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Green Oxidative

Synthesis of Alcohols and Phenols

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1.1 Introduction

Alcohol and phenol derivatives are among the most important and common organic chemicals used for industrial materials such as polymers and commodity chemicals, and are the core structures of many biologically active compounds, including pharmaceuticals, agrochemicals, and natural products. The development of synthetic methods for introducing hydroxyl groups into organic compounds is a fundamental task in organic chemistry. Due to the sustainable chemistry and environmentally friendly manufacturing techniques extensively demanded in society today, development of new synthetic methodologies and novel reaction conditions without compromising product selectivity, energy efficiency, and environmental safety has become the main theme of current chemical research. Over the past decades, numerous methods have been reported, the most important and straightforward strategy is the oxidation of various C–H, C–C, and C=C bonds to hydroxyl groups. In this review, we will focus on the latest developments adopting green oxidative strategies with aerobic (O₂ and air), hydrogen peroxide, enzymatic oxidation, and photocatalytic oxidation for synthesis of alcohol and phenol derivatives that have happened since 2008. Mechanistic studies of the novel transformations including the preparation and isolation of reaction intermediates will also be discussed. Our intention is to highlight here the interesting achievements in green oxidative synthesis of alcohols and phenols over the last 10 years. There may be important literature reports that have escaped our attention, for which we extend our sincere apologies.

1.2 C–H Hydroxylation via Aerobic Oxidant

C–H hydroxylation is considered as one of the most straightforward approaches to preparing alcohols and phenols. During this process, various oxidants, such as inorganic salt, TBHP, Phl(OAc)₂, K₂S₄O₈, and IBX, are used. For green and sustainable chemistry, molecular oxygen is considered as an ideal oxidant due to its natural, inexpensive, and environmentally friendly characters, and therefore offers attractive academic and industrial prospects. In addition, it exhibits a highly atom-efficient oxidant per weight.
In this context, various significant progress in catalytic C—H hydroxylation via aerobic oxidant has been achieved over the past 10 years, especially in transition metal- (such as palladium, copper, and cobalt) catalyzed oxidation reactions employing molecular oxygen as the sole oxidant. In the next section, we will illustrate the recent advances over the last 10 years in C—H hydroxylation using molecular oxygen or air as an oxidant.

1.2.1 Synthesis of Phenols by C\((sp^2)\)-H Hydroxylation

An intriguing example of employing transition metals to catalyze ortho-hydroxylation involving strong coordination of the carbonyl group was reported by Yu and co-workers in 2009 [1]. Notably, hydroxylation proceeded using 1 atm of air as the sole oxidant under nonacidic conditions in high yields with variously substituted benzoic acids such as trifluoromethyl, acetyl, cyanide, and nitro. Preliminary mechanistic investigations strongly supported the proposal that the aryl-Pd species could be directly oxygenated by molecular O\(_2\) (Scheme 1.1).

In 2012, Lei’s group reported a copper-catalyzed “oxygenase-type” oxidation of arenes and heteroarenes at room temperature by the oxidation of O\(_2\) from air (1 atm). The authors proposed a mechanism of a novel combination of single-electron transfer (SET) initiation and organometallic catalytic cycle for this copper-catalyzed aerobic oxidation reaction (Scheme 1.2) [2].

**Scheme 1.1** Pd(II)-catalyzed hydroxylation of arenes with 1 atm of O\(_2\) or air.

**Scheme 1.2** Copper-catalyzed oxidation of arenes and heteroarenes.
In 2013, Jiao’s group reported a novel PdCl₂ and N-hydroxyphthalimide co-catalyzed direct C(sp²)-H hydroxylation of 2-phenyl-pyridines. Molecular oxygen was employed as a reagent and the sole oxidant under neutral conditions without the addition of any other stoichiometric oxidant and base. This transformation provided a green and practical method to synthesize a variety of substituted 2-(pyridin-2-yl)phenols. Its synthetic use has been exemplified in further applications in the preparation of a series of biologically active molecules from 2-(pyridin-2-yl)phenols. Based on extensive mechanistic studies, a novel combination of transition-metal-catalyzed C–H activation and a NHPI-initiated radical process was proposed as the mechanism (Scheme 1.3) [3].

Scheme 1.3 PdCl₂ and N-hydroxyphthalimide co-catalyzed C(sp²) by dioxygen activation.
In 2015, Yu and co-workers reported Cu(II)-mediated ortho-C–H hydroxylation using a removable directing group. The reaction tolerates a wide range of functional groups, and the use of O$_2$ as the oxidant presents a significant advantage. The practicality of this new methodology has been proven by gram-scale synthesis of 2-hydroxybenzamide [4]. Very recently, the author developed a similar reaction to generate the corresponding phenols via a weakly coordinating monodentate directing group with the assistance of an external oxazoline ligand (Scheme 1.4) [5].

In 2016, Guin and co-workers reported a Pd-catalyzed direct C–H hydroxylation of 2-arylpyridines. This method offered easy access to a broad range of substituted 2-(pyridin-2-yl)phenols in good isolated yields. The $^{18}$O labeling experiment proved that the oxygen atom of the hydroxyl group originated from molecular oxygen, and the use of molecular oxygen as a sole oxidant makes the process environmentally attractive. A possible reaction pathway is depicted in Scheme 1.5. The catalytic cycle begins with the chelation-assisted C–H activation through ortho palladation of 1a with a palladium catalyst to form the complex E. Meanwhile, aerobic oxidation of n-butyraldehyde to n-butyric acid produces an active acyl peroxy-radical intermediate B. The oxidative addition of the radical B to Pd$^{II}$-complex E may lead to a transient peroxo-palladium species that decomposes to the most likely Pd$^{IV}$-intermediate, F. Finally, reductive elimination of F furnishes the hydroxylated product 2a and regenerates the catalyst [6].

Due to multicopper proteins that bind and activate O$_2$ exhibiting highly selective oxidative transformations and playing important roles in a number of biological processes, the multicopper(II) complex has received much interest from researchers in chemistry fields that range from coordination chemistry to synthetic methods. Arising from these studies, three basic Cu$_2$O$_2$ core structures have been widely described [7]. Recently, Ribas and co-workers systematically studied O$_2$ activation and selective phenolate ortho-hydroxylation by an unsymmetric di-copper $\mu$-$\eta^1$: $\eta^1$-peroxido complex, which represented a novel di-copper complex based on a heptadentate ligand that gave rise to an asymmetric N$_3$Cu$^{II}$N$_4$Cu$^{II}$($\mu$-$\eta^1$: $\eta^1$-O$_2$) core and hitherto exhibited reactivity patterns not observed for symmetric analogs [8]. The combined experimental and computational evidence indicated that the ortho-hydroxylation of a phenolate by a Cu$_2$O$_2$ species can occur by adjacent binding of phenolate and O$_2$ at a common N$_3$Cu site without requiring the peroxide to be side-on bound, thus offering a conceptually new understanding of O$_2$ activation at di-copper sites (Scheme 1.6) [9].
Scheme 1.5 Pd-catalyzed direct C–H hydroxylation of 2-arylpyridines.

Scheme 1.6 O₂ activation and selective phenolate ortho-hydroxylation by an unsymmetric di-copper.
1.2.2 Synthesis of Alcohol by C(sp)$^3$-H Hydroxylation

Inspired by discovery and mechanism evaluation of previously unknown Pd-(III)-Pd(III) complexes [10], Ritter and co-workers developed a chemo- and regioselective α-hydroxylation reaction of carbonyl compounds by oxygen transfer from O$_2$, catalyzed by a dinuclear Pd(II) complex in 2011 (Scheme 1.7) [11]. The hydroxylation reaction was regioselective and compatible with other electrophilic and nucleophilic oxygen transfer reagents such as double bonds and sulfides. A broad range of carbonyl compounds were smoothly transformed to tertiary alcohols with good yields under very mild conditions. It is interesting to note that the dinuclear Pd(II) complex functions as an oxygen transfer catalyst, reminiscent of an oxygenase. On the basis of an oxygen uptake experiment, both oxygen atoms from O$_2$ were incorporated into the product. Hence, this oxidation proceeded without generation of stoichiometric amounts of waste except for solvent. This reaction represents the first example of the catalytic hydroxylation of C–H bonds with a bimetallic palladium(III) catalysis.

In 2012, Tan and co-workers described pentanidium-catalyzed α-hydroxylation of 3-substituted-2-oxindoles using molecular oxygen with good yields and enantioselectivities (Scheme 1.8) [12]. Several 3-hydroxyl-2-oxindoles with excellent enantioselectivities (85–98% ee) were obtained. The reaction was demonstrated to consist of two steps: an enantioselective formation of hydroperoxide oxindole and a kinetic resolution of the hydroperoxide oxindole via reduction with enolates generated from the oxindoles. This reaction does not require an additional reductant such as triethyl phosphite, which was typically added to reduce the peroxide intermediate. This chiral phase-transfer catalysis operated with a high degree of efficiency and selectivity that made it a valuable tool for constructing highly enantiopure 3-hydroxyl-2-oxindoles in organic synthesis.

\[
\text{R}^1\text{O} + \text{O} + \text{R}^2\text{R}^3 \xrightarrow{1 \text{ atm O}_2, \text{ 5 mol} \% \text{ 1, 30 mol} \% \text{ 2}} \text{THF 0-6 °C, 12-24h} \quad \text{R}^1\text{OH} + \text{R}^2\text{R}^3
\]

\[
\text{Pd}^2\text{hpp}_4 (1) \quad \text{hpph(2) (1) (2)}
\]

Scheme 1.7 Dinuclear palladium catalyst for α-hydroxylation of carbonyls with O$_2$. 

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5, 96%  
6, 94%  
7, kjellmanianone, 97%$^b$  
5, 90%$^b$  
5, 68%$^c$  
5, 77%  
5, 71%  
5, 70%  
5, 70%  
5, 70%  
5, 70%  

$^a$A total of 2.5 mol% of 1 was used. $^b$No 2 was added. $^c$A total of 10 mol% of 1, and 60 mol% of 2 were used.
In 2015, Gu and co-workers reported efficient ionic liquid ([bmIm]OH)-catalyzed α-hydroxylation of phosphonates using O₂ as the oxygen source (Scheme 1.9) [13]. The procedure was environmentally friendly, avoiding hazardous organic solvents and toxic catalysts. This method provided a novel and convenient methodology for the construction of quaternary α-hydroxy phosphonates.
A significant number of transition-metal-catalyzed autoxidation and aerobic oxidative hydroxylation reactions have been proved to be environmentally friendly strategies for the preparation of various phenols and alcohols. However, main group metal-catalyzed C─H hydroxylation has been rarely reported. Recently, Jiao and co-workers described a transition-metal-free Cs₂CO₃-catalyzed α-hydroxylation of carbonyl compounds with O₂ as the oxygen source to give tertiary α-hydroxycarbonyl compounds, which are highly valued chemicals and widely used in the chemical and pharmaceutical industries (Scheme 1.10) [14]. The simple conditions and the use of molecular oxygen as both the oxidant and the oxygen source make this protocol very environmentally friendly and practical. This transformation is highly efficient and selective for tertiary C(sp³)─H bond cleavage. Remarkably, its synthetic utilities have been exemplified in further late-stage modification of several drug substrates such as ketoprofen, ibuprofen, and naproxen. Shortly after this report, the authors applied a similar CsOH-catalyzed aerobic oxidation to efficiently access various p-quinols from multi-alkyl phenols with moderate to good yields [15].

In 2015, Zhao and co-workers demonstrated an efficient and enantioselective α-hydroxylation of acyclic as well as cyclic ketones using molecular oxygen (Scheme 1.11) [16]. Synthetically valuable acyclic ketones could be hydroxylated in modest to good yields with good enantioselectivities, whereas a wide range of cyclic α-hydroxy ketones could be obtained with excellent yields and enantiopurity.
In 2016, Schoenebeck and co-workers developed a selective aerobic hydroxylation of tertiary α-C—H bonds in ketones without C—C cleavage (Scheme 1.12) [17]. They found that α-alkyl-substituted ketones selectively generated α-hydroxy ketones under Cu$_2$O/DMSO/hppH conditions, and the hydroxylated products were formed under these conditions, tolerating different ring sizes, heteroatoms, and substituents at the aromatic ring. Furthermore, the experimental and computational studies uncovered the role of hppH [1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine] to act not only as a base in the transformation but also as a reductant of the peroxide to the corresponding α-hydroxy ketone.

In 2016, Kanai and co-workers reported that a radical N-oxyl directing activator promoted the aerobic oxygenation of benzylic, propargylic, tertiary, and unactivated acyclic methylene C(sp$^3$)—H bonds in aliphatic alcohols with γ- (or δ-) selectivity under mild conditions (room temperature to 50℃) (Scheme 1.13) [5]. Molecular oxygen was used as the stoichiometric oxidant, and the reactions proceeded regioselectively at the γ- (and δ-) position(s), whereas the α, β, and other positions beyond the δ position remained intact. This regioselectivity can be explained in terms of the intramolecular accessibility of the reactive N-oxyl radical site, despite the low regioselectivity between γ- and δ-positions in electronically nonbiased substrates is a current limitation that
must be solved in future studies. Preliminary structural tuning of the DA led to an alteration of the regioselectivity, providing a selective ultraremote aerobic C–H oxygenation.

Following the pioneering report by Schönecker and co-workers on the Cu-mediated C–H oxidation for the synthesis of 12β-hydroxy steroids [18], Baran and co-workers reinvestigated this fascinating Cu-mediated Schönecker oxidation; the only practical solution to the challenge of site-specific steroidal C12 functionalization was dramatically improved (Scheme 1.14) [19]. The new imine directing group and alternative reducing agent rendered this an operationally simple reaction that was no longer limited to a 50% maximum yield with long reaction times. Various types of ketone-derived substrates were prepared with acceptably isolated yields and short reaction time under the derived procedure.

A new mechanistic picture was proposed based on a series of NMR studies. Following initial Cu binding to give 16, additional uncoordinated Cu(I) and O2 could complex to form the imine complex 17, a [Cu2O2] species. The active Cu-species was likely the bis(μ-oxo)di-copper(III) complex 18, which could also be the mixed bis(μ-oxo)Cu(II)/Cu(III) complex. Oxidation of the proximal C–H bond then presumably occurred through an oxygen-rebound mechanism. The resulting Cu(II) that was not directly ligated to the substrate in the [Cu2O2] complex 19 was then reduced by ascorbate to Cu(I) and released, allowing for further substrate engagement. In 2017, Holthausen and co-workers reported a detailed mechanistic DFT study of Schönecker’s reaction [20].

### 1.2.3 Oxidative Aromatization for Synthesis of Phenols

In 2011, Stahl and co-workers developed a palladium(II) catalyst system, incorporating an unconventional ortho-dimethylaniloinopyridine ligand, for the conversion of substituted cyclohexanones to the corresponding phenols (Scheme 1.15) [21]. This approach proved to be effective in the preparation of a number of substituted phenol derivatives. These reactions achieved high conversions and product yields, and the catalyst tolerated useful substrate functional groups, including aromatic and heteroatom substituents. This reactivity demonstrates a versatile and efficient strategy for the synthesis of substituted aromatic molecules with fundamentally different selectivity constraints from numerous known synthetic methods that rely on substitution of a pre-existing aromatic ring.
In palladium-catalyzed aerobic oxidation reactions, this transformation involves initial dehydrogenation of cyclohexanones via sequential Pd-mediated C–H activation and β-hydride elimination steps, followed by tautomerization of the resulting dienone product. This strategy is appealing because Pd(II)–hydride intermediates formed in this mechanism could be oxidized by molecular oxygen, thereby enabling the overall process to be catalytic in Pd with water as the sole by-product (Scheme 1.16).

In 2013, Stahl’s group disclosed that kinetic and mechanistic studies of these reactions revealed the key role of the dimethylsulfoxide (DMSO) ligand in controlling this chemoselectivity [22]. DMSO had minimal kinetic influence on the rate of Pd(TFA)₂-catalyzed dehydrogenation of cyclohexanone to cyclohexenone, while it strongly inhibited the second dehydrogenation step, the conversion of cyclohexenone to phenol. These contrasting kinetic effects of DMSO provided the basis for chemoselective formation of cyclohexenones.
Scheme 1.15 Palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Phenol</th>
<th>%Yield</th>
<th>Entry</th>
<th>Substrate</th>
<th>Phenol</th>
<th>%Yield</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 70 | 4 | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{Ph}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 93 |
| 2     | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 76 | 5 | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{Ph}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 73 |
| 3     | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 79 | 6 | \[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{Ph}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph}
\end{array}
\] | 95 |

Scheme 1.16 Catalytic mechanism whereby cyclohexanone dehydrogenation can be achieved with O₂ as the terminal oxidant.
1.2 C—H Hydroxylation via Aerobic Oxidant

In the synthesis of phenol, various oxidative aromatizations of cyclohexenones are straightforward procedures for the preparation of multi-substituted phenol derivatives. Following this strategy, Nishina and co-workers developed a catalytic oxidative aromatization of 2-cyclohexen-1-ones for synthesis of phenol derivatives in the presence of a catalytic amount of copper salt and aqueous HBr under molecular oxygen in 2013 (Scheme 1.17) [23]. Various mono-, di-, and trisubstituted phenols with substituents at the desired positions could be synthesized under cheap and simple conditions. The authors proposed that copper(II) species involved generation of molecular bromine along with reduced copper(I) species, followed by bromination and dehydrobromination of 2-cyclohexen-1-one to give the desired phenol. The reduced copper(I) would be oxidized by molecular oxygen and HBr to regenerate the copper(II) species.

1.2.4 Oxygenation of Alkenes for Synthesis of Alcohols

Following the pioneering report by Feldman and Parvez on the thiol-olefin co-oxygenation reaction, Naito and co-workers developed a domino effect of reactions of vinylcyclopropyl oxime ethers involving thyl radical addition, ring-opening, and hydroxylation reactions to form highly functionalized ε-thio-δ,γ-unsaturated-β-hydroxy oxime ethers in 2009, which are versatile intermediates in organic synthesis and play an important role in biological and chemical processes (Scheme 1.18) [24]. Importantly, this multi-component reaction provided a single and efficient operation to form the allyl sulfide containing 1,3-amino alcohol compounds.

On the other hand, various saturated-β-hydroxy oxime ethers have been prepared by an intermolecular hydroxylation of α,β-unsaturated imines (Scheme 1.19) [25]. This reaction proceeds via two key transitional steps such as Et₃B-mediated regioselective alkyl radical addition and subsequent hydroxylation with molecular oxygen. This approach is characterized by mild conditions, is straightforward, and allows for the efficient and concomitant construction of a C—C bond and a C—O bond. In the proposed
reaction pathway, the first step involved regioselective alkyl radical addition assisting Et₃B for trapping of the enaminyl radical. The borylenamine was followed the oxidation by molecular oxygen to generate the desired alcohol.

In 2011, Taniguchi and co-workers reported a Fe-catalyzed oxidative arylation of alkenes by oxygen-mediated formation of aryl radicals from arylhydrazines (Scheme 1.20) [26]. Both peroxides and alcohols were smoothly obtained in satisfactory yields from a simple alkene in the presence of a catalytic amount of potassium ferrocyanide.
1.2 C–H Hydroxylation via Aerobic Oxidant

This reaction showed excellently reactivity, regioselectivity, and good functional-group tolerance. Due to the involvement of environmentally friendly and inexpensive reagents (K₄[Fe(CN)₆]·3H₂O, oxygen gas, and water), this provided a mild and economical approach for the synthesis of peroxides and alcohols through C–C bond formation.

In 2013, Jiao and co-workers developed a novel highly chemoselective coupling and oxygenation of alkenes for the direct synthesis of alcohols (Scheme 1.21) [27]. Various 1,2-diarylethanols were obtained in moderate to good yields from the corresponding aryl hydrazines and substituted styrenes. Remarkably, molecular oxygen not only participated
as an oxidant, but also underwent dioxygen activation through a radical process. The proposed mechanism for this transformation involved initial dehydrogenation of hydrazine via molecular oxygen and iodine to form phenyl radical \(8\) and a large amount of hydroperoxyl radical (HOO) with the release of \(N_2\) in the presence of base, followed by the addition of alkene and molecular oxygen to generate the benzyl peroxy radical \(10\), which captured a H atom from the strong H-donor \(6\) to provide hydroperoxide \(12\), along with the formation of radical intermediate \(7\) to complete the chain propagation step. Subsequently, the hydroxylation product \(5a\) was generated by hydroperoxide \(12\) through the Landolt reaction with the regeneration of iodine.

In 2014, Taniguchi’s group reported a unique 1,4-hydroxylation reaction of aliphatic alkenes by iron-catalyzed aerobic hydration and C\(^{sp^3}\)-H hydroxylation (Scheme 1.22) [28]. Notably, this reaction enabled oxidation of all types of C\(^{sp^3}\)─H bonds (methyl/primary,
methylene/secondary, and tertiary carbon centers) and allowed efficient generation of various 1,4-diols from simple alkenes using nontoxic and inexpensive reagents under mild conditions. The catalysis systems consisted of a user-friendly iron phthalocyanine complex, sodium borohydride. Molecular oxygen was the source for the two oxygen atoms of the 1,4-diols. This transformation of simple molecules into functionalized compounds was realized with a convenient and common reaction system. Based on their experiments, they proposed that a putative iron(III) hydride complex A, which was formed from iron phtholocyanine and sodium borohydride in the presence of oxygen, followed by the oxidation of molecular oxygen to initiate tertiary-carbon-centered radical B and iron peroxide complex C. Subsequently, highly reactive alkoxy radical D was able to undergo a [1,5]hydrogen shift to provide alkyl radical intermediate E, which was transformed into the resulting 1,4-diol through a similar pathway as the formation of complex C from alkyl radical B.

In 2015, Lei’s group developed a selective radical dioxygenation of alkenes using hydroxamic acid and O₂, and cobalt was used as the catalyst without assistance from any additional ligands or bases (Scheme 1.23) [29]. Various α-oxo-tertiary alcohols were achieved from 1,1-disubstituted alkenes with good yields under mild conditions.

In 2015, Li and co-workers developed a general and practical method for hydroxy-sulfenylation of alkenes through an aerobic copper catalysis (Scheme 1.24) [30]. This method presented a selective and efficient synthesis of β-hydroxysulfides bearing

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**Scheme 1.23** Cobalt-catalyzed radical dioxygenation of 1,1-disubstituted alkenes.

**Scheme 1.24** Copper-catalyzed hydroxy-sulfenylation of alkenes.
electron-withdrawing groups, and a broad range of alkenes were applied smoothly for
the hydroxysulfenylation under optimized conditions, including α,β-unsaturated esters,
amides and ketone, styrenes, and the conjugated diene.

In 2010, Taniguchi and co-workers reported the Fe(III)-catalyzed oxidative addition of
alkoxycarbonyl radicals to alkenes in air to give β-hydroxylesters (Scheme 1.25) [31].
This approach represents an environmentally friendly reaction, which employed the
use of a cheap and nontoxic iron catalyst, readily available carbazate precursors, and an
oxygen molecule green oxidant. Based on the knowledge that radical species could be
generated from hydrazine compounds through the oxidative formation of diazenes, the
alkoxycarbonyl radical is likely to be generated through a similar diazene pathway.

In 2015, Jiao and co-workers described the synthesis of β-azido alcohols through
an efficient Mn-catalyzed aerobic oxidative hydroxyazidation of olefins at room tem-
perature (Scheme 1.26). This approach showed broad substrate scope, inexpensive Mn

![Scheme 1.25 Iron-catalyzed oxidative addition of alkoxy carbonyl radicals to alkenes with carbazates and air.]

![Scheme 1.26 Mn-catalyzed aerobic oxidative hydroxyazidation of olefins.]
1.3 C–H Hydroxylation via Hydrogen Peroxide

1.3.1 Synthesis of Phenols by C(sp²)-H Hydroxylation

In 2009, Rybak-Akimova and co-workers described the regioselective hydroxylation of aromatic acids with hydrogen peroxide in the presence of iron(II) complexes with tetradeutate aminopyridine ligands (Scheme 1.29) [34]. The hydroxylation of the aromatic ring occurred exclusively in the vicinity of the carboxylate functional group.
Scheme 1.28  Aerobic acetoxyhydroxylation of alkenes co-catalyzed by organic nitrite and palladium.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Position</th>
<th>Yield of hydroxylated product [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>2-</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>3-</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>4-</td>
<td>22</td>
</tr>
<tr>
<td>Cl</td>
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<td>98</td>
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<td></td>
<td>4-</td>
<td>60</td>
</tr>
<tr>
<td>Cl</td>
<td>2-</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>3-</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>4-</td>
<td>68</td>
</tr>
</tbody>
</table>

Scheme 1.29  Iron-promoted ortho- and/or ipso-hydroxylation of benzoic acids with H₂O₂.
ortho-hydroxylation afforded salicylates, whereas 2- and, to a lesser extent, 4-substituted substrates tended to undergo ipso-hydroxylation through decarboxylation yielding phenolates.

As a continuous study of C—H hydroxylation, in 2012, Mizuno’s group reported a divanadium-substituted phosphotungstate, \([\gamma-PW_{10}O_{38}V_2(m-OH)_2]^{3-}\) catalyzed oxidation system to direct hydroxylation of various structurally diverse arenes to phenols with H\(_2\)O\(_2\) under mild conditions (Scheme 1.30) [35]. This study provided the first example of a synthetic catalyst that could chemoselectively hydroxylate the aromatic ring C\((sp^2)\)—H bonds without causing the oxidation of the more reactive aromatic side-chain C\((sp^3)\)–H bonds. With an excess of substrate relative to H\(_2\)O\(_2\), the reaction exhibited high H\(_2\)O\(_2\) efficiency.

In 2012, Zhao’s group reported benzene hydroxylation catalyzed by vanadyl(IV) complex grafted PMOs using hydrogen peroxide as the terminal oxidant (Scheme 1.31). The PMO catalyst could be recovered and reused [36]. Under the best conditions, the benzene conversion could reach 27.4 with 100% selectivity to form phenol. A reversible V\(^{4+}/V^{5+}\) redox mechanism was proposed for the hydroxylation of benzene to phenol as depicted in Scheme 1.17.

In 2014, Kühn’s group reported the hydroxylation of benzene and toluene by an Fe\(^{II}\) NHC complex using aqueous H\(_2\)O\(_2\) as the oxidant (Scheme 1.32) [37]. The authors suspected that the reaction underwent an electrophilic mechanism by an Fe=O species. Under the reported conditions, benzene was hydroxylated with a high selectivity to phenol and toluene was hydroxylated to cresols with a good selectivity for the ortho and para positions. However, this reaction showed low H\(_2\)O\(_2\) efficiency with less than 13% total conversion, even in the presence of 10 equiv. H\(_2\)O\(_2\).

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**Scheme 1.30** Hydroxylation of arenes with H\(_2\)O\(_2\) catalyzed by a divanadium-substituted phosphotungstate.

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**Scheme 1.31** Hydroxylation of benzene to phenol with H\(_2\)O\(_2\) by vanadyl(IV) complex grafted PMOs.
In 2015, Itoh’s group reported a benzene hydroxylation reaction employing nickel complexes supported by pyridylalkylamine ligands as the catalysts and H₂O₂ as the oxidant under mild conditions (Scheme 1.33) [38]. The maximum yield of phenol was 21% based on benzene without the formation of quinone or diphenol. However, high catalyst loading (10 mol%) and a large excess of H₂O₂ (500 equiv.) was employed. This catalyst could also be used for the hydroxylation of toluene, in which cresol was obtained as the major product with 90% ortho and para selectivity in the presence of 1 mol% catalyst and 5 equiv. H₂O₂.

In 2016, Fukuzumi reported the benzene hydroxylation with hydrogen peroxide in the presence of catalytic amounts of Cu(II) complexes ([Cu(tmpa)]²⁺) in acetone to yield phenol at room temperature. The author also demonstrated the incorporation of the Cu(II) into mesoporous silica–alumina (Al-MCM-41) to make it a heterogeneous catalyst.

1.3.2 Synthesis of Alcohol by C(sp³)-H Hydroxylation

As a great master of chemical synthesis, nature has devised many elegant metalloenzymes such as the heme-containing cytochrome P450 and the nonheme methane monooxygenase to enable biologically essential transformations under mild conditions.
Iron-containing cytochrome P450 selectively hydroxylates the long aliphatic side chain of cholesterol and thus plays an important role in the biosynthesis of the female hormone progesterone. Inspired by the extremely fine craftsmanship of enzyme active sites, continuous efforts have been devoted to the development of nonheme iron catalysts mimicking enzyme activities for selective C–H hydroxylations.

Based on the principles in oxidation catalysis with heme complexes and the seminal work reported by White, Costas’ group in 2009 designed a chemically robust nonheme iron catalyst for the alkane hydroxylation using H$_2$O$_2$ as the oxidant (Scheme 1.34) [39]. The catalyst was proved to be highly efficient; by using 1 mol% of this iron complex, stereospecific, and site-predictable hydroxylation of alkanes was achieved in synthetically useful yields. The catalytic hydroxylation preferentially occurred at tertiary C–H bonds to give the 3° alcohol stereoselectively. The authors observed the formation of monomeric [LFe$_{III}$(OR)(CF$_3$SO$_3$)]$^+$ (OR = OH, OAc) species by mass spectroscopy, thus it was presumed that the formation of high-valent iron–oxo species was responsible for catalytic activity.

A small-molecule, nonheme iron hydroxylation catalyst possessing mixed hydroxylase/desaturase activity with carboxylic acid containing aliphatic substrates by using H$_2$O$_2$ as the terminal oxidant was reported by White’s group in 2011 (Scheme 1.35) [40].

Scheme 1.34 Iron(II) catalyzed stereospecific C–H oxidation with H$_2$O$_2$.

Scheme 1.35 Aliphatic C–H hydroxylations with H$_2$O$_2$ catalyzed by non-heme iron catalyst.
Under standard Fe(PDP)/H₂O₂ conditions, besides the anticipated butyrolactone products, unexpected hydroxylactone products derived from in situ generated olefins by the Fe(PDP) catalyst via desaturation were observed across a series of carboxylic acid substrates. Through the rearrangement of a taxane-based radical trap under Fe(PDP) oxidation, the authors provided the first direct evidence for the formation of a substrate radical using this class of stereoretentive hydroxylation catalysts.

Hitomi and co-workers demonstrated the first example of an iron(III)–monoamidate complex catalyzed efficient aliphatic C–H bond hydroxylation with H₂O₂ in 2012 (Scheme 1.36) [41]. The experimental result suggests that the reaction undergoes an iron(V) oxo mechanism. The catalytic system exhibited a high stereoretention rate and good regioselectivity. Previous examples mostly occupied acetic acid to increase both the selectivity and the efficiency. The acetic acid was supposed to facilitate the heterolytic scission of the O–O bond of Fe³⁺OOH species to form iron(V) oxo species, while in this case acetic acid was not needed.

In 2013, White’s group reported a nonheme iron catalyst catalyzed aliphatic C–H oxidation over a range of topologically diverse substrates by hydrogen peroxide (Scheme 1.37) [42]. In most cases, the catalytic oxidation system gave a ketone in a good yield and a small amount of tertiary C–H bonded oxidation products (alcohol). However, the reaction could stop at the alcohol stage for some substrates.

In 2010, Mizuno’s group reported the hydroxylation of alkanes through a bis(m-hydroxo) divanadium-substituted phosphotungstate/H₂O₂ system in high yields [43]. The bulky polyoxometalate framework of the catalyst showed an unusual selectivity to oxidize secondary rather than the weaker tertiary C–H bonds to give 2° alcohols in most cases. The oxidation system demonstrated mild conditions and good H₂O₂ efficiency ranging from 56 to 98%. Based on experimental observation, the authors proposed a catalytic cycle as shown in Scheme 1.38. First, the catalyst reacts with H₂O₂ to

![Scheme 1.36 Iron(III)–monoamidate complex catalyzed alkane C–H bonds hydroxylation with H₂O₂.](image)

![Scheme 1.37 Catalyst-controlled aliphatic C–H oxidations with H₂O₂.](image)
generate $[\gamma$-PV$_2$W$_{10}$O$_{38}$(OH)(OOH)]^{3-}$, which then goes through the dehydration to form the active oxidant. Eventually, that oxidant selectively oxidizes the alkane C–H bonds to furnish the hydroxylation product and the regenerated catalyst for the next turnover.

In addition to iron catalysts, copper and copper complexes have also been continuously studied for catalyzing the oxidation of alkanes by H$_2$O$_2$. In 2013, Pérez and co-workers reported that mononuclear Cu complexes bearing a trispyrazolylborate ligand could catalyze the oxidation of alkyl C–H bonds providing alcohols and/or ketones as the major products with small amounts of the alkenes in moderate yields (Scheme 1.39) [44]. Based on experimental data, the authors excluded the hydroxyl radical pathway. DFT studies supported the viability of the oxidation process through a copper-oxo active species.

In 2016, Siegler’s group reported that Cu(I) salts, combined with commercially available ligand systems and H$_2$O$_2$, could catalyze the oxidation of C–H bonds with high efficiency (Scheme 1.40) [45]. This approach can be successfully applied to the oxidation of cyclohexane to produce cyclohexyl hydroperoxide as the main product and a 1:1 ratio of cyclohexanol and cyclohexanone at a roughly 50–60% total yield. Retention of the configuration was not observed in the tertiary C–H oxidation of cis-1,2-dimethylcyclohexane under these conditions, which excludes the mechanism of oxygen transfer from high-valent metal–oxo species. Combining other experimental evidence, the authors proposed that the mechanism involved C- and O-centered radical formation.

Scheme 1.38 Stereo- and regioselective hydroxylation of alkanes catalyzed by a bulky polyoxometalate.
Perfluorinated oxaziridines and dioxiranes have been known to be able to convert select alkanes to alcohols. However, the difficulties associated with the preparation or the inconvenience in using dilute solutions of these compounds prepared in advance have limited their use. Efforts have been made in the development of an analogous catalytic hydroxylation by using corresponding imine or ketone-based compounds to generate perfluorinated oxaziridines or dioxiranes in situ under oxidative conditions. As a result of continuous efforts seeking imine-based catalysts with application potential, in 2009, Du Bois' group described the catalytic reaction processes for selective C—H bond hydroxylation by using a benzoxathiazine catalyst and aqueous H₂O₂ (Scheme 1.41) [46]. The active oxidant was highly selective for tertiary C—H bonds over secondary C—H bonds.

In 2014, Hilinski's group introduced the first example of ketone-catalyzed oxidation of aliphatic C—H bonds to furnish the hydroxylation of tertiary C—H bonds using hydrogen peroxide as the terminal oxidant (Scheme 1.42) [47]. This catalytic hydroxylation reaction showed high selectivity for tertiary C—H bonds in trans-decalin and other
substrates. In contrast, the oxidation of trans-decalin by stoichiometric amount of TFDO gave a 2:1 ratio of 3°:2° oxidation products. The selectivity difference with traditional dioxirane oxidation may represent the advantage of this approach.

In 2016, Hilinski’s group reported an example of aliphatic C─H hydroxylation by an iminium salt catalysis at room temperature using hydrogen peroxide as the terminal oxidant (Scheme 1.43) [48]. The reaction shares a similar catalytic mechanism with the previously mentioned benzoxathiazine catalysts.

In 2017, Takashi Ooi and co-workers reported an asymmetric α-hydroxylation of 3-substituted oxindoles under the catalysis of chiral 1,2,3-triazolium salts using
aqueous hydrogen peroxide as a terminal oxidant (Scheme 1.44) [49]. The combination of trichloroacetonitrile and H₂O₂ was crucial for the smooth transformation.

**1.4 Photocatalytic Oxidation for Synthesis of Alcohols and Phenols**

In 2010, Matsumura and co-workers proved that benzene could be oxidized by TiO₂ with UV light and oxygen to give the intermediate phenol (Scheme 1.45). However, the phenol was easily over-oxidized to carbon dioxide and water [50, 51]. In 2013, Sano’s group further optimized the reaction conditions [52]. The layered silicate could be an excellent partner of a TiO₂ photocatalyst for efficient and selective green fine-chemical synthesis. The titanosilicate zeolites, a coexisting adsorbent composed of a silica framework and highly dispersed TiO₂, can promptly and selectively absorb phenol from a mixture solution, and efficiently prevent the over-oxidation of the phenol. Interestingly, in 2010 Ogawa’s group found a benzene ring could be transformed into phenol with Au-nanoparticle-supported layered titanate as a visible-light-induced photocatalyst. The Au-nanoparticle selectively first oxidized benzene to phenol, thus obtaining a 62% yield and 96% selectivity for phenol formation under UV irradiation.

In 2015, Zhao and co-workers developed a visible-light-induced method for the hydroxytrifluoroethylation of styrenes under a molecular oxygen atmosphere in the

**Scheme 1.45** Oxidation of Benzene on TiO₂ Photocatalysts in Aqueous Solutions.
1.4 Photocatalytic Oxidation for Synthesis of Alcohols and Phenols

The presence of water (Scheme 1.46). The hydroxyl and trifluoroethyl groups were efficiently installed in one step, which is difficult to obtain by the conventional strategy [53]. The reaction was very compatible with various styrenes possessing electron-donating and halogen substituents at the aryl rings and also with substituents at the β-positions of double bonds. Importantly, the oxygen atom in the product originates from molecular oxygen in this radical reaction.

In 2016, Fu and co-workers illustrated a visible-light photoredox borylation of aryl halides and subsequent aerobic oxidative hydroxylation at room temperature (Scheme 1.47) [54]. The methods show some advantages including simple equipment, mild conditions, easy operation, and wide substrate scope. In this reaction, commercially available aryl halides and bis(pinacolato)diboron as the starting materials, fac-Ir(ppy)₃ as the photocatalyst, and corresponding arylboronic esters and phenols were obtained in good yields. When the borylation was complete, the reaction was allowed to be exposed to air, and subsequent aerobic oxidation hydroxylation of arylboronic ester provided the corresponding phenols.

In 2016, Gao and co-workers reported a photo-organocatalytic enantioselective α-hydroxylation of β-dicarbonyl compounds by a series of Cinchona-derived N-oxide phase-transfer catalysts (Scheme 1.48) [55]. Moreover, the catalysts could be recycled and reused six times for such reactions with almost the original reactivity and enantioselectivity. Molecular oxygen was the sole oxidant in this reaction.

In 2016, Tung and co-workers came up with a blueprint for aromatic C—H functionalization via a combination of photocatalysis and cobalt catalysis (Scheme 1.49) [56]. They described the utility of this strategy for benzene hydroxylation as well as amination. As shown in Scheme 1.49, photocatalyst(PC⁺) uses as the form of onium. When irradiated by UV light, the onium could generate excited state(s) of photocatalyst(PC⁺⁺), which could then undergo single-electron transfer from benzene to produce benzene radical cation and photocatalyst radical(PC•). This may have then given an electron to
the metal cocatalyst to produce Co II and ground state photocatalyst (PC+), completing the photocatalysis cycle. They used the dual catalyst system to produce phenol directly from benzene and water with evolution of hydrogen gas under unusually mild conditions in good yield and selectivity. These synthetic reactions show significant atom economy and step economy.

Scheme 1.48 Asymmetric α-hydroxylation of β-keto esters and β-keto amides by Cinchona-derived N-oxide phase-transfer catalysts.

Scheme 1.49 Visible-light-induced hydroxytrifluoroethylation of styrenes under a molecular oxygen atmosphere.
1.5 Enzymatic Oxidation and Electrochemical Oxidation for Synthesis of Alcohols

In 2011, Reetz and co-workers reported region- and stereoselectivity of P450-catalyzed hydroxylation of steroids (Scheme 1.50) [57]. According to the previous result, cytochrome P450 enzymes could enable C—H activation at non-activated positions. However, the simultaneous control of both region and stereoselectivity is problematic. In this work, starting from P450 BM(F87A) and using progesterone as a substrate, they demonstrated a series of mutagenesis could obtain 96–97% selectivity for either of the two regioisomers. The result showed the mutants could selectively oxidize them without performing an additional mutagenesis experiment. The shapes of the binding pockets of mutants have been evolved to enforce, in each case, a single active positional orientation of the substrate, setting the stage for the respective regio- and diastereoselective oxidation.

In 2014, Siegel's group demonstrated a protocol to generate phthaloyl peroxide in flow for the hydroxylation of arenes (Scheme 1.51) [58]. Improving on earlier batch procedures, the flow protocol they developed could directly yield phthaloyl peroxide in high purity (>95%) and be used to bypass the need to isolate and recrystallize phthaloyl peroxide. The flow protocol for the formation of phthaloyl peroxide could be combined with arene hydroxylation reactions and provided a method for the consumption of peroxide as it was generated to minimize the accumulation of large quantities of peroxide so as to make this protocol more efficient and environmentally friendly.

<table>
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<tr>
<th>Mutant</th>
<th>Library</th>
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<th>3</th>
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<tr>
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<td>2</td>
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<tr>
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<tr>
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<tr>
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<td>81</td>
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<tr>
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Conditions: 1 mM progesterone, 24 h, 25 °C, resting cells containing expressed P450 mutants. *Traces of side products were identified as 17a, 21-dihydroxyprogesterone and 21-hydroxyprogesterone by HPLC. †Wild-type amino acid was retained in at least one position; mutant KSA-9 contains a silent mutation V78V (GTA GTG). ‡Mutant KSA-4 was used as a parent and site B was addressed. Mean values are given, standard deviation for conversion is ±5% and for selectivity ±1%. Differences from 100% occur from rounding.

Scheme 1.50 Regio- and stereoselectivity of P450-catalyzed hydroxylation of steroids controlled by laboratory evolution.
1.6 Conclusion and Perspectives

During the past few years, the green oxidative approach has emerged as an increasingly viable tool for the step-economical and sustainable functionalization and assembly for alcohols and phenols. The results summarized in this review highlight numerous important advances that have been made in the development of green oxidative reaction for synthesis of alcohols and phenols using molecular oxygen, air, and hydrogen peroxide as the oxidants. Furthermore, other green strategies such as the enzymatic reaction, photoredox reaction, and electrochemical oxidation were illustrated here. We have highlighted this progress in the areas of C=H hydroxylation, oxygenation of alkenes, dehydrogenative oxidation, and photoredox oxidation.

Despite momentous achievements, green oxidative synthesis of alcohols and phenols is still in an early stage of development, being used to install a hydroxyl group in some limited position and some simple scaffolds. We should recognize that only a small part of the transformation in these oxidative processes uses green oxidants as the terminal oxidant. However, these approaches provide environmentally friendly and step-economical methods. Many challenges remain to be addressed in the future development of green oxidative approaches, such as unactivated C(sp³)-H hydroxylation, photocatalysis, and enzymatic reaction. A lot of effort is still required in order to extend in this field. It is believed that further research into new, highly active, and selective reaction development in the green oxidative synthesis of alcohols and phenols will continue to contribute toward the future progression of newly sustainable chemistry, which will, in turn, extend the utility of organic synthesis.
References


