

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

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Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

The Logic of Organic Synthesis

Retrosynthetic analysis:

The construction of a *synthetic tree* by *working backward* from the *target molecule* (TM) is called *retrosynthetic analysis* or *antithesis*.

The symbol \implies signifies a reverse synthetic step and is called a transform.

The main transforms are disconnections, or cleavage of C-C bonds, and functional group interconversions (FGI).

Retrosynthetic analysis involves the *methodical disassembly* of a TM into *available starting materials* by sequential disconnections and FGI.

Structural changes in the retrosynthetic direction should lead to substrates that are more readily available than the TM.

The success of a retrosynthetic analysis depends upon known or conceivable reactions that can be used to prepare these substrates. Application of this procedure requires a basic knowledge of organic chemistry and rather strict adherence to certain rules.

Disconnection of carbon-carbon bonds of the TM results in *synthons* - these are *idealised charged fragments* that may or may not be actual intermediates in the synthetic route.

The actual substrates used for the forward synthesis are the *synthetic equivalents* (SEs) or *reagents*.

Also, reagents derived from *inverting the polarity* (IP) of synthons may serve as SEs.



Synthetic design involves two distinct steps: (1) retrosynthetic analysis (*a mental operation*) and (2) subsequent translation of the analysis into a "forward direction" synthesis (*a physical execution* of the strategy devised in the retrosynthetic analysis).

In the analysis, the chemist *recognizes the functional groups* in a molecule and disconnects at the suitable site. Identification of the potential site for disconnection will depend on the experience and existing knowledge of the chemist. This disconnection generates synthons. The SEs corresponding to these synthons must combine between themselves in the forward synthesis through a *known and reliable method* to construct the bond that was targeted at the disconnection step.



R. Robinson
(1886-1975)



R. B. Woodward
(1917-1979)

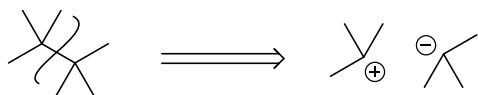


E. J. Corey
(1928-)

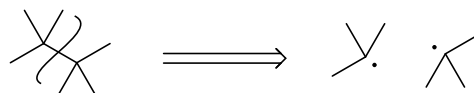
Retrosynthetic analysis:

Chemical bonds can be cleaved either heterolytically or homolytically, or through concerted transform (into two neutral, closed-shell fragments). The following discussion will focus on heterolytic and cyclic disconnections.

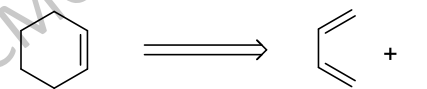
heterolytic disconnection:



homolytic disconnection:



concerted transform:



Donor and acceptor synthons:

Heterolytic retrosynthetic disconnection of a carbon-carbon bond in a molecule breaks the TM into an acceptor synthon, a carbocation, and into a donor synthon, a carbanion.

In a formal sense, the reverse reaction - the formation of a C-C bond - then involves the union of an **electrophilic acceptor synthon (a)** and a **nucleophilic donor synthon (d)**.

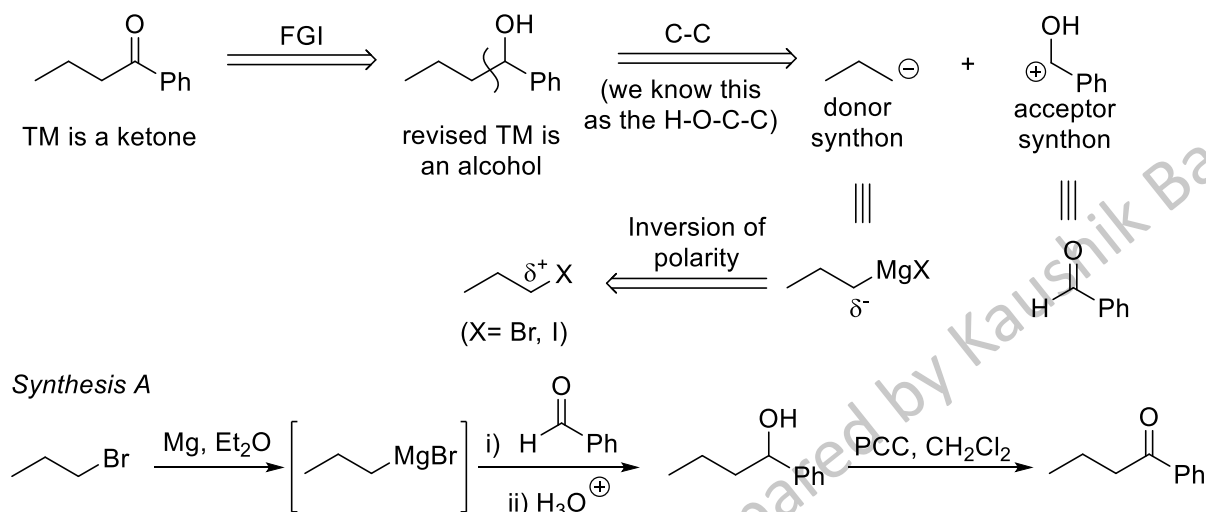
The following tables show some important acceptor and donor synthons and their synthetic equivalents.

Acceptor Synthons	Synthetic Equivalent(s)	Acceptor Synthons	Synthetic Equivalent(s)	Donor Synthons	Synthetic Equivalent(s)	Donor Synthons	Synthetic Equivalent(s)
R^+	$R-X$ (X = Cl, Br, I, OTs)	H_2C^+-OH	$H_2C=O$	R^-	$R-M$ (M = metal)	$R-C=O$	
Ar^+	$Ar-N_2^+$	$R-C^+-OH$	$R-C=O$	$R-C\equiv C^-$	$R-C\equiv C-M$ (M = metal)	$COOH^-$	CN^-
$H-C^+=O$	$H-C(=O)-X$ (X = OR, NR ₂)	$R-C^+-OH$	$R-C=O$	Ar^-	$Ar-M$ (M = metal)	$H_2C-COOH^-$	H_2C-CO_2Et
$R-C^+=O$	$R-C(=O)-X$ (X = Cl, OR, NR ₂)	H_2C^+-C-OH		$H_2C-C(=O)^-$	$H_3C-C(=O)-R$	H_2C-CO_2Et	H_2C-CO_2Et
$HO-C^+=O$	$O=C=O$	$H_2C^+-C(=O)-R$	$X-C(=O)-R$ (X = Cl, Br)	$R-C(=O)NO_2^-$	$R-C(=O)NO_2$	$H_2C-C(=O)CH_3^-$	$H_2C-C(=O)CH_3$
$H_2C^+-C(=O)-R$	$H_2C=C(=O)-R$			$R-C(=O)^-$	$R-C(=O)-Li$		

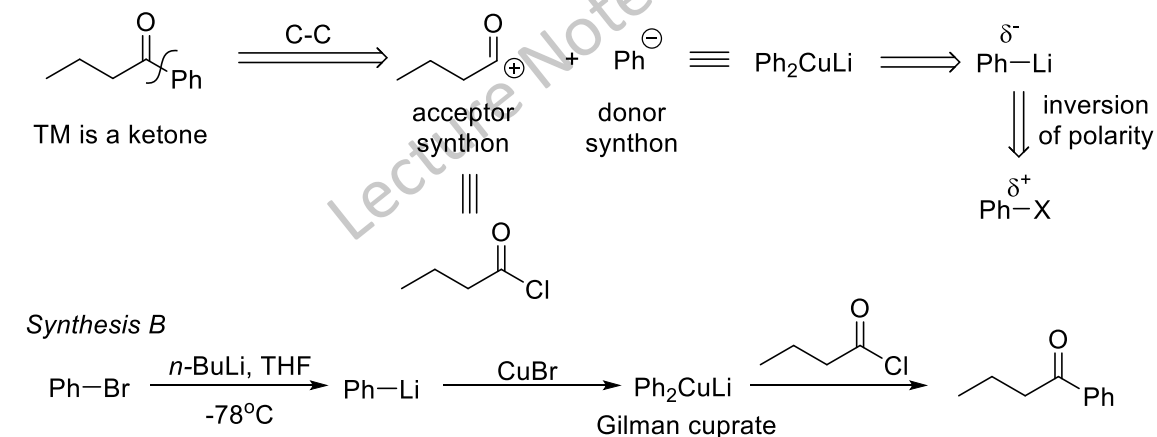
Retrosynthetic analysis:

Often, more than one disconnection for a particular TM is feasible, as depicted in retrosynthetic analyses A and B below. In the synthesis, a plan for the sequence of reactions is drafted according to the analysis by adding reagents and conditions.

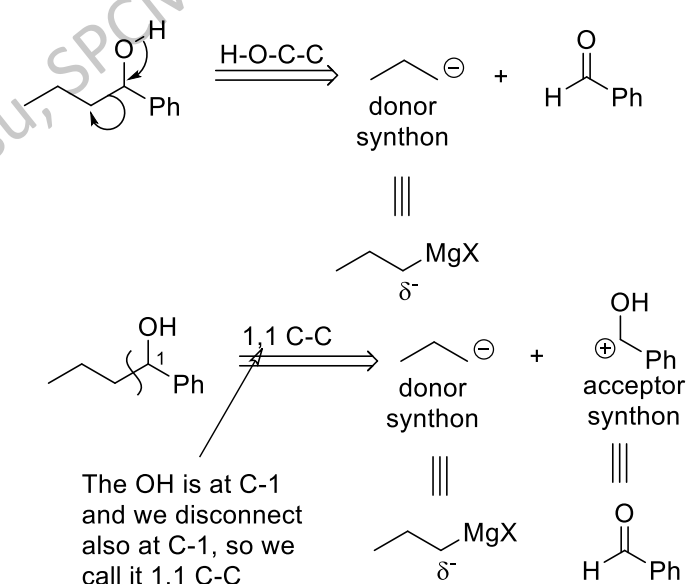
Retrosynthetic analysis A



Retrosynthetic analysis B



Same disconnection - just different name:



The Logic of Organic Synthesis

Alternating Polarity Disconnections:

As we have seen many times, a number of C-C disconnection can be envisaged for construction of a given carbon-made backbone.

However, among these possibilities, some are better than the others. In general, how one chooses a particular disconnection is related to functional group manipulations, since the distribution of formal charges in the carbon skeleton is controlled by the presence of functional groups.

The presence of a heteroatom, i.e. a functional group imparts an alternating acceptor-donor reactivity network (pattern) along the carbon backbone (skeleton).

One of the first to highlight this was Arthur Lapworth who proposed (1920) a theory of alternating polarity. His model was based upon the polarised character of organic bonds and the "*alternating latent polarities*", induced by the presence of some "key-atoms" or heteroatoms (such as oxygen or nitrogen) in a chain of atoms.

The idea behind Lapworth's model was revived by David A. Evans fifty years later where he posited that a synthetic target molecule may be viewed in terms of its "ionic components", the alternating polarities being assigned according to the electronic character of the functional group or heteroatom attached to the carbon chain.

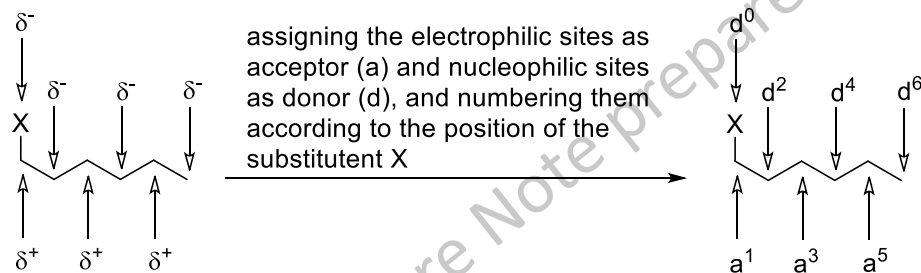
To illustrate this point, let us consider a carbon chain where one of the carbons is attached to a heteroatom 'X' which is electron-withdrawing in nature and thus, makes the carbon right next to it partially positive, i.e. electrophilic in nature:



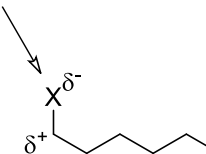
Arthur Lapworth
(1872-1941)



D. A. Evans
(1941-)



X is a heteroatom, EW in nature, but itself has partial negative charge - so it is a donor site



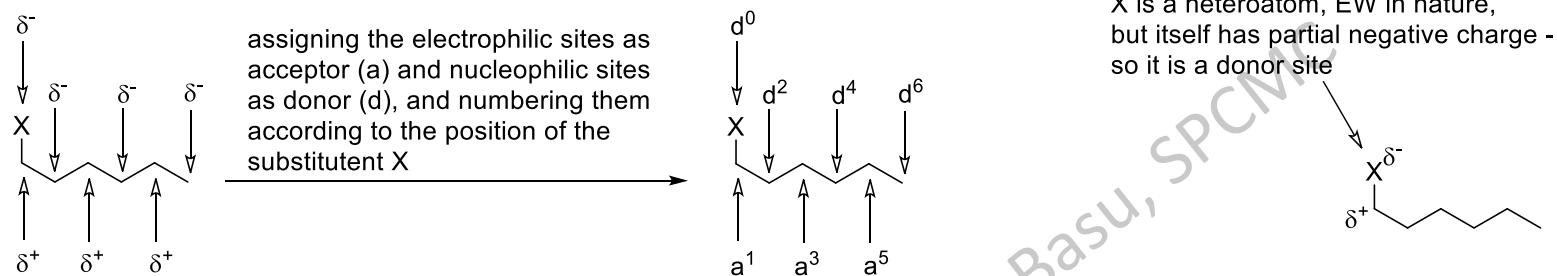
It is to be noted that -

- the acceptor and donor sites occur *alternately*, X being a donor site itself, and the carbon to which it is attached being an acceptor,
- donor atoms are characterized by even numbers (2,4,6..., 2n) while acceptors are by odd number (1,3,5..., 2n+1).

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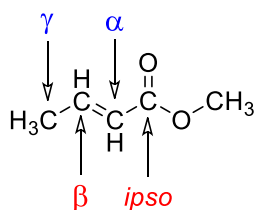
Alternating Polarity Disconnections:

Let us consider a carbon chain where one of the carbons is attached to a heteroatom 'X' which is electron-withdrawing in nature and thus, makes the carbon right next to it partially positive, i.e. electrophilic in nature:



It is to be noted that - i) the acceptor and donor sites occur *alternately*, X being a donor site itself, and the carbon to which it is attached being an acceptor, ii) donor atoms are characterized by even numbers (2,4,6...) while acceptors are by odd number (1,3,5...).

Let us now take a real example and try to see if this theory of alternating polarity really holds. Consider the molecule methyl crotonate:



The carbonyl carbon (i.e. the *ipso* carbon) and the β-carbon both are **electrophilic**.

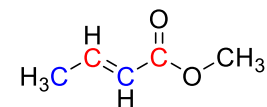
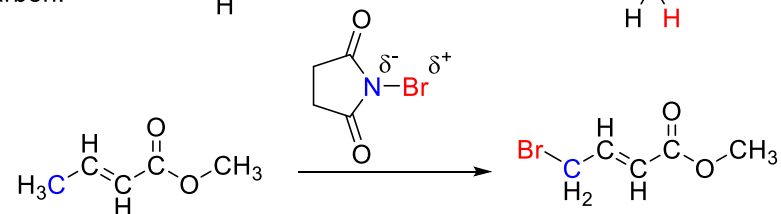
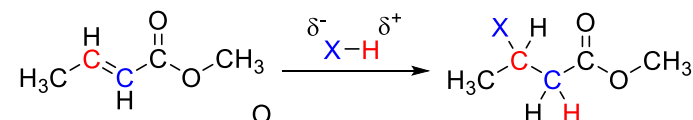
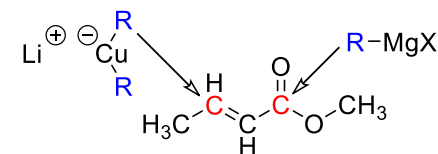
If we add a **Grignard reagent**, the organometallic attacks the carbonyl carbon.

If we add a **Gilman reagent**, the organometallic attacks the β-carbon.

On the other hand, both the α- and the γ-carbons are **nucleophilic**.

An **electrophile** such as a proton reacts with the **nucleophilic** α-carbon atom e.g. the addition of hydrogen halide across the olefinic double bond, where the halide goes to the β-carbon and the hydrogen to the α-carbon.

Again, a positive bromine ion will react with the nucleophilic γ-carbon atom, as evident from the ready substitution of hydrogen by bromine when this compound is refluxed with *N*-bromosuccinimide in CCl_4 .



The pattern of alternating polarity is thus clear from these examples.

The Logic of Organic Synthesis

Alternating Polarity Disconnections:

What is the use of this concept? How may this help us?

The concept of alternating or latent polarities enables one to identify the best position to make the disconnection within a complex molecule, because the donor-acceptor properties of synthons are affected by the functional group present in that fragment.

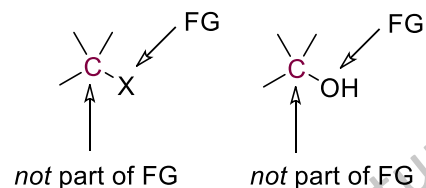
To understand which functional group affect or induce the latent polarity in a carbon chain in what manner, it is necessary first to classify the functional groups themselves.

Evans (1971) divided the groups into the following three categories:

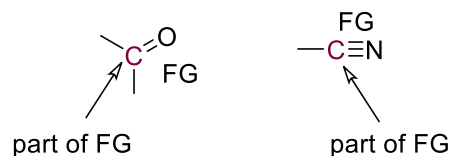
Note carefully that classical organic chemistry incorporates the carbon atom to which the heteroatom is attached as part of the functional group when that ipso carbon is either sp^2 or sp hybridized, but when the said carbon is sp^3 hybridized, it is not considered to be a part of the functional group.

Type	Nature	Example
E class	Confers electrophilic character to the ipso carbon atom to which they are attached (+).	-OH, -OR, -NH ₂ , =O, =NR, X (halogen)
G class	Confers nucleophilic character to the ipso carbon atom to which they are attached (-).	-Li, -MgX, -AlR ₂ , -SiR ₃
A class	These groups exhibit ambivalent nature, and confers both electrophilic and nucleophilic character to the ipso carbon. Whichever character will be manifest depends upon reaction condition and/or the structure of the molecule to which these are attached (+ or -).	-NO ₂ , =NOH, ≡N, +NR ₃ -SR, -S(O)R, -SO ₂ R, -BR ₂ , =CR ₂ , ≡CR,

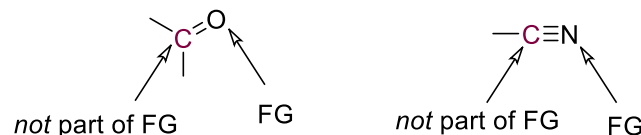
Case in point is organohalides and alcohols, where the functional groups are halogens (X) and the hydroxyls (OH) respectively.



On the other hand, ketones and alkylcyanides have C=O and CN functional groups, where the ipso carbons are sp^2 and sp hybridized respectively.



In Evans' classification, however, *only the heteroatom is considered to the functional group in all cases*, irrespective of the state of hybridization of the ipso carbon.

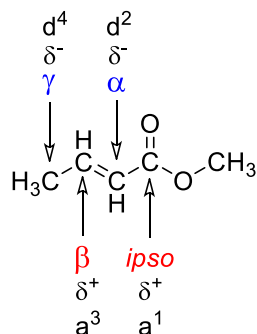


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Alternating Polarity Disconnections:

Let us now take a close look at each of the three classes of functional groups and see how they induce the pattern of alternating polarity in the carbon skeleton by taking specific examples:

i) E class: Take, for example methyl crotonate, the molecule that we have already seen:

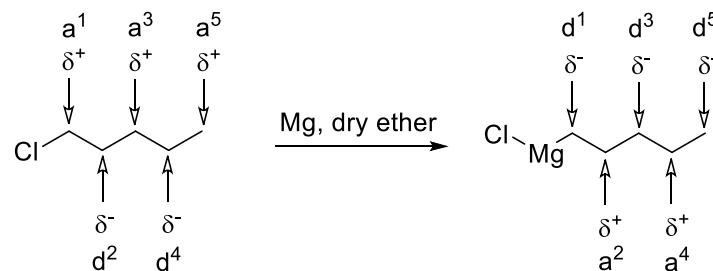


ii) G class: Consider the following Grignard reagent derived from 1-chloropentane:

Recall that a Grignard reagent is prepared from the corresponding organohalide. As the halogen is an E class functional group, this transformation of RX to RMgX reverses the latent polarity of every carbon in the chain.

This is a classic example of what Seebach termed as "umpolung" or reversal of reactivity:

It is to be noted that in the organomagnesium reagent the donor sites carry odd number while the acceptor sites are odd numbered. This indicates umpolung, i.e. the electrophilic organohalide is transformed into a nucleophilic organometallic reagent.



D. Seebach
(1937-)

Also note that whereas compounds with E class functional groups are relatively stable and storable organic chemicals such as alcohols, ethers, aldehydes, ketones, acids, esters, amines, etc., compounds with G class functional groups of "reagents" that must usually be prepared in situ, such as organolithiums, Grignard reagents, etc.

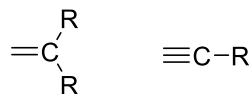
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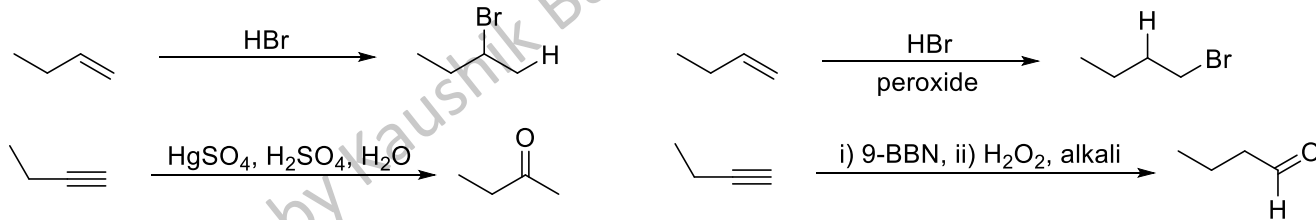
Alternating Polarity Disconnections:

iii) A class: With regard to functional groups of this class, their interest lies in the *ambivalent character* exhibited by such groups, which confers a double electrophilic and nucleophilic character to each of the carbon atom of the carbon chain.

Take, for instance, the alkenes' and alkynes' double and triple bonds.



Unsymmetrical reagents such as water or hydrogen bromide may add across these bonds in either Markovnikov or anti-Markovnikov fashion, demonstrating that the latent polarities of the carbon chain changes with the reaction conditions.

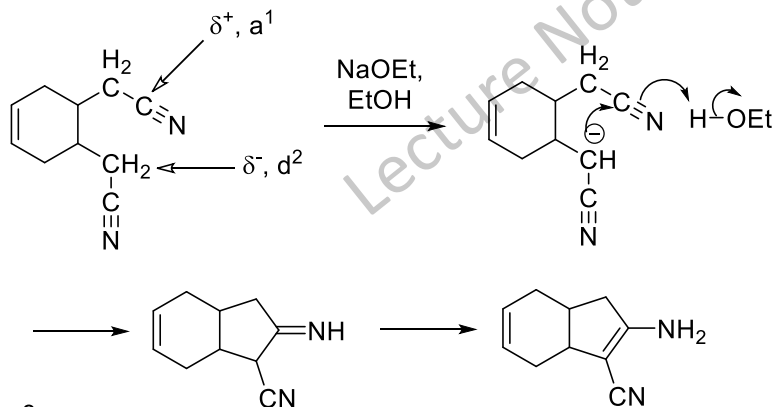


Markovnikov regioselectivity

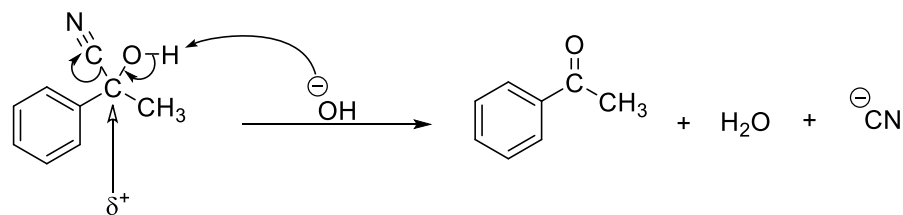
anti-Markovnikov regioselectivity

Another important group is cyanide (functional group CN).

On one hand, it stabilizes a negative charge on α -carbon and shows the typical reactivity of an electrophile at the digonal carbon in Thorpe-Ziegler condensation:



On the other hand, owing to the stability of cyanide ion it may behave as a leaving group conferring then an electrophilic character upon the α -carbon atom. Although the instance of cyanide as a leaving group in nucleophilic substitution is relatively rare owing to the strength of C-CN bond, cyanide does leave when a relatively strong bond is formed to compensate its cleavage. For example, consider the breakdown of cyanohydrins in basic mediums where a strong C=O bond forms at the expense of C-CN bond cleavage. The carbon next to CN in cyanohydrin is thus polarised as electrophilic:



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Alternating Polarity Disconnections:

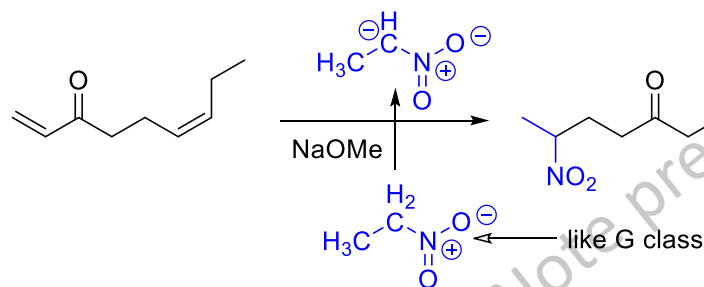
iii) A class: With regard to functional groups of this class, their interest lies in the *ambivalent character* exhibited by such groups, which confers a double electrophilic and nucleophilic character to each of the carbon atom of the carbon chain.

Another synthetically versatile group in A class is nitro. The nitro group can stabilize a carbanion adjacent to it but it can also sometimes act as a leaving group.

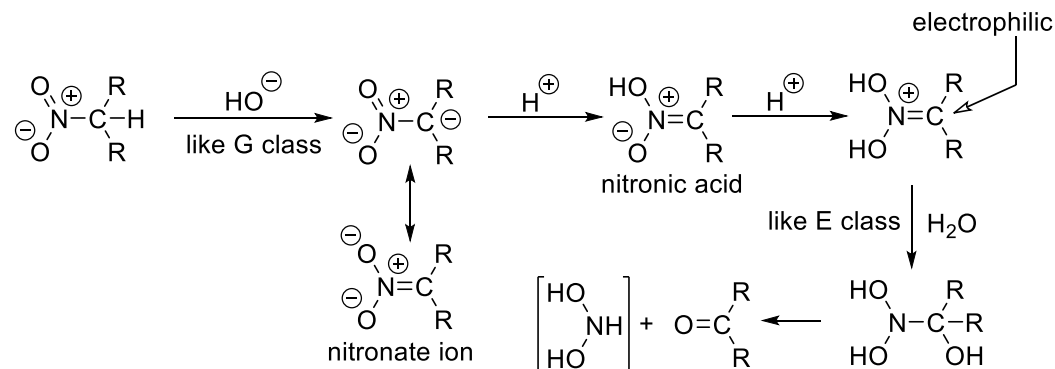
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Thus it can promote both nucleophilic and electrophilic character at the carbon next to it, depending upon the reaction used.

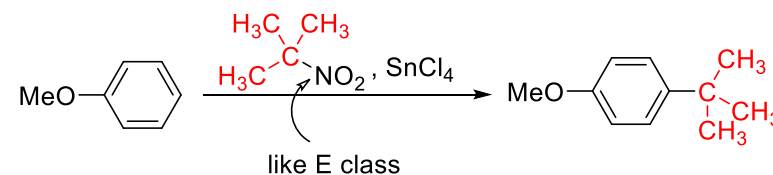
Consider the following examples, first, a Michael addition where nitro behaves like a G class substituent and promotes carbanion formation next to it:



The following is another illustration of the nitro group exerting its ambivalent character. This is the Nef carbonyl synthesis, an old method for converting nitro to carbonyl:



and second, an aromatic electrophilic substitution where it makes the adjacent carbon electrophilic, thus behaving like a E class functional group:



The Logic of Organic Synthesis

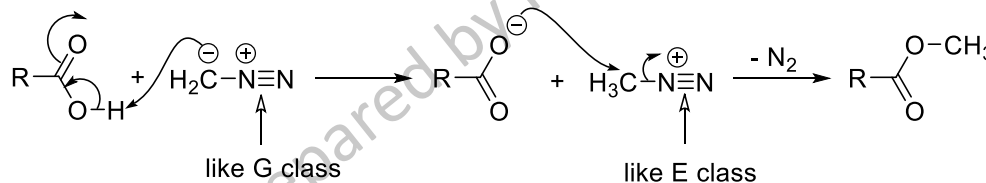
Alternating Polarity Disconnections:

iii) A class: With regard to functional groups of this class, their interest lies in the *ambivalent character* exhibited by such groups, which confers a double electrophilic and nucleophilic character to each of the carbon atom of the carbon chain.

Another classic demonstration of A function is provided by the diazo group.

Type	Nature	Example
E class	Confers electrophilic character to the ipso carbon atom to which they are attached (+).	-OH, -OR, -NH ₂ , =O, =NR, X (halogen)
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Recall that diazomethane is used to prepare methyl esters. The reaction is believed to proceed in the following way where the diazo group exhibits its ambivalent nature in successive steps:



We would do well to keep in mind that the Evans' classification is *purely heuristic*, in the sense that it works, and its purpose is not to give a rigid classification based on theoretical considerations about the reactivity of organic molecules, but to differentiate between those groups strongly polarised either towards typical E or typical G behaviour.

A heuristic technique, or a heuristic, is any approach to problem solving or self-discovery that employs a practical method that is not guaranteed to be optimal, perfect, or rational, but is nevertheless sufficient for reaching an immediate, short-term goal or approximation.

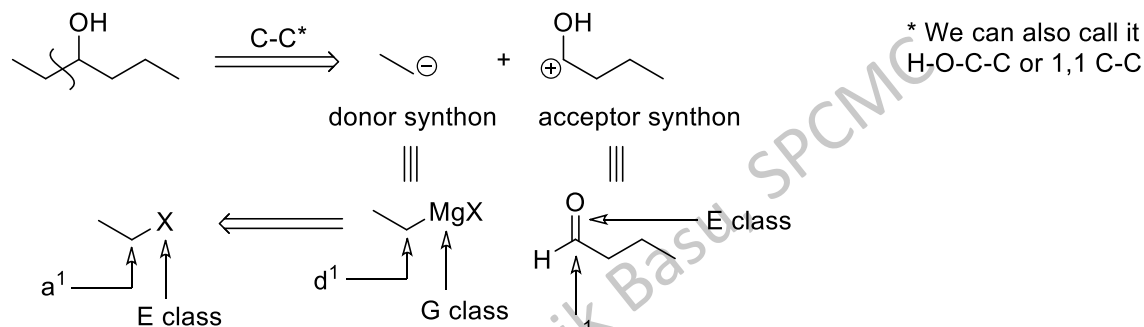
Let us now tackle some examples of choosing reasonable disconnections for functionally substituted target molecules based on the concept of alternating polarity.

The Logic of Organic Synthesis

Alternating Polarity Disconnections:

Examples of choosing reasonable disconnections for functionally substituted target molecules based on the concept of alternating polarity:

Retrosynthesis of target molecule with only one functional group:



Retrosynthesis of Bifunctional compounds:

From a synthetic point of view, it is convenient to analyse the organic molecules in terms of paired functional group relationships.

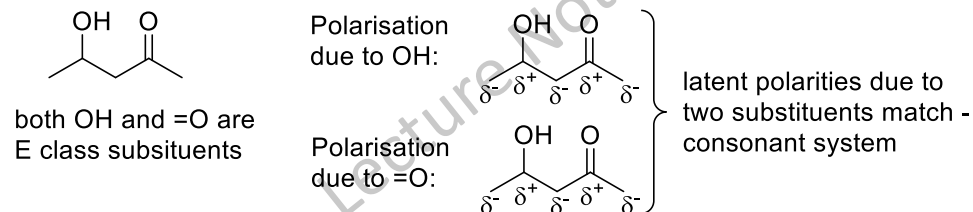
Since there are two hypothetical "ideal" groups, E and G, according to Evans it is possible to define two different bifunctional relationships:

the "*consonant systems (or molecules)*", in which the alternating latent polarities *always match* whatever the starting functional group from which the polarities are assigned,

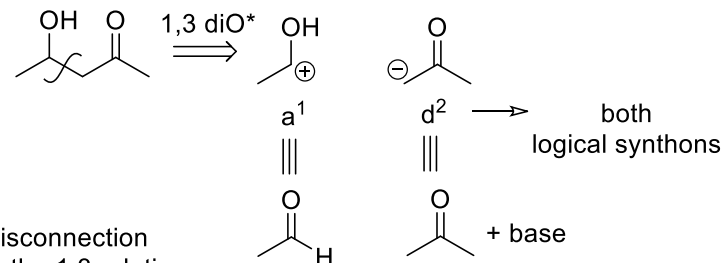
and the "*dissonant systems (or molecules)*" in which the alternating latent polarities *do not match*.

Consider the following examples:

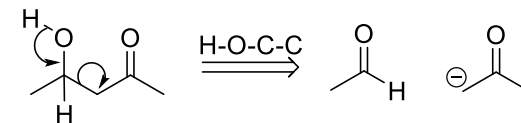
1,3-bifunctional compound:



Retrosynthetic analysis:



*1,3 diO as disconnection is done using the 1,3 relation b/w two heteroatoms. We can also call it H-O-C-C if we treat the TM as an alcohol.

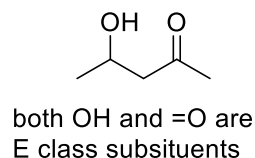


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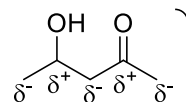
Alternating Polarity Disconnections:

Examples of choosing reasonable disconnections for functionally substituted target molecules based on the concept of alternating polarity:

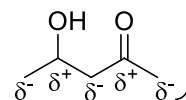
1,3-bifunctional compound:



Polarisation due to OH:

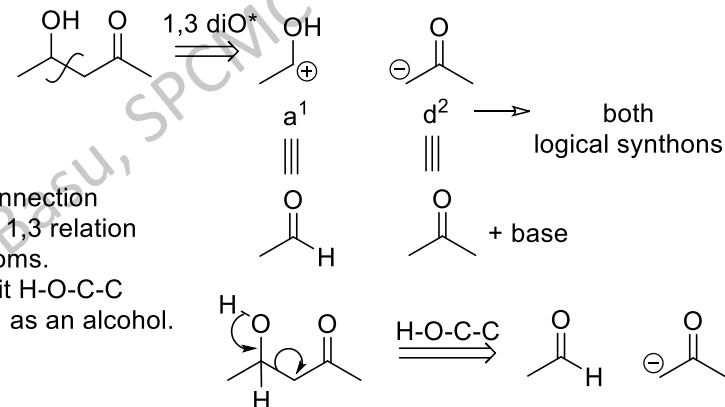


Polarisation due to =O:



latent polarities due to two substituents match - consonant system

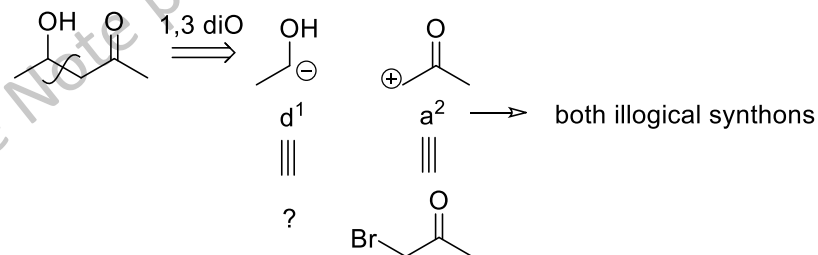
Retrosynthetic analysis:



The synthesis would involve a directed aldol addition of acetone enolate to acetaldehyde.

Of course, it would not be wise to disconnect this target into a combination of d^1 and a^2 synthons because both of these would require umpolung strategy as both are illogical in the sense that the charged carbon is not in harmony with the latent polarity induced by the substituent present in that fragment.

Bad disconnection:



We can generalise from this analysis that any two E-class substituents in a 1,3-relation in a target molecule is a consonant system and thus will not require any umpoled reagents.

The Logic of Organic Synthesis

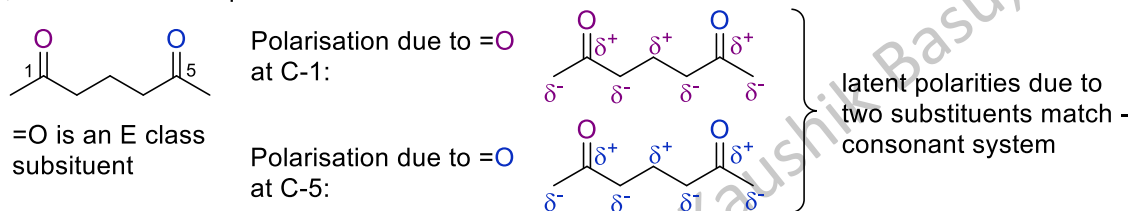
Alternating Polarity Disconnections:

Examples of choosing reasonable disconnections for functionally substituted target molecules based on the concept of alternating polarity:

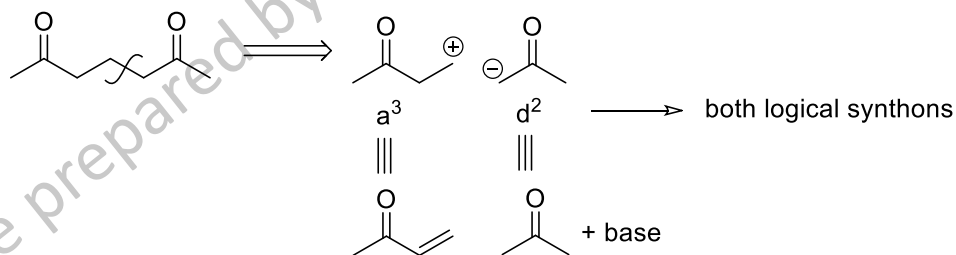
We have seen that any two E-class substituents in a 1,3-relation in a target molecule is a consonant system and thus will not require any umpoled reagents.

Similarly, an analysis of a 1,5-dicarbonyl compound would reveal two logical synthons derived by heterolytic retrosynthetic cleavage of the C3-C4 bond - a^3 and d^2 , i.e. a Michael addition of an enolate to an α,β -unsaturated carbonyl.

1,5-bifunctional compound:



Retrosynthetic analysis:



As stated for 1,3-bifunctional relationship, a 1,5-dicarbonyl, or for that matter any two E class substituents in 1,5-relation in a target molecule represent a consonant system and their synthesis would not require umpolung strategy.

Synthesis of these consonant systems is therefore a relatively simple problem.

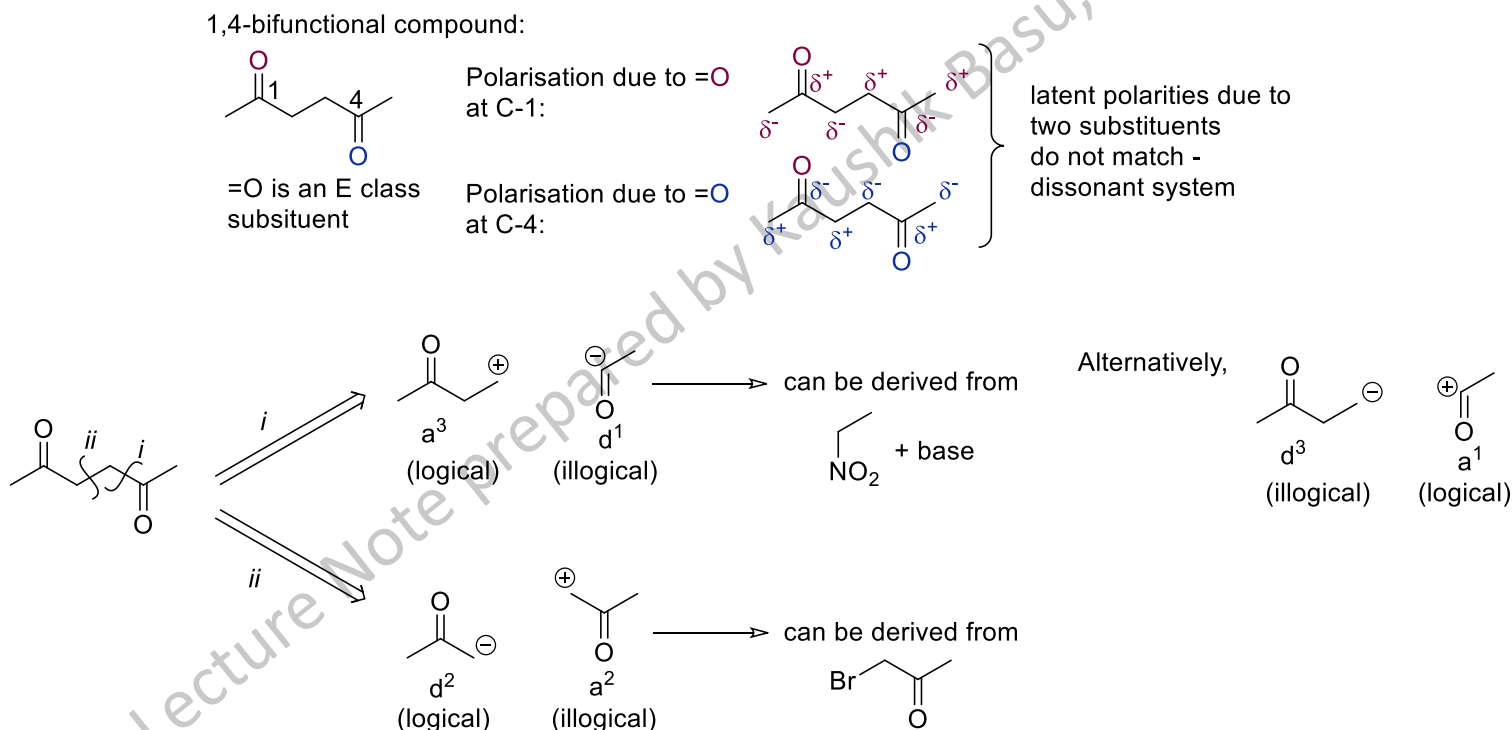
The Logic of Organic Synthesis

Alternating Polarity Disconnections:

Examples of choosing reasonable disconnections for functionally substituted target molecules based on the concept of alternating polarity:

We have seen that any two E-class substituents in a 1,3- or in a 1,5-relation in a target molecule is a consonant system and thus will not require any umpoled reagents.

On the other hand, dissonant systems usually involve umpolung reagents and their synthesis is not as straightforward as those for consonant ones. Consider the following 1,4-dicarbonyl compound:



Both strategies (i and ii) would therefore require reversal of polarity on at least one of the reagents.

Synthesis of dissonant systems like 1,4-bifunctional compounds would not be as easy as that for 1,3- or 1,5-bifunctional compounds.