Homework 4 – 2017/04/24

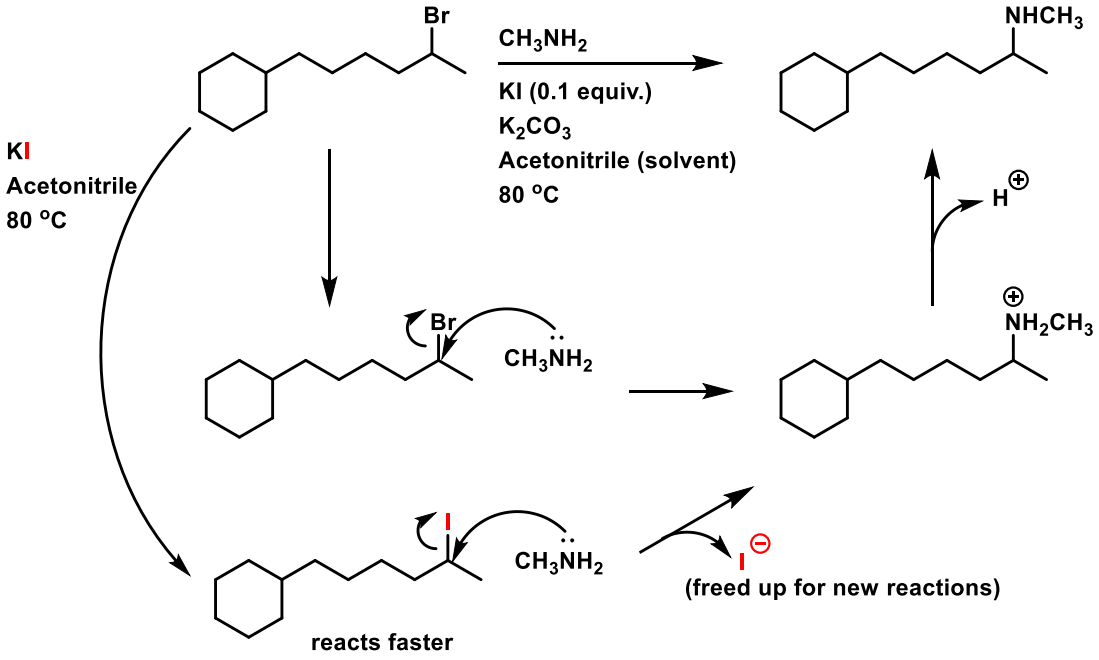
1) Often people will add a catalytic amount (~0.1 stoichiometric equivalent, 10%) of an iodide salt, usually KI, to nucleophilic substitution reactions. For an example, see below.

a) Based on what you know about the mechanisms of these reactions, suggest an explanation for why this is a good idea.

Proposed explanation:

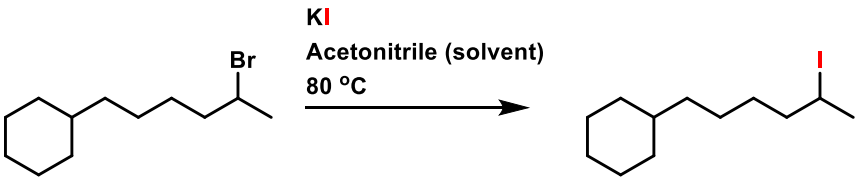
The rate of nucleophilic substitutions depends on the electrophile. What happens in these reactions is that the added iodide acts as an external nucleophile, and generates a highly reactive alkyl iodide species. This reacts faster than the alkyl bromide.

Alkyl iodides are more expensive than alkyl bromides, so it's nice that you can use the cheap stuff as the stoichiometric reagent. Additionally, there might be toxicity/carcinogenicity problems with some really reactive alkyl iodides, which means that you might not want to handle them on a large scale.

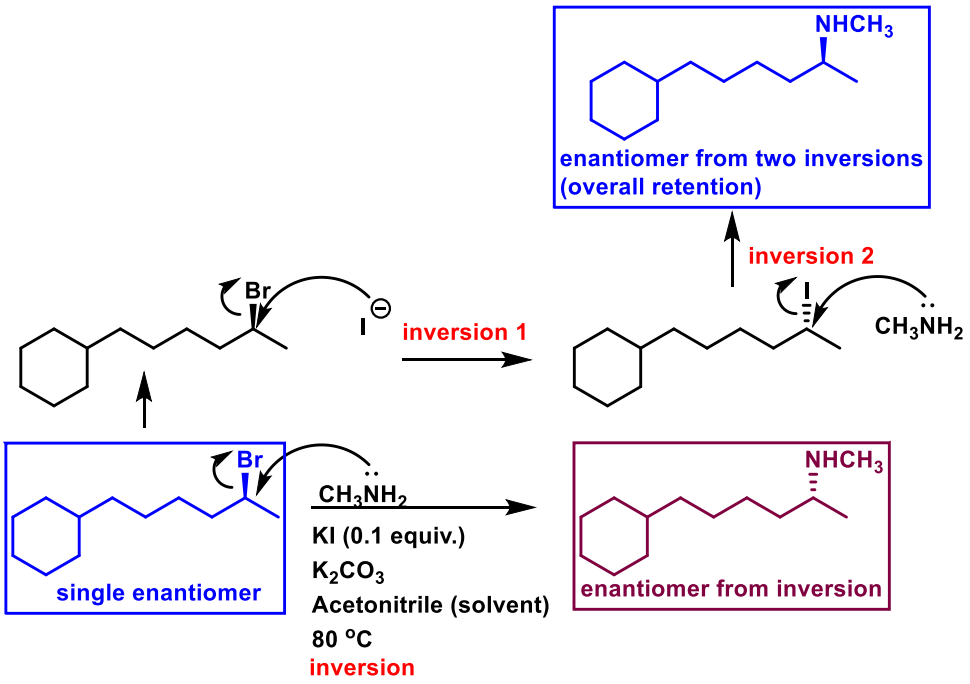


b) How would you confirm your suggestion?

- You can add KI to your alkyl bromide, and see if you see any replacement of the bromide with iodide. You can do this by simply stirring your alkyl bromide with iodide for a while, and then stopping the reaction and analyzing the product. If it's a bromide-iodide mixture, that's consistent with the hypothesis.



- You can also start from a single enantiomer of a chiral alkyl halide (see below). Then, the iodide will replace the bromide in an S_N2 reaction, which inverts the stereochemistry. Then, the iodide gets replaced with the nucleophile, again in an S_N2 reaction, which inverts the alkyl iodide intermediate's stereochemistry. Two inversions mean retention, so if you find that adding iodide both speeds up you reaction and results in a (at least) partial racemization of the product, that's a good support for the hypothesis.



c) Are there reactions where this is just a waste of iodide? If not, why not? If yes, give an example, and explain.

For S_N1 reactions, the rate determining step is the formation of the carbocation, so, while the leaving group is still important, going from Br^- to I^- may not make a huge difference. Also, if you're keen to do a clean S_N2 reaction with inversion of configuration (e.g. because you're working with an enantiomerically pure sample), adding iodide, and risking retention during alkylation would not be a good idea at all.

d) What is the by-product of the reaction?

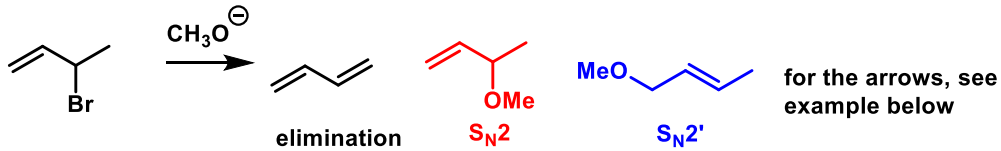
In the first step you displace Br^-, and then the amine loses a proton. Overall, it's HBr.

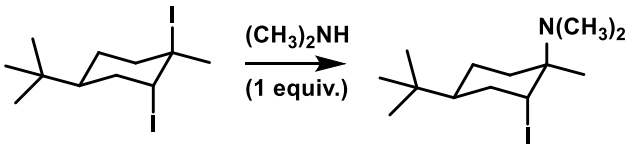
e) What is the role of the K_2CO_3?

It's a base. The HBr by-product is a strong acid & can protonate CH_3NH_2, a basic amine. Protonation kills the amine's nucleophilicity, as it forms a positively charged protonated species. When you've transformed half your starting material, you've produced 0.5 equivalent of HBr, which protonates 0.5 equivalents of the amine – exactly the amount you had remaining. This basically stops the reaction halfways.

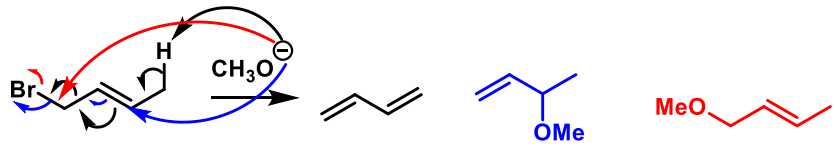
This means that if you have a cheap amine, you can use at least two equivalents (1 equiv. as nucleophile, 1 equiv. as base). Alternatively, you can add a cheap base (e.g. K_2CO_3) to mop up the acidic by-product.

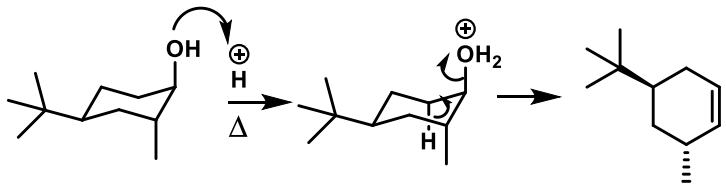
2) Nucleophilic substitution and elimination reactions can occur under similar conditions, and are often competing with each other. In the reactions below, draw the most likely product (or products), with a very short explanation about why you think it (they) will be dominant. Pay attention to the stereochemistry, when relevant!



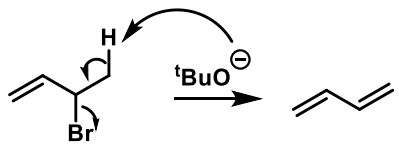


S_N1 substitution is fastest. The other iodide does only slow S_N2 (secondary carbon with a lot of stuff nearby, bulky nucleophile), so it probably gets outcompeted by the S_N1 (which the tertiary iodide does really well)

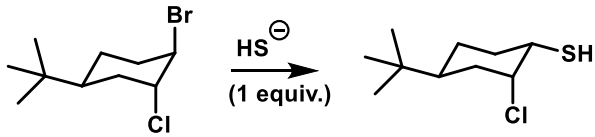




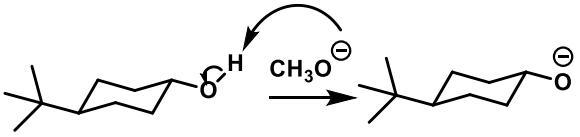
(there are other alternatives which are not covered in this course)



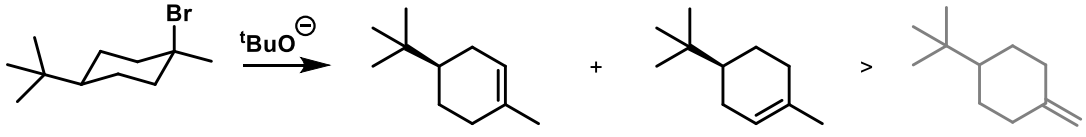
***tert*-butoxide is a really lousy nucleophile, but it's a lovely base**



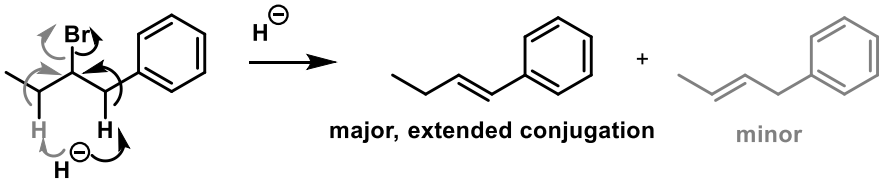
the bromide is a better leaving group, and is easier displaced in an S_N2-reaction than the chloride. Also, the bromide is in a sterically less hindered position.



yes. this is precisely *this* boring.

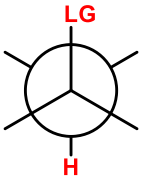


major products, enantiomers

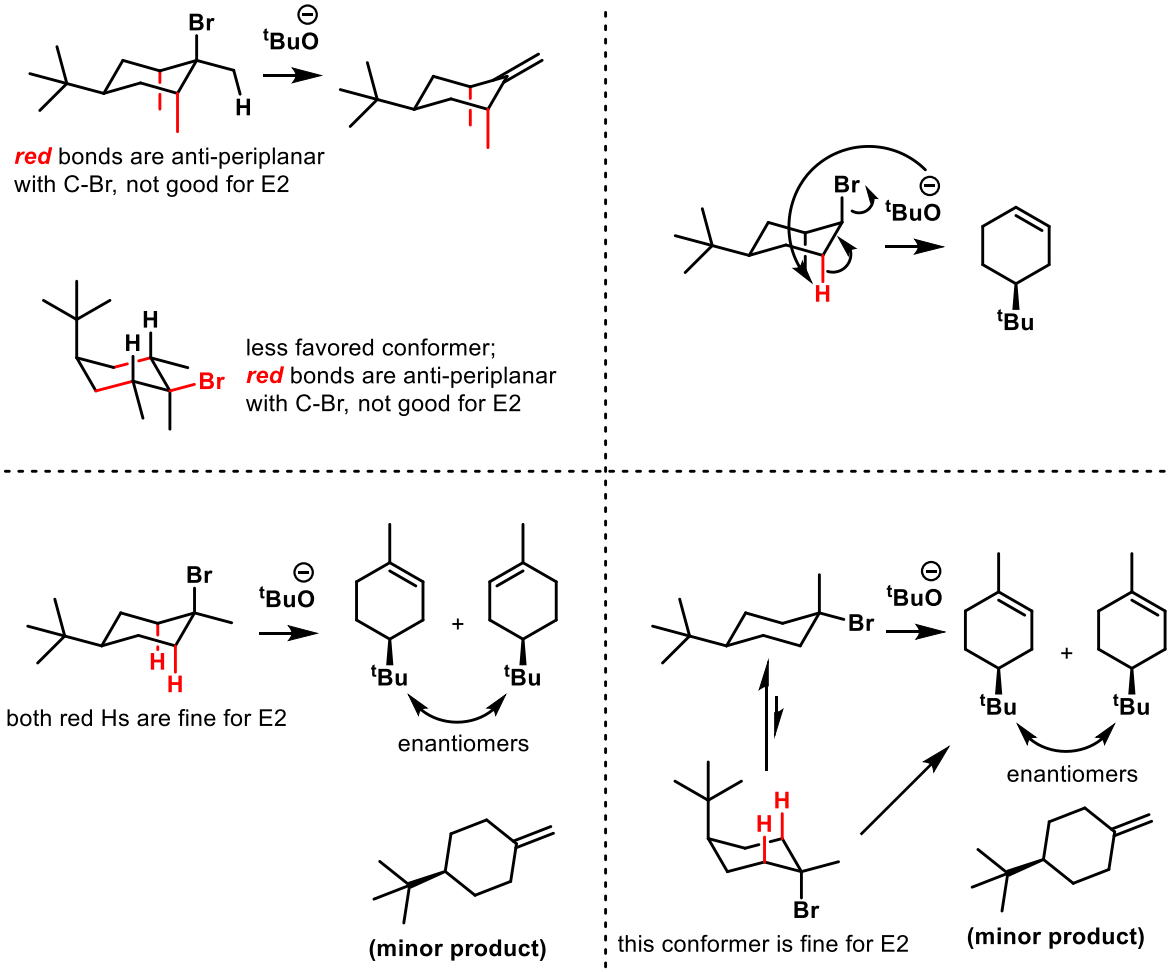


major, extended conjugation

3) For E2 reactions the leaving group and the H have to be in a so-called anti-periplanar conformation (see below). This means, that if such a conformation is inaccessible for the molecule, then there will be no E2. (There might be substitution or E1 taking place of course.)



a) Of the compounds below, which ones can do E2? Draw all the possible E2-products.



b) Which one of the cyclohexane derivatives reacts faster in an E2-reaction? (Hint: think about the favored chair-conformations of cyclohexanes, and how large substituents like to be placed in a chair.)