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Heterogeneous oxidative synthesis of quinazolines over OMS-2 under ligand-free conditions

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Manganese oxide octahedral molecular sieve (OMS-2) prepared using urea as additive was found to be an efficient recyclable catalyst for the synthesis of quinazolines via oxidation/cyclization. A broad of substituted quinazolines were obtained from alcohols and amidines in good yields under ligand-free conditions. OMS-2 was characterized by XRD, BET, ICP-AES, SEM, TEM and XPS, which indicates that the superior catalytic ability might arise from enhanced surface area and crystallinity.

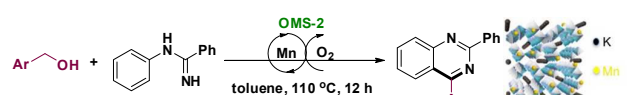
Introduction

Quinazolines are important nitrogen heterocycles because they have showed remarkable bioactivities as anticancer, antiviral and antitubercular reagents and they are cores of HIV reverse transcriptase inhibitors.¹ Over the past years, the synthesis of quinazolines was realized through condensation of 2-aminobenzophenones with aldehydes, acyl chloride and benzylamines.² Recently, amidines were employed as starting materials to construct quinazolines with aldehydes catalyzed by Pd or promoted by microwave.³ Notably, nano-CuO-catalyzed aerobic oxidative synthesis of quinazolines from amidines and alcohols that acted as stable and cheap precursors of aldehydes was developed with the help of ligand.⁴ From an environmentally-friendly and economic point of view, the development of heterogeneous catalytic system based on elegantly designed recyclable catalysts under ligand-free conditions for the synthesis of important heterocyclic compounds is still desirable and challenging.

Manganese oxide octahedral molecular sieve (OMS-2) that is composed of 2x2 edge- and corner-shared MnO₆ octahedral chains and tunnel K⁺ ions (Scheme 1), in recent years, has captured broad attention because it demonstrates outstanding practical ability in terms of catalysis, absorption, battery materials and ion-exchange.⁵ Especially, due to its excellent redox ability and existence of mixed valent manganese (Mn⁴⁺,

Mn³⁺ and Mn²⁺), OMS-2 has widely applied in oxidation of alcohols, oxidative dehydrogenation, imination, cylation, amidation, oxidative cyclization, and environmental catalysis.^{6,7} Very recently, our group reported that several practical and clean synthesis of N-containing heterocycles catalyzed by OMS-2 which was prepared by different methods with green oxidants under additive-, base- and ligand-free conditions.⁸ Therefore, it is desirable to synthesize OMS-2-based materials and construct the efficient and simple catalytic systems based on them for the sustainable organic molecular transformation.

In continuation of our research toward sustainable catalysis,⁹ herein, we would like to describe that OMS-2-based materials were prepared by different methods and employed as heterogeneous catalysts for the aerobic synthesis of quinazolines under ligand-free conditions (Scheme 1). The optimal catalyst was fully characterized, which shows that enhanced surface area and crystallinity resulted into the excellent catalytic ability.



Scheme 1 OMS-2-catalyzed heterogeneous oxidative synthesis of quinazolines under ligand-free conditions.

Results and Discussion

OMS-2-based materials were synthesized through oxidation of Mn²⁺ or reduction of Mn⁴⁺ by H₂O₂ under reflux conditions. First of all, X-ray diffraction (XRD) was employed to characterize the crystal structure and crystallinity of conventional OMS-2, OMS-2-U and OMS-2-H. As shown in Figure 1, all materials exhibited typical cryptomelane-type manganese oxides with 2x2 tunnel (JCPDS 29-1020).⁵

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Specifically, OMS-2-U possessed higher crystallinity compared with others because sharper and more intense diffraction peaks were observed. Subsequently, the textural properties of OMS-2-based materials were investigated by nitrogen adsorption-desorption measurements and the corresponding information was listed in Table 1. Three OMS-2 materials all exhibited type-II isotherm (Figure S1). Notably, conventional OMS-2 and OMS-2-H exhibited similar surface area (75-79 m²/g), while OMS-2-U demonstrated significantly enhanced surface area (113 m²/g) due to the use of urea as the additive. Next, morphology and microstructure of them were probed using SEM and TEM. From the images of SEM, it was found that all materials exhibited nano-fiber morphology although slight differences were observed (Figure 2). OMS-2-U and OMS-2 shared very similar nano-fiber morphology on length and width. OMS-2-H showed more uniform, thinner and longer fiber-like morphology, which means it possessed the smallest particle sizes. Similarly, TEM images illustrated typical uniform nanorod morphologies, which was in agreement with previous research (Figure 3).^{9a,10,11} More characterization information of OMS-2-based materials was concluded in supporting information.

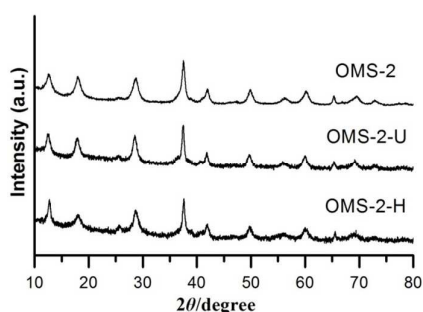


Figure 1 XRD patterns of OMS-2-based materials.

Table 1 Texture properties of OMS-2, OMS-2-H and OMS-2-U

Entry	Catalyst	BET surface area (m ² /g)	Total pore volume (cm ³ /g)	Average pore size (nm)
1	OMS-2	79	0.26	12
2	OMS-2-H	75	0.14	7
3	OMS-2-U	113	0.33	11

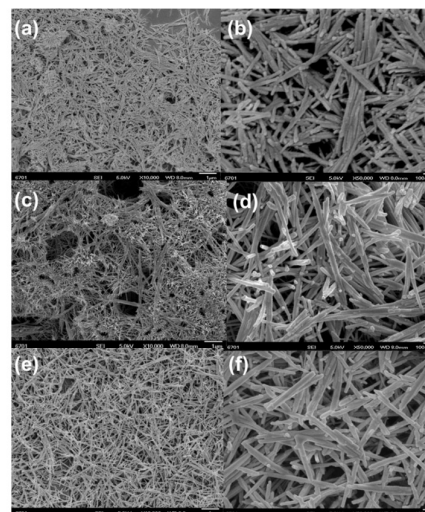


Figure 2 SEM images of OMS-2 (a and b), OMS-2-U (c and d) and OMS-2-H (e and f).

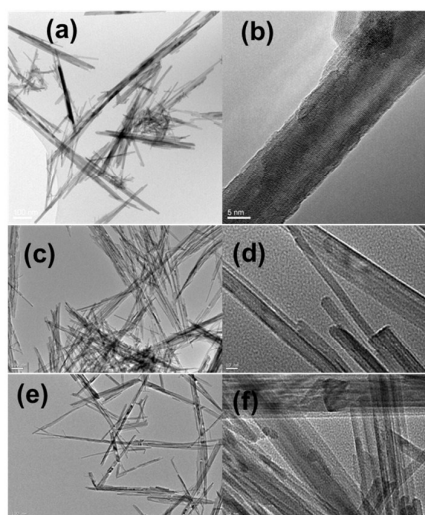


Figure 3 TEM images of OMS-2 (a and b), OMS-2-U (c and d) and OMS-2-H (e and f).

After investigation of physical properties of conventional OMS-2, OMS-2-H and OMS-2-U, the oxidative synthesis of quinazolines **3a** between benzyl alcohol **1a** and N-phenylbenzimidamide **2a** was studied in toluene under ligand-free conditions (Table 2). Initially, blank experiment indicated that the reaction did not occur in the absence of catalyst, while α -MnO₂ with short nanorod-like morphology¹² could not catalyze the oxidation at all in toluene at 110 °C (entries 1 and 2). Delightedly, conventional OMS-2 proceeded the reaction very well and the quinazoline **3a** was obtained in 75% yield under O₂ (entry 3). Next, experiments indicated KMnO₄ (10 mol%) or MnSO₄ (10 mol%) which are raw of OMS-2 could not play a role of catalyst in the reactions (entries 4 and 5). However, when OMS-2-H was used as the catalyst, a very low yield of desired product was observed (entry 5). It was found that OMS-2-H hardly proceeded the oxidation of benzyl alcohol even using O₂ as the oxidant due to the unique surface

properties (entry 6), such as the existence of different planes, which was in agreement of the results of Suib's group on the research of OMS-2-H.¹³ Nevertheless, OMS-2-U with enhanced surface area and crystallinity successfully catalyzed the reaction and led to 82% yield of **3a** under the standard conditions (entry 7). Then, we found that OMS-2-U-catalyzed reaction could not work very well under N₂ and a very poor result was obtained, which means that the reaction was aerobic oxidation and O₂ played a role of the terminal oxidant (entry 8). On the other hand, a slightly low yield was realized using air as the terminal oxidant instead of O₂ and H₂O₂ failed the reaction at all (entries 9 and 10). It was worthy to note that the reaction temperature affected the reaction significantly and the reaction did not occur below 110 °C because OMS-2-catalyzed oxidation of benzyl alcohol **1a** barely carried out (entry 11). Very recently, we reported that Cu/OMS-2-catalyzed synthesis of dihydro-1,3,5-triazines using the same substrates at 90 °C, which indicates that the interaction between Cu and Mn made oxidation of alcohols occur at a low temperature (90 °C) and resulted into the synthetic selectivity between alcohols and N-phenyl amidines. Therefore, the

Table 2 Optimization of oxidative synthesis of quinazoline **3a** from alcohol **1a** and N-phenyl amidine **2a**^a

Entry	Catalyst	Oxidant	Solvent	Yield ^b (%)
1	-	O ₂	toluene	N.R.
2	α-MnO ₂	O ₂	toluene	0
3	OMS-2	O ₂	toluene	75
4	KMnO ₄	O ₂	toluene	0
5	MnSO ₄	O ₂	toluene	0
6	OMS-2-H	O ₂	toluene	29
7	OMS-2-U	O ₂	toluene	82
8 ^c	OMS-2-U	-	toluene	15
9	OMS-2-U	air	toluene	70
10	OMS-2-U	H ₂ O ₂	toluene	0
11 ^d	OMS-2-U	O ₂	toluene	N.R.
12	OMS-2-U	O ₂	DMSO	0
13	OMS-2-U	O ₂	Dioxane	0
14	OMS-2-U	O ₂	EtOH	0
15 ^e	OMS-2-U	O ₂	toluene	38 (85 ^f)

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol), catalyst (20 mg, 13 mol%) was used for OMS-2, solvent (1 mL), 12 h, O₂ balloon or under air. ^b Isolated yields. ^c Under N₂ (1 atm). ^d At 90 °C. ^e OMS-2-U (5 mg, 3 mol%) was used. ^f OMS-2-U (50 mg, 32 mol%) was used.

catalytic method we described here could complement the approach we reported previously. More optimizations proved that toluene was the best solvent for the reaction (entries 12–14). Moreover, controlled experiments showed that decreasing amounts of catalyst led to poor yield and further increasing amounts of OMS-2-U could not obviously better the yield of **3a** (entry 15). Finally, the optimal reaction conditions were using OMS-2-U as the catalyst in toluene at 110 °C under O₂.

After the optimization, we wondered whether the observed catalysis was derived from the solid OMS-2-U rather than the leached manganese species in the solution. The hot-filtration experiment was performed, which proved that the catalysis was truly heterogeneous (For experimental details, see SI). Therefore, the recyclability of OMS-2-U was examined on the synthesis of quinazoline **3a** (Table 3). After each run, the catalyst was filtered, washed by water and dried at 120 °C for the next run. It was found that the catalyst remained the catalytic ability and was able to reuse at least 4 times. Meanwhile, the retrieved catalyst after the first run was characterized by XRD, which indicates that the crystal structure of OMS-2-U remained very well (Fig. 4).

Table 3 The recyclability of OMS-2-U^a

Run	1	2	3	4	5
Isolated yield (%)	82	86	83	80	82

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol), OMS-2-U (20 mg, 13 mol%), toluene (1 mL), O₂ balloon, 110 °C, 12 h.

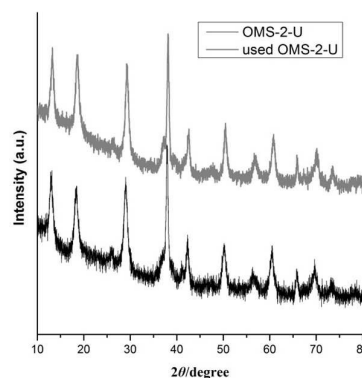
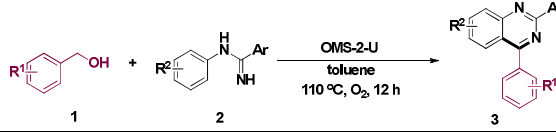


Figure 4 XRD patterns of fresh OMS-2-U and OMS-2-U after the first run.

With the optimized conditions in hand, the scope of reaction was investigated by performing the reaction with substituted alcohols and amidines in toluene with OMS-2-U. Generally, substituted benzyl alcohols reacted with various N-phenyl amidines smoothly and corresponding quinazolines with good to excellent yields were obtained (Table 4). On the other hand, a broad of benzyl alcohols with different functional groups were able to react with N-phenylbenzimidamide **2a** (Table 5). Specifically, steric hindrance effect influenced the reaction very much and 2-chloro benzyl alcohol gave desired product **3n** in moderate yield (entry 3). Furthermore, benzyl alcohols with electron-withdrawing groups resulted into better results than ones with electron-donating groups. (3,4-Dimethoxyphenyl)methanol failed the reaction and the corresponding aldehyde was observed after the reaction (entry 8). And, aromatic heterocyclic alcohol also participated the reaction successfully and the corresponding quinazoline **3t** were observed in 71% yield (entry 9).

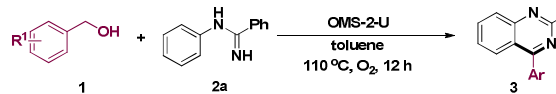
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Table 4 Scope of reactions between alcohols and substituted N-phenyl amidines^a


Entry	R ¹ =	R ² =	Ar =	Compound	Yield ^b (%)
1	H	H	4-OMe-Ph	3b	85
2	4-Br	H	4-OMe-Ph	3c	81
3	4-Et	H	4-OMe-Ph	3d	91
4	4-CF ₃	H	4-OMe-Ph	3e	75
5	H	H	3-OMe-Ph	3f	86
6	H	4-Br	4-Cl-Ph	3g	78
7	H	4-OCF ₃	4-Cl-Ph	3h	82
8	H	4-OEt	4-Cl-Ph	3i	86
9	4-CF ₃	H	3-OMe-Ph	3j	88
10	3,4-di-Cl	H	3-OMe-Ph	3k	95

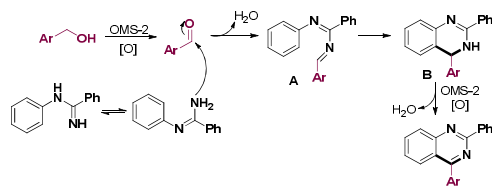
^a Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), OMS-2-U (20 mg, 13 mol%), toluene (1 mL), O₂ balloon, 110 °C, 12 h. ^b Isolated yields.

Table 5 Scope of reactions between alcohols and N-phenylbenzimidamide^a


Entry	R ¹ =	Compound	Yield ^b (%)
1	4-Cl	3l	90
2	3-Cl	3m	88
3	2-Cl	3n	56
4	3,4-di-Cl	3o	92
5	4-Br	3p	87
6	4-F	3q	90
7	4-Me	3r	75
8	3,4-di-OMe	3s	0
9	pyridin-2-yl	3t	71

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.25 mmol), OMS-2-U (20 mg, 13 mol%), toluene (1 mL), O₂ balloon, 110 °C, 12 h. ^b Isolated yields.

Based on our previous work¹³ and reports from other groups⁴, we proposed the reaction mechanism in Scheme 2. Benzyl alcohol firstly was oxidized by OMS-2 with O₂ to corresponding benzaldehyde.^{6,14} After that, benzaldehyde reacted with tautomeric amidine with the help of OMS-2, which gave intermediate **A**. Next, intermediate **B** was generated *via* cyclization of **A**. Finally, OMS-2/O₂-catalyzed oxidative dehydrogenation occurred on intermediate **B** to give desired product quinazoline.

**Scheme 2** Proposed reaction route.

Conclusions

In summary, OMS-2-catalyzed heterogeneous oxidative synthesis of quinazolines from alcohols and amidines under ligand-free conditions was achieved. The characterization of the catalyst indicated that enhanced surface area and crystallinity might result into the excellent catalytic activity. Moreover, the catalyst could be reused for many times without the loss of activity. The exploration of more ligand- and additive-free catalytic systems based on OMS-2 for the sustainable organic synthesis is going on in our laboratory.

Experimental Section

General information

All reagents were purchased from commercial suppliers and used without further purification. All experiments were carried out under air or using O₂ balloon. Flash chromatography was carried out with Merck silica gel 60 (200-300 mesh). Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ¹H NMR and ¹³C NMR (400 and 100 MHz respectively) spectra were recorded in CDCl₃. Chemical shifts (δ) are reported in ppm using TMS as internal standard, and spin-spin coupling constants (J) are given in Hz.

Preparation of MnO₂-based catalysts

Conventional OMS-2 was prepared according to our previous works.^{9a}

OMS-2 synthesized using urea as the template was designated as OMS-2-U and prepared according to the literature procedure with minor modification.¹⁰ In a typical procedure, KMnO₄ (32 mmol, 5.04 g) was dissolved in 80 mL of deionized water. Urea (112 mmol, 6.72 g) was added to the above solution, and the mixture was stirred at r.t. for 30 mins. Then, the resulting solution was added dropwise to a vigorously stirred mixture of 60 mL of MnSO₄ (42 mmol, 7.08 g) solution and concentrated HNO₃ (2.4 mL). Next, the reaction mixture was refluxed for 24 h. Finally, the catalyst was filtered, washed by water, dried at 120 °C and calcined at 350 °C for 2 h.

OMS-2 synthesized using H₂O₂ as the reductant in acidic condition was designated as OMS-2-H and prepared according to the literature procedure with minor modification.¹¹ H₂O₂ (40 mL, 3.0 wt%) was added to a buffer solution consisting of HOAc (5 mL) and 40 mL of KOAc (0.05 mol, 5 g) solution. 150 mL of KMnO₄ (0.04 mol, 6.5 g) solution was then added dropwise to the above mixture while stirring. The resulting solution was refluxed for 24 h, and the product was finally filtered, washed and dried under air at 120 °C.

General procedure for OMS-2-U-catalyzed quinazolines synthesis

The aerobic oxidative synthesis of quinazolines was generally performed as follows: MnO₂-based catalyst (20 mg), alcohol (0.3 mmol) and amidine (0.2 mmol) were added into a Schlenk tube with a stir bar. Then, the tube was sealed followed by the removal of air and O₂ was charged into it. Toluene (1 mL) was added into the reaction mixture using a syringe under O₂. Subsequently, the reaction mixture was allowed to react at 110 °C for 12 h. After the reaction was completed, the catalyst was isolated by filtration and washed with EtOH and deionized water. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography to yield corresponding product.

Conflicts of interest

There are no conflicts to declare.

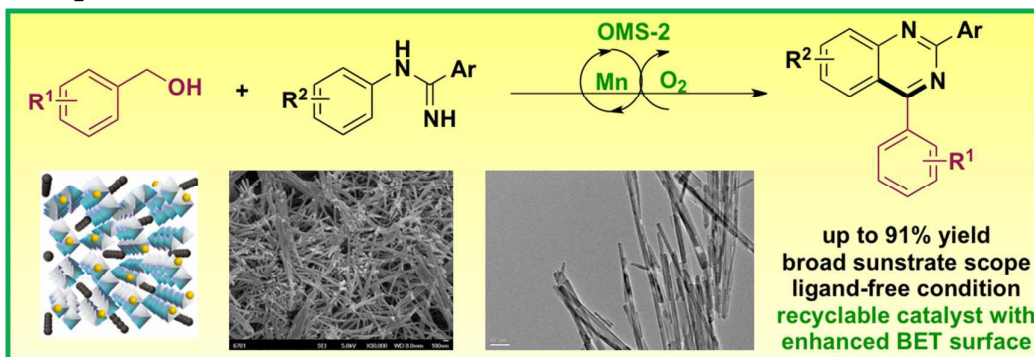
Acknowledgements

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Graphic Abstract



OMS-2 is employed to synthesize heterocycles through selective oxidation without the help of ligands.