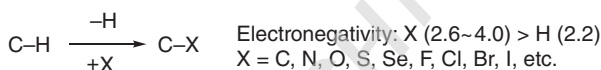


1

Introduction

1.1 What Is Oxidation of C–H Bonds?

Oxidation of C–H bonds is to transform the C–H bonds to various C–X bonds, in which X is a nonmetal atom with higher electronegativity than hydrogen, including carbon, nitrogen, oxygen, sulfur, selenium, fluorine, chlorine, bromine, iodine, etc. in this book [1]. In a typical oxidation process, it usually involves a cleavage of the covalent C–H bond and an oxidative functionalization of the carbon by a reagent (Scheme 1.1).



H 2.2					
		C 2.6	N 3.0	O 3.4	F 4.0
				S 2.6	Cl 3.2
				Se 2.6	Br 3.0
					I 2.7

Scheme 1.1 Oxidation of C–H bond.

1.2 Chemical Synthesis and Oxidation of C—H Bonds

1.2.1 Transformation of Organic Compounds

Organic compounds are a kind of carbon molecules containing at least one C—H, C—C, or single C—heteroatom bond, which are very important substances to provide chemical energy, to construct organisms, to act as the functional materials in human life, and so on. Actually, many transformations are happening spontaneously among these organic compounds and other carbon-containing compounds every day, leading to a big carbon cycle on the Earth. Meanwhile, man-made organic compounds including agrochemicals, pharmaceuticals, and various organic functional materials are prepared enormously through a series of reactions from the raw materials such as methane, ethylene, and benzene, affecting the human being's daily life and human beings themselves remarkably. The preparation of target products (complex molecules) from substrates (simple molecules) is called chemical synthesis normally involving multiple-step reactions in one way (Scheme 1.2).

1.2.2 Ideal Chemical Synthesis

An ideal chemical synthesis is a process with minimal impact on external environment. There are two simple aspects in the process: mass and energy. In theory, at the end of the most ideal process, there are no other substances transformed except the desired products generated from substrates and no other energy consumed except the reaction heat ΔH for product generation. Although there is a large gap between the current chemical processes and the ideal ones in most cases, it is necessary to give some concise suggestions on the estimation of a practical process. Five rules for a HELLO process are listed as follows:

- 1) *High Yield* When the product is obtained in high yield, it indicates that the utilization of substrate is highly sufficient and effective during the transformation.
- 2) *Efficient Pathway* In an efficient pathway of chemical synthesis, a multiple-step process is usually replaced by a one-step reaction, a few reactions in one pot, or a cascade reaction to avoid or reduce the consumption of both

Carbon cycle in Nature



Chemical synthesis



Scheme 1.2 Carbon cycle and chemical synthesis.

substance and energy in the reactions and posttreatments. Furthermore, the substrates, intermediates, and products should be tolerant to the reaction systems without protection treatment on functional groups, and no external substances are consumed to initiate, accelerate, or control any reactions in the process.

- 3) *Low Loading* If it is possible, to save substance, energy, and space, quantitative reactants are employed, and other necessary materials including catalysts, additives, and solvents are used at a minimum during the whole chemical process.
- 4) *Low Complexity in Operation* It is highly required that a chemical process is carried out easily without special protection and caution, under normal pressure in air, and at an ambient temperature. In such a process, all expenses are reduced on safety, equipment, energy, and so on.
- 5) *Only Target Products* In some cases, high selectivity such as high stereoselectivity is more important than high yield. Thus, it is the key symbol for an excellent and elegant process to obtain target products only. In other words, a HELLO process could become a HELL one with a poor selectivity because the wastes or by-products generated could decrease obviously the quantity and/or quality of products and increase largely the cost of substance and energy in the reactions as well as in the product purifications.

To set up such a HELLO process, it mainly depends on the discovery and development of every single perfect reaction, that is, an ideal chemical synthesis is an ideal reaction indeed or consists of a series of ideal reactions.

1.2.3 Oxidation of C—H Bonds for Ideal Chemical Synthesis

According to the aforementioned description, oxidation of C—H bonds should be one of the most promising reactions in an ideal chemical synthesis. There are three main factors as follows to support it strongly:

- 1) *Rich Resources* Since the C—H bonds are fundamental, ubiquitous, and substantial in the saturated and unsaturated organic compounds, especially in the raw materials such as simple alkanes, olefins, and arenes, the oxidation of C—H bonds to form the C—C bonds or C—heteroatom bonds is the most popular method in organic synthesis. For example, aryl sp^2C-H bonds are very common and abundant in various aromatic compounds, so it is the most convenient method for the direct oxidative coupling of two aryl sp^2C-H bonds to give a new aryl sp^2C-sp^2C bond in the preparation of biaryls.
- 2) *High Mass Efficiency* A direct oxidation of C—H bonds to give the desired product is a process in a high mass efficiency (ME). The ME is the ratio of the mass of products to the mass of all transformed substances including reactants, reagents, oxidants or reductants, additives, etc. in

the synthetic process. Obviously, the highest ME must be 100% in all addition or rearrangement reactions, like the atom economy [2]. In the substitution or elimination reactions, however, the highest ME can be achieved just when hydrogens, the lightest elements, are replaced or eliminated from the substrates and the wastes or by-products are produced at a minimum. The oxidations of C–H bonds *via* the cleavage of C–H bonds belong to these reactions giving the highest ME values, which may be close to the ideal processes.

Mass Efficiency

$$\text{ME} = \frac{\text{Mass of product}}{\text{Mass of all transformed substances}} \times 100\%$$

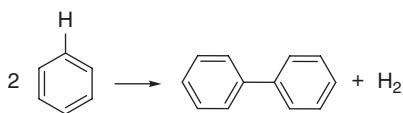
When the transformed substances are just the reactants, the ME is equal to the atom efficiency (AE).

For example, in the formation of biphenyl from benzene, the highest ME is 99% in the dehydrogenative coupling reaction, in which the by-product is only H₂. When dioxygen is employed as an oxidant, the ME is 90% with H₂O generated in the direct oxidative coupling reaction. In contrast, the total ME is decreased sharply to just 39% because of more wastes produced in the sequentially oxidative bromination of benzene using dioxygen as the terminal oxidant and the reductive coupling (Ullmann coupling) of bromobenzene using zinc as reductant (Scheme 1.3).

It is notable that the preparations of different products cannot be compared with each other by their ME values because one process in synthesis has its own highest ME values. For instance, the highest ME is 99% in the formation of biphenyl (C₆H₅–C₆H₅) from benzene (C₆H₆), but that is 94% in the formation of ethane (CH₃–CH₃) from methane (CH₄).

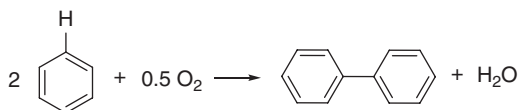
- 3) *High Energy Efficiency* A direct oxidation of C–H bonds to give the desired product is also a process with a high energy efficiency (EE). The EE is the ratio of the reaction heat just for the products (ΔH) to all consumed energy (ΣE) in the synthetic process. The EE is a small value in a practical one due to all consumed energy including not only the reaction heat but also a large part for keeping reaction temperature, mechanical stirring, purifying substances, treating wastes, and so on though it is close to 100% in an ideal reaction. Thus, if the process is just a one-step reaction running under mild conditions, especially to generate no or less wastes like a HELLO process, it usually shows a high EE. The aerobic oxidation of C–H bonds expresses a unique merit in EE when its by-product is only H₂O which should not be considered to deal with specially. In contrast, since the multiple-step synthesis often requires the external energy consumption in the separation of intermediates and/or the regeneration of some important additives to enhance the ME, it is not a process in good EE.

I. Dehydrogenative coupling of benzene



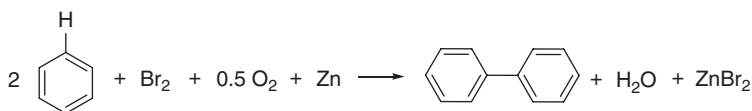
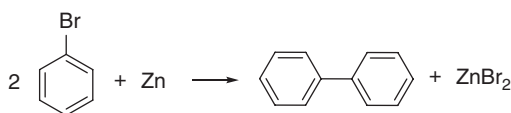
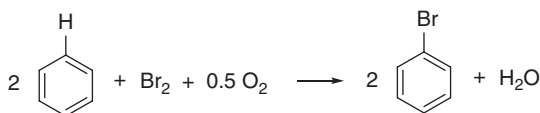
ME = 99% (highest)

II. Oxidative coupling of benzene



ME = 90%

III. Oxidative bromination of benzene and reductive coupling of bromobenzene



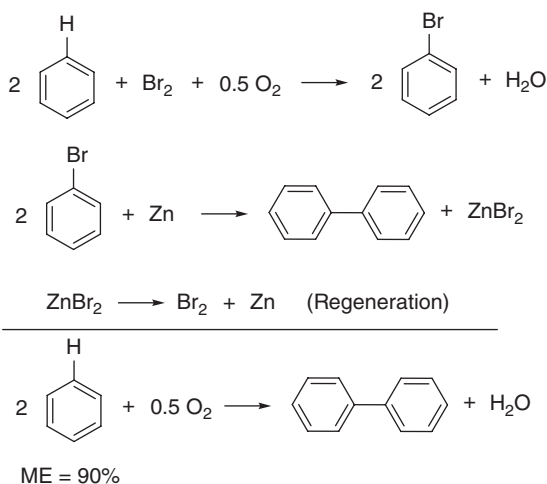
ME = 39%

Scheme 1.3 Preparation of biphenyl from benzene and ME.

Energy Efficiency

$$\text{EE} = \frac{\text{Reaction heat for products } |\Delta H|}{\text{All consumed energy } \Sigma E} \times 100\%$$

For example, in the cases of biphenyl prepared from benzene mentioned earlier, if the regeneration of Zn and Br₂ from ZnBr₂ is carried out after the oxidative bromination/reductive coupling reaction, the total ME can be up to 90% as in the aerobic oxidative coupling reaction (Scheme 1.4). However, the three-step process apparently requires more energy consumption for the treatments of intermediates and wastes than that one-step process, a



Scheme 1.4 Oxidative bromination/reductive coupling and regeneration.

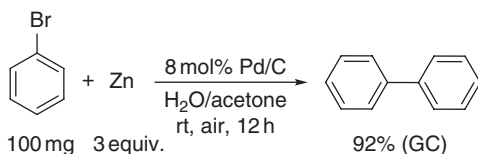
direct oxidation of C—H bonds, even though their total reaction heats for the products could be the same.

Overall, it is undoubted that direct oxidation of C—H bonds is the simplest and most effective method to form the carbon backbones and to introduce a lot of functional groups or heteroatoms in the synthesis. However, at present, either the realization or the application of direct oxidation of C—H bonds is insufficient, and it is far away to be a HELLO process with high ME and EE. For example, the preparation of biphenyl by the coupling of aryl C—halogen bonds and aryl reagents is very effective and applicable, such as the Ullmann coupling [3] and the Suzuki coupling [4], but the development of the aerobic oxidative coupling of aryl C—H bonds under mild conditions is still underway because the normal aryl C—H bonds are more inert than the aryl C—halogen, C—B, and C—metal bonds in these reactions [5] (Scheme 1.5).

1.3 C—H Bonds

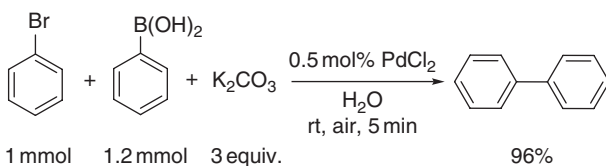
In general, C—H bond is a covalent bond having one electron pair shared by the carbon and the hydrogen. According to the hybridization of carbon atom in the organic molecules, the C—H bonds can be divided into three kinds, that is, $\text{sp}^3\text{C—H}$, $\text{sp}^2\text{C—H}$, and spC—H bonds. The $\text{sp}^3\text{C—H}$ bonds are from the alkanes, so they are named alkyl $\text{sp}^3\text{C—H}$ bonds, correspondingly. When the $\text{sp}^2\text{C—H}$ bonds are found in olefins and arenes, they are called alkenyl (vinyl) $\text{sp}^2\text{C—H}$ bonds and aryl (phenyl) $\text{sp}^2\text{C—H}$ bonds, respectively. The spC—H bonds of alkynes are alkynyl spC—H bonds. These basic C—H bonds are normally inert

The Ullmann coupling



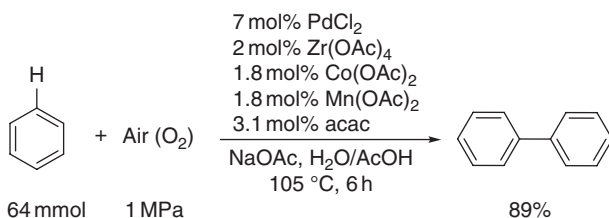
Venkatraman and Li [3b]

The Suzuki coupling



Sarmah et al. [4b]

Direct oxidative coupling of aryl C—H bonds



Mukhopadhyay et al. [5b]

Scheme 1.5 Preparation of biphenyl.

in the reactions except the alkynyl $spC-H$ bonds. If the heteroatoms or some functional groups connect to the carbon atom or the aromatic ring, the characters of $C-H$ bonds would be changed obviously.

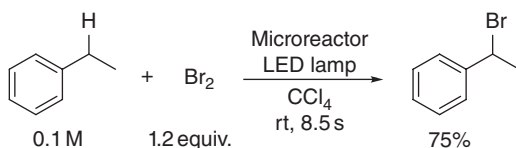
1.3.1 Reactivity

It is well known that the reactivity of covalent bonds can be expressed partially by their bond strength, that is, the bond dissociation energy (BDE). A $C-H$ bond with a high BDE value indicates it is very difficult to cleave in homolysis, such as methyl or primary sp^3C-H bond, alkenyl or aryl sp^2C-H bond, and alkynyl $spC-H$ bond (BDE > 400 kJ/mol). However, if an electron-donating group is attaching directly to the $C-H$ bond and/or a resonance stabilization can affect the $C-H$ bond, its BDE value decreases apparently, and the $C-H$ bond is highly active especially in the radical reactions [6] (Scheme 1.6). For example, the

sp ³ C–H bond	BDE ₂₉₈ (kJ/mol)	sp ² C–H bond	BDE ₂₉₈ (kJ/mol)
CH ₃ –H	439	Ph–H	472
C ₂ H ₅ –H	420	CH ₂ =CH–H	464
(CH ₃) ₂ CH–H	410	CH ₃ C(O)–H	374
(CH ₃) ₃ C–H	400		
CH ₃ C≡CCH ₂ –H	379		
PhCH ₂ –H	375		
CH ₂ =CHCH ₂ –H	369		
Ph(CH ₃)CH–H	357		
		spC–H bond	BDE ₂₉₈ (kJ/mol)
H–CH ₂ NO ₂	415	CH ₃ C≡C–H	557
H–CH ₂ CN	405	H–CN	528
H–CH(CH ₃)CN	393		
H–CH ₂ NH ₂	392		
H–CH ₂ OCH ₃	402		
H–CH ₂ OH	401		
H–CH ₂ C(O)CH ₃	401		
H–CH ₂ C(O)H	394		
H–CH ₂ Cl	419		
H–CHCl ₂	400		
H–CCl ₃	392		

Scheme 1.6 Bond dissociation energies of C–H bonds.

Benzylic sp³C–H bond, BDE = 357 kJ/mol


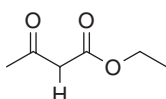


Manabe et al. [7]

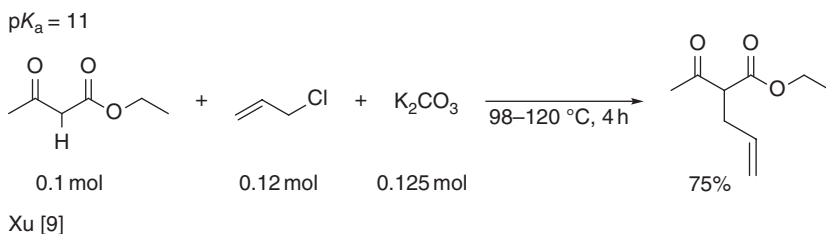
Scheme 1.7 Bromination of benzylic sp³C–H bond.

bromination of a benzylic sp³C–H bond of ethylbenzene is much faster than that of alkyl sp³C–H bonds and aryl sp²C–H bonds under mild conditions [7] (Scheme 1.7).

On the other hand, since a C–H bond can be broken to give a proton as an acid in heterolysis, the reactivity of a C–H bond is also determined quantitatively by its acid strength, that is, the acid dissociation constant (p*K*_a) [8]. A C–H bond with a high p*K*_a value (p*K*_a > 40) is a very weak acid in the reactions, which is from the simple alkanes, alkenes, or arenes. In contrast, when the C–H bond is

sp ³ C–H bond	pK _a	sp ² C–H bond	pK _a
CH ₃ –H	48	Ph–H	43
C ₂ H ₅ –H	50	CH ₂ =CH–H	50
(CH ₃) ₂ CH–H	51		
(CH ₃) ₃ C–H	53		
		spC–H bond	pK _a
PhCH ₂ –H	41	CH ₃ C≡C–H	24
CH ₂ =CHCH ₂ –H	43	H–CN	9.4
H–CH ₂ NO ₂	10		
	19~20		
	11		

Scheme 1.8 Acid dissociate constants of C–H bonds.



Scheme 1.9 Alkylation of methylene sp³C–H bond in ethyl acetoacetate.

connecting to an electron-withdrawing group, its pK_a value decreases sharply, and it becomes an effective nucleophile in the presence of base in the reactions (Scheme 1.8). For example, a methylene sp³C–H bond of ethyl acetoacetate or a β-dicarbonyl compound is very active to undergo the alkylation with an alkyl halide to afford a C–C bond just in the presence of K₂CO₃ as base [9] (Scheme 1.9).

Based on BDE and the pK_a, the C–H bonds can also be divided into two classes simply in their transformations: active and inert (Chart 1.1). For the active C–H bonds usually linking to the functional groups as mentioned earlier, they have either low BDE (<400 kJ/mol) or low pK_a (<40) and can be broken by the attacking of radicals or bases without any catalysts, special reagents, and additives under normal conditions in the current synthesis. For the inert C–H bonds with both high BDE and pK_a, however, the functionalizations of

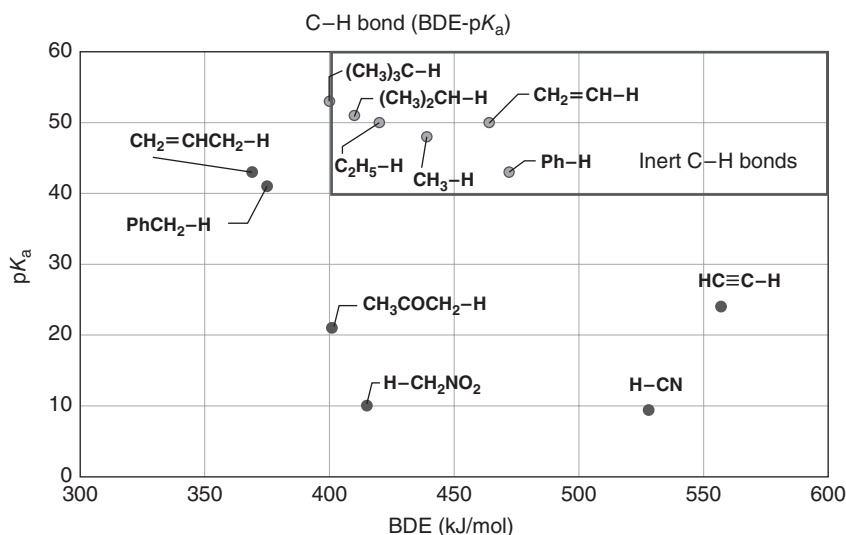


Chart 1.1 C—H bonds expressed by BDE and pK_a .

them are seriously limited. According to the different characteristics of inert C—H bonds mainly found in the simple alkanes, alkenes, and arenes, respectively, some corresponding methods to cleave or to activate them have been realized and applied in the oxidations.

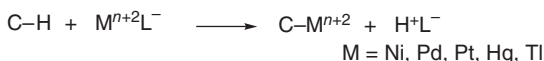
1.3.2 Cleavage of Inert C—H Bonds

The cleavage of inert C—H bonds having high bond strength can occur definitely in the cracking at high temperature but with low selectivity. However, some species at high-energy states, such as radicals, carbenes, superacids, and transition metal complexes are also available to make the C—H bonds break directly not only at high temperature but also at an ambient temperature. On the other hand, the indirect cleavage of inert sp^2C-H bonds can be achieved by means of the reversible conversions at their unsaturated groups.

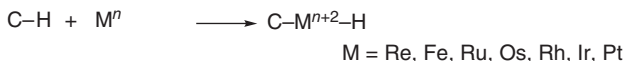
1.3.2.1 Direct Cleavage

According to the formation of intermediates, there are two common ways for the cleavage of the inert C—H bonds. One is C—H bond activation by transition metal complexes, in which C—H bonds are transformed to be the C—M bonds at lower carbon oxidation states (Scheme 1.10). The other is non-C—H activation to give intermediates or products at higher oxidation states such as the carbon radicals or carbocations and C—C bonds (Scheme 1.11).

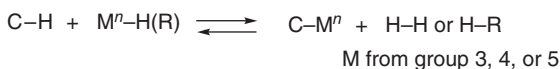
I. Electrophilic activation



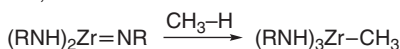
II. Oxidation addition



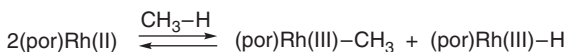
III. Sigma-bond metathesis



IV. 1,2-Addition



V. Metal radical activation



Scheme 1.10 Direct cleavage of C–H bonds (C–H activation).

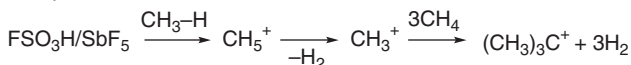
I. Radical pathway



II. Carbene or nitrene insertion



III. Superacid abstraction



Scheme 1.11 Direct cleavage of C–H bonds (non-C–H activation).

1) *C–H Activation* For the simple alkyl $\text{sp}^3\text{C-H}$ and aryl $\text{sp}^2\text{C-H}$ bonds, their organometallic complexes containing C–M bonds can be found as intermediates in the presence of some certain transitional metals by either electrophilic activation or oxidative addition processes. In the former one, the high-valent, late, or posttransition metal species $[\text{M}^{n+2}(\text{L}^-)]$ (Ni^{2+} , Pd^{2+} , Pt^{2+} , Pt^{4+} , Hg^{2+} , or Tl^{3+}) are chosen to undergo electrophilic attack on C–H bonds to form the $[\text{C-M}^{n+2}]$ complexes usually in an acid [10]. Since L^- abstracts H^+ from the C–H bond like an acid–base reaction in some cases, it is also called a concerted metalation–deprotonation (CMD) process [11]. However, in the latter one, the reactive species are the low-valent late transition metal complexes $[\text{M}^n]$ (Re, Fe, Ru, Os, Rh, Ir, Pt) generated from their precursors *in situ* under thermal or photochemical conditions [12]. During these processes, it is thought that the formed intermediates are the $[\text{C-M}^{n+2}\text{-H}]$ complexes.

Another method to cleave alkyl sp^3C-H bonds is using alkyl or hydride transition metal complexes $[M^n-R]$ or $[M^n-H]$ to form $[M^n-C]$ species, which is a sigma-bond metathesis process, where M is commonly from group 3, 4, or 5 [13]. In addition, it is also found that sp^3C-H bonds of methane or sp^2C-H bonds of benzene reacted with $Zr=N$ complexes through a 1,2-addition reaction to generate $NH-Zr-C$ species [14] and sp^3C-H bonds of methane underwent a radical process with rhodium(II) porphyrin complexes to give (por)Rh(III)-C species, respectively [15].

- 2) *Non-C-H Activation* In fact, some strong radicals, generated by the transition metal complexes (Pd, Cu, Co, V), oxo-metal complexes $[M=O]$, peroxides, hypervalent iodine reagents, etc., can abstract hydrogens of alkyl sp^3C-H bonds effectively to lead to the formation of alkyl radicals at not high temperature [16]. Meanwhile, carbenes and nitrenes are able to insert into the alkyl sp^3C-H bonds, especially the secondary ones with electron-rich carbons and less steric hindrance to form C-C bonds [17]. Moreover, a superacid FSO_3H-SbF_5 can protonate methane to give a tertiary-butyl carbocation, involving the formation of a methyl carbocation intermediate through an acid-base reaction between the superacid and a hydride of methyl sp^3C-H bond [18].

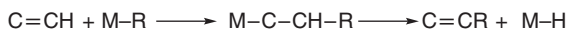
1.3.2.2 Indirect Cleavage of Inert sp^2C-H Bonds

In the cleavage of alkenyl sp^2C-H bonds, a very common and effective method is insertion/ β -hydride elimination in organometallic chemistry. Certainly, this is a two-step pathway involving an insertion of the alkenyl $C=CH$ double bond into an $M-R$ bond of an organometallic compound to form an $M-C-CH-R$ complex followed by a β -hydride elimination of the complex to give a substituted olefin $C=CR$ and an $M-H$. The whole process can be carried out under mild conditions.

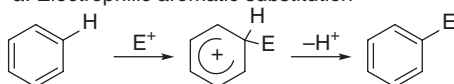
For the aryl sp^2C-H bonds, the classic electrophilic aromatic substitution shows that an electrophile E^+ attacks an aromatic ring $Ar-H$ easily, especially an electron-rich one to form a cationic intermediate but not aromatic, then a substituted aromatic ring $Ar-E$ can be regenerated quickly after losing a proton, which is the cleavage of an aryl sp^2C-H bond. Moreover, several special species such as aryl radicals generated from aryl halides with bases can cleave the aryl sp^2C-H bonds also through a radical pathway including dearomatization and rearomatization under mild conditions [19].

These indirect methods usually involve a conversion of sp^2C to sp^3C by electrophilic attack and a regeneration of sp^2C accompanying the cleavage of $C-H$ bond as well as the formation of the final product (Scheme 1.12).

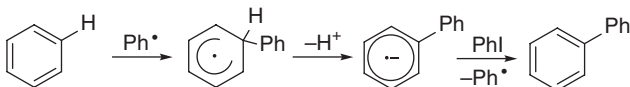
Apparently, those substances mentioned earlier such as metal complexes and special reagents are employed to promote and control the $C-H$ bond cleavage

I. Alkenyl sp^2C-H (insertion/ β -hydride elimination)II. Aryl sp^2C-H

a. Electrophilic aromatic substitution



b. Radical process

Scheme 1.12 Indirect cleavage of sp^2C-H bonds.

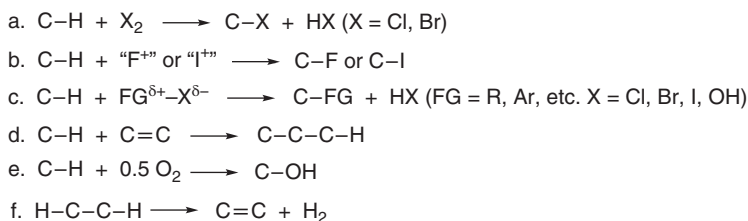
under mild conditions. Thus, to set up a catalytic system may be the first task in the oxidation of C—H bonds, especially for inert C—H bonds.

1.3.3 Oxidation

Based on whether an external oxidant is necessary or not, the oxidation of C—H bonds is an oxidative process or a redox process, correspondingly.

1.3.3.1 Redox Processes

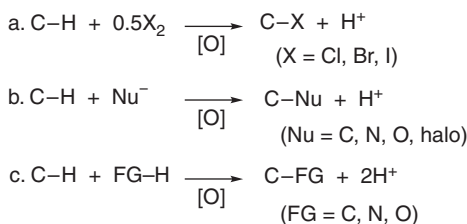
In a redox process, C—H bonds are oxidized to be C—C or C—heteroatom bonds just by the reaction partners as oxidants in the presence or absence of catalysts. Since the oxidation states of C—H bonds increase to form the products, those of the reaction partners should decrease at the end of these processes. The molecules or reagents with high redox potential are suitable to be used as oxidants or reactants in the oxidations of C—H bonds. For example, in the halogenation of alkyl and aryl C—H bonds, halogens including Cl_2 and Br_2 are often employed directly, but only half of the available halogen atoms can be transformed into the C—halogen bonds without external oxidants and the HCl or HBr are formed as by-products. In the cases of fluorination and iodination, the special F^+ and I^+ reagents at high oxidation states are normally used. Other electrophiles such as alkyl or aryl halides, alcohols, alkenes, alkynes, and carbenes can be used with or without catalysts to produce various C—C bonds effectively. It is the simplest and cleanest method in the preparation of alcohols and phenols, that is, to oxidize the alkyl and aryl C—H bonds by using dioxygen as reactant directly. Another clean way in the oxidation of C—H bonds is dehydrogenation in the absence of any external oxidants. However, it is normally carried out to produce alkenes from alkanes under harsh conditions, which is an endothermic process (Scheme 1.13).



Scheme 1.13 Redox processes.

1.3.3.2 Oxidative Processes

Compared with the redox process, an oxidative process in the oxidation of C-H bonds is to employ external oxidants to change nucleophilic reactants to electrophilic ones *in situ*, to make carbon radicals or carbon cations from C-H bonds to accept electrophiles, or to regenerate transition metal catalysts in the catalytic cycle, etc. For example, in the halogenation of C-H bonds, the external oxidants can be useful to enhance the ME or to extend the scope of reactants through the oxidation of halogen anions to halogens or even cations. A more important utilization of external oxidants is in the catalytic processes especially *via* C-H activation. In organometallic chemistry, C-Mⁿ⁺² bonds generated from C-H bonds and transition metal catalysts Mⁿ⁺² often undergo reductive elimination with various anionic ligands L or carbon groups to give C-halogen, C-O, C-N, or C-C bonds, and Mⁿ species; then, the Mⁿ may be reoxidized by the external oxidants to the catalysts Mⁿ⁺² for the next reaction cycle. Furthermore, it is possible that C-H bonds can couple with other C-H, O-H, or N-H bonds from hydrocarbons, alcohols, amines, or amides to afford the corresponding products in the presence of catalysts and external oxidants through an oxidative dehydrogenation, which is a favorably exothermic process. Apparently, if dioxygen from air is the terminal oxidant in the catalytic oxidation of C-H bonds currently by using some special oxidants such as peroxides, hypervalent iodine reagents, and metal oxidants to regenerate catalysts, the whole process especially the dehydrogenation is close to an ideal one with both high MEs and EEs (Scheme 1.14).

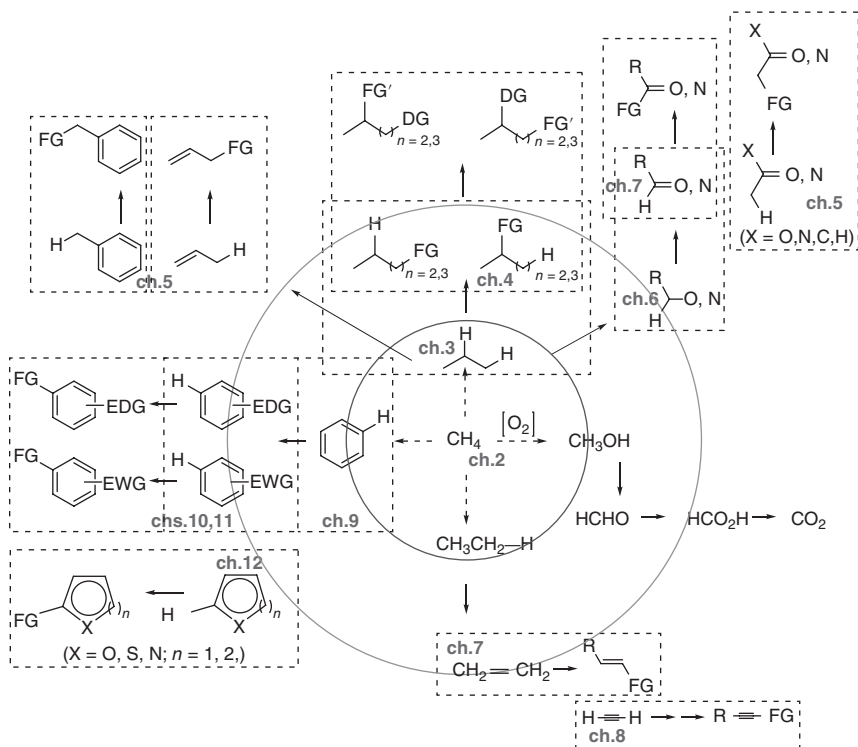


Scheme 1.14 Oxidative processes.

1.4 Concepts in This Book

In Chapters 2–12, the transformations of some C–H bonds to C–C, C–N, C–O, C–halogen bonds, and others will be described, including the reaction systems and mechanisms. For the inert C–H bonds of simple alkanes and arenes, it is emphasized that their catalytic oxidative reactions are carried out under mild conditions. For the non-inert or active C–H bonds, it is concerned that the ideal processes involve the common reaction partners, dioxygen as oxidant, not toxic solvents or additives, operation under normal conditions, and so on. Of course, the product yield and selectivity are always focused mainly for chemical synthesis.

As illustrated in Scheme 1.15, the description starts at methane, the simplest hydrocarbon compound, in Chapter 2. In theory, any important or complex organic compounds, especially the fundamental chemicals including ethylene, benzene, methanol, acetic acid, etc., can be prepared from it



Scheme 1.15 Oxidation of C–H bonds from CH₄ to various organic compounds.

by means of the oxidations of C—H bond. In Chapter 3, the simple alkyl $\text{sp}^3\text{C—H}$ bonds are discussed for the efficiency and selectivity of their oxidations. After a functional group, such as alcohol, carbonyl, imine, amide group, is formed in the hydrocarbon compound, the selective oxidation of the inert $\text{sp}^3\text{C—H}$ bonds at β , γ , or other far positions of the functional group is feasible in organometallic catalysis. It is called the oxidation of $\text{sp}^3\text{C—H}$ bonds assisted by directing groups in Chapter 4. Meanwhile, the reactivity of $\text{sp}^3\text{C—H}$ bonds adjacent to unsaturated groups or heteroatoms increases largely, and the oxidations of these active $\text{sp}^3\text{C—H}$ bonds are shown in Chapters 5 and 6, respectively. Subsequently, in Chapter 7, the $\text{sp}^2\text{C—H}$ bonds of alkenes and aldehydes are introduced. The alkenyl $\text{sp}^2\text{C—H}$ bonds and the carbonyl $\text{sp}^2\text{C—H}$ bonds are very different; the former ones are inert but the latter ones are not. In the oxidations of alkenyl $\text{sp}^2\text{C—H}$ bonds, transition-metal catalysts are used effectively to form C—C, C=O, and C—N bonds, such as in the Heck reaction, the Wacker process, and the aza-Wacker process. In contrast, since the spC—H bonds of alkynes and hydrogen cyanides are more acidic, their oxidations can be achieved in the presence of bases, even weak bases in the catalytic processes, as mentioned in Chapter 8. In Chapters 9–13, various aryl $\text{sp}^2\text{C—H}$ bonds from benzene, substituted benzenes, heteroarenes, and polyfluoroarenes are described in their oxidations. Since benzene is the typical aromatic compound, many methods have been developed in the functionalization of its phenyl $\text{sp}^2\text{C—H}$ bonds, including alkylation, alkenylation, arylation, carbonylation, hydroxylation, nitration, and halogenation, as described in Chapter 9. Similarly to those in alkyl $\text{sp}^3\text{C—H}$ bonds, the substituted functional groups not only change the reactivity and selectivity of aryl $\text{sp}^2\text{C—H}$ bonds on the phenyl rings but also play the assistance roles for transition metal catalysts to cause the oxidations happening at certain aryl $\text{sp}^2\text{C—H}$ bonds. These performances can be found in Chapters 10 and 11. Compared with the normal arenes, heteroarenes and polyfluoroarenes show different properties in the oxidations of their special C—H bonds, which are introduced in Chapter 12. Although the oxidative cross-coupling reaction of two inert C—H bonds is a very convenient, effective, and clean method to form new C—C bonds in chemical synthesis, it is still a big challenge to researchers. In Chapter 13, some developments related to the couplings of one simple aryl C—H bond with another inert C—H bond are shown and discussed.

In summary, the main concepts of this book are about the methodologies of oxidation in both the first functionalization of inert C—H bonds from hydrocarbons such as methane, simple alkanes, and arenes and the second functionalization of C—H bonds connecting to or assisted by other functional groups including heteroatoms, double bonds, and triple bonds.

References

- [1] Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215–221.
- [2] Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.
- [3] (a) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2185; (b) Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133–1135.
- [4] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440; (b) Sarmah, G.; Mondal, M.; Bora, U. *Appl. Organomet. Chem.* **2015**, *29*, 495–498.
- [5] (a) Helden, R. V.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1263–1273; (b) Mukhopadhyay, S.; Rothenberg, G.; Lando, G.; Agbaria, K.; Kazanci, M.; Sasson, Y. *Adv. Synth. Catal.* **2001**, *343*, 455–459.
- [6] Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*. CRC Press, Boca Raton, **2007**.
- [7] Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. *Chem. Eur. J.* **2014**, *20*, 12750–12753.
- [8] Perrin, D. D.; Dempsey, B.; Serjeant, E. P. Chapter 3: Methods of pK_a prediction; *pK_a Prediction for Organic Acids and Bases*. Springer, the Netherlands. **1981**, p. 21–26 (Evans pK_a Chart).
- [9] Xu, Z.; Xu, C. *Chin. J. Org. Chem.* **1987**, *1*, 56–59.
- [10] Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.
- [11] Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1119–1126.
- [12] Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352–354.
- [13] (a) Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491–6493; (b) Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarsiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203–219; (c) Vidal, V.; Théolier, A.; Thivolle-Cazat, J.; Basset, J.; Corker, J. *J. Am. Chem. Soc.* **1996**, *118*, 4595–4602; (d) Niccolai, G. P.; Basset, J. M. *Appl. Catal. A* **1996**, *146*, 145–156.
- [14] Cummins, C. C.; Baxter, S. M.; Wolczansk, P. T. *J. Am. Chem. Soc.* **1988**, *110*, 8731–8733.
- [15] (a) Sherry, A. E.; Wayland, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 1259–1261; (b) Wayland, B. B.; Ba, S.; Sherry, A. E. *J. Am. Chem. Soc.* **1991**, *113*, 5305–5311.
- [16] (a) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2–24; (b) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859–861; (c) Walling, C.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1963**, *85*, 2084–2090.
- [17] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904; (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724.
- [18] Olah, G. A.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 2726–2727.
- [19] Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5018–5022.

