state control; $A^{1,3}$ strain is minimized



Attack trajectory of electrophile is determined by
- steric effects (vs Si)
- electronic effects (antiperiplanar to C-Si bond)

chiral allylsilanes react antarafacially (JACS **1982***, 104*, 4963):



He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. "Enantioselective total synthesis of aspidophytine." *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

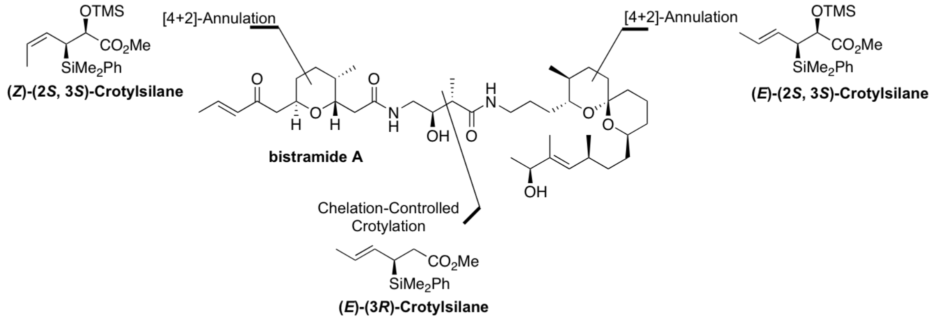
Key Cyclization Mechanism:

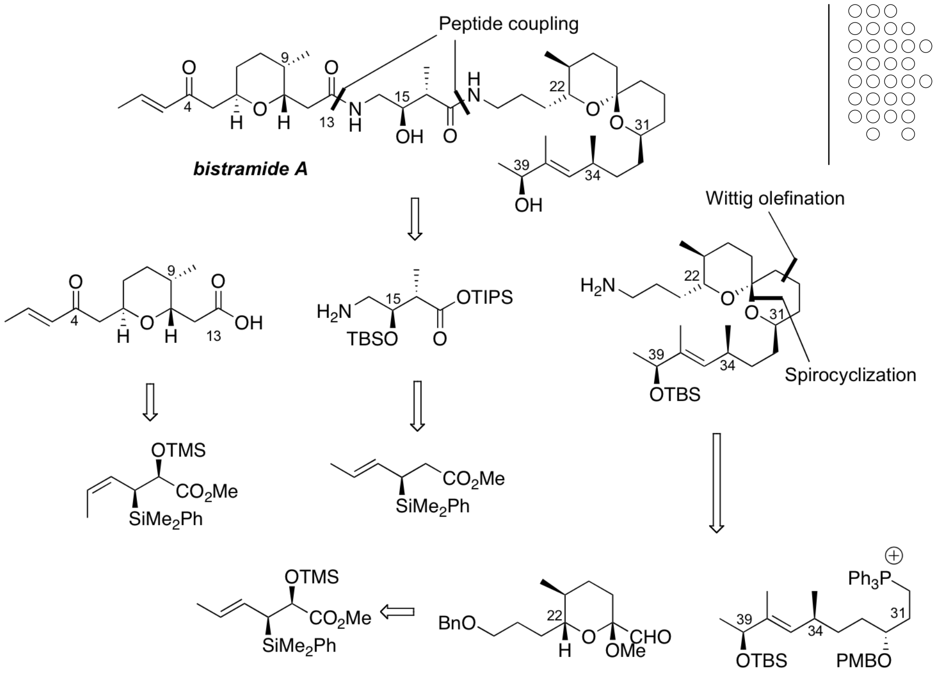
Reactions with sugar acetals and ketals

(Kishi, JACS **1982**, *104*, 4976):

Carba-Ferrier (Danishefsky, JACS **1987**, *109*, 8117)

Lowe, Jason T.; Wrona, Iwona E.; Panek, James S. **Total Synthesis of Bistramide A.** Organic Letters ACS ASAP.

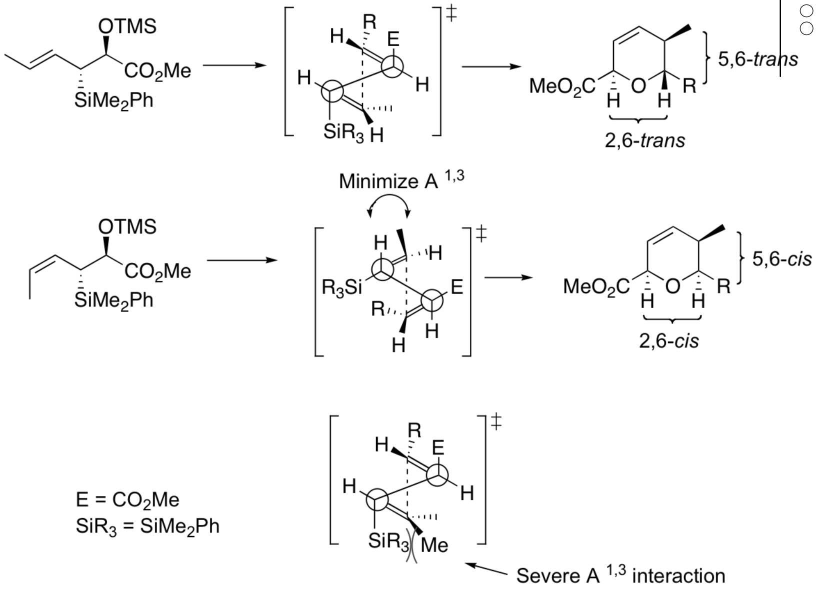




Preparation of *cis*- and *trans*-Silyl Epoxy Esters

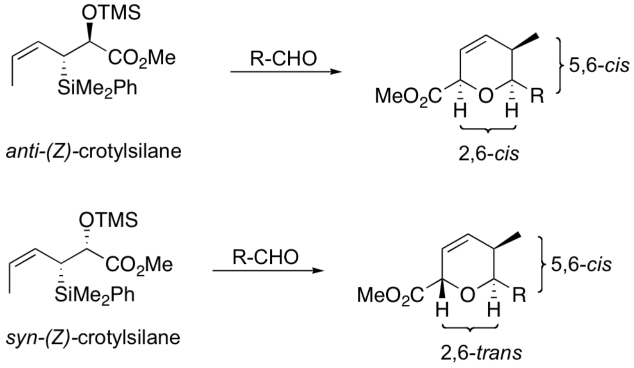
Preparation of *cis*- and *trans*-Silyl Epoxy Esters

Comparison of (*E*)- and (*Z*)-Crotylsilanes in [4+2]-Annulation



E = CO_2Me
SiR_3 = $SiMe_2Ph$

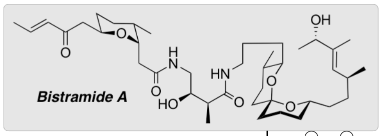
Comparison of (*E*)- and (*Z*)-Crotylsilanes in [4+2]-Annulation



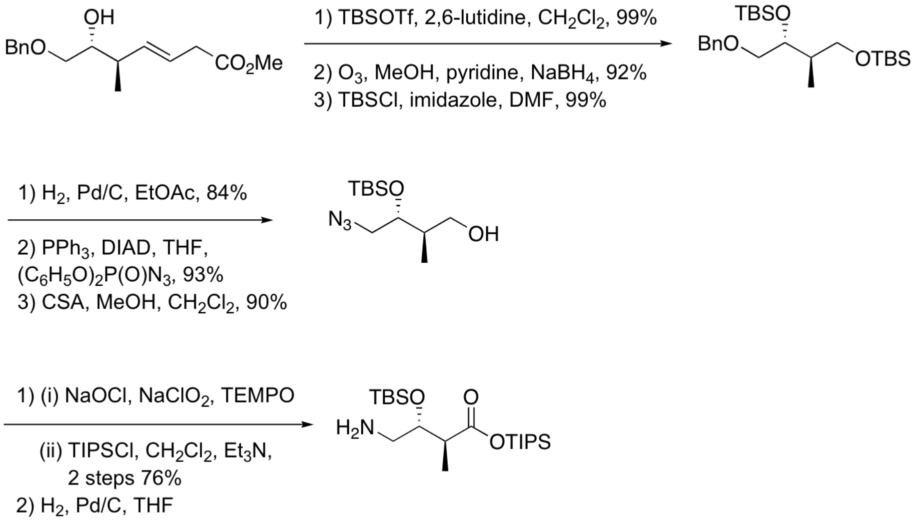
anti-(Z)-crotylsilane

syn-(Z)-crotylsilane

Synthesis of the C1-C13 Fragment of Bistramide A



Bistramide A



1) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%

2) O_3, MeOH, pyridine, $NaBH_4$, 92%

3) TBSCl, imidazole, DMF, 99%

1) H_2, Pd/C, EtOAc, 84%

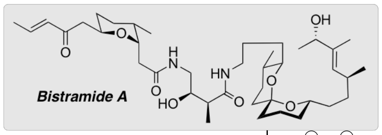
2) PPh_3, DIAD, THF, $(C_6H_5O)_2P(O)N_3$, 93%

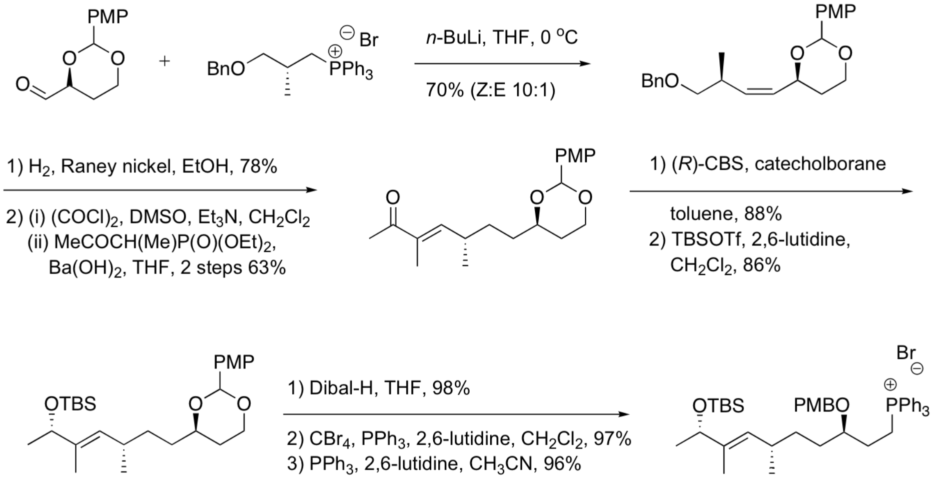
3) CSA, MeOH, CH_2Cl_2, 90%

1) (i) NaOCl, $NaClO_2$, TEMPO

(ii) TIPSCl, CH_2Cl_2, Et_3N, 2 steps 76%

2) H_2, Pd/C, THF





n-BuLi, THF, 0 °C

70% (Z:E 10:1)

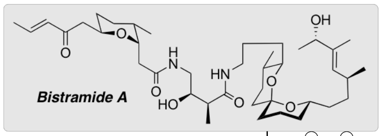
1) H_2, Raney nickel, EtOH, 78%

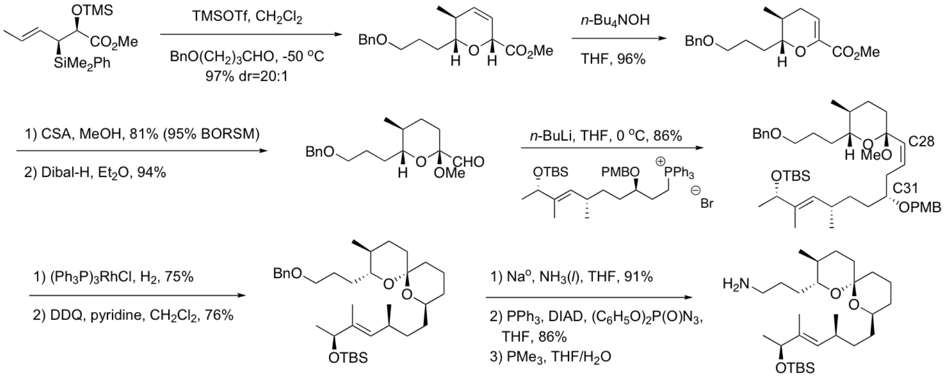
2) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
(ii) $MeCOCH(Me)P(O)(OEt)_2$, $Ba(OH)_2$, THF, 2 steps 63%

1) (*R*)-CBS, catecholborane toluene, 88%
2) TBSOTf, 2,6-lutidine, CH_2Cl_2, 86%

1) Dibal-H, THF, 98%

2) CBr_4, PPh_3, 2,6-lutidine, CH_2Cl_2, 97%
3) PPh_3, 2,6-lutidine, CH_3CN, 96%





TMSOTf, CH_2Cl_2

$BnO(CH_2)_3CHO$, -50 °C
97% dr=20:1

n-Bu_4NOH

THF, 96%

1) CSA, MeOH, 81% (95% BORSM)

2) Dibal-H, Et_2O, 94%

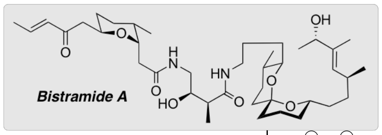
n-BuLi, THF, 0 °C, 86%

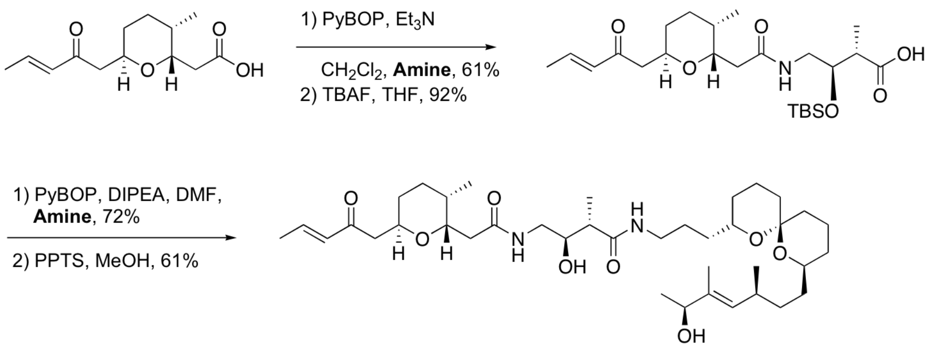
1) $(Ph_3P)_3RhCl$, H_2, 75%

2) DDQ, pyridine, CH_2Cl_2, 76%

1) Na°, $NH_3(l)$, THF, 91%

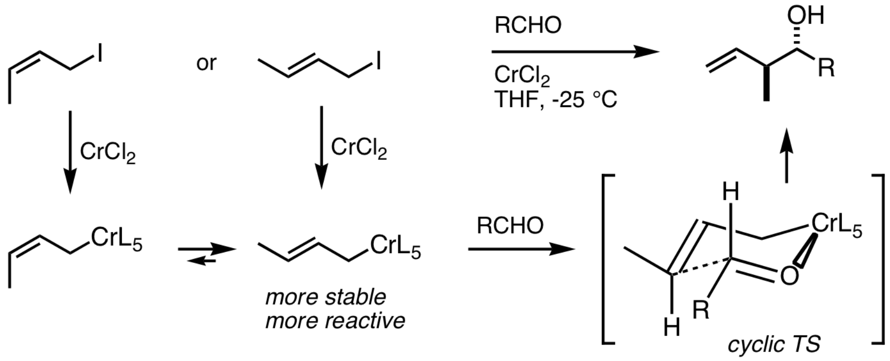
2) PPh_3, DIAD, $(C_6H_5O)_2P(O)N_3$, THF, 86%
3) PMe_3, THF/H_2O





III. anti-selective irrespective of olefin geometry (Ti, Cr, Zr, In, Zn).

Heathcock-Hiyama (1978):

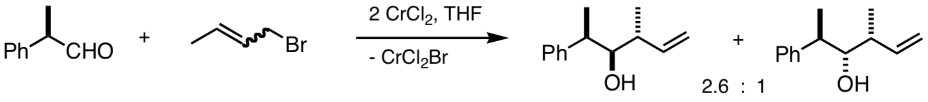


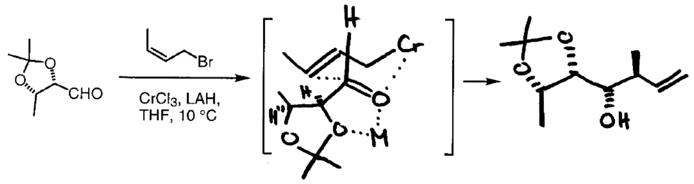
The principal difference between type I and type III crotyl organometallics is the lack of configurational integrity of type III species.

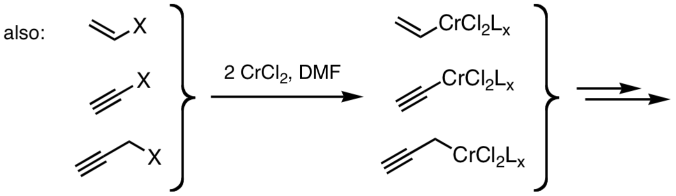
Chromium

- Cintus, P. *Synthesis* **1992**, 248.
- Wessjohann, L. A., "Recent advances in chromium(II)- and chromium(III)-mediated organic synthesis." *Synthesis* **1999**, 1.
- Fürstner, A., "Carbon-carbon bond formations involving organochromium(III) reagents." *Chem. Rev.* **1999**, *99*, 991.

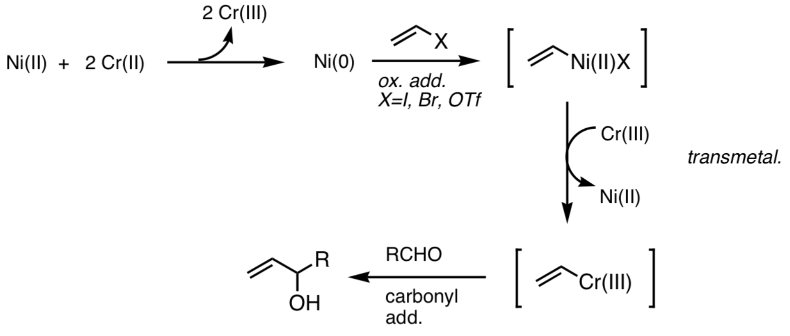
Nozaki-Takai-Hiyama-Kishi reaction:







Kishi: 0.1 - 1% of Ni(II) is beneficial:



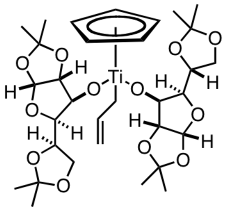
the functional group compatibility of this reagent is excellent:

W.C. Still, JOC **1983**, *48*, 4785. Asperdiol.

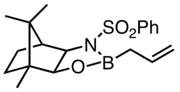
Wipf, P.; Kendall, C., "Tandem zirconocene homologation – aldimine addition." *Org. Lett.* **2001**, *3*, 2773-2776. Hydrozirconation of internal and terminal alkynes followed by *in situ* transmetalation to dimethylzinc and treatment with diiodomethane leads to chain extended allylic organometallics. Addition to *N*-phosphinoyl or *N*-sulfonyl aldimines provides homoallylic amines in 48-87% yield and 3:2 to >20:1 diastereomeric ratios favoring *anti*-products.

Chiral Allyl Transfer Reagents

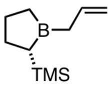
Selectivities are for PhCHO



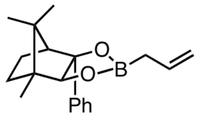
Duthaler, ACE **1989**, *29*, 494
90% ee



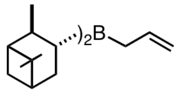
Reetz, PAC **1988**, *60*, 1607
36% ee



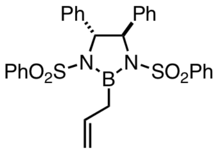
Masamune, JACS **1989**, *111*, 1892
96% ee



Hoffmann, Chem. Ber. **1981**, *114*, 375
96% ee



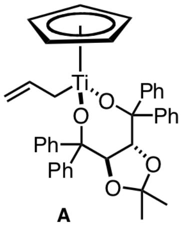
Brown, JACS **1983**, *105*, 2092
94% ee



Corey, JACS **1989**, *111*, 5495
94% ee

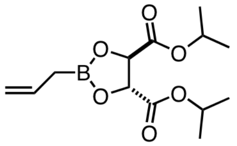
Chiral Allyl Transfer Reagents

Selectivities are for PhCHO

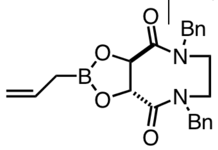


A

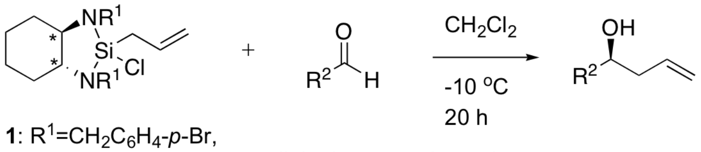
Duthaler, JACS **1992**, *114*, 2321
95% ee



Roush, JACS **1985**, *107*, 8186
72% ee



Roush, JACS **1988**, *110*, 3979
85% ee

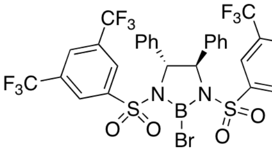


1: $R^1=CH_2C_6H_4$-*p*-Br,
95-98% *ee*

2: $R^1=CH_3$,
90-95% *ee*

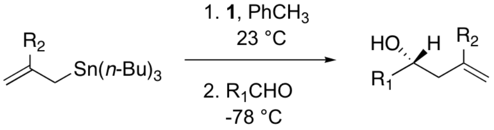
aliphatic, aromatic, and
conjugated aldehydes

Leighton ACIEE **2003**, *42*, 946.



1

Corey, THL **1990**, *31*, 3715
85% ee



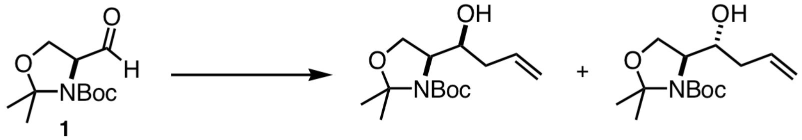
aldehyde	R_2	yield (%)	ee (%)
PhCHO	H	92	96
PhCHO	Cl	80	90
c-C_6H_{11}CHO	H	84	92
c-C_6H_{11}CHO	Cl	76	88

Williams, D. R.; Brooks, D. A.; Berliner, M. A., "Total synthesis of (-)-hennoxazole A." *J. Am. Chem. Soc.* **1999**, *121*, 4924.

Carreira: *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363.

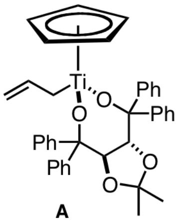
Taylor, R. E.; Haley, J. D. *Tetrahedron Lett.* **1997**, *38*, 2061 (using the Keck protocol: Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827).

Double Diastereodifferentiation



1

$Cp(i\text{-}PrO)_2Ti\text{-}CH_2CH{=}CH_2$	37%	63%
$H_2C{=}CHCH_2MgCl$	55.1%	44.9%
(*R*,*R*)-**A**	98.1%	1.9%
(*S*,*S*)-**A**	0.5%	99.5%



A