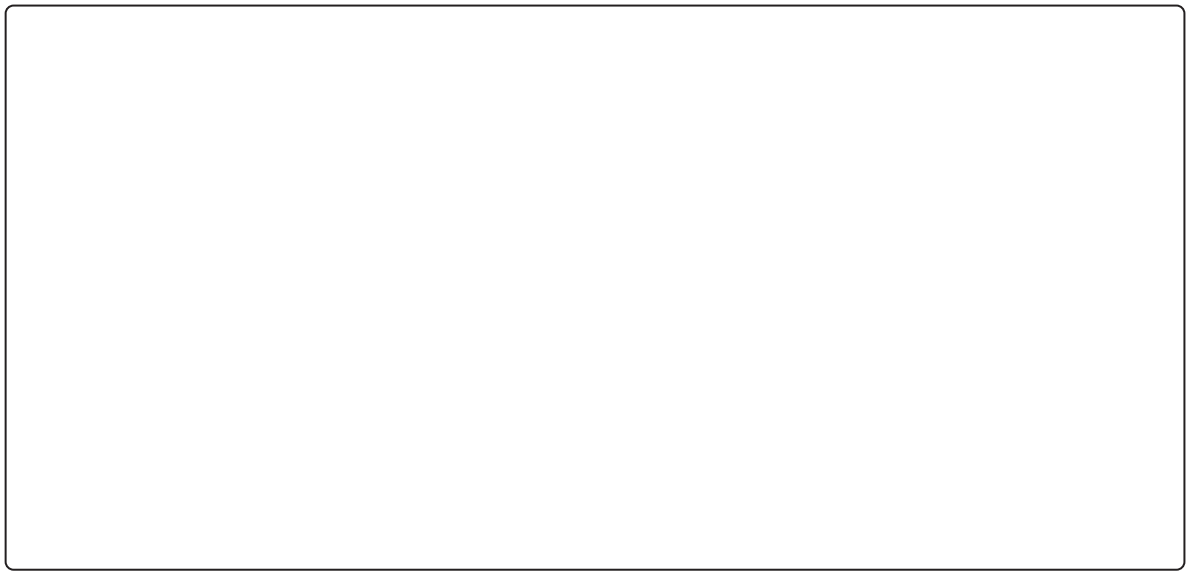
C Allylation

Objectives:

By the end of this section you will:

1) appreciate the importance of the allylation reaction in natural product synthesis;
2) be able to differentiate two major classes of allyl metal reagents;
3) be able to account for the stereospecificity of Type I allyl metal reagents;
4) use Type I allyl metal reagents in enantioselective synthesis;
5) be able to use Type II allyl metal reagents in stereoselective synthesis;
6) have gained an understanding of the complexities involved in the mechanism involving Type II allyl metals.

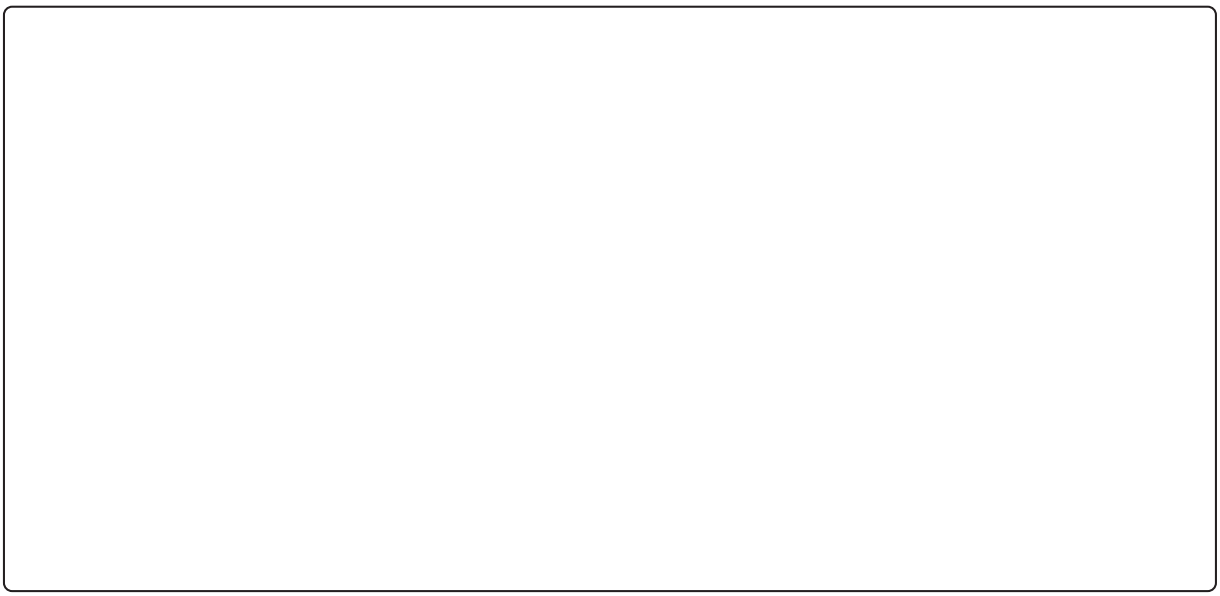
General Reaction



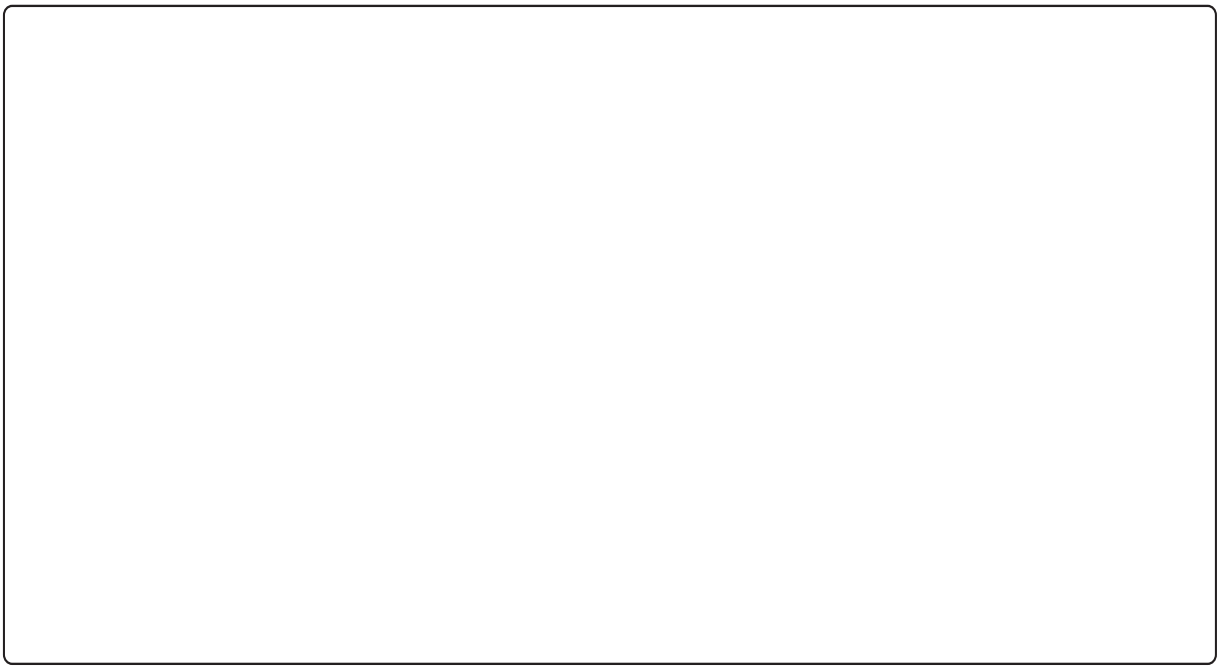
Need to address/consider a number of issues:

1. Chemoselectivity – frequently we want a selective reaction with aldehydes, leaving other functionality elsewhere in the molecule intact.
2. When $R^2 = R^3 = H$ (allyl metal), we need to consider *absolute* stereocontrol.
3. When $R^2 = H$, $R^3 = Me$ (or *vice versa*), the allyl metal is known as a **crotyl** metal. In this case we must consider not only absolute, but also *relative* stereocontrol. Crotyl metals

can react with aldehydes to produce 4 diastereoisomers (2 *syn*, 2 *anti*) assuming they react only through an S_E2' pathway.

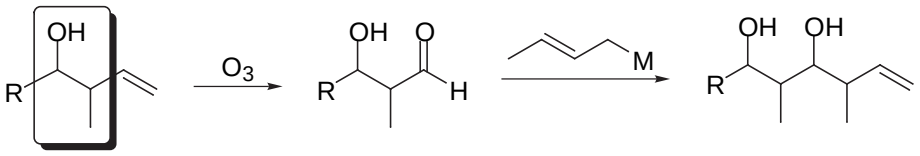


4. Allyl metals are *ambident* nucleophiles *i.e.* they can react through two different atoms. The choice of metal and reaction conditions will dictate which reaction pathway is adopted. Normally the S_E2' reaction pathway is desired.



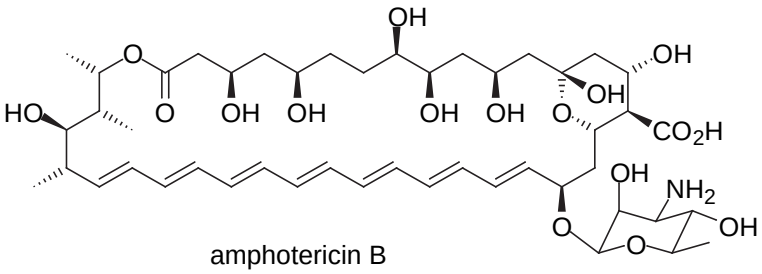
Why is the allylation reaction so important?

The reaction between an allyl metal and an aldehyde generates a motif that is widespread in numerous natural products derived from the polyketide biosynthetic pathway. An allyl reagent can function as a masked aldehyde enolate:

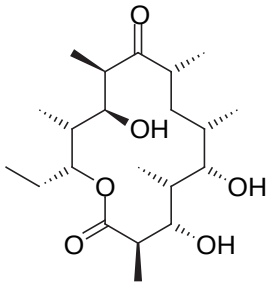


propionate

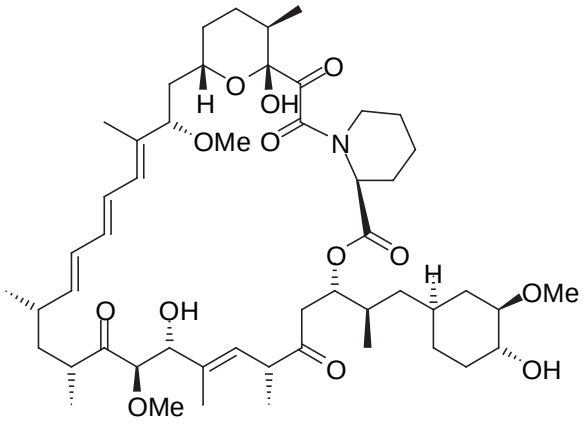
iterative assembly of polyketide natural products



amphotericin B



6-deoxyerythronolide



rapamycin

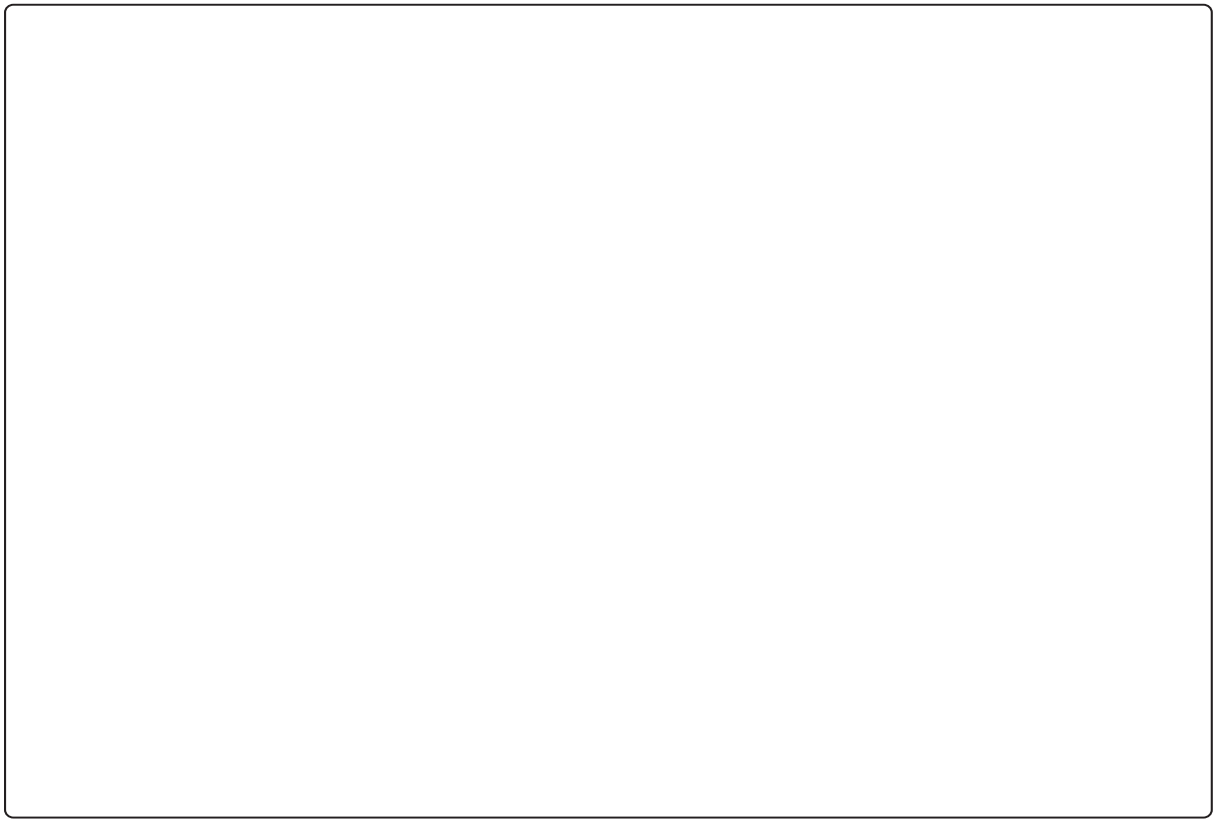
Classification of Allyl Metal reagents

Allyl reagents of most metals are known. They may be classified according to the way they react (mechanism) with aldehydes (this also depends on the precise reaction conditions *e.g.* allylstannanes can behave as Type I or Type II allyl reagents depending on the reaction conditions). Three types are distinguished; only the first two (the most widely used) will be discussed here.

C.1 Type I Allyl Metal Reagents

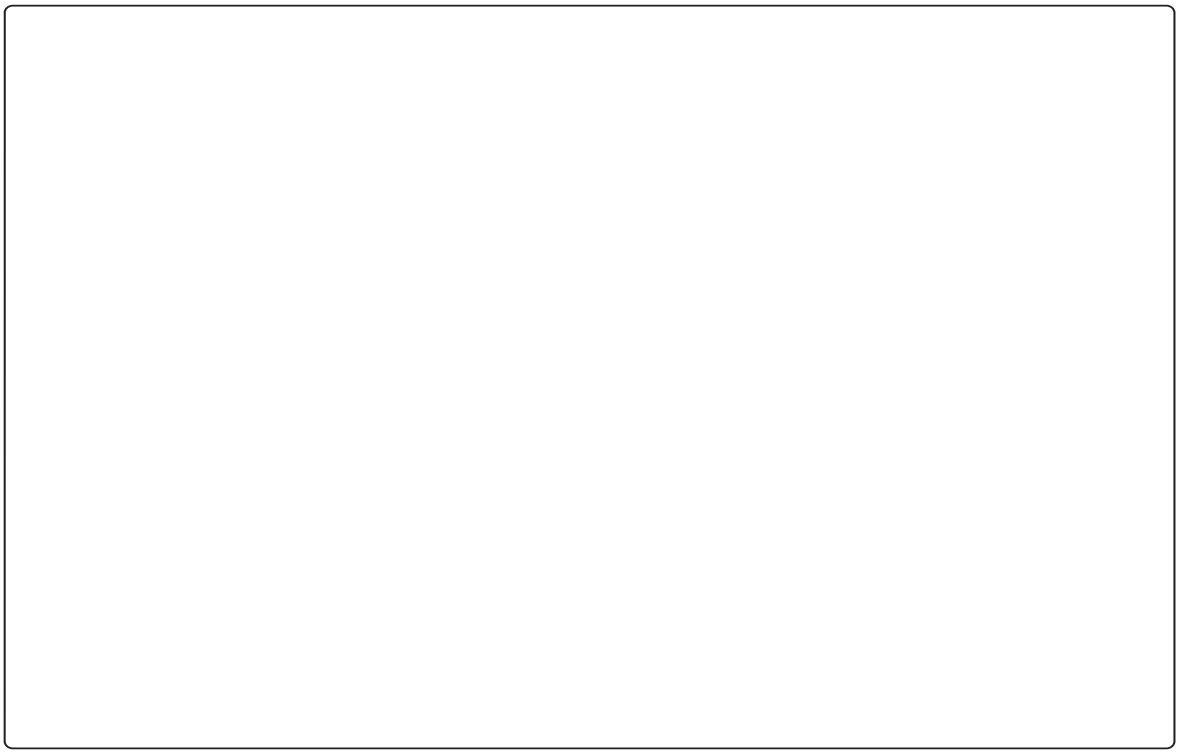
The most important Type I allyl metal reagents are **allyl boranes** and **allyl boronates**. In this class, the addition reaction is *stereospecific*; thus the (*E*)/(*Z*) ratio of the crotyl metal determines the *syn/anti* ratio of the homoallylic alcohol products.

Reaction proceeds through a CLOSED or CYCLIC (6-membered ring Zimmerman-Traxler) Transition State.



Reaction through a 6-membered cyclic chair T.S. is supported by computational studies.
Y. Li, K. N. Houk, *J. Am. Chem. Soc*., 1989, **111**, 1236-1240.

(*Z*)-crotyl boron reagents provide *syn* addition products; (*E*)-crotyl boron reagents give the corresponding *anti* addition products.

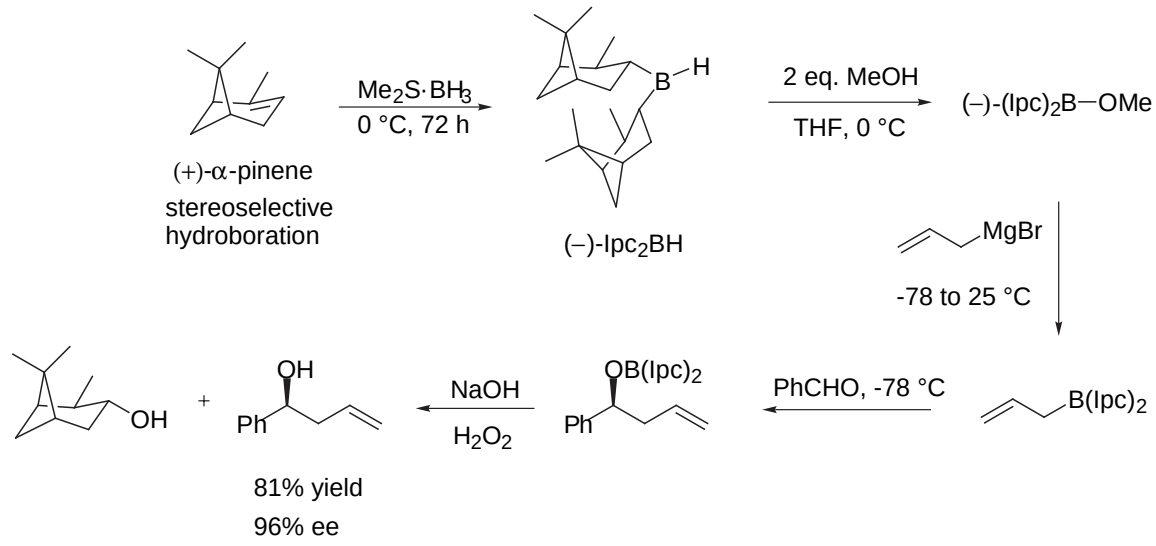


Providing the starting crotyl reagents can be prepared with high stereoselectivity (see below), then crotyl boron reagents can provide either *syn* or *anti* products by appropriate choice of the (*E*)- or (*Z*)-reagent.

Absolute Stereocontrol

A number of *chiral* allyl boranes and boronates have been prepared. Chirality is best incorporated by using chiral dummy ligands (*i.e*. ligands which aren't transferred). We will just consider the chiral allyl boranes developed by *Brown*.

Brown has developed a wide variety of chiral allyl boranes derived from naturally occurring terpenes. The most widely used reagents are those derived from α-pinene and provide some of the best enantioselectivities for allylation reactions to date.



Notes.

1. $(Ipc)_2B(OMe)$ is commercially available in both enantiomeric forms (Ipc = isopinocampheyl).

2. The allyl borane is normally prepared *in situ* and used directly, although it can be isolated.

H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.,* 1983, **105**, 2092-2093.
P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem*., 1986, **51**, 432-439.

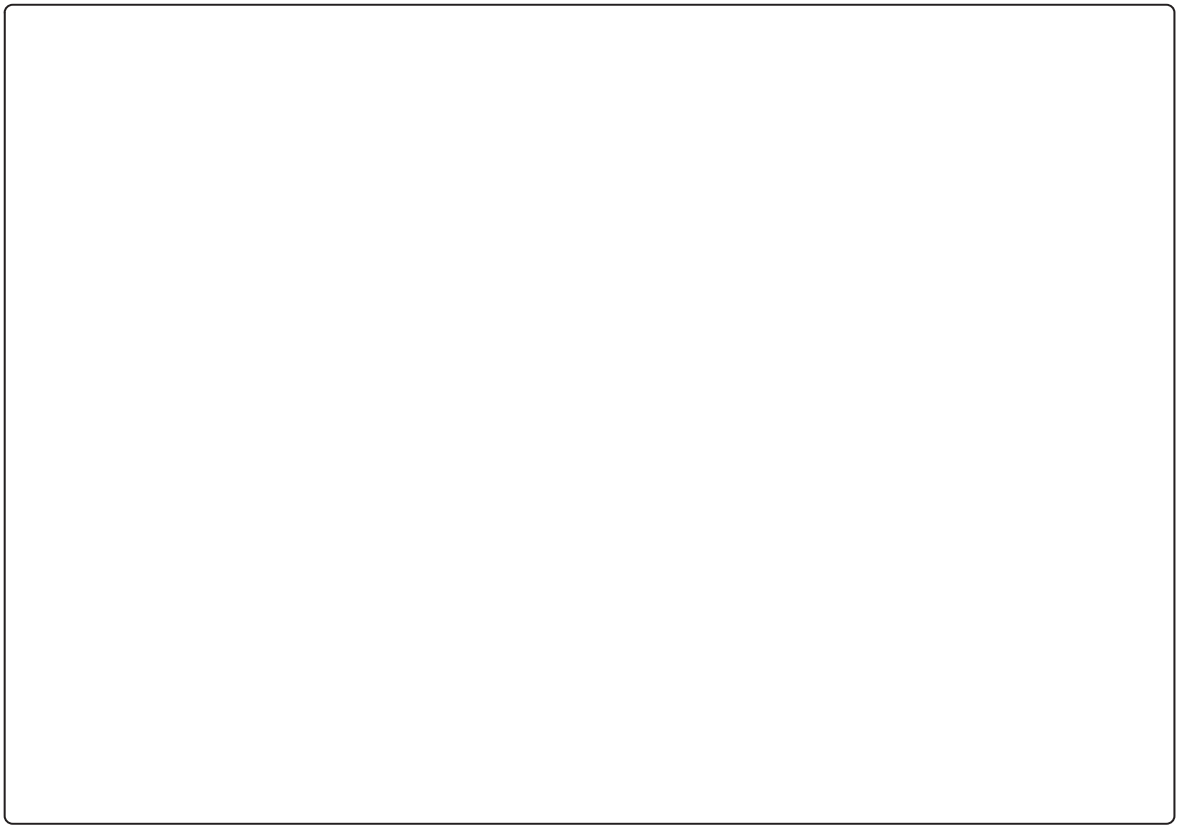
3. The enantioselectivity of the reaction tends to increase on decreasing the temperature, although at –100 °C, the reaction is quite slow. However by removing the magnesium salts (Mg(OMe)Br) from the reaction by pentane extraction, reaction at –100 °C is instantaneous!

U.S. Racherla, H. C. Brown, *J. Org. Chem*., 1991, **56**, 401-404.

4. The basic peroxide work-up destroys the auxiliary. Alternative work-up protocols have been developed which allow recycling of the chiral reagent.

H. C. Brown, U. S. Racherla, V. V. Khanna, *J. Org. Chem*., 1992, **57**, 6608-6614.

Basic peroxide method – an oxidative work-up:



cf. Baeyer-Villiger reaction. We will meet this mechanism again in the Tamao-Fleming oxidation. What about crotyl-(Ipc)boranes? The crotyl analogues of $(Ipc)_2$(allyl)B are readily prepared and undergo highly stereospecific and enantioselective addition reactions with aldehydes.

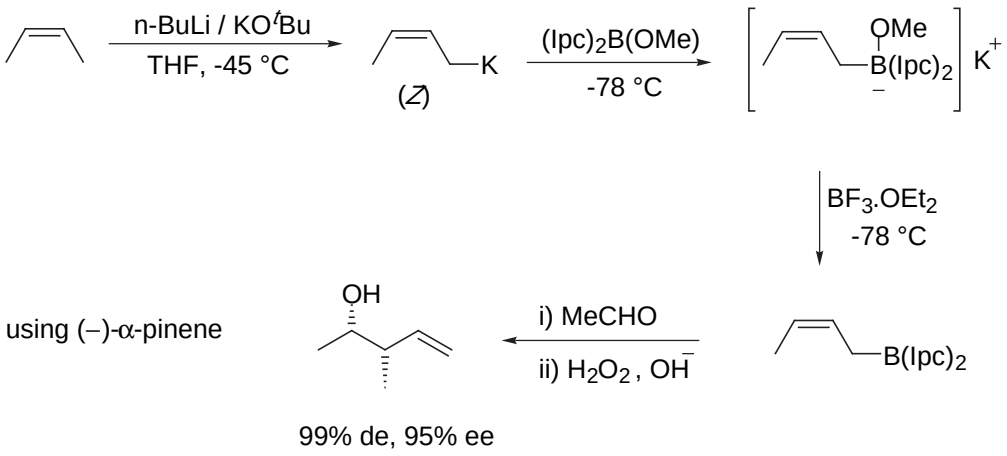
Preparation of Stereodefined Crotyl Boranes.

Use chemistry developed by Schlosser: a 1:1 mixture of n-BuLi and KO^{t}Bu forms a very basic species (its exact constitution is not well understood), which is capable of metallating relatively non-acidic sites *e.g*. the allyl position [pK_a(propene) = 35].

Schlosser has shown that low temperature metallation of (*Z*)-but-2-ene provides the (*Z*)-crotyl potassium species while (*E*)-but-2-ene generates the (*E*)-isomer. Significantly, at low temperature their interconversion is very slow.

M. Schlosser, J. Hartmann, *J. Am. Chem. Soc.* 1976, **98**, 4674-4676.

Preparation and reaction of (Z)-crotyl(Ipc)$_2$borane



99% de, 95% ee

Starting from (*E*)-but-2-ene, the *anti* product is obtained in 99% de and 95% ee. The reaction is therefore under complete **reagent control**; in other words it is the stereochemical information (chirality) contained in the reagent that controls the stereochemical outcome of the reaction.

Disadvantages of Brown's allyl reagents

1. They are very reactive, which can pose a problem with handling.
2. The alcohol by-product (oxidised auxiliary) can be difficult to separate from the desired product.
3. The crotyl reagents are not configurationally stable at room temperature.

Summary

1. Allylboranes are important allylating reagents in organic synthesis.

2. The Lewis acidic nature of tricoordinate boron ensures allylation with aldehydes and ketones proceeds through a closed, cyclic transition state. The internal coordination of boron to the carbonyl oxygen in this reaction mechanism:
   - 'intramolecularises' the allylation reaction;
   - increases the electrophilicity of the aldehyde (formally positively charged);
   - increases the nucleophilicity of the allylating reagent (formally negatively charged);
   - ensures a high degree of stereospecificity in the reaction of crotyl boranes.

3. The use of chiral ligands on the boron atom provides a method for controlling the absolute stereochemical outcome of the reaction (Brown allylation).

4. The strength of the B–O bond means that simple protolytic work-up is insufficient for releasing the alcohol product from the boron product. However, by exploiting the vacant p AO of the neutral boron species a Baeyer-Villiger-type oxidative work-up with peroxide provides a solution.