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Transition Metal-Catalyzed Carboxylation reactions with Carbon Dioxide

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Abstract: Driven by the inherent synthetic potential of CO2 as an abundant, inexpensive and renewable C1 chemical feedstock, the recent years have witnessed renewed interest in devising catalytic CO₂ fixations into organic matter. Although the formation of C-C bonds via catalytic CO₂ fixation remained rather limited for a long period of time, a close look into the recent literature data indicates that catalytic carboxylation reactions have entered a new era of exponential growth, evolving into a mature discipline that allows for streamlining the synthesis of carboxylic acids, building blocks of utmost relevance in industrial endeavours. These strategies have generally proven broadly applicability and convenient to perform. However, substantial challenges still need to be addressed reinforcing the need to cover metal-catalyzed carboxylation arena in a conceptual and concise manner, delineating the underlying new principles that are slowly emerging in this vibrant area of expertise.

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1. Introduction

Since the industrial revolution, the burning of fossil fuels and deforestation, among other human activities, have significantly disrupted the carbon cycle of our planet, releasing substantial amounts of carbon dioxide (CO₂) into the atmosphere. Although the safe upper limit for atmospheric CO₂ is estimated to be no more than 350 ppm,¹ its concentration has steadily increased at an average growth of 2 ppm/year since the pre-industrial era, currently exceeding 408 ppm in January 2018,² thus causing a serious society concern. Unfortunately, our society strongly depends on fossil fuels, which represent 80% of the world's energy sources and account for the production of approximately 95% of all organic chemical commodities.³ Although one might argue that the implementation of CO₂ fixation in synthetic methods will unlikely reduce its concentration in the atmosphere, CO₂ is an abundant, inexpensive and renewable C1 feedstock. thus providing an added value that might be able to compensate the potential costs of its capture and recyclability.³ It is evident that the recent years have witnessed significant progress in CO₂ reduction events, rapidly accessing a new generation of fuels such as methanol or hydrocarbons.⁴ However, their low market value leaves some doubt whether their production from CO2 could be competitive or economically-viable, at least in the short term.



Scheme 1. Industrial CO₂ fixation into chemicals.

Driven by the abundance and availability of CO₂, chemists have been challenged to design technologies for converting CO2 into fine chemicals.⁵ However, the scope of fine chemicals available from CO₂ is certainly negligible when compared to current available petrochemicals (Scheme 1). IError! Marcador no definido. At present, the vast majority of these catalytic processes remain primarily confined to C-O or C-N bond-forming reactions such as the synthesis of polycarbonates, cyclic carbonates or the production of urea by the Bosch-Meiser process, among others. In sharp contrast, the ability to promote a catalytic CO₂ fixation via formation of C-C bonds, possibly the most fundamental linkages in organic molecules, still remains largely underdeveloped. Among the different alternatives, particularly attractive would be the ability to promote a catalytic CO₂ conversion into carboxylic acids, building blocks of utmost relevance on the manufacture of cosmetics, soaps, detergents, rubbers, dyes, animal feed, plastics, agrochemicals or pharmaceuticals, among others (Scheme 2).⁶ Indeed, the prospective social and economic impact of carboxylic acids is illustrated by a global market value that will likely reach €16 billion by 2024.7

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Scheme 2. Carboxylic acids in chemical industry.

As judged by the wealth of literature data reported in recent years, catalytic CO₂ fixation techniques en route to carboxylic acids might represent, practicality and conceptuality aside, a straightforward alternative to classical synthetic routes based on the acid-mediated hydrolysis of nitriles,⁸ oxidation of primary alcohols⁸ or carbonylation of organic halides with toxic and hazardous carbon monoxide, among others.⁹ While recognizing the prospective impact of preparing added-value carboxylic acids from CO₂, we identified the need for a more up-to-date, yet comprehensive, review in this topic of expertise. Beyond any reasonable doubt, spectacular advances have been reported in the electrochemical¹⁰ and heterogeneous arena;¹¹ however, the purpose of this review is to focus on the most important developments in transition metal-catalyzed carboxylation reactions with CO2.¹² Specifically, we have structured this review based on the type of bond where the CO₂ insertion occurs, ranging from the utilization of stoichiometric and highly polarized C-metal bonds to less-polarized C-(pseudo)halide bonds, unsaturated hydrocarbons and C-H bonds. This account will not only provide a detailed description of the current methods, but also highlight the remaining, yet notorious, challenges of these processes, without losing sight mechanistic considerations, when appropriate. The selected examples highlighted in this review are meant to showcase our conviction that these unorthodox, yet powerful, technologies are in the midst of a transition that might impact the practice of organic chemistry when preparing carboxylic acids.

2. Molecular Features of CO₂ and Binding Modes to Transition Metals

Taking into consideration that catalytic CO₂ fixation technologies typically involve the coordination of CO₂ to a metal center, it is particularly important to understand the basic features associated to the molecule of CO2 and its binding modes to transition metals. In its ground state, CO2 is a linear triatomic molecule with D_{wh} symmetry in which the central carbon atom possesses sp hybridization as a consequence of possessing two C=O bonds with a C-O bond distance of 1.16 Å.^{iError! Marcador no} definido. Such linearity results in two dipole moments opposite each other, making CO₂ a non-polar molecule that shows a remarkable kinetic and thermodynamic stability. The main molecular orbitals (MO) that are primarily responsible for the reactivity of CO₂ are the $1_{\pi a}$ -occupied MO (HOMO) and $2_{\pi u}$ -unoccupied MO (LUMO).¹³ While the former is centered on the oxygen atoms, the latter preferentially lies at the carbon atom. This dichotomy confers an ambiphilic character to CO₂, both exhibiting Lewis basic character at oxygen and Lewis acidic character at carbon as a consequence of having two adjacent electronegative oxygen atoms (Scheme 3). These features govern the binding of CO₂ to transition metals; in particular, metals in low oxidation states typically bind CO2 to the carbon atom, whereas highly oxidized metals predominantly interact with the oxygen atoms.





As the molecule of CO₂ contains two C=O bonds, it possesses two sets of orthogonal π -orbitals that can interact with the d electrons of transition metals. Although CO₂ can bind multiple metal complexes, the majority of catalytic carboxylation technologies can be rationalized by four basic coordination modes to CO2 (Scheme 3).13 The $\eta^1\!-\!C$ coordination mode is typically observed with rather electron-rich metal complexes possessing a relatively high in energy do-type orbital, in which the interaction takes place via charge transfer between the anti-bonding π^* orbital of CO_2 and a d_z^2 metal orbital. The binding at the carbon atom might also occur in a $\eta^2(C,O)$ side-on coordination mode, a situation that is typically favored by a high-energy $d\pi$ -type orbital. In this particular case, there is a σ bond from the π -orbital of CO₂ to an empty d_z^2 metal orbital as well as a π -back bonding situation from a d_{xy} metal orbital to an empty π^* orbital of CO₂. If electronpoor metal complexes are involved in, these typically bind the molecule of CO_2 in either a η^1 –O end-on coordination mode or in a $\eta^2(0,0)$ fashion, the latter being commonly observed for alkali metals. Among all binding modes, the $\eta^2(C,O)$ coordination is probably the most popular, as illustrated by the multiple number of metal complexes that have been isolated and unambiguously characterized by X-ray diffraction. Indeed, the first transition metal complex that could be structurally characterized contained a $\eta^2(C,O)$ coordination mode and was reported by Aresta and colleagues $(Cy_3P)_2Ni(CO_2)$.¹⁴



Scheme 4. Common catalytic scenarios when converting CO₂ into RCO₂H.

With the exception of the η^1 –O end-on mode, that typically adopts a quasi-linear geometry, the binding of the metal center to CO₂ causes a significant deviation of the O–C–O angle from linearity. This observation can hardly be underestimated, as the binding significantly lowers down the activation energy required for CO₂ activation, thus setting the basis for promoting the targeted C–C bond-forming event. Although other pathways are potentially conceivable, the conversion of CO₂ into the targeted carboxylic acid can formally be explained via three different pathways (Scheme 4): (a) initial coordination of the metal center to CO₂ followed by reaction with the substrate; (b) interaction of the substrate to the metal center prior to CO₂ binding or insertion; (c) dual coordination of the substrate and CO₂ to the metal center. Regardless of the pathway employed, it is inevitable to establish a parallelism between the Aresta complex (Cy₃P)₂Ni(CO₂)^{iErrort}

Marcador no definido. and the recent popularity gained by Ni catalysts.¹⁴ As judged by the wealth of literature data, the Ni-catalyzed carboxylation arena includes a rather vast portfolio of coupling partners that includes organometallic reagents, organic (pseudo)halides or (un)saturated hydrocarbons, among others. However, such success should by no means indicate that other metal complexes cannot be utilized in catalytic carboxylation reactions; as it will become evident from the results compiled in this review, Rh, Ru, Ir, Co, Cu, Au or Fe catalysis have enabled a series of reactions that are oftentimes complementary, or even beyond reach, to commonly employed Ni-catalyzed carboxylation events.

3. Metal-Catalyzed Carboxylation of Well-Defined Organometallic Reagents

In the early twentieth century, the high thermodynamic stability and kinetic inertness of CO_2 contributed to the perception that a highly energetic coupling partner would be required for promoting the fixation of CO_2 fixation into organic matter. This notion was reinforced by the observation that insertion of CO_2 across a metalcarbon bond could be promoted with stoichiometric and highly nucleophilic organometallic entities such as Grignard reagents or organolithium derivatives, thus furnishing the corresponding carboxylic acids upon hydrolytic workup.¹⁵ Ironically, the advantage of using highly polarized Grignard reagents or

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organolithiums for CO₂ activation could not be translated into a more prolific use in organic synthesis due their poor chemoselectivity. Gratifyingly, the meteoric progress in catalytic cross-coupling reactions, ¹⁶ together with the multiple binding modes of CO₂ to transition metals created an avalanche of opportunities for designing chemoselective metal-catalyzed carboxylation techniques with less-basic organometallics such as organoborons, organotins and organozinc reagents.

3.1. Catalytic carboxylation of organotin derivatives

first report of metal-catalyzed carboxylation The of organometallic compounds with CO_2 was reported by Shi and Nicholas in 1997.¹⁷ Specifically, it was found that allyl stannanes could be easily converted into the corresponding allyl tin esters upon exposure to Pd(PPh₃)₄ at 70 °C under high pressure of CO₂ (Scheme 5, top). Intriguingly, parasitic isomerization to the corresponding α , β -unsaturated ester was observed depending on the nature of the allyl stannane. Although undoubtedly a stepforward, this protocol required high pressures of CO₂ and could not be extended to more substituted analogues, as crotyl stannanes failed to provide the targeted tin esters. Few years later, Wendt and Johansson observed that the utilization of palladium pincer catalysts afforded otherwise identical products under milder reaction conditions (Scheme 5, bottom).¹⁸ The authors observed a non-negligible role exerted by the nature of the pincer ligand, with less-sterically encumbered backbones bearing electron-withdrawing motifs providing the best results, even at room temperature under 4 atm CO2. In this case, olefin isomerization to the $\alpha,\beta\text{-unsaturated ester}$ was not observed. The versatility of the corresponding allyltin carboxylates was further illustrated by Nicholas¹⁹ and Bao,²⁰ showing that these species could be treated with either allyl or benzyl chlorides, thus generating the corresponding allyl esters in good yields.



Scheme 5. Initial Pd-catalyzed studies of allyl stannanes.

In 2011, the Hazari group extended the family of Pd catalysts that can be utilized in the carboxylation of allyl stannanes (Scheme 6).²¹ In particular, it was found that the utilization of well-defined η^3 -allyl Pd(II) complexes supported by *N*-heterocyclic carbenes (NHC) allowed for promoting the reaction in excellent yields under remarkably mild conditions. Shortly after,²² a new family of Pd(I)-bridging allyl dimers (**Pd-3**) was employed for similar purposes, with the advantage of their ease of synthesis

and increased stability when compared to the corresponding monomeric intermediates. Wendt²³ and Hazari²⁴ elucidated the mechanism of this transformation, concluding that it might proceed via the intermediacy of η^1 -allyl Pd(II) intermediates (I) generated upon transmetallation of the allyl stannane to the initial Pd(II) precatalyst. Of particular interest was the observation that CO₂ insertion does not occur via direct insertion into the Pd-C bond, but rather from the nucleophilic attack of the olefin to CO₂ (**TS1**). Such a pathway leads to a zwitterionic intermediate II that ultimately generates back the corresponding η^1 -allyl Pd(II) intermediate (I) by transmetallation of III with allyl stannane (Scheme 6, *bottom*).



Scheme 6. Initial Pd-catalyzed studies of allyl stannanes.

3.2. Catalytic carboxylation of organoboron reagents

Metal-catalyzed cross-coupling reactions with organoboron reagents has attracted considerable attention in both academic and pharmaceutical laboratories. Such popularity is largely due to the ready availability and stability of the corresponding boronic acids or boronic esters to heat, oxygen and moisture as well as the ease of handling boron-byproducts. Not surprisingly, this discipline has also found application in the area of catalytic carboxylation reactions. The first metal-catalyzed carboxylation of organoboron reagents was reported by Iwasawa and co-workers in 2006.²⁵ The authors observed that a Rh catalyst supported by bidentate phosphine ligands was particularly suited for their purposes, allowing for the carboxylation of a wide range of neopentyl glycol boronic esters under atmospheric pressure of CO2 (Scheme 7). The addition of large amounts of cesium fluoride was found to be critical, an aspect that is likely correlated with the intermediacy of four-coordinate boron 'ate' complexes that accelerate transmetalation while enhancing the nucleophilicity of the corresponding aryl rhodium species prior to CO₂ insertion.

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Scheme 7. Rh-catalyzed carboxylation of organoboron compounds



Scheme 8. Cu-catalyzed carboxylation of aryl and vinyl boronates.

Subsequently, it was found that cheaper copper catalysts could be employed for similar purposes when combined with bisoxazoline ligands, resulting in a protocol that significantly improved the functional group compatibility when compared to the previous Rh-catalyzed carboxylation reaction (Scheme 8, Cond. A).²⁶ Shortly after, Hou described that a similar transformation can be effected with NHC ligands in the presence of 1 equivalent tBuOK, thus avoiding the use of excess amounts of additives (Scheme 8, Cond. B).²⁷ The utilization of IPr as ligand allowed for dramatically lowering down the catalyst loadings, resulting in a rather robust protocol that improved the applicability of the reaction. More importantly, the authors isolated and characterized the putative copper species within the catalytic cycle, demonstrating their competence as reaction intermediates. These results can hardly be underestimated, as the study of the reactivity of the intermediate metal species within the catalytic cycle still constitutes an important gap in a myriad of catalytic carboxylation reactions. The conclusions extracted from these studies could be

corroborated in a subsequent theoretical study by DFT calculations,²⁸ reinforcing the notion that the reaction is initiated by transmetallation via a B–O–Cu bridged intermediate to afford a IPrCu-aryl complex **IV**. Such complex precedes CO₂ insertion, that turned out to be the rate-determining step. Final transmetalation with the tetracoordinated boron ate complex delivers the targeted potassium carboxylate while reinitiating the catalytic cycle. Riss and co-workers further extended this strategy to the construction of radiotracers by employing ¹¹CO₂ as counterpart.²⁹ In this case, TMEDA was found to be the ligand of choice, allowing for the synthesis of ¹¹C-labelled benzoic acids in high radiochemical yields. In 2013, Li described the competence of pH-responsive NHC copper(I) catalysts in carboxylation reactions of neopentyl glycol boronic esters, thus establishing the basis for homogeneous catalyst recycling.³⁰



Scheme 9. Ag- and Ni-catalyzed carboxylation of aryl and vinyl boronates.

While the available literature data reinforced the unique ability of copper and rhodium complexes to effectively promote carboxylation reactions of aryl boronic esters, Lu showed that the combination of AgOAc, PPh₃ and *t*BuOK was equally effective (Scheme 9 *top*),³¹ with excellent functional group tolerance. More recently, Nolan developed an efficient Ni-catalyzed carboxylation of both aryl and vinyl neopentyl glycol boronic esters (Scheme 9, *bottom*),³² with allyl-nickel(II) catalysts supported by sterically hindered NHC ligands (L2) being critical for success.

Although the previous examples demonstrated the utilization of well-defined aryl or vinyl boronates in carboxylation events, Kimura offered a multicomponent approach en route to polysubstituted acrylic acids with terminal alkynes as coupling partners (Scheme 10).³³ The authors proposed that this reaction proceeds through an alkynyl boron 'ate' complex that undergoes a stereoselective [1,2]-alkyl migration, delivering a vinyl boronate species that triggers a CO₂ insertion under Hou's conditions²⁹ based on IPrCuCI (Scheme 8). Although the reaction was limited

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to aryl-substituted acetylenes, the authors showed that not only commercially available trialkyl boranes, but also those arising from hydroboration of simple alkenes could be employed as substrates. Despite its inherent synthetic potential, it would be particularly important to significantly reduce the large amounts of borane required.



Scheme 10. Cu-catalyzed synthesis of acrylic acids.



Scheme 11. Cu-catalyzed carboxylation of allyl pinacol boronates

The considerable success in designing metal-catalyzed carboxylation of organoboranes suggested that these reactions should by no means be limited to aryl or vinyl boronic esters. Such observation was confirmed by Hazari when implementing a catalytic carboxylation of allyl boronic esters by well-defined allyl palladium complexes Pd-2 and Pd-3.^{21,22} While previous catalytic carboxylations necessarily required the presence of a neopentyl unit on the organoborane, the utilization of pinacol or diisopropyl boronate motifs proved to be equally effective. In 2013, Duong applied Hou's conditions for the carboxylation of allyl pinacol boronic esters,³⁴ resulting in a transformation that delivers the corresponding branched β ,y-unsaturated carboxylic acids with exquisite regioselectivity (Scheme 11). The ability to obtain otherwise identical products from regioisomeric allyl boronates suggest that a common copper intermediate comes into play, triggering a carboxylation at the γ -position via a classical S_E'-type pathway. Consistent with such interpretation, the inclusion of large substituents at the γ -position had a detrimental impact in reactivity.



Scheme 12. Cu-catalyzed synthesis of secondary and malonic acids.

Despite the advances realized in catalytic carboxylation reactions of organoboranes, the available portfolio exclusively included the activation of either sp² C–B bonds or rather activated sp³ allylic C–B motifs. Aiming at extending these reactions beyond activated allylic boronic esters, Sawamura 35 and Hou 36 independently reported a two-step sequence consisting of alkene hydroboration followed by a subsequent carboxylation event (Scheme 12, top). Intriguingly, the utilization of 9-BBN turned out to be essential for the reaction to occur, an observation that is in sharp contrast with the preferred reactivity of neopentyl boronic esters in the aryl series. While Sawamura's protocol is based on a CuOAc/1,10-phenanthroline couple, Hou exploited the high reactivity of IPrCuCl. Regardless of the copper catalyst utilized, the reaction likely proceeds via the intermediacy of a bridged Cu-O-B species that is somewhat reminiscent of the scenario shown in Scheme 8 (IV). Although the use of unactivated alkenes is a bonus from both synthetic and conceptual standpoint, it is worth noting that internal alkenes could not be employed as counterparts, an observation that probably is associated to the inherent difficulty of promoting carboxylation at an unactivated aliphatic secondary alkyl positions. This drawback has been recently tackled by Skrydstrup in which a protocol based on CsF at 120 °C was found to be rather critical for success (Scheme 12, bottom). 37 Under these conditions, a range of olefins could formally be carboxylated via alkyl borane intermediates generated upon initial exposure to 9-BBN. Notably, excellent stereo- and regioselectivity was obtained with both trisubstituted alkenes or stilbene derivatives, with CO₂ insertion occurring preferentially at the most electron-deficient position. Of particular interest was the

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ability to access malonic acids from terminal alkynes via a tandem double hydroboration followed by carboxylation. The synthetic utility of the method was showcased by its application to a series of natural products containing internal olefins.

3.3. Catalytic carboxylation of other organometallic species

The popularity of organozinc derivatives in a myriad of metalcatalyzed C–C bond-formations have made them indispensable vehicles for further functionalization.³⁸ However, the employment of organozinc species in catalytic carboxylation reactions has found little echo compared to the prolific use of organoboron reagents for similar purposes. In 2008, Dong³⁹ and Oshima⁴⁰ independently reported Pd and Ni-catalyzed protocols for the carboxylation of aromatic organozinc reagents (Scheme 13), showcasing the need for particularly electron-rich and stericallyhindered PCy₃. Interestingly, aliphatic organozinc reagents could only be coupled under a Ni/PCy₃ regime when combined with LiCl. While there was no rationale behind the superior reactivity of Ni when compared to Pd catalysts in the aliphatic series, the role exerted by LiCl was attributed to an enhanced nucleophilicity of the organozinc derivative.⁴¹



Scheme 13. Catalytic carboxylation of organozinc derivatives.

The generation of a latent nucleophile via hydrometalation of unsaturated hydrocarbons holds promise to build up molecular complexity from simple and available precursors.⁴¹ Prompted by the successful hydroboration/carboxylation sequence highlighted in Scheme 8, Hou described a new route to α , β -unsaturated carboxylic acids via stereoselective carbon(hydro)alumination of alkynes followed by carboxylation in the presence of Cu catalysts (Scheme 14, *top*).⁴² Subsequently, Xi extended this methodology to the intermediacy of alkenyl zirconium species.⁴³ In this case, however, the reaction turned out to be less-general than the corresponding route involving alkenyl aluminum reagents. Following Uchiyama's seminal studies on lithium aluminates,⁴⁴

Hou developed a new Cu-catalyzed carboxylation protocol via the intermediacy of aromatic and allylic aluminates, thus formally constituting a C–H carboxylation event (Scheme 14, *bottom*).^{45,46} However, a directing group was still required when dealing with aromatic aluminates whereas a 2-aryloxy motif was essential for the preparation of allylic carboxylic acids. The ligand exerted a non-negligible role on reactivity, with IPr providing the best results for the carboxylation of aryl aluminates and IMes for the allyl series. As expected, the presence of DBU as base resulted in a quantitative isomerization of the pending olefin, resulting in the corresponding α , β –unsaturated carboxylic acids.



Scheme 14. Cu-catalyzed carboxylation of organoaluminum species.

As judged by the wealth of literature data, it is evident that considerable knowledge has been gathered in the catalytic carboxylation of organometallic reagents, establishing new design principles for direct CO_2 fixation into polarized C-metal bonds. Among these, particularly attractive is the ability to utilize air- and moisture-stable organometallic reagents as counterparts, thus improving the practicality of these processes. However, numerous challenges remain in this field of expertise: (a) the coupling of simple boronic acids still remains unexplored; (b) the design of an enantioselective carboxylation of organometallic reagents still remains an elusive goal, and (c) despite their inherent synthetic potential, the design of in situ generated organometallic reagents is at its infancy.

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4. Catalytic Reductive Carboxylation of C– (Pseudo)Halide Bonds

Despite the spectacular advances realized in catalytic carboxylation of organometallic species, these techniques necessarily require stoichiometric amounts of organometallic reagents, an observation that might potentially hamper the implementation of these rather appealing scenarios in synthetic endeavours. Driven by the observation that organometallic reagents are oftentimes prepared from the corresponding organic halides via classical metalation techniques,47 chemists have been challenged to design direct carboxylation of organic (pseudo)halides with CO2. However, such a process is counterintuitive to say the least; unlike classical cross-coupling reactions based on nucleophile/electrophile regimes,48 the direct carboxylation of organic (pseudo)halides formally falls into the category of cross-electrophile coupling processes,49 as both CO2 and C-(pseudo)halide bonds possess an electrophilic carbon atom. This notion necessarily implies that the redox properties have to be balanced by the presence of an appropriate reducing agent.⁵⁰ However, such a scenario is expected to be particularly problematic, as the reducing agent might react preferentially with the putative oxidative addition species prior to CO₂ insertion, resulting in non-productive and to-be-avoided reduction events. If successful, however, these catalytic carboxylation reactions might represent, practicality and conceptuality aside, a powerful alternative to commonly-employed organometallic reagents. As it will become apparent from the results compiled in the following sections, the catalytic reductive carboxylation arena has reached remarkable levels of sophistication, becoming an attractive tool for synthetic chemists due to its exquisite chemoselectivity profile in the presence of numerous functional groups, including organometallic reagents. The latter is particularly attractive, as it might lead to the foundation of orthogonal cross-coupling scenarios.

4.1. Catalytic Carboxylation of Organic Halides

In 1994, pioneering studies by Osakada and Yamamoto tacitly demonstrated that stoichiometric amounts of PhNiBr(bpy), readily prepared by simple exposure of PhBr to Ni(cod)₂ and bipyiridine, could effectively react with CO₂ at atmospheric pressure to afford benzoic acid in moderate yield. ⁵¹ This experiment confirmed not only the unique ability of nickel complexes to trigger CO₂ insertion into putative oxidative addition complexes, but also establishing the basis for designing an integrated catalytic platform for preparing carboxylic acids from simple organic halides. As judged by the exponential growth in metal-catalyzed carboxylation technologies, this seemingly innocent finding triggered an avalanche of new reactivity principles when fixating CO₂ into organic matter via C-C bondforming reactions. Surprisingly, however, Osakada's findings found little echo and this field of expertise remained dormant until 2009, when Martin reported the first catalytic carboxylation of aryl bromides with CO₂ (1-10 atm) by using Et₂Zn as terminal reductant (Scheme 15). 52 Particularly important was the observation that bulky and electron-rich phosphine (*t*BuXPhos) was critical for success, minimizing parasitic Negishi-type crosscoupling reaction as well as unproductive reduction pathways. Although one might argue that the presence of Et_2Zn might limit the application profile of these methods, the reaction exhibited an excellent functional group tolerance; indeed, epoxides could be tolerated under these conditions. Preliminary mechanistic experiments ruled out the intervention of intermediate organozinc species, thus suggesting a direct CO_2 insertion into the corresponding ArPd(II)Br oxidative addition species.

Pd-catalyzed carboxylation of aryl bromides



Scheme 15. Pd-catalyzed carboxylation of aryl bromides.

While this method constituted the genesis of reductive catalytic carboxylation of organic halides with CO₂, the need for high pressures, pyrophoric reducing agent (Et₂Zn) and the limitation to aryl bromide counterparts were important drawbacks to be overcome. In 2012, the group of Tsuji and Fujihara extended the scope of catalytic carboxylations to the more challenging and readily available aryl and vinyl chlorides at atmospheric pressure of CO₂ (Scheme 16).⁵³ It was shown that a mild and air-stable reducing agent (Mn) in combination with ammonium salts (Et₄NI) as additives were critical for success. Although tentative, the success of the former is likely attributed to its role as reducing agent (E = -1.18V) whereas a rational explanation for the later still remains speculative. As it will become apparent in the following sections, the use of additives has not only been critical for achieving reactivity in the reductive carboxylation arena, but also for establishing site-selectivite protocols. It is particularly noteworthy that PhNiCl(PPh₃)₂ did not react with CO₂ (1 bar) unless a single-electron reductant was utilized (Co(η^5 -C₅H₅)₂; E = -0.89V). This result was particularly intriguing taking into consideration the CO_2 insertion found by Osakada and Yamamoto with PhNiBr(bpy) in the absence of reductant, thus providing compelling evidence about the unique role exerted by the ligand backbone depending on the oxidation state of the Ni center. Theoretical calculations supported a CO2 insertion into the Ar-Ni(I)(PPh₃)₂⁵⁴ that could be generated upon Mn-mediated single electron transfer (SET), which can be facilitated by the presence of appropriate additives. 55

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Ni-catalyzed carboxylation of aryl and vinyl chlorides



Scheme 16. Ni-catalyzed carboxylation of aryl chlorides.

In 2013, Daugulis reported the Cu-catalyzed reductive carboxylation of aryl iodides using a Cul/TMEDA or Cul/DMEDA regime when combined with Et₂Zn as reducing agent (Scheme 17).^{56,57}In contrast to previous catalytic carboxylations of aryl halides, the presence of particularly sterically hindered substrate combinations did not pose any problem, even at room temperature. The authors favoured a mechanism that is somewhat reminiscent of that shown by Martin with aryl bromides,⁵²(Scheme 15) with CO₂ being directly inserted into an Ar-Cu(I)L_n oxidative addition intermediate.



Scheme 17. Cu-catalyzed carboxylation of aryl iodides.

Aiming to expand the catalytic reductive carboxylation portfolio beyond the utilization of aryl halides, Martin described a Nicatalyzed protocol of primary, secondary or even tertiary benzyl halides with CO₂ at atmospheric pressure (Scheme 18).⁵⁸ In this case, highly electron-rich phosphines such as PCp₃ and PCy₃ were found to be critical in the presence of Zn as reducing agent (E = -0.72V). Although not yet fully understood, the presence of additives was found to play a profound influence on reactivity; while the presence of TBAI mediated the coupling of primary benzyl halides, the addition of MgCl₂ proved particularly useful for secondary and tertiary benzyl halides. The authors performed stoichiometric studies with a putative η^3 -benzylnickel(II) complex, revealing that the reaction did not proceed in the absence of Zn. Additionally, control experiments argued against a mechanism consisting of the intermediacy of benzyl zinc reagents or styrene derivatives obtained via β -hydride elimination. Taking together, these experiments suggest a one-electron reduction of in situ generated η^3 -benzylnickel(II) complexes mediated by either Zn or comproportionation with Ni(0)L₂, resulting in Ni(1) intermediates that would subsequently insert CO₂ at the sp^3 C–Ni bond.⁵⁹ Although not conclusive, an initial SET was proposed based on the inhibition found in the presence of radical scavengers as well as the observed racemization if an enantiopure benzyl bromide was utilized as substrate. In 2014, a detailed DFT study suggested that the addition of MgCl₂ might accelerate CO₂ insertion while favouring SET-type processes.⁶⁰





Scheme 18. Ni-catalyzed carboxylation of benzyl halides.



Scheme 19. Pd-catalyzed carboxylation of primary benzyl chlorides.

In line with the ability of electron-rich and bulky phosphines to mediate the Pd-catalyzed carboxylation of aryl bromides,⁵² He reported the catalytic carboxylation of primary benzyl chlorides using a Pd precatalyst and SPhos as ligand (Scheme 19).⁶¹ Once again, the addition of MgCl₂ turned out to be important, improving the overall catalytic efficiency of the reaction. In this case, however, DFT calculations favoured a pathway consisting of a Lewis acid coordination to CO₂, thus lowering down its activation energy and setting up the stage for a CO₂ insertion into the *sp*² C–Pd(II) bond.





Scheme 20. Pd/photoredox-catalyzed carboxylation of aryl halides.

Over the recent years, visible light photoredox catalysis has emerged as a powerful tool for building up molecular complexity under remarkably mild reaction conditions. 62 Driven by the ability to generate transient radical intermediates via non-invasive outersphere SET processes, photoredox catalysis might open new vistas in catalytic reductive carboxylation reactions by avoiding the need for stoichiometric amounts of metallic single-electron reductants.⁶³ Recently, Iwasawa and Martin described the merger of Pd and photoredox catalysis for the direct carboxylation of aryl bromides and chlorides (Scheme 20). ⁶⁴As initially anticipated from previous Pd-catalyzed carboxylations,⁵² a particularly bulky and electron-rich phosphine (tBuXPhos) was found to be wellsuited for the carboxylation of aryl chlorides, whereas PhXPhos proved to be superior when coupling aryl bromides. In line with other carboxylation reactions, the addition of additives was necessary for the reaction to occur; indeed, the utilization of Cs₂CO₃ was found to be particularly important for minimizing the formation of hydrodehalogenated products. Preliminary mechanistic studies showed a mismatch between the reduction potentials of PhPdBr(XPhos) (-2.28 V vs Fc/Fc⁺) and the photocatalyst utilized (-1.87 V vs Fc/Fc⁺). Interestingly, however, CV measurements in CO₂ atmospheres (1 bar) indicated a way lower reduction potential for the oxidative addition complex (-1.4 V). Although tentative, this result suggested that the coordination of CO₂ to the Pd(II) center might facilitate a subsequent singleelectron transfer en route to a Ar-Pd(I)XPhos intermediate prior to CO₂ insertion into the sp^2 C–Pd bond.

In 2014, metal-catalyzed reductive carboxylations remained confined to the utilization of aryl, benzyl or allyl (pseudo)halides as coupling partners. This observation indirectly suggested that extending the scope of these technologies beyond substrates that easily undergo oxidative addition might be more problematic than initially anticipated. Despite the advances realized in metalcatalyzed cross-coupling reactions of unactivated alkyl halides,65 the vast majority of these technologies make use of particularly reactive, in many instances homogenous, precursors that can effectively intercept the in situ generated alkyl metal species. Unfortunately, CO₂ is thermodynamically stable, kinetically inert and not particularly soluble in the classical solvents required for effecting cross-coupling reactions.^{iError! Marcador no definido.} Therefore, it was anticipated that the direct carboxylation of unactivated alkyl halides would be hampered by the particularly low concentration of CO₂ in solution, thus making particularly difficult to intercept the in situ generated alkyl metal species with CO2 prior unproductive β -hydride elimination and/or homodimerization pathways.⁶⁶







Scheme 21. Ni-catalyzed carboxylation of unactivated alkyl halides.

X = Br or CI

dr = 1:1

The Martin group offered a solution to this challenge by utilizing 1,10-phenanthroline ligands possessing substituents adjacent to the nitrogen atom (Scheme 21, top).⁶⁷ While a full rationale behind these results will likely require future efforts at molecular level, it was suggested that the presence of such substituents prevented parasitic β-hydride elimination while favouring the formation of putative alkyl-Ni(I) intermediates prior to CO₂ insertion. Although the reaction exhibited a remarkable functional group tolerance, this technique did not include neither the coupling of secondary (or tertiary) alkyl bromides nor the more accessible unactivated alkyl chlorides. These limitations were overcome in 2016 in a new Ni-catalyzed carboxylation of primary, secondary or even tertiary alkyl chlorides (Scheme 21, middle),68 constituting the first time that such coupling partners could be employed in catalytic reductive cross-couplings. As anticipated, a more electron-rich ligand was expected to accelerate the oxidative addition whereas the inclusion of ortho-substituents would prevent parasitic reaction pathways prior CO₂ insertion into the alkyl C-metal bond. As for other carboxylation reactions, the addition of additives turned out to be essential for the reaction to occur, with a cocktail based on *n*Bu₄NBr (TBAB) and LiCl providing the best results. Although merely speculative, the former might facilitate SET processes, whereas the later could significantly enhance the nucleophilicity of the transient alkyl nickel intermediates. Labelling deuterium experiments with diastereomerically-pure substrates revealed that this reaction likely operates via SET processes via Ni(I) species, inevitably obtaining statistical mixtures of the corresponding carboxylic acids (Scheme 21, bottom). This notion was further corroborated in a series of stoichiometric experiments with well-defined and isolable 18-electron species Ni(0)L₂ not only revealing that the reaction does not require reducing agent but also ruling out the intervention of organomanganese species.



Scheme 22. Ni-catalyzed carboxylation of cyclopropyl motifs

Aiming at extending the scope of catalytic carboxylation reactions, the Martin group described the use of cyclopropyl motifs in these endeavours (Scheme 22).⁶⁹ The success of this reaction is intimately associated to the exceptional ring strain and orbital rehybridization of cyclopropyl rings,⁷⁰ thus facilitating the CO_2 insertion at the sp^3 hybridized carbon. In line with previous carboxylation reactions, subtle structural differences in the 1,10-phenanthroline backbone were found to be critical for the carboxylation to occur. Indeed, inclusion of LiCl was essential to prevent competitive ring-opened products. Although a variety of cyclopropyl backbones could be coupled with similar ease, the

presence of aliphatic substituents failed to furnish the targeted carboxylic acids. Notably, variable *cis/trans* ratios were found for unsymmetrically-substituted substrates, pointing towards SET processes and Ni(I) intermediates.

Ni-catalyzed divergent cyclization/carboxylation of unactivated alkyl halides



Scheme 23. Ni-catalyzed cyclization/carboxylation of unactivated alkyl halides.

Although one might argue that the loss of stereochemical integrity observed in carboxylation reactions via SET processes might inherently limit their application profile, these undesired pathways can be turned into a strategic advantage. Specifically, the Martin group reported a cyclization/ carboxylation of unactivated alkyl halides possessing an alkyne on the side-chain, resulting in polycyclic carboxylic skeletons. The rationale behind such reactivity was attributed to an initial SET, triggering a rapid 5-exo-trig cyclization prior recombination with the Ni(I) complex, delivering a vinyl-Ni(II) intermediate that can subsequently be intercepted with CO₂ (Scheme 23).^{68,71} While primary alkyl halides rendered the syn-product exclusively, anti-products were predominantly observed with secondary alkyl halides. The nature of the ligand and substrate influenced such site-selectivity. These results were tentatively ascribed to the nature of the corresponding vinyl radical species; upon 5-exo-trig cyclization, sp²-vinyl radical species could coexist in rapid equilibrium, each of these possessing a priori different recombination rates with Ni(I) complexes. Such kinetic behaviour represents an ideal Curtin-Hammett situation, in which the lower steric repulsions at the recombination step might lead to a lower activation energy, thus dictating the regioselectivity pattern. The rapid equilibration of vinyl radical intermediates was empirically observed by exposing a cyclic, vinyl iodide with a low E/Z ratio, obtaining a single regioisomer via formal anti-motion (Scheme 23, bottom).

Driven by the Pd-catalyzed photoredox carboxylation of aryl halides (Scheme 20),⁶⁴ the König group recently described the merger of Ni catalysis within the photoredox arena for the carboxylation of aryl as well as alkyl bromides (Scheme 24).⁷² Unlike the iridium polypyridyl sensitizers utilized in the Pd/photoredox couple, an organic photosensitizer (4CzIPN) turned out to be particularly useful when combined with Hantzsch ester (HEH) as sacrificial reductants and K₂CO₃ as the inorganic base. As to previous carboxylation reactions,⁶⁷⁻⁶⁹ the employment of *ortho*-substituted 1,10-phenanthrolines was required for the reaction to occur. Electrochemical experiments suggested that both oxidative and reductive quenching of the excited state of 4CzIPN may be operating, although the latter was expected to be considerably faster than the former.



Scheme 24. Nickel/photoredox carboxylation of bromides.

Although metal-catalyzed cross-couplings of unactivated alkyl halides have enabled new paradigms for introducing saturated hydrocarbon chains into organic motifs,65 these processes require prefunctionalization at the initial reaction site. Recently, the Martin group designed a method by which unactivated alkyl halides can be used as vehicles for promoting remote carboxylation events at distal sp³ C–H reaction sites (Scheme 25).⁷³ Such a design principle is based on the ability of an in situ generated alkyl-Ni(II) intermediate to accelerate β -hydride elimination while preventing CO₂ insertion at the initial reaction site. A key contributory factor for success was the design of a 1,10-phenanthroline ligand possessing large ortho-substituents and arene motifs at C4 & C7. While the former likely favours halide dissociation and triggers a fast β-hydride elimination, the latter enhances the electrophilicity at the Ni(II) center, facilitating the binding of the intermediate alkene. These features cause a "chain-walking" ⁷⁴ via iterative β hydride elimination/migratory insertion sequence, thus setting the basis for a CO₂ insertion at distal sites. As the selectivity is controlled by the "chain-walking" motion, similar reactivity was observed regardless of the location of the halide function within the alkyl chain. This notion was used for converting alkanes or unrefined mixtures of olefins into fatty acids by a two-step sequence consisting of bromination/"chain-walking" carboxylation. Notably, a bidirectional motion could be established by a subtle temperature modulation. enabling the regiochemical discrimination between multiple sp³ C-H bonds within an alkyl chain. It is worth noting that substrates containing pre-existing

stereogenic centers substantially preserved their chiral integrity, suggesting that the Ni catalyst remains bound to the olefin during the "chain-walking" event.⁷⁵





Scheme 25. Ni-catalyzed remote carboxylation of halogenated hydrocarbons.

4.2 Catalytic reductive carboxylation of C-O electrophiles

Prompted by the ready availability and natural abundance of phenols and aliphatic alcohols, the utilization of C-O electrophiles as organic halides surrogates in cross-coupling reactions has gained considerable momentum.⁷⁶ Practicality and accessibility aside, these technologies offer the advantage of lower toxicity as well as the opportunity to design orthogonal techniques in the presence of aryl halides. Unlike cross-coupling reactions with aryl halides that are typically conducted with Pd catalysts, the higher activation energy required for C-O cleavage is commonly achieved with Ni catalysts. These favourable attributes have been adopted within the carboxylation arena. In particular, Tsuji and Fujihara reported the catalytic carboxylation of activated aryl sulfonates under otherwise similar conditions to that shown for aryl chlorides based on PPh₃ as the ligand (Scheme 26, top).⁵³ Extensions to more sterically hindered substrates or vinyl triflates could be applied recently with either a Ni or Co regime in which an appropriately ortho-substituted 1,10-phenanthroline was critical for the reaction to occur, an observation that parallels other carboxylation reactions (Scheme 26, *bottom*).⁷⁷

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Scheme 26. Ni-catalyzed carboxylation of aryl triflates.

Ni-catalyzed carboxylation of aryl tosylates CO₂H NiBr₂(bpy) (10 mol%) CO₂ R R (1 atm) Mn (2.0 equiv) DMF, 60°C CO₂H O₂H F₃C CO₂H ;O₂H CO₂Me MeO 56% 58% 53% 54% Ni-catalyzed carboxylation of unactivated alkyl sulfonates [NiBr₂·glyme] (10 mol%) OR L5 (26 mol%) Ĥ. N + Mn (2.4 equiv) Μe L5 CO2 (1 atm) DMF, 50 °C .OPiv .OMe Me CO₂H CO₂H CO₂H CO₂H 74% (**R** = Ts) 76% (R = Ts) 62% (R = Ts) 69% (**R = Ts**) 61% (R = Ms)

Scheme 27. Ni-catalyzed carboxylation of organic tosylates.

In 2016, Durandetti showed that the carboxylation of aryl tosylates could be conducted with NiBr₂(bpy) as precatalyst without the need for neither ammonium salts nor phosphine ligands (Scheme 27, *top*).⁷⁸ Although the transformation afforded moderate yields, it is worth noting that the coupling of *ortho*-substituted aryl tosylates was equally effective. The Martin group extended these processes to the utilization of unactivated alkyl mesylates and tosylates (Scheme 27, *bottom*).⁶⁷ As expected, it was found that a slight increase in temperature when compared to the utilization of alkyl bromides was necessary for the reaction to occur.⁶⁷ The loss of the stereochemical integrity when employing α , β -bisdeuterated alkyl tosylates suggested the involvement of single-electron transfer (SET) processes.

Unlike activated organic sulfonates, less-attention has been devoted to simpler ester derivatives as C–O counterparts. Despite the high activation energy required for C–O scission and propensity for acyl C–O cleavage, the Martin group designed a reductive carboxylation of aryl and benzyl ester derivatives (Scheme 28).⁷⁹ As expected, the choice of the ligand exerted a profound effect on the reactivity, with dppf being particularly suited for the carboxylation of aryl pivalates and PMe₃ for the corresponding benzyl esters. Although non- π -extended aryl or benzyl esters failed to furnish the targeted carboxylic acids, this limitation could be partially alleviated by using hemilabile groups, enabling a faster oxidative addition into the C–O bond while opening up vacant coordination sites for CO₂ binding at the Ni centre.⁸⁰



Scheme 28. Ni-catalyzed carboxylation of C(sp²)- and C(sp³)-O bonds.



Scheme 29. Co-catalyzed carboxylation of propargyl acetates

The carboxylation of ester derivatives was also explored by Tsuji and Fujihara utilizing propargylic counterparts by means of cobalt catalysis (Scheme 29).⁸⁰ In contrast to related Ni-catalyzed methods, the influence of the ligand backbone was not particularly important on both reactivity and selectivity, with 1,10-phenanthroline providing the best results. The carboxylation could be executed with both secondary and tertiary propargyl acetates, with sterically-encumbered groups located at the alkyne terminus. Regardless of the substrate utilized, propargyl rather than allenyl carboxylic acids were observed.

The ability to fundamentally alter and control the site-selectivity of cross-coupling reactions from common precursors constitutes an important goal in organic synthesis.⁸¹ In 2014, a Ni-catalyzed regiodivergent reductive carboxylation of allyl acetates with CO₂ was reported by the Martin group, with site-selectivity dictated by the coordination geometry of the ligand utilized (Scheme 30).⁸² In this manner, both α -branched or linear carboxylic acids could be accessed regardless of the allyl acetate regioisomer utilized. While not fully understood, the reactivity could also be modulated by the appropriate selection of both reductant and additive, with Mn/MgCl₂ and Zn/Na₂CO₃ being particularly suited for the carboxylation of linear and α -branched allyl acetates, respectively. Stoichiometric experiments with Ni(0)(L5)2 and Ni(0)L13, both of which characterized by X-ray diffraction, were particularly illustrative (Scheme 31). While the former necessarily required Mn for the reaction to occur, non-negligible yields of abranched product were observed with the latter in the absence of Zn. These results suggested a linear carboxylation via Ni(I) intermediates with L5, whereas a CO_2 insertion at the γ -position of well-defined alkyl-Ni(II) intermediates seems the most plausible avenue for L13, an interpretation that gains credence when comparing with the reactivity found by Hazari⁸³ and Iwasawa⁸⁴ with σ -bound Pd(II) pincer complexes.



Scheme 30. Ni-catalyzed regiodivergent carboxylation of allyl acetates.



Scheme 31. Ni-catalyzed regiodivergent carboxylation of allyl acetates.

Given that C-O electrophiles ultimately derive from the corresponding alcohols, one could envision the possibility for effecting a direct carboxylation of these counterparts. However, the high polarizability of the O-H bond, together with the high activation energy required for effecting sp³ C–OH cleavage left a reasonable doubt that such a transformation would be viable.85 Mita and Sato described the first efforts towards this goal, culminating in a Pd-catalyzed carboxylation of allylic alcohols with Et₂Zn as reducing agent, affording α-branched carboxylic acids regardless of the regioisomer of the allylic alcohol utilized. (Scheme 32).⁸⁶ It was proposed that the high Lewis acidity of the Zn(II) reagent triggered the formation of an alkoxylate that reacts reversibly with CO₂, lowering down the activation energy for C-OH cleavage. The observed selectivity is indicative of π-allyl Pd(II) species that are in equilibrium with n¹-allyl Pd(II), setting the stage for a CO_2 insertion at the γ -position of the alkene.





Scheme 32. Pd-catalyzed carboxylation of allyl alcohols.

Recently, the Martin group described an alternative method in the absence of pyrophoric/air-sensitive Et₂Zn based on the ability of CO₂ to react reversibly with alcohols to form carbonic acids (Scheme 33, top).⁸⁷ As carbonic acids possess weaker sp³ C–O bonds than allyl alcohols, it was hypothesized that a Lewis acid capable of switching such equilibrium would facilitate C-O scission. It was found that the ligand geometry controlled the siteselectivity, with linear carboxylic acids obtained with bidentate L10 whereas tridentate L14 affording exclusively α -branched derivatives. The addition of NEt₃ in the latter was found to be particularly important, likely acting as an acid scavenger to prevent parasitic reduction events. No conversion was observed upon exposure to Ni(0)(L10)₂ or [Ni(cod)₂]/L14, thus reinforcing the notion that CO₂ was used with dual roles, both as C1 source and as a mediator to facilitate C-O scission. The proposed mechanism is otherwise analogous to that shown for allyl acetates,⁸² in which the coordination geometry of the ligand dictates whether a η^1 -Ni(I) or a η^1 -Ni(II) regime intervenes or not. Independently from Martin's work, Mei described a related Nicatalyzed carboxylation strategy based on L5, delivering exclusively linear carboxylic acids (Scheme 33, bottom).⁸⁸ In this case, an ammonium salt (nBu₄NOAc) was used instead of a Lewis acid to facilitate C-O bond-cleavage. Mechanistic investigations with propargyl alcohol as coupling partner suggested the involvement of Ni(II)-hydride species generated from advantageous water, leading to a formal semi hydrogenation of the triple bond prior to sp^3 C–O cleavage.



Scheme 33. Ni-catalyzed carboxylations of allyl and propargyl alcohols.

4.3 Catalytic reductive carboxylation of C-N electrophiles

As evident from the results compiled in previous sections, the catalytic reductive carboxylation of organic halides and C-O electrophiles has provided new vistas in CO₂ fixation techniques via C-C bond-formation. However, the carboxylation of benzyl electrophiles is not as commonly practiced as one might anticipate. This is likely due to the attenuated nucleophilicity of the η^{1} -Ni(II) benzylic species that are in equilibrium with η^{3} -Ni(II) intermediates. Furthermore, a limited set of substitution patterns can be utilized when using benzyl halides or benzyl C-O electrophiles.58,79 These drawbacks prompted the development of benzyl ammonium salts as counterparts in carboxylation reactions via sp³ C-N cleavage (Scheme 34).⁸⁹ Once again, the inclusion of ortho-substituents to the nitrogen atom in 1,10phenanthroline ligands exerted a non-negligible influence in both yield and selectivity. Unlike benzyl halides or C-O counterparts, the presence of aliphatic side-chains or non- π -extended systems did not have a deleterious effect on reactivity. Mechanistic investigations revealed that well-defined Ni(0)(L7)2 and Ni(I)(L7)2 were catalytically competent as reaction intermediates. While stoichiometric experiments strongly suggested the participation of SET processes mediated by either Mn or comproportionation events with Ni(0)(L7)2, it was not possible to rule out the involvement of η^1 -Ni(II) species prior to CO₂ insertion.



Scheme 34. Ni-catalyzed carboxylations of benzyl ammonium salts.

In light of the results accomplished, it is evident that the seminal studies from Osakada triggered an avalanche of new catalytic carboxylation methodologies for the coupling of aryl, benzyl, vinyl, allyl or even unactivated alkyl electrophiles. Despite the considerable knowledge acquired and the ability to expand horizons within the photoredox arena, this field has by no means yet reached its full maturity. Indeed, in depth mechanistic understanding is still lacking, and the utilization of ubiquitous and naturally-abundant phenols, anisoles or simple unactivated aliphatic alcohols as coupling partners is still beyond reach. Therefore, it is inevitably to predict that efforts aimed at meeting these challenges will have a considerable impact, conceptuality and practicality aside, in this area of research.

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5. Catalytic Carboxylation of Unsaturated Hydrocarbons

The development of catalytic cross-coupling reactions of organometallic reagents and organic (pseudo)halides with CO_2 has led to a wide variety of synthetic alternatives to prepare valuable carboxylic acid derivatives via C–C bond-formation. Although robust and efficient protocols, the need for well-defined, stoichiometric organometallic reagents or pre-functionalized organic (pseudo)halides might hamper the application profile of these procedures. From a synthetic standpoint, the direct carboxylation of non-particularly polarized substrates would be particularly advantageous. To such end, the use of simple unsaturated hydrocarbons is particularly attractive, constituting an opportunity to combine two chemical feedstocks en route to valuable carboxylic acids. The following section describes the progress made in the last 30 years on the site-selective incorporation of CO_2 into using unsaturated hydrocarbons.

5.1. Catalytic carboxylation of alkynes

The first studies on the catalytic carboxylation of alkynes with CO₂ were reported by Inoue in the late 70's.⁹⁰ Specifically, it was found that Ni and Co catalysts supported by phosphine ligands triggered a cycloaddition of CO₂ with terminal or internal alkynes, resulting in 2-pyrone derivatives in low to moderate yields (Scheme 35, top). The initial mechanistic proposal involved the formation of nickelacyclopentadienes via oxidative cyclization of two alkynes with the Ni(0) catalyst prior to CO₂ insertion (Scheme 35, bottom). Mechanistic investigations by Walther, however, revealed the formation of oxanickelacyclopentene via the coupling of alkyne and CO₂ with Ni(0) active species.⁹¹ Subsequently, Rh catalysts were found to provide an otherwise analogous reactivity⁹² and the reaction could be expanded to diynes giving rise to the corresponding cyclic pyrones.⁹³ Shortly after Inoue's work and contemporary to the discovery of nickelalactones with alkenes and CO2, Hoberg and co-workers first isolated oxanickelacyclopentene derivatives via the oxidative cyclization of alkynes and CO2 with Ni(0) complexes and diamine ligands (Scheme 36, top).94



Scheme 35. Catalytic formation of 2-pyrone derivatives.

Oxanickelacyclopentenes are particularly stable compounds with versatile reactivity (Scheme 36, *bottom*). While direct protonolysis leads to the formation of acrylic acid derivatives,^{94c} the coupling with CO and other aliphatic unsaturated compounds affords the preparation of products with different molecular complexity.^{94a-b} Recently, oxanickelacyclopentenes ⁹⁵ or

structurally-related oxazirconacyclopentenes 96 have shown to react with alkyl electrophiles to afford fully substituted acrylic acids. The formation of oxanickelacyclopentenes was studied by DFT calculations, and indicated that unlike the coupling of alkenes and CO₂, the reaction proceeds through an associative mechanism, involving the coordination of both alkyne and CO₂ to the Ni(0) complex prior to the cyclization.⁹⁷



Scheme 36. Oxanickelacyclopentenes formation and reactivity.





In 1999, Saito and Yamamoto reported the preparation of β substituted acrylic acids from the cross-coupling of terminal alkynes with CO₂ via protonolysis of oxanickelacyclopentenes (Scheme 37, a).⁹⁸ Regardless the electronic nature of the substrates, almost exclusive formation of the β -substituted isomer was observed. The regioselectivity was later rationalized by DFT calculations, suggesting a subtle thermodynamic vs kinetic control. Specifically, oxanickelacyclopentene resulting from CO₂ attack to the substituted carbon is thermodynamically favoured, whereas the insertion at a distal position is kinetically preferred (Scheme 37, b).97 As for other cross-couplings, Iwasawa demonstrated that the nature of the ligand might dictate the regioselectivity pattern in Ni-mediated carboxylations of terminal alkynes (Scheme 37, c).99 In particular, methylene-substituted bis(amidine)ligands selectively afforded *β*-substituted acrylic acids whereas less-sterically encumbered ligands resulted in a regioselectivity switch, giving rise to α -substituted acrylic acids in low vields. Regioselectivity control with internal alkynes could also be achieved using electronically biased motifs. Sato and Saito reported a Ni(0)-mediated carboxylation of alkoxyacetylenes¹⁰⁰ and vnamides ¹⁰¹ (Scheme 37, d). The electron-donating character of the ether and amide motif triggered the formation of a nickelacyclopentene that resulted from the CO₂ insertion onto the most nucleophilic carbon, resulting in an opposite siteselectivity to that found in Saito & Yamamoto's method. 98



Scheme 38. Catalytic hydrocarboxylation of alkynes with well-defined hydrides.

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In retrospect, it is evident that these stoichiometric experiments set the basis for designing catalytic carboxylation of alkynes with CO₂. Among these, considerable research has been devoted to the implementation of hydrocarboxylation reactions, as it might constitute a rapid entry to acrylic acids, and an alternative to the existent oxidative coupling of olefins with CO2 that remain primarily restricted to the coupling of ethylene as counterpart.¹⁰² In 2011, Ma disclosed a Ni-catalyzed alkyne hydrocarboxylation with Et₂Zn as reductant (Scheme 38, top).¹⁰³ If unsymmetrically substituted alkynes were utilized, CO2 insertion occurred adjacent to the aromatic substituent. This is consistent with a formal Markovnivkov hydrozincation, where the metal center is adjacent to the arene prior to CO₂ insertion. Later, the same authors reported a related methyl-carboxylation of homopropargylic alcohols.¹⁰⁴ Independently, Tsuji and Fujihara described a Cucatalyzed hydrocarboxylation of alkynes with similar yields and regioselectivities (Scheme 38, middle).¹⁰⁵ In this case, the active metal hydride species was generated with silanes and copper catalysts bearing N-heterocyclic carbene ligands. Cheng recently described the ability to promote a tandem Fe-catalyzed hydromagnesiation of aromatic alkynes with EtMgBr followed by CO₂ insertion into the C–Mg bond (Scheme 38, bottom).¹⁰⁶

Challenged by the need for either well-defined organometallic reagents or high-molecular silanes as formal hydride precursors, the Martin group described two Ni-catalyzed hydrocarboxylation protocols using more available and benign hydride sources. In 2015, it was found that simple alcohols can be used as formal sources in a mild Ni-catalyzed regioselective hvdride hydrocarboxylation of alkynes, a finding that allowed to expand significantly the functional group tolerance of these protocols (Scheme 39, top).¹⁰⁷ Interestingly, an opposite regioselectivity pattern to that observed in previous hydrocarboxylations of alkynes (Scheme 38) was observed. Apparently, CO2 insertion took place exclusively at a distal position to the aromatic site, independently of the substitution pattern at the alkyne terminus. Such an intriguing regioselectivity profile can be attributed to the formation of two electronically and sterically-differentiated oxanickelacyclopentene intermediates that might be in rapid equilibrium prior selective protonation with the alcohol motif. A final reduction event with Mn recovers back the active Ni(0)Ln species. Following a similar mechanistic rationale, aliphatic terminal and internal alkynes could also be employed as counterparts, using water as the formal hydride source, ultimately generating α -branched aliphatic carboxylic acids (Scheme 39, middle).¹⁰⁸ Such outcome is consistent with the formation of an intermediate oxanickelacyclopentene that locates the metal catalyst at the less-hindered site followed by reductive protonation with water and Mn as the terminal reductant. Subsequent reduction with H₂ over Pd/C delivers the targeted carboxylic acid. More recently, Sato reported the hydrocarboxylation of ynamides with water and Zn as reducing agent.¹⁰⁹ In this case, mixtures of regioisomers were obtained, with a reverse site-selectivity when compared to their previous stoichiometric reaction. Although the mechanism is currently unclear, the change in selectivity might indicate the presence of other pathways, such as nickel hydrides that can insert into the triple bond (Scheme 39, bottom).

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Scheme 39. Catalytic hydrocarboxylation of alkynes using alcohols and water.

The site-selective controllable addition of a both carbon synthon and CO₂ across an alkyne would be a particularly attractive endeavour in the carboxylation arena. To such end, Mori reported a Ni-catalyzed alkylative carboxylation of silyl-substituted alkynes using organozinc reagents as nucleophilic partners (Scheme 40, top). ¹¹⁰ The method allows rapid access to tetrasubstituted acrylic acids, likely via nickelalactone intermediates, in which the nickel catalyst is located distal to the silyl group due to both electronic and steric effects. Such interpretation was later corroborated by theoretical calculations.⁹⁷ In 2016, Hou described a Cu-catalyzed alkylative carboxylation of ynamides with organozinc reagents (Scheme 40, *middle*).¹¹¹ The regioselectivity pattern was controlled by a preferential syn-carbozincation across the alkyne, with CO₂ insertion occurring adjacent to the amine moiety. Tsuji and Fujihara demonstrated the feasibility of triggering multiple CO₂ insertions across the alkyne, obtaining the corresponding maleic anhydrides with Zn as reducing agent (Scheme 40, bottom).¹¹² The presence of Lewis acidic MgBr₂ was essential for the second carboxylation to occur, suggesting that the Lewis acid might facilitate the ring opening of the oxanickelacyclopentene intermediate prior CO2 insertion into the Ni-C bond.



Scheme 40. Catalytic alkylative carboxylation of alkynes.



Scheme 41. Catalytic carboxyzincation/functionalization of alkynes.

Tsuji and Fujihara described an elegant Co-catalyzed carboxyzincation of alkynes en route to acrylic acids bearing tetrasubstituted alkenes (Scheme 41).¹¹³ First, carboxyzincation of the alkyne with $Zn(OAc)_2$ occurs via transmetallation of an in situ generated oxacobaltacyclopentene. The corresponding alkenylzinc intermediate was then engaged in multiple number of transformations in the presence of strong electrophiles or aryl halides in Negishi-type cross-coupling reactions. The method is both versatile and robust, as differently substituted acrylic acids can be obtained with high regioselectivities.

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Scheme 42. Cu-catalyzed bora- and silacarboxylation of alkynes.

While nickel catalysts proved to be particularly competent for hydrocarboxylations and dicarbofunctionalizations of alkynes with CO₂, copper catalysts turned out to be suited for effecting heterocarboxylation reactions. In 2012, Hou developed a Cucatalyzed boracarboxylation of internal alkynes with B₂pin₂ under basic conditions, resulting in the preparation of a variety of α,β unsaturated β -boralactone derivatives (Scheme 42, top).¹¹⁴ Shortly after, Tsuji and Fujihara disclosed a structurally-related Cu-catalyzed silacarboxylation of alkynes with PhMe₂SiBPin en route to α,β -unsaturated β -silalactones (Scheme 42, *bottom*).¹¹⁵ Both reactions are believed to proceed via similar pathways in which the presence of the base mediates the formation of either Cu-Bpin or Cu-SiMe₂Ph species which are added across the alkyne prior to CO₂ insertion. As anticipated, the regioselectivity can be interpreted on the basis of a preferential boryl or silyl cupration in which the Cu atom is located adjacent to the arene or a π -component, invariably leading to the targeted carboxylic acid by CO₂ insertion into the C-Cu bond.

5.2. Catalytic carboxylation of alkenes

The first catalytic procedure for incorporating CO₂ into alkenes was reported in 1978 by Lapidus and co-workers.¹¹⁶ Specifically, the authors demonstrated the feasibility of a previously considered inaccessible transformation, allowing to access propionic acid from ethylene and CO₂ by using Rh and Pd heterogeneous catalysts. This discovery fuelled a revolution, setting the basis for new developments in this area. For instance, Höberg showed that electron-rich Ni(0) complexes could be engaged in an oxidative cyclization of olefins with CO₂ in the presence of imine, diimine and phosphine ligands, giving rise to nickelalactones that afforded propionic acids upon protonolysis in good yields (Scheme 43).¹¹⁷



Scheme 43. Nickelalactone formation and reactivity.



Scheme 44. Regioselectivity in the formation of nickelalactones.

Nickelalactones turned out to be superb reaction intermediates, resulting in a formal homologation reaction that allowed to access high-ordered carboxylic acids by coupling with styrenes, 1,3dienes, allenes or carbon monoxide, among others (Scheme 43).¹¹⁸ Although regioselectivity issues might arise when using monosubstituted olefins, the site-selectivity could be controlled by a subtle temperature modulation and/or the electronic features of the alkene (Scheme 44).¹¹⁹ For example, styrenes form preferentially nickelalactones with the metal center located at the most stable benzylic position. In sharp contrast, α-olefins give rise to a mixture of nickelalactones at room temperature that are in dynamic equilibrium. A seemingly trivial raise in temperature favours the formation of the less-sterically congested nickelalactone. As anticipated, the ligand played a crucial role on site-selectivity. Specifically, good yields could be obtained with phosphines and electron-rich imines whereas disproportionation of CO₂ to form CO was observed when using bipyridine ligands. More recently, an improved site-selectivity with aliphatic olefins was observed with more sophisticated pyridyl-phosphine ligands, 120 and even the rather elusive trisubstituted alkenes could be within reach as well.¹²¹ The formation of nickelalactones via oxidative cyclization has also been investigated by DFT calculations, concluding that the metalacycle is formed by an ethylene-coordinated Ni(0) intermediate.¹²² Subsequently, CO₂ formally attacks the olefin followed by an outer sphere pathway in which previous coordination of CO₂ to the metal center is not indispensable for the nickelalactone formation.¹²³

The formation of five-membered metallalactones should by no means be limited to the oxidative cyclization of unsaturated hydrocarbons with Ni(0) species. Indeed, Ti(II)¹²⁴, Zr(II)¹²⁵ and Fe(0)¹²⁶ complexes have shown to be competent for the formation of oxametallacyclopentanones with ethylene and CO₂ as coupling partners. Interestingly, the use of Fe(0) supported by phosphine ligands (Scheme 45) showed that the ligand utilized was a contributory factor on regioselectivity, with monodentate phosphine ligands giving rise to 1,1-dicarboxylic acids whereas chelating phosphine ligands furnished the regioisomeric 1,2-dicarboxylic acids. The latter is particularly interesting, as nickelalactones derived from alkenes do not typically trigger multiple CO₂ insertion reactions.



Scheme 45. Oxidative cyclization of ethylene, CO₂ and Fe(0) species.





challenging

B-hvdride

elimination

Scheme 46. Acrylate formation from ethylene and CO₂.

The cross-coupling reaction of ethylene and CO_2 for the preparation of acrylic acid, a building block of utmost relevance in industry, ranks amongst the most studied reactions in both academic and industrial laboratories. ¹²⁷ Although important milestones have been achieved during the last 30 years, the oftentimes denominated 'dream reaction' is still considered a rather challenging process.¹²⁸ The origin of such interest can be traced back from the pioneering studies reported by Hoberg, that observed the formation of α , β -unsaturated carboxylic acids from nickelalactones upon raising the temperature to 85 °C (Scheme 46, *top*).^{117c} This result demonstrated the feasibility for promoting a β -hydride elimination from nickelalactones, a rather intriguing observation taking into consideration that such a complex might not easily establish the required syn conformation required for β -elimination events. Driven by these precedents, one could easily

envision a catalytic cycle for preparing acrylic acid from CO_2 and ethylene (Scheme 46, *bottom*).



Scheme 47. Strategies to promote β-hydride elimination in nickelalactones.

However, the implementation of a catalytic route for the preparation of acryclic acid from ethylene is considerably more complicated that one might anticipate. This is due to the fact that (a) the overall transformation is highly endothermic; ¹²⁹ (b) the kinetic barrier for β -hydride elimination is particularly high and (c) the ethylene/acrylic acid ligand exchange that recovers back the active Ni(0) species is not trivial to say the least. In 2006, Walther studied the formation of acrylate from nickelalactones in the presence of bidentate ligands.¹³⁰ Interestingly, the presence of acrylate was detected with bis(diphenylphosphino)methane, resulting in the formation of a rather stable Ni(I)-Ni(I) dimer. Similar results were also found using Mo and W.131 Encouraged by these empirical evidences, theoretical calculations were carried out to shed light on the critical features that assist the β -hydride elimination step. ¹³² As anticipated, DFT studies confirmed that the agostic Ni-H interaction in the corresponding nickelalactone is energetically uphill due to a considerable ring strain. Consequently, it was predicted that an elongation of the Ni–O bond would facilitate β -hydride elimination, thus serving as an inspiration for designing a catalytic route for producing acrylic acids from CO₂. Riecker and Kühn showed that β -hydride elimination could be effected by exposure to a methylating agent (MeI), delivering the corresponding methyl acrylate (Scheme 47, top).¹³³ Subsequently, DFT calculations¹³⁴ suggested a more electrophilic MeOTf could promote this reaction at a faster rate. Bernskoetter and co-workers devised a different strategy consisting of ring-opening of the nickelalactone intermediate by Lewis acids (Scheme 47, middle).¹³⁵ Specifically, coordination of a Lewis acid to the carboxylate fragment expedites β -hydride elimination, resulting in a four-membered nickelacycle. Subsequent theoretical investigations disclosed that the addition of a base was decisive to capture the Ni hydride intermediate and deliver the desired acrylate (Scheme 47, bottom).^{134,136}

In 2012, Limbach and co-workers put together all these stoichiometric investigations and attempted the first catalytic carboxylation of ethylene with CO₂ using a bidentate phosphine ligand and Na^tBuO as the exogenous base.¹³⁷ It became quickly apparent that a subtle balance of all of the elementary steps within the catalytic cycle would be critical for success. For example, while nickelalactone formation typically proceed at high pressures of CO₂, the subsequent steps needed to be carried out at lower pressures of CO₂ due to the formation of carbonic acid esters with the base. Although other reaction conditions were reported, including the use of metal alkoxides as bases,138 the following investigations were directed to find a base with a subtle balance of nucleophilicity and basicity, which could be compatible with all of the individual steps within the catalytic cycle. In this context, Schaub and Limbach found that the use of substituted metal phenoxides efficiently promote the formation of the acrylate Ni(0) complex in the presence of CO₂, allowing to obtain the targeted metal acrylates from ethylene and CO₂ in up to 107 TONs.¹³⁹ Following a different strategy, Vogt and co-workers tackled the critical *B*-hydride elimination step by using a strong Lewis acid such as lithium iodide in the presence of trimethylamine as base. obtaining the corresponding lithium acrylates.¹⁴⁰ It is worth mentioning that although Ni catalysts are commonly employed in these reactions. Pd complexes have been also utilized for similar purposes.¹⁴¹ In this regard, Schaub reported that TONs higher than 500 in a single run could be accomplished by using a Pdbased catalyst by removing the catalyst regeneration step between runs.¹⁴² Despite the advances realized, there is ample consensus that these protocols are still far from being implemented at an industrial scale, suggesting that more research should be conducted for a more efficient production of acrylic acid from CO₂.

Prompted by the stoichiometric studies by Höberg, chemists have been challenged to devise catalytic carboxylations of alkenes other than ethylene. In 2008, Rovis reported the Nicatalyzed hydrocarboxylation of styrenes by using Et₂Zn as reducing agent, resulting in the corresponding phenyl acetic acids (Scheme 48).¹⁴³ The authors excluded the intermediacy of nickelalactones, favoring a mechanism consisting of putative nickel hydride intermediates generated upon transmetalation/βhydride elimination with Et₂Zn. Such interpretation gained credence by deuterium labelling experiments, thus ruling out a mechanism consisting of an initial oxidative cyclization. DFT calculations by Lin and Yuan subsequently revealed that while the generation of nickelalactone was thermodynamically favored, the involvement of nickel hydrides was kinetically driven. 144 Moreover, theoretical calculations confirmed a dual role for Et₂Zn, acting both as hydride source and as Lewis acid that might facilitate the reaction of the transient benzyl nickel(II) intermediate with CO₂. Following this strategy but using bis(acetylacetonato)cobalt(II) as a catalyst and Et₂Zn as a reducing agent, the Yamada Group reported the hydrocarboxylation of α , β -unsaturated nitriles and amides with excellent selectivities, obtaining the insertion of the CO₂ at the α position.¹⁴⁵



Scheme 48. Rovis' hydrocarboxylation of styrenes.

In 2012, Hayashi and Shirakawa reported an Fe/Cu-catalyzed tandem hydromagnesiation/carboxylation of a variety of alkenes via iron hydride intermediates.¹⁴⁶ Of particular relevance was the ability to use unactivated alkenes as substrates, resulting in the corresponding primary alkyl Grignard reagents that ultimately generate, upon exposure to CO₂, the targeted linear carboxylic acids with excellent levels of regioselectivity (Scheme 49, top). Prompted by these studies, Thomas reported a similar approach towards phenyl acetic acids from electron-rich styrenes using an Fe/(bis)imino-pyriridine couple and Grignard reagents as hydride sources (Scheme 49, middle).¹⁴⁷ The use of EtMgBr resulted in preferential formation of branched carboxylic acids. Intriguingly, a linear selectivity was predominantly observed with cyclopentyl magnesium bromide, revealing the non-innocent character of the hydride source on site-selectivity. While the authors did not include a rationale behind these results, one might argue that this finding is likely due to the binding of the cyclopentene to the iron intermediate, increasing the steric hindrance of the hydride entity and favoring the hydrometalation at the homobenzylic position. Prompted by these precedents, Xi showed that titanium precatalysts could be used in an alkene hydromagnesiation followed by carboxylation in the presence of Grignard reagents (Scheme 49, bottom).¹⁴⁸ As for Hayashi and Shirakawa, the utilization of terminal olefins gave rise to the corresponding linear carboxylic acids.

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Scheme 49. Catalytic hydromagnesiation/carboxylation reactions.

Rh-catalyzed carbonylation of olefins with CO₂ and H₂

Ru-catalyzed carbonylation of olefins with CO₂ and alcohols

Scheme 50. Rh- and Ru-catalyzed hydrocarboxylation of unactivated olefins.

The major drawback associated to these strategies, however, relies on the utilization of stoichiometric amounts of highly reactive, yet not particularly chemoselective, organozinc or Grignard reagents. Following up a hydroformylation/reduction sequence of unactivated alkenes with CO₂ by Sasaki, ¹⁴⁹ Leitner ¹⁵⁰ and Beller ¹⁵¹ described a direct Rh- or Ru-catalyzed hydrocarboxylation of olefins with CO₂ and hydrogen or alcohols that gave rise to the targeted carboxylic acids. Note, however, that these techniques fall into the carbonylation arena, as the presence of H₂ or alcohols results in a reverse water-shift reaction that releases CO as the active C1 synthon. Although undoubtedly

a step-forward, the need for elevated temperatures and high pressures, together with the lack of regiochemical discrimination of CO_2 incorporation into the olefin backbone still continued important challenges to be overcome (Scheme 50).



Scheme 51. Ni-catalyzed hydrocarboxylation of olefins with CO₂ and H₂O.

Aimed at fundamentally alter the effective discrimination of CO₂ incorporation across an alkene backbone in the absence of either organometallic reagents or hazardous CO, the Martin group has recently described the ability of harnessing water as an inexpensive hydride source in catalytic hydrocarboxylation of a wide range of alkene derivatives with CO2 at atmospheric pressure (Scheme 51, top).¹⁰⁸ The mild conditions achieved could be translated into a high chemoselectivity profile in the presence of multiple number of functional groups. This protocol could be extended to unactivated olefins, compounds produced in bulk from the ethylene oligomerization,¹⁵² providing an opportunity to repurpose three chemical feedstocks (H₂O, alkene and CO₂) in a controllable fashion (Scheme 51, middle). In a formal sense, this is complementary to that shown for method the hydrocarboxylation of terminal alkynes in which branched carboxylic acids were exclusively obtained under otherwise similar conditions (Scheme 39, middle). 108 As alkynes and alkenes can be easily interconverted by common chemical methods, these results constitute a formal regiodivergent scenario by which either linear or branched carboxylic acids can be accessed from simple unsaturated hydrocarbons. This

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technique could be extended to the coupling of ethylene, the largest volume chemical produced annually, thus affording propionic acid, albeit with low TONs. Mixtures of internal olefins could also be carboxylated under otherwise identical reaction conditions, obtaining exclusively the linear carboxylic acid (Scheme 51, bottom). This result arises from a "chain-walking" migration of the Ni catalyst throughout the aliphatic chain prior to the carboxylation step,⁷⁴ suggesting that water can be used in lieu of commonly-employed stoichiometric organometallic reagents or high-molecular weight silanes as hydride sources in chainwalking scenarios.153

Recently, Yu have reported the direct copper-catalyzed hydroxymethylation of styrenes using silanes and CO₂ (Scheme 52).¹⁵⁴ The reaction likely proceeds via generation of a putative copper hydride intermediate that promotes a regioselective hydrofunctionalization across the double bond prior to CO₂ fixation at the benzylic position. The presence of excess amounts of silane triggers an in situ reduction of the carboxyl function, ultimately affording the hydroxymethylation product in good yields. In line with the seminal work reported by Buchwald in related Cucatalyzed hydrofunctionalization techniques, ¹⁵⁵ the utilization of the SEGPHOS family of bidentate phosphine ligands enabled the development of an asymmetric version, resulting in the corresponding hydroxymethylated products with remarkable levels of enantioselectivity. These results are particularly the development of noteworthy. as metal-catalyzed enantioselective carboxylation reactions still remains a largely underdeveloped terrain.156



Scheme 52. Cu-catalyzed enantioselective hydroxymethylation of styrenes.

Very recently, the Iwasawa¹⁵⁷ and the König¹⁵⁸ group described the merger of transition metal catalysis and photocatalysis for the hydrocarboxylation of styrenes and electrondeficient alkenes. Specifically, the Iwasawa group found that the utilization of a tertiary amine as terminal reductant allows for the in situ generation of a rhodium hydride that triggered a regioselective hydrometalation followed by subsequent CO₂ insertion to afford the corresponding phenyl acetic acid (Scheme 53, top). On the other hand, the König group found that a protocol based on Hantzsch ester as terminal reductant and 4CzIPN as photosensitizer provided the best results under high-intensity Blue-LED irradiation when combined with a cocktail of inorganic bases such as K₂CO₃ and LiOAc (Scheme 53, bottom). Apart from

providing a powerful alternative to classical carboxylation technologies based on the utilization of metal reductants, the authors found that regiodivergency can be dictated by the ligand employed; while bidentate phosphines provided access to linear carboxylic acids, 1,10-phenanthrolines possessing orthosubstituents (L5) afforded phenyl acetic acids instead. While the requirement for 4CzIPN, Hantzsch ester as well as the combination of K₂CO₃ and LiOAc is not yet fully understood, the observed outcome is consistent with a dual pathway by which nickel hydride species are obtained with a L5 regime whereas the intermediacy of nickelalactones are the most plausible scenario with dppb.





CO₂H

.CO₂Et

N H Me

H-1

R

Ŕ

R = carbazole

4CzIPN

EtO₂C

O₂H С CN

ĊΝ

CO₂H

R

electrondeficient alkenes with CO₂,

As to the utilization of alkyne counterparts, a particularly attractive endeavour would consist of the development of a catalytic technique capable of simultaneously adding either a carbon or heteroatom synthon together with CO₂ in a controllable manner across the alkene backbone. Prompted by Hou's studies in related Cu-catalyzed boracarboxylation of alkynes,¹¹⁴ Popp described a related transformation with styrenes as coupling partners, leading to the formation of versatile boron-functionalized α -aryl carboxylic acids that can be further derivatized via crosscoupling reactions (Scheme 54).¹⁵⁹ The reaction proceeds via addition of Cu-BPin active species across the alkene prior to CO2 insertion at the benzylic position.

CO₂H

CO₂H

10.1002/anie.201803186

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Scheme 54. Cu-catalyzed boracarboxylation of styrenes.

In 2017, the Martin group reported a photocatalytic dicarbofunctionalization of styrenes mediated by visible light in which a carbon-based radical precursor is added across the alkene with concomitant CO₂ insertion, thus enabling the access to highly substituted phenyl acetic acids from simple precursors under mild conditions (Scheme 55, top). 160 This technique allowed for introducing fluorinated analogues from sulfinate salts whereas regular carbon backbones could be inserted by using readily available organotrifluoroborates or simple oxalate salts derived from tertiary alcohols. Preliminary mechanistic experiments suggested the intermediacy of in situ generated benzyl anions, an assumption that was corroborated by isotopelabelling and by the favourable exergonic process by which a benzyl radical ($E_{red} \sim -1.40V$) is reduced by Ir(II) ($E_{red} \sim -1.51V$) generated upon reductive quenching. Independently from Martin's work, Yu described the use of FeCl₃ in combination with an aromatic thiol under visible light irradiation to perform the thiocarboxylation of styrenes and acrylates (Scheme 55, *bottom*).¹⁶¹ In this case, CO₂ was inserted at the homobenzylic site, thus suggesting the intermediacy of CO2 radical anion. This strategy is reminiscent of a recent work developed by Jamison and co-workers, in which CO₂ radical anion formed by organophotocatalysis was coupled with amines and styrenes to yield the corresponding carboxylic acids.¹⁶²

dicarbofunctionalization of styrenes with CO₂ and radical precursors





Scheme 55. Photocatalytic difunctionalization of styrenes with CO₂.

5.3. Catalytic carboxylation of dienes and other polyunsaturated systems

Unlike alkenes or alkynes, 1,3-dienes offer the advantage of possessing an additional unsaturated backbone that could be used for further functionalization. Such seemingly trivial observation can hardly be underestimated, as it might set the basis for promoting conceptually novel carboxylation reactions that would be beyond reach otherwise. The first reports aimed at unravelling the potential of 1,3-dienes in carboxylation technologies appeared in the 80's, when Behr¹⁶³ and Höberg¹⁶⁴ reported the telomerization of butadiene in presence of CO_2 catalyzed by either palladium or nickel precatalysts (Scheme 56). As shown, the choice of metal exerted a profound influence on both reactivity and selectivity, obtaining either a lactone or a carboxylic acid, albeit in low to moderate yields.



Scheme 56. Telomerizarion of 1,3-butadiene with CO₂.

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Despite the inherent potential of 1,3-dienes in carboxylation reactions, it was not until 2002 that Mori described the Nicatalyzed carboxylation of bis-1,3-dienes with CO₂ and organozinc reagents, resulting in a protocol that is somewhat reminiscent of the classical cycloisomerization reactions (Scheme 57).¹⁶⁵ Two years later, the authors described the feasibility of promoting an enantioselective reaction with (*S*)-MeOMOP as chiral ligand. This result is particularly noteworthy, as it constituted the first metal-catalyzed enantioselective transformation described with CO₂ as coupling partner.¹⁶⁶



Scheme 57. Cycloisomerization of bis-1,3-dienes with CO2.

In 2011, Iwasawa described an elegant and rather efficient hydrocarboxylation of 1,3-dienes (Scheme 58, top).^{88b} Critical for success was the employment of a pincer-type Pd(II) precatalyst (Pd-4) and Et₃Al as the terminal reducing agent to form the corresponding β , γ -unsaturated carboxylic acids. Intriguingly, the utilization of 1,3-dienes in metal-catalyzed carboxylation endeavors remained dormant until early 2018, at which time the Martin group described a Ni-catalyzed protocol for the synthesis of adipic acids from 1,3-dienes and CO₂ in a site-selective manner (Scheme 58).¹⁶⁷ Although 1,3-dienes are inherently predisposed to telomerization reactions (Scheme 56), it was found that a catalytic couple based on a 1,10-phenanthroline ligand possessing substitution adjacent to the nitrogen atom enabled the site-selective 1,4-dicarboxylation reaction without traces of neither competitive telomerization nor 1,2-dicarboxylation. The transformation turned out to be widely applicable and could be coupled with a hydrogenolysis event, including the coupling of 1,3-dienes substituted with either aromatic or aliphatic backbones. This technology could be extended to 1,3-butadiene, piperylene or isoprene, chemical feedstocks that are produced on a large scale from the steam cracking in the production of ethylene. Mechanistic experiments with both Ni(0)(L16)₂ or well-defined Ni-1 suggested a mechanism that exploited the carbogenic nucleophilicity of in situ generated π -allyl nickel carboxylate prior to CO₂ insertion via SET processes or comproportionation with Ni(0)L16.



Scheme 58. Metal-catalyzed carboxylation of 1,3-dienes with CO2.

Ni-catalyzed dicarboxylation of allenes





Scheme 59. Catalytic carboxylation of allenes with CO_2 .

The first catalytic carboxylation of 1,2-dienes (allenes) was described in 2005 by Mori and co-workers using Ni(cod)₂ as catalyst and Me₂Zn as reducing agent (Scheme 59, *top*). ¹⁶⁸ Of particular importance was the requirement for a large excess of DBU and a silyl end-capped allene, the latter being attributed to a combination of stereoelectronic effects. More recently, an intramolecular reductive arylative carboxylation of allenes with CO₂ was reported by Sato (Scheme 59, *bottom*).¹⁶⁹ Unlike Mori's protocol, the reaction was promoted by palladium catalysts supported by electron-poor phosphines with Et₂Zn as a stoichiometric reducing agent.

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Scheme 60. Pd-catalyzed hydrocarboxylation of allenes with CO2.

In 2008, Iwasawa reported the hydrocarboxylation of allenes using **Pd-4** and Et₃Al as stoichiometric reductant (Scheme 60, *top*).^{88a} The proposed mechanism followed an otherwise similar rationale to that shown previously for 1,3-dienes.^{88b} Such interpretation gained credence in an elegant study reported by the Hazari group that isolated and characterized the putative reaction intermediates within the catalytic cycle.⁸⁷ In line with this notion, the mechanism likely is initiated by the generation of a Pd(II) hydride followed by hydrometalation to yield an allylic Pd(II) intermediate (Scheme 60, *bottom*). CO₂ insertion followed by transmetalation gives rise to an aluminium carboxylate while regenerating the Pd(II) hydride via β -hydride elimination.

Prompted by Mori's cycloisomerization with CO₂ and nickel catalysts,¹⁶⁵ Sato described the reductive carboxylation of 1,7enynes as a means to access the core of (–)-Corynantheidine (Scheme 61, *top*).¹⁷⁰ Subsequently, the groups of Ma¹⁷¹ and Diao¹⁷² independently showed the ability of 1,6-enynes and 1,7enynes to participate in related catalytic reductive carboxylations, furnishing the five-membered or six-membered ring, respectively (Scheme 61, *bottom*). These conceptions were followed up by Ma in a Ni-catalyzed hydrocarboxylation of 1,6-diynes to give access to α , β , γ , δ -unsaturated carboxylic acids in excellent yields and regioselectivities (Scheme 62).¹⁷³





Scheme 61. Catalytic carboxylation of enynes with CO2.



Scheme 62. Catalytic carboxylation of 1,6-diynes with CO2.

In light of these results, the catalytic incorporation of CO2 into unsaturated hydrocarbons undoubtedly holds promise to give a rapid and reliable access to carboxylic acids from simple and abundant precursors. These processes are essentially based on the generation of a transient organometallic reagent via the siteselective addition of a hydrogen, carbon or heteroatom across the π -component. Despite the knowledge acquired, however, a nonnegligible number of methods still require the utilization of either stoichiometric metal complexes or metal reductants, and the development of enantioselective variants are still at their infancy. Although these limitations have partially been met by the merger of photocatalysis with metal catalysis, it is worth noting that the number of photocarboxylation processes is still rather limited to particularly activated substrates, requiring in multiple cases the utilization of large amounts of additives. Additionally, the maturity of these reactions has not yet been demonstrated within the context of polyunsaturated systems, as a myriad of transformations can easily be envisioned by harnessing the inherent reactivity of the in situ generated organometallic reagents.

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6. Catalytic carboxylation techniques via C–H functionalization

The last decades have witnessed an exponential growth in catalytic C–H functionalization reactions. ¹⁷⁴ Unlike classical cross-coupling technologies, C–H functionalization offers the advantage of replacing either the nucleophile or electrophile by an *in situ* generated organometallic reagent. Such seemingly trivial modification avoids prefunctionalization, increasing the efficiency of the process. Although spectacular advances have been realized in the area of C–H functionalization, the discrimination among multiple C–H bonds still represent a considerable challenge – particularly in saturated hydrocarbons – to be overcome. The next section describes efforts aimed at promoting metal-catalyzed C–H carboxylation reactions with CO₂ as coupling partner. Although undoubtedly important for preparing salicylic acid, the Kolbe-Schmitt reaction doesn't fall into such category and it will not be treated in this account.¹⁷⁵

6.1. Metal-catalyzed sp C-H carboxylation

Prompted by the acidity of sp C-H bonds, it comes as no surprise that multiple efforts have been made for effecting the catalytic carboxylation of terminal alkynes. These reactions typically proceed via the intermediacy of a well-defined organometallic reagent via in situ deprotonation with an appropriate base, thus setting the stage for a CO₂ insertion into the sp C-metal bond that ultimately results in the corresponding carboxylate intermediate. The first example of a metal-mediated carboxylation of alkynes was reported in 1974 by Saegusa (Scheme 63, top),¹⁷⁶ in which a copper or silver acetylide (formed in situ by exposing a terminal alkyne to either CuOtBu or CuOtBu) triggered a CO₂ fixation in the presence of electron-rich ligands such as tributyl phosphine. Surprisingly, this result was not "revisited" until 20 years later when Inoue described the first catalytic carboxylation of terminal alkynes using Ag(I) or Cu(I) salts in the presence of excess amounts of exogenous bases at high temperatures (Scheme 63, middle). 177 The presence of electrophilic partners resulted in the formation of alkyl or benzyl esters.

Saegusa metal-mediated carboxylation of terminal alkynes



Scheme 63. Metal mediated carboxylation of terminal alkynes.

In 2008, Anastas described a Ag-catalyzed tandem cycloisomerization/carboxylation via in situ generated 1,6-diynes under basic conditions and high temperatures (Scheme 64).¹⁷⁸ This rather intriguing technique showed the potential of promoting multiple C–C bond-formations with concomitant CO_2 insertion in a tandem fashion. Although regioisomeric mixtures were inevitably obtained, this technology allowed for rapidly obtaining scaffolds with anticancer or antiviral properties.¹⁷⁹



Scheme 64. Selected examples of the alkyne carboxylation/cyclazation.

Inspired by the pioneering work of Saegusa and Inoue, 176-177 Gooßen, ¹⁸⁰ Lu, ¹⁸¹ and Zhang¹⁸² independently reported the use of copper catalysts for the direct carboxyation of terminal alkynes with CO₂ under basic conditions (Scheme 65, top & middle). Gooßen utilized a heteroleptic Cu(I) complex containing a 1,10phenanthroline and triarylphosphine (I and II) whereas Lu and Zhang dealt with (IPr)CuCl or TMEDA-Cu(I) complexes. Prompted by the lower yields obtained with electron-withdrawing alkynes, Zhang developed a protocol based on a polymeric NHC ligand.¹⁸³ The inherent versatility of this platform set the basis for designing Ag and Pd-catalyzed carboxylations of acetylenes in the presence of both CO₂ and H₂, furnishing the corresponding cinnamic acid derivatives.¹⁸⁴ Subsequently, Lu and coworkers described an otherwise similar, transformation using a ligand-free Ag(I) catalyst instead (Scheme 65, bottom).¹⁸⁵ These results reinforced the superior reactivity of Ag(I) catalysts, particularly at low catalyst loadings.^{186, 187} Recently, a silver tungstate catalyst has been shown to promote a dual activation of both CO2 and the alkyne in a synergistic fashion, even with electron-deficient alkynes (Scheme 66). ¹⁸⁸ Aimed at improving catalytic recyclability, ¹⁸⁹ chemists have focused their attention on a more prolific use of Cu and Ag nanoparticles and on the discovery of more efficient protocols in the presence of greener solvents such as ethylene carbonate¹⁹⁰ or supercritical CO₂.¹⁹¹ Similarly, Cucatalyzed multicomponent reactions ¹⁹² and rare-earth metals have also been used for the carboxylation of terminal alkynes.¹⁹³

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Scheme 65. Cu- and Ag-catalyzed carboxylation of sp C-H bonds.



Scheme 66. Silver tungstate-catalyzed carboxylation of sp C-H bonds.

6.2. Metal-catalyzed *sp*² C–H carboxylation

The success of promoting a direct carboxylation of terminal alkynes is inherently linked to the remarkably high acidity of the targeted sp C–H bond. However, the acidity of sp² C–H bonds typically rank from $pK_a \sim 25$ (electron-poor heterocycles) to $pK_a = 50$ of ethylene. Such a wide range of pK_a values indirectly suggests that different strategies should be implemented depending on the acidity of the targeted sp^2 C–H bond. In 2012,

Nolan reported a carboxylation of acidic sp² C–H bonds based on [(IPr)AuOH] as catalyst under basic conditions (Scheme 67, top).¹⁹⁴ Shortly after, Nolan¹⁹⁵ and Hou¹⁹⁶ independently reported an otherwise similar reaction with Cu(I) complexes (Scheme 67, top & middle), albeit requiring higher catalyst loadings than the Au-regime. More recently, Hou reported an improved Cu-based protocol based on a different NHC ligand with a variety of electron-poor heteroaromatics. 197 The mechanism of these transformations is believed to proceed via either copper or gold hydroxides that subsequently trigger a deprotonation of the sp² C-H bond in the electron-poor arene (Scheme 67, bottom). CO2 insertion into the carbon-metal bond followed by base treatment regenerates the catalytically competent species. DFT studies by Ahlquist and Werd suggested that the reactivity of (NHC)AuAr complexes might occur via an oxidative mechanism, leaving some doubt whether the Au-C bond could promote CO2 insertion.¹⁹⁸ Similarly, Yates suggested that a more reactive carbene intermediate VII could undergo nucleophilic attack to CO2 in the Cu series to afford a copper carboxylate.¹⁹⁹

The first carboxylation of less-acidic sp^2 C–H bonds lacking directing groups in the vicinity was described in 1984 by Fujiwara (Scheme 68).²⁰⁰ Specifically, it was found that carboxylic acids were within reach by exposure of arenes with Pd(OAc)₂ and tBuOOH under CO2 atmospheres. While the mechanism still remains rather unclear and one might argue that the efficiency of the reaction was rather low (TON ~ 1.3), this reaction set a new ground in the carboxylation arena. Indeed, this seminal work tacitly showed the viability for obtaining benzoic acids from benzene and CO2, a reaction that a priori would be thermodynamically uphill. These conceptions were taken by Iwasawa, demonstrating that chelation control could alternatively be employed for tackling the challenge of promoting a carboxylation event at less-acidic sp² C-H bonds (Scheme 69, top). 201 Specifically, it was shown that Rh(I) precatalysts in combination with AIMe₂OMe could be used for the carboxylation of 2-pyridyl or 2-pyrazoyl arenes under atmospheric pressure of CO₂. The proposed catalytic cycle is initiated by $L_n Rh(I)$ -Me species that are formed in situ via transmetalation of Rh(I) precatalysts with AIMe2(OMe) (Scheme 69, middle). A subsequent binding to the nitrogen atom facilitates an oxidative addition into the proximal sp² C-H bond, thus setting the stage for a reductive elimination that releases methane while forming a fivemembered Rh(I) metallacycle. A final CO₂ insertion into the sp² C-Rh bond and metathesis with AIMe2(OMe) recovers back the active LnRh(I)-Me species while delivering an aluminium carboxylate. No dicarboxylation was detected, an observation that is likely attributed to the presence of the carboxyl acid function that prevents the Rh(I) catalyst to be in close proximity to the targeted sp² C–H bond. In 2016, Ma took advantage of Iwasawa's report for functionalizing aromatic rings contained in a metal organic framework (MOF), thus modulating the properties of the resulting MOF.202

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Scheme 67. Au or Cu-catalyzed carboxylation of acidic sp^2 C–H bonds.

Ar -H (solvent)	+	CO₂ (1 atm)	Pd(OAc) ₂ (1 equiv)	Ar -CO₂H 40 - 127%
			tBuOOH (40 equiv)	

Scheme 68. Fujiwara carboxylation of arenes.





Scheme 69. Rhodium and palladium-catalyzed "directed" carboxylation of sp^2 C-H bonds

Although a step-forward, the need for a non-particularly trivial to modify *ortho*-pyridine as well as the presence of stoichiometric amounts of organometallic reagents still represented a drawback to be overcome. To such end, Iwasawa has recently described an alternative carboxylation of arenes with 2-hydroxystyrenes under basic conditions, furnishing the corresponding α , β -unsaturated δ -lactones (Scheme 69, *bottom*).²⁰³ The authors could isolate a sixmembered alkenyl Pd(II) intermediate and study its reactivity, establishing a mechanistic rationale that incorporates an additional molecule of 2-hydroxystyrene prior CO₂ insertion. Reaction with Cs₂CO₃ ultimately leads to the formation of the corresponding lactone product. Recently, the Yu group has shown a similar reactivity with related precursors in the absence of Pd catalysts.²⁰⁴



Scheme 70. "non-directed" Rh-catalyzed carboxylation of sp² C–H bonds.

Recently, Iwasawa described an alternative to the "non-directed" Fujiwara carboxylation of benzene, showing that Rh(I) catalysts supported by bidentate phosphine ligands could promote this transformation effectively (Scheme 70).²⁰⁵ It was found that higher temperatures and methyl aluminium complexes were ultimately required to obtain good turnover (TON) numbers. Moderate to excellent site-selectivities were obtained when promoting the direct carboxylation of toluene or xylene. Recent mechanistic investigations suggested an otherwise identical pathway to that shown previously for directing group protocols in which in situ generated $L_nRh(I)$ -Me complexes come into play.²⁰⁶

6.3. Metal-catalyzed sp³ C–H carboxylation

While catalytic sp^2 or sp C–H functionalization has matured to a robust discipline in organic synthesis, less research has been focused on the activation of sp^3 C–H bonds.²⁰⁷ Although a priori conceivable, the functionalization of sp^3 C–H bonds is considerably more challenging than the corresponding sp^2 C–H bonds. This is due to the fact that the former lacks empty low-energy orbitals or filled high-energy orbitals that could interact with the metal center, making these techniques particularly challenging from a both conceptual and practical standpoint.

Prompted by the knowledge acquired when promoting the photocarboxylation of ortho-alkylated aryl ketones,²⁰⁸ Murakami described the merger of organic photocatalysts with (IPr)CuCl for tackling the carboxylation of allylic sp³ C-H bonds (Scheme 71). 209 Photoexcitation of PC-1 under UV-light irradiation generates a triplet excited state upon intersystem crossing, setting the basis for a hydrogen-atom abstraction (HAT) that upon recombination with the ketyl radical results in a tertiary homoallyl alcohol. Deprotonation with in situ generated [Cu]OtBu delivers a copper alkoxide that triggers a β -carbon elimination that ultimately furnishes the targeted potassium carboxylate via CO₂ insertion. Although low TON's were unfortunately obtained, such a technique is unique in its own right, providing a step-forward in the sp³ C–H carboxylation arena. More recently, Sato developed an alternative approach for the carboxylation of allylic sp^3 C–H bonds based on the cobalt catalysts and AIMe₃ (Scheme 72).²¹⁰ The proposed mechanism for this transformation follows a similar rationale to that shown for the Rh-catalyzed carboxylation of arenes (Scheme 69), in which L_nCo(I)Me intermediates undergo an oxidative addition followed by loss of methane, generating allyl-Co(I) species prior to CO₂ insertion, generating the corresponding β , γ -unsaturated carboxylic acid. Although siteselectivity issues come into play when olefins lacking π -components adjacent to the targeted sp^3 C–H bond are utilized, this method certainly provides the basis for future developments in this area of expertise.



Scheme 71. Light-induced carboxylation of allylic sp^{3} C–H bonds.



Scheme 72. Cobalt-catalyzed carboxylation of allylic *sp*³ C-H bonds.

Beyond any reasonable doubt, the most attractive case scenario would be the development of a technology capable of promoting the catalytic carboxylation of unactivated sp^3 C–H

bonds in alkane feedstocks. However, this functionalization is particularly problematic due to the presence of multiple, yet similar, sp^{3} C–H bonds in a saturated hydrocarbon side-chain. Such goal could a priori be tackled by the utilization of directing group protocols or radical-type C–H functionalizations; however, the former requires the installation (and detachment at later stages) of directing groups whereas the latter typically results in the activation of relatively weak C–H bonds. Efforts towards this goal have recently been shown by the Martin group in a reactivity relay that makes use of either alkyl halides or internal olefins as substrates, thus resulting in a formal carboxylation event at distal and previously unfunctionalized sp^{3} C–H sites via "chain-walking" of an *in situ* generated organometallic Ni complexes (Scheme 25 & Scheme 51, *bottom*).^{73,108}

7. Summary and Outlook

The catalytic conversion of abundant, inexpensive and renewable CO2 into chemicals via C-C bond-forming reactions has gained considerable momentum as it might not only create an added value that balances the costs of CO₂ capture, but also represent a sustainable opportunity to fossil fuels. Among various conceivable scenarios, particular attention has been devoted for the conversion of CO₂ into carboxylic acids given their important role on the manufacture of a myriad of products of utmost relevance for our chemical industry. Any attempt at using CO₂ as raw material in synthetic endeavours, however, has to cope with its significant kinetic inertness and thermodynamic stability (ΔG_{f}^{o} = - 94.6 Kcal/mol). For a considerable long time, these features suggested that heavily polarized and particularly reactive, organometallic intermediates would be needed for converting CO2 into carboxylic acids, contributing to the perception that the design of catalytic technologies would be a futile effort. Fortunately, chemists share the romantic idea that anything is possible and that science progresses when curiosity, ambition, passion, conviction and creativity go hand-to-hand to alter our prevailing, yet not invincible, preconceptions. As judged by the exponential growth experienced in metal-catalyzed carboxylation reactions, it is evident that this field has evolved into a mature discipline within organic synthesis, and that a variety of coupling partners can now be employed in these endeavours. Even modern "chain-walking" scenarios are within reach, holding promise to gravitate toward CO₂ insertion at distal reaction sites, enabling strategic, yet counterintuitive, new approaches for installing the carboxylic acid function. In view of the superb functional-group compatibility of these methods, it is fair to predict that carboxylation reactions will gain even more importance in the years to come, and that immediate applications will slowly start to appear, particularly within the context of total synthesis of biologically-relevant molecules

In view of the current carboxylation portfolio, one might wonder whether there are any substantial shortcomings left that need to be overcome. The following aspects are most daunting: (a) despite the low cost, availability and lack of toxicity of phenols, anisoles or simple *unactivated* aliphatic alcohols, the *ipso*-

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carboxylation of these attractive counterparts via C-O bondcleavage is still beyond reach; (b) while the merger of metal catalysis with photocatalysis has recently alleviated the need for stoichiometric metal precursors, these methods still face notorious challenges, particularly when using unactivated unsaturated hydrocarbons as starting precursors; (c) the development of catalytic carboxylation reactions at unactivated sp² or sp³ C-H bonds lacking directing groups, or "control elements" on the side-chain have found little echo. Arguably, the biggest deficit in synthetic terms is the virtual lack of enantioselective carboxylation reactions; if successful, such technologies would gain tremendous popularity, constituting a significant step-forward for preparing valuable pharmaceutical ingredients. These untoward features notwithstanding, it is inevitable to predict that the fine-tuning of the catalysts will close many of these gaps in coverage and that brave efforts aimed at meeting these challenges will not be in vain.

As evident from the results compiled in this review, seemingly subtle modifications on the ligand backbone marked changes in the reaction outcome. Likewise, the unique role exerted by the additives and coordinating solvents (e.g., DMF) still remains enigmatic and speculative. Although these features could be turned into a strategic advantage for reaction optimization, allowing to establish certain "structure-reactivity" relationships, they provide case-specific solutions. At present, progress in this arena is unfortunately based on empirical evidences and unravelling the mechanistic intricacies of catalytic carboxylation reactions still remains "terra incognita" due to the presence of short-lived, yet exceptionally sensitive, entities, the highly heterogeneous nature of these processes and the low solubility of CO₂ in organic solvents. Additionally, there is ample consensus that multiple redox manifolds might intervene depending on both the substrate and the catalyst employed. As the reader might anticipate, the exact nature of the putative active species remains speculative and uncertainty prevails on whether "inner-sphere" mechanisms via CO₂-bound metal complex or "outer-sphere" CO₂ insertions into in situ generated organometallic intermediates come into play. Therefore, it is fair to say that the lack of mechanistic understanding can be termed as the "Achilles heel" of this field of expertise. However, history has showed that there are no invincible armies and that every great advance in science has always issued from an innate desire for truth. We certainly anticipate that efforts aimed at providing fundamental knowledge at the molecular level will not only be a rewarding ground for innovation but also will provide additional momentum, setting the basis for the full adaptation of these rather appealing events while enabling the transition from comprehension to prediction. It is therefore safe to state that catalytic carboxylation reactions have not reached their full potential and that spectacular developments are likely expected in the near future.

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With a certain lag time, metal-catalyzed carboxylation reactions of organic matter with CO_2 as C1 feedstock have entered a new era of exponential growth. These C-C bond-formations are characterized by its mild conditions and excellent chemo- and site-selectivity for a wide range of coupling partners, holding promise to streamline synthetic sequences en route to carboxylic acids. These favorable attributes are expected to foster advanced applications in the near future.

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Transition Metal-Catalyzed Carboxylation reactions with Carbon Dioxide