ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

N-Dimethylation and *N*-Functionalization of Amines Using Ru Nanoparticle Catalysts and Formaldehyde or Functional Aldehydes as the Carbon Source

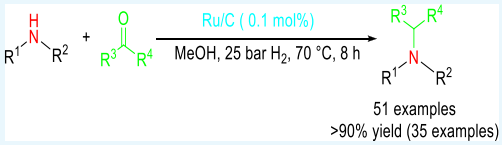
Jianguo Liu,*,# Yanpei Song,# Xiang Wu, and Longlong Ma*

Cite This: *ACS Omega* 2021, 6, 22504−22513

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: *N*-methylated amines are essential bioactive compounds and have been widely used in the fine and bulk chemical industries, as well as in pharmaceuticals, agrochemicals, and dyes. Developing green, efficient, and low-cost catalysts for methylation of amines by using efficient and easily accessible methylating reagents is highly desired yet remains a significant challenge. Herein, we report the selective *N*-dimethylation of different functional amines with different functional aldehydes under easy-to-handle and industrially applicable conditions using carbon-supported Ru nanoparticles (Ru/C) as a heterogeneous catalyst. A broad spectrum of amines could be efficiently converted to their corresponding *N*,*N*-dimethyl amines with good compatibility of various functional groups. This method is widely applicable to *N*-dimethylation of primary amines including aromatic, aliphatic amines with formaldehyde, and synthesis of tertiary amines from primary, secondary amines with different functional aldehydes. The advantage of this newly described method includes operational simplicity, high turnover number, the ready availability of the catalyst, and good functional group compatibility. This Ru/C catalyzed *N*-dimethylation reaction possibly proceeds through a two-step *N*-methylation reaction process.



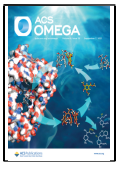
INTRODUCTION

N-Functionalized amines, especially *N*-methyl amines and form-amides, are very important intermediates and building blocks as they are widely used in the synthesis of dyes, perfumes, pesticides, and pharmaceutical products.[1] *N*-methylated compounds generally prepared from the *N*-methylation method, which is an efficient and powerful method for regulating the biological and pharmaceutical properties by incorporating into a magic methyl group, are also prevalent in naturally occurring and synthetic biologically active compounds.[1d2] As reported by Njarqarson and co-workers in the top 200 Small Molecule Pharmaceuticals by Retail Sales in 2018, there were more than 25 of the top 200 prescribed pharmaceutical products containing *N*-monomethyl or *N*-dimethyl groups.[3] Specifically, since the global pandemic of novel corona-virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2) widely spread worldwide, *N*-methylated functional drugs especially azithromycin showed to be highly effective in the control of COVID-19 infection (Figure 1).[4]

Since methyl-substituted amines exist frequently as bioactive compounds and pharmaceutical drugs, the development of more efficient, green, economical, and sustainable methylation processes continuously attracted the attention of chemists in the last few decades.[1d,2a,e,5] Until then, several methodologies for the synthesis of *N*-methylamines have been developed and widely used in academics and industry. The traditional methodologies for *N*-methylation typically employ the methylation of amines with activated methyl compounds, such as toxic methyl iodide,[6] dimethyl sulfoxide,[2d7] or dimethyl carbonate.[8] These processes have serious issues that are operationally problematic and generally suffer from narrow scopes of amines and generation of byproducts and a large amount of waste. 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 C_1 sources.[1d,2a−c,5h,j,l,9] In recent years, with the environmental problem issues and the green, sustainable chemistry, the C_1 sources used in transition-metal-catalyzed *N*-methylation of amines have predominantly more environmentally benign and safer methylation reagents, such as MeOH,[5j10] CO_2,[1d,e,2c,5e,f,l,9i,11] HCOOH,[12] (*para*)-formaldehyde,[9f1314] and so on (Figure 2a,b). Until now, various homogeneous and heterogeneous metal catalysts have been reported.

As for the homogeneous catalyst system, Ru complex catalysts have been widely used and studied for the direct *N*-methylation of amines using CO_2 as a C_1 source. In 2013, Beller and co-workers did pioneer work on the combination of homogeneous catalyst systems, applying commercially available $RuCl_2(dmso)_4$ and $BuPAd_2$ ligands for the general

Received: April 12, 2021
Accepted: July 8, 2021
Published: August 26, 2021



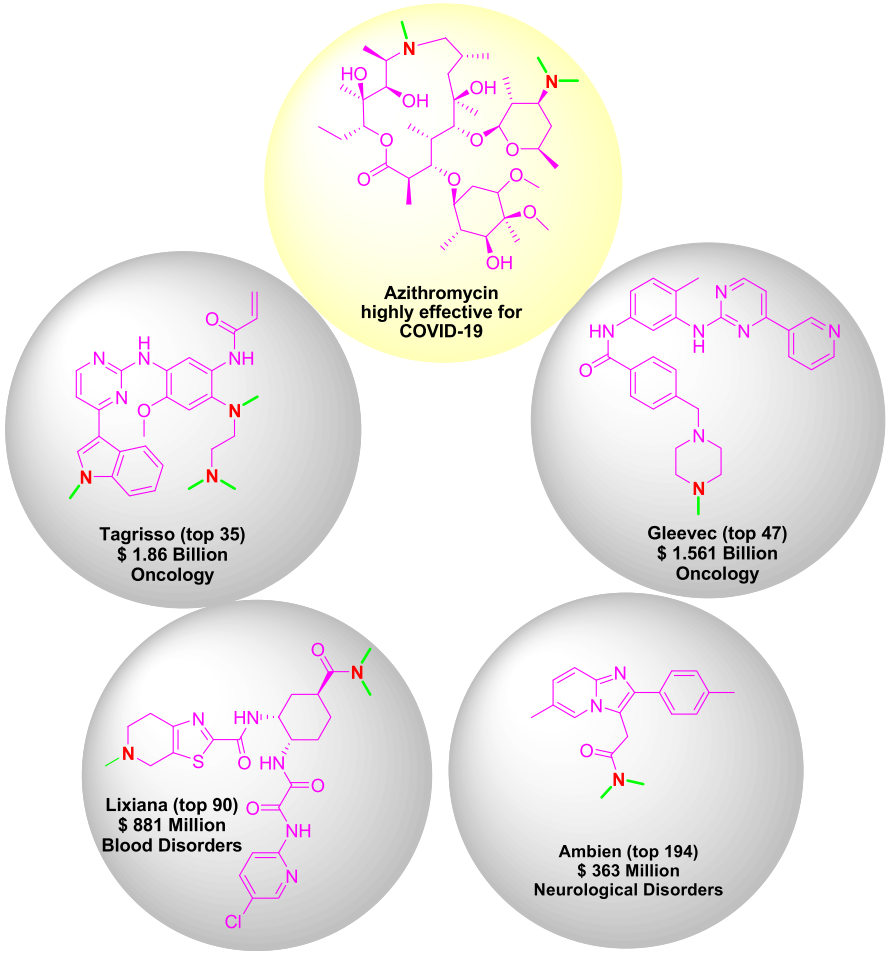


Figure 1. Pharmaceuticals containing *N*-methylated and *N*-dimethylated drugs.

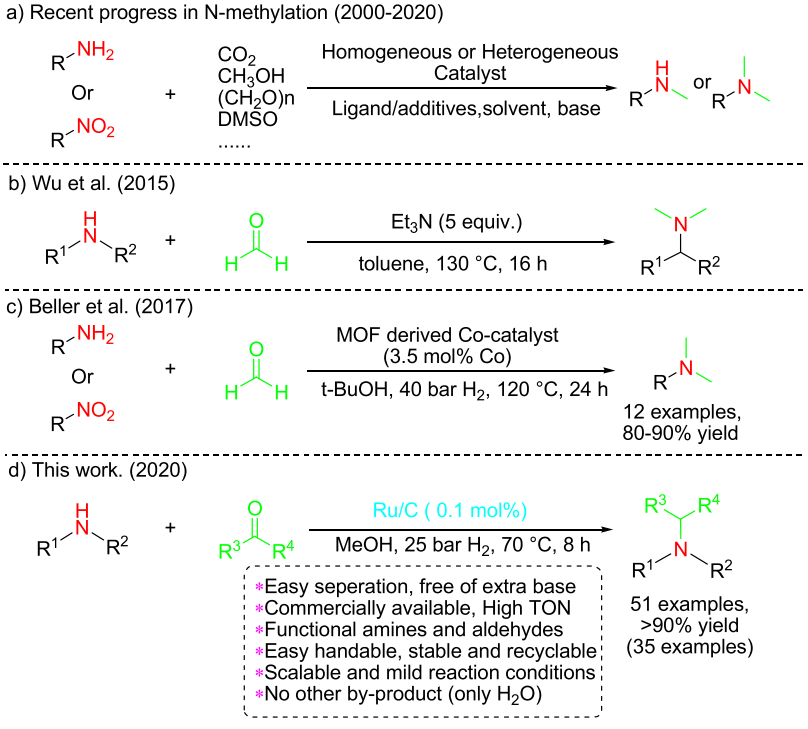


Figure 2. *N*-Methylation of amines or nitrobenzenes with various methylation agents.

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

methylation of amines using $PhSiH_3$ and CO_2.[1d] Many aromatic and aliphatic, secondary, and primary amines with various functional groups were well tolerated under the optimized reaction conditions (30 bar CO_2, 4 equiv $PhSiH_3$, toluene, 100 °C, and 16 h). In the meantime, they also demonstrated highly selective *N*-methylation of amines using an in situ combination of commercially available Ru $(acac)_3$, triphos, and acid or LiCl additives.[2c] Various kinds of monomethylation and dimethylation products were obtained in good to excellent yields under the optimized reaction conditions (20 atm CO_2, 60 atm H_2, THF, 140 °C, 24 h). Later, Klankermayer and co-workers also found that the readily commercially available Ru (triphos)(tmm) complex and the $HNTf_2$ acid served as a highly efficient homogeneous catalyst system for catalytic reductive *N*-methylation of imines using CO_2 and H_2.[2e] Some tertiary *N*-methyl amines were produced with moderate to excellent yields in the three-component coupling reaction of primary amines, aldehydes, and CO_2. From then on, not only various homogeneous Ru-catalyzed *N*-methylation systems $[RuCp^*Cl_2]_2$/dpePhos[10a] and $[Ru(p\text{-cymene})I_2]_2$[13b] but also other transition-metal homogeneous catalyst systems such as Fe,[5m,9h,15] Karstedt's complex,[8b16] Ir,[5j17] Rh,[5n] Cu,[5l,9d,12c] Co,[10c] and Mn[5h,9g,18] have been successively developed.

It is known that homogeneous catalysts normally suffer from several disadvantages such as difficult separation of the catalyst/product, the necessity for additives (ligands, acids, and salts), and difficulty to reuse. As such, from both economic and environmental perspectives, effective heterogeneous catalysis has also been developed and widely used in transition-metal-catalyzed *N*-methylation reactions. In 1951, Pearson and Bruton reported the reductive methylation of amines with the pre-reduced Adams catalyst Pt using H_2 and HCHO.[19] 79% yield of *N*,*N*-dimethylglycine was obtained from the reductive methylation of glycine. Half a decade later, in 2009, Li and co-workers[20] described pretreated Raney Ni-catalyzed *N*-methylation of nitroarenes with methanol under 170 °C and 3 MPa Ar. Methanol served as a hydrogen source, alkylating reagent, and solvent simultaneously. Several years later, Rong and co-workers[21] reported the one-pot synthesis of *N*,*N*-dimethyl anilines with HCHO and nitroarenes catalyzed by the quenched skeletal Cu catalyst. Many *N*,*N*-dimethyl aniline products were obtained in good to excellent selectivity under the optimized reaction condition (nitroarenes: 6 mmol, HCHO: 18 mmol, 0.5 g skeletal Cu catalyst, 13 bar H_2, 70−100 °C, 37−127 min). Recently, Shi and co-workers[5c,9a] found that two simple heterogeneous catalysts $CuAlO_x$ and Pd/$CuZrO_x$, which showed high reactivity and selectivity for the transformation of primary and secondary amines as well as nitro compounds into *N*-methyl or *N*,*N*-dimethyl products with CO_2 and H_2 (reaction conditions: 30−100 bar, 150−170 °C, 30−48 h). They also developed the efficient TiO_2-supported nano-Pd catalyzed *N*-methylation of nitro compounds with MeOH under UV irradiation at room temperature.[22] In 2015, Cao and co-workers[23] reported the first heterogeneous Au/rutile catalyst for the one-pot *N*-methylation of nitroarenes. A variety of amines including aromatic, aliphatic, secondary, and primary amines were converted smoothly to the corresponding methylation products with good to excellent yields under the optimized reaction conditions (2 MPa CO_2, 6 MPa H_2, 140−170 °C, 7 h). Recently, much more efficient transition-metal heterogeneous catalyst systems such as Pt-MoOx/TiO_2,[9b] Au/Al_2O_3,[23] PdZn/TiO_2,[9i] and Pd/TiO_2,[24] have been successively developed. Specifically, inexpensive copper-[9f] and cobalt-based[25] (Figure 2c) heterogeneous catalysts are found to be good alternatives of palladium-base catalysts or iron-, nickel-, copper-, and cobalt-based homogeneous catalysts with toxic ligands in recent years. In 2019, Yang and co-workers[9f] developed an inexpensive heterogeneous Cu nanoparticle catalyst derived from CuAl-layered double hydroxide via an *in situ* topotactic transformation process. The heterogeneous catalyst Cu/Al_2O_3 demonstrated excellent efficiency for one-pot reductive *N*-methylation of easily available nitroarenes with *para*-formaldehyde with good compatibility of various functional groups under the optimized reaction conditions (nitroarenes: 0.5 mmol, Cu/Al_2O_3 12 mg, 27 mol % Cu, 15 equiv $(CH_2O)_n$, 2 equiv Na_2CO_3, 130 °C). So far, the state of reported works has one or several of the following issues: transition-metal-based homogeneous catalysts generally need complex or even toxic ligands and also tedious product separation processes; earth-abundant transition-metal-based heterogeneous catalyzed *N*-methylation usually was carried out under harsh conditions; a high equivalent of base and/or reducing agents was required in many of the homogeneous and heterogeneous catalyst systems. To overcome these problems, specifically in the sustainable and environmental perspective, several factors are required for developing a new methodology of *N*-methylamines, including the use of a cheap, green reagent and green byproduct generation (in general, H_2O) or a fully atom-economic process without any byproduct formation; fairly cheap and industrially scalable heterogeneous catalysts; and mild conditions, easy and convenient procedures of product separation, and downstream processing.

Recently, we found that the graphene sphere-encapsulated uniform Ni/NiO nanoalloy catalysts Ni/NiO@C were efficient in the reductive amination of carbonyl compounds.[26] Surprisingly, several *N*,*N* dimethylation products were obtained in excellent yield using aromatic amines and formaldehyde. In the meantime, we also found that the commercially available Ru/C showed excellent reactivity and selectivity for *N*,*N*-dimethyl benzylamine. To the best of our knowledge, commercially available Ru/C has remained unexplored for *N*-methylation of aromatic amines using inexpensive, readily available formaldehyde as a C_1 source and a H_2 source. This Ru/C has a lot of benefits such as the following: (1) it is air-stable, easy to handle, and readily available; (2) it shows excellent catalytic activity in the absence of a ligand and base; (3) it can be easily separated from the reaction medium by simple filtration; and (4) the only byproduct is H_2O. Inspired by the abovementioned developments on *N*-methylation and based on the attractive catalytic features of Ru/C, we describe here an efficient *N*-methylation reaction utilizing different functional aldehydes and amines. Using this commercially available heterogeneous catalyst and starting from inexpensive, readily available aldehydes, primary and secondary amines, and molecular hydrogen, we undertook the synthesis of >50 functionalized, structurally diverse linear and branched benzylic and aliphatic *N*-methylation products.

EXPERIMENTAL SECTION

The reaction was conducted in a stainless steel autoclave (Anhui Kemi Machinery Technology Co., Ltd., China) with six wells (10 mL per well), one thermocouple, and one set of circulating water cooling equipment. Each well has a glass lining and loaded with one 10 mm magnetic stirring bar, 0.5

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

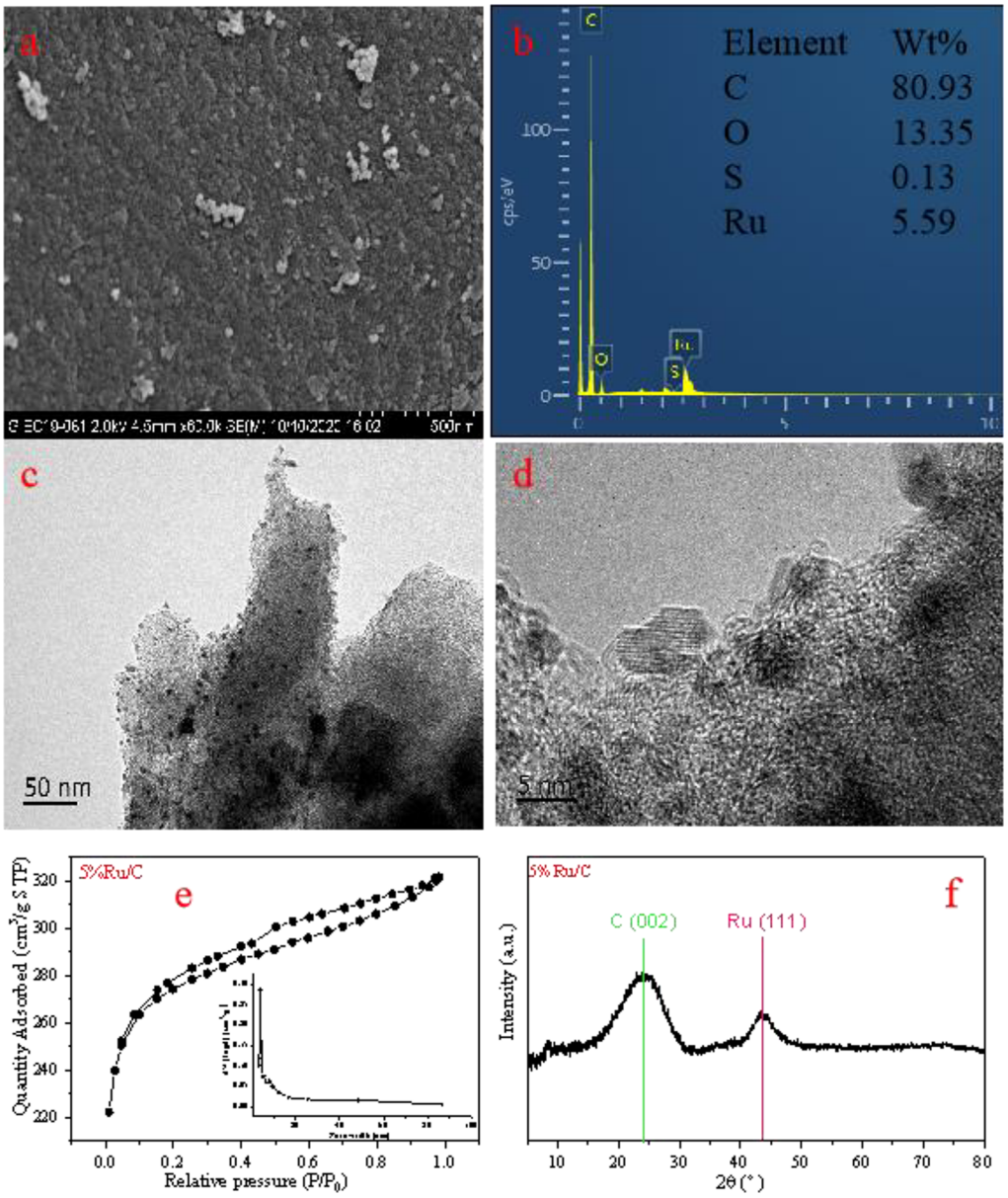


Figure 3. Characterization of Ru/C. SEM images of 5% Ru/C (a), EDS elemental analysis of 5% Ru/C (b), HRTEM images of 5% Ru/C (c and d), N_2 adsorption and desorption isotherm curves and pore size distribution profile of 5% Ru/C (e), and XRD images of 5% Ru/C (f).

mmol of the corresponding amine, 3 mmol of the corresponding aldehyde, 0.05 mmol of 1,3,5-trimethoxybenzene, 10 mg of catalyst, and 5 mL of methanol. Then, the autoclave was sealed and purged with H_2 three times at 2.5 MPa pressure and was pressurized with 2.5 MPa H_2. The autoclave was placed into a heating mantle, and the stirring rate was set at 300 rpm. The autoclave was preheated from room temperature to the target temperature (inside temperature detected by the thermocouple) at a rate of 2 °C·min^{-1}. The target temperature was used as the reaction temperature. The reaction was proceeding at the reaction temperature for the required time. After the reaction, the remaining gas was discharged after the autoclave was cooled down to room temperature. The reaction solutions were collected with a dropper and filtered. The catalyst was immobilized on a magnetic stirring bar and washed thoroughly with ethanol and water. The catalyst (together with a magnetic stirring bar) was then dried at −48 °C for 12 h in vacuum by using a freeze dryer.

The reaction products were identified by GC−MS and ^{1}H NMR, and the yields of reaction products were determined by GC with 1,3,5-trimethoxybenzene as the internal standard. For ^{1}H NMR analysis, about 2 mL of reaction solutions was concentrated by rotary evaporation, and then 0.5 mL of $CDCl_3$ was added (preneutralized with basic Al_2O_3).

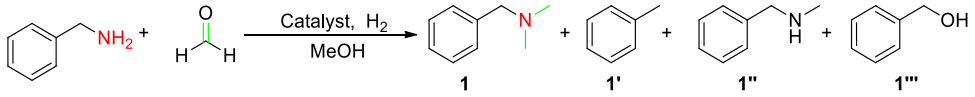
The source of the chemicals, specific reaction steps, analysis methods, etc. are described in detail in the Supporting Information.

RESULTS AND DISCUSSION

The scanning electron microscopy (SEM) images for the Ru/C sample (Figure 3a) showed small catalyst particles. Elemental analysis indicated that the catalyst consisted of 5.5 wt % Ru. The TEM measurements were performed to investigate the morphology and distribution of Ru species in

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

Table 1. Optimization of Transition-Metal-Catalyzed *N*-Methylation of Benzylamine[a]



entry	catalyst	H_2 pressure (bar)	temperature (°C)	time (h)	conversion (%)	yield of **1** (%)
1	Ru/C	20	90	12	>99	93
2	Ru/C	20	80	12	>99	93
3	Ru/C	20	70	12	>99	98
4	Ru/C	20	60	12	>99	71
5	Ru/C	20	50	12	88	45
6	Ru/C	20	r.t.	12	63	nd
7	Ru/C	20	70	8	>99	97
8	Ru/C	20	70	4	>99	70
9	Ru/C	20	70	2	>99	43
10	Ru/C	25	70	8	>99	99
11	Ru/C	15	70	8	>99	89
12	Ru/C	10	70	8	>99	52
13	Pt/C	25	70	8	>99	99
14	Pd/C	25	70	8	>99	95
15	Rh/C	25	70	8	>99	76
16	NiO	25	70	8	>99	nd
17	Fe	25	70	8	80	nd
18	Zn	25	70	8	93	12
19	Raney-Ni	25	70	8	>99	99
20	Raney-Co	25	70	8	>99	99

[a]Reaction conditions: 10 mg of catalyst, 5% Ru/C catalyst, 0.5 mmol of benzylamine, 3 mmol of formaldehyde, 5 mL of methanol. Yields and conversion were determined by GC using 1,3,5-trimethoxybenzenen as an internal standard.

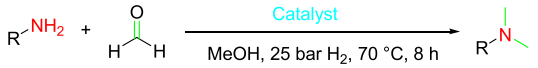
the catalyst Ru/C. It was observed that Ru NPs with an average size of 10 nm are non-uniformly dispersed on carbon and some Ru nanoparticles were agglomerated at some parts (Figure 3c). The nitrogen physisorption measurements for the Ru/C catalyst in the specific surface area (Brunauer–Emmett–Teller method) were following the SEM phenomenon. The Ru/C catalyst has quite a large surface area with 1061.8 $m^2\ g^{-1}$ with an almost identical pore size distribution (>95% micropores with a total pore volume of 0.498 $cm^3\ g^{-1}$ and average pore width of 1.87 nm) (Figure 3e). The XRD spectra showed that the graphitic carbon shell and the Ru nanoparticles phases are present in the Ru/C sample (Figure 3f). The weak and broad C (002) peak also confirm that thin graphene shells have been formed, which agrees with the statistical analysis of layers in TEM (Figure 3d). For the Ru/C catalyst containing a small amount of Ru species, a diffraction peak was observed at about 44.3° corresponding to the Ru (111) plane.

Initially, heterogeneous transition-metal-catalyzed *N*-methylation was evaluated using benzylamine and formaldehyde. In the beginning, we investigated different reaction temperatures of Ru/C catalyzed *N*-methylation and it turns out that the *N*-methylation can be carried out in excellent selectivity under a fairly mild reaction temperature of 70 °C. Further optimization showed that Ru/C catalyzed benzylamine smoothly to the corresponding *N*-dimethyl products in 8 h. As shown in Table 1, the hydrogen pressure had a great effect on the production of *N*-dimethyl products (entry **8**–**12**). Interestingly, unlike previously reported processes,[27,28] the commercially available Pt/C, Raney-nickel, and Raney-cobalt as well as Pd/C showed excellent reactivity and selectivity of >99% yield of *N*-dimethyl product **1**. NiO, iron powder, and zinc were not active in the methylation of benzylamine under the chosen conditions.

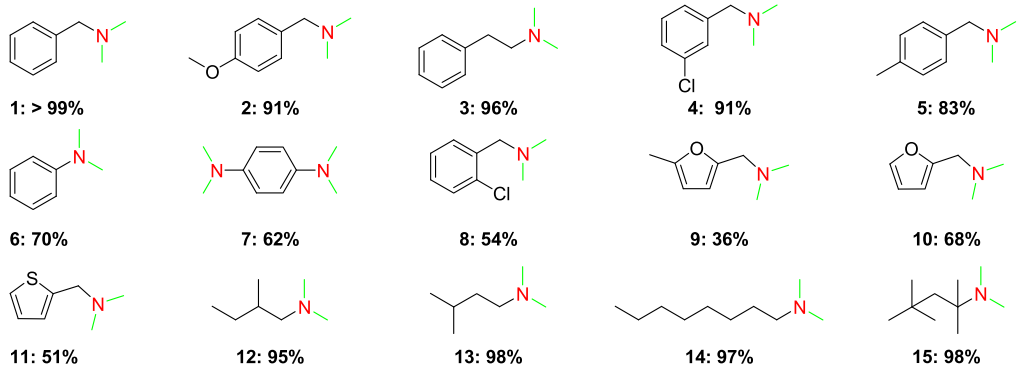
After having a convenient protocol in hand for the benchmark reaction, we explored the substrate scopes of Ru/C-catalyzed *N*-methylation of different functional primary amines with formaldehyde (Table 2). At first, 15 kinds of aromatic, heterocyclic, and aliphatic amines having different functional groups were converted to the corresponding *N*,*N*-dimethylamines in good to excellent yields using Ru/C. The strong electron-donating group −OMe in the *para* position has little effect on the catalytic reactivity and *N*,*N*-dimethylamine product **2** selectivity. The aromatic amine with an aliphatic chain was transformed to the corresponding dimethylation product **3** with excellent yield (96%). The *meta*-halo-substituted aromatic amine was also tolerated in this reaction and can be transformed to the *meta*-halo-substituted *N*,*N*-dimethylamine product **4** in excellent yield. The substrate having a weak electron-donating group −Me in the *para* position had a lower yield of 83% for the dimethylation product **5** compared with the one having a strong electron-donating group −OMe. Interestingly, the *N*,*N*-dimethylaniline **6** and N_1,N_1,N_4,N_4-tetramethylbenzene-1,4-diamine **7** could also be obtained in good yields of 70 and 62%, respectively. Probably due to the steric effect, the *ortho*-halo-substituted *N*,*N*-dimethylamines product **8** was only obtained in 54% yield. Interestingly, the biomass derivative reductive amination product cyclopenta-1,3-dienylmethanamine, prepared from the previous report process,[26] could also give the desired product **10** in 68% yield. Linear and branched aliphatic *N*,*N*-dimethylated products, which were previously seldom reported and some with low yield,[5c2329] were obtained in excellent yield under the optimized mild reaction conditions. The commercially available Pt/C, which showed an excellent capacity of catalyzing *N*-methylation of anilines and aromatic imines with formic acid in the presence of $PhSiH_3$ under 80 °C after 15 h,[12b] was also investigated under the present optimized

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

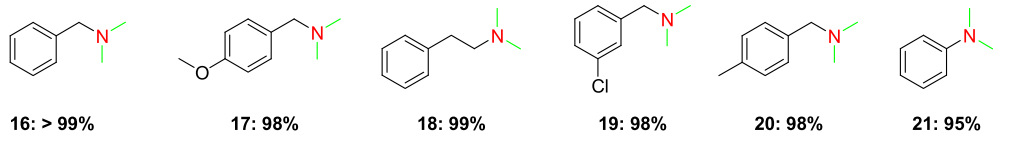
Table 2. Synthesis of Tertiary Amines by Transition-Metal-Catalyzed *N*-Methylation of Primary Amine[a]



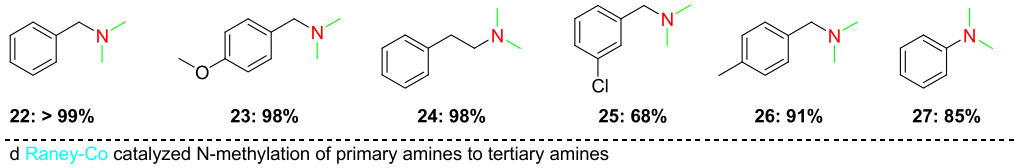
a 5% Ru/C catalyzed N-methylation of primary amines to tertiary amines



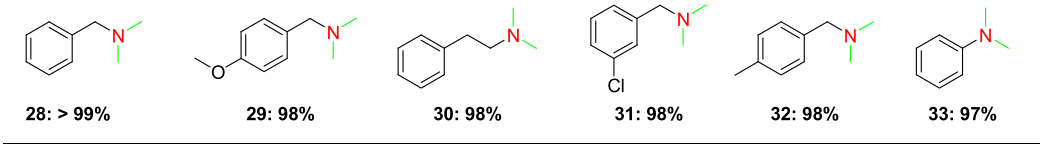
b 5% Pt/C catalyzed N-methylation of primary amines to tertiary amines



c Raney-Ni catalyzed N-methylation of primary amines to tertiary amines



d Raney-Co catalyzed N-methylation of primary amines to tertiary amines



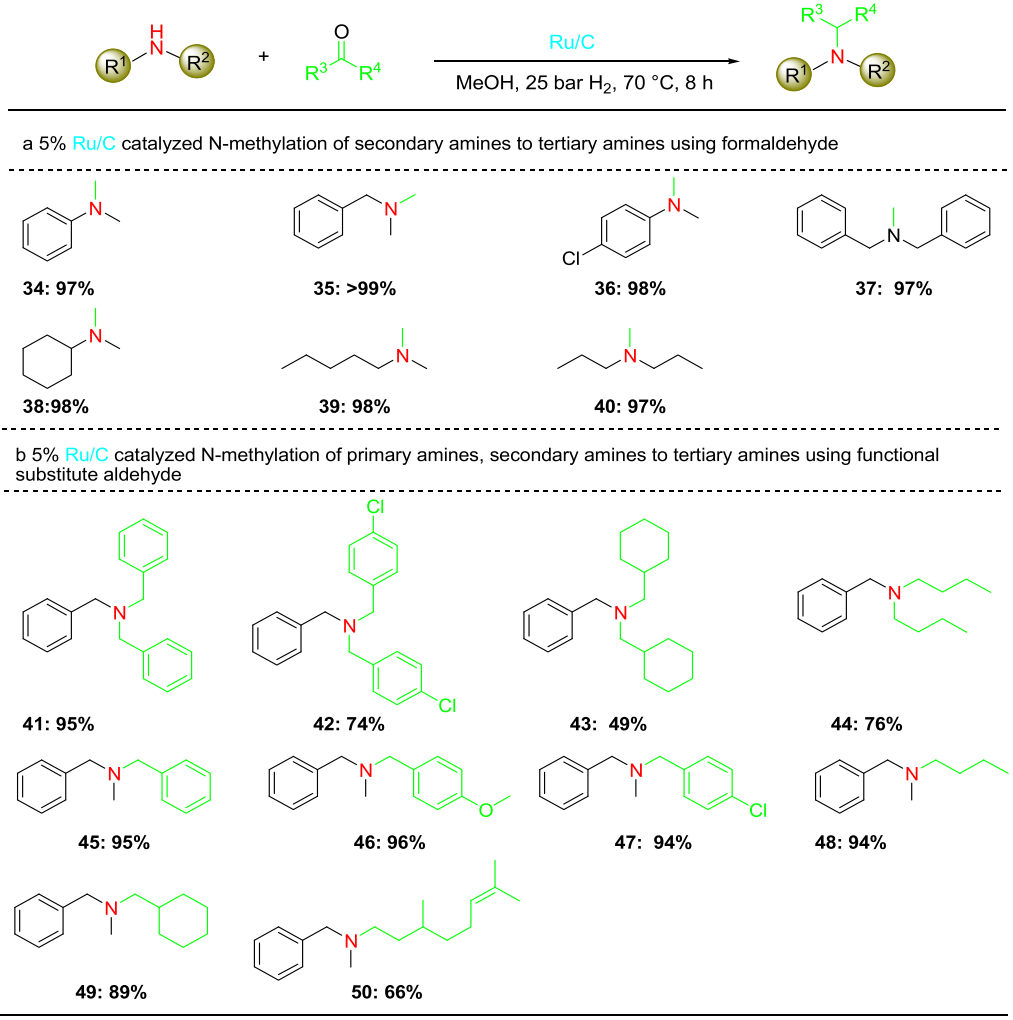
[a]Reaction conditions: 10 mg of catalyst, 5% Ru/C catalyst, 5% Pt/C catalyst, 0.5 mmol of amine substrate, 3 mmol of formaldehyde, 5 mL of methanol. Yields and conversion were determined by GC using 1,3,5-trimethoxybenzenen as an internal standard.

reaction conditions using green reducing reagent H_2. Notably, the presence of electron-donating or electron-withdrawing groups in the *para* position of the aromatic ring did not have a significant influence on the product yield (**17** and **20**). Nevertheless, the *meta* chloro-substrate was also well tolerated under the same reaction conditions (**19**). The commercially available Raney Ni and Raney Co catalysts were also investigated in this *N*-methylation reaction (**22**−**33**). Excellent yields were obtained for most of the tested substrates except for the *meta* chloro-substrate using Raney Ni as a catalyst.

Encouraged by the success in the synthesis of tertiary amine by *N*-methylation of primary amine catalyzed by Ru/C with formaldehyde, we then explored the synthesis of tertiary amine starting with secondary amine with formaldehyde or primary and secondary amines with different functional group-substituted aldehydes, which were seldom reported previously.(Table 3) To our delight, the non-substituted and halo-substituted aromatic secondary amines, *N*-methyl(phenyl)-methanamine, and aliphatic amines were converted to the corresponding tertiary amines with excellent yields using formaldehyde (**34**−**40**). Tertiary amines with different functional groups are important building blocks in bioactive molecule synthesis and materials application. In this context, we applied the Ru/C-catalyzed *N*-methylation methodology to synthesize tertiary amines using primary and secondary amines with different functional group-substituted aldehydes. Primary amines can react with benzaldehyde, halo-substituted benzaldehyde, and aliphatic aldehydes to give the tertiary amines in moderate to excellent yields (**41**−**45**). To the best of our knowledge, very limited work illustrated the synthesis of tertiary amines starting with secondary amines and functional aldehydes using the transition-metal catalyst *N*-methylation method. Notably, the Ru/C catalyst also showed excellent activity in the *N*-alkylation of secondary amines with aromatic, *para*-substituted aromatic aldehydes as well as linear and cyclic aliphatic aldehydes (**46**−**50**). Meanwhile, we also tested the catalyst's reusability, and after three recycle tests, the yield of **1** was dropped from 99 to 60% due to the leaching of the transition metal. Thus, we are still focusing on designing and preparing more suitable catalyst supports, like graphene-encapsulated transition-metal catalysts, which were reported

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

Table 3. Synthesis of Tertiary Amines by Ru/C-Catalyzed *N*-Methylation of Primary, Secondary Amines with Different Functional Aldehydes[a]



[a]Reaction conditions: 10 mg of 5% Ru/C catalyst, 0.5 mmol of amine, 3 mmol of aldehyde, 5 mL of methanol. Yields and conversion were determined by GC using 1,3,5-trimethoxybenzenen as an internal standard based on amine.

previously by our group, to avoid metal leaching and enhance the catalytic activity and reusability.

Mechanism Study. Based on the scope studies and the results from the control experiments, unlike the previously reported *N*-methylation process using the formaldehyde–formic acid process, CO_2 was not observed in this process. Thus, a possible proposed mechanism of Ru/C-catalyzed *N*-methylation of phenylmethanamine with formaldehyde is similar to the reported two-step *N*-methylation process,[9f,27] As depicted in Figure 4, first, phenylmethanamine reacted with one molecule of formaldehyde to form the intermediate (benzylamino) methanol then followed by a dehydration reaction to give the imine, enamines, or iminium ions. In the meantime, the H–H bond is activated on the surface of Ru/C, and the imine intermediate is also absorbed on Ru/C. Then, the imine was reduced by H–H to form *N*-methyl(phenyl)-methanamine. Surprisingly, the aliphatic amines also showed excellent reactivity in this Ru/C *N*-methylation reaction. They were unreactive in the previous reported Pt/C *N*-methylation reaction, probably due to the weak adsorption on Pt/C, which was caused by the lack of aromatic π–Pt interaction.[12b] In the second step of *N*-methylation of *N*-methyl(phenyl)-methanamine, it is slightly different from the first one. *N*-Methyl-*N*-methylene(phenyl)methanaminium is more stable in the alkaline aqueous after dehydration. Reduction of the iminium intermediate with H_2 and desorption deliver the *N*-methylation product *N*,*N*-dimethyl (phenyl) methanamine.

CONCLUSIONS

In conclusion, we have demonstrated a simple, practical, and highly efficient ruthenium heterogeneous catalyst for the *N*-methylation of a variety of amines with different functional aldehydes under mild conditions. Both primary and secondary amines with various functional groups including aromatic, aliphatic, halo-substituted, furan, and thiophene substituents can be methylated in the presence of formaldehyde at a temperature of 70 °C. Importantly, a variety of tertiary amines were synthesized in excellent yield up to 96% by Ru/C-catalyzed *N*-methylation of primary and secondary amines with different functional aldehydes. The obvious advantage of the presented method includes operational simplicity, high TON, the ready availability of the catalyst, and also good functional group compatibility. Since the simple catalyst system offers highly selective *N*-methylation under mild conditions but with

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504–22513

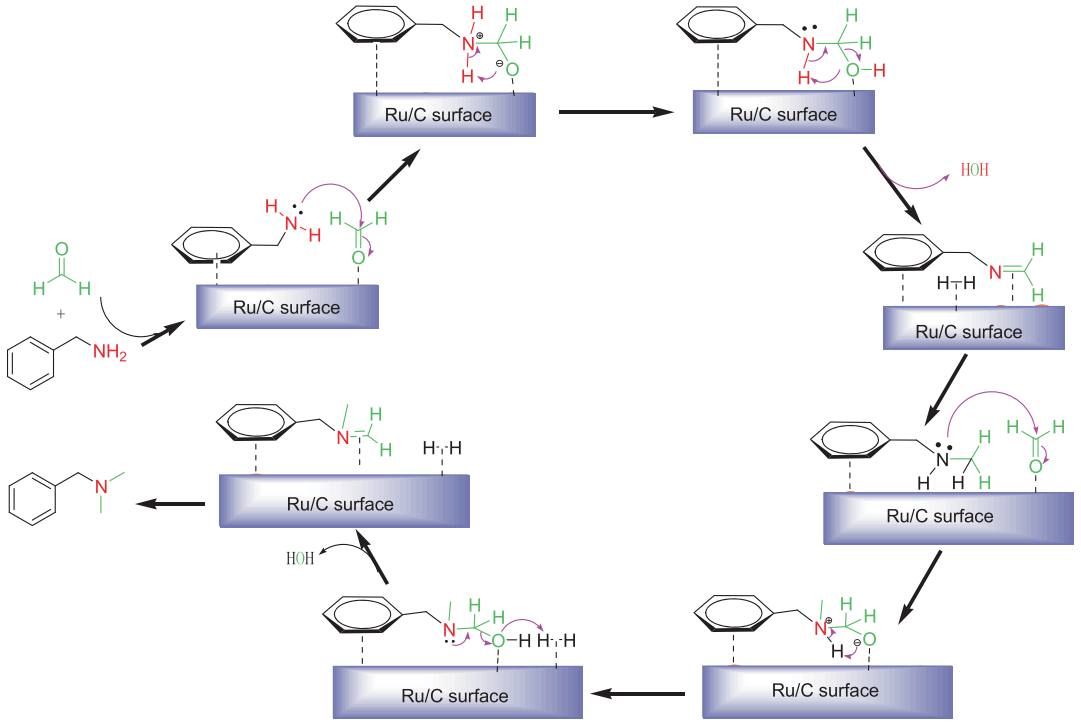


Figure 4. Possible pathway for Ru/C-catalyzed *N*-methylation of amines and aldehydes

moderate reusability due to catalysts metal leaching, it would be useful and important for further investigation in the design and preparation of a highly stable Ru-based catalyst avoiding leaching. At present, our laboratory is conducting design and research on the prevention of catalyst leaching and other related aspects.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01961.

Experimental materials and methods, physicochemical properties of catalysts, and synthetic products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jianguo Liu − *Key Laboratory of Energy Thermal Conversion and Control of Ministry of Education, School of Energy and Environment, Southeast University, Nanjing 210096, PR China; Dalian National Laboratory for Clean Energy, Chinese Academy of Sciences, Dalian 116023, P. R. China;* orcid.org/0000-0001-5105-5114; Email: liujg@ms.giec.ac.cn

Longlong Ma − *Key Laboratory of Energy Thermal Conversion and Control of Ministry of Education, School of Energy and Environment, Southeast University, Nanjing 210096, PR China; 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;* orcid.org/0000-0003-3848-5149; Email: mall@ms.giec.ac.cn

Authors

Yanpei Song − *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*

Xiang Wu − *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*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c01961

Author Contributions

[#]J.G.L. and Y.P.S. contributed equally to this work.

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. X.W. performed substrate scope experiments. J.G.L. and Y.P.S wrote the paper. All authors discussed the results and assisted during manuscript preparation.

Notes

The authors declare no competing financial interest.
Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

■ ACKNOWLEDGMENTS

This work was supported financially by the National Key R&D Program of China (2018YFB1501500), the National Natural Science Foundation of China (51976225), the DNL Cooperation Fund, and the Chinese Academy of Sciences (DNL201916).

REFERENCES

(1) (a) Kalasz, H. Biological Role of Formaldehyde, and Cycles Related to Methylation, Demethylation, and Formaldehyde Production. *Mini-Rev. Med. Chem.* **2003**, *3*, 175−192. (b) 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.* **2004**, *126*, 7368−7377. (c) Waterman, K. C.; Arikpo, W. B.; Fergione, M. B.; Graul, T. W.; Johnson, B. A.; Macdonald, B. C.; Roy, M. C.; Timpano, R. J. N-methylation and N-formylation of a secondary amine drug (Varenicline) in an osmotic tablet. *J. Pharm. Sci.* **2008**, *97*, 1499−1507. (d) Li, Y.; Fang, X.; Junge, K.; Beller, M. A General Catalytic Methylation of Amines Using Carbon Dioxide. *Angew. Chem., Int. Ed.* **2013**, *52*, 9568−9571. (e) 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. *Nat. Protoc.* **2017**, *12*, 417−428. (f) Dasgupta, S.; Castro, L. M.; Tashima, A. K.; Fricker, L. Quantitative Peptidomics Using Reductive Methylation of Amines. In *Peptidomics*; Humana Press 2018, *1719*, 161−174.

(2) (a) 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. Ed.* **2013**, *52*, 9554−9557. (b) Jacquet, O.; Frogneux, X.; Das Neves Gomes, C.; Cantat, T. CO_2 as a C_1-building block for the catalytic methylation of amines. *Chem. Sci.* **2013**, *4*, 2127. (c) Li, Y.; Sorribes, I.; Yan, T.; Junge, K.; Beller, M. Selective Methylation of Amines with Carbon Dioxide and H_2. *Angew. Chem., Int. Ed.* **2013**, *52*, 12156−12160. (d) Atkinson, B. N.; Williams, J. M. J. Dimethylsulfoxide as an N-Methylation Reagent for Amines and Aromatic Nitro Compounds. *ChemCatChem* **2014**, *6*, 1860−1862. (e) 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. Ed.* **2014**, *53*, 11010−11014.

(3) Njardarson, J. *Top 200 Small Molecule Pharmaceuticals by Retail Sales in* 2018. https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Small%20Molecule%20Pharmaceuticals%202018V4.pdf (accessed 2020-10-27).

(4) (a) Whitehead, C. L.; Walker, S. P. Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. *Lancet* **2020**, *395*, No. e92. (b) Wu, R.; Wang, L.; Kuo, H.-C. D.; Shannar, A.; Peter, R.; Chou, P. J.; Li, S.; Hudlikar, R.; Liu, X.; Liu, Z.; Poiani, G. J.; Amorosa, L.; Brunetti, L.; Kong, A.-N. An Update on Current Therapeutic Drugs Treating COVID-19. *Curr. Pharmacol. Rep.* **2020**, *6*, 56−70. (c) Sanders, J. M.; Monogue, M. L.; Jodlowski, T. Z.; Cutrell, J. B. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). *Jama* **2020**, DOI: 10.1001/jama.2020.6019. (d) Gautret, P.; Lagier, J.-C.; Parola, P.; Hoang, V. T.; Meddeb, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V. E.; Tissot Dupont, H.; Honoré, S.; Colson, P.; Chabrière, E.; La Scola, B.; Rolain, J.-M.; Brouqui, P.; Raoult, D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents* **2020**, *56*, 105949.

(5) (a) Barclay, M. G.; Burawoy, A.; Thomson, G. H. A new method of nuclear methylation of aromatic amines and phenolic substances. *Nature* **1943**, *151*, 615−616. (b) Banerjee, S. P.; Snyder, S. H. METHYLTETRAHYDROFOLIC ACID MEDIATES N-METHYLATION AND O-METHYLATION OF BIOGENIC-AMINES. *Science* **1973**, *182*, 74−75. (c) Cui, X.; Dai, X.; Zhang, Y.; Deng, Y.; Shi, F. Methylation of amines, nitrobenzenes and aromatic nitriles with carbon dioxide and molecular hydrogen. *Chem. Sci.* **2014**, *5*, 649−655. (d) 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. Ed.* **2014**, *53*, 12876−12879. (e) Li, Y.; Yan, T.; Junge, K.; Beller, M. Catalytic methylation of C-H bonds using CO_2 and H_2. *Angew. Chem., Int. Ed.* **2014**, *53*, 10476−10480. (f) Tlili, A.; Frogneux, X.; Blondiaux, E.; Cantat, T. Creating added value with a waste: methylation of amines with CO_2 and H_2. *Angew. Chem., Int. Ed.* **2014**, *53*, 2543−2545. (g) Chen, W. C.; Shen, J. S.; Jurca, T.; Peng, C. J.; Lin, Y. H.; Wang, Y. P.; Shih, W. C.; Yap, G. P.; Ong, T. G. Expanding the Ligand Framework Diversity of Carbodicarbenes and Direct Detection of Boron Activation in the Methylation of Amines with CO_2. *Angew. Chem., Int. Ed.* **2015**, *54*, 15207−15212. (h) Elangovan, S.; Neumann, J.; Sortais, J. B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, 12641. (i) Dorko, E.; Szabo, M.; Kotai, B.; Papai, I.; Domjan, A.; Soos, T. Expanding the Boundaries of Water-Tolerant Frustrated Lewis Pair Hydrogenation: Enhanced Back Strain in the Lewis Acid Enables the Reductive Amination of Carbonyls. *Angew. Chem., Int. Ed.* **2017**, *56*, 9512−9516. (j) Liang, R.; Li, S.; Wang, R.; Lu, L.; Li, F. N-Methylation of Amines with Methanol Catalyzed by a Cp*Ir Complex Bearing a Functional 2,2 '-Bibenzimidazole Ligand N. *Org. Lett.* **2017**, *19*, 5790−5793. (k) Yan, T.; Feringa, B. L.; Barta, K. Direct N-alkylation of unprotected amino acids with alcohols. *Sci. Adv.* **2017**, *3*, No. eaao6494. (l) Li, X.-D.; Xia, S.-M.; Chen, K.-H.; Liu, X.-F.; Li, H.-R.; He, L.-N. Copper catalysis: ligand-controlled selective N-methylation or N-formylation of amines with CO_2 and phenylsilane. *Green Chem.* **2018**, *20*, 4853−4858. (m) Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal.* **2018**, *8*, 6440−6445. (n) Lam, R. H.; McQueen, C. M. A.; Pernik, I.; McBurney, R. T.; Hill, A. F.; Messerle, B. A. Selective formylation or methylation of amines using carbon dioxide catalysed by a rhodium perimidine-based NHC complex. *Green Chem.* **2019**, *21*, 538−549.

(6) (a) 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. *J. Org. Chem.* **2008**, *73*, 4705−4708. (b) 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.* **2019**, *880*, 232−240.

(7) Jiang, X.; Wang, C.; Wei, Y.; Xue, D.; Liu, Z.; Xiao, J. A General Method for N-Methylation of Amines and Nitro Compounds with Dimethylsulfoxide. *Chem. − Eur. J.* **2014**, *20*, 58−63.

(8) (a) Tundo, P.; Selva, M. The Chemistry of Dimethyl Carbonate. *Acc. Chem. Res.* **2002**, *35*, 706−716. (b) Li, Y.; Sorribes, I.; Vicent, C.; Junge, K.; Beller, M. Convenient Reductive Methylation of Amines with Carbonates at Room Temperature. *Chem. − Eur. J.* **2015**, *21*, 16759−16763.

(9) (a) Cui, X.; Zhang, Y.; Deng, Y.; Shi, F. N-Methylation of amine and nitro compounds with CO_2/H_2 catalyzed by Pd/CuZrO(x) under mild reaction conditions. *Chem. Commun.* **2014**, *50*, 13521−13524. (b) Kon, K.; Siddiki, S. M. A. H.; Onodera, W.; Shimizu, K.-i. Sustainable Heterogeneous Platinum Catalyst for Direct Methylation of Secondary Amines by Carbon Dioxide and Hydrogen. *Chem. − Eur. J.* **2014**, *20*, 6264−6267. (c) Rezayee, N. M.; Huff, C. A.; Sanford, M. S. Tandem amine and ruthenium-catalyzed hydrogenation of CO_2 to methanol. *J. Am. Chem. Soc.* **2015**, *137*, 1028−1031. (d) Santoro, O.; Lazreg, F.; Minenkov, Y.; Cavallo, L.; Cazin, C. S. J. N-heterocyclic carbene copper(I) catalysed N-methylation of amines using CO_2. *Dalton Trans.* **2015**, *44*, 18138−18144. (e) Zhen, W.; Li, B.; Lu, G.; Ma, J. Enhancing catalytic activity and stability for CO_2 methanation on Ni@MOF-5 via control of active species dispersion. *Chem. Commun.* **2015**, *51*, 1728−1731. (f) Dong, X.; Wang, Z.; Yuan, Y.; Yang, Y. Synergistic catalysis of Cu^+/Cu^0 for efficient and selective N-methylation of nitroarenes with para-formaldehyde. *J. Catal.* **2019**, *375*, 304−313. (g) Huang, Z.; Jiang, X.; Zhou, S.; Yang, P.; Du, C.-X.; Li, Y. Mn-Catalyzed Selective Double and Mono-N-Formylation and N-Methylation of Amines by using CO_2. *ChemSusChem* **2019**, *12*, 3054−3059. (h) Li, W.-D.; Zhu, D.-Y.; Li, G.; Chen, J.; Xia, J.-B. Iron-Catalyzed Selective N-Methylation and N-Formylation of Amines with CO_2. *Adv. Synth. Catal.* **2019**, *361*, 5098−5104. (i) Lin, W.; Cheng, H.; Wu, Q.; Zhang, C.; Arai, M.; Zhao, F. Selective N-Methylation of N-Methylaniline

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513

with CO_2 and H_2 over TiO_2-Supported PdZn Catalyst. *ACS Catal.* **2020**, *10*, 3285−3296.
(10) (a) Dang, T. T.; Ramalingam, B.; Seayad, A. M. Efficient Ruthenium-Catalyzed N-Methylation of Amines Using Methanol. *ACS Catal.* **2015**, *5*, 4082−4088. (b) Tsarev, V. N.; Morioka, Y.; Caner, J.; Wang, Q.; Ushimaru, R.; Kudo, A.; Naka, H.; Saito, S. N-Methylation of Amines with Methanol at Room Temperature. *Org. Lett.* **2015**, *17*, 2530−2533. (c) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol. *Adv. Synth. Catal.* **2017**, *359*, 4278−4283. (d) Jamil, M. A. R.; Touchy, A. S.; Rashed, M. N.; Ting, K. W.; Siddiki, S. M. A. H.; Toyao, T.; Maeno, Z.; Shimizu, K.-i. N-Methylation of amines and nitroarenes with methanol using heterogeneous platinum catalysts. *J. Catal.* **2019**, *371*, 47−56. (e) Zhang, S.; Ibrahim, J. J.; Yang, Y. A pincer ligand enabled ruthenium catalyzed highly selective N-monomethylation of nitroarenes with methanol as the C1 source. *Org. Chem. Front.* **2019**, *6*, 2726−2731.
(11) Lu, C.; Qiu, Z.; Zhu, Y.; Lin, B.-L. Scalable direct N-methylation of drug-like amines using $^{12}CO_2/^{13}CO_2$ by simple inorganic base catalysis. *Sci. Bull.* **2019**, *64*, 723−729.
(12) (a) Savourey, S.; Lefevre, G.; Berthet, J.-C.; Cantat, T. Catalytic methylation of aromatic amines with formic acid as the unique carbon and hydrogen source. *Chem. Commun.* **2014**, *50*, 14033−14036. (b) 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. *Catal. Sci. & Technol.* **2016**, *6*, 6172−6176. (c) 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 CO_2. *Org. Lett.* **2017**, *19*, 1490−1493.
(13) (a) da Silva, R. A.; Estevam, I. H. S.; Bieber, L. W. Reductive methylation of primary and secondary amines and amino acids by aqueous formaldehyde and zinc. *Tetrahedron Lett.* **2007**, *48*, 7680−7682. (b) van der Waals, D.; Heim, L. E.; Gedig, C.; Herbrik, F.; Vallazza, S.; Prechtl, M. H. Ruthenium-Catalyzed Methylation of Amines with Paraformaldehyde in Water under Mild Conditions. *ChemSusChem* **2016**, *9*, 2343−2347. (c) Wang, H.; Huang, Y.; Dai, X.; Shi, F. N-Monomethylation of amines using paraformaldehyde and H_2. *Chem. Commun.* **2017**, *53*, 5542−5545.
(14) Men, N. Y. T.; Li, W.; Stewart, S. G.; Wu, X.-F. Transition Metal-free Methylation of Amines with Formaldehyde as the Reductant and Methyl Source. *Chimia* **2015**, *69*, 345−347.
(15) (a) Zheng, J.; Darcel, C.; Sortais, J.-B. Methylation of secondary amines with dialkyl carbonates and hydrosilanes catalysed by iron complexes. *Chem. Commun.* **2014**, *50*, 14229−14232. (b) Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. Well-Defined Phosphine-Free Iron-Catalyzed N-Ethylation and N-Methylation of Amines with Ethanol and Methanol. *Org. Lett.* **2018**, *20*, 5985−5990.
(16) Sorribes, I.; Junge, K.; Beller, M. General Catalytic Methylation of Amines with Formic Acid under Mild Reaction Conditions. *Chem. − Eur. J.* **2014**, *20*, 7878−7883.
(17) (a) 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* **2018**, *37*, 3353−3359. (b) Huang, S.; Hong, X.; Cui, H.-Z.; Zhou, Q.; Lin, Y.-J.; Hou, X.-F. N-Methylation of ortho-substituted aromatic amines with methanol catalyzed by 2-arylbenzo d oxazole NHC-Ir(iii) complexes. *Dalton Trans.* **2019**, *48*, 5072−5082. (c) Gonzalez-Lainez, M.; Jimenez, M. V.; Passarelli, V.; Perez-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. *Catal. Sci. Technol.* **2020**, *10*, 3458−3467. (d) Meng, C.; Liu, P.; Nguyen Thanh, 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. *J. Org. Chem.* **2020**, *85*, 5815−5824.
(18) Neumann, J.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. Improved and General Manganese-Catalyzed N-Methylation of Aromatic Amines Using Methanol. *Chem. − Eur. J.* **2017**, *23*, 5410−5413.
(19) Pearson, D. E.; Bruton, J. D. REDUCTIVE METHYLATION OF AMINES. *J. Am. Chem. Soc.* **1951**, *73*, 864−864.
(20) Xu, L.; Li, X.; Zhu, Y.; Xiang, Y. One-pot synthesis of N,N-dimethylaniline from nitrobenzene and methanol. *New J. Chem.* **2009**, *33*, 2051−2054.
(21) Rong, Z.; Zhang, W.; Zhang, P.; Sun, Z.; Iv, J.; Du, W.; Wang, Y. One-pot synthesis of N,N-dimethylanilines from nitroarenes with skeletal Cu as chemoselective catalyst. *Catal. Commun.* **2013**, *41*, 115−118.
(22) Zhang, L.; Zhang, Y.; Deng, Y.; Shi, F. Light-promoted N,N-dimethylation of amine and nitro compound with methanol catalyzed by Pd/TiO_2 at room temperature. *RSC Adv.* **2015**, *5*, 14514−14521.
(23) Du, X.-L.; Tang, G.; Bao, H.-L.; Jiang, Z.; Zhong, X.-H.; Su, D. S.; Wang, J.-Q. Direct Methylation of Amines with Carbon Dioxide and Molecular Hydrogen using Supported Gold Catalysts. *ChemSusChem* **2015**, *8*, 3489−3496.
(24) Wang, L.-M.; Jenkinson, K.; Wheatley, A. E. H.; Kuwata, K.; Saito, S.; Naka, H. Photocatalytic N-Methylation of Amines over Pd/TiO_2 for the Functionalization of Heterocycles and Pharmaceutical Intermediates. *ACS Sustainable Chem. Eng.* **2018**, *6*, 15419−15424.
(25) Jagadeesh, R. V.; Murugesan, K.; Alshammari, A. S.; Neumann, H.; Pohl, M.-M.; Radnik, J.; Beller, M. MOF-derived cobalt nanoparticles catalyze a general synthesis of amines. *Science* **2017**, *358*, 326.
(26) Liu, J.; Zhu, Y.; Wang, C.; Singh, T.; Wang, N.; Liu, Q.; Cui, Z.; Ma, L. Facile synthesis of controllable graphene-co-shelled reusable Ni/NiO nanoparticles and their application in the synthesis of amines under mild conditions. *Green Chem.* **2020**, 7387.
(27) 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.* **2014**, *4*, 43195−43203.
(28) Goyal, V.; Gahtori, J.; Narani, A.; Gupta, P.; Bordoloi, A.; Natte, K. Commercial Pd/C-Catalyzed N-Methylation of Nitroarenes and Amines Using Methanol as Both C_1 and H_2 Source. *J. Org. Chem.* **2019**, *84*, 15389−15398.
(29) 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. *Chem. Sci.* **2016**, *7*, 3432−3442.

https://doi.org/10.1021/acsomega.1c01961
ACS Omega 2021, 6, 22504−22513