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# Copper(II)-Catalyzed Selective Reductive Methylation of Amines with Formic Acid: An Option for Indirect Utilization of $CO_2$

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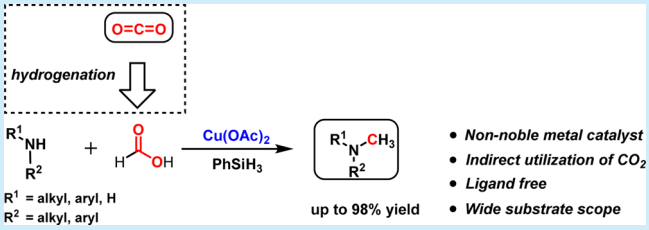
Supporting Information

**ABSTRACT:** A copper-catalyzed protocol for reductive methylation of amines and imine with formic acid as a C1 source and phenylsilane as a reductant is reported for the first time, affording the corresponding methylamines in good to excellent yields under mild conditions. This protocol offers an alternative method for indirect utilization of $CO_2$, as formic acid can be readily obtained from hydrogenation of $CO_2$.

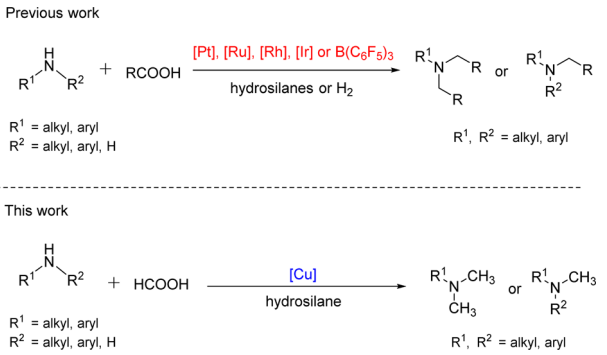



Methyl-substituted amines have found wide applications in pharmaceuticals, agrochemicals, dyes, and materials.[1] Thus, the methylation of amines is of high interest in both academia and industry.[2] Recently, methodologies for *N*-methylation of amines using $CO_2$[3] as methylating agent has been flourished due to its abundant, cheap, and nontoxic characters. As an easily available C1 source, formic acid can be prepared from $CO_2$ through catalytic hydrogenation.[4] In this perspective, methylation with formic acid as C1 synthon can be considered as indirect utilization of $CO_2$, thus providing an alternative synthetic method and promising field for $CO_2$ chemistry.

Seminal work on *N*-methylation of amines with formic acid as C1 source and hydrosilane as a reductant was reported in 2014 by utilizing Pt/dppp [dppp = bis(phenylphoshino)-propane] at room temperature.[5] Soon after, a broad range of alkylated secondary and tertiary amines has been obtained by *N*-alkylation of amines with carboxylic acid using similar platinum/diphosphine-based catalyst in the range of room temperature to 120 °C.[6,7] Since then, other metal catalysts including Ru,[8] Rh,[9] Ir,[10] and heterogeneous Pt/C[11] have successfully been developed to promote this C−N bond formation reaction employing hydrosilane as reductant. Notably, borane i.e. $B(C_6F_5)_3$ serving as an metal-free catalyst has also been demonstrated to be effective.[12] Furthermore, the Ru/triphos [triphos = 1,1,1-tris(diphenylphosphinomethyl)-ethane] system is also proven efficient for *N*-alkylation of amines with different kinds of carboxylic acids as alkylating agents and $H_2$ (60 bar) as reductant at 160 °C.[13] On the other hand, it should be noted that Eschweiler−Clarke reaction (reductive amination using excess formaldehyde as C1 source and formic acid as reductant) has been reported to obtain *N*-methylamines,[14] which is quite different from the above-mentioned reaction with formic acid as C1 source and hydrosilane or hydrogen molecule as reductant.

Despite the achievements in this field as shown in Scheme 1, most of the reported catalysts are mainly based on noble metals

**Scheme 1. Reductive *N*-Alkylation of Amines with Carboxylic Acid**




with complicated ligands. Thus, the development of easily available and cost-effective catalysts especially based on non-noble metal under mild conditions is highly desirable but still remains a challenge. Herein, we report $Cu(OAc)_2$ as a robust catalyst for efficient *N*-methylation of amines/imine with formic acid as renewable C1 building block and phenylsilane as reductant at 80 °C.[15] Copper salts with oxygen/fluoride-containing anion show good selectivity toward methylamines, while copper halides (halogen = Cl, Br, I) exhibit high exclusivity for formamides. To the best of our knowledge, this is the first example that non-noble metal catalyst is applied to *N*-methylation of amines using formic acid and hydrosilane.

Our study commenced with the methylation of *N*-methylaniline (**1a**) with formic acid as C1 source and phenylsilane as reductant at 80 °C as listed in Table 1. In the absence of any catalyst, *N*-methylformanilide (**2a**) was obtained in 32% yield (entry 1). $Cu(OAc)_2$ showed excellent activity and exclusive formation toward *N*,*N*-dimethylaniline (**3a**) (entry 2), while

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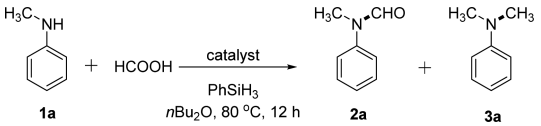
**Table 1. Screening of Various Non-noble Metal Salts**[a]




| entry | catalyst | conv (%) | yield of **2a** (%)[b] | yield of **3a** (%)[b] |
|---|---|---|---|---|
| 1 | | 32 | 32 | 0 |
| 2 | $Cu(OAc)_2$ | >99 | 0 | 99 (97)[c] |
| 3 | $Fe(OAc)_2$ | 50 | 50 | 0 |
| 4 | $Co(OAc)_2$ | 48 | 48 | 0 |
| 5 | $Ni(OAc)_2$ | 76 | 73 | 2 |
| 6 | $Zn(OAc)_2$ | >99 | 99 | 0 |
| 7 | $Cu(NO_3)_2{\cdot}2.5H_2O$ | 97 | 73 | 22 |
| 8 | $CuSO_4{\cdot}5H_2O$ | >99 | 58 | 40 |
| 9[d] | $Cu(acac)_2$ | >99 | 19 | 76 |
| 10 | $Cu(OTf)_2$ | >99 | 0 | 99 |
| 11 | $CuF_2$ | >99 | 0 | 99 |
| 12 | $CuCl_2$ | 75 | 74 | 0 |
| 13 | CuCl | 83 | 83 | 0 |
| 14 | CuBr | 70 | 70 | 0 |
| 15 | CuI | 66 | 66 | 0 |
| 16[e] | $Cu(OAc)_2$ | >99 | 0 | 99 (98)[c] |

[a]Unless otherwise specified, all the reactions were performed with **1a** (0.5 mmol), HCOOH (1.5 equiv), $PhSiH_3$ (3.0 equiv), catalyst (5 mol %), $nBu_2O$ (1.0 mL), 80 °C, 12 h, argon atmosphere. [b]Determined by GC using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield of **3a**. [d]acac = acetyl acetonate. [e]Open air in 10 mL flask.

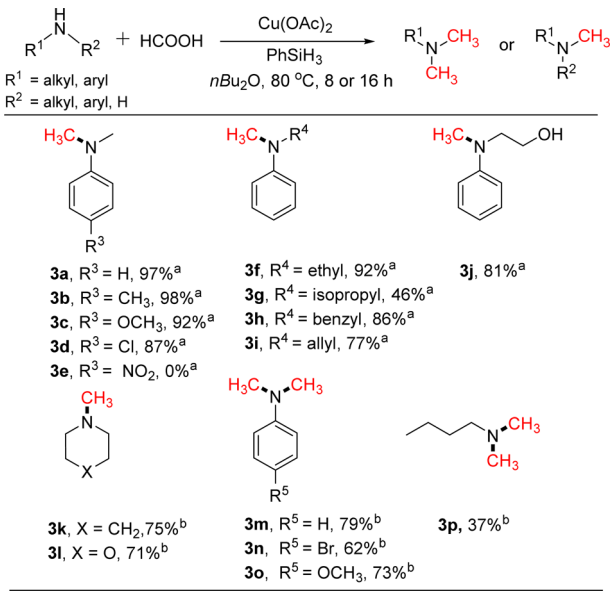
other metal acetates including $Fe(OAc)_2$, $Co(OAc)_2$, $Ni(OAc)_2$, and $Zn(OAc)_2$ could only result in the formation of formamide **2a** (entries 3−6), indicating the obvious superiority of copper salt for this *N*-methylation reaction, which may be attributed to the compatibility of the newly formed copper hydride with acidic system. Subsequently, the influence of anions were evaluated, and only the ones containing oxygen, including $Cu(NO_3)_2{\cdot}2.5H_2O$, $CuSO_4{\cdot}5H_2O$, $Cu(acac)_2$, and $Cu(OTf)_2$ (entries 7−10), could promote the *N*-methylation. $CuF_2$ also allowed the reaction to afford quantitative yield of **3a** successfully (entry 11). This may be because the oxygen-[16] or fluoride-containing[3f,17] anion could activate the hydrosilane via the interaction of oxygen or fluoride with silicon. This is in sharp contrast with that of $CuCl_2$ or CuX (X = Cl, Br, I), which only led to the formation of **2a** with high selectivity. It may be explained that halide has no facilitation for copper hydride generation, thus forbidding the following-up reduction and terminating the reaction at formamide **2a** (entries 7−10 vs 12−15). Even at 60 °C, $Cu(OAc)_2$ could still give 84% yield of **3a** and was more active than $Cu(OTf)_2$ (OTf = trifluoromethanesulfonate) and $CuF_2$ (Table S3). Notably, this protocol was air-tolerant (entry 16).

Miscellaneous parameters were intensively screened on the reaction outcome. Among the hydrosilanes tested in Table S5, only phenylsilane allowed this reaction to proceed smoothly (Table S5, entry 2), being consistent with reducing ability of hydrosilanes tested.[12a,18] Non- and low-polar solvents such as toluene and ethers were favorable solvents for this methylation reaction (Table S4, entries 1−4) compared with polar solvents such as DMF (*N*,*N*-dimethylformamide) and acetonitrile (Table S4, entries 5 and 6). Such a solvent effect may be attributed to the relative stability of the copper hydride species in ether and arene solvent.[19] In addition, the *N*-methylation reaction was completed within 8 h (Figure S1).

With the optimal conditions in hand, we evaluated the scope of this newly established Cu-catalyzed *N*-methylation protocol. As shown in Scheme 2, the reaction of para-substituted *N*-methylanilines proceeded smoothly to deliver *N*,*N*-dimethylaniline derivatives in high to excellent yields (**3b−d**). However, *N*-methyl-4-nitroaniline was unreactive with almost full recovery of the substrate, probably due to the strong electron-withdrawing effect. *N*-Ethyl-, *N*-isopropyl-, and *N*-benzylanilines were successfully methylated with formic acid (**3f−h**), but the amine with bulky group showed lower reactivity (**3g**) ascribed to the steric hindrance. *N*-Substituted anilines with alkenyl or hydroxyl were transformed into the corresponding methylated products with the sensitive group intact, showing good functional group compatibility (**3i,j**). This protocol was also applicable to aliphatic amines such as piperidine and morpholine (**3k,l**). In addition, primary amines worked in a fashion similar to that for secondary amines, resulting in the dominant formation of dimethylated products by increasing the amount of hydrosilane and doubling the reaction time (**3m−p**). However, monomethylated byproducts were inevitably present, which led to low yield of dimethylated products (see the Supporting Information (SI)). Notably, imine benzylidene phenylamine is a suitable substrate for this Cu-catalyzed methylation protocol to afford the corresponding *N*-methylated amine in 82% yield (Scheme S1). Furthermore, a gram-scale experiment of **1a** (10 mmol, 1.0707 g) results in 86% isolated yield of **3a**, which shows the practicality of this methodology on a gram scale (see the SI).

Several control experiments were conducted as shown in Scheme 3 to probe the reaction mechanism. Initially, *N*-methylformanilide (**2a**) was tested under the optimized reaction conditions, and only 9% yield of *N*,*N*-dimethylaniline

**Scheme 2. *N*-Methylation of Various Amines with Formic Acid and $PhSiH_3$***




*Reaction conditions: secondary amine (0.5 mmol), HCOOH (1.5 equiv), $PhSiH_3$ (3.0 equiv), $Cu(OAc)_2$ (5 mol %, 4.6 mg), $nBu_2O$ (1.0 mL), 80 °C, 8 h. Primary amine (0.2 mmol), HCOOH (2.5 equiv), $PhSiH_3$ (6.0 equiv), $Cu(OAc)_2$ (5 mol %, 1.9 mg), $nBu_2O$ (1.0 mL), 80 °C, 16 h. [a]Isolated yield. [b]Yield was determined by $^1H$ NMR using 1,3,5-trimethoxybenzene as an internal standard.



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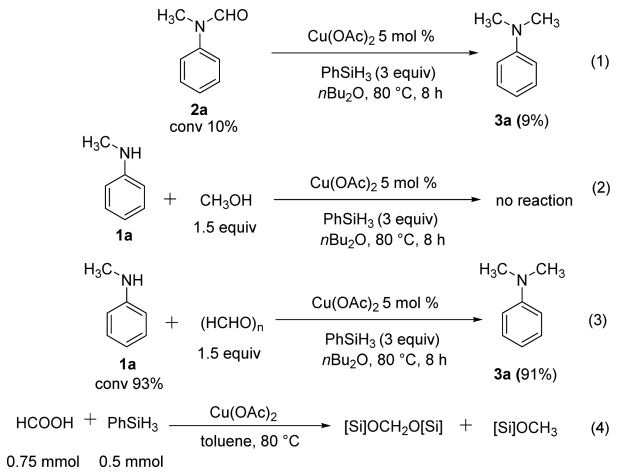
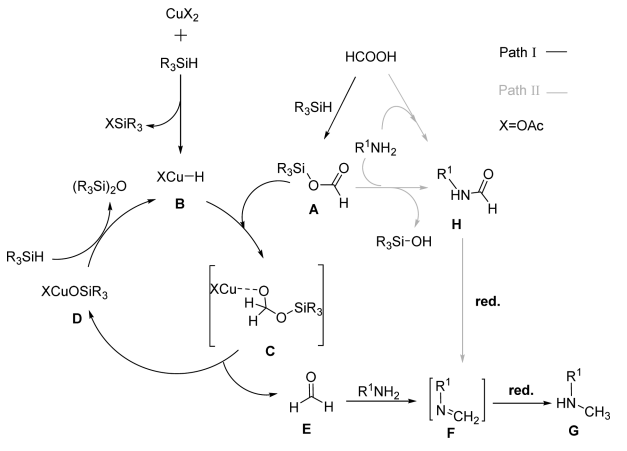
**Scheme 3. Control Experiments**




(**3a**) was obtained (eq 1). Then, methanol was used as C1 source to replace formic acid under otherwise identical conditions, and no *N*-methylated product **3a** was detected at all (eq 2). When paraformaldehyde was employed, the desired product **3a** was obtained in 91% yield (eq 3), indicating that formaldehyde could be a possible intermediate. We then verified the feasibility of the reduction of formic acid to formaldehyde, and the reaction of formic acid and phenylsilane in the absence of *N*-methylaniline was conducted (Figure S2). It revealed that formic acid could be reduced to the silyl acetal and methoxide under our reaction conditions (eq 4).[20] Therefore, formaldehyde might be present in the reaction mixture as a transient species.

Based on the above experimental results and previous reports on reductive alkylation of amines with carboxylic acid and hydrosilane,[5,6,8−13] two possible reaction pathways for this copper acetate catalyzed methylation of amines with formic acid are proposed as shown in Scheme 4. In path I,

**Scheme 4. Proposed Mechanism**




dehydrogenative coupling between formic acid and hydrosilane leads to formoxysilane **A**. In parallel, the copper hydride species **B** is initially generated by metathesis between copper acetate and hydrosilane in which oxygen of acetate interacts with silicon of hydrosilane and promotes hydride transfer to copper.

Two such species (**A** and **B**) could readily deliver the silyl acetal **C**, which is further converted into formaldehyde **E** with release of the copper ether **D**. Then, **E** reacts with the amine in the presence of hydrosilane to furnish the methylation product **G** through reductive amination. On the other hand, **D** is reduced by hydrosilane to regenerate the copper hydride **B** to finish the catalytic cycle. This path is deemed as the major one because a nearly quantitative yield of *N*,*N*-dimethylaniline (**3a**) was obtained when paraformaldehyde was employed (Scheme 3, eq 3). Path II explains the formation of formamide **H**, which follows by a conventional amide reduction process.[21,22] Though a low yield of *N*,*N*-dimethylaniline (**3a**) was obtained with *N*-methylformanilide (**2a**) (Scheme 3, eq 1), this route cannot be excluded. With copper halide (excluding $CuF_2$) as catalyst, only formamide **H** was obtained in high selectivity. This may be because the presence of halide seems to be disfavorable for the formation of the copper hydride **B**, thus suppressing subsequent reduction and rendering the reaction terminated at formamide **2a**.

In conclusion, we have established the first non-noble-metal-catalyzed methylation of amines with formic acid using phenylsilane as a reducing agent. Primary amines, secondary amines, as well as imine are suitable substrates and give corresponding methylamines in 37−98% yields under relatively mild conditions. Formic acid, which can be easily obtained by hydrogenation of $CO_2$, is employed as a sustainable methylating agent in this protocol, providing a new option for indirect utilization of $CO_2$. Therefore, this copper-catalyzed protocol represents an environmentally friendly, readily operational, and highly efficient example for methylation of amines.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00551.

Experimental procedures; characterization of all products (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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