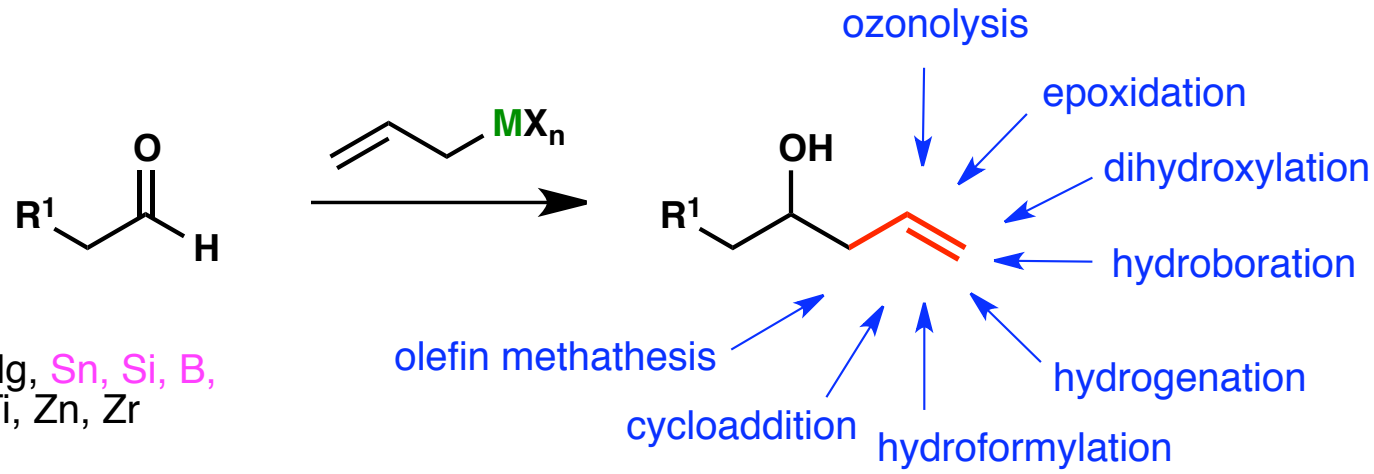
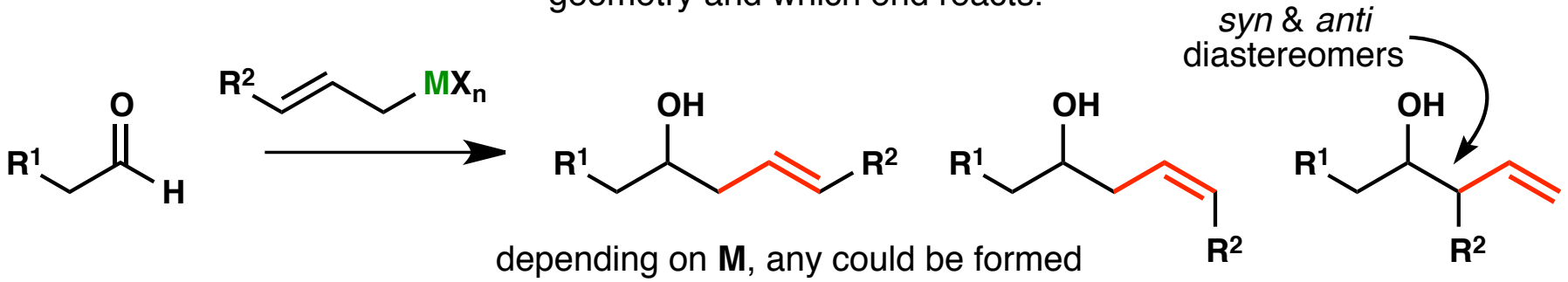
Allylation of C=O Bonds

Carreira: Chapter 5.1 – 5.9

Of all of the alkyl groups that can be introduced into a molecule, the allyl group is arguably the most versatile. The double bond can participate in a number of synthetically useful transformations.



While simple allyl Grignard or allyllithium reagents can be used as the nucleophile, they are often far too reactive to be used in stereoselective reactions. Can be quite basic, and reaction rate is too fast to be overly selective. With substituted allyl groups (e.g., crotyl), there is also the question of olefin geometry and which end reacts.

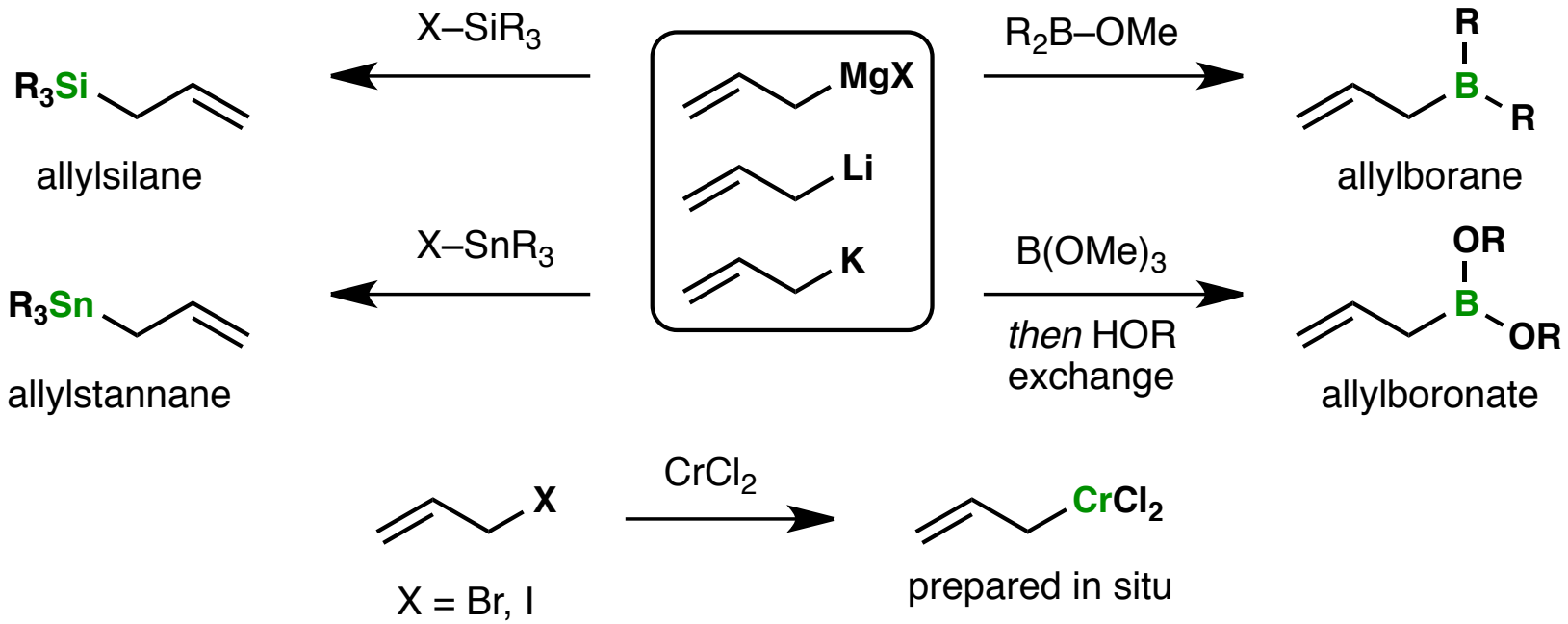


depending on **M**, any could be formed

Reviews: Schinzer, D. *Synthesis* **1988**, 263–273; Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575; Hoffman, R. W. *Pure Appl. Chem.* **1988**, *60*, 123–130; Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316 (chiral allyl & allenyl silanes); Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774–7854 (enantioselective catalysis)

Preparation and Reactivity

The reactivity of the reagents derived from the alkali and alkaline earth metals can be tamed by swaping the metal with a main group and transition metal element. Of particular importance are reagents derived from silicon, boron, tin, and chromium.



The above allyl reagents display a wide range of reactivities toward aldehydes and ketones:

allylsilanes: typically no reaction in the absense of a strong Lewis acid activation

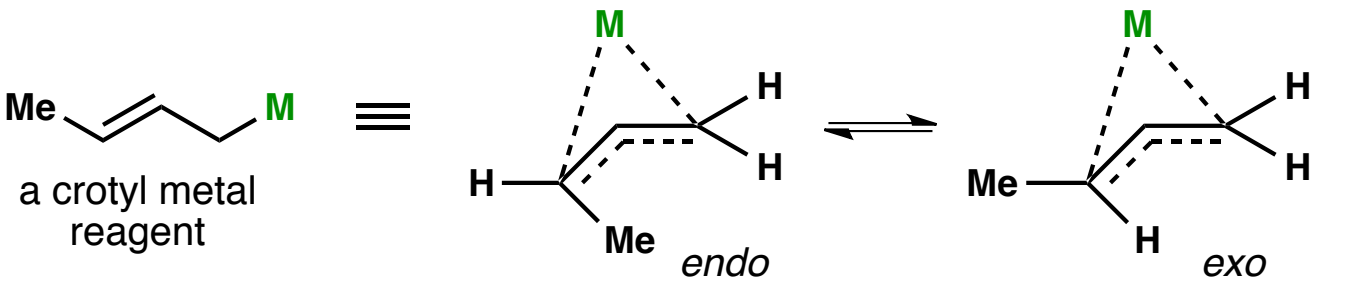
allylstannanes: will react with heating or in the presence of modest Lewis acid activation

allylboronates: can react with aldehydes in the absence of activators at room temp (slow)

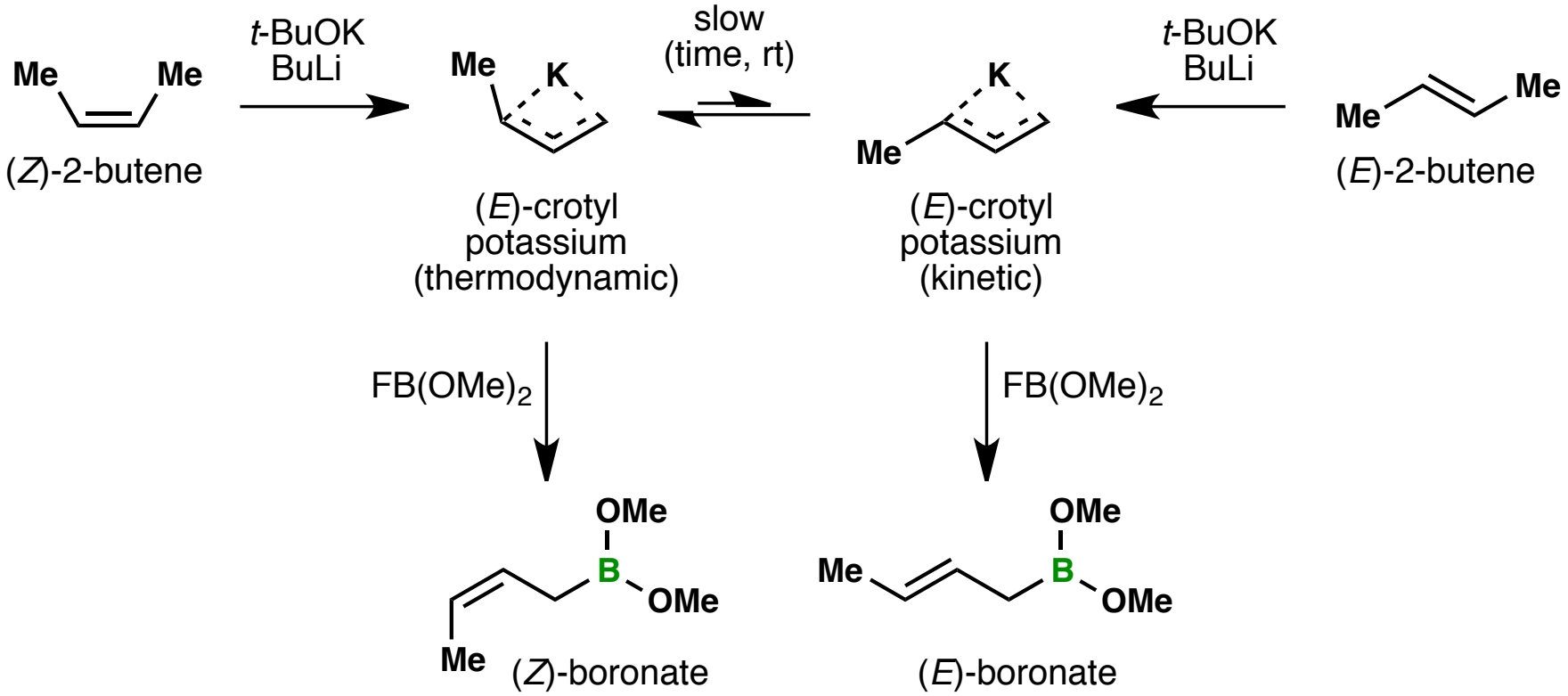
allylboranes: can react with aldehydes in the absence of activators even at –100 ºC

Crotyl Metal Reagents

Both (*Z*)- and (*E*)-crotyl metal reagents can be prepared from 2-butene and an alkali metal reagent. The degree of selectivity depends on the metal used and how easily it isomerizes.

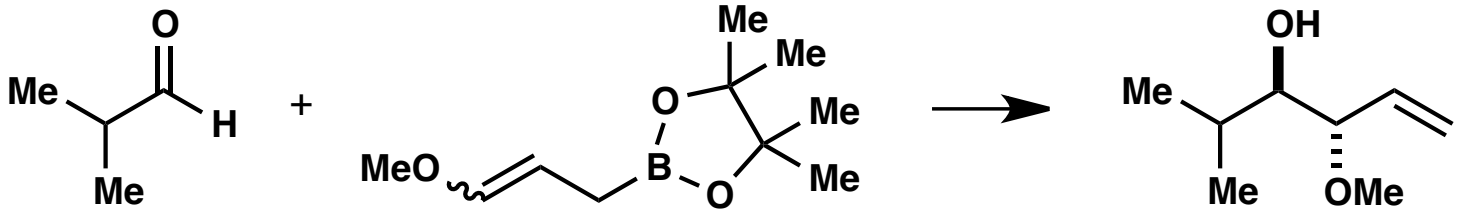


M	endo:exo
MgBr	1:3
Li	3:1
Na	10:1
K	125:1 (slow)
Ca	500:1



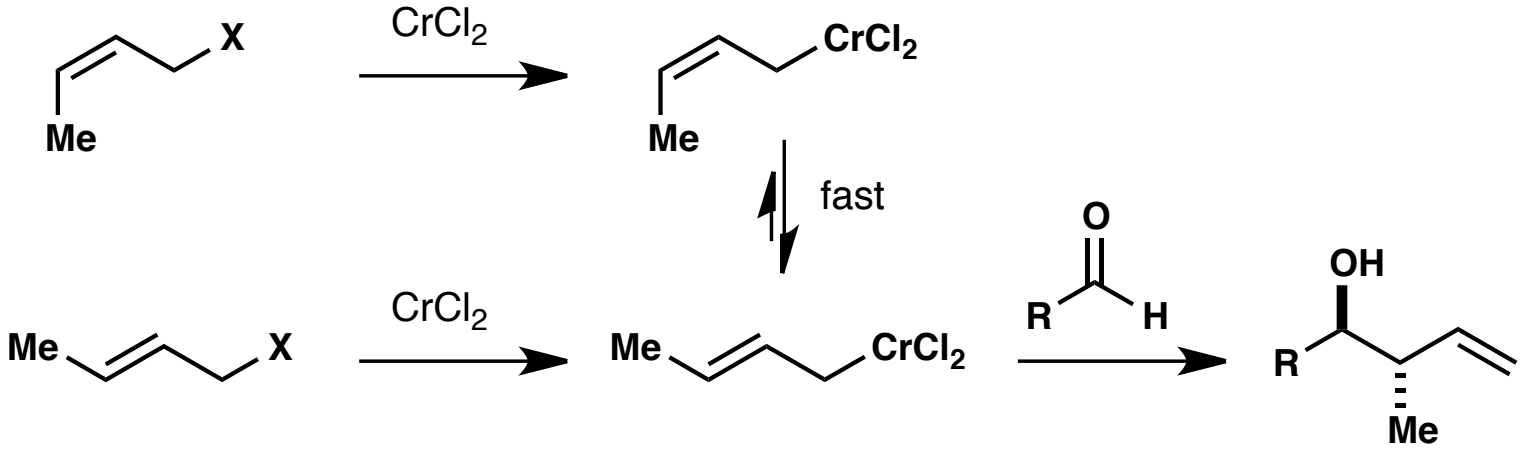
Reactivity of (E)- & (Z)-allyl reagents

(*E*)-substituted reagents tend to react faster than the (*Z*) stereoisomers. For other substitution patterns a kinetic resolution can be used to enrich the allylmetal reagent.



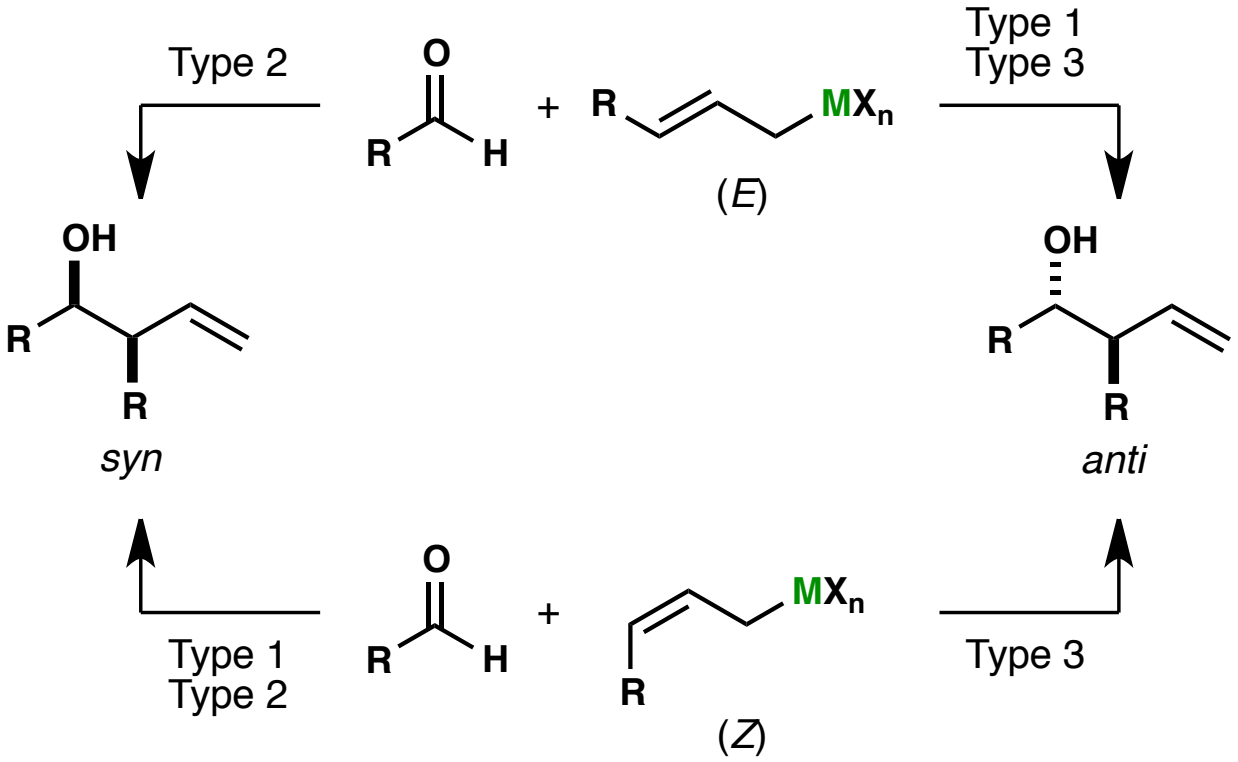
0.9 equiv 90:10 *E* : *Z* > 98 : 2 *anti* : *syn*

Allylchromium reagents are stereoselective irrespective of the starting configuration of the allyl halide precursor. Both halide isomers react, but the allylchromium reagent undergoes *rapid* equilibration to form the thermodynamically favored (*E*)-isomer.



Reactivity Trends

The transition state that is thought to be active and the observed stereoselectivity is dependent on the type of allylation reagent used. The different reactivity tpes arise from how Lewis acidic the metal is and how configurationally stable the reagent is.



Seems like a lot of information, but the mechansism of each tells the stroy

Type 1

E → *anti* & *Z* → *syn*

closed, cyclic T.S.

MX$_n$ = BR_2, BX_2, $B(OR)_2$
SnX_3, SiX_3

Type 2

E & *Z* → *syn*

open T.S.

MX$_n$ = $SnBu_3$, $SiMe_3$

Type 3

E & *Z* → *anti*

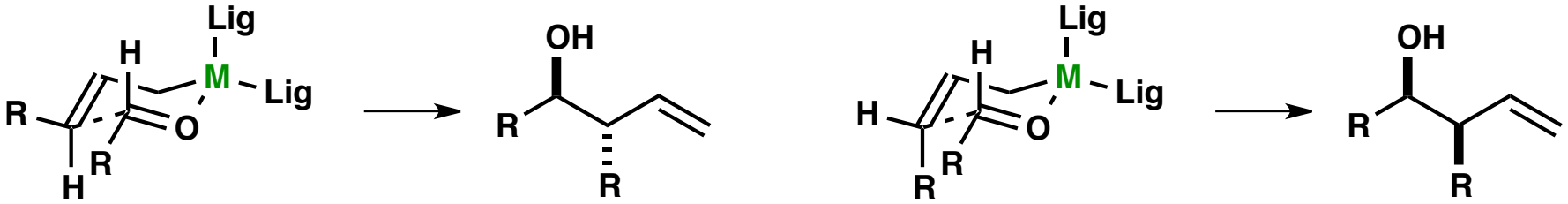
closed, cyclic T.S.

MX$_n$ = $CrCl_2$, Cp_2TiX
Cp_2ZrX

Transition States

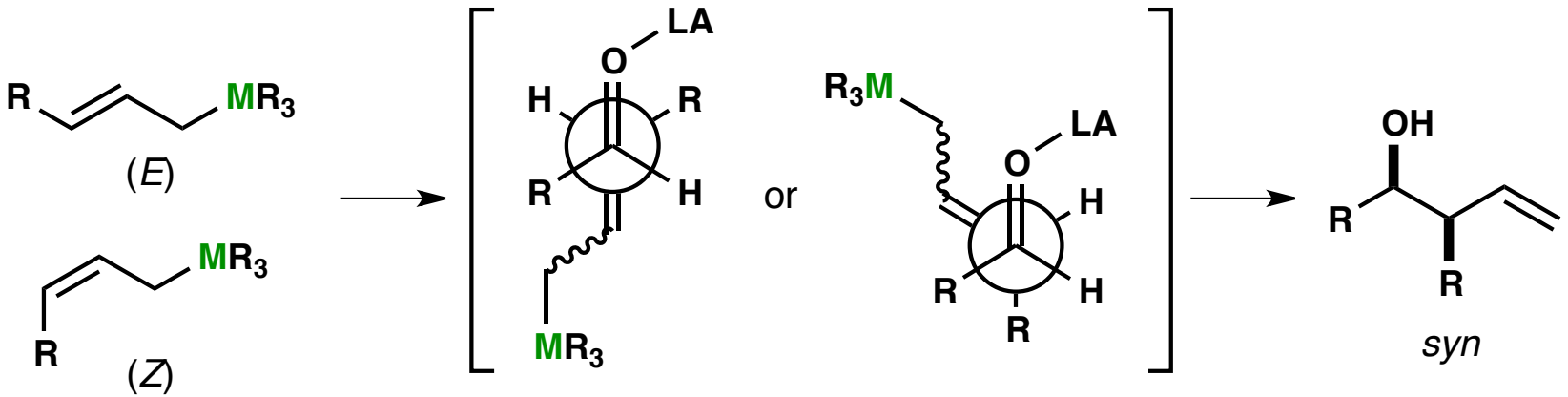
Several different mechanisms/transition states are possible. All based on the nature of the metal.

Type 1 & 3 reagents are Lewis acidic enough to activate the aldehyde without additional promoters. This results in a closed, six-membered transition state (Zimmerman-Traxler).



from (*E*)-reagent *anti* from (*Z*)-reagent *syn*

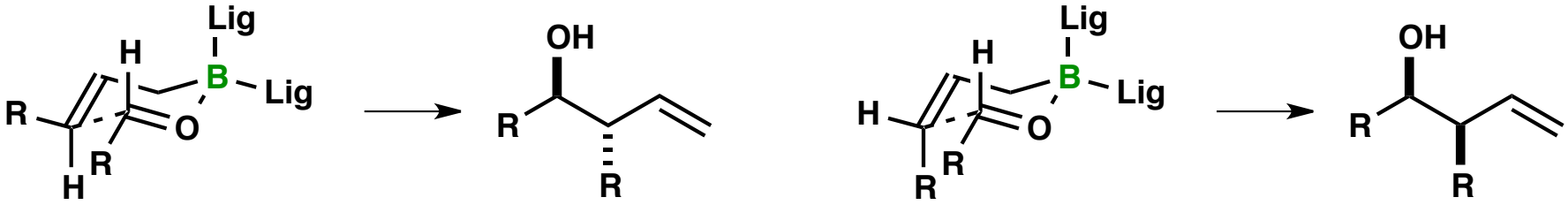
Type 2 reagents do not activate the aldehyde by themselves and require an additional Lewis acid promoter. This results in a open transition state. Two have been proposed. Either can be used depending on the sterics of the specific system.



antiperiplanar synclinal (favorable orbital interactions)

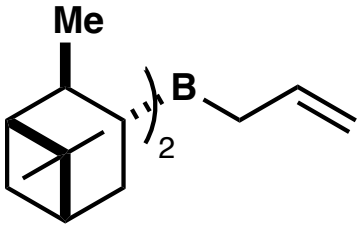
Allylation with Boron Reagents

All are type 1 reagents and react through a Zimmerman-Traxler-type transition state. (*E*)-substituted reagents lead to *anti* products, while (*Z*)-substituted reagents lead to *syn* products.

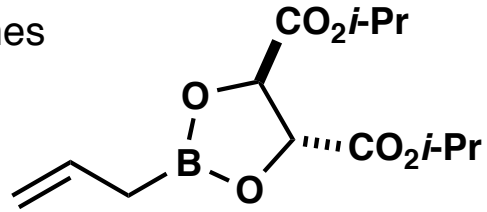


from (*E*)-reagent *anti* from (*Z*)-reagent *syn*

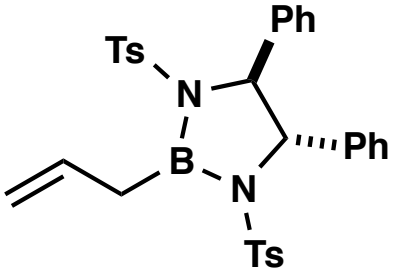
The greatest utility of the boron reagents are the different reagents available for carrying out enantioselective reactions. These use stoichiometric amounts of the source of chirality, but all are reasonably inexpensive.



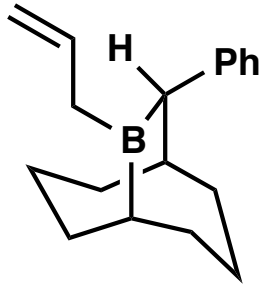
allyl diisopinocampheylboranes
($Ipc_2BAllyl$)
Brown



tartrate-derived allylboronates
Roush



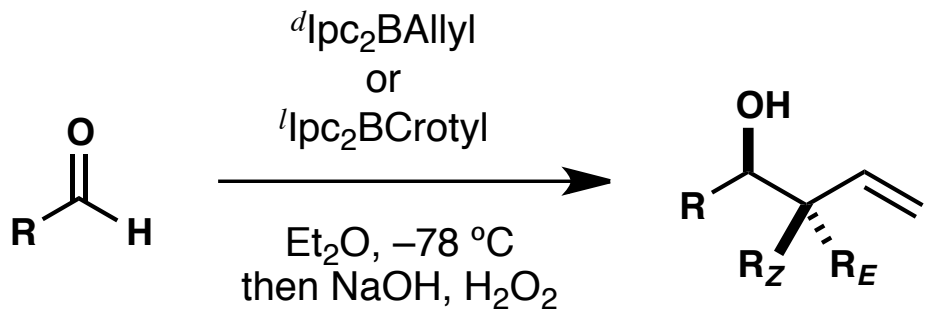
Corey

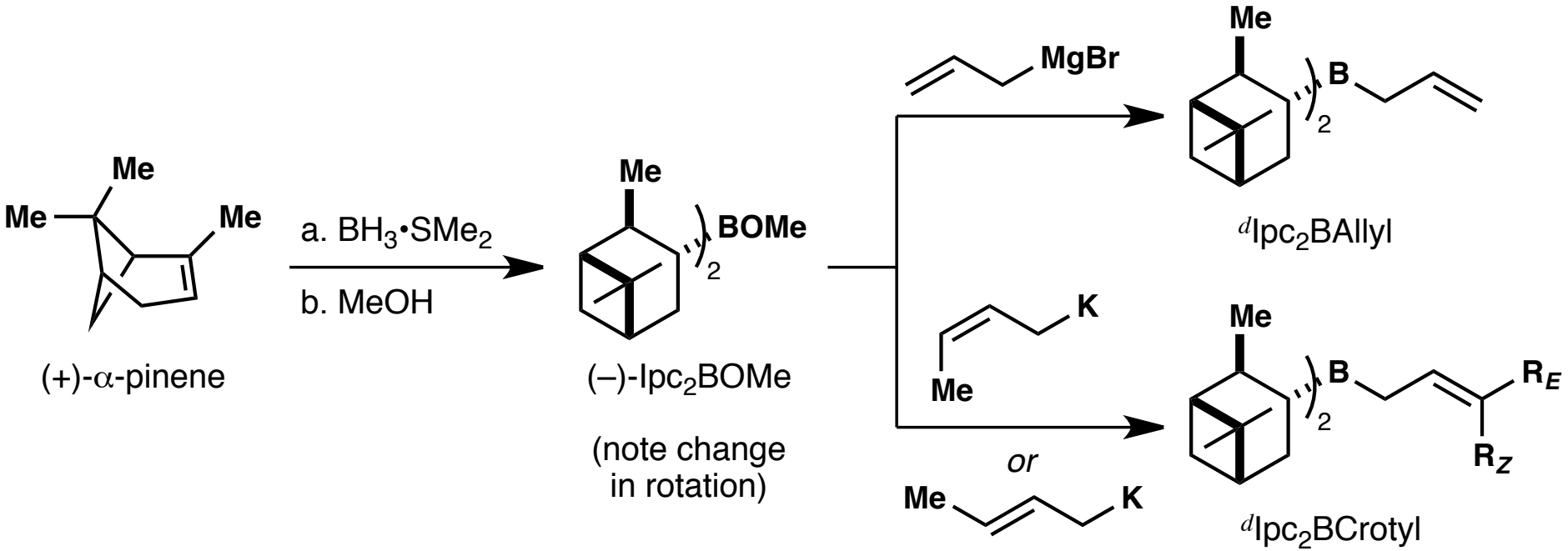


9-BBN-derived reagents
Soderquist

Brown Allylation

Prepared easily from either (+)- or (–)-α-pinene. The allyl reagent is stable under inert atmosphere as a stock solution. The crotyl reagents isomerize upon storage and must be generated and used in situ.



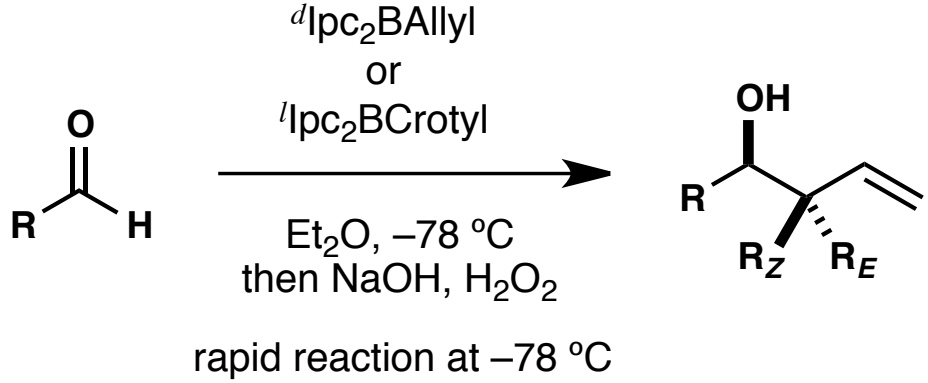


Preparation of allyl: *J. Am. Chem. Soc.* **1983**, *105*, 2092. (*Org. Synth.* **2011**, *88*, 87.)
Preparation of crotyl: *J. Am. Chem. Soc.* **1986**, *108*, 5919

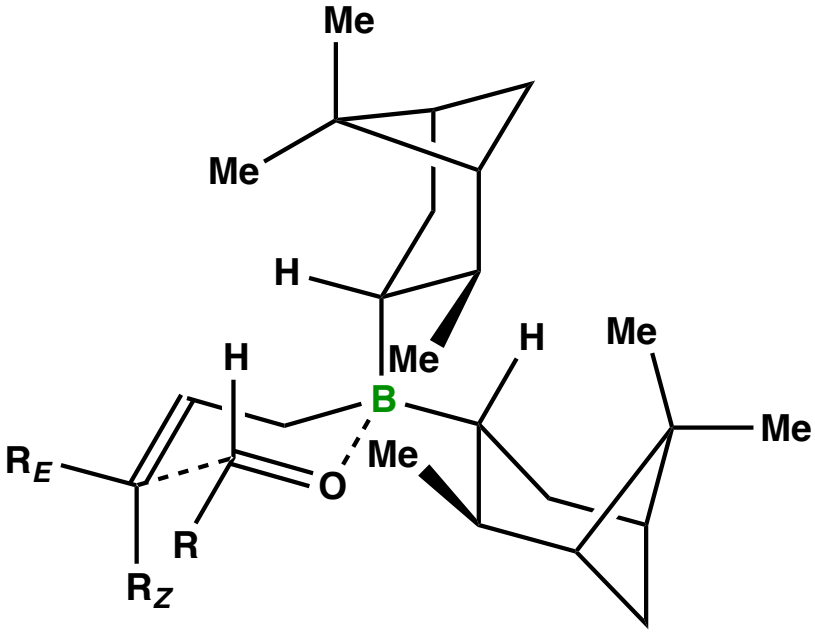
^{d}Ipc$_2$ from (+)-α-pinene
^{l}Ipc$_2$ from (–)-α-pinene

Brown Allylation

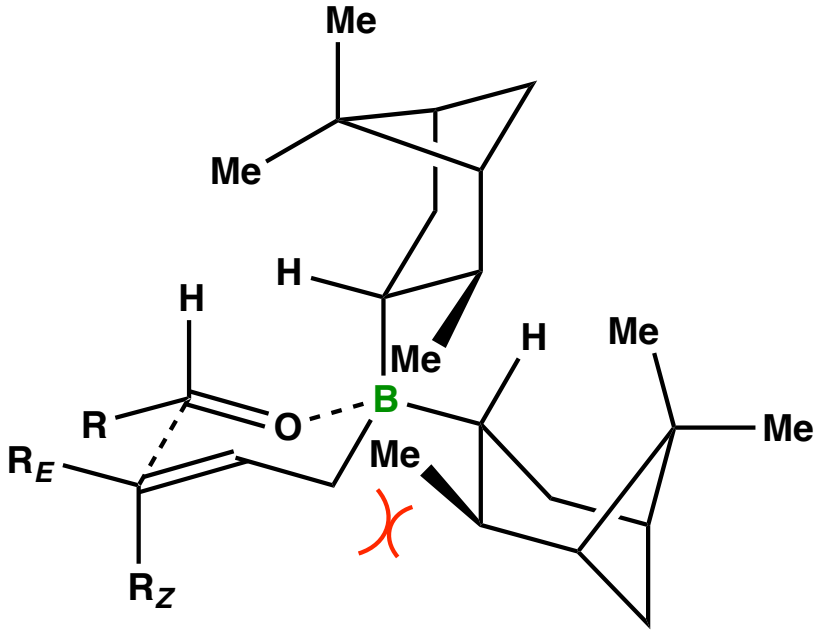
Stereoselectivity model



w/ ^{d}Ipc$_2$BAllyl		w/ ^{d}Ipc$_2$B-*E*-Crotyl	
R	**% ee**	**R**	**% ee**
CH_3	>99	CH_3	90
Bu	96	Ph	88
Ph	96	CH_2=CH	90
t-Bu	99		
		dr 95:5	



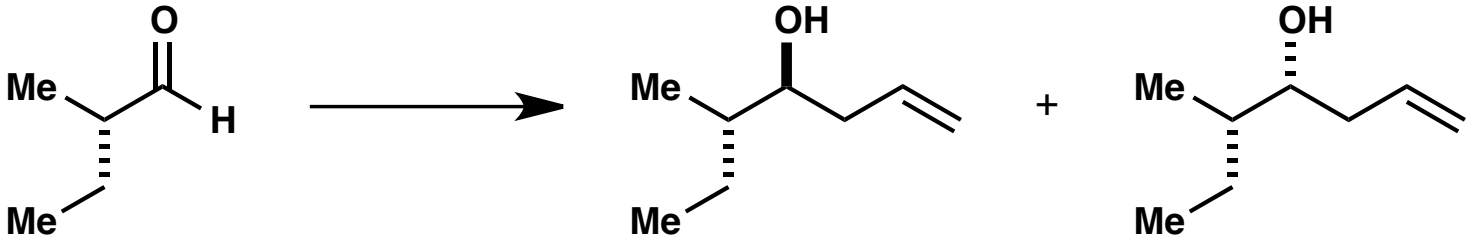
Favored transition state
(*Si* face addition)



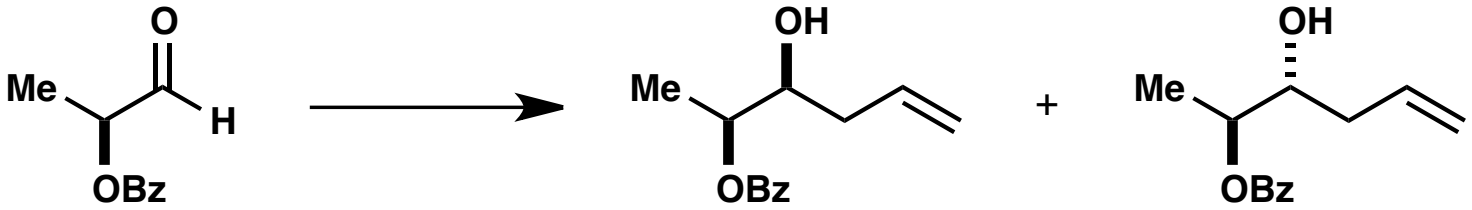
Disfavored transition state
(*Re* face addition)

Brown Allylation of α-Chiral Aldehydes

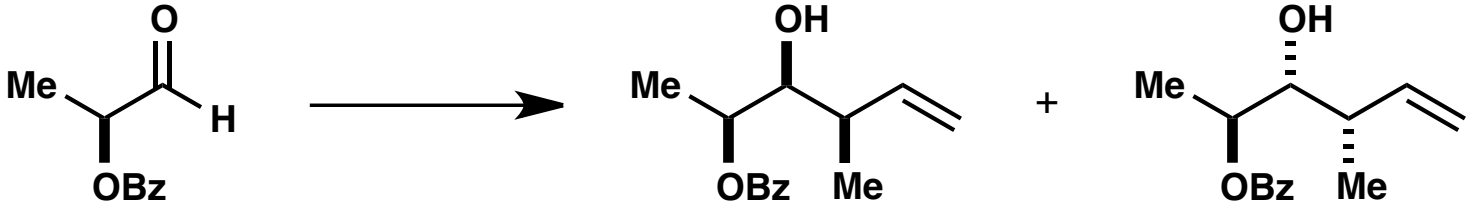
The selectivity of the Brown reagents typically overrides any facial preference of the aldehyde.



^{d}Ipc$_2$BAllyl	96 : 4
^{l}Ipc$_2$BAllyl	5 : 95



^{d}Ipc$_2$BAllyl	94 : 6
^{l}Ipc$_2$BAllyl	4 : 96

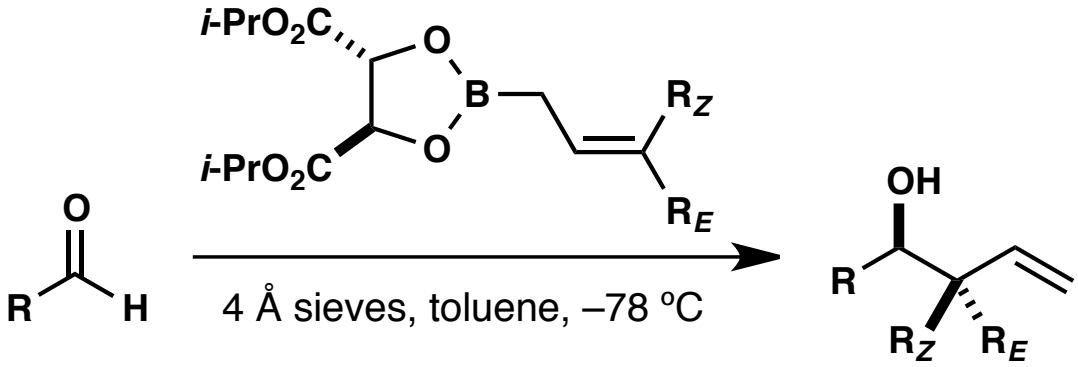


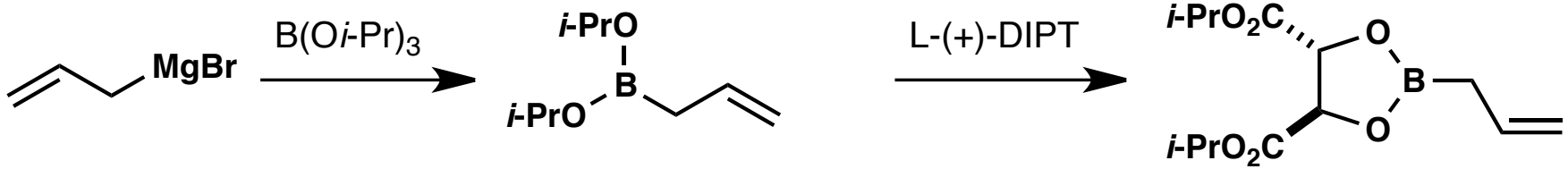
^{d}Ipc$_2$B-(*Z*)-Allyl	73 : 27
^{l}Ipc$_2$B-(*Z*)-Allyl	1 : 99

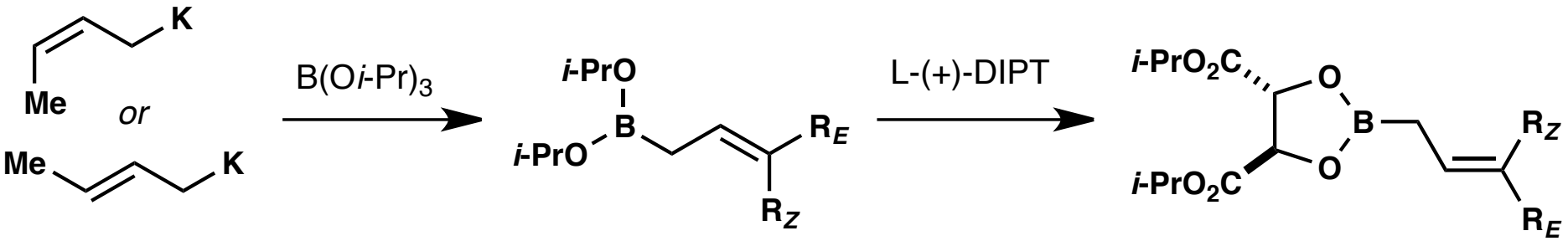
J. Org. Chem. **1987**, *52*, 319.
J. Org. Chem. **1989**, *54*, 1570.

Roush Allylation

Prepared from either (+)- or (–)-DIPT and the allyl boronic ester. The boronate reagent is sensitive to moisture, but can be distilled and stored under inert atmosphere at –10 ºC.



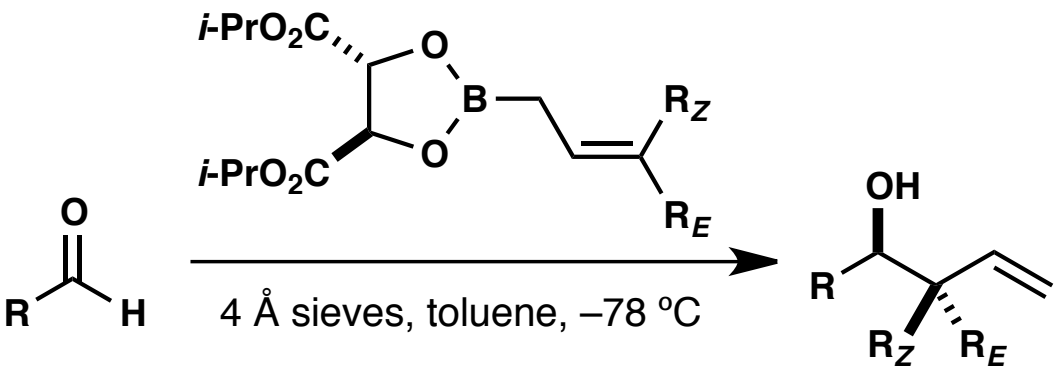




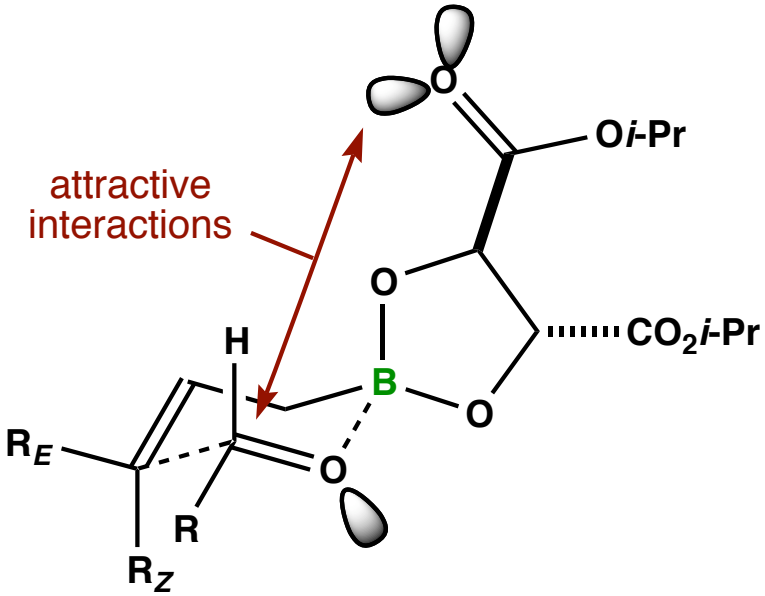
Preparation of allyl: *J. Am. Chem. Soc.* **1985**, *107*, 8186
Preparation of crotyl: *J. Am. Chem. Soc.* **1990**, *112*, 6339 (*Org. Synth.* **2011**, *88*, 181.)

Roush Allylation

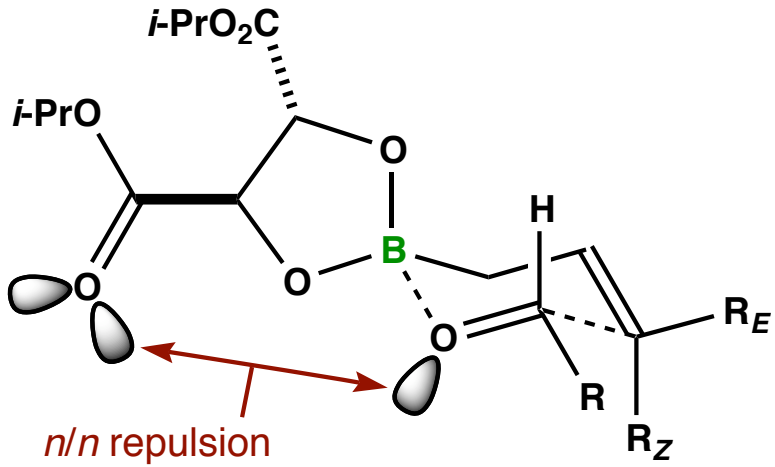
Stereoselectivity model



R	w/ Allyl % ee	w/ *E*-Crotyl dr >97:3 % ee	w/ *Z*-Crotyl dr >97:3 % ee
n-C_9H_{19}	79	88	86
c-C_6H_{11}	87	91	83
t-Bu	82	73	70
Ph	71	66	55



Favored T.S.
(*Si* face addition)

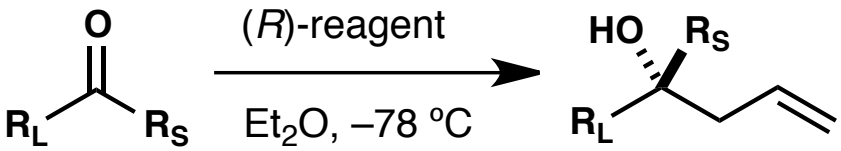


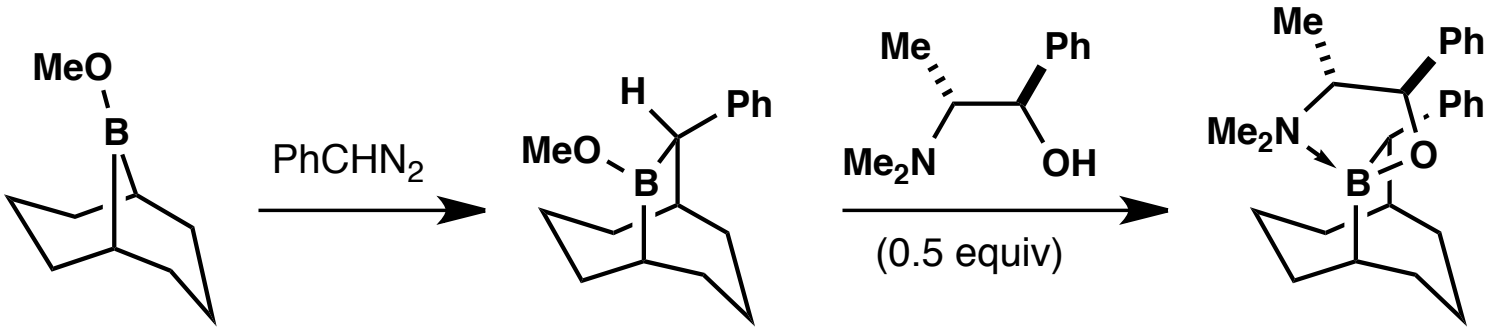
Disfavored T.S.
(*Re* face addition)

Model calculations: *J. Am. Chem. Soc.* **2002**, *124*, 10692

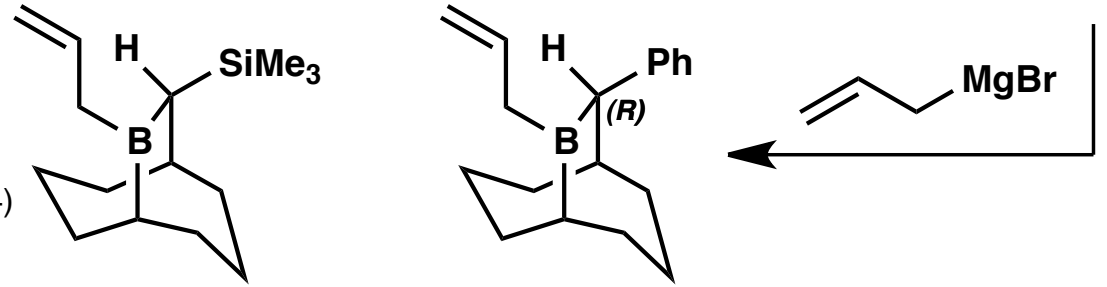
Soderquist Allylation of Ketones

Asymmetric allylation of ketones has been a difficult problem. To address this Soderquist has developed an allyl borane based on 9-BBN. The TMS-substituted version works well for allylation of aldehydes (94-99% ee), >98:2 dr), but their reactivity with ketones is very slow (2 days, 25 °C) and less selective (62% ee). The phenyl substituted reagent was designed to be more reactive toward ketones.





resolution

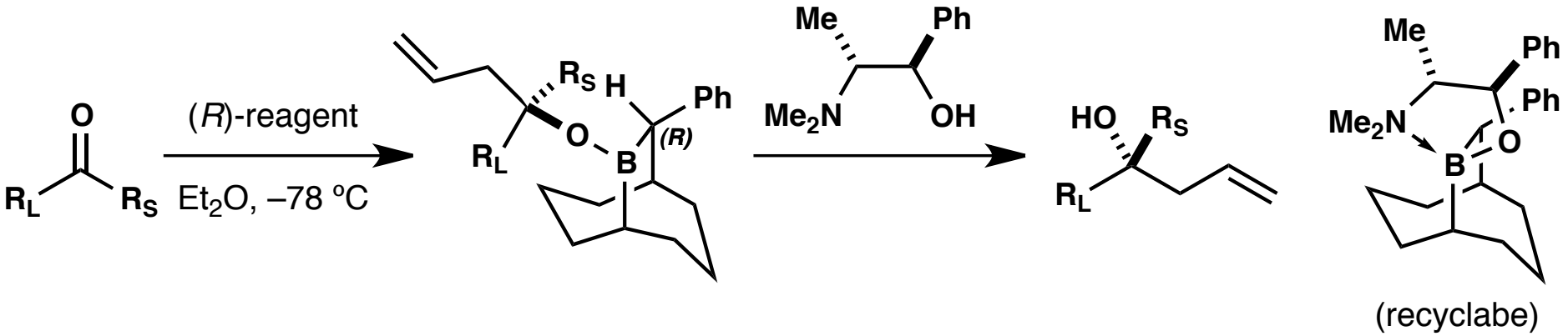


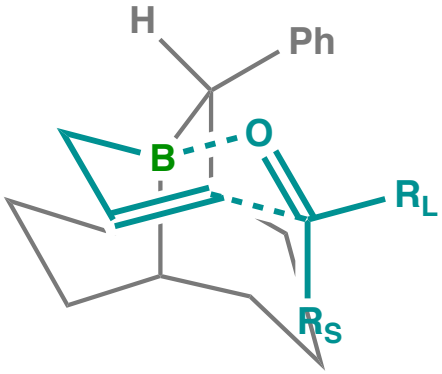
The TMS derivative is also a useful reagent for aldehyde allylations (*J. Am. Chem. Soc.* **2005**, *127*, 8044)

J. Am. Chem. Soc. **2005**, *127*, 11572

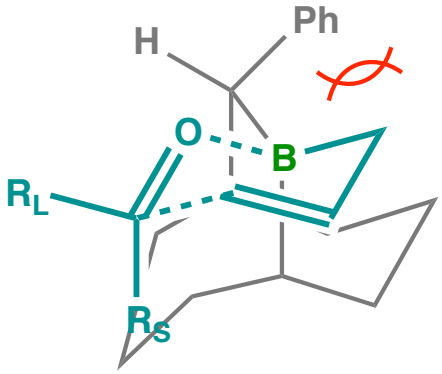
Soderquist Allylation of Ketones

Stereoselectivity model





Favored T.S.
(*Re* face addition)

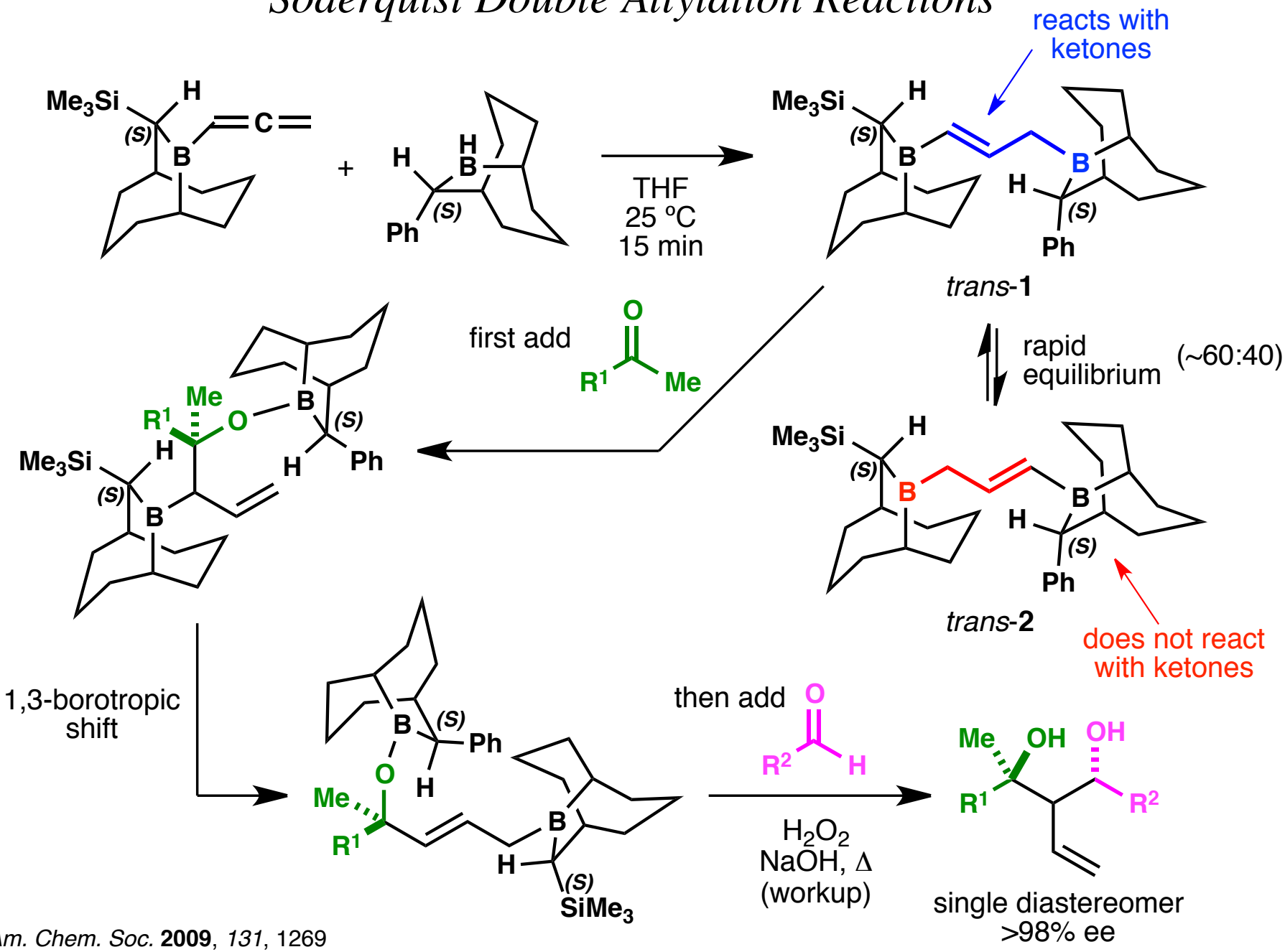


Disfavored T.S.
(*Si* face addition)

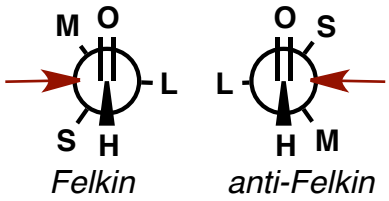
R_L	R_S	% ee
Ph	Me	96
Ph	Et	94 (w/ S-reagent)
4-BrC_6H_4	Me	98 (w/ S-reagent)
Et	Me	87 (w/ S-reagent)
CH_2=CH	Me	81 (w/ S-reagent)
i-Pr	Me	92 (w/ S-reagent)
Ph	H	90

J. Am. Chem. Soc. **2005**, *127*, 11572

Soderquist Double Allylation Reactions



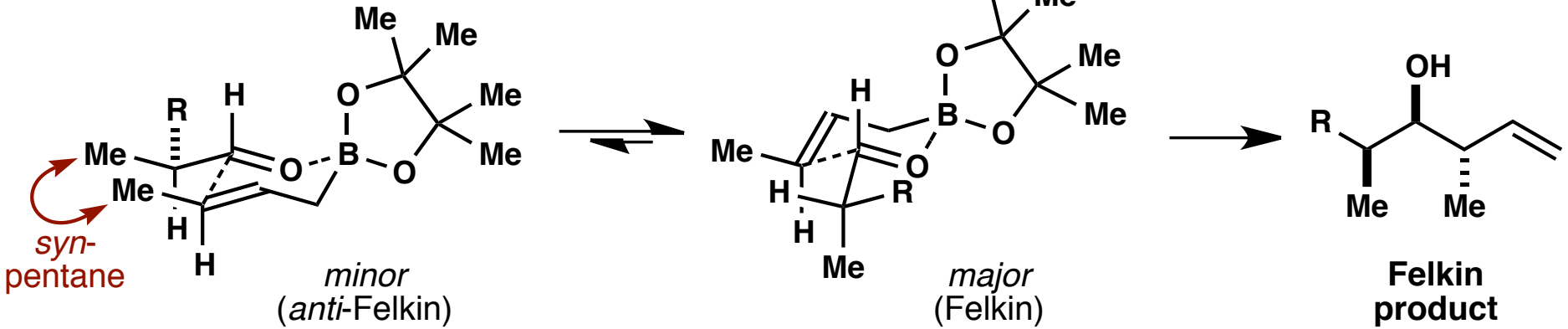
J. Am. Chem. Soc. **2009**, *131*, 1269



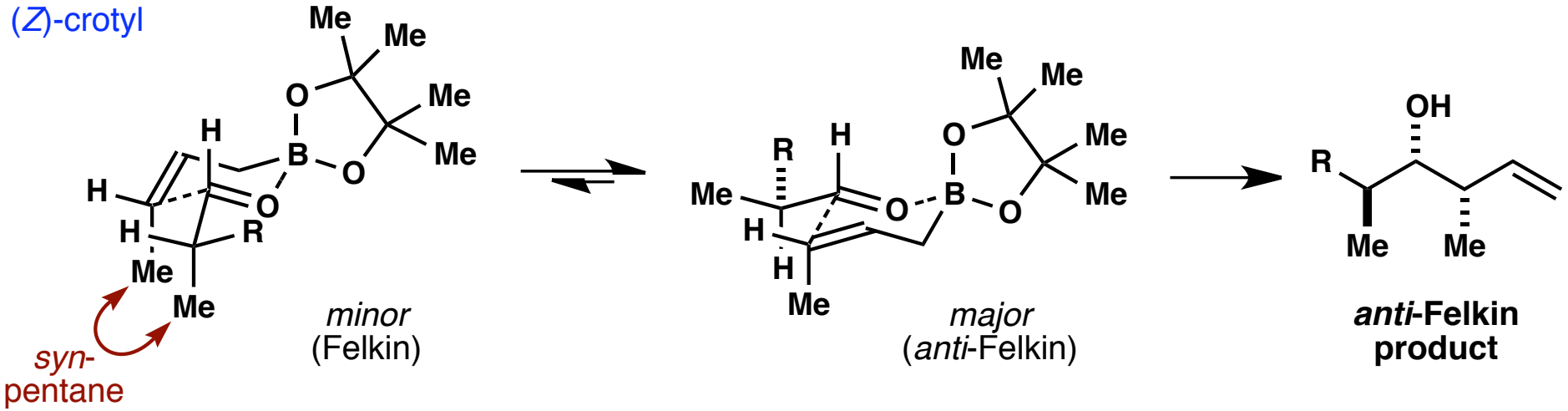
Diastereoselective Boron Allylation Reactions

Reactions of allyl- and crotylboron reagents with chiral aldehydes are subject to the Cram and Felkin-Ahn models described previously. But we must also take into account the added sterics of the crotyl group.

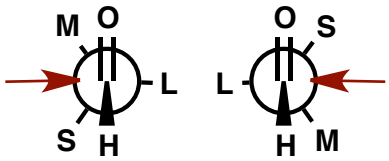
(*E*)-crotyl



(*Z*)-crotyl

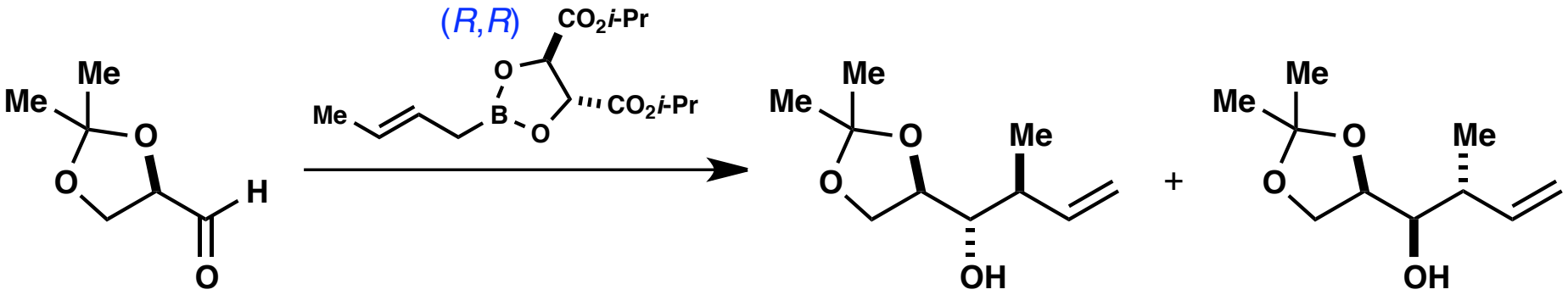


Diastereoselective Boron Allylation Reactions



Felkin *anti-Felkin*

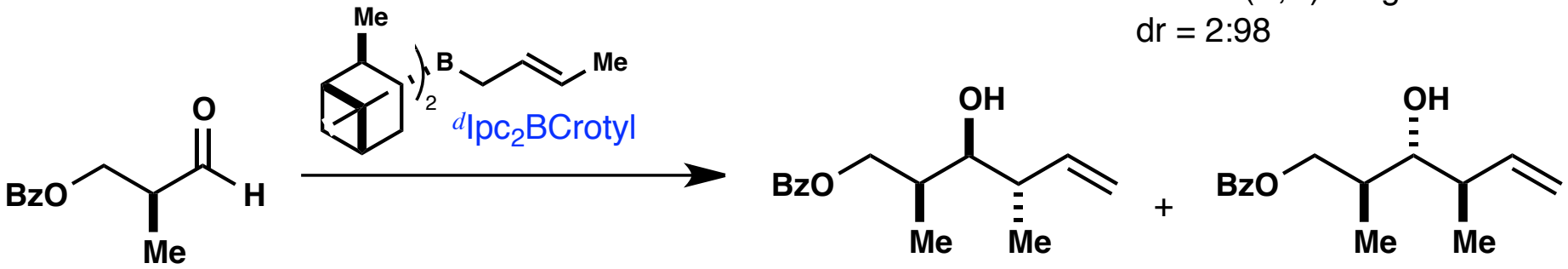
With chiral boron reagents, the facial selectivity of the chiral aldehyde is often overruled by the chiral reagent.



Felkin product ***anti*-Felkin product**

J. Org. Chem. **1990**, *55*, 4117

matched case: (*R*,*R*)-reagent (shown)
dr = 91:9
mismatched case: (*S*,*S*)-reagent
dr = 2:98



Felkin product ***anti*-Felkin product**

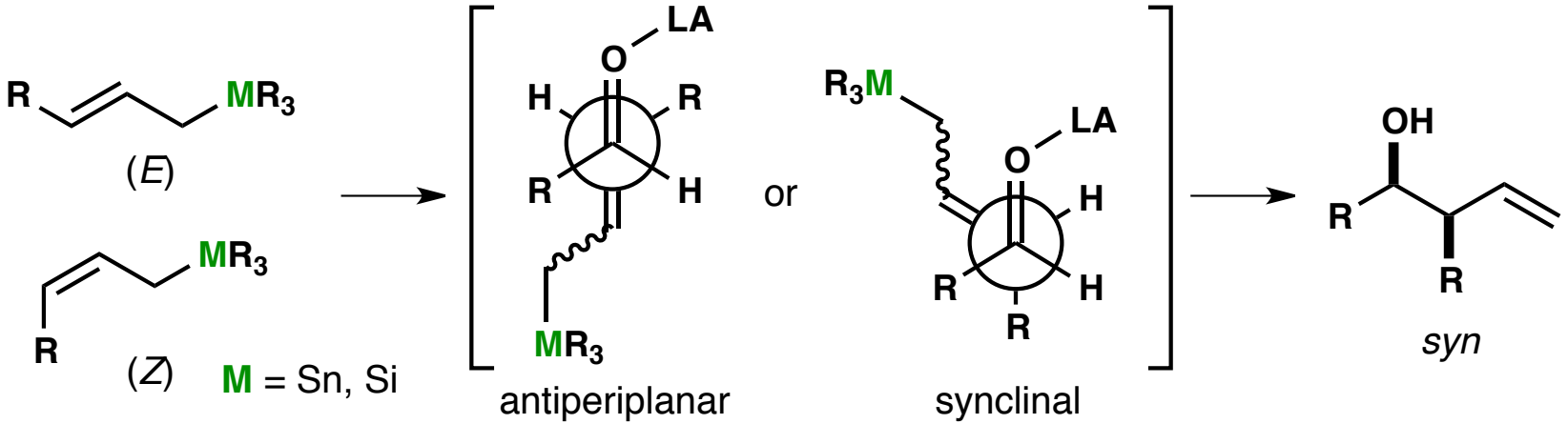
J. Org. Chem. **1989**, *54*, 1570

matched case: ^{d}Ipc$_2$BCrotyl (shown)
dr = 98:2
mismatched case: ^{l}Ipc$_2$BCrotyl
dr = 5:95

similar results with *Z*-crotyl

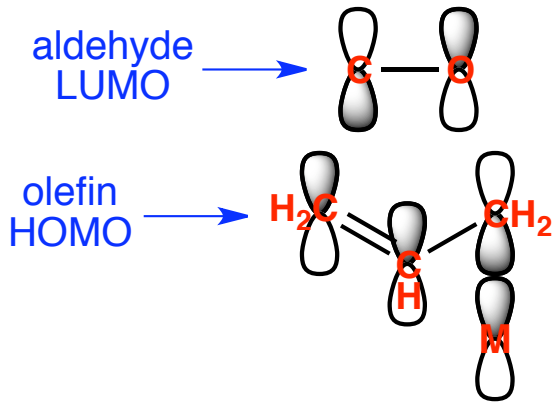
Allylation with Silicon and Tin Reagents

Allylsilanes and allyl stannanes are not Lewis acidic. Because of this they cannot activate the aldehyde themselves and so require an external Lewis acid promotor. They react through an open transition state. Both antiperiplanar and synclinal transition state have been proposed and either can be employed depending on the sterics of the system. With crotyl reagents, the sense of diastereoselectivity is often independent of the olefin geometry (though the ratio may differ).



The synclinal transition state is thought to take advantage of secondary orbital interactions

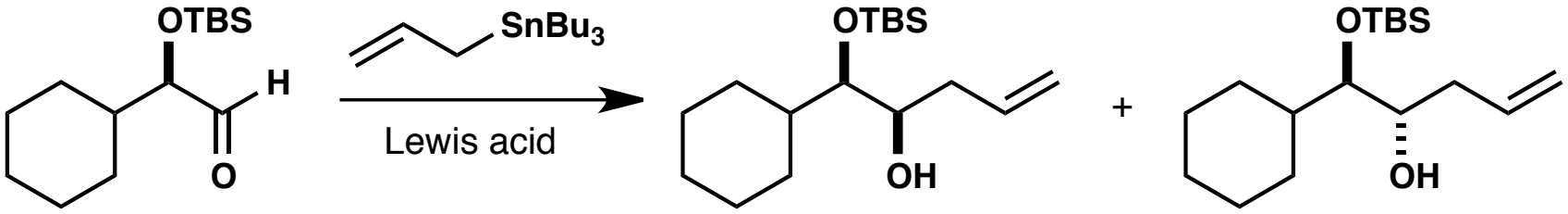
In general the allylsilanes are popular due to their stability over allylboranes.



J. Am. Chem. Soc. **1980**, *102*, 7107; *J. Org. Chem.* **1994**, *59*, 7889; *Tetrahedron Lett.* **1983**, *24*, 2865

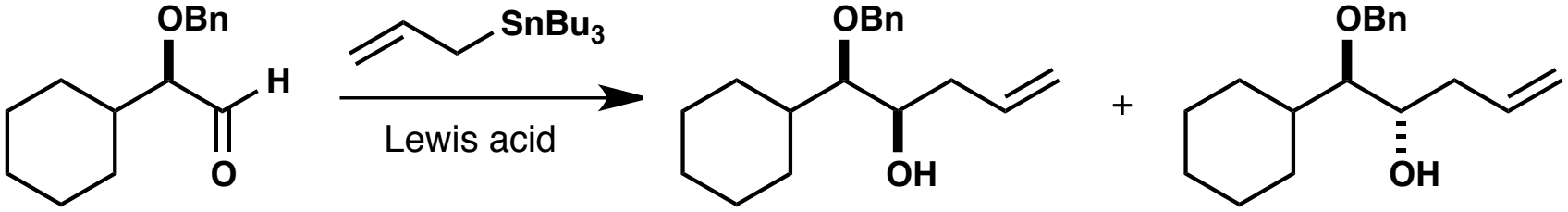
Allylation Reactions With Chiral Aldehydes

Because Si and Sn are not directly involved in the transition state, we must consider both Cram chelation and Felkin-Ahn models in allylation reactions with chiral aldehydes.



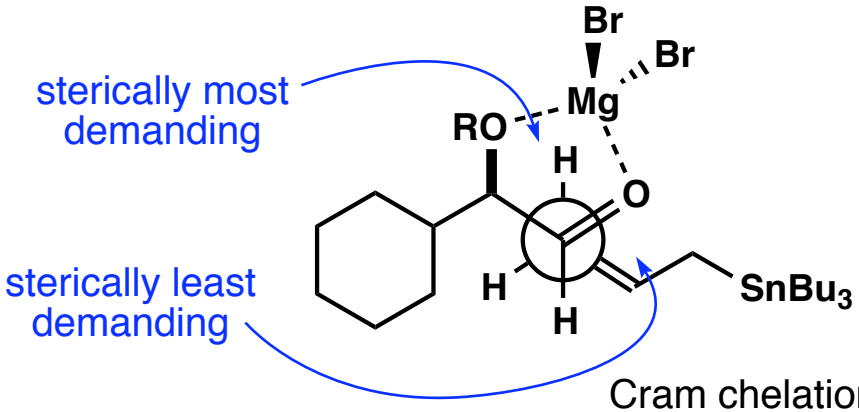
BF_3•OEt_2: dr = 5:95
$MgBr_2$: dr = 21:79

Felkin product

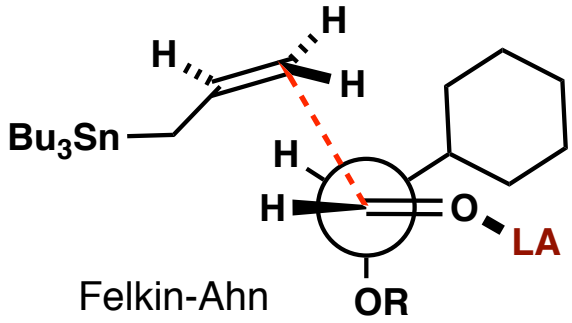


BF_3•OEt_2: dr = 39:61
$MgBr_2$: dr = >250:1

Felkin product



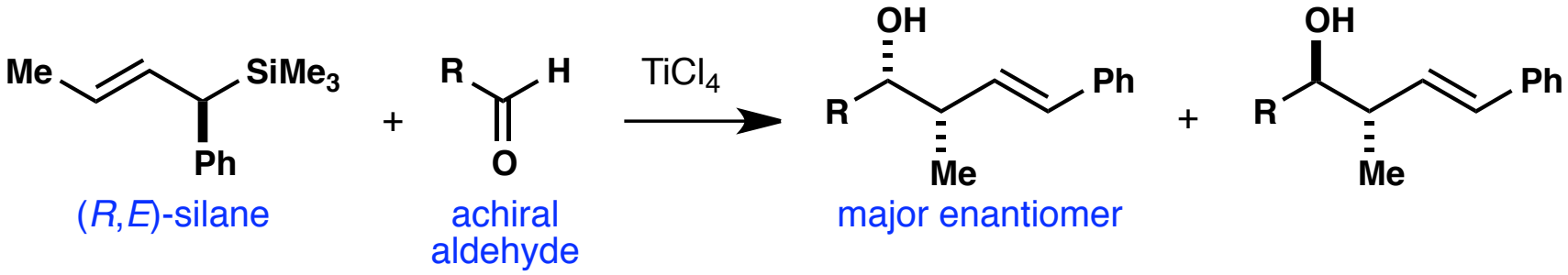
Cram chelation

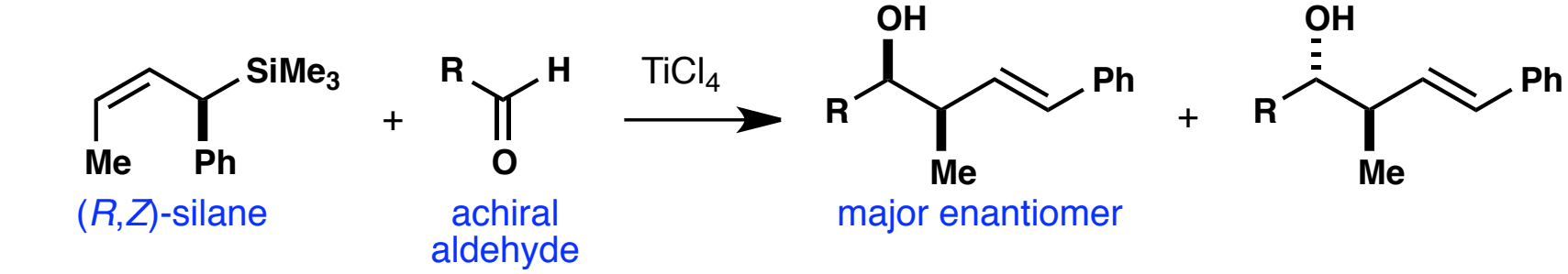


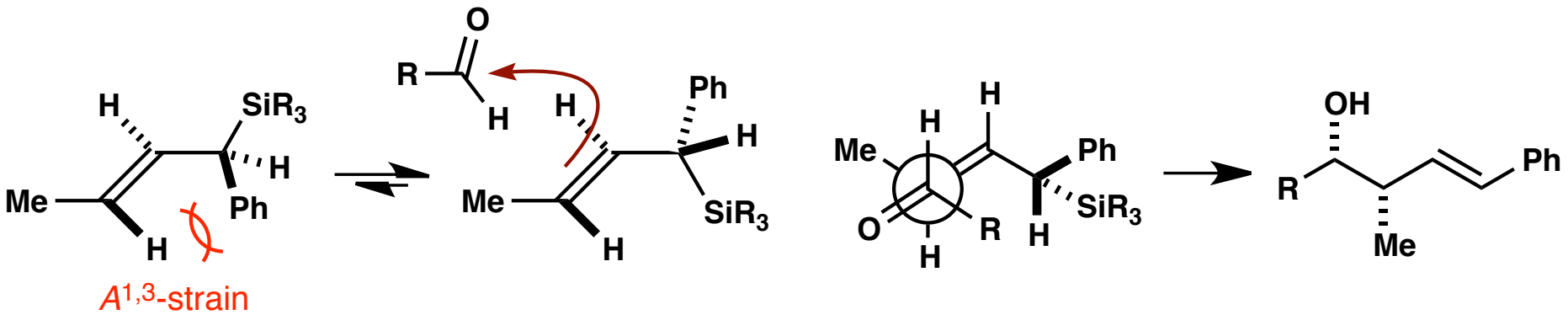
Felkin-Ahn

Chiral Allylsilanes and Allylstannanes

There are also several methods available for preparing chiral allyl silanes and stannanes. These undergo diastereoselective reactions with aldehydes. The chirality is transferred from the allylsilane/stannane to the product.



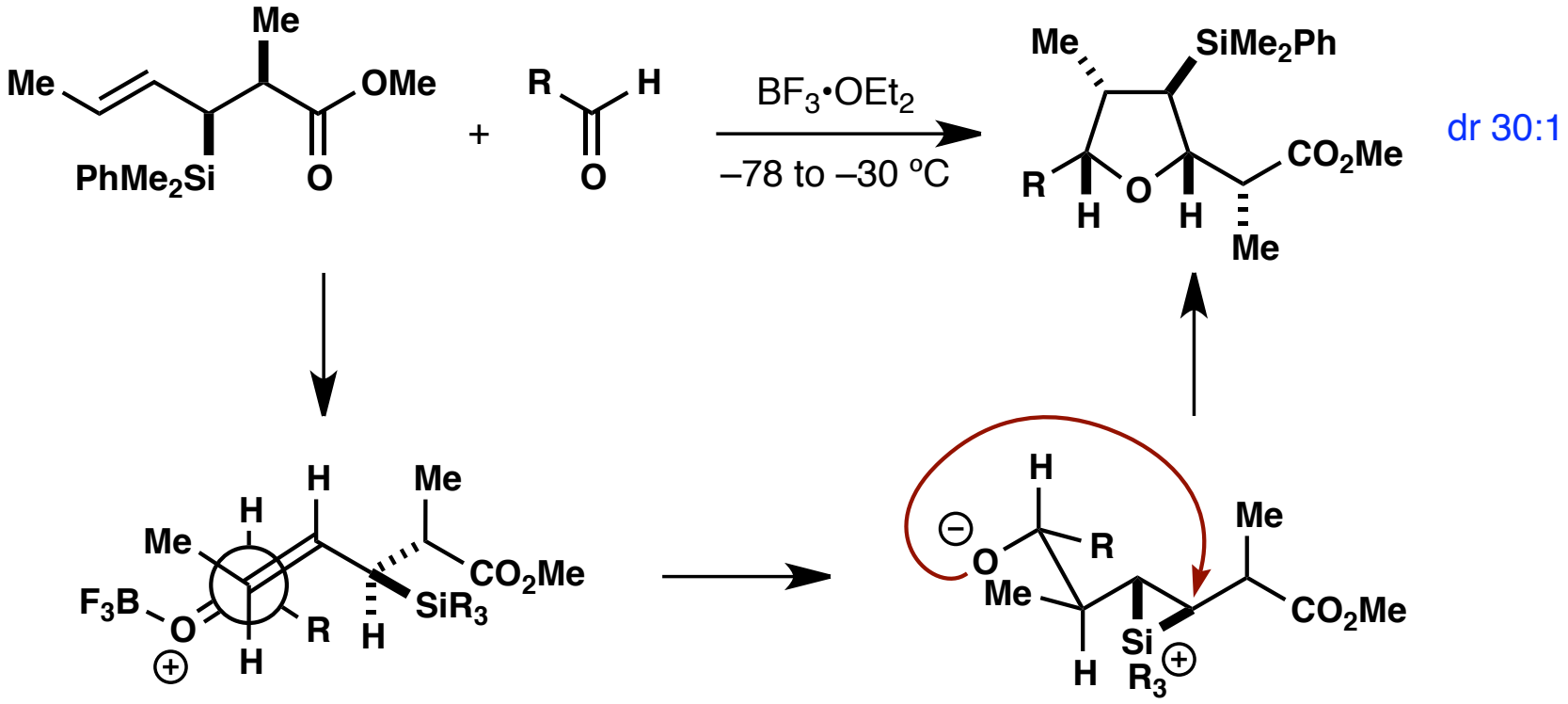




J. Am. Chem. Soc. **1982**, *104*, 4962 & 4963

Formation of Tetrahydrofuran rings

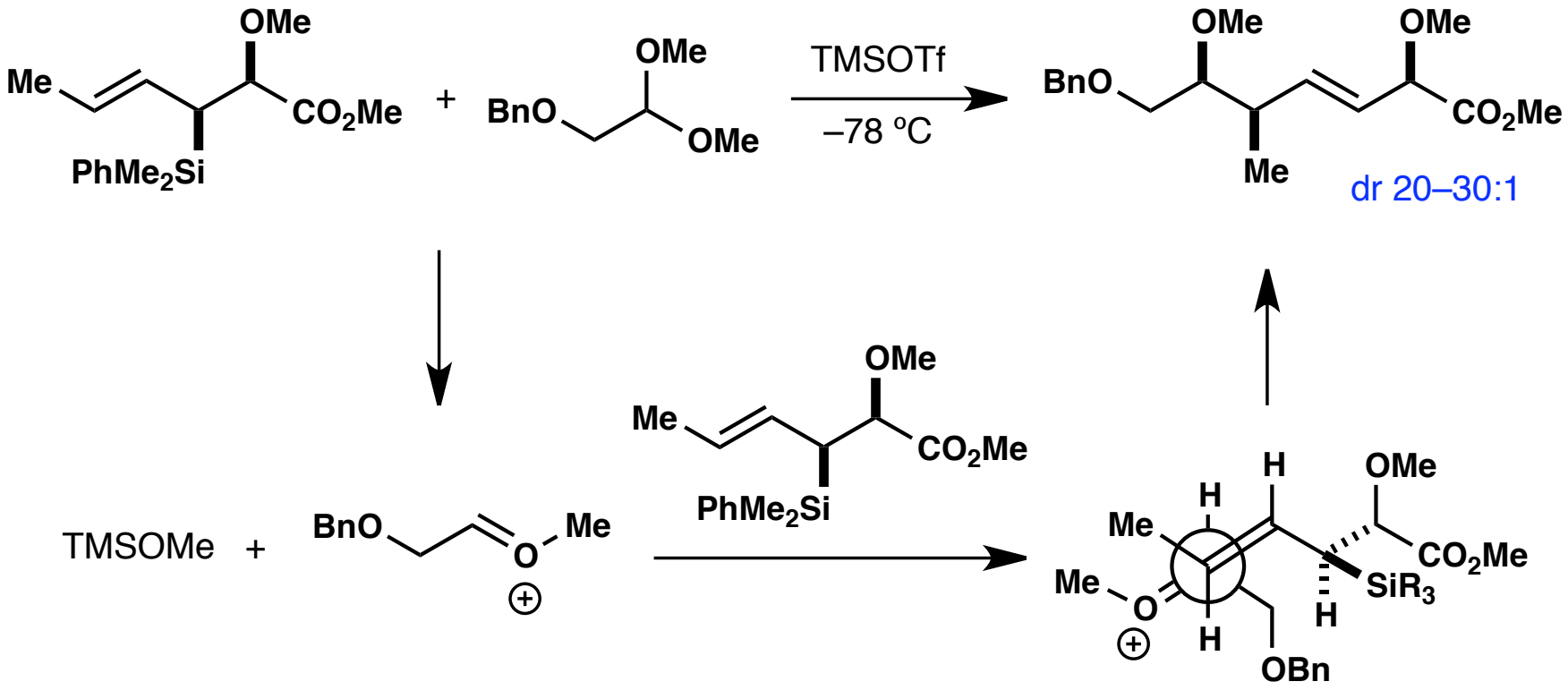
Slightly different reactivity can be achieved if dimethylphenylsilanes (Me_2SiPh, DMPS) are used. Here a 1,2-silyl shift competes with elimination.



J. Am. Chem. Soc. **1991**, *113*, 9868

Allylation of acetals

Allylsilanes can also react with acetals. Here the electrophile is an oxocarbenium ion. Using TMSOTf as the Lewis acid gives higher yields. Similar selectivities observed with other Lewis acids.

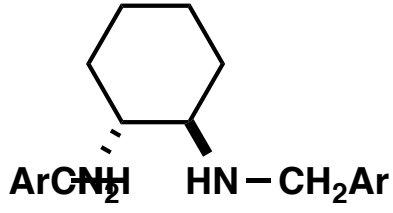


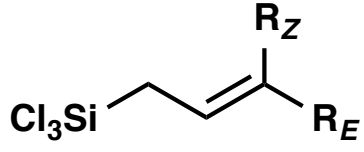
J. Am. Chem. Soc. **1991**, *113*, 6594; *J. Org. Chem.* **1991**, *56*, 5755.

Enantioselective Allylation with Allylsilanes

Jim Leighton (Columbia) has developed several chiral silicon-based reagents for enantioselective allylations of aldehydes, ketones, and imines. They likely react through a closed transition state.

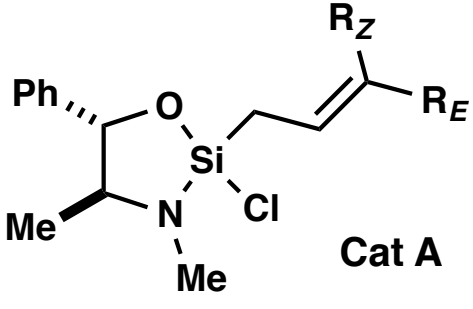
(1*S*,2*S*)-pseudoephedrine





Et_3N, CH_2Cl_2

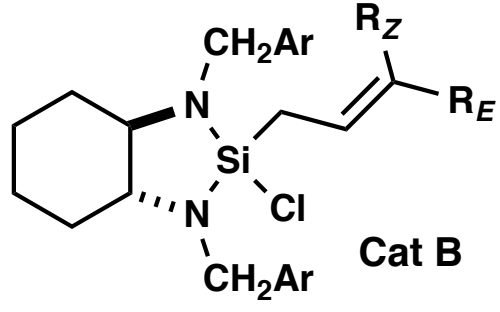
DBU, CH_2Cl_2



Cat A

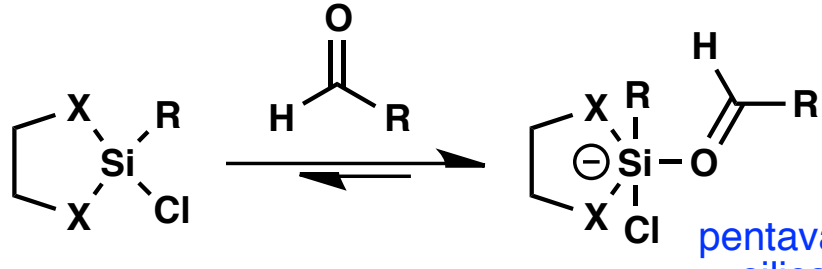
2:1 dr @ Si

Both can be prepared in high yield and purity and on large scale. The strain associated with silacycle makes the silicon atom more Lewis acidic.



Cat B

1 stereoisomer

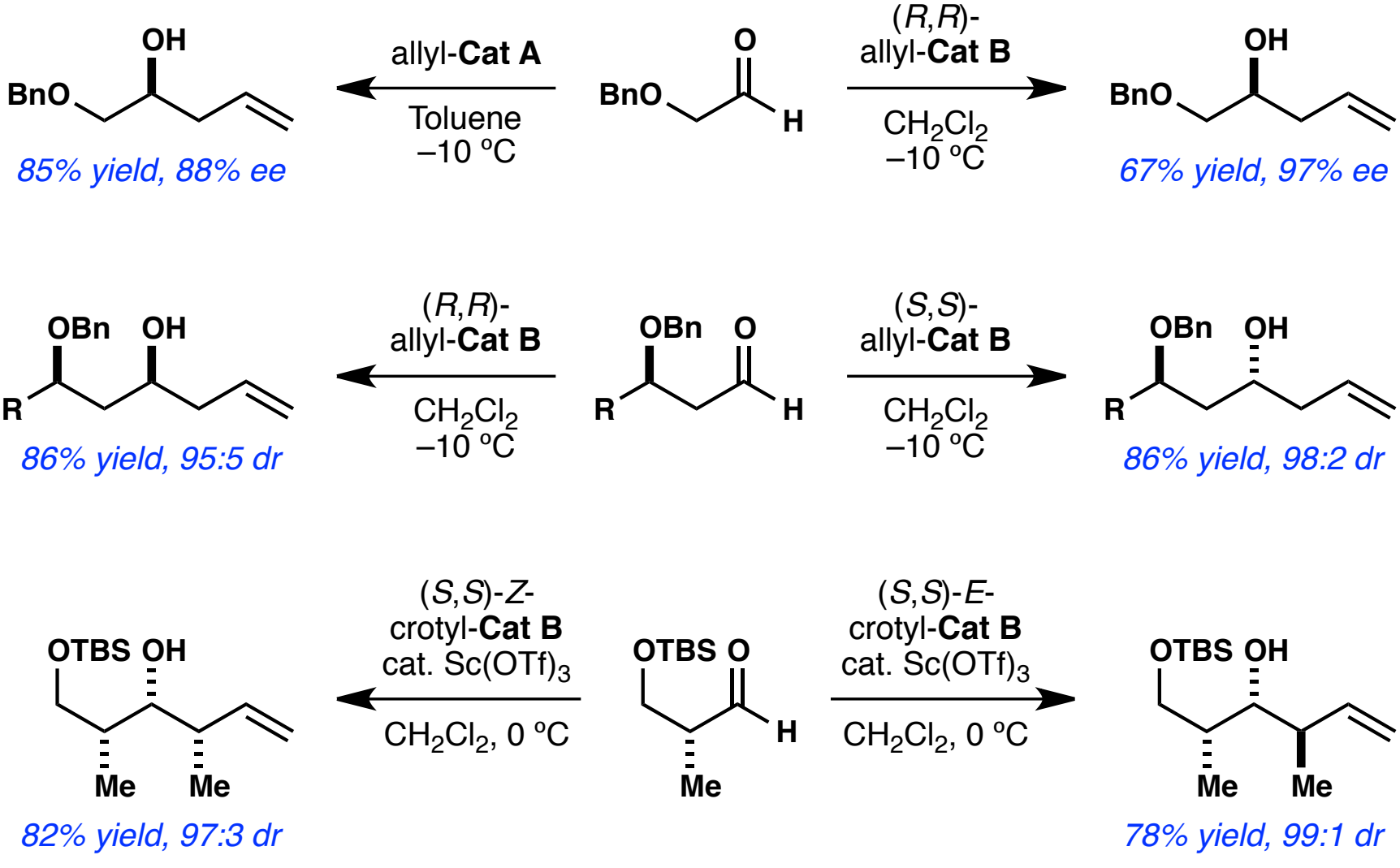


pentavalent silicate
• less strained

J. Am. Chem. Soc. **2002**, *124*, 7920; *Angew. Chem. Int. Ed.* **2003**, *42*, 946
Angew. Chem. Int. Ed. **2006**, *45*, 3811; *J. Am. Chem. Soc.* **2011**, *133*, 6517

Enantioselective Allylation with Allylsilanes

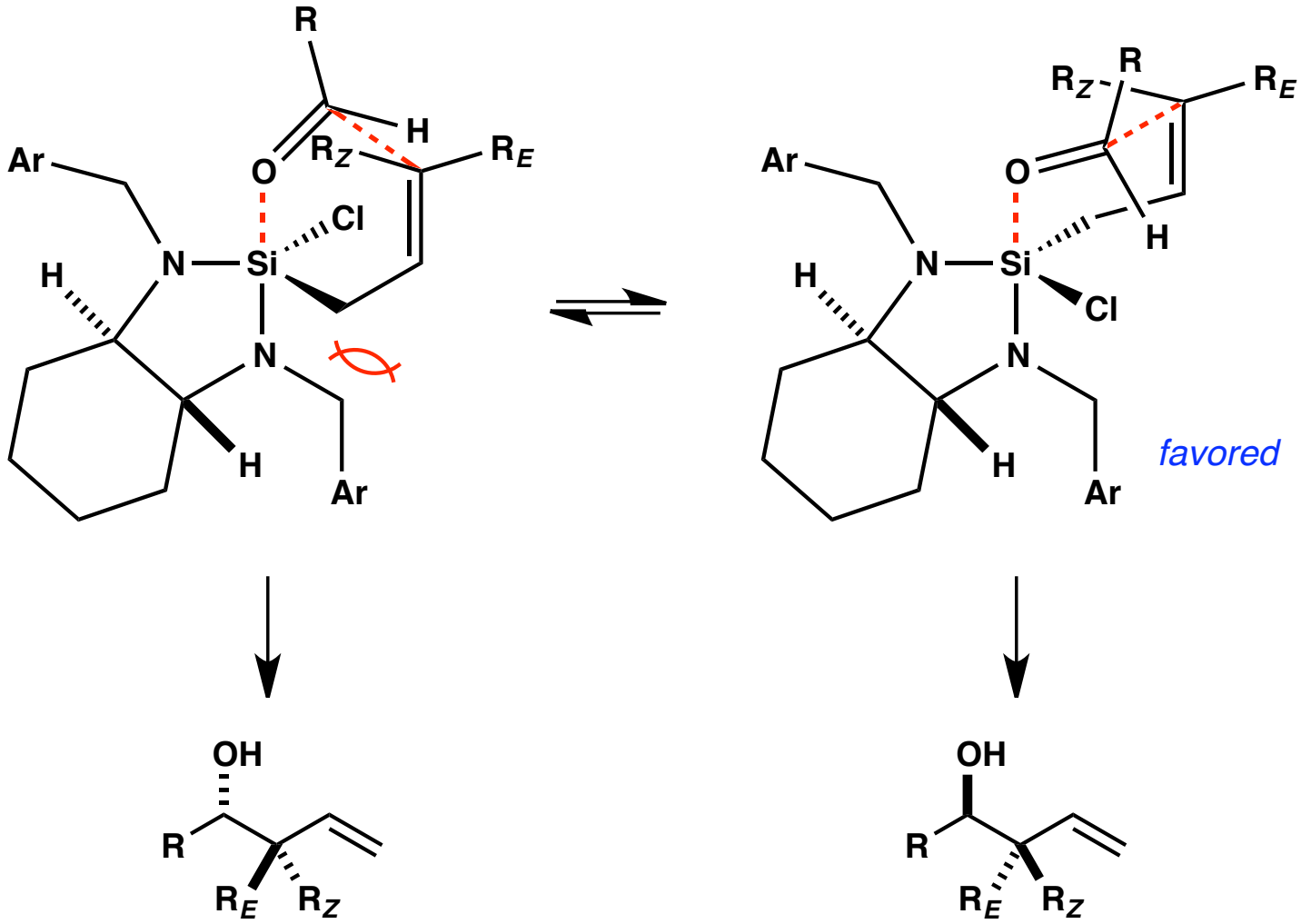
Some examples...



J. Am. Chem. Soc. **2002**, *124*, 7920; *Angew. Chem. Int. Ed.* **2003**, *42*, 946
Angew. Chem. Int. Ed. **2006**, *45*, 3811; *J. Am. Chem. Soc.* **2011**, *133*, 6517

Selectivity Model with Diamine Reagents

A similar model could be envisioned for the pseudoephedrine reagents, but is more complicated due to the stereogenic silicon and pseudorotation processes. The diamine ligand can be recovered in >90% yield after the reaction.



J. Am. Chem. Soc. **2002**, *124*, 7920; *Angew. Chem. Int. Ed.* **2003**, *42*, 946
Angew. Chem. Int. Ed. **2006**, *45*, 3811; *J. Am. Chem. Soc.* **2011**, *133*, 6517