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Recent progress in reductive carboxylation of C–O bonds with CO₂

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Transformation of carbon dioxide (CO₂) into value-added organic compounds has attracted increasing interest of scientific community in the last few decades, not only because CO₂ is the primary greenhouse gas that drives global climate change and ocean acidification, but also because it has been regarded as a plentiful, nontoxic, nonflammable and renewable one-carbon (C1) feedstock. Among the various CO₂-conversion processes, carboxylation reactions represent one of the most beautiful and attractive research topics in the field, since it offers the possibility for the construction of synthetically and biologically important carboxylic acids from various easily accessible (pseudo)halides, organosilicon, and organoboron compounds. The purpose of this review is to summarize the available literature on deoxygenative carboxylation of alcohols and their derivatives utilizing CO₂ as a carboxylative reagent. Depending on the C–O compounds employed, the paper is divided into five major sections. The direct dehydroxylative carboxylation of free alcohols is discussed first. This is followed by reductive carboxylation of carboxylates, triflates, and tosylates. In the final section, the only reported example on catalytic carboxylation of fluorosulfates will be covered. Notably, special attention has been paid on the mechanistic aspects of the reactions that may provide new insights into catalyst improvement and development, which currently mainly relies on the use of transition metal catalysts.

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1. Introduction

The catalytic fixation of carbon dioxide (CO₂) into value-added organic compounds is an extremely important and hot research topic in synthetic organic chemistry and green chemistry from the viewpoint of developing this plentiful greenhouse gas as an inexpensive, nontoxic, and renewable one-carbon (C1) feedstock.¹ Among the various CO₂-fixation reactions,² carboxylation and decarboxylation reactions represent one of the most attractive and promising transformations, since it offers the possibility for the construction of valuable carboxylic acids, from various organic substrates in one step and eco-friendly manner.³ Needless to say that compounds containing the carboxylic acid functional group play a cardinal role in drug discovery programs due to their broad spectrum of biological

activities including diuretic, antibacterial, antiretroviral, anti-hypertensive, anti-inflammatory, antiarrhythmic, antipsychotic, and antihistamine activities (Scheme 1). The classical synthesis of carboxylic acids from CO₂ involves the stoichiometric conversion of an electrophilic organic halide to a nucleophilic Grignard reagent followed by carboxylation and subsequent acidic workup of the resulted halomagnesium carboxylate.⁴ However, poor compatibility of Grignard reagents with a verity of functional groups, limited the utility of this synthetic procedure. In order to bypass the need for highly reactive and difficult to handle Grignard reagents, the direct catalytic carboxylation of organohalides with CO₂ has thus been developed as one of the most sustainable and efficient synthesis strategies to carboxylic acid derivatives.⁵ Although, considerable successes have been achieved using this synthetic approach, some inherent limitations such as the high cost of organic bromides and iodides, low reactivity of organic chlorides, and environmental toxicity of some organic halides, might limit the application profile of this page of carboxylic acid synthesis.⁶

Considering the above considerations, from a sustainable chemistry point of view, there is a need for new protocols for the preparation of carboxylic acids from CO₂ that are truly efficient, high yielding, eco-friendly, byproduct-free, and responsive to mild reaction conditions. In this regard, alcohols and their activated derivatives (e.g., carboxylates, tosylates, and fluorosulfates), which, as

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Scheme 1 Selected examples of FDA-approved drugs containing a carboxylic acid moiety.

compared to organohalides, offer more sustainable starting materials because most of them are easily accessible from biomass,⁷ have recently applied as viable alternative to halides in CO₂-fixation reactions. Needless to say that not all activated alcohols meet the criteria of green chemistry and may also be potentially toxic (*e.g.*, triflates, due to the formation of genotoxic triflic acid).

Although several nice reviews articles were briefly covered some aspects of this topic,⁸ a comprehensive review on this highly active research arena has not appeared in the literature to date. As a part of our ongoing review papers of the CO₂-fixation reactions,^{2b,c,3c-e,9} herein, we will highlight the most important developments on the preparation of carboxylic acid derivatives through the reductive carboxylation of respective (activated) alcohols with CO₂ (Fig. 1).

2. Carboxylation of free alcohols

The direct dehydroxylative functionalization of free alcohols has recently become one of the most impactful areas of research in synthetic chemistry because it is an economic, powerful and eco-friendly strategy for the fabrication of various valuable

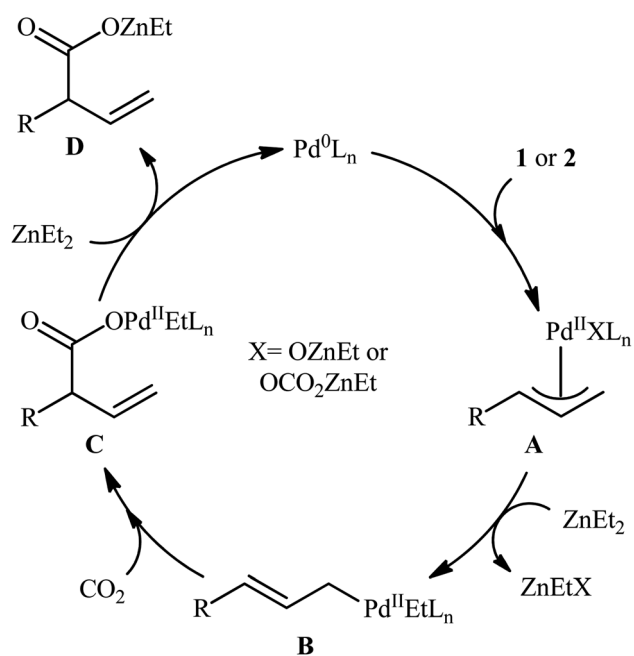
functionalized organic compounds from inexpensive, environmentally benign, and naturally abundant feedstocks without pre-functionalization of starting materials and isolation of intermediates.¹⁰

One of the earliest reports of the direct dehydroxylative carboxylation of allylic alcohols using CO₂ as the carboxyl source was published by Mita, Higuchi, and Sato in 2015,¹¹ who unfolded that the treatment of allylic alcohols with a catalytic amount of PdCl₂/PPh₃ under a CO₂ atmosphere in the presence of ZnEt₂ as a stoichiometric transmetalation reagent/reductant, resulted in the regioselective formation of branched α,β -unsaturated carboxylic acids in good to excellent yields after hydrolysis. To facilitate the isolation process, the obtained carboxylic acids were derivatized into their methyl esters by methyl esterification with TMSCHN₂. Thus, a library of branched α,β -unsaturated methyl esters **3** were efficiently synthesized through the sequential carboxylation of various linear and branched allylic alcohols **1** and **2** with CO₂ and subsequent methyl esterification of the generated carboxylate with TMSCHN₂ (Scheme 2). In order to demonstrate the synthetic applicability of their mythology, the authors



Fig. 1 Reductive carboxylation of C–O bonds with CO₂.



Scheme 2 Pd-catalyzed carboxylation of allylic alcohols **1** and **2** with CO₂ developed by Mita *et al.*

Scheme 3 Plausible mechanism for the reaction in Scheme 2.

performed the synthesis of baclofen, a pain-relieving medication, starting from 2-(4-chlorophenyl)prop-2-en-1-ol using their carboxylation strategy as a key step. A possible mechanism for

this Pd-catalyzed dehydroxylative carboxylation is illustrated in Scheme 3. The reaction starts with the generation of η^3 -allylpalladium **A** through the activation of allylic alcohol **1/2** by Lewis acidic ZnEt₂ or by carbonate formation with CO₂. Subsequently, this intermediate undergoes transmetalation with ZnEt₂ to give the nucleophilic η^1 -allylpalladium **B**, which after nucleophilic attack to CO₂ at the γ -position affords palladium carboxylate **C**. Finally, reduction of this complex by ZnEt₂ leads to the formation of zinc carboxylate **D** and regenerates Pd⁰.

Two years later, Mei's research group described an alternative carboxylation of allylic alcohols with atmospheric CO₂ in the absence of pyrophoric Et₂Zn using the ability of ⁿBu₄NOAc to facilitate C–O bond-cleavage.¹² Thus, by using Ni(acac)₂/2,9-dimethyl-1,10-phenanthroline (dmphen)/Mn powder/ⁿBu₄NOAc combination as a catalytic system in DMF, various linear and branched allylic alcohols **4** and **5**, respectively, carboxylated regioselectively to afford branched α,β -unsaturated carboxylic acids **6** exclusively (Scheme 4). Notably, the reaction displayed high degree of stereoselectivity in which both *cis*-allylic and *trans*-allylic alcohols predominantly provided (*E*)-configured carboxylic acids, which suggests that the reaction occurred *via* π -allylnickel intermediates. Interestingly, the electronic effects of the substituents had no significant influence on the outcome of the reaction. On the other hand, the steric effect was very strong, as the allylic alcohols wherein the alkene is conjugated

Scheme 4 Ni-catalyzed carboxylation of allylic alcohols **4** and **5** with CO₂.



Scheme 5 Ni-catalyzed, switchable site-selective carboxylation of allylic alcohols **7** with CO₂ by using either a Ni/L3 or Ni/L8 couple.

with an arene or is trisubstituted afforded low yields of the desired products. In this study, the authors also provided further examples of α,β -unsaturated carboxylic acids preparation *via* hydrogenation of propargylic alcohols to allylic alcohols using water as an H atom source, followed by carboxylation under the identical conditions.

Concurrently, Martin and co-workers screened a series of bi- and tridentate ligands for the ligand-controlled, site-selective Ni-catalyzed carboxylation of allylic alcohols **7** (or **7'**) with CO₂.¹³ Their results revealed that different ligands can control site-selectivity pattern. Therefore, the use of bidentate ligands was selective toward linear products **8**. Among the bidentate ligands examined, commercially available bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) **L3** afforded the highest regioselectivity towards linear derivatives. On the other hand, tridentate 4,4'',6,6''-tetramethyl-2,2':6',2''-terpyridine **L8** provided exclusively branched products **9** (Scheme 5).

Very recently, Xi and co-workers disclosed that the merge of a Ni catalyst with a photoredox catalysis can be used as effective metallaphotoredox catalytic system for regioselective carboxylation of allylic alcohols with CO₂ without consuming any stoichiometric metallic reductant.¹⁴ The optimal reaction

employed 4CzIPN/Ni(OTf)₂ as the metallaphotoredox catalyst, dmphen as a ligand, Hantzsch ester (HEH) as the reductant and LiOAc as an additive. Under optimized conditions, a variety of linear α,β -unsaturated carboxylic acids **12** were prepared in moderate to good yields from the corresponding mono-substituted allylic alcohols **10** and **11** (Scheme 6). However, π -conjugated substrates were sluggish to participate in this protocol. Based on several control experiments, the authors suggested that this C–C bond forming reaction proceeds through the following key steps (Scheme 7): (i) excitation of 4CzIPN under visible light irradiation to form excited state of 4CzIPN* (ii) reductive quenching of 4CzIPN* by HEH to generate 4CzIPN^{•-}; (iii) reduction of Ni^{II} in the presence of L1 through a single electron transfer (SET) from 4CzIPN^{•-} to form to L₁Ni⁰ and regenerate ground state 4CzIPN; (iv) preactivation of allylic alcohol to the corresponding allylic hydrogen carbonate **A** in the presence of water and CO₂; (v) coordination and oxidative addition of active catalytic species to the allylic hydrogen carbonate **A** to give π -allylnickel intermediate **B**; (vi) ligand exchange of **B** with LiOAc to generate intermediate **C**; (vii) reduction of complex **C** by 4CzIPN^{•-} to produce Ni^I intermediate **D**; (viii) insertion of CO₂ into the Ni–C bond of **D** to afford nickel



Scheme 6 Visible-light-driven carboxylation of allylic alcohols **10** and **11** by the combined use of nickel and photoredox catalysts.





Scheme 7 Possible mechanism of dual photoredox/nickel-catalyzed carboxylation of allylic alcohols **11** with CO_2 .



Scheme 8 Ni-catalyzed carboxylation of propargylic alcohols **13** with CO_2 .

carboxylate **E**; and (ix) single electron reduction of **E** to provide the corresponding carboxylate **F** and regenerate the catalytic Ni^0 .

In a significant contribution in this field, Kimura and co-workers found that treatment of propargylic alcohols **13** containing a silyl group at the terminal position with CO_2 (1 atm) in the presence of $\text{Ni}(\text{acac})_2/\text{dppbz}/\text{Et}_2\text{Zn}$ combination as a catalytic system, resulted in the formation of the corresponding β,γ -alkynyl carboxylic acids **14** in high yields within 24 h (Scheme 8).¹⁵ The results indicated that the presence of a silyl group at the terminal acetylenic carbon atom was crucial for this coupling reaction. No products were obtained by 3-phenyl and 3-ethyl substituted propargylic alcohols under the same reaction



Scheme 9 Proposed mechanistic pathway for the formation of β,γ -alkynyl carboxylic acids **14**.





(Het)Ar= Ph, 4-Me-C₆H₄, 4-Ph-C₆H₄, 4-ⁱBu-C₆H₄, 4-OMe-C₆H₄, 4-CO₂Me-C₆H₄, 4-CN-C₆H₄, 4-CF₃-C₆H₄, 4-(4-ⁱBu-C₆H₄)-C₆H₄, 4-(2-thienyl)-C₆H₄, 3-OMe-C₆H₄, 3-OPh-C₆H₄, 3-CF₃-C₆H₄, 2-CF₃-C₆H₄, 2-Me-3-Ph-C₆H₃, 2-OMe-4-Ph-C₆H₄, 3-F-4-Ph-C₆H₃, 1-naphthyl, 2-naphthyl, 2-(6-OMe)-naphthyl, 2-benzofuryl

R¹= H, Me
 R²= H, Me, Et, Ph
 R¹ + R²= -(CH₂)₄-

Scheme 10 Visible-light photoredox-catalyzed carboxylation of benzylic alcohols **15** with CO₂.

conditions. Furthermore, the presence of functionalities at the C1-position of 3-silylated propargyl alcohols prevented carboxylation, and no reaction proceeded at all. According to the author proposed mechanism (Scheme 9), this reaction proceeds through the formation of an allenyl metal intermediate and the presence of silyl group is important for stabilization of this key intermediate. Moreover, it was suggested that CO₂ playing a dual role in this transformation; a C1 source and an accelerator for the C–O bond cleavage.

In 2022, Liao, Yu and co-workers described an elegant visible-light photoredox-catalyzed dehydroxylative carboxylation of benzyl alcohols **15** with atmospheric CO₂ under ambient temperature.¹⁶ No transition-metal was used and only 2 mol% of organic dye 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile

(4DPAIPN) was enough for preparation of a panel of 30 functionalized aryl acetic acids **16** in 30–92% yields (Scheme 10). Various primary-, secondary-, as well as tertiary benzylic alcohols were well tolerated under the reaction conditions, thus indicating the broad applicability of this synthetic strategy. It is worthwhile to note that beside benzylic alcohols, benzylic carbonates were also successfully applied as C–O compounds under the identical conditions. Mechanistically, after a series of control experiments, it was confirmed that this CO₂-fixation reaction most likely proceeds *via* a radical pathway through the key benzylic radical intermediate **B** (Scheme 11).

Another independent benzylic alcohol carboxylation method was published by Lan, Xia and co-workers *via* activation of free alcohols with neutral diphenyl boryl radical (Ph₂B[•]) generated



Scheme 11 Mechanistic explanation for the formation of aryl acetic acids **16**.





Scheme 12 Lan-Xia's synthesis of carboxylic acid derivatives 18.

from sodium tetraphenylborate (NaBPh₄) under mild visible light photoredox conditions.¹⁷ They showed that the treatment of various benzyl alcohols 17 with NaBPh₄ under CO₂ atmosphere and visible light irradiation in the presence of a catalytic amount of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ afforded the corresponding carboxylic acid derivatives 18 in modest to high yields within 40 h (Scheme 12). Interestingly, all the three kinds of benzyl alcohols (primary, secondary, and tertiary benzyl alcohols) were applicable to this reaction. Intriguingly, this synthetic strategy has also been successfully applied for the preparation of various commercialized drugs (*i.e.*, flurbiprofen, naproxen, and felbinac) from the corresponding free alcohols. However, nonbenzylic alcohols, 1-phenylpropan-2-ol, and 2-methyl-1-phenylpropan-2-ol, did not furnish the desired products.

In summary, despite significant progress in recent years, numerous challenges remain in this field of expertise. For example, the majority of methodologies are relayed on the use of Ni and Pd catalysts. Therefore, these approaches cannot be attractive from an industrial perspective because Pd and Ni are expensive and toxic.¹⁸ Although in order to overpass these limitations, recently, Liao, Yu and co-workers¹⁶ developed an innovative transition metal-free method for the photoredox-

catalyzed dehydroxylative carboxylation of free alcohols. However, their synthetic strategy appears to be limited to only benzylic alcohol derivatives. Thus, further research should be focused on development of inexpensive, non-toxic, and highly active catalytic systems with much broader substrate scope. Along this line, first-row transition metals are low-cost and naturally abundant and could be promising candidates for catalyst development in dehydroxylative carboxylation of free alcohols.

3. Carboxylation of esters

Reductive functionalization of alcohols through the pre-activation of C–OH bonds by converting to the reactive esters is a well-documented and useful synthetic protocol.¹⁹ In 2014, the group of Martin documented one of the earliest methods for the reductive carboxylation of esteric C–O bonds with CO₂ to generate carboxylic acids.²⁰ Here, NiCl₂(dppf) [dppf = 1,1'-bis(diphenylphosphino)ferrocene] was used as the catalyst and Mn powder as a reducing reagent. The reaction scope appears to be broad as various aromatic esters 19 with either electron-donating or electron-withdrawing substituents were tolerated and provided the corresponding carboxylic acids 20 in

Scheme 13 Ni-catalyzed carboxylation of esteric C–O bonds with CO₂.



Scheme 14 Proposed mechanism for the formation of aromatic carboxylic acids **20**.

moderate to good yields (Scheme 13). However, the results indicated that the steric effects of the substituents on the acyl terminus played a crucial role on the success of this transformation. Generally, the presence of a bulky substituent (*e.g.*, *t*-butyl, adamantyl) on the acyl terminus is necessary for the reaction to proceed efficiently; esters bearing less hindered acyl substrates such as acetate and carbamate failed to enter into this C–C bond forming reaction. The authors explained this observation by possible stabilization of the transient Ni species within the catalytic cycle by the bulkier substituent on the acyl terminus which might prevent decomposition pathways. Notably, carboxylation of more challenging C(sp³)–O bonds were also found to be feasible by this synthetic strategy, as exemplified by the preparation of 28 benzylic carboxylic acids from the respective benzyl esters. It should be mentioned that unlike the carboxylation of C(sp²)–O bonds that was found to be

specific for sterically demanding ester derivatives, the nature of the leaving group on the carboxylation of C(sp³)–O bonds did not have such a profound effect on reactivity. Scheme 14 depicted the possible mechanistic cycle for this reaction. First, reduction of the Ni(II) precatalyst with Mn generates active catalytic species **A**, which undergo oxidative addition into the C–O bond of ester **19** to afford the Ni(II) intermediate **B**. Subsequently, reduction of the newly formed complex **B** in the presence of Mn leads to the formation of more nucleophilic Ni(I) species **C**. Next, the insertion of CO₂ into the nickel–carbon bond of complex **C** yields the nickel carboxylate **D**. Finally, transmetalation of intermediate **D** with Mn regenerates the active Ni(0)L species **A** and the manganese carboxylate **E** that upon hydrolytic workup delivers the expected carboxylic acid **20**.

Shortly afterwards, the same research team reported an interesting Ni-catalyzed ligand-controlled regiodivergent reductive carboxylation of allyl acetates **21** and **22** with atmospheric CO₂ which allow the introduction of the carboxylic motif at any site of the allyl terminus depending on the coordination geometry of the ligand employed.²¹ Utilizing oct-2-en-1-yl acetate as the reactant and NiBr₂·glyme as a catalyst, optimization revealed two sets of suitable reaction conditions: (i) the bidentate ligand dmphen in the presence of Mn (a reductant) and MgCl₂ (an additive); and (ii) the tetradentate ligand 2,2':6',2'':6'':2'''-quaterpyridine (qtpy) in the presence of Zn (a reductant) and Na₂CO₃ (an additive). The first system was found to be highly selective toward linear products **23**. While performing the process under the second catalytic system resulted in the predominant formation of α -branched carboxylic acids **24** regardless of whether linear or α -branched allyl acetates were utilized (Scheme 15). Unfortunately, a plausible mechanistic scheme to explain this regiodivergent process has not been proposed.

Concurrently, the combination of CoI₂(phen) and Mn was found by Fujihara, Tsuji, and co-workers as efficient catalytic



Scheme 15 Ni-catalyzed ligand-controlled regiodivergent reductive carboxylation of allyl acetates **21** and **22** with CO₂.





R¹ = TMS, TBS, C(Me)₂OTBS, ^tBu, Cy
 R² = H, Me, ⁿPr, ⁿBu, CH₂Bn, (CH₂)₄CO₂Me, (CH₂)₄Cl, (CH₂)₃CH=CH₂, CH₂CH(Me)-2-(5-Me-furyl)
 R³ = H, Me, Hex
 R² + R³ = -(CH₂)₅-, -(CH₂)₂NAc(CH₂)₂-

Scheme 16 Co-catalyzed carboxylation of propargyl acetates **25** with atmospheric CO₂.

system for carboxylation of propargyl acetates with atmospheric CO₂ at room temperature.²² In this reaction, various α -unsubstituted, α -mono-substituted, and α,α -disubstituted propargyl acetates **25** proceeded well to afford the desired 3-butynoic acid derivatives **26** with fair to excellent yields after hydrolysis (Scheme 16). The best product yields were obtained for the substrates possessing a silyl group on the alkyne terminus. The authors demonstrated that the silyl group (TMS) can be easily removed in a single step procedure by protodesilylation in the presence of a suitable base and the obtained terminal alkynes then could be subjected to Sonogashira coupling reactions. In this study, an optically pure propargyl acetate was also subjected to the carboxylation. However, chirality-transfer products were not observed, and the carboxylated product was obtained as a racemic form.

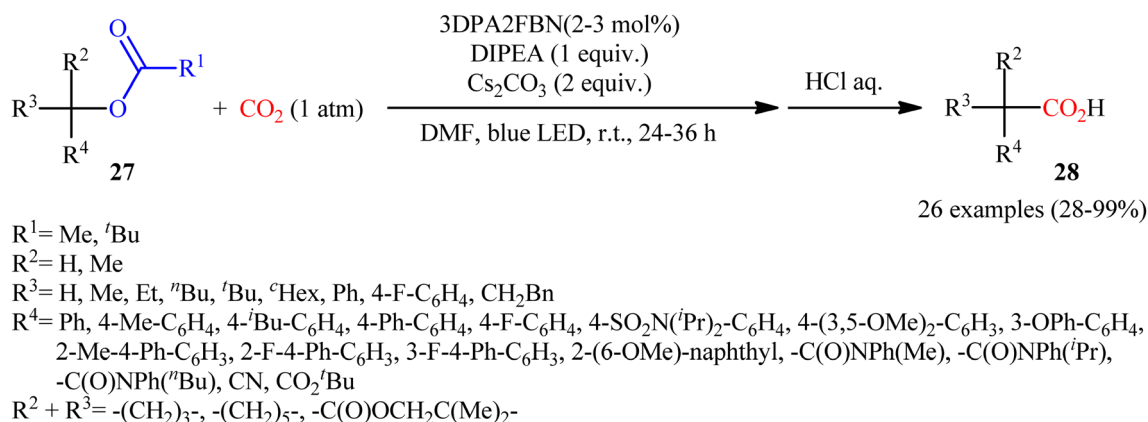
Quite recently, in the same paper describing the direct dehydroxylative carboxylation of benzylic alcohols to aryl acetic acids in the presence of catalytic amounts of an organo dye, Liao, Yu and co-workers reported the successful visible-light photoredox-catalyzed preparation of aliphatic carboxylic acids from the corresponding carboxylates.¹⁶ Thus, in the presence of catalytic amount of 2,4,6-tris-(diphenylamino)-3,5-difluorobenzonitrile (3DPA2FBN) under irradiation of visible light, deoxygenative carboxylation of various alkyl/benzylic carboxylates **27** with atmospheric CO₂ furnished the corresponding aliphatic acids **28** in moderate to quantitative yields (Scheme 17). A variety of primary, secondary, and tertiary benzylic carboxylates were compatible under the reaction conditions, indicating the general applicability of this synthetic

procedure. Furthermore, some drug molecules such as ibuprofen, (\pm)naproxen, fenoprofen, and flubiprofen were also effectively constructed under the optimal reaction. Beside good yields and broad substrate scope, scale ability can be considered as the advantages of this photoredox-catalyzed carboxylation process. Another independent visible-light-enabled benzyl carboxylates reductive carboxylation method was published by Iwasawa and co-workers using a palladium/iridium dual catalyst under visible light irradiation.²³ However, in this method, the reaction was heated at 80–100 °C using DMA as solvent (Scheme 18).

4. Carboxylation of triflates

Due to the excellent leaving ability of trifluoromethanesulfonate anion (triflate, TfO⁻), triflates are known as one of the superior C–O electrophiles and have widely been employed as alternatives and/or replacements for organic halides.²⁴ Despite their several inherent drawbacks such as instability and toxicity,²⁵ they are still among the most widely used electrophiles in the pharmaceutical industry.²⁶

After pioneering work by Tsuji and co-workers on the synthesis of a small library (two examples) of benzoic acid derivatives through the Ni-catalyzed carboxylation of aryl triflates employing CO₂,²⁷ the first general and practical example of the carboxylation of triflates with CO₂ was published by the same research team in 2015.²⁸ In this study, twelve α,β -unsaturated carboxylic acids **32** were selectively synthesized through the treatment of various cyclic alkenyl triflates **31** with atmospheric CO₂ in the presence of CoI₂(dmphen)/Mn combination as the catalytic system in DMA at room temperature (Scheme 19a). Intriguingly, the triflate moiety was selectively carboxylated even in the presence of tosylate and chloro functionalities which could be potentially reactive under the reductive carboxylation conditions. However, owing to extensive side reactions, oct-1-en-2-yl trifluoromethanesulfonate did not take part in the reaction and therefore no other *exo*-methylene containing substrates were examined in the protocol. It is worthwhile to note that carboxylation of a series of electron-rich aryl triflate derivatives **33** was also achieved with use of similar



R¹ = Me, ^tBu
 R² = H, Me
 R³ = H, Me, Et, ⁿBu, ^tBu, ^cHex, Ph, 4-F-C₆H₄, CH₂Bn
 R⁴ = Ph, 4-Me-C₆H₄, 4-^tBu-C₆H₄, 4-Ph-C₆H₄, 4-F-C₆H₄, 4-SO₂N(ⁱPr)₂-C₆H₄, 4-(3,5-OMe)₂-C₆H₃, 3-OPh-C₆H₄, 2-Me-4-Ph-C₆H₃, 2-F-4-Ph-C₆H₃, 3-F-4-Ph-C₆H₃, 2-(6-OMe)-naphthyl, -C(O)NPh(Me), -C(O)NPh(ⁱPr), -C(O)NPh(ⁿBu), CN, CO₂^tBu
 R² + R³ = -(CH₂)₃-, -(CH₂)₅-, -C(O)OCH₂C(Me)₂-

Scheme 17 Visible-light photoredox-catalyzed carboxylation of alkyl/benzylic carboxylates **27** with CO₂.



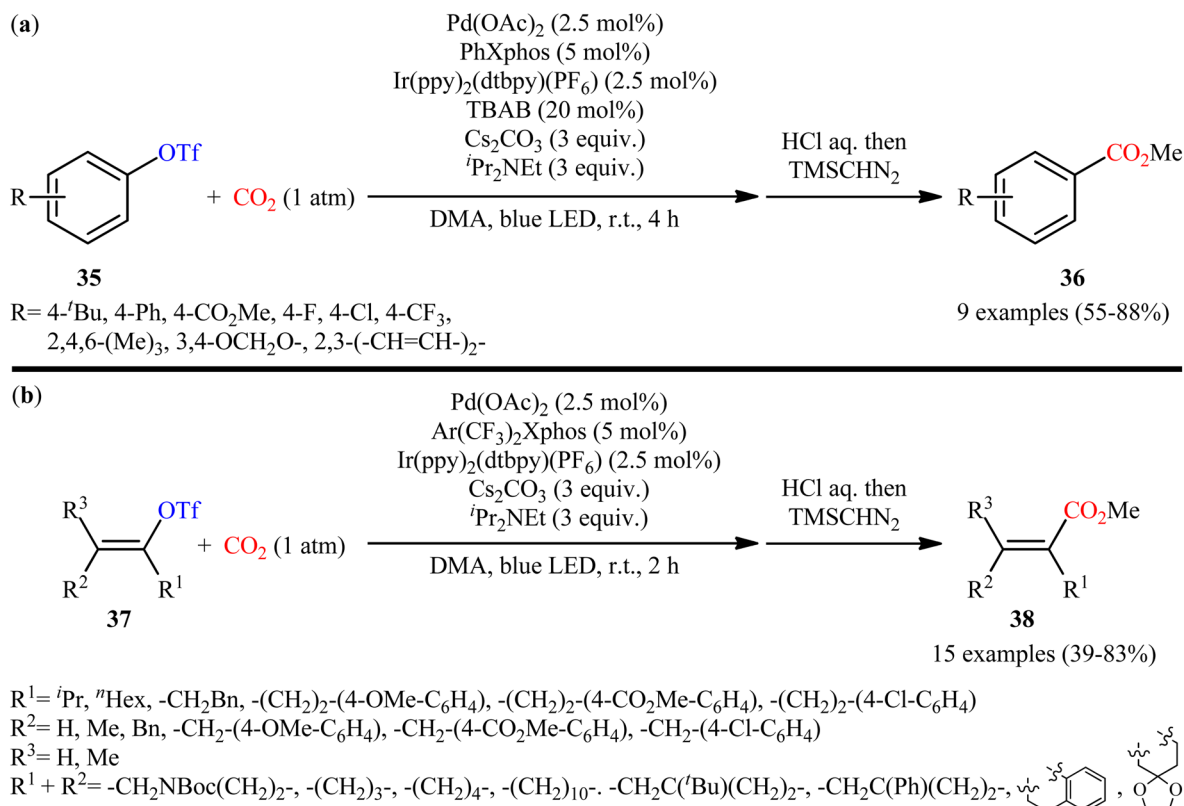
Scheme 18 Visible-light-enabled Pd/Ir-catalyzed carboxylation of benzyl alcohol derivatives **29** with CO_2 .

reaction conditions (Scheme 19b). Unfortunately, the authors did not unravel the plausible mechanistic cycle for this CO_2 -fixation reaction.

Four years later, the innovative research group of Iwasawa realized an efficient metallaphotoredox-catalyzed carboxylation of aryl triflates **35** employing atmospheric CO_2 under ambient conditions.²⁹ In this protocol, the combination of $\text{Ir}(\text{ppy})_2(\text{-dtbbpy})(\text{PF}_6)$ as a photocatalyst and $\text{Pd}(\text{OAc})_2$ as a transition-

metal-catalyst upon irradiation of blue LEDs was found to be significant for this carboxylation reaction. The presented methodology exhibited good functional group compatibility and the target carboxylic acid derivatives **36** were obtained in moderate to high yields within 4 h (Scheme 20a). Inspired by this success, the authors further extended the scope of their methodology to the more challenging alkenyl triflates. It was shown that under the identical conditions, a panel of 15 cyclic

Scheme 19 Co-catalyzed carboxylation of (a) alkenyl triflates **31** and (b) aryl triflates **33** with CO_2 .

Scheme 20 (a) Metallaphotoredox-catalyzed carboxylation of aryl triflates **31** and (b) alkenyl triflates **33** with atmospheric CO₂.

Scheme 21 Proposed mechanism for the reaction in Scheme 20.

and acyclic alkenyl triflates **37** underwent selective carboxylation and subsequent methylation to afford the desired α,β -unsaturated methyl esters **38** in satisfactory yields (Scheme 20b). Importantly, *exo*-methylene containing alkenyl triflates which were not compatible substrates under the condition developed by Tsuji, were successfully carboxylated in this protocol. Recently, the same authors conducted a detailed DFT study to understand the reaction mechanism of this palladium-catalyzed visible light-driven carboxylation.³⁰ The computations revealed that the active species for photoredox-catalyzed reduction was cationic ArPd(II)⁺ species to generate

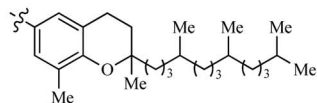
nucleophilic ArPd(I) or its further reduced ArPd(0)⁻ species, which reacted with CO₂ to give carboxylic acids. Based on these findings and experimental results, they suggested that the reaction may proceed through the catalytic cycle as depicted in Scheme 21, which was started with the oxidative addition of ArOTf to Pd(0)(Xphos) **A** to form neutral ArPd(II)(OTf)(Xphos) **B**, followed by ligand exchange to produce cationic [ArPd(II)(Sol)(Xphos)]⁺ **C**. Then, one-electron reduction of this complex by Ir(II) species generated nucleophilic ArPd(I)(Xphos) **D** or its X⁻-coordinated anionic ArPd(I) species. Subsequently, this Pd(I) species reacted with CO₂ to yield the corresponding (ArCO₂)Pd(II)(Xphos) species **E**, which is finally reduced to Pd(0)(Xphos) **A** with release of ArCO₂⁻. In another possibility, intermediated **D** would be further reduced to anionic [ArPd(0)(Xphos)]⁻ **F** and the carboxylation would be proceeded with **F**.

In a closely related investigation, Jana and co-workers also described that a diverse range of (hetero)aromatic triflates **39** were converted to the corresponding (hetero)aryl carboxylic acids **40**, *via* carboxylation with CO₂ using the same palladium and visible-light-photoredox catalysts and replacing PhXphos with davephos ligand (Scheme 22).³¹ In this transformation, a wide panel of important functional groups, such as halide, cyano, amine, ketone, ether, and ester functionalities were well tolerated, thus provided the opportunity to further functionalize the carboxylic acid products using other convenient reactions. In addition, a tolerance for an alkenyl triflate was also demonstrated. To demonstrate the practical utility of this methodology, one-pot version of this reaction using an *in situ*





(Het)Ar= Ph, 4-Ph-C₆H₄, 4-OMe-C₆H₄, 4-F-C₆H₄, 4-Cl-C₆H₄, 4-CN-C₆H₄, 4-CF₃-C₆H₄, 4-OCF₃-C₆H₄, 4-OBn-C₆H₄, 4-Cl-OC₆H₄, 3-COMe-C₆H₄, 3-NHBoc-C₆H₄, 2-Me-C₆H₄, 2-allyl-C₆H₄, 2-Ph-C₆H₄, 2,4,6-(Me)₃-C₆H₂, 3,5-(OMe)₂-C₆H₃, 2-ⁱPr-5-Me-C₆H₃, 2-Me-4-ⁱPr-C₆H₃, 2-OMe-5-allyl-C₆H₃, 3,4-OCH₂O-C₆H₃, 3,4-(CH₂)₂-C₆H₄, 3,4-(CH₂)₄-C₆H₃, 1-naphthyl, 2-naphthyl, 2-(6-OMe)-naphthyl, 2-(6-Br)-naphthyl, 4-(N-Boc)-indolyl, 3-(2-CO₂Me)-thienyl, 2-(N-Me)-carbazolyl,



Scheme 22 Jana's synthesis of (hetero)aryl carboxylic acids 40.

generated aryl triflate from the corresponding phenol was performed and the desired product was obtained in good yield. Unfortunately, neither benzylic nor allylic triflates were effectively reacted under the conditions employed. Furthermore, when tosylate, mesylate, and nonaflates were employed under the optimal reaction conditions, only trace amounts of carboxylated products were observed.

Recently, Sun *et al.* developed an interesting electrochemically enabled nickel-catalyzed methodology for carboxylation of aryl triflates **41** with CO₂ using electron as the clean reductant.³² The efficient combination of NiBr₂·DME, dtbbpy, DMAP, KO^tBu, MgBr₂, and NaI with a carbon felt anode and a Zn plate cathode in an undivided cell, under constant current of 8–10 mA, provided the benzoic acid derivatives **42** in good yields (Scheme 23). Apart from triflates, other activated alcohols such as tosylates and mesylates were also compatible with this scenario. Although only two examples were disclosed, this paper represents the first example of the electrocatalytic carboxylation of triflates with CO₂.

5. Carboxylation of tosylates

Tosylates (OTs) are one of the viable C–O electrophiles and widely used in certain organic reactions such as nucleophilic substitution and cross-coupling reactions. Although they are more attractive than triflates in terms of cost, stability, and availability of reagents, but they tend to be less reactive than triflates as electrophiles.³³

Compared with triflates, carboxylation of tosylates with CO₂ is considerably less explored. In fact, to the best of our knowledge, only two practical examples of such a CO₂-fixation reaction were reported in literature thus far. In 2014, Martin and colleagues realized the first metal-catalyzed carboxylation of tosylates with CO₂ by the combination of NiBr₂·glyme, dmphen, and Mn powder as catalyst, ligand, and reducing agent, respectively.³⁴ The transformation proceeded under atmospheric pressure of CO₂ in DMF, tolerated a series of alkyl tosylates **43** containing other potentially reactive functionality such as OPiv and OMe groups, and provided the



Scheme 23 Electrochemical carboxylation of aryl triflates **41** with CO₂.



Scheme 24 Ni-catalyzed carboxylation of alkyl tosylates **43** with CO_2 .Scheme 25 Ni-catalyzed carboxylation of aryl tosylates **45** with CO_2 .

corresponding aliphatic carboxylic acids **44** in good yields, ranging from 62% to 76% (Scheme 24). Notably, the carboxylation of alkyl mesylates and trifluoroacetates was also feasible, albeit in lower yields.

Two years later, the group of Durandetti extended the scope of this chemistry to carboxylation of aryl tosylates employing $[\text{NiBr}_2(\text{bipy})]/\text{Mn}$ combination as a catalytic system and DMF as the solvent.³⁵ A variety of electron deficient- and donating-substituted aryl tosylates **45** easily took part in this transformation and produced the desired carboxylic acid derivatives **46** in moderate to good yields (Scheme 25); in addition, a tolerance for aryl iodide as well as aryl bromide was also demonstrated. In this report, several control experiments, such as electrochemical investigations, DFT calculation and others, were conducted for the insight of the reaction mechanism, which indicated the formation of key Aresta-type $\text{Ni}-\eta^2\text{-CO}_2$ complex in the catalytic cycle (Scheme 26).

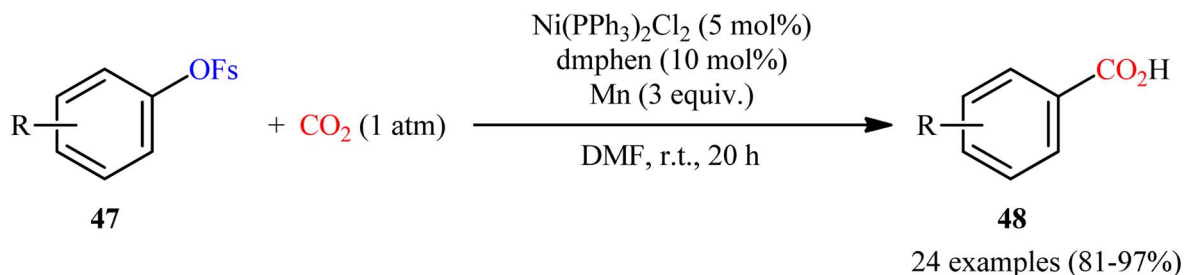
6. Carboxylation of fluorosulfates

Fluorosulfates (OFs) as a more stable and eco-friendly alternative of triflates, have recently gained increasing attention as versatile electrophilic partners in cross-coupling reactions.³⁶ They are easily and conveniently prepared from alcohols using sulfuryl fluoride (SO_2F_2) as an inexpensive sulfonyl fluoride provider.

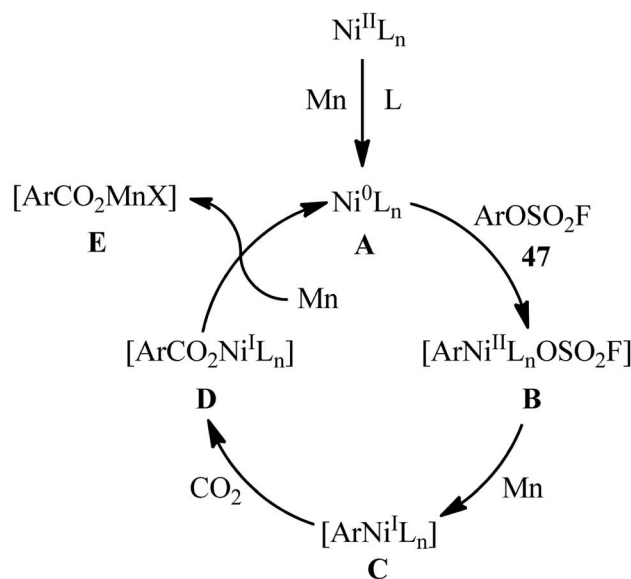
In 2019, Mei's research group demonstrated for the first time the usefulness of aryl fluorosulfates as coupling partners in carboxylation reactions using CO_2 , providing a novel opportunity to construction of carboxylic acids.³⁷ To evaluate various parameters, such as catalyst and ligand, 4-(*tert*-butyl)

phenylfluorosulfate was chosen as the model reactant. The combination of $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ with dmphen and Mn powder was found to be more effective catalytic system, which afforded a better yield of the desired 4-(*tert*-butyl)benzoic acid. Under the optimized conditions, 24 benzoic acid derivatives **48** were obtained in high to almost quantitative yields from the respective aryl fluorosulfonates **47** (Scheme 27). Apart from aryl fluorosulfonates, heteroaryl derivatives (e.g., pyridine, quinoline) were also compatible with this scenario. Notably, the authors also disclosed one-pot version of the same reaction where the requisite aryl fluorosulfonates were prepared *in situ* from the corresponding phenols and SO_2F_2 .

Scheme 26 Mechanistic proposal for the formation of carboxylic acid derivatives **46**.



R = H, 4-Me, 4-Ph, 4-OMe, 4-COMe, 4-CO₂Me, 4-SO₂Me, 4-CF₃, 4-Cl, 4-CN, 4-NHCOMe, 3-F, 3-OMe, 3-CN, 2-Me, 2-Ph, 2-F, 3,5-(Me)₂, 3,5-(F)₂, 3,4-(-CH=CH-)₂-, 3,4-(CH₂)₃C(O)-,



Scheme 27 Ni-catalyzed carboxylation of aryl fluorosulfates **47** with CO_2 developed by Mei.

7. Conclusion

The ubiquity of carboxylic acids in nature and a myriad of applications in the fields of agriculture, pharmaceuticals, medicine, food, and other industries inspire constant development of complementary and alternative routes for their synthesis, which are green and sustainable. In this regard, catalytic carboxylation of alcohols and some of their derivatives with CO_2 via C–O bond cleavage has received remarkable attention. This page of carboxylic acid synthesis not only benefits from the use of CO_2 as an inexpensive, nontoxic, and renewable one-carbon (C1) feedstock, but also allows the use of alcohol derivatives as far more sustainable and safer alternatives of the conventionally employed organohalides. Intriguingly, without exception, all deoxygenative carboxylations covered in this review were performed under atmospheric pressure of CO_2 and majority of them at room temperature. Interestingly, some of these reactions were performed under

metal-free condition which is highly desirable from the standpoint of green chemistry. These results clearly indicate the potential application of this page of carboxylic acid synthesis in industry. Despite notable recent advances, this interesting research arena is still in infancy and there are still many challenges to be addressed in this synthetic strategy. Some of these are listed below: (i) the application of this methodology in the enantioselective synthesis of chiral carboxylic acids remains elusive, and therefore development of asymmetric catalytic systems will be still highly desirable task in this field; (ii) the direct dehydroxylative carboxylation of free alcohols are mainly limited to the use of only aliphatic alcohols. Therefore, the development of new catalytic systems that being able to catalyze carboxylation of (hetero)aromatic alcohols is highly desirable; and (iii) the utilized activated alcohols are mainly limited to esters, triflates, tosylates, and fluorosulfates. Therefore, of course, expanding of the scope of C–O reagents are necessary.



Conflicts of interest

There are no conflicts to declare.

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