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Ruthenium Nanoparticles Catalyzed Selective Reductive Amination of Imine with Aldehyde to Access Tertiary Amines

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Reductive amination is one of the most frequently used transformations in organic synthesis. Herein, by developing a novel ruthenium nanoparticles embedded within ordered mesoporous carbon catalyst (Ru-OMC) and a new hydrosilylation process for the synthesis of tertiary amines. We present a direct reductive amination of imines (C=N bond) with aldehydes (C=O bond) using hydrosilane as reducing reagent under mild conditions. Moreover, the Ru-OMC catalytst can be reused up to 14 runs without noticeable losing activities.

The development of synthetic strategies to access tertiary amines is of significant importance due to their widespread occurrence in natural products, agrochemicals, pharmaceuticals, and valuable fine chemicals¹. Pioneered by *N*-alkylation using alcohols or haloalkanes with amines², amine-carbonyl reductive amination³, or C-N cross coupling are simple methods for the synthesis and functionalization of tertiary amines⁴. Despite these significant achievement, the control of the degree of N-alkylation, the limitation of molecular diverse of tertiary amides still remains elusive and highly challenging. Importantly, reductive amination has become the sixth most frequently used transformation in medical chemistry from a recent analysis of drug candidate synthesis by three pharmaceutical companies⁵. Very recently, Doyle reported an efficient Ni-catalyzed reductive amination to access tertiary alkylamines with Ntrimethylsilyl amines.⁶ Within the mild conditions and good chemoselectivities, transition metal catalyzed reductive amination using hydrosilane as a suitable hydrogen donor has emerged as a competitive alternative method to access tertiary amines⁷, which compared to the classical hydrogenation⁸ and hydrogen transfer reactions9.

During the last few years, the amine synthesis *via* reductive amination of aldehydes with primary amines under hydrosilylation conditions has been developed by using some transition metal

catalysts¹⁰ (Scheme 1). However, these transformations always stopped in the first reductive amination step to formation of secondary amines, and the second reductive amination of aldehydes with secondary amines is always slower, this mainly because of the reaction difficulty on the steric effect and p- π conjugated effect between nitrogen atom and aromatic ring. Furthermore, compared to the reductive amination of secondary amines with carbonyl derivatives, the direct reductive amination of imine with carbonyl derivatives is a more "greener" process without amine pre-reduction step in the area of tertiary synthesis. We envisioned a new synthetic protocol to produce tertiary amines from the reaction of imines and aldehydes under hydrosilylation conditions (Scheme 1). Hence, to achieve selective generation of tertiary amine product, at least three challenging issues have to be solved: (1) There should be an compatible catalytic system able to perform two times hydrosilylation of imine or iminium. (2) This catalytic system ensure the reducing rate of C=N bond is much faster than reduction of C=O bond. (3) This catalytic system could also react with aromatic aldehydes which overcome the steric effect and p- π conjugated effect between nitrogen atom and aromatic ring, thus enrich the molecular diversities of tertiary amine products.



Scheme 1. Previous work and new synthetic protocol

Recently, heterogenous metal oxide nanocatalysts have attracted more and more attention on organic transformations, mainly because of their high stability, easy recyclability and different reaction pathway, such as hydrogenation or transfer hydrogenation

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of nitro compounds¹¹, selective reduction of *N*-heteroaromatics¹², oxidation of alcohols to esters¹³. Ordered mesoporous carbon (OMC) is a kind of mesoporous material¹⁴, with typical mesoporous structures like a 2-D hexagonal ordered structure. After introducing Ru, to some extent, parts of pore may be blocked by RuOx. However, the large amount of mesopore volume with high specific surface area still benefit for decreasing diffusion resistance and increasing mass transfer. The another advantage is that this material can be prepared with adjustable pore diameter by changing raw material ratio, which would offer a promising way in the field of organic synthesis. Herein, nanoparticles embedded within ordered mesoporous carbon catalyst (Ru-OMC), and demonstrate for the first application in catalytic reductive amination of imines and aldehydes to selective access tertiary amine derivatives using hydrosilane as the hydrogen source.

The new Ru-OMC catalyst was prepared using RuCl₃ as the ruthenium precursor and resorcinol formaldehyde resin precursor as the sources of carbon material. As depicted in Fig. 1, resorcinol formaldehyde resin precursor synthesized using soft template procedure. Next, the RuCl₃ was then added to this resorcinol formaldehyde resin precursor with 5 wt% Ru contents by impregnating method. Finally, the resulting composites were dried in an oven at 90 °C for 12 h and then carbonized at 1000 °C for 2 h under a N₂ atmosphere. Finally, the Ru-OMC catalysts were obtained after cooling down the materials to room temperature.



Fig. 1. Schematic illustration for the preparation of catalyst.

Fig.2 shows the SEM–EDS micrographs of surfaces of particle morphology of Ru-OMC materials after calcination. As shown in the Figure 2(a), the porous structure in the material, which has loose network micro structure, is still be obviously observed after the impregnation of Ru. The Ru nanoparticles were dispersed on the surface of OMC almost without aggregation. As seen in Fig.2(a)-(c), lots of ruthenium oxide composite crystallites distribute evidently inside or on the surface of the carbon matrix. The EDS mapping results shown in Fig. 2(d)-(f) confirm that C, O, and Ru elements are highly dispersed in Ru-OMC catalyst.



Fig. 2. SEM photograph and elemental mapping images of assynthesized Ru-OMC catalyst for C, O, and Fe with color superposition (C = red; O = green; and Ru = blue).



Fig. 3. XPS results of as-synthesized Ru-OMC catalysts.

X-ray photoelectron spectroscopy (XPS) was employed to investigate the oxidation state of Ru and the surface composition of the catalysts. The C 1s, O 1s and Ru 3d for Ru-OMC catalysts are shown in Fig.3, indicating the Ru-OMC catalyst was composed of C, O and Ru elements. Due to the strong overlap of the C 1s and Ru 3d peaks around 284.6 eV, it can be seen from Fig. 3a that the C 1s high-resolution spectrum, revealed a peak at 284.6 eV ascribed to the sp 2 RuC bond of pure carbon. The C 1s signal is deconvoluted into two distinguishable component peaks. The peak at about 284.6 eV is assigned to aromatic carbon and RuC while the peak at about 285.9 eV is assigned to single C-O bonds (hydroxyl group)¹⁵. The deconvolution of the O 1s spectra yielded the following three peaks: peak I (531.0 eV), metal oxides such as RuO₂; peak II (532.3 eV), carbonyl oxygen atoms in esters, anhydrides and oxygen atoms in hydroxyl groups; peak III (533.1 eV), non-carbonyl (ether-type) oxygen atoms in esters or aromatic ring. Fig. 3d shows the absorptions located at 284.6 eV for Ru 3d, revealing the Ru element that covered on the surface of Ru-OMC exists as metallic Ru¹⁶.

To test the catalytic efficiency of the prepared novel Ru-OMC material, we selected imine **1a** and benzaldehyde **2a** as the model substrates to evaluate different reaction parameters, such as solvents, silane and temperature. (Table 1) As shown in table 1, no

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GC-yield of tertiary amine 3a was detected in the absence of catalyst (table 1, entry 1). 27 % GC-yield of tertiary amine 3a was obtained by using 1 mol% of Ru-OMC catalyst, 1.5 equiv. of Ph₂SiH₂ as hydrogen source in CH₃CN at 80 $^{\circ}$ C for 16 h (Table 1, entry 2). Next, after tested different hydrosilanes under similar conditions for this reductive amination, PhSiH₃ as the best hydrosilane was found, and yielding tertiary amine 3a in 83% yield (table 1, entry 10), other hydrosilanes including Et₂SiH₂, TMDS (1,1,3,3-tetramethyldisiloxane), PMHS (polymethylhydroxysiloxane), PhMe₂SiH, Ph₂ClSiH, PhMeSiH₂, (MeO)₃SiH can not give the better results (Table 1, entries 3-9). However, when this reaction was performed in MeOH instead of CH₃CN at 40°C, almost complete conversion was reached and tertiary amine 3a was obtained in 82% isolated yield (Table 1, entries 13). By contrast, other solvents such as EtOAc, EtOH, DMC were disfavor for this reductive amination (Table 1, entries 11, 12, 14).

group containing imines afforded the desired tertiary amine products in higher yields (see **3a** and **3b**) than the electron-poor one (**3p** and **3q**). Moreover, the reaction also proceeded well with the heteroaromatic aldehydes, including thiophene-2-carbaldehyde, 2furaldehyde and 2-chloronicotinaldehyde leading to corresponding tertiary amines (**3k-3n**) in good yields. More importantly, the functional ester group on imine aryl ring could be tolerated, and the corresponding tertiary amine **3r** were directly obtained without the reduction of the carbonyl moiety. Additionally, the reaction of different imines containing thiophene, benzyl and alkyl groups with aldehydes were well performed and produce corresponding tertiary amines (**3s-3u**) in 64-80% yields. However, when using acetophenone instead of aldehyde react with imine, no desired tertiary amine was occurred. This indicated that the reductive amination of imine with ketone is more difficult than aldehydes.

Ru-OMC (5 wt%, 1 mol%)

Rz

Table 1. Optimization of the Ru-OMC catalyzed selective reductive					
amination of benzaldehyde and imine 1a ^[a]					

Ĉ	N	осн ₃ о +	Ru-OMC (5 wt%, 1 mol%)	N CCH3
Ť		~	Solvent (2 mL),	\bigvee
	1a	2a	80 °C, 16 h	3a
	Entry	Solvent	Silane	GC-yield. (%)
	1	CH_3CN	Ph_2SiH_2	
	2	CH_3CN	Ph ₂ SiH ₂	27
	3	CH ₃ CN	Et_2SiH_2	24
	4	CH₃CN	TMDS	
	5	CH ₃ CN	PMHS	6
	6	CH₃CN	PhMe₂SiH	12
	7	CH_3CN	Ph ₂ ClSiH	60
	8	CH₃CN	PhMeSiH ₂	63
	9	CH₃CN	(MeO)₃SiH	
	10	CH₃CN	PhSiH ₃	83
	11	EtOAc	PhSiH ₃	60
	12	EtOH	PhSiH ₃	61 ^[b]
	13	MeOH	PhSiH ₃	96 ^[b] (82 ^[c])
_	14	DMC	PhSiH ₃	

[a] imine **1a** (0.5 mmol), benzaldehyde **2a** (0.75 mmol), Ru-OMC catalyst (5 wt%, 1 mol%), Silane (1.5 equiv.), Solvent (2 mL), at 80° C for 16 h. [b] at 40 °C. [c] Isolated yield of **3a**.

Within the optimal conditions (table 1, entry 13), the scope and limitations of this first Ru-OMC catalyzed reductive amination of imines 1 with aldehydes 2 were then explored. Various imines 1 and aldehydes 2 were applied to synthesize tertiary amines 3, and the results were shown in scheme 2. As shown in scheme 2, different aromatic and alkyl aldehydes 2 were reacted with imines 1a or 1b to successfully produce tertiary amines 3a-3j in 45-86% isolated yields. Notably, no dehalogenation occurred during the reductive amination process. It is noteworthy that the electron-donating



lmine (0.5 mmol), aldehyde (0.75 mmol), Ru-OMC (5 wt%, 1 mol%), PhSiH_3 (1.5 equiv.), CH_3OH (2 mL), at 40 $^\circ$ C, under air for 16 h.

Scheme 2. Ru-OMC catalyzed reductive amination of imines with aldehydes.

Further, we examined the stability and reusability for our developed new Ru-OMC catalyst with the reaction of imine **1a** and benzaldehyde **2a** under the reductive amination conditions. The results listed in Fig. 4, and shown the catalytic system could be reused up to 14 runs while retaining the catalytic activity, without substantially decrease of the yield. However, after 14 times consecutive experiments, the surface of RuOx particles appeared some matters, which was corresponding with the surface scaling formation. Morphological information of the used Ru-OMC catalyst catalyst shows that the active RuOx component could not uniformly disperse on the surfaces of Ru-OMC catalyst. (see in Figure S1).

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Conclusions

In summary, we have developed a novel ruthenium nanoparticles embedded within ordered mesoporous carbon catalyst, and demonstrated a direct reductive amination to produce tertiary amines of imines with aldehydes under hydrosilylation conditions for the first time. Many functional groups, such as halides, ester, furan, thiophene are tolerated under this reductive amination. Moreover, the Ru-OMC catalytst can be easily separated and recovered from the reaction mixture by filtration and reuse up to 14 runs without noticeable losing activities. Further development of metal-OMC nanocatalysts and exploitation of their applications in selective hydrosilylation systems are currently underway.

Conflicts of interest

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There are no conflicts to declare.

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