Abstract

New ways of generating carbon-carbon bonds (C–C) are continually being developed in the field of organic synthesis. For the production of different C-C bonds, transition metal-catalyzed (palladium or nickel) cross-couplings have been extensively studied and employed in the synthesis of several key compounds in the area of synthetic chemistry. Decarbonylative coupling processes have evolved as an efficient alternative to classic cross-coupling methods in recent years, owing to the environmental benefits of utilizing electrophiles with carbonyl-containing functionalities rather than extensively utilized organohalide or sulphate. As a result, we have mostly discussed about transition metal-catalyzed processes that make C–C bonds through decarbonylative coupling, and we have also discussed the limitations involved with these approaches.

Keywords: Transition metals, palladium, nickel, C-C bond formation, decarbonylation
1. Introduction

Cross-coupling methods that use transition metals to make both carbon–carbon and carbon–heteroatom bonds make it easy to make structurally diverse molecules that are needed to make modern medicines and functional materials.\textsuperscript{1-3} Richard F. Heck, Ei-ichi Negishi and Akira Suzuki earned Nobel Prize for their contribution in palladium catalysis-based synthetic approaches in the year of 2010. Over the last 50 years, scientists have researched about how most of the organohalides and sulphates are used in the common electrophiles for catalyzed by metal or metal-mediated reactions. Despite the fact that they are expensive, availability, and transformability, as well as the halogen and sulphur synthesis are on the corrosive compounds byproducts, these are unfavorable in both synthetic and environmental aspects.\textsuperscript{4-7} As a result, it is extremely desirable to investigate alternate cross-coupling equivalents with increased practical application and flexibility.

Organohalide analogues to the carbonyl functions of acyl chlorides and anhydrides have recently been proven to be carbonyl functions like esters, amides, aldehydes, and ketones.\textsuperscript{8,9} Carbonyl compounds have several benefits as coupling substrates, including their low cost, ease of procurement, absence of halogenated waste, and the possibility for interconversion between functional groups. Recent chemical research has seen the activation and functionalization of acyl C-C and C-heteroatom links by transition metals.\textsuperscript{10-12} For the reasons stated above, as well as the omnipresent ability to decarbonize carbonyl functionalities based on their type essential substitute for conventional techniques.

In modern days, there has been a surge of interest in decarbonylative coupling processes that employ carbonyl group moieties as starters. However, a complete mechanistic insight has yet to be attained, researchers have devoted significant efforts to conduct illuminating experimental and theoretical investigations. Considering the existing mechanistic aspects, the proposed fundamental mechanism for coupling of carbonyl derivatives by transition metal catalysis through decarbonylation can be postulated (Scheme 1). Initially, the acyl C-X bond in aryl moieties is oxidatively attached to the poor valent metal (n) entity, yielding an acyl metal (n+2) intermediate which was then CO evacuated subsequently. In the absence of an external nucleophile, the corresponding aryl metal (n+2) entity either discharges the decarbonylated product R-X by path A, or initiates transmetalation with following reductive elimination to deliver the desired cross-coupling product by replenishing the active low metal (n) entity by path B. Nevertheless, the order of CO extrusion vs transmetalation is yet uncertain.
Scheme 1. Plausible transition metal catalyzed coupling through decarbonylation mechanism.

However, the mechanistic evidence was corroborated with some theoretical calculations and laboratory results which supports decarbonylation occurring antecedent to transmetalation. For instance, Sanford carried out comprehensive stoichiometric reactions of benzoyl fluoride with Ni(cod)$_2$ and PCy$_3$ in THF. The results obliged that decarbonylation occurs proceeding to the transmetalation $^{13}$. Moreover, Rueping documented acylnickel moieties were more susceptible to decarbonylation with minimum barrier of energy than transmetalation $^{14}$.

In addition, interestingly, Ritter and his group discovered that reactions with acyl(chloro)palladium could not carry out via decarbonylation step prior to transmetalation at room temperature, whereas, difluoromethylated complex underwent faster decarbonylation even below room temperature confirms the occurrence of transmetalation prior to decarbonylation. Likewise, several investigations are currently being conducted to determine the sequence of decarbonylation and transmetalation $^{15}$.

Decarbonylative coupling methods that utilize carbonyl functionalities as precursors have received a lot of attention in recent years. In this minireview, we concentrate on recent advances in the past three years in decarbonylative coupling procedures are catalyzed by transition metals that use diverse carbonyl-containing moieties as coupling electrophiles, especially palladium and nickel, to form C-C bonds. In this tutorial, we have
categorized this review into seven subunits such as arylation, cyanation, difluoromethylation, trifluoromethylation alkylation, alkynylation, and alkenylation.

2. Arylation

Zhou et al. 16 reported for the first time in 2019 a palladium-based catalytic system Pd(dppf)Cl₂ for the amide decarbonylative coupling to synthesise biaryls via selective N-(CO) bond activation of amides (Scheme 2). This new method is based on quick sequence engineering of the catalytic cycle, in which decarbonylation takes place prior to the phase of transmetallation. N-benzoyl glutarimide 1 and 4-methoxyphenyl boronic acid 2 start to mix together at first, different Pd catalytic systems was carried out to find the optimization condition. Surprisingly, the Pd(dppf)Cl₂ catalytic system gave 90% yield with a biaryl: ketone selectivity of more than 10:1. Having optimized conditions in hand, a broad range of boronic acids reacted with N-cyclic and acyclic amides, given important for biaryls 3 to excellent product. DFT investigations support an oxidative addition, decarbonylation, and transmetalation mechanism while also shedding light on the strong selectivity in the activation of N–C(O) bonds.

![Scheme 2. Pd-catalyzed Cross-coupling of Suzuki-Miyaura decarbonylation of amides (C sp²-sp²).](image)

Szostak et al. in 2020 17 procured biaryls 6 through the decarbonylation of aroyl chlorides 4 utilising Suzuki-Miyaura cross coupling. This approach works with a broad variety of prevalent aryl boronic acids 5 and chlorides. To speed up transmetalation, this method uses [Pd(n^3-1-t-Bu-ind)Cl]₂/PPh₃ as a weak base, use DPEPhos with NaHCO₃ (Scheme 3). There are many ways that natural products and pharmaceuticals can be made more useful by focusing on how close the decarbonylation takes place of both the carboxylic acid and
biaryl moiety. Finally, they have conducted extensive mechanistic as well as DFT investigations to explain the mechanistic process and give a foundation for long-term synthetic tactic development.

![Chemical structure](image)

**Scheme 3.** Decarbonylation of aroyl chlorides utilizing Suzuki-Miyaura reaction.

Traditional coupling partners via CO or CO₂ loss, termed as decarbonylative and decarboxylative couplings, have been devised as practical proxies for benzoic acids and their derivatives. Within this method, amongst the most important is the production of synthetic techniques for biaryls, which is of great importance. In this regard, Nishihara et al. in 2021¹⁸ addressed the synthesis of biaryls 9 which is unsymmetrical from the decarbonylation of acyl chlorides 7 with that of potassium perfluorobenzoates 8 utilizing a palladium catalyst (Scheme 4). The first redox-neutral cross-coupling that included both decarbonylation and decarboxylation
was made with this framework. Both precursors can be prepared directly from carboxylic acids, resulting in an eco-friendly and productive cross-coupling reaction.

![Scheme 4](image)

**Scheme 4.** Decarbonylative coupling of aroyl chlorides with potassium perfluoroborates.

### 3. Cyanation Reactions

Shi and Szostak\(^1\) in 2017 reported, for the first time, palladium catalyzed cyanation of various amides 10 using Zn(CN)\(_2\) 11 through decarbonylation to synthesize a broad range of valuable aryl nitriles 12 by highly selective cleavage of C-N bond. In this protocol, a very broad range of amide substrates 10 were tolerated, and yields ranged from fair to outstanding in most cases (Scheme 5). Palladium metal was inserted into the N-C bond as part of the mechanism without forming an acyl cyanide. This new methodology is further utilized in the isotopically labelled interconversion of amides to nitriles via the exchange of carboxylic acid, formal carbon starting material.

Rueping and his coworkers came up with the nickel-based system Ni(cod)\(_2\) to make it easier to cyanate aryl esters 13, cinnamoyl esters, and amides 14 through decarbonylation, which led to the formation of corresponding nitriles 15 (Scheme 6).\(^2\) The active implementation of the CN group was achieved in this reaction by the use of Zn(CN)\(_2\). The advantage of this protocol was the suppression of poisoning of the catalyst, undesired nitrile product formation and decomposition.
Scheme 5. Palladium-catalyzed decarbonylative cyanation of amides.

Further, the same group extended the catalytic application in the intramolecular cyanation of aroyl nitriles 16 to corresponding aryl nitriles 17 via decarbonylation without using an external cyanide source. This strategy...
was effectively implemented by employing Ni(II) catalyst (10 mol%), assemblage of dctype there as ligand (20 mol%) as well as Mn as a reducing agent (2 equiv) in the decarbonylative cyanation of benzoyl nitrile derivatives to corresponding all nitriles are classified as aryl, heteroaryl, or alkenyl nitriles (Scheme 7).

Scheme 7. Intramolecular cyanation via decarbonylation catalyzed by nickel of benzoyl nitrile derivatives.

Scheme 8. Decarbonylative cyanation of acyl chlorides through Ni based catalytic system.
Wang and Nishihara's group developed an efficient protocol (Scheme 8) for the cyanation of acyl chlorides 19 (commercially available or in-situ formed) with TMSCN (trimethylsilyl cyanide) using the Ni-based catalytic system Ni(cod)$_2$ in 2019. Acyl chlorides have been prepared for the chlorination of carboxylic acids 18. In this transformation, various functional group substrates were well tolerated to produce corresponding aryl, alkyl and alkenyl nitrile products 20 with good to excellent yields under neutral and milder environments. Mechanistic studies revealed that oxidative addition of acyl chlorides takes place, in the presence of TMSCN, transmetalation happens before to the decarbonylation process. Finally, reductive elimination occurred to obtain the desired product. Herein, the authors reported that the role of PPh$_3$ was to boost the decarbonylation and reductive elimination steps.

4. Trifluoromethylation

Keaveney and Schoenebeck explored trifluoromethylation of aroyl fluorides 21 through decarbonylation by a Pd/Xantphos catalytic system to get trifluoromethyl arenes (ArCF$_3$) 22 (Scheme 9). Triethyl(trifluoromethyl)silane, TMSCF$_3$, was used as a trifluoromethylating agent. Several functional group substrates were effectively beared and provided good results. This newly developed methodology avoids the need for the addition of exogenous fluoride and adverse over-transmetalation steps by allowing Xantphos to act as an efficient catalyst. Also, the authors reported that Pd(II)-F is an important intermediate for introducing a variety of functionalities through selective and additive-free transmetalations. For effective decarbonylation, a high temperature of 170 °C was necessary to drive the transformation.

![Scheme 9. Trifluoromethylation through decarbonylation by Pd catalytic system.](image_url)
5. Difluoromethylation

A new strategy for the effective difluoromethylation of acyl chlorides 23 to corresponding difluoromethylated arenes 24 at room temperature through decarbonylation has been developed by Ritter et al. in 2018, rather than the other literature works, which required high temperatures and longer reaction times. This new synthetic route could be achieved using Pd(dba)$_2$ and the RhPhos catalytic system (Scheme 10). The reported method enabled the efficient difluoromethylation of excellent results across a wide variety of substrates. The phosphine ligand was shown to have a significant impact on the speed of reaction. Here bulky monodentate phosphines being vital for an effective transformation and also that the RuPhos ligated complex offered an open coordination site, ensuring rapid decarbonylation by accepting carbonyl ligand.

![Scheme 10. Decarbonylative difluoromethylation of acyl chlorides by palladium catalysis.]

6. Alkynylation

Chen et al. in 2018 developed a Pd catalyzed Sonogashira coupling type reaction that uses amides 25 and terminal alkynes 26 as coupling partners and resulted in a decarbonylative alkynylated product, i.e., internal
alkynes 27, through C-N bond activation, rather than the already published Ni/Cu catalyst system, which commenced only smoothly using silylacetylenes. But a new system of Pd(OAc)$_2$, Na$_2$CO$_3$, dppp, and dioxane made it easier to remove carbon from alkyl, aryl, and silyl terminal alkynes, and it worked well with a wide range of alkyl, aryl, and silyl terminal alkynes (Scheme 11). This confirmed its wide substrate tolerability and also ensured straightforward synthesis to produce diverse internal alkynes.

Scheme 11. Alkynylation of amides with terminal alkynes by decarbonylation catalysed by Pd.

Chen et al. $^{25}$ described Pd catalyzed Sonogashira type coupling reaction of carboxylic acids 28 with terminal alkynes 29 via direct decarbonylative strategy to give alkynylated products 30. The reported method was documented as a redox-neutral reaction which surmounts the usage of over stoichiometric oxidants thus avoiding the homocoupling of terminal alkynes. Under the appropriate reaction conditions as described in (Scheme 12). The synthesis was established to be applicable to a broad range of functional groups such as alkynes bearing electronic substituents like alkyl, phenyl, F, Cl, CF$_3$, CN, etc. as well as heterocyclic aromatic alkynes, aliphatic and conjugated alkynes are well sustained in this strategy. Furthermore, both electron deficient and donating benzoic acids as well as bioactive carboxylic acids underwent decarbonylation with terminal alkynes smoothly.
Scheme 12. Pd catalyzed Sonogashira type decarbonylative alkynylation of aryl acids with terminal alkynes.

7. Alkylation

In 2018, Nishihara et al.\textsuperscript{26} addressed the alkylation of aroyl fluorides \textbf{31} by decarbonylation when used in conjunction with a Lewis acid. A nickel catalyst can be used to create organoboranes (Scheme 13). The researchers used aroyl fluorides, which are thought to be quite chemically robust like aroyl chlorides that can be easily made from the carboxylic acids that make them up. The fluoronickel intermediate produced by Lewis-acidic trialkylboranes \textbf{32} is the product of oxidative addition, which results in decarbonylative alkylation \textbf{33}. When BF bonds are made, they speed up the thermodynamic process, which is important for making sure that aroyl fluorides are turned into aroyl halides exactly. This novel synthetic technique allows for the palladium-catalyzed ortho-C-H arylation is used to 1,2-bifunctionalize aromatic carboxylic acids.
Scheme 13. Ni catalyzed decarbonylative alkylation by organoboranes.

Newman and coworkers in 2018 $^{27}$ documented Pd mediated aryl esters 34 and alkyl boranes 35 cross-coupling leading to decarbonylative alkylated arene products 36 when dctype ligand was used (Scheme 14). Utilization as an N-heterocyclic carbene ligand resulted in a carbonyl retentive coupling product, which accounts for the reaction switchable selectivity. The Bidentate dctype ligand enabled the coordination site to be opened, requiring CO extrusion and resulting in a decarbonylated coupling product. Electronic substrates, heteroaryl esters, and aliphatic boranes were sustained well, resulting in the desired coupling product with appreciable yield.

In 2020, Nishihara and his colleagues $^{28}$ achieved decarbonylative Pd(acac)$_2$/DPPE catalyzed alkylation of acyl fluoride 37 with alkylboranes 38, resulting in C(sp$^2$)-C(sp$^3$) bond formation 39 (Scheme 15). DPPE is a hemilabile bidentate ligand was critical in suppressing unfavorable -hydride elimination. Even at extremely high temperatures, the decarbonylation process is capable of being carried out, Numerous functional groups were identified to stay strong and work.

Scheme 15. Alkylation with acyl fluorides through decarbonylation alkyl boranes facilitated by Pd.
Thioesters are flexible fundamental units they are used in organic synthesis quite often. For peptide linkage, Corey-Nicolaou macro lactonizations with native chemical grafting are used. While so many attempts have been undertaken to build innovative reactions using thioesters, their use in organic synthesis is prevalent especially in comparison toward other carboxylic acid derivatives. Herein, Han et al. in 2021 formulated a palladium(0)-catalyzed, ligand-promoted asymmetric dearomatization reaction of indole derivatives 40 to produce indolines 41 in high yields. Phosphine ligands play a key role in the thioesters decarbonylation and the succeeding asymmetric reductive Heck process. A plethora of functional groups were tolerated, resulting in moderate to better yields (Scheme 16).

Scheme 16. Asymmetric dearomatization via decarbonylation.

8. Alkenylation

Heck coupling is a highly effective process for the synthesis of alkenes that has extensively purposes for natural and manufactured chemicals, medicines, and functional material molecules. Researchers have observed their conversion in order to develop useful compounds. Instead, using them as the aryl source in Heck couplings would speed up the process of making high-efficiency alkenes a lot. In this work, Yu et al. in 2020 accomplished Palladium catalysis by decarbonylative alkenylation of aromatic carboxylic acids 42. Various benzoic acids, when used with functional groups attached to the terminal alkenes 43, led to higher yields of the internal alkenes 44 under the conditions (Scheme 17).
Scheme 17. Decarbonylative Alkene-carboxylic acid Heck coupling.

9. Conclusions

Because of the distinct benefits of carbonyl functionalities, chemists have lately devised a number of fresh and intriguing procedures that could not previously be produced using standard techniques. In this Minireview, we have attempted to highlight recent advances in the field of transition-metal-catalyzed decarbonylative coupling processes especially Pd and Ni that have effectively produced a series of carbonyl functional group replacements including decarbonylative alkylation, arylation, difluoromethylation, trifluoromethylation, alkenylation, alkynylation and cyanation reactions resulting C-C bond formation. This synthetic technique is hoped to open new avenues for organic synthesis. However, several intriguing but difficult challenges remain unexplored. It is still difficult to employ unactivated aliphatic aroyl derivatives in decarbonylative cross-coupling. High temperatures are often employed, constraining industrial uses. Nonetheless, the results represent a significant advancement in the field of functional group interconversion and broaden the repertory of synthetic approaches that may be addressed in critical stage functionalizations, as well as synthesis and retrosynthesis in particular.
Precatalysts now play a key part in the coupling reactions catalyzed by traditional palladium, but their growth was aided by a deeper knowledge of the mechanism of these reactions and the properties of the active species. Because the identity of the active species in many novel reactions is uncertain, precatalysts are reluctant to be produced until mechanistic uncertainties are resolved. Another issue is that most of the modern coupling reactions employ first transition metal catalysts, that were more prone to generate paramagnetic species. Mechanistic investigations of these systems are complex, necessitating more collaboration between modern synthetic and inorganic physical chemists with competence in fields including EPR spectroscopy.

In a similar vein, deciphering metallaphotoredox reactions is challenging and will demand collaboration amongst disciplines that have previously had little overlap. Addressing offcycle activities is another key aspect of constructing better catalysts. This encompasses both the activation of the precatalyst and the dissolution of the catalyst. Substantial advances in productivity can be made if these largely overlooked processes are fully understood. Technological advancements, like elevated research, could make great strides in cross-coupling and associated reactions.

References

   https://doi.org/10.1021/cr100346g
   https://doi.org/10.1007/3-540-45313-X
   https://doi.org/10.3762/bjoc.9.34
   https://doi.org/10.1039/C1CS15093F
   https://doi.org/10.1039/C2CS20312J
   https://doi.org/10.1007/s11426-012-4791-7
   https://doi.org/10.1039/C7CS0182G
   https://doi.org/10.1039/C1CS15109F
    https://doi.org/10.1021/acscatal.6b03277
    https://doi.org/10.1002/chem.201605012
    https://doi.org/10.1002/chem.201704670.
    https://doi.org/10.1038/s41586-018-0628-7
https://doi.org/10.1021/jacs.7b12865

https://doi.org/10.1002/anie.201811139

https://doi.org/10.1039/C9SC03169C

https://doi.org/10.1021/acs.orglett.0c02250

https://doi.org/10.1039/D1CC00202C

https://doi.org/10.1021/acs.orglett.7b01199

https://doi.org/10.1021/acs.orglett.7b01905

https://doi.org/10.1021/acs.orglett.9b02398

https://doi.org/10.1002/anie.201800644

https://doi.org/10.1002/ange.201811139

https://doi.org/10.1021/acs.orglett.8b00949

https://doi.org/10.1021/acs.orglett.1c00768

https://doi.org/10.1021/acsomega.8b02155

https://doi.org/10.1021/acsorganlett.8b01646

https://doi.org/10.1021/acs.orglett.0c00542

https://doi.org/10.1021/acs.orglett.0c03897

https://doi.org/10.1021/acs.orglett.0c02462
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