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Journal Name

COMMUNICATION

Reductive N-methylation of Quinolines with Paraformaldehyde and H_2 for Sustainable Synthesis of N-methyl Tetrahydroquinolines

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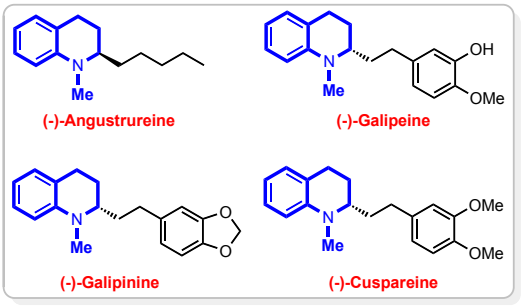
A new and straightforward method was developed for the synthesis of N-methyl-1,2,3,4-tetrahydroquinolines by one-pot reductive N-methylation of quinolines with paraformaldehyde and H_2 over Pd/C catalyst. A series of functional MTHQs, including (±)-Galipinine and (±)-Angustrureine were successfully synthesized in good to excellent yields by applying this simple catalyst system.

1,2,3,4-Tetrahydroquinolines (THQs) derivatives are valuable backbones in natural alkaloids and are widely utilized in fine chemicals, pharmaceuticals, agrochemicals, dyes, fragrances, and hydrogen-storage materials.[1,2] Among these, the N-methyl substituted ones are especially attractive and powerful motifs of biologically active molecules and pharmaceuticals because the incorporation of methyl group into molecules is of significant importance to regulate their biological and pharmaceutical activities.[3,4] For example, N-methyltetrahydroquinoline (MTHQ) motif is observable in many natural alkaloids such as angustureine, galipeine, galipinine and cuspareine, which displayed excellent antiplasmodial and cytotoxic activity (Scheme 1).[5-8]



Scheme 1 Several examples of pharmaceuticals containing a MTHQ motif.

Due to their significance, extensive efforts have been paid to develop effective synthetic methodologies for the preparation of MTHQs over the past few decades. Traditionally, THQs are usually employed as starting materials for the synthesis of MTHQs with a variety of methylating agents, such as MeX, CO_2,[9-14] dimethylcarbonate (DMC),[15,16] HCOOH,[17,18] HCHO,[19] and others.[20] Although a number of above methods have been established, there is still room for the development of facile, straightforward procedures toward MTHQs.

It is well-known that the reduction of quinolines is one of the most commonly used approaches to synthesize THQs.[2, 21] Thus, direct N-methylation of readily available quinolines offers a straightforward and promising approach to access MTHQs in term of its simplicity and high step efficiency. To date, however, only a few catalytic systems dealing with N-methylation of quinolones have been reported. In 2009, Perumal and co-workers demonstrated that reaction of quinoline and CH_3I with Hantzsch dihydropyridine ester could be used for the synthesis of MTHQs.[22] Recently, Han and co-workers developed a nice method for the N-methylation of quinolines with CO_2/H_2 as methylating agent using a homogeneous Ru/triphos catalyst system.[23] Compared with the homogeneous catalysts, heterogeneous counterparts can be more facilely separated and recycled. Till now, only one example of N-methylation of quinoline with methanol was reported using zinc as a reductant in the presence of Pd/C catalyst at 150 °C.[24] However, the employment of zinc as a reductant and rigorous reaction conditions significantly reduced the appeal of this method in industrial applications. Therefore, the development of straightforward, facile, cost-effective heterogeneous catalyst system for the N-methylation of quinolines under mild conditions is highly demanded. Herein, we describe the first examples of N-methylation of quinolines with paraformaldehyde and H_2 in the presence of a simple Pd/C catalyst (Scheme 2). Two main steps were involved in the reaction. The first step is the catalytic hydrogenation of quinoline to THQ, and the second step is the reductive N-methylation of THQ to N-methyl MTHQ.[25] The Pd/C catalyst is

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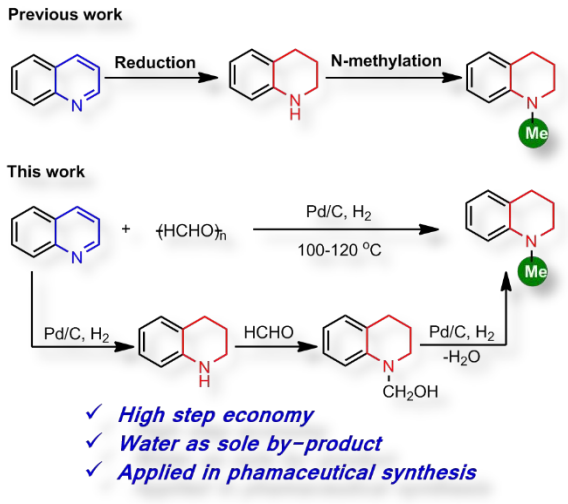
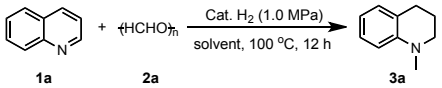
crucial to realize the whole reaction. The one-pot reductive N-methylation of quinolines avoids the synthesis of THQ, so it is simpler and more economic.



Scheme 2 Reductive N-methylation of quinolines to MTHQs.

We began our exploration with reductive N-methylation of quinoline with paraformaldehyde and H_2 as the model reaction (Table 1). The catalysts used here were prepared by a deposition–precipitation method and followed by reduction with hydrazine hydrate solution. Prompted by our reductive N-monomethylation of nitroarene and formaldehyde using Pd/TiO_2 as catalyst,[26] the reductive N-methylation reaction was initially investigated with quinoline and the paraformaldehyde in the presence of 40 mg 2 wt% Pd/TiO_2 under 1.0 MPa H_2 in 1,4-dioxane at 100 °C. To our delight, 52% conversion with 41% yield for N-methyl-1,2,3,4-tetrahydroquinoline was obtained (entry 1). The influence of the solvent on the reactivity and selectivity of this reaction was further evaluated (entries 2–4). It was discovered that EA was the optimal choice and much higher conversion (89%) of quinoline and 85% yield to N-methyltetrahydroquinoline were obtained when EA was used as the solvent. Following, the catalytic performance of nano-Pd catalysts with different supports was tested (entries 5–7). Clearly, Pd/C exhibits the best catalytic performance, achieving 99% conversion with 97% yield towards the desired product. (entry 5). The excellent performance of this catalyst might be attributed to the π-π interaction between π electron of active carbon and aromatic ring of quinolone.[27,28] If other catalysts including $Pd/\gamma\text{-}Al_2O_3$, and Pd/SiO_2 were employed, lower conversion or no conversion of quinoline was observed. Interestingly, 99% conversion with 98% yield to methylated product was still observed if reducing the H_2 pressure to 0.4 MPa, affording the desired product in 89% isolated yield (entry 9). However, conversion decreased from 99% to 82% if further reducing of the H_2 pressure to 0.2 MPa (entry 10). Furthermore, reducing the reaction time led to a lower conversion and yield to desired product (entry 11). Notably, this catalyst is easily recoverable by simple filtration, and it can be reused directly without further treatment. To our delight, a 99% conversion of quinoline with 96% yield for N-methyltetrahydroquinoline was maintained when it was used at the 3rd run (entry 9). Thus, this catalyst exhibits nice reusability. Meanwhile, the Pd loadings of Pd/C before and after recycling were tested by ICP-AES. The results suggested that the Pd loadings decreased from 2.46 wt% to 2.38 wt% after the 1st run, then it maintained stable after the 2rd run (2.12 wt%, Table S1).

Table 1 Reaction condition optimization for reductive N-methylation of quinoline with $HCHO/H_2$[a]



1a 2a 3a

Entry	Cat.	Solvent	Conv.[b](%)	Yield (%)
1	Pd/TiO_2	1,4-dioxane	52	41
2	Pd/TiO_2	toluene	55	43
3	Pd/TiO_2	MeOH	43	34
4	Pd/TiO_2	EA	89	85
5	Pd/C	EA	99	97
6	$Pd/\gamma\text{-}Al_2O_3$	EA	80	69
7	Pd/SiO_2	EA	n.r.	--
8[c]	Pd/C	EA	99	98
9[d]	**Pd/C**	**EA**	**99(99)[e]**	**98(96)[e]**
10[f]	Pd/C	EA	82	69
11[g]	Pd/C	EA	87	77

[a] Reaction conditions: quinoline 1a (1.0 mmol), paraformaldehyde 2a (1.2 mmol), catalyst (40 mg), H_2 (1.0 Mpa), solvent (4.0 mL), 100 °C, 12 h. [b] Determined by GC-FID using biphenyl as the internal standard material. [c] H_2 (0.7 MPa). [d] H_2 (0.4 MPa). [e] The catalyst was recovered and reused at the 3rd run. [f] (0.2 MPa). [g] 9 h.

The supported Pd catalysts were characterized by XPS, XRD, TEM and N_2 adsorption–desorption instruments to reveal their structures. Firstly, the XPS studies of the catalysts were performed to determine the chemical state of Pd nanoparticles. As shown in Fig. 1a and Fig. S1, weak peaks of Pd $3d_{5/2}$ were found in Pd/TiO_2, Pd/Al_2O_3, and Pd/SiO_2 but not observable in fresh Pd/C, which might be attributed to the low Pd content on the catalyst surface. The Pd $3d_{5/2}$ signals of Pd/TiO_2, Pd/Al_2O_3, and Pd/SiO_2 appeared at 335.0, 335.3, and 335.9 eV, respectively. These results suggested that metallic Pd was mainly formed on the surface of Pd/TiO_2, Pd/Al_2O_3, and Pd/SiO_2. Besides, the N1s spectra at 400.1 eV and the Pd $3d_{5/2}$ signals at 336.3 eV, which were usually assigned to N-coordinated metallic Pd,[29] can be observed after recycling of the Pd/C catalyst (Fig. S1-2). Therefore, we speculated that the N-coordinated Pd might be the active species in-situ generated during the reaction.

Moreover, the XRD patterns of the catalysts are shown in Fig. 2b and Fig. S3. The Pd/C and Pd/SiO_2 catalyst shows diffraction peaks at 40.1°, 46.7°, 68.1°, and 82.1°, which can be ascribed to the diffraction peaks of Pd(111), Pd(200), Pd(220), Pd(311). However, neither palladium oxide nor metallic palladium diffraction pattern was detectable in Pd/TiO_2 and $Pd/\gamma\text{-}Al_2O_3$ catalysts (Fig. S3). So, the Pd species in these catalysts were amorphous or highly dispersed. Compared with fresh Pd/C, the intensity of the diffraction peaks of reused samples increases somewhat, indicating a slight increase in the crystalline order.

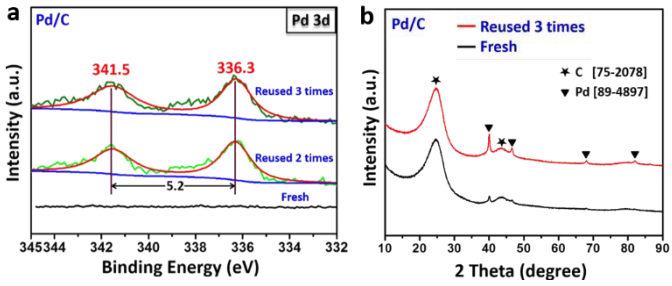


Fig. 1 XPS spectra of fresh and reused Pd/C (a). XRD patterns of fresh and reused Pd/C (b).

TEM and HAADF-STEM images of Pd/C before and after being used for 3 times, and their corresponding particle size distributions are shown in Fig. 2. The TEM and HAADF-STEM results revealed that the Pd nanoparticles are homogeneously dispersed on carbon surface and possess an average diameter of 1.0–2.5 nm and 1.0-3.0 nm in fresh and used Pd/C, respectively. The slight increase in nanoparticle size does not influence the catalytic performance remarkably. Compared with Pd/C, much bigger Pd nanoparticles were found on SiO_2 (Fig. S4). The poor activity of Pd/SiO_2 might be attributed to the bigger Pd nanoparticle size, and more importantly, the weak interaction between nan-Pd and the SiO_2. The N_2 adsorption–desorption tests (Fig. S5) showed that the BET surface areas of the Pd/C, Pd/TiO_2, Pd/γ-Al_2O_3, and Pd/SiO_2 were 198.49, 59.16, 146.66, 270.95 $m^2\ g^{-1}$, respectively. Based on the FT-IR analysis and Boehm titration results, lactone group, which is 0.62 mmol/g, and carboxylic group, which is 0.27 mmol/g, were detectable on the carbon surface (Fig. S6).

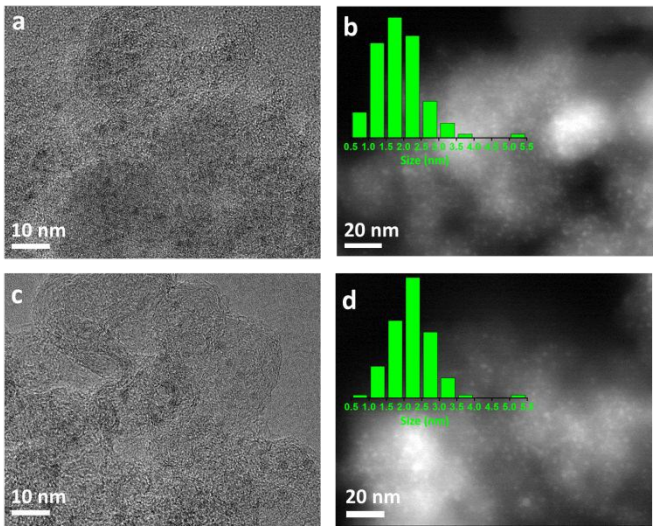
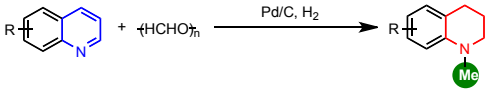
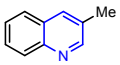
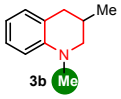
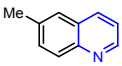
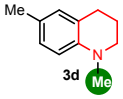
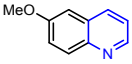
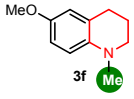
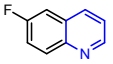
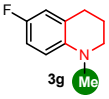
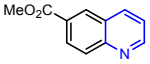
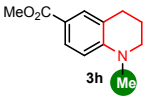
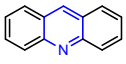
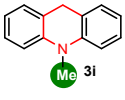
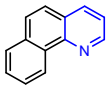
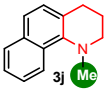


Fig.2 TEM (a, c) and HAADF-STEM (b, d) images of the fresh Pd/C (a, b), reused Pd/C (c, d).

With these optimized conditions in hand, we proceeded to examine the substrate scope of the Pd/C catalyst for the reductive N-methylation reaction. As shown in Table 2, the quinolines with both electron-withdrawing and electron-donating groups on the phenyl ring were well tolerated under the current conditions. Importantly, the catalyst could be reused for this reaction for at least three catalytic cycles producing the desired product in 88% yield (**3a**). Reductive N-methylation of electron rich methyl- and methoxy substituted quinolines proceeded smoothly to provide the corresponding products in 72-84% yields (**3b**–**3f**). Electron-deficient nitroarenes bearing fluoride and ester groups also proceeded well, affording their corresponding products in 82% and 77% yields, respectively (**3g**–**3h**). In addition, the fused-ring acridine was also successfully converted to the corresponding N-methylated product in 81% yield (**3i**). Gratifyingly, benzoquinoline led to the corresponding product in decent yield, too (**3j**). Only 8% GC yield of N-methylpiperidine was observed when pyridine was used as substrate. Therefore, this catalyst can not be applied in the reductive N-methylation of pyridine.

Table 2 Results of the N-monomethylation of quinolines[a]



Entry	Substrates	Products	Yield[b] (%)
1		 **3a**	89 (88%)[c]
2[d]		 **3b**	72
3[e]		 **3c**	84
4		 **3d**	75
5[d]		 **3e**	81
6		 **3f**	80
7		 **3g**	82
8		 **3h**	77
9		 **3i**	81
10[e]		 **3j**	68

[a] Quinolines (1.0 mmol), paraformaldehyde (1.2 mmol), Pd/C (40 mg), H_2 (0.4 MPa), Ethyl acetate (4.0 mL), 100 °C, 12 h. [b] Isolated yields. [c] Catalyst was recovered and reused at the third run. [d] H_2 (0.4 MPa), 120 °C. [e] Pd/C (80 mg), H_2 (0.4 MPa), 120 °C, 24 h.

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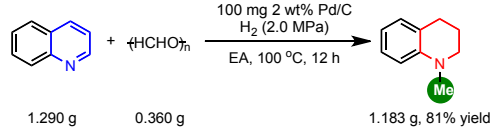
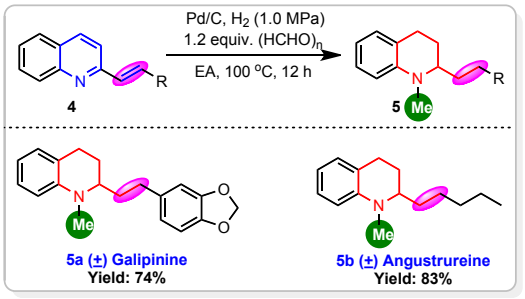
In addition, this reaction was easily performed with a gram-scale and N-methyl tetrahydroquinoline was obtained in 81% yield when 10 mmol (1.290 g) quinoline was used as the starting material (Scheme 3). This result demonstrates the scalability of this reaction.



Scheme 3 The scaled-up reaction for synthesis of N-methyl tetrahydroquinoline

To demonstrate synthetic application, a concise and efficient synthesis of tetrahydroquinoline alkaloids (±)-Galipinine and (±)-Angustrureine was developed (Scheme 4). One-pot reductive N-methylation of 2-alkenylquinoline derivatives **4**[30] proceeded smoothly to produce the (±)-Galipinine and (±)-Angustrureine in 74% and 83% yields, respectively.



Scheme 4 Synthesis of THQ alkaloids (±)-Galipinine and (±)-Angustrureine

In conclusion, we have developed first example of Pd/C catalyzed one-pot reductive N-methylation of quinolines with paraformaldehyde and H_2, providing facile access to N-methyl-1,2,3,4-tetrahydroquinolines in good to excellent yields. This work offers a straightforward, step economic, and clean methodology for the synthesis of MTHQs. Furthermore, the synthetic utility of this reaction is specifically demonstrated by successful synthesis of (±)-Galipinine and (±)-Angustrureine.

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Conflicts of interest

There are no conflicts to declare.

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