ChemPubSoc Europe

DOI: 10.1002/chem.201502917

CHEMISTRY
A European Journal
Communication

Methylation |Hot Paper|

Convenient Reductive Methylation of Amines with Carbonates at Room Temperature

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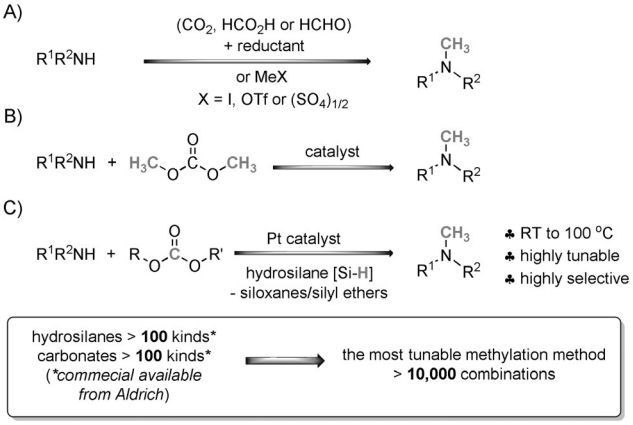
Abstract: Methylation of amines is a fundamental and commonly used reaction in organic synthesis. Many methods are known including various reductive methylations using formaldehyde, formic acid, or carbon dioxide in the presence of reductants. However, several of these methods suffer from limited substrate scope and chemoselectivity because of the different nucleophilicities of substrates. In this respect, the combination of carbonates and hydrosilanes is a valuable methylation source in the presence of Pt-based catalysts. This highly tunable method allows for methylation of both aromatic and aliphatic amines, and chemoselective methylation of aminoalcohols and diamines. Notably, the in situ-formed catalyst can also be used for the reduction of carbonates to methanol at room temperature. Mechanistic insights on intermediates formed during the reaction pathway were obtained by using ESI mass spectrometry.

N-methyl amines are key intermediates and important building blocks in organic synthesis. Hence, the discovery of more efficient and selective methylation methods continuously attracts the attention of chemists.[1] Other than the use of toxic formaldehyde or activated methylation reagents, recently CO_2,[2] CH_3OH,[3] and HCO_2H[4] have been disclosed as interesting C1 building blocks for the synthesis of *N*-methylamines. Despite these important developments, improvements are desired due to drawbacks such as limited substrate scope, inconvenient employment of pressure operations, or the necessity to apply high temperatures or acidic conditions.

Organic carbonates (carbonic acid esters) constitute an important and versatile class of compounds that are easily available from CO or CO_2. These "nontoxic", biodegradable compounds are used more and more in chemical and material industries, for example, as solvents even in organic (reduction) reactions.[5] Nonetheless, recently the selective reduction of carbonates also attracted interest in the context of reductive CO_2 valorization. In this regard, the hydrogenation of organic carbonates to methanol, as reported by the groups of Milstein[6a] and Ding,[6b] is noteworthy. Although the use of dimethyl carbonate as a green methylation reagent is an important issue for a sustainable chemical industry,[7a–d] only one example of reductive methylation of amines by carbonates is known, which interestingly employed photoactivation in the presence of Fe complexes.[7e] Nevertheless, we assumed that under the appropriate catalytic conditions, the C=O moiety could be used for efficient methylation of amines by selective substitution and reduction reactions in the absence of photoactivation. Herein, we report a general and selective homogeneous system for this type of reaction under mild conditions. Compared to the recent work with CO_2 or formaldehyde, the use of different carbonates allows the performance of reductive methylation under ambient conditions without any specific high-pressure equipment (Scheme 1).



Scheme 1. *N*-Methylation methods: A) and B) Known methods; C) use of carbonates as methylating reagents under reductive conditions (this work).

At the start of our work, we investigated the reaction of *N*-methylaniline (**1a**) and dimethyl carbonate (**2a**) in toluene in the presence of transition metals and silanes as a model system.[8a,b] To identify effective catalysts, different metal precursors, including Ru, Ir, Rh, Ni, Pd, In, and Pt complexes, were tested by using phenylsilane as a reducing agent (Table 1 and Table S5 in the Supporting Information). Commercially available Pt complexes proved to be the most active catalyst precursors, giving dimethylaniline (**3a**) in near 70% yield (Table 1, entries 7–9), whereas no reaction took place in the absence of

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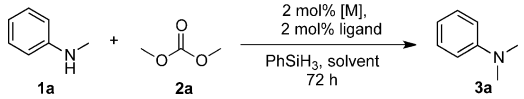
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201502917.

Table 1. Transition metal-catalyzed methylation of **1a** with **2a** and phenysilane.[a]



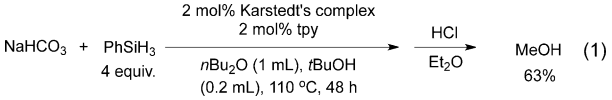
1a **2a** **3a**

Entry	[M]	Ligand	T [°C]	Conv. [%][b]	Yield [%][b]
1	$[RuCl_2(dmso)_4]$	–	80	26	25
2	$[\{Ir(cod)Cl\}_2]$	–	80	46	46
3	$[RhCl(PPh_3)_3]$	–	80	34	33
4	$[Ni(cod)_2]$	–	80	35	34
5	$[Pd(OAc)_2]$	–	80	8	6
6	$In(OTf)_3$	–	80	2	2
7	H_2PtCl_6	–	80	73	66
8	$[Pt(PPh_3)_4]$	–	80	72	66
9	Karstedt [Pt]	–	80	72	67
10	Karstedt [Pt]	–	80	76	71
11[c,d]	Karstedt [Pt]	tpy	RT	78	76
12[c,e]	Karstedt [Pt]	tpy	RT	39	37
13[c,d,f]	Karstedt [Pt]	tpy	RT	96	92
14[g]	Karstedt [Pt]	tpy	RT	99	93
15[h]	Karstedt [Pt]	tpy	100	26	24

[a] Reaction conditions (unless otherwise stated): **1a** (0.5 mmol), **2a** (2 equiv), $PhSiH_3$ (2.5 equiv), solvent (1 mL); Karstedt [Pt] = platinum(0) 1,3-divinyl-1,1,3,3-tetramethyldisiloxane; entries 1–9: solvent = toluene; entries 10–13: solvent = nBu_2O; [b] determined by GC using *n*-hexadecane as an internal standard; [c] t = 18 h; [d] 1 mol% [Pt] and tpy; [e] 0.1 mol% [Pt] and tpy; [f] **2a** (4 equiv), $PhSiH_3$ (5 equiv); [g] carbon source = propylene carbonate; [h] carbon source = $NaHCO_3$, t = 24 h.

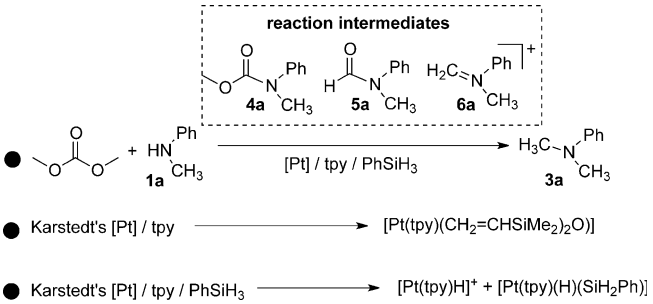
catalyst (see the Supporting Information, Table S1).[8c] A moderate improvement in the conversion and yield was observed on changing the solvent to nBu_2O (Table 1, entry 10). Next, to improve the product yield various commercially available ligands were tested in combination with Karstedt's complex ($[Pt(CH_2{=}CHSiMe_2)_2O]$; see the Supporting Information, Table S2). The most effective catalyst was formed by using 2,2′:6′,2″-terpyridine (tpy) as a ligand, with which 76% yield of **3a** was obtained at room temperature (Table 1, entry 11).[8d,e] Notably, even at 0.1 mol% catalyst loading, this system showed significant activity (Table 1, entry 12). Next, the methylation of **1a** was investigated in the presence of different silanes (see the Supporting Information, Table S3). Basically, all tested silanes proved to be less active than $PhSiH_3$. For example, with polymethylhydrosiloxane (PMHS) and Ph_2SiH_2, 10% and 9% yields were observed, respectively, and no reaction occurred with other silanes under the otherwise same conditions. However, by using phenyl silane and adjusting the amount of dimethyl carbonate (**2a**) and reductant to 4 and 5 equivalents, respectively, 96% conversion of **1a** was achieved affording dimethylaniline (**3a**) in 92% yield (Table 1, entry 13). Reaction monitoring over time revealed the formation of **3a** in 62% yield in 1 h, whereas after 4 h the reaction was almost finished (>85% yield; see the Supporting Information, Scheme S1). In the meantime, 0.8 mmol of methanol could be produced by quenching the reaction solution with acidic aqueous solution.

Without amine present, smooth reduction of various carbonates, such as dimethyl carbonate or ethylene carbonate, to methanol was achieved at room temperature (see the Supporting Information, Scheme S2). For example, full conversion was observed for the reduction of dimethyl carbonate to methanol within 20 h in the presence of 0.5 mol% catalyst and 2.5 equivalents of $PhSiH_3$.[9] Furthermore, 63% yield of MeOH could be obtained after acidic work-up in the reduction of $NaHCO_3$ [Eq. (1)].



Hence, bicarbonate and propylene carbonate were also tested for reductive methylation of amines. Whereas bicarbonate gave only a low yield of **3a** (24%), in the presence of propylene carbonate excellent activity (93% yield) was observed (Table 1, entries 14 and 15). However, given its easy availability, dimethyl carbonate (DMC) was used for the subsequent mechanistic studies and the evaluation of the substrate scope.

Mechanistic insights on this multicomponent catalytic reaction were gathered from electrospray ionization mass spectrometry (ESI-MS) experiments.[10] **1a** and **3a** and proton adducts of potential carbamate or amide intermediates might be easily detected by ESI(+)-MS. Thus, we envisaged this technique as a highly sensitive analytical tool for reaction monitoring in the present system. Performing the model reaction in THF under optimized conditions (Table 1, entry 13 and Figure S1 in the Supporting Information) gave almost full conversion of the substrate after 4 h. After 30 min, prominent peaks had formed in the mass spectrum that were assigned to proton adducts of carbamate **4a** and formamide **5a**,[11] as well as the iminium **6a** cation (Scheme 2). However, Pt-containing



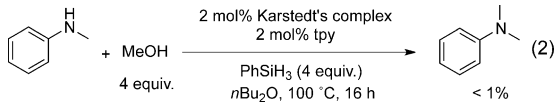
Scheme 2. Reaction intermediates **4a**–**6a** under catalytic conditions and species detected from reactivity studies of the Karstedt's complex with tpy and $PhSiH_3$.

species could not be detected by ESI-MS, due to strong ion-suppression effects.[12] The effect of each component ([Pt], tpy, **1a**, DMC, $PhSiH_3$) on the chemical speciation was investigated separately and is summarized in Scheme 2 (see also the Supporting Information, Figures S2–S5). The reaction of Karstedt's complex and tpy afforded the $[Pt(tpy)(CH_2{=}CHSiMe_2)_2O)]$ complex [$(CH_2{=}CHSiMe_2)_2O$ = 1,3-divinyl-1,1,3,3-tetramethyl disiloxane].

Upon reaction of Karstedt's complex with tpy and $PhSiH_3$, besides the Pt^{II} hydride $[Pt(tpy)H]^+$ cation (m/z 429.1), the hy-

dridoplatinum silyl complex [Pt(tpy)H($PhSiH_2$)] is also detected as the proton adduct (*m/z* 537.1), which supports oxidative addition of the silane to the Pt^0 complex. In this respect, it is interesting to note that hydridometal silyl complexes and iminium **6a** cations are key intermediates in the Ir–[13] or Pt–silane[14] mediated reduction of tertiary amides to amines (a transformation formally corresponding to the **5a** to **3a** step). Based on the detection of intermediates **1a**–**6a**, we propose an initial addition of **1a** to DMC to form the carbamate intermediate **4a**. Subsequent Pt-catalyzed reduction of **4a** by formamide **5a** and iminium cation **6a** should afford amine **3a**.

Meanwhile, a control experiment of the model reaction using MeOH as the carbon source was carried out. Even at 100 °C, no methylated product was formed in the presence of phenylsilane [Eq. (2)].



After investigating the model reaction, the substrate scope and limitation of various amines were tested (Table 2). In general, arylalkylamines showed higher methylation reactivity compared to diaryl, dialiphatic or primary amines (see also the Supporting Information, Table S6). When using aromatic secondary amines as substrates, in most cases the methylation reaction worked at room temperature affording the corresponding *N*-methylated anilines in up to 94% yield (Table 2, entries 1–9). However, an increased temperature and higher amount of DMC (**2a**) were needed for primary amines, as well as benzylic and aliphatic amines (58–95% yield; Table 2, entries 10–15).

Notably, the presence of electron-donating or electron-withdrawing groups in the *para* position of the aromatic ring in *N*-methylanilines did not have a significant influence on the reactivity. Nevertheless, *ortho* substituents on the aryl ring had a major steric and electronic influence, lowering the general reactivity under otherwise the same reaction conditions (Table 2, entries 5–7).

Of course, many bioactive amines contain other sensitive functional groups, such as hydroxy or alkenyl groups. Selective *N*-methylation of them might provide a useful route for efficient amine modification in organic synthesis. For example, the hydroxy group is well tolerated, even after 16 h of reaction time, and **3q** was obtained in 83% yield [Eq. (3)], whereas the reduction of the unsaturated amine resulted in **3r** in 41% yield.

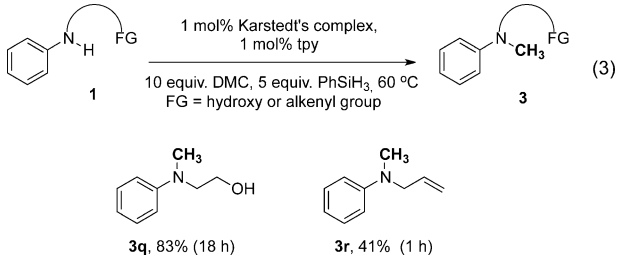
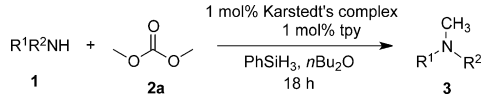
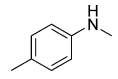
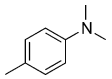
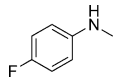
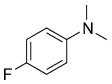
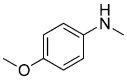
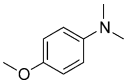
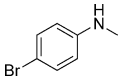
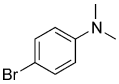
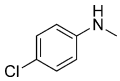
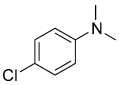
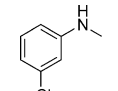
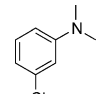
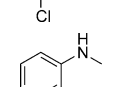
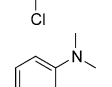
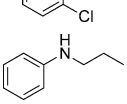
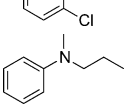
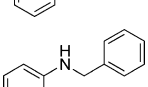
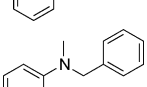
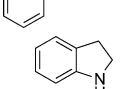
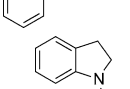
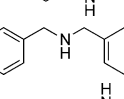
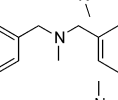
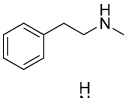
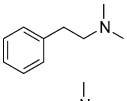
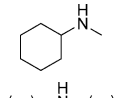
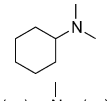
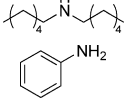
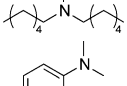
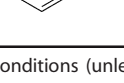
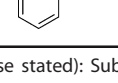


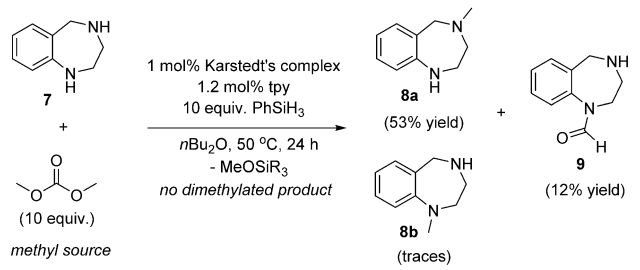
Table 2. Pt-catalyzed methylation of amines from DMC.[a]



Entry	Substrate		Product		T [°C]	Conv. [%][b]	Yield [%][b]
1	**1b**		**3b**		RT	93	87
2	**1c**		**3c**		RT	94	93
3	**1d**		**3d**		RT	81	(70)
4	**1e**		**3e**		RT	88	82
5	**1f**		**3f**		RT	92	90
6	**1g**		**3g**		RT	81	81
7	**1h**		**3h**		RT	57	56
8	**1i**		**3i**		RT	96	94
9	**1j**		**3j**		RT	88[c]	(81)
10[d]	**1k**		**3k**		100	89	(76)
11[d]	**1l**		**3l**		60	95	95
12[d]	**1m**		**3m**		100	59	58
13[d]	**1n**		**3n**		100	92	92
14[d]	**1o**		**3o**		100	89	87
15[e]	**1p**		**3a**		100	86	58

[a] Reaction conditions (unless otherwise stated): Substrate (0.5 mmol), **2a** (4 equiv), $PhSiH_3$ (5 equiv), nBu_2O (1 mL); [b] determined by GC using *n*-hexadecane as an internal standard; yields in parentheses refer to isolated products; [c] determined on isolation of the starting material after reaction; [d] **2a** (10 equiv), $PhSiH_3$ (5 equiv); [e] **2a** (20 equiv), $PhSiH_3$ (10 equiv).

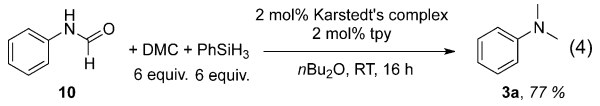
Selective monomethylation of di- and polyamines is challenging and often needs careful control of the reaction conditions. As shown in Scheme 3, the desired monomethylated product **8a** was obtained from the heterocyclic diamine **7** (53%) after purification by simple column chromatography.



Scheme 3. Highly selective monomethylation of **7**.

Notably, the main byproduct was the formamide derivative **9** and almost no formation of other methylated products was observed. It should be noted here that higher methylation reactivity was obtained for the dialkylamine site, which was further established by competitive experiments between **1a** and **1n**. With respect to the results in Table 2, the presence of dialkylamines accelerates the reduction of carbonates to form silyl methoxides, most likely through interaction with carbonates and/or the Pt center. Hence, in these cases, considering competitive reductions of the carbon source, higher amounts of carbonates and higher temperatures were needed to achieve reasonable *N*-methylation yields.

Finally, a domino reduction/methylation sequence of formamides was investigated. Due to the formation of formamides as the reaction intermediate, such direct modification should be possible. Indeed, the reaction of amide **10** at room temperature for 16 h gave the desired product **3a** in 77% yield [Eq. (4)].



In summary, a selective methylation of amines applying convenient and inexpensive carbonates has been achieved at room temperature. Key to success is the in situ combination of commercially available Karstedt's complex and tpy to form the catalyst. For most substrates, reactions proceed efficiently under mild conditions, using phenylsilane as reductant and dimethyl carbonate as the C1 source. Moreover, other carbonates, including propylene carbonate and sodium bicarbonate, could be used as the source of methyl group. Mechanistic studies based on ESI-MS experiments revealed that the reaction proceeded by nucleophilic substitution of the carbonate with the amine to form the corresponding carbamate followed by Pt-catalyzed reduction. Notable features of this method are the mild reaction conditions and convenient operation mode.

Experimental Section

General procedure for methylation reaction: In a dry 25 mL Schlenk tube containing a stirring bar, tpy (1.2 mg, 5 μmol) was dissolved with nBu$_2$O (1 mL) under Ar atmosphere and Karstedt's complex (57 μL, 5 μmol) was added without any apparent color change. After the mixture was stirred for 10 min, dimethylcarbonate (169 μL, 2.0 mmol) and $PhSiH_3$ (309 μL, 2.5 mmol) were added, leading to the formation of a red precipitate, which progressively disappeared with the fast addition of the amine substrate (0.5 mmol) and *n*-hexadecane (50 μL) as internal standard. Next, the reaction mixture was stirred at room temperature (or up to 100 °C) for a given time period, diluted with ethyl acetate (15 mL), and carefully quenched by aqueous NaOH solution (5 mL, 3 M) with vigorous stirring for 3 h at room temperature. Then, a sample was taken to be injected into the GC to determine the yield. All catalytic reactions were performed at least twice to ensure reproducibility. To allow determination of the yields of the isolated methylated amines, no internal standard was added. The mixture was extracted with ethyl acetate (2×25 mL) and the combined organic layers were died over anhydrous $MgSO_4$. Then, the organic phase was filtered, concentrated and purified by column chromatography on silica gel (eluent: *n*-heptane/ethyl acetate mixtures) to give the corresponding methylated amines.

Acknowledgements

We thank the state of Mecklenburg-Vorpommern and the BMBF for financial support. Technical support from Bianca Wendt is also acknowledged.

Keywords: alkylation · carbonates · platinum · reduction · silanes

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[9] These results represent the first example for reduction of carbonates under mild conditions in the presence of hydrosilanes.

[10] The versatility of ESI-MS experiments for identification of reaction intermediates in catalysis is exemplified in the following: a) D. Schröder, *Acc. Chem. Res.* **2012**, *45*, 1521; b) L. P. E. Yunker, R. L. Stoddard, J. S. McIndoe, *J. Mass Spectrom.* **2014**, *49*, 1; c) K. Vikse, Z. Ahmadi, J. S. McIndoe, *Coord. Chem. Rev.* **2014**, *279*, 96 or the discovery of new catalytic reactions is well-documented; see for example D. W. Robbins, J. F. Hartwig, *Science* **2011**, *333*, 1423.

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Received: July 24, 2015
Published online on October 9, 2015