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Cooperative Multifunctional Catalysts for Nitrone Synthesis: Platinum Nanoclusters in Amine-Functionalized Metal-Organic Frameworks

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Abstract: Nitrones are key intermediates in organic synthesis and the pharmaceutical industry. The heterogeneous synthesis of nitrones with multifunctional catalysts is extremely attractive but rarely explored. Herein, we report ultrasmall platinum nanoclusters (Pt NCs) encapsulated in amine-functionalized UiO-66-NH_2 (Pt@UiO-66-NH_2) as a multifunctional catalyst in the one-pot tandem synthesis of nitrones. By virtue of the cooperative interplay among the selective hydrogenation activity provided by the ultrasmall Pt NCs and Lewis acidity/basicity/nanoconfinement endowed by UiO-66-NH_2, Pt@UiO-66-NH_2 exhibits remarkable activity and selectivity, in comparison to Pt/carbon, Pt@UiO-66, and Pd@UiO-66-NH_2. Pt@UiO-66-NH_2 also outperforms Pt nanoparticles supported on the external surface of the same MOF (Pt/UiO-66-NH_2). To the best of our knowledge, this work demonstrates the first examples of one-pot synthesis of nitrones using recyclable multifunctional heterogeneous catalysts.

Nitrones are versatile reagents central to a wide range of cycloaddition reactions to form biologically active nitrogen heterocycles.[1] Significant efforts have been devoted towards the development of efficient syntheses of nitrones including the condensation of *N*-methyl hydroxylamine hydrochloride with aromatic aldehydes,[2] the oxidation of amines[3] or imines,[4] the reduction of *N*-hydroxy amides,[5] the alkylation of oximes,[6] and the Cope-type hydroamination of alkenes.[7] However, these aforementioned methods are either non-catalytic or rely on homogeneous transition metal catalysts that are difficult to reuse and can contaminate the nitrone product. The development of heterogeneous catalysts for nitrone synthesis is attractive due to the relative ease with which heterogeneous catalysts can be separated and recycled. Nevertheless, only a few heterogeneous catalysts have been reported for the synthesis of nitrones,[8] and these heterogeneous routes require the use of expensive hydroxylamine precursors. Bearing these limitations in mind, we envisioned that hydroxylamines, which are often unstable intermediates,[9] could be generated *in situ* from the selective hydrogenation of inexpensive and readily available nitroalkanes in the presence of a heterogeneous catalyst. The subsequent condensation of the resulting hydroxylamine with aromatic aldehydes would produce nitrones. This rationally-designed tandem reaction, combining two individual reactions (hydrogenation and condensation) in a single pot, is highly attractive as a synthetic route to nitrones, since it eliminates the need to isolate and purify the unstable hydroxylamine intermediates.[10] To accomplish the proposed tandem reaction, we envisioned the development of a multifunctional heterogeneous catalyst capable of promoting both reduction and condensation process while minimizing undesired reaction pathways.

Metal-organic frameworks (MOFs) are a burgeoning class of crystalline organic-inorganic porous materials that have attracted increasing interest due to their large surface area, facile tunability/tailorability, and their numerous applications in gas storage and separation,[11] chemical sensors,[12] catalysis,[13] drug delivery,[14] and proton conductivity.[15] Of particular interest to this study, MOFs have been widely utilized as a host matrix for metal nanoparticles (metal NPs@MOF), serving as advanced heterogeneous catalysts with multiple functions.[16] Metal NPs@MOF holds specific advantages as multifunctional catalysts including (i) the uniform and small cavities of MOFs restrict the overgrowth of metal NPs affording more surface metal sites; (ii) multiple active sites (i.e., metal NPs and Lewis acid/base sites on MOFs) enable the flexible design of multifunctional catalysts;[17] (iii) the highly porous nature of MOFs facilitates rapid mass transportation of substrates to access the encapsulated metal NPs; and (iv) the nanoconfinement endowed by MOFs can lead to enhanced catalytic performance. Despite intensive efforts intended to elucidate the role of metal NPs@MOFs in heterogeneous catalysis,[18] only a limited number of studies on multifunctional NPs@MOF catalysts of tandem reactions have been reported.[12,19] Therefore, the development of multifunctional metal NPs@MOF catalysts for tandem catalysis is highly desired but remains a significant challenge.

Herein, we report for the first time a facile, one-pot synthesis of nitrones catalyzed by Pt NCs encapsulated inside a Zr-MOF, UiO-66-NH_2 (denoted as Pt@UiO-66-NH_2). The multifunctional Pt@UiO-66-NH_2 catalyzes the tandem reaction of nitromethane with aromatic aldehydes to form *N*-methyl-α-aryl nitrones with

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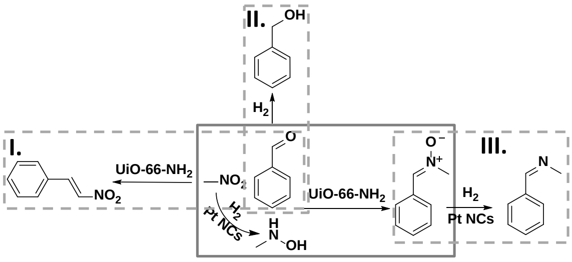
high activity and selectivity. This tandem reaction was achieved by coupling the hydrogenation activity of Pt NCs, the Lewis acidic/basic sites of UiO-66-NH_2, and the nanoconfinement endowed by the effective encapsulation of Pt NCs inside UiO-66-NH_2. By virtue of the cooperative interplay among ultrasmall Pt NCs and UiO-66-NH_2, Pt@UiO-66-NH_2 exhibits superior catalytic performance in the tandem nitrone synthesis in comparison to Pt/carbon, Pt@UiO-66, Pt/UiO-66-NH_2 (Pt NPs supported on the external surface of UiO-66-NH_2) and Pd@UiO-66-NH_2. To the best of our knowledge, this study demonstrates the first example of one-pot tandem synthesis of nitrone using heterogeneous multifunctional catalysts.



Scheme1. A plausible mechanism of nitrone synthesis through hydrogenation of nitromethane and condensation of benzaldehyde (solid rectangle) and possible side reactions indicated by the dashed rectangles, including I) the condensation reaction between benzaldehyde and nitromethane, II) the direct hydrogenation of benzaldehyde, and III) further hydrogenation of the nitrone.

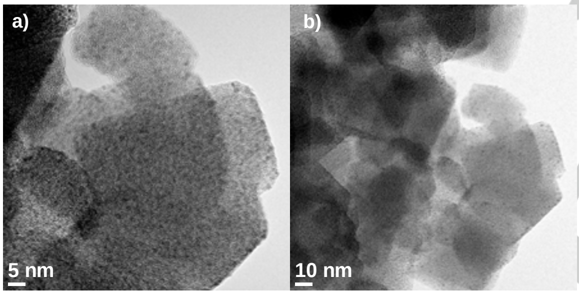
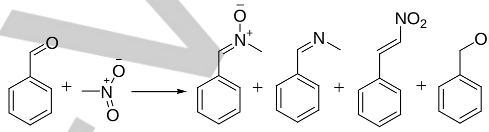


Figure 1. TEM images of 2.0 wt% Pt@UiO-66-NH_2 at different resolutions.

We used UiO-66-NH_2 as the MOF host matrix, which contains uniform and ultrasmall cavities (~1.2 nm). These cavities could serve as rigid templates to encapsulate metal NCs with a matching size.[13d] Following a reported protocol,[20] UiO-66-NH_2 was prepared solvothermally from $ZrCl_4$ and 2-aminoterephthalic acid. The powder X-ray diffraction (PXRD) pattern of the as-synthesized UiO-66-NH_2 was identical to that of the simulated UiO-66 (Figure S1). Using UiO-66-NH_2 as the host, we immobilized Pt NCs exclusively inside its cavities via a solution impregnation approach developed by our group (Details in the Supporting Information).[21] The PXRD analysis indicates that the crystallinity of UiO-66-NH_2 was well retained upon metal loading and reduction (Figure S1). The actual Pt content in Pt@UiO-66-NH_2 was quantitatively determined to be 2.0 wt% by inductively coupled plasma mass spectrometry (ICP-MS). Transmission electron microscopy (TEM) images clearly show that the Pt NCs are evenly dispersed over the UiO-66-NH_2 crystals with a mean diameter of ~1.1 nm and no observable aggregation on the external surface of UiO-66-NH_2 (Figure 1). Moreover, we have confirmed that most of the Pt NCs are indeed encapsulated inside at different angles.[21]

Nitrogen sorption isotherms show that both UiO-66-NH_2 and 2.0 wt% Pt@UiO-66-NH_2 display a Type I curve (Figure S2), suggesting the existence of micropores. Pt@UiO-66-NH_2 has a Brunauer–Emmett–Teller (BET) surface area of 869 $m^2\ g^{-1}$ with a micropore volume of 0.35 $cm^3\ g^{-1}$. These values are smaller than those of the parent UiO-66-NH_2 (BET surface area of 931 $m^2\ g^{-1}$ and micropore volume of 0.38 $cm^3\ g^{-1}$). The decrease in the surface area and pore volume of Pt@UiO-66-NH_2 is attributed to the partial occupation of the cavities in UiO-66-NH_2 by the Pt NCs. It is worth noting that the loaded metal occupies less than one percent of the total internal volume of the MOF and the Pt@UiO-66-NH_2 remains highly porous for the diffusion of reactant and product molecules.

Table 1. Identification of Reaction Conditions by Pt@UiO-66-NH_2.[a]



entry	Pt	H_2 (psi)	solvent	conv. (%)	nitrone sel. (%)
1	1 mol%	200	Toluene	99	97
2[b]	1 mol%	200	Nitromethane	99	98
3	1 mol%	200	Trifluorotoluene	93	94
4[c]	1 mol%	200	MeOH	98	80
5	1 mol%	200	1,4-dioxane	90	60
6	1 mol%	200	Cyclohexane	98	91
7	1 mol%	100	Toluene	95	82
8	1 mol%	500	Toluene	94	94
9[d]	1 mol%	200	Toluene	31	86
10	0	200	Toluene	/	/

[a] Reaction conditions: benzaldehyde (0.1 mmol), nitromethane (1.5 mmol), toluene (1 mL), metal/substrate = 1 mol%, ambient temperature, 12 hours, stirring at 600 rpm. [b] 1 mL of nitromethane was used. [c] Benzaldehyde dimethyl acetal was formed. [d] Nitromethane is 3 eq. of benzaldehyde.

We next set out to evaluate Pt@UiO-66-NH_2 in the tandem reaction of benzaldehyde, nitromethane, and hydrogen at ambient temperature. A plausible mechanism of this tandem reaction involves two steps (Figure S3):[22] i) the selective hydrogenation of nitromethane to yield *N*-methyl hydroxylamine on the Pt NCs surface and ii) the subsequent condensation of hydroxylamine and benzaldehyde to afford *N*-methyl-α-phenyl nitrone by UiO-66-NH_2 (solid rectangle in Scheme 1). Other possible side reactions are indicated by the dashed rectangles in Scheme 1, including I) the condensation of benzaldehyde and nitromethane to form β-nitrostyrene, II) the direct hydrogenation of benzaldehyde into benzyl alcohol, and III) the further hydrogenation of *N*-methyl-α-phenyl nitrone to *N*-methyl-1-phenylmethanimine. A variety of solvents, hydrogen pressures, and feed ratios of nitromethane have been evaluated in an effort to optimize reaction conditions. When toluene was used as solvent with 200 psi H_2 and 15 equivalents of nitromethane to benzaldehyde, Pt@UiO-66-NH_2 gave 99% conversion of benzaldehyde and 97% selectivity for nitrone formation. Tandem catalysis in nitromethane without toluene (entry 2) also led to high conversion (99%) and selectivity (98%) to nitrone. Analogous reactions in methanol, trifluorotoluene, cyclohexane, and 1,4-dioxane occurred with decreased conversion and/or selectivity

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(Table 1, entries 3-6). Decreasing the H_2 pressure to 100 psi led to a lower selectivity, while a higher H_2 pressure of 500 psi did not improve the selectivity (entries 7 and 8). It is notable that decreasing the concentration of nitromethane from 1.5 M to 0.3 M (15 to 3 equivalents) led to significantly decreased activity and a lower selectivity at 86% (entry 9). UiO-66-NH_2 alone resulted in the negligible conversion of benzaldehyde, indicating that Pt NCs are essential in the tandem catalysis (Table 1, entry 10). Time-dependent studies of the tandem reaction under the optimum conditions revealed that Pt@UiO-66-NH_2 showed high selectivity to nitrone initially. With the reaction proceeding, the activity gradually increased without significant decrement of the selectivity (Figure S4).

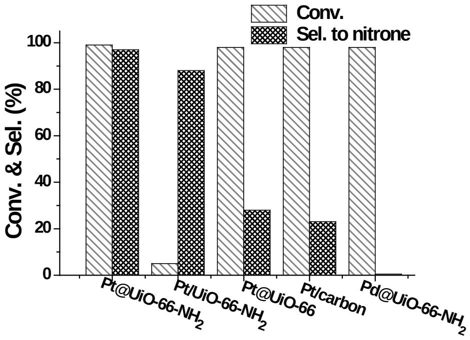


Figure 2. Tandem nitrone synthesis by various heterogeneous catalysts. PVP-Pt/UiO-66-NH_2, Pt/UiO-66-NH_2, Pt@UiO-66 and Pd@UiO-66-NH_2 gave benzyl alcohol as the major product; Pt/Carbon gave β-nitrostyrene as the major product.

To elucidate the origin of the excellent catalytic performance of Pt@UiO-66-NH_2 in this tandem reaction, we systematically tested a series of control catalysts under identical conditions (toluene, 200 psi H_2, ambient temperature, 12 hours, Figure 2). To probe the role of -NH_2 substituents on the benzene dicarboxylic acid (BDC) linker in this tandem reaction, we synthesized UiO-66, an isoreticular analog of UiO-66-NH_2, using unsubstituted BDC as the linker. UiO-66 and UiO-66-NH_2 have the same structure but different chemical functionality. Pt@UiO-66 prepared from UiO-66 gives similar Pt NCs size measured by TEM (Figure S5). To our surprise, the nitrone selectivity of Pt@UiO-66 is significantly lower (28%) than that of Pt@UiO-66-NH_2 (97%), and the major product formed is benzyl alcohol (53%). This result highlights the critical role of –NH_2 in the high selectivity to nitrone in the tandem reaction, inhibiting the direct hydrogenation of benzaldehyde. To probe the role of Lewis acidity in the tandem catalysis, we added a base probe molecule (triethylamine) when the reaction has proceeded for 2 hours. The activity and selectivity decreased significantly compared to the reaction without the base (Table S1), which demonstrates the importance of Lewis acidity of MOFs on the catalytic performance. Using Pt/carbon as the catalyst led to low selectivity for the nitrone product (23%) and the formation of β-nitrostyrene (25%) as the major product.

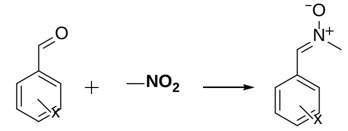
Nanoconfinement effects are often key factors in heterogeneous catalysis to enhance selectivity.[23] To explore the nanoconfinement effect rendered by the UiO-66-NH_2, we deposited Pt NPs on the external surface of UiO-66-NH_2 via two preparation protocols - traditional impregnation and loading polyvinylpyrrolidone (PVP)-capped Pt NPs on MOFs, serving as a comparison to investigate the effect of Pt NC location on catalysis. Following the traditional impregnation method with slight modification, we deliberately deposited Pt NPs on the external surface of MOFs (designated as Pt/UiO-66-NH_2) and the TEM image of Pt/UiO-66-NH_2 shows the average size of the Pt NPs to be 3.8 ± 0.7 nm, which is larger than the largest cavity of UiO-66-NH_2 (Figure S6). Pt/UiO-66-NH_2 showed an inferior activity (69%) and selectivity (84%) in comparison to Pt@UiO-66-NH_2 (Figure 2). We also deposited PVP-capped Pt NPs (~2.7 nm) onto the surface of MOF (Figure S7) using a polyol reduction method (termed PVP-Pt/UiO-66-NH_2). PVP-Pt/UiO-66-NH_2 showed strikingly low activity (6%) and selectivity (60%, the major byproduct is benzyl alcohol) in comparison to Pt@UiO-66-NH_2 (Figure 2). The location of Pt in these two control samples and Pt@UiO-66-NH_2 was confirmed by the hydrogenation of two probe molecules of different sizes, styrene and tetraphenylethylene (Figure S8). These results clearly highlight the advantages of nanoconfinement effects in MOFs. Apart from the nanoconfinement effect, we cannot completely exclude that the smaller Pt particle size in the Pt@UiO-66-NH_2 contributes to the enhanced activity than those control catalysts.

The metal selection was also evaluated by replacing Pt with Pd. Surprisingly, Pd@UiO-66-NH_2, which possesses similar ultrasmall NCs (Figure S9) did not lead to the formation of the nitrone. Instead, high selectivity for benzyl alcohol (99%) was observed under otherwise identical conditions (Figure 2). This strikingly different catalytic performance clearly demonstrates the unique properties of Pt NCs in this tandem reaction. We infer that Pt and Pd NCs possess different adsorption strength concerning nitromethane and benzaldehyde. For Pd NCs, benzaldehyde molecules preferentially adsorb on the metal surface in comparison to nitromethane, and thus, likely undergo the hydrogenation to yield benzyl alcohol (reaction II in Scheme 1). In contrast, absorption of nitromethane on the surface of Pt is favored over benzaldehyde leading to the reduction of nitromethane to form hydroxylamine and subsequent formation of the nitrone upon condensation with benzaldehyde. These results suggest that the competitive adsorption of reactants (benzaldehyde and nitromethane) over different metal NPs (Pt and Pd) could alter the product selectivity in this tandem reaction. A similar effect has been experimentally and computationally proven in selective phenol hydrogenation.[24] Kinetics studies of tandem catalysis with varied benzaldehyde to nitromethane ratio show that the reaction is first order to benzaldehyde and zero order to nitromethane, indicating the nitromethane or its hydrogenation products, hydroxylamine, is the dominant species on the surface of the catalysts under investigated conditions (Figure S10-11).[25] A more detailed study to reveal how catalytic pathways vary in this tandem nitrone synthesis is ongoing.

Pt@UiO-66-NH_2 is unique that can avoid the three byproducts (I – III) showing in Scheme 1 and only lead to the nitrone product. To test the scope of this multifunctional catalyst, we conducted the tandem reaction of a variety of substituted benzaldehydes with nitromethane over Pt@UiO-66-NH_2 under optimized conditions. As illustrated in Table 2, we found that reactions of halogenated benzaldehydes (2-F, 4-Cl, and 4-Br) and benzaldehydes containing electron-withdrawing groups (3-CN, 4-CN) occurred with good-to-high conversions and selectivities. Benzaldehydes containing electron-donating groups (4-Me, 4-

OMe) gave moderate conversions and selectivities, indicating the generality of the multifunctional catalyst.

Table 2. Tandem Catalysis with Various Substituted Benzaldehyde and Nitromethane over Pt@UiO-66-NH_2.



Entry	X	Conv.(%)	Sel. to nitrone (%)
1	2-F	99	90
2	4-Cl	87	58
3	4-Br	90	47
4	3-CN	99	88
5	4-CN	97	82
6	4-Me	81	77
7	4-OMe	76	60

Reaction conditions: Substituted benzaldehyde (0.1 mmol), nitromethane (1.5 mmol), toluene (1 mL), metal/substrate = 1 mol%, ambient temperature, 12 hours, stirring at 600 rpm.

Stability and recyclability of heterogeneous catalysts are prerequisite criteria for practical applications. We performed the recyclability test of Pt@UiO-66-NH_2 by isolating the catalyst from the reaction media at partial conversion and reusing the catalyst in the subsequent runs. The Pt@UiO-66-NH_2 was used at partial conversion for 4 times without significant decrease in activity and only a slight decrease in selectivity (Figure S12). The PXRD analysis shows that the crystalline structure of the MOF was retained after the recyclability test (Figure S13), indicating the catalyst is robust under our reaction conditions. At full conversion, the Pt@UiO-66-NH_2 can be used for 3 times without any noticeable decrease in activity and selectivity (Figure S14). A leaching test was also performed to confirm the heterogeneity of the catalyst. Upon removal of the catalyst, no further increase in the conversion of benzaldehyde was observed (Figure S15). Furthermore, ICP-MS analysis of the reaction supernatant showed only negligible Pt (< 0.01% of added Pt) leaching out into the solution. In combination, these results show the multifunctional Pt@UiO-66-NH_2 to be an active, selective, reusable, and robust catalyst for nitrone synthesis by a tandem reaction manifold.

In conclusion, we have developed for the first time a one-pot synthesis of nitrones with high activity and selectivity by virtue of a cooperative multifunctional heterogeneous catalyst. By combining the *in situ* formation of *N*-methyl hydroxylamine and subsequent condensation with aromatic aldehydes, the Pt@UiO-66-NH_2 catalyst shows excellent catalytic performance in the tandem catalysis and significantly outperforms Pt/carbon, Pt@UiO-66, Pt/UiO-66-NH_2 and Pd@UiO-66-NH_2, presumably due to the synergetic cooperation among the ultrasmall Pt NCs, Lewis acid/basic sites on UiO-66-NH_2, and nanoconfinement effects. Furthermore, the multifunctional Pt@UiO-66-NH_2 catalyst is recyclable. This facile and rational design will open new opportunities for MOF-based multifunctional catalysts for the broader production of fine chemicals.

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Keywords: MOFs, tandem catalysis, heterogeneous catalysis, cooperative catalysis, nanoparticles.

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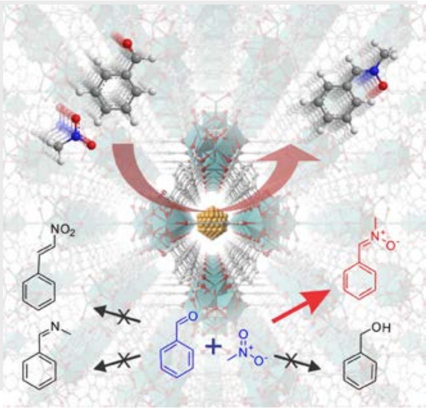
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Nitrones are key intermediates in organic synthesis and the pharmaceutical industry. We report platinum nanoclusters (Pt NCs) encapsulated in amine-functionalized UiO-66-NH$_2$ (Pt@UiO-66-NH$_2$) as a multifunctional catalyst in the one-pot tandem synthesis of nitrones. By the cooperative interplay among the selective hydrogenation activity provided by Pt NCs and Lewis acidity/basicity/nanoconfinement endowed by the MOF, Pt@UiO-66-NH$_2$ exhibits remarkable activity and selectivity.



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Page No. – Page No.

Cooperative Multifunctional Catalysts for Nitrone Synthesis: Platinum Nanoclusters in Amine-Functionalized Metal–Organic Frameworks