VIP Homogeneous Catalysis Very Important Paper

DOI: 10.1002/anie.201306850

Selective Methylation of Amines with Carbon Dioxide and H_2**

*Yuehui Li, Iván Sorribes, Tao Yan, Kathrin Junge, and Matthias Beller**

Carbon dioxide is the most abundant carbon source responsible for the construction of all organic compounds in nature. Because of the rising anthropogenic emission of CO_2, its use as a cheap and renewable C_1 feedstock is of increasing interest for the production of value-added bulk chemicals such as methanol, polycarbonates, as well as fine chemicals.[1–3] In recent years, important developments to convert the thermodynamically stable CO_2 molecule into formates, methanol, and methane have been reported using different reductants.[4–15] In addition to these methods, very recently interesting methylations using CO_2 were reported by Cantat et al.[16] and us.[17] Unfortunately, in both cases hydrosilanes had to be used as the reductant for the production of methylated amine products in the presence of either a Zn/NHC or Ru/BuPAd$_2$ catalyst.

Since methyl-substituted amines exist frequently as bioactive compounds and have been widely utilized as key intermediates and important chemicals, the development of more efficient methylation methods continuously attracted the attention of chemists in the last decades.[18] Still, the most common methylation of amines in industry makes use of toxic formaldehyde, whereas in organic synthesis less benign methylation reagents, for example, methyl iodide, and dimethyl sulfate, prevail.[19,20] Thus, the application of more sustainable reagents with good selectivity (e.g. functional-group tolerance and monomethylation) is highly desired. Obviously, catalytic methylations using CO_2 and H_2 represent an elegant and viable method with H_2O as the only byproduct (Figure 1).[21] Herein we describe a general and selective ruthenium-catalyzed methylation of both aromatic and aliphatic amines using carbon dioxide/hydrogen to N-methylated products.

The present work was motivated by the efficiency of ruthenium-catalyzed hydrogenation of CO_2 and carboxylic acid derivatives as well as N-alkylation from alcohols previously reported by us and other groups.[14,22–28] Initially, we investigated the reaction of carbon dioxide, H_2, and aniline (**1a**) in the presence of in situ formed ruthenium complexes as a model system (Table 1 and Tables S1–S4 in the Supporting Information). The most active catalyst was formed from ruthenium acetylacetonate [Ru(acac)$_3$] and 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos; **4f**), and afforded full

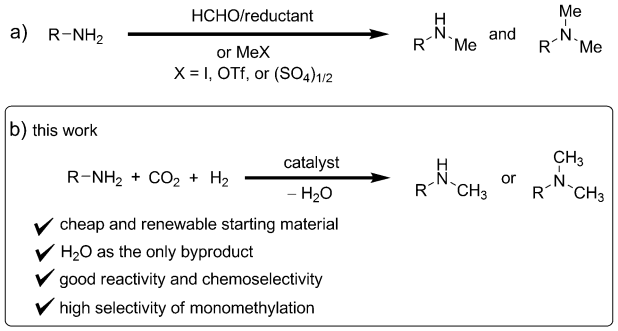


Figure 1. A) Known methods for N-methylation. B) N-methylation using CO_2 and H_2. Tf = trifluoromethanesulfonyl.

conversion with 96% yield of *N*,*N*-dimethylaniline (**3a**) and 4% of *N*-methylaniline (**2a**) in the presence of a catalytic amount of a Brønsted acid (Table 1, entry 8).[29] This combination was found to be critical (Table 1, entries 1–7, 9–14). Interestingly, the pressure of CO_2 could be lowered to only 2 atm, thus generating 88% of **2a** and 4% of **3a**, and indicating methylation of **1a** is favored over methylation of **2a** (Table 1, entry 15). Notably, this reaction system is robust and not sensitive to air. Hence, it is not necessary to work under inert conditions before introducing carbon dioxide.

To understand the mechanism of this methylation reaction, control experiments were studied to identify the key intermediates. Since it is known that CO_2 can be hydrogenated to formic acid and methanol in the presence of ruthenium complexes, the reduction of the formamide **5a** and methylation from methanol were investigated. As shown in Scheme 1a, **5a** was fully converted and **2a** was the major product in 64% yield.[30a] Meanwhile, it was found that methanol can also act as the source of the methyl group. Interestingly, this reaction occurred in low yield in the presence of H_2 (Scheme 1b). To further understand the methylation process, a reaction profile of **1a** was performed (see Figure S1 in the Supporting Information). Under the standard reaction conditions, no obvious incubation period was observed. During the reaction, **5a** is not detected as an intermediate. However, significant amounts of methanol were generated (up to 9.5 mmol MeOH produced). In contrast, at a lower pressure of H_2 (30 atm), **5a** is detected in low yield (< 5%). Under the same reaction conditions, using benzyl amine as the substrate, only traces of the corresponding methylated product can be obtained with a significant amount of formamide byproduct. These results are consistent with the work of Cole-Hamilton and Leitner et al. for the reduction of N-aliphatic amides compared to that of N-aromatic amides.[26]

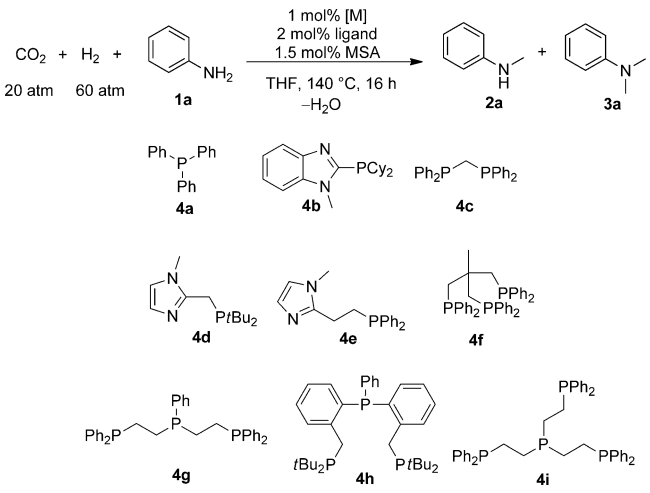
To understand the influence of electronic effects, the competition reaction of *para*-substituted aniline derivatives

[*] Dr. Y. Li, Dr. I. Sorribes, T. Yan, Dr. K. Junge, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V.
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
E-mail: matthias.beller@catalysis.de
Homepage: http://www.catalysis.de

[**] This work was supported by the state of Mecklenburg-Vorpommern and the BMBF. We thank Prof. Kuiling Ding for fruitful discussions.

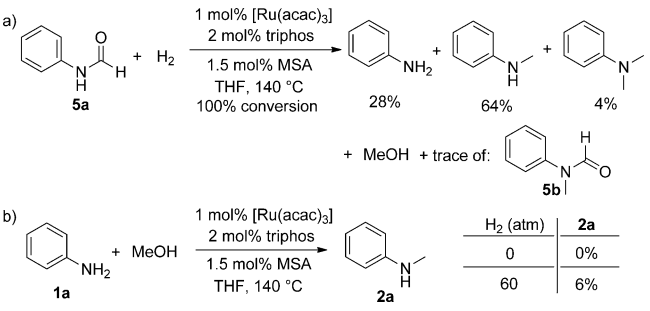
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306850.

Table 1: Ruthenium-catalyzed methylation of **1a** with carbon dioxide and H_2.[a]



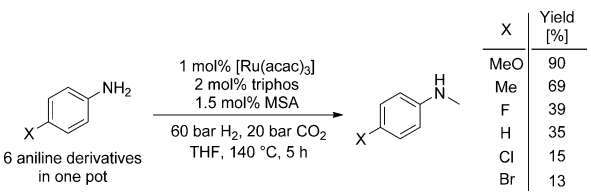
Entry	[M]	Ligand	Yield [%][b]	
			2a	**3a**
1	$[Ru(acac)_3]$	–	0	0
2	$[Ru(acac)_3]$	**4a**	<1	0
3	$[Ru(acac)_3]$	**4a**	4	<1
4	$[Ru(acac)_3]$	**4b**	4	0
5	$[Ru(acac)_3]$	**4c**	0	0
6	$[Ru(acac)_3]$	**4d**	<1	0
7	$[Ru(acac)_3]$	**4e**	2	0
8	$[Ru(acac)_3]$	**4f**	4	96
9	$[Ru(acac)_3]$	**4g**	0	0
10	$[Ru(acac)_3]$	**4h**	0	0
11	$[Ru(acac)_3]$	**4i**	0	0
12	$[\{Ru_2Cl_3(triphos)_2\}Cl]$	–	10	16
13	$[Ru(triphos)(CO)H_2]$	–	55	<1
14	[Ru-MACHO-BH]	–	8	1
15[c]	$[Ru(acac)_3]$	**4f**	88	4

[a] Reaction conditions: 0.5 mmol **1a**, 1 mol% catalyst, 2 mol% ligand, 1.5 mol% methanesulfonic acid (MSA), 20 atm CO_2, 60 atm H_2, 2 mL solvent, 140 °C, 16 h. [b] Determined by GC using *n*-hexadecane as an internal standard. [c] 2 atm CO_2 and 60 atm H_2 were used. THF = tetrahydrofuran.



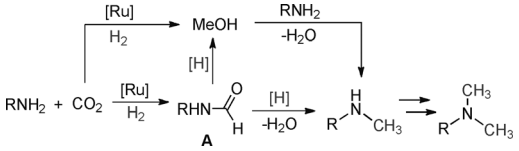
Scheme 1. Control experiments.

was investigated. As shown (Scheme 2; see the Supporting Information), the reactivity correlates well with the electron density on the N-aromatic ring. Such a correlation was not observed in the ruthenium/triphos-catalyzed amide reduction.[26]



Scheme 2. Competition reactions for methylation of different anilines.

Based on these results, we propose that the consecutive methylation reaction proceeds under our reaction conditions with both formamide (major) and methanol (minor) as intermediates (Scheme 3). The formamide intermediate **A** is favorably formed, and then rapidly reduced to the corresponding methylated product. Compared to this pathway, methylation from methanol contributes to an insignificant extent.[30]

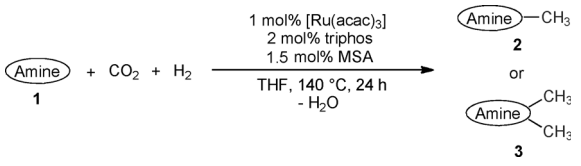


Scheme 3. Proposed reaction pathway for methylation of amines using carbon dioxide.

With good reactivity for anilines in hand, the methylation of different types of amines was studied in detail (Table 2). A variety of aromatic amines can be smoothly methylated and the corresponding dimethylated products were obtained with good to excellent yields (Table 2, entries 1–23). Notably, by tuning the reaction time and catalyst loading highly selective monomethylation was achieved over dimethylation with a ratio of >10:1 (Table 2, entries 7 versus 15). However, under similar reaction conditions the reactivity of aliphatic amines was strongly suppressed.[29b,31a,b] To our delight, this problem was successfully solved after careful study of the effect of the additive. Replacing MSA simply with LiCl is critical and dimethylated products were obtained with good to excellent yields for various aliphatic amines (Table 2, entries 24–30).[31c] Remarkably, good functional-group tolerance was observed for ester, ether, heterocyclic, and hydroxy groups.

Inspired by the results of the competition reactions, we explored the selective monomethylation of diamines, a reaction which represents a challenging task for traditional methylation methods because of the high chemical similarity of the two amine moieties. As an example, the reaction of **6a** can generate more than 20 kinds of products. Gratefully, moderate to good yields were obtained with good selectivity for monomethylation, which was the combined result of both electronic and steric effects (Scheme 4; for details see the Supporting Information).[32] The structure of the products was determined by ^{1}H NOESY based on the interaction of N-CH_3 and CH on the phenyl ring. The best result was obtained for **6c**, since the desired reaction site is more nucleophilic and less sterically hindered. These examples demonstrate that our

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



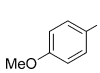
Entry	Substrate		Product		Yield [%][b]
1[c,d]		**1a**		**3a**	98
2[c,d]		**1b**		**3b**	87
3[c,d]		**1c**		**3c**	96
4[c]		**1d**		**3d**	99
5[c]		**1e**		**3e**	89
6[c]		**1f**		**3f**	95
7[c]		**1g**		**3g**	99
8[c,d]		**1h**		**3h**	69
9[c,d]		**1i**		**3i**	82
10[d]		**1j**		**3j**	96
11[c,d]		**1k**		**3k**	89
12[c,d]		**1l**		**3l**	96
13[c]		**1m**		**2m**	70
14		**1n**		**2n**	71
15[c,e]		**1g**		**2g**	78
16[c]		**1o**		**2o**	85
17[c]		**2a**		**3a**	80
18		**1p**		**2p**	92
19[c]		**1q**		**2q**	99

Table 2: (Continued)

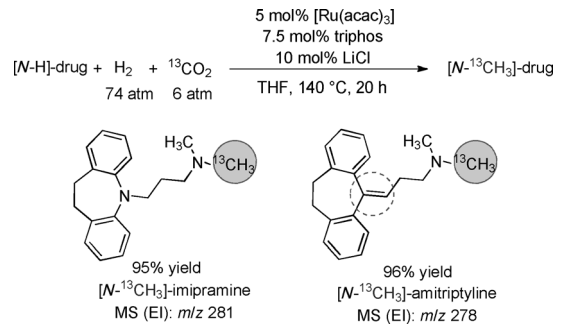
Entry	Substrate		Product		Yield [%][b]
20		**1r**		**2r**	89
21		**1s**		**2s**	93
22		**1t**		**2t**	72
23[d]		**1u**		**2u**	67
24[c,f]		**1v**		**3v**	75
25[c,f]		**1w**		**3w**	77
26[c,f]		**1x**		**3x**	87
27[c,f]		**1y**		**3y**	82
28[c,f]		**1z**		**3z**	60
29[c,f]		**1aa**		**2aa**	83
30[c,f]		**1ab**		**2ab**	81

[a] Reaction conditions: 0.5 mmol substrate, 20 atm CO_2, 60 atm H_2, 2 mL THF, 24 h. [b] Yield of isolated product. [c] Determined by GC using *n*-hexadecane as an internal standard. [d] Reaction time was 36 h. [e] Reaction time was 5 h. [f] 5 mol% of $[Ru(acac)_3]$, 7.5 mol% triphos, and 7.5 mol% LiCl were used.

Scheme 4. Selective N-monomethylation of diamines.

methodology allows selective (mono)methylation of diamines and even multiamines.

Isotopically labelled compounds such as drug molecules are frequently used for medical reasons.[33] To show the application potential, our method was finally tested for the synthesis of ^{13}C-labelled amines. Using the protocol described before, starting from desipramine and nortriptyline two important ^{13}C-labelled drugs, imipramine and amitriptyline, respectively, were synthesized with excellent yields (Scheme 5). Notably, in the latter case the C=C bond was



Scheme 5. Direct synthesis of [*N*-$^{13}CH_3$]drugs from $^{13}CO_2$.

completely retained. It should be noted that $^{13}CO_2$ can be much easier handled and is much cheaper than other activated methylation reagents (e.g. $^{13}CH_3I$).[34] Meanwhile, this direct methylation method is apparently more effective compared to the two-step condensation/reduction method (e.g. $H^{13}CHO/NaBH_4$).[33] Considering the high efficiency and the selectivity demonstrated above, this novel catalytic method holds promise for ^{13}C-labelling of important intermediates.

In summary, we have demonstrated the efficient methylation of both aromatic and aliphatic, both primary and secondary amines using CO_2 with H_2 as the methylation reagent. Applying an in situ combination of a ruthenium(III) precursor, triphos, and either acid additives or LiCl, the desired methylated amines were obtained with good to excellent yields. Notably, under these conditions, various functional groups are tolerated. Furthermore, selective monomethylation of diamines and convenient synthesis of ^{13}C-labelled drugs show the promising application potential of this novel method.

Experimental Section

General procedure for methylation reaction in a 300 mL autoclave: inside the autoclave, the 4 mL glass vial containing a stirring bar was charged with $[Ru(acac)_3]$ (2.0 mg, 5 μmol), **4 f** (6.2 mg, 10 μmol), and MSA (0.51 μL, 7.5 μmol). Dry THF (2.0 mL) and the amine substrate (0.5 mmol) were added to the vial, sealed by a septum, with a syringe needle. The autoclave was sealed, purged (30 atm CO_2, twice), and pressurized with CO_2 (20 atm) and H_2 (60 atm). Then the autoclave was seated in an aluminum block on a stirring machine and heated to 140 °C for a certain time period. After that the reaction mixture was cooled in cold water and the gas was carefully released. The reaction mixture was analyzed by GC-MS and GC with *n*-hexadecane as an internal standard, or purified through silica gel columns to give the corresponding methylated amines.

Received: August 5, 2013
Published online: September 25, 2013

Keywords: homogeneous catalysis · hydrogen · methylation · reduction · ruthenium

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[29] a) A reaction temperature of 140 °C was found to be crucial for obtaining good reactivity, even though moderate yields were obtained at 120 °C with a higher catalyst loading. b) For details, see the Supporting Information.
[30] a) Under otherwise the similar reaction conditions, but without H_2 and CO_2, **1a** reacted well with formic acid and **5a** was obtained in 81% yield. b) These results only showed the involvement of formamide and MeOH as the intermediates detected. In fact, there may exist other intermediates such as carbamate salts or formaldehyde (further formation of imines with amines) which could not be detected. c) For the reactions of both **1a** and benzyl amine using $^{13}CO_2$ with and without addition of MeOH, no obvious difference on the ratio of $^{13}C/^{12}C$ was observed in the methylated products by MS(EI) and HRMS-(ESI).
[31] a) Under the same reaction conditions, only 2% of *N*-methyl benzylamine was obtained. b) The control experiments for benzylamine in the presence of LiCl was also done and similar results were obtained as **1a** in Scheme 1. c) The mechanism study on details of the activation effect of Lewis acid such as LiCl is undergoing.
[32] From GC-MS, more than 20 byproducts from di- and trimethylation mixed with formylation were detected. Full conversion was obtained for all the cases (**6a–c**) and the main byproducts are the dimethylated and trimethylated ones (verified by GC-MS and/or NMR spectroscopy after isolation).
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