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COMMUNICATION

Heterogeneous Manganese-Catalyzed Oxidase C–H/C–O Cyclization to Access Pharmaceutically Active Compounds

Francesco Ferlin[a], Alberto Marini[a], Nicola Ascani[a], Lutz Ackermann[b], Daniela Lanari[c], and Luigi Vaccaro*[a]

Dedication ((optional))

Abstract: Heterogeneous manganese-catalyzed C–H oxidative couplings were accomplished to gain access to pharmaceutically relevant 2-aminophenoxazin-3-ones and to diaminophenazine and purpurogallin moieties in excellent yields. The user-friendly K-OMS-2 oxidase strategy proved to be more versatile and robust than enzymatic catalysts-based procedures allowing a wider substrate scope and being effectively reusable as proven by leaching measurements and XRD analyses.

Oxidative C–H activation/functionalization represents one of the most powerful tools for creating or decorating with high precision organic compounds and access target molecular structures.[1], [2] The development of innovative metal catalytic systems able to directly functionalize carbon–hydrogen (C–H) bonds continues to progress at a rapid pace due to the significant chemical and environmental advantages offered by these transformations over traditional synthetic methods based on pre-functionalization strategies.[3]

At this concern, besides the major efforts and contributions from chemists, Nature is undoubtedly a magnificent source of inspiration when it comes to the ability of creating complex molecular systems. Enzymes oxidases and peroxidases can highly selective recognize substrates and promote specific reactions, including C–H activation/functionalization processes.[4]-[5] Some representative targets for the definition of bio-inspired C–H oxidation processes are reported in Figure 1.

While the development of specific enzymatic processes is an important goal of synthetic chemistry,[6] there are significant challenges to be considered for their practical application e.g. enzyme expression/purification, cofactor supply, but above all, stability to organic solvents, oxygen tolerance, and substrate scope.[7]

A strategic challenge would be the development of metal catalytic systems able to promote key oxidative C–H functionalizations mimicking the selectivity of enzymes while offering higher chemical stability, versatility and durability. Heterogeneous catalytic systems based on carbon-[8] or inorganic materials[9]-[12] such as ferromagnetic nanoparticles,[9] or nanostructured metal oxides,[10] noble metals,[11] or a combination of those,[12] represent some prominent examples of this tendency.

We have been inspired by the fact that, to the best of our knowledge, there is no example in the literature reporting the use of manganese-based nanostructured materials for C–H oxidative process able to mimic peroxidase ability in the synthesis of phenoxazinones or flavins (Figure 1).

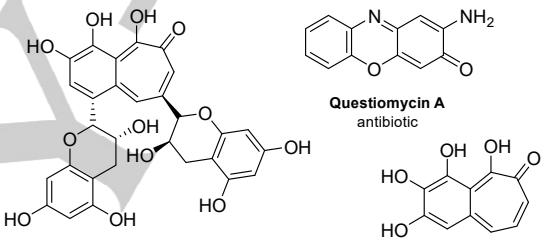

Figure 1. Relevant APIs prepared by a bio-synthetic approach.

In this contribution we report that the manganese oxide molecular sieve K-OMS-2, with a rigid MnO_2 framework composed of MnO_6 octahedral building blocks and one-dimensional square tunnel structure (4.6 Å), which contain guest cations (in the present case, K+) are highly effective in mimicking peroxidase properties.[13] In particular, we have focused our study on potassium-containing Octahedral-Molecular-Sieves (K-OMS) first prepared and developed by Suib.[14]

These structures are composed by manganese oxide tunnels with cryptomelane-type morphology.[15] The structure of this entities can be tuned by exchanging the ions into the tunnels as well as by isomorphic substitution. Recently, it has been demonstrated that such materials can catalyze, among others, a plethora of oxidation reactions and possess a great ability to reduce oxygen. Furthermore, they are air- and moisture-stable and many methodologies for their synthesis are described in literature.[16]

Herein, we report on the use of K-OMS as a heterogeneous oxidase system for the C–H oxidation/dimerization reaction of *o*-aminophenols. This process allows the access to 2-aminophenoxazin-3-one and related diaminophenazine and purpurogallin moieties and it is classically promoted by peroxidase enzymes (e.g. Horseradish peroxidase enzyme, HRP).[17] The typical narrow substrate scope of these processes limit the access to the corresponding pharmaceutically relevant active compounds.

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We have therefore aimed our study to prove the higher stability of K-OMS oxidase systems over enzymes, paying attention to expand the scope of the accessible molecular structures and towards the identification of the optimal reaction conditions allowing the minimal metal leaching and the full recovery and reuse of the heterogeneous inorganic catalytic system.
Following the reported methodology,[15b] we have prepared the K-OMS system as illustrated in Figure 2. The catalyst we have used in this study, was first calcined and, after being washed, isolated by size exclusion filtration. ICP-AES analysis of the resulting material gave a manganese loading of 62% w/w. The manganese average oxidation state was calculated to be 3.8 and the synthesized K-OMS-2 features the crystal cryptomelane tunnel structure as proven by XRD spectra, being in accordance with literature.[18]

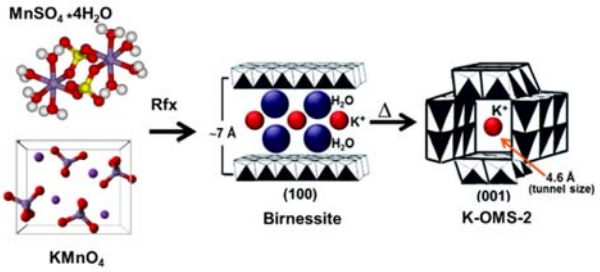


Figure 2. Schematic overview for the synthesis of K-OMS-2

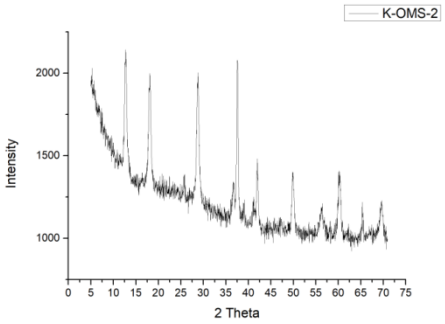
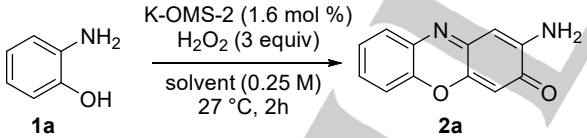


Figure 3. XRD-pattern of synthesized K-OMS-2

Table 1. Manganese leaching in different solvent

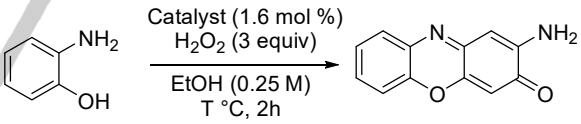


Entry[a]	Medium	Conversion[b] (Isolated yield)	Mn leaching (ppm)[c]
1	pH 7 Buffer	> 99 %	20
2	H_2O	> 99 %	31
3	DMF	82 %	8
4	DMC	> 99 %	13
5	Toluene	> 99%	6
6	EtOH	> 99 % (97 %)	7

[a] Reaction conditions: 2-aminophenol **1a** (1 mmol), H_2O_2 (3 mmol, 3 equiv.), K-OMS-2 (1.3 mg, 1.6 mol %), solvent (4mL, 0.25 M), 27 °C, 2h. [b] Determined by GC analysis using sample of pure compounds as references. [c] Determined by ICP-AES analysis.

By taking *o*-aminophenol (**1a**) as representative substrate, we started our study on the influence of different media and oxidants on the reaction (Table 1). On each final reaction mixture, we have also evaluated the leaching of the manganese species in the different media used and the manganese content in the recovered catalysts, in order to have information on the nature of the mechanism of the reaction. The results are illustrated in Table 1. In ethanol, toluene or DMF manganese dissolved poorly, whilst, aqueous pH 7 phosphate buffer represents the medium in which the highest content of metal was found after the reaction completion.
EtOH was therefore selected as medium for further optimization of the reaction conditions being the safest medium that also gave the best combination of high chemical efficiency and low leaching. The optimal conditions (Table 1, entry 6) resulted in complete conversion of the starting material in 2 h, with 97% isolated yield of the desired product **2a**.
Moreover EtOH can easily solubilize aminophenols **1** and it is also compatible with Horseradish peroxidase enzyme (HRP), allowing the direct comparison of K-OMS-2 with this enzyme under the same reaction conditions.
In fact, when H_2O_2/O_2 system was used as oxidant K-OMS-2 and HRP efficiencies resulted to be comparable in terms of initial reaction rate and kinetic of product formation (see ESI). It is also noteworthy that the use of K-OMS is not strictly limited to the classical temperature range stability of HRP. In fact, increasing the temperature from 27 °C to 50 °C or 70 °C, HRP activity decreases due to its denaturation process, while the K-OMS remains, as expected, highly active (Table 2).

Table 2. Comparison of reaction between HRP and K-OMS-2.



Entry[a]	Catalyst (2 mol%)	T (°C)	Conversion[c] (Isolated yield)
1	K-OMS-2	27	> 99 % (97 %)
2	K-OMS-2	50	> 99 % (97 %)
3	K-OMS-2	70	> 99 % (97 %)
4	HRP[b]	27	> 99 % (97 %)
5	HRP[b]	50	95 % (90 %)
6	HRP[b]	70	13 %

[a] Reaction conditions: 2-aminophenol **1a** (1 mmol), H_2O_2 (3 mmol, 3 equiv.), K-OMS-2 (1.3 mg, 1.6 mol %), EtOH 4mL (0.25 M), 27 °C, 2h. [b] HRP (2 mol %, 0.02 equiv, 10 µL of a 12 µM ethanolic solution), EtOH 4mL (0.25 M), 27 °C, 2h. [c] Determined by GC analysis using sample of pure compounds as references.

As for the enzyme catalyzed process, to fully regenerate the K-OMS catalyst a terminal oxidizing agent is needed.

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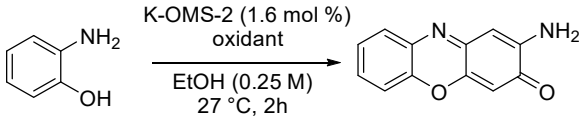
The recoverability and reusability of K-OMS-2 was therefore investigated by using different conditions and terminal oxidants and the data are illustrated in Table 3.
It should be noted that when the reaction of 2-aminophenol (**1a**) was catalyzed by K-OMS-2 without any other additional oxidizing agent a yield of **2a** of only 63% was obtained (Table 3, entry 1). Nonetheless, using H_2O_2 as terminal oxidant, deactivation of K-OMS-2 occurred after the 4th recycle run (Table 3, entry 2). A similar behavior was observed when molecular oxygen (1 atm) was used as the sole sacrificial oxidant (Table 3, entry 3). Further control experiments also evidenced that higher pressure of oxygen and inert atmosphere did not facilitated the recoverability of the catalytic system. A combination of both oxygen (1 atm) and H_2O_2, resulted to be, very effective and successful reuse the K-OMS-2 was confirmed for representative 10 runs without any loss in catalyst efficiency (Table 3, entry 4).

Table 3. Different oxidizing system and related recycling runs



1a **2a**

Entry[a]	Oxidant	Reuse of K-OMS	Conversion each run[b] (Yield)
1	-[c]	1 run	63 % (58 %)
2	H_2O_2 (3 eq)	4 runs	> 99 % (97 %)
3	O_2 (1 atm)	3 runs	> 99 % (97 %)
4	H_2O_2 (3 eq)/ O_2 (1 atm)	10 runs	> 99 % (97 %)
5	O_2 (3 atm)	4 runs	> 99 % (94 %)
6	N_2 (1 atm)	1 run	52 % (50 %)
7	Argon (1 atm)	1 run	50 % (46 %)

[a] Reaction conditions: 2-aminophenol **1a** (1 mmol), K-OMS-2 (1.3 mg, 1.6 mol %), EtOH (4mL, 0.25 M), 27 °C, 2h. [b] Determined by GC analysis using sample of pure compounds as references. [c] the reaction was carried out in closed vial.
After experimenting different options and oxidants, we concluded optimal recovery and reuse of the catalyst is achieved by centrifugation of the reaction mixture, washing and drying the catalyst (see SI).

XRD analyses of the catalyst recovered after each were performed to possibly reveal any change in the crystal structure that could be related to the its efficiency. It was found that the combined use of molecular oxygen and H_2O_2 is crucial to maintain an unchanged oxidation state of the catalyst and therefore its tunnel structure (Figure 4). On the contrary, when no terminal oxidant was used the XRD analysis of the used material revealed a significant loss in crystallinity and therefore justify the impossibility of its reuse for further reactions. These results also suggested that the catalyst efficiency is closely linked to its 3D tunnel structure. With these results in hand, we were interested into the comparison of the catalytic parameters between K-OMS-2 and HRP. To this end, by calculating TON and TOF for the two system we were pleased to note that, while for one run the data are similar (TON_{HRP} = 83, TOF_{HRP} = 41 and TON_{OMS} = 63, TOF_{OMS} = 31), if considering that we have been recycled our catalytic system up to 10 times the TON associated to the K-OMS-2 catalyst rise up to 630.

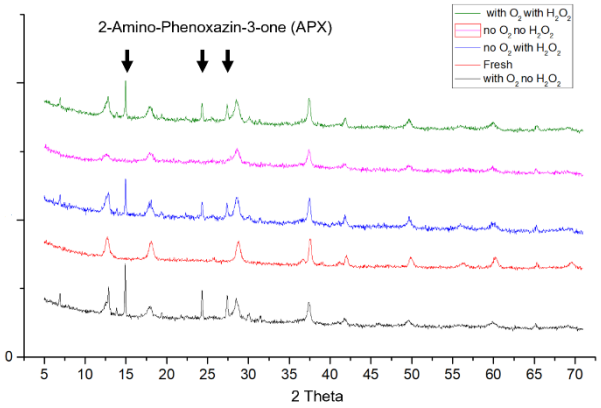
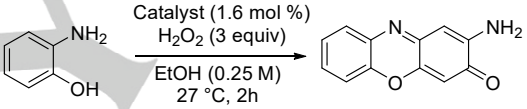


Figure 4. XRD-pattern of fresh and used catalysts

After the definition of optimized reaction conditions (Table 3, entry 4), we compared the activity of our catalytic system with other common oxidation catalysts (Table 4).

Table 4. Different catalysts/oxidants used in the reaction



1a **2a**

Entry[a]	Catalyst	Conversion[b] (Yield)	Reusability
1	-	12 %	-
2	K-OMS-2	> 99 %	YES
3	MnO_2[c]	84 %	NO
4	$KMnO_4$	90 %	NO
5	$Mn(OAc)_2$ tetrahydrate	86 %	NO
6	p-benzoquinone	68 %	NO
7	$FeCl_3$	89 %	NO
8	Fe(II) Phtalocyanine	90 %	NO

[a] Reaction conditions: 2-aminophenol **1a** (1 mmol), H_2O_2 (3 mmol, 3 equiv.), O_2 (1 atm, balloon), catalyst (1.6 mol %), EtOH 4mL (0.25 M), 27 °C, 2h. [b] Determined by GC analysis using sample of pure compounds as references. [c] β-MnO_2 is used as commercially available polymorph structure.

It is noteworthy that none of the catalysts proved to be a valuable choice in terms of stability and recyclability of the catalyst. Control experiment (Table 4, entry 1) in the absence of catalyst revealed that the oxidation rate ion the presence of H_2O_2 only is small and 2-amino-phenoxazin-3-one (**2a**) was formed in only 12% conversion. Iron catalyst/oxidant system were also used in order to compare the most similar system to the active heme-type site of HRP enzyme (Table 4 entries 7 and 8). It is important to notice

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that MnO_2 and $KMnO_4$ (Table 4, entry 3 and 4) showed a very low efficiency compared to K-OMS-2. This evidence additionally suggests that the optimal reaction conditions are guaranteed by the three-dimensional framework of the catalyst and not by its single subunits.

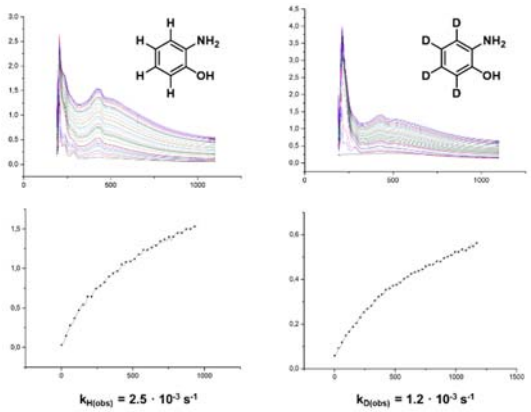
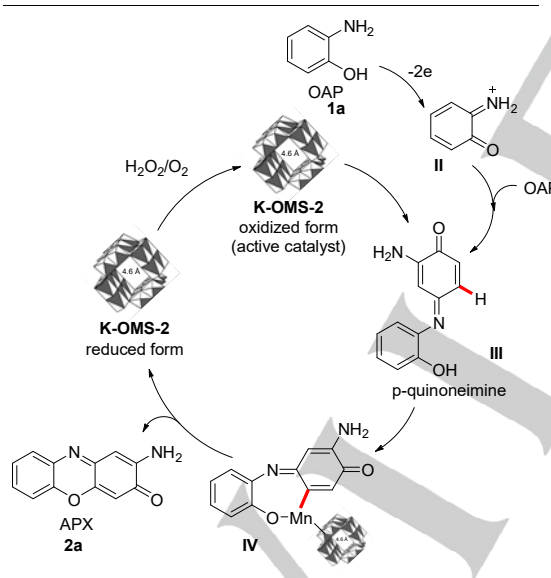


Figure 5. Uv-vis absorption and plot for determination of k_{obs}.

In order to elucidate the mechanism of action of the K-OMS-2 in the oxidative dimerization of *o*-aminophenol (**1a**) we performed kinetics studies using deuterium labeled *o*-aminophenol (d_4-**1a**). This experiment revealed that a relevant KIE (k_H/k_D= 2.1) is operative suggesting that dissociation of proton from the *p*-quinoneimine intermediate constitutes the rate determining step in which the actual C–H activation takes place.



Scheme 1. Plausible mechanism

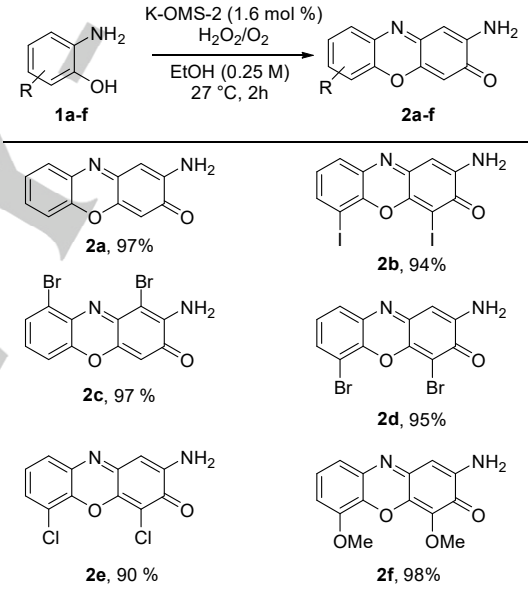
These experimental evidences suggest a plausible mechanism as follows: hydrogen peroxide mediated oxidation of *o*-aminophenol (**1a**) forms the highly electrophilic species quinone-iminium ion (**II**) which reacts with another *o*-aminophenol molecule to form the key intermediate *p*-quinone imine (**III**) which undergoes manganese catalyzed C–H activation to give the corresponding mangana-cycle (**VI**) in which proto-demetalation occurs to give 2-aminophenoxazin-3-one as product (**2a**).

At this stage, as shown by the reusability experiments with related XRD patterns, the reduced form of the catalyst is being oxidized by H_2O_2/O_2 to maintain the optimal mixed-manganese oxide network.

We finally extended the substrate scope of our protocol using different substituted-aminophenols **1** (Table 5). The applicability of K-OMS-2 using our reaction conditions was demonstrated for the synthesis of various 2-aminophenoxazin-3-ones **2** always achieving excellent yields. The presence of a halogen atom in the core structure was tolerated and paves the way for further modification of the Questiomycin A scaffold, allowing for the synthesis of architecturally more complex pharmaceuticals.

To additionally prove the capability of K-OMS-2 to act as enzyme mimicking system, we extended the scope of the reaction to specific substrates that are commonly converted by HRP. We found that, K-OMS-2 can effectively convert *o*-phenylenediamine(**1g**) and pyrogallol (**1h**) to the corresponding diaminophenazine (**2g**) and purpurogallin (**2h**) respectively, as illustrated in Table 6.

Table 5. Substrates scope with substituted *o*-aminophenols**1a-g**.



[a] Reaction conditions: substituted aminophenol **1** (1 mmol), H_2O_2 (3 mmol, 3 equiv.), O_2 (1 atm, balloon), K-OMS-2 (1.3 mg, 1.6 mol %), EtOH 4mL (0.25 M), 27 °C, 2h.

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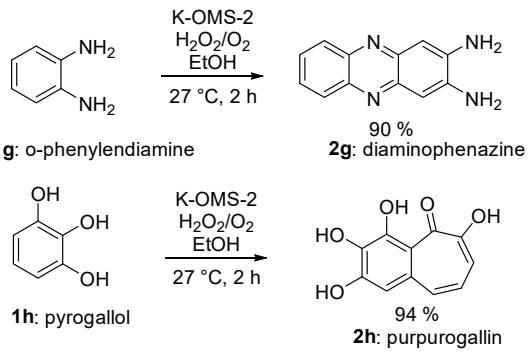
Table 6. Use of K-OMS-2 for accessing diaminophenazine and purpurogallin skeletons.



[a] Reaction conditions: substrates **1g** or **1h** (1 mmol), H_2O_2 (3 mmol, 3 eq.), O_2 (1 atm, balloon), K-OMS-2 (1.3 mg, 1.6 mol %), EtOH 4mL (0.25 M), 27 °C, 2h.

In conclusion, we have demonstrated that manganese-based inorganic-oxide framework can efficiently mimic the microenvironment of peroxidase enzymes in the synthesis of valuable compounds. K-OMS-2 is and effective heterogeneous manganese oxidase system more stable than an enzymatic catalyst and allows the preparation in excellent yields of novel substituted phenoxazinones derivatives that are not accessible by classic enzyme catalysis. The 3D tunnel structure is of key importance for the overall high efficiency of the C–H oxidative coupling and also for the reusability of the catalyst. The heterogeneous nature of manganese-based catalyst was proved by leaching measurements and XRD analyses. Re-oxidation and recycling of the active catalyst was optimized leading to asimple and efficient methodology. We believe that these results might be of general interest and inspire further application of manganese-based heterogeneous catalysts in processes of key interest for both industry and academia.

Acknowledgements

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Keywords: manganese • heterogeneous catalysis • C–H functionalization •

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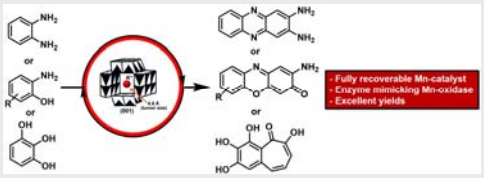

Heterogeneous manganese-catalyzed C–H oxidative couplings were accomplished to access pharmaceutically relevant 2-aminophenoxazin-3-ones and proving the access diaminophenazine and purpurogallin molecular moieties, always in excellent yields. The user-friendly K-OMS-2 oxidase strategy proved to be more versatile and stable than enzymatic catalysts opening to a wider substrate scope and being effectively reusable as proven by leaching measurements and XRD analyses

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Heterogeneous Manganese-Catalyzed Oxidase C–H/C–O Cyclyzation to Access Pharmaceutically Relevant Phenoxazinones