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*Review*

# Selectivity in the Aliphatic C–H Bonds Oxidation (Hydroxylation) Catalyzed by Heme- and Non-Heme Metal Complexes—Recent Advances

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**Abstract:** The oxyfunctionalization of non-activated C-H bonds has attracted considerable attention for several years. Following the example of enzymatic systems, a multitude of catalytic systems capable of carrying out such a transformation efficiently and selectively have been described. The great discoveries in this area were described at the beginning of the 21st century, but due to the growing demand for precise syntheses (e.g., for the needs of the pharmaceutical industry), new solutions or new applications for already known catalytic systems are constantly being sought. This review article summarizes the development of metal complex-catalyzed selective functionalization of saturated C-H bonds since 2010. However, brief references to previous studies are also made for clarity. There is a huge amount of literature reports in this area, so we intend to highlight only the most important findings in the selective hydroxylation of saturated C–H bonds. Their practical applications in synthesis will also be pointed out.

**Keywords:** metal complexes; C-H functionalization; porphyrin-ligands; non-heme ligands



**Citation:** Siedlecka, R. Selectivity in the Aliphatic C–H Bonds Oxidation (Hydroxylation) Catalyzed by Heme- and Non-Heme Metal Complexes—Recent Advances. *Catalysts* **2023**, *13*, 121. https://doi.org/10.3390/catal13010121

Academic Editor: Mauro Bassetti

Received: 30 November 2022
Revised: 28 December 2022
Accepted: 1 January 2023
Published: 5 January 2023



## 1. Introduction

Selective oxidation of organic molecules, especially those widely available and cheap but relatively inert chemically, is an essential process for preparing high-value-added compounds such as alcohols, aldehydes, and ketones used in organic and polymer synthesis [1]. The saturated C–H bonds due to the high dissociation energy (96–105 kcal/mol), if not activated in any manner (adjacent $\pi$ electron systems, heteroatoms, etc.), are among the less reactive in organic chemistry [2]. For years, the development of methods for direct selective hydroxylation (oxygenation) has been a great challenge. However, this reaction extensively occurs in the metabolism of all living aerobic organisms. Heme and nonheme iron enzymes efficiently perform such transformations with a high level of chemo-, regio-, and stereoselectivity using $O_2$ or $H_2O_2$ as terminal oxidants. The goal of biomimetic studies is to develop a catalytic system that can generate a selective metal-based oxidant analogous to those employed, i.e., by cytochrome P450, rather than via HO• or RO• radicals that easily initiate the radical chain of aerobic autoxidation. The paradoxical challenge lies in discovering a catalyst that is both highly reactive and predictably selective for oxidizing the inert C–H bonds present in each organic compound. Due to the fact that the formation of a C-M intermediate is a key step in the reaction, the process is referred to as C–H activation rather than C–H transformation. Structurally developed and electronically differentiated coordination complexes of transition metals constitute a versatile platform for catalyst designing. Several series of coordination complexes have the proven ability to catalyze the oxidation of aliphatic C–H bonds. After the first exploitation of biomimetic oxidative catalytic systems by Groves in the hydroxylation and epoxidation of olefins with iodosylbenzene as an oxidant [3], the number of reports significantly increased. In this paper, we will focus on reviewing catalytic oxidation reports that have been published since 2010,

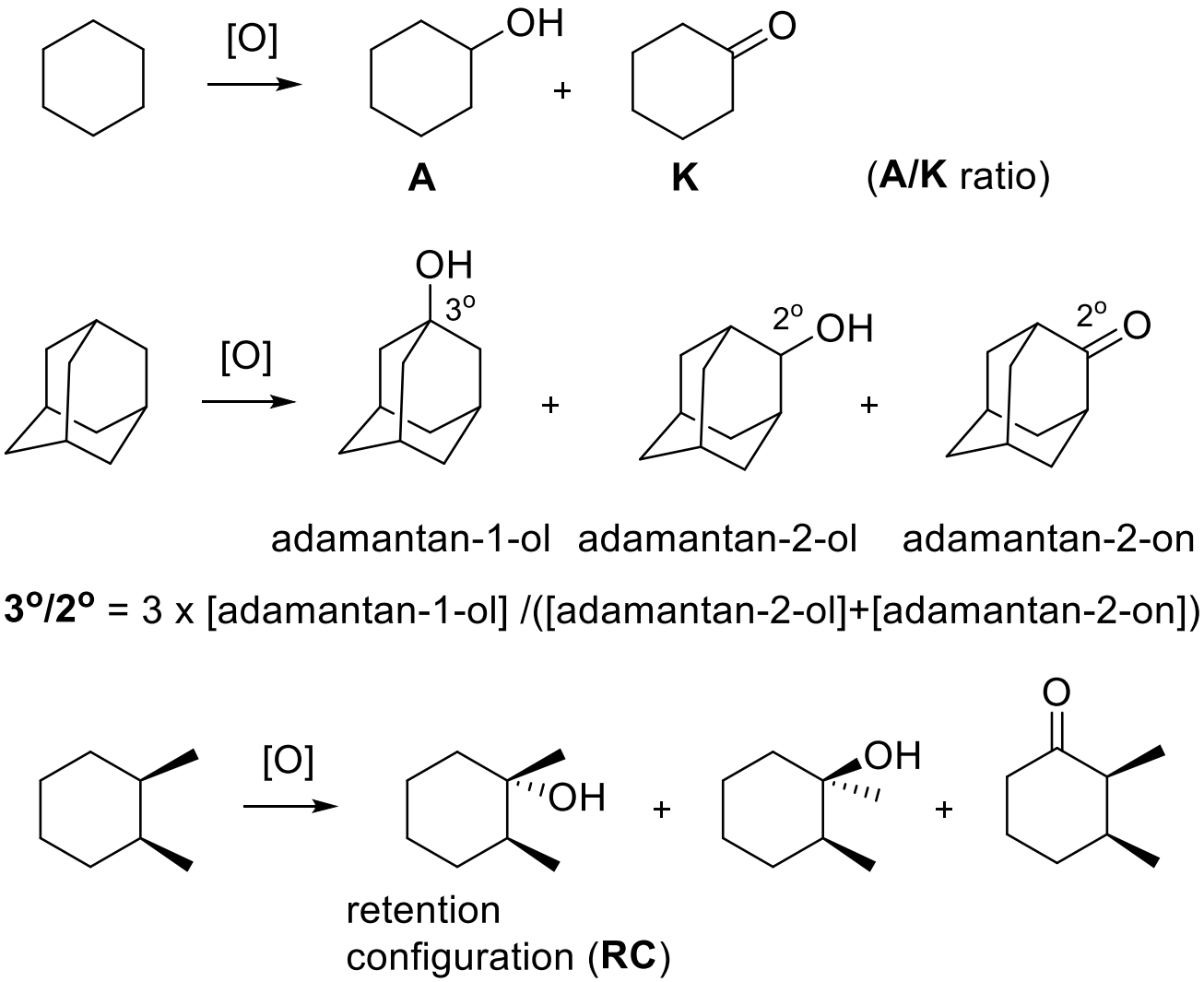
with particular emphasis on the applications of iron and manganese complexes. The influence of metal, ligand structure, and particularly the oxygen donor agent has been reported. Several available oxygen donors, which include *m*-chloroperoxybenzoic acid (*m*CPBA), alkyl peroxides (ROOH), sodium hypochlorite (NaOCl), iodosylbenzene (PhIO), hydrogen peroxide ($H_2O_2$), and oxygen ($O_2$), were investigated. The latter are both definitely the most attractive in terms of accessibility, convenient handling, and environmental impact [4]. The mainly used metal-based oxidants are transition-metal oxo species, often suggested as reactive intermediates in various oxidation processes [5–9].

## 2. Tools to Evaluate the Selectivity and Usability of Catalytic Systems

A critical issue within catalytic oxidation is chemo-selectivity because the primary products (alcohols) are typically more oxidizable than the hydrocarbon substrates and are therefore, over-oxidized or obtained in relatively low yields. Since the catalytic system's selectivity and possible synthetic applications strongly depend on its mechanism of action, the explanation of the oxidation pathway has huge importance. Obtaining useful reactivity and chemo-, site-, and stereoselectivity in their direct transformations remains a difficult task, both via the organometallic pathway and via a radical-mediated process. A few tools/test procedures have been elaborated for its cognition (see Scheme 1). Oxidation of cyclohexane is the first of the three widely used "test reactions" for catalytic systems. In cases when the substrate was used in large excess compared to the oxidant, the experimentally obtained ratio of the oxygenated products (A/K ratio means alcohol/ketone) allows to qualitatively distinguish between free-radical or metal-mediated oxidation mechanisms. The A/K value close to 1 indicates a radical reaction pathway involving the formation of long-lived cyclohexyl radicals, while A/K > 1 may indicate the action of a metal-based oxidant [7]. A more detailed discussion of these "tests" can be found in the literature [6,10]. Cyclohexane oxidation is also a convenient test reaction for quantitative evaluation of the sensitivity of the electrophilic metal-based oxidants to electronic effects. The more reactive and less stable high valency species are expected to be less discriminative between cyclohexane with its strong C–H bonds (bond dissociation energy, BDE = 99.3 kcal/mol) and cyclohexanol with its weaker C(OH)-H bond (BDE = 92.4 kcal/mol) [11,12]. The influence of the binding force was quantified by comparing the rate of the cyclohexanol overoxidation reaction to the rate of the primary reaction, i.e., cyclohexane oxidation. Such measurements were performed, inter alia, for the catalytic systems based on Fe(PDP)-type iron complexes and $H_2O_2$ in the presence of acetic acid [13]. In most cases, the observed values varied depending on the reaction atmosphere: somewhat higher under an inert atmosphere than under ambient air. The introduction of $O_2$ usually altered the yields of alcohol and ketone.

Direct functionalization of saturated C–H bonds through the formation of M-C bonds is an attractive strategy in organic synthesis. Therefore, there has been a clear increase in interest in the development of metal catalysts that are sufficiently reactive and show significant selectivity, taking into account different types of carbons (e.g., 1°, 2°, 3°, or allyl) in a substrate molecule. Adamantane is the second model substrate in CH oxidations (see Scheme 1), used to test the sensitivity of electrophilic oxidants to electronic factors and selectivity in the hydrogen transfer process. The latter is reflected by the regioselectivity 3°/2° of adamantane oxidation (indicated by the ratio), which shows a preference for the oxidation of more electron-rich 3° CH groups (to yield 1-adamantanol) compared to less electron-rich 2° CH bonds (to yield 2-adamantanol and 2-adamantanone), corrected for the 3-fold statistical prevalence of the CH bonds. The low values of this ratio (3°/2° < 6) indicate a free-radical mechanism, while $3^0/2^0$ ratios higher than 13–15 strongly indicate a metal-based mechanism. For cytochrome P450 and heme catalysts, the adamantane regioselectivity can be as high as 48:1 [6]. The oxidation of the cis and trans isomers of 1,2-dimethylcyclohexane is the third way to probe the catalyst nature and the lifetime of the nascent alkyl radical in alkane hydroxylation reactions. The ratio of cis and trans tertiary alcohol products after oxidation depends on the competition between the epimerization of

the putative tertiary alkyl radical intermediate and the "oxygen rebound" step (C-O bond formation). Reactions that give rise to long-lived free radicals (higher than ~$10^{-9}$ s) afford comparable amounts of both cis and trans alcohols with a cis*:* trans ratio close to 1.2. It is estimated that the tertiary carbon radical epimerizes with a first-order rate constant of $10^{9}$ $s^{-1}$ [14]. On the other hand, short-lived alkyl radicals, where the "oxygen-rebound" step is extremely fast, should afford a tertiary alcohol where the original configuration is retained. Therefore, stereospecific hydroxylation (with stereo retention) is observed with such catalysts. Metal-based oxidation provides mostly high configuration retention (RC: 90–99%).

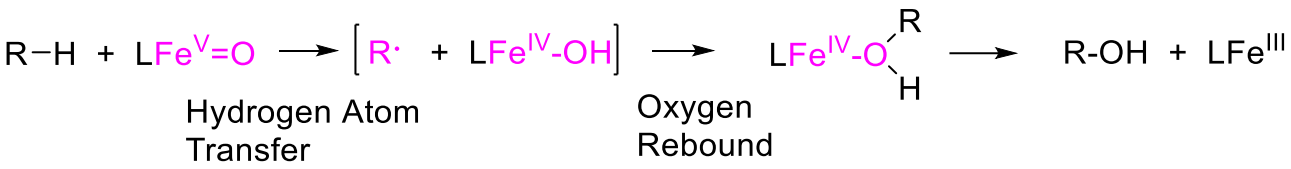



**Scheme 1.** The main test reactions and parameters help to explore the mechanism of catalytic oxidation.

### 3. Oxidation with Metalloporphyrin Complexes

Metalloporphyrin catalysts were intended to mimic natural processes in the laboratory and have been exploited for a long time [15,16]. Several characteristics of metalloporphyrins increase their importance as effective catalysts for the selective functionalization of saturated C–H bonds, including the ability to decorate the ligand with bulky groups or functional groups, modifying the electronic properties, and even chiral components, resulting in different types of selectivity, a high product turnover number (TON), etc. [17]. Moreover, metalloporphyrins are coordinated and thermally stable. After the formation of the complex molecule, dissociation of the metal ion is difficult or almost impossible under most reaction conditions. This significantly extends the lifetime of the catalyst and facilitates the elimination of metal contamination in the products. Various oxidants have been

successfully used in catalytic hydroxylation attempts to produce alcohols using different metalloporphyrins as catalysts. In summary, the catalytic abilities of metalloporphyrins depend on the type of metal center, the three-dimensional structure of macrocycle rings, the type and amount of substituents on the porphyrin ring, and sometimes on the presence and type of axial ligand. Experimental evidence suggests the involvement of porphyrin metal-oxo complexes as key intermediates in catalytic processes [18,19]. The general mechanism for alkane oxidation by the high-heme-$Fe^{V}$-oxo catalyst can be separated into two steps. The C–H bond cleavage and hydrogen atom transfer (HAT) step is followed by the oxygen rebound to the radical cage and the C-O bond formation step, as depicted in Scheme 2.




**Scheme 2.** Mechanism of the metalloporphyrin-catalyzed hydroxylation of alkanes.

These two steps can occur simultaneously, or alternatively, the C–H bond is cleaved to form an alkyl radical, which is very quickly captured to form the C–O bond [6]. The mechanism of the C–H bond activation by manganese-oxo analogs is not so well understood and fully explained. An exhaustive discussion of the reaction mechanisms covering both iron and manganese complexes was presented in a review from 2019 [20]. The iron-porphyrin complexes (the closest precursors of natural iron monooxygenases) are well investigated and probably constitute the largest alkane hydroxylation-active "synthetic enzymes". Their structure, the link between the structure and reactivity or selectivity, as well as the modes of action, was the subject of extensive investigation in several research groups [6,19,21]. Iron complexes have long been considered one of the most promising catalysts [22], but also complexes of other transition metals, e.g., Mn [23], Co [24,25], Cu [26,27], Ru [28], and Os [29], have been studied as catalysts for the oxidation of alkanes [30]. The structures of selected porphyrin complexes are depicted in Figure 1.

The first iron-porphyrin catalyst applied for hydroxylation was **1a** ($Fe^{III}$(TPP)Cl), used with iodosylbenzene (PhIO) as the terminal oxidant. Results were not impressive: cyclohexane and adamantane were selectively oxidized to the corresponding alcohols in 8 and 13% yields, respectively [31]. Since then, porphyrin ligands have been tuned in various ways to modulate the steric environment or electrophilicity, resulting in new generations of metalloporphyrin catalysts. Nakagaki and co-workers have designed an acetal phenyl-substituted iron-porphyrin complex **1f** (see Figure 1) for the oxidation of cyclohexane with PhIO, obtaining 27% of alcohol and 8% of ketone yields [32]. The same catalyst immobilized on silica was slightly less active. The second generation of metalloporphyrin catalysts (e.g., **1b**,**1c**, **2**, Figure 1) was designed in such a way that electron-withdrawing substituents (mainly halides) were introduced at the ortho, meta, and para positions of the phenyl ring attached to the macrocycle meso positions. After the introduction of fluorine atoms into the phenyl ring of the porphyrin ($Fe^{III}$(TPFPP)Cl, **1b**), the durability of the catalyst and its effectiveness significantly increased (19 TON). With the use of **1b** and *t*BHP as the oxidants in the reaction with cyclohexane, alcohol was obtained in a 47% yield [33]. The same fluorinated ligand was used with ruthenium as the metal center, resulting in a more active catalyst **1c** (70 TON) [33]. Using 2,6-dichloropyridine N-oxide (2,6-$Cl_2$pyNO) as the oxidant with **1c,** the secondary C–H bonds of benzylic substrates were over-oxidized, giving the corresponding ketones as the final products in moderate yields (46–70%), while **1c** in the presence of mCPBA resulted in the benzylic alcohols with a 78–81% yield [34]. Furthermore, Ru(TPFPP)(CO) supported on polyethylene glycol (PEG) macromolecules were applied with 2,6-$Cl_2$pyNO, but the catalytic activity decreased (50 TON). However, in this case, the tertiary C–H bond in adamantane was converted to the tertiary alcohol only (65% conversion, 80% yield) [35].

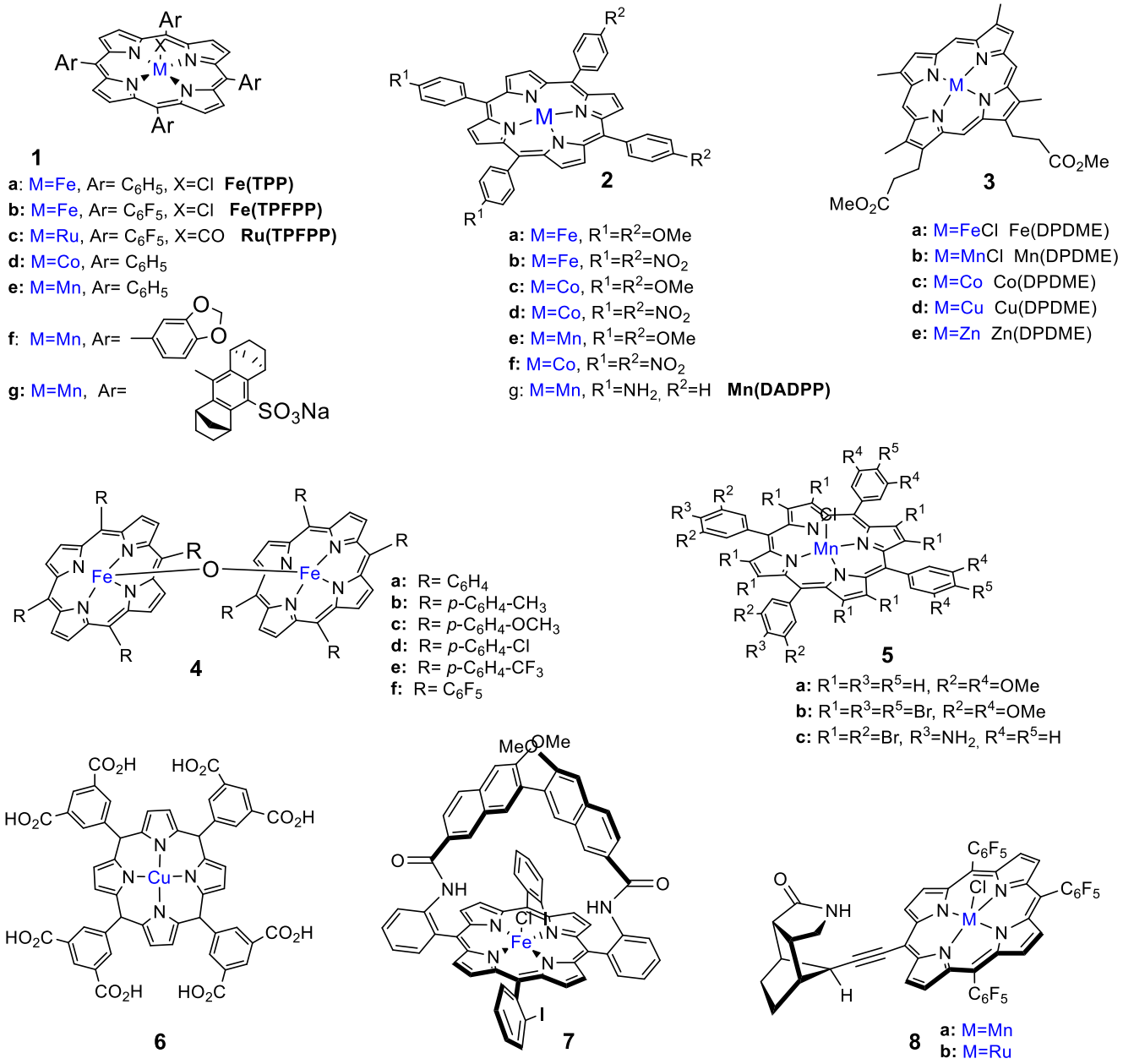
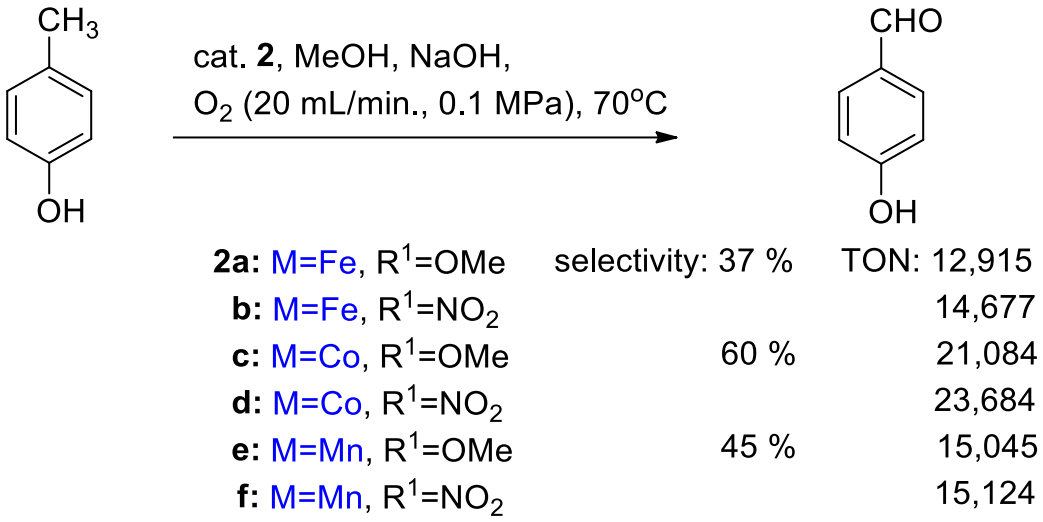


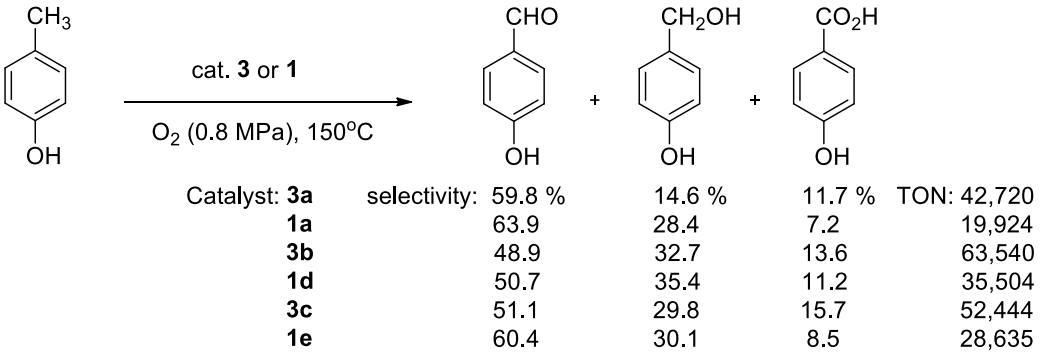

**Figure 1.** Structures of selected metalloporphyrin complexes.

Much effort was made to study the use of metalloporphyrin catalysts with $O_2$ as the oxidant, checking both the effect of substituents on the periphery of the metalloporphyrin ligand and the type of metal in the center. Base hydrolysis of the type Fe(TPP)Cl (**1**) complexes affords the "μ-oxo dimers" with the formula $[Fe(TPP)]_2O$ (**4**). She et al. have tested Fe-catalysts type **1** and **4** in the oxidation of *p*-nitrobenzene as a substrate with $O_2$ (0.1 MPa) without the solvent [36]. The experiments proved that the monomers **1a**,**d**, and **e** were the most active (up to 56% conversion for cobalt catalyst **1d**), while the lowest reactivity was shown by the **4a** dimer (29%). The study expanded to evaluate the effect of electron-withdrawing vs. -donating groups present in the aromatic ring. In the oxidation to ketones, better activities and selectivities were obtained with complexes having strong electron-withdrawing substituents, according to the obtained sequence methoxy < hydrogen < bromine < acyl < nitro (conversion from 9% to 54%, respectively). Wang et al. investigated the oxidation of *p*-cresol catalyzed by $Fe^{III}$, $Mn^{III}$, and $Co^{III}$ complexes with porphyrins (**2**, see Scheme 3) modified with a donor group ($OCH_3$) or an electron-withdrawing group

($NO_2$), respectively. Both the selectivity and yield of *p*-hydroxybenzaldehyde followed the sequence Co > Mn > Fe, while Fe porphyrins performed better in *o*-cresol oxidation [25,37]. Although, independent experiments proved that the central metal was the most relevant issue for the catalyst activity using metallo-deuteroporphyrins ($Co^{II}$ > $Mn^{III}$ > $Fe^{III}$) in the oxidation of alkylbenzenes (see Scheme 4). The $Co^{II}$ complexes were the best and most active catalysts, giving up to ~63 540 TON [38]. The iron complexes **4** have been investigated also by Tabor et al. in catalytic oxidation with molecular oxygen at 20 °C, 10 atm. [39]. Cycloalkanes were converted to ketones (mainly) and alcohols. For cyclohexane, **4a** yielded 17.4% and 3.4%, respectively, and for cyclooctane, there was a 40.3% yield of ketone and an 8.0% yield of alcohol (A/K = 0.16; TON 108,660). The catalytic performance of μ-oxo dimers can be modified by the substituents introduced in meso-aryl positions of porphyrin macrocycles. It was depicted that either electron-withdrawing or electron-donating substituents can improve the catalytic activity toward the oxyfunctionalization. The best results were delivered with **4d** cyclooctanone, with a 46% yield, and cyclooctanol, with an 8.5% yield (A/K = 0.18; TON 122,640) [17]. Although, it was slightly lower than in the case of the respective monomers.




**Scheme 3.** Influence of ligand periphery substitution on the catalyst activity in the oxidation of *p*-cresol.

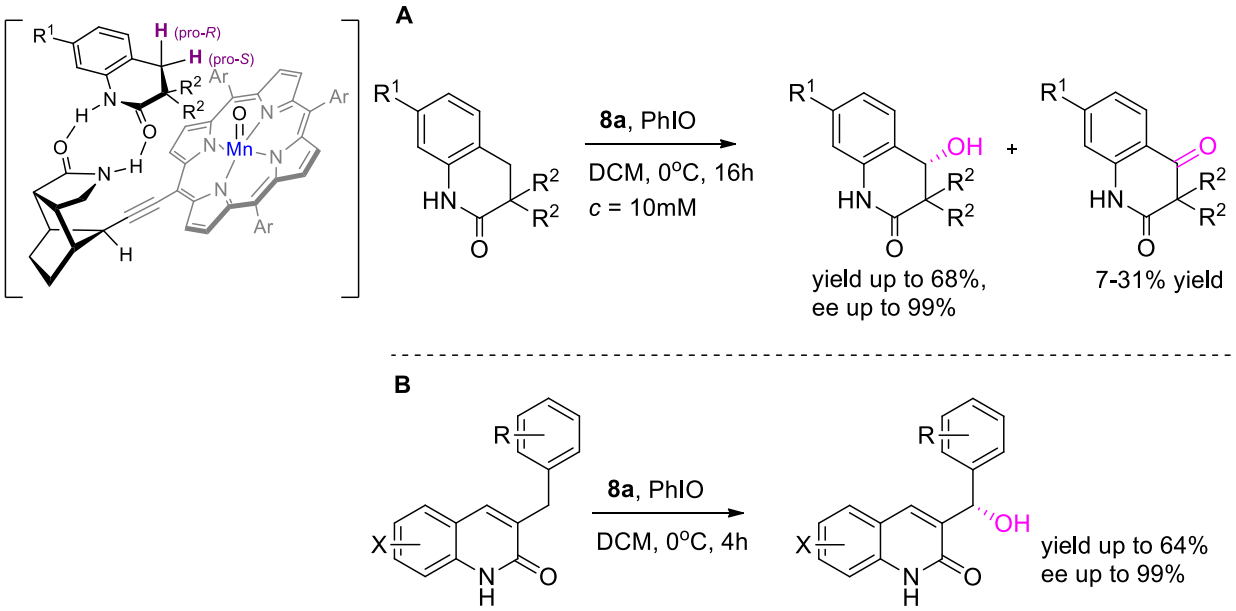



**Scheme 4.** Influence of central metal on the catalyst activity in the oxidation of *p*-cresol.

The third generation of porphyrin catalysts broadened the idea of electronic modifications by introducing halide substituents at the β-position of pyrroles also. It resulted in large, positive shifts in the FeIII/FeII redox couple, while at the same time protecting the porphyrin structure from oxidative destruction. It also enables the formation of oxo-bridged dimeric structures. Further interference with the electronic properties by introducing electron-withdrawing nitro- or 4-(N-methylpyridinium) groups led to the formation of even more reactive species in hydroxylation reactions [29]. DeFreitas-Silva

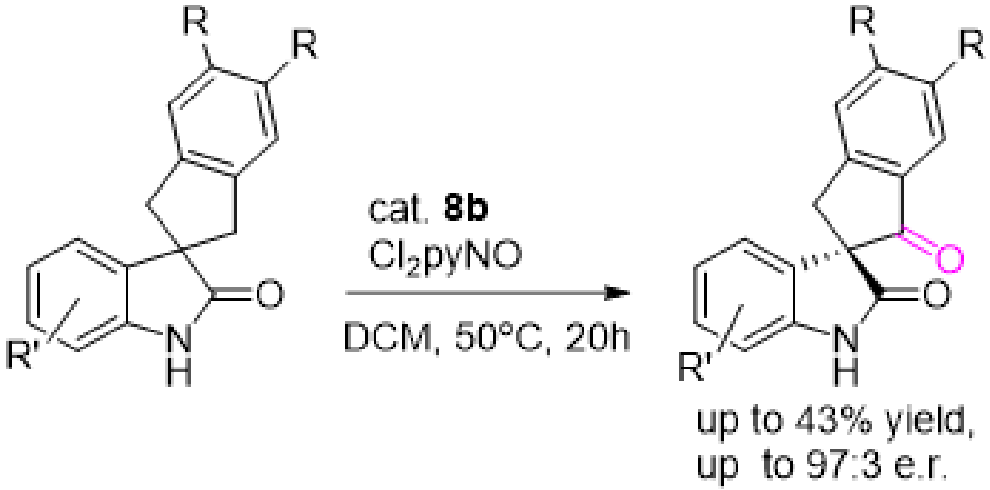
evaluated the efficiency of metalloporphyrins **5** with $PhI(OAc)_2$ (alternative oxidant to PhIO). **5b**, as a third-generation catalyst, was more selective in the cyclohexane oxidation (86% of cyclohexanol) and had a higher total yield (65%) compared to **5a** (7% and 19%, respectively). The oxidation of adamantane **5a** resulted in a slightly higher $3^0/2^0$ ratio than that of **5b** (8.33 vs. 1.57), while the latter gave a better overall yield (36% vs. 28%). Both of these catalysts were more efficient compared to [$Fe^{III}$ TPP]Cl (**1a**) [40]. The authors found that **5b** underwent more extensive destruction as compared with **5a**, possibly due to the presence of bulky bromine atoms in the β-pyrrole positions of the porphyrin ring, causing some distortions. The addition of imidazole or water to the catalytic system significantly improved the total product yield [41]. It has been observed that complex cis-[$Mn^{III}$DADPP]Cl (**2g**, second generation), when water was added, was more selective for alcohols (71%) than **5a**, however, not as much as **5b**. It is likely that the amino groups in **2g** could coordinate with the metal center of the second molecule of the complex and make the high-valent active form of $Mn^V$ = O more reactive and increase the selectivity towards alcohol [40]. A convenient way to recover and reuse an organometallic catalyst is to prepare and use it in a heterogeneous form. In addition to the attempts to immobilize catalysts on silica gel or chitosan, polymer structures of catalysts were also built. Recently, Zhao and Wu received a metal-organic-framework (MOF), in which $Cu^{II}$ meso-tetrakis (3,5-dicarboxyphenyl)-porphyrinate (**6**) was immobilized onto the porous framework [41]. The new MOF was applied in the oxidation of ethylbenzenes using $O_2$ as an oxidant (24 h at 50 °C), resulting in up to 99% yield. Moreover, a complete selectivity was obtained for the corresponding ketones [42]. Enantioselective oxidation results are strongly favored by the rigid geometry of the catalyst molecule. The influence of other parameters, such as solvent, polar, electronic, and torsional effects, has also been investigated. Although many complexes of different metals have been studied, most synthetic applications in enantioselective hydroxylation involve manganese rather than iron catalysts. The first enantioselective oxidation catalyzed by metalloporphyrin was described by Groves and Viski [43]. Chiral benzyl alcohols were obtained (up to 77% ee) in the oxidation of ethylbenzenes with PhIO in the presence of a chiral iron-porphyrin catalyst (**7**). The occurrence of asymmetric induction is evidence of a non-radical hydroxylation mechanism. There are not many examples of metalloporphyrin complex-catalyzed enantioselective oxidations with $H_2O_2$. The reason can be: (i) the synthesis of optically active water-soluble chiral metalloporphyrins having high enough catalytic activity; (ii) the requirement of high activity of metalloporphyrin complexes in the homolytic cleavage of the peroxidic O–O bond resulting in the formation of hydroxyl radical; (iii) the high thermal stability of the C–H bond, which is one of the most difficult to transform. The first asymmetric hydroxylation catalyzed by Mn porphyrins in the presence of $H_2O_2$ in water was performed by Simonneaux. The treatment of ethylbenzene (1 equivalent) with $H_2O_2$ (5 equivalent) in the presence of complex **1g** in $H_2O$/MeOH (1/1) afforded (88% conversion) a mixture of 1-phenyl ethanol (57% yield, 38% ee) and acetophenone (43% yield) [44]. Cyclic alkanes such as indane and tetrahydronaphthalene are more reactive substrates, giving a high conversion (85 and 90%), but the obtained enantioselectivities decreased to 32% and 43%, respectively. The $SO_3Na$ group (in **1g**) was the most suitable substituent; its replacement with H, $NMe_2$, or $NO_2$ afforded less chemo- and enantioselective catalysts [45]. Another way to obtain asymmetric induction was to develop catalysts that show a specific binding mode for a given substrate and thus enable a selective interaction of the reactants. Developed by Bach and coworkers, complex **8** has an octahydro-1H-4,7-methanoisoindol-1-one motif, suitable for two-point hydrogen bonding interactions during the oxidation of 3,3-disubstituted 3,4-dihydroquinolones.

When supramolecular catalyst **8a** was applied with PhIO in dichloromethane, it gave the benzyl type of alcohols efficiently (up to 68% yield) with remarkable enantioselectivity (up to 99% ee), as shown in Scheme 5, part A [46]. In the later report [47], a series of 3-substituted quinolones were hydroxylated adjacent to the 3-position of the heterocyclic ring with outstanding site- and enantioselectivity (up to 99% ee, up to 64% yield, see Scheme 5 part B).




**Scheme 5.** Asymmetric hydroxylation of 3,4-dihydroquinolones (**A**) and 3-substituted quinolones (**B**) with **8a**.

The same authors previously employed a supramolecular ruthenium catalyst **8b** with 2,6-$Cl_2$pyNO as an oxidant for the oxidation of spirocyclic oxindoles, resulting in a conversion of 60%, and an e.r. of 95:5 in favor of ketone (Scheme 6) [48]. The high enantioselectivity of the described system is, to some extent, limited by substrate specificity.



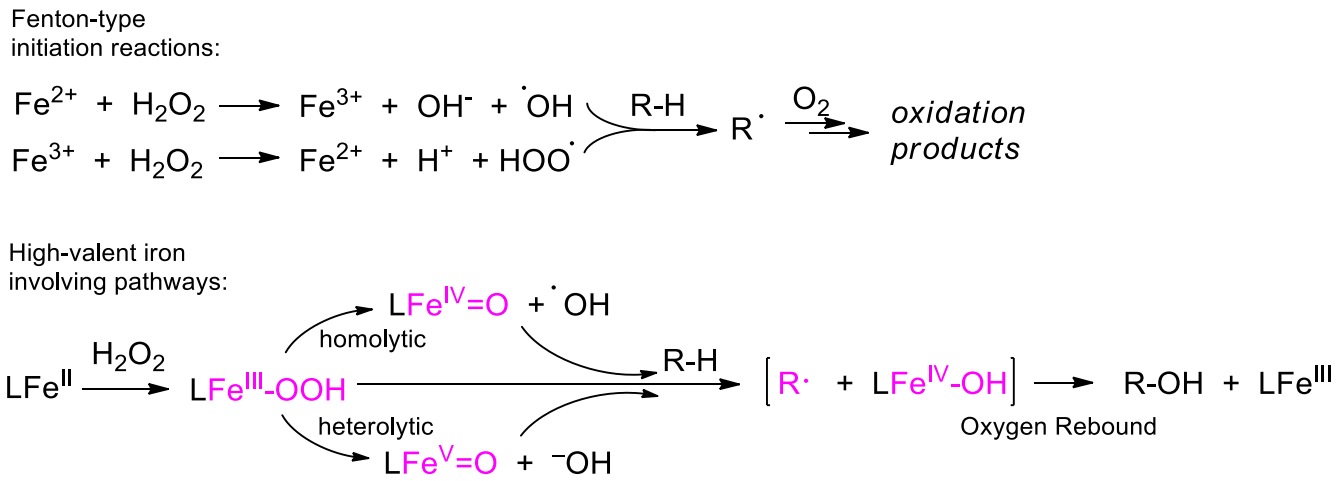

**Scheme 6.** Asymmetric desymmetrization of spirocyclic ketones catalyzed by a supramolecular ruthenium complex **8b**.

## 4. Oxidation with Non-Heme Complexes

In the field of C–H oxidations, numerous synthetic non-heme complexes have been designed and prepared. Generally, they are more flexible for structural modification compared to metalloporphyrins. Most of the discovered effective iron catalysts are supported by tetradentate N4 ligands and possess two cis-oriented sites on the metal center for peroxide binding and activation. The importance of the cis-labile coordination sites and cis-α coordination of the ligand for the stability of the catalyst and its catalytic abilities has been highlighted based on analogous tests of several differently substituted TPA-ligands (**10b**,**10c**,**11**–**13**) [19]. The first stereospecific oxidation of alkanes was performed using

Fe(TPA) (**10a**) and $H_2O_2$ as the terminal oxidant [10]. In this reaction, cyclohexane gave mainly alcohol (A/K = 4.3), and cis-1,2-dimethylcyclohexane gave almost 100% RC (which revealed the metallocentric and not the radical mechanism).

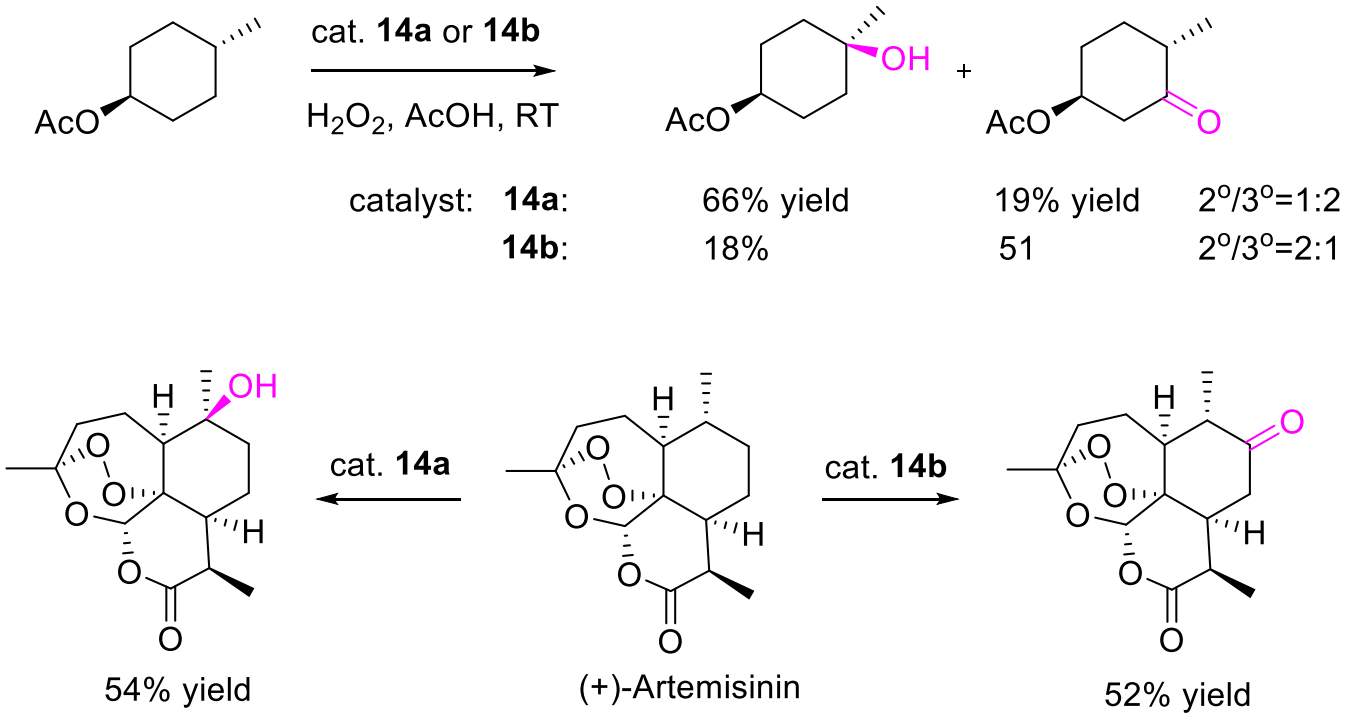
In order to clarify the nature of the active metal-based oxidant, detailed studies of the mechanism engaged in catalytic hydroxylation of alkanes were needed (see Scheme 7). [10,19,49,50] High-valent metal-oxo species could be also accessed by a nonheme ligand environment [51,52]. Since then, a large number of nonheme oxo-iron(IV) complexes with a wide range of tetradentate and pentadentate ligands have been designed. A few selected examples are shown in Figure 3. The investigations of the iron(BMEP) complex **9** (BMEP is N,N′-dimethyl-N,N′-bis(2-pyridylmethyl)-ethane-1,2-diamine) showed its better activity than the iron-TPA complex (**10a**) in the oxidation of cyclohexane with $H_2O_2$ (65% yield and an A/K ratio of 9.5) [53]. It was established that **9** has a high tolerance towards functional groups in substrates; furthermore, it operates via the electrophilic metal oxidant and has a bulky ligand framework amenable to modification, which gives a base to the design of its modifications [54]. Topological variations of the BPMEN ligands were studied by the Britovsek group [53,55].




**Scheme 7.** Free-radical and metal-based oxidation pathways.

Based on collected experience, the ground-breaking results in the field of nonheme iron-catalyzed oxidation were reported by Chen and White [56,57]. The authors have demonstrated that the site of oxidation in complex organic substrates with **14a** can be predicted by knowing the electronic and steric environment of the C–H bond in a substrate. Hydroxylation with **14a** in all examined cases occurred preferentially at the most electron-rich C–H bond, the tertiary one. If the 3° C–H bond was part of the stereogenic center, complete retention of stereochemistry was observed (see Scheme 8). In substrates where 3° C–H bonds were not available, oxidation proceeded with methylene hydrogens to give the keto product via the 2° alcohol. The site selectivity and stereochemical oxidation result of **14a** correspond to a concerted mechanism mediated by an electrophilic oxidant. The Fe(*S*,*S*-PDP) complex contains a rigid, non-labile tetradentate ligand, that significantly improves the site selectivity and yield of aliphatic C–H bond oxidation compared to similar iron complexes bearing more flexible, labile ligands. Moreover, it turned out the catalyst was less susceptible to decomposition and sensitive to unselective Fenton-type oxidation chemistry. The 'isolation of the metal site' by adding sterically demanding substituents (e.g., pinene fragment) at distant positions to the ligand pyridyl units increased the stability and could modulate, at the same time, the activity of the catalyst. The control of the site selectivity could be shifted from the substrate to the ligand [58,59]. The **14b** (possessing aromatic substituent with two $CF_3$ groups) diverts reactivity toward the electronically disfavored 2° sites by restricting access of the 3° sites to the oxidant. The inverted site selectivity was observed for the oxidation of trans-4-methylcyclohexyl acetate or (+)-Artemisinin with **14b**

compared to **14a** (Scheme 8). Substitution of the ligand's pyridine ring at the 6-position suppressed the reactivity, confirming previous reports that sterically hindered catalysts near the oxo show significantly reduced C–H oxidation reactivity [60]. On the basis of steric, electronic, and stereoelectronic effects, the principles of selectivity for the C-H oxidation reaction were clearly defined, and the mechanism of this reaction was proposed, taking into account the initial hydrogen abstraction step.




**Scheme 8.** Chemo- and site-selective oxidation with Fe(PDP)-type catalysts.

Due to the predictable reactivity, the modified type **14** catalysts have found wide application for the hydroxylation of neutral C-H bonds as one of the key steps in the total synthesis of compounds with known biological activity, e.g., (+)-2-oxo-Sclareolide [55], controlled oxidation of (+)-Artemisinin [60], (+)-Pseudoanisatine [61], Vancomycin aglycone core [62], Scaparvins [63], Cyanthiwigin core [64], Illicium sesquiterpenes [65], Illisimonin A [66], and Streptovitacin A [67] (see Figure 2). The practical application of the Fe(PDP) complex in the oxidation of a series of nitrogen-containing molecules (amides, imides, pyridines) was presented by White [67,68].

Bryliakov and coworkers displayed the selectivity patterns of iron catalysts of the Fe(TPA) and Fe(PDP) families in aliphatic C–H oxidation with $H_2O_2$. According to them, the studied catalytic systems generated low-spin (S = 1/2) $Fe^V$ = O(OAc) intermediates or high-spin (S = 3/2) $Fe^V$ = O(OAc) intermediates (see Scheme 9), depending on the electron-donating abilities of the remote substituents at the pyridine rings via iron-complex dimerization [13,69]. The detected (by EPR Spectroscopy) low-spin perferryl intermediates demonstrate lower stability and higher reactivity toward aliphatic C-H groups of cyclohexane than their high-spin congeners. Additionally, Costas and coworkers put in a lot of effort to study the active form of the oxidant generated by the reaction of the iron complex with an excess of the oxidant (peroxyacid). They have managed to collect a number of spectroscopic data on identification (UV-vis, EPR, cryospray-HRMS) and a set of data on the unprecedented reactivity of this $Fe^V$–oxo intermediate [70,71].

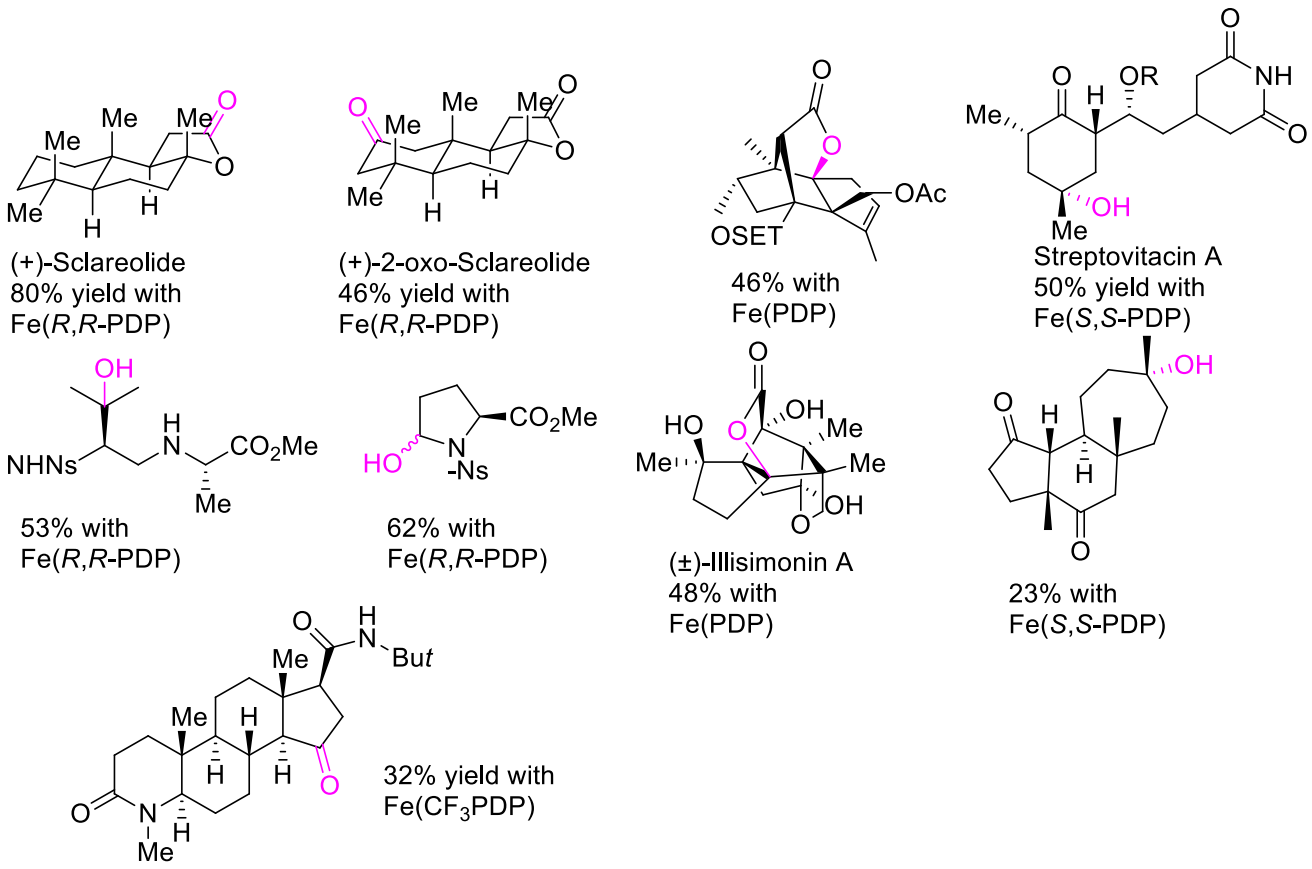
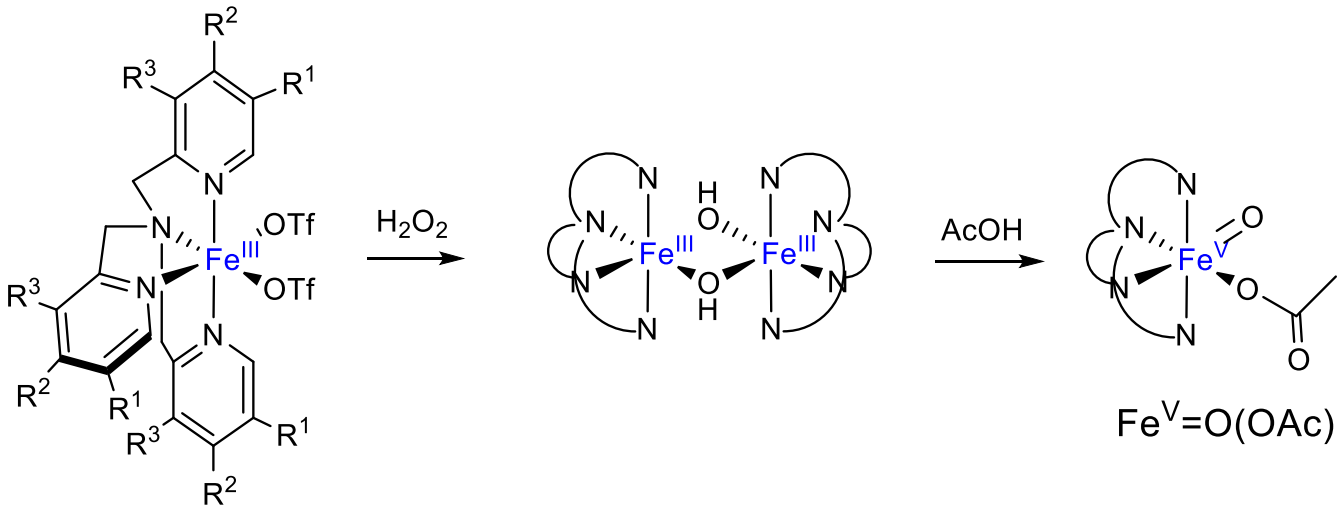



**Figure 2.** Selected compounds obtained by iron complex catalyzed oxidation.

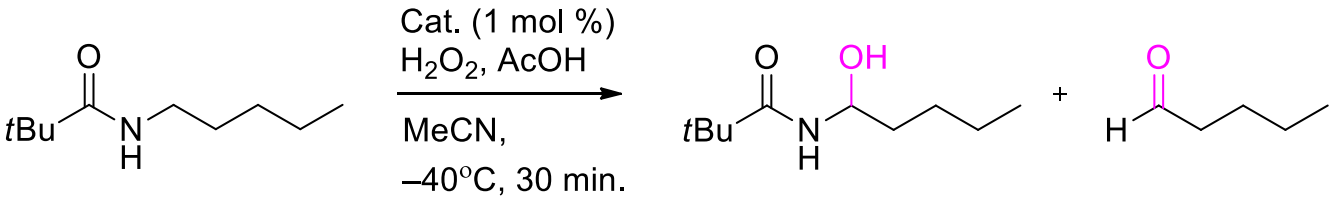



**Scheme 9.** Postulated formation of the elusive $Fe^{V}$ = O(OAc) intermediates in selective catalytic oxofunctionalizations.

Hitomi reported a $Fe^{III}$(DPAQ) complex (**15**; DPAQ = 2-[bis(pyridin-2-ylmethyl)]amino-N-quinolin-8-yl-acetamidate, Figure 2) which was able to catalyze the selective hydroxylation of inert C–H bonds with $H_2O_2$ as the oxidant [72,73]. The distribution of the products (cyclohexanol + cyclohexanone) over time has changed; initially, the A/K ratio was 36:1 but gradually decreased to 11.3:1. This result indicates the formation of cyclohexanone by further oxidation of cyclohexanol. Different derivatizations of the quinoline unit of the ligand yielded a series of complexes possessing adjustable electronic properties. An increase in catalytic turnovers and selectivity for the reaction of tertiary bonds in the case of

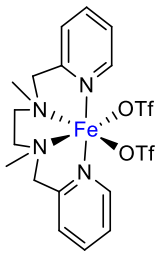
adamantane oxidation was observed, while the electron deficiency of the catalyst increased. (TON from 75.1 for R = $OCH_3$ up to 108.1 for R = $NO_2$) [73], probably because of the weaker coordination of the amide group with the iron center. Pentadentate TPA-derived complex **16** exhibited a moderate catalytic activity in the cyclohexane oxidation with $H_2O_2$, probably because of the short lifetime of the primary $Fe^{IV}$-oxo species, which dimerize to form a $\mu$-oxo bridged iron(III)-complex [74]. Application of complex **17**, with the rigid pentadentate N-donor ligand, did not work much better. Cyclohexane was oxidized with $H_2O_2$ resulting in a 25% yield (with respect to the oxidant), and an A/K ratio of 1.3 was observed, indicating the possibility of free radicals occurring during the reaction [75].

From a practical perspective, Mn-aminopyridine complexes (for selected structures, see Figure 3 and Figure 5) demonstrate higher oxidation efficiencies as compared to nonheme iron catalysts: they perform up to ca. 1000 catalytic turnovers (versus hundreds for Fe counterparts) and require as little as a 1.3-fold excess of $H_2O_2$ (versus typically 2 equivalent of $H_2O_2$ for Fe complexes) [76–79]. The mechanisms of Mn-catalyzed C–H oxidations are rather underinvestigated. However, the data available give evidence for close similarities to oxofunctionalization in the presence of Fe-aminopyridine complexes, proving indirectly the formation of $Mn^{V}$-oxo active species during the reaction [80]. Reactants capable of oxidizing C-H generally show a strong electrophilic character, therefore, C–H bonds near electron-donating groups such as amines, amides, ethers, and alcohols are more likely to react with these reagents than those near electron-withdrawing groups. By using electronic, steric, and stereoelectronic effects, it was possible to achieve highly chemoselective oxidation of aliphatic C–H bonds in N-alkylamides and N-alkylphthalimides in the catalyzed by manganese-complexes reactions, applying $H_2O_2$ as the oxidant. However, different site selectivity was observed [79]. Amides show a decreased nucleophilicity at the nitrogen center and can not only be tolerated in metal-catalyzed oxidation (contrary to amine substrates), but the amide functionality has the potential to be developed into a versatile directing group for C–H functionalization [81]. In the case of N-pentylpivalamide used as a substrate, the α-hydroxylation was observed mainly. Electron-donating substituents in the ligand's pyridine rings also increased the activity of oxidation in the case of iron catalysts (see Scheme 10).



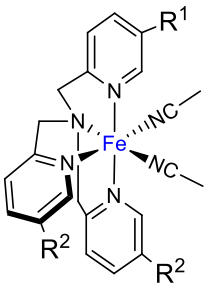

| Catalyst: | | | |
|---|---|---|---|
| **14a** | conversion: <2% | | |
| **14e** | 64% | 41% | 15% |
| **14c** | 15% | 6% | 5% |
| **14f** | 99% | 60% | 11% |
| **18e** | 97% | 42% | 10% |
| **18g** | 65% | 58% | 4% |
| **18h** | 22% | 8% | 11% |

**Scheme 10.** Amide functionality as directing group in C–H functionalization of N-pentylpivalamide.



**9**

**Fe(BPMEN)**

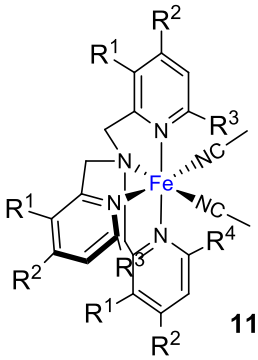


**10**

**a:** $R^1$=$R^2$=H **Fe(TPA)**

**b:** $R^1$=$R^2$=Me

**c:** $R^1$=H, $R^2$=$CO_2$Me



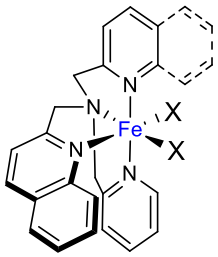
**11**

**a:** $R^1$=Me, $R^2$=$R^3$=$R^4$=H

b: $R^1$=$R^2$=$R^3$=H, $R^4$=Me

**c:** $R^1$=$R^2$=$R^4$=H, $R^3$=Me

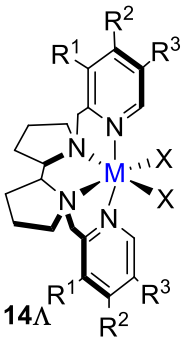
**d:** $R^1$=$R^2$=H, $R^3$=$R^4$=Me



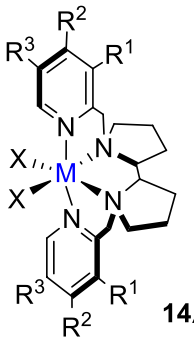
**12**

a: X= OTf **Fe(BPQA)**

b: X=$H_2O$, $ClO_4$- **Fe(BQPA)**



**14**Λ



**14**Δ

**a:** M=Fe, $R^1$=$R^2$=$R^3$=H **Fe(PDP)**

**b:** M=Fe, $R^1$=$R^2$=H, $R^3$=2,6-$(CF_3)_2C_6H_3$,

**c:** M=Fe, $R^1$=$R^3$=Me, $R^2$=OMe **Fe(**$^{DMM}$**PDP)**

**d:** M=Fe, $R^1$=$R^2$=H, $R^3$=Si(*i*Pr)$_3$ **Fe(**$^{TIPS}$**PDP)**

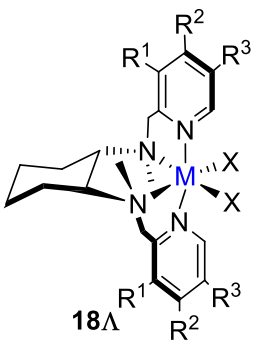
**e:** M=Mn, $R^1$=$R^2$=$R^3$=H **Mn(PDP)**

**f:** M=Mn, $R^1$=$R^3$=Me, $R^2$=OMe **Mn(**$^{DMM}$**PDP)**

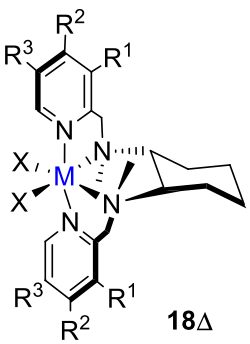
**g:** M=Mn ,$R^1$=$R^3$=H, $R^2$=$NMe_2$ **Mn(**$^{Me2N}$**PDP)**

**h:** M=Mn ,$R^1$=$R^2$=H, $R^3$=Si(*i*Pr)$_3$ **Mn(**$^{TIPS}$**PDP)**

**i:** M=Mn ,$R^1$=Me, $R^2$=$OCH_2CF_3$, $R^3$=H



**18**Λ



**18**Δ

**a:** M=Fe, $R^1$=$R^2$=$R^3$=H **Fe(MCP)**

**b:** M=Fe, $R^1$=$R^2$=H, $R^3$=2,6-$(CF_3)_2C_6H_3$

**c:** M=Fe, $R^1$=$R^3$=Me, $R^2$=OMe **Fe(**$^{DMM}$**MCP)**

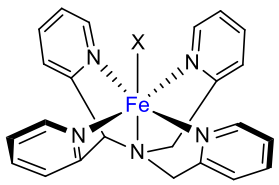
**d:** M=Fe ,$R^1$=$R^2$=H, $R^3$=Si(*i*Pr)$_3$ **Fe(**$^{TIPS}$**MCP)**

**e:** M=Mn, $R^1$=$R^2$=$R^3$=H **Mn(MCP)**

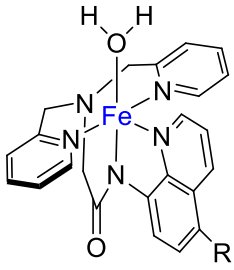
**f:** M=Mn, $R^1$=$R^3$=Me, $R^2$=OMe **Mn(**$^{DMM}$**MCP)**

**g:** M=Mn ,$R^1$=$R^2$=H, $R^3$=Si(*i*Pr)$_3$ **Mn(**$^{TIPS}$**MCP)**

**h:** M=Mn, $R^1$=$R^3$=Me, $R^2$=Cl **Mn(**$^{Cl}$**MCP)**



**13**



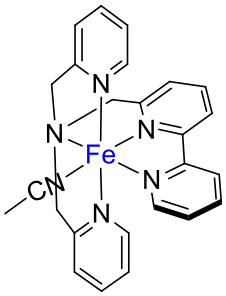
**15**

**a:** R=H **Fe(DPAQ)**

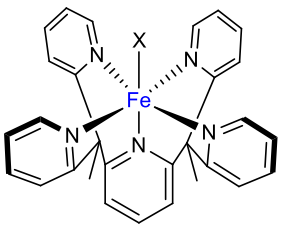
**b:** R=OMe

**c:** R= Cl

**d:** R=$NO_2$



**16**



**17**

**Figure 3.** Structures of selected nonheme complexes.

Application of Fe($^{DMM}$PDP) (**14c**) provides oxidation products but in low yield compared to the values obtained with the manganese analog (**14f**, gave 99% yield and A/K = 5.5). On the other hand, the more electron-poor catalyst, Mn($^{Cl}$MCP) (**18h**), only delivered very low product yields. When the *t*Bu group in the substrate was changed to $CF_3$ (EWG), or N-pentylphthalimide was used as a substrate, the γ-hydroxylation occurred predominantly. The selectivity toward hydroxylation of aliphatic C-H bonds is strongly supported by the hydrogen bonding ability of the solvent used. Trifluoroethanol (TFE), as well as 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), form the hydrogen bonds with alcohol (the primary formed product), thus preventing its overoxidation to the ketone via polarity reversal and consequent deactivation of the α-C–H bond. Cyclohexane-subjected oxidation with **18g** and $H_2O_2$ in MeCN, TFE, or HFIP resulted in hydroxylation selectivity at 40%, 96%, and 97%, respectively [82]. Fluorinated alcohol solvents applied in the oxidation of C-H bonds in 1,2-diols with (*S*,*S*)-**18g** or (*R*,*R*)-**14d** complex and $H_2O_2$, due to strong hydrogen bonds formation, cause polarity reversal and strong deactivation of proximal C-H bonds in HAT-initiated oxidation. As a consequence, site-selective and chemoselective oxidation of complex multi-functional molecules (sugars, steroids, and pharmaceuticals) occurs, in which the hydroxylation of C-H bonds at a distant and nonactivated site of the molecule predominates [83].

During the oxidation of adamantylacetic acid, Costas and co-workers observed and excellently described the influence of the carboxyl group in the substrate on the stereoselectivity of the hydroxylation [84]. Discrimination between the two enantiotopic C–H bonds of an inactivated methylene group was observed, resulting in γ-lactones in high enantiomeric excess (up to 99% ee, up to 88% yield, with **14h** as a catalyst). Coordination of the carboxylic acid group to the bulky Mn complex (see Figure 4) ensures the rigidity needed for high enantioselectivity and dictates the outstanding γ site-selectivity. When the respective methyl acetate was subjected to oxidation, the product of $3^0$ C–H hydroxylation was isolated exclusively. Thanks to the observed interactions, a general method for site-selective lactonization of γ-C-H bonds of natural and unnatural α-amino acids was developed [85]. The effect of the carboxyl group was used in the synthesis for the diastereoselective $C^2$ hydroxylation of taxane with simultaneous lactonization resulting in (+)-Taxol (see Scheme 11) [86]. Interactions of a chiral substrate with the chiral iron catalyst (*S*,*S*)-**14a** afford matched/mismatched selectivity in C–H oxidation; the use of **14a** antipode, (Fe (*R*,*R*-PDP)), resulted in a decreased yield of Taxol (25%) and a more complex mixture of oxidation products.

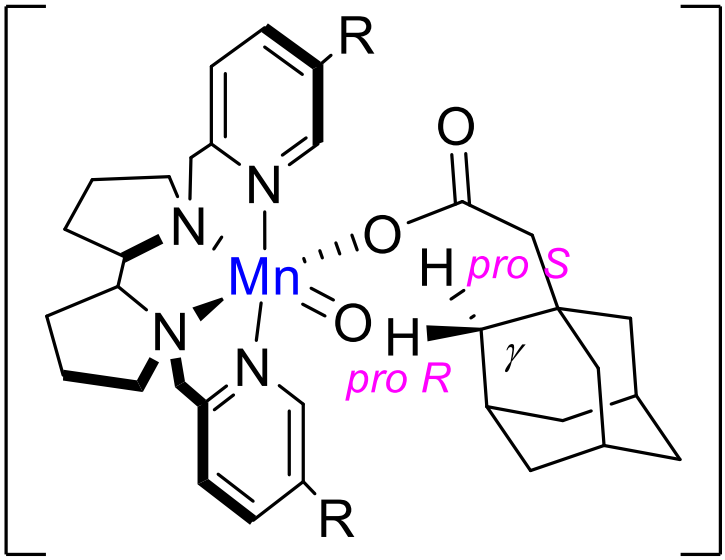
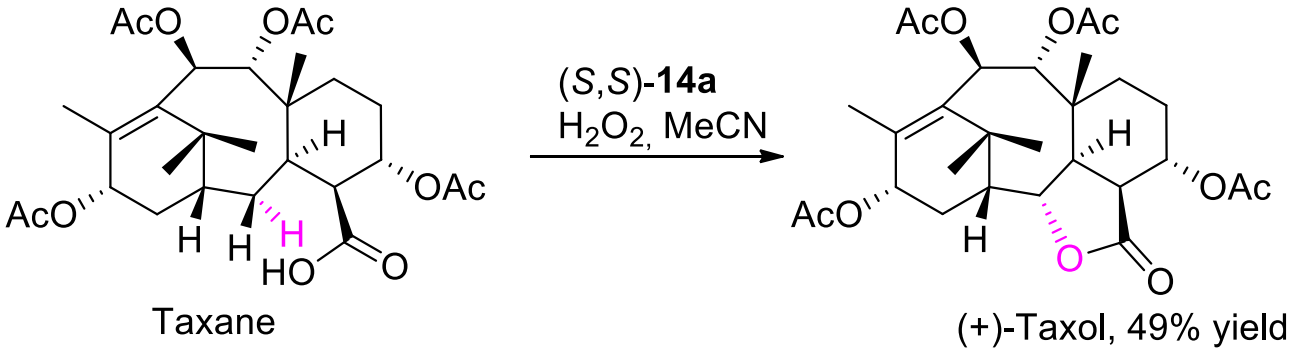
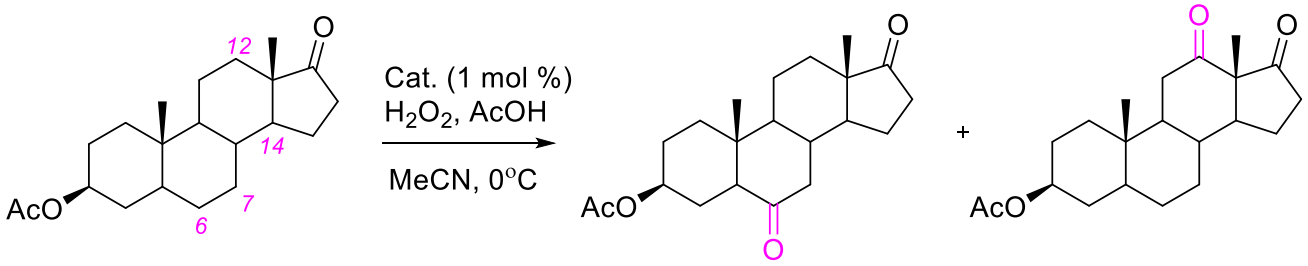



**Figure 4.** Directing effect of the carboxylic group in the substrate.




**Scheme 11.** Diastereoselective hydroxylation of Taxane with simultaneous lactonization resulting (+)-Taxol.

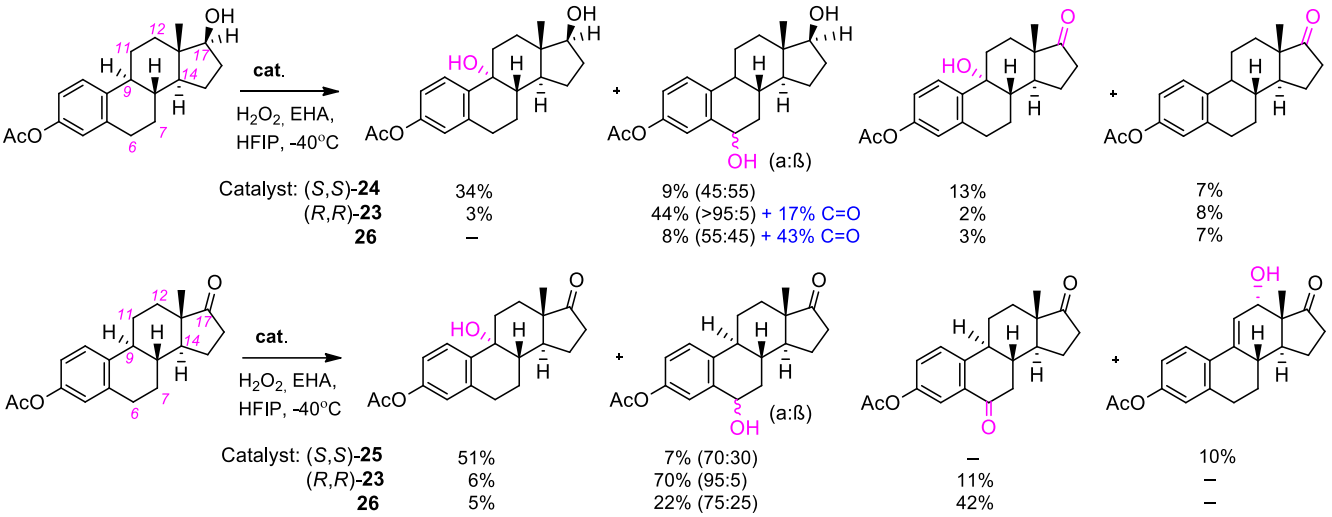
Complexes **14** and **18** are chiral at the metal (Λ or Δ series), which in turn is determined by the chirality of the diamine backbone (*S*,*S*′ and *R*,*R*′, respectively). Costas and Gebbink proved that the nature of the backbone systematically has a contributing role in enhancing selectivity towards the less sterically hindered C–H bond. According to their report, application in oxidation complexes substituted with bulky tris-(isopropyl)silyl groups (TIPS) can more strongly modulate their regioselectivity and may also enhance the stereoselectivity in C–H oxidation reactions. Both catalysts (**14d** and **18d**) provide improved product yields compared to the parent catalysts, **14a** and **18a**. Furthermore, TIPS-modified catalysts oxidize preferentially 2° over 3° C–H bonds, giving ketones. However, most remarkably, their chirality endows them with the ability to determine site selectivity among distinct methylene groups in the oxidation of complex molecules, as shown for steroids (Scheme 12). The (*S*,*S*′)-catalyst favors oxidation in the $C^6$ position while (*R*,*R*′)-catalyst reacts in $C^{12}$ [87]. Very thorough studies and interesting results regarding the influence of ligand architecture on the result of oxidative transformation were presented lately by Bryliakov and co-workers [88,89].




| | | C6 : C7 : C12 : C14 |
|---|---|---|
| Catalyst: (*S*,*S*)-**14d** | yield 70% | 72 : 5 : 23 : - |
| (*R*,*R*)-**14d** | 80 | 11 : 1 : 88 : - |
| (*S*,*S*)-**18d** | 60 | 82 : 12 : 3 : 3 |
| (*R*,*R*)-**18d** | 28 | 22 : 6 : 69 : 3 |

**Scheme 12.** Oxidation of trans-androsterone acetate.

A general synthetic protocol for late-stage selective oxidative C-H functionalization of estrone 3-acetate, 17α-estradiol 3-acetate, and 17β-estradiol 3-acetate (female hormones) with $H_2O_2$, relying on bioinspired Mn nonheme complexes with tetradentate N-donor ligands, has been developed. By tuning the ligand steric and absolute chirality, the reaction can be effectively directed towards either $C^9$-hydroxylation, $C^6$-hydroxylation, $C^6$-ketonization, or 9,11-desaturation/$C^{12}$-hydroxylation (selected examples in Scheme 13).



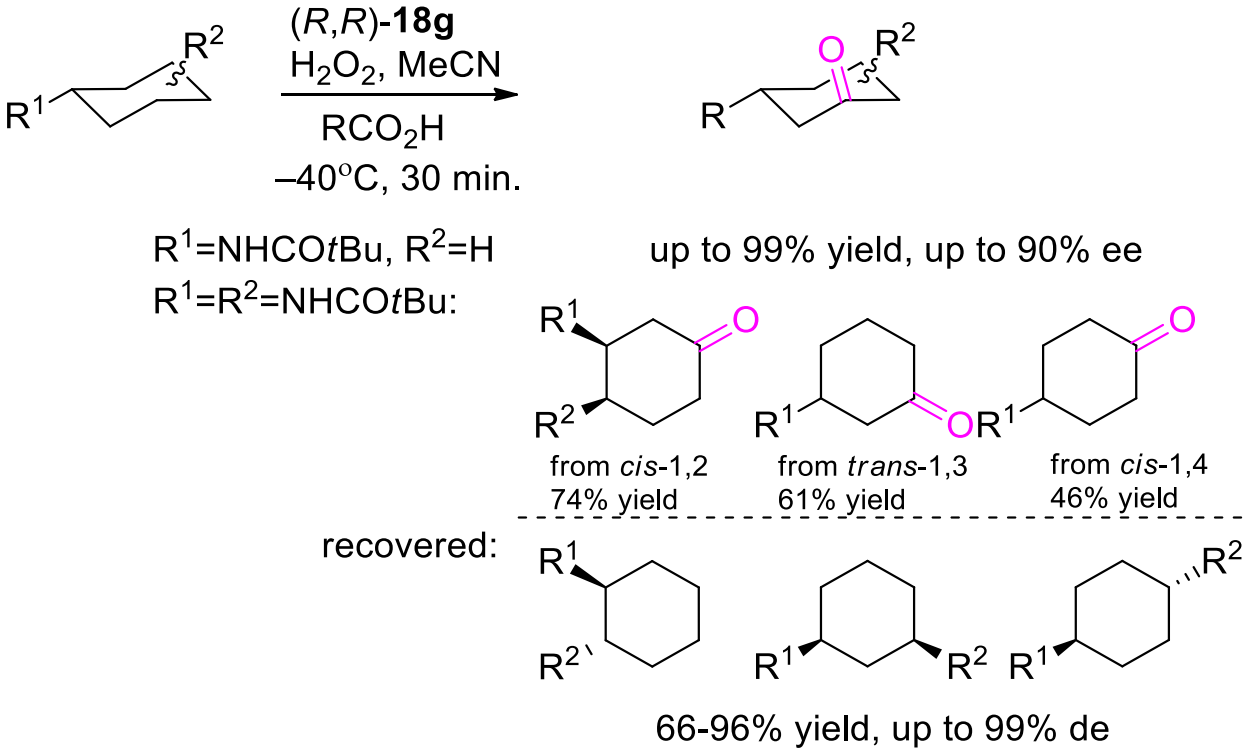

**Scheme 13.** Examples of selectivity of manganese catalysts depending on absolute chirality and ligand decoration.

The aromatic ring remains intact under these conditions, and ketonization of the hydroxo groups at $C^{17}$ is effectively prevented by using HFIP as a strong hydrogen bond donor reaction solvent [88]. The significance of the possibility of universal substitution and ligand compatibility for the development of efficient oxofunctionalization catalysts based on common transition metals was described in detail in the papers of Sun [90] and Costas [91].

The next challenge was to explore the ability of chiral complexes to affect the enantioselectivity of C–H oxidation. Since it has been shown that secondary alcohols are rapidly oxidized by several Fe- and Mn-complexes to the corresponding achiral ketones, it was decided to select substrates for the C–H oxidation, which can result in an asymmetric desymmetrization. The screening of related iron and manganese complexes as catalysts in the oxidation of tert-butylcyclohexane with $H_2O_2$ proved the superiority of manganese catalysts, especially those with TIPS-substituents on the pyridine rings (up to 44% ee). Significant improvements in enantioselectivity were observed when N-cyclohexylpivalamide was applied as the substrate (90% yield, up to 85% ee) [78,81]. As expected, the use of the opposite enantiomers of catalysts ((*S*,*S*′) or (*R*,*R*′)) provides the oxidation product with comparable optical purity (ee) but with the opposite absolute configuration. Carboxylic acid, used as a cocatalyst, strongly impacts the stereoselectivity due to its binding to the metal center (cis to the site where $H_2O_2$ is activated) and contributes to defining the active site. The best result was delivered by the application of propanoic and cycloproanecarboxylic acids (90 and 99% yield, 89 and 90% ee, respectively, $K^3/K^4$ = 45) [78]. This is considered the first example of nonenzymatic, highly enantioselective oxidation of nonactivated methylenic sites (Scheme 14).

Using previous observations, several N-cyclohexyl amides were oxidized under the same conditions. Unexpectedly, kinetic separation in the oxidation of C–H bonds in disubstituted cyclohexane derivatives has been observed [92]. Only cis-1,2-, cis-1,4-, and trans-1,3-cyclohexanediamides underwent selective oxidation with **18g** to ketones, while the other diastereoisomers were unreactive under the same conditions and can be recovered in good to excellent yields (66–96%) (see Scheme 14). Overall, the kinetic resolution in C–H bond oxidation of cyclohexane derivatives gave a powerful tool for organic synthesis. Moreover, it can successfully be used to isolate pure diastereomers from different cis—trans mixtures of commercially available starting materials, with a relatively low material loss. The carboxylic acid additive was found crucial for achieving a high A/K ratio and high enantioselectivity. While the use of simple achiral or racemic carboxylic acids results in low to moderate enantioselectivities (10–50% ee), the optically pure additive N-Boc-(*S*)-proline, in combination with **14i**, affords benzyl-type alcohols with up to 86% ee (A/K = 0.5–3.4,

TON = 25–340) [93,94]. The influence of the type of acid used as the cocatalyst has been studied recently by Wang's team [95]. After optimization, they developed a catalytic system using Mn(MCP) (**18e**), along with $H_2O_2$ as the oxidant, and with the addition of bromoacetic acid. The crucial features of the reported system are the excellent catalytic activity in hydroxylation (up to 98%), a low catalyst loading (0.1–1.0 mol%), a short reaction time, a broad substrate scope, and an easy scale-up. The catalytic system also showed excellent stereoretention (up to 98% ee) [95].




**Scheme 14.** Oxidation of cyclohexane derivatives with Mn($^{TIPS}$MCP) (**18g**).

Nam, San, and coworkers reported an enantioselective oxidation of benzylic methylene C–H bonds in spirocyclic substrates. Different manganese catalysts bearing a tetradentate N4 ligand (**19**–**21**, see Figure 5) were tested together with aqueous $H_2O_2$ as an oxidant. A series of chiral spirocyclic $\beta,\beta'$-diketones in high yields with excellent site- and enantioselectivities (up to 80% yield and up to 94% ee) were obtained when **21a** was used, and 2,2-dimethylbutanoic acid (DMBA) was applied as a cocatalyst (see part A of Scheme 15) [96]. To demonstrate the synthetic usefulness of the presented catalytic system, a gram-scale oxidation experiment was carried out. Oxidation of spirocyclic indanones under the same conditions afforded corresponding spirocyclic $\beta,\beta'$-spirobiindanones with good to excellent enantioselectivities (68%−98% ee). The authors studied the scope of the developed oxidation procedure more widely, namely, in the asymmetric oxidation of spirocyclic oxindoles and dihydroquinolinones, as shown in part B of Scheme 15 [97]. In optimized reaction conditions (two additions of catalyst for 2 h, at −20 °C), chiral alcohol was isolated (up to 41% yield, up to 99% ee). This result confirmed that the ketone product arises from the oxidation of the corresponding chiral alcohol.

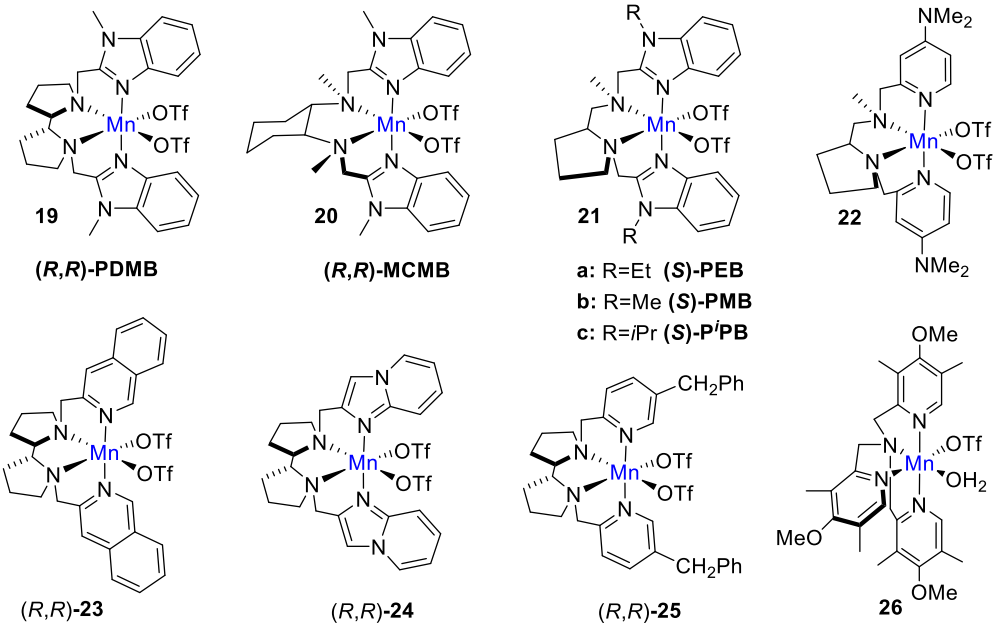
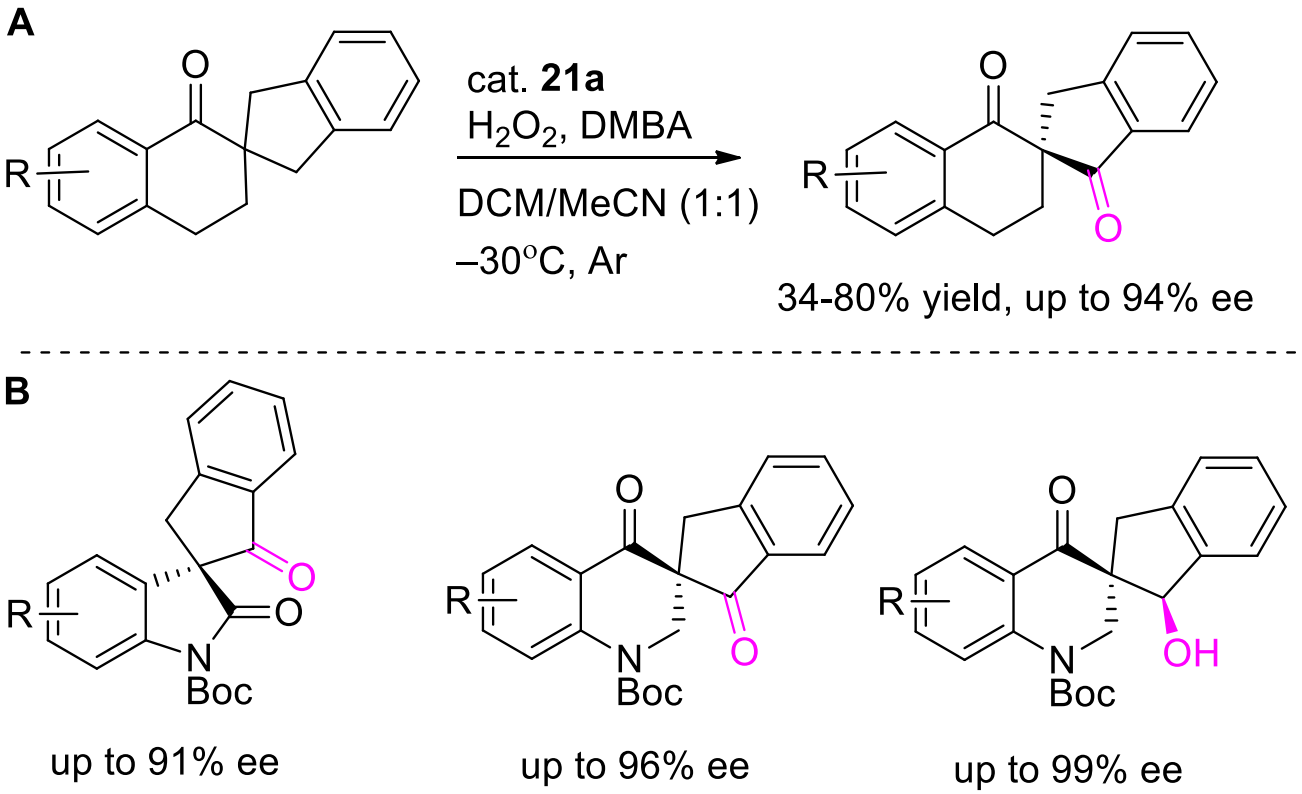


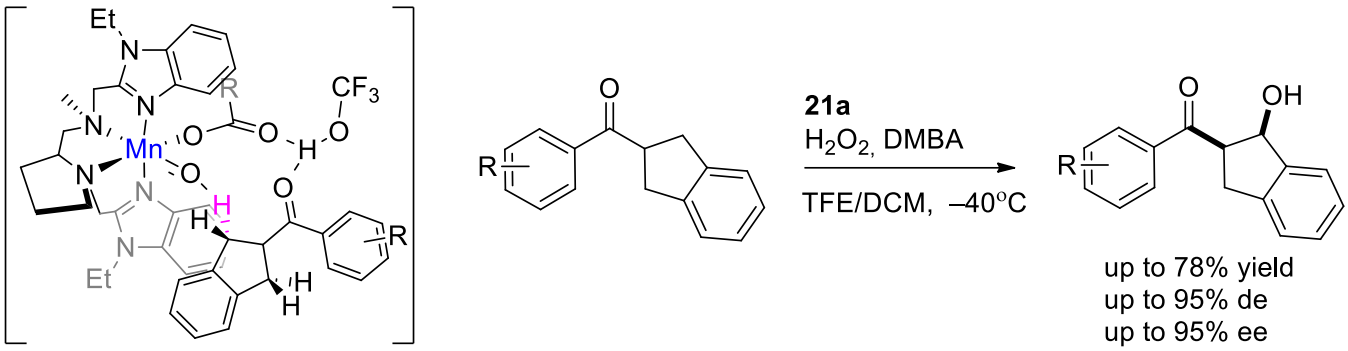

**Figure 5.** Selected structure of active Manganese complexes.




**Scheme 15.** Enantioselective oxidation of benzylic methylene C–H bonds in spirocyclic substrates with **21a**.

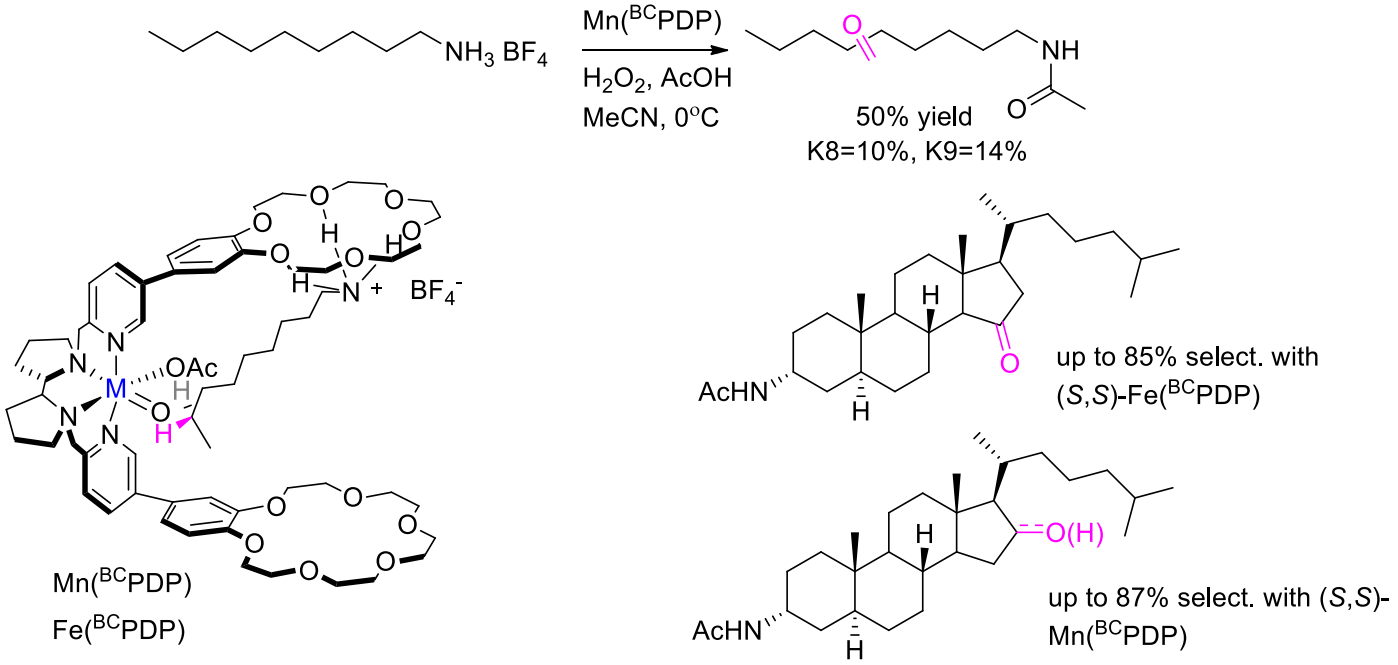
Sun has developed a direct, diastereo- and enantioselective C–H hydroxylation of the indan-type substrates bearing a carbonyl group. Catalyzed by a complex **21a** reaction, a series of benzylic alcohols were successfully obtained as the only product with high enantioselectivity (up to 95% ee) in TFE [98]. By modifying the amount of additive acid (DMBA), high diastereoselectivity of C–H hydroxylation was also obtained. Furthermore, a mechanism involving hydrogen bond interactions between the Mn(V)-oxo species, TFE, and the reaction substrate has been suggested (depicted in Scheme 16). Fluorinated alcohol

(TFE) has become the solvent of choice in oxidation reactions due to its mild acidity, high polarity, and strong hydrogen bonding, thus inhibiting further oxidation of the secondary alcohols formed.




**Scheme 16.** Application of **21a** in enantioselective hydroxylation of benzyl C-H bonds; the transition state responsible for the high enantioselectivity is shown.

Costas et al. introduced a supramolecular recognition strategy into the site-selective C–H oxidation of a simple alkyl chain with nonheme catalysts [99]. To achieve the site-selective oxidation, they designed iron- and manganese-PDP complexes bearing the 18-benzocrown-6 ether (BC) motif and investigated the oxidation of alkylammonium salts as a BC receptor (see Scheme 17). For short-chain substrates, both catalysts worked non-selectively, giving a mixture of ketones. However, for longer-chain substrates, the supramolecular-directed manganese-catalyzed oxidation (on $C^8$ and $C^9$) proceeded. Moreover, the Mn(PDP-BC) complex enabled the oxidation of alkylammonium salts selectively from various alkane mixtures [100]. The same strategy was applied to the late-stage C-H oxidation of aminosteroids at $C^{15}$ (or $C^{16}$) positions, with a selectivity tunable by modification of catalyst chirality and metal [101].




**Scheme 17.** Supramolecular recognition in the nonheme complex catalyzed oxidation.

Kadera and coworkers reported the preparation and application of catalytic oxidation in $\mu$-oxodiaquadiiron(III) complex **27** (see Figure 6) [102]. They discovered that in the presence of $H_2O_2$, complex **27** is converted to high-spin $\mu$-oxodiaquadiiron(IV) complex **27b**, which undergoes a fast transformation from synoxo to more active antioxo form. Due to the presence of the bis-TPA-type ligand, the binuclear structures **27a**–**27b** were stable enough for isolation as solid materials and were therefore possible to investigate. Species antidioxo-**27b** showed relatively high activity in the cleavage of a C-H bond, which was 620 times more reactive than the most reactive di-iron system reported to date. It was found that antidioxo-**27b** enabled quantitative alkane oxidation with reasonably high selectivity and gave large turnover numbers in the catalytic cycle (for cyclohexane TON = 104, for adamantane TON = 188, for cis-1,2-dimethylcyclohexane TON = 12.5). Lately, a series of nonheme $\mu$-oxo-bridged dinuclear $Fe^{III}$-complexes, with tripodal 4N ligands with pyridine (**28**–**30**), imidazole (**31**–**32**), and sterically demanding quinoline moieties (**33**), were prepared and their catalytic activity toward the hydroxylation of alkanes has been studied using *m*CPBA as an oxidant [103]. All of these complexes were characterized; moreover, molecular structures of **29** and **32** have been successfully determined by single crystal X-ray diffraction analysis. The most active in the cyclohexane oxidation was complex **31**, giving 448 TON of cyclohexanol (A) and 51 TON of cyclohexanone (K), and 12 TON of 3-caprolactone (A/K, 7.1) with 73% conversion.

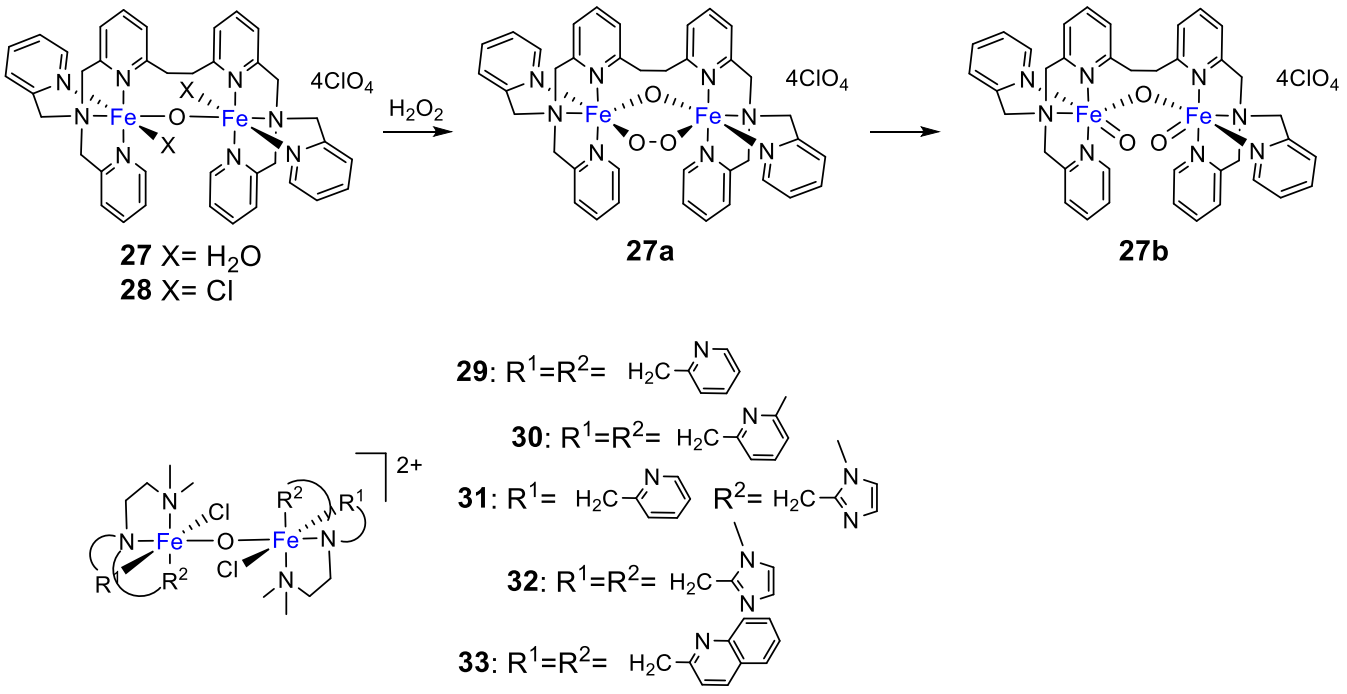
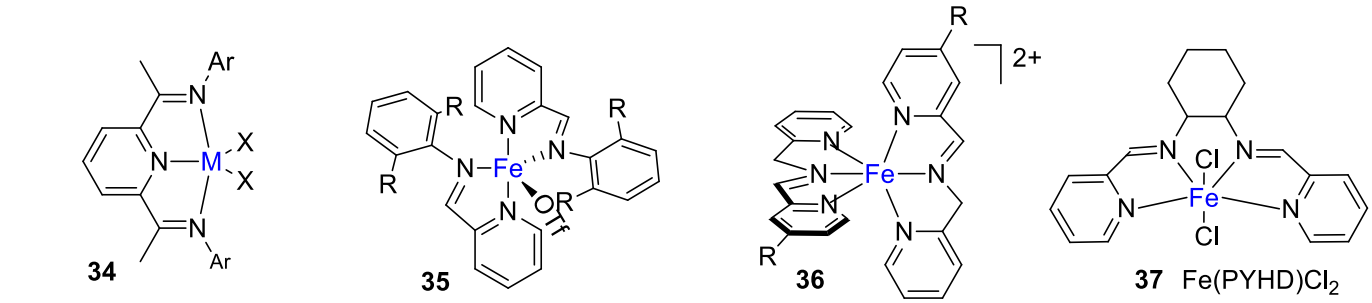



**Figure 6.** High reactive $\mu$-oxodioxodiiron(IV) active species and $\mu$-oxodiaquadiiron(III) complexes.

Research on iron catalysts based on nonheme amines was accompanied by parallel studies on iron complexes based on nonheme imines. However, the latter has received considerably less attention, possibly due to the conviction that imines are not robust enough to be successfully and widely used under typical oxidation conditions. The imine ligands are good sigma donors and allow a high degree of $\pi$-backbonding, so they have been used for the coordination of various transition metals. The first iron complexes **34** (see Figure 7) applied in the oxidation of cyclohexane exhibited only moderate activity. The A/K ratios closely suggest radical formation and indicate that the reaction mechanism is driven mainly by Fenton-type chemistry [104]. Bauer et al. described the synthesis and application of iron complexes bearing **35** bidentate iminopyridine ligands. These complexes showed rather low activity in the oxidation of cyclohexane with $H_2O_2$ or *t*BHP, compared to the activities of iron complexes with tetradentate N-coordinating ligands. However, activated methylene

groups can be oxidized by applying **35** with *t*BHP (catalyst loading 3 mol%) for up to 91% yield (fluorene to fluorenone) [105]. An effective catalyst for the oxidation of C-H bonds of hydrocarbons by $H_2O_2$, even at low catalyst loads (as low as 1%), turned out to be the nonheme imine-based iron(II) complex **36** developed by Di Stefano. The authors assume that the octahedral complex, easily prepared in situ from commercially available starting materials, is the pre-active form in the catalytic sequence. Its reaction with an oxidant leads to the $Fe^{III}$-OOH form, which is finally transformed into an active oxo-complex capable of carrying out the oxidation of cyclohexane (24% yield, A/K = 1.4), adamantane (47% yield, 3o/2o up to 13), and 1,2-cis-dimethylcyclohexane (RC 97%) [106,107].




**a:** M=Fe, Ar=2,6-*i*$Pr_2C_6H_3$
**b:** M=Fe, Ar=2,6-$Me_2C_6H_3$
**c:** M=Mn, Ar=2,6-*i*$Pr_2C_6H_3$
**d:** M=Mn, Ar=2,6-$Me_2C_6H_3$
**e:** M=Co, Ar=2,6-*i*$Pr_2C_6H_3$
**d:** M=Co, Ar=2,6-$Me_2C_6H_3$

**a:** R=H
**b:** R=$OCH_3$
**c:** R=$CH_3$
**d:** R=$NO_2$

**Figure 7.** Selected imine-based iron complexes.

Contrarily, high selectivity towards the formation of cyclohexanol using $H_2O_2$ as an oxidant was achieved with complex **37**, although nonactivated C–H bond oxidation required nitric acid as a cocatalyst. The overall yield of cyclohexane oxidation was 17.5%, but the A/K ratio was 74.5 (TON 16.7) [108].

## 5. Conclusions

Over the past decades, the direct and selective functionalization of nonreactive C–H bonds of alkanes and cycloalkanes has become an attractive approach to obtaining various functionalized organic compounds with high added value from cheap and ubiquitous starting materials. Among the various types of transformation, one of the most widely exploited was direct oxidation/hydroxylation. By discovering how enzymes work in nature, we are able to construct systems that mimic their action. For this purpose, complexes of transition metals with porphyrin ligands and nonheme ligands have been designed, and since then they have been constantly modified, improved, or new ones are created. In recent years, apart from activity requirements, the catalytic systems under development are expected to be chemo-, site-, or even enantioselective. By exploring the nature of the electrophilic oxidant and its mechanism of action, it is possible to reach for the design of appropriately substituted structures that will have the desired properties. Porphyrin ligands were the first to offer such a modeling opportunity, but the introduction of polydentate aminopyridine ligands (nonheme) provided much wider possibilities. The development of Mn complexes with multi-dentate, structure-modulated, and aminopyridine ligands was another milestone in bioinspired transition metal-catalyzed selective oxidation of aliphatic C–H groups with environmentally acceptable final oxidants. The usefulness of iron and manganese complexes as catalysts in oxyfunctionalization has been repeatedly proven by their use in key stages of the synthesis of many compounds of proven importance. In some respects (catalytic efficiency, selectivity, and oxidant economy), Mn catalysts seem to have even higher potential compared to their iron counterparts. Calculations and available experimental data prove the similarity of the mechanisms of C–H oxidation catalyzed by

Fe- and Mn-aminopyridine complexes, i.e., the formation of high-value $M^V$–oxo species. Despite the proven catalytic efficiency and efforts made, the detection of the same active intermediates involved in the mechanism of oxidation by catalysts based on late transition metals, such as cobalt, nickel, or copper, is rather rare. Concerning catalyst-controlled site-divergent and chemo-selective C–H bond functionalization, future research should focus on the development of new ligand structures for transition metal-catalyzed oxidation procedures that enable the oxidation of currently inaccessible C–H bonds. Work should be continued to expand the more useful C–H bond functionalization.

**Funding:** This research received no external funding.

**Data Availability Statement:** Publicly available datasets were analyzed in this study.

**Acknowledgments:** The authors are grateful for the financial support given by the Polish Ministry of Science and Higher Education by subvention activity for the Faculty of Chemistry at Wrocław University of Science and Technology.

**Conflicts of Interest:** The author declares no conflict of interest.

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