$NaHCO_3$ AS CO_2 SOLID SURROGATE FOR CARBOXYLATION REACTIONS UNDER MECHANOCHEMICAL CONDITIONS

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Abstract

The valorization of CO_2, the most abundant waste product of human activities, has become a priority for modern society. This study explores the innovative use of sodium bicarbonate ($NaHCO_3$) as a solid source of CO_2 for carboxylation reactions performed under mechanochemical conditions. We demonstrate that $NaHCO_3$ can be effectively used to produce high-value chemicals such as cyclic carbamates and carbonates *via* ball milling with propargylamines and epoxides. This approach not only avoids the handling of gaseous CO_2 and high-pressure cylinders but also highlights the potential of $NaHCO_3$ in synthesizing pharmaceutically active molecules without the massive use of solvents. Our findings suggest that the use of $NaHCO_3$ as a solid CO_2 surrogate could significantly contribute to reducing greenhouse gases and enhancing the valorization of CO_2 in industrial applications.

Introduction

CO_2 is the main greenhouse gas and the main responsible of the global warming. From the beginning of the industrial revolution, the increasing impact of human activities has been causing irreversible effects on the planet and, currently, the reduction of CO_2 emissions has become one of the main priorities for society.[1] The reduction of CO_2 emission likely needs the implementation of technological, societal and political actions at the same time. From the technological point of view, Carbon Capture and Storage (CCS),[2] Direct-Air Capture (DAC)[3] and BioEnergy with Carbon Capture and Storage (BECCS)[4] are some of the most promising solutions. Fortunately, CO_2 is also a renewable source of carbon, which in principle might become useful for the synthesis of a large variety of industrially relevant products, including chemicals, fuels and materials (Fig. 1A).[5] On one side, high volume commodities lead to a consistent amount of fixed CO_2, while small volume and high value-added chemicals can ensure a superior financial return. Additionally, CO_2 serves as the primary carbon source for plants, enabling the synthesis of complex molecules essential for their survival. Overall, it should be noted that the chemical fixation of CO_2, besides affording useful products from a waste, could significantly help mitigate the greenhouse effect of anthropogenic CO_2 emissions by 7-10%.[6]

One promising solution to mitigate the rise of CO_2 in the atmosphere is the storage of carbon dioxide in disused carbon sinks, though this approach presents significant challenges. A more efficient and nature-inspired strategy involves converting CO_2 into bicarbonate (Fig. 1B). This process not only stabilizes and safely stores CO_2 but also provides a reliable carbon source for future applications. Bicarbonate's stability and safety make it an attractive option for long-term carbon management and utilization. In this context, $NaHCO_3$ is manufactured during the Solvay process, aimed to produce soda ash (Na_2CO_3). Compared to Na_2CO_3, $NaHCO_3$ is marketed in much lower amount (2 Mt/y *vs*

65 Mt/y) being sold for small-scale domestic and industrial applications, including uses in the food industry, medicine, and as a component of dry-chemical fire extinguishers.[7] In chemical syntheses, it is primarily used as a base for the neutralization of acids and only sporadically as a CO_2 surrogate in solvent-based reactions, often with poor results.[8-10] We envisage that $NaHCO_3$ has the potentiality to be largely exploited for the manufacture of chemicals under solvent-free conditions, contributing both to the indirect valorisation of CO_2 as well as to the reduction of greenhouse gases in a sustainable way.

While bicarbonate can serve as a carbon source, its low solubility in common organic solvents poses a challenge. However, mechanochemistry can address this by bypassing traditional solubility limitations. Moreover, it allows for the design of synthetic transformations that require minimal amounts of solvents, and often none at all, greatly increasing the sustainability of chemical reactions.[11] It has been also demonstrated that mechanochemistry can promote alternative reactivity and may improve safety of chemical reactions.[12] For example, although solid-gas reactions are reported to be a viable synthetic strategy under ball milling conditions,[13] researchers have turned to mechanochemical techniques for the *in-situ* generation of gases, starting from solid surrogates (Fig. 1C).[14-18] This approach avoids the storage of potentially hazardous gases and the use of specialized equipment, allowing one to further improve the safety of a process while reducing, at the same time, its complexity and cost.

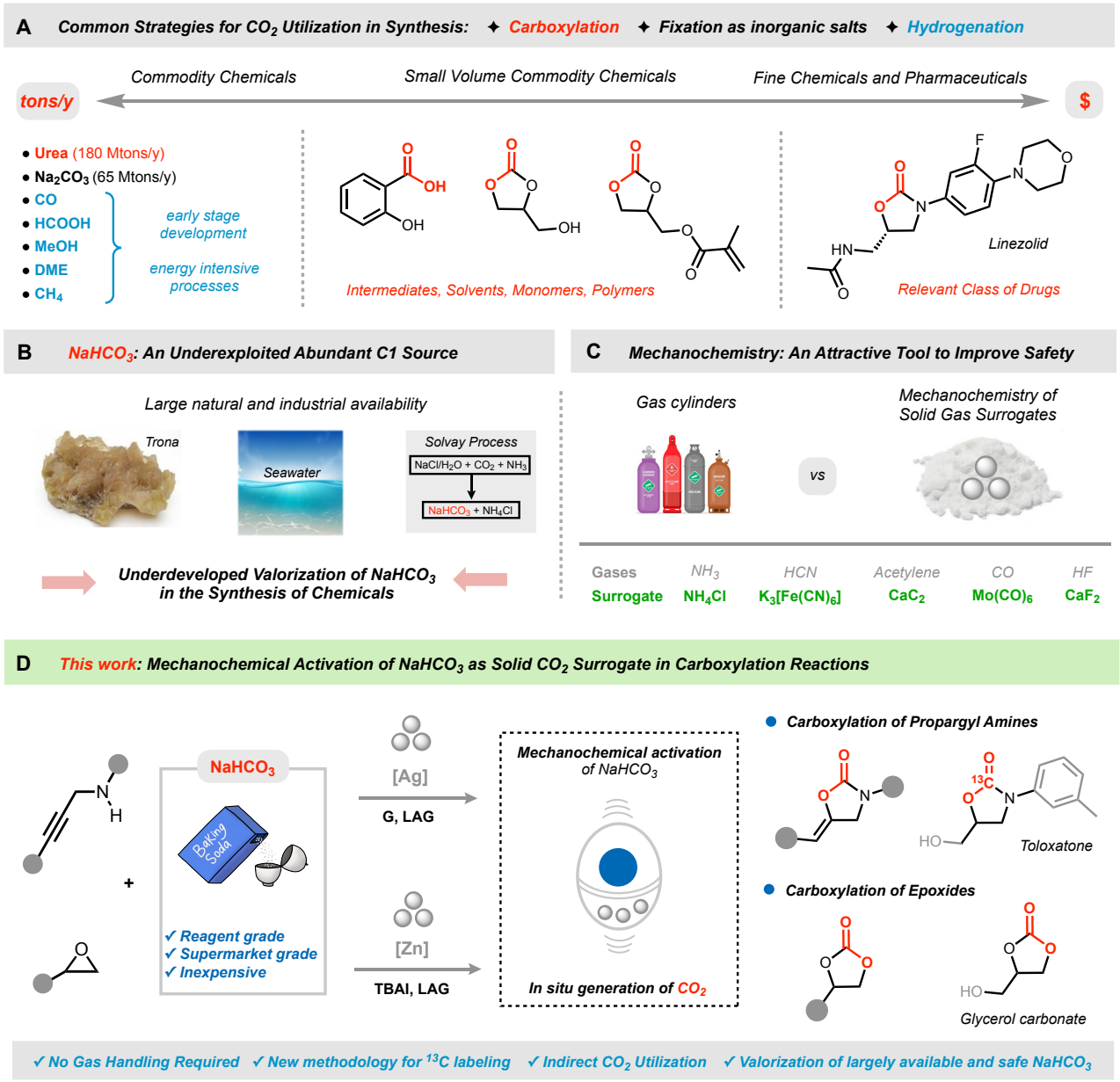


Fig. 1. A) CO_2 as valuable source of carbon for chemicals and fuels; B) $NaHCO_3$ as a natural and safe CO_2 surrogate; C) Mechanochemical strategies to replace gaseous reactants; D) *This work*.

The implementation of mechanochemical carboxylative reactions that employ solid CO_2 surrogates remains restricted to a few investigations. For instance, in 2011 Pinhas *et al.* utilized dry ice as a solid source of CO_2 for the synthesis of oxazolidinones from aziridines *via* High-Speed Ball Milling (HSBM) technique.[19] In the same year, the same method was used to obtain dialkyl carbonates from organic halides and potassium/caesium carbonate, in the presence of cation complexing reagents and dry ice.[20] The generation of diethyl carbonate from inorganic carbonates and ethyl trifluoromethanesulfonate under mechanochemical conditions, has been recently elucidated by Borchardt and coworkers through implementation of both *ex-situ* and *in-situ* monitoring

techniques.[21] Sodium Methyl Carbonate (SMC) has been employed in conjunction with Grignard reagent by Bolm's group for the synthesis of carboxylic acids under ball milling conditions.[22]

Herein, we describe the use of $NaHCO_3$ as an attractive solid CO_2 surrogate for mechanochemical carboxylations (Fig. 1D). As a widely accessible source of CO_2, $NaHCO_3$ is inexpensive, safe, easy to handle, and eliminates the need for high-pressure equipment. Industrially relevant chemicals such as cyclic carbamates and carbonates can be efficiently obtained from $NaHCO_3$ and the corresponding propargylamines/epoxides under nearly solventless conditions. Notably, pharmaceutically active molecules such as Toloxatone and a Linezolid-like precursor can be obtained in their ^{13}C labelled form in good to high yields without handling high-pressure cylinders of ^{13}C-labelled gases. Moreover, our unprecedented $NaHCO_3$-based carboxylative protocol represent an invaluable tool to access the thermodynamic product (cyclic carbonate) over the kinetic one (copolymer) in the reaction of epoxides with CO_2 (*vide infra*).

Results

The synthesis of oxazolidinones from $NaHCO_3$ and propargylic amine

We started our investigation working on a well-studied transformation: the synthesis of the oxazolidinone from propargylamine and CO_2.[23] The oxazolidinone fragment is found in pharmaceutical compounds such as Linezolid,[24] agrochemicals[25] and Evans auxiliaries.[26] Straightforward methodologies to access this valuable scaffold from propargylamines may involve the utilization of metallic catalysts (i.e. Ag, Cu, Pd, Zn, Au) often in combination with strong bases (amidines, guanidines).[27-32] In a limited number of examples, oxazolidinones can be obtained *via* carboxylation using caesium or potassium hydrogencarbonate as CO_2 surrogates with the use of large amount of organic solvent.[9,10,33,34] Our laboratory reported for the first time the exploitation of $NaHCO_3$ as a CO_2 surrogate for the synthesis of oxazolidinones from propargylamines by the use of guanidines in water.[8] From this expertise, we initially set out to develop a versatile method to mechanochemically activate $NaHCO_3$ for the incorporation of the -CO_2- moiety into a propargylamine with a minimal amount of solvent and short reaction times. An extensive optimization study (Table S1-4, SI) allowed to identify the optimal reaction conditions and the most relevant deviations (Fig. 2). The selected catalytic system ($AgNO_3$ and guanidine **G**) enabled the almost complete consumption of propargylamine **S1** and $NaHCO_3$, delivering the corresponding oxazolidinone **1** in 95% yield (Fig. 2, entry 1). Alternative commercially available superbases, such as DBU, TBD and MTBD were slightly less efficient under mechanochemical conditions (Table S1, SI). Notably, a comparative reaction carried out in solution (2 ml of dry DCE at room temperature for

4 hours) did not yield any product (Fig. 2, entry 2). Control experiments revealed the importance of the simultaneous presence of the silver catalyst, guanidine, and LAG (Fig. 2, entries 3-5). The use of Na_2CO_3 in place of $NaHCO_3$ was completely ineffective (Fig. 2, entry 6). Similarly, the reaction was hindered in the absence of $NaHCO_3$ (Fig. 2, entry 7).[35] The milling frequency was found to be crucial for a productive transformation as only 11% of **1** was observed at 30 Hz (Fig. 2, entry 8). However, recent observations indicate that increasing the temperature during the grinding process, known as "Heat & Beat," can significantly enhance outcomes. By raising the temperature by just a few degrees, the results can be markedly improved, sometimes leading to the complete conversion of the reagents. In particular, when the temperature was increased to 60 °C, 30 Hz were good enough to produce an excellent 93% yield of compound **1** (Fig. 2, entry 9). The yield of oxazolidinone **1** dropped to 44% using 4 equiv. of $NaHCO_3$ (Fig. 2, entry 10). On the other hand, by increasing the reaction time to 4 h, an excellent 95% yield of the desired cyclic carbamate was obtained (Fig. 2, entry 11). Additional experiments varying the catalyst nature and its loading, the base and other parameters are included in the SI file (Table S1-4).

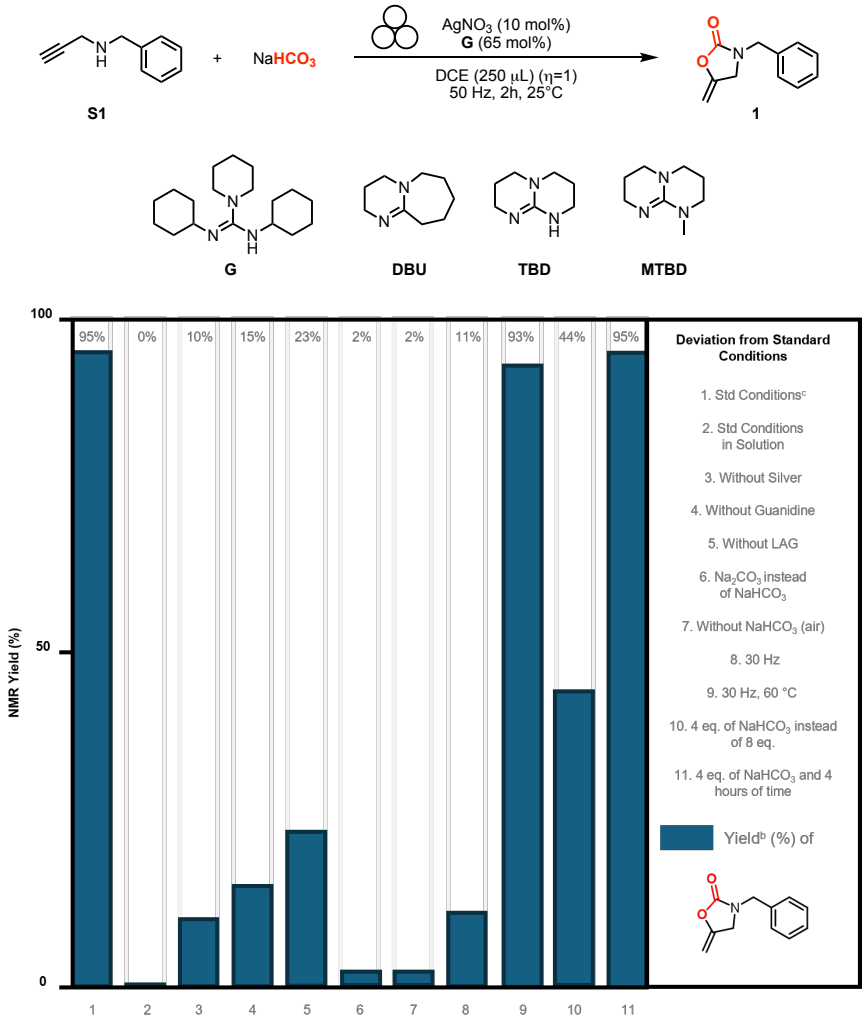


Fig. 2. Effect of the most relevant parameters in the mechanochemical carboxylation of propargyl amine **S1** to oxazolidinone **1**. [a] *Reaction conditions*: Stainless-steel jar of 15 mL, stainless-steel ball (10 mm, 13.5 g), 2 hours, 50 Hz, **S1** (0.3 mmol), **G** (0.195 mmol), $NaHCO_3$ (2.4 mmol), dry DCE as LAG (250 μL, η=1). [b] Yield determined by ^1H NMR with dimethyl maleate as internal standard. [c] Yield after isolation.

Substrate scope for the synthesis of oxazolidinones

After obtaining suitable reaction conditions, we explored the substrate scope for the Ag/**G**-catalyzed cyclocarboxylation of propargylic amines using $NaHCO_3$ as substitute of gaseous CO_2 (Fig. 3). Electron-rich and electron-poor benzyl moieties on the N nucleus gave good to excellent yields of the products, including those with sterically hindered *ortho* positions (**1**-**6**). Notably, even supermarket-grade $NaHCO_3$ proved to be equally effective in the reactions, demonstrating its practicality and accessibility for use in these synthetic transformations. The anthracenyl unit is less compatible (**7**), whereas heteroaromatic rings such as pyridine and thiophene can be incorporated into the final product with high yields (**8**-**9**). As expected, a less nucleophilic phenyl ring directly attached to the N affords only 35% yield of the corresponding oxazolidinone (**10**).[23] Increasing the temperature of the system to 60 °C, along with an improved electron density on the aromatic ring, results in fully satisfactory outcomes (**11**-**12**). Remarkably, compound **12** is present in the core structure of Linezolid. Propargyl amine bearing an alkyl chain gave quantitatively compound **13**. Importantly, product **14** containing the D-phenylalanine fragment was obtained in 78% yield. Propargyl amines with an internal triple bond were compatible with this transformation, as arenes substituted with both electron-donating (Me, OMe) and electron-withdrawing groups (CF_3, CN, COMe, CO_2Me, NO_2) on the phenylacetylene unit were nicely tolerated (**15**-**22**). In these cases, an *endo*/*exo* mixture of isomers was observed with electron-withdrawing groups (CF_3, CN, COMe, CO_2Me), whereas the *Z*-isomers of the *exo* product were selectively formed using more electron-enriched arenes (**15**-**17**). *Endo* isomers, that were successfully separated from their analogues, may derive from the tautomerization of *exo* isomers under basic conditions.[36] Steric congestion generated by double substitution at the *ortho* position of the aromatic ring (**22**) or at the propargylic position (**23**) led to lower yields. However, the unreacted starting material can be recovered in these cases. Stable labelled pharmaceutical molecules are essential for accurately tracking and studying drug distribution, metabolism, and elimination in biological systems.[37] They help researchers understand how drugs interact with specific targets and tissues, leading to safer and more effective therapeutic interventions.[38] Indeed, with good yields for the reaction using $NaHCO_3$, we attempted the incorporation of ^{13}C isotope into bioactive compounds using $NaH^{13}CO_3$. The present method, allowing to consume a controlled amount of expensive ^{13}C isotope containing CO_2 surrogate,

provided labelled oxazolidinones **24** and **25** in good to excellent yields. Moreover, labelled compound **26** was obtained with 97% yield and subsequently converted into the corresponding antidepressant *toloxatone* **27** by hydroboration/oxidation sequence with complete carbon isotope incorporation (see SI).

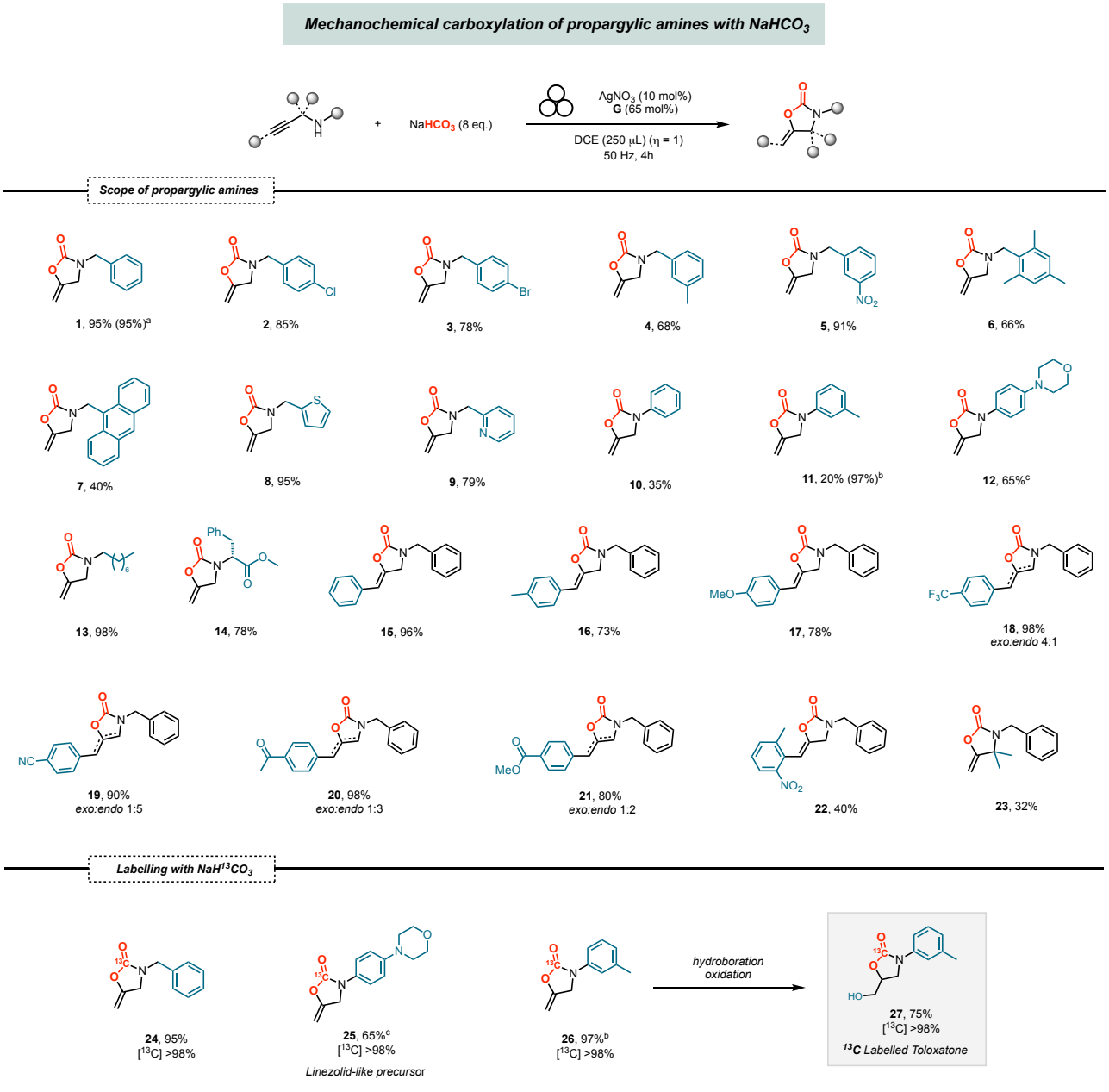
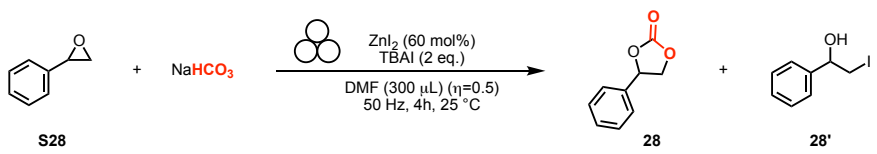


Fig. 3. Reaction conditions: Stainless-steel jar of 15 mL, stainless-steel ball (10 mm, 13.5 g), 4 hours, 50 Hz, propargylic amine (0.3 mmol), **G** (0.195 mmol), $NaHCO_3$ (2.4 mmol), dry DCE as LAG (250 μL, η = 1). All reported yields are intended after isolation. [a] $NaHCO_3$ purchased from supermarket. [b] Modified condition: 4 hours, 50 Hz, 60 °C, propargylic amine (0.3 mmol), **G** (0.6 mmol), $NaHCO_3$ (2.4 mmol), dry DCE as LAG (250 μL, η = 1). [c] Modified condition: 4 hours, 50 Hz, 60 °C, propargylic amine (0.3 mmol), **G** (0.3 mmol), $NaHCO_3$ (2.4 mmol), dry DCE as LAG (250 μL, η = 1).

The synthesis of cyclic carbonates from $NaHCO_3$ and epoxides

From an industrial point of view, the synthesis of cyclic carbonates by carboxylation of epoxides is one of the most relevant CO_2-based processes.[39] Cyclic carbonates are used as electrolytes in lithium-ion batteries, in pharmaceuticals and agrochemicals, and as monomers for polycarbonates. We started our research by investigating the most used metal catalysts with the potential to effectively carboxylate styrene oxide. An extensive experimental investigation (Tables S5-11, SI) led us to concluded that the most efficient activation system relied on utilizing commercially accessible ZnI_2 and tetrabutylammonium iodide (TBAI) as a source of iodide (Fig. 4). In particular, the standard conditions enabled the formation of styrene carbonate (**28**) in almost quantitative yield (Fig. 4, entry 1). TBAI was found to promote the formation of the desired product (Fig. 4, entry 2). No consumption of styrene oxide was observed in the absence of either ZnI_2 or TBAI, or without LAG (Fig. 4, entries 3-4). A careful investigation of the kinetic profile of the reaction revealed that compound **28'** is an intermediate (Fig. 4, entries 5-7, see SI for independent conversion of **28'** to **28**). The milling frequency is also crucial to achieve a high reaction rate together with full selectivity (Fig. 4, entries 8-10). Byproducts formed at lower frequency could reasonably be kinetically favoured polymeric materials.[40]



S28 **28** **28'**

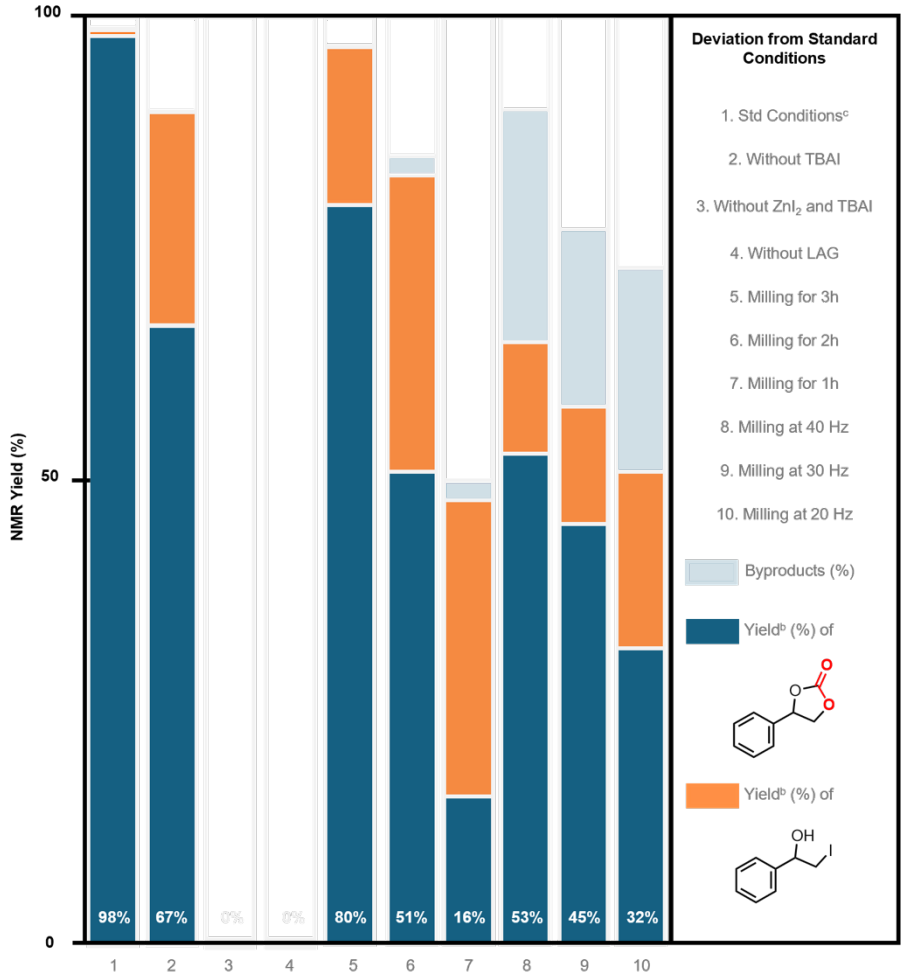


Fig. 4. Effect of the most relevant parameters in the mechanochemical carboxylation of styrene oxide **S28**. [a] *Standard conditions*: Stainless-steel jar of 15 mL, stainless-steel ball (10 mm, 13.5 g), 4 hours, 50 Hz, **S28** (0.3 mmol), TBAI (0.6 mmol), $NaHCO_3$ (6.0 mmol), dry DMF as LAG (300 μL, η = 0.5). [b] Determined by ^1H NMR with dimethyl maleate as internal standard. [c] Yield after isolation.

Substrate scope for the synthesis of cyclic carbonates

With the optimized conditions in our hands a series of terminal epoxides was studied and the results are summarized in Fig. 5. Monosubstituted epoxides were converted into cyclic carbonates under standard conditions in good to excellent yields. Similarly to styrene oxide, 4-bromostyrene oxide, bearing a useful substituent for versatile derivatization, afforded the corresponding cyclic carbonate **29** in 90% yield. Reactions of alkyl-substituted epoxides proceeded smoothly and generated cyclic carbonates **30**-**33** in high yields. Apparently, the presence of the benzyl substituent hinders the cycloaddition to a certain extent, while a bromide on the alkyl chain is fully tolerated. Different ether-substituted epoxides reacted nicely and gave cyclic carbonates **34**–**37** in 48–80% yields. Remarkably, the methacrylate unit, which is commonly used in the production of copolymers, is highly compatible

with this transformation (**38**). An epoxide derivative containing a free OH group led to the corresponding product **39** in near quantitative yield. Synthetically useful handles, such as NHTs and Cl substituents, were also tolerated as compounds **40** and **41** were isolated in 83 and 90% yield, respectively. Symmetric substrate **S42**, displaying two epoxide units, underwent mono cyclocarboxylation on one ring and iodohydrin formation on the other. Although with limited conversion, biologically relevant spirooxindole carbonate **43** was accessed from the corresponding spirooxindole epoxide with high selectivity.[41] Finally, a polyhedral oligomeric silsesquioxane (POSS) bearing the epoxide function has been successfully converted into the desired cyclic carbonate **44** together with its functionalized precursor **44'**. POSS are regarded as ideal building blocks for fabricating hybrid materials in biomedical applications.[42]

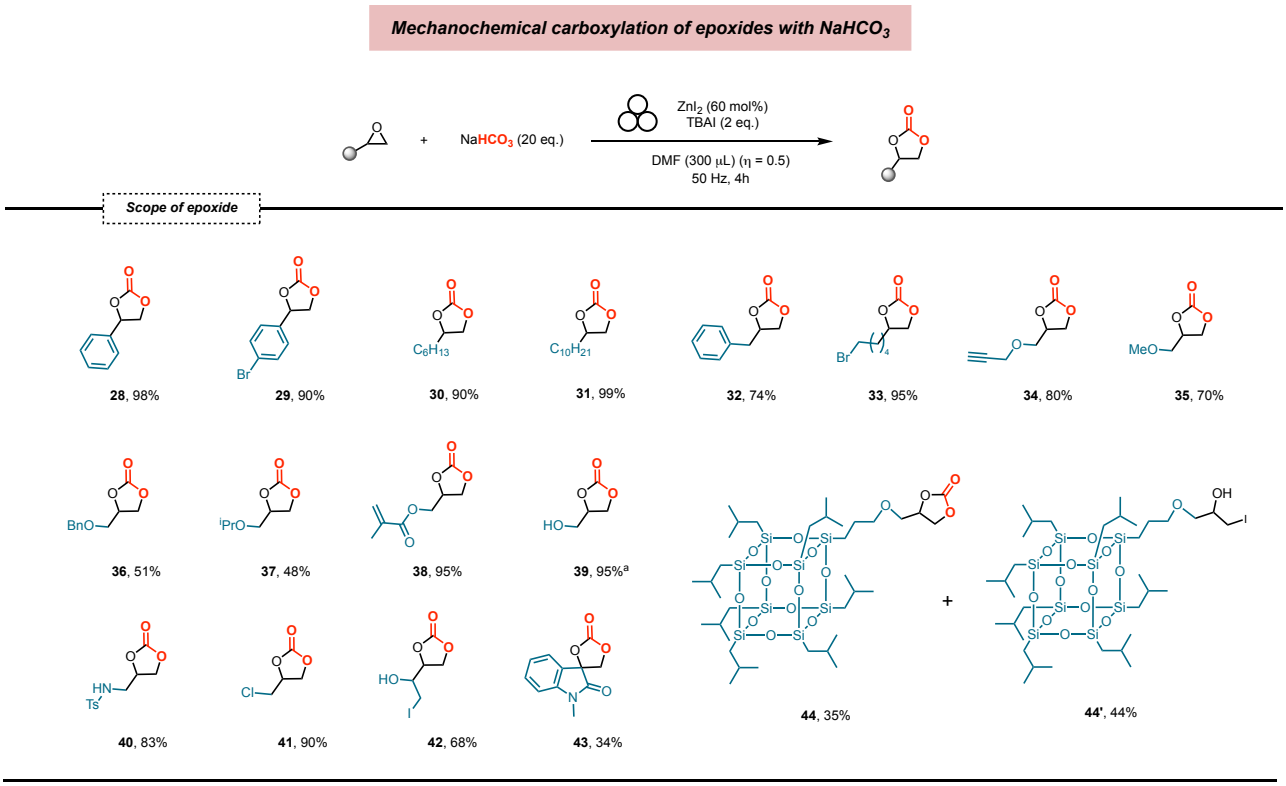


Fig. 5. Reaction conditions: Stainless-steel jar of 15 mL, stainless-steel ball (10 mm, 13.5 g), 4 hours, 50 Hz, starting epoxide (0.3 mmol), TBAI (0.6 mmol), $NaHCO_3$ (6.0 mmol), dry DMF as LAG (300 µL, η = 0.5). All reported yields are intended after isolation. [a] NMR yield.

Proposed reaction pathway

It is well known that $NaHCO_3$ starts to slowly release CO_2 at 80 °C with the concomitant formation of Na_2CO_3.[43] However, to the best of our knowledge, the mechanochemical decomposition of $NaHCO_3$ into CO_2 and Na_2CO_3 has been rarely studied. In particular, it is reported

that the decomposition of $NaHCO_3$ is accelerated by grinding the substance in a ball mill.[44] In this study, we employed powder X-ray diffraction (PXRD) to understand the nature of solid material resulting from the exposure of $NaHCO_3$ to 50 Hz ball-milling for 2 hours.

The Fig. 6A compares the XRD patterns of $NaHCO_3$ collected before (black) and after grinding carried out without (green line) and with (blue line) guanidine. The majority of the $NaHCO_3$ remains unaffected, except for the expected decrease of the crystal size. This reduction in crystal size is accompanied by the partial decomposition of $NaHCO_3$, resulting in the formation of a small yet significant amount of Na_2CO_3. These results indicate that ball milling action can cause, albeit partially, the release of CO_2 and H_2O and consequent formation of Na_2CO_3. Moreover, the presence of **G** is found to promote this process.[45] Fig. 6B shows the Lebail fitting performed on XRD data collected from the inorganic carbonates obtained after mechanosynthesis. The potential presence of an amorphous phase was not considered, and the smoothed background was modeled using a polynomial function. Therefore, the fitting in Fig. 6B aims to identify the most prevalent carbonate phases rather than to conduct a quantitative analysis. The significant presence of the $Na_2CO_3 \cdot 3NaHCO_3$ (Wegscheiderite) double salt indicates again the decomposition of $NaHCO_3$. Previous studies demonstrated that this double salt is an intermediate during $NaHCO_3$ decomposition.[46] Additionally, the formation of $Na_2CO_3 \cdot 3NaHCO_3$ is favored by moderate temperature increases and low water vapor pressure. These conditions seem to be met during the milling operations conducted within the jar at a frequency of 50Hz.

These preliminary findings clearly support a scenario in which ball-milling induces the *in-situ* generation of CO_2. We then demonstrated that gaseous CO_2 can be incorporated in the oxazolidinone core under standard milling conditions in the absence of $NaHCO_3$ (Fig. 6C-1). In addition, a synthesized guanidine-hydrogencarbonate adduct $\mathbf{GH^+HCO_3^-}$ (Fig. 6C-2)[47] was used under standard conditions affording the corresponding carboxylated compound in 95% yield (Fig. 6C-3). Collectively, these data provide support for a plausible mechanism that starts with the generation of CO_2 and proceeds with its further catalytic incorporation in organic substrates (propargyl amines) through $\mathbf{GH^+HCO_3^-}$ (Fig 6D).[8,23] As further evidence, temperature can promote the reaction likely by boosting $NaHCO_3$ decomposition to CO_2 (Fig. 2, entry 9). In this context, the complete inefficiency of Na_2CO_3 (Fig. 2, entry 6) can be explained by its high decomposition temperature (up to 780 °C for pure Na_2CO_3).

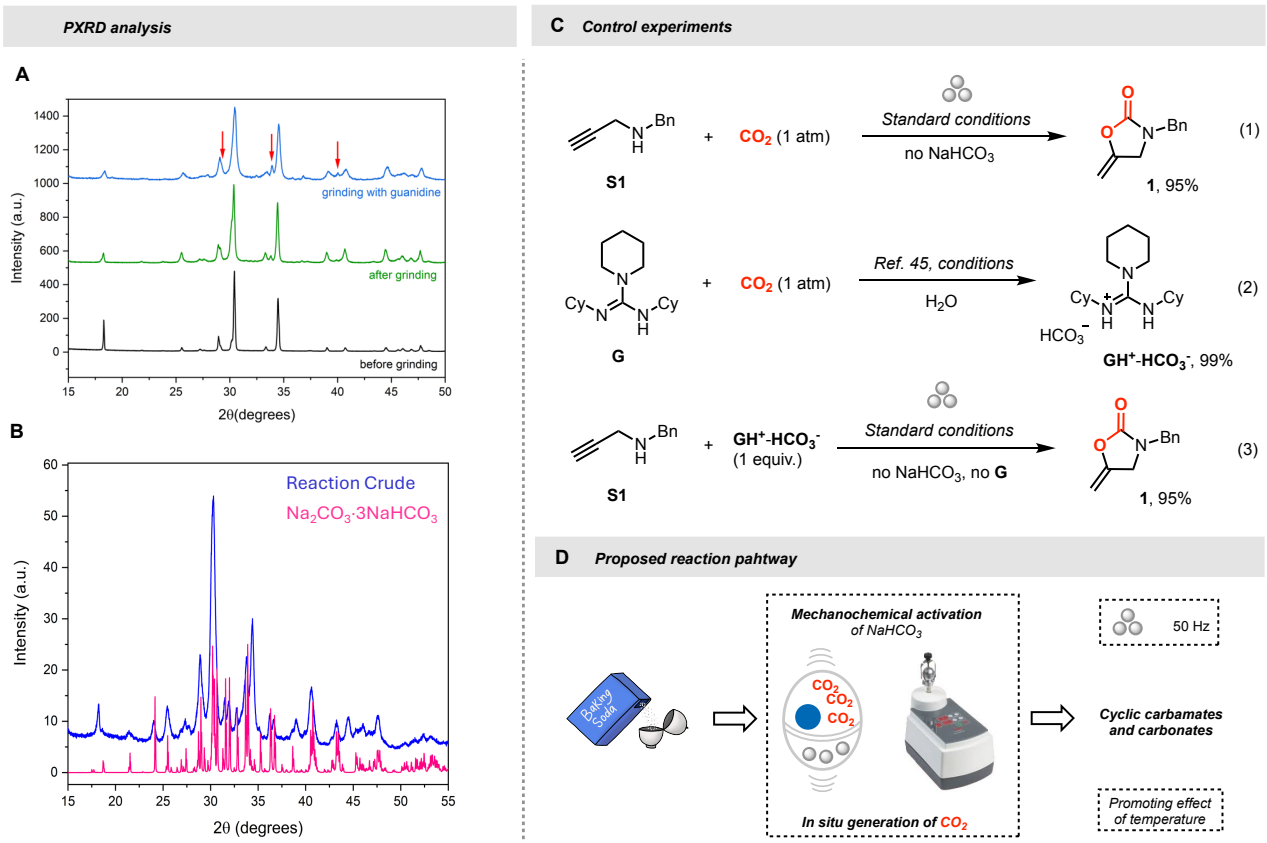


Fig. 6. A) Direct comparison of the X-ray diffraction patterns of $NaHCO_3$ before (black) and after grinding without (green) and with guanidine (blue). The reflections characteristic of Na_2CO_3 are indicated by the red arrows. B) Powder x-ray diffraction pattern of the crude after the mechanosynthesis process. The pink line represents the calculated pattern of the compound $Na_2CO_3{\cdot}3NaHCO_3$ (Wegscheiderite). C) Control experiments. D) Proposed reaction pathway.

Conclusions

In summary, we have described the unprecedent use of $NaHCO_3$ as cheap and safe solid CO_2 surrogate for carboxylation reactions under mechanochemical conditions. High value-added chemicals such as cyclic carbamates and carbonates can be efficiently obtained ball-milling $NaHCO_3$ and the corresponding propargylamines/epoxides. Labelled $NaH^{13}CO_3$ is equally effective to provide pharmaceutically active molecules such as Toloxatone and a Linezolid-like precursor without handling gases and high-pressured cylinders. Beyond the synthesis of oxazolidinones and cyclic carbonates from CO_2, including the small-scale synthesis of labelled bioactive compounds, this work lays the foundation for ample future developments. The valorization of $NaHCO_3$ as a solid CO_2 surrogate holds for vast synthetic application, from high-value pharmaceuticals to polymer chemistry. We hope that present proof-of-concept will thus contribute to the collective effort connected with the valorization of the most abundant, renewable, C1 carbon source.

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