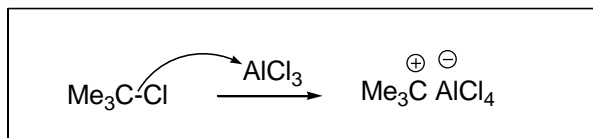


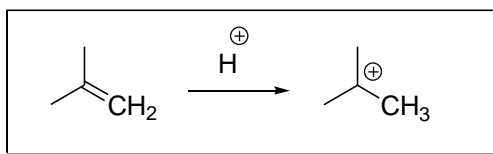
Lecture 3 Acid Catalyzed Reactions I

2.1 Principles

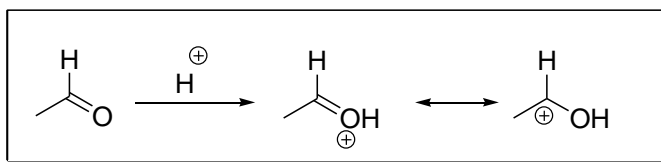
The reaction involves the generation of an electrophilic species with the aid of an acid which undergoes reaction with nucleophile. The electrophiles may be formed from an alkyl or acyl halide by treatment with a Lewis acid, e.g.



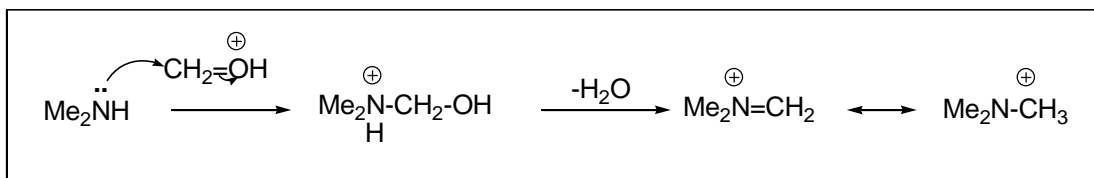
or, more generally, by the addition of a proton to a double bond.



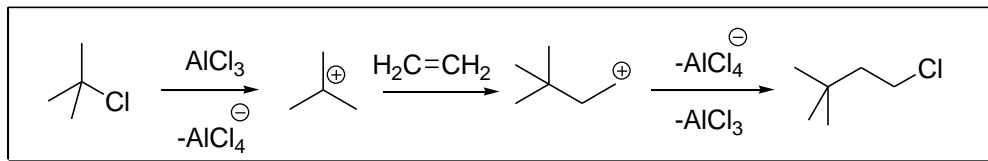
or a carbonyl group, as in the self-condensation of aldehydes and ketones, e.g.



The electrophiles in the Mannich reaction are generated from an aldehydes and an amine in the presence of an acid e.g.

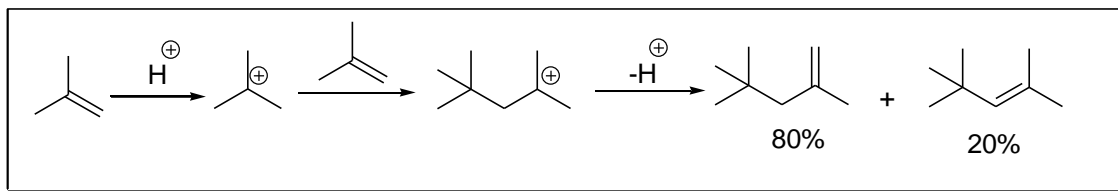


The nucleophiles may be an alkene, an enol or a compound of related type.

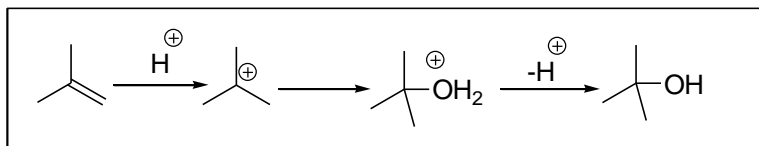


2.2 Self-Condensation of Alkenes

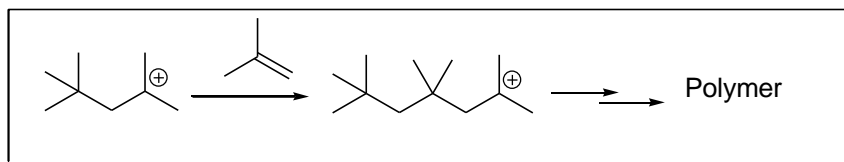
Alkenes undergo protonation with acid to give a carbocation that can add with second molecule of alkene to generate new carbocation which could eliminate a proton to give alkene. For an example, isobutylene with 60% sulfuric acid affords a 4:1 mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene. The reaction takes place by protonation of one molecule of the alkene to provide a carbocation that adds to the methylene group (Markonovkov's rule) of a second molecule. The new carbocation eliminates a proton to afford the products.



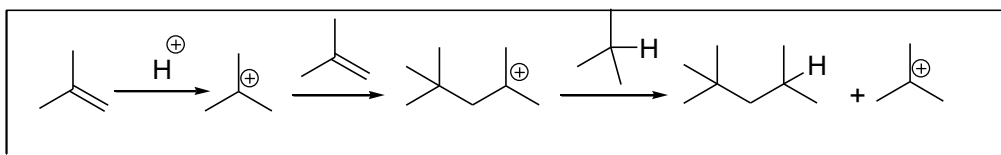
The reaction condition is crucial for the selectivity of the products. For an example, when dilute sulfuric acid is used, the first carbocation undergoes reaction preferentially with water to afford t-butanol as a major product.



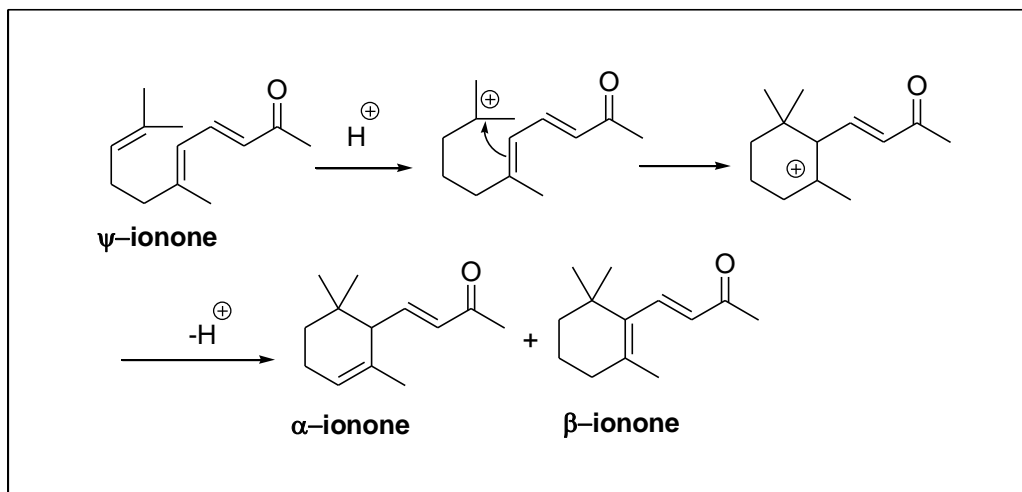
Alternatively, when more concentrated sulfuric acid is used, the second carbocation reacts with a further molecule of isobutylene to lead polymerization.



Furthermore, isooctane (used as high-octane fuel) is formed in the presence of isobutene. Under these conditions, the carbocation formed by dimerization of isobutylene abstracts hydride ion from isobutane. During the process a new t-butyl carbocation is generated which adds to isobutylene to lead a chain propagation.



Dienes may undergo acid-catalyzed cyclizations provided the product is a stereochemically favored five or six membered ring. For example, in the presence of acid, ψ -ionone cyclizes to give a mixture of α - and β -ionones.

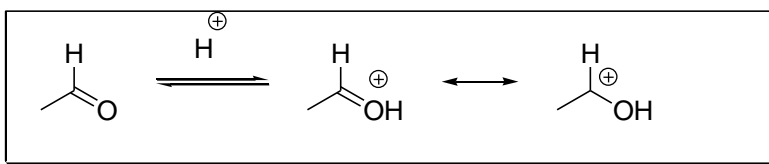


2.3 Reactions of Aldehydes and Ketones

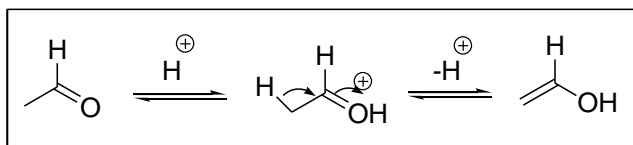
The acid-catalyzed reactions of aldehydes and ketones can be broadly divided into four types: self-condensation, crossed-condensation, reactions of ketones with acid chlorides and acid anhydrides and reactions of 2-methyl pyridines and related compounds.

2.3.1 Self-Condensation

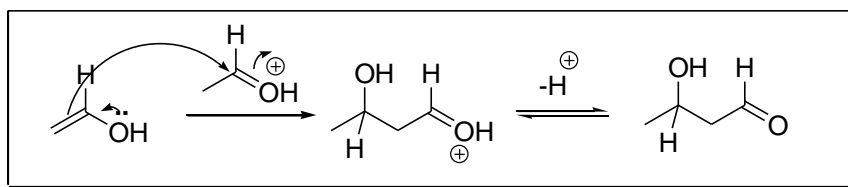
Aldehydes and ketones which are prone to undergo enolization proceed self-condensation in the presence of acids. The acid has dual functions: first, it enhances the reactivity of the carbonyl group towards the addition of a nucleophile, e.g.



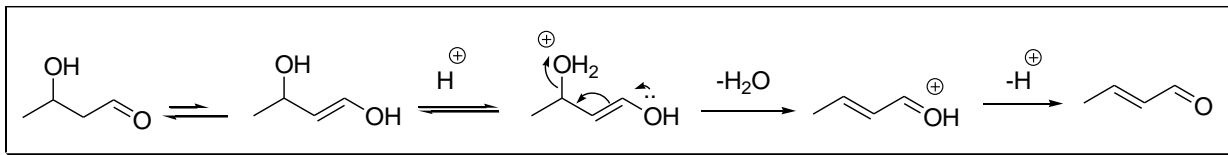
Next, it catalyzes the enol formation of the carbonyl compound, e.g.



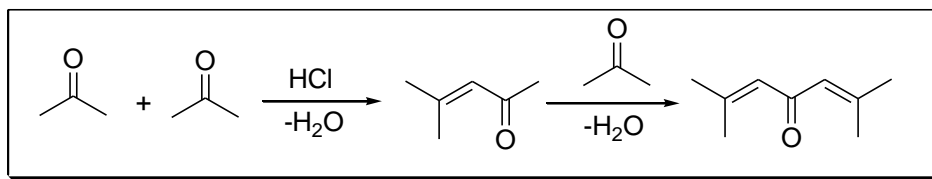
A molecule of enol then reacts with a molecule of the activated carbonyl compound.



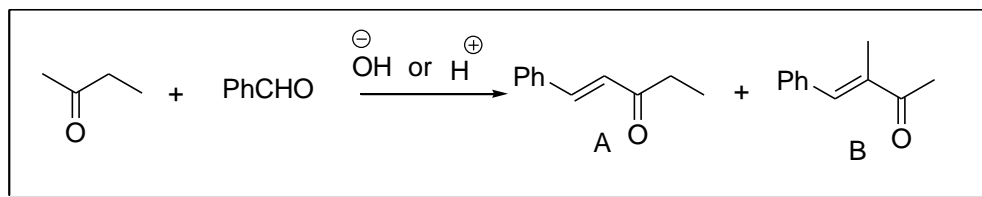
Dehydration via the enol generally follows:



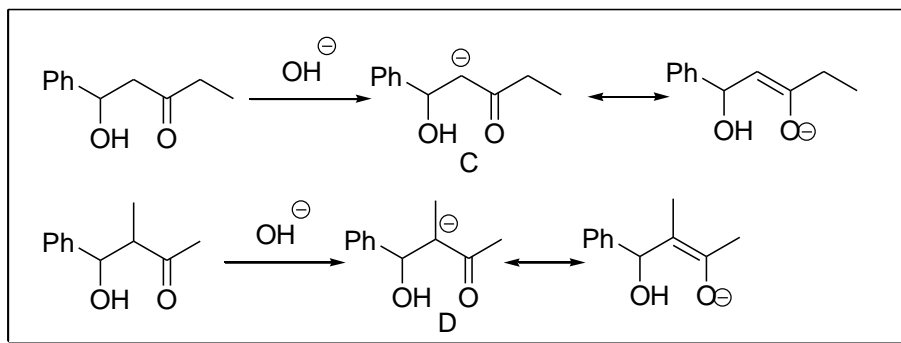
In case of ketones having α -hydrogen, further reaction possible. For an example, in presence of hydrogen chloride, acetone proceeds reaction to afford a mixture of mono- and di-condensation products.



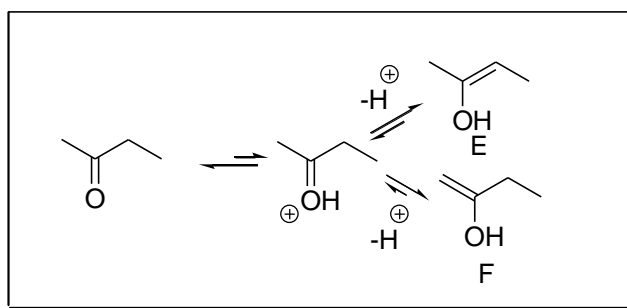
The product yield is usually low in acid-catalyzed reaction compared to that of the base-catalyzed reactions. However, in some instances the products are different, where the acid-catalyzed reactions are useful. For an example, the base-catalyzed reaction of benzaldehyde with butanone gives A as a main product whereas the acid-catalyzed reaction affords B as the major product.



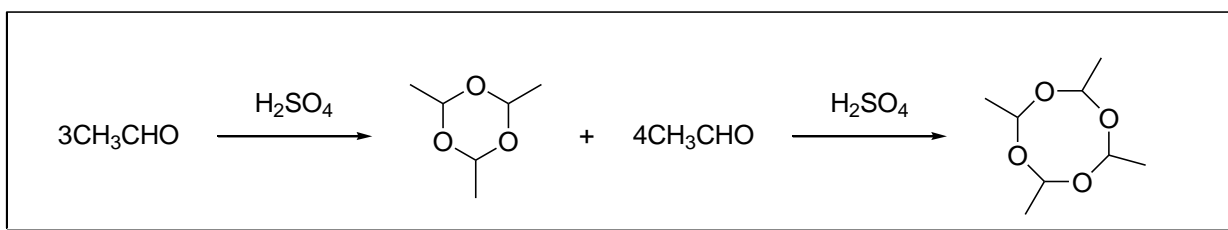
This is because, in the former, equilibria are established with the two possible aldol adducts and the main product is determined by the ease of dehydration to provide an aryl-conjugated product. Thus, the formation of A is favored since the enolate C is generated faster compared to that of the more substituted enolate D.



In contrast, in acid-catalyzed reaction the crucial step is not dehydration but the formation of the new C-C bond and the regioselectivity is governed by the rapid formation of the more substituted enol E compared to monoalkylated enol F. Thus, the formation of B is favoured compared to that of A.



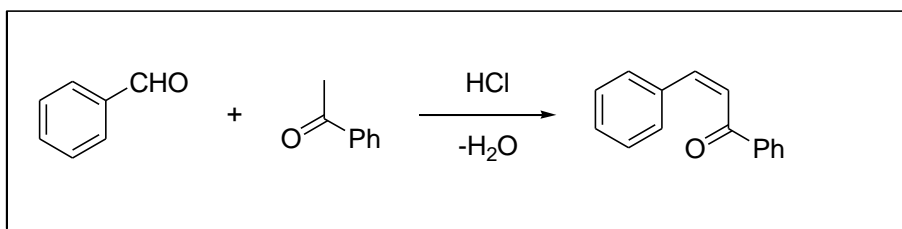
Finally, some aldehydes give cyclic polymers with acids. For example, acetal with trace of concentrated sulphuric acid provides the cyclic trimer, paraldehyde, and some of the cyclic tetramer, metaldehyde.



It is reversible and the aldehyde can be generated prior to use by warming with dilute acid. In case of ketones, acetone undergoes similar kind of polymerization with concentrated sulfuric acid producing 1,3,5-trimethylbenzene.

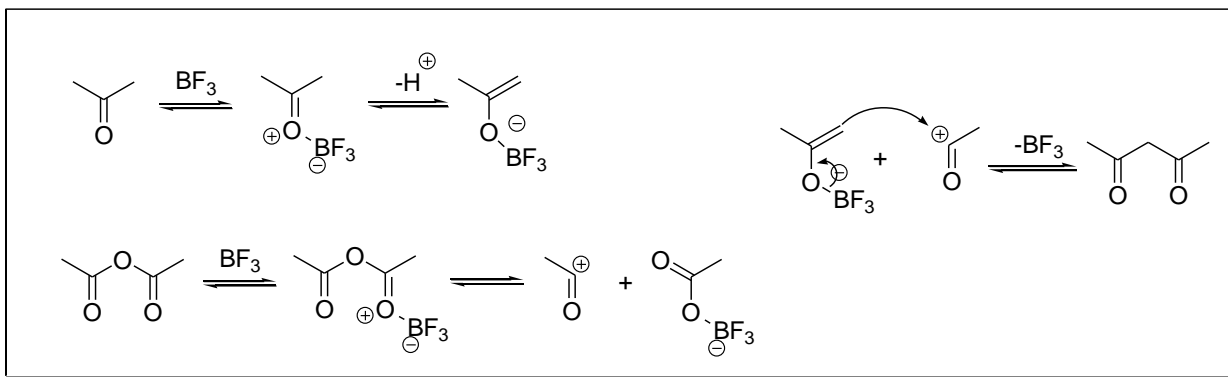
2.3.2 Crossed-Condensation

Similar to base-catalyzed reactions, crossed reactions between two enolizable carbonyl compounds may result in a mixture of four products. However, if only one of the two compounds can enolize and the other has the more reactive carbonyl group, a single product may then be formed. For example, the reaction of enolizable acetophenone with non-enolizable more reactive benzaldehyde can give single product in good yield.



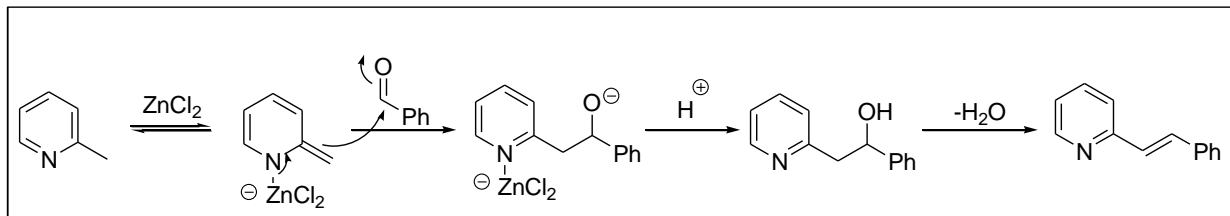
2.3.3 Reactions between Ketones and Acid Chlorides or Anhydrides

Ketones react with compounds having more reactive carbonyl groups such as acid chloride or anhydrides. For example, the reaction of acetone with Ac_2O in presence of BF_3 gives 2,4-pentanedione.



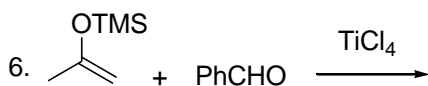
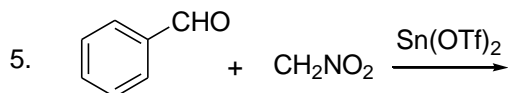
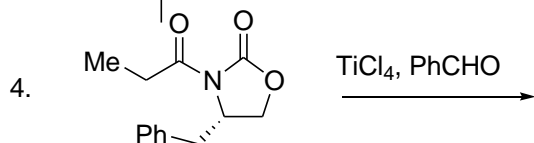
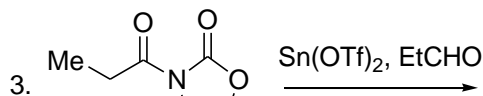
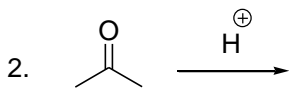
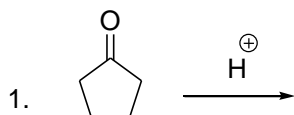
2.3.4 Reactions of 2-Methylpyridine and Analogue

Compounds such as 2- and 4-methylpyridines, and 2- and 4-methylquinolines react with aldehydes in presence of ZnCl_2 which catalyzes their conversion into the nitrogen-analogue of an enol. For example, 2-methylpyridine proceeds reaction with benzaldehyde in presence of ZnCl_2 .



Problems:

Complete the following reactions.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Ellerd, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

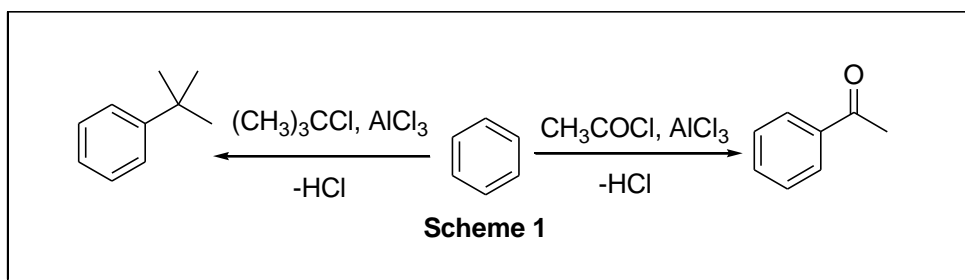
J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.



Lecture 4 Acid Catalyzed Reactions II

2.4 Friedel-Crafts Reactions

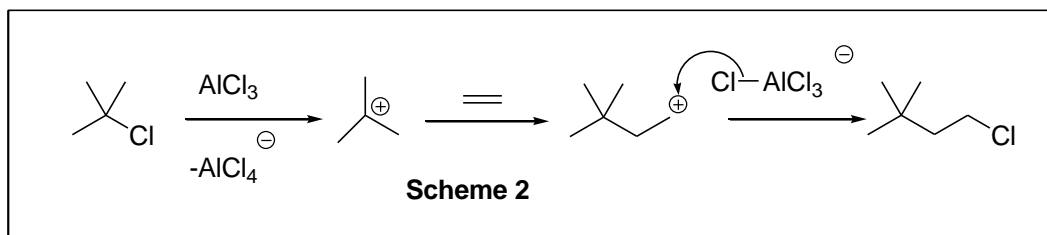
Friedel and Crafts reactions are associated with the acylation and alkylation of aromatic systems in presence of Lewis acids (Scheme 1).



Analogous reactions also occur with alkenes, although they are not widely useful.

2.4.1 Alkylation

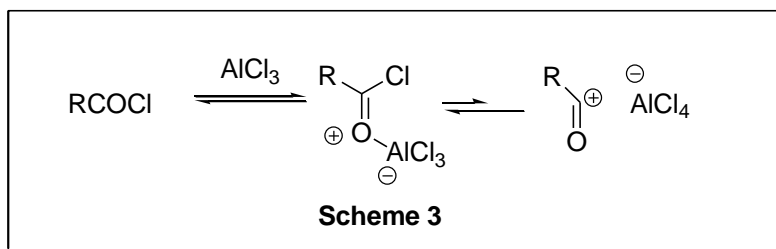
The simplest example is the reaction of *t*-butyl chloride with ethylene to afford neohexyl chloride at $-10\text{ }^{\circ}\text{C}$ in presence of AlCl_3 (Scheme 2).



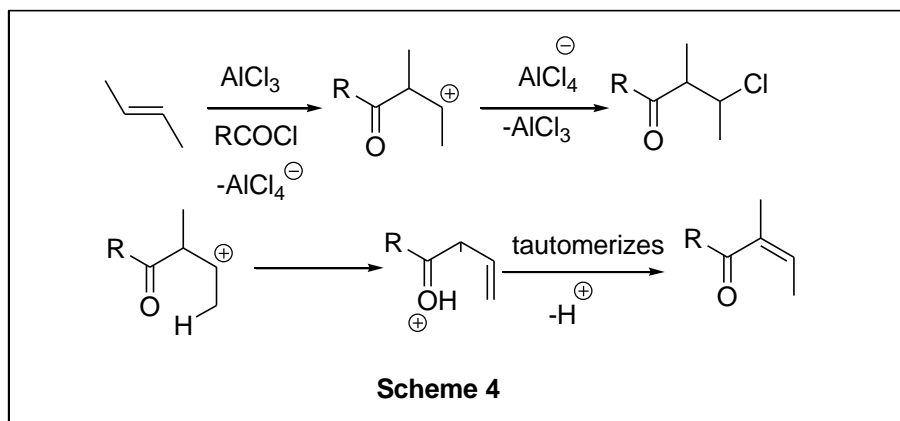
However, several side reactions are usually encountered in alkylation. First, alkene often isomerizes in presence of AlCl_3 . Second, alkyl halide may rearrange. In addition, the halide produced may undergo further reaction. These aspects limit their applications.

2.4.2 Acylation

The acylation of alkene can be brought using acid chloride or anhydride as acylating agent in presence of Lewis acid. The electrophilic reagent can be either a complex of the acid chloride and Lewis acid or an acylium cation (Scheme 3).



The reaction may end with the uptake of chloride ion to give a β -chloroketone or by elimination to give β,γ -unsaturated ketone which rearranges using the released acid to yield the more stable conjugated ketone (Scheme 4).

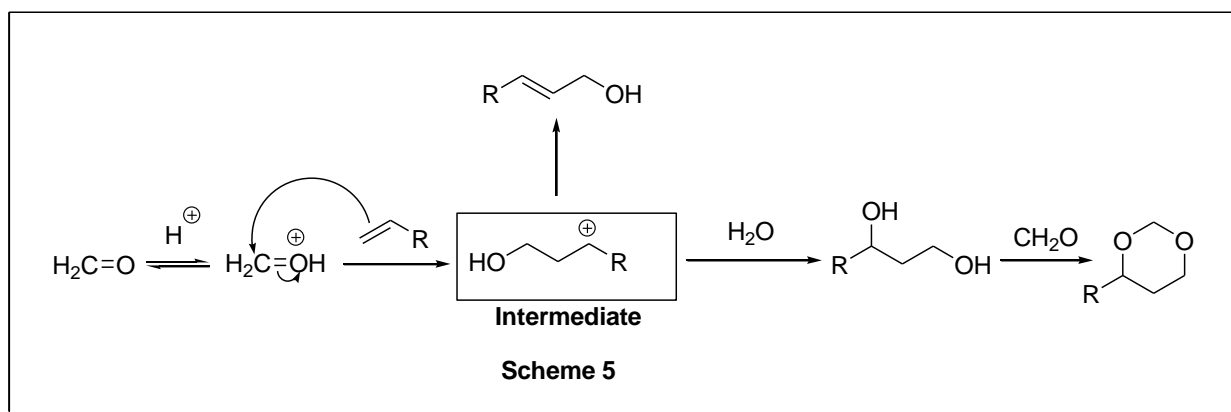


Acylation also suffers due to rearrangement of the alkenes in presence of AlCl_3 . Thus, the use of less vigorous Lewis acid such as SnCl_4 will be useful to minimize the side reactions.

2.5.1 Prins Reaction

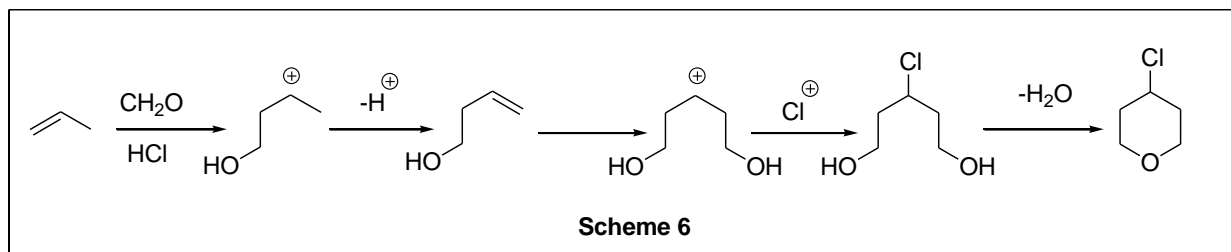
2.5.1.1 The Original Prins Reaction

Prins reaction has remarkable scope which sometimes affords useful molecules that are difficult to prepare by other methods. The reaction involves an electrophilic addition (Markovnikov) of aldehyde or ketone to an alkene in presence of an acid followed by capture of a nucleophile. The outcome of the reaction depends on nature of the substrates and reaction conditions. For examples, with water and protic acid, the reaction product is a 1,3-diol. In absence of water, dehydration takes place to give an allyl-alcohol. With an excess of HCHO, the reaction product is dioxane. When water is replaced by acetic acid, corresponding esters are formed (Scheme 1).



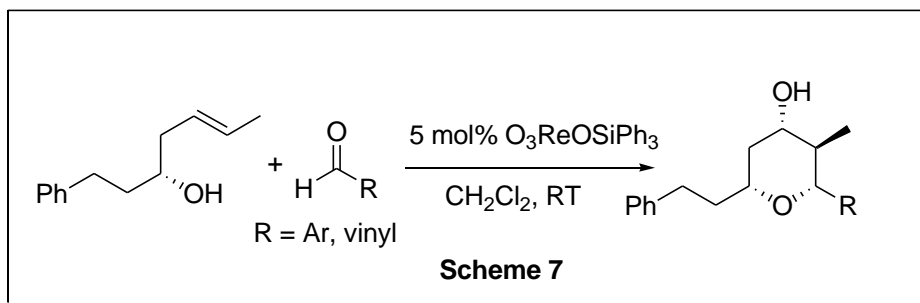
2.5.1.2 The Formation of Tetrahydropyrans

Aliphatic alkenes undergo Prins reaction. For example, the reaction of propene, HCHO and HCl gives 4-chloro-tetrahydropyran in good yield (Scheme 6).

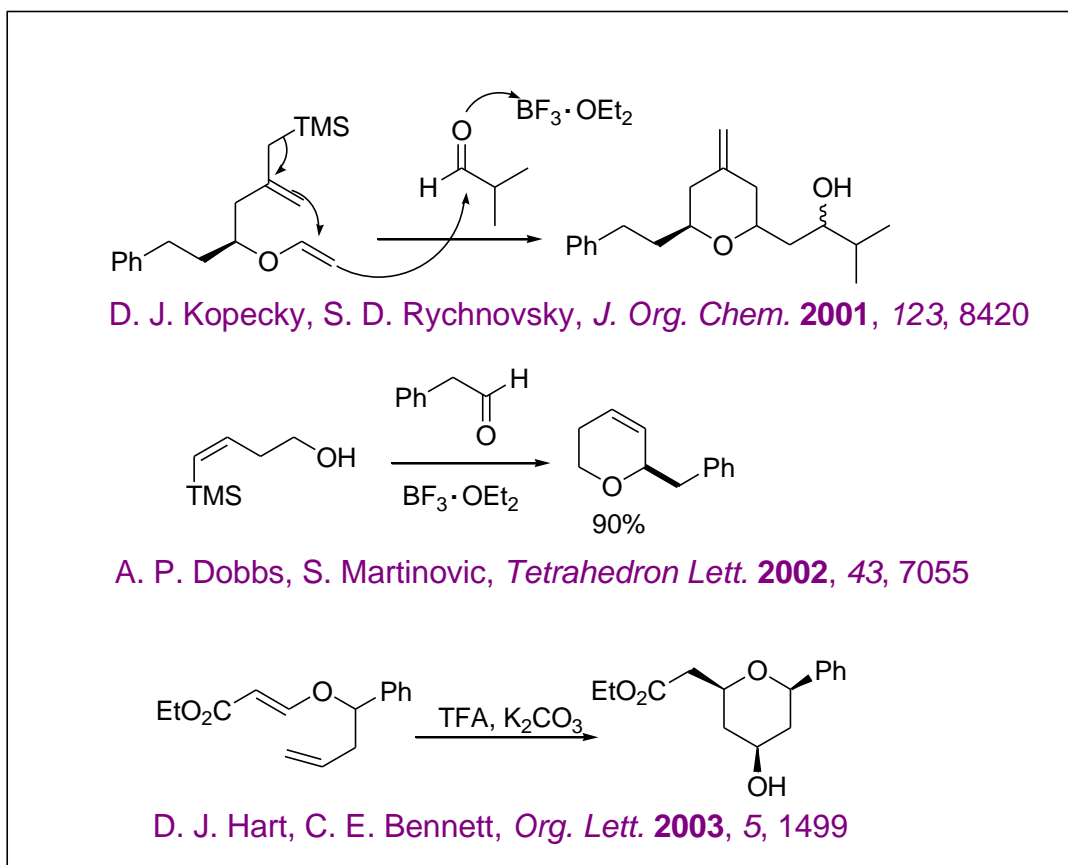


Diastereoselective version of this reaction has also been considerably explored. For example, the synthesis of highly substituted 4-hydroxytetrahydropyran can be

accomplished using rhenium(VII) complex, $\text{O}_3\text{ReOSiPh}_3$, as a catalyst under milder conditions (Scheme 7).

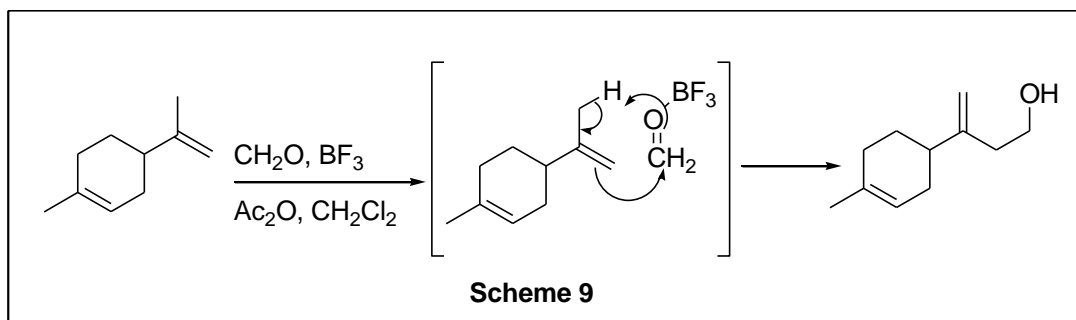
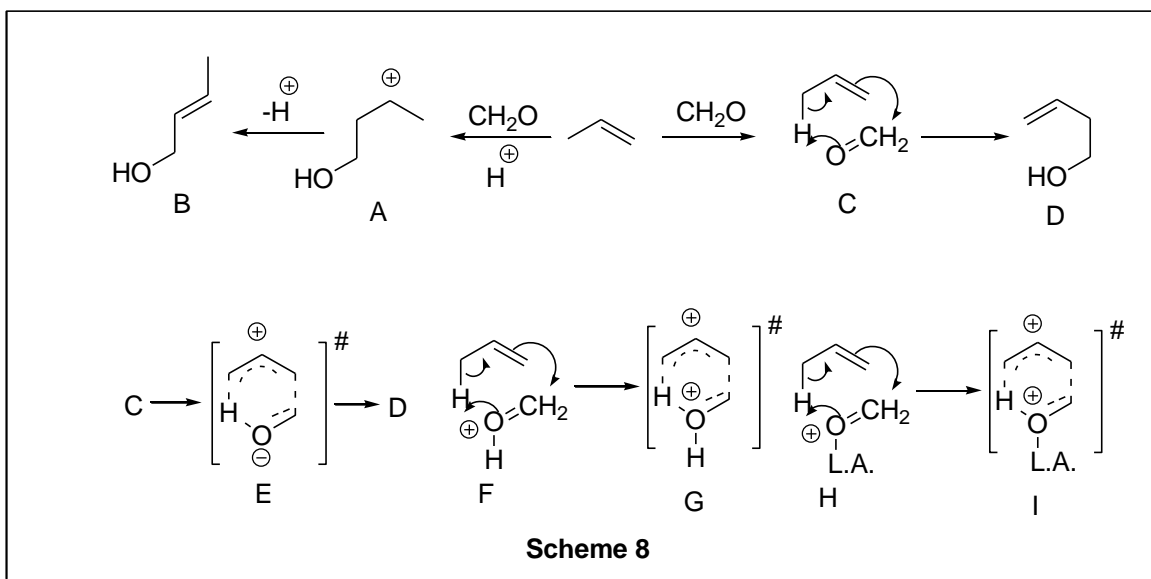


Examples:



2.5.1.3 The Carbonyl-Ene Mechanism

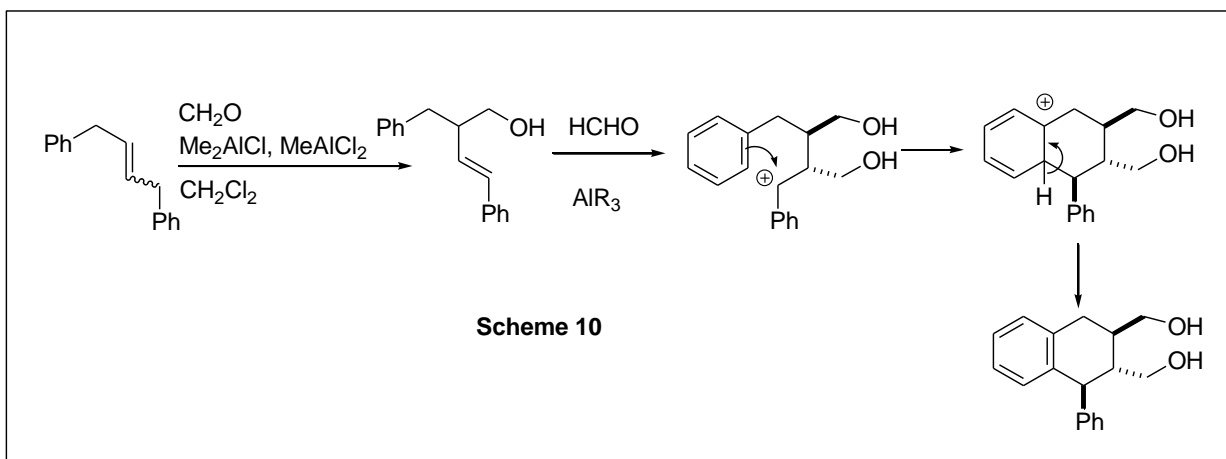
Let us analyze the mechanism described in Scheme 6 again. The formation of terminal alkene D takes place compared to the more stable internal alkene B. These results suggest that the mechanism is similar to that of a carbonyl ene reaction having the hydrogen transfer and addition of HCHO concerted C (B. J. Snider, *Comp. Org. Syn.* Vol. 2, p. 527). The intermediate C is polar having partial charges E that could be stabilized and the reaction accelerated by protic acids G and Lewis acids I (Scheme 8).



Lewis acids are found to be excellent catalysts and the reaction can be stopped after the first step. This is advancement in the Prins reaction because otherwise a mixture of products is generally obtained. For example, the addition of HCHO to limonene using BF_3 selectively affords a single compound in good yield with excellent chemo- and regioselectivity (Scheme 9).

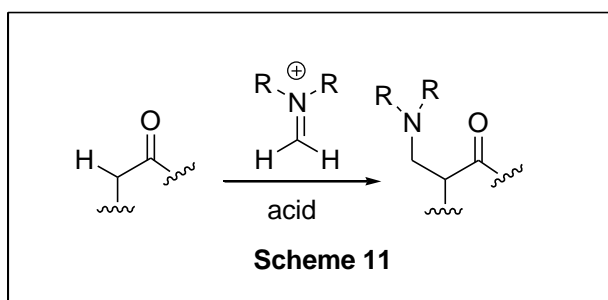
2.5.1.4 Stereoselectivity

The stereochemistry of the product can be controlled. For example, a mixture of E and Z 1,4-diphenylbut-2-enes with formaldehyde in presence of a mixture of MeAlCl_2 and Me_2AlCl gives cyclized product with anti-selectivity in 50% yield. Irrespective of the geometry of the starting alkene a single anti product is obtained. This reaction involves a carbonyl ene reaction followed by Friedel-Crafts alkylation (Scheme 10).

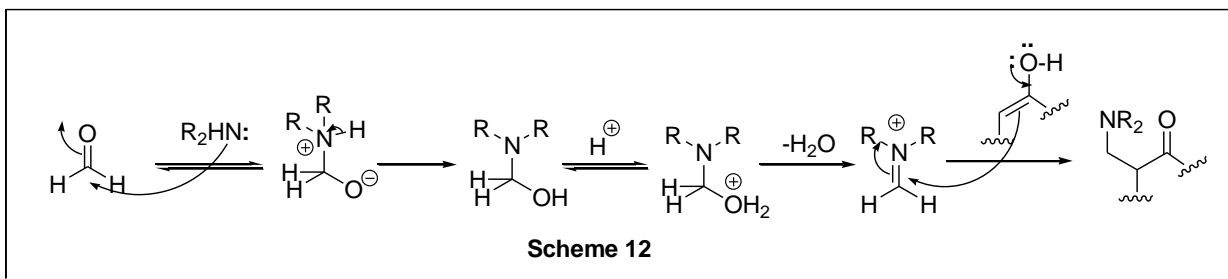


2.5.2 Mannich Reaction

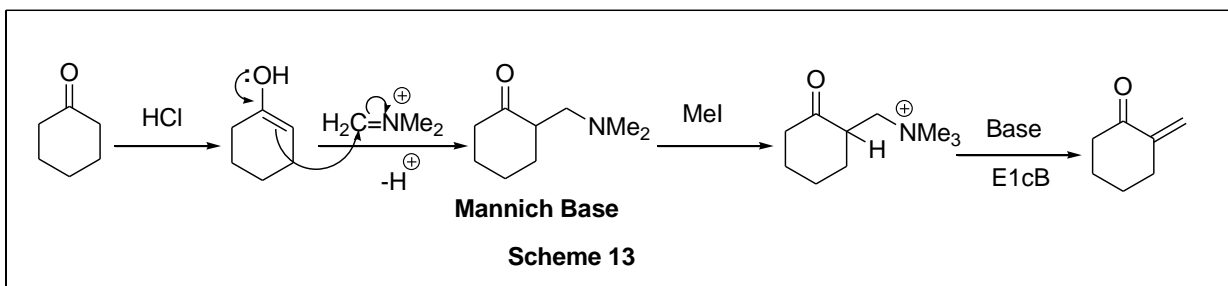
Compounds that are enolic react with a mixture of an aldehydes and a primary or secondary amine in the presence of acid (Scheme 11).



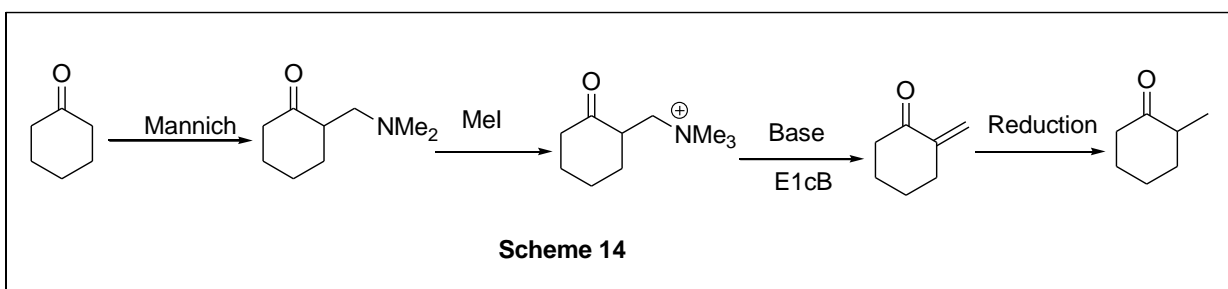
Amines react with aldehydes in the presence of acid to give an adduct that eliminates water to form an electrophiles, and the acid also catalyzes the conversion of ketone into its enol tautomer. The enol then reacts with the electrophiles and the resulting adduct tautomerizes to the amine salt (Scheme 12).

Mechanism

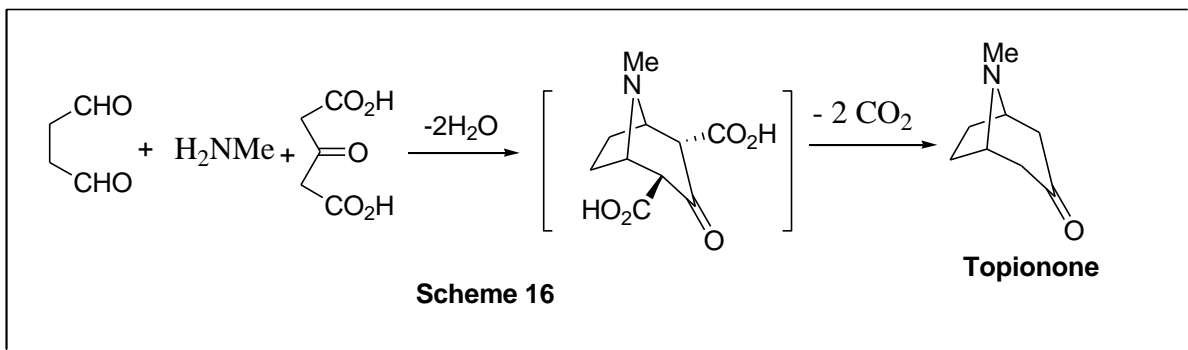
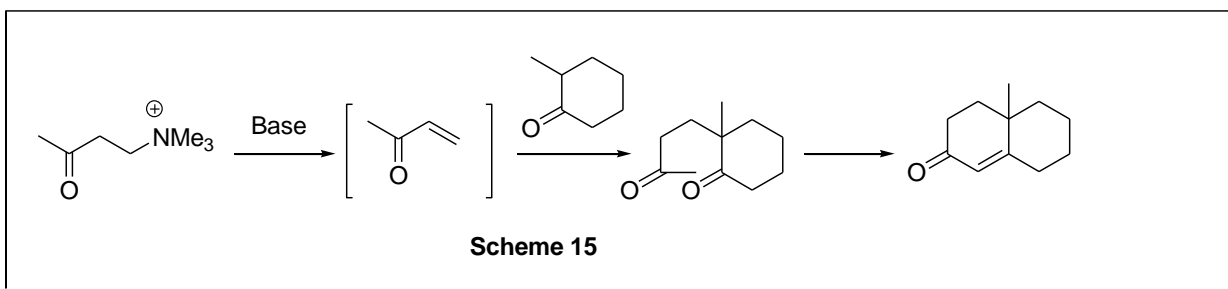
Mannich reaction is one of important reactions in organic synthesis. It provides a simple route for the preparation of amino-ketones and many drug molecules belong to this class. Furthermore, the Mannich products can be converted into enones. For examples, the most reliable method for making enone is to alkylate the Mannich base with MeI and then treat with base (Scheme 13).



Although the reaction is similar to the Hofmann elimination of a quaternary ammonium salt, Mannich base--hydrochlorides undergo elimination readily because the double-bond which is generated is conjugated with unsaturated group. Eliminations of this type have advantages. For example, the reduction of C=C bond gives the next highest homologue of the ketone from which the Mannich base was derived (Scheme 14).

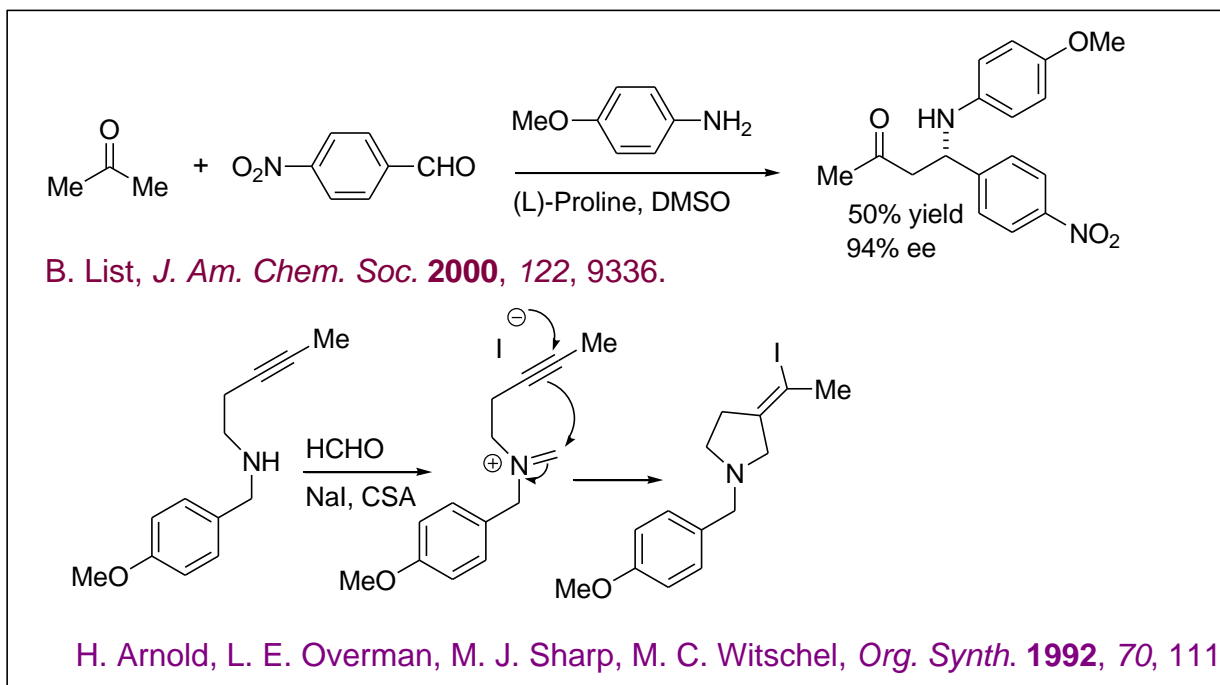


Furthermore, the quarternary salts of Mannich bases are latent sources of α,β -unsaturated carbonyl compounds required for condensation reactions. For example, for a base-catalyzed reaction utilizing but-3-en-2-one, it is better to employ the quarternized Mannich base derived from acetone, from which the unsaturated ketone is generated in situ by the action of a base, than to use the free but-3-en-2-one which is prone to undergo polymerization. The best example of this application is the **Robinson annelation** in steroid synthesis.



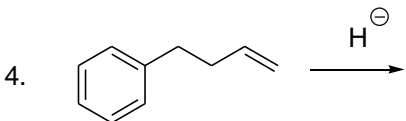
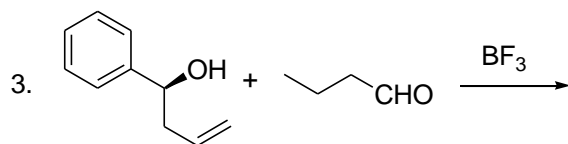
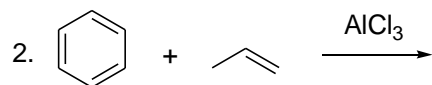
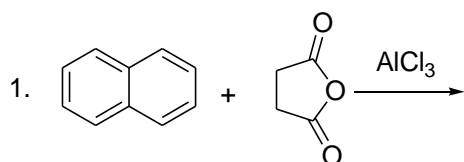
Mannich reaction finds huge applications in alkaloid synthesis. For example, the Robinson's synthesis of tropionone from calcium acetonedicarboxylate, methylamine and succindialdehyde gives the product in 90% yield (Scheme 16). It consists of two Mannich reactions, followed by spontaneous decarboxylation of the dibasic β -keto acid.

Examples:

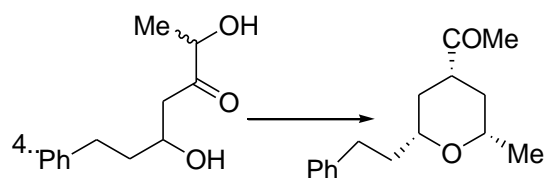
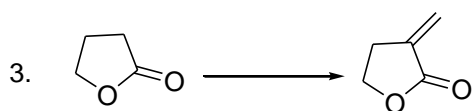
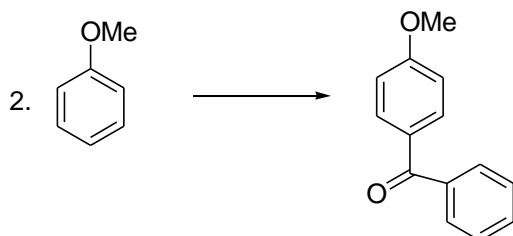
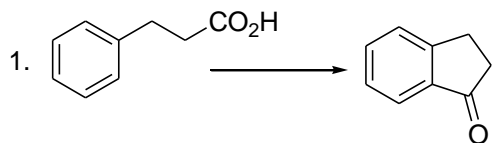


Problems:

A. What products would you expect from the following?



B. How would you use acid catalysis in the following conversions?



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

I. L. Finar, *Organic Chemistry*, Vol. 2, 5th edition, ELBS, England, 1975.

P. Wyatt, S. Warren, *Organic Synthesis*, Wiley, England, 2007.