Exploitation of Intrinsic Confinement Effects of MOFs in Catalysis
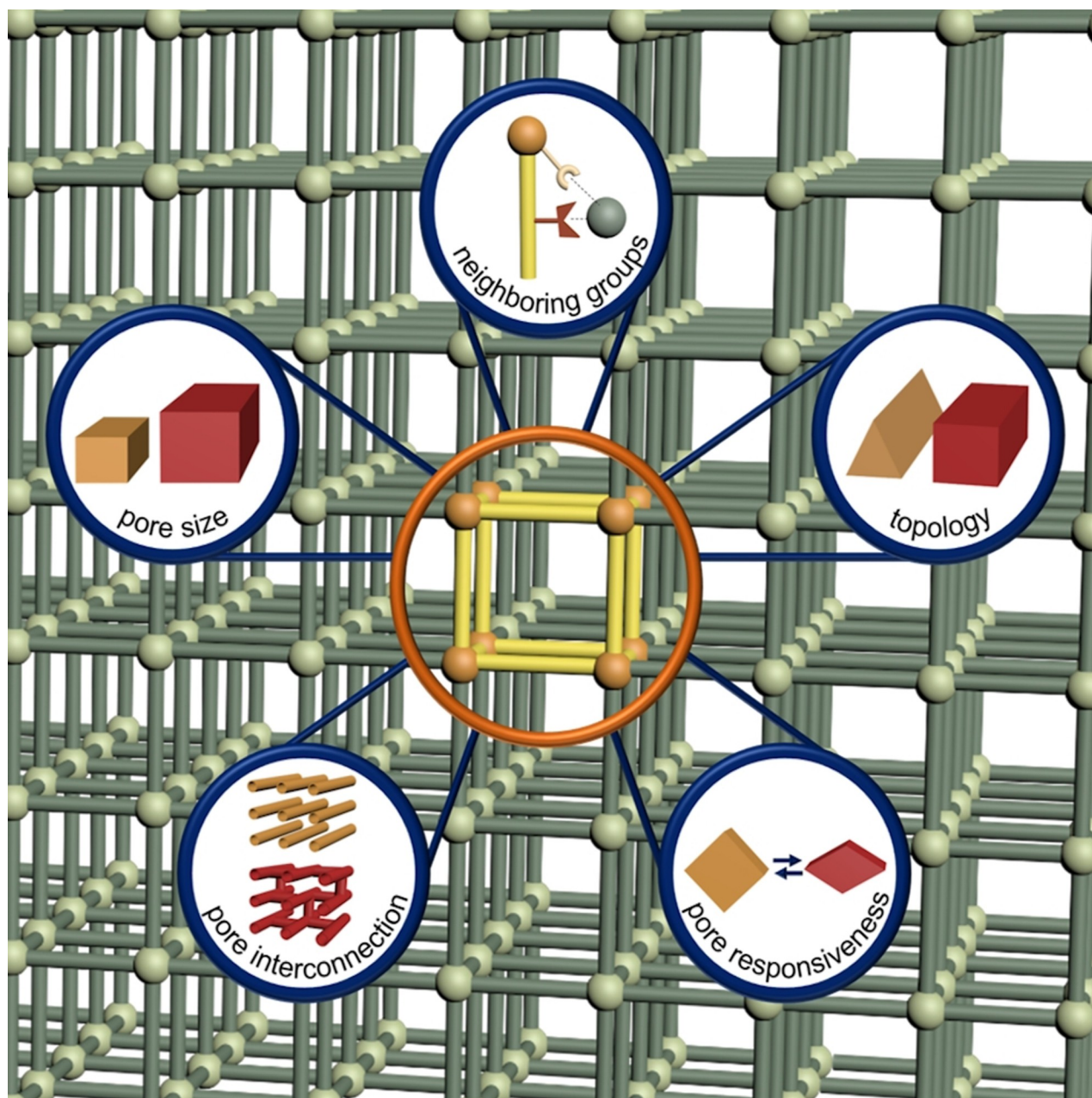
Karina Hemmer,[a] Mirza Cokoja,[a] and Roland A. Fischer*[a]

In catalysis research the design of bio-inspired, 'artificial enzymes' is a field of huge interest. These catalysts are distinguished by their high catalytic efficiency resulting from a close proximity of several active sites and secondary substrate-catalyst interactions enabled by functional groups in the catalytic pocket. A class of materials which meets these requirements are metal-organic frameworks (MOFs). Here, the pores confine a reaction environment where several functionalities can be incorporated and spatially positioned in a tunable fashion. Recently, a number of reports revealed the importance of such confinement effects for the control of catalytic activity and selectivity by exploiting the intrinsic properties like pore size and neighboring group effects and the alignment and distance of different active sites within one MOF pore. Thus, this concept aims to accentuate the potential of the exploitation of those effects in MOFs for the design of sophisticated catalysts.

Introduction

In nature, organic transformations are catalyzed by enzymes with high efficiency and excellent selectivity, which is essential for life on Earth. One major reason for this outstanding performance – at low reaction temperatures – is the precise arrangement of the catalytic pockets of enzymes. Here, the different active centers are located in close and defined proximity facilitating the alignment of different substrates. This is further supported by various amino acid residues, which are able to coordinate to the substrates and placing them via secondary interactions in a preferred orientation resulting in the observed high activity and (stereo-)selectivity.[1] For decades, mimicking enzyme catalysis by the design of artificial analogs has been addressed by several homogeneous and heterogeneous systems.[2] Multifunctionality and an enzyme pocket-like reaction environment are thus beneficial material properties. Nevertheless, creating bio-inspired, artificial materials, which exhibit similar properties on a supramolecular level is rather difficult in terms of stability or control over selectivity. Although molecular complexes with sophisticated (chiral) ligands are able to mimic enzymes in first and second coordination spheres, the performance control by higher coordination spheres comparable to enzymes has not been achieved yet. Moreover, a targeted design of pocket and porosity in structurally more extended (solid) systems is not readily feasible so far.

Metal-organic frameworks (MOFs) are a class of hybrid materials, which principally allow for a controlled design of local reactive sites and confined environments of pores and channels, which could potentially be exploited for catalytic bio-inspired reactions. MOFs are built from inorganic metal nodes or clusters (so-called secondary building units, SBUs) and organic linker molecules and exhibit excellent properties which can be strategically exploited for this purpose. Here, either the node or functionalities incorporated into the structure as part of the linker can act as catalytically active sites.[3,4] Beside using MOFs as a support for homogeneous catalysts – which has been revealed elaborately during the last years[4–6] – especially the intrinsic MOF properties and the potential multifunctionality are beneficial for designing confined environments similar to enzymes. The multifunctionality allows for secondary substrate – catalyst interactions and specific substrate alignment by neighboring groups, which can be either integrated into the existing framework or are intrinsically given, strengthening the potential of this material for the design of artificial enzymes. The porous network defines a specific reaction space geometry and shape (topology) which influences the distance between the active sites enabling cooperative activation of substrates. Simultaneously, positioning active sites in an ideal distance inside the MOF prevents the deactivation or inhibition of both centers which is crucial for acid/base reactions.[7,8] Moreover, the arrangement of substrates relative to the active centers is supported by the neighboring group effects placing the substrate in close proximity to the catalytic center comparable to the amino acids and their side groups in the enzymatic pockets.

It has to be mentioned here, that 'confinement' in this case is not applied for the incorporation of nanoparticles or homogeneous catalysts in which context this word is often utilized in literature.[6] Here, 'confinement' refers to the inherent structural and functional properties of the MOF cavity, which is defined by the composition of a MOF from its building blocks. The pore 'walls' (in Figure 1 given in dark green restricting a cubic space) affect the selectivity in the simplest way by size

[a] K. Hemmer, Dr. M. Cokoja, Prof. R. A. Fischer
Chair of Inorganic and Metal-Organic Chemistry
Catalysis Research Center and Department of Chemistry
Technical University of Munich
Ernst-Otto-Fischer-Straße 1
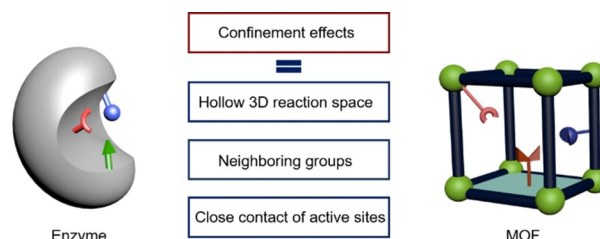D-85748 Garching (Germany)
E-mail: roland.fischer@tum.de

Figure 1. Schematic representation of confinement effects with a comparison of an active enzyme pocket (left) and a simplified MOF with different functional groups or catalytically active sites able to coordinate and convert substrates which are located in the pocket and pores, respectively.

ChemCatChem

Concepts
doi.org/10.1002/cctc.202001606

Chemistry Europe
European Chemical
Societies Publishing

exclusion of substrates or products which is nowadays widely applied in heterogeneous systems especially with porous catalysts like zeolites and can be extended to the targeted control of activity and selectivity of a reaction by affecting the respective transition states.[4,9] The shape of the cavity space, i.e. the environment and accessibility of the catalytically active sites (see Figure 1, the MOF node in light green) are tunable by precise modification by functionalities at the linker (shown in Figure 1 in red and blue) creating a selective reaction space inside the material. However, the investigation of the effect of the confinement of MOFs and the design of confined spaces on reaction selectivity has so far not been studied in much detail, which has been a driving force to bring it to attention with this article. In principle, three factors can be identified to use confinement effects to steer the selectivity of a MOF-catalyzed reaction:

(1) the influence of pore size,
(2) neighboring group effects and
(3) the influence of topology and alignment of active sites

According to these criteria, it is important to assess and understand the origin of the observed selectivity, looking at the relevant publications in the MOF catalysis field. However, this remains challenging, since the catalytic performance of such systems is often assumed to be caused by more than one of those factors. In other cases, the exact reason for the observations is still not completely elucidated due to the challenging characterization of the underlying phenomena and interactions. Thus, a systematic division into subchapters has proven to be difficult for this complex topic at this point of early development. However, a deeper understanding of those underlying principles of the confinement effects and exploiting them in catalysis will enable the specific design of pore environments of sophisticated catalysts and will provide a way to control the (stereo-)selectivity and activity by space restric-tions and directing substrate – catalyst interactions inside the cavities.

Pore Size Effects

The very first reports on confinement effects of MOF catalysts focused on polymerization reactions. This reaction type partic-ularly allows for the investigation of these effects due to the polymer characteristics like tacticity and cross linking which are influenced by the catalyst. This has been shown by Kitagawa et al. for the polymerization of monosubstituted acetylenes using a $[Cu_2(pzdc)_2(L)]_n$ (pzdc = pyrazine-2,3-dicarboxylate, L = pillar ligands) porous coordination polymer (PCP).[10] Here, the acetylene substrate is anchored by the carboxylic oxygens of the material which are directed into the one-dimensional nanochannels (Figure 2). Beside acceleration of the reaction, an increased selectivity towards the *trans*-polymerization product is achieved since the limitation of the reaction space by the channel size inhibits the formation of the *cis*-product.

This principle of reaction environment restriction was further applied for the polymerization of divinylbenzene (DVB), where a concrete correlation between pore size and selectivity can be drawn using the PCP $[M_2(1,4-bdc)_2(ted)]_n$ (bdc = benzenedicarboxylate; ted = triethylenediamine) with M = Zn(II) or Cu(II).[11] In the small nanochannels of this material the molecules form desired topotactic linear polymers, whereas in larger channels the selectivity is drastically decreased obtaining cross-linked polymers (Figure 3). Therefore, by limiting the space for the polymerization and thus the transition states for the formation of the respective isomers a control of selectivity is possible. These early examples already highlight the effect of channel size.

Karina Hemmer received her M. Sc. degree from the Technical University Munich (TUM) in 2019. In her Master's Thesis under the guid-ance of Prof. Roland A. Fischer, she worked on intermetallic Ni/Ga clusters in alkyne semi-hydrogenation reactions. Currently, she is a Ph.D. student in the group of Prof. Roland A. Fischer at TUM. Her research focuses on metal-organic frameworks for catalysis, in particular the exploitation of intrinsic MOF properties for catalytic performance control.

Mirza Cokoja received his Dr. rer. nat. from the Ruhr-University Bochum in 2007 under the guidance of Roland A. Fischer. In 2008, he joined the team of Bruno Chaudret at the CNRS Laboratoire de Chimie de Coordination in Toulouse, France. Since 2009, he has been a research group leader at TUM. His research interests focus on nano-scaled catalysts for multiphase oxidation and hydrogenation reac-tions, and their targeted design for controlling key functions, such as catalyst-substrate inter-actions, reaction selectivity, and catalyst re-covery.

Roland A. Fischer received his Dr. rer. nat. from TUM in 1989. After a postdoc at the University of California, Los Angeles, he returned to TUM in 1990, where he obtained his Habilitation in 1995. He was Associate Professor at Heidelberg University (1996–1997) and Full Professor for Inorganic Chemistry at Ruhr-University Bochum (1997–2015). In 2016 he returned to TUM and took the Chair of Inorganic and Metal-Organic Chemistry. Since 2016, he is Vice President of the Deutsche Forschungsgemeinschaft (DFG). Since 2017, he is Director of the TUM Catalysis Research Center. His research focuses on group 13/transition metal compounds and clusters, precursors for chemical vapor deposi-tion (CVD) and the materials chemistry of metal-organic frameworks (MOFs).
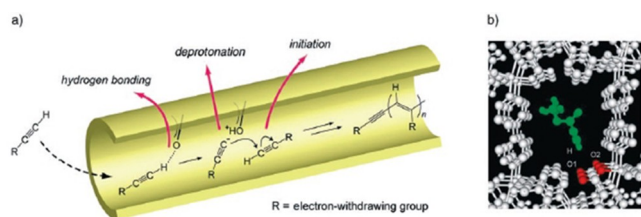
Figure 2. a) Representation of the polymerization mechanism of acidic acetylenes inside the nanochannels of $[Cu_2(pzdc)_2(L)]_n$. b) Optimized structure of methyl propiolate (depicted in green) in the channels of the porous coordination polymer. Oxygen atoms of the PCP are depicted in red. Reproduced from Ref. [10] with permission of Wiley-VCH.
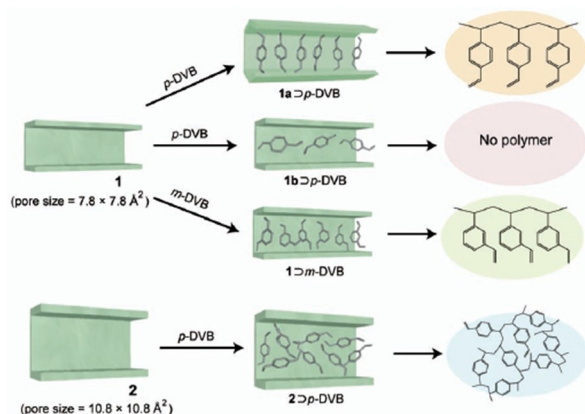

Figure 3. Illustration of DVB polymerization inside the different channels of the porous coordination polymers. Reproduced from Ref. [11] with permission of Wiley-VCH.

Beside influencing polymer properties, stereoselective catalysis offers high potential for the investigation of confinement effects, since the formation of one specific isomer or enantiomer is aspired, which is, in most cases, accomplished by catalyst design. This confinement of the reaction space was also investigated for the MOFs Cr-MIL-100/-101 with addition of different ligands as activators for the polymerization of isoprene.[12] Depending on the coordinating ability of the different activators (Ph_3C versus $PhNMe_2$) the channel size is altered leading to different polymerization products. In the case of the non-coordinating activator Ph_3C cyclic polyisoprene (PIP) is obtained via β-H elimination side reactions due to the increased pore space. In contrast, for the $PhNMe_2$ activator with coordinating ability a confinement effect is observed decreasing the reaction space and thus forming linear cis-1,4-PIP with high molecular weights. This example sheds a light on the effects of reaction space limitation achieved by MOF modification with coordinating versus non-coordinating additives on product selectivity.

Instead of the addition of further coordinating molecules to confine the reaction space, the alteration of the organic MOF linker can provoke similar effects. For two chiral MOFs built from copper SBUs and BINOL-derived (BINOL = 1,1'-bis-2-naphthol) phosphoric acid linkers a confinement of the porous environment has been reported.[13] Changing the substitution of the BINOL

linker and therefore its steric demand and the location of carboxylate groups able to coordinate to the SBU results in different topologies of those chiral MOFs and thus different restricted porous environments (Figure 4). The MOFs were applied in the enantioselective Friedel-Crafts reaction of imines and indole. In comparison to the 3,3',6,6'-tetrabenzyl-BINOL derivative, the 4,4'- substituted linker results in larger MOF pores and therefore, due to varied steric demands, in a decreased enantioselectivity in the described reaction. Simultaneously, for the MOF with the 3,3'-substituted linker, a flip of product handedness is observed compared to the homogeneous analog where the (S)-enantiomer is primarily formed, since in the MOF catalyzed reaction the (R)-enantiomer dominates. This change of enantioselectivity is ascribed to the interaction of the substrate with the walls of the MOF pores affecting the transition states which was identified by QM/MM (Quantum Mechanics/Molecular Mechanics) calculations. In contrast, for the MOF exhibiting larger pores with the 4,4'-substituted linker, the enantioselectivity remains unchanged in comparison to the homogeneous counterpart – both forming the (R)-product. Similarly, Janiak et al. incorporated L-proline as a homogeneous catalyst in the porous network of MIL-53(Al), DUT 5(Al) and MIL-101(Al), differing in channel size, to be applied in the aldol reaction of 4-nitrobenzaldehyde and acetone (Figure 5).[14] Interestingly, for MIL-101 with the largest channel size a reversal of
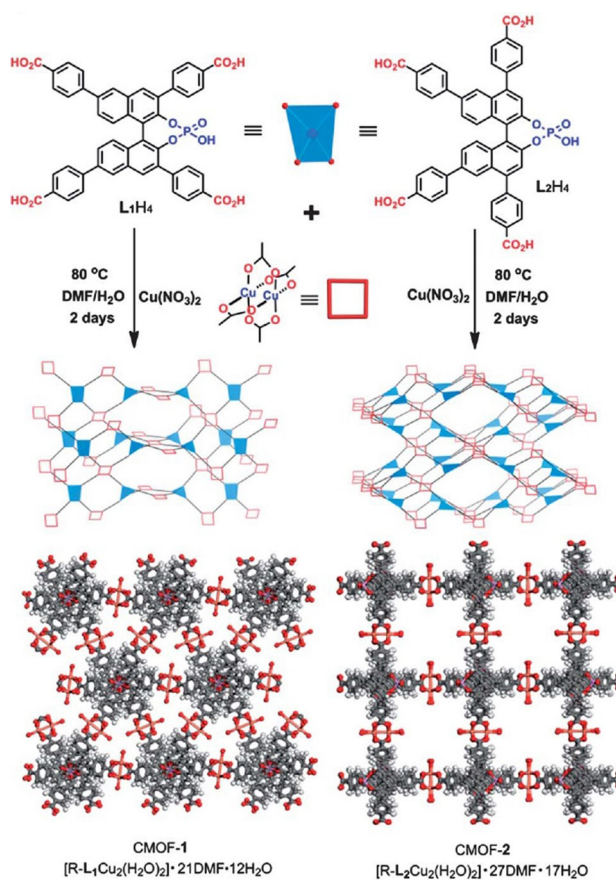

Figure 4. CMOF-1 (left) and CMOF-2 (right) built from ligand L1 and L2, respectively, and a $[Cu_2(carboxylate)_4]$ SBU, forming different topologies. Reproduced from Ref. [13] with permission of the Royal Society of Chemistry.

ChemCatChem

Concepts
doi.org/10.1002/cctc.202001606

Chemistry Europe
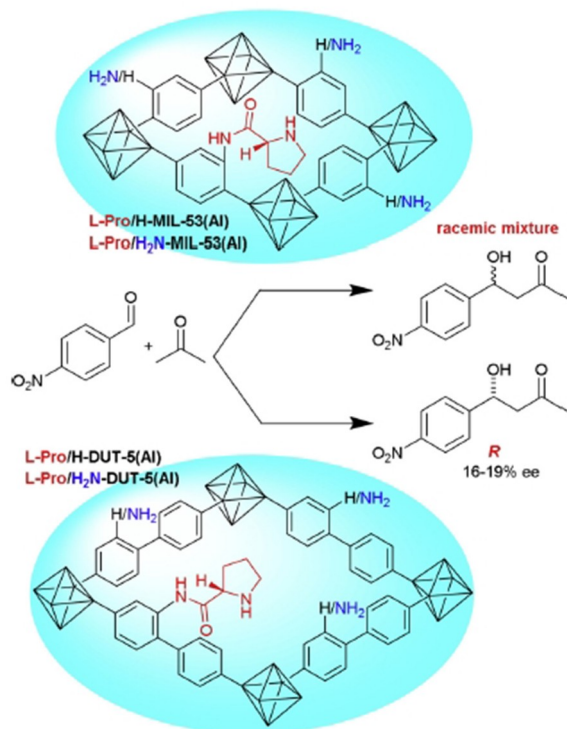European Chemical
Societies Publishing

Figure 5. Depiction of the pore environment of L-Pro-MIL-53(Al) and L-Pro-DUT-5(Al) highlighting the effect of the pore space restriction on the stereoselectivity. Reproduced from Ref. [14] with permission of Elsevier B.V.

stereoselectivity from the (*R*)- to (*S*)-enantiomer compared to the other two MOFs and the homogeneous system is observed. Moreover, for the proline-functionalized MIL-53 with very narrow pores a racemic product mixture was obtained. These results indicate that a too restricted environment prohibits the necessary alignment of the substrate. Contrary, providing enough reaction space for sufficient orientation of the substrate can even allow for a reversal of chiral information. Thus, the specific design of MOF pores and therefore the confinement effect is a powerful tool to control the stereoselectivity in catalysis – similar to transformations catalyzed by different enzymes – which is of high importance in particular for pharmaceutical and fine chemical synthesis.

Neighboring Group Effects on Catalytic Performance

The reversal of stereoselectivity achieved by MOFs was also observed by Kaskel et al. for the isoreticular, chiral UiO-67 and UiO-68 MOFs functionalized with L-proline, which were applied as catalysts in diastereoselective aldol addition of cyclohexanone with 4-nitrobenzaldehyde.[15] Here, a difference in reaction kinetics was observable, since the larger pores of UiO-68 enhanced the adsorption and desorption processes and thus, the yield of the reaction. In comparison to L-proline in homogeneous catalysis, where the (racemic) *anti*-product is favored, both MOF catalysts

achieved an inversed selectivity towards the *syn*-product. Although the exact underlying reason for the observed behavior was not determined, it is likely that the restricted porous environment influences the transition state of the reaction in both cases. However, recent results of this group have shown for proline-functionalized DUT-67 that the *syn*-selectivity in the same aldol addition arises from missing linker defects of Lewis acidic Zr nodes of the MOF (Figure 6).[16] Further investigations on the proline-functionalized MIL-101(Al) system also supported the impact of the metal nodes on the stereoselectivity – however, indicating that the substrate is not coordinated to the node next to the catalytically active site but to a more distant one (Scheme 1).[17] This approach of affecting the stereochemical preference of catalysts incorporated in MOFs by the spatial environment was also followed for MUF-77. This MOF consists of three different linker molecules which are modified with L-proline as a catalyst and different modulators to systematically create a reaction space inside the pores, which is crystallographically identical, to promote the catalytic performance by secondary, non-covalent interactions via neighboring group effects. The impact of the environment around the active sites was followed by the comparison of catalytic results and molecular modeling. Depending on the linker modification and combination applied for MUF-77 and thus the spatial surrounding of the catalytically active site, the enantiomeric excess (*ee*) of the asymmetric aldol reaction can be enhanced. Moreover, a reversal of the type of preferentially formed enantiomer is possible. In contrast to the (*S*)-enantiomer which is formed with the other heterogeneous MOF systems used in this study, here, the (*R*)-enantiomer is preferred. The latter is also typically obtained in the homogeneous system.[18]
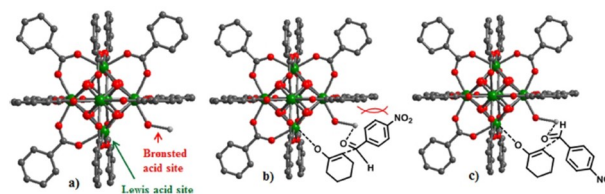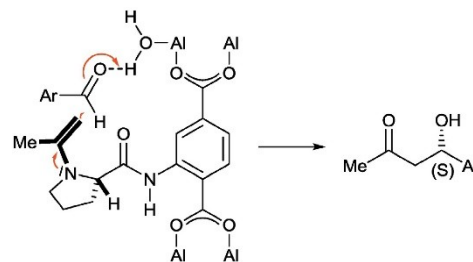

Figure 6. a) Brønsted (—OH) and Lewis acid (Zr(IV)) sites in a Zr-oxo-cluster containing defect sites. b) Supposed coordination for the *anti*-product formation due to steric effects. c) Supposed coordination for the formation of the *syn*-product. Reproduced from Ref. [16] with permission of Elsevier B.V.

Scheme 1. Proposed mechanism for the of L-Pro/H₂N-MIL-101(Al) catalyzed aldol addition of acetone and nitrobenzaldehyde resulting in the (*S*)-enantiomer. Reproduced from Ref. [17] with permission of Elsevier B.V.

ChemCatChem

Concepts
doi.org/10.1002/cctc.202001606

**Chemistry
Europe**
European Chemical
Societies Publishing

This importance of neighboring group effects on selectivity has also been studied by Long et al.[19] The Fe(II)-based frameworks Fe$_2$(dobdc) (dobdc^{4-} = 2,5-dioxido-1,4-benzenedicarboxylate), Fe$_2$(dobpdc) (H$_4$dobpdc = 4,4′-dihydroxy-[1,1′-biphenyl]-3,3′-dicarboxylic acid), and Fe$_2$(dotpdc) (H$_4$dotpdc = 4,4″-dihydroxy-[1,1′:4′,1″-terphenyl]-3,3″-dicarboxylic acid) with increasing pore sizes were applied in the oxidation of cyclohexane to the respective alcohol and ketone. While the altered pore sizes rather influence the catalyst stability and diffusion, the introduction of neighboring group effects plays a major role for controlling product selectivities resulting in increased alcohol formation. Therefore, the functionalities −H, −F, −CH$_3$ and −^{t}Bu (tert-butyl) have been introduced to Fe$_2$(dotpdc) as the most promising candidate and investigated in terms of conversion and alcohol selectivity. Both parameters are drastically increased for non-polar functional groups like ^{t}Bu due to the reduction of channel size towards the active Fe centers (Figure 7) suggested by structural modelling. Therefore, a directing effect of ^{t}Bu for the cyclohexane substrates towards these centers via van der Waals interactions is assumed which is supported by an increased adsorption enthalpy of cyclohexane. This affects the local substrate concentrations close to the Fe sites, which are unequally restricted for the two MOFs. Thereby, an increase in alcohol selectivity for the ^{t}Bu-functionalized Fe$_2$(dotpdc) in comparison to the non-functionalized analog is observed. In addition to increased product selectivity also the stability of the Fe sites is increased by those neighboring group effects without changing the active site structure. These works demonstrate the capability of exploiting the intrinsic possibility of high tunability and multifunctionality of MOFs by designing sophisticated, enzyme-inspired coordination environments with neighboring groups which offers new strategies for approaching challenging transformations in organic synthesis.

Influence of Topology and Alignment of Active Sites

The importance of confinement effects in terms of the alignment of the active centers and in particular the distance of those has also been highlighted, in contrast to the influence of
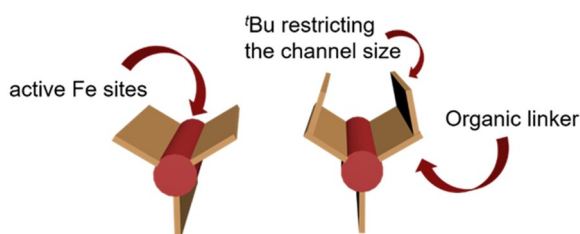
pore size described above where only one catalytically active site is involved. Cui et al. synthesized a Co(salen) functionalized MOF providing a close arrangement of the catalytically active Co sites.[20] This enables cooperative interactions between both centers which is necessary for the simultaneous activation of water and epoxide as substrates. The close contact of these active sites located into the direction of the MOF pores results in an increased catalytic activity in the hydrolytic kinetic resolution and achieves higher enantioselectivities compared to the homogeneously catalyzed system. This impact of the proximity of active sites for catalysis with MOFs has been further studied by Duan et al. for a Zn-BCTA-MOF (BCTA = bis[4-(5-carboxy-2-thienyl)-phenyl](4-carboxyphenyl)amine) applied in the photocatalytic sulfonylation and cyclization of alkenes. The proximity between the Zn-node and the photocatalytic center of the BCTA^{3-} linker, given by the twofold interpenetration of the framework, offers the possibility to fixate the substrate resulting in an enhanced catalytic efficiency (see Figure 10). Moreover, the spatial confinement resulting from the porous MOF environment enables a control of stereoselectivity, since higher diastereoselectivities with respect to the homogeneous analog are obtained.[21] Thus, the concomitant substrate fixation and activation as a consequence of the confinement effects MOFs provide has been shown to improve the performance of the catalyst. In general, suitable MOFs for the study of confinement effects are porphyrin-based MOFs, since these materials can be synthesized from the same building blocks (Zr-oxo metal nodes and porphyrin linkers) but depending on the reaction conditions form different structures (Figure 8). This has been shown by Deng et al. who reported on the dependence of the photocatalytic activity of the dehydrogenation of tetrahydroquinoline on the interactive site distance in the framework of different MOFs (Figure 9). Therefore, they investigated several porphyrin-based MOFs (namely PCN-221, PCN-222, PCN-223, PCN-224, MOF-525 and Al-PMOF) only
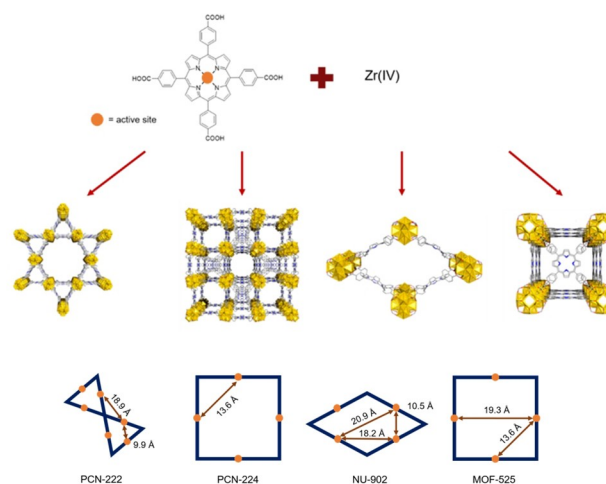

Figure 7. Environment of active Fe centers in Fe$_2$(dotpdc) (left) and tert-butyl functionalized Fe(dotpdc^{tBu}) (right). The addition of −^{t}Bu results in a more restricted size of the channel which enables the direction of the substrate to the active sites.[19]

Figure 8. Selection of porphyrin MOFs PCN-222, PCN-224, NU-902 and MOF-525 which are all built from porphyrin linkers and Zr-oxo metal nodes (Zr(IV)). Beside the MOF topology, a schematic representation of the pores with inter active site distances is depicted. The distances are taken from ref. [22] and [23].
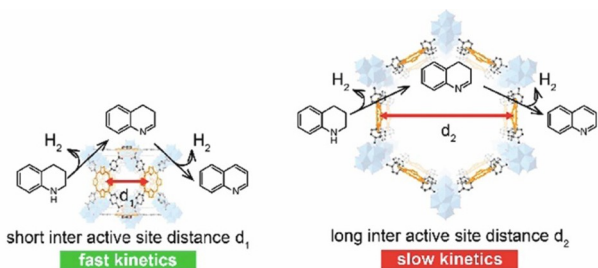
ChemCatChem

Concepts
doi.org/10.1002/cctc.202001606

**Chemistry
Europe**

European Chemical
Societies Publishing

Figure 9. Illustration of the reaction kinetics of the photocatalytic dehydrogenation of tetrahydroquinoline depending on the inter active site distance of the different porphyrin MOFs. Reproduced from Ref. [23] with permission of Wiley-VCH.

differing in their topology and thus in the spatial arrangement of the active sites. Noteworthy, the activity of this reaction linearly correlates with the distance between the active centers. Therefore, a shorter distance between two porphyrin linkers resulted in an increased reactivity in the above mentioned reaction and thus highlights the potential of confinement and spatial arrangement in catalysis.[23]

The principle of a favorable alignment of active sites to raise the activity of a catalytic reaction has also been suggested for a twofold interpenetrated In-TBP MOF (TBP = tetrakis(4-benzoic acid)porphyrinato) where the porphyrin ligands are metalated with cobalt (Figure 10). These active Co(III) centers are aligned in a parallel fashion with a inter active site distance of 8.8 Å enabling the cooperative activation of the two substrates – methanol and an aromatic alkyne – to obtain the desired ketone as the hydrated product. By this simultaneous activation, possible by the targeted confinement of active Co centers, the activity of the reaction is drastically increased compared to the homogeneous counterparts. At the same time, this close proximity of the Co atoms prohibits the conversion of meta-substituted aromatic alkynes due to the increased steric hindrance.[8] Thus, the confinement is not only exploited to achieve an increase in activity but also to affect the selectivity of a catalytic reaction. This influence on the catalyst selectivity has been addressed in a similar approach by Zhang, Su et al. who synthesized an Ir(III)-metalated porphyrin MOF acting as a molecular nanoreactor, which is defined by four Ir-porphyrin ligands restricting the reaction space and acting as catalytically
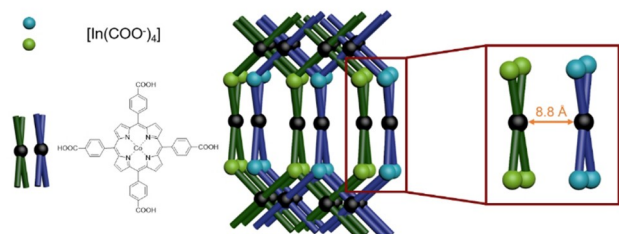
active centers (Figure 11). This smaller cavity is surrounded by larger cavities facilitating reactant diffusion. Using this crystalline nanoreactor, an unexpected chemoselectivity towards the primary silanes in the insertion of a carbenoid into Si−H bonds is observed in contrast to conventional catalytic systems in homogeneous phase where tertiary silanes show the highest reactivity.[24] Besides affecting the chemoselectivity of a reaction, the MOF itself can also be applied to induce stereoselectivity.[25–29] In such cases, the porous environment itself has been exploited to control the diastereoselectivity of a reaction without bearing any further stereoinformation (i.e. no chiral auxiliaries). Similar to the catalytic pockets of enzymes, the confinement effects are assumed to direct specific substrate coordination at the active site. This has been shown for MIL-101 (Cr) as a support for Pd nanoparticles.[25] The Cr(III) sites catalyze the cyclization of citronellal to isopulegol, which is further hydrogenated by Pd to the desired (−)-menthol with a diastereoselectivity of 81%. Similarly, the cyclopropanation of alkenes with ethyl diazoacetate (EDA) using HKUST-1 as a catalyst has been studied.[26] For styrene a diastereoselectivity of 71% for the *trans*-isomer was obtained. The synthesis of estradiol from estrone by direct reduction with a diastereoselectivity of 40:60 (*alpha:beta*) is catalyzed by MOF-808 where coordinatively unsaturated Zr(IV) sites are crucial for the catalytic reactivity.[27] The observed diastereoselectivity is ascribed to the MOF pores confining the reaction space and influencing the steric hindrance of the transition states. The control of diastereoselectivity by reaction space confinement has recently been published by Fischer et al. in a comparative study for the porphyrin linker-based MOFs PCN-222 and PCN-224 – both metalated with Rh. In this work, the catalytic cyclopropanation of styrene and its derivatives using those
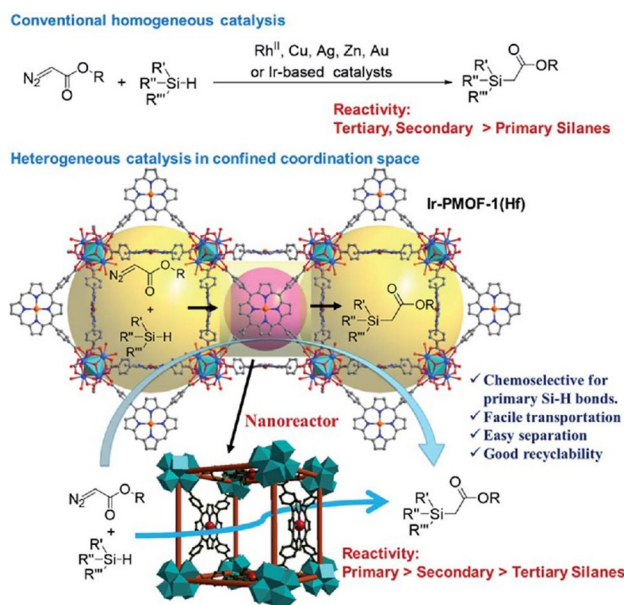

Figure 10. Schematic representation of the twofold interpenetrated In-TBP MOF built from [In(COO−)₄] and a Co-metalated porphyrin linker. This twofold interpenetration results in an active Co−Co site distance of 8.8 Å.[8]

Figure 11. Si−H insertion reaction catalyzed by an Ir-metalated porphyrin MOF as a nanoreactor with confined reaction space (bottom) in comparison to the homogeneously catalyzed system (top). Reproduced from Ref. [24] with permission of the Royal Society of Chemistry.

ChemCatChem

Concepts
doi.org/10.1002/cctc.202001606

Chemistry Europe
European Chemical
Societies Publishing

MOFs was investigated (Figure 12). Noteworthy, the selectivity towards the *trans*-isomer is drastically increased by functional groups present at the appropriate position of the styrene substrate. The possibility of amino or hydroxy groups of the substrate to coordinate to a neighboring Rh center allows for a specific alignment of the olefin group facilitating the reaction with the active Rh carbene species of an adjacent Rh-porphyrin in the same pore. This situation is favored in the specific Kagomé topology of PCN-222 in contrast to PCN-224. The Rh–Rh distance between two neighboring centers is approximately 10 Å for PCN-222, which coincides with the length of an amino-functionalized styrene and the Rh-carbene, thus, increasing the *trans*-isomer formation.[28] The effect of topology on catalytic performance has also been highlighted by Hupp, Farha et al. for zinc-metalated porphyrin MOFs PCN-222, NU-902 and MOF-525 differing in their structure (Figure 8) and also the density of Lewis acidic zinc sites.[22] These MOFs were applied as catalysts in the acyl transfer reaction with different pyridylcarbinols (PC). It has been shown that orientation effects in the different MOF structures affect the preconcentration (influenced by the number of single porphyrin sites per volume) and alignment of the substrates (affected by the number of porphyrin pairs per volume of MOF) and thus, the initial reaction rates. The importance of substrate alignment in the different MOF topologies for increased catalytic activity has been elucidated by DFT calculations. Therefore, the orientation of the substrates which varies due to altered Zn-porphyrin locations is crucial, placing them in a suitable distance and orientation to enable the formation of the required transition state. With this study, the authors accentuated the impact of the density of catalytically active sites and their distribution over the framework facilitating beneficial secondary coordination effects for in-creased activity – combining the importance of substrate alignment, neighboring group effects, and network topology.

Conclusions and Outlook

Although still in its infancy and with a limited number of pertinent publications, the examples covered in this concept article outline the effects of confined reaction spaces and highlight the potential of exploiting these effects for catalysis. Moreover, these studies also indicate the challenging characterization of those effects which requires the application of several analytical techniques in combination with theoretical calculations and model simulations to elucidate various interactions or transition states present inside the material. However, even with detailed analysis, the exact elucidation – if the confinement effects are indeed the reason for the catalytic behavior – and the specific control of those parameters remains challenging. Especially, the introduction of functionalities in MOF catalysts like the porphyrin-based systems which intrinsically differ in topology might be beneficial for future studies of confinement effects. An understanding of the fundamental, underlying principles will pave the way for catalysis optimization and the control of activity and selectivity by designing sophisticated catalytic systems and desirable catalyst-substrate interactions inspired by enzyme catalysis. At this point we highlight the emerging power of data science, machine learning and artificial intelligence computational tools and concepts, which may boost the field in the future. Based on current knowledge, machine learning is already applicable for the optimization of synthesis procedures.[30] Although so far it has not been implemented in MOF catalysis, this will be of high importance in the future for the realization of catalyst design strategies.[31]
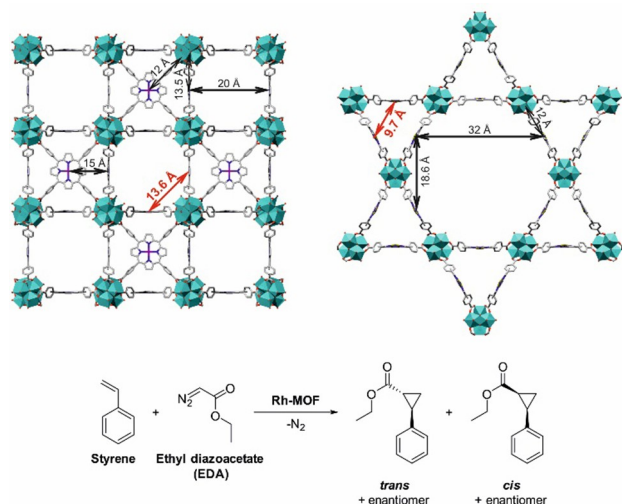
Conflict of Interest

The authors declare no conflict of interest.

Keywords: Artificial Enzymes · Confinement Effects · Heterogeneous Catalysis · Metal-organic Frameworks · Porous Materials

Figure 12. Top: Depiction of the two topologies of Rh-metalated PCN-224 (left) and PCN-222 (right) with the Rh–Rh site distances (bold arrows) in the framework necessary for simultaneous substrate fixation and activation. The shortest Rh–Rh distance is highlighted in red. Bottom: Reaction scheme of the cyclopropanation of styrene using a Rh-MOF (namely PCN-222 and PCN-224) as catalyst resulting in the formation of the *cis*- and *trans*-cyclopropane derivative. Reproduced from Ref. [28] with permission of the Royal Society of Chemistry.

[1] a) G. G. Hammes, *Biochemistry* **2002**, *41*, 8221–8228; b) G. G. Hammes in *Enzyme catalysis and regulation*, Academic Press, New York, **1982**, pp. 99–109.
[2] E. Kuah, S. Toh, J. Yee, Q. Ma, Z. Gao, *Chem. Eur. J.* **2016**, *22*, 8404–8430.

[3] a) S. M. J. Rogge, A. Bavykina, J. Hajek, H. Garcia, A. I. Olivos-Suarez, A. Sepúlveda-Escribano, A. Vimont, G. Clet, P. Bazin, F. Kapteijn, M. Daturi, E. V. Ramos-Fernandez, F. X. Llabrés i Xamena, V. van Speybroeck, J. Gascon, *Chem. Soc. Rev.* **2017**, *46*, 3134–3184; b) A. Dhakshinamoorthy, M. Opanasenko, J. Čejka, H. Garcia, *Catal. Sci. Technol.* **2013**, *3*, 2509–2540; c) D. Yang, B. C. Gates, *ACS Catal.* **2019**, *9*, 1779–1798; d) H.-C. Zhou, J. R. Long, O. M. Yaghi, *Chem. Rev.* **2012**, *112*, 673–674.

[4] A. Dhakshinamoorthy, Z. Li, H. Garcia, *Chem. Soc. Rev.* **2018**, *47*, 8134–8172.

[5] a) J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen, J. T. Hupp, *Chem. Soc. Rev.* **2009**, *38*, 1450–1459; b) Q. Yang, Q. Xu, H.-L. Jiang, *Chem. Soc. Rev.* **2017**, *46*, 4774–4808.

[6] Y.-B. Huang, J. Liang, X.-S. Wang, R. Cao, *Chem. Soc. Rev.* **2017**, *46*, 126–157.

[7] Z. Niu, W. Zhang, P. C. Lan, B. Aguila, S. Ma, *Angew. Chem. Int. Ed.* **2019**, *58*, 7420–7424.

[8] Z. Lin, Z.-M. Zhang, Y.-S. Chen, W. Lin, *Angew. Chem. Int. Ed.* **2016**, *55*, 13739–13743; *Angew. Chem.* **2016**, *128*, 13943–13947.

[9] X. Jia, W. Khan, Z. Wu, J. Choi, A. C. K. Yip, *Adv. Powder Technol.* **2019**, *30*, 467–484.

[10] T. Uemura, R. Kitaura, Y. Ohta, M. Nagaoka, S. Kitagawa, *Angew. Chem. Int. Ed.* **2006**, *45*, 4112–4116; *Angew. Chem.* **2006**, *118*, 4218–4222.

[11] T. Uemura, D. Hiramatsu, Y. Kubota, M. Takata, S. Kitagawa, *Angew. Chem. Int. Ed.* **2007**, *46*, 4987–4990; *Angew. Chem.* **2007**, *119*, 5075–5078.

[12] F. Gao, L. Zhang, C. Yu, X. Yan, S. Zhang, X. Li, *Macromol. Rapid Commun.* **2018**, *39*, 1800002.

[13] M. Zheng, Y. Liu, C. Wang, S. Liu, W. Lin, *Chem. Sci.* **2012**, *3*, 2623–2627.

[14] S. Nießing, C. Janiak, *Mol. Catal.* **2019**, *467*, 70–77.

[15] C. Kutzscher, G. Nickerl, I. Senkovska, V. Bon, S. Kaskel, *Chem. Mater.* **2016**, *28*, 2573–2580.

[16] K. D. Nguyen, C. Kutzscher, S. Ehrling, I. Senkovska, V. Bon, M. de Oliveira Jr., T. Gutmann, G. Buntkowsky, S. Kaskel, *J. Catal.* **2019**, *377*, 41–50.

[17] S. Nießing, C. Czekelius, C. Janiak, *Catal. Commun.* **2017**, *95*, 12–15.

[18] L. Liu, T.-Y. Zhou, S. G. Telfer, *J. Am. Chem. Soc.* **2017**, *139*, 13936–13943.

[19] D. J. Xiao, J. Oktawiec, P. J. Milner, J. R. Long, *J. Am. Chem. Soc.* **2016**, *138*, 14371–14379.

[20] C. Zhu, G. Yuan, X. Chen, Z. Yang, Y. Cui, *J. Am. Chem. Soc.* **2012**, *134*, 8058–8061.

[21] T. Zhang, Y. Shi, S. Zhang, C. Jia, C. He, C. Duan, *New J. Chem.* **2018**, *42*, 18448–18457.

[22] P. Deria, D. A. Gómez-Gualdrón, I. Hod, R. Q. Snurr, J. T. Hupp, O. K. Farha, *J. Am. Chem. Soc.* **2016**, *138*, 14449–14457.

[23] X. Gong, Y. Shu, Z. Jiang, L. Lu, X. Xu, C. Wang, H. Deng, *Angew. Chem. Int. Ed.* **2020**, *59*, 5326–5331.

[24] Y. Wang, H. Cui, Z.-W. Wei, H.-P. Wang, L. Zhang, C.-Y. Su, *Chem. Sci.* **2017**, *8*, 775–780.

[25] F. G. Cirujano, F. X. Llabrés i Xamena, A. Corma, *Dalton Trans.* **2012**, *41*, 4249–4254.

[26] A. Corma, M. Iglesias, F. X. Llabrés i Xamena, F. Sánchez, *Chem. Eur. J.* **2010**, *16*, 9789–9795.

[27] H.-H. Mautschke, F. Drache, I. Senkovska, S. Kaskel, F. X. Llabrés i Xamena, *Catal. Sci. Technol.* **2018**, *8*, 3610–3616.

[28] K. Epp, B. Bueken, B. J. Hofmann, M. Cokoja, K. Hemmer, D. de Vos, R. A. Fischer, *Catal. Sci. Technol.* **2019**, *9*, 6452–6459.

[29] V. L. Rechac, F. G. Cirujano, A. Corma, F. X. Llabrés i Xamena, *Eur. J. Inorg. Chem.* **2016**, *27*, 4512–4516.

[30] P. Chen, Z. Tang, Z. Zeng, X. Hu, L. Xiao, Y. Liu, X. Qian, C. Deng, R. Huang, J. Zhang, Y. Bi, R. Lin, Y. Zhou, H. Liao, D. Zhou, C. Wang, W. Lin, *Matter* **2020**, *2*, 1651–1666.

[31] T. Toyao, Z. Maeno, S. Takakusagi, T. Kamachi, I. Takigawa, K. Shimizu, *ACS Catal.* **2020**, *10*, 2260–2297.