Science Bulletin

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Citation: Science Bulletin **64**, 723 (2019); doi: 10.1016/j.scib.2019.04.032

View online: http://engine.scichina.com/doi/10.1016/j.scib.2019.04.032

View Table of Contents: http://engine.scichina.com/publisher/scp/journal/SB/64/11

Published by the Science China Press

Science Bulletin 64 (2019) 723–729

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Article

Scalable direct *N*-methylation of drug-like amines using $^{12}CO_2/^{13}CO_2$ by simple inorganic base catalysis

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ARTICLE INFO

Article history:
Received 22 February 2019
Received in revised form 31 March 2019
Accepted 1 April 2019
Available online 26 April 2019

Keywords:
N-Methylation
Sabatier principle
$^{12}CO_2/^{13}CO_2$
Drug-like amines
Inorganic base catalysis

ABSTRACT

With the growing urgency of potential catastrophic climate changes due to anthropogenic CO_2 emissions, numerous efforts have been devoted to development of synthetic protocols using CO_2 as a building block in organic reactions, but the general applicability to complex drug-like substrates remains a challenge. We develop a general protocol for scalable direct *N*-methylation of a wide-scope drug-like amines using CO_2 and polymethylhydrosiloxane—a nontoxic, aerobically-stable hydrosilane considered as an industrial waste—via simple inorganic base catalysis. A rare application of the Sabatier principle in organic chemistry led to the discovery of cheap, nontoxic K_3PO_4 as an efficient catalyst. Preparations of a wide-scope drug-like amines with carbon-isotope label were also successfully achieved, enabling direct use of CO_2 in studies of drug absorption, distribution, metabolism and excretion.

1. Introduction

Limiting the rise of average global temperature relative to preindustrial levels not exceeding 1.5–2 °C via abatement of CO_2 emissions [1,2] is imperative in order to avoid irreversible catastrophic climate changes [3–5]. The ongoing trend to exhaust the remaining carbon budget for the temperature-control targets in the next ca. 10–20 years [6,7] requires immediate collective actions from all socioeconomic fields to contribute to abatement of CO_2 emissions. Pharmaceutical industry may potentially contribute to abatement of CO_2 emissions via chemical utilization of CO_2 as a C1 building block. Industrial production of aspirin via carboxylation of phenoxide using CO_2 directly to form salicylic acid has been successfully practiced for over a century (Fig. 1a) [8]. However, in spite of the tremendous progress in the field of direct chemical utilization of CO_2 in organic reactions [9–15], development of synthetic protocol with a general applicability to complex drug-like compounds ubiquitous in pharmaceutical industry remains a significant challenge [16].

Classical *N*-methylation of amines is well known as one of the most used reactions in medicinal chemistry [17] owing to the high prevalence of methyl amine moiety in drugs or related compounds [18,19], but rarely is the reaction recognized as an application of chemical utilization of CO_2 in pharmaceutical industry. To overcome the thermodynamic stability and the kinetic inertness of CO_2, industrial *N*-methylation of drug-like amines employs a multiple-step strategy to pre-activate CO_2 via a complex six-electron process under harsh conditions, such as high temperature, high-pressure H_2 [20] and strong reductant [21], to form toxic and unstable methylation agents (Fig. 1b). Additionally, since CO_2 is the primary source of carbon isotopes [22], such a multiple-step strategy has also found widespread applications in preparations of important isotope-labelling compounds, including $^{13}C/^{14}C$-methylated drugs for studies of their absorption, distribution, metabolism and excretion (ADME) [23,24] and ^{11}C-methylated drug-like compounds for positron emission tomography (PET) [25,26]. Remarkable recent progress on catalytic direct *N*-methylation of amines using CO_2 and various reductants [27–31], including high-pressure H_2, hydrosilanes and boranes, in one step provides a promising alternative protocol. However, we questioned whether it might be possible to develop a practical strategy to enable the application of such a one-step protocol to a wide scope of drug-like compounds using CO_2 and its carbon isotopologues under mild conditions.

In general, six-electron reduction of CO_2 to form the final *N*-methylated products selectively in one step is accomplished via cascade reductions of CO_2 and relevant intermediates with unsaturated carbonaceous functional groups, such as ester and amide, to break C—O σ and π bonds [28,32,33]. Nevertheless, conditions

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https://doi.org/10.1016/j.scib.2019.04.032
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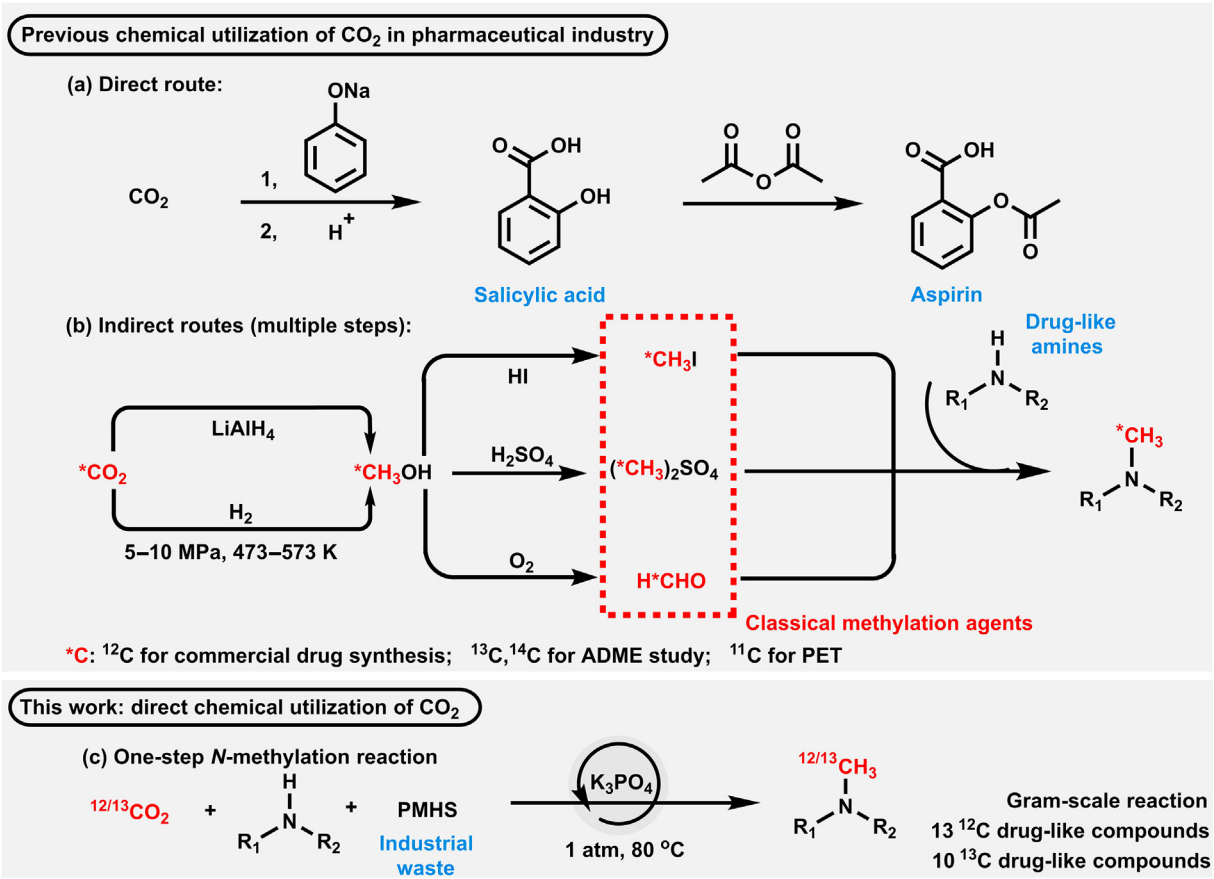

Fig. 1. (Color online) Comparison between previous chemical utilizations of CO_2 in pharmaceutical industry and the present method. (a) Direct CO_2 chemical utilization in industrial production of aspirin. (b) Indirect utilization of CO_2 in industrial *N*-methylation of drug-like amines with a multiple-step strategy. (c) Direct chemical utilization of CO_2 in this present one-step *N*-methylation reaction.

capable of reducing ester or amide also tend to reduce more reactive functional groups containing unsaturated bonds such as C=O or C=N bonds, leading to limited functional group tolerance that disallows the application of the reaction to a wide scope of complex drug-like compounds. We reasoned that such a compatibility issue should be inherent to over-reducing conditions, including high-pressure H_2 and strong reductants (e.g., phenyl hydrosilanes and boranes), which are typically required in previous direct reduction of CO_2 to form *N*-methylated amines. Development of a catalytic strategy that endows weak reductants with a just-right reducing power to drive the reactions selectively under mild conditions appears to be the key to solving this issue.

The Sabatier principle—that the interaction between the catalyst and the reactant should not be too strong or too weak—is a qualitative strategy commonly used to guide the design of heterogeneous catalysis [34], albeit the application of such a principle in the field of organic synthesis is rarely explored [35,36]. Upon adjusting the reducing power of Si—H bonds to two distinctive levels via judicious selection of reaction conditions, we recently reported a protocol featuring a rare controllable selectivity for direct *N*-formylation or *N*-methylation using a simple inorganic carbonate as the catalyst [32]. Mechanistic studies suggested that the catalytic reactions should be promoted via nucleophilic activation of phenyl hydrosilanes by the base. Encouraged by these preliminary results and inspired by the Sabatier principle, we hypothesized that nucleophilic activation of weakly reducing Si—H bonds, especially less hydrdic hydrosiloxanes due to the presence of electron-withdrawing siloxy substituents [37], by other simple inorganic bases with diversified basicities might be a more direct strategy to further manipulate the reducing power of Si—H bonds to the desired just-right level. Herein, we report a general protocol via simple inorganic base catalysis for scalable direct *N*-methylation of drug-like amines using polymethylhydrosiloxane (PMHS), a nontoxic and aerobically-stable hydrosilane that's considered as an industrial waste [38,39], and a stoichiometric amount of $^{12}CO_2$/$^{13}CO_2$ under mild conditions (Fig. 1c).

2. Experimental

2.1. General information

Commercial reagents were purchased from Adamas, Macklin reagent, TCI, J&K chemical and Alfa Aesar, and were used as received. CH_3CN was treated by a solvent purification system before use. $^{13}CO_2$ were purchased from CIL. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 or 400 spectrometer at ambient temperature. HRMS analysis was performed on ThermoFisher Q-Exactive Focus.

2.2. Representative procedures for the methylation of amines using CO_2 and PMHS

In a glovebox, K_3PO_4, 18-crown-6, PMHS, amine and CH_3CN were added into a Schlenk tube equipped with a stir bar. The Schlenk tube was sealed in the glovebox and then the vessel was degassed by three freeze-pumpthaw cycles and then sealed after being filled with ca.1 atmosphere of CO_2 on a Schlenk line. The

mixture was stirred at 80 °C. After the reaction was completed, the mixture was filtered, concentrated, and purified by silica gel or Isolera Flash Chromatography to give the pure product. Detailed experimental procedures and characterizations of the products are provided in the Supplementary Information (online).

2.3. Representative procedures for the methylation of amines using $^{13}CO_2$ and PMHS

In a glovebox, K_3PO_4, 18-crown-6, PMHS, amine and CH_3CN were added into a Schlenk tube equipped with a stir bar. The Schlenk tube was sealed in the glovebox and then the vessel was degassed by three freeze-pumpthaw cycles on a Schlenk line and ca.1 atmosphere of $^{13}CO_2$ was injected into the Schlenk tube via a syringe. The mixture was stirred at 80 °C. After the reaction was completed, the mixture was filtered, concentrated, and purified by silica gel or Isolera Flash Chromatography to give the pure product. Detailed experimental procedures and characterizations of the products are provided in the Supplementary Information (online).

3. Results and discussion

We first probed the validity of the Sabatier principle in the direct *N*-methylation of a model substrate, *N*-methyl aniline, using PMHS and CO_2 via studies of a series of simple inorganic salts with a wide range of basicities. Remarkably, most of the salts successfully catalyzed the selective formation of *N*,*N*-dimethylaniline (**1**) under the assistance of a catalytic amount of 18-crown-6 that presumably enhanced the solubility of the salts, while the *N*-formylation species was also observed as a minor product (Table S1 online). To our delight, the highest yield was achieved by a cheap and nontoxic salt—K_3PO_4. Isolated yields up to 95% were obtained in 24 h at 80 °C under ambient pressure. A volcano-type curve characteristic of the Sabatier principle [34] was observed upon plotting the yields over corresponding pK_a' (pK_a of conjugate acids of salts) (Fig. 2), indicating that pK_a' may be used as a descriptor for simple inorganic base catalysis qualitatively.

With the promising performance of K_3PO_4 in hand, we next explored the scope of secondary amines to evaluate the tolerability of various functional groups (**1**–**28**, Fig. 3). In spite of the simplicity of K_3PO_4, a remarkable wide scope of common functional groups, including, but not limited to, various unsaturated ones (**9**–**13**, **22**, **23**, **26**, **28**: ester, ketone, amide, cyano, nitro and olefinyl groups), are well tolerated by this new catalytic protocol. Several other prominent features are also notable: (i) the substitution position at the anilinic phenyl ring, *ortho*-, *meta*- *or para*-, only has a small impact onto the reaction (**2**–**4**); (ii) both electron-donating and electron-withdrawing groups are well tolerated, including chloro, bromo, fluoro, methyl, methoxyl, cyano, ester, cabonyl, amide and nitro (**4**–**13**); (iii) steric hindrance in diisopropylamine (**27**) or substrates with the *N*-methyl group for derivatives of aniline/benzyl amine replaced by ethyl, isopropyl, cyclohexyl, benzyl, and cyclopropyl group (**14**–**17**, **24**–**26**) is also well tolerated; (iv) cyclic amine (**18**) and diphenyl amine (**19**) are also suitable substrates; and (v) chemoselective functionalization of substrates with multiple nucleophilic sites is a classical challenge in organic synthesis [40]. Surprisingly, the present simple inorganic base catalysis allows for selective *N*-monomethylation of anilinic N—H in the presence of another nucleophilic site, boc-protected NH (**20**) or hydroxyl group (**21**), in the same substrate without any condition optimization; (vi) selective methylation of bicyclic aliphatic amine was also successfully achieved in the presence of ketone (**28**).

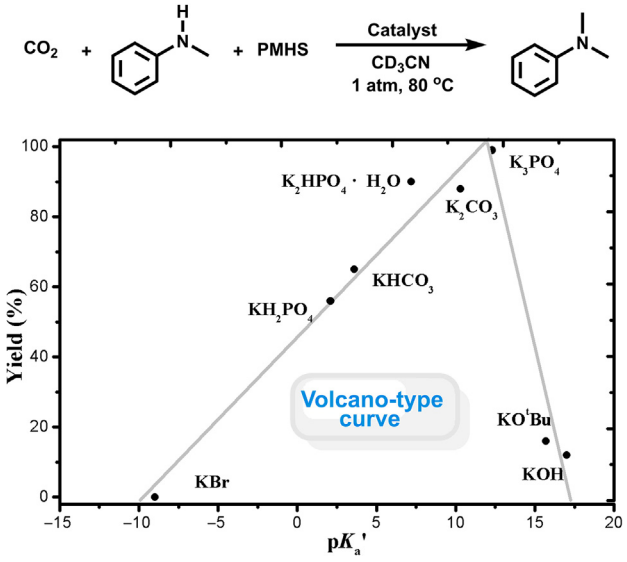

Fig. 2. (Color online) Plot of the *N*-methylation yield over corresponding pK_a' values of the inorganic salts. pK_a' = pK_a of conjugate acid of the salts.

As shown in Fig. 3, the catalytic system is also applicable to primary amines (**29**–**40**). However, *N*,*N*-dimethylation is the favored selectivity for both aryl amines (**29**–**36**) and aliphatic amines (**37**–**40**), which may be attributed to the enhanced nucleophilicity of the monomethylated intermediate relative to the starting amine. In contrast to their secondary counterparts, the reactions of aryl amines with various *para*-substituents are fairly sensitive to remote electronic effects. Electron-withdrawing groups presumably lower the nucleophilicity of the amine, leading to significantly lower conversion rates and yields (**34**–**36**). Notably, the successful *N*,*N*-dimethylation of *tert*-butylamine with a good yield (**38**) further indicates that the present protocol has an excellent tolerability of steric encumbrance.

Encouraged by the wide applicability of this new methodology among simple amines, we next examined the utility of the simple inorganic base catalysis in direct *N*-methylation of drug-like amines using CO_2 and PMHS for 9 commercial drugs, including Fluoxetine, Amoxapine, Tomoxetine, Duloxetine, Sertraline, Cinacalcet, Tetrahydropapaverine, Olanzapine and Rasagiline (**41**–**49**, Fig. 3). A gram-scale reaction was attempted for Rasagiline (**49b**), leading to an isolated yield almost identical to its small-scale counterpart (**49a**). This promising result shows that the simple inorganic base catalysis is fairly scalable even for drug-like amines.

To further demonstrate its potential utility in medicinal chemistry, we next applied the present methodology to the syntheses of 4 commercial drug molecules, including the parasympathomimetic drug Nicotine, the ganglion-blocking drug Pempidine, the antidepressant drug Amitriptyline and the antifungal drug Naftifine (**50**–**53**, Fig. 3). All of them can be conveniently synthesized with good to excellent yields (50%–90%) via the direct *N*-methylation reaction of their precursors using CO_2 and PMHS. It should be noted the relatively low yields of some primary amines and drug-like amines are due to the competitive formation of *N*-formylation by-products.

Having successfully established the simple inorganic base catalysis as a general tool for drug-like amines, we next explored the utility of this protocol in preparations of drug-like compounds with carbon isotope label. Only $^{13}CO_2$ was examined here given that both ^{11}C and ^{14}C are radioactive. Direct *N*-^{13}C-methylation was successfully achieved with moderate to excellent yields in 6–24 h for 10 drug-like amines, including Nicotine, Naftifine, Amitriptyline, Rasagiline, Cinacalcet, Tomoxetine, Amoxapine, Fluoxetine, Duloxetine and Sertraline (**54**–**63**, Fig. 3). These results indicate that the present methodology should also be useful for

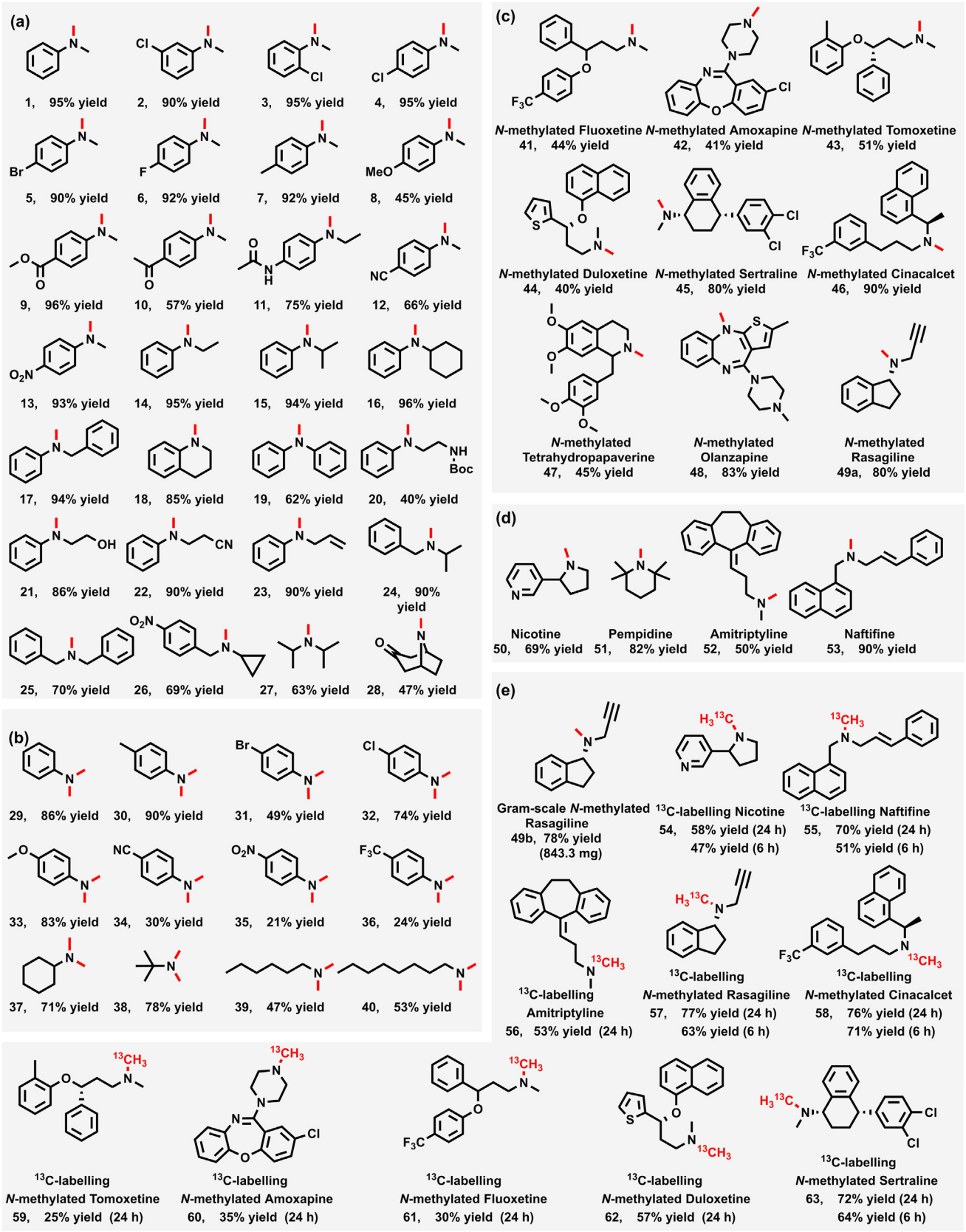

Fig. 3. (Color online) Substrate scope for *N*-methylation of simple amines and complex drug-like amines with $^{12/13}CO_2$. (a) *N*-methylation of secondary amines. (b) *N*-methylation of primary amines. (c) *N*-methylation of drug molecules. (d) Synthesis of drug molecules. (e) Gram-scale and ^{13}C-labelling reactions. General reaction conditions: CO_2 (1 atm), catalyst (2.5 mol%–20 mol%), 18-crown-6 (5 mol%–40 mol%), 80 °C. See the supplementary material for details (online).

N-^{14}C-methylation of drug-like amines considering the half-lives of carbon isotopes (^{11}C: ca. 20 min; ^{14}C: ca. 5,700 years). It should be noted that an excessive amount of CO_2 is typically needed in previous direct *N*-methylation of amines [27], which precludes their practical application in carbon isotope-labelling reactions due to the high cost of CO_2 isotopologues. In contrast, a stoichiometric amount of CO_2 (8 equivalents) is sufficient in the present protocol despite the simplicity of the catalyst and the mildness of the reaction conditions.

The transformation of CO_2 to *N*-methyl groups must involve a sequence of 2-electron reduction events considering that Si—H bond is a 2-electron reductant. Along such a reduction cascade, the formal oxidation state of the carbon center should experience four different stages: +4, +2, 0 and − 2. The C—N bond formation may occur at any of these stages, leading to four possible reaction pathways (Fig. 4a): (i) C—N bond forms first between CO_2 and amine to afford the corresponding carbamate, followed by 6-electron deoxygenative reduction to the product; (ii) CO_2 is first reduced by 2 electrons to formate, followed by a C—N bond formation to formamide and subsequent 4-electron deoxygenative reduction to the product; (iii) CO_2 is first reduced by 4 electrons to acetal, followed by a C—N bond formation to aminal and subsequent 2-electron reduction to the product; and (iv) CO_2 is first reduced by 6 electrons to methoxide, followed by a C—N bond formation to the product.

We then interrogated the potential reaction mechanism for the simple inorganic base catalysis using *N*-methylaniline as the substrate (Fig. 4b). The carbamate was not observed for a reaction mixture without PMHS, indicating that the present catalytic conditions are thermodynamically unfavorable for the formation of carbamate from CO_2 and *N*-methylaniline (Fig. 4b, Eq. (1)). Furthermore, it was shown recently that carbamate cannot be reduced to the *N*-methylation product [41]. Thus, pathway (i) is a less-likely pathway for the reaction, but a minor amount of carbamate might be involved as a nucleophile to activate the silane. As for pathway (ii), we found that the amide remained unreacted under the present catalytic conditions (Fig. 4b, Eq. (2)). As such, the *N*-methylated product should not be produced via pathway (ii). In the absence of amine, reduction of CO_2 by PMHS to form corresponding silyl methoxide was observed. But the lack of conversion of the methoxides to the *N*-methylated product upon treatment with *N*-methylaniline (Fig. 4b, Eq. (3)) rules out pathway (iv). Thus, reduction of aminal appears to be the only viable pathway to furnish the *N*-methylated product under current conditions. This notion is further supported by direct observation of bis(*N*-methyl-*N*-phenyl)aminal (**65**) upon carrying out the reaction at room temperature, which can be further reduced to *N*,*N*-dimethylaniline (**1**) at 80 °C by PMHS using K_3PO_4 as the catalyst (Fig. 4b, Eq. (4)). Such a mechanistic possibility was recently pro-

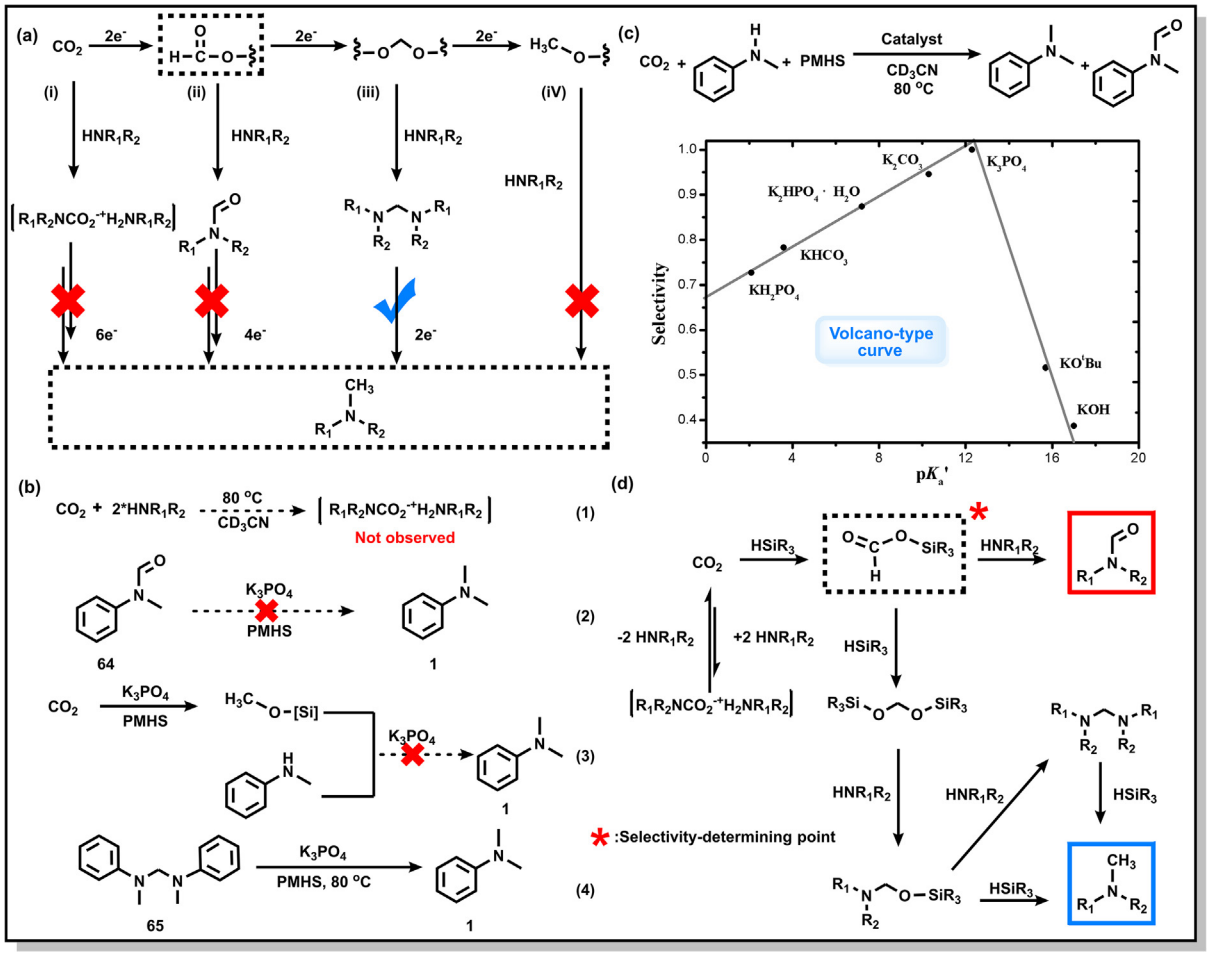

Fig. 4. Potential pathways for the methylation of amines with CO_2 and the selectivity of methylation product. (a) Four possible reaction pathways for *N*-methylation reaction. (b) Experiments suggest that pathway (iii) is the operational mechanism in the K_3PO_4 catalysis. (c) Plot of the selectivity of *N*,*N*-dimethylaniline, defined as the molar ratio of *N*-methylation/(*N*-methylation + *N*-formylation), over corresponding pK_a' values of the inorganic salts. (d) Competitive formamide/acetal-forming reactions of the silyl formate.

posed for an organocatalytic system [42,43]. Thus, we preferred pathway (iii) as the operational mechanism for the K_3PO_4 catalysis.

These mechanistic insights suggest that inhibition of the formamide-forming side-reaction pathway is a prerequisite for efficient direct *N*-methylation. We next purposefully examined the likely formation of formamide for the reaction of *N*-methylaniline catalyzed by different simple inorganic salts. Interestingly, only K_3PO_4 fully suppresses the formation of *N*-formyl-*N*-methylaniline (**64**) and a plot of selectivity of *N*, *N*-dimethylaniline, defined as the molar ratio of **1** to the sum of **1** and **64**, over pK_a' reveals another volcano-type curve (Fig. 4c). The "just-right" basicity of K_3PO_4 appears to play a critical role at the selectivity-determining point in the catalysis, at which competitive formamide/acetal-forming reactions of the silyl formate occur (Fig. 4d). It was previously shown that such an amide-forming reaction proceeds under the assistance of a concerted deprotonation of amine by base [44]. The dual promotion effects of base onto both formamide/acetal-forming reactions appear to be the underlying reason for the present unusual volcano-type curves characteristic of the Sabatier principle.

4. Conclusion

In summary, we developed a general catalytic protocol for direct chemical utilization of CO_2 as a C1 feedstock in syntheses of a wide scope of drug-like compounds. This work clearly shows that appropriate methodological development can greatly expand the potential applications of CO_2 utilization in pharmaceutical industry. Considering the immediate urgency to meet the CO_2 mitigation target in the next couple decades or so, it is crucial for all socioeconomic sectors to prepare practical enabling technologies for CO_2 utilizations and contribute collectively to emission reductions no matter how insignificant the current contribution might appear to be.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (U1532135). We thank Center of Instrumentation Analysis of School of Physical Science and Technology of ShanghaiTech University for instrumentation supports and Mr. Shimin Zhou of ShanghaiTech University for the drawing of TOC image.

Author contributions

Bo-Lin Lin conceptualized and directed the project. Chunlei Lu designed and carried out most of the experiments. Bo-Lin Lin, Zetian Qiu, Chunlei Lu and Yiling Zhu co-wrote the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2019.04.032.

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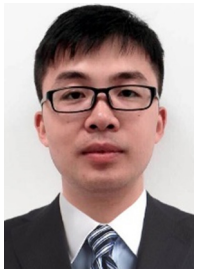

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