Lab 6A • 02/01/12

We have the Grignard reaction and the Wittig reaction that are both ways of forming carbon-carbon bonds. The main difference between the two is a Grignard reaction forms a carbon-carbon single bond, whereas a Wittig reaction forms a carbon-carbon double bond. What we're about to see is an example of a Grignard reaction, but also an example of how you might have difficulties using a Grignard reaction to get to the product that you want, and therefore seeing why we might want to use the Wittig approach instead.

I've started out with a ketone, 3-methylbutan-2-one, and I'm throwing an alkylmagnesium halide at it; this is a classic example of a Grignard reagent, an organometallic reagent. You might recall that that is effectively going to act as if it is methyl minus. So methyl group attacks the carbonyl, pushes it open. We initially end up with an alkoxide. Normally, you do a very gentle acid work-up, which will get you to the alcohol; in this case, if we left it in acid and heated it up, we could cause a dehydration to occur. This is the normal product, the most favorable product we might expect from that dehydration. The first steps would be for the alcohol to get protonated and come off, which in this case would form a tertiary carbocation. Rearrangement is not impossible but unlikely because you already have a tertiary carbocation. When elimination occurs under heat like this, it tends to be the more substituted alkene that forms because it's the one that's more favorable thermodynamically. We have learned eliminations, but there are two eliminations that can occur. One is the thermodynamic product – that's known as a Zaitsev elimination, whenever the more substituted alkene, the more thermodynamically favored alkene forms, that's Zaitsev elimination. But [you can cause] the opposite behavior, where you have elimination to form a double bond that's not the most substituted one. Sometimes that's referred to as anti-Zaitsev behavior; sometimes it's called Hoffmann elimination.

Let's say that we wanted to make an alkene out of this intermediate alcohol, but make it such that the double bond goes to the terminal position. That would leave only two substituents on the double bond, which is less favorable than the four that I formed a minute ago. But we can force that reaction to happen, if we use the right kind of reagents. First, I'll turn this into a leaving group, because I need a leaving group to do elimination. But then, I'll use potassium t-butoxide. That t-butoxide, because it's so bulky, it makes it more difficult for it to access the tertiary proton it would need to in order to eliminate and make the product that I showed originally. Thermodynamically, yes, it would still be more favorable to eliminate to the interior. But, if you had a bulky reagent like this, and let's add to that, let's say that we do this reaction at low temperatures. At low temperature, it's going to be the activation barrier that really controls what kind of reaction is going to happen; in other words, only those reactions that there's enough energy to happen will be the ones that tend to happen; that's kinetic control. Low temperature and using a hindered base like this, making the approach more difficult, will steer this to reacting with a primary hydrogen instead, because it's more accessible. This will give us the Hoffmann elimination product.

This is the thermodynamic product. Just like we have the term Markovnikov to describe the usual pattern of substitution we get when we add something to a double bond; Zaitsev is the term we use to describe the thermodynamic formation of a double bond. Down below here, this is the kinetic product; Hoffmann is the name often give to this kind of elimination, or it's sometimes called anti-Zaitsev as well. At low temperatures, only those reactions with lower activation barriers tend to predominate, even if they result in products that may not be as favorable thermodynamically. When a large, bulky base is used to perform eliminations, a less favorable product may be formed because of the difficulty the base has at accessing a more sterically-hindered hydrogen. That's exactly what we did in this example: we used t-butoxide, bulky base, would more easily grab just that primary proton in this example than the tertiary that would have otherwise given us the thermodynamically more stable product.

We were able to get to the product in this case, but there could be other cases where we might imagine we want to make an alkene where elimination might get us three different potential products. Is there a way we could force this particular reaction to occur? The answer turns out to be yes: that's what we can do with a Wittig reaction. The Wittig reaction has a unique type of reagent normally used, just like a Grignard reaction generally has those alkylmagnesium halides as reactants. First I'm going to show you how [a Wittig reaction] is normally done. In generally for a Wittig reaction, you start with an alkyl halide or an alkyl tosylate, and you react it with a compound called triphenylphosphate. A benzene ring is sometimes abbreviated with the symbol Ph, because a benzene ring, when it's a substituent, is called a phenyl group. Ph, we can also write that as the Greek letter phi – it makes it a heck of a lot easier to abbreviate compounds that have lots of benzene rings in them, like triphenylphosphine. So, I can write triphenylphosphine as Pphi3. That phosphorus is even more nucleophiilic than a nitrogen would be, even though this phosphorus is not as basic; it's the same story that we have with oxygen versus sulfur – sulfur, being lower on the periodic table, is squishier (that's the technical word) and therefore able to start bond formation during a substitution reaction. Same thing here; this is a relatively easy Sn2 reaction. The general name for this is a tetraalkylphosphonium salt, that we initially make.

The next step is to deprotonate this compound. This compound deprotonates just a little more easily than a standard old alkane cause we do have this positive charge next door that would interact favorable with a negative charge if one were to form next to it.

Phosphorus already has an octet as written, but phosphorus being on the third row of the periodic table can have an expanded octet – that's our watered-down phrase for meaning a complicated orbital interaction can occur – in other words you can put more than eight electrons into the valence shell of phosphorus. Although this is more acidic than an standard alkane, you still usually need a pretty hefty base to deprotonate one of these compounds. If you're doing a general Wittig reaction, the reagent that often is used is n-butyllithium. The 'n' in n-butyl means 'normal', which means unbranched. n-Butyllithium is butane with a lithium sticking off of it. It's similar to a Grignard reagent, where it acts as if it is a carbanion, it is a carbon with a negative charge, and carbanions are really, really basic. What we could show is n-butyllithium deprotonating this tetraalkylphosphonium salt, which will make something that has two different names we could call it. The general term for a compound that has both a plus and a minus charge on it is zwitterion, which literally means 'twin ion'. Where you'll more commonly see that term is with amino acids. They're called amino acids because they have an amine portion – which is a base, a nitrogen – and you have a carboxylic acid portion – which is an acid. They therefore can self-neutralize in solution, forming both a carboxylic acid salt and an ammonium salt, so you get both a plus and a minus on the same molecule. This is an even more special version of one called an ylide. If you think about the ending -yl, you often see that in names like the methyl group or the methyl carbocation, so yl itself doesn't mean positive charge, but it's often used in names with positive charges. The -ide ending, think of halide, oxide, nitride – negatively charged. So this ylide is really plusminus, right next door to each other – which, because phosphorus could have more than a standard octet, we could write a resonance structure for this compound and show it as being a neutral, doubly-bound compound. There is no difference between those two structures; they're just two different ways to write it.

How does this critter react? Let's throw it at the same ketone that I used in the Grignard example. A Grignard reagent, as you might expect, is fairly polarized, because it has both a positive and a negative terminus. A negative carbon, that's very likely to attack a carbonyl, that's what a Grignard reagent does. So, I'll have this attack the carbonyl, push it open. Once that occurs, recognize that they're not connected to each other, but in space there's a positive and a negative charge that are practically right next door to each other. Very rapidly, you'll end up forming a four-membered ring. Not normally favorable to make a four-membered ring, but because of the opposite charges, it does occur. There is a naming system for what are called heterocyclic compounds. You might remember that the term heteroatom means something besides carbon and hydrogen – if you have hydrocarbons and you modify them, those extra atoms are called heteroatoms. Using similar terminology, a ring that has something other than carbon as part of the ring is called a heterocycle. There's a special nomenclature that doesn't have number endings; they're just words that they created that they in themselves mean three- or four- or five- or six-membered ring. This intermediate has the name oxaphosphetane. The -etane ending means four-membered ring, the phos- portion of it means you've replaced a carbon with phosphorus; the oxa- means you've replaced carbon with oxygen. Oxaphosphetane is just a complicated way of saying four-membered-ring-with-an-oxygen-and-phosphorus-in-it.

In this case, when you have that kind of structure, it rapidly decomposes, because it is enormously favorable to form an oxygen-phosphorus double bond. That's what drives the decomposition of this intermediate; you don't even isolate this, just reacts and decomposes. One of the things that's spit out is triphenylphosphine oxide, which is a thermodynamic brick, meaning it's very favorable to form. Anything that's favorable to form, which might imply the release of energy, that's why something would want to occur. At the same time, notice that we end up with an alkene, not a single bond, and there's no more oxygen there, but a double bond directly. Just the Wittig reaction by itself gave us exactly what we would have wanted from a Grignard reaction followed by an elimination. Since there is no rearrangement that occurs, this lets you make the double bond in a very specific location; that's part of the synthetic advantage of using a Wittig reaction.

[comment that triphenylphosphine is a neurotoxin and therefore not used in lab]

[review of common names – phenyl, benzyl, vinyl, allyl, aspargyl]

Benzyl compounds are unusually reactive because if you dissociate and put a carbocation on there, the carbocation is delocalized, heavily. In fact, you can form a carbocation there, even though it's primary, because you don't have hyperconjugation from the benzene ring, you have full-on conjugation with the benzene ring. Similarly, it is easier than normal to form an anion that that benzyl position, again because of delocalization (resonance) with the benzene ring.

[lab directions]

Because we have a benzene ring right next door, and because we have the positive charge on the phosphorus, both of them together make that proton that's between the two acidic enough that, with long-term heating in sodium hydroxide, we can get sodium hydroxide to do the deprotonation. It's an unusual reaction that we can use hydroxide here instead, and that's the advantage of using this benzyl reagent[, benzyltriphenylphosphonium bromide].

We have this deprotonated salt, the ylide, which I'll write in zwitterionic form. We're going to react that with benzaldehyde. The anion's going to attack. Once that attack occurs .... Be careful with the number of carbons that you're writing; it's very easy in a Wittig reaction to accidentally leave something out. There is the four-membered ring that is going to form. Notice that I wrote this with the two benzene rings on opposite sides of the single bond from each other.

I could have written the two benzene rings on the same side as each other, which doesn't matter as long as there's a single bond because you can freely rotate around a single bond. But as soon as you close up and make that four-membered ring, you've locked in the relative position of the two benzene rings. Let me show you the two possibilities that can result. I have two different stereochemical possibilities; for either of them, we technically could have enantiomers as well, but we're about to make a double bond, so that gets rid of the worry about enantiomers. But, when that double bond forms, if the two phenyl rings are pointed the same way versus the opposite way, then when the decomposition of this oxaphosphetane occurs, we're going to have the possibility of forming both the cis product and the trans product.

[lab procedure – washes: water, to remove ionic impurities; bisulfite, to remove triphenylphosphine oxide]
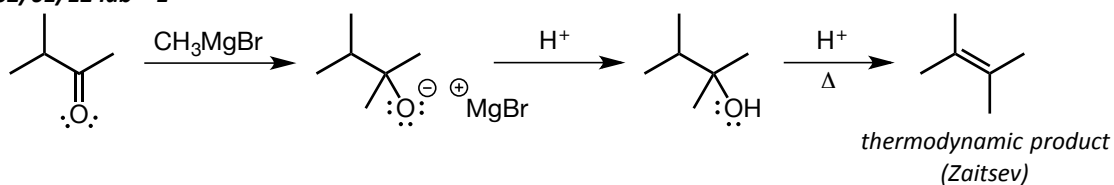
————

At low temperatures, only those reactions with lower activation barriers tend to predominate, even if they result in products that may not be as favorable thermodynamically. When a large, bulky base is used to perform eliminations, a less favorable product can be obtained due to the difficulty of that hindered base in removing a more sterically-hindered hydrogen.
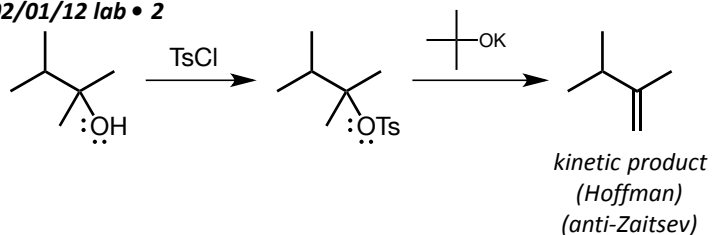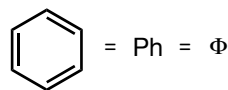
Wittig

zwitterion   – "twin ion"
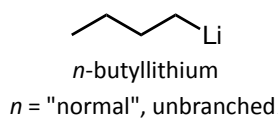
————

Structures

02/01/12 lab • 1

H⁺ → H⁺ Δ → **thermodynamic product (Zaitsev)**

02/01/12 lab • 2

TsCl → OK →

kinetic product (Hoffman) (anti-Zaitsev)

02/01/12 lab • 3

= Ph = Φ

02/01/12 lab • 4

n-butyllithium

n = "normal", unbranched

02/01/12 lab • 7

phenyl   benzyl   vinyl   allyl   aspargyl

02/01/12 lab • 5

triphenylphosphine → *tetraalkylphosphonium salt* → *ylide*

02/01/12 lab • 6

oxaphosphetane → + triphenylphosphine oxide

02/01/12 lab • 8

unusually acidic due to resonance stabilization of the resulting anion

530