Ultrahigh Loading Copper Single Atom Catalyst for Palladium-free Wacker Oxidation

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Wacker oxidation is an industry-adopted process to transform olefins into value-added epoxides and carbonyls. However, traditional Wacker oxidation involves the use of homogeneous palladium and copper catalysts for the olefin addition and reductive elimination. Here, we demonstrated an ultrahigh loading Cu single atom catalyst(14% Cu, mass fraction) for the palladium-free Wacker oxidation of 4-vinylanisole into the corresponding ketone with *N*-methylhydroxylamine hydrochloride as an additive under mild conditions. Mechanistic studies by ^{18}O and deuterium isotope labelling revealed a hydrogen shift mechanism in this palladium-free process using *N*-methylhydroxylamine hydrochloride as the oxygen source. The reaction scope can be further extended to Kucherov oxidation. Our study paves the way to replace noble metal catalysts in the traditional homogeneous processes with single atom catalysts.

Keywords Single atom catalyst; Wacker oxidation; Ultrahigh loading; High valued chemical; Organic catalysis

1 Introduction

Wacker oxidation is probably one of the most studied organic transformations since it affords carbonyl compounds from readily available olefins at an industrial level[1,2]. A typical procedure of Wacker oxidation involves a homogeneous $PdCl_2/CuCl_2$ mixture under aerobic and acidic conditions, where the initial Pd(II) species is reduced to Pd(0) and re-oxidized to Pd(II) by the Cu(II) co-catalyst[3]. Under such conditions, the Markovnikov addition of water is usually achieved, affording the corresponding methyl ketones when terminal alkenes are employed as substrates. Despite its convenience, traditional Wacker oxidation suffers from the use of homogeneous noble metal species, adding cost and difficulty in separation from the reaction system[4,5]. Many attempts have been devoted to more sustainable non-noble complexes[6,7] and heterogeneous Pd catalysts[4,8−10] to promote the Wacker oxidation, however, the process is still dominated by the classical Pd/Cu catalyst.

The last decade has witnessed the emergence of single atom catalyst(SAC) to emulate the coordination environment of homogeneous catalysts, while retaining its structural integrity on a heterogeneous solid support for the ease of separation[11,12]. Successful demonstrations in many oxidative and hydrogenative reactions have evident the feasibility to replace the homogeneous variants by SACs[13,14]. The utility in complex organic transformations, such as cross-coupling, diboration, hydroformylation and cyclization to produce bioactive medicines has recently been realized by palladium or copper-based SACs[15−18]. Particularly, Cu SAC has demonstrated high efficiency in the C—N coupling reaction, which shares a similar oxidative addition-reductive elimination pathway to Wacker oxidation[19]. Nonetheless, the scope of SAC in such organic transformations is restricted by the sluggish sequential activation process at the same metal site[14,20,21]. It is therefore important to design an ultrahigh metal loading SAC(preferably Cu) to realize cooperative activation of reactants by two(or more) nearby metal sites to promote the Wacker oxidation.

Herein, we reported the fabrication of an ultrahigh loading Cu SAC in a nitrogen-rich carbon matrix[Cu-N-C, 14.5%, mass fraction, Cu by inductively coupled plasma-optical emission spectrometry(ICP-OES)] by the pyrolysis of Cu precursor. Such a Cu SAC presented excellent activity and selectivity(up to 86%) for the Wacker oxidation of 4-vinylanisole to the corresponding ketone using *N*-methylhydroxylamine hydrochloride as an additive under mild oxidative conditions. Further studies employing ^{18}O and deuterium isotope labelling revealed a hydrogen shift mechanism in this palladium-free process. Such a strategy can be extended to Kucherov oxidation.

2 Experimental

2.1 Synthesis of Cu SAC

Copper(II) acetate(2.5 mmol, 98%, Sigma) and *L*-glutamic acid(1 mmol, 99%, Sigma) were dissolved in 100 mL of DI water. 1,3,5-Benzenetricarboxylic acid(3 mmol, 95%, Sigma) was dissolved in another 100 mL of DI water at 60 °C. Two

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solutions were mixed and stirred at room temperature for 2 h. After filtration of the excess Cu precursor, the blue precipitate was rinsed with DI water and ethanol, and dried at 70 °C overnight. Then 1 g of the precipitate was annealed at 800 °C for 3 h at 3 °C/min under argon. The as-obtained black powder was washed with 2 mol/L HCl solution for 12 h to remove unwanted Cu nanoparticles. Cu SAC was collected by filtration, rinsing with DI water and ethanol, and drying at 70 °C overnight. The black powder of Cu SAC was sent for ICP to determine the Cu loading, for structural characterization, as well as for further catalytic performance study.

2.2 Cu SAC Catalysed Wacker-type Oxidation

Typically, 4-vinylanisole(0.1 mmol, 13.7 mg, 97%, Sigma), Cu SACs(4%, molar fraction, 1.8 mg), *N*-methylhydroxylamine hydrochloride(0.2 mmol, 17.2 mg, 98%, Sigma), dioxane (0.7 mL, anhydrous, Sigma) and H_2O(90 μL) were added to a Schlenk tube(5 mL). The reaction was conducted at 90 °C in the air for 24 h. After the reaction, 2 mL of deionized water was added to the mixture and the catalyst was recycled by centrifugation. The solution was extracted with CH_2Cl_2 three times. The combined organic layer was dried with anhydrous Na_2SO_4 and then evaporated under reduced pressure. The pure product was obtained by thin layer chromatography (TLC) and verified by gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance(NMR). The yield was calculated by dividing the amount of pure product to the theoretical yield.

2.3 Material Characterization

The following equipments were used: atomic-resolution scanning transmission electron microscope(STEM, JEOL ARM200F equipped with an ASCOR probe corrector at 80 kV), transmission electron microscope(TEM, JEM 2010F, 200 kV), X-ray photoelectron spectrometer(XPS, AXIS UltraDLD, monochromatic Al *Kα*), X-ray diffraction instrument(XRD, Bruker D8), ICP-OES(Perkin Elmer Avio 500, ppm level accuracy), GC-MS(Agilent 5975 C inert MSD with a triple-axis detector), NMR(Bruker AV400). X-Ray absorption near-edge structure spectroscopy-extended X-ray absorption fine structure spectroscopy(XANES/EXAFS): 100 mg of sample was first ground into a fine powder using a mortar and pestle before being pressed into a 10 mm pellet. Measurements were carried out at Singapore Synchrotron Light Source(SSLS) for X-ray absorption fine structure for catalysis(XAFCA) beamline. Data analysis and simulation were carried out on Athena, Artemis, and Hephaestus(Version 0.9.23).

3 Results and Discussion

3.1 Synthesis and Characterization of Cu SAC

The Cu SAC was synthesized by a modified method using tridentate *L*-glutamic acid and copper acetylacetonate to form a Cu precursor, followed by the pyrolysis at 800 °C to convert it into a thermally stable Cu-N-C matrix[22]. The introduction of *L*-glutamic acid is critical to prevent aggregation pyrolysis as reflected in the control experiment without ligand. The morphology of Cu SAC was carefully investigated by STEM. As shown in Fig.1, the Cu SAC presented an ultrathin nanosheet morphology. The existence of Cu single atoms was identified by the bright spots in the high-resolution STEM images. No significant particle aggregation can be observed throughout the matrix, suggesting the major existence of a single Cu atom in our catalyst.

    XPS was employed to verify the oxidation state of Cu. Two peaks featured at 932 and 935 eV for Cu $2p_{3/2}$ can be assigned to the Cu^I(*ca.* 60%) and Cu^{II}(*ca.* 40%) species in Fig.2(A). Such a mixed valence state of Cu is important for the dynamic redox process during the oxidative addition and reductive elimination in Wacker oxidation. The formation of the Cu-N-C structure is confirmed by the characteristic peaks of the pyridinic N and graphitic N at 398.5 and 400.8 eV in the N 1*s* core-level XPS spectrum in Fig.2(B). Furthermore, the electronic and coordination structures of Cu in SAC were examined by X-ray absorption spectroscopy(XAS). In the near-edge region, XANES spectra show that the absorption edge falls between Cu foil and Cu(II) porphyrin, indicating a positively charged Cu species. The mixed valance state of Cu is confirmed by the white-line intensity of Cu SAC, which is in-between Cu_2O and CuO. The single atom nature of our
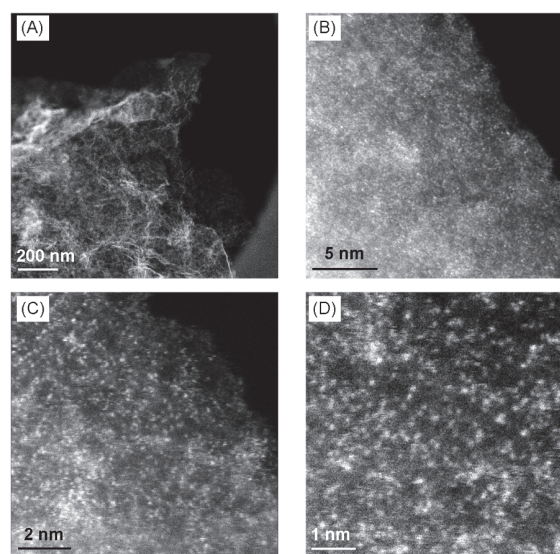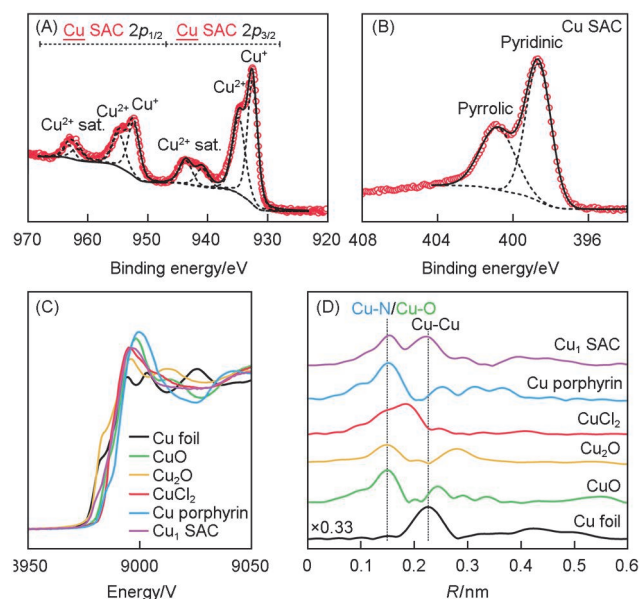

Fig.1 STEM images of the Cu SAC at various magnifications

Fig.2 Chemical composition of the Cu SAC
(A) Cu 2p core-level XPS; (B) N 1s core-level XPS; (C) Cu K-edge XANES spectra; (D) Cu K-edge EXAFS spectra.

Table 1 Catalyst screening on the Wacker oxidation of olefin[a]

Entry	Addictive	Oxidant	Catalyst	Yield(%)
1	——	Air	Cu SAC	0
2	——	H_2O_2	Cu SAC	92[b]
3	$CH_3NHOH \cdot HCl$	Air	Cu SAC	56
4	$CH_3NHOH \cdot HCl$	O_2(1 atm)	Cu SAC	54
5	$CH_3NHOH \cdot HCl$	H_2O_2	Cu SAC	55
6	$CH_3NHOH \cdot HCl$	Ar	Cu SAC	53
7	$CH_3NHOH \cdot HCl$	Air	——	0
8	$CH_3NHOH \cdot HCl$	Air	10% Cu/C	0
9	$CH_3NHOH \cdot HCl$	Air	CuI	32[c]
10	$CH_3NHOH \cdot HCl$	Air	Cu(OAc)$_2$	27[c]
11	$CH_3NHOH \cdot HCl$	Air	Cu SAC(6 mg)	87
12	$CH_3NHOH \cdot HCl$	Air	Cu SAC[d]	50

a. Reaction condition: 4-vinylanisole(0.1 mmol, 1.0 eqv.), catalyst(4% Cu, molar fraction), *N*-hydroxy-*N*-methylamine hydrochloride(0.2 mmol), dioxane(0.7 mL), H_2O(90 μL), 90 °C for 24 h; Isolated yield was obtained; *b*. 3 equiv. of H_2O_2. Product is benzoic acid rather than compound **2**a; *c*. GC yield; *d*. recycled.

3.2 Wacker Oxidation of Olefin to Ketone

Typical Wacker oxidation was conducted by using a dioxane/H_2O solvent mixture with a catalytic amount of Cu SAC in air at 90 °C. However, no product could be obtained due to the worse activity of Cu SAC than Pd catalysts(Table 1, entry 1). The use of a more aggressive oxidant(hydrogen peroxide) leads to the formation of benzoic acid at a high yield(92%) *via* oxidative cleavage of alkene, rather than the desired acetophenone product(entry 2). With the knowledge of tuning the reaction pathway and product selectivity by the addition of additives[23,24], the acetophenone product **2**a can be obtained at a 56% isolated yield with 2 equivalents of *N*-methylhydroxylamine hydrochloride($CH_3NHOH \cdot HCl$) under an oxidative condition, such as O_2 or air(Table 1, entries 3—5). It is worth noting that both Cu SAC and additive are essential for such Wacker oxidation, where blank control or commercial 10% Cu/C failed to catalyze the reaction(entries 7 and 8). The use of homogeneous CuI or Cu(OAc)$_2$ can promote the reaction at a lower yield(*ca*. 30% in entries 9 and 10). Increasing the usage of Cu SAC from 4%(molar fraction) to 10%(molar fraction) significantly improves the isolated yield to 87%(entry 11). The

stability of the catalyst is proven by the recycling test without significant loss in catalytic activity(entry 12). Additional reaction screening on the nature of additive and solvent is provided in Table S1(see the Electronic Supplementary Material of this paper), where the presence of acid and *N*-hydroxyl group is the key factor for product formation. Importantly, we can extend the reaction scope of Cu SAC-catalysed Wacker oxidation to other similar reactions. As shown in Fig.3(C), Kucherov oxidation of terminal alkyne can happen under the identical condition of Wacker oxidation to produce the 4-methoxyacetophenone at a lower isolated yield of 41%. This paves the way for the use of SAC in the advanced oxidative process to produce valuable chemicals.

Isotope labelling experiments using ^{18}O and deuterated reagents were conducted to gain more reaction insights. In such a catalytic system, O_2, dioxane, H_2O and $CH_3NHOH \cdot HCl$ are the four possible oxygen sources for the carbonyl oxygen in the final product. The occurrence of reaction in the absence of O_2 excludes the possibility of O_2 as a carbonyl oxygen source(Table 1, entry 6). Dioxane is also excluded as the reaction occurs when using toluene or acetonitrile as the solvent, albeit much lower yields were observed(Table S1). As shown in Fig.3(A), the use of $H_2^{18}O$ will not introduce the ^{18}O isotope label in the product, proving the oxygen in ketone does not originate from water. It is conceivable to deduce *N*-methylhydroxylamine hydrochloride as the oxygen source in the final product. To assess the hydrogen transformation during the reaction, deuterium oxide was charged to the reaction system in Fig.3(A). Tri-deuterated product 3D-**2**a was found due to fast proton-deuterium exchange with solvent for α-proton in carbonyl compound[25].

A plausible mechanism is given in Fig.3(B) based on the
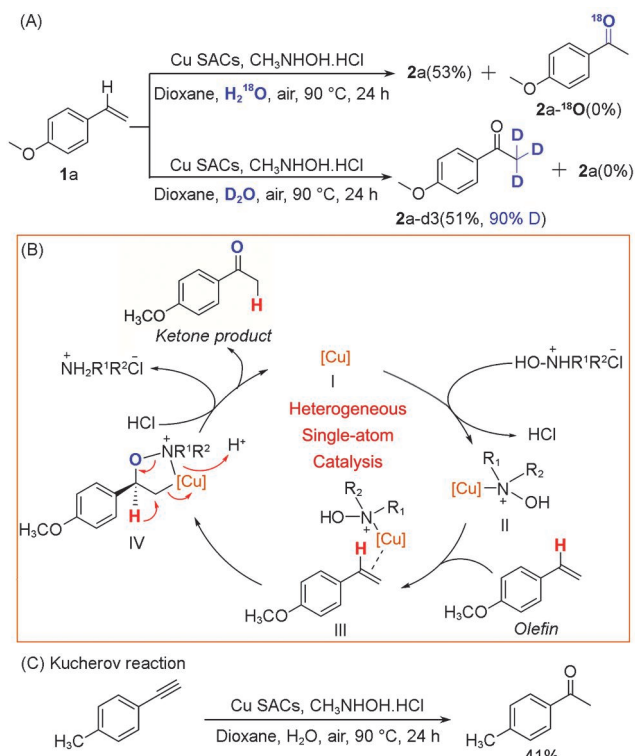
Fig.3 Mechanistic studies by ¹⁸O and deuterium isotope labelling(A), plausible reaction pathway involving the hydrogen shift and reductive elimination(B) and extended reaction scope for Kucherov reaction using terminal alkyne(C)

above observations. The first step of the reaction involves the binding of *N*-methylhydroxylamine hydrochloride on the Cu single atom to yield a Cu-N-OH complex II. Such species are coordinated with olefin *via* oxidative addition(III). Subsequent hydroxylaminometallation of olefin forms a pseudo-five-membered ring of the hydroxylaminometalic intermediate IV. This is followed by the cleavage of the N—O bond and a hydride shift to afford the α-methyl ketone product[5,26]. The dissociation of the ammonium salt from the Cu single atom under acidic conditions regenerates the catalytic site and then closes the catalytic cycle.

4 Conclusions

In summary, we have developed an ultrahigh loading Cu single atom catalyst, which is more cost-effective and environment-friendly than the typical palladium catalyst for Wacker oxidation of olefin to ketone. The existence of Cu single atoms was confirmed by atomic-resolution STEM and X-ray absorption. In the presence of *N*-methylhydroxylamine hydrochloride additive, such olefin oxidation can be performed in an almost identical yield using Cu SACs under mild conditions. Further mechanistic studies by isotope labelling illustrated the oxygen source and hydrogen

transformation during the reaction process. This work is strategically valuable as it can offer a new approach for the Wacker-type oxidation of aryl alkenes toward high-value-added chemicals.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-022-2130-x.

Conflicts of Interest

The authors declare no conflicts of interest.

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