Transition Metal-Catalyzed Decarbonylative Cross Coupling Reactions - Concepts, Classifications and Applications

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Dedication ((optional))

Abstract: Transition metal-catalyzed decarbonylative cross-coupling reactions have emerged as a powerful alternative to conventional cross-coupling protocols due to the advantages associated with the use of carbonyl-containing functionalities as coupling electrophiles instead of commonly used organohalides or sulfates. A wide variety of novel transformations based on this concept have been successfully achieved, including decarbonylative carbon-carbon and carbon-heteroatom bond forming reactions. In this Review, we summarize the recent progress in this field and present a comprehensive overview of metal-catalyzed decarbonylative cross-couplings with carbonyl derivatives.

1. Introduction

Transition-metal-catalyzed cross-coupling reactions for the construction of carbon-carbon and carbon-heteroatom bonds enable the facile preparation of structurally diverse molecules essential for the development of modern pharmaceuticals and functional materials.^[1] The well-established synthetic methodologies by palladium catalysis have exerted an ubiquitous influence on the synthesis community and have been honored with the 2010 Nobel Prize in Chemistry. As judged by the wealth of literature reports in the past half-century, organohalides and sulfates have become the most conventionally employed coupling electrophiles in metal mediated or catalyzed transformations. However, their high-cost, accessibility, transformable nature, as well as the production of corrosive halogen and sulfur wastes are disadvantageous from both synthetic and environmental points of view.^[2] Therefore, it is highly desirable to further explore alternative cross-coupling counterparts with improved practicability and generality. In recent years, carbonyl functionalities (e.g. acyl chlorides, anhydrides, esters, amides, aldehydes, ketones) have shown their potential as alternatives to the conventionally used organohalides.^[3] Regarding the advantages of carbonyl compounds as coupling partners, these include low-cost, easy availability, the lack of halogenated waste as well as the potential for functional group interconversion. Importantly, modern chemical research has witnessed the development of acyl C-C and C-heteroatom bond activation and functionalization mediated by transition metals.^[4] In view of the mentioned reasons and based on the ubiquitous nature of carbonyl functionalities, decarbonylative processes provide an important surrogate for traditional methods (Scheme 1).

Scheme 1. Traditional metal-catalyzed cross-couplings versus newly-developed decarbonylative cross-couplings.

Recent years have witnessed an increasing interest in decarbonylative cross-coupling reactions using carbonyl functionalities as precursors. Although a detailed mechanistic understanding has not yet been fully achieved, chemists made great efforts towards performing elucidative theoretical and experimental studies.^[5] Combining the mechanistic aspects known to date, the following general mechanism can be proposed for the transition-metal-catalyzed decarbonylative cross-coupling of carbonyl derivatives (Scheme 2): initially, oxidative addition of the acyl C-X bond (X = Cl, O, N, H, C, S, or P) of aryl compounds to the low-valent metal (n) species gives an acyl metal (n+2) intermediate, which subsequently undergoes transmetalation. The following CO extrusion step results in an aryl metal (n+2) species and reductive elimination delivers the desired cross-coupling product while regenerating the active low-valent metal (n) species.

Scheme 2. Proposed general reaction mechanism for metal-catalyzed decarbonylative cross-coupling reactions.

It is noteworthy to mention that a series of carbonyl-retaining acyl cross-coupling reactions have also been developed via C(acyl)-X bond cleavage by transition metals, representing another intriguing class of reactions with carbonyl functionalities.^[6] In comparison with these well-established carbonyl-retaining transformations, decarbonylative cross-coupling reactions typically require relatively harsh conditions (> 130 °C) to release the carbonyl group in the form of carbon monoxide (Scheme 3).^[7] However, the occurrence of the CO

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extrusion event can also be dependent on the nature of both, the metal catalyst and the ligand employed.

Carbonyl-retaining cross-coupling

- relatively facile transformation
- mild reaction conditions
- ketone, ester and amide formation

Decarbonylative cross-coupling

VS

- unconventional cross-coupling
- harsh reaction conditions (> 130 °C)
- C-C and C-heteroatom bond formation

Scheme 3. Two types of cross-coupling reactions, carbonyl retaining and decarbonylative pathways.

In this review, we focus on the recent progress in metal-catalyzed decarbonylative cross-coupling reactions using different carbonyl-containing functionalities as coupling electrophiles. The use of acids as coupling partners, which results in decarboxylative reactions, will not be discussed. According to the reaction type, this review is organized into four main sections: 1) decarbonylative carbon-carbon bond forming reactions; 2) decarbonylative carbon-heteroatom bond forming reactions; 3) reductive decarbonylation; and 4) retro-hydrocarbonylation.

2. Carbon–Carbon Bond Forming Reactions

Carbon-carbon bond construction represents the basis of whole organic chemistry. Since the 1970s, transition-metal-catalyzed cross-coupling reactions have provided a straightforward route for the construction of carbon-carbon bonds and have been widely used in applications that range from complex natural product synthesis to drug discovery and manufacturing. Within the realm of transition-metal-catalyzed decarbonylative cross-coupling reactions, carbon-carbon bond formation with various aroyl compounds has been at mostly explored.

2.1. Suzuki-Miyaura-Type Reaction

In 2004, an interesting rhodium-catalyzed Suzuki-type decarbonylative cross-coupling of aromatic carboxylic anhydrides with arylboroxines was achieved by Gooßen and coworkers.^[8] This novel decarbonylative coupling process is distinguished by the use of $[\text{Rh}(\text{ethylene})_2\text{Cl}]_2/\text{KF}$ catalytic system with a broad range of substrates (Scheme 4), potentially opening up new perspectives for the use of carboxylic acid derivatives in biaryl synthesis. Notably, the use of boroxines as coupling nucleophiles proved to give the best yields, whereas the use of boronic acids, esters or borates gave unfavorable results.

Scheme 4. Rh-catalyzed decarbonylative cross-coupling of anhydrides with arylboroxines.

Later, Sames and coworkers reported a ruthenium-catalyzed decarbonylative arylation reaction of cyclic 2-amino esters, which allows the replacement of ester groups at sp^3 -carbon centers.^[9] In a decarbonylative fashion, pyrrolidine, piperidine and piperazine heterocycles bearing methyl ester functionalities could be coupled with aromatic and heteroaromatic boronic esters (Scheme 5). The utilization of a cyclic amidine group, which proved to be far superior to other commonly employed functionalities such as amides and carbamates, is crucial for success as it acts as a strong directing group for the ruthenium insertion. The proposed mechanistic hypothesis indicated that the catalytic cycle was initiated by chelation-assisted C(acyl)-O bond activation of ester group followed by decarbonylation and transmetalation of the respective intermediates to ultimately produce the α -arylated product while regenerating the active Ru species.

Scheme 5. Amidine-directed Ru-catalyzed decarbonylative arylation reaction of cyclic 2-amino esters with boronic esters.

In another interesting approach, a novel Rh-catalyzed decarbonylative cross-coupling of ethyl benzo[*h*]quinoline-10-carboxylate and organoboron compounds was further developed by Wang and coworkers.^[10] A wide variety of functional groups was tolerated in the reaction, and the desired products were obtained in good to excellent yields (Scheme 6).

The mechanism of the reaction was explained by DFT calculations, indicating that the oxidative addition of rhodium occurred through chelation-assisted C(acyl)-C(aryl) bond activation rather than C(acyl)-O bond activation, and that CuCl played a crucial role in the CO extrusion process.

Scheme 6. Rh-catalyzed decarbonylative coupling of ethyl carboxylate with arylboronic acids via chelation-assisted C-C bond activation.

In a significant contribution, Itami and Yamaguchi reported an inexpensive and user-friendly nickel-based catalytic system $[\text{Ni}(\text{OAc})_2/\text{P}(n\text{-Bu})_3]$ for the decarbonylative biaryl synthesis using carboxylic esters as coupling partners.^[7] A wide range of phenyl esters of aromatic carboxylic acids reacted with boronic acids to give biaryls in good to excellent yields (Scheme 7). Moreover, this newly developed methodology could be effectively applied to heteroaromatic and benzylic esters. A gram-scale coupling as well as a one-pot coupling protocol starting directly from carboxylic acids were also successfully performed in a decarbonylative fashion. Furthermore, theoretical calculations revealed that the crucial transmetalation step was accelerated by the addition of Na_2CO_3 as base, and the decarbonylation was supposed to be the rate-determining step under the optimized conditions.

Scheme 7. Ni-catalyzed decarbonylative organoboron cross-coupling of esters.

However, this well-developed $\text{Ni}^{(II)}/\text{P}(n\text{-Bu})_3$ catalytic system was found not to be applicable to 2-azinecarboxylates. To solve this issue, the group further developed a palladium-catalyzed decarbonylative coupling of phenyl 2-azinecarboxylates and arylboronic acids (Scheme 8).^[11] The process features a $\text{Pd}^{(II)}/\text{dcype}$ catalytic system for the acyl C-O bond activation followed by transmetalation, decarbonylation, and reductive elimination.

Scheme 8. Pd-catalyzed decarbonylative coupling of azinecarboxylates with arylboronic acids.

Following the recent breakthrough on acyl C-N bond activation and functionalization by nickel catalysis,^[4b,4c] an intriguing decarbonylative cross-coupling of amides with boronic acids was reported by Szostak and coworkers.^[12] It is worth noting that the utilization of a sterically distorted amide was the key to success for this Suzuki-Miyaura type cross-coupling, resulting in 83% yield of the desired product, while the use of less distorted amides gave rather unsatisfactory results (Scheme 9). In addition, a cost-effective and air-stable $\text{Ni}^{(II)}$ precatalyst was employed. Furthermore, the protocol is characterized by a broad substrate scope with regard to both amide and boronic acid components, and even shows high tolerance towards water.

Scheme 9. Ni-catalyzed decarbonylative biaryl synthesis of amides with arylboronic acids.

The introduction of alkyl groups by transition metal catalysis has always been very difficult due to the competing β -hydride elimination. As a part of research interest aimed at promoting alkylation protocols via C–O bond activation and functionalization,^[13] Rueping group demonstrated the possibility to achieve a Suzuki–Miyaura type decarbonylative alkylation reaction of carboxylic acid esters.^[14] With 10 mol% $\text{Ni}(\text{cod})_2$ as catalyst and 20 mol% *dcype* as the supporting ligand, a wide variety of aromatic and heteroaromatic esters were coupled with structurally diverse *B*-alkyl-9-BBNs possessing β -hydrogens in good to moderate yields (Scheme 10). The utility of this protocol has been demonstrated by the broad functional group tolerance and application to the synthesis of bioactive compounds. At the same time, the authors also demonstrated that switching the ligand from *dcype* to P^nBu_3 favors the ketone formation rather than decarbonylative coupling.^[14]

Scheme 10. Ni-catalyzed decarbonylative alkylation reaction of esters with *B*-alkyl-9-BBNs.

2.2. Negishi-Type Reaction

Organozinc compounds have been considered as very useful and versatile reagents for a broad variety of transformations in organic synthesis owing to their straightforward preparation, high reactivity/selectivity and excellent functional group tolerance. In 2003, Rovis group presented a stoichiometric nickel-mediated decarbonylative cross-coupling of cyclic *meso*-anhydrides with diarylzinc compounds, which constitutes an extraordinary example of $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling that generates stereochemistry.^[15] As shown in Scheme 11, a wide range of cyclic anhydrides successfully underwent the decarbonylative ring-opening reaction with good reactivity. Interestingly, the authors suggested that two different ligands, *dppb* and *neocuproine*, were both necessary for the formation of the desired product as explained by the following mechanistic scheme (Scheme 11). Oxidative addition of $\text{Ni}^{(0)}/\text{neocuproine}$ species into the acyl C–O bond of anhydride gives an acyl $\text{Ni}^{(II)}$ intermediate, which subsequently undergoes CO migration in a reversible manner. At this stage, a second $\text{Ni}^{(0)}/\text{dppb}$ complex with a much greater affinity for CO (more electron-rich) could permanently remove CO from the metal center. At last, the

transmetalation by diphenylzinc with the following reductive elimination provides the final coupling product.

Scheme 11. Stoichiometric Ni-mediated decarbonylative cross-coupling of cyclic anhydrides with organozinc compounds and its proposed mechanism.

A similar strategy was then extended to a stoichiometric nickel-mediated decarbonylative coupling of phthalimide derivatives with diorganozinc reagents by the Johnson group.^[16] As shown in Scheme 12a, a variety of *ortho*-substituted benzamides were efficiently produced via a decarbonylative process with excellent tolerance of diverse functionalities including alkyl, aryl, and heteroatom-containing substituents.

Scheme 12. a) Stoichiometric Ni-mediated decarbonylative cross-coupling of phthalimides with organozinc compounds; b) Catalytic decarbonylative cross-coupling of phthalimides with organozinc compounds.

In order to achieve the catalytic decarbonylative coupling of phthalimides with diorganozinc reagents, the same group recently reported a modified protocol by introducing an electron-deficient group (Ts, OH, electron-deficient aromatics, etc.) onto the phthalimide nitrogen atom (Scheme 12b).^[17]

Recently, Rueping and colleagues developed a Negishi-type decarbonylative alkylation of carboxylic esters by nickel catalysis.^[18] With the use of 10 mol% Ni(cod)₂ as catalyst and 10 mol% dcype as ligand, this protocol proceeded smoothly with easily prepared alkylzinc bromides as nucleophilic reagents and was characterized by an excellent functional group tolerance with regard to both coupling partners (Scheme 13). The authors also discovered that the unique catalytic system Ni⁽⁰⁾/dcype, allows the selective introduction of alkyl groups to the carboxylic acid component via decarbonylative acyl C-O bond cleavage or phenol component via aryl C-O bond cleavage.

Scheme 13. Ni-catalyzed decarbonylative alkylation reaction of carboxylic esters with organozinc compounds.

2.3. Mizoroki-Heck-Type Reaction

Mizoroki-Heck cross-coupling has found extensive application in transformations that do not require stoichiometric amounts of organometallic reagents for the desired carbon-carbon bond formation, which is a major advantage compared with other cross-coupling procedures. As early as in the late 1970s, chemists conducted investigations on the Ni- or Pd-catalyzed Mizoroki-Heck reaction of aryl chlorides with methyl acrylate, and observed the formation of decarbonylative coupling product.^[19] Later on, Spencer and Miura have independently extended the Mizoroki-Heck-type decarbonylative methodology with various aryl chlorides and olefins to palladium and rhodium catalysis.^[20]

In 1998, de Vries and coworkers developed a Heck-type decarbonylative olefination of anhydrides with terminal and internal alkenes.^[21] Notably, the loading of palladium^(II) chloride catalyst can be reduced to 0.25 mol%, and ligands are not required in this protocol (Scheme 14). Anhydrides bearing a heterocycle as well as 1,2-disubstituted olefins also successfully underwent the reaction with good *E*-selectivity.

Scheme 14. Pd-catalyzed decarbonylative Heck olefination of anhydrides.

The first ester to alkene interconversion via palladium-catalyzed Heck-type decarbonylative reaction was reported by Gooßen and coworkers in 2002.^[22] *Para*-nitrophenyl ester was selected as the most reactive coupling partner after screening various ester protecting groups. With the optimized PdCl₂/LiCl catalytic system, a variety of aromatic and heteroaromatic *p*-nitrophenyl esters could be converted into structurally diverse olefins in good to moderate yields. Two years later, the same group further developed the concept by demonstrating that enol esters could be utilized as precursors under base-free conditions (Scheme 15).^[23] In contrast to the traditional Mizoroki-Heck reactions, this method only produced volatile, flammable by-products (acetone and CO) instead of waste salts. Importantly, the regioselectivity of these two methods was nicely illustrated by the fact that linear coupling products were favorably formed, rather than the branched ones.

*Numbers in the parentheses refer to the relative amounts of 1,2- and 1,1-substituted vinyl arenes which determined by gas chromatography.

Scheme 15. Pd-catalyzed decarbonylative Heck olefination of enol esters.

In 2015, the Szostak group developed the first palladium-catalyzed decarbonylative Heck olefination of amides.^[24] Notably, the utilization of the highly reactive *N*-glutarimide amides was the key to success. After thoroughly examining the reaction conditions, the authors obtained the best result when employing palladium^(II) chloride as catalyst and lithium bromide as additive (Scheme 16). A wide range of aryl, heteroaryl and alkenyl *N*-glutarimide amides could be efficiently reacted with diverse olefins to give the desired products in good yields (65–94%) as well as excellent stereoselectivity (*E/Z* > 98/2 in all cases) and regioselectivity (linear product favored). The same group recently further demonstrated that *N*-acylsaccharins are also applicable in the Pd-catalyzed decarbonylative Heck reactions.^[25]

Scheme 16. Pd-catalyzed decarbonylative Heck olefination of amides.

2.4. Sonogashira-Type Reaction

Alkynes are recurring structural motifs in a variety of natural products, bioactive molecules and functional materials. Among the established methods for the synthesis of substituted alkynes, the transition-metal-catalyzed Sonogashira coupling has proven to be one of the most popular and efficient procedures.

In 2016, Itami and Yamaguchi group reported a palladium-catalyzed alkylation reaction of aromatic esters with terminal alkynes in a decarbonylative manner.^[26] The transformation is distinguished by its wide substrate scope with respect to the electrophilic partner, including aromatic and heteroaromatic substituted ester substrates (Scheme 17). There is no doubt that this methodology represented an impressive advance in this field, however, the nucleophilic reagent scope of this Pd-catalyzed Sonogashira-type reaction was to some extent restricted to terminal bulky silylacetylenes. The use of other alkynes, such as arylacetylenes and alkylacetylenes resulted in poor yields.

Scheme 17. Pd-catalyzed decarbonylative alkylation reaction of esters with terminal alkynes.

Recently, Rueping and coworkers achieved a nickel-catalyzed amide to alkyne interconversion via a decarbonylative pathway.^[27] A variety of *N*-glutarimide amides featuring aromatic and heteroaromatic motifs are tolerated in this protocol (Scheme 18). The resulting silylated alkynes might undergo

protodesilylation to afford terminal alkynes which hold great potential for further transformations, setting the basis for designing iterative cross-coupling procedures as well as further derivatization techniques via C(sp)-Si cleavage.

Scheme 18. Ni-catalyzed decarbonylative alkylation reaction of amides with terminal alkynes.

2.5. Decarbonylative C-H Coupling

In 2008, Yu and coworkers developed a ligand-free rhodium catalytic system for the decarbonylative C-H functionalization of benzo[*h*]quinolines or 2-aryl pyridines with acyl chlorides.^[28] This protocol is distinguished by the use of 5 mol% of [Rh(cod)₂Cl]₂ and is applicable to a broad range of substrates (Scheme 19). Later on, new transformations using the same strategy were gradually developed and expanded to cinnamoyl chlorides,^[29] anhydrides^[30] and aldehydes.^[31]

Scheme 19. Rh-catalyzed decarbonylative cross-coupling of acyl chlorides with active C-H nucleophiles.

In 2012, Itami's group reported the first nickel-catalyzed decarbonylative C-H biaryl coupling of aryl esters with azoles.^[32] In this work, a selective decarbonylative C-H coupling occurs in the presence of Ni(cod)₂ and dcypt. A wide range of heteroaromatic esters could be reacted with (benz)oxazoles and thiazoles under the optimized conditions to give the biheteroaryl

products in good to excellent yields (Scheme 20). Aromatic esters, such as phenyl 2-naphthoate, could also be coupled with azole compounds under the reaction conditions. In addition to these preliminary results, the authors successfully applied the newly developed protocol to a convergent formal synthesis of the antibacterial natural product muscoride A.

Scheme 20. Ni-catalyzed decarbonylative C-H biaryl coupling of esters with azoles.

2.6. Cyanation Reaction

A new palladium-catalyzed decarbonylative cyanation reaction of carboxylic amides was recently developed by Szostak and coworkers.^[33] A key challenge in the cyanation protocols is the risk of hazardous hydrogen cyanide gas generation. To circumvent this, the authors applied zinc cyanide, which is commonly recognized as a cheap and harmless cyanating agent. The new amide to nitrile interconversion is characterized by its high efficiency and excellent functional group tolerance, providing a practical and versatile approach to a wide range of aryl, heteroaryl, and alkenyl nitriles (Scheme 21).

Scheme 21. Pd-catalyzed decarbonylative cyanation reaction of amides with zinc cyanide.

Simultaneously, Rueping's group reported a similar decarbonylative cyanation reaction of carboxylic esters and amides by using a Ni⁽⁰⁾/dcype catalytic system.^[34] This newly developed protocol successfully suppressed the undesired acyl cyanide formation, nitrile product decomposition, and catalyst

poisoning process and is characterized by its high efficiency, chemoselectivity and excellent functional group tolerance (Scheme 22).

Scheme 22. Ni-catalyzed decarbonylative cyanation reaction of esters and amides with zinc cyanide.

Continuing their research, Rueping and coworkers then explored an external-cyanide-free and directing-group-free decarbonylative cyanation of benzoyl cyanide derivatives.^[34] With the utilization of 10 mol% nickel^(II) catalyst, 20 mol% dcype as ligand, and 2.0 equivalents of manganese as reducing agent a wide variety of acyl cyanides could be transferred into the corresponding aryl-, heteroaryl-, and alkenyl-nitriles by intramolecular decarbonylation and cyanation (Scheme 23).

Scheme 23. Ni-catalyzed intramolecular decarbonylative cyanation reaction of aryl cyanides.

2.7. Intramolecular Decarbonylation of Ketones

While the synthetic methods presented so far have involved transition-metal-catalyzed acyl carbon-heteroatom bond cleavage prior to decarbonylation, new transformations via decarbonylative carbon-carbon bond cleavage of ketones would be of interest.^[4d] In 1994, Murakami reported a pioneering work on rhodium-catalyzed decarbonylation of cyclic ketones via selective C-C bond cleavage.^[35] With the utilization of a high loading of a Cp* rhodium complex, Brookhart observed a unique decarbonylation process of simple biaryl ketones to achieve the corresponding biaryls.^[36]

Based on these developments, Shi and coworkers reported an efficient rhodium-catalyzed decarbonylation process via double C-C bond cleavage of ketones.^[37] With the assistance of 2-

pyridine as a directing group for the oxidative addition of rhodium^(I), a large range of substrates was successfully applied and various aryl, alkenyl, and even alkyl moieties were compatible (Scheme 24).

Scheme 24. Pyridine-directed Rh-catalyzed decarbonylation of ketones.

Following the successful CO extrusion research, Dong and coworkers realized an elegant decarbonylation of diyones to produce 1,3-diynes via Rh-catalyzed carbon-carbon activation.^[38] The same group later extended the methodology to the formation of disubstituted alkynes from monoyones.^[39] With the use of a Rh/Xantphos catalytic system, the scope and limitations were thoroughly investigated, and a broad range of functionalities including heterocycles were compatible under the developed conditions (Scheme 25). Furthermore, mechanistic explorations by applying DFT calculations indicated that the reaction proceeds via Rh-catalyzed C(acyl)-C(alkyne) bond activation, rather than C(acyl)-C(aryl) bond cleavage.

Scheme 25. Rh-catalyzed decarbonylation of conjugated ynone.

While the synthetic methods presented so far have successfully achieved the activation of highly inert carbon-carbon bonds, drawbacks have also been found in that noble rhodium metal species had to be utilized and substrates were restricted to strained ketones or ketones with specific directing groups.

Recently Chatani and Tobisu made a significant contribution in developing a stoichiometric nickel-mediated reaction for the decarbonylation of simple aromatic ketones that proceeds via unstrained C-C bond cleavage (Scheme 26).^[40] This protocol represents the first earth-abundant nickel-mediated decarbonylation of unstrained ketones.

Scheme 26. Ni-catalyzed decarbonylation of unstrained simple ketones.

2.8. Ring-Opening and Alkyne/Alkene Insertion

In 2008, Kurahashi and Matsubara reported a nickel-catalyzed decarbonylative ring-opening/alkyne insertion reaction of cyclic anhydrides.^[41] This coupling reaction, accomplished with a $\text{Ni}^{(0)}/\text{PMe}_3$ catalyst as well as a Lewis acid (ZnCl_2), exhibits high reactivity and broad substrate scope with respect to both cyclic anhydrides and alkynes. Diverse isocoumarins and α -pyrones could be synthesized in good yields and regioselectivities under the reaction conditions (Scheme 27).

Scheme 27. Ni-catalyzed decarbonylative ring-opening/alkyne insertion of cyclic anhydride.

A plausible reaction pathway to account for the formation of isocoumarins is outlined in Scheme 28. The catalytic cycle is supposed to consist of an oxidative addition of the anhydride C(acyl)-O bond to nickel, followed by decarbonylation and coordination of the alkyne. The favored intermediate could be achieved when the steric repulsive interaction between the bulkier R_L group and the PMe_3 ligand on the nickel is minimal. Following the alkyne insertion into the $\text{C}(\text{sp}^2)\text{-Ni}$ bond, reductive

elimination proceeds from the resulting 7-membered ring complex to produce the corresponding isocoumarin and $\text{Ni}^{(0)}$.

Scheme 28. Proposed reaction mechanism for Ni-catalyzed decarbonylative ring-opening/alkyne insertion of cyclic anhydride.

Another approach for the synthesis of isocoumarins and α -pyrones via Ru-catalyzed decarbonylative addition reaction of anhydrides with alkynes was reported by Gogoi and Boruah.^[42] They revealed that $[\text{RuCl}_2(p\text{-cymene})_2]$ (2.5 mol%) alone can efficiently catalyze the reaction in a similar ring-opening/alkyne insertion manner. An interesting decarbonylative ring-opening/alkyne insertion reaction of phthalimides by nickel catalysis was also reported by Kurahashi and Matsubara.^[43] The reaction proceeded through C(acyl)-N bond cleavage followed by decarbonylation and alkyne insertion. Notably, investigation of the substituent effects on the nitrogen atom revealed that phthalimide substrate requires an electron-deficient group, such as pyridine, pyrrole, pyrazine, and pentafluorobenzene. Similarly to the above isocoumarin synthesis, this cycloaddition reaction successfully proceeded in a regioselective fashion when unsymmetrical alkynes were employed (Scheme 29).

Scheme 29. Ni-catalyzed decarbonylative ring-opening/alkyne insertion of phthalimides.

In 2010, Kurahashi and Matsubara reported the first example of a decarbonylative cycloaddition of phthalimides with alkenes

using nickel catalysis (Scheme 30).^[44] Under the reaction conditions, electron-deficient *N*-arylphthalimides were found to react with 1,3-dienes. Moreover, the presented cycloadditions displayed excellent regio- and chemo-selectivity in the presence of functional groups, which may open the way for a facile divergent synthesis of functionalized isoquinolones.

Scheme 30. Ni-catalyzed decarbonylative cycloaddition of phthalimides with 1,3-dienes.

3. Carbon-Heteroatom Bond Forming Reactions

While decarbonylative carbon-carbon bond forming reactions of carboxylic acid derivatives have been well established, carbon-heteroatom bond formations also attracted increasing attention as carbon-heteroatom bond containing compounds are widely utilized. For example, natural products, pharmaceuticals and conductive polymers contain amine C-N or ether C-O bonds. Ligands exhibiting C-N or C-P bonds are used in the organometallic catalysis and coordination chemistry. C-B, C-Si or C-Sn bonds-containing functionalities are widely recognized as valuable synthetic intermediates. Taking into consideration their widespread use, chemists are challenged to implement new and sustainable protocols for carbon-heteroatom bond formations.

3.1. C-O Bond Formation

In 2017, Itami, Yamaguchi and coworkers developed the first decarbonylative ether synthesis from carboxylic acid esters by applying nickel or palladium catalysis.^[45] With the utilization of 5 mol% of either $\text{Ni}(\text{cod})_2$ or $\text{Pd}(\text{OAc})_2$ as catalyst, a wide variety of aryl azinecarboxylates could be transferred into the corresponding 2-arenoxyazines via intramolecular decarbonylation and etherification (Scheme 31). Notably, the supporting ligands, dcypt and dcpt, are critical for success. Additional alcohol nucleophiles are not needed for this protocol. The decarbonylative etherification method can also be applied on gram-scale. Although this discovery constitutes a step forward, the substrate scope is limited to 2-azinecarboxylates.

As a plausible reason the author proposed a faster reductive elimination step for 2-azinecarboxylates compared to other carboxylates.

Scheme 31. Decarbonylative diaryl ether synthesis by Pd and Ni catalysis.

3.2. C–N Bond Formation

The first catalytic decarbonylative amination protocol was recently developed by Rueping's group,^[46] which allows the direct conversion of aroyl compounds into the corresponding amines and represents a good alternative to classical Buchwald-Hartwig aminations which make use of aryl halides. The reaction with aromatic esters and commercially available benzophenone imine was successfully performed using 10 mol% Ni^(II) catalyst and 20 mol% dcyte ligand, giving the desired primary amines in good to moderate yields upon acidic hydrolysis (Scheme 32). Moreover, the methodology could be effectively extended to the synthesis of heteroaromatic aniline derivatives. It is noteworthy that the corresponding secondary amines could also be obtained by reductive hydrogenation (work up by sodium borohydride) of the ketimine intermediate instead of acidic hydrolysis.

Scheme 32. Ni-catalyzed decarbonylative amination of esters.

The synthetic concept could also be extended to *N*-glutaramide amide as coupling electrophile.^[46,47] A simple modification of the reaction conditions by exchanging the supporting ligand from dcyte to dppe allowed the decarbonylative amination reaction of amides with benzophenone imine to proceed. These initial results demonstrated the potential of this protocol and the use of versatile carbonyl functionalities as coupling partners (Scheme 33).

Scheme 33. Ni-catalyzed decarbonylative amination of amides.

In another interesting approach, an intramolecular decarbonylative amination reaction of amides was further achieved by Rueping and coworkers.^[48] The unconventional amination process is distinguished by the use of an inexpensive Ni^(II) catalyst and *N*-heterocyclic carbene ligand with high efficiency and perfect functional group tolerance, allowing the amide to amine interconversion in the absence of reducing reagents and additional amine source (Scheme 34). Similar to Itami and Yamaguchi's results,^[45] this protocol indicated that 2-azinecarboxamides were more effective coupling electrophiles as compared to other amides.

Scheme 34. Ni-catalyzed intramolecular decarbonylative amination of amides.

3.3. C–Si Bond Formation

Taking into consideration that organosilicon compounds constitute a crucial class of intermediates in the synthesis of many pharmaceuticals and natural products, chemists are highly motivated to search for novel and effective routes for their synthesis.

As early as in the beginning of the 1990s, Krafft and Rich observed the formation of arylsilanes by palladium-catalyzed decarbonylative coupling of acyl chlorides with disilanes.^[49] Later, Tsuji and coworkers reported a palladium-catalyzed 1,4-carbosilylation reaction via three-component coupling of acyl chlorides, disilanes, and 1,3-dienes.^[50] A naked Pd⁽⁰⁾ complex, Pd(dba)₂ without donating ligand, was selected as the catalyst and showed high catalytic activity (Scheme 35). The reaction proceeds with high regio- and stereoselectivity to afford various *E*-allylic silanes as the main products. A bulky acyl chloride such as adamantane-1-carbonyl chloride did not undergo the decarbonylation but afforded allylic silanes containing the carbonyl functionality.

Scheme 35. Synthesis of allylic silanes via Pd-catalyzed 1,4-carbosilylation reaction.

A possible mechanism for the palladium-catalyzed 1,4-carbosilylation reaction was proposed by the authors, as shown in Scheme 36.

Scheme 36. Proposed reaction mechanism for Pd-catalyzed 1,4-carbosilylation reaction.

In analogy to previous literature reports, the elementary steps involve oxidative addition of Pd⁽⁰⁾ to C(acyl)-Cl bond followed by decarbonylation and η^3 -coordination to provide η^3 -allylchloropalladium^(II) intermediate. Subsequent transmetalation of disilane and reductive elimination releases the allylic silane product and regenerates the active Pd⁽⁰⁾ species.

Given the need to develop new and more sustainable procedures for the formation of C–Si bonds, Rueping and coworkers decided to develop a metal-catalyzed decarbonylative silylation starting from cheap and readily available carboxylic esters as coupling partners. In 2016 the group reported the first combined nickel and copper catalyzed silylation reaction by employing silylboranes.^[51] This new ester to silane interconversion is characterized by its efficiency and good functional group tolerance, providing a practical and versatile approach to a wide range of aromatic and heteroaromatic silanes (Scheme 37). Regarding the mechanistic aspects, a copper silane complex that is *in situ* generated from copper and silylborane efficiently facilitates the crucial transmetalation step. In a similar approach, Shi and coworkers also developed a nickel-catalyzed decarbonylative silylation reaction with silylborane compound as coupling partner, where a bidentate phosphine ligand (dcype) with catalytic Ni⁽⁰⁾ species was utilized.^[52]

Scheme 37. Ni-catalyzed decarbonylative silylation reaction of esters.

Based on these developments, Rueping and coworkers recently developed a Ni-catalyzed decarbonylative silylation reaction of amides.^[47] In the presence of copper^(II) fluoride as co-catalyst, a wide range of *N*-glutarimide amides successfully underwent the reaction to generate aryl and heteroaryl silanes exhibiting various functional moieties such as -F, -OMe, and -CO₂Me (Scheme 38).

Scheme 38. Ni-catalyzed decarbonylative borylation of amides.

3.4. C–B Bond Formation

Organoboron compounds are generally considered as valuable synthetic building blocks in modern organic synthesis. The introduction of a boron group via nickel-catalyzed decarbonylative cross-coupling of esters was recently developed by Rueping's group.^[53] This protocol provides a new possibility to cleave a stable ester group while forming a versatile boron derived entity. Functional groups, such as methoxy, amine, fluoride, trifluoromethyl, dioxole, ketone, methyl ester and amide, were perfectly tolerated under the reaction conditions (Scheme 39). Interestingly, the previous borylation events through C-OMe, C-F and C-NCOR cleavage by nickel catalysis^[54] did not compete with this decarbonylative borylation reaction. Identical reaction conditions were also successfully applied to α,β -unsaturated esters and unactivated aliphatic esters.

Scheme 39. Ni-catalyzed decarbonylative borylation reaction of esters.

At the same time a nickel/*N*-heterocyclic carbene catalytic system was established for the decarbonylative borylation of amides by Shi and coworkers.^[55] Employing $B_2(nep)_2$ [bis(neopentyl glycolato)diboron] as an efficient borylating agent, the authors successfully transformed a series of *N*-Boc amides into arylboronate esters, setting the basis for late-stage functionalization of amide groups in complex molecules. This transformation also allows access to alkenyl and alkyl boronate esters with good reactivity (Scheme 40).

Scheme 40. Ni-catalyzed decarbonylative borylation of amides.

In addition, relevant mechanistic studies were carried out by the authors (Scheme 41). Intriguingly, the treatment of amide **A** with

stoichiometric $Ni^{(0)}$ catalyst and NHC ligand resulted in the formation of acylnickel^(II) species **B**. Furthermore, complex **B** undergoes decarbonylation to produce the arylnickel^(II) species **C** in full conversion by simply raising the reaction temperature to 50 °C. Both nickel complexes (**B** and **C**) could be isolated and their structures were confirmed by NMR and X-ray analysis. Upon treatment with $B_2(nep)_2$, arylnickel^(II) species **C** can be converted into the corresponding arylboronate **D** at 60 °C in 82% yield in the presence of K_3PO_4 . Overall, these mechanistic experiments and two well-characterized nickel intermediates nicely provided evidence for the ligand-promoted C(acyl)-N bond insertion and the subsequent decarbonylation process.

Scheme 41. Decarbonylative stoichiometric reaction of amides with $Ni(cod)_2$ and ICy HCl ligand.

Thioesters are widely recognized as an important class of carboxylic acid derivatives due to the highly chemoselective cleavage of C(acyl)-S bonds via oxidative addition to a low-valent transition metal. For example, Niwa and Hosoya recently developed a mild Rh-catalyzed borylation of aromatic thioesters (Scheme 42).^[56]

Scheme 42. Rh-catalyzed decarbonylative borylation of thioesters.

Compared to the previously reported decarbonylative borylation reactions by Rueping and Shi, this newly developed transformation enables a two-step borylation reaction starting from aromatic carboxylic acids. The reaction proceeds at significantly lower temperature (80 °C). Furthermore,

mechanistic studies indicated that the addition of KOAc was crucial in the catalytic process in that it contributed to the regeneration of the rhodium catalyst.

3.5. C–P Bond Formation

Organophosphorous compounds are not only recognized as essential supporting ligands in organic synthesis and catalysis, but have also found widespread applications in medicinal chemistry and material synthesis. Thus, new synthetic routes towards organophosphorous compounds are always of interest. In 2017, Wang and coworkers developed the first decarbonylative carbon-phosphorus bond formation by employing a nickel-catalyzed intramolecular transformation of acylphosphines which can be readily prepared from carboxylic acid chlorides and phosphines (Scheme 43).^[57] The authors showed that a carboxyl group can serve as an important surrogate for the commonly used halides or triflates. The transformation is distinguished by its generality, accommodating aromatic, heteroaromatic, and even aliphatic acylphosphines in the presence of various functional groups. Regarding the mechanism, an acyl C–P bond insertion by the Ni⁽⁰⁾ species and a following CO extrusion were proposed.

Scheme 43. Ni-catalyzed intramolecular decarbonylation of acylphosphines.

Very recently, the Szostak group developed a new Hirao-type cross-coupling of *N*-glutarimide amides and dialkyl phosphites in a decarbonylative fashion using palladium or nickel catalysis.^[58] The present method constitutes the first example of transition-metal catalyzed generation of C–P bonds from amides. The reaction with aromatic *N*-glutarimide amides and phosphites was successfully performed using either Pd^(II)/dppb catalyst, or Ni(dppp)Cl₂, giving the desired aryl phosphonates in good to moderate yields (Scheme 44). Mechanistic studies suggested an oxidative addition / transmetalation / decarbonylation / reductive elimination pathway, in which transmetalation proceeds prior to decarbonylation under both Pd and Ni catalytic conditions.

3.6. C–S Bond Formation

In an interesting approach, Rueping's group recently developed a nickel-catalyzed decarbonylative thiolation reaction of esters.^[59] Optimal reaction conditions for the C–S bond formation were realized by the utilization of nickel^(II) chloride as catalyst and

dppp as ligand. Sodium carbonate proved to be the most effective base. Despite the high temperature needed, a wide range of aryl-, heteroaryl-, and alkenyl-esters with various functional groups including ketones, fluorides, and trifluoromethyl groups were tolerated in this transformations. The protocol is also applicable to structural diverse amides as coupling electrophiles by replacing the base with trisodium phosphate (Scheme 45a). Furthermore, based on previous studies by Yamamoto and Wenkert,^[60] the same group later demonstrated the possibility to achieve a Ni-catalyzed intramolecular decarbonylation of thioesters (Scheme 45b).

Scheme 44. Ni-catalyzed intramolecular decarbonylation of acylphosphines.

Scheme 45. Ni-catalyzed decarbonylative thiolation of esters and amides.

3.7. C–Sn Bond Formation

It is highly desirable to develop new and efficient approaches for the formation of C–Sn bonds as organotin compounds are valuable intermediates and building blocks in the synthetic chemistry. As early as in 2000, when Shirakawa and Hiyama conducted research on nickel-catalyzed stannylation reaction, they found that phenyltin compound can be achieved via decarbonylation of acylstannane (Scheme 46).^[61]

Scheme 46. Ni-catalyzed intramolecular decarbonylation of acylstannane.

Recently, Rueping's group developed the first Ni-catalyzed decarbonylative stannylation reaction using carboxylic acid esters. Specifically the highly-inert methyl esters were considered as coupling partners together with a silylstannane reagent.^[62] The transformation is distinguished by its high reactivity and wide substrate scope, including the coupling of aryl and heteroaryl substrates, setting the basis for further derivatization via C–Sn cleavage (Scheme 47).

Scheme 47. Ni-catalyzed decarbonylative stannylation of esters.

4. Reductive Decarbonylation

The transition metal catalyzed aroyl-group-defunctionalization of readily available carboxylic acid derivatives was recognized as one of the most important transformations in synthetic chemistry. Recently, significant advances have been achieved to enable the removal of carbonyl functionalities, which could be useful for the late-stage modification of complex molecules in that carbonyl groups are initially used as directing groups for *ortho*-lithiation or C–H functionalization.

In 2017, Maiti and coworkers reported a Ni-catalyzed reductive deamidation reaction.^[63] With Ni(cod)₂ as catalyst, EtPPh₂ as ligand and tetramethyldisiloxane (TMDSO) as hydride source, a reductive deamidation of planar and non-distorted amides was successfully achieved with formation of the corresponding hydrocarbons (Scheme 48). Although the reaction scope seems to be restricted to π -extended aromatic

amide derivatives, this methodology still stands for an important advance in the area of decarbonylation.

Scheme 48. Ni-catalyzed reductive deamidation of planar amides.

Later, Rueping's group reported a nickel-catalyzed reductive cleavage of ester and amide groups using the cheap, nontoxic and air-stable polymethylhydrosiloxane (PMHS) as a reducing agent.^[64] After screening various parameters, Ni(II)/dcype was selected as the most effective catalytic system. While the reductive defunctionalization of various aromatic esters and amides invariably resulted in good yields of the corresponding arenes, the use of heterocyclic frameworks was also possible (Scheme 49). In addition, a scale-up experiment and a synthetic application based on the use of a removable carbonyl directing group highlighted the usefulness of this protocol.

Scheme 49. Ni-catalyzed reductive decarbonylation of esters and amides.

5. Retro-Hydrocarbonylation

The retro-hydrocarbonylation reaction is an intriguing class of decarbonylative transformations. In 2015, Dong reported an elegant example of rhodium-catalyzed retro-hydroformylation of aliphatic aldehydes en-route to structurally diverse olefins.^[65] The authors found that a Rh(Xantphos)(benzoate) catalyst could trigger C(acyl)–C bond cleavage to generate olefins by selective activation of the aldehyde C–H bond (Scheme 50). This protocol

proved to be applicable to complex molecules synthesis and was used to achieve a three-step synthesis of (+)-yohimbenone. In the same year, a similar transformation was achieved with an iridium complex by Nozaki and colleagues.^[66]

Scheme 50. Rh-catalyzed retro-hydroformylation of aliphatic aldehydes.

The retro-hydrocarbonylation strategy has also contributed to the perception that aliphatic amides can be successfully employed to achieve olefins in a decarbonylative fashion.

Scheme 51. Ni-catalyzed retro-hydroamidocarbonylation of aliphatic amides.

Recently, the group of Shi established an interesting Ni/NHC-catalytic system for retro-hydroamidocarbonylation of aliphatic amides to olefins.^[67] Besides the advantage to realize the acyl C-N bond insertion, the authors also developed a powerful synthetic tool for obtaining olefins from a wide range of readily available amides (Scheme 51).

5. Conclusion and Outlook

Owing to the unique advantages of carbonyl functionalities, chemists have recently developed a series of novel exciting protocols that have not been achieved with traditional methods before. In this Review, we have tried to emphasize the recent progress in the field of transition-metal-catalyzed decarbonylative cross-coupling reactions in which a series of carbonyl functional group substitutions have been successfully achieved, including decarbonylative arylation, alkylation, olefination, alkynylation, cyanation, etherification, amination, silylation, borylation, thiolation, phosphination, stannylation, reduction and retro-hydrocarbonylation. This synthetic approach is desired to offer new opportunities for organic synthesis. But, still, some interesting yet challenging problems remain unsolved. The use of unactivated aliphatic aroyl derivatives in decarbonylative cross-coupling is still a challenge. Often high temperatures are used which restrict industrial applications. Nevertheless, the developments stand for a great advance in the area of functional group interconversion and expand the repertoire of synthetic methods which can be considered in late stage functionalizations as well as synthesis and retrosynthesis in general.

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Keywords: decarbonylative cross-coupling • metal catalysis • carbonyl derivatives • cleavage reactions • functionalization

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REVIEW

Lin Guo, Magnus Rueping*

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**Transition Metal-Catalyzed
Decarbonylative Cross Coupling
Reactions - Concepts, Classifications
and Applications**

In view of the great advantages of using carbonyl-containing functionalities as coupling electrophiles instead of the commonly used organohalides or sulfates, transition-metal-catalyzed decarbonylative cross-coupling reactions have emerged as powerful alternatives to the conventional cross-coupling protocols. A wide variety of novel transformations based on this concept have been successfully achieved, including decarbonylative carbon-carbon and carbon-heteroatom bond forming-reactions. Mechanistic studies revealed that this intriguing reaction methodology proceeds through metal-catalyzed acyl C-X bond cleavage with a subsequent CO extrusion step. In this Review, we summarize the recent progress in this field and present a comprehensive overview of transition-metal-catalyzed decarbonylative cross-couplings with carbonyl derivatives.