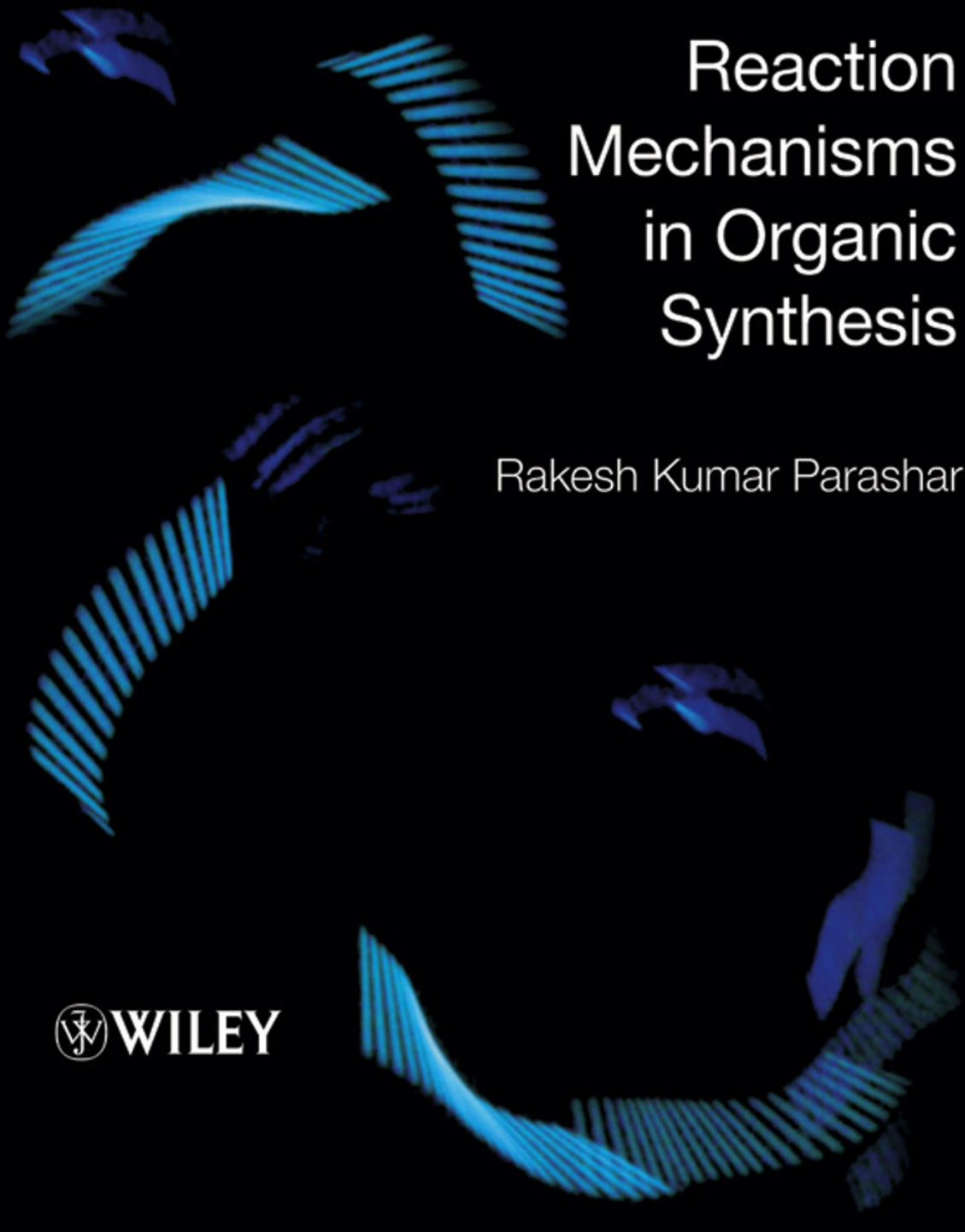
Postgraduate Chemistry Series

Reaction Mechanisms in Organic Synthesis

Rakesh Kumar Parashar



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Reaction Mechanisms in Organic Synthesis

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Reaction Mechanisms in Organic Synthesis

Rakesh Kumar Parashar

Reader, Chemistry Department,
Kirori Mal College, University of Delhi, India

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To Riya, Manya and Indu with love and to
my parents with immense respect

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Foreword

Exciting new methods and reagents are being discovered and used everyday in the synthesis of organic molecules. Knowing the mechanism of these reactions is very important, without which it is almost impossible to carry out the synthesis of important molecules in the laboratory or in industry. Thus, the importance of organic reaction mechanisms continues to increase, and this book is a welcome addition to the available sources on the subject.

While teaching organic synthesis and practicing it in the laboratory, a need is often felt of a handy book combining organic synthesis and mechanisms of reactions employed in synthesis instead of large volumes or monograms on synthesis. There are not many such books covering these two very essential aspects of organic chemistry.

Writing a textbook for any level is always a challenge. However, Dr Parashar deserves praise for undertaking this project and interlinking these two areas of organic chemistry so well throughout the book.

The book is designed to provide fundamental aspects of organic chemistry in a flexible way rather than presenting a traditional approach. The mechanisms and stereochemical features of common reactions used in organic synthesis are discussed in a qualitative and quantitative manner. Specific examples are taken from the latest literature.

The contents of the book give a general impression about what is dealt with. The selection of topics has been done very carefully and judiciously. The material is condensed to a manageable text of 363 pages and presented in a clear and logical fashion over eight chapters. This is done by focusing purely on the basics of the subject without going through exhaustive detail or repetitive examples.

This book would be of immense help to students at the postgraduate level as well as to research workers because of its contents and the way those have been dealt with. I sincerely hope that the book will go a long way to satisfy the long-felt need of students and teachers who inspire the students to take up synthetic organic chemistry as their research topic and career.

I hope practitioners and professionals will be benefited from the experience of learning reaction mechanisms of important synthetic reactions.

I am happy to recommend this book as a self-guide for students and professionals.

Virinder S. Parmar, PhD, FRSC
Professor and Head, Department of Chemistry, and
Chairman of the Board of Research Studies
University of Delhi, India

Preface

An organic chemist is primarily concerned with (a) the synthesis of organic molecules of particular interest to the pharmaceutical and agrochemical industries and (b) the way these molecules interact in biological pathways.

Synthesis involves a careful selection of reactions; new reactions are being developed everyday. Knowing how structure affects a reaction, a rational sequence of transformations can be used to synthesize target molecules. An understanding of organic reaction mechanisms is essential without which it is impossible to plan organic synthesis. It is also required to extend one's knowledge of different areas related to organic chemical reaction mechanisms. The vital importance of the organic synthesis processes is established by the fact that many Nobel laureates have been associated with this field.

Beginning with basic introductory course, this book covers all aspects of organic reaction mechanisms, expands on the foundation acquired in chemistry courses, and enables students and research workers to understand the mechanisms and then to plan syntheses. This book will help postgraduate students to write reasonable mechanisms for organic chemical transformations, which are arranged according to an ascending order of difficulty.

Established reactions are being subjected to both technical improvements and increasing number of applications. For example, intense efforts are made in industry and university laboratories to devise innovative ways to speed up reactions, to carry them out in a continuous fashion and to provide for separation of complex mixtures. For example, ultrasound can dramatically affect the rates of chemical reactions. Microwave-assisted protocols often result in high yields and time efficiency. Solid-phase synthesis allows for easy separation of the resulting products while providing for libraries of compounds to be made. Although these methods have been discussed in special monographs and review articles, there is no recent single book covering reactions (modern or newer) with latest procedural modifications and also simultaneously explaining reaction mechanism and covering stereospecificity and regiospecificity.

The book contains examples from recently published research work to illustrate the important steps involved in synthesis. The discussion is organized by the conditions under which the reaction is executed rather than by the types of mechanisms as is the case in most textbooks at the graduate level.

The author believes that students are well aware of the basic reaction pathways such as substitutions, additions, eliminations, aromatic substitutions, aliphatic nucleophilic substitutions and electrophilic substitutions. Students may follow undergraduate books on reaction mechanisms for basic knowledge of reactive intermediates and oxidation and reduction processes. *Reaction Mechanisms in Organic Synthesis* provides extensive coverage of various carbon–carbon bond forming reactions such as transition metal catalyzed reactions; use of stabilized carbanions, ylides and enamines for the carbon–carbon bond forming reactions; and advance level use of oxidation and reduction reagents in synthesis.

Thus, this book may prove to be an excellent primer for advanced postgraduates in chemistry. This book will be useful both for instructors and those who are preparing for examinations.

Following is a brief account of the contents of the eight chapters of this book.

Chapter 1 is devoted to exploring strategies involved in organic synthesis. It seeks to explain concepts like retrosynthetic analysis, atom economy, umpolung approach, click chemistry and asymmetric synthesis. On the basis of interesting and relevant examples, protection and deprotection of different functional groups are explained and the most probable mechanism is also mentioned for important reactions.

Chapter 2 includes complete discussion on reaction intermediates including carbocations, carbanions, free radicals, carbenes, nitrines and benzynes. The structure, methods of generation and important reactions of all the intermediates are discussed in this chapter. The author has emphasized on their applications in the asymmetric synthesis.

Chapter 3 discusses ylides and enamines, and also deals with the extended examples of carbanions.

Chapter 4 reviews the role of various reagents used in organic synthesis for the formation of carbon–carbon double bond. Specific examples are included at each stage to illustrate the mechanism under discussion.

Chapter 5 includes complete coverage of the transition metals-mediated carbon–carbon bond forming reactions. Pd-, Ni-, Cr-, Zr- and Cu-catalyzed reactions such as Heck, Negishi, Sonogashira, Suzuki, Hiyama, Stille, Kumada reactions are covered in adequate details including the applications of these reactions in organic synthesis.

Chapter 6 focuses on selected examples of reduction methods and their mechanisms in detail. The chapter gives a detailed account of reducing reagents and their applications in organic synthesis.

The oxidation examples in **Chapter 7** are arranged to elucidate key aspects of organic reaction mechanisms. The importance of oxidation reagents in synthesis and their mechanism of action have been explained in detail.

Chapter 8 covers extensively pericyclic reactions and also includes the aromatic transition state theory. Most of the examples are taken from latest literature and are useful for postgraduate and research students.

As an academic convenience to readers all reaction mechanisms leading to stereospecific products are highlighted. The book will also serve as an excellent reference book since references are offered at the end of each chapter.

The book seeks to cover the postgraduate syllabi of almost all the universities. Students will be spared the tedium of collecting all the information on the subject scattered in various books and journals. Even though a comprehensive effort was made to gather information from all sources, it is inevitable that some relevant papers and reviews may be left unscanned.

The author hopes that the book proves to be an easy-to-use general organic chemistry textbook and finds a place in libraries and personal bookshelves of the academic community.

All comments and suggestions will be received with gratitude.

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About the Author

Dr Rakesh Kumar Parashar completed his PhD in 1990 from the University of Delhi, Delhi, in the field of synthetic organic chemistry. He is a Reader in Chemistry at Kirori Mal College, University of Delhi, Delhi. He has done his postdoctorate from the University of Barcelona, Spain. He has published 22 papers in various national and international journals and has delivered several lectures in India and abroad. He is also the author of several books. He is actively involved in teaching and research for the past 18 years.

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I sincerely thank Prof. Jim Coxon who inspired me to take up this project. He also generously helped me to improve this book at the writing stage.

My special thanks are to Prof. Virinder S. Parmar, Head of Chemistry Department, University of Delhi, for writing foreword of this book. I acknowledge Prof. J. M. Khurana, University of Delhi, for his fruitful suggestions that helped me throughout the preparation of this manuscript. I also thank Dr S. Gera and Dr Geetanjali Pandey, Chemistry Department, Kirori Mal College, University of Delhi, for reviewing several chapters.

And, finally, I thank my wife, Indu, and daughters, Riya and Manya, for their love and encouragement during the lengthy, seemingly interminable period of writing this book.

Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
All	allyloxycarbonyl
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BHT	butylated hydroxytoluene (2,6-di-*t*-butyl-*p*-cresol)
BINAL-H	2,2′-dihydroxy-1,1′-binaphthyllithium aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bis-2,2-naphthol
bipy	2,2′-bipyridyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
Bs	brosyl (4-bromobenzenesulfonyl)
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bu	*n*-butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
cat.	catalyst
Cbz	benzyloxycarbonyl
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
CIP	Cahn–Ingold–Prelog priority rules
cod	cyclooctadiene
m-CPBA	*m*-chloroperbenzoic acid or *m*-chloroperoxybenzoic acid
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
d	density
DABCO	1,4-diazabicyclo[2.2.2]octane
DAIPEN	1,1-dianisyl-2-isopropyl-1,2-ethylenediamine
DAST	*N,N*-diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*′-dicyclohexylcarbodiimide
DCE	dichloroethane

DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
De	diastereomeric excess
DEG	diethylene glycol
DET	diethyl tartrate
$(DHQ)_2PHAL$	1,4-bis(9-*O*-dihydroquinine)phthalazine
$(DHQD)_2PHAL$	1,4-bis(9-*O*-dihydroquinidine)phthalazine
DIBAH or DIBAL-H	diisobutylaluminum hydride $(i\text{-}Bu_2AlH)_2$
DIEA	=DIPEA
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane or 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane
DIPAMP	bis[(2-methoxyphenyl)phenylphosphino]ethane
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane, glyme or dimethyl glycol
DMEU	1,3-dimethylimidazolidin-2-one
DMF	dimethylformamide
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPEN	diphenylethylenediamine
Dppe	1,2-bis(diphenylphosphino)ethane
DMMP	Dimethyl methylphosphonate
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppm	1,1-bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
Dod-S-Me	Dodecyl methyl sulfide
DTBP	di-*t*-butyl peroxide
E1cB	*e*limination *c*onjugate *b*ase
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
EWG	electron-withdrawing group
Fmoc	9-fluorenylmethoxycarbonyl
h	hour(s)
HMDS	hexamethyldisilazane or 1,1,1,3,3,3,-hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HWE	Horner–Wadsworth–Emmons
i	iso
Ipc	isopinocampheyl
isc	intersystem crossing
IR	infrared
kcal	kilocalorie
KHDMS	potassium hexamethyldisilazide

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	LiHMDS
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tretramethylpiperidide
LTA	lead tetraacetate
LTEAH	lithium triethoxyaluminohydride
LVT	low-valent titanium
2,6-Lutidine	2,6-dimethylpyridine
M	metal; also molar
Me	methyl
MEM	(2-methoxyethoxy)methyl
min	minutes
mL	millilitre
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
mp	melting point
Ms	mesyl or methanesulfonyl
MS	molecular sieves
MTM	methylthiomethyl
MW	molecular weight; microwave
NaHMDS	sodium hexamethyldisilazide
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
OTf	Triflate or trifluoromethanesulfonate, functional group with the formula $CF_3SO_3^-$
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhH	benzene
pent	pentyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
pmIm	1-methyl-3-pentylimidazolium
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
PTC	phase transfer catalyst/catalysis
PTSA	*p*-toluenesulfonic acid
py	pyridine
R	alkyl group

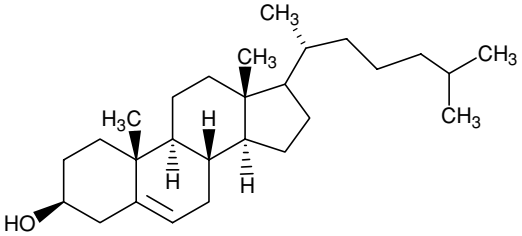
R	clockwise (R, for rectus)
rt	room temperature
S	counterclockwise (S, for sinister)
S_N1	nucleophilic substitution reaction unimolecular
S_N2	nucleophilic substitution reaction bimolecular
salen	bis(salicylidene)ethylenediamine
SET	single electron transfer
SMEAH	red-Al or sodium bis(2-methoxyethoxy)aluminum hydride
t	tertiary
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAP	tetrabutylammonium perruthenate
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	$N,N,N'N'$-tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	*p*-tolyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	tosyl or *p*-toluenesulfonyl; also transition state
TSOH	*p*-toluenesulfonic acid (PTSA)
TTBS	tri-t-butylsilyl

Chapter 1

Synthetic Strategies

1.1 An introduction to organic synthesis

Organic synthesis is the construction of complex organic compounds from simple starting compounds by a series of chemical reactions. The compounds synthesized in nature are called **natural products**. Nature provides a plethora of organic compounds and many of these possess interesting chemical and pharmaceutical properties. Examples of natural products include cholesterol (**1.1**), a steroid found in most body tissues; limonene (**1.2**), a terpene found in lemon and orange oils; caffeine (**1.3**), a purine found in tea leaves and coffee beans; and morphine (**1.4**), an alkaloid found in opium.



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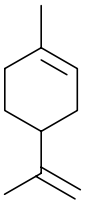

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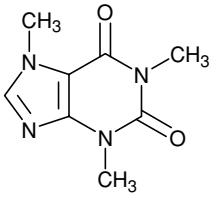

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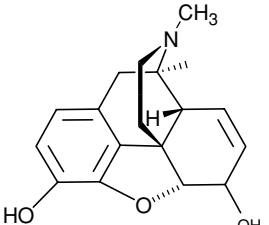
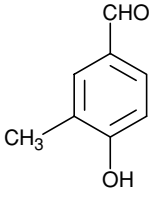


1.4

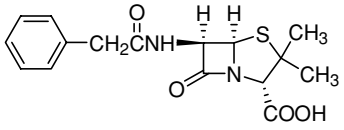
The synthesis of organic molecules is the most important aspect of organic chemistry. There are two main areas of research in the field of organic synthesis, namely **total synthesis** and **methodology**. A total synthesis is the complete chemical synthesis of complex organic molecules from simple, commercially available or natural precursors. Methodology research usually involves three main stages, namely discovery, optimization and the study of scope and limitations. Some research groups may perform a total synthesis to showcase the new methodology and thereby demonstrate its application for the synthesis of other complex compounds.

The compound to be synthesized may have a small carbon framework such as vanillin (**1.5**) (vanilla flavouring) or have more complex carbon framework such as penicillin G (**1.6**) (an antibiotic) and taxol (**1.7**) (used for the treatment of certain types of cancer). However, three challenges must be met in devising a synthesis for a specific compound: (1) the carbon atom framework or skeleton that is found in the desired compound must be assembled;

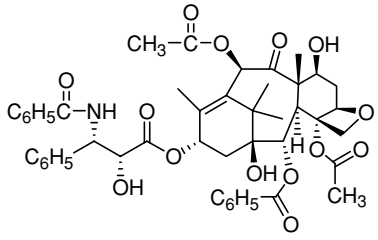
(2) the functional groups that characterize the desired compound must be introduced or transformed from other groups at appropriate locations; and (3) if stereogenic centres are present, they must be fixed in a proper manner.



1.5



1.6



1.7

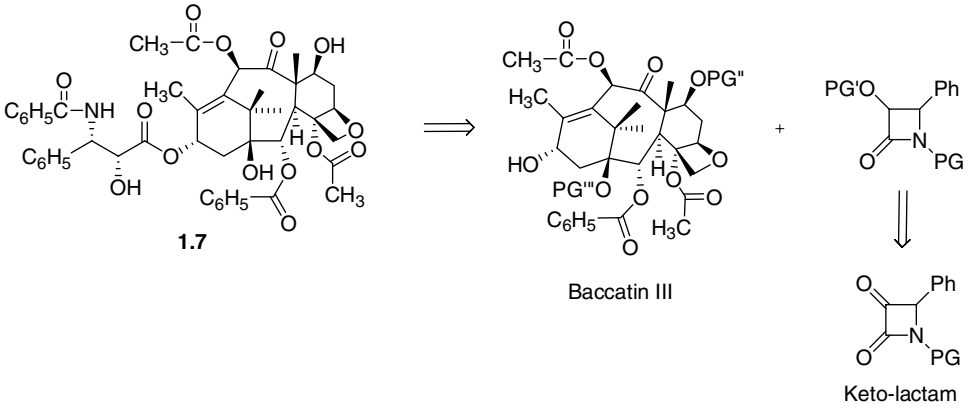
Thus, in order to understand the synthesis of a complex molecule, we need to understand the carbon–carbon bond forming reactions, **functional groups interconversions** and **stereochemistry** aspects.

Carbon–carbon bond forming reactions are the most important tool for the construction of organic molecules. The reaction in which one functional group is converted into another is known as functional group interconversion. The spatial arrangements of the substituents can have a significant impact on the reactivity and interaction towards other molecules. Many chiral drugs must be made with high enantiomeric purity because the other enantiomer may be inactive or has side effects. Thus, there is a need to develop methods to synthesize organic compounds as one pure enantiomer and the use of these techniques is referred to as **asymmetric synthesis** (section 1.5).

Therefore, carbon–carbon bond forming reactions, asymmetric synthesis, the design of new chiral ligands, environmental-friendly reactions and atom economical syntheses are the major aims of present-day research.

1.2 Retrosynthetic analysis (disconnection approach)

E. J. Corey[1,2] brought a more formal approach to synthesis design, known as retrosynthetic analysis. The analysis of synthesis in reverse manner is called **retrosynthetic analysis** or alternatively a **disconnection approach.** Retrosynthetic analysis or retrosynthesis is a technique for solving problems in synthesis planning, especially those presented by complex structures. In this approach, the synthesis is planned backwards starting from a relatively complex product to available simpler starting materials (Scheme 1.1). This approach requires construction of a carbon skeleton of the target molecule, placing the functional groups and appropriate control of stereochemistry.



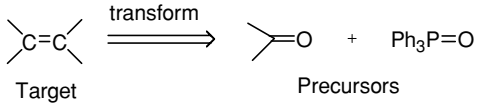
Scheme 1.1 Retrosynthetic analysis of taxol

Table 1.1 Synthetic versus retrosynthetic analysis

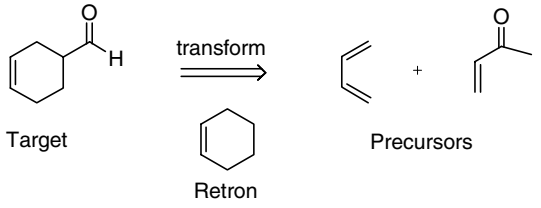
Direction	Synthetic	Retrosynthetic
Step	Reaction	Transform or retro-reaction
Arrow used in graphical depiction	$\longrightarrow$	$\Longrightarrow$
Starting structure	Reactant	Target
Resulting structure	Product	Precursor
Substructure required for operation	Reacting functionality	Retron

The terminology used in synthetic and retrosynthetic analysis is shown in Table 1.1.

A transform in the case of the retrosynthetic counterpart of the Wittig reaction is shown below:



In a similar manner, the retrosynthetic analysis of the Diels–Alder reaction is represented below:

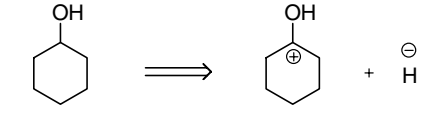


The retrosynthetic step involving the breaking of bond(s) to form two (or more) **synthons** is referred to as a **disconnection**. A synthon is an idealized fragment, usually a cation, anion or radical, resulting from a disconnection. One must select disconnections which correspond to the high yielding reactions.

Functional group interconversion is the process of the transformation of one functional group to another to help synthetic planning and to allow disconnections corresponding to appropriate reactions. In planning a synthetic strategy, apart from devising means of

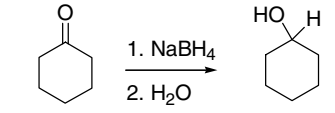
constructing the carbon skeleton with the required functionality, there are other factors which must be addressed including the control of regiochemistry and stereochemistry.

The above points are explained by discussing retrosynthetic analysis of cyclohexanol:



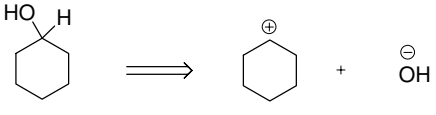
Cyclohexanol

The hydroxycarbocation and the hydride ion formed after disconnection of cyclohexanol are synthons. The synthetic equivalents of hydroxycarbocation and the hydride ion are cyclohexanone and sodium borohydride, respectively. Thus, the target molecule cyclohexanol can be prepared by treating cyclohexanone with sodium borohydride.



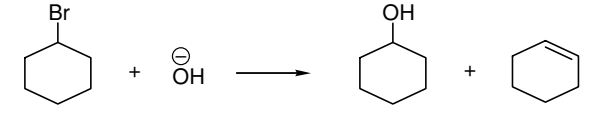
Cyclohexanone Cyclohexanol

The C–C bond of cyclohexanol can also be disconnected as shown below:



Cyclohexanol

The synthetic equivalent for the cyclohexyl carbocation is cyclohexyl bromide. Thus, cyclohexanol can be prepared by the reaction of cyclohexyl bromide with hydroxide ion.



Cyclohexyl bromide Cyclohexanol Cyclohexene

However, in this case cyclohexene is also formed; thus, this method may not be considered as effective as the previous one.

A **retrosynthetic tree** is a directed acyclic graph of several (or all) possible retrosyntheses of a single target. Retrosynthetic analysis, then, consists of applying transforms to a given target, thereby generating all precursors from which that target can be made in a single step. The analysis can be repeated for each precursor, generating a second level of precursors. Each precursor molecule so generated is in some way simpler than the target from which it was derived and then considered to be a target and analyzed similarly. The analysis terminates when precursors are elaborated, which are considered to be relatively simple or readily available, generating a tree of synthetic intermediates.

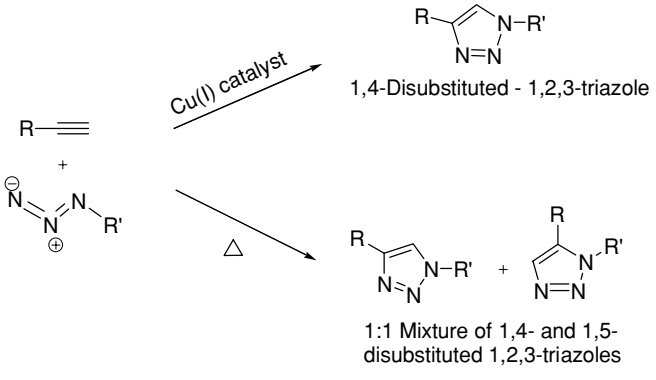
The final result is a complete retrosynthetic tree that will contain all possible syntheses of the given target – reasonable and unreasonable, efficient and cumbersome. Of course, such a tree would be unmanageably large both for humans and computers, even when the number of precursor levels is limited. To keep the size of the retrosynthetic tree under control, examine all possible disconnections – check which are chemically sound (corresponding to known reactions, reagents, directing effects). The guiding principles for this selection are called **strategies**.

Some **guidelines for retrosynthesis** are given below:

1. It is better to use convergent approach rather than divergent for many complex molecules.
2. Use only disconnections corresponding to disconnect C–C bonds and C–X bonds wherever possible.
3. Disconnect to readily recognizable synthons by using only known reactions (transform).
4. The synthesis must be short.
5. It is better to use those reactions which do not form mixtures.
6. The focus is on the removal of stereocentres under stereocontrol. Stereocontrol can be achieved through either mechanistic control or substrate control.

The computer-assisted synthetic analysis designated **OCSS** (*o*rganic *c*hemical *s*imulation of *s*ynthesis) and **LHASA** (*l*ogic and *h*euristics *a*pplied to *s*ynthetic *a*nalysis) were designed to assist chemists in synthetic analysis by Corey *et al.*[3,4]. LHASA generates trees of synthetic intermediates from a target molecule by analysis in the retrosynthetic direction.

Click chemistry is a modular synthetic approach towards the assembly of new molecular entities. The nature has overall preference for carbon–heteroatom bonds over carbon–carbon bonds; e.g. all the proteins are created from 20 building blocks that are joined via reversible heteroatom links. Thus following nature's lead, the term 'click chemistry'[5] was coined by Kolb, Finn and Sharpless in 2001 for synthesis restricted to molecules that are easy to make. The click chemistry as defined by Sharpless is reactions that are modular, wide in scope, high yielding, create only inoffensive products, are stereospecific, simple to perform and require the use of only benign solvent. Of all the reactions which fall under the umbrella of click chemistry, the Huisgen 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles is undoubtedly the premier example of a click reaction. The reaction is accelerated under copper(I) catalysis, requires no protecting groups, and almost complete conversion takes place. The reaction is selective, as only 1,4-disubstituted 1,2,3-triazole is the only product formed and there is no formation of 1,5-disubstituted triazole, which is also formed in the thermally induced Huisgen cycloaddition (Scheme 1.2).

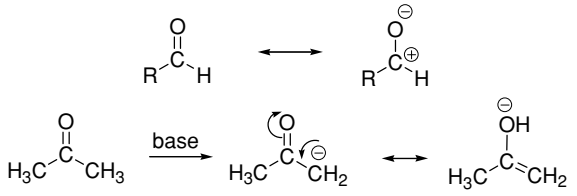


Scheme 1.2

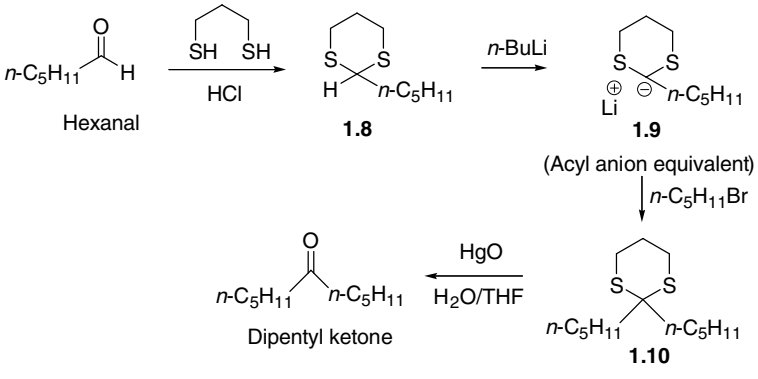
Due to the reliability, specificity and biocompatibility of **click chemistry**, its application is found in nearly all areas of modern chemistry from drug discovery to material science.

1.3 Umpolung strategy

Umpolung is a general class of reactions in which the characteristic reactivity of a group or an atom is temporarily reversed. The concept of umpolung is helpful especially with carbonyl groups. But to understand this concept, it is important to understand the normal reactivity of the carbonyl group. For example, under normal conditions carbonyl carbon is electrophilic and the α-carbon is nucleophilic because of the resonance, as shown below:



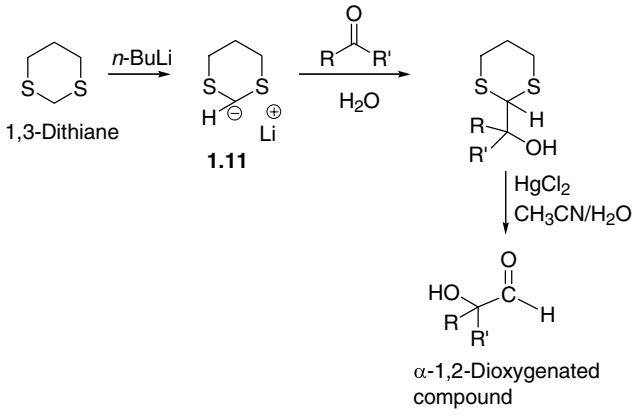
But if the polarity of a carbonyl compound is reversed, the acyl carbon becomes nucleophilic. This is achieved by first converting the carbonyl group into dithianes **1.8**, and then the carbon becomes nucleophilic. The strong base can remove the hydrogen adjacent to the sulfur in the dithiane to give 2-lithio-1,3-dithiane **1.9**. The acyl anion equivalent **1.9** generated in this manner reacts with an alkyl halide to give the alkylated product **1.10**. Finally, the carbonyl group is regenerated by unmasking the dithiane (Scheme 1.3). Thus, this type of inversion of the normal polarization of a functional group atom is known as umpolung.



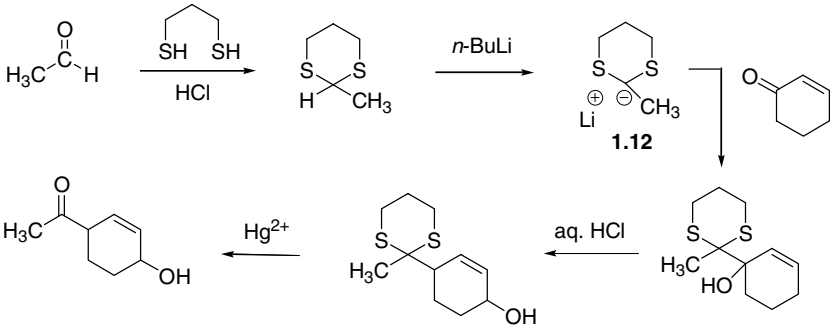
Scheme 1.3 Conversion of hexanal into dipentyl ketone (corey-seebach reaction)

In Scheme 1.3, hexanal on reaction with 1,3-propanedithiol gives the 1,3-dithiane derivative **1.8**. A strong base such as *n*-butyllithium abstracts the proton to give the corresponding 2-lithio-1,3-dithiane **1.9**, which reacts with 1-bromopentane to give alkylated product **1.10**. Treatment of **1.10** with HgO and BF_3 (boron trifluoride) in aqueous THF (tetrahydrofuran) yields the dipentyl ketone (the corey-seebach reaction[6]). Thus, dithianyllithium (2-lithio-1,3-dithiane) **1.9** is an 'acyl anion' synthetic equivalent.

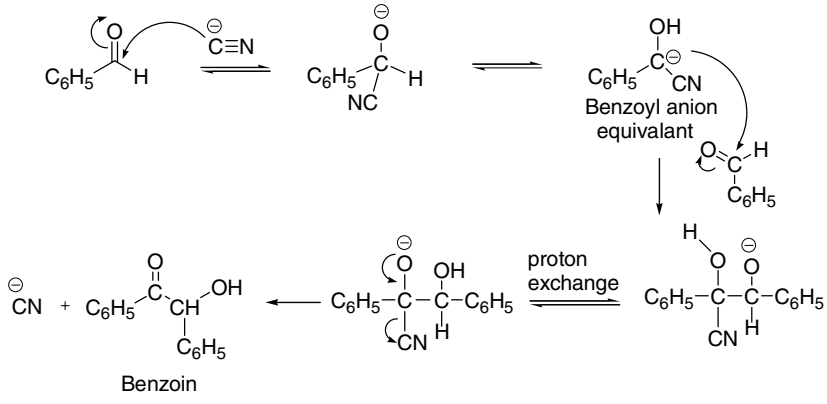
The dithiane anion **1.9** also reacts with acyl halides, ketones and aldehydes to give the corresponding dioxygenated compounds. Schemes 1.4 and 1.5 show the reaction of dithiane anions **1.11** and **1.12** with ketones. The most common example of umpolung reactivity of a carbonyl group is the benzoin condensation (Scheme 1.6).



Scheme 1.4

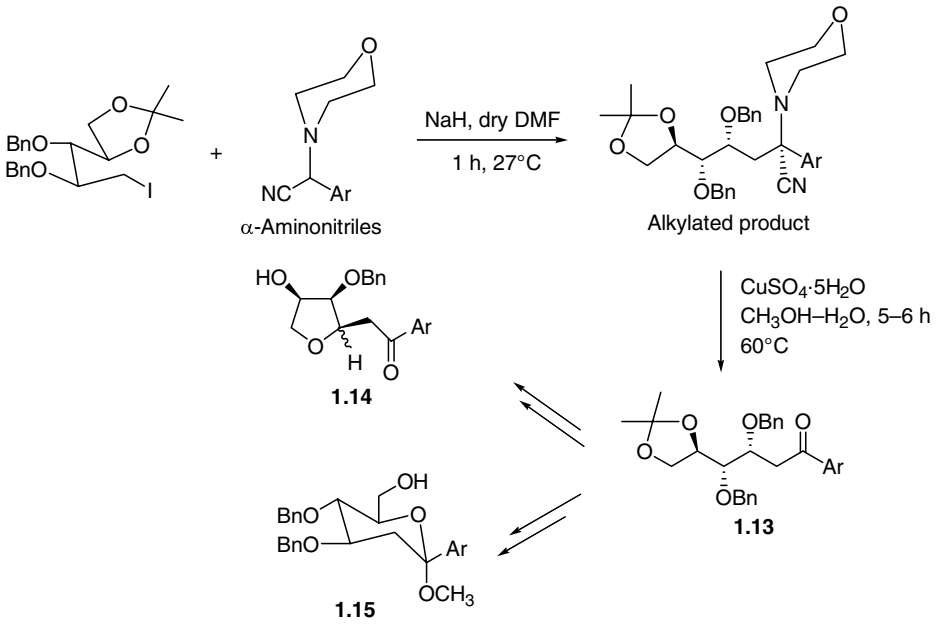


Scheme 1.5



Scheme 1.6 Mechanism of benzoin condensation

A synthetic route for the synthesis of 2-deoxy-*C*-aryl glycosides using an umpolung strategy has been reported by Aidhen and co-worker[7] (Scheme 1.7). The synthetic endeavour led to a versatile intermediate aryl ketone **1.13**, which has paved the way for two important classes of *C*-glycosides, i.e. *C*-alkyl furanosides **1.14** and methyl 2-deoxy-*C*-aryl pyranosides **1.15**.



Scheme 1.7 Synthesis of *C*-aryl glycosides

1.4 Atom economy

The concept of atom economy was developed by B. M. Trost[8,9] which deals with chemical reactions that do not waste atoms. Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. It is widely used to focus on the need to improve the efficiency of chemical reactions.

A logical extension[10] of B. M. Trost's concept of atom economy is to calculate the **percentage atom economy**. This can be done by taking the ratio of the mass of the utilized atoms to the total mass of the atoms of all the reactants and multiplying by 100.

$$\text{Percentage atom economy} = \frac{\text{Mass of atoms in the final product}}{\text{Mass of atoms in reactants}} \times 100$$

R. A. Sheldon[11] has developed a similar concept called **percentage atom utilization**. For instance, the percentage atom economy and percentage atom utilization calculation for the oxidation reaction of benzene to maleic anhydride is given below: