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Tandem functionalization-carboxylation reactions of π -systems with CO₂

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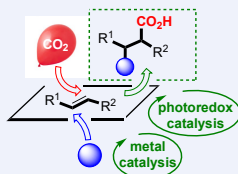
Keywords

Catalysis | Carboxylation | CO₂ | Tandem reaction | π -Systems

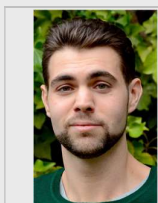
Abstract

The tandem catalytic functionalization/carboxylation of double as well as triple carbon-carbon bonds with CO₂ represent an emerging research area in synthetic organic methodology. In particular, the combination of mild reaction conditions, stoichiometric acceptor/donorless conditions (visible light photoredox catalytic) and chiral catalysts contributed to a rapid development of this intriguing research area capable of creating chemical diversity/complexity from readily available unsaturated hydrocarbons and in the presence of CO₂ as a C1-binding block. The most recent developments in the field have been collected in the present review article and organized, based on the different sets of π -systems/intermediates/reactive partners employed (*i.e.* nickelalactones, organo-halides) as well as synthetic strategies targeted (*i.e.* visible-light photo redox catalysis).

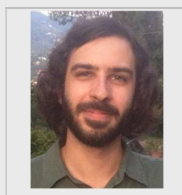
Comprehensive Graphic Content



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Lorenzo Lombardi was born in Jesi, Italy in 1994. He obtained his Bachelor's degree in 2006 from the University of Camerino under the supervision of Prof Enrico Marcantoni. Then he moved to Bologna where he got the Master in Chemistry (2018) and entered the PhD programme under the supervision of Prof. Marco Bandini. His research interests deal with the development of new metal and carbocatalytic methodologies in organic transformations (middle-right).



Marco Bandini received the PhD in Chemistry from the University of Bologna in the 2000. After some research periods abroad (University of Chapel Hill, USA and University of York, UK) he got a permanent position at the Alma Mater Studiorum – Università di Bologna where he is currently holding the position of full Professor in organic chemistry. Authors of more than 130 publications, his research interests deal with the development of catalytic systems in synthetic organic chemistry (right).



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1. Introduction

Carbon dioxide has emerged in the past decades as a green and abundant C1-synthon in organic chemistry.^[1] Overcoming the challenge of CO₂ intrinsic inertness has brought chemists to develop different activation methods, applying it successfully in metal-, light- or base-promoted processes.^[2] This continuous interest has turned this ubiquitous gas from a dull by-product to a versatile building-block. Direct carboxylation of reactive functional groups, such as aryl/alkyl (pseudo)halides, alcohols, amines and radical precursors, as well as hydrocarboxylation of olefins can rapidly give access to pre-functionalized carboxylate-containing scaffolds of great synthetic interest.^[3] However, the possibility of enhancing molecular complexity and, at the same time, introducing CO₂ as a carboxylate precursor has recently emerged, giving rise to a number of **tandem functionalization-carboxylation processes**. The advantage of applying this reactive concept is to employ a single activation method (that is, a complete set of catalysts, additives, and solvents) to achieve both molecular modification and carboxylation of the same scaffold. This review focuses on these reactive sequences, highlighting the elegance and the potential of the single strategies. As it emerges from the collected examples, the types of functionalizations that have been productively coupled with CO₂-based carboxylation are wide and diversified, ranging from carbo-functionalizations to the introduction of various heteroatoms such as B, F, Si, S, and P. The processes are divided into three categories, depending on the type of activation employed, namely: light-promoted processes, metal or base-promoted processes and reactions involving nickelalactone intermediates. This is useful for a reader that looks at the disclosed examples with a critical point of view, giving a reasoned idea of the reactive panorama as well as stimulating further applications. Closely related, but conceptually different are carboxylation-ring closure reactions that employ CO₂ as a “double” building block, creating two bonds with the reactive partner. These strategies are undoubtedly highly useful as well as widely developed; they however suffer from a restricted number of functional groups that can be introduced, namely lactones, carbonates, lactams, ureas and more rarely ketones, that can readily derive from CO₂ capture. These processes are collected in some recent reviews and are not presented here.^[4]

2. Light-promoted alkene carboxylative functionalizations with CO₂

The chemistry of carboxylative functionalizations of (isolated) alkenes has recently been dominated by light-promoted processes,

showing the versatility of the synthetic strategies and the tolerability of a variety of substrates and functional groups.^[5]

The first report of light-mediated functionalization-carboxylation reaction of olefins was disclosed in 2017 by the group of Martin.^[6] This consists in a catalytic dicarbofunctionalization of styrenes **1** with radical precursors and CO₂, in the presence of Ir-photocatalyst **A** and blue-light irradiation. This redox-neutral reaction was conveniently developed under stoichiometric donorless conditions or using organic (pseudo)halides, making it complementary to other carboxylation strategies (Figure 1). The process was mainly optimized for a trifluoromethylation-carboxylation reaction towards phenylacetic acids **2**, employing the Langlois reagent (CF₃SO₂Na) as a precursor for the trifluoromethyl radical. However, it was extended, with slight modifications (catalyst **B**), to CHF₂SO₂Na, benzyl trifluoroborates or *tert*-alkyl oxalates, resulting in a quite general and diversified protocol. The reaction could accommodate α,α -disubstituted or α -unsubstituted styrenes, as well as β -substituted ones, along with a broad variety of functional groups, including aromatic boronates, halides or pseudohalides, useful for subsequent cross-coupling-based functionalizations. Preliminary mechanistic studies pointed to the sequence highlighted in Figure 1 where the reaction of the Langlois reagent with excited **A** generates a trifluoromethyl radical, which is added across the styrene double bond, forming an intermediate bearing a benzyl radical. A single-electron-transfer (SET) process from the reduced photocatalyst to this intermediate generates a carbanion responsible for the trapping of CO₂ and consequent delivery the final product **2**.

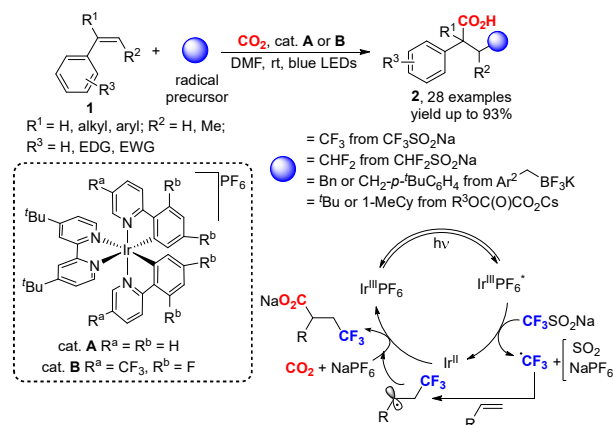


Figure 1 Early studies in the dicarbofunctionalization of alkenes with CO₂ via visible-light photoredox catalysis.

A modification of the previous protocol was recently reported by Yu and Lan.^[7] Specifically engineered substrates **3** underwent a trifluoromethylation-1,5-hydrogen atom transfer (HAT)-carboxylation sequence in the presence of photocatalyst **A**, the Langlois reagent as a trifluoromethyl radical source, Cs₂CO₃ and KOPiv as auxiliary bases, and blue light irradiation (Figure 2). Products **4**, bearing the ubiquitous α -amino acid moiety, were produced in high yields for a variety of starting materials, showing a broad functional group toleration. A mechanism similar to the one proposed by Martin is also operating here. However, between the addition of the trifluoromethyl radical to the olefin and the reduction-carboxylation events, a 1,5-HAT occurs, with the formation of an α -amino benzyl radical.

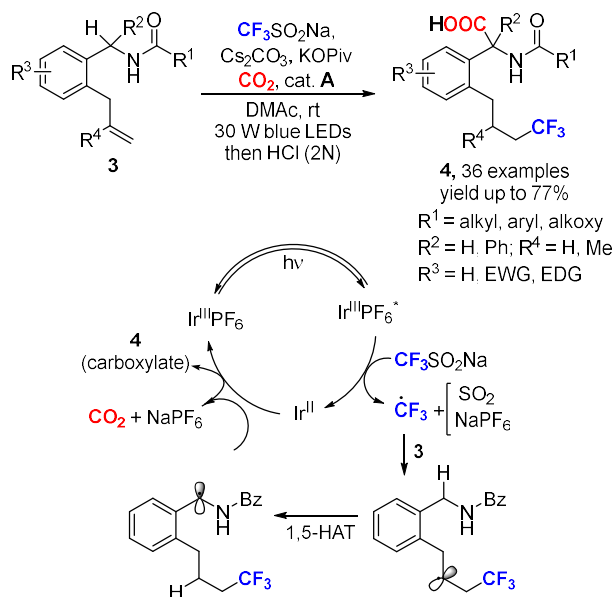


Figure 2 Visible-light promoted intramolecular remote double functionalizations of alkenes with CO_2 .

Shortly after the first report by Martin in 2017, Yu and co-workers disclosed a three-component thiocarboxylation of conjugated olefins **5** with thiophenols **6** and CO_2 for the formation of β -thioacids **7**.^[8] This redox-neutral process is promoted by a catalytic amount of FeCl_3 and proceeds in the presence of blue light irradiation and an excess of a strong base (KO^tBu). A variety of functionalized styrenes, including α,α -disubstituted, β -substituted ones and vinyl-heterocycles, as well as acrylates (**5**) were well tolerated. However, the process was found to be restricted to electron-rich or electron-neutral aromatic thiols only (Figure 3). Products **7** were also subjected to a variety of transformations to prove their synthetic relevance. The prominent feature of this reaction is the unusual regioselectivity observed, giving rise to β -substituted hydrocinnamic acids **7**, instead of usual phenylacetic acids (*vide infra*). This is explained through an inverted carboxylation-functionalization sequence, where carboxylation occurs first. Mechanistic studies corroborated the hypothesis of the formation of CO_2 radical anion ($\text{CO}_2^{\cdot-}$) as well as the presence of an alkyl radical in the reaction mechanism. The authors indeed suggested that, upon irradiation of a Fe-S complex (presumably an iron(III) thiolate) and its reaction with CO_2 , a thiophenyl radical (ArS^\cdot) and $\text{CO}_2^{\cdot-}$ are formed. The latter reacts with the olefin for the formation of a stabilized benzylic radical, captured by the ArS^\cdot to give the observed product. An inverted sequence, where thiolation occurs first, was ruled out by the observed regiochemistry.

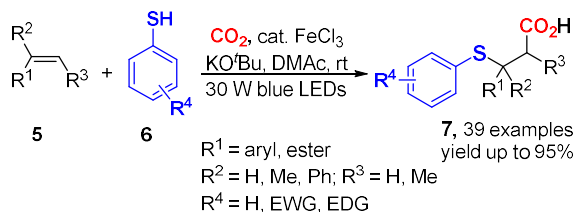


Figure 3 Iron-promoted thiocarboxylation of alkenes with CO_2 under visible light assistance.

The interest by Yu for light-driven functionalization-carboxylation reactions led to the disclosure of additional protocols. In 2019, they reported a metal-free phosphonocarboxylation of a variety of alkenes **8** or **9** with H-P(O) compounds **10** in the presence of organic photocatalyst **C** (4-CzIPN), blue light irradiation and a base (Figure 4).^[9] A careful optimization stage of the reaction conditions was pivotal to ensure high yields over a very large volume of compounds, showing a broad and diversified protocol. In particular, di-alkyl and diaryl phosphine oxides as well as phosphites could serve as phosphonylating agents. Moreover, an impressive variety of olefins **8** or **9** could productively undergo the desired process, such as: electron rich enamides and enolsilanes, electron-neutral broadly substituted styrenes, and electron-poor acrylates. This resulted in the formation of diversified products **11** or **12**, among which enamides-derived β -phosphono- α -amino acids are particularly noteworthy due to the presence of this motif in natural products and pharmaceuticals. Derivatizations of the obtained compounds were also achieved. Mechanistic studies pointed towards SET from **10** to the excited catalyst, followed by addition of the radical to the olefin, reduction of the so-formed stabilized radical by a second SET from the reduced form of the photocatalyst and finally CO_2 trapping from the reduced form of the photocatalyst and finally CO_2 trapping.

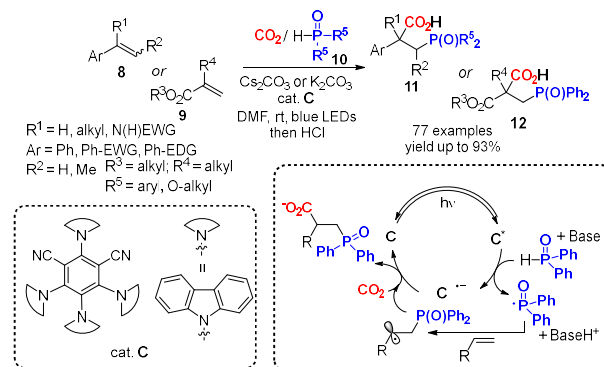


Figure 4 Phosphonocarboxylation of alkenes with CO_2 under metal-free visible light photoredox regime.

In 2020, the same group developed an intramolecular dearomatic arylcarboxylation of indoles **13** for the preparation of valuable indoline-3-carboxylic acids **14**, overcoming, at the same time, the thermodynamic stability of aromaticity and CO_2 inertness.^[10] Differentiating to similar reports by this and other groups, this reaction relies on a reductive protocol, proceeding in the presence of photocatalyst **C**, DIPEA as a sacrificial reductant and Cs_2CO_3 as a base. High yields and very good diastereoselectivities were observed for a variety of 1-(2-bromobenzoyl)-1H-indole-2-carboxylates (**13** X = CO), bearing multiple substituents both on the indole (including challenging C-3 and C-4 positions) and the aromatic rings. Other functional groups at the C-2 position are tolerated (such as amides, methyl and phenyl units) and the reaction could be extended to 1-(2-bromobenzoyl)-1H-indoles-2-carboxylates (**13** X = CH_2) albeit with a drop in the diastereoselectivity (Figure 5). Mechanistic studies pointed to a photoredox-catalyzed successive single electron transfer (SSET) process where DIPEA generates a

reduced form of excited photocatalyst **C**, reacting with the Ar-Br moiety for the formation of an aryl radical (first SET). This is rapidly trapped by the indole double bond, generating a benzyl radical, subsequently reduced to a carbanion by reaction with another molecule of reduced **C** (second SET). Ultimately, this carbanion undergoes carboxylation with electrophilic CO₂.

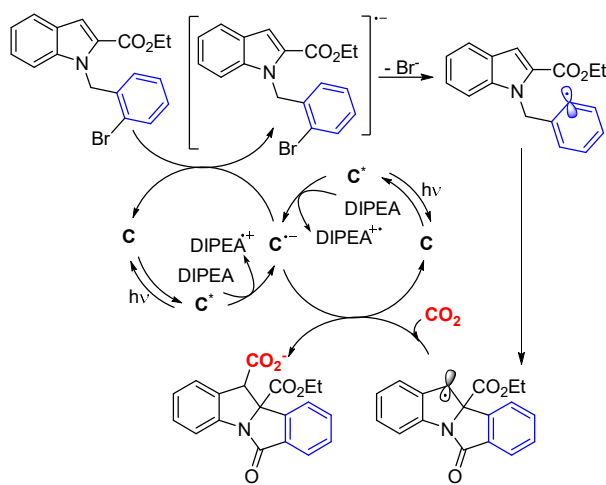
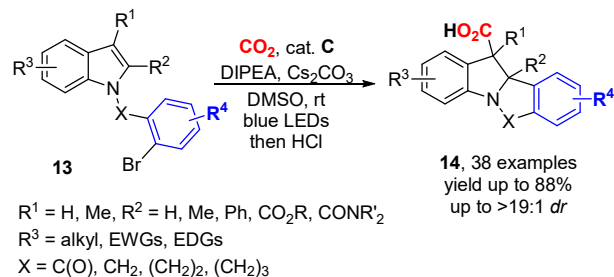


Figure 5 Reductive dearomatization of indoles with CO₂.

Continuing their interest for light-driven functionalization-carboxylation reactions, in 2021, Yu and co-workers developed a carbo-carboxylation of alkenes **15** employing α -amino acids **16** as bifunctional reagents.^[11] Thus, γ -aminobutyric acids **17** were synthesized through a light-promoted process (cat. **B**) where α -amino acids **16** are first decarboxylated, generating an alkyl radical that is added onto the double bond of **15** (carbofunctionalization). Then, the so-formed CO₂ is “recycled” in the final step where, after reduction of the intermediate to a carbanion, the carboxylation step occurs (Figure 6). A great variety of styrenes, as well as acrylates, could productively be employed as olefins **15**, while proline, proline-derived peptides as well as other natural and non-natural amino acids **16** were found to be suitable bifunctional reagents for the disclosed process.

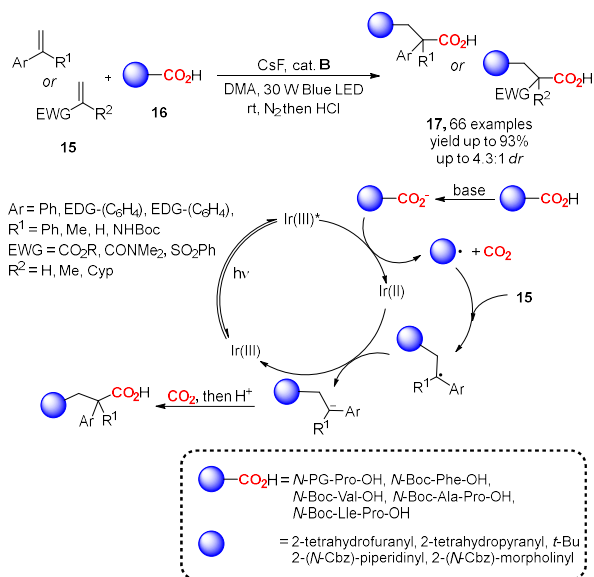
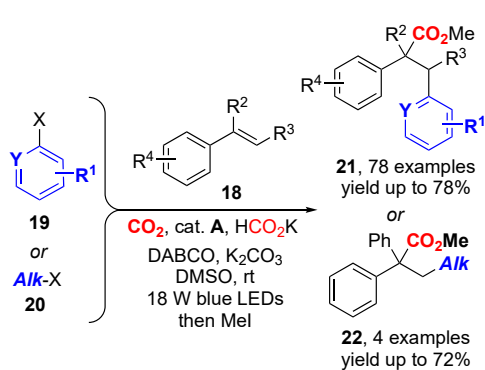


Figure 6 Photocatalyzed synthesis of γ -amino acids/peptides via carboxylation with recycled CO₂.

With respect to carbo-carboxylation reactions, the group of Li reported a very significant contribution in 2020.^[12] They disclosed a reductive Meerwein-type difunctionalization of alkenes **18** using organic halides **19** or **20** as radical sources and CO₂ for the preparation of functionalized phenylacetic acids **21** or **22**. The reaction proceeds under light irradiation with the intermediacy of catalyst **A**, DABCO as a HAT catalyst, potassium formate as a terminal reductant and K₂CO₃ as a base. Aryl iodides and bromides along with electron-deficient aryl chlorides **19** could be productively engaged in the desired process, that could be extended to secondary alkyl bromides or iodides **20** as well. α,α -Disubstituted or α -unsubstituted styrenes, as well as β -substituted ones could be efficiently employed as olefins **18**. Functional groups such as aromatic chlorides and boronates were well tolerated, demonstrating a process of high applicability and synthetic utility. Mechanistic studies suggested quenching of the excited photocatalyst **A** by DABCO, followed by HAT from potassium formate to generate the CO₂ radical anion and protonated DABCO (regenerated by K₂CO₃ acting as sacrificial base). The CO₂ radical anion then generates the aryl(alkyl) radical from the corresponding halide and is transformed into CO₂. The alkyl radical then adds to the olefin, leaving a benzyl radical, subsequently reduced to a carbanion by reduced photocatalyst **A**. Quenching of the carbanion finally occurs *via* carboxylation with CO₂. The proposed mechanism leaves the question whether the CO₂ trapped in the carboxylation step is the one generated from potassium formate or the one introduced into the reaction mixture. On the one hand, the reaction proceeds well in the absence of CO₂, suggesting the possibility of employing the one formed in the reduction of potassium formate. On the other hand, running the reaction with ¹³CO₂ resulted in 74% ¹³C incorporation, revealing that atmospheric CO₂, if present, is usually preferentially trapped.



For X = Br, I; Y = CH, N; R¹ = EDGs and EWGs
 For X = Cl; Y = CH, N; R¹ = EWGs;
 R² = H, Me, aryl; R³ = H, Me; R⁴ = EWGs, EDGs
 Alk = Cy, Ad, 4-*N*-Boc-piperidyl, 4-tetrahydropyryl

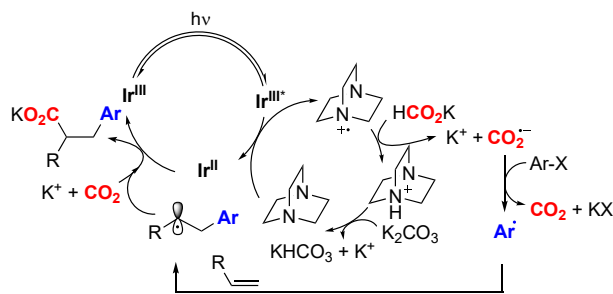


Figure 7 Reductive carboxylation for styrenes with CO₂.

In 2018, Wu and co-workers disclosed a visible-light-mediated sila-carboxylation and carbo-carboxylation of alkenes **23** or **24** towards β-sila carboxylic acids **27** or **28**, or acids bearing γ-heteroatoms **29** or **30**, respectively.^[13] The reaction proceeds in the presence of catalyst **C** and a catalytic amount of quinuclidin-3-yl acetate or aryl-dialkyl silanes **25**, a vast number of heteroatom-stabilized, carbon-centered radical precursors **26** were productively engaged in the carbo-carboxylation process: nitrogen-, oxygen- or sulfur-containing aliphatic heterocycles could be easily added to alkenes **23** or **24**. Electron-poor styrenes **23** and acrylates **24** could serve as olefins. Importantly, the process could be scaled-up to gram quantities employing continuous-flow technologies. The peculiar feature of this protocol is the absence of a sacrificial base, which is usually needed in SET processes for the generation of radicals from "R-H" sources. Instead, quinuclidin-3-yl acetate could serve as a HAT-catalyst. Mechanistic investigations suggested that oxidation of this species by the excited photocatalyst is followed by a HAT from radical precursors **25** or **26**. Then, olefins **23** or **24** can undergo addition of the radical, reduction from the reduced photocatalyst and carboxylation with CO₂. The carboxylate product acts then as a base, regenerating the HAT catalyst.

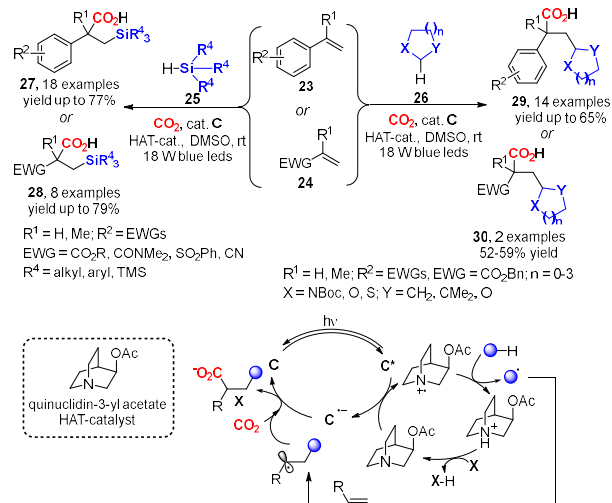


Figure 8 Visible-light-mediated tri-component difunctionalization of styrenes with CO₂.

The light-mediated carbo-carboxylation of alkenes with nitrogen-stabilized, carbon-centered radical precursors and CO₂ was deeply investigated by the group of Xi in 2020.^[14a] In the presence of catalyst **C**, LiCl and an excess of anilines **31**, styrenes **32** underwent the desired sequence towards γ-amino carboxylic acids **33** (Figure 9). A high functional group tolerance on both substrates was demonstrated in a broad scope showing generally very high yields. The process is believed to follow a mechanism close to the one proposed by Wu in 2018, with the exception of the absence of the HAT catalyst. In this particular case, one equivalent of amine **31** acts as a sacrificial base while the other one is added onto the double bond of the olefin.

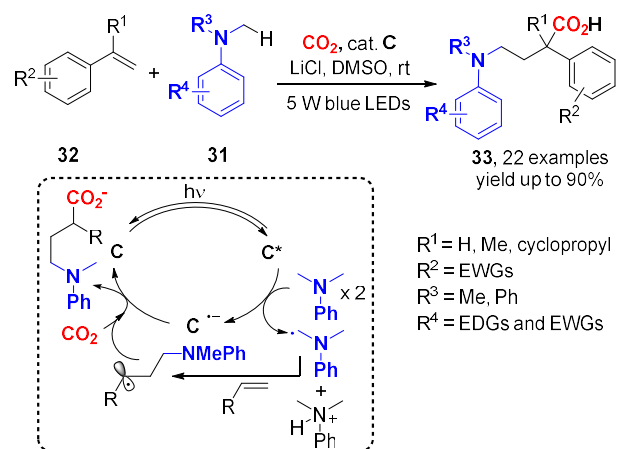


Figure 9 Synthesis of γ-amino acids via photoredox catalyzed difunctionalization of styrenes with CO₂.

3. Metal/base-promoted alkene carboxylative functionalizations with CO₂

Strategies for the double functionalization-carboxylation of alkenes are not limited to light-promoted reactions. A number of excellent examples, either promoted by metal catalysts or bases were recently disclosed, highlighting how versatile and productive these tandem reactions can be, as they can be run under a variety of different conditions. Some metal-catalyzed examples of sequential functionalization-carboxylations of olefins^[15] have also been reported, however, not being strictly tandem one-pot protocols these will not be discussed here in detail.

3.1 Organo-halides in metal-catalyzed carboxylative difunctionalizations of π -systems

In 2015 Martin, and co-workers developed a substrate-based stereodivergent intramolecular cyclization-carboxylation protocol to convert bromides **34** into cyclo-fused acrylic acids **35**.^[16] The reaction was promoted by sterically demanding ligand **D** coupled with catalytic nickel, and manganese as stoichiometric reductant. Labeling experiments revealed that the selectivity in the cyclization step, which determines the configuration of the double bond, is closely related to the nature of the substrate. Specifically, the *syn*-addition will be obtained when $R_2 = \text{H/D}$, while the *anti*-product is produced by the steric repulsion with $R_2 = \text{alkyl, aryl}$. The protocol tolerates variously substituted aryl-alkynes **34**, and also aliphatic substrates where successfully subjected to the desired cyclization-carboxylation sequence (Figure 10). Mechanistically, after the insertion of the Ni(0) to the C-Br bond, a fast *syn*-insertion to the triple bond occurs forming intermediate **36**. Here the nature of the substrate induces the isomerization of the *in-situ* formed alkene. From previous reports disclosed by the same group, insertion of CO₂ on the Ni-C bond is accessible for the more nucleophilic Ni(I) species, with respect to the Ni(II) complexes. Thus, after the Mn-mediated mono-electronic reduction (intermediates **36'**), CO₂ is trapped and a second reduction re-generates the Ni(0) active species liberating the product as a Mn-carboxylate.

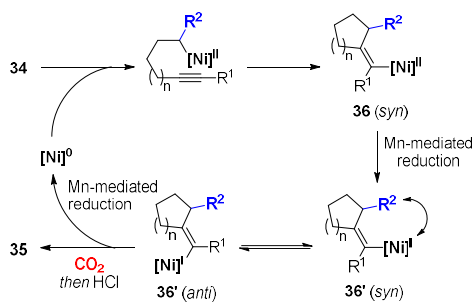
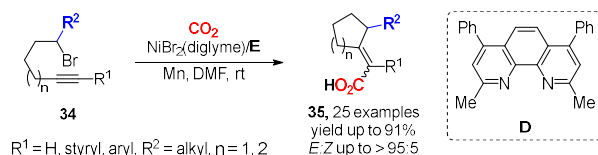


Figure 10 Divergent intramolecular carboxylative cyclizations of alkyl halides under Ni-catalysis.

A palladium-catalyzed synthesis of 3-methyleneindoline-2-carboxylates **54** and analogues was disclosed by the group of Sato in 2017 through a Heck-carboxylation sequence on N-allenyl-2-

iodoanilines **53** (Figure 11).^[17] The reaction was promoted by the use of slightly electron-poor monodentate phosphine ligands, and Et₂Zn as sacrificial reductant for the turnover of the catalyst. The protocol could accommodate the use of iodoanilines of different electronic nature- and 2-iodophenols-tethered allenes. Moreover, when 2-iodobenzylamines were subjected to the target di-functionalization, other heterocyclic scaffolds could be productively accessed. The determining step for the formation of the product is the Et₂Zn mediated activation of the η^3 -allylpalladium intermediate **55** generating the less sterically hindered η^1 -allylpalladium **56**, which can capture atmospheric carbon dioxide at the γ -position. Finally, the product is obtained as a Zn-carboxylate through Et₂Zn-induced β -hydride elimination of the Pd(II) intermediate **56** and concomitant reduction of the catalyst. This mechanism interestingly forms the non-aromatic product mainly, and the methylene moiety can be easily functionalized to obtain complex indole-2-carboxylates derivatives through rearomatization.

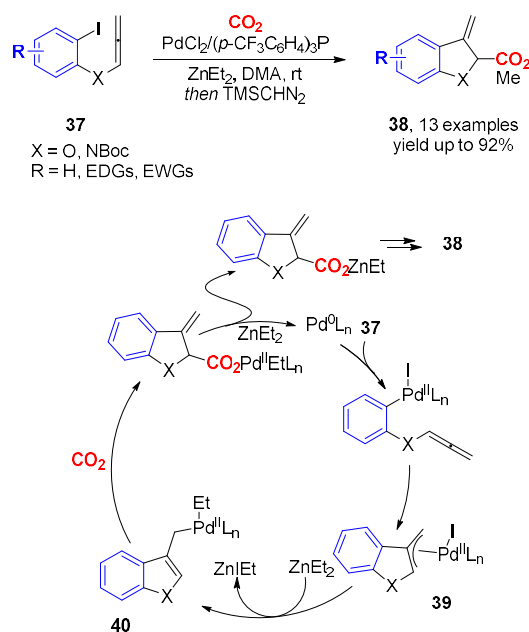


Figure 11 Pd-catalyzed arylative carboxylation of allenes with CO₂.

In 2020, the group of Martin disclosed a novel nickel-catalyzed remote C(sp²)-H carboxylation of arenes (see Figure 12).^[18] Tethered *o*-alkynylaryl bromides **41** underwent cyclization on the triple bond moiety, to generate the alkenyl-nickel complex **42**. Here the carboxylation pathway occurs after a faster 1,4-Ni migration, to give the aryl-nickel intermediate **43** which finally traps the CO₂ to give the final product **45** (Figure 12a). The protocol could produce a variety of densely functionalized cyclo-fused styrene-2-carboxylates **45**, with a well-defined geometry of the formed alkene, and sterically or electronically demanding substrates are nicely accommodated. Worth of notice is the use of silyl linkages between the arene and the alkyl bromide moieties in **41**, giving access to interesting orthogonal functionalizations of carboxylated adducts **45**. Mechanistic insight showed a significant isotopic effect when the deuterated starting material **42** is engaged in the cascade process, corroborating the [1,4]-Ni migration hypothesis (Figure 12b). Moreover, differently from the majority of the previous studies, in

this case the insertion of CO₂ on the Ni-C bond looks to be accessible from the Ni(II) center. In fact, when the pre-formed Ni(II) complexes **43** and **44** are subjected at the carboxylation protocol, in the absence of the sacrificial reductant, the desired benzoic acid **45** is still obtained. This unusual reactivity could be attributed to particular electronic and steric properties of the substrate, but still represents an important information to add to the Ni-catalyzed reductive coupling portfolio.

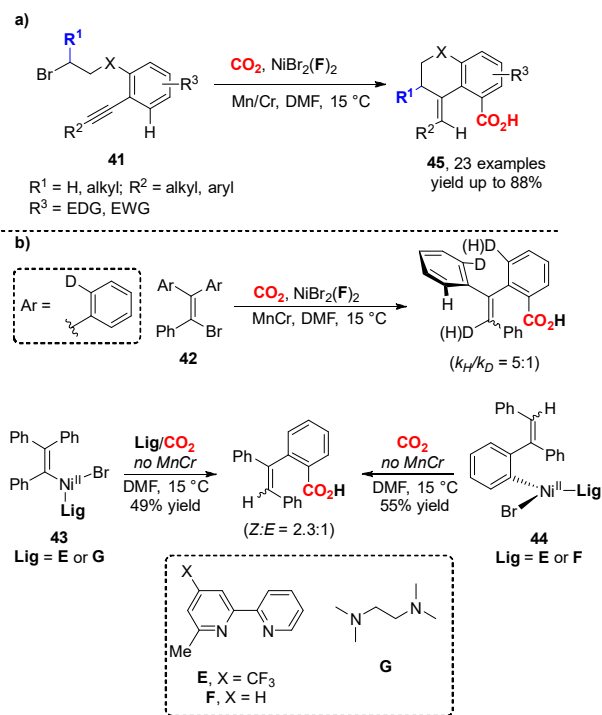


Figure 12 Remote Csp²-H carboxylation with CO₂ under Ni-catalysis.

The unprecedented nickel-catalyzed enantioselective intramolecular Heck-carboxylation cascade process has been firstly described by our group in 2021.^[19] The process gave access to enantioenriched 2,3-dihydrobenzofurans, indolines and indanes **47** bearing a defined quaternary stereogenic center, starting from simple 2-iodoarenes tethered with unactivated alkenes **46**. The stereoselectivity was achieved by using a pre-formed nickel complex **H** bearing an electron-rich pyridine-imidazoline chiral ligand (Figure 13). Mechanistically, after the insertion on the aryl iodide a regioselective stereodiscriminating cyclization occurs, to form an alkyl-Ni(I) intermediate **48**, which can insert to the CO₂. The reduction of the nickel complex operated by zinc metal gives the product as a Zn-carboxylate and regenerates the catalyst. A range of differently decorated of iodo-arenes **46** were accessible by the protocol. Bulky and/or coordinating groups, even as substituents of the internal position of the olefin, were well tolerated, and the stereoselectivity was maintained almost untouched. The mechanism has been deeply investigated via combined experimental and computational tools. A proposal, involving the formation of aryl-Ni(I) species **48** before the Heck process, was corroborated by the identification of benzoic acid **49** as by-product of the reaction.

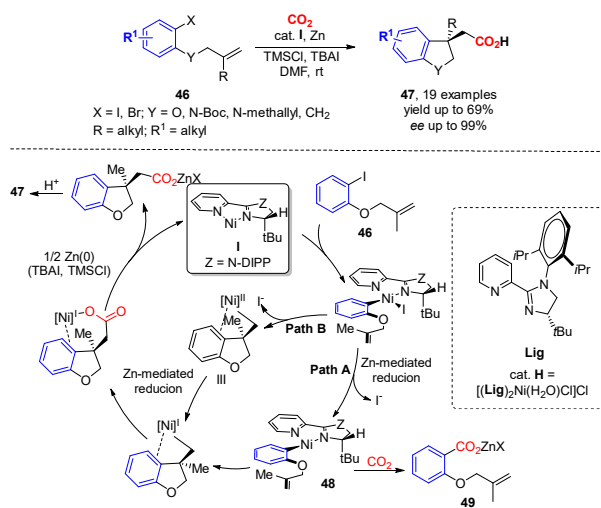


Figure 13 Enantioselective Ni-catalyzed cascade Heck/carboxylation reaction with CO₂.

Simultaneously to our group, Kong and Yu reported the nickel-catalyzed enantioselective intramolecular carbo-carboxylation of methacrylanides **50** for the synthesis of oxindole 3-acetic acids **51** bearing a defined C3-quaternary stereogenic center.^[20] In this case the PN chiral ligand **I** gave the best performances, and, similarly to our methodology, sterically demanding substituents on the aromatic ring or on the alkene motif were well tolerated (Figure 14). This protocol was applicable not only to activated aryl bromides, but also *o*-chloroaniline derivatives were amenable with a similar chemical output. Differently, aryl triflate derivatives were less efficient, but still able to undergo the cyclization-carboxylation sequence with more moderate yields and comparable enantioselectivity. The mechanism proposed by the authors is coherently based on the same observations reported by our group, such as the presence of the *ipso*-carboxylation product in the reaction media. This makes the hypothesis that the enantio-determining 5-*exo* cyclization is conducted by a Ni(I) complex more valuable.

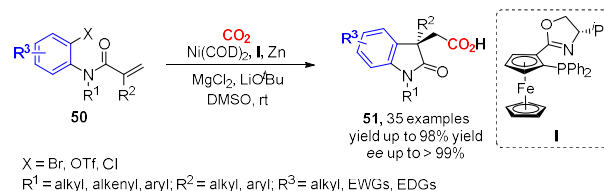


Figure 14 Enantioselective Ni(0)-catalyzed intramolecular carboxylative/Heck coupling with CO₂.

3.2 Nickelalactones intermediates

The capability of Ni(0) species to engage oxidative cycloadditions, which yields a nickelacycle complex with concomitant formation of a C-C bond between two unsaturated partners,^[21] has been the first exploited strategy for CO₂ fixation. Nickelalactone complexes (see for example Figure 15) are readily obtained via

direct oxidative cyclization of CO₂ and monounsaturated systems (alkenes, alkynes, allenes) or via oxidative intramolecular cyclization and subsequent CO₂ insertion with polyunsaturated systems (dienes, diynes). Implementing a reductive transformation of the nickelalactone complex allows turnover of the nickel catalyst: this approach has prompted the development of catalytic methodologies for the functionalization-carboxylation of unsaturated substrates, either by incorporation of an organic group from an organometallic reductant or by reductive cyclization of the nickelalactone.

On the basis of previously studied co-oligomerization of 1,3-dienes and CO₂ catalyzed by nickel or palladium, in 2002 the group of Mori reported the nickel catalyzed intramolecular ring closing-carboxylation of bis-1,3-dienes **52**.^[22a] The reaction proceeded in the presence of a catalytic amount of Ni(acac)₂ and triphenylphosphine, using an excess of a diorganozinc compound as both reductant and transmetalating agent. The selectivity was observed to be absolute: cyclized products **53** or **53'** (*vide infra*) were obtained as single regio- and stereoisomers, as shown in Figure 15. Shortly after, the same group reported an enantioselective version of the protocol by using (S)-MeO-MOP as ligand, with excellent yields and enantioselectivity.^[22b] Various tethering units were found to be competent in the transformation, and unsymmetrical dienes **52**, bearing a terminal methyl group reacted smoothly as well, with carboxylation occurring exclusively at the unsubstituted diene. The proposed mechanism involves oxidative cyclization of the diene to form a bis-η³-allyl nickel complex, which undergoes CO₂ insertion followed by transmetalation with the organozinc species. Reductive elimination allows the catalyst turnover and furnishes the desired product as methyl ester upon treatment with diazomethane.

For the racemic version, an interesting chemo-divergency was observed, depending on the organozinc reagent employed. As a matter of fact, while Me₂Zn and Ph₂Zn furnished products **53**, Et₂Zn yielded products **53'** due to β-H elimination prior to reductive elimination. In the enantioselective methodology, Et₂Zn furnishes the ethylated product **53** over **53'** in good selectivity, showing that β-H elimination is less competitive in this case.

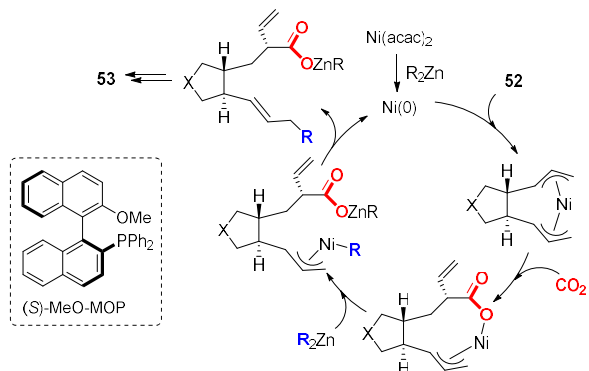
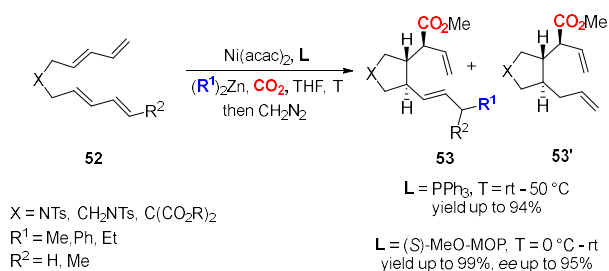


Figure 15 Nickel catalyzed carbocyclization of bis-dienes with final CO₂ trapping.

To show how in some cases CO₂-cyclizations and tandem functionalization-carboxylation processes can be connected, and a slight modification of the reaction partners can lead to one or the other, we will briefly compare the previous report with a similar one, employing diynes **54**, instead of bis-1,3-dienes **52**. This was described by the group of Louie in two reports, addressing respectively symmetric and unsymmetric substrates.^[23] The reaction used Ni(cod)₂ as the catalyst and IPr (1,3-bis-(2,6-diisopropylphenyl)imidazolidene) as the ligand, delivering densely functionalized pyrones **55** via formal carboxylative [2+2+2]-cycloaddition reactions. Different types of tethering units worked equally well in the process, and excellent regioselectivity was achieved for unsymmetrical diynes, bearing bulky substituents (*i.e.* tBu, TMS, Figure 16).

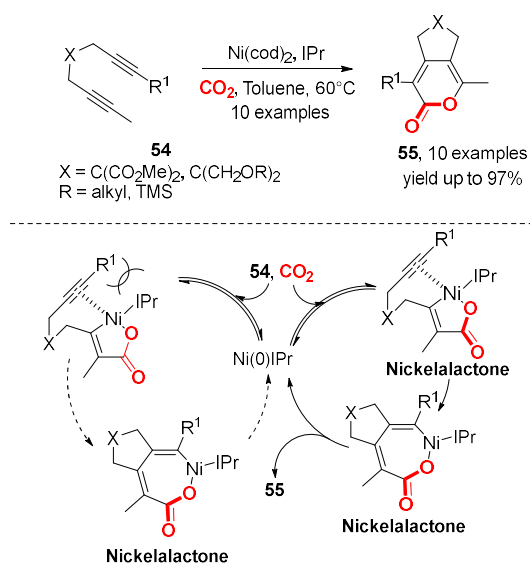


Figure 16 Nickel catalyzed [2+2+2]-cycloaddition reaction involving diynes with CO₂.

The proposed mechanism starts with the oxidative cycloaddition of one pendant alkyne and CO₂, followed by insertion on the other alkyne moiety to yield a 7-membered nickelalactone complex. Reductive elimination from this species turns over the nickel catalyst and furnishes the pyrone products **55**. Mechanistic studies rule out an inverted pathway involving first ring closure of the diyne and subsequent CO₂ insertion in a 5-membered nickelalactone complex. Regioselectivity for unsymmetrical diynes **54** likely arises from the steric interaction between the IPr ligand and the terminal group on the alkyne in the 5-membered nickelalactone intermediate. When this substituent is large, insertion leading to the 7-membered nickelacycle is significantly slower. The initial oxidative cyclization is proposed to be reversible, so that the intermediate derived from initial insertion on the alkyne bearing the smaller substituent would not react further, undergoing cycloreversion instead and eventually leading to the observed regioisomer in a Curtin-Hammett scenario.

The Mori group also reported a nickel catalyzed carbo-carboxylation of disubstituted alkynes **56** with organozinc reagents, for the synthesis of tetrasubstituted α,β -unsaturated esters **57**. The reaction proceeded in the presence of a catalytic amount of Ni(acac)₂ or Ni(cod)₂ and an excess of both diorganozinc compounds and DBU.^[24] The latter is thought to coordinate the organozinc compound, forming a more activated species for transmetalation. Interestingly, both possible regioisomers of **57** could be accessed with good regioselectivity, depending on the alkyne substitution: for TMS-alkyl disubstituted alkynes **56**, carboxylation occurred predominantly at the TMS-bearing carbon, whereas for *t*-Bu-alkyl or aryl-alkyl substituted alkynes **56** the formation of the opposite regioisomer was observed to be preferred. Various functionalized and unfunctionalized alkyl chains were well tolerated in the protocol (Figure 17).

The proposed mechanism consists in an oxidative cycloaddition between Ni, the alkyne and CO₂, yielding the nickelalactone complex, followed by transmetalation and reductive elimination of the carboxylic acid product. Regioselectivity is thought to be

controlled by the electronic effect of the substituents, modulating the relative energies of the two possible nickelalactone isomers.

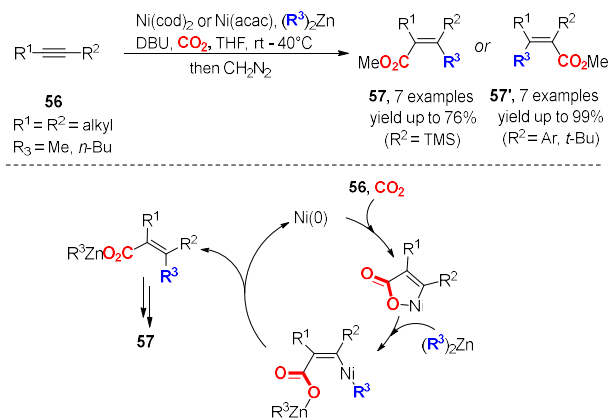


Figure 17 Nickel catalyzed carboxylative synthesis of tetrasubstituted alkenes from TMS-alkynes.

3.3 Other metal- or base-catalyzed tandem functionalization-carboxylation protocols

In 2014 the group of Tsuji developed a copper-catalyzed regio-divergent sila-carboxylation of allenes **58** with PhMe₂Si-Bpin and CO₂.^[25] In the presence of *rac*-Me-DuPhos ligand (conditions A), carboxylated vinyl silanes **59** were obtained as the only regioisomer; however, in the presence of PCy₃ (conditions B) regioisomeric silylated methacrylates **60** were obtained exclusively (Figure 18). The reversal in regioselectivity might be attributed to the difference in relative steric bulkiness of the CuL (L = Me-DuPhos or PCy₃) and SiMe₂Ph moieties. Indeed, when mono-substituted allenes were employed, the regioselectivity under conditions B dropped sensibly, highlighting the steric hindrance at the C-1 position of allenes **58** as a key factor for a high selectivity. The process showed generally high yield, with functional groups such as ketal, alkenyl, bromo and ester being well-tolerated. Products **59** and **60** were also amenable of selective transformations.

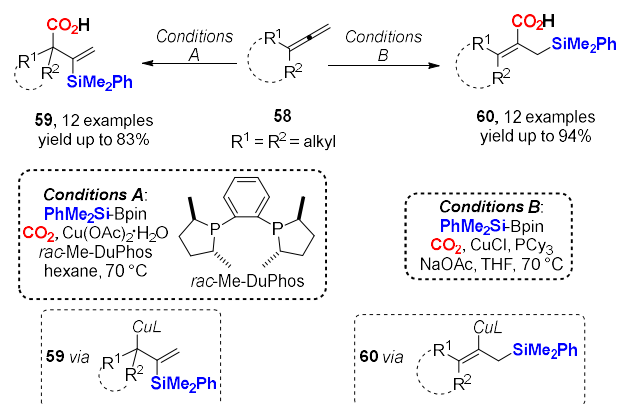


Figure 18 Regio-divergent copper catalyzed sila-carboxylation of allenes with CO₂.

In 2016, Popp and co-workers disclosed the first hetero-element functionalization-carboxylation of alkenes by developing a redox-neutral copper-catalyzed regioselective bora-carboxylation of styrenes **61**.^[26a] The process relied on an olefin boryl-cupration by a Cu-B species, followed by CO₂ insertion into the Cu-C bond. The reaction proceeded in the presence of B₂pin₂ as a boron source, catalyst **J** and NaO^tBu as a base (conditions **A**, Figure 19). Under these reaction conditions electron-rich and electron-neutral styrenes could undergo efficiently the desired process for the formation of a variety of α-aryl-β-boryl carboxylic acids **62**. However, electron-poor styrenes **61** failed in delivering any product, suggesting the nucleophilicity of the Cu-alkyl intermediate as a key factor for the carboxylation step. Nevertheless, in 2019, the same group disclosed an improved protocol (conditions **B**) relying on the addition of PPh₃ as a co-catalyst. Under these conditions some electron-poor styrenes afforded the desired products **62** in moderate yields.^[26b]

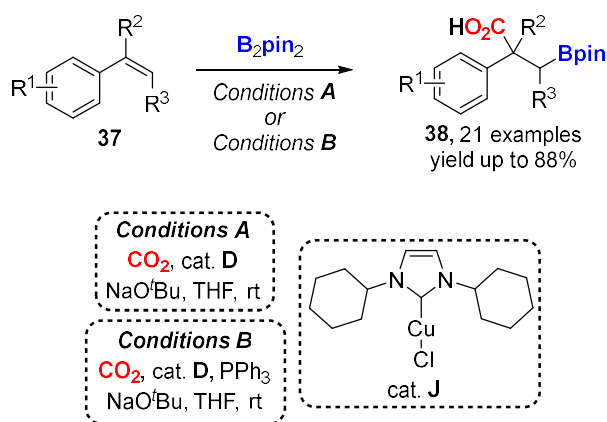


Figure 19 Borylative difunctionalization of vinyl arenes with CO₂ under copper catalysis.

In 2019 Kobayashi and co-workers developed a simple and straightforward procedure for the fluorocarboxylation of gem-difluoroalkenes **63**.^[27] This catalyst- and additive-free protocol, proceeding in the presence of nucleophilic CsF and CO₂, was facilitated by the presence of polar solvents such as DMSO (Figure 20). Although providing useful yields at atmospheric pressure of CO₂, the reaction efficiency became excellent at 20 atm. Products **64**, namely α-trifluoromethyl carboxylic acids, were obtained through a domino process beginning with nucleophilic fluorination of **63**. This leaves a benzylic carbanion, capable of CO₂ trapping. Electron-poor as well as electron-rich *gem*-difluorostyrenes **64** were well tolerated and afforded the respective products in good to excellent yields. Difluoroalkenes **63** bearing strong electron-donating substituents required slightly higher reaction temperatures to facilitate the addition of the fluoride anion as trigger of the reactive sequence.

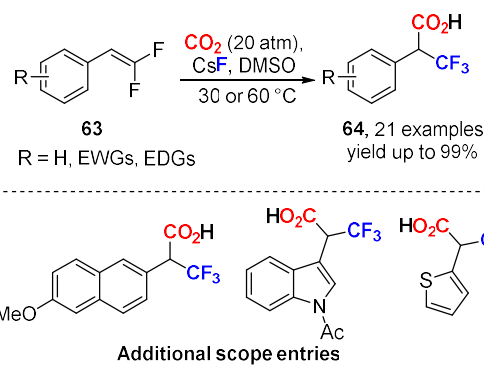


Figure 20 CsF mediated fluoro-carboxylation of difluoroalkenes with CO₂.

In 2020, Li and coworkers disclosed a Rh(I)-catalyzed aryl-carboxylation of acrylamides **65** with arylboronic acids **66** and CO₂.^[28] This elegant strategy envisioned the productive merging of 1,4-additions of organometallic reagents to α,β-unsaturated compounds and metal-catalyzed carboxylation reactions, with the aid of a single catalytic species capable of both processes, namely [Rh(cod)Cl]₂. Malonate derivatives **67** were thus obtained in high yields when different **65** and substituted **66** were reacted with the abovementioned Rh(I) catalyst. The use of Cs₂CO₃, PMDETA (*N,N,N',N''*-pentamethyldiethylenetriamine) as bases and AgOTf as a co-catalyst completed the reaction conditions (Figure 21). In particular, the addition of silver salts improved the selectivity of the process greatly, thus increasing the yield in desired products **67** as well. Control experiments pointed to the presence of rhodium-enolates as the nucleophilic species undergoing CO₂ trapping.

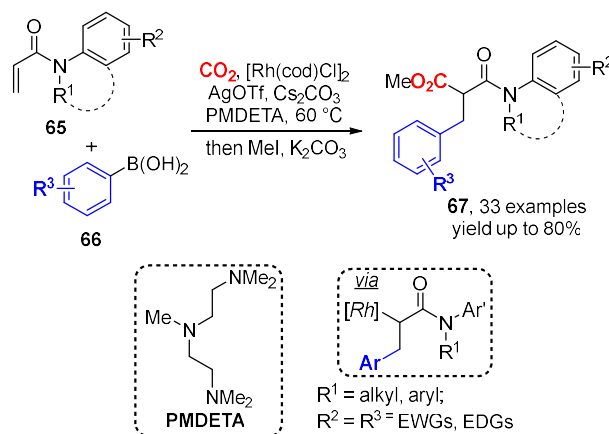


Figure 21 Rhodium catalyzed arylcarboxylation of acrylates with CO₂.

In 2020, Zhang, Luo, Hou and co-workers demonstrated that the bora-carboxylation strategy for the tandem functionalization of π-systems is not restricted to C-C double bonds but can be productively achieved on imines **68** as well (Figure 22)^[29]. The protocol

relies on a copper-catalyzed addition of a B(pin) unit, followed by *N*-carboxylation with atmospheric CO₂ for the preparation of cyclic lithium boracarbamates **69** that can be isolated as such. Alternatively, reaction with Meerwein's salt affords α -amino boronic esters **70** in good to excellent yields.

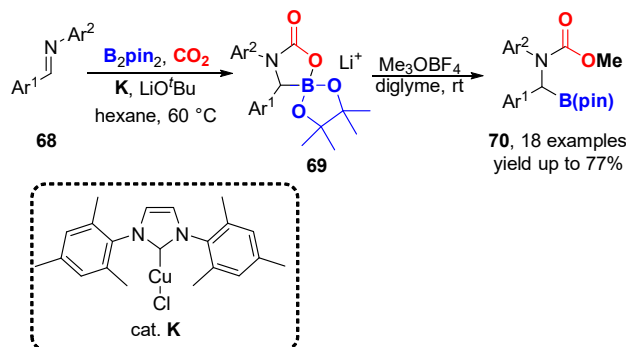


Figure 22 Bora-Carboxylation of imines by Cu-catalysis.

4. Conclusions and Perspectives

In conclusion, the direct access to organic carboxylic acids via CO₂-mediated carboxylation of readily available starting materials is becoming a *hot topic* in synthetic methodology. The field is facing an exponential growth and it is boosted by the always more sustainable and selective enabling techniques available in organic synthesis. The area has predominantly permeated the functionalization of π -systems both in inter- as well as intramolecular matter. In the present minireview article, the most salient and recent discoveries in the carboxylative difunctionalization of double/triple C-C bonds with CO₂ are presented. Despite the undoubted level of excellence already achieved in the topic, the continuous demand for sustainable synthetic protocols capable of temporary capturing and subsequently releasing low-pressure volumes of CO₂ into value-added organic scaffolds could suggest more developments in the area to be foreseen in the near future.

Acknowledgement

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