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## Sustainability spotlight

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The current efforts for CO<sub>2</sub> capture and sequestration require the development of new chemical processes devote to use this carbon dioxide as raw material. Carboxylation reactions are of key interest in Industrial Chemistry, requiring the use of CO<sub>2</sub> and reactant and allowing the incorporation of these carbon atoms into chemical products. We revise in this article the current situation of thermo-, photo-, and electrochemical processes for upgrading CO<sub>2</sub> via carboxylation reactions.

Our article is related to the following UN sustainable development goals: affordable and clean energy (SDG 7), industry, innovation, and infrastructure (SDG 9), climate action (SDG 13).



## ARTICLE

# Carboxylation reactions for the sustainable manufacture of chemicals and monomers

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Carboxylation stands out as one of the most versatile and viable routes for carbon dioxide fixation, a crucial chemical transformation essential for advancing capture technologies and fostering a sustainable industry. The carboxylic acids and derivatives produced through this process hold considerable interest for various sectors, including pharmaceuticals and polymers. Presently, most of these chemicals are derived from non-renewable resources, underscoring the imperative to develop sustainable pathways for their synthesis. The inherent stability of the CO<sub>2</sub> molecule, owing to its high oxidation state and linear configuration, poses significant challenges for activation. Diverse approaches, including photochemical, electrochemical, enzymatic, and thermochemical carboxylation have been explored. While noteworthy results have been achieved across these methods, substantial efforts are still required to facilitate their scalability. This review provides a comprehensive overview of each of these routes, elucidating their respective strengths and weaknesses. Emphasis is placed on thermochemical routes, given their proximity to potential industrial-scale application.

## Introduction

Carbon dioxide (CO<sub>2</sub>) is a non-toxic, non-combustible and non-flammable gas. It is a crucial component of Earth's atmosphere, playing a pivotal role in regulating the planet's temperature and sustaining life. However, the rapid and constant increase in atmospheric CO<sub>2</sub> concentration, primarily due to human activities (combustion of fossil fuels, deforestation, industrial processes, agriculture), has raised serious environmental concerns, including climate change, ocean acidification, and impacts on biodiversity. Thus, the decline in CO<sub>2</sub> concentration in the atmosphere may be considered one of the most significant challenges of the early decades of the 21st century.

Several alternatives have been proposed for its capture (absorption, adsorption, membranes, etc).<sup>1,2</sup> Although there are technically viable solutions, the economic viability of these technologies is subordinated to the development of efficient routes for the direct (i.e., not chemically altered) or indirect (i.e., transformed) use of this CO<sub>2</sub>.<sup>3</sup> Chemically, this compound provides an environmentally friendly and readily available source of carbon. Its use as a C1 building block in organic synthesis (emulating natural photosynthesis) is the most attractive alternative for a sustainable industry, combining the mitigation of climate change with reducing the need for fossil fuels as raw materials in various industrial applications.<sup>4</sup>

CO<sub>2</sub> is a linear and highly oxidized molecule, two properties that hinder its reactivity and restrict its utility as a reagent in chemical

industrial processes. However, CO<sub>2</sub> takes part in well-established and relevant processes, such as the synthesis of urea and its derivatives,<sup>5,6</sup> the salicylic acid production;<sup>7,8</sup> and, in the last years, the production of organic carbonates.<sup>9</sup>

Despite its low reactivity, CO<sub>2</sub> oxygen atoms show a weak Lewis basicity, while the carbon atom is electrophilic. Therefore, the reactions involving CO<sub>2</sub> are dominated by nucleophilic attachment at the carbon atom and reaction with electron-donating reagents.<sup>10</sup> In other words, CO<sub>2</sub> is necessarily reduced in any chemical carbon fixation reaction. Organic chemistry offers different reactions that fulfil these conditions, see **Scheme 1**, and the optimization of these reactions could open the range of possibilities for CO<sub>2</sub> utilization.

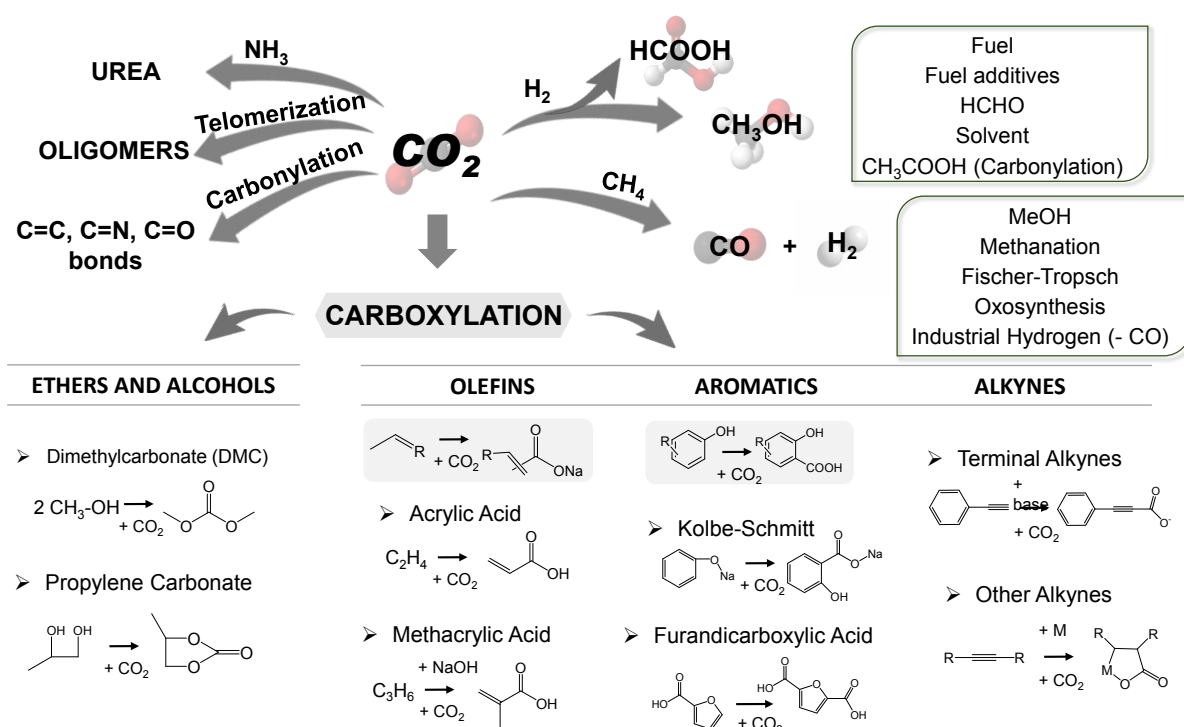
Almost all these alternatives are still at the lab scale, requiring strong efforts to optimize them and make them attractive for the scale-up. Because of the versatility and the high value of the chemicals that could be obtained, carboxylation, the topic of this review, is identified as one of the most promising routes for CO<sub>2</sub> chemical valorisation.

This work reviews the state of the scientific research on carboxylation using CO<sub>2</sub>, including electrochemical, photochemical, enzymatic, and catalytic approaches. General aspects about the mechanisms, reaction conditions, and the current advances and drawbacks of each alternative are discussed, highlighting those specific processes that have more potential for a near future scale-up to industrial applications. Catalytic carboxylation is examined in greater detail since, as will be discussed in the subsequent sections, it is the only pathway currently providing sufficient feasibility conditions to be considered as a potential sustainable route for the industrial production of chemical products.

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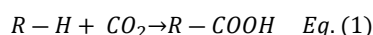
in this reaction has been constant, the current environmental  
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**Scheme 1.** Summary of the most promising chemical routes for the CO<sub>2</sub> valorisation, highlighting carboxylation, the objective of this review. Adapted from <sup>11</sup>

## General aspects of carboxylation

Carboxylation is a chemical reaction that involves the incorporation of a carboxyl group (-COOH) to an organic compound, typically in the form of a CO<sub>2</sub> molecule, as represented in Eq. 1:



Where R represents the organic molecule, and R-COOH is the carboxylated product.

The carboxylic group consists of a carbonyl group (C=O) and a hydroxyl group (OH) connected to the same carbon atom. This unique structure imparts several key properties, being one of the most versatile functional groups. The carboxylic group is highly polar, and the oxygen atoms can form hydrogen bonds, making carboxylic acids and related compounds excellent at solvating other polar molecules. When dissolved in water, they release H<sup>+</sup> ions, making them acids. Based on these properties, carboxylic acids are fundamental in various industrial sectors, including chemistry, biochemistry, pharmacology, and plastic.

The history of carboxylation can be traced back to the late 19th century when scientists began to explore the reaction of carbon dioxide (CO<sub>2</sub>) with various organic compounds. The Kolbe-Schmitt reaction, discovered by Hermann Kolbe and Rudolf Schmitt in 1860, marked an early milestone in carboxylation.<sup>12</sup> Although the interest

pressure has pushed an increasing interest in this reaction, not only from a chemical viewpoint but also from the biotechnological and industrial ones.

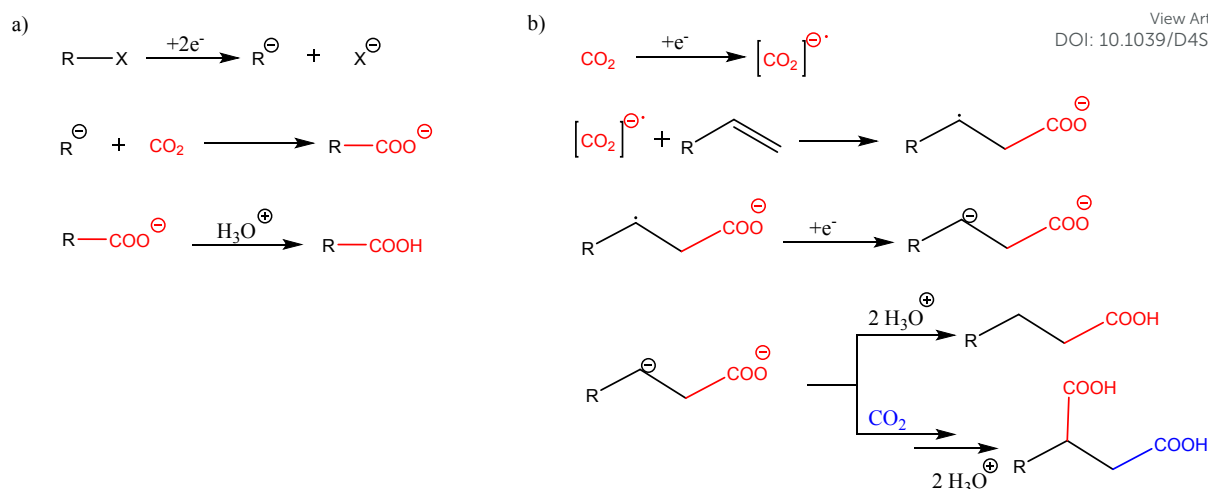
When CO<sub>2</sub> is participating in a reaction, the thermodynamic barrier ( $\Delta H \approx -400 \text{ kJ/mol}$ ) that must be overcome requires homogeneous or heterogeneous catalysts, energetic reaction partners, or energy inputs to the process. The different alternatives to surpass this energy barrier have led to approaches to carboxylation through electrochemical, photochemical, enzymatic, and catalytic pathways.

## Electrochemical carboxylation

Electrochemical fixation of CO<sub>2</sub> to generate carboxylic acids is a feasible method in which the redox reaction replaces the utilization of traditional reducing agents. It is performed at atmospheric pressure and room temperature, decreasing the reaction costs, and suppressing side reactions, i.e., obtaining a high atom economy, and being environmentally friendly. However, from the industrial viewpoint, the use of electrocarboxylation is not very promising, due to the difficulty of scaling up the results obtained in batch configuration or microreactors, usually performed in milligrams.

Electrocarboxylation can occur by two general pathways, as shown in **Scheme 2**. If the reduction potential of an organic substrate is



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DOI: 10.1039/D4SU00482E**Scheme 2:** Two different pathways in electrochemical fixation of carbon dioxide with C-C bond formation

more positive than that of  $\text{CO}_2$ , electrochemical reduction of the organic compound predominantly occurs, yielding anionic species. The subsequent nucleophilic attack on carbon dioxide yields the carboxylic acid. On the contrary, if the reduction potential of the organic molecule is more negative than that of  $\text{CO}_2$ , one electron reduction of carbon dioxide predominantly takes place, generating the radical anion of  $\text{CO}_2$  that reacts with the organic substrate. This second route typically occurs with alkenes.

Electrochemical carboxylation has received attention since the last decades of the XX century, concluding that it takes place efficiently when a sacrificial anode such as magnesium or aluminium is used as an anode.<sup>13</sup> After several studies with different organic molecules, such as alkenes, alkynes, enynes, aromatic and aliphatic halides, benzyl carbonates, aldehydes, and ketones, this configuration remains the optimum one.<sup>14-17</sup> The oxidation of the anode metal, resulting in the dissolution of the metal, proceeds at the anode during electrolysis and it prevents any species from oxidizing at the anode. Furthermore, the formation of a metal salt of the carboxylate ion with the metal ion generated from the anode is an essential factor for obtaining carboxylic acids in good yields. However, contamination due to these metals is a serious drawback from the viewpoint of green chemistry.

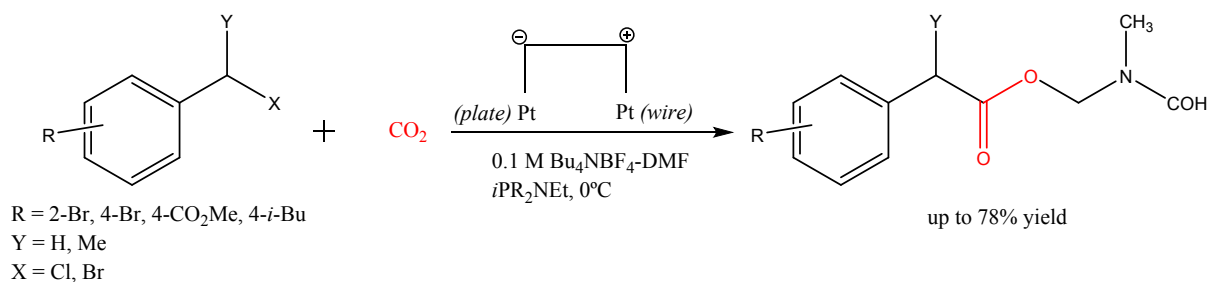
In the last decade, sacrificial anode-free electrocarboxylation was also demonstrated as promising.<sup>18,19</sup> For example, the carboxylation of benzylic halides using a quasi-divided cell (an undivided cell equipped with a much smaller counter electrode than the working

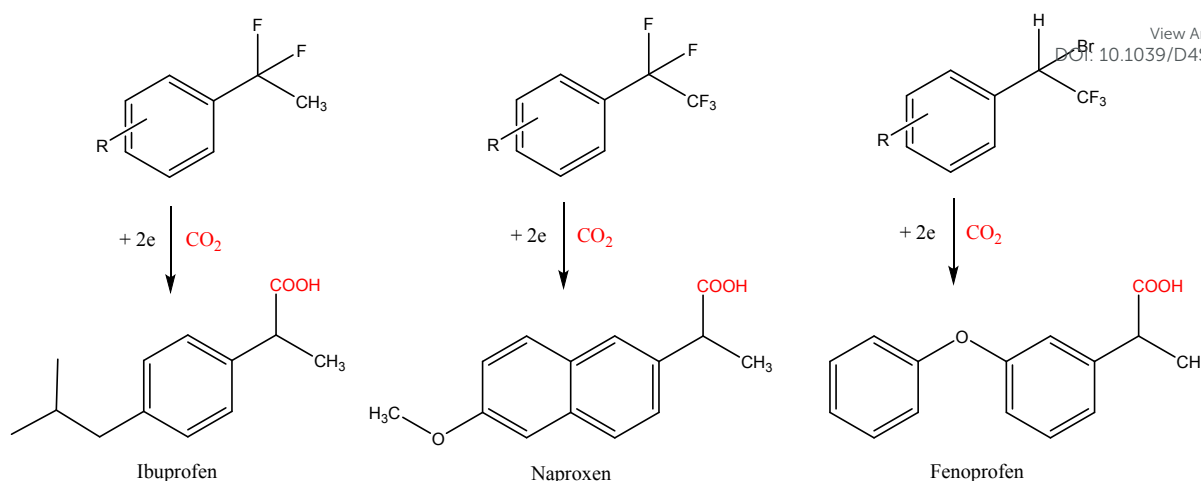
electrode) with a Pt plate cathode and a Pt wire anode yielded up to 78%, working at 0°C in a THF medium, see **Scheme 3**.

Considering these relevant results, this sacrificial anode-free reaction has been also tested using a microreactor, a configuration that has several advantages, such as high-speed mixing, a large surface-to-volume ratio, and precise temperature control. Once the electrode distance was optimized (20  $\mu\text{m}$ ), a 90% yield was reached working with a 0.6 mL/min flowrate.<sup>20</sup> Other studies extend this no sacrificial anode configuration to the C-H carboxylation of arenes, using graphite felt electrodes, and obtaining yields up to 87%.<sup>21</sup>

Among all the molecules tested, electrochemical fixation of  $\text{CO}_2$  is of great importance for synthesizing nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, ibuprofen, and their precursors and derivatives, see **Scheme 4**.

According to the last data available, ibuprofen was prescribed more than 16.5 million times in 2020, whereas naproxen total prescriptions overcome 8.1 million.<sup>22</sup> The classical synthesis of ibuprofen (developed in the 1960s) has six steps, including the use of toxic aluminium chloride.<sup>23</sup> This original method has been improved to the current three-step procedure (Hoechst process), based on cumene (coal and oil-derived compound) and with several drawbacks from the environmental viewpoint.<sup>24</sup> The traditional synthesis of naproxen (1976) was based on the traditional Friedel-Crafts alkylation, obtaining the naproxen after a four-step process using homogeneous catalysts (strong acid, NaOH, chlorides,

**Scheme 3:** Sacrificial anode-free electrocarboxylation of benzylic halides using a quasi-divided cell<sup>18</sup>

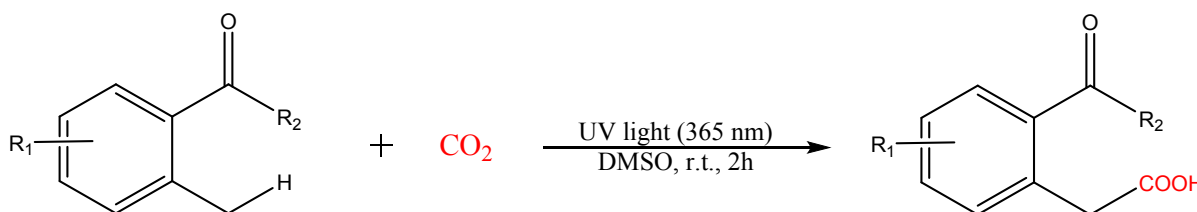


**Scheme 4:** Potential synthesis of NSAID from organic halides<sup>16</sup>

iodides).<sup>25</sup> In the last decades, the development of simpler, more efficient, stereospecific, and sustainable routes for these two drugs has been a hot topic in the pharmaceutical sector.<sup>26</sup> In both cases, electrochemical carboxylation offers promising results, being a friendly alternative that does not require stoichiometric metals or external reducing agents. As relevant results, Yang and coworkers

### Photochemical carboxylation

Photocatalytic carboxylation relies on the photochemical reduction of CO<sub>2</sub>, often using sunlight or artificial light sources. The



**Scheme 5:** Photoinduced carboxylation of *o*-alkylphenyl ketones with CO<sub>2</sub><sup>37</sup>

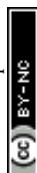
reached yields up to 87% of ibuprofen by electrochemical carboxylation of benzyl trimethylammonium bromide using commercially available carbon cloth and platinum on carbon (Pt/C) as cathode and anode, respectively, and bubbling CO<sub>2</sub> in a DMF solution (room temperature, -4.5V).<sup>27</sup> The electrocarboxylation route to synthesize naproxen has not been proposed since the asymmetric electrochemical carboxylation (required in this case because of the optical activity of naproxen) is one of the issues that remains to be investigated and resolved.<sup>19</sup> However, preliminary studies with aromatic ketones<sup>28,29</sup> and aryl epoxides<sup>30</sup> suggest that naproxen synthesis will be possible shortly.

Despite these promising results, the scale-up of electrocarboxylation faces several challenges related to the low CO<sub>2</sub> solubility at working conditions, mass transfer issues, the high cost of electrodes (more relevant in the sacrificial anode configuration), and, and more relevant nowadays, the involved energy costs. At this point, the wider extent of renewable energy opens a new window for this kind of processes

photocatalyst, typically a semiconductor material, absorbs photons and generates electron-hole pairs, which can then be used to drive the carboxylation. Photo-carboxylation is a very attractive approach because of its mild conditions, high activity, facile operation, and scalability. It can also be integrated into energy storage systems since using solar energy to convert CO<sub>2</sub> into energy-dense molecules, such as formate or other organic fuels, contributes to the development of renewable energy storage technologies. Thus, relevant contributions in this field have been reported in the last two decades, being summarized and analysed in very complete reviews.<sup>31-34</sup>

Photochemical carboxylation can occur via two mechanisms: 1) the insertion of CO<sub>2</sub> as an electrophile or, 2) the single-electron reduction of CO<sub>2</sub>, generating a radical-anion species that acts as a nucleophile.<sup>35</sup> For later, the reduction potential of CO<sub>2</sub> is quite high ( $E^0 = -2.21$  V),<sup>36</sup> which triggers the process of CO<sub>2</sub> assimilation under mild conditions. Nowadays, photocatalytic carboxylation has relevant advances for the selective functionalization of benzylic bonds (C(sp<sup>3</sup>)-H) but also C(sp<sup>2</sup>)-H, and C(sp)-H ones.

One of the most interesting studies was presented in 2015 by Murakami and co-workers, dealing with the photocatalytic carboxylation of alkylphenyl ketones to produce acylphenylacetic acids using LED lamp (365 nm, 2h).<sup>37</sup> This reaction occurs at room



temperature using DMSO solvent, and high yields (61-95%) are obtained, even when working with CO<sub>2</sub> atmospheric pressure, see **Scheme 5**. The reaction is so effective that no need for any catalyst or sacrificial reagent. Even if LED light is substituted by solar irradiation, a relevant yield of 72% is reached after 7 h. The most interesting application of this reaction is the production of 2,3-benzodiazepines. In this case, Cs<sub>2</sub>CO<sub>3</sub> catalyst is needed, an extended intermediate in some biologically active pharmaceutical molecules, including anxiolytics.<sup>38</sup> The broad market of this drug (valued at USD 2.96 billion in 2021<sup>39</sup>) justifies the high relevance of substituting the current petrol-derived synthesis process by a sustainable one.

Based on these works, this strategy has been extended to the photoinduced carboxylation of benzylic and aliphatic C-H bonds with CO<sub>2</sub> using aromatic ketone and nickel complex catalysts under UV light,<sup>40</sup> an interesting and selective route to obtain mono-carboxylated products even in those compounds that have more than one benzylic C-H bonds. However, using benzene solvent is a relevant drawback of these studies.

As to the single-electron reduction strategy, the synthesis of  $\alpha$ -amino acids from different amines, very relevant for the food sector, is one of the most interesting applications. The reduction potential of most transition metal photocatalysts is insufficient in this case, so these reactions require an organic photosensitizer *para*-terphenyl, which in addition to being an electron donor acts as a free radical precursor.<sup>41</sup> Preliminary analyses in batch configurations yielded up to 92% in 10 min, whereas the continuously bubbling CO<sub>2</sub> (**Scheme 6**) only provided a 30% yield after 2h irradiation, requiring the development of more active sensitizers or catalysts.

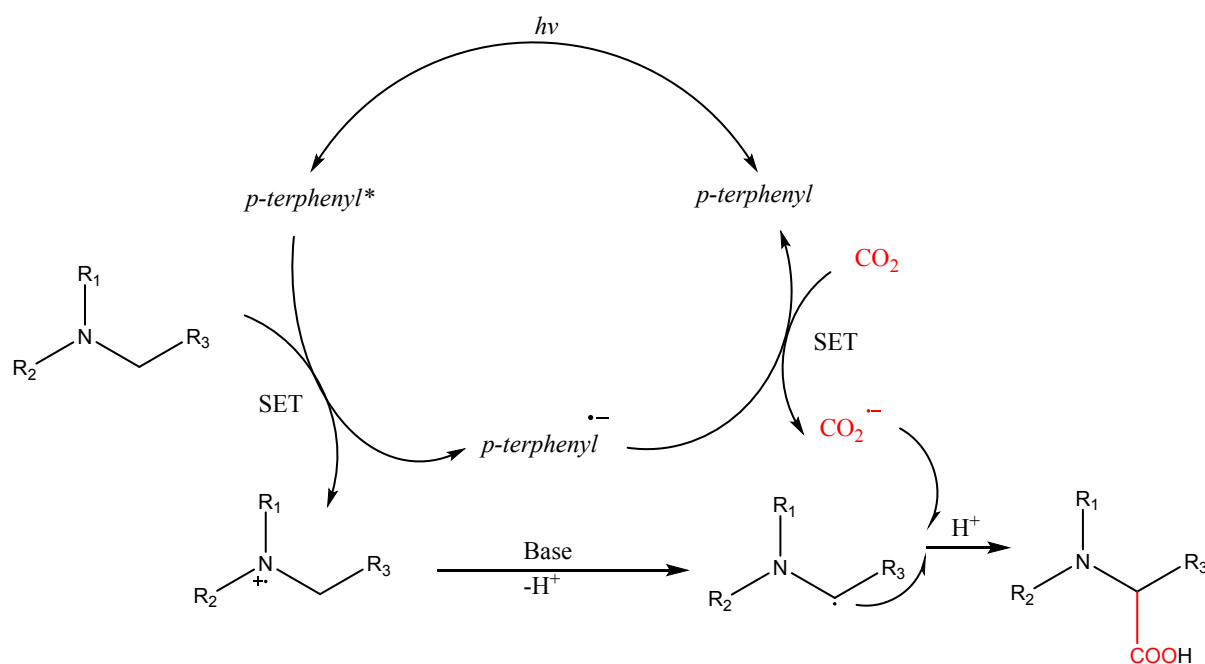
Modifications of this strategy define the hydrogen atom transfer (HAT), which allows for obtaining bioactive molecules, such as fenoprofen, naproxen, and flurbiprofen, from benzylic compounds,

but in moderate yields.<sup>42</sup> For example, 53% of fenoprofen, or 38% of naproxen are obtained using high-power blue LED light for 24 h in the presence of a photosensitizer, and complex catalysts, when the reaction is carried out in DMS at 0°C. This strategy has been deeply studied for many different chemicals, defining a huge number of catalysts (based on Ni, Ti, and Zn, among others). Despite the chemical interest and the deep mechanistic studies proposed in the literature, discussed in detail in,<sup>32</sup> these routes are not specifically defined for the synthesis of any valuable chemical, and the complexity, high price, and potential toxicity of chemicals involved hinder their scaling.

By combining SET and HAT steps, the photoinduced carboxylation concept has been also proposed for the carboxylation of alkyl halides at remote C(sp<sup>3</sup>)-H sites, activated and common C(sp<sup>3</sup>)-X (X = H, N) bonds, C(sp<sup>2</sup>)-X (X = H, N, (pseudo)halide) bonds and, in less extension, C(sp)-H bonds. The C(sp<sup>2</sup>)-X group includes the hydrocarboxylation of alkenes, imines, and aromatic halocarbons. In most cases, using stoichiometric amounts of organometallic reductant is indispensable to provide active metal hydride species, including Zn, Al, Ni, Ir, Pd, Ru, and Rh complexes and photocatalysts. These reactions are deeply studied in excellent reviews published on this topic.<sup>31-34</sup> Despite the high academic relevance of these works, the industrial interest in these reactions is quite low.

The carboxylation of alkynes (C(sp)-H) using CO<sub>2</sub> is a promising method to prepare  $\alpha,\beta$ -unsaturated acids. Acrylic acid is the most relevant example of this kind of acids, the industrial interest to develop a sustainable route for its synthesis being out of any doubt. This route has been studied since the 1980s<sup>43</sup> and the last studies offer interesting results using visible light with the aid of an iridium/cobalt dual catalysis, avoiding utilizing metallic reagents.<sup>44</sup>

To sum up, while photocatalytic carboxylation holds significant

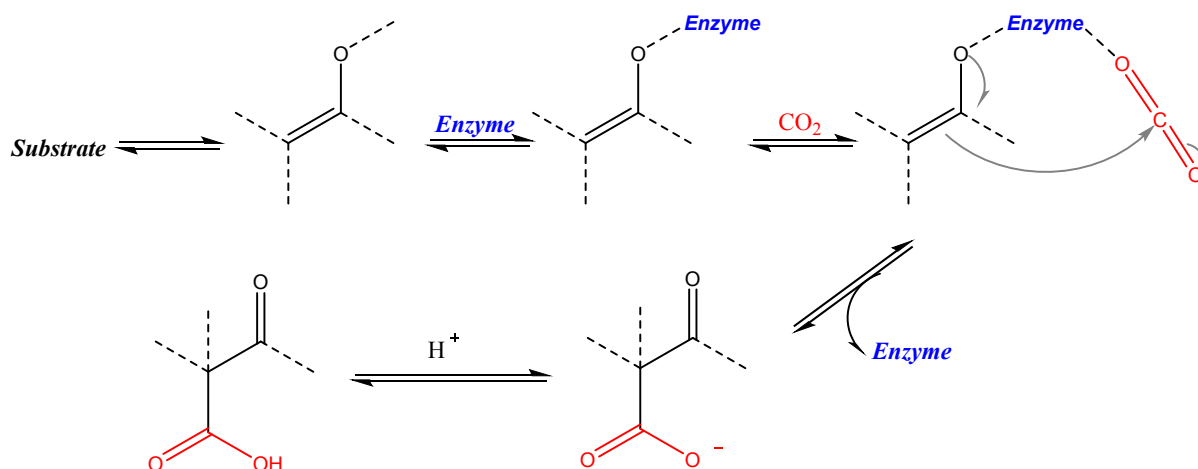


**Scheme 6:** Photocatalytic  $\alpha$ -carboxylation of amines with CO<sub>2</sub> in continuous flow<sup>41</sup> (SET = single-electron transfer)



promise, the efficiency of the process using UV light must be improved. Relevant results are reached with C(sp<sup>3</sup>)-X (X = N, H) bond

affinity permits working under low CO<sub>2</sub> concentrations and the broad portfolio of carboxylases allows different binding and activation



**Scheme 7:** General mechanistic steps of enzymatic carboxylations<sup>50</sup>

and styrene, whereas not with olefin without activation. The selectivity of carboxylation products and the stability of the photocatalysts are among the key areas of concern. Avoiding the utilization of noble-metal photosensitizer and organic solvents is in favour of these systems to meet the need for green chemistry. There are promising results for its application to many different substrates, but nowadays, photocatalytic carboxylation has more academic than industrial interest.

A possible scale-up of these routes presents several challenges, primarily due to the complexity and sensitivity of photochemical reactions. Requirements in terms of light penetration, distribution and stability are difficult to fulfil in large scale, requiring complex reactor designs (geometry, materials, cooling systems). Photochemical reactions are highly sensitive to variations in light intensity, wavelength, and reaction conditions, parameters more difficult to control at industrial scale, challenging the quantum efficiency. The energy and material costs are also very relevant, especially working with UV light.

## Enzymatic carboxylation

Enzymatic carbon dioxide fixation is one of the most important metabolic reactions as it allows the capture of inorganic carbon from the atmosphere. Natural enzymatic reactions also include carboxylation, and the knowledge of these mechanisms has suggested many studies to extend these procedures to biotechnology contexts.<sup>45-47</sup> Biocatalytic carboxylation is applied to overcome the most relevant obstacles of using CO<sub>2</sub> in a chemical reaction: its highest oxidation state and the difficulty to activate it, the CO<sub>2</sub> low concentration in nature that does not allow direct use of atmospheric air, and its reactivity with water that hinders the reactions in aqueous solution because of the formation of bicarbonates. The high efficiency of enzymes and the substrate

modes of CO<sub>2</sub> (including as a bicarbonate) and different attack modes of the carbon nucleophile, yielding high selective reactions.<sup>48</sup>

Despite the carboxylase used, almost all the enzymatic carboxylations follow the same general five-step mechanism,<sup>49</sup> shown in **Scheme 7**: (1) generation of an enol/enolate to create a nucleophile, (2) binding and stabilization of the enol/enolate; (3) accommodation and activation of CO<sub>2</sub>; (4) C-C bond formation via nucleophilic attack of the enol/enolate onto the carbon of CO<sub>2</sub>; and (5) potential follow up reactions such as cleavage of the product from the cofactor.

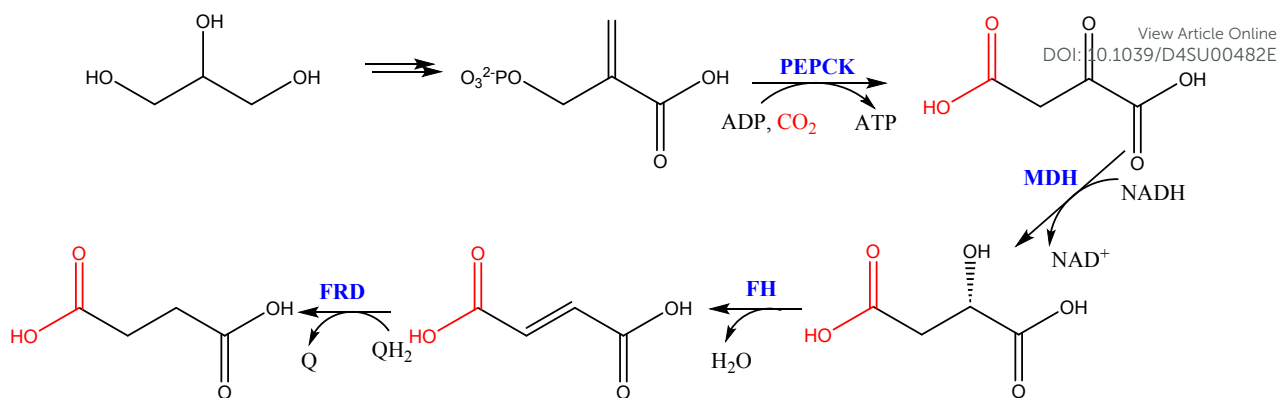
Since carboxylation is a thermodynamically controlled reaction, enzymatic carboxylation (both nature and synthesis) is accomplished either by reducing the required reaction energy or by shifting the reaction equilibrium. Strategies to render carboxylations more favourable include: (i) using high energy starting materials (electron-rich substrates); (ii) the activation of CO<sub>2</sub> by the interaction with the enzyme (carboxyphosphate, binding to biotin, coordination); (iii) supply of external reducing equivalents, such as NADPH or ferredoxins; and (iv) formation of low energy products, such as in the case of the carboxylation of phenolic compounds.<sup>50</sup>

Recent reviews detail the most relevant enzymatic carboxylations.<sup>50,51</sup> Maybe the most promising biosynthetic carboxylation for implementation at a medium scale is the fermentation production of succinic acid,<sup>52</sup> an important building block for the synthesis of polyesters, see **Scheme 8**. This route uses glycerol as a carbon source and fixes one CO<sub>2</sub> molecule by the carboxylation of phosphoenolpyruvate.

Enzymatic carboxylations have relevant drawbacks that discourage their implementation at a large scale. On the one hand, their low productivity and incomplete conversion, are mainly due to the high amount of energy that is required. Moreover, their sensitiveness since the operational window of enzymes is usually quite narrow







**Scheme 8:** Fermentative production of succinic acid from glycerol and CO<sub>2</sub>. (PEPCK = phosphoenolpyruvate carboxykinase; MDH = malate dehydrogenase; FH = fumarate hydratase; FRD = fumarate reductase; QH = quinol)<sup>52</sup>

(temperatures, solvent, pH, pressure, inhibitors). This directly clashes with the variable conditions that might occur in an industrial process. Moreover, the cost of these enzymes is quite high, and the recovery and reuse of enzymes and cofactors are crucial to render the process economically feasible. Each singular enzyme would require its specific immobilization strategy (encapsulation, adsorption, covalent immobilization) and, although some works evaluate the heterogenization of enzymes,<sup>48,53,54</sup> these procedures are far from being prepared for their scale-up.

Despite these limitations, biotechnology has several advantages concerning chemo-catalytic industry, such as the use of non-toxic compounds, and the soft conditions in terms of pH, temperature, and pressure. Considering these strong points, several authors have made relevant efforts to overcome the inherent disadvantages of enzymatic routes. Most of these studies have the objective of increasing the yield, affected by the thermodynamics but also by the irreversible production of bicarbonates since reactions occur in the aqueous medium. Different strategies for pushing the equilibrium to the target compounds are developed,<sup>55</sup> but most of these solutions are not applicable in the context of reaction engineering.

Working with temperature or pressure to increase the CO<sub>2</sub> available is difficult due to the irreversible deactivation that most carboxylases suffer under these conditions.<sup>56</sup> Few natural carboxylases can survive these conditions, but enzyme engineering has found an interesting research niche in generating variants of carboxylases with enhanced stability and activity.<sup>49,57</sup> However, the current state-of-art of these studies is far from being applied at an industrial scale and the high costs of these mutations limit the future application to high-value fine chemicals, the pharmaceutical sector being the main candidate. This fact reduces the application of enzymatic carboxylation as a large-scale capture and utilization (CCU) technology. An exception to this general situation is the pyrrole carboxylation, already tested in continuous flow at high pressure (65 bar), achieving a space-time yield of  $24 \pm 7 \mu\text{mol}\cdot\text{h}^{-1}$  using immobilized *B. metagerium* (Pyr2910).<sup>58</sup>

Another option proposed in the literature is product removal, with the subsequent displacement of the reaction equilibrium. This solution is useful when the carboxylic acid is not the final product but

an intermediate, such as in the synthesis of methionine (carboxylation + amination)<sup>59</sup> or when carboxylic acid derivatives form insoluble salts, such as in the case of benzoic acid. An interesting increase in conversion (from 37% to 97%) was observed by adding 50 mM of tetrabutylammonium bromide to the reaction medium.<sup>60</sup>

### Thermocatalytic carboxylation

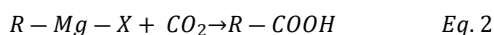
The chemical approach of CO<sub>2</sub> fixation is considered one of the most versatile strategies to produce carboxylic acids from quite different substrates, including alcohols, olefins, aromatics, and alkynes. The extensive bibliography about this topic has been analysed and discussed in several comprehensive reviews, analysing the main advances in terms of some of them structured based on the substrates,<sup>61-66</sup> the mechanisms,<sup>67,68</sup> and the catalysts.<sup>69-73</sup>

The success of a carboxylation reaction depends on various factors, including temperature, pressure, and the need for a catalyst or a precursor. Different carboxylation reactions require specific conditions, being mainly influenced by the reactivity of the organic compound (the acidity of the C-H bond). Thus, carboxylation can occur in the liquid phase, at soft temperatures using organometallic catalysts (homogeneous catalysis); or at higher temperatures, with a solvent-free configuration, using inorganic salts as precursors.

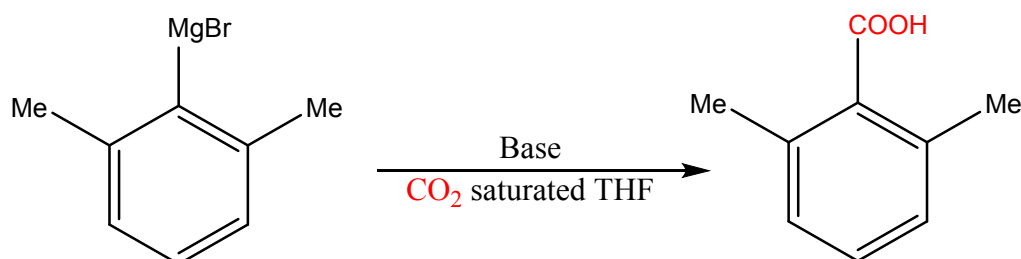
In general, thermocatalytic carboxylation can follow two opposite mechanisms, mainly depending on the specific reaction conditions and the nature of the organic compound involved: the nucleophilic addition and the electrophilic one. The first mechanism involves the attack of a nucleophile on the organic compound by CO<sub>2</sub>. Common nucleophiles include organometallic reagents, such as Grignard reagents or organolithium compounds. By the second mechanism, CO<sub>2</sub> is activated by a strong electrophile, often a metal catalyst. The metal site polarizes the CO<sub>2</sub> molecule, making it more reactive and susceptible to electrophilic attack by the organic compound. The Kolbe-Schmitt reaction is a typical example of this type of carboxylation. A first introduction of these two reactions is needed to identify those aspects that have focused the attention of the researchers in the last decades, trying to develop suitable reactions that can have a crucial role in a future sustainable industry.



**Grignard Carboxylation.** The Grignard reaction, discovered by Victor Grignard in the early 20<sup>th</sup> century (Nobel Prize in 1912), involves the addition of an organomagnesium compound (Grignard reagent) to a variety of electrophilic substrates, leading to the formation of new carbon-carbon bonds. This reaction is described by the following general equation, where R represents an organic group bonded to a magnesium atom, X is a halide or other leaving group, and R-COOH is the carboxylic acid:



The high reduction potential of Grignard reagents in the presence of



**Scheme 9:** 2,6-dimethylphenylmagnesium bromide carboxylation at room temperature, using different bases and THF saturated in CO<sub>2</sub>. Maximum yield of 77% obtained after 30 min using DBU (1,8-diazabicycloundec-7-ene) 50mol%<sup>74</sup>

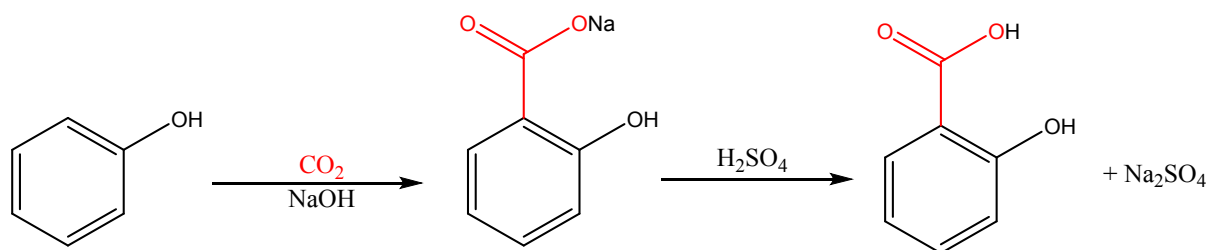
nucleophilic bases allows the formation of C-C bonds to spontaneously afford carboxylic acids from gaseous or solid-state CO<sub>2</sub>. The reaction at room temperature is one of the strongest points of this reaction. However, the limited availability of the parent reagents (these reactions are not compatible with sensitive functional groups, such as aldehydes, ketones, or nitriles, as they rapidly react with organolithium or Grignard reagents), as well as their chemical reactivity and complex manipulation makes CO<sub>2</sub> fixation by this method unattractive for industrial implementation. Some authors consider this mechanism to study possible carboxylations, mainly of aromatic compounds (**Scheme 9**), and relevant knowledge about mechanisms, conditions, and catalysts has been obtained from these studies.<sup>64</sup> However, the relevance of these studies is limited to the academic interest.

mixture of phenol and sodium under an atmosphere of CO<sub>2</sub>, see **Scheme 10**.<sup>7</sup> This first experiment was extended to the production of p-cresotic and o-thymotic acids, from p-cresol and o-thymol, respectively. In all the cases, this solid-state reaction was carried out by contacting dry CO<sub>2</sub> with alkali metal aryloxides or by passing CO<sub>2</sub> through the melted aryloxides. Schmitt reported in 1885 an improved version of the original procedure, working with high CO<sub>2</sub> pressures (80-130 bar), increasing the yields above 80%.<sup>75</sup>

One of the drawbacks of this method is that the reaction mixture is a waxy solid or a highly viscous liquid, which limits the contact surface between alkali metal phenoxide and CO<sub>2</sub>. Different studies propose the Kolbe-Schmitt reaction in solution or suspension, proposing polar

media such as phenol, ketones, dimethylsulfoxide (DMSO), or THF, among others.<sup>64</sup> However, it was demonstrated that solvents, although improving the reaction's rate constants by dissolving the reactants, would also allow the reverse reaction to take place because the final product was retained in the reactive phase.<sup>76</sup>

Most of the current Kolbe-Schmitt reactions are based on the optimized process patented by Marassé in 1893: the reaction is performed at high temperature, with a mixture of free phenol and anhydrous potassium, rubidium, or cesium carbonate under CO<sub>2</sub> pressure, the best results being obtained when using the caesium salt.<sup>77</sup> This reaction is limited by the requirement of a dry phenoxide since the presence of moisture can bind with the metal cation, thereby the coordination between CO<sub>2</sub> and alkali metal cation is prevented.<sup>78</sup>



**Scheme 10:** Synthesis of salicylic acid by phenol carboxylation

**Kolbe-Schmitt synthesis.** Kolbe-Schmitt is the oldest organic synthesis using CO<sub>2</sub>. Kolbe reported in 1860 the synthesis of 2-hydroxy-benzoic acid (also known as salicylic acid) by heating a

**Recent advances in thermochemical carboxylation.** This topic has garnered significant attention from the academic community in



recent decades, with numerous comprehensive reviews analysing the main conclusions of the hundreds of works published studying the carboxylation mechanisms of different aromatic compounds. Considering that most of these works adopt a more academic than practical approach, in this review they are only briefly analysed considering the different types of catalysts used, with specific sections discussing the reactions that generate more industrial interest, both in the present and next future.

**Base-mediated carboxylation:** The C-H bond carboxylation of aromatic heterocycles can be performed solely in the base medium under suitable reaction conditions.<sup>79</sup> In this preliminary study, using benzothiazole and 1.4 bar of CO<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub> was the most active base, whereas other compounds like NaOH, KOH, K<sub>2</sub>CO<sub>3</sub>, and K<sub>3</sub>PO<sub>4</sub> were not active. This reaction was studied for different hetero aromatics containing electron-withdrawing groups (EWG) or electron-donating groups (EDG), obtaining good yields.<sup>64</sup> Due to the instability of the synthesized carboxylic acids, the final compounds were received in their methyl esters form or, the carboxylation was combined with other steps. For these tandem configurations, other salts, such as K<sub>2</sub>CO<sub>3</sub> or tBuOLi were also very active.<sup>80,81</sup>

Alternatively, the carboxylation of phenol with CO<sub>2</sub> (1 atm) in the presence of NaOH and additive 2,4,6-trimethylphenol (TMP) was reported by Larrosa and co-workers, see **Scheme 11**.<sup>82</sup> The high yields obtained with several phenol derivatives (up to 90%) represent a relevant improvement of the original Kolbe-Schmitt configuration allowing the carboxylation at atmospheric pressure (easier to implement at high scale in combination with CO<sub>2</sub> capture techniques). Additionally, it offers other advantages since it does not generate water and the isolation of the phenoxide intermediate is not required. However, this reaction is inactive in the presence of EWG on the aromatic ring. The carboxylation of aromatic compounds was also proposed in the presence of organic bases, the diazabicyclo[5.4.0]undec-7-ene (DBU) being the most used one.<sup>83</sup> Excellent yields of salicylic derivatives (>99%) are obtained under atmospheric CO<sub>2</sub> pressure at soft temperatures.

All these studies consider the reaction with high acidic C-H or N-H bonds of aromatic heterocycles, concluding that the presence of highly energetic substances (strong base or highly reducing metal) is imperative for the construction of nucleophilic carbons, a needed step to react with the CO<sub>2</sub>. Thus, to perform the carboxylation of less acidic C-H bond (pKa>40) with CO<sub>2</sub> is very challenging. This problem

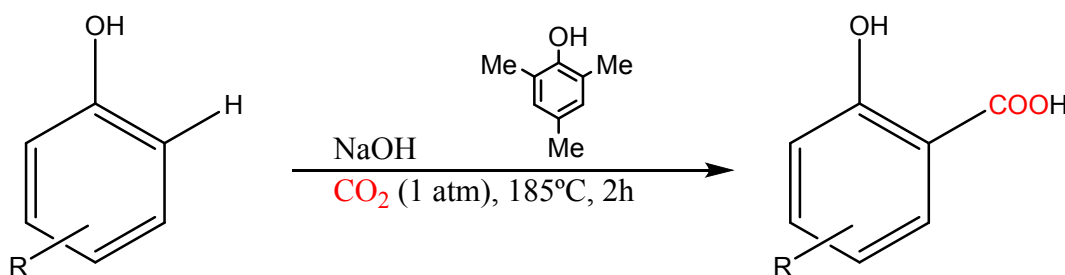
was solved in 2016, using molten Cs<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub>, obtaining good yields of furan-2,5-dicarboxylic acid (FDCA) when furfural was used as the reactant.<sup>84</sup> Considering the industrial interest of this compound for the polymer industry, an independent section of this review is dedicated to this reaction.

**Lewis acid carboxylation:** Transition metal catalysts have shown very high activity for several carboxylations, but the harmful reaction conditions and the corrosion of the reactor require an alternative solution. Lewis acid catalysts are good candidates to replace them since Lewis sites effectively activate the aromatic ring so that the CO<sub>2</sub> can be fixed. The origin of this approach is the Friedel-Crafts reaction, where a small amount of benzoic acid was obtained using aluminium chloride to introduce different functionalities in aromatics.<sup>85</sup>

After a broad screening of different aromatics with several Lewis and Bronsted acid catalysts,<sup>64</sup> only AlCl<sub>3</sub> performed the carboxylation successfully. However, the low reactivity of CO<sub>2</sub> and the high reactive character of organoaluminium (intermediate in the reaction) afforded low yields, with the formation of undesired products. This drawback was solved using an Al<sub>2</sub>Cl<sub>6</sub>/Al system.<sup>86</sup> The role of additive Al was defined as very crucial to direct the reaction for the selective formation of the carboxylic acid by scavenging the HCl to produce AlCl<sub>3</sub>, which further participated in the reaction and assisted the carboxylation process. The effect of temperature, CO<sub>2</sub> pressure, the amount of catalyst, and the reaction mechanisms was investigated thoroughly, obtaining in all the cases softer conditions than those reported for basic systems. Experimental and theoretical studies based on the density functional theory (DFT) concluded that the activation of CO<sub>2</sub> takes place by super-electrophilic AlCl<sub>3</sub> followed by a reaction with aromatic compounds. Based on these results, other authors proposed the use of organic catalysts with Lewis acidity, and good results were reached with different dialkyl aluminium chlorides (Me<sub>2</sub>AlCl, Et<sub>2</sub>AlCl), at room temperature and medium CO<sub>2</sub> pressure (30 bar).<sup>87,88</sup> AlCl<sub>3</sub>-derived catalysts are the most studied ones, and only a few references to other Lewis acids are reported, as discussed by Rawal and coworkers.<sup>64</sup>

As a common drawback of this approach, carboxylation catalyzed by Lewis acids is moisture sensitive, so it must be performed in inert atmosphere, reducing the potential for a possible scale-up.

**Transition metal carboxylation:** The carboxylation using metals is very interesting since the coordination of CO<sub>2</sub> with metal alters the



**Scheme 11:** Phenol carboxylations using TMP additive<sup>82</sup>



molecular and electronic distribution of CO<sub>2</sub>, leading to significant changes in its reactivity and, subsequently, allowing carboxylations at mild conditions.<sup>64</sup> Metal catalysts allow the direct synthesis of aryl carboxylic acids and, even more relevant, the site-selective C-H carboxylation, obtaining relevant improvements in terms of atom economy and reaction efficiency. These metals are also relevant to produce acrylic acid by ethene carboxylation.

The first-row transition metal ions are easily available and their price is quite low; 3d transition metal-based catalysts are the most active ones, but 4d and 5d can be used under milder conditions.

The earliest coupling reaction of CO<sub>2</sub> and ethene (the 1980s) already considered the use of nickelalactone, using donor ligands to be potential activators of the β-hydride elimination reaction, see **Scheme 12**. This reaction has been the basis for an extensive bibliography about mechanisms, activators, and conditions to optimize the yields obtained. Other transition metal complexes have also been utilized for the acrylate formation, highlighting molybdenum, tungsten, palladium, platinum, and, with significantly lower relevance, iron, and ruthenium. All these contributions are discussed in a very comprehensive review.<sup>69</sup> Group VI metal centres induce more facile oxidative coupling of CO<sub>2</sub> and ethene than Ni, which has a direct influence on the reaction conditions. Thus, carboxylation can occur at ambient temperature and pressures with Mo/W complexes, whereas high gas pressures are required with Ni.

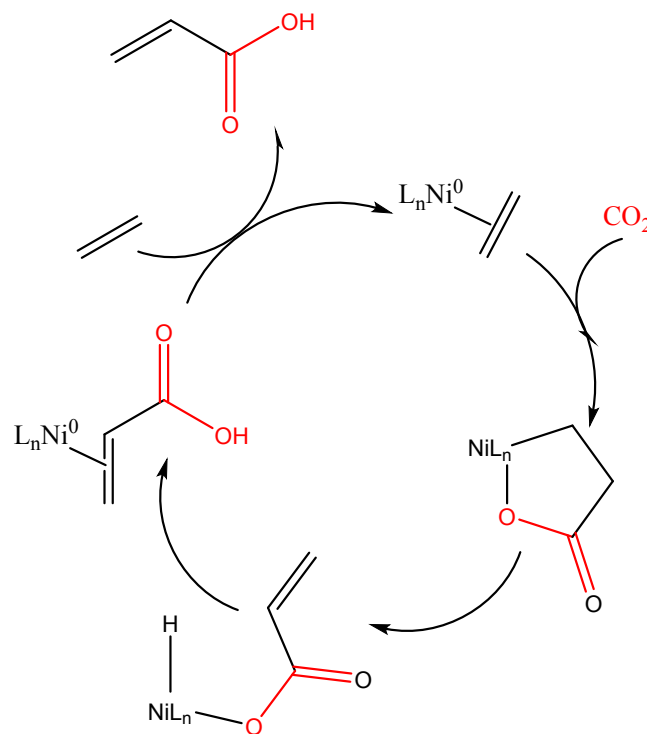
As for the carboxylation of aryl compounds, copper is one of the most used metals. In the first studies, the in situ generation of copper complexes between CuCl and organic precursors was proposed, using tetrahydrofuran (THF) or dimethylfurane (DMF) solvents and mild temperatures.<sup>89,90</sup> Other authors demonstrate a high activity of gold(I) complexes containing strong donor ligands, for different aromatic systems, even when C-H bonds are not very acidic (pKa < 30.3).<sup>92</sup> To a lesser extent, many other transition metals have been considered, including Ag, Zn, or Ru.<sup>70</sup>

The use of transition metal catalysts is an efficient strategy to obtain high activity for many different substrates (high functional group tolerance), providing high selectivity at mild conditions. However, organic solvents, basic salts, and organic precursors are needed to stabilize the complexes that activate the CO<sub>2</sub>, resulting in difficult methodologies that are not easy to apply on medium or large scale. Maybe the most promising future of this strategy is photocatalysis, i.e., using these transition metals but obtaining the required energy from a light source.

**Heterogeneous catalysis: MOFs.** One of the requirements of Green Chemistry is the use of heterogeneous catalysts instead of homogeneous ones. Working with solid catalysts has many advantages, including simple product purification, recyclability, etc. The development of optimum catalysts for carboxylation must consider not only the activity, selectivity, and stability, but also the cost and the moisture sensitivity. The special characteristics of metal-organic frameworks (MOFs) are very interesting, and these catalysts have attracted a lot of attention.<sup>93,94</sup> These materials have a well-

structured organic frame (structural flexibility, porous nature, tunability size) enriched in metal ions and ligands that introduce Lewis acid and basic character.

Liu and colleagues reported the first study about the carboxylation of terminal alkynes with CO<sub>2</sub> to propiolic acid by using Ag@MIL-101, obtaining high efficiency as a bifunctional material, for the CO<sub>2</sub> capture and the carboxylation at 100°C and atmospheric pressure.<sup>95</sup> The use of heterogeneous catalysts allowed its recovery and reuse.



**Scheme 12:** Ni mediated catalytic cycle as discussed by Fisher and coworkers<sup>91</sup>

This study demonstrates that this MOF can be recycled up to five times without any significant change in the catalytic ability or the structure. The use of Cs<sub>2</sub>CO<sub>3</sub> is required to abstract a proton from C(sp)-H bond, leading to the formation of silver acetylide followed by the insertion of adsorbed CO<sub>2</sub> into the Ag-C bond to form carboxylic acid. This study paves the way for other researchers, proposing the use of this MOF with Ag, Cu, and Pd@Cu nanocrystals.<sup>96-100</sup> In all the cases, terminal alkynes (hetero aromatics and aromatic ring consisting of EWG or EDG) were used as substrates. Other MOFs, such as UiO67(dcppy) and ZIF-8 have been also proposed in preliminary approaches, using organic solvents and always at a very small scale.

The optimum situation implies the use of metal-modified MOFs that could be active, selective, and stable in aqueous-phase carboxylations or solvent-free conditions. These aspects are crucial for establishing carboxylation as a green route to obtain carboxylic acids at an industrial scale.



## Main Industrial Processes Involving Carboxylation

Carboxylic acids and their derivatives are used in the formulation of solvents, surfactants, and emulsifying agents due to their amphiphilic nature. This property is crucial in the creation of stable emulsions and the development of cleaning products and cosmetics. Carboxylic groups are commonly incorporated into drug molecules because they enhance the drug's solubility, influence its adsorption and distribution in the body, and participate in specific interactions with target proteins. Aspirin (acetylsalicylic acid) is the most relevant example of a carboxylic-derived drug. Its production includes a key step of CO<sub>2</sub> incorporation, being the reference of carboxylation at an industrial scale.

For the next future, carboxylation reactions hold significant potential for reducing the environmental impact of chemical processes. The Principles of Green Chemistry, which focus on designing sustainable and environmentally friendly reactions, can be applied to carboxylation: (1) **Atom Economy**: Carboxylation reactions often lead to the incorporation of CO<sub>2</sub> into valuable products, maximizing the use of starting materials and minimizing waste; (2) **Renewable Feedstocks**: CO<sub>2</sub> is a renewable feedstock that can be harnessed to create valuable organic compounds, reducing the reliance on fossil-based resources; (3) **Reduced Hazardous Substances**: By using CO<sub>2</sub> as a feedstock and employing mild reaction conditions, carboxylation can reduce the generation of hazardous waste and by-products.

Although the academic interest in carboxylation is very relevant, only a few chemicals have real potential to be suitable for scaling in a next future. This selected group includes pharmaceutical chemicals, such as ibuprofen and naproxen, that could be obtained by enzymatic routes, and green polymers that can be obtained by thermocatalytic strategies. This group includes polyacrylic acid and polyethylene furanoate (PEF). Polyacrylic acid and its derivatives are used in a range of applications, from superabsorbent materials in diapers to drug delivery systems. Acrylic acid can be synthesized through carboxylation of propylene with CO<sub>2</sub>. PEF is the green substitute of polyethylene terephthalate (PET), one of the most used polymers, a basic material for plastic bottles and packaging. The last part of the review is dedicated to summarizing the main aspects of these processes from an engineering perspective.

### Salicylic acid

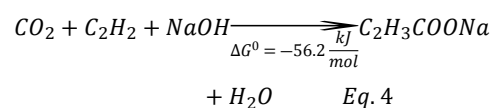
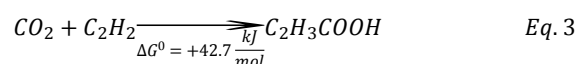
The production of salicylic acid is the main exponent of an industrial application of the Kolbe-Schmitt reaction. In this process, dry sodium phenoxide obtained from phenol and soda is contacted with CO<sub>2</sub> under 50 bar and at temperatures around 100°C. Once approximately one molar equivalent of CO<sub>2</sub> is absorbed, the temperature is raised and held at 150-160°C for several hours to fulfil the reaction. The final "technical-grade" salicylic acid is obtained after successive purification steps (filtration, precipitation, separation, drying) including acidification with sulfuric or hydrochloric acid.

According to the latest reports, the salicylic acid market was valued at \$431.1 million in 2020 and is projected to reach almost \$890 million by 2030.<sup>101</sup> Large-scale use of this compound in the pharmaceutical sector is the major driver of this market in Asia-Pacific and Africa areas, whereas a more stable situation is considered for Europe and North America, where its softer increase is mainly due to the use of salicylic acid in the food & beverage industry for packaging.

### Acrylic acid

Acrylic acid is a crucial monomer in the polymer industry and a relevant intermediate in producing paints, adhesives, and hygienic products, among other examples. Currently, this acid is industrially produced at a multimillion-ton scale by a two-step process using propylene as raw material. This route has several drawbacks, highlighting the high corrosive conditions and the low E-factor of this pathway, yielding acetic acid and CO<sub>2</sub> as subproducts. Ethylene carboxylation has emerged as the main sustainable alternative to this process, receiving relevant attention from the scientific and industrial communities.

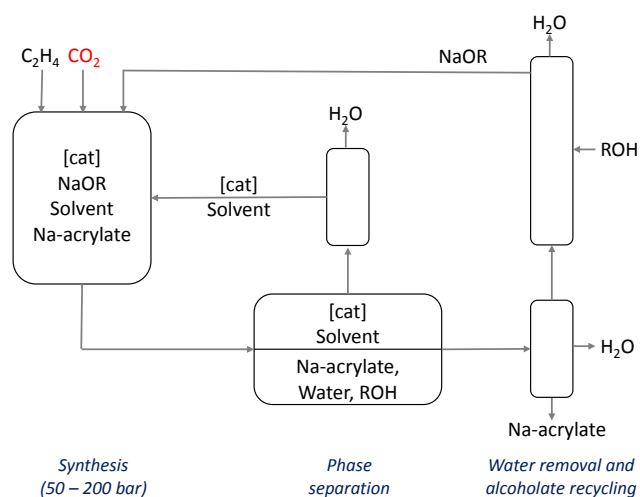
This reaction was reported for the first time in 1987, using homogeneous iron salts as metal catalysts. This preliminary approach was performed at -78°C, using THF solvent, obtaining a metal lactone complex that stabilizes the ethylene, allowing the reaction with the CO<sub>2</sub> stream (1 bar).<sup>102</sup> This pioneering study was rediscovered in the first decade of the 21st century, with a relevant number of studies that deepen the reaction conditions, the mechanism, and possible catalysts. Mo and W complexes were identified as the optimum homogeneous catalysts, the carboxylation being possible at room temperature and pressure,<sup>103,104</sup> whereas more severe conditions are required with Ni.<sup>105</sup> THF is the most studied solvent, and, in all the cases, a base is required to stabilize the intermediates since, due to thermodynamics, acrylic acid is unfavourable to obtain, and the equilibrium must be shifted,<sup>106</sup> see equations 3 and 4.



The use of NaOH itself is not recommended because of the formation of a stable carbonate (NaHCO<sub>3</sub>) that is significantly more favourable from the thermodynamics point of view ( $\Delta G^0 = -826.4 \text{ kJ/mol}$ ). Therefore, this reaction requires sodium bases that are basic enough to produce the sodium acrylate but not to form irreversible carbonates. In addition, these bases should be capable of regeneration by using NaOH. Promising results are reported with certain sodium phenolates and alkoxides (NaO-*t*-Bu, NaO-*i*-Pr) using homogeneous nickel or palladium catalysts.<sup>62</sup>



Based on these results, Manzini and colleagues proposed the first continuous process using amide solvents, NaO-iPr, and Pd-catalysts at 145°C, see **Scheme 13**.<sup>107</sup> In this concept, water is added to a continuous stream from the reactor after depressurization to separate the sodium acrylate from the catalyst. The alcohol that is formed in the reaction can be distilled from the product phase and recycled with NaOH, leaving the pure sodium acrylate behind. The catalyst and the organic solvent could also be recycled, improving the sustainability of the process.



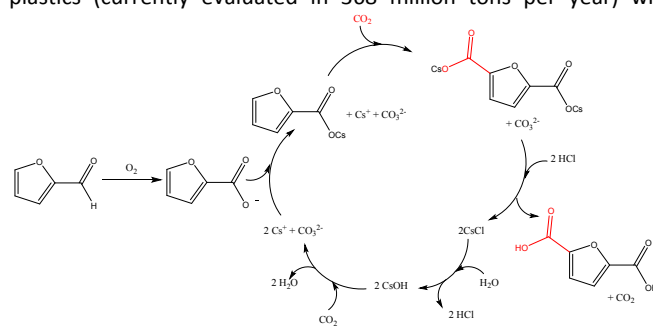
**Scheme 13:** Process concept for the Pd-catalyzed synthesis of sodium acrylate from ethylene and CO<sub>2</sub> using amide solvents and NaO-iPr<sup>107</sup>

This route is an interesting alternative to propylene oxidation. From an economic perspective, the CO<sub>2</sub> route could result in significant raw material savings, mainly because of the increase in ethane cracking that produces ethylene and only minor amounts of propylene. Ethylene can also be obtained by ethanol dehydration, and the production of ethanol by sugar fermentation is a well-known process, already established at an industrial scale. Thus, this route has a double benefit from the sustainability point of view, capturing CO<sub>2</sub> and using a biomass-derived compound as the raw material. However, the overall energy consumption must also be considered since the CO<sub>2</sub> route is a net steam consumer (base regeneration) whereas propylene oxidation produces steam (highly exothermic reaction). Moreover, this approach still has significant drawbacks, highlighting the low turnover numbers (<0.1 h<sup>-1</sup>), the stoichiometric amount of base required, and the use of solvents.<sup>108</sup>

### Furandicarboxylic acid

Carboxylation deserves special attention as a sustainable pathway for producing polymer precursors, especially for plastics. The current plastic industry heavily relies on petroleum, resulting in significant environmental impacts throughout their lifecycle, including their production and their long life as wastes because of their slow biodegradability. A transformation is imperative for this sector, with

an ambitious goal of substituting 50% of these petroleum-derived plastics (currently evaluated in 368 million tons per year) with



**Scheme 14:** Overview of the reaction steps for the conversion of furfural to FDCA using the carboxylation route<sup>65</sup>

renewable and biodegradable alternatives over the next 25 years.<sup>109</sup>

One of the main candidates to lead this transition is polyethylene 2,5-furandicarboxylate (PEF), the renewable substitute of the most used plastic (polyethylene terephthalate, PET). The most advanced route to produce FDCA converts edible fructose into 5-hydroxymethylfurfural (HMF) and oxidizes it to FDCA. This route is treated as a benchmark process, with plans for a 5kt/a pilot plant operational in 2023.<sup>110</sup> However, a future scale-up of this approach is restricted by the high price of HMF, conditioned by the use of edible biomass and the purity requirements.

An alternative route to produce FDCA is based on furfural (FFL), the cyclic aldehyde obtained by the acidic hydrolysis of pentoses, i.e., with a non-edible origin. This route is a two-step process involving a first partial oxidation of furfural yielding furoic acid and a second step that can imply three different catalytic routes: (1) disproportionation (Henkel reaction), (2) carbonylation, or (3) carboxylation. The first option has a limited selectivity because of the simultaneous production of furan. The second one is a complex process using non-sustainable chemicals. Thus, furoic acid carboxylation is the most promising one according to the principles of Green Chemistry.

Considering the current state of art, the acidic approach is discarded since poor yields are obtained<sup>86</sup> and, despite the ambient temperature, high CO<sub>2</sub> pressures are needed, making it not possible to implement this reaction in a possible capture system. The complexity of the process also discourages the transition-metal strategy, although some studies are proposed using Cu and Pd salts.<sup>63</sup>

The base-mediated furoic acid carboxylation was first reported in 2016, as a particular application of the Kolbe-Schmitt reaction.<sup>84</sup> The carboxylation was studied in a free-solvent configuration, using Cs<sub>2</sub>CO<sub>3</sub> as a melting salt, as shown in **Scheme 14**. Further studies were focused on the study of the mechanism, mainly to understand the role of Cs<sup>+</sup>.<sup>65</sup>

Dick and co-workers have tried the first study in a fixed-bed flow reactor (mole-scale), yielding almost 90% of FDCA working at 260–285°C and with 8 bar of CO<sub>2</sub>.<sup>111</sup> To complete these studies, Wang and colleagues, in a very complete study, optimized the reaction



conditions, concluding that maximum yield is obtained with a furoic acid:salt molar ratio of 3:5 (higher excess reduces the activity), and at 270°C (higher temperatures promote decomposition).<sup>112</sup>

The substitution of  $\text{Cs}_2\text{CO}_3$  is of key interest because of economic reasons. Preliminary results suggest that, modifying the conditions, this salt could be substituted by  $\text{K}_2\text{CO}_3$ .<sup>113</sup> This strategy indicates a relevant role of formates, also corroborated by DFT studies.<sup>114</sup>

Another strategy considers the FDCA production by the simultaneous reaction of HMF and furfural, considering that both aldehydes are obtained in the same hydrolytic process. This approach allows the production of more than 71% of FDCA after 36 h at 260°C, using a bimetallic-lignin complex in the presence of  $\text{Cs}_2\text{CO}_3$ .<sup>115</sup>

All these studies demonstrate the promising future of this perspective. However, relevant drawbacks must be overcome, including the narrow range of reaction conditions to produce the FDCA preventing the decomposition, the development of effective heterogeneous catalysts, the optimization of reaction conditions, and a relevant cost reduction.

According to the last data available, in 2022, the market volume of furfural amounted to over 365.24 metric tons worldwide.<sup>116</sup> By the year 2030, it is forecast to grow to nearly 505.41 metric tons. This global production capacity is still far from substituting the current PET demand, estimated at almost 35.3 million metric tons,<sup>117</sup> but the development of an efficient process of furfural valorisation can push its production. Increasing the furfural production can have a direct impact on the economy of the process since, according to preliminary studies of Dubbink and coworkers, a cost cut of 75% is required to meet the target FDCA selling price for a profitable design.<sup>118</sup>

### Main challenge for future green carboxylations

All advanced studies about carboxylations (already industrially implemented or with an expected near scale-up) use high-purity  $\text{CO}_2$  (specially manufactured for this purpose) and, in general, at high pressure. This makes the processes costly and environmentally unsustainable. Therefore, the greatest challenge is adapting these processes to use  $\text{CO}_2$  captured directly from the atmosphere (DAC) or from industrial processes that produce it (exhaust gases, CCU).

The significant number of possible technologies for capturing  $\text{CO}_2$  from exhaust gas as well as their relevant technical and economic drawbacks that difficult their industrial implementation are well known, and its analysis is out of the scope of this work.<sup>119</sup> Carboxylation highlights as one of the most promising alternatives for the  $\text{CO}_2$ -capture-and-utilization technologies (CCU). Although those capture technologies that are affected by technical limitations (too high flowrate, low concentration, potential catalytic impurities) need to be optimized, the development of an efficient valorisation process could be the impulse required for some others to reach the required economic feasibility.

Another option is direct air capture (DAC) of  $\text{CO}_2$ , which involves extracting  $\text{CO}_2$  from the atmosphere.<sup>120</sup> While this approach addresses the  $\text{CO}_2$  directly relevant to the environment, it also presents significant barriers to the large-scale implementation, mainly related to the low concentration of  $\text{CO}_2$  in the air, requiring highly efficient, advanced and costly capture equipment.

With this scenario, carboxylation using atmospheric or captured residual  $\text{CO}_2$  is far from becoming a reality, and there are no scientific articles that consider this configuration. Therefore, the analysis of the potential consequences or additional difficulties of using these streams remains incomplete.

### Conclusions and Outlook

The demand for  $\text{CO}_2$  sequestration to value-added products is high, and carboxylation stands out as one of the most attractive options to obtain commodity chemicals. Carboxylic acids or their esters play a crucial role in the synthesis of relevant biologically active molecules, polymers, and natural products, many of which are currently produced using non-renewable resources.

The high stability of the  $\text{CO}_2$  molecule, attributed to its highest oxidation state and linear configuration, introduces relevant thermodynamic and kinetic limitations. Activating  $\text{CO}_2$  is challenging, and various techniques have been developed to overcome this drawback. These include energy activation through electrochemical and photochemical approaches, biological and chemical activation, using enzymes and catalysts, respectively; or a combination of both philosophies, utilizing chemical catalysts to improve the electrochemical or photochemical route. These routes have been well documented over the last few decades, proposing and optimizing procedures for the synthesis of hundreds of chemicals.

Despite the wealth of research studies, the large-scale transformation of  $\text{CO}_2$  into value-added products remains a significant challenge. While these studies are academically interesting, their limited industrial application is due to various reasons hindering economic feasibility. These include the difficult scaling of some configurations, the use of complex, non-commercial catalysts, the need for too harsh conditions and toxic compounds, and the low yields obtained, mainly for asymmetric carboxylations.

From an industrial viewpoint, catalytic routes are the most promising ones. In fact, this is the only methodology already implemented on a large scale (production of salicylic acid) and it is expected that this approach will be extended to the sustainable production of other compounds, such as renewable polymers.

Despite notable recent advances, common drawbacks that must focus the research on this field for the next future include the development of cheap and sustainable (metal-free if possible) catalysts, active for carboxylations under atmospheric pressure of  $\text{CO}_2$  and mild temperature. Sustainable methods, such as photocatalysis and electrocatalysis still have a long way to go before being scalable whereas, nowadays, enzymatic and transition metal-



catalyzed carboxylation are the most suitable configurations from the industrial viewpoint.

The most ambitious goal in this field is the development of industrially viable carboxylation processes working with CO<sub>2</sub> captured either directly from the atmosphere or from waste streams.

### Conflicts of interest

There are no conflicts to declare

### Acknowledgements

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No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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