

Investigation on the stoichiometry of carbon dioxide in isotope exchange reactions with phenyl acetic acids

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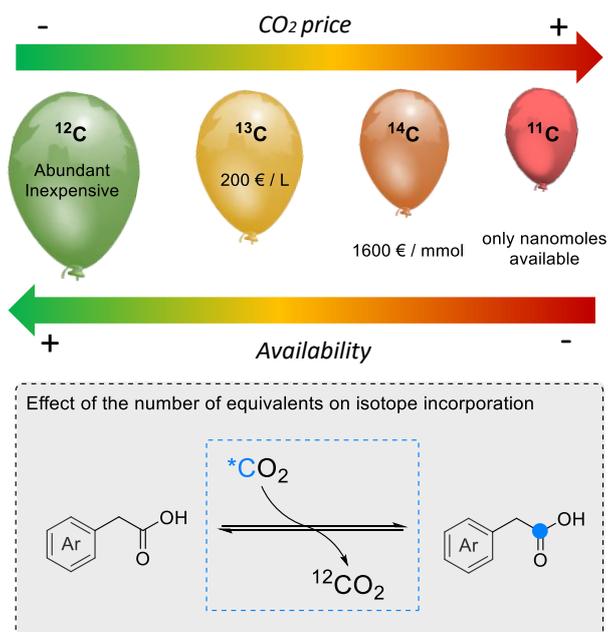
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Abstract The functionalization of carbon dioxide (CO₂), as C1 building block has attracted enormous attention. Carboxylation reactions in particular are of major interest for applications in isotope labeling. Due to the inexpensive nature of CO₂, information about its stoichiometric use is most often unavailable in the literature. Because of the rarity and limited availability of CO₂ isotopomers, this parameter is of concern for applications to carbon isotope labeling. Here, we investigated the effects of the stoichiometry of labeled-CO₂ on carbon isotope exchange of phenyl acetic acids. Both thermal and photocatalytic procedures were studied, providing insight on product outcome and isotope incorporation. Preliminary results on isotope dilution effects of carbonate bases in photocatalytic carboxylation reactions have also been obtained.

Key words carbon dioxide, isotope labeling, photoredox catalysis, decarboxylation, carboxylation

Carbon dioxide (CO₂) is highly abundant C1 building block with a low toxicity profile in respect to other C1 sources commonly employed in industry and academy.^{1,2} While recent work by Ofial, Mayr and co-workers has demonstrated that the electrophilicity of CO₂ is comparable to that of benzaldehyde,³ the lack of thermodynamic driving force poses a synthetic challenge for its functionalization.⁴ The interest in CO₂ transformations has witnessed a remarkable progress in recent years and a large variety of novel reactions has been reported.⁵ In particular, new approaches towards carboxylation have been investigated.⁶

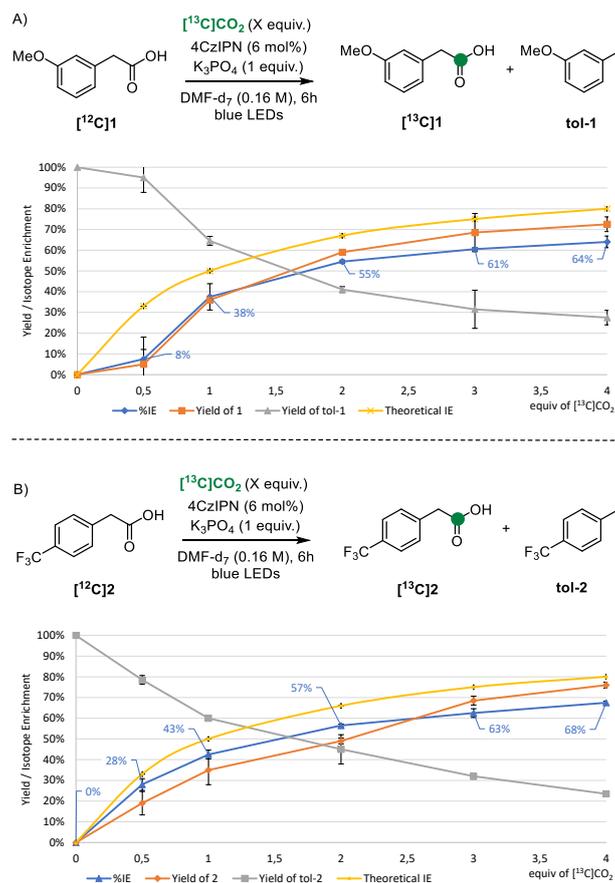
Transformations involving CO₂ are commonly optimized towards the development of efficient recyclable catalysts exhibiting high turnover numbers, the use of non-toxic reagents and mild conditions.⁷ On the opposite, poor attention is usually given to the conversion of CO₂ into the final product of the reaction and its stoichiometry is a most often a neglected parameter. This is not surprising given the natural abundance and the low price of this greenhouse gas. On the other hand, the stoichiometry of CO₂ is a major parameter of concern when high-value CO₂ carbon-labeled isotopomers are used.⁸ In carbon isotope chemistry, CO₂ represents the primary synthetic building block.⁹⁻¹¹ As the processes to obtain isotopically pure material are energy-intensive and/or time consuming and/or technically challenging, costs associated to these sources are far from negligible. These considerations are a key concern when application of CO₂ methodologies to isotope chemistry is required. It is somehow significant that between the myriad of known transformations involving CO₂, only a limited number of them have found application to carbon isotope labeling.¹²



Scheme 1 Top. Availability and costs related to the four major carbon isotope utilized for applications in life science. Bottom. Aim of this study: investigation of CO₂ stoichiometry in isotope exchange reactions of phenyl acetic acids.

Recently, Carbon Isotope Exchange (CIE) using CO₂ has emerged as an attractive technology.¹³ By replacing a ¹²C-¹²COOH bond with a ¹²C-^{11/13/14}C¹³COOH, this concept is particularly attractive as it avoids the synthesis of functionalized precursors and accelerates the availability of C-labeled pharmaceuticals for drug development studies.¹⁴

In 2020, a thermal CIE procedure to access phenyl acetates was independently reported by Lundgren's and our group.¹⁵⁻¹⁷ This transformation opens a direct access to labeled Nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen, ketoprofen, fenclofenac. In 2021, an improved photocatalytic version of this CIE reaction was reported by the same groups. This method has the advantage of proceeding under milder conditions utilizing 4CzIPN as an organic photo-catalyst.^{18,21} In the course of these studies, we realized that these reactions constitute a suitable platform to study the impact of the stoichiometry of the gas reagent delivered on the outcome of the reaction both in terms of yield, isotope incorporation and/or by-product formation.



Scheme 2 Effects of the stoichiometry of $[^{13}\text{C}]\text{CO}_2$ on the outcome of the CIE photocatalytic procedure using K_3PO_4 . Green colored circles denote the positions of the carbon atoms labeled. See supporting information for detailed conditions.

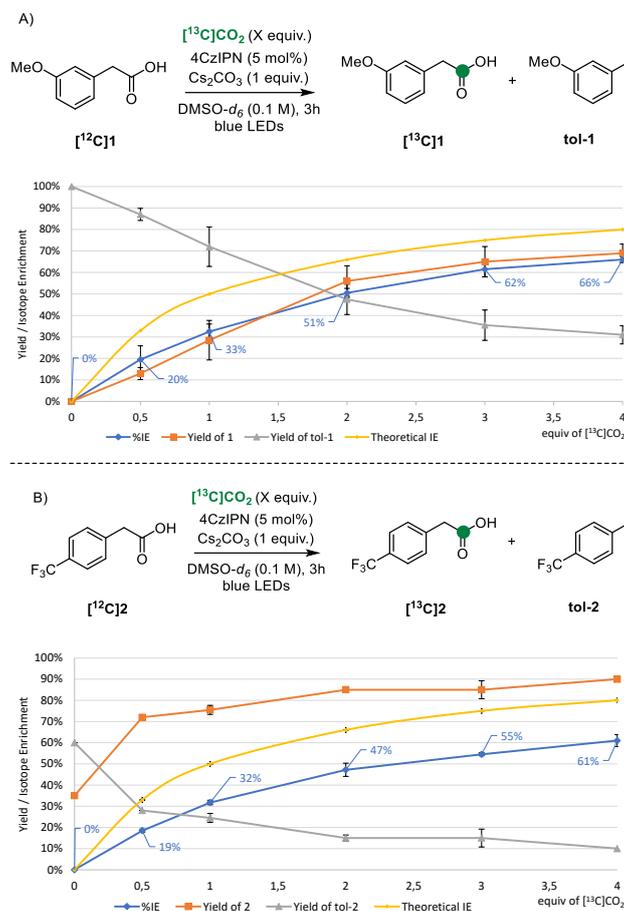
In preliminary results,¹⁸ we observed that in presence of 2-(3-methoxyphenyl)acetic acid $[^{12}\text{C}]\mathbf{1}$, the outcome of the photocatalytic CIE was influenced by the stoichiometry of $[^{13}\text{C}]\text{CO}_2$. As shown in Scheme 2A, the isotopic enrichment (% I.E.) of $[^{13}\text{C}]\mathbf{1}$ follows closely the theoretical values (1 equiv. of $[^{12}\text{C}]\text{CO}_2$ is generated from the substrate), particularly when > 1.5 equiv. of $[^{13}\text{C}]\text{CO}_2$ was present. On the other hand, the ratio between $[^{13}\text{C}]\mathbf{1}$ and proto-decarboxylation product **tol-1** is strongly influenced by the amount of $[^{13}\text{C}]\text{CO}_2$ present in the reactor. When carbon dioxide is lower than 1.5 equiv., we observed the proto-decarboxylation as major process in the transformation.²⁰

In order to learn from this result and understand whether this behavior is substrate dependent or more general, we decided to investigate it in more details. In this letter, we report the results on the both thermal and photoredox-catalyzed CIE of phenyl acetic acids.

At first, we selected electron-poor acid $[^{13}\text{C}]\mathbf{2}$ and determined its behavior under identical CIE protocol. The reaction was performed in a 2 mL schlenk flask that was connected to a RC Tritec[®] carboxylation manifold, to allow for a precise addition of $[^{13}\text{C}]\text{CO}_2$ into the flask. This is a noticeable difference compared to common carboxylation procedures found in the literature, where the gas is often added to the reaction by purging a CO_2 -filled balloon in an undetermined excess.¹⁹

In analogy with acid **1**, full proto-decarboxylation was observed when CO_2 is replaced by N_2 and **tol-2** was the major product of the reaction unless 2 equiv. of labeled- CO_2 are added (Scheme 2B).²⁰ On the

other hand, with more than 2 equiv. of labeled gas, [^{13}C]2 was observed in more the 50% yield. Once again, the measured ^{13}C -isotope incorporation followed quite closely the expected theoretical values.



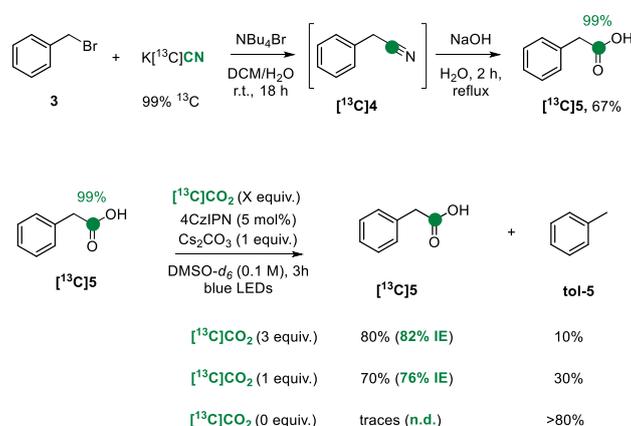
Scheme 3 Effects of the stoichiometry of [^{13}C]CO₂ on the outcome of the CIE photocatalytic procedure using Cs₂CO₃. Green colored circles denote the positions of the carbon atoms labeled. See supporting information for detailed conditions.

The group of Lundgren has shown that this CIE proceeds well also in presence of carbonate base (Cs₂CO₃ in place of K₃PO₄) in DMSO as aprotic polar solvent, under slight more diluted conditions and shorter reaction time (3h in place of 6h). In addition, they proved that the method is compatible to β -carboxy amides, β -carboxy lactams, malonate half-esters, and β -carboxy nitriles.²¹ To estimate how such modifications might affect the outcome of the reaction, we performed it under increasing [^{13}C]CO₂ stoichiometry. In the case of [^{12}C]1 (Scheme 3A), it was observed a very similar behavior compared to what we have previously noted (Scheme 2A). Proto-decarboxylation product **tol-1** was the predominantly formed product with less than 2 equiv. of CO₂. Above this amount of gas, the labeled-phenyl acetic acid was obtained with good yield, up to 72%. The percentage of isotope incorporation was found to be consistent with what previously observed in presence of K₃PO₄ and DMF (Scheme 2). Though isotope dilution between the [^{13}C]CO₂ and Cs₂[^{12}C]CO₃ might have been expected, these results suggest this process is not occurring with acid **1**, at the time scale of the reaction.

Interestingly, in the case of electron-poor acid **2**, we found that in the absence of CO₂ the unlabeled [^{12}C]2 was recovered in 35% yield while the formation of the **tol-2** was limited to less than 30% starting

from 0.5 equiv. of $[^{13}\text{C}]\text{CO}_2$ (Scheme 3B). On the opposite, the yield of $[^{13}\text{C}]\mathbf{2}$ was consistently higher but isotope incorporation was found in all cases lower compared to the $\text{K}_3\text{PO}_4/\text{DMF}$ conditions (Scheme 2B). A drop of an average of 9% is observed for all points: 19% vs 28% (for 0.5 equiv.), 32% vs 43% (for 1 equiv.), 47% vs 57% (for 2 equiv.), 55% vs 63% (for 3 equiv.) and 61% vs 68% (for 4 equiv.), thus supporting the hypothesis of isotope dilution due to the presence of Cs_2CO_3 .

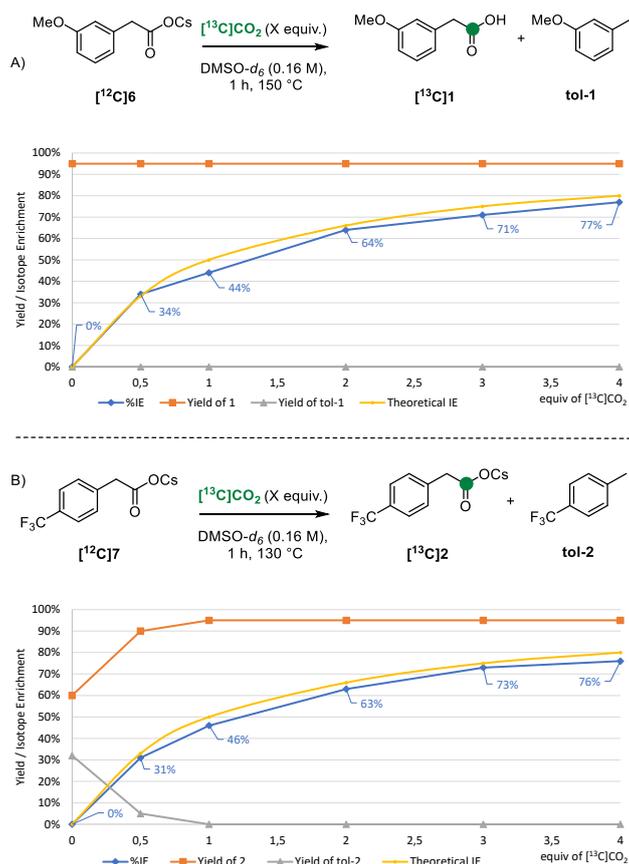
It has been showed by Yu's and König's groups that Cs_2CO_3 and K_2CO_3 can partially act as a source of CO_2 .^{22,23} In the photocatalytic carboxylation reported by Yu, 14% yield of desired acid product was observed when CO_2 was replaced by nitrogen in presence of 1.3 equiv. of Cs_2CO_3 . The report on dual visible-light–nickel catalysed carboxylation by König shows that in presence of K_2CO_3 (1 equiv.) up to 37% of carboxylic acid can be formed. Interestingly, the authors showed that optimization of the amount of K_2CO_3 has a negligible effect on the reactivity and the use of a balloon filled with CO_2 was necessary to increase the yield.



Scheme 4 Evaluation of isotope dilution of $[^{13}\text{C}]\mathbf{5}$, in presence of unlabeled carbonate base $\text{Cs}_2[^{12}\text{C}]\text{CO}_3$.

In order to quantify the contribution of Cs_2CO_3 towards isotope dilution, we designed an experiment using fully ^{13}C -labeled $[^{13}\text{C}]\mathbf{5}$ (99% ^{13}C incorporation), which was prepared by cyanation of benzyl bromide and hydrolysis starting from $\text{K}[^{13}\text{C}]\text{CN}$ (Scheme 4). When phenyl acetic acid $[^{13}\text{C}]\mathbf{5}$ (99% IE) was reacted under photocatalytic CIE conditions in presence of $[^{13}\text{C}]\text{CO}_2$ (3 equiv.) and unlabeled Cs_2CO_3 (1 equiv.) as the only source of $[^{12}\text{C}]\text{CO}_2$, $[^{13}\text{C}]\mathbf{5}$ was formed in good yield but in 82% IE, thus indicating an isotopic dilution of 18%. When the amount of $^{13}\text{CO}_2$ was reduced to 1 equiv., we observed a slight decrease in the yield and in isotopic enrichment to 76% IE (70% yield). The reaction performed without $^{13}\text{CO}_2$ unfortunately conducted to only traces of the acid making isotopic enrichment measurements impossible.

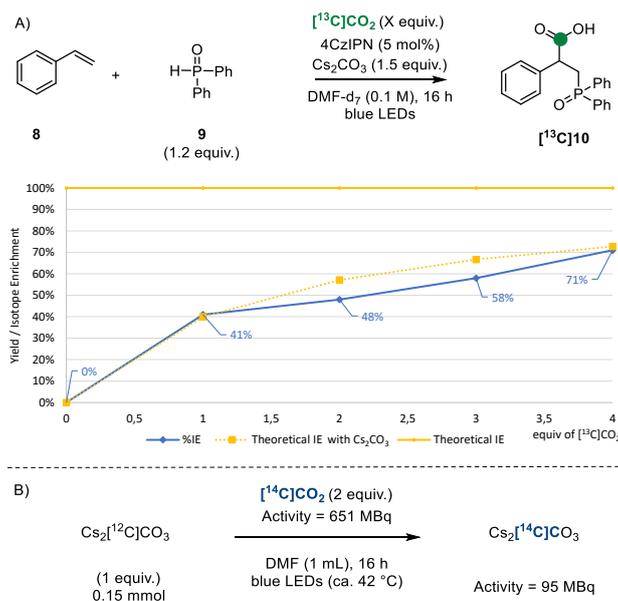
Next, we compared the effects of different $[^{13}\text{C}]\text{CO}_2$ stoichiometry on the thermal CIE.^{15,24} When cesium carboxylate $[^{12}\text{C}]\mathbf{6}$ was reacted with $[^{13}\text{C}]\text{CO}_2$ in DMSO at 150 °C (1h), we did not observe the formation of proto-decarboxylation by-product **tol-1** and the acid was obtained in all cases in > 95% yield, even in the absence of $[^{13}\text{C}]\text{CO}_2$ (Scheme 5A). These results are consistent with the absence of the carboxylic acid proton in the starting material, thus significantly reducing by-product formation. More importantly, in all reactions we observed that the desired acid $[^{13}\text{C}]\mathbf{1}$ was labeled in high % IE, which follows quite closely the theoretical expected values (34% to 77% instead of 33 to 80%).



Scheme 5 Effects of the stoichiometry of $[^{13}\text{C}]\text{CO}_2$ on the outcome of the thermal CIE procedure from carboxylates. Green colored circles denote the positions of the carbon atoms labeled. See supporting information for detailed conditions.

When electron-poor salt **[^{12}C]7** was reacted in analogous thermal conditions (at 130 °C, Scheme 5B), once more isotope incorporation was found to follow the theoretical CO_2 ratio at equilibrium and are consistent with **[^{13}C]1** (Scheme 5A). A slight decrease in the yields was observed using less than 1 equiv. of $[^{13}\text{C}]\text{CO}_2$ and the formation of the proto-decarboxylation product **tol-2** was detected : 5% with 0.5 of $[^{13}\text{C}]\text{CO}_2$ and 32% when it was replaced by nitrogen.

Finally, we decided to evaluate the effects of CO_2 stoichiometry on a carboxylation reaction that does not imply CO_2 isotope exchange. Between the myriad of reactions reported, photo-catalytic styrene carboxylations seemed pertinent. In particular, the work of Yu *et al.*²⁵ on phosphonocarboxylation of alkenes attracted our attention, as the procedure is reminiscent of the photo-redox CIE. It utilizes 4CzIPN as photocatalyst and generates β -phosphono carboxylic acids whose relevance could be of interest for ^{14}C -labeling.²⁶ Importantly, their optimized procedure utilizes 1.5 equiv. of carbonate base for the reaction to proceed. As shown in Scheme 6A, in presence of precise amounts of $[^{13}\text{C}]\text{CO}_2$, we observed the formation of desired product **[^{13}C]10** with a discreet amount of isotope dilution. Interestingly, in this transformation we have observed almost a complete equilibration between the ^{12}C -labeled carbonate and the $[^{13}\text{C}]\text{CO}_2$.



Scheme 6 A) Effects of the stoichiometry of $^{13}\text{C]CO}_2$ on the outcome of the phosphonocarboxylation of styrene. Green colored circles denote the positions of the carbon atoms labeled. B) Isotopic dilution of carbonate in presence of ^{14}C -labeled CO_2 . See supporting information for detailed conditions.

To verify whether partial isotope dilution occurs under anhydrous organic conditions (in dry DMF), we run a control experiment in presence of non-labeled $\text{Cs}_2\text{[}^{12}\text{C]CO}_3$ (1. equiv.) and radioactive $^{14}\text{C]CO}_2$ (2 equiv., activity 651 MBq) in DMF on a 0.15 mmol scale reaction. To mimic the photocatalytic temperature, the reaction was irradiated with blue LED (ca. 40 °C). After 16h, carbon dioxide was released and after dilution in water, scintillation measurements revealed the presence of 95 MBq in the basic phase.²⁷ This result (Scheme 6B) shows that ^{12}C -carbonate/ $^{14}\text{C]CO}_2$ dilution occurs under mild anhydrous conditions. This was further confirmed by a $^{13}\text{C]CO}_2$ experiment, where after dilution of the $\text{Cs}_2\text{[}^{12}\text{C]CO}_3$ in D_2O , a characteristic resonance signal was observed by ^{13}C -NMR corresponding to a ^{13}C -enriched carbonate species (singlet δ 160.5 ppm).²⁸ At present, we cannot exclude that substrate and reaction dependent effects might influence the dilution.

For applications in isotope labeling, the percentage of isotope incorporation is a major parameter to consider. In particular for ^{13}C , where the need for internal standards for MS qualification require high isotope purity (> 99%). Since a large variety of carboxylation reactions utilize a carbonate,²⁹ these results indicated that this has to be taken into consideration especially when high isotope incorporation is required.

In conclusion, we studied the precise impact of the number of equivalent of $^{13}\text{C]CO}_2$ on CIE of phenyl acetic acids. From these preliminary results, we found that this parameter, often neglected in standard carboxylation reactions, affects the outcome of the transformation both in terms of isotope incorporation and in some cases also product yield and byproduct formation. The utilization of carbonate bases might also be a parameter of selection, depending on the isotope utilized and the application contemplated. These results are also of interest in the field of non-isotopically labeled carboxylation, as oftentimes the setup of the addition of CO_2 onto the reaction is not standardized.

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K₃PO₄ (0.1 mmol, 1.0 equiv.), 4CzIPN (0.006 mmol, 6 mol%), substrate (0.1 mmol, 1.0 equiv.) were loaded into a microreactor, followed by the addition of 0.6 mL of dry DMF-*d*₇. ¹³CO₂ was added to the suspension with a RC Tritec carboxylation manifold. The mixture was then irradiated with two LED blue lights (455 nm) and stirred at 42 °C for 6 hours. A 1 M solution of 1,3,5-trimethoxybenzene in DMF-*d*₇ (50 μL, 0.5 equiv.) was added and the suspension was filtrated through a pad of cotton. The final filtrate was directly analysed by NMR with no further purification.
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Cesium salt of acids (0.1 mmol, 1.0 equiv.) was loaded into a microreactor, then 1 mL of DMSO-*d*₆ and ¹³CO₂ were added to the suspension, which was then heated at the indicated temperature for 1 hour. A 1 M solution of 1,3,5-trimethoxybenzene in DMSO-*d*₆ (50 μL, 0.5 equiv.) was added and the suspension was filtrated through a pad of cotton. The final filtrate was directly analysed by NMR with no further purification.
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