

CARBONYL COMPOUNDS

PART-26, PPT-26, SEM-3

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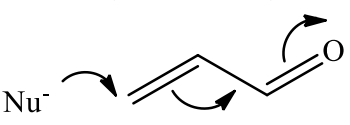
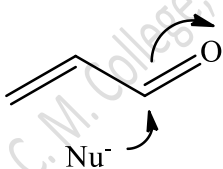
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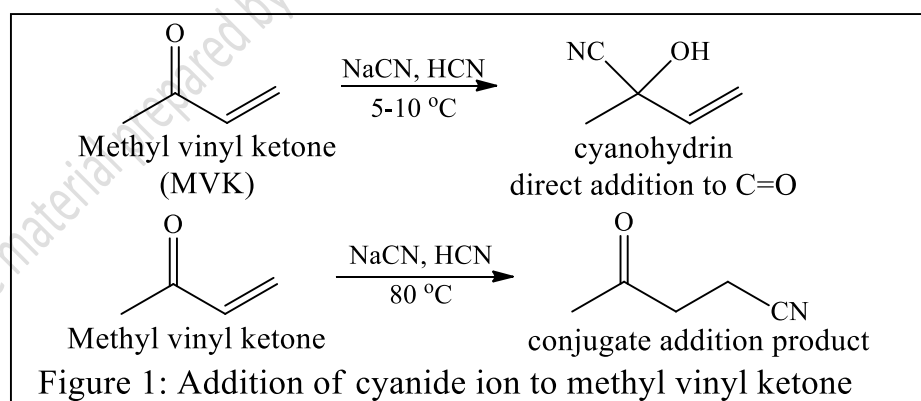
Factors Affecting Direct Addition or Conjugate Addition to Carbonyl Group

Several factors are involved for the nucleophiles to undergo conjugate addition (1,4-addition) and to add directly to the carbonyl group (1,2-addition). These are summarized in the following Table 1.

Table 1: Factors Affecting Direct vs Conjugate Addition		
conjugate addition to C=C (1,4-addition)	conjugate addition to C=O (1,2-addition)	
	or	
The way that nucleophiles react depends on:		
1. the conditions of the reaction		
2. the nature of the α, β -unsaturated carbonyl compound		
3. the type of nucleophile		

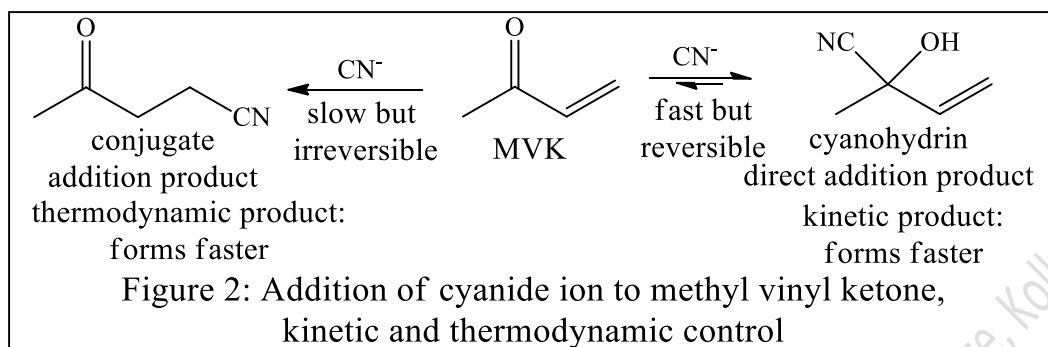
1. Reaction Conditions

On treating an enone with cyanide and an acid catalyst at low temperature gives a cyanohydrin by direct attack at C=O, while heating the reaction mixture leads to conjugate addition (Figure 1).



Direct addition to the carbonyl group turns out to be faster than conjugate addition, so the reaction ends up with the formation of cyanohydrin.

Kinetic and Thermodynamic Control



The cyanohydrin formation is reversible. Even if the equilibrium for cyanohydrin formation lies well over to the side of the products, at equilibrium there will still be a small amount of unreacted enone remaining. At the same time, some cyanohydrin will decompose back to enone and cyanide ion. But every now and then, the starting enone will undergo a conjugate addition with the cyanide at a much slower rate than that of the direct addition.

Now the situation is different. Conjugate addition is essentially an irreversible reaction, so once a molecule of enone has been converted to conjugate addition product, it cannot go back to enone again. Very slowly, therefore, the amount of conjugate addition product in the mixture will build up. In order for the enone - cyanohydrin equilibrium to be maintained, any enone that is converted to conjugate addition product will have to be replaced by reversion of cyanohydrin to enone and cyanide.

Even at room temperature, it is, therefore, expected that the cyanohydrin will be converted slowly to the conjugate addition product. This may take a very long time, but reaction rates are faster at higher temperatures, so at 80°C this process becomes faster and, after a few hours, the cyanohydrin is converted into conjugate addition product.

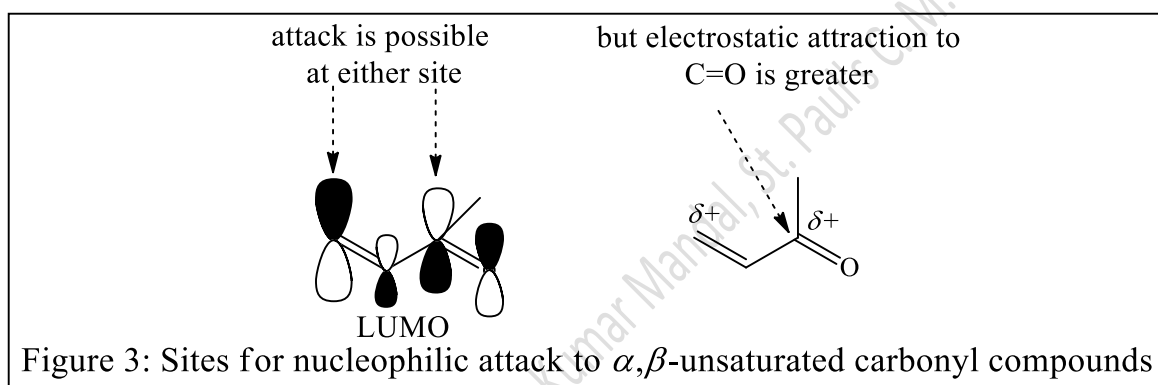
The contrast between the two products is this: cyanohydrin is formed faster than the conjugate addition product, but the conjugate addition product is the more stable compound. Typically, kinetic control involves lower temperatures and shorter reaction times, which ensures that only the fastest reaction has the chance to occur.

On the contrary, typically, thermodynamic control involves higher temperatures and long reaction times to ensure that even the slower reactions have a chance to occur, and all the material is converted to the most stable compound. The kinetic versus thermodynamic control in nucleophilic addition to α,β -unsaturated carbonyl compound is summarized in Table 2.

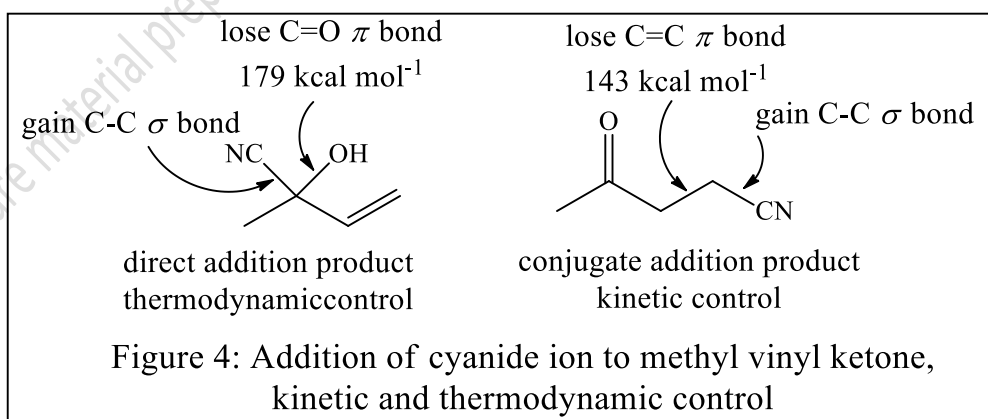
Table 2: Kinetic and thermodynamic control

- * The product that forms faster is called the kinetic product.
- * The product that is the more stable is called the thermodynamic product.
- * Conditions that give rise to the kinetic product are called kinetic control.
- * Conditions that give rise to the thermodynamic product are called thermodynamic control.

The reason for the faster rate of direct addition compared to that of conjugate addition is that although the carbon atom β to the C=O group carries some positive charge, the carbon atom of the carbonyl group carries more, and so electrostatic attraction for the charged nucleophiles will encourage it to attack the carbonyl group directly rather than undergo conjugate addition. The sites for the nucleophilic attack to the α,β -unsaturated carbonyl compounds is shown in Figure 3.

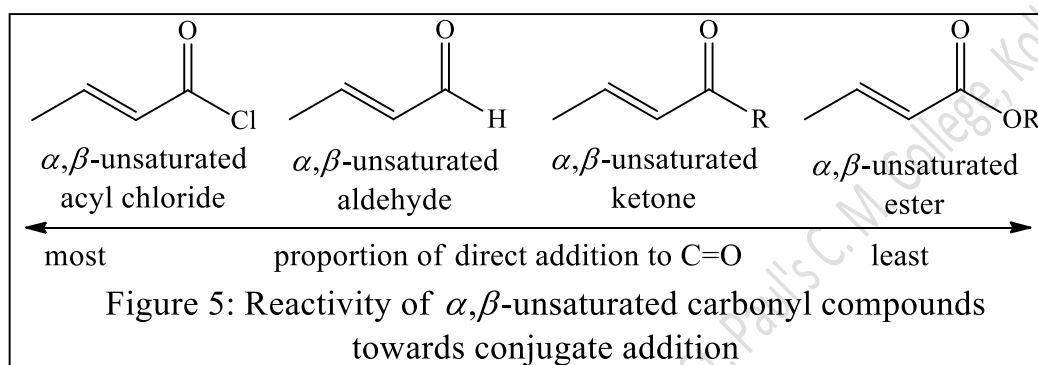


The conjugate addition product is more stable. In the conjugate addition product, a C–C σ bond is formed losing a C=C π bond, but the C=O π bond remains intact. With direct addition, still a C–C bond is formed, but the C=O π bond is lost and it keeps the C=C π bond intact. As the C=O π bond is stronger than C=C π bond, so the conjugate addition product is more stable. The result is shown pictorially in Figure 4.

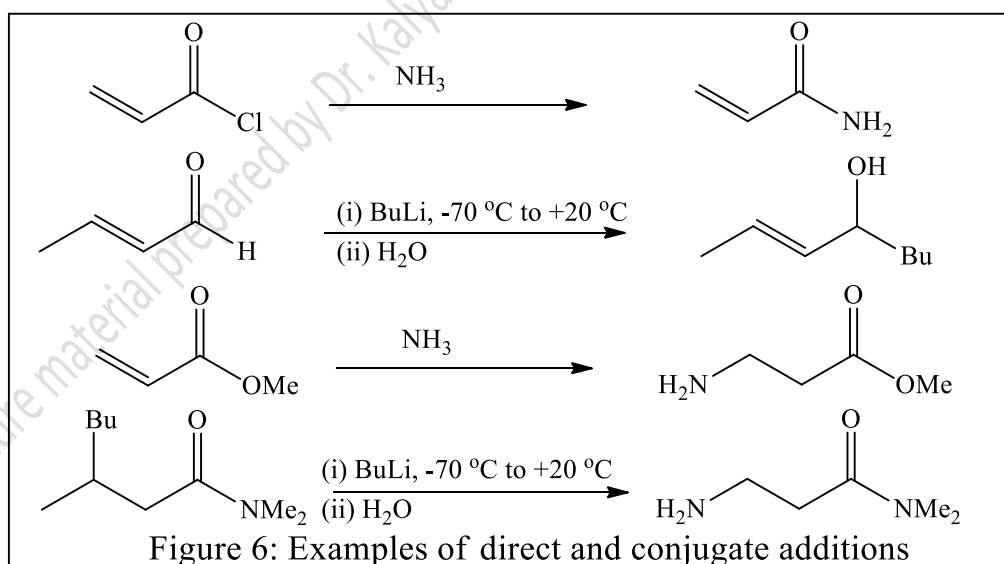


2. Structural Factors

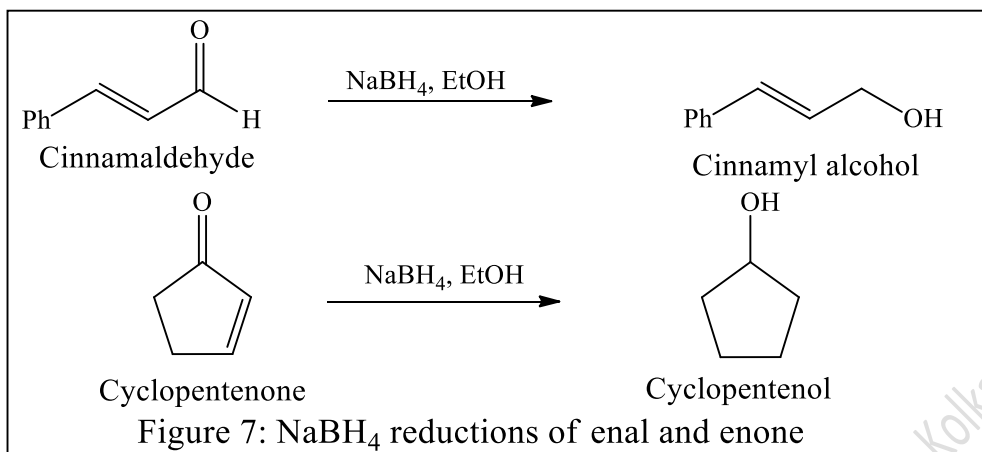
Not all additions to carbonyl groups are reversible, e.g., additions of organometallics. In such cases, the site of nucleophilic attack is determined simply by reactivity: the more reactive the carbonyl group, the more direct addition to C=O will result. The most reactive carbonyl groups are those that are not conjugated with O or N (as they are in esters and amides), and particularly reactive are acyl chlorides and aldehydes. For esters and other less reactive carbonyl compounds conjugate addition is the only reaction that occurs. In general, the proportion of direct addition to the carbonyl group follows the reactivity as follows:



The additions of butyllithium to an α,β -unsaturated aldehyde and α,β -unsaturated amide are irreversible and BuLi attacks the reactive carbonyl group of the aldehyde, but prefers conjugate addition to the less reactive amide. Similarly, ammonia reacts with this acyl chloride to give an amide product that derives from direct addition to the carbonyl group, while with the ester it undergoes conjugate addition to give an amine.

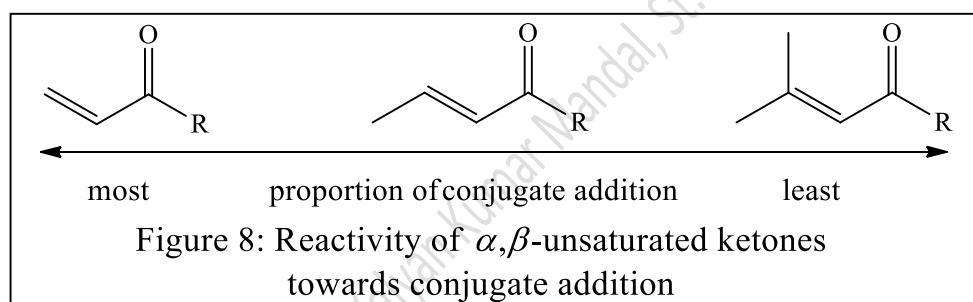


Sodium borohydride is a nucleophile that reduces simple aldehydes and ketones to alcohols, and it usually reacts with α,β -unsaturated aldehydes in a similar way, giving alcohols by direct addition to the carbonyl group (Figure 7).



In α,β -unsaturated ketones, e.g., cyclopentenone the borohydride reduces not only the carbonyl group but the double bond as well. In fact, it is the double bond that is reduced first in a conjugate addition, followed by addition to the carbonyl group.

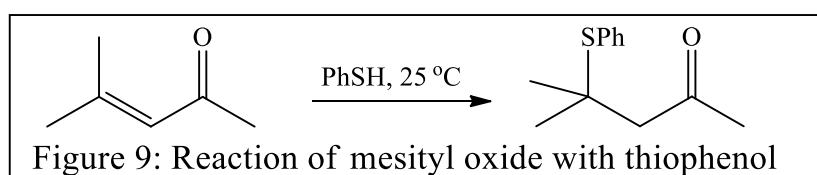
Steric hindrance also plays a role in conjugate addition. The more substituents there are at the β carbon, the less likely a nucleophile is to attack there (Figure 8).



For ketones of the type $R^1\text{-CH=CH-CO-R}^2$, the predominant factor in deciding the course of reaction is steric hindrance. When both R^1 and R^2 are large, R^2 has greater influence than R^1 (the first step in 1,2-addition is addition to the C=O group). On the other hand, 1,4-addition can be made to predominate by carrying out the reaction in the presence of copper(I) salts.

3. The Nature of the Nucleophile: Hard and Soft

Among the best nucleophiles of all carrying out conjugate addition are thiols, the sulphur analogues of alcohols. In this example (Figure 9), the nucleophile is thiophenol (PhSH). In this reaction, no acid or base catalyst is needed, and the product is obtained in a very good yield under quite mild reaction conditions.



The attraction between nucleophiles and electrophiles is governed by two related interactions - electrostatic attraction between positive and negative charges and orbital overlap between the HOMO of the nucleophile and the LUMO of the electrophile. Successful reactions usually result from a combination of both, but sometimes reactivity can be dominated by one or the other.

The dominant factor, be it electrostatic or orbital control, depends on the nucleophile and electrophile involved. Nucleophiles containing small, electronegative atoms (such as O or Cl) tend to react under predominantly electrostatic control, while nucleophiles containing larger atoms (e.g., sulphur of thiols) are predominantly subject to control by orbital overlap. The terms 'hard' and 'soft' have been introduced to describe these two types of reagents.

Hard nucleophiles are typically from the early rows of the periodic table and have higher charge density, while soft nucleophiles are from the later rows of the periodic table - they are either uncharged or have larger atoms with higher-energy, more diffuse orbitals. Few common hard and soft nucleophiles are listed in Table 3.

Hard nucleophiles	Borderline	Soft nucleophiles
F ⁻ , HO ⁻ , RO ⁻	N ₃ ⁻ , CN ⁻	I ⁻ , RS ⁻
H ₂ O, ROH, ROR	RNH ₂ , R ₂ NH	RSH, RSR, R ₃ P
NH ₃ , RMgBr, RLi	Br ⁻	Alkenes, Aromatic rings

Not only can nucleophiles be classified as hard or soft, but electrophiles can too. For example, H⁺ is a very hard electrophile because it is small and charged, while Br₂ is a soft electrophile, its orbitals are diffuse and it is uncharged.

The carbon atom of a carbonyl group is also a hard electrophile because it carries a partial positive charge due to polarization of the C=O bond. On the other hand, the β -carbon of α,β -unsaturated carbonyl compound is relatively softer in nature.

In general, hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles with soft electrophiles. Hard nucleophiles therefore prefer the carbonyl carbon undergoing direct addition whereas softer nucleophiles will go for the β -carbon for a conjugate addition.

Though the β carbon atom to the C=O group in α,β -unsaturated carbonyl system carries some positive charge, yet the carbonyl carbon carries more, and so electrostatic attraction for a hard nucleophile (which has high charge/size ratio) encourages it to attack the carbonyl group at a faster rate and consequently, a kinetically controlled 1,2-addition will take place.

So, for example, water (a hard nucleophile) reacts with aldehydes (hard electrophiles) to form hydrates in a reaction largely controlled by electrostatic attraction.

Hard/soft reactivity

- * Reactions of hard species are dominated by charges and electrostatic effects
- * Reactions of soft species are dominated by orbital effects
- * Hard nucleophiles tend to react well with hard electrophiles
- * Soft nucleophiles tend to react well with soft electrophiles

An α,β -unsaturated carbonyl compound has two electrophilic sites, one is hard and the other is soft. The carbonyl group has a high partial charge on the carbonyl carbon and will tend to react with hard nucleophiles, such as organolithium and Grignard reagents, that have a high partial charge on the nucleophilic carbon atom.

Conversely, the β carbon of the α,β -unsaturated carbonyl system does not have a high partial positive charge but is the site of the largest coefficient in the LUMO. This makes the β carbon a soft electrophile and likely to react well with soft nucleophiles such as thiols.

Hard/soft - direct/conjugate addition

- * Hard nucleophiles tend to react at the carbonyl carbon (hard) of an enone
- * Soft nucleophiles tend to react at the β -carbon (soft) of an enone and lead to conjugate addition

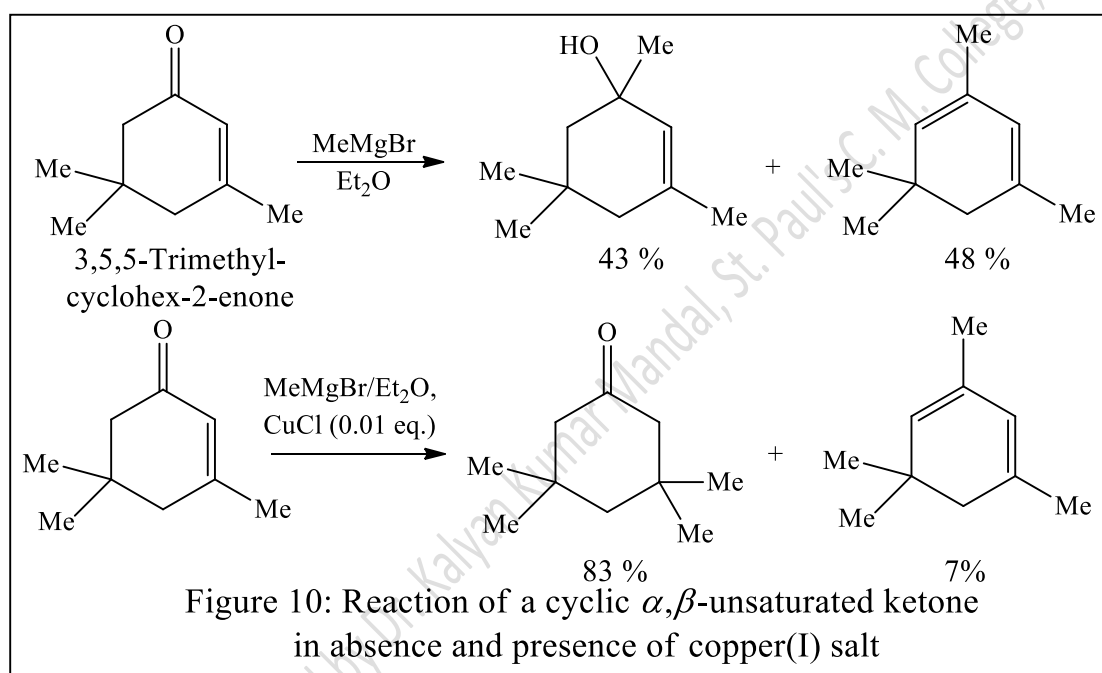
Summary

	Conjugate addition favoured by	Direct addition to C=O favoured by
Reaction conditions (for reversible addition):	thermodynamic control: * high temperatures, * long reaction times	kinetic control: * low temperatures, * long reaction times
Structure of α,β -unsaturated compound	*unreactive C=O group (amide, ester) *unhindered β -carbon	* reactive C=O group (aldehyde, acyl chloride) * hindered β -carbon
Type of nucleophile	soft nucleophiles	hard nucleophiles
Organometallic	organocoppers or catalytic Cu(I)	organolithiums, Grignard reagents

Reaction of α,β -Unsaturated Ketones with Organometallic Reagents in presence of traces of Copper(I) salts

Grignard reagents add directly to the carbonyl group of α,β -unsaturated aldehydes and ketones to give allylic alcohols. This is because the hard Grignard reagent prefers to attack the harder C=O rather than the softer C=C electrophilic centre.

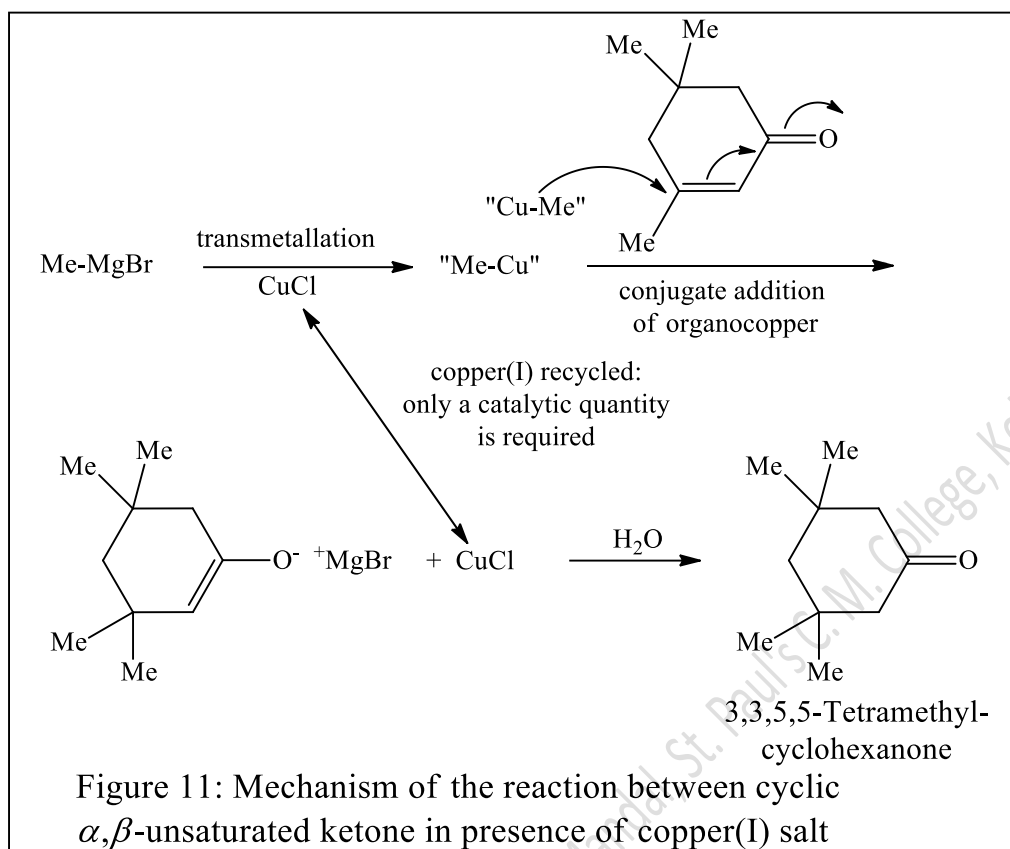
The addition of MeMgI to a cyclic ketone, shown in Figure 10, gives an allylic alcohol, additionally a diene is also obtained which arises from this alcohol by loss of water (dehydration). However, if the same reaction is carried out in presence of a very small amount (just 1%) of copper(I) chloride, the Grignard reagent undergoes conjugate addition predominantly, with only a trace of the diene.



Organocopper reagents undergo conjugate addition

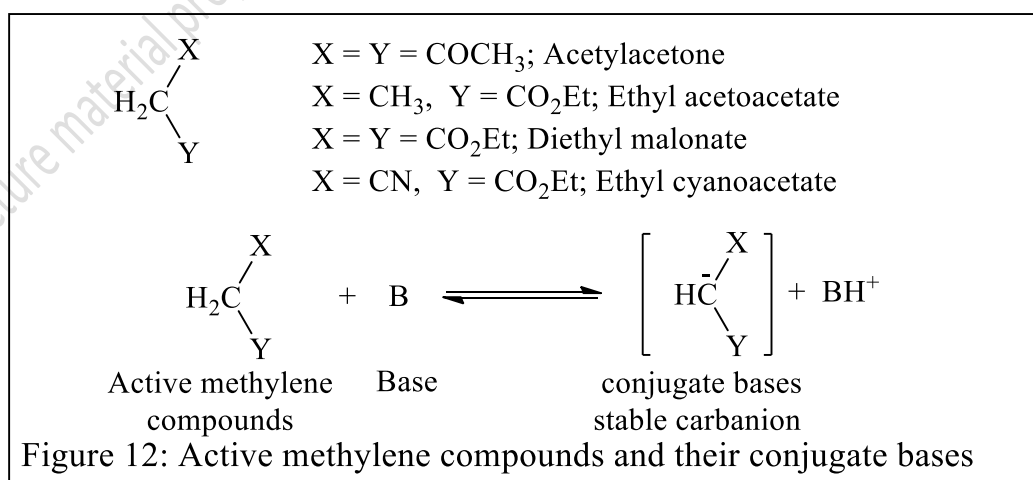
The copper works by transmetallating the Grignard reagent to give an organocopper reagent. Organocoppers are softer than Grignard reagents because copper is less electropositive than magnesium (electronegativities: Mg, 1.3; Cu, 1.9.), so the C–Cu bond is less polarized than the C–Mg bond, giving the carbon atom less of a partial negative charge.

Therefore, the organocopper reagents add in a conjugate fashion to the softer C=C double bond. Once the organocopper has added, the copper salt is available to transmetallate some more Grignard, and consequently, only a catalytic amount is required. The mechanism involving the transmetallation reaction is shown in Figure 11.



Stable Enolate Ions: Nucleophiles Promoting Conjugate Addition

An important source of nucleophile undergoing conjugate addition to α,β -unsaturated carbonyl compounds is the carbanion generated from an active methylene compound, such as acetylacetone, ethyl acetoacetate, diethyl malonate, ethyl cyanoacetate, etc. In presence of base, each of these compounds forms a relatively stable carbanion as illustrated in Figure 12.



Since the carbanion obtained from an active methylene compound is - a) a softer base, and b) relatively stabilized, it is expected that an active methylene compound will undergo 1,4-addition with an α,β -unsaturated carbonyl compound in presence of a suitable base (B:). Figure 14 illustrates the course of the reaction.

