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# Selective aerobic oxidation of halides and amines with an inorganic-ligand supported zinc catalyst\*

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A practical, efficient and environmentally benign catalytic protocol for the oxidative cross-coupling reaction of halides with amines, oxidative self-coupling of amines and oxidation of halides was developed with inorganic-ligand supported ZnPOM (NH<sub>4</sub>)<sub>4</sub>[ZnMo<sub>6</sub>O<sub>18</sub>(OH)<sub>6</sub>] using molecular oxygen. This method mainly utilizes an inorganic polymolybdate ligand to support the Zn<sup>2+</sup> ion, avoiding the use of complicated organic ligands.

Zinc metal is abundant in the Earth's crust and it has a certain biological relevance as an essential trace element in humans.<sup>1</sup> Recently, great progress in the use of cheaper and low toxicity zinc complexes to replace precious metal catalysts (e.g. Rh, Pd, Ir, Ru, etc.) has been made in modern chemistry. In 2008, Nicholas and co-workers reported that benzylic and allylic C-H bonds are successfully converted to related secondary amines in good yields.<sup>2</sup> In 2012, the Wu group reported a general and efficient zinc catalyzed oxidation of benzyl alcohol to aldehydes which are important intermediates for fragrances and many drugs.3 The examples impressively show the potential of zinc catalysts in oxidation chemistry. In general, the catalytic effect can only be produced by the interaction of the metal center with organic ligands which often suffer from severe problems including cost, toxicity, air/moisture sensitivity and being commercially unavailable (Fig. 1a).<sup>4</sup> Moreover, it is difficult to separate the catalyst from the reaction system. Therefore, developing an efficient, stable, and recyclable zinc catalytic system is of great significance.<sup>5</sup>

Catalytically active, stable complexes involving low-valence metal ions supported/coordinated by metal oxides are potential candidates. Many of these inorganic-ligand coordinated complexes contain well-dispersed metal ions bound with the inorganic scaffold via a variable number of metal-oxygen bonds, thus providing complexes which are more stable than organometallic catalysts. Inspired by this idea, polyoxometalates (POMs),<sup>6</sup> types of discrete metal-oxo clusters, are considered to be inorganic alternatives to synthesize classical transition-metal complexes. The catalytic function of POMs has attracted much attention because of their multiple active sites, including protons, oxygen atoms, and metals allows for "fine-tuning" of their redox activities and acidic properties at the atomic or molecular levels. Recently, our group reported firstly that the Anderson-type POMs can be used as the inorganic-ligand supported metal catalysts for highly efficient aerobic oxidation of aldehydes to carboxylic acids in water, or the oxidation of amines to imines under mild conditions.7 Herein, we report an efficient and environmentally friendly transformation from organic halides to aldehydes/ketones and imines to amines using an inorganic-ligand supported zinc catalyst,  $(NH_4)_4[ZnMo_6O_{18}(OH)_6]$  (1) (Fig. 1b) (for characterization see the ESI<sup>†</sup>). Catalysis is performed under mild conditions with molecular oxygen as the terminal oxidant, and it shows good





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stability and reusability. And the catalytic oxidation could readily be scaled up to the gram-scale with little loss of catalytic activity.

Imines, known as Schiff bases, are key synthetic intermediates in the synthesis of biologically and fragrances, agricultural chemicals and pharmaceuticals.<sup>8</sup> In recent years, the crosscoupling reaction of alcohols with amines has been one of the most popular synthesis approaches due to its use of green molecular oxygen as the terminal oxidant and water being the only by-product.<sup>9</sup> But alcohols are mainly obtained by the hydrolysis of halogenated hydrocarbons both in the laboratory and in industry.<sup>10</sup> From the point of view of atom economy, we present here an inorganic-ligand supported zinc-catalyst for the oxidative cross-coupling reaction of halides with amines and oxidation reactions of various halides with oxygen acting as the sole oxidant (Scheme 1).

Initially, we selected benzylamine and benzyl chloride as model substrates for the oxidative cross-coupling reaction and gained N-benzylidenebenzylamine 3a with 32% yield and 47% selectivity (Table S1,† entry 1). By screening the solvent, acetonitrile is the best solvent with 89% yield and 90% selectivity (Table S1,† entries 1-9). Moreover, both shortening and prolonging the reaction time have an impact on the yield (Table S1,† entries 10 and 11). 60 °C is the optimum reaction temperature (Table S2,† entries 1-3). When taking ZnSO<sub>4</sub>·7H<sub>2</sub>O, (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>·4H<sub>2</sub>O as the catalyst alone or in the absence of a catalyst, no desired product was detected (Table S2,† entries 4-6). 1.0 mol% is the optimal catalyst loading (Table S2,† entries 7 and 8). Switching from a pure oxygen atmosphere to air under the same atmospheric pressure also led to 18% yield (Table S2,† entry 9). When the reaction was carried out under a nitrogen atmosphere, a very low yield was obtained (<10%), implying a stoichiometric oxidation reaction (Table S2,† entry 10).

With the optimal conditions in hand, the general applicability for the oxidative coupling reaction of various amines and halides was examined, as shown in Table 1. Benzyl chloride, benzyl bromide and benzyl iodide were smoothly crosscoupled with benzylamine to yield *N*-benzylidenebenzylamine with a yield of 93%, 94% and 89%, respectively (compound



**Scheme 1** Oxidation of halides to aldehydes or ketones and amines to imines.

 $\label{eq:table_$ 



<sup>*a*</sup> Reaction conditions: 1.0 mol% cat. 1, 1.0 mmol amines, 1.0 mmol halides,  $O_2$  (1 atm, balloon), 2.0 mL MeCN, and 60 °C for 24 h. <sup>*b*</sup> Determined by GC and confirmed by GC-MS.

3a). When coupling with benzylamine, benzyl chloride with electron-donating substituents generally resulted in higher yields than substrates bearing electron-withdrawing substituents, probably due to the higher nucleophilicity of the former (compounds 3b-3f). The reaction of benzylamine with heterocyclic functionalized chloride such as 3-(chloromethyl)pyridine and 2-(chloromethyl)thiophene produced the corresponding imines in 88% and 89% yields, respectively (compounds 3g and 3h). In view of more challenging aliphatic chloride, (chloromethyl)cyclohexane and 1-chloropentane gave the corresponding imines in 86% and 80% yields, respectively (compounds 3i and 3j). Switching from benzylamine to other amines, the catalytic coupling of benzyl chloride with aniline under analogous reaction conditions yielded 90% of the corresponding imines (compound 3k). Benzyl chloride with aniline substrates containing both electron-donating and electron-withdrawing groups also has good tolerance (compounds 31 and 3m). Both cyclic and aliphatic amines reacted efficiently with benzyl chloride to produce the imine products in excellent yields (compounds 3n-3p). Notably, the most challenging coupling of aliphatic chlorides and aliphatic amines was also promoted by catalyst (1) to afford the corresponding imines, albeit in relatively lower but reasonable yields (compound 3q).

Inspired by this study, we next checked the applicability of this aerobic protocol in the synthesis of symmetrical imines under the optimal conditions (Table S3†). This reaction is very well tolerated. Benzylamines which have electron-donating or -withdrawing substituents were converted into their corresponding products with high yields by a zinc catalyst (Table 2, compounds 5a–5p). However, benzylamines with electrondonating groups (compounds 5h–5j) showed more efficiency than those with electron-withdrawing groups (compounds 5b–5g). In addition, the benzylamine having a methyl group at

 Table 3
 Investigation of substrate scope on the oxidation of benzyl

 halides<sup>a</sup>
 Investigation of substrate scope on the oxidation of benzyl



<sup>*a*</sup> Reaction conditions: 1.0 mol% cat. 1, 1.0 mmol amines, O<sub>2</sub> (1 atm, balloon), 2.0 mL MeCN, and 60 °C for 24 h. <sup>*b*</sup> Determined by GC and confirmed by GC-MS. Values in parentheses are the isolated yields.

an ortho position (compound 5j) showed a slight decrease in product yield in comparison to the para isomer (compound 5i) owing to steric hindrance. Heterocyclic amine compounds such as furan-2-ylmethanamine and thiophene-methylamine were also examined (compounds 5k and 5l) and gave modest yields. It was found that inert 1-butylamine can also be converted to related imine (compound 5m). Secondary dibenzylamine also yielded the corresponding imine with moderate yield (compound 5n). To our satisfaction, 1,2,3,4-tetrahydroquinoline was also successfully converted to the corresponding imine in 85% yield, which is an important pharmaceutical intermediate (compound 50). Moreover, dibenzylamine was converted to N-benzylidenebenzylamine with 90% yield (compound **5p**). These results suggest that the inorganic-ligand supported zinc catalyst is promising to promote the oxidative coupling reactions of various amines.

To demonstrate the general applicability of the inorganicligand supported zinc catalyst, various primary and secondary halides were investigated to produce aldehydes or ketones under the optimal reaction conditions (Table S4†). As depicted in Table 3, various primary and secondary halides react to give the desired products in good yields (compounds 7a-7y). No matter what electron-withdrawing or electron-donating substrates, all gave related aldehyde or ketone products. Aryl halides possessing electron-withdrawing substrates such as 4-F, 4-Cl, 4-Br, and 4-NO<sub>2</sub> provided excellent yields, respectively (compounds 7b-7h). But aryl halides with electron-rich groups like  $-CH_3$ ,  $-OCH_3$ ,  $-C(CH_3)_2$ , and -CN produced 95%, 95%, 92%, and 93% yields, respectively (compounds 7i-7k and 7m).



<sup>*a*</sup> Reaction conditions: 1.0 mol% cat. 1, 1.0 mmol halides,  $O_2$  balloon, 2.0 mL MeCN/H<sub>2</sub>O (1:1), and 60 °C for 12 h. <sup>*b*</sup> Determined by GC and confirmed by GC-MS. Values in parentheses are the isolated yields.

On the whole, the former has a lower impact than the latter on yield, probably because the latter increases the electron cloud density on the aromatic ring, which the latter have the presence of the electron donating group. Moreover, we discover that this reaction has a certain steric effect. Among the para-, meta- and ortho-substituents, the para-substituent shows a slightly better yield (compounds 7b, 7e, 7f, 7d and 7g). Despite this, 2-(chloromethyl)-1,3,5-trimethylbenzene afforded 2,4,6-trimethylbenzaldehyde in 90% yield (compound 71). 2-(Chloromethyl)naphthalene produced the corresponding products in good yields (compound 7n). What's more, as for inert cyclic or aliphatic halides, we also obtained the corresponding aldehyde products in moderate yields (compounds 70 and 7p). Notably, this may be accompanied by by-products of the corresponding acid. Moreover, we conducted secondary benzyl halide oxidation to ketones (compounds 7q-7y). Secondary benzyl chlorides with electron-withdrawing groups (-Cl, -F) or an electron-donating group (-CH<sub>3</sub>) provided good yields (compounds 7r-7t). The heterocyclic secondary benzyl chloride also generated related ketones in good yields (compounds 7u-7w). In addition, 2-(chloromethyl)naphthalene and chlorodiphenylmethane gave 90% and 85% yields of the corresponding desired ketones (compounds 7x and 7y).

On the basis of the above experiments and existing literature,<sup>11</sup> we propose a plausible mechanism, as shown in Fig. 2. In the first step Zn-POM activates oxygen molecules to form the peroxo intermediates  $\mathbf{B}$ .<sup>12</sup> The active component  $\mathbf{B}$  is then subjected to the reaction path producing compound  $\mathbf{C}$  with a high oxidation state that is from the heterolytic cleavage of the O–O bond. Subsequently the amine substrate reacts with  $\mathbf{C}$  to generate active intermediate  $\mathbf{D}$ , which can further form the



Fig. 2 Proposed mechanism for the formation of aldehydes, ketones and imines.

NH-imine intermediate. In other words, the amine substrate is activated under the action of the catalyst and then dehydrogenated to afford the NH-imine intermediate. The unstable intermediate was decomposed by the release of NH<sub>3</sub>, followed by coupling with another amine substrate, forming the final imine product and completing the catalytic cycle. Similar to the halide oxidation process and the oxidative coupling of halides with amine substrates, the alcohol substrate derived from the hydrolysis of halides can also coordinate with the active substance C to produce the active intermediate E, which in turn gives the aldehyde intermediate. If there is no other substance in the system, dehydes are formed. But in addition to halides, if there are amines in the reaction system, condensation can occur to produce an asymmetric imidized product. According to the above assumption of the mechanism, the key to the success of the catalytic reaction is the formation of intermediate C. Furthermore we detected the presence of aldehydes in the course of the experiment by GC-MS, and this also verified the reliability of the mechanism.

To identify the effectiveness and reusability of ZnPOM, 10 mmol scale 4-methylbenzyl chloride and benzylamine, 10 mmol scale self-coupling of (4-methoxyphenyl)methanamine and 10 mmol scale oxidation of 4-methylbenzyl chloride were performed under optimal reaction conditions. The reaction produced the desired products in 78%, 81% and 84% yields (Scheme S1†). What's more, the inorganic ligand supported zinc catalyst was still efficient even if the catalyst was recycled six times. The FT-IR, XRD and ICP-AES analysis proved that the recycled catalyst still has the original structure and stability (Fig. S5, S6 and Table S5†). This demonstrates that the ZnPOM is a potential catalyst to be applied at the industrial level.

In conclusion, a one-pot protocol to achieve the oxidative cross-coupling of halides and amines, self-coupling of primary and secondary amines, and oxidation of halides using inorganic ligand supported zinc catalyst- $(NH_4)_4$  [ZnMo<sub>6</sub>O<sub>18</sub>(OH)<sub>6</sub>], which was cheap, efficient and environmentally friendly was developed. Although the reaction used a single oxygen as the oxygen source, related imines and aldehydes or ketones can be efficiently prepared. The inorganic-ligand supported zinc catalyst is not only easy to prepare by the hydrothermal method

but also conveniently-recoverable because of heterogeneous reaction. In addition, compared with precious metals such as rhodium, ruthenium and palladium, the inorganic ligand catalysts avoid the use of toxic, air and water-sensitive organic ligands. Hence, we believe that inorganic ligand-modified heteropolyacids still have great potential as heterogeneous catalysts in organic synthesis. This work is currently underway in our laboratory.

#### Conflicts of interest

There are no conflicts to declare.

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