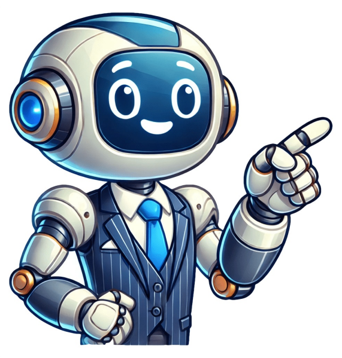

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 10.6), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the C=O bond, Grignard reaction involves addition of a carbanion nucleophile (R:+MgX).The nucleophilic addition reaction of Grignard reagents to carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction does have an indirect biological counterpart, for well see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carboncarbon bonds.As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, H!C=O, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as LiAlH4 reduction of an ester adds two hydrogens.Carboxylic acids dont give addition products when treated directly with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.Carboxylic acids do, however, react with Grignard reagents to give ketones if they are first treated with i-Pr2NMgCl-LiCl, called the turbo-Hauser base, to form a complex and increase the electrophilicity of the carboxylate anion toward nucleophilic addition with a Grignard reagent.The Grignard reaction, although useful, does have limitations. One major problem is that a Grignard reagent cant be prepared from an organohalide if other reactive functional groups are present in the same molecule. For example, a compound that is both an alkyl halide and a ketone cant form a Grignard reagent because it would react with itself.Similarly, a compound that is both an alkyl halide and a carboxylic acid, alcohol, or amine cant form a Grignard reagent because the acidic RCO2H, ROH, or RNH2 hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents cant be prepared from alkyl halides that contain the following functional groups (FG):As with the reduction of carbonyl compounds discussed in the previous section, well defer a detailed treatment of the Grignard reactions until Chapter 19. For the moment, its sufficient to note that Grignard reagents act as nucleophilic carbanions (:R) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H3O+ in a second step.Worked Example 17.3Using a Grignard Reaction to Synthesize an AlcoholHow could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2- butanol?StrategyDraw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone.Solution2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group (C6H5) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.Worked Example 17.4Using a Grignard Reaction to Synthesize an AlcoholHow could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?StrategyDraw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound could be either a ketone or an ester.SolutionIn the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone.Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.Problem 17-9Show the products obtained from addition of methylmagnesium bromide to the following compounds:(a) Cyclopentanone (b)Benzophenone (diphenyl ketone) (c)3-Hexanone Problem 17-10Use a Grignard reaction to prepare the following alcohols: (a)2-Methyl-2-propanol (b)1-Methylcyclohexanol (c)3-Methyl-3-pentanol (d)2-Phenyl-2-butanol(e)Benzyl alcohol (f)4-Methyl-1-pentanol Problem 17-11Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound:Last updated: February 5th, 2025 | All About The Reactions of Grignard ReagentsGrignard reagents are excellent carbon-based nucleophiles as well as strong bases.They will add to aldehydes and ketones to form alcohols (after a protonation step)They will addtwiceto esters to give tertiary alcohols.They will add to the less-substituted side of epoxidesGrignard reagents will also react with carbon dioxide (CO2) to give carboxylic acids (after acid workup).Grignard reagents will not perform SN2 reactions with alkyl halides. They are also not compatible with carboxylic acids or alcohols.Table of Contents 1. Reminder: Grignard Reagents Are NucleophilesSo far in this series weve introduced organometallic compounds and said that their carbons tend to be nucleophilic. Weve learned how to make them from alkyl, alkenyl or aryl halides (along with some ways not to make them!) and saw that they are very strong bases.Most interesting about Grignards is that they are carbon-based nucleophiles and we can thus combine Grignard reagents with various electrophilic carbon species to form new carbon-carbon bonds.And since carbon-carbon bonds constitute the backbone of molecules in organic chemistry, it turns out that this class of reactions is very useful. As a matter of fact, it won its discoverer, Victor Grignard, the Nobel Prize for Chemistry back in 1912.For our purposes, the key carbon-based electrophiles that Grignard reagents react with are epoxides, aldehydes, ketones, and esters. Lets go through them in turn.2. Addition of Grignard Reagents To EpoxidesEpoxides (oxiranes if you are an IUPAC stickler) are 3-membered cyclic ethers which possess considerable ring strain. As weve seen, this ring strain makes them somewhat spring loaded toward attack by nucleophiles, which will result in formation of a new bond to carbon and opening of the ring.Negatively charged nucleophiles (such as Grignards) tend to react with epoxides in a manner similar to the SN2 reaction: attack occurs at theleast substitutedcarbon of the epoxide. Heres an example:Note the bonds that formed and broke here: weformed a new C-C bond (between carbons A and B), andbrokea C-O bond (between carbon A and the oxygen). This resulted in a negatively charged oxygen (alkoxide): to produce final alcohol product, we typically quench the reaction with a source of acid, forming OH.Heres how the reaction works. The hard thing is to recognize that the nucleophile is the pair of electrons in the C-Mg bond: remember from previous posts that carbon is strongly- (nucleophilic) because of its greater electronegativity as compared to magnesium.It might be helpful to imagine the Grignard reagent below as CH3CH2. Other than that the reaction is fairly straightforward if youve seen an SN2 reaction before: we simultaneously form C-C and break C-O.Note that this reaction also forms an alkoxide. In order to obtain our neutral alcohol product at the end, we must perform second step: a workup (quench) with a source of acid. This is written a variety of ways H+, H3O+, H2O, or just acid workup. This step occursafter our key Grignard reaction, for what should be obvious reasons being strong bases, Grignard reagents are destroyed by acid.Another thing to keep in mind is stereochemistry of the epoxide.Consistent with an SN2 reaction, if the reaction occurs at a secondary carbon, we will observeinversion of configuration:3. Reaction of Grignards With Aldehydes and KetonesA second class of important electrophiles that react with Grignards (and arguably THE most important class of electrophiles) is aldehydes and ketones. If you havent covered the reactions of these functional groups yet, a short summary would be this: the carbonyl carbon is an electrophile, and when nucleophiles react at this carbon, its accompanied by cleavage of the C-O pi bond (bond). (For more on the addition mechanism to carbonyls, see post: Nucleophilic Addition)Here are some examples of reactions of Grignards with aldehydes and ketones. Note that in each case we are forming a new bond between the carbonyl carbon (labelled A) and the carbon bound to magnesium (labelled B), and we are breaking the C-O pi bond in the process.So how does this reaction work?Lets get familiar with a VERY important mechanism called addition (sometimes called, 1,2-addition). This is by far the most important reaction of the carbonyl group, and if you give yourself a chicken for every time you will see variations of it in Org 2, you will have a lot of eggs in your room by the end of the semester.Note that this reaction also forms an alkoxide. In order to obtain our neutral alcohol product at the end, we must perform a workup (quench) with a source of acid, forming O-H.4. Reaction of Grignard Reagents With EstersEsters are close relatives of aldehydes and ketones: they consist of a carbonyl group directly attached to an OR group. As you might expect, they react with Grignards in a similar fashion to aldehydes and ketones: with formation of a new C-C bond and breakage of a C-O (pi bond).However, theres a twist with the reaction of esters that isnt present with aldehydes and ketones. Look carefully: whats different?Note that in both cases we addedtwo equivalents of our Grignard reagent to the ester, forming a tertiary alcohol.Wait a minute how did this happen?!5. Why Is There Double AdditionWith Esters? The MechanismThis reaction incorporates the second most important mechanism of carbonyls (next to addition), namely, elimination. In fact elimination is the exact reverse of addition ! Lets walk through it. There are 4 stepsIn the first step,the Grignard performs an addition reaction on the ester, forming C-C and breaking C-O (pi), giving us an intermediate with a negatively charged oxygen. Weve seen this type of reaction before in the addition of Grignards to aldehydes and ketones.Now comes the new step: elimination (sometimes, 1,2 elimination).This intermediate has a reasonably goodleaving group(OCH2CH3 in the case below). What happens next is reformation of the C-O pi bond with expulsionof the leaving group (CH3CH2O in the case below). In other words, we form CO and break a CO single bond. The new product is aketone.Together, these two steps are often referred to as Nucleophilic Acyl Substitution (See post: Nucleophilic Acyl Substitution)Elimination does not occur in addition to aldehydes and ketones because the leaving group would have to be the extremely strong bases H(-) or R(-). It is reasonably favorable for esters because the leaving group RO(-) is of comparable basicity to the negatively charged oxygen of the tetrahedral intermediate. [Note 1]But wait! Theres more!After Step 2, we have a new ketone. As weve seen before, Grignards will react quickly with ketones in yet anotheraddition reaction[Step 3]. Here, as in Step 1, we form CC and break CO (pi).The result is a tertiary alkoxide (the conjugate base of a tertiary alcohol).[Wait, you might ask. If we just use one equivalent of Grignard reagent, is it possible to get the reaction to stop at the ketone stage? The short answer is no. [See Note 3for the long answer]]Finally, protonation of this tertiary alkoxide yields the tertiary alcohol (Step 4).Heres the graphical walkthrough:6. Summary: Reactions of Grignard ReagentsThat does it for the key reactions of Grignard reagents youll see in most Org 1 and Org 2 courses.In the next post well talk about yet another way to screw up formation of Grignard reagents, and it involves the reactions in this post.Next Post: Protecting Groups In Grignard Reactions Notes Note 1: Although alkoxides (RO, the conjugate base of alcohols, pKa 16-18) are not on anyones list of Great Leaving Groups, they are some 25 orders of magnitude better leaving groups than hydrides (H, the conjugate base of hydrogen, pKa 40) and more than 30 orders of magnitude better than alkyl groups (R- , the conjugate base of alkanes, pKa 50). Thus, when the alkoxide intermediate is formed in Step 1, there is not any deep energetic penalty for the C-O pi bond to reform and for RO- to be expelled: after all, we are simply replacing a strong base (the O-) with one of comparable basicity.Note 2. Why are ketones more reactive towards Grignard reagents than esters? This requires understanding the phenomenon of pi donation. The lone pair on oxygen donates electron density into the carbonyl carbon. This is worthy of a separate post, but heres the bottom line:Note 3. Alas, no. Using 1 equivalent of Grignard will result in 0.5 equivalents of a tertiary alcohol and 0.5 equivalents of the starting ester. The reason why is that Step 2 [elimination] is quite fast!Once elimination occurs, we will have ketone in the presence of an ester. For interesting reasons [see Note 2] ketones are more reactive than esters toward Grignard reagents, which means they will be consumed more quickly. Quiz Yourself! Click to Flip Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. (Advanced) References and Further Reading:The Grignard ReagentsDietmar SeyferthOrganometallics200928 (6), 1598-1605DOI: 10.1021/om900088zA historical overview on Grignard reagents by the late Prof. Dietmar Seyferth (MIT), founding editor of the journal Organometallics.Secondary and Tertiary Alkyllithium Compounds and Some Interconversion Reactions with ThemHenry Gilman, Fred W. Moore, and Ogden BaineJournal of the American Chemical Society 1941, 63 (9), 2479-2482DOI: 1021/ja01854a046Prof. Henry Gilman (Iowa State) was a pioneer in organometallic chemistry in the first half of the 20th century. In this paper he describes the synthesis and reactivity of various alkyllithiums (n-butyllithium, s-butyllithium, isopropyllithium, and t-butyllithium). The synthesis is from the alkyl halide and lithium metal, as can be seen in the experimental section.t-ButyllithiumPaul D. Bartlett, C. Gardner Swain, and Robert B. WoodwardJournal of the American Chemical Society 1941, 63 (11), 3229-3230DOI: 1021/ja01856a501This communication is from some legendary figures in organic chemistry and describes the preparation of t-butyllithium.2-PHENYLPYRIDINE C. W. Evans and C. F. H. AllenOrg. Synth. 1938, 18, 70DOI: 10.15227/orgsyn.018.0070The first step in this procedure is a preparation of phenyllithium from bromobenzene and lithium metal. Organic Syntheses is a reputable source of reproducible and independently tested synthetic organic procedures.The mechanism of the lithium halogen Interchange reaction : a review of the literatureBailey, W. F.; Patricia, J. J. Organomet. Chem. 1988, 352 (1-2), 1-46DOI: 10.1016/0022-328X(88)83017-1In modern organic chemistry, organolithium reagents are rarely prepared from scratch (i.e. using Li metal), due to the ready availability of alkyllithium reagents from vendors (e.g. MeLi, the BuLi reagents, PhLi, etc.). Instead, these reagents can be used to form other organolithium species through a process known as lithium-halogen exchange.Whats Going on with These Lithium Reagents?Hans J. ReichThe Journal of Organic Chemistry 2012, 77 (13), 5471-5491DOI: 1021/jo3005155Prof. Hans Reich (U. Wisconsin-Madison) has spent his career studying the behavior of organolithium species, and this is an account of his research and the surprising findings he made. This is classic Physical Organic chemistry. Share copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. In this post, we will talk about the Grignard reaction a fundamental reaction in organic chemistry discovered by Victor Grignard in 1912 which gave him the Nobel prize award.The most common and important Grignard reaction is the one with compounds containing a carbonyl group. Grignard reagents react with aldehydes, ketones, and ester to form alcohols. Aldehydes and ketones form secondary and tertiary alcohols respectively, while esters are reacted with an excess Grignard reagent to produce tertiary alcohols: Grignard reagents can also react with acid chlorides, anhydrides, nitriles and epoxides. These reactions are slightly different so lets first discuss the principle of the Grignard reaction. Grignard Reaction MechanismLets discuss the mechanism of the Grignard reaction by starting with aldehydes and ketones. The origin of the Grignard reaction is the great imbalance of electron distribution. On the one hand, we have the C-Mg non-metal-metal polar bond which is almost ionic, and on the other hand, we have the C=O bond where the electron density is on the oxygen and the carbon is highly electrophilic: When these two are mixed, the strongly Grignard reagent uses the C-Mg electron pair to form a bond to the carbon atom of the carbonyl. This nucleophilic attack pushes the electron pair of the carbonyl bond to the oxygen forming an alkoxide. The resulting alkoxide ion associated with Mg2 and the halide is then neutralized by reacting with water or an acid: At this point,t it is important to mention that Grignard reagents are very strong bases. The high electron density on the C-Mg carbon atom makes it not only a good nucleophile but also a strong base.This brings up a very important rule that you need to always follow when working with a Grignard reagent or any other organolithium. And that is making sure the reaction is carried out in dry conditions no trance of water should be present because it will react with the Grignard before the nucleophilic attack happensThis essentially kills the Grignard reagent and the reaction wont work: This restriction is not only applied for water but also for any compound that contains a proton, acidic enough to react with the Grignard reagent. That can be, for example, an alcohol or a carboxylic acid.You may want to check this post about the protonation-deprotonation principle in acid-base reactions.Nevertheless, sometimes it is needed to prepare a Grignard reagent that contains an alcohol group or react it with a carbonyl that contains an OH group: What you need to remember is that these two groups are incompatible as they will react immediately. To prevent this undesired reaction, protecting groups of alcohols are used which is covered in this post.Therefore, it is crucial to add the water (or acid) after the Grignard reagent already reacted with the electrophile. The reaction must be shown in two steps first the nucleophilic attack of the Grignard and then the acidic work-up: Grignard Reaction with EstersGrignard reagents also react with esters to produce tertiary alcohols by a similar mechanism to the aldehydes and ketones: However, there is one important difference! Esters react with two equivalents of Grignard forming a tertiary alcohol.Lets see how this happens.In the first step, we have the nucleophilic attack of the Grignard making the C-C bond and shifting the electrons of the bond to the oxygen.The difference with aldehydes and ketones is that the product of this addition reaction to the carbonyl contains an alkoxy group on the tetrahedral intermediate. This group is a relatively good leaving group (more stable than the Grignard reagent) since it is a weaker base than the alkyl groups on the tetrahedral carbon. And the lone pairs of the oxygen can move down to expel this group and restore the carbonyl bond: This forms a ketone which are more reactive than esters since the electrophilicity of the carbon atom of the ester is partially suppressed by the lone pair of the oxygen through resonance stabilization: After the first addition to the carbonyl, we have the Grignard reagent, ester, and a ketone in the reaction mixture. The ketone reacts further to form a tertiary alcohol as we have seen earlier. In addition, the ester being in a much higher concentration still reacts with the Grignard as well.This demonstrates why two equivalents of Grignard are needed when reacted with esters.If one equivalent was used, a mixture of a tertiary alcohol, ketone, and unreacted ester would have been obtained after the acidic work-up: Nitriles contain a polar carbon-nitrogen triple bond. Remember, in a triple bond we have two bonds and this makes it a great candidate for reacting in a Grignard reaction. The product of this reaction is a ketone: Doesnt this look strange since we have been saying all this time that ketones react with the Grignard?Here is how it happens.In the first step, we have the nucleophilic attack forming the C-C bond. The product of this step is an imine in deprotonated form: And even though the imine contains a C=N bond, it does not undergo another nucleophilic attack by the Grignard since that would put a double negative charge on the nitrogen which highly unstable: Instead, the reaction is stopped at this point by adding water or an acid since the Grignard cannot react with the negatively charged imine. The protonation of the imine quenches also the Grignard reagent: Wait, this does not show how the ketone is obtainedYou may not have covered this in your class, but imines undergo hydrolysis to form a ketone which is the final product of the reaction. The mechanism of imine hydrolysis is shown below: Epoxides react with Grignard reagents to form alcohols: The difference with other Grignard reactions is that the epoxide does not contain a bond and its reactivity is a result of the ring strain. Three-membered rings are susceptible to nucleophilic attacks as we have seen in the reactions of alkenes such as the chlorination and oxymercuration of alkenes and alkynes. Check this post for details and examples of epoxide ring-opening reactions with additional practice problems.With this said, the carbon atom in the epoxide is still partially positively charged which makes it an electrophilic center for the Grignard reagent. The nucleophilic attack of the Grignard reagent opens the epoxide ring forming an alkoxide which is then protonated to produce an alcohol: Grignard reagents are good nucleophilic and the attack on unsymmetrical epoxides occurs at the less substituted carbon: Notice that there stereochemical considerations to the reaction as well. We have a dedicated post on the reactions of epoxides with Grignard reagents to discuss these and other features in more detail.To summarize what we have discussed, the Grignard reaction works for compounds containing a carbonyl such as aldehydes, ketones, esters, nitrile, carbon dioxide, and epoxides due to the ring strain.It is a great tool in organic synthesis and there is a variety of ways it can be used to achieve synthetic reformations. Check the next post for more details and specific examples:Grignard Reaction in Organic Synthesis with Practice ProblemsIn the following practice exercise, we will determine the major product of a Grignard Reagent with an aldehyde, ketone, ester, carbon dioxide, an ether a nitrile. 1. Predict the major organic product(s) for the following Grignard reactions of a ketone, aldehyde, ester, carbon dioxide and an epoxide: a) b) c) d) e) 2. Unlike aldehydes, ketones, and esters, nitriles do not produce an alcohol in the Grignard reaction and formation of carbonyl compounds is observed instead.Draw the mechanism, to determine the product, of the following Grignard reaction ofbenzonitrile with ethylmagnesium bromide: The product of this reaction is a ketone (Propiophenone). The mechanism is shown in the solution. 3. In the following practice problem, we will use the Grignard reaction to synthesize a primary, secondary or a tertiary alcohol. This is a retrosynthetic Grignard reaction as the product is given and you need to identify the starting material. Each synthesis has more than one way of combing the correspondingcarbonyl or another electrophilewith a Grignard reagent. a) b) c) d) e) f) Victor Grignard is best known for two things. One hell of a mustache he sports on every picture of him on the Internet, and the reaction named after him which earned him a Nobel Prize in 1912. In this tutorial, well discuss the details of the Grignard reaction, how to approach those on the test, and common mistakes to avoid. Before we jump into the discussion of the Grignard reagent reactivity, lets talk about how we make the Grignard reagent itself and what exactly it is. We make the Grignard reagent by reacting an alkyl halide with magnesium shavings in anhydrous ether or THF (tetrahydrofurane). The exact mechanism of this reaction goes beyond the scope of this tutorial, but if you really want to know, let me know in the comments below, and Ill make a video about this mechanism as well. From the reactivity perspective, the iodine and bromine containing halides are the most reactive, chlorides are ok but not the best choice for the reagent, and fluorides are comparatively unreactive, so youll never see those in your course. In the original research, Victor Grignard used isobutyl iodide. Another important thing to keep in mind is that were virtually not limited by the nature of our alkyl halides. Your halogen can be a simple chain with a halogen on an sp3-hybridized atom, or a complex molecule with the halogen on even an sp2-hybridized atom! The sky is the limit here, making the Grignard reagent truly a Swiss army knife of nucleophiles! When it comes to the Grignard reagent structure, things are not as simple as they may seem. Good news is, within the scope of a typical sophomore organic chemistry, we dont need to know the gory details of how the Grignard reagent really looks like. So, well use a simplified approach to its structure which works just fine for our purposes. So, due to the direct C-Mg bond, carbon atom has a very high electron density on it. The electronegativity of magnesium is about 1.3, while the carbons electronegativity is roughly 2.5. This means that we have a very significant difference in the electronegativity making this bond so polar, its close to an ionic bond in its behavior. So, you can think of a Grignard reagent as, essentially, a carbanion in terms of its reactivity and overall behavior. Depending on how your textbook and your instructor wants to treat it, we can see it depicted as an ionic pair (which is an oversimplification), or as a covalent bond between carbon and magnesium. In this tutorial, Ill stick to the covalent bond depiction. As Ive mentioned earlier, due to the high electron density around the carbon atom and a carbocationic character of the organic portion of the Grignard reagent, these substances are very basic and very nucleophilic. So, first, lets look at the acid-base properties of the Grignard reagent. Lets look at a reaction between the butyl magnesium bromide and a hypothetical acid of some sort. The pKa value of our conjugate acid in this reaction is somewhere in the vicinity of 60. This means that anything with the pKa lower than that will be acidic enough to easily react with our Grignard reagent. If we look at all common acidic (and not so acidic) species we commonly see in organic chemistry: carboxylic acids, alcohols, water, amines, even terminal alkynesthey all are too acidic to peacefully coexist with the Grignard reagent! Which means that when youre working with the Grignard reagent, you shouldnt have anything even remotely acidic anywhere in your system. Remember, the proton transfer reactions have a very low activation barrier, so they will typically happen before anything else can happen to your reagents. So, if lets say, you have a molecule with a carbonyl and an alcohol functional group, the alcohol will react with the Grignard reagent before the carbonyl. This is also why we always must emphasize the anhydrous conditions for the reaction, as water kills the Grignard reagent. This is also a very common trick instructors love to implant into the tests hoping you wont notice an acidic group and go with the nucleophilic attack instead of the proton transfer. Now, if the acid-base chemistry is not an issue, we can actually talk about the namesake reaction itself. The Grignard reaction truly revolutionized the field of organic chemistry when it was discovered. Victor Grignard discovered it in the 1900 as a part of his doctoral, and it was such a big deal, that he got a Nobel Prize for it in 1912. Just think how cool it would be to get a Nobel prize for your PhD work just 10 years after you get your PhD! Most people barely have a tenure at that point in their career. But I digress. So, what exactly is the Grignard reaction? The classic Grignard reaction is the reaction between the Grignard reagent and a carbonyl like an aldehyde or a ketone giving a corresponding alcohol. Since the reaction is done in highly basic conditions, well initially end up with the alkoxide, which we then protonate in the acidic workup step. The reaction is extremely useful as it makes a new carbon-carbon bond. So, you can easily construct complex molecules from simple ones. The resulting product is an alcohol, so you can further functionalize your molecule using the alcohol chemistry. Lets look at the mechanism details of this reaction. Since the Grignard reagent is a strong nucleophile, itll readily react with electrophiles such as aldehydes and ketones. Here, I have a reaction between butyl magnesium bromide and acetophenone. The reaction starts with the nucleophilic attack from the Grignard reagent onto the carbonyl. Traditionally, we show it by taking the electrons from the C-Mg bond and pushing them towards the carbon of the carbonyl. However, if your instructor likes to show it as a carbocation, well then show an electron pair on the carbon atom instead of the covalent bond between carbon and magnesium. As I mentioned above, Ill stick to the bond version of the mechanism. Heres also the important thing to keep in mindsince carbon of the carbonyl is already fully satisfied with the electrons and has a full octet, we cannot just add those electrons to it and make a new bond. If we want that carbon to accept those electrons, it needs to push some electrons away. And thats precisely what it does with the -bond to the oxygen. Remember to do that when youre working through the mechanism of this reaction, or youll end up with a carbon with too many bonds around it. This step makes a new carbon-carbon bond and a negatively charged oxygen. In the next step, were going to do the acidic workup protonating the O-. The acidic workup is always going to be the second step in this reaction. Some instructors skip it or assume it but its always there even if they dont show it. In this case, the resulting alcohol is chiral. At this point in your course, your instructor will most likely expect you to indicate the stereochemistry of your products when relevant. So, make sure you do so and dont forget about it. Here, if I wanted to indicate my stereochemistry, I would either write racemic under my molecule or show both stereoisomers which are enantiomers for this molecule. Lets look at another example. In this case were reacting the phenyl magnesium bromide with pentane-3-one. This reaction makes a tertiary (3) alcohol similar to the last example. However, in this case, were going to get an achiral molecule. And the mechanism is going to be very similar to the previous example as well. Well start by attacking our carbonyl making a new carbon-carbon bond. And once that part is done, well protonate our molecule in the acidic workup step. How would this reaction proceed with an aldehyde? Well, a reaction with an aldehyde gives us a secondary (2) alcohol. For instance, in the reaction of the methyl magnesium bromide with butanal, well get a pentane-2-ol after the acidic workup. This molecule is chiral as well, so Ill say racemic or show both possible stereoisomers. The Grignard reagent can react with a whole range of various electrophiles. Another common example is going to be the reaction with esters and acid chlorides. If I take a Grignard reagent, butyl magnesium bromide, and react it with, for instance, benzoyl chloride, the first step in this reaction is going to be exactly what we would expect from itthe nucleophilic attack on the carbon of the carbonyl. However, we now have a leaving group which can be easily pushed off our molecule. This recreates the C=O and the reaction can happen one more time! So, the next equivalent of butyl magnesium bromide will come in and attack again. This makes another carbon-carbon bond yielding the alkoxide like if we did this reaction with a ketone. And only after that wed be able to do our acidic workup giving us the tertiary (3) alcohol as the final product. So, important thing to remember here is that the Grignard reaction with acid chloride happens twice. And for as long as youre working with a simple Grignard reagent, you wont be able to stop if after the first round of addition. There are, of course, ways how we can prevent it, but it would require special conditions and additional components in our reaction mixture which goes beyond the scope of this tutorial. What about the esters? The reaction proceeds in a similar fashion. If I treat ethyl acetate with phenyl magnesium bromide, Ill first do the first round of the addition giving me the negatively charged intermediate. That intermediate will push away an alkoxide leaving group restoring the C=O and the reaction can happen one more time with another equivalent of phenyl magnesium bromide, eventually giving us a tertiary alcohol as a final product. So, the idea here is the samereaction happens twice and you end up with a tertiary alcohol. While there are other variations of this reaction with carboxylic acid derivatives, Ill limit our discussion here just to these two reactions. But youll also learn how the Grignard reagent reacts with nitriles and amides later in your course. Another variation of the Grignard reaction you are likely to encounter in your course, is the reaction with an epoxide. This is a useful reaction from the synthetic perspective as it can give us a new carbon-carbon bond one carbon away from the -OH group in the resulting alcohol. So, if I react phenyl magnesium bromide with 2,2-dimethyloxirane, Im going to attack the less substituted carbon of my epoxide. This creates a new carbon-carbon bond opening the epoxide ring. And since the oxygen is still connected to the other atom, it makes an alkoxide with the oxygen one atom removed from the place where we have attached our Grignard reagent. Of course, here like in all of these reactions, well need to do an acidic workup to protonate the resulting anionic species. The Grignard reaction is an incredibly versatile method of making new carbon-carbon bonds. For many years, it was the premiere method of the carbon-carbon bond formation. Its made such a profound impact on the field of organic chemistry, that early 1900s to about 1960 is known as the Grignard era of organic chemistry. And while this reaction is over 120 years old, it is still regularly used in the modern research and synthetic strategies in organic chemistry. Its also going to be one of the premier carbon-carbon bond-making methods in your course. So, whenever youre looking at a synthesis problem and see that there was a new carbon-carbon bond added, chances are, the key step in that synthesis is the Grignard reaction. Victor Grignard is best known for two things. One hell of a mustache he sports on every picture of him on the Internet, and the reaction named after him which earned him a Nobel Prize in 1912. In this tutorial, well discuss the details of the Grignard reaction, how to approach those on the test, and common mistakes to avoid. Before we jump into the discussion of the Grignard reagent reactivity, lets talk about how we make the Grignard reagent itself and what exactly it is. We make the Grignard reagent by reacting an alkyl halide with magnesium shavings in anhydrous ether or THF (tetrahydrofurane). The exact mechanism of this reaction goes beyond the scope of this tutorial, but if you really want to know, let me know in the comments below, and Ill make a video about this mechanism as well. From the reactivity perspective, the iodine and bromine containing halides are the most reactive, chlorides are ok but not the best choice for the reagent, and fluorides are comparatively unreactive, so youll never see those in your course. In the original research, Victor Grignard used isobutyl iodide. Another important thing to keep in mind is that were virtually not limited by the nature of our alkyl halides. Your halogen can be a simple chain with a halogen on an sp3-hybridized atom, or a complex molecule with the halogen on even an sp2-hybridized atom! The sky is the limit here, making the Grignard reagent truly a Swiss army knife of nucleophiles! When it comes to the Grignard reagent structure, things are not as simple as they may seem. Good news is, within the scope of a typical sophomore organic chemistry, we dont need to know the gory details of how the Grignard reagent really looks like. So, well use a simplified approach to its structure which works just fine for our purposes. So, due to the direct C-Mg bond, carbon atom has a very high electron density on it. The electronegativity of magnesium is about 1.3, while the carbons electronegativity is roughly 2.5. This means that we have a very significant difference in the electronegativity making this bond so polar, its close to an ionic bond in its behavior. So, you can think of a Grignard reagent as, essentially, a carbanion in terms of its reactivity and overall behavior. Depending on how your textbook and your instructor wants to treat it, we can see it depicted as an ionic pair (which is an oversimplification), or as a covalent bond between carbon and magnesium. In this tutorial, Ill stick to the covalent bond depiction. As Ive mentioned earlier, due to the high electron density around the carbon atom and a carbocationic character of the organic portion of the Grignard reagent, these substances are very basic and very nucleophilic. So, first, lets look at the acid-base properties of the Grignard reagent. Lets look at a reaction between the butyl magnesium bromide and a hypothetical acid of some sort. The pKa value of our conjugate acid in this reaction is somewhere in the vicinity of 60. This means that anything with the pKa lower than that will be acidic enough to easily react with our Grignard reagent. If we look at all common acidic (and not so acidic) species we commonly see in organic chemistry: carboxylic acids, alcohols, water, amines, even terminal alkynesthey all are too acidic to peacefully coexist with the Grignard reagent! Which means that when youre working with the Grignard reagent, you shouldnt have anything even remotely acidic anywhere in your system. Remember, the proton transfer reactions have a very low activation barrier, so they will typically happen before anything else can happen to your reagents. So, if lets say, you have a molecule with a carbonyl and an alcohol functional group, the alcohol will react with the Grignard reagent before the carbonyl. This is also why we always must emphasize the anhydrous conditions for the reaction, as water kills the Grignard reagent. This is also a very common trick instructors love to implant into the tests hoping you wont notice an acidic group and go with the nucleophilic attack instead of the proton transfer. Now, if the acid-base chemistry is not an issue, we can actually talk about the namesake reaction itself. The Grignard reaction truly revolutionized the field of organic chemistry when it was discovered. Victor Grignard discovered it in the 1900 as a part of his doctoral, and it was such a big deal, that he got a Nobel Prize for it in 1912. Just think how cool it would be to get a Nobel prize for your PhD work just 10 years after you get your PhD! Most people barely have a tenure at that point in their career. But I digress. So, what exactly is the Grignard reaction? The classic Grignard reaction is the reaction between the Grignard reagent and a carbonyl like an aldehyde or a ketone giving a corresponding alcohol. Since the reaction is done in highly basic conditions, well initially end up with the alkoxide, which we then protonate in the acidic workup step. The reaction is extremely useful as it makes a new carbon-carbon bond. So, you can easily construct complex molecules from simple ones. The resulting product is an alcohol, so you can further functionalize your molecule using the alcohol chemistry. Lets look at the mechanism details of this reaction. Since the Grignard reagent is a strong nucleophile, itll readily react with electrophiles such as aldehydes and ketones. Here, I have a reaction between butyl magnesium bromide and acetophenone. The reaction starts with the nucleophilic attack from the Grignard reagent onto the carbonyl. Traditionally, we show it by taking the electrons from the C-Mg bond and pushing them towards the carbon of the carbonyl. However, if your instructor likes to show it as a carbocation, well then show an electron pair on the carbon atom instead of the covalent bond between carbon and magnesium. As I mentioned above, Ill stick to the bond version of the mechanism. Heres also the important thing to keep in mindsince carbon of the carbonyl is already fully satisfied with the electrons and has a full octet, we cannot just add those electrons to it and make a new bond. If we want that carbon to accept those electrons, it needs to push some electrons away. And thats precisely what it does with the -bond to the oxygen. Remember to do that when youre working through the mechanism of this reaction, or youll end up with a carbon with too many bonds around it. This step makes a new carbon-carbon bond and a negatively charged oxygen. In the next step, were going to do the acidic workup protonating the O-. The acidic workup is always going to be the second step in this reaction. Some instructors skip it or assume it but its always there even if they dont show it. In this case, the resulting alcohol is chiral. At this point in your course, your instructor will most likely expect you to indicate the stereochemistry of your products when relevant. So, make sure you do so and dont forget about it. Here, if I wanted to indicate my stereochemistry, I would either write racemic under my molecule or show both stereoisomers which are enantiomers for this molecule. Lets look at another example. In this case were reacting the phenyl magnesium bromide with pentane-3-one. 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Its made such a profound impact on the field of organic chemistry, that early 1900s to about 1960 is known as the Grignard era of organic chemistry. And while this reaction is over 120 years old, it is still regularly used in the modern research and synthetic strategies in organic chemistry. Its also going to be one of the premier carbon-carbon bond-making methods in your course. So, whenever youre looking at a synthesis problem and see that there was a new carbon-carbon bond added, chances are, the key step in that synthesis is the Grignard reaction. 17.5 Alcohols from Carbonyl Compounds: Grignard Reaction Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 10.6), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the C=OC=O bond, Grignard reaction involves addition of a carbanion nucleophile (R:+MgX). The nucleophilic addition reaction of Grignard reagents to carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction does have an indirect biological counterpart, for well see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carboncarbon bonds. As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, H2C=OH2C=O, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols. Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as LiAlH4 reduction of an ester adds two hydrogens. Carboxylic acids dont give addition products when treated directly with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid. Carboxylic acids do, however, react with Grignard reagents to give ketones if they are first treated with i-Pr2NMgCl-LiCl, called the turbo-Hauser base, to form a complex and increase the electrophilicity of the carboxylate anion toward nucleophilic addition with a Grignard reagent. The Grignard reaction, although useful, does have limitations. One major problem is that a Grignard reagent cant be prepared from an organohalide if other reactive functional groups are present in the same molecule. For example, a compound that is both an alkyl halide and a ketone cant form a Grignard reagent because it would react with itself. Similarly, a compound that is both an alkyl halide and a carboxylic acid, alcohol, or amine cant form a Grignard reagent because the acidic RCO2H, ROH, or RNH2 hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents cant be prepared from alkyl halides that contain the following functional groups (FG): As with the reduction of carbonyl compounds discussed in the previous section, well defer a detailed treatment of the Grignard reactions until Chapter 19. For the moment, its sufficient to note that Grignard reagents act as nucleophilic carbanions (:R) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H3O+ in a second step. How could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2-butanol? Strategy Draw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone. Solution 2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group (C6H5) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone. How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol? Strategy Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound could be either a ketone or an ester. Solution In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone. Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate. Problem 17-9 Show the products obtained from addition of methylmagnesium bromide to the following compounds: (b) Benzophenone (diphenyl ketone) Problem 17-10 Use a Grignard reaction to prepare the following alcohols: Problem 17-11 Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound: Organometallic coupling reactionClassical Grignard reactionNamed afterVictor GrignardReaction typeCoupling reactionReactionMethanal/Higher aldehyde/Ketone+ R-MgX+ (H3O+)Primary/Secondary/Tertiary alcoholsIdentifiersOrganic Chemistry Portalgrignard-reactionRSC ontology IDRXNO:0000014A solution of a carbonyl compound is added to a Grignard reagent. (See gallery)An example of a Grignard reaction (R2 or R3 could be hydrogen)The Grignard reaction (French: [ia]) is an organometallic chemical reaction in which, according to the classical definition, carbon alkyl, allyl, vinyl, or aryl magnesium halides (Grignard reagent) are added to the carbonyl groups of either an aldehyde or ketone under anhydrous conditions.[1][2][3] This reaction is important for the formation of carboncarbon bonds.[4][5]Grignard reactions and reagents were discovered by and are named after the French chemist Franois Auguste Victor Grignard (University of Nancy, France), who described them in 1900.[6] He was awarded the 1912 Nobel Prize in Chemistry for this work.[7] The reaction of an organic halide with magnesium is not a Grignard reaction, but provides a Grignard reagent.[8] Although Grignard reagents undergo many reactions, the classical Grignard reaction refers only to the reaction of RMgX with ketones and aldehydes, shown in red. X = Cl, Br, I.Classically, the Grignard reaction refers to the reaction between a ketone or aldehyde group with a Grignard reagent to form a primary or tertiary alcohol.[1] However, some chemists understand the definition to mean all reactions of any electrophiles with Grignard reagents.[9] Therefore, there is some dispute about the modern definition of the Grignard reaction. In the Merck Index, published online by the Royal Society of Chemistry, the classical definition is acknowledged, followed by "A more modern interpretation extends the scope of the reaction to include the addition of Grignard reagents to a wide variety of electrophilic substrates."[9] This variety of definitions illustrates that there is some dispute within the chemistry community about the definition of a Grignard reaction. Shown below are some reactions involving Grignard reagents, but they themselves are not classically understood as Grignard reactions.Additional reactions which involve Grignard reagents, but are not considered to be Grignard reactions by the classical definition. X = Cl, Br, I.See also: Grignard reagents Reactions of Grignard reagentsBecause carbon is more electronegative than magnesium, the carbon attached to magnesium acts as a nucleophile and attacks the electrophilic carbon atom in the polar bond of a carbonyl group. The addition of the Grignard reagent to the carbonyl group typically proceeds through a six-membered ring transition state, as shown below.[10]The mechanism of the Grignard reaction.Based on the detection of radical coupling side products, an alternative single electron transfer (SET) mechanism that involves the initial formation of a ketyl radical intermediate has also been proposed.[11] A recent computational study suggests that the operative mechanism (polar vs. radical) is substrate-dependent, with the reduction potential of the carbonyl compound serving as a key parameter.[12]If a Grignard reaction is performed in the presence of water, or any labile proton, the labile proton will quench the Grignard reagent as shown in the figure above.[3]The Grignard reaction is conducted under anhydrous conditions.[3] Otherwise, the reaction will fail because the Grignard reagent will act as a base rather than a nucleophile and pick up a labile proton rather than attacking the electrophilic site. This will result in no formation of the desired product as the R-group of the Grignard reagent will become protonated while the MgX portion will stabilize the deprotonated species. To prevent this, Grignard reactions are completed in an inert atmosphere to remove all water from the reaction flask and ensure that the desired product is formed.[13] Additionally, if there are acidic protons in the starting material, as shown in the figure on the right, one can overcome this by protecting the acidic site of the reactant by turning it into an ether or a silyl ether to eliminate the labile proton from the solution prior to the Grignard reaction.Other variations of the Grignard reagent have been discovered to improve the chemoselectivity of the Grignard reaction, which include but are not limited to: Turbo-Grignards, organocerium reagents, and organocuprate (Gilman) reagents.Turbo-Grignards are Grignard reagents modified with lithium chloride. Compared to conventional Grignard reagents, Turbo-Grignards are more chemoselective; esters, amides, and nitriles do not react with the Turbo-Grignard reagent.[14]An example reaction of forming a Turbo-Grignard with an ester group.A conjugated 1,4 addition using a Gilman reagent with an arbitrary R groupThe behavior of Grignard reagents can be usefully modified in the present of other metals. Copper(I) salts giveorganocuprates that preferentially effect 1,4 addition.[15] Cerium trichloride allows selective 1,2-additions to the same substrates. Nickel and palladium halides catalyze cross coupling reactions.Wikimedia Commons has media related to Grignard reactions.Grignard reagentWittig reactionHornerWadsworthEmmons reactionBarbier reactionBodrouxChichibabin aldehyde synthesisFujimotoBelleau reactionOrganolithium reagentsSakurai reactionIndium-mediated allylationAlkynylation^ a b Smith, Michael B.; March, Jerry (2007), Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (6thed.), New York: Wiley-Interscience, ISBN978-0-471-72091-1^ Chapter 19: Carboxylic Acids. Organic Chemistry 4e Carey. mhhe.com^ a b c Ouellette, Robert J.; Rawn, J. David (January 1, 2014), Ouellette, Robert J.; Rawn, J. David (eds.), "15 - Alcohols: Reactions and Synthesis", Organic Chemistry, Boston: Elsevier, pp.491534, doi:10.1016/b978-0-12-800780-8.00015-2, ISBN978-0-12-800780-8, retrieved November 6, 2023^ Shirley, D. A. (1954). "The Synthesis of Ketones from Acid Halides and Organometallic Compounds of Magnesium, Zinc, and Cadmium". Org. 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"Comprehensive Study of the Enhanced Reactivity of Turbo-Grignard Reagents*". Angewandte Chemie International Edition. 62 (25): e202302489. doi:10.1002/anie.202302489. PMID36971042. S2CID257765567.^ Woodward, Simon (January 1, 2000). "Decoding the 'black box' reactivity that is organocuprate conjugate addition chemistry". Chemical Society Reviews. 29 (6): 393401. doi:10.1039/B002690P. ISSN1460-4744.Retrieved from " reagent reaction with alcohol. What happens when grignard reagent reacts with water. Can grignard reagent react with alcohol. Does grignard reagent react with alcohol. Grignard reagent to alcohol.