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Additional Information

Epoxidation vs. dehydrogenation of allylic alcohols: Heterogenization of the VO(acac)₂ catalyst in a metal-organic framework

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Allylic alcohol epoxidation and dehydrogenation reactivity is distinguished when VO(acac)₂ is used in solution or anchored in a metal organic framework (MOF). The chemical mechanism depends on the electronic profile of alkene substituents when the vanadyl complex is used in homogenous phase. However, confinement effects imparted by MOF channels allow to gain control on the chemoselectivity toward the dehydrogenation product.

The development of catalytic and selective methods for oxidation reactions is extremely important in organic synthesis. Among several oxidizing systems,¹ metal-catalysed methodologies² have experienced ever increasing growth and application over the years. One of the best examples reported so far is the VO(acac)₂/TBHP (vanadyl acetylacetonate/*tert*-butyl hydroperoxide) system,³ developed by Sharpless and Michaelson, for the highly regio- and stereoselective epoxidation of allylic alcohols.⁴ This catalytic system has been also extensively employed in a wide plethora of reactions,⁵ such as the chemoselective dehydrogenation of acyclic and cyclic secondary alcohols to the corresponding ketones,⁶ or the oxidation of *o*-alkenyl phenols to *o*-hydroxybenzyl ketones.⁷ However, to the best of our knowledge, it has not been clearly specified yet the exact conditions where the corresponding epoxidation or alcohol dehydrogenation takes place.

Metal-organic frameworks⁸ (MOFs) have blossomed in recent years in catalysis as a direct consequence of their unique characteristics,⁹ such as a fascinating host-guest chemistry¹⁰ and the possibility to use single-crystal X-ray diffraction (SC-XRD)¹¹ to unveil the nature of catalytically active species and reaction mechanisms.¹² MOFs catalytic activity can be

¹⁵ This matrix-isolation strategy^{11,13} offers clear benefits over homogenous solution, such as structural characterisation and higher reusability.¹⁵ However, much work needs to be done to understand how chemical and steric environment offered by the host matrix affects the chemical nature of guest species and the concomitant effects on their catalytic activity.

Here, we aim to shed light on both open questions. Thus, firstly, we demonstrate that when VO(acac)₂ is in solution, the selection of the reaction pathway of allylic alcohols with TBHP – underpinned by activation energy evaluations – depends on the electronic profile (electron donating/withdrawing groups) of alkene substituents, which set the preference toward either the corresponding epoxide or aldehyde product. Then, we present the post-synthetic insertion of VO(acac)₂ within a preformed MOF of formula {Ca^{II}Cu^{II}}_6[(*S,S*)-methox]_3(OH)_2(H₂O)} · 16H₂O (**4**) (methox = (*S,S*)-oxaloyl-bis(*N*-methioninate)),^{16,17} to lead to the hybrid material [V^{VO}(acac)(H₂O)]@{Ca^{II}Cu^{II}}_6[(*S,S*)-methox]_3(OH)_3} · 8H₂O (**VO(acac)(H₂O)@4**), whose crystal structure is unveiled by single-crystal X-ray crystallography. The confinement effect of MOFs channels in **VO(acac)(H₂O)@4** plays a key role, considerably reducing the substrate-dependence and imparting a preference toward the less-sterically demanding dehydrogenation reaction.

VO(acac)₂ is able to catalyse the epoxidation and the dehydrogenation of allylic alcohols.¹⁸ However, as far as we know, a structure-activity relationship has not been clearly specified in the open literature. A plausible reaction mechanisms for both reactions, could indicate that the coordination either of the alkene or final alcohol functionalities to the vanadyl site dictates the final reaction (Fig. S1, ESI[†]).¹⁹ In order to confirm the absence of one of the acac ligands in the active species, we performed the reaction using 1 equivalent of extra acac⁻ ligand (Fig S2a). The low conversion obtained can be attributed to the saturated positions of the VO(acac)⁺, blocking the position to the allylic alcohol. Moreover, acac ligand signals were observed by NMR in the reaction solution (Fig S2b). With these mechanisms in hand, electron donating groups (EDG) on the alkene (R) should favour coordination of the alkene to the vanadyl and epoxidation, while electron withdrawing groups (EWG) should favour alcohol coordination and dehydrogenation.

Fig. 1 shows the results obtained for the reaction of different allyl alcohols with TBHP in the presence of VO(acac)₂, under typical reaction conditions.⁴ We observe that the product obtained for allyl alcohol **1a** with an aliphatic substituent, is epoxide **2a**. On the contrary, the major product for allyl alcohol **1b** with an aromatic substituent, is aldehyde **3b** (Fig. 1). Interestingly, when an additional CH₃ group substituent is

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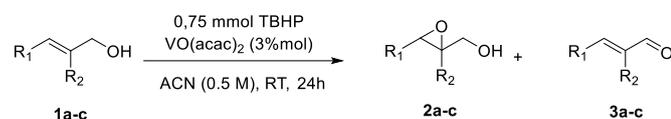
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originated intrinsically – arising from open metal sites and/or the organic linkers constituting the coordination network –, extrinsically – emerging from guest active species hosted in their channels^{11,13} – and a synergic combination of both of them.¹² Dealing with guest active species, different examples showing the encapsulation of active metal-based species of different chemical nature and nuclearity have been reported recently.¹²⁻

present in the allylic alcohol, the selectivity of **1c** reverts back to the epoxidation product **2c**, though in very low yield (Fig. 1). Blank experiments for compound **1b**, without catalyst and with **4**, showed reaction conversions below 8 and 15%, respectively, (Table S1).



	R ¹	R ²	Conversion %	Selectivity 2 %	Selectivity 3 %
1a	Propyl	H	90.3	97.9	2.1
1b	Ph	H	87.7	22.9	77.1
1c	Ph	Me	8.6	51.3	48.7

Fig. 1. Reaction scheme for allylic alcohol epoxidation/dehydrogenation of aliphatic **1a**, aromatic **1b**, and both aliphatic and aromatic allylic alcohol **1c**. ACN: acetonitrile.

With the aim to rationalize these results, we have evaluated the activation energy for both reactions in substrates containing either an aliphatic (EDG) or aromatic (EWG) substituent (Fig. S3 and Figs. S4-S5 for complete calculations). We obtained that the epoxidation was favoured by almost 60 KJ mol⁻¹ respect to the dehydrogenation for 2-hexenol (**1a**) (Fig. S3a and S4), 28.9 and 88.6 KJ·mol⁻¹, respectively. However, this was inverted for cinnamyl alcohol **1b**, where the dehydrogenation showed an activation energy of 50.3 KJ mol⁻¹ while the epoxidation was less favoured (53.9 KJ mol⁻¹, Fig. S3b and Fig. S5 for complete calculations). Thus, these energetic differences explain why changing the benzene by an alkyl substituent (**1a**), or just adding a methyl substituent in the other carbon atom of the alkene (**1c**), the reactivity can be reversed so easily from the dehydrogenation to the epoxidation.

Considering these findings, we have extended our study to different starting materials with modulated electronics of substituents (Fig. S6), where we further confirm the observed trend. Thus, with these results in hand, it seems that the epoxidation vs. dehydrogenation reaction of allyl alcohols catalysed by VO(acac)₂, in solution, is natively controlled by the substrate, which leave little room for improvement.

Heterogenization of metal Schiff base catalyst has attracted great interest in recent years,²⁰ being mostly used to improve the performance of hydrogen peroxide as an oxidant for alkene epoxidation.^{21,22} Among them, expanded research has been performed on vanadium Schiff base complexes, owing to its amazing structural features and catalytic purpose.²³ However, as far as we know, despite the interest, the ultimate catalyst after VO(acac)₂ heterogenization in MOFs have not been atomically-precisely well-characterised, which limit the knowledge on the real active catalyst and difficult the rationalization of structure-properties relationships.²⁴

In this work, we report the postsynthetic²⁵ insertion of the vanadyl acetylacetonate complex VO(acac)₂¹⁸ within the preformed MOF **4**^{16,17} (Fig. 2). **4** present functional hexagonal channels decorated by the highly flexible ethylenethiomethyl chains of the methionine amino acid (Fig. 2a), which are prone for a high loading of vanadyl complexes. This results in a homogenous distribution of them along the pores, anchored to these functional thioalkyl groups, as confirmed by SC-XRD, to lead to [V^{IV}O(acac)(H₂O)]@{Ca^{II}Cu^{II}₆[(S,S)-methox]₃(OH)_{3}}} · 8H₂O (VO(acac)(H₂O)@**4**). Compound VO(acac)(H₂O)@**4** was synthesised by soaking crystals of **4** in an acetonitrile solution of the VO(acac)₂ complex during three days in open air (see Experimental Section, ESI[†]). This insertion process was followed through inductively coupled plasma mass spectrometry (ICP-MS) and scanning electron microscopy-energy dispersive X-ray spectroscopy (SEM-EDX) (Table S2).

VO(acac)(H₂O)@**4** crystallized in the chiral P6₃ space group of the hexagonal system (Table S3) like the precursor **4** (Fig. 2). The crystal structure of VO(acac)(H₂O)@**4** allowed to confirm the presence of VO(acac)(H₂O)⁺ moieties, being recognized by the flexible²⁶ thioether arms of the methionine residues and confined into the channels through S...vanadyl interactions (Figs. 2b-d). In this complex vanadium is penta-coordinated (Fig. 2d), linked by one acac ligand, a terminal solvent molecule and being grasped by sulfur atom from methionine amino acid residues (Figs. S6-S10). The vanadium environment is highly distorted, resembling a trigonal bipyramidal geometry with a very bent apical position occupied by water molecule. This is likely because of the steric constrains imposed by the network (Fig. S9). The values of VO-acac bond lengths [2.00(3) and 2.01(3) Å] are in agreement with previously reported ones.²⁷ On the contrary, the vanadium...S [2.83(10) Å] and vanadyl...O_{water} [2.69(14) Å] bond distances are longer than those reported so far.^{28,29} A second water molecule reside close to the VO(acac)(H₂O) moiety at a distance of 2.96(3) Å, longer than expected, but still low than sum of van der Waals radii (Fig. S10).

Complementary to the above described structural characterization, the chemical nature of the final host-guest adsorbate VO(acac)(H₂O)@**4** was also determined by different characterization techniques. The atom composition was established by elemental (C, H, S, N) analysis, SEM-EDX and ICP-MS (ESI[†]). The integrity of the framework and solvent contents by powder X-ray diffraction (PXRD) and thermo-gravimetric (TG) analyses (Figs. S12 and S13). The oxidation state of vanadium atoms was definitively established by XPS (Fig. S14). N₂ adsorption isotherm at 77 K revealed the permanent microporosity of VO(acac)(H₂O)@**4** (Fig. S15).

The XPS spectra of VO(acac)(H₂O)@**4** and VO(acac)₂ (Fig. S14), showed identical binding energy (BE) of 516.6 eV (V2p_{3/2} line) in both cases, which confirms the V(IV)-valence state in VO(acac)(H₂O)@**4**, as previously reported.³⁰ This can be extended to V2p_{1/2} and O1s bands (Fig. S14), exhibiting similar BEs, further confirming the proposed oxidation state (IV).

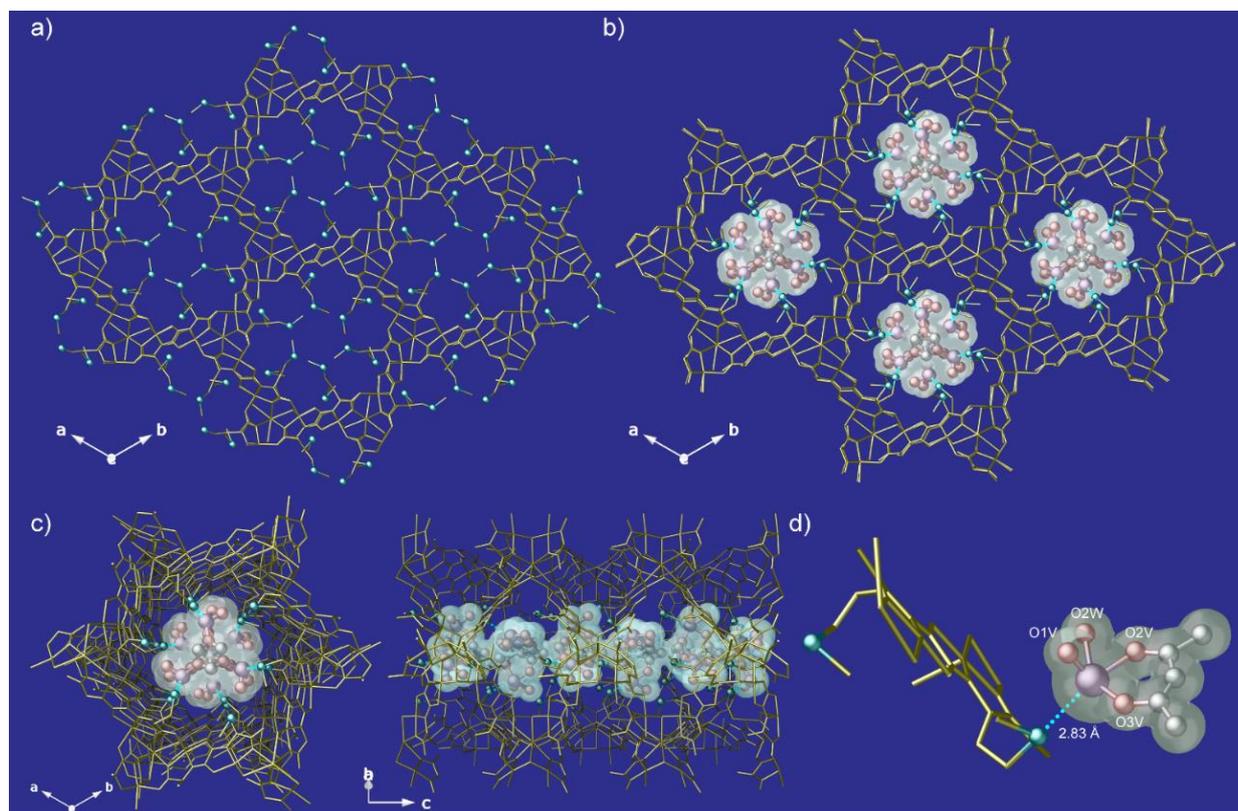


Fig. 2. Views of the 3D open-framework of **4** (a) and $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ (b) along the *c* axis (crystallization water molecules are omitted for clarity). The 3D network is depicted as gold sticks, with the only exception of sulphur atoms, which are represented as blue spheres. For the guest $\text{VO}(\text{acac})(\text{H}_2\text{O})^+$ species hosted in the channels (b), vanadium, carbon and oxygen atoms are represented as purple, grey and red spheres, respectively. Surfaces are used to highlight these guest species. c) Top (left) and side (right) perspective views of a single channel of $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$. (d) Fragment of $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ emphasising the host-guest interactions. Dashed blue lines represent the S–V interaction

$\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ can be seen as a pre-activated catalyst, which has already released the unnecessary acac^- ligand, but influenced by the constraints of MOF channels. Thus, it could be expected that the less sterically-demanding dehydrogenation reaction takes preferentially. Indeed, Fig. 3 shows an increase in the selectivity towards the dehydrogenation of allyl alcohols not only with EWG substituents (products **3b** and **3f**) but also with EDG (products **3a** and **3e**). Thus, it can be said that the MOF structure allows to control the chemoselectivity of the reaction beyond the native structure of the reactant allyl alcohol toward the dehydrogenation product. This selectivity is not total, and some substrate-control persists and, for instance, the methyl substituent in **1c** is still enough to increase the selectivity towards the epoxide. But, when the substituent is larger (**1i**), the EWG benzene is sufficient to reverse the selectivity to the dehydrogenation (see Fig. S16 for comparison between $\text{VO}(\text{acac})_2$ and $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$). The better reactivity of **1c** and **1g** with $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ may be explained by any sort of favoured π -interactions between the aromatic part of substrates and the catalytic site within the MOF channels. However, compounds **1b** and **1f** does not react so efficiently. Thus, it is difficult at this point to explain the different reactivity on the basis of selective adsorptions on the catalytic site.

No leaching processes were observed during reaction (Fig. S17). $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ could be reused up to seven times for the epoxidation of **1c** without depletion in the final yield, while retaining the crystallinity as PXRD supported (Fig. S12c). The

presence of the active species within the MOF and the stability of $\text{VO}(\text{acac})(\text{H}_2\text{O})@4$ during the reaction was checked by FT-IR (Fig. S18-S19). We observed an oxidation of the sulphur groups when the reaction proceeds in low yields. In the reaction of **1i** appear new peaks at 1207 and 1440 cm^{-1} , corresponding to S=O bands, while the intensity of these new peaks is very low for **1h**, maintaining also the peaks of the original S at 1287 and 1370 cm^{-1} . Moreover, when we just impregnated a solution of $\text{VO}(\text{acac})_2$ either in neat **4** or in a second isostructural MOF with hydroxyl-residues decorating the channels instead of the thioether-arms ($\{\text{Ca}^{\text{II}}\text{Cu}^{\text{II}}\}_6\{(\text{S,S})\text{-serimox}\}_3(\text{OH})_2(\text{H}_2\text{O})\} \cdot 39\text{H}_2\text{O}$ (**5**), where $\text{serimox} = (\text{S,S})\text{-oxaloyl-bis}(N\text{-serineninate})$),³¹ we also observed high catalytic activities (Fig. S20). However, the vanadyl active species leached out from the structure (Fig. S21), being the material only active for 2 uses. Even when the $\text{VO}(\text{acac})_2$ was impregnated on SiO_2 , we could observe the leaching of the active species (Fig. S22). These results confirm the requisite of encapsulating, not impregnating, the $\text{VO}(\text{acac})_2$ inside **4** for obtaining a robust solid catalyst.

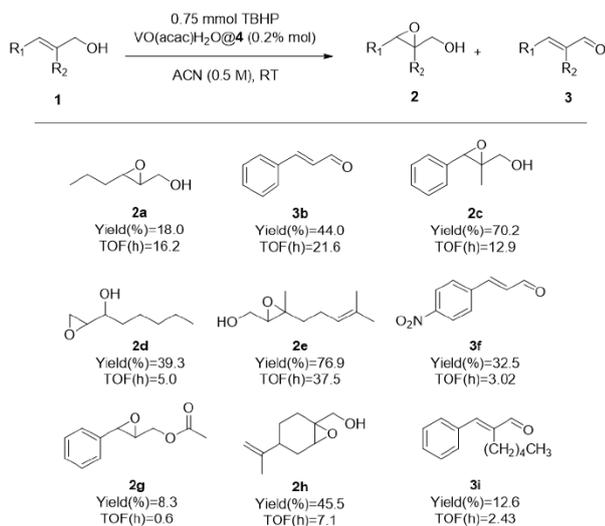


Fig. 3. Scope of the reaction using VO(acac)₂·H₂O@4 as a catalyst.

Overall, we have observed in homogenous phase (VO(acac)₂/TBHP) the selectivity of allylic alcohols towards the epoxidation or dehydrogenation reactions is subtly controlled by the substituents around the allylic alcohol functionalities. A MOF encapsulating VO(acac)(H₂O) species has been synthesized and atomically-resolved by SC-XRD. VO(acac)(H₂O)@4 as a heterogeneous catalyst, taking advantage of the steric constraints induced by the solid network on the catalyst, allow to gain some control on the chemoselectivity of the reaction toward the dehydrogenation product.³² These studies are representative of the change in reactivity imparted by a well-defined structured solid in organometallic catalysts, and expand the study of vanadium catalyst within MOFs channels.^{33,34}

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