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Chapter 2

# Recent Highlights in Green Oxidative Chemical Processes Applied to Steroid Chemistry

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Additional information is available at the end of the chapter

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**Abstract**

Steroids and their oxidation products are widely distributed in living organisms and are important intermediates for the synthesis of many biologically active molecules. Due to their pharmacological and synthetic relevance, several oxidative chemical processes for the functionalization of the steroid nucleus have been developed. Green chemistry principles have been incorporated in some oxidative transformations of steroids, allowing significant advances in synthetic chemistry applied to these compounds. This chapter presents a selection of relevant applications of pharmaceutical green chemistry to steroid's oxidative processes. Special emphasis is given to catalytic processes encompassing heterogeneous nanocatalysts, whose application in this context is increasing over the past years. This chapter is organized according to the reaction type that includes alcohol oxidation, epoxidation of alkenes, and allylic oxidation of alkenes to enones, among other relevant oxidative transformations. Biocatalytic oxidative methods applied to steroid synthesis are not included in this review.

**Keywords:** green pharmaceutical chemistry, steroids, catalysis, oxidation, green technologies, nanocatalysts

## 1. Introduction

### 1.1. Basic steroid chemistry and relevance of oxygenated steroids

Steroid compounds are found in almost all living organisms [1, 2], having an important role in their vital activity [1–4]. The steroid hormones were discovered and characterized during the 1930s, and since then, it has been realized that steroid compounds can control important

physiopathological conditions, being therefore important starting point for the development of new medicines [3]. Indeed, several natural and synthetic steroids are important therapeutic options for a wide range of diseases. These include sex and corticosteroid hormones, bile acids, vitamin D derivatives, and cardiotonic steroids, among others, that have shown unique therapeutic value for a broad array of medical conditions [1]. Due to their relevance, over the last decades, hundreds of steroid compounds have been isolated from natural sources, whereas many thousands of them have been obtained synthetically [2, 4] and their study has continued until present days in both chemical and biological perspectives.The steroidal basic structure constitutes a common chemical skeleton of four fused rings, consisting of three six-membered rings and a five-membered ring [1, 2, 5]. This hydrocarbon scaffold contains 17 carbons and has the cyclopentaneperhydrophenanthrene basic structure. The four steroid rings are labeled as A, B, C and D and their carbon atoms are numbered according to the universal convention according to the IUPAC-IUB (International Union of Pure and Applied Chemistry/International Union of Biochemistry) Joint Commission on Biochemical Nomenclature [6]. Angular methyl groups at C13 and C10 are designated as 18-$CH_3$ and 19-$CH_3$, respectively, and alkyl substituents at C17 are the steroid side-chain. The 18- and 19-methyl groups stand above the plane of the steroid skeleton and, by convention, have β-configuration. Therefore, as stated, other atoms or substituents located above this plane also have β-configuration, while those below it have $\alpha$-configuration (**Figure 1**) [1, 2, 5, 6].

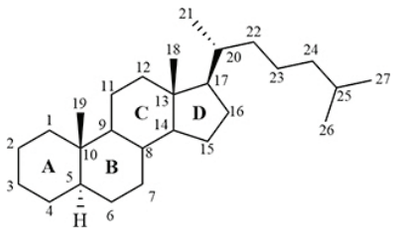


**Figure 1.** Chemical structure of the 5$\alpha$-cholestane nucleus.

The preparation of steroids containing oxygenated functions in the steroid nucleus is of high relevance and can be performed by means of several oxidative processes. Among the large variety of available methods, the allylic oxidation and epoxidation of alkenes and the alcohol oxidation are probably the most commonly used oxidative transformations [1, 2]. In fact, the allylic oxidation of steroidal alkenes to the corresponding enones, such as $\Delta^5$-7-ketones, is of great importance because of their significant biological properties. The diastereoselective epoxidation of steroidal alkenes is a relevant challenge because of the difficulty in the preparation of pure epoxides. This transformation is also very important not only because the epoxide moiety is of high synthetic interest for further elaboration but also because this functionality has been found in several biologically active steroids. The oxidation of steroidal alcohols is also considered in this chapter. A relevant example of high industrial interest is the transformation of $\Delta^5$-3β-hydroxylated steroids into the corresponding $\Delta^4$-3-ketones, a typical functionality of the major class of steroidal hormones [1, 2].

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### 1.2. The green chemistry concept and green nanotechnologies

According to the Environmental Protection Agency, green or sustainable chemistry has been defined as "the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances" [7]. In fact, over the years, a large development in this field was observed and several new greener procedures are now being used in the chemical industry [8]. In the pharmaceutical industry, due to the complexity of the products involved as well as the characteristics/issues associated with their uses, the application of the green chemistry principles in the production of medicines has been an enormous challenge [8, 9]. Considering that the major sources of waste in the chemical/pharmaceutical industry are the use of stoichiometric reagents and solvent losses, and the clear solution to this problem is the development of catalytic reactions in alternative reaction media. Additionally, the possibility of recovery and reuse of the reactants/catalysts/solvents and the use of inexpensive, renewable and non-toxic materials are key issues in this context. Accordingly, over the years several greener approaches for the majority of chemical reactions have been developed [10–12].

The development of catalytic processes has been the most explored strategy in green and sustainable chemistry, avoiding the use of numerous hazardous and/or expensive stoichiometric reactants. According to their nature, catalysts can be classified as metallic, organometallic, organocatalysts and biocatalysts. On the other hand, based on their physical state, catalysts can be grouped as homogeneous and heterogeneous [10–13]. In this context, the use of heterogeneous catalysts (either metallic or non-metallic) has the important advantage of allowing their recovery and reuse [14, 15]. Furthermore, of major relevance in the pharmaceutical industry is the synthesis of organic compounds devoid of metal contamination, which can be achieved by using organo- [16, 17] and biocatalytic [18] procedures. Biocatalysis also has several advantages in the context of green chemistry, including the fact that reactions are frequently performed under mild conditions of temperature, pressure and pH and using water as solvent. Moreover, the catalyst is biodegradable and derived from renewable raw materials. Noteworthy, biocatalysis frequently leads to higher chemo-, regio- and stereoselectivities, than traditional chemical processes [10].

A special advance in green chemistry is the use of nanotechnologies. According to McKenzie and Hutchison, "Green nanoscience/nanotechnology involves the application of green chemistry principles to the design of nanoscale products, the development of nanomaterial production methods, and the application of nanomaterials" [19]. In organic chemical synthesis, the main application of this concept is the use of nanomaterials as nanocatalysts, being considered sustainable alternatives to conventional materials. In fact, the nanosized particles can offer some of the advantages of homogeneous catalysts because of an increased exposed surface area of the active component of the catalyst, which enhances dramatically the contact between reactants and catalyst. In addition, similarly to heterogeneous catalysts, their insolubility in the reaction solvents renders them easily separable from the reaction mixture, which consequently makes the product isolation stage effortless. Moreover, the activity and selectivity of nanocatalysts can be manipulated by tailoring chemical and physical properties such as size, shape, composition and morphology [20]. Due to these interesting properties, the use of nanocatalysts has been increasing over the years [21].

Solvent selection is another important issue in the development of new synthetic processes, in the chemical and pharmaceutical industries [8, 22]. Actually, the highest part of the material usage for active pharmaceutical ingredient (API) manufacture is usually constituted by solvents. In fact, it was estimated that their use consumes more than 50% of the overall energy and accounts for half of the post-treatment green-house gas emissions. Ideally, reactions should be performed without any solvent (neat conditions). However, solvents are critical for the reaction rates and selectivities and are often required for heat and mass transfer. Consequently, solvents should be readily available, non-volatile, non-flammable, non-toxic, recyclable and cheap [8, 10, 22]. Attractive solvents from both economical and environmental point of view can include water [23, 24], ionic liquids [25, 26], fluorous solvents [27] as well as supercritical fluids (e.g., supercritical $CO_2$) [28, 29].

Green chemistry also deals with the minimization of energy usage. In fact, the addition of energy, mostly thermal, is necessary for the majority of organic reactions. For this reason, the strategy to develop chemical transformations under mild reaction conditions has been exploring alternative energy sources such as microwaves (MW), ultrasounds and even light [11, 12, 30]. In fact, successful advances have been made over the years mainly on MW-promoted reactions [30, 31] but also on sonochemistry [30, 32] and photochemistry [33].

### 1.3. Scope and organization of this chapter

Due to the above referred biological and synthetic importance of steroids, several new green chemical processes for the preparation and/or functionalization of the steroid nucleus have also been developed over the years [34, 35]. In this chapter, relevant applications of green oxidative chemical processes in steroid chemistry are described. Special emphasis is given to catalytic processes involving the use of heterogeneous catalysts, including nanocatalysts. Other green approaches, such as MW technologies as well as the use of ionic liquids as solvents, are presented. This chapter is organized according to the reaction type that includes alcohol oxidation, epoxidation, allylic oxidation and miscellaneous oxidative transformations.

## 2. Alcohol oxidation

The most common oxidative transformation in steroid chemistry is probably the oxidation of alcohols [34, 35]. Actually, not only several important natural and synthetic steroids have carbonyl groups but also this oxidation is frequently used as an intermediary step in the preparation of a large variety of bioactive steroids. For this reason, several oxidative processes for this reaction have been developed over the years. The most employed oxidants are transition metals, particularly chromium(VI) reagents. Nonetheless, other oxygen- and halogen-based oxidants as well as other oxidizing conditions, frequently combined with suitable catalysts, have been described [34, 35].

As a relevant example, a heterogeneous catalyst described for the successful oxidation of 5$\alpha$-cholestan-3$\beta$-ol to 5$\alpha$-cholestanone (**Scheme 1**) was chromium exchanged zeolite (CrE-ZSM-5) combined with 70% aqueous *tert*-butyl hydroperoxide (TBHP), an oxygen-based oxidant. However, it was shown that the reaction was, at least partially, homogeneously catalyzed by

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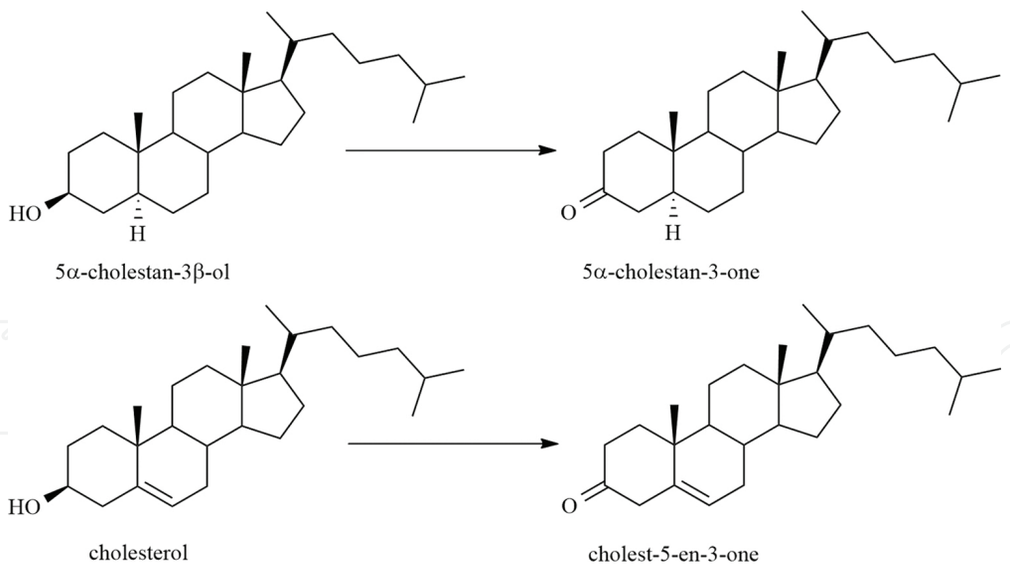
leached chromium [36]. Recently, metal-monocatecholate species were immobilized in a Zr(IV)-based metal-organic framework (MOF) to create new efficient heterogeneous catalysts. Within these, Cr-metalated MOFs revealed to be useful in the oxidation of a wide range of alcohols to ketones with TBHP (80% TBHP in di-*t*-butyl peroxide/water 3:2 solution). Catalysis could be achieved with very low metal loadings (0.5−1 mol %), and these MOF-based catalysts were completely recyclable and reusable [37]. In spite of the fact that 5α-cholestan-3β-ol is too large to diffuse into the pore cage of this catalyst, this steroidal alcohol was also efficiently oxidized with this system and probably the catalysis occurred on the surface of the particles. The oxidation of several alcohols, including cholesterol (**Scheme 1**), was also reported in aqueous conditions using the same oxidant and vanadyl sulfate as catalyst. Noteworthy, after completion of the oxidation and isolation of the product by extraction, the catalyst was recovered in the aqueous layer and reused in a new reaction by simply adding $CH_3CN$, substrate and TBHP [38]. The immobilization of a $RuCl_3$ complex in an aluminum metal-organic framework (MOF), MOF-253, by post-synthetic modification, afforded an heterogeneous catalyst (MOF-253-Ru) that was used in the oxidation of primary and secondary alcohols with $PhI(OAc)_2$ as the oxidant, under very mild reaction conditions. When applied to 5α-cholestan-3β-ol (**Scheme 1**), a fast and high-yielding reaction was observed and after 4 hours of reaction, the corresponding ketone was obtained in 89% yield. Interestingly, due to the structure of the catalyst, it seems that its pore size is large enough to accommodate this complex substrate. Moreover, the MOF-253-Ru could be successively recycled up to six times without significant loss of activity [39].




**Scheme 1.** Oxidation of 5α-cholestan-3β-ol and cholesterol to the corresponding 3-ketone derivatives.

Of high interest in the context of green chemistry is the use of molecular oxygen combined with recoverable and reusable heterogeneous catalysts in the transformation of alcohols to carbonyl compounds. An important example is the use of the heterogeneous Pd catalyst consisting on the palladium(II) acetate-pyridine complex supported on hydrocal-

cite in the aerobic oxidation of 5α-cholestan-3β-ol (**Scheme 1**) by air at atmospheric pressure as the sole oxidant under mild conditions. This catalyst was easily prepared using only commercially available reagents and could be reused several times [40]. Later, diverse nanocatalyts were reported to be effective in this transformation under aerobic conditions. These include gold nanoparticles immobilized in aluminum oxyhydroxide [41] or supported in hydrotalcite [42], and palladium nanoparticles entrapped in aluminum hydroxide [43]. Other steroidal alcohols including 3α-hydroxy-5α-pregnan-20-one and nandrolone were oxidized under aerobic conditions catalyzed by *in situ* generated Pd nanoparticles from $Pd(O_2CCF_3)_2$ and neocuproine. Interestingly, this reaction was performed in aqueous solvent [44]. The use of fluorinated solvents is another relevant strategy in this context not only because they can be recovered and reused, but also because of the fact that the solubilization of oxygen is favored in fluorinated solvents. A relevant example was the aerobic oxidation of 5α-cholestan-3β-ol to 5α-cholestanone by molecular oxygen (**Scheme 1**) in a fluorinated biphasic system composed by perfluorodecalin and toluene, under catalysis by palladium(II) acetate combined with a perfluoroalkylated-pyridine ligand [pyridine-3-carbaldehyde bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl) acetal]. Of high interest is the fact that the fluorinated phase containing the active palladium species was easily separated and reused several times without significant loss of catalytic activity [45].

The use of a readily available organic compound as hydrogen acceptor can provide an interesting alternative to aerobic conditions namely by overcoming safety concerns linked to the use of flammable solvents. A relevant example of this strategy is the use of styrene as hydrogen acceptor in the oxidation of steroidal alcohols such as 3β-hydroxy-5α-androstan-17-one catalyzed by a low loading supported copper catalyst ($Cu/Al_2O_3$) [46]. More recently, Mitsudome et al. described the successful oxidation of 5α-cholestan-3β-ol to 5α-cholestanone promoted by two different nanocatalysts (**Scheme 1**). These included hydrotalcite-supported copper nanoparticles [47] and hydrotalcite-supported silver nanoparticles [48], which were used in combination with mesitylene or *p*-xylene as hydrogen acceptor, respectively.

Several ionic liquids can be used as compatible supports for or catalyst/reagent immobilization with the advantage of allowing its recovery and recycling. In this context, an organosulfoxide anchored on imidazolium ionic liquid scaffold was used in the oxidation of 5α-cholestan-3β-ol to 5α-cholestanone (**Scheme 1**) in 85% yield, under Swern oxidation conditions. This ionic liquid-supported reagent has the advantages of being non-volatile and odorless but also recoverable and reusable after reoxidation of the sulfide with periodic acid [49]. The oxidation of several alcohols including 5α-cholestan-3β-ol using ion-supported methyl sulfoxides and methyl sulfides through Swern and Corey-Kim reaction conditions, respectively, was also reported. Again, unpleasant odor was not detected in both procedures, and good yields and high purity of the products were achieved after straightforward work-ups. Moreover, the reactants could also be recovered and reused [50]. A similar strategy involved the use of ion-supported (diacetoxyiodo)benzenes (IS-DIB) in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO) to efficiently transform a large variety of alcohols including 5α-cholestan-3β-ol (**Scheme 1**) under mild conditions. Ion-supported iodobenzenes, the co-products derived from IS-DIB in this oxidation, were recovered in good

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yields by a simple extraction and were then re-oxidized with sodium peroxoborate, for reuse in the same transformation [51].

The preparation of oxandrolone intermediates required the oxidation of 17$\alpha$-methylandrostan-3$\beta$,17$\beta$-diol, which was accomplished by means of several mild, efficient and eco-friendly oxidizing conditions involving the use of NaOCl or $H_2O_2$/catalytic $Na_2WO_4$ under phase transfer conditions [52]. The oxidation of this substrate was also studied using the environmentally benign ionic liquid [bmim][Br] and mild and inexpensive reagent 2-iodoxybenzoic acid (IBX). Interestingly, it was observed that the relative amount of oxidant determined the products obtained. In effect, using 1.2 eq. of IBX, mestanolone was the only product, however, with 2.4 eq., a 1,2-dehydrogenation occurred along with the oxidation to the carbonyl functionality, affording 17$\beta$-hydroxy-17$\alpha$-methyl-$\Delta^1$-androsten-3-one as the major product in a one-pot reaction. Moreover, by simply concentrating the filtrate under reduced pressure, the ionic liquid was recovered and effectively reused up to three times [53].

In addition to the previously described use of fluorinated solvents and ionic liquids, subcritical water may also be useful to replace environmentally unacceptable solvents in numerous organic reactions, including in oxidations of alcohols. This fact results from a dramatic decrease in solvent viscosity and an increase in substrate solubility observed with its use. Similarly to the observed with fluorinated solvents, molecular oxygen has a relevant solubility in subcritical water. In this context, Ozen and Kus reported a metal-free procedure using this solvent in several oxidations, including in the transformation of alcohols to carbonyl compounds. Under these conditions, cholesterol originated cholest-5-en-3-one (**Scheme 1**) in high yields [54].

The use of MW technology for the oxidation of alcohols to the corresponding carbonyl functions was also reported. Among other relevant substrates, diosgenin and cholesterol (**Scheme 1**) were oxidized to their $\Delta^5$-3-ketone derivatives in high isolated yields and after 2 minutes of reaction with pyridinium chlorochromate (PCC) and under MW irradiation [55].

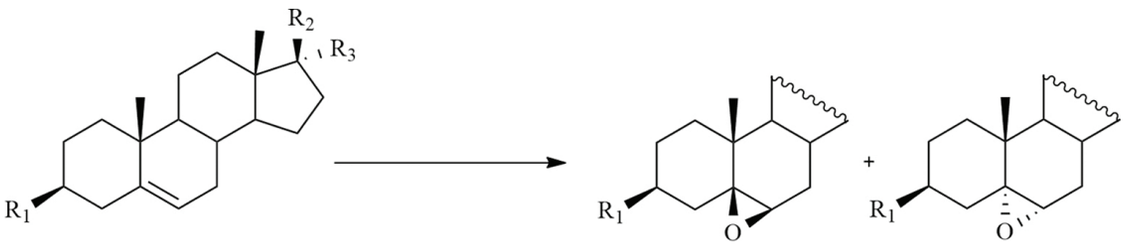
## 3. Epoxidation

Epoxysteroids, namely several withanolides and oxysterols, exhibit diverse biological activities [34, 35, 56, 57]. In addition, the epoxide functional group has high synthetic interest because the facile ring opening allows the stereoselective introduction of various functionalities into the steroidal nucleus.

Classically, the preparation of epoxysteroids involves the use of peroxacids, such as meta-chloroperoxybenzoic acid (MCPBA), usually originating $\alpha$-epoxides [58]. The stoichiometric combination of $KMnO_4$ and metal salts, on the other hand, allows the successful selective synthesis of $\beta$-epoxides. Steroidal epoxides can also be prepared using other oxidative procedures involving, for example, the use of isolated or *in situ* generated dioxiranes, aziridines and peroxides, frequently combined with adequate promoters. More recently, due to their greener nature, several catalytic epoxidations have been reported as well as various procedures using more environmental friendly oxidants in combination with metal and non-metal

catalysts [34, 35]. For example, new iron- and manganese-based catalysts were recently reported to efficiently epoxidize several unsaturated steroids in combination with $H_2O_2$ [59–62]. In addition, the possibility of the recovery and reuse of the catalysts as well as the use of alternative solvents were also considered greener approaches to perform this transformation [34, 35].

Stereoselective syntheses of several β-epoxysteroids were described with combinations of oxidant/catalysts including 2,6-dichloropyridine *N*-oxide (DCPNO)/Ru-based catalysts and iodosylbenzene (PhIO)/Mn-porphyrins [34, 35]. In this context, among other interesting and advantageous heterogeneous catalytic procedures, the use of a polymer-supported manganese(III) porphyrin as heterogeneous catalyst and PhIO as oxidant has been reported for the β-selective epoxidation of several $\Delta^4$- and $\Delta^5$-steroids (**Scheme 2**) [63] Similar results were observed using DCPNO as oxidant combined with a ruthenium(II) tetrafluorophenylporphyrin (TFPP) carbonyl complex [Ru(TFPP)CO] covalently attached to functionalized silica [64] or with [$Ru^{II}$(F20-TPP)CO] (TPP = tetraphenylporphyrin) covalently attached to poly(ethylene glycol) [65]. Other green approach for the effective preparation of 5β,6β-epoxides from $\Delta^5$-steroids (**Scheme 2**) involves the use of $O_2$ combined with a sacrificial aldehyde (Mukaiyama reaction conditions) and heterogeneous catalysts mainly bearing cobalt as the metal centre [66, 67]. Later, a $SiO_2$-supported Ru-monomer complex was described as catalyst for the epoxidation of cholesteryl benzoate under similar oxidative conditions [68].




**Scheme 2.** Epoxidation of $\Delta^5$-steroids affording 5β,6β- and 5α,6α-epoxides.

An alternative strategy to allow the recovery and efficient reuse of the catalysts is their use in perfluorinated compounds to mediate the oxidative reactions, being the fluorinated solvents also recoverable and reusable. Accordingly, it was reported that both 2,4-bisperfluorooctylphenyl butylselenide combined with $H_2O_2$ [69] and a ruthenium-pyridine-benzimidazole complex bearing perfluorinated 'ponytails' under Mukaiyama reaction conditions [70] catalyzed the epoxidation of various olefins, including 3β-chlorocholest-5-ene in a fluorous biphasic system.

The epoxidation of $\Delta^5$-steroids (**Scheme 2**) mediated by organocatalysts has been reported as an interesting approach to obtain these biological and pharmaceutical interesting steroids avoiding the contamination with metal compounds. A representative example is the regio- and stereoselective epoxidation of cholesteryl benzoate performed with $O_2$ in the presence of benzhydrol catalyzed by *N*-hydroxyphthalimide (NHPI) and hexafluoroacetone. Among other epoxides, this metal-free aerobic procedure allowed the selective preparation of 5α,6α-

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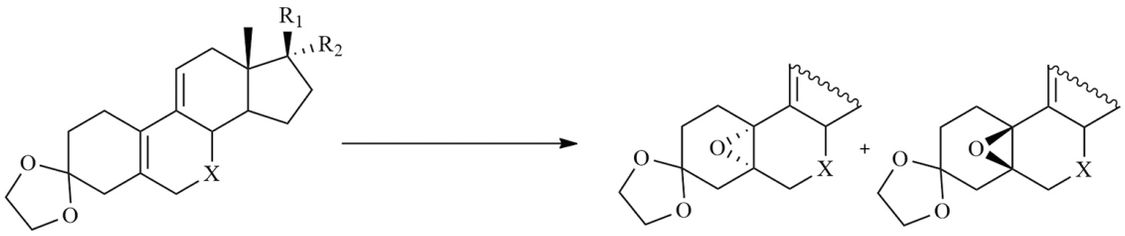
epoxycholesteryl benzoate in moderate yield [71]. Additionally, other 5β,6β-epoxysteroids (**Scheme 2**) were efficiently prepared using chiral ketones [e.g. 1,1,3(*S*),5(*R*)-tetramethyl-4-oxo-2(*R*),6(*S*)-diphenylpiperidinium triflate] as organocatalysts and Oxone™ as oxidant [72]. More recently, Dansey et al. [73] reported the application of a chiral and bulky fructose-derived ketone as catalyst also combined with Oxone™ for the regio- and stereoselective epoxidation of a diene A-homosteroid that occurred in the steroidal A-ring and afforded the corresponding β-epoxide as the only product in 35% yield [73].

The previously referred hexahaloacetones, including hexafluoroacetone, can be used as catalysts in combination with $H_2O_2$ for the epoxidation of several estra-5(10),9(11)-dienes to obtain the corresponding 5α,10α-epoxy derivatives (**Scheme 3**) as the major reaction products. An improvement of the α:β ratio of isomers to 7:1 was observed in the epoxidation of the substrate 3,3-ethylenedioxo-17α-(1-propynyl)estra-5(10),9(11)-dien-17β-ol using chiral ammonium salts derived from cinchona alkaloids as phase-transfer enantioselective catalysts under similar oxidation conditions [74]. Other oxidative conditions to perform this transformation (**Scheme 3**) used stoichiometric MCPBA or metal catalysts under homogeneous conditions. These included methylrhenium trioxide combined with $H_2O_2$ or urea-hydrogen peroxide or $Fe^{II}$-phthalocyanine and PhIO. However, the results were poorer than those observed with the combination of hexahaloacetones and $H_2O_2$ [75].




**Scheme 3.** Regioselective epoxidation of 3,3-ethylenedioxo-$\Delta^{5(10),9(11)}$-steroidal dienes.

Guggulsterones are natural steroids with high potential therapeutic interest namely as hypocholesterolemic agents, and therefore it is important to study their chemical reactivity including under oxidative conditions. For this purpose, the use of $H_2O_2$ combined with different 5,10,15,20-tetraarylporphyrinatoiron(III)chlorides (e.g., iron(III) 5,10,15,20-tetrakis(2′,6′-dichloro-3′-sulfonatophenyl)porphyrin, [$Cl_8TPPS_4Fe$(III)]) in dichloromethane as well as in the ionic liquid [bmim]$BF_4$ was evaluated by Singhal and Chauhan. Interestingly, in both solvents the 17,20-epoxide was formed in moderate yields along with minor hydroxylated products and it was observed that the reaction was more effective with *Z*-guggulsterone than its geometric isomer *E*-guggulsterone. In addition, the use of ionic liquid allowed the easy isolation of the products from the reaction mixture, leaving behind the water-soluble iron(III)porphyrin catalyst immobilized in it [76].

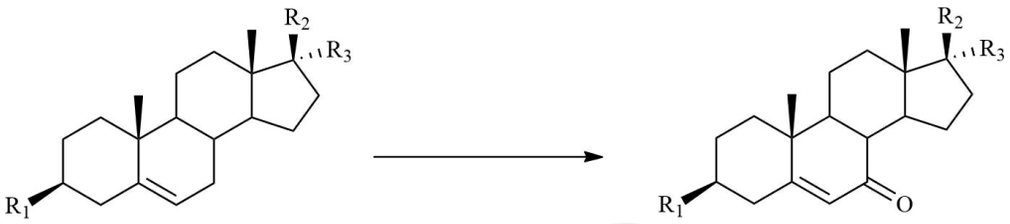
A recent and interesting example involving nanotechnologies was reported by Banerjee et al., who developed a heterogeneous $Co_xO_y$–N/C (*x*=1,3; *y*=1,4) catalyst composed by cobalt oxide nanoparticles with varying size along with very few large particles with a metallic Co core and an oxidic shell. This catalyst was applied to efficient epoxidation reactions of aromatic and

aliphatic olefins using TBHP as the terminal oxidant. Interestingly, among the substrates included in the study, only the linear double bond of 20-oxopregn-5-en-3β-yl *trans*-styrylates was epoxidized. This cobalt oxide catalyst can be recycled up to five times without significant loss of activity or change in structure [77].

## 4. Allylic oxidation

The allylic oxidation allows the synthesis of allylic alcohols, esters, ethers and α,β-unsaturated carbonyl compounds and has attracted interest over the years [78]. In the steroids field, the oxidation of alkenes to the corresponding enones, such as $\Delta^5$-7-ketones (**Scheme 4**), is an important reaction, not only because this functionality can be found in biologically active compounds, namely in the nutraceutical 7-oxodehydroepiandrosterone, but also because of its synthetic interest, associated with the further functionalization of the intact double bond or of the carbonyl group [78–80].

Typically, the oxidation of $\Delta^5$-steroids to $\Delta^5$-7-ketones (**Scheme 4**) has been performed using either chromium(VI) reagents in stoichiometric conditions or with TBHP combined with metal catalysts under homogeneous conditions [34, 35]. Very recently vanadyl acetylacetonate [81] or activated manganese dioxide [82] was explored as interesting catalysts for this reaction, using a 70% aqueous solution of TBHP. In addition, this oxidant was combined with the catalysts NHPI and $Co(OAc)_2$ in another optimized protocol described by Zhao et al. [83] for the regio- and chemoselective allylic oxidation of several functionalized $\Delta^5$-steroids.




**Scheme 4.** Allylic oxidation of $\Delta^5$-steroids to $\Delta^5$-7-ketones.

Greener approaches to prepare $\Delta^5$-7-oxosteroids from $\Delta^5$-steroids (**Scheme 4**) involved the use of catalysts immobilized on heterogeneous supports, which may allow their recovery and reuse. In fact, several heterogeneous catalysts including $KMnO_4/SiO_2$ in benzene or chromium(VI) adsorbed on $SiO_2/ZrO_2$, cobalt(II), copper(II), manganese(II) and vanadium(II) immobilized on silica and $BiCl_3$/montmorillonile K-10 were described for the allylic oxidation of $\Delta^5$-steroids in combination with TBHP as oxidant [34, 84].

The use of recyclable/reusable acetylacetone-metal catalysts modified by a pyridinium salt as co-catalysts in a NHPI-catalyzed oxidation of cholesteryl acetate by molecular oxygen under mild conditions was described. The pyridinium salt interacting with the acetylacetone ligand behaved as an electron-withdrawing group and as a co-catalyst for the decomposition of the alkyl hydroperoxides formed, allowing the relevant isolated yields. Interestingly, the catalyst

$[Co(acac\text{-}py)_2][Cl_2]$ could be easily recovered by a water wash method and reused at least four times with only a slight loss of catalytic activity [85].

Recently, the preparation of multifunctional core-shell nanospheres consisting of a core of metal clusters and an outer microporous silica shell was described. Interestingly, the Pd clusters encapsulated in hybrid core-shell structures exhibit exceptional size-selective catalysis in aerobic allylic oxidations of substrates. In fact, after 60 minutes, conversions of 23.1% and 9.8% were observed for cyclohexene and cholesteryl acetate, respectively, affording mainly allylic oxidation products. These reactivities can be explained by the different sizes of these substrates (cyclohexene ~0.5 nm, cholesteryl acetate ~1.91 nm), which can determine their diffusion to inside the pores of the catalyst [86].

As previously referred, synthetic transformations avoiding the use of toxic and expensive metals are especially attractive for the preparation of compounds that do not tolerate metal contamination such as APIs [87]. A relevant application of this concept was the use of household laundry bleach and aqueous TBHP at sub-ambient temperature for the oxidation of steroidal olefins (**Scheme 4**) and benzylic compounds to $\alpha,\beta$-enones. This procedure is not only simple and economical but also has the advantage of using water as solvent [88]. Later, our group described that various $\Delta^5$-steroids could be selectively oxidized to $\Delta^5$-7-ketones (**Scheme 4**) by sodium chlorite associated with NHPI as catalyst in aqueous solvents, achieving good yields [35, 89].

The use of water as solvent was also described in the preparation of several steroidal $\Delta^4$-3,6-diketones from $\Delta^4$-3-ketones (**Scheme 5**) catalyzed by dirhodium caprolactamate $[Rh_2(cap)_4]$ and 70% TBHP in water [90]. This allylic oxidation was also carried out with 5 mol% of $CrO_3$ as catalyst combined with the same oxidant but using benzotrifluoride as a recoverable fluorous solvent [91].


**Scheme 5.** Allylic oxidation of $\Delta^4$-3-ketone steroids to $\Delta^4$-3,6-diketones.

The oxidation of 3β-cholesteryl benzoate to the corresponding $\Delta^5$-4-ketone derivative was also described involving the same fluorous solvent and perfluorooctylseleninic acid as catalyst along with $PhIO_2$ as oxidant. Interestingly, this catalyst could be recovered by fluorous extraction as bis(perfluorooctyl)diselenide, which served as a catalyst precursor [92].

Alternative energy sources such as light can also be useful in allylic (**Scheme 4**) and benzylic oxidation reactions. In this context, the irradiation of olefins such as cholesteryl acetate with UV light in open flasks in the presence of HgBr or *N*-bromosuccinimide originated the corresponding allylic oxidation products in high yields [93]. More recently, the same trans-

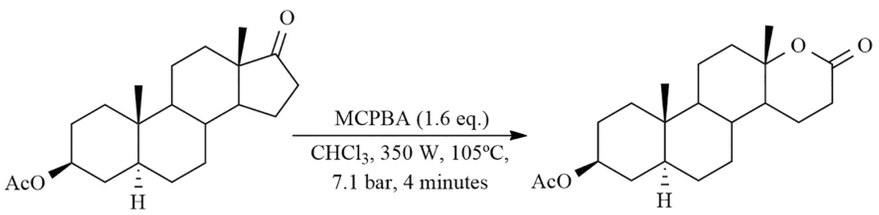
formation was performed by means of a photocatalytic system consisting on the combination of a recoverable graphitic carbon nitride (*g*-$C_3N_4$) and *N*-hydroxy compounds (e.g., NHPI) to activate $O_2$. Despite the low to moderate conversions, this mild photocatalytic strategy also has the advantages of avoiding the employment of metal derivatives or organic oxidizing agents [94].

Several electrochemical methods were applied in the oxidation of cholesterol and derivatives affording, namely, allylic acetoxylation or hydroxylation products [95, 96]. In effect, an electrochemical system for the aerobic oxidation of cholesteryl acetate induced by iron picolinate complexes was reported by Okamoto et al. Interestingly, this procedure mainly afforded 7-hydroxylated products with high stereoselectivity ($\alpha$:β ratio > 100:9), despite relatively low yields [97]. Later, it was described that cholesterol can undergo direct electrochemical oxidation on platinum electrode in glacial acetic acid containing sodium perchlorate and sodium acetate as supporting electrolytes. This preparative electrolysis mainly led to 7$\alpha$- and 7β-acetoxycholesterol in a 10:3 ratio. These products were also found when sodium acetate was replaced by sodium trifluoroacetate, but the stereoselectivity of the reaction was lost and the yields of the oxidized products were low to moderate [95].

## 5. Other oxidation reactions

Electrochemical methods were also developed and applied in the halogenation of steroids [96, 98–100], including $\Delta^5$-steroids, to afford 5$\alpha$,6β-halogenated derivatives that have high biological interest and can be useful in the protection of the double bond in synthetic chemistry. In addition, these procedures can be valuable alternatives to the use of less green reagents namely chlorine gas.

Another important oxidation reaction to which new sustainable procedures have been developed is the Baeyer-Villiger rearrangement [101]. However, within the steroidal field, this reaction is classically performed by means of peroxyacids, such as MCPBA. In this context, the use of MW irradiation to accelerate the oxidation of several steroidal ketones was described. In fact, after few minutes of reaction, the corresponding esters/lactones were successfully obtained (**Scheme 6**) [102]. A more sustainable oxidant used to perform this reaction is $H_2O_2$ which, in combination with the lipophilic catalyst $Ca[B(C_6F_5)_4]_2$ allowed, for example, the preparation of estrolactone from estrone in 88% yield after 4 hours of reaction [103].



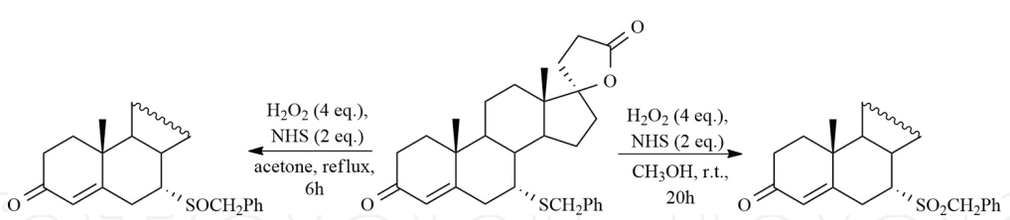

**Scheme 6.** Baeyer-Villiger oxidation of 17-oxo-5$\alpha$-androstan-3β-yl acetate by MCPBA under MW.

http://dx.doi.org/10.5772/62381

The dihydroxylation of olefins is an important reaction because the 1,2-diol functionality is present in many synthetic and natural relevant molecules and is a very useful synthetic building block. The most efficient approach for the preparation of steroidal *syn*-diols is the direct dihydroxylation of olefins, [35, 75], whereas the *trans*-dihydroxylation of olefins occurs mainly by epoxidation and hydrolysis [104]. Recently, the Brønsted acid *p*-toluenesulfonic acid (PTSA) was described as a catalyst for the direct *trans*-dihydroxylation of olefins including cholesterol affording the 5$\alpha$,6$\beta$-diol derivative in 56% yield, in aqueous media. This procedure has the advantages of being mild and metal-free and compatible with a considerable range of organic functional groups, and the catalyst could be recycled and reused [105].

Water was also used as solvent in combination with Aliquat 336 and sand for several reactions of very sparingly soluble high melting-point organic substrates, such as steroids. In this system, Aliquat 336 works as both catalyst and solvent, and its efficiency is enhanced by the moving sand under mechanical stirring. This mixture was successfully applied in the good-yield oxidation of pseudosapogenins into 16-dehydropregnenolone acetate and its analogues using $H_2O_2$ and catalyzed by $V_2O_5$ [106]. This transformation is of high impact because 16-dehydropregnenolone acetate and similar compounds are important starting materials for the preparation of several semisynthetic steroid drugs [2].

The metal-free oxidation of spironolactone-related sulfides to corresponding sulfoxides and sulfones was performed by the green oxidant $H_2O_2$ in the presence of the organocatalyst *N*-hydroxysuccinimide (NHS). In this high-yielding process, a full oxidation to sulfones occurred in methanol at room temperature, whereas sulfoxides could be selectively obtained using acetone as solvent under reflux temperature (example in **Scheme 7**). Both processes were compatible with the presence of sensitive groups including ketones, alkenes, hydroxyl groups and benzylic carbons under the described reaction conditions [107].




**Scheme 7.** Organocatalytic oxidation of 7$\alpha$-(phenylmethylthio)-17-hydroxy-3-oxo-17$\alpha$-pregn-4-ene-21-carboxylic acid $\gamma$-lactone by $H_2O_2$.

## 6. Conclusions and future perspectives

Currently, pharmaceutical chemistry is moving towards the incorporation of the sustainable chemistry principles into the development of new reactions and processes. In the oxidation of steroids, however, green approaches are still relatively limited and mostly involving catalytic methods. In addition, the application of nanocatalysts to steroid chemistry has started to emerge.

Considering the importance of sustainability in oxidative process research and development and the biological and synthetic relevance of oxygenated steroid compounds in medicinal chemistry, it is mandatory to increase the efforts to enlarge the scope of the new green chemistry tools, such as novel catalysts, solvents and technologies. Therefore, in the near future, it can be expected an increase in the use of greener solvents, such as water and fluorous solvents. The application of alternative energy sources, including microwaves, sonochemistry and photo irradiation, will contribute to reduce reaction times and overall energy consumption. Furthermore, the continuous replacement of stoichiometric methods by catalytic reactions, preferably avoiding metal catalysts and involving heterogeneous catalysts is also expected.

In spite of some limitations, such as the shape and complexity of steroid compounds, which are responsible for their singular chemo-, regio- and stereoselectivities, their solubility problems and their rigid molecular framework, nanocatalysts, will certainly be increasingly applied in catalytic oxidative processes namely in steroid chemistry.

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