Nickel-catalyzed Reductive Carboxylation and Amidation Reactions

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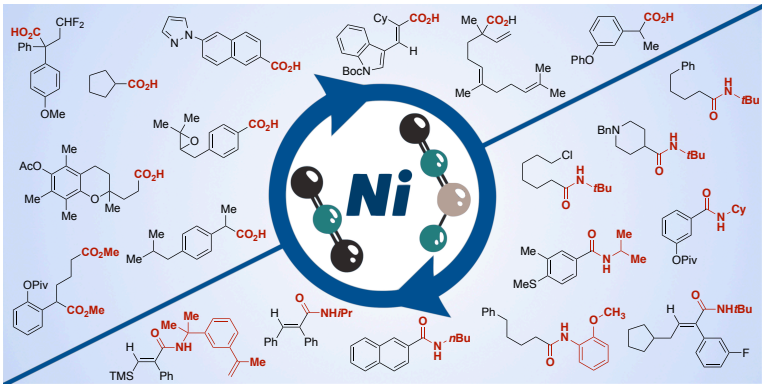
CONSPECTUS

The ubiquity and importance of carboxylic acids and amides in peptides, pharmaceuticals, agrochemicals and synthetical materials has challenged chemists to design *de novo* catalytic carboxylation and amidation protocols. They represent a powerful alternative to canonical oxidation of alcohols and aldehydes, hydrolysis of nitriles, transamidation reactions or condensation techniques for the synthesis of these functional groups. Among various scenarios,

the recent years have witnessed considerable advances in Ni-catalyzed reductive carboxylation and amidation reactions utilizing carbon dioxide and isocyanate counterparts. This account aims to highlight the progress made in this arena with a historical perspective, with a particular emphasis of the methodologies that have emanated from our laboratories without losing sight of the underlying principles by which these reactions operate, with the ultimate goal of allowing the transition from comprehension to prediction in this exciting field.

Unlike the utilization of conventional polar, yet highly reactive, organometallic reagents in carboxylation or amidation reactions, the utilization of nickel catalysts has allowed the use of carbon dioxide and isocyanates with less reactive and less-polarized counterparts for the formations of carboxylic acids and amides. These less reactive groups include organic halides and pseudohalides (i.e. alkyl bromides and chlorides, esters, alcohols and ammonium salts), unsaturated hydrocarbons (i.e. alkynes, styrenes, unactivated alkenes and dienes) or even C–H bonds, where forging the targeted C–C bond at previously unfunctionalized C–H linkages was possible, thus giving access to densely functionalized compounds that would be difficult to access otherwise. The C–H functionalization include chain-walking scenarios, where subtle changes in the ligand and reaction conditions marked the selectivity of the transformations, and reactions via a [1,4]-Ni shift, where selective carboxylation in aromatic rings could be achieved. Conceptuality and practicality aside, these transformations have even offered the possibility of modulating and dictating the site-selectivity pattern, thus not only providing new vistas when controlling the selectivity of bond-forming reactions at specific sites within the sidechain, but also new knowledge in retrosynthetic analysis when accessing carboxylic acids and amide backbones. Importantly, these techniques have shown to be particularly suited for the preparation of isotopically labelled molecules when using $^{13}CO_2$ or even $^{14}CO_2$, thus becoming a useful endeavor in the drug discovery

pipeline. Although mechanistic understanding at the molecular level still constitutes the "*Achiles heel*" of these transformations, the recent empirical discoveries and the rapid adoption of these protocols by the Community augurs well for the widespread utilization of reductive carboxylation and amidation reactions in both academic and industrial laboratories.



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INTRODUCTION

Carboxylic acids and amides rank among the most prevalent functional groups in natural products, biologically-relevant compounds and pharmaceuticals.[5,6] Conventional protocols for the preparation of amides include transamidation reactions[7] or dehydrative condensation of carboxylic acids and amines either thermally or in the presence of coupling reagents,[8–10] whereas carboxylic acids are typically prepared from the oxidation of alcohols/aldehydes or the hydrolysis of nitriles.[11] However, the recent years have witnessed the development of alternative catalytic methods for the synthesis of carboxylic acids and amides. Among these, particular attention has been devoted to reductive coupling reactions with carbon dioxide or isocyanates, as these techniques offer a complementary new approach to the synthesis of high-value added carboxylic acids and amides from simple and readily available precursors.

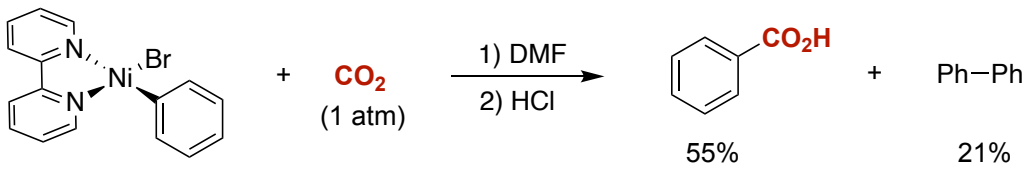
While carbon dioxide is an abundant, inexpensive and renewable C1 synthon,[12] its zero dipolar moment, high thermodynamic stability and kinetic inertness makes its utilization particularly problematic in catalytic endeavors.[13] In contrast, isocyanates are considerably more reactive entities due to the polarization induced by the nitrogen atom on the heterocumulene backbone, making the central carbon amenable for functionalization events with metal complexes.[14] Although this can offer a broader synthetic scope, more frequently the susceptibility of isocyanates for binding transition metals makes them particularly vulnerable for decomposition pathways such as dimerization or trimerization pathways.[15] Despite all these drawbacks, the recent advances in nickel catalysis have alleviated most of the challenges associated with these endeavors,[16] culminating in a series of conceptually novel Ni-catalyzed protocols en route to aliphatic or aromatic carboxylic acids and amides.[17,18] Although significant progress has also been made through the utilization of other transition metals, this account highlights the work that our group

has carried out during the last years in Ni-catalyzed reductive carboxylation and amidation reactions, including mechanistic considerations when appropriate. We expect that the underlying principles by which these reactions operate will set the basis for designing even more powerful catalytic processes with CO_2 and isocyanates as coupling counterparts as a means to synthesize scaffolds of interest for both pharmaceutical and academic laboratories.

Reductive carboxylation and amidation of organic halides and pseudo-halides

In 1994, a seminal disclosure by Osakada and Yamamoto demonstrated that a well-defined Ni(II) oxidative addition complex Ni(II)Br(Ph)(bpy) reacted with CO_2 at atmospheric pressure in DMF, providing non-negligible amounts of benzoic acid (Scheme 1).[19] This finding can hardly be underestimated, as it tacitly showed that a priori unreactive CO_2 could be inserted into organometallic sp^2 C–Ni linkages, thus establishing the basis for designing *de novo* catalytic carboxylation reactions.

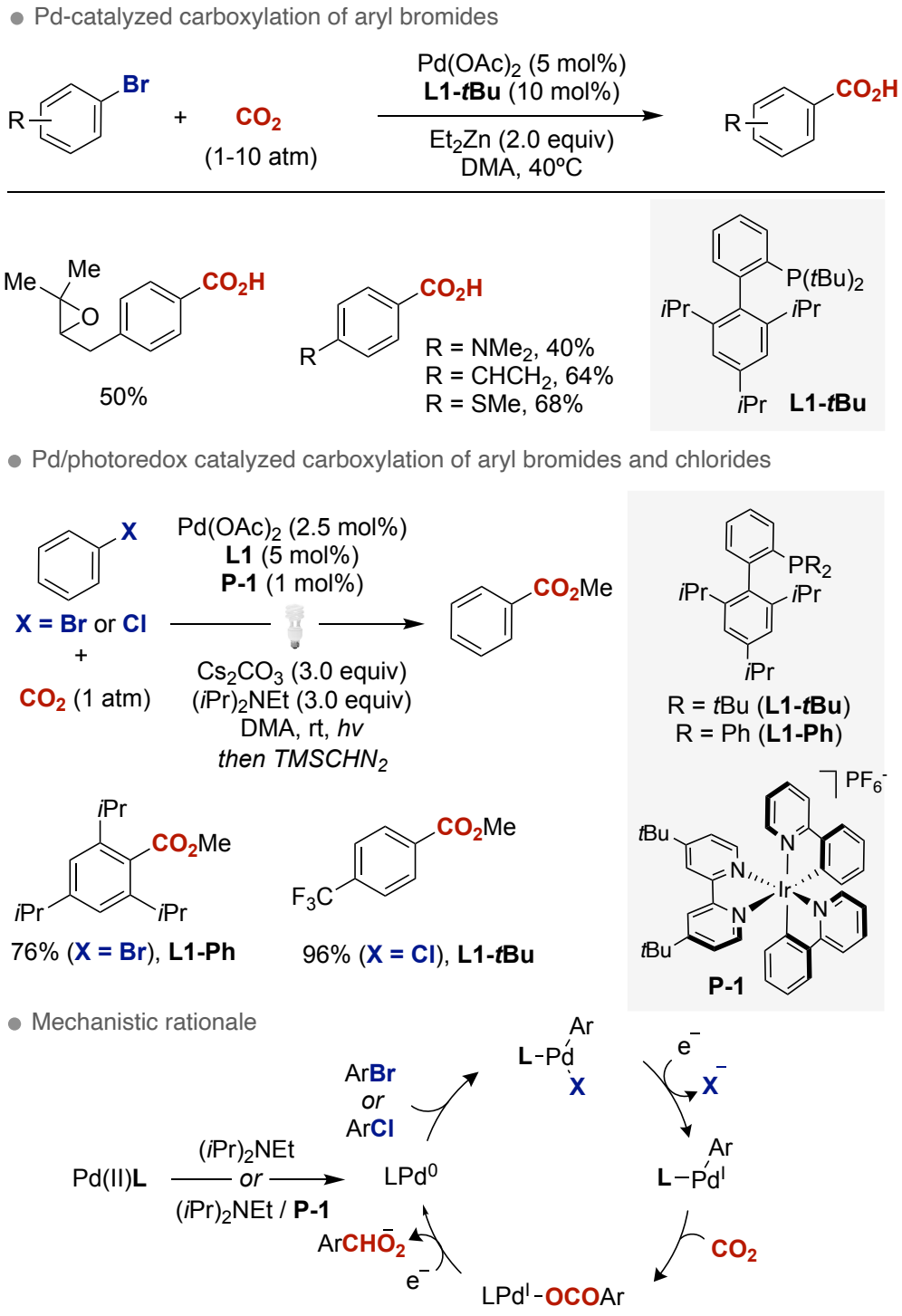
Scheme 1. Pioneering stoichiometric carboxylation of a Ni(II) complex.



Surprisingly, Osakada's findings remained dormant for nearly 15 years, and it was not until 2009 when our group reported the first catalytic carboxylation of aryl bromides with CO_2 by using a Pd catalyst and Et_2Zn as terminal reductant. Although one might argue that the use of a pyrophoric organometallic reductant might limit the scope of the transformation, the reaction exhibited an excellent functional group tolerance and allowed the carboxylation of molecules containing esters, ketones or epoxides (Scheme 2, *top*).[20] The inability of PhZnBr to insert CO_2 under the catalytic conditions and the absence of deuterium incorporation after quenching the model reaction with

D_2O ruled out the intermediacy of organozinc species, suggesting an analogous pathway to that showed by Osakada consisting of a direct CO_2 insertion into the corresponding sp^2 C–Ni bond. Recently, a collaboration between Iwasawa and our group described that the combination of Pd catalysts and photoredox endeavors might represent a fertile ground in the catalytic carboxylation of aryl halides, avoiding the utilization of organometallic species as reducing agents (Scheme 2, *middle*).[21] As expected, bulky and electron-rich phosphine ligands were found to be particularly suited for this reaction. Experimental and theoretical studies showed ArPd(II)X as the active species that generate ArPd(I) intermediates via SET prior to reaction with CO_2 (Scheme 2, *bottom*).[22]

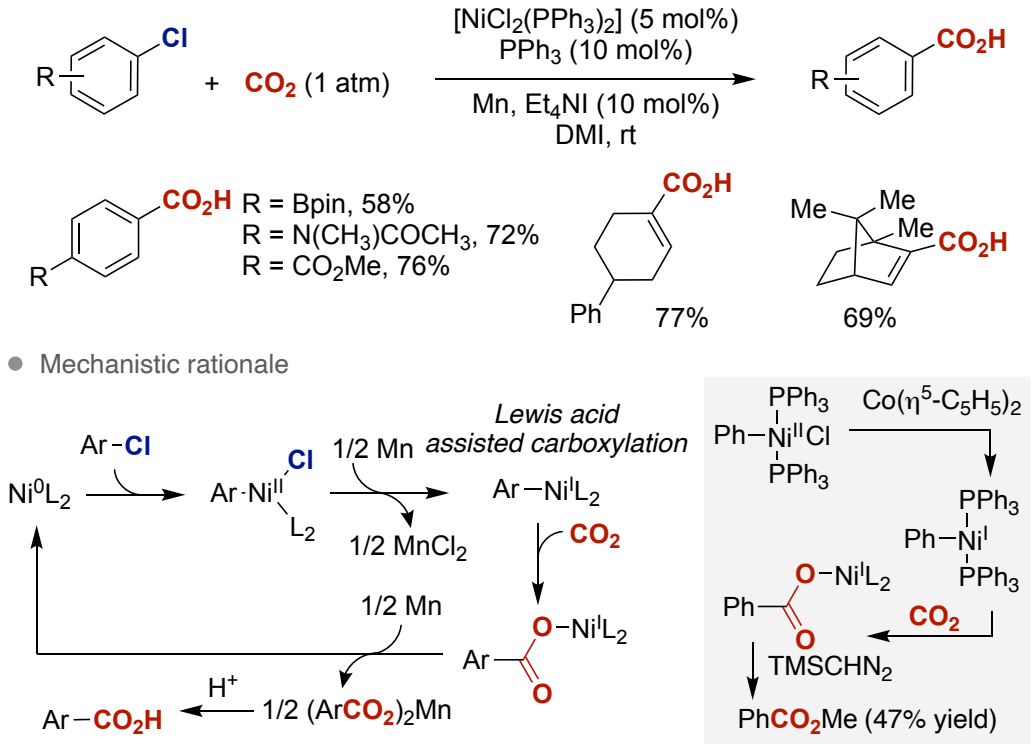
Scheme 2. Palladium catalyzed carboxylation of aryl bromides



In 2012, Tsuji and Fujihara extended the scope of catalytic carboxylation reactions to more challenging aryl and vinyl chlorides with Mn as reductant and Et_4NI as additive (Scheme 3).[23] Stoichiometric experiments already pointed out the possible intermediacy of Ni(I) species in this

reaction. While Mn was initially considered merely as an electron donor, recent investigations by Hazari showed that the MnX_2 obtained in every turnover played a non-negligible role in the rate of CO_2 insertion into the Ni(I) aryl intermediates. The inclusion of ammonium salts likely undergoes ligand-exchange processes, thus facilitating reduction of in situ generated Ni(I) carboxylates while recovering back the propagating Ni(0) species. As it will become evident in the following sections, certain additives play a non-negligible role, yet not fully understood, in both reactivity and site-selectivity.

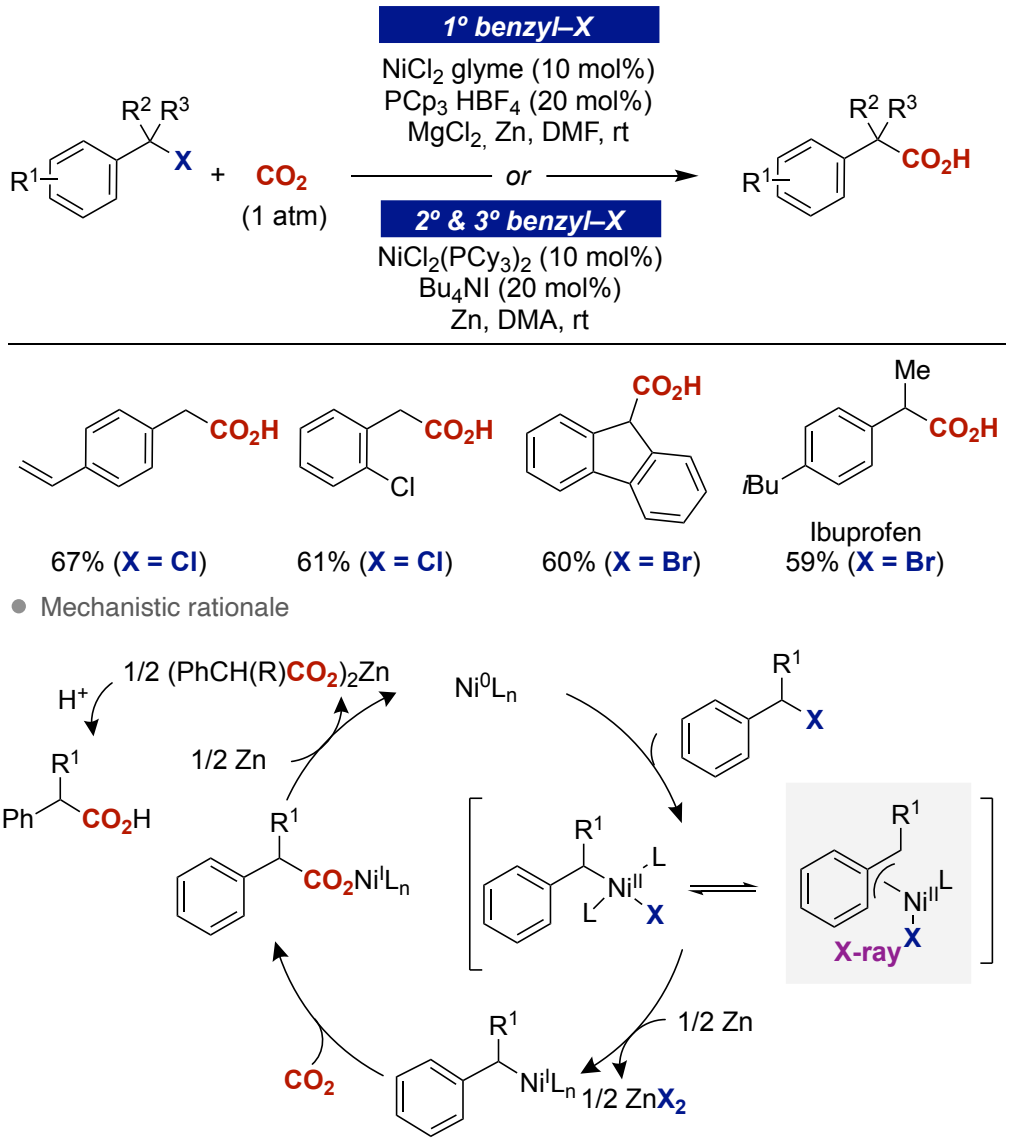
Scheme 3. Nickel catalyzed carboxylation of aryl and vinyl chlorides



Although these investigations set the basis for modern catalytic reductive carboxylation techniques, the field remained confined to aryl and vinyl electrophiles. Aimed at extending the carboxylation portfolio beyond sp^2 counterparts, our group described a Ni-catalyzed reductive carboxylation of primary, secondary and tertiary benzyl halides (Scheme 4).[24] The use of highly

electron-rich phosphines as PCp_3 and PCy_3 in combination with Zn as reducing agent was found to be critical for success. In line with Hazari's recent mechanistic studies, the utilization of $MgCl_2$ as additive was highly beneficial for the carboxylation of primary benzyl halides – likely facilitating SET-type processes, an observation that could be indirectly corroborated by DFT calculations[25] and that agrees with the role of salts observed in other cross electrophile couplings with metallic reductants[26] –, while the presence of TBAI improved significatively the carboxylation of secondary and tertiary benzyl halides. Stoichiometric experiments with an isolated η^3-benzylnickel(II) complex indicated that carboxylation does not occur unless Zn is employed, suggesting a CO_2 insertion event at Ni(I) intermediates that are generated upon single electron transfer or comproportionation events.[27]

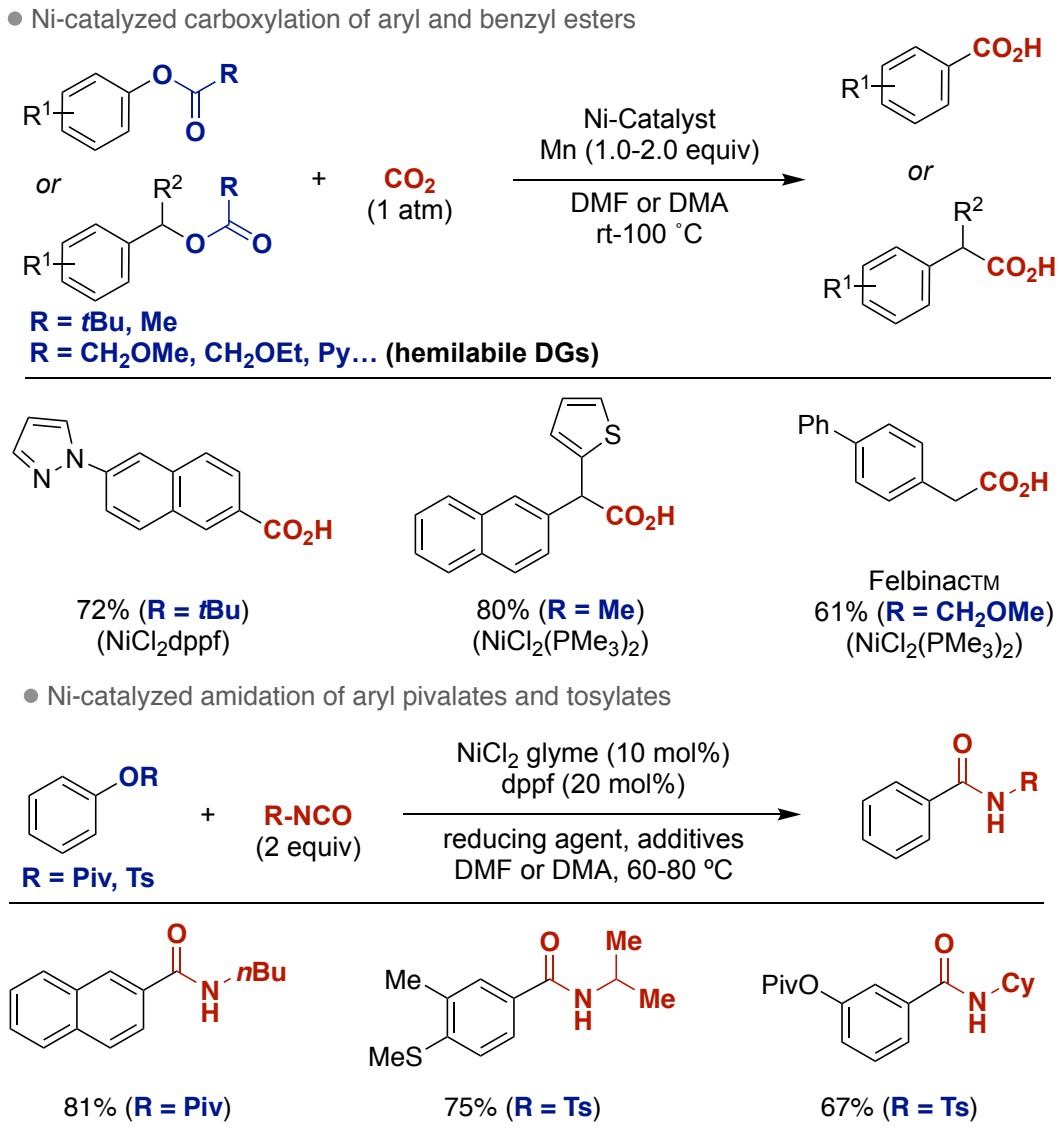
Scheme 4. Nickel catalyzed carboxylation of benzyl bromides and chlorides



Prompted by the natural abundance and ready availability of phenols and alcohols, it comes as no surprise that C-O electrophiles has gained considerable momentum as alternative counterparts to organic halides in cross-coupling reactions. While considerable progress has been made with particularly activated C-O electrophiles such as sulfonates, tosylates or triflates,[28] the utilization of simpler, yet more robust, ester derivatives as C–O electrophiles poses significant challenges such as the higher activation energy required for effecting sp^2 C–O cleavage, site-selectivity issues

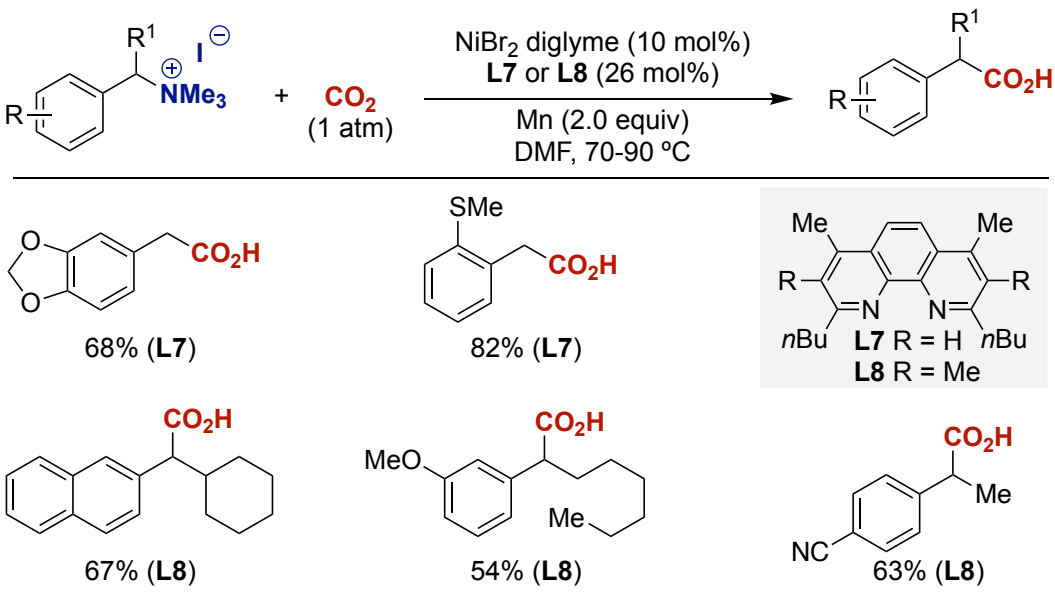
in the presence of two competing C–O bonds and the proclivity of the acyl C–O bonds towards competitive hydrolysis.[29] Despite these drawbacks, our group succeeded in developing a Ni-catalyzed carboxylation of aryl and benzyl ester derivatives (Scheme 5, *top*).[30] It was found that the ligand had a profound effect on the reactivity, with dppf being particularly suited for the carboxylation of aryl pivalates whereas the utilization of monodentate PMe_3 was critical for promoting the carboxylation of benzyl ester derivatives. Although non-extended π-systems remained unreactive under these conditions – an observation typically found in a myriad of C–O functionalization reactions –, this limitation could be alleviated by employing hemilabile directing groups that likely increase the rate of oxidative addition while enabling a rapid CO_2 insertion by opening up coordination sites at the nickel center. Driven by the inherent similar electronic structure of CO_2 and isocyanates, an otherwise related Ni-catalyzed reductive amidation of aryl and benzyl ester derivatives could be developed with similar ease (Scheme 5, *bottom*).[31] As for the previous carboxylation event, dppf was critical to allow the coupling of a wide variety of alkyl isocyanates with benzyl or aryl esters whereas the inclusion of K_2HPO_4 minimized undesired trimerization of the isocyanate. Notably, non-extended arenes could be employed as substrates by using slightly more activated aryl tosylates or aryl chlorides in combination with NaI as additive.

Scheme 5. Nickel catalyzed carboxylation and amidation of esters.



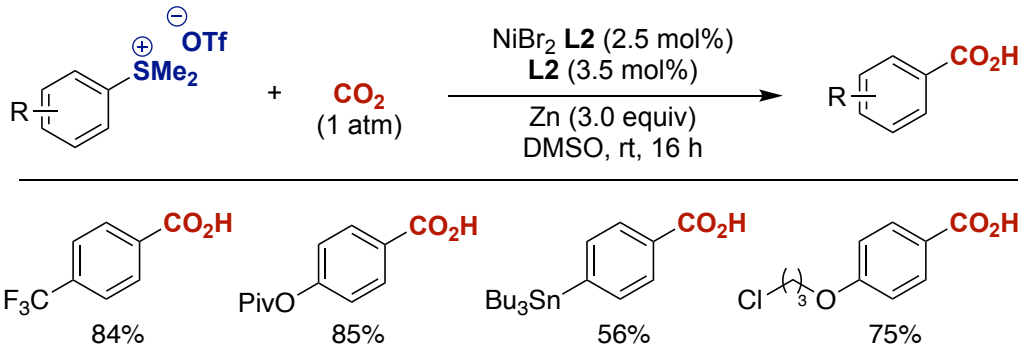
Prompted by the prevalence of benzyl amines in a myriad of pharmaceuticals and biologically-relevant molecules, we showed the viability of their corresponding ammonium salts as counterparts in a catalytic deaminative carboxylation event (Scheme 6).[32] As for previous carboxylation protocols, the utilization of 1,10-phenanthroline ligands possessing substituents adjacent to the nitrogen atom were critical for success, allowing the coupling of primary and secondary benzylic ammonium salts with CO_2.

Scheme 6. Nickel catalyzed carboxylation of ammonium salts.



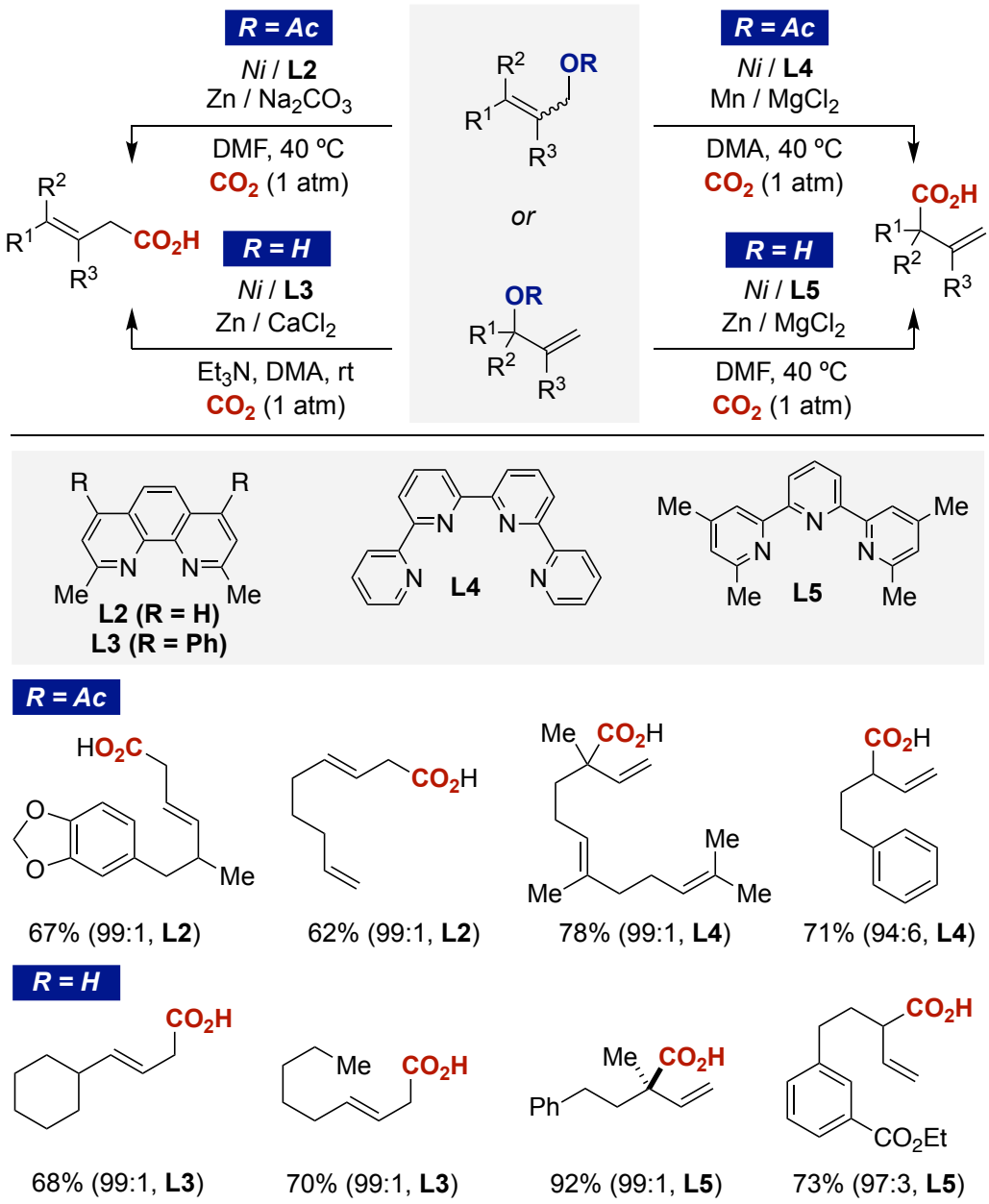
Recently, a collaborative effort with Prof. Yorimitsu showed the possibility to utilize bench-stable aryl sulfonium salts – easily accessed from simple aryl sulfides – as coupling counterparts in catalytic carboxylation reactions with Zn as stoichiometric reductant (Scheme 7).[33] In contrast to other carboxylation reactions, initial mechanistic studies advocated the notion that organozinc intermediates are generated in situ. These findings do not only suggest the involvement of a Ni-to-Zn transmetallation but also indicate that different mechanistic pathways may intervene depending on the nature of the coupling partner utilized.

Scheme 7. Ni-Catalyzed Carboxylation of C(sp^2)–S Bonds with CO_2.



The development of regiodivergent protocols that control and predict the site-selectivity pattern of cross-coupling reactions still constitutes a formidable challenge in catalytic endeavors.[34] Aiming at unraveling the potential of catalytic reductive carboxylation events, our group found that α-branched or linear carboxylic acids could be within reach from simple allyl esters by discriminating both ends of the initially generated π-allyl metal complex, with site-selectivity dictated by the denticity of the ligand employed. Specifically, while bidentate 1,10-phenanthroline ligands resulted in linear carboxylic acids, the utilization of tetradentate backbones gave rise to the corresponding α-branched compounds exclusively, thus suggesting the formation of two distinctive Ni intermediates which promote CO_2 insertion at different reaction sites (Scheme 8).[35] Given that allylic esters are ultimately prepared from the corresponding allyl alcohols, the ability to promote an otherwise similar site-selective carboxylation event by employing the latter as substrates would represent a bonus from a practical standpoint. However, the high activation energy required for effecting C-OH bond cleavage and the high polarizability of the hydroxyl group left some doubts whether such a technology could ever be implemented. We hypothesized that CO_2 might play a dual role by lowering down the activation energy of the targeted sp^3 C–O bond upon reversible formation of carbonic acids and as C1 source for the carboxylation event. As for the previous carboxylation of allylic esters, a careful choice of the ligands dictated the site-selectivity pattern, with 1,10-phenanthrolines affording linear carboxylic acids whereas the inclusion of terpyridine ligands resulted in an exclusive α-branched selectivity pattern (Scheme 8).[36]

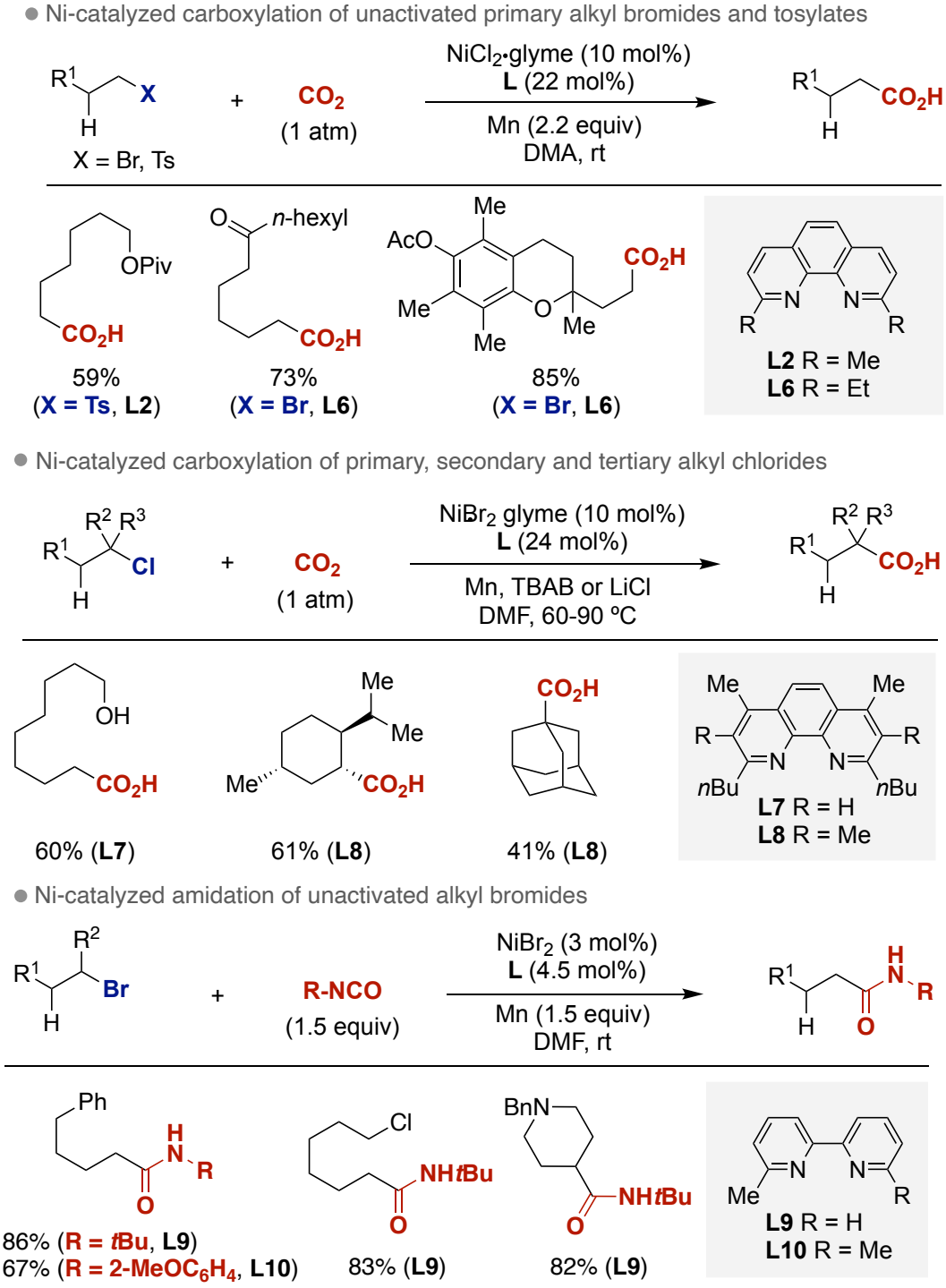
Scheme 8. Nickel catalyzed carboxylation of allyl acetates and alcohols.



In 2014, the catalytic carboxylation portfolio remained restricted to the utilization of particularly activated aryl, benzyl or allylic electrophiles, thus contributing to the perception that extending these conceptions to unactivated alkyl electrophiles would be particularly problematic. While the difficulty for triggering an oxidative addition of alkyl electrophiles to low-valent metal centers and/or the proclivity of in situ generated alkyl metal intermediates for parasitic β–hydride elimination and/or homodimerization pathways constituted a serious barrier for the

implementation of these processes, our group found that 1,10-phenanthroline ligands bearing substituents adjacent to the nitrogen atom efficiently promoted a Ni-catalyzed reductive carboxylation of unactivated primary alkyl bromides (Scheme 9, *top*).[1] However, secondary, tertiary alkyl bromides or even more accessible alkyl chlorides failed to react under these conditions. These challenges were finally met by utilizing an appropriately substituted 1,10-phenanthroline with either *n*Bu_4NBr (TBAB) or LiCl as additives (Scheme 9, *middle*).[37] Stoichiometric experiments with well-defined Ni(0) complexes and Ni(I) species confirmed the intermediacy of the latter as key species prior to CO_2 insertion into the C–Ni bond.[38] Careful ligand optimization demonstrated that the utilization of substituted 2,2'-bipyridine ligands enabled a Ni-catalyzed reductive amidation of unactivated primary, secondary or even tertiary alkyl bromides with a wide range of aliphatic and aromatic isocyanates (Scheme 9, *bottom*).[2] As expected, the utilization of enantioenriched alkyl electrophiles or α,β-bisdeuterated substrates in both reductive amidation or carboxylation events resulted in the loss of the stereochemical integrity, thus suggesting that single-electron transfer (SET) processes come into play.

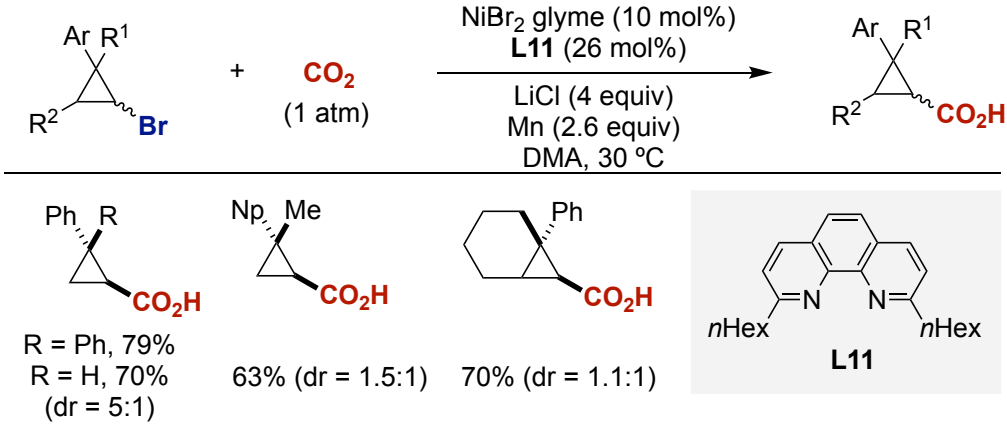
Scheme 9. Nickel catalyzed carboxylation and amidation of unactivated alkyl (pseudo)halides.



Recently, our group extended the range of catalytic carboxylation reactions to the utilization of cyclopropyl bromides, thus giving access to added-value strained carboxylic acids (Scheme 10).[39]

As expected, 2,9-substitution at a 1,10-phenanthroline ligand backbone was critical for success, with LiCl being essential for avoiding competitive ring-opening processes.

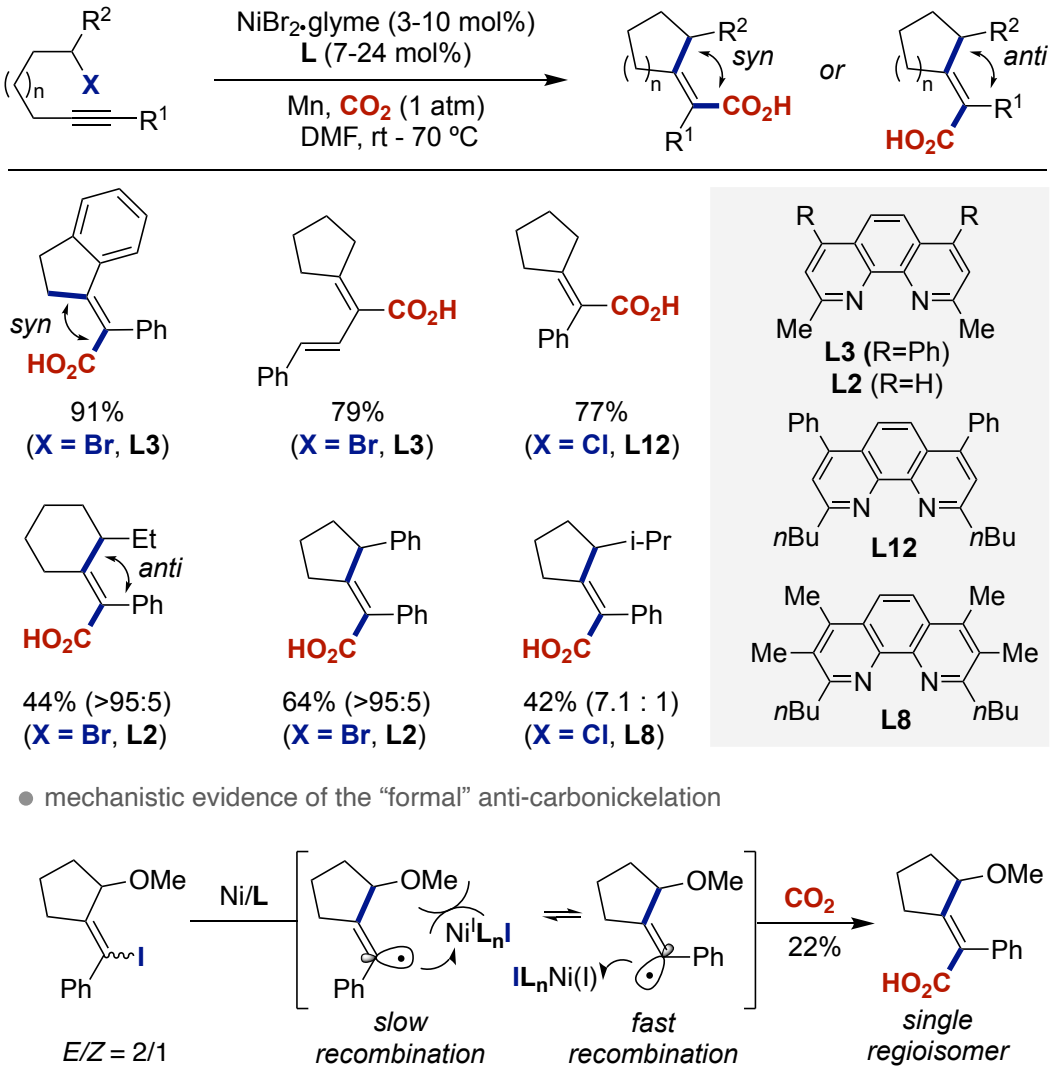
Scheme 10. Nickel catalyzed carboxylation of cycloporpyl bromides.



While the ability to enable SET processes at *sp*^{3} C–halide bonds results in the loss of stereochemical integrity, this apparent drawback can be turned into a strategic advantage by triggering cascade-type processes via open-shell intermediates. Specifically, we found that unactivated alkyl halides possessing an alkyne on the side chain enabled the formation of five- or six-membered rings via formal 5-exo or 6-exo-dig cyclization *en route* to tetrasubstituted olefins containing a carboxylic acid function (Scheme 11).[40] Interestingly, the regioselectivity at the alkene backbone can be tuned and controlled by an appropriate selection of both the ligand employed and the substitution pattern at the alkyl halide motif. While the carboxylation of primary alkyl halides resulted in *syn*-products exclusively, the employment of secondary alkyl halides afforded *anti*-products predominantly. The origin of this divergence can be rationalized through the intermediacy of two vinyl radicals that can rapidly interconvert and recombine at different rates with the corresponding LNi(I)X species. The observed *anti*-selectivity switch with secondary alkyl

halides can be rationalized by a selective recombination of a vinyl radical that avoids the steric clash with the proximal alkyl substituents within the carbocyclic skeleton.

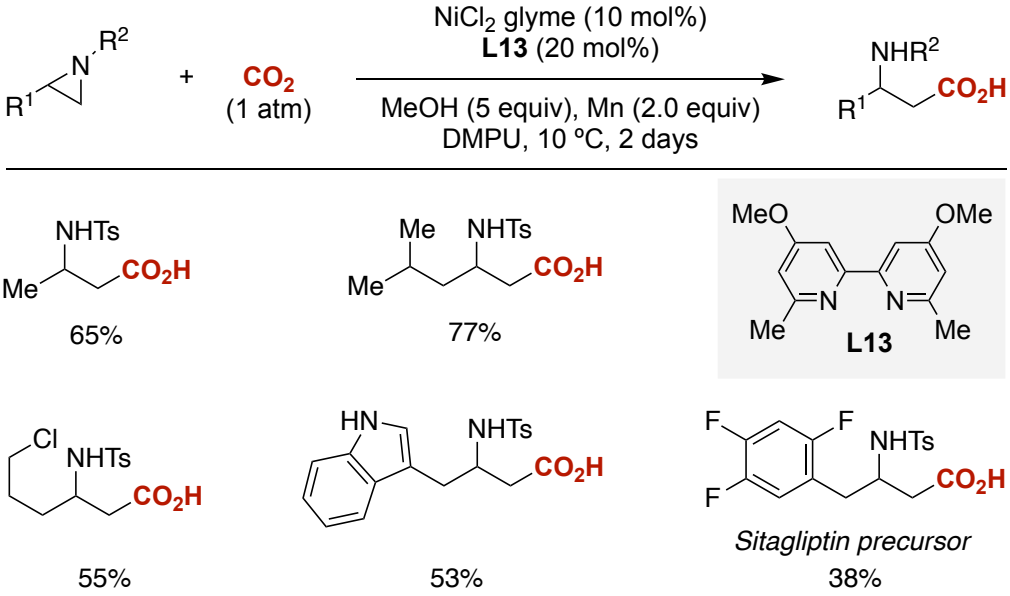
Scheme 11. Nickel catalyzed cyclization-carboxylation of alkyl bromides and chlorides.



Convinced about the relevance of carboxylation reactions for preparing added-value chemicals, we recently extended our interest in deaminative cross-coupling reactions towards the development of a Ni-catalyzed reductive carboxylation of aziridines with CO_2 at atmospheric pressure en route to β-amino acids, important building blocks with considerable potential of peptidomimetics (Scheme 12).[41] Importantly, the protocol was suited for the utilization of $^{13}CO_2$,

resulting in a de novo technique to obtain biologically-relevant molecules such as ^{13}C-Sitagliptin precursors.

Scheme 12. Ni-Catalyzed Carboxylation of Aziridines.

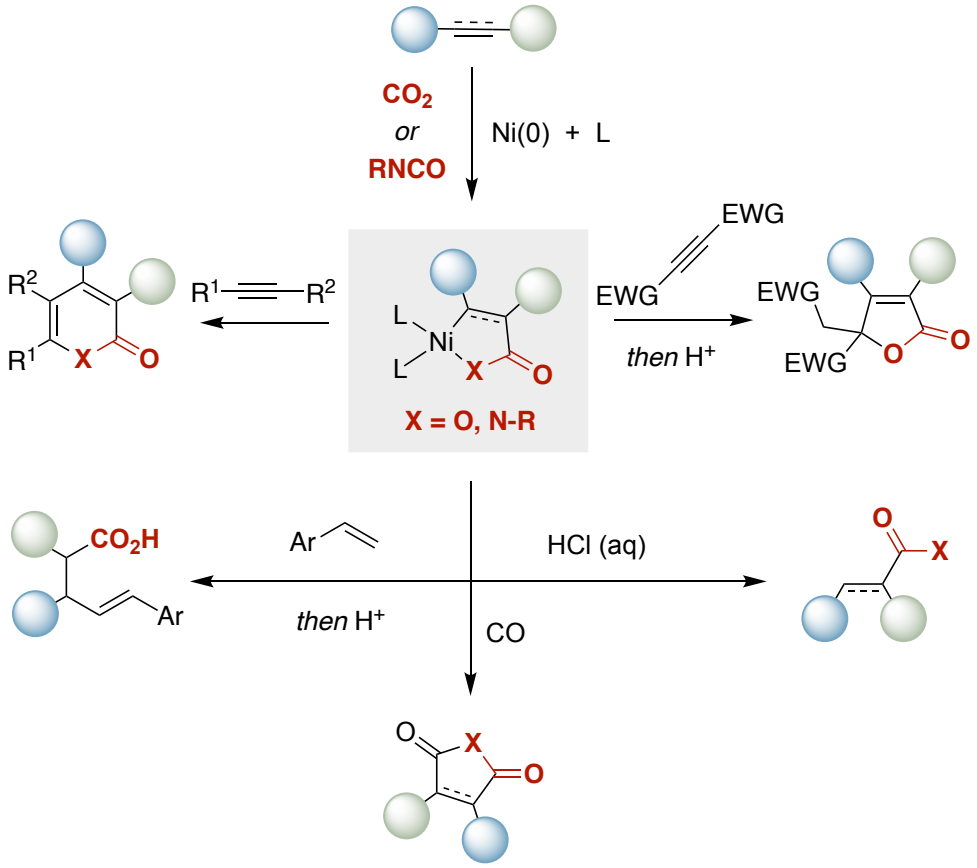


Reductive carboxylation/amidation of alkynes, alkenes and dienes

While the means to promote catalytic carboxylation of organic halides, ammonium salts, aryl sulfides or C–O electrophiles offered new opportunities in both the reductive coupling arena and CO_2 fixation, these methodologies inevitably required prefunctionalization at either the sp^2 or sp^3 reaction site, thus lowering down the practicality and potential applicability of these techniques. These observations served as an inspiration to develop catalytic carboxylation reactions of simple unsaturated hydrocarbons, as these manifolds offer the opportunity to repurpose two available feedstocks en route to added-value chemicals. Over the last 40 years, considerable progress has been made in this regard, either in a stoichiometric or in a catalytic fashion. The first reports on the carboxylation of unsaturated hydrocarbons can be traced back from the seminal work of Inoue and Hoberg in the 1970's.[42–48] Specifically, it was reported the formation of relatively stable

nickelacycles by oxidative cyclization of simple alkynes, alkenes or heteroallenes with nickel (0) and CO_2 or isocyanates, thus setting up the basis for preparing useful carbocyclic skeletons and/or aliphatic carboxylic acid derivatives (Scheme 13).

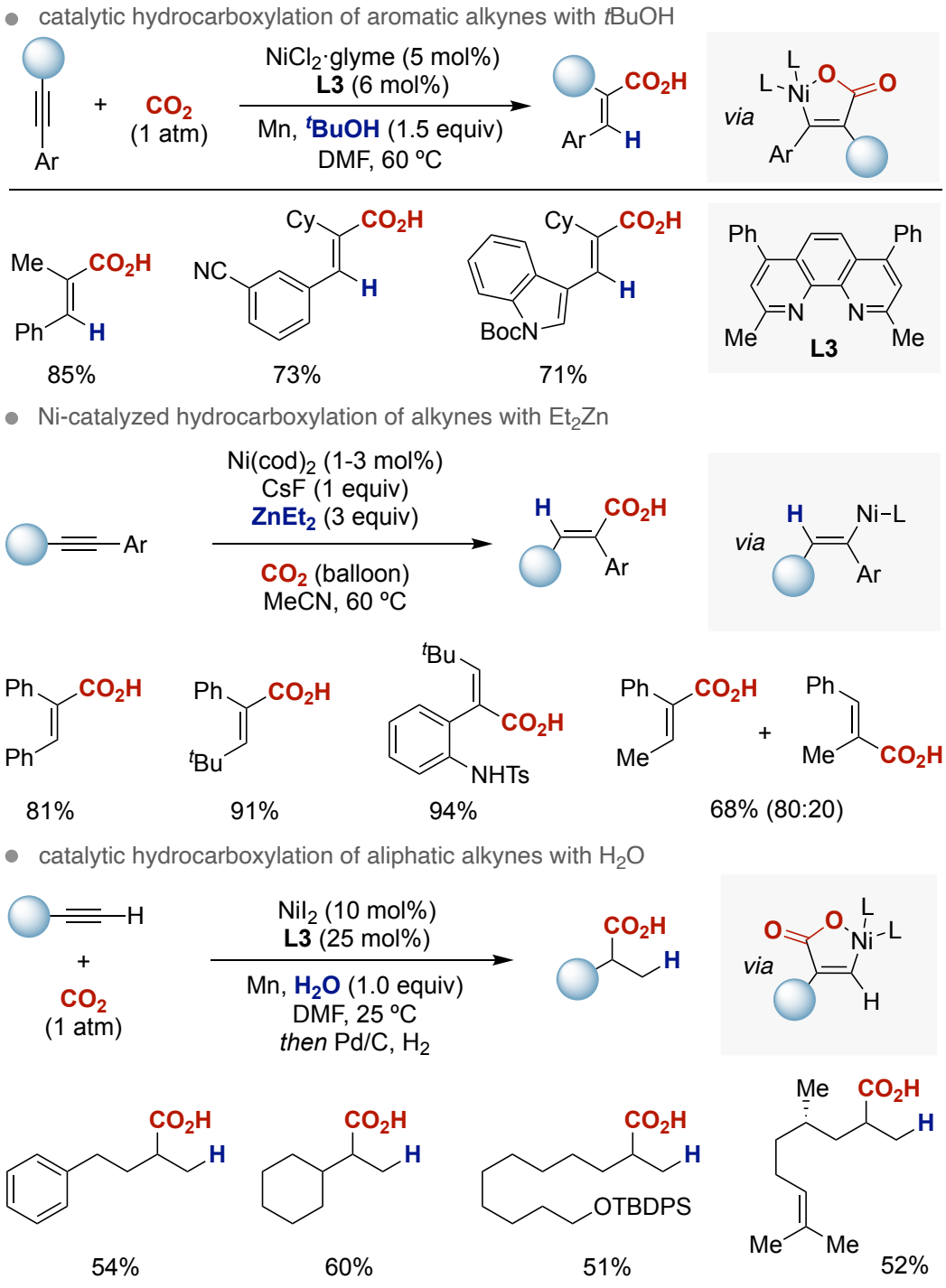
Scheme 13. Synthesis and reactivity of nickelacycles.



Inspired by these seminal studies, our group decided to investigate the catalytic carboxylation and amidation of unsaturated motives without recourse to stoichiometric, yet highly reactive, organometallics or air sensitive reagents. Specifically, we envisioned that the catalytic hydrocarboxylation of alkynes with CO_2 could be achieved by using alcohols or water as formal hydride sources, offering not only a powerful alternative to known procedures based on stoichiometric amounts of organometallics or silanes as hydride sources, but also a platform for preparing acrylic acids with a different site-selectivity pattern (Scheme 14, *top*).[49] Indeed, the

regioselectivity was found to be independent of the substitution pattern of the substrate, with CO_2 insertion taking place exclusively at the distal position to the aromatic site. These results are in sharp contrast with the site-selectivity pattern observed by Ma when using Ni(0) precatalysts and Et_2Zn as reducing agents (Scheme 14, *middle*).[50] The observed regioselectivity suggested a protonation of the oxanickelacyclopentene intermediate with a bulky alcohol, giving rise to the targeted hydrocarboxylation product as a single isomer. Following a similar mechanistic rationale, aliphatic terminal alkynes underwent hydrocarboxylation under similar Ni-catalyzed conditions using water as formal hydride source (Scheme 14, *bottom*).[51] In this case, α–substituted acrylic acids are obtained selectively, an observation that goes in line with the formation of an oxanickelacyclopentene that locates the metal center distal to the aliphatic substituent prior to protonation with water. Subsequently, the corresponding acrylic acid can be reduced by exposure to H_2 over Pd/C to deliver the corresponding saturated branched carboxylic acids.

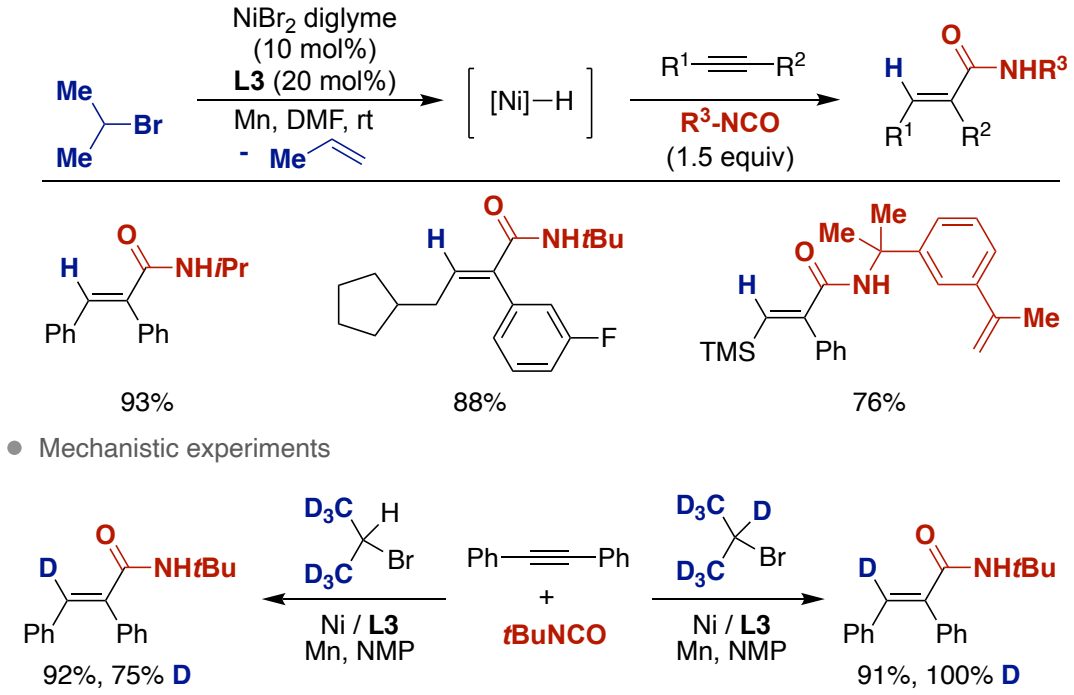
Scheme 14. Nickel catalyzed hydrocarboxylation of alkynes.



Although an analogous catalytic reductive hydroamidation of alkynes could a priori be enabled by utilizing isocyanates as counterparts, the need for hydride sources or acids to generate the intermediate metal hydrides posed a significant challenge, as these species can readily react with

isocyanates to obtain ureas, carbamates or oligomerization products. To such end, we envisioned that nickel hydrides could be generated in situ via β-hydride elimination of a sacrificial alkyl halide, thus allowing to promote a chemo- and regioselective migratory insertion of a nickel hydride to the alkyne while leaving the isocyanate entity intact.[52] As shown in Scheme 15, this protocol could be put into practice by using isopropyl bromide as hydride precursor, thus giving rise to the targeted acrylamides with propene as byproduct. Deuterium-labelling experiments with either $(CD_3)_2CHBr$ or $(CH_3)_2DBr$ unambiguously showed that the hydride source derived from a β-hydride elimination pathway from in situ generated alkyl nickel intermediates.

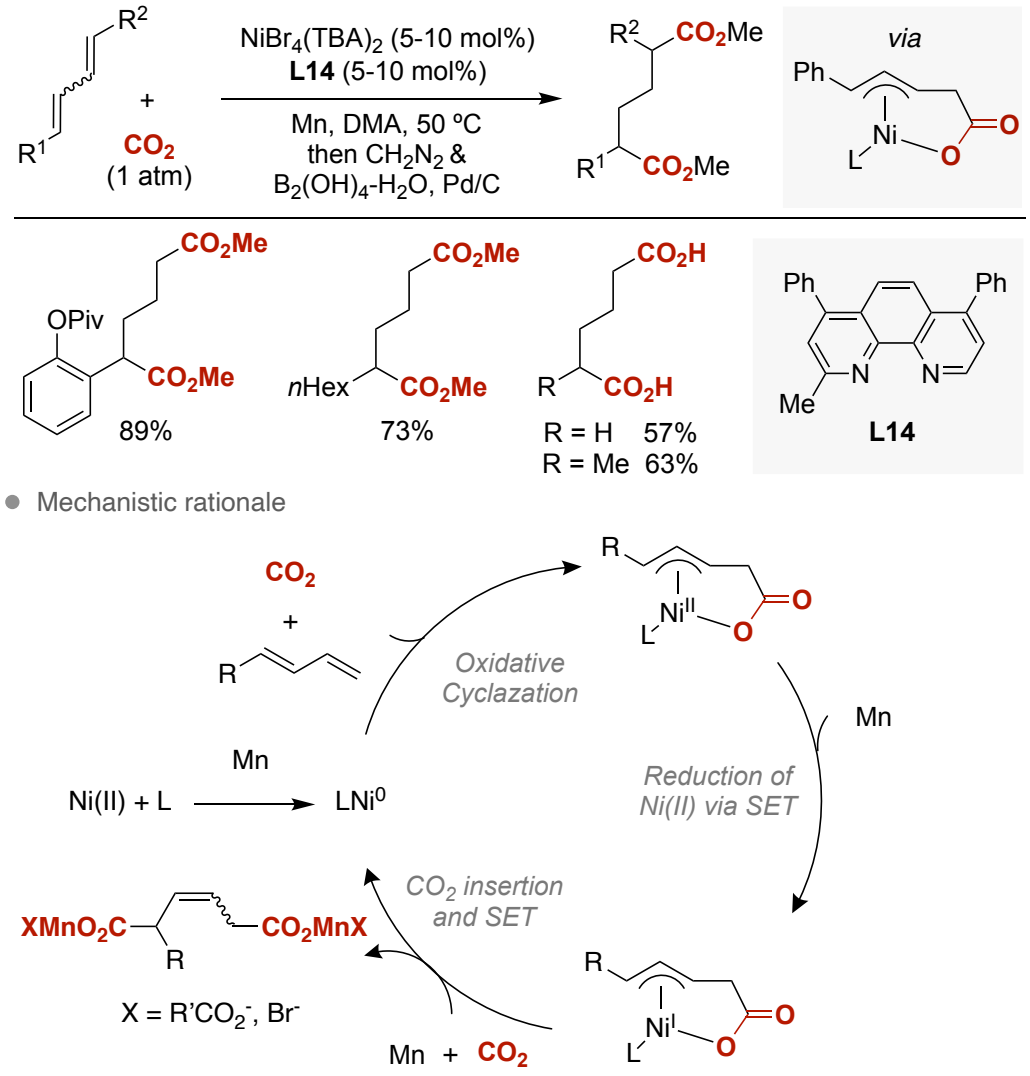
Scheme 15. Nickel catalyzed hydroamidation of alkynes.



Although 1,3-dienes are particularly prone to trigger telomerization reactions in the presence of transition metals and CO_2,[53–55] we anticipated that adipic acids – molecules of utmost synthetic relevance in the production of plastics and adhesives – might a priori be beyond reach via a site-selective catalytic dicarboxylation of 1,3-dienes in the absence of stoichiometric organometallic

reagents.[56] In line with other catalytic carboxylation reactions, 1,10-phenanthroline ligands bearing substituents adjacent to the nitrogen atom were perfectly suited for the reaction to occur, exclusively affording adipic acids upon hydrogenolysis of the pending olefin (Scheme 16).[57] Importantly, the technology could be applied for 1,3-butadiene, piperylene or isoprene, chemical feedstocks that are produced on a large scale from the steam cracking in the production of ethylene. Recent DFT studies supported our mechanistic hypothesis based on an initial oxidative cyclization of Ni(0) with the terminal olefin and CO_2 followed by SET to generate a Ni(I) intermediate prior to insertion of a second molecule of CO_2.[58]

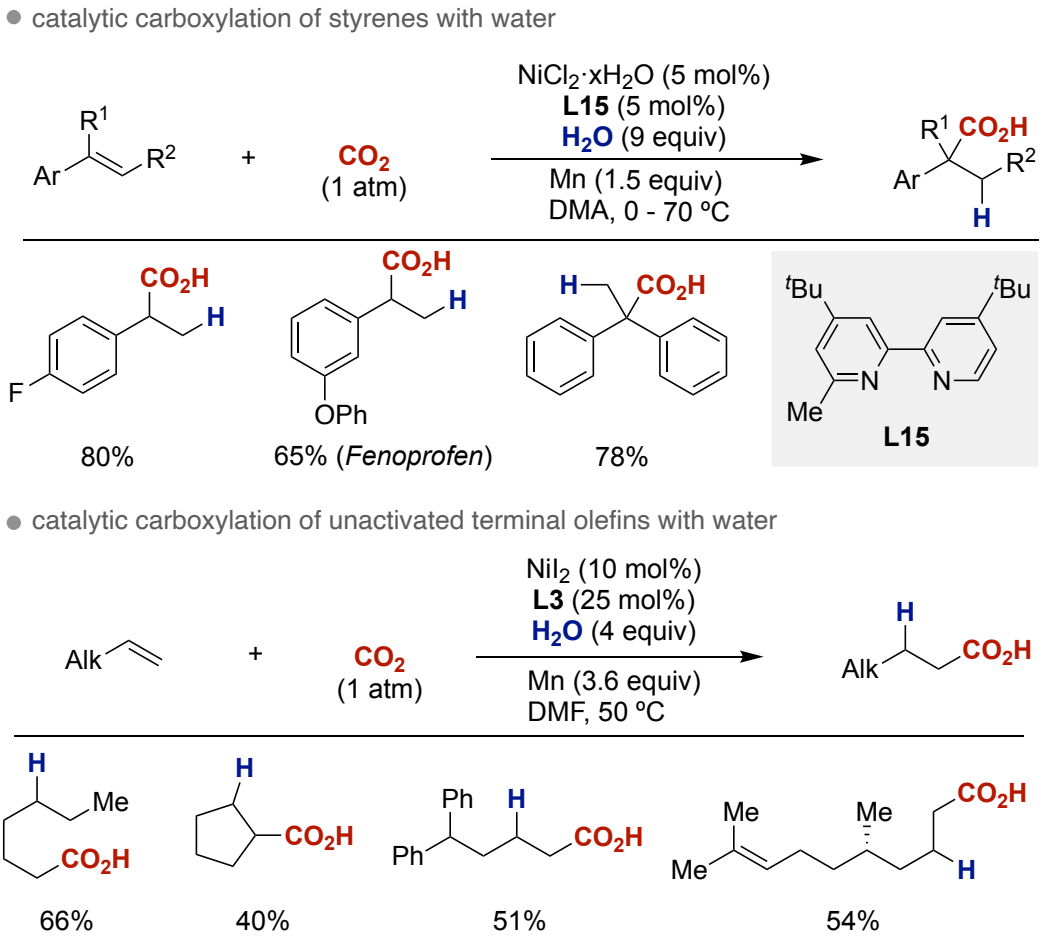
Scheme 16. Nickel catalyzed double carboxylation of 1,3-dienes.



Following up our interest in the catalytic valorization of unsaturated hydrocarbons, we described the means to enable a catalytic reductive carboxylation of simple olefins. Interestingly, this technique offered a complementary site-selectivity to that observed for alkyne congeners, as the hydrocarboxylation of styrenes delivered phenyl acetic acids whereas the use of unactivated α-olefins resulted in primary carboxylic acids (Scheme 17).[51] This change in site-selectivity could be rationalized by a different mechanism that does not invoke the formation of nickelalactones, but rather nickel hydride species that trigger a selective migratory insertion prior to CO_2 insertion. The

selective migratory insertion into styrenes delivered benzyl nickel intermediates on thermodynamic grounds whereas the utilization of α-olefins results in anti-Markovnikov insertion that locates the Ni center at the less-sterically encumbered site of the olefin.

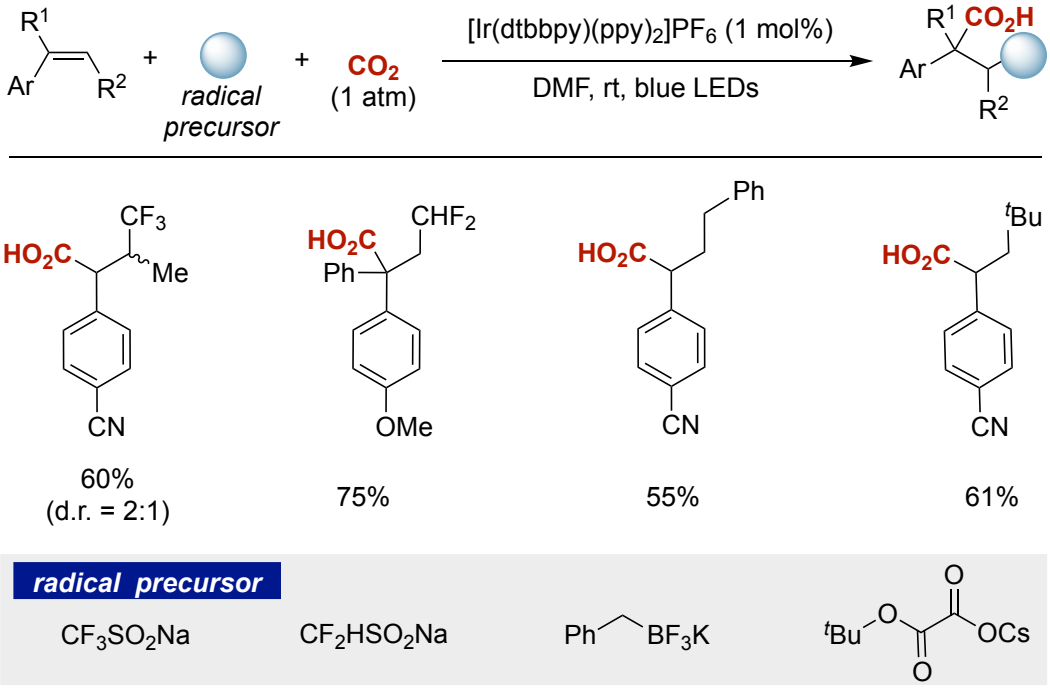
Scheme 17. Nickel catalyzed hydrocarboxylation of alkenes.



In 2017, our group described a dicarbofunctionalization of styrenes by photoredox catalysis with CO_2 as coupling partner, thus extending the carboxylation of unsaturated hydrocarbons beyond hydrofunctionalization reactions (Scheme 18).[59] Such a technique allowed to incorporate a series of radical precursors into the alkene backbone via SET oxidation such as di(tri)fluoromethyl sulfinates, potassium trifluoroborates salts or cesium oxalates in good yields. Preliminary mechanistic experiments suggested the involvement of benzyl anions generated upon SET

reduction of an in situ generated 1,1-diphenyl 3,3,3-trifluoro- propane radical (E_{red} = -1.34V vs SCE in MeCN)[60] by the reduced form of the Ir(II) photocatalyst (E_{red} = -1.51V vs SCE in MeCN)[61] that trigger a subsequent nucleophilic attack to CO_2. It is worth noting that these conceptions have been taken by others, showing the viability of generating benzyl anion intermediates for forging C–C bonds under photochemical reactions with or without CO_2.[62]

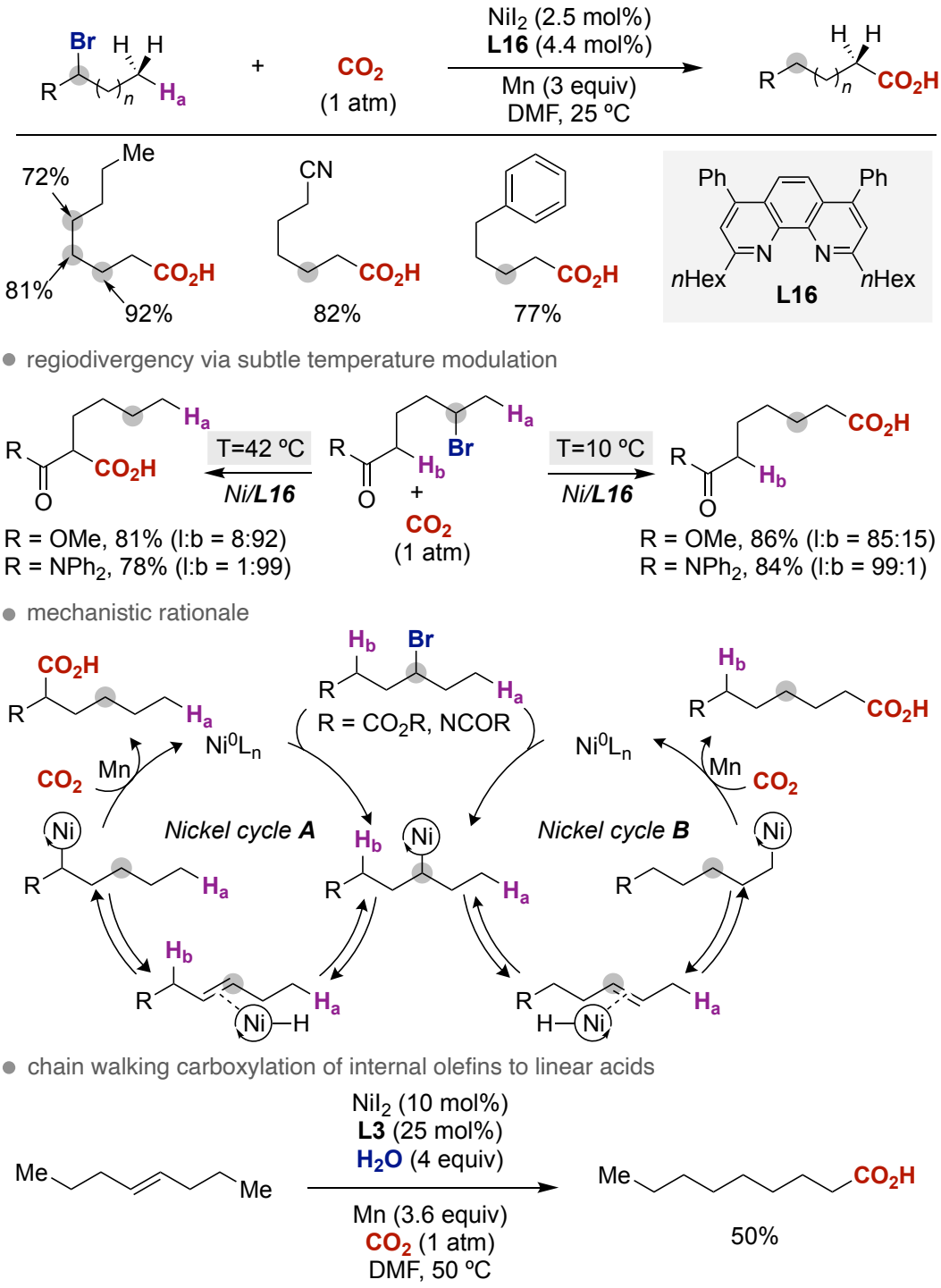
Scheme 18. Dicarbofunctionalization of styrenes with CO_2 and radical precursors.



Reductive carboxylation at remote *sp²* and *sp³* C–H sites

As shown in Scheme 15, the propensity of alkyl halides to undergo β-hydride elimination turned out to be a worthwhile endeavor for chemical invention, as the corresponding nickel hydrides could easily be intercepted by alkyne congeners. In the absence of unsaturated moieties, such nickel hydrides might trigger a chain-walking throughout the alkyl side chain via iterative migratory insertion/β-hydride elimination, thus allowing to formally translocate the metal center at a distal, yet previously unfunctionalized, *sp³* C–H site prior to CO_2 insertion. In 2017, we demonstrated the successful realization of this concept by triggering a catalytic carboxylation of unactivated alkyl halides at distal *sp³* C–H sites by means of a tunable and controllable Ni-catalyzed chain-walking event. Importantly, CO_2 insertion took place exclusively at primary *sp³* C–H sites – the strongest linkages in the alkyl C–H series –, thus reinforcing the notion that our protocol is dictated by kinetic grounds and therefore complementary to radical type scenarios that would otherwise result in the functionalization at weaker benzylic *sp³* C–H sites (Scheme 19, *top*).[3] It is worth noting that site-selectivity could be modulated by a subtle change in the reaction temperature with alkyl halides possessing carbonyl-type compounds on the side-chain, with linear carboxylic acids obtained at low temperatures whereas high temperatures resulted in α-branched carboxylic acids selectively, suggesting that site-selectivity arises from a subtle thermodynamic vs kinetic control that could be modulated by the temperature of the reaction. Furthermore, chain-walking carboxylation was not limited to alkyl halide counterparts, as a similar endeavor could be implemented with unactivated internal olefins with water as the formal reducing agent (Scheme 19, *bottom*). [51]

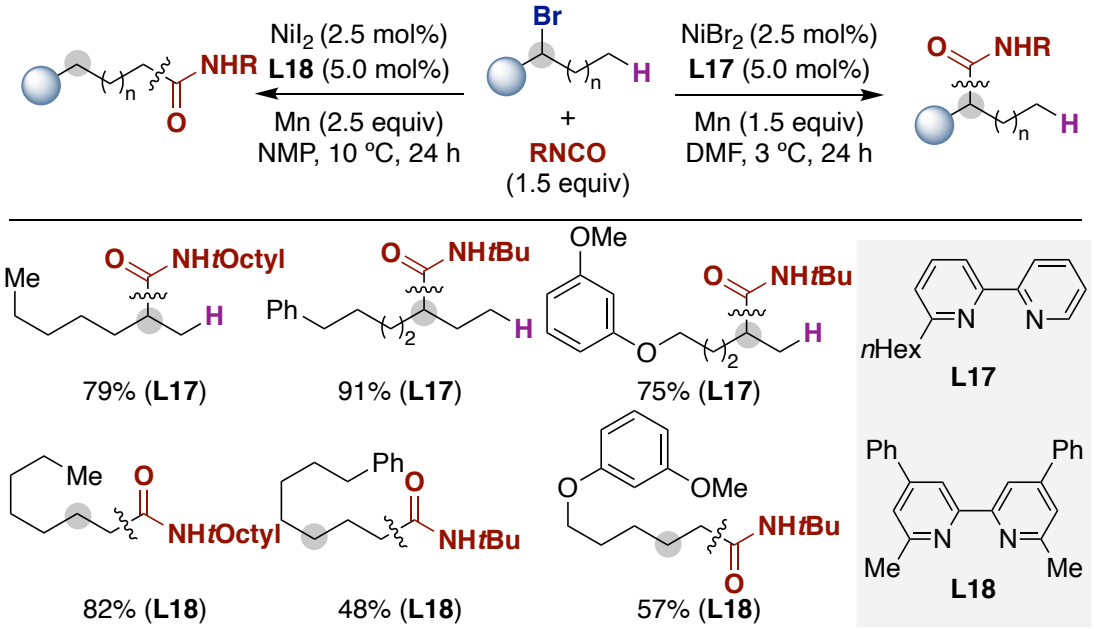
Scheme 19. Nickel catalyzed carboxylation of remote C-H bonds.



Continuing our quest for achieving site-selective transformations, the amidation of secondary alkyl bromides allowed us the development of a new regiodivergent reaction. The selectivity of

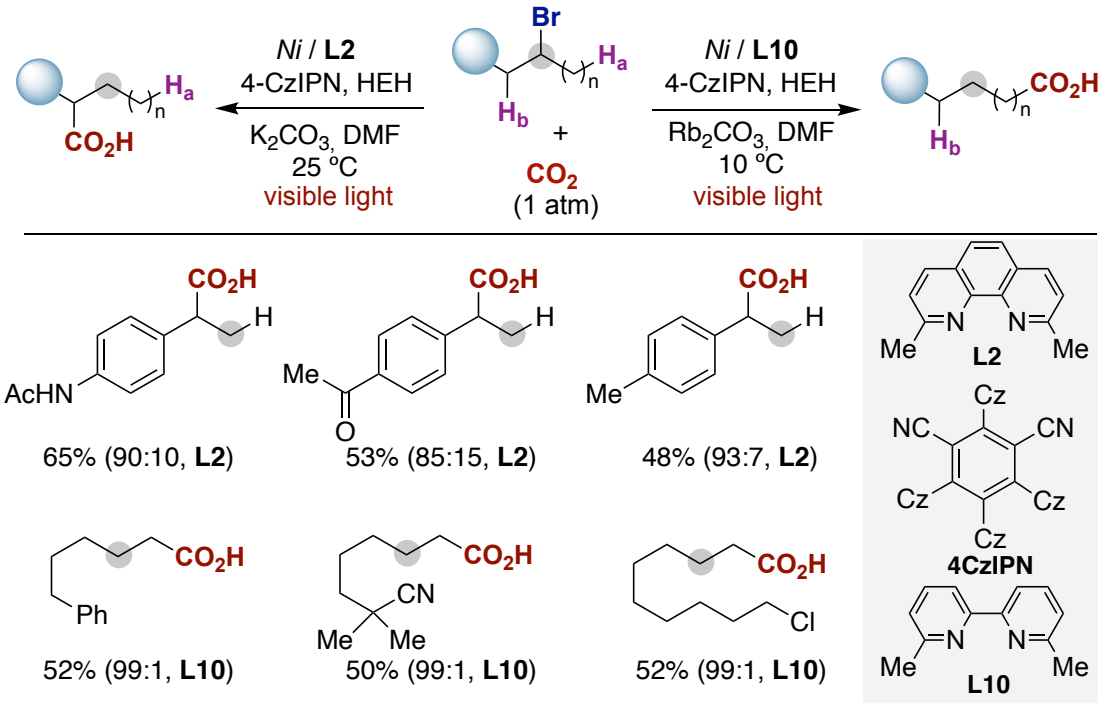
the amidation event could be modified by subtle changes in the backbone of the bipyridine ligand, allowing the functionalization of the initial sp^3 C–Br bond or the remote terminal position via chain-walking scenarios to achieve the corresponding amides with good selectivity (Scheme 20).[63]

Scheme 20. Regiodivergent nickel catalyzed amidation of secondary alkyl bromides.



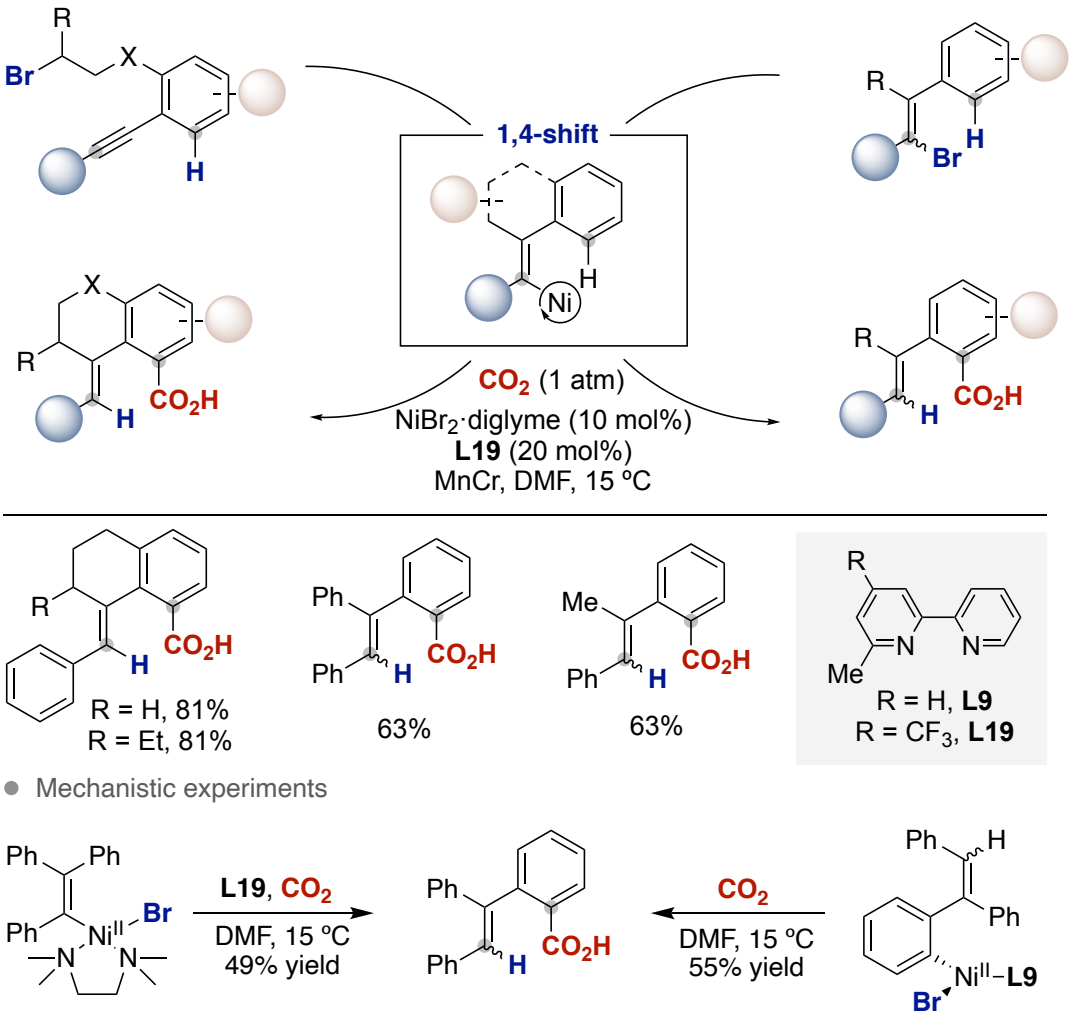
While this technology required stoichiometric metal reductants, one might a priori anticipate that the key SET to generate Ni(I) intermediates might be enabled within the context of photoredox catalysis. This protocol could be delineated in the context of a collaboration with Prof. König, showing that the combination of organic photocatalyst 4-CzIPN with inexpensive Hantzsch esters was particularly suited for these purposes, enabling a formal sp^3 C–H carboxylation event by means of chain-walking scenarios (Scheme 21).[64]

Scheme 21. Nickel catalyzed carboxylation of remote C–H bonds.



The means to promote remote carboxylation events should by no means be limited to sp^3 C–H sites. Driven by this observation, our group has recently found that an alkyl halide decorated with an aryl moiety and a pending alkyne could trigger a 6-exo-dig cyclization, resulting in a vinyl nickel intermediate evolves via [1,4]-Ni shift, thus allowing to translocate the Ni center at a previously unfunctionalized sp^2 C–H site prior to CO_2 insertion (Scheme 22).[65] Stoichiometric reactions with well-defined Ni(II) oxidative addition species suggested that both [1,4]-Ni migration and CO_2 insertion occurred at Ni(II) centers, thus challenging the prevailing perception that carboxylation occur exclusively at Ni(I)-carbon motifs.

Scheme 22. Remote C(sp^2)–H Carboxylation via 1,4-Nickel Migration with CO_2.

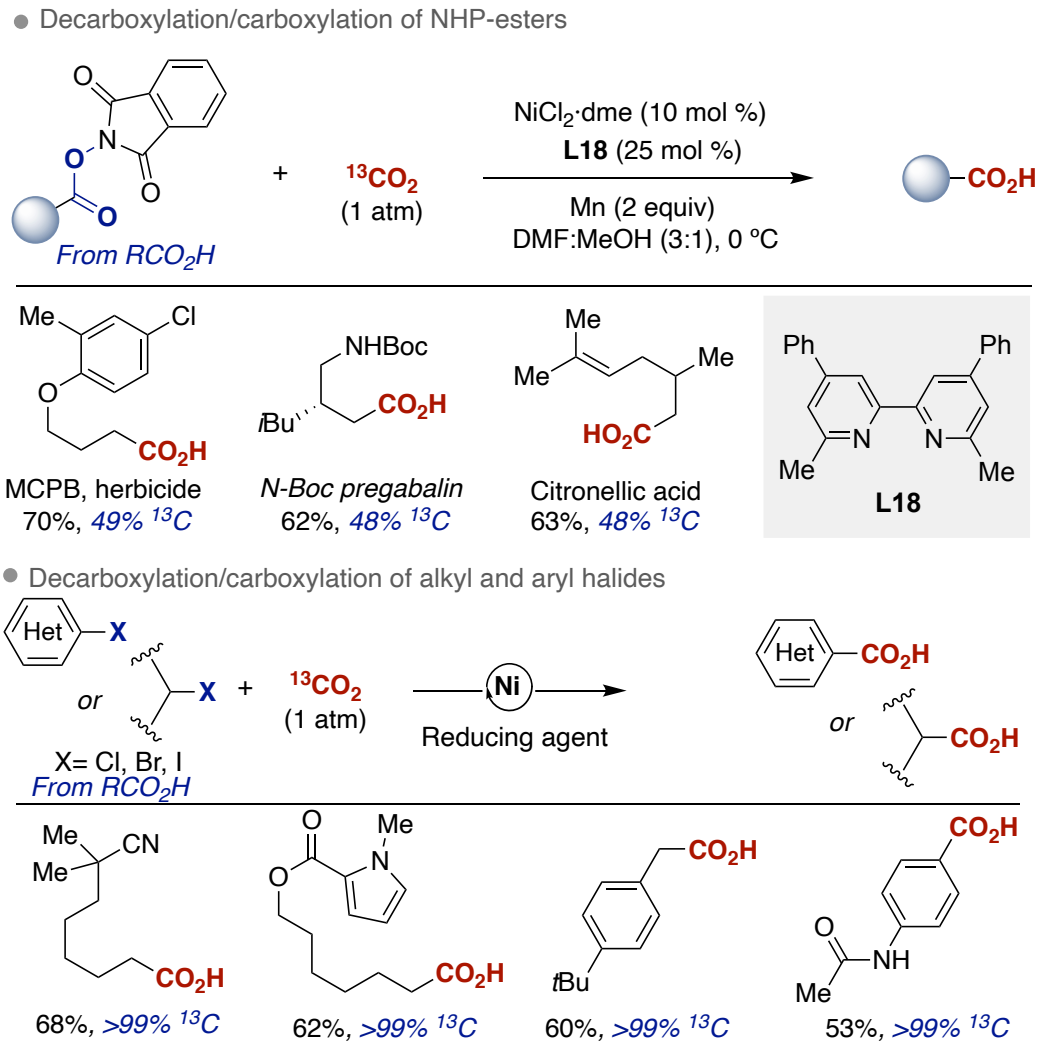


Application to isotope labeling

The discovery and development of new drugs is a time-consuming process, taking on average more than 10 years and over $ 2600 million.[66] A crucial aspect when designing new potential drugs is the understanding of how the active ingredient behaves in biological systems, including the evaluation of the pharmacokinetics and its metabolic profile, thus avoiding unnecessary costly clinical trials.[67] These studies oftentimes required the synthesis of a radiolabelled version of the drug to generate preclinical data.[68] However, its preparation is oftentimes more problematic than that of the parent compound, making necessary in most cases to design of a de novo new synthetic

route, thus raising the costs and requested time for research and development. Undoubtedly, the abundance of $^{13}CO_2$ and $^{14}CO_2$ makes carbon dioxide particularly attractive in isotope-labelling techniques. Taking into consideration that carboxylic acids rank amongst the most prevalent structural units in pharmaceuticals,[5] an efficient, robust and inexpensive technique for incorporating both $^{13}CO_2$ and $^{14}CO_2$ into organic matter without changing the already established synthetic sequence for preparing the non-labelled drug would represent a highly rewarding scenario for industrial laboratories. To such end, an independent disclosure by Baran[69] and our group[4] demonstrated the viability of promoting a formal decarboxylation/carboxylation event by means of Ni-catalyzed reductive coupling of redox-active *N*-hydroxyphthalimide (NHP) esters with labelled CO_2 (Scheme 23, *top*). Given the inherent limitation of the protocol to alkyl carboxylic acids and the modest isotope exchanges observed due to unavoidable hydrolysis of the parent NHP ester or carboxylation with *in situ* generated $^{12}CO_2$, an alternative procedure consisting of a decarboxylative halogenation/carboxylation was designed. Importantly, this method allows to extend the scope of this labelling event to aliphatic, benzylic or even aromatic carboxylic acids in good yields and quantitative ^{13}C-transfer (Scheme 23, *bottom*). [4]

Scheme 23. Isotopic labeling carboxylation reactions.



Conclusion and perspective

The catalytic reductive coupling of CO_2 or isocyanates with electrophilic counterparts has gained momentum as a powerful alternative to the preparation of carboxylic acids and amides. Such interest arises from the historical perception that functionalization of these compounds might require heavily polarized and particularly reactive organometallic reagents. Recent advances have demonstrated the considerable synthetic potential that reductive carboxylation and amidation

reactions might have in synthetic endeavors, both in terms of the broad application profile and the ability to dictate the site-selectivity of the overall reaction. Taking into consideration the recent advances realized, including the implementation of photoredox catalysis as an alternative to the conventional utilization of stoichiometric metal reductants, it is reasonable to predict that these rather appealing scenarios will gain further importance in the next years to come. Indeed, the ability to utilize these techniques for accessing isotopically-labelled drug candidates is particularly noteworthy, thus holding promise for the rapid adoption of these methodologies in industry.

Despite the advances realized, there exists substantial challenges that still need to be addressed in reductive carboxylation and amidation reactions. The following aspects are particularly important: (a) the utilization of aryl methyl ethers – the simplest derivatives of the phenol series – , phenols or unactivated aliphatic alcohols is still beyond reach in catalytic reductive amidation or carboxylation reactions. If successful, these reactions would offer a significant step-forward towards the broad adoption of these processes in industrial endeavors by using non-toxic and available precursors; (b) unlike the utilization of prefunctionalized C–X (X = halide, pseudohalide) linkages, the catalytic reductive carboxylation and amidation reactions within the context of sp^3 C–H functionalization has found little echo; (c) the means to enable enantioselective carboxylation or amidation reactions still represents *terra incognita*; (d) the potential of catalytic reductive carboxylation or amidation reactions of unsaturated hydrocarbon feedstocks still represent a considerable challenge, particularly when promoting difunctionalization of unactivated olefins with a tunable, controllable and switchable site-selectivity pattern. Although there exists a certain consensus on how these reactions operate at the molecular level, these reactions are poorly understood in mechanistic terms and progress in this field is mainly based on empirical discoveries. Although tentative, we predict that the prospective potential of these reactions would be realized

if the mechanistic intricacies of these reactions are unraveled by combining experimental and computational studies. Beyond any reasonable doubt, efforts towards this goal will not only bring comprehension, but also predictive tools for the new generation of chemists willing to improve upon existing reductive amidation and carboxylation reactions.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Biography

Andreu Tortajada Navarro graduated with a B.Sc. in Chemistry with maximum honors in 2015 at the University of València. In October 2015 he began doctoral studies under the supervision of Prof. Ruben Martin at ICIQ, where he earned his MSc from the University Rovira i Virgili in July 2016 and his PhD in 2020. His work while at ICIQ focused on the study of new site-selective catalytic CO_2 fixations into organic matter, including the implementation of isotope-labelling techniques.

Marino Börjesson Carazo studied chemistry at the University of Granada. In 2014 he joined the group of Prof. Ruben Martin at ICIQ, where he obtained his MSc from the University Rovira i Virgili. In 2015 he began his PhD studies in the same group, where he worked on the development of new metal-catalyzed transformations for the incorporation of carbon dioxide into organic molecules. In 2020 he joined Syngenta as a Postdoctoral Research Chemist and subsequently Evotec as a Senior Research Scientist.

Ruben Martin received his PhD in 2003 from the University of Barcelona under the guidance of Prof. Antoni Riera. In 2004, he moved to the Max-Planck Institut für Kohlenforschung as a Humboldt postdoctoral fellow with Prof. Alois Fürstner. In 2005, he undertook further postdoctoral studies at MIT with Prof. Stephen L. Buchwald as a MEC-Fulbright fellow. In 2008, he initiated his independent career as an assistant professor at the ICIQ (Tarragona), where in 2013, he was promoted to associate professor and subsequently to ICREA Research Professor.

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