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Single-atom catalysis for organic reactions

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ABSTRACT

Metal-based catalysis, including homogeneous and heterogeneous catalysis, plays a significant role in the modern chemical industry. Heterogeneous catalysis is widely used due to the high efficiency, easy catalyst separation and recycling. However, the metal-utilization efficiency for conventional heterogeneous catalysts needs further improvement compared to homogeneous catalyst. To tackle this, the pursing of heterogenizing homogeneous catalysts has always been attractive but challenging. As a recently emerging class of catalytic material, single-atom catalysts (SACs) are expected to bridge homogeneous and heterogeneous catalytic process in organic reactions and have arguably become the most active new frontier in catalysis field. In this review, a brief introduction and development history of single-atom catalysis and SACs involved organic reactions are documented. In addition, recent advances in SACs and their practical applications in organic reactions such as oxidation, reduction, addition, coupling reaction, and other organic reactions are thoroughly reviewed. To understand structure-property relationships of single-atom catalysis in organic reactions, active sites or coordination structure, metal atom-utilization efficiency (*e.g.*, turnover frequency, TOF calculated based on active metal) and catalytic performance (*e.g.*, conversion and selectivity) of SACs are comprehensively summarized. Furthermore, the application limitations, development trends, future challenges and perspective of SAC for organic reaction are discussed.

1. Introduction

Single-atom catalyst (SAC) is a recently emerging class of catalytic material featured with unique single-atom dispersion and maximum atomic utilization of active metal. The atomically dispersed metal anchored on support brings SAC similar catalytic behavior to homogeneous catalyst, in which metal is usually covalently bonded to ligand. These structural features endow SACs with well-defined catalytic sites and high atomic efficiency of active metal species. Additionally, the heterogeneous nature of SACs makes them easy to be separated from the liquid-phase reaction mixture and achieves convenient recovery as well as recycling. Therefore, SAC is considered as homogenized heterogeneous catalysts and bridge the gap between homogeneous and heterogeneous catalysts (Fig. 1) [1].

In literatures, catalysts with supported active single-atom metal centers are also often called "SACs" [2], "single-atom site catalysts (SASCs)" [3], "isolated single-atom-site catalysts (ISAS)" [4], "single atomic site catalysts (SASC)" [5] or "atomically dispersed metal catalysts (ADCs)" [6], all of which are emphasizing the atomic dispersion of the active metal species. For most discussions in this review, we use the terms "SACs" and "single-atom catalysis" to highlight the importance of atomic isolation of active metal sites on supports. Although research in SACs has only begun to grow rapidly in recent years, single-atom catalysis has become the most active new frontier in the catalysis field [7,8]. Pioneering research for SAC participation in organic reaction can be traced back to 1995, Thomas *et al.* prepared a single Ti atom-based catalyst by grafting metallocene complexes onto mesoporous silica. They demonstrated that four coordinated Ti was the active center for epoxidation of cyclic alkenes [9]. In 1999, Asakura *et al.* synthesized an atomically dispersed Pt catalyst by supporting Pt ions on the MgO for propane combustion [10]. In 2000, Abbet *et al.* fabricated a series of Pd_n ($1 \le n \le 30$) clusters including single Pd atoms ($n = 1$) on MgO support. Their findings showed that a single Pd atom was active enough to catalyze acetylene cyclotrimerization [11]. In 2003, Fu *et al.* demonstrated that cationic Au and Pt were responsible for the water-gas shift reaction [12]. In 2005, Zhang *et al.* loaded isolated Au^{3+} ions on a zirconia (ZrO_2) support with very low loading (<0.1%) for selective hydrogenation of

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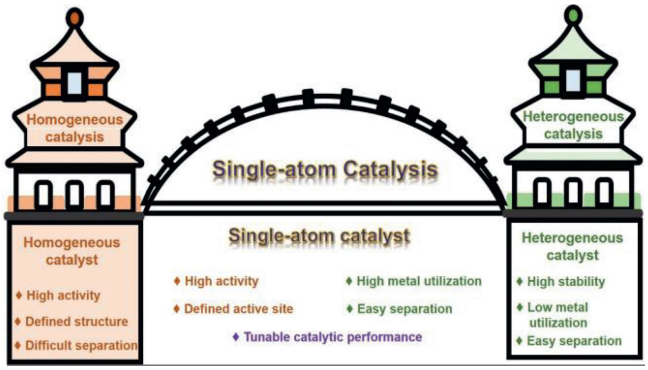
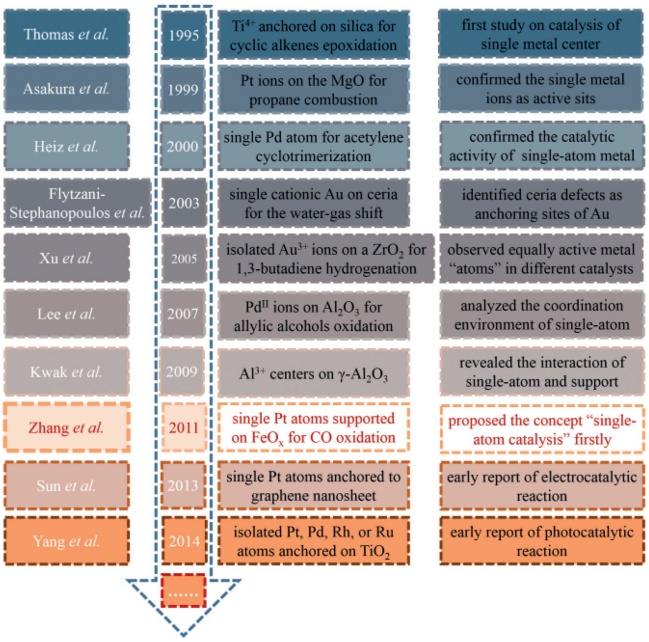


Fig. 1. Schematic illustration of the features for different catalysts and corresponding catalytic process. The features of homogeneous catalysis, heterogeneous catalysis and single-atom catalysis.



Thomas *et al.*	1995	Ti^{4+} anchored on silica for cyclic alkenes epoxidation	first study on catalysis of single metal center
Asakura *et al.*	1999	Pt ions on the MgO for propane combustion	confirmed the single metal ions as active sits
Heiz *et al.*	2000	single Pd atom for acetylene cyclotrimerization	confirmed the catalytic activity of single-atom metal
Flytzani-Stephanopoulos *et al.*	2003	single cationic Au on ceria for the water-gas shift	identified ceria defects as anchoring sites of Au
Xu *et al.*	2005	isolated Au^{3+} ions on a ZrO_2 for 1,3-butadiene hydrogenation	observed equally active metal "atoms" in different catalysts
Lee *et al.*	2007	Pd^{II} ions on Al_2O_3 for allylic alcohols oxidation	analyzed the coordination environment of single-atom
Kwak *et al.*	2009	Al^{3+} centers on γ-Al_2O_3	revealed the interaction of single-atom and support
Zhang *et al.*	2011	single Pt atoms supported on FeO_x for CO oxidation	proposed the concept "single-atom catalysis" firstly
Sun *et al.*	2013	single Pt atoms anchored to graphene nanosheet	early report of electrocatalytic reaction
Yang *et al.*	2014	isolated Pt, Pd, Rh, or Ru atoms anchored on TiO_2	early report of photocatalytic reaction
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Fig. 2. The development history and breakthroughs of SACs. Time axis of the major breakthroughs regarding SACs and single-atom catalysis from 1995 to 2014.

1,3-butadiene. The turnover frequencies (TOFs) were similar for the catalysts containing 0.01%, 0.05%, and 0.08% of gold, indicating that the active Au species were dispersed as isolated atoms on the surface of the zirconia support [13]. In 2007, Hackett *et al.* synthesized a single-site Pd^{II} catalyst loaded on mesoporous Al_2O_3. The atomically dispersed Pd^{II} centers exhibited exceptional catalytic performance in the selective aerobic oxidation of allylic alcohols [14]. In 2009, Kwak *et al.* prepared the γ-Al_2O_3 supported Pt SAC by anchoring Pt atom onto pentacoordinate Al^{3+} centers on γ-Al_2O_3 surface [15]. They provided an in-depth understanding of the strong interactions between active metal sites and oxide support materials. In 2011, Qiao *et al.* fabricated a defective FeO_x supported Pt SAC with excellent CO oxidation activity. In this work, they firstly proposed the concept of "single-atom catalysis" [16], which has been widely accepted by the catalysis community and triggered extensive research interest in recent years. The above-mentioned works consisted of the early stage of the single-atom catalysis [17]. Fig. 2 shows the time axis of the breakthroughs regarding SACs and single-atom catalysis.

Earlier works on SACs mainly focused on optimizing the synthetic conditions to integrate the metal atoms onto the support with a decent loading. It should be noted that the majority of the SACs were utilized in organic reactions [9–11,13,14]. With the development of advanced characterization techniques, the synthesis strategy was further accelerated and the application scope has been extended to photocatalytic reactions [18–20], electrocatalytic reactions [21–23], organic synthesis [24] *etc.* Although research in SACs has only begun to grow rapidly in the last decade, single-atom catalysis has become the most active new frontier in the catalysis field. In recent years, with the incensement of loading amount of atomic metal to over 10 wt% [25], 20 wt% [26], 30 wt% [27], and 40 wt% [28], SACs have shown great potential for practical catalytic applications.

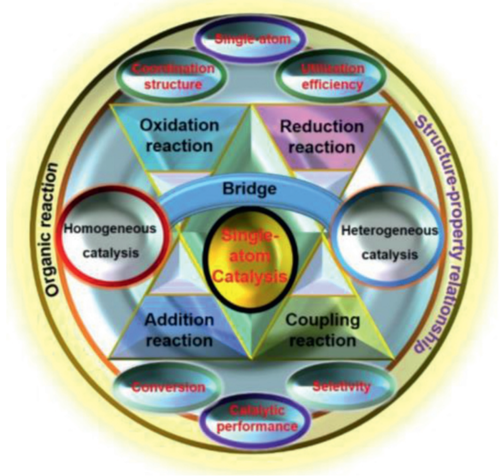

Fig. 3. Overview of the topics covered in this review.

This review focuses on the application in organic reactions of SACs from the viewpoint of their performance advantages. The unique features of single-atom catalysts and brief developmental history single-atom catalysis for organic reactions are illustrated. Furthermore, the catalytic application of SACs in organic reactions (*e.g.*, oxidation, reduction, addition, coupling, and other organic reactions) and the corresponding performance advantages (*e.g.*, conversion, selectivity and TOF) are systematically summarized and discussed (Fig. 3). In addition, the current critical challenges in SACs for catalytic organic reactions are pointed out, and perspectives are also proposed. Thus, this review covers the key aspects of SACs for organic transformations, including loading and utilization of metal, as well conversion and selectivity of the reactions. We believe it is of great importance and interest to the development of SACs for the application of organic reactions, and it can be extended to other fields as well.

2. Catalytic performance and active sites of SACs

Over the past years, various SACs have been developed and utilized in many liquid-phase organic reactions due to the heterogenized catalytic properties and maximum atom efficiency of active metal [29–34]. The important SACs-catalyzed organic reactions such as hydrogenation, oxidation, and coupling are mainly discussed in this review.

2.1. Oxidation reaction

Oxidation reaction is crucial for producing high-value-added oxygenates, such as phenols, aldehydes, ketones, carboxylic acid, or carboxylic acid derivatives. SACs have been widely utilized in selective oxidation reactions due to their high activity and unique selectivity.

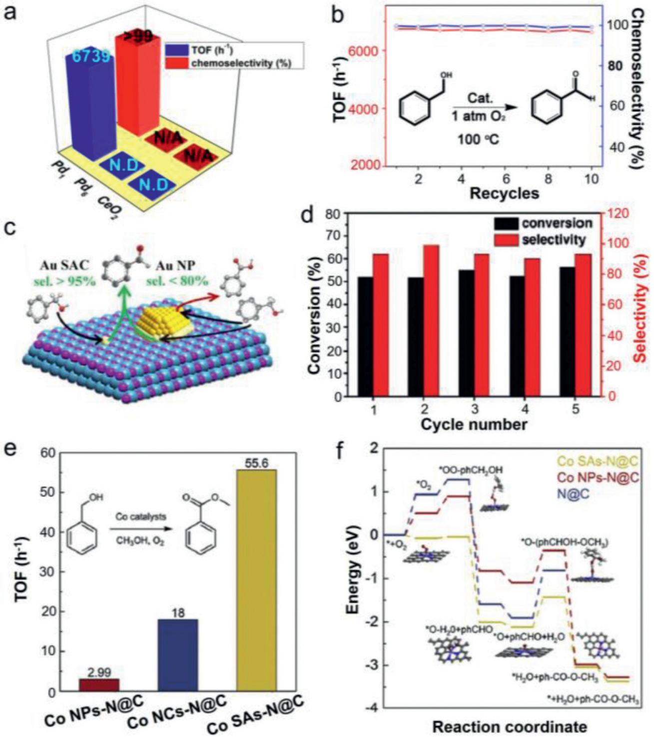

Fig. 4. Oxidation reactions of benzyl alcohol by SACs. (a) TOF and chemoselectivity of Pd_1/CeO_2 SAC for benzyl alcohol oxidation. (b) Recycle experiments for Pd_1/CeO_2 SAC. Reproduced with permission [35]. Copyright 2018, Wiley. (c) The comparison of selectivity of Au SAC and its NP counterpart for benzyl alcohol oxidation. (d) Conversion and selectivity of benzyl alcohol oxidation over Au_1/CeO_2 catalyst in recycling. Reproduced with permission [36]. Copyright 2018, Wiley. (e) Catalytic performances of Co catalysts, TOF values were calculated with methyl benzoate yield. (f) Energy profile and corresponding structures of oxidative esterification of benzyl alcohol catalyzed by Co SAs-N@C SAC. Reproduced with permission [37]. Copyright 2019, Elsevier.

Pd-based SACs showed excellent performance in the selective oxidation of alcohols. In 2007, Hackett *et al.* demonstrated that atomically dispersed Pd^{II} centers loaded on mesoporous alumina (Pd/meso-Al_2O_3) showed an exceptional catalytic performance toward the aerobic oxidation of three allylic alcohols (benzyl, cinnamyl, and crotyl alcohol) to corresponding aldehydes under mild conditions [14]. In order to recognize the true active species of Pd-based catalysts, Wang and coworkers further compared the catalytic properties of palladium-cerium oxide (Pd_1/CeO_2) SAC and hexapalladium cluster-cerium oxide (Pd_6/CeO_2) nanocatalyst in aerobic selective oxidation of benzyl alcohol or substituted alcohols [35]. Their findings showed that Pd_1/CeO_2 SAC achieved an extremely high catalytic activity with a turnover frequency (TOF) as high as 6739 h^{-1}, while Pd_6/CeO_2 was inactive, confirming that the single Pd atoms were the true active species (Figs. 4a and b). A similar phenomenon was also observed for single-atom Au and Au nanoparticle (NP) supported on CeO_2 (Au_1/CeO_2 and Au NP/CeO_2) in the selective oxidation of benzyl alcohol to benzaldehyde (Figs. 4c and d) [36]. Zhou *et al.* examined the catalytic efficiency of different kinds of active Co sites, including single-atom Co supported on nitrogen-doped carbon (Co SAs-N@C), Co nanoclusters supported on N-doped carbon (Co NCs-N@C), and Co NPs supported on N-doped carbon (Co NPs-N@C) [37]. Their findings showed that alcohols could also be oxidized into esterification under the catalysis of SACs. Co SAs-N@C SAC possessed extraordinary catalytic activity for the oxidative esterification of primary alcohols *via* aldehyde intermediates, achieving a high TOF of 55.6 h^{-1} for benzyl alcohol, which was much higher than that of Co nanoclusters and NPs (Fig. 4e). Theoretical reaction mechanism studies showed that the reaction energy barriers of benzyl alcohol activation for Co SAs-N@C was much lower than that for Co nanoclusters and NPs (Fig. 4f). The individually dispersed atoms not only maximized their metal utilization but also showed totally different catalytic properties compared with their nano-scaled counterparts (*e.g.*, clusters and NPs), demonstrating unique catalytic behaviors due to the size effect. Recent literature also reported that Zn-N_x sites anchored on N-doped carbon were effective for aerobic oxidative cleavage and esterification of C(CO)-C bonds and converting acetophenone to methyl benzoate quantitatively [38]. In addition, the application of SACs can be extended to oxidation reactions with high activity and exceptional chemoselectivity, such as Ag [39] or Al [40] SAC catalyzed HCHO oxidation, Co SAC catalyzed sulfide oxidation [41], and Fe SAC catalyzed oxidation of ethylbenzene to acetophenone [42] or oxidation of amine to nitrile [43].

Among varieties of oxidation reactions, direct oxidation of C—H bond is one of the most important and challenging organic transformations. As a typical sp^2 unsaturated C—H bond oxidation reaction, epoxidation of alkene in the presence of SACs was also investigated. Li and coworkers revealed that both single-atom Fe [27] and dual-atom Pt catalysts [44] were effective for the epoxidation of styrene. Besides, uniformly distributed Cu single ions on mesoporous graphitic carbon nitride (g-C_3N_4) were catalytically active in liquid-phase aerobic oxidation of cyclohexene. Although the selective cyclohexene oxidation was somewhat difficult due to the presence of two active bonds in the molecule, they promoted the formation of epoxidation products and shifted the allylic selectivity toward 2-cyclohexene-1-one by increasing the reaction temperatures [45]. The Cu oxo species (a pair of Cu atoms without direct Cu-Cu interaction) were identified as active sites for CH_4 partial oxidation to methanol [46].

The challenging benzene oxidation reaction (BOR) can also be achieved with favorable conversions *via* single-atom catalysis. Fe atoms anchored by four-coordinating N atoms (Fe-N_4) on carbon supports exhibited high performance in the catalytic BOR at mild conditions with the highest benzene conversion of 78.4% and phenol selectivity of 100% (Figs. 5a and b) [47]. As a matter of fact, the atomic structure of Fe-N_4 centers was firstly revealed by Bao and coworkers in 2015 [48]. They reported that confined atomic Fe sites gained satisfying benzene conversion (23.4%) and phenol yield (18.7%) in catalytic direct BOR at room temperature (Fig. 5c). Besides Fe sites, single Cu sites anchored on heteroatoms doped carbon material or graphitic carbon nitride (g-C_3N_4) are catalytically active to BOR. It is believed that Cu single-atoms inserted into the crystal structure of hollow g-C_3N_4 spheres (Cu-SA/HCNS) and exhibited a relatively high catalytic efficiency for selective BOR at room temperature [49]. At a higher reaction temperature (60°C for 12 h), an unexpected benzene conversion (86%) and outstanding high phenol selectivity of 96.7% can be achieved (Fig. 5d). When S and N dual-decorated Cu single-atom (Cu SAC/S-N) was used as a catalyst, 42.3% benzene conversion and 93.4% phenol selectivity were obtained (Fig. 5e) [50]. Similarly, Co single-atoms embedded in ultrathin 2D porous N-doped carbon nanosheets (Co-ISA/CNS) exhibited high activity for C-H bond activation in the direct catalytic BOR [51]. The benzene conversion and phenol yields were 68% and 61%, respectively (Fig. 5f).

Considering the unique feature of SAC, Zhang and coworkers explored the catalytic performance of Fe-N-C SAC in selective sp^3 saturated C-H bond oxidation of a broad scope of substrates, including aromatic, heterocyclic, and aliphatic alkanes [52]. The selectivity of related products reached as high as 99% even at room temperature due to Fe's single-atom dispersion and high oxidation state. Li and coworkers anchored Fe ISAS on a covalent organic framework (COF)-derived N-doped carbon nanospheres [53]. The resultant Fe-ISAS showed high reactivity, high selectivity and good recyclabil-

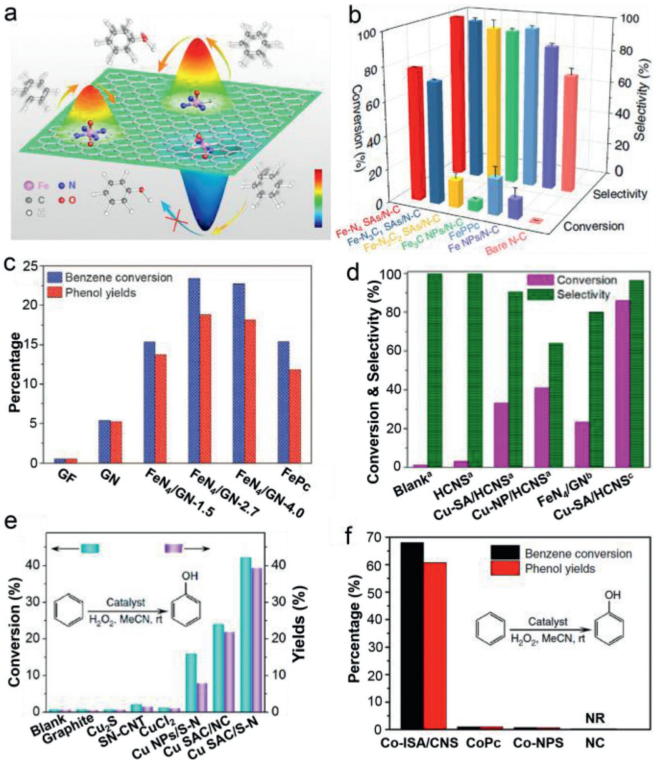

Fig. 5. Oxidation reactions of benzene by SACs. (a) The coordination effect of single-atom Fe-N_xC_y catalytic sites for BOR. (b) Comparison of BOR performance of the as-synthesized Fe-N_xC_y SAC and control catalysts. Reproduced with permission [47]. Copyright 2019, Springer Nature. (c) The performance of the direct BOR by FeN_4/GN samples compared with control catalysts. Reproduced with permission [48]. Copyright 2015, AAAS. (d) Comparison of BOR performance of the as-synthesized Cu SAC and control catalysts. Reproduced with permission [49]. Copyright 2018, American Chemical Society. (e) Conversion rates and yields of BOR catalyzed by Cu SAC and control catalysts. Reproduced with permission [50]. Copyright 2020, American Chemical Society. (f) A comparison of BOR catalyzed by the Co-ISA/CNS SAC and control catalysts. Reproduced with permission [51]. Copyright 2018, Springer Nature.

ity for oxidation of ethylbenzene to acetophenone. They also found that single-atom Co sites embedded on CN supports (Co SAC/CN) showed excellent catalytic properties for oxidation of ethylbenzene in air, while the nanosized or homogenous Co catalysts are inert to this reaction [54]. These works revealed that the fine structure of metal atom anchored on support played a crucial role in reaction energy barrier, which resulted in a robust catalytic performance of SACs. Therefore, many transition metals should be catalytically active for varieties of oxidation reactions if they are isolated as single-atom sites with suitable coordination structures or anchoring microenvironments. In order to understand advantages of single-atom catalysis, the coordination structure of single-atom sites and the catalytic performance (*e.g.*, conversion, selectivity and TOF) of SACs toward oxidation reactions are summarized in Table S1 (Supporting information).

2.2. Reduction reaction

Reduction of unsaturated compounds (*e.g.*, aldehydes/ketones, nitroarenes) represents a family of industrially important reactions to produce fine chemicals, including pharmaceutical, agrochemical, and fragrance compounds.

H_2 involved hydrogenation is the most common reduction system. For instance, acetophenone can be reduced to 1-phenylethanol with a 98.7% selectivity over Pt/Al_2O_3 SAC-H_2 system [55]. Single Rh atoms anchored to the edges of 2D MoS_2 sheets (Rh_1/MoS_2) can efficiently catalyze the reduction of crotonaldehyde to crotyl alcohol with 100% selectivity in the presence of H_2 [56]. Single atomic Pt, Pd and Au supported on oxygen defective Nb_2O_5 can efficiently catalyze the hydrogenation of 5-(hydroxymethyl)furfural to 5-methylfurfural using H_2 as the reducing agent with a selectivity of >99% at complete conversion [57]. Alcohols (*e.g.*, ethanol, *n*-propyl alcohol, 2-propyl alcohol, *n*-butyl alcohol, 2-butyl alcohol) were also used as the hydrogen source for single-atom catalyzed reduction of aldehydes/ketones. Single-atom Ni was efficient for catalytic transfer hydrogenation of furfural to furfuryl alcohol (Fig. 6a) [58]. Ni SAC with unique Ni–N_4 sites in N-doped carbon ($Ni_{2.1}$/CN) was efficient for the transfer hydrogenation reaction of aldehydes/ketones to produce alcohols using ethanol as the H donor (Figs. 6b–d) [59]. Similarly, under the catalysis of single-site Ru (Ru_1/NC) species, aldehydes/ketones can be converted into primary amines *via* a reductive amination reaction with high activity and selectivity [60].

SACs are highly active and chemoselective toward the reduction of substituted nitroarenes even when reducible groups (*e.g.*, unsaturated bonds) or sensitive groups (*e.g.*, halogen) coexist in their molecules [61–63]. Zhang and coworkers revealed that the coordination structure of Pt sites as well as the interaction between single or pseudo-single Pt atoms and the FeO_x support was crucial to the catalytic performance [64,65]. Strong metal-support interaction resulted in significant electron transfer from the Pt atoms to the FeO_x support, leading to a chemoselective reduction of substituted nitroarenes containing -C=C, -C=O, -C≡N and -X functional groups. It should be noted that single-site metal (*e.g.*, Sn) was acted as a promoter to enhance the catalytic performance in nitroarenes (Fig. 6e) [66]. Besides, it is effective to regulate the performance by constructing confined structure of active atom sites. Metal single-atoms encaged or trapped in pores or interfaces of inorganic materials (*e.g.*, zeolite [67], metal oxides [68], C_3N_4 [69], amorphous or graphitic carbon [70]) exhibited unique properties for nitroarenes reduction. The confinement of metal atoms in the cavities of porous support materials may result in strong metal-support interactions, and show significant influence on the catalytic performance. In addition to the conventional reduction method with a reducing agent (*e.g.*, H_2, $NaBH_4$), nitroarenes can also be catalytically reduced by SACs *via* the transfer hydrogenation approach, in which hydrazine hydrate [71], formic acid [72], isopropanol [73], *N*-heterocycles [74] can be employed as the H sources for hydrogen transfer. Moreover, Choi and coworkers reported that iron SAC was efficient and durable for selective electrocatalytic reduction of nitric oxide into hydroxylamine [75]. The coordination structure of single-atom sites and the catalytic performance (*e.g.*, conversion, selectivity and TOF) of SACs toward reduction reactions are summarized in Table S2 (Supporting information).

2.3. Addition reaction

Addition reaction is one of the most widely used organic synthesis approaches in producing fine chemicals. Addition reactions involved an unsaturated substrate, such as alkyne, alkene, or conjunct alkene. In recent years, SACs have been applied in addition reactions, including hydrogenation, hydrochlorination, hydrosilylation, hydroboration, distannylation, *etc.*

Catalytic hydrogenation is one of the best-studied categories and most important industrial reactions catalyzed by metal-based catalysts. Compared to nano-scaled metals, atomically dispersed ones would show remarkably high activity and selectivity by maximizing metal utilization and/or suppressing the conversion of by-products (Fig. 7a) [2]. Zheng and coworkers demonstrated that the catalyst with atomically dispersed palladium on titanium (Pd_1/TiO_2) exhibited high catalytic activity in hydrogenation of C=C

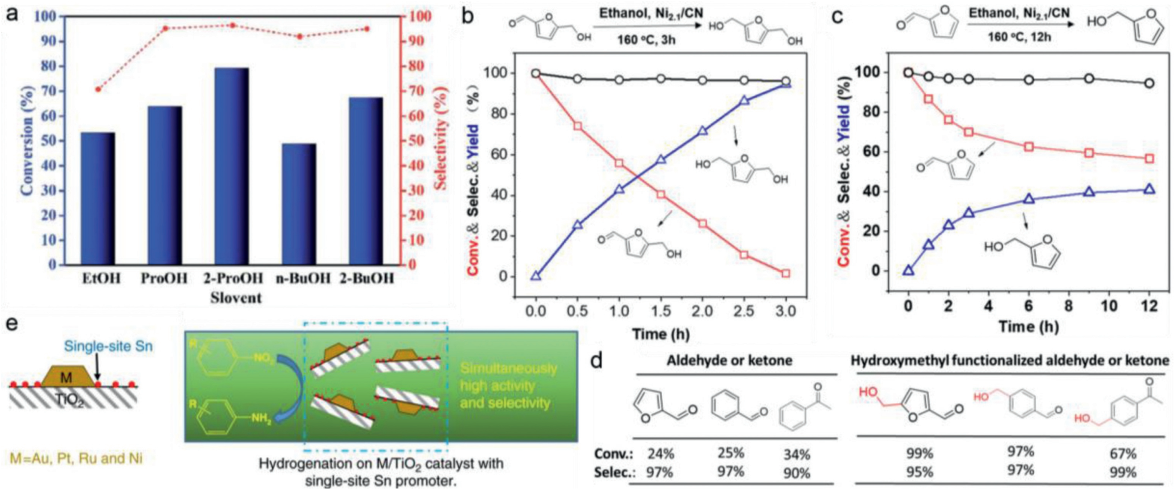

Fig. 6. Reduction reactions of aldehydes, ketones or nitroarenes. (a) Effect of solvents on the hydrogenation of furfuryl alcohol over Ni SAC Reproduced with permission [58]. Copyright 2021, Royal Society of Chemistry. Time course of hydrogenation of (b) 5-hydroxymethylfurfural, (c) furfural, and (d) biomass-derived aldehyde/ketone with/without the -CH_2OH group over $Ni_{2.1}$/CN. Reproduced with permission [59]. Copyright 2021, American Chemical Society. (e) M/TiO_2 catalysts with single-site Sn promoters in reduction of substituted nitroarenes. Reproduced with permission [66]. Copyright 2018, Springer Nature.

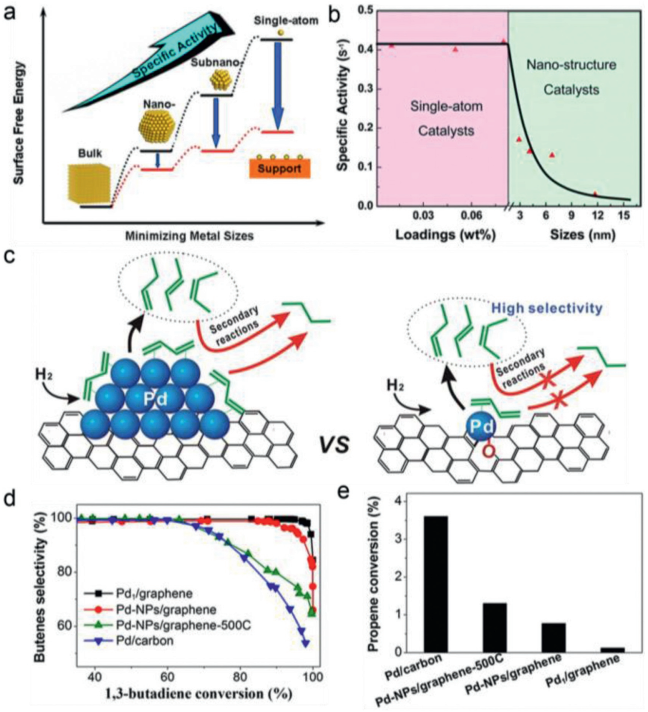

Fig. 7. Size and the support effect of single-atoms and hydrogenation reactions catalyzed by SACs. (a) Schematic illustrate the changes of surface free energy and specific activity per metal atom with metal particle size and the support effects on stabilizing single atoms. Reproduced with permission [2]. Copyright 2013, American Chemical Society. (b) Specific activity as a function of metal loadings/sizes. Reproduced with permission [13]. Copyright 2005, Wiley. (c) Catalytic performances of Pd_1/graphene and its NPs counterparts in selective hydrogenation of 1,3-butadiene. (d) Butenes selectivity as a function of conversion by changing the reaction temperatures. (e) Propene conversion of 1,3-butadiene hydrogenation in the presence of propene. Reproduced with permission [78]. Copyright 2015, American Chemical Society.

bonds, far exceeding that of commercial Pd NPs catalysts [76]. Their findings proved that upgrading catalytically active components from NPs to single-atoms not only boosted the catalytic reaction because of the high atom efficiency, but also endowed SACs with remarkable catalytic capability that conventional nanocatalysts did not possess. Yan and coworkers synthesized a series of polyoxometalate-supported Pt SACs and comparatively studied their catalytic properties in the hydrogenation of propene, 1,3-butadiene, and phenylacetylene. They found that molecular hydrogen and propene co-adsorbed and activated on the single Pt atom. One H from the H_2 unit transferred to propene and preferentially produced isopropyl, while the migration of the remaining H atom led to the formation of propane. Their investigation further unveiled how the metal-support interaction influenced the catalytic behavior of Pt SACs and establish the structure–activity relationships [77].

Selective hydrogenation of 1,3-butadiene has long been an important model reaction catalyzed by metal-based catalysts. Xu and coworkers discovered that isolated surface-type Au^{3+} ions supported on ZrO_2 support (Au/ZrO_2) were actually the active sites for the selective hydrogenation of 1,3-butadiene [13]. More importantly, the catalytic efficiencies were nearly the same (TOFs were *ca.* 0.40 s^{-1}) for the different catalysts with varied Au loadings (*e.g.*, 0.08, 0.05, and 0.01 wt%) (Fig. 7b). These results demonstrated that the atomically dispersed and isolated gold atoms in these three samples were equally active for the catalytic hydrogenation. It is noteworthy that it was the first work that reported the maximum atomic efficiency of SAC. Satisfied selectivity can also be achieved with the catalysis of SAC. For instance, isolated Pd supported on graphene (Pd_1/graphene) exhibited excellent performance in the hydrogenation of 1,3-butadiene with superb conversion (~95%) and butenes selectivity (~100%) (Figs. 7c–e) [78]. Besides to linear unsaturated carbon-carbon bond hydrogenation, a wide range of aromatic and heterocyclic compounds can also be hydrogenated over SACs. Atomically dispersed Ir (up to 10 wt%) supported on mesoporous sulfur-doped carbons (meso_S-C) [79], single Ru site supported on nitrogen-doped porous carbon (Ru SAs/N-C) [80], and S, N co-doped carbon supported Co single atom catalysts (Co/SNC) [81] can effectively and selectively catalyze the hydrogenation of quinolines. Atomic Ru decorated with Na^+ ions (Na^+-Ru1/Al_2O_3) was also highly active for the hydrogenation of a wide range of aromatic and heterocyclic substrates, such as phenol, guaiacol, di(2-ethylhexyl)phthalate, 4,4′-methylenedianiline, and pyridine [82].

The selective semi-hydrogenation of acetylene to ethylene in an ethylene-rich gas stream is an important process in the chemical industry [83,84]. Recent studies showed that single-atom catalysis

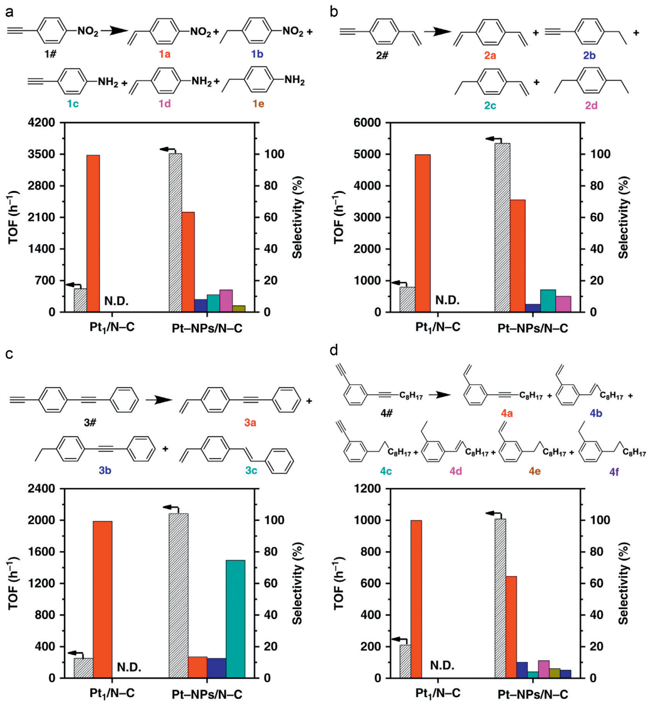

Fig. 8. Catalytic performance comparison of Pt SAC and Pt NPs catalyst in hydrogenation of alkynes. Reaction results for the hydrogenation of (a) 1-nitro-4-ethynylbenzene, (b) 1-ethynyl-4-vinylbenzene, (c) 1-ethynyl-4-(phenylethynyl)benzene, (d) 1-(dec-1-yn-1-yl)-3-ethynylbenzene on Pt_1/N-C and Pt-NPs/N-C. Reproduced with permission [91]. Copyright 2019, Springer Nature.

could suppress the undesirable over-hydrogenating of ethylene to ethane. Pioneer researcher Javier Pérez-Ramírez has conducted a series of researches about selective alkyne semi-hydrogenation *via* g-C_3N_4 stabilized Pd SACs [69,85,86]. Using the same support material, they further incorporated atomically dispersed noble metals (*e.g.*, Pd, Ag, Ir, Pt, and Au) and achieved a 100% selectivity to the desired product [87], outperforming the commercial Lindlar-type Pd-Pb/$CaCO_3$ catalyst (78%) [88]. Huang and coworkers anchored Pd single-atoms on nanodiamond /graphene hybrid for selective hydrogenation of acetylene [89,90]. To explore a general synthesis method, they introduced different metals (M = Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Ga, Zr, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Er, W, Ir, Au and Bi) on N doped carbon (N-C) to synthesize a series of SACs with different surface atom densities, bi-metallic sites, and metal aggregation states [91]. Compared with Pt-NPs/N-C, Pt_1/N-C showed excellent regioselectivity in the hydrogenation of alkynes, only converting terminal alkynes to alkenes while keeping other reducible functional groups such as alkenyl, nitro group, and even internal alkyne intact (Fig. 8). Similarly, single-atom Pd supported on mesoporous NC nanosphere exhibited high activity, excellent ethylene selectivity, and good long-term stability in semi-hydrogenation of acetylene [92]. Besides, N-containing support materials, P- or S-containing supports can be employed to stabilize metal single-atoms (*e.g.*, Ni [93], Pt [94,95]) and enhance the activity of acetylene semi-hydrogenation. As sintering and coke formation usually occur in the hydrogenation of acetylene, leading to the deactivation of catalysts. Lu and coworkers solved this problem by synergizing metal-support interactions and spatial confinement of single-atom Ni and thus achieved extraordinary catalytic performance [96]. Interestingly, selective acetylene hydrogenation can also be achieved through a photothermal single-atom catalytic process induced by light irradiation. Zhang and coworkers firstly reported that atomically dispersed Pd on nitrogen-doped graphene exhibited outstanding activity and selectivity for the hydrogenation of acetylene with H_2 in the presence of excess ethylene under full spectrum Xe lamp irradiation [97].

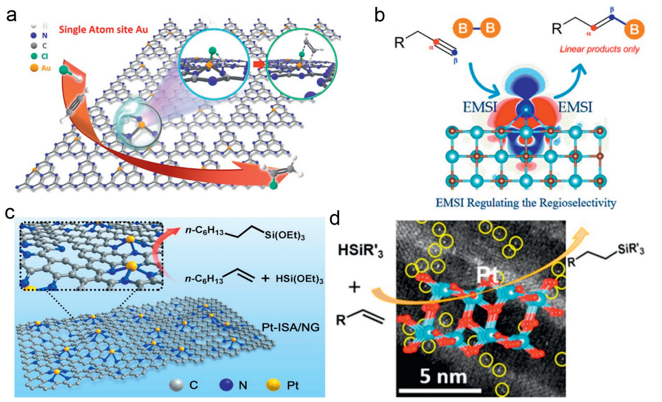

Fig. 9. Addition reactions (*e.g.*, hydrochlorination, hydroboration and hydrosilylation) catalyzed by SACs. (a) Au SAC for acetylene hydrochlorination reaction. Reproduced with permission [101]. Copyright 2020, American Chemical Society. (b) Cu SAC for hydroboration of terminal alkynes. Reproduced with permission [103]. Copyright 2021, American Chemical Society. (c) Pt SAC for anti-Markovnikov alkene hydrosilylation. Reproduced with permission [106]. Copyright 2018, American Chemical Society. (d) Pt SAC as heterogeneous catalyst for alkene hydrosilylation. Reproduced with permission [108]. Copyright 2018, American Chemical Society.

Isolated noble metal (*e.g.*, Pt, Au) sites can also provide an efficient pathway for sustainable vinyl chloride production *via* acetylene hydrochlorination [98–100]. The positive charged single Au site with N coordinated electronic structure endowed the corresponding SAC with remarkable catalytic performance toward acetylene hydrochlorination reaction (Fig. 9a) [101]. In recent work, Pt(II)−Cl was identified as the active site for the same reaction [102]. Acetylene addition with other substrates was also realized through single-atom catalysis. For instance, selective hydroboration of terminal alkynes (Fig. 9b) [103] and azide-alkyne cycloaddition of 4-ethynylanisol with benzyl azide [99], diboration of alkynes [104], as well as distannylation of terminal alkynes [105], can be achieved under the catalysis of Cu, Pt and Pd SACs, respectively. In addition, the addition of C=C bond was also achieved under the catalysis of SAC. Ding and coworkers reported that SACs are effective for alkene hydrosilylation, the addition reaction of a silicon hydride (Si-H) to the C=C bond. Efficient and selective anti-Markovnikov hydrosilylation of various terminal alkenes with silanes (Figs. 9c and d) was also achieved under the catalysis of atomic Pt recently [106–108]. Besides to the addition of carbon-carbon unsaturated bonds, selective hydrogenation of nitriles can be realized in the presence of atomically dispersed Pd species stabilized on the defect-rich nanodiamond-graphene (ND@G) hybrid (Pd1/ND@G). The Pd1/ND@G SAC preferentially generated secondary amines, exhibiting different catalytic behavior from its Pd cluster-base counterpart, over which primary amines were selectively generated products [109]. This work elucidated the different mechanisms of the Pd catalysts (*e.g.*, Pd single-atom, Pd cluster) induced by structural variation and established structure-performance relationship over atomically dispersed Pd catalysts. The coordination structure of single-atom sites and the catalytic performance (*e.g.*, conversion, selectivity and TOF) of SACs toward addition reactions are summarized in Table S3 (Supporting information).

2.4. Coupling reaction

Coupling reaction has been considered one of the most straightforward and effective pathways for constructing carbon-carbon, carbon-oxygen, carbon-nitrogen, or nitrogen-nitrogen bonds in or-

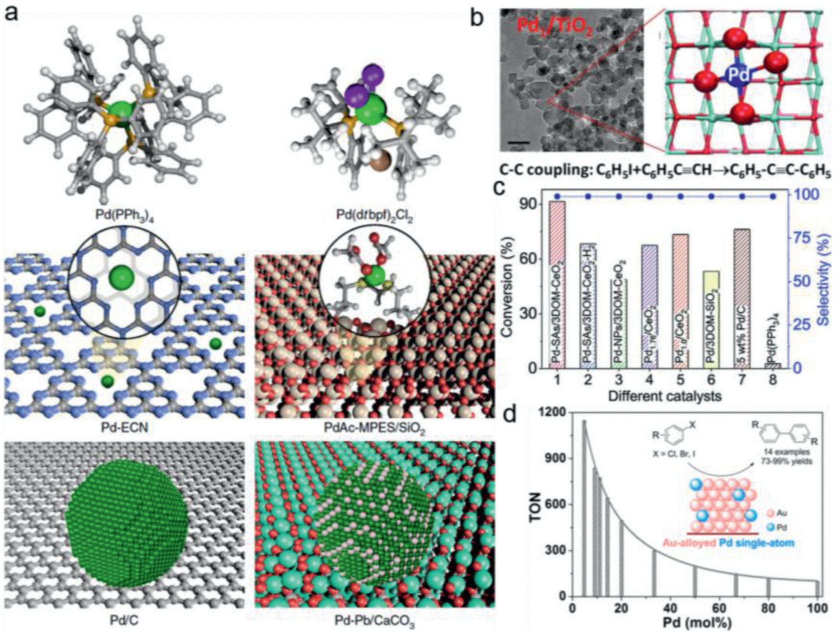

Fig. 10. Coupling reactions (*e.g.*, Suzuki, Sonogashira, and Ullmann reactions) catalyzed by SACs. (a) Structural comparison of different homogeneous and heterogeneous palladium catalysts for Suzuki reaction. Reproduced with permission [110]. Copyright 2018, Springer Nature. (b) Pd_1/TiO_2 SACs for Sonogashira C–C coupling reactions. Reproduced with permission [114]. Copyright 2018, American Chemical Society. (c) Conversion of iodobenzene and selectivity for producing biphenyl over different catalysts. Reproduced with permission [111]. Copyright 2020, Wiley. (d) TON values of Au-Pd/resin for the Ullmann reaction. Reproduced with permission [115]. Copyright 2014, American Chemical Society.

ganic synthesis. Single metal atom usually has uniform and identified reactive sites, leading to unique catalytic behavior for coupling reactions, including Suzuki, Sonogashira, Ullmann, *etc.*

Pd-based SACs have been widely used in C-C bond formation to produce biphenyl compounds (*e.g.*, Suzuki coupling). Isolated Pd atoms anchored on exfoliated graphitic carbon nitride (Pd-ECN) demonstrated a high activity, chemoselectivity, stability, and broad functional group tolerance. The Pd-ECN SAC surpassed the performance of state-of-the-art homogeneous catalysts and conventional heterogeneous catalysts [*e.g.*, palladium acetate ($Pd(OAc)_2$), tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) and [1,1′-bis(di-*tert*-butylphosphino) ferrocene]dichloropalladium(II) ($Pd(dtbpf)Cl_2$)] and commercial heterogeneous catalysts [*e.g.*, $Pd(OAc)_2$ anchored on silica functionalized by 3-mercaptopropyl ethyl sulfide ($PdAc\text{-}MPES/SiO_2$), Pd/C or even strongly modified Lindlar-type $Pd\text{-}Pb/CaCO_3$)] for Suzuki couplings (Fig. 10a) [110]. A similar comparative study was conducted by Xiong and coworkers [111]. They found that Pd single-atoms anchored in 3D ordered macroporous structural ceria ($Pd\text{-}SAs/3DOM\text{-}CeO_2$) exhibited outstanding activity and durability toward Suzuki reactions for a broad scope of substrates, far outperforming the other control heterogeneous catalysts and the homogeneous $Pd(PPh_3)_4$ catalyst (Fig. 10c). It was believed that single Pd atom kinetic-feasibly dissociated the chemisorbed halogenobenzene and thus motivated C-halogen bond cleavage [112]. Besides to Pd, Pt single-atoms are also active to Suzuki coupling reaction. Lee *et al.* reported that Pt dispersed on thiolated multi-walled nanotubes (Pt-S-MWNT) exhibited extremely high activity for the ligand-free Suzuki coupling reaction [113].

In addition, SAC can be employed for C≡C coupling reaction. Single Pd atom (Pd_1O_4) sites anchored on TiO_2 (Pd_1/TiO_2) exhibited high activity and selectivity for Sonogashira coupling reaction (Fig. 10b) [114]. Resin-supported Au alloyed Pd single atoms (Au-Pd/resin) served as an effective and robust catalyst for the Ullmann reaction of aryl chlorides. The surface Pd sites were isolated by Au atoms and exhibited high activity and excellent durability for Ullmann reactions of aryl chlorides with broad substrate scope and functional group tolerance (Fig. 10d) [115]. Similarly, atomically dispersed Ir on MgO showed remarkable activity in coupling benzene and ethylene into styrene [116]. Recently, reduced graphene oxide (rGO) supported molybdenum dioxo (rGO/MoO_2) SAC was demonstrated to be effective for reductive carbonyl coupling to afford the C–O–C bond [117]. Furthermore, SACs were proved to be catalytically active for the construction of C–N [118,119], C=N [120], and N=N [121] bonds *via* coupling reactions. Recently, metal-N-C typed centers (*e.g.*, V-N-C and Co-N-C) in SACs were also identified to be active to the coupling reactions. The coordination structure of single-atom sites and the catalytic performance (*e.g.*, conversion, selectivity and TOF) of SACs toward coupling reactions are summarized in Table S4 (Supporting information).

2.5. Other organic reactions

Besides to the common organic reactions mentioned above, SACs exhibited distinct performance in other specialized chemical reactions, such as alkane dehydrogenation, hydroformylation, hydrogenolysis, hydrodeoxygenation.

Hydroformylation of olefins is one of the most important organic reactions for aldehyde synthesis [122]. Single-atom Rh exhibited remarkable catalytic activity and selectivity when supported on metal oxides, such as ZnO [123], CoO [124], CeO_2 [125]. In addition, phosphorus coordination [126] and ionic-liquid (IL)-immobilization [127,128] were also proved to be effective strategies for stabilizing the single-atom Rh on support materials, and thus enhanced the catalytic performance and the metal utilization efficiency. The electronic metal-support interaction played a crucial role in improving catalytic performance *via* the coordination bonding between atomic metal and support [129,130]. Incorporation of single-atom Pt with other metals was an effective method to enhance the catalytic performance in high temperature (>500 °C) propane dehydrogenation reactions [131]. Non-noble metals played vital roles in promoting the dispersion of Pt *via* separating Pt atoms and forming intermetallic compounds [132] or single-atom alloy [133]. Fe and Co SACs showed excellent activity and selectivity for dehydrogenation of 1,2,3,4-tetrahydroquinoline [134]. In addition, atomic Ni [135], Pt [136], Ru [137], Pd [138], Ru [139], Cu [140], and Ag [141] could serve as efficient and chemoselective SACs for the hydrogenolysis of cellulose, hydrogenolysis of glycerol, hydrogenolysis of catechyl lignin, hydrodeoxygenation of vanillin, reduction of CO_2 to methanol or methane, and borylation of aryl iodides, respectively. Recently, SAC was used in catalyzing alcohol [142] or ammonia borane [143] dehydrogenation and H/D exchange and isomerization of alkenes [144]. It is believed that the investigation of metal-site's fine structure of and reaction intermediate facilitate the understanding of the structure-activity relationship in the single-atom catalytic system [145]. The coordination structure of single-atom sites and the catalytic performance (*e.g.*, conversion, selectivity and TOF) of SACs toward the above-mentioned organic reactions are summarized in Table S5 (Supporting information). It is worth noting that the catalytic applications of SACs are not limited to the above-mentioned organic reactions. With the development of single-atom catalysis, SACs will be applied in a wider scope of organic reactions.

3. Conclusions and perspectives

3.1. Conclusions

Over the past few years, SACs have been successfully used in a variety of organic reactions, including oxidation, reduction, addition, coupling, and other kinds of organic transformations. With the advantages of homogeneity and low-coordination environment of the atomic metal sites, SAC has been viewed as a bridge between homogeneous and heterogeneous catalysts, thus enabling single-atom catalysis to position along the development history of heterogeneous catalysis. The unique structural properties of atomically dispersed metal sites endow SAC with distinctive catalytic performance, such as activity, selectivity, and stability. By benefitting from the advancement of synthesis strategy, high loading SACs can be easily prepared at a gram-scale or even kilogram-scale, which paves the way to practical industrial applications.

3.2. Perspectives and challenges

SACs have many possible applications in varieties of organic reactions. In the following, we highlight some specific fields for which SACs have not been explored yet, but where their use could be advantageous:

(1) The preparation of SACs mainly focused on transition metals, namely Au, Pt, Pd, Fe, Co, Ni, *etc.* Nevertheless, the preparation and application of main group elements (*e.g.*, Al, Hg, Os) or lanthanide elements-based SACs are merely reported. Although high loading SACs and specific scale-up manufacture techniques have been developed, the commercialization and industrial usage of SACs need to be pushed forward in the future. Furthermore, the SACs with various solid supports still await exploration to expand the member number of the family and extend the scope of applications.

(2) SACs have been widely used in varieties of organic reactions; however, they still face some limitations: not all organic reactions can be catalyzed by SACs. In addition to some conventional organic reactions, asymmetric synthesis catalyzed by SACs has not been achieved yet. This should be ascribed to the absence of chiral centers in SACs, which is different from their homogeneous counterparts with chiral ligands. The incorporation of chiral sources into the SACs should be a solution to break through the limitation.

(3) Besides to SACs, double-atom and triple-atom catalysts have been fabricated. The co-existence of non-single atom or even different type of metal elements make the catalytic properties more complicated than that of mono-metal-based SACs. The interactions between the adjacent atoms and different metal species need further investigation. The catalytic behaviors of single-atom, double-atom, triple-atom, and even subnanocluster need further comparative study.

(4) SACs have been extensively studied for electrocatalytic applications (*e.g.*, hydrogen evolution reaction, oxygen reduction reaction) and catalytic organic reactions. However, SACs for electrochemical and photochemical organic reactions were merely explored. Electrocatalytic and photocatalytic organic transformations based on SACs should be of great interest and importance for the further development of in green synthesis of fine chemicals.

Based on the developmental history and the discussion of recent progress in the SACs and single-atom catalysis for organic reactions, it is believed that extending the scope of organic reaction and precisely regulation the catalytic behavior by modulating the chemical and/-or physical environments of active metal atoms will be promising directions. In terms of industrial application, tireless pursuits for the four guidelines, referring to safety, performance, cost, and environmental friendliness, are still underway.

Declaration of competing interest

I would like to declare on behalf of my co-authors that there is no conflict of interest exists in the submission of this manuscript, and the manuscript has been approved by all authors for publication. All of the authors listed have approved the manuscript that is enclosed.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107959.

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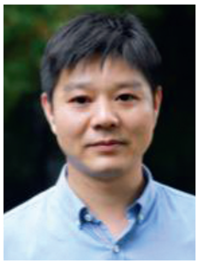

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