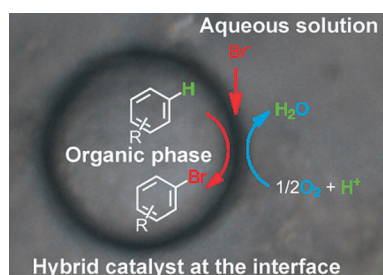


COMMUNICATIONS

Workin' in a bromine: A palladium–polyoxometalate amphiphilic hybrid material serves as catalyst for oxidative brominations. The emulsion-based process avoids the use of toxic and corrosive bromination agents such as Br₂ or HBr, and uses molecular oxygen as oxidant. The only side product is water, which is also the reaction medium. The catalyst offers good recoverability and recyclability.



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**A Sustainable Process for Catalytic
Oxidative Bromination with Molecular
Oxygen**



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A Sustainable Process for Catalytic Oxidative Bromination with Molecular Oxygen

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The twelve principles of green chemistry are valuable benchmarks when developing chemical products and processes that are more ecofriendly and sustainable.^[1] The sustainability of a chemical process, as promoted by the European Technology Platform on Sustainable Chemistry (ETP SusChem),^[2] is relevant to process intensification. A core technology of process intensification is the development of new catalysts. Such developments can allow improvements in yields/productivity, abate process costs through longer catalyst life, enable milder reaction conditions, and reduce costs associated with separation and environmental requirements.^[3]

The importance of halogenated organic compounds in chemistry is evident from the fact that they are essential starting compounds and intermediates in organic synthesis, and are also widely applied as building-block molecules in materials science, industrial chemistry, and medicinal compounds.^[4] Most often, brominated compounds are used because they have a relatively high activity and acceptable costs. However, the synthesis of brominated molecules generally requires hazardous, toxic, and corrosive bromine in chlorinated solvents. Other synthesis processes involve modifying bromination reagents (*N*-bromosuccinimide; NBS), bromine-carrying agents (mainly derivatives of pyridinium perbromides), and oxidative bromination. If hydrogen peroxide or oxygen is selected as oxidant, one bromine atom can be incorporated into the molecule while bromine can be regenerated from the residual HBr by oxidation, and water is the only byproduct.^[5] An excellent Review by Iskra et al. describes “green” oxidative halogenation.^[6] Approximately 4500 naturally occurring organohalogen compounds have been reported, the biological production of which involves halogenating enzymes.^[7] Processes based on haloperoxidases^[8] and halogenases^[9] are potentially the most effective and ecofriendly routes. In halogenations by enzymes, hydrogen peroxide and molecular oxygen serve as oxidants. Such biological halogenation processes offer a refreshing perspective on developing sustainable, biomimetic oxidative halo-

genation catalysts, based on metal centers such as iron, vanadium, and molybdenum.

Herein, we report the development of a sustainable oxidative halogenation process based on a well-designed palladium catalyst. The catalytic reaction proceeds in microemulsions suspended in an aqueous solution, offering high activity and selectivity under mild reaction conditions. The catalysts are dispersed over the interface between the lipophilic droplets and the aqueous solution. Molecular oxygen is used as oxidant. The products in the lipophilic phase are easily separated by destroying the microemulsion, causing the reaction mixture to form three phases: an organic phase, containing products; the used catalyst; and an aqueous phase. The catalyst can be recovered and recycled into the next batch without much effort.

The hybrid multifunctional catalyst was prepared according to the procedure illustrated in Figure 1. A rigid tripodal anion receptor, based on a 1,3,5-trisubstituted benzene spacer (**1**; 1,3,5-tris[(3-methylimidazolio) methyl]-2,4,6-trimethylbenzene tribromide^[10]) was used as the organic structure-directing agent. **1** was precipitated from the aqueous solution by introducing $[\text{PdCl}_4]^{2-}$. After reduction, palladium nanoparticles stabilized by **1** were dispersed in water, resulting in a black suspension. Polyoxometalate anion $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ was then added and the hybrid organic–inorganic nanocomposites gradually precipitated. The solids were collected by centrifugation. The transmission electron microscopy (TEM) image in Figure 1 reveals the morphology of the as-synthesized nanocomposites. The porous nanostructures result from self-assembly between the rigid tripodal ligands and polyoxometalate anions, directed by electrostatic interactions. The palladium nanoparticles are embedded in the nanostructure, and kept in the monodispersed state. The chemical composition of the nanocomposite was characterized by X-ray photoelectron spectroscopy (XPS; Figure S1), allowing to detect the chemical elements comprising the tripodal ligand, polyoxometalate anion ($[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$), and palladium nanoparticles, and identify their chemical states. The binding energy of the palladium species was 334.9 eV ($\text{Pd } 3d_{5/2}$), which was indexed to zero-valent palladium nanoparticles (Figure S1 c). The palladium nanoparticles were further characterized by high-resolution TEM (Figure 2a). The particle size was about 10 nm. Porous substructures surround the nanoparticles.

Oxidative bromination experiments were then performed by mixing organic substrate and catalyst in an aqueous buffer solution ($\text{MeCOONa}/\text{MeCOOH}$) containing NaBr. Dibutyl ether was used as organic solvent for the microemulsion system. Molecular oxygen was provided by using a balloon. The reaction mixture was stirred gently to form the microemulsion.

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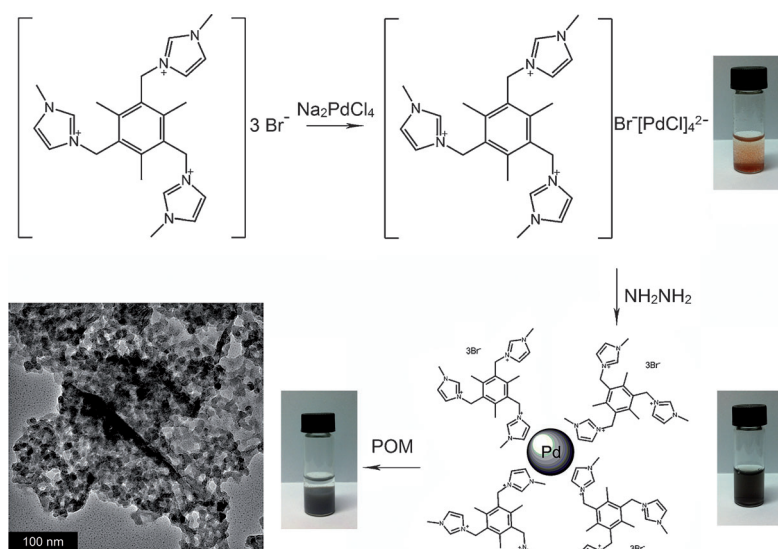


Figure 1. Preparation and TEM image of the hybrid multifunctional catalyst.

Seven typical benzene derivatives were tested over the catalyst (Table 1). The process exhibited high activity, and high selectivity in converting the substrates to *para*-brominated products. For active substrates with strong electron-donor groups, the yields to *para*-brominated product reached more than 99%. For the inactive substrates toluene and ethyl benzene, the yield of 4-bromo-toluene was 78% and the yield of 4-bromo-ethyl-benzene was 83%. Composites of $\text{H}_3\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ with dimethyl ethers of ethylene glycol oligomers were used as the catalyst for the bromination of organic compounds with gaseous

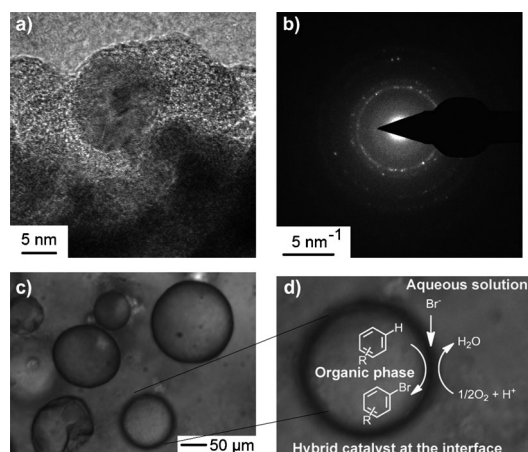


Figure 2. a) High-resolution TEM image of the embedded palladium nanoparticles. b) Corresponding electron diffraction pattern. c) Optical microscopy image of the microemulsion system. d) Schematic illustration of the multiphase reaction model for oxidative bromination.

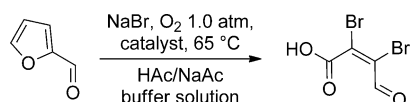
Microdroplets containing organic substrates were suspended in the aqueous solution and the hybrid catalyst was dispersed over the interface of the two phases (Figure 2c). The catalytic reaction proceeded over the interface through a multiphase reaction model (Figure 2d). The organic substrate and product were contained within the microdroplets. The aqueous solution served as bromine source while the oxidant was from the gas phase. The organic-inorganic hybrid catalyst was amphiphilic. After reaction, a small amount of diethyl ether was added, causing the reaction mixture to separate into an organic, aqueous, and catalyst phase as mentioned above. The three-phase mixture was easily separated by using a separatory funnel. The catalyst was recovered by washing with water and directly recycled to the next batch.

Table 1. Oxidative bromination of benzene derivatives. ^[a]			
Entry	R	Yield [%]	
		<i>para</i>	<i>ortho</i>
1	–OMe	> 99	–
2	–Me	78	11
3	–Et	83	9
4	–NHCOMe	> 99	–
5	–N(Me) ₂	> 99	–
6	–OH	> 99	–
7	–NH ₂	> 99	–

[a] Reaction conditions: 10 mL HAc/NaAc buffer solution, 0.1 mL dibutyl ether, 1.0 mmol substrate, 10 mg catalyst (approximately 1.0 mol% of the substrate), oxygen balloon, 5.0 mmol NaBr, reaction temperature: 45 °C, reaction time: 5.0 h.

hydrogen bromide and molecular oxygen.^[5f] However, the catalyst showed no activity towards toluene. In this work, the activity and sustainability of the oxidative bromination are greatly improved. Toxic and corrosive bromination agents (Br_2 and HBr) are avoided by using NaBr in aqueous solution. Molecular oxygen is used as oxidant and the only side product is water. The reaction medium is water and the catalyst is an amphiphilic nanocomposite with good recoverability and recyclability. The process exhibits high activity and selectivity to monobrominated products, which can be easily separated from the reaction mixture.

Mucobromic acid (CAS: 488-11-9) is an important intermediate in the synthesis of heterocycles. Its preparation involves the bromination of furoic acid or furfural with a large amount of bromine.^[11] The hybrid catalyst described herein enables a sustainable synthesis of mucobromic acid directly from furfural, as shown in Scheme 1. The reaction was performed at



Scheme 1. Oxidative bromination of furfural to mucobromic acid.

65 °C during approximately 8.0 h. The yield of mucobromic acid was 87%, higher than that of direct bromination (5.0 equiv Br₂, 75–83%).^[11]

The catalyst comprises palladium nanoparticles and polyoxometalate anion [PV₂Mo₁₀O₄₀]⁵⁻, which are sensitive to changes in the chemical and physical parameters of the reaction mixture. Sharp fluctuations of the pH value may lead to decomposition of the polyoxometalate. The involvement of bromine in the catalytic cycle may cause leaching of palladium species. These factors may impact the stability of the catalyst. The stability and recyclability were investigated by a five-run recycling test (Table 2). After the fifth recycling test, the catalyst lost approximately 3.3% of its activity. From a practical perspective,

Table 2. Recycling of the catalyst.		
Run	para	ortho
1	99.5	–
2	98.7	–
3	97.6	–
4	96.5	–
5	96.2	–

such a slight decrease of catalytic activity is unavoidable. Firstly, manual laboratory operations can not guarantee 100% recycling of the catalyst. Inevitably, catalyst will be lost during operations such as transfer between containers, cleaning, separation, and purification. Secondly, the performance of catalysts is time- and process-dependent. Interactions between the adsorbate and catalyst during catalytic reactions may lead to reconstruction and, in turn, variations in local compositions, which have a subtle impact on the performance of heterogeneous catalysts. The concentrations of leached palladium and molybdenum species in the final aqueous solution were detected by inductively coupled plasma-atomic emission spectroscopy (ICP-OES), and the measured amounts for each test run proved negligible (Tables S1). The morphology of the used catalysts was characterized by TEM (Figure S2), and the nanostructures appeared constant.

The catalytic roles of the palladium nanoparticles, polyoxometalates, and tripodal ligand (**1**) were further investigated by control experiments over eight model catalysts: blank, tripodal ligand (**1**), poly(vinylpyrrolidone)-stabilized palladium nanoparticles (Pd/PVP), tripodal ligand (**1**)-stabilized palladium nanoparticles (Pd/**1**), polyoxometalate (POM), polyoxometalate/tri-

podal ligand composite (POM/**1**), POM/**1** + Pd/PVP, and the as-synthesized catalyst (Pd/**1**/POM) (Table S2). The samples without polyoxometalate [PV₂Mo₁₀O₄₀]⁵⁻ did not show catalytic activity. Polyoxometalate anions [PV₂Mo₁₀O₄₀]⁵⁻ are the main catalyst, but their catalytic activity is relatively low. The tripodal ligand (**1**) functions as the structure-directing agent and counter-ion to heterogenize the polyoxometalate anions. Also, **1** is a rigid tripodal anion receptor, which can trap bromide anions from aqueous solution and facilitate the following generation of the halogenation agent. The catalytic performance of the polyoxometalate/tripodal ligand composite (POM/**1**) was greatly improved. Palladium nanoparticles activate molecular oxygen and promote the oxidative bromination cycle. The catalytic conversion reached approximately 100%. However, only palladium nanoparticles embedded in the polyoxometalate/tripodal ligand composite matrix exhibit this synergetic catalytic effect.

The catalytic reaction proceeded in an aqueous emulsion, with amphiphilic organic particles acting as microreactors for the reaction. The organic-inorganic hybrid catalyst is dispersed over the interface of the microemulsion. The organic substrates and products are contained within the microdrops. Bromine sources are from aqueous solution and the oxidant is from the gas phase. The catalytic oxidative bromination proceeds over the interface through a multiphase reaction model. The combination of these promoting effects and advanced properties has successfully realized a sustainable process for oxidative bromination with molecular oxygen.

In summary, a sustainable process is developed for oxidative bromination with molecular oxygen. A multifunctional catalyst is prepared by electrostatic-interaction-directed self-assembly of a rigid tripodal ligand and a polyoxometalate anion [PV₂Mo₁₀O₄₀]⁵⁻. Palladium nanoparticles are embedded in the nanostructure and kept in a monodisperse state. Molecular oxygen is used as oxidant and the only side product is water, which is also the reaction medium. The catalytic process has a high activity and the selectivity to monobrominated products is more than 99% for some active substrates. The catalyst exhibits good recoverability and recyclability during a five-run recycling test.

Experimental Section

To a 25 mL Schlenk tube were added HAc/NaAc buffer solution (10 mL), dibutyl ether (0.1 mL), substrate (1.0 mmol), catalyst (10 mg; approximately 1.0 mol% relative to the substrate), and NaBr (5.0 mmol). The tube was flushed with oxygen and connected to an oxygen balloon. The reaction mixture was heated to 45 °C in a water bath and stirred by a magnetic stirrer. After the required reaction time, diethyl ether (1.0 mL) was added and the organic layer was separated by a separatory funnel. The five-run recycling test was performed with the same procedure and the catalyst was recovered by washing with water, after which it was directly recycled to the next batch. Reaction products were analyzed by GC and GC-MS. GC was performed on a GC-2014 (SHIMADZU) equipped with a high-temperature capillary column (MXT-1, 30 m, 0.25 mm ID) and a FID detector. GC-MS was performed on a GCT

Premier/Waters instrument equipped with a capillary column (DB-5MS/J&W Scientific, 30 m, 0.25 mm ID).

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Keywords: bromine · oxidation · palladium · phase-transfer catalysis · polyoxometalates

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