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## Toward ideal carbon dioxide functionalization

Yang Yang and Ji-Woong Lee \*

This *Perspective* recapitulates recent developments of carbon dioxide utilization in carbon–carbon bond formation reactions, with an intention of paving a way toward sustainable CO<sub>2</sub>-functionalization and its tangible applications in synthetic chemistry. CO<sub>2</sub> functionalization reactions possess intrinsic drawbacks: the high kinetic inertness and thermodynamic stability of CO<sub>2</sub>. Numerous procedures for CO<sub>2</sub> utilization depend on energy-intensive processes (*i.e.* high pressure and/or temperature), often solely relying on reactive substrates, hampering its general applications. Recent efforts thus have been dedicated to catalytic CO<sub>2</sub>-utilization under ambient reaction conditions, however, it is still limited to a few activation modes and the use of reactive substrates. Herein, ideal CO<sub>2</sub>-functionalization with particular emphasis on sustainability will be discussed based on the following sub-categories; (1) metal-catalyzed ‘reductive’ carboxylation reaction of halides, olefins and allyl alcohols, (2) photochemical CO<sub>2</sub>-utilization, (3) redox-neutral CO<sub>2</sub>-functionalization, and (4) enantioselective catalysis incorporating CO<sub>2</sub> to form C–CO<sub>2</sub> bonds (excluding strain mediated reactions with epoxide- and aziridine-based substrates). Recent progress in these fields will be discussed with the proposed reaction mechanisms and selected examples, highlighting redox-neutral, umpolung, and asymmetric carboxylation to postulate ideal CO<sub>2</sub> functionalization reactions to be developed in the near future.

## 1. Introduction

Carbon is an essential element for all living organisms, and is present in carbohydrates, amino acids, proteins, and lipids. These biomolecules are synthesized with specific selectivities controlled by the natural molecular foundry – enzymes – to sustain forms of life. The sustainability of bio- and chemical networks in living organisms is powered by the seemingly

unlimited solar energy. Owing to the evolution of cyanobacteria and their photosynthesis,<sup>1</sup> our planet became a unique biosphere where water was split into oxygen and hydrogen, while consuming (or fixating) CO<sub>2</sub> to generate reduced organic matter.

Photosynthesis and CO<sub>2</sub> fixation operate under ambient conditions; artificial photosynthesis is yet to be realized,<sup>2</sup> and can ensure sustainable growth of the human civilization. The challenge lies in overcoming the thermodynamic stability and kinetic inertness of CO<sub>2</sub>, which possesses the highest oxidation state of carbon. Therefore, it is inevitable to employ reducing

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Ji-Woong Lee (right) received his BSc and MSc in chemistry from Sungkyunkwan University under the guidance of Prof. Choong Eui Song (2009). In 2013 he obtained his PhD under the supervision of Prof. Dr Benjamin List at the Max-Planck-Institute für Kohlenforschung. After postdoctoral research at the Weizmann Institute of Science with Prof. Rafal Klajn and at UC-Berkeley with Prof. Jeffrey R. Long, he has been an

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reagents (reactive metals, H<sub>2</sub>, electricity, and highly reducing chemicals) to overcome the intrinsic reaction barrier of CO<sub>2</sub>-activation, particularly to enable the reactions to be operative under mild reaction conditions.

Recently, the global society has raised concerns related to excessive energy consumption and uncontrollable anthropogenic CO<sub>2</sub> emission.<sup>3</sup> Although CO<sub>2</sub> functionalization can provide ideal solutions, chemical reactions with CO<sub>2</sub> currently suffer from low efficiency, making it impossible to mitigate the overwhelmingly large quantity of accumulated CO<sub>2</sub> in the atmosphere at low concentrations.<sup>4</sup> Yet, chemical recycling of carbon dioxide has been recognized as a promising supplement to the natural carbon cycle,<sup>5</sup> while producing value-added fine chemicals.<sup>6</sup> In this context, CO<sub>2</sub> can serve as an inexpensive and non-toxic renewable C1-building block.<sup>4,7</sup> For example, light hydrocarbons and C<sub>1</sub>- or C<sub>2</sub>-units (*i.e.* carbon

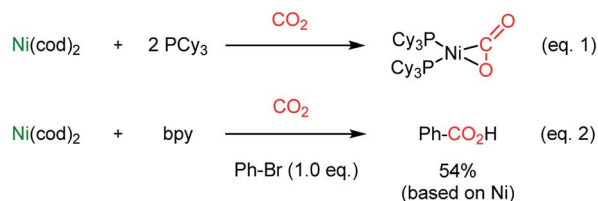
monoxide, formic acid, formaldehyde, methanol, and oxalic acid) are accessible from CO<sub>2</sub>, mostly catalyzed by heterogeneous materials (semiconductors,<sup>8</sup> zeolites,<sup>9</sup> COFs,<sup>10</sup> MOFs,<sup>11</sup> and g-C<sub>3</sub>N<sub>4</sub> (ref. 12)). On the other hand, homogeneous catalysis has shown remarkable potential in C–C bond formation reactions, *via* formal insertion of CO<sub>2</sub> at C–H bonds. The utility of carboxylic acids and their derivatives is certainly applicable with broad interest in organic synthesis<sup>13</sup> and pharmaceutical chemistry.<sup>14</sup>

As categorized in Table 1, catalytic CO<sub>2</sub>-functionalization reactions have been reviewed, particularly transition-metal catalyzed C–C bond formation reactions,<sup>15</sup> carboxylation reactions catalyzed by palladium,<sup>16</sup> silver,<sup>17</sup> copper<sup>18</sup> or copper–NHC (N-heterocyclic carbene) complexes,<sup>19</sup> and nickel/iron<sup>20</sup> catalysts, asymmetric CO<sub>2</sub>-functionalization reactions<sup>21</sup> and photocatalytic CO<sub>2</sub>-functionalization.<sup>22</sup> Other types of reactions are

**Table 1** A summary of recent reviews cited regarding CO<sub>2</sub>-utilization related subjects

Year (ref.)	Title	Keywords
2014 (ref. 3a)	Catalysis for the valorization of exhaust carbon: from CO <sub>2</sub> to chemicals, materials, and fuels. Technological use of CO <sub>2</sub>	CO <sub>2</sub> emission and utilization
2014 (ref. 3b)	Porous inorganic membranes for CO <sub>2</sub> capture: present and prospects	CO <sub>2</sub> capture
2001 (ref. 3c)	Catalysis research of relevance to carbon management: progress, challenges, and opportunities	CO <sub>2</sub> emission and utilization
2007 (ref. 4)	Transformation of carbon dioxide	CO <sub>2</sub> conversion
2018 (ref. 7)	Sustainable conversion of carbon dioxide: an integrated review of catalysis and life cycle assessment	Catalysis, carbon life cycle assessment
2018 (ref. 8a)	Cocatalysts in semiconductor-based photocatalytic CO <sub>2</sub> reduction: achievements, challenges, and opportunities	Photocatalytic CO <sub>2</sub> reduction
2013 (ref. 8b)	Photocatalytic reduction of CO <sub>2</sub> on TiO <sub>2</sub> and other semiconductors	
2014 (ref. 8c)	Photocatalytic conversion of CO <sub>2</sub> into renewable hydrocarbon fuels: state-of-the-art accomplishment, challenges, and prospects	
2017 (ref. 11a)	The chemistry of metal–organic frameworks for CO <sub>2</sub> capture, regeneration and conversion	MOFs in CO <sub>2</sub> utilization
2017 (ref. 11b)	Metal organic framework based catalysts for CO <sub>2</sub> conversion	g-C <sub>3</sub> N <sub>4</sub> in CO <sub>2</sub> utilization
2015 (ref. 12a)	A review on g-C <sub>3</sub> N <sub>4</sub> for photocatalytic water splitting and CO <sub>2</sub> reduction	Metal-catalyzed carboxylation
2018 (ref. 15a)	Transition metal-catalyzed carboxylation reactions with carbon dioxide	
2016 (ref. 15b)	Metal-catalyzed carboxylation of organic (pseudo)halides with CO <sub>2</sub>	
2018 (ref. 15c)	Transition metal-catalyzed carboxylation of unsaturated substrates with CO <sub>2</sub>	
2018 (ref. 16)	Recent advances in palladium-catalyzed carboxylation with CO <sub>2</sub>	
2016 (ref. 17)	Silver-catalyzed carboxylation	
2016 (ref. 18)	Copper-catalyzed carboxylation reactions using carbon dioxide	
2013 (ref. 19)	N-heterocyclic carbene (NHC)–copper-catalysed transformations of carbon dioxide	
2016 (ref. 20)	Ni- and Fe-catalyzed carboxylation of unsaturated hydrocarbons with CO <sub>2</sub>	
2015 (ref. 23a)	Recent advances in the catalytic preparation of cyclic organic carbonates	Cyclic organic carbonates
2018 (ref. 23b)	Catalytic strategies for the cycloaddition of pure, diluted, and waste CO <sub>2</sub> to epoxides under ambient conditions	
2015 (ref. 23c)	Synthesis of cyclic carbonates from epoxides and carbon dioxide by using organocatalysts	
2018 (ref. 24a)	Catalytic reductive N-alkylations using CO <sub>2</sub> and carboxylic acid derivatives: recent progress and developments	Catalytic alkylation
2017 (ref. 24b)	Utilization of CO <sub>2</sub> as a C1 building block for catalytic methylation reactions	
2017 (ref. 21a)	Enantioselective incorporation of CO <sub>2</sub> : status and potential	Asymmetric functionalization
2016 (ref. 21b)	CO <sub>2</sub> -mediated formation of chiral fine chemicals	Photocatalytic carboxylation using CO <sub>2</sub>
2018 (ref. 22a)	Photoredox catalysis as a strategy for CO <sub>2</sub> incorporation: direct access to carboxylic acids from a renewable feedstock	Formic acid and methanol derivatives
2017 (ref. 22b)	Photochemical carboxylation of activated C(sp <sup>3</sup> )–H bonds with CO <sub>2</sub>	
2017 (ref. 85a)	Reversible hydrogenation of carbon dioxide to formic acid and methanol: Lewis acid enhancement of base metal catalysts	
2015 (ref. 85b)	CO <sub>2</sub> hydrogenation to formate and methanol as an alternative to photo- and electrochemical CO <sub>2</sub> reduction	
2014 (ref. 85c)	Recycling of carbon dioxide to methanol and derived products-closing the loop	



Scheme 1 Stoichiometric CO<sub>2</sub>-functionalization using Ni(0).

also tabulated to guide the readers for further reading in specific topics of interest. For example, carbonate formation reactions with epoxides and ring-strain mediated reactions,<sup>23</sup> catalytic alkylation with CO<sub>2</sub>,<sup>24</sup> etc., will not be discussed in this *Perspective*.

The purpose of *this Perspective* is the following: providing a general concept of catalytic CO<sub>2</sub>-functionalization by exemplifying recent progress (up to 2018). Section 2 will discuss transition-metal catalysis with a hint of sustainability. Sections 3 and 4 will explore recently reported photochemical redox catalysis by utilizing synthetic dyes with the aid of pre-established transition metal catalysis, and single-electron

reduction of CO<sub>2</sub> via a redox-neutral mechanism. Section 5 will focus on a handful but remarkable examples of asymmetric C–C bond formation reactions by the action of metal-chiral ligand complexes. The future perspective on ideal CO<sub>2</sub>-functionalization will also be discussed in the context of umpolung carboxylation, redox-neutral photochemistry and asymmetric CO<sub>2</sub>-activation to reduce the prevailing energy input or highly reactive species. This discussion will lead to an alternative platform for sustainable CO<sub>2</sub> recycling, to mimic the natural carbon cycle by utilizing the combined knowledge in organic, inorganic, photo- and materials chemistry, and enzymatic engineering for improved carbon fixation as well.

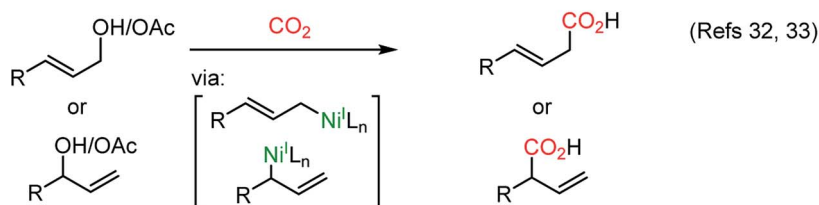
## 2. Metal-catalyzed reductive carboxylation with halides, olefins and allyl alcohols

The catalytic application of transition metals for carboxylation with CO<sub>2</sub> was triggered by the seminal work by Nobile<sup>25</sup> (Scheme 1, eqn (1)) and Osakada<sup>26</sup> (Scheme 1, eqn (2)), where stoichiometric Ph–Ni(L)–Br (L = 2,2'-bipyridine (bpy))

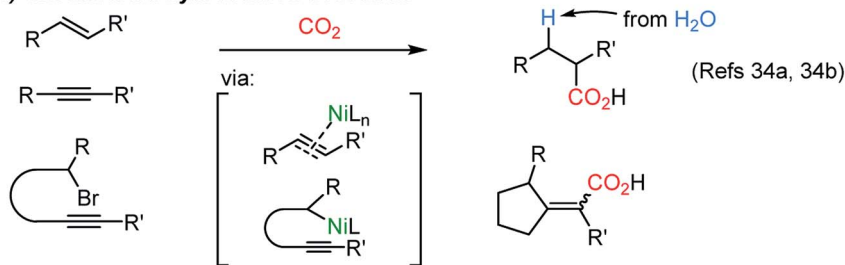
### a) Ni-Catalyzed reductive R–CO<sub>2</sub> coupling reactions



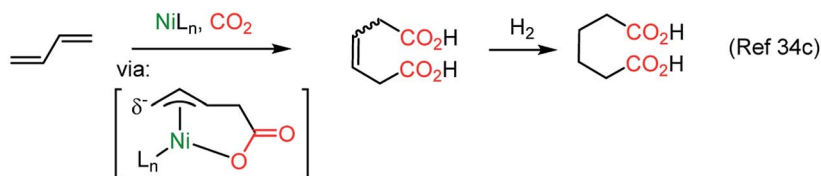
### b) Ligand-controlled carboxylation of allyl esters



### c) Unsaturated hydrocarbon activation



### d) Dicarboxylation of 1,3-dienes

Scheme 2 Ni-catalyzed reductive CO<sub>2</sub>-functionalization reactions.

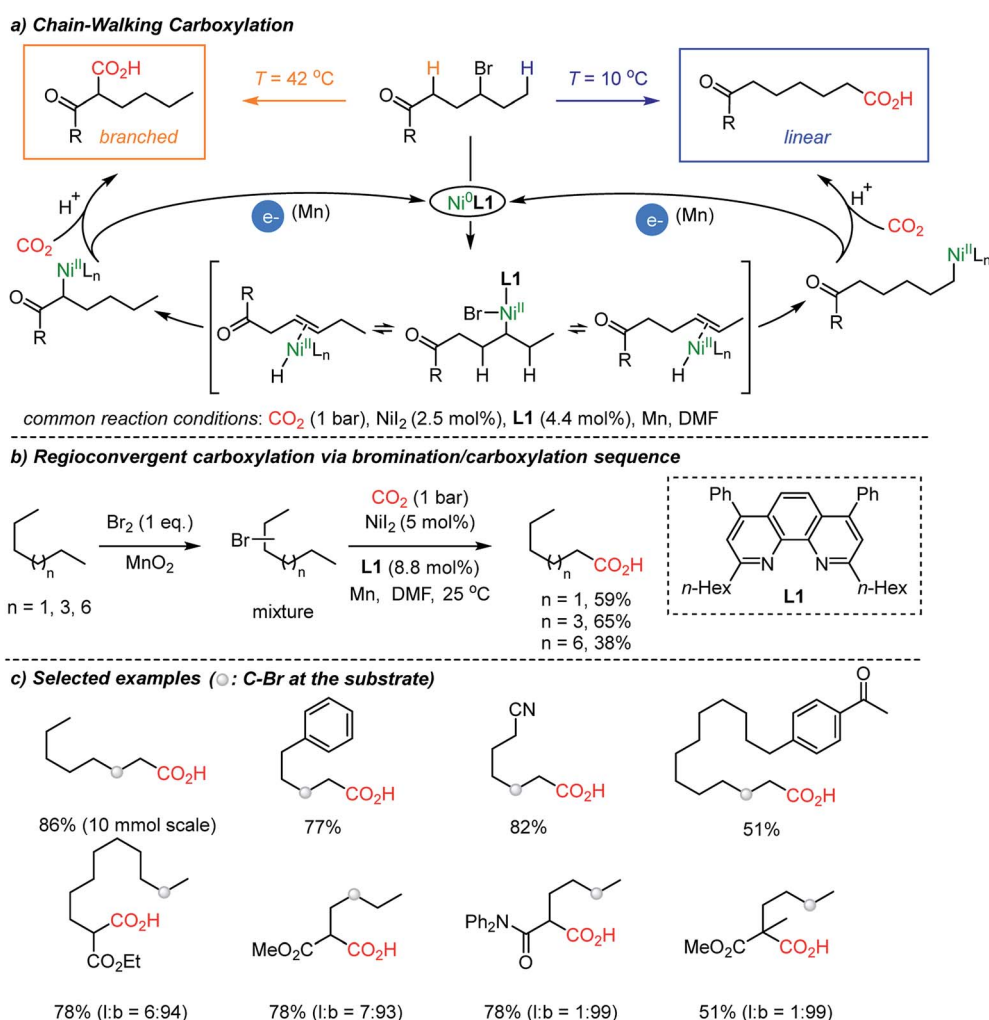
participated in CO<sub>2</sub> insertion at the Ph–Ni bond, affording benzoic acid as the final product.

The Martin group employed a Pd(II)–Pd(0) cycle in the catalytic carboxylation reaction of aryl bromides using ZnEt<sub>2</sub> as a terminal reducing reagent.<sup>27</sup> This methodology was further expanded to abundant Ni(II) catalysis by the Tsuji group,<sup>28</sup> realizing carboxylation of aryl chloride with Mn powder as a reducing reagent. New reductive carboxylation reactions were developed later by the Martin group with a broad range of substrate scope, including organic halides,<sup>29</sup> sulfonates,<sup>29b</sup> esters,<sup>30</sup> benzylic ammonium salts<sup>31</sup> (Scheme 2a), allyl acetates,<sup>32</sup> allyl alcohols<sup>33</sup> (Scheme 2b), and unsaturated hydrocarbons (Scheme 2c and d).<sup>34</sup> The facile insertion of CO<sub>2</sub> into R–Ni was tested with olefin substrates, enabling olefin activation without an apparent hydride donor (Scheme 2). These protocols provided a broad substrate scope and high functional group tolerance. However, it is necessary to use (over) stoichiometric amounts of reducing reagents (*i.e.* Mn, Zn, ZnR<sub>2</sub>, and *etc.*) to complete the catalytic cycle.

In 2017, a breakthrough CO<sub>2</sub>-functionalization was reported by the Martin group proposing a ‘chain-walking’ mechanism with catalytic Ni–H species (Scheme 3).<sup>35</sup> Although the β-hydride

elimination is undesired in transition metal-catalyzed coupling reactions,<sup>36</sup> in the proposed reaction mechanism, a chain-walking process was key to generate thermodynamically more stable species, thus contributing to the high regio- and chemoselectivity of the targeted insertion reactions.<sup>37</sup> For carboxylation reactions with CO<sub>2</sub>, the Martin group showed temperature-controlled site-selectivity affording linear and branched carboxylated products (1 : b ratios). The authors suggested a Curtin–Hammett scenario, where the reaction proceeded through common intermediates or transition states under fast equilibrium (Scheme 3a). More strikingly, the chain-walking mechanism was translated to a useful method starting from a mixture of alkyl bromides – expanding the utility of the protocol significantly. Regardless of regioisomers, linear alkanes were smoothly converted to carboxylated products under a bromination/carboxylation reaction sequence (1 atm of CO<sub>2</sub>). The iterative reversible β-hydride elimination/insertion reactions occurred, converging regioisomers of alkyl bromides into a single carboxylated product (Scheme 3b).

The proposed chain-walking process with high site-selectivity represents a significant potential toward fatty-acid syntheses from bulk petroleum raw materials. In this context,



Scheme 3 Chain-walking carboxylation of halogenated hydrocarbons.





Scheme 4 Site-selective carboxylation dictated by the degree of unsaturation.

the same group extended the methodology with olefin substrates, enabling carboxylation reactions in the presence of water as a proton source.<sup>34b</sup> In the case of alkenes, water served as a way to access metal-hydride species,<sup>38</sup> namely Ni-H species, which in turn can participate in the above-mentioned chain-walking mechanism. Indeed, a linear carboxylic acid was the main product with high selectivity (b : l = 1 : 99) even from an unrefined mixture of olefin isomers (Scheme 4a). As for alkynes, however, only a branched carboxylation product was obtained (Scheme 4b). The authors proposed that the Ni-L2 complex favored the formation of a thermodynamically more stable  $\alpha,\beta$ -unsaturated nickelalactone (Ni-1) with internal alkynes in a CO<sub>2</sub> environment. Therefore, a branched carboxylic acid was obtained with high selectivity (b : l = 99 : 1) after reduction with H<sub>2</sub> and Pd/C. The 'uni-directional' chain-walking mechanism highlights the potential application of this process in producing added value chemicals from CO<sub>2</sub> and crude industrial feedstock.

It is noteworthy that the variation of the ligand is critical in Ni-catalyzed reactions. The substituent adjacent to the nitrogen atoms in bidentate ligands (L1 and L2), such as bipyridine and phenanthroline, differentiates the site-selectivity of the carboxylation reaction. High site-selectivity is a pre-requisite for many organic transformations, for example in allylic substitution reactions. Catalytic metal-ligand complexes govern chemo-, regio- and even enantioselectivity.<sup>39</sup> Allyl alcohol is a substrate class with high accessibility yet low chemical utility for allylation reactions due to the apparently low leaving group ability of the hydroxide. It has been proved that *in situ* activation of allylic alcohol with 'activating reagents' can mediate various types of transformation,<sup>40</sup> shortening the synthetic steps avoiding the preparation of activated substrates<sup>41</sup> (like amines,<sup>41a</sup> ammonium salts,<sup>41b</sup> carbamates,<sup>41c</sup> carbonates,<sup>41d</sup> esters,<sup>41e</sup> ethers,<sup>41f</sup> nitro compounds,<sup>41g</sup> phosphates,<sup>41h</sup> and sulfones<sup>41i</sup>). For example, CO<sub>2</sub> was involved in the asymmetric Pd-catalyzed direct  $\alpha$ -allylation of ketones.<sup>40a</sup> The use of CO<sub>2</sub> as a catalyst is noticeable although only a 'catalytic'-amount of it would be necessary for the process.

The Martin group employed CO<sub>2</sub> as an activating reagent as well as a C1 source for the carboxylation of allylic alcohols to afford  $\beta,\gamma$ -unsaturated carboxylic acids (Scheme 5a).<sup>33</sup> Once again, ligand-controlled selectivity was observed starting from

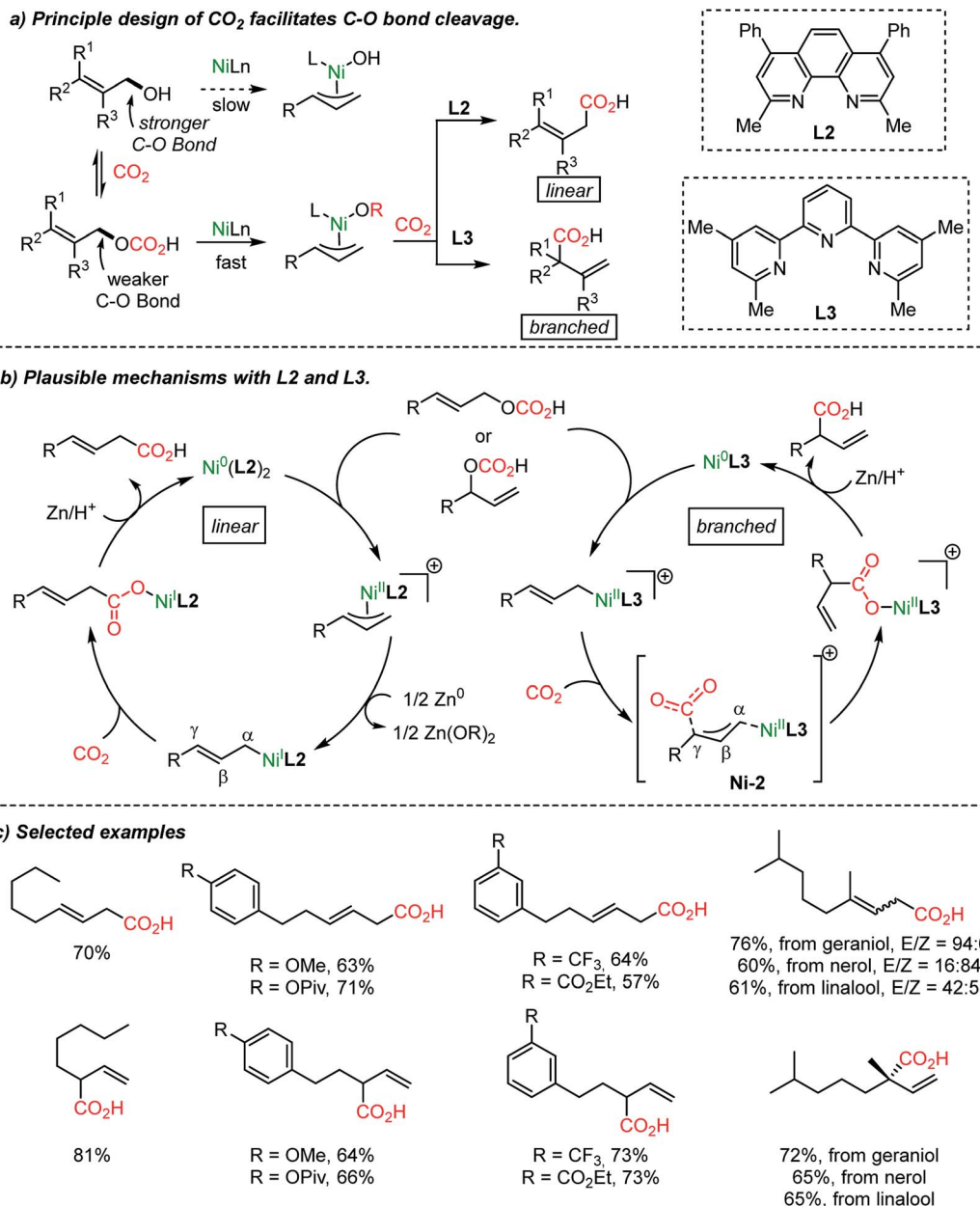
linear or branched allylic alcohols affording high yields of linear and branched carboxylation products (Scheme 5b). The former resulted from CO<sub>2</sub> insertion between the  $\alpha$ -carbon and Ni(I) center. Alternatively,  $\alpha$ -branched acids were obtained when the tridentate ligand L3 was employed. The critical role of the ligands was rationalized by stoichiometric studies of active NiL2 or NiL3 species in the absence of Zn metal (yields: linear, 0%; branched 73%). The transition-state, Ni-2, was proposed for the nucleophilic attack from the  $\gamma$ -carbon of an  $\eta^1$ -allyl Ni(II) intermediate to CO<sub>2</sub>. Also, a six-membered cyclic conformation can be suggested, similar to the reported nucleophilic addition of Pd( $\pi$ ) allyl intermediates to CO<sub>2</sub> or carbonyl substrates.<sup>42,43</sup> The utility of the reaction was further verified by producing useful intermediates for the synthesis of  $\gamma$ -lactone-based bioactive compounds.<sup>44</sup>

Dienes, abundant and accessible chemical feedstocks, have the same oxidation states as allylic alcohols. However, activation of dienes and conjugated olefins poses a great challenge. Recently, Ni-based catalysts were evaluated for a catalytic carboxylation reaction of dienes toward carboxylated or dicarboxylated products in stoichiometric amounts of a Ni(0) complex.<sup>45</sup> Although limited only to activated substrates, alkynes<sup>46</sup> and silylallenes<sup>47</sup> were transformed to the desired dicarboxylated products. The Martin group successfully implemented a catalytic dicarboxylation reaction for 1,3-dienes with high site-selectivity (up to 90%), to furnish diesters (Scheme 6a).<sup>34c</sup> Various functional groups were tolerated including heterocycles, organotin, nitrile, and esters. Structurally simple dienes such as butadiene, isoprene, and piperylene – major byproducts of steam cracking in ethylene production plants – were converted to the corresponding terminal diacids with excellent site-selectivity in moderate yields (up to 65% yield, 99 : 1 selectivity, Scheme 6b). Single crystal structure analysis determined the formation of monocarboxylated  $\eta^3$ -Ni nickelalactone (Ni-3). The corresponding dicarboxylation product could be obtained when Ni-3 was treated with CO<sub>2</sub> under optimized reaction conditions (also see Mori group's work<sup>45c</sup>), shedding some light on the reaction mechanism (Scheme 6c).

The transition metal-catalyzed carboxylation reactions of the above-mentioned recent examples showed unprecedented catalytic performances with a variety of substrates, yet they require stoichiometric reducing reagents to sustain the catalytic cycle.







Scheme 5 Site-selective catalytic carboxylation of allylic alcohols.

Certain improvements have been attempted by utilizing insoluble reducing reagents (Mn, and Zn powder) replacing highly reactive RMgX, Et<sub>2</sub>Zn, or AlMe<sub>3</sub>. In an ideal CO<sub>2</sub> functionalization process, a redox-neutral mechanism would be more desirable,<sup>48</sup> where no additional oxidants or reductants are required. In this context, the next two sections will describe reactions utilizing photocatalysts, demonstrating sustainable light-induced chemical reduction reactions, mimicking photosynthesis.

### 3. Photocatalytic carboxylation with CO<sub>2</sub>

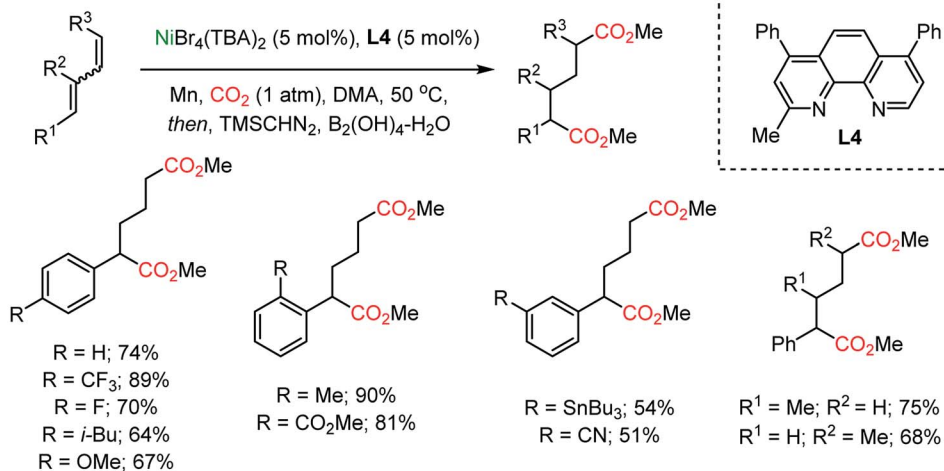
Photosynthesis is the master process in the realm of CO<sub>2</sub>-functionalization, as it is called CO<sub>2</sub>-fixation. This ideal process

operates *via* multi-step electron transfer and chemical transformation reactions,<sup>49</sup> resulting in somewhat limited CO<sub>2</sub>-fixation efficiency, constraining the capacity of nature's carbon cycle (Fig. 1 highlighted in green).<sup>50</sup> Recent efforts in enzymatic engineering in chemical biology for *in vitro* CO<sub>2</sub> fixation<sup>51</sup> would potentially lead to enhanced photosynthesis.<sup>52</sup>

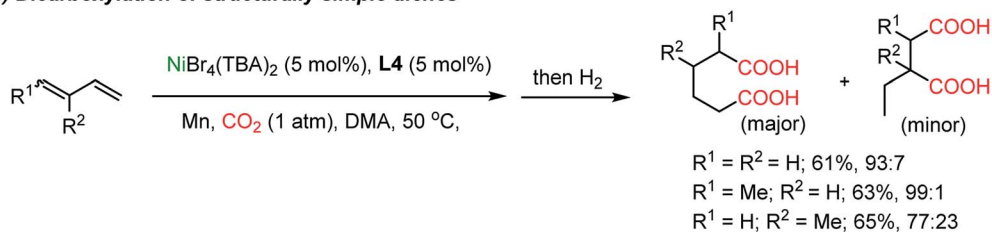
Solar energy obviously represents one of the most promising and limitless energy sources, which can be harnessed using a photosensitizer. In the late 1970s, seminal studies were reported regarding photocatalytic CO<sub>2</sub> reduction by the Tazuke, Fujishima, Honda, and Lehn groups,<sup>53</sup> which formed the basis of the modern photoredox activation of CO<sub>2</sub>. Further developments in photocatalysts played a significant role in CO<sub>2</sub> reduction reactions mainly targeting industrial feedstock



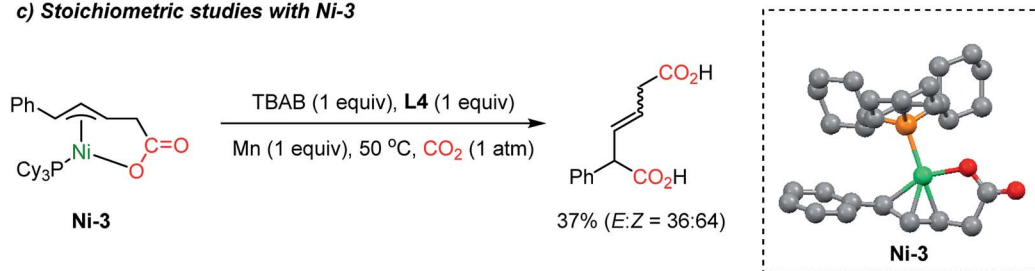
## a) Scope of dicarboxylation



## b) Dicarboxylation of structurally simple dienes



## c) Stoichiometric studies with Ni-3



Scheme 6 Ni-catalyzed dicarboxylation of 1,3-dienes and a mechanistic study.

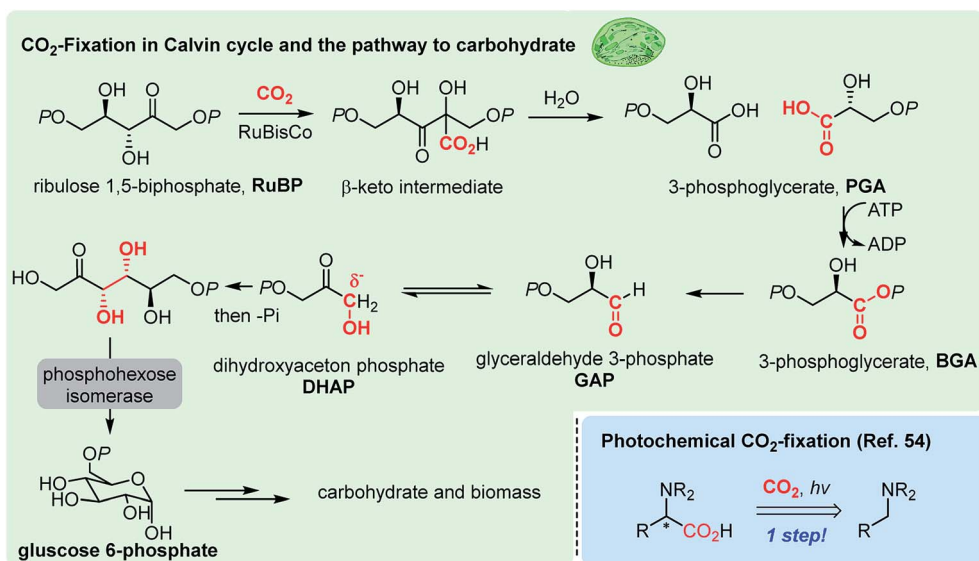


Fig. 1 Natural photosynthesis and an example of artificial photosynthesis.







Scheme 7 Carboxylation of aryl halides by Pd/Ir dual catalysis.

molecules, such as carbon monoxide, methanol, methane and formic acid.<sup>8</sup> In this regard, artificial CO<sub>2</sub> functionalization reactions have shown elegant modes of action in C-C bond

formation reactions.<sup>22</sup> For example, a photochemical CO<sub>2</sub>-fixation provided  $\alpha$ -amino acid derivatives in a one-step reaction (Fig. 1 bottom right<sup>54</sup>). The key to the success of this field will be



Scheme 8 Photoredox cycles and carboxylation cycles in a co-catalysis system.



to maintain mild reaction conditions to conserve complex molecular structures of products, while providing appropriate reduction potential for the reductive CO<sub>2</sub>-functionalization.

The Iwasawa group demonstrated a dual catalytic system with a Pd/Ir-photocouple for carboxylation reactions of aryl halides in the absence of metallic reducing reagents (Scheme 7).<sup>55</sup> Hünig's base (3 eq.) served as a sacrificial electron donor in photoredox cycles, generating Pd(0)-complexes in the proposed catalytic carboxylation cycles (Scheme 10b). Although Ar-Pd(II)-Br(XPhos) possesses a high reduction potential (−2.28 V, vs. Fc/Fc<sup>+</sup>), a new peak at −1.4 V was observed from cyclic voltammetry (CV) measurements. The coordination of CO<sub>2</sub> on Pd might influence the redox chemistry of the metal complex, therefore reducing the required reduction potential. In addition to the common insertion of CO<sub>2</sub> into the active Pd(II)-C bond, the authors suggested the formation of two intermediates, a Pd(I)- or Pd(II)-CO<sub>2</sub> complex (Scheme 7b, path b). After methylation with TMSCHN<sub>2</sub>, various carboxylic acid esters were obtained including a sterically hindered acid (*i.e.* 2,4,5-triisopropyl carboxylic acid methyl ester).

Starting from simple feedstocks, Ar-Br and alkyl-Br, the König group reported visible light-induced carboxylation mediated by nickel catalysts (Scheme 8).<sup>56</sup> The plausible

reaction mechanism could be divided into two distinct catalytic cycles. The first one involved a one electron delivery to a Ni(II) or Ni(I) complex from the anion radical (4CzIPN<sup>•−</sup>). Hantzsch ester (HEH, 2 equiv. required) was used as a terminal reducing agent in the presence of a reducing excited sensitizer (4CzIPN\*) and light (left circle, Scheme 8b). Second, the oxidative addition to a Ni(0) complex was suggested, which undergoes reduction and then an insertion reaction with CO<sub>2</sub> (right circle, Scheme 8b). The catalytically active Ni(0) species can be regenerated from Ni(I) with electron sources produced from the left circle.

The same group expanded the dual catalysis strategy to the carboxylation of styrenes,<sup>57</sup> affording Markovnikov (branched) or anti-Markovnikov (linear) products selectively controlled by the choice of the ligand (Scheme 9). The suggested reaction mechanism explained that the observed chemoselectivity (branched/linear) was controlled by the different ligands (L6, neocuproine and L7, dppb). According to DFT calculations, Ni(0) species with the more sterically demanding ligand dppb (L7) tend to coordinate with CO<sub>2</sub>, forming a 5-membered nickel-elactone (Ni-4) with styrene. With the less hindered neocuproine ligand (L6), the reaction proceeds *via* hydrometalation of styrene to afford Ni(II), which is subsequently reduced by the catalytic action of the photosensitizer (4CzIPN, Scheme 9b). The



Scheme 9 Site-selective photocatalytic carboxylation controlled by ligands.



electrons generated from the photocatalytic cycle are used to reduce Ni(II) or Ni(I) to Ni(0), which can diverge to the hydro-metalation step (left) and CO<sub>2</sub> activation step (right) to generate branched and linear products respectively while completing the catalytic cycles.

The Jamison group reported styrene functionalization reactions in a CO<sub>2</sub> atmosphere to generate β-aryl carboxylic acids (Scheme 10).<sup>58</sup> In this case PMP (1,2,2,6,6-pentamethylpiperidine) was employed as a sacrificial organic electron donor, while utilizing water as an additive under modified reaction conditions. Although it is unclear, the addition of water induced high selectivity toward the mono-carboxylated product compared to other tested hydride or proton donors. The suggested reaction mechanism shows that the carboxylation with CO<sub>2</sub><sup>•-</sup> results in the formation of a stabilized benzylic radical ( $E^0$  = from -1.82 to -0.71 V vs. SCE). Therefore, further reduction is feasible leading to the generation of carboxylated benzylic anion species, which could be protonated upon addition of water.

Photoactivation of organic substrates has been a successful transformation with high chemoselectivity to produce Markovnikov (branched) or anti-Markovnikov (linear) carboxylic acids. Also, the Murakami group reported a carboxylation reaction with α-alkyl ketones and CO<sub>2</sub> via a Norrish type II activation mechanism.<sup>59</sup> The carboxylation reactions at toluenyl carbon were also conducted in natural sunlight at ambient temperature with good isolated yields of the desired products. The authors suggested an energetically feasible [4 + 2]cycloaddition reaction by DFT calculations, which was determined by the thermal reaction of benzocyclobutenol to generate an *o*-quinodimethane intermediate.

Recently, Hou *et al.* reported carboxylation reactions of internal and terminal alkynes promoted by Co/Ir dual catalysis (Scheme 11).<sup>60</sup> The authors proposed that the reaction proceeded via functionalization of alkynes to generate an (*E*)-Co-CO<sub>2</sub> complex which is an intermediate for various products – carboxylic acids, pyrones, α,β-unsaturated γ-lactones, coumarins, and 2-quinolones, by sharing a common intermediate, (*E*)-int

(Scheme 11a). Pyrones were formed through a formal [2 + 2 + 2] cycloaddition with terminal alkynes (R<sup>1</sup>=H). In the case of internal alkynes, pharmaceutically vital heterocycles such as coumarins and 2-quinolones were obtained with high selectivity. The suggested mechanism proceeded *via* intramolecular cyclization of acrylic acid intermediates. The *E/Z* isomerization of acrylic acid was confirmed by control experiments with (or without) the Ir-photoredox catalyst under irradiation (or in the dark). Also, this newly developed carboxylation/acyl-migration cascade reaction is feasible for alkyne difunctionalization, highlighting its utility in the field of light-driven CO<sub>2</sub>-fixation.

The Yu group reported the photocatalytic hydrocarboxylation of enamides and imines to afford α-amino acids with excellent chemo- and regio-selectivity (Scheme 12).<sup>61</sup> The pre-equilibrium of enamides and imines was combined with photocatalytic reduction. Despite the inherent nucleophilicity of enamides, kinetic studies indicated that the imines underwent the desired hydrocarboxylation faster than the competitive β-carboxylation reaction. The authors proposed an umpolung reaction of the α-amino carbanion under metal-free conditions. The carboxylated products were obtained with a broad substrate scope regardless of the electronic and steric properties of substituents. In addition, the enamide and imine starting materials were equally effective, confirming the fast pre-equilibrium before the reduction/carboxylation steps.

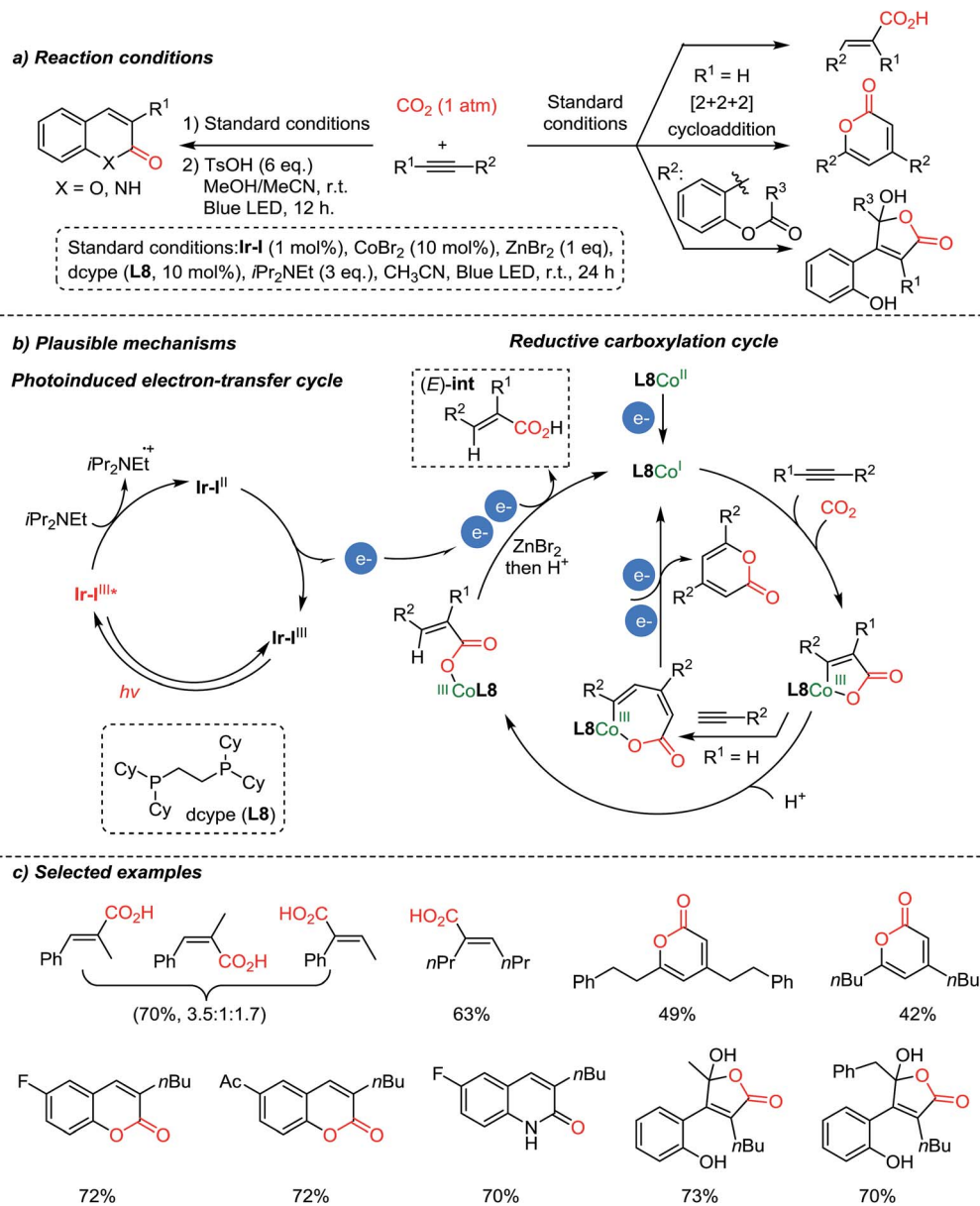
Very recently, the Walsh group presented photocatalytic carboxylation of benzophenone-derived ketimines by employing an Ir-complex (Ir-I) under mild conditions (Scheme 13).<sup>62</sup> The radical anion was generated by single electron transfer (SET) from [Ir-I]\* to ketimines, which was facilitated by the coordination between the imine and Cy<sub>2</sub>MeN<sup>+</sup>.<sup>63</sup> Spin density calculation was carried out to evaluate the radical anions (**A**, **B**) suggesting that the carbon atom was more negatively charged than the nitrogen atom (spin density, radical probability on C: 0.05–0.18 and N: 0.37).<sup>64</sup> Subsequently, the more reactive *N*-centered radical species abstracts a hydrogen atom from Cy<sub>2</sub>MeN<sup>+</sup> to form an α-amino carbanion and an iminium cation



Scheme 10 Photocatalytic direct β-selective hydrocarboxylation of styrenes.







Scheme 11 Carboxylation of alkynes by Co/Ir dual catalysis.

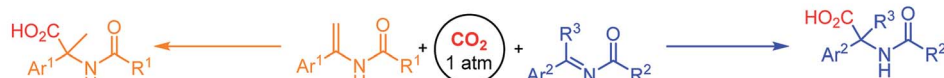
$[\text{Cy}_2\text{N}=\text{CH}_2]^+$  via an umpolung reactivity (Scheme 13b). The carbanion then undergoes nucleophilic addition to  $\text{CO}_2$  affording the desired carboxylation product. The obtained  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acid shows potential application of the protocol in asymmetric synthesis to generate quaternary stereogenic centers, which are often difficult to control.<sup>65</sup>

Direct carboxylation of imines and amines with  $\text{CO}_2$  represents a very promising pathway to afford  $\alpha$ -amino acids, especially those promoted by photoredox catalysts as shown above (Schemes 12, 13 and 17). Compared to tertiary amines, however,  $\alpha$ -functionalization (*i.e.*  $\alpha$ -carboxylation) of primary amines still remains a great challenge due to the lower reactivity of the  $\alpha$ -C-H bond. Besides carboxylation reactions,  $\text{CO}_2$  has been used as an activating group,<sup>33,40</sup> a directing group<sup>66</sup> and a protecting

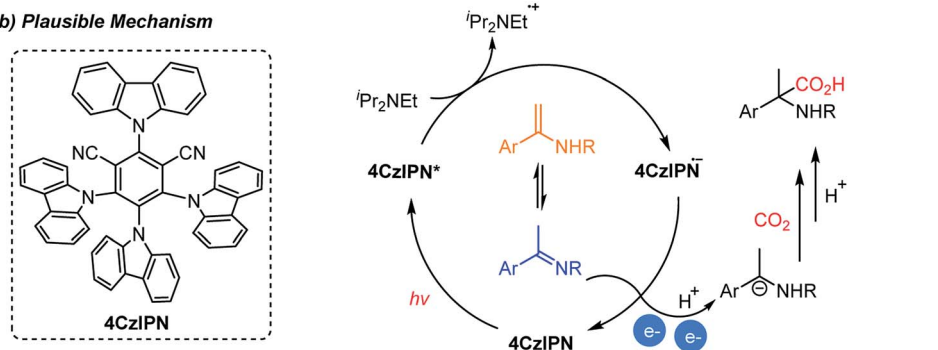
group<sup>67</sup> in organic synthesis. Ye *et al.* recently reported the photocatalytic  $\alpha$ -alkylation of primary amines to yield  $\gamma$ -lactams with  $\text{CO}_2$  as a temporary activator and as a protecting group (Scheme 14).<sup>68</sup> Various  $\alpha,\beta$ -unsaturated esters were tolerated in the presence of an Ir-II photosensitizer. Quinuclidine was employed as a sacrificial electron donor. According to the suggested reaction mechanism,  $\text{CO}_2$  was regenerated after releasing lactam products via an intramolecular cyclization reaction. The *in situ* carbamate formation reaction suppressed the reactivity of primary amines while increasing the reactivity of  $\alpha$ -C-H bonds according to the computational studies. The generation of the  $\alpha$ -radical of the substrate is highly intriguing due to the potential applications toward various electrophiles and radical-radical coupling reactions. Furthermore, the use of



## a) Reaction conditions

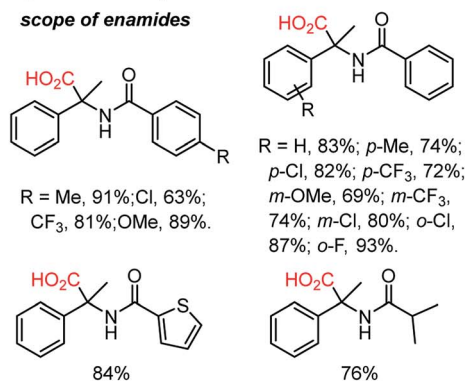


## b) Plausible Mechanism

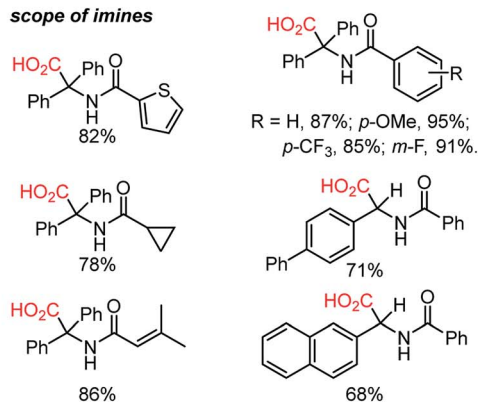


## c) Selected examples

## scope of enamides

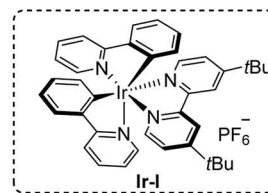
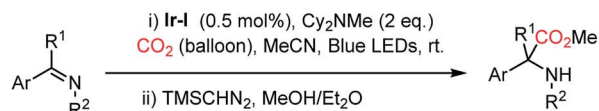


## scope of imines

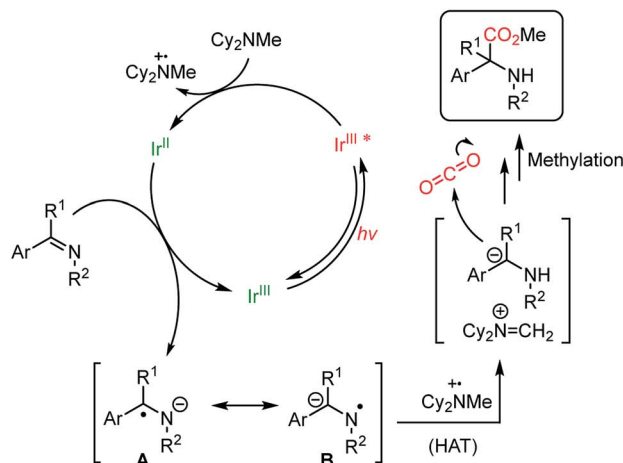


Scheme 12 Photocatalytic hydrocarboxylation of enamides and imines.

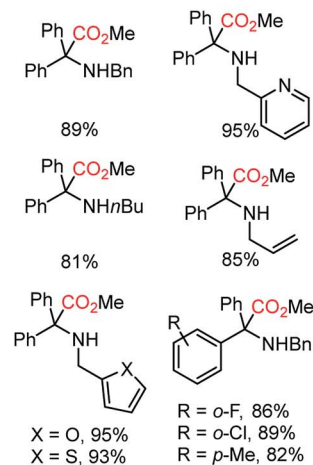
## a) Reaction conditions



## b) Plausible mechanism

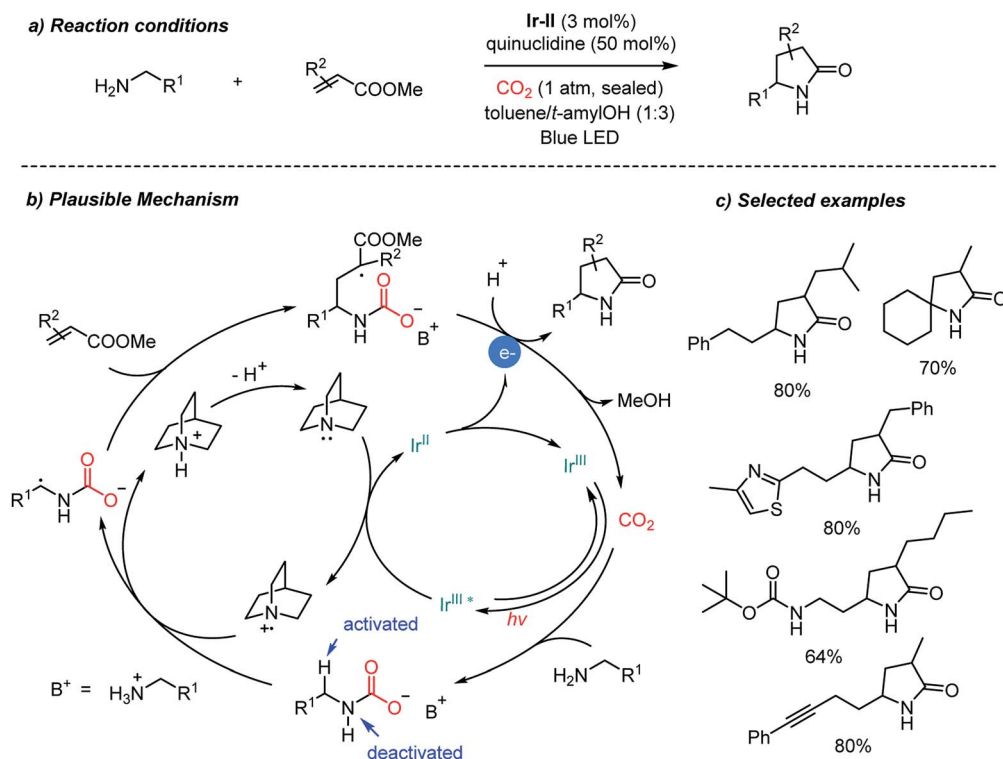


## c) Selected examples



Scheme 13 Photocatalytic carboxylation of ketimines.



Scheme 14 Catalytic application of CO<sub>2</sub> for photocatalytic  $\alpha$ -alkylation of primary amines.

tertiary amines as a base will enable a potential asymmetric catalysis to afford enantioenriched products.

This section summarizes recent progress in photo-CO<sub>2</sub>-functionalization without strong metallic reducing agents. Instead, an organic sacrificial electron source or a reducing reagent was employed (*i.e.* triethylamine, piperidine, Hünig's base and Hantzsch esters) in the presence of photocatalysts with an appropriate reduction potential to complete the catalytic cycles. Various types of substrates underwent C–CO<sub>2</sub> bond formation reactions to provide unique molecular structures under ambient photosynthetic conditions (low CO<sub>2</sub> pressure, and accessible light sources). However, there is still plenty of room to develop more elegant methodologies in terms of

sustainability. The next section will discuss redox-neutral carboxylation without external reductants.

## 4. Recent developments in redox-neutral CO<sub>2</sub>-functionalization

It is thought that catalytic carboxylation of non-activated organic substrates would be an ideal approach to CO<sub>2</sub>-utilization, avoiding reactive organometallic reagents (RMgX, RLi, R<sub>2</sub>Zn, R<sub>4</sub>Sn, *etc.*). For example, solar energy provides chemical reduction potential to enable CO<sub>2</sub> conversion in the Calvin cycle, where actual CO<sub>2</sub>-fixation and C–CO<sub>2</sub> bond formation reaction occur under mild conditions *via* an  $\alpha$ -ketol



Fig. 2 Calvin–Benson–Bassham (CBB) cycle at the RubisCo enzyme reaction center. Note that the C–CO<sub>2</sub> H bond formation reaction occurs at the ketone functional group, and the two glyceric acid products are enantiomerically enriched.





rearrangement (Fig. 2).<sup>50,69</sup> This “enantioselective” CO<sub>2</sub>-fixation process generates a new C–C bond while creating additional stereogenic center(s) *via* a redox-neutral pathway. Accordingly, recent progress in photo-redox catalysis offers a promising platform to develop sustainable CO<sub>2</sub> utilization reactions under mild conditions in the absence of additional reducing reagents.<sup>54,70</sup> When combined with practicability and scalability, redox-neutral CO<sub>2</sub>-functionalization strategies will provide a tangible scenario of sustainable artificial carbon fixation.

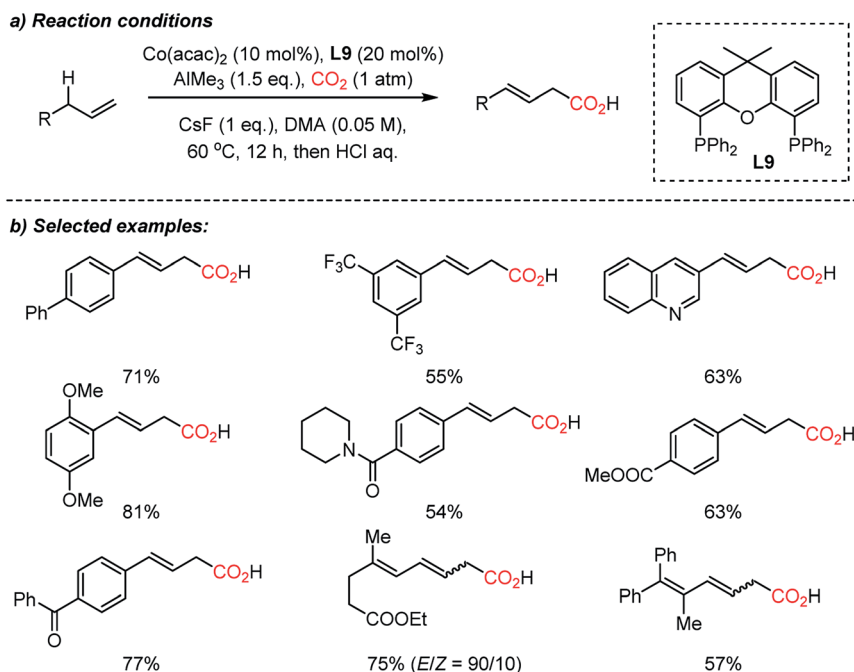
The following examples in this section represent their redox-neutral reaction profile in terms of the proposed reaction mechanisms – no terminal reducing or oxidizing reagents. Despite the fact that these reactions require activated substrates or radical initiators or a strong base, the generation of C–CO<sub>2</sub> bonds with CO<sub>2</sub> is a remarkable step toward truly ideal CO<sub>2</sub>-functionalization. Keeping in mind that solar energy might be the only and truly sustainable energy source, a few examples of redox-neutral photocatalytic CO<sub>2</sub>-functionalization reactions are also highlighted in this section.

The Sato group recently reported a direct carboxylation reaction at the allylic C(sp<sup>3</sup>)–H bond (Scheme 15).<sup>71</sup> The use of the AlMe<sub>3</sub> – non-nucleophilic base – was ascribed to the initial generation of catalytically active Co(I) species, therefore the catalytic cycle is free from an external reducing reagent. The carboxylation reaction of allylarenes and 1,4-dienes was proven to be effective with a nucleophilic η<sup>1</sup>-allyl-Co(I) catalyst after intensive screening of transition metal catalysts such as Cr(II), Mn(I), Fe(III), Rh(I), Ir(I), Ni(II) and Cu(I). The role of the ligand was critical; Xantphos (L9) showed high selectivity without the formation of isomerization or methylation byproducts by the use of AlMe<sub>3</sub>. Various terminal alkenes were smoothly converted to β,γ-unsaturated acids with excellent functional group

tolerance, including amides, esters, and ketones. The authors suggested that the presence of the low-valent Co(I)-complex was the key to the successful carboxylation reaction with high selectivity. This protocol expands upon the scope of carboxylation to C(sp<sup>3</sup>)–H bonds, which represents atom- and step-economic approaches to construct molecular complexity by incorporating CO<sub>2</sub>.

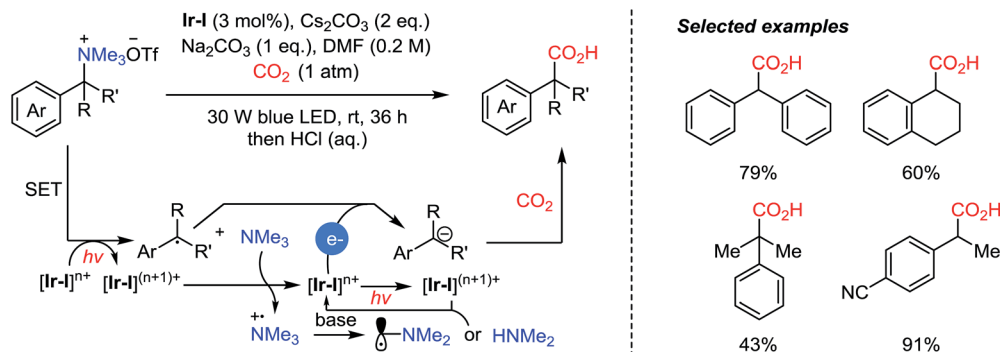
Very recently, the Yu group reported photocatalytic carboxylation of tetraalkyl ammonium salts *via* C–N bond cleavage (Scheme 16).<sup>72</sup> Trimethylamine was generated *in situ* by single-electron transfer (SET) from the excited Ir-I to the substrates. In turn, the resulting active Ir-I species could be reduced by the tertiary amine. Afterwards, carbanions undergo a carboxylation reaction after another SET step between the excited photoredox catalyst and the alkyl radical. The authors suggested that the oxidized trimethylamine was transformed to amine species, like α-radical [Me<sub>2</sub>NCH<sub>2</sub>·], or dimethylamine after hydrolysis. As electron donors, trimethylamine and dimethylamine accounted for 2 equivalents of reducing reagents required to complete the catalytic cycle. This built-in reductant was generated and demonstrated carboxylation reactions without additional reducing reagents, compared to Ni-catalyzed reductive carboxylation of benzylic C–N bonds.<sup>31</sup>

In the above-mentioned cases, organic amines act as sacrificial electron donors, where the resulting radical cation trialkyl amines have dramatically reduced pK<sub>a</sub> at the α-protons.<sup>73</sup> In the presence of a base, a deprotonation reaction would generate an amine with an α-radical, which can couple with other reactive species. The single-electron reduction of CO<sub>2</sub> to CO<sub>2</sub><sup>•-</sup> is in general a rate-determining step due to the high reduction potential (–2.21 V vs. SCE (saturated calomel electrode) in DMF (N,N-dimethylformamide)).<sup>74</sup> A viable C–C bond formation



Scheme 15 Cobalt-catalyzed direct carboxylation of allylic C(sp<sup>3</sup>)–H bonds.



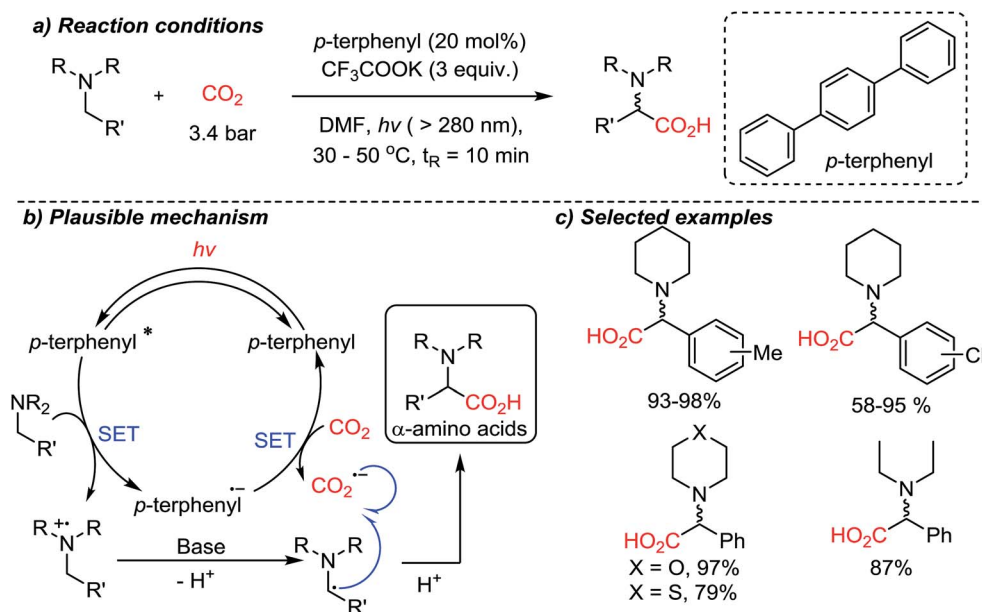


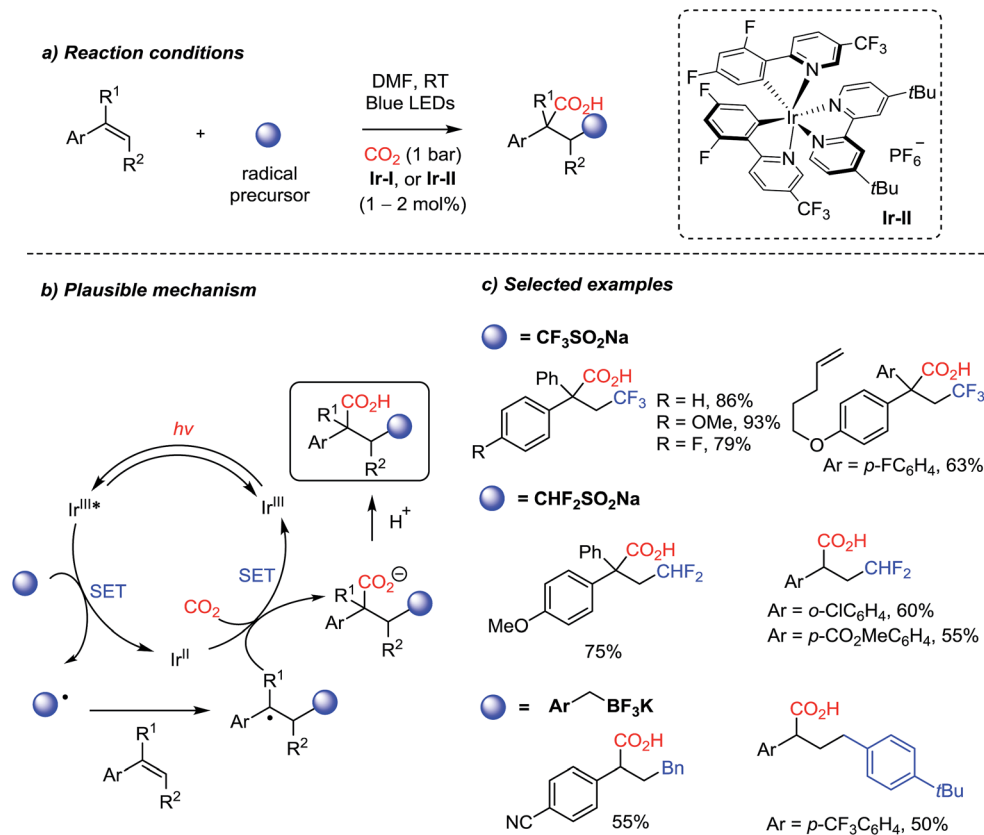
Scheme 16 Photocatalytic carboxylation with a built-in reductant as the electron donor.

reaction with  $\text{CO}_2^{\cdot-}$  and amine based  $\alpha$ -radicals would afford  $\alpha$ -amino acids as the product. This was realized by the Jamison group demonstrating a metal-free photoredox conversion of  $\text{CO}_2$  (Scheme 17).<sup>54</sup> An organic sensitizer, *p*-terphenyl, mediated single electron transfer reactions (reduction potential:  $-2.63$  V vs. SCE in DMF) to perform the suggested one-electron reduction of  $\text{CO}_2$ , providing  $\alpha$ -amino acids in the absence of additional reducing reagents. Various aryl-substituted  $\alpha$ -amino acids were prepared in good to excellent yields. The convenience of continuous flow chemistry<sup>75</sup> was an added benefit of the photocatalysis to provide essential synthetic building blocks from carbon dioxide. The generation of  $\text{CO}_2$ -radical anion is highly attractive, considering its vast application potential in organic synthesis for carboxylation reactions. This photocatalysis mediated by *p*-terphenyl showed promise toward metal-free  $\text{CO}_2$ -functionalization *via* a single-electron reduction mechanism in terms of atom-economy (redox-neutral), feasibility (continuous flow setups), and utility of the final products ( $\alpha$ -amino acids) containing stereogenic centers.

Owing to the recent developments in organic photosynthesis and photosensitizers,<sup>22,76</sup> unprecedented reactivity patterns were achieved with  $\text{CO}_2$  as a C1 source. For example, the Martin group showed photocatalytic dicarbofunctionalization of styrene derivatives initiated by radicals under mild reaction conditions, where stabilized benzyl carbanions react with  $\text{CO}_2$  (Scheme 18).<sup>70a</sup> Various radical initiators, such as trifluoro- and difluorosulfonates, and trifluoroborate salts, were proven to be effective under photochemical reaction conditions. The photocatalytic redox cycle was mediated by an Ir-complex (**Ir-II**). This protocol provides two new C–C bonds with a stereogenic center in the absence of additional stoichiometric reducing reagents. Trisubstituted alkenes were also employed to afford carboxylic acids with a quaternary stereogenic center. The convenient introduction of the (di)trifluoromethyl group highlights potential applications of radical carboxylation reactions in drug discovery and pharmaceutical industry.<sup>77</sup>

The Yu group developed the first thiocarboxylation of styrenes by using an Fe/S complex as the photosensitizer

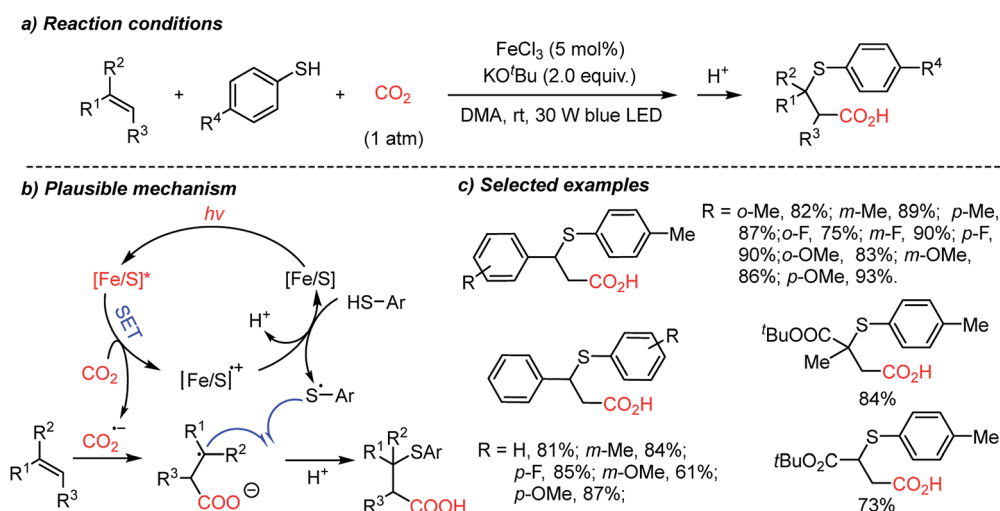
Scheme 17 Photoredox  $\text{CO}_2$ -activation to access  $\alpha$ -amino acids using a *p*-terphenyl photosensitizer.



Scheme 18 Structural diversity of carboxylation with radical initiators.

(Scheme 19).<sup>70b</sup> Various  $\beta$ -thioacids were synthesized selectively with different regioselectivities from the previous protocol (Scheme 18). Mechanistic studies revealed that single-electron reduction of CO<sub>2</sub> can be initiated by the excited Fe/S complex, yielding the CO<sub>2</sub> radical anion (CO<sub>2</sub><sup>•-</sup>). This radical intermediate was trapped subsequently by an alkene substrate to generate a stabilized alkyl radical, which led to anti-Markovnikov regioselectivity. Thiolation of alkyl radicals was

mediated by the [Fe/S] radical cation, highlighting the application potential of the methodology in the synthesis of  $\beta$ -thioacids – an intermediate for the antidepressant drug thiazemim.<sup>78</sup> Also, considering the Fe- and S-rich environment in the prebiotic era, the presented reaction could help us to rethink the CO<sub>2</sub> chemistry in the primordial soup, potentially affording complicated photoredox reactions with CO<sub>2</sub> to furnish chiral molecules.



Scheme 19 Fe–S catalyzed thiocarboxylation induced by visible light.





The progress in redox-neutral CO<sub>2</sub> functionalization showed elegant reaction mechanisms operating under mild conditions, for example, *via* CO<sub>2</sub> insertion into metal–carbon bonds or CO<sub>2</sub><sup>•-</sup> captured by activated substrates. This represents a promising and ideal mode of action, whereby no additional sacrificial redox agents were applied to construct multiple C–C, and C–X bonds. Thus, high atom economy and step-efficiency are expected in constructing molecules with CO<sub>2</sub> as a non-toxic C1 source, boosting research in CO<sub>2</sub>-utilization from recently developed dicarbofunctionalization.<sup>79</sup> Meanwhile, the structural diversity of recent CO<sub>2</sub>-functionalization reactions shows the significant potential of CO<sub>2</sub> in asymmetric synthesis and catalysis. Further investigations on the asymmetric activation of CO<sub>2</sub> and its utilization in CO<sub>2</sub>-functionalization will allow us to achieve higher values of products while recycling CO<sub>2</sub>.

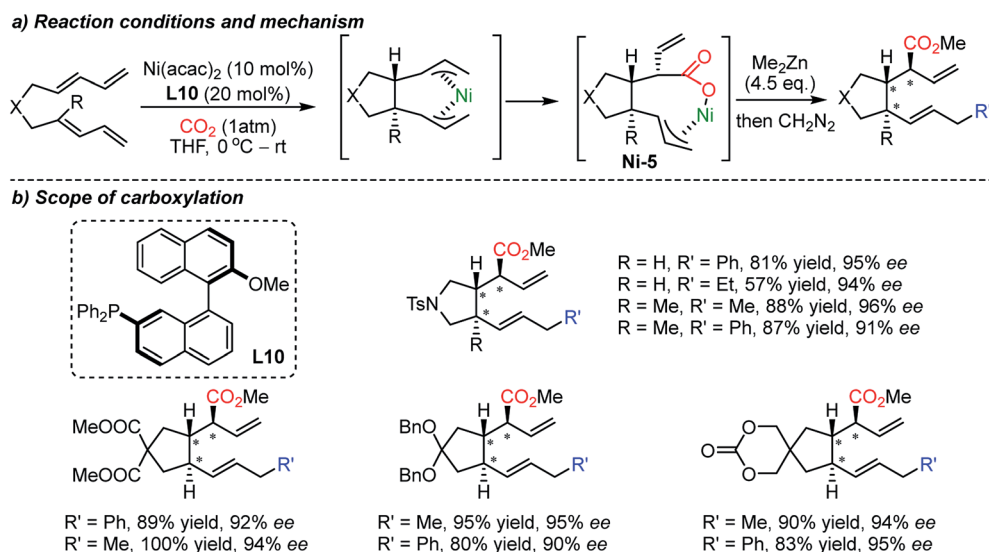
## 5. Asymmetric catalytic carboxylation with CO<sub>2</sub>

Besides the asymmetric synthesis of cyclic carbonates or polycarbonates with epoxides or diols,<sup>21b,80</sup> the construction of enantioselective C–CO<sub>2</sub> bonds using CO<sub>2</sub> has been a formidable challenge under the influence of chiral catalysts or chiral environments. This is due to the high stability of CO<sub>2</sub>, limiting the scope of reaction partners; highly reactive organometallic species and/or harsh reaction conditions are necessary thus low stereoselectivity is in general expected.<sup>21a</sup> In 2004, the Mori group reported the carboxylative cyclization reaction of bis-1,3-dienes catalyzed by a Ni catalyst (Scheme 20).<sup>81</sup> The authors performed facile 5-membered ring formation reactions in the presence of excess amounts of dialkyl zinc (4.5 equiv.). The obtained products possess three consecutive stereogenic centers with absolute diastereoselectivity with good yield and excellent enantioselectivity.

In 2017, the Marek group developed an enantioselective Cu-catalyzed carbomagnesiation reaction of cyclopropenes, which could be selectively carboxylated with CO<sub>2</sub> as an electrophile (Scheme 21).<sup>82</sup> High diastereoselectivity was observed which is not fully understood yet based on the control experiment without the copper catalyst (racemic but moderate diastereoselectivity, 9 : 1 dr). Other electrophiles such as iodine, bromine and allylbromide were smoothly incorporated to furnish the desired products. Although Grignard reagents are reactive nucleophiles, the sequential addition of the alkene and CO<sub>2</sub> prevented direct attack of these nucleophiles on CO<sub>2</sub> at low reaction temperature (0 °C) in the presence of a copper catalyst. The observed stereoselectivity was attributed to the stability of the stereogenic center at the carbon–Cu moiety, explaining the *cis* geometry between the nucleophile and electrophilic CO<sub>2</sub>.

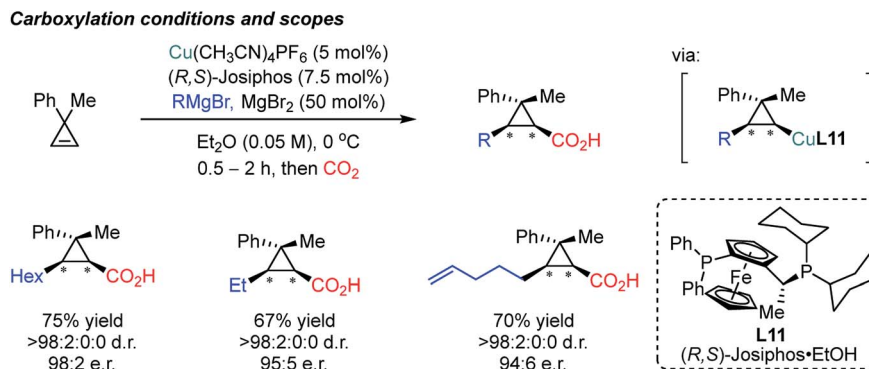
The Yu group<sup>83</sup> recently reported a highly regio- and enantioselective copper-catalyzed CO<sub>2</sub>-functionalization reaction of olefins owing to enantioselective Cu–H catalysis<sup>84</sup> (Scheme 22). Inspired by the CO<sub>2</sub> reduction reaction to methanol<sup>85</sup> and other higher alcohols,<sup>86</sup> the authors developed the sequential enantioselective Cu–H addition, carboxylation and reduction reactions to achieve hydroxymethylation of olefins. A preliminary mechanistic study revealed that the **L12** Cu–R (C) species showed no reactivity toward reduced CO<sub>2</sub> (R<sub>3</sub>Si–OCOH) (dashed arrow), indicating the direct carboxylation of C in the chiral environment to ensure the obtained high enantioselectivity. Furthermore, the developed methodology was applied to 1,3-dienes, affording (*Z*)-selective homoallylic alcohols with good enantioselectivities. Further derivatization of the hydroxymethylation products afforded elegant syntheses of enantioenriched (*R*)-(–)-curcumen<sup>87</sup> and (*S*)-(+)-ibuprofen, starting from CO<sub>2</sub> as a C1 building block.

Although asymmetric catalytic C–C bond formation has achieved relatively considerable progress,<sup>88</sup> only a few methodologies have been reported with CO<sub>2</sub> as a sustainable C1 source while creating stereogenic center(s) with high stereoselectivity.



Scheme 20 Asymmetric carboxylative cyclization of bis-1,3-dienes.





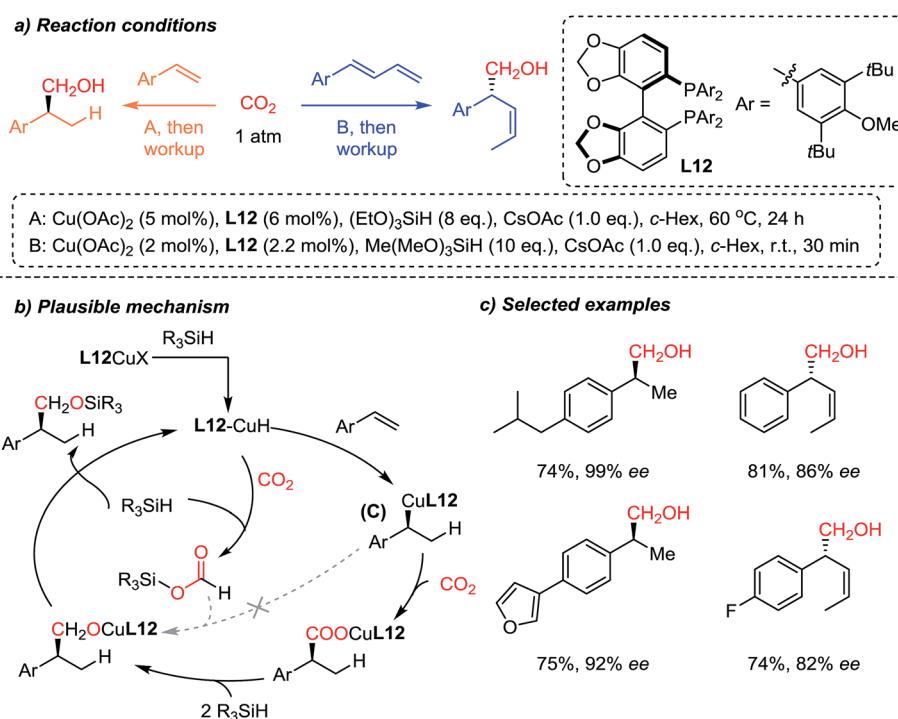
Scheme 21 Asymmetric carbomagnesiation/carboxylation of cyclopropenes.

Considering that the carbon fixation process produces carbohydrates and biomass with absolute enantioselectivity, it is a logical extension to implement asymmetric carboxylation reactions in artificial  $\text{CO}_2$  fixation. Chemical synthesis offers various synthetic pathways and tools that can be easily tested, potentially providing a playground for facile screening and method development. For example, photochemical reactions with chiral catalysts including a chiral iridium catalyst<sup>89</sup> or Lewis-acid assisted photocatalysis<sup>90</sup> for  $\text{CO}_2$ -functionalization are seemingly feasible methods to be developed. Considering the mode of action of RubisCo enzyme, redox-inactive metals and ligands (*e.g.* Mg–biotin complex) would be critical to improve the availability of  $\text{CO}_2$  in organic reactions.<sup>91</sup> On the other hand, it could be inferred that chiral  $\text{CO}_2$ -complexes may play a significant role in  $\text{CO}_2$ -activation *via* bifunctional

asymmetric catalysts.<sup>92</sup> It would be exciting to see the development of  $\text{CO}_2$ -functionalization, with foreseeable sustainability and increased utility of the final products in organic synthesis.

## 6. Conclusion and outlook: umpolung reactivities towards $\text{CO}_2$

It is a formidable challenge to define an “ideal” carbon dioxide functionalization considering that many factors – environmental impact, atom-economy, sustainability, utility of products, and reaction conditions – are involved in designing reaction processes. Harnessing the full capacity of  $\text{CO}_2$ -functionalization can be envisaged with sustainable and accessible chemical feed stocks, catalysts, and reaction conditions.

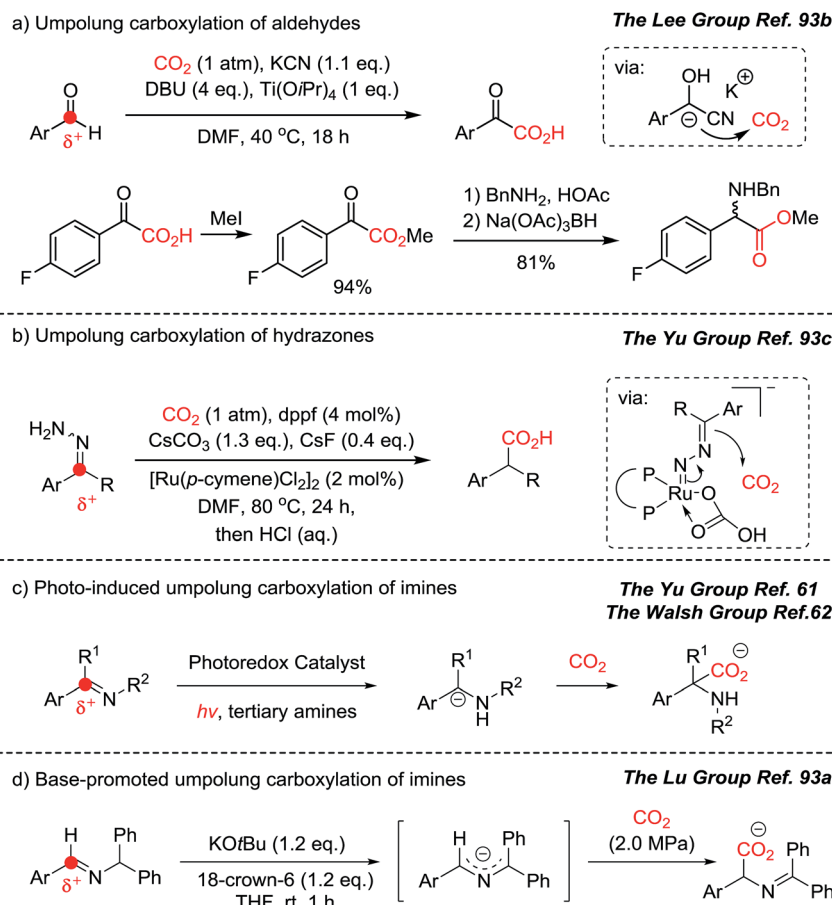
Scheme 22 Enantioselective incorporation of  $\text{CO}_2$  *via* hydrocarboxylation of styrene derivatives and dienes.

Victor Grignard, in 1912, stated this in his Nobel Lecture – “Willstatter in fact recognized that ...organic magnesium compounds must form and that the absorption of CO<sub>2</sub> gas by chlorophyll would in every way be comparable to the Grignard reaction”. The mode of action of magnesium compounds in chlorophyll differs from what Grignard speculated, however, one of the earliest umpolung reactions with CO<sub>2</sub> and Grignard reagents paved a way for modern CO<sub>2</sub> functionalization to date. Considering the formation of Grignard reagents, an umpolung process utilized polarized bonds, C<sup>δ+</sup>-X<sup>δ-</sup>, by inverting the electronic nature of the carbon to nucleophilic by forming C<sup>δ-</sup>-Mg-X.

In this context, recent developments in umpolung carboxylation reactions have shown unprecedented reaction patterns (Scheme 23):<sup>61,62,93</sup> for example, umpolung reactivity has been implemented to functionalize CO<sub>2</sub> for an aldehyde carboxylation reaction through a redox-neutral mechanism (Scheme 23a).<sup>93b</sup> The obtained product, α-keto acid, was smoothly converted to the corresponding α-amino acid under reductive amination reaction conditions mimicking the biosynthesis of various amino acids. The use of nitrogen-containing nucleophiles offers direct synthesis of α-amino acid derivatives (Scheme 23c–e). By employing cyanohydrin, hydrazone, photocatalysts, and a base, *in situ* generated umpolung species were transformed to the desired carboxylated products under mild

reaction conditions, with or without reducing agents. This is particularly interesting to hypothesize the evolution of α-amino acids from the CO<sub>2</sub>-rich prebiotic environment. It has been postulated that cyanide is an abundant source of a carbon nucleophile in the synthesis of biologically active molecules in the primordial soup.<sup>94</sup> The use of aldehydes, cyanide, and CO<sub>2</sub> in synthesizing biologically active molecules is a promising step toward answering the important question: what is the origin of life? Was there an involvement of photochemical CO<sub>2</sub>-activation? Was it promoted by an optically pure component to induce homochirality? The forthcoming ideal CO<sub>2</sub>-functionalization may answer these conundrums.

In summary, this *Perspective* collects the recent literature in CO<sub>2</sub> functionalization and groups it into four categories: (1) metal catalyzed direct carboxylation, (2) photocatalytic carboxylation reactions, (3) redox-neutral carboxylation, and (4) asymmetric introduction of catalytic CO<sub>2</sub> for C–C bond formation reactions. Even a broad scope of substrates and remote site functionalization were achieved; transition metal-catalyzed reductive carboxylation is mostly limited to CO<sub>2</sub> insertion reaction with (over)stoichiometric amounts of reducing reagents. However, photoredox catalysts present promising access to more diversified CO<sub>2</sub> reactions, like dicarboxylation, single-electron reduction and radical coupling *via*



**Scheme 23** Direct umpolung carboxylation. (a) Umpolung carboxylation of aldehyde and reductive amination of α-keto acids to α-amino acids; (b) umpolung carboxylation of hydrazones; (c) photo-induced and (d) base-promoted umpolung carboxylation of imines.



a redox-neutral mechanism. Thanks to these developments of methodologies, as discussed at the end of Section 5, more examples in challenging enantioselective C–CO<sub>2</sub> bond formation will be realized in the near future. Although enzymatic CO<sub>2</sub> functionalization reactions are not covered in this *Perspective*, they have shown their very promising application in artificial carbon recycling processes.<sup>51,95</sup> Synergetic and interdisciplinary CO<sub>2</sub> fixation with biological and chemical catalysts will be particularly interesting in (asymmetric) photocatalytic conversion of CO<sub>2</sub>, truly mimicking photosynthesis to provide ideal CO<sub>2</sub> functionalization reactions.

## Conflicts of interest

There are no conflicts to declare.

## References

- (a) G. Drews, in *Bioenergetic Processes of Cyanobacteria: From Evolutionary Singularity to Ecological Diversity*, ed. G. A. Peschek, C. Obinger and G. Renger, Springer Netherlands, Dordrecht, 2011, p. 265; (b) R. M. Soo, J. Hemp, D. H. Parks, W. W. Fischer and P. Hugenholtz, *Science*, 2017, **355**, 1436.
- (a) D. Gust and T. A. Moore, *Science*, 1989, **244**, 35; (b) X. Liu, S. Inagaki and J. Gong, *Angew. Chem., Int. Ed.*, 2016, **55**, 14924.
- (a) M. Aresta, A. Dibenedetto and A. Angelini, *Chem. Rev.*, 2014, **114**, 1709; (b) M. Pera-Titus, *Chem. Rev.*, 2014, **114**, 1413; (c) H. Arakawa, M. Aresta, J. N. Armor, M. A. Barteau, E. J. Beckman, A. T. Bell, J. E. Bercaw, C. Creutz, E. Dinjus, D. A. Dixon, K. Domen, D. L. DuBois, J. Eckert, E. Fujita, D. H. Gibson, W. A. Goddard, D. W. Goodman, J. Keller, G. J. Kubas, H. H. Kung, J. E. Lyons, L. E. Manzer, T. J. Marks, K. Morokuma, K. M. Nicholas, R. Periana, L. Que, J. Rostrup-Nielsen, W. M. H. Sachtler, L. D. Schmidt, A. Sen, G. A. Somorjai, P. C. Stair, B. R. Stults and W. Tumas, *Chem. Rev.*, 2001, **101**, 953.
- T. Sakakura, J.-C. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365.
- G. A. Olah, G. K. S. Prakash and A. Goeppert, *J. Am. Chem. Soc.*, 2011, **133**, 12881.
- (a) O. Jacquet, C. Das Neves Gomes, M. Ephritikhine and T. Cantat, *J. Am. Chem. Soc.*, 2012, **134**, 2934; (b) C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine and T. Cantat, *Angew. Chem., Int. Ed.*, 2012, **51**, 187.
- J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow and W. Leitner, *Chem. Rev.*, 2018, **118**, 434.
- (a) J. Ran, M. Jaroniec and S.-Z. Qiao, *Adv. Mater.*, 2018, **30**, 1704649; (b) S. N. Habisreutinger, L. Schmidt-Mende and J. K. Stolarczyk, *Angew. Chem., Int. Ed.*, 2013, **52**, 7372; (c) W. Tu, Y. Zhou and Z. Zou, *Adv. Mater.*, 2014, **26**, 4607.
- (a) P. Gao, S. Li, X. Bu, S. Dang, Z. Liu, H. Wang, L. Zhong, M. Qiu, C. Yang, J. Cai, W. Wei and Y. Sun, *Nat. Chem.*, 2017, **9**, 1019; (b) J. Wei, Q. Ge, R. Yao, Z. Wen, C. Fang, L. Guo, H. Xu and J. Sun, *Nat. Commun.*, 2017, **8**, 15174; (c) J. Wang, A. Zhang, X. Jiang, C. Song and X. Guo, *J. CO<sub>2</sub> Util.*, 2018, **27**, 81.
- (a) S. Lin, C. S. Diercks, Y.-B. Zhang, N. Kornienko, E. M. Nichols, Y. Zhao, A. R. Paris, D. Kim, P. Yang, O. M. Yaghi and C. J. Chang, *Science*, 2015, **349**, 1208; (b) S. Yang, W. Hu, X. Zhang, P. He, B. Pattengale, C. Liu, M. Cendejas, I. Hermans, X. Zhang, J. Zhang and J. Huang, *J. Am. Chem. Soc.*, 2018, **140**, 14614; (c) Z.-J. Mu, X. Ding, Z.-Y. Chen and B.-H. Han, *ACS Appl. Mater. Interfaces*, 2018, **10**, 41350.
- (a) C. A. Trickett, A. Helal, B. A. Al-Maythaly, Z. H. Yamani, K. E. Cordova and O. M. Yaghi, *Nat. Rev. Mater.*, 2017, **2**, 17045; (b) J. W. Maina, C. Pozo-Gonzalo, L. Kong, J. Schütz, M. Hill and L. F. Dumée, *Mater. Horiz.*, 2017, **4**, 345.
- (a) S. Ye, R. Wang, M.-Z. Wu and Y.-P. Yuan, *Appl. Surf. Sci.*, 2015, **358**, 15; (b) S. Yin, J. Han, T. Zhou and R. Xu, *Catal. Sci. Technol.*, 2015, **5**, 5048.
- L. J. Gooßen, N. Rodríguez and K. Gooßen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100.
- (a) E. Proschak, P. Heitel, L. Kalinowsky and D. Merk, *J. Med. Chem.*, 2017, **60**, 5235; (b) H. Maag, in *Prodrugs: Challenges and Rewards Part 1*, ed. V. J. Stella, R. T. Borchardt, M. J. Hageman, R. Oliyai, H. Maag and J. W. Tilley, Springer New York, New York, NY, 2007, p. 703.
- (a) A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas and R. Martin, *Angew. Chem., Int. Ed.*, 2018, **57**, 15948; (b) M. Börjesson, T. Moragas, D. Gallego and R. Martin, *ACS Catal.*, 2016, **6**, 6739; (c) S.-S. Yan, Q. Fu, L.-L. Liao, G.-Q. Sun, J.-H. Ye, L. Gong, Y.-Z. Bo-Xue and D.-G. Yu, *Coord. Chem. Rev.*, 2018, **374**, 439.
- J. Song, Q. Liu, H. Liu and X. Jiang, *Eur. J. Org. Chem.*, 2018, **2018**, 696.
- K. Sekine and T. Yamada, *Chem. Soc. Rev.*, 2016, **45**, 4524.
- S. Wang, G. Du and C. Xi, *Org. Biomol. Chem.*, 2016, **14**, 3666.
- L. Zhang and Z. Hou, *Chem. Sci.*, 2013, **4**, 3395.
- F. Juliá-Hernández, M. Gaydou, E. Serrano, M. van Gemmeren and R. Martin, *Top. Curr. Chem.*, 2016, **374**, 45.
- (a) J. Vaitla, Y. Guttormsen, J. K. Mannisto, A. Nova, T. Repo, A. Bayer and K. H. Hopmann, *ACS Catal.*, 2017, **7**, 7231; (b) X.-B. Lu, *Top. Organomet. Chem.*, 2016, **53**, 171.
- (a) Y. Charles, *Angew. Chem., Int. Ed.*, 2018, DOI: 10.1002/anie.201806285; (b) Y.-Y. Gui, W.-J. Zhou, J.-H. Ye and D.-G. Yu, *ChemSusChem*, 2017, **10**, 1337.
- (a) C. Martín, G. Fiorani and A. W. Kleij, *ACS Catal.*, 2015, **5**, 1353; (b) R. R. Shaikh, S. Pornpraprom and V. D'Elia, *ACS Catal.*, 2018, **8**, 419; (c) M. Cokoja, M. E. Wilhelm, M. H. Anthofer, W. A. Herrmann and F. E. Kühn, *ChemSusChem*, 2015, **8**, 2436.
- (a) J. R. Cabrero-Antonino, R. Adam Ortiz and M. Beller, *Angew. Chem., Int. Ed.*, 2018, DOI: 10.1002/anie.201810121; (b) Y. Li, X. Cui, K. Dong, K. Junge and M. Beller, *ACS Catal.*, 2017, **7**, 1077.
- M. Aresta, C. F. Nobile, V. G. Albano, E. Forni and M. Manassero, *J. Chem. Soc., Chem. Commun.*, 1975, 636.
- K. Osakada, R. Sato and T. Yamamoto, *Organometallics*, 1994, **13**, 4645.
- A. Correa and R. Martín, *J. Am. Chem. Soc.*, 2009, **131**, 15974.





- 28 T. Fujihara, K. Nogi, T. Xu, J. Terao and Y. Tsuji, *J. Am. Chem. Soc.*, 2012, **134**, 9106.
- 29 (a) T. León, A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 1221; (b) Y. Liu, J. Cornella and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 11212; (c) T. Moragas and R. Martin, *Synthesis*, 2016, **48**, 2816; (d) M. Börjesson, T. Moragas and R. Martin, *J. Am. Chem. Soc.*, 2016, **138**, 7504.
- 30 A. Correa, T. León and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 1062.
- 31 T. Moragas, M. Gaydou and R. Martin, *Angew. Chem., Int. Ed.*, 2016, **55**, 5053.
- 32 T. Moragas, J. Cornella and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 17702.
- 33 M. van Gemmeren, M. Börjesson, A. Tortajada, S. Z. Sun, K. Okura and R. Martin, *Angew. Chem., Int. Ed.*, 2017, **56**, 6558.
- 34 (a) X. Wang, Y. Liu and R. Martin, *J. Am. Chem. Soc.*, 2015, **137**, 6476; (b) M. Gaydou, T. Moragas, F. Juliá-Hernández and R. Martin, *J. Am. Chem. Soc.*, 2017, **139**, 12161; (c) A. Tortajada, R. Ninokata and R. Martin, *J. Am. Chem. Soc.*, 2018, **140**, 2050.
- 35 F. Juliá-Hernández, T. Moragas, J. Cornella and R. Martin, *Nature*, 2017, **545**, 84.
- 36 (a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062; (b) N. Kambe, T. Iwasaki and J. Terao, *Chem. Soc. Rev.*, 2011, **40**, 4937; (c) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417.
- 37 (a) A. Vasseur, J. Bruffaerts and I. Marek, *Nat. Chem.*, 2016, **8**, 209; (b) H. Sommer, F. Juliá-Hernández, R. Martin and I. Marek, *ACS Cent. Sci.*, 2018, **4**, 153.
- 38 O. V. Ozerov, *Chem. Soc. Rev.*, 2009, **38**, 83.
- 39 (a) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (b) J. Thomas and F. Peter, *Chem.–Eur. J.*, 2009, **15**, 9632; (c) J. Tsuji, H. Takahashi and M. Morikawa, *Tetrahedron Lett.*, 1965, **6**, 4387; (d) B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385.
- 40 (a) G. Pupo, R. Properzi and B. List, *Angew. Chem., Int. Ed.*, 2016, **55**, 6099; (b) S. Masato, S. Isao and Y. Akio, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1065; (c) S. B. Lang, T. M. Locascio and J. A. Tunge, *Org. Lett.*, 2014, **16**, 4308; (d) I. Starý, I. G. Stará and P. Kočovský, *Tetrahedron Lett.*, 1993, **34**, 179; (e) I. Starý, I. G. Stará and P. Kočovský, *Tetrahedron*, 1994, **50**, 529; (f) R. Kumareswaran and Y. D. Vankar, *Tetrahedron Lett.*, 1997, **38**, 8421.
- 41 (a) K. E. Atkins, W. E. Walker and R. M. Manyik, *Tetrahedron Lett.*, 1970, **11**, 3821; (b) T. Hirao, N. Yamada, Y. Ohshiro and T. Agawa, *J. Organomet. Chem.*, 1982, **236**, 409; (c) I. Minami, Y. Ohashi, I. Shimizu and J. Tsuji, *Tetrahedron Lett.*, 1985, **26**, 2449; (d) B. M. Trost and M. H. Hung, *J. Am. Chem. Soc.*, 1983, **105**, 7757; (e) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4730; (f) J. Tsuji, Y. Kobayashi, H. Kataoka and T. Takahashi, *Tetrahedron Lett.*, 1980, **21**, 1475; (g) R. Tamura and L. S. Hegedus, *J. Am. Chem. Soc.*, 1982, **104**, 3727; (h) Y. Tanigawa, K. Nishimura, A. Kawasaki and S.-I. Murahashi, *Tetrahedron Lett.*, 1982, **23**, 5549; (i) B. M. Trost, N. R. Schmuff and M. J. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 5979.
- 42 H.-W. Suh, L. M. Guard and N. Hazari, *Chem. Sci.*, 2014, **5**, 3859.
- 43 N. Solin, J. Kjellgren and K. J. Szabó, *J. Am. Chem. Soc.*, 2004, **126**, 7026.
- 44 (a) H. Takahata, Y. Uchida and T. Momose, *J. Org. Chem.*, 1995, **60**, 5628; (b) Y. Zhang, X. Wang, M. Sunkara, Q. Ye, L. V. Ponomereva, Q.-B. She, A. J. Morris and J. S. Thorson, *Org. Lett.*, 2013, **15**, 5566.
- 45 (a) H. Hoberg and B. Apotecher, *J. Organomet. Chem.*, 1984, **270**, c15; (b) H. Hoberg, K. Jenni, C. Krüger and E. Raabe, *Angew. Chem., Int. Ed.*, 1986, **25**, 810; (c) M. Takimoto and M. Mori, *J. Am. Chem. Soc.*, 2001, **123**, 2895.
- 46 T. Fujihara, Y. Horimoto, T. Mizoe, F. B. Sayyed, Y. Tani, J. Terao, S. Sakaki and Y. Tsuji, *Org. Lett.*, 2014, **16**, 4960.
- 47 M. Takimoto, M. Kawamura, M. Mori and Y. Sato, *Synlett*, 2005, **2005**, 2019.
- 48 J. Xie, A. H. Jin and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2017, **46**, 5193.
- 49 (a) M. Hervás, J. A. Navarro and M. A. De la Rosa, *Acc. Chem. Res.*, 2003, **36**, 798; (b) S. Nishitani, N. Kurata, Y. Sakata, S. Misumi, A. Karen, T. Okada and N. Mataga, *J. Am. Chem. Soc.*, 1983, **105**, 7771.
- 50 N. J. Claassens, *Microb. Biotechnol.*, 2017, **10**, 31.
- 51 T. Schwander, L. Schada von Borzyskowski, S. Burgener, N. S. Cortina and T. J. Erb, *Science*, 2016, **354**, 900.
- 52 (a) D. R. Ort, S. S. Merchant, J. Alric, A. Barkan, R. E. Blankenship, R. Bock, R. Croce, M. R. Hanson, J. M. Hibberd, S. P. Long, T. A. Moore, J. Moroney, K. K. Niyogi, M. A. J. Parry, P. P. Peralta-Yahya, R. C. Prince, K. E. Redding, M. H. Spalding, K. J. van Wijk, W. F. J. Vermaas, S. von Caemmerer, A. P. M. Weber, T. O. Yeates, J. S. Yuan and X. G. Zhu, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 8529; (b) D. C. Ducat and P. A. Silver, *Curr. Opin. Chem. Biol.*, 2012, **16**, 337.
- 53 (a) S. Tazuke and H. Ozawa, *J. Chem. Soc., Chem. Commun.*, 1975, 237; (b) S. Tazuke and N. Kitamura, *Nature*, 1978, **275**, 301; (c) T. Inoue, A. Fujishima, S. Konishi and K. Honda, *Nature*, 1979, **277**, 637; (d) J.-M. Lehn and R. Ziessel, *Proc. Natl. Acad. Sci. U. S. A.*, 1982, **79**, 701; (e) J. Hawecker, J.-M. Lehn and R. Ziessel, *J. Chem. Soc., Chem. Commun.*, 1983, 536.
- 54 H. Seo, M. H. Katcher and T. F. Jamison, *Nat. Chem.*, 2016, **9**, 453.
- 55 K. Shimomaki, K. Murata, R. Martin and N. Iwasawa, *J. Am. Chem. Soc.*, 2017, **139**, 9467.
- 56 Q.-Y. Meng, S. Wang and B. König, *Angew. Chem., Int. Ed.*, 2017, **56**, 13426.
- 57 Q.-Y. Meng, S. Wang, G. S. Huff and B. König, *J. Am. Chem. Soc.*, 2018, **140**, 3198.
- 58 H. Seo, A. Liu and T. F. Jamison, *J. Am. Chem. Soc.*, 2017, **139**, 13969.
- 59 Y. Masuda, N. Ishida and M. Murakami, *J. Am. Chem. Soc.*, 2015, **137**, 14063.
- 60 J. Hou, A. Ee, W. Feng, J.-H. Xu, Y. Zhao and J. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 5257.
- 61 T. Ju, Q. Fu, J.-H. Ye, Z. Zhang, L.-L. Liao, S.-S. Yan, X.-Y. Tian, S.-P. Luo, J. Li and D.-G. Yu, *Angew. Chem., Int. Ed.*, 2018, **57**, 13897.



- 62 X. Fan, X. Gong, M. Ma, R. Wang and P. J. Walsh, *Nat. Commun.*, 2018, **9**, 4936.
- 63 S. Humbel, I. Côte, N. Hoffmann and J. Bouquant, *J. Am. Chem. Soc.*, 1999, **121**, 5507.
- 64 M. Li, O. Gutierrez, S. Berritt, A. Pascual-Escudero, A. Yeşilçimen, X. Yang, J. Adrio, G. Huang, E. Nakamaru-Ogiso, M. C. Kozłowski and P. J. Walsh, *Nat. Chem.*, 2017, **9**, 997.
- 65 (a) K. Bera and I. N. N. Namboothiri, *Asian J. Org. Chem.*, 2014, **3**, 1234; (b) S. Fustero, M. Sánchez-Roselló, C. Báez, C. del Pozo, J. L. García Ruano, J. Alemán, L. Marzo and A. Parra, *Amino Acids*, 2011, **41**, 559; (c) C. Spino and C. Gobdout, *J. Am. Chem. Soc.*, 2003, **125**, 12106.
- 66 M. Kapoor, D. Liu and M. C. Young, *J. Am. Chem. Soc.*, 2018, **140**, 6818.
- 67 (a) V. Laserna, G. Fiorani, C. J. Whiteoak, E. Martin, E. Escudero-Adán and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2014, **53**, 10416; (b) A. Peeters, R. Ameloot and D. E. De Vos, *Green Chem.*, 2013, **15**, 1550.
- 68 J. Ye, I. Kalvet, F. Schoenebeck and T. Rovis, *Nat. Chem.*, 2018, **10**, 1037.
- 69 H. Wu, R. Andres, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 499.
- 70 (a) V. R. Yatham, Y. Shen and R. Martin, *Angew. Chem., Int. Ed.*, 2017, **56**, 10915; (b) J.-H. Ye, M. Miao, H. Huang, S.-S. Yan, Z.-B. Yin, W.-J. Zhou and D.-G. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15416.
- 71 K. Michigami, T. Mita and Y. Sato, *J. Am. Chem. Soc.*, 2017, **139**, 6094.
- 72 L.-L. Liao, G.-M. Cao, J.-H. Ye, G.-Q. Sun, W.-J. Zhou, Y.-Y. Gui, S.-S. Yan, G. Shen and D.-G. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 17338.
- 73 X. Zhang and F. G. Bordwell, *J. Org. Chem.*, 1992, **57**, 4163.
- 74 (a) E. Lamy, L. Nadjo and J. M. Saveant, *J. Electroanal. Chem. Interfacial Electrochem.*, 1977, **78**, 403; (b) A. M. Appel, J. E. Bercaw, A. B. Bocarsly, H. Dobbek, D. L. DuBois, M. Dupuis, J. G. Ferry, E. Fujita, R. Hille, P. J. A. Kenis, C. A. Kerfeld, R. H. Morris, C. H. F. Peden, A. R. Portis, S. W. Ragsdale, T. B. Rauchfuss, J. N. H. Reek, L. C. Seefeldt, R. K. Thauer and G. L. Waldrop, *Chem. Rev.*, 2013, **113**, 6621.
- 75 (a) K. Booker-Milburn, *Nat. Chem.*, 2012, **4**, 433; (b) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio and R. J. Ingham, *Angew. Chem., Int. Ed.*, 2015, **54**, 10122; (c) J. Britton, S. Majumdar and G. A. Weiss, *Chem. Soc. Rev.*, 2018, **47**, 5891.
- 76 (a) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (b) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (c) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (d) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052.
- 77 (a) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (b) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.
- 78 S. Y. Dike, D. H. Ner and A. Kumar, *Bioorg. Med. Chem. Lett.*, 1991, **1**, 383.
- 79 (a) J.-H. Ye, L. Zhu, S.-S. Yan, M. Miao, X.-C. Zhang, W.-J. Zhou, J. Li, Y. Lan and D.-G. Yu, *ACS Catal.*, 2017, **7**, 8324; (b) T. Koike and M. Akita, *Acc. Chem. Res.*, 2016, **49**, 1937.
- 80 (a) M. I. Childers, J. M. Longo, N. J. Van Zee, A. M. LaPointe and G. W. Coates, *Chem. Rev.*, 2014, **114**, 8129; (b) Y. Liu, W.-M. Ren, K.-K. He and X.-B. Lu, *Nat. Commun.*, 2014, **5**, 5687.
- 81 M. Takimoto, Y. Nakamura, K. Kimura and M. Mori, *J. Am. Chem. Soc.*, 2004, **126**, 5956.
- 82 L. Dian, D. S. Müller and I. Marek, *Angew. Chem., Int. Ed.*, 2017, **56**, 6783.
- 83 Y.-Y. Gui, N. Hu, X.-W. Chen, L. L. Liao, T. Ju, J.-H. Ye, Z. Zhang, J. Li and D.-G. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 17011.
- 84 (a) C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916; (b) M. T. Pirnot, Y.-M. Wang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2016, **55**, 48.
- 85 (a) W. H. Bernskoetter and N. Hazari, *Acc. Chem. Res.*, 2017, **50**, 1049; (b) W.-H. Wang, Y. Himeda, J. T. Muckerman, G. F. Manbeck and E. Fujita, *Chem. Rev.*, 2015, **115**, 12936; (c) A. Goepfert, M. Czaun, J.-P. Jones, G. K. Surya Prakash and G. A. Olah, *Chem. Soc. Rev.*, 2014, **43**, 7995.
- 86 Y. Tani, K. Kuga, T. Fujihara, J. Terao and Y. Tsuji, *Chem. Commun.*, 2015, **51**, 13020.
- 87 A. Gualandi, P. Canestrari, E. Emer and P. G. Cozzi, *Adv. Synth. Catal.*, 2014, **356**, 528.
- 88 (a) P. Renaud and P. Leong, *Science*, 2008, **322**, 55; (b) T. Yasukawa, H. Miyamura and S. Kobayashi, *Chem. Soc. Rev.*, 2014, **43**, 1450; (c) T. Tetsu, I. Takanori and K. Shū, *Angew. Chem., Int. Ed.*, 2013, **52**, 6590; (d) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (e) R. Mahrwald, in *Enantioselective Organocatalyzed Reactions II: Asymmetric C-C Bond Formation Processes*, Springer Netherlands, Dordrecht, 2011.
- 89 H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt and E. Meggers, *Nature*, 2014, **515**, 100.
- 90 T. R. Blum, Z. D. Miller, D. M. Bates, I. A. Guzei and T. P. Yoon, *Science*, 2016, **354**, 1391.
- 91 T. M. McDonald, J. A. Mason, X. Kong, E. D. Bloch, D. Gygi, A. Dani, V. Crocellà, F. Giordanino, S. O. Odoh, W. S. Drisdell, B. Vlasisavljevich, A. L. Dzubak, R. Poloni, S. K. Schnell, N. Planas, K. Lee, T. Pascal, L. F. Wan, D. Prendergast, J. B. Neaton, B. Smit, J. B. Kortright, L. Gagliardi, S. Bordiga, J. A. Reimer and J. R. Long, *Nature*, 2015, **519**, 303.
- 92 (a) J.-A. Ma and D. Cahard, *Angew. Chem., Int. Ed.*, 2004, **43**, 4566; (b) M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187.
- 93 (a) C.-X. Guo, W.-Z. Zhang, H. Zhou, N. Zhang and X.-B. Lu, *Chem.-Eur. J.*, 2016, **22**, 17156; (b) M. Juhl and J.-W. Lee, *Angew. Chem., Int. Ed.*, 2018, **57**, 12318; (c) S.-S. Yan, L. Zhu, J.-H. Ye, Z. Zhang, H. Huang, H. Zeng, C.-J. Li, Y. Lan and D.-G. Yu, *Chem. Sci.*, 2018, **9**, 4873.
- 94 B. H. Patel, C. Percivalle, D. J. Ritson, C. D. Duffy and J. D. Sutherland, *Nat. Chem.*, 2015, **7**, 301.
- 95 J. Martin, L. Eisoldt and A. Skerra, *Nat. Catal.*, 2018, **1**, 555.

