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Article

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# Selective Formylation and Methylation of Amines Using Carbon Dioxide and Hydrosilane Catalyzed by Alkaline Metal Carbonates

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ABSTRACT: The formylation and methylation of amines with carbon dioxide and hydrosilanes are emerging yet important types of transformations for $CO_2$. Catalytic methods effective for both reactions with wide substrate scopes are rare because of the difficulty in controlling the selectivity. Herein, we report that simple and readily available inorganic bases—alkaline metal carbonates, especially cesium carbonate—catalyze both the formylation and methylation reactions efficiently under mild conditions. The selectivity can be conveniently controlled by varying the reaction temperature and silane. A "cesium effect" on both reactions was observed by comparing the catalytic activity of various alkaline metal carbonates. Combined experimental and computational studies suggested the following reaction mechanism: (*i*) an activation of Si–H by $Cs_2CO_3$, (*ii*) insertion of $CO_2$ into Si–H, (*iii*) formylation of amines by silyl formate, and (*iv*) reduction of formamides to methylamines.

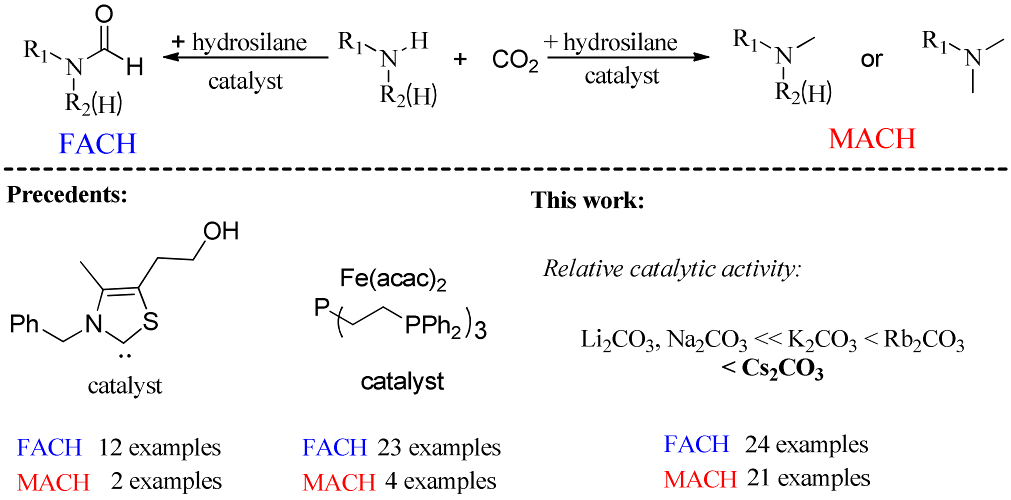
KEYWORDS: $CO_2$, hydrosilanes, amines, $Cs_2CO_3$, formylation, methylation

## Introduction

Recent years have witnessed great advances in the activation of $CO_2$ as a renewable, low-cost C1 feedstock in the synthesis of value-added chemicals.[1] However, to overcome the thermodynamic and/or kinetic barriers in the activation, reductive transformations of $CO_2$, e.g., hydrogenation of $CO_2$,[2,3] usually require relatively forceful conditions, such as high temperatures and high pressures as well as stoichiometric amounts of basic additives.

Growing research attention has been devoted to the development of new catalytic methodologies for the conversion of $CO_2$ using hydrosilanes as the reductants. Compared with dihydrogen, many hydrosilanes are more convenient to use in laboratory syntheses partially due to safety reasons and their hydrogen–silicon bonds are weaker and more polar than the hydrogen-hydrogen bond, which allows for milder reaction conditions.[4] Furthermore, the formation of strong Si–O bonds in the products provides an extra thermodynamic driving force.[5]

Although many catalysts leading to the formation of various products, such as formate, methanol, and methane, have been developed,[3] few have been shown to catalyze efficiently the formylation and methylation of amines with $CO_2$ and hydrosilanes. The latter two transformations, featuring the formation of a new carbon–nitrogen bond, have expanded the scope of value-added products from $CO_2$. The products, formamides and methylamines, are important intermediates widely used in the domains of medicines, agrochemicals and dyes.[6] In particular, *N*-methylation of amines has been shown to increase significantly the cytotoxicity of drug molecules.[7]



**Scheme 1.** Known catalysts that can catalyze both the formylation and methylation of amines using $CO_2$ and hydrosilanes. [15,17]

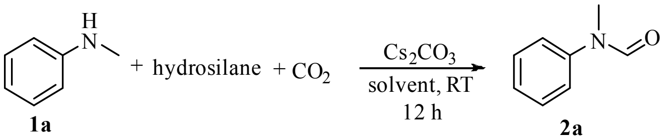
Cantat and co-workers[8] described initially an organocatalyst that mediated the formylation of amines with $CO_2$ and hydrosilanes (FACH) in 2012. Subsequently, in 2013, Cantat et al.[9a] and Beller et al.[9b] reported Zn-based and Ru-based catalysts, respectively, for the methylation of amines with $CO_2$ and hydrosilanes (MACH). Since then, several organic bases[10–15] and transition metal complexes[16–22] have emerged as effective catalysts for either the formylation or methylation of various amines.[23–25] To date, however, only two examples have been shown to catalyze both FACH and MACH, with limited substrate scopes for the latter, presumably because of the difficulty in obtaining selective MACH in the presence of FACH in the same system (**Scheme 1**).[17] Identifying catalytic systems with distinctive selective conditions for the two reactions appears to be a key challenge.

Herein, we report a new methodology using simple and readily available inorganic bases—especially cesium carbonate—as efficient catalysts for the construction of C–N bonds from $CO_2$ and amines under mild conditions. Interestingly, remarkable selectivities for both FACH and MACH have been achieved.[26–28] The substrate scope covers more than 20 different nitrogenous substrates for both reactions with yields up to 99%. A remarkable "cesium effect" unprecedented for the reduction of $CO_2$ by hydrosilane was observed. Combined experimental and computational studies provided insights into the reaction mechanisms. Notably, a related "cesium effect" was also reported very recently in a carbonate-promoted C–H carboxylation using $CO_2$ under molten-salt conditions.[29] Combined experimental and computational studies provided insights into the reaction mechanisms.

## Results and Discussion

We reasoned that effective catalysts for the hydrosilylation of aldehydes, ketones, or amides are promising candidates to catalyze FACH because they all share the same key step—the activation of a carbon–oxygen double bond. Because Cui and co-workers[30] have shown that cesium carbonate can effectively catalyze the hydrosilylation of aldehydes, ketones, and amides, it appears reasonable to postulate that inorganic carbonates may also catalyze FACH. The initial conditions were explored using *N*-methylaniline (**1a**) as the substrate and 1 equiv of $PhSiH_3$ (relative to **1a**) as the reductant. The reactions were performed with 5 mol % $Cs_2CO_3$ under 1 bar of $CO_2$ at RT for 12 h. As shown in **Table 1** (Entries 1–8), the best yield for *N*-formanilide (**2a**, 94% GC yield; 90% isolated yield) was obtained when using acetonitrile as the solvent. In contrast to the hydrosilylation of aldehydes, ketones, and amides,[30a] no reaction was detected under the solvent-free condition. When we decreased the amount of $PhSiH_3$ to 0.33 equiv (1 equiv of Si–H corresponding to **1a**), the yield of *N*-formanilide reduced to 30% (Entry 9, **Table 1**). Notably, yields greater than 90% can still be obtained even after decreasing the catalyst loading to 2.5 mol % or 1 mol % (Entries 10, 11, **Table 1**), although a further reduction of the loading to 0.5 mol % gave a significantly lower yield (80%) (Entry 12, **Table 1**). The performance of various hydrosilanes was probed next. The use of $Ph_2SiH_2$ as the reductant led to a 24% yield of **2a** (Entry 13, **Table 1**), while no reaction was observed when using 1,1,4,4-tetramethyldisiloxane (TMDS), polymethylhydrosiloxane (PMHS), or triethylsilane ($Et_3SiH$) (Entries 14–16, **Table 1**). Thus, $PhSiH_3$ appeared to be the best reductant for the current reaction and was used in further investigations.

**Table 1.** Optimization of reaction conditions for the *N*-formylation of *N*-methylaniline using $CO_2$.[a]



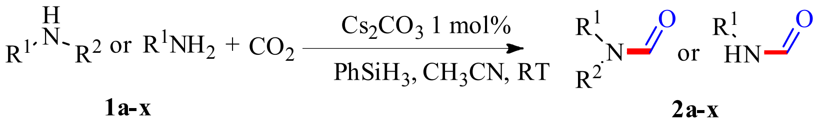
| Entry | Silane | Solvent | Catalyst loading (%) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $PhSiH_3$ | – | 5 | <1 |
| 2 | $PhSiH_3$ | $CH_3CN$ | 5 | 94(90)[c] |
| 3 | $PhSiH_3$ | $CH_2Cl_2$ | 5 | <1 |
| 4 | $PhSiH_3$ | EtOAc | 5 | <1 |
| 5 | $PhSiH_3$ | 1,4-dioxane | 5 | <1 |
| 6 | $PhSiH_3$ | THF | 5 | <1 |
| 7 | $PhSiH_3$ | DME[d] | 5 | 48 |
| 8 | $PhSiH_3$ | toluene | 5 | <1 |
| 9 | $PhSiH_3$[e] | $CH_3CN$ | 5 | 30 |
| 10 | $PhSiH_3$ | $CH_3CN$ | 2.5 | 91 |
| 11 | $PhSiH_3$ | $CH_3CN$ | 1 | 90 |

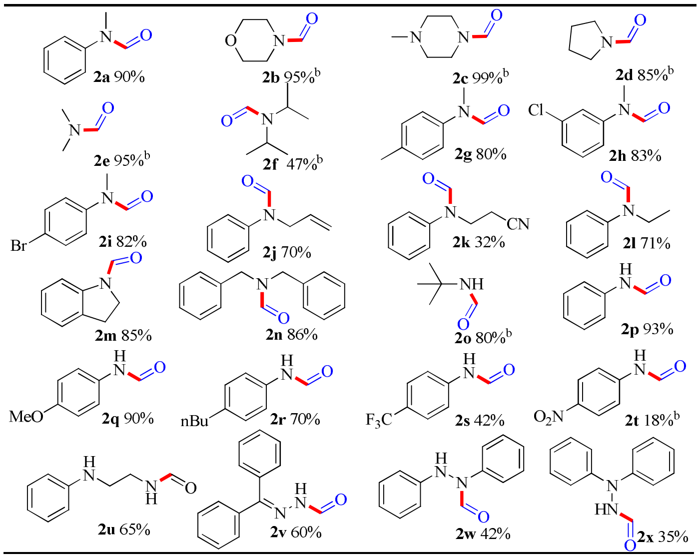
| | | | | |
|---|---|---|---|---|
| 12 | $PhSiH_3$ | $CH_3CN$ | 0.5 | 80 |
| 13 | $Ph_2SiH_2$ | $CH_3CN$ | 5 | 24 |
| 14 | TMDS | $CH_3CN$ | 5 | <1 |
| 15 | PMHS | $CH_3CN$ | 5 | <1 |
| 16 | $Et_3SiH$ | $CH_3CN$ | 5 | <1 |

[a] Reaction conditions: **1a** (0.5 mmol), hydrosilane (0.5 mmol or 3 equiv Si–H), $Cs_2CO_3$ (0.5–5.0 mol %), solvent (1 mL), $CO_2$ (1 bar), 12 h, RT. [b] Yield was determined by $^1H$ NMR spectroscopy using ferrocene as the internal standard. [c] Isolated yield in the parentheses. [d] DME= dimethoxyethane. [e] 0.17 mmol.

The scope of amines was subsequently studied with 1 equiv $PhSiH_3$ and 1 mol % of $Cs_2CO_3$ in acetonitrile under 1 bar of $CO_2$ at RT for 12 h (**Table 2**). Most secondary amines were successfully formylated with good to excellent yields (**2a–2n**). Tolyl, aryl chloride, aryl bromide, allyl, and cyano groups (**2g–2n**) were well tolerated in the reaction, while only a moderate yield was obtained with the sterically hindered diisopropylamine (**2f**). In addition to the secondary amines, primary amines can also be selectively transformed to the monoformylated products (**2o–2u**). Both tert-butylamine and aniline gave excellent yields (**2o, 2p**). A strong remote substituent effect was observed for aniline and its derivatives. Compounds with electron-donating groups on the para-position showed much higher reactivity than those with electron-withdrawing groups (**2q–2t**). It is noteworthy that *N*-benzylmethanediamine was selectively converted to *N*-((benzylamino)methyl)formamide in good yield presumably owing to the stronger basicity and smaller steric hindrance of the terminal alkylamine group (**2u**). Modest formylating yields for phenylhydrazine compounds were observed (**2v–2x**), indicating that the present method is also applicable to nonamine nitrogenous compounds.

**Table 2.** Substrate scope for the *N*-formylation of various amines with $CO_2$.[a]

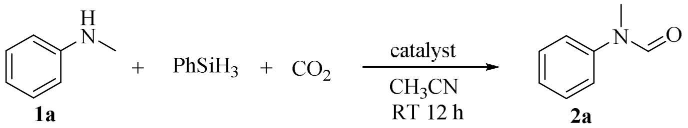




[a] Reaction conditions: substrate (0.5 mmol), $PhSiH_3$ (1 equiv), $Cs_2CO_3$ (1 mol %), $CO_2$ (1 bar), $CH_3CN$ (1.0 mL), RT, 12 h; Isolated yields are shown. [b] Yields were determined by $^1H$ NMR spectroscopy of the crude reaction mixture using ferrocene as the internal standard.

A remarkable size effect on the activity was observed after comparing the catalytic activity of various alkaline metal carbonates for the FACH reaction of **1a** and phenylsilane. For the small-sized alkaline metals—$Li_2CO_3$ or $Na_2CO_3$—no reaction was observed. As the size of the cation increased, a modest yield of **2a** was obtained for $K_2CO_3$, while $Rb_2CO_3$ further enhanced the yield and $Cs_2CO_3$ gave the highest yield (**Table 3**). Such an activity trend is reminiscent of the classical "cesium effect"[31] and may be attributed to the increased solubility and/or nucleophilicity of the carbonates due to the aggravating mismatch between the hard oxygen base and the softening acid as the cation changes from $Li^+$ to $Cs^+$. To probe these two factors, 15-Crown-5 ether was added to the $Na_2CO_3$-based system and surprisingly, the yield of **2a** was increased to 21% (Entry 6, **Table 3**), suggesting that the solubility of the carbonates be an important factor. In the carbonate-promoted C-H carboxylation using $CO_2$ under molten-salt conditions,[29] the higher reactivity of $Cs_2CO_3$ compared with $K_2CO_3$ was attributed to the lower melting point of the cesium salt mixture during the reaction.

**Table 3.** The *N*-formylation of *N*-methylaniline using $CO_2$ catalyzed by various alkaline metal carbonates.[a]



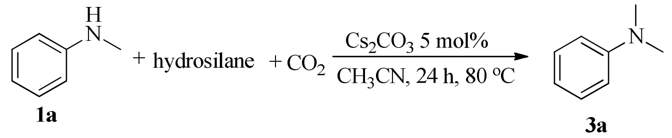
| Entry | Catalyst | Yield of **2a** (%)[b] |
|---|---|---|
| 1 | $Li_2CO_3$ | <1 |
| 2 | $Na_2CO_3$ | <1 |
| 3 | $K_2CO_3$ | 65 |
| 4 | $Rb_2CO_3$ | 81 |
| 5 | $Cs_2CO_3$ | 94 |
| 6 | $Na_2CO_3$/ 15-Crown-5 ether[c] | 21 |

[a] Reaction conditions: **1a** (0.5 mmol), $PhSiH_3$ (0.5 mmol), catalyst (5.0 mol %), $CH_3CN$ (1 mL), $CO_2$ (1 bar), 12 h, RT. [b] Yields were determined by $^1H$ NMR spectroscopy of the crude reaction mixture using ferrocene as the internal standard. [c] 15-Crown-5 ether (10 mol %).

Further reduction of formamides to form methylamines was observed upon elevating the reaction temperature. Using 5 mol % $Cs_2CO_3$ as the catalyst, the initial MACH reaction was studied with **1a** as the substrate and 2 equiv $PhSiH_3$ as the reductant in acetonitrile. Encouragingly, a 71% yield of *N*-dimethylaniline (**3a**) was obtained after 24 h at 80 °C (Entry 1, **Table 4**). Notably, a limited amount of $CO_2$ (4 equiv) was used in the present MACH instead of large excess amounts, i.e. constant pressures of $CO_2$, used in previous examples.[9,11,14,15,17,22] Other hydrosilanes were then screened (Entries 2-9, **Table 4**). Given the same number of Si–H bonds relative to **1a** (6 equiv), $Ph_2SiH_2$ exhibited the highest yield of **3a** (92%). In contrast, other silanes, such as $Ph_3SiH$ and $(EtO)_3SiH$, led to poor or no yields of **3a**. As such, $Ph_2SiH_2$ was used for further studies. The effects of temperature and stoichiometry of the starting materials were examined next. The yield of **3a** increased from 76% to 92% as the temperature rose from 50 °C to 80 °C, while no further improvement of the yield was observed at 95 °C (Entries 2, 10–12, **Table 4**). In additon, decreasing the equivalents of $CO_2$ (Entries 2, 13, 14, **Table 4**) or $Ph_2SiH_2$

(Entries 2, 15-16, **Table 4**) lowered the yields of **3a** significantly. A "cesium effect" similar to that observed in the FACH (supra infra) was also observed in the MACH (**Table S1**).

**Table 4.** Optimization of reaction conditions for the *N*-methylation of *N*-methylaniline using $CO_2$.[a]



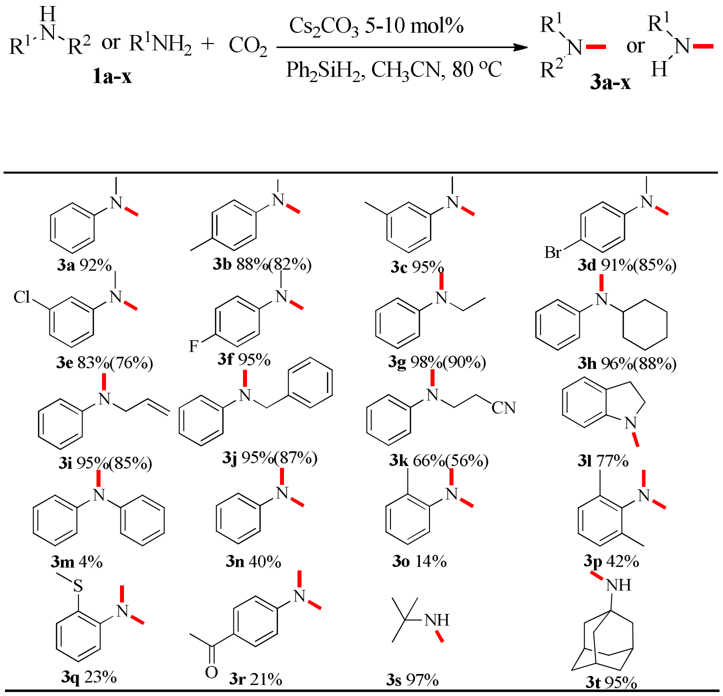
| Entry | Temp (°C) | Silane | Equiv ($CO_2$) | Equiv (silane) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 80 | $PhSiH_3$ | 4 | 2 | 71 |
| 2 | 80 | $Ph_2SiH_2$ | 4 | 3 | 92 |
| 3 | 80 | $Ph_3SiH$ | 4 | 6 | <1 |
| 4 | 80 | $Et_3SiH$ | 4 | 6 | <1 |
| 5 | 80 | PMHS | 4 | 2 | 7 |
| 6 | 80 | $Me(EtO)_2SiH$ | 4 | 6 | 8 |
| 7 | 80 | $(Me_2SiH)_2O$ | 4 | 3 | 1 |
| 8 | 80 | $(EtO)_3SiH$ | 4 | 6 | 2 |
| 9 | 80 | $Me(Me_3SiO)_2SiH$ | 4 | 6 | 1 |
| 10 | 50 | $Ph_2SiH_2$ | 4 | 3 | 76 |
| 11 | 65 | $Ph_2SiH_2$ | 4 | 3 | 86 |
| 12 | 95 | $Ph_2SiH_2$ | 4 | 3 | 90 |
| 13 | 80 | $Ph_2SiH_2$ | 1 | 3 | 20 |
| 14 | 80 | $Ph_2SiH_2$ | 2 | 3 | 60 |
| 15 | 80 | $Ph_2SiH_2$ | 4 | 2.5 | 76 |
| 16 | 80 | $Ph_2SiH_2$ | 4 | 2 | 57 |
| 17 | 80 | $Ph_2SiH_2$ | 4 | 1.5 | 25 |

[a] Reaction conditions: **1a** (0.5 mmol), hydrosilane (6 equiv Si–H), $Cs_2CO_3$ (5 mol %), $CH_3CN$ (1.6 mL). [b] Yield was determined by GC using anisole as the internal standard.

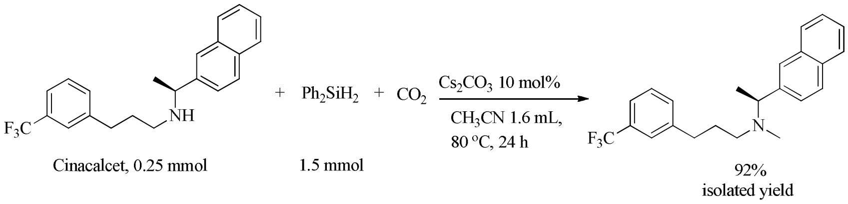
Most of secondary monoaromatic amines can be successfully methylated and the corresponding methylated products were obtained with excellent yields (**3a–3l**, **Table 5**), while only a poor yield was observed for diphenylamine (**3m**, **Table 5**). In contrast to secondary monoaromatic amines, dimethylation was observed for primary aromatic amines with much lower reactivity (**3n–3r**, **Table 5**) presumably due to the lower basicity. Such low reactivity is consistent with the lack of their monomethylation products, likely intermediates that are more basic and thus consumed faster than the starting materials. Interestingly, selective monomethylation can be achieved with excellent yields for primary substrates with strong basicity and large steric hindrance (**3s**, **3t**, **Table 5**). To examine the potential application of the present methodology, we next evaluated the *N*-methylation of a drug molecule—Cinacalcet. An excellent isolated yield (92%) was obtained for the reaction (**Scheme 2**).

The methylation may occur via three possible pathways (**Scheme 3**). A) An acid-base reaction between $CO_2$ and an amine forms a carbamate salt, followed by a dehydration to generate a urea. Reduction of the urea then leads to the methylation product.[32] B) FACH occurs first to generate a formamide, followed by deoxygenative reduction to produce the corresponding methylamine. C) $CO_2$ may initially be hydrosilylated to generate a methoxide intermediate. The resultant methyl group might be attacked nucleophilically by an amine to furnish the methylamine.

**Table 5.** Substrate scope for *N*-methylation of various amines with $CO_2$.[a]



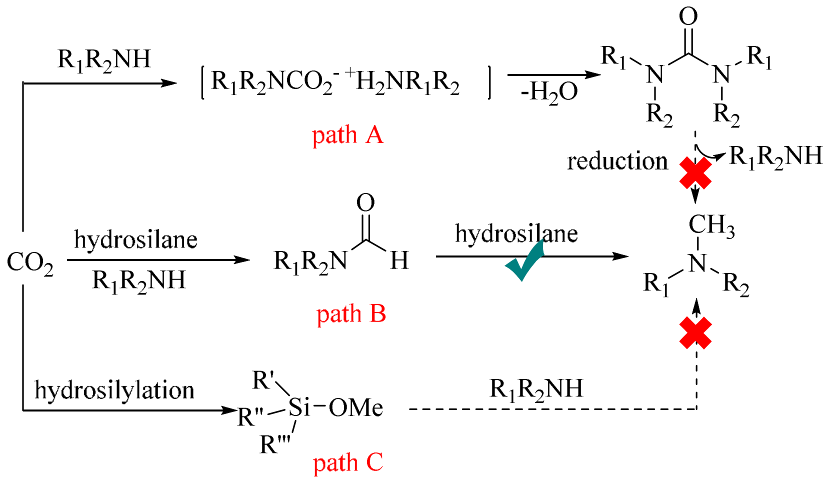
[a] Reaction conditions: substrate (0.25–0.5 mmol), $Ph_2SiH_2$ (3.0–6.0 equiv), $Cs_2CO_3$ (5–10 mol %), $CO_2$ (4 equiv), $CH_3CN$ (1.6 mL), 80 °C, 24-72 h; Yield was determined by $^1H$ NMR spectroscopy of the crude reaction mixture using ferrocene as the internal standard. Isolated yields in parentheses.



**Scheme 2.** The *N*-methylation of Cinacalcet using $CO_2$.

Because virtually no reaction was observed for *N,N′*-diphenyl-*N,N′*-dimethylurea under the optimized conditions of MACH (**Scheme S1**), path A was ruled out. Path B was supported by the further reduction of **2a** to **3a** (**Scheme S2**, **Figs S1–S3**) upon heating the product mixture of the formylation reaction of **1a** with an exogenous amount of silane. Although a significant amount of silyl methoxides was formed in $Cs_2CO_3$-catalyzed hydrosilylation of $CO_2$ in the absence of amine, subsequent addition of amine did not convert the methoxide to the methylation product (**Scheme S3**, **Figs S4–S7**), disfavoring path C. These observations suggest that path B should be the most likely path for the present MACH reaction.

Recent experimental evidence[12,13,18–20,33–35] suggested that FACH might involve two steps: (i) hydrosilylation of $CO_2$ to form silyl formates and (ii) formylation of amines with the formates to yield formamides (**Scheme S4**). Consistent with this mechanistic proposal, we found that $Cs_2CO_3$ catalyzed the reaction of $PhSiH_3$ and $CO_2$ to form silyl formates, which yielded **2a** upon addition of 1a (**Figs S8–S12**). Step (i) could occur with or without the transfer of hydrogen from Si–H to $Cs^+$ (**Fig. S13**). Our DFT calculations suggested that the formation of a precomplex between $PhSiH_3$ and $Cs_2CO_3$ to activate the Si–H bond before the insertion of $CO_2$ is a more favorable pathway (**Fig. 1**, **Fig. S14**).[36] But since Cs(OCOH), a hypothetical intermediate in the catalytic cycle of the CsH pathway (path 3, **Fig. S14**), was also an active catalyst, albeit with a relatively lower activity than $Cs_2CO_3$ (**Scheme S5**), the CsH pathway cannot be firmly excluded. In addition, DFT calculations also indicated that different cations show little influence on the energy barriers ($K_2CO_3$ *vs* $Cs_2CO_3$, **Fig. S15**), so the influence of the cations on the nucleophilicity of the oxygen atom can be ruled out as an important factor controlling the catalytic activity, further supporting that the "cesium effect" may result from the increased solubility of its carbonate salt. Interestingly, the calculated energy barrier drops 2.5 kcal/mol when the solvent is changed to THF (**Fig. S15**), which ostensibly contradicts to the experimental observation that MeCN is a better solvent. This again indicates that the solubility factor dominates when it comes to the activity of cesium salts.



**Scheme 3.** Potential pathways for the methylation of amines with $CO_2$ and silane catalyzed by $Cs_2CO_3$.

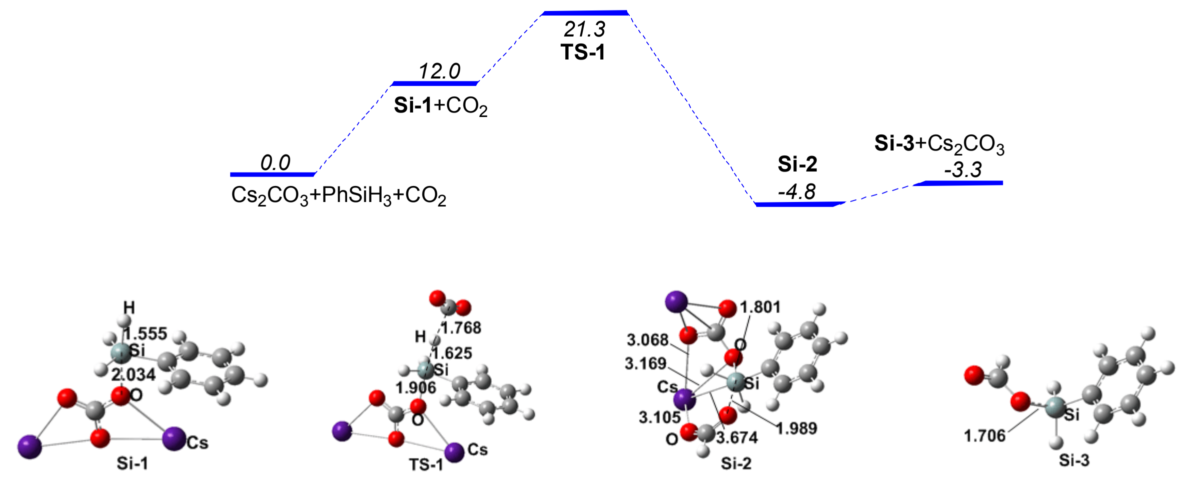


**Figure 1.** The reaction free-energy profile (in kcal/mol) for the computationally favorable pathway forming silyl formate and the optimized structures of the silyl species along with key bond lengths (in Å).

## Conclusion

Collectively, we have found that cesium carbonate, albeit simple, is a remarkably efficient catalyst for the formylation/methylation of amines with $CO_2$ and silane to produce formamides/methylamines under mild conditions. Upon changing the reaction temperature and the relative amount of silanes, the formylation/methylation selectivity can be controlled conveniently. The excellent yield for the methylation of a drug molecule, Cinacalcet, using the present methodology demonstrates its potential application in syntheses of complex molecules. An interesting "cesium effect" on the catalytic activity of alkaline metal carbonates was observed for both formylation and methylation. Further explorations of such an effect on related reductive transformations of $CO_2$ is ongoing.

ASSOCIATED CONTENT

**Supporting Information**. Experimental details, spectra, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

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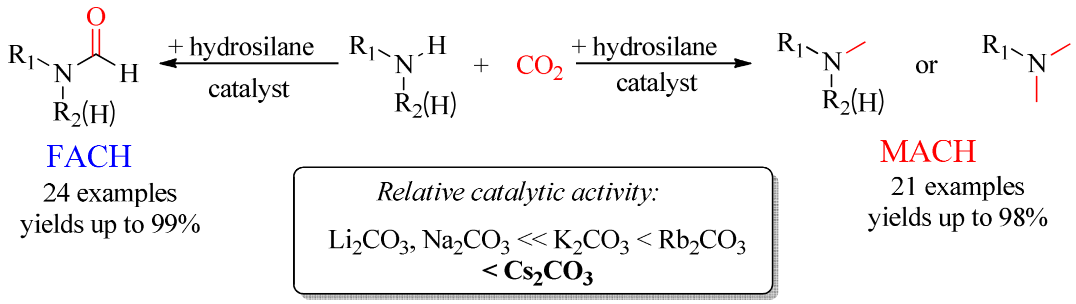

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