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Highly Practical and Efficient Preparation of Aldehydes and Ketones from Aerobic Oxidation of Alcohols with an Inorganic-ligand Supported Iodine Catalyst†

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Herein, we divulge an efficient protocol for aerobic oxidation of alcohols with an inorganic-ligand supported iodine catalyst, $(\text{NH}_4)_5[\text{IMo}_6\text{O}_{24}]$. The catalyst system is compatible with a wide range of groups and exhibits high selectivity, and shows excellent stability and reusability, thus serving as a potentially greener alternative to the classical transformations.

Over the past two decades, hypervalent organo-iodine compounds have attracted significant interest as selective, versatile and environmentally benign oxidants and have been applied to many organic transformations.¹ The most important representatives of this class of compounds, iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP), are employed extensively as mild and highly selective stoichiometric oxidation reagents for the oxidation of alcohols to aldehydes or ketones.² However, the use of stoichiometric hypervalent iodine compounds is problematic for large-scale application because of their high cost, potentially shock-sensitive explosiveness, the generation of large amounts of aryl iodides as inevitable waste products and/or poor solubility in common organic solvents.³ Catalytic oxidation can potentially alleviate these problems, and some progress in the oxidation of alcohols catalyzed by hypervalent iodine reagents has been achieved.⁴ One of the earliest examples is the iodine(V)-catalyzed oxidation of alcohols in the presence of oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) as an oxidizing agent was reported by vinod and co-workers in 2005.^{5a} The primary alcohols were oxidized cleanly to the corresponding carboxylic acids, while secondary alcohols were oxidized to ketones. Schulze and

Giannis^{5b} reported another high yielding IBX-catalyzed approach for the oxidation of alcohols using tetra-*n*-butylammonium oxone as an oxidant in an ethyl acetate/water solvent system. Benzylic primary and secondary alcohols were oxidized into benzaldehydes and ketones, whereas carboxylic acids are generated in the oxidation of aliphatic primary alcohols. Some progress in the oxidation of aliphatic alcohols was reported recently by Page et al.^{5c} albeit still using tetraphenylphosphonium monoperoxysulfate (TPPP) as the oxidant.

Despite the advantages of these reactions, the use of stoichiometric oxidants, such as oxone or TPPP to generate the iodine (III) or iodine (V) species in situ, and complicated IBX derivatives as the catalysts, has limited their use in traditional synthetic chemistry applications. Molecular oxygen is an ideal oxidant with a high atom economy and its use results in the production of water as the only byproduct. Indeed, significant progress has been made in the development of catalytic methods for aerobic alcohol oxidation.⁶ Nevertheless, the use of hypervalent

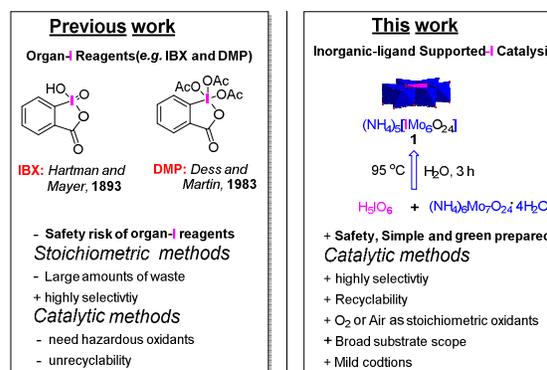
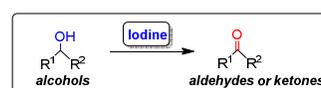


Fig. 1 Representative organic-iodine catalyst systems and inorganic-ligand supported iodine-catalyst for aerobic oxidation of alcohols.

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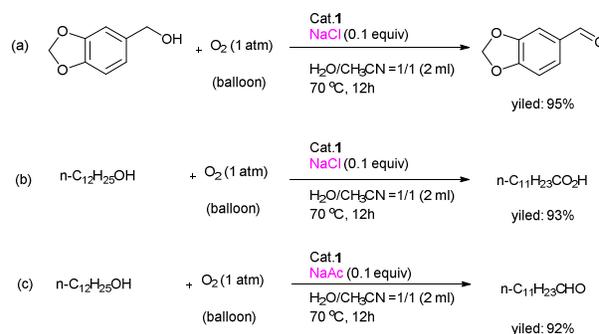
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iodine catalyst systems with molecular oxygen as a terminal oxidant remains challenging.⁷ Therefore, the development of a sustainable and environmentally friendly organo-iodine catalytic oxidation of alcohol compounds with molecular oxygen as the terminal oxidant is greatly desired.

Ligand-supported iodine catalysts, in which an inorganic ligand is used instead of the organic ligand, can potentially provide alternative methodologies to overcome the problems associated with hypervalent organic iodine catalyzed oxidations of alcohol systems. Polyoxometalates (POMs),^{8, 9} as a class of metal-oxide clusters with unmatched molecular structural diversity and versatile functions, possess high redox and acidic properties at the atomic or molecular levels as well as resistance toward hydrolysis and oxidative degradation. They can offer great potential as stable inorganic ligands for coordination with metal ions differing from classical transition-metal complexes.¹⁰ Very recently, our group reported the first Anderson-type polyoxometalate¹¹ (POM) as an inorganic-ligand supported metal catalyst for the highly efficient aerobic oxidation of aldehydes to carboxylic acids in water,^{12a} or oxidation of amines to imines under mild conditions.^{12b} These types of inorganic-ligand supported metal catalyst have a unique structure with a Mo^{VI}O₆ inorganic scaffold supported by a central metal atom, which greatly enhances the Lewis acidity of the catalytically active sites, as well as enables the edge-sharing MoO₆ unit to act as ligands analogous to those used in traditional organometallic complexes. These properties make them ideal candidates for solving the problems associated with the instability and activity of complex catalysts commonly encountered in organo-iodine catalyst systems, and thus provides a potential alternative for the aerobic oxidation of alcohols. Herein, we report the preparation of the inorganic-ligand supported iodine catalyst **1**, (NH₄)₅[IMo₆O₂₄]¹³ (Figure 1B), which possesses an iodine ion core supported with a Mo^{VI}O₆ inorganic scaffold. The catalyst can be readily synthesized in one simple step in aqueous solution at 95°C (Figures S1 to S5, ESI†). The catalyst **1** can efficiently catalyze the oxidation of various aromatic and aliphatic alcohols to aldehydes or ketones using O₂ as the sole oxidant. This catalyst exhibits high catalytic efficiency and possesses excellent stability during the catalytic cycle. Compared with organic-iodine catalyst systems, this inorganic-ligand supported iodine catalyst offers significant advantages in that it is robust to auto-oxidation, easily recovered and recycled, and avoids the use of complicated/sensitive organic ligands and toxic oxidants.

Various additives are often employed to improve the activity and selectivity of the oxidation of alcohols in homogeneous transition metal complex catalytic systems. Additives have been employed in our system to evaluate their influence on the iodine-POM catalyzed oxidation of alcohol, which proved to be successful in our previous research.¹² The additive, solvent, temperature and catalyst loading were evaluated with the oxidation of pepper alcohol or lauryl alcohol as a model substrate using the iodine-POM catalyst **1** and one atmospheric pressure O₂ as the sole oxidant (Table S1-S8, ESI†).

When piperitol was treated with 1 mol% (NH₄)₅[IMo₆O₂₄] and 10 mol% NaCl with an O₂ balloon in an acetonitrile/water solvent system (MeCN/H₂O=1/1) at 70 °C for 12 h, piperonal was formed in 95% yield (Scheme 1a). However, when lauryl alcohol was treated

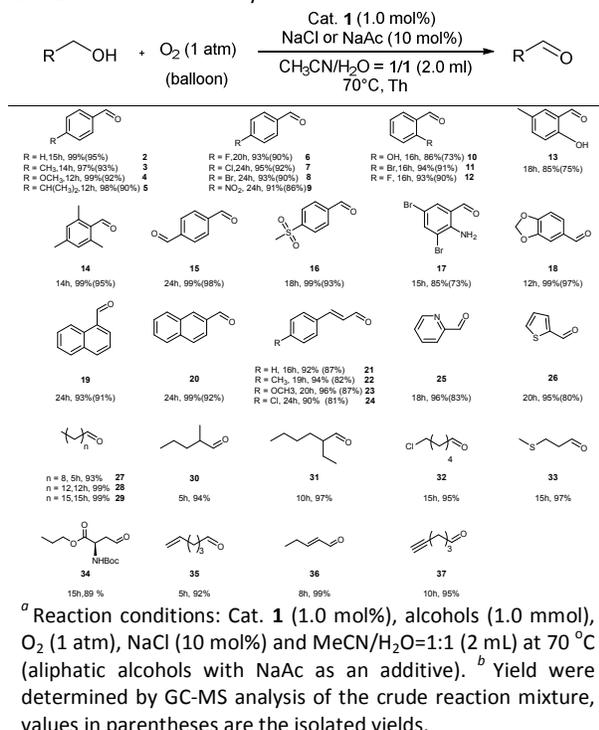


Scheme 1 Selective Oxidation of pepper alcohol and lauryl alcohol

with the same reaction conditions for 12 h, lauric acid was formed in 93% yield, and no lauraldehyde product was obtained, demonstrating that the aerobic oxidation of alkyl aliphatic alcohols does not stop at the aldehyde stage and is prone to further oxidation to the corresponding acid (Scheme 1b). After further optimization of the reaction conditions for the oxidation of alkyl aliphatic alcohols (Table S4, ESI†), this problem was circumvented by replacing NaCl with NaAc as the additive, affording lauraldehyde in a yield of 92% (Scheme 1c). These results indicate that the type of additive is able to control the selectivity of the alcohol oxidation reaction, with the redox properties of the catalytic system being changed by the additive. The cyclic voltammograms of catalyst **1**, catalyst **1**/NaCl (1:10) and catalyst **1**/NaAc (1:10) in the H₂O/CH₃CN (1:1) solvent system support this hypothesis (Fig. S14, ESI†).

Due to the structure of the POMs being pH dependent, the selectivity of the oxidation was also tested at different pH values. The desired product was obtained in good yield and with good selectivity when the reaction medium had a pH in the range of 4-9; moving out of this region significantly reduced both the conversion and selectivity (Fig. S15, ESI†) due to the decomposition of the catalyst **1** in strongly acidic or basic solution.

Under the optimized reaction conditions, excellent product yields are obtained for the oxidation of a wide range of primary alcohols bearing diverse functional groups, including ethers, heterocycles, amines, alkenes, and alkynes (Table 1). All substituted benzyl alcohols with electron-donating and -withdrawing groups were easily oxidized into the corresponding aldehydes or ketones with excellent yields (compounds **2-20**). Electron-donating substituents on the phenyl group accelerated the reaction, while reactions of alcohols with electron-withdrawing groups required longer reaction times. It is worth noting that primary benzylic alcohols can be quantitatively oxidized to the corresponding aldehydes. For unsaturated aromatic alcohols, cinnamyl alcohol, bearing a carbon-carbon double bond, also provided excellent yields of the desired products (compounds **21-24**). Heteroaromatic alcohols containing nitrogen or sulfur atoms, usually regarded as difficult substrates to oxidize, could also be transformed to the corresponding aldehydes in quantitative yields (compounds **25** and **26**). Some limitations of the method resemble those observed with the iodine-POM catalyst **1**. For example, reaction inhibition and/or poor yields are observed with phenols, primary homobenzylic alcohols, and substrates bearing amines. For aliphatic primary alcohols, the reaction tolerates many oxidatively sensitive functional groups, such as internal alkenes and alkynes as well as thioethers. Oxidation of Boc-

Table 1 Oxidation of Primary Alcohols ^{a,b}

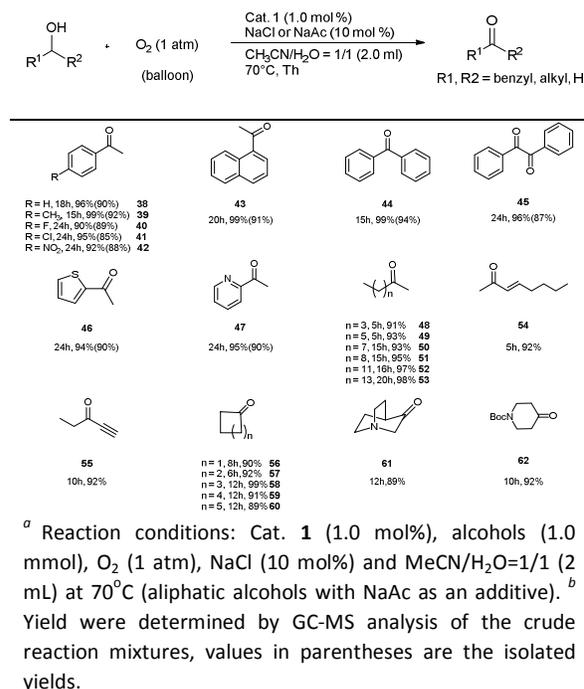
protected β -amino alcohols proceeds without epimerization of the stereocenter (compounds **34**).

Having obtained good results for the oxidation of primary alcohols, we next examined the ability of the (NH₄)₅[IMo₆O₂₄]/NaX catalytic system to catalyze the oxidation of certain secondary alcohols. The results revealed a similarly broad scope and catalytic efficiency for the oxidation of a diverse array of secondary alcohols, including allylic, benzylic, and aliphatic substrates (Table 2). The reactions display functional-group compatibility similar to that observed with primary alcohols, including tolerance of sulfur and nitrogen heterocycles. Alkene as well as alkyne substrates undergo oxidation in excellent yields (compounds **54** and **55**), a feature that likely reflects the regioselectivity of catalysts **1**. Linear and annular primary alcohols were smoothly oxidized to the desired ketones with high yields. Moreover, the oxidation of challenging hindered secondary alcohols furnished the expected products in excellent yields (compounds **61**).

To further demonstrate the practicality of the catalytic system, a 60 mmol reaction of benzyl alcohol was conducted using pure O₂ to give 5.724 g of benzaldehyde in 90% isolated yield with 99% selectivity within 16 h. These results suggest that in the case of a low catalytic amount of iodine-POM catalysts **1**, high activity and selectivity is retained allowing for the scalable aerobic oxidation of alcohols. Next, the ability of the catalyst **1** to be recycled and used in successive reactions was also evaluated. The solid catalyst was isolated by filtration (precipitation of catalyst after the addition of ether to the reaction system) and used directly for the subsequent oxidation of benzyl alcohol without further purification. The catalyst **1** could be used at least six times and the catalyst performance was not deactivated (Figure S11, ESI[†]). To confirm the high stability of the catalyst and its associated performance, the

structure and morphology of the catalyst were further investigated using FTIR spectroscopy. The structure and morphology of the recycled catalyst remains unchanged from its original state (Figures S12 and S13, ESI[†]).

In order to unveil the mechanism, some control experiments were conducted. When iodine catalyst **1** was used stoichiometrically under an inert atmosphere for the oxidation of benzyl alcohol, the corresponding benzaldehyde was obtained in 96% yield, indicating that catalyst **1** is an active oxidant. It should be noted that H₅IO₆ and (NH₄)₆Mo₇O₂₄ = (NH₄)₆[MoMo₆O₁₈(O)₆] (also considered to be an isomerized Anderson-structured POM with an Mo core instead of iodine as the central atom), when used as catalysts alone, gave only trace amounts of product even at a prolonged reaction time of up to 24 h. When a mixture of 1.0 mol% of H₅IO₆ and 1.0 mol% of the (NH₄)₆Mo₇O₂₄ was used as the catalyst, the corresponding product was obtained in a low yield of 32%. The superior aerobic oxidation efficiency of the combined catalyst platform indicates that every constituent plays a vital role in the inorganic-ligand supported iodine catalyst. The kinetic isotope effect was investigated to gain greater insight into the present alcohol oxidation system. The KIE value for this iodine POM-catalyzed oxidation of RCDHOH is 2.2, and the intramolecular competition experiment for the oxidation of RCH₂OH and RCD₂OH is 3.9. These data show that C-H cleavage is turnover limiting for the oxidation of PhCH₂OH (Fig. 2 and Fig. S16).

Table 2 Oxidation of Secondary Alcohols ^{a,b}

Based on these experimental results, a tentative mechanism for the oxidation of alcohols using our catalyst system has been proposed (Fig. 3). (NH₄)₅[I^{VII}Mo^{VI}₆O₂₄]-catalyzed aerobic oxidation reactions are similar to enzymatic oxidases in that the catalytic mechanism can be separated into two independent half-reactions:

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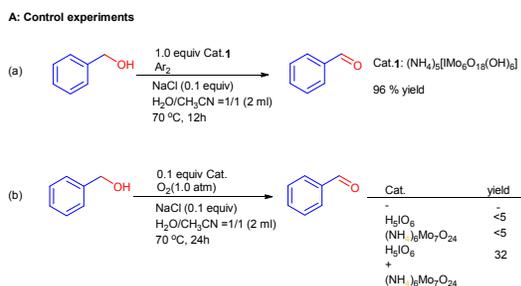


Fig. 2 Experimental studies providing insight into the mechanism of the iodine-catalyzed oxidation of alcohols.

Iodine-POMs-mediated oxidation of the alcohols and dioxygen-coupled oxidation of [I^VMo^{VI}₆O₂₄]⁷⁻. For the inorganic-ligand supported iodine catalysts, the two oxidizing equivalents required for oxidation are stored at the iodine center. The addition of additives can significantly influence the reaction; this is most likely due to the Cl⁻ or Ac⁻ acting as an electron-transfer mediator to improve the electron transfer efficiency of the iodine-POMs catalyst system. This mechanism has important implications for the development of new catalytic oxidation reactions.

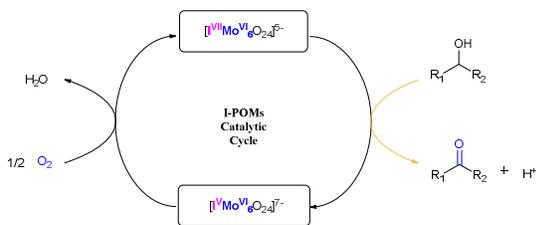


Fig. 3 Proposed mechanism for the iodine-POM-catalyzed oxidation of alcohols

In summary, we have developed a highly efficient and mild inorganic-ligand coordinated iodine-POM-catalyzed oxidation system for a variety of alcohols. The catalyst system exhibits a wide substrate tolerance with excellent selectivity and recoverability. This catalytic system takes safety into account and avoids using any organic ligand and toxic oxidants, which is beneficial for its use in pharmaceuticals, fragrances, and food additives. The generality of this methodology gives it the potential to be used on an industrial scale.

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