Decarbonylative Cross-Coupling of Amides

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REVIEW

Decarbonylative Cross-Coupling of Amides

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Cross-coupling reactions are among the most powerful C–C and C–X bond forming tools in organic chemistry. Traditionally, cross-coupling methods rely on the use of aryl halides or pseudohalides as electrophiles. In the last three years, decarbonylative cross-couplings of amides have emerged as an attractive method for the construction of a wide variety of carbon–carbon and carbon–heteroatom bonds, allowing for the synthetically-valuable functional group inter-conversion of the amide bond. These previously elusive reactions hinge upon selective activation of the N–C(O) acyl amide bond, followed by CO extrusion, in a formal double N–C/C–C bond activation, to generate a versatile aryl-metal intermediate as an attractive alternative to traditional cross-couplings of aryl halides and pseudohalides. In this perspective review, we present recent advances and key developments in the field of decarbonylative cross-coupling reactions of amides as well as discuss future challenges and potential applications for this exciting field.

1. Introduction

The amide bond is among the important functional groups in chemistry.[1–4] The development of new methods for functionalization of the N–C(O) bond in amides is a critical area of research due to the ubiquitous presence of the amide bond in essentially every field of chemical science, including drug discovery, agrochemistry, biochemistry, structural chemistry, and polymer science.[2–4] Historically, activation of the amide N–C(O) bond by transition metals has been a major challenge due to amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, resonance of 15-20 kcal/mol, planar amides).[5] Recent structural studies demonstrated that modulation of amidic resonance is in fact, in contrast to the established dogma, quite straightforward,[6,7] which opens the door for utilization of the amide component as an electrophile in cross-coupling reactions of broad synthetic interest.[8] In this context, cross-coupling reactions of amides hold a tremendous potential as a new manifold in organic chemistry that could enable (1) late-stage functionalization of amide-containing synthetic intermediates, (2) site-selective functionalization of biomolecules, and (3) the development of new orthogonal cross-coupling precursors derived from carboxylic acids with selectivity unattainable to other acyl electrophiles.

Mechanistically, activation of the amide bond proceeds via selective metal insertion into the N–C(O) amide bond to generate acyl metal intermediate (Fig. 1).[9] The resulting acyl-metal intermediate can undergo direct transmetallation (ligand exchange), followed by reductive elimination to afford acyl cross-coupling product.[10,11] Alternatively, the acyl-intermediate resulting from the selective oxidative addition of a low-valent metal into the N–C(O) amide bond can be subject to decarbonylative pathway (Fig. 2), prior to or after the transmetallation step. This process, which ultimately depends on the ability of acyl-metal to undergo carbon monoxide de-insertion[12] and can be regarded as a formal double N–C/C–C bond activation, generates a versatile aryl-metal intermediate as an attractive alternative strategy to traditional cross-couplings of aryl halides and pseudohalides.

The field of decarbonylative cross-coupling of amides has been launched with Pd-catalyzed decarbonylative Heck cross-coupling of amides reported by our group in 2015.[13] This was quickly followed by the first examples of Rh-catalyzed[14] and Ni-catalyzed[15] decarbonylative cross-couplings of amides also reported by our group. In the last three years, this technology has experienced a rapid growth. At present, decarbonylative cross-couplings of amides represent an attractive method for the construction of a wide variety of carbon–carbon and carbon–heteroatom bonds, allowing for synthetically-valuable

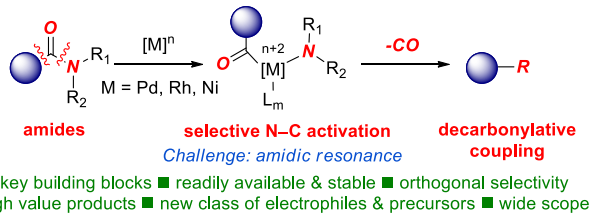

Figure 1 Decarbonylative cross-coupling of amides.

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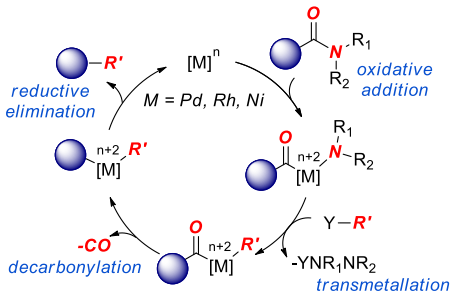


Figure 2 Mechanism of decarbonylative cross-coupling of amides.

functional group inter-conversion of amides. In this perspective review, we present recent advances and key developments in the field of decarbonylative cross-coupling reactions of amides as well as discuss future challenges and potential applications for this exciting field.

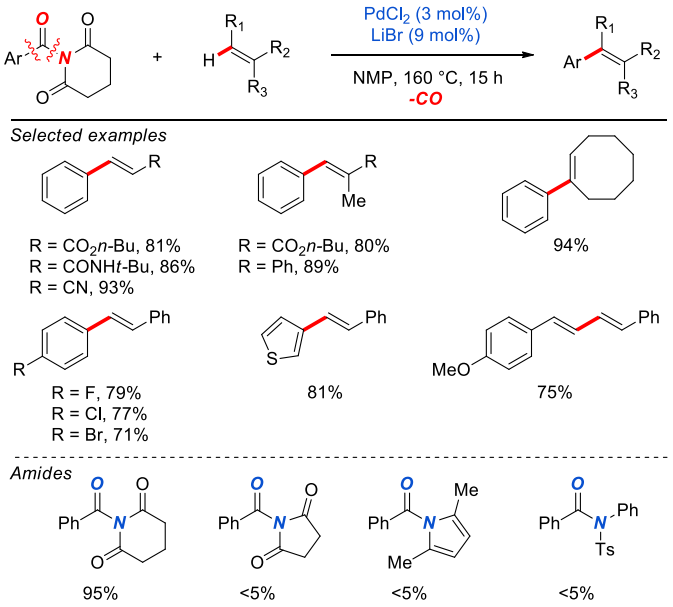
The review is arranged by the type of metal that promotes the cross-coupling. Furthermore, throughout the review, we give special attention to the type and electronic properties of the amide electrophile that undergoes the cross-coupling. The inherent properties of the amide bond in addition to the catalyst system employed are critical to the current success that this field enjoys, while further modifications and improvements are likely to establish this manifold as a prevalent cross-coupling method for the synthetic community.

2. Palladium-catalyzed decarbonylative cross-coupling of amides

There is no doubt that at present palladium is the most versatile metal in homogeneous catalysis.[8] Palladium-catalyzed cross-coupling reactions have been widely recognized by the 2010 Nobel Prize in Chemistry. Therefore, it comes as no surprise that the development of decarbonylative cross-couplings of amides catalyzed by palladium represents a highly attractive research strategy.

2.1. Decarbonylative Heck cross-coupling. Heck reaction is one of the classic cross-coupling reactions,[16] which is broadly used to construct C–C bonds under academically and industrially-appealing conditions. Following our establishment of the ground-state amide-bond destabilization concept for acyl-cross-coupling,[17] in 2015, we have reported a Pd-catalyzed decarbonylative Heck cross-coupling of amides via N–C bond activation (Scheme 1).[15] The reaction represented the first method for decarbonylative cross-coupling of amides. Typical conditions involved 3 mol% $PdCl_2$ as a catalyst and 9 mol% of LiBr as an additive. A TON of 700 at 0.10 mol% of $PdCl_2$ was achieved. Notably, this method accomplished base-free and ligand-free olefin synthesis with amides as benign aryl electrophiles in the absence of toxic aryl halides. As a demonstration of the synthetic utility of decarbonylative amide cross-coupling, a broad scope with respect to both the amide and olefin components was established.

Interestingly, the developed $PdCl_2$/LiBr catalytic system was found to work very well with N-acyl-glutarimides, which due to disrupted n_N to $\pi^*_{C=O}$ stabilization (RE, resonance energy, of ca. 1-3

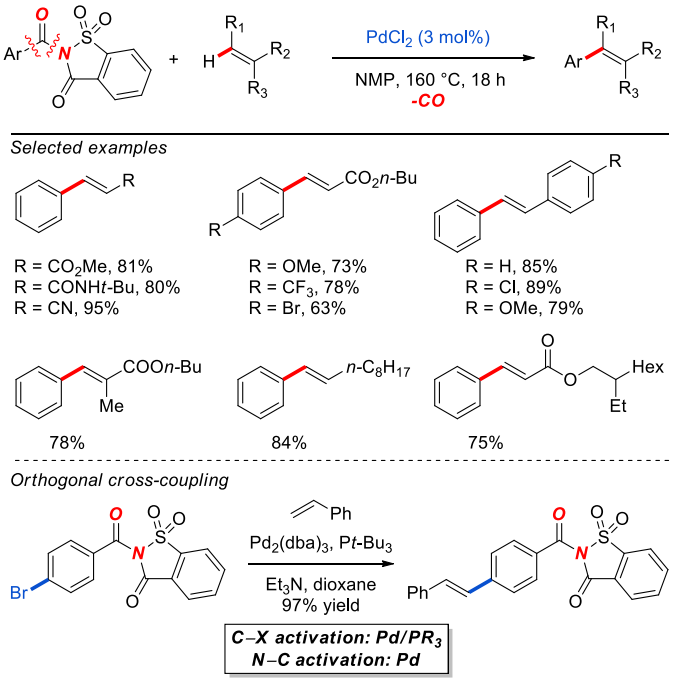


Scheme 1 Pd-catalyzed decarbonylative Heck cross-coupling of amides reported by our group.

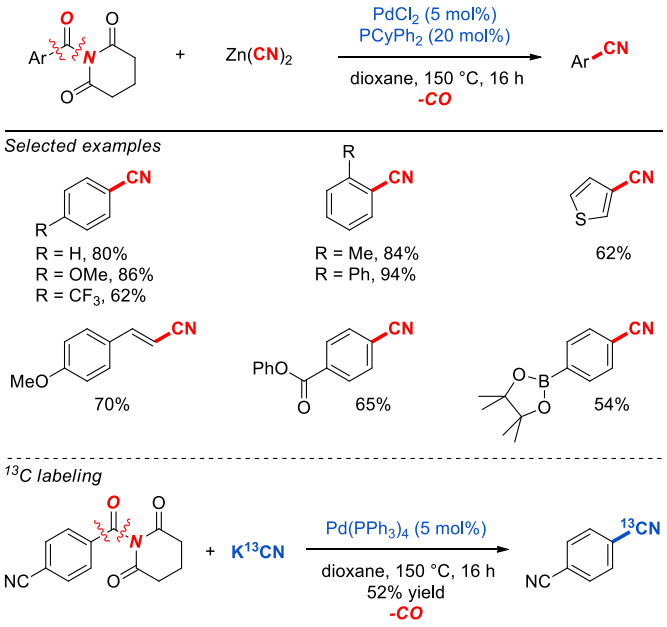
kcal/mol),[6b,e,18] feature a significantly weakened amide bond (vide infra). Other amide precursors were also tested, including Weinreb amide, N-acylpyrrole,[19] N-acyl-succinimide, N-Ts-sulfonamide as well as N-acyl-aziridine and N-acyl-azetidine;[20] however, only traces of the desired cross-coupling product were formed. The high chemoselectivity for N–C(O) activation rationally guided by amide bond distortion[6,7] is one of the attractive features of this cross-coupling manifold. The high stability of the amide bond compares favorably with other acyl precursors,[8,9] contributing to the high utility of amides as aryl-transfer reagents.

2.2. Decarbonylative Heck cross-coupling of N-acyl-saccharins. To expand the generality of decarbonylative Heck cross-coupling of amides, in 2016, we have reported a Pd-catalyzed decarbonylative Heck cross-coupling of N-acyl-saccharins as electrophilic reagents (Scheme 2).[21] N-Acylsaccharins, introduced simultaneously by our group and Zeng and co-workers, represent convenient, crystalline, benign, cheap and bench-stable reagents that are selectively activated at the exo-cyclic N–C bond by transition metals.[22] We demonstrated that a broad range of diverse amides and olefins could be selectively cross-coupled in good to excellent yields, and with exclusive decarbonylation selectivity. As one of the highlights of this method, we have established the feasibility of iterative decarbonylative cross-couplings of amides as demonstrated by site-selective C–X Heck cross-coupling/C–N(O) decarbonylative Heck.

2.3. Decarbonylative cyanation of amides. In our pursuit of new decarbonylative cross-coupling methods with broad scope, in 2017, we have reported the first decarbonylative cyanation of amides (Scheme 3).[23] Aromatic nitriles are routinely used to generate a broad wealth of organic molecules (aldehydes, ketones, heterocycles, imines, amines), and as such are widely considered as versatile building blocks. Transition-metal-catalyzed cyanation of

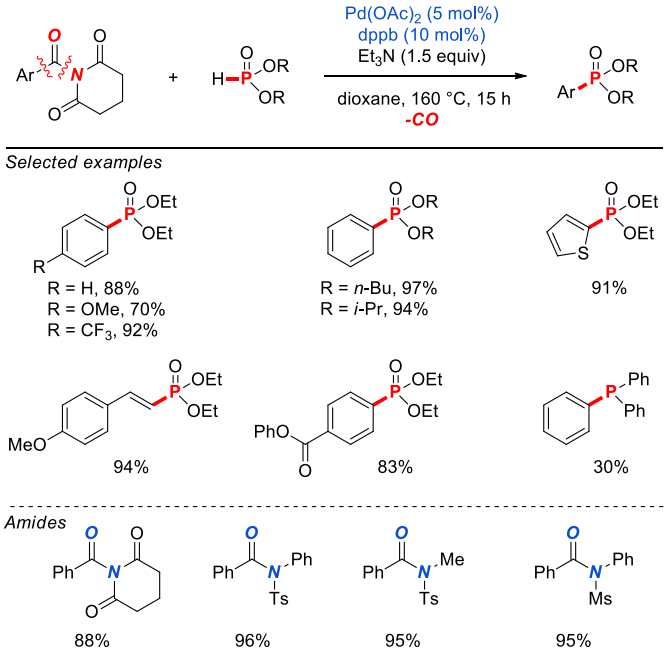


Scheme 2 Pd-catalyzed decarbonylative Heck cross-coupling of N-acyl-saccharins reported by our group.



Scheme 3 Pd-catalyzed decarbonylative cyanation of amides reported by our group.

aryl halides represents an important methodology for the construction of aromatic nitriles, which have found numerous applications in the synthesis of pharmaceuticals, dyes and agrochemicals.[24] In our method, zinc cyanide was employed as a benign cyanating reagent, which in combination with the use of amides (cf. toxic halides) provides a means of accessing valuable cross-coupling reactivity. This transformation showed excellent functional group tolerance, including the synthesis of functionalized aryl, heteroaryl, and vinyl nitriles in generally high yields. The



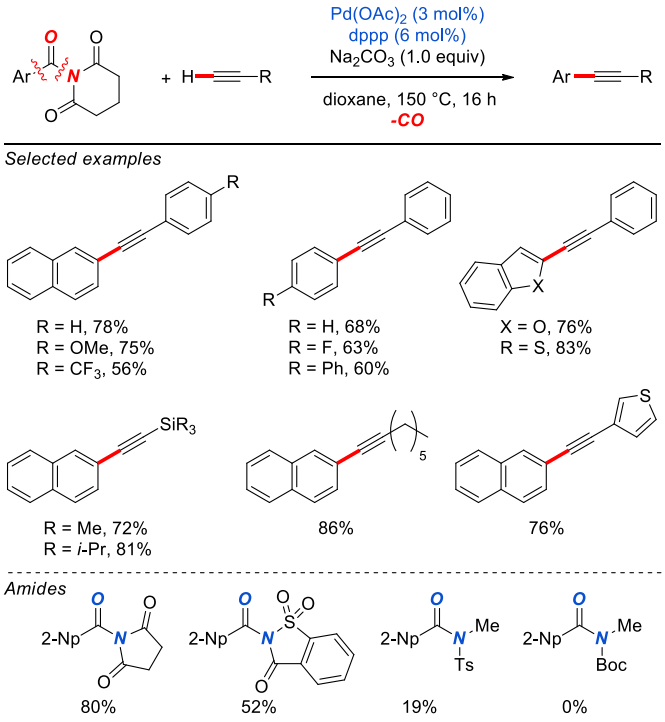
Scheme 4 Pd-catalyzed decarbonylative phosphorylation of amides reported by our group.

potential of this formal 'carbon exchange' reaction was demonstrated in the synthesis of isotopically-labeled nitriles.

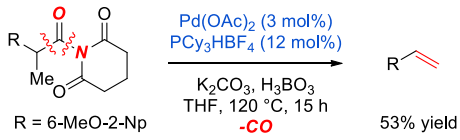
2.4. Decarbonylative phosphorylation of amides. To establish the broad applicability of Pd-catalyzed decarbonylative cross-couplings of amides, in 2017, we have reported the first decarbonylative phosphorylation of amides, dubbed as 'amide Hirao cross-coupling' (Scheme 4).[25] Organophosphorus compounds have profound implications as efficient supporting ligands in synthesis and catalysis as well as feature key applications in drug discovery, agrochemistry and functional materials. While the classic Hirao cross-coupling has been widely adopted for the synthesis of C–P bonds,[26] the current methods suffer from toxicity, low efficiency and limited functional group tolerance. The 'amide Hirao cross-coupling' exploits an alternative source of benign, abundant and bench-stable amide aryl electrophiles. The reaction tolerates a broad range of electronically-diverse and functionalized aromatic as well as vinyl and heterocyclic substrates providing the coupling products in good to excellent yields. Mechanistic studies indicated an oxidative addition/ transmetalation/decarbonylation pathway with transmetalation prior to decarbonylation under the developed conditions. The synthetic potential of this redox-neutral protocol was highlighted in several iterative C–X/C–N(O) cross-coupling reactions.

Importantly, both N-cyclic amides like N-acyl-glutarimides and N-acyclic amides, such as N-Ts and N-Ms sulfonamides,[27] can be employed using this highly general catalytic system. This highlights a key consideration in the development of decarbonylative cross-couplings of amides to include simple N-acyclic amides that can be readily prepared from common 1° or 2° amides.

2.5. Decarbonylative alkynylation of amides. In 2018, the Chen group reported an elegant Pd-catalyzed decarbonylative



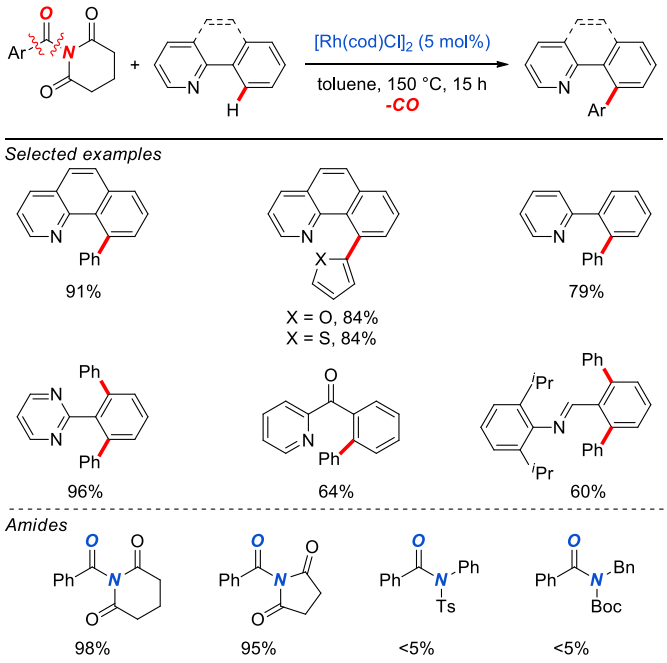
Scheme 5 Pd-catalyzed decarbonylative alkynylation of amides reported by Chen and co-workers.



Scheme 6 Pd-catalyzed retro-hydroamidocarbonylation reported by our group.

alkynylation of amides with terminal alkynes via C–N(O) bond activation (Scheme 5).[28] Considering that internal alkynes are fundamental structural motifs in a variety of natural products and common synthetic intermediates, the development of new, highly efficient and functional group tolerant protocols for their synthesis is an important endeavor. In this respect, the method developed by Chen and co-workers proceeds with broad substrate generality that is inherent to palladium catalysis and would be difficult to achieve with base-metals (vide infra). The reaction proceeds well with aromatic, aliphatic and silylated terminal alkynes. Under the developed conditions, N-acyl-glutarimides showed the best reactivity; however, promising results were also achieved with N-acyl-succinimide[29] and N-acyl-saccharine amides.[22] The authors suggested that the reaction involves the following steps: (i) oxidative addition, (ii) decarbonylation, (iii) ligand exchange, and (iv) reductive elimination; however, additional studies need to be conducted to elucidate the reaction mechanism.

2.6. Pd-catalyzed retro-hydroamidocarbonylation. During our studies on Pd-catalyzed ketone synthesis by acyl-cross-coupling of amides,[15b,17] we established the first example of a tandem decarbonylation/β-hydride elimination to form the olefin product from a substrate containing an activated β-hydrogen (Scheme 6). It



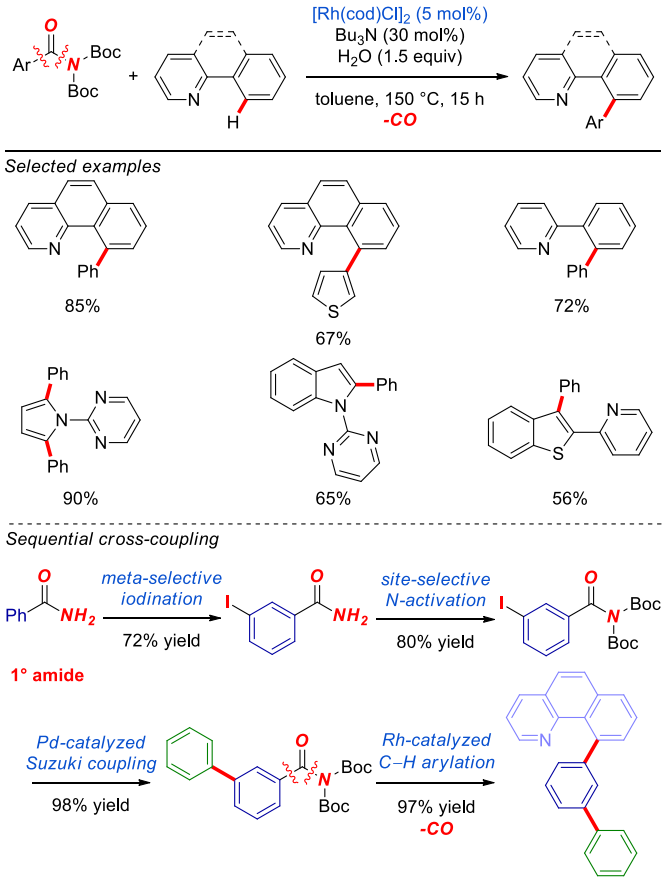
Scheme 7 Rh-catalyzed decarbonylative C–H bond functionalization using amides reported our group.

is noteworthy that while the olefin synthesis has been well-established using aliphatic carboxylic acids,[30] the present method paves the way for utilizing amides as alternative CO–X electrophiles.

3. Rhodium-catalyzed decarbonylative cross-coupling of amides

Originally discovered by William Hyde Wollaston in 1803, shortly after his discovery of palladium, in recent years, rhodium has been particularly effective in promoting a variety of C–H functionalization reactions.[31] Significant advancements have also been made in the development of C–C bond functionalizations using rhodium catalysis.[32] While rhodium is more expensive that palladium, rhodium-catalyzed reactions stand out as particularly versatile owing to exceptional functional group tolerance, high reactivity and the ability to promote cleavage of strong σ bonds, including in a non-directed fashion. We were attracted to rhodium catalysis in decarbonylative cross-coupling of amides because these methods would be complementary to palladium catalysis.

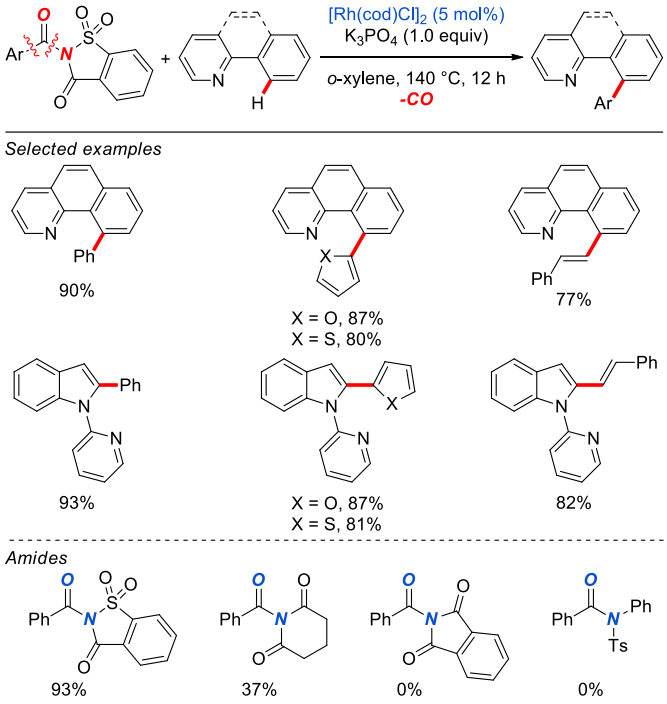
3.1. Rh-catalyzed decarbonylative C–H bond functionalization of amides. In 2016, we reported the rhodium-catalyzed decarbonylative C–H functionalization with amides as coupling partners via double C–H/N–C(O) bond activation (Scheme 7).[14] The transformation constituted the first catalytic activation of the N–C(O) amide bond by rhodium catalysis, and still represents the most functional group tolerant and the most efficient method for decarbonylative cross-coupling of amides of any type reported to date. There are several advantages of using amides as cross-coupling partners in C–H functionalization, including broad availability, low price, wide substrate scope, excellent functional group tolerance, facile



Scheme 8 Rh-catalyzed decarbonylative C–H bond functionalization using N,N-Boc$_2$-amides reported our group.

decarbonylation, and operational simplicity because the reaction is tolerant to air and moisture. A TON of 1,000 was demonstrated for this cross-coupling, consistent with efficient activation of both C–H and N–C(O) bonds. Due to the beneficial character of direct functionalization of arenes, C–H bond activation methods have attracted tremendous attention. Site-selective C–H functionalizations using amides as cross-coupling partners offer promising perspectives for the efficient assembly of complex molecules of broad interest.

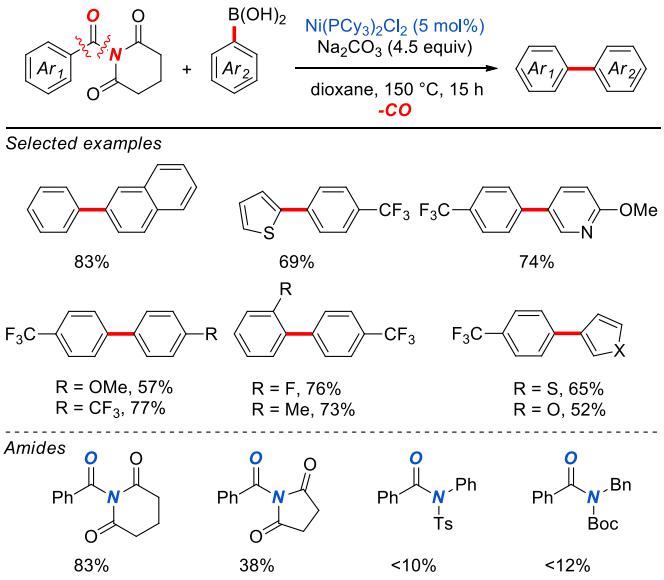
3.2. Rh-catalyzed decarbonylative C–H bond functionalization of primary amides. In our efforts to develop broadly useful cross-coupling reactions of amides, we quickly recognized that cross-coupling of amides readily derived from common 1° amides would be particularly attractive. Unfortunately, decarbonylative cross-couplings of N-acyclic amides represent a major challenge because they typically require more demanding conditions than acyl-cross-couplings. To date, there are very few methods that efficiently engage N-acyclic amides in decarbonylative cross-couplings due to the facile scission of the N-activating group (N–Ts. N–Boc, etc).[10,11] In this context, cross-coupling of N,N-Boc$_2$ amides, which are readily prepared from primary carboxamides and arguably among the most useful amide derivatives in light of late-stage and biomolecule functionalization,[6d] represents an even more formidable challenge.



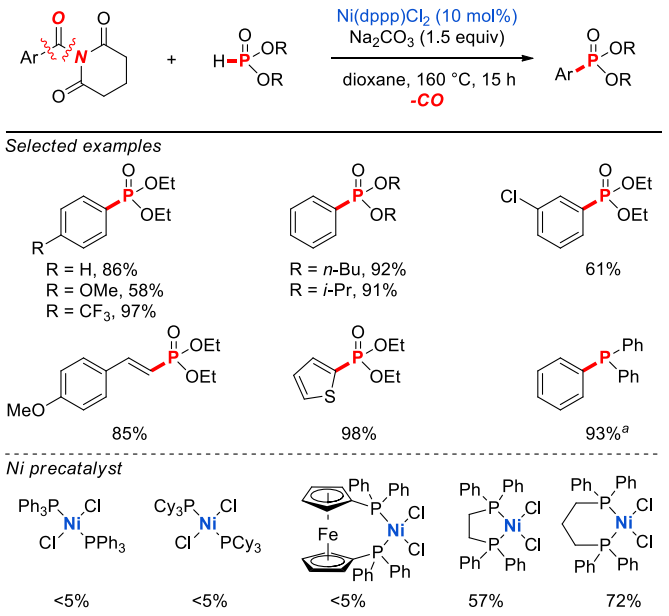
Scheme 9 Rh-catalyzed decarbonylative C–H bond functionalization using amides reported by Zeng and co-workers.

In 2017, we reported the first and only to date method for decarbonylative cross-coupling of primary amide derivatives (Scheme 8).[33] Inspired by the success of C–H functionalization with N-cyclic amide precursors,[14] we designed a process that proceeds via decarbonylative C–H coupling of N,N-Boc$_2$ amides through C–H/N–C(O) cleavage. The cooperative combination of rhodium catalysis and Lewis base catalysis[10c] plays an important role to promote activation of the inert N–C(O) bond by forming acyl-ammonium intermediate, thus obviating the high energy, direct activation of the amide bond. The transformation showed wide substrate scope and excellent functional group tolerance, which provides an attractive avenue for designing future C–H functionalization methods. The synthetic potential was demonstrated through sequential functionalizations enabled by 1° amide bond. The feasibility of the method to activate N-acyclic amides readily derived from 2° amides has also been documented.

3.3. Rh-catalyzed decarbonylative C–H bond functionalization of N-acyl-saccharins. N-Acylsaccharins have proved as efficient functional group transfer reagents in acylation[22] and arylation[21] reactions. Considering the great success of N-acyl-glutarimides in C–H functionalization, in 2016, the Zeng group developed an elegant Rh-catalyzed decarbonylative C–H functionalization of N-acyl-saccharins via C–H/N–C(O) bond activation (Scheme 9).[34] The reaction tolerates a wide range of functional groups, such as chloro, bromo, formyl, ester, vinyl and heterocyclic groups. Thus, this protocol provides another attractive alternative for transition-metal-catalyzed decarbonylative C–H activation of amides via selective N–C(O) cleavage.



Scheme 10 Ni-catalyzed decarbonylative Suzuki-Miyaura biaryl coupling of amides reported our group.



Scheme 11 Ni-catalyzed decarbonylative phosphorylation of amides reported our group. [a]Using $HPPh_2$, 48 h.

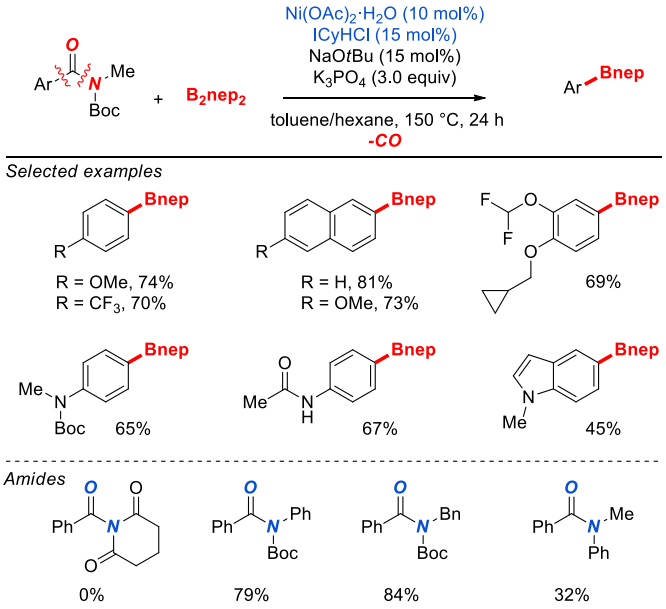
4. Nickel-catalyzed decarbonylative cross-coupling of amides

Recently, nickel-catalysis has been successfully established as one of the dominant directions in cross-coupling owing to the low price of nickel and the capacity of Ni(0) to promote challenging oxidative additions.[35] At present, there is a strong tendency to replace precious metal catalysts with inexpensive base metals. In this regard, cheap, highly efficient and environmentally-friendly nickel catalysis has met with significant attention from the cross-coupling community. Despite this progress, it should be clearly emphasized that nickel catalysis is typically less general than palladium in terms of functional group tolerance and catalytic turnover, both of these factors critical from the operational standpoint.

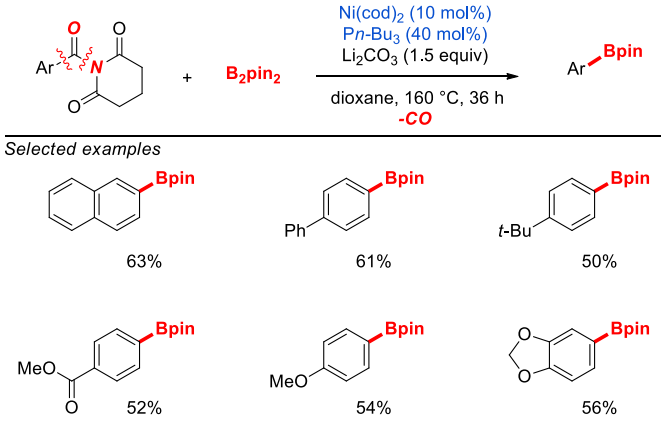
4.1. Ni-catalyzed decarbonylative Suzuki-Miyaura biaryl coupling of amides. The first Ni-catalyzed decarbonylative cross-coupling of amides was reported by our group in 2016 (Scheme 10).[15] Considering that Ni has been incredibly useful in promoting cleavage of unreactive C–X bonds,[35] after the establishment of the acyl-Suzuki cross-coupling of amides,[17] we hypothesized that nickel might be beneficial in developing generic activation modes of the amide bond. The biaryl Suzuki cross-coupling represented the first example of a transition-metal-catalyzed direct arylation from amides via N–C(O) bond cleavage, and as such, a significant advance in using amides as benign, bench-stable, readily accessible, environmental-friendly and orthogonal cross-coupling partners for the generation of biaryl motifs. We found that the 'amide biaryl coupling' is promoted by a cheap, user-friendly and air-stable $Ni(PCy_3)_2Cl_2$ precatalyst. A wide range of electron-poor, electron-neutral, and electron-rich substituents on both the amide and boronic acid coupling partners were tolerated to accomplish the biaryl synthesis in good to excellent yields. A mechanism involving transmetalation prior to decarbonylation was proposed to be operative in this process. Electronic activation and ground-state distortion in N-acyl-glutarimides promoted the reactivity of the amide bond. Notably, nickel catalysis was found to be much preferred to promote the decarbonylation step, while palladium catalysis typically generated acyl cross-coupling products.

Since the traditional Suzuki-Miyaura biaryl coupling is one of the most important and reliable C–C bond forming reactions in organic synthesis, which has been extensively incorporated by the pharmaceutical, agrochemical and polymer industry,[36] the emergence of amides as alternative cross-coupling partners brings the prospects of new synthetic disconnections in biaryl synthesis using base-metal catalysis.

4.2. Ni-catalyzed decarbonylative phosphorylation of amides. On the basis of the excellent performance of nickel catalysts in decarbonylative biaryl cross-coupling of amides, in 2017, we reported the first decarbonylative phosphorylation of amides catalyzed by nickel (Scheme 11).[25] This transformation provides an alternative method to generate C–P bonds[26] using carboxylic acid derivatives as electrophiles. Compared with the palladium-catalyzed process (Scheme 4), nickel can also perform with similar efficiency for simple substrates, and even better cross-coupling capability for select amide and phosphite substrates. Mechanistic studies indicated a similar catalytic mechanism under both Ni- and Pd-catalytic conditions, with transmetallation occurring prior to decarbonylation in both cases. Notably, acyl-phosphine cross-coupling products were not detected under either Ni or Pd catalytic conditions. However, the major limitation of Ni, a corollary of its high nucleophilicity,[35] is the low tolerance with respect to the N-amide activating group, with N-acyl-glutarimides vastly preferred for the majority of decarbonylative cross-couplings of amides reported to date.



Scheme 12 Ni-catalyzed decarbonylative borylation of amides reported by Shi and co-workers.



Scheme 13 Ni-catalyzed decarbonylative borylation of amides reported by Rueping and co-workers.

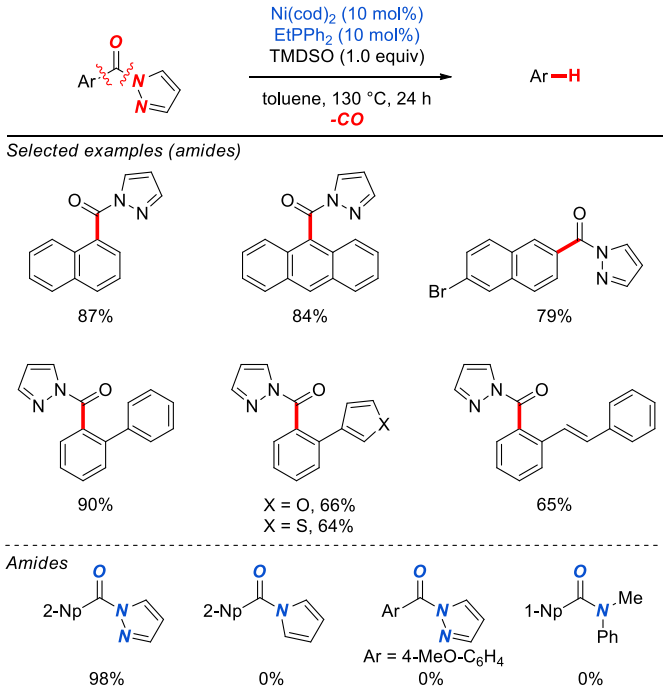
4.3. Ni-catalyzed decarbonylative borylation of amides. Organoboron compounds are robust and versatile building blocks in modern organic chemistry.[36] In 2016, the Shi group developed a decarbonylative borylation of N-Boc-activated amides using a nickel/N-heterocyclic carbene catalytic system (Scheme 12).[37] They used N-Boc functional group to decrease amidic resonance and activate the N–C(O) bond towards catalytic activity.[6a] There are several highlights of their protocol: (1) the transformation forms weaker C–B bonds from typically more stable N–C bonds; (2) the use of N-Boc amides provides advantage to manipulate common 2° amides; (3) arylboronate products do not react with the unreacted amide starting materials via Suzuki-Miyaura reaction.[38] Intriguingly, the group was able to isolate the acyl-nickel(II) intermediate after ligand exchange. This intermediate underwent decarbonylation upon increasing the reaction temperature. Both acyl-nickel(II) and aryl-nickel(II) complexes have been isolated and their structures confirmed by X-ray crystallography. The scope of the reaction is impressive with respect to functional group tolerance; however, the method appears to be limited to the less synthetically useful Bnep esters, offering potential for further improvements. This reaction provides a new, highly important addition to the suit of modern borylation methods, enabling the formation of versatile arylboranes from amides.

Independently, the Rueping group reported a nickel-catalyzed decarbonylative borylation of N-acyl-glutarimides using a combination of Ni(0) and P*n*-Bu$_3$ (Scheme 13).[39] This user-friendly catalytic system exhibits broad functional group tolerance. The method generates widely useful Bpin esters, which represents an excellent alternative to the Ni/NHC-catalyzed decarbonylative borylation of amides.

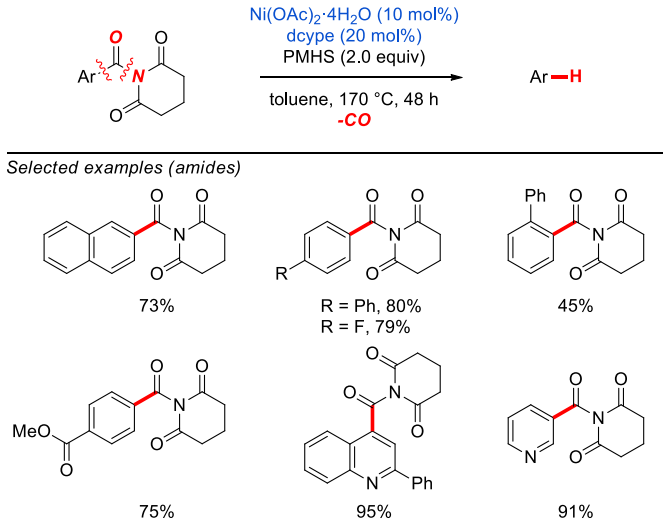
4.4. Ni-catalyzed decarbonylative reduction of amides. In 2017, two excellent methods for decarbonylative reduction of amides by selective N–C(O) cleavage mediated by Ni have been reported.[40,41] In the first approach, the Maiti group reported a nickel-catalyzed decarbonylative reduction of planar N-pyrazolyl amides (Scheme 14),[40] which includes a one-pot N–C bond cleavage followed by decarbonylation in the presence of tetramethyldisiloxane (TMDSO). Notably, this reaction represented the first example of a decarbonylative transition-metal-catalyzed N–C(O) bond activation of planar amides.[42] Amide destabilization by conjugating the Nlp with the π-aromatic system[6c] increases the reactivity of the N–CO acyl amide bond. Furthermore, in their design the N2 atom of the pyrazole coordinates to Ni, resulting in the efficient delivery of the transition metal to the weakened amide bond. Interestingly, a broad range of ligands was found to promote the reduction in high yields (PPh_3, 87%; $EtPPh_2$, 98%' IMes, 90%). The present transformation presenting a coplanar N–CO bond opens the possibility of using novel amide-based reagents in decarbonylative cross-coupling reactions.[42]

Independently, in an alternative approach exploiting amide bond destabilization, the Rueping group reported a decarbonylative reduction of N-acyl-glutarimides catalyzed by Ni in the presence of a bidentate phosphine ligand (dcype) and commercially available, nontoxic polymethylhydrosiloxane (PMHS) (Scheme 16).[41] This reaction provides an important protocol for decarbonylative reductive de-functionalization[43] of aryl and heteroaryl amides. The authors suggested that the reaction mechanism involves the following steps: (i) oxidative addition, (ii) CO de-insertion, (iii) transmetalation, (iv) reductive elimination, and (v) CO extrusion. The transition-metal-catalyzed reductive de-functionalization of readily available amides reported by Maiti and Rueping is one of the most fundamental and promising transformations in organic synthesis.

4.5. Ni-catalyzed decarbonylative amination of amides. In 2017, the Rueping group reported the first nickel-catalyzed decarbonylative amination of amides using benzophenone imine as the aminating reagent and N-acyl-glutarimides as amide electrophiles (Scheme 16).[44] The method permits the direct transformation of amides to the corresponding aryl amines after in situ hydrolysis, in an analogy to the classic



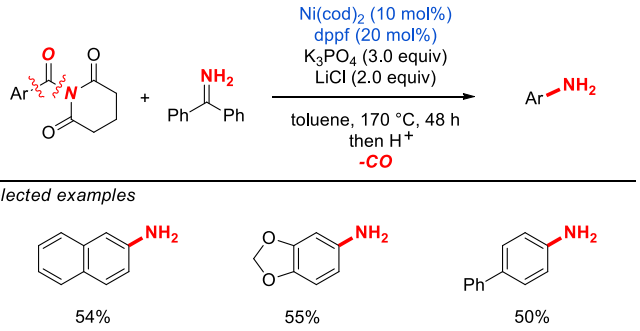
Scheme 14 Ni-catalyzed decarbonylative reduction of amides reported by Maiti and co-workers.



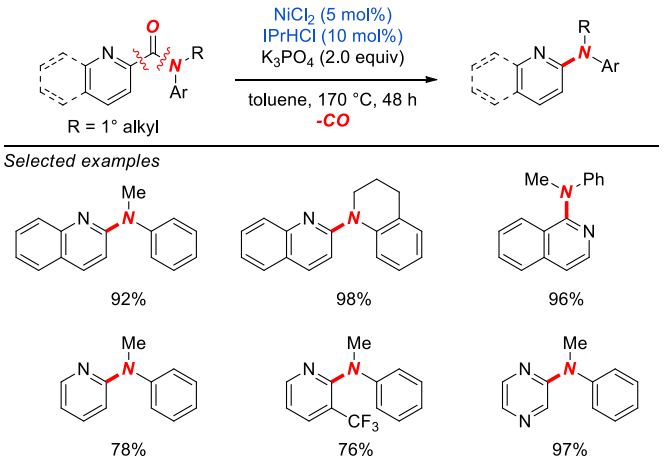
Scheme 15 Ni-catalyzed decarbonylative reduction of amides reported by Rueping and co-workers

rearrangements of carboxylic acids derivatives (Schmidt, Curtius, Lossen). The $Ni(cod)_2$/dcype catalytic system was found to provide optimum reactivity in this coupling.

The second example to directly inter-convert amides to amines was reported shortly thereafter by Rueping and co-workers (Scheme 17).[45] In this case, the intramolecular decarbonylation of amides consisting of a straightforward CO extrusion and recombination of resonance destabilized anilides[6c] bearing a conjugating six-membered N-heterocycle at the α-carbon position of the amide bond allowed to overcome the decarbonylation barrier, while exhibiting excellent functional group tolerance. The reaction was efficiently promoted by $NiCl_2$ in the presence of an NHC ligand.



Scheme 16 Ni-catalyzed decarbonylative amination of amides reported by Rueping and co-workers.

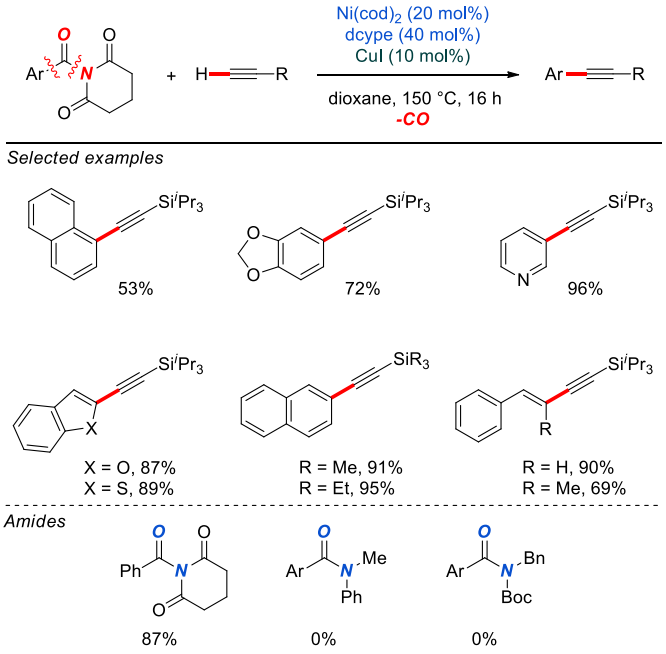


Scheme 17 Ni-catalyzed decarbonylative amination of amides reported by Rueping and co-workers.

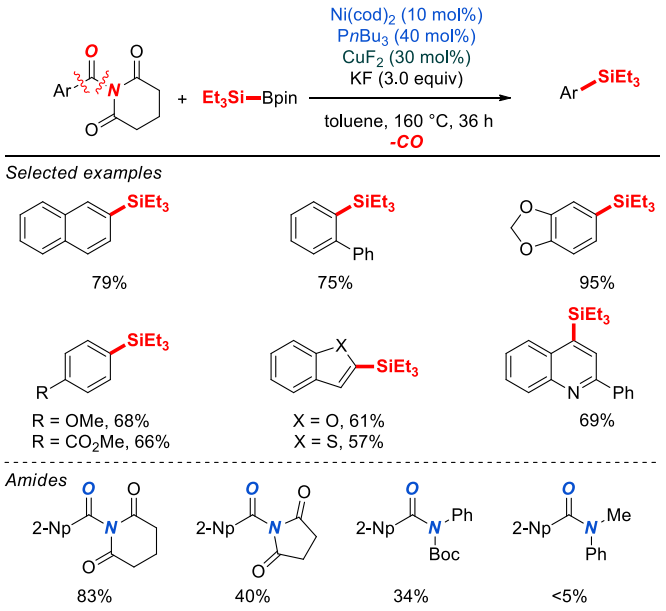
The decarbonylative amination methods reported by Rueping represent an attractive alternative to Buchwald-Hartwig N–C cross-coupling using amide electrophiles.[46,47]

4.6. Ni-catalyzed decarbonylative alkynylation of amides. The Sonogashira cross-coupling is an exceptionally versatile method for the synthesis of alkynes.[48] In 2017, the Rueping group reported a Ni/Cu-co-catalyzed decarbonylative Sonogashira-type alkynylation of amides (Scheme 18).[49] The catalytic systems consisting of $Ni(cod)_2$ and CuI catalysts and dcype ligand can successfully achieve the inter-conversion of amides to internal aryl and heteroaryl alkynes in good to excellent yields. N-acyl-glutarimides are the preferred amide precursors in this decarbonylative alkynylation. Furthermore, due to facile polymerization of aryl and alkyl terminal acetylenes, this reaction proceeds well with silylacetylenes. The potential to prepare enynes by cross-coupling of alkenyl amides was also demonstrated. The reported 'amide Sonogashira' cross-coupling readily generates $C(sp^2)$-C(sp) bonds using amides as cheap, bench-stable and environmentally-friendly electrophilic coupling partners.

4.7. Ni-catalyzed decarbonylative silylation of amides. A cooperative Ni/Cu co-catalytic system was also employed by Rueping in the development of the decarbonylative silylation of amides by N–C(O) bond cleavage (Scheme 19).[39]

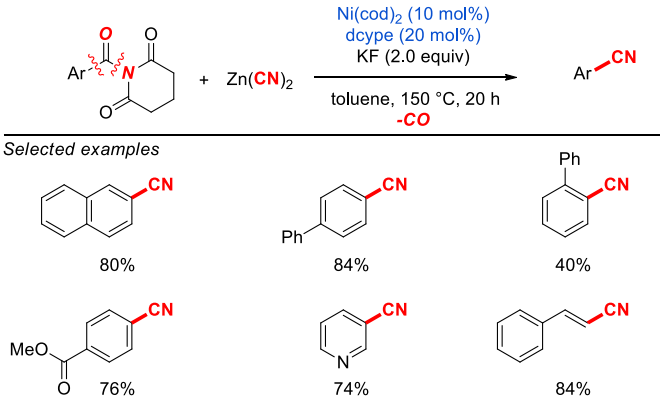


Scheme 18 Ni/Cu-catalyzed decarbonylative alkynylation of amides reported by Rueping and co-workers.

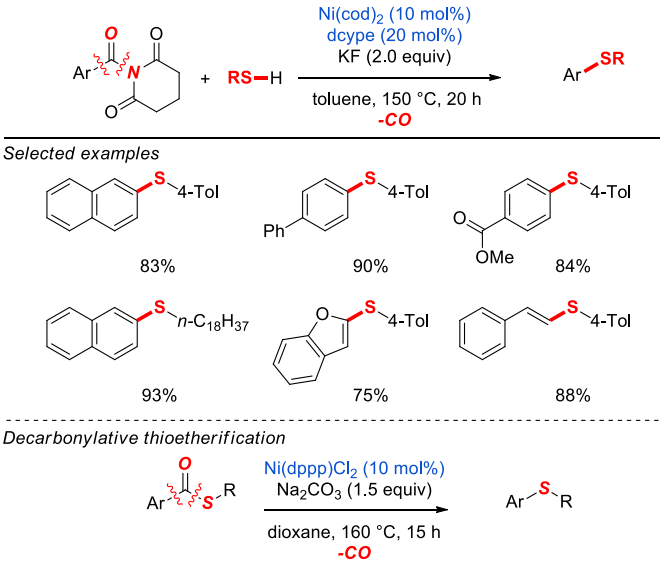


Scheme 19 Ni/Cu-catalyzed decarbonylative silylation of amides reported by Rueping and co-workers.

The challenge in preparing aryl-silanes lies in the low nucleophilicity of silicon. The authors addressed this issue by using $Et_3Si–Bpin$ in the presence of CsF as a selective nucleophilic Si transfer reagent. The reaction works well with N-acyl-glutarimides; however, preliminary optimization showed promising reactivity also with N-acyl-succinimides[29] and N-Boc-carbamates.[6a] This transformation represents a complementary strategy for C–Si bond formation from amides by a decarbonylative pathway.



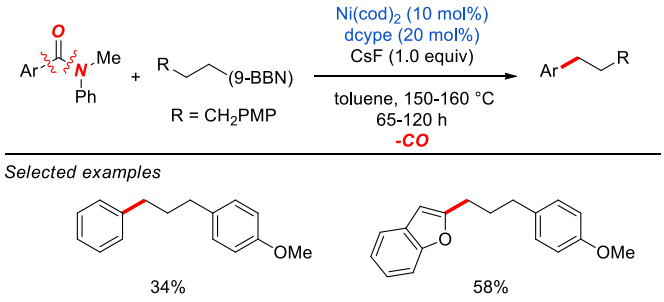
Scheme 20 Ni-catalyzed decarbonylative cyanation of amides reported by Rueping and co-workers.



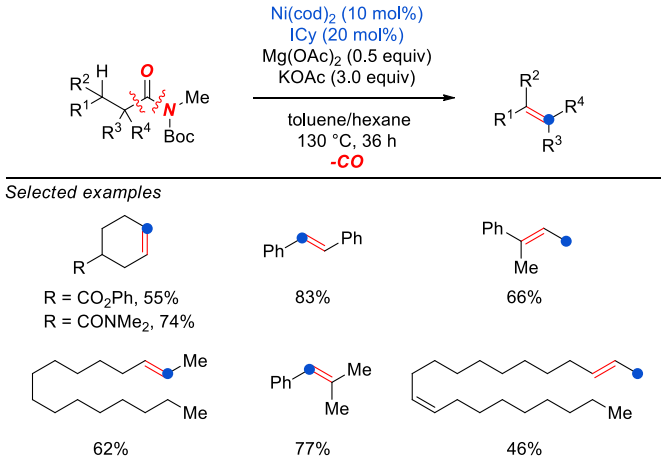
Scheme 21 Ni-catalyzed decarbonylative thioetherification of amides reported by Rueping and co-workers, and decarbonylative thioetherification of thioesters reported by our group.

4.8. Ni-catalyzed decarbonylative cyanation of amides. Following our discovery of Pd-catalyzed decarbonylative cyanation of amides,[23] the Rueping group reported Ni-catalyzed decarbonylative cyanation of N-acyl-glutarimides using zinc cyanide as a CN source (Scheme 20).[50] The reaction employs the previously field-tested in the decarbonylative cross-coupling of amides $Ni(cod)_2$/dcype catalyst system. The reaction shows good functional group tolerance; however, in several examples the selectivity using Pd-catalysis is better. Nevertheless, the method should be considered as an efficient strategy for inter-conversion of amides to nitriles, especially given the broad applicability of nitriles in pharmaceutical and functional material industry.[24]

4.9. Ni-catalyzed decarbonylative thioetherification of amides. Thioethers are considered as important motifs in organic synthesis. In 2018, the Rueping group reported a Ni-catalyzed decarbonylative thioetherification of N-acyl-glutarimides by selective N–C(O) bond cleavage using $NiCl_2$ in combination with dppp as a ligand and Mn as a stoichiometric



Scheme 22 Ni-catalyzed decarbonylative alkylation of amides reported by Rueping and co-workers.



Scheme 23 Ni-catalyzed retro-hydroamidocarbonylation reported by Shi and co-workers.

reductant (Scheme 21, top).[51] The main challenge lies in the C–S bond forming decarbonylation of the highly stable thioester.[52] The reaction most likely proceeds via transition-metal-free[53] thioesterification of the amide bond, followed by thioester decarbonylation. This approach provides a facile route for metal-catalyzed decarbonylative thioetherification of amides. Independently, in 2018, we have reported a direct decarbonylative thioetherification of thioesters using bench-stable $Ni(dppp)Cl_2$ precatalyst in the presence of Na_2CO_3 (Scheme 21, bottom).[54] This complementary method allows to directly interconvert thioesters to thioethers with vastly improved substrate scope and operational simplicity.

4.10. Ni-catalyzed decarbonylative alkylation of amides. Two examples of decarbonylative alkylation of N-anilides have been reported by Rueping in 2018 using an alkyl organoboron reagent (Scheme 22).[55] Despite modest yields, the present transformation provides an important proof-of-concept for incorporation of $C(sp^2)$-$C(sp^3)$ bond forming strategy from amides by a straightforward decarbonylative pathway.

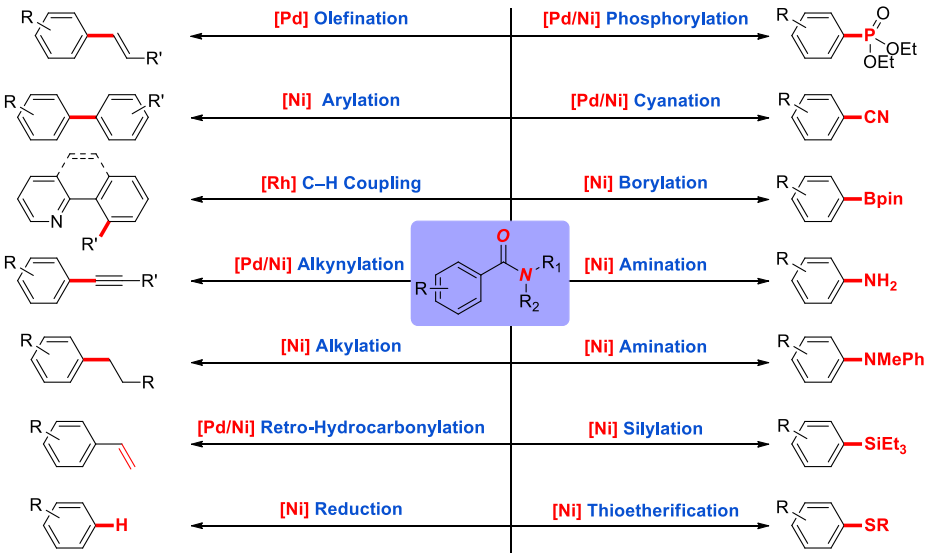
4.11. Ni-catalyzed retro-hydroamidocarbonylation of amides. Olefins are key synthetic intermediates that are broadly applied in the production of fine chemicals and drug molecules.[16] In this context, β-hydride elimination from acyl substrates containing β-hydrogens has been established as an efficient reaction to convert carboxylic acids into olefins.[30] In 2017, the Shi group reported a Ni-catalyzed retro-hydroamido-carbonylation of aliphatic amides via N–C(O) bond cleavage, decarbonylation and β-hydride elimination pathway (Scheme 23).[56] The previously established $Ni(cod)_2$/ICy catalytic system[37] was found to work best in this reaction. The olefin products were obtained in generally good yields with broad functional group tolerance; however, the process is less regioselective with respect to the olefin isomer than related protocols utilizing carboxylic acids. A nice highlight of this work included inter-conversion of complex amides to functionalized olefins with potential applications in natural product synthesis. This method shows how the decarbonylative amide bond coupling strategies could be incorporated into late-stage synthesis of pharmaceuticals and natural products.

5. Conclusions

In the past three years tremendous progress has been made in the development of decarbonylative cross-coupling reactions of amides. These reactions are typically initiated by selective N–C(O) bond cleavage driven by destabilization of amidic resonance, which allows for a wide variety of broadly useful cross-coupling transforms with excellent functional group tolerance. Since the initial studies reported in 2015, this mode of activation of the amide bond has provided more than 15 previously unknown reaction types of amides catalyzed by Pd, Rh and Ni in conjunction with various ligands. A summary of the feasible transformations of amides by decarbonylative cross-coupling is presented in Scheme 24.

The advantages of decarbonylative cross-couplings of amides are clear. These methods utilize new orthogonal cross-coupling precursors derived from carboxylic acids with selectivity unattainable to other acyl electrophiles due to superior stability of the amide bond. Ultimately, this mode of activation is likely to be utilized in late-stage functionalization of amide-containing synthetic intermediates and site-selective functionalization of biomolecules, and promising preliminary results have already been secured. From the sustainability point of view, the use of benign amides leads to a decrease of toxic halide waste and typically operationally-simple protocols.

Despite progress has been remarkable, several challenges need to be addressed: (1) the scope of amide component has been mostly limited to N-cyclic amides; (2) the functional group tolerance of Ni-catalysis should be improved; (3) there is few methods that employ the most useful Pd-catalysis, and fewer yet that operate at high TON; (4) there is a general lack of in-depth mechanistic studies[57] that could lead to refinement and further improvements in catalysis. The challenge is thus to define more reactive yet stable amide precursors that would be amenable to decarbonylative cross-couplings and at the same time readily prepared from common 1° and 2° amides. Addressing properties of non-planar amides is the key to apply resonance destabilized amide precursors in cross-couplings via N–C(O) amide bond cleavage. The evaluation of new ligand classes in combination with different metals and discrete reaction types will lead to the establishment of general cross-coupling protocols in this important field.



Scheme 24 Current state-of-the-art in transition-metal-catalyzed decarbonylative cross-coupling of amides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Chengwei Liu was born and raised in Yantai, China. He received his B.Eng. degree from Zaozhuang University in 2011 and his M.Sc. degree from Soochow University in 2014. Following graduation, he worked for WuXiAppTec and ChemPartner. In 2015, he joined the group of Prof. Michal Szostak at Rutgers University as a PhD student. His research interests are focused on transition-metal-catalyzed cross-coupling of amides.

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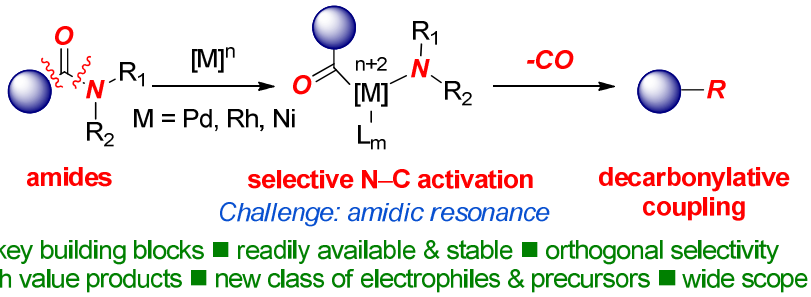

Cross-coupling reactions are among the most powerful C–C and C–X bond forming tools in organic chemistry. Traditionally, cross-coupling methods rely on the use of aryl halides or pseudohalides as electrophiles. In the last three years, decarbonylative cross-couplings of amides have emerged as an attractive method for the construction of a wide variety of carbon–carbon and carbon–heteroatom bonds, allowing for the synthetically-valuable functional group inter-conversion of the amide bond. These previously elusive reactions hinge upon selective activation of the N–C(O) acyl amide bond, followed by CO extrusion, in a formal double N–C/C–C bond activation, to generate a versatile aryl-metal intermediate as an attractive alternative to traditional cross-couplings of aryl halides and pseudohalides. In this perspective review, we present recent advances and key developments in the field of decarbonylative cross-coupling reactions of amides as well as discuss future challenges and potential applications for this exciting field.