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***N*-Methylation of amine and nitro compounds with CO₂/H₂ catalyzed by Pd/CuZrO_x under mild reaction conditions†**

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An active Pd/ZrCuO_x catalyst was prepared for the reductive amination of CO₂. The *N*-methylation of amines and nitro compounds with CO₂/H₂ can be realized with up to 97% yield under relatively mild reaction conditions. *N*-Formylation becomes the main reaction if the reaction was performed under milder conditions or using Pd/ZnZrO_x as the catalyst.

With depleting fossil resources, carbon recycling is becoming an essential operation for realizing sustainable chemistry, in which the utilization of CO₂ for highly valuable chemical synthesis is one of the key steps.¹ However, the application of CO₂ as feed stock in chemical industry is severely retarded because of the low energy of its molecule. Therefore, classical transformations regarding CO₂ normally involve high-energy molecules such as epoxide, aziridine, alkyne and others, as starting materials.² To extend the application of CO₂, various processes have been explored; CO₂ is commonly used as a carbonyl source for the synthesis of carboxylic acid, ester, lactone, *N*-substituted urea, carbamate, methanol, hydrocarbons and polymers.³

N-Functionalized amines, such as *N*-methyl amines and formamides, represent important intermediates for the synthesis of dyes, perfumes, pesticides and others.⁴ In industry, *N*-methyl amines are usually synthesized by the reaction of amines with methanol or formaldehyde, and formamides are produced by the reaction of amine with CO in several million tonnes.⁴ Alternatively, CO₂ can be used as the carbon source for *N*-formylation and *N*-methylation reactions. At the beginning, the synthesis of *N,N*-dimethyl formamide using CO₂/H₂ as a carbonyl source was realized.⁵ Then, *N*-formylation reactions of amines with different structures were reported with CO₂ using silanols or H₂ as reducing agents in the presence of homogeneous catalysts.^{3i,6} The *N*-methylation reactions

were also reported and excellent results were obtained with homogeneous Ru catalysts.⁷ Recently, the *N*-formylation and *N*-methylation reactions were realized with heterogeneous catalysts in our groups catalyzed by Pd/Al₂O₃-NR and CuAlO_x, respectively.⁸ However, the reaction conditions of the *N*-methylation reaction using CO₂/H₂ as the methyl source were still very harsh (2.5 MPa CO₂ and 6 MPa H₂). The controllable preparation of active heterogeneous catalysts for the CO₂ amination reactions under mild conditions is highly desirable.

As revealed in previous publications, *N*-alkyl formamide might be an intermediate in the synthesis of *N*-methyl amine, which can be obtained *via* further hydrogenation of *N*-alkyl formamide.^{7,8} If this mechanism is correct, the catalyst for *N*-alkyl formamide synthesis should be less active for the hydrogenation of carbonyl compound, whereas a catalyst with suitable activity for the hydrogenation of carbonyl group to methyl group should be prepared for the synthesis of *N*-methyl amine. However, there is still limited research on the variation between the synthesis of *N*-alkyl formamide and *N*-methyl amine with CO₂ as the carbon source. In the synthesis of methanol from CO₂ using H₂, Cu was often selected as a key species in the preparation of multi-metal oxides.^{3b,9} In addition, ZrO₂, ZnO and other transitional metals were proven to be effective co-catalysts for the selective synthesis of methanol.^{3a,10} Therefore, the preparation of active catalysts for *N*-methyl or *N*-formamide synthesis by combining Cu oxide and other transitional metal oxides can be a potential option. As revealed in our previous work, Pd is a potentially active component for these transformations.^{3a} Thus, to develop active heterogeneous *N*-methyl or *N*-formamide synthesis catalysts *via* CO₂ recycling, the supported nano-Pd catalyst can be used for realizing CO₂ activation under mild conditions. Based on our continuous study on the amine functionalization reactions, here we present our new results regarding the preparation of active heterogeneous catalysts by varying the composition of metal oxide supports for the syntheses of *N*-methyl amine or *N*-formamide using CO₂/H₂ as the methyl and carbonyl sources (Fig. 1).

As discussed previously, Cu and Zr are potential components for the synthesis of methanol from CO₂/H₂ under relatively mild reaction conditions, *i.e.* 1 MPa CO₂ and 2.5 MPa H₂. Thus, the exploration

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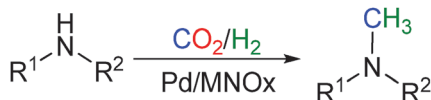


Fig. 1 *N*-Methylation of amine with CO₂/H₂.

started with Pd/CuO_x and Pd/ZrO_x using **1a** as the starting material. However, the major product was **1c** instead of **1b** (Table S1, entries 1 and 2). Thus, we tried to improve catalytic performance by combining other metal oxides with Cu or Zr. First, the addition of Al, Zr, Zn, Fe, Mg and Ni elements into Pd/CuO_x catalyst was tried. Clearly, the addition of a second transition metal influenced the catalytic performance remarkably (entries 3–7). The combination of Cu and Zr generated an active catalyst, and both the conversion and selectivity were improved significantly using Pd/CuZrO_x as the catalyst, in which the conversion of **1a** was 95% with an 86% yield to **1b**. Unfortunately, the introduction of other metal oxides, such as ZnO_x, FeO_x, MgO_x and NiO_x, resulted in lower activity. Product distribution could be tuned efficiently if AlO_x, ZnO_x or NiO_x was added into the Pd/ZrO_x catalyst (entries 8–10). The major product using these catalysts was **1c**. Therefore, Pd/CuZrO_x was a suitable catalyst for amine *N*-methylation with CO₂/H₂. Other noble metals, including Pt, Rh and Ru, were also supported on CuZrO_x, and the *N*-methylation product was major if Pt/CuZrO_x was used as a catalyst. However, it is less active than Pd/CuZrO_x, while lower activity was observed by applying Rh or Rh/CuZrO_x as catalysts (entries 12–14). The variation of palladium loadings was also screened. A similar result was obtained with 4 wt% Pd/CuZrO_x as catalyst, but lower yields were detected with 0.5 or 1 wt% Pd/CuZrO_x (entries 15–17). If using CuZrO_x as catalyst, 85% conversion of **1a** was obtained but the ratio of **1b** to **1c** was about 1 to 1. Finally, the reusability of the catalyst was tested, and an 81% yield to **1b** was maintained at the third run (entry 4). Thus, this catalyst is relatively stable under the reaction conditions.

Next, the typical catalysts were characterized by XPS, XRD, BET, ICP-AES and TEM. The XPS spectra of Pd_{3d} suggested a significant difference in surface Pd on the catalysts Pd/CuO_x, Pd/ZrO_x and Pd/CuZrO_x, although metallic palladium formed on all the catalyst surfaces with a binding energy of 333.4 eV (Fig. S1, ESI[†]). Both Cu and Zr were in the oxide state with binding energies of 933.6 and 182.3 eV. Strangely, almost no palladium species can be observed on the surface of Pd/CuO_x, which implies that almost all of the palladium species were encapsulated inside the bulk catalyst. In contrast, palladium species were enriched on the surface of Pd/ZrO_x, in which the molar ratio of Pd to Zr was 1:2.3. On the surface of the catalyst Pd/CuZrO_x, the ratio of Pd to Cu and Zr was 1:1.7:2.1. Simultaneously, catalyst Pd/CuZrO_x possessed a good mesoporous structure with an average pore diameter of 10.2 nm and a relatively high BET surface area of 89.3 m² g⁻¹ (Fig. S2, ESI[†]). The BET surface area of Pd/CuO_x was only 1.2 m² g⁻¹ without mesopore formation (Table S2, ESI[†]). For Pd/ZrO_x, although a mesoporous structure with an average pore diameter of 3.5 nm was formed, its surface area was only 25.7 m² g⁻¹ (Table S1 and Fig. S3, ESI[†]). Thus, high surface area and mesoporous structure might be other factors for the high catalytic activity of Pd/CuZrO_x. The catalysts were also characterized by XRD, which suggested that the catalysts Pd/CuO_x, Pd/ZrO_x

and Pd/CuZrO_x were all amorphous (Fig. S4, ESI[†]). ICP-AES analysis showed that Pd loadings in these typical catalysts were 1.8, 2.0 and 1.9 wt%. From the TEM and HAADF images of these catalysts, it is difficult to observe nano-Pd particles, although the crystal lattices of CuO and ZrO₂ can be observed clearly (Fig. S5, ESI[†]). By considering the XRD diffraction patterns of the catalysts, we can expect that palladium particles were highly dispersed in the bulk catalyst or on the catalyst surface. Except for the specific structure of Pd/CuZrO_x, the combination of Pd, Cu and Zr might be important for high activity, *i.e.* the presence of ZrO_x should favour the adsorption of carbon dioxide to the catalyst surface. In addition, the incorporation of Cu is helpful to retain the lower oxidation state of Pd and can promote the preferential hydrogenation of the carbonyl group in *N*-formamide.^{3b,9}

Next, the generality of Pd/CuZrO_x in the *N*-methylation of other amines were studied with the *N*-methylation of secondary amines (Table 1). The *N*-methylation of **1a** can be realized smoothly with

Table 1 *N*-Methylation of secondary amines with CO₂/H₂^a































Entry	Substrates	Products	Yields ^b /%
1	1a	1b	97
2	2a	2b	93
3	3a	3b	97
4	4a	4b	91
5	5a	5b	87
6	6a	6b	93
7	7a	7b	95
8	8a	8b	71
9	9a	9b	83 ^c
10	10a	10b	76 ^c
11	11a	11b	74 ^c
12	12a	12b	94

^a Reaction conditions: 1.0 mmol amine, 40 mg 2 wt% Pd/CuZrO_x (0.75 mol% Pd to amine), 2 mL octane, 1.0 MPa CO₂, 2.5 MPa H₂, 150 °C, 30 h.

^b The yields were determined by GC-FID using biphenyl as an external standard material. ^c Isolated yields.

97% yield to **1b** by extending the reaction time to 30 h (entry 1). For the cyclic secondary amines, including **2a–7a**, the *N*-methylation products, *i.e.* **2b–7b**, can be synthesized with 87–97% yields (entries 2–8). The presence of an aromatic ring did not influence the activity of the cyclic secondary amine. 71%, 83% and 76% isolated yields to **8b**, **9b** and **10b** can be obtained when using **8a**, **9a**

Table 2 *N*-Methylation of primary amine and nitrobenzene with CO₂/H₂^a

Entry	Substrates	Products	Yields ^b /%
1	 13a	 13b	75
2	 14a	 14b	73 ^c
3	 15a	 15b	75
4	 16a	 16b	67
5	 17a	 17b	73
6	 18a	 18b	49
7	 19a	 19b	79 ^c
8	 20a	 20b	57
9	 21a	 21b	54 ^c
10	 22a	 22b	48
11 ^d	 23a	 23b	68 ^c
12	 24a	 24b	70
13	 25a	 25b	69
14	 26a	 26b	67
15	 27a	 27b	75 ^c

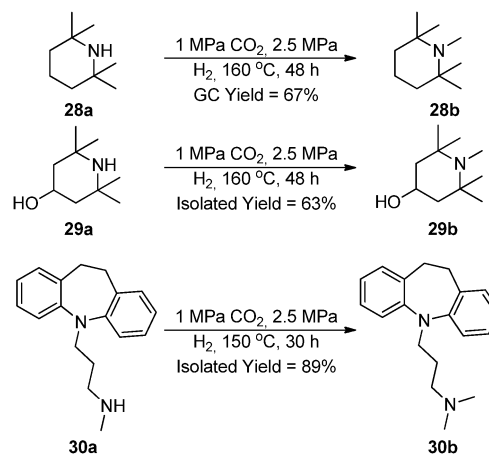
^a Reaction conditions: 1.0 mmol amine, 40 mg 2 wt% Pd/CuZrO_x (0.75 mol% Pd to amine), 2 mL octane, 1.0 MPa CO₂, 2.5 MPa H₂, 150 °C, 30 h. ^b The yields were obtained by GC-FID using biphenyl as external standard material. ^c Isolated yields. ^d 48 h.

and **10a** as starting materials (entries 9 and 10), respectively. Good yield was also obtained when an aliphatic secondary amine **11a** was employed with 74% yield to **11b** (entry 11). Finally, *N,N'*-dimethylation reaction of **12a** can progress well with 94% yield to the desired product (entry 12). Thus, the Pd/CuZrO_x catalyst exhibits excellent generality in the *N*-methylation reactions of secondary amines.

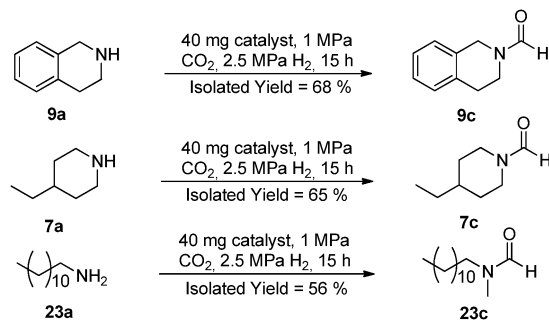
The *N*-methylation reactions of primary amines and nitro compounds were then explored (Table 2). For primary aromatic amines containing various functional groups, *i.e.* **14a–21a**, the *N*-methylation products can be obtained selectively with up to 79% isolated yields (entries 1–8). For aliphatic amines, such as benzyl amine, *p*-Me-benzyl amine and dodecylamine, *N,N*-dimethylation occurred and good to moderate yields were obtained (entries 9–11). Note that the reductive amination of CO₂/H₂ can be carried out with nitro compounds with up to 75% isolated yields (entries 12–15). Thus, Pd/CuZrO_x can be used in the *N*-methylation reactions of aromatic amine, secondary amine and nitro compounds with CO₂/H₂ and *N,N*-dimethylation of primary amines under relatively mild reaction conditions.

Interestingly, Pd/CuZrO_x was observed to be very active in the synthesis of some unique functional N-containing compounds (Scheme 1). For example, pempidine, which is a ganglion-blocking drug, can be synthesized efficiently through the *N*-methylation of **28a** with 67% yield. Simultaneously, the typical hindered amine light stabilizer, *i.e.* 1,2,2,6,6-pentamethyl-4-piperidinol, can be synthesized by the *N*-methylation of **29a**. However, a higher temperature is required because of the higher resistance of starting materials. It is noteworthy that imipramine, which is a typical tricyclic antidepressant, can also be synthesized with 89% isolated yield. Thus, our methodology exhibits good generality in the synthesis of various *N*-methyl amines.

It has been suggested that *N*-alkyl formamide might be an intermediate in the synthesis of *N*-methyl amine *via* further hydrogenation of *N*-alkyl formamide.^{8,9} Thus, we expect that *N*-formamides might be obtained if the reactions were performed under relatively milder reaction conditions. Herein, three typical



Scheme 1 Synthesis of pempidine (ganglion-blocking drug), 1,2,2,6,6-pentamethyl-4-piperidinol (hindered amine light stabilizer) and imipramine (tricyclic antidepressant) catalyzed by Pd/CuZrO_x.



Scheme 2 Results of the *N*-formamide intermediates during the *N*-methylation of different amines catalyzed by 2 wt% Pd/CuZrO_x.

amines, *i.e.* 1,2,3,4-tetrahydroisoquinoline, 4-ethylpiperidine and dodecylamine, were used as the starting materials to test the aforementioned hypothesis (Scheme 2). Hence, the corresponding *N*-formamides intermediates, *i.e.* 9c, 7c and 23c, can be synthesized with 56–68% isolated yields when the reactions were carried out with 15 h. Regarding the *N*-formamide, we expected that it was generated *via* carbenium ion intermediate (RNH[⊕]C=O), which was formed through the dehydration of carbamic acid (RNHCO₂H), and a detailed description of the reaction mechanism is given in the ESI† in Fig. S6.

In conclusion, an active Pd/CuZrO_x catalyst for the reductive amination of CO₂ using molecular hydrogen as a reducing agent was prepared by varying the composition of metal oxide supports. In the presence of this catalyst, the *N*-methylation reactions of amine and nitro compounds can be carried out smoothly under relatively mild reaction conditions without any additional co-catalyst. *N*-Methyl or *N,N'*-dimethyl amines with various structures can be synthesized with yields of up to 97%. *N*-Formylation becomes the main reaction if the reaction was performed under milder conditions or using Pd/ZnZrO_x as a catalyst. These results should be valuable for the development of a novel catalyst for CO₂ activation under mild conditions.

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