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Review

Molecular Oxygen Beyond Oxidation: Non-Oxidative and Borderline Transformations in Organic Synthesis

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Abstract

Dioxygen is vital for life and a key oxidant in biological systems. Its importance, however, extends beyond living processes; it has been harnessed for diverse applications since antiquity. In synthetic chemistry, oxygen-mediated oxidations are fundamental transformations. Nevertheless, molecular oxygen can also facilitate reactions without a net oxidative outcome. Intriguingly, this role, which defies conventional portrayal of oxygen as an oxidizing agent, has occasionally been noted in the literature. In some cases, oxygen mediates or induces reactions in which the oxidation state of the target organic compound remains unchanged, or the overall transformation does not involve the net incorporation of oxygen or the removal of hydrogen (or hydrogen equivalents) from the organic substrate. In these transformations, oxygen facilitates formally redox-neutral reactions or processes in which the combined number of heteroatoms, π bonds, and ring structures in the product does not exceed that in the reactant. This review covers oxygen-mediated or -induced reactions that meet these criteria. By presenting mechanistic insights and experimental investigations, it highlights behavior of dioxygen in these transformations. This analysis broadens our understanding of versatility of oxygen in synthetic chemistry and supports the development of more sustainable chemical processes.

Keywords: molecular oxygen; biocatalysts; radical initiators; radical polymerization; diimide reduction; singlet oxygen

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1. Introduction

Oxygen is the most abundant element in the Earth's crust (46%), in the bodies of water that cover it (rivers, seas, and oceans, 86%), and, after hydrogen and helium, the most abundant element in the universe (1%). As dioxygen or molecular oxygen, thanks to photosynthesis, it makes up 21% of the atmosphere that covers our planet. As is well established, dioxygen is indispensable for the life of aerobic organisms (again, the vast majority) through respiration or aerobic metabolism, a process that operates in cellular mitochondria and oxidizes different organic materials such as sugars and fats, thereby generating considerably more energy than anaerobic organisms do, for example, through fermentation [1,2]. Thus, the role of dioxygen as an oxidant is intrinsically linked to life as we know it. Moreover, even setting aside the decisive role of combustion in human development, oxidation processes involving molecular oxygen have been used since ancient times in a wide range of applications. These include synthetic chemical transformations such as the oxidation of alcohols and carbonyl compounds, the hydroxylation of arenes, the

oxygenation of alkanes, the oxidative dimerization of alkynes, and the oxidative cleavage of unsaturated hydrocarbons [3–5]. Such processes are also used on an industrial scale, as illustrated by the production of phthalic anhydride and acetic acid [6,7]. Representative examples of oxidative processes using molecular oxygen as the oxidant are shown in Figure 1.

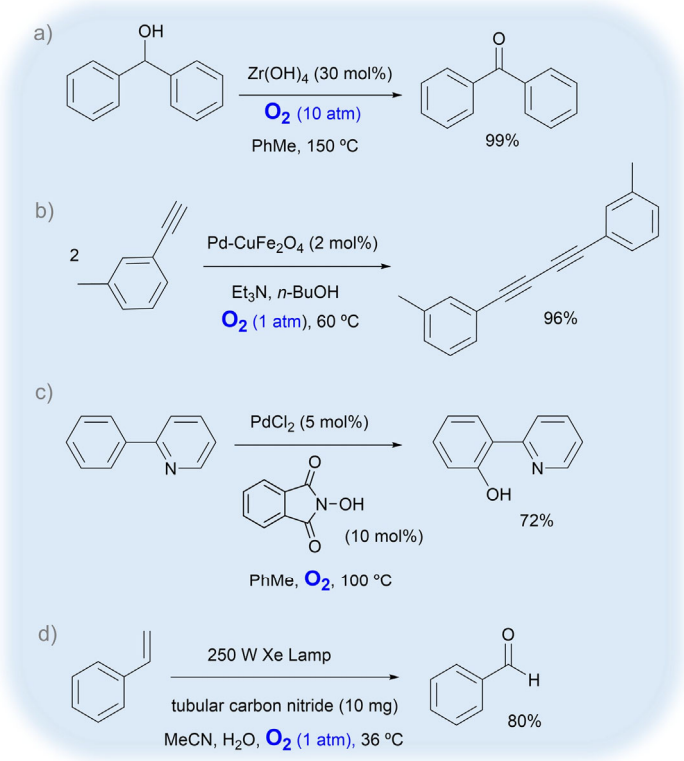


Figure 1. Oxidative transformations carried out using dioxygen as the oxidant. (**a**) Oxidation of benzhydrol to benzophenone as a representative example of the oxidation of alcohols [8]; (**b**) Glaser-Hay oxidative dimerization of terminal alkynes [9]; (**c**) Arene hydroxylation catalyzed by palladium/N-hydroxyphthalimide [10]; (**d**) Oxidative cleavage of styrene to benzaldehyde as an illustrative example of the preparation of carbonyls from unsaturated hydrocarbons [11].

Despite this well-established role as a terminal oxidant, molecular oxygen can also participate in organic transformations in which the organic substrate undergoes no net oxidation. In such processes, O_2 may serve as a source of reactive oxygen species, a ligand or promoter for metal catalysis, an initiator of radical chains, a trapping agent, or a component of a catalytic redox cycle, while the overall oxidation state of the main organic product remains unchanged. These transformations are chemically counterintuitive for a molecule so closely associated with oxidation, yet they offer attractive synthetic opportunities: they can exploit the abundance, low cost, and favorable environmental profile of O_2 without requiring stoichiometric oxidants or producing large quantities of oxidized by-products. Examples include oxygen-mediated rearrangements, cyclizations, additions, fragmentations, and redox-neutral functionalizations, in which dioxygen enables bond formation, cleavage, or relocation without increasing the overall degree of oxidation of the substrate. Recognizing and systematizing these reactions is essential not only to understand the full reactivity of O_2, but also to identify new, more sustainable synthetic strategies based on this ubiquitous molecule.

Although such reactions remain less developed and less systematically classified than oxidative transformations, they reveal a broader and more nuanced reactivity profile of molecular oxygen. Their identification is nevertheless complicated by the fact that many

processes involving O_2 are formally oxidative, while others are mechanistically oxygen-dependent but redox-neutral with respect to the organic substrate. To this end, we present, analyze, and categorize a series of formally non-oxidative reactions involving dioxygen, thereby providing new insights into the remarkable and unconventional functions of this ubiquitous diatomic molecule. In this regard, the oxidative nature of any synthetic transformation can be analyzed from the point of view of the oxidation degree of both reagents and products as well as from the reaction pathway or mechanism involved [12,13]. In addition, a straightforward method to distinguish oxidation from reduction involves calculating the combined count of heteroatoms, π-bonds and ring structures in each organic reactant and product. If the product total exceeds that of the reactant, oxidation likely took place; a lower total suggests reduction [14]. When analyzing only the starting organic reagent and the target compound while disregarding side reactions, borderline cases may arise. In these edge cases, although the degree of unsaturation is preserved in the final product, the nature of the by-products warrants classifying the process as partially oxidative. Overall, the nature of the process can be inferred from preservation or change in the degree of unsaturation, combined with the heteroatom count in relation to the main product(s) of the reaction.

Accordingly, preservation or decrease in the degree of unsaturation will be the criterion adopted for classifying reactions as non-oxidative. This operational definition provides a consistent framework for categorizing the diverse transformations discussed in this review, even in borderline cases. To the best of our knowledge, the literature currently lacks a review specifically dedicated to the use of O_2 in formally non-oxidative transformations. While molecular oxygen is well established as a sustainable terminal oxidant and has been extensively discussed in this context, considerably less attention has been given to its synthetic involvement in processes that do not entail an overall oxidation of the organic substrate. In view of the growing adoption of molecular oxygen as a reagent across a broad range of synthetic methodologies, a structured overview of these non-oxidative applications is both relevant and timely.

This review provides the first dedicated overview of molecular-oxygen-mediated or induced organic transformations that are formally non-oxidative with respect to the main organic substrate. We define these reactions as those in which the degree of unsaturation of the principal organic product is conserved or decreased relative to the organic starting material, and we analyze their mechanisms, the role played by O_2, and the boundary cases that challenge conventional oxidative/non-oxidative classifications. By organizing this dispersed literature according to transformation type and mechanistic manifold (Table 1), we aim to establish a practical framework for identifying, designing, and classifying O_2-enabled non-oxidative synthetic methodologies. Mechanistic considerations will be highlighted in most instances, accompanied by an analysis of experimental investigations aimed at unraveling the specific involvement of dioxygen in these processes.

2. Enzymatic Processes

The functioning of living organisms is heavily reliant on a wide range of oxidases and other oxidoreductases that use dioxygen as the electron acceptor. However, in a limited number of cases, these enzymes catalyze formally redox-neutral processes that are mediated or co-catalyzed by molecular oxygen. In these instances, dioxygen functions both as a catalyst activator or redox mediator and, in some cases, as the source of the transferred oxygen atom. In this regard, oxalate decarboxylase catalyzes the redox-neutral dissociation of oxalate into formate and carbon dioxide (Figure 2) [15,16]. Following previous reports on the complex interplay between manganese oxidation states, molecular oxygen, and substrate binding in the catalytic mechanism of oxalate decarboxylase for this dissociative

transformation [17,18], Angerhofer and co-workers confirmed that the enzyme contains tightly bound Mn(II) in its resting state, but Mn(III) formation is crucial for its catalytic function. Molecular oxygen is believed to oxidize Mn(II) to Mn(III), which is essential for the catalytic activity of the enzyme. In addition, Mn(III) formation in oxalate decarboxylase occurs only in the presence of both oxalate (substrate) and molecular oxygen under acidic conditions. In this regard, the authors observed that the redox cycling between Mn(II) and Mn(III) is pH-dependent. Indeed, Mn(III) formation is favored at lower pH values and correlates with the enzyme's optimal activity at pH 3. The research suggests that molecular oxygen binds to the C-terminal Mn ion, rather than the *N*-terminal one, as previously assumed, and electrons are transferred from the *N*-terminal Mn site through a long-range electron-transfer pathway. Moreover, the study provides direct spectroscopic evidence for the formation of hexacoordinate Mn(III) during catalytic turnover, supporting the hypothesis that Mn(III) is involved in removing an electron from the substrate to form a radical intermediate [19]. In this case, O_2 may be regarded as a catalyst activator and, more specifically, as a redox mediator.

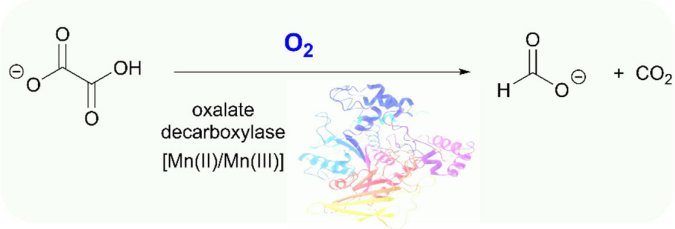


Figure 2. General scheme for the oxalate decarboxylase-catalyzed reaction. Radical intermediates, including a carbon dioxide radical anion, have been detected during catalysis, supporting a proton-coupled electron transfer mechanism. Because it degrades oxalate without producing hydrogen peroxide, oxalate decarboxylase is of interest for applications in food, agriculture, and medicine (e.g., reducing oxalate in foods or reducing the risk of kidney-stone formation).

Cyanobacterial aldehyde-deformylating oxygenases (ADOs) are part of the ferritin-like diiron-carboxylate superfamily. The ADO-catalyzed transformation stands out among reactions in this enzyme superfamily due to its lack of net oxidation of the primary substrate. Its connection to other members of the family becomes apparent only when considering two key aspects: the strict requirement for an external reducing system and the incorporation of one oxygen atom from O_2 into the formate byproduct. This combination of features sets the ADO reaction apart while still maintaining fundamental links to its enzymatic relatives [20]. Indeed, they convert saturated or monounsaturated fatty aldehydes into formate and alkanes or alkenes, with four electrons required per turnover to reduce one oxygen atom to water and incorporate the other into formate. Research by Booker, Krebs, Bollinger and co-workers on ADO from cyanobacterium *Nostoc punctiforme* shed light on the mechanism of this formally hydrolytic (redox-neutral) process. Thus, they proposed that, as a result of the O_2 addition to the reduced $Fe_2^{II}/^{II}$ cofactor in the ADO·aldehyde complex, an $Fe_2^{III}/^{III}$ complex with a bound peroxide is formed. In addition, the reductive splitting of the corresponding peroxyhemiacetal peroxide triggers a free-radical C1-C2 β-scission reaction (Figure 3) [21,22]. The conversion of long-chain fatty aldehydes (C_n) into alkanes or alkenes (C_n-1), with concomitant release of formate as a co-product, is carried out in water as the sole solvent. This reaction is a key step in the biosynthesis of hydrocarbons in cyanobacteria and is unusual among oxygenases because it results in carbon–carbon bond cleavage rather than the typical oxidation of the substrate. In this enzyme system, O_2 therefore serves both as the source of the oxygen atom incorporated into formate and as the terminal electron acceptor.

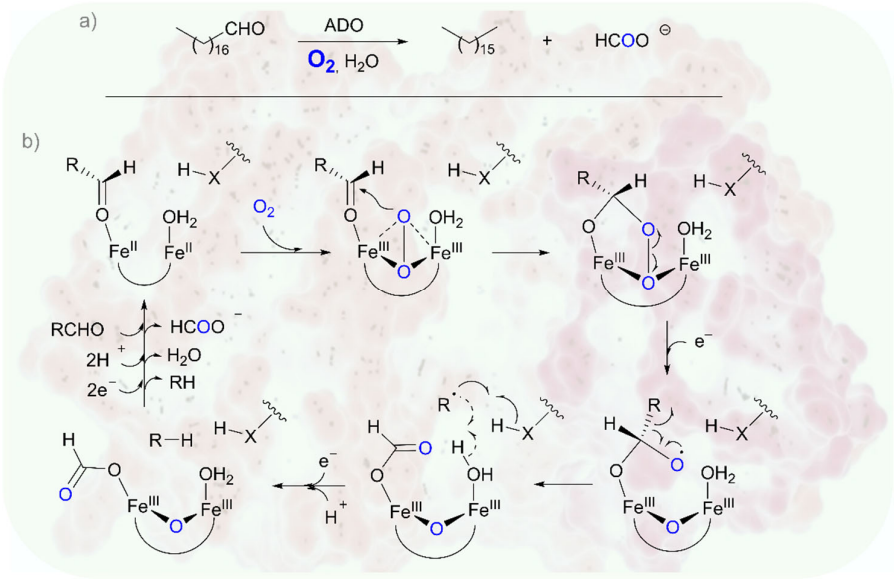


Figure 3. Cyanobacterial aldehyde-deformylating oxygenases efficiently catalyze the formation of alkanes and formate from aldehydes. (**a**) Transformation of stearyl aldehyde (octadecanal) into heptadecane and formate. (**b**) Proposed mechanism for the ADO-catalyzed transformation. The enzyme contains a di-iron center and requires molecular oxygen (O_2) as a co-substrate, as well as a reducing system that provides four electrons per turnover. Biological reducing systems include ferredoxin, ferredoxin reductase, and nicotinamide adenine dinucleotide phosphate (NADPH), while chemical systems such as phenazine methosulfate and nicotinamide adenine dinucleotide can also support activity.

3. Radical Functionalizations Using Organoboron Compounds as Precursors and Initiators

Organoboranes, particularly triethylborane (Et_3B), are potent radical initiators [23]. The Et_3B/O_2 system initiates radical reactions through a homolytic substitution (S_H2) mechanism, generating alkyl radicals that propagate the chain reaction. This system is highly efficient even at low temperatures (−78 °C), making it valuable for stereoselective radical reactions and processes involving thermally unstable compounds. The ability of organoboranes to initiate radical reactions at low temperatures sets them apart from other classical radical initiators [24]. Additionally, the organoborane/oxygen radical initiator system has garnered significant attention for its versatility in radical-based reactions, including the addition of xanthates to alkenes, the reduction of alcohols using water as a hydrogen source, and multiple conventional and controlled radical polymerization techniques. In all these cases, dioxygen plays an essential role in the radical initiation process.

Boivin and Nguyen presented an operationally simple procedure for the intermolecular radical additions of (*S*)-2-oxoalkyl-thionocarbonates [(S-xanthates)] to olefins initiated by the system Et_3B/air in dichloromethane or 1,2-dichloroethane as solvents. Depending on the substrates employed, the reactions were conducted at room temperature or 40–83 °C [25]. As a more convenient and safer alternative to the classic Barton–McCombie reaction initiated by organotin hydrides, Wood and co-workers reported the selective reduction of O-alkyl thiocarbonate esters (xanthates), using water or deuterium oxide as the source of hydrogen or deuterium (Figure 4). In this case, Me_3B/air (0.8 equiv. of O_2) initiated the reaction, which was conducted in benzene as the solvent. Despite the use of this unsafe solvent, the study highlighted a fundamentally new reactivity mode for water and trialkylboranes, offering a safer and more environmentally benign alternative to traditional deoxygenations based on tin hydrides [26].

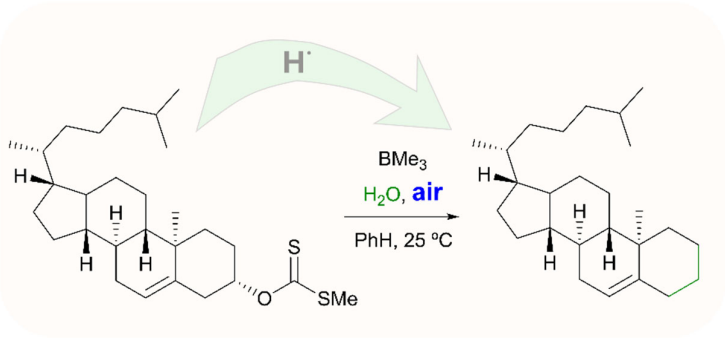


Figure 4. Selective reduction of xanthate esters under aerobic conditions. The authors presented a tin-free method for the deoxygenation of alcohols using water as the hydrogen atom source. That protocol transformed methyl cholesteryl xanthate into the corresponding 3-deoxy derivative. Ab initio calculations revealed that the trialkylborane–water complex has an unusually low O–H bond dissociation energy (73 kcal/mol), which facilitates the reaction and supports a radical chain mechanism.

Concerning conventional radical polymerizations, the organoboranes most frequently used in this field include tributylborane and triethylborane, each used in combination with a low concentration of dioxygen. For certain reactions, such as styrene polymerization, a bicomponent transfer system consisting of triethylborane and a methyl vinyl ketone complex was employed [27]. As mentioned above, the generally accepted steps of alkylborane autoxidation are shown in Figure 5. However, it is important to note that this reaction may involve additional processes and intermediates. Recent computational studies using density functional theory have proposed that this autoxidation is an autocatalytic process [28].

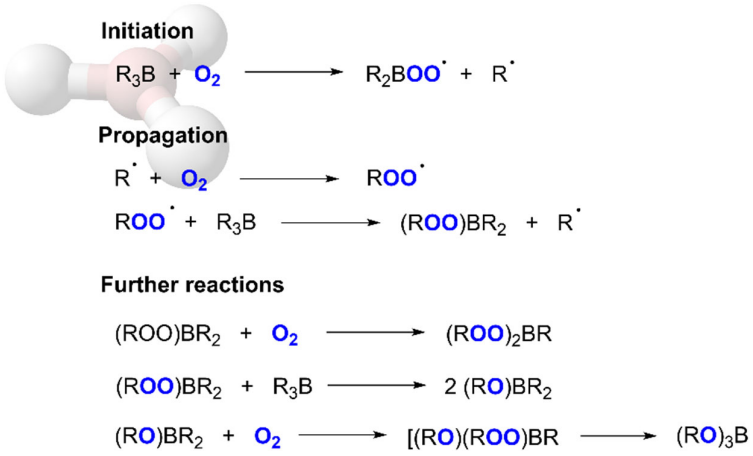


Figure 5. Presumed mechanism for the autoxidation of alkylboranes. Recent computational studies using density functional theory have proposed that the autoxidation of alkylboranes proceeds via an autocatalytic mechanism, where intermediates generated during the reaction accelerate subsequent steps. Thus, this autocatalytic loop would involve alkyl radicals acting as both intermediates and catalysts.

Given the reactivity of trialkylboranes with air, researchers developed various methods to enhance their stability. One approach involved forming complexes with ammonia and amines, such as the 1,3-diaminopropane-triethylborane complex. When exposed to light in the presence of a photoinitiator, this complex can liberate trialkylborane, which then can trigger conventional radical polymerization reactions. Additionally, scientists conducted comprehensive studies on the thermal decomposition behavior of different amine-trialkylborane complexes [29]. Controlled radical polymerization, also referred

to as "living" radical polymerization or reversible-deactivation radical polymerization, offers a practical approach to synthesizing polymers with precise characteristics. This method allows for the creation of well-defined polymeric materials with predetermined molecular weights and specific structural features. Initially developed in academic research, these methods were rapidly adopted by industry, resulting in the large-scale manufacture of multiple commercial products, particularly well-characterized block copolymers with thermoplastic elastomer properties [30]. In this particular area, bicyclic borane derivatives, such as 2-isopropyl-2-boraadamantane, 8-borahydrindane and 1-octyl-9-borabicyclo[3.3.1]nonane have been frequently used [31,32]. Recently, more selective organoboranes, such as β-alkylcatecholboranes, have been observed to undergo autoxidation to provide only one alkyl radical thereby enabling a high degree of polymerization control in the synthesis of ultrahigh-molecular-weight polymers [33]. In all the reactions described in this section, molecular oxygen functions primarily as a radical initiator.

4. Dioxygen-Initiated Reductions with Diimide

The reduction of unsaturated carbon-carbon bonds is a critical transformation in organic synthesis. Traditional methods often employ hydrogen gas with heterogeneous catalysts such as Pd/C, PtO_2, Rh/C, or Raney® Nickel, or with homogeneous metal complexes of Rh, Pd, Pt, and Cu. The homogeneous complexes are also used for asymmetric hydrogenation. However, these approaches can suffer from selectivity issues, such as hydrogenolysis of a number of sensitive functional groups (benzylic, allylic, and propargylic alcohols and amines; removal of Cbz and Alloc protecting groups), reduction of other functionalities (nitro groups, benzylic ketones, and aryl halides, among others), alkene migration, or racemization [34,35].

An alternative is diimide or diazene (N_2H_2), a transfer hydrogenation agent used for over a century [36]. Diimide selectively reduces nonpolarized carbon-carbon double bonds while avoiding common side reactions. It is typically generated in situ through methods such as the decarboxylation of dipotassium azodicarboxylate, thermal decomposition of sulfonylhydrazides or base-induced eliminations. A more atom-efficient method involves oxidizing hydrazine using agents such as H_2O_2, $NaIO_4$, $K_3[(FeCN)_6]$, or molecular oxygen (Figure 6) [37,38]. Although hydrazine is oxidized aerobically, the organic substrate undergoes reduction; therefore, this transformation also meets the requirements of this review.

Diimide is valuable because of its chemoselectivity and simplicity, offering a metal-free alternative to catalytic hydrogenation. Its utility has been demonstrated at pilot scale, notably in the diastereoselective reduction of artemisinic acid carried out under pilot-scale conditions [39]. However, while it is possible to generate diimide through uncatalyzed oxidation of hydrazine with molecular oxygen, this approach is less practical. It often requires prolonged reaction times and a large excess of hydrazine due to the low reaction rate. Additionally, the process is hindered by the tendency of the reactive intermediate to undergo disproportionation to hydrazine and nitrogen or overoxidation to nitrogen [40,41]. Therefore, efficient oxidation of hydrazine with molecular oxygen typically relies on catalysts to accelerate the process. Historically, copper salts have been employed to achieve high reaction rates. More recently, iron salts and organocatalysts, such as guanidine salts or flavin derivatives, have emerged as well-established alternatives [42]. In line with the works by Imada and Naota on the generation of diimide from hydrazine hydrate and oxygen using flavin-based compounds as organocatalysts [43,44], Minnaard and co-workers employed 5-ethylriboflavin, readily prepared from riboflavin (vitamin B_2), as an advantageous catalyst for the reduc-

tion of cyclooctene. A combined anaerobic–aerobic mechanism has been proposed for flavin-based organocatalysts in this reaction. Initially, reduction of the flavin catalyst leads to the formation of a flavin-diimide complex. This complex can hydrogenate olefins while concomitantly releasing a flavin species, which reacts with O_2 to generate a hydroperoxyflavin intermediate. The latter then reacts with hydrazine to form a hydroxyflavin-diimide complex, which can further reduce olefins. Finally, dehydration of the hydroxyflavin derivative regenerates the organocatalyst, thereby completing the catalytic cycle [43]. A number of internal and terminal alkenes were reduced by this method. Good results were obtained in most cases, although internal trisubstituted alkene moieties reacted much more slowly and tetrasubstituted olefins were not reduced at all (Figure 7) [45]. In addition to being performed in the absence of precious metal catalysts and mediated with dioxygen, the use of environmentally friendly ethanol as the solvent should be pointed out. Following their previous research on the in situ generation of diimide from hydrazine monohydrate and molecular oxygen in continuous-flow mode [46], Kappe and co-workers applied this method to the synthesis of active pharmaceutical ingredients. After a diastereoselective reduction of artemisinic acid to dihydroartemisinic acid [47], a precursor of the currently marketed antimalarial agent artemisinin, they carried out the selective reduction of thebaine combined with hydrolysis leading to hydrocodone (Figure 8), a semi-synthetic opioid used primarily for pain management and as a cough suppressant [48]. All the reactions described in this section are based on the role of O_2 as the terminal oxidant that oxidizes hydrazine (N_2H_4) to diimide.

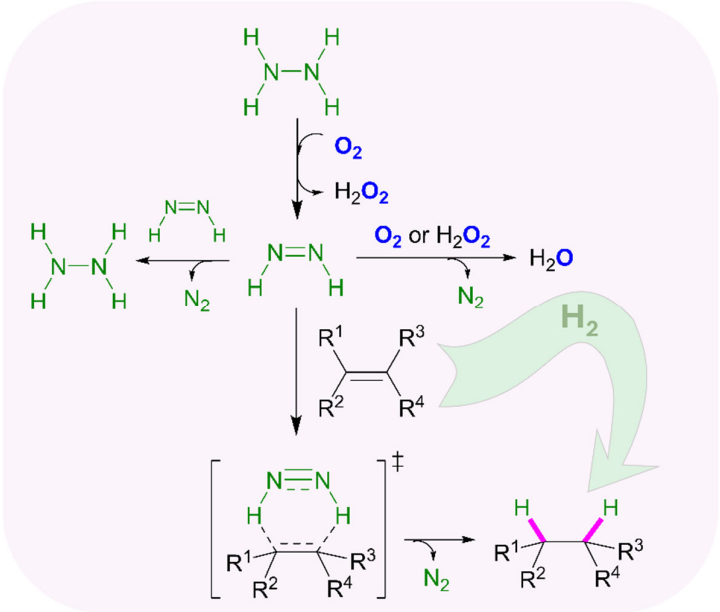


Figure 6. Olefin reduction through N_2H_4/O_2-generated diimide. Hydrazine reacts with molecular oxygen under aerobic conditions, often catalyzed by Brønsted acids, to produce diimide (N_2H_2) in situ. Diimide is unstable and must be generated in the presence of the substrate to be reduced. Diimide acts as a hydrogen donor, transferring two hydrogen atoms across the C=C double bond of the olefin in a concerted, *syn*-addition manner.

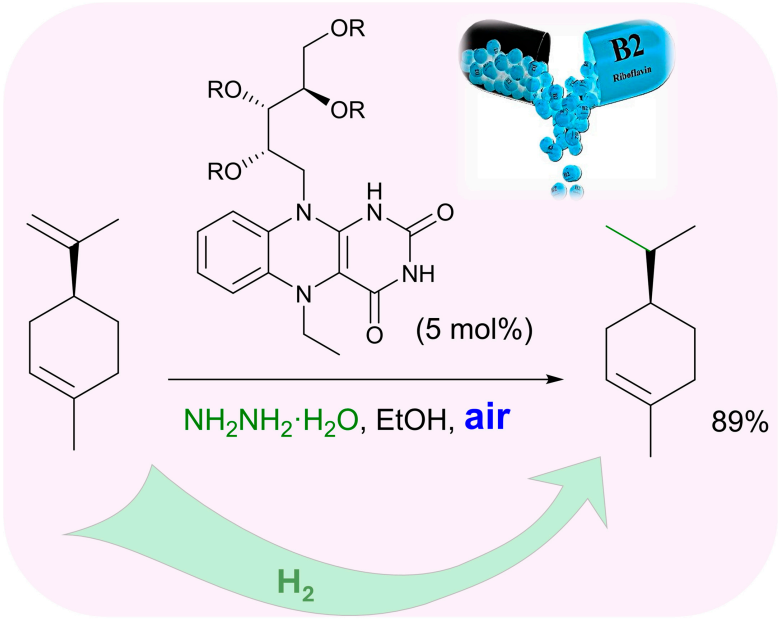


Figure 7. 5-Ethylriboflavin acts as a redox organocatalyst, facilitating the aerobic oxidation of hydrazine (N_2H_4) to generate diimide (N_2H_2) in situ. Under aerobic conditions, hydrazine is oxidized, with molecular oxygen as the terminal oxidant. The flavin catalyst accelerates this process, enabling efficient and controlled production of diimide, which is otherwise unstable and must be generated in the presence of the substrate. Diimide selectively reduces the endocyclic double bond of (*S*)-limonene through a *syn*-addition of hydrogen atoms, forming the corresponding saturated product (dihydrolimonene) and releasing nitrogen gas as the only by-product.

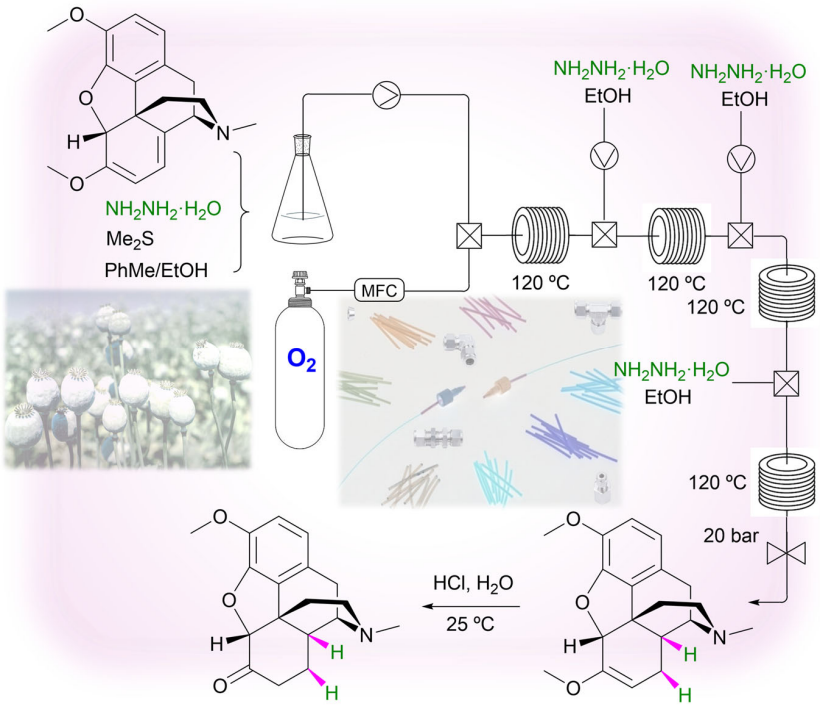


Figure 8. Gas–liquid continuous-flow approach to hydrocodone from thebaine. Thebaine, also known as paramorphine, is a naturally occurring opioid alkaloid found in the opium poppy (*Papaver somniferum*). Diimide-mediated regio- and stereoselective hydrogenation of thebaine followed by acidic hydrolysis under mild conditions provides hydrocodone.

5. Processes Mediated by Singlet Oxygen Species

Reactive oxygen species are highly reactive species that occur naturally in biological systems, environmental processes, and various chemical reactions. This group encompasses several key players, including singlet oxygen, superoxide radical anion, hydroxyl radical, and hydroperoxyl radical. Among these, singlet oxygen occupies a unique position in terms of reactivity. While it is generally less reactive than the hydroxyl radical, it is more reactive than the superoxide radical anion toward many organic molecules. Singlet oxygen represents the lowest-energy electronically excited state of molecular oxygen, yet it remains a potent oxidizing agent. It has the capacity to trigger oxidation processes in organic compounds and biological molecules, making it a crucial player in various chemical and biological systems [49]. This ability to initiate oxidative reactions underscores its importance in both natural processes and potential applications in fields such as organic synthesis, materials science, and biomedicine. The most well-known and frequently discussed reactions involving singlet oxygen and organic molecules typically result in the initial formation of peroxides. While these peroxide intermediates can be isolated and studied at low temperature, they are often transient in biologically complex systems such as living cells. The key characteristic of these peroxides is the inherent instability of their oxygen-oxygen bond. This bond has a relatively low dissociation energy, making it prone to cleavage. When this bond breaks, it generates oxygen-centered radicals, with hydroperoxides, for example, producing hydroxyl radicals. These newly formed radicals are highly reactive and can initiate chain reactions. They have the potential to create a diverse array of reactive intermediates through various propagation steps. As a result, the initial singlet oxygen reaction can lead to the production of a broad range of final products, often quite different from the original peroxide intermediate [50,51].

Among the synthetic processes involving singlet oxygen species [52–54], some examples of transformations that conserve the overall degree of unsaturation can be found in the literature. Vassilikogiannakis and coworkers reported a one-pot, consecutive approach to several benzo- and heterofused 8*a*-alkylhexahydroindolizin-3(2*H*)-ones, including several 10*b*-alkyl-1,5,6,10*b*-tetrahydropyrrolo [2,1-*a*]isoquinolin-3(2*H*)-ones, from simple mono- and polysubstituted furans and β-(hetero)arylethylamines. Using rose Bengal (RB) as photosensitizer, a 300 W lamp, and Me_2S as the reducing agent for the hydroperoxy group, the authors generated singlet oxygen, which promoted the formation of 1-alkyl-1,3-dihydro-2*H*-pyrrol-2-one derivatives that, in the presence of a Brönsted acid (trifluoroacetic or formic acid) or Lewis acid ($AlCl_3$) underwent a Pictet-Spengler cyclization through an *N*-acyliminium intermediate, as depicted in Figure 9 [55,56]. A similar strategy was designed by the authors to develop an efficient approach for synthesizing erythrinane alkaloids, starting from 4-(furan-2-yl)butanal. This one-pot methodology relied on the photochemical generation of singlet oxygen, which reacted with the furan substrate to form a versatile 1,4-enedione intermediate. After condensation of the latter dielectrophile with an arylethylamine, enamide cyclization took place, followed by acid-catalyzed formation of an *N*-acyliminium ion, and finally a Pictet-Spengler cyclization to construct the tetracyclic erythrinane skeleton [57].

An unprecedented acyl group migration in *N*-arylenaminoketones was described by Wu and coworkers. Thus, the authors introduced a novel strategy for constructing a quaternary carbon center via an intramolecular 1,2-acyl migration. This mild and straightforward reaction was carried out under aerobic conditions at room temperature. Upon irradiation of a platinum(II) polypyridyl complex with visible light (λ = 450 nm) in the presence of molecular oxygen, enaminones reacted with alcohols to produce alkyl 2-methyl-3-oxo-2-(phenylamino)butanoates, containing a quaternary carbon center, through a combination of 1,2-acyl migration and esterification (Figure 10). Experimental evidence from electron

paramagnetic resonance (EPR) measurements, crossover experiments, and isotope labeling confirmed that singlet oxygen played a crucial role in enabling this unique intramolecular 1,2-acyl migration. Furthermore, it was demonstrated that the carbonyl oxygen of the newly formed ester originated from molecular oxygen [58].

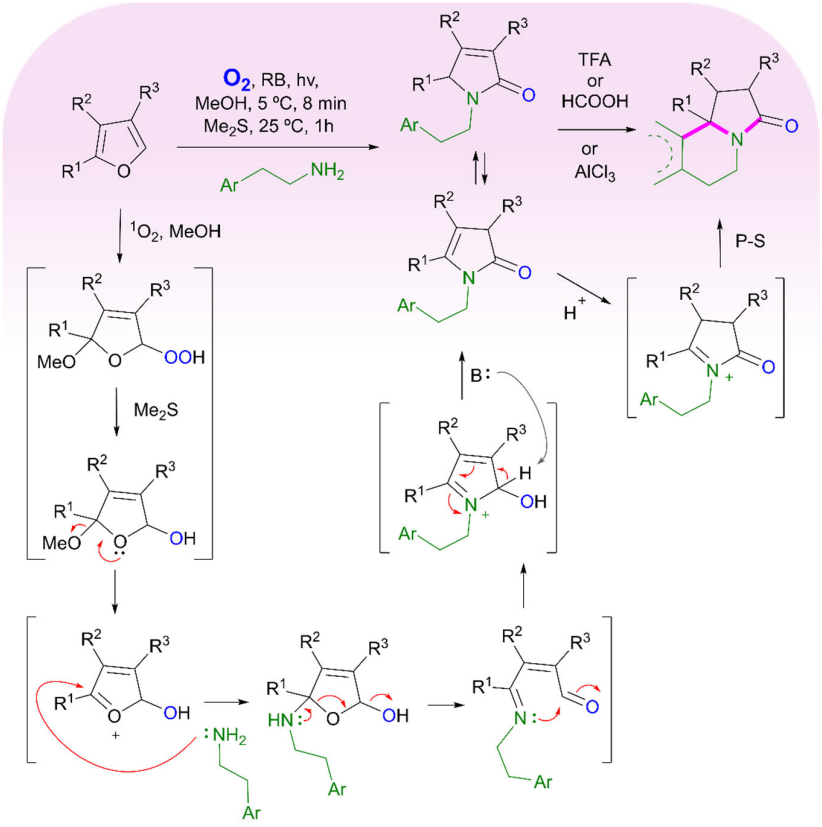


Figure 9. Singlet oxygen-mediated one-pot approach to nitrogen-bearing aromatic polycycles. It is postulated that photooxygenation of a furan derivative in methanol using singlet oxygen generates a 1,4-dielectrophile species, which interacts with an amine bearing a pendant aromatic ring. After condensation to form the corresponding pyrrolidinone, the key *N*-acyliminium intermediate would be formed upon addition of a Brønsted or Lewis acid, and an intramolecular 6-*endo*-cyclization involving the arene moiety analogous to the Pictet-Spengler reaction would then occur to yield the final nitrogen-containing aromatic polycycle.

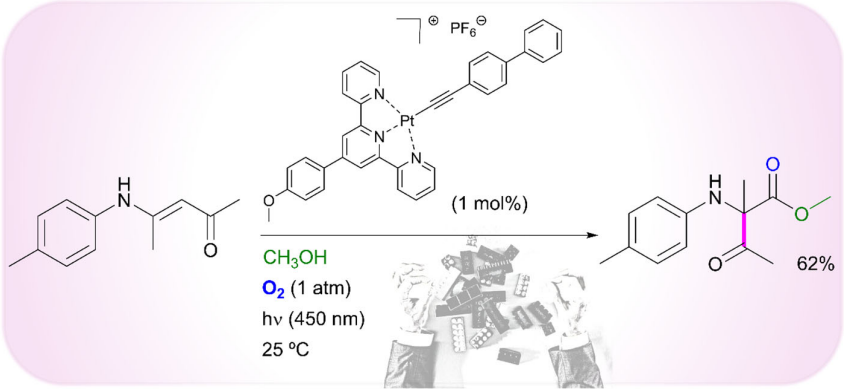


Figure 10. 1,2-Acyl migration/esterification of (*E*)-4-(*p*-tolylamino)pent-3-en-2-one. Upon exposure to visible light, a platinum(II) polypyridyl complex facilitates the reaction between *N*-arylenaminones and alcohols, producing alkyl 2-methyl-3-oxo-2-(phenylamino)butanoates bearing a quaternary carbon center through 1,2-acyl migration coupled with simultaneous ester formation.

The incorporation of aryl groups into heterocyclic structures plays a pivotal role in medicinal chemistry, natural product synthesis, and the development of functional materials. This process, known as arylation of heterocycles, has been a subject of extensive research due to its ability to significantly alter the physicochemical properties and biological activities of the resulting compounds [59]. Traditionally, transition-metal-catalyzed cross-coupling reactions have been the standard method, utilizing organic (pseudo)halides and organometallic reagents as coupling partners. While substantial advancements have been made in transition-metal-catalyzed C–H arylation, concerns about potential residual metal contamination in the final products persist [60]. In response, radical-based C–H arylation has emerged as a promising alternative, offering the advantage of generating reactive aryl radicals under mild conditions without the need for specific ligands [61]. Recently, a visible-light-driven method for the arylation and alkylation of quinoxalin-2(1*H*)-ones and quinolines was reported by Jiang, Song, and co-workers. Building upon the observation that singlet oxygen ($^1O_2$) is readily generated from air or molecular oxygen in the presence of quinoxalin-2(1*H*)-ones or their analogs when illuminated with 400 nm light, the authors optimized the phenylation of 1-methylquinoxalin-2(1*H*)-one with phenylhydrazine under air in MeCN at room temperature and then extended this procedure to the preparation of a series of 3-aryl- and 3-aryl quinoxalin-2(1*H*)-ones. No additional photocatalyst was required (Figure 11). In order to perform the C-2 arylation of quinoline derivatives, eosin Y (0.5 mol%) was added and the irradiation wavelength was changed to 455 nm. Based on experiments using employing radical scavengers, singlet-oxygen quenchers, and electron spin resonance spectroscopy, the researchers suggested that the quinoxalin-2(1*H*)-one substrate, or the corresponding arylated or alkylated product, was excited by irradiation from a purple LED (400 nm), resulting in the generation of a triplet excited state. The triplet excited state then transferred energy to molecular oxygen, thereby converting ground-state molecular oxygen into singlet oxygen. The highly oxidizing singlet oxygen species then oxidized organic hydrazines, generating carbon-centered radicals and simultaneously producing superoxide radical anions. Subsequently, these carbon-centered radicals added to the substrate, forming nitrogen-centered radicals. These nitrogen-centered radicals were then oxidized by the superoxide radical anions, ultimately yielding the desired product [62]. In all the reactions described in this section O_2 serves as a source of ROS.



Figure 11. Visible-light-induced phenylation of 1-butylquinoxalin-2(1*H*)-one with phenylhydrazine. Control experiments demonstrated that light irradiation was essential for achieving optimal reaction efficiency in this reaction leading to 1-butyl-3-phenylquinoxalin-2(1*H*)-one. Furthermore, performing the reaction under different atmospheres -nitrogen, air, and oxygen- indicates that oxygen is vital to the mechanism.

6. Miscellaneous

6.1. Radical Polymerization

The discovery of a practical method for synthesizing polyethylene in 1933 by Fawcett and Gibson at Imperial Chemical Industries was accidental and initially difficult to reproduce. The crucial breakthrough came in 1935 when, by chance, a leak in their equipment introduced trace amounts of oxygen into the ethylene feed. This accidental introduction of oxygen, which contributed to the formation of radical species under the reaction condi-

tions, proved essential for successful polymerization. The resulting process, involving high temperatures and pressures, led to the production of low-density polyethylene (LDPE). Remarkably, modern LDPE production still relies on conditions very similar to those accidentally discovered, with oxygen serving as an initiator in the polymerization process [63]. The role of O_2 in these cases is that of a radical initiator.

6.2. Activation of Lewis Acids

Lewis acids play a crucial role in chemistry as activating agents for organic substrates, with widespread applications in synthetic processes. The past two decades have witnessed a surge in research focused on developing metal-containing Lewis acids based on elements across the periodic table and exploring their catalytic potential across diverse reactions [64]. The effectiveness of Lewis acids can be modulated by several factors, including the choice of metal center, the presence of coordinating additives, and the nature of the counteranion. For instance, substituting a highly coordinating halide anion with a less nucleophilic triflate anion is a common strategy to enhance Lewis acidity of the metal center [65]. However, beyond these conventional approaches, novel methods to augment Lewis acidity are limited. Kobayashi and coworkers introduced an innovative Lewis acid system reported to be activated by molecular oxygen, thereby providing a distinct approach to Lewis-acid activation. While dinuclear molybdenum compounds [$Mo_2(OAc)_4$] had been investigated as inorganic complexes, their synthetic applications remained largely unexplored [66]. Notably, the researchers successfully employed this catalyst to facilitate a previously unreported Diels-Alder reaction between a large number of aromatic acyl hydrazones and Danishefsky dienes. In addition to demonstrating Mukaiyama aldol and Mannich-type reactions, the authors provided evidence for a Strecker reaction between (*E*)-*N*-benzylideneaniline and trimethylsilyl cyanide (Figure 12) mediated by this Lewis acid catalyst activated by molecular oxygen [67]. As discussed above, O_2 serves as a catalyst activator in the reactions described in this subsection.

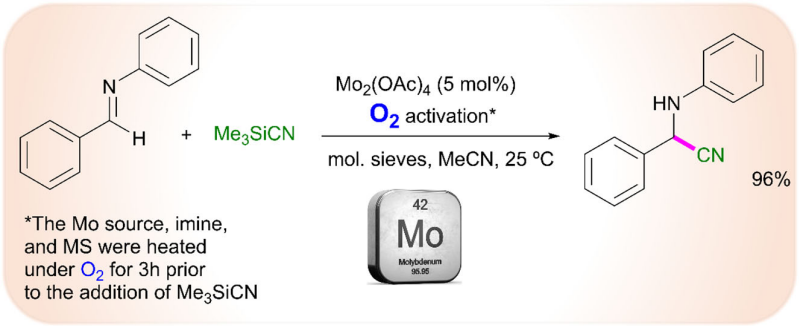


Figure 12. Molybdenum-catalyzed aerobic Strecker synthesis. This molybdenum-catalyzed preparation of α-aminonitriles from aldimines and trimethylsilyl cyanide was strongly dependent on activation of the catalyst under aerobic conditions prior to the addition of the cyanide source. Furthermore, the same system also catalyzed Mukaiyama aldol and Mannich-type reactions.

6.3. Photocatalytic Processes

In recent years, the field of photocatalysis has experienced an exponential increase in the field of photocatalysis. In addition to its use in the degradation of organic pollutants in aqueous and gaseous effluents, photocatalysis has also been successfully applied to the large-scale synthesis of high-value molecules [68]. Initially focused on cycloadditions, enantioselective organocatalytic transformations, the photoreductive generation of radicals from alkyl halides, and other oxidative and reductive processes, the field of photocatalysis has since expanded to encompass a wide range of transformations, including the construction of diverse carbon–carbon bonds involving different hybridization states

(sp^2-sp^2, sp^2-sp^3, and sp^3-sp^3), as well as numerous carbon–heteroatom bonds (C-O, C-N, C-S) [69]. Apart from typical photocatalysts such as $Ru(bpy)_3Cl_2$], *fac*-$Ir(ppy)_3$, eosin Y or flavin, other chemical entities that alter the rate of a chemical reaction upon irradiation have appeared with improved applications [70]. In this context, Griesbeck, Schmalz *and co-workers* investigated the intramolecular [2 + 2] cycloaddition of coumarins bearing an unsaturated alkyl substituent at the 3-position (Figure 13). After verifying that this transformation had not been described in the literature, they realized that the presence of molecular oxygen dramatically improved the reaction yields and accelerated the process. They also observed that the addition of a common singlet oxygen sensitizer, Rose Bengal or other sensitizers, such as tetraphenylporphyrin did not have a significant effect on the reaction yield. From these and other experiments, they concluded that this reaction, in which dioxygen acts as a key redox catalyst, goes through an initial light absorption followed by intersystem crossing, generating a triplet transient species from the starting compound. This transient then undergoes a single-electron transfer reaction with triplet molecular oxygen ($^3O_2$). The resulting radical cation subsequently participates in a 5-*exo*-trig radical cyclization, forming a distal radical-cation intermediate. This intermediate is then reduced by the superoxide radical anion, which was produced in the earlier single-electron transfer step, leading to the formation of a biradical species. In the final step, this biradical undergoes a radical recombination, resulting in the creation of a four-membered ring and yielding the isolated racemic cycloaddition product [71]. Thus, O_2 functions as a redox mediator.

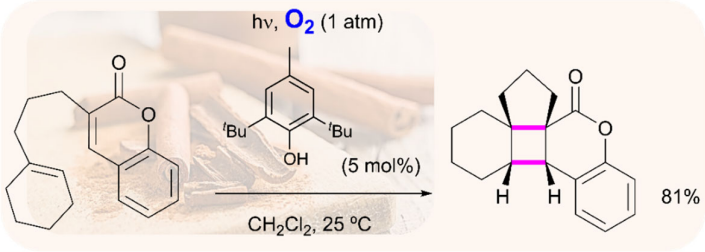


Figure 13. Intramolecular photocycloaddition of coumarin. A pentacyclic lactone is directly obtained from a coumarin derivative bearing an unsaturated alkyl group at the 3-position in the presence of a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol. The suggested pathway for the intramolecular [2 + 2] photocycloaddition of coumarins with an unsaturated alkyl group at the 3-position, in which oxygen acts as a redox catalyst, was supported by transient absorption spectroscopy and electrochemical studies.

6.4. Decarboxylative Cross-Couplings

Decarboxylative cross-coupling has seen significant advancement in recent decades. This approach utilizes various catalysts and oxidants to promote coupling reactions that release carbon dioxide as a benign by-product. Therefore, decarboxylative cross-coupling is a promising route for the large-scale synthesis of valuable aromatic compounds from sustainable feedstocks. While challenges such as equipment needs and catalyst stability remain, these methods render decarboxylative arylation increasingly practical for industrial applications [72]. Researchers have employed copper, silver, iridium, persulfate, hypervalent iodine, and hydroperoxide oxidants, as well as photocatalysts, to facilitate these reactions [73,74]. In some instances, dioxygen at atmospheric pressure has yielded superior results. For example, Zhang et al. developed a copper-catalyzed method for the *N*-arylation of carboxamides and sulfonamides with *ortho*-substituted benzoic acid derivatives (Figure 14). After evaluating several oxidants, they found that dioxygen produced the best outcomes [75]. As with the other processes discussed thus far, the total numbers of heteroatoms, π-bonds, and ring structures re-

main unchanged between the organic reactants and the *N*-arylated product, indicating that no formal oxidation has occurred. In these cases, O_2 acts as the terminal oxidant reoxidizing the catalyst (and/or oxidizing carboxylate-derived intermediates) to sustain the catalytic cycle.

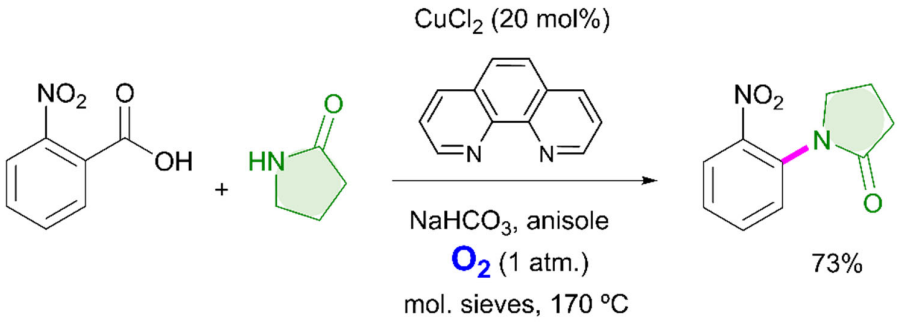


Figure 14. Copper-catalyzed decarboxylative C-N coupling. This effective strategy for N-arylation employs a straightforward copper(II)–phenanthroline catalytic system, enabling efficient cross-coupling of various benzoic acids with appropriate ortho-substituents and diverse nitrogen nucleophiles, such as 2-nitrobenzoic acid and pyrrolidin-2-one. Among the oxidants tested, molecular oxygen proved to be the most effective, whereas alternatives such as peroxides, peroxydisulfates, quinones, metal-based oxidants, and hypervalent iodine reagents resulted in lower yields of the targeted coupling products.

6.5. Other Light-Induced Processes

Oderinde, Johannes, and co-workers presented significant findings on the role of molecular oxygen in Ir-photoredox/Ni dual-catalyzed cross-coupling reactions. Their research demonstrated that dioxygen is crucial for catalyst activation when air-stable Ni(II) precatalysts are used in *N*,*N*-dimethylformamide (DMF) under compact fluorescent (CF) lamp irradiation (Figure 15); it likely promotes the rapid reduction of Ni(II) to Ni(0) by Ir(II). The study also explored the effects of solvent and light source (CF or blue LED) on the development of reproducible and efficient iridium-photoredox/nickel dual-catalyzed sp^3-sp^2 carbon-carbon bond-forming reactions [76]. In this case, O_2 functions as a catalyst activator. Following their initial work on the visible-light-induced three-component selenofunctionalization of alkenes, which included the selenoarylation of styrene to provide a (2,2-diarylethyl)(phenyl)selane [77], Oh, Kim, and co-workers reported a selenocyclization of *ortho*-vinylanilides that involved a visible-light-induced, oxygen-controlled synthesis of 4*H*-3,1-benzoxazines. From the beginning, the authors observed that this newly established visible light-induced selenocyclization of ortho-vinylanilides depended on the critical role of reduced oxygen levels, which favored the formation of 4*H*-3,1-benzoxazines through selenocyclization without the need for photocatalysts or promoters. Moreover, this innovative approach employed light and O_2, producing only a half equivalent of water as a by-product. After preparing an extensive array of 4*H*-3,1-benzoxazine derivatives by this protocol, the authors conducted several experiments for mechanistic studies. As a result, a plausible mechanism for this process is outlined in Figure 16 [78]. Given the slightly lower electronegativity of selenium (2.4 on the Pauling scale) and the preservation of π-bonds and ring structures from the substrate to the 4*H*-3,1-benzoxazine product, no net oxidation is observed. O_2 acts as the terminal oxidant that oxidizes selenol/selenolate intermediates generated in situ, closing the catalytic cycle and allowing cyclization.

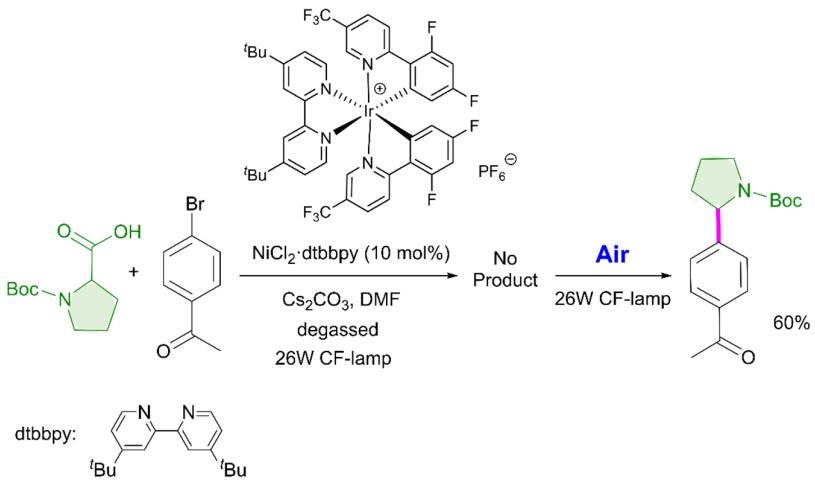


Figure 15. Ir-photoredox/Ni dual-catalyzed decarboxylative cross-coupling. The authors explored how molecular oxygen combined with a light source (either a compact fluorescent lamp or blue LED) affects various Ir-photoredox-driven transformations, including decarboxylative cross-coupling of (tert-butoxycarbonyl)proline and 1-(4-bromophenyl)ethan-1-one. The results showed that O_2 is crucial for activating the catalyst when air-stable Ni(II) precursors are used in DMF under CF lamp illumination; however, when $Ni(COD)_2$ is employed, O_2 is unnecessary for catalysis under the same conditions.

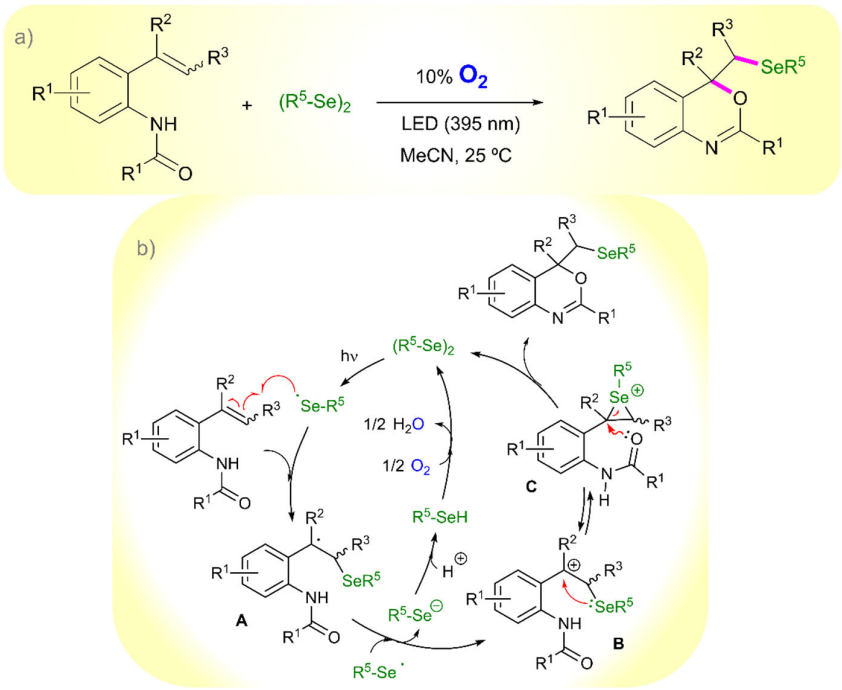


Figure 16. Selenofunctionalization of alkenes provides an atom-economic pathway to benzoxazines that are suitable for further modification. (**a**) Visible light-mediated selenocyclization of *N*-(2-alkenylaryl)anilides leading to 4-(selanyl)alkyl-4*H*-benzo[*d*][1,3]oxazines. The reaction is not limited to aryl diselenides; alkyl and heteroaryl diselenides also undergo smooth cyclization, expanding the diversity of accessible selenylated benzoxazines. Moreover, the *ortho*-vinylanilide substrates tolerate a wide range of substituents on the aromatic ring. (**b**) Suggested mechanistic route for visible-light-mediated selenocyclization under low O_2 concentration.

Some of the above examples outline the increasing relevance of the combination of visible light and dioxygen. However, visible-light-driven photochemical processes that generate reactive oxygen species (ROS) or peroxides pose significant safety hazards—such as fire, explosion, and human health risks from exposure—especially when scaled to

bulk or open systems, due to the highly reactive nature and accumulation potential of these intermediates. The literature highlights that the uncontrolled generation of ROS (e.g., hydroxyl radicals, superoxide, hydrogen peroxide) during photocatalysis can induce oxidative stress, damage materials, and, in biological contexts, cause cytotoxicity and genotoxicity, reinforcing the need for careful risk management in industrial settings. To mitigate these hazards, best practices include using closed reactor systems, real-time ROS monitoring, selection of oxidation-resistant materials, and catalyst modification, all underpinned by robust process safety assessments and operator training to address scale-up challenges. These strategies are essential for safely advancing photochemical synthesis and remediation technologies from laboratory to industrial applications, where uncontrolled ROS formation could otherwise compromise product quality, equipment integrity, and operator safety [79,80].

6.6. Alkylation Reactions

A radical α-alkylation of ketones with unactivated alkenes under catalytic conditions was described by Leyva-Pérez and co-workers. After an extensive screening of peroxides and metal catalysts, they found that catalytic amounts (2 mol%) of $Mn(OAc)_2 \cdot 4H_2O$ - either as a soluble salt or supported on zeolites- combined with molecular oxygen at low pressure (1–4 atm) in the presence of biomass-derived *n*-hexanoic acid induced the aerobic α-alkylation of both cyclic and acyclic ketones with allyl and alkyl alkenes (Figure 17). Peracid radicals, generated in situ by reaction of dioxygen with the manganese catalyst under these acidic conditions, are key to understanding this process, which offers a less aggressive alternative to current industrial protocols, thus opening avenues for sustainable aerobic catalytic systems. Comprehensive reactivity and mechanistic investigations reveal that larger cyclic ketones better stabilize α-positioned radicals due to increased polarizability, steric factors, and the absence of proximity effects. To demonstrate practical applicability, the industrial fragrance exaltolide was synthesized on a gram scale using the above Mn^{2+} catalysts in air, surpassing previous methods in terms of safety, environmental impact, synthetic efficiency, and overall yield [81]. The role of O_2 in this reaction is related to its ability to act as both a radical initiator and the terminal oxidant that enables the Mn-mediated generation of radical oxidants.



Figure 17. Radical α-alkylation of cyclododecanone with 1-dodecene. In addition to 1-dodecene, the protocol enables the direct coupling of cyclododecanone with other alkenes, such as allyl acetate, allyl hexanoate, and other allyl derivatives, to form α-alkylated cyclododecanone products.

6.7. Amide Formation

Amidation reactions constitute the most abundant group of transformations in medicinal chemistry. However, the development of more efficient methods with greater atom economy for the synthesis of amides is still considered a priority objective. Despite the large number of existing methods for preparing amides, the need in many cases to use stoichiometric amounts of harmful reagents (acyl chlorides, anhydrides, carbodiimides, benzotriazoles, carbon tetrachloride, α,α-dichlorodiarylmethanes, thiosulfonates) for amide formation has motivated continued intensive research in this field [82]. In this context, transamidation reactions become a highly attractive alternative, considering the abundance

and diversity of amides as very convenient acylating agents. However, the amidation of planar or non-activated amides (unlike non-planar or activated amides -that is, amides in which N-CO conjugation has been blocked, such as *N*-acylamides, *N*-acylimides, *N*-Boc amides and other *N*-acylcarbamates, *N*-tosylamides, etc.) is problematic due to the stability of these amides based on the strong $n_N \rightarrow \pi^*_{C=O}$ interaction and the thermoneutral nature of the reaction. As a result, high temperatures and prolonged reaction times are necessary, especially for secondary and tertiary amides. Different strategies have been described to overcome this limitation, and regarding transition-metal-catalyzed transamidations, they are usually limited to primary amides and ureas as substrates, require the aforementioned high temperatures, and provide mixtures of amides as a result of partial equilibrium [83]. SanMartin and co-workers observed that the presence of molecular oxygen strikingly accelerated the palladium-catalyzed transamidation of *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide with benzylamine. After optimizing the reaction conditions (10^{-4} mol% of dichloro(1,5-cyclooctadiene)palladium(II), 10^{-4} mol% 1-benzyl-1,2,3-triazole, pivalic acid, O_2 (1 atm), diethyl carbonate, 120 °C), these conditions were applied to a wide variety of amides (including primary, secondary, and tertiary amides, as well as imides, carbamates, and ureas) and aliphatic and aromatic amines. Good yields were obtained in most cases (Figure 18). In addition to the generality of the procedure, its high efficiency should be highlighted (10^{-4} mol% of the palladium source was used, so that the products were isolated free of palladium traces) and the use in this case of a sustainable and biodegradable solvent, diethyl carbonate. A thorough analysis of the results obtained from a series of experiments (kinetic studies, experiments performed in the presence of other oxidants and radical inhibitors, analysis of other potentially active metals, catalyst poisoning-inhibition tests, isolation of reaction intermediates, transmission electron microscopy imaging, electron paramagnetic resonance spectroscopy analysis, and high-resolution ultra-performance liquid chromatography coupled with electrospray ionization analysis of the reaction crude, etc.) led the authors to propose a complex mechanistic pathway based on the insertion of dioxygen to generate a palladium hydroperoxide intermediate. Thus, initial acylation of benzylamine by diethyl carbonate in the acidic medium provided by pivalic acid releases ethanol, which is incorporated as a ligand, along with the pivalate anion and the triazolyl ligand, in the generation of an initial palladium(II) complex. This complex undergoes several transformations involving molecular oxygen insertion, nucleophilic attacks, and ligand exchanges. The reaction proceeds through multiple intermediates, including palladium hydrides and various complexes. The mechanism includes alternative pathways to the final product, involving different types of nucleophilic attacks and protonation steps. In addition to the electron transfer of the Pd(II)-Pd(0) cycle and the release of H_2O_2 and finally water through a Radziszewski-type process, the use of an excess of amine constitutes one of the driving forces of the reaction [84].

The same group reported a highly effective method for the iron-catalyzed direct acylation of amines with carboxylic esters and acids. This scalable and atom-efficient procedure employed molecular oxygen as a reaction initiator and pivalic acid as an additive. The versatility of the above approach was evidenced by its successful application to a diverse array of primary and secondary amines, as demonstrated through over 65 examples presented in the paper. Furthermore, the reaction was again conducted in diethyl carbonate, a more environmentally friendly solvent. To elucidate the roles of various components in the reaction, a detailed mechanistic proposal was put forward, centered on an Fe(II)/Fe(III) cycle and the interaction between Fe(II) and dioxygen (Figure 19). This innovative procedure represented a significant advancement in amine acylation chemistry, offering both practical and environmental benefits [85]. Furthermore, given the low catalyst loading and the use of a sustainable solvent, both amidation protocols—oxygen-induced transamidation and

acylation of amines—demonstrate strong potential as candidates for pilot-plant trials or large-scale production. In these two cases, O_2 acts as a catalyst activator.

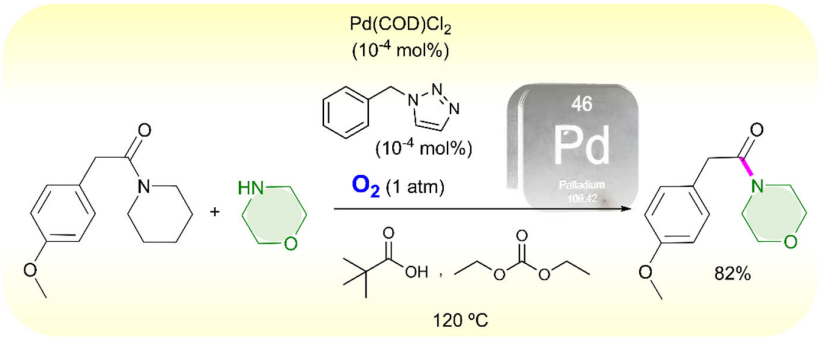


Figure 18. Palladium-catalyzed transamidation of a tertiary amide with morpholine. Transamidation of 2-(4-methoxyphenyl)-1-(piperidin-1-yl)ethan-1-one with morpholine takes place in the presence of infinitesimal amounts of dichloro(1,5-cyclooctadiene)palladium(II) and 1-benzyl-1*H*-1,2,3-triazole, using diethyl carbonate as a convenient solvent.

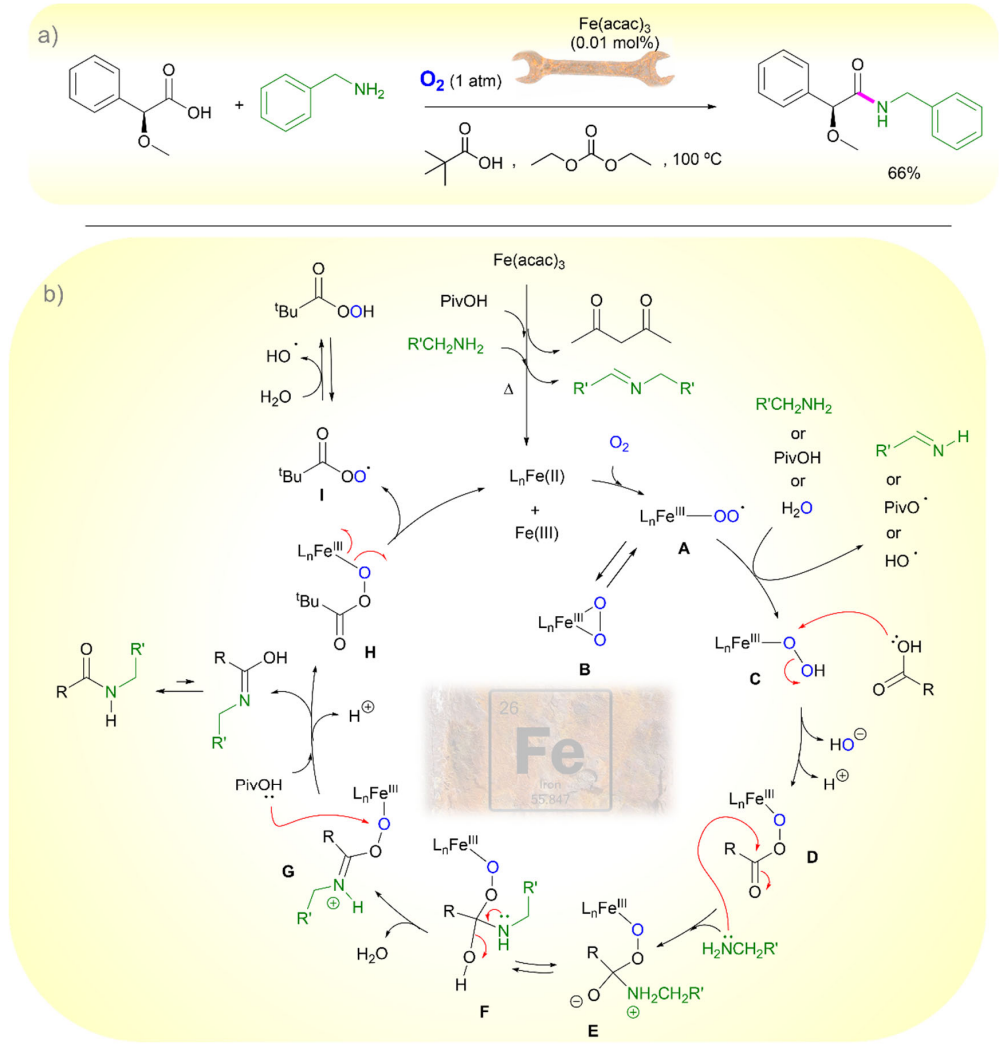


Figure 19. Catalytic direct acylation of amines with carboxylic acids and esters has emerged in response to the growing demand for more efficient and environmentally friendly alternatives to traditional amidation protocols. (**a**) Iron-catalyzed aerobic acylation of benzylamine with (*S*)-2-methoxy-2-phenylacetic acid. (**b**) Mechanistic proposal for the iron-catalyzed aerobic direct amidation of carboxylic acids and amines.

Table 1. Summary of unsaturation-conserving transformations involving molecular oxygen.

Reaction Type	Role of O_2	Net Redox Nature	References
Enzymatic processes Radical functionalizations using organoboron compounds Diimide-mediated reductions	Activation/oxidation of the metal center at the enzyme Radical initiator (generation of alkyl radicals) Oxidation of hydrazine	Neutral (cleavage to provide reduced substrate and CO_2/formate) Neutral (reduction/polymerization of the substrate with borates as by-products)	[15–18,20–22]
Processes involving singlet oxygen species	Source of singlet oxygen-> generation of radical species/oxygen atom insertion into the product	Neutral (reduction/hydrogenation of the substrate with dinitrogen and hydrogen peroxide as by-products) Neutral/Partly oxidative (cyclication/coupling/rearrangement of the substrates with peroxides as by-products)	[25,27,28,33]
Enzymatic processes Radical functionalizations using organoboron compounds Diimide-mediated reductions Processes involving singlet oxygen species	Activation/oxidation of the metal center at the enzyme Radical initiator (generation of alkyl radicals) Oxidation of hydrazine Source of singlet oxygen-> generation of radical species/oxygen atom insertion into the product	Neutral (polymerization/nucleophilic addition/[2 + 2] cycloaddition/decarboxylative coupling/selenocyclization/α-alkylation/amidation with peroxides/CO_2/peracids as by-products) Neutral (cleavage to provide reduced substrate and CO_2/formate) Neutral (reduction/polymerization of the substrate with borates as by-products	[41,45–47,49,50]
Miscellaneous Enzymatic processes	Catalyst/reagent activation Activation/oxidation of the metal center at the enzyme	Neutral (reduction/hydrogenation of the substrate with dinitrogen and hydrogen peroxide as by-products) Neutral/Partly oxidative (cyclication/coupling/rearrangement of the substrates with peroxides as by-products)	[55–58,62]
Radical functionalizations using organoboron compounds	Radical initiator (generation of alkyl radicals)	Neutral (polymerization/nucleophilic addition/[2 + 2] cycloaddition/decarboxylative coupling/selenocyclization/α-alkylation/amidation with peroxides/CO_2/peracids as by-products)	[63,67,71,75,76,78,81,84,85]

7. Conclusions and Outlook

Molecular oxygen is widely regarded as a terminal oxidant, yet the transformations discussed in this review demonstrate that it can also enable organic reactions in which the degree of unsaturation of the principal organic substrate and product is conserved or decreased. These formally non-oxidative processes reveal functions of O_2 beyond conventional oxygen-atom transfer or substrate oxidation. The main conclusions and future perspectives of this review are as follows:

O_2 can mediate or induce organic transformations without net oxidation of the main organic substrate. Enzymatic processes, radical functionalizations, polymerizations, singlet-oxygen reactions, and selected amide syntheses illustrate that molecular oxygen can participate in bond-forming, bond-cleaving, rearrangement, and reduction processes while conserving or decreasing the unsaturation number.

The role of O_2 is highly system-dependent and may be multiple within a single transformation. It can activate metals, generate reactive intermediates, supply singlet

oxygen, or act as a direct redox catalyst. In many systems, its functions as oxygen-atom source, reactive-intermediate precursor, catalytic intermediate, terminal oxidant, or radical initiator are intertwined and must be established experimentally for each case.

Metal activation is a recurrent function of molecular oxygen. Through oxidation, reduction, or complexation, O_2 can generate or regulate active metal species, as illustrated by enzyme activation, iron and palladium peroxo complexes in amidation, and metal activation in cross-coupling reactions.

O_2 is a versatile precursor to reactive intermediates. It can generate alkyl and peracid radicals, diimines, and imines, which enable radical reductions, organoborane-initiated polymerizations, and olefin reductions through diimide. In this regard, singlet oxygen enables selective transformations beyond conventional oxidation. O_2-derived singlet oxygen participates in the arylation of quinoline and quinoxalinone derivatives and in cascade formation of pyrroloisoquinolinones from furans and β-(hetero)arylethylamines.

Mechanistic certainty remains a central challenge. Whether O_2 is incorporated, consumed, reversibly bound, or regenerated should be determined through quantitative oxygen-balance experiments, $^{18}O_2$ labeling, operando spectroscopy, kinetic analysis, and radical-trapping controls, rather than inferred solely from product structures. The relationship between O_2 activation and preservation of substrate unsaturation also requires further study, particularly in catalytic systems where O_2 regulates metal oxidation state, coordination environment, or catalyst deactivation.

Future development depends on expanding scope, ensuring safety, and establishing predictive design principles. O_2-enabled non-oxidative methodologies offer attractive opportunities for sustainable synthesis, including their potential use as reversible redox mediators, spin-state or energy-transfer partners, and catalyst-activation reagents in photochemical, electrochemical, and transition-metal-catalyzed reactions. However, scale-up requires rigorous management of the hazards associated with O_2, organic solvents, heat, visible light, reactive oxygen species, and peroxides. Closed systems, real-time monitoring, appropriate materials and catalyst design, comprehensive safety assessment, and operator training will be essential for safe industrial implementation.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

acac	Acetylacetonate
ADOs	Cyanobacterial aldehyde-deformylating oxygenases
Alloc	Allyloxycarbonyl
Boc	*tert*-Butyloxycarbonyl
bpy	2,2′-Bipyridyl
Cbz	Carbobenzyloxy

CF	Compact fluorescent lamp
COD	1,5-Cyclooctadiene
DMF	*N*,*N*-Dimethylformamide
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-bipyridine
equiv.	Equivalents
LED	Light-emitting diode
LDPE	Low-density polyethylene
MFC	Mass Flow Controller
mol. sieves	Molecular sieves
ppy	Phenylpyridine
P-S	Pictet-Spengler
RB	Rose Bengal
ROS	Reactive oxygen species
S_H2	Bimolecular homolytic substitution

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