Liu, L.; Corma Canós, A. (2021). Isolated metal atoms and clusters for alkane activation: translating knowledge from enzymatic and homogeneous to heterogeneous systems. Chem. 7(9):2347-2384. https://doi.org/10.1016/j.chempr.2021.04.001

Isolated Metal Atoms and Clusters for alkane activation: translating knowledge from enzymatic and homogeneous to heterogeneous systems

Lichen Liu[1,2] and Avelino Corma[1]*†

[1] *Instituto de Tecnología Química, Universitat Politècnica de València-Consejo Superior de Investigaciones Científicas (UPV-CSIC), Av. de los Naranjos s/n, Valencia 46022, Spain*

[2] *Department of Chemistry, Tsinghua University, Haidian District, Beijing 100084, China*

*Corresponding author. E-mail: acorma@itq.upv.es

†Lead contact

Summary

Activation of alkanes can be achieved with different types of catalysts, spanning over enzymes, homogeneous and heterogeneous metal catalysts. Though a tremendous amount of knowledge has been accumulated in the literature, the connections between different types of catalysts are rarely discussed due to the differences among the three catalysis fields in terms of catalyst structures, reaction conditions and catalytic performances. There are also similarities among the various systems in terms of the structural features of the active sites and reaction mechanisms. In this Review, we attempt to show the interconnections among the three catalysis fields regarding the nature of active sites and reaction mechanism for metal-catalysed alkane activation reactions. We will show the lessons obtained from well-defined enzymatic and molecular catalysts developed in bio- and homogeneous catalysis, and how can be translated into fundamental understanding and further developments of heterogeneous metal catalysts, for practical applications related to alkane activation.

Keywords: Alkane, C-H activation, Enzyme, Isolated metal atoms, Metal clusters

UN Sustainable Development Goals

SDG7: Affordable and clean energy

SDG12: Responsible consumption and production

1. Introduction

The conversion of alkanes, especially light alkanes (methane, ethane, propane and butane), into chemicals (such as olefins, aromatics, alcohols) and fuels have tremendous significance for chemical industry[1]. Among the numerous approaches for activation of alkane molecules, the use of a homogenous or heterogeneous metal catalyst or a combination of both is one of the most important routes[2-5]. The activation of the inert C-H and C-C bonds in alkane molecules and selective transformation of the intermediates into value-added products are also the key chemical problems in this field, which are strongly associated with fundamental understandings on the nature of the active sites and development of more efficient catalysts and catalytic processes[6].

Looking into the literature, the activation of alkanes has been intensively studied by chemists in bio-, homogeneous and heterogeneous catalytic systems, resulting in a tremendous accumulation of knowledge[7, 8]. However, the link between these three fields are not well established, which could be caused by the different reaction conditions (liquid-phase reaction vs. fix-bed gas-solid reactions, relatively low temperature vs. high temperature), distinct catalysts used (enzymes, molecular metal compounds vs. solids), and different reaction pathways[9].

From the point view of homogeneous catalysis, the mainstream works on metal-catalysed alkane conversion are to synthesize new molecular metal complexes and study the reaction mechanism with those well-defined molecular metal catalysts[10]. However, taking into account the catalyst cost, feasibility for scale-up, catalyst stability and other related practical problems, it is not always possible to use homogeneous catalysts for alkane conversion at the industrial level. Meanwhile, in the heterogeneous catalysis field, the majority of the research efforts are devoted to the development of solid catalysts and to study how the alkane molecules interact with the catalyst's surface as well as the structural evolution of the solid catalysts during the catalytic process[11, 12]. The intrinsic complexity of solid catalysts makes it very difficult to identify the exact nature of the active sites in the working catalyst under reaction conditions. The recent advances on subnanometric supported metal catalysts (containing isolated metal atoms and clusters with a few atoms with sizes below 1 nm) have made promising progress on the precise control of the structure of the metal centres at atomic and molecular levels[13, 14]. However, for some challenging reactions, such as selective oxidation of methane to methanol, the performances of currently reported catalysts are still far below the standards for large-scale industrial applications, though the reaction mechanism has been studied at the molecular level[15]. Certainly, more research efforts are required to improve the performance of current heterogeneous systems and to deepen the fundamental understanding on how the geometric and electronic structures of the metal species and their environment can influence the reactivity for reactions related to alkane activation.

In terms of the active sites, there are some similarities between the three fields if we are considering the use of isolated metal atoms or subnanometric metal clusters (with a few atoms) as the active sites for alkane activation reactions. For enzymes, the metal centres are surrounded by the protein scaffold, which assists the activation of the substrate molecule. For homogeneous catalysts, the metal centre is coordinated by the ligand, solvent or reactant. In these two fields, the metal centres show well-defined geometric and electronic structures. In the case of heterogeneous metal catalysts, the solid support serves as the "ligands" for the metal entities to modulate their geometric and electronic structures[16, 17]. Despite the solid support is much more rigid than the protein scaffold in biocatalysis and organic ligands in homogeneous molecular catalysts, the insights and knowledge accumulated with bio- and homogeneous catalysis should also be applied, or at least partially, to the studies with heterogeneous catalysis. Indeed, some examples are showing the common chemistry principles in the two different fields. For instance, binuclear/trinuclear Cu centres are proposed to be the active sites in methane monooxygenase (pMMO), which can catalyse the selective oxidation of methane to methanol under ambient conditions[18]. Inspired by nature, chemists have prepared binuclear and trinuclear Cu complexes for oxidation of methane and other alkanes[19, 20]. Interestingly, in heterogeneous systems, Cu clusters with two or three atoms confined in zeolites have also been reported to be the active sites for oxidation of methane to methanol. We would like to show the interconnections among the three fields on the active sites and reaction mechanisms for alkane activation, by highlighting the representative works done with enzymatic and homogeneous metal catalysts and comparing the similarity and dissimilarity with the solid catalysts and their chemical behaviour.

2. Learning from the enzymes

As mentioned before, natural enzymes can transform a broad range of alkanes (C1 to C40 and even longer) into oxygenates and other products to sustain microbes[21]. In this section, we will briefly summarize and discuss the general mechanism of enzymatic oxidation of alkanes and the structure of the active sites.

2.1 Monooxygenase for alkane oxidation

Taking the monooxygenase as an example, two types of enzymes have been widely founded in microbes for alkane oxidation reaction: the particulate methane monooxygenase (pMMO) as a membrane protein, and the soluble methane monooxygenase (sMMO). From a mechanistic point of view, in the presence of cofactor such as NADPH (nicotinamide adenine dinucleotide phosphate reduced), both enzymes can catalyse the aerobic oxidation of alkanes using binuclear metal sites. Though the metal component (Cu for pMMO and Fe for sMMO) and the protein scaffold conformation is different in the two type of enzymes, the mechanism for O_2 activation is similar, involving the formation of peroxide intermediate and subsequent cleavage of O-O bond, as illustrated in **Figure 1A**[22]. The C-H activation is believed to be a critical step for alkane oxidation by enzymes, as confirmed by kinetic isotopic effect (KIE) on oxidation of methane[23]. Besides, the oxidation states of the metal centre can vary between +4, +3 and +2 during the catalytic cycle, as observed with Fe-sMMO[24] (see **Figure 1A**).

One important feature of enzymatic catalysis is its very high chemoselectivity for transforming a specific reactant to target product, which is also reflected in the enzyme-catalysed alkane oxidation reactions. Increasing the chain length of the alkane substrate from methane to C2+ alkanes will cause a clear decrease of reactivity[25]. For instance, by introduction of an artificial mutation to enlarge the "pocket" of the scaffold, the substrate scope can be extended from methane to larger molecules such as ethane and propane. Interestingly, when switching the substrate from methane to propane, the KIE studies indicate that the bonding of substrate on the active sites becomes a more rate-limiting step rather than the C-H activation[26].

By introduction of additional functional components to the monooxygenase, the alkane hydroxylase systems can convert longer alkanes (e.g. C5-C12 alkanes) into the corresponding alcohols, indicating the importance of the surrounding environment of the metal active sites in enzymes[27]. The synergy of different functional components in terms of mass transfer of the intermediates and electron transport pathways is critical for achieving the above transformation. Tandem transformations of alkanes have also been reported with homogeneous and heterogeneous systems (as will be discussed later in this Review). However, the organization of different functional components is not as ordered as that in enzymatic system, which could be one of the reason accounting for its unique selectivity and high efficiency.

2.2 Cytochrome P450 for alkane oxidation

Changing the nuclearity of the abovementioned binuclear sites into mononuclear sites gives another type of enzymes (cytochrome P450), which are also capable of oxidizing alkanes. Notably, the Fe centre is stabilized in the porphyrin ring of cytochrome P450 while the binuclear Fe centre is coordinated by the scaffold of the peptide chain in monooxygenase. The basic catalytic redox cycle shares common principles for both cytochrome P450 and monooxygenase, which could be caused by the similarity between the electronic feature of the Fe centres in the two types of enzymes[28, 29]. Noted that, the activation of O_2 on sMMO and cytochrome P450 shares a similar mechanism, in which superoxide and peroxide species are the intermediates (see **Figure 1B**)[30]. Notably, the activation of O_2 is facilitated by hydrogen bonding between the secondary coordination sphere and the reactant[31]. Though the alkane oxidation is an exothermic reaction, the use of a cofactor as reduction agent for regeneration of the oxidized metal centres into reduced state is required. The flexible transformation between the oxidized and reduced state of the metal centre is considered to the key for the enzyme-catalysed alkane oxidation reaction.

The change of enzyme's catalytic behaviour can be caused by a single mutation in its structure, as demonstrated by switching a histidine residue to a phenylalanine in the P450 CYP101B1 enzyme. This mutation makes the active site more hydrophobic, therefore improving its activity for catalysing the oxidation of cycloalkanes to corresponding alcohols[32]. If more sites are changed, the scaffold surrounding the active centre will be modified accordingly, leading to distinct catalytic properties. For instance, the reaction rate and regioselectivity in the reaction of oxidation of cycloalkanes into corresponding alcohols by two P450 enzymes are quite different, though they share a common electron transfer system that performing the catalytic reactions[33]. The difference is caused by the geometric shape of the scaffold surrounding the active centres, which further influenced the binding orientation of the substrate molecules. Another successful showcase is the engineering of a medium-chain (C12–C18) fatty acid monooxygenase into an alkane hydroxylase suitable for alkanes of medium chain length (C3–C8) by introducing 11 mutations in the original enzyme (from the cytochrome P450 enzyme family)[34]. Remarkably, the evolved enzyme can directly catalyse the conversion of alkanes to alcohols without the assistance of other proteins while the natural alkane hydroxylase is a complex of several functional enzymes. The critical role of the scaffold surrounding the active sites inspire us to prepare solid catalysts through an "ab initio" strategy based on mimicking the transition states of the target reaction, which will be discussed later in this Review.

As mentioned before, the oxidation of alkane requires the energy input from co-factors such as NADPH. For oxidation of linear alkane into terminal alcohol catalysed by soluble cytochrome P450 relays on the electron and proton transfer by Fdx ferredoxin and FdxR ferredoxin reductase[35]. The intermolecular energy transfer system in enzymes is quite unique because of the high efficiency and high accuracy. This feature is even more amazing in natural enzymes involved in photosynthesis systems, which is superior to the energy transfer systems constructed by either molecular complexes or solid materials[36]. Indeed, this is a direction in which researchers are trying to imitate artificial systems to achieve high efficiency in chemical transformation and energy conversion[37].

In conclusion, the enzymatic oxidation catalysts contain binuclear and mononuclear metallic (for instance Cu and Fe) centres stabilized by proteomic or porphyritic groups that allow reversible changes in the oxidation state of the metal species. This structural feature together with the scaffold, that helps to activate or stabilize adsorbed reactants or transition states and to facilitate the electron transfer across the enzyme, are the two key factors to explain enzymatic activity and selectivity.

2.3 Anaerobic oxidation of alkanes

Besides the aerobic oxidation of alkanes, some microorganisms can convert alkanes into chemicals under anaerobic conditions[38]. For instance, over 3×10^8 tons of methane is estimated to be removed by anaerobic oxidation in ocean by microbes[39]. There are several types of mechanisms reported for anaerobic oxidation of methane based on Ni-containing enzymes, by employing sulfate, nitrite or sulphide as the oxidant. The substrate can also be extended to long-chain alkanes (C3-C16), though the reaction mechanism at the molecular level is not fully revealed[40]. The capabilities of microbes for utilization of alkanes depend on their environment, which is the driving force to gain desired capabilities through evolution.

2.4 Directed evolution of enzymes

The concept of “directed evolution” is widely applied in the biocatalysis field, which can accelerate the discovery of more efficient enzymes for targeted reactions[41, 42]. The “directed evolution” strategy relies on the iterative mutation of the enzymes, resulting in an efficient optimization of the enzyme’s performance for chemo-, stereo- and regioselectivity[43]. The mutation can occur either at the binding pocket or at a remote site of the binding pocket[44]. For an enzyme with multiple mutations, the cooperative effects among different mutated sites within the three-dimensional protein structure can be understood by combining experimental and theoretical studies and the design of new enzymes can be guided by machine learning[45].

It can be expected that, starting with a concept and carrying out the preparation and reactivity test of heterogeneous catalysts with high-throughput experimental setups, the discovery of a new catalyst could also be dramatically shorten[46]. However, the successful implementation of “directed evolution” for heterogeneous catalysis will be more difficult than that in biocatalysis because of the complexity of solid catalysts, which makes it very challenging to describe the structural features of the solid catalysts by a group of parameters.

3. Learning from homogeneous systems

Activation and selective transformation of alkanes have been a long-standing field in homogeneous catalysis, in which numerous molecular metal complexes have been developed for various purposes[47]. Compared to the heterogeneous systems that will be discussed later, the homogeneous systems have superior advantages in constructing C-X bonding (e.g. C-C, C-N, C-O, C-B, etc.) through metal-catalysed C-H activation[48]. The core concept in the homogeneous systems is to modify the electronic structure of the metal centres by ligands and therefore influence the reactivity and selectivity for desired reactions with alkanes[49]. In most of the cases, the homogeneous catalytic reactions occur in an organic solvent at higher temperatures than enzyme-catalysed alkane activation reactions, which usually offers higher reaction rates and wider scope of reactions.

3.1 Metal complexes for methane oxidation

Inspired by natural enzymes, numerous Cu complexes with two or more Cu atoms have been developed for oxidation of methane to methanol with a mixture of O_2 and H_2O_2 [19, 20]. The role of H_2O_2 is to regenerate the oxidized trinuclear Cu complex ($Cu^{I}Cu^{II}Cu^{II}$) into its reduced state ($Cu^{I}Cu^{I}Cu^{I}$), which is similar to the role of the co-factor in the enzyme-catalysed methane oxidation reaction. This model catalyst has been employed to clarify the structure of the active sites in pMMO enzyme, whose structure and catalytic mechanism is still not fully consented[50-54]. The results are consistent with the biochemistry of pMMO, inferring a plausible presence of trinuclear Cu species as active sites in pMMO. Among the related literature, the binuclear copper model is widely used while the mononuclear copper model is supported by the evidence obtained from electron paramagnetic resonance and mass spectrometry in recent works[53, 54]. There are other works on molecular Cu complexes for selective oxidation reactions (such as ortho-hydroxylation-defluorination of 2-fluorophenolates), showing the tunable reactivity by modulating the ligands and Cu nuclearity[49, 55]. In particular, it has been shown that tetranuclear Cu complex is more active than binuclear and trinuclear Cu complexes for oxidation of alkanes with H_2O_2[44]. Those results/insights are helpful to understand how the coordination configuration and composition of the metal centres can affect the catalytic properties.

Oxidation of methane to methanol by molecular Pt complex in concentrated or fuming sulfuric acid can achieve high single-pass yield (72%) for conversion of methane to methyl bisulfate, which can be further converted to methanol through hydrolysis. In this system, the mononuclear Pt complex is the active species while H_2SO_4/SO_3 act as transfer oxidants[56, 57]. By adjusting the ligand of Pt in the complex and optimizing the reaction medium, a high reaction rate can be reached[58]. Formation a Pt(II) intermediate is proposed as the active species for C-H activation[59], and an electrophilic electron transfer mechanism between the Pt(II) and Pt(IV) intermediate complex is proposed to clarify the missing piece of the whole catalytic mechanism. It will be interesting to consider the abovementioned inter-molecular charge transfer in the heterogeneous analogue of the molecular Pt complex, which consists of isolated Pt atoms on N-doped carbon support[60]. It could be the metal-support interaction or the interaction between neighbouring Pt atoms that participate in the process to maintain the Pt(II) species. It should be noted that inter-molecular charge transfer mechanism as well as structural evolution of molecular metal complexes is commonly observed in homogeneous metal catalysts as examples of the synergistic effect of multiple active sites, while it is rarely observed in enzymes[61]. Of course, the mechanisms for selective oxidation of alkanes by different metal complexes could be more complicated than the above-mentioned aspects, for which the intrinsic electronic structure of the metal elements, the secondary coordination environment of the metal species and the reaction intermediates should be considered[62]. Interestingly, the formation of binuclear Pd(III) complexes are found as active species for Pd-catalysed activation of methane in H_2SO_4/SO_3 medium, indicating the importance of the formation of metal-metal bonding and the difference in the oxidation states of different metal elements[63].

For the abovementioned two reactions for methane valorisation, the one-electron transfer process occurs within the oxidation of methane to methanol with Cu complexes, as observed within the enzymatic systems. While in the case of Pt-catalysed oxidation of methane to methyl bisulfate, a two-electron transfer process is involved during the transformation between Pt(II) and Pt(IV). Such difference could be caused by the intrinsic electronic properties of the metal centres (first-row transition metals vs. noble metals) and the ability of the oxidant used in the reaction (O_2 vs. H_2SO_4/SO_3).

3.2 Alkane metathesis

Another interesting application of molecular catalysts for alkane activation is alkane metathesis, which involves the coupling of alkane dehydrogenation to alkene and alkene metathesis reactions in a tandem process for converting light alkanes into heavier ones, as described in **Figure 2A**[65]. Alkane metathesis has not been reported with natural enzymes, which could be related to the absence of natural enzymes for olefin metathesis. Using Ir complex as the catalyst for alkane dehydrogenation reaction, alkanes can be converted into terminal alkenes and further transformed into long-chain olefins through olefin metathesis on either heterogeneous (e.g. Re/Al_2O_3) or homogeneous catalyst (molecular Mo catalyst) (Ref. [66, 67]). The initial dehydrogenation of alkane into alkene intermediate is proposed to proceed via a classic σ-bond metathesis ([2σ + 2σ] cycloaddition reaction to generate metal-alkyl intermediate) and subsequent β-elimination[68, 69]. It should be mentioned that the isomerization of terminal alkene to internal alkene via a π-Allylic mechanism may also occur[70]. These olefins with longer carbon chains can be hydrogenated into alkanes, or even further react by olefin metathesis with other intermediates, resulting in a broad range of alkene and alkane products (see **Figure 2C-D**).

The alkane metathesis can also be catalysed by a single type of metal species, i.e. organometallic complexes (such as tungsten, tantalum and zirconium complexes) grafted on solid carriers (as displayed in **Figure 2B**), through a similar process as the abovementioned tandem process[64]. The reactivity of different isolated metal species for alkane metathesis could be influenced by the reactivity of the alkyl alkylidene intermediates[71]. Though the isolated metal species (such as tantalum hydride complexes) need to be grafted on solid carriers, the physicochemical properties of the support have limited impacts on the catalytic performance of supported tantalum hydride species, which is quite different to the marked support-dependent behaviour observed with heterogeneous metal catalysts[72]. Such distinction could be caused by the lower degree of interaction between the grafted organometallic complexes and the solid carrier compared to the metal-support interaction in conventional supported metal catalysts.

3.3 Role of coordination configuration of the metal centres

The abundance of C-H bonds in alkane molecules and the high stability of the C-H bonds make the C-H activation as a key scientific issue for alkane activation. One important lesson we can learn from homogeneous catalysis is the numerous strategies developed for C(sp^3)-H activation reactions, including ligand-assisted C-H activation[73], hydrogen atom transfer[74] and radical-involved C-H activation[75]. In particular, the remote activation of C(sp^3)-H bond achieved with a transient directing group has similarity to the enzymatic C-H activation process[76], in which the scaffold surrounding the metal centre also participates in the substrate recognition and activation process (see **Figure 3**).

In a similar manner as observed with the "pocket effect" in enzymatic catalysis, the vacant sites in molecular metal complexes can influence the adsorption and activation of the substrate molecule, as revealed by the low-temperature NMR spectroscopic and X-ray crystallographic studies[77, 78]. Captured by ultrafast spectroscopy, metal complexes with under-coordinated configuration can easily react with alkane molecule[79]. When tuning the ligands coordinated to the metal centres, the reactivity of the organometallic complex towards the activation of alkane can be improved, as demonstrated with the comparison between [Re(Cp)(CO)(PF_3)] and [Re(Cp)$(CO)_2$] for the interaction with n-pentane[80].

In addition to the geometric factors, the electronic properties of the metal centres can also be influenced in a remarkable manner by the ligands. For instance, it is demonstrated that the reactivity of Pd-catalysed C-H activation reaction can be greatly improved by playing with the functional groups in the quinone ligands[81]. The complex electronic properties of transition metal elements cause difficulties to rationalize the relationships between electronic structure and reactivity in a simple way because both spin and oxidation state should be considered when carrying out theoretical studies[82].

3.4 Gas-phase model catalyst for alkane activation

Gas-phase metal atoms or clusters generated by physical methods are ideal model systems to understand the elementary steps of the activation of alkane molecules in a detailed way[83]. The related works have clearly revealed that, for a single atom or a single metal cluster in a specific reaction, changes in atomicity (number of the atoms in the cluster), charge or geometric structure can lead to marked changes in its reactivity accordingly[84]. Such structure-dependent reactivity is exhibited in a more remarkable way than the homogeneous metal complexes, which should be related to the simple, but sensible, structural feature of the gas-phase metal species. Moreover, thanks to their well-defined structures, the reactivity of gas-phase model systems can be correlated with the orbital structures of the active sites[85, 86]. For instance, by infrared spectroscopy and first-principles calculations, the reaction mechanism of CH_4 activation on Au clusters has been revealed, which involves the formation of hydrido methyl complexes, H-Au_x(I)-CH_3 as the intermediates[87]. More related works show that the activation of methane on gas-phase metal clusters can lead to other reaction pathways and various products, depending on the chemical components of the metal clusters[88]. Obviously, gas-phase metal atoms and clusters are quite different to supported isolated atoms and clusters on solid carriers. Nevertheless, we believe the detailed mechanistic information acquired in studies with gas-phase metal species can provide insightful clues on the reaction mechanisms of heterogeneous metal catalysts.

4. Alkane activation with supported isolated atoms and clusters

Alkane activation with supported metal catalysts has also been intensively studied in the heterogeneous catalysis community, as reflected in a large number of publications for various types of reactions. Notably, most of the reactions involved in alkane activation processes are structure-sensitive reactions, meaning that the catalytic properties of the metal species are related to the particle size and their coordination environment[89]. Such effects have been firstly studied with single-crystal surface and supported metal catalysts based on nanoparticles[90, 91]. Nevertheless, it is quite likely that catalysts developed in early works already consisted of isolated atoms or clusters smaller than 1 nm, which were not well characterized due to limitations with the existing techniques[92]. As stated in the **Introduction** section, we are going to focus on the recent progress achieved with subnanometric metal catalysts (i.e. isolated metal atoms and clusters with a few atoms) and we will attempt to extract the insights on the structure-reactivity correlation on those works.

4.1 Methane activation

As one of the most intensively studied reactions for alkane activation, methane valorisation with supported isolated metal atoms and clusters have been reported with numerous types of materials (as summarized in **Figure 4**), which can be referred to some related reviews[1, 5, 16, 93]. Herein, we would like to mention some representative works and compare them in terms of the reaction mechanism and structure of the active sites.

By the non-oxidative routes, it usually requires very high temperatures to activate the C-H bond in methane and subsequently transform it into value-added products. For instance, using isolated Fe atoms bonded to C and Si atoms on silica support as the catalyst, methane can be directly converted into ethylene, aromatics and H_2 at very high temperature (1223-1363 K)[94]. Mechanistic studies indicate that radicals ($\bullet CH_3$) are formed in the gas phase, which further form C-C bonds. Using isolated Pt atoms supported on CeO_2 as the catalyst, methane can be directly converted into ethylene with high selectivity (>75% at 950 ^oC)[95]. Considering the wide scope of currently available supported single-atom catalysts reported in the literature, it will be interesting to study how the metal element and support perform in the direct conversion of methane[13]. Certainly, considering the harsh conditions employed for this reaction, it is also crucial to study the stability of those single-atom species during the catalytic processes.

When the active species are confined in porous materials, e.g. Mo-zeolite catalyst, the conversion of methane to benzene can be readily achieved at 700 ^oC though a fast deactivation due to coke cannot be avoided in reported works[96]. Both theoretical and experimental studies suggest that Mo clusters (probably in the form of Mo_xC_y, with 2-4 Mo atoms) are the active sites for methane activation and subsequently form intermediates (e.g. ethylene) and aromatic products (benzene and naphthalene) inside the 10 member-ring micropores[97, 98]. The microporous environment is critical for stabilizing the subnanometric Mo species and the formation of aromatics, which makes this system different to the enzymatic and homogeneous systems.

In the presence of O_2, the activation of methane is thermodynamically easier, though a high energy input is still necessary. For instance, subnanometric Rh clusters confined in zeolites are selective for partial oxidation of methane to CO and H_2 at above 450-600 ^oC[99]. Switching the continuous reaction into stepwise chemical looping, methane can be converted into methanol with Cu-zeolite and Cu-MOF samples at 150-450 ^oC, though the productivity is quite low[15, 100]. The anaerobic oxidation of methane with H_2O can also be achieved with Cu-zeolite materials, showing a similar concept as the anaerobic oxidation of methane process in nature[101]. Interestingly, the active sites in the majority of reactions related to methane activation are composed of isolated metal atoms or binuclear metal species as observed in enzymes or most molecular metal complexes, with a few other reports on larger clusters such as trinuclear Cu clusters[102, 103]. Though theoretical studies have clarified the correlation between the electronic structure of the metal species and their capability for C-H activation[104], other elementary steps such as the desorption of methoxy species in the presence of H_2O could also play a critical role[105]. Nevertheless, in the Cu-zeolite materials prepared via impregnation or ion-exchange method, a considerable portion of the Cu species exist as nanoparticles (>1 nm), and their role in the oxidation of methane is not clarified[106]. Thus, improving the purity of desired Cu species (either in the form of isolated Cu or Cu clusters) will be crucial for the fundamental understanding and practical application[107].

If the methane activation is processed in the presence of CO, acetic acid is obtained as the product of C-C coupling reaction between the $*CH_3$ intermediate and CO, which are both bonded to the isolated Rh sites dispersed on metal oxide or zeolites[108, 109]. Similar to the counterpart industrial process (Monsanto process) for production of acetic acid from CO and methanol[110], which relies on the homogeneous Rh complex as the catalyst together with iodide promotor, the C-C coupling step between CO and $*CH_3$ intermediate occurs on the supported isolated Rh sites, inferring a partially shared mechanism between the two processes. If so, the optimization experiences accumulated in the industrial process can be translated to the direct oxidative carbonylation of methane for further development.

As can be seen in the literature, tremendous efforts have been devoted into the direct conversion of methane into chemicals and fuels, there is still a large gap to cross for large-scale applications[111], though the oxidative coupling of methane into ethane and ethylene has been tested in pilot plant reactors for years[112]. One may argue that the current catalysts are not optimized and the reaction pathways are not fully explored, but the fundamental physicochemical characteristics of the methane molecule could be the intrinsic barrier that limits the performance of heterogeneous catalysts under current reaction conditions. Nevertheless, the future landscape of the global energy supply market also has decisive influence on the utilization of methane for producing fuels and chemicals. From the point view of fundamental research, it is of much interest to develop new catalysts and to understand the reaction mechanism at atomic and molecular level. But to make a breakthrough in this direction, it probably requires a new research paradigm based on new reaction pathways to lower the activation barrier or changing the conventional thermal catalysis into new forms such as photocatalytic/electrocatalytic/photoelectrocatalytic methane activation, as will be discussed later in this Review.

4.2 Alkane oxidation

Gas-phase Oxidation of alkanes into oxygenate products or olefins through oxidative dehydrogenation are well-established processes, usually carried out with metal oxide catalysts[113]. Traditionally, metal oxides are considered to be different catalytic materials compared to supported metal particles. However, taking the widely used polyoxometalates as an example, their Keggin-type structure can also be considered as isolated sites for selective oxidation of alkanes into aldehydes or acids[114, 115]. In the case of supported metal oxides, the catalytic performance is also related to the size of the domain. For instance, vanadium dimers were proposed to be the active species for oxidative dehydrogenation of propane to propylene, instead of isolated vanadium species or vanadium oxide particles[116, 117]. If this knowledge can be translated from supported vanadium catalysts to polyoxometalate catalysts, it will be quite interesting to study the catalytic performance of polyoxometalate clusters (~1 nm or even smaller) confined in microporous or mesoporous supports for oxidation of alkanes. Those materials comprising isolated Keggin-type structures may lead to distinct reactivity compared to bulk polyoxometalate materials.

In terms of oxidation of liquid alkanes, it usually follows a radical-involved mechanism and the role of the metal catalyst is to produce oxygen radicals to initiate the chain reaction. In this context, the difference among different catalysts is their efficiency to generate radicals and sustain the chain reaction[118]. For instance, subnanometric Au clusters stabilized in MWW zeolite have been reported as more efficient species than Au nanoparticles to initialize the radical oxidation of cyclohexane into cyclohexanone and cyclohexanol[119]. In another example, isolated binuclear Fe species confined in zeolites show promising activity for oxidation of alkanes (also for functionalization of aromatics, such as the oxidation of benzene to phenol) into oxygenates when using peroxides or N_2O as oxidant[120]. The introduction of Cu into Fe-zeolite catalyst was found to suppress the over-oxidation of methanol into formic acid and CO_2 for selective oxidation of methane to methanol. Considering the cost of H_2O_2, it is more favourable to carry out the selective oxidation of long-chain alkanes by H_2O_2 into oxygenates as achieved with enzymes[121] or to use a small amount of H_2O_2 as an initiator for oxidation of alkanes with O_2[122].

Using H_2O_2 as the oxidant, oxidation of alkanes has been explored with homogeneous metal complexes. For instance, the Fe-catalysed oxidation of cyclohexane to cyclohexanone and cyclohexanol also follows a radical-type mechanism, being similar to the heterogeneous systems[123]. Such a feature makes it difficult to control the product distributions for alkane oxidation reactions by homogeneous metal catalysts. Nevertheless, one major advantage of homogeneous Fe catalysts for alkane oxidation reaction is exhibited in the stereospecific oxidation on the $C(sp^3)$-H bonds, which is based on the development of structurally rigid bipyrrolidine-based Fe complex as the catalyst[124]. This work indicates that the key to achieve highly specific reactivity for alkane activation reaction is to construct the active site with suitable geometric structure, which is a great challenge for heterogeneous systems.

Besides O_2, other oxidants such as CO_2, can also react with alkanes to give reforming products. One of the most intensively studied reactions is the dry reforming of CH_4 with CO_2 with supported metal nanoparticles (such as Rh, Ni and Ru). Recent works show that isolated metal species and metal clusters can be highly active catalysts for this reaction, being superior to conventional nanoparticulate catalysts[125-127]. Replacing methane with ethane or propane, the reforming reaction between alkane and CO_2 results in the formation of corresponding olefins. Mechanistic studies on supported bimetallic nanoparticles suggest that metal-oxide interfaces are the active sites and it is possible to modulate the selectivity of ethane reforming with CO_2 to syngas or ethylene via tuning the catalyst's chemical composition[128]. Notably, C3 oxygenates can be obtained when employing supported RhCo bimetallic nanoparticles for the reforming of ethane with CO_2 through the C-C coupling reaction between ethylene and CO (by-product in the reforming reaction)[129]. The abovementioned mechanistic studies clearly show the involvement of multiple sites in the reforming reaction between CO_2 and alkanes, and these works infer the potential of developing heterogeneous metal catalysts based on subnanometric metal clusters, which may show different catalytic behaviour to conventional nanoparticulate catalysts.

The cleavage or formation of saturated C-C bonds in long carbon chains (such as fatty acids) can be achieved by mutated cytochrome P450[130]. Such transformation involves the oxidation of two neighbouring C-H into C-OH bonds and a subsequent C-C cleavage, resulting in the formation of two aldehyde molecules. By homogeneous metal complexes, the oxidative C-C cleavage of alkane molecules is also feasible. In the case of heterogeneous metal catalysts, the selective cleavage of saturated C-C bonds in alkane molecules is more challenging due to the over-oxidation of the primary products. To improve the chemoselectivity, one strategy is to take advantage of the shape-selective properties of microporous materials to modulate the accessibility of the reactant, as demonstrated with the oxidation of hexane to adipic acid with CuOx clusters encapsulated in SAPO-34 zeolite nanosheets[131]. The shape-selective property of two-dimensional SAPO-34 zeolite suppresses the C-C cleavage of C-C bonds in adipic acid, therefore lowering the formation of CO_2 by-product.

4.3 Alkane hydrogenolysis and hydroisomerization

Selective ring-opening of cycloalkanes through hydrogenolysis is an important catalytic route to improve the fuel's quality[133]. Mechanistic studies indicate the size of the metal particles has significant regioselectivity for C-C cleavage in this reaction[134]. Compared to large Ir nanoparticles, Ir clusters of ~0.7 nm supported on amorphous silica can give higher selectivity to ring-opening and branched products for the hydrogenolysis of substituted cyclohexane. Prepared by conventional ion-exchange method, small Ir nanoparticles (~1 nm) supported on mesoporous Beta zeolite have already shown remarkable performance for selective ring opening of decalin[135]. In a recent work, it is shown that subnanometric Ir clusters of 0.5-0.7 nm are the optimized species for hydrogenolysis of alkanes in comparison with smaller Ir clusters and large Ir nanoparticles (see **Figure 5**)[132]. If the size of the Ir clusters can be precisely controlled in the subnanometric regime, we expect a further enhanced reactivity of the Ir-Beta catalyst for ring-opening reactions of alkanes.

In the presence of acid sites, linear alkanes can be converted into branched alkanes through hydroisomerization, which results from the synergistic effect of the metal and acid sites[136]. In the scenario of homogeneous catalysis, a molecular acid compound is required to assist the transformation, and it is believed that the acid co-catalyst is working together with the metal complex by forming a coordination complex as intermediate to achieve the multi-step elementary reactions. However, in a heterogeneous system, it is found that the intimacy between the metal and acid sites does not follow the rule of "the closer, the better"[137]. There is an optimized distance between the two functional sites to avoid the undesired hydrogenolysis of C-C bonds[138], though it requires more work to address such effects in a more quantitative way.

Notably, in the above-mentioned works related to metal-zeolite materials, a considerable amount of subnanometric metal clusters is present inside the zeolites, though a broad range of size distribution is observed. We expect that new findings can be obtained if the catalytic studies can be done with catalysts comprising narrow size distribution of metal species and finer structural characterizations to establish the structure-reactivity correlation[139].

As mentioned before, the cleavage of aliphatic C-C bonds in nature can be realized by oxidative reactions instead of hydrogenolysis reaction. In terms of homogeneous systems, the cleavage of C-C bonds via hydrogenolysis is also rarely reported. One possible explanation can be the high activation energy required for breaking C-C bonds through the hydrogenolysis pathway by natural enzymes or homogeneous metal complexes. According to the above discussion and the reaction mechanism for hydrogenolysis reaction, it is inferred that supported metal clusters can show their superior activity than homogeneous complex and natural enzymes because of the participation of multiple metal atoms in the metal clusters for simultaneous activation of H_2 and C-C bond in the alkane molecule[64, 140].

4.4 Alkane dehydrogenation

Direct dehydrogenation of alkanes into corresponding olefins is an efficient way to utilize the shale gas resource. Indeed, dehydrogenation of light alkanes has been commercialized in several industrial processes based on either supported Pt or CrOx catalysts[142]. In terms of the Pt catalyst, which gives much higher specific activity than the CrOx catalyst, fast deactivation and the use of a large quantity of Pt are the remaining issues to be further improved. The endothermic nature of the alkane dehydrogenation reaction requires high energy input. Therefore, materials with high structural stability against sintering during high-temperature oxidation-reduction treatments are desired. Imposing constraints on isolated metal atoms or metal clusters by confining them in microporous materials can be a promising solution to the above challenges since C-H activation, the rate-limiting step is more favourable on smaller metal particles[143]. It has been demonstrated that subnanometric Pt clusters can be stabilized in the pores of microporous zeolites, which can deliver enhanced activity and stability than conventional supported Pt nanoparticles[144]. Such effects are more profound when the Pt clusters are regioselectively located in the 10 member-ring (10 MR) sinusoidal channels of pure-silica MFI zeolite structure, as presented in **Figure 6** (Ref.[141]). The Pt and PtSn bimetallic clusters confined in the channels show superior activity and stability than the Pt and PtSn nanoparticles.

The reaction mechanism of dehydrogenation of light alkanes on metal nanoparticles (>1 nm) is usually believed to follow the reverse Horiuti−Polanyi Mechanism, involving the formation of alkyl intermediate through C-H activation and a subsequent β-elimination. Taking the dehydrogenation of propane to propylene as an example, according to a microkinetic study, CH_3-*CH-CH_3 (the "*" notation refers to the carbon atom adsorbed on Pt site) is formed on Pt(111) surface with well-coordinated Pt atoms as primary intermediate while *CH_2-*C-CH_3 is formed on Pt(211) surface with under-coordinated Pt atoms due to the removal of two β-H atoms and one α-H[145]. This study inters that the reaction mechanism on subnanometric Pt clusters could be largely different to that on Pt nanoparticles, which deserves to be experimentally investigated in detail.

By substituting Pt by a more oxyphilic metal (such as In and Ga), isolated metal atoms can be preserved in the extra-framework positions within zeolites even after high-temperature reduction treatment (>500 ^{o}C) and are able to active light alkanes[146, 147]. For instance, isolated indium atoms stabilized CHA zeolite can transform into isolated indium hydride species and show high activity and stability for dehydrogenation of ethane to ethylene[147]. The appearance of $[InH_2]^+$ intermediate is supported by several spectroscopic characterization techniques and such active species are similar to those observed with metal complexes in homogeneous dehydrogenation of alkanes[148]. Compared to other metals such as Zn and Ga, which are also present as isolated metal hydride species within CHA zeolite, the indium hydride species are initially less active but show a much lower deactivation rate during the ethane dehydrogenation reaction. Considering the deactivation mechanism, the faster deactivation rates observed with isolated Zn and Ga species could be associated with their stronger acidity[149]. Furthermore, the reactivity of extra-framework species can be modulated by tuning the chemical composition of the zeolite framework (such as the Si/Al ratio, the doping of heteroatoms) or the location of the extra-framework within the zeolite structure, being similar to the concept for modifying the ligands of homogeneous metal complexes[150].

If comparing the metal-zeolite catalysts reported for alkane dehydrogenation reaction, one will notice that noble metals (such as Pt and Pd) exist as small clusters or nanoparticles within zeolite structure[141,151,152] while non-noble metals (such as Ga, Sn, In, Fe) mainly exist as isolated metal atoms under reduction conditions[147,153]. This leads to one question: how are the performances of non-noble metal clusters compared to their single-atom counterparts?

In principle, isolated metal atoms or clusters confined in zeolites can also be applied to dehydrogenation of long-chain alkanes (i.e. middle distillate fractions, C9-C14), which can be operated at a relatively lower temperature (450-500 ^{o}C)[154]. Future efforts in this direction can be made to extend this concept to other pure-silica zeolites to match the size of various reactants and study the influence of the location of subnanometric metal species on the catalytic performance.

Despite the well-established industrial processes for dehydrogenation of short alkanes, organometallic Ir complexes can proceed with the reactions under milder conditions to avoid thermal cracking of C-C bonds[155]. The reaction mechanism on homogeneous metal complexes follows a similar process as the heterogeneous single-site metal catalysts, which involves the activation of C-H bonds and formation of metal-alkyl intermediates. Indeed, by supporting those mononuclear Ir complexes on a solid carrier, it is possible to perform the dehydrogenation of n-butane into butenes under continuous flow conditions at 300 °C.[156] Though the stability of such system is lower than the solid catalysts, it is worthy to dedicate further efforts on studying the deactivation mechanism and improving the reactivity and stability. Considering the numerous examples of the application of metal clusters for alkane dehydrogenation, it is interesting to develop multinuclear metal complexes and to compare their behaviour with mononuclear metal complexes and supported metal clusters.

4.5 Alkane dehydroaromatization

The alkane dehydroaromatization reaction involves the alkane dehydrogenation and subsequent cyclization reaction to form aromatics, which has also been commercialized using Pt catalyst supported on KL zeolite (LTL-type zeolite modified with K) for converting n-hexane into aromatics[158]. The working principle is the combination of dehydrogenation of alkanes on subnanometric Pt clusters and the confinement effect of the zeolite structure for shape-selective transformation of the intermediates into aromatics. Therefore, it can be expected, the location of Pt clusters in the KL zeolite has a significant influence on the product distribution[157]. Besides, since the hydrogenolysis of C-C bonds can be suppressed with subnanometric Pt catalysts[159], precise control on the size distribution of Pt clusters encapsulated inside the zeolite structure can be another key for promoting selectivity to aromatics.

When using light alkanes for dehydroaromatization, the presence active sites for dehydrogenation of alkanes into alkenes is critical. For instance, the presence of NiGa alloys can facilitate the dehydrogenation of ethane into ethylene, which can be further converted into aromatics (benzene, toluene, and xylene) by the isolated Ga species confined in ZSM-5 zeolite[160]. Considering the dehydrogenation of light alkanes to corresponding olefins is more favourable on subnanometric metal clusters, loading a small amount of subnanometric metal clusters (such as Pt or Ni) on Ga-zeolite crystallites to enhance the initial step (dehydrogenation of alkane to olefin) may lead to improvements in the yields of aromatics.

The dehydroaromatization of alkanes can also be achieved with homogeneous metal catalysts. In the presence of sacrificial alkenes, n-alkanes can be directly transformed into aromatics with pincer-ligated Ir complexes at a much lower temperature (165 ^{o}C) compared to the heterogeneous process (>400 ^{o}C), though the reaction rate is lower when using homogeneous metal catalysts[161]. Interestingly, the homogeneous Ir catalysts offer different product distributions in the dehydroaromatization reaction. Taking the reforming of n-octane as an example, 75% of meta-xylene is obtained with Ir complex while much lower selectivities to xylenes (<10% in total hydrocarbon products) are obtained with a heterogeneous Pt/KL catalyst (see **Figure 7**) because benzene and toluene are the major aromatic products[162]. The distinct selectivities of Ir complex and Pt/KL catalyst could be associated with the different reaction conditions and the confinement effect of the KL zeolite.

The reaction mechanism for dehydroaromatization of n-hexane has been studied with homogeneous metal catalysts and supported metal catalysts. When using metal-zeolite catalysts, the aromatization of n-hexane is suggested to proceed via the pathway shown in **Figure 10c** because the acid sites in the zeolite support can favour the cyclization of 1-hexene[163]. While in the case of homogeneous Ir-catalysed aromatization reaction, it is inferred by theoretical studies that the reaction follows the reaction pathway described in **Figure 10d**, in which the cyclization reaction occurs with the 1,3,5-hexatriene intermediate [164].

To avoid the use of sacrificial alkenes, one alternative strategy is to carry out the dehydrogenation/dehydroaromatization reaction under photocatalytic conditions, as demonstrated with the dehydrogenation of octane to octenes[165] and transformation of amines into aniline through the dehydroaromatization of an enamine intermediate[166]. Translating this lesson into a heterogeneous system, it could be interesting to immobilize a metal complex on solid photocatalyst as a hybrid catalyst for photocatalytic dehydrogenation/dehydroaromatization of alkanes.

4.6 Alkane metathesis

As mentioned before, alkane metathesis is an effective route to modulate the chain length of alkanes, especially to convert short-chain alkanes into higher homologues[167]. Isolated Ta hydride species supported on silica was firstly reported for converting ethane into methane and propane at 150 ^{o}C and atmosphere pressure[168]. Mechanistic studies indicate that, for metathesis of propane, Ta-carbenic species are firstly formed, followed by the formation of cyclobutanes due to the reaction between Ta-carbenic species and propylene formed from dehydrogenation of propane. The subsequent hydrogenolysis of the intermediates lead to the production of various alkanes[169].

Since the alkane metathesis requires several elementary steps to complete the catalytic cycle, it can also be catalysed by a combination of due active sites instead of a single type metal sites to facilitate the global reaction. For example, as shown in **Figure 8**, isolated W and Ti sites can give much higher activity than spatially separated metal sites because the C-H activation and subsequent β-elimination occur on Ti while the olefin metathesis occurs on W, resulting in a significant improvement in activity when increasing the intimacy of the two metal sites[170].

Despite the above works on alkane metathesis, the current catalysts are not stable enough and most of the reported catalysts give a broad product distribution when using C4+ alkanes. Considering the active sites are proposed to be isolated organometallic species and mechanistic studies with well-defined homogeneous metal catalysts, controlling the metal-support interaction and the coordination environment of the metal centres by loading the metal species onto regular solid surfaces should be an effective approach. Replacing the open-structure solid carrier into porous supports with a well-defined micro-environment for the accommodation of the metal species can be a promising strategy to narrow the product distribution. Nevertheless, tuning the intimacy of the two functional sites (dehydrogenation and olefin metathesis site) at a more accurate level will also be quite helpful, which also requires a high-precision control of the solid catalyst's structure.

4.7 Challenging reactions

Besides the above reactions that have been intensively studied and practiced, there are also some challenging reactions related to alkane activation which are quite attractive but less investigated in the literature. We would like to mention some representative ones and discuss the current limitations as well as promising future developments.

Direct reaction between methane and CO_2 to form acetic acid is a highly desired reaction observed in marine sediment but also quite tough to proceed[171, 172]. It has been reported that formation of acetic acid can be achieved with Cu-zeolite samples when reacting with CO_2 and CH_4 at 425-525 ^{o}C, though the yield is low and declines with time on stream[173]. Theoretical studies indicate that the simultaneous activation of CO_2 and CH_4 is related to the coordination environment of Cu atom and Cu clusters[174]. Progress on this reaction requires a deeper understanding on the active sites and catalytic studies on various Cu-zeolite materials with controlled atomicity and distributions in zeolite structures.

Alkylation of benzene with olefins has been well established by zeolite catalysts. Since olefins can be produced from dehydrogenation of alkanes, the direct coupling of light alkanes with benzene can be a route for the production of alkylbenzene. Bifunctional catalysts such as Pt/MFI and Pt/$H_4SiW_{12}O_{40}$/SiO_2 catalyst have been reported for this reaction with >80% selectivity to the desired alkylbenzene at 400-500 ^oC, but the conversion of light alkane is not high (<10 %)[175, 176]. Though Pt species mainly exist as nanoparticles in those reported works, using subnanometric Pt clusters confined in the zeolite structures and modulating the position and distribution of acid sites can be an effective approach to further improve the activity and selectivity to alkylbenzene.

Selective halogenation of alkanes is an important route for the production of useful raw materials for manufacturing chemicals, pharmaceuticals and polymers[177]. The radical-involved reaction mechanism and multiple possible reaction pathways make it quite difficult to control the product distributions. For instance, numerous supported Cu catalysts have been studied for ethane oxychlorination into vinyl chloride monomer (VCM), though the active sites are not fully revealed[177]. Since single-site Au catalysts have been proposed as the active sites for hydrochlorination of acetylene into VCM[178], it will be interesting to clarify the reactivity of isolated Cu species and subnanometric Cu clusters for oxyhalogenation of alkanes and the role of metal-support interaction and confinement effect in selectivity control[179].

Activation and conversion of waste plastics into fuels and chemicals plays a central role towards a circular economy with sustainability. Polymers such as polyethylene and polypropylene can be considered as macromolecule alkanes very long carbon chains. It has been reported that polyethylene and polypropylene can be decomposed into diesel and lower alkanes with single-site Zr species supported on silica[64]. The degradation of polyethylene has also been achieved with the combination of homogeneous Ir complex and supported rhenium catalyst through a cross-alkane metathesis pathway by adding an excess amount of light alkanes (such as n-hexane) to react with polyethylene for production of liquid fuels and wax[180]. The application of a catalyst comprising Pt nanoparticles supported on $SiTiO_3$ has also been reported for hydrogenolysis of polyethylene into liquid lubricants or wax[181]. Considering the higher ability of Pt nanoclusters for hydrogenation reactions and the potential synergistic effect between Pt nanoclusters and single-site Lewis acid species, a bifunctional solid catalyst consisting of Pt clusters and isolated metal species (such as Zr, Ta or W) can be potential catalysts for selective conversion of polyolefins into lower alkanes or aromatics[182].

The activation of C-H bonds in alkane molecules through the insertion of carbene and nitrene is a promising method to directly functionalize the inert alkane molecules, as demonstrated by the Rh-catalysed carbene insertion reaction shown in **Figure 9**, which can be proceeded by the carbene transfer from metal sites or through the free carbene intermediates[183, 184]. Currently, this type of reaction has to proceed with molecular metal complexes (such as Rh, Cu and Ag) and the regioselectivity and enantioselectivity can be modulated with the ligands[185-187]. Taking into account the application of Pd-MOF catalyst for carbene-mediated Buchner reaction of benzene derivatives to give cycloheptatrienes[188], it will be interesting to incorporate Rh or other metal complexes into MOF structures for catalysing carbene-mediated activation of alkanes. MOFs are versatile hosts to stabilize isolated metal species either in the organic linkers or inorganic nodes, though the stability of MOF structures during catalytic reactions should be carefully examined.

For enzymatic and homogeneous systems, there are also some challenging reactions/issues related to alkane activation that are of interest to be explored or considered in future works. Considering the cost of homogeneous metal catalysts and enzymes, their strength can be maximized when being applied to transform alkanes into highly value-added products such as enantioselective oxidation of alkanes into alcohols, C-C coupling reaction and cascade transformations (for instance, hydroformylation of the olefins derived from the dehydrogenation of alkanes[189]). Great efforts should be devoted to decrease the cost of the biocatalytic and homogeneous systems and to improve the robustness of the catalysts/enzymes to compete with heterogeneous systems. These targets could be achieved by improving the recyclability of the catalysts and performing the reactions in a continuous way if the catalysts/enzymes can be immobilized on solid carriers.

5. Comparison of the enzymatic, homogeneous and heterogeneous systems

In the above sections, we have summarized the applications of isolated metal atoms and metal clusters for alkane activation. There are some similarities among different systems, in terms of the key active centres, catalytic mechanism and the principles of reactivity modulation by tuning the coordination environment (see **Figure 10**). For instance, selective oxidation of methane to methanol has been observed with Cu sites in enzymes, Cu complex and supported Cu catalyst. According to the literature, the active sites are associated to binuclear Cu species in most of the works and the insertion of O into the C-H bond is commonly proposed to be the critical elementary step. As mentioned in the above discussion, the rich knowledge accumulated in organic chemistry for metal-catalysed C(sp^3)-H activation reactions can be translated into the development of new heterogeneous metal catalysts. However, we would like to emphasize the dramatic differences between different systems, which can further impact the design principles for supported metal catalysts.

5.1 Coordination environment of the active sites

The three types of catalysts discussed in this review have intrinsically different chemical structures. The coordination environment of metal centres in enzymes and molecular metal complexes is quite flexible while the inorganic support in heterogeneous metal catalysts is much more rigid. On one hand, supported metal catalysts also show the strongest interaction between the metal centre and coordination environment, which leads to much higher stability[190]. On the other hand, the metal-support interaction could also limit the reactant's accessibility to the supported isolated atoms or metal clusters due to the limited exposure of those species, which may further influence their reactivity. Nevertheless, due to harsher reaction conditions, dynamic structural transformation of supported subnanometric metal clusters can play a critical role during the catalytic cycles while the structure of the metal sites in enzymes and molecular metal complexes are relatively more stable[191].

Confinement effects are widely observed in enzymes and molecular metal catalysts and such effects are subtler than those observed in heterogeneous metal catalysts, which should originate from the well-defined interaction between the metal active site neighbouring atoms and substrate molecule[192, 193]. Regarding the confinement effect in solid catalysts, isolated atoms and clusters confined in zeolites are the most typical examples, which are strongly dependent on the location of the metal species within the zeolite structures. The heterogeneity of site distribution and non-uniform coordination environment surrounding the subnanometric metal species on solids preclude the molecular recognition with supported metal catalysts[194], which leads to the difficulty to carry out enantioselective reactions with solid catalysts.

Compared to the flexible structure of molecular metal catalysts and enzymes, the rigid framework structures of zeolites can provide strong confinement effect to facilitate the conversion of small molecules (such as methane and propane) into larger ones such as aromatics (benzene, toluene and xylenes), which is rarely observed with homogeneous and enzymatic catalysts. MOFs can be the supports that combine the regular porosity and the relatively flexible framework, which offer the opportunities to carry out chiral catalytic reactions related to alkane activation[195].

5.2 Atomicity

In nature enzymes, the active sites usually consist of one or two metal atoms and the vast majority of molecular metal catalysts are also mononuclear or binuclear complexes. The much lower stability of multinuclear structures could be the reason accounting for that phenomena. However, owing to the presence of the solid carrier, the formation of metal clusters comprising a few or even 10-20 atoms are feasible. From a geometric point of view, in some reactions, it may require multiple atoms to interact with C2+ alkane or O_2/H_2 molecules. As a result, metal clusters could be more efficient catalysts than isolated atoms[196]. Respecting to that point, studying the size effect, especially in the subnanometric region, of supported metal catalysts for alkane activation will still be an important topic.

5.3 Oxidation states

Mechanistic studies indicate that the oxidation states of metal sites in enzymes vary between M(II) and M(IV) during the catalytic cycle while it may vary from M(0) to M(IV) for most cases of molecular metal catalysts. In this sense, the oxidation states of the metal species are closed in these two systems. Shifting to supported metal atoms and clusters, their oxidation states are usually lower than their homogeneous counterparts, especially in the cases of supported metal clusters due to the formation of metal-metal bonding and metal-support electronic interaction. For instance, as proposed in the literature, Cu species may plausibly show Cu(III)/Cu(II) variance in pMMO enzyme for methane oxidation reaction while the Cu species (either in the form of binuclear or trinuclear clusters) confined in zeolites mainly show the variance of Cu(II)/Cu(I)[197, 198]. Indeed, the high-valence metal species formed in enzymes and molecular complexes are rarely observed in supported metal catalysts. When the atomicity grows to higher than 4, the formation of metallic bonding within the metal clusters lead to the shift of oxidation states closed to 0, and thus give to different catalytic properties. This difference also infers that, if the unfeasible oxidation states of the metal species on solid carriers can be stabilized, unique catalytic properties could be achieved, as reported with Zr(III), Hf(III) and Pt(I) species stabilized in MOFs[199, 200].

5.4 Reaction conditions

The reactions achieved with enzymes and molecular metal catalysts are usually performed in the liquid phase and under relatively mild conditions, especially for enzymes. As a consequence, the reaction rate could be very slow, as limited by kinetics. The vulnerable nature of enzymes and low robustness of molecular metal complexes almost ban their applications for large-scale conversion of alkanes. In the case of heterogeneous catalysts, it is feasible to operate the alkane activation reactions under high-temperature and/or high-pressure conditions to accelerate the catalytic processes. The large difference in reaction conditions will cause discrepancies in reaction kinetics and even in reaction mechanisms. Because of the presence of solid-gas or solid-liquid interface when using supported metal catalysts, the mass transportation and reactant-catalyst contact time in heterogeneous system will be dramatically different to the homogeneous systems and such influences can cause differences in product distributions, as discussed before in this Review for the alkane dehydroaromatization reaction. In this context, modulating the catalyst-reactant interface to control the diffusion of reactant and product should also be considered to optimize the catalyst's performance[201].

6. Development of subnanometric heterogeneous metal catalysts for alkane activation

The above discussions on the similarities and dissimilarities between the different catalytic systems on alkane activation have attempted to give some insights on how the different catalytic systems work. Based on those understandings, we will make perspectives on future developments for establishing/designing new heterogeneous catalytic systems comprising isolated metal atoms and clusters for reactions related to alkane activation.

6.1 Material design

One approach to combine the advantages of different materials is to prepare hybrid materials. For instance, by immobilizing a molecular metal complex on an inorganic support, it will be possible to carry out the alkane activation reactions under flow conditions, avoiding the problem of catalyst recovery. This concept has been well established with supported organometallic complexes for various reactions, though the stability can still be an issue in some cases[93]. If the molecular metal catalysts can be grafted to "soft" carriers such as polymers or inorganic-organic hybrid materials, the flexible support may improve the accessibility of larger alkane molecules and the formation of micelles in the solvent may also facilitate the reaction of hydrophobic alkanes in green solvents like water[202, 203]. This stabilization strategy has already been applied to supported Rh atoms in organic polymer for hydroformylation reaction and we expect this concept will be extended to other reactions such as metal-catalysed oxidative carbonylation of methane[204].

The critical role of scaffold surrounding the active sites has been repeatedly emphasized in the above discussion in this Review. For the target reaction, the synthesis of solid catalyst can follow an "ab initio" strategy by mimicking the transition states of the target reaction. The candidate catalysts are synthesized in the presence of structure-directing agents that sharing similar structural conformation as transition states of the target reaction. In this way, the micro-environment surrounding the active sites can be similar to the geometric structure of the transition states, which can give better performance than the catalysts prepared without such pre-stabilized micro-environment. Considering the positive results obtained in the previous works on methanol-to-olefins, Diels-Alder reaction and other acid-catalysed reactions [205-207], this “ab initio” strategy deserves to be tested for some reactions related to alkane activation, such as selective oxidation of long-chain alkanes and C-H functionalization of alkanes.

When dealing with some very large reactants, such as polyolefin, the design of the scaffold should consider the accessibility of the reactants to active sites and the way how the active sites can interact with the reactants. In natural enzymes, a processive mechanism is found in the reactions for destruction of macromolecules. Translating this knowledge into heterogeneous catalysis, a core-shell $mSiO_2/Pt/SiO_2$ catalyst is developed for hydrogenolysis of high-density polyethylene[208]. The linear chain of polyethylene can access Pt nanoparticles through the mesoporous SiO_2 channels and contact between the long-chain polyethylene is limited to a narrow range. As a result, the chain-length distribution of the hydrocarbon products is narrower than those obtained with conventional Pt/SiO_2 catalysts. If the porous scaffold surrounding the Pt catalysts, which can also be replaced to be isolated Pt atoms or clusters, can be controlled in a more precise manner, better control on the product distribution can be achieved.

The importance of the interfaces between the reactant, product and solid catalyst is well recognized in heterogeneous catalysis, as shown in the direct aerobic oxidation of toluene to benzaldehyde with colloid iron oxide nanoparticles in a biphasic system. A remarkably high selectivity to benzaldehyde (>99%) is obtained in this catalytic system, which is suggested to be related to the unique interface between the monodispersed iron oxide nanoparticles and the hexadecylphosphate ligand coordinated to the nanoparticles[209]. The presence of multiple interfaces in the reaction mixture is common for liquid-phase transformation of alkanes. Therefore, it is highly recommended to investigate the adsorption of reactants and desorption of products in those heterogeneous systems, especially when ligands are involved in the metal-catalysed alkane activation reactions.

Liquid alkanes can be activated by numerous molecular metal catalysts via C-H functionalization to form C-X bonding (e.g. C-C, C-N, C-O, C-B, etc.)[48, 210]. An alternative approach to heterogenize this type of reaction is to anchor the isolated metal species in a metal-organic framework. For instance, inspired by molecular Ir complex used for alkane borylation, mononuclear Ir species were anchored on the organic linker in a Zr-MOF support, and the resultant catalysts can afford very high chemoselectivity to monoborylated methane due to the shape-selectivity of the MOF structure[211]. Inspired by the ligand-assisted C-H activation in homogeneous catalysis, preparing metal-organic framework (MOF) materials containing isolated metal atoms with suitable ligands can be an alternative approach to transform the homogeneous metal catalysts into a heterogeneous form. This concept has been demonstrated by Pd-MOF materials for oxidative coupling of arenes[212]. As a flexible backbone material, it is possible to stabilize the unfeasible oxidation states (such as Fe(IV) and Cu(III) species) in MOF structure[213], which are proved to be critical intermediates for alkane activation by enzymes. Those species are rarely observed and difficult to be generated on conventional solid carriers (such as carbon and oxide materials) due to their low stability.

The framework stabilization sites and confinement effect are claimed to stabilize isolated metal atoms and clusters in porous materials for the conversion of alkanes under harsh conditions in various examples. Controlling the coordination environment of isolated atoms in porous materials is critical to obtain highly active catalyst, as shown with Fe-CHA catalysts for oxidation of methane to methanol with N_2O, in which the sitting of Al species can influence the stabilization of isolated α-Fe^{II} redox active site[214]. For some reactions employing bimetallic nanoclusters as active sites, such as the dehydrogenation of alkane to alkenes or hydrogenolysis reaction, the precise control of the chemical composition of the bimetallic clusters in porous materials is still a challenge[215]. To further develop this concept into catalysts for cascade reactions, one needs to anchor two or more types of metal species in the specific location of the porous matrix and control their spatial intimacy in order to achieve a synergistic effect. This strategy can be applied to design multifunctional materials for reactions involving tandem reactions, such as alkane metathesis. In addition to tuning the intimacy of different metal entities, putting the same metal element but with different atomicity could be another way to generate active sites with different functions for cascade transformations[216, 217]. For instance, the hydrogenolysis of alkane may require multiple metal atoms for activation of H_2 and C-C bond cleavage while the formation of radical hydrocarbon intermediates could be more favourable on isolated metal atoms or very small metal clusters. The combination of both types of metal species could facilitate the transformation of long-chain hydrocarbons into desired products by using well-controlled supported metal catalysts. Thinking from another angle, the initial reaction can be catalysed by a molecular metal complex, followed by a subsequent transformation on solid catalyst. If the metal complex is immobilized on the solid catalyst, the two-step transformation can be carried out in a one-pot process. This strategy has been applied to combine pincer-ligated Ir complex and zeolite catalyst for alkyl-aryl coupling reaction[218].

The practical catalysts used in industrial processes are usually shaped solids comprising functional components, binder and additives. Obviously, there is a large materials gap between the atomic control of the coordination environment of the support subnanometric metal catalysts and the macroscopic materials.

Taking the encapsulated subnanometric metal catalysts in porous materials as an example, considering the size of the porous matrix can span over tens to hundreds of nanometres[219], the precise control of the chemical composition in the whole matrix can also be a quite challenging task, requiring both sophisticated synthesis methodologies as well as advanced structural characterization techniques for mapping the chemical compositions with atomic-level resolution[215, 220]. One way to improve the homogeneity of supported subnanometric metal catalysts is to perform the materials synthesis under flow conditions or by additive manufacturing techniques, which allows the production of solid materials in the continuous mode under well-controlled process management.

6.2 Introduction of an external field

As discussed before, enzymatic and homogeneous catalysts are superior to heterogeneous catalysts when dealing with radical-involved reactions due to their uniform and well-defined structures. Indeed, photocatalysis and electrocatalysis based on molecular metal complexes are emerging fields in organic chemistry, which widely broaden the reaction scope of C-H activation reactions[221, 222]. In a recent work, the selective oxidation of methane to methanol is achieved by integrating C-H activation on low-valence Rh complex and oxygen activation on Si nanowire electrode[223]. In a similar concept, biocatalysis is coupled to electrocatalysis for oxidation of alkane into alcohol by coupling an alkane monooxygenase (binuclear Fe species the active sites), a soluble electron transfer protein (rubredoxin) and toluidine blue O (TBO) as an electrochemical mediator[224]. The above integration can realize the electron transfer from the electrode to the working enzyme for oxidation aliphatic C-H bonds to hydroxyl groups. The geometric conformation of the enzymes (alkane hydroxylase (AlkB) and rubredoxin-2 (AlkG)) can be partly changed when interacting with the electrode, as inferred by kinetic studies for hydroxylation of C3–C12 n-alkanes[225]. Such subtle changes in geometric structures cause the expansion of the substrate scope of the hydroxylation reaction to small alkanes such as propane and butane. We expect that the electron-transfer efficiency can be improved if the metal complex-electrode and enzyme-electrode interface can be further optimized, leading to improved catalytic performances. Such interface optimizations can be achieved via installing chemical bonding/interaction between the catalyst (metal complexes or enzymes) and the solid electrode[226, 227].

High-temperature fuel cells are also promising devices for the conversion of alkanes into value-added chemicals. The high-temperature fuel cells based on methane have already been intensively studied both in terms of the device fabrication and catalyst design[228]. By translating that knowledge into fuel cells using other alkanes as the fuel, it may be possible to transform alkanes into oxygenates rather than CO_2 in methane-based fuel cells[229]. The high-temperature fuel cells for oxidative coupling of methane to ethane and ethylene is also desired[230]. The key to achieve that goal can be the controllable oxidation of alkanes by the oxygen ions from the solid electrolyte, which involves a selective catalyst to avoid the over-oxidation reaction and a suitable device design for the separation of the primary oxygenate products. In respect to the electrocatalyst, isolated atoms/clusters that show high selectivity in partial oxidation of methane/alkanes can be the candidates. It has been reported that isolated Ru and Ni atoms supported on CeO_2 are active and stable for reforming of methane to CO and H_2 within a high-temperature solid oxide fuel cells[231].

Photocatalysis and electrocatalysis based on supported single-atom or cluster catalysts also show great potential for activation of small molecules (CO_2, N_2, H_2O, etc.)[232, 233], as promising approaches for delocalization utilization of renewable energy for the production of chemicals and fuels[234]. Besides, the introduction of external electric or photo-generated electric fields can modulate the electronic structures of the supported subnanometric metal catalysts, making them closer to those in nature enzymes or molecular metal complexes. Therefore, we can expect the deployment of supported subnanometric metal catalysts in electrocatalysis or photocatalysis can greatly extend the reaction scope of conventional thermal catalysis for catalytic transformation of alkanes.

One possible research paradigm can be replacing the homogeneous metal catalysts into heterogeneous metal catalysts comprising isolated metal atoms or clusters in current developed photocatalytic and electrocatalytic systems. For instance, selective functionalization of methane and other alkanes has been achieved with cerium photocatalysis, which can enable the amination of alkanes at room temperature under irradiation of a LED light source[235]. Direct functionalization of $C(sp^3)$-H bonds has also been achieved in numerous other photocatalytic systems using transition metal complexes as photosensitizer and/or catalyst[236-238]. Besides, solid materials such as colloid quantum dots or other semiconductor nanoparticles have also been reported for photocatalytic activation of $C(sp^3)$-H bonds[239]. For instance, by employing decatungstate complex ($W_{10}O_{32}^{4-}$) as a photosensitizer and then abstract H from alkane molecule to form carbon-centred radicals, which can subsequently react with olefins to form C-C bond[240]. Inspired by these works, the immobilization of metal catalyst in the form of either isolated metal atoms or metal clusters on semiconductors, can be a promising strategy to realize the above reactions with heterogeneous catalysts[241]. In such a way, the scaling-up of these catalytic systems will be more feasible and the charge transfer between the immobilized metal entities and the semiconductor support may also bring new physicochemical properties. For instance, it has been reported that the combination of homogeneous Ni complex and a solid semiconductor (C_3N_4) can mitigate the sintering of Ni catalyst during photoredox C-N coupling reaction[242]. Another solution for that purpose can be implanting the photosensitizer and the metal catalyst within the porous structure of MOF[243]. Under this circumstance, energy transfer between the photosensitizer and the anchored isolated metal species can be facilitated when they are regularly confined in the MOF structure, which could contribute to the realization of photocatalytic activation of alkanes under continuous flow conditions[244].

Another strategy can be substituting the reactant in the established photocatalytic or electrocatalytic systems by alkane molecules. For instance, it has been reported electrocatalytic hydrogenation and oxidation of biomass-derived compounds into value-added products by supported metal catalyst[245, 246]. In principle, the hydrogenolysis of alkane and selective oxidation of alkane should also be feasible by using supported metal catalysts, which could be achieved by replacing the solid carrier of conventional catalysts from insulator supports (such as metal oxides) to carbon-based materials. Though the reaction mechanisms are different and the active sites may also vary accordingly, the knowledge generated in conventional thermal catalysis can be translated into this direction and can facilitate the improvement of catalytic performance.

In terms of photocatalysis, there are already various solid catalysts reported for reactions related to methane activation[247], such as oxidative coupling of methane to ethane by Ga-zeolite under UV light[248], oxidation of methane with CO_2 for production of oxygenates[249] and photocatalytic or photoelectrocatalytic conversion of methane to benzene or ethane[250, 251]. However, for all those works, the reactivity is quite low, which could be limited by the reaction temperature and the use of metal catalyst without optimized particle size. The recent advances on photo-thermal catalytic activation of inert molecules (N_2, CO_2, CH_4, etc.) infer the potential of using supported single-atom or cluster catalysts for photo-thermal conversion of alkanes[125, 252, 253]. A core-shell type structure comprising a light-absorbent (semiconductor or plasmonic metal) and subnanometric metal catalysts on the external surface is therefore proposed for such reactions.

Another type of external field that could be applied for alkane activation is non-thermal plasmas, in which highly energetic electrons with an electron temperature of 1-10 eV can interact and activate inert molecules such as N_2, CO_2 and methane[254]. With conventional supported metal catalysts ($Cu/\gamma\text{-}Al_2O_3$, $Au/\gamma\text{-}Al_2O_3$ and $Pt/\gamma\text{-}Al_2O_3$) methane and CO_2 can be converted into oxygenates, such as acetic acid, methanol, ethanol, acetone and formaldehyde, under ambient conditions[255]. To the best of our knowledge, the application of supported subnanometric metal catalysts for plasmas-assisted catalysis is barely explored yet. We expect new findings in this direction in the near future to clarify the activation of alkanes on isolated atoms and clusters in a plasma environment.

Nevertheless, the introduction of microwave irradiation is also recently shown to be effective for destruction of polyethylene and polypropylene into H_2 and multiwall carbon nanotubes using Fe/Fe_3C nanoparticles supported on alumina as the catalyst[256]. The microwave irradiation can accelerate the activation of C-H in the polymers. These advances encourage the coupling of supported subnanometric metal catalysts and external microwave irradiation for alkane activation.

6.3 Reaction engineering

As discussed in **Section 4**, the major challenges of reactions related to the conversion of light alkanes (methane, ethane and propane) are reactivity and catalyst stability. While for long-chain alkanes, improving selectivity to desired products is the major challenge. Despite the efforts on materials design and introduction of an external field, reactor engineering is also an effective way to surpass the limitation of a conventional thermal reactor, especially in the case of challenging reactions related to alkane activation.

Cascade reactions in fix-bed reactors have shown great potential for conversion of syngas into chemicals and fuels, by separating the hydrogenation of CO/CO_2 and the subsequent transformation of intermediates (methanol or ketene) on metal oxides and zeolites, respectively[257, 258]. The spatial distribution of two catalyst components in the fix-bed reactor has a profound influence on product distributions. If one attempts to perform cascade reactions to transform alkanes into some target products, the optimization of the spatial distributions of the catalyst components is a critical issue. Perhaps, additive manufacturing can be an alternative option for transforming supported metal catalysts as well as other components into well-defined practical granular catalysts[259]. Moreover, the pristine materials for additive manufacturing are better to be prepared in a continuous way, because this can help to control the reproducibility and quality of the final catalysts[260, 261].

The combination of conventional fix-bed reactor and membrane reactor is a quite promising strategy to surpass the thermodynamic equilibrium of the conventional thermal process. For instance, the integration of Mo-zeolite catalyst with an oxygen-conducted membrane enables the removal of H_2 from the product mixture and the combustion of coke on Mo-zeolite catalyst, which dramatically improves the yield of benzene and alleviated the catalyst deactivation[262]. This concept can also be extended to other reactions such as oxidative coupling of methane[230] and alkane dehydrogenation reaction[263], which should be able to shift the thermodynamic equilibrium by extracting H_2 from the product mixture. It can be expected that the low-temperature performance of the newly developed catalysts containing subnanometric metal species can be further promoted by the deployment with a membrane permselective to hydrogen, in order to decrease the energy consumption. Moreover, the prompt separation of desired products can mitigate the selectivity limitations by avoiding the subsequent overreaction. The application of oxygen-permeable membrane reactors has been shown effective for improving the selectivity to olefins in oxidation of light alkanes[264].

Chemical looping is a versatile route to carry out some chemical transformations in a more selective way than conventional catalytic routes, as discussed above with Cu-zeolite materials for methane oxidation[265]. In a recent work, TiO_2 supported Ag-phosphotungstic acid has been reported to be an efficient material for selective conversion of methane into ethane and propane under photothermal conditions through a chemical looping mechanism[266]. AgO_x nanoparticles of 1-2 nm can activate methane and carry out the C-C coupling reaction under the assistance of phosphotungstic acid and then will be reduced to metallic Ag accordingly. The AgO_x nanoparticles are easily recovered by exposure to air under light irradiation, and the optimized material are reused for more than 10 cycles without deactivation. Considering the interaction of alkane with metal particles is strongly related to the atomicity, it will be of great interest to study the chemical looping performance with isolated Ag atoms and Ag clusters supported on various semiconductor carriers.

7. Conclusions

We have summarized some representative works on alkane activation with supported isolated metal atoms and clusters and discussed the similarities and dissimilarities between enzymatic, homogeneous and heterogeneous catalytic systems. Despite the large difference among the three systems, some concepts from bio- and homogeneous catalysis can be translated into heterogeneous systems for potential large-scale practical applications. To facilitate the translation, interdisciplinary studies and integration of different systems are promising approaches to overcome current limitations.

References

1. Schwach, P., Pan, X. and Bao, X. (2017) Direct conversion of methane to value-added chemicals over heterogeneous catalysts: challenges and prospects. *Chem. Rev.* 117, 8497-8520.
2. Kondratenko, E.V., Peppel, T., Seeburg, D., Kondratenko, V.A., Kalevaru, N., Martin, A. and Wohlrab, S. (2017) Methane conversion into different hydrocarbons or oxygenates: current status and future perspectives in catalyst development and reactor operation. *Catal. Sci. Technol.* 7, 366-381.

3. Labinger, J.A. and Bercaw, J.E. (2002) Understanding and exploiting C-H bond activation. *Nature* 417, 507-514.
4. Coperet, C. (2010) C-H bond activation and organometallic intermediates on isolated metal centers on oxide surfaces. *Chem. Rev.* 110, 656-680.
5. Olivos-Suarez, A.I., Szécsényi, À., Hensen, E.J.M., Ruiz-Martinez, J., Pidko, E.A. and Gascon, J. (2016) Strategies for the direct catalytic valorization of methane using heterogeneous catalysis: challenges and opportunities. *ACS Catal.* 6, 2965-2981.
6. Liu, L. and Corma, A. (2018) Metal catalysts for heterogeneous catalysis: from single atoms to nanoclusters and nanoparticles. *Chem. Rev.* 118, 4981-5079.
7. Sterckx, H., Morel, B. and Maes, B.U.W. (2019) Catalytic Aerobic oxidation of C(sp^3)-H bonds. *Angew. Chem. Int. Ed.* 58, 7946-7970.
8. Bordeaux, M., Galarneau, A. and Drone, J. (2012) Catalytic, mild, and selective oxyfunctionalization of linear alkanes: current challenges. *Angew. Chem. Int. Ed.* 51, 10712-10723.
9. Corma, A. (2011) Attempts to fill the gap between enzymatic, homogeneous, and heterogeneous catalysis. *Catal. Rev.* 46, 369-417.
10. Sivaramakrishna, A., Suman, P., Veerashekhar Goud, E., Janardan, S., Sravani, C., Sandeep, T., Vijayakrishna, K. and Clayton, H.S. (2013) Review: active homogeneous reagents and catalysts inn-alkane activation. *J. Coord. Chem.* 66, 2091-2109.
11. Weaver, J.F., Hakanoglu, C., Antony, A. and Asthagiri, A. (2014) Alkane activation on crystalline metal oxide surfaces. *Chem. Soc. Rev.* 43, 7536-7547.
12. Senanayake, S.D., Rodriguez, J.A. and Weaver, J.F. (2020) Low temperature activation of methane on metal-oxides and complex interfaces: insights from surface science. *Acc. Chem. Res.* 53, 1488-1497.
13. Ji, S., Chen, Y., Wang, X., Zhang, Z., Wang, D. and Li, Y. (2020) Chemical synthesis of single atomic site catalysts. *Chem. Rev.* 120, 11900-11955.
14. Wang, A., Li, J. and Zhang, T. (2018) Heterogeneous single-atom catalysis. *Nat. Rev. Chem.* 2, 65-81.
15. Ravi, M., Ranocchiari, M. and van Bokhoven, J.A. (2017) The direct catalytic oxidation of methane to methanol-a critical assessment. *Angew. Chem. Int. Ed.* 56, 16464-16483.
16. Copéret, C. (2019) Fuels and energy carriers from single-site catalysts prepared via surface organometallic chemistry. *Nat. Energy* 4, 1018-1024.
17. Li, X., Rong, H., Zhang, J., Wang, D. and Li, Y. (2020) Modulating the local coordination environment of single-atom catalysts for enhanced catalytic performance. *Nano Res.* 13, 1842-1855.
18. Balasubramanian, R., Smith, S.M., Rawat, S., Yatsunyk, L.A., Stemmler, T.L. and Rosenzweig, A.C. (2010) Oxidation of methane by a biological dicopper centre. *Nature* 465, 115-119.
19. Haack, P. and Limberg, C. (2014) Molecular Cu(II)-O-Cu(II) complexes: still waters run deep. *Angew. Chem. Int. Ed.* 53, 4282-4293.
20. Chan, S.I., Lu, Y.J., Nagababu, P., Maji, S., Hung, M.C., Lee, M.M., Hsu, I.J., Minh, P.D., Lai, J.C., Ng, K.Y. *et al.* (2013) Efficient oxidation of methane to methanol by dioxygen mediated by tricopper clusters. *Angew. Chem. Int. Ed.* 52, 3731-3735.
21. Ayala, M. and Torres, E. (2004) Enzymatic activation of alkanes: constraints and prospective. *Appl. Catal. A: Gen.* 272, 1-13.
22. Sirajuddin, S. and Rosenzweig, A.C. (2015) Enzymatic oxidation of methane. *Biochemistry* 54, 2283-2294.
23. Kopp, D.A. and Lippard, S.J. (2002) Soluble methane monooxygenase: activation of dioxygen and methane. *Curr. Opin. Chem. Bio.* 6, 568-576.

24. Wallar, B.J. and Lipscomb, J.D. (1996) Dioxygen activation by enzymes containing binuclear non-heme iron clusters. *Chem. Rev.* 96, 2625-2658.
25. Elliott, S.J., Zhu, M., Tso, L., Nguyen, H.H.T., Yip, J.H.K. and Chan, S.I. (1997) Regio- and stereoselectivity of particulate methane monooxygenase from methylococcus capsulatus(Bath). *J. Am. Chem. Soc.* 119, 9949-9955.
26. Brazeau, B.J., Wallar, B.J. and Lipscomb, J.D. (2001) Unmasking of deuterium kinetic isotope effects on the methane monooxygenase compound Q reaction by site-directed mutagenesis of component B. *J. Am. Chem. Soc.* 123, 10421-10422.
27. Schmid, A., Sonnleitner, B. and Witholt, B. (1998) Medium chain length alkane solvent-cell transfer rates in two-liquid phase,Pseudomonas oleovorans cultures. *Biotechnol. Bioeng.* 60, 10-23.
28. Dey, A., Okamura, T.A., Ueyama, N., Hedman, B., Hodgson, K.O. and Solomon, E.I. (2005) Sulfur K-edge XAS and DFT calculations on P450 model complexes: effects of hydrogen bonding on electronic structure and redox potentials. *J. Am. Chem. Soc.* 127, 12046-12053.
29. Schwartz, J.K., Wei, P.P., Mitchell, K.H., Fox, B.G. and Solomon, E.I. (2008) Geometric and electronic structure studies of the binuclear nonheme ferrous active site of toluene-4-monooxygenase: parallels with methane monooxygenase and insight into the role of the effector proteins in O_2 activation. *J. Am. Chem. Soc.* 130, 7098-7109.
30. Guengerich, F.P. (2018) Mechanisms of cytochrome P450-catalyzed oxidations. *ACS Catal.* 8, 10964-10976.
31. Shook, R.L. and Borovik, A.S. (2010) Role of the secondary coordination sphere in metal-mediated dioxygen activation. *Inorg. Chem.* 49, 3646-3660.
32. Sarkar, M.R., Lee, J.H.Z. and Bell, S.G. (2017) The oxidation of hydrophobic aromatic substrates by using a variant of the P450 monooxygenase CYP101B1. *ChemBioChem* 18, 2119-2128.
33. Sarkar, M.R. and Bell, S.G. (2020) Complementary and selective oxidation of hydrocarbon derivatives by two cytochrome P450 enzymes of the same family. *Catal. Sci. Technol.* 10, 5983-5995.
34. Glieder, A., Farinas, E.T. and Arnold, F.H. (2002) Laboratory evolution of a soluble, self-sufficient, highly active alkane hydroxylase. *Nat. Biotechnol.* 20, 1135-1139.
35. Moreno, R. and Rojo, F. (2017) Aerobic Utilization of Hydrocarbons, Oils and Lipids. 1-25.
36. Barber, J. (2009) Photosynthetic energy conversion: natural and artificial. *Chem. Soc. Rev.* 38, 185-196.
37. Proppe, A.H., Li, Y.C., Aspuru-Guzik, A., Berlinguette, C.P., Chang, C.J., Cogdell, R., Doyle, A.G., Flick, J., Gabor, N.M., van Grondelle, R. *et al.* (2020) Bioinspiration in light harvesting and catalysis. *Nat. Rev. Mater.* 5, 828-846.
38. Callaghan, A.V. (2013) Enzymes involved in the anaerobic oxidation of n-alkanes: from methane to long-chain paraffins. *Front. Microbiol.* 4, 89.
39. Reeburgh, W.S. (2007) Oceanic methane biogeochemistry. *Chem. Rev.* 107, 486-513.
40. Sünwoldt, K., Knack, D. and Heider, J. (2012) New reactions in anaerobic alkane and alkene metabolism. *in DFG-Priority Programme 1319 Third Meeting: Biological Transformations of Hydrocarbons without Oxygen: from the Molecular to the Global Scale. (Freiburg: Deutsche Forschungsge-meinschaft).*
41. Arnold, F.H. (2018) Directed evolution: bringing new chemistry to life. *Angew. Chem. Int. Ed.* 57, 4143-4148.
42. Acevedo-Rocha, C.G., Hollmann, F., Sanchis, J. and Sun, Z. (2020) A pioneering career in catalysis: Manfred T. Reetz. *ACS Catal.* 10, 15123-15139.
43. Reetz, M.T. (2001) Combinatorial and evolution-based methods in the creation of enantioselective catalysts. *Angew. Chem. Int. Ed.* 40, 284-310.

44. Li, G. and Reetz, M.T. (2016) Learning lessons from directed evolution of stereoselective enzymes. *Org. Chem. Front.* 3, 1350-1358.
45. Yang, K.K., Wu, Z. and Arnold, F.H. (2019) Machine-learning-guided directed evolution for protein engineering. *Nat. Methods* 16, 687-694.
46. Coley, C.W., Eyke, N.S. and Jensen, K.F. (2020) Autonomous discovery in the chemical sciences Part II: Outlook. *Angew. Chem. Int. Ed.* 59, 23414-23436.
47. Crabtree, R.H. (2001) Alkane C–H activation and functionalization with homogeneous transition metal catalysts: a century of progress—a new millennium in prospect. *J. Chem. Soc. Dalton Trans.*, 2437-2450.
48. Mkhalid, I.A., Barnard, J.H., Marder, T.B., Murphy, J.M. and Hartwig, J.F. (2010) C-H activation for the construction of C-B bonds. *Chem. Rev.* 110, 890-931.
49. Serrano-Plana, J., Garcia-Bosch, I., Company, A. and Costas, M. (2015) Structural and reactivity models for copper oxygenases: cooperative effects and novel reactivities. *Acc. Chem. Res.* 48, 2397-2406.
50. Chen, Y.-H., Wu, C.-Q., Sung, P.-H., Chan, S.I. and Chen, P.P.-Y. (2020) Turnover of a methane oxidation tricopper cluster catalyst: implications for the mechanism of the particulate methane monooxygenase (pMMO). *ChemCatChem*. 12, 3088-3096.
51. Chan, S.I., Wang, V.C., Lai, J.C., Yu, S.S., Chen, P.P., Chen, K.H., Chen, C.L. and Chan, M.K. (2007) Redox potentiometry studies of particulate methane monooxygenase: support for a trinuclear copper cluster active site. *Angew. Chem. Int. Ed.* 46, 1992-1994.
52. Himes, R.A., Barnese, K. and Karlin, K.D. (2010) One is lonely and three is a crowd: two coppers are for methane oxidation. *Angew. Chem. Int. Ed.* 49, 6714-6716.
53. Ross, M.O., MacMillan, F., Wang, J., Nisthal, A., Lawton, T.J., Olafson, B.D., Mayo, S.L., Rosenzweig, A.C. and Hoffman, B.M. (2019) Particulate methane monooxygenase contains only mononuclear copper centers. *Science* 364, 566-570.
54. Ro, S.Y., Schachner, L.F., Koo, C.W., Purohit, R., Remis, J.P., Kenney, G.E., Liauw, B.W., Thomas, P.M., Patrie, S.M., Kelleher, N.L. *et al.* (2019) Native top-down mass spectrometry provides insights into the copper centers of membrane-bound methane monooxygenase. *Nat. Commun.* 10, 2675.
55. Kirillova, M.V., Kozlov, Y.N., Shul’pina, L.S., Lyakin, O.Y., Kirillov, A.M., Talsi, E.P., Pombeiro, A.J.L. and Shul’pin, G.B. (2009) Remarkably fast oxidation of alkanes by hydrogen peroxide catalyzed by a tetracopper(II) triethanolaminate complex: promoting effects of acid co-catalysts and water, kinetic and mechanistic features. *J. Catal.* 268, 26-38.
56. Shilov, A.E. and Shul'pin, G.B. (1997) Activation of C-H bonds by metal complexes. *Chem. Rev.* 97, 2879-2932.
57. Periana, R.A., Taube, D.J., Gamble, S., Taube, H., Satoh, T. and Fujii, H. (1998) Platinum catalysts for the high-yield oxidation of methane to a methanol derivative. *Science* 280, 560-564.
58. Zimmermann, T., Soorholtz, M., Bilke, M. and Schuth, F. (2016) Selective methane oxidation catalyzed by platinum salts in oleum at turnover frequencies of large-scale industrial processes. *J. Am. Chem. Soc.* 138, 12395-12400.
59. Mironov, O.A., Bischof, S.M., Konnick, M.M., Hashiguchi, B.G., Ziatdinov, V.R., Goddard, W.A., 3rd, Ahlquist, M. and Periana, R.A. (2013) Using reduced catalysts for oxidation reactions: mechanistic studies of the "Periana-Catalytica" system for CH_4 oxidation. *J. Am. Chem. Soc.* 135, 14644-14658.
60. Soorholtz, M., Jones, L.C., Samuelis, D., Weidenthaler, C., White, R.J., Titirici, M.-M., Cullen, D.A., Zimmermann, T., Antonietti, M., Maier, J. *et al.* (2016) Local platinum environments in a solid analogue of the molecular Periana catalyst. *ACS Catal.* 6, 2332-2340.

61. Shul'pin, G. (2016) New trends in oxidative functionalization of carbon–hydrogen bonds: a review. *Catalysts* 6, 50.
62. Shteinman, A.A. (2017) Activation and selective oxy-functionalization of alkanes with metal complexes: Shilov reaction and some new aspects. *J. Mol. Catal. A: Chem.* 426, 305-315.
63. Kim, R.S., Nazemi, A., Cundari, T.R. and Surendranath, Y. (2020) A Pd^{III} sulfate dimer initiates rapid methane monofunctionalization by H atom abstraction. *ACS Catal.* 10, 14782-14792.
64. Basset, J.M., Coperet, C., Soulivong, D., Taoufik, M. and Cazat, J.T. (2010) Metathesis of alkanes and related reactions. *Acc. Chem. Res.* 43, 323-334.
65. Basset, J.M., Coperet, C., Soulivong, D., Taoufik, M. and Thivolle-Cazat, J. (2006) From olefin to alkane metathesis: a historical point of view. *Angew. Chem. Int. Ed.* 45, 6082-6085.
66. Nawara-Hultzsch, A.J., Hackenberg, J.D., Punji, B., Supplee, C., Emge, T.J., Bailey, B.C., Schrock, R.R., Brookhart, M. and Goldman, A.S. (2013) Rational design of highly active "hybrid" phosphine–phosphinite pincer iridium catalysts for alkane metathesis. *ACS Catal.* 3, 2505-2514.
67. Goldman, A.S., Roy, A.H., Huang, Z., Ahuja, R., Schinski, W. and Brookhart, M. (2006) Catalytic alkane metathesis by tandem alkane dehydrogenation-olefin metathesis. *Science* 312, 257-261.
68. Waterman, R. (2013) σ-Bond Metathesis: A 30-Year Retrospective. *Organometallics* 32, 7249-7263.
69. Perutz, R.N. and Sabo-Etienne, S. (2007) The σ-CAM Mechanism: σ-complexes as the basis of σ-bond metathesis at late-transition-metal centers. *Angew. Chem. Int. Ed.* 46, 2578-2592.
70. Liu, F., Pak, E.B., Singh, B., Jensen, C.M. and Goldman, A.S. (1999) Dehydrogenation of n-alkanes catalyzed by iridium "pincer" complexes: regioselective formation of α-olefins. *J. Am. Chem. Soc.* 121, 4086-4087.
71. Sautet, P. and Delbecq, F. (2010) Catalysis and surface organometallic chemistry: a view from theory and simulations. *Chem. Rev.* 110, 1788-1806.
72. Rataboul, F., Coperet, C., Lefort, L., de Mallmann, A., Thivolle-Cazat, J. and Basset, J.M. (2007) Synthesis, characterization and propane metathesis activity of a tantalum-hydride prepared on high surface area "silica supported zirconium hydroxide". *Dalton Trans*, 923-927.
73. He, J., Wasa, M., Chan, K.S.L., Shao, Q. and Yu, J.Q. (2017) Palladium-catalyzed transformations of alkyl C-H bonds. *Chem. Rev.* 117, 8754-8786.
74. Chu, J.C.K. and Rovis, T. (2018) Complementary strategies for directed $C(sp^3)$-H functionalization: a comparison of transition-metal-catalyzed activation, hydrogen atom transfer, and carbene/nitrene transfer. *Angew. Chem. Int. Ed.* 57, 62-101.
75. Yi, H., Zhang, G., Wang, H., Huang, Z., Wang, J., Singh, A.K. and Lei, A. (2017) Recent advances in radical C-H activation/radical cross-coupling. *Chem. Rev.* 117, 9016-9085.
76. Zhang, F.L., Hong, K., Li, T.J., Park, H. and Yu, J.Q. (2016) Functionalization of $C(sp^3)$-H bonds using a transient directing group. *Science* 351, 252-256.
77. Young, R.D., Lawes, D.J., Hill, A.F. and Ball, G.E. (2012) Observation of a tungsten alkane sigma-complex showing selective binding of methyl groups using FTIR and NMR spectroscopies. *J. Am. Chem. Soc.* 134, 8294-8297.
78. Torres, O., Calladine, J.A., Duckett, S.B., George, M.W. and Perutz, R.N. (2015) Detection of σ-alkane complexes of manganese by NMR and IR spectroscopy in solution: $(\eta^5\text{-}C_5H_5)Mn(CO)_2$(ethane) and $(\eta^5\text{-}C_5H_5)Mn(CO)_2$(isopentane). *Chem. Sci.* 6, 418-424.
79. Wasserman, E.P., Moore, C.B. and Bergman, R.G. (1992) Gas-phase rates of alkane C-H oxidative addition to a transient CpRh(CO) complex. *Science* 255, 315-318.
80. Ball, G.E., Brookes, C.M., Cowan, A.J., Darwish, T.A., George, M.W., Kawanami, H.K., Portius, P. and Rourke, J.P. (2007) A delicate balance of complexation vs. activation of alkanes interacting with

[Re(Cp)(CO)(PF_3)] studied with NMR and time-resolved IR spectroscopy. *Proc. Natl. Acad. Sci. USA* 104, 6927-6932.
81. Salazar, C.A., Flesch, K.N., Haines, B.E., Zhou, P.S., Musaev, D.G. and Stahl, S.S. (2020) Tailored quinones support high-turnover Pd catalysts for oxidative C-H arylation with O_2. *Science* 370, 1454-1460.
82. Nandy, A. and Kulik, H.J. (2020) Why conventional design rules for C–H activation fail for open-shell transition-metal catalysts. *ACS Catal.* 10, 15033-15047.
83. Lang, S.M. and Bernhardt, T.M. (2012) Gas phase metal cluster model systems for heterogeneous catalysis. *Phys. Chem. Chem. Phys.* 14, 9255-9269.
84. Luo, Z., Castleman, A.W., Jr. and Khanna, S.N. (2016) Reactivity of metal clusters. *Chem. Rev.* 116, 14456-14492.
85. Ferrari, P., Vanbuel, J., Janssens, E. and Lievens, P. (2018) Tuning the reactivity of small metal clusters by heteroatom doping. *Acc. Chem. Res.* 51, 3174-3182.
86. Boronat, M., Leyva-Perez, A. and Corma, A. (2014) Theoretical and experimental insights into the origin of the catalytic activity of subnanometric gold clusters: attempts to predict reactivity with clusters and nanoparticles of gold. *Acc. Chem. Res.* 47, 834-844.
87. Lang, S.M., Bernhardt, T.M., Chernyy, V., Bakker, J.M., Barnett, R.N. and Landman, U. (2017) Selective C-H bond cleavage in methane by small gold clusters. *Angew. Chem. Int. Ed.* 56, 13406-13410.
88. Zhao, Y.X., Li, Z.Y., Yang, Y. and He, S.G. (2018) Methane activation by gas phase atomic clusters. *Acc. Chem. Res.* 51, 2603-2610.
89. Bond, G.C. (2002) Strategy of research on supported metal catalysts. Problems of structure-sensitive reactions in the gas phase. *Acc. Chem. Res.* 26, 490-495.
90. Gillespie, W. (1981) The structure sensitivity of n-heptane dehydrocyclization and hydrogenolysis catalyzed by platinum single crystals at atmospheric pressure. *J. Catal.* 70, 147-159.
91. Alayoglu, S., Aliaga, C., Sprung, C. and Somorjai, G.A. (2011) Size and shape dependence on Pt nanoparticles for the methylcyclopentane/hydrogen ring opening/ring enlargement reaction. *Catal. Lett.* 141, 914-924.
92. Crampton, A.S., Rötzer, M.D., Ridge, C.J., Yoon, B., Schweinberger, F.F., Landman, U. and Heiz, U. (2016) Assessing the concept of structure sensitivity or insensitivity for sub-nanometer catalyst materials. *Surf. Sci.* 652, 7-19.
93. Samantaray, M.K., D'Elia, V., Pump, E., Falivene, L., Harb, M., Ould Chikh, S., Cavallo, L. and Basset, J.M. (2020) The comparison between single atom catalysis and surface organometallic catalysis. *Chem. Rev.* 120, 734-813.
94. Guo, X., Fang, G., Li, G., Ma, H., Fan, H., Yu, L., Ma, C., Wu, X., Deng, D., Wei, M. *et al.* (2014) Direct, nonoxidative conversion of methane to ethylene, aromatics, and hydrogen. *Science* 344, 616-619.
95. Xie, P., Pu, T., Nie, A., Hwang, S., Purdy, S.C., Yu, W., Su, D., Miller, J.T. and Wang, C. (2018) Nanoceria-supported single-atom platinum catalysts for direct methane conversion. *ACS Catal.* 8, 4044-4048.
96. Ismagilov, Z.R., Matus, E.V. and Tsikoza, L.T. (2008) Direct conversion of methane on Mo/ZSM-5 catalysts to produce benzene and hydrogen: achievements and perspectives. *Energy Environ. Sci.* 1, 526-541.
97. Gao, J., Zheng, Y., Jehng, J.M., Tang, Y., Wachs, I.E. and Podkolzin, S.G. (2015) Catalysis. Identification of molybdenum oxide nanostructures on zeolites for natural gas conversion. *Science* 348, 686-690.

98. Li, G., Vollmer, I., Liu, C., Gascon, J. and Pidko, E.A. (2019) Structure and reactivity of the Mo/ZSM-5 dehydroaromatization catalyst: an operando computational study. *ACS Catal.* 9, 8731-8737.
99. Hou, Y., Ogasawara, S., Fukuoka, A. and Kobayashi, H. (2017) Zeolite-supported rhodium sub-nano cluster catalyst for low-temperature selective oxidation of methane to syngas. *Catal. Sci. Technol.* 7, 6132-6139.
100. Ikuno, T., Zheng, J., Vjunov, A., Sanchez-Sanchez, M., Ortuno, M.A., Pahls, D.R., Fulton, J.L., Camaioni, D.M., Li, Z., Ray, D. *et al.* (2017) Methane oxidation to methanol catalyzed by Cu-oxo clusters stabilized in NU-1000 metal-organic framework. *J. Am. Chem. Soc.* 139, 10294-10301.
101. Sushkevich, V.L., Palagin, D., Ranocchiari, M. and van Bokhoven, J.A. (2017) Selective anaerobic oxidation of methane enables direct synthesis of methanol. *Science* 356, 523-527.
102. Woertink, J.S., Smeets, P.J., Groothaert, M.H., Vance, M.A., Sels, B.F., Schoonheydt, R.A. and Solomon, E.I. (2009) A $[Cu_2O]^{2+}$ core in Cu-ZSM-5, the active site in the oxidation of methane to methanol. *Proc. Natl. Acad. Sci. USA* 106, 18908-18913.
103. Grundner, S., Markovits, M.A., Li, G., Tromp, M., Pidko, E.A., Hensen, E.J., Jentys, A., Sanchez-Sanchez, M. and Lercher, J.A. (2015) Single-site trinuclear copper oxygen clusters in mordenite for selective conversion of methane to methanol. *Nat. Commun.* 6, 7546.
104. Latimer, A.A., Kulkarni, A.R., Aljama, H., Montoya, J.H., Yoo, J.S., Tsai, C., Abild-Pedersen, F., Studt, F. and Norskov, J.K. (2017) Understanding trends in C-H bond activation in heterogeneous catalysis. *Nat. Mater.* 16, 225-229.
105. Narsimhan, K., Iyoki, K., Dinh, K. and Roman-Leshkov, Y. (2016) Catalytic oxidation of methane into methanol over copper-exchanged zeolites with oxygen at low temperature. *ACS Cent. Sci.* 2, 424-429.
106. Tomkins, P., Mansouri, A., Bozbag, S.E., Krumeich, F., Park, M.B., Alayon, E.M., Ranocchiari, M. and van Bokhoven, J.A. (2016) Isothermal cyclic conversion of methane into methanol over copper-exchanged zeolite at low temperature. *Angew. Chem. Int. Ed.* 55, 5467-5471.
107. Dinh, K.T., Sullivan, M.M., Serna, P., Meyer, R.J., Dincă, M. and Román-Leshkov, Y. (2018) Viewpoint on the partial oxidation of methane to methanol using Cu- and Fe-exchanged zeolites. *ACS Catal.* 8, 8306-8313.
108. Tang, Y., Li, Y., Fung, V., Jiang, D.E., Huang, W., Zhang, S., Iwasawa, Y., Sakata, T., Nguyen, L., Zhang, X. *et al.* (2018) Single rhodium atoms anchored in micropores for efficient transformation of methane under mild conditions. *Nat. Commun.* 9, 1231.
109. Shan, J., Li, M., Allard, L.F., Lee, S. and Flytzani-Stephanopoulos, M. (2017) Mild oxidation of methane to methanol or acetic acid on supported isolated rhodium catalysts. *Nature* 551, 605-608.
110. Cheung, H., Tanke, R.S. and Torrence, G.P. (2011) Acetic acid. *in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KGaA*.
111. Huang, K., Miller, J.B., Huber, G.W., Dumesic, J.A. and Maravelias, C.T. (2018) A general framework for the evaluation of direct nonoxidative methane conversion strategies. *Joule* 2, 349-365.
112. Galadima, A. and Muraza, O. (2016) Revisiting the oxidative coupling of methane to ethylene in the golden period of shale gas: A review. *J. Ind. Eng. Chem.* 37, 1-13.
113. Grant, J.T., Venegas, J.M., McDermott, W.P. and Hermans, I. (2018) Aerobic oxidations of light alkanes over solid metal oxide catalysts. *Chem. Rev.* 118, 2769-2815.
114. Millet, J.-M.M. and Védrine, J.C. (2001) Importance of site isolation in the oxidation of isobutyric acid to methacrylic acid on iron phosphate catalysts. *Top. Catal.* 15, 139-144.
115. Zhang, Z., Zhu, Q., Sadakane, M., Murayama, T., Hiyoshi, N., Yamamoto, A., Hata, S., Yoshida, H., Ishikawa, S., Hara, M. *et al.* (2018) A zeolitic vanadotungstate family with structural diversity and ultrahigh porosity for catalysis. *Nat. Commun.* 9, 3789.

116. Le Bars, J., Auroux, A., Forissier, M. and Vedrine, J.C. (1996) Active sites of V_2O_5/γ-Al_2O_3 catalysts in the oxidative dehydrogenation of ethane. *J. Catal.* 162, 250-259.
117. Rozanska, X., Fortrie, R. and Sauer, J. (2014) Size-dependent catalytic activity of supported vanadium oxide species: oxidative dehydrogenation of propane. *J. Am. Chem. Soc.* 136, 7751-7761.
118. Hermans, I., Jacobs, P.A. and Peeters, J. (2006) To the core of autocatalysis in cyclohexane autoxidation. *Chem. Eur. J.* 12, 4229-4240.
119. Liu, L., Arenal, R., Meira, D.M. and Corma, A. (2019) Generation of gold nanoclusters encapsulated in an MCM-22 zeolite for the aerobic oxidation of cyclohexane. *Chem. Commun.* 55, 1607-1610.
120. Hammond, C., Forde, M.M., Ab Rahim, M.H., Thetford, A., He, Q., Jenkins, R.L., Dimitratos, N., Lopez-Sanchez, J.A., Dummer, N.F., Murphy, D.M. *et al.* (2012) Direct catalytic conversion of methane to methanol in an aqueous medium by using copper-promoted Fe-ZSM-5. *Angew. Chem. Int. Ed.* 51, 5129-5133.
121. Olmedo, A., Aranda, C., Del Rio, J.C., Kiebist, J., Scheibner, K., Martinez, A.T. and Gutierrez, A. (2016) From Alkanes to Carboxylic Acids: Terminal Oxygenation by a Fungal Peroxygenase. *Angew. Chem. Int. Ed.* 55, 12248-12251.
122. Agarwal, N., Freakley, S.J., McVicker, R.U., Althahban, S.M., Dimitratos, N., He, Q., Morgan, D.J., Jenkins, R.L., Willock, D.J., Taylor, S.H. *et al.* (2017) Aqueous Au-Pd colloids catalyze selective CH_4 oxidation to CH_3OH with O_2 under mild conditions. *Science* 358, 223-227.
123. Retcher, B., Costa, J.S., Tang, J., Hage, R., Gamez, P. and Reedijk, J. (2008) Unexpected high oxidation of cyclohexane by Fe salts and dihydrogen peroxide in acetonitrile. *J. Mol. Catal. A: Chem.* 286, 1-5.
124. Chen, M.S. and White, M.C. (2007) A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. *Science* 318, 783-787.
125. Zhou, L., Martirez, J.M.P., Finzel, J., Zhang, C., Swearer, D.F., Tian, S., Robatjazi, H., Lou, M., Dong, L., Henderson, L. *et al.* (2020) Light-driven methane dry reforming with single atomic site antenna-reactor plasmonic photocatalysts. *Nat. Energy* 5, 61-70.
126. Akri, M., Zhao, S., Li, X., Zang, K., Lee, A.F., Isaacs, M.A., Xi, W., Gangarajula, Y., Luo, J., Ren, Y. *et al.* (2019) Atomically dispersed nickel as coke-resistant active sites for methane dry reforming. *Nat. Commun.* 10, 5181.
127. Zuo, Z., Liu, S., Wang, Z., Liu, C., Huang, W., Huang, J. and Liu, P. (2018) Dry reforming of methane on single-site Ni/MgO catalysts: importance of site confinement. *ACS Catal.* 8, 9821-9835.
128. Xie, Z., Tian, D., Xie, M., Yang, S.-Z., Xu, Y., Rui, N., Lee, J.H., Senanayake, S.D., Li, K., Wang, H. *et al.* (2020) Interfacial active sites for CO_2 assisted selective cleavage of C–C/C–H bonds in ethane. *Chem* 6, 2703-2716.
129. Xie, Z., Xu, Y., Xie, M., Chen, X., Lee, J.H., Stavitski, E., Kattel, S. and Chen, J.G. (2020) Reactions of CO_2 and ethane enable CO bond insertion for production of C3 oxygenates. *Nat. Commun.* 11, 1887.
130. Cryle, M.J. and De Voss, J.J. (2004) Carbon-carbon bond cleavage by cytochrome p450(BioI)(CYP107H1). *Chem. Commun.*, 86-87.
131. Guo, X., Xu, M., She, M., Zhu, Y., Shi, T., Chen, Z., Peng, L., Guo, X., Lin, M. and Ding, W. (2020) Morphology-reserved synthesis of discrete nanosheets of CuO@SAPO-34 and pore mouth catalysis for one-pot oxidation of cyclohexane. *Angew. Chem. Int. Ed.* 59, 2606-2611.
132. Liu, L., Lopez-Haro, M., Meira, D.M., Concepcion, P., Calvino, J.J. and Corma, A. (2020) Regioselective generation of single-site iridium atoms and their evolution into stabilized subnanometric iridium clusters in MWW zeolite. *Angew. Chem. Int. Ed.* 59, 15695-15702.

133. McVicker, G., Daage, M., Touvelle, M.S., Hudson, C.W., Klein, D.P., Jr., W.C.B., Cook, B.R., Chen, J.G., Hantzer, S., Vaughan, D.E.W. *et al.* (2002) Selective ring opening of naphthenic molecules. *J. Catal.* 210, 137-148.
134. Flaherty, D.W., Uzun, A. and Iglesia, E. (2015) Catalytic ring opening of cycloalkanes on Ir clusters: alkyl substitution effects on the structure and stability of C–C bond cleavage transition states. *J. Phys. Chem. C* 119, 2597-2613.
135. Suárez, N., Arribas, M.A., Moreno, A. and Martínez, A. (2020) High-performing Ir- and Pt-containing catalysts based on mesoporous beta zeolite for the selective ring opening of decalin. *Catal. Sci. Technol.* 10, 1073-1085.
136. Weitkamp, J. (2012) Catalytic hydrocracking-mechanisms and versatility of the process. *ChemCatChem* 4, 292-306.
137. Weisz, P.B. (1962) Polyfunctional heterogeneous catalysis. *Adv. Catal.* 13, 137-190.
138. Zecevic, J., Vanbutsele, G., de Jong, K.P. and Martens, J.A. (2015) Nanoscale intimacy in bifunctional catalysts for selective conversion of hydrocarbons. *Nature* 528, 245-248.
139. Liu, Y., Li, Z., Yu, Q., Chen, Y., Chai, Z., Zhao, G., Liu, S., Cheong, W.C., Pan, Y., Zhang, Q. *et al.* (2019) A general strategy for fabricating isolated single metal atomic site catalysts in Y zeolite. *J. Am. Chem. Soc.* 141, 9305-9311.
140. Shi, H., Gutiérrez, O.Y., Haller, G.L., Mei, D., Rousseau, R. and Lercher, J.A. (2013) Structure sensitivity of hydrogenolytic cleavage of endocyclic and exocyclic C–C bonds in methylcyclohexane over supported iridium particles. *J. Catal.* 297, 70-78.
141. Liu, L., Lopez-Haro, M., Lopes, C.W., Li, C., Concepcion, P., Simonelli, L., Calvino, J.J. and Corma, A. (2019) Regioselective generation and reactivity control of subnanometric platinum clusters in zeolites for high-temperature catalysis. *Nat. Mater.* 18, 866-873.
142. Sattler, J.J., Ruiz-Martinez, J., Santillan-Jimenez, E. and Weckhuysen, B.M. (2014) Catalytic dehydrogenation of light alkanes on metals and metal oxides. *Chem. Rev.* 114, 10613-10653.
143. Sattler, A., Paccagnini, M., Lanci, M.P., Miseo, S. and Kliewer, C.E. (2019) Platinum catalyzed C–H activation and the effect of metal–support interactions. *ACS Catal.* 10, 710-720.
144. Liu, L., Diaz, U., Arenal, R., Agostini, G., Concepcion, P. and Corma, A. (2017) Generation of subnanometric platinum with high stability during transformation of a 2D zeolite into 3D. *Nat. Mater.* 16, 132-138.
145. Xiao, L., Shan, Y.-L., Sui, Z.-J., Chen, D., Zhou, X.-G., Yuan, W.-K. and Zhu, Y.-A. (2020) Beyond the reverse Horiuti–Polanyi mechanism in propane dehydrogenation over Pt catalysts. *ACS Catal.* 10, 14887-14902.
146. Phadke, N.M., Van der Mynsbrugge, J., Mansoor, E., Getsoian, A.B., Head-Gordon, M. and Bell, A.T. (2018) Characterization of isolated Ga^{3+} cations in Ga/H-MFI prepared by vapor-phase exchange of H-MFI zeolite with $GaCl_3$. *ACS Catal.* 8, 6106-6126.
147. Maeno, Z., Yasumura, S., Wu, X., Huang, M., Liu, C., Toyao, T. and Shimizu, K.I. (2020) Isolated indium hydrides in CHA zeolites: speciation and catalysis for nonoxidative dehydrogenation of ethane. *J. Am. Chem. Soc.* 142, 4820-4832.
148. Kumar, A., Bhatti, T.M. and Goldman, A.S. (2017) Dehydrogenation of alkanes and aliphatic groups by pincer-ligated metal complexes. *Chem. Rev.* 117, 12357-12384.
149. Schreiber, M.W., Plaisance, C.P., Baumgartl, M., Reuter, K., Jentys, A., Bermejo-Deval, R. and Lercher, J.A. (2018) Lewis-Bronsted acid pairs in Ga/H-ZSM-5 to catalyze dehydrogenation of light alkanes. *J. Am. Chem. Soc.* 140, 4849-4859.

150. Harris, J.W., Bates, J.S., Bukowski, B.C., Greeley, J. and Gounder, R. (2020) Opportunities in catalysis over metal-zeotypes enabled by descriptions of active centers beyond their binding site. *ACS Catal.*, 9476-9495.
151. Sun, Q., Wang, N., Fan, Q., Zeng, L., Mayoral, A., Miao, S., Yang, R., Jiang, Z., Zhou, W., Zhang, J. *et al.* (2020) Subnanometer bimetallic platinum-zinc clusters in zeolites for propane dehydrogenation. *Angew. Chem. Int. Ed.* 59, 19450-19459.
152. Choi, M., Wu, Z. and Iglesia, E. (2010) Mercaptosilane-assisted synthesis of metal clusters within zeolites and catalytic consequences of encapsulation. *J. Am. Chem. Soc.* 132, 9129-9137.
153. Yang, Z., Li, H., Zhou, H., Wang, L., Wang, L., Zhu, Q., Xiao, J., Meng, X., Chen, J. and Xiao, F.S. (2020) Coking-resistant iron catalyst in ethane dehydrogenation achieved through siliceous zeolite modulation. *J. Am. Chem. Soc.* 142, 16429-16436.
154. He, S., Wang, B., Dai, X., Sun, C., Bai, Z., Wang, X. and Guo, Q. (2015) Industrial development of long chain paraffin (n-C10^o–C13^o) dehydrogenation catalysts and the deactivation characterization. *Chem. Eng. J.* 275, 298-304.
155. Gupta, M., Hagen, C., Flesher, R.J., Kaska, W.C. and Jensen, C.M. (1996) A highly active alkane dehydrogenation catalyst: stabilization of dihydrido rhodium and iridium complexes by a P–C–P pincer ligand. *Chem. Commun.*, 2083-2084.
156. Sheludko, B., Cunningham, M.T., Goldman, A.S. and Celik, F.E. (2018) Continuous-flow alkane dehydrogenation by supported pincer-ligated iridium catalysts at elevated temperatures. *ACS Catal.* 8, 7828-7841.
157. Xu, D., Wang, S., Wu, B., Huo, C., Qin, Y., Zhang, B., Yin, J., Huang, L., Wen, X., Yang, Y. *et al.* (2018) Tailoring Pt locations in KL zeolite by improved atomic layer deposition for excellent performance in n-heptane aromatization. *J. Catal.* 365, 163-173.
158. Tauster, S. (1990) Molecular die catalysis: Hexane aromatization over Pt/KL. *J. Catal.* 125, 387-389.
159. Zhu, Y., An, Z. and He, J. (2016) Single-atom and small-cluster Pt induced by Sn (IV) sites confined in an LDH lattice for catalytic reforming. *J. Catal.* 341, 44-54.
160. Fadaeerayeni, S., Shan, J., Sarnello, E., Xu, H., Wang, H., Cheng, J., Li, T., Toghiani, H. and Xiang, Y. (2020) Nickel/gallium modified HZSM-5 for ethane aromatization: Influence of metal function on reactivity and stability. *Appl. Catal. A: Gen.*
161. Ahuja, R., Punji, B., Findlater, M., Supplee, C., Schinski, W., Brookhart, M. and Goldman, A.S. (2011) Catalytic dehydroaromatization of n-alkanes by pincer-ligated iridium complexes. *Nat. Chem.* 3, 167-171.
162. Jongpatiwut, S. (2003) n-Octane aromatization on a Pt/KL catalyst prepared by vapor-phase impregnation. *J. Catal.* 218, 1-11.
163. Davis, B.H. (1999) Alkane dehydrocyclization mechanism. *Catal. Today* 53, 443-516.
164. Thawani, A., Rajeev, R. and Sunoj, R.B. (2013) On the mechanism of the dehydroaromatization of hexane to benzene by an iridium pincer catalyst. *Chem. Eur. J.* 19, 4069-4077.
165. Chowdhury, A.D., Weding, N., Julis, J., Franke, R., Jackstell, R. and Beller, M. (2014) Towards a practical development of light-driven acceptorless alkane dehydrogenation. *Angew. Chem. Int. Ed.* 53, 6477-6481.
166. S, U.D., Julia, F., Luridiana, A., Douglas, J.J. and Leonori, D. (2020) A photochemical dehydrogenative strategy for aniline synthesis. *Nature* 584, 75-81.
167. Soulivong, D., Coperet, C., Thivolle-Cazat, J., Basset, J.M., Maunders, B.M., Pardy, R.B. and Sunley, G.J. (2004) Cross-metathesis of propane and methane: a catalytic reaction of C-C bond cleavage of a higher alkane by methane. *Angew. Chem. Int. Ed.* 43, 5366-5369.

168. Vidal, V.V., Theolier, A., Thivolle-Cazat, J. and Basset, J.M. (1997) Metathesis of alkanes catalyzed by silica-supported transition metal hydrides. *Science* 276, 99-102.
169. Basset, J.M., Coperet, C., Lefort, L., Maunders, B.M., Maury, O., Le Roux, E., Saggio, G., Soignier, S., Soulivong, D., Sunley, G.J. *et al.* (2005) Primary products and mechanistic considerations in alkane metathesis. *J. Am. Chem. Soc.* 127, 8604-8605.
170. Samantaray, M.K., Kavitake, S., Morlanes, N., Abou-Hamad, E., Hamieh, A., Dey, R. and Basset, J.M. (2017) Unearthing a well-defined highly active bimetallic W/Ti precatalyst anchored on a single silica surface for metathesis of propane. *J. Am. Chem. Soc.* 139, 3522-3527.
171. Huang, W., Xie, K.C., Wang, J.P., Gao, Z.H., Yin, L.H. and Zhu, Q.M. (2001) Possibility of direct conversion of CH_4 and CO_2 to high-value products. *J. Catal.* 201, 100-104.
172. Hoehler, T.M., Alperin, M.J., Albert, D.B. and Martens, C.S. (1994) Field and laboratory studies of methane oxidation in an anoxic marine sediment: Evidence for a methanogen-sulfate reducer consortium. *Global Biogeochemical Cycles* 8, 451-463.
173. Rabie, A.M., Betiha, M.A. and Park, S.-E. (2017) Direct synthesis of acetic acid by simultaneous co-activation of methane and CO_2 over Cu-exchanged ZSM-5 catalysts. *Appl. Catal. B: Environ.* 215, 50-59.
174. Wang, S., Guo, S., Luo, Y., Qin, Z., Chen, Y., Dong, M., Li, J., Fan, W. and Wang, J. (2019) Direct synthesis of acetic acid from carbon dioxide and methane over Cu-modulated BEA, MFI, MOR and TON zeolites: a density functional theory study. *Catal. Sci. Technol.* 9, 6613-6626.
175. Wong, K.S., Vazhnova, T., Rigby, S.P. and Lukyanov, D.B. (2013) Temperature effects in benzene alkylation with ethane into ethylbenzene over a PtH-MFI bifunctional catalyst. *Appl. Catal. A: Gen.* 454, 137-144.
176. Alotaibi, A., Bayahia, H., Kozhevnikova, E.F. and Kozhevnikov, I.V. (2015) Selective alkylation of benzene with propane over bifunctional Pt-heteropoly acid catalyst. *ACS Catal.* 5, 5512-5518.
177. Lin, R., Amrute, A.P. and Perez-Ramirez, J. (2017) Halogen-mediated conversion of hydrocarbons to commodities. *Chem. Rev.* 117, 4182-4247.
178. Malta, G., Kondrat, S.A., Freakley, S.J., Davies, C.J., Lu, L., Dawson, S., Thetford, A., Gibson, E.K., Morgan, D.J., Jones, W. *et al.* (2017) Identification of single-site gold catalysis in acetylene hydrochlorination. *Science* 355, 1399-1403.
179. Paunovic, V., Zichittella, G., Moser, M., Amrute, A.P. and Perez-Ramirez, J. (2016) Catalyst design for natural-gas upgrading through oxybromination chemistry. *Nat. Chem.* 8, 803-809.
180. Jia, X., Qin, C., Friedberger, T., Guan, Z. and Huang, Z. (2016) Efficient and selective degradation of polyethylenes into liquid fuels and waxes under mild conditions. *Sci. Adv.* 2, e1501591.
181. Celik, G., Kennedy, R.M., Hackler, R.A., Ferrandon, M., Tennakoon, A., Patnaik, S., LaPointe, A.M., Ammal, S.C., Heyden, A., Perras, F.A. *et al.* (2019) Upcycling single-use polyethylene into high-quality liquid products. *ACS Cent. Sci.* 5, 1795-1803.
182. Zhang, F., Zeng, M., Yappert, R.D., Sun, J., Lee, Y.H., LaPointe, A.M., Peters, B., Abu-Omar, M.M. and Scott, S.L. (2020) Polyethylene upcycling to long-chain alkylaromatics by tandem hydrogenolysis/aromatization. *Science* 370, 437-441.
183. Pérez, P.J. (2012) Alkane C-H activation by single-site metal catalysis, Springer.
184. Demonceau, A., Noels, A.F. and Hubert, A.J. (1989) Catalytic functionalisation of alkanes: evidence for attractive steric effects in reactions of rhodium carbenoids. *J. Mol. Catal.* 57, 149-152.
185. Liu, Z., Cao, S., Yu, W., Wu, J., Yi, F., Anderson, E.A. and Bi, X. (2020) Site-selective C–H benzylation of alkanes with N-triftosylhydrazones leading to alkyl aromatics. *Chem* 6, 2110-2124.
186. Reddy, R.P. and Davies, H.M. (2006) Dirhodium tetracarboxylates derived from adamantylglycine as chiral catalysts for enantioselective C-h aminations. *Org. Lett.* 8, 5013-5016.

187. Despagnet-Ayoub, E., Jacob, K., Vendier, L., Etienne, M., Álvarez, E., Caballero, A., Díaz-Requejo, M.M. and Pérez, P.J. (2008) A new perfluorinated F_{21}-Tp scorpionate ligand: enhanced alkane functionalization by carbene insertion with (F_{21}-Tp)M Catalysts (M = Cu, Ag). *Organometallics* 27, 4779-4787.
188. Fortea-Perez, F.R., Mon, M., Ferrando-Soria, J., Boronat, M., Leyva-Perez, A., Corma, A., Herrera, J.M., Osadchii, D., Gascon, J., Armentano, D. *et al.* (2017) The MOF-driven synthesis of supported palladium clusters with catalytic activity for carbene-mediated chemistry. *Nat. Mater.* 16, 760-766.
189. Tang, X., Gan, L., Zhang, X. and Huang, Z. (2020) n-Alkanes to n-alcohols: Formal primary C horizontal line H bond hydroxymethylation via quadruple relay catalysis. *Sci. Adv.* 6, eabc6688.
190. Zhang, J., Zheng, C., Zhang, M., Qiu, Y., Xu, Q., Cheong, W.-C., Chen, W., Zheng, L., Gu, L., Hu, Z. *et al.* (2020) Controlling N-doping type in carbon to boost single-atom site Cu catalyzed transfer hydrogenation of quinoline. *Nano Res.* 13, 3082-3087.
191. Liu, L. and Corma, A. (2020) Evolution of isolated atoms and clusters in catalysis. *Trends Chem.* 2, 383-400.
192. Grommet, A.B., Feller, M. and Klajn, R. (2020) Chemical reactivity under nanoconfinement. *Nat. Nanotechnol.* 15, 256-271.
193. Mitschke, B., Turberg, M. and List, B. (2020) Confinement as a unifying element in selective catalysis. *Chem* 6, 2515-2532.
194. Ariga, K., Ito, H., Hill, J.P. and Tsukube, H. (2012) Molecular recognition: from solution science to nano/materials technology. *Chem. Soc. Rev.* 41, 5800-5835.
195. Ma, L., Falkowski, J.M., Abney, C. and Lin, W. (2010) A series of isoreticular chiral metal-organic frameworks as a tunable platform for asymmetric catalysis. *Nat. Chem.* 2, 838-846.
196. Liu, L., Meira, D.M., Arenal, R., Concepcion, P., Puga, A.V. and Corma, A. (2019) Determination of the evolution of heterogeneous single metal atoms and nanoclusters under reaction conditions: which are the working catalytic sites? *ACS Catal.* 9, 10626-10639.
197. Ikuno, T., Grundner, S., Jentys, A., Li, G., Pidko, E., Fulton, J., Sanchez-Sanchez, M. and Lercher, J.A. (2019) Formation of active Cu-oxo clusters for methane oxidation in Cu-exchanged mordenite. *J. Phys. Chem. C* 123, 8759-8769.
198. Citek, C., Gary, J.B., Wasinger, E.C. and Stack, T.D. (2015) Chemical plausibility of Cu(III) with biological ligation in pMMO. *J. Am. Chem. Soc.* 137, 6991-6994.
199. Rivero-Crespo, M.A., Mon, M., Ferrando-Soria, J., Lopes, C.W., Boronat, M., Leyva-Perez, A., Corma, A., Hernandez-Garrido, J.C., Lopez-Haro, M., Calvino, J.J. *et al.* (2018) Confined Pt_1^{1+} water clusters in a MOF catalyze the low-temperature water-gas shift reaction with both CO_2 oxygen atoms coming from water. *Angew. Chem. Int. Ed.* 57, 17094-17099.
200. Ji, P., Feng, X., Veroneau, S.S., Song, Y. and Lin, W. (2017) Trivalent zirconium and hafnium metal-organic frameworks for catalytic 1,4-dearomative additions of pyridines and quinolines. *J. Am. Chem. Soc.* 139, 15600-15603.
201. Jin, Z., Wang, L., Zuidema, E., Mondal, K., Zhang, M., Zhang, J., Wang, C., Meng, X., Yang, H., Mesters, C. *et al.* (2020) Hydrophobic zeolite modification for in situ peroxide formation in methane oxidation to methanol. *Science* 367, 193-197.
202. Cortes-Clerget, M., Akporji, N., Zhou, J., Gao, F., Guo, P., Parmentier, M., Gallou, F., Berthon, J.Y. and Lipshutz, B.H. (2019) Bridging the gap between transition metal- and bio-catalysis via aqueous micellar catalysis. *Nat. Commun.* 10, 2169.
203. Garcia-Garcia, P., Moreno, J.M., Diaz, U., Bruix, M. and Corma, A. (2016) Organic-inorganic supramolecular solid catalyst boosts organic reactions in water. *Nat. Commun.* 7, 10835.

204. Li, C., Yan, L., Lu, L., Xiong, K., Wang, W., Jiang, M., Liu, J., Song, X., Zhan, Z., Jiang, Z. *et al.* (2016) Single atom dispersed Rh-biphephos&PPh$_3$@porous organic copolymers: highly efficient catalysts for continuous fixed-bed hydroformylation of propene. *Green Chem.* 18, 2995-3005.
205. Gallego, E.M., Portilla, M.T., Paris, C., Leon-Escamilla, A., Boronat, M., Moliner, M. and Corma, A. (2017) "Ab initio" synthesis of zeolites for preestablished catalytic reactions. *Science* 355, 1051-1054.
206. Li, C., Paris, C., Martínez-Triguero, J., Boronat, M., Moliner, M. and Corma, A. (2018) Synthesis of reaction-adapted zeolites as methanol-to-olefins catalysts with mimics of reaction intermediates as organic structure-directing agents. *Nat. Catal.* 1, 547-554.
207. Gallego, E.M., Paris, C., Cantin, A., Moliner, M. and Corma, A. (2019) Conceptual similarities between zeolites and artificial enzymes. *Chem. Sci.* 10, 8009-8015.
208. Tennakoon, A., Wu, X., Paterson, A.L., Patnaik, S., Pei, Y., LaPointe, A.M., Ammal, S.C., Hackler, R.A., Heyden, A., Slowing, I.I. *et al.* (2020) Catalytic upcycling of high-density polyethylene via a processive mechanism. *Nat. Catal.*
209. Li, L., Lv, J., Shen, Y., Guo, X., Peng, L., Xie, Z. and Ding, W. (2014) Hexadecylphosphate-functionalized iron oxide nanoparticles: mild oxidation of benzyl C–H bonds exclusive to carbonyls by molecular oxygen. *ACS Catal.* 4, 2746-2752.
210. Chen, H., Schlecht, S., Semple, T.C. and Hartwig, J.F. (2000) Thermal, catalytic, regiospecific functionalization of alkanes. *Science* 287, 1995-1997.
211. Zhang, X., Huang, Z., Ferrandon, M., Yang, D., Robison, L., Li, P., Wang, T.C., Delferro, M. and Farha, O.K. (2018) Catalytic chemoselective functionalization of methane in a metal‒organic framework. *Nat. Catal.* 1, 356-362.
212. Van Velthoven, N., Waitschat, S., Chavan, S.M., Liu, P., Smolders, S., Vercammen, J., Bueken, B., Bals, S., Lillerud, K.P., Stock, N. *et al.* (2019) Single-site metal-organic framework catalysts for the oxidative coupling of arenes via C-H/C-H activation. *Chem. Sci.* 10, 3616-3622.
213. Simons, M.C., Vitillo, J.G., Babucci, M., Hoffman, A.S., Boubnov, A., Beauvais, M.L., Chen, Z., Cramer, C.J., Chapman, K.W., Bare, S.R. *et al.* (2019) Structure, dynamics, and reactivity for light alkane oxidation of Fe(II) sites situated in the nodes of a metal-organic framework. *J. Am. Chem. Soc.* 141, 18142-18151.
214. Devos, J., Bols, M.L., Plessers, D., Goethem, C.V., Seo, J.W., Hwang, S.-J., Sels, B.F. and Dusselier, M. (2019) Synthesis–structure–activity relations in Fe-CHA for C–H activation: control of Al distribution by interzeolite conversion. *Chem. Mater.* 32, 273-285.
215. Liu, L., Lopez-Haro, M., Lopes, C.W., Rojas-Buzo, S., Concepcion, P., Manzorro, R., Simonelli, L., Sattler, A., Serna, P., Calvino, J.J. *et al.* (2020) Structural modulation and direct measurement of subnanometric bimetallic PtSn clusters confined in zeolites. *Nat. Catal.* 3, 628-638.
216. Sancheti, S.P., Urvashi, Shah, M.P. and Patil, N.T. (2020) Ternary catalysis: a stepping stone toward multicatalysis. *ACS Catal.* 10, 3462-3489.
217. Climent, M.J., Corma, A., Iborra, S. and Sabater, M.J. (2014) Heterogeneous catalysis for tandem reactions. *ACS Catal.* 4, 870-891.
218. Dinh, L.V., Li, B., Kumar, A., Schinski, W., Field, K.D., Kuperman, A., Celik, F.E. and Goldman, A.S. (2016) Alkyl–aryl coupling catalyzed by tandem systems of pincer-ligated iridium complexes and zeolites. *ACS Catal.* 6, 2836-2841.
219. Liu, L. and Corma, A. (2021) Confining isolated atoms and clusters in crystalline porous materials for catalysis. *Nat. Rev. Mater.* 6, 244–263.

220. Liu, L., Lopez-Haro, M., Lopes, C.W., Meira, D.M., Concepcion, P., Calvino, J.J. and Corma, A. (2020) Atomic-level understanding on the evolution behavior of subnanometric Pt and Sn species during high-temperature treatments for generation of dense PtSn clusters in zeolites. *J. Catal.* 391, 11-24.
221. Yan, M., Kawamata, Y. and Baran, P.S. (2017) Synthetic organic electrochemical methods since 2000: on the verge of a renaissance. *Chem. Rev.* 117, 13230-13319.
222. Twilton, J., Le, C., Zhang, P., Shaw, M.H., Evans, R.W. and MacMillan, D.W.C. (2017) The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* 1, 0052.
223. Natinsky, B.S., Lu, S., Copeland, E.D., Quintana, J.C. and Liu, C. (2019) Solution catalytic cycle of incompatible steps for ambient air oxidation of methane to methanol. *ACS Cent. Sci.* 5, 1584-1590.
224. Yuan, M., Abdellaoui, S., Chen, H., Kummer, M.J., Malapit, C.A., You, C. and Minteer, S.D. (2020) Selective electroenzymatic oxyfunctionalization by alkane monooxygenase in a biofuel cell. *Angew. Chem. Int. Ed.* 59, 8969-8973.
225. Tsai, Y.F., Luo, W.I., Chang, J.L., Chang, C.W., Chuang, H.C., Ramu, R., Wei, G.T., Zen, J.M. and Yu, S.S. (2017) Electrochemical hydroxylation of C3-C12 n-alkanes by recombinant alkane hydroxylase (AlkB) and rubredoxin-2 (AlkG) from pseudomonas putida GPo1. *Sci. Rep.* 7, 8369.
226. Kumar, A., Hsu, L.H.-H., Kavanagh, P., Barrière, F., Lens, P.N.L., Lapinsonnière, L., Lienhard V, J.H., Schröder, U., Jiang, X. and Leech, D. (2017) The ins and outs of microorganism–electrode electron transfer reactions. *Nat. Rev. Chem.* 1, 0024.
227. Gentil, S., Serre, D., Philouze, C., Holzinger, M., Thomas, F. and Le Goff, A. (2016) Electrocatalytic O_2 reduction at a bio-inspired mononuclear copper phenolato complex immobilized on a carbon nanotube electrode. *Angew. Chem. Int. Ed.* 55, 2517-2520.
228. Ruiz-Morales, J.C., Canales-Vazquez, J., Savaniu, C., Marrero-Lopez, D., Zhou, W. and Irvine, J.T. (2006) Disruption of extended defects in solid oxide fuel cell anodes for methane oxidation. *Nature* 439, 568-571.
229. Atkinson, A., Barnett, S., Gorte, R.J., Irvine, J.T., McEvoy, A.J., Mogensen, M., Singhal, S.C. and Vohs, J. (2004) Advanced anodes for high-temperature fuel cells. *Nat. Mater.* 3, 17-27.
230. Farrell, B.L. and Linic, S. (2016) Oxidative coupling of methane over mixed oxide catalysts designed for solid oxide membrane reactors. *Catal. Sci. Technol.* 6, 4370-4376.
231. Chen, Y., deGlee, B., Tang, Y., Wang, Z., Zhao, B., Wei, Y., Zhang, L., Yoo, S., Pei, K., Kim, J.H. *et al.* (2018) A robust fuel cell operated on nearly dry methane at 500 °C enabled by synergistic thermal catalysis and electrocatalysis. *Nat. Energy* 3, 1042-1050.
232. De Luna, P., Hahn, C., Higgins, D., Jaffer, S.A., Jaramillo, T.F. and Sargent, E.H. (2019) What would it take for renewably powered electrosynthesis to displace petrochemical processes? *Science* 364.
233. Chen, Y., Ji, S., Chen, C., Peng, Q., Wang, D. and Li, Y. (2018) Single-atom catalysts: synthetic strategies and electrochemical applications. *Joule* 2, 1242-1264.
234. Martín, A.J. and Pérez-Ramírez, J. (2019) Heading to distributed electrocatalytic conversion of small abundant molecules into fuels, chemicals, and fertilizers. *Joule* 3, 2602-2621.
235. Hu, A., Guo, J.J., Pan, H. and Zuo, Z. (2018) Selective functionalization of methane, ethane, and higher alkanes by cerium photocatalysis. *Science* 361, 668-672.
236. Rohe, S., Morris, A.O., McCallum, T. and Barriault, L. (2018) Hydrogen atom transfer reactions via photoredox catalyzed chlorine atom generation. *Angew. Chem. Int. Ed.* 57, 15664-15669.
237. Perry, I.B., Brewer, T.F., Sarver, P.J., Schultz, D.M., DiRocco, D.A. and MacMillan, D.W.C. (2018) Direct arylation of strong aliphatic C-H bonds. *Nature* 560, 70-75.
238. Chu, J.C. and Rovis, T. (2016) Amide-directed photoredox-catalysed C-C bond formation at unactivated sp^3 C-H bonds. *Nature* 539, 272-275.

239. Caputo, J.A., Frenette, L.C., Zhao, N., Sowers, K.L., Krauss, T.D. and Weix, D.J. (2017) General and efficient C-C bond forming photoredox catalysis with semiconductor quantum dots. *J. Am. Chem. Soc.* 139, 4250-4253.
240. Laudadio, G., Deng, Y., van der Wal, K., Ravelli, D., Nuno, M., Fagnoni, M., Guthrie, D., Sun, Y. and Noel, T. (2020) C(sp^3)-H functionalizations of light hydrocarbons using decatungstate photocatalysis in flow. *Science* 369, 92-96.
241. Zhang, Z., Rogers, C.R. and Weiss, E.A. (2020) Energy transfer from CdS QDs to a photogenerated Pd complex enhances the rate and selectivity of a Pd-photocatalyzed Heck reaction. *J. Am. Chem. Soc.* 142, 495-501.
242. Gisbertz, S., Reischauer, S. and Pieber, B. (2020) Overcoming limitations in dual photoredox/nickel-catalysed C–N cross-couplings due to catalyst deactivation. *Nat. Catal.* 3, 611-620.
243. Lan, G., Quan, Y., Wang, M., Nash, G.T., You, E., Song, Y., Veroneau, S.S., Jiang, X. and Lin, W. (2019) Metal-organic layers as multifunctional two-dimensional nanomaterials for enhanced photoredox catalysis. *J. Am. Chem. Soc.* 141, 15767-15772.
244. Garlets, Z.J., Nguyen, J.D. and Stephenson, C.R. (2014) The development of visible-light photoredox catalysis in flow. *Isr. J. Chem.* 54, 351-360.
245. Liu, W., You, W., Gong, Y. and Deng, Y. (2020) High-efficiency electrochemical hydrodeoxygenation of bio-phenols to hydrocarbon fuels by a superacid-noble metal particle dual-catalyst system. *Energy Environ. Sci.* 13, 917-927.
246. Lopez-Ruiz, J.A., Andrews, E., Akhade, S.A., Lee, M.-S., Koh, K., Sanyal, U., Yuk, S.F., Karkamkar, A.J., Derewinski, M.A., Holladay, J. *et al.* (2019) Understanding the role of metal and molecular structure on the electrocatalytic hydrogenation of oxygenated organic compounds. *ACS Catal.* 9, 9964-9972.
247. Yuliati, L. and Yoshida, H. (2008) Photocatalytic conversion of methane. *Chem. Soc. Rev.* 37, 1592-1602.
248. Li, L., Cai, Y.Y., Li, G.D., Mu, X.Y., Wang, K.X. and Chen, J.S. (2012) Synergistic effect on the photoactivation of the methane C-H bond over Ga^{3+}-modified ETS-10. *Angew. Chem. Int. Ed.* 51, 4702-4706.
249. Shi, D., Feng, Y. and Zhong, S. (2004) Photocatalytic conversion of CH_4 and CO_2 to oxygenated compounds over Cu/CdS–TiO_2/SiO_2 catalyst. *Catal. Today* 98, 505-509.
250. Li, L., Fan, S., Mu, X., Mi, Z. and Li, C.J. (2014) Photoinduced conversion of methane into benzene over GaN nanowires. *J. Am. Chem. Soc.* 136, 7793-7796.
251. Amano, F., Shintani, A., Tsurui, K., Mukohara, H., Ohno, T. and Takenaka, S. (2019) Photoelectrochemical homocoupling of methane under blue light irradiation. *ACS Energy Lett.* 4, 502-507.
252. Liu, L., Puga, A.V., Cored, J., Concepción, P., Pérez-Dieste, V., García, H. and Corma, A. (2018) Sunlight-assisted hydrogenation of CO_2 into ethanol and C2+ hydrocarbons by sodium-promoted Co@C nanocomposites. *Appl. Catal. B: Environ.* 235, 186-196.
253. Shoji, S., Peng, X., Yamaguchi, A., Watanabe, R., Fukuhara, C., Cho, Y., Yamamoto, T., Matsumura, S., Yu, M.-W., Ishii, S. *et al.* (2020) Photocatalytic uphill conversion of natural gas beyond the limitation of thermal reaction systems. *Nat. Catal.* 3, 148-153.
254. Mehta, P., Barboun, P., Go, D.B., Hicks, J.C. and Schneider, W.F. (2019) Catalysis enabled by plasma activation of strong chemical bonds: A review. *ACS Energy Lett.* 4, 1115-1133.
255. Wang, L., Yi, Y., Wu, C., Guo, H. and Tu, X. (2017) One-step reforming of CO_2 and CH_4 into high-value liquid chemicals and fuels at room temperature by plasma-driven catalysis. *Angew. Chem. Int. Ed.* 56, 13679-13683.

256. Jie, X., Li, W., Slocombe, D., Gao, Y., Banerjee, I., Gonzalez-Cortes, S., Yao, B., AlMegren, H., Alshihri, S., Dilworth, J. *et al.* (2020) Microwave-initiated catalytic deconstruction of plastic waste into hydrogen and high-value carbons. *Nat. Catal.* 3, 902-912.
257. Jiao, F., Li, J., Pan, X., Xiao, J., Li, H., Ma, H., Wei, M., Pan, Y., Zhou, Z., Li, M. *et al.* (2016) Selective conversion of syngas to light olefins. *Science* 351, 1065-1068.
258. Cheng, K., Gu, B., Liu, X., Kang, J., Zhang, Q. and Wang, Y. (2016) Direct and highly selective conversion of synthesis gas into lower olefins: design of a bifunctional catalyst combining methanol synthesis and carbon-carbon coupling. *Angew. Chem. Int. Ed.* 55, 4725-4728.
259. Parra-Cabrera, C., Achille, C., Kuhn, S. and Ameloot, R. (2018) 3D printing in chemical engineering and catalytic technology: structured catalysts, mixers and reactors. *Chem. Soc. Rev.* 47, 209-230.
260. Liu, Z., Zhu, J., Peng, C., Wakihara, T. and Okubo, T. (2019) Continuous flow synthesis of ordered porous materials: from zeolites to metal–organic frameworks and mesoporous silica. *React. Chem. Eng.* 4, 1699-1720.
261. Zhao, C.-X., He, L., Qiao, S.Z. and Middelberg, A.P.J. (2011) Nanoparticle synthesis in microreactors. *Chem. Eng. Sci.* 66, 1463-1479.
262. Morejudo, S.H., Zanon, R., Escolastico, S., Yuste-Tirados, I., Malerod-Fjeld, H., Vestre, P.K., Coors, W.G., Martinez, A., Norby, T., Serra, J.M. *et al.* (2016) Direct conversion of methane to aromatics in a catalytic co-ionic membrane reactor. *Science* 353, 563-566.
263. Itoh, N. (2015) Membrane reactors for the dehydrogenation of alkanes to alkenes. *Membrane Reactors for Energy Applications and Basic Chemical Production*, Elsevier.
264. Yang, W., Wang, H., Zhu, X. and Lin, L. (2005) Development and application of oxygen permeable membrane in selective oxidation of light alkanes. *Top. Catal.* 35, 155-167.
265. Zeng, L., Cheng, Z., Fan, J.A., Fan, L.-S. and Gong, J. (2018) Metal oxide redox chemistry for chemical looping processes. *Nat. Rev. Chem.* 2, 349-364.
266. Yu, X., Zholobenko, V.L., Moldovan, S., Hu, D., Wu, D., Ordomsky, V.V. and Khodakov, A.Y. (2020) Stoichiometric methane conversion to ethane using photochemical looping at ambient temperature. *Nat. Energy* 5, 511-519.

Acknowledgement

We are grateful for the financial supports from the European Union through the European Research Council (grant ERC-AdG-2014-671093, SynCatMatch) and the Spanish government through the "Severo Ochoa Program" (SEV-2016-0683).

Competing Interests

The authors declare no competing interests.

Author Contributions

A.C. conceived the review, and L.L. and A.C. wrote this review together.

Figure Captions

Figure 1. Mechanism of alkane activation by enzymes. (A) Reaction mechanism of selective oxidation of methane to methanol by soluble methane monooxygenase (sMMO) with binuclear Fe species as the active centres. (B) Reaction mechanism of alkane oxidation by cytochrome P450. In this figure, intermediates (1 to 9) are illustrated to show how alkane and oxygen are activated on the isolated Fe site in cytochrome P450. (A) Reprinted with permission from Kopp et al.[23] copyright 2002 Elsevier. (B) Reprinted with permission from Guengerich et al.[30] copyright 2018 American Chemical Society.

Figure 2. Metathesis of alkane. (A) Mechanism of alkane metathesis reaction for transforming propane into ethane and butane through a three-step process: dehydrogenation of alkane into olefin, olefin metathesis of propylene and hydrogenation of olefin products into alkanes. (B) Schematic illustration of the single-site Ta species supported on SiO_2. Three types of Ta species could be present, depending on the coordination of the Ta centres. (C) Reaction mechanism of the metathesis of propane for the production of CH_4, C_2H_6 and linear higher alkanes (n-butane and n-pentane). (D) Reaction mechanism of the metathesis of propane for the production of CH_4, C_2H_6 and branched alkanes (isobutane and 2-methyl-butane). (B-D) Reprinted with permission from Basset et al.[64] copyright 2010 American Chemical Society.

Figure 3. Schematic illustration of ligand-assisted C(sp^3)-H activation. In this example shown in (a), a directing group is present in the reactant, which can coordinate with the metal species (such as Pd) and then activate a C-H bond in the saturated carbon chain. A general reaction mechanism for ligand-directing C-H functionalization is illustrated in (b). The target C-H bond is activated by the metal coordinated by the directing group. The functional group will transfer from the metal centre to the activated C-H bond. DG, directing group; M, metal catalyst; FG, function group.

Figure 4. Several strategies for conversion of methane into chemicals and fuels. The corresponding commonly used catalysts are indicated in this figure.

Figure 5. Ir clusters confined in pure-silica MWW zeolite for hydrogenolysis of propane. (A) High-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) images of the

0.24Ir@MWW sample (prepared by one-pot synthesis with an Ir loading of 0.24 wt%) after reduction by H_2 at 650 ^oC, showing the good dispersion of Ir clusters in the MWW zeolite crystallite. (B) HAADF and (C) the corresponding integrated differential phase contrast (iDPC) image of the 0.24Ir@MWW sample, showing the location of Ir cluster at the 10MR window between the two neighbouring 12MR supercages. (D) Catalytic performance of 0.24Ir@MWW and 0.07Ir/MWW-imp (prepared by conventional impregnation with an Ir loading of 0.07 wt%) for hydrogenolysis of propane to methane and ethane. As a result of the preparation method, the spatial distribution of the two samples is distinct, as illustrated in (D). Each catalyst was pre-reduced by H_2 at different temperatures to tune the size distribution of Ir species, in order to correlate the size distribution and the catalytic performance. According to the catalytic results, Ir clusters of 0.5-0.7 nm are the most active species for hydrogenolysis of propane. Reprinted with permission from Liu et al.[132] copyright 2020 Wiley-VCH.

Figure 6. Catalytic performance of Pt–zeolite materials for propane dehydrogenation. (A) Initial turnover frequency (TOF) of various Pt–zeolite materials for propane dehydrogenation reaction at 600 °C based on the exposed Pt sites determined by the average particle size derived from electron microscopy and EXAFS results. (B) Initial reaction rates of various Pt–zeolite materials for propane dehydrogenation reaction at 600 °C based on the mass of Pt in the solid catalyst. The K-containing Pt–zeolite samples (K-Pt–MFI and K-PtSn–MFI) show higher rates than the K-free samples, indicating the significant promotion effect of potassium and higher reactivity of subnanometric Pt clusters. (C) Deactivation constant of PtSn–MFI, K-Pt–MFI and K-PtSn–MFI samples in the first 10 hours during the first catalytic cycle of the propane dehydrogenation reaction. (D) Initial propane conversion on PtSn–MFI, K-Pt–MFI and K-PtSn–MFI catalysts in different catalytic cycles (C1, C2 and C3 denote the first, second and third catalytic cycles). The initial conversion of propane decreases significantly when the K-free PtSn–MFI sample is regenerated for the second and third catalytic test, which is caused by the sintering of Pt. Notably, both K-Pt–MFI and K-PtSn–MFI show good recyclability in three consecutive reaction-regeneration cycles, indicating the high stability of subnanometric Pt clusters confined in the sinusoidal 10-membered-ring channels. (E–H) HAADF-STEM images of various pristine Pt–MFI catalysts after reduction by H_2 at 600 °C: (E) Pt–MFI, (F) K-Pt–MFI, (G) PtSn–MFI and (H) K-PtSn–MFI. (I–L) HAADF-STEM images of various pristine Pt–MFI catalysts after propane dehydrogenation: (I) Pt–MFI, (J) K-Pt–MFI, (K) PtSn–MFI and (L) K-PtSn–MFI. By comparing the size of Pt particles in the pristine and used catalyst, the sintering of Pt nanoparticles in the K-free samples is observed. By contrast, in the K-promoted samples,

subnanometric Pt clusters can be preserved after the catalytic tests for propane dehydrogenation. EXAFS, extended X-ray absorption fine structure; HAADF-STEM, high-angle annular dark-field scanning transmission electron microscopy. Reprinted with permission from Liu et al.[141] copyright 2019 Springer Nature.

Figure 7. Dehydroaromatization of n-heptane to aromatics with Pt/KL catalyst. (A) Preparation of Pt/KL catalysts by controlling the conditions for atomic layer deposition of Pt particles on the KL zeolite support. When tuning the exposure time to organometallic Pt precursor, it is possible to vary the Pt loading in the KL support. With a longer exposure time, more Pt species can enter into the KL zeolite crystallites. (B) Catalytic performance of Pt/KL catalysts for dehydroaromatization of n-heptane into aromatics. Reaction conditions: 420 ^{o}C, atmosphere pressure and H_2/n-heptane=6. The Pt/30Al-KL sample was prepared by depositing Pt on Al-modified KL zeolite, in which the Pt particles are mainly located on the external surface of the KL zeolite crystallites. These catalytic results indicate that Pt particles located inside the KL zeolite are more active and selectivity for the conversion of n-heptane into aromatics. (C, D) Proposed reaction mechanisms for aromatization of n-hexane to benzene. In the mechanism shown in (C), cyclization reaction occurs after the formation of 1-hexene, followed by the subsequent dehydrogenation of cyclohexane to benzene. In the mechanism shown in (D), 1,3,5-hexatriene is formed after consecutive dehydrogenation reactions and then transformed into benzene by cyclization reaction. Reprinted with permission from Xu et al.[157] copyright 2018 Elsevier.

Figure 8. Metathesis reaction of propane with bifunctional supported organometallic catalysts. (A) Preparation of isolated Ti and W sites on amorphous silica support via surface grafting of organometallic complexes. (B) Different types of catalyst packing methods for continuous metathesis of propane. (C) Influence of the spatial distribution of the Ti and W sites on the catalytic performance of metathesis of propane. When the W and Ti sites were closely generated in the solid carrier, high activity for propane metathesis reaction could be obtained. On the contrary, when the two types of sites are separated, very low activity was observed. Reprinted with permission from Samantaray et al.[170] copyright 2017 American Chemical Society.

Figure 9. **Rhodium-catalysed alkane functionalization by carbene insertion into the C-H bond.** (a) The product distribution observed with the carbene insertion reaction with n-pentane. (b) Proposed

reaction routes of the carbene transfer steps. In Route A, the carbene specie is transferred from the metal sites to the alkane while the C-C coupling reaction occurs between alkane and free carbene in Route B. The reaction pathway is dependent on the functional groups of the carbene intermediates.

Figure 10. Comparison of the enzymatic, homogeneous and heterogeneous catalysts for alkane activation. In this figure, three types of Fe-containing catalysts are illustrated to represent the three different systems. The features of three catalytic systems are also summarized. (A) enzyme, (B) molecular metal complex and (D) isolated metal atom supported on solid carrier.