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Article

CuH-Catalyzed Selective N-Methylation of Amines Using Paraformaldehyde as a C1 Source

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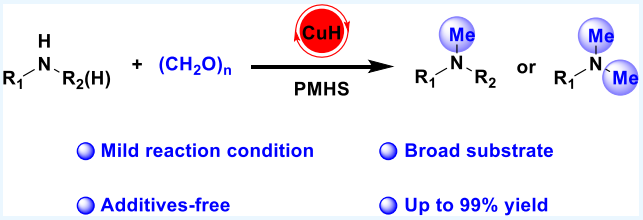
ABSTRACT: Copper hydride (CuH) complexes have been proposed as key intermediates in synthesis and catalysis. Herein, we developed a highly efficient strategy for CuH-catalyzed N-methylation of aromatic and aliphatic amines using paraformaldehyde and polymethylhydrosiloxane (PMHS) under mild reaction conditions. The reaction proceeded smoothly without additives to furnish the corresponding N-methylated products using cyclic(alkyl)(amino)carbene (CAAC)CuH as a reaction intermediate, which results from a reaction between PMHS and (CAAC)CuCl.



1. INTRODUCTION

The selective synthesis of *N*-methylamines or *N*,*N*-dimethylamines is significant because these compounds are widely applied in the synthesis of medicines, biomolecules, and dyes.[1−7] In particular, bestselling drugs such as enzalutamide, tofacitinib, osimertinib, and cariprazine contain *N*-methylamine or *N*,*N*-dimethylamine groups (Figure 1).[8] The N-methylation of amines to produce *N*-methylamines and *N*,*N*-dimethylamines has been traditionally performed using methylation reagents such as methanol,[9,10] dimethyl carbonate,[11,12] formic acid,[13,14] and carbon dioxide.[15,16] However, the increasing demand for *N*-methylamines and *N*,*N*-dimethylamines has prompted intensive research on the development of more efficient industrial synthesis methods. For instance, since the pioneering work of Eschweiler−Clarke, the N-methylation of amines with formaldehyde remains an attractive approach for the industrial production of *N*-methylamines and *N*,*N*-dimethylamines.[17]

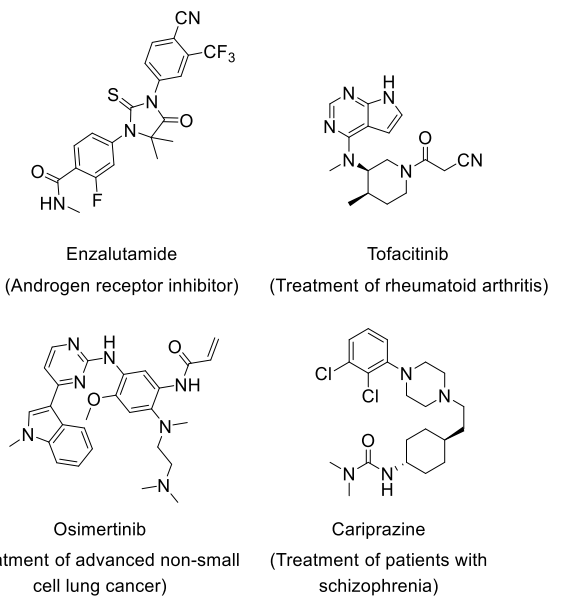


Figure 1. Selected significant medicines containing *N*-methyl or *N*,*N*-dimethyl amines.

In the selective N-methylation of amines with formaldehyde, the activation of formaldehyde, a carbonyl reagent, is a key step in the selective N-methylation of amines with formaldehyde. So far, only a few catalytic systems have been reported for this reaction.[18−22] In 2014, Qian et al.[18] disclosed a Raney Ni-catalyzed N-methylation of amines with paraformaldehyde to obtain various *N*-methylamines and *N*,*N*-dimethylamines in 21−97% yields at 100−180 °C under a H_2 pressure of 1.3−2.0 MPa. In 2016, Métay et al.[19] used Pd/C as the catalyst and CaH_2 as the reductant for synthesizing *N*-methylamines and *N*,*N*-dimethylamines; however, the use of CaH_2 hindered the application of this method to industrial production of these amines. Simultaneously, Shi et al.[20] used Au/Al_2O_3 as the catalyst and H_2O as the reducing agent for this reaction, obtaining *N*-methylamines in yield up to 99% at 112 °C. Later on, the same group[21] reported a $CuAlO_x$ catalyst with satisfactory performance in *N*-monomethylation reactions

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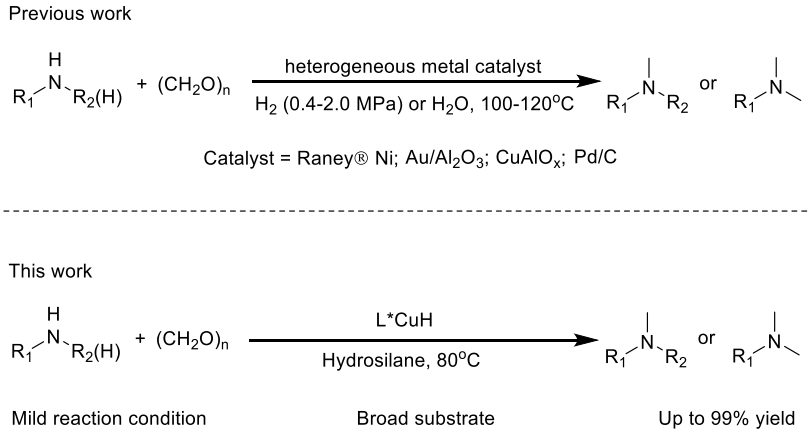

Figure 2. N-Methylation of amines with paraformaldehyde.

with H_2 as the reductant. Various aromatic and aliphatic primary amines smoothly reacted to produce the corresponding *N*-methylamines were obtained in 61−89% yields at 120 °C/140 °C under a H_2 pressure of 0.5 MPa. In 2019, they reported another Pd/C catalyst for the selective synthesis of *N*-methyl-1,2,3,4-tetrahydroquinolines via the N-methylation of quinolines with paraformaldehyde/H_2.[22] Remarkably, all reported catalysts for selective N-methylation of amines with formaldehyde are heterogeneous metal catalysts. Moreover, the aforementioned reactions require harsh reaction conditions (H_2 or H_2O serving as the reductant) or cannot be industrialized. Compared with heterogeneous metal catalysts, homogeneous metal catalysts are gathering increasing interest owing to their high activity and selectivity as well as the requirement of mild reaction conditions. However, examples of homogeneous metal catalysts used for the selective N-methylation of amines with formaldehyde are scarce,[23−25] more examples of N-methylation of amines mainly use methanol or CO_2 as methylation reagents.[26−29] Previously, we successfully developed a tandem copper hydride(CuH)-Lewis pair synergistic homogeneous catalytic system that displayed excellent catalytic performance in the hydrogenation of CO_2 to formic acid reaction (turnover numbers up to 1881).[30] The critical step in this reaction is the insertion of CO_2 as the carbonyl reagent into the CuH and the regeneration of the latter using H_2 as a reducing agent (H_2). In addition, CuH has been widely used as an efficient catalyst for the activation of carbonyl reagents such as CO,[31,32] ketones,[33,34] and carboxylic acids.[35,36]

Inspired by the aforementioned results, herein, we used CuH as the catalyst and hydrosilane as the reducing agent for the selective N-methylation of aromatic and aliphatic amines with formaldehyde. In this reaction, which proceeded smoothly to furnish the corresponding N-methylated products without additives, cyclic(alkyl)(amino)carbene CuH [(CAAC)CuH] was produced as an intermediate from the reaction between polymethylhydrosiloxane (PMHS) and cyclic (alkyl)(amino)-carbene CuCl [(CAAC)CuCl]. This homogeneous CuH catalytic system has the merits of mild reaction conditions, broad substrate scope, and high yields up to 99% compared with previously reported heterogeneous catalysts for the N-methylation reaction (Figure 2). In particular, this method does not require the participation of gas and can be synthesized at atmospheric pressure. Finally, based on the results of this study and those of previous research, a possible mechanism for the N-methylation reaction is proposed.

2. RESULTS AND DISCUSSION

We started to investigate the solvent effect on the N-methylation reaction using *N*-heterocyclic carbene (NHC)-CuCl (**cat 1**) as the catalyst, PMHS as the reductant, *N*-methylaniline (**1**) as the model substrate, and paraformaldehyde as the formaldehyde source (Table 1). When weakly polar solvents such as tetrahydrofuran (THF), diglyme, or toluene were used, only moderate yields of the corresponding N-methylated product (**1a**) were obtained (Table 1, entries 1−3). The yield of **1a** in strongly polar *N*,*N*-dimethylformamide (DMF) was only 15%, whereas that of *N*-methylformamide (**1b**) was 41% for reasons that are not yet clear (entry 4). The yield of **1a** increased significantly to 86% when the more polar CH_3CN was used as the solvent, which may be attributed to the increased basicity and nucleophilicity of **1** (entry 5).[37,38] Importantly, the conversion of **1** and the yield of **1a** were both higher than 99% in dibutyl ether (nBu_2O), which may be attributed to the relative stability of **cat 1** and the appropriate basicity and nucleophilicity of **1** (entry 6).[13,39] Upon reducing the dosage of **cat 1** to 1.0 mol %, both the conversion of **1** and the yield of **1a** were significantly lower (71 and 70%, respectively) (entries 6 and 7). Subsequently, **cat 2**, **cat 3**, and **cat 4** were used to catalyze this N-methylation reaction (entries 8−10). When **cat 3** was used, the conversion of **1** and the yield of **1a** increased (75 and 73%, respectively) compared with when **cat 1** and **cat 2** were used, which may attributed to the presence of stronger metal-carbene bonds in **cat 3** because CAACs are more electrophilic and nucleophilic than NHCs (entries 7 and 9).[40,41] Interestingly, after increasing the amount of **cat 3** to 2.5 mol %, both the conversion of **1** and the yield of **1a** improved significantly to >99% (entries 9 and 11).

To gain more insights into the role of the CAAC and NHC ligands, CuCl was used as a catalyst for the N-methylation reaction; however, **1a** was obtained only in a low 7% yield (entry 12). These results suggest that the CAAC and NHC ligands play a crucial facilitating role in this reaction (entries 6−12). Although fluorine- and oxygen-containing anions are known to afford higher yields of N-methylated products via the activation of hydrosilanes,[13,42−45] the yields of **1a** was as low as 11 and 4% when using Cu(OTf) (OTf = trifluoromethanesulfonate) and Cu(OAc) as catalysts (entries 13 and 14). The yield of **1a** in the reaction catalyzed by **cat 4** containing the OTf anion was also lower than that in the reaction catalyzed by **cat 3** (entries 9 and 10). These results demonstrate that the

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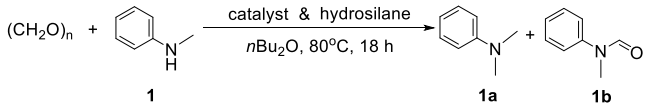
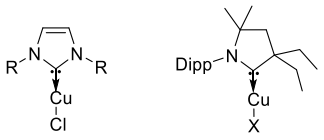
Table 1. Optimization of Reaction Conditions[a]





cat 1 R = 1-(2,3,6-trimethylphenyl)
cat 2 R = 1-(2,6-diisopropylphenyl)
cat 3 X = Cl
cat 4 X = OTf

entry	solvent	catalyst (mol %)	hydrosilane	con. of **1** (%)[b]	yield of **1a** (%)[b]	yield of **1b** (%)[b]
1	THF	**cat 1** (2.5)	PMHS	45	40	5
2	diglyme	**cat 1** (2.5)		48	48	0
3	toluene	**cat 1** (2.5)		73	57	16
4	DMF	**cat 1** (2.5)		56	15	41
5	CH_3CN	**cat 1** (2.5)		88	86	2
6	nBu_2O	**cat 1** (2.5)		>99	>99	0
7	nBu_2O	**cat 1** (1.0)		71	70	1
8	nBu_2O	**cat 2** (1.0)		61	54	7
9	nBu_2O	**cat 3** (1.0)		75	73	2
10	nBu_2O	**cat 4** (1.0)		65	62	3
11	nBu_2O	**cat 3** (2.5)		>99	>99	0
12	nBu_2O	CuCl (2.5)		10	7	3
13	nBu_2O	$Cu(OTf)_2$ (2.5)		17	11	6
14	nBu_2O	$Cu(OAc)_2$ (2.5)		19	4	15
15[c]	nBu_2O	**cat 3** (2.5)		68	61	7
16	nBu_2O		$PhSiH_3$	>99	>99	0
17	nBu_2O		Ph_2SiH_2	76	74	2
18	nBu_2O		Ph_3SiH	33	15	18
19	nBu_2O		$(EtO)_3SiH$	88	82	6
20[d]	nBu_2O		PMHS	76	76	0
21[e]	nBu_2O			53	48	5
22	nBu_2O	catalyst-free		12	11	1

[a]Reaction conditions: amine (**1**, 0.5 mmol), solvent (2 mL), hydrosilane (1.5 mmol), $(CH_2O)_n$ (1.5 mmol), 80 °C, 18 h. [b]The yields were determined by GC/MS using dodecane as the internal standard substance. [c]PMHS (0.6 mmol). [d]9 h. [e]50 °C.

CAAC and NHC ligands play a dominant role in the selective generation of N-methylated products.

The N-methylation reactions using various hydrosilanes as reducing agents, i.e., $PhSiH_3$, Ph_2SiH_2, and $(EtO)_3SiH$, proceeded smoothly to produce **1a** in 99, 74, and 82% yields, respectively, whereas a mere 15% yield of **1a** was obtained when using Ph_3SiH as the reductant (entries 16−19). Reducing the dosage of PMHS, the reaction time, and the reaction temperature resulted in a significant decrease in both the conversion of **1** and the yield of **1a** (entries 15, 20, 21). Notably, the conversion of **1** and an 11% yield of **1a** were low (12 and 11%, respectively) when the reaction was performed in the absence of a catalyst (entry 22). Finally, the conditions, as shown in entry 11, Table 1, were selected as the optimal reaction conditions for the (CAAC)CuH-catalyzed N-methylation.

After determining the optimal reaction conditions, we explored the application scope of the newly established (CAAC)CuH-catalyzed N-methylation scheme (Table 2). Interestingly, various aromatic and aliphatic amines were suitable for the reaction and afforded the corresponding *N*-methylamines and *N*,*N*-dimethylamines in moderate to excellent yields. Remarkably, the electronic nature of the functional group on the benzene ring exerted a considerable effect on the reactivity of the amines. Among them, the introduction of methyl groups either at the ortho-, meta-, or para-position of the benzene ring caused a decrease in the yield of the corresponding N-methylated products (Table 2, entries 1−4). However, the effect of the position of the methyl group on the benzene ring on the reactivity of the amines was not noticeable (entries 2−4). *N*-Methylanilines containing sensitive groups such as hydroxyl, ether, fluorine atoms, or chlorine atoms showed satisfactory functional group compatibility in this reaction and afforded the corresponding *N*,*N*-dimethylamines in 72−99% yields (entries 5−8). However, the introduction of a nitro group at the para position of the benzene ring hampered the reaction, most likely owing to the strong electron-withdrawing effect of the nitro group (entry 9). Diphenylamine could be successfully N-methylated with paraformaldehyde, but only moderate yields of the N-methylated products were obtained owing to the steric hindrance (entry 10). Meanwhile, because of its weak basicity and nucleophilicity, aniline exhibited poor activity in the N-methylation reaction (Table 2, entry 11).

Aliphatic amines are considerably more reactive than aromatic amines. Accordingly, *N*-methylbenzylamine and dibenzylamine successfully reacted with paraformaldehyde to afford the corresponding N-methylated products in 92% and 91% yields, respectively (entries 12 and 13). Heterocyclic amines exhibited highly activity, furnishing the corresponding N-methylated products in 94−96% yields (entries 14−16). In particular, 2,2,6,6-tetramethylpiperidine, which has a large steric hindrance, was converted to the corresponding *N*-methylamine in 95% yield (entry 16). Dibutylamine also smoothly underwent N-methylation with paraformaldehyde to furnish the corresponding N-methylated products in 90% yield (entry 17). The two amine groups of 1,2-bis(methylamino)-ethane were also successfully N-methylated to produce *N*,*N*,*N*,*N*-tetramethylethylenediamine in 67% yield (entry 18). Importantly, the drug molecules 1,2,3,4-tetrahydroquinoline and indoline were suitable for this (CAAC)CuH-catalyzed N-methylation reaction, affording the corresponding *N*-methylamines in 68 and 74% yields, respectively (entries 19 and 20). Furthermore, both *N*-methylcyclohexylamine and cyclohexylamine produced dimethylaminocyclohexane in yields of 94 and 65%, respectively (entries 21 and 22). To examine the potential application of the present methodology, we next evaluated the *N*-methylation of a drug molecule *N*-methyl-1-(naphthalen-1-yl)methanamine and achieved a yield of 88% under optimized conditions (Scheme S1). In particular, the reaction can be scaled up to the gram level, giving *N*,*N*-dimethylaniline (**1a**) in a yield of 93% (Scheme S2).

Considering that CuH is regarded as a key intermediate in the hydrosilylation reaction,[46,47] we attempted to isolate the CuH monomer via the replacement reaction between (CAAC)CuCl and hydrosilanes. Unfortunately, our efforts have failed so far because the CuH intermediate is highly unstable.[30] To gain insights into the mechanism of the reaction, we performed a controlled experiment involving a

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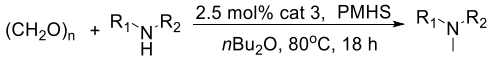
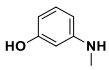
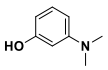
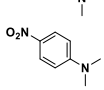
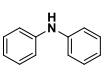
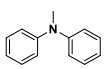
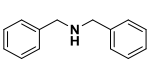
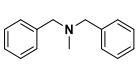
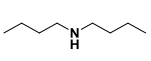
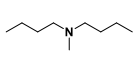
Table 2. N-Methylation of Amines with Paraformaldehyde and PMHS[a]



Entry	Substrate	Product	Yield(%)[b]
1			98
2			73
3			61
4			68
5			72
6			97
7			99
8			78
9			0
10			54
11			43
12			92
13			91
14			96
15			94
16			95
17[c]			90
18			67
19			68
20			74
21			94
22			65

[a]Conditions: amines (0.5 mmol), nBu$_2$O (2 mL), (CAAC)CuCl (2.5 mol %), PMHS (1.5 mmol), (CH$_2$O)$_n$ (1.5 mmol), 80 °C, 18 h. [b]Isolated yield. [c]PMHS (3.0 mmol), (CH$_2$O)$_n$ (3.0 mmol).

step-by-step reaction (see the Supporting Information). The imine salt was generated in 27% yield via the direct condensation reaction between *N*-methylaniline and paraformaldehyde. It was confirmed that polyoxymethylene decom-

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posed to produce formaldehyde at high temperatures. Subsequently, the (CAAC)CuCl catalyst and the PMHS reducing agent were added, and the imine salt and unreacted *N*-methylaniline were converted into *N*,*N*-dimethylaniline in 91% yield.

According to the aforementioned results and the results of previous research,[28−33] a possible mechanism for the N-methylation reaction was proposed (Figure 3). First, the

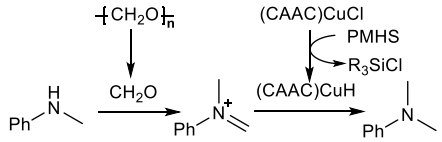

Figure 3. Proposed reaction mechanism.

reaction between (CAAC)CuCl and hydrosilane produces a key intermediate (CAAC)CuH. Subsequently, polyoxymethylene decomposes to produce formaldehyde and then condenses with *N*-methylaniline to furnish an imine cation. After the imine cation reacts with the pregenerated (CAAC)-CuH, *N*,*N*-dimethylaniline is generated via reductive elimination in the presence of PMHS, with the concomitant regeneration of the (CAAC)CuH. Notably, the yield of the imine cation directly obtained from the reaction between *N*-methylaniline and paraformaldehyde was only 27%, which suggests that (CAAC)CuCl might promote the decomposition of polyoxymethylene.

3. CONCLUSIONS

We demonstrated that a (CAAC)CuH catalyst produced via a reaction between PMHS and (CAAC)CuCl exhibited high efficiency for the selective N-methylation of amines with paraformaldehyde in the absence of additives. Interestingly, various aromatic and aliphatic amines were suitable for the reaction and afforded the corresponding *N*-methylamines or *N*,*N*-dimethylamines in moderate to excellent yields. A plausible mechanism for the N-methylation reaction was suggested based on the results of this study and those of previous research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c04332.

Details on preparation of catalysts, synthetic method for selective *N*-methylation of amines, and the NMR information for the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Chatterjee, J.; Gilon, A. C. N-methylation of peptides: A new perspective in medicinal chemistry. *Acc. Chem. Res.* **2008**, *41*, 1331−1342.

(2) Goldberg, A. D.; Allis, C. D.; Bernstein, E. Epigenetics: A landscape takes shape. *Cell* **2007**, *128*, 635−638.

(3) Yan, F.; Cai, S.; Wen, W.; Wen, W.; Li, B.; Wang, L.; Zhu, L. Recent advances and applications in N-methylation of amines and imines. *Chin. J. Org. Chem.* **2020**, *40*, 1874−1890.

(4) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The methylation effect in medicinal chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246.

(5) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. Advances in the chemistry of tetrahydroquinolines. *Chem. Rev.* **2011**, *111*, 7157−7259.

(6) Chen, L.; Liu, R.; Yan, Q. Polymer meets frustrated Lewis pair: Second-generation CO_2-responsive nanosystem for sustainable CO_2 conversion. *Angew. Chem., Int. Ed.* **2018**, *57*, 9336−9340.

(7) Li, W.; Zhou, X. J. Methylation extends the reach of liquid biopsy in cancer detection. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 655−656.

(8) https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster.

(9) 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.

(10) Liu, P.; Yang, J.; Ai, Y.; Hao, S.; Chen, X.; Li, F. Recyclable covalent triazine framework-supported iridium catalyst for the N-methylation of amines with methanol in the presence of carbonate. *J. Catal.* **2021**, *396*, 281−290.

(11) 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.
(12) Cabrero-Antonino, J. R.; Adam, R.; Junge, K.; Beller, M. A general protocol for the reductive N-methylation of amines using dimethyl carbonate and molecular hydrogen: mechanistic insights and kinetic studies. *Catal. Sci. Technol.* **2016**, *6*, 7956−7966.
(13) 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.
(14) Huang, Y.; Deng, W.; Lin, B.-L. Air-tolerant direct reductive N-methylation of amines using formic acid via simple inorganic base catalysis. *Chin. Chem. Lett.* **2020**, *31*, 111−114.
(15) Yang, Z.; Yu, B.; Zhang, H.; Zhao, Y.; Ji, G.; Ma, Z.; Gao, X.; Liu, Z. $B(C_6F_5)_3$-catalyzed methylation of amines using CO_2 as a C1 building block. *Green Chem.* **2015**, *17*, 4189−4193.
(16) Lin, W.; Cheng, H.; Wu, Q.; Zhang, C.; Arai, M.; Zhao, F. Selective N-methylation of N-methylaniline with CO_2 and H_2 over TiO_2-supported PdZn catalyst. *ACS Catal.* **2020**, *10*, 3285−3296.
(17) Eschweiler, W. Ersatz von an stickstoff gebundenen wasserstoffatomen durch die methylgruppe mit hülfe von formaldehyd. *Chem. Ges.* **1905**, *38*, 880−882.
(18) 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.
(19) Guyon, C.; Duclos, M.-C.; Métay, E.; Lemaire, M. Reductive N-methylation of amines with calcium hydride and Pd/C catalyst. *Tetrahedron Lett.* **2016**, *57*, 3002−3005.
(20) Ke, Z.; Cui, X.; Shi, F. Water as Co-hydrogen donor in reductive aminations. *ACS Sustainable Chem. Eng.* **2016**, *4*, 3921−3926.
(21) Wang, H.; Huang, Y.; Dai, X.; Shi, F. N-monomethylation of amines using paraformaldehyde and H_2. *Chem. Commun.* **2017**, *53*, 5542−5545.
(22) Wang, H.; Huang, Y.; Jiang, Q.; Dai, X.; Shi, F. Reductive N-methylation of quinolines with paraformaldehyde and H_2 for sustainable synthesis of N-methyl tetrahydroquinolines. *Chem. Commun.* **2019**, *55*, 3915−3918.
(23) Goyal, V.; Naik, G.; Narani, A.; Natte, K.; Jagadeesh, R. V. Recent developments in reductive N-methylation with base-metal catalysts. *Tetrahedron* **2021**, *98*, 132414.
(24) Liu, J.; Song, Y.; Zhuang, X.; Zhang, M.; Ma, L. Simplified preparation of a graphene-co-shelled Ni/NiO@C nano-catalyst and its application in the Ndimethylation synthesis of amines under mild conditions. *Green Chem.* **2021**, *23*, 4604−4617.
(25) Irrgang, T.; Kempe, R. Transition-metal-catalyzed reductive amination employing hydrogen. *Chem. Rev.* **2020**, *120*, 9583−9674.
(26) 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.
(27) Zhang, H.; Zhang, Y. M.; Gao, K. DIC-borane-catalyzed selective methylation of primary amines with CO_2 using boranes as reducing agents. *Org. Chem. Front.* **2023**, *10*, 2491−2497.
(28) Maji, S.; Das, A.; Mandal, S. K. Mesoionic N-heterocyclic olefin catalysed reductive functionalization of CO_2 for consecutive N-methylation of amines. *Chem. Sci.* **2021**, *12*, 12174−12180.
(29) Choi, G.; Hong, S. H. Selective N-formylation and n-methylation of amines using methanol as a sustainable C1 source. *ACS Sustainable Chem. Eng.* **2019**, *7*, 716−723.
(30) Romero, E. A.; Zhao, T.; Nakano, R.; Hu, X.; Wu, Y.; Jazzar, R.; Bertrand, G. Tandem copper hydride-Lewis pair catalysed reduction of carbon dioxide into formate with dihydrogen. *Nat. Catal.* **2018**, *1*, 743−747.
(31) Wu, F.-P.; Wu, X.-F. Copper-catalyzed borylative methylation of alkyl iodides with CO as the C1 source: advantaged by faster reaction of CuH over CuBpin. *Angew. Chem., Int. Ed.* **2021**, *60*, 11730−11734.
(32) Zhao, S.; Mankad, N. Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO To Provide One-Carbon-Extended Alcohols. *Angew. Chem., Int. Ed.* **2018**, *57*, 5867−5870.
(33) Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-catalyzed reactions. *Chem. Rev.* **2008**, *108*, 2916−2927.
(34) Xu, G.; Leloux, S.; Zhang, P.; Meijide Suárez, J.; Zhang, Y.; Derat, E.; Ménand, M.; Bistri-Aslanoff, O.; Roland, S.; Leyssens, T.; Riant, O.; Sollogoub, M. Capturing the monomeric (L)CuH in NHC-capped cyclodextrin: Cavity-controlled chemoselective hydrosilylation of α,β-unsaturated ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 7591−7597.
(35) Zhou, Y.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Asymmetric Reduction of α,β-Unsaturated Carboxylic Acids to β-Chiral Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 606−609.
(36) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. Enantioselective CuH-catalyzed hydroacylation employing unsaturated carboxylic acids as aldehyde surrogates. *J. Am. Chem. Soc.* **2017**, *139*, 8126−8129.
(37) Lv, H.; Xing, Q.; Yue, C.; Lei, Z.; Li, F. Solvent-promoted catalyst-free N-formylation of amines using carbon dioxide under ambient conditions. *Chem. Commun.* **2016**, *52*, 6545−6548.
(38) Song, J.; Zhou, B.; Liu, H.; Xie, C.; Meng, Q.; Zhang, Z.; Han, B. Biomass-derived γ-valerolactone as an efficient solvent and catalyst for the transformation of CO_2 to formamides. *Green Chem.* **2016**, *18*, 3956−3961.
(39) Rendler, S.; Oestreich, M. Polishing a diamond in the rough: "Cu-H" catalysis with silanes. *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504.
(40) Tomás-Mendivil, E.; Hansmann, M. M.; Weinstein, C. M.; Jazzar, R.; Melaimi, M.; Bertrand, G. Bicyclic (alkyl)(amino)carbenes (BICAACs): Stable carbenes more ambiphilic than CAACs. *J. Am. Chem. Soc.* **2017**, *139*, 7753−7756.
(41) Morvan, J.; Mauduit, M.; Bertrand, G.; Jazzar, R. Cyclic (alkyl)(amino)carbenes (CAACs) in ruthenium olefin metathesis. *ACS Catal.* **2021**, *11*, 1714−1748.
(42) Liu, X.-F.; Ma, R.; Qiao, C.; Cao, H.; He, L.-N. Fluoride-catalyzed methylation of amines by reductive functionalization of CO_2 with hydrosilanes. *Chem.—Eur. J.* **2016**, *22*, 16489−16493.
(43) Motokura, K.; Naijo, M.; Yamaguchi, S.; Miyaji, A.; Baba, T. Reductive transformation of CO_2 with hydrosilanes catalyzed by simple fluoride and carbonate salts. *Chem. Lett.* **2015**, *44*, 1217−1219.
(44) Hulla, M.; Bobbink, F. D.; Das, S.; Dyson, P. J. Carbon dioxide based N-formylation of amines catalyzed by fluoride and hydroxide anions. *ChemCatChem* **2016**, *8*, 3338−3342.
(45) Revunova, K.; Nikonov, G. I. Base-catalyzed hydrosilylation of ketones and esters and insight into the mechanism. *Chem.—Eur. J.* **2014**, *20*, 839−845.
(46) Zhang, L.; Cheng, J. H.; Hou, Z. M. Highly efficient catalytic hydrosilylation of carbon dioxide by an N-heterocyclic carbene copper catalyst. *Chem. Commun.* **2013**, *49*, 4782−4784.
(47) Zhou, L.; Peng, L. L.; Ji, J. L.; Ma, W. T.; Hu, J. L.; Wu, Y. T.; Geng, J.; Hu, X. B. Cyclic (alkyl)(amino)carbene-copper supported on SBA-15 as an efficient and recyclable catalyst for CO_2 hydrogenation to formate. *J. CO_2 Util.* **2022**, *58*, 101910.

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