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Carboxylations

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Metal-Catalyzed Carboxylation of Organometallic Reagents with Carbon Dioxide**

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carbon dioxide · carboxylation · homogeneous catalysis · organometallics · sustainable chemistry

Since the late 18th century, our society has altered the pace of the carbon cycle by extracting and burning fossil fuels, such as oil, gas, or coal. As a result, billions of tones of greenhouse gases such as carbon dioxide (CO_2) have been released to our atmosphere. Indeed, there is an increasing pressure for carbon capture and sequestration as CO_2 emissions are today a matter of genuine public concern. From an academic point of view, chemists are currently being challenged to devise processes that utilize CO_2 to produce chemicals (e.g. carboxylic acids, ureas, urethanes, or carbonates[1]) because such sustainable methodologies would reduce waste and make a better use of energy and carbon.

The ubiquity of carboxylic acids in a vast array of medicinally important compounds as well as the tremendous utility as a synthon in organic synthesis makes them particularly attractive targets for fine-chemical synthesis.[2] For instance, numerous valuable compounds bearing a carboxylic acid motif exhibit remarkable therapeutic activities, such as acetylsalicylic acid or 2-(4-isobutylphenyl)propionic acid, worldwide commercialized as aspirin and ibuprofen, respectively. Likewise, water absorbing properties of polyacrylic acids are of great utility in the production of diapers. A plethora of well-established methods for the preparation of carboxylic acids includes the well-known hydrolysis of nitriles and related derivatives or the oxidation of preoxidized substrates, such as alcohols or aldehydes.[2] Despite the efficiency of these conventional procedures, however, the most straightforward method for accessing carboxylic acids is the direct carboxylation of carbon nucleophiles using CO_2 as the electrophilic partner (Scheme 1). Among their advantages is that harsh conditions are generally avoided and that CO_2 is non-toxic, abundant, cheap and has an appealing potential as a renewable source.[3]

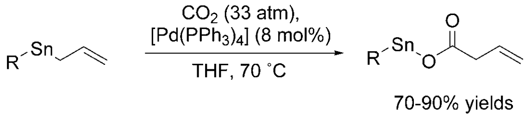
$$\mathrm{R{-}M} \;+\; \mathrm{CO_2} \xrightarrow{[\mathrm{M'}]\,(\mathrm{cat.})} \mathrm{R{-}CO_2H}$$

$$\mathrm{M = Li, Mg, Cu, Mn, Sn, Zn, B}$$

Scheme 1. Carboxylations of organometallic reagents with CO_2.

The typical nucleophilic coupling partners in carboxylation reactions are organolithium or Grignard reagents as their high reactivity can easily overcome the kinetic inertness associated with CO_2. Indeed, these carboxylation reactions proceed smoothly even in the absence of transition-metal catalysts.[4] As a result, the use of organolithium or organomagnesium halides still represents an excellent method for the low-cost synthesis of carboxylic acids. However, despite the advances made, these reactions are not compatible with sensitive functional groups, such as aldehydes, ketones, or nitriles, as they rapidly react with organolithium or Grignard reagents. Therefore, the use of alternate organometallic methods that operate under milder reaction conditions and with high chemoselectivity would be desirable. Herein, we describe the major breakthroughs reported recently in the field, illustrating the importance of using CO_2 as a carbon source for more sustainable chemical processes.

One of the early attempts to activate CO_2 by using less polarized metal–carbon bonds was reported in 1997 by Shi and Nicholas. In this report, allyl stannanes smoothly underwent carboxylations when mixing up with 8 mol% of $[Pd(PPh_3)_4]$ as catalyst at high pressures (33 atm) of CO_2 (Scheme 2).[5] Although this was a significant discovery from a fundamental point of view, the synthetic application profile was highly limited owing to the severe substrate restrictions.



Scheme 2. Palladium-catalyzed carboxylation of allystannanes.[5]

Surprisingly, the topic remained dormant for years and it was only recently that carboxylation reactions regained considerable attention by using alternate methods with more convenient nucleophilic coupling reagents. In 2006, Iwasawa introduced the use of rhodium catalysts to conduct carboxylations of organoboronic esters under an atmospheric pressure of CO_2.[6,7] Interestingly, the synthesis of the

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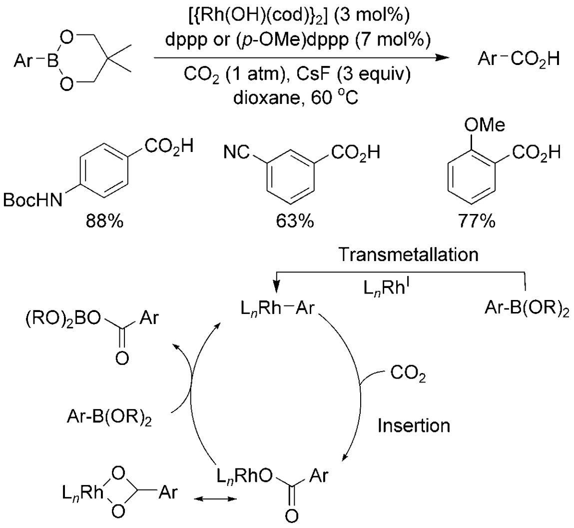
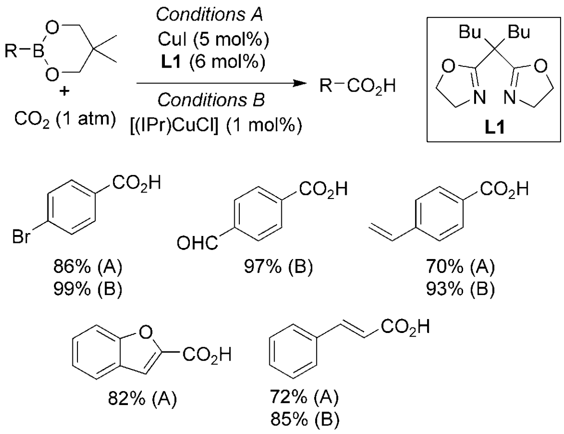
nucleophilic components was highly modular as it was accomplished by means of the palladium-catalyzed cross-coupling of diboron reagents and aryl halides[8] or, alternatively, by the hydroboration of alkynes.[9] It was anticipated that the oxophilicity of boron compounds would enable the regeneration of the active catalyst by assisting the exchange of rhodium carboxylates to the corresponding boron carboxylates (Scheme 3).



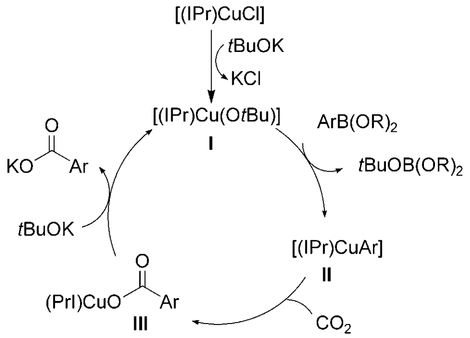
Scheme 3. Rhodium-catalyzed carboxylation of boronic esters.[6]

It was observed that the presence of CsF and of dppe-type ligands (dppe = 1,2-bis(diphenylphosphino)ethene) played a crucial role in delivering the desired carboxylic acids in high yields. Importantly, potentially sensitive functional groups such as esters, ketones, nitriles, and protected amines, were all tolerated under such reaction conditions. In striking contrast, boronic esters bearing bromo, nitro, alkynyl, and vinyl substituents were entirely inert under otherwise identical reaction conditions. Some of these drawbacks have recently been circumvented by the research groups of Iwasawa[10] and Hou[11] who independently introduced the less-expensive and readily available copper-catalysts to perform the carboxylation of such boron-type compounds. Iwasawa and co-workers identified the combination of CuI and **L1** in the presence of three equivalents of CsF as a highly active system for the conversion of a wide variety of boronic esters into the corresponding carboxylic acids (conditions A, Scheme 4). They reasonably assumed a similar mechanism to the related rhodium-catalyzed process (Scheme 3). The crucial role of CsF may be rationalized as a result of its influence on either transmetallation or on the carboxylation step by forming arylfluoroborates and fluorocuprates, respectively.

Hou and co-workers described an alternate copper-catalyzed method using N-heterocyclic carbene supported ligands.[11] Initial observations indicated that the combination of CuCl (5 mol%), *t*BuOK (2 equiv), and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl, 5 mol%) was optimal, thus rendering an efficient catalyst for the carboxylation of boronic esters. Remarkably, they further observed that the isolated carbene complex [(IPr)CuCl][12] was even more active under lower catalyst loadings (conditions B, Scheme 4). In accordance with the findings reported by Iwasawa,[10] this copper-catalyst system showed a broader substrate scope than the rhodium-catalyzed methods and allowed for the synthesis of a wide range of functionalized carboxylic acids including those bearing aldehydes, alkenes, aryl halides, nitro groups, oxiranes, and even alkyne moieties. This compatibility is particularly noteworthy as the more commonly used organolithium or Grignard reagents would result in undesired addition to these functional groups. The postulated mechanism for this transformation is shown in Scheme 5. Initial metathesis reaction of complex [(IPr)CuCl] and *t*BuOK furnishes the complex **I**,[13] which subsequently transmetallates affording organocopper complexes of type **II**. Insertion of CO_2 into the Cu–C bond followed by reaction with *t*BuOK regenerates the propagating catalytic species **I** and simultaneously releases the potassium carboxylate. Interestingly, some reaction intermediates could be isolated, thus resulting in an empirical evidence of the proposed mechanistic pathway.



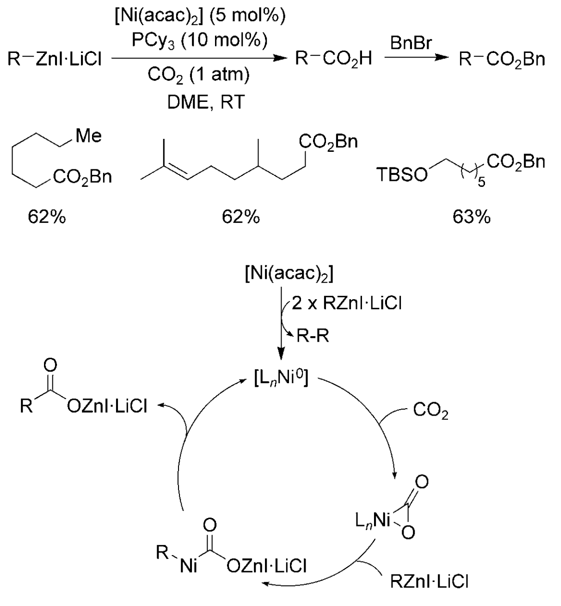
Scheme 4. Copper-catalyzed carboxylation of boronic esters.[10,11]



Scheme 5. Mechanistic proposal for copper-catalyzed carboxylation of boronic esters using [(IPr)CuCl].[11]

As an alternative to the use of boron compounds, Oshima, Yorimitsu, and co-workers have recently reported a nickel-catalyzed reaction for the coupling of organozinc reagents with CO_2 at room temperature (Scheme 6).[14] Unlike the boron-based methods, the prime interest of the organozinc method relies on the assembly of previously inaccessible aliphatic carboxylic acids under mild reaction conditions. However, aromatic zinc reagents such as PhZnI·LiCl, reacted with CO_2 in lower yields, which shows that further improvements are required to make the method more general in terms of scope. Particularly noteworthy is the influence of LiCl on the reaction outcome; although the nature of its role has not yet been rationalized it is believed that it favors the transmetallation step by coordination to the zinc center. Concerning the reaction mechanism, it was proposed that the initially generated nickel(0) species undergoes oxidative addition of CO_2, thus delivering a carbon dioxide complex.[15] Subsequent transmetallation and reductive elimination afforded the corresponding zinc carboxylate, which upon hydrolytic work-up delivered the desired carboxylic acids.

Dong and Yeung have recently reported the carboxylation of organozinc reagents with both palladium and nickel catalysts.[16] They first successfully utilized Aresta's complex, $[Ni(\eta^2\text{-}CO_2)(PCy_3)_2]$, to transform PhZnBr into the corresponding benzoic acid in quantitative yields. The use of an in situ catalyst resulting from the reaction of either $[Ni(PCy_3)_2(N_2)]$ or $[Ni(cod)_2]$ (cod = cyclooctadiene) with PCy_3 was also found to be effective for the carboxylation of PhZnBr with CO_2. Interestingly, the replacement of the nickel complexes by $Pd(OAc)_2$ proved to be beneficial for the carboxylation of some substituted aryl zinc bromides.[17,18] However, generally, the nickel-based catalysts are superior to palladium as they are active for both aromatic and alkyl zinc reagents.[19] In this case, it is reasonable to assume an analogous mechanism to the one depicted in Scheme 6 consisting of oxidative addition of nickel (0) to CO_2, transmetallation with the organozinc reagent and reductive elimination to afford the corresponding zinc carboxylate which is finally hydrolyzed during the acidic work-up.[14]



Scheme 6. Nickel-catalyzed carboxylations of organozinc reagents.[14]

In conclusion, the preparative aspects of using CO_2 in organic synthesis as C_1 source undoubtedly represent a key strategy for the development of greener chemical processes. In recent years, substantial advances in the field of carboxylation of organometallic reagents have allowed the use of relatively less-reactive nucleophilic components, such as boron or zinc-type reagents. These methods are distinguished by their wide scope and functional group tolerance and therefore may importantly emerge as competitive and convenient methods for the syntheses of carboxylic acid derivatives.[20] We certainly speculate a continued growth in this promising area of research and we anticipate that impressive advances in the field of CO_2 have yet to come.

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