Organic synthesis

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The making of an organic compound from simpler starting materials.

Role in chemistry

Organic synthesis plays an important role in chemistry, biochemistry, medicine, agriculture, molecular biology, physics, materials science, electronics, and engineering by allowing for the creation of specific molecules for scientific and technological investigations. In some cases the target molecule has an unusual structure whose characterization may advance understanding of various theoretical aspects of chemistry. Such a molecule may possess particularly unusual patterns of bonding, such as a strained ring system or unique symmetry; examples are cubane (1), prismane (2), and dodecahedrane (3).

Once a structurally unusual molecule has been synthesized, its properties can be studied to elucidate concepts of chemical bonding, spectroscopy, and reactivity. *See also:* CHEMICAL BONDING; ORGANIC CHEMISTRY; STERIC EFFECT (CHEMISTRY).

There are other reasons for synthesizing a particular molecule. For example, a molecule may be isolated as a natural product from some obscure organism, and a synthesis of the molecule in the laboratory can provide larger quantities of it for testing for properties that might indicate its usefulness, such as in medicine or agriculture. Another reason for synthesizing a molecule is because its structure is different from any known compound and the molecule is predicted to possess some useful property, such as selective ion-binding ability or biological activity such as antibiotic, herbicidal, insecticidal, anticancer, or antiviral activity. In the study of polymers, a particular monomeric subunit might be chosen for synthesis because, upon polymerization, it might yield a polymer having useful physical properties. By hypothesizing that a certain molecule will have a particular property, then obtaining that molecule by synthesis, a chemist can test that hypothesis and thus obtain a better

understanding of the relationship between molecular structure and function, and at the same time producing—if the synthesized molecule does possess the desired property—a novel chemical that can be used to better the human condition. *See also:* POLYMER; POLYMER COMPOSITE; POLYMERIZATION.

Finally, a chemist might devise and carry out the synthesis of an already-known compound in order to introduce one or more radioactive isotopes of some of the constituent elements into the product. Such labeled molecules are useful in biology for studying metabolic processes and for isolating enzymes and proteins that bind specifically to that molecule. *See also:* RADIOISOTOPE (BIOLOGY).

Synthetic strategy

The heart of organic synthesis is designing synthetic routes to a molecule. Organic synthesis can be compared with architecture and construction, where the chemist must devise a synthetic route to a target molecule (a "blueprint"), then utilize a repertoire of organic reactions (the "tools") to complete the "construction project." Along the way, the synthetic chemist must make extensive use of analytical techniques for purifying and characterizing intermediate products as well as the final product. *See also:* CHROMATOGRAPHY; CRYSTALLIZATION; DISTILLATION; INFRARED SPECTROSCOPY; MASS SPECTROMETRY; NUCLEAR MAGNETIC RESONANCE (NMR).

The simplest synthesis of a molecule is one in which the target molecule can be obtained by submitting a readily available starting material to a single reaction that converts it to the desired target molecule. However, in most cases the synthesis is not that straightforward; in order to convert a chosen starting material to the target molecule, numerous steps that add, change, or remove functional groups, and steps that build up the carbon atom framework of the target molecule may need to be done.

Retrosynthetic analysis. A systematic approach for designing a synthetic route to a molecule is to subject the target molecule to an intellectual exercise called a retrosynthetic analysis. This involves an assessment of each functional group in the target molecule and the overall carbon atom framework in it; a determination of what known reactions form each of those functional groups or that build up the necessary carbon framework as a product; and a determination of what starting materials (synthetic precursors or synthetic intermediates) for each such reaction are required. The resulting starting materials are then subjected to the same retrosynthetic analysis, thus working backward from the target molecule until starting materials that are commercially available (or available by synthesis following an already published procedure) are derived.

The retrosynthetic analysis of a target molecule usually results in more than one possible synthetic route. It is therefore necessary to critically assess each derived route in order to choose the single route that is most feasible (most likely to proceed as written, with as few unwanted side reactions as possible) and most economical (involving the fewest steps and using the least expensive starting materials). The safety of each possible synthetic route (the toxicity and reactivity hazards associated with the reactions involved) is also considered when assessing alternative synthetic routes to a molecule.

Stereoselectivity. Selectivity is an important consideration in the determination of a synthetic route to a target molecule. Stereoselectivity refers to the selectivity of a reaction for forming one stereoisomer of a product in preference to another stereoisomer. Stereoselectivity cannot be achieved for all organic reactions; the nature of the mechanism of some reactions may not allow for the formation of one particular configuration of a chiral (stereogenic) carbon center or one particular geometry (cis versus trans) for a double bond or ring. When stereoselectivity can be achieved in a reaction, it requires that the reaction proceed via a geometrically defined transition state and that one or both of the reactants possess a particular geometrical shape during the reaction. For example, if one or both of the reactants is chiral, the absolute configuration of the newly formed stereogenic carbon center can be selected for in many reactions. Nucleophilic substitution is an example of a reaction that can proceed stereoselectively when the starting material is chiral. Pericyclic reactions also proceed stereoselectively, because they involve transition states that have well-defined geometries. The achievement of stereoselectivity is an important aspect of organic synthesis, because usually a single stereoisomer of a target molecule is the desired goal of a synthesis. Sometimes the target molecule contains a chiral (stereogenic) carbon center; that is, it can exist as either of two possible enantiomers. The possible synthetic routes to the target molecule may not be selective for forming a single enantiomer of the target molecule; each would form a racemic mixture. In some cases, such nonstereoselective synthetic routes to a molecule are acceptable. However, if a synthesis of a single stereoisomer of a target molecule is required, the stereoselectivity of the reactions derived during the retrosynthetic analysis would need to be considered. The development of stereoselective reactions is an active area of research in organic synthesis. *See also:* ASYMMETRIC SYNTHESIS; ORGANIC REACTION MECHANISM; PERICYCLIC REACTION; RACEMIZATION; STEREOCHEMISTRY.

Chemoselectivity. This term refers to the ability of a reagent to react selectively with one functional group in the presence of another similar functional group. An example of a chemoselective reagent is a reducing agent that can reduce an aldehyde and not a ketone. In cases where chemoselectivity cannot be achieved, the functional group that should be prevented from participating in the reaction can be protected by converting it to a derivative that is unreactive to the reagent involved. The usual strategy employed to allow for such selective differentiation of the same or similar groups is to convert each group to a masked (protected) form which is not reactive but which can be unmasked (deprotected) to yield the group when necessary. The development and usage of protecting groups is an important aspect of organic synthesis.

Other strategies. Most target molecules for synthesis are complicated, and their syntheses require many steps. An important aspect of the strategy for synthesizing complex molecules is to devise a convergent synthesis, where relatively large subunits of the target molecule are synthesized individually and then attached together to form the complete or nearly complete target. A convergent synthesis strategy is more economical than the alternative linear synthesis strategy, where the target molecule is built up step by step, one group at a time.

Synthetic reactions

A retrosynthetic analysis can be done by using sophisticated computer programs in order to derive as comprehensive a list of possible synthetic routes to a target molecule as possible. One important aspect of synthetic planning is that it depends upon a knowledge (by a chemist, or programmed into a computer program) of known synthetic transformations, reactions that build up carbon skeletons or introduce functional groups or interconvert functional groups. A large variety of organic reactions that can be used in syntheses are known. They can be categorized according to whether they feature a functional group interconversion or a carbon-carbon bond formation.

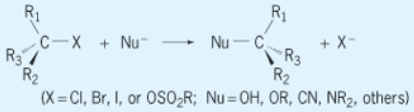
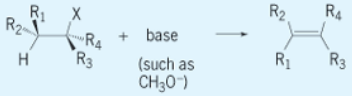
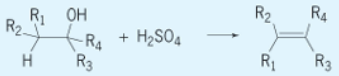
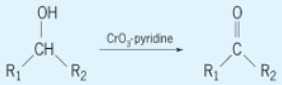
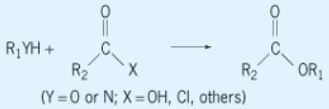
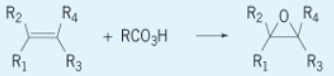
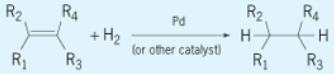
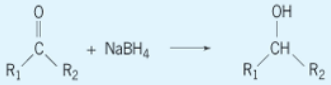
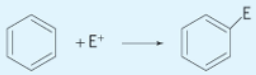
Functional group interconversions (**Table 1**) are reactions that change one functional group into another functional group. A functional group is a nonhydrogen, non-all-singly-bonded carbon atom or group of atoms. Included in functional group interconversions are nucleophilic substitution reactions, electrophilic additions, oxidations, and reductions. *See also:* COMPUTATIONAL CHEMISTRY; ELECTROPHILIC AND NUCLEOPHILIC REAGENTS; OXIDATION-REDUCTION; OXIDIZING AGENT; SUBSTITUTION REACTION.

Carbon-carbon bond-forming reactions (**Table 2**) feature the formation of a single bond or double bond between two carbon atoms. This is a particularly important class of reactions, as the basic strategy of synthesis—to assemble the target molecule from simpler, hence usually smaller, starting materials—implies that most complex molecules must be synthesized by a process that builds up the carbon skeleton of the target by using one or more carbon-carbon bond-forming reactions.

Nucleophilic reactions. An important feature of many common carbon-carbon bond-forming reactions is the intermediacy of a carbanionic intermediate, a molecule bearing a carbon-metal bond formed by deprotonation, by a strong base, of a carbon-hydrogen bond that is relatively acidic because of a nearby electron-withdrawing group or because of the insertion of a metal into a carbon-halogen bond. Such carbanionic intermediates are good nucleophiles (electron-rich, partly negatively charged centers) and thus react readily with added aldehydes, alkyl halides, esters, or other electrophilic (electron-poor, partly positively charged) carbon centers to form the carbon-carbon bond. For example, Grignard reagents are formed by the reaction of an organohalide with magnesium metal in ether solvents in the absence of water. Grignard reagents react with aldehydes or ketones by adding the nucleophilic carbon bound to the magnesium to the electrophilic carbonyl carbon of the aldehyde functional group (Table 2). The resulting magnesium alkoxide intermediates will, upon subsequent addition of an acid (usually dilute aqueous hydrochloric acid), undergo protonation to yield neutral alcohol products whose carbon frameworks bear both the carbons of the aldehyde or ketone and the carbons of the organohalide. *See also:* REACTIVE INTERMEDIATES.

By changing the metal associated with a carbanionic reagent, the reactivity of the reagent can be altered for synthesis. For example, an organocopper (Gilman) reagent will react more readily in nucleophilic substitution reactions with alkyl halides than will organomagnesium (Grignard) reagents (Table 2). Gilman reagents, which

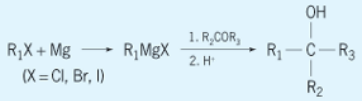
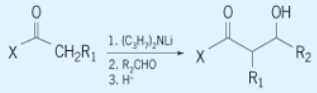
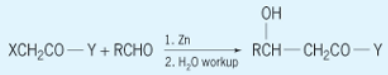
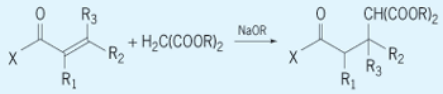
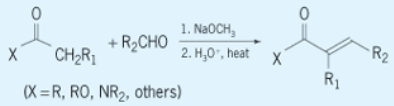
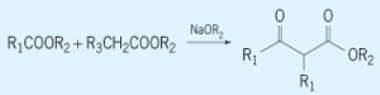
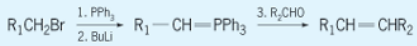
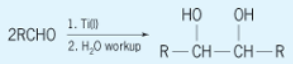
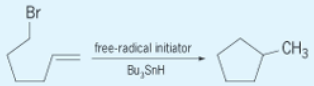
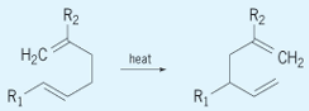
TABLE 1. Examples of some functional-group interconversions

General equation for the reaction*	Net transformation (name)
 (X = Cl, Br, I, or OSO_2R; Nu = OH, OR, CN, NR_2, others)	Alkyl halide to various functional groups (alcohols, ethers, nitriles, amines, others)
	Alkyl halide to alkene (elimination)
$ROH + HX \rightarrow RX$ (X = Cl, Br, I)	Alcohol to alkyl halide
	Alcohol to alkene (dehydration)
	Oxidation of alcohol to ketone or aldehyde
 (Y = O or N; X = OH, Cl, others)	Alcohol and carboxylic acid derivative to ester (esterification); amine and carboxylic acid derivative to amide
	Alkene to epoxide (epoxidation)
	Alkene to alkane (hydrogenation)
	Reduction of ketone or aldehyde to alcohol
$R_1COOR_2 \xrightarrow[2.\ H_2O\ workup]{1.\ LiAlH4} R_1CH_2OH + R_2OH$	Reduction of ester to two alcohols
$R_1COOR_2 \xrightarrow{H_2O,\ acid\ or\ base} R_1COOH + R_2OH$	Ester to carboxylic acid and alcohol (ester hydrolysis)
$R-CN \xrightarrow[2.\ H_2O\ workup]{1.\ LiAlH4} RCH_2NH_2$	Reduction of nitrile to amine
 (E = Br, NO_2, R, RCO, others)	Benzene to substituted benzene (electrophilic aromatic substitution)

*R = any organic group (alkyl, aryl, alkenyl) or a hydrogen atom. Nu = nucleophile.

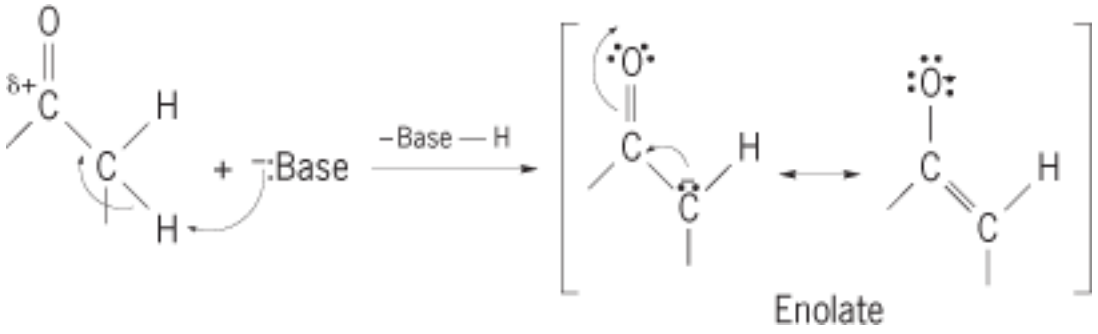
are lithium diorganocopper salts, can be formed by the reaction of organohalides, in the absence of water and oxygen, with lithium metal to form the organolithium reagent (RLi), followed by the addition of copper(I) iodide to form the lithium diorganocopper reagent. Subsequent addition of an alkyl halide results in a nucleophilic substitution reaction, where the carbon bound to the copper displaces a halide ion to form a coupled product

TABLE 2. Examples of some carbon-carbon bond-forming reactions

General equation for the reaction	Name of reaction
	Grignard
	Gilman
	Aldol addition
	Reformatsky
	Michael addition
	Aldol condensation
	Claisen condensation
	Wittig
	Pinacol coupling
	Free-radical cyclization
	Diels-Alder
	Cope rearrangement

consisting of the carbon framework of the organohalide precursor to the Gilman reagent connected to the carbon framework of the alkyl halide by a carbon-carbon single bond. *See also:* ORGANOMETALLIC COMPOUND.

Addition reactions. The Grignard reaction is an example of an addition reaction, where the carbanionic reagent adds itself to the carbon-oxygen double bond of the aldehyde or ketone. A similar addition reaction between a carbanionic reagent and a carbonyl group is the aldol addition reaction (Table 2), where the carbanionic reagent is an enolate formed by the removal, by a strong base, of a hydrogen from a carbon that is bound to a carbonyl group. The electropositive nature of the carbonyl group enhances the acidity of the carbon-hydrogen (C-H) bond next to it, thus allowing such a deprotonation (removal of the hydrogen) to occur, as shown in reaction (1).

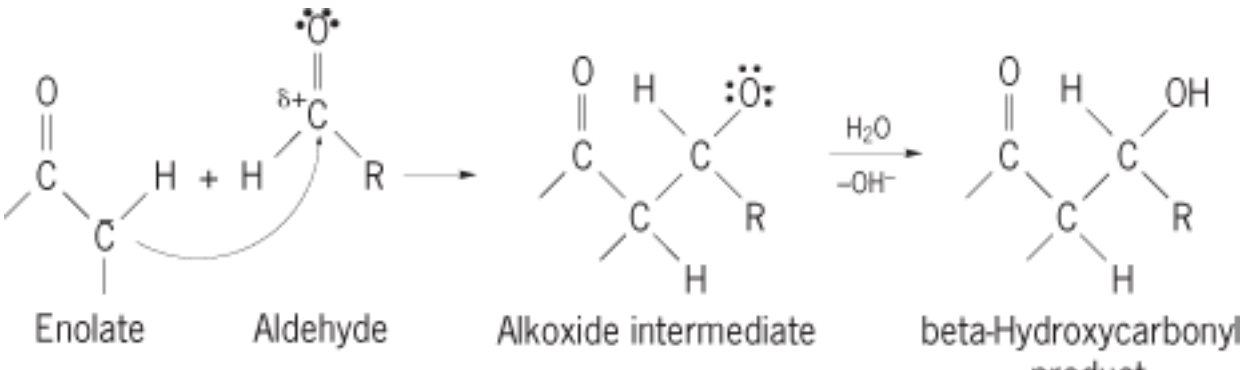


(1)

See also: GRIGNARD REACTION.

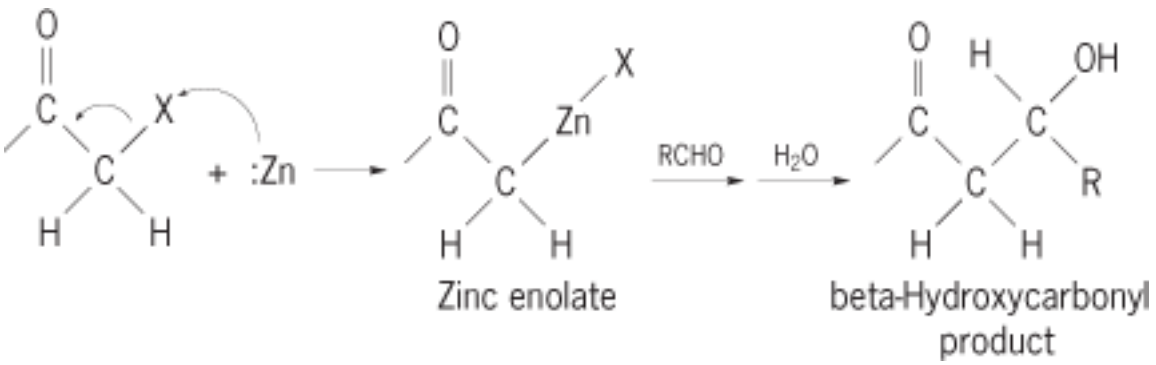
Enolates can be formed by using lithium amide bases (such as lithium diisopropylamide) or, in equilibrium with the carbonyl precursor (most often a ketone, ester, or amide), by using alkoxide bases (such as sodium methoxide). Their structures are resonance hybrids between two resonance structures, one having the negative charge of the enolate centered on the oxygen and the other having the negative charge centered on the carbon. Most of the reactions of enolates used in synthesis involve the anionic carbon atom of the enolate acting as a nucleophile. Enolates can be formed by using weaker bases when the enolate precursor bears two carbonyl groups. *See also:* RESONANCE (MOLECULAR STRUCTURE).

In the case of the aldol addition reaction, the enolate formed by deprotonation of a carbonyl precursor is allowed to react with an aldehyde; the enolate reacts like a Grignard reagent, adding to the carbonyl carbon atom of the aldehyde to form an alkoxide intermediate. Subsequent addition of water results in the protonation of the alkoxide, thus producing a beta-hydroxycarbonyl product, as shown in reaction (2).



(2)

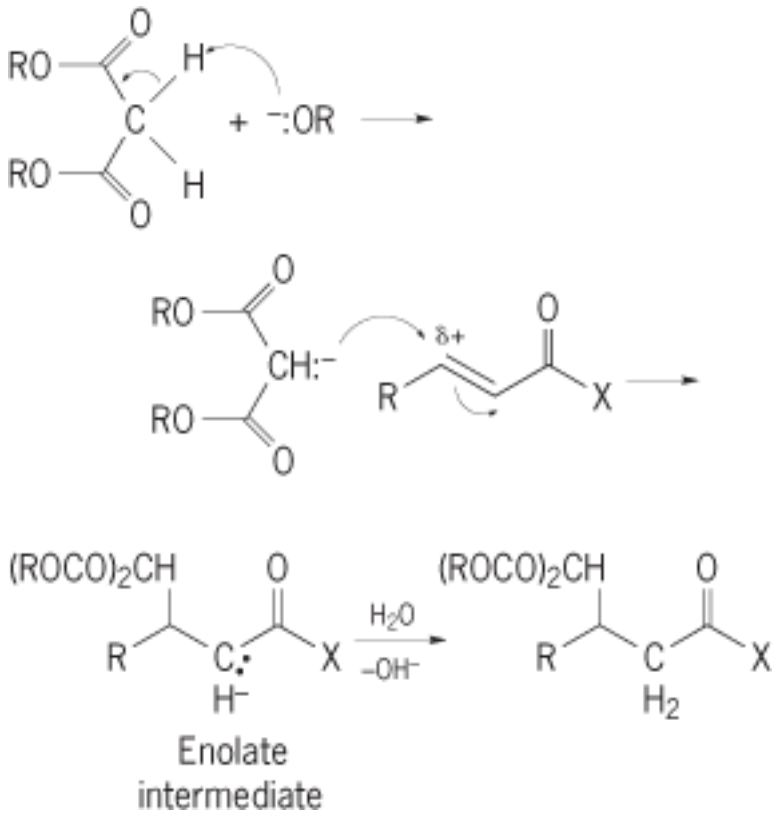
A similar addition reaction is the Reformatsky reaction (Table 2), where a zinc enolate is formed by the insertion of a zinc metal atom into the carbon-halogen bond of an alpha-halocarbonyl precursor. The zinc enolate is then allowed to react with an aldehyde, adding to it in a manner analogous to the Grignard reaction and aldol addition reaction to yield a zinc alkoxide intermediate which, upon subsequent addition of water, undergoes protonation (addition of a hydrogen) to yield a beta-hydroxycarbonyl product, as shown in reaction (3).



(3)

The Michael addition reaction (Table 2) is similar to the aldol addition in that it involves the formation of an enolate, which then acts as a nucleophile. In the Michael reaction, however, the enolate is formed by deprotonation of a carbon next to two carbonyl groups (usually a diester), and the reaction is typified by the addition of the enolate to a carbon-carbon double bond that is activated by being attached to a carbonyl group (an alpha, beta-unsaturated system). The double bond is polarized by the carbonyl group so that it is electrophilic enough to react with the nucleophilic enolate, thus forming an intermediate enolate which is subsequently

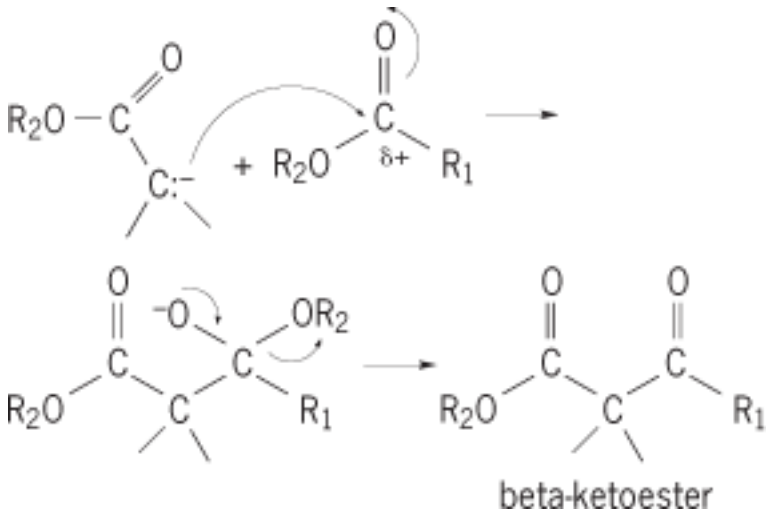
protonated to yield an addition product, as shown in reaction scheme (4).



(4)

Condensation reactions. Numerous carbon-carbon bond-forming reactions are classified as condensation reactions, referring to the fact that the reaction combines the two reactants with a net loss of a small fragment, usually water or an alcohol by-product. Condensation reactions typically proceed in a manner similar to that of the Grignard reaction, the aldol reaction, and the Michael addition reaction, involving the initial addition of a carbanionic intermediate to a carbonyl group. The addition step is followed by the loss of the water (as hydroxide) or alcohol (as an alkoxide). For example, the aldol condensation (Table 2) proceeds initially in the same manner as the aldol addition reaction, an enolate adding to an aldehyde to form a beta-hydroxycarbonyl intermediate, but subsequent addition of an acid to the reaction mixture causes the beta-hydroxyl group to eliminate (a dehydration reaction; Table 1) to form an alkene product (specifically, an alpha,beta-unsaturated carbonyl compound). The Claisen condensation (Table 2) involves the addition of an enolate to an ester to form initially an alkoxide intermediate similar to the intermediates formed by enolates adding to an aldehyde. However, this alkoxide intermediate subsequently undergoes an eliminationlike reaction where the alkoxy group of the ester is displaced by the negative charge of the alkoxide to form a ketone carbonyl group; thus the final

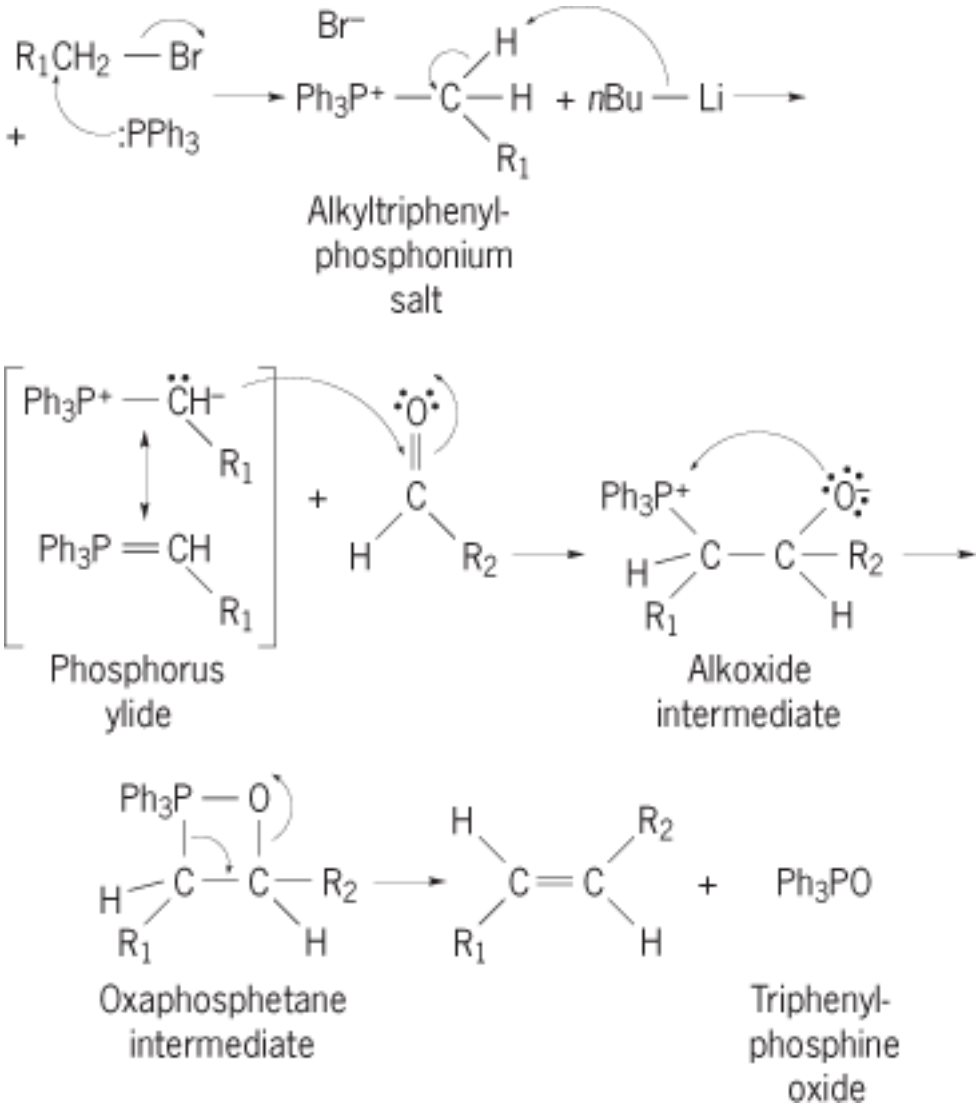
product of the Claisen condensation is a beta-ketoester, as shown in reaction (5).



(5)

The Wittig reaction (Table 2) also proceeds by way of a net condensation process. It starts with an alkyl halide, which is first treated with triphenylphosphine to form, by a nucleophilic substitution reaction, an alkyltriphenylphosphonium salt. This salt is then treated, in the absence of water, with a strong base such as *n*-butyllithium, which removes a proton from the carbon attached to the phosphorus atom. As in the case with the formation of enolates, the electropositive nature of the positively charged phosphorus atom enhances the acidity of the C-H bond next to it, allowing the deprotonation to occur. The resulting deprotonated intermediate, which is called a phosphorus ylide, has an anionic carbon center that can add to an electrophile. Thus, when an aldehyde is subsequently added to the reaction mixture, the nucleophilic carbon atom of the ylide adds to the carbonyl carbon to form an alkoxide intermediate. This intermediate then cyclizes to a four-membered oxaphosphetane intermediate, which then undergoes an elimination reaction to form the alkene product along

with triphenylphosphine oxide as a by-product, as shown in reaction scheme (6).

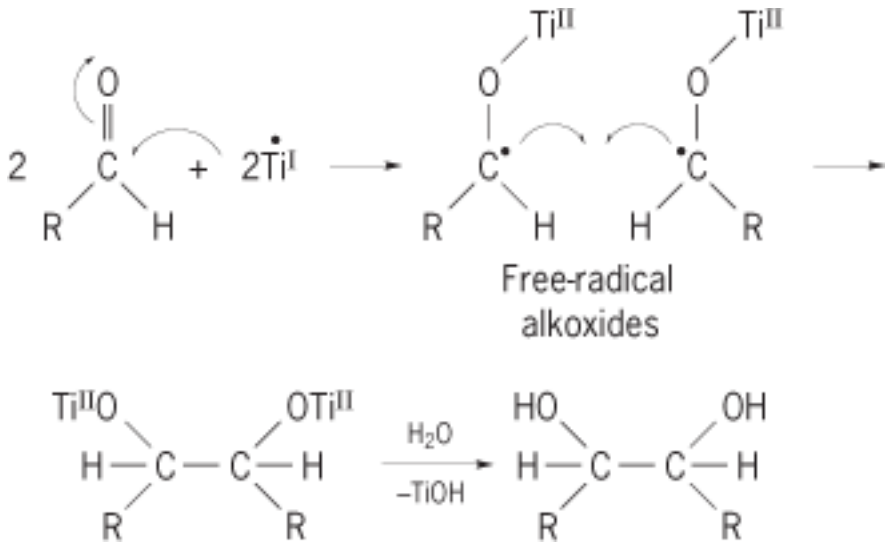


(6)

See also: YLIDE.

Free-radical intermediates. Some carbon-carbon bond-forming reactions involve free-radical intermediates, where a carbon-centered free radical is an intermediate. The free radicals involved in such reactions are molecules that bear a neutral carbon atom that has three bonds to other atoms and a single, unpaired electron. For example, in the pinacol coupling (Table 2) two aldehyde groups are coupled to each other to form, upon subsequent treatment with water as a proton source, a 1,2-diol product. This reaction requires a reduced metal reagent such as titanium(I), and this metal reagent acts to add an electron to the aldehyde group to form a carbon-centered free-radical metal alkoxide (the metal undergoes oxidation as a result of this electron transfer). The free-radical metal alkoxides then couple to each other (a typical reaction of free radicals) to form a coupled dialkoxide product. Subsequent addition of water results in protonation of the dialkoxide to yield the 1,2-diol product, as

shown in reaction scheme (7),

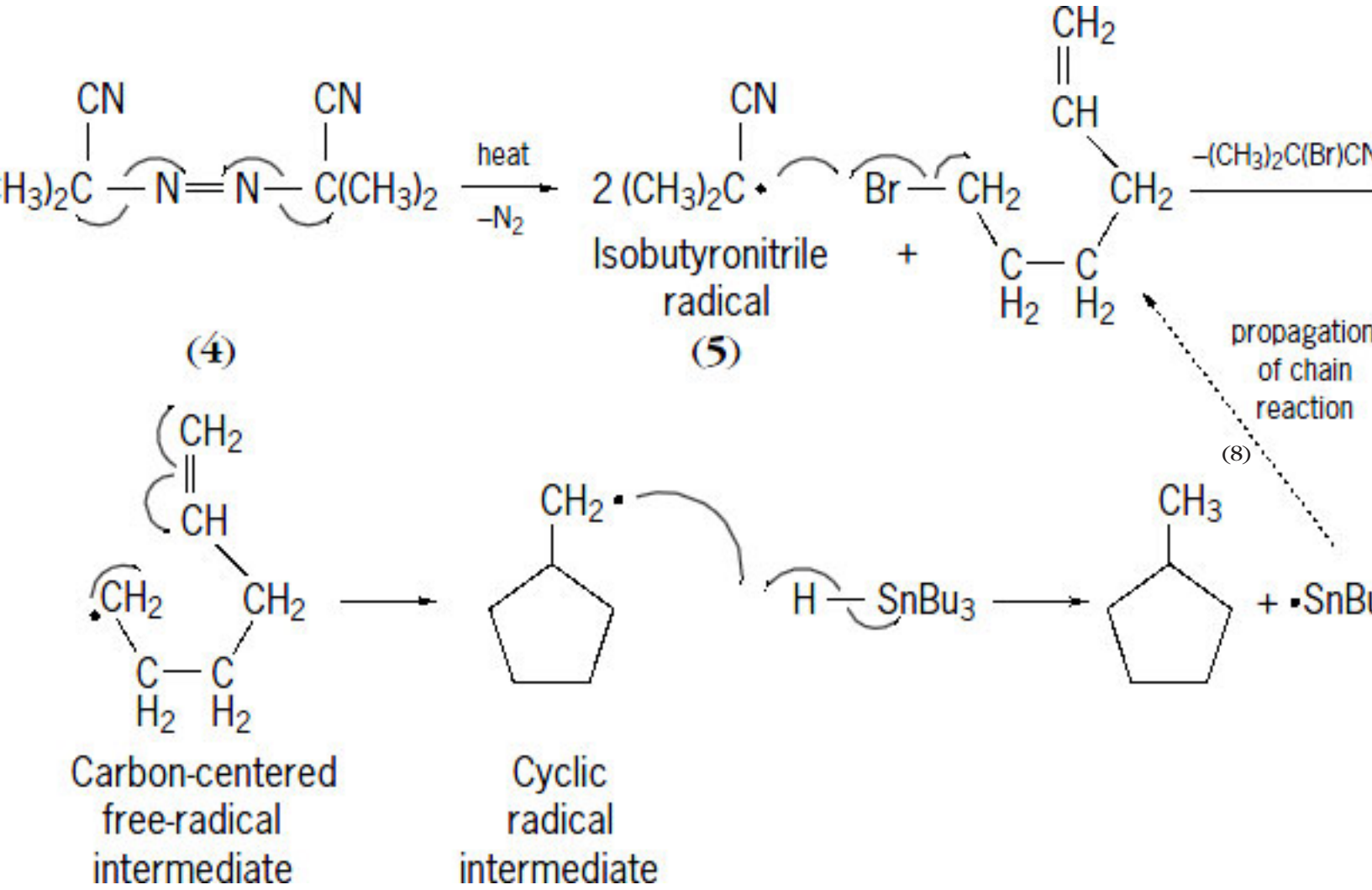


(7)

where Ph represents the phenyl group (C_6H_5). *See also:* FREE RADICAL.

Another common carbon-carbon bond-forming reaction that involves free radical intermediates is the addition of a carbon-centered free radical to an alkene. The form of this reaction that has found greatest utility for organic synthesis is the intramolecular addition of the radical to an alkene group in the presence of tributyltin hydride to form a reduced cyclic product, a cyclization that proceeds most efficiently when it forms a five-membered ring (Table 2). In these cyclizations, the carbon-centered free radical is usually formed by the cleavage of a carbon-bromine bond by a free-radical initiator [usually the isobutyronitrile radical (5), which is formed by heating azobisisobutyronitrile, or AIBN (4), a commonly used free-radical precursor]. The free-radical initiator abstracts the bromine from the carbon-bromine bond to form the carbon-centered radical, which then attacks the alkene group tethered to it to form a cyclic radical intermediate. This intermediate then abstracts a hydrogen atom from the tin hydride reagent to form the reduced cyclic product and a tin-centered free-radical, which then acts as a radical initiator by abstracting (withdrawing) a bromine atom from another molecule of the starting material. Thus the reaction is a free-radical chain reaction, where free radicals (alternatively, carbon-centered and tin-centered) are continuously produced in a chain, which continues until either the bromine-containing starting

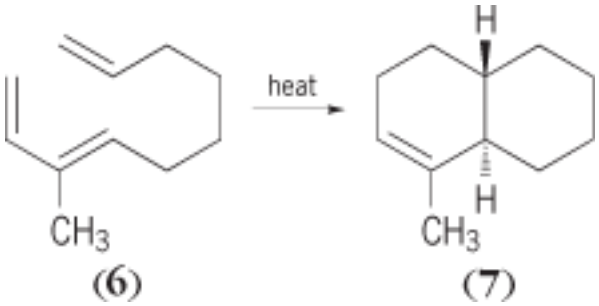
material or the tin hydride reagent is consumed, as in reaction scheme (8)



where the symbol · identifies a free radical. *See also:* CHAIN REACTION (CHEMISTRY).

Other reactions. Other carbon-carbon bond-forming reactions proceed in a concerted fashion and do not involve charged or free-radical intermediates. For example, the Diels-Alder reaction (Table 2) is a reaction between a 1,3-diene and an isolated alkene that simultaneously forms two new carbon-carbon bonds and changes the bond order (double bond to single bond, single bond to double bond) of three other carbon-carbon bonds. The Cope rearrangement (Table 2) is a reaction that simultaneously forms and breaks carbon-carbon single bonds while shifting the positions of a carbon-carbon double bond. These concerted reactions are examples of pericyclic reactions, a class of reactions that are notable for their stereoselectivity. When a diene is tethered to an alkene group in a starting material, an intramolecular Diels-Alder reaction can proceed, thus forming several rings in a single step. For example, by heating the triene (6), the bicyclic product (7) can be formed as a single

stereoisomer, as shown in reaction (9).



(6) (7)

(9)

Such intramolecular processes are very useful for the synthesis of complex organic molecules. *See also:* DIELS-ALDER REACTION; WOODWARD-HOFFMANN RULE.

Robert D. Walkup

Protecting groups

A successful chemical synthesis results in a product with a specified structure and set of properties. In designing a chemical synthesis, it is necessary to develop a strategy that will result in a product with these characteristics. In the course of a chemical synthesis, the usual practice is to use compounds with several functional groups. While one of these serves as the reactive center for one reaction, others are saved for later use in the sequence. It is imperative that the conditions required for the desired reaction do not lead to reactions at other groups. Thus, some groups must be protected by first converting them to unreactive derivatives, accomplished with the use of protecting (protective) groups.

A protecting group is a functional group that is attached to a second functional group during a synthesis to prevent interference by or reaction at that site during subsequent chemical transformations. The group should have certain specific properties: (1) It must be possible to install and remove the group in high yield so as not to compromise the efficiency of a synthesis. Every time a protective group is used, it adds two steps to a synthesis. Even if both reactions proceed in 95% yield, the total yield is only 90%. (2) The group should not introduce new stereocenters so that diastereomers are not produced that would complicate analysis by nuclear magnetic resonance and purification. (3) The reagents for its introduction should be low in cost since these ultimately do not add value or carbon to a synthesis. (4) The reagents used for removal of the group should have a high degree of specificity for that group.

Protection of alcohols, phenols, and thiols. Among the protective groups, those for alcohols and amines provide the greatest diversity and will serve to illustrate some more general principles involved in protection and deprotection. Protection of an alcohol usually is accomplished by some modification of a reaction known as the Williamson ether synthesis; that is, the alcohol is treated with a base and a suitable alkylating agent to form an

TABLE 3. Protection for alcohols

Protection group	Deprotection method
Ethers	
$-CH_3$	HI or BBr_3
$-C(CH_3)_3$	Solvolysis in strong acid (CF_3CO_2H)
$-CH_2Ph$	Hydrogenolysis (H_2, Pd−C)
$-CH_2C_6H_4OCH_3$	Oxidation (dichloro-dicyanoquinone, DDQ)
$-CH_2C_6H_4-2-NO_2$	Photolysis
$-CH_2CH=CH_2$	Isomerization-hydrolysis [$Rh(Ph_3P)_3Cl$; $HgCl_2$, H_2O]
Acetals	
$-CH_2OCH_3$	Strong acid
$-CH_2OCH_2CH_2OCH_3$	Lewis acid ($ZnCl_2$)
$-CH_2OCH_2CH_2TMS$	Fluoride ion $(n\text{-}Bu)_4NF$
$-CH_2OCH_2CCl_3$	Reduction with zinc
$-CH_2OCH_2Ph$	Hydrogenolysis (H_2, P−C)
$-CH_2OCH_2SiPh(CH_3)_2$	Oxidation (AcOOH, KBr)
$-CH_2OCH_2C_6H_4OCH_3$	Oxidation (DDQ)
$-CH_2OCH_2CH_2CH_2CH=CH_2$	*N*-Bromosuccinimide
$-CH_2OC_6H_4OCH_3$	Oxidation (DDQ)
$-CH_2SCH_3$	$HgCl_2$, $CaCO_3$, H_2O

ether. Methods that rely on carbonium-ion chemistry are also employed, but they are restricted to substrates that stabilize cations. *See also:* ALCOHOL.

The greatest variability in protective group chemistry occurs in the methods for deprotection, so that any group in a given molecule can be removed in the presence of the others. This concept is known as orthogonality. Simple ethers or acetals are used as protective groups for alcohols (**Table 3**). The simple ethers are considered the most robust with respect to most synthetic reagents. The methylene acetals (Table 3) offer a large measure of variability in deprotection methods, and consequently greater discrimination is possible when choosing conditions for carbon-carbon bond formation in a synthesis when these are used. *See also:* ACETAL; ETHER.

A third group consists of silyl ethers ($R_1R_2R_3SiOR$). These have the advantage that they can be introduced and removed with great facility under very mild conditions while maintaining excellent stability to a wide array of synthetic reagents. *See also:* ORGANOSILICON COMPOUND.

Esters (RCO_2R') are also extensively used to protect alcohols, and they are usually introduced through the acid chloride or anhydride in the presence of a base. Cleavage is normally effected by basic hydrolysis, and the rate of hydrolysis is dependent upon both electronic and steric effects. By introducing electron-withdrawing groups on the carbon in the alpha position relative to the carbonyl, the rate of base hydrolysis is increased, and this increase can be used to advantage to obtain good cleavage selectivity between several esters. As the crowding or steric demand increases around a particular ester, the rate of hydrolysis decreases because the accessibility to the carbonyl is greatly reduced. For example, the large tertiary butyl ester is much more difficult to hydrolyze with

sodium hydroxide than the much smaller methyl ester. As a result, in the case of a substance that contains both these esters only the methyl ester will be hydrolyzed with sodium hydroxide. One advantage of increased steric demand is that it greatly improves the selectivity of protection in polyfunctional substrates. *See also:* ACID ANHYDRIDE; ESTER.

For alcohol protection, some carbonates have proven to be useful since they are introduced with the ease of an esterification, but can be cleaved by some of the methods used to cleave ethers, thus avoiding the use of basic conditions. Carbonates are generally more stable to base hydrolysis than esters, and thus they can also provide a good level of selectivity in the protection of multiple hydroxyl groups.

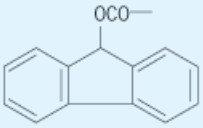
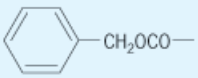
Thiol protection is analogous to alcohol protection. The major differences are that with the increased nucleophilicity of a thiol many of the ether-type derivatives are more easily formed, but they are sometimes more difficult to cleave. This is especially true for situations that employ the noble-metal catalysts which are often poisoned with sulfur compounds. As with the methylthio methyl ether, many of the thioether-based protective groups are cleaved with mercury salts. Strong acids such as trifluoroacetic or hydrobromic acid are also frequently used. Protection of a thiol through disulfide formation is an option not available to alcohols. Disulfides are easily prepared by oxidation and cleaved by reduction. *See also:* CATALYSIS; ORGANOSULFUR COMPOUND.

Protection of amines. Amine protection has its origin in peptide synthesis, where the nucleophilic amine must be rendered temporarily nonnucleophilic in order to activate the carboxylic acid end for coupling with the amine of another amino acid. An amino acid attached to a polymer is coupled with an amino acid protected at the amine and activated at the carboxylate end to form a dipeptide. Deprotection then leads to a new amine, which can then be reacted with a different activated and protected amino acid to form a tripeptide. After the desired number of iterations of the process, the polypeptide is cleaved from the polymer; this step is also a deprotection. *See also:* PEPTIDE.

The most useful protecting groups for amines are based on carbamates [R′RNC(=O)OR″]. Numerous methods exist for their preparation, with the most common method being through reaction of an amine with a chloroformate or activated carbonate in the presence of a base. The carbamate protecting groups (**Table 4**) exhibit a high degree of orthogonality in that most can be deprotected in the presence of the others. It should be noted that there is a strong correlation between the amine protective groups and the simple ethers used to protect alcohols. Both are often cleaved under the same conditions.

Although it is easy to convert an amine to an amide, most are not useful as protective groups because they are too difficult to hydrolyze. The exception is the trifluoroacetamide, which because of its three strongly electron withdrawing fluorine atoms is relatively easy to hydrolyze. A large number of other methods exist for amine protection, but many of these are of a very specialized nature and are used infrequently. In thinking about amine protection, it is necessary to consider the difference between normal primary and secondary amines and heterocyclic amines such as imidazole and tryptophan. Because of their increased acidity, these are often more

TABLE 4. Carbamate protective groups

Abbreviation	Structure	Deprotection method
BOC	*t*-BuOCO—	Strong acid
Fmoc		Base
Alloc	$H_2C{=}CHCH_2OCO{-}$	Pd $(Ph_3P)_4$, nucleophile
Cbz		Hydrogenolysis
Troc	$CCl_3CH_2OCO{-}$	Reduction with zinc

easily deprotected. This is especially true of acyl derivatives which can be cleaved with hydroxide under very mild conditions in contrast to normal amides which are very difficult to hydrolyze. *See also:* AMIDE; AMINE.

Protection of carbonyls. The most commonly used method for the protection of the carbonyl is by ketal formation. The most common derivatives are the dimethylacetals, 1,3-dioxolanes and 1,3-dioxanes. These are easily prepared by treating a ketone or aldehyde with methanol, ethylene glycol, or 1,3-propane diol respectively and an acid catalyst, while scavenging water either azeotropically with benzene or toluene or chemically with a suitable drying agent. The most frequently employed ketal is the 1,3-dioxolane, for which numerous methods exist for both its introduction and cleavage. Acid-catalyzed hydrolysis is the most commonly employed cleavage method, but many methods that avoid the use of aqueous conditions are also available. For cases where a very robust protective group is required, the carbonyl can be protected as the 1,3-dithiolane or the 1,3-dithiane. These are very resistant to acid cleavage and are usually cleaved with mercury or silver salts, but many other methods have also been developed, the best of which is probably by visible-light photolysis in the presence of the dye methylene green. *See also:* ALDEHYDE; AZEOTROPIC DISTILLATION; KETONE; PHOTOLYSIS.

Protection of acids. Carboxylic acids are usually protected as an ester (RCO_2R') which serves to tie up the acidic proton, thus avoiding unwanted acid-base reactions. Most commonly the methyl or ethyl ester is used in this capacity. These are easily hydrolyzed with hydroxide. In the event that basic conditions cannot be used to cleave the ester, several other options are available. The allyl and a variety of benzyl esters are often used. These may be cleaved by using conditions similar to the related ethers and carbamates previously discussed. To prevent nucleophilic addition to the carbonyl, sterically hindered esters (that is, esters having bulky substituents near the carbonyl group) such as the *t*-butyl ester are normally used, because they are easily prepared and conveniently cleaved with strong acid. Since hindered esters are not always effective in preventing nucleophilic additions, a

second alternative exists: an orthoester can be prepared that completely blocks both the acidity and the carbonyl's susceptibility to nucleophilic attack.

Phosphate protection. This is an exercise in selective deprotection, since phosphoric acid is a trivalent acid. The importance of phosphates has centered on the synthesis of oligonucleotides, that is, gene synthesis. Some of the methods used to protect alcohols and acids such as the use of allyl and various benzyl esters are quite effective. Unlike carboxylic acids, simple phosphate esters are not easily cleaved with mild acid and base. They are often cleaved with trimethylsilylbromide. As the leaving group ability (that is, the ability to stabilize a negative charge) of the ester increases, nucleophilic reagents become much more effective. *See also:* OLIGONUCLEOTIDE; ORGANOPHOSPHORUS COMPOUND.

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