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Merrifield resin-supported quinone as an efficient biomimetic catalyst for metal-free, base-free, chemoselective synthesis of 2,4,6-trisubstituted pyridines†

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Metal-free, base-free, biomimetic and chemoselective synthesis of 2,4,6-trisubstituted pyridines was developed under mild conditions for the first time. The heterogeneous biomimetic catalyst – recoverable Merrifield resin-supported quinone – was fully characterized by Fourier transform infrared spectroscopy (FT-IR), X-ray photoelectron spectrometry (XPS) and energy dispersive X-ray spectroscopy (EDX). This supported quinone catalyst exhibited excellent catalytic reactivity for chemoselective synthesis of 2,4,6-trisubstituted pyridines, providing an efficient and green method for the synthesis of pyridine derivatives under mild conditions. Mechanistic investigations were conducted to gain insights into the heterogeneous biomimetic catalyst as well as the resulting transformation. The successful capture of intermediates offered direct and clear evidence for the proposed mechanism.

Introduction

Quinones are useful building blocks and important precursors for a wide range of biological compounds, such as pharmaceuticals, antibiotics, anticancer drugs, pigments and dyes.[1] Scientists have put in a lot of effort and achieved great progress in this area.[2] Notably, scientists have found the significant use of quinones in organic catalysis in recent years.[3] For example, Stahl *et al.* reported the quinone-catalyzed aerobic oxidative coupling of primary benzylic amines to afford secondary imines and the dynamic self-sorting of imine products in good yields.[4] Later, they developed a new method for the aerobic oxidation of secondary amines which employs 1,10-phenanthro-line-5,6-dione as a bifunctional *o*-quinone catalyst *via* a biological pathway involving a hemiaminal intermediate.[5a] In 2016, Kim and Oh reported a highly modular aerobic dehydrogenation protocol for primary and secondary amines, and cross-couplings of amines were obtained through the utilization of *o*-naphthoquinone catalysts in the presence of cocatalysts such as acids and bases.[6a] Afterward, the same group identified an *o*-naphthoquinone-catalyzed oxidative deamination reaction where molecular oxygen and water serve as the sole oxidant and nucleophile respectively.[6b] In 2017, Clift and co-workers developed a sequential quinone-catalyzed oxidative decarboxylation/Mukaiyama–Mannich addition, which provided a highly efficient route for α-amino acid homologation under mild reaction conditions.[7] Luo *et al.* proved that a simple *ortho*-quinone catalyst could effectively facilitate the oxidative synthesis of heterocycles such as quinoxalines, benzoxazoles and benzimidazoles from primary amines in good yields with oxygen as the oxidant.[8a] In 2019, Luo *et al.* identified the mechanism of aerobic oxidation of α-branched cyclic tertiary amines, secondary amines, and primary amines in a bioinspired *ortho*-quinone catalytic system.[8c] From a sustainable-development and green chemistry standpoint, there is an urgent need to develop a recoverable catalytic system to achieve atom economical reactions with higher selectivity and under more environmentally benign conditions, such as dehydrogenation reactions.[9,10]

Functionalized 2,4,6-trisubstituted pyridines are one of the most important and useful heterocyclic compounds in modern industry.[11] These are important intermediates that find wide applications and have been diversified into subunits such as anti-oxidation materials, anti-bacterial materials and anticancer drugs in pharmaceuticals and pesticides in agriculture. The conventional method for the synthesis of 2,4,6-tri-

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substituted pyridines is based on the modified multicomponent pyridine transformation from an enolizable ketone and aldehyde and uses ammonium salt as the nitrogen source in the presence of a catalyst at high reaction temperature.[12] Recently, several methodologies have been developed for the synthesis of 2,4,6-triarylpyridines, such as the condensation of keto-oximes with aryl aldehydes,[13a,b] the reaction of amino acids with aryl ketones,[13c] taking Eosin Y[13d] as a photoredox agent or using HOTf,[13e,f] copper,[13g–i] iron,[13j] palladium,[13k] Iodine,[13l] $B(C_6F_5)_3$,[13m] and 4,6-dihydroxysalicylic acid[13n] as catalysts. Based on the previous dehydrogenation and borrowing hydrogen reactions,[14–16] we recently developed several ruthenium and iridium catalysts and studied their catalytic activity.[17] However, these ruthenium and iridium complexes are costly and lack reusability, resulting in huge waste for dehydrogenation reactions.[18] As part of our continuing efforts in the development of green methods for borrowing hydrogen reactions and quinone transformations,[19] herein, we report that heterogeneous Merrifield resin-supported quinone can effectively catalyze the synthesis of 2,4,6-trisubstituted pyridines in high yields with good recovery performance.

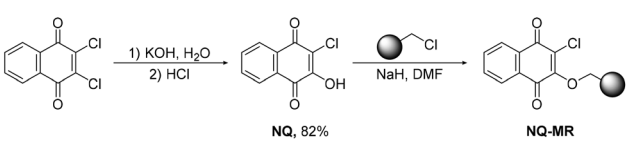
Results and discussion

Preparation of the NQ-MR catalyst

First, 2,3-dichloro-1,4-naphthoquinone was added into KOH aqueous solution. The reaction mixture was stirred at 70 °C for 3 hours and then acidified with a few drops of concentrated hydrochloric acid until pH ≈ 2. After purification, a yellow solid was obtained, which is the target product 2-chloro-3-hydroxy-1,4-naphthoquinone (NQ, up to 82% yield). Then, an appropriate amount of NQ was mixed with the Merrifield resin (MR) swollen in DMF solution and processed for 18 hours at 60 °C in the presence of NaH according to Williamson's synthesis (Scheme 1).[20] Finally, after ultrasonic washing and drying, the desired catalyst Merrifield resin-supported naphthoquinone (NQ-MR) was acquired (for the detailed preparation process, please see the ESI†).

Characterization of the NQ-MR catalyst

After NQ-MR synthesis, Fourier transform infrared spectroscopy (FT-IR), energy dispersive X-ray spectroscopy (EDX) and X-ray photoelectron spectrometry (XPS) were used to characterize the supported catalyst NQ-MR. The FT-IR spectra of the Merrifield resin, NQ-MR and NQ are shown in Fig. 1. The Merrifield resin (Fig. 1a) shows two characteristic peaks at 1265 and 676 cm^{-1}, corresponding to the chloromethyl group



Scheme 1 The synthesis of supported NQ-MR.

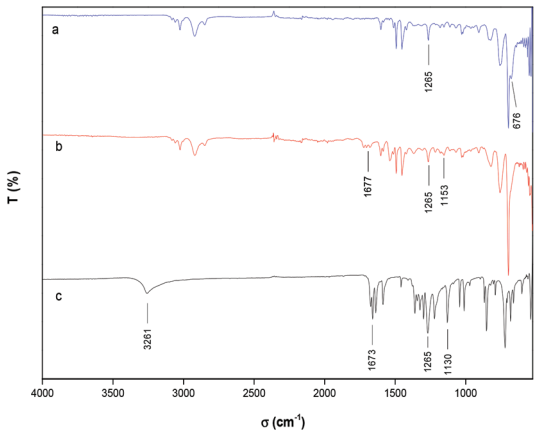


Fig. 1 FT-IR spectra of (a) the Merrifield resin, (b) NQ-MR, and (c) NQ.

on the benzene ring. For NQ (Fig. 1c), the broad peak around 3261 cm^{-1} belonged to –OH and the strong peak at 1130 cm^{-1} (characteristic absorption peak of the C–O bond) reflected the stable existence of the phenolic hydroxyl group in NQ compounds. Delightfully, a peak at 1677 cm^{-1} was found for the supported catalyst NQ-MR (Fig. 1b) which was similar to the carbonyl (C═O) absorption in NQ, thereby indicating the successful coupling of NQ on the Merrifield resin. Meanwhile, the disappearance of the hydroxyl characteristic peak from the NQ-MR spectrum and the emergence of a C–O bond (1153 cm^{-1}) in the fingerprint region can further confirm the successful conversion of NQ to NQ-MR.

The energy-dispersive X-ray (EDX) spectra of the MR and NQ-MR (Fig. 2) reveal the existence of the expected elements (C, O, and Cl) in the structure. An increase in the oxygen content could be attributed to the addition of carbonyl oxygen in the quinones. Next, Fig. 3 clearly displays the uniform distribution of Cl atoms on the surface of the carrier material (for more details, see the ESI†).

Finally, the surface elemental chemical states and the contents of the resin-loaded chloride quinone catalyst were investigated by XPS. As shown in Fig. 4a, the characteristic peaks of O 1s, C 1s and Cl 2p for NQ-MR appear at ~532.8 eV, ~284.8

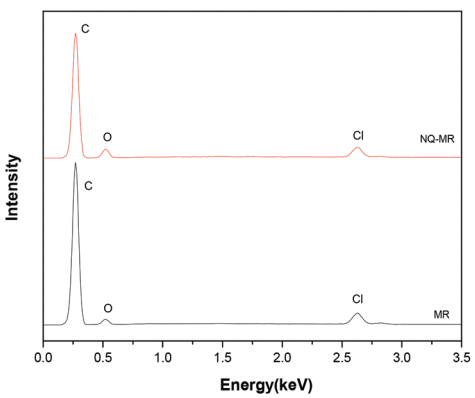


Fig. 2 EDX pattern of the Merrifield resin and NQ-MR.

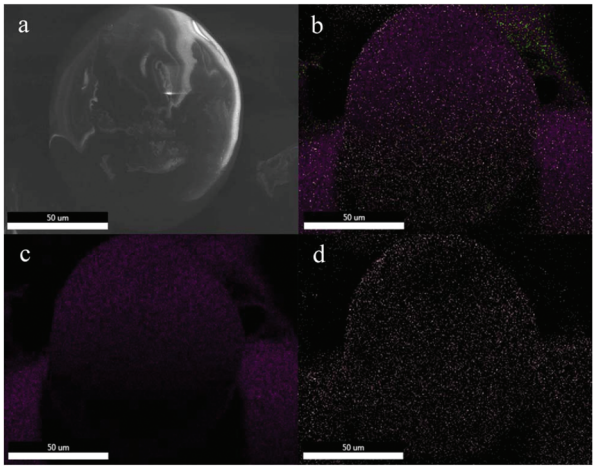


Fig. 3 SEM image of (a) the MR and EDX elemental maps of (b) MR, (c) C atoms, and (d) Cl atoms.

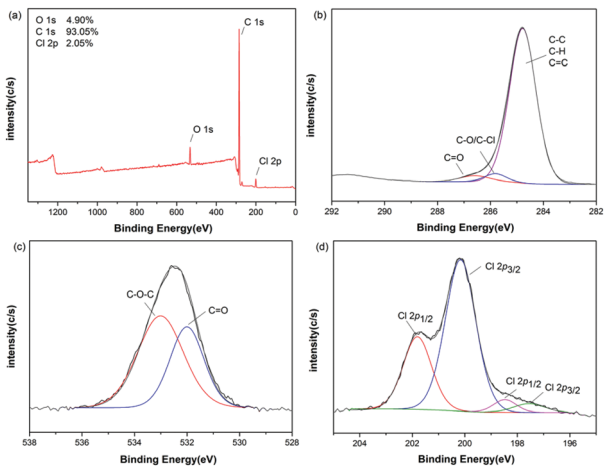


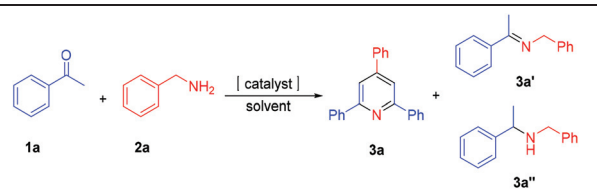
Fig. 4 XPS spectra of NQ-MR (a) surface. C 1s (b), O 1s (c) and Cl 2p (d) core-level spectra of catalyst surface.

eV and ~200.8 eV, respectively, which is consistent with the chemical composition of the sample. The Gaussian curve of the C 1s core-level spectrum (Fig. 4b) after the initial fitting was deconvoluted into three peaks of varying intensities at 286.6 eV (C═O), 285.8 eV (C–O/C–Cl) and 284.8 eV (C–C/C–H/C═C), in agreement with original expectation. The O 1s signal (Fig. 4c) shows two peaks at 532.0 eV and at 533.0 eV, corresponding to the C═O bond in chloride quinone and a C–O–C bond produced in the resin and catalyst reaction. The Cl 2p region (Fig. 4(d)) shows four distinct peaks: the Cl $2p_{1/2}$ main peak at 201.8 eV and its satellite at 198.4 eV, as well as the Cl $2p_{3/2}$ main peak at 200.2 eV and its satellite at 197.5 eV. Therefore, it is certain that most of the chloromethyl groups on the surface of the Merrifield resin were consumed in the reaction, as can be seen from the two minor satellite peaks belonging to free Cl^{-1} (198.4 eV and 197.5 eV). These results well confirmed the previous speculations. Furthermore, combining the elemental content and the resulting peak area, we confirmed the fact that a quinone relative resin was obtained, which was grafted to the surface of a support at a weight percentage of 32% approximately (for more details, see the ESI†).

Catalytic activity

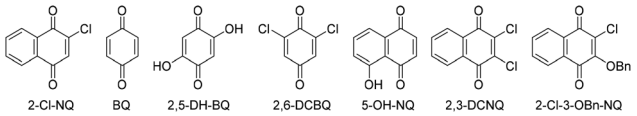
Initially, we investigated the synthesis of 2,4,6-triphenylpyridine (**3a**) using simple acetophenone (**1a**) and benzylamine (**2a**) in the presence of 10 mol% 2-chloro-1,4-naphthoquinone at 80 °C in MeOH (Table 1, entry 1), resulting in 45% product yield. Unfortunately, 1,4-benzoquinone exerted very poor efficiency towards **3a** (Table 1, entry 2). Compared with the unsubstituted benzoquinone (Scheme 2), catalysts containing hydroxyl groups and chlorine were able to achieve **3a** in yields of 25% and 38%, respectively (Table 1, entries 3 and 4 *versus* entry 2). Further experiments demonstrated that monosubstituted naphthoquinones tend to exhibit good catalytic performance in this reaction. It was worth noting that the yield of **3a** was up to 72% when taking 2-Cl-3-OB*n*-NQ as the catalyst, probably due to the co-effect of oxygen and chlorine in the *ortho* position of the carbonyl group in the naphthoquinone structure (Table 1, entry 7). Subsequently, with the loaded cata-

Table 1 Screening of reaction conditions[a]



Entry	Catalyst	Solvent	Ratio(**3a**/**3a′**/**3″**)	Yield(**3a**)[b] [%]
1	2-Cl-NQ	MeOH	96/4/0	45
2	BQ	MeOH	—	<5
3	2,5-DH-BQ	MeOH	—	25
4	2,6-DCBQ	MeOH	93/7/0	38
5	5-OH-NQ	MeOH	85/15/0	31
6	2,3-DCNQ	MeOH	—	20
7	2-Cl-3-OB*n*-NQ	MeOH	90/10/0	72
8	NQ-MR	MeOH	94/6/0	74
9	NQ-MR	MeCN	78/19/3	62
10	NQ-MR	DCE	—	23
11	NQ-MR	EtOH	100/0/0	78
12	NQ-MR	Toluene	87/13/0	66
13	NQ-MR	H_2O	—	7
14	—	EtOH	—	<5
15	NQ-MR	none	—	<5

[a] Reagents and conditions: **1a** (2.0 mmol), **2a** (1.5 mmol), catalyst (10 mol%), solvent (3.0 mL), 80 °C or reflux, air, 24 h, "—" = not determined; the ratio was determined by GC. [b] Yields of the isolated product.

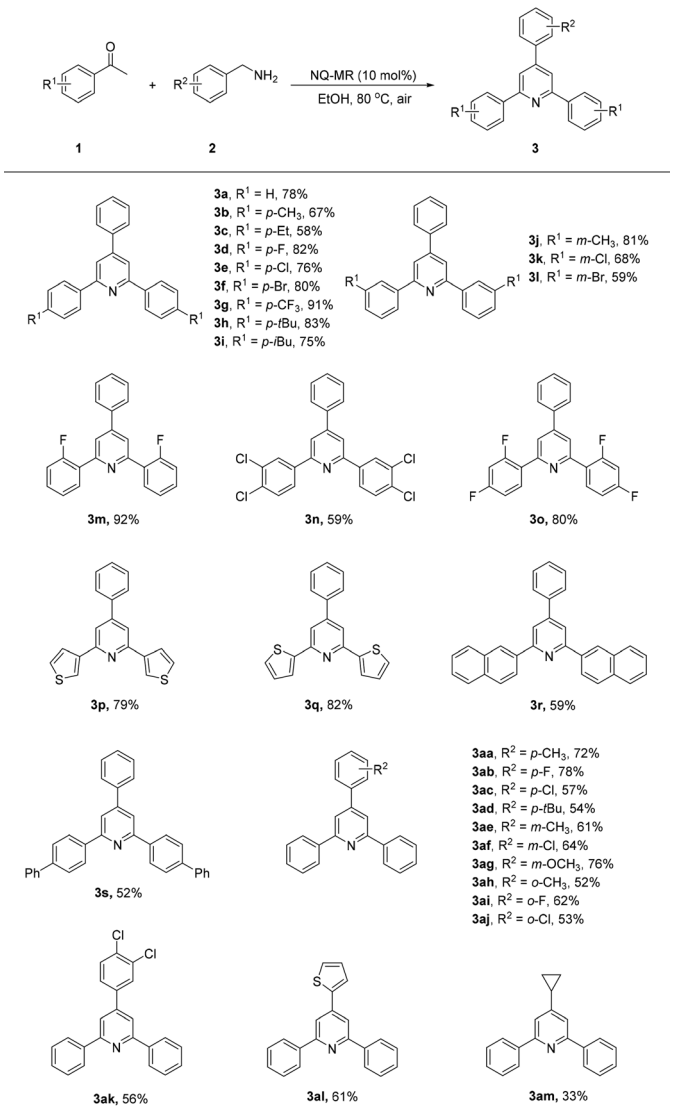


Scheme 2 Several benzoquinones and naphthoquinones.

lyst NQ-MR in hand, our efforts were focused on improving the catalytic efficiency of NQ-MR. To our delight, the supported quinone achieved relatively high yield in MeOH, under the same reaction conditions (Table 1, entry 8). Inspired by this result, solvent impacts on this system were taken into consideration and investigated next. Solvents including MeOH, MeCN, DCE, EtOH, toluene and water were tested as the reaction media specifically, and EtOH was found to be the best solvent for this reaction (Table 1, entries 8 to 13). Furthermore, at 80 °C in EtOH, no **3a** product was formed in the absence of a catalyst, suggesting that a catalyst was crucial to this reaction (Table 1, entry 14). It should be noted that the reaction could not take place under solvent-free conditions (entry 15).

Next, we studied the scope of this reaction with respect to different functional group components (Table 2). Different *para*- and *meta*-substituted acetophenones, containing electron-donating and electron-withdrawing groups, could be converted to the corresponding 2,4,6-triarylsubstituted symmetrical pyridines in 58–91% yields (**3a–3l**). In particular, the *ortho*-substituted aromatic ethyl ketone reacts only with 4-fluoroacetophenone (**3m**), possibly due to steric hindrance. Furthermore, 3,4-dichloro and 2,4-difluoro substituted aryl ketones yielded the desired products **3n** and **3o** in 59% and 80% yields. In addition, the use of the heterocyclic ethyl ketone, naphthalene ketone and biphenyl ketone can also promote the synthesis of symmetric pyridines (**3p–3s**). For amine substrates, both substitutions at the *para*- (**3aa–3ad**), *meta*- (**3ae–3ag**) and *ortho*- (**3ah–3aj**) positions were all well-tolerated. It was noteworthy that in the amine substrate part, polysubstituted benzylamine, heterocyclic methylamine and alkyl amine provided the corresponding products (**3ak**, **3al** and **3am**) under the reaction conditions. However, it was observed that only a mixture was obtained, when the reaction was set up with two different ketones in one reaction.

Table 2 Substrate expansion of reactions[a,b]



[a] Reagents and conditions: **1a** (2.0 mmol), **2a** (1.5 mmol), catalyst (10 mol%), EtOH (3.0 mL), 80 °C, air, 24 h. [b] Yields of the isolated product.

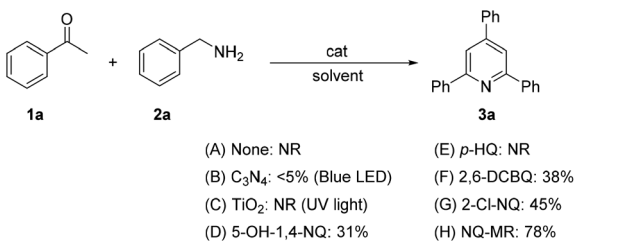
Mechanism exploration

Catalyst investigation

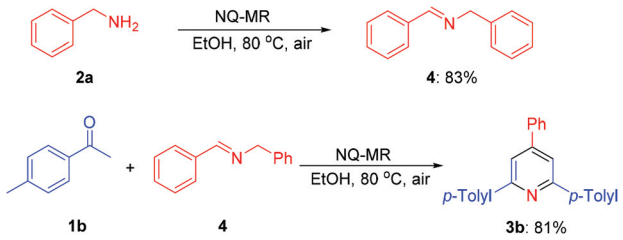
This metal-free and base-free catalytic system revealed high activity in the synthesis of 2,4,6-triphenylpyridine derivatives without photosensitizers and light. It was observed in the following control experiments that simple benzoquinones are ineffective in catalyzing this reaction and all kinds of naphthoquinones are only able to produce a low-to-moderate yield of 2,4,6-triphenylpyridine. A further control experiment revealed that the carrier Merrifield resin could not promote this reaction. Meanwhile, the blank experiment disclosed that the reaction could not take place without a catalyst (Scheme 3). When supported NQ-MR was applied to the synthesis with no photosensitizers or light implemented, a high catalytic activity was obtained as anticipated, most likely due to the synergistic effect of the 1,4-naphthoquinone and Merrifield resin.

Capture of intermediates

The detection, trapping, and even separation of key intermediates are considered as an efficient means to explore the possible pathway or the reaction mechanism. A control reaction of benzyl amine without acetophenone under NQ-MR conditions was conducted and the results showed an 83% yield for the



Scheme 3 The catalyst exploration experiments.



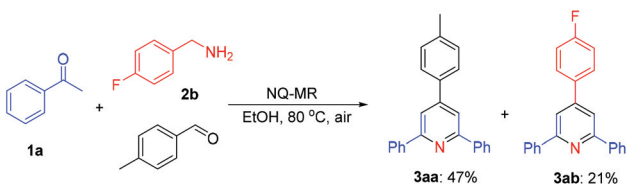
Scheme 4 The capture of intermediates.

N-benzyl-1-phenylmethanimine intermediate (**4**). Further investigation demonstrated that *p*-methyl-acetophenone (**1b**) could continue to react with *N*-benzyl-1-phenylmethanimine to produce **3b** in a slightly higher yield (81%). Therefore, *N*-benzyl-1-phenylmethanimine is believed to be the key reaction intermediate to understand the reaction mechanism (Scheme 4).

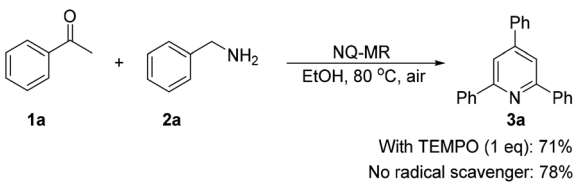
To gain insights into the reaction pathway, *p*-methylbenzaldehyde was selected as a partner to examine the reaction. The mixture of acetophenone (**1a**), *p*-fluoro-benzylamine (**2b**) and *p*-methylbenzaldehyde was stirred under the optimal conditions with NQ-MR as the catalyst. The results showed that both products **3aa** and **3ab** were obtained in 47% and 21% yields, respectively. This disclosed that an aldehyde was a possible intermediate during the synthesis of 2,4,6-triphenylpyridine derivatives (Scheme 5).

Further mechanism exploration was also performed using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1 eq.), a useful radical scavenger, to investigate the possibility of the radical process in this reaction (Scheme 6). The experimental results disclosed that TEMPO could not prevent the production of 2,4,6-triphenylpyridine **3a**, implying that the involvement of free-radical intermediates should be ruled out during this NQ-MR catalyzed reaction.

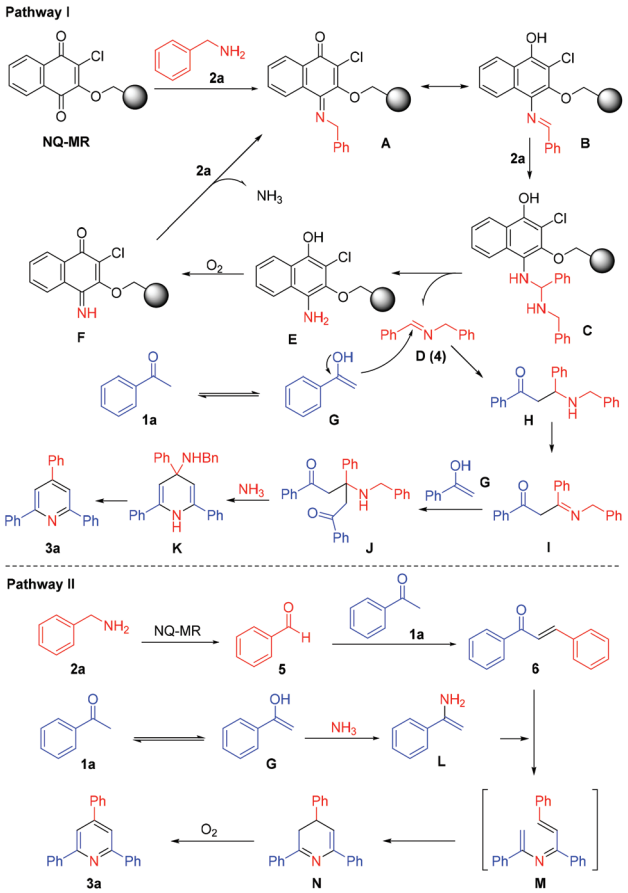
Based on the above explorations and previous references,[13a,b,d] we proposed two plausible reaction mechanisms for the synthesis of 2,4,6-triphenylpyridine derivatives, as shown in Scheme 7. The first step of pathway I was the condensation of benzyl amine (**2a**) with NQ-MR to generate intermediate **A**. After isomerization, imine **B** was attacked by another benzyl amine to produce **C**. Subsequently, intermediate **C** could easily release imine **D**, which underwent isomerization and gave again the first intermediate (**A**). Next, imine **D** reacted with enolate (**G**) to give compound **H**. After dehydrogenation, intermediate **I** successively reacted with enolate (**G**) and ammonia to form tetrahydropyridine (**K**), which underwent the second dehydrogenation to complete the reaction. For the second pathway, benzyl amine was easily converted into an aldehyde (**5**) under NQ-MR conditions. Next, the unsaturated ketone (**6**) was generated through the condensation of benzyl amine (**2a**) with acetophenone (**1a**). After isomerization, enolate (**G**) could react with ammonia to form enamine (**L**), which could attack the unsaturated ketone (**6**) to give intermediate **N**. After oxidation in air, the desired product (**3a**) was formed. In this methodology, *N*-benzyl-1-phenylmethanimine (**4**), benzaldehyde (**5**) and chalcon (**6**), which are the most important key intermediates, were all detected, indicating that two pathways were both possible (Scheme 7). These results were in line with previous results[13h] and supported by the literature.[13i]



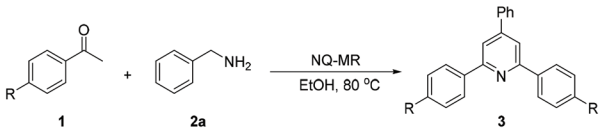
Scheme 5 Mechanism exploration experiments.



Scheme 6 Mechanism exploration experiments.



Scheme 7 The possible reaction mechanism.



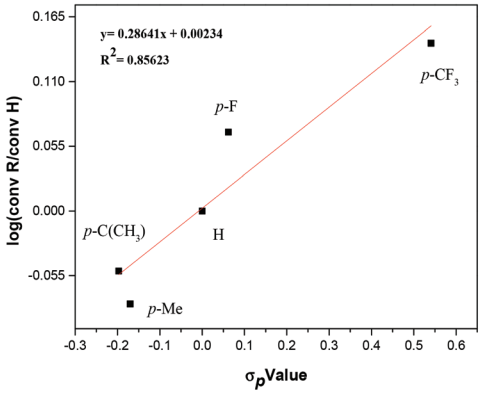
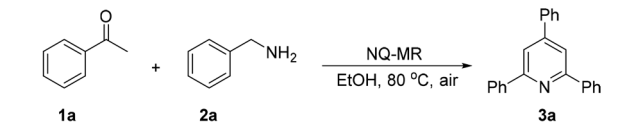


Fig. 5 Hammett plot of *para*-substituted ketones.

To gain more insights into the possible reaction mechanism, we employed the Hammett plot equation and used several typical starting materials to build the Hammett plot equation (Fig. 5). The results revealed that this reaction was greatly impacted by the electronic effect, and a negative charge on substrates might be favored during the supposed transition state.

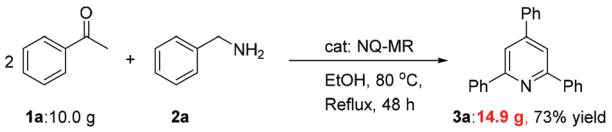
Reusability of the catalyst

In addition, the catalyst NG-MR was dealt and centrifuged several times with water, dried and recycled for reuse in the synthesis of 2,4,6-triphenylpyridine. We found that the reaction yield of **3a** gradually decreased with the number of cycles increased, despite the fact that good yield was still attainable even after five trials (Scheme 8). To better illustrate this NQ-MR catalyst, the hot filtration experiments were set up. The amount of the NQ-MR catalyst leaching into water for the coupling of acetophenone and benzylamine at 80 °C was detected by comparing the content of the carbonyl group before and after each reaction cycle. The results revealed that the amount of the carbonyl group leaching after the fifth run



Recycled times	0	1	2	3	4	5
Yields	78%	73%	72%	72%	71%	70%

Scheme 8 The recycle experiments for the synthesis of 2,4,6-triphenylpyridine with NQ-MR.



Scheme 9 The synthesis of 2,4,6-triphenylpyridine on a gram scale.

was 3.12% (w/w). Therefore, the results revealed that the leaching of NQ-MR was negligible, and NQ-MR showed good stability for the synthesis of 2,4,6-trisubstituted pyridines.

Finally, the gram-scale synthesis of 2,4,6-triphenylpyridine was carried out with NQ-MR as the catalyst. Over 10 g of desired pyridine derivative can be separated in 73% yield, suggesting that NQ-MR was a truly excellent catalyst for this transformation under mild conditions (Scheme 9).

4. Conclusions

In conclusion, we developed a class of novel heterogeneous chloride quinones, to be supported on the Merrifield resin as an efficient catalyst. It was thoroughly characterized by Fourier transform infrared spectroscopy (FT-IR), X-ray photoelectron spectrometry (XPS) and energy dispersive X-ray spectroscopy (EDX). This supported quinone catalyst exhibited good catalytic efficiency for the chemoselective synthesis of 2,4,6-trisubstituted pyridines under mild conditions. Compared with strong acid or metal catalysts, this NQ-MR system was a much greener and milder catalyst for the synthesis of 2,4,6-trisubstituted pyridines, which provided a new idea for organic catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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