Supported Single Atom Catalysts for C–H Activation: Selective C–H Oxidations, Dehydrogenations and Oxidative C–H/C–H Couplings

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The activation of C–H bonds in hydrocarbons (saturated, unsaturated and aromatics) by single atom catalysts immobilized in a solid support is an active research front in catalysis. On the one hand, different examples of transition metal catalysts atomically dispersed on inorganic, organic and hybrid supports are constantly designed, synthesized and characterized using advanced microscopy and spectroscopic techniques. On the other hand, active, selective and stable single metal sites are recently developed as high performant heterogeneous catalysts for the C–H activation of organic molecules. This review covers recent examples of selective alkane and arene C–H oxidations, dehydrogenations of alkanes, as well as C–H/C–H oxidative couplings involving arenes, alkenes and alkynes, based on the use of supported single atom catalysts.

1. Introduction

During the last decade, there was an enormous interest in the synthesis and understanding of single metal atoms as the ultimate size for catalytic entities in the transformation of organic molecules.[1,2] At the nanoscale, the chemical reactivity of bulk metals changes with the size of the aggregate of atoms that compose such metal (e.g. nanoparticles, subnanometric clusters, single atoms). When decreasing the size of the aggregates, the bandgap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) is different from bulk metals. This modifies the reactivity of single atom catalysts (SAC) with respect to nanoparticles or even subnanometric clusters. Moreover, the size of the active metal aggregates is inversely proportional to the surface/volume ratio and the number of unsaturated metal atoms exposed. Therefore, interesting and useful chemical properties arise in the case of a single metal atom, which implies improvements in catalytic applications. Besides reactivity, the atom utilization efficiency of high cost noble metals, such as those of the platinum group (Rh, Pd, Pt, and Au), is maximized when they are atomically dispersed. Thus, low loading supported metals can now be designed with atomic level precision.[3,4]

Supported SAC combines activity with stability since, on the one hand, a support allows for the decrease in surface free energy of the metal by immobilization of SAC, thus avoiding the sintering into larger nanoparticles. On the other hand, in supported single atom catalyst the metal support interaction is maximum, which provides more interface and active sites. Common materials employed as support for anchoring the SAC and controlling the electronic and steric environment of the metal center are graphitic carbon, metal oxides, porous silicates (e.g. zeolites), porous organic or metal-organic polymers (e.g. MOFs).[5,6] Importantly, the crystalline nature of the support allows for a catalyst design with atomic level precision. Indeed, the structures of SAC, diatomic sites, multiatomic (homo- and hetero-nuclear) sites, and atomic interfaces can be manipulated in order to control the catalytic activity and selectivity, obtaining valuable structure-performance relationships.

Transition metal SAC have been widely studied in traditional oxidation and reduction steps of industrial relevance, such as CO oxidation, CO$_2$ electroreduction, hydrogenations of unsaturated organic groups, etc. However, little attention had been payed to the synthesis of fine chemicals and related applications.[7] Among all organic transformations, the process of C–H scission is very challenging due to the high dissociation energy of this fundamental bond present in basic hydrocarbons for the chemical industry. In this regard, important knowledge on supported SAC that promotes C–H bond scission in alkanes, alkenes and alkynes has been generated during recent years. Among the different C–H activation methodologies, the use of transition metals under oxidant conditions is the most widely employed. Different examples of selective C–H oxidation, dehydrogenation and C–H/C–H oxidative couplings occur with high efficiency and under mild conditions thanks to the use of atomically dispersed metals. The oxygenated, unsaturated or C–C coupling products generated are of importance as basic compounds (e.g. methanol, phenol, biaryls, etc.) in bulk and fine chemistry. To our knowledge, no revision of the use of supported SAC in the specific topic of C–H activation of organic
molecules (particularly hydrocarbons) is reported. Thus, it is our aim here to approach this topic through the selection of relevant examples of selective C–H bond oxidations, dehydrogenations and oxidative couplings from recent literature, which are summarized in Scheme 1.

This minireview covers, on the one hand, the supported SAC-promoted selective oxidation and dehydrogenation of hydrocarbons through single C–H activation steps. Two industrially relevant examples have been selected in this part due to their importance: the selective oxidation of methane and benzene. On the other hand, recent examples of the performance of SAC in oxidative couplings of unsaturated hydrocarbons (aromatics, olefins and alkynes) are revised in the second part of the review, given the synthetic importance of C–C bond formations directly from the coupling of two C–H bonds via double C–H/C–H activation under mild conditions. Surface characterization techniques and computational modeling of the dynamic catalytic process at the atomic scale will be discussed in order to understand reaction mechanisms involving rate limiting C–H activation steps.

The literature revised is divided into two sections, according to the type of organic transformation catalyzed by the supported SAC: The first one (section 2) focuses on the topic of C–H activation in sp² and sp³ carbons of light alkanes and aromatics. For this part, we selected the proof-of-concept selective oxidation of methane into methanol (section 2.1), dehydrogenation of methane and propane (section 2.2) and the selective oxidation of benzene into phenol (section 2.2), promoted by supported SAC. The second section (section 3) reviews the recent contributions to the use of supported SAC for C–C bond formations through direct C–H/C–H couplings of sp² carbons in arenes (section 3.1) and/or olefins (section 3.2), as well as oxidative couplings of sp carbons in alkynes (section 3.3), focusing on the very few examples reported on the use of supported SAC.

2. Supported SAC for selective C–H oxidations and dehydrogenations

2.1. Supported SAC for the C(sp³)–H activation of alkanes: Selective oxidation of methane

The most widely studied C–H activation of alkanes is the selective oxidation of this particular bond into a C-OH bond (and/or CH₃ coupling) with the help of an oxidant and a catalyst. This part will be focused only on methane as a representative alkane due to the abundance of works on its SAC-promoted selective oxidation, with respect to other light alkanes of industrial relevance (such as ethane or propane), which mostly focuses their dehydrogenation into light olefins and will be briefly reviewed on the following section 2.2. The selective transformation of methane into C1 oxygenate products, such as the industrially relevant methanol, is a challenging process. This is due to the weakly polarized tetrahedral structure and strong C–H bonds in CH₄ (ΔH_C–H = 104 kcal mol⁻¹). Thus, highly active SAC is needed to be synthesized and characterized in order to activate the C–H bond in methane.

One example of experimental characterization of such type of supported SAC was carried out for Pd/Pt dispersed on Al₂O₃ using X-ray absorption fine structure (XAFS). The study indicated the presence of single Pt atoms binding to oxygen, with an average coordination number of 4.2. This corresponded to an average cluster diameter of 0.4 nm, below the 1 nm resolution limit of high-angle annular dark-field imaging with scanning transmission electron microscope (HAADF-STEM). The predicted lower surface free energies of Pd with respect to Pt, favored its aggregation in larger clusters. Moreover, this metal reacted under oxidant atmospheres at T = 500 °C, forming Pd→η¹→2-O species, according to CO-FTIR and electron diffraction. Such large clusters with a Pt-rich core and a PdO shell (> 5 nm) were more active than single Pt atoms, resulting in methane C–H activation energies as low as 8 kcal mol⁻¹, much lower than monometallic PdO or Pt catalysts. The Pt-rich core increased the reactivity of the surface Pd–O electrophilic-nucleophilic pairs, which promoted the C–H scission through a four-center transition state (H₄C⁰→Pd²⁺→H⁺→O³⁻). In these large clusters, the nucleophilicity of the O atoms was enhanced when Pt valence electrons are incorporated. This was due to the lower d band with respect to the 2p states of adsorbed O atoms, which decrease the Pd–O overlap and thus weakened the binding of the oxygen to the Pd surface.

The selective C–H activation of methane via oxidation to methanol has been attempted in the solid-liquid-gas interface, instead of the traditional solid-gas phases. For that, an aqueous solution of H,O₂ was employed at mild temperatures (50–95 °C) in the presence of Pd₁O₂ single-sites (0.01 wt.% Pd) anchored on the internal surface of the micropores of ZSM-5. This was done through incipient wetness impregnation-calcination of the zeolite, using 2 wt.% of CuO as a co-catalyst to...
promote the H₂O₂ dissociation into H₂O and O₂. Each Pd site converted ca. 2 molecules of methane into methanol per second (TOF of ca. 7·10⁻⁴ h⁻¹). No PdO nanoparticles were observed by transmission electron microscope (TEM), X-ray diffraction (XRD) or X-ray photoelectron spectroscopy (XPS) techniques. Extended X-ray absorption fine structure (EXAFS) analysis showed no signals associated with Pd-O-Pd nanoclusters or Pd–Pd nanoparticles. This fact, together with the coordination number (CN)=4 obtained, pointed to the presence of PdO single sites in the zeolite, which are responsible for the C–H activation in methane.

Rhodium was a widely employed metal for the selective oxidation of methane into methanol. Kwon et al. obtained a performance in the methane activation and conversion (1 molecule of methanol obtained per Rh atom and per hour) for the C–H activation in methane.

Scheme 1. Selected examples of oxidative (O) C–H activations (selective oxidations and dehydrogenations in the red box, and oxidative couplings in the blue box) in sp², sp³ and sp carbons, using transition metals as single atom catalysts (SAC) discussed in this minireview.

Rhodium was a widely employed metal for the selective oxidation of methane into methanol. Kwon et al. obtained a single Rh atom supported on ZrO₂ via wet impregnation and calcination. The supported SAC exhibited a moderated catalytic activity increased 4-fold when the Rh loading was decreased from 2 wt.% to 0.3 wt.%, in line with the disappearance of Rh–Rh interactions in EXAFS. This fact confirmed the single atomic nature and high oxidation state between + 3 and + 4 (according to XPS) of the sites in the low loaded sample. Fourier transform infrared spectroscopy with CO adsorption (CO-FITR) also confirmed the presence of single atoms stabilized by the hydroxyl groups of zirconia, based on the geminal CO adsorption peaks with a 90° angle between the two CO. Methane was dissociatively adsorbed on the Rh single atoms, generating adsorbed CH₃⁺, which can react with H₂O₂ to give MeOOH. The ZrO₂ support promoted the decomposition of both H₂O₂ and MeOOH intermediate, producing MeOH and CO₂, this last product in much lower amounts with respect to the use of larger Rh nanoparticles. Ethane was observed when the reaction was performed at 260 °C in the presence of an O₂ flow, due to the migration of the methyl group from the Rh atom to an adjacent O atom, and subsequent exothermic coupling with a second CH₃⁺ group.

Besides ZrO₂, CeO₂ nanowires (6.2×260 nm) were employed as support of Rh single atom catalysts, via hydrothermal process, for the conversion of methane in the presence of H₂O₂ at 50 °C. XRD patterns and TEM images indicated the atomic dispersion of Rh on the CeO₂ support, while XPS analysis of the single atoms suggested electron transfer from Rh to CeO₂ (metal-support interaction). In fact, density functional theory (DFT) calculations confirmed the coupling between Rh-4d and Ce-4d orbitals. As occurs with ZrO₂, the CeO₂ nanowires in H₂O₂ triggered the formation of *CH₃, *OOH, and *OH radicals, which were observed by electron paramagnetic resonance (EPR) and in situ diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). The adsorbed *OH radicals on neighboring Ce(III) atoms oxidized the adsorbed CH₃ at the Rh atoms into *CH₄, which in turn formed oxygenated C1 products after combination with oxygenated radicals.

As in the case of Pd, Rh single atom sites were supported in porous aluminosilicates such as the medium pore zeolite ZSM-5. Shan et al. introduced 0.5 wt.% of isolated mononuclear Ru⁺ species inside the zeolite micropores, according to HAADF/STEM, XPS, CO-DRIFTS and XANES analysis. This species facilitated the activation of methane in water by O₂, forming Rh-CH₃ intermediates which produced methanol or acetic acid after oxygen or CO insertion, respectively, and hydrolysis of the Rh-OCH₃ intermediates. Tang et al. incorporated Rh single atoms in ZSM-5 by exchange with singly dispersed Brønsted acid sites of the zeolite. The supported Rh atoms with a single coordination sphere of 5 O atoms at the framework micropores, did not self-interacted due to the absence of Rh–Rh or Rh–O–Rh bonding observed by EXAFS. Only 2% of the Rh atoms leached from the zeolite to the reaction media after 12 h at 150 °C.

Scheme 1. Selected examples of oxidative (O) C–H activations (selective oxidations and dehydrogenations in the red box, and oxidative couplings in the blue box) in sp², sp³ and sp carbons, using transition metals as single atom catalysts (SAC) discussed in this minireview.
Moreover, soluble Ru$^{13+}$ exhibited a much lower TOF with respect to the supported single atoms, thus confirming the heterogeneous nature of the catalysis. DFT modeling of Rh$_2$O$_5$ active sites indicated that the C–H bond activation of methane presented an energy barrier of 30 kcal mol$^{-1}$, forming a methyl and hydroxyl adsorbed on the Rh atom.

Besides the Ni SAC previously described, other first-row transition metals have been proposed as SAC for the C–H activation in methane. Filonowich et al. employed these metals supported in phthalocyanine/porphyrin-functionalized graphene surfaces.[19] The hydrogen abstraction energies (difference between the formation energies of metal-OH and metal-oxo species) and transition state energies for methane activation through radical-type mechanism were studied by DFT calculations. Among all the metal tested, Co was the optimal one in terms of breaking the C–H bond (activation) followed by the formation of metal-oxo species (regeneration). N-doping and ligand exchange affected both parameters. Interestingly, these values were related to electronic descriptors, such as the metal d-band center (obtained from partial density of states calculations of metal-oxo species), metal charge and charge on the reactive oxygen at the active site. Both the distance to the Fermi surface and electron excess on the O atom influenced the C–H activation. However, the different local environments created by various organic linkers/ligands in metal-organic systems did not correspond with the charges on the metal sites. In a related work, Cui et al. employed iron as supported SAC obtained through ball milling of graphene and iron phthalocyanine.[14] The resulting single FeN$_4$ sites on graphene nanosheets (2.7 wt.% Fe) activated methane at room temperature using H$_2$O as oxidant of the C–H bond, with a TOF of 0.5 h$^{-1}$ (considering all C1 oxygenates). The reaction mechanism consisted of the H$_2$O$_2$ decomposition and O adsorption at the Fe sites (O–FeN$_4$–O). The C–H bonds of methane were activated through the generation of methyl radicals that reacted with the hydroxyl or peroxyl radicals to form the C1 oxidized products.

In addition to iron, non-noble single chromium atoms (1 wt.%), supported on TiO$_2$ nanoparticles, through incipient wetness followed by calcination in air.[13] This SAC selectively oxidized 58 molecules of methane per Cr atom, with a 93% selectivity to methanol, after 20 h at 50 °C. Isolated bright dots corresponding to individual Cr atoms dispersed on the TiO$_2$ support were observed by HAADF-STEM. Moreover, XPS and H$_2$-TPR (temperature programmed reduction) confirmed the III/VI oxidation states of Cr and the shift of Ti binding energies due to metal-support interactions. The high-valent Cr(VI) species played a crucial role in the mechanism since their loss decreases the activity upon reuses, requiring the calcination of the spent material for recovering its activity and maintain the single Cr atom catalysts. EPR analysis of the reaction mixture detected CH$_4$ and OH radicals, due to the formation of Ti-OOH and Cr-OH species after interacting with H$_2$O$_2$. The CH$_4$ reacted with Ti-OOH* or with the OH* to form CH$_3$OOH or CH$_3$OH as the primary products, which were further over-oxidized with time.

### 2.2. Supported SAC for the C(sp$^3$)-H activation of alkanes: Dehydrogenation of methane and propane

In the previous section, we have shown that different single metal atoms (instead of clusters or nanoparticles) supported in different materials have been reported during the past decade to tackle the challenging C–H activation of methane via its selective oxidation into C1-oxygenates. We would like to comment on other (not necessarily oxidative) C–H activations on light alkanes such as methane or propane. We will first start with the C–H scission of methane into CH$_x$ fragments (dehydrogenation) and C–C coupling products and then finish the section with some of the reported examples of supported SAC for the activation of propane via dehydrogenation into propylene.

Darby et al. reported that a single Pt atom allowed to tune the activity and selectivity of single non-doped pure metal atoms, such as Ag.[16] In these single metal alloyed catalysts, the C–H bond was activated over the dopant (i.e. Pt atoms) top site after CH$_4$ physisorption through van der Waals interactions. While the CH$_3$ fragment remained there, the H migrated to a hollow shared at the dopant. The Pt/Ag(111), showed in Figure 1, presented a C–H activation energy of 22 kcal mol$^{-1}$.

After this rate limiting C–H scission, the entropy-favored spill-over of the activated CH$_4$ fragments into the support material gave rise to C–C coupling processes.

Another interesting single-atom alloy consisting of small amounts of Pt single atoms (0.01 and 1 monolayers) as catalytic sites for methane C–H activation on the surface of a Cu (111) host, facilitated C–C couplings over coking processes.[15] The single-atoms were observed by high-resolution scanning tun-
neling microscopy (STM), while the study of the surface reactivity of the single crystal was measured under ultra-high vacuum using temperature programmed reaction (TPR) of methyl iodide. Lower temperatures for methane and carbon coupling products (i.e. ethene, ethane and propene) desorption were obtained for the Pt/Cu with respect to pure (and less reactive) Cu. Interestingly, the C–H bond activation readily occurred without further C–C coupling on the 1 monolayer alloy, in contrast to the extensive C–C coupling observed at the pure Pt (111) crystal. Thus, the amount of coupling products dropped as the amount of Pt was increased above 0.01 monolayers in the alloy. This was in agreement with DFT calculations of transition state energies during the C–H activations and adsorption energies of the resulting CH₂ species. Kinetic Monte Carlo simulations indicated the favored formation of adsorbed CH₄ and C⁺ coke precursors in pure Pt, preventing the C–C coupling of CH₄ and CH₃⁺ fragments from methane dehydrogenation. Continuous flow C–H activation of butane via deuteration of one C–H bond proved the adequate activity and stability of PtₓCu/y with respect to non-reactive Cu or easily deactivated Pt (via carbon formation/deposition) pure system.

First-row nickel atoms in the form of Niₓ/TiC (001) were prepared via room temperature vapor deposition of small coverages, 0.2–0.3 monolayers, of nickel on the carbide. The metal-support interactions and catalytic activity maximized with respect to large Ni coverages, due to the minimum content of metal neighbors in the 2D-few Ni atom clusters. The reactivity of the Ni cluster increased inversely to their size, with the Niₓ/TiC as the optimal structure. Thus, the energy barrier of CH₄ dehydrogenation was only 4 kcal · mol⁻¹, due to the electron density polarization and lability of the Niₙ cluster. This low energy barrier allowed the room temperature C–H bond activation when methane was deposited as CH₄ species on the surface at Ni or Ni-Carbide interfaces, according to the shifts of the XPS signals of the element. The synergistic effect between the metal and the support was clear when comparing the activation barriers for either bulk Ni(111) metal (27 kcal · mol⁻¹) or TiC(001) support (28 kcal · mol⁻¹).

A somewhat different reaction pathway during the C–H activation of methane is the non-oxidative conversion of methane into ethylene and aromatics. This reaction proceeded at the single-atom active center of Feₓ@SiCₓ, where the CH₃ and H were adsorbed at Fe site and C sites, respectively, after the C–H bond scission in methane. Both sites acted synergistically through a C–H(CH₃)–Fe four-centered transition state structure, according to molecular dynamics simulation and crystal orbital Hamilton population analysis of the C–H bond in methane. This was composed of 2p orbitals of the C atom in CH₃ and SiCₓ, the 1 s orbital of the H atom in CH₃, and the 3d orbital of the Fe atom. Then, the methyl fragments could desorb from the catalyst into the gas phase, where the high temperatures (1000 °C) favored radical/molecule collisions. Alternatively, they could remain during a few picoseconds as metastable chemisorbed on top of the Fe sites (Fe–CH₃ length of ca. 2 Å), and subsequently migrate to an adjacent C site. Static DFT calculations of the activation energies for the C–H cleavage and methyl transfer resulted in 42 and 15 kcal · mol⁻¹, respectively. Not just the kinetics but also the thermodynamics of the methyl transfer was also favorable, with a calculated exothermic reaction energy of −3 kcal · mol⁻¹. These lower energies with respect to the gas phase reaction pointed to the surface-based mechanism, which was > 4000 times faster. Subsequent hydrogen transfer from an adjacent Fe site transformed the C=CH₂ intermediate into ethylene through an exothermic reaction (−11 kcal · mol⁻¹) with an activation barrier of 22 kcal · mol⁻¹.

To finish this part, we will comment on some of the recent reports on the C–H activation, via dehydrogenation, of higher alkanes, such as propane. The oxidative dehydrogenation of light alkanes is a promising route towards highly demanded light olefins. Selective catalysts for the dehydrogenation vs. deep oxidation (e.g. CO₂) and/or cocking (e.g. C deposits) steps have been proposed based on the use of single site supported metals, such as vanadium. Atomically dispersed and well-defined monovanadate species on silica were prepared through a surface organometallic methodology and characterized by FT-IR, solid-state NMR, UV–vis, Raman, EPR and XAS spectroscopies. The resultant supported SAC exhibited a better performance in terms of propane conversion and propylene productivity than traditionally impregnated catalysts, which contained mixtures of mononeric and polymeric species. DFT calculations of vanadium SAC supported on graphic carbon nitride attributed its high activity to the free-atom like V3d states. The propylene selectivity was ascribed to the structural confinement of the V atoms, interacting weakly with propylene through π-bonding (inhibiting di-π binding mode), and thus favoring its desorption from the catalyst surface.

Alumina was an adequate support of mononeric Ga sites, with much higher activity in the propane dehydrogenation at 550 °C than its dinuclear counterparts obtained when using silica as support. This highlighted the importance of proximity between Al and Ga in the mechanism of alkane dehydrogenation, probably because of the role that Lewis acid sites on the alumina surface played in stabilizing highly dispersed Ga sites under the reaction conditions, or even in the propane C–H activation itself. Other metal SAC such as Zn species were also atomically dispersed from the gas phase into high-surface-area silica. The resultant open shell 16-electron, tri-coordinate ethyl zinc-silica sites were much active and selective to propylene in the propane dehydrogenation at 550 °C, with respect to 18-electron, tetra-coordinate zinc oxide-type centers.

Recently, γ-alumina was employed as support of atomically dilute platinum/copper oxides for the activation of propane under atmospheric pressure at 520 °C. A PtCu single atom alloy (SAA) was obtained after reduction under H₂ atmosphere for 1 h at 600 °C. On the one hand, CO-DRIFTS indicated the interaction of CO with Pt atoms on the surface of Cu nanoparticles suggesting individually dispersed Pt–Cu bonds. On the other hand, EXAFS showed the presence of Pt–Cu bonds but not Pt–Pt bonds in the case of isolated Pt (for high Cu:Pt ratios). The SAA catalysts prepared by incipient wetness coimpregnation method (with a high copper to platinum ratio) showed excellent stability during more than 120 h of operation under atmospheric pressure at 520 °C.
Another example of Pt single atom for the same type of C–H activation was proposed for SiO₂-supported PtGa–Pb catalyst. The material was prepared by an impregnation-reduction method (H₂ at 700 °C) and tested in propane dehydrogenation at high temperatures (600 °C). This resulted in 30% conversion with full selectivity to propylene for 96 h without lowering the performance, in contrast to the deactivation occurring with Pt–Ga/SiO₂. XPS, EXAFS and FTIR with CO adsorption proved the Pb location at the surface of the PtGa nanoparticles and the presence of single Pt atoms, without any Pt–Pt ensembles.

Finally, we will comment on the reported size dependence of Pt catalysts in the propane dehydrogenation at 575 °C, which was demonstrated using hierarchically structured nanoalumina as a Pt catalyst support. The turnover frequency (TOF) of the atomically dispersed Pt/Al₂O₃ catalyst was approximately 3-fold and 7-fold higher than the subnanometer-sized clusters and the nanoparticles, respectively. In fact, the activation energy for the propane dehydrogenation over the supported Pt nanoparticles decreased from 56 kJ·mol⁻¹ to 41 kJ·mol⁻¹ on small clusters and 26 kJ·mol⁻¹ on atomically dispersed Pt. Additionally, the absence of multiple Pt–Pt sites resulted in effectively inhibiting C–C cracking that requires the combination of multiple Pt atoms, which improved the propylene selectivity and anticokeing ability.

2.3. Supported SAC for the C(sp²)–H activation of arenes: Selective oxidation of benzene

The direct C–H activation of aromatics, e.g. benzene, allow the green obtention of industrially relevant phenol through one-step selective oxidation using oxygen at mild temperatures. Given the strong C–H bonds in benzene (110 kcal·mol⁻¹), a catalyst of the scission is needed, as described earlier with methane. Pioneering works by Tada et al. reported the oxidation of benzene with oxygen by using an N-containing Re cluster introduced inside ZSM-5 zeolite by chemical vapor deposition (0.58 wt.% Re). The activation barrier was as low as 6 kcal·mol⁻¹ due to the Re-activation of the O–O dissociation, O-addition to C of benzene and O-insertion into the C–H bond of benzene. The 0.56 nm pore size of the zeolite could accommodate the Re cluster and the O–Re and Phenol-Re transition intermediates.

The oxygen in the reaction conditions oxidized the Re₉₀ clusters into ReO₂ monomers, at the same time that oxidized the benzene substrate. NH₃ had a decisive role in the regeneration of the Re cluster from the resulting Re monomer after the reaction, an interesting observation that highlights the higher activity of clustered Re particles over single Re species. DFT and EXAFS investigations of the Re₉₀ clusters in the ZSM-5 zeolite provided detailed information of the phenol synthesis steps. The competitive co-adsorption of oxygen and benzene was key in the mechanism. On the one hand, the adsorbed oxygen at a bridge site in the end-on form was subsequently dissociated in a bridge-bonded O and a terminal O=Re. On the other hand, benzene was coordinated to a Re atom at the para position of the carbon that will be bonded to the O on the atop site. This co-adsorption allowed the concerted O insertion into the benzene C–H bond to form phenol (H=C=O-Re → C=O+Re), liberating the catalytic Re site.

First-row transition metals were also employed as an available alternative to precious metals catalysts of the C–H activation in benzene. One example of Cu SAC reported by Zhang et al. consisted of the thermal polymerization of a supramolecular melamine-Cu complex and cyanuric acid. This protocol generated single Cu₅N₇ atoms (0.85 wt.% Cu) isolated in a porous hollow structure (ca. 3 nm pore). The activity and selectivity of the single Cu atoms in the room temperature benzene oxidation to phenol were higher than for Cu nanoparticles.

The same authors reported single-atom Cu₅N₇ moieties on hollow carbon nitride microspheres (HCNS). This SAC was obtained after Cu impregnation/reduction with NaBH₄ and subsequent acid leaching to eliminate the CuO nanoclusters and leave only the single Cu atoms coordinated to N (0.23 wt.% Cu). These atoms are seen as bright spots by HAADF-STEM image and showed a shift in the XPS Cu 2p signal due to strong metal-support interactions. They exhibited a TON of ca. 6.5·10⁳ for the benzene oxidation into phenol (> 90% selectivity) with H₂O₂ at 60 °C, with an activation energy of 4 kcal·mol⁻¹. The single Cu sites demonstrated to be active catalysts to (i) decompose the H₂O₂, (ii) adsorb the O atoms and (iii) transfer them to benzene.

Single copper atom species (0.43 wt.% or 0.14 atoms·nm⁻²) at the edge-rich defects of hollow carbon nanotubes were employed in the room temperature oxidation of benzene. A TOF of 123 h⁻¹ was obtained with the single Cu atoms with respect to the 11 h⁻¹ obtained with the Cu nanoparticles. The proposed methodology of cation-exchange and thermal treatments of Cu₅S/CdS/aminophenol-formaldehyde starting compounds allowed Cd evaporation and S/N-doped carbon formation. The abundant carbon defects were introduced by the pyridine/graphitic N and S-thiophene, according to NEXAFS and Raman spectra. N/S heteroatoms interacted with the Cu single atoms, with an oxidation state between 0 and +2 in and a Cu₅N₇ coordination, according to XPS and EXAFS. Characterization of the spent catalysts confirmed no aggregation of the atomically dispersed Cu active sites. Two steps were modeled: (i) H₂O₂→OOOH⁺+H⁺; (ii) C₆H₆+OOOH⁺→C₆H₅OH+OH⁺, where the S, N-electronically modified copper sites participated in the generation and dissociation of the *OOH radicals in order to decrease the energy barrier of the C–H activation.

Besides copper, iron was widely studied as an Earth-abundant catalyst for the selective oxidation of benzene, as previously reported for methane oxidation. In this sense, single atom coordinatively unsaturated Fe₅N₇ sites dispersed in a graphene matrix were obtained through ball milling of iron phthalocyanine and graphene nanosheets. The well-defined atomic structure of the material was evident by HRTEM images of the single atom, which appeared as well-dispersed small black dots on the graphene matrix or as bright dots in HAADF-STEM. Those Fe atoms were atomically coordinated to N atoms according to electron energy loss spectroscopy (EELS) atomic
spectra of the spot. Low temperature scanning tunneling microscopy (STM) suggested the presence of FeN₄ macrocycles embedded in the plane of the graphene sheet (probably bonded at defective C sites during high energy ball milling), which resulted in strong metal-support interactions, as further confirmed by XPS and EXAFS.

Another type of single Fe atoms (0.9 wt.%) on hollow nitrogen-doped carbon materials was prepared from the pyrolysis (700 °C) and acid leaching of dopamine-derived polymer-coated iron hydroxide nanorods. The hollow pipes of graphitized carbon had a high surface BET area (891 m²·g⁻¹) and an average pore diameter of 2.4 nm. The Fe single atoms were seen as homogeneously distributed bright dots by HAADF-STEM, with an oxidation state between 2⁺ and 3⁺ and a Fe-N₄ structure, according to XANES. The material was active in the benzene hydroxylation to phenol at 60 °C, in contrast to the negligible activity of iron in the form of nanoparticles, chloride or phthalocyanine. A key step in the mechanism was the dissociation of H₂O₂ into *OH radicals co-adsorbed at the Fe single site, which formed the activated O* (detected Fe⁶⁺=O species by EPR) by releasing a molecule of water. This step had lower activation energy (18 kcal · mol⁻¹) and was highly exothermic (51 kcal · mol⁻¹). In contrast, Fe nanoparticles exhibited a higher activation barrier (38 kcal · mol⁻¹) and endothermicity (46 kcal · mol⁻¹). The same trend was observed for the rate limiting C–H activation step in benzene by the O* generated, being 25 kcal · mol⁻¹ in the case of single atoms, with respect to 40 kcal · mol⁻¹ for the nanoparticles. This was attributed to stronger charge interactions between the hydroxyl species and Fe₆ nanoparticles (0.9 e⁻) with respect to that of a single Fe atom (0.68 e⁻), as well as the higher electronic chemical potential that hindered charge transfer to the adsorbed species.

The role of the N, C atoms in the active sites of Fe-NₓCₙ atomically dispersed materials prepared at different temperatures (500–700 °C) was investigated by experimental and theoretical methods. A direct relation was found between the Fe–N coordination number and the catalytic activity in the C–H activation of benzene. DFT, EXAFS, EPR and ⁵⁷Fe Mössbauer spectroscopy pointed to the favored formation of O=Fe=O intermediate species upon H₂O₂ activation by the FeN₄ single sites, with respect to the C containing ones (Figure 2). This O-FeN₄ intermediate served as the active site for the oxidation of benzene, given the weak O–Fe bonding strength but strong charge transfer (highly concentrated charge density at the O atom).

3. Supported SAC for oxidative C–H/C–H couplings

3.1. Supported SAC for the double C(sp²)–H/C(sp²)–H activation or arenes: Oxidative coupling of aromatics

The C–C coupling of two C–H bonds is the most direct, atom economic and low-cost strategy to elongate or functionalize this fundamental bond. However, the high cost of the catalytic metals employed in this process requires the minimization of metal utilized. SAC is then an interesting strategy, especially when supported to facilitate recovery and recycle. An example of C–H/C–H coupling is the synthesis of biaryls from aromatics,
given the high relevance of these compounds in the chemical industry.

Liu et al. prepared highly electrophilic single atomic Pd species (2.2 wt.% Pd) dispersed in a bifunctional -COOH/-SO$_3$H porous organic polymer.[39] The supported SAC promoted the heterogeneous oxidative coupling of benzene using oxygen (8 atm) as oxidant and CF$_3$SO$_3$H/HAc as additives, achieving a maximum turnover number (TON) of 487 and turnover frequency (TOF) of 352 h$^{-1}$ at 120°C. Those values were much higher than the palladium acetate Pd(OAc)$_2$, homogeneous catalyst (TON = 212; TOF = 53 h$^{-1}$), thanks to the atomically dispersed and unique structure of the heterogeneous system. The Pd interaction with the -COOH and -SO$_3$H surface sites of the polymer allowed a compromise between stability and electrophilicity of the single atoms. On the one hand, the stability of the Pd(OAc)$_2$ molecular species was enhanced by coordination to double -COOH sites through H$^+$ exchange with Pd, according to a new COO–Pd peak appearing in the FTIR. On the other hand, the -SO$_3$H groups enhanced the electrophilicity of Pd by week interactions, according to the shift of the S(2p)-XPS signal and DFT calculated Pd charges. No Pd nanoparticles were observed by TEM or XAS, even at the high Pd loading of 2.2 wt.%.

The authors employed H$_2$PMO$_{12}$V$_2$O$_{40}$ as an additive of the same polymer-supported Pd(II) single sites, aiming at milder reaction conditions of temperature and pressure.[39] For atmospheric O$_2$ pressures and mild temperatures (90°C), the maximum TON of the heterogeneous Pd SAC was 62, with respect to the TON of 55 in the case of homogenous Pd(OAc)$_2$ under similar conditions. The formation of inactive Pd(0) nanoparticles upon reuse was the cause of activity loss (by covering the remaining Pd(II) active sites), although no Pd leaching was detected.

Similar mild conditions were employed (80°C, 1 atm O$_2$) for the C–H/C–H homocoupling of benzene using Pd(II) (3.8 wt.%) species on graphene oxide, achieving a TON of 66. This value was not far from the one obtained with the porous organic polymer described, but in this case, no co-catalysts or co-solvent was needed.[35] The highly dispersed hydrated PdO clusters were prepared by wet Pd(NO$_3$)$_2$ impregnation of graphene oxide and subsequent calcination. No metallic palladium was detected and only Pd(III) species interacting with surface -COOH and -C–O groups were present in the material, as the XPS, TEM, XRD and FTIR analysis indicated. However, there was a substantial loss in activity upon recycles, probably due to the formation of inactive Pd nanoparticles. DFT calculations indicated an energy barrier for the C–H activation rate limiting step of 38 kcal·mol$^{-1}$, corresponding to a transition state where a carbon atom of benzene was coordinated by Pd. This stabilized the phenyl ion after the scission of the C–H bond with the participation of the acetate oxygen atom, forming the O–H bond in the adsorbed acetic acid molecule that was formed.

Vercammen et al. confined well-isolated cationic Pd(II) species in the pores of zeolite Beta as a catalyst for the shape-selective oxidative coupling of toluene (80% to the p,p′-diaryl), overcoming the regioselectivity and reusability problems associated with homogeneous Pd species.[80] The double C–H activation at the para position took place with significant activity in hydrophobic zeolites (e. g. Si/Al of 75), with TON of 422 at 110°C and 16 bar O$_2$, which was four times higher than the values obtained with TsOH as homogeneous acid. XANES and NMR characterization of the Pd@Beta pointed to a strong interaction of the spatially isolated Pd(OAc) molecular species (after losing one of the acetates) with the zeolite framework, thus compensating one or two anionic O$^-$ charges.

The C–H activation took place through a concerted metatation-deprotonation mechanism, with the activation at the para carbon as the lower energy barrier, according to DFT calculations. The intermediates resembled that proposed via XAS analysis of toluene-loaded zeolite samples. These numbers also supported a C–C bond formation through migratory insertion reaction, in agreement with the experimental first-order rate dependence on Pd. The Pd–H regeneration occurred via O$_2$ insertion and H abstraction to form Pd–O–OH species and release of H$_2$O$_2$.

Most of the examples previously commented rely on the use of supports or hosts of SAC (e.g. metal oxides, graphitic carbon, zeolites, etc.) which do not enable full control of the nuclearity (mono/multi-nuclear) of the metal species and its order within the support. This creates ambiguities in the synthesis and activation processes, and distinguishing active from inactive segregated species is a challenging task. MOFs, as zeolites, present high porosity and crystallinity, which allows characterization by single crystal and/or powder-diffraction techniques.[80–82] The advantages of MOFs over zeolites are the well-defined nature of their atomically dispersed active sites (every metal site is endowed with the same nuclearity, oxidation state and coordination environment) and unique electronic properties and reactivity of the metal-oxo clusters.

In this sense, the group of Prof. De Vos anchored isolated palladium single atoms at the Zr vacancies of MOF-808, having 6 open metal sites per cluster.[83] The Pd@MOF was employed in the oxidative coupling of o-xylene using oxygen (16 bar) at 110°C. A TON of 436 was obtained, which was the best reported Pd-supported catalyst for the C–H activation of xylene, higher than porous organic polymers (TON of 383) at 120°C.
The MOF-808 support was superior to other MOFs containing groups with a strong affinity for Pd(II), such as carboxylic acids or bipyridines. A cumulative TON of 1218 with overall regioselectivity of 73% for 3,3',4,4'-tetramethylbiphenyl was obtained after three runs, with only 5% Pd leached, which was well beyond the state-of-the-art. The isolation of the molecular Pd(OAc) species occurred at the open Zr sites associated with acetate defects, which exchanges the OH/H\textsubscript{2}O by the Pd species, according to FTIR analysis. EXAFS data fitted to a model where monomeric Pd(II) was anchored to the MOF after one of the acetate ligands in Pd(OAc)\textsubscript{2} gets protonated by one of the protons at the Zr open sites. HAADF-STEM and EDX analysis of the spent MOF showed that the Pd(0) nanoparticle formation (and thus deactivation of the catalyst) was minimized by the Pd(II) anchoring to the MOF support (Figure 4). Furthermore, a similar \( k_1/k_2 \) kinetic isotope effect in the case of homogeneous and heterogeneous catalysts suggested similar rate limiting steps in both systems.

### 3.2. Supported SAC for the double C(sp\textsuperscript{2})=H/C(sp\textsuperscript{2})=H activation or arenes: Alkenylation of aromatics

The C–H bond of benzene can be activated to form a C–C heterocoupling product with a different C–H containing molecule, such as an olefin in the presence of a Pd(II) catalytic site and an oxidant to regenerate the reduced Pd(0) sites during the cycle. This alkenylation or olefination of aromatics is known as the oxidative Heck or Fujiwara-Moritani reaction. A pioneering work about the design and application of single-site supported Pd(II) catalyst consisted of grafting 2,2'-bipyridine to a periodic mesoporous organosilica via co-polymerization and subsequent Pd(OAc)\textsubscript{2} loading (1.2 wt.%) in DMSO at room temperature.\(^{[44]}\) This avoided the generation of Pd(0) nanoparticles, as confirmed by TEM and XAS analysis. Interestingly, the authors did not detect the formation of Pd nanoparticles even after the reaction in acetic acid at 80°C using tert-butyl hydroperoxide as oxidant and ethyl acrylate as coupling partner.
of benzene. The stabilization of the Pd(II) sites at the bipyridine moieties (preventing agglomeration into nanoparticles) and their accessibility and dispersion in the mesoporous framework resulted in a TON of 128 (with a cumulative TON of 420 after 4 cycles), with respect to the 56 obtained with homogeneous Pd(OAc)$_2$. The reaction exhibited zero order (no dependence) with respect to the olefin or the oxidant, and first order with the Pd concentration. This indicated that the rate limiting step was the C–H bond cleavage of benzene by Pd, and not the olefin insertion or Pd re-oxidation, supported also by kinetic isotope effect ($K_{\text{H}}/K_{\text{D}} = 3.6$).

Oxidative coupling of a biphenyl moiety with an olefin was achieved by dispersing Pd single atoms in post-synthetically sulfated or phosphated Hf$_6$ nodes of Hf-MOF-808. Characterization of the appended metal by XPS indicated the higher stability of Pd via immobilization at the acid sites of the SO$_4$/PO$_4$-functionalized MOF. The authors also reported the presence of only Pd(II) sites at the functionalized MOF-808 in contrast to the parent Hf-MOF-808, where both Pd(II/0) sites were observed by TEM. Raman spectroscopy indicated that the Pd(II) interacts with the oxygen holes of the MOF clusters (2.2 Pd per cluster according to ICP) since the intensity of P=O and S=O stretching vibration modes became weaker with respect to the parent material. Acetate was also attached to the MOF cluster replacing OH/H$_2$O groups, in addition to the varied electrostatic interactions of Pd with the conjugated bases of the P and S-acids incorporated at the Hf-oxo cluster, being 0.9 Pd per cluster according to single crystal and modeling studies (Figure 5). The supported Pd SAC exhibited a 5 and 15-fold rate enhancement for Pd@Hf-MOF-808-SO$_4$ and Pd@Hf-MOF-808-PO$_4$ respectively, when comparing with Pd@Hf-MOF-808. DFT studies of the Pd containing clusters showed that the enhancement of catalyst lifetime with respect to the parent MOF was due to the adequate functionalization of the nodes with isolated Pd(II) species. Moreover, a key point was the decreased mobility of the resulting Pd(0) atoms (i.e. more exergonic Pd binding), preventing their agglomeration into nanoparticles during the catalytic cycle.

The group of Prof. De Vos designed a well-defined thioether ligand anchored into the Zr$_6$ clusters of MOF-808, according to the short distance relations (proved by solid NMR) and the homogeneous distribution at the adamantane cages (proved by N$_2$ physisorption). Pd(II) sites were located in the vicinities of the N, O-coordinating groups of the ligand, due to the strong affinity for Pd(II), which fitted the XANES spectra. The activity of the MOF in the alkenylation of 2,6-dimethylanisole, using tert-butyl peroxybenzoate as oxidant, was higher than that of Pd/MOF-808 without the S, N ligand. The TOF = 8.4 h$^{-1}$ was threefold higher than that of the homogeneous Pd(OAc)$_2$ catalyst. This confirmed that the MOF-supported S, O-moieties increased the catalytic activity of Pd(II). The leaching of the ligand and Pd after 2 h was only 3% and 1%, respectively. However, Pd(0) nanoparticles started to form after 2 h of reaction, deactivating the catalyst for further recycling. A similar type of Pd single atoms uniformly attached to thioether ligands on titanium oxide-bisphosphonate materials were employed in...
the C–H/C–H coupling of 2,6-dimethylanisole with n-butyrylacrylate, using tert-butyl peroxybenzoate as oxidant.\cite{47} The Pd(II) sites were accessible and isolated through the binding to the S-, O- sites of the immobilized thioether ligand within the porous material (with fitted interatomic Pd–O and Pd–S distances of 1.95 Å and 2.25 Å, according to EXAFS). This resulted in the highest TOF = 13 h\(^{-1}\) reported for such heterogeneously catalyzed oxidative coupling. The enhanced activity for the C–H bond activation step was due to the low surface density of the S, O-containing linker. The deactivation occurring after 1 h of reaction at 100 °C was attributed to the formation of Pd(0) nanoparticles, evidenced by HAADF-STEM, despite the good structural stability of the material and low Pd leaching (1%).

An alternative to homogenous Pd(OAc)\(_2\)/acid for the alkenylation of aromatic N-heterocycles, e.g. indole, was the copper-containing MOF-74.\cite{48} This system is attractive due to its pore dimensions of 1 × 1.4 nm and the redox-active properties in the presence of tert-butyl hydroperoxide. No damage to the MOF structure was observed after the encapsulation of Pd(OAc)\(_2\) and H\(_3\)PW\(_{12}\)O\(_{40}\) (POM) into the porous architecture. The number of alkenylated indole molecules generated per Pd atom was three times higher when those sites were in the MOF (TON\(_{Pd}=15\)) with respect to the homogeneous catalyst. Interestingly, a linear trend between catalytic activity (TON\(_{Pd}\)) and reduction potential (E\(^0\)) of the divalent metals at the MOF oxoclusters (i.e. Mg, Mn, Ni, Co, Cu) was observed. This suggested the favored re-oxidation of the electrophilic Pd(II) sites by the redox-active Cu sites present at the MOF (top part of Figure 6),

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**Figure 5.** Reaction network and \(\Delta G^\circ\) (kcal/mol) for the formation of Pd(II)@Hf-MOF-808 and Pd(0)@Hf-MOF-808 with or without phosphate or sulfate modification. Reprinted with permission from reference [45]. Copyright (2019) American Chemical Society.
which maintained its crystalline structure after the C–H/C–H coupling. Even under continuous flow conditions, the lifetime of Pd(II) sites was increased by more than 270% for the Pd/POM–Cu-MOF support in comparison with silica (bottom part of Figure 6). The decrease in activity after 1 h of was attributed to the reduction of the Pd(II) encapsulated to inactive Pd(0). The Pd–Pd EXAFS band observed in the Pd-MOF after the reaction confirmed this point.

Figure 6. Alkenylation of indole with butyl acrylate catalyzed by POM/Pd(OAc)$_2$@MOF-74 in batch or continuous flow mode. Reprinted with permission from reference [48]. Copyright (2018) Wiley.
3.3. Supported SAC for the double C(sp)–H/C(sp)–H activation of alkynes: oxidative coupling of phenylacetylene

The last part of this review will briefly highlight a few reported C–H activation of terminal alkynes using supported SAC. The alkyno carboxylation using CO$_2$, a base and a SAC will serve as an introductory example of this last part. Yang et al. prepared a mesoporous CN-based copper single atom catalyst by grinding Cu(NO$_3$)$_2$ with urea, with subsequent calcination and acid leaching.$^{[36]}$ On the one hand, the copper coordination (Cu–N) with an oxidation state between 0 and +2 was studied by Raman, FTIR, XPS and XAS spectroscopies. On the other hand, the 1.4 Å size of the Cu single atoms was determined by HAADF-STEM images. The 8 wt.% Cu-containing sample exhibited the highest TOF of 9.7 h$^{-1}$, maintaining the activity in five cycles without neither Cu leaching nor structural damage. CuCN was modeled by replacing one C site with the Cu dopant coordinated to 3 N atoms. DFT calculations provided activation energies for the rate limiting step of CO$_2$ insertion in the copper acetylde on Cu–CN (20 kcal·mol$^{-1}$) or CN (53 kcal·mol$^{-1}$) surfaces. However, due to the presence of a base (CsCO$_3$), the deprotonation of the alkyne was not a rate limiting step at the Cu single atoms.

One example of double C(sp)–H activation is the oxidative coupling of alkynes. Ren et al. reported atomically dispersed unsaturated Cu–N active sites on hierarchically N-doped graphitized defect containing carbon (characterized by HAADF-STEM, XPS, XAFS and Raman spectrum) obtained from the pyrolysis of biochar and Cu(NO$_3$)$_2$. The supported single atom species (1.3 wt.% Cu) were employed for the double C–H activation of alkynes through the Glaser-Hay coupling using air as the oxidant (no base required). The resulting Cu-supported SAC showed 5.4-fold higher catalytic activity in the formation of 1,3-dienes with respect to samples containing metallic Cu phases on carbon. The stability, activity and selectivity were maintained after 5 recycles, without leaching of active sites. DFT calculations indicated that the Cu–alkyne interaction was stronger at the single atom catalyst. This favored the rate limiting step for the subsequent C–H activation of the unsaturated Cu sites without steric hindrance for the key Cu-acetylide intermediate species. The reductive elimination and catalyst regeneration in air generated the diyn by deprotonation of the alkyne.

MOFs have been recently employed as supports of single metal sites for the activation of C–H bonds in alkynes.$^{[31,52]}$ For example, the MIL-101-SO$_2$H was exchanged with Cu(II) to generate well-isolated MIL-101-SO$_2$Cu, compensating the charges of 14 mol% of the SO$_2$H groups.$^{[33]}$ No metallic Cu nanoparticles were observed by TEM; instead, a homogeneous distribution of Cu within the MOF in oxidation state +2 was present, according to EDS mapping and XPS. The SAC showed an extremely high TOF of 7×10$^{4}$ h$^{-1}$ for the A3 coupling of phenylacetylene, paraformaldehyde and piperidine, overcoming state-of-the-art MOF-based copper catalysts.$^{[54,55]}$ The material was recycled 5 times without structural collapse or metal leaching. Despite the extremely low Cu content, the copper remained totally exposed at the MOF support and thus catalytically active due to its good atomic isolation within the MOF framework. The key step of C–H activation of phenylacetylene took place at the unsaturated Cu sites without steric hindrance for its coordination to the triple bond of the alkyne.

We will finally comment on the dimerization of alkynes using atomically dispersed Pd sites on hollow ZIF-derived structures.$^{[36]}$ This type of supported SAC was prepared by (i) Pd coordination to the surface unsaturated dangling N groups (PdN$_2$), (ii) subsequent reduction (200 °C, H$_2$) and (iii) core dissolution (H$_2$O, 100 °C). EDS and STEM images showed the Pd atoms (1.8 wt.%) in the remaining shell, highlighting the stronger Pd–N coordination over Co–N of the starting MOF and the absence of Pd nanoparticles, according to XRD. XANES and XPS analysis indicated that the Pd valence was between 0 and 2. Such single Pd(II) catalysts promoted the dimerization of phenylacetylene into 1,4-diphenyl-1,3-butadiene at the surface of the catalyst. The supported SAC maintained high activity and selectivity after six reaction cycles, with no Pd leaching. Experiments using the 1,3-enzyme as starting product for its hydrogenation into the 1,3-diene indicated that this step was faster than the activation of a terminal C–H bond in phenylacetylene, which was the rate limiting step (favored for lower H$_2$ concentrations).

4. Conclusions and outlook

The activation, cleavage and C-hydroxylation, dehydrogenation or C-coupling of C–H bonds of hydrocarbons has been widely explored using supported single metal atoms (<2 wt.%) as catalysts. On the one hand, the atomic dispersion was thoroughly characterized by advanced techniques such as high-resolution electron microscopy, X-ray absorption and X-ray photoelectron spectroscopies. On the other hand, the supported SAC was tested in the C–H activation of methane, benzene and other aromatics, as well as alkynes and alkynes. A deep understanding of the reaction mechanism was experimentally and computationally provided in many examples, with estimated activation barriers for the C–H bond scission step.

In the first place, the selective hydroxylation of methane into methanol was promoted in the presence of precious or first-row transition metal single atoms atomically dispersed on different supports. For the C–H activation of methane (via either hydroxylation or dehydrogenation), the activation energies of the C–H scission varied from 4 to 22 kcal·mol$^{-1}$, for Ni/TiC and Pt/Ag(111), respectively; with TOFs as high as 7·10$^4$ h$^{-1}$ for Pd@ZSM-5. In the second place, the selective oxidation of benzene into phenol has been possible thanks to single metal atoms of Cu or Fe supported on N-doped carbon. TOFs up to 123 h$^{-1}$ and TONs up to 6.5·10$^3$ were reported, with C–H activation energies of 25 kcal·mol$^{-1}$. Besides the rate limiting C–H scission, the dissociation of the oxidant (e.g. O$_2$ or H$_2$O) at the metal site was a key step in order to generate activated Metal-O species able to transfer the O into the C–H bond.

Double C–H/C–H activations in the presence of an electrophilic metal, i.e. Pd, and an oxidant, i.e. O$_2$, to regenerate the Pd(0) into Pd(II), were discussed in detail. The coupling of
aromatics, (e.g. benzene, toluene, xylene) resulted in C–C bond formations towards biaryl, catalyzed by supported single Pd sites on silicates, organic and metal-organic polymers. TOFs up to 352 h$^{-1}$ and TONs up to 436 were reported, due to the high electrophility of the sites, which are immobilized at the support, avoiding the fast deactivation of Pd(II) single atoms into Pd(0) nanoparticles. In the same line, the alkenylation of arenes was also explored with similar supported SAC but using hydroperoxides as oxidants. These systems performed with TONs and TOFs close to 15 h$^{-1}$. Finally, the oxidative coupling of alkynes using supported Cu SAC was briefly commented, highlighting the improved performance with respect to Cu nanoparticles.

In general, we have highlighted how the use of metal SAC allows for higher catalytic performances than aggregate clusters or nanoparticles, in the context of the C–H activations. A key factor in the catalytic performance of the heterogeneous catalysts employed for such endeavors is the selection of a support that strongly interacts with the SAC. This improves its reactivity and stabilizes the active sites, allowing a simple recovery and recycle, with minimum metal leaching. All the accumulated knowledge on catalyst synthesis and characterization will allow for further improvement on the design of tunable supported single atoms. The optimal compositions and structures will result in better supported SAC systems, requiring milder and greener reaction conditions. Moreover, the preparation of SAC using more sustainable synthesis from Earth-aborundant metals and low-cost supports should be pursued. We are confident that these pioneering examples of supported SAC for C–H activation of hydrocarbons will pave the way towards direct functionalization of organic molecules, replacing halogenated hydrocarbons as starting products for C–C couplings.

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Conflict of Interest

The authors declare no conflict of interest.

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