An efficient strategy for halogenation addition of olefins catalyzed by Polyoxometalate-based Iron Catalyst

Junting Zhou
Shanghai Institute of Technology

Mengjie Deng
Shanghai Institute of Technology

Ya Xie
Shanghai Normal University

Sheng Han
Shanghai Institute of Technology

Han Yu
hanyu2023@shnu.edu.cn

Shanghai Normal University

Research Article

Keywords: Olefin, N-bromosuccinimide, Polyoxomolybdate catalyst, Halogenated products

Posted Date: April 22nd, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4260116/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.
Abstract

The halogenation of alkenes is a crucial pathway in forming C-X bonds, with significant impact in organic synthesis and pharmaceuticals. However, traditional methodologies present potential hazards to both the environment and human health, making the quest for green and efficient halogenation methods paramount. In this study, we introduce a novel iron catalyst based on a polyoxomolybdate, \((\text{NH}_4)_3[\text{FeMo}_6\text{O}_{18}(\text{OH})_6]\), simplified as Fe(III)Mo6. Employing this catalyst, a plethora of styrene derivatives and alcohols were efficiently and successfully converted to the corresponding halogenated products. Also, our catalysts showed excellent performance towards the reaction with various substrates. Moreover, it demonstrates high stability and activity in cycle test. In addition, we also described the reaction mechanism based on the control experiment. The catalyst exhibits non-toxic, green, and environmentally friendly characteristics that provide future industrialization potential.

1. Introduction

Alkenes, owing to their unsaturated double bonds, are amongst the most versatile organic compounds, facilitating a myriad of chemical transformations\[1\]. The presence of their unsaturated double bonds enables the selective introduction of various functional groups, thereby expanding the applicability of olefins across diverse sectors\[2, 3\]. It is worth noting that bromides with C-X bonds produced by the halogenation of alkenes are crucial in the fields of organic chemistry, pharmaceuticals, and industry\[4–6\]. The targeted introduction of C-X bonds via olefin halogenation is a quintessential approach, enabling the diversification of functional groups\[7, 8\]. In essence, alkene halogenation is not only a fundamental reaction pathway but the resultant halogenated compounds are indispensable in contemporary chemical research and applications\[9\].

The halogenation of alkenes via electrophilic addition is a commonly practiced reaction. Although molecular halogens (X2, where X = Cl, Br, I) have traditionally been employed, concerns about their environmental and health impacts have driven the search for safer alternatives\[10, 11\]. Alternative halogen sources such as inorganic salts like sodium bromide or ferrous bromide, as well as N-halo-succinimides (NXS), which are a type of reagents used for halogenation reactions in organic synthesis, have been explored for these reactions\[12–14\]. The employment of metal halides in alkene reactions is another significant synthetic approach, particularly avoiding the use of molecular halogens, and offers an efficient alternative strategy for the synthesis of halogenated products. Nevertheless, this method often demands a stoichiometric amount of metal compounds. Dewkar et al. used metal halides to substitute traditional molecular halogens for halogenating alkenes, resulting in halogenated products. This substitution may limit the yield and selectivity of the reaction\[15\]. Previous research has identified several drawbacks, such as the complex synthesis of organometallic catalysts\[16, 17\], the high cost associated with noble metal catalysts\[18\], and the use of organic reagents that are not amenable to recovery\[19\] (Fig. 1 (a)). Electrochemical catalysis provides an intriguing alternative for such reactions, as electric current can serve as both an oxidant and a reductant. However, current electrochemical methods also face challenges, such as low yields after the use of large amounts of additives or replacement of...
nucleophilic reagents[20], Zhang et al. presented an electrochemical method for the alkoxyhalogenation of alkenes using organic halides as the halogen source. However, the yields of the resulting haloethers were unsatisfactory, and the reaction conditions, such as the type of electrolyte and the applied current, were not fully optimized. This lack of optimization may impact the scalability and applicability of the method in industrial settings[21]. Thus, the development of a high efficient, high region-selective, low-cost and recyclable catalyst for stereoselective halogenation with potential industrial applications, remains important and challenging [22].

Polyoxometalates (POMs) represent a class of metal oxides that encompass three or more transition metal atoms interconnected via bridging oxygen atoms [23–25]. In comparison to traditional inorganic acids such as H₂SO₄, HNO₃, and HCl, POM exhibits stronger bronsted acidity, which is mainly attributed to its larger size and high degree of charge delocalization[26]. Moreover, the unique structure of POM allows for precise design at the molecular and atomic level, giving it tunable acidity, superior redox potential, and enhanced stability. Due to these characteristics, POM has garnered widespread attention in the field of acid catalysis[27–29], the application of green catalysts contributes to reduced waste and energy consumption, thereby diminishing environmental impact[30, 31]. Our research group has documented catalytic reactions mediated by Anderson-type polyoxometalate catalysts. These catalysts have proficiently enabled the selective oxidation of olefins to aldehydes, ketones, and acids[32]; alcohols to carboxylic acids[33]; aldehydes to carboxylic acids[34]; and amines to imines[35].

In the present study, we have reported an Anderson-type polyoxometalate catalyst, Cat.1, with a simplified chemical formula of Fe(III) Mo₆ (Fig. 1(b)). This catalyst facilitates a direct engagement between alkenes and NBS/NCS (N-chlorosuccinimide) agents under mild conditions, culminating in the genesis of the corresponding halogenated ethers. Additionally, based on experimental research, we proposed a possible reaction mechanism. Meanwhile, we conducted recycling experiments and gram-scale reactions, and the catalyst demonstrated commendable stability in its activity, yielding satisfying results.

2. Experimental Section

2.1 Preparation and characterizations of catalyst

Synthesis of [NH₄]₃[FeMo₆O₁₈(OH)₆] • 7H₂O: [NH₄]₃[FeMo₆O₁₈(OH)₆] • 7H₂O was synthesized that depicted in earlier works[36, 37]. Firstly, [NH₄]₆Mo₇O₂₄ • 4H₂O weighed a certain amount (5.0 g) was dissolved in 80 mL water, then stirring at 100°C in oil-filled magnetic stirrer. Secondly, Fe₂(SO₄)₃ • 9H₂O (1.24 g) was dissolved in 20 mL water, then added into the above solution drop by drop. Finally, a slight yellow precipitation formed and was extracted and filtered by Buchner funnel, and the filtrate was placed at room temperature for 72 h for crystallization. Then, the crystallized crude samples were dried to produce white crystals at room temperature for a few days and precipitated the white crystals. It is worth mentioning that the hydrogen ion concentration (pH) of the mixed solution was conducting in 2.5, using nitric acid to adjust by pH indicator paper to monitor.
2.2 Reaction process

To a Schlenk tube were added styrene (104.2 mg, 1.0 mmol), Cat. 1 (12 mg, 0.01 mmol), NBS (177.9 mg, 1.0 eq) and CH$_3$OH (2 mL). The Schlenk tube was then stirred at 60°C until completion of the reaction as monitored by GC (12 h). The crude reaction mixture was extracted with ethyl acetate (5 mL). When finished the reaction, a small amount of ethyl acetate was added into the reaction mixture and the solution was quickly filtered. The filtered solid was washed with ether, dried and redispersed for recyclability tests. Finally, the solvent was removed in vacuum, and the corresponding product was purified by washing through silica gel column. (EA: PE = 1:30)

3. Results and discussion

3.1 Screening of Optimal Reaction Conditions

Initially, we synthesized the molecular catalyst (NH$_4$)$_3$[FeMo$_6$O$_{18}$(OH)$_6$][36,37], and its structure was confirmed through FT-IR (Figure S2), which demonstrated its characteristic spectral profile. We initiated our studies by probing various reaction conditions for the POM catalyzed alkene halogen addition in an environmentally-friendly way. At first, we attempted to screen the catalysts by replacing the central ion with various metals such as Co, Ni, and Cu (Table S1), and found that when Fe was used as the central ion, the yield of product 4 was the highest. Next, we screened the parameters of "Br" source, temperature, reaction time, and solvent (as shown in Table S2 and S3). After optimizing the other conditions, the yield of brominated ether could reach 49% (Table S2, entry 4) under the condition using 1.0 mol% Cat.1 and 0.1 eq. NBS at 60°C to react for 12 hours. Therefore, we attempted to clarify the importance of NBS as a bromine source compared with other brominating reagents such as NaBr, KBr, and TBAB. The results showed that 0.1 eq. of NBS as a brominating agent yielded the best results in reaction (Table S2, entries 1-3). This could be attributed to the fact that NBS is capable of continuously generating active bromine atoms at low concentrations, thereby reducing the risk of multiple halogenations and unwanted side reactions. On the other hand, when using KBr or NaBr, it is typically necessary to add other oxidizing agents (such as H$_2$O$_2$) to generate active bromine atoms, which may increase the chances of multiple halogenations or other side reactions. Furthermore, we noticed that as the amount of NBS gradually increased, the yield of product 4 also increased. Finally, we determined that using 1.0 eq. of NBS facilitated the smooth bromination addition of styrene, yielding product 4 with a 99% yield (Table S2, entries 5-10). Upon further screening of solvents (Table S3), we discovered that the optimal solvent is methanol. When we changed the solvent, we interestingly observed that if acetic acid is used as the solvent, although the desired ether is not produced, the reaction can generate esters as product.

In the following experiments, we found only a small amount of product was detected in the absence of the Fe catalyst (Table 1, Entry 2). Without methanol, no corresponding product was detected, indicating that methanol plays a dual role as both solvent and reactant in this reaction (Table 1, Entry 3). When using other types of Fe catalysts, such as iron sulfate Fe$_2$(SO$_4$)$_3$ to replace Cat.1 or simply using the raw materials of Cat.1 to catalyze the reaction, the isolated yield did not achieve the expected results (Table 1,
Entries 4-6). These results indicate that Fe and polyoxometalate ligands exhibit a synergistic catalytic effect.

3.2 Expanding Substrate Range

Under optimized conditions, we explored the types of olefins (Table 2) to determine the universality of the current catalyst, testing the yields of corresponding bromoethers from different olefin substrates through isolated yields. Both electron-donating and electron-withdrawing groups can obtain relatively high yields of products under the optimized reaction conditions. For substrates with electron-donating groups, such as -CH₃, -¹Bu, -OCH₃, the yields of corresponding products were 95%, 97%, and 99%, respectively (Table 2, compounds 5, 8, 9). Compounds containing electron-withdrawing groups, including -Br, -F, -Cl, can also yield corresponding halogenated ethers (Table 2, compounds 12-18). At the same time, we found that if the electron-withdrawing or electron-donating groups are located at the ortho, meta, or para positions of styrene, the reactants can still be reasonably converted into corresponding halogenated ethers through olefin difunctionalization. When -OCH₃ is at the para and ortho positions (Table 2, compounds 5, 6), it can be seen that the yield of the para position products is higher, similar to the situation for electron-withdrawing groups such as -Br, -Cl (Table 2, compounds 12-13, 15-17). From this, we can infer that as the steric hindrance decreases, the yield of the product will correspondingly increase. However, we were pleasantly surprised to find that when using the bulky -Ph as a substitute, the yield was still quite good (Table 2, compounds 11, 21), indicating that the steric hindrance effect on this reaction is not very significant. Although steric hindrance typically influences reaction yields, in this instance, the presence of the -Ph group seems to have no significant impact on the yield. This could be attributed to the unique electronic characteristics of the -Ph group, which potentially enhance the reactivity of alkenes via conjugative effects. Next, we tried to introduce groups at two different positions on the benzene ring at the same time, such as introducing -OCH₃ at the meta and para positions (Table 2, compound 23), or using 2,5-Dimethylstyrene (Table 2, compound 24) as a raw material for the reaction and the yields were satisfactory. Despite the introduction of two substituents on the phenyl ring, these groups may not impose significant steric hindrance, thus not adversely affecting the reaction outcome. The reaction conditions also apply to allylbenzenes or polycyclic olefins (Table 2, compounds 20, 22). In comparison to aromatic olefins, aliphatic and heterocyclic olefins have also been applied in this reaction with reasonable yields achieved (Table 2, compounds 25-27). Furthermore, when 2-Phenyl-1-propene and 4-Chloroisopropenylbenzene are used as raw materials, the yields are 91% and 89%, respectively (Table 2, compounds 18, 19). Similarly, by changing different types of halogenating reagents, such as replacing the NBS to NCS (N-chlorosuccinimide) and simultaneously attempting to replace different types of olefins, the excellent catalytic effect of Fe(III) Mo₆ can also be demonstrated (Table 2, compounds 28-33).

Subsequently, we assessed the versatility of alcohol substrates in their reaction with styrene and NBS (Table 3). For instance, methanol was separately replaced with ethanol, n-propanol, isopropanol, n-butanol, etc. It was readily observed that styrene and NBS could smoothly generate their corresponding products (Table 3, compounds 34-37). In order to further verify reaction efficiency of alkenes with
different nucleophiles, ethanol and n-propanol were separately employed as nucleophiles, with different alkenes being substituted. Interestingly, it was discovered that regardless of whether the substituents were in ortho or para positions, alkenes with an -OCH$_3$ group could successfully generate their corresponding products (Table 3, compounds 39, 40, 44). The presence of the -OCH$_3$ group, which is a known electron-donating substituent, may enhance the reactivity of the alkene due to conjugation, resulting in the expected outcomes. Whether with electron-donating groups or electron-withdrawing groups, satisfactory results were obtained after the replacement of aliphatic monohydric alcohols (Table 3, compounds 39-45). In addition to this, we also experimented with diols. The yields of ethylene glycol, propylene glycol, and butylene glycol were just barely satisfactory (Table 3, compounds 46-49).

3.3 Catalyst recycling experiments and gram-scale experiments

Moreover, the stability, effectiveness, and recyclability of the catalyst are also significant aspects that must be considered during industrial chemical reactions, leading us to conduct recovery experiments. It is worth noting that, despite multiple rounds of catalyst recycling experiments, structural studies of the catalyst conducted using FT-IR and XRD reveal that the recovered catalyst retains a form and properties similar to its initial state, with its catalytic activity remaining high (see SI). In organic synthesis and drug design, bromoethers play a pivotal role as intermediates. Their flexibility allows them to participate in various cross-coupling reactions and interactions with diverse nucleophilic reagents, thus enabling the introduction or formation of novel functional groups. This ability makes it a powerful tool in synthetic strategies, with potential industrial application value.

This leads us to carry out the gram-scale reaction under optimized conditions using 3.124g (30mmol) of styrene, we obtained bromoether with a corresponding yield of 93%. Therefore, this catalyst demonstrates excellent catalytic performance and versatility (Scheme 2).

3.4 Proposed Reaction Mechanism

To further investigate the reaction mechanism, control experiments were conducted on the halogenation of styrene. When no catalyst Cat.1 was used in the reaction, the yield was not satisfactory (Fig 3a (1)). However, when the iron catalyst reacted proportionally in an inert gas, such as nitrogen, it was found that the yield was not significantly different from that in air, indicating that oxygen does not participate in the reaction. And the yield was not affected by other components in the air (Fig 3a (2)). In the presence of a radical scavenger (TEMPO), the reaction still occurred, suggesting that the current halogenation reaction does not involve a radical pathway (Fig 3a (3)). Additionally, experiments conducted with AIBN as a free radical initiator did not yield the anticipated results, indicating that the catalytic efficiency of Fe(III) Mo$_6$ is superior for this reaction(Fig 3a (4)). By using different brominating reagents, it was found that NBS exhibited higher reaction yield, possibly due to its attack on the α-H bonded to the double bond, which other bromine-containing reagents could not do (Fig 3a (5-6)).

To investigate the coordination between styrene and the iron catalyst, we employed UV-visible spectroscopy for testing. (Fig 3b). Spectroscopic results indicate that Fe(III) Mo$_6$ exhibits a certain degree
of solvent stability towards styrene. As observed in the figure, the characteristic UV absorption peak of the mixture of the catalyst and styrene shifts towards shorter wavelengths. This shift could be attributed to the cage-like structure of the catalyst, which facilitates electron transfer, thereby rendering styrene more susceptible to protonation. The protonation process increases the polarization of \( \pi \) electrons in the molecule, leading to an elevation in the energy required for \( \pi-\pi^* \) transitions.

Based on the above-mentioned comparative test results and literature, the following reaction mechanism is proposed (Fig 3c). Under the reaction conditions, based on the structure of the POM catalyst, we speculate that a complex A is formed between Fe(III) Mo\(_6\) and styrene\(^{[39]}\), followed by the addition of NBS, which forms an intermediate B with the alkene\(^{[40]}\). NBS and olefins are activated by Cat.1 and form an intermediate B through coordination. At this point, \( \text{Br}^+ \) attacks the double bond. Subsequently, the alcohol nucleophile attacks the three-membered ring bromide ion intermediate C. This structure exhibits enhanced stability compared to conventional carbocations, attributed to the stabilizing interaction between the halogen and carbon atoms within the bond. In alcohol solutions, nucleophiles can open the bromide ion intermediate to produce product 4, completing the catalytic process\(^{[41]}\).

**4. Conclusions**

In summary, we have developed an Anderson-type polyoxometalate catalyst with inorganic ligands. The reaction conditions were optimized with the model reaction. Further, the substrates have been extended. Under certain conditions, the catalyst can convert olefin derivatives into the corresponding halogenated ethers with good functional group tolerance and high conversion efficiency. After replacing different halogenating agents and nucleophilic reagents, the catalytic efficiency of the catalyst remains satisfactory. Moreover, the catalyst structure was detected by FT-IR and X-ray diffractometer, and proved its high stability in activity. At the same time, when the reaction is scaled up to gram level, the yield is still satisfactory, indicating that Fe(III) Mo\(_6\) has potential application prospects. At last, the reaction mechanism has been proposed based on the optimization and control experiments. This provide an alternative method for future halogenation addition in industrial plants.

**Declarations**

**Author Contribution**

Conceptualization: Han Yu and Sheng Han; Catalyst preparation and characterization and carry out related experiments: Ya Xie, Junting Zhou and Mengjie Deng; Investigation: Ya Xie, Junting Zhou and Mengjie Deng; Writing: Junting Zhou ; Supervision: Han Yu and Sheng Han.

**Acknowledgement**
Conceptualization: Han Yu and Sheng Han; Catalyst preparation and characterization and carry out related experiments: Ya Xie, Junting Zhou and Mengjie Deng; Investigation: Ya Xie, Junting Zhou and Mengjie Deng; Writing: Junting Zhou; Supervision: Han Yu and Sheng Han.

Declaration of Interest Statement

There are no competing conflicts of interest to declare.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (No. 21961003 and 21871183), Shanghai Natural Science Foundation of China (No. 18ZR1437900).

References

38. K. Nomna, T. A. Shirai, and M. Miwa, (n.d.).

Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures
(a) Previous work:

Phukan, 2006  
Karada, 2007  
Yu, 2014  
Lin, 2018  
Matsuo, 2020

(b) This work:

Cat 1: (NH₄)₂[FeMo₄O₄(OH)₈]  
- Readily available, cheap, Fe catalyst
- Organic ligand free
- Efficient recyclable
- Broad substrate scope

Figure 1

The halogenation addition of alkenes

\[
\begin{align*}
\text{R}_1 & = \text{aryl, alkyl} \\
\text{R}_1 & = \text{aryl, alkyl} \\
\text{NXS} & = \text{halogenating agent} \\
\text{Cat. 1a} & = \text{catalyst} \\
\text{Solvent, T, t} & = \text{reaction condition} \\
X & = \text{Br, Cl} \\
R & = \text{alkyl, Et, n-Pr, i-Pr, Bu}
\end{align*}
\]

Figure 2

Gram-scale reaction.
Figure 3

Control experiments and a plausible mechanism

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• Sl.docx
• Table123.docx