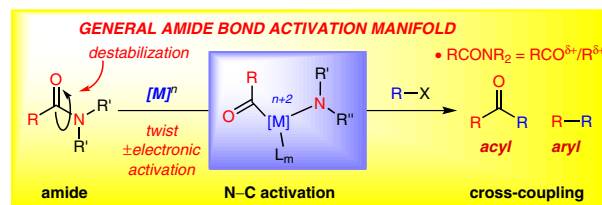


Cross-Coupling of Amides by N–C Bond Activation

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Abstract In recent years, significant conceptual advances have taken place in the field of amide bond cross-coupling. Mild and selective functionalization of amides by transition-metal catalysis has an enormous potential for widespread applications in both industry and academia due to the unparalleled prevalence of amide-containing molecules. However, direct metal insertion into the N–C(O) amide bond is extremely difficult as a consequence of amidic resonance. In this account, we summarize our work on the development of new cross-coupling reactions of amides by N–C bond activation, and briefly discuss other modern developments in this area.

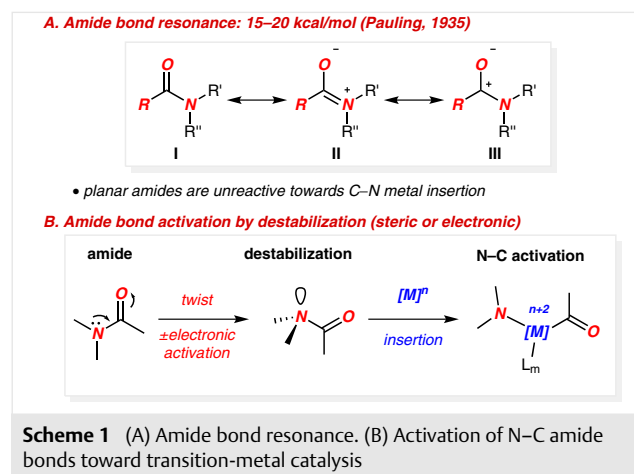
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Key words amides, cross-coupling, N–C bond activation, Suzuki coupling, decarbonylative coupling, C–H activation, palladium, nickel

1 Introduction

The amide bond is one of the most important functional motifs in chemistry and biology.^{1,2} Amide bonds are unique from all other functional groups in that they form the essential links in peptides and proteins. Amides feature as prevalent pharmacophores in small-molecule pharmaceuticals.³ It is estimated that the amide functional group is

present in 55% of potential drugs, while approximately 25% of all registered pharmaceuticals contain amides.^{4,5} A recent survey estimates that reactions involving amide bonds are among the most commonly performed processes by industrial organic chemists.⁶ Amides are present as key motifs in synthetic polymers, agrochemicals and functional materials.^{7,8} Moreover, amides serve as versatile, cheap and bench-stable intermediates in organic synthesis that are often derived from a different pool of precursors than carboxylic acids and halides.^{9,10} However, despite the central role of amides as extremely common pharmacophores in medicinal chemistry, and equally importantly as bench-stable intermediates in organic synthesis and basic monomer units in peptides and proteins, transition-metal-catalyzed transformations of amides by N–C bond activation remain vastly underutilized (Schemes 1–3).^{11,12}



The major challenge in transition-metal-catalyzed transformations of amides by N–C cleavage is the high activation energy required for the N–C(O) bond scission due to

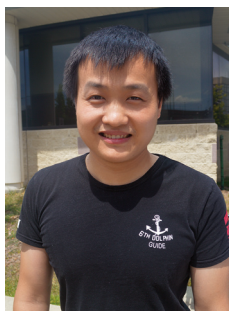
n_{N} to $\pi_{\text{C=O}}$ conjugation.¹³ Classic studies by Pauling demonstrated that planar amide bonds contain approximately 40% double-bond character as a consequence of resonance, which led to the breakthrough prediction of the α -helix.¹⁴ Amide delocalization is critical for the structure of proteins, but it also makes direct metal insertion into the N–C amide bond extremely difficult (Scheme 1).^{11,12}

Over the past four decades, transition-metal-catalyzed reactions have had a tremendous impact on the progress in synthetic organic chemistry, with the indisputable significance of these methods recognized by the 2010 Nobel Prize in Chemistry.¹⁵ The transition-metal-catalyzed activation of amide N–C bonds holds an enormous potential for widespread practical applications in organic synthesis due to: (1) the inherent benefits of amides as acyl or aryl electrophilic precursors in general metal-catalyzed reaction manifolds;^{11,12} (2) myriad potential metal-catalyzed transformations that could be discovered after the fundamental steps for N–C activation have been demonstrated and the ratio-

nale for the development of new reactions has been outlined;¹⁵ (3) the potential to employ the amide bond activation platform for late-stage drug modification and in molecular biology for site-selective peptide cleavage, which is not feasible with other acyl electrophiles.^{2–6}

Recently, significant conceptual advances have taken place in the field of amide bond cross-coupling (Scheme 2).^{16,17} In this account, we summarize our work on the development of new cross-coupling reactions of amides via N–C bond activation, and briefly discuss other modern developments in the area. We focus both on the mechanistic aspects of the amide bond distortion and the reactions mediated by different reaction manifolds by the N–C bond cleavage (i.e., acyl-type vs decarbonylative cross-couplings). We provide the reader with an overview of the area and its emerging, but crucial role to other methods of transition-metal-catalyzed cross-coupling to forge carbon–carbon bonds (Scheme 3).¹⁸ Moreover, we review the recent outstanding developments in the formation of carbon–oxygen,

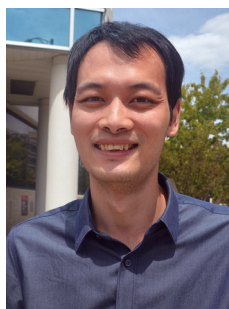
Biographical Sketches



Guangrong Meng was born in Shandong Province, P. R. of China, and received his B.Sc. degree from Dalian Medical University in 2011. He received

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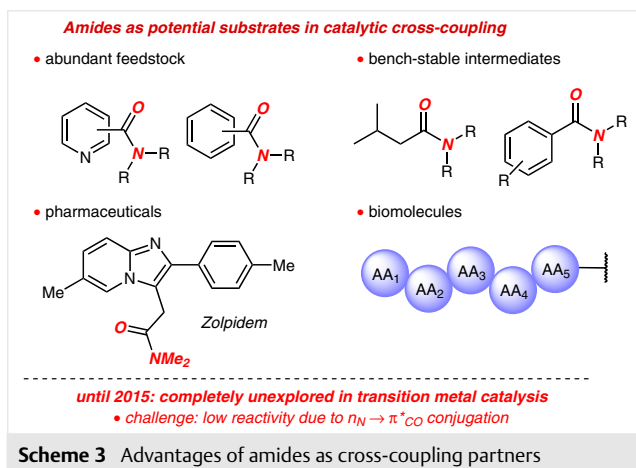
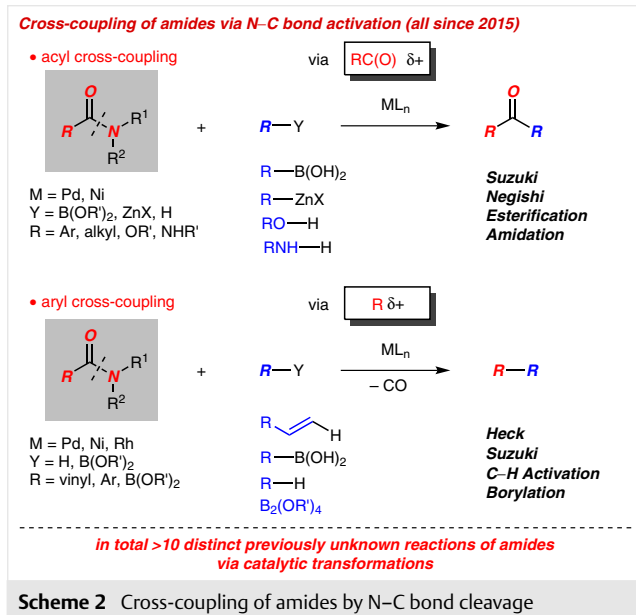


Michal Szostak received his Ph.D. from the University of Kansas with Professor Jeffrey Aubé in 2009. After postdoctoral stints at Princeton University with Professor David MacMillan

and at the University of Manchester with Professor David Procter, in 2014, he joined the faculty at Rutgers University. His research group is focused on the development of new syn-

thetic methodology based on transition-metal catalysis, transition-metal-mediated free-radical chemistry, and application to the synthesis of biologically active molecules.

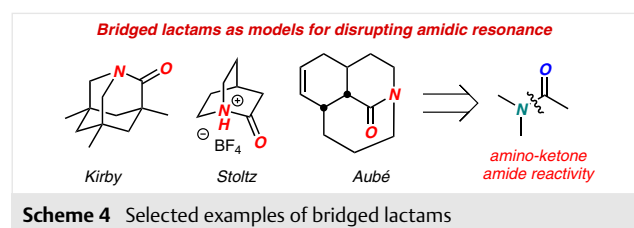
carbon–nitrogen and carbon–boron bonds by the amide N–C bond activation reported by Garg and Shi. The amide bond activation area is experiencing rapid growth; these transformations collectively demonstrate more than 10 previously undocumented reaction types of the amide bond published since the first reports in 2015.



2 Amide Bond Ground-State Distortion

In 2015, our laboratory introduced a new generic mode of activation of amide bonds by geometric distortion, whereby metal insertion into an inert amide bond (amide bond resonance of 15–20 kcal/mol in planar amides, ca. 40% double bond character) can proceed only if the classic Pauling amide bond resonance has been disrupted (Scheme 1B).^{19,20}

In consideration of the amide bond planarity¹³ and our own expertise in the area,²¹ we recognized that low-valent metal insertion into the effectively ‘double bonds’ in planar amides to afford versatile acyl-metal intermediates represents an unlikely scenario.²² Furthermore, we recognized that for the amide bond activation mode to be generally useful, the method must be mild, selective, and employ bench-stable, readily accessible reagents. In addition, it would be highly desirable if the rate of metal insertion could be controlled by both the substrate and catalyst system, which could potentially lead to a powerful cross-coupling selectivity by the judicious choice of reaction parameters and coupling partners.²³



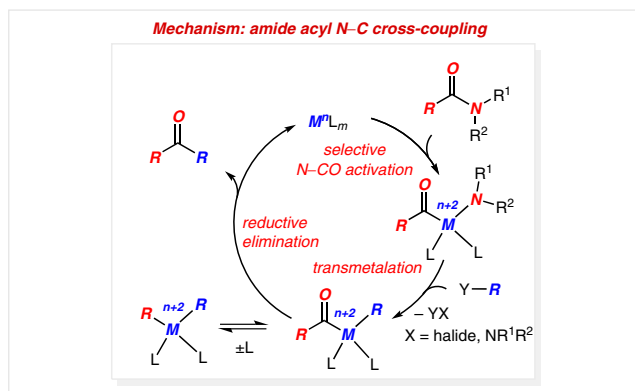
The work of Kirby, Stoltz, Aubé and others on twisted amides was significant in realizing the concept (Scheme 4).²⁴ These researchers showed that amide distortion in conformationally restricted cyclic lactams can be applied as a controlling feature to alter amidic resonance. Accordingly, we hypothesized that in amides in which amidic resonance is disfavored by steric or electronic reasons,²⁵ metal insertion into the N–CO bond should be feasible. On the basis of literature precedents²⁶ and our own studies on the N-/O-protonation aptitude of bridgehead bicyclic lactams,²⁷ we considered that in amides in which the additive Winkler–Dunitz distortion parameter ($\Sigma\tau + \chi_N$)^{27,28} is close to 50°, metal insertion should be thermodynamically favorable under mild, synthetically useful reaction conditions. A strong caveat of this model is that it seemingly contradicts the classic Pauling’s amide bond resonance, which assumes coplanarity of typical acyclic amides.

However, the emergence of bridged twisted lactams and the increased understanding of the structure–reactivity relationship of non-planar amide bonds realized in the last decade^{21,24} brought the possibility of effecting synthetically useful distortion in simple acyclic amides. Indeed, literature reports describe various examples of specific electronically and sterically distorted amides.²¹ However, most crucial to the success of the amide bond N–C cross-coupling is the massively underestimated fact that steric and electronic activation of the amide bond in simple generally accessible acyclic amides is relatively straightforward to achieve. All examples of amides reported to date undergoing the N–C bond cross-coupling feature markedly destabilized amide bonds. It should be noted that all these amides are bench-stable and readily available from carboxylic acid precursors by standard methods.⁹ The ability to promote previously elusive

transformations of amides via generic transition-metal-catalyzed activation modes represents a new powerful amide bond disconnection in organic synthesis with great relevance to biology, medicinal chemistry, polymers and materials science.

3 Acyl Amide N–C Cross-Coupling

The generic cycle for the cross-coupling of amides by acyl-metal intermediates is shown in Scheme 5. The key step involves a controlled metal insertion into the N–C amide bond. In this mechanism, bench-stable, readily accessible amides serve as acyl precursor equivalents to other acyl electrophiles, such as aroyl halides, anhydrides, thioesters, and esters.²⁹ The advantages of using amides as cross-coupling electrophilic partners include: (i) low price; (ii) stability; (iii) low toxicity; (iv) orthogonal cross-coupling conditions; (v) the potential to functionalize biologically active amide-containing molecules.



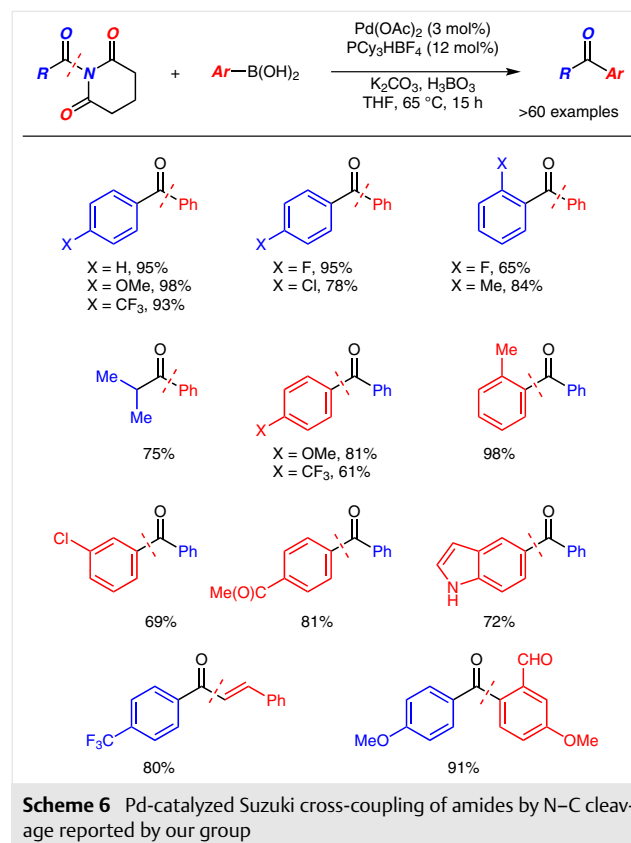
Scheme 5 Cross-coupling of amides via acyl-metal intermediates

3.1 Suzuki Cross-Coupling

We reported the first Suzuki cross-coupling of twisted amides with boronic acids using *N*-glutarimide amides as substrates (Scheme 6).^{19,20} These reactions proceeded smoothly in the presence of Pd(OAc)₂, PCy₃HBF₄ as a practical bench-stable trialkyl phosphonium salt, H₃BO₃ and K₂CO₃ in THF at 65 °C. Cross-coupling with a broad range of electrophilic substituents at both the amide and the boronic acid component occurred with high selectivity. The oxidative addition into the amide N–C bond over the aryl chloride was preferred under these conditions. Moreover, the cross-coupling of heterocycles and 1° and 2° alkyl amides was possible, affording ketone products in good to excellent yields.

Interestingly, we found that the use of acid was critical to obtain high reactivity. We propose that the switchable N-/O-amide bond coordination³⁰ might be responsible for this effect. In support of this mechanism, a good correlation be-

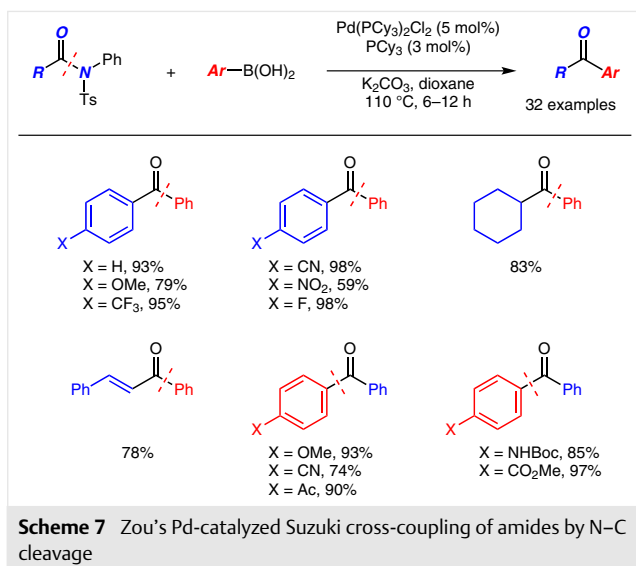
tween the reaction efficiency and the pK_a of acidic additives used in the cross-coupling at room temperature was observed. 2-Nitrobenzoic acid (pK_a = 2.16) afforded the best results. To our knowledge, this reaction represents the first example of the Suzuki cross-coupling of amides by N–C activation at room temperature, thus setting the stage for further developments of this synthetically valuable process.



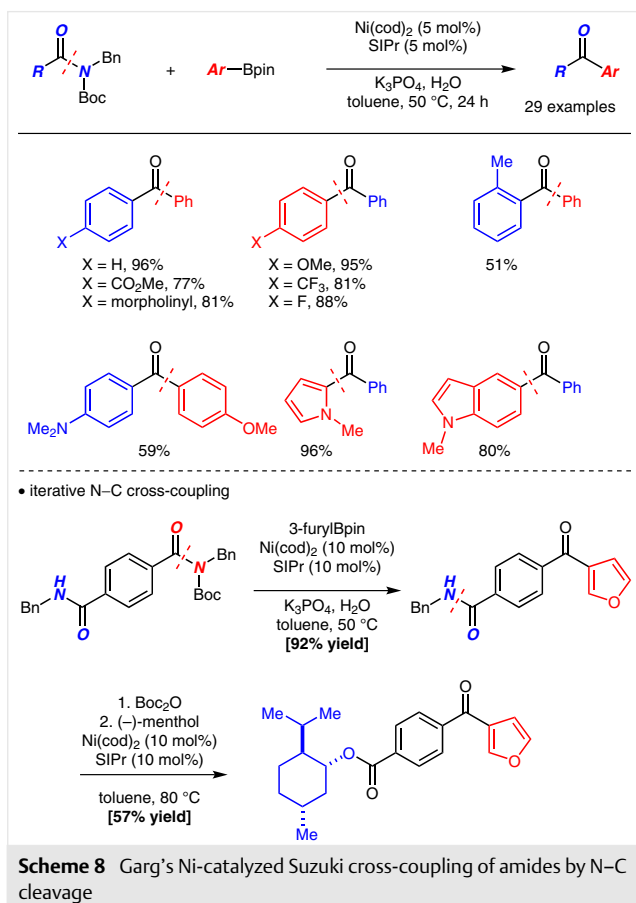
Scheme 6 Pd-catalyzed Suzuki cross-coupling of amides by N–C cleavage reported by our group

In the reaction development we screened the coupling of approximately >20 derivatives, including various sterically and electronically activated amides. We consistently found that the best results were obtained with *N*-glutarimide amides, while the related *N*-succinimide amides were found to be less reactive. A distinct advantage of these amide precursors relies on the exquisite steric distortion, which in combination with the electronic activation enables the high reactivity that cannot be easily achieved with other non-planar amides.

Independently, the Suzuki cross-coupling by amide N–C cleavage was reported by Zou³¹ (Scheme 7) and Garg³² (Scheme 8). The conditions reported by Zou employ *N*-Ts/Ar amides in the presence of Pd(PCy₃)₂Cl₂, K₂CO₃ and boronic acids in dioxane at 110 °C, while Garg reported the use of *N*-Boc/alkyl amides, Ni(cod)₂, SIPr [1,3-bis(2,6-di-*i*-propylphenyl)-4,5-dihydroimidazol-2-ylidene], K₃PO₄ and boronate esters in aqueous PhMe at 50 °C. In general, broad



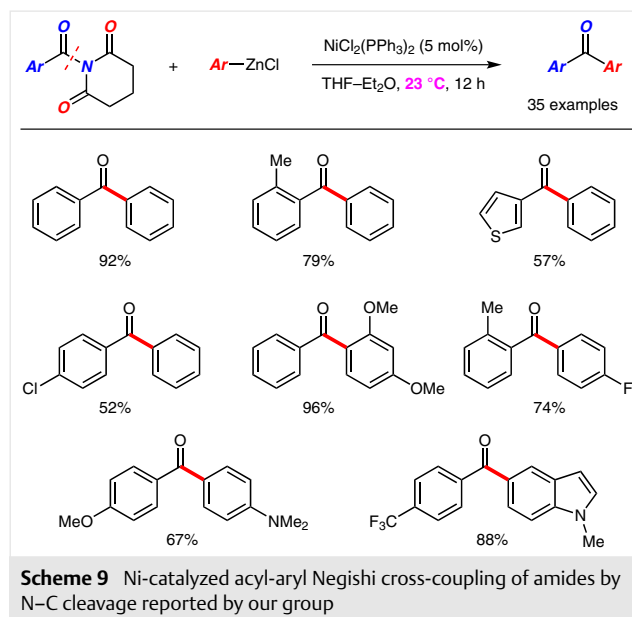
scope and good functional group tolerance was demonstrated. The Garg group showcased the utility of the amide bond N–C disconnection in sequential alternating C–C/C–O cross-couplings in high yields. It should be noted that all



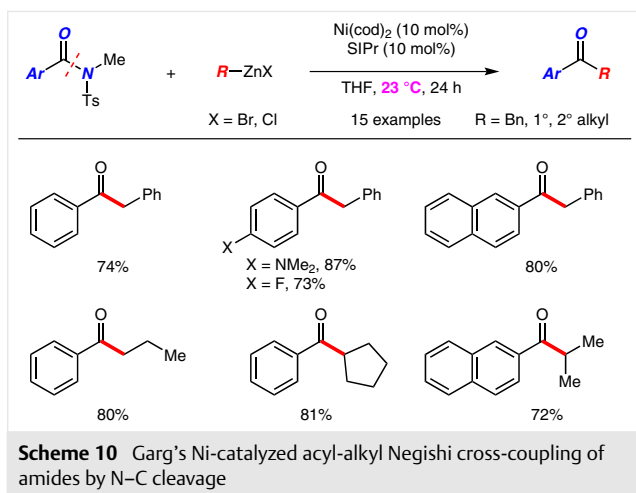
three types of amides are prepared from the same synthetic precursors, while the reactions should be considered as complementary in terms of substrate scope, reaction conditions, catalyst system and operational simplicity.³³

3.2 Negishi Cross-Coupling

Expanding the theme of ketone synthesis from amides, we developed the first Negishi diaryl ketone synthesis by N–C cleavage with good functional group tolerance (Scheme 9).³⁴ Notably, using bench-stable Ni(PPh₃)₂Cl₂ as the catalyst, the cross-coupling was accomplished within 15 minutes at room temperature. To our knowledge, this reaction represents the mildest conditions for the N–C amide bond cross-coupling reported thus far. The high functional group tolerance, low cost, and operational simplicity are attractive features of this protocol. The bench stability of amides and ready access to functionalized arylzinc reagents, also on an industrial scale, should make this method easily accessible to the synthetic community. It is worth noting that acyl-aryl Negishi-type and Fukuyama-type cross-couplings are less preceded due to different reactivity in oxidative addition/transmetalation steps.

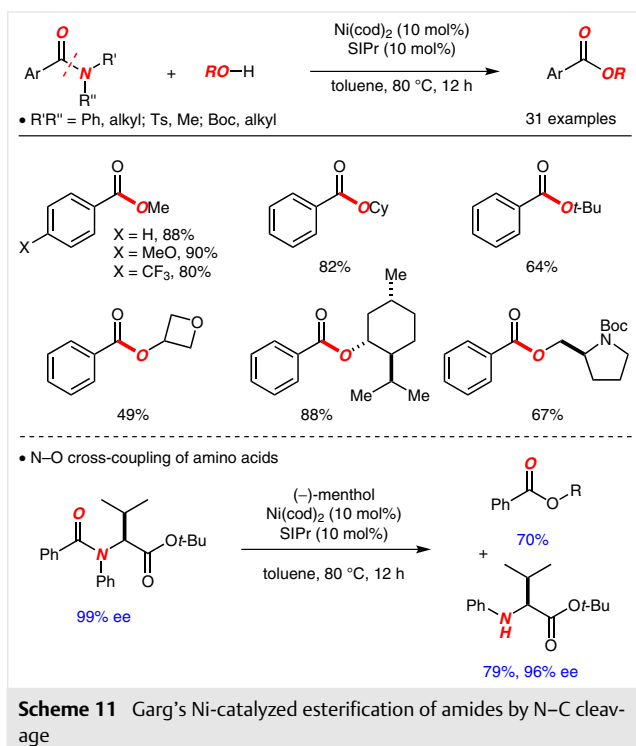


The Garg group reported an acyl-alkyl Negishi cross-coupling of aromatic amides using N-Ts/alkyl amides, Ni(cod)₂ and SIPr at room temperature (Scheme 10).³⁵ The coupling of benzyl, 1° and 2° alkyl organozinc reagents proceeded in high yields. This reaction represents the first use of alkyl nucleophiles in the transition-metal-catalyzed N–C amide cross-coupling. As in the Suzuki cross-coupling of amides, the two simultaneous reports on the acyl-aryl and acyl-alkyl Negishi cross-couplings convincingly demonstrate the potential of this reactivity platform in catalysis.³⁶



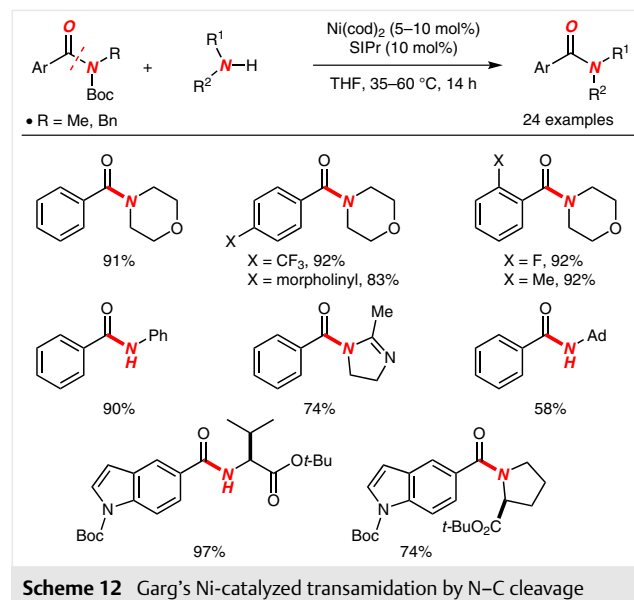
3.3 Esterification and Amidation via N–C Cross-Coupling

In their seminal 2015 report, the Garg group reported esterification of amides using $\text{Ni}(\text{cod})_2$ and SIPr in toluene at 80 °C (Scheme 11).^{37,38} A series of aromatic amides (e.g., anilides, *N*-Boc/alkyl) and an impressive range of alcohols underwent the cross-coupling in high yields and with retention of configuration when chiral substrates were used. From DFT calculations, it was suggested that the rate-determining step of the reaction involves oxidative addition of the N–C amide bond into $\text{Ni}(0)\text{-NHC}$ via a three-membered



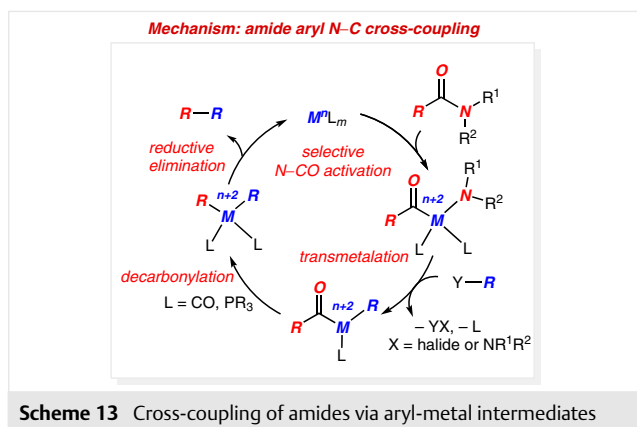
transition state (not shown). Interestingly, this mechanism appears to be different from the Pd-catalyzed Suzuki and Ni-catalyzed decarbonylative Suzuki reactions through N–C amide cleavage. Importantly, the putative transition state suggests that less distorted amides might become available as substrates for metal-catalyzed N–C activation reactions. The synthetically useful order of reactivity: *N*-Me,Ar-benzamide > *N*-H,Ar-benzamide, *N*-Me,alkyl-benzamide, *t*-Bu-alkyl ester was demonstrated.

More recently, this protocol has been extended to transamidation of aryl *N*-Boc/alkyl amides using $\text{Ni}(\text{cod})_2$ and SIPr in toluene at 35–60 °C (Scheme 12).³⁹ Heteroatom-containing, aromatic, sterically hindered and chiral amines readily furnished cross-coupling products in high yields. High chemoselectivity and the mildness of these procedures are noteworthy.



4 Decarbonylative Amide N–C Cross-Coupling

The general mechanism for decarbonylative amide N–C cross-coupling is shown in Scheme 13. In general, decarbonylative cross-couplings⁴⁰ are significantly more challenging than acyl cross-couplings as the success must accommodate selective metal insertion into the N–C bond, and controlled decarbonylation. The major advantage of using amides as aryl electrophile equivalents involves low price and stability of amide precursors (air, moisture), halide-free cross-coupling manifolds, and the potential for orthogonal C–N/C–X cross-coupling. To date, four previously unknown reactions of amides by decarbonylative cross-coupling have been reported (cf. ketone synthesis by acyl cross-coupling). This mode of amide bond activation has been achieved using Pd, Ni and Rh catalysis.

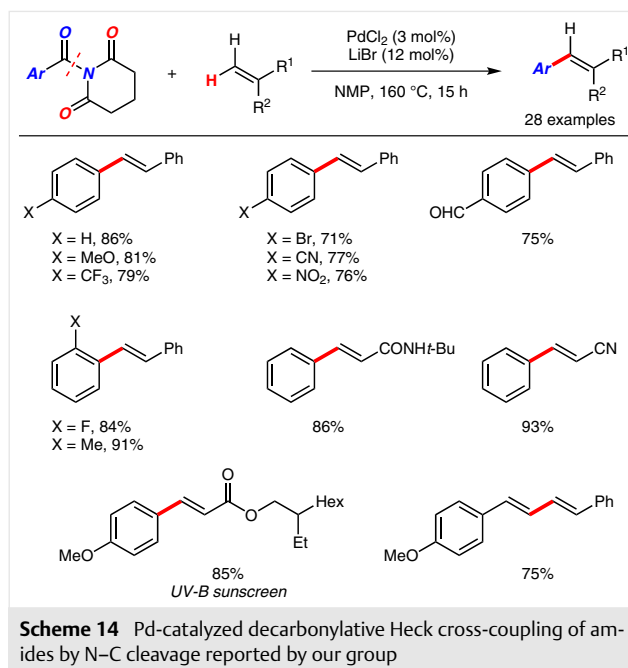


4.1 Heck Cross-Coupling

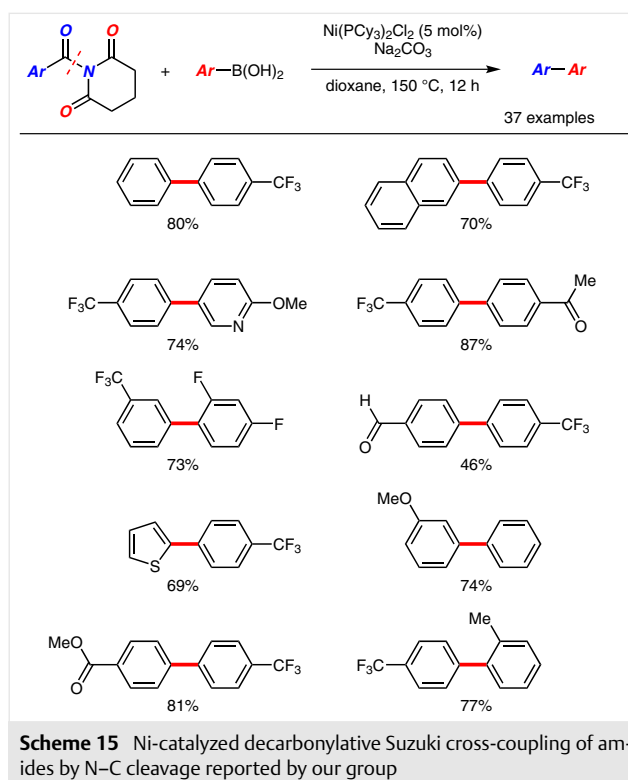
In 2015, we demonstrated the first decarbonylative cross-coupling by amide N–C bond cleavage using catalytic PdCl₂ and LiBr in NMP at 160 °C to deliver functionalized olefins in high yields and with excellent selectivity (Scheme 14).⁴¹ This Heck protocol was characterized by a broad substrate scope with respect to both coupling partners. A diverse array of electrophilic functional groups, such as chlorides, bromides, esters, ketones and even aldehydes remained intact under the reaction conditions, attesting to the high selectivity of the N–C amide bond cleavage. Moreover, this reaction is effective for the cross-coupling of styrenes, acrylic esters, amides, nitriles, α,α -disubstituted olefins, cyclic and aliphatic olefins. In addition, the coupling of an α,β -unsaturated substrate afforded the diene product with excellent selectivity. Through kinetic studies, we established that the reactivity of amides in comparison with other aryl precursors is in the following order: Ar–C(O)NR₂ \approx (Ar–CO)₂O \gg Ar–CO₂R. Moreover, the order of reactivity with respect to aryl halides is as follows: Ar–I $>$ Ar–C(O)NR₂ \gg Ar–Br. The reaction was applied to the gram-scale synthesis of a common UV-B sunscreen. Considering the industrial role of olefins, the reaction represents an exciting advance in decarbonylative Heck reaction protocols.

4.2 Suzuki Cross-Coupling

The Suzuki biaryl synthesis is among the most important synthetic reactions as a result of its efficiency, operational simplicity and reliability.^{11,15} In 2016, we disclosed the first decarbonylative Suzuki cross-coupling by N–C bond cleavage using bench-stable Ni(PCy₃)₂Cl₂ and Na₂CO₃ in dioxane at 150 °C (Scheme 15).⁴² Interestingly, the reaction proceeded with high decarbonylation selectivity, while the insertion occurred selectively at the N–C bond, with cleavage of the alternative σ N–C bond not observed under these reaction conditions. The reaction proved to be remarkably robust to the electronic nature of the reaction



components. A series of electron-neutral, electron-donating and electron-withdrawing substituents on the amide and the boronic acid coupling partner underwent the reaction in high to excellent yields. The synthesis of fluorine-containing biaryls was accomplished using electron-deficient,



generally less reactive in transmetalation boronic acids, highlighting the potential of this protocol. In terms of functional group tolerance (esters, ketones, aldehydes, heterocycles, ethers), the reaction showed good complementarity to C–O couplings, while using the bench-stable catalyst system and readily available amide precursors. Stoichiometric ESI-MS measurements were used to detect the presence of Ni-aryl, as well as ArCONiCO_3^{2-} intermediates, suggesting a key role of carbonate to facilitate transmetalation.

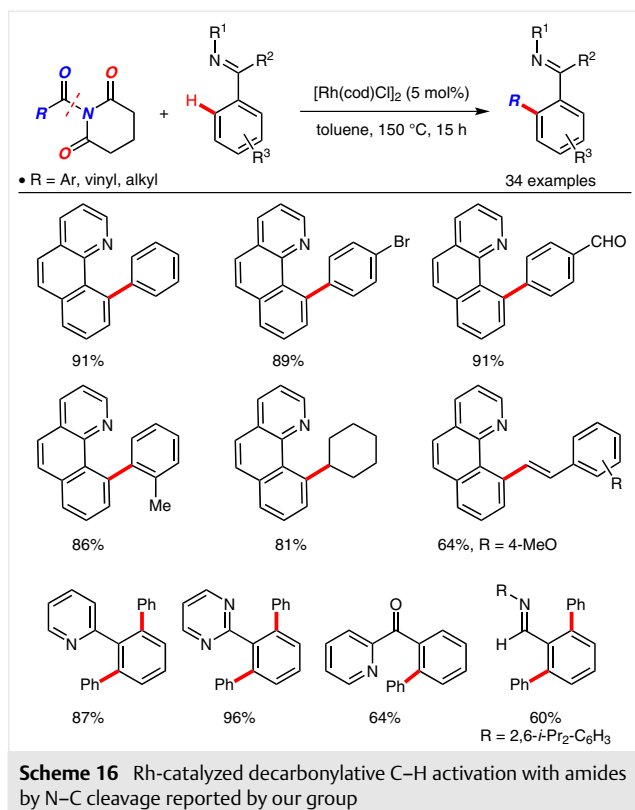
4.3 C–H Activation

The first example of directed sp^2 C–H bond functionalization with amides as coupling partners was reported by our group in 2016 using catalytic $[\text{Rh}(\text{cod})\text{Cl}]_2$ in toluene at 150 °C (Scheme 16).⁴³ Using this protocol, aryl, vinyl and even alkyl amides underwent efficient insertion/decarbonylation to provide direct C–H functionalization products with substrates containing a variety of directing groups, including quinolines, pyridines, pyrazoles, pyrimidines, 2-carboxypyridines and imines. Sensitive functionalities (bromide, aldehyde, ketone, ester) were well-tolerated under the reaction conditions. Notably, C–H activation through the inherently difficult six-membered metallacycle

was readily accomplished, while the use of imines furnished synthetically valuable biaryl aldehydes after hydrolysis. Perhaps most remarkably, the turnover number of >1,000 demonstrated in this reaction is the highest reported to date in amide N–C activation reactions, a finding which bodes well for the application of amides as coupling partners in a broad range of C–H activation protocols.

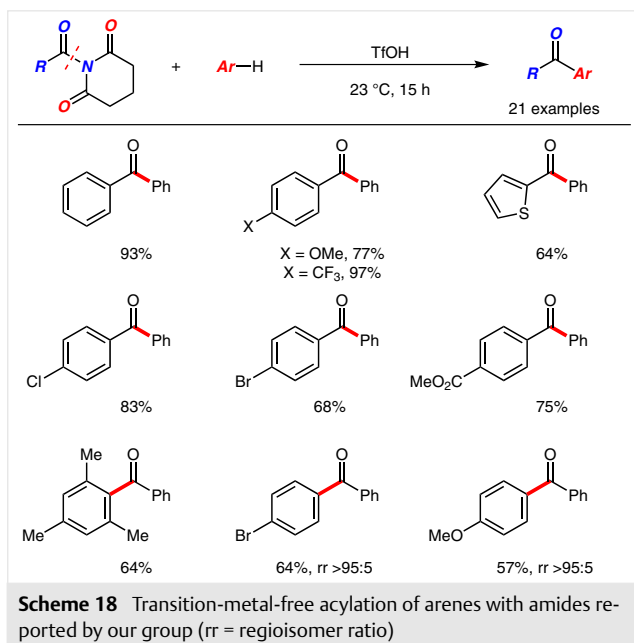
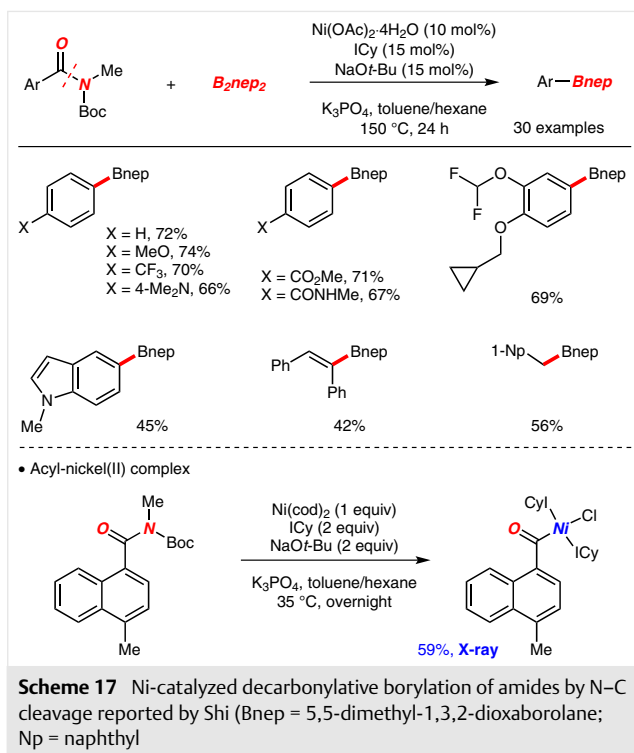
4.4 Decarbonylative Borylation

In 2016, the Shi group reported the first decarbonylative borylation of amides by N–C bond cleavage in the presence of B_2nep_2 , $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, commercially available 1,3-dicyclohexylimidazolium chloride (ICy), NaOt-Bu and K_3PO_4 in toluene/hexane at 150 °C (Scheme 17).⁴⁴ The broad functional group tolerance of this protocol is noteworthy. The authors found that aryl *N*-Boc/alkyl amides afforded the highest yields in the reaction. Vinyl and benzyl borylation by amide scission was also accomplished using this method. From a stoichiometric study with $\text{Ni}(\text{cod})_2$, the NHC ligand, NaOt-Bu and K_3PO_4 in toluene/hexane at 35 °C, the nickel-acyl species was isolated and the structure was determined by X-ray crystallography. The acyl-nickel intermediate was found to be stable at room temperature. The complex exhibited similar reactivity to that observed in the borylation reaction, and was converted into the final product in the presence of K_3PO_4 at 60 °C. The isolation of the Ni-acyl complex suggests that ligand exchange on the Ni(II) might be facile, while decarbonylation/transmetalation might be limiting. The study provides valuable insight into the amide N–C cross-coupling. The complex was found to be catalytically active in the N–C borylation.



5 Transition-Metal-Free Activation of Amide Bonds

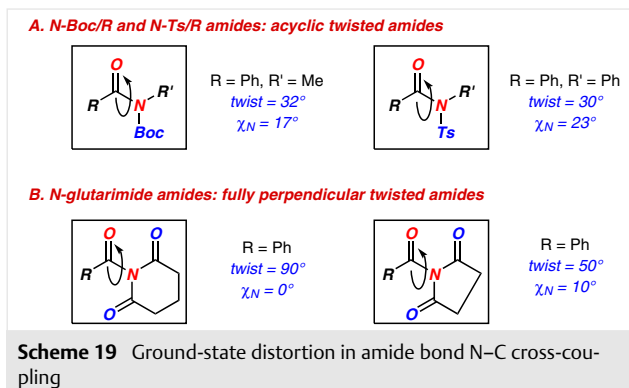
Recently, there has been a strong impetus to develop transition-metal-free carbon–carbon bond-forming reactions.⁴⁵ Metal-free reactions are often cheaper than the metal-catalyzed variants, while removal of trace metal impurities can provide a significant manufacturing issue. In this context, we considered the use of amides as acyl equivalents in the classic Friedel–Crafts reaction. We found that when *N*-glutarimide amides were treated with TfOH in the presence of an appropriate arene at room temperature or at 60 °C for electron-deficient arenes, the corresponding diaryl ketones were formed in good yields and with excellent regioselectivity (Scheme 18).⁴⁶ The reaction showed good functional group compatibility, tolerating sensitive aryl chlorides and bromides on either of the coupling partners.



To our knowledge, this method represents the first general Friedel–Crafts acylation using acyclic amides as substrates.

6 Mechanistic Studies

In our general mechanistic hypothesis, low-valent metal insertion into the N–C amide bond can occur only after the amide has been destabilized (Scheme 1B). This is in agreement with the energetic barrier required to activate otherwise inert planar amide bonds. To gain insight into the structures of amides undergoing N–C cross-coupling, we performed detailed mechanistic investigation of the ground-state amide distortion in relevant amides (Scheme 19).^{47,48}



Using DFT and crystallographic studies, we determined that *N*-acyl-*tert*-butyl carbamates (Boc) and *N*-acyl-tosylamides (Ts), two classes of amides that have been used as prototypes in the amide bond cross-coupling, contain significantly distorted amide N–C bonds in the ground state (Scheme 19A).⁴⁷ For example, *N*-Boc/alkyl and *N*-Ts/Ar amides that have been shown to be particularly reactive in amide N–C cross-coupling feature amide bonds approaching one-third maximum amide distortion ($\tau = 32.06^\circ$, $\chi_N = 17.36^\circ$, $\tau = 30.39^\circ$; $\chi_N = 22.28^\circ$, respectively). We determined that these *N*-Boc/alkyl and *N*-Ts/Ar amides can freely rotate around the N–CO axis.

Furthermore, we established that *N*-glutarimide amides employed by us as models for N–C cross-coupling contain uniformly twisted (close to $\tau = 90^\circ$) amide bonds irrespective of the steric demand at the amide carbon side (Scheme 19B).⁴⁸ These *N*-glutarimide amides are distorted by a new destabilization mechanism of the amide bond, which features an inverted rotational profile of the amide linkage. The high reactivity observed in N–C activation reactions of *N*-glutarimide amides correlates with structural ground-state distortion. Collectively, these results strongly support the amide bond destabilization as a blueprint for activation of amides toward transition-metal-catalyzed N–C bond cleavage.^{49,50}

7 Conclusions and Outlook

In conclusion, the field of amide bond N–C cross-coupling has experienced an exponential growth over the past two years and huge conceptual advances have been made in this area. The results reviewed here demonstrate that the formation of carbon–carbon, carbon–oxygen, carbon–nitrogen and carbon–boron bonds has been successfully accomplished. These new methods are of considerable interest given the central importance of amides in organic chemistry and biology. At present, steric distortion and/or electronic activation appear to be required for the efficient N–C metal insertion, in agreement with Pauling's resonance theory. An especially exciting functionalization involves the use of simple anilides, as in the Ni-catalyzed esterification. Furthermore, the progress in decarbonylative cross-couplings is noteworthy. Future research in the field will need to address the practical aspects of the amide N–C bond cleavage. Moreover, mechanistic investigations focused on the interplay between catalysts and substrates will enable the design of more efficient catalytic processes. We are convinced that the amide bond N–C activation platform will reach its maturity in the coming years. Ultimately, general reactions involving amide N–C bond activation will be of significant utility to organic chemists.

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