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Homogeneous Catalysis

General Catalytic Methylation of Amines with Formic Acid under Mild Reaction Conditions

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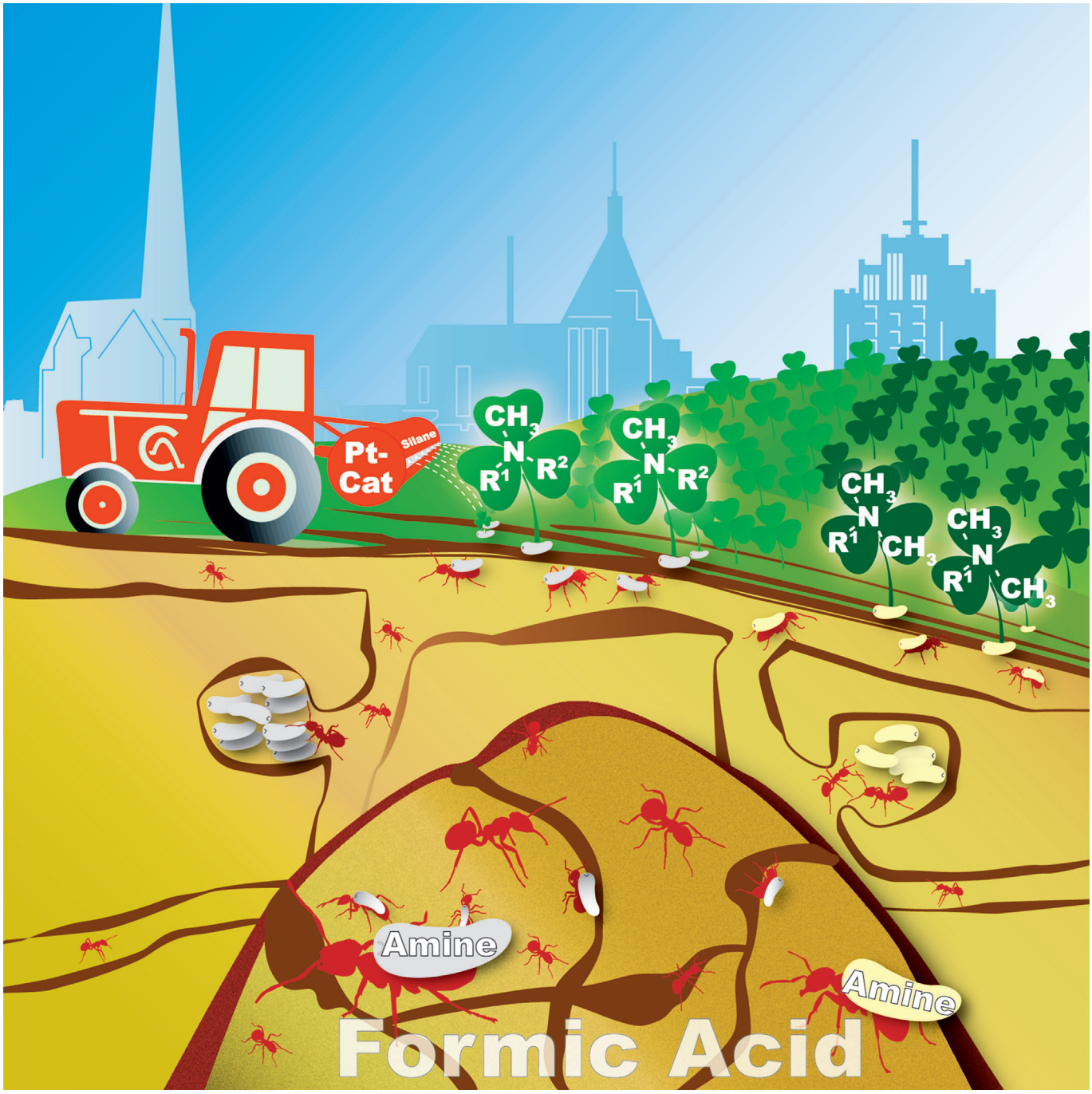


Abstract: A general catalytic protocol for the methylation of amines has been developed applying, for the first time, formic acid as the C_1 building block and silanes as reducing agents. A broad range of aromatic and aliphatic, both primary and secondary, amines has been converted to the corresponding tertiary amines including [*N*-^{13}C]-labelled drugs in good to excellent yields under mild conditions.

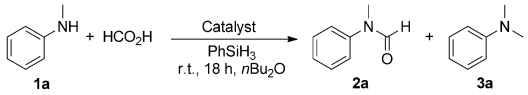
Methyl-substituted amines are valuable organic compounds in both the bulk and fine chemical industries because of their use in the manufacture of pharmaceuticals, agrochemicals, dyes, etc.[1] Although the classic Eschweiler–Clarke methodology using toxic formaldehyde as the C_1 source prevails in industry,[2] the most common methodology for methylations of amines on the laboratory scale still makes use of activated methyl compounds, such us methyl iodide, dimethyl sulfate, MeOTf (OTf = trifluoromethanesulfonate) or diazomethane.[3] Besides toxicity, the main drawback of these conventional methylating reagents is the generation of stoichiometric amounts of wasteful (in)organic salts. Thus, the development of more environmentally acceptable processes that make use of eco-friendly reagents is highly desired. In this regard, during the last decade, dimethyl carbonate and methanol have been presented as interesting green alternatives.[4] In addition, very recently interesting *N*-methylations using CO_2 have been reported by Cantat et al., Klankermayer and Leitner et al., as well as our group.[5–7] Unfortunately, so far the use of these attractive green alternatives requires high-temperature and/or pressure operations, which make the laboratory-scale synthesis difficult.

Formic acid (FA) is one of the major products formed in biomass processing and also easily accessible by hydrolysis of methyl formate or by CO_2 hydrogenation. Notably, it is a non-toxic liquid, which is used for food preservation. In organic synthesis, FA is well established in transfer hydrogenation reactions,[8] and more recently formic acid has been intensely investigated as a suitable liquid for hydrogen production and as a potential hydrogen storage material.[9] The reaction of amines with formic acid to form the corresponding formamides is well known.[10] Owing to its non-toxicity, biodegradability, and good reactivity with amines, FA offers great potential as a benign C_1 feedstock for the synthesis of *N*-methylamines after catalytic deoxygenation. However, to the best of our knowledge, methylation reactions using formic acid as a building block remain elusive under both heterogeneous and homogeneous catalysis.

Herein, we describe for the first time a general and selective Pt-catalyzed methylation of a range of amines employing formic acid and silanes for the construction of the methyl group under mild reaction conditions. At the start of our work, the reaction of *N*-methylaniline (**1a**) with formic acid in the presence of silanes at room temperature was investigated as a benchmark system.[11] To identify active catalysts, we tested different metal precursors by using phenylsilane as reductant. As shown in Table 1, Pt metal precursors were the most active catalysts (Table 1, entries 8–10) and to our delight, full conversion with 99% yield of *N,N*-dimethylaniline (**3a**) was achieved in the presence of 0.5 mol% of the commercially available so-called Karstedt's catalyst ([Pt(CH_2=$CHSiMe_2$)$_2$O]) in the absence of any additional ligand (Table 1, entry 8). Interestingly, even at 0.1 mol% catalyst loading, **3a** was afforded in 92% yield (Table 1, entry 11; see also Supporting Information, Table SI3).[12] Without catalyst, *N*-methylformanilide (**2a**) was formed in 76% yield and only traces of the dimethylated product **3a** (2%) were detected (Table 1, entry 12). Next, the methylation of **1a** was studied in the presence of different arylsilanes, polymethylhydrosiloxane (PMHS) and alkoxysilanes (Table SI1 in the Supporting Information). Among the various silanes tested, the initially used phenylsilane remained as the best reagent, which led to quantitative yield. Reaction in the absence of phenylsilane gave no conversion towards the dimethylated product **3a**. Notably, use of non-protic solvents, such as nBu$_2$O, Et$_2$O, THF, toluene, or 1,4-dioxane have no noticeable influence on the conversion and only slightly lower yields were obtained for the last two solvents (Table SI2 in the Supporting Information). Finally, optimal quantities of phenylsilane and formic acid were found to be 2.5 and 1.5 equivalents, respectively (Table 1, entry 8; see also Supporting Information, Table SI4).

After investigating the benchmark system, we were interested in the reaction of more challenging primary amines. By

Table 1. Methylation of *N*-methylaniline (**1a**): Testing different metal precursors.[a]



1a 2a 3a

Entry	Catalyst	Conversion [%][b]	Yield [%][b] 2a	3a
1	$Fe(CF_3SO_3)_2$	91	81	4
2	Me_2SAuCl	87	64	14
3[c]	$Pd(acac)_2$	99	35	54
4[c]	$Ru(acac)_3$	98	88	5
5	$(NH_4)_2IrCl_6$	99	88	6
6	$MeReO_3$	85	78	3
7	$In(CF_3SO_3)_3$	90	85	1
8[d]	[Pt] Karstedt's catalyst	>99	–	>99
9	$Pt(PPh_3)_4$	>99	–	94
10	Na_2PtCl_4	>99	6	86
11[e]	[Pt] Karstedt's catalyst	99	5	92
12[f]	–	83	76	2

[a] Reaction conditions: **1a** (0.5 mmol), HCO_2H (2 equiv), $PhSiH_3$ (3 equiv), catalyst (1 mol%), nBu$_2$O (1 mL). [b] Determined by GC using *n*-hexadecane as an internal standard. [c] acac = acetylacetonate. [d] HCO_2H (1.5 equiv), $PhSiH_3$ (2.5 equiv), catalyst (0.5 mol%). [e] Catalyst (0.1 mol%). [f] Without catalyst.

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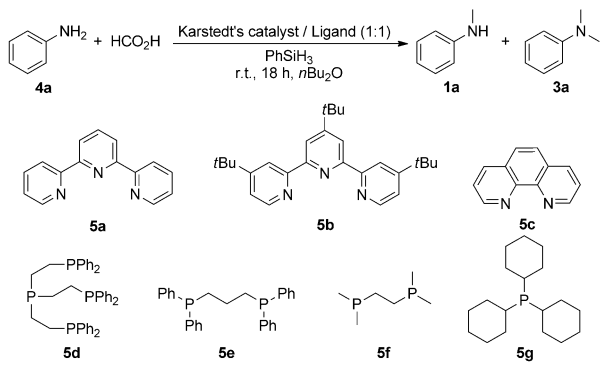
Table 2. Platinum-catalyzed methylation of aniline with formic acid and phenylsilane.[a]



Entry	Ligand	Conversion [%][b]	Yield [%][b]	
			1a	3a
1[c]	–	>99	–	90
2	5a	>99	–	91
3	5b	>99	2	86
4	5c	>99	3	81
5	5d	>99	2	8
6	5e	>99	–	95
7	5f	>99	–	93
8	5g	>99	2	78
9[c]	5e	>99	–	>99
10[d]	5e	42	1	–
11[e]	5e	79	19	38

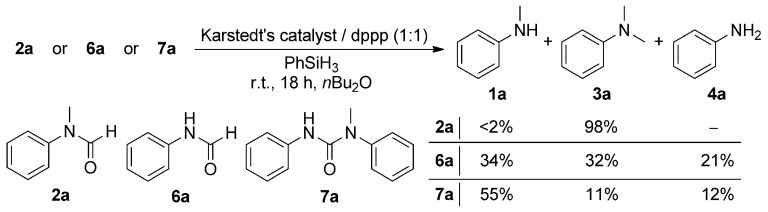
[a] Reaction conditions: **4a** (0.5 mmol), HCO_2H (3 equiv), $PhSiH_3$ (4 equiv), catalyst (1 mol%), ligand (1 mol%), nBu_2O (1 mL). [b] Determined by GC using *n*-hexadecane as an internal standard. [c] HCO_2H (3 equiv), $PhSiH_3$ (5 equiv). [d] Ligand (2 mol%). [e] HCO_2H (1 equiv), $PhSiH_3$ (2.5 equiv), catalyst (0.5 mol%), ligand (0.5 mol%).

using higher amounts of silane, FA, and catalyst loading, methylation of aniline (**4a**) afforded full conversion with a 90% yield of *N,N*-dimethylaniline (**3a**) (Table 2, entry 1). To improve the product yield, various commercially available phosphine and nitrogen-based ligands were tested in combination with Karstedt's catalyst (Table 2). Fortunately, by using 1 mol% of dppp (1,3-bis(diphenylphosphino)propane) the desired yield was improved to 99% (Table 2, entry 9). Notably, in the presence of an excess of ligand (Pt/dppp ratio = 1:2), no reactivity to *N*-methylated products was observed (Table 2, entry 10).

As it is known that the reaction of amines with formic acid affords the corresponding formamides,[10] we decided to perform some control experiments to clarify the elementary steps involved in this methylation of primary and secondary amines. As shown in Scheme 1, the reaction of *N*-methylformanilide (**2a**) with phenylsilane afforded **3a** in 98% yield with only traces of the monomethylated product **1a** (<2%). However, under the same reaction conditions, formanilide (**6a**) gave three major products: 34% *N*-methylaniline (**1a**), 32% *N,N*-dimethylaniline (**3a**), and 21% aniline (**4a**). It is easy to envision a route for the formation of dimethylated product **3a** by condensation of the initially formed **1a** and the starting formamide **6a** to produce *N*-methyl-*N,N'*-diphenylurea (**7a**) first, followed by reduction of this intermediate. In fact, the reduction of the urea **7a** affords the dimethylated product **3a** in 11% yield without further optimization of reaction conditions (Scheme 1).[13]

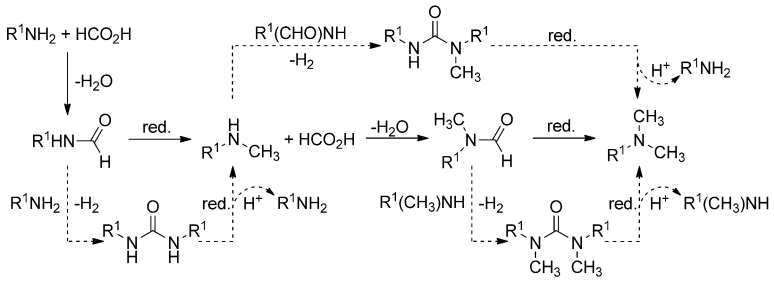
Interestingly, when **6a** was reacted in the presence of a 2-fold excess of aniline, the formation of the dimethylated product **3a** (14% yield) was strongly suppressed and **1a** was obtained in 70% yield. Under these reaction conditions, formanilide (**6a**) preferentially reacts with aniline (**4a**) to produce the corresponding urea derivate, which is subsequently reduced to give **1a** and **4a**. Based on these results, we propose that methylation of amines with formic acid under our reaction conditions proceeds with both formamide and urea derivates as reaction intermediates (Scheme 2). The occurrence of this reaction pathway avoids the possibility of the monomethylation of primary amines because dimethylated products will always be generated. In fact, the reaction of aniline with only one equivalent of formic acid in the presence of phenylsilane afforded **3a** as major product in 38% yield (Table 2, entry 11).

Next, to demonstrate the applicability of this novel catalytic transformation for the methylation of amines, we tested more than 35 different primary and secondary amines, affording the corresponding *N*-methylated products with good to excellent yields (Table 3). In general, primary and secondary substituted anilines were smoothly methylated at room temperature to afford the corresponding *N,N*-dimethylanilines in up to 99%



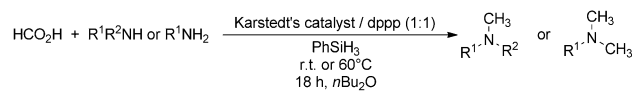
	1a	3a	4a
2a	<2%	98%	–
6a	34%	32%	21%
7a	55%	11%	12%

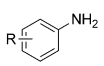
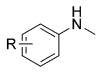
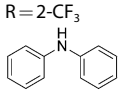
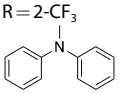
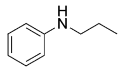
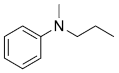
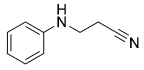
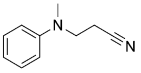
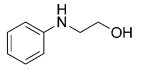
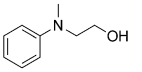
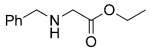
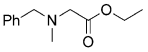
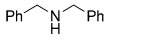
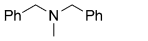
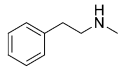
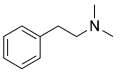
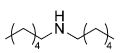
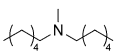
Scheme 1. Control experiments.[14]



Scheme 2. Proposed pathways for the Pt-catalyzed methylation of amines with formic acid.

Table 3. A general catalytic methylation of amines from HCO_2H.[a]



Entry	Substrate	T [°C]	Product	Conv. [%][b]	Yield [%][b]
					
1	R = 4-Me	r.t.	R = 4-Me	> 99	98
2	R = 4-F	r.t.	R = 4-F	> 99	98
3	R = 4-Cl	r.t.	R = 4-Cl	> 99	93
4	R = 4-Br	r.t.	R = 4-Br	> 99	98
5	R = 4-SMe	r.t.	R = 4-SMe	> 99	99 (85)
6	R = 3-Cl	r.t.	R = 3-Cl	> 99	97
7[c]	R = 2-Cl	r.t.	R = 2-Cl	> 99	> 99
8	R = 2,5-Me	r.t.	R = 2,5-Me	> 99	(80)
9	R = 2,5- *i*Pr	r.t.	R = 2,5- *i*Pr	> 99	> 99
10	R = 2-Ph	r.t.	R = 2-Ph	> 99	(86)
					
11[d]	R = 4-CN	60	R = 4-CN	> 99	73
12	R = 4-OMe	r.t.	R = 4-OMe	> 99	(71)
13[d]	R = 3-OMe	r.t.	R = 3-OMe	> 99	72
14[d,e]	R = 4-COOMe	r.t.	R = 4-COOMe	> 99	94
15[d]	R = 2-CF_3	r.t.	R = 2-CF_3	> 99	(78)
16[d]		60		> 99	99[f]
17		r.t.		> 99	99 (83)
18[d]		60		> 99	70
19[d]		r.t.		> 99	87
20[c,e]		60		> 99	(68)
21[d]		60		97	90
22		60		> 99	93
23		60		> 99	(84)
24		60		> 99	> 99
25		60		> 99	92
26		60		> 99	97
27		60		> 99	96
28		60		> 99	97
29		60		> 99	> 99
30		60		> 99	87

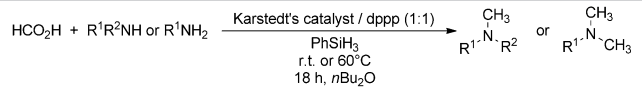
yield (Table 3, entries 1–20). However, for anilines bearing a cyanide group and for the least reactive diphenylamine, a higher amount of $PhSiH_3$ and HCO_2H and an increased temperature (60 °C) were needed (Table 3, entries 11, 16, and 18). Interestingly, *N,N′*-dimethyl-1,2-phenylenediamine, which is a substrate that also gave important mechanistic information (see Table SI5 in the Supporting Information), was successfully methylated to give the corresponding diamine in good yield (Table 3, entry 20).

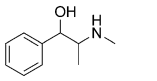
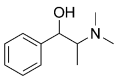
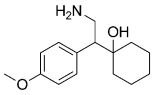
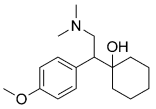
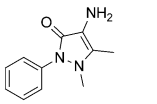
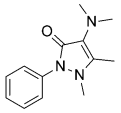
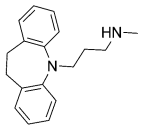
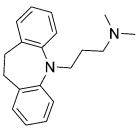
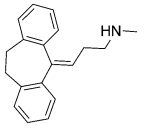
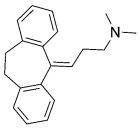
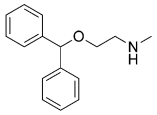
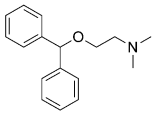
Moreover, this catalytic system also allows for convenient methylation of aliphatic amines. Under mild conditions (60 °C), excellent reactivity towards the desired products was achieved, affording the corresponding methylated amines in up to 99% yield (Table 3, entries 22–36). In addition to benzyl amines, linear aliphatic, and even branched compounds, were smoothly methylated. Notably, good functional-group tolerance was observed for nitrile, ester, ether, thiol, olefin, heterocyclic, hydroxy, and even for highly functionalized formamide groups. As *N*-methylation reactions are of major importance in the synthesis of a wide variety of drug molecules for many therapeutic areas, we next focused our attention in this direction. Hence, five current drug molecules, including venlafaxine, 4-dimethylaminoantipyrine, imipramine, amitriptyline, and diphenhydramine, were synthesized in high yields starting from the corresponding primary or secondary aliphatic amine (Table 3, entries 32–36).

Finally, we investigated the use of our catalytic protocol for the preparation of [*N*-^{13}C]-labelled drugs, which are of significant importance in medical biology for tracking metabolites and their quantitative analysis by mass spectrometry and ^{13}C NMR spectroscopy.[15] Thus, two drug precursor molecules, 4-aminoantipyrine and 2-(diphenylmethoxy)-*N*-methylethylamine, were reacted under the protocol described above by using $H^{13}CO_2H$ as an inexpensive and convenient labelling reagent. To our delight, the corresponding [*N*-^{13}C]-labelled drugs were obtained with excellent yields (Scheme 3 and Table 3, entries 33 and 36).

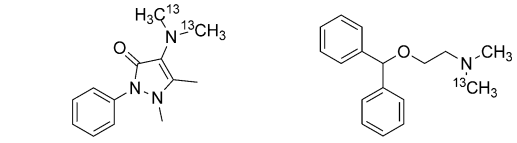
In conclusion, we have developed a general and highly efficient protocol for the methylation of aromatic and aliphatic, both primary and secondary amines. To the best of our knowledge, this methodology demonstrates for the first time that HCO_2H can act as a C_1 building block for methylation by using silanes as reducing agents. In the presence of the commercially available Karstedt's catalyst and dppp as ligand combined in situ, the methylation of the desired amines proceeds easily under mild reaction conditions (room temperature or 60 °C, ambient pressure) in good to excellent yield. Furthermore, it is shown that this protocol can be applied for the convenient synthesis of [*N*-^{13}C]-labelled drugs, too.

Table 3. (Continued)



Entry	Substrate	T [°C]	Product	Conv. [%][b]	Yield [%][b]
31[d]		60		>99	91
32[e,g]		60		>99	65
33[e]		60		>99	94 91[h]
34[e]		60		>99	92
35[e]		60		>99	94
36[e]		60		>99	92 85[h]

[a] Reaction conditions for primary amines: substrate (0.5 mmol), HCO_2H (1.5 equiv), $PhSiH_3$ (2.5 equiv), catalyst (0.5 mol%; metal/ligand ratio 1:1), nBu_2O (1 mL); for secondary amines: HCO_2H (3 equiv), $PhSiH_3$ (5 equiv), catalyst (1 mol%; metal/ligand atio 1:1), nBu_2O (1 mL). [b] Determined by GC using *n*-hexadecane as an internal standard; yield of isolated product in parenthesis. [c] 7.5 equiv of $PhSiH_3$ and 4.5 equiv of HCO_2H. [d] 5 equiv of $PhSiH_3$ and 3 equiv of HCO_2H. [e] THF used as a solvent. [f] Dodecane used as an internal standard. [g] 10 equiv of $PhSiH_3$ and 6 equiv of HCO_2H. [h] Yield of [*N*-^{13}C]-labelled products.



Scheme 3. [*N*-^{13}C]-labelled drugs synthetized from $H^{13}CO_2H$.

Experimental Section

The general procedure for the methylation reaction of aniline is as follows: dppp (2.1 mg, 0.005 mmol) was dissolved in dry nBu_2O (1 mL) in a Schlenk tube under argon atmosphere and Karstedt's catalyst (57 μL, 0.005 mmol) was added, leading to the formation of a slightly yellow solution. After the mixture had been stirred for 10 min, $PhSiH_3$ (309 μL, 2.5 mmol) was added and the solution turned colorless. Immediately, aniline (45.6 μL, 0.5 mmol), *n*-hexadecane (50 μL) as an internal standard, and HCO_2H (57 μL, 1.5 mmol) were added and a bubble gas generation was observed. After the reaction mixture had been stirred for 18 h at room temperature, ethyl acetate (15 mL) was added and then a sample was taken to be injected into the GC to determinate the yield. For methylated amines containing a hydroxyl group (Table 3, entries 19, 31–32), the sample for GC was taken after dilution of the reaction mixture with CH_2Cl_2 (15 mL), slow addition of NaOH (3 M (aq.), 5 mL) and vigorous stirring for 3 h at room temperature. All catalytic reactions were performed at least twice to ensure reproducibility. To determine the isolated yield of the methylated amines no internal standard was added. After completion and dilution with ethyl acetate (15 mL), NaOH (3 M (aq.), 5 mL) was slowly added and the reaction mixture was vigorously stirred for 3 h at room temperature. The mixture was then extracted with ethyl acetate (three times) and the combined organic layers were dried over $MgSO_4$ anhydrous. Finally, the organic phase was filtered, concentrated, then purified by silica gel column chromatography (*n*-hexane/ethyl acetate mixtures) to give the corresponding methylated amines.

Acknowledgements

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Keywords: formic acid · homogeneous catalysis · methylation · platinum · silanes

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[14] Reduction of **2a** and **6a** was carried by using 2.5 equivalents of phenylsilane.

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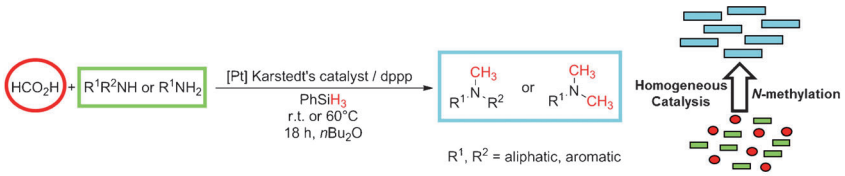


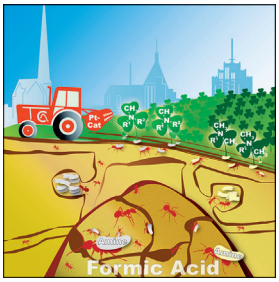
Methylation made easy: A general catalytic protocol for the methylation of amines has been developed applying, for the first time, formic acid as the C_1 building block and silanes as reducing agents. A broad range of aromatic and aliphatic, both primary and secondary, amines has been converted to the corresponding tertiary amines, including [*N*-^{13}C]-labelled drugs, in good to excellent yields at mild conditions (see scheme: dppp = (1,3-bis(diphenylphosphino)propane)).

Homogeneous Catalysis

*I. Sorribes, K. Junge, M. Beller**

■■ – ■■

General Catalytic Methylation of Amines with Formic Acid under Mild Reaction Conditions



Amine Methylation

In their Communication on page ■■ ff., M. Beller et al. describe a general catalytic protocol for the methylation of amines that applies, for the first time, formic acid as the C_1 building block and silanes as reducing agents, which is represented here as mono and dimethylated amines growing from the corresponding amine seeds after being irrigated with the mixture catalyst/silane. The hard-working ants secrete the formic acid starting material for attack and defense purposes.