Homogeneous Catalysis

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A General Catalytic Methylation of Amines Using Carbon Dioxide**

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Dedicated to the Bayer company on the occasion of its 150th anniversary

Carbon dioxide is the most abundant carbon source responsible for the generation of all organic compounds in nature. Its use as an inexpensive and nontoxic C_1 feedstock is of increasing interest for the production of value-added chemicals.[1] Owing to its high stability, well designed activation of CO_2 and a thermodynamic driving force are required for efficient transformations. In this respect, in recent years important developments in the conversion of carbon dioxide into formates, methanol (methoxides), and methane have been reported.[2–5] For example, under hydrosilylation conditions CO_2 is reduced to silyl formates in the presence of catalytic amounts of organic bases, Ru complexes, or Cu complexes;[6–9] its reduction to silyl methoxides can be catalyzed by N-heterocyclic carbenes;[10] and, when catalyzed by $Zr^{IV}/B(C_6F_5)_3$, frustrated Lewis pairs/$B(C_6F_5)_3$, or Ir-pincer complexes, it can even be reduced to methane.[11–13] Notably, using hydrogen, the reduction of CO_2 to formic acid derivatives can be catalyzed by Rh, Ir, Ru, and Fe complexes.[14–18] More recently, its reduction to methanol has been achieved using Ru^{II}-pincer complexes and multi-catalyst cascade catalysis.[19]

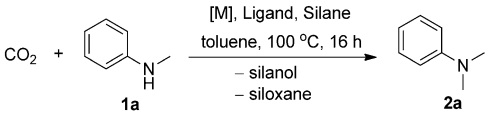
Though there exists numerous reactions between amines and CO_2, to the best of our knowledge there is only one example known that describes the synthetically interesting methylation of amines by CO_2. More specifically, Vaska and co-workers reported the formation of methylamine as a minor product using Ru or Os complexes.[20] However, it was later suspected that an alkyl group exchange was (partially) responsible for the methylamine product.[21] Hence, it remains that no general catalytic methylation reactions using carbon dioxide is known to date. Instead, activated methyl compounds, such as methyl iodide, dimethyl sulfate, MeOTf, diazomethane, and reductive amination systems (HCHO/reductant), are often used for this purpose.[22] However, the toxicity of most of these reagents and/or the limited substrate scope attract organic chemists to extend this research area. In this regard, it is interesting to note that the use of dimethyl carbonate or methanol as eco-friendly alternatives has been more recently reported as well.[23]

Herein, we describe for the first time a single Ru complex that is able to convert carbon dioxide and amines into various kinds of *N*-methylated products. Our initial design was motivated by previous reports on the dehydration of primary amides using silanes and the hydrosilylation of carboxylic acid derivatives by us and other groups.[24–30] Hence, we started to investigate the reaction of carbon dioxide and *N*-methylaniline (**1a**) in the presence of silanes as a model system (Table 1). To identify active catalysts around 15 different metal precursors including Ru, Rh, Cu and Fe complexes and 12 phosphine and nitrogen ligands were tested using phenyl silane as reductant (Figure S1 and Table S2).

As shown in Table 1, commercially available $[RuCl_2(dmso)_4]$ (dmso = dimethylsulfoxide) proved to be the best catalyst precursor, giving dimethylaniline in 70% yield (Table 1, entry 3); no reaction occurred without the catalyst. To our delight, using *n*BuPAd$_2$ (4 mol%; Ad = adamantyl) improved the yields up to 92% (Table 1, entry 5; see also the Supporting Information, Figure S1).[31] Using other types of metal complexes, hydrosilanes, or solvents led to much lower reactivity (2–63% yield; Table 1, entries 6–9). However, when using highly polar acetonitrile as the solvent, the best reactivity was obtained (98% yield; Table 1, entry 10).[32]

Methylation reactions of nitrogen compounds are of major importance in biology, for example, in epigenetics, embryonic development, and some cancer growth. Therefore, the methylation of different types of amines was studied in

Table 1: Ruthenium-catalyzed methylation of **1a** with carbon dioxide and phenylsilane.[a]



Entry	[M]	Ligand	Silane	Yield [%][b]
1	$Cu(OTf)_2$	–	$PhSiH_3$	–
2	$Fe(OAc)_2$	–	$PhSiH_3$	–
3	$[RuCl_2(dmso)_4]$	–	$PhSiH_3$	70
4	$[RuCl_2(dmso)_4]$	PPh_3	$PhSiH_3$	53
5	$[RuCl_2(dmso)_4]$	*n*BuPAd$_2$	$PhSiH_3$	92
6	$[Ru(acac)_3]$	*n*BuPAd$_2$	$PhSiH_3$	2
7	$[\{RuCl_2(C_6H_6)\}_2]$	*n*BuPAd$_2$	$PhSiH_3$	23
8	$[RuCl_2(dmso)_4]$	*n*BuPAd$_2$	$PhSiH_3$[c]	63
9	$[RuCl_2(dmso)_4]$	*n*BuPAd$_2$	$(EtO)_2MeSiH$	21
10[d]	$[RuCl_2(dmso)_4]$	*n*BuPAd$_2$	$PhSiH_3$	98

[a] Reaction conditions, unless otherwise noted: 1.0 mmol **1a**, catalyst (2 mol%), ligand (4 mol%), silane (4 equiv), toluene (10 mL), CO_2 (30 bar), 100°C, 16 h. [b] Determined by GC using *n*-hexadecane as an internal standard. [c] Silane (2 equiv) was used. [d] MeCN as solvent. Ac = acetyl, acac = acetylacetonate, Ad = adamantyl, Tf = trifluoromethanesulfonyl.

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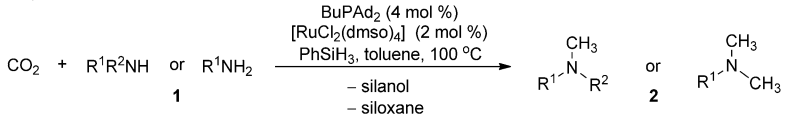
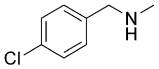
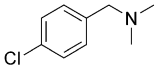
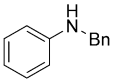
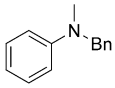
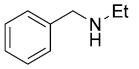
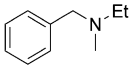
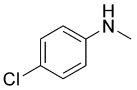
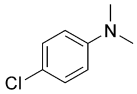
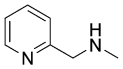
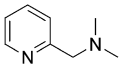
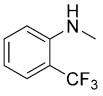
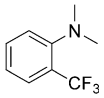
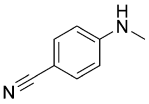
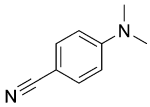
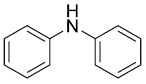
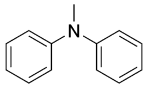
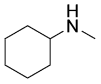
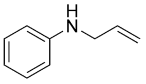
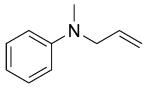
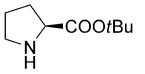
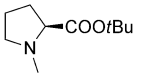
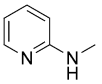
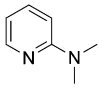
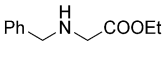
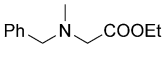
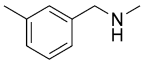
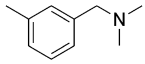
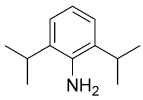
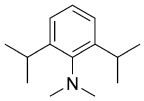
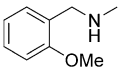
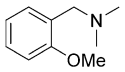
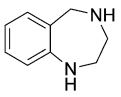
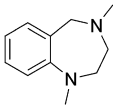
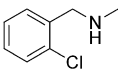
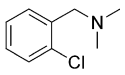
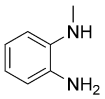
Table 2: A general catalytic methylation of amines from CO_2.[a]



Entry	1	2	Yield [%][b]	Entry	1	2	Yield [%][b]
1			86	12			81
2			81	13[c]			85
3			75	14[c]			82
4[c]			97	15[c]	Bn_2NH	Bn_2NMe	98
5[c]			76	16[c]	$nHex_2NH$	$nHex_2NMe$	99
6[c]			73	17[c]			94
7[c]			71	18			75
8[c]			61	19			72
9			72	20[c]			84
10[c]			70	21			83
11			82	22			63

[a] Reaction conditions: substrate (0.5 mmol), silane (4 equiv to amine moiety), toluene (2–10 mL), 10–36 h. [b] Yield of isolated product. [c] Determined by GC using *n*-hexadecane as an internal standard. Bn = benzyl.

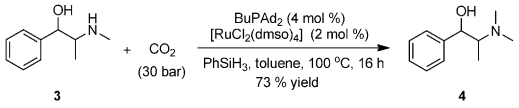
more detail (Table 2). When aromatic secondary amines were used as substrates, the desired products were obtained in 71–97% yield (Table 2, entries 1–7). A slight drop in reactivity to 61% yield is seen for the methylation of the heterocyclic 2-*N*-methylaminopyridine (Table 2, entry 8). In general, dialkylamines showed higher reactivity than aniline derivatives (Table 2, entry 16 vs. entry 6).

For most of the cases, full and clean conversion was observed, with yields of 70–99% in 10 h (Table 2, entries 9–17). From a biochemical point of view, it is interesting to note that the methylation process also proceeds well with amino acid esters, thus demonstrating the potential chemoselectivity of this method. Indeed, under our reducing conditions good tolerance to other types of reducible groups such as nitriles, olefins, and esters was obtained, which is not achievable with other known reductions for carbon dioxide.

Next, we were interested in the reactions of more challenging primary amines. Gratifyingly, these compounds also proved to be good substrates with somewhat longer reaction times. Even sterically hindered 2,6-di-isopropyl aniline was fully converted after 24 h and the dimethylated product was obtained in 84% yield (Table 2, entry 20). Moreover, reactions of diamine substrates gave the corresponding di- and trimethylated diamines in good to excellent yields. Although more than three kinds of byproducts were found in both cases, 83% and 63% yields of the desired products were obtained, respectively, after increasing the

reaction time to 36 h (formamide byproducts were obtained in up to 10% yield; Table 2, entries 21–22).

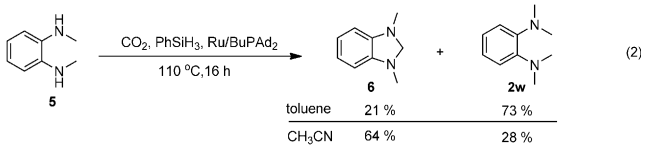
After the successful methylation of the different types of amines, we were interested in exploring the selective methylation of amino alcohols, a structural motif that occurs widely in natural amines and manmade bioactive compounds. As an example, ephedrine (**3**) was used as a substrate and provided the desired *N*-methylephedrine (**4**) in 73% yield with a chemoselectivity of >7:1 [Eq. (1)], although full conversion



(1)

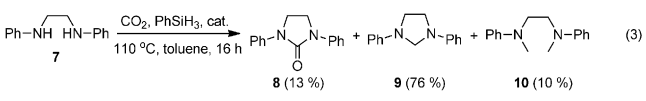
was not obtained, owing to the production of trace amounts of *N*-formylephedrine. Thus, the selective methylation of amino alcohols without protection/deprotection steps is indeed possible with this method.

With respect to the mechanism, CO_2 may be first reduced to formamide, which is then reduced to the methylamine product in a route similar to known reductive amination methods using HCHO.[31] However, under dehydrating conditions, ureas should be formed as the major products from CO_2 and amines.[33] To understand the sequential transformation in more detail, control experiments were carried out by using specific 1,2-diamines as starting material to capture key intermediates.[33] After testing different 1,2-diaminobenzenes and 1,2-ethylendiamines, we were able to isolate some interesting intermediates, such as the corresponding methylene diamines from the reduction of ureas. Under the standard conditions using *N*,*N*′-dimethyl-1,2-phenylenediamine (**5**) as substrate, the dimethylated compound **2w** was obtained as the main product, accompanied by the methylene diamine (**6**) in 21% yield [Eq. (2)]. Interestingly,



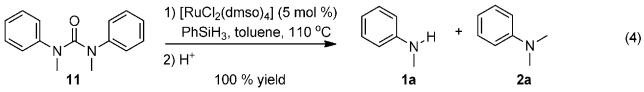
(2)

when changing the solvent from toluene to acetonitrile, the chemoselectivity is inverted to give **6** as the major product, which should be formed through deoxygenative reduction of the corresponding urea. Otherwise, strong base and higher temperature are required for the synthesis of this product from **5** or reaction intermediates and byproducts.[34] Under catalytic conditions, the more bulky aromatic diamine **7** gave three major products: 13% of *N*,*N*′-diphenylethyleneurea (**8**), 76% of 1,3-diphenylimidazolidine (**9**), and 10% of the dimethylated product **10** [Eq. (3)]. In this reaction sequence



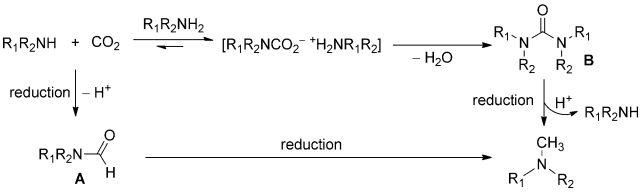
(3)

urea **8** is formed first, followed by reduction to **9**. Finally, slow ring opening forms the monomethylated intermediate, which immediately undergoes further methylation to yield the dimethylated product **10**. To further support this assumption, we performed the reduction of **8** independently with phenylsilane (2 equiv). Indeed, using $[RuCl_2(dmso)_4]$ (5 mol%) at 110 °C in toluene gave **9** and **10** in 71% and 28% yield, respectively, in the presence of CO_2 (30 bar). As shown in Equation (4), other ureas such as *N*,*N*′-diphenyl-*N*,*N*′-dimethylurea (**11**) can also be quantitatively reduced to give dimethylaniline (**2a**) and *N*-methylaniline (**1a**).[31]



(4)

With this data in hand, we propose the following two reaction pathways for direct methylation with carbon dioxide (as shown in Scheme 1): 1) Formation of formamide occurs



Scheme 1. Proposed pathways for the methylation of amines with carbon dioxide.

through direct reduction of CO_2 to generate **A**, followed by deoxygenative reduction to produce the corresponding methylamine product. 2) Dehydration of ammonium carbamate under hydrosilylative conditions to generate urea **B**, followed by reduction to the desired product and one molecule of starting material in the presence of a proton.[35]

In conclusion, we have demonstrated for the first time that the general methylation of organic substrates using silanes and CO_2 as a simple carbon source is possible. Applying a readily available ruthenium complex and a commercially available ligand, various kinds of aromatic and aliphatic, secondary and primary amines were successfully transformed into the desired tertiary amines and diamines with good to excellent yields. Notably, various functional groups are tolerated under these conditions, which is not known for other methods of carbon dioxide reduction. Furthermore, the selective reduction of ureas is possible under similar reaction conditions. An important goal for the future is the development of similar reactions using more benign H_2 as the reductant.[36]

Experimental Section

General procedure for the methylation reaction in a parallel pressure reactor: $RuCl_2(dmso)_4$ (4.9 mg, 10 μmol) and *n*$BuPAd_2$ (7.2 mg, 20 μmol) were added to an autoclave containing a stirring bar. Under Ar flow, dry toluene (1.5 mL), $PhSiH_3$ (250 μL, 2.0 mmol), and amine substrate (0.5 mmol) were added. After pressurizing with CO_2 to 30 bar, the mixture was stirred at 100 °C for a certain time period.

The yield can be determined by GC using *n*-hexadecane as an internal standard. To isolate the products, the reaction mixture was cooled to 15 °C and transferred to a 50 mL round bottom flask followed by the slow addition of NaOH (2 N aq.; 3 mL). After the mixture was vigorously stirred for 3 h at room temperature, the mixture was extracted by ethyl ether. After removal of the organic solvent followed by washing with a mixture of ethyl ether/pentane (1:10), the organic phase was concentrated and purified by silica gel column chromatography to give the corresponding methylated amines.

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