Methylation Hot Paper

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# Metal-Free Catalyst for the Chemoselective Methylation of Amines Using Carbon Dioxide as a Carbon Source**

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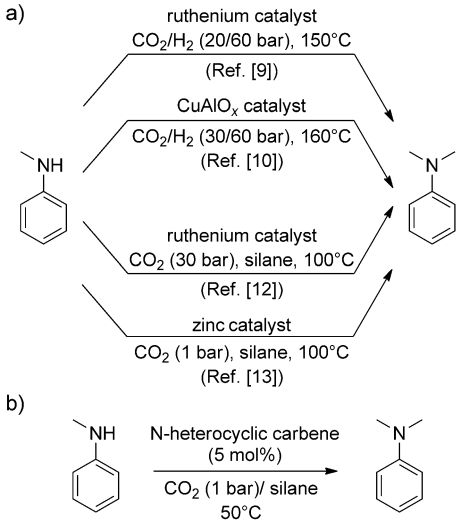
***Abstract:*** *N-methylation of amines is an important step in the synthesis of many pharmaceuticals and has been widely applied in the preparation of other key intermediates and chemicals. Therefore, the development of efficient methylation methods has attracted considerable attention. In this respect, carbon dioxide is an attractive $C_1$ building block because it is an abundant, renewable, and nontoxic carbon source. Consequently, we developed a highly chemoselective, metal-free catalytic system that operates under ambient conditions for the N-methylation of amines.*

Carbon dioxide is an abundant, safe, and renewable carbon source and therefore an attractive $C_1$ building block for the formation of organic molecules.[1–5] Indeed, much progress has been made in the catalytic activation of $CO_2$ by reactive substrates, such as epoxides, alcohols, amines, and alkynes, to form new C–O and C–C bonds and, in some cases, industrial processes have been developed.[6] In contrast, the formation of C–N bonds using $CO_2$ as a $C_1$ source to afford N-methylated compounds remains challenging, although several promising systems have been reported (Scheme 1). Nonetheless, the development of highly active catalysts for this transformation could have a significant impact on future chemical resources, with the sustainable replacement of toxic organic reagents in a number of chemical processes.

N-methylated compounds are important intermediates in the chemical industry,[7] the functionality being found in medicines, agrochemicals, dyes, and perfumes. Currently, formaldehyde is used in industrial N-methylations, whereas methyl iodide and dimethylsulphates are usually employed in methods on a small scale.[8] As $CO_2$ is cheap, abundant and, nontoxic, it represents an ideal alternative to these environmentally hazardous and toxic reagents.

In seminal papers, Beller et al. and Leitner et al. described ruthenium-based catalysts that mediated the N-methylation of amines using $CO_2$ and $H_2$ as sources for the methyl group.[9] Subsequently, Shi et al. reported a new heterogeneous catalyst for the synthesis of N-methylated compounds from amines, nitriles, and nitro compounds, also employing $CO_2$ and $H_2$ to generate the methyl group.[10]

Harsh reaction conditions and poor functional-group tolerance led to the application of other reducing agents, such as hydrosilanes,[11] which, when applied with homogeneous ruthenium- and zinc-based catalysts, afforded N-methylated compounds under comparatively mild reaction conditions.[12,13] Nevertheless, the development of new efficient and chemoselective catalysts for this type of reaction (employing $CO_2$ as a $C_1$ source) remains important.




***Scheme 1.*** Methods of N-methylation using $CO_2$ as a $C_1$ source. a) Currently known routes. b) New route using commercially available reagents, enabling gram-scale reactions, and characterized by unprecedented functional-group tolerance.

We decided to evaluate suitable organocatalysts for this type of transformation,[14] in part because of their low cost and low toxicity. Notably, N-heterocyclic carbenes (NHCs) have attracted much interest,[15] as they can behave as nucleophiles and may activate $CO_2$ to form imidazolium carboxylates.[16] The propensity of NHCs to form carboxylates could be exploited to give metal-free catalysts for the transformation of $CO_2$.

In the course of identifying and optimizing key reaction parameters for the reaction of *N*-methylaniline (**1a**) with $Ph_2SiH_2$ as a model system, several NHCs were investigated as potential catalysts (Table 1). In the presence of 5 mol% of NHC **B** and 3 equiv of diphenylsilane, the corresponding *N*,*N*-

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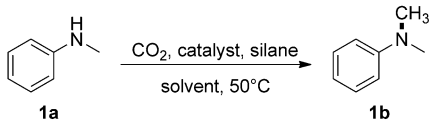
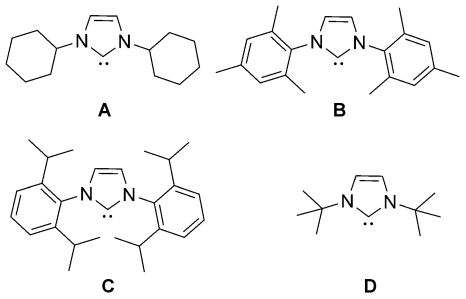
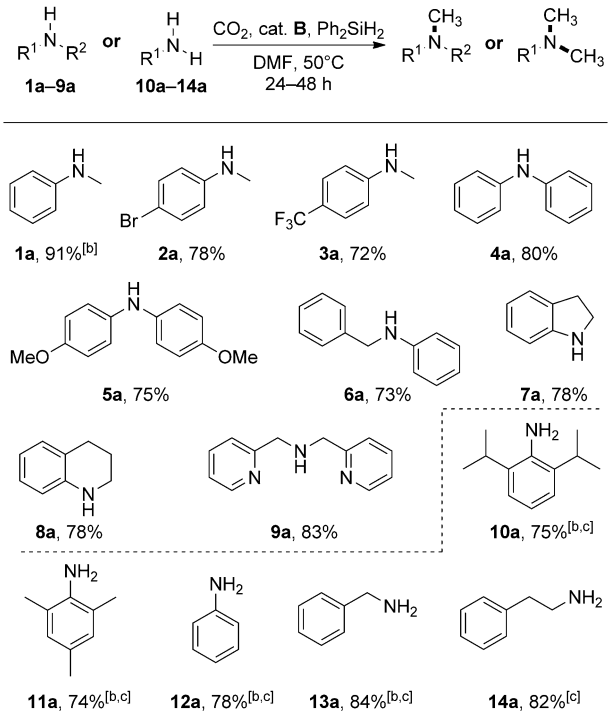
***Table 1:*** Optimization of the reaction conditions for *N*-methylaniline (**1a**) as a model substrate.[a]




| Entry | Catalyst | Silane | Solvent | Yield [%][b] |
|---|---|---|---|---|
| 1 | – | $Ph_2SiH_2$ | DMF | 19 |
| 2 | **A** | $Ph_2SiH_2$ | DMF | 25 |
| 3 | **B** | $Ph_2SiH_2$ | DMF | 91 |
| 4 | **C** | $Ph_2SiH_2$ | DMF | 79 |
| 5 | **D** | $Ph_2SiH_2$ | DMF | 78 |
| 6 | **B** | $PhSiH_3$ | DMF | 84 |
| 7 | **B** | $Me(OEt)_2SiH$ | DMF | 33 |
| 8 | **B** | PMHS | DMF | 48 |
| 9 | **B** | TMDSO | DMF | 32 |
| 10 | **B** | $Ph_2SiH_2$ | acetonitrile | 87 |
| 11 | **B** | $Ph_2SiH_2$ | toluene | 0 |
| 12 | **B** | $Ph_2SiH_2$ | 1,4-dioxane | 0 |
| 13 | **B** | $Ph_2SiH_2$ | THF | 7 |

[a] Reaction conditions: *N*-methylaniline (0.5 mmol), catalyst (5 mol%), silane (1.5 mmol), solvent (4 mL), $CO_2$ (1 atm), 50°C, 24 h. [b] Yield determined by GC using decane as an internal standard. PMHS = polymethylhydrosiloxane and TMDSO = tetramethyldisiloxane.




***Scheme 2.*** Catalytic N-methylation of amines **1a**–**14a** using $CO_2$ and $Ph_2SiH_2$ as the source of the methyl group. Reaction conditions: substrate (0.5 mmol), catalyst **B** (5 mol%), $Ph_2SiH_2$ (3 equiv), DMF (4 mL), $CO_2$ (1 atm), 50°C, 24–48 h. Please note: shown structures are those of substrates **1a**–**14a**, the yields are those of the corresponding N-methylated products. [b] Yields determined by GC using decane as an internal standard. [c] 4 equiv of silane were used.

dimethylaniline (**1b**) was obtained in 91% yield (Table 1, entry 3). Other NHCs also showed activity, but gave the product in lower yields.

We also investigated the influence of different silanes (Table 1, entries 6–9) and solvents (entries 10–13) on the reaction. Other silanes, such as TMDSO, PMHS, and $MeSi(OEt)_2H$, were less effective reducing agents under the optimized reaction conditions, although $PhSiH_3$ showed good activity in the formation of **1b**. Catalysis was suppressed in other solvents, such as toluene, THF, and 1,4-dioxane, whereas the use of acetonitrile led to only a slightly decreased yield compared to that observed in DMF. DMF is known to activate $CO_2$, which could be the case in this reaction.[17]

Based on the optimized reaction conditions, the scope of the NHC-catalyzed methylation reaction was explored using catalyst **B** (Scheme 2). Aromatic, heteroaromatic, and aliphatic amines reacted smoothly and the corresponding products were obtained with yields of up to 84%. Aromatic amines with both electron-donating and electron-withdrawing substituents at the *para* position reacted well, whereas amines with electron-withdrawing groups were sluggish. Steric hindrance on both sides of the amine (substrates **10a** and **11a**) has a minimal effect on the product yield. Different symmetric and nonsymmetric amines were also subjected to the optimized reaction conditions, and the reaction worked well with these substrates (substrates **4a**–**6a**). Moreover, a *para*-bromo-substituted amine (substrate **2a**) gave the corresponding product in 78% yield. It is noteworthy that reductive dehalogenation was not observed. The catalyst is also tolerant toward heteroaromatic amines such as picoline, indoline, and 1,2,3,4-tetrahydroquinoline (substrates **7a**–**9a**). Additionally, primary amines react in a similar fashion to secondary amines, forming dimethylated products (substrates **10a**–**14a**). Notably, the reaction may also be performed on a multigram scale without any special precautions.

As N-methylation has been shown to significantly increase the cytotoxicity of drug molecules, we next evaluated the use of NHC **B** in the N-methylation of complicated molecules (Figure 1).[18–20] For this purpose, nortryptyline, cinacalcet, duloxetine, and sertraline were selected, as they have different complex structures that include aromatic, aliphatic, heterocyclic, and alicyclic groups. It was possible to N-methylate these substrates and obtain pure products in good yields without special precautions regarding degradation.

The functional-group tolerance of the catalyst was studied using some particularly challenging substrates with different functional groups attached to different parts of the substrate. By positioning these functionalities either at the

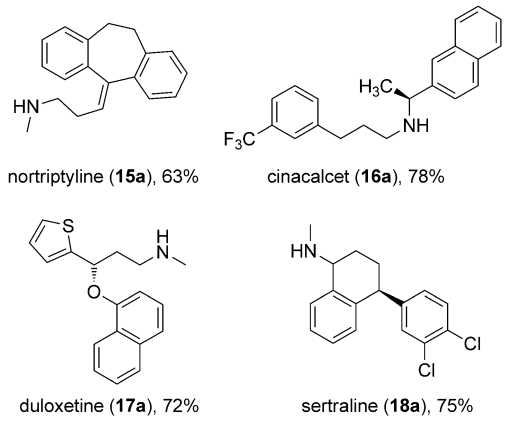
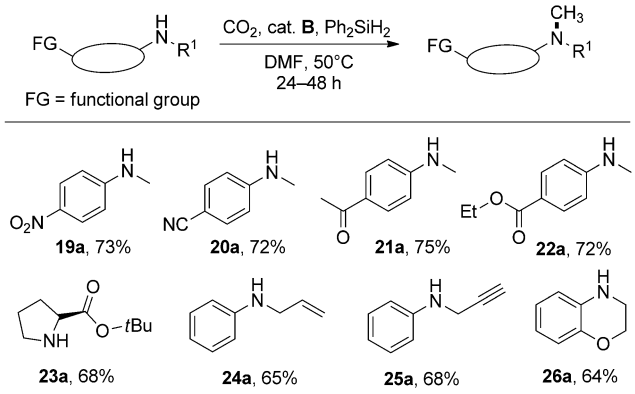
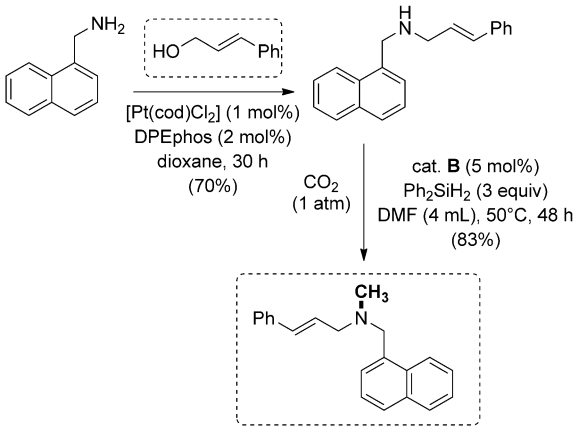



*Figure 1.* Pharmaceuticals **15a–18a**, which were subjected to the catalytic N-methylation using $CO_2$ and $Ph_2SiH_2$ as the source for the methyl group. Please note: shown structures are those of substrates **15a–18a**, the yields are those of the corresponding N-methylated products, obtained using the optimized reaction conditions (Table 1, entry 3).




*Scheme 3.* Functional-group tolerance of the N-methylation of amines **19a–26a** using $CO_2$ and $Ph_2SiH_2$ as the source of the methyl group. Reaction conditions: substrate (0.5 mmol), catalyst **B** (5 mol%), $Ph_2SiH_2$ (3 equiv), DMF (4 mL), $CO_2$ (1 atm), 50°C, 24–48 h. Please note: shown structures are those of substrates **19a–26a**, the yields are those of the corresponding N-methylated products.

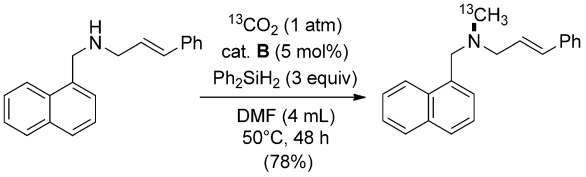
aryl or at the amine moieties, steric influences were minimized (Scheme 3). Remarkably, without further optimization, nitrile and nitro groups, double and triple bonds, and ether- and ester-substituted amines were well tolerated, providing the corresponding N-methylated amines in good to excellent yields. Moreover, the methylation was chemoselective, even in the presence of a ketone group, which is known to be much more reactive toward reduction.[21] The reduction of other functional groups was not observed in any of these reactions, thus demonstrating the excellent chemoselectivity of the catalyst. To the best of our knowledge, this chemoselectivity is unparalleled, that is, it cannot be achieved by other catalysts/routes, and was further verified by exploring reactions of 1:1 mixtures of acetophenone, benzonitrile, methyl benzoate, and nitrobenzene with *N*-methylaniline under the optimized conditions. Again, while the amines were N-methylated, the other substrates were not reduced.




*Scheme 4.* Demonstration of chemoselectivity in an N-methylation reaction.

To demonstrate this chemoselective potential, catalyst **B** was used to prepare naftifine (Scheme 4), an antifungal drug for the topical treatment of fungal infections.[21] Most of the previous routes to this drug include the use of stoichiometric reagents, although catalytic routes have been reported.[22,23] We prepared naftifine in two catalytic steps with an overall yield of 58%. First, (*E*)-*N*-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine was obtained in 70% yield from naphthalen-1-ylmethanamine and cinnamyl alcohol using 1 mol% $[Pt(cod)Cl_2]$.[23] Second, the application of our N-methylation protocol gave the product in 83% yield.

Isotopically labelled bioactive compounds are widely used to study interactions with lipid membranes, proteins, nucleic acids, etc.[24] Thus, catalyst **B** was used to prepare $^{13}C$-labelled naftifine in 78% yield (Scheme 5) using $^{13}CO_2$. The catalyst showed excellent selectivity as the double bond was not reduced. Indeed, this methodology is attractive compared to alternative routes, which require expensive labelled alkylating reagents, for example, $^{13}CH_3I$.[25]




*Scheme 5.* Chemoselective synthesis of [*N*-$^{13}CH_3$]-naftifine using $^{13}CO_2$.

In summary, we have employed a metal-free catalyst for the efficient methylation of various amines using $CO_2$ as a $C_1$ source combined with hydrosilane as the reducing agent. The catalyst tolerates a broad range of substrates/functional groups. In addition, selective N-methylation of several drug molecules and the synthesis of naftifine was also achieved. As demonstrated in the chemoselective synthesis of naftifine, this catalyst could find uses in the sustainable synthesis of highly functionalized molecules including natural products and in the selective labelling of molecules with $^{13}CH_3$ groups.

## Experimental Section

General procedure for the methylation reaction: Imidazolium salt (0.10 mmol) and sodium hydride (0.10 mmol) were dissolved in 2 mL of solvent in a 10 mL Schlenk flask and stirred for 30 min to generate the carbene (0.05 mmol $mL^{-1}$ solution). The solution was then kept under nitrogen atmosphere without stirring until the inorganic salts settled at the bottom of the Schlenk flask. 1 mL of this carbene solution was transferred into a dry three-neck flask (after three vacuum and $CO_2$-purge cycles), already charged with the starting materials and connected to the $CO_2$ balloon. Next, 3 mL of solvent and 3 equiv of diphenylsilane were introduced. The reaction was monitored by TLC and GC-MS. Upon completion, 3 mL of a saturated aqueous solution of $NH_4F$ were added and the reaction mixture stirred at room temperature overnight. Excess ethyl acetate was added to afford a clear solution and aqueous work-up was performed. The combined organic layers were dried with anhydrous sodium sulfate, and the product was purified by column chromatography using ethyl acetate/pentane and 1 vol% of triethylamine. Note: the silanol by-product ($Ph_2SiHOH$) was removed during the chromatographic step and, as the amount of silane reagent increased, the rate of the reaction increased.

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