Efficient and selective N-dimethylation of amines with functional aldehydes catalysed by Ru nanoparticles heterogeneous catalyst

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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 easily handle-able 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 proceed through a twice N-methylation reaction process.

Key words: *Amines; N-dimethylation; Functional aldehydes; Ru nanoparticles*

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 pharmaceuticals products [1]. N-methylated compounds generally prepared from N-methylation methods, which 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. As reported by Jon T. 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-mono-methyl or N-di-methyl 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 highly effective in the control of COVID-19 infection[4].
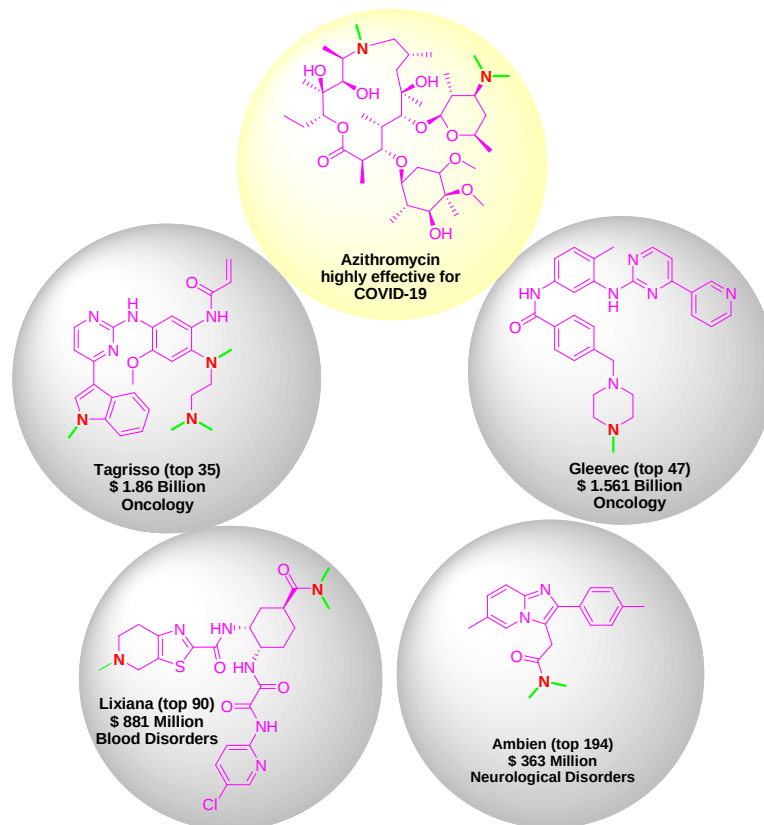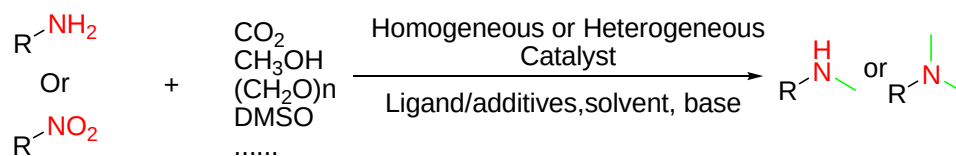
Figure 1. Pharmaceuticals containing N-methylated and N-di-methylated drugs

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 decades . 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 , or dimethyl carbonate [8]. These processes have serious issues that are operationally problematic and generally suffer from narrow scopes of amines and generation of by-products 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 . In recent years, with the environmental problems issues and the "green, sustainable chemistry", the C_1 sources used in transition metal-catalyzed N-methylation of amines were predominantly with more environmentally benign and safer methylation reagents, such as MeOH , CO_2, HCOOH [12], (para)formaldehyde [14] and so on (**Fig.2a**, **Fig.2b**). Until now, various homogeneous and heterogeneous metal catalysts have been reported.
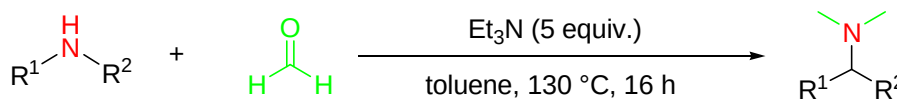
As for the homogeneous catalyst system, Ru complex catalysts have been widely used and studied for the direct N-methylation of amines used CO_2 as a C_1 source. In 2013, Beller and co-workers did pioneer work for the combination homogeneous catalyst system applying commercially available $RuCl_2(dmso)_4$ and $BuPAd_2$ ligand for the general 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 that 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 mono-methylation and di-methylation products were obtained in good to excellent yield 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 homogenous 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 system [RuCp*Cl$_2$]$_2$/dpePhos [10a], [Ru(p-cymene)I$_2$]$_2$ [13b], but also other transition metal homogeneous catalyst systems such as Fe , Karstedt's complex , Ir , Rh [5n], Cu , Co [10c], Mn , have been successively developed.
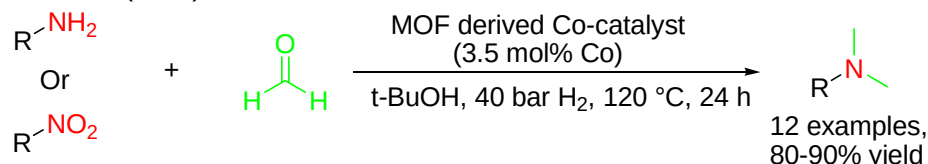
a) Recent progress in N-methylation (2000-2020)

b) Wu et al. (2015)

c) Beller et al. (2017)
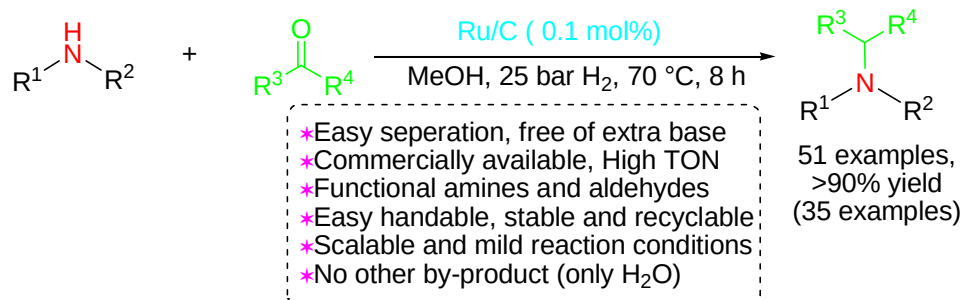
d) This work. (2020)

★Easy seperation, free of extra base
★Commercially available, High TON
★Functional amines and aldehydes
★Easy handable, stable and recyclable
★Scalable and mild reaction conditions
★No other by-product (only H_2O)

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

As it is known that homogeneous catalysts normally suffer from several disadvantages of difficult separation of catalyst/product, the necessity of 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 reaction. 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. The methanol was 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-di-methyl anilines with HCHO and nitroarenes catalyzed by the quenched skeletal Cu catalyst. Many N, N-dimethyl anilines 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 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 methanol under UV irradiation at room temperature [22]. In 2015, Cao and co-workers [23] reported the first heterogeneous Au/rutile catalyst for 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], Pd/TiO_2 [24], have been successively developed. Specifically, inexpensive copper- [9f] and cobalt-based [25] (**Fig.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 nanoparticles 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 have one or several of the following issues: transition metal-based homogeneous catalysts generally need complex or even toxic ligands and also tedious product separation process; earth-abundant transition metal-based heterogeneous catalyzed N-methylation usually were carried out under harsh conditions; the high equivalent of base and/or reducing agents were 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 using cheap, green reagent and green by-product generation (in general H_2O) or fully atom-economic without any byproduct formation; fairly cheap and industrial scalable heterogeneous catalysts; mild conditions, easy and convenient procedures of product separation and downstream processing.

Recently, we found that the graphene spheres encapsulate uniform Ni/NiO nanoalloy catalysts Ni/NiO@C were efficient in the reductive amination of carbonyl compounds [26]. Surprisingly, several N, N di-methylation products were obtained in excellent yield using aromatic amines and formaldehyde. In the meantime, we also found that the commercial available Ru/C showed excellent reactivity and selectivity for N, N-di-methyl benzylamine. To the best of our knowledge, commercial available Ru/C has remained unexplored for N-methylation of aromatic amines using inexpensive, readily available formaldehyde as a C_1 source and an H_2 source. This Ru/C has a lot of benefits such as: (1) it is fairly cheap, air-stable, easy to handle, and readily available, (2) it shows excellent catalytic activity in the absence of ligand and base, and (3) it can be easily separated from the reaction medium by simple filtration and reused, and (4) the only by-product was H_2O. Inspired by the above-mentioned 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, secondary amines, and molecular hydrogen, we undertook the synthesis of >50 functionalized, structurally diverse linear and branched benzylic, and aliphatic N-methylation products. Furthermore, the catalyst can be easily recycled with filtration and reused.
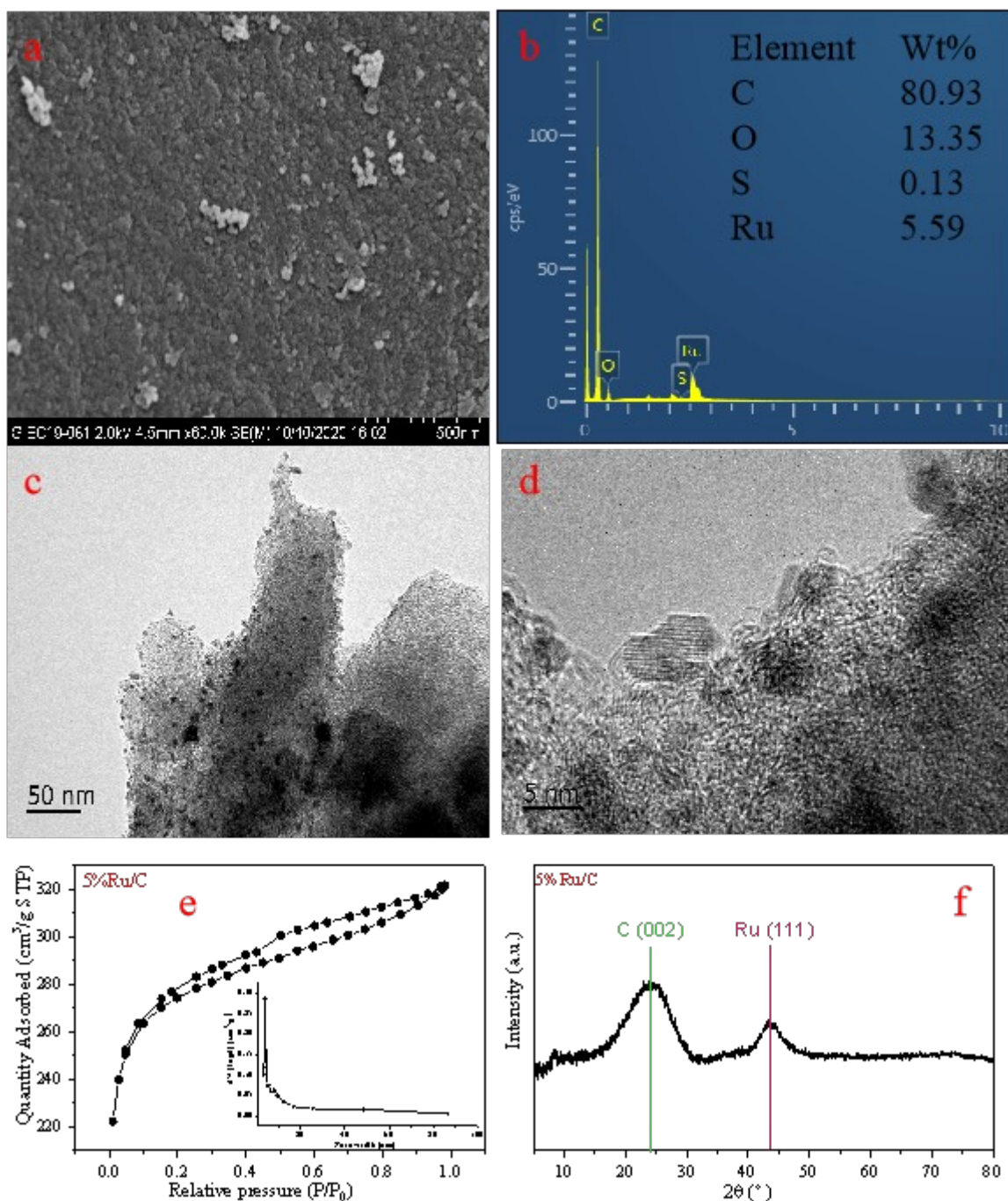
Results and discussion

Figure 3. Characterization of Ru/C

The scanning electron microscopy (SEM) images for the Ru/C sample (**Fig. 3a**) showed small catalyst particles. Element 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 the catalyst Ru/C. It was observed that Ru NPs with an average size of 10 nm are un-uniformly dispersed on carbon and some Ru nanoparticles were agglomerated at some parts (**Fig. 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) (**Fig. 3e**). The XRD spectra showed that the graphitic carbon shell and the Ru nanoparticles phases are present in the Ru/C sample (**Fig. 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 (**Fig. 3d**). For Ru/C

catalyst containing a small amount of Ru species, 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 the N-methylation can be carried out in excellent selectivity under fairly mild reaction temperature 70 °C. Further optimization showed that Ru/C catalyzed benzylamine smoothly to the corresponding N-dimethyl products in 8 h. As showed in the Table 1, the hydrogen pressure had a great effect on the production of N-dimethyl products (entry **8-12**). Interestingly, unlike previously reported process [27] [28], the commercially available Pt/C, Raney-nickel, Raney-cobalt as well as Pd/C showed excellent reactivity and selectivity of > 99% yield of N-dimethyl product **1**. The NiO, iron powder and Zinc were not active in the methylation of benzylamine under the chosen conditions.
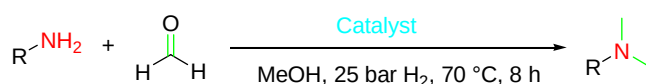
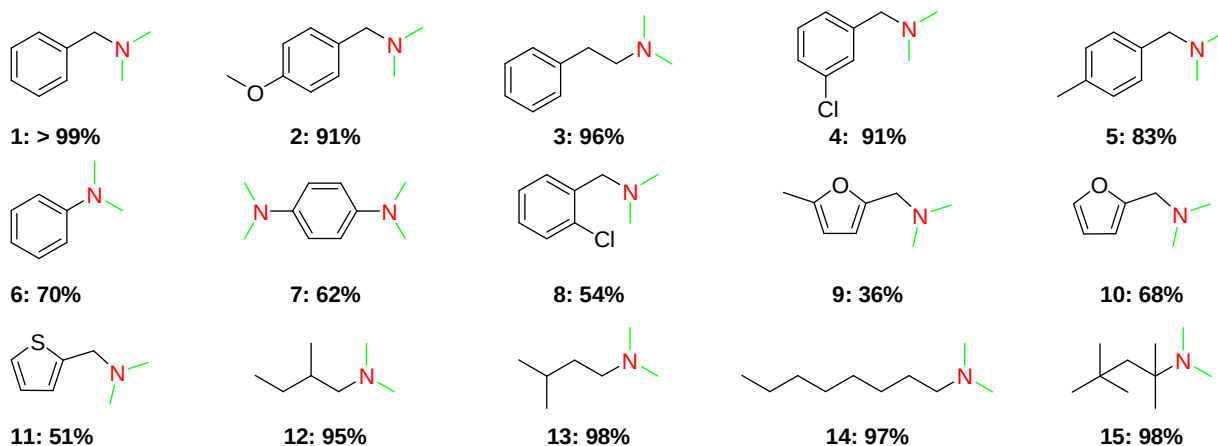**Table 1 Optimization of transition metal catalysed N-methylation of benzylamine** [a]
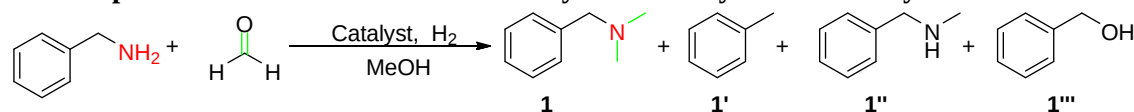
Entry	Catalyst	H$_2$ Pressure(bar)	Tempreture(°C)	Time(h)	Conversion(%)	Yield of **1**(%)
1	**Ru/C**	20	90	12	>99	93
2	**Ru/C**	20	80	12	>99	93
3	**Ru/C**	20	70	12	>99	98
4	**Ru/C**	20	60	12	>99	71
5	**Ru/C**	20	50	12	88	45
6	**Ru/C**	20	r.t.	12	63	nd
7	**Ru/C**	20	70	8	>99	97
8	**Ru/C**	20	70	4	>99	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 catalyst, 0.5 mmol benzylamine, 3 mmol formaldehyde, 5 mL methanol. Yields and conversion were determined by GC using 1, 3, 5-trimethoxybenzenen as an internal standard.
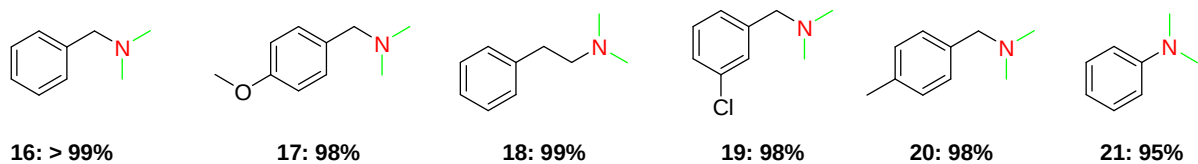
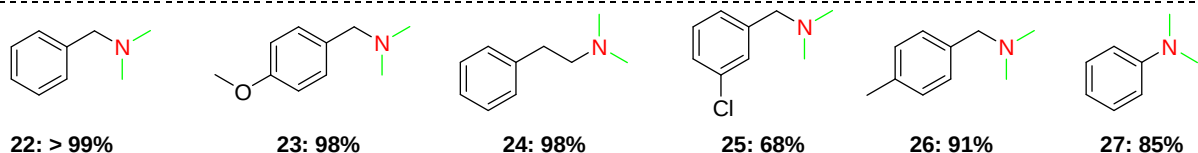**Table 2 Synthesis of tertiary amines by transition metal catalyzed N-methylation of primary amine** [a]

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

1: > 99%	2: 91%	3: 96%	4: 91%	5: 83%
6: 70%	7: 62%	8: 54%	9: 36%	10: 68%
11: 51%	12: 95%	13: 98%	14: 97%	15: 98%

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

| 16: > 99% | 17: 98% | 18: 99% | 19: 98% | 20: 98% | 21: 95% |

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

| 22: > 99% | 23: 98% | 24: 98% | 25: 68% | 26: 91% | 27: 85% |

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

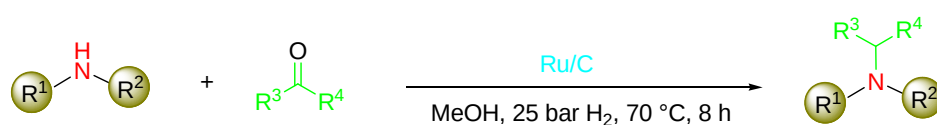| 28: > 99% | 29: 98% | 30: 98% | 31: 98% | 32: 98% | 33: 97% |
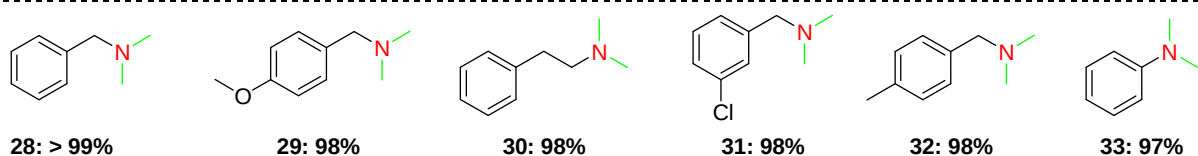
[a] Reaction conditions: 10 mg catalyst, 0.5 mmol amine substrate, 3 mmol formaldehyde, 5 mL methanol. Yields and conversion were determined by GC using 1, 3, 5-trimethoxybenzenen as an internal standard.

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-di-methylamines in good to excellent yields using Ru/C. The *meta*-halo substituted aromatic amine was also tolerated in this reaction and can be transformed to the meta-halo substitute N, N-di-methylamine product **4** in excellent yield. Probably due to the steric effect, the *ortho*-halo substituted N, N-di-methylamines product **8** was only obtained in 54% yield. Interestingly, the biomass derivatives 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-di-

methylated products, which were previously seldom reported and some with low yield [5c] [23] [29], were obtained in excellent yield under the optimized mild reaction conditions. The commercial 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 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.
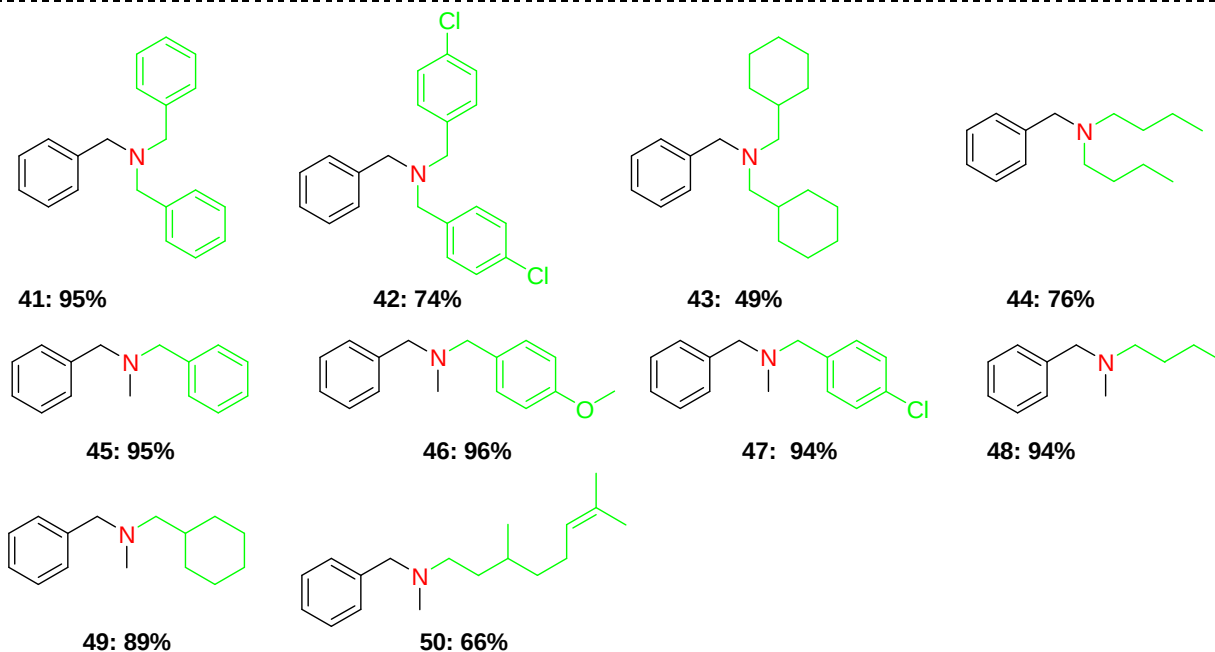
Table 3 Synthesis of tertiary amines by Ru/C catalyzed N-methylation of primary, secondary amines with different functional aldehydes [a]

a 5% Ru/C catalyzed N-methylation of secondary amines to tertiary amines using formaldehyde

34: 97% **35: >99%** **36: 98%** **37: 97%**

38: 98% **39: 98%** **40: 97%**
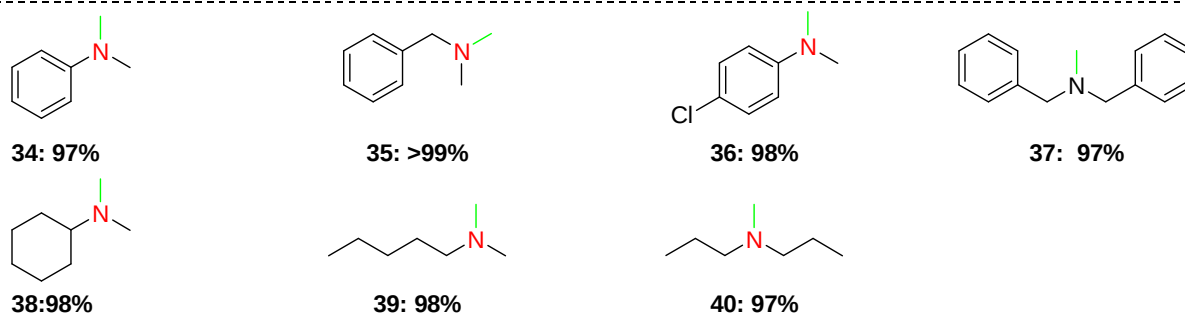
b 5% Ru/C catalyzed N-methylation of primary amines, secondary amines to tertiary amines using functional substitute aldehyde

41: 95% **42: 74%** **43: 49%** **44: 76%**

45: 95% **46: 96%** **47: 94%** **48: 94%**

49: 89% **50: 66%**

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

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, secondary amines with different functional substituted aldehydes, which were seldom reported previously. To our delight, the non-substituted and halo substituted aromatic secondary amines, N-methyl (phenyl) methanamine, 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 molecules synthesis and materials application. In this context, we applied the Ru/C catalyzed N-methylation methodology to synthesis tertiary amines using primary, secondary amines with different functional substituted aldehydes. Primary amines can react with benzaldehyde, halo substituted benzaldehyde, aliphatic aldehydes to give the tertiary amines moderate to excellent yields (**41-45**). To the best of our knowledge, very limit 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 liner and cyclic aliphatic aldehydes (**46-50**). Meanwhile, we also tested the catalyst's re-usability, after three recycle tests, the yield of **1** was dropped from 99% to 60% due to the leaching of the transition metal. So, we are still focusing on designing and preparing more suitable catalyst support, like graphene encapsulated transition metal catalyst which was reported previously by our group, to avoid metal leaching and enhance the catalytic activity and re-usability.
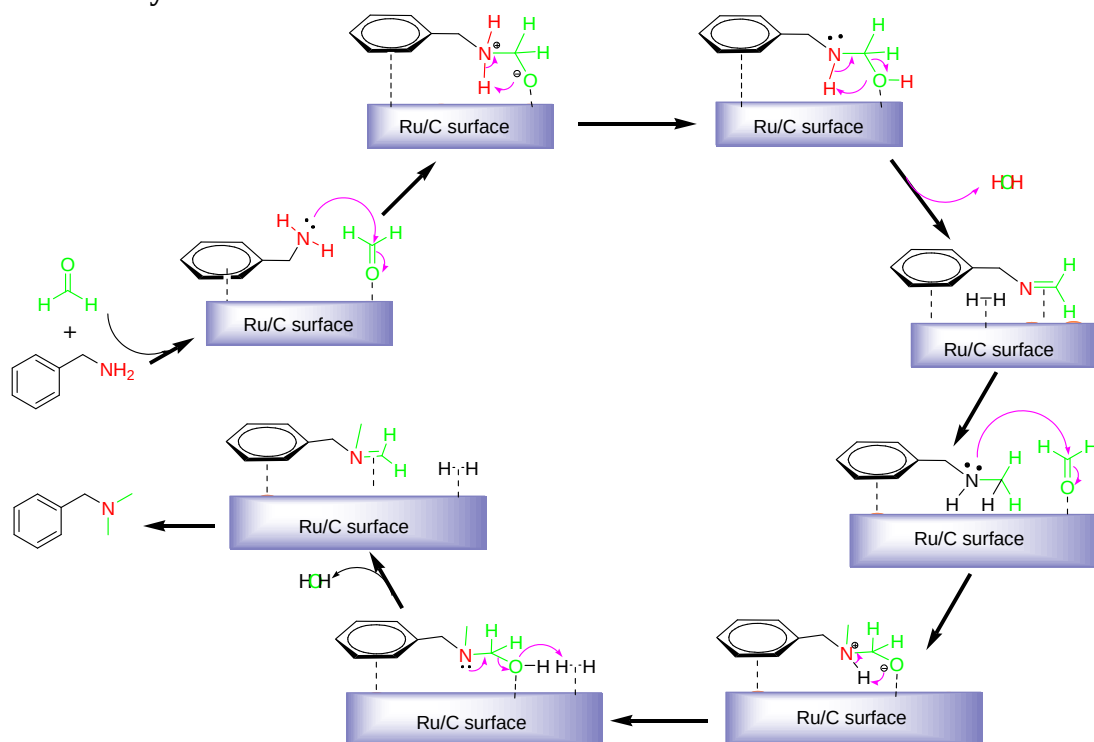
Mechanism study.

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

Based on the scope studies and the results from the control experiments, unlike the previous reported N-methylation process using formaldehyde, formic acid process, CO_2 was not observed in this process. So, a possible proposed mechanism of Ru/C catalyzed N-methylation of phenylmethanamine with formaldehyde is similar to the reported twice N-methylation process [9f] [27]. As depicted in **Fig. 4**, first, the 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 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. The 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.

Conclusion

In conclusion, we have demonstrated that 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 temperatures 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, 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 moderate re-usability due to catalyst metal leaching, it would be useful and important for further investigation in the design and preparation of highly stable Ru-based catalyst avoiding leaching. At present, our laboratory is conducting design and research on prevention of catalyst leaching and other related aspects.

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 substrates scope experiments. J. G. L. and Y. P. S wrote the paper. 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.

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