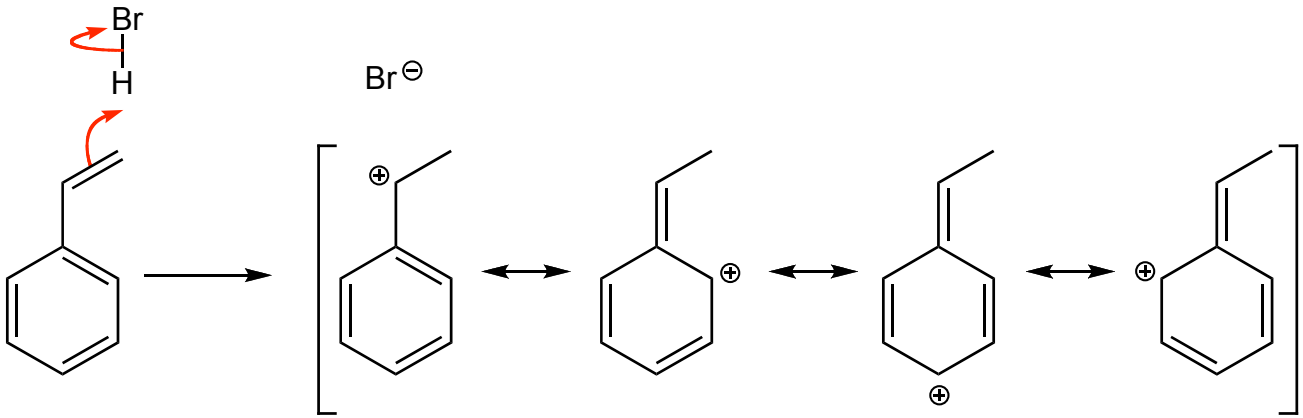
Ben Mills, University of Bristol, 4 March 2008

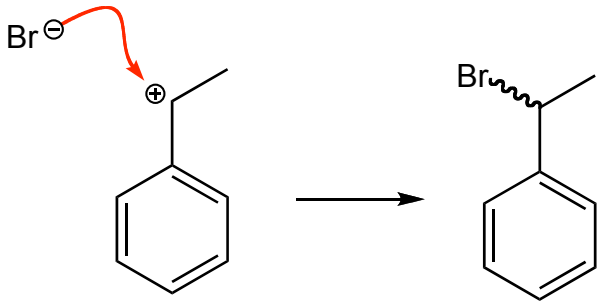
Organic Chemistry: Structure and Reactivity Tutorial Six

Question 1

Hydrobromination of styrene



hydrogen adds to the terminal carbon, so that the carbocation can be stabilised by delocalisation over the benzene ring

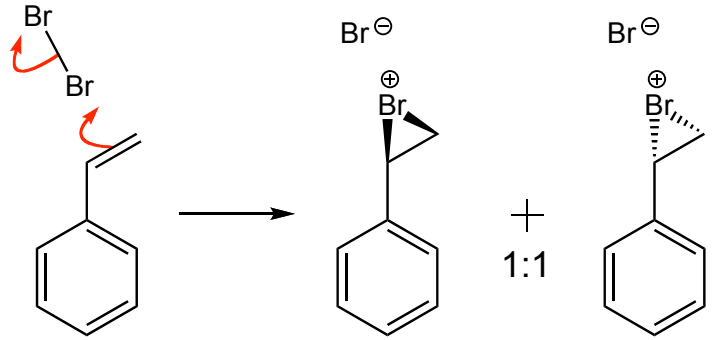


bromide adds to the planar carbocation
from either side, forming a racemic product

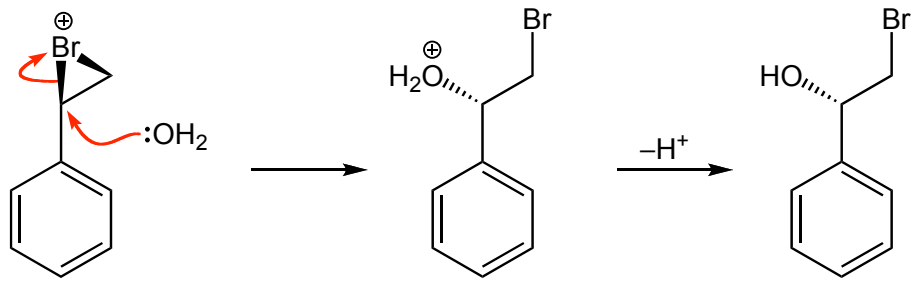
Bromide does not add at any of the ring positions, because the resulting compound would not be aromatic and would therefore be much less stable than the phenyl product.

Ben Mills, University of Bristol, 4 March 2008

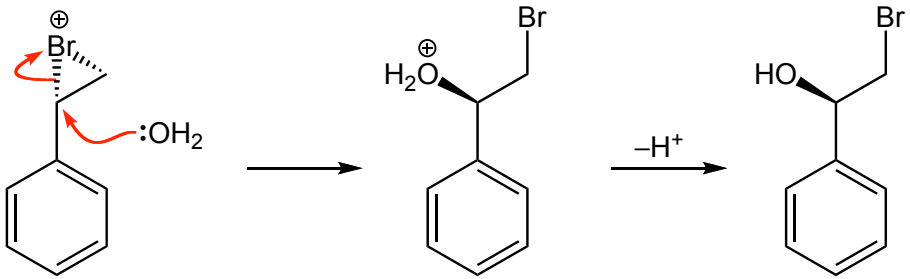
Bromohydration of styrene



bromine attacks styrene's C=C bond from either face of the molecule with equal likelihood, forming a racemic mixture of two bromonium ions

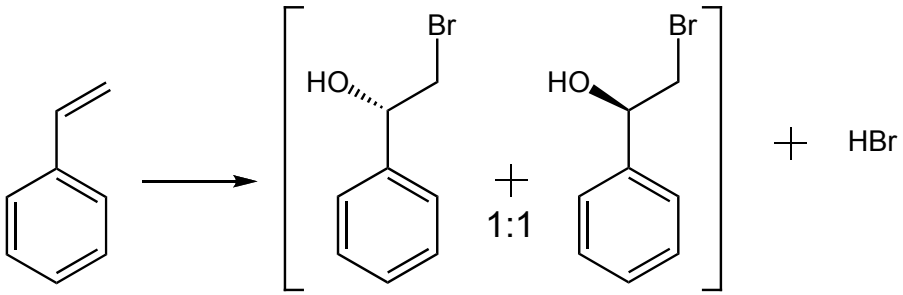


Water is present in much greater concentration than bromide, so is much more likely to attack the bromonium ion first. It attacks the more substituted carbon of the bromonium ion, because this end is more electrophilic.



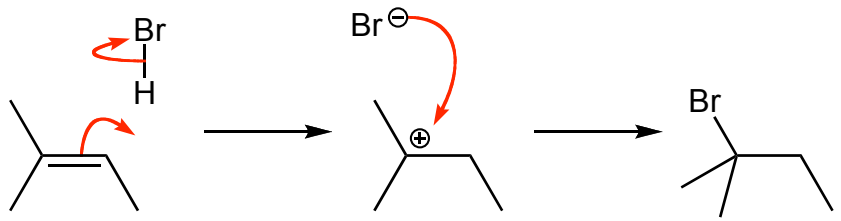
water always adds *anti* to the bromide group, because of the backside attack required on the bromonium ion due to the shape and location of its C-Br σ* orbital

The final products are the two enantiomers, (*S*)-2-bromo-1-phenylethanol and (*R*)-2-bromo-1-phenylethanol:



Ben Mills, University of Bristol, 4 March 2008

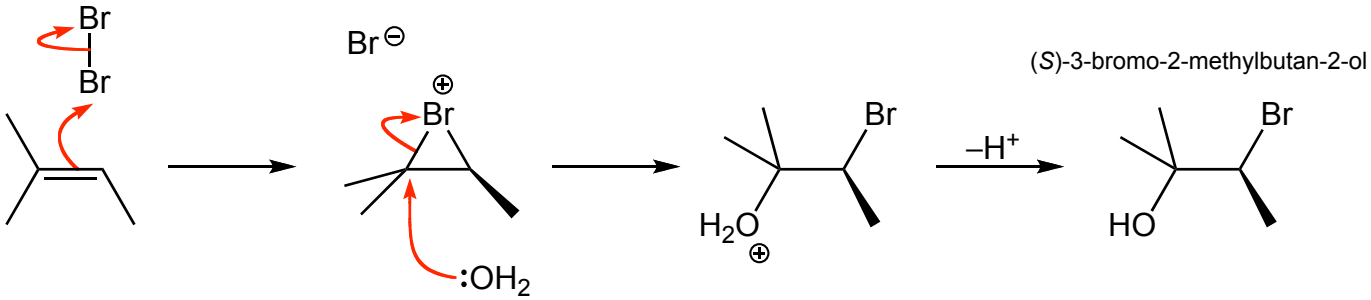
Hydrobromination of 2-methylbut-2-ene



hydrogen adds to less substituted carbon, because the more substituted carbon better stabilises a positive charge, by hyperconjugation from two (rather than one) methyl groups

2-bromo-2-methylbutane
(tert-amyl bromide)

Bromohydration of 2-methylbut-2-ene

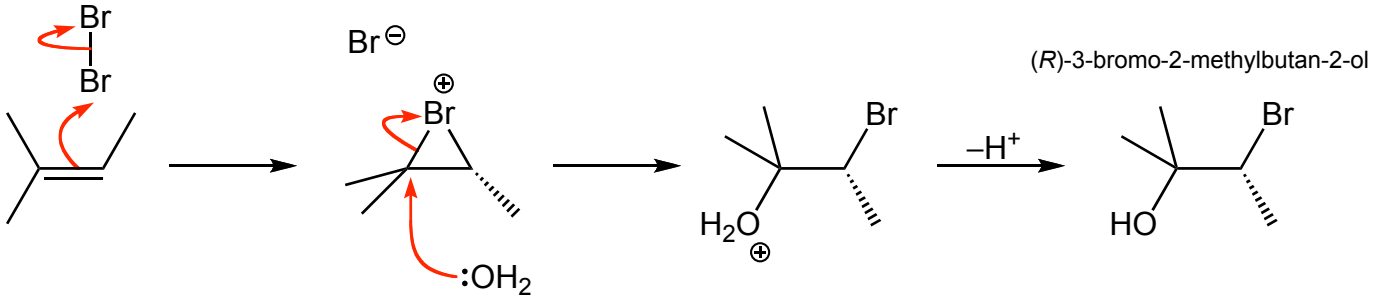


(*S*)-3-bromo-2-methylbutan-2-ol

C=C π orbital overlaps with the Br-Br σ* orbital, forming a bromonium ion and bromide. Water then attacks the more substituted carbon, because it can better stabilise positive charge.

Water has to attack the bromonium ion from behind to allow one of its lone pairs to overlap maximally with the C-Br σ* orbital

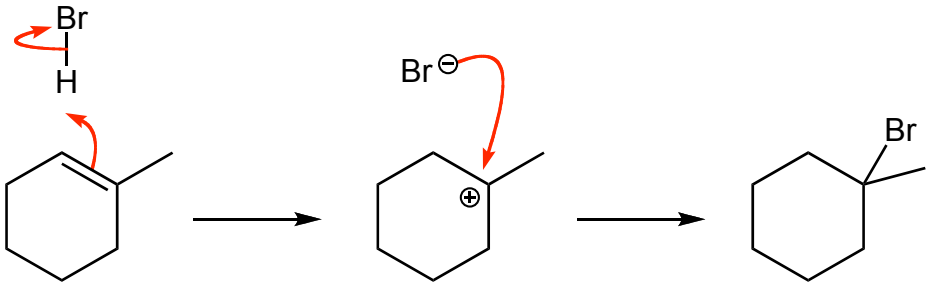
Bromine can attack the alkene from either face, so both enantiomers are formed:



(*R*)-3-bromo-2-methylbutan-2-ol

Ben Mills, University of Bristol, 4 March 2008

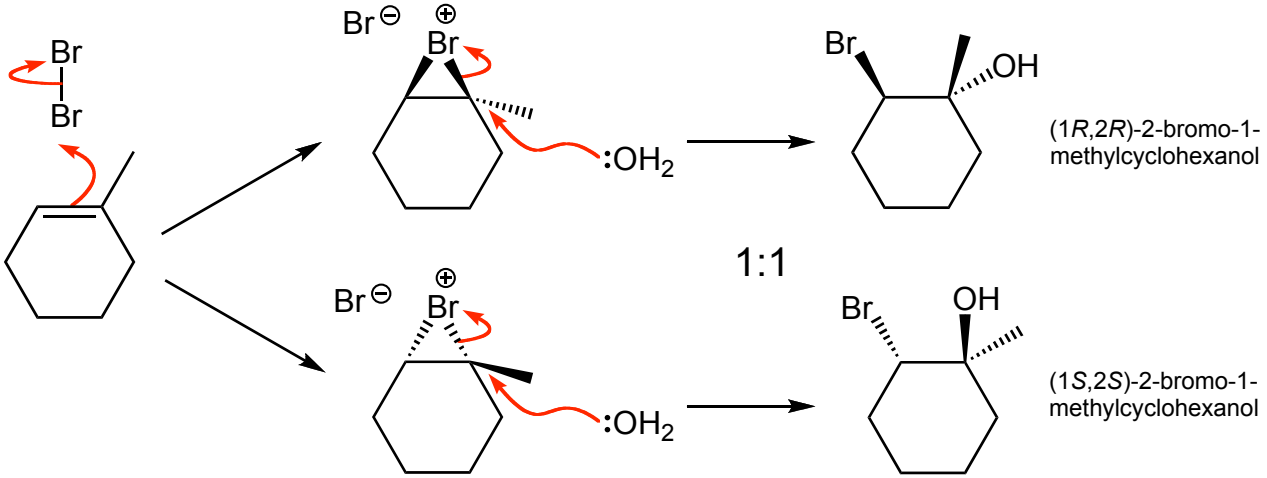
Hydrobromination of 1-methylcyclohex-1-ene



hydrogen adds to the less subtituted carbon, because this results in the positive charge forming on the more substituted carbon, which better stabilised the charge by sigma donation from three (rather than two) alkyl groups

the bromide ion can add to the carbocation from either side, but the product is the same (achiral) either way: 1-bromo-1-methylcyclohexane

Bromohydration of 1-methylcyclohex-1-ene



(1*R*,2*R*)-2-bromo-1-methylcyclohexanol

(1*S*,2*S*)-2-bromo-1-methylcyclohexanol

bromine attacks the C=C bond from either face of the molecule with equal likelihood, forming a racemic mixture of two bromonium ions

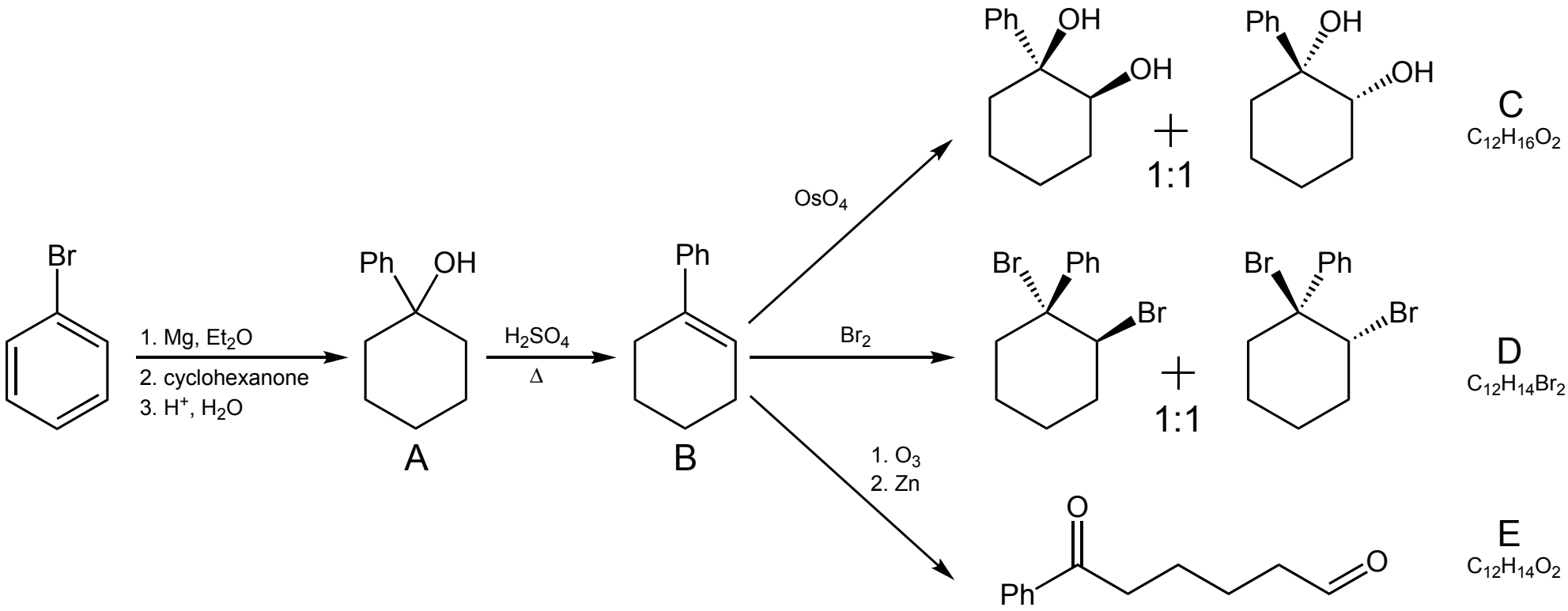
water attacks the more electrophilic, more substituted carbon of the bromonium ion

A racemic mixture of the two *anti*-bromohydrins is formed.

Ben Mills, University of Bristol, 4 March 2008

Organic Chemistry: Structure and Reactivity Tutorial Six

Question 2

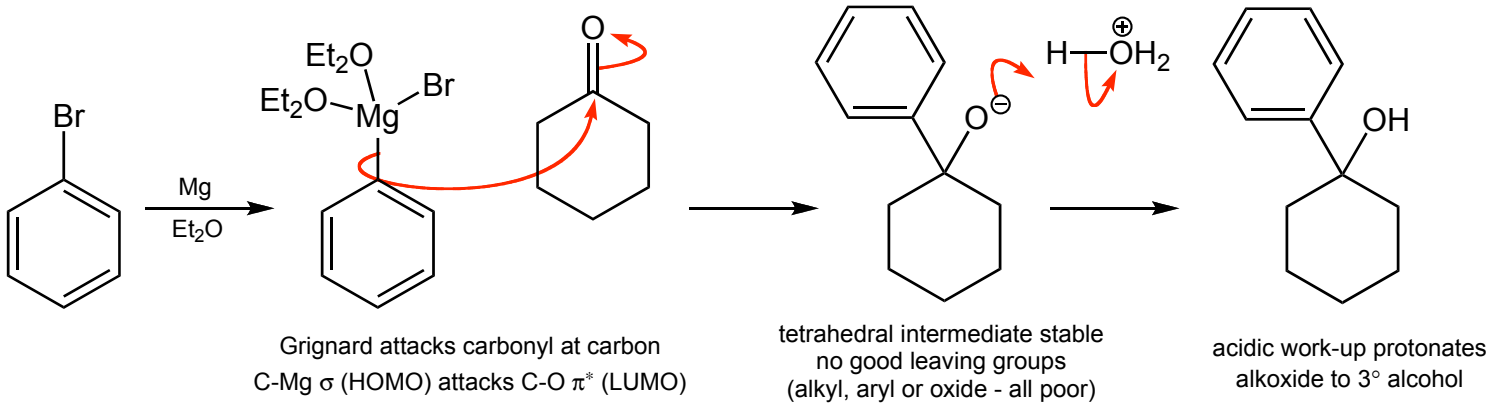


C is a racemic mixture of two *cis*-diols: (1*S*,2*S*)-1-phenylcyclohexane-1,2-diol and (1*R*,2*R*)-1-phenylcyclohexane-1,2-diol.

D is racemic mixture of two *trans*-dibromides: ((1*R*,2*S*)-1,2-dibromocyclohexyl)benzene and ((1*S*,2*R*)-1,2-dibromocyclohexyl)benzene.

E is a 1,6-dicarbonyl: 6-oxo-6-phenylhexanal.

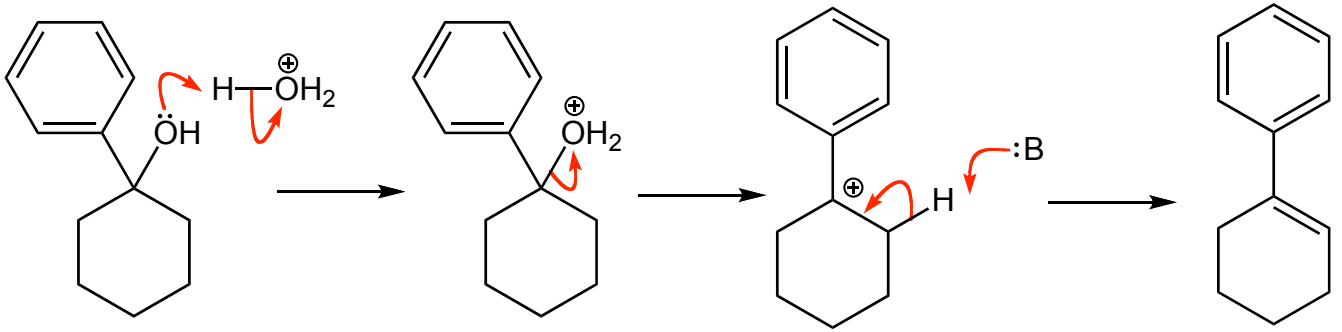
Mechanism of formation of A by Grignard addition to carbonyl



(Mg oxidatively inserts into the C-Br bond of the organobromide, forming a Grignard reagent – mechanism not fully understood)

Ben Mills, University of Bristol, 4 March 2008

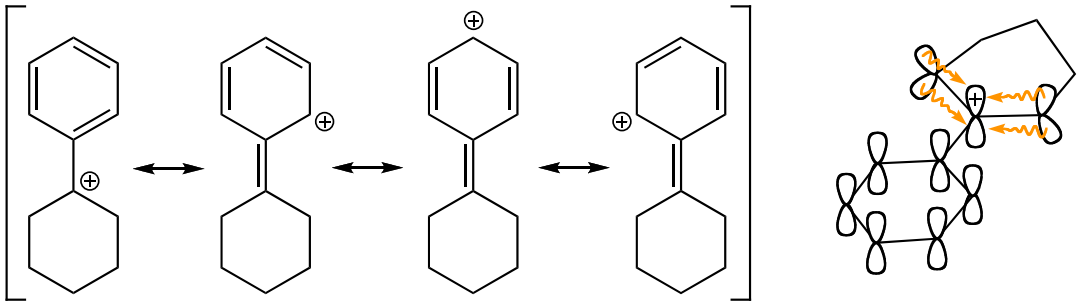
Mechanism of dehydration of A to B



acid protonates hydroxyl group, making it a good leaving group

water leaves, the remaining carbenium ion stablised by delocalisation of the positive charge over the benzene ring (and some sigma conjugation from four cyclohexane C-H bonds)

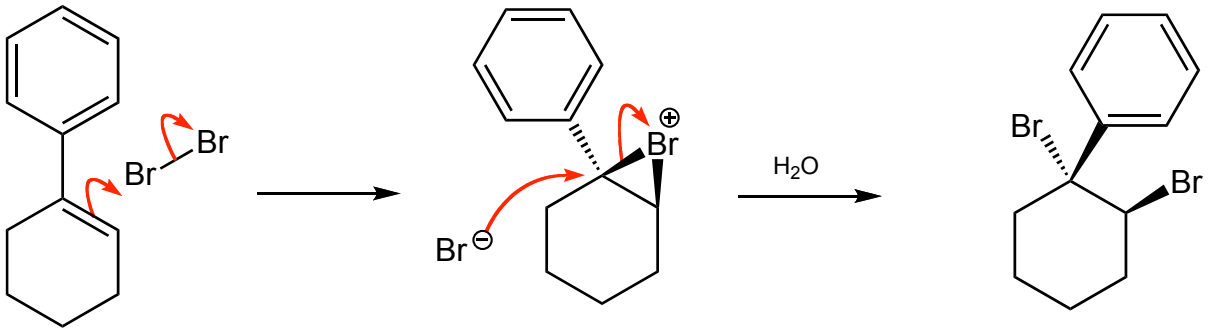
any base (water, sulfate, etc.) can remove the alpha proton from a carbocation, forming a C-C double bond (which is conjugated to the benzene ring)



carbenium ion stablised by π-conjugation to benzene ring and σ-conjugation to C-H bonds

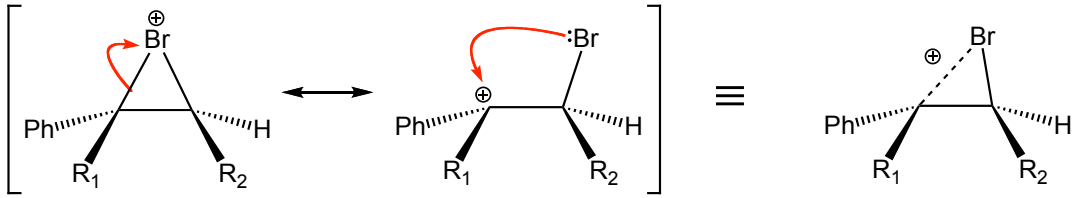
Ben Mills, University of Bristol, 4 March 2008

Mechanism of *anti*-dibromination of B to D with bromine

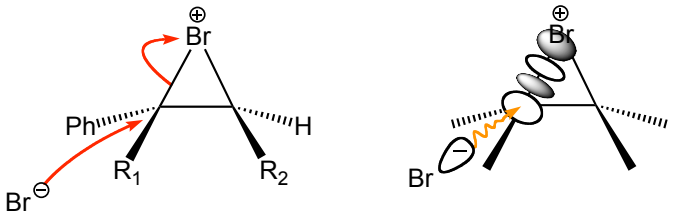


alkene π bond (HOMO) attacks Br-Br σ* (LUMO), forming a three-membered cyclic bromonium ion

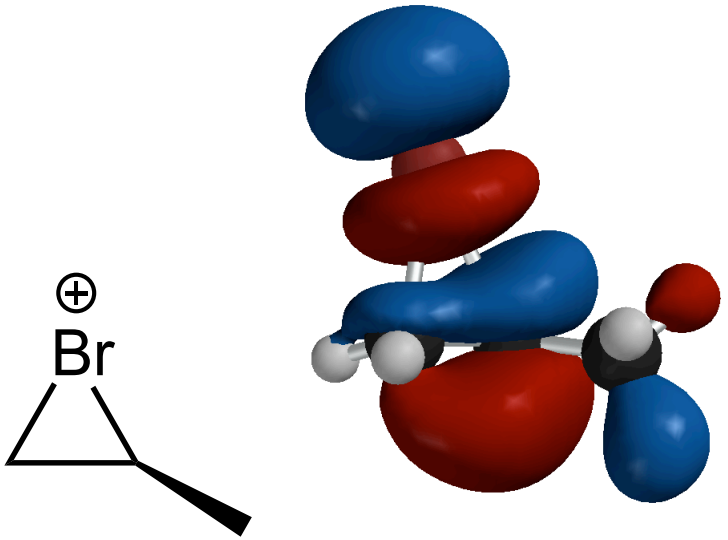
bromide attacks one C-Br σ* of the bromonium ion, cleaving the three-membered ring



The more substituted carbon of bromonium ion is better able to stablise a positive charge and thus has a greater partial positive charge than the other carbon, so it is more electrophilic and is therefore preferentially attacked by nucleophiles, despite the greater steric hindrance at this carbon.



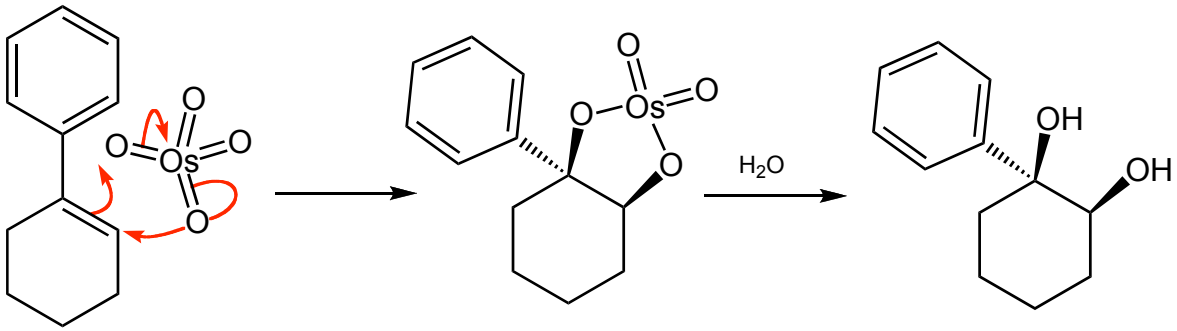
The bromide nucleophile can only attack the electrophilic carbon from below – this backsite attack is required for optimal overlap of the bromide lone pair with the bromonium C-Br antibond (σ* MO).



This isosurface of the LUMO of one of the bromonium ions propylene can form, (*S*)-2-methylbromiranium, shows the lowermost red lobe is more on the more substituted carbon – this is why nucleophiles attack there.

Ben Mills, University of Bristol, 4 March 2008

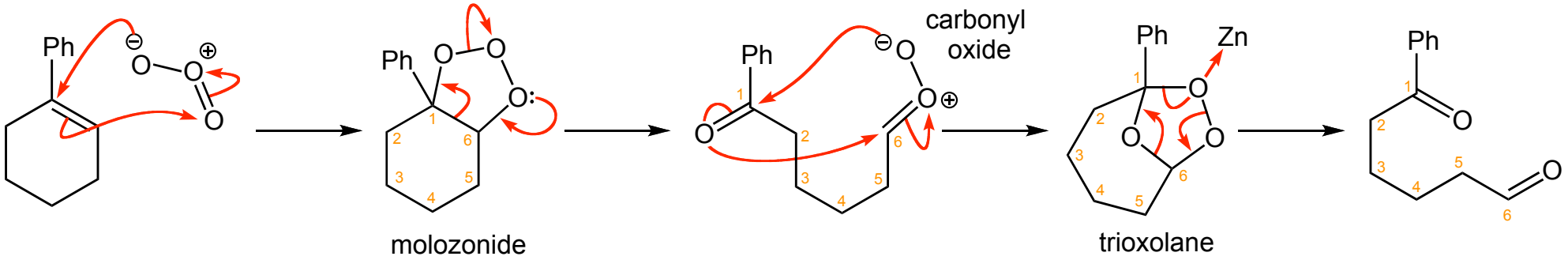
Mechanism of *syn*-dihydroxylation of B to C with osmium tetroxide



cycloaddition of OsO_4 to one face of the alkene, forming an osmate ester

hydrolysis of the osmate ester yields the vicinal *syn*-diol and H_2OsO_4, which can be oxidised back to OsO_4 (by e.g. NMO) to make the reaction catalytic

Mechanism of conversion of B to E by ozonolysis



molozonide

trioxolane

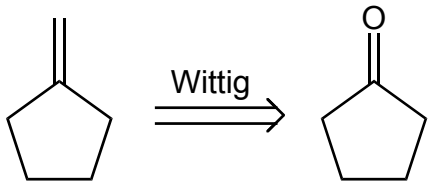
Ozone adds to the alkene via a 1,3-dipolar cycloaddition, forming a molozonide. It then undergoes a retro-1,3-dipolar cycloaddition to a ketone and a carbonyl oxide, the so-called Criegee intermediate. This intermediate then reacts with itself by another 1,3 cycloaddition to yield a trioxolane. The trioxolane is reduced to a ketone and an aldehyde with zinc.

Ben Mills, University of Bristol, 4 March 2008

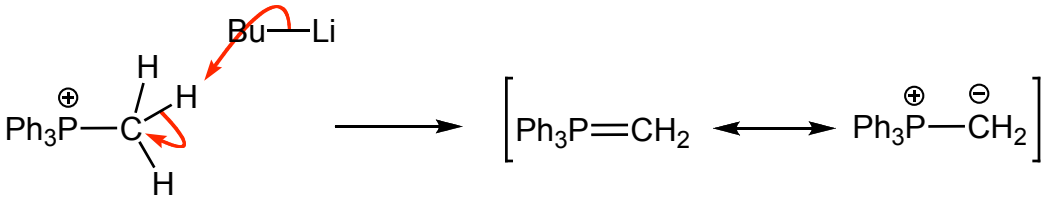
Organic Chemistry: Structure and Reactivity Tutorial Six

Question 3

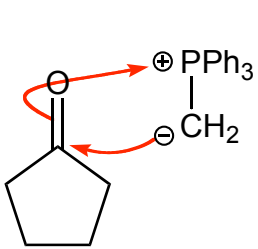
Methylenecyclopentane from cyclopentanone



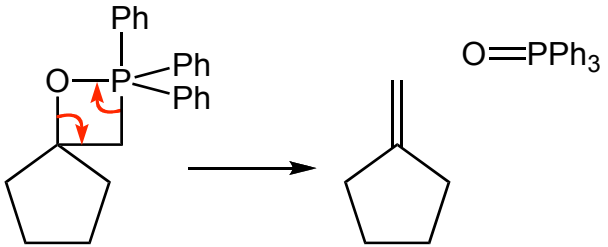
a powerful methylating agent such as methyl iodide will methylate triphenylphosphine to the methyltriphenylphosphonium cation



methyltriphenylphosphonium can be deprotonated by a strong base (e.g. BuLi) to the Wittig reagent, which can be considered as a phosphorane or a phosphonium ylide



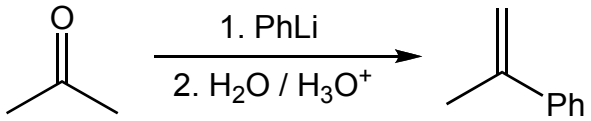
The Wittig reagent is nucleophilic at carbon and attacks the electrophilic ketone - while the alkoxide that forms attacks the positively charged phosphorus, which can accomodate five bonds



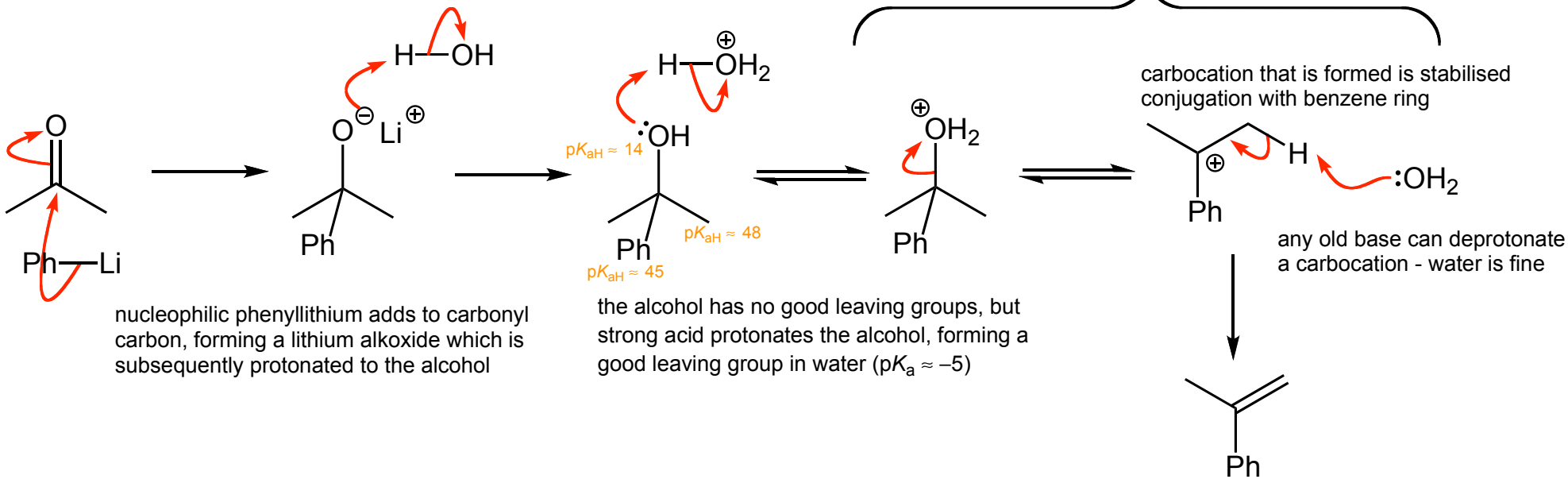
an oxephosphetane intermediate is formed, which decomposes to an alkene and triphenylphosphine oxide - Ph_3PO is very stable, and its formation is the thermodynamic driving force for the reaction

Ben Mills, University of Bristol, 4 March 2008

Prop-1-en-2-ylbenzene from acetone



E1 elimination

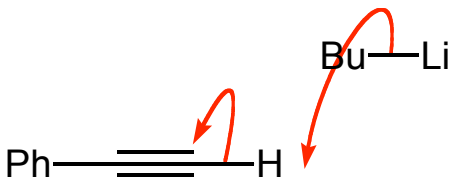


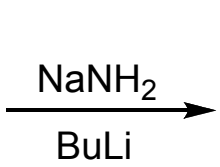
nucleophilic phenyllithium adds to carbonyl carbon, forming a lithium alkoxide which is subsequently protonated to the alcohol

the alcohol has no good leaving groups, but strong acid protonates the alcohol, forming a good leaving group in water ($pK_a \approx -5$)

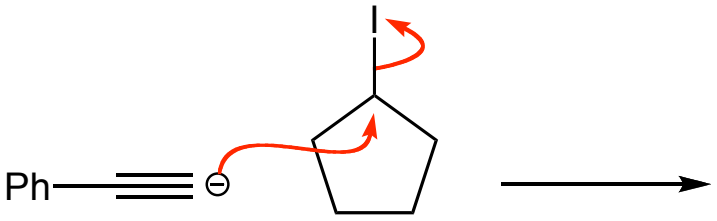
Ben Mills, University of Bristol, 4 March 2008

(*Z*)-(2-cyclopentylvinyl)benzene from phenylacetylene

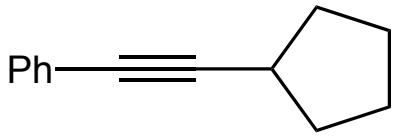




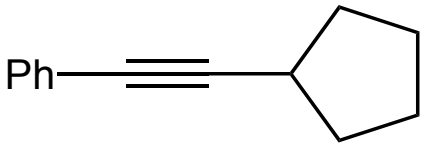
terminal alkynes have a fairly acidic proton ($pK_a \approx 25$) that can be removed by a strong base such as BuLi

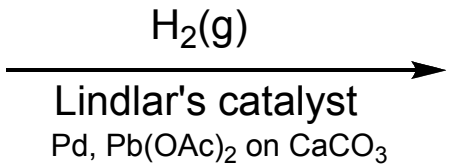


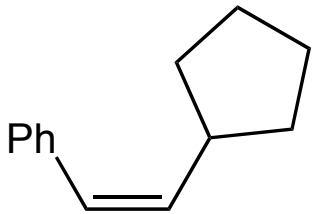
the acetylide anion formed is a powerful nucleophile, which can attack an electrophile such as an alkyl iodide, in this case via S_N2 - although probably quite slow as the iodide is quite sterically hindered



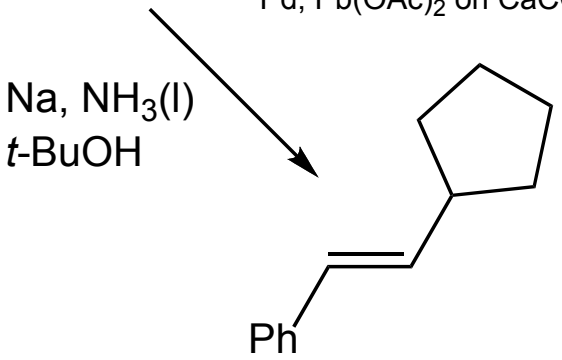
a disubstituted acetylene is formed







Lindar's catalyst forms only the *Z*-alkene, since it delivers two hydrogen atoms simultaneously to the same face of the alkyne

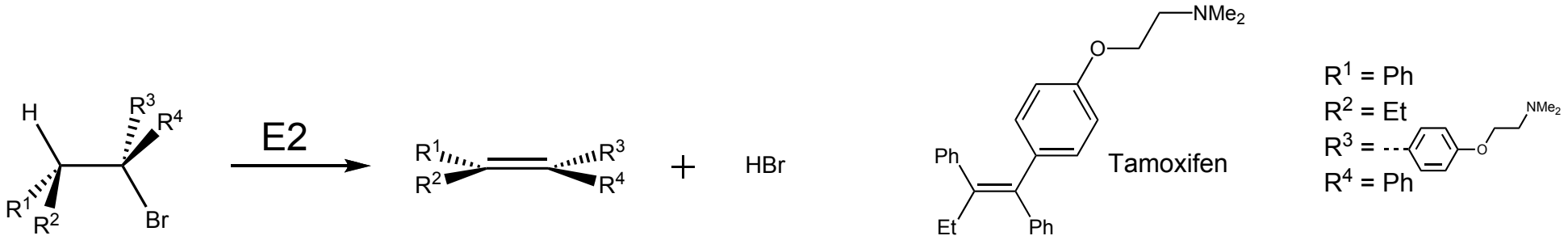


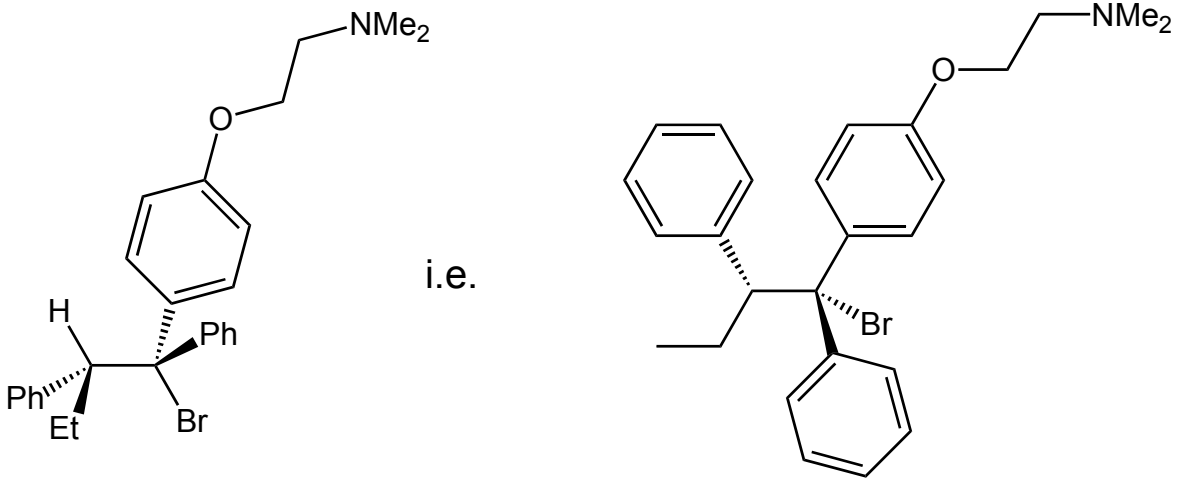
Sodium in liquid ammonia ensures *anti* addition and thus forms the *E*-alkene, due to the reaction's radical mechanism (Clayden, p. 819)

Organic Chemistry: Structure and Reactivity Tutorial Six

Question 4

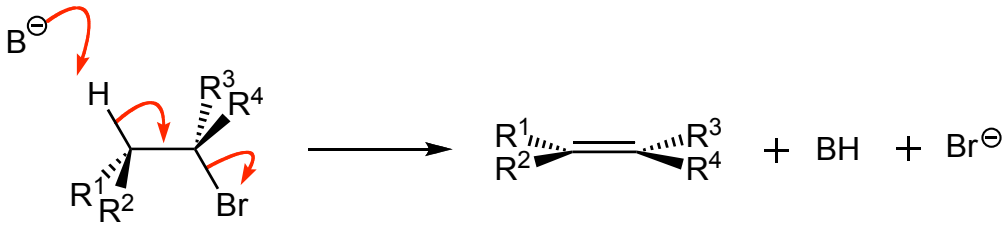
Tamoxifen by elimination of a bromide



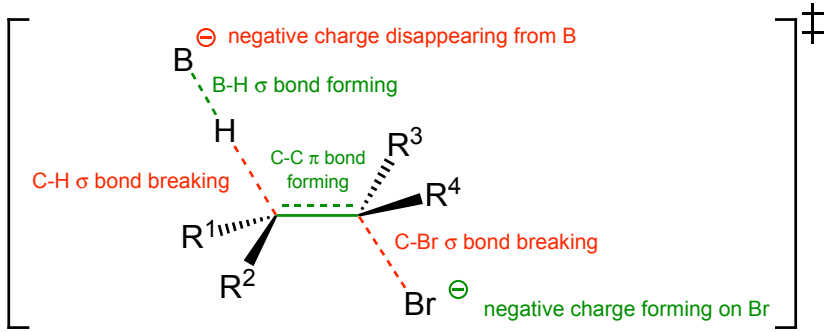


Starting bromide: 2-(4-((1*S*,2*R*)-1-bromo-1,2-diphenylbutyl)phenoxy)-*N*,*N*-dimethylethanamine

It might be difficult to prevent E1 elimination occurring simultaneously, leading to a mixture of two stereoisomers (racemic if 100% E1, otherwise ratio depends on ratio of E1:E2) – bromide could leave, resulting in a carbocation stabilised by conjugation with two aromatic groups. The question only mentions E2 elimination, so I'll go with the flow.



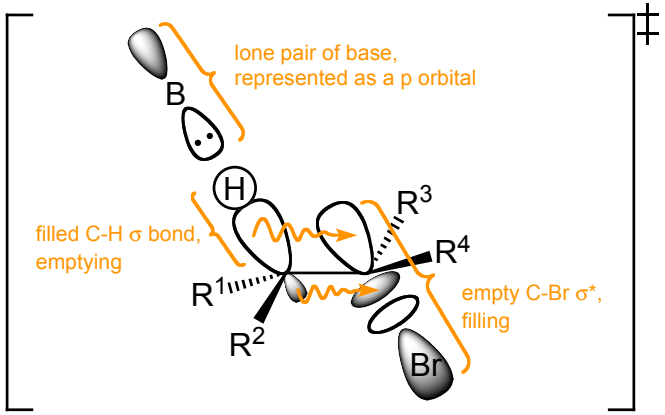
A strong base is required to effect E2 elimination, whereas the weakest of bases can deprotonate a carbocation in E1. A bulky, non-nucleophilic but strong base is ideal, such as *t*-BuOK. In this particular case, the bromide is tertiary, so even a nucleophilic base would be unable to perform S_N2 instead of the required E2. So here, any strong base will do.



anti-periplanar transition state for E2 elimination

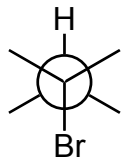
The new π bond is formed as the C-H σ bond overlaps with the C-Br σ* antibonding orbital.

The lone pair on the base becomes a B-H σ bond, the C-H σ bond electrons become the C-C π bond electrons, and C-Br σ bond electrons become Br lone pair electrons.

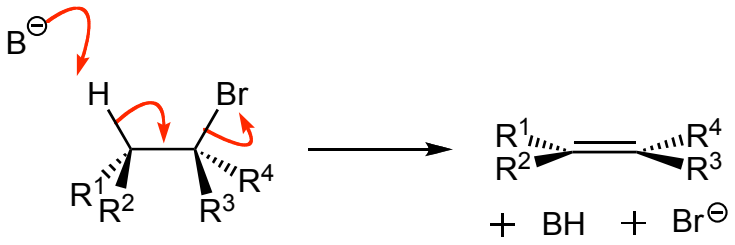


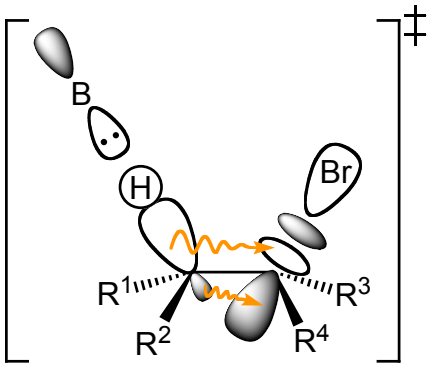
Orbital picture of the anti-periplanar E2 transition state. Orbital symmetry requires a transition state in which the C-H σand C-X σ* are parallel.

With the anti-periplanar transition state, only one geometrical isomer of the alkene forms. Orbital overlap is optimal in this geometry, so E2 eliminations go via this TS if at all possible.



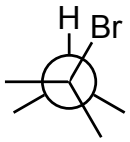
a Newman projection of the anti-periplanar conformation shows it is sterically the most stable conformer, and an orbital picture shows it is electronically the favoured geometry, too





Orbital picture of the syn-periplanar E2 transition state.

With a syn-periplanar transition state, the other geometrical isomer of the alkene would form - this is not observed in E2 unless the starting material is constrained and thus has no choice but to adopt a syn-periplanar TS. E2 eliminations are much slower in such a situation, e.g. *endo*-*cis*-2,3-dichloronorbornane.



a Newman projection shows the steric hindrance in a syn-periplanar conformation, due to replusion between substituents