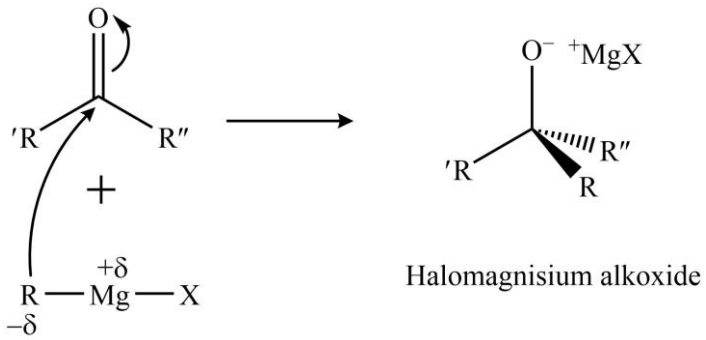
❖ Addition of Grignard Reagents, Organozinc and Organolithium Reagents to Carbonyl and Unsaturated Carbonyl Compounds

As far as the addition to carbon-heteroatom multiple bonds is concerned, three organometallic reagents are much more important than the others; organomagnesium (Grignard reagents), organozinc, and oreganolithium compounds. In this section, we will discuss the addition of these three types of reagents to carbonyl and unsaturated carbonyl compounds.

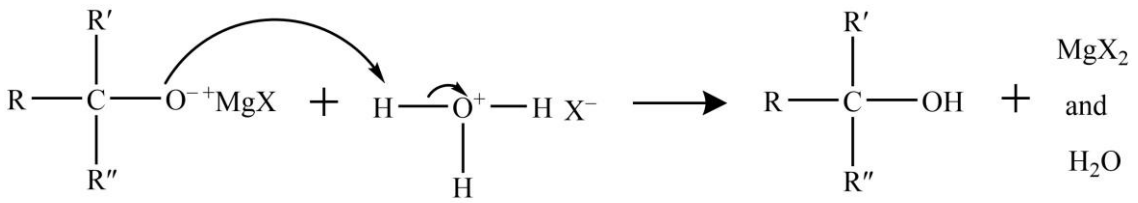
➢ *Addition of Grignard Reagents to Carbonyl and Unsaturated Carbonyl Compounds*

The typical addition mode of organomagnesium compounds (Grignard reagent) to common carbonyl compounds like ketone and aldehydes is given below.

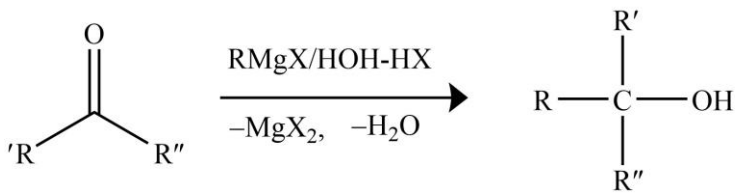


Halomagnisium alkoxide

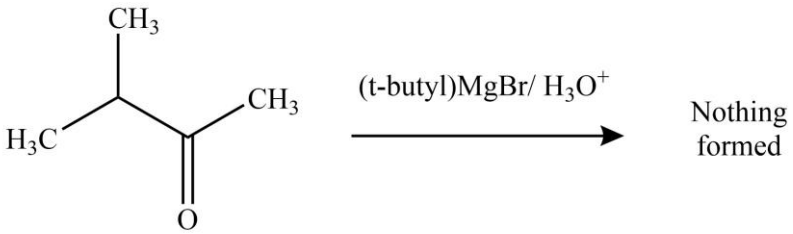
The halomagnesium alkoxide thus formed can react with H_2O (when an HX type mineral acid is available) to result in alcohols; which in turn, could be susceptible to dehydration (acid-catalyzed) if it is tertiary-type. To stop the alcohol's dehydration, we need to add some ammonium chloride (NH_4Cl) to the water so that because its acidic character can be employed to transform ROMgX to ROH.

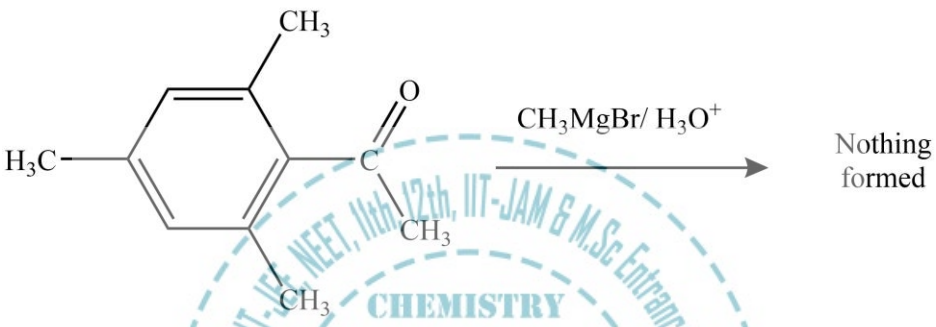


or

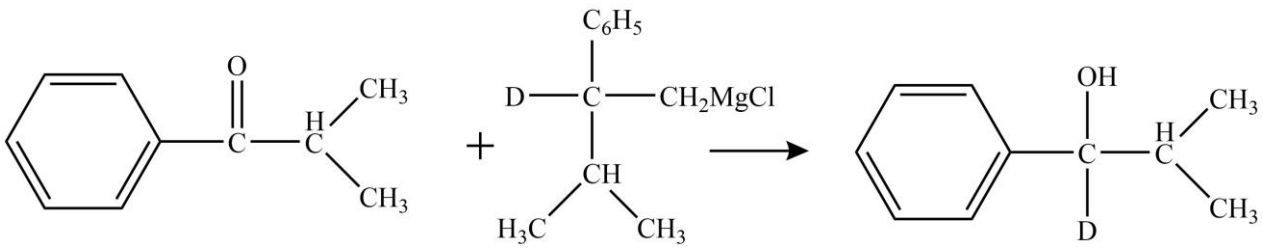


It is also worthy to note that bulky groups in the keto group, or in the reagent itself, greatly affect the nucleophilic addition in a negative way, or gets completely prohibited in some cases.

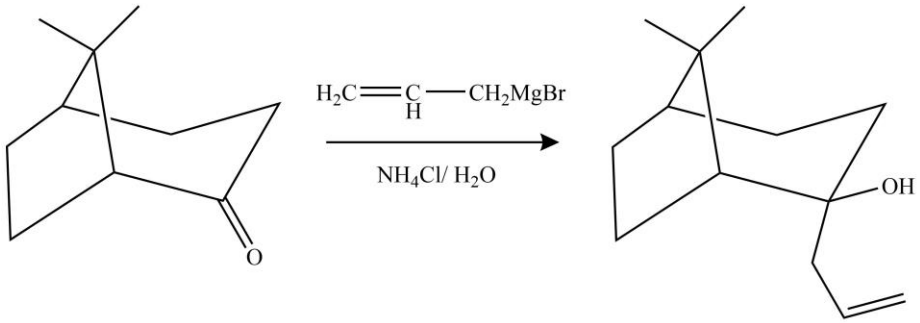


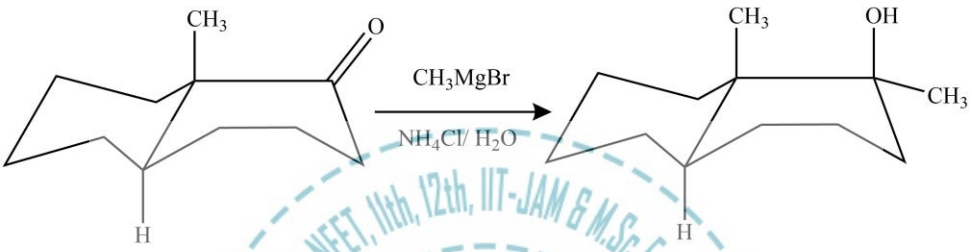


However, if a β-hydrogen is present in the bulky group of Grignard reagent, the transfer of hydride ion can result in the reduction of even highly hindered ketones. Moreover, if this is carried out via chiral Grignard reagent, the resulting product will also become optically active proving that the transfer of hydride ion does take place via the generation of cyclic transition state having six members.

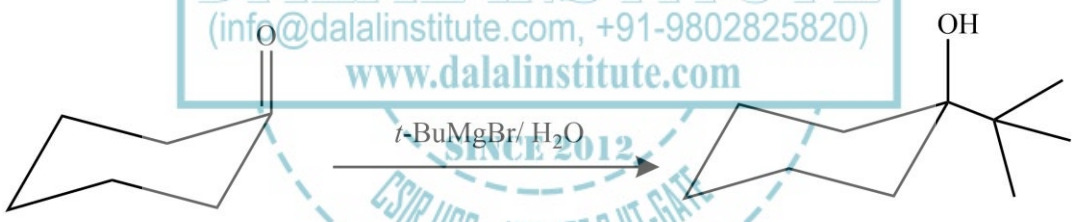


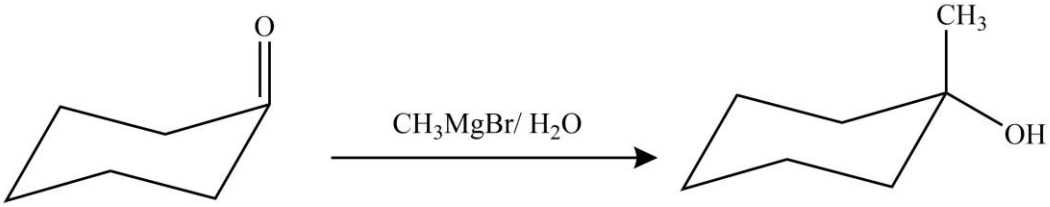
Also, if the Grignard addition takes place in cyclic ketones, the nucleophilic attack will happen from the carbonyl's face with less steric hindrance.



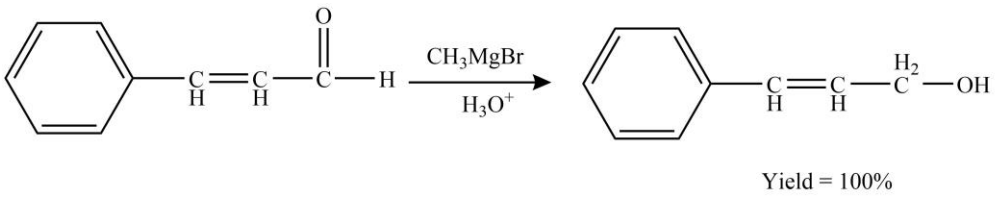


Since the organomagnesium reagent moves towards the substrate from a less hindered end, the final products' nature is also a function of the Grignard reagent used as it will push the hydroxy group to the axial site. On the other hand, a less bulky R (in comparison to OH) will make the hydroxy group occupy an equatorial site.

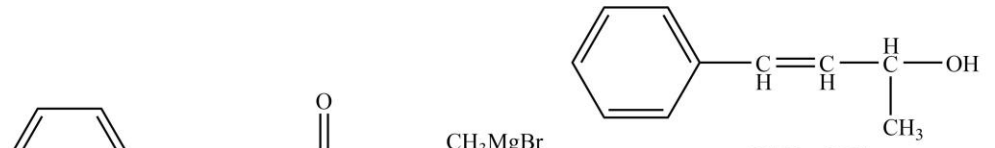




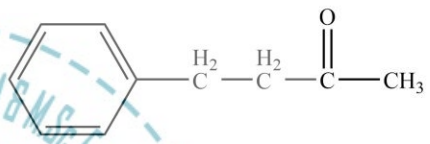
On a final note, if the aldehyde or the ketone used is α-, β-unsaturated, the nucleophilic addition of Grignard reagents becomes must faster and effective than normal carbonyl compounds, yielding 1, 4- and 1, 2-adddition products simultaneously. Moreover, these α-, β-unsaturated ketone and aldehydes give 1, 4- and 1, 2- adducts as the major products, respectively.



Yield = 100%

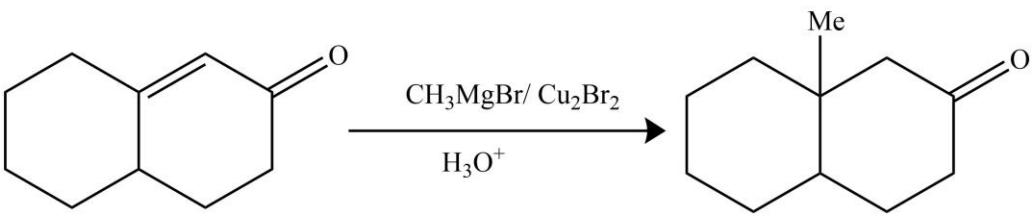


Yield = 30%



Yield = 70%

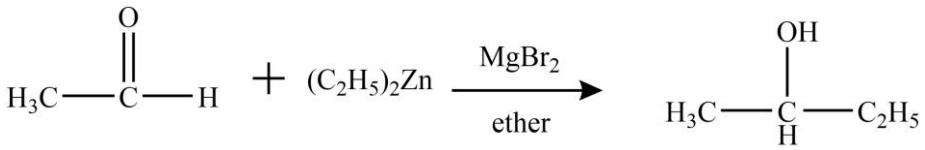
Nevertheless, it should also be noted that only 1, 4-adduct will be obtained if the addition over ketone is carried out in the presence of Cu_2Br_2.



Since the Grignard reagents are very strong bases, they are not suitable to act as nucleophiles with substrate containing acidic hydrogens. In other words, Grignard reagents will act as a base and will abstract the acidic hydrogen instead of participating as a nucleophile to attack the carbonyl group.

➢ ***Addition of Organozinc Reagents to Carbonyl and Unsaturated Carbonyl Compounds***

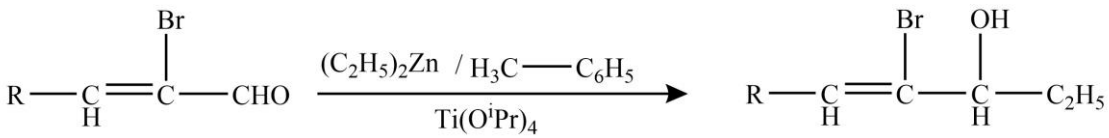
The rate of reaction for carbonyl compounds with dialkylzinc reagents is quite slow. It has also been observed that the rate for higher dialkylzinc is even lesser than lower dialkylzinc reagents. For instance, the reaction of diethylzinc with acetaldehyde takes hours for completion whereas the higher homologs may even take weeks. Nevertheless, allylzinc reagents show greater reactivity towards nucleophilic addition than normal dialkylzinc systems. Furthermore, the metal halide Lewis acids have been shown to enhance the rate of addition via dialkylzinc reagents.

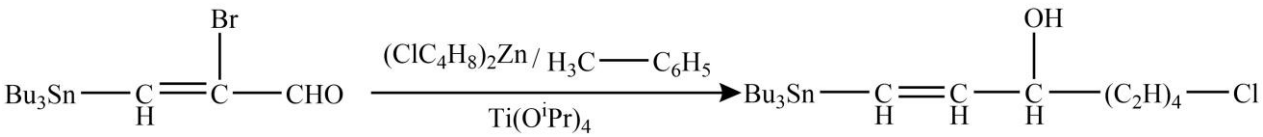


Yield = 60%

The heteroatom's presence at the α-site (relative to CO group) has also been found to be supportive of nucleophilic addition organozinc reagents.

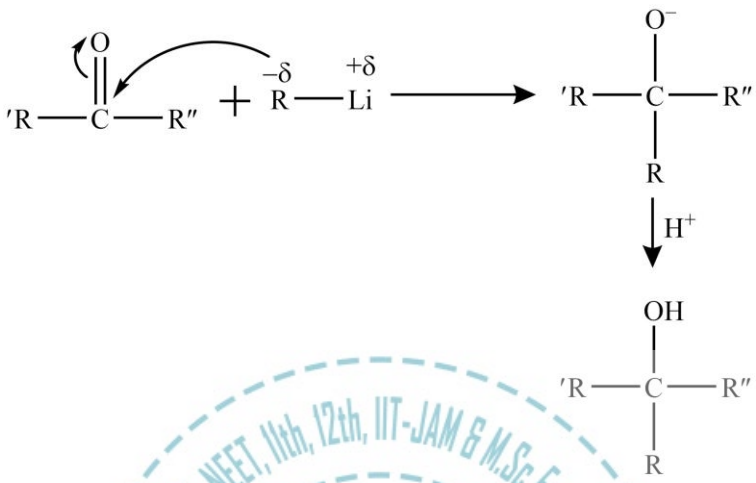
On a final note, it has also been proved that many titanium catalysts are supportive of the reactivity of organozinc reagents, specially $TiCl_4$ and $Ti(O^iPr)_4$.





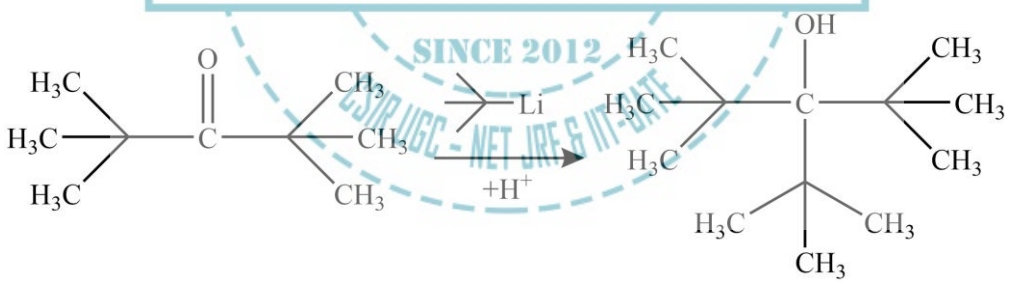
➢ ***Addition of Organolithium Reagents to Carbonyl and Unsaturated Carbonyl Compounds***

Organolithium reagents react with organic carbonyl derivatives to generate lithium alkoxide, which in turn gives rise to alcohols upon hydrolysis.

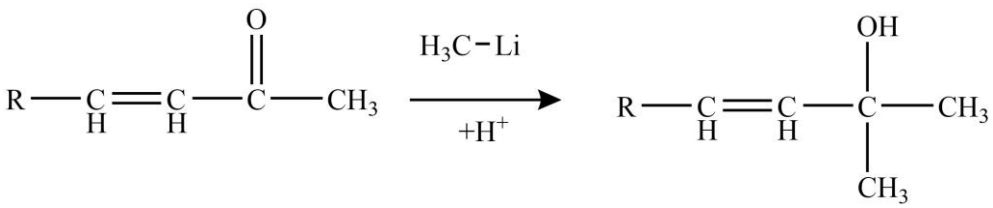


Sometimes a bioproduct via the α-deprotonation can also be obtained because besides being a nucleophilic attacker, organolithium is a powerful base too.

Furthermore, it is also worthy to note that organolithium reagents are better than their organomagnesium counterparts; and therefore, some highly hindered carbonyls (who were unable to react at all with Grignard reagents) can also be used as a substrate to produces quite stable products.



On a final note, the conjugated addition doesn't happen in the case of organolithium, leaving 1, 2-adducts as the only products.



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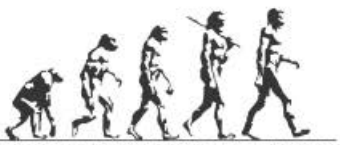

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