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 valuable bulk chemicals such as methanol, polyesters, as well as fine chemicals.[1–3] In recent years, important developments to convert the thermodynamically stable CO$_2$ molecule into formates, (Figure 1).[21] Herein we describe a general and selective 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 methylation processes using CO$_2$ and H$_2$ represent an elegant and viable method with H$_2$O 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 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.[30] 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.[36]

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

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]

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 1H NOESY based on the interaction of N-CH3 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
methodology allows selective (mono)methylation of diamines and even multiamines.

Isotopically labelled compounds such as drug molecules are frequently used for medical reasons. 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

**Table 2:** A general catalytic methylation of amines from CO$_2$.$^{[4]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [%]$^{[5]}$</th>
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<tbody>
<tr>
<td>1$^{[c,d]}$</td>
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<td>$^{3}$a</td>
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<td>2$^{[c,d]}$</td>
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<td>$^{3}$b</td>
<td>87</td>
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<tr>
<td>3$^{[c,d]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$c</td>
<td>96</td>
</tr>
<tr>
<td>4$^{[i]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$d</td>
<td>99</td>
</tr>
<tr>
<td>5$^{[i]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$e</td>
<td>89</td>
</tr>
<tr>
<td>6$^{[i]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$f</td>
<td>95</td>
</tr>
<tr>
<td>7$^{[i]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$g</td>
<td>99</td>
</tr>
<tr>
<td>8$^{[c,d]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$h</td>
<td>69</td>
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<td>9$^{[c,d]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$i</td>
<td>82</td>
</tr>
<tr>
<td>10$^{[i]}$</td>
<td>$^{1}$NH$_2$</td>
<td>$^{3}$j</td>
<td>96</td>
</tr>
<tr>
<td>11$^{[c,d]}$</td>
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<td>12$^{[c,d]}$</td>
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<td>$^{3}$l</td>
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<td>$^{1}$NH$_2$</td>
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</tr>
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</table>

[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.
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$_3$I).[34] Meanwhile, this direct methylation method is apparently more effective compared to the two-step condensation/reduction method (e.g. $^{13}$CH$_2$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(cacac)$_3$] (2.0 mg, 5 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 aluminium 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.

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

[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 H₂ and CO₂, 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 1³CO₂ with and without addition of MeOH, no obvious difference on the ratio of ¹³C/¹²C 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).