

Efficient, green, and renewable N-di-methylation synthesis of amines by a novel

nano-catalyst of NiNiO@C

Jianguo Liu^{1,2*#}, Yanpei Song^{1,3#}, Xiuzheng Zhuang^{1,3}, Mingyue Zhang^{1,3}, Longlong Ma^{1*}

¹ CAS Key Laboratory of Renewable Energy, Guangdong Provincial Key Laboratory of New and Renewable Energy Research and Development, Guangzhou Institute of Energy Conversion, Chinese Academy of Sciences, Guangzhou 510640, P. R. China.

² Dalian National Laboratory for Clean Energy, Dalian 116023, P. R. China.

³ University of Chinese Academy of Sciences, Beijing 100049, P. R. China.

* Corresponding authors e-mail: liujg@ms.giec.ac.cn; mall@ms.giec.ac.cn

These authors contributed equally to this work.

Abstract: The development of Earth-abundant reusable and no-toxic heterogeneous catalyst applied in the pharmaceutically, bio-active relevant compounds synthesis as well as other organic syntheses still remains as the most important goal of the general chemical research. N-methylated compounds, as one of the most essential bioactive compounds, have been widely used in the fine and bulk industries for the production of high-value chemicals including pharmaceuticals, agrochemicals, and dyes. As their reports, activated toxic methyl iodide and dimethyl sulfoxide were usually employed in the traditional N-methylation, which easily suffer from narrow scopes of amines, generation of by-products, and a large amount of waste. Very recently, transition metal-catalyzed methylation of amines has become an efficient, practical, and cost-effective method for the one-pot selective synthesis of N-methylamines with C₁ sources. Herein, we first developed a simple and environmentally friendly method for the preparation of efficient, reusable, and low-cost graphene spheres encapsulated Ni/NiO nanoalloy catalysts (Ni/NiO@C) for highly selective synthesis of the N-methylated compounds by using various functional amines and aldehydes under easily handle-able and industrially applicable conditions. A large number of

primary, secondary amines (more than 70 examples) could be converted smoothly to the corresponding N, N-dimethylamines with the participation of different functional aldehydes. The gram-scale synthesis was also demonstrated in an excellent yield; not only that, the catalyst was further proved that it could be easily recycled by its intrinsic magnetism and reused up to ten times without losing activity and selectivity. Both of them are the great advantages in contrast to other catalysts reported previously. And also, for the first time, we have developed the highly efficient, cost-effective tandem synthesis of N, N-dimethylamines products in a one-pot process by means of aldehydes and NH₃. As far as we know, this is the first example of the synthesis of tertiary amines with the combined reaction process of reductive amination of aldehydes and N-methylation of primary amines only with the single one earth-abundant metal catalyst. Overall, the advantages of this newly developed method including operational simplicity, high stability, easily recyclable, cost-effective of the catalyst, and good functional group compatibility for the synthesis of N-methylation products, as well as the highly efficient and industrial applicable tandem synthesis process.

Key words: *Graphene shell encapsulated; Ni nanoparticles; tandem synthesis; N-methylation*

Introduction

In recent years, green, efficient, and sustainable processes are urgently preferred in the chemical, pharmaceutical, and agrochemical industries owing to the increasingly strict standards required by environmental and economic issues. One of the most popular way is to use earth-abundant transition metal catalysts for the organic syntheses, especially with the help of nanomaterials^{1,2}. N-Functionalized amines, N-alkylamines in particular, are a sort of important compound in the synthesis of pharmaceuticals, dyes, detergents, and fine chemicals³⁻⁹. Transition metal-catalyzed

N-methylation has been an efficient and powerful method for the synthesis of N-methylated compounds, which regulated the biological and pharmaceutical properties by incorporating them into a magic methyl group¹⁰. For instance, the methylated compound (i.e., LASSBio-785) was much superior to the corresponding non-methylated compound (i.e., LASSBio-294) in producing an endothelium-independent vasodilator effect¹¹. As listed in the top 200 Small Molecule Pharmaceuticals by Retail Sales in 2018, there were more than 25 prescribed pharmaceutical products containing N-mono-methyl or N-di-methyl groups¹². Moreover, the N-methylated functional drugs especially Azithromycin showed highly effective in the control of the global pandemic of novel coronavirus disease infection in 2019^{13,14} (**Figure 1**). Since N-methylated amines exist widely as bioactive compounds, pharmaceutical drugs, and so on, the development of more efficient, environmentally friendly, economical, and sustainable N-methylation processes attracted chemists' attention continuously over the last decades^{3,4,6,8,15-26}. Until then, many methodologies for the synthesis of N-methylamines have been developed and widely used in academics and industry, applying formaldehyde²⁷, CO₂^{4,6,26,28,29}, alcohols (mostly methanol)³⁰⁻³², paraformaldehyde^{33,34}, dimethyl sulfoxide (DMSO)^{35,36}, dimethyl carbonate^{37,38}, alkyl halides or halogenated benzenes^{39,40} as methylation agents. Traditional N-methylation reactions generally encounter drawbacks including narrow scopes of amines, operationally problematic, and generation of by-products; this process may also cause a large amount of waste since the utilization of some of the activated methyl compounds, such as toxic methyl iodide, dimethyl sulfoxide, or dimethyl carbonate, is not recommendable. For this reason, transition metal-catalyzed methylation of amines by using the more environmentally benign and safer methylation reagents C₁ sources like MeOH^{30,41}, CO₂^{4,6,29,42}, HCOOH⁴³⁻⁴⁵, formaldehyde^{27,33,34} has become an efficient, practical, and cost-effective method for the one-pot selective synthesis of N-methylamines (**Figure**

2a). In this yield, both homogeneous and heterogeneous catalysts have been developed rapidly to achieve a specific target.

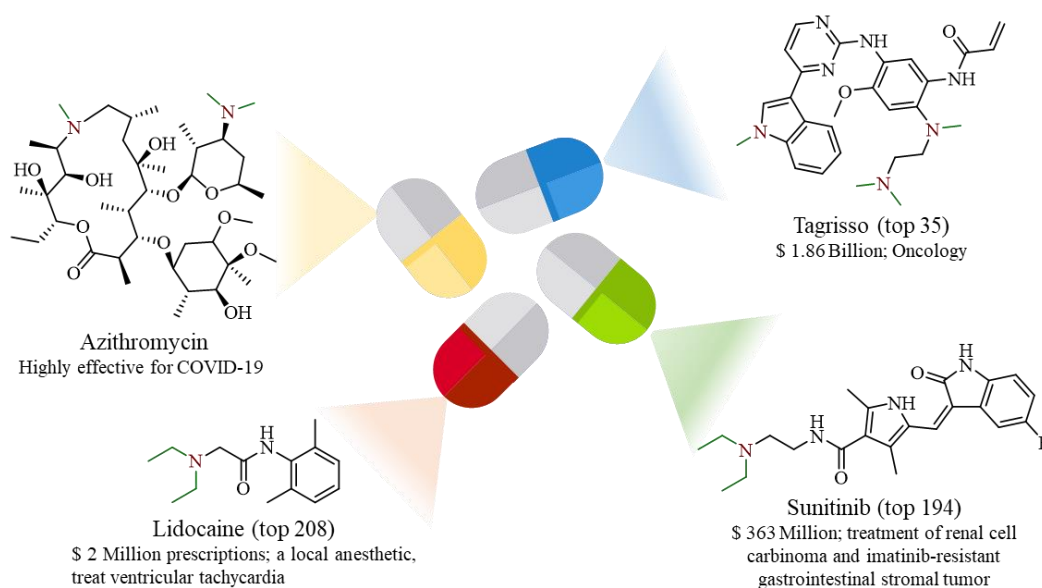


Figure 1. Pharmaceuticals containing N-methylated and N-di-methylated drugs

Ru complex have been developed as homogeneous catalyst for the direct N-methylation of amines which used CO_2 as a C_1 source. In 2013, Beller and co-workers reported an efficient method for the methylation of amines that employs commercially available $\text{RuCl}_2(\text{dms})_4$ and BuPAD_2 ligand as the catalyst, PhSiH_3 as the hydrogen source, and CO_2 as the methylation reagent²². Number of N-methylation products with different functional groups were obtained in good to excellent yield under optimized reaction conditions (30 bar CO_2 , 4 equiv. PhSiH_3 , toluene, 100 °C, and 16 h). They also built an in-situ combined catalyst system where $\text{Ru}(\text{acac})_3$, triphos, and acid or LiCl additives were highly selective for N-methylation of amines²³. Under the optimized reaction conditions (20 atm CO_2 , 60 atm H_2 , THF, 140 °C, 24 h), an attractive yield of mono-methylation and di-methylation products was obtained in their report. Klankermayer and co-workers¹⁷ also found that the readily commercially available $\text{Ru}(\text{triphos})(\text{tmm})$ complex and HNTf_2 acid were another highly efficient homogeneous catalyst system for the N-methylation of imines through CO_2 and H_2 . From then on, not only various homogeneous Ru-catalyzed ($[\text{RuCp}^*\text{Cl}_2]_2/\text{dpePhos}$ ³⁰, $[\text{Ru}(\text{p-cymene})\text{I}_2]_2$ ³³) N-methylation reaction process have been

developed successively, but also other homogeneous transition metal like Fe^{24,46,47}, Ir^{31,32,48,49}, Rh²⁰, Cu^{28,43,50}, Co⁵¹, and Mn^{19,52,53} catalyst systems have been rapidly studied.

Compared with the homogeneous catalyst system, the heterogeneous catalyst system has the advantages of better separation of catalyst/product, the no-necessity of additives (ligands, acids, and salts), and catalyst recyclable, re-useable ability, which matches very well with the economic and environmental perspectives. Pears and Bruton first applied the pre-reduced Adams heterogeneous catalyst Pt for the reductive methylation of amines with H₂ and HCHO⁵⁴. They obtained N, N-dimethylglycine in 79% yield from the reductive methylation of glycine. Half a decade later, Li and co-workers⁵⁵ used the pre-treated Raney Nickel for catalyzing N-methylation of nitroarenes with MeOH, which served as a hydrogen source, alkylating reagent, and solvent simultaneously (170 °C, 3 MPa Ar). Recently, Shi and co-workers^{56,57} designed two heterogeneous catalysts, namely CuAlO_x and Pd/CuZrO_x, whose results showed that both of them have high activity and selectivity for the N-methylation of amines and nitro compounds with CO₂ and H₂ (reaction conditions: 30-100 bar, 150-170 °C, 30-48 h). A more efficient TiO₂ supported nano-Pd catalyst was subsequently developed for the N-methylation of nitro compounds with MeOH under UV irradiation at room temperature⁵⁸. In 2015, Wang and co-workers⁵⁹ innovatively described the one-pot N-methylation of nitroarenes with the help of the heterogeneous Au/rutile catalyst. A variety of aromatic, aliphatic, and different functional groups of methylation products was obtained with good to excellent yields (2 MPa CO₂, 6 MPa H₂, 140-170 °C, 7 h). From then on, many more efficient transition metal-based catalyst systems such as Pt-MoO_x/TiO₂⁶⁰, Au/Al₂O₃⁵⁹, PdZn/TiO₂²⁹, Pd/TiO₂⁶¹, have been developed successively. To be more specific, inexpensive Cu-⁶² and Co-based⁷ (**Figure 2b**) heterogeneous catalysts are found to be good alternatives of Pd-based catalysts or Fe-, Ni-, Cu- and Co-based homogeneous catalysts with toxic ligands in recent years. Yang and co-workers⁶² reported a synthesis method via an in-situ topotactic transformation process

for Cu nanoparticles catalyst Cu/Al₂O₃ preparation derived from CuAl-layered double hydroxide (**Figure 2c**). The heterogeneous catalyst of Cu/Al₂O₃ showed excellent activity for the one-pot reductive N-methylation of nitroarenes with para-formaldehyde. Various functional groups of N-methylamines were obtained in good to excellent yield under the optimized reaction conditions (nitroarenes: 0.5 mmol, Cu/Al₂O₃ 12 mg, 27 mol% Cu, 15 equiv. (CH₂O)_n, 2 equiv. Na₂CO₃, 130 °C). However, high temperature (120~140 °C), high pressure (2-6 MPa) or excess bases (2 equiv. Na₂CO₃) are necessary for the insurance of the high yield of target products; meanwhile, the N-mono-methylation and the N, N-di-methylation products are always generated simultaneously, leading to extra needs for separation.

So far, the current state of reported works commonly has one or several of the following problems: 1) noble metals-based homogeneous catalysts need complex or even toxic ligands, tedious product/catalyst separation process, difficult catalyst recycles and re-usability; 2) heterogeneous catalysts with earth-abundant transition metal can induce N-methylation but usually required harsh conditions (high temperature and high pressure); 3) the high equivalent of base and/or reducing agents were needed in many of the homogeneous and heterogeneous catalyst systems. To overcome these problems, especially for the development perspectives with sustainable and environmental goals in the near future, several main factors are required for seeking a relatively brand-new methodology of N-methylamines, i.e., green reacting reagent, a fully atom-economic process without any byproduct formation or less green by-product generation (in general H₂O); fairly cheap and possible widely applied industrial scalable heterogeneous catalysts; mild conditions, easy and convenient procedures of product separation and downstream processing.

Hence, the development of easily accessible, eco-friendly, highly active, and earth-abundant transition metal heterogeneous catalysts for N-methylation is increasingly important as these

reactions allow for the cost-efficient production chain and sustainable green chemistry. Perfectly matched with the above goals, nanomaterials supported non-noble metal catalysts have been drawn attentions as their highly active single-atom sites and economic production for the N-methylation industrial application^{7,63,64}. Simple metal-supported nanoparticles are mainly prepared via the thermal (pyrolysis or calcination) or chemical reduction of several respective metal salts loaded on the nanomaterial supports⁶⁵⁻⁷⁰. Unfortunately, traditional metal-based catalysts often reflect sleepy reactivity and poor selectivity in challenging synthetic availability or stability in an acid environment as a result of leaching⁷¹⁻⁷³. A key to the more rational preparation of active nanoparticle catalysts may be the use of structural templates to control a predesign framework of catalyst bond strongly to the respective metal ion that can effectively avoid the metal leaching during the synthesis processes^{67,74,75}. In an attempt to fulfill this respect, a type of nanoparticle catalyst with a graphitic shell which tightly encapsulates the metal ions represents a well-matched concept for maintaining the satisfying activity and stability of catalysts in an acidic medium and has recently been applied in a variety of catalytic systems⁷⁶⁻⁷⁸. Beller and co-workers synthesized a highly efficient graphitic shell encapsulated nanoscale Co particles and single atoms supported on carbon catalyst which was derived from the pyrolysis and calcination of a metal-organic framework (MOF)-derived Co precursor catalyst⁷. The Co-DABCO-TPA@C-800 catalyst was active for the preparation of N-methylamines with good to excellent yield; however, fairly harsh conditions (120 °C, 4 MPa H₂) and high-cost solvent *t*-BuOH were still inevitable for this reaction (**Figure 2b**). What is more, during the preparation of active Co-DABCO-TPA@C-800 catalyst, the unacceptable consumption of necessary energy for the complex step of preparation and the non-environmental solvent DMF were also required, posing a potential fault for scale-up performance. Stability and recyclability are crucial features for any heterogeneous catalyst. As they mentioned, they observed a slight decrease in catalytic activity after six times catalyst

recycles. Thus, it is clear that a fundamental and economic principle to achieve a convenient and practical chemical synthesis relies on that the catalyst should be simple, effective, stable, and easily accessible^{7,79-81}.

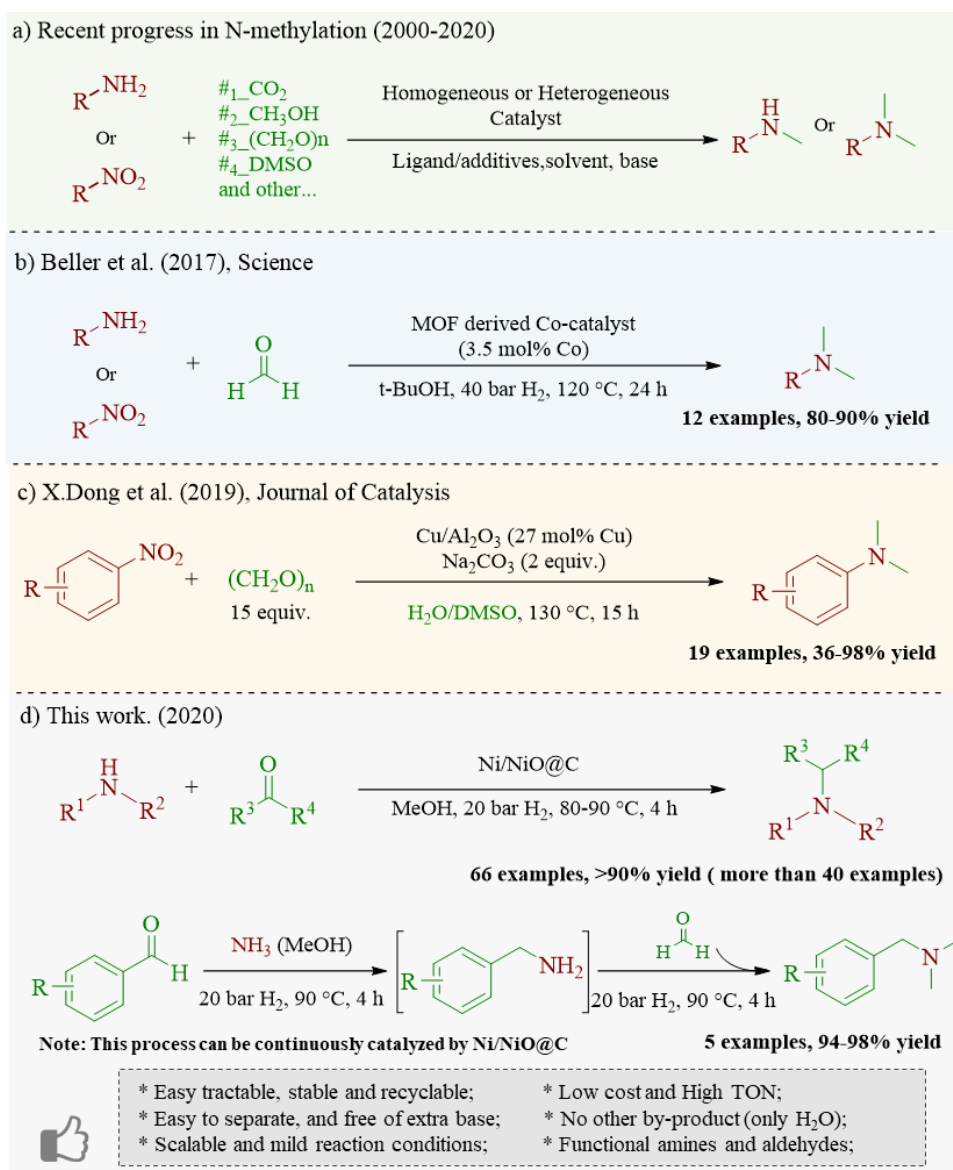


Figure 2. N-methylation of amines or nitrobenzenes with various methylation agents

Herein, we developed an environmentally friendly method, using less hazardous solvent EtOH, in fewer easily practical synthetic steps with low energy consumption, for the preparation of graphitic shell encapsulated nano-scale Ni/NiO particles (the single atoms supported on carbon catalyst). The most outstanding advantage of this method is undoubtedly the precise regulation of the properties of the graphene structure. Generally speaking, the carbon shells for relevant catalysts reported previously are comprised of multilayer graphitic carbon or composites thereof,

which may significantly reduce the catalytic activity. This occurs since the electronic structure of outermost carbon layer is only modulated by the electron which is transferred from the encapsulated metal-core when the shell consists of no more than three to four carbon layers⁸²⁻⁸⁴. Hence, the synthesis of carbon-encapsulated Ni-based catalyst with a controllable number of graphene layers, especially for the catalysts with less than three layers of graphene, is crucial for the construction of transition metal catalysts with superior activity⁸⁵. To the best of our knowledge, controllable thin graphene layers encapsulated Ni/NiO@C catalyst has remained unexplored for the N-methylation of amines. As a result, we have applied the encapsulated Ni-based nanoparticles into N-methylation reaction in this work, by utilizing different functional aldehydes and amines as reagents. In contrast to the previous synthesis routes of catalyst that heterogeneous materials were generally prepared by impregnation or immobilization, a better in-situ pyrolysis precursor and graphene encapsulated metal nanoparticles formation, eco-friendly and low energy-consuming process was better defined and proved. Using this facile synthesis of graphene encapsulated nanocatalyst Ni/NiO@ and starting from inexpensive, readily available aldehydes, primary, secondary amines, we undertook the synthesis of more than 65 functionalized, structurally diverse linear and branched benzylic, and aliphatic N-methylation/N-ethylation products under mild reaction conditions (80 °C and 2 MPa H₂ pressure, 4 h). We have also successfully demonstrated the scale-up of heterogeneous N-methylation protocol to gram-scale syntheses. Subsequently, starting from aldehydes, for the first time, we also developed an efficient method for the preparation of several N-methylation products via tandem reductive amination and N-methylation without purification of the intermediate by using the single catalyst highly active Ni/NiO@C (**Figure 2d**). And surprisingly, this catalyst can be immobilized on the magnetic stirring bar and be conveniently recycled up to ten times without any loss of catalytic activity and selectivity of the desired product. Overall, the developed catalyst of Ni/NiO@C has several significant advantages

as below: 1) based on the earth-abundant transition metal Ni, it is cheap, air-stable, easy to synthesis, and easy to handle; 2) it shows excellent catalytic activity for N-methylation in the absence of ligand and base; 3) it can be easily separated from the reaction medium by simple filtration and reused; 4) the reaction is carried out under industrially applicable conditions and the only by-product was H₂O.

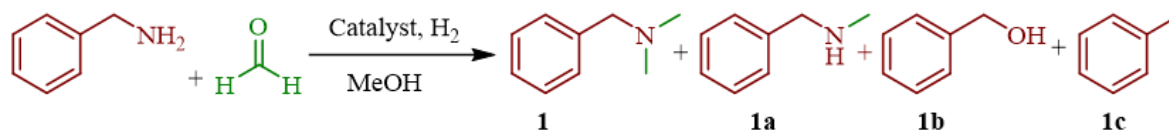
Results and Discussion.

The Ni/NiO@C catalysts were synthesized following simple modified three-step procedure reported in our previous literature⁸⁶. All the prepared Ni/NiO@C catalysts and other commercial catalysts such as Pd/C, Rh/C, Ru/C, Pt/C, and Raney Ni were evaluated in the N-methylation reaction of benzylamine with formaldehyde under the H₂ atmosphere as reducing agent. The solvent adopting for the preparation of catalyst precursors had a great effect on the catalyst characterization and catalytic activity, as shown in Table 1. For instance, catalyst **A**, **B** which were synthesized by employing H₂O as medium showed higher catalytic activity than the corresponding catalyst **C** and **D** using EtOH. Furthermore, the oxidation step had a big effect on the catalytic activity of the catalysts with EtOH (**C**, **D**, **G**, and **H**). The optimized catalyst **H** exhibited excellent reactivity and selectivity for the desired product (> 99% conversion, 99% yield of **1**). As the reaction temperature decreased from 80 to 60 °C, the reaction product yield dropped rapidly from 99% to 30% (entries 8-10). The reaction could be carried out in a short time but with acceptable selectivity (entry 11). When the reaction pressure decreased from 20 to 10 bar, the reaction product yield dropped from 99% to 73% (entries 11, 13, and 14). Moreover, the catalyst **H** showed excellent reactivity and stability even up to ten times the recycling test (entry 15). Other commercially available noble catalysts also showed good to excellent reactivity (entries 16-18, 20, and 21). However, the catalyst Ru/C reactivity and selectivity dropped dramatically only after 3 times the recycling test (entry 19). Compared with the commercially available noble catalyst Ru/C,

the Ni/NiO@C catalyst prepared in this work had a big breakthrough and obvious advantages in catalyst cost, reactivity, and stability. We also characterized the catalyst before and after the recycling test. According to the high resolution Transmission Electron Microscope (TEM) analysis, the Ni metal nanoparticles (NPs) that were completely coated by graphene shells (**Figure 3a**) even after the recycling test (**Figure 3b, 3c**). The H catalyst which was after the oxidation step treatment, not only had the (111) plane of the Ni alloy but also had the (110) plane of the NiO alloy with a d-spacing of 0.24 nm. Based on the statistical analysis by TEM, the graphene shells on the Ni NPs are thin (>90% consist of few layers), and this tendency kept unchanged although the catalyst H was reused up to 10 times. We also did the energy dispersive spectrometer to explore the elemental distribution of C with white color, Ni with yellow color, and O with blue color on the nanoparticle surface, whose results found that the oxidized Ni somehow become dominant after a long-time recycle (**Figure 3d, 3e, 3f**), in according with the subsequent analysis of X-ray photoelectron spectroscopy (XPS) and X-ray diffraction (XRD) aimed at the electronic and structural properties of the catalyst H. As shown in the XPS spectrums (**Figure 3g**), both metallic Ni⁰ and Ni²⁺ species were observed on the catalyst surface (**Figure 3h**). The intensity of Ni²⁺ combined with O²⁻ increased after the ten times recycling test., indicating that the catalyst active species Ni⁰ was transformed to a more stable, higher oxidation state of Ni²⁺ species but still have an obvious active for the N-methylation reaction. As further shown in the XRD spectra, the graphitic carbon shell, the Ni alloy (111), Ni (200), NiO (220) and NiO (111) phases were all presented in the catalyst H before and after recycling reaction (**Figure 3h**), but with different intensities. The weak peaks of NiO in the XRD pattern confirmed that the metals were presented as nanosized particles. It was also founded that the intensity of Ni decreased after ten times recycling, and this was consistent with the TEM statistical analysis and XPS analysis. From the weak and broad C (002) peaks in

XRD spectrums, thin graphene shells had been formed and this matched well with the statistical analysis of the number of layers in TEM.

Table 1. Optimization of catalysts and conditions for reductive N-methylation of benzylamine to N,N-dimethylbenzylamine^a



Entry	Catalyst	H ₂ pressure (bar)	Temperature (°C)	Time (h)	Yield of 1 (%)
1	Ni@C-600-H ₂ O (A)	20	80	6	92
2	Ni@C-700-H ₂ O (B)	20	80	6	99
3	Ni@C-600-EtOH (C)	20	80	6	42
4	Ni@C-700-EtOH (D)	20	80	6	77
5	Ni/NiO@C-600-200-1h-H ₂ O (E)	20	80	6	94
6	Ni/NiO@C-700-200-1h-H ₂ O (F)	20	80	6	95
7	Ni/NiO@C-600-200-1h-EtOH (G)	20	80	6	96
8	Ni/NiO@C-700-200-2h-EtOH (H)	20	80	6	99
9	Same as entry 8 (H)	20	70	6	85
10	Same as entry 8 (H)	20	60	6	30
11	Same as entry 8 (H)	20	80	4	99
12	Same as entry 8 (H)	20	80	2	72
13	Same as entry 8 (H)	15	80	4	84
14	Same as entry 8 (H)	10	80	4	73
15 ^b	Same as entry 8 (H)	20	80	4	99
16	Pd/C	25	70	8	95
17	Rh/C	25	70	8	74
18	Ru/C	25	70	8	99
19 ^c	Ru/C	25	70	8	59
20	Pt/C	25	70	8	99
21	Raney Ni	25	70	8	99

^a Reaction conditions: 10 mg catalyst, 0.5 mmol benzylamine, 3 mmol formaldehyde (37% aq), 5 mL methanol. Yields and conversion were determined by GC using 1, 3, 5-trimethoxybenzenen as an internal standard. ^b Recycling test of the Ni-based nano-catalyst after 10 times. ^c Recycling test of the Ru/C after 3 times.

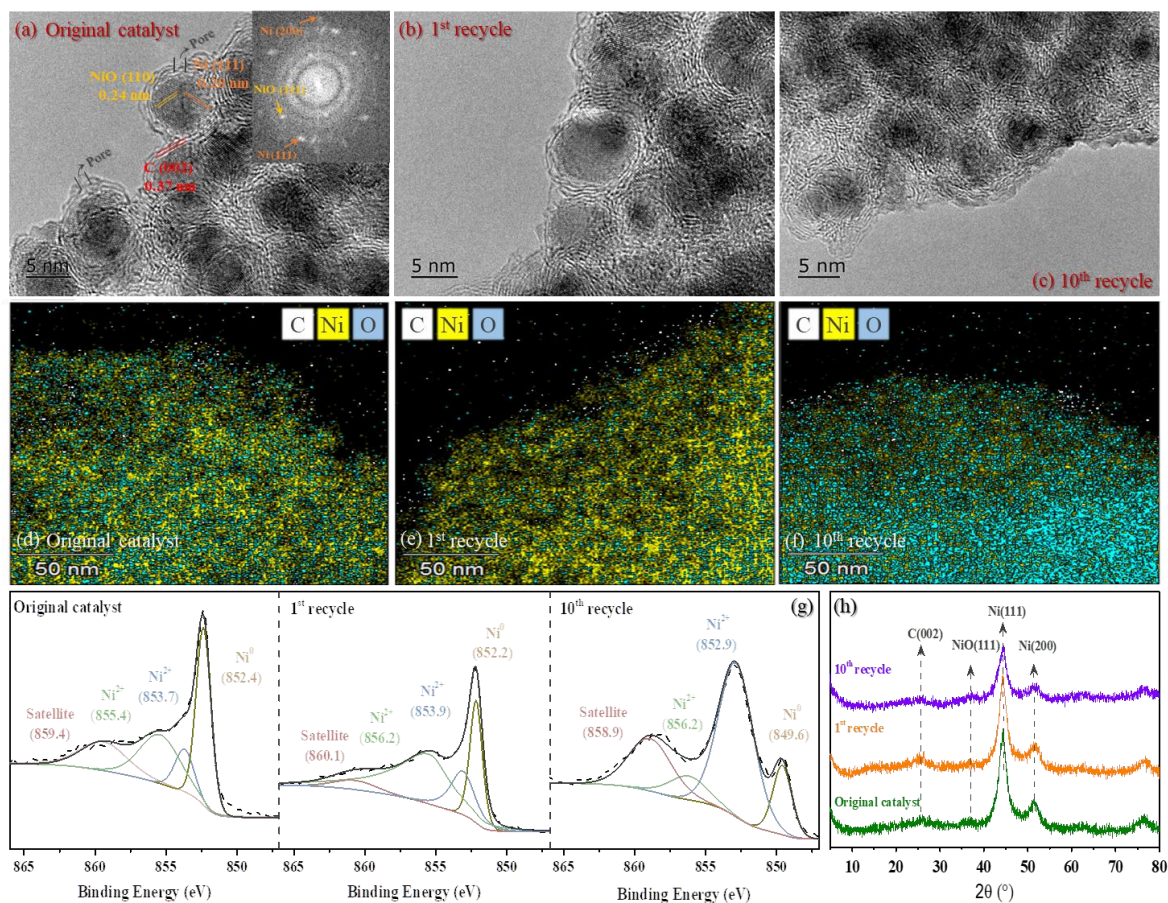
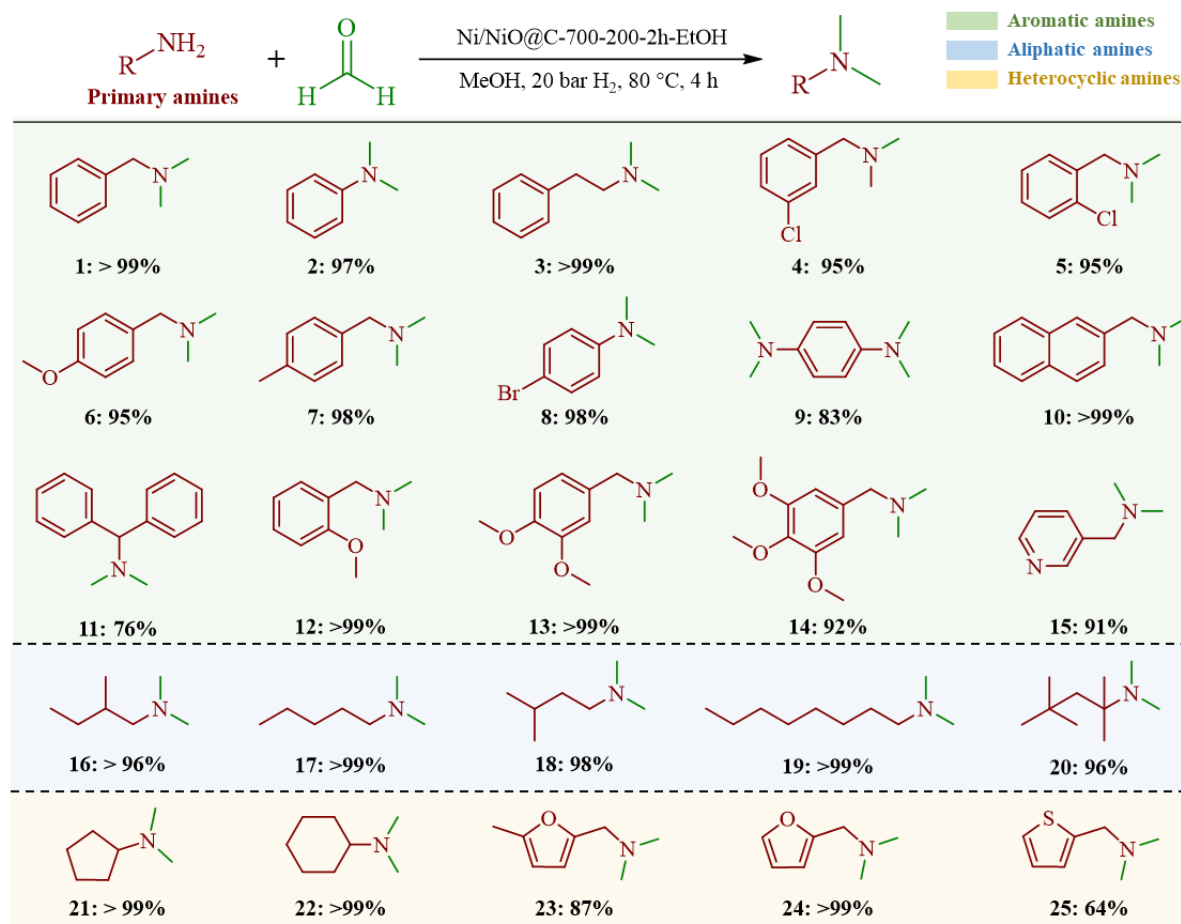


Figure 3. Catalyst characterization. TEM images of fresh H catalyst (a), TEM images of the after 1 times recycle H catalyst (b); TEM images of the after 1 times recycle H catalyst (c); EDS mapping images of the fresh H catalyst (d), the after 1 times recycle H catalyst (e), and the after 10 time recycle H catalyst (f); XPS images of the H catalyst before and after recycle (g); XRD images of the fresh H catalyst, after 1 times recycle H catalyst, after 10 times recycle H catalyst (h).

After having the optimized reaction conditions in hand for the benchmark reaction, we next explored the substrate scopes of Ni/Ni@C-700-200-2h-EtOH catalyzed N-methylation of different functional primary amines with formaldehyde (Table 2). Surprisingly, 21 examples of the 25 tested aromatic, heterocyclic, and aliphatic amines having different functional groups were converted to the corresponding N, N-di-methylamines in above 90% yields under the standard mild reaction conditions (20 bar H₂, 80 °C, and 4 h). The halo-substituted aromatic amines, which are the important building blocks in pharmaceutical and material synthesis, no matter where the halogen is located, were well tolerated in this reaction (4, 5, and 8). The biomass derivatives reductive amination products (12, 13, 14, 23 and 24) can also be converted to the corresponding N,

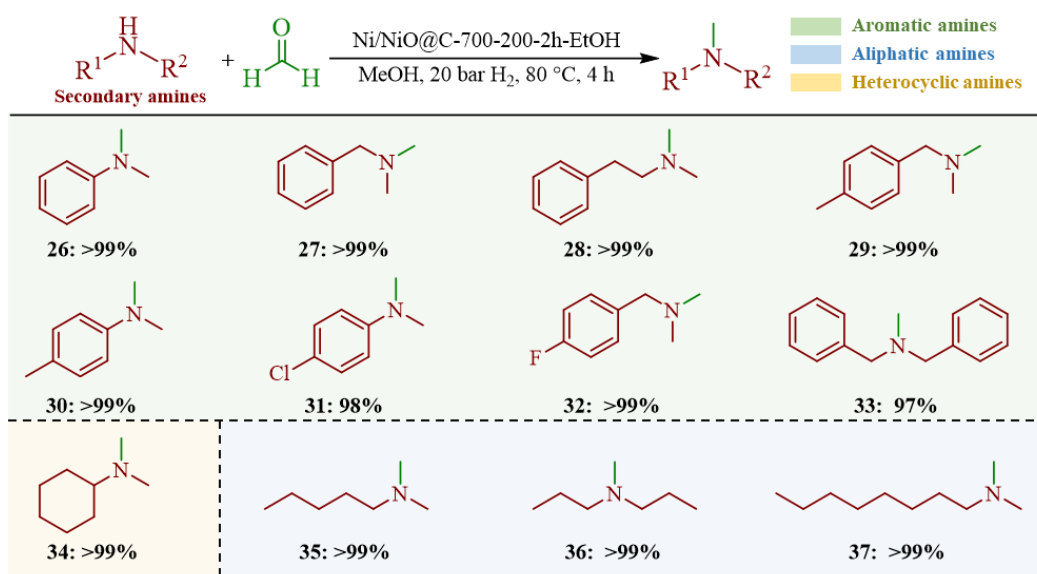
N-di-methylamines products in good to excellent yield. What is more, the linear, branched and cyclic aliphatic amines, which were the challenging substrates and previously seldom reported or with low yield^{56,59,87}, were transformed to the corresponding N, N-di-methylated products in excellent yield (**16-22**). Encouraged by this success in the N-methylation of primary amines with formaldehyde, we subsequently explored the secondary amines substrates. As showed in the table 3, to our delight, all the evaluated substrates, such as the aromatic, halo-substituted aromatic, cyclic, linear and branched aliphatic secondary amines gave the target products in excellent yields (**26-37**) as expected.

Table 2. Synthesis of tertiary amine by N-methylation of primary amine catalyzed by Ni/NiO@C-700-200-2h-EtOH



Reaction conditions: 10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol primary amine, 3 mmol formaldehyde (37% aq), 5 mL methanol, 20 bar H₂, 80 °C, 4 h. Yields and conversion were determined by GC based on amine. The types of products were determined by GCMS and ¹H NMR.

Table 3. Synthesis of tertiary amine by N-methylation of secondary amine catalyzed by Ni/NiO@C-700-200-2h-EtOH

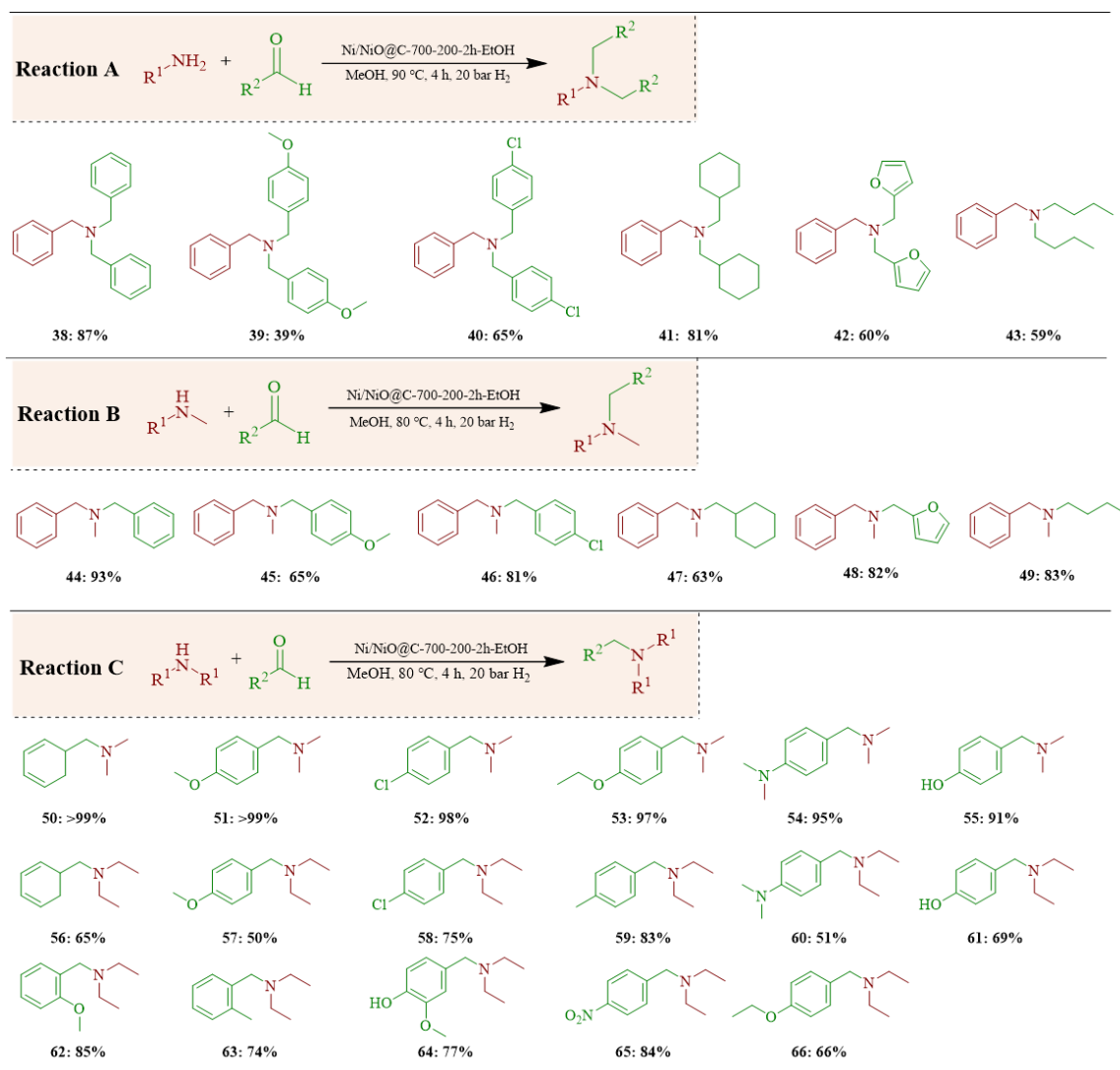


Reaction conditions: 10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol secondary amine, 3 mmol formaldehyde (37% aq), 5 mL methanol, 20 bar H₂, 80 °C, 4 h. Yields and conversion were determined by GC based on amine. The types of products were determined by GCMS and ¹H NMR.

Similarly, encouraged by the successful synthesis of tertiary amine by the N-methylation of primary or secondary amines with formaldehyde catalyzed with catalyst H, we kept on exploring the synthesis of tertiary amine starting from primary, secondary amines or dimethylamine and diethylamine with different functional substituted aldehydes, which were seldom reported previously. To our delight, most of the aromatic primary and secondary amines were converted to the corresponding tertiary amines in moderate to excellent yields using different functional aromatic, aliphatic, cyclic, heterocyclic aldehydes (**38-49**). To the best of our knowledge, few works reported the synthesis of tertiary amines using secondary amines and functional aldehydes via transition metal catalyzed N-methylation method. To develop this method more practically for wide application, we sequentially investigated aromatic aldehydes with different functional groups. As exhibited in the Table 3, for the para-substituted aromatic aldehydes, no matter the electron-withdrawing group or electron with donating group, all of them could be reacted with dimethylamine and converted smoothly to the corresponding N-dimethylation product with

excellent yield (**50-55**). When the amine sources changed from dimethylamine to diethylamine, moderate to a good yield of N-diethylation product (**56-63**) could still be obtained under the optimized reaction conditions (20 bar H₂, 80 °C, 4 h). Moreover, the ortho-substituted aromatic aldehydes **64**, **65**, and the biomass-derived platform compound **66** could also well-tolerated and gave the tertiary amines in good yields.

Table 4. Screening aldehydes for Synthesis of tertiary amine by N-methylation of amine catalyzed by Ni/NiO@C-700-200-2h-EtOH



Reaction conditions: ^a10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol primary amine, 3 mmol aldehyde, 5 mL methanol, 20 bar H₂, 90 °C, 4 h. ^b10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol secondary amine, 3 mmol aldehyde, 5 mL methanol, 20 bar H₂, 80 °C, 4 h. ^{a,b}Yields and conversion were determined by GC based on amine. ^c10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol aldehyde, 0.5 ml dimethylamine solution (2 M in methanol), 4.5 mL methanol, 20 bar H₂, 80 °C, 4 h. ^d10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol aldehyde, 1 mmol diethylamine, 5 mL methanol, 20 bar H₂, 80 °C, 4 h. ^{c,d}Yields and

conversion were determined by GC based on aldehyde. The types of products were determined by GCMS and ^1H NMR.

Gram-scale reactions and recycling of the catalyst. After developed the successful synthesis of tertiary amines via the N-methylation of functional amines and functional aldehydes, we hope to apply this method in the future industry. And here we were delighted to show three substrates were well performed in this Ni-catalyzed N-methylation reaction at the 1-g scale. They were similar to those small-scale reactions and excellent yields of the desired product were obtained for all the three substrates. Furthermore, we also evaluated the catalyst stability and recycle ability using the benchmark reaction under the optimized reaction conditions. Surprisingly, compared with the other previously reported catalysts^{7,29,62}, our thin layer graphene shell encapsulated Ni/NiO@C catalyst showed excellent activity, product selectivity and exhibited excellent stability. It could be easily recycled ten times without any significant loss of activity (**Figure 4**). We have currently applied this highly active, stable, easily hand-able and low-cost Ni-based catalyst in kg-scale/day and Ton-scale/Year of tertiary amines' synthesis.

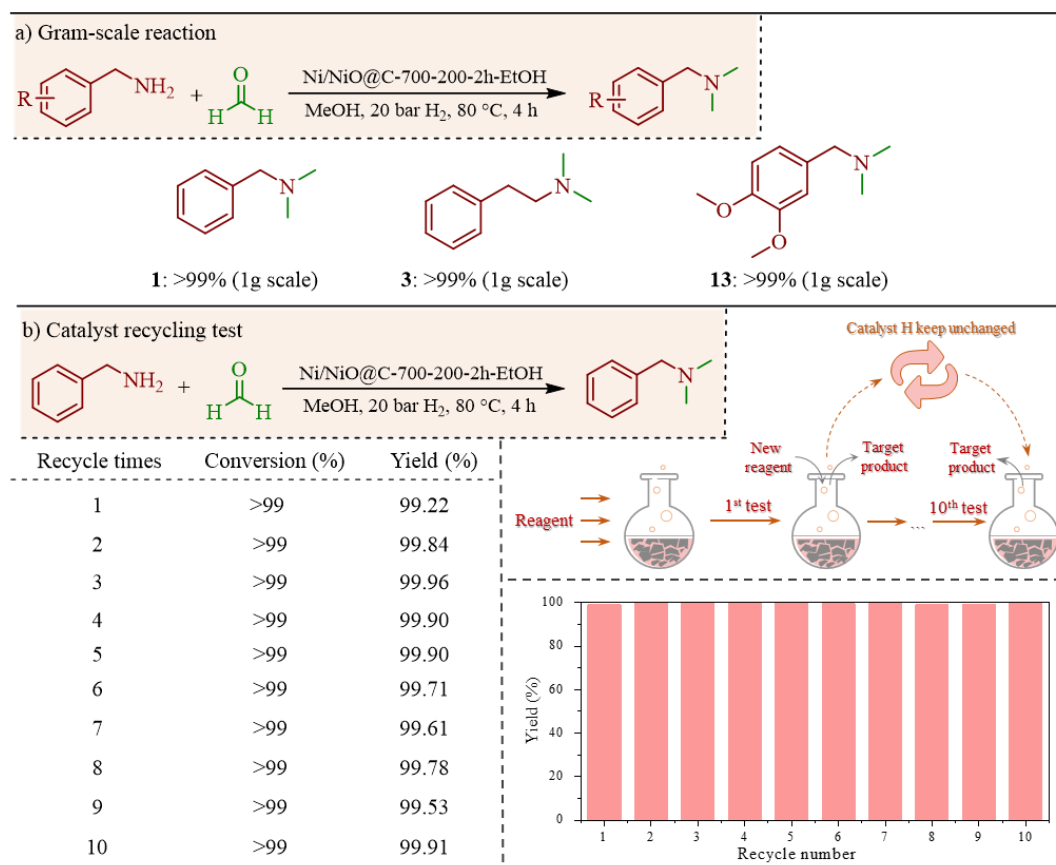
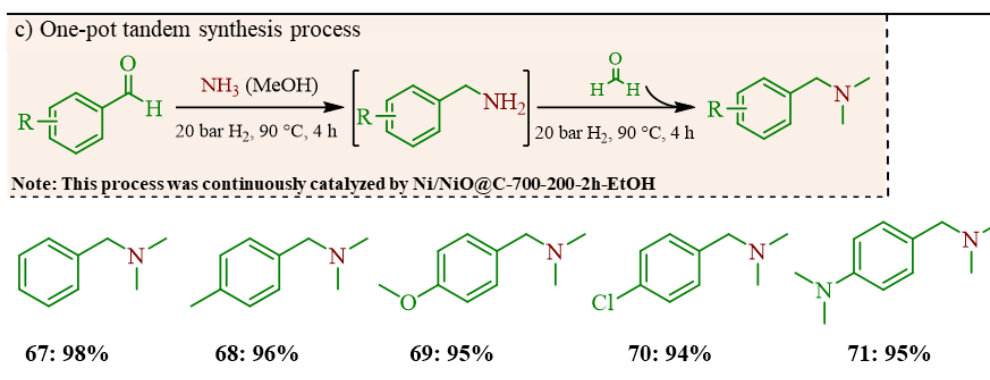


Figure 4. Gram-scale reactions and recycling of the catalyst. a) Gram-scale reaction conditions: 200 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 10 mmol amine, 60 mmol formaldehyde (37% aq), 100 mL methanol, 20 bar H₂, 80 °C, 4 h. Yields and conversion were determined by GC based on amine. The types of products were determined by GCMS and ¹H NMR; b) Catalyst recycling test reaction conditions: 10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol benzylamine, 3 mmol formaldehyde (37% aq), 5 mL methanol, 20 bar H₂, 80 °C, 4 h. Yields and conversion were determined by GC using 1, 3, 5-trimethoxybenzenen as an internal standard based on amine. The types of products were determined by GCMS and ¹H NMR.

To make this efficient N-methylation process more applicable, we also developed the more cost-effective and highly practical tandem synthesis of tertiary amines which starts from the easily accessible aromatic aldehydes and NH₃. We combined the reductive amination of aldehydes and N-methylation of the formed primary amines into an one-pot tandem synthesis process as depicted in Table 5, by using the only catalyst of Ni/NiO@C without any purification. Excellent yields of N-diethylation products were obtained for all the tested *para*-substituted aromatic aldehydes (67-71). This process is highly cost-efficient, easily separation, high yielding of the desired product and gave less by-product which matches the sustainable and green chemistry very well.

Table 5. Tandem synthesis of tertiary amines via reductive amination and N-methylation in one-pot process



Reaction conditions: 10 mg Ni/NiO@C-700-200-2h-EtOH catalyst, 0.5 mmol benzaldehyde, 5 ml ammonia solution (2 M in methanol), 20 bar H₂, 90 °C, 4 h; After the reaction was completed, add 3 mmol formaldehyde (37% aq), 20 bar H₂, 90 °C, 4 h. Yields and conversion were determined by GC using 1, 3, 5-trimethoxybenzenen as an internal standard based on amine. The types of products were determined by GCMS and ¹H NMR.

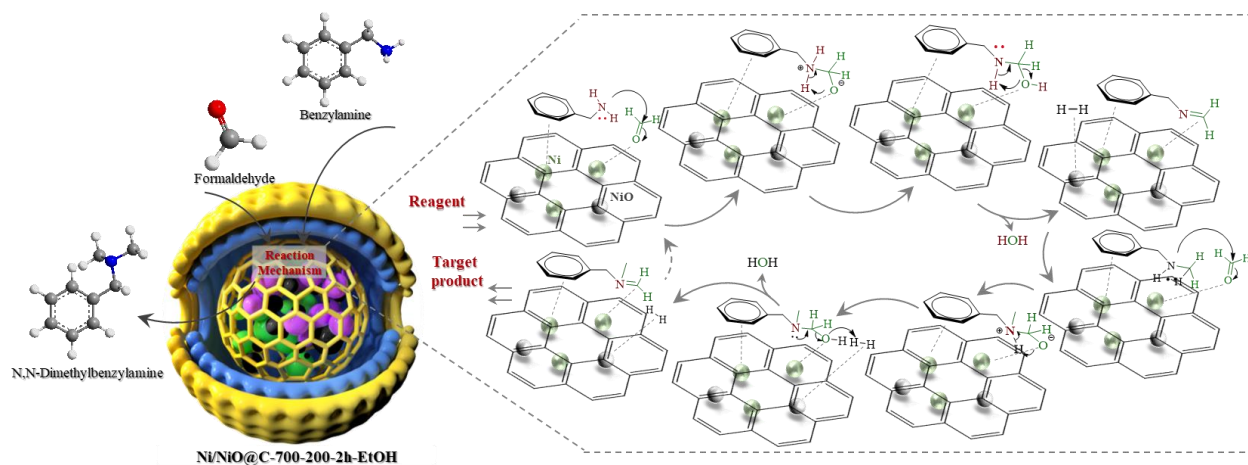


Figure 5. A possible pathway for Ni/NiO catalyzed N-methylation of amines and aldehydes

Here, according to our studies and controlled experiments, we proposed the mechanism of Ni/NiO@C catalyzed N-methylation of amines using formaldehyde as the C₁ source. In this reaction process, CO₂ which was normally occurred in the previous reported formic acid process mechanism, was not observed. So, it could be similar to the reported combination of reductive amination and twice N-methylation process^{62,88}. As shown in Figure 5, the phenylmethanamine reacted with formaldehyde first to form the intermediate (benzylamino) methanol, and then after a dehydration reaction, the imine, enamines, or iminium ions was formed. In the following step, the H-H bond is activated on the surface of Ni/NiO, and in the meantime, the imine intermediate is also absorbed on Ni/NiO catalyst surface. So, the imine was reduced to N-methyl (phenyl) methanamine by H-H. Aliphatic amines, which were unreactive in the previously reported Pt/C N-methylation reaction, also showed excellent reactivity in this Ni/NiO N-methylation reaction. The second N-methylation process step is slightly different from the first one. In the alkaline aqueous after the dehydration process, the N-methyl-N-methylene (phenyl) methanaminium is more stable. Finally, the iminium intermediate was reduced with H₂ and after the desorption process, the N, N-dimethyl (phenyl) methanamine product was formed eventually. The most accepted reductive amination pathway refers to the nucleophilic addition of amine and carbonyl groups to yield an imine. The imine was then hydrogenated to the desired amine. However, as for

the second amine (such as N, N-dimethylamine), imine cannot be formed according to the above pathway. A possible intermediate of N, N-dimethylamines in the Ni/NiO@C catalyzed N-methylation reaction could be a nitrogen cation. A *in situ* Raman experiment was used to record the presence of intermediate species during the reaction under 80 °C.

Conclusion

In summary, we have demonstrated a simple, practical, and eco-friendly method for the preparation of thin graphene spheres encapsulated uniform Ni/NiO nanoalloy catalysts. The high stable and recyclable heterogeneous catalyst were highly efficient for the N-methylation of a variety of amines with different functional aldehydes under mild conditions. Both of the primary and secondary amines (more than 70 examples) with various functional groups including aromatic, aliphatic, halo-substituted, furan, and thiophene substituents can be converted smoothly to N, N-dimethylamines or N, N-diethylamines utilizing different functional aldehydes under mild reaction conditions. The protocol also exhibited an excellent reactivity for the gram-scale synthesis. Not only that, compared with other previous reported catalysts, the catalyst can be easily recycled and reused up to ten times without losing any activity and selectivity. And more importantly, for the first time, we have demonstrated the highly efficient, cost-effective tandem synthesis of N, N-dimethylamines products via reductive amination of aldehydes and N-methylation of amines in an one-pot synthetic process. These aforementioned findings open a pathway for an available and the feasible preparation of cheap but high-performance catalysts toward the N-methylation. By and large, the advantage of this brand-new method is beneficial for the operational simplicity, high stability, easily recyclable, cost-effective of Ni/NiO@C catalyst, and good functional group compatibility for the synthesis of N-methylation products, as well as the highly efficient and industrial applicable tandem synthesis process.

Acknowledgment This work was supported financially by the National Key R&D Program of China (2018YFB1501502), National Natural Science Foundation of China (51976225), DNL Cooperation Fund, and Chinese Academy of Sciences (DNL201916).

Author contributions J. G. L. and L. L. M supervised and designed the research. Y. P. S. performed most of the experiments and data analysis. M. Y. Z. performed substrates scope experiments. J. G. L. and Y. P. S wrote the paper. X. Z. Z. reviewed and wrote the original manuscript. All authors discussed the results and assisted during manuscript preparation.

Competing interests The authors declare no competing financial interests.

Data availability Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Additional information Correspondence and requests for materials should be addressed to L. L. M or J. G. L.

References

- 1 Irrgang, T. & Kempe, R. 3d-Metal Catalyzed N- and C-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chemical Reviews* **119**, 2524-2549, doi:10.1021/acs.chemrev.8b00306 (2019).
- 2 Wang, D. & Astruc, D. The recent development of efficient Earth-abundant transition-metal nanocatalysts. *Chemical Society Reviews* **46**, 816-854, doi:10.1039/c6cs00629a (2017).
- 3 Beydoun, K., vom Stein, T., Klankermayer, J. & Leitner, W. Ruthenium-Catalyzed Direct Methylation of Primary and Secondary Aromatic Amines Using Carbon Dioxide and Molecular Hydrogen. *Angew Chem Int Edit* **52**, 9554-9557, doi:10.1002/anie.201304656 (2013).
- 4 Bobbink, F. D., Das, S. & Dyson, P. J. N-formylation and N-methylation of amines using metal-free N-heterocyclic carbene catalysts and CO(2) as carbon source. *Nature protocols* **12**, 417-428, doi:10.1038/nprot.2016.175 (2017).
- 5 Dasgupta, S., Castro, L. M., Tashima, A. K. & Fricker, L. Quantitative Peptidomics Using Reductive Methylation of Amines. *Methods in molecular biology (Clifton, N.J.)* **1719**, 161-174, doi:10.1007/978-1-4939-7537-2_10 (2018).
- 6 Jacquet, O., Frogneux, X., Das Neves Gomes, C. & Cantat, T. CO₂ as a C₁-building block for the catalytic methylation of amines. *Chemical Science* **4**, 2127-2131, doi:10.1039/C3SC22240C (2013).
- 7 Jagadeesh, R. V. *et al.* MOF-derived cobalt nanoparticles catalyze a general synthesis of amines. *Science* **358**, 326-+, doi:10.1126/science.aan6245 (2017).
- 8 Oku, T., Arita, Y., Tsuneki, H. & Ikariya, T. Continuous Chemoselective Methylation of Functionalized

- Amines and Diols with Supercritical Methanol over Solid Acid and Acid–Base Bifunctional Catalysts. *J Am Chem Soc* **126**, 7368-7377, doi:10.1021/ja048557s (2004).
- 9 Waterman, K. C. *et al.* N-methylation and N-formylation of a secondary amine drug (Varenicline) in an osmotic tablet. *J Pharm Sci-U.S.* **97**, 1499-1507, doi:10.1002/jps.21119 (2008).
- 10 Feng, J. X. & Pan, H. Electronic state optimization for electrochemical N(2)reduction reaction in aqueous solution. *J Mater Chem A* **8**, 13896-13915, doi:10.1039/d0ta04709k (2020).
- 11 Silva, A. G. *et al.* Synthesis and vasodilatory activity of new N-acylhydrazone derivatives, designed as LASSBio-294 analogues. *Bioorgan Med Chem* **13**, 3431-3437, doi:10.1016/j.bmc.2005.03.003 (2005).
- 12 Njarđarson, J. Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2018. 2018 [cited 2020-10-27]; Available from: <https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Small%20Molecule%20Pharmaceuticals%202018V4.pdf>.
- 13 Mehra, M. R., Desai, S. S., Kuy, S., Henry, T. D. & Patel, A. N. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *New Engl J Med* **382**, doi:ARTN e10210.1056/NEJMoa2007621 (2020).
- 14 Sanders, J. M., Monogue, M. L., Jodlowski, T. Z. & Cutrell, J. B. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. *Jama-J Am Med Assoc* **323**, 1824-1836, doi:10.1001/jama.2020.6019 (2020).
- 15 Banerjee, S. P. & Snyder, S. H. Methyltetrahydrofolic Acid Mediates N-Methylation and O-Methylation of Biogenic-Amines. *Science* **182**, 74-75, doi:DOI 10.1126/science.182.4107.74 (1973).
- 16 Barclay, M. G., Burawoy, A. & Thomson, G. H. A new method of nuclear methylation of aromatic amines and phenolic substances. *Nature* **151**, 615-616, doi:DOI 10.1038/151615a0 (1943).
- 17 Beydoun, K., Ghattas, G., Thenert, K., Klankermayer, J. & Leitner, W. Ruthenium-Catalyzed Reductive Methylation of Imines Using Carbon Dioxide and Molecular Hydrogen. *Angew Chem Int Edit* **53**, 11010-11014, doi:10.1002/anie.201403711 (2014).
- 18 Das, S., Bobbink, F. D., Laurenczy, G. & Dyson, P. J. Metal-Free Catalyst for the Chemoselective Methylation of Amines Using Carbon Dioxide as a Carbon Source. *Angew Chem Int Edit* **53**, 12876-12879, doi:10.1002/anie.201407689 (2014).
- 19 Elangovan, S. *et al.* Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat Commun* **7**, doi:ARTN 1264110.1038/ncomms12641 (2016).
- 20 Lam, R. H. *et al.* Selective formylation or methylation of amines using carbon dioxide catalysed by a rhodium perimidine-based NHC complex. *Green Chemistry* **21**, 538-549, doi:10.1039/C8GC03094D (2019).
- 21 Li, Y., Yan, T., Junge, K. & Beller, M. Catalytic methylation of C-H bonds using CO₂ and H₂. *Angewandte Chemie (International ed. in English)* **53**, 10476-10480, doi:10.1002/anie.201405779 (2014).
- 22 Li, Y. H., Fang, X. J., Junge, K. & Beller, M. A General Catalytic Methylation of Amines Using Carbon Dioxide. *Angew Chem Int Edit* **52**, 9568-9571, doi:10.1002/anie.201301349 (2013).
- 23 Li, Y. H., Sorribes, I., Yan, T., Junge, K. & Beller, M. Selective Methylation of Amines with Carbon Dioxide and H₂. *Angew Chem Int Edit* **52**, 12156-12160, doi:10.1002/anie.201306850 (2013).
- 24 Polidano, K., Allen, B. D. W., Williams, J. M. J. & Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catalysis* **8**, 6440-6445, doi:10.1021/acscatal.8b02158 (2018).
- 25 Purse, B. W., Ballester, P. & Rebek, J. Reactivity and molecular recognition: Amine methylation by an introverted ester. *J Am Chem Soc* **125**, 14682-14683, doi:10.1021/ja036595q (2003).
- 26 Tlili, A., Frogneux, X., Blondiaux, E. & Cantat, T. Creating Added Value with a Waste: Methylation of

- Amines with CO₂ and H₂. *Angewandte Chemie International Edition* **53**, 2543-2545, doi:<https://doi.org/10.1002/anie.201310337> (2014).
- 27 Man, N. Y., Li, W., Stewart, S. G. & Wu, X. F. Transition Metal-free Methylation of Amines with Formaldehyde as the Reductant and Methyl Source. *Chimia* **69**, 345-347, doi:10.2533/chimia.2015.345 (2015).
- 28 Li, X. D. *et al.* Copper catalysis: ligand-controlled selective N-methylation or N-formylation of amines with CO₂ and phenylsilane. *Green Chemistry* **20**, 4853-4858, doi:10.1039/c8gc02280a (2018).
- 29 Lin, W. *et al.* Selective N-Methylation of N-Methylaniline with CO₂ and H₂ over TiO₂-Supported PdZn Catalyst. *ACS Catalysis* **10**, 3285-3296, doi:10.1021/acscatal.9b04677 (2020).
- 30 Dang, T. T., Ramalingam, B. & Seayad, A. M. Efficient Ruthenium-Catalyzed N-Methylation of Amines Using Methanol. *ACS Catalysis* **5**, 4082-4088, doi:10.1021/acscatal.5b00606 (2015).
- 31 González-Lainez, M., Jiménez, M. V., Passarelli, V. & Pérez-Torrente, J. J. Effective N-methylation of nitroarenes with methanol catalyzed by a functionalized NHC-based iridium catalyst: a green approach to N-methyl amines. *Catalysis Science & Technology* **10**, 3458-3467, doi:10.1039/D0CY00707B (2020).
- 32 Meng, C., Liu, P., Tung, N. T., Han, X. & Li, F. N-Methylation of Amines with Methanol in Aqueous Solution Catalyzed by a Water-Soluble Metal-Ligand Bifunctional Dinuclear Iridium Catalyst. *The Journal of Organic Chemistry* **85**, 5815-5824, doi:10.1021/acs.joc.9b03411 (2020).
- 33 Van der Waals, D. *et al.* Ruthenium-Catalyzed Methylation of Amines with Paraformaldehyde in Water under Mild Conditions. *ChemSuschem* **9**, 2343-2347, doi:10.1002/cssc.201600824 (2016).
- 34 Wang, H., Huang, Y., Dai, X. & Shi, F. N-Monomethylation of amines using paraformaldehyde and H₂. *Chemical communications (Cambridge, England)* **53**, 5542-5545, doi:10.1039/c7cc02314f (2017).
- 35 Atkinson, B. N. & Williams, J. M. J. Dimethylsulfoxide as an N-Methylation Reagent for Amines and Aromatic Nitro Compounds. *ChemCatChem* **6**, 1860-1862, doi:<https://doi.org/10.1002/cctc.201400015> (2014).
- 36 Jiang, X. *et al.* A General Method for N-Methylation of Amines and Nitro Compounds with Dimethylsulfoxide. *Chemistry – A European Journal* **20**, 58-63, doi:<https://doi.org/10.1002/chem.201303802> (2014).
- 37 Li, Y., Sorribes, I., Vicent, C., Junge, K. & Beller, M. Convenient Reductive Methylation of Amines with Carbonates at Room Temperature. *Chemistry* **21**, 16759-16763, doi:10.1002/chem.201502917 (2015).
- 38 Tundo, P. & Selva, M. The chemistry of dimethyl carbonate. *Accounts of chemical research* **35**, 706-716, doi:10.1021/ar010076f (2002).
- 39 Fatemeh, N. H., Farasat, Z., Nabavizadeh, S. M., Wu, G. & Abu-Omar, M. M. N-methylation versus oxidative addition using MeI in the reaction of organoplatinum(II) complexes containing pyrazine ligand. *J Organomet Chem* **880**, 232-240, doi:10.1016/j.jorganchem.2018.11.002 (2019).
- 40 Santhapuram, H. K. R., Datta, A., Hutt, O. E. & Georg, G. I. N-Methylation of the C3' Amide of Taxanes: Synthesis of N-Methyltaxol C and N-Methylpaclitaxel. *The Journal of Organic Chemistry* **73**, 4705-4708, doi:10.1021/jo800173h (2008).
- 41 Tsarev, V. N. *et al.* N-methylation of amines with methanol at room temperature. *Org Lett* **17**, 2530-2533, doi:10.1021/acs.orglett.5b01063 (2015).
- 42 Lu, C., Qiu, Z., Zhu, Y. & Lin, B.-L. Scalable direct N-methylation of drug-like amines using 12CO₂/13CO₂ by simple inorganic base catalysis. *Science Bulletin* **64**, 723-729, doi:<https://doi.org/10.1016/j.scib.2019.04.032> (2019).

- 43 Qiao, C., Liu, X.-F., Liu, X. & He, L.-N. Copper(II)-Catalyzed Selective Reductive Methylation of Amines with Formic Acid: An Option for Indirect Utilization of CO₂. *Organic Letters* **19**, 1490-1493, doi:10.1021/acs.orglett.7b00551 (2017).
- 44 Savourey, S., Lefèvre, G., Berthet, J. C. & Cantat, T. Catalytic methylation of aromatic amines with formic acid as the unique carbon and hydrogen source. *Chemical communications (Cambridge, England)* **50**, 14033-14036, doi:10.1039/c4cc05908e (2014).
- 45 Zhu, L., Wang, L.-S., Li, B., Li, W. & Fu, B. Methylation of aromatic amines and imines using formic acid over a heterogeneous Pt/C catalyst. *Catalysis Science & Technology* **6**, 6172-6176, doi:10.1039/C6CY00674D (2016).
- 46 Li, W. D., Zhu, D. Y., Li, G., Chen, J. & Xia, J. B. Iron-Catalyzed Selective N-Methylation and N-Formylation of Amines with CO₂. *Adv Synth Catal* **361**, 5098-5104, doi:10.1002/adsc.201900906 (2019).
- 47 Zheng, J., Darcel, C. & Sortais, J. B. Methylation of secondary amines with dialkyl carbonates and hydrosilanes catalysed by iron complexes. *Chemical communications (Cambridge, England)* **50**, 14229-14232, doi:10.1039/c4cc05517a (2014).
- 48 Deng, D., Hu, B., Yang, M. & Chen, D. Methylation of Amines and Ketones with Methanol Catalyzed by an Iridium Complex Bearing a 2-Hydroxypyridylmethylene Fragment. *Organometallics* **37**, 3353-3359, doi:10.1021/acs.organomet.8b00575 (2018).
- 49 Huang, S. *et al.* N-Methylation of ortho-substituted aromatic amines with methanol catalyzed by 2-arylbenzo[d]oxazole NHC-Ir(III) complexes. *Dalton T* **48**, 5072-5082, doi:10.1039/C9DT00218A (2019).
- 50 Santoro, O., Lazreg, F., Minenkov, Y., Cavallo, L. & Cazin, C. S. N-heterocyclic carbene copper(I) catalysed N-methylation of amines using CO₂. *Dalton transactions (Cambridge, England : 2003)* **44**, 18138-18144, doi:10.1039/c5dt03506f (2015).
- 51 Liu, Z. *et al.* Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol. *Adv Synth Catal* **359**, 4278-4283, doi:<https://doi.org/10.1002/adsc.201701044> (2017).
- 52 Huang, Z. *et al.* Mn-Catalyzed Selective Double and Mono-N-Formylation and N-Methylation of Amines by using CO(2). *ChemSuschem* **12**, 3054-3059, doi:10.1002/cssc.201900152 (2019).
- 53 Neumann, J., Elangovan, S., Spannenberg, A., Junge, K. & Beller, M. Improved and General Manganese-Catalyzed N-Methylation of Aromatic Amines Using Methanol. *Chemistry – A European Journal* **23**, 5410-5413, doi:<https://doi.org/10.1002/chem.201605218> (2017).
- 54 Pearson, D. E. & Bruton, J. D. Reductive Methylation of Amines. *J Am Chem Soc* **73**, 864-864, doi:10.1021/ja01146a522 (1951).
- 55 Xu, L., Li, X., Zhu, Y. & Xiang, Y. One-pot synthesis of N,N-dimethylaniline from nitrobenzene and methanol. *New Journal of Chemistry* **33**, 2051-2054, doi:10.1039/B905656D (2009).
- 56 Cui, X., Dai, X., Zhang, Y., Deng, Y. & Shi, F. Methylation of amines, nitrobenzenes and aromatic nitriles with carbon dioxide and molecular hydrogen. *Chemical Science* **5**, 649-655, doi:10.1039/C3SC52676C (2014).
- 57 Cui, X., Zhang, Y., Deng, Y. & Shi, F. N-Methylation of amine and nitro compounds with CO₂/H₂ catalyzed by Pd/CuZrO_x under mild reaction conditions. *Chemical Communications* **50**, 13521-13524, doi:10.1039/C4CC05119J (2014).
- 58 Zhang, L., Zhang, Y., Deng, Y. & Shi, F. Light-promoted N,N-dimethylation of amine and nitro compound with methanol catalyzed by Pd/TiO₂ at room temperature. *Rsc Adv* **5**, 14514-14521, doi:10.1039/C4RA13848A (2015).

- 59 Du, X.-L. *et al.* Direct Methylation of Amines with Carbon Dioxide and Molecular Hydrogen using Supported Gold Catalysts. *Chemsuschem* **8**, 3489-3496, doi:<https://doi.org/10.1002/cssc.201500486> (2015).
- 60 Kon, K., Siddiki, S. M., Onodera, W. & Shimizu, K. Sustainable heterogeneous platinum catalyst for direct methylation of secondary amines by carbon dioxide and hydrogen. *Chemistry* **20**, 6264-6267, doi:10.1002/chem.201400332 (2014).
- 61 Wang, L.-M. *et al.* Photocatalytic N-Methylation of Amines over Pd/TiO₂ for the Functionalization of Heterocycles and Pharmaceutical Intermediates. *Acs Sustain Chem Eng* **6**, 15419-15424, doi:10.1021/acssuschemeng.8b03855 (2018).
- 62 Dong, X., Wang, Z., Yuan, Y. & Yang, Y. Synergistic catalysis of Cu⁺/Cu⁰ for efficient and selective N-methylation of nitroarenes with para-formaldehyde. *Journal of Catalysis* **375**, 304-313, doi:<https://doi.org/10.1016/j.jcat.2019.06.022> (2019).
- 63 Hahn, G., Kunnas, P., de Jonge, N. & Kempe, R. General synthesis of primary amines via reductive amination employing a reusable nickel catalyst. *Nature Catalysis* **2**, 71-77, doi:10.1038/s41929-018-0202-6 (2019).
- 64 Murugesan, K., Chandrashekhar, V. G., Senthamarai, T., Jagadeesh, R. V. & Beller, M. Reductive amination using cobalt-based nanoparticles for synthesis of amines. *Nature protocols* **15**, 1313-1337, doi:10.1038/s41596-019-0258-z (2020).
- 65 Corma, A. & Serna, P. Chemoselective hydrogenation of nitro compounds with supported gold catalysts. *Science* **313**, 332-334, doi:10.1126/science.1128383 (2006).
- 66 Hughes, M. D. *et al.* Tunable gold catalysts for selective hydrocarbon oxidation under mild conditions. *Nature* **437**, 1132-1135, doi:10.1038/nature04190 (2005).
- 67 Munnik, P., de Jongh, P. E. & de Jong, K. P. Recent Developments in the Synthesis of Supported Catalysts. *Chemical Reviews* **115**, 6687-6718, doi:10.1021/cr500486u (2015).
- 68 Sankar, M. *et al.* Designing bimetallic catalysts for a green and sustainable future. *Chem Soc Rev* **41**, 8099-8139, doi:10.1039/c2cs35296f (2012).
- 69 Torres Galvis, H. M. *et al.* Supported iron nanoparticles as catalysts for sustainable production of lower olefins. *Science* **335**, 835-838, doi:10.1126/science.1215614 (2012).
- 70 Zecevic, J., Vanbutsele, G., de Jong, K. P. & Martens, J. A. Nanoscale intimacy in bifunctional catalysts for selective conversion of hydrocarbons. *Nature* **528**, 245-248, doi:10.1038/nature16173 (2015).
- 71 Deng, D. *et al.* Iron encapsulated within pod-like carbon nanotubes for oxygen reduction reaction. *Angewandte Chemie (International ed. in English)* **52**, 371-375, doi:10.1002/anie.201204958 (2013).
- 72 Haslam, G. E., Chin, X. Y. & Burstein, G. T. Passivity and electrocatalysis of nanostructured nickel encapsulated in carbon. *Physical chemistry chemical physics : PCCP* **13**, 12968-12974, doi:10.1039/c1cp20701f (2011).
- 73 Lefèvre, M., Proietti, E., Jaouen, F. & Dodelet, J. P. Iron-based catalysts with improved oxygen reduction activity in polymer electrolyte fuel cells. *Science* **324**, 71-74, doi:10.1126/science.1170051 (2009).
- 74 Jagadeesh, R. V., Junge, H. & Beller, M. Green synthesis of nitriles using non-noble metal oxides-based nanocatalysts. *Nat Commun* **5**, 4123, doi:10.1038/ncomms5123 (2014).
- 75 Luo, W. *et al.* High performing and stable supported nano-alloys for the catalytic hydrogenation of levulinic acid to γ -valerolactone. *Nat Commun* **6**, 6540, doi:10.1038/ncomms7540 (2015).
- 76 Chen, T.-C. *et al.* In Situ Monitoring the Role of Working Metal Catalyst Nanoparticles for Ultrahigh Purity Single-Walled Carbon Nanotubes. *Advanced Functional Materials* **23**, 5066-5073, doi:<https://doi.org/10.1002/adfm.201300614> (2013).

- 77 Deng, J. *et al.* Highly active and durable non-precious-metal catalysts encapsulated in carbon nanotubes for hydrogen evolution reaction. *Energ Environ Sci* **7**, 1919-1923, doi:10.1039/C4EE00370E (2014).
- 78 Liu, Y., Jiang, H., Zhu, Y., Yang, X. & Li, C. Transition metals (Fe, Co, and Ni) encapsulated in nitrogen-doped carbon nanotubes as bi-functional catalysts for oxygen electrode reactions. *J Mater Chem A* **4**, 1694-1701, doi:10.1039/C5TA10551J (2016).
- 79 Friedfeld, M. R. *et al.* Cobalt precursors for high-throughput discovery of base metal asymmetric alkene hydrogenation catalysts. *Science* **342**, 1076-1080, doi:10.1126/science.1243550 (2013).
- 80 Jagadeesh, R. V. *et al.* Nanoscale Fe₂O₃-based catalysts for selective hydrogenation of nitroarenes to anilines. *Science* **342**, 1073-1076, doi:10.1126/science.1242005 (2013).
- 81 Prieto, G., Zečević, J., Friedrich, H., de Jong, K. P. & de Jongh, P. E. Towards stable catalysts by controlling collective properties of supported metal nanoparticles. *Nature materials* **12**, 34-39, doi:10.1038/nmat3471 (2013).
- 82 Chen, H.-A. *et al.* Measurement of Interlayer Screening Length of Layered Graphene by Plasmonic Nanostructure Resonances. *The Journal of Physical Chemistry C* **117**, 22211-22217, doi:10.1021/jp312363x (2013).
- 83 Guinea, F. Charge distribution and screening in layered graphene systems. *Physical Review B* **75**, 235433, doi:10.1103/PhysRevB.75.235433 (2007).
- 84 Stauber, T., Peres, N. M. R. & Guinea, F. Electronic transport in graphene: A semiclassical approach including midgap states. *Physical Review B* **76**, 205423, doi:10.1103/PhysRevB.76.205423 (2007).
- 85 Deng, J., Ren, P., Deng, D. & Bao, X. Enhanced electron penetration through an ultrathin graphene layer for highly efficient catalysis of the hydrogen evolution reaction. *Angewandte Chemie (International ed. in English)* **54**, 2100-2104, doi:10.1002/anie.201409524 (2015).
- 86 Liu, J. *et al.* Facile synthesis of controllable graphene-co-shelled reusable Ni/NiO nanoparticles and their application in the synthesis of amines under mild conditions. *Green Chemistry* **22**, 7387-7397, doi:10.1039/D0GC02421J (2020).
- 87 Cabrero-Antonino, J. R., Alberico, E., Junge, K., Junge, H. & Beller, M. Towards a general ruthenium-catalyzed hydrogenation of secondary and tertiary amides to amines. *Chemical Science* **7**, 3432-3442, doi:10.1039/C5SC04671H (2016).
- 88 Ge, X., Luo, C., Qian, C., Yu, Z. & Chen, X. RANEY® nickel-catalyzed reductive N-methylation of amines with paraformaldehyde: theoretical and experimental study. *Rsc Adv* **4**, 43195-43203, doi:10.1039/C4RA04414B (2014).