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Metal-Organic Frameworks Invert Molecular Reactivity: Lewis Acidic Phosphonium Zwitterions Catalyse The Aldol-Tishchenko Reaction

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ABSTRACT: The influence of metal-organic frameworks (MOFs) as additives is herein described for the reaction of *n*-alkyl aldehydes in the presence of methylvinylketone and triphenylphosphine. In the absence of a MOF, the expected Morita-Baylis-Hillman product – a *β*-hydroxy enone – is observed. In the presence of MOFs with UMCM-1 and MOF-5 topologies, the reaction is selective to Aldol-Tishchenko products - the 1 and 3 *n*-alkylesters of 2-alkyl-1,3-diols - that is unprecedented in organocatalysis. The (3-oxo-2-butenyl)triphenylphosphonium zwitterion, a commonly known nucleophile, is identified as the catalytic active species. This zwitterion favours nucleophilic character in solution, whereas once confined within the framework, it becomes an electrophile yielding Aldol-Tishchenko selectivity. Computational investigations reveal a structural change in the phosphonium moiety induced by the steric confinement of the framework that makes it accessible and an electrophile.

Metal-organic frameworks (MOFs) are becoming increasingly relevant for catalytic applications.[1] Their structural versatility, tuneable pore size and modularity gives a nearly infinite number of structures.[2] MOFs feature active sites as intrinsic parts of the inorganic nodes or organic linkers. Reactive intermediates may also be trapped inside the pores.[1a] These features can be thought of providing host-guest properties similar to enzymes giving them potential beyond simple heterogenisation of homogeneous catalysts. Reactivity and selectivity of reactions can be tuned by exploiting the environment around the active site.[3] For instance, a chiral binaphthyl copper MOF with phosphoric acid functionality can reverse the stereoselectivity in the Friedel-Crafts reaction between indoles and imines.[4] The cobalt salen-catalysed intramolecular epoxide ring opening in the presence of a MOF results in the formation of the 6-membered ring, whereas the homogeneous analogue yielded the 5-membered ring product.[5] Molecular confinement within a phosphine MOF with IRMOF-9 topology has also proven to sterically induce intermediate selectivity to determine which reactions occur.[6] One can also tune the environment *around* active sites to affect regioisomer reactivity as demonstrated by amino MixMOFs with IRMOF-9 topology that catalyse the Knøvenagel condensation of nitrobenzaldehydes.[7] The common underlying feature is the anchoring of reaction intermediates to the framework which consequently alters the reaction pathway. We show that we can use the MOF's porous environment to completely alter the reactivity of a catalytic intermediate from nucleophile to electrophile, yielding an as yet unprecedented catalytic pathway.

Hereby, phosphines play a central role in catalytic processes to achieve high reactivity and selectivity. Although their main application lies in the field of transition metal catalysed reactions,[8] e.g. the hydroformylation of olefines[9] and the asymmetric synthesis of fine chemicals and bioactive compounds,[10] phosphorous compounds gain increasing interest in organocatalytic reactions.[11] Phosphines as organocatalysts facilitate the reaction with unsaturated carbon atoms to form phosphonium zwitterions.[11d] Such species are reactive towards nucleophilic attack and catalyse a variety of C-C bond forming reactions like the Michael addition and the Morita-Baylis-Hillman (MBH) reaction. [11a, 11d] The phosphonium ion activates the adjacent carbon atoms. Free phosphonium cations are also active Lewis acid catalysts.[12] The low lying σ* orbitals of the P-C bonds make the phosphorous electrophilic.[13] Even though phosphonium cations have shown to catalyse different coupling reactions,[14] they are rarely – if ever – the reactive moiety when placed in a zwitterion. Hence, electrophilic reactions, like the Aldol-Tishchenko (AT) reaction,[15] are usually not accessible via phosphonium zwitterions.

In this contribution, we describe a triphenylphosphonium zwitterionic species that features electrophilicity *only* when MOFs are present. These findings show that MOFs can completely alter the reactivity of an organocatalyst from a nucleophile in solution to an electrophile in the framework, enabling the AT reaction: an as yet unprecedented reaction in organocatalysis. The role of the framework was subsequently studied by experimental and computational methods. This work shows the capability of MOFs to completely switch the reactivity of the phosphonium zwitterions, thus enabling otherwise inaccessible reaction pathways.

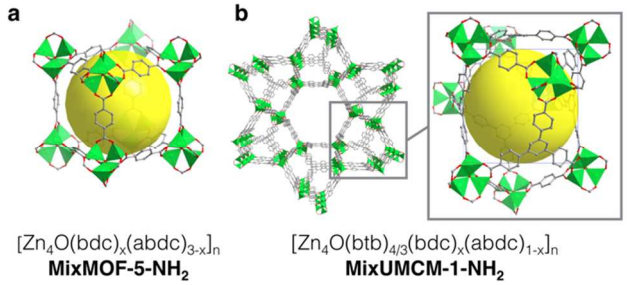

Figure 1. Structures and molecular formulas of the MOFs used in this work: (a) MixMOF-5-NH_2 and (b) MixUMCM-1-NH_2. bdc = 1,4-benzenedicarboxylate; abdc = 2-amino-1,4-benzenedicarboxylate, btb = 4,4′,4″,-benzene-1,3,5-triyl-trisbenzoic acid (hydrogen and nitrogen atoms were omitted for clarity).

Phosphines are commonly used as organocatalysts in the MBH reaction: electron deficient olefines, such as methyl vinyl ketone (MVK), react in the presence of the nucleophilic PPh_3 and aldehydes to form *β*-hydroxy enones.[16] The influence of amino containing MixMOF systems with MOF-5 topology as co-catalysts[17] in the PPh_3-catalysed MBH reaction was investigated at first. Experiments in solution of *n*-pentanal and MVK with catalytic amounts of PPh_3 showed 15% conversion of the starting aldehyde with a selectivity of >99% towards the corresponding MBH product, the 4-hydroxy-3-methylene-2-octanone (**3-C_4**) (Table 1, Entry 1). When the same reaction was performed with *n*-butanal as substrate in the presence of MixMOF-5-NH_2 (13 mol% NH_2; Figure 1a) three products were observed.[18] In addition to the expected MBH product, the AT products, the 1- and 3- butanoic acid esters of 2-ethyl-1,3-hexandiol (**1-C_4** and **2-C_4**),[15] were observed as major products with 76% selectivity (Table 1, Entry 2). The formation of **1-C_4** and **2-C_4** was confirmed by independent synthesis and analysis of the AT products.[19]

The addition of the amino containing MIL-101(Al)[20] and DMOF-1-NH_2,[21] yielded only the MBH product **3-C_4**.[19] When MixUMCM-1-NH_2 (28 mol% NH_2; Figure 1b)[21-22] was used as additive, the conversion increased to 70% and the AT selectivity to 82% (Table 1, Entry 3). The role of the amino substituent was further investigated. MixUMCM-1-NH_2 with 28 to 100 mol% NH_2 were employed (Table 1, Entries 3 - 5). Increasing the amino content in the MOF to 52 mol% NH_2 (Table 1, Entry 4) enhanced the AT selectivity to 84% with an 87% conversion. The fully functionalised UMCM-1-NH_2 (Table 1, Entry 5) significantly reduced conversion to 14% with an AT selectivity of 63%. Reaction with non-functionalised UMCM-1 showed a conversion of 84% with a respective AT selectivity of 75% (Table 1, Entry 6). These results indicate that the amino residue influence AT reactivity and selectivity. The UMCM-1 with around 50 mol% NH_2, equivalent of one functional group per pore, is optimal for conversion and selectivity.

The substrate scope was then extended using a series of different *n*-aliphatic aldehydes with increasing chain lengths. The use of *n*-pentanal and *n*-hexanal reduced the overall conversion to 58% and 56%, respectively, with an AT selectivity of 84% in both cases (Table 1, Entries 7 and 8). *n*-Heptanal yielded a conversion of 34% with a corresponding AT selectivity of 62% (Table 1, Entry 9). Increasing the chain length of the aldehyde limits the conversion, giving further evidence that AT catalysis takes place inside the framework. Blank reactions using dimethyl aminoterephthalate – as a substitute for the amino containing MOF – and Zn^{2+} precursors were also performed (Table S8).[19] All reactions yielded only the MBH product underlining the pivotal role of the MOF in forming the AT product. The formation of an imine between the dimethyl aminoterephthalate and the aldehyde was not observed. In addition, the amino-free UMCM-1 (Table 1, Entry 6) also showed to induce the selectivity change towards AT reaction, which excludes the formation and the involvement of imines as catalytically relevant entities (Table S8). When MVK and/or PPh_3 were omitted from the reaction, neither reaction occurred.[19] Previous studies showed that PPh_3 reacts with MVK to form the zwitterionic species **4** (Figure 2).[16, 19, 23] The presence of **4** was independently detected by UPLC/MS in the crude reaction mixture.[19] Molecule **4** is an active intermediate in the MBH reaction and normally acts as a nucleophile. However, in the presence of amino MOFs with MOF-5 and UMCM-1 topologies, this zwitterion becomes an electrophile as required in the AT reaction.[15]

Table 1. Reactivity and selectivity of various *n*-aliphatic aldehydes in the presence of PPh_3 and MVK using different MixMOF-NH_2 systems as co-catalysts.

Entry	MOF	Aldehyde	Conv. [%][a]	Selectivity [%][b]		
				1-C_n 2-C_n	**3-C_n**	Other
1	--	*n*-pentanal (R=C_3H_7)	15	0	>99	0
2	MixMOF-5-NH_2 (13 mol% NH_2)	*n*-butanal (R=C_2H_5)	47	76	14	10
3	MixUMCM-1-NH_2 (28 mol% NH_2)	*n*-butanal (R=C_2H_5)	70	82	14	4
4	MixUMCM-1-NH_2 (52 mol% NH_2)	*n*-butanal (R=C_2H_5)	87	84	13	3
5	UMCM-1-NH_2 (100 mol% NH_2)	*n*-butanal (R=C_2H_5)	14	63	30	7
6	UMCM-1	*n*-butanal (R=C_2H_5)	84	75	21	4
7	MixUMCM-1-NH_2 (28 mol% NH_2)	*n*-pentanal (R=C_3H_7)	58	84	13	3
8	MixUMCM-1-NH_2 (28 mol% NH_2)	*n*-hexanal (R=C_4H_9)	56	84	14	2
9	MixUMCM-1-NH_2 (28 mol% NH_2)	*n*-heptanal (R=C_5H_{11})	34	62	38	0

[a] Conversions were determined via GC or UPLC: the starting material was calibrated prior to the analyses, [b] The amount of product were determined via GC: the values are based on the C-ratios of the respective products.

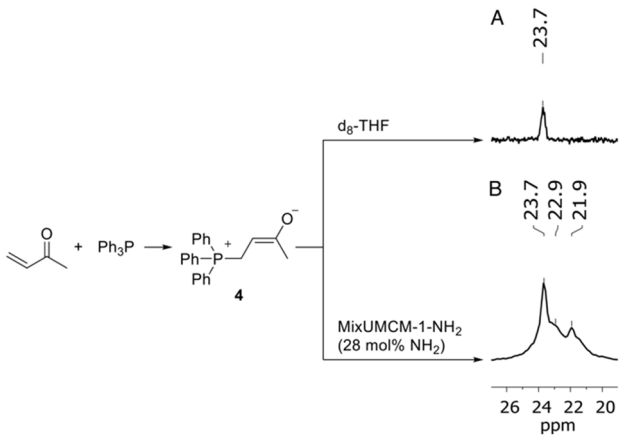

Figure 2. Formation of (3-oxo-2-butenyl) triphenylphosphonium (**4**) as catalytic active species: (**A**) MVK (0.25 mmol) + PPh_3 (0.16 mmol) in d_8-THF (0.5 mL), (**B**) Formation and interaction **4** with MixUMCM-1-NH_2 (28 mol% NH_2).

To further prove that (a) the catalytic intermediate is trapped within the MOF and that (b) leads to AT raectivity, MixUMCM-1-NH_2 (28 mol% NH_2) was pretreated with PPh_3 and MVK in tetrahydrofuran (THF) overnight. It was then intensively washed to remove the excess MVK and PPh_3. A solution with *n*-butanal in THF was introduced thereto. Under these conditions exclusively the AT product was formed (Table S8).[19] The absence of the MBH product excludes the leaching of the catalytic intermediate from the framework. Furthermore it shows the central role of the MOF in the selectivity change. The interaction between active species and the MOF was then investigated. A stoichiometric mixture of PPh_3 and MVK in d_8-THF was measured by ^{31}P NMR spectroscopy showing the formation of a new species at 23.7 ppm, which corresponds to the zwitterionic phosphonium species, (3-oxo-2-butenyl)triphenylphosphonium (Figure 2, spectrum A).[19, 23b] When dimethyl aminoterephthalate was added to the solution, the signal shifted downfield to 24.2 ppm.[19] This is indicative of an interaction between the zwitterion **4** and the amino moiety. Subsequently, the presence of **4** in the MOF structure was confirmed by pretreating MixUMCM-1-NH_2 (28 mol% NH_2) with PPh_3 and MVK in THF after removal of the excess PPh_3 and MVK. Solid state ^{31}P NMR spectroscopy (Figure 2, Spectrum B)[19] shows the formation of three species at 21.9, 22.9 and 23.7 ppm with chemical shifts comparable to solution spectra of the zwitterion **4** demonstrating that the zwitterion is trapped relatively strong within the MOF pores. ^{1}H NMR spectroscopy after digestion of **4** within MixUMCM-1-NH_2 (42 mol% NH_2) revealed a formula $[Zn_4O(btb)_{4/3}(bdc)_{0.58}(abdc)_{0.42}(\mathbf{4})_{0.27}]_n$ with 0.64 ratio between **4** and amino groups (Figure S9-S11).[19] The structure of the MOF is maintained upon reaction with intermediate **4**, and a surface area decrease of 50% is observed (Figures S3 and S4).[19]

To understand the role of the framework in the activation of the AT reaction pathway, we compared the catalytically active phosphonium zwitterion **4** in solution as well as in the UMCM-1 environment using a mix of density functional theory (DFT) and force field calculations. Intermediate **4** can either bind to defect sites in the crystal lattice, enabling a direct coordination to Zn^{2+} ions, or via hydrogen bonding to the amine group dispersed within the framework. The coordination of the Zn-sites cannot be excluded *a priori* but it was shown exprimentally that the amine group plays a central role in the anchoring of **4**. Further evidence of the stabilising role of hydrogen bonds in phosphonium zwitterions is also evidenced in the enantioselective phosphine organocatalysis literature.[16] Hence, we focused on H-bond stabilisation and studied stability of **4** in the presence of MixUMCM-1-NH_2 (50 mol% NH_2; system **A**) and in solution with dimethyl aminoterephthalate (system **B**; Figure 3). The optimised geometry of systems **A** and **B** was computed using DFT. Inside the MOF, the zwitterion can adopt two different configurations: (**A1**) pointing towards the pore or (**A2**) pointing towards the channel (Figure 3). Starting from these configurations, classical molecular dynamics (MD) was used to verify the strength of the H-bond and the possibility of a transition between the states **A1** and **A2**. All the simulations consider liquid *n*-butanal as explicit solvent. In both MixUMCM-1-NH_2 systems (**A1**, **A2**) and the unhindered system (**B**) the H bond was found to be stable, i.e., the zwitterion stayed bound to the amine group for the entire simulation (50 ns). A transition between the pore and the channel conformation was not observed, suggesting that a possible transformation from **A1** to **A2** only goes via the cleavage of the hydrogen bond.

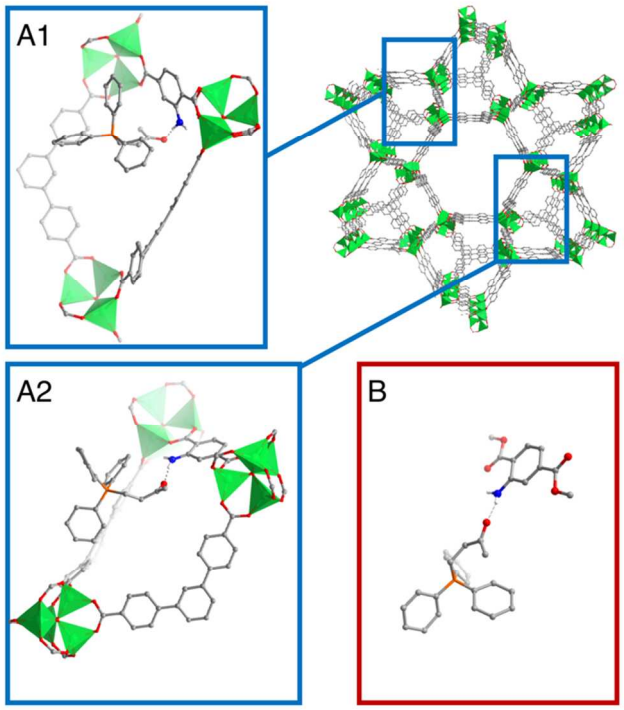

Figure 3. Two different configurations in which the zwitterion (**4**) can be found inside MixUMCM-NH_2, anchored by an H bond to the amino group: **4** is trapped inside the pore (**A1**); **4** points toward the channel (**A2**). The dimethyl aminoterephthalate system (**B**, "solution"). H atoms were omitted for clarity reasons.

To derive different reaction pathways the C···C and the O···P (Figure S12)[19] distances were investigated in systems **A1**, **A2** and **B**. These distances represent the first step of MBH and AT reaction pathway, respectively.[24] In this analysis we consider that the transition state of the reactions is reached when the $d_{Cc\text{-}C\beta}$ and $d_{O\text{-}P}$ distances are smaller than the respective C···C and O···P van der Waals distances, i.e., 3.47 Å and 3.36 Å. The probability of the transition state can therefore be compared between the different systems. The probability of the C···C distance between the zwitterion and the carbonyl to be shorter than the respective van der Waals distance is in a similar range for the system **A2** and **B** (Table S9). Hence, the steric confinement of the MOF does not play a major role in the suppression of the MBH pathway. On the

other hand, the d_{O-P} distance shows a remarkable enhancement inside the MOF: in system **A2** the probability related to the formation of the AT precursor is 26-times higher than in systems **B.** This difference in the binding of the O···P arises from the interaction between the phenyl groups of the phosphonium and the steric confinement of the MOF. The three phenyl groups cause a significant steric hindrance, which results in the shielding the phosphorous from the *n*-butanal. However, the MOF limits the freedom of movement of **4**, distorting the tetrahedral configuration of the phosphonium moiety. This distortion enables the oxygen attack by the *n*-butanal due to the attractive electrostatic interaction between the oppositely charged O (-0.278) and P (0.523) atoms. On the other side, the configuration with the zwitterion shielded inside the pores of the MOF (**A1**), are shown not to be reactive, giving similar results to the B system (Table S9). MD simulations confirm the active role of the MOF in alternating the zwitterion's reactivity in **A2** as result of the steric interaction arising between between the ligands of the frameworks and the phenyl rings.

We have shown that MOFs can effectively bind reaction intermediates and influence the reactivity of catalytic systems. In our case the Morita-Baylis-Hillman (MBH) reaction of *n*-aliphatic aldehydes with methyl vinyl ketone and PPh_3 can be switched to exclusively yield the Aldol-Tishchenko (AT) reaction in the presence of amino containing MixMOFs. This change in reactivity was shown on a series of different *n*-aliphatic aldehydes in various framework systems. The (3-oxo-2-butenyl)triphenylphosphonium zwitterion (**4**), a commonly known nucleophile, was identified as catalytic active species. MixUMCM-1-NH_2 confines the zwitterionic organocatalyst and influences the geometry around the tetrahedral phosphonium moiety. Simulations suggested the MOF to affect the fine structure around the phosphonium through new steric interactions between the host (MOF) and the guest (zwitterion), which opens the phosphonium moiety to nucleophilic attack. This work shows a novel way of doing catalysis where MOFs can be used as additive to trap reaction intermediates yielding unprecedented reactivity inaccessible under standard reaction conditions.

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18. *Mol% NH_2 refers to % aminoterephthalate to total terephthalate content.*

19. *See the supporting information.*

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