A Categorical Guide to Basic Terminologies, Principles, and Disconnections in Retrosynthesis

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Abstract: Retrosynthesis is a powerful tool for the synthetic analysis of organic compounds. Although it is a relatively newly proposed idea, it has now been put into wide use. All compounds can have several possible retrosynthetic paths, but the feasibility and practicality of a path is determined by certain concepts and principles. This paper is an introduction to retrosynthesis, starting with basic concepts, reactions, and guiding principles, and proceeding to a detailed guide to basic disconnections categorized with regard to the class of target molecules. This work attempts to provide introductory-level students of organic chemistry with a handbook allowing them to quickly learn to recognize and design basic retrosynthetic strategies.

1 INTRODUCTION

Retrosynthetic analysis was proposed by American organic chemist E. J. Corey of Harvard University, who later won the Nobel prize in Chemistry in 1990 for the proposal (Shampo, 2012). The period between 1960 and 1990 witnessed the evolution of retrosynthesis, and the concept developed into a mature subject that now deserves a separate space in university courses. Early development focused on the idea of antagonistic methods and perfected the disconnections (Rao, 2020).

The importance of retrosynthetic analysis lies in its wide applicability. For example, natural products including alkaloids, rubber, as well as dyes and fragrances. Chemists soon starts to separate, purify, analyze and determine the structure of these compounds. These substances can be applied in various fields, such as medicine, plastics, electronics, etc. (Divakaran, 2008). Retrosynthesis provides a means for the large-scale production of compounds, and makes them available for research and use in a low-cost method for the benefit of mankind.

2 WHAT IS RETROSYNTHESIS?

Retrosynthesis is the process of recursively decomposing a target molecule into simpler and available starting materials (Ghosh, 2020). For instance, a hexagon can be made by first imagining its constituent pieces, as shown in Figure 1.

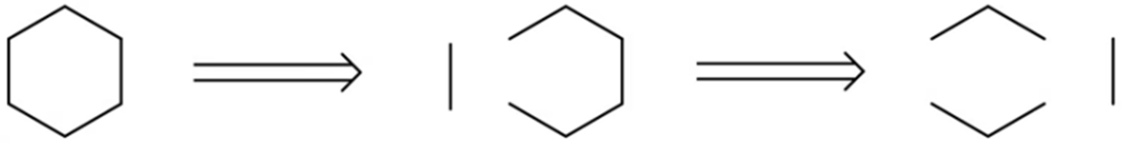

Figure 1: Decomposing a hexagon.

Chemical molecules can be made in a similar way, except that instead of breaking down shapes at random as done with geometric shapes, molecules can be deconstructed by disconnecting bonds, as shown in Figure 2.

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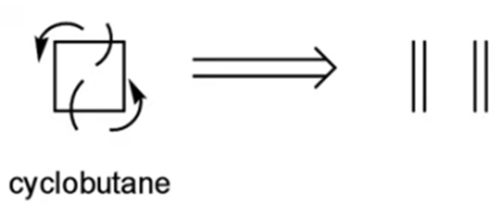


Figure 2: Disconnecting a cyclobutene.

In retrosynthesis, the symbol "⟹"represents the reverse of a synthetic reaction, the symbol "(" indicates the disconnection of bonds, and " ↝ " indicates electron transfer.

3 CONCEPTS

3.1 Target Molecule (T.M.)

The target molecule is the desired molecule, and the molecule whose synthesis is being analyzed.

3.2 Disconnection

A disconnection is an analytical operation which involves the imaginary cleavage of a bond that deconstructs a molecule into simpler pieces; the reverse of a synthetic reaction.

Disconnections are in essence the transfer of electrons. There are two possibilities: after the disconnection of a single bond, the electrons are either retained by respective atoms, or they are both transferred to a single atom (see Figure 3). However, the latter is more common in retrosynthesis.

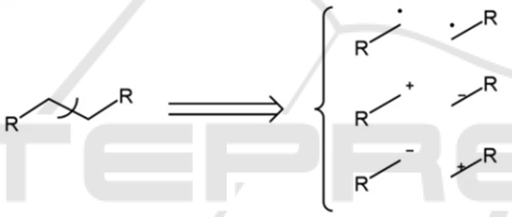


Figure 3: Three possibilities of a disconnection

3.3 Synthon

A synthon is a fragment resulting from a disconnection, usually a cation or an anion (Ghosh, 2020). (It may sometimes be used interchangeably with "synthetic equivalent".) There are two kinds of synthons, namely the negatively charged nucleophiles and the positively charged nucleophiles, as shown in Figure 4.

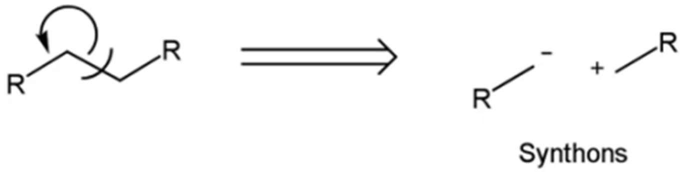


Figure 4: Synthons.

3.4 Synthetic Equivalent

A synthetic equivalent carries out the functions of a synthon which cannot be used itself, usually because it is too unstable (Warren, 2002). The concept will be discussed in more detail in a later section.

3.5 "Fine tuning"

"Fine tunings" are operations on functional groups that facilitate disconnections. The first and most common type of fine tuning is functional group interconversion, or FGI (see Figure 5). It is the operation of converting a functional group into another, usually through oxidation. FGI can also be used for protection of certain functional groups from unwanted reactions. FGI is the most frequently used fine tuning method, and most retrosynthesis involve a sequence of disconnections and functional group interconversions. The second is functional group addition, or FGA (see Figure 6), often used to guide disconnections, or to enable the installation of other functional groups (Singh, 2013). The third is functional group removal, or FGR, which is the operation of removing a functional group (see Figure 7).

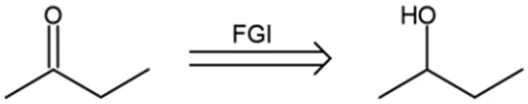


Figure 5: Functional group interconversion.

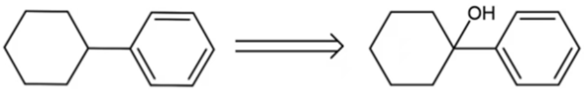


Figure 6: Functional group addition.

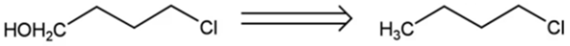


Figure 7: Functional group removal.

3.6 Guiding Principles

A molecule can have several possible retrosynthetic routes. While all of them may be correct, certain strategies are better than others. The following guiding principles will help you recognize and design strategic disconnections. The first rule is greatest simplification. Resulting compounds after a disconnection should be easier to make than the target molecule. A disconnection should also have a reasonable mechanism: a strategic disconnection should give stable and recognizable synthons, as will be demonstrated in subsequent examples. The third principle is minimal fine tuning. While fine tuning does facilitate disconnections to a certain extent, they are not simplifying, and frequent use of fine tuning may lead to redundancy. Lastly, good strategies should have maximum convergency. Since most chemical reactions do not have full efficiency, a synthesis with too many steps will have a low yield. (Warren, 2002) To avoid the problem, convergent instead of linear strategies should be employed, as shown in Figure 8.

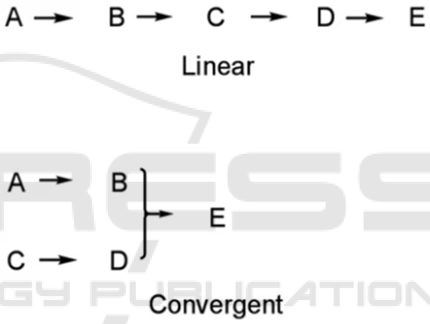


Figure 8: Linear and convergent strategies.

Other concepts and principles will be introduced in application in later sections.

4 DISCONNECTING STRATEGIES

4.1 One-Group Disconnections

4.1.1 Alcohols

As mentioned previously, disconnections are the transfer of electrons. Lone pair electrons can serve as a guide. For instance, the disconnection of alcohols can start with the transfer of a lone pair electron on the oxygen atom, as shown in Figure 9.

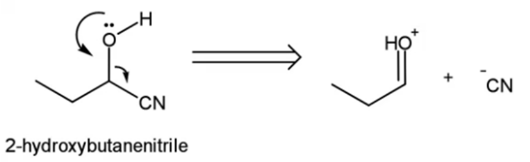


Figure 9: Disconnection of an alcohol.

Both ions are stable, so this is considered a strategic disconnection. Figure 10 shows an alternative route, where the electron goes the other way. But the resulting anion is clearly unstable, so this is an undesirable strategy.

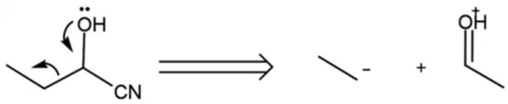


Figure 10: Undesired disconnection for an alcohol.

However, most of the times, there may not be a disconnection that gives stable synthons. The problem can be solved by using stable synthetic equivalents. For instance, Grignard reagents (see Figure 11) are good synthetic equivalents for unstable carbanions, while $NaBH_4$ and $LiAlH_4$ are equivalent to the hydrogen anion H^-. (Warren, 2002)

Figure 11: Grignard reagent as synthetic equivalent

4.1.2 Acids

The disconnection of acids can also start from the oxygen, as shown in Figure 12.

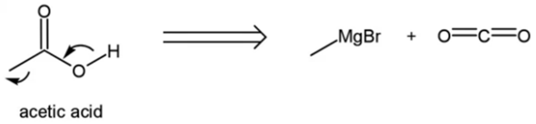


Figure 12: Disconnection of an acid.

4.1.3 Ketones

A simple retrosynthesis for ketones is to first convert them to alcohols, and then make the disconnection (see Figure 13).

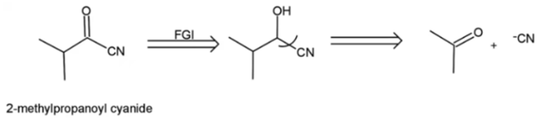


Figure 13: Disconnection of a ketone.

4.1.4 Olefins

Olefins can be made by simply disconnecting the double bond (see Figure 14).

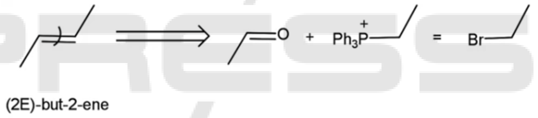


Figure 14: disconnection of an olefin

This is the Wittig reaction, with its mechanism presented in Figure 15.

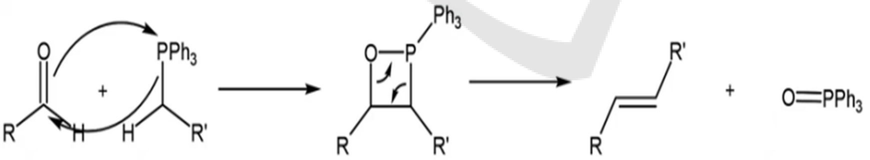


Figure 15: mechanism of the Wittig reaction

4.2 Two-Group Disconnections

When a compound contains two oxygenation groups, they can be used together to guide disconnections.

4.2.1 1, 3-dioxygenated Compounds

Figure 16 shows a few of the variations of the 1,3-dioxygenation pattern. Note that a double bond is equivalent to a hydroxy group.

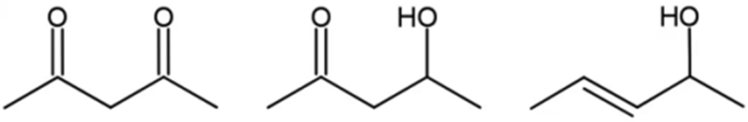


Figure 16: 1, 3-dioxygenated compounds

1, 3-dioxygenated compounds can generally be disconnected at the α, β bond (see Figure 17).

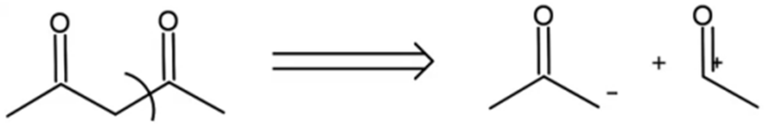
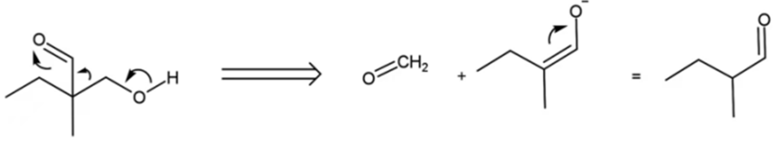


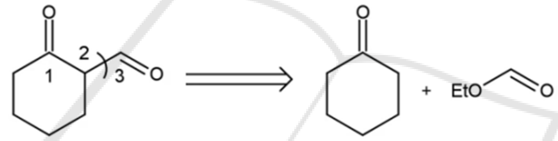
Figure 17: General disconnection strategy for 1,3-dioxygenated compounds.

For instance, the β-hydroxy carbonyl (see Figure 18), 1,3-dicarbonyl (see Figure 19), and α, β-unsaturated carbonyl (see Figure 20) compounds can all be disconnected following the pattern shown in Figure 17.



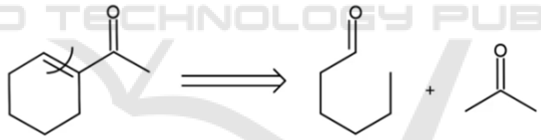
2-(hydroxymethyl)-2-methylbutanal

Figure 18: Disconnection of a β-hydroxy carbonyl.



2-oxocyclohexane-1-carbaldehyde

Figure 19: Disconnection of a 1,3-dicarbonyl.



1-(cyclohex-1-en-1-yl)ethan-1-one

Figure 20: Disconnection of an α,β-unsaturated carbonyl.

4.2.2 1,5-dioxygenation

The mechanism of the disconnection of 1,5-dioxygenation pattern is mostly similar to that of the 1,3-dioxygenation pattern. The compound can be disconnected at any of its two middle bonds, as shown in Figure 21.

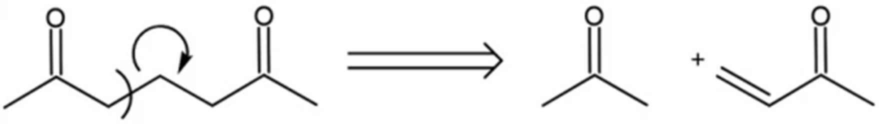


Figure 21: Disconnection of a 1,5-dioxygenation.

The reverse of this disconnection—the reaction using α, β-unsaturated carbonyl compounds as electrophiles—is called the Michael reaction.

Figure 22 shows a more integrated example, in which the α,β-unsaturated ketone has both 1,3- and 1,5-dioxygenation patterns. A good retrosynthetic path is to first disconnect the C-C double bond, and then the β, γ bond in the 1,5-dioxygenation pattern, as shown in Figure 22.

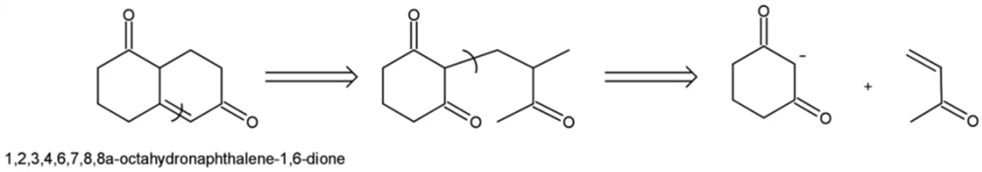


Figure 22: Integrated example of disconnection for a compound with 1,3- and 1,5-dioxygenation patterns.

4.3 Illogical Disconnections

Disconnections resulting in synthons in which the normal polarity is reversed are called illogical disconnections (Ghosh, 2020). As a rule of thumb, compounds with an even number of C atoms between two functional groups produce illogical synthons because of a dissonance of charges arising from their oxidation patterns (Šunjić, 2016). For instance, while disconnecting the middle bond of a 1,3-dicarbonyl results in logical synthons (see Figure 23), a 1,2-dicarbonyl produces two illogical synthons that react unfavorably due to a like charges (see Figure 24).

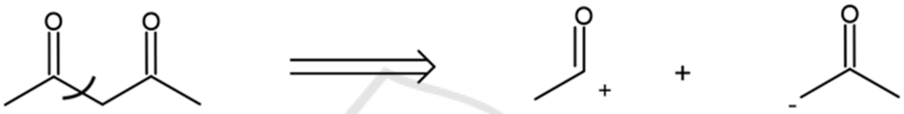


Figure 23: Disconnection of a 1,3-dicarbonyl.

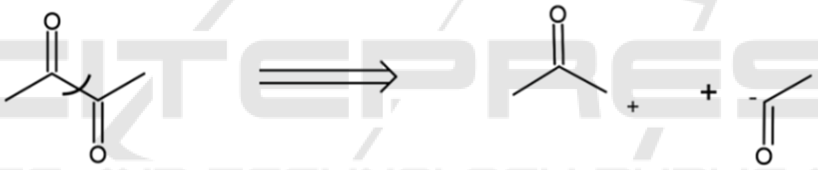


Figure 24: Disconnection of a 1,2-dicarbonyl.

4.3.1 Illogical Synthons

The key to illogical disconnections is recognizing illogical synthons and replacing them with their corresponding synthetic equivalents. The synthetic equivalent of a positively charged illogical synthon is called an illogical electrophile (see Figure 25), while that of a negatively charged illogical synthon is an illogical nucleophile (see Figure 26).

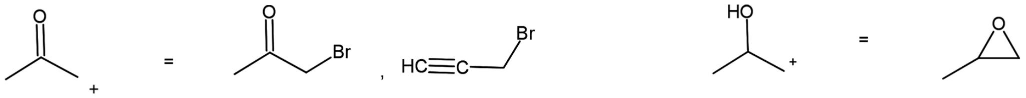


Figure 25: Illogical electrophiles and their synthetic equivalents.

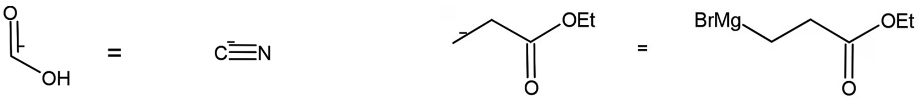


Figure 26: Illogical nucleophiles and their synthetic equivalents.

4.3.2 1,2-dioxygenation

An α-hydroxy-carbonyl can be disconnected in the middle, resulting in a benzyl alcohol electrophile and an illogical nucleophile equivalent to a benzaldehyde, as shown in Figure 27.

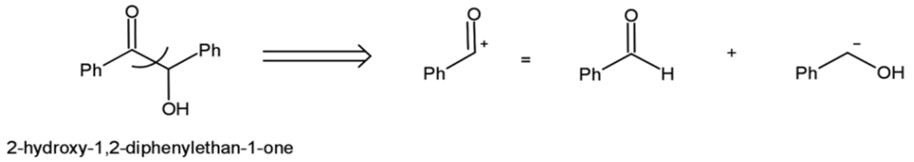


Figure 27: Disconnection of an α-hydroxy-carbonyl.

The strategy for 1,2-dicarbonyl compounds is similar. The most convenient way to make a 1,2-dicarbonyl is to convert it to an α-hydroxy-ketone first, and then synthesize it from there (see Figure 28).

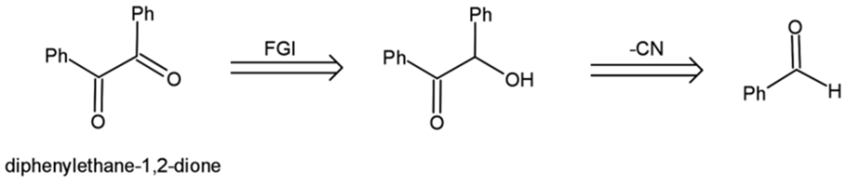


Figure 28: Disconnection of a 1,2-dicarbonyl.

The disconnection of 1,2-diols is slightly different. Figure 29 shows a good approach, which is to use an olefin as the intermediate and disconnect the double bond by the Wittig reaction.

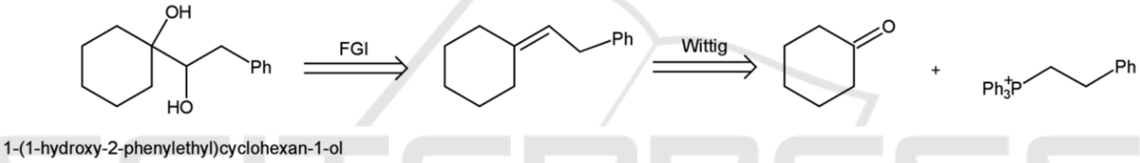


Figure 29: Disconnection of a 1,2-diols.

4.3.3 1,4-dixoygenation

The disconnecting strategy for the 1,4-dioxygenation pattern is similar to that of 1,2-dioxygenated compounds in essence: disconnection of the β,γ bond results in two synthons, one of them illogical.

The disconnection of the 1,4-dicarbonyl shown in Figure 30 results in a stable acetone nucleophile and an illogical electrophile, which can be substituted by its corresponding synthetic equivalent.

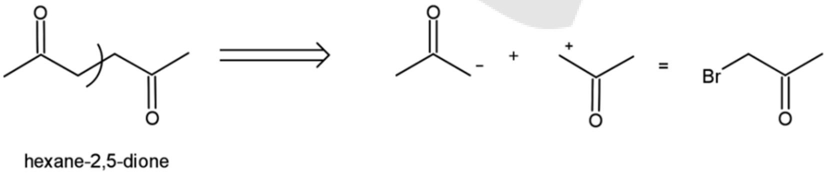


Figure 30: Disconnection of a 1,4-carbonyl.

γ -hydroxy-carbonyl compounds can be disconnected in a similar fashion (see Figure 31).

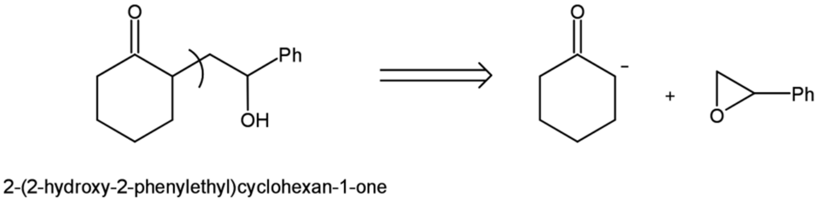


Figure 31: Disconnection of an α-hydroxy-carbonyl.

4.3.4 1,6-Dioxygenation

1,6-dioxygenated compounds have a different synthetic strategy. Instead of disconnecting bonds in the usual sense, a general strategy is to disconnect the two oxygenation groups, as shown in Figure 32.

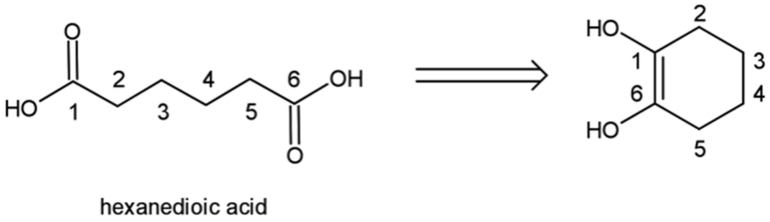


Figure 32: Disconnection of a 1,6-dioxygenated compound.

Subsequent disconnections of the ring structure will be introduced in a later section.

All compounds with a 1,6-oxygenation pattern can be made by first converting the corresponding functional groups to carbonyl groups, and then reconnecting the bonds in a similar fashion.

4.4 Pericyclic Disconnections

Pericyclic reactions are concerted reactions with cyclic transition states.

4.4.1 The Common Atom Approach

The common atom approach is a guiding principle for the retrosynthesis of polycyclic compounds. The most strategic disconnections are made by breaking bonds connecting atoms that are common to more than one ring, for they lead to maximum simplification. For instance, in the compound shown in Figure 33, the common atoms are marked in bold along with the most strategic bonds.

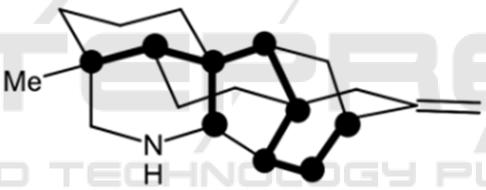


Figure 33: A hetidine analyzed with the common atom approach.

4.4.2 Diels-Alder Reaction

The Diels-Alder reaction is one of the most important reactions in organic synthesis. It occurs between a conjugated diene and a dienophile (an alkene or alkyne), and is sometimes referred to as a [2+4]-cycloaddition (Gunawardena, 2020). Its disconnection is easily recognizable as the reverse of the reaction. Below are the mechanisms of the disconnection (Byrne, 2013):

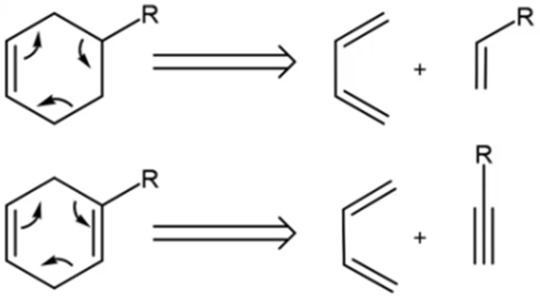


Figure 34: Mechanisms of the Diels-Alder reaction.

Below are some examples (Figure 35):

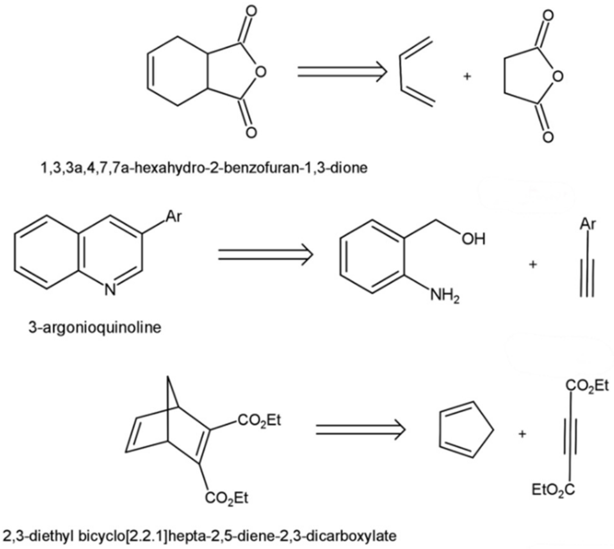


Figure 35: Examples of the Diels-Alder reaction.

However, it is important to note that although different types of disconnections have different mechanisms, they are under the same theoretical backdrop and are guided by the same principles, and it is important, therefore, to look at them as a whole instead of simply treating them as separate operations.

5 CONCLUSION

This work introduces basic retrosynthetic concepts including terminologies and guiding principles, and gives a categorical and detailed overview of disconnections of molecules with different functionalities. This work summarizes and builds upon previous introductory works, and can serve as a guide to retrosynthesis for beginning students of organic chemistry, providing them with the knowledge base which will help them in further studies in the field. However, this paper only covers representative concepts, disconnections, and strategies currently, and there will be continued efforts to make the work more comprehensive and readable.

REFERENCES

Byrne, P. A., & Gilheany, D. G. (2013, May 14). *The modern interpretation of the Wittig reaction mechanism*. Chemical Society Reviews. https://pubs.rsc.org/en/content/articlelanding/2013/cs/c3cs60105f.

Divakaran, G. (2008). *Retrosynthetic Analysis*. science blogs. https://science-blogs.ucoz.com/resources/notes/msc/theory/Retrosynth.pdf.

Ghosh, D. C. (2020). *The Logic of Organic Synthesis*. Sajaipuria College. http://www.sajaipuriacollege.in/wp-content/uploads/2020/04/SEM-4_Chemistry-Hons_Organic-Synthesis_Module-1_Dinesh-Ch.-Ghosh-converted.pdf.

Gunawardena, G. (2020, August 24). *Diels-Alder reaction*. Chemistry LibreTexts. https://chem.libretexts.org/Ancillary_Materials/Reference/Organic_Chemistry_Glossary/Diels-Alder_Reaction.

Rao, R. B. (2020, August 11). *Chapter 18: Organic synthesis*. Chemistry LibreTexts. https://chem.libretexts.org/Courses/Purdue/Purdue%3A_Chem_26605%3A_Organic_Chemistry_II_(Lipton)/Chapter_18%3A_Organic_Synthesis.

Shampo, M. A., Kyle, R. A., & Steensma, D. P. (2012). *Elias James Corey—Nobel Prize for Retrosynthetic Analysis*. Mayo Clinic Proceedings. https://www.mayoclinicproceedings.org/article/S0025-6196(12)01042-7/fulltext.

Singh, R., & Rarh, V. (2013.). *14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)*. BSc Chemistry. http://epgp.inflibnet.ac.in/epgpdata/uploads/epgp_content/S000005CH/P000669/M019143/ET/1515665975CHE_P14_M1_etext.pdf.

Šunjić, V., & Petrović Peroković, V. (2016). Illogical disconnections with participation of two groups. *Organic Chemistry from Retrosynthesis to Asymmetric Synthesis*, 103–141. https://doi.org/10.1007/978-3-319-29926-6_5

Warren, S. G. (2002). *Designing organic syntheses: A programmed introduction to the synthon approach*. Wiley & Sons.