Applications of Phosphorus, Sulfur, Silicon and Boron Chemistry:

Stereo- and Regioselective Synthesis and Reactions of Alkenes

Semester 1

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3. PETERSON OLEFINATION
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6. SCHLOSSER MODIFICATION OF THE WITTIG REACTION
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18. SILYL ETHERS: HYDROXYL PROTECTING GROUPS

Suggested reading

- *Organic Chemistry*, J. Clayden, N. Greeves, S. Warren and P. Wothers, Oxford University Press. 1st Edition: Chapters 31, 46 and 47; 2nd Edition: Chapter 27 and sections of Chapters 11 and 26 (and 17 good for revision).
- *Organic Synthesis: the Roles of Boron and Silicon*, S.E. Thomas, (Oxford Primer No. 1)
- *Organosulfur Chemistry*, G.H. Whitham, (Oxford Primer No. 33)

Learning outcomes:

At the end of the course you should be able to:

1. Formulate the P, S or Si product formed from a given set of reagents (as covered in the course), e.g. synthesis of phosphonates, phosphonium salts, ylids etc.
2. Identify the alkene-forming reaction type for a given set of reagents, e.g. "Peterson olefination" or "Wittig: stabilized ylid"

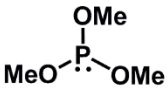
3. Work out the structure of the alkene product(s) arising from given reagents (see LO2)
4. Predict the stereochemistry of the (major) alkene product (see LO3)
5. Rationalize your deductions using a mechanistic argument (see LO3 and 4)
6. Formulate the alkyl- or alkenylborane product arising from reaction of borane, or a borane derivative, with an alkene or alkyne.
7. Formulate the product arising from oxidation, protonolysis, halogenation or amination of an alkyl- or alkenylborane.
8. Formulate the *cis* or *trans* alkene product arising from reaction of alkenylboranes *via* a boronate intermediate.
9. Predict the stereochemistry of the product(s) arising from reactions covered (see LO6, 7 and 8) using reaction mechanisms to explain the stereochemical outcome of the transformations.
10. Show how silyl ethers can be used as hydroxyl protecting groups in organic chemistry.

These notes, self-study workbook problems with answers, and sample past exam paper questions (some with solutions) are available for download at:

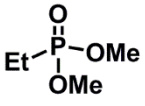
http://www.hull.ac.uk/php/chsanb/teaching.html

Some Important Sulfur and Phosphorus Functional Groups 1a

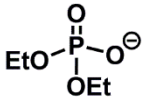
There are a plethora of functional groups in S and P chemistry. This is due to the possibility using d-orbitals for bonding and a variety of oxidation states are therefore accessible. Some of the important functional groups that will crop up in this course are shown below.



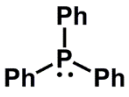
Trimethyl phosphite



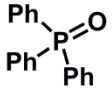
Dimethyl ethylphosphonate



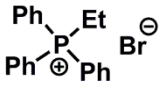
Diethyl phosphate



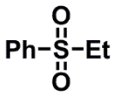
Triphenyl phosphine



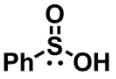
Triphenyl phosphine oxide



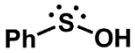
Ethyl triphenyl phosphonium bromide



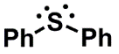
Ethyl phenyl sulfone



Benzenesulfinic acid

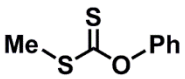


Benzenesulfenic acid



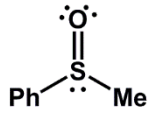
Diphenyl sulfide

Benzene thiol



S-Methyl O-phenyl xanthate

As the O(2p)-S(3d) or O(2p)-P(3d) orbital overlap is poor compared to 2p-2p overlap, as in the C=O bond, so the π-bonds are not so strong. Often S=O bonds, in sulfoxides in particular, are represented as single bonds with charge separation. These are just resonance or canonical representations of the same molecule.

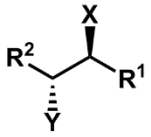
phenyl methyl sulfoxide 

Either representation is valid and both will be encountered in text books and this course

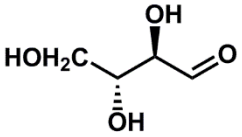
Isomeric descriptors for molecules with neighbouring stereocentres 1b

The terms *erythro* and *threo* (from the names of two isomeric sugars, erythrose and threose) are often used to describe the two diasteroisomers of a molecule with adjacent asymmetric centres.

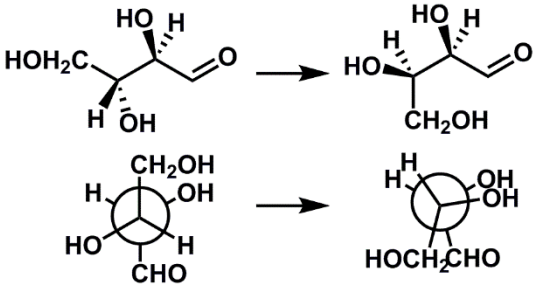
Erythrose



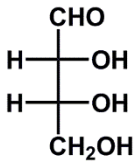
erythro isomer



anti OHs

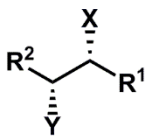


Newman projections

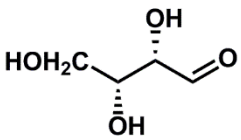


Fischer projections

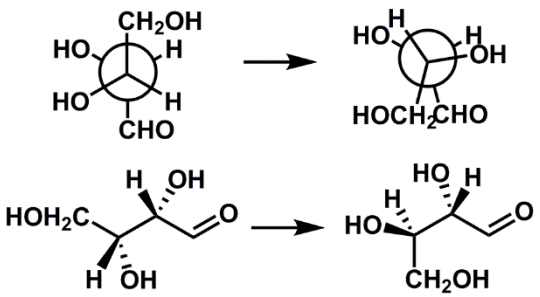
Threose

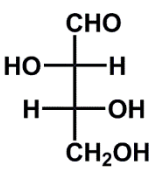


threo isomer



syn OHs



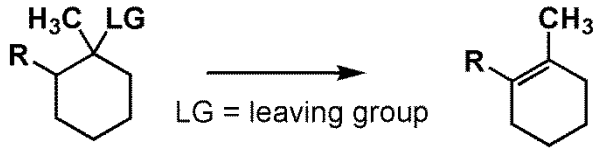


Confidence with interconverting the different projections will assist in your understanding of this course

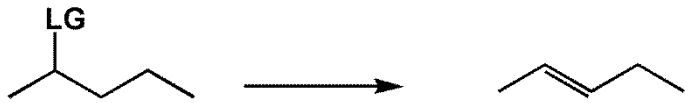
Synthesis of Alkenes

2a

Alkenes can be made *via* elimination reactions, e.g. from alcohols using acid catalysis, or from alkyl halides using a base. Such elimination reactions can lead to the new double bond being located in different positions, i.e. regio- or positional isomers may be formed. The *REGIOSELECTIVITY* of the reaction is therefore of interest.



Alkenes may be also formed as a mixture of geometric (*E/Z*) isomers. The *STEREOSELECTIVITY* of the reaction is of interest.



QUESTION: How can we make alkenes *regioselectively*?
How can we make alkenes *stereoselectively*?
Can we make them *connectively* (by joining two molecules together)?

We can using sulfur, silicon and phosphorus chemistry !

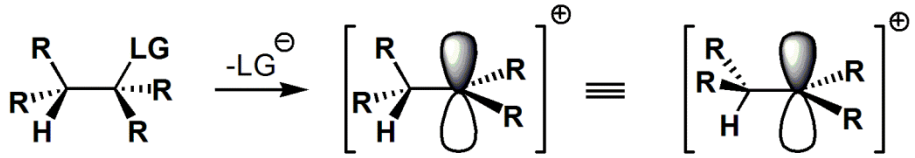
Elimination pathways

2b

Alkenes can be made *via* elimination reactions, e.g. of alcohols (using acid catalysts) or alkyl halides (using base). The two common mechanistic pathways you have encountered before are E1 and E2.

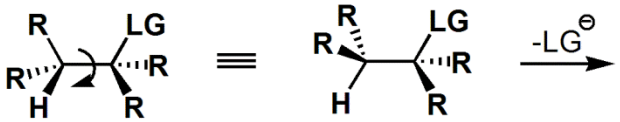
E1 - two steps > stepwise reaction, cation formation followed by loss of a proton

C-H bond must be in the same plane as the empty orbital for elimination.



associated problems > re-arrangement of the cation

E2 - one step > concerted reaction, occurs *via* the lowest energy anti periplanar (a.p.p.) conformation



an anti elimination:
H must be a.p.p. to bromide for elimination.

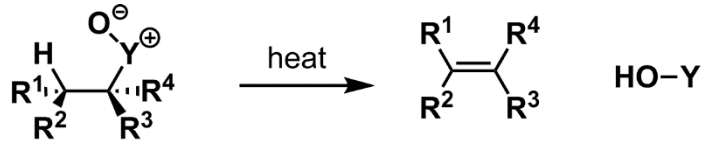
associated problems > may have competing substitution pathways if base is also nucleophilic

Syn elimination - the E*i* reaction

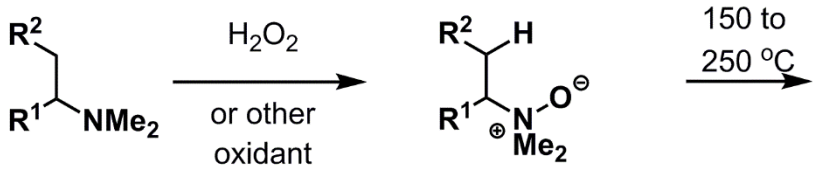
3a

Overall transformation

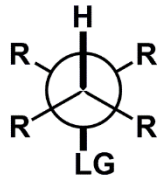
Y = NR_2
Y = SR
Y = SeR



An alternative to the E1 and E2 elimination mechanisms is the E*i* process. Here the *i* stands for intramolecular. These eliminations are thermally driven and, depending on the functional group, may need high temperatures to work. Amine oxides are examples of such a leaving group.



These reactions are stereospecific concerted processes, like the E2 mechanism, but occur from the less stable *syn* periplanar conformation. The *syn* periplanar conformation is an eclipsed (less stable) conformation and so explains the need often for higher temperatures.



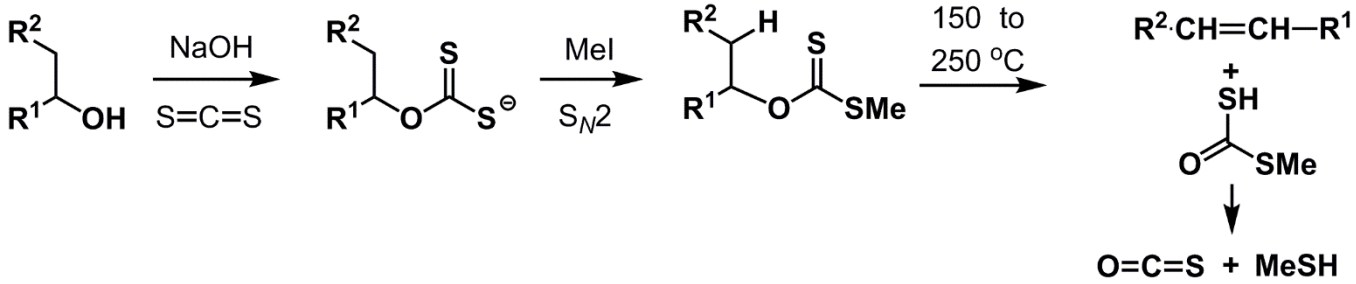
E2
H&LG are *anti periplanar*
(LG = leaving group)

Ei
H&LG are *syn periplanar*
(LG = leaving group)

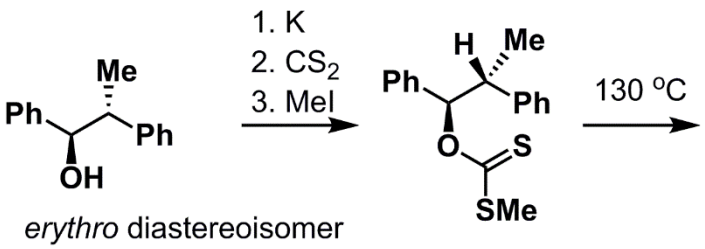
The Chugaev reaction

3b

The Chugaev (Tschugaeff or Tschugaev) reaction is a thermal *syn* elimination of a xanthate group.



Example

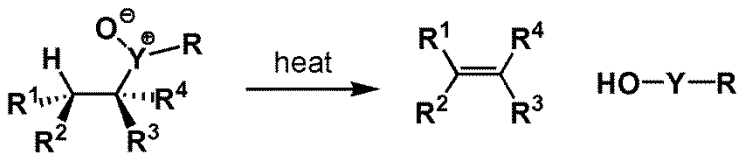


erythro diastereoisomer

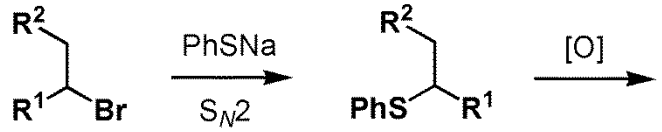
The recent development of related sulfur and selenium chemistry means that the required temperatures for elimination are lower, and in some cases only moderate warming is needed. The risk of double bond isomerisation caused by higher temperatures is therefore reduced, and means that the method is compatible with a wider range of functional groups.

Syn elimination of sulfoxides and selenoxides

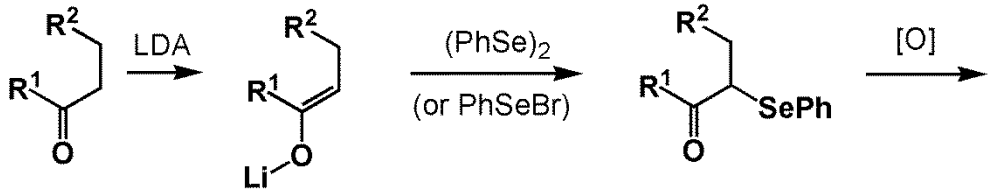
Overall transformation Y = S, Y = Se

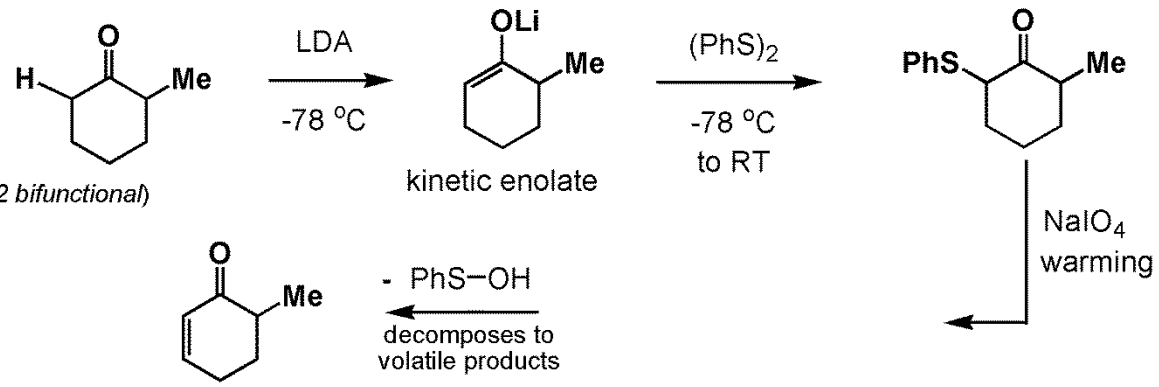


Sulfoxides, and the related selenoxides, can be prepared by a variety of methods. The thiolate and selenate ions are excellent nucleophiles and participate in S_N2 reactions. Thio and selenoethers can be then be oxidised very easily with a range of oxidants.



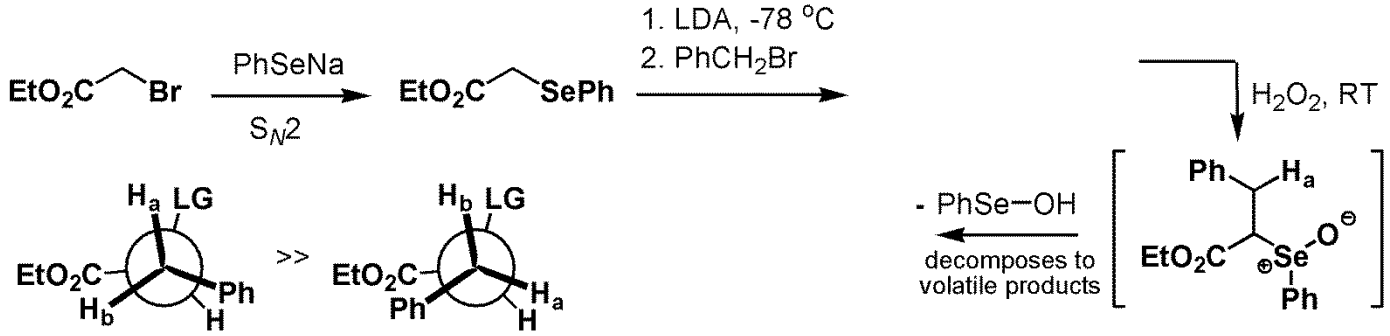
An alternative approach is by the reaction of organometallic reagents with disulfides or diselenides, with the latter acting as electrophiles.





(see Y2 bifunctional)

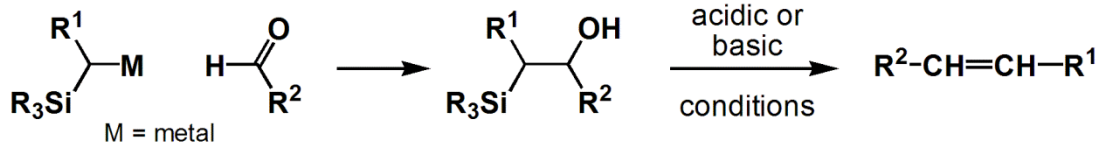
Selenoxides with a β-hydrogen are thermally unstable and readily undergo the *syn* elimination process. Usually the selenoxides are not even isolated as they spontaneously undergo the elimination at room temperature.



Where there is a choice, the thermodynamically favoured *E* alkene is formed as it comes from the more stable of the two possible *syn* periplanar conformations.

The Peterson Olefination

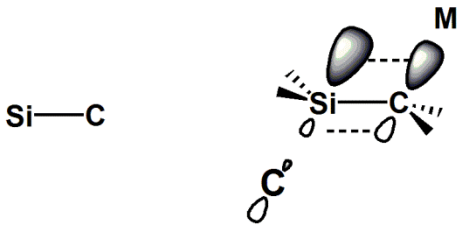
Overall transformation



The Peterson olefination was developed in the late 1960s. It involves the elimination of a β-trialkylsilyl alcohol and can be conducted under either acidic or basic conditions.

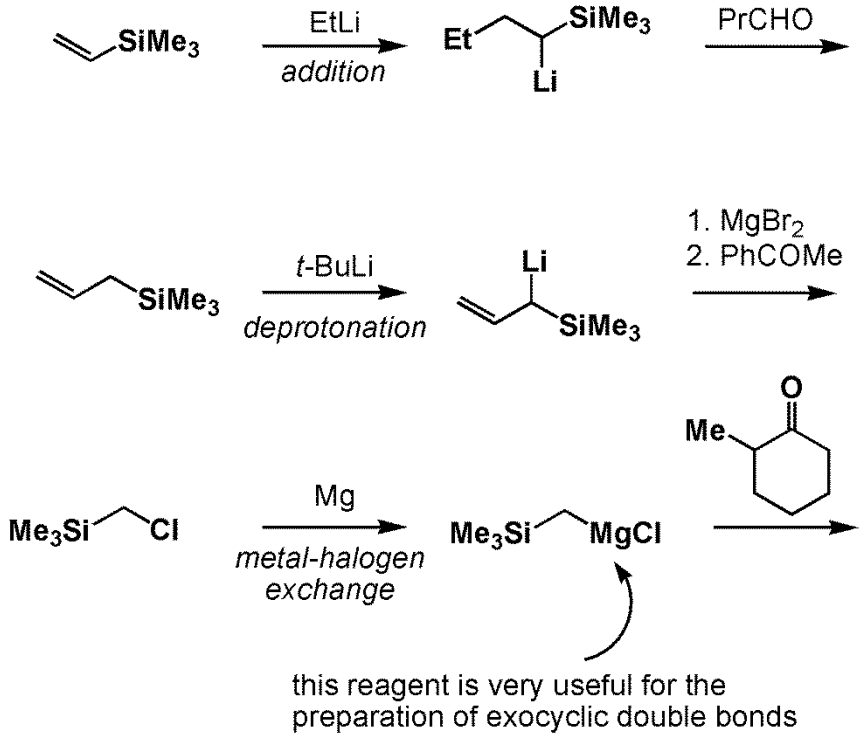
Synthesis of silyl alcohols

Silicon is much more electropositive than carbon and so the C-Si bond is polarised towards the carbon. A silyl group can be used to stabilize a carbanion α- to the silicon atom.



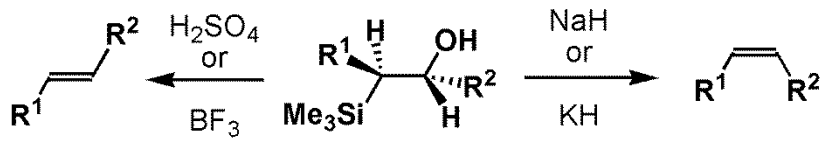
The stabilization of a negative charge α- to silicon has been attributed to contributions from the overlap of the carbon-metal σ bond with the σ* orbital of the C-Si bond, and / or overlap with a silicon *d* orbital.

As organometallic silicon reagents are readily available they can be used to generate substrates for the Peterson olefination by reaction with carbonyl-containing groups.

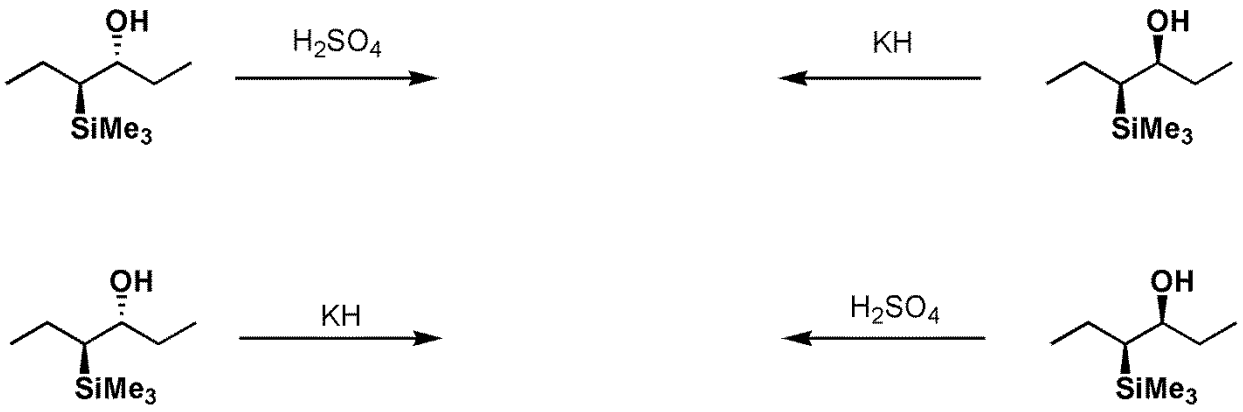


The Peterson Olefination - part 2

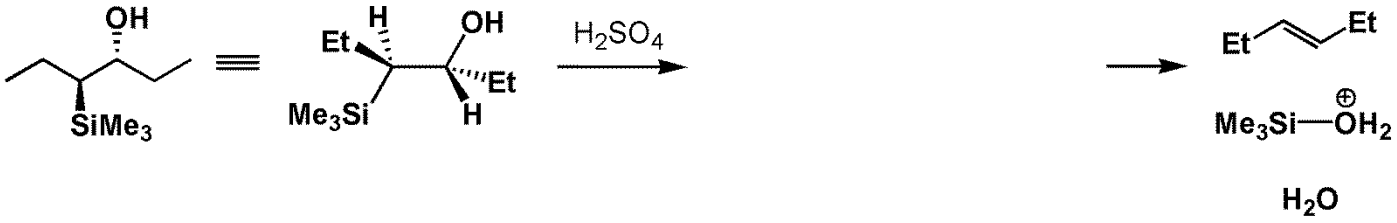
Overall transformation



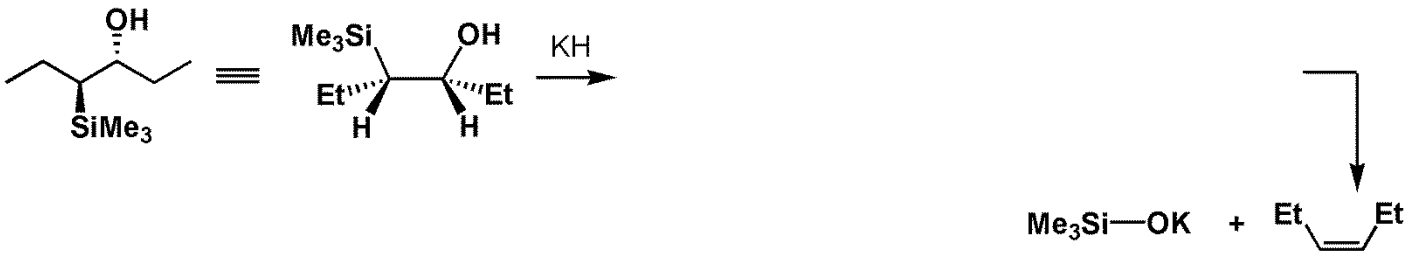
The elimination step of the Peterson reaction can be conducted under either acidic or basic conditions, and in each case the reaction is stereospecific. Thus a single diasteroisomer of the starting β-hydroxysilane gives a single isomer of the alkene.



Mechanism - acidic conditions



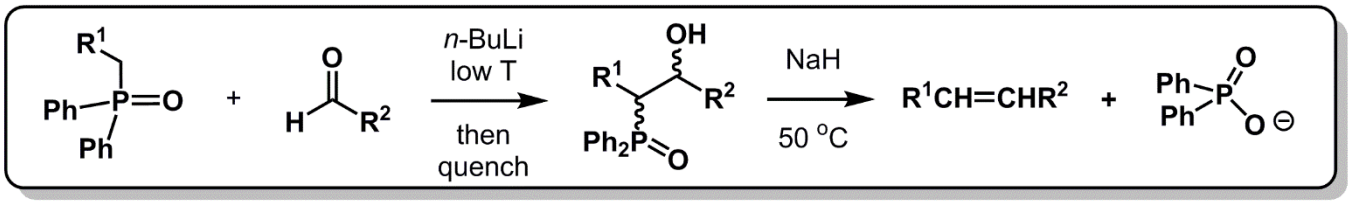
Mechanism - basic conditions



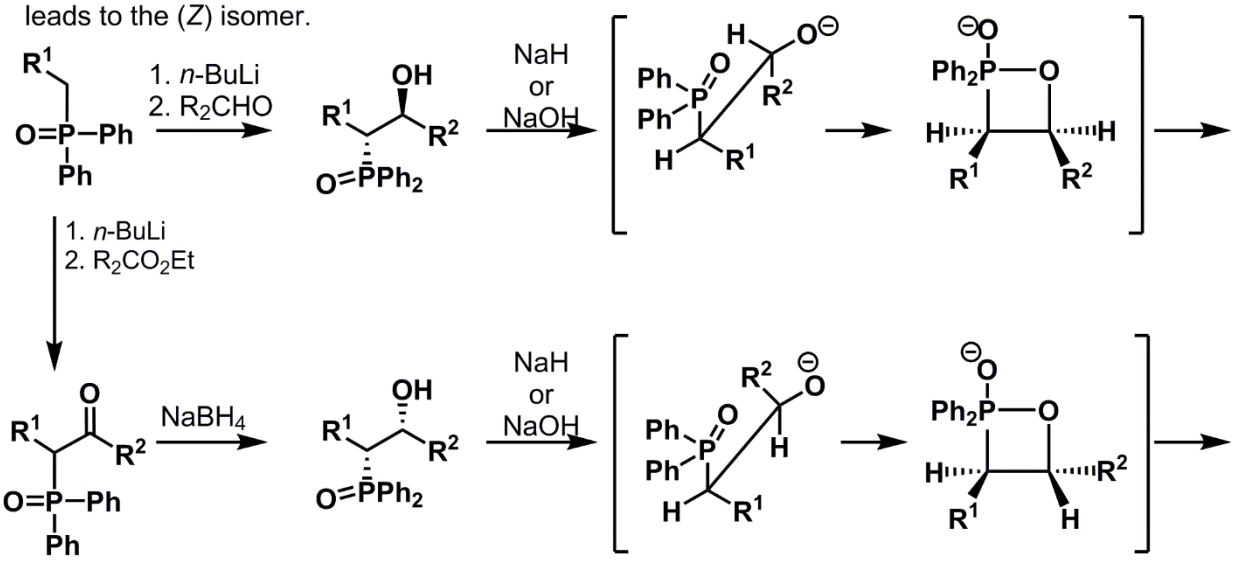
Thus it is the diasteroselectivity in the synthesis of the β-hydroxysilane which ultimately controls the *E*/*Z* ratio of the alkene. However if these diasteroisomers can be separated before the elimination then the alkenes can be produced as single isomers. Under acidic conditions. H^+ catalysed isomerisation of the double bond may also be a problem with certain substrates, and so a base-catalyzed route is preferred in these cases.

The Horner-Wittig Reaction

7a



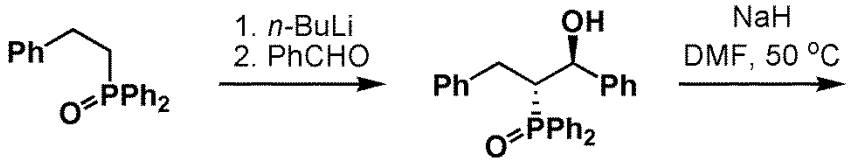
The Horner-Wittig reaction uses phosphoryl-stabilized anions to generate β-oxy phosphine oxides by condensation with aldehydes. If the alcohol is isolated, and diastereoisomers are separated, a stereospecific elimination can be triggered using base at higher temperatures (developed by Warren in the 1980s). As with the conceptually-related Peterson reaction, the *threo* diastereoisomer leads to the (*E*) alkene and the *erythro* leads to the (*Z*) isomer.

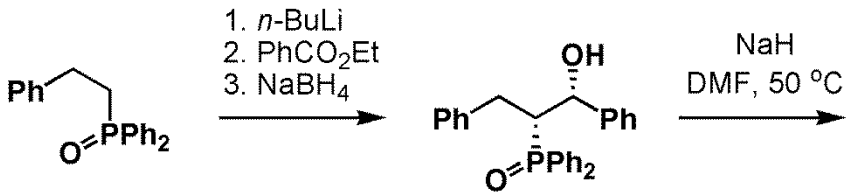


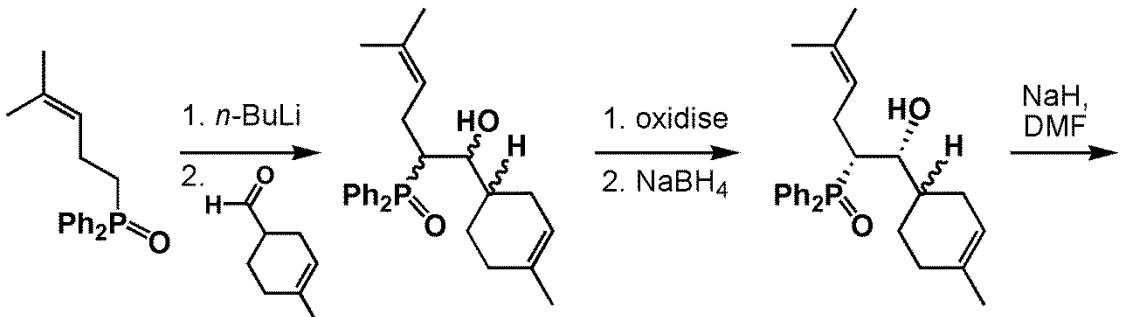
7b

In almost all cases a mixture of diasteroisomers of the β-hydroxy phosphine oxides are obtained. Synthesis of (*Z*) alkenes *via* selective synthesis of the *erythro* isomer is difficult if the aldehyde or phosphine oxide is branched α- to the reaction centres. In these cases a route *via* acylation and reduction using "Luche conditions" ($NaBH_4$, $CeCl_3$) is better.

Examples





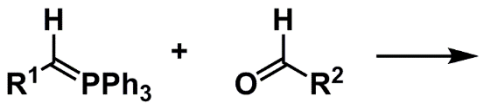


mixture of isomers
(3 stereocentres)

75% yield of *threo* isomer
after purification

The Wittig reaction

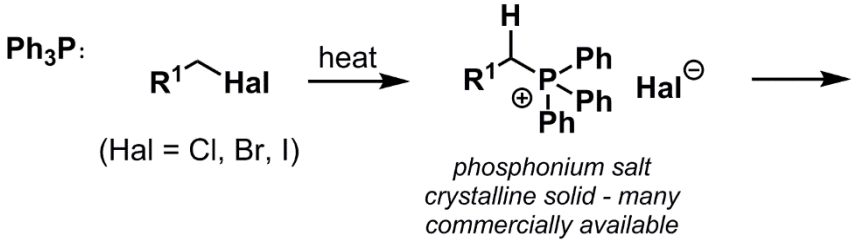
Overall transformation



(*Z*) : (*E*) ratio depends on R^1, R^2 and the conditions.

The Wittig reaction was developed in the 1950s by Georg Wittig (Nobel Prize in 1979). It is a connective method used to make di- and tri-substituted alkenes stereoselectively from a phosphorous ylid (ylide) and an aldehyde or ketone. The stereoselectivity is subject to both substrate structure and metal (M+) counterion effects. The driving force of the reaction is attributed to the formation of the strong P=O bond in the by-product, which is a phosphine oxide.

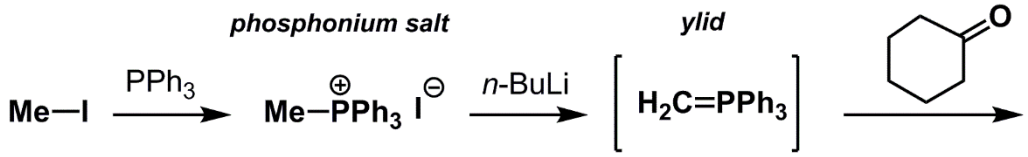
Preparation of phosphorus ylids

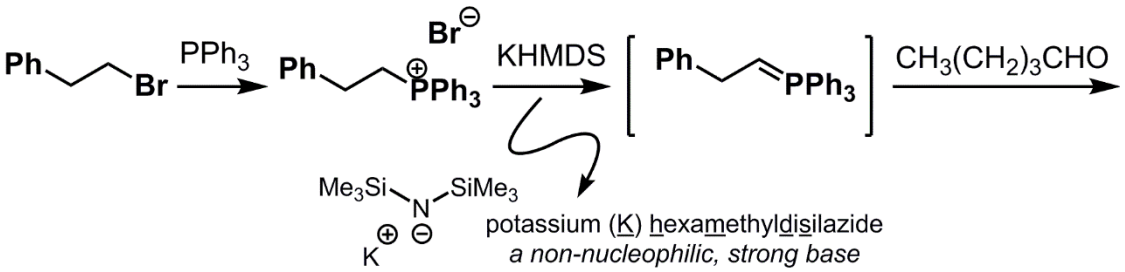


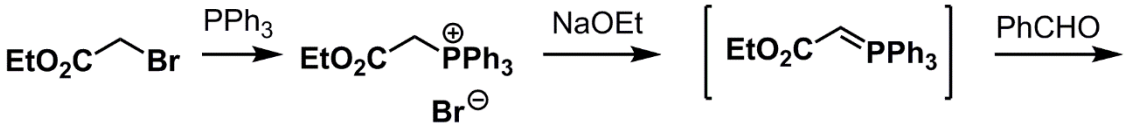
The phosphorus ylids are most commonly derived from triphenylphosphine. This is a good nucleophile which reacts with a primary alkyl halide to make a phosphonium salt. Yields are often poor with secondary halides. Deprotonation of this salt $\alpha-$ to the charged P atom then forms the ylid.

If the R^1 group is an electron withdrawing, e.g. CO_2Et , then a so-called "stabilized ylid" is formed. If R^1 is a simple aliphatic group then an "unstabilized ylid" is formed. The reaction outcome is different for these two cases where, in general, *E*-alkenes are formed from stabilized ylids, and Z-alkenes from unstabilized ylids.

Examples of the Wittig reaction

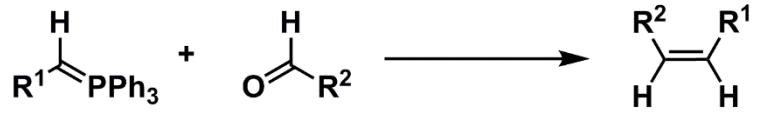






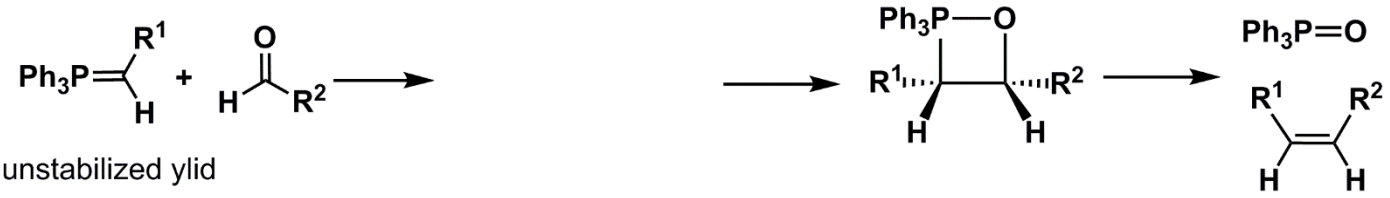
The Wittig reaction - unstabilized ylids

Overall transformation



Mechanism of the Wittig reaction.
Explanation for the Z-selectivity with unstabilized ylids

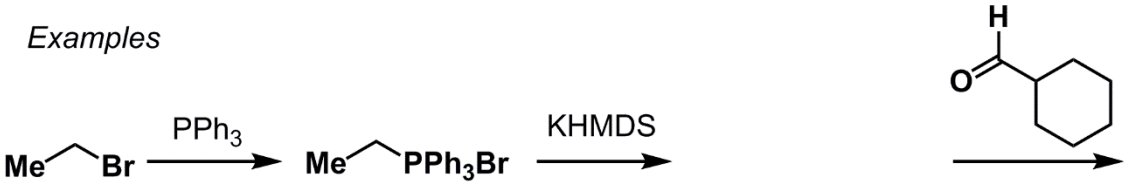
The stereoselectivity of the Wittig reaction with different ylids has been the subject of controversy over years. To explain this we need to consider possible intermediates in the reaction.



unstabilized ylid

Under Li^+ free conditions, the reaction is now believed to proceed under kinetic control *via* irreversible formation of the four-membered oxaphosphetane intermediate. Consideration of the symmetry of the orbitals concerned predicts that the two double bonds approach at an angle, with the bulky R groups kept apart. This leads to the *syn* oxaphosphetane which then decomposes to the observed *Z* alkene in a process analogous to the Peterson reaction under basic conditions.

Examples

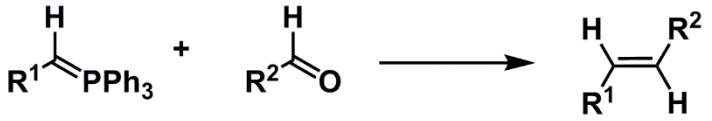


With ketones the *Z* selectivity may be reduced, as the lowest energy transition state in forming the oxaphosphetane is less clear cut. Nevertheless there are some apparently anomalous reactions where the *Z* selectivity can be high, such as with α-alkoxy ketones. Selectivity may also be different when the phosphorus atom has one or more alkyl groups in place of the phenyl substituents.

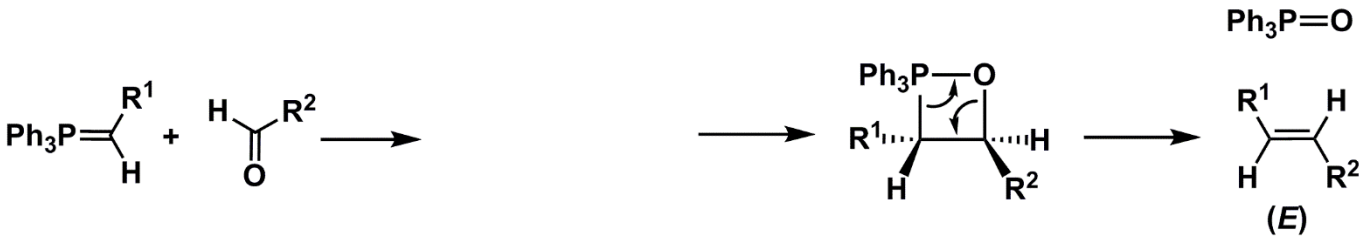
reaction with ketones

The Wittig reaction - stabilized ylids

Overall transformation



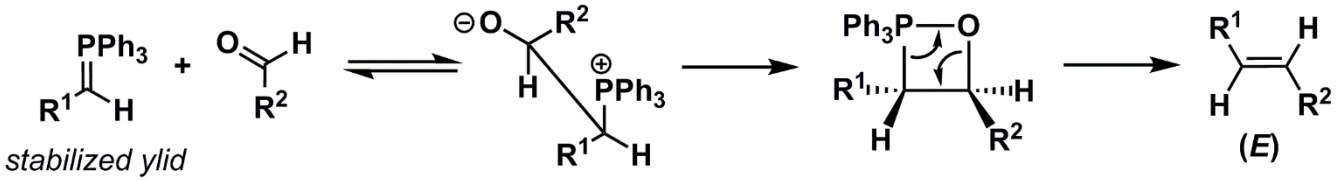
The mechanism for (*E*)-selective formation of alkenes from stabilized ylids has undergone revision in the last ten years or so. Previously, the selectivity was explained by reversible addition of the ylid to the aldehyde forming an intermediate called a betaine (see later). This mechanism is stIll common in many older text books.



It is now believed that the formation of the oxaphosphetane from a stabilized ylid is also concerted ***under lithium free conditions***, as with an unstabilized ylid, but that the reactants are aligned so as to oppose the dipole moments of the C-O and C-R^1 bonds (remember that R^1 is electron withdrawing). Whether the C-C and P-O bond formations are asynchronous or not, this mechanism, backed up by computational studies, can account for the anomalies seen in certain cases, as well as when phosphines other than triphenylphosphine are used.

The Wittig reaction - betaines and the effect of $Li^{\oplus}$

On reaction of an ylid with an aldehyde, if the C-C bond forms first then a betaine (a neutral, but charged separated species) would be created as the first intermediate. Originally it was thought that betaine formation was reversible with stabilized ylids, and so the *threo* and *erythro* diastereoisomers could equilibrate to form a thermodynamically controlled isomer mixture leading to the (*E*)-alkene *via* the *trans* oxaphosphetane.

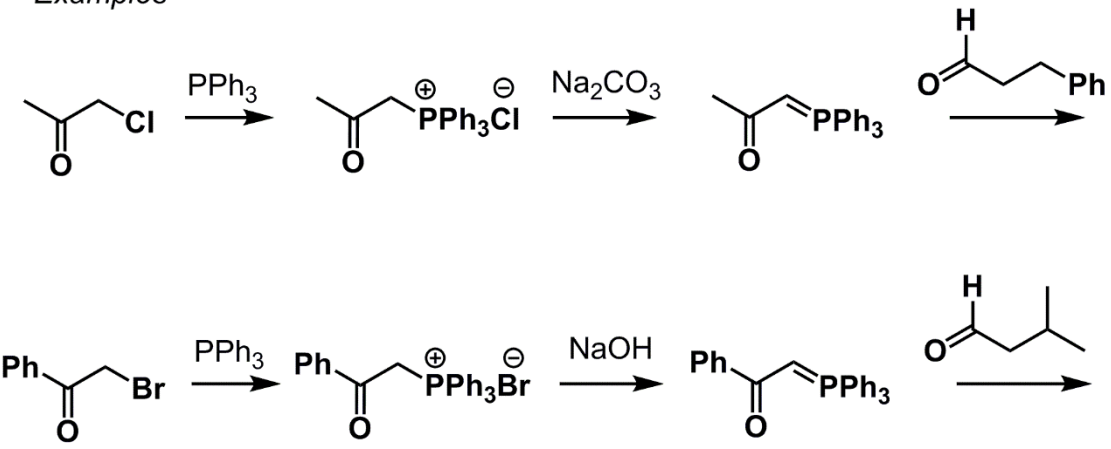


Calculations have indicated that betaines are too high in energy to be significant in the mechanism of a *normal* Wittig reaction, but they may be generated by alternative routes (e.g. deprotonation of the corresponding alcohol). From these studies it was found that there is no evidence that betaines can equilibrate between *threo* and *erythro* forms *via* the ylid.

However, what is clear from experimental evidence is that the presence of lithium ions (commonly originating from bases such as *n*-BuLi or LDA [lithium diisopropylamide]) have a significant effect on the stereoselectivity of the reaction. Lithium salts are more soluble in organic solvents, and may possibly assist in soulbilizing betaine-like salts (as above). The effects of Li+ ions on the stereoselectivity of the reaction are still not fully understood.

The Wittig reaction - stabilized ylids (cont.)

Examples

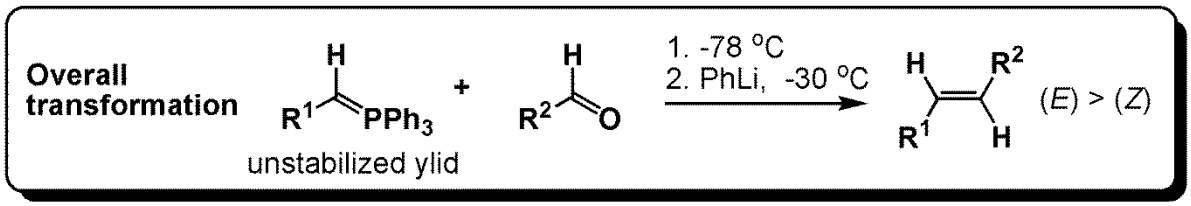


Wittig reaction summary. Irrespective of the detail of the debate surrounding the mechanism, it is generally safe to assume that:

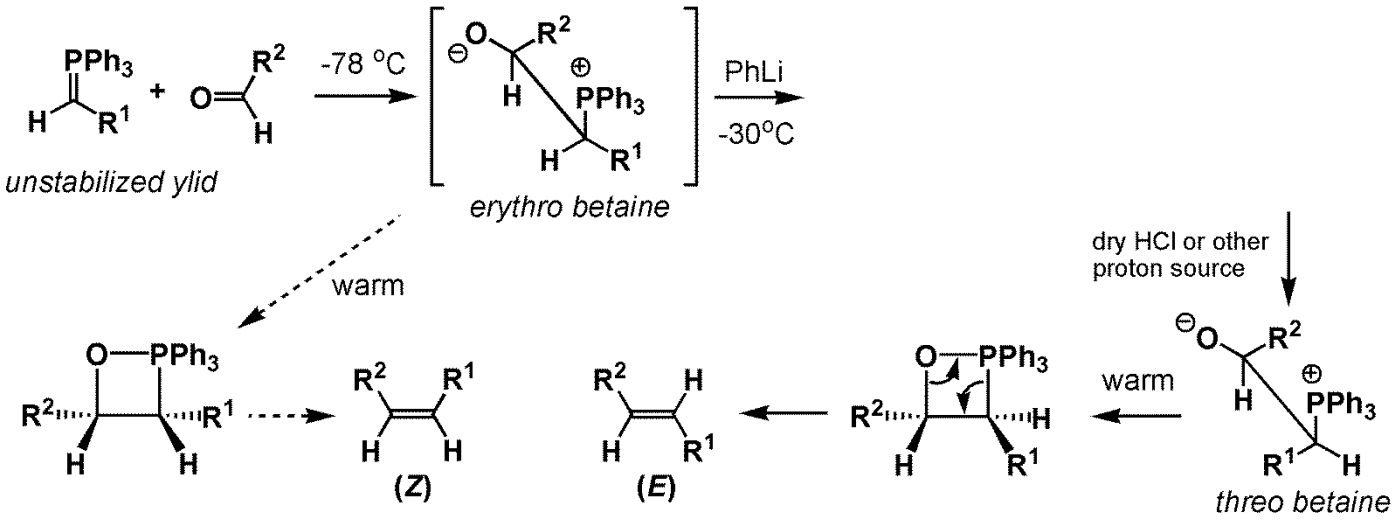
1. with unstabilized ylids, the (*Z*) isomer is the major isomer
2. with stabilized ylids, the (*E*) isomer is the major isomer
3. the presence of lithium ions will affect the stereoselectivity of the reaction

NB using a phosphine other than PPh_3 may well change the stereoselectivity of a reaction too.

The Wittig reaction - The Schlosser modification

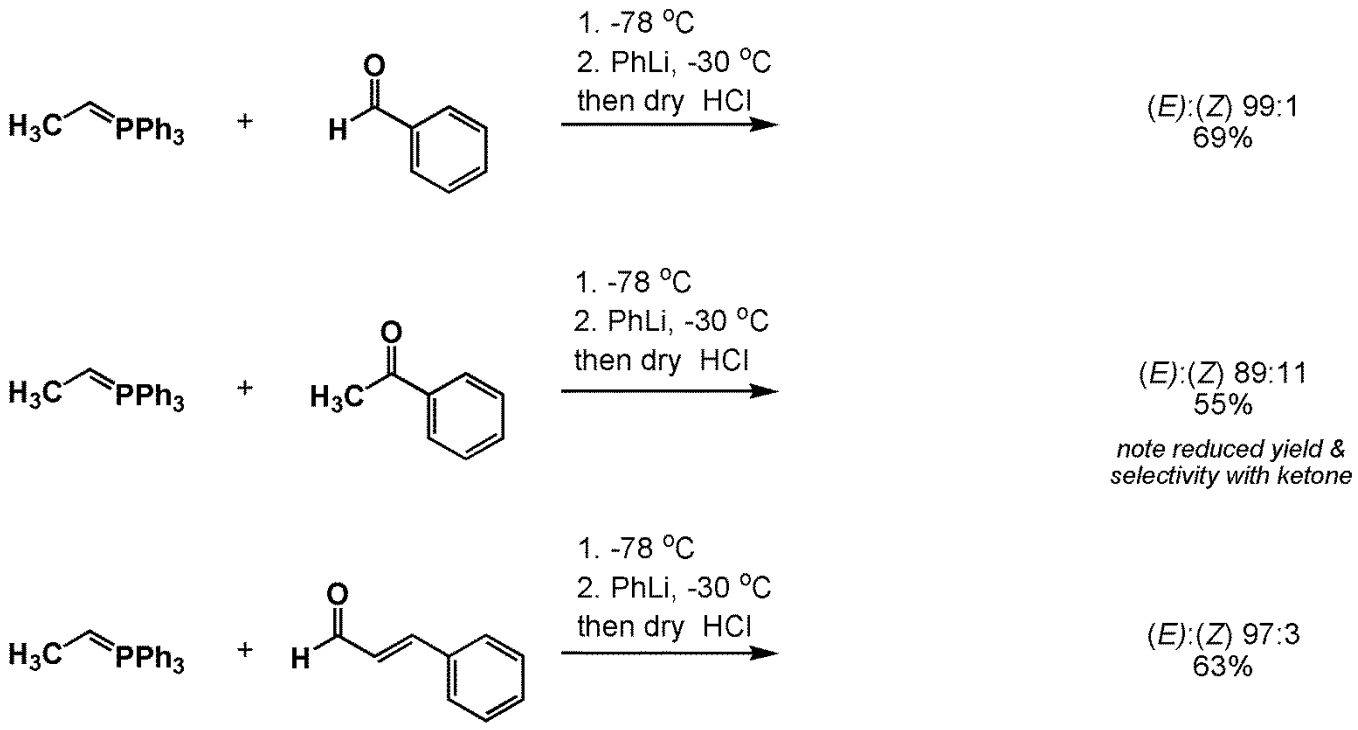


The Schlosser modification to the Wittig reaction (from 1966) is a method for the stereoselective formation of *E* alkenes from unstabilized ylids (when the *Z* isomers would normally be expected to predominate). Addition of butyl or phenyllithium to the betaine at low temperatures can be used to equilibrate the *erythro* to the *threo* isomer via formation of a second ylid.

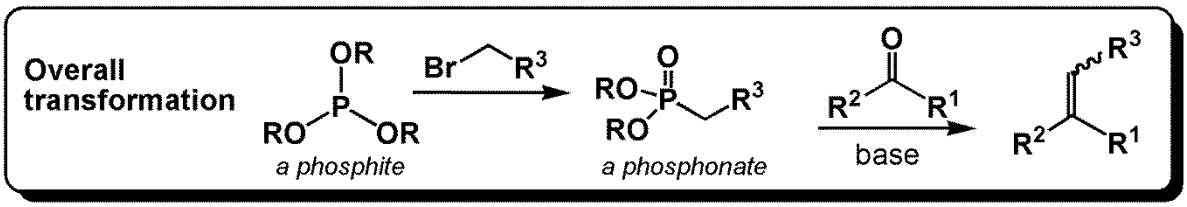


The Wittig reaction - The Schlosser modification (cont.)

Examples



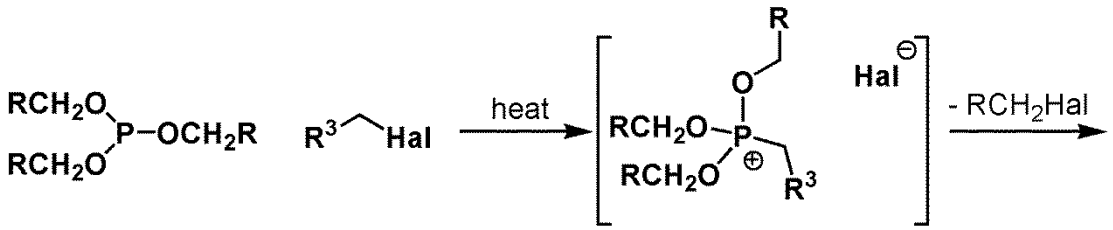
The Arbuzov and Horner-Wadsworth-Emmons Reactions



The Horner-Wadsworth-Emmons (HWE) reaction utilises a phosphonate stabilized anion in a Wittig-type olefination. It is also related to, and may be confused with, the Horner-Wittig reaction which uses phosphine oxide stabilized anions (slide 7a). Classical conditions lead to the alkenes directly, however depending on conditions and substituents, the β-hydroxyphosphonate may be isolated. Harsher / longer reaction conditions would then give the alkene.

Synthesis of phosphonates - the Arbuzov reaction

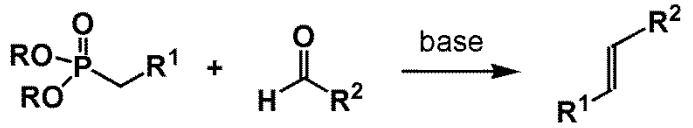
The Arbuzov reaction, also known as the Michaelis-Arbuzov reaction, is a method for making phosphonates from alkyl halides and a phosphite.



cf. Year 3 lab experiment

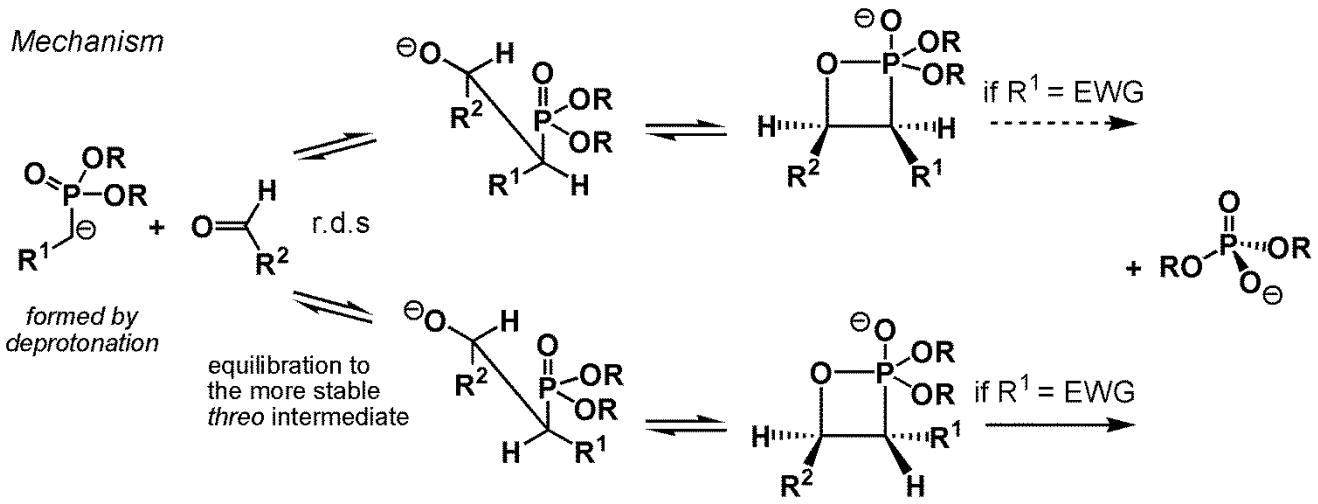
The Horner-Wadsworth-Emmons Reaction

Overall transformation



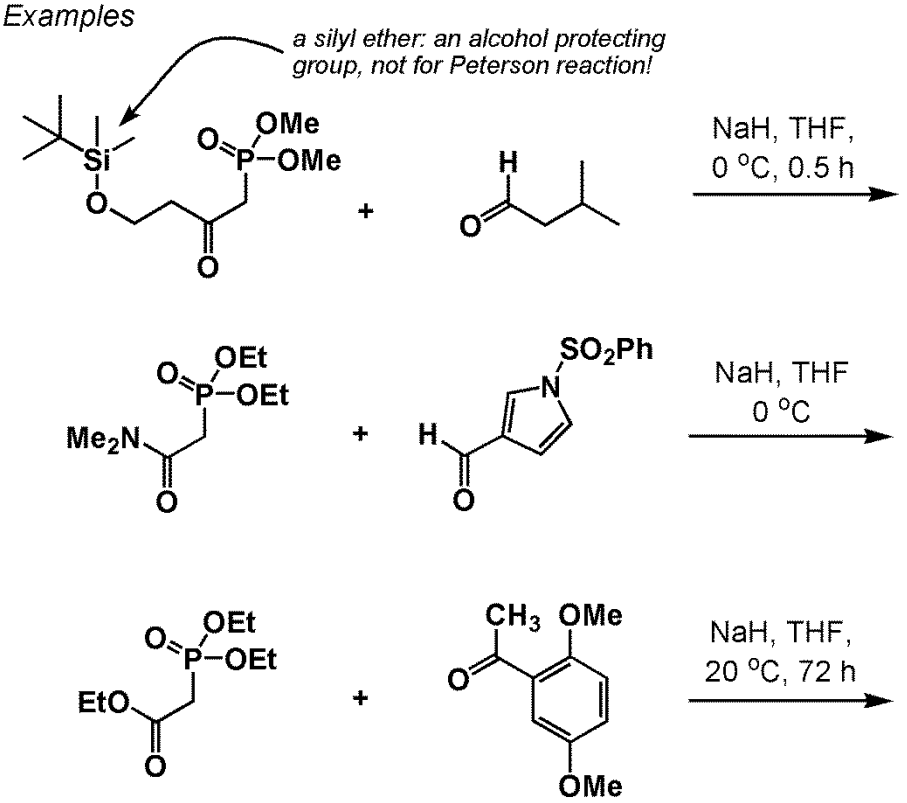
The HWE reaction utilises a phosphonate stabilized anion. The HWE may be used instead of the Wittig reaction where ketones are involved, as the reactions are otherwise often slow and poor yielding (especially when stabilized ylids are involved). The reaction can be thought of as being like the Wittig reaction with stabilized ylids but with added advantages. The phosphate salt by-product is easily extracted using an aqueous wash (unlike the phosphine oxide by-product of the Wittig reaction).

Mechanism

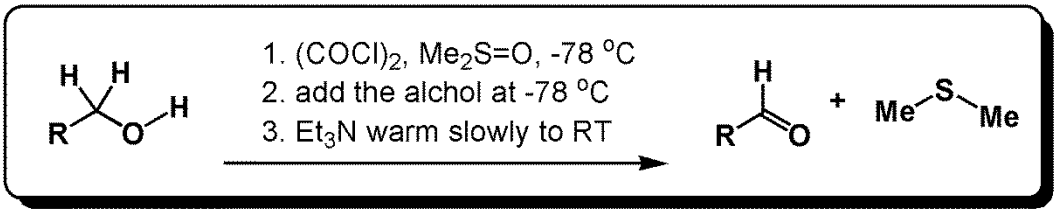


In the HWE reaction the elimination step will only take place *in situ* if the R^1 group is an electron withdrawing group (EWG), otherwise the hydroxy phosphonate is obtained. As can be predicted with this mechanism, bulky R^1 and R^2 groups enhance (*E*) selectivity.

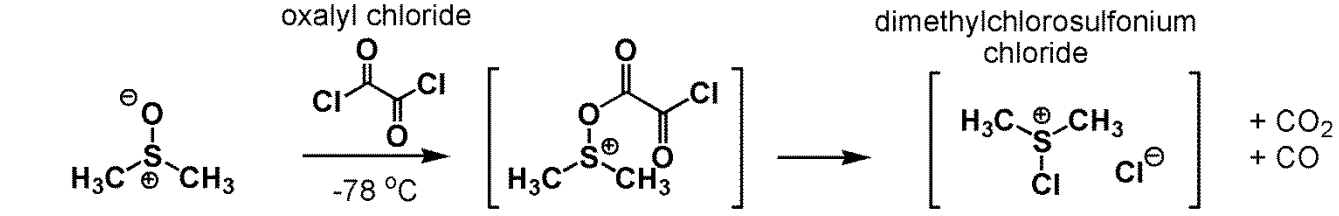
Examples

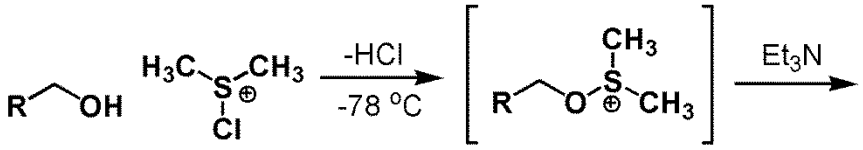


The Swern oxidation and related chemistry

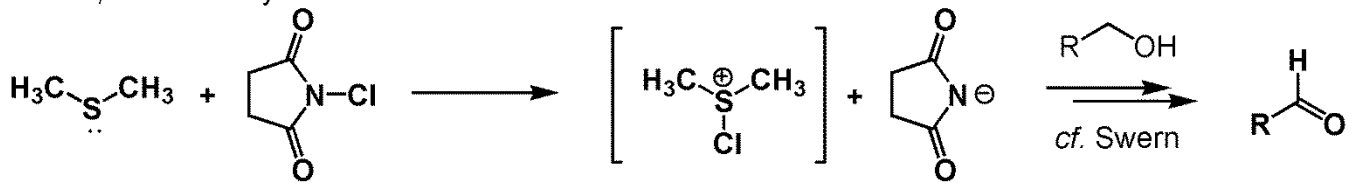


This oxidation was developed in the mid-late1970s and has since become one of the most widely used methods for the mild oxidation of alcohols to aldehydes. It uses oxalyl chloride to activate dimethyl sulfoxide (DMSO) though an alternative uses trifluoroacetic anhydride. The relevance of this reaction here, other than it is also an example of versatile sulfur chemistry, is that the mechanism is analogous to the sulfoxide / selenoxide elimination seen previously, i.e. it also follows an orbital-controlled, concerted reaction pathway.

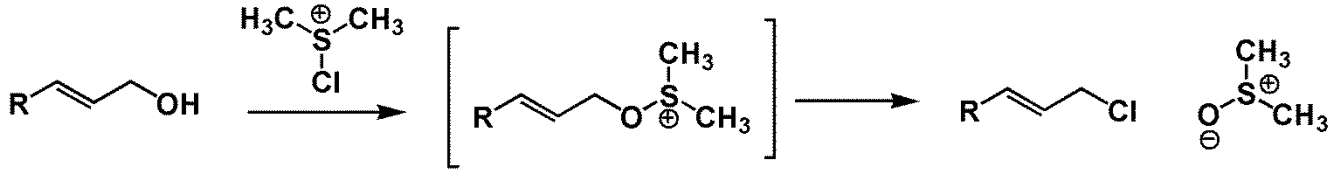




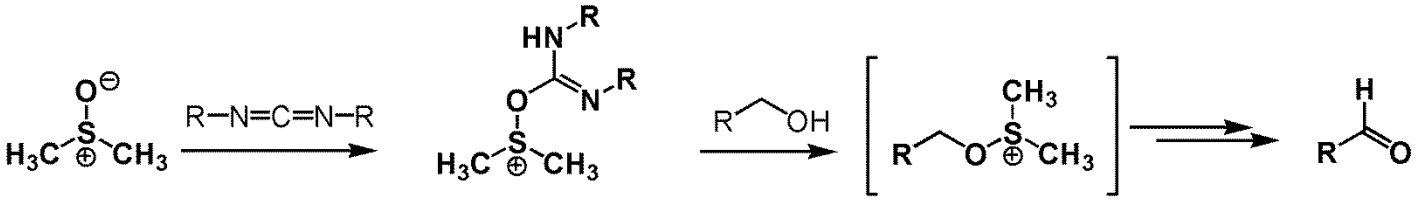
A related method is the Corey-Kim oxidation which uses *N*-chlorosuccinimide, instead of oxalyl chloride, and dimethyl sulfide.



When applied to allylic and benzylic alcohols, these reagents may lead to the corresponding chloride. Omission of the Et_3N in the final step leads to the alkyl dimethylsulfonium salt undergoing a nucleophilic substitution by the chloride ion upon warming. Dimethyl sulfide is also very smelly!

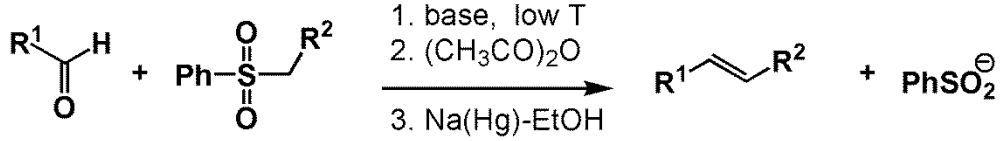


A related oxidation is the Pfitzner Moffatt oxidation which uses dicyclohexylcarbodiimide (R = *c*-C_6H_{11}) to activate the DMSO. The Pfitzner Moffatt is generally less 'clean' than the Swern process and so is not as commonly used nowadays.



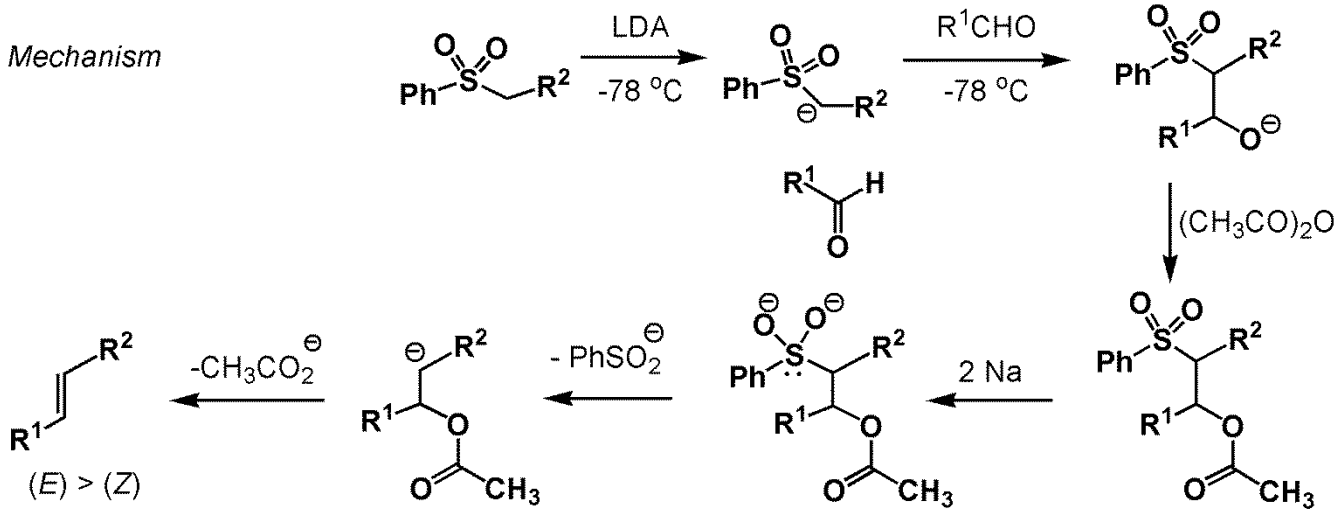
The Julia olefination

Overall transformation



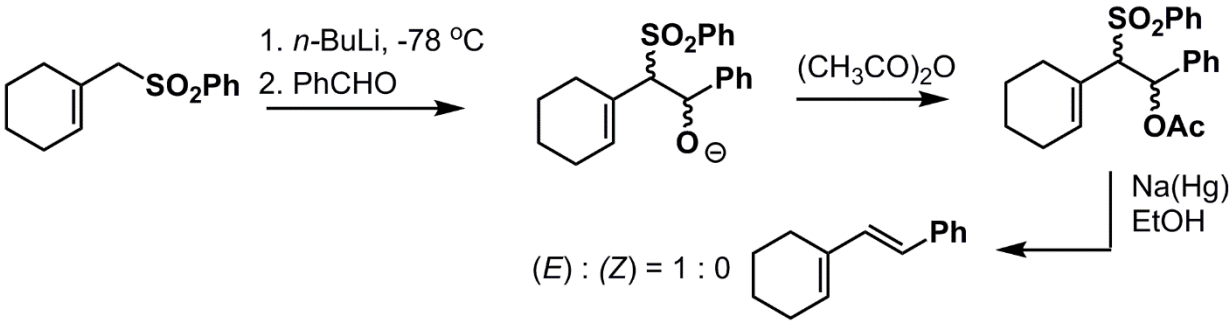
The Julia olefination (also known as the Julia-Lythgoe olefination) is a connective, (*E*)-selective method for forming alkenes. The first step is similar to the Horner-Wittig reaction, where a stabilized (by a sulfone in this case) anion is condensed with an aldehyde. Further modification is required to obtain the alkene from the intermediate hydroxysulfone, which normally involves acetylation (or benzoylation) followed by reduction with a sodium-mercury amalgam.

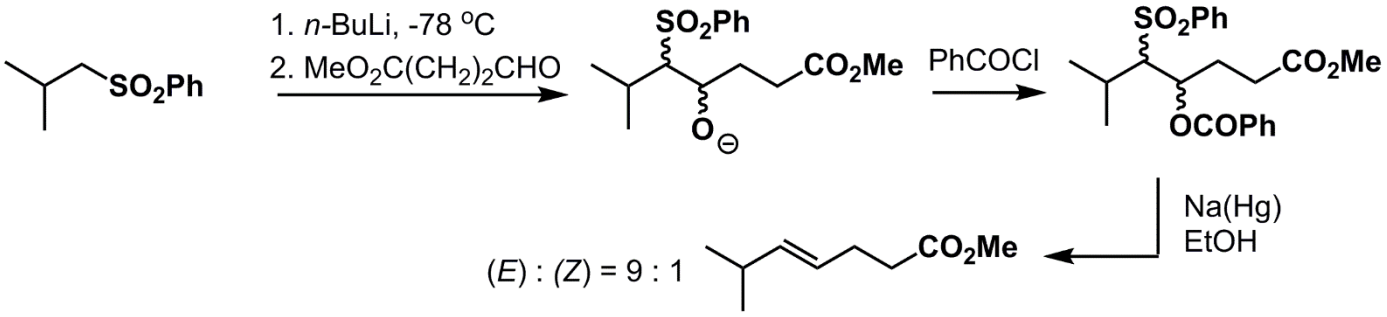
Mechanism



The reaction is (*E*)-selective (*not* stereospecific) due to the mechanism of the reduction with sodium-mercury amalgam. Both the *threo* and *erythro* diastereoisomers of the intermediate ***A*** give the same (*E*):(*Z*) ratio of the alkene, implying a common intermediate, ***B***, to both reactions.

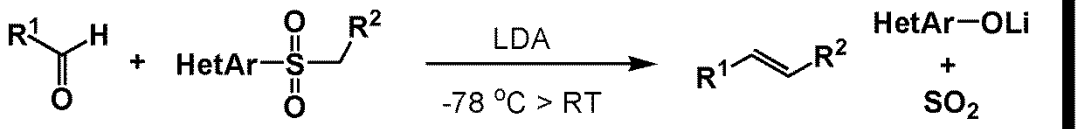
Examples





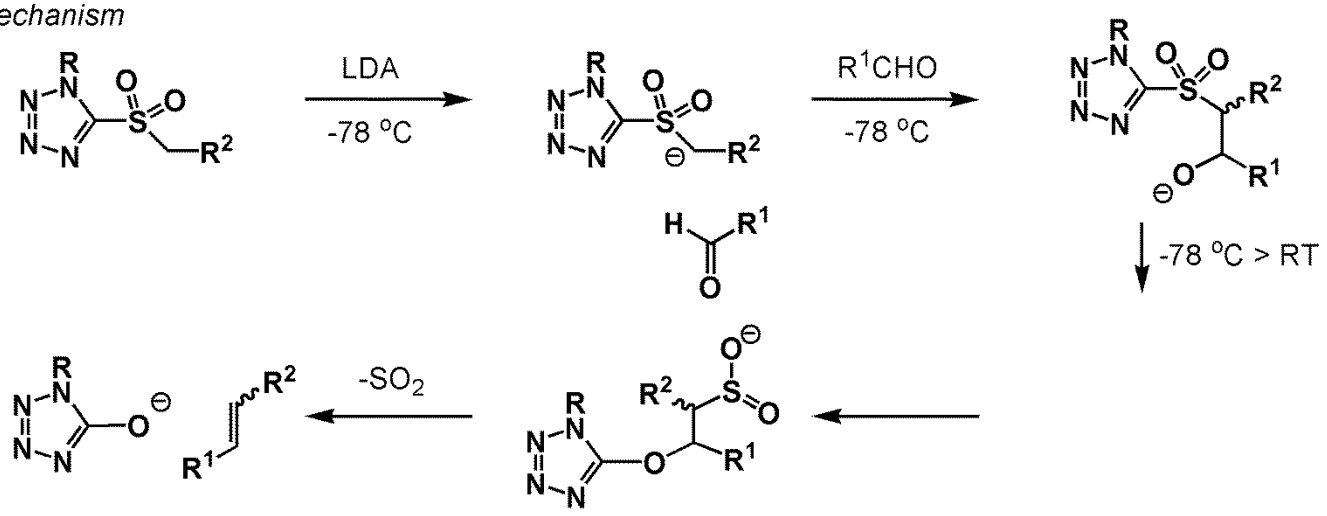
The Modified Julia olefination

Overall transformation



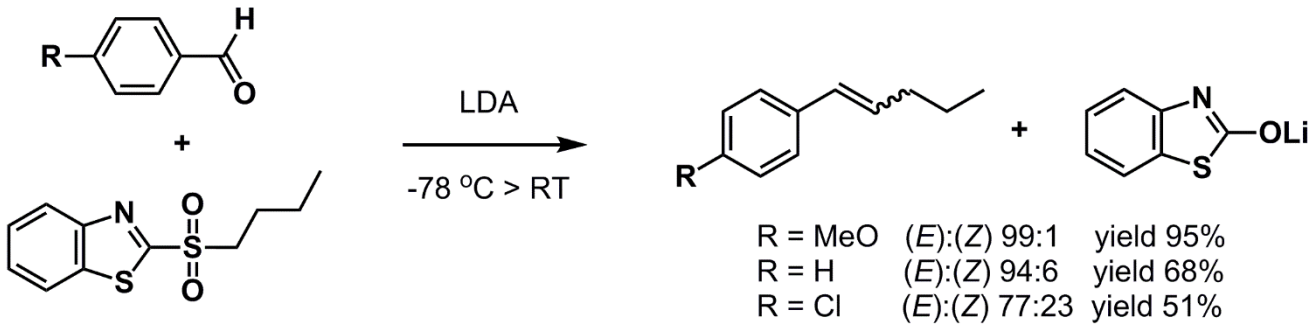
The Julia-Kocienski olefination is an example of a modified Julia reaction, which are 'one-pot' alkene syntheses. There are several variations on this theme, each using a different heterocycle to the tetrazole (the J.-K. olefination) shown below. However, the basic mechanism, as shown below, is the same for all cases. Here the key step is an example of the Smiles re-arrangement which converts ***A*** to ***B***.

Mechanism

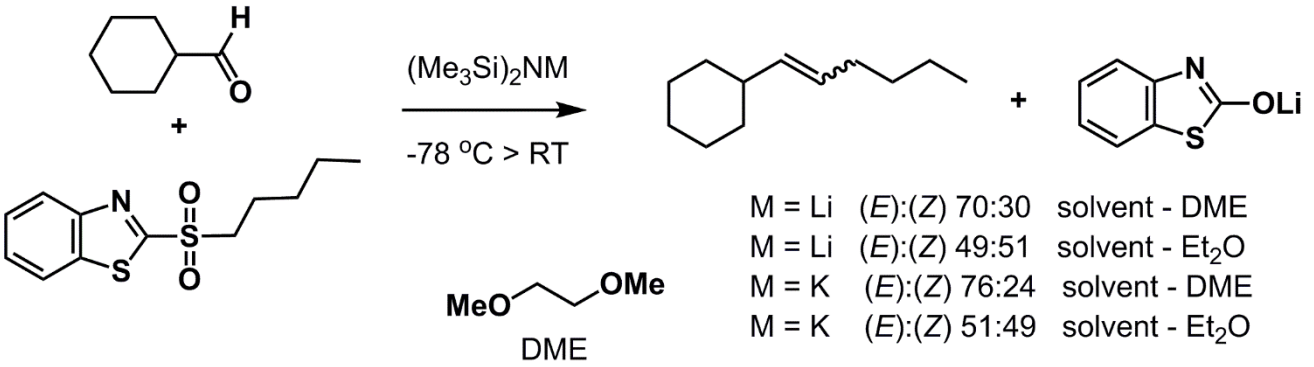


None of the intermediates are formed in equilibria processes and so the (*E*):(*Z*) ratio is dependent on the diastereoselectivity of the initial addition to the aldehyde.

Examples



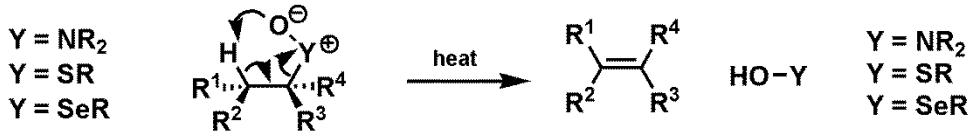
R = MeO (*E*):(*Z*) 99:1 yield 95%
R = H (*E*):(*Z*) 94:6 yield 68%
R = Cl (*E*):(*Z*) 77:23 yield 51%



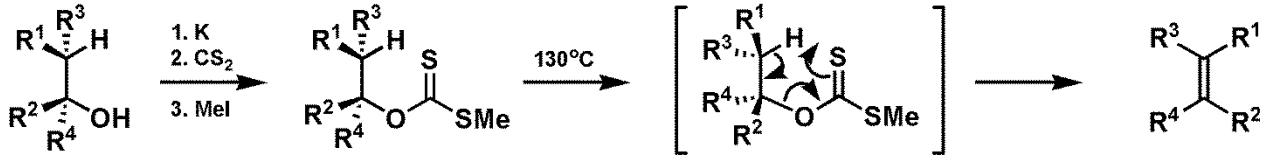
M = Li (*E*):(*Z*) 70:30 solvent - DME
M = Li (*E*):(*Z*) 49:51 solvent - Et_2O
M = K (*E*):(*Z*) 76:24 solvent - DME
M = K (*E*):(*Z*) 51:49 solvent - Et_2O

Applications of Phosphorus, Sulfur and Silicon Chemistry: Stereo- and Regioselective Synthesis of Alkenes

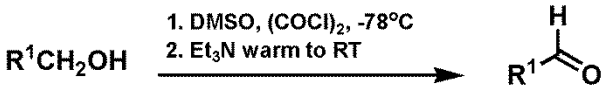
Syn eliminations - thermal decomposition of sulfoxides, selenoxides and amine oxides



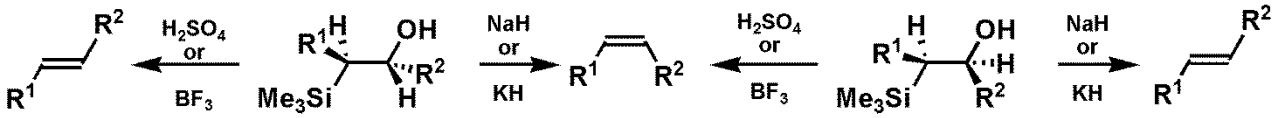
Syn eliminations - the Chugaev Reaction



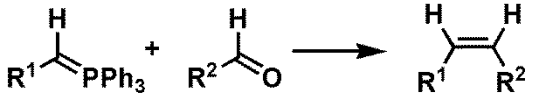
Swern oxidation - a *syn* elimination type mechanism



Peterson reaction - *anti* elimination with acid and *syn* elimination with base

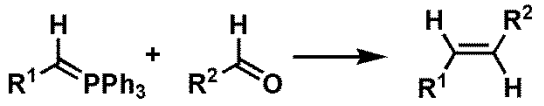


Wittig reaction - *unstabilized ylid*



(*Z*) > (*E*)

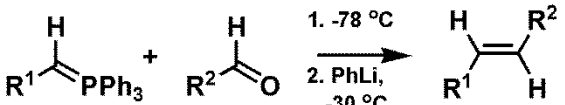
Wittig reaction - *stabilized ylid*



R1 = EWG

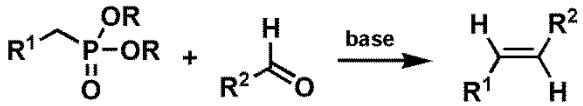
(*E*) > (*Z*)

Wittig-Schlosser reaction - *unstabilized ylid*



(*E*) > (*Z*)

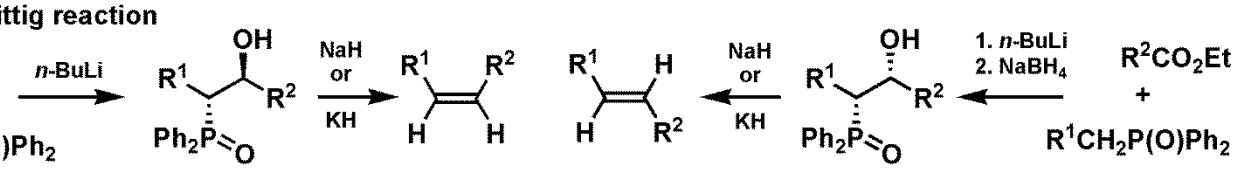
Horner-Wadsworth-Emmons reaction



R1 = EWG

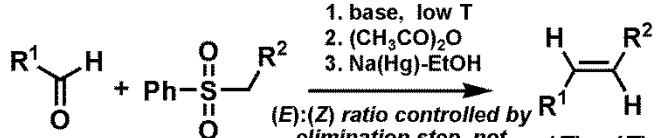
(*E*) > (*Z*)

Horner-Wittig reaction



major isomer *major isomer*

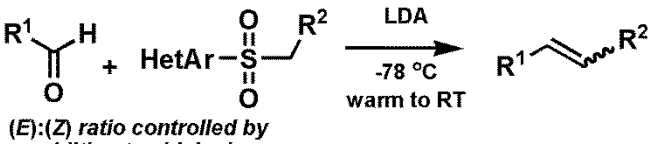
Julia olefination



(*E*):(*Z*) *ratio controlled by elimination step, not addition to aldehyde*

(*E*) > (*Z*)

modified Julia olefination

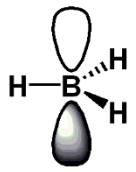


(*E*):(*Z*) *ratio controlled by addition to aldehyde*

Boron and borane

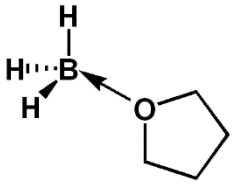
17a

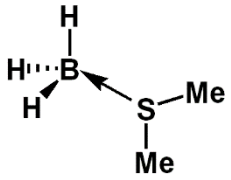
Boron is in group 13 of the periodic table and thus can form neutral compounds with 6-electrons in its outer shell. Borane, BH_3, is such an example and due to the empty p-orbital these compounds can act as Lewis acids (cf. $AlCl_3$)



Due to its electron deficiency borane forms the dimer diborane (B_2H_6). Two-electron three-centre bonds (i.e bridging hydrogen atoms) are used to explain the bonding in this species.

Borane is also commercially available in a variety of forms as a 'complex' with an electron pair donator - i.e. a Lewis base. The coordinate bond is formed between the vacant 2p oribtal of boron and the lone pair of a small molecule such as an ether - e.g. diethyl ether or THF (tetrahydrofuran).



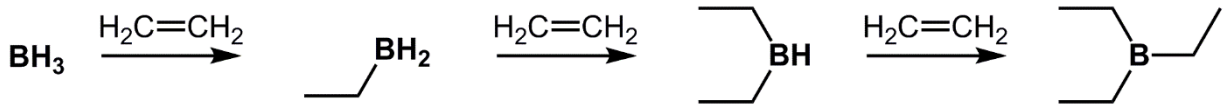


$BH_3.OEt_2$

Alkylboranes and hydroboration or alkenes

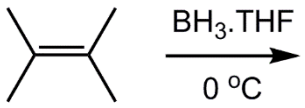
17b

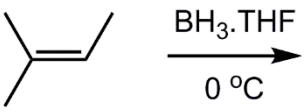
The reactions of borane are dominated by those with alkenes in which the C-H bond is replaced with a C-R bond by addition of the B-H across the C=C of the alkene. This is known as hydroboration of the alkene. You can consider this in simple terms by the replacement of the electron neutral H atom with a +I alkyl group. With borane and simple unhindered alkenes multiple additions can take place in which all B-H bonds are replaced with B-C bonds.



borane *alkylborane* *dialkylborane* *trialkylborane*

Hindered alkenes may undergo controlled mono- or dihydroboration reactions. Two useful alkylboranes which will feature later in the course are shown below.





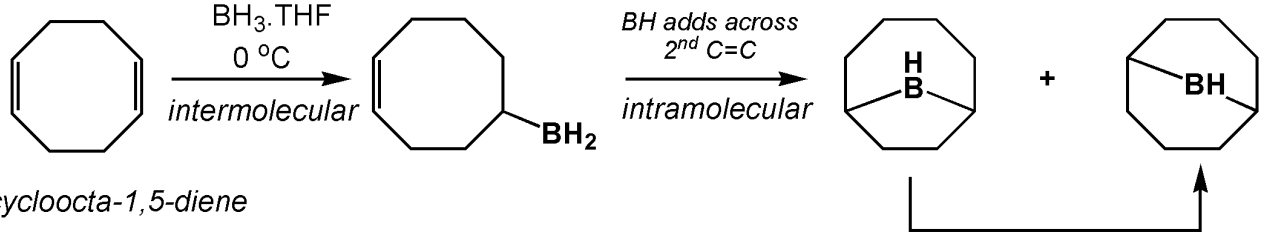
thexylborane

disiamylborane
$(Sia)_2BH$

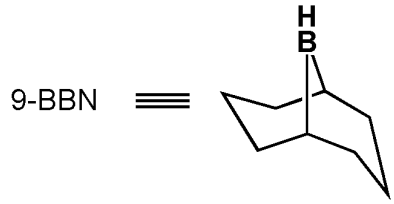
Hydroboration of dienes

Borane can also react with dienes to form cyclic boron compounds.

9-borabicyclo[3.3.1]nonane

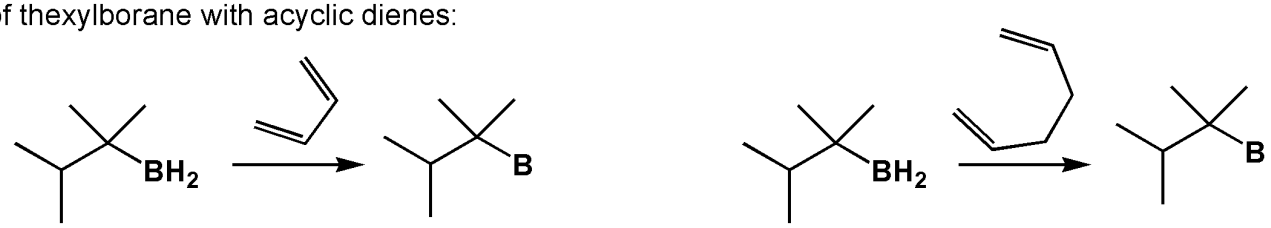


cycloocta-1,5-diene



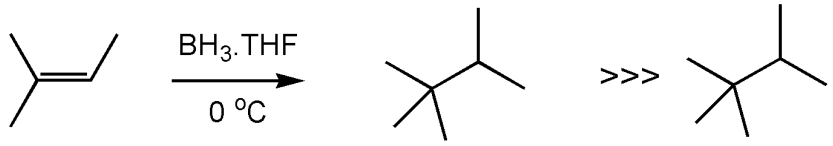
9-BBN is another commercially available important borane which will be encountered during the course.

Mono alkyl boranes can also react with dienes to form trialkylboranes. Here the examples are reactions of thexylborane with acyclic dienes:

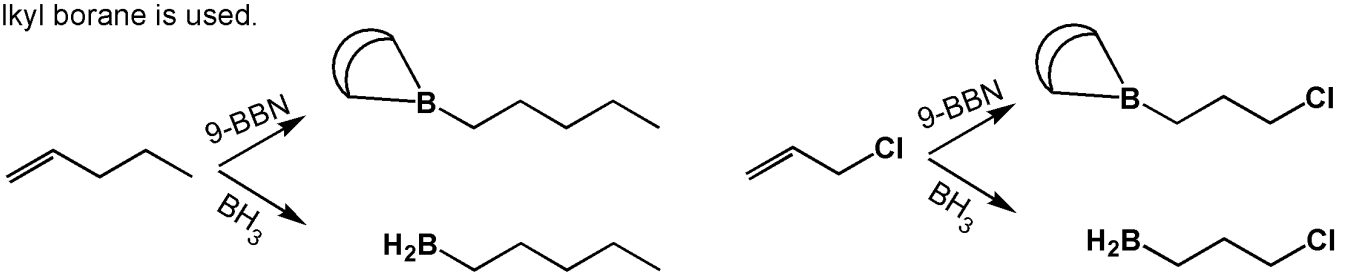


Regiochemistry of alkene hydroboration

The regiochemical outcome of the hydroboration reaction is that the boron adds preferentially to the least hindered carbon of the C=C bond.

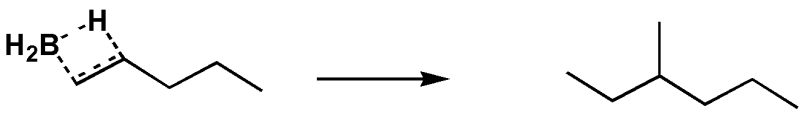


Addition of BH_3.THF across simple alkenes is **regioselective**, but even more so if a more hindered alkyl borane is used.



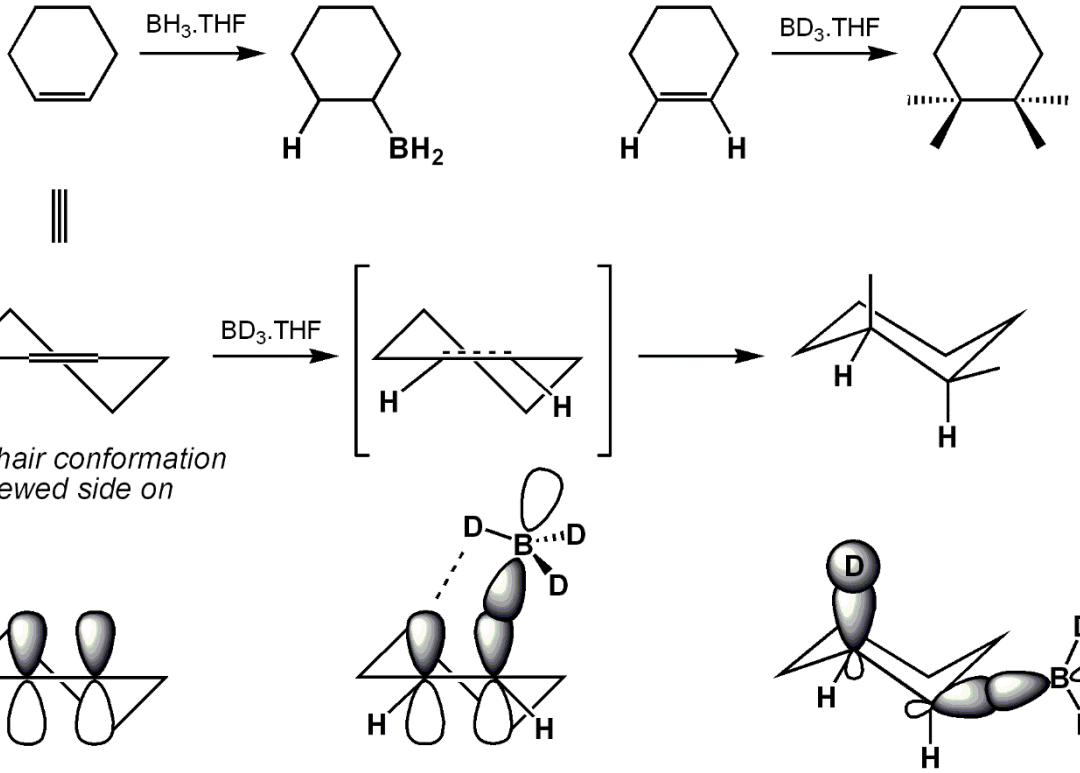
Electronic factors also play a role in the regiochemical outcome of the reaction. As can be seen below, there is build up of positive charge on the more substituted carbon in the transition state.

cf. Markovnikov addition of HX to alkenes

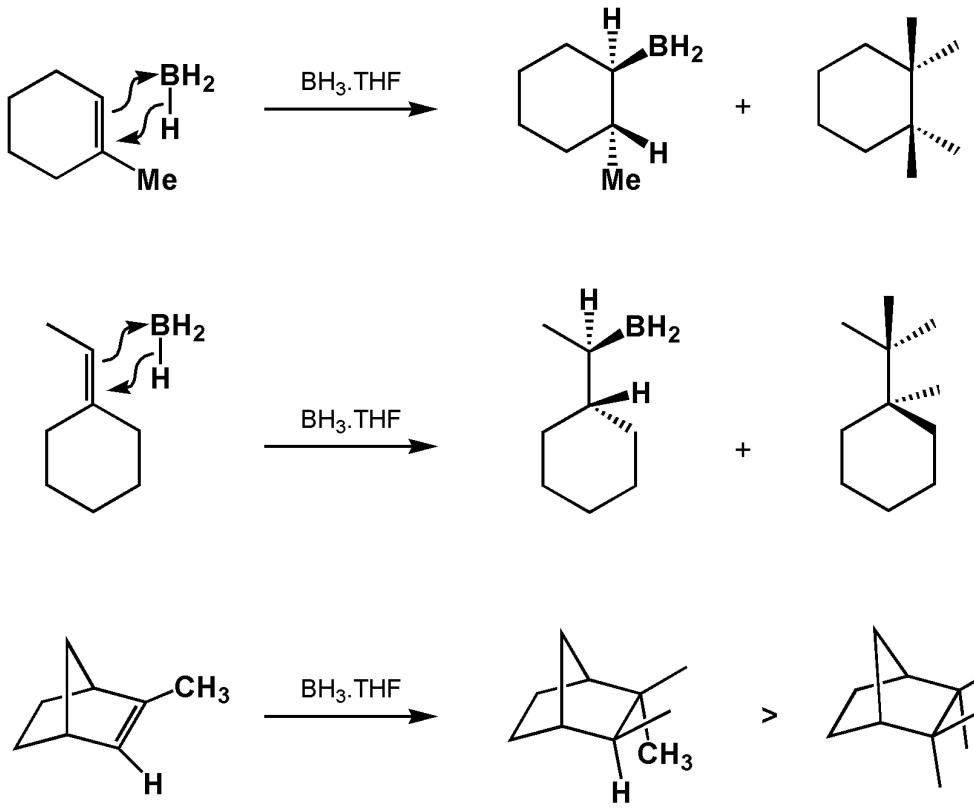


Stereochemistry of alkene hydroboration

The addition of a B-H across a carbon-carbon double (or triple) bond is a concerted process. The addition has been shown to be ***syn*-stereospecific** with the use of deuterated boranes or alkenes.



Hydroboration of alkenes: examples



The addition is *syn* stereospecific, but the borane adds equally to each face.

A *racemic mixture* is produced.

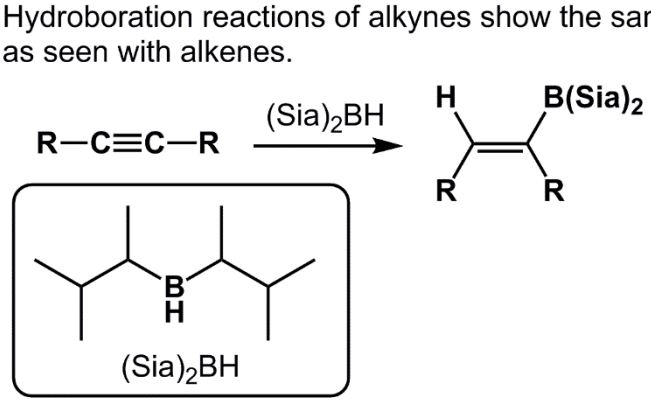
Addition to each face is different. Unequal amounts of *diasteroisomers* are produced.

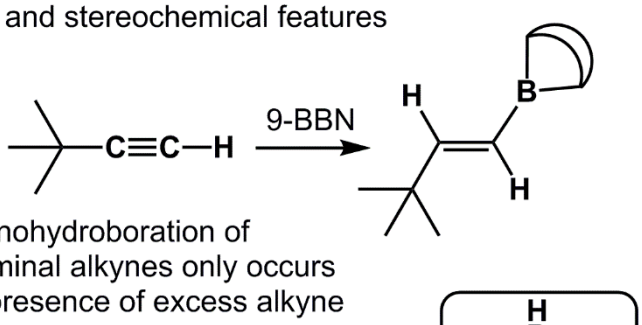
regioselective and *diastereoselective* addition

Hydroboration of alkynes

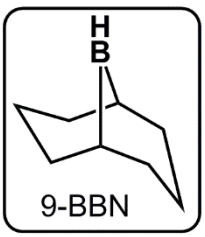
20a

Hydroboration reactions of alkynes show the same regio- and stereochemical features as seen with alkenes.

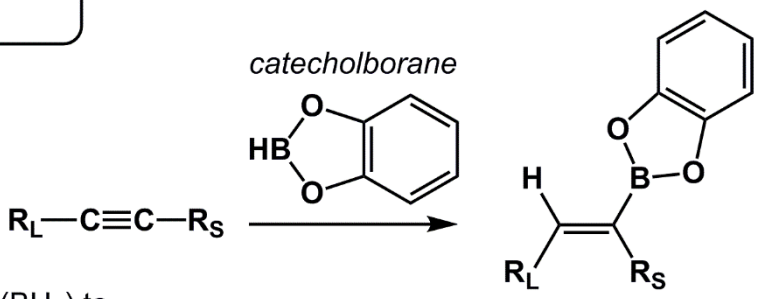




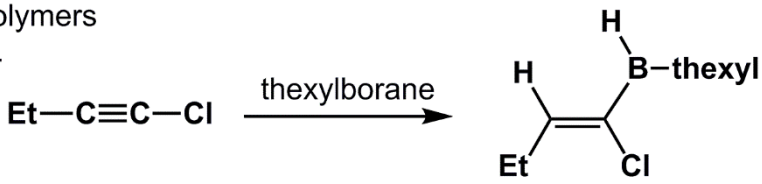
monohydroboration of terminal alkynes only occurs in presence of excess alkyne

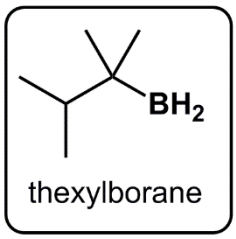


catecholborane



addition of **borane** (BH_3) to alkynes can form polymers by multiple addition.





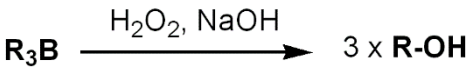
note regiochemistry: H adds to the C atom stabilised in the transition state by the +I Et (not the -I Cl)

Reactions of alkylboranes

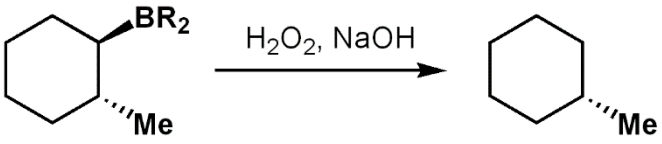
20b

The carbon boron bond in alkylboranes may be cleaved in a variety of ways. Coupling the alkene hydroboration with further reaction provides a range of very useful functional groups interconversions.

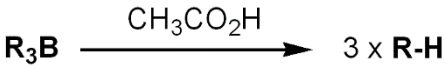
Oxidation

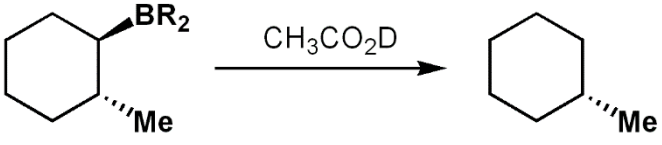


Examples

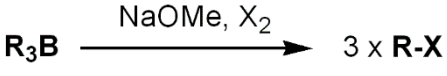


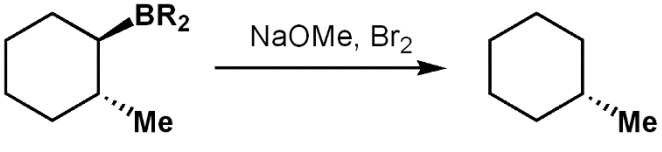
Protonolysis



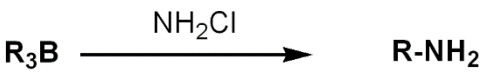


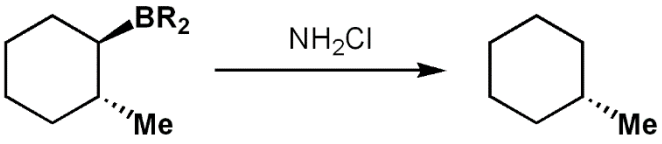
Halogenation





Amination



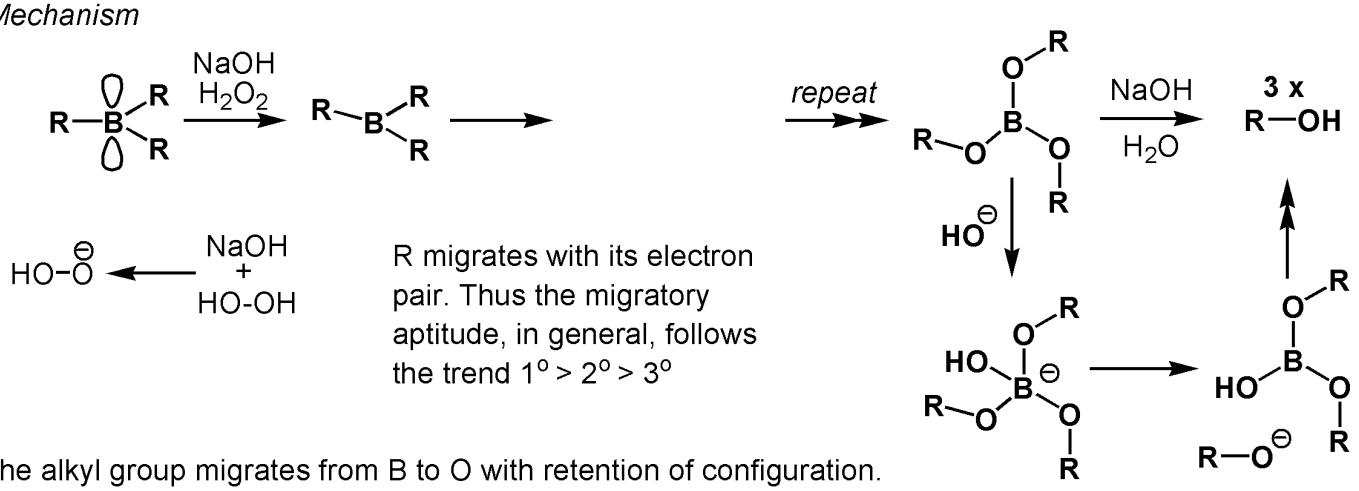


Reactions of alkylboranes - oxidation

21a

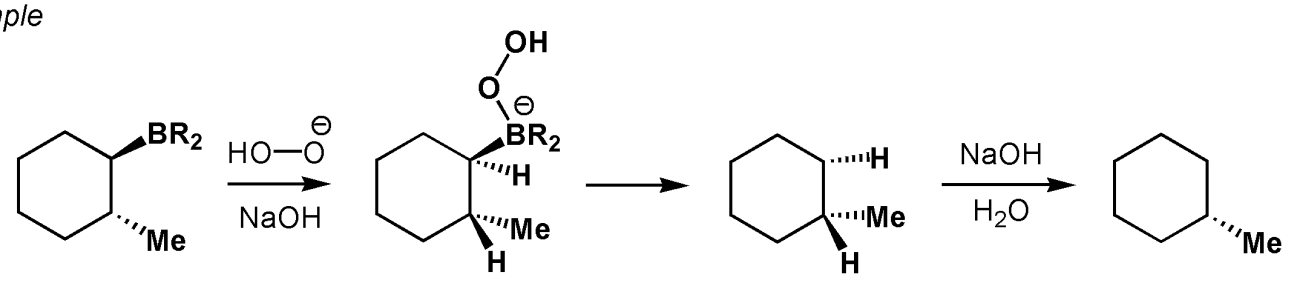
The oxidation reaction of alkylboranes proceeds *via* formation of a boronate complex.

Mechanism



The alkyl group migrates from B to O with retention of configuration.

Example

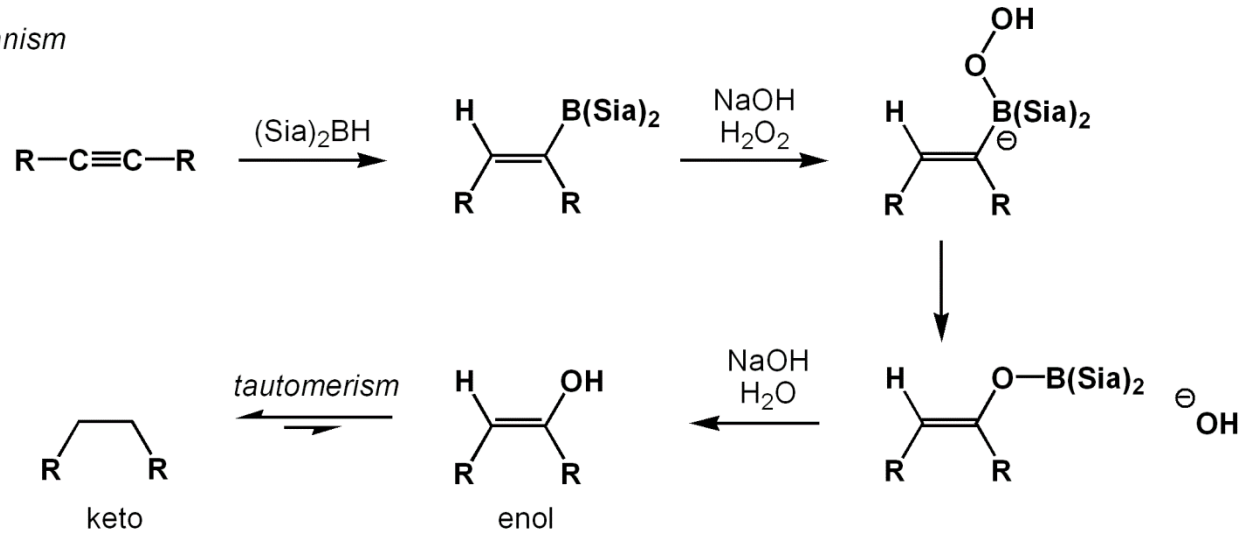


Reactions of alkenylboranes - oxidation

21b

The oxidation of alkenylboranes proceeds as with the alkylboranes, however the enol product typically tautomerises to the more stable keto form.

Mechanism



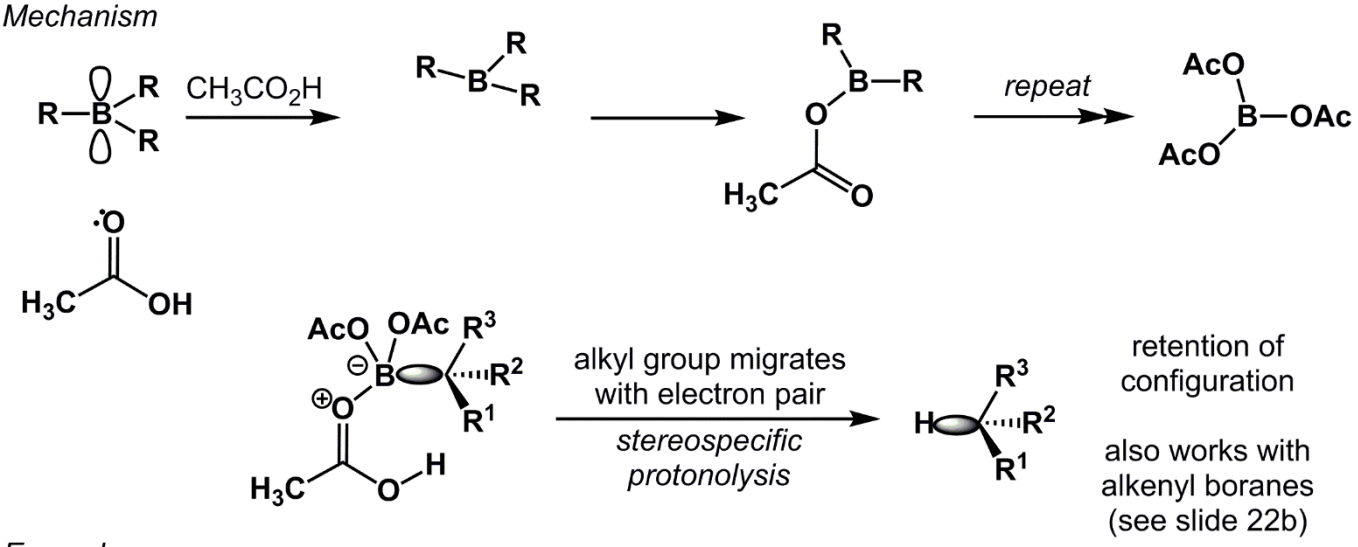
Example

Reactions of alkylboranes - protonolysis

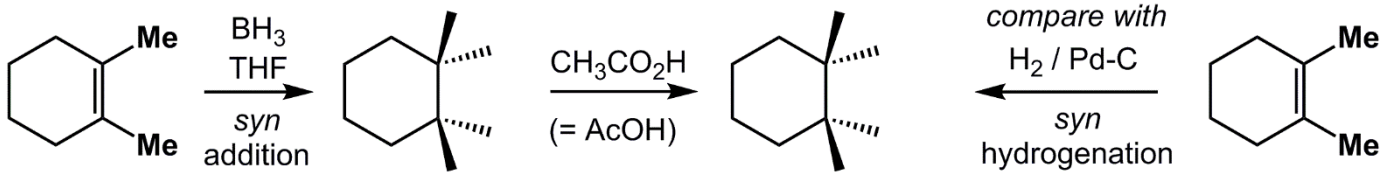
22a

The protonolysis of alkyl- and alkenylboranes using acetic acid produces alkanes or alkenes *via* a stereospecific reaction with retention of configuration in the migrating R group.

Mechanism



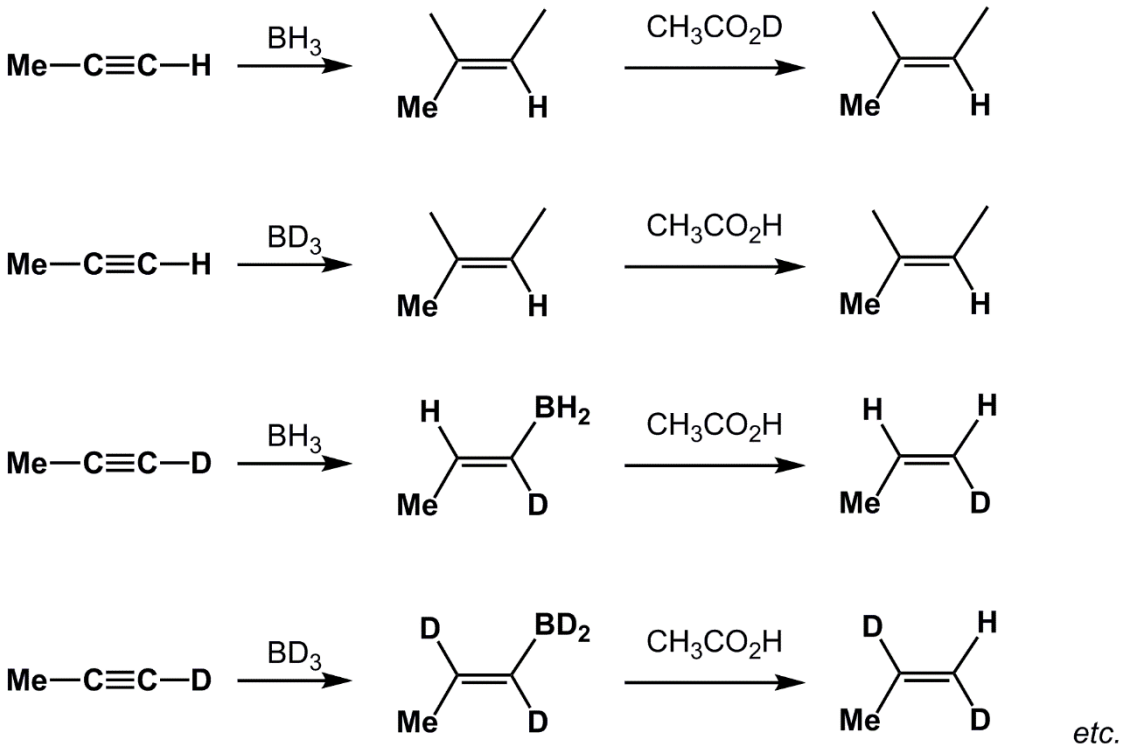
Example



Reactions of alkenylboranes - protonlysis

22b

The stereospecific protonolysis of boranes is a useful method for preparing isotopically labelled compounds with control over which isomer is produced. This can be illustrated with the following examples which are protonolysis reactions of alkenylboranes.

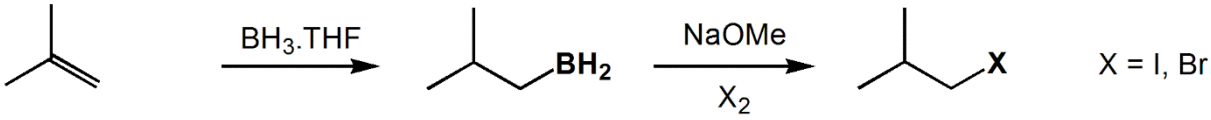


Reactions of alkylboranes - halogenation

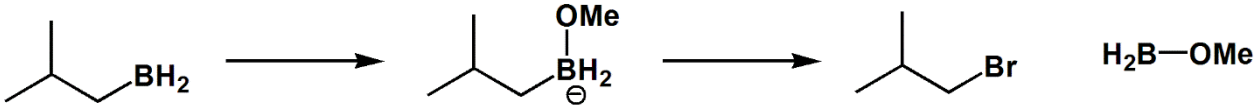
23a

Carbon-boron bonds are not usually cleaved as easily as seen in protonolysis. As found in the oxidation reaction, however activation of the C-B bond can be acheived by making a boronate complex. This can be seen in the halogenation reactions below.

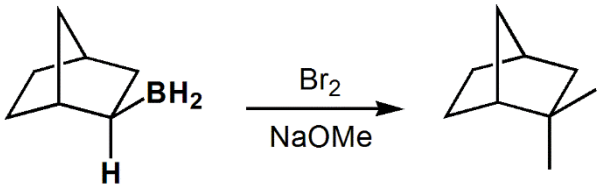
Example



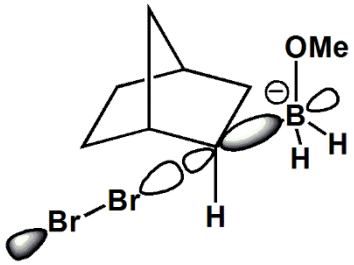
Mechanism



Stereochemical implications - this reaction proceeds with **inversion of configuration** at the C-B centre.



inversion of configuration

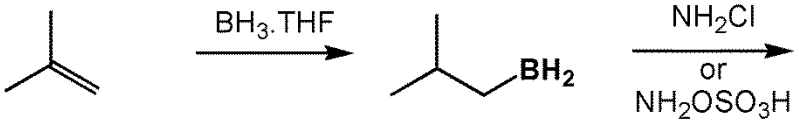


Reactions of alkylboranes - amination

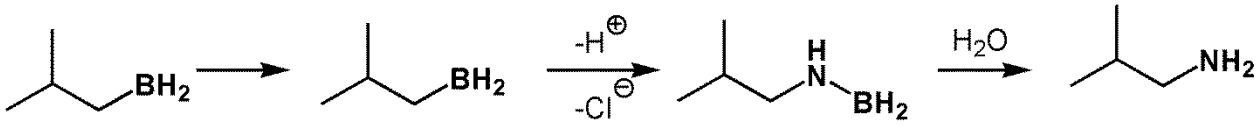
23b

Activation of the C-B bond by forming a boronate complex is also a key step in the following amination process in which an *N*-chloroamine (or similar) is reacted with an alkylborane.

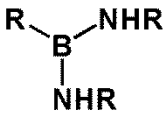
Example



Mechanism



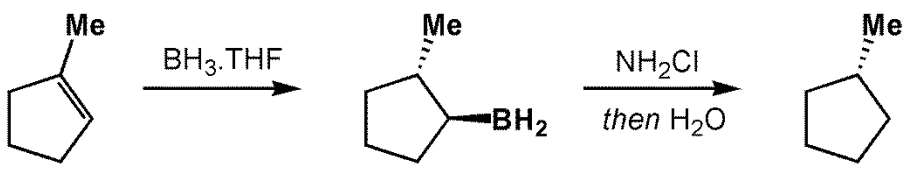
With trialkylboranes the reaction stops at the second amination



so only **two moles** of amine can be made

Stereochemical implications

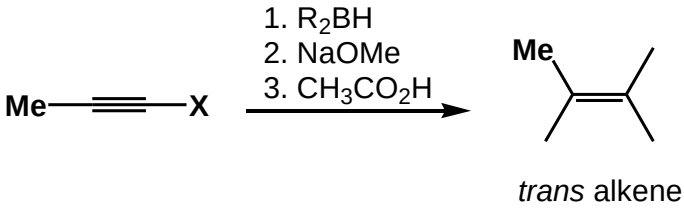
As with the oxidation process this reaction, with the same mechanism, proceeds with retention of configuration in the intramolecular migration step.



Reactions of alkenylboranes - synthesis of (*E*)-alkenes

Hydroboration of 1-haloalk-1-ynes, followed by reaction with NaOMe followed by acetic acid gives rise to (*E*)-alkenes via a R-B to R-C migration.

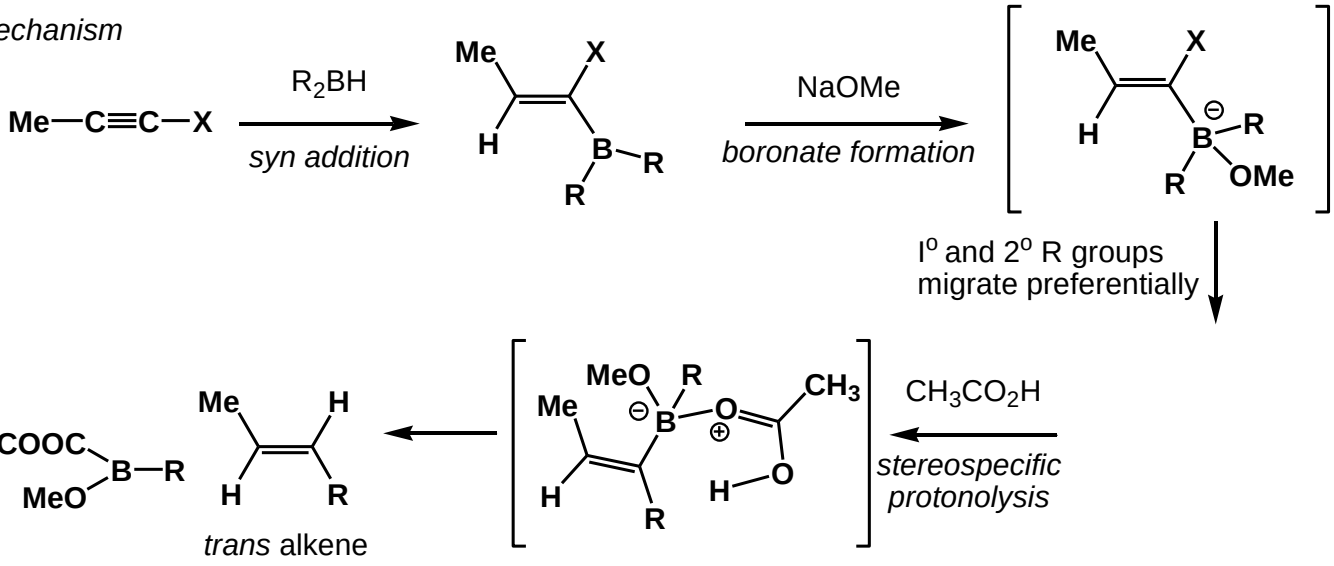
Overall



trans alkene

migration occurs with retention of configuration in the R group but inversion of the alkenyl geometry

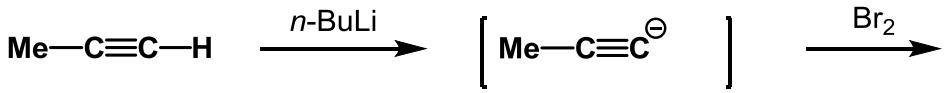
Mechanism



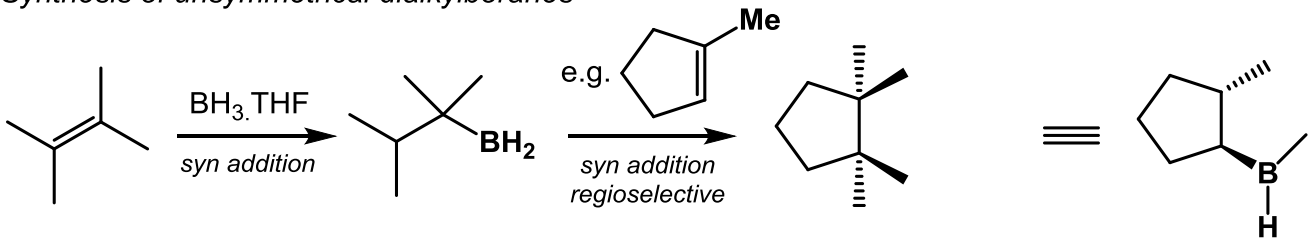
Synthesis of (*E*)-alkenes - continued

This method is extremely useful for making alkenes if an unsymmetrical borane R^1-BH-R^2 is used ***and*** you can control which R group migrates to the alkenylcarbon atom. With a thexylborane derivative this is possible as the 3° alkyl thexyl group is less prone to migrate under these reaction conditions.

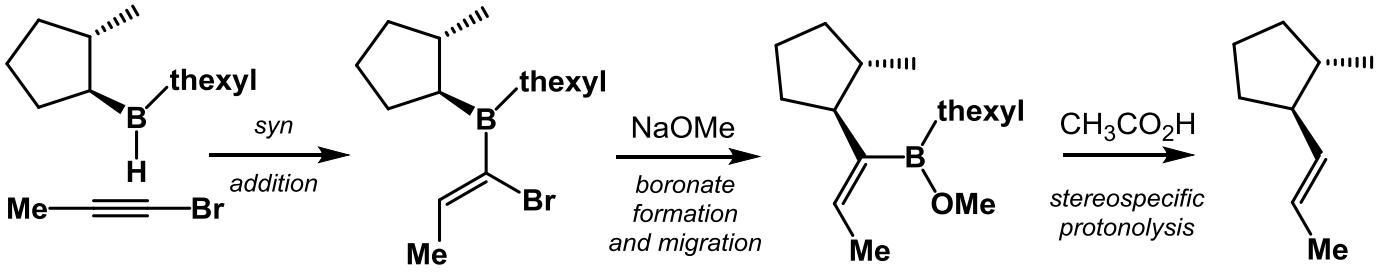
Synthesis of 1-halogenoalkynes



Synthesis of unsymmetrical dialkylboranes



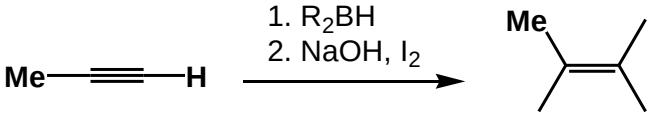
Putting it all together



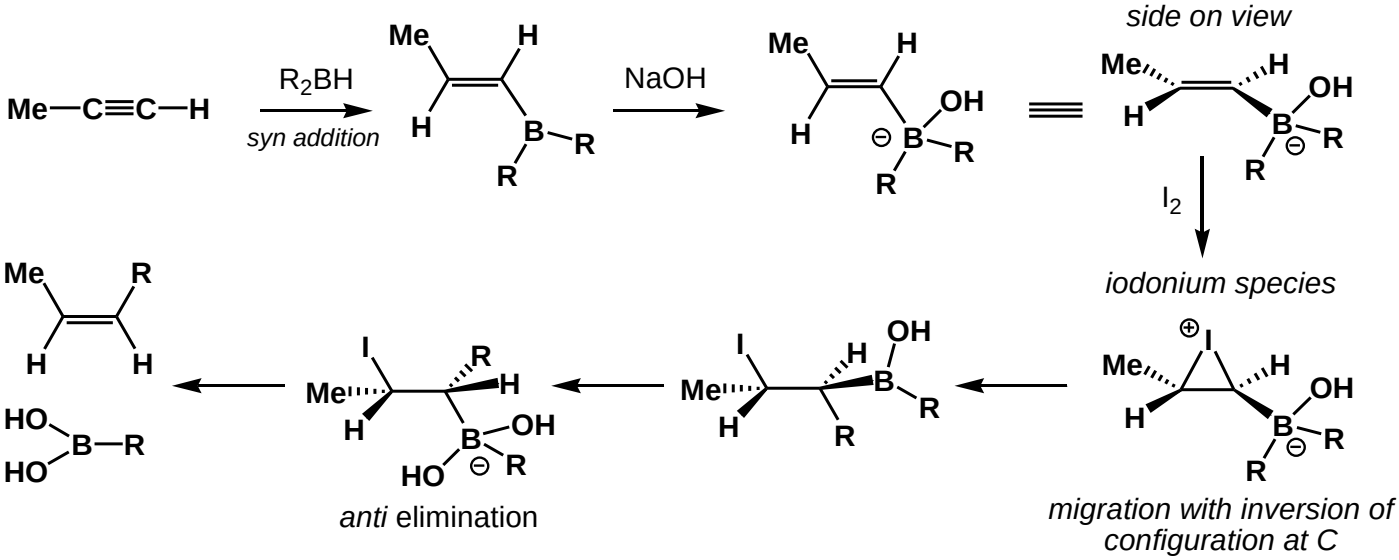
Reactions of alkenylboranes - synthesis of (*Z*)-alkenes 25a

Hydroboration of alk-1-ynes, followed by reaction with $NaOH/I_2$ gives rise to (*Z*)-alkenes

Overall

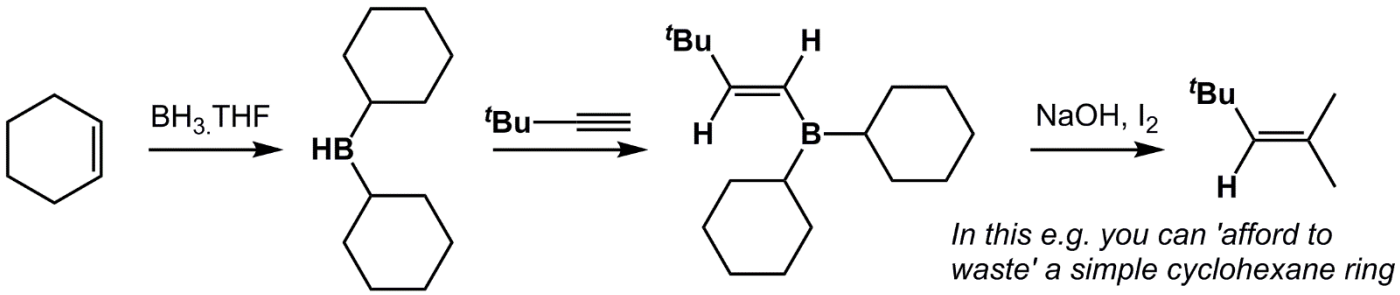


Mechanism

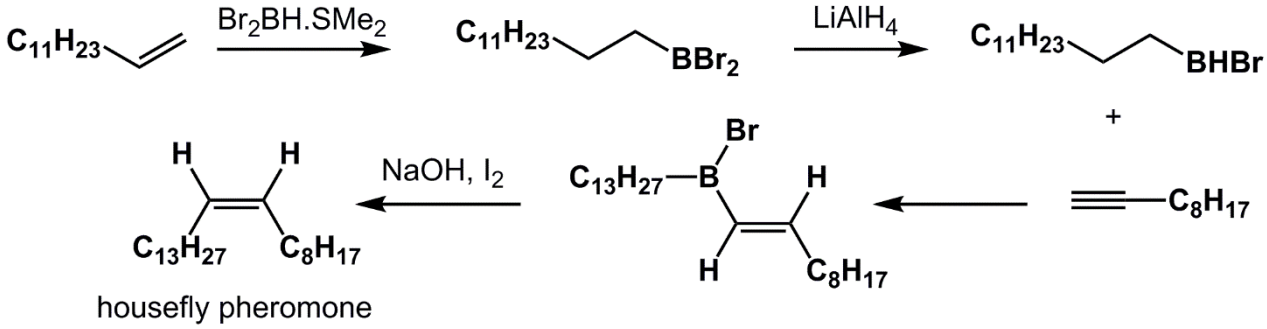


Synthesis of (*Z*)-alkenes - continued 25b

As before, this method would extremely useful for making alkenes if an unsymmetrical borane R^1-BH-R^2 was used ***and*** you could control which R group migrates to the carbon atom. Unfortunately this is not possible as even the 3° thexyl group has been observed to migrate in this reaction. Thus symmetrical boranes are used - if 'wastage' of one of the R groups can be justified.

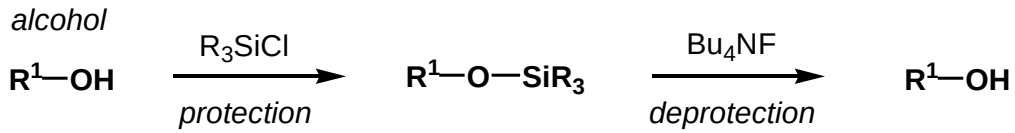


An alternative approach is more 'long winded' going via a *mono*bromo-*mono*alkylborane. Here ***only*** the alkyl group can migrate thus making this route unambiguous.



Silyl ethers: temporary hydroxyl protecting groups

Silicon is a versatile element in organic chemistry, as typified by the Peterson reaction seen before. One ubiquitous application is the use of silyl ethers for the temporary protection of hydroxyl (alcohol/ phenol) groups when the presence of a free alcohol may interfere with a chemical transformation.

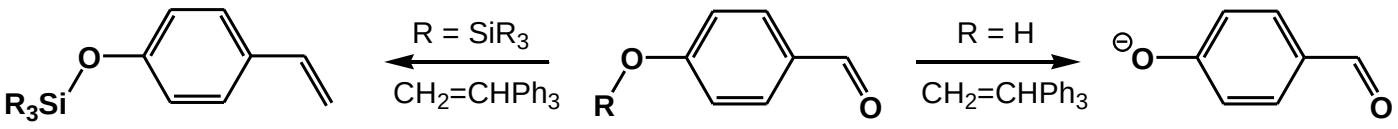


This protection / deprotection chemistry takes advantage of the particularly strong Si-O and S-F bonds. The relevant bond dissociation energies are shown below.

C—C	**C—Si**	**C—F**
335 kJ / mol	320 kJ / mol	450 kJ / mol
C—Si	**O—Si**	**Si—F**
320 kJ / mol		

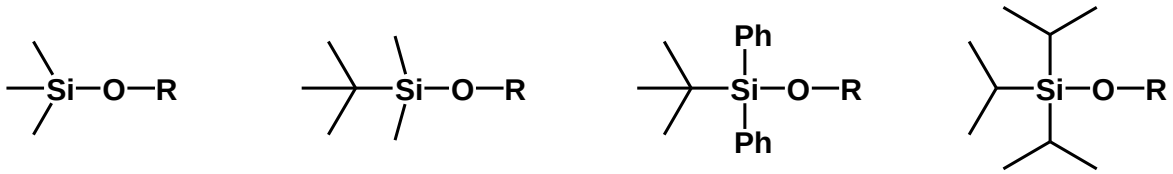
*R^1 is now amenable to chemical transformation without interference by the OH group, for example:

unstablised ylids can act as bases



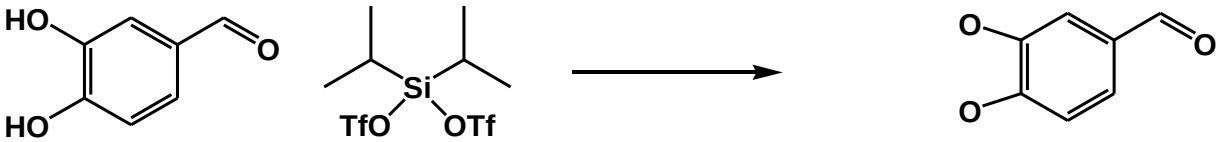
Silyl ethers

The following silyl ethers are commonly used as protecting groups



trimethylsilyl	*t*butyldimethylsilyl	*t*butyldiphenylsilyl	triisopropylsilyl
Me_3Si-OR	$^tBuMe_2Si$-OR	$^tBuPh_2Si$-OR	$^iPr_3Si$-OR
TMS	TBDMS -*or*- TBS	TBDPS	TIPS

Also encountered are triethylsilyl, TES, and dichlorosilanes which can be used for protecting 1,2-diols

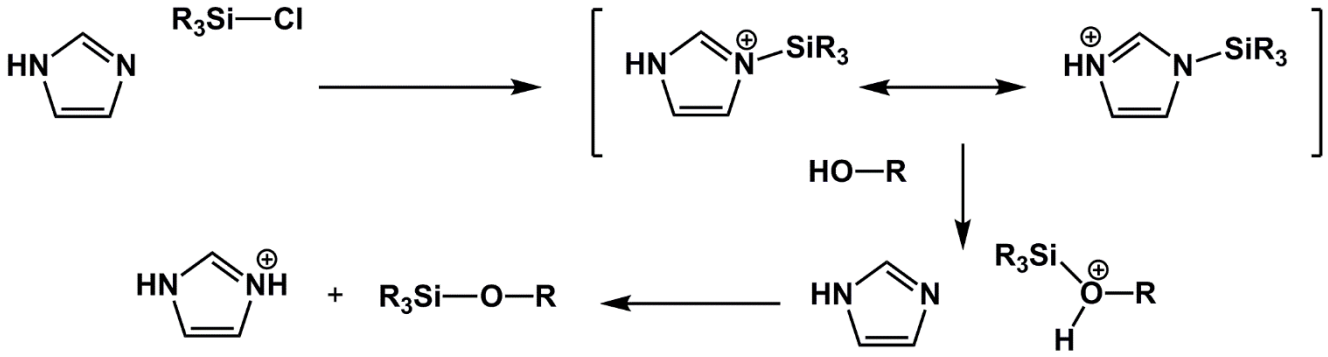


TfO = CF_3SO_2O (trifluoromethanesulfonate, or triflate)

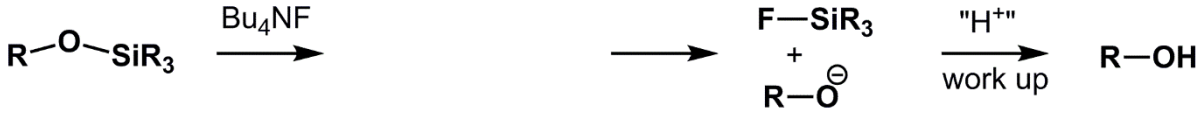
Making and cleaving silyl ethers: protection and deprotection

27a

The protection of alcohols as silyl ethers uses a silyl chloride and a base, commonly imidazole.



Deprotection of silyl ethers uses fluoride ion, commonly Bu_4NF which is soluble in organic solvents. This is also known as 'TBAF' - tetrabutyl ammonium fluoride. TMS and TES ethers are quite labile and can be easily cleaved using acids, sometimes too easily in the case of TMS ethers where very weak acids or bases can lead to deprotection. TBAF is usually required for TBDPS or TIPS ethers.

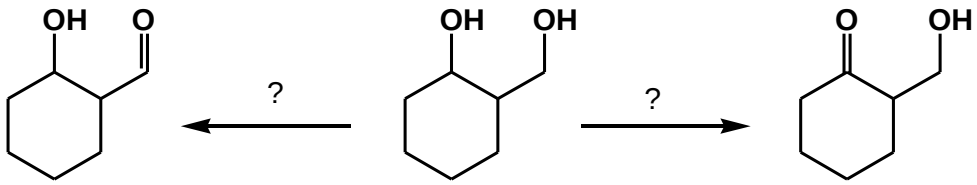


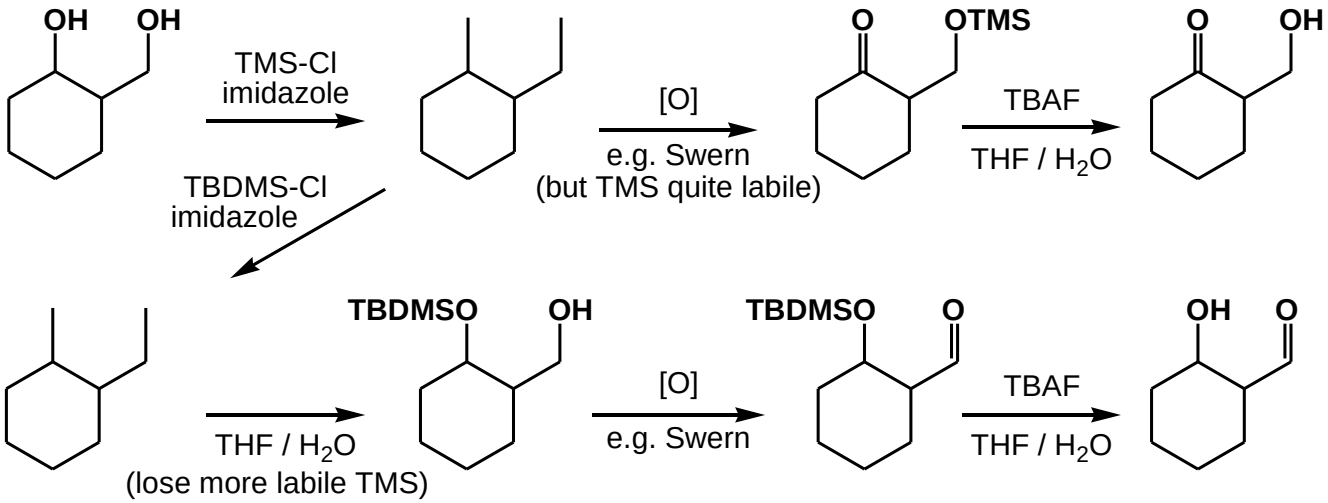
This mechanism is often shown on paper as an S_N2 process. The pentacoordinate Si is accessible due to the longer C-Si bonds and also nucleophile attacks an accessible d orbital, not the C-O σ^* orbital.

Selective protection using silyl ethers

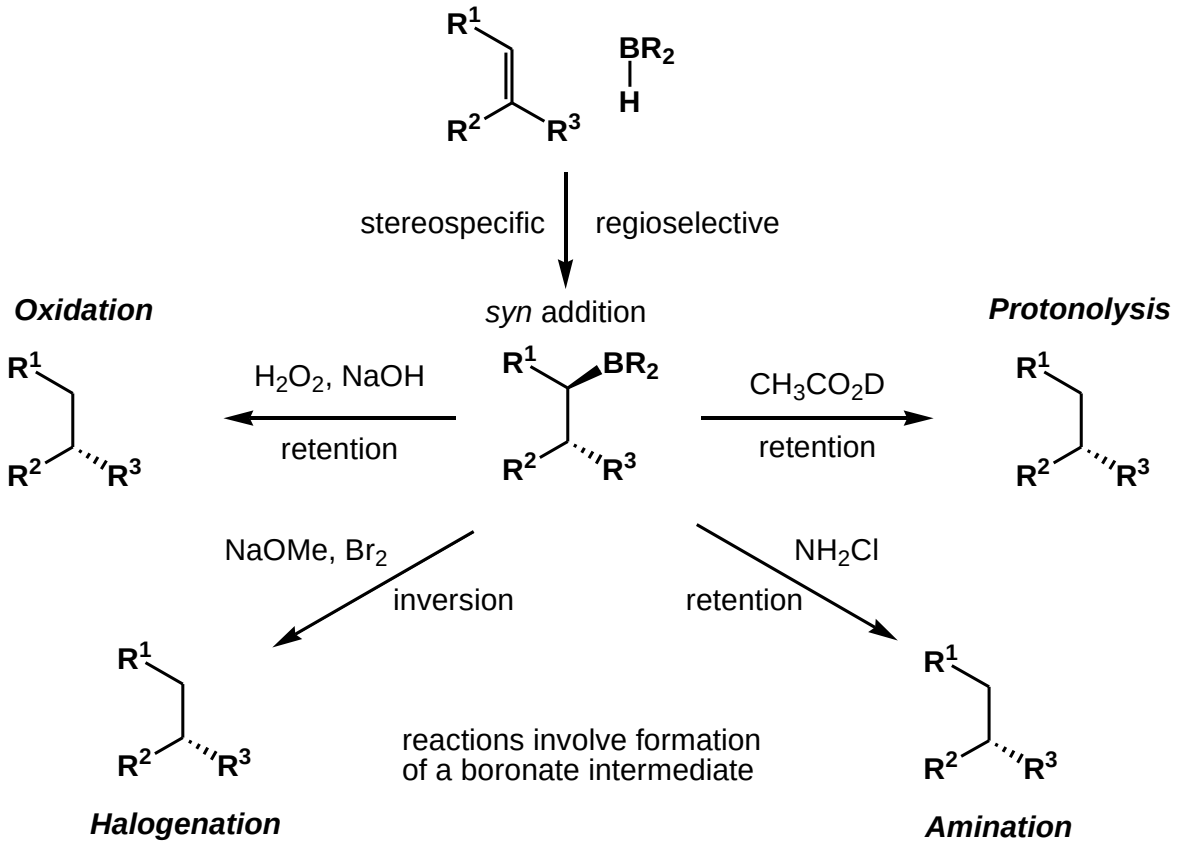
27b

Silyl chlorides, especially bulky TBDPSCl, TIPSCl and TBDMSCl, can be used to selectively protect 1^o alcohols in the presence of 2^o or 3^o alcohols. This can be illustrated in the following example, showing how polyfunctional molecules may be selectively manipulated with the correct protection strategy.

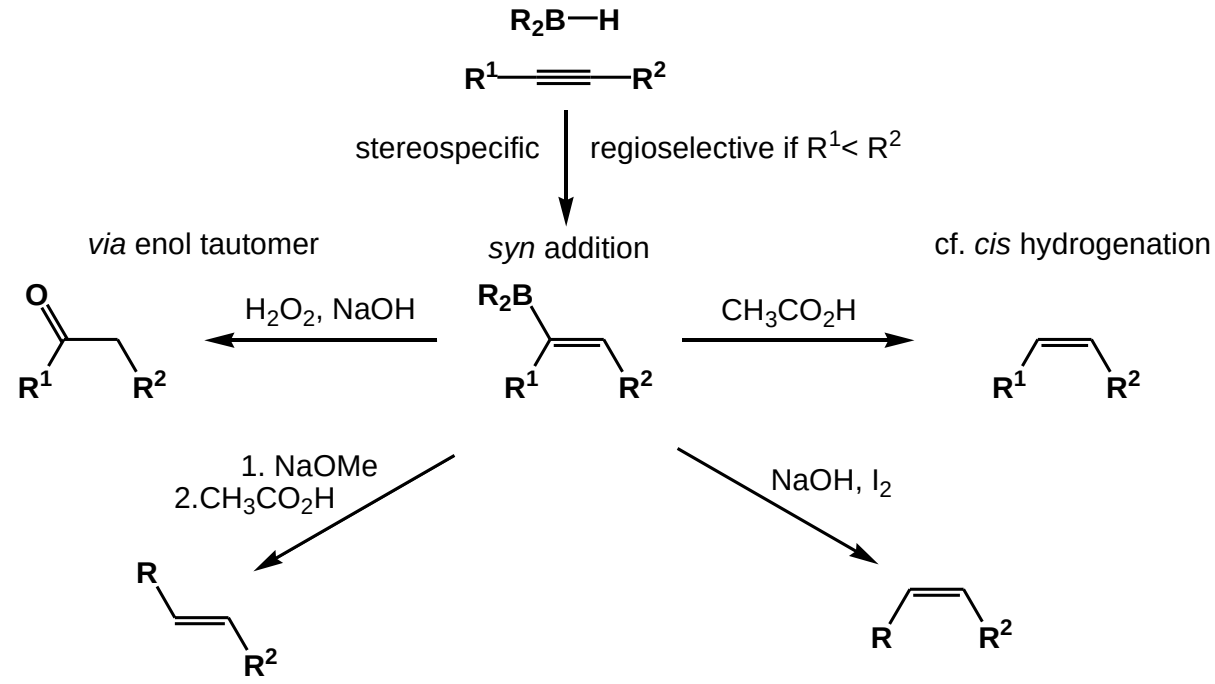




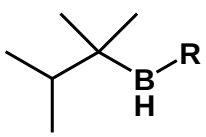
Reactions of alkylboranes - summary



Reactions of alkenylboranes - summary



Only one R group migrates so using thexylborane prevents wastage. The 3° thexyl group migrates slower than a 1° or 2° R group.



The thexyl group is known to migrate in this reaction so there is no advantage in using unsymmetrical boranes.