



Umpolung



new
reactivity



Dr. Harish R. Talele

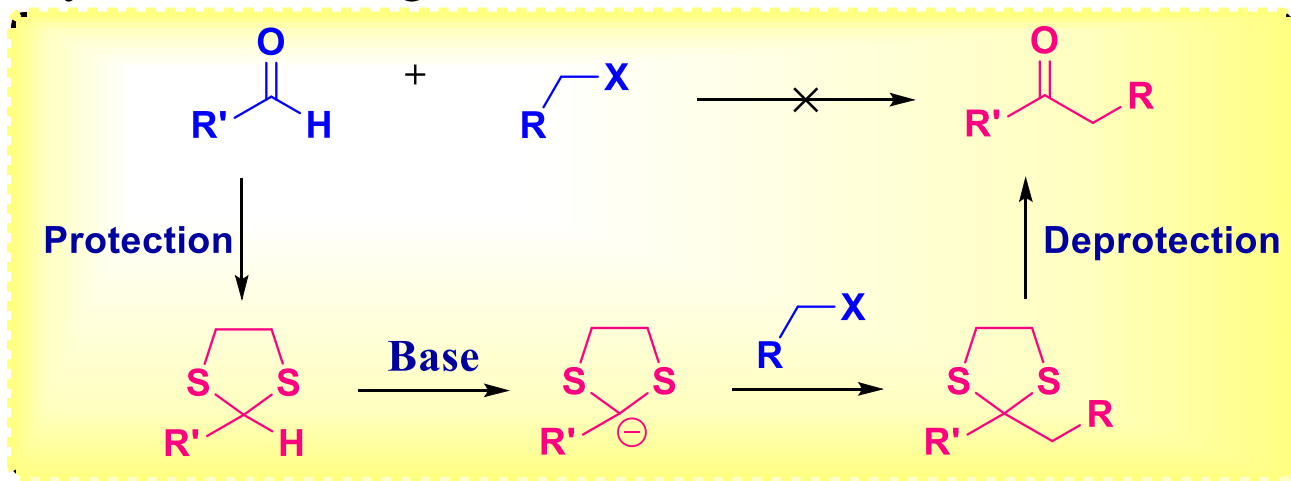
Department of Chemistry

TVES'S D. N. College, Faizpur, 425503

What is an Umpolung?

Polarity inversion in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group.

The concept was introduced by **D. Seebach** (hence the German word *umpolung* for reversed polarity) and **E. J. Corey**. Polarity analysis during retrosynthetic analysis tells a chemist when umpolung tactics are required to synthesize a target molecule



The temporary modification of a carbonyl group so that the carbon atom behaves as a nucleophile in displacement and addition reactions would be of great utility in organic synthesis.

Angew. Chem. Int. Ed. **1965**, *4*, **1075**.

Angew. Chem. Int. Ed. **1965**, *4*, **1077**.

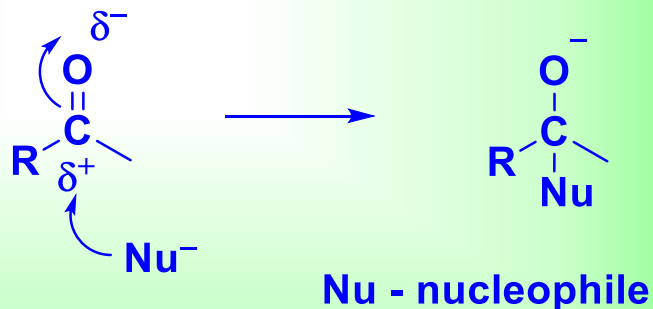
J. Am. Chem. Soc. **1967**, *89*, **434**.

J. Org. Chem. **1968**, *33*, **300**.

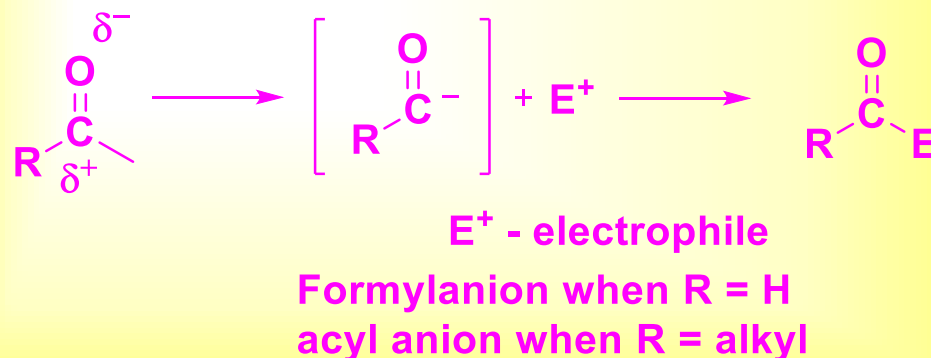
J. Org. Chem. **1966**, *31*, **4303**.

Reversal of carbonyl group polarity (Umpolung)

Traditional approach



Umpolung approach

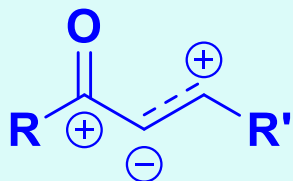


The carbonyl group is electrophilic at the carbon atom and hence is susceptible to attack by nucleophilic reagents. Thus, the carbonyl group reacts as a **formyl cation** or as an **acyl cation**. A reversal of the positive polarity of the carbonyl group so it acts as a **formyl or acyl anion** would be synthetically very attractive. To achieve this, the carbonyl group is converted to a derivative whose carbon atom has the negative polarity. After its reaction with an electrophilic reagent, the carbonyl is regenerated.

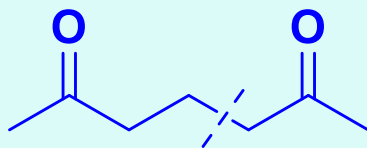
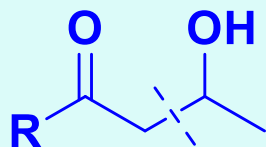
Umpolung in a synthesis usually requires extra steps. Thus, one should strive to take maximum advantage of the functionality already present in a molecule

Carbonyl group reactivity and Target Molecule

Traditional approach

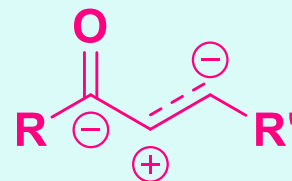


Normal reactivity

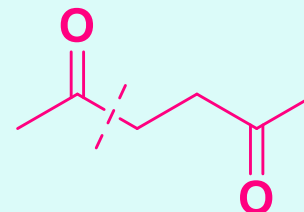
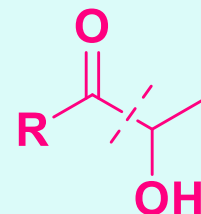


odd number of carbons
between functional groups

Umpolung approach

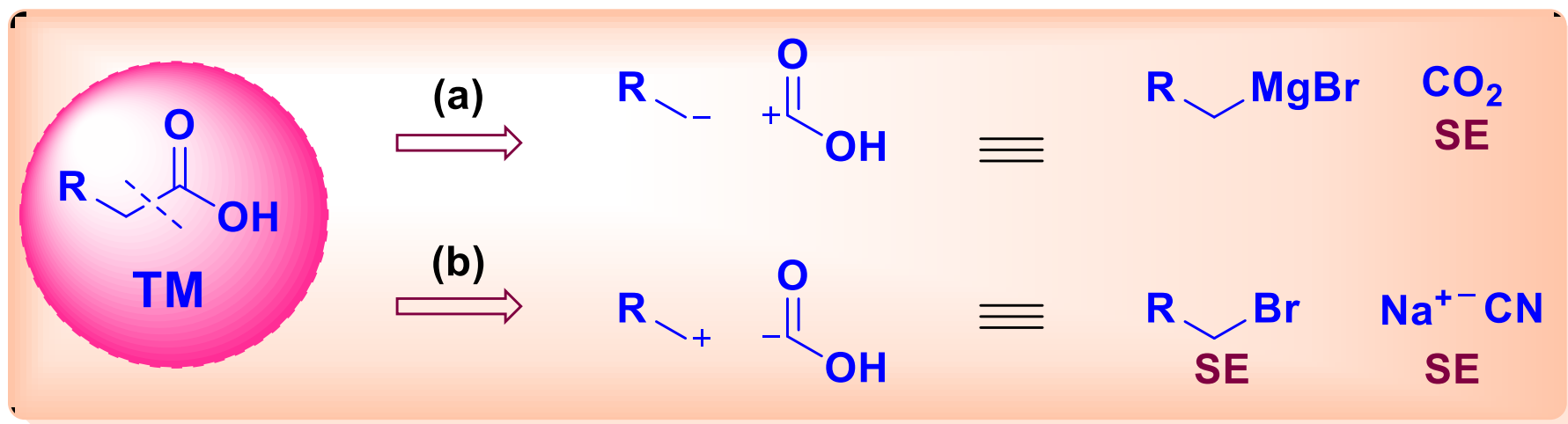


Inverted reactivity



even number of carbons
between functional groups

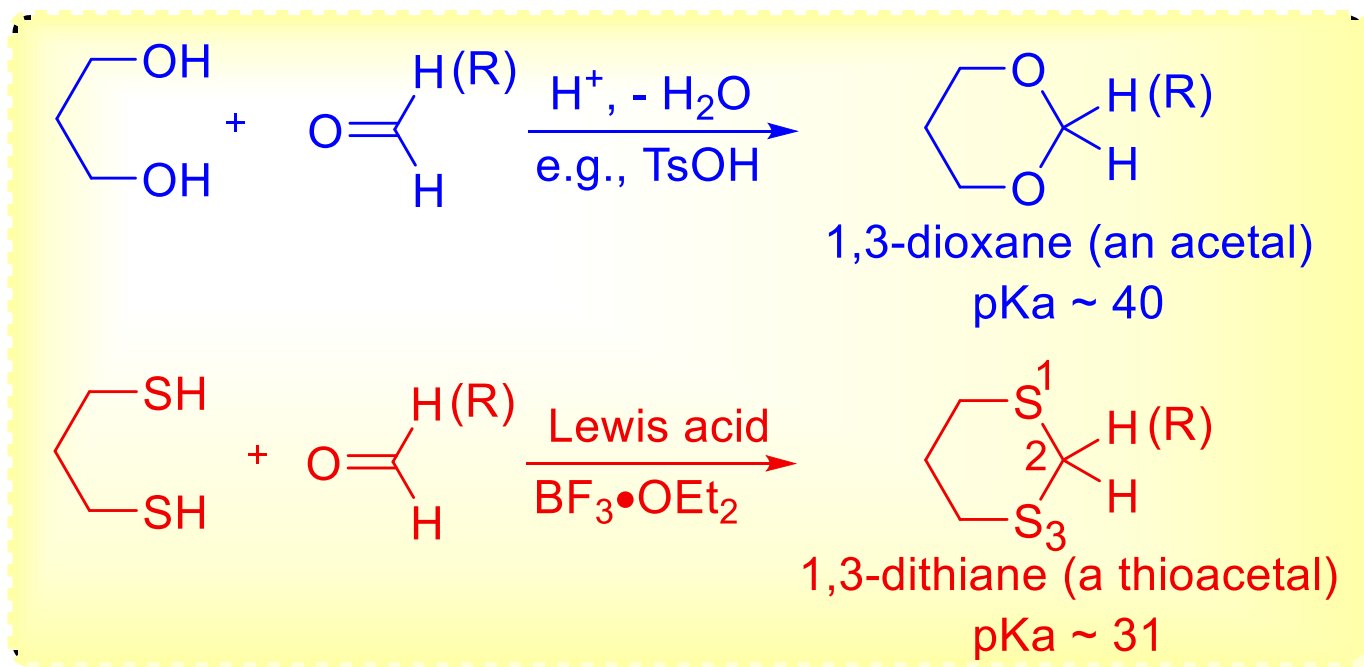
The normal disconnection pattern of a carboxylic acid with a Grignard reagent and carbon dioxide as SEs (path a) and a disconnection leading to a carboxyl synthon with an "unnatural" negative charge (path b). Cyanide ion can act as an SE of a negatively charged carboxyl synthon. Its reaction with R-Br furnishes the corresponding nitrile, which on hydrolysis produces the desired TM.



Since formyl and acyl anions are not accessible, one has to use synthetic equivalents of these anions. Several reagents are synthetically equivalent to formyl or acyl anions, permitting the Umpolung of carbonyl reactivity.

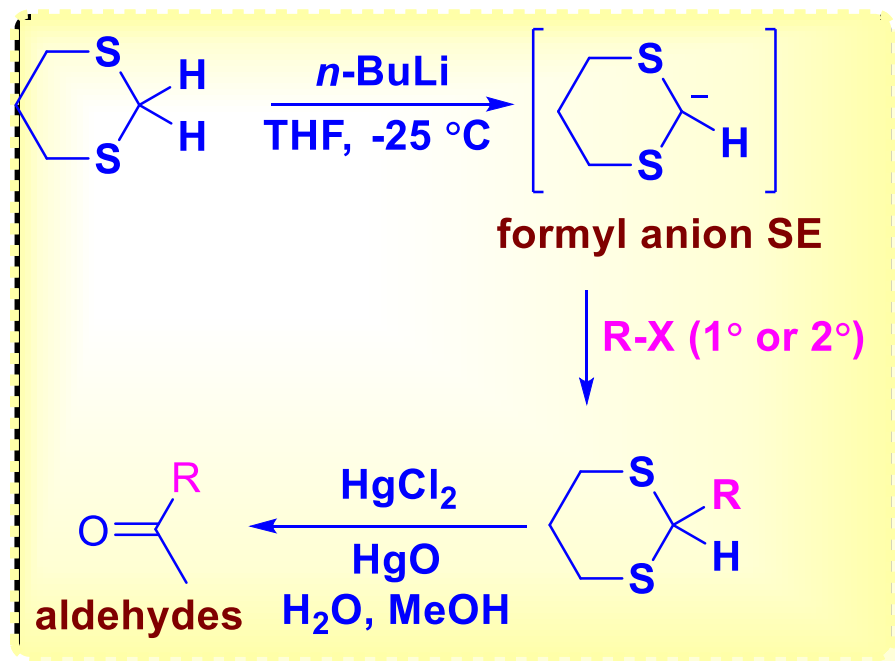
Formyl and Acyl Anions Derived from 1,3-Dithianes

The most utilized Umpolung strategy is based on formyl and acyl anion equivalents derived from 2-lithio-1,3-dithiane species. These are readily generated from 1,3-dithianes (thioacetals) because the hydrogens at C(2) are relatively acidic (pK_a : ~31). In this connection it should be noted that thiols (EtSH , pK_a : 11) are stronger acids compared to alcohols (EtOH , pK_a : 16).

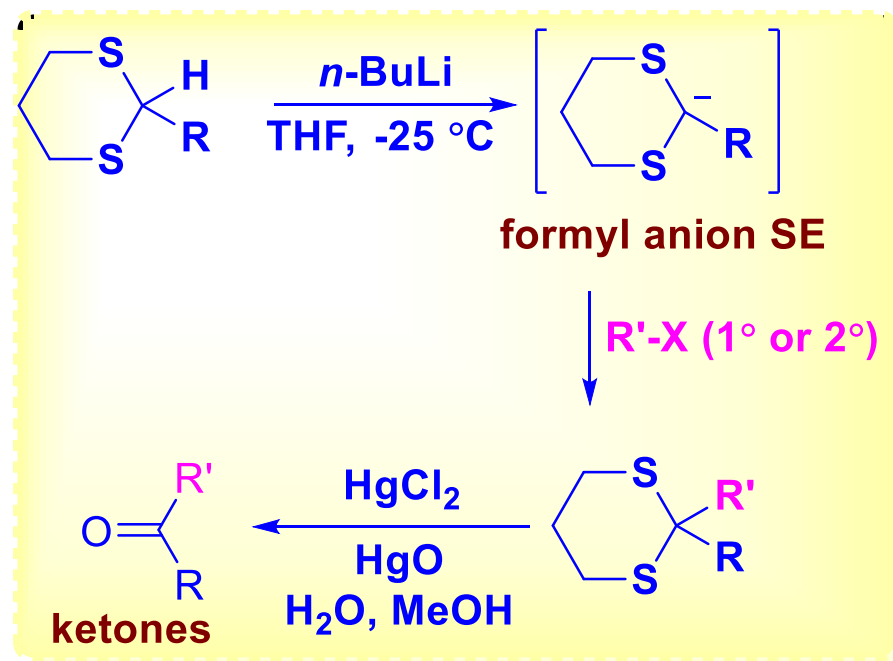


The lower ionization potential and the greater polarizability of the valence electrons of sulfur compared to oxygen make the divalent sulfur compounds more nucleophilic in $\text{S}_\text{N}2$ reactions. The polarizability factor may also be responsible for the stabilization of carbanions α to sulfur.

The anions derived from dithianes react with alkyl halides to give the corresponding alkylated dithianes. After hydrolysis produced aldehydes or ketones.

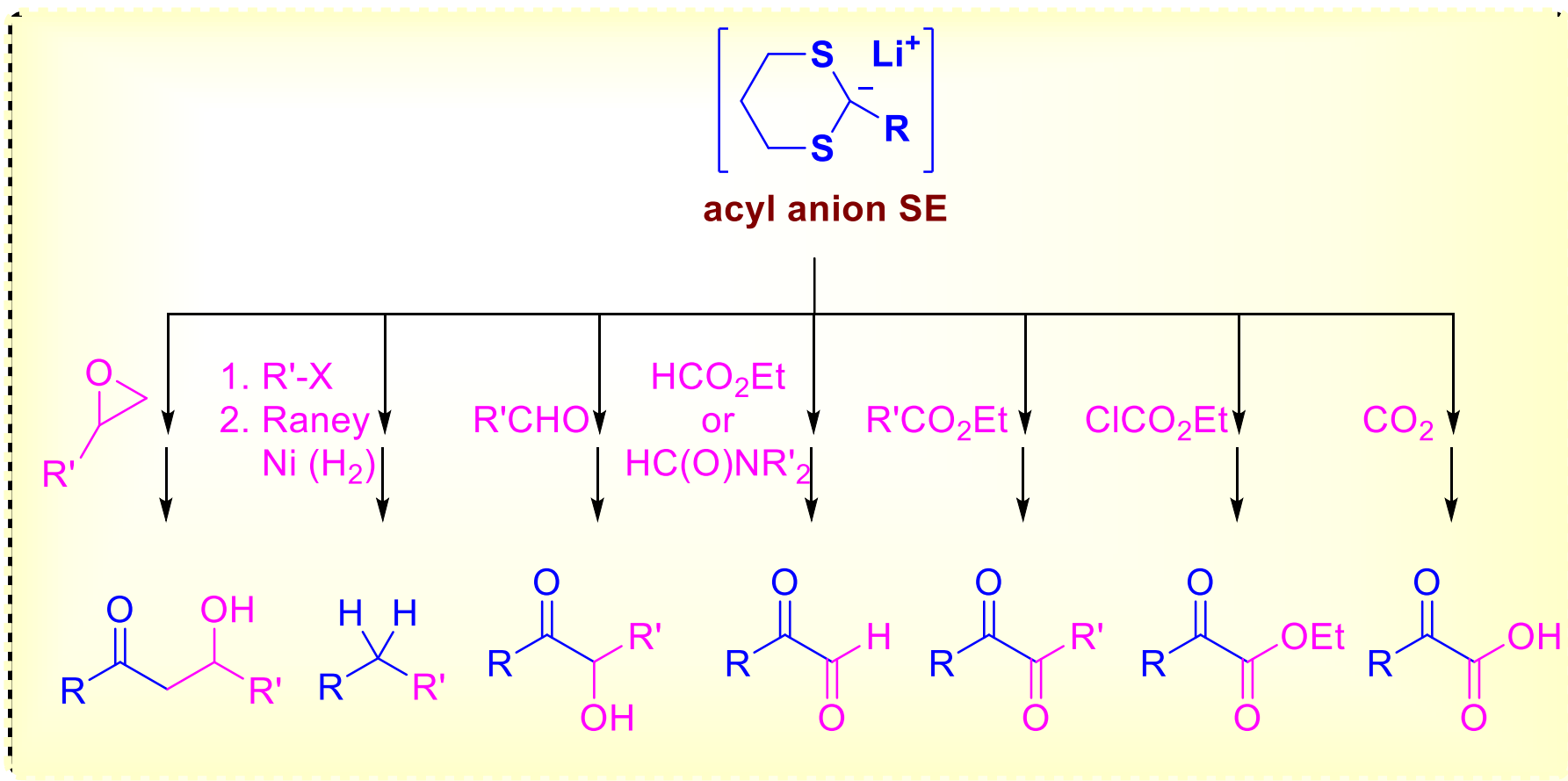


Formyl anions to aldehydes



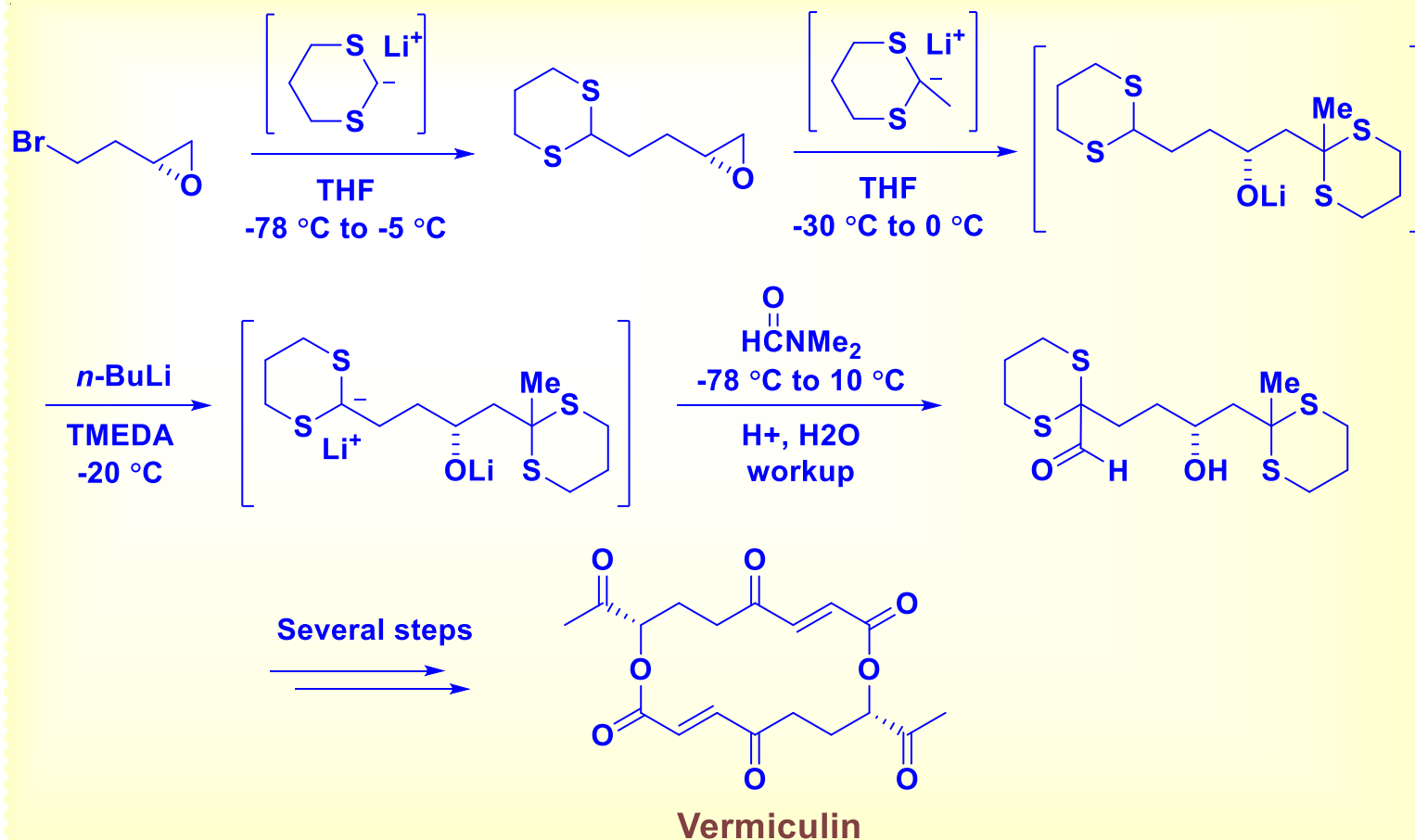
Acyl anions to ketones

Umpolung in various transformations



Dithiane-derived carbanions can be hydroxyalkylated or acylated to produce, after removal of the propylenedithiol appendage, a variety of difunctional compounds.

Synthesis of Vermiculin using Umpolung concept



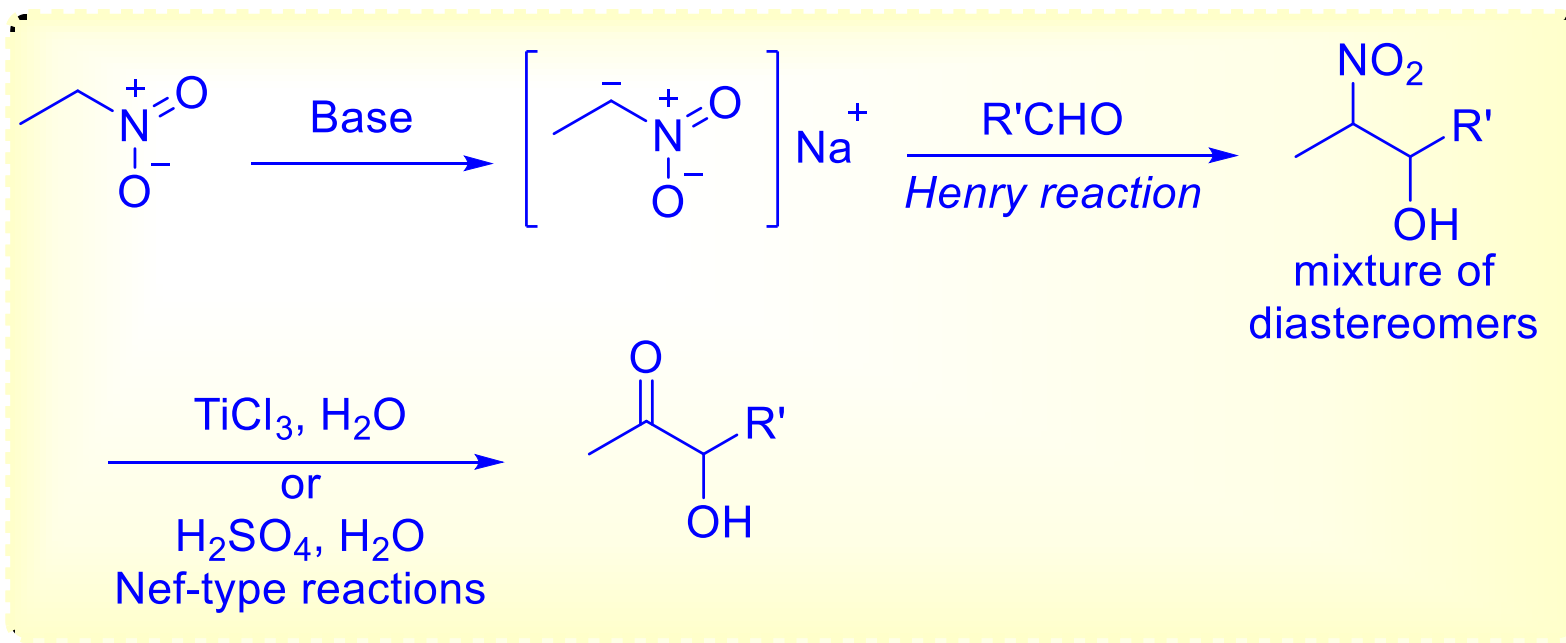
TMEDA = N,N,N',N' -tetramethylethylenediamine ($\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$);
used to sequester Li^+ and disrupt $n\text{-BuLi}$ aggregate

An instructive example of using a dithiane Umpolung approach to synthesize a complex natural product is the one-pot preparation of the multifunctional intermediate, which ultimately was elaborated to the antibiotic vermiculin.

Boeckmann, R. K., Jr.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1974**, *96*, 5954.

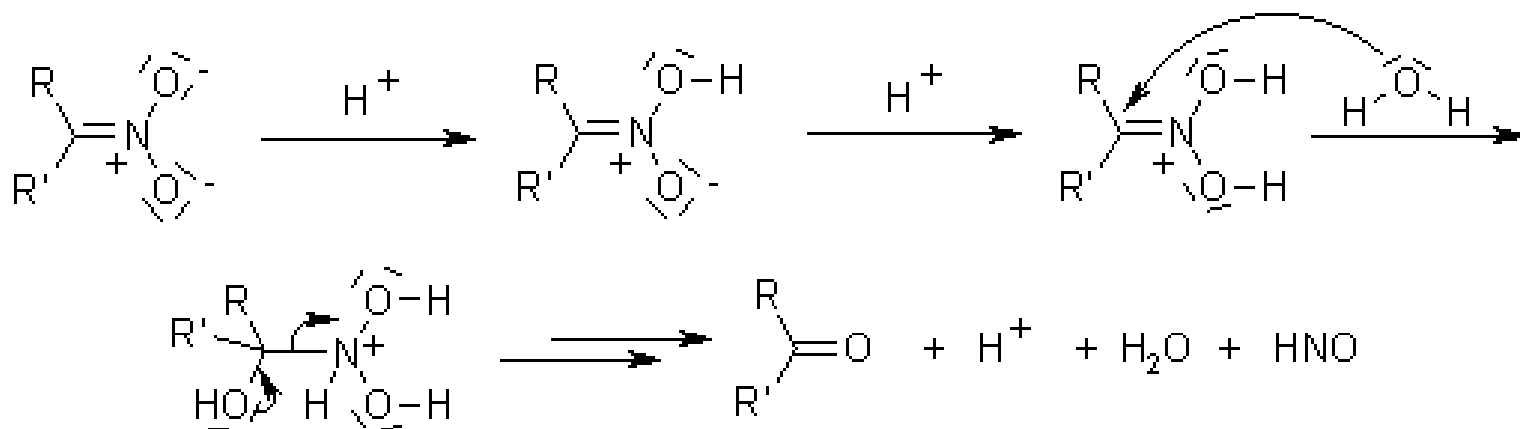
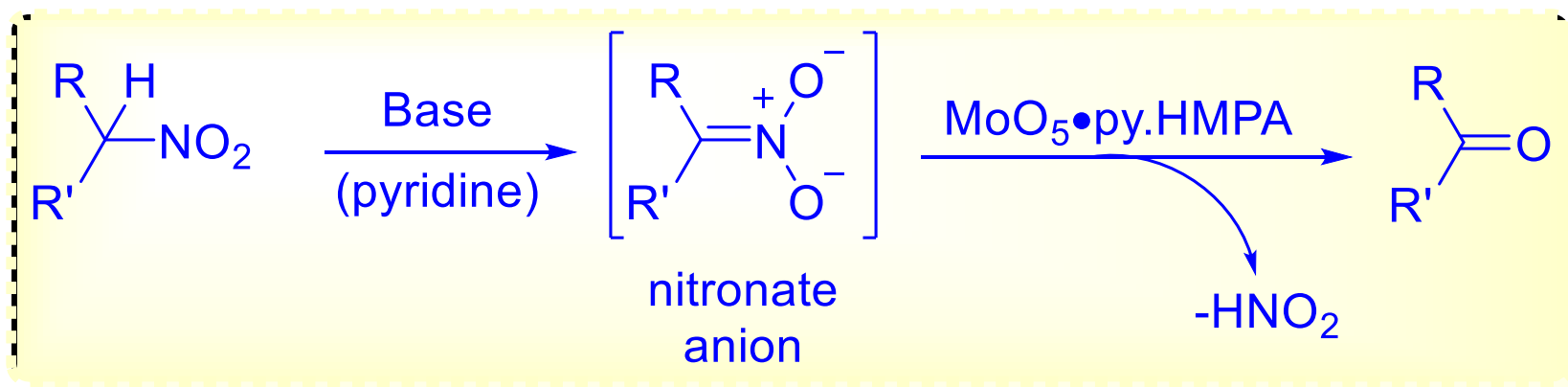
Acyl Anions Derived from Nitroalkane

The α -hydrogens of nitroalkanes are appreciably acidic due to resonance stabilization of the anion CH_3NO_2 , pK_a : 10.2; $\text{CH}_3\text{CH}_2\text{NO}_2$, pK_a : 8.51. The anions derived from nitroalkanes give typical nucleophilic addition reactions with aldehydes (the Henry-Nef tandem reaction).



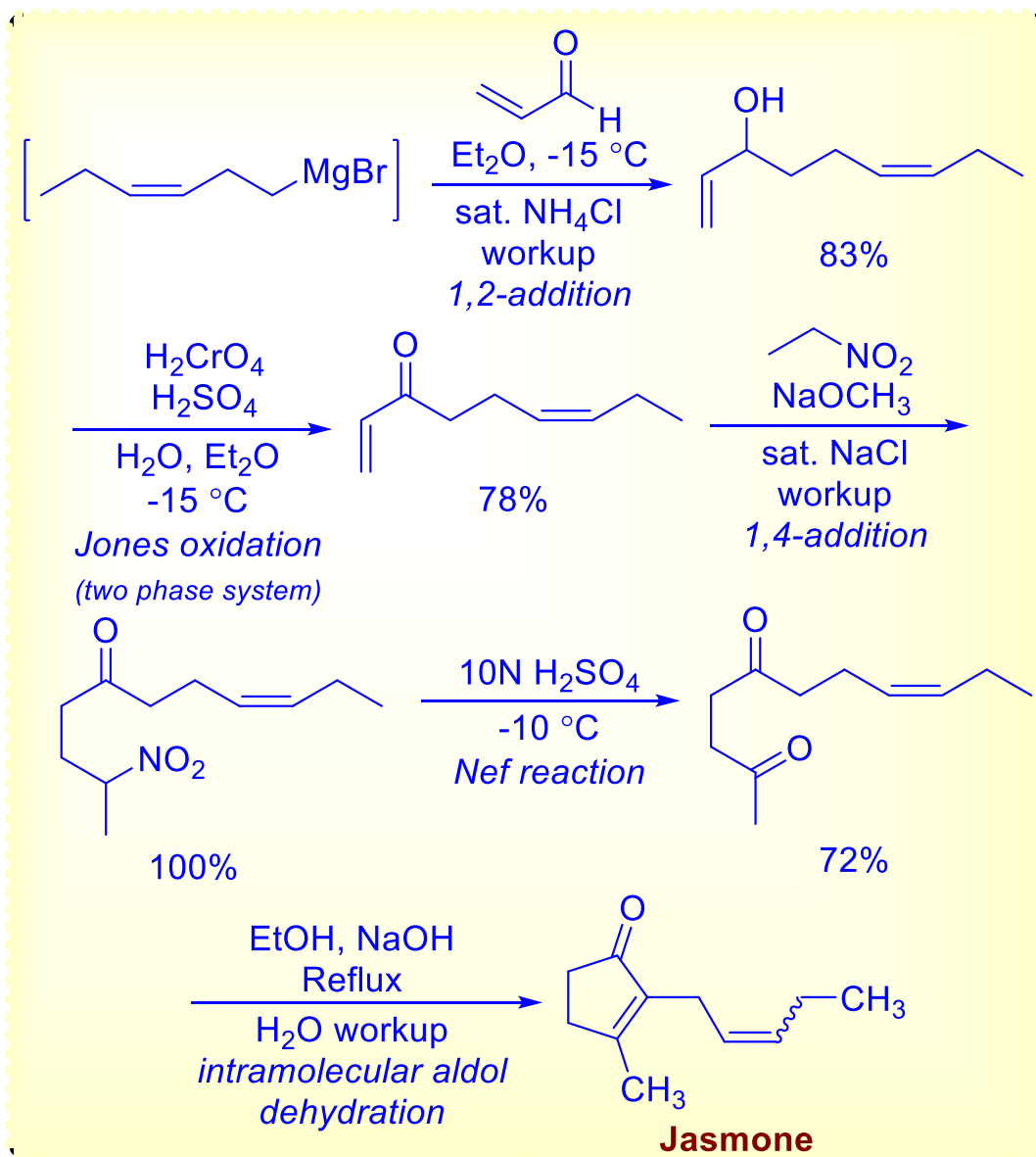
Note that the nitro group can be changed directly to a carbonyl group via the Nef reaction (under acidic conditions).

Under basic conditions, salts of secondary nitro compounds are converted into ketones by the pyridine-HMPA complex of molybdenum (VI) peroxide. Nitronates from primary nitro compounds yield carboxylic acids since the initially formed aldehyde is rapidly oxidized under the reaction conditions.



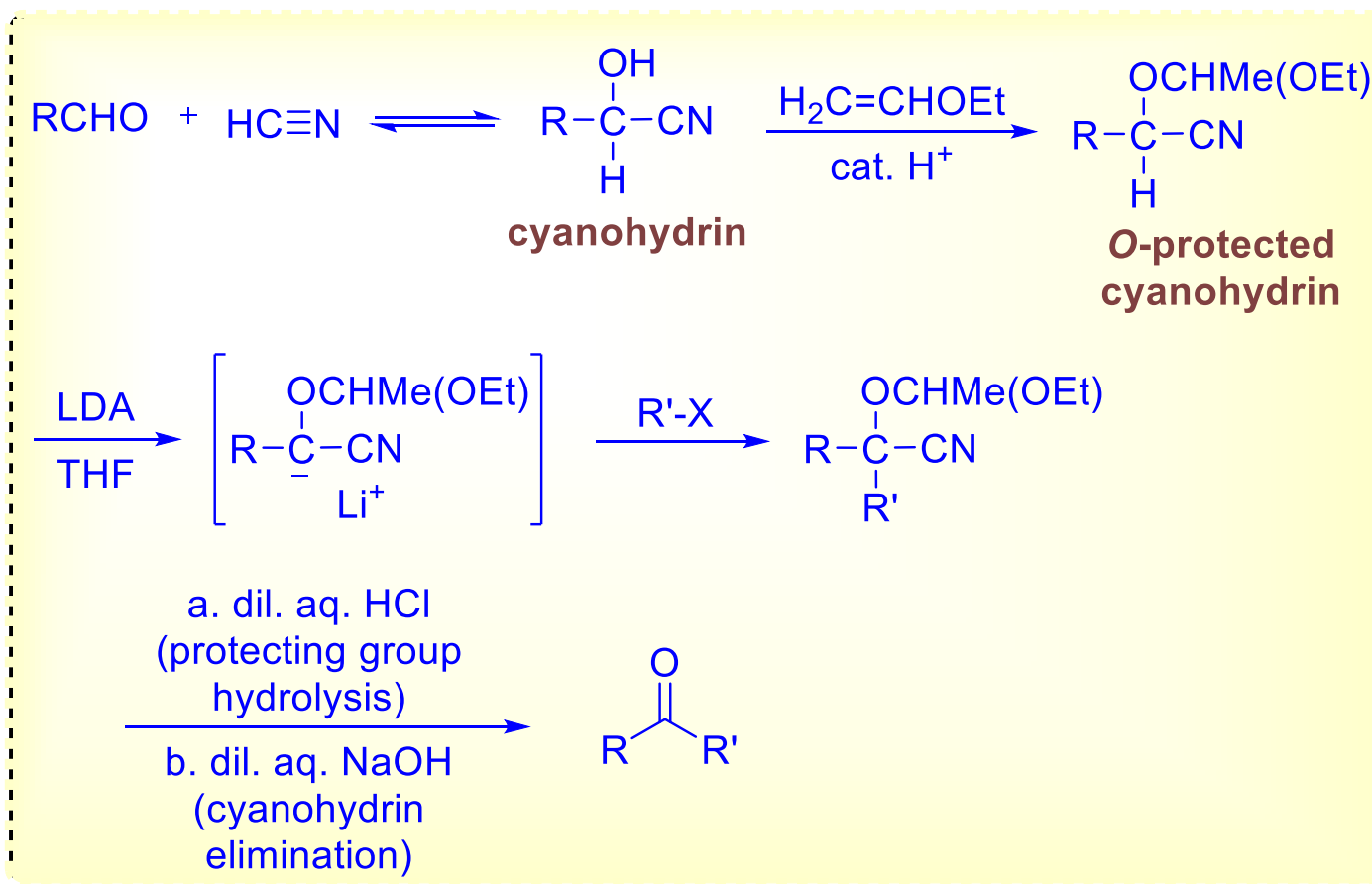
α -nitro anion Umpolung in the synthesis of Jasmone (TM)

Synthesis

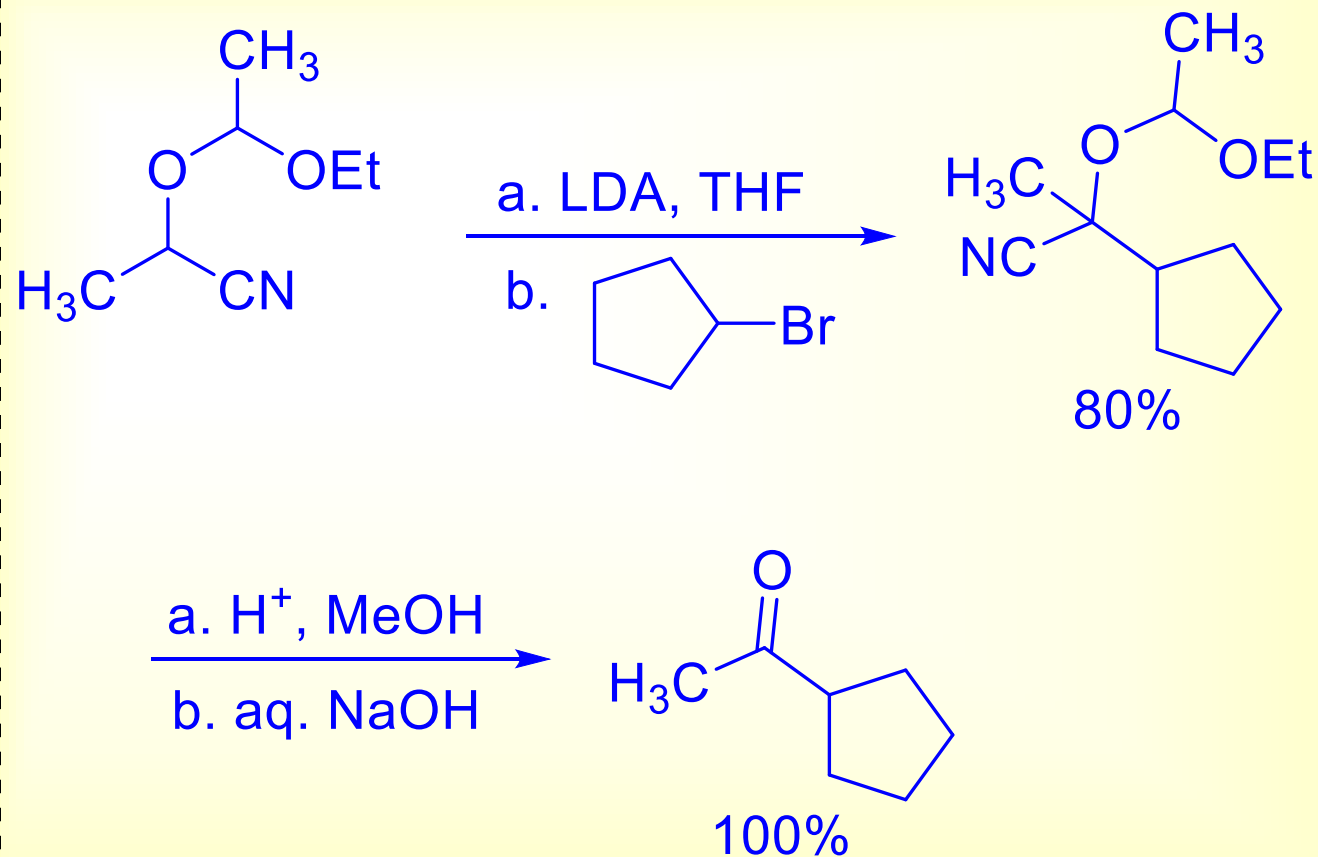


Acyl Anions Derived from Cyanohydrins

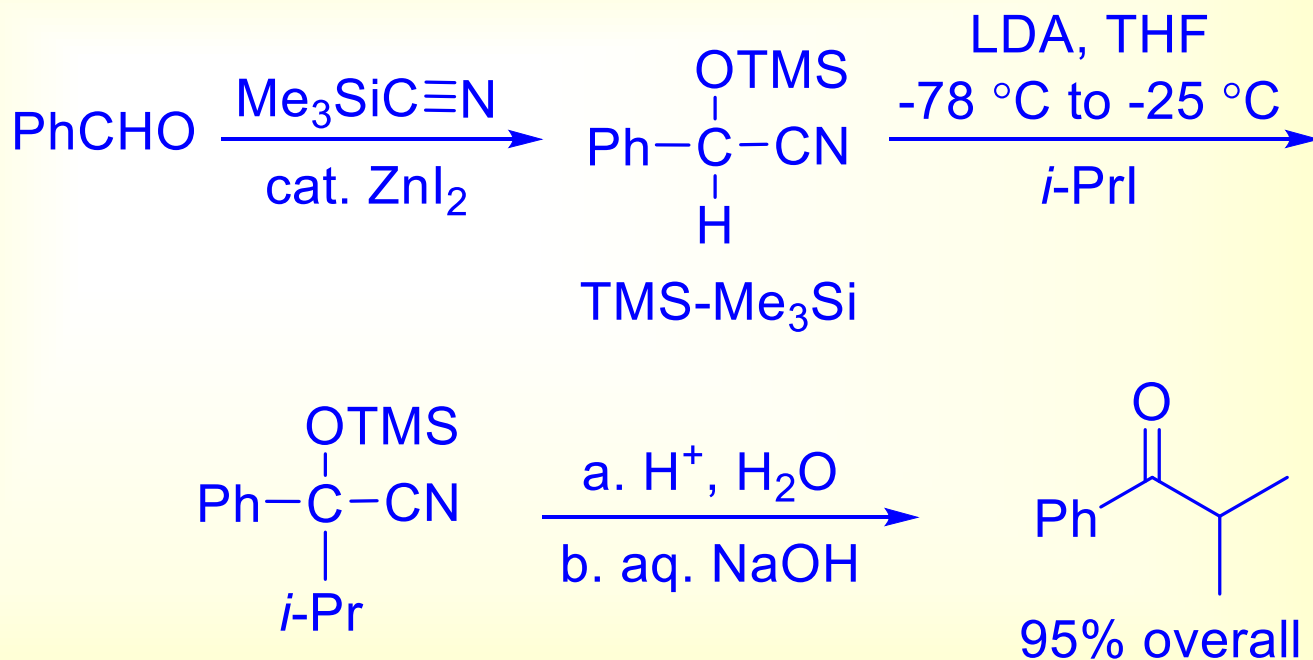
O-Protected cyanohydrins contain a masked carbonyl group with inverted polarity. The α -carbon of an *O*-protected cyanohydrin is sufficiently activated by the nitrile moiety ($\text{CH}_3\text{CH}_2\text{CN}$, pK_a : 30.9) so that addition of a strong base such as LDA generates the corresponding anion. Its alkylation, followed by hydrolysis of the resultant alkylated cyanohydrin, furnishes the ketone.



The overall reaction represents alkylation of an acyl anion equivalent as exemplified for the synthesis of methyl cyclopentyl ketone.

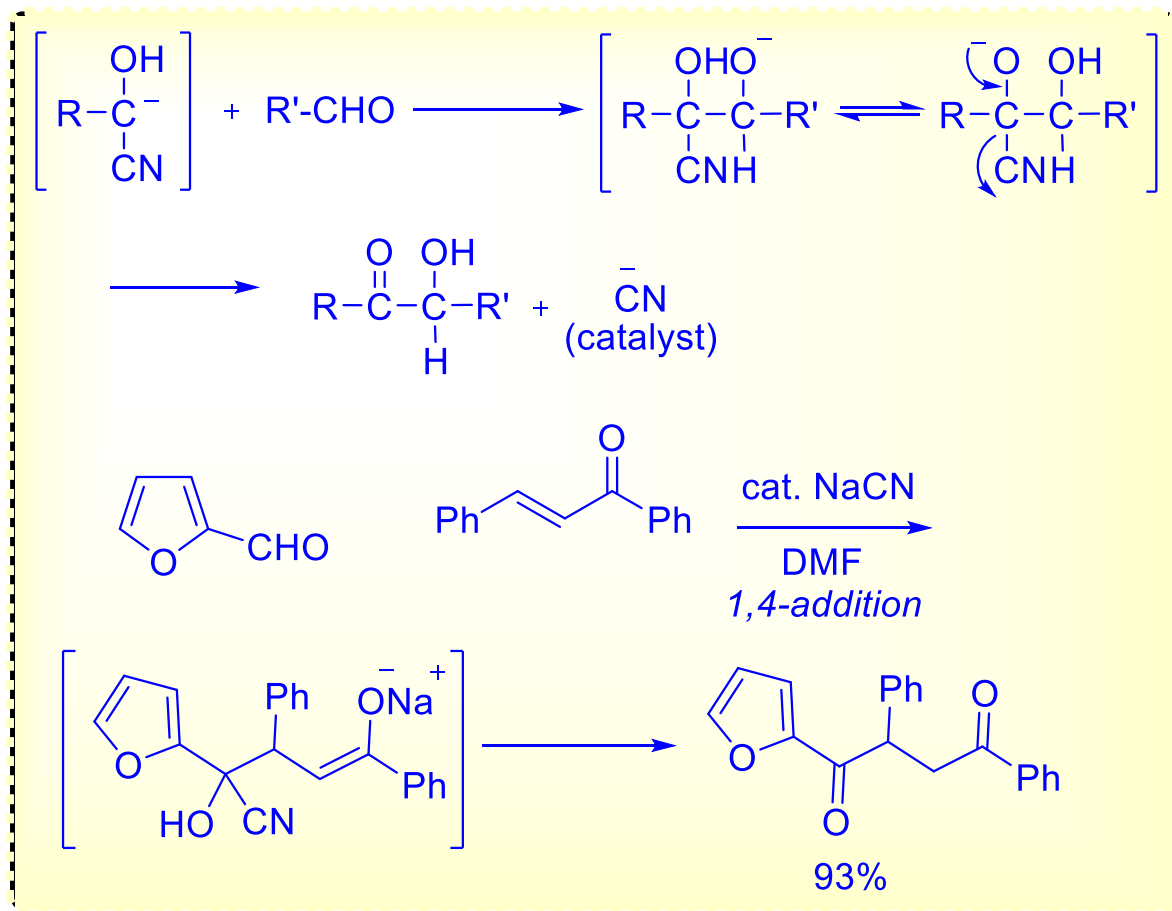


An attractive alternative to the above protocol involves the nucleophilic acylation of alkylating agents with aromatic and heteroaromatic aldehydes via trimethylsilyl-protected cyanohydrins.



Stetter reaction using Umpolung concept

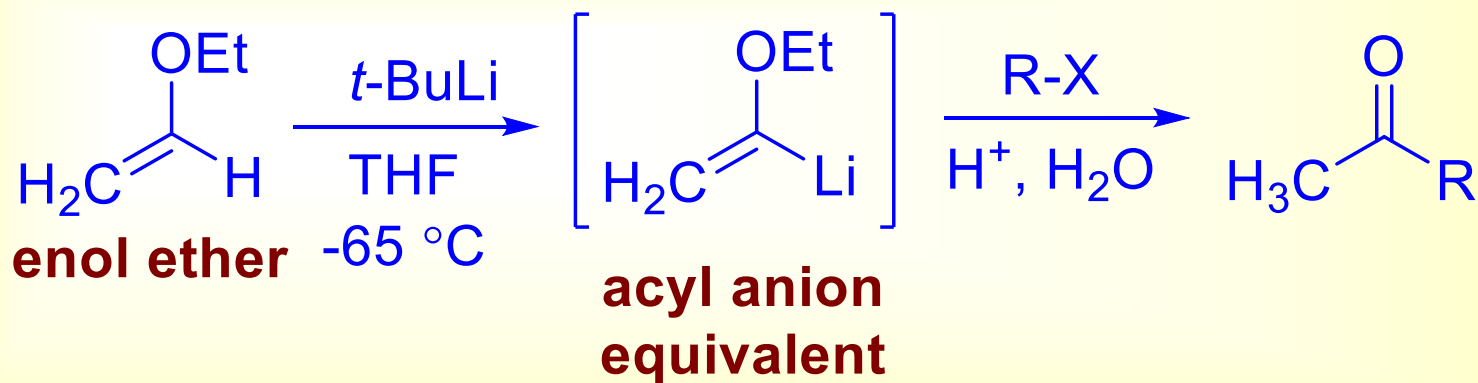
Acyl anion synthons derived from cyanohydrins may be generated catalytically by cyanide ion via the Stetter reaction. However, further reaction with electrophiles is confined to carbonyl compounds and Michael acceptors.



Stetter, H. Schreckenberger, M. *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 81
Stetter, H. *Angew. Chem. Int. Ed.* **1976**, 15, 639.

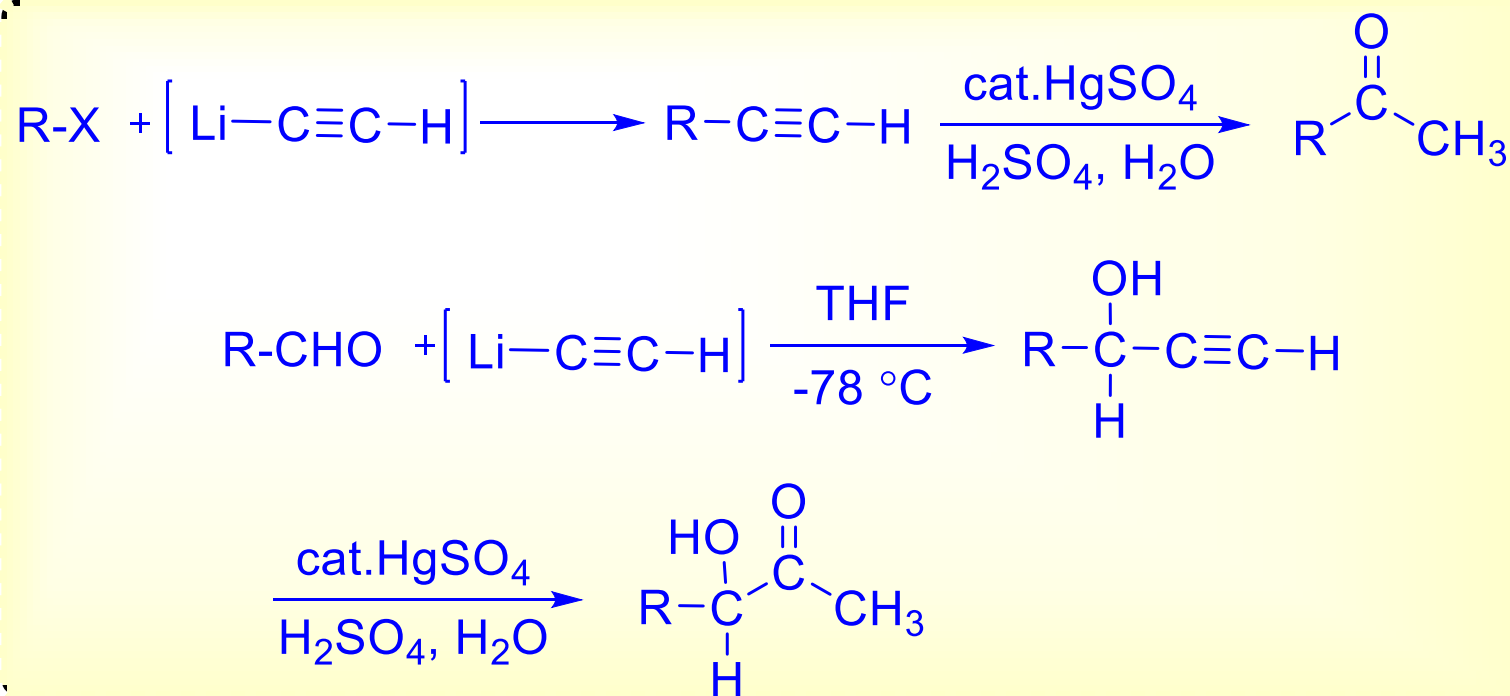
Acyl Anions Derived from Enol Ethers

The α -hydrogens of enol ethers may be deprotonated with *tert*-BuLi. Alkylation of the resultant vinyl anions followed by acidic hydrolysis provides an efficient route for the preparation of methyl ketones.



Acyl Anions Derived from Lithium acetylide

Treatment of lithium acetylide with a primary alkyl halide (bromide or iodide) or with aldehydes or ketones produces the corresponding monosubstituted acetylenes or propargylic alcohols. Mercuric ion-catalyzed hydration of these furnishes methyl ketones and methyl α -hydroxy ketones, respectively



Thank You