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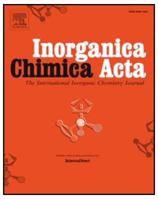

Research paper

Manganese complex catalyst for valencene oxidation: The first use of metalloporphyrins for the selective production of nootkatone

Carla Nunes de Melo[a], Alexandre Moreira Meireles[a], Vinicius Santos da Silva[b], Patrícia Robles-Azocar[a], Gilson DeFreitas-Silva[a,*]

[a] *Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais, 31.270-901 Belo Horizonte, MG, Brazil*
[b] *Centro de Formação de Professores, Universidade Federal do Recôncavo da Bahia, 45.300-000 Amargosa, BA, Brazil*

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ABSTRACT

This work describes the oxidation of valencene, a sesquiterpene easily obtained from citrus fruits, and responsible for the fresh odor of oranges. The reactions were catalyzed by manganese porphyrins derived from 5,10,15,20-tetrakis(3,5-dimethoxyphenyl)porphyrin ($H_2T3,5DMPP$): [Mn^{III}(T3,5DMPP)Cl] (**MnP1**) and [Mn^{III}($Br_{12}T3,5DMPP$)Cl] (**MnP2**), using iodosylbenzene (PhIO), iodobenzene diacetate [$PhI(OAc)_2$], and molecular oxygen as oxidants. The systems **MnP1**/O_2/acetonitrile and **MnP1**/O_2/diethyl carbonate led to higher yields of valencene oxidation products (44% and 48%, respectively) as compared with **MnP2** (9% and 7%, respectively), with nootkatone being the major product. The addition of a small amount of imidazole (molar **MnP1**: imidazole ratio of 1:5) to the **MnP1**/O_2/diethyl carbonate led to superior yields (64%) as compared with systems without the additive. A mechanism for the formation of the two products obtained was also proposed.

1. Introduction

Valencene (**1**, Fig. 1), the chemical responsible for the fresh odor of oranges, is a sesquiterpene that is easily obtained from citrus fruits [1]. It is an inexpensive raw material that can be oxidized into high value products such as nootkatone [2,3] (**2**, Fig. 1). Nootkatone is an allylic ketone first isolated from the heartwood of Alaskan yellow cedar [4,5]. Currently, this substance is widely used in the food industry, as a beverage flavoring, and the fragrance industry [1]. Recent studies have also demonstrate its potential use as a natural repellent against mosquitoes and other pathogenic insects to humans and animals [6,7].

Despite the great industrial demand for this molecule, its most common extraction source, the grapefruit, contains a low concentration of this substance (0.05 to 0.2%), causing the process to be costly [2,8,9]. Studies on obtaining nootkatone are generally related to valencene biotransformation. Although the commonly used processes lead to satisfactory yields, it requires a long processing time, due to the need for inoculation and cultivation of microorganisms, and results in the formation of a large number of byproducts, which causes their industrial application to be unfeasible [1,5,10–12]. Therefore, investing in simpler routes that can provide good yields of nootkatone in a shorter time becomes a promising research field.

Metalloporphyrin catalysts have been investigated in several studies as biomimetic models of cytochrome P450 in oxidation reactions of organics substrates [13,14]. Metalloporphyrin catalysts are classified into first, second, and third-generation, based on the catalytic activity of these compounds in the reaction medium and their ability to resist oxidative processes [15]. Complexes derived from tetraphenylporphyrin are classified as first-generation catalysts, while second and third-generation catalysts are characterized by having substituents (such as –Cl, –Br, –NO_2, and –OCH_3) in the aryl group of the *meso*-positions or the β-pyrrolic positions of the macrocycle, respectively.

In reactions catalyzed by metalloporphyrins, several oxidants can be used, including iodosylbenzene (PhIO), iodobenzene diacetate [$PhI(OAc)_2$], hydrogen peroxide (H_2O_2), and molecular oxygen (O_2) [16–20]. The use of molecular oxygen in place of classical oxidants typically used for catalyzing these reactions, such as PhIO, is an interesting proposal [19–21]. This oxidant is attractive due to its low cost, ready availability, and it is environmentally harmless because it generates water as a byproduct. The oxidation of olefins in value-added compounds using O_2 is already widely used in several catalytic systems [22–25]. Rayati and Nafarieh studied the oxidation of alkenes and alkanes with molecular oxygen in the presence of Fe(III)- and Mn(III)-porphyrins supported onto multi-wall carbon nanotubes as catalysts [21]. The Mn-catalyst was shown to have higher catalytic activity

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[*] Corresponding author at: Departamento de Química – Instituto de Ciências Exatas – Universidade Federal de Minas Gerais, Belo Horizonte, MG 31270-901, Brazil.
E-mail address: gilsonufmg@ufmg.br (G. DeFreitas-Silva).

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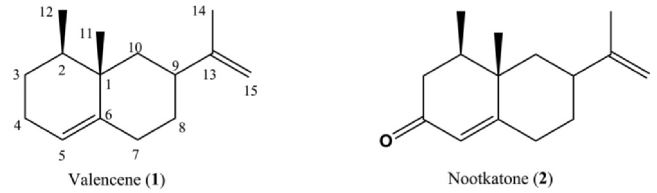

Fig. 1. Structural representation of valencene (**1**) and nootkatone (**2**).

compared with the Fe-catalyst in styrene oxidation. In this case, the reactions were carried out with acetonitrile as a solvent at 40 °C and resulted in the formation of styrene oxide with a conversion of 87% and selectivity of 64% [21].

In addition to the oxidant, the choice of solvent represents one of the fundamental aspects within the principles of green chemistry since it represents up to 90% of the total mass for the synthesis of many products of industrial interest [26]. Thus, toxic solvents, whenever possible, should be replaced by solvents with less toxicity in chemical reactions. Organic carbonates, such as diethyl carbonate, have been attractive as substitutes for volatile organic compounds (VOC) because of their low toxicity and they do not bioaccumulate [27]. This solvent has only been broadly employed in electrochemical and extraction processes [26,27]. However, this scenario has been modified, and it is already possible to find works in which catalyzed reactions such as Heck [26] and hydrogenation [28] and even oxidation [29] are performed using carbonates as solvents.

In this context, we decided to evaluate the oxidation of the sesquiterpene valencene using second and third-generation manganese porphyrins as biomimetic catalysts derived from 5,10,15,20-tetrakis(3,5-dimethoxyphenyl)porphyrin, H_2T3,5DMPP: [Mn^{III}(T3,5DMPP)Cl] (**MnP1**) and [Mn^{III}(Br_{12}T3,5DMPP)Cl] (**MnP2**) (Fig. 2), which have shown efficient catalytic activity for the activation of inert C—H bonds in alkanes with high selectivity [30,31]. Based on these studies, the oxidation of valencene was carried out using the classical oxidants PhIO and $PhI(OAc)_2$. In an attempt to develop catalytic systems more sustainable for this substrate oxidation, molecular oxygen as an oxidant and diethyl carbonate as a solvent were also evaluated.

2. Materials and methods

2.1. Chemicals

Analytical grade dichloromethane was obtained from Aldrich and distilled before use. PhIO was prepared according to a previously described method and assayed periodically by iodometric titrations [32]. All the other reagents and solvents were analytical grade and used without further purification unless stated otherwise.

2.2. Catalysts

The [Mn^{III}(T3,5DMPP)Cl] (**MnP1**) and [Mn^{III}(Br_{12}T3,5DMPP)Cl] (**MnP2**) (Fig. 2) were obtained and characterized as previously reported by Silva et al. [30].

2.3. Catalytic reactions

Reactions were carried out in a 100 mL homemade stainless-steel reactor with a magnetic stirrer. In a typical run, a mixture of valencene (1 mmol), dodecane (GC internal standard, 0.5 mmol), **MnP1** or **MnP2** (1 µmol), and solvent (acetonitrile or diethyl carbonate, 4.8 mL) was vigorously stirred (300 rpm) at 80 °C under an oxygen pressure of 10 atm. At appropriate time intervals, stirring was stopped, and samples were collected from the reactor and analyzed by gas chromatography (GC) using a Shimadzu QP2010-Plus instrument fitted with an apolar RTx −5MS (Crossbond –Carbowax –polyethylene glycol) capillary column and a flame ionization detector. All the reactions were carried out at least two times, and the data reported represent the average of these reactions. The reactions that presented the best results were performed two more times, and the data reported represent the average of these four reactions. For these systems, the standard deviation was 2% of the average value. The conversion of the substrate and the yield of the reaction products were monitored over time. A time of 4 h achieved the maximum conversion of the substrate. Control reactions, in the absence of either oxidant or catalyst, were performed under the same conditions as the catalytic runs.

Gas chromatography (GC) mass balance was carried out using dodecane as an internal standard. Deviations from the complete mass balance were attributed to the formation of high boiling point products from the polymerization reactions [33], which were not determined by GC analysis. The details about the mass balance are given in the Supplementary Material.

Reactions with PhIO or $PhI(OAc)_2$ were similar to the described process using molecular oxygen. In this case, a mixture of valencene (1 mmol), dodecane (GC internal standard, 0.5 mmol), **MnP1** (1 µmol), PhIO (10, 25, 50, or 100 µmol) or $PhI(OAc)_2$ (10 or 100 µmol), and dichloromethane (4.8 mL) was vigorously stirred (300 rpm) at 80 °C, and the reactor was kept under atmospheric pressure.

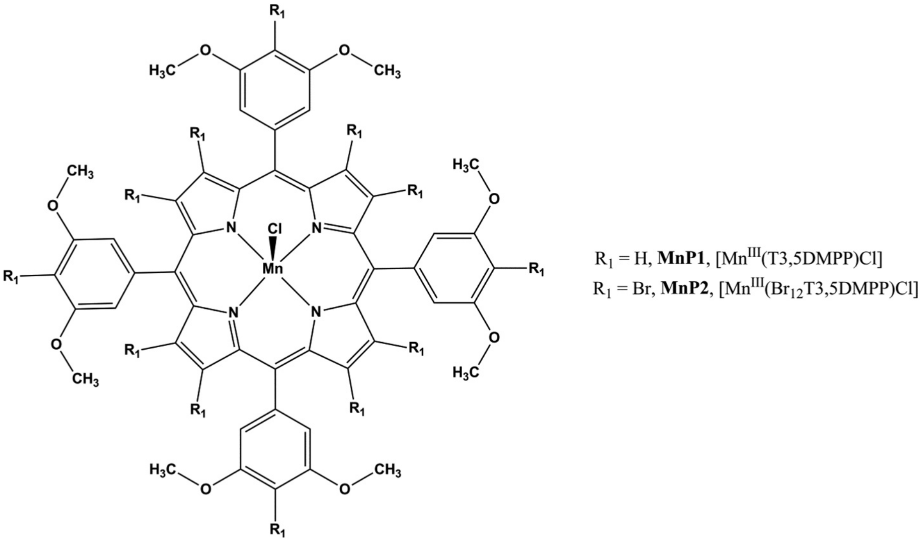

Fig. 2. Structural representation of the metalloporphyrin catalysts used in this work.

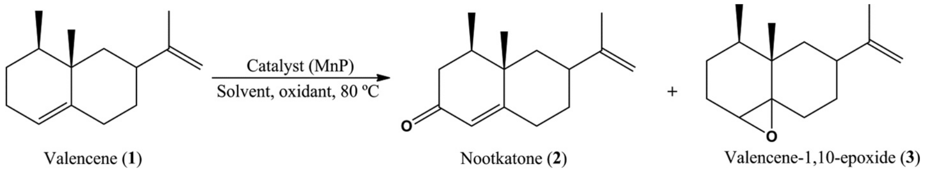

Fig. 3. Oxidation of valencene by different oxidants (PhIO, PhI(OAc)$_2$, or O$_2$) catalyzed by manganese porphyrins (MnP).

2.4. Product characterization

Products **2** and **3** (Fig. 3) were isolated by column chromatography (Aprolab®, 60G, 70–230 Mesh) using mixtures of hexane and ethyl acetate (5:1) as eluents and identified by GC/MS (Shimadzu QP2010-PLUS instrument, 70 eV). Product **2** was characterized by NMR (Bruker DRX-400 instrument, tetramethylsilane, CDCl$_3$).

Nootkatone (**2**, Fig. 1): ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS), δ = 0.97 (d, 3H, C^{12}H$_3$, ^2J = 6.78); 1.12 (s, 3H, C^{11}H$_3$); 1.24–1.28 (s, 1H, C^{2}H); 1.74 (s, 3H, C^{15}, H$_3$); 1.87–2.09 (m, 4H, C^8*H*H, C^{8}H*H*, C^{10}*H*H, C^{10}H*H*); 2.22–2.41 (m, 4H, C^3*H*H, C^{3}H*H,* C^7*H*H, C^{7}H*H*); 2.46–2.58(m, 1H, C^{9}H); 4.71–4.76 (m, 2H, C^{15}*H*H, C^{15}H*H*); 5.78 (s, 1H, C^{5}H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C, TMS), δ = 200.00 (C^4); 170.7 (C^6); 149.3 (C^{13}); 125.2 (C^5); 109.5 (C^{15}); 44.17 (C^{10}); 42.29 (C^3); 40.71 (C^9); 40.57 (C^1); 39.58 (C^2); 33.26 (C^7); 31.88 (C^8); 21.02 (C^{14}); 17.08 (C^{11}); e 15.10 (C^{12}) ppm. MS (*m/z*/rel. int.): 218/38 (M$^+$); 203/40 (M$^+$ − CH$_3$); 175/50; 161/78; 147/100; 133/74; 121/80; 105/62; 91/79; 79/78; 55/36.

Valencene-1,10-epoxide (**3**, Fig. 3): MS (*m/z*/rel. int.): 220/35 (M$^+$); 205/20 (M$^+$ − CH$_3$); 91/95; 121/96; 177/100; 105/93; 121/87; 107/75; 79/61; 135/59; 79/72; 67/50; 109/41; 55/73. The data are consistent with those reported by Sowden et al. [34].

3. Results and discussion

3.1. Oxidation of valencene employing MnP1 and MnP2 as catalysts

The oxidation of valencene results in products of great commercial value, such as nootkatone, which is widely used in the flavor and cosmetic fields due to its grapefruit odor. To the best of our knowledge, this is the first work describing the use of manganese porphyrins as catalysts for valence oxidation. The vast majority of reports employ the use of various biocatalysts, which are characterized by low conversion rate and yield, costly culture conditions, the formation of various byproducts, and inhibition of enzymes by these byproducts. These characteristics hamper the industrial application of these biocatalysts [10,12,35]. Therefore, we decided to evaluate valencene oxidation using **MnP1** as the catalyst. This compound was synthesized by our group [30]. It showed good activity in linear and cyclic alkanes oxidation, and the presence of methoxy-groups at the *meso*-aryl positions of the porphyrinic macrocycle tends to be beneficial in systems involving the oxidation of alkenes [36–38].

The reaction was first evaluated using the classic oxidant, PhIO, and employing dichloromethane (CH$_2$Cl$_2$) as the solvent (Table 1). This solvent is typically used in reactions catalyzed by metalloporphyrins since it can efficiently solubilize the catalyst, and additionally, it is a non-coordinating solvent [30,31,39,40].

The control reaction, in the absence of **MnP1** (Table 1, Run 1), exhibited a small conversion of valencene (7%). Moreover, only traces of nootkatone (**2**, Fig. 3) were detected. These results demonstrated the need for a catalyst to obtain functionalized products. In Run 2, the oxidation of valencene was carried out in the absence of PhIO, and nootkatone (**2**) was formed with high selectivity (75%) and a yield of 7%. This result suggests the incorporation of molecular oxygen in the substrate, even in the absence of PhIO as the oxidant. The experiment under aerobic condition, employing a molar **MnP1**:PhIO:valencene ratio of 1:10:1000 (Run 3), led to a yield of 10% for nootkatone with the selectivity of 60%. To verify the influence of atmospheric oxygen in the system, the reaction was performed under an argon atmosphere (Run 4, Table 1). In this case, there was a significant decrease in the selectivity of **2** (10%), showing that the formation of this product strongly depended on the presence of O$_2$. Furthermore, according to GC–MS data, an oxygenated product (*m/z* (%): 220 (35) [M$^+$]) was detected in a similar amount to ketone (selectivity of 10 and 11%, respectively). The product was attributed to the transformation of endocyclic π-bond of valencene, resulting in the valencene-1,10-epoxide formation (**3**, Fig. 3), the most common product reported in the literature for this transformation type [6,34]. This system indicated that the formation of epoxide was favored in anaerobic conditions, although the combined yield for the two oxygenated products was a little higher than 1%. Thus, it is possible that higher yields were achieved when there was both PhIO and atmospheric O$_2$ in the reaction medium. Nascimento et al. reported a similar system for cyclohexene oxidation reactions. The high yields for the allylic products derived from cyclohexene were attributed to the ability of PhIO to act as a radical chain initiator in the presence of O$_2$, mediated (or not) by the MnP catalyst [41].

Table 1

Oxidation of valencene by PhIO and PhI(OAc)$_2$ catalyzed by **MnP1** in CH$_2$Cl$_2$.[a]

Run	Oxidant (μmol)	Conversion (%)	Selectivity (%)		Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
			2	**3**			
1[e]	PhIO (10)	7	Tr.	0	0	–	–
2[f]	–	9	75	0	7	90	9
3	PhIO (10)	16	60	0	10	160	40
4[g]	PhIO (10)	6	10	11	1.3	60	15
5	PhIO (25)	27	42	0	11	270	68
6	PhIO (50)	29	33	0	10	290	73
7	PhIO (100)	14	31	0	4	140	35
8	PhI(OAc)$_2$ (10)	12	40	0	5	120	30
9	PhI(OAc)$_2$ (100)	37	43	0	16	370	93

[a] Conditions: valencene = 1.0 mmol; **MnP1**: 1 μmol; CH$_2$Cl$_2$ = 4.8 mL; 80 °C, reaction time: 4 h. Conversion and selectivity were determined by GC. Tr = traces.

[b] Theoretical yield calculated by the ratio: (conversion) × (selectivity 2 + 3)/100.

[c] TON (turnover number) was calculated as the amount of substance of valencene (mol) reacted per amount of substance of **MnP1** (mol).

[d] TOF (Turnover frequency).

[e] Reaction in the absence of catalyst; reaction time: 10 h.

[f] Reaction in the absence of oxidant; reaction time: 10 h.

[g] Reaction in an argon atmosphere.

In the attempt to obtain the highest yields and conversions, reactions were carried out with higher amounts of PhIO (Runs 5 to 7), keeping the amounts of **MnP1** and valencene fixed. When the reaction was carried out with 25 and 50 μmol of oxidant, very little difference was observed in the product yield (Runs 5 and 6 *versus* Run 3). However, the selectivity for nootkatone decreased considerably (42 and 33%, respectively) when compared to the experiment with 10 μmol of PhIO (60%; Run 3, Table 1). The increase in the amount of PhIO (100 μmol) did not lead to more efficient systems for obtaining oxidized products (yield of 4%, Run 7). Based on these results, we hypothesize that with higher amounts of PhIO, there should be an increase in the catalyst destruction process, leading to a decrease in the amount of active catalytic species available for the oxidation of the substrate [42] or by the occurrence of by-side reactions, responsible for consuming part of the oxidant [39,43]. Additionally, PhIO is a very strong oxidant, which can lead to the formation of products with higher molar mass (polymerization) that are not detectable by GC [44]. These data present the drawback of using PhIO as an oxygen source for the valencene oxidation reaction. It is poorly soluble in most of the organic solvents, toxic, potentially explosive [45], and not recommended by Green Chemistry principles [46,47].

We also evaluated the catalytic efficiency of **MnP1** using $PhI(OAc)_2$ as the oxidant (Table 1). This oxidant has the advantage of being soluble in most of the organic solvents commercially available and safer than PhIO [48,49]. Under aerobic conditions and employing a molar **MnP1**: $PhI(OAc)_2$:valencene ratio of 1:10:1000, the yield and selectivity for nootkatone were 5% and 40%, respectively (Run 8, Table 1). This system was less effective for valencene oxidation than the one using PhIO (Run 3, Table 1). This could be due to the fact that the reactions with $PhI(OAc)_2$ are slower than those with PhIO [48]. This observation could explain the lower catalytic efficiency of this system.

In an attempt to increase the efficiency of the reactions with $PhI(OAc)_2$, we also verified the effect of the amount of oxidant in this system, similar to the reactions of PhIO (Table 1). When a molar **MnP1**:$PhI(OAc)_2$:valencene ratio of 1:100:1000 was employed, no significant differences in the selectivity of **2** (43%) was observed compared to lower amounts of oxidant; however, the reaction yield had a considerable increase (16%, Run 9, Table 1). As proposed by In and co-workers, the systems with $PhI(OAc)_2$ can generate the active oxidant PhIO *in situ* in the presence of a small amount of water [48]. This controlled hydrolysis could avoid the side reactions responsible for removing part of the active oxidant from the reaction. In this way, we carried out the reaction with $PhI(OAc)_2$ in the same conditions as Run 9, with the presence of 5 μL of water as an additive. This system reached a maximum total yield of 21% in only 2 h, while the system in the absence of this additive presented a total yield of 16% in 4 h. At this point, we could suggest that even in the absence of water (as observed for the reactions in Run 8 and 9 (Table 1)), the $PhI(OAc)_2$ could be hydrolyzed by the presence of water from the solvent [40,50] since the solvent was not previous dried.

However, the system with $PhI(OAc)_2$ presents higher values of catalyst destruction, favored by a large amount of oxidant used [51]. Also, one of the byproducts of this oxidant is acetic acid [48,49], which reduced the atomic economy of the process [46].

The reactions with PhIO and $PhI(OAc)_2$ in the presence of dichloromethane as the solvent exhibited low values of valencene conversion and low yields for the oxidized products. These systems present reagents that should be avoided, according to Green Chemistry principles. In this way, searching to develop a more environmentally-friendly system, we verified the effect of a green oxidant and solvents for valencene oxidation reactions.

As an alternative to PhIO and $PhI(OAc)_2$, we evaluated the efficiency of **MnP1** to catalyze the oxidation of valencene by molecular oxygen, O_2 (Table 2). Oxidation of organic compounds with molecular oxygen has the advantages of promoting an eco-friendly environment and being an abundant reagent. Initially, we carried out the reaction in the presence of acetonitrile. This solvent, besides being safer than dichloromethane (boiling point 82 *versus* 39.6 °C, respectively, and it is not a halogenated solvent), is also able to solubilize the catalyst and the substrate, which facilitates the interaction between the components of the reaction.

The oxidation of valencene under 10 atm of O_2 was firstly evaluated in the absence of a catalyst (Run 10, Table 2). In this system, almost no conversion was observed, and only traces of nootkatone (**2**) were detected, indicating that the presence of the catalyst has an important role in the reaction.

The reaction in the presence of the second-generation manganese porphyrin **MnP1** and with acetonitrile as the solvent (Run 11, Table 2), led to the formation of nootkatone (**2**) and product **3** (in smaller amounts). In this reaction, the total yield of the oxygenated products was 48%, with the highest value of TON values (860) among the studied systems.

When we employed the green solvent diethyl carbonate (DEC) in the presence of O_2, there was a slight decrease in reaction yield (44%) when compared to the system with acetonitrile and a TON value (740) was verified (Run 12, Table 2). The high TON values showed the stability of the catalyst under the conditions employed. The slight decrease in reaction yield could be related to the lower solubility of MnP1 in DEC than acetonitrile since we verified that the catalyst was not completely solubilized at the beginning of the reaction; however, the catalyst was solubilized during the reaction, and at the end of 4 h we verified a homogeneous system in the reactor vessel. These solvents present distinct properties, such as the dielectric constant (37.5 and 2.82 for acetonitrile and DEC, respectively) and the dipole moment (3.75 and 1.07 D for acetonitrile and DEC, respectively), which could justify the difference between these two systems. Guimarães and co-workers verified that in solvents with higher dielectric constants, the active species responsible for transferring the oxygen atom to the substrate could be formed faster than those present in the solvents with lower dielectric constants [31]. In this way, acetonitrile could promote a more effective system for the oxidation of valencene. However, DEC has the advantage of being a biodegradable solvent that fits in the Green Chemistry principles when compared to acetonitrile [46,52]. Thus, the replacement of acetonitrile by DEC can ensure a greener system for valencene oxidation, in addition to not promoting large losses in the total reaction yield.

In an attempt to obtain a more effective catalytic system, imidazole was used as an additive (Run 13, Table 2). The addition of imidazole at a molar MnP:Im ratio of only 1:5 to the system led a total product yield of 64% *versus* 44% in the system with an absence of this additive (Run 12, Table 2). As reported by the literature, the co-catalyst, imidazole (or other axial ligands), is responsible for favoring the epoxidation of alkenes due to the intermediary type formed in the oxidation reactions by single oxygen donors [53,54]. Surprisingly, we verified that the addition of imidazole promoted a more selective system for nootkatone production. Gunter and Turner proposed that a second type of the intermediary is responsible for the high levels of allylic oxidations when the catalyst presents a radical centered in the porphyrin ligand (a typical π-cation radical $[\mathrm{Mn(IV)P{=}O}]^{\cdot+}$) [54]. In this way, we suggest that the formation of this radical intermediary could be responsible for promoting an increase in nootkatone selectivity. Also, imidazole pulls the metal into the plane of the porphyrin ligand, increasing steric hindrance around the metal center and, therefore, decrease its reactivity toward valencene (low epoxide yield). In another way, binding of imidazole can modify the redox potential of the metal center [55], activate O_2, or weaken the oxygen bond to the metal center [56,57] favoring the occurrence of the autooxidation reaction, which leads to the formation of the ketone in the reaction medium. It is important to emphasize that the effect of imidazole in systems employing O_2 as the oxidant (without co-oxidant) has not been extensively studied and the amount of imidazole employed in this work was very small, showing that it is not necessary to use a large excess of this additive [40].

In previous studies, it has been demonstrated that third-generation metalloporphyrins usually present better catalytic efficiency than second-generation complexes [30,37]. Therefore, we decided to evaluate the catalytic efficiency of **MnP2**.

The reactions were carried out under the same conditions as employed in Runs 11 and 12 (Table 2). When acetonitrile was used as the solvent (Run 16, Table 2), the combined yield for the products **2** and **3** was only 9%. With the green solvent DEC (Run 8, Table 2), the combined yield for the products showed no significant difference (yield of 7%). Thus, it was verified that the introduction of bulky electron-withdrawing bromine substituents in the β-pyrrolic positions of **MnP2** led to a less efficient catalyst than the second-generation **MnP1** to oxidize valencene, counteracting results obtained by our group when it was used for the oxidation of alkanes [30]. Low reaction yields may be

Table 2
Oxidation of valencene by O_2 catalyzed by **MnP1** and **MnP2**.[a]

Run	Catalyst	Solvent	Conversion (%)	Selectivity (%)		Yield[b] (%)	TON[c]	TOF[d] (h^{-1})
				2	3			
10[e]	–	CH_3CN	9	Tr.	0	0	–	–
11	**MnP1**	CH_3CN	86	35	21	48	860	215
12	**MnP1**	DEC	74	38	21	44	740	185
13[f]	**MnP1**	DEC	75	68	17	64	750	188
14[g]	**MnP1**	DEC	12	–	–	–	–	–
15[h]	**MnP1**	DEC	63	–	89	56	630	158
16	**MnP2**	CH_3CN	46	17	3	9	460	115
17	**MnP2**	DEC	42	11	5	7	420	105

[a] Conditions: valencene = 1.0 mmol; Catalyst: 1 μmol; solvent = 4.8 mL; 80 °C, 10 atm of O_2, reaction time: 4 h. Conversion and selectivity were determined by GC. Tr = traces.

[b] Theoretical yield calculated by the ratio: (conversion) × (selectivity 2 + 3)/100.

[c] TON (turnover number) was the amount of substance of valencene (mol) reacted per amount of substance of **MnP1** or **MnP2** (mol).

[d] TOF (Turnover frequency).

[e] The reaction in the absence of the catalyst.

[f] The reaction in the presence of imidazole as additive; molar **MnP1**:imidazole ratio of 1:5.

[g] The reaction was performed at room temperature (25 °C).

[h] The reaction was performed with butylated hydroxytoluene (BHT) as a radical scavenger.

attributed to the difficulty for interactions between valencene and **MnP2** due to the presence of bulky groups, such as the bromine atoms, in β-pyrrolic positions of the porphyrinic macrocycle. Besides, the high-valence active species [MnP = O] has a different reactivity when comparing second and third-generation catalysts, as already observed by Bartoli et al. [36], with **MnP1** being more active for alkenes oxidation and **MnP2** for alkanes oxidation. The greater activity of **MnP1** can be explained by the higher electronic density of this catalyst, compared to **MnP2** [36–38].

To the best of our knowledge, no studies have reported valencene oxidation by manganese porphyrins similar to this work. Most studies involved substrate biotransformation. Kolwek et al. recently obtained nootkatone in a combined system using a unique dye–decolorizing peroxidase (Ftr-DyP) obtained from basidiomycetes *Funalia trogii*. In this system, the authors reached a yield of 36% for nootkatone after 24 h of incubation and 48 h of reaction [35]. In the work of Palmerín-Carreño et al., the efficiency of several microorganisms that can convert valencene into nootkatone using different bioconversion systems such as water, organic and biphasic systems was evaluated. It was noted that *Botryodiplodia theobromae*, *Yarrowia lipolytica*, and *Phanerochaete chrysosporium* have oxidized valencene to nootkatone, reaching maximum yields of 25%, 29%, and 27%, respectively after 4 days of incubation and 5 days of reaction [12]. Although the reported works have shown satisfactory yields, the need for inoculation and cultivation of microorganisms can make the process relatively slow.

The oxidation system proposed in our study is capable of generating ketone with yields comparable to previous systems in the literature. Results obtained in our catalytic system led to a yield of nootkatone in 28% and 16% for the epoxide, resulting in a combined yield of 44% in only 4 h of reaction employing the green solvent diethyl carbonate. When small amounts of imidazole were added to the system, yields of **2** and **3** increased to 51% and 13%, respectively, leading a combined yield of 64%, also in 4 h of reaction.

It is interesting to highlight that although epoxide **3** has been produced in smaller amounts, the epoxidation of olefins has received considerable attention, because they are key intermediates in the organic synthesis of fine chemicals [19,58–60]. As far as we are concerned, the few studies present in the literature related to the epoxidation of valencene employ environmentally harmful oxidants and the product is obtained via slower methodologies [1,34]. Thus, the use of second-generation metalloporphyrin, **MnP1**, might be an alternative to obtain this product using green and sustainable chemistry principles.

In this work, the conditions employed in the classical system (i.e., PhIO or $PhI(OAc)_2$ as the oxidants and dichloromethane as the solvent, Table 1) and the green system (i.e., O_2 as oxidant and acetonitrile and DEC as solvent) were different, preventing a direct comparison between these two systems. The classical system produced a higher amount of nootkatone (**2**) than valencene-1,10-epoxide (**3**), although low conversions and total yields were obtained employing the iodosylarenes. The green systems had higher conversion values and total yields, with higher productions of **2** and **3** simultaneously. In this sense, the results obtained indicated that the replacement of a classical system by a green system employing O_2 as the oxygen source and imidazole as an additive can generate a positive effect on the formation of products derived from valencene. This also shows the potential for a green solvent (DEC) and molecular oxygen to be used in oxidation systems of other terpenes catalyzed by metalloporphyrins aiming at the valorization of the raw material.

3.2. Mechanism for the oxidation of valencene employing manganese porphyrins as catalysts

The proposed mechanisms for **MnP1** catalyzing the oxidation of valencene by molecular oxygen are presented in Figs. 4 and 5. The variations in quantities of the obtained products (**2** and **3**) can be explained by different radical mechanisms. The first mechanism (Fig. 4) involves a preferred route that explains the higher yields of nootkatone (**2**) in relation to valencene epoxide (**3**). This mechanism is consistent with that proposed by Melodnicka [61]. In this case, the initiation occurs via a direct reaction of MnP with valencene via an initial electron transfer followed by the loss of a hydrogen ion and formation of an alkyl radical (Step Ia). It is interesting to note that the allylic position to the valencene double terminal bond remained unchanged. The transfer of an allylic hydrogen atom from valencene to the alkylperoxide radical depends on the C—H bond reactivity. In the case of valencene, the allylic hydrogen of the endocycle double bond appears to be more reactive than the allylic hydrogen at the terminal double bond, since no products derived from the transformation of that position were observed. The regeneration of the catalyst (Step IIa) is carried out directly by molecular oxygen that leads to the formation of the superoxide anion ($O_2^{\cdot-}$). The termination step (IIIa) occurs via reaction of the superoxide anion and the alkyl radical that, in the presence of hydrogen ion, leads to the formation of alkyl hydroperoxide. The decomposition of alkyl hydroperoxide leads to nootkatone (**2**) and water.

The mechanism for the epoxidation of valencene is described in Fig. 5. The oxidation of organic substrates by O_2 in the presence of

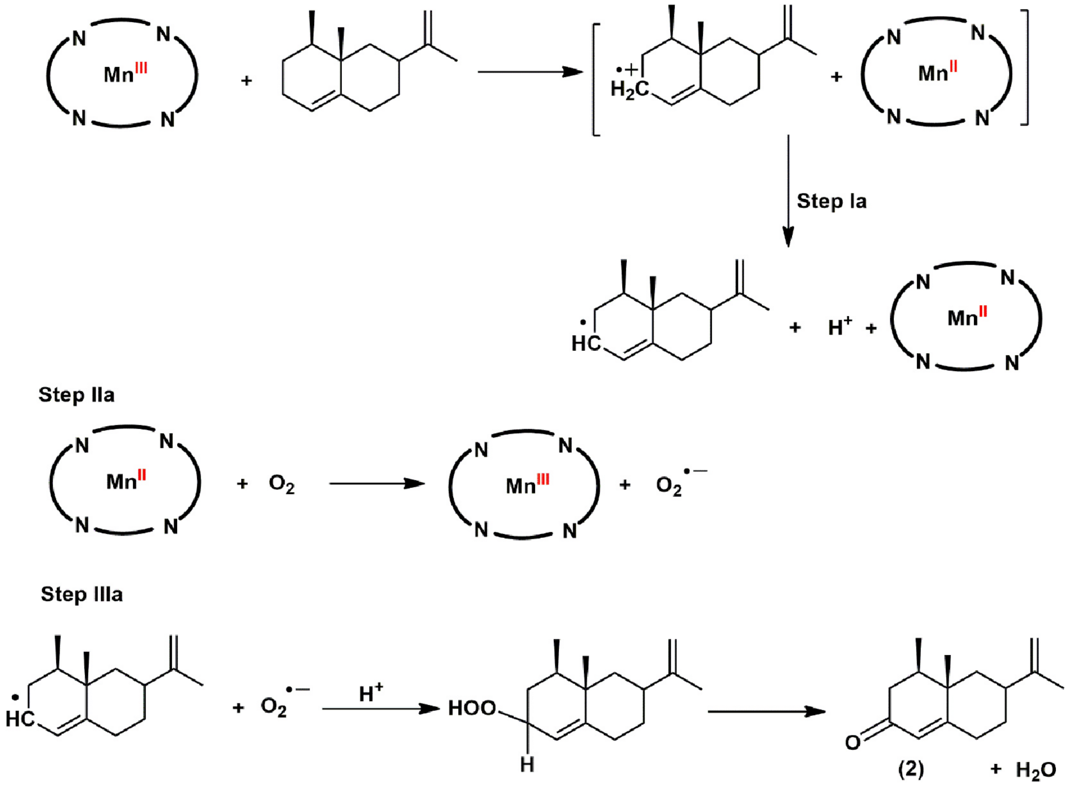

Fig. 4. Proposed mechanism for the formation of nootkatone (**2**) by molecular oxygen and MnP as the catalyst.

synthetic metalloporphyrins remains a challenge since the literature reports the autooxidation pathway as the major route for oxidized product obtention [62–66] and no evidence of high-valence [Mn(V)P=O] species formation.

As reported in the literature, Fe(II)- and Mn(II)-porphyrins can bind the O_2 (similar to the monooxygenase CIP450 pathway) [67]. In the proposed catalytic cycle, the first step involves the reduction of [Mn(III)P] catalyst by the substrate, as observed in the step Ia (Fig. 4). This step is facilitated by high temperatures [68], and the alkyl radical generated could be responsible for nootkatone formation. The reduced form of the catalyst is a fundamental intermediary responsible for generating the $O_2^{\bullet-}$ anion, its able to coordinate to the catalyst as observed in Step IIb, resulting in the $[Mn(III)P(O_2)]^-$ complex. Then, the coordination of another [Mn(II)P] to the terminal oxygen atom leads to the mixed-valence oxo-dimer complex in Step IIIb. This species has been characterized by EPR spectroscopy in systems involving Mn(II)-porphyrins and

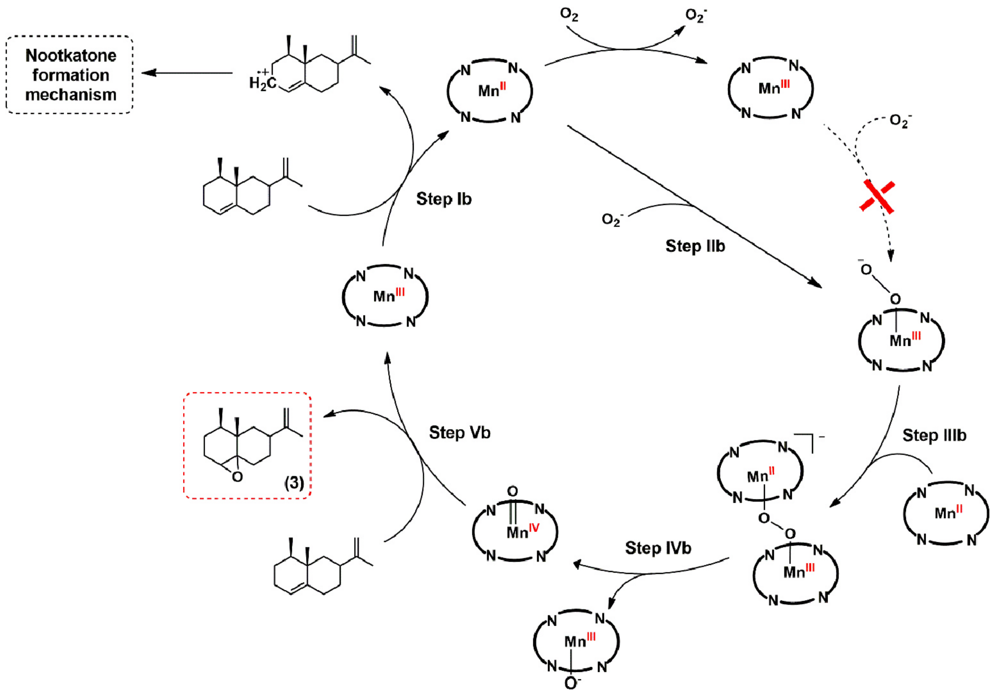

Fig. 5. Proposed mechanism for the formation of valencene epoxide (**3**) by molecular oxygen and MnP as the catalyst.

O_2 [62,69,70]. At this point, the O—O bond in the dimeric complex can be cleaved, generating the high-valence [Mn(IV)P=O] species (Step IVb). In our work, we suggest that the [Mn(IV)P=O] is responsible for transferring the oxygen atom to the endocyclic double bond of the valencene, resulting in the formation of 3 (Step Vb). In step Vb, a mechanism involving the concerted insertion of an "oxene" into the endocyclic double bond of the substrate has been proposed [54]. Hyun and co-workers proposed that different active species are responsible for oxidizing alkenes, with the [Mn(IV)P=O] may be formed in the presence of aprotic solvents and when the catalyst presents electron-donating groups in the macrocycle periphery [49,71].

To reinforce these hypotheses, we carried out reactions at room temperature (25 °C; Run 14, Table 2) and with butylated hydroxytoluene (BHT) as a radical scavenger (under 80 °C; Run 15, Table 2). The reactions carried out at 25 °C did not lead to the formation of products, indicating that the reduction of the catalyst did not occur at low temperatures, inhibiting the O_2 molecule coordination to the [Mn(III)P] and the alkyl radical formation (Fig. 5). The reactions in the presence of BHT led to the exclusive formation of **3**, indicating that this product can be generated, preferably, by a route that does involve metal-oxo species.

4. Conclusion

Oxidation of valencene employed second-generation porphyrin, $[Mn^{III}(T3,5DMPP)Cl]$ (**MnP1**) as a catalyst, and its activity was firstly evaluated employing the classic oxidant PhIO. Aiming to develop eco-friendly systems for this reaction, PhIO was replaced by molecular oxygen, and the solvent CH_2Cl_2 by acetonitrile and the green solvent diethyl carbonate. Diethyl carbonate was shown to be a suitable solvent for the reactions, without a significant loss of yield compared to the reactions in acetonitrile. Besides that, the effect of the addition of small amounts of imidazole additive was also studied. There was a significant increase in the reaction yield. We believe that these results may stimulate the development of systems for the transformation of different organic substrates, mainly, more complex sesquiterpenes. The third-generation porphyrin $[Mn^{III}(Br_{12}T3,5DMPP)Cl]$ (**MnP2**) was also studied as a catalyst for the oxidation of valencene, and its catalytic activity was lower than **MnP1**. Thus we have shown that to obtain nootkatone, it is better to use a second-generation catalyst (**MnP1**), which is cheaper and easier to obtain.

CRediT authorship contribution statement

Carla Nunes Melo: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Visualization. **Alexandre Moreira Meireles:** Methodology, Writing - review & editing. **Vinicius Santos Silva:** Methodology, Writing - review & editing. **Patrícia Robles-Azocar:** Resources, Writing - review & editing, Supervision, Funding acquisition. **Gilson DeFreitas-Silva:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.F. Urusawa, T.H. Ashimoto, Y.N. Oma, Y.A. Sakawa, Chem. Pharm. Bull 53 (2005) 1513–1514.
[2] C. Letizia, Food Chem. Toxicol. 38 (2000) s165–s167.
[3] G.W. Shaffer, E.H. Eschinasi, K.L. Purzycki, A.B. Doerr, J. Org. Chem. 40 (1975) 2181–2185.
[4] Y. Erdtman, H. Hirose, Acta. Chem. Scand. 16 (1962) 1311–1314.
[5] K. Cankar, A. Van Houwelingen, M. Goedbloed, R. Renirie, R.M. De Jong, H. Bouwmeester, D. Bosch, T. Sonke, J. Beekwilder, FEBS Lett. 588 (2014) 1001–1007.
[6] S. Umezawa, H. Akao, M. Kubota, K. Kino, Biosci. Biotechnol. Biochem. 84 (2020) 780–788.
[7] M. Milhim, P. Hartz, A. Gerber, R. Bernhardt, J. Biotechnol. 301 (2019) 52–55.
[8] K. Tsoyi, H.J. Jang, Y.S. Lee, Y.M. Kim, H.J. Kim, H.G. Seo, J.H. Lee, J.H. Kwak, D.U. Lee, K.C. Chang, J. Ethnopharmacol. 137 (2011) 1311–1317.
[9] W.D. Macleod, N.M. Buigues, J. Food Sci. 29 (1964) 565–568.
[10] I. Plagemann, U. Krings, R.G. Berger, Zeitschrift Fur Naturforsch. C 69 C (2014) 149–154.
[11] A.B. Omarini, I. Plagemann, S. Schimanski, U. Krings, R.G. Berger, Bioresour. Technol. 171 (2014) 113–119.
[12] D.M. Palmerín-carreño, C.O. Castillo-araiza, M. Olga, R.V. Calvo, G.M. Trejo-aguilar, S. Huerta-ochoa, J. Chem. Technol. Biotechnol. 91 (2015) 1164–1172.
[13] H. Lu, X.P. Zhang, Chem. Soc. Rev. 40 (2011) 1899–1909.
[14] M. Costas, Coord. Chem. Rev. 255 (2011) 2912–2932.
[15] B. Meunier, Chem. Rev. 92 (1992) 1411–1456.
[16] A.A. Guedes, J.R.L. Smith, O.R. Nascimento, D.F. Costa, J. Braz. Chem. Soc. 16 (2005) 835–843.
[17] R.R.L. Martins, M.G.P.M.S. Neves, A.J.D. Silvestre, M.M.Q. Simões, A.M.S. Silva, A.C. Tomé, J.A.S. Cavaleiro, P. Tagliatesta, C. Crestini, J. Mol. Catal. A Chem. 172 (2001) 33–42.
[18] H. Srour, P. Le Maux, S. Chevance, G. Simonneaux, Coord. Chem. Rev. 257 (2013) 3030–3050.
[19] K. Berijani, A. Farokhi, H. Hosseini-Monfared, C. Janiak, Tetrahedron 74 (2018) 2202–2210.
[20] M. Perrée-Fauvet, A. Gaudemer, J. Chem. Soc. Chem. Commun. 1 (1981) 874–875.
[21] S. Rayati, P. Nafarieh, Appl. Organomet. Chem. 33 (2019) 1–11.
[22] M. De Fátima Teixeira, O.A.C.A. Gomes, J. Mol. Catal. A Chem. 121 (1997) 145–155.
[23] K. Berijani, H. Hosseini-Monfared, Inorganica Chim. Acta 471 (2018) 113–120.
[24] A. Farokhi, H. Hosseini Monfared, J. Catal. 352 (2017) 229–238.
[25] M. Mukherjee, A. Dey, ACS Cent. Sci. 5 (2019) 671–682.
[26] C.M. Alder, J.D. Hayler, R.K. Henderson, A.M. Redman, L. Shukla, L.E. Shuster, H.F. Sneddon, Green Chem. 18 (2016) 3879–3890.
[27] B. Scha, F. Scha, A. Bo, Chem. Rev. 110 (2010) 4554–4581.
[28] A. Gamez, K. Jochem, J. Bradley, Catal. Letters 55 (1998) 73–77.
[29] M.H. Ali, M. Hashmat, Synthesis (Stuttg). 48 (2015) 429–436.
[30] V.S. Da Silva, S. Nakagaki, G.M. Ucoski, Y.M. Idemori, G. DeFreitas-Silva, RSC Adv. 5 (2015) 106589–106598.
[31] A.S. Guimarães, B. Schmitberger, A.M. Meireles, D. Carvalho, G. Defreitas-silva, Polyhedron 163 (2019) 144–152.
[32] J.G. Sharefkin, H. Saltzman, Org. Synth. 43 (1963) 62–64.
[33] M.J. da Silva, J.A. Villarreal, Catal. Lett. 147 (2017) 1646–1653.
[34] S. Sowden, R.J. Yasmin, N.H. Rees, S. Bell, L. Wong, Org. Biomol. Chem 3 (2005) 57–64.
[35] J. Kolwek, C. Behrens, D. Linke, U. Krings, R.G. Berger, J. Ind. Microbiol. Biotechnol. 45 (2017) 89–101.
[36] J.F. Bartoli, O. Brigaud, P. Battioni, D. Mansuy, J. Chem. Soc. Chem. Commun. (1991) 440–442.
[37] C.G. Enrico Baciocchi, Tristano Boschi, Tetrahedron 53 (1997) 4497–4502.
[38] S. Zakavi, F. Heidarizadi, S. Rayati, Inorg. Chem. Commun. 14 (2011) 1010–1013.
[39] A.M. Meireles, V.S. da Silva, J.S. Rebouças, D.C. da Silva Martins, ChemistrySelect 4 (2019) 3275–3280.
[40] V.S. Da Silva, A.M. Meireles, D.C. Da Silva Martins, J.S. Rebouças, G. Defreitas-Silva, Y.M. Idemori, Appl. Catal. A Gen. 491 (2015) 17–27.
[41] E. do Nascimento, G. de F Silva, F.A. Caetano, M.A.M. Fernandes, D.C. da Silva, M.E.M.D. de Carvalho, J.M. Pernaut, J.S. Rebouças, Y.M. Idemori, J. Inorg. Biochem. 99 (2005) 1193–1204.
[42] C.L.H. Robert, B. Brown Jr., J. Org. Chem 53 (1988) 5762–5768.
[43] D.R. Leanord, J.R.L. Smith, J. Chem. Soc. Perkin Trans. 2 (1991) 25–30.
[44] D.F. Banks, Chem. Rev. 66 (1966) 243–266.
[45] V.V. Zhdankin, P.J. Stang, Chem. Rev. 108 (2008) 5299–5358.
[46] P. Anastas, N. Eghbali, Chem. Soc. Rev. 39 (2010) 301–312.
[47] M.S. Yusubov, V.V. Zhdankin, Curr. Org. Synth. 9 (2012) 247–272.
[48] J. In, S. Park, R. Song, W. Nam, Inorg. Chim. Acta 343 (2003) 373–376.
[49] K.W. Kwong, T. Chen, W. Luo, H. Jeddi, R. Zhang, Inorg. Chim. Acta 430 (2015) 176–183.
[50] V. Santos da Silva, Y.M. Idemori, G. Defreitas-silva, Appl. Catal. A, Gen. 498 (2015) 54–62.
[51] G.M. Ucoski, K.A.D.D.F. Castro, K.J. Ciuffi, G.P. Ricci, J.A. Marques, F.S. Nunes, S. Nakagaki, Appl.Catal. A Gen. 404 (2011) 120–128.
[52] P.T.F. Aricò, Usp. Khim 79 (2010) 532–543.
[53] M.J. Gunter, P. Turner, J. Mol. Catal. 66 (1991) 121–141.

[54] F.G. Doro, J.R.L. Smith, A.G. Ferreira, M.D. Assis, J. Mol. Catal. A Chem. 164 (2000) 97–108.
[55] Z. Solati, M. Hashemi, S. Hashemnia, E. Shahsevani, Z. Karmand, J. Mol. Catal. A Chem. 374–375 (2013) 27–31.
[56] K.A.P.S. Jrgensen, Acta. Chem. Scand. 43 (1989) 822–824.
[57] Y. Sun, X. Hu, H. Li, A.F. Jalbout, J. Phys. Chem. C 113 (2009) 14316–14323.
[58] V. Maraval, J.E. Ancel, B. Meunier, J. Catal. 206 (2002) 349–357.
[59] R. Chakrabarty, B.K. Das, J. Mol. Catal. A Chem. 223 (2004) 39–44.
[60] R. Hajian, A. Ehsanikhah, Chem. Phys. Lett. 691 (2018) 146–154.
[61] T. Mlodnicka, Met. Catal. Oxidations, Marcel Dekker Inc., New York, 1994, pp. 261–287.
[62] V.L. Pecoraro, M.J. Baldwin, A. Gelasco, Chem. Rev. 94 (1994) 807–826.
[63] J. Haber, T. Mlodnicka, J. Mol. Catal. 74 (1992) 131–141.
[64] P. Battioni, J.F. Bartoli, P. Leduc, M. Fontecave, D. Mansuy, J. Chem. Soc. Chem. Commun. (1987) 791–792.
[65] C. Sun, B. Hu, Z. Liu, Chem. Eng. J. 232 (2013) 96–103.
[66] T. Mlodnicka, J. Mol. Catal. 36 (1986) 205–242.
[67] D. Mansuy, P. Battioni, Met. Catal. Oxidations, Marcel Dekker Inc., New York, 1994, pp. 99–132.
[68] Q.L., C.G. Guofang Jiang, in: Anne George (Ed.), Biomim. Based Appl., Chicago, 2011, pp. 31–57.
[69] C.J. Weschler, B.M. Hoffman, F. Basolo, J. Am. Chem. Soc. 97 (1975) 5278–5280.
[70] M. Perree-Fauvet, A. Gaudemer, J. Bonvoisin, J.J. Girerd, C. Boucly-Goester, P. Boucly, Inorg. Chem. 28 (1989) 3533–3538.
[71] M.Y. Hyun, Y.D. Jo, J.H. Lee, H.G. Lee, H.M. Park, I.H. Hwang, K.B. Kim, S.J. Lee, C. Kim, Chem. Eur. J. 19 (2013) 1810–1818.