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Mesoporous Poly(melamine–formaldehyde): A Green and Recyclable Heterogeneous Organocatalyst for the Synthesis of Benzoxazoles and Benzothiazoles Using Dioxygen as Oxidant

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A simple, highly efficient, and sustainable strategy for the synthesis of benzoxazole and benzothiazole derivatives was developed by using inexpensive, green, readily available, and recyclable mesoporous poly(melamine–formaldehyde) as a green, heterogeneous organocatalyst. The corresponding substituted benzoxazoles and benzothiazoles were obtained in good to excellent yields by aerobic oxidation of *o*-substituted aminobenzenes with various aldehydes under dioxygen atmosphere. The catalyst can be completely recovered through simple filtration to be reused more than six times without significant loss of catalytic activity.

Introduction

N-Heterocycles widely occur in natural products and biologically active molecules. Especially, they are often considered as the privileged targets by pharmaceutical industries and medicinal chemists. As a consequence, the ongoing interest for developing versatile and more efficient approaches for the synthesis of heterocycles has always been a thread in the synthetic community. As the important N-heterocycles, benzoxazole and benzothiazole derivatives are found in a variety of natural products and pharmacological agents. For example, UK1 is a structurally unique bisbenzoxazole (natural product),[1] NSC693638 is used as an anticancer agent,[2] IDD552 is a well-known aldol reductase inhibitor,[3] and RWJ-51084 is a potent cationic trypsin precursor[4] (Figure 1). In the past few decades, many significant methods to construct the two important motifs have been subsequently developed. Traditionally, the synthesis of benzoxazoles involves two approaches. One is the metal-catalyzed intramolecular O-arylation of *o*-haloanilides.[5] Another method mainly involves the condensation of 2-aminophenol derivatives with carboxylic acids or carboxylic halides under strong-acid/high-temperature conditions.[6] These methods are successful, however, the uneasily available precursors and undesired byproducts can limit their wide applications, which thus stimulates chemists to search for more effective processes.

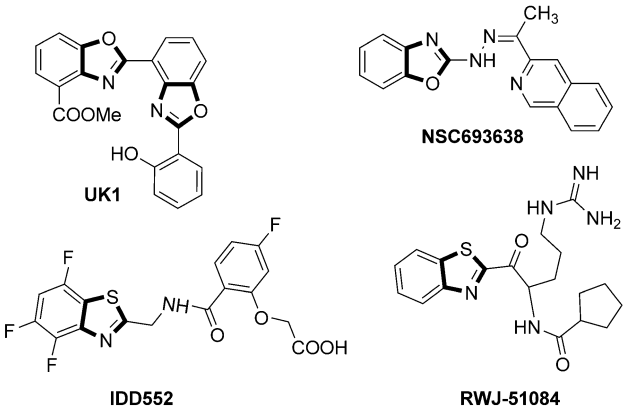

Figure 1. Benzoxazole and benzothiazole derivatives of related natural products and drugs.

Aldehydes are important and common building blocks, and they are easily prepared from readily available materials. Recently, condensation of *o*-aminophenol with aldehydes under oxidative conditions has caught considerable attention. In this regard, the special reaction conditions, such as using undesirable stoichiometric oxidants, toxic metal catalysts, the use of strong acid, and the residual of the trace amounts of metal catalyst in the end products, may limit their wide applications.[7] Therefore, it would be highly desirable to develop a more effective and environmentally friendly process.

In view of the principles of green chemistry, the proposal of the reaction conditions, media and catalysts, is still challenging.[8] Optimization of existing chemical transformations to-

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gether with the development of practical, environmentally friendly processes depend greatly on improvement of catalyst performance.[9,10] In particular, the recovery of catalysts after the catalytic reaction and reusing them to minimize waste production represent the central idea of the green chemistry movement. Recently, heterogeneous organocatalysts have drawn great interest in organocatalysis owing to their potential advantages over homogeneous catalysts, such as efficient activity, ease in recovery, and potential reusability.[11] Among them, porous organic polymers (POPs), a new class of porous materials with a cross-linked amorphous organic framework, have emerged as a sustainable catalyst support owing to their advantages in synthetic diversity, pore size controllability, high specific surface area, easy pore-surface modifiability and facile separation by filtration.[12]

Very recently, poly(melamine–formaldehyde) (mPMF) material has been successfully synthesized by Zhang and co-workers, and there is great progress in its application in CO_2 capture,[13] toxic metal removal,[14] and organic catalytic synthesis.[15] Importantly, the aminal (–NH–CH_2–NH–) and triazine groups existing in the mPMF organic frameworks can have dual roles in Brønsted acidity and Lewis basicity. Therefore, mPMF can act as a bifunctional organocatalyst, which can activate the carbonyl functional groups by means of double hydrogen bonding (Figure 2). For green and sustainable chemistry, there is an

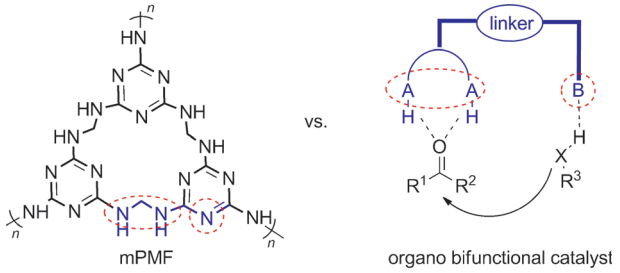
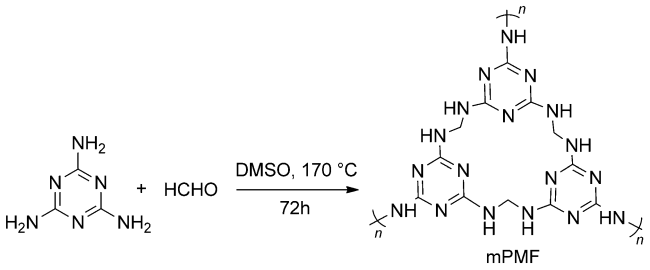


Figure 2. Chemical structure and bifunctional motif of mPMF.

increasing demand for the use of dioxygen as an oxidant owing to its natural, inexpensive, and environmentally friendly characteristics. Herein, we describe the use of green, efficient, recyclable mPMF as a heterogeneous organocatalyst for the synthesis of substituted benzoxazoles and benzothiazoles using dioxygen as oxidant.

Results and Discussion

Poly(melamine–formaldehyde) (mPMF) was prepared according to the literature procedure and the chemical process to mPMF is described in the Experimental Section and Scheme 1.[13–15] As can be seen from the TEM images (Figure 3a), mPMF has a foam-like interconnected mesoporous network structure. It consists of numerous spherical aggregates of submicron-sized particles, as evidenced by SEM (Figure 3b). The unique mesoporous particle structure with high surface-to-volume ratio of



Scheme 1. Synthesis of mPMF.

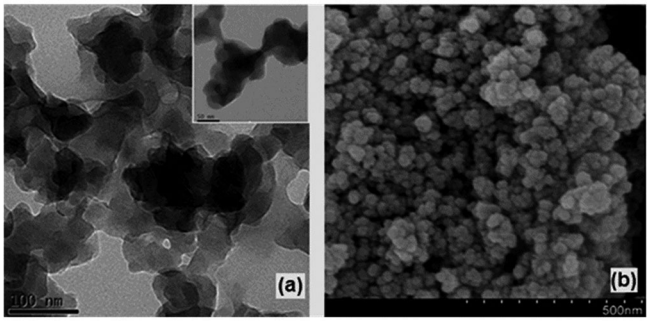


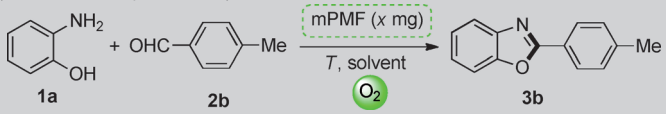
Figure 3. Characterization of mPMF by a) TEM and b) SEM. Scale bars = a) 100 nm (inset: 50 nm) and b) 500 nm.

mPMF could be expected to achieve high catalysis efficiency in the synthetic reactions of benzoxazole derivatives.

Initially, 2-aminophenol (**1a**) and 4-methylbenzaldehyde (**2b**) were chosen as the model substrates to optimize the reaction conditions including the amounts of catalyst, solvents, and reaction temperatures under dioxygen atmosphere (Table 1). First, six solvents were tested in the presence of mPMF (10 mg), and xylenes gave the highest yield (95%), Interestingly, the absence of solvent could also afford **3b** in 80% yield (Table 1, entries 1–7). If the amount of the catalyst was changed to 2.0 mg from 10.0 mg, the reaction yield decreased, only 31% yield was provided (entries 6, 9, 10). Control experiments confirmed that only a trace amount of target product was observed in the absence of the catalyst (entry 8). We attempted different temperatures (compare entries 6, 11–14), and 110 °C was optimal. The reaction under air also gave a good yield (79%, entry 15). Therefore, the standard reaction condition for the mPMF-catalyzed synthesis of benzoxazole derivatives is as follows: A catalyst quantity of 10 mg of mPMF particles and xylenes as the solvent under oxygen atmosphere.

We then investigated the scope of mPMF-catalyzed reactions of substituted 2-aminophenols (**1**) with benzaldehydes (**2**) under the optimized catalytic conditions determined above. As shown in Table 2, most of the examined substrates provided good to excellent yields of products. For the substituted benzaldehydes, substrates with electron-withdrawing groups, such as 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, and 4-bromobenzaldehyde (Table 2, **3c–f**), gave better yields than the benzaldehyde substrate with the electron-donating substituent (**3b**). For the substituted 2-aminophenols, electron-withdraw-

Table 1. mPMF-catalyzed condensation of 2-aminophenol (**1a**) with 4-methylbenzaldehyde (**2b**) leading to 2-*p*-tolylbenzo[*d*]oxazole (**3b**): optimization of conditions.[a]



1a 2b 3b

Entry	Solvent	Temp. [°C]	Yield [%][b]
1	H_2O	100	0
2	EtOH	80	0
3	CH_3CN	80	0
4	THF	80	0
5	toluene	110	90
6	xylenes[c]	110	95
7	–	110	80
8	xylenes	110	10[d]
9	xylenes	110	31[e]
10	xylenes	110	64[f]
11	xylenes	25	0
12	xylenes	60	40
13	xylenes	90	65
14	xylenes	100	74
15	xylenes	110	79[g]
16	xylenes	110	38[h]

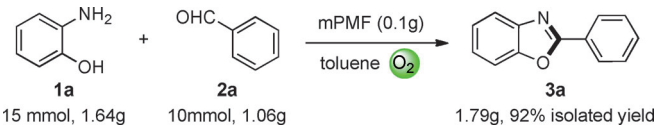
[a] Reaction conditions: 2-aminophenol (**1a**, 0.75 mmol), benzaldehyde (**2b**, 0.5 mmol), catalyst (10.0 mg), solvent (0.5 mL) reaction time, 10 h; under oxygen atmosphere. [b] Isolated yield. [c] Mixture of *o*-, *m*-, and *p*-xylene. [d] Without catalyst. [e, f] In the presence of catalyst (2.0 mg; 5.0 mg; respectively). [g] Under air conditions. [h] Using melamine as the catalyst.

ing as well as electron-donating substituents did not significantly affect the catalytic activity. The steric hindrance in the benzaldehydes significantly affected the catalytic efficiency (**3b′**). Although aromatic aldehydes displayed high reactivity, aliphatic ones were poor substrates. If aliphatic aldehydes such as butyraldehyde, heptanal, and cyclohexanecarbaldehyde were used as the substrates under the optimal reaction conditions, no desired product was obtained. The reason might be the weak hydrogen bonding between aliphatic aldehyde and mPMF (see the reaction mechanism in Scheme 3). Under similar conditions, the methodology was extended to the synthesis of various benzothiazoles from *o*-aminothiophenol. The results are also summarized in Table 2. Unfortunately, treatment of benzene-1,2-diamine (**1g**) with benzaldehyde (**2a**) under the optimized conditions produced 2-phenyl-1H-benzo[*d*]imidazole (**3c′**) in a very low yield. To explore the reason for this transformation, control experiments were performed. Upon treatment of benzene-1,2-diamine only under the standard conditions, the reaction detected by TLC was messy and no benzene-1,2-diamine was recovered, and the results showed that benzene-1,2-diamine could be oxidized into other substrates in this transformation. The mPMF-catalyzed domino reactions could tolerate some functional groups such as alkyl group, C–F bonds, C–Cl bonds, C–Br bonds, which could be used for further modifications at the substituted positions.

We also studied the recyclability of the catalyst. For this, we investigated the mPMF-catalyzed cyclization of 2-aminophenol (**1a**) with benzaldehyde (**2a**) under the optimized conditions. After completion of the reaction, the reaction mixture was cooled to room temperature, and the catalyst was filtered from the reaction mixture, washed with ethanol, and dried at 170 °C for 2 h and then used directly for further catalytic reactions. No significant loss of catalytic performance was observed as illustrated in Figure 4.

Further, we explored the synthetic applicability of the method. As shown in Scheme 2, the gram-scale reaction was performed in the usual laboratory setup with a one-neck round-bottomed flask fitted with a dioxygen balloon, and the reaction afforded **3a** in 92% yield. This example clearly demonstrates the practical aspect of this newly developed method.

To explore the mechanism on mPMF-catalyzed condensation of *o*-aminophenols with aldehydes, a control experiment was



1a 2a 3a
15 mmol, 1.64g 10mmol, 1.06g 1.79g, 92% isolated yield

Scheme 2. Synthesis of **3a** on a gram scale.

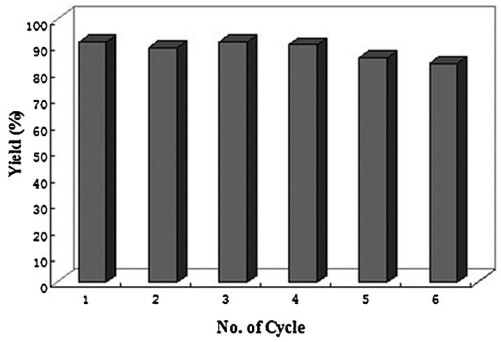


Figure 4. Recycling of the mPMF catalyst.

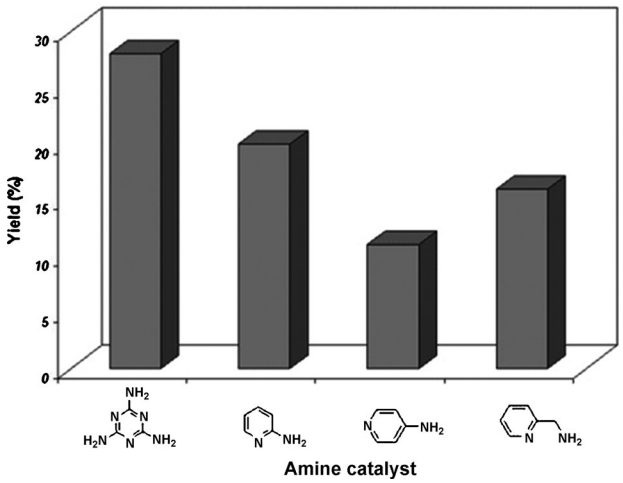
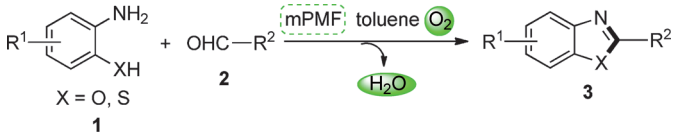
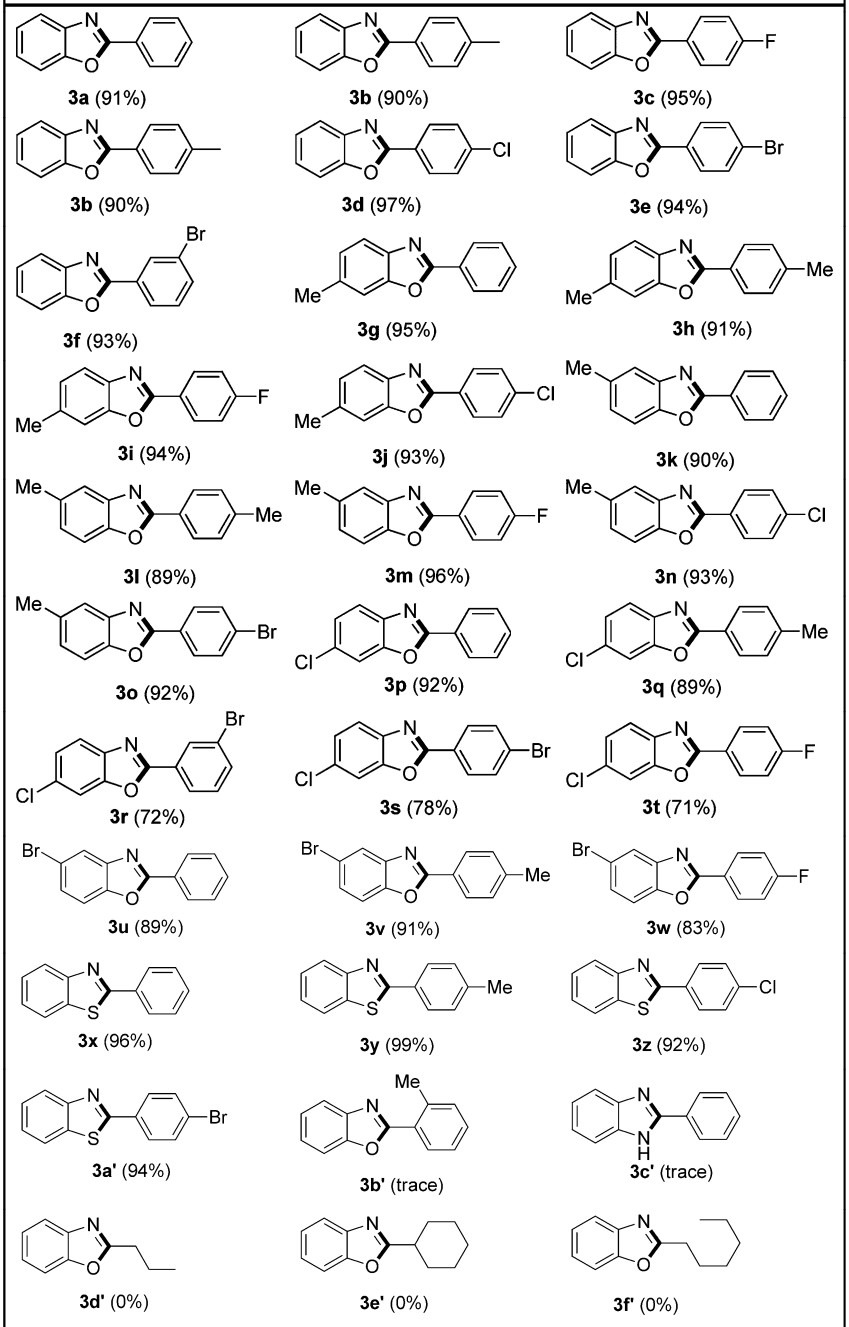


Figure 5. Control experiments using different amine catalysts.

Table 2. mPFM-catalyzed synthesis of benzoxazoles and benzothiazoles, showing products and isolated yields.[a]





[a] Reaction conditions: *o*-substituted aminobenzene (**1**, 0.75 mmol), benzaldehyde (**2**, 0.5 mmol), catalyst (10 mg), solvent (0.5 mL) under oxygen atmosphere.

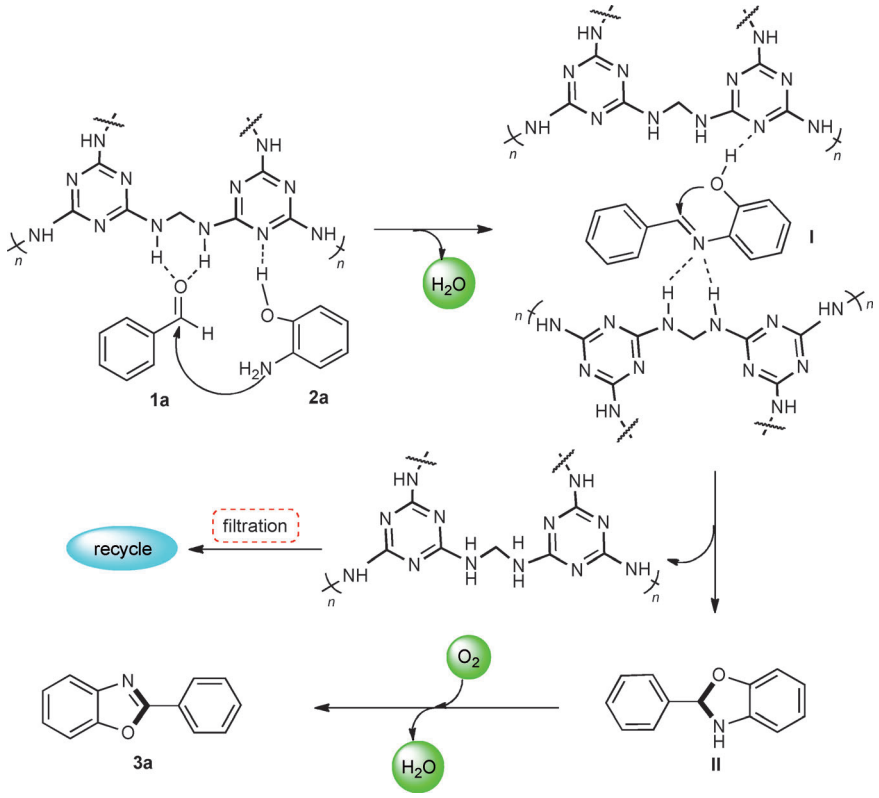
performed as shown in Figure 5. Treatment of *o*-aminophenol (**1 a**) with benzaldehyde in the presence of other small amine-based molecules under dioxygen for 36 h gave very low reaction activity. In contrast, mPMF provided superior activity. The results indicated that mPMF containing of the high density of aminal (–NH–CH_2–NH–) groups and triazine rings plays the dual roles of Brønsted acidity and Lewis basicity. The interaction between the triazine rings and the hydroxyl on *o*-aminophenol could shorten the distance between the two molecules, so as to make it suitable for nucleophilic attack.

We also calculated the structures and bonding energies of mPMF system and melamine system using Gaussian 03 program package[16] (Figure 6). Calculations were conducted in the framework of DFT by use of the hybrid B3LYP functional[17] combined with the standard basis set 6-31G(d,p). The calculated structure confirmed that benzaldehyde formed two H bonds with mPMF and only one with melamine. Hydrogen bonding interaction played a dominant role between the reactants and the catalyst, and the hydrogen bonding energy in the mPMF system (23.27 kcal mol^{-1}) was higher than that in the melamine system (19.65 kcal mol^{-1}, Figure 6).

On the basis of these results above and according to the previous report, a possible mechanism is thus proposed as illustrated in Scheme 3. First, coordination of mPFM to the benzaldehyde (binding and activation), followed by the nucleophilic attack of amino of *o*-aminophenol gives (*E*)-2-(benzylideneamino)phenol (**I**) with elimination of water, and **I** transforms into **II** in the presence of mPMF, which presents dual functionalities of Brønsted acidity and Lewis basicity. The intermediate **II** then subsequently undergoes aromatization by dioxygen oxidation under the reaction conditions to afford the desired products.

Conclusion

We have developed a simple, green, and efficient strategy for the synthesis of benzoxazoles and benzothiazoles. The couplings were performed by using readily available starting materials (*o*-substituted aminobenzene and various aldehydes), recyclable heterogeneous organocatalyst mPMF as the catalyst, and dioxygen as the green oxidant, importantly, organic oxidizing agents, strong acids, or bases were not necessary. The present method shows eco-friendly, economical, and practical advantages over the previous methods. Further applications of mPFM in organic transformations are in progress in our laboratory.



Scheme 3. Proposed mechanism for the direct transformation.

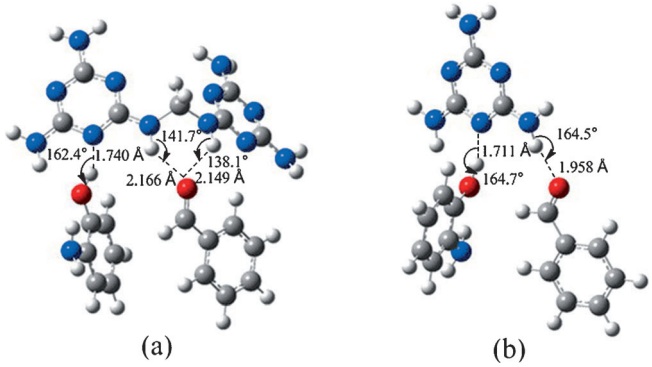


Figure 6. DFT modeling for benzaldehyde and *o*-aminobenzaldehyde with a) mPMF (binding energy = 23.27 kcal mol^{-1}) and b) melamine (binding energy = 19.65 kcal mol^{-1}). ●: C, ●: N, ●: O, and ●: H atoms.

Experimental Section

Synthesis of compounds 3 a–d′

General procedure: A 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with mPMF (10 mg), substituted *o*-substituted aminobenzene (**1**, 0.75 mmol), and various aldehydes (**2**, 0.5 mmol). The tube was evacuated twice and backfilled with oxygen, and toluene (0.5 mL) was added to the tube under oxygen atmosphere. The tube was sealed with a balloon and then the mixture was allowed to stir under oxygen atmosphere at 110 °C for 24 h. After completion of the reaction, the resulting solution was cooled to room temperature, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel by using petroleum ether/ethyl acetate as the eluent to provide the desired product (**3**).

Recycling of the mPMF catalyst

After completion of the reaction, the reaction mixture was transferred to a centrifugal tube, and then was filtered after centrifugation. The residue solid was washed with ethanol (3×5 mL) to remove all traces of product or reactant present, dried at 170 °C in an oven for 2 h to provide the recycling mPMF about 9.84 mg. The recovered solid catalyst was used for further catalytic reactions.

Acknowledgements

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Keywords: green chemistry · mesoporous materials · nitrogen heterocycles · organocatalysis · oxidation

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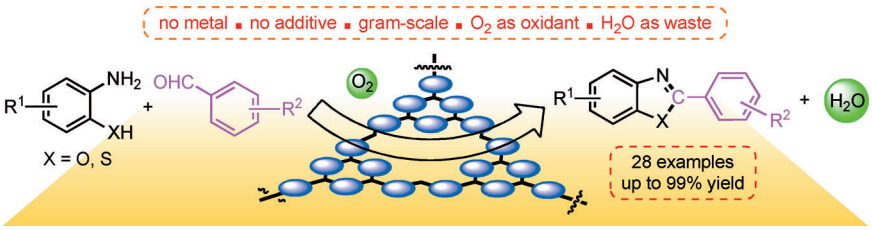

Going round in heterocycles: Benzoxazole and benzothiazole derivatives are synthesized by using mesoporous poly(melamine–formaldehyde) as a green and recoverable catalyst. This heterogeneous organocatalytic method can provide a novel and efficient strategy for the synthesis of other N-heterocycles.

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Mesoporous Poly(melamine–formaldehyde): A Green and Recyclable Heterogeneous Organocatalyst for the Synthesis of Benzoxazoles and Benzothiazoles Using Dioxygen as Oxidant