Classes of Amides that Undergo Selective N–C Amide Bond Activation: The Emergence of Ground-State-Destabilization

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ABSTRACT: Ground-state-destabilization of the N–C(O) linkage represents a powerful tool to functionalize the historically inert amide bond. This burgeoning reaction manifold relies on the availability of amide bond precursors that participate in weakening of the $n_N \rightarrow \pi^*_{C=O}$ conjugation through N–C twisting, N pyramidalization and n_N electronic delocalization. Since 2015, acyl N–C amide bond activation through ground-state-destabilization of the amide bond has been achieved by transition-metal-catalyzed oxidative addition of the N–C(O) bond, generation of acyl radicals and transition-metal-free acyl addition. This Featured Review summarizes contributions of our laboratory in the development of new ground-state-destabilized amide precursors enabled by twist and electronic activation of the amide bond, and synthetic utility of ground-state-destabilized amides in cross-coupling reactions and acyl addition reactions. The use of ground-state-destabilized amides as electrophiles enables a plethora of previously unknown transformations of the amide bond, such as acyl coupling, decarbonylative coupling, radical coupling and transition-metal-free coupling to forge new C–C, C–N, C–O, C–S, C–P and C–B bonds. Structural studies of activated amides and catalytic systems developed in the last decade enable to change the view of the amide bond from the "traditionally inert" to "readily modifiable" functional group with continuum of reactivity dictated by ground-state-destabilization.

1. Amide Bonds as Inherently Stable Linkages in Organic Synthesis

The amide motif represents the most fundamental building block in chemistry and biology.[1-6] In drug discovery, 25% of registered drugs and 55% of medicinal candidates contain amide functionality, while amide bond forming reactions are the most common synthetic method performed by medicinal chemists.[7-8] Compared to other carboxylic acid derivatives, typical amide bonds feature high resonance energy (15-20 kcal/mol) due to strong $n_N \rightarrow \pi^*_{C=O}$ conjugation, resulting in approximately 40% double bond character.[9-13] This conjugation results in high stability of the amide bond, making direct activation of the N–C(O) linkage a formidable challenge.

However, as an immensely valuable building block in organic synthesis, selective activation of amide bonds is a popular field of research and has historically attracted broad interest of synthetic chemists. In order to unlock ground-state-destabilization of amides, two strategies can be generally considered: (1) geometric alteration of the amide bond by twist and pyramidalization; and (2) electronic activation. The origin of ground-state-destabilization of amides can be traced to the landmark contributions made by Lukeš, Kirby, Stoltz, Greenberg, Aubé and others in the area of bridged lactams.[14-17] By placing the amide bond in a rigid bridged ring system, these cyclic twisted amides feature structural deformation of the amide bond, thus disrupting its planarity and resonance.[18-22]

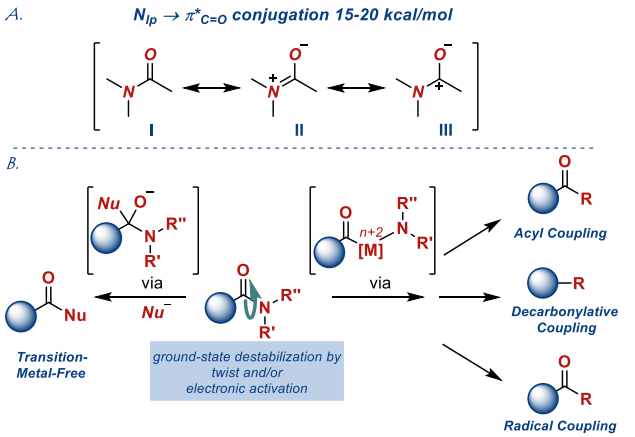
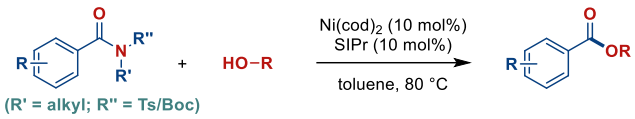


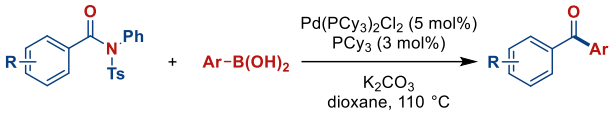
Figure 1. (A) Amide bond resonance. (B) Amide bond N–C(O) activation enabled by ground-state-destabilization.

As another important avenue, acyclic twisted amides have been developed by placing sterically bulky substituents at the nitrogen atom of the amide bond.[23-24] These strategies often overlap with electronic activation of the amide bond by n_N electronic delocalization.[23-24] By installing electron-withdrawing groups on the nitrogen atom of the amide bond, amidic resonance decreases by reverting the traditional $n_N \rightarrow \pi^*_{C=O}$ conjugation to an exocyclic activating group. As a result, destabilized amide bonds feature weaker N–C(O) resonance with more electrophilic character of the carbonyl group, which permits to achieve selective activation of amides.

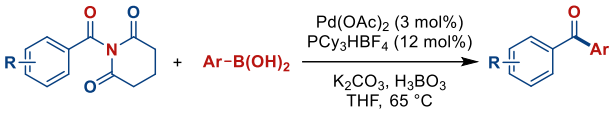
Scheme 1. Esterification of *N*-Ts and *N*-Boc Activated Amides



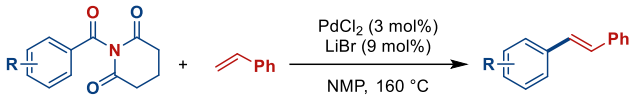
Scheme 2. Suzuki–Miyaura Cross-Coupling of *N*-acyl-tosylamides



Scheme 3. Suzuki–Miyaura Cross-Coupling of *N*-acyl-glutarimides



Scheme 4. Decarbonylative Heck Cross-Coupling of *N*-acyl-glutarimides



Among amide activation strategies in organic synthesis, direct transition-metal-insertion and transition metal-free addition are widely applied in amide bonds activation.[25-36] Spectroscopic, crystallographic and computation techniques have been used to garner structural and energetic parameters of ground-state destabilization of the amide bond in comparison with their planar analogues.[37-43]

Since 2015, remarkable progress has been achieved in selective acyl N–C activation reactions of readily prepared acyclic ground-state-destabilized amides (Figure 1). This area was launched by three independent reports by Garg,[44] Zou,[45] and our group[46,47] on Ni-catalyzed esterification and Pd-catalyzed Suzuki cross-coupling of acyclic activated amides as electrophiles (Schemes 1-3). This was quickly followed by the first example of decarbonylative cross-coupling of amides reported by our group (Scheme 4).[48]

These studies sparked tremendous progress in amide bond activation by the synthetic community.[25-36] Among the early studies, the Garg group focused on non-precious Ni catalysis for amide bond activation.[28] With the rationalization of selective amide activation via ground-state destabilization,[24] our group developed a user-friendly Pd–NHC catalysis platform[25] and highly reactive amide bond precursors, such as *N*-acyl-glutarimides.[49] In parallel, transition-metal-free reactions of ground-state-destabilized amides have been rapidly developed, providing an alternative disconnection in organic synthesis.[26]

In a broader context of amide bond activation, the acyl N–C activation by ground-state-destabilization should also be compared with a tremendously important field of electrophilic activation of amides.[31,32] These reactions proceed by initial O-functionalization and typically retain N–C bond in the products. These two classes of functionalizations of amides can regarded as complementary in terms of amide bond properties that are required for each pathway (O-nucleophilic vs. electrophilic amides).

In this Featured Review, we summarize contributions of our laboratory in the development of new ground-state-destabilized amide precursors enabled by twist and electronic activation of the amide bond, and synthetic utility of ground-state-destabilized amides in cross-coupling reactions and acyl addition reactions. Structural studies of activated amides and catalytic systems developed in the last decade enable to change the view of the amide bond from the "traditionally inert" to "readily modifiable" functional group with continuum of reactivity dictated by ground-state-destabilization of broad interest to organic synthesis. The present review is focused on classes of amides that undergo distortion and their structural effects that enable amide bond activation. For mechanistic studies in amide bond activation, the Reader is encouraged to consult already published reviews.[37–39]

2. Amides that Undergo N–C Bond Activation: The Emergence of Ground-State-Destabilization

In general, ground-state-destabilized amides that undergo N–C bond activation can be divided into the following classes: (1) cyclic imides; (2) *N*-acyl-sulfonamides; (3) *N*-mono-Boc-amides; (4) *N*,*N*-Boc$_2$-amides; (5) *N*-acyl-amides; (6) anilides; (7) *N*-heterocyclic amides. The common feature is decrease of $n_N \rightarrow \pi^*_{C=O}$ conjugation by a combination of twist and electronic activation. It is worth noting that *N*-mono-Boc and *N*,*N*-Boc$_2$-amides represent the most wide-ranging method of activation of 2° and 1° amide bonds, while *N*-aryl and *N*-heterocyclic amides can be electronically-activated in the absence of geometric alterations of amide bond.[23–25]

Synthesis of Activated Amides. A critical point in discussing amide bond destabilization is synthetic access to twisted amides. In general, two major synthetic routes can be employed: (1) acylation of amines with activated carboxylic acid derivatives; (2) direct N-acylation of primary or secondary amides. In terms of synthetic utility, the second route is a vastly preferred method to activate planar amide bonds since it enables to utilize common primary and secondary amides in cross-coupling manifolds. The most useful examples of activating groups that can be accessed by this route are mono-Boc and di-Boc amides (sections 2.3. and 2.4.). These amides should always be tested in developing new technologies for cross-coupling of amides. In contrast, amides accessed by the standard amine acylation route, such as cyclic amides (section 2.1.) or N-acyl-sulfonamides (section 2.2.) often offer advantages in terms of stability of the N-activating group. These amides are recommended for the development of new technologies, where the cleavage of the activating N–C bond becomes an alternative pathway.

2.1. Cyclic Imides

2.1.1. *N*-Acyl-Glutarimides. Since the first reported example by our group in 2015,[46] *N*-acyl-glutarimides have become the most frequently used amides in acyl and decarbonylative N–C(O) cross-couplings.[49] The synthesis of *N*-acyl-glutarimides is by direct nucleophilic substitution of acyl chlorides with glutarimide.

As the most reactive amide derivative in catalytic N–C(O) cross-coupling, X-ray diffraction study revealed the critical structural features of *N*-benzoyl-glutarimide, such as perpendicular twist of the amide bond (τ = 85.7°; χ_N = 5.6°) and very long N–C(O) bond (1.474 Å), indicating significant weakening of the amide bond (Figure 2). The distortion parameters of amides discussed can be compared with a planar benzamide, N–C(O) of 1.342 Å, τ = 0.0°, χ_N = 0.1°. Note that Winkler-Dunitz parameters of the amide bond in Figures 2-24 correspond to the exocyclic N-acyl bond. For an extended discussion of accessible geometric bond distortion of acyclic twisted amides, see ref. 23. An intriguing question pertains to from what geometric and energetic parameters an amide is considered twisted. Recent studies demonstrate a continuum of structural deformations of the amide bond and their impact on reactivity.[23] The distortion values should always be compared with the theoretical maximum distortion of $\Sigma_{(\tau + \chi N)}$ = 150°; however, the highest values achieved so far for acyclic amides are closer to 90°, which is likely close to the highest achievable distortion in the absence of geometric constraints, such as in bridged lactams. In general, values of $\Sigma_{(\tau + \chi N)} \approx 50°$ are in the range of O-/N-switch of protonation of amide bonds, and amides in this range should be considered twisted.[41] However, it is worth pointing out that electronic activation will additionally activate amide bonds towards N–C(O) reactivity.

Perhaps most importantly, these amides feature very high rotational energy barrier (ΔE = 13.73 kcal/mol) of the twisted conformation, indicating that *N*-acyl-glutarimides show strong preference to remain in the highly twisted ground-state-destabilized state irrespective of the sterics at the α-carbon atom. This high rotational barrier is unique among all derivates of acyclic twisted amides discovered to date, and arises from a steric interaction of the R–C(O) amide carbonyl group with the exocyclic N–C(O) glutarimide substituents. Furthermore, ^{15}N NMR analysis revealed that electron-donating substituents on the aromatic ring result in elongation of the N–C(O) bond, which could make the amide more reactive towards activation reactions.[50]

Energetic characteristics of the amide bond in *N*-acyl-glutarimides were determined at the B3LYP/6-311++G(d,p) level. Using the COSNAR method,[18,19] resonance energy (E_R) of the amide bond in *N*-acyl-glutarimides (E_R = -1.49 kcal/mol) practically disappeared[51] (note that amidic resonance of planar *N*,*N*-dimethylacetamide is E_R = 18.3 kcal/mol). Proton affinities (PA) and differences between *N*- and *O*-protonation affinities of *N*-acyl-glutarimides (ΔPA = 16.5-23.5 kcal/mol) showed that these amides strongly favor *O*-protonation. Computations also revealed the possibility of intramolecular *O*-/*O*-protonation switch between the amide and glutarimide oxygens, further activating the amide bond towards metal insertion.

Structural analogues of *N*-acyl-glutarimides, such as 3,3-dimethyl, 3,3-tetramethylene, 3,3-pentamethylene, 3-phenyl-glutarimide and 1,8-napthalimide have been reported.[52] The effect of glutarimide ring in these structures affect the twist angle from 77.7 to 89.1°, while rotational barriers from 11.77 to 11.98 kcal/mol.

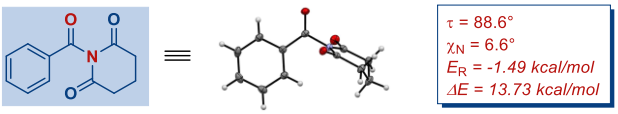


Figure 2. Structure of *N*-acyl-glutarimide (CCDC 1483077).

2.1.2. *N*-Acyl-Succinimides. *N*-Acyl-succinimides represent five-membered ring analogues of perpendicularly twisted *N*-acyl-glutarimides.[46] *N*-Acyl-succinimides were characterized as half-twisted amides by our group in 2017.[53-55] The synthesis of *N*-acyl-succinimides is by direct nucleophilic acyl substitution of acyl chlorides and succinimides. X-ray diffraction showed approximately half-rotated amide bond (τ = 46.1°; χ_N = 9.5°) with the N–C(O) amide bond length of 1.439 Å (Figure 3), indicating stronger amide bond than in *N*-acyl-glutarimides. Resonance energy (E_R = -1.49 kcal/mol) and rotational barrier (ΔE = 7.42 kcal/mol) are consistent with complete disappearance of amidic resonance and high reactivity in N–C(O) amide bond activation.[51] ΔPA (21.0-28.8 kcal/mol) demonstrated similar *O*-protonation preference to *N*-acyl-glutarimides. These structural features render several inherent advantages of *N*-acyl-succinimides, such as (1) higher stability of the amide bond; (2) more sterically-accessible N–C(O) bond surrounded by the compact five-membered ring; and (3) potential for selective tuning of metal insertion into N–C(O) amide bond by twist.

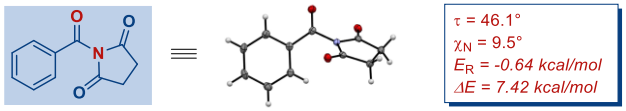


Figure 3. Structure of *N*-acyl-succinimide (CCDC 1487224) .

2.1.3. *N*-Acyl-Saccharins. In 2016, our and Zeng group reported Pd-catalyzed Suzuki-Miyaura coupling and decarbonylative Heck reaction with *N*-acyl-saccharin amides.[56-58] This design was inspired by the high reactivity of *N*-acyl-glutarimides[46] and the studies by Zou on acyclic *N*-acyl-sulfonamides.[45] The X-ray structure demonstrated that *N*-acyl-saccharin contains a moderately distorted amide bond (τ = 23.0°; χ_N = 12.5°) with the N–C(O) bond length of 1.421 Å (Figure 4). Resonance energy and rotational barrier were determined to be 2.0 kcal/mol and 4.87 kcal/mol. Similar to *N*-acyl-glutarimides, *N*-acyl-

saccharins favor protonation at the oxygen atom (ΔPA = 11.8 kcal/mol). Interestingly, protonation of the exocyclic *N*-acyl group is preferred over the ring oxygen (ΔPA > 5.0 kcal/mol). Thus, structural and energetic parameters of *N*-acyl-saccharins confirm ground-state-destabilization of the amide bond in these systems. *N*-Acyl-saccharins are derived by acylation from cheap, abundant and non-toxic sweetener saccharin. The key feature differentiating *N*-acyl-saccharins is strong electronic activation of N–C(O) in presence of an electron-withdrawing sulfonyl moiety, rendering these amides highly reactive in N–C(O) amide bond activation.

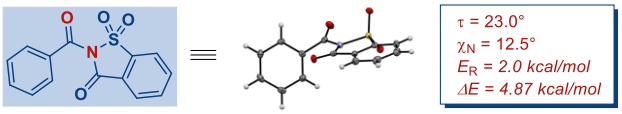


Figure 4. Structure of *N*-acyl-succinimide (CCDC 1487224).

2.1.4. *N*-Acyl-Phthalimides. Similar to *N*-acyl-succinimides, *N*-acyl-phthalimides can be characterized as half-twisted, electronically-activated amides.[59] Crystallographic studies showed high amide bond twist (τ = 55.0°; χ_N = 8.4°).[50] Resonance in these amides completely disappears (E_R = -1.83 kcal/mol), indicating electronically-disconnected amide bond (Figure 5).[51] Furthermore, ΔPA (18.1-25.1 kcal/mol) indicates a strong preference for *O*-protonation. Compared with aliphatic *N*-imide activators, such as *N*-acyl-glutarimides and *N*-acyl-succinimides, a challenge of using *N*-acyl-phthalimides in catalytic N–C(O) activation is unselective cleavage of benzylic bonds. This side reaction can typically be overcome by using Pd–NHC catalysis (NHC = N-heterocyclic carbenes) owing the strong σ-donating property of NHC ancillary ligands in the presence of mild bases, which leads to selective N–C(O) acyl cleavage.[59]

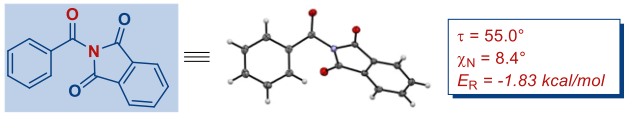


Figure 5. Structure of *N*-acyl-phthalimide (CCDC 1483079).

2.1.5. *N*-Acyl-Hydantoins. In 2018, our group reported structural and energetic properties of *N*-acyl-hydantoins as heteroatom analogues of *N*-acyl-succinimides.[60] *N*-Acyl-hydantoins contain highly distorted acyclic amide bonds (τ = 46.1°, χ_N = 9.5°) with the N–C(O) bond length of 1.440 Å in the parent *N*-benzoyl-hydantoin, and further increased distortion in *N*-acyl-5,5-dimethylhydantoin (τ = 49.5°, χ_N = 13.3°; N–C(O) = 1.447 Å for) (Figure 6). Resonance energy is non-existent (E_R = -0.1 kcal/mol), while the high rotational barrier (ΔE = 6.07 kcal/mol) indicates strong preference for non-planar geometry. Interestingly, heteroatom substitution of the activating ring (C to N) increases distortion of the exocyclic acyl bond, with *N*-pyramidalization as the main alteration (cf. succinimide). Thus, *N*-acyl-hydantoins represent another class of electronically-disconnected amides. The presence of the free NH group on hydantoin is tolerated in N–C(O) activation as shown by our and Zeng group in Suzuki–Miyaura cross-coupling using Pd–NHCs or Pd–phosphines.[61-62]

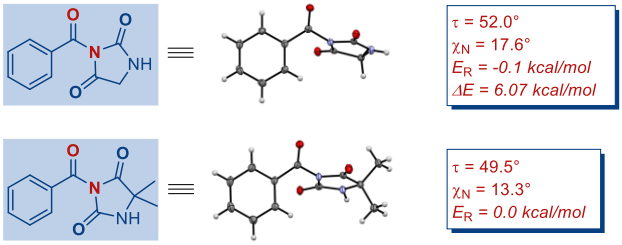


Figure 6. Structures of *N*-acyl-hydantoins (CCDC 1860546, 1860547).

2.1.6. *N*-Acyl-Oxazolidinones. In 2020, the Zeng group reported *N*-acyl-oxazolidinones for palladium-catalyzed Suzuki–Miyaura cross-coupling by N–C(O) activation.[63] *N*-Acyl-oxazolidinones are comparatively less twisted (τ = 18.2°; χ_N = 5.6°) than *N*-acyl-succinimides and *N*-acyl-hydantoins (Figure 7). Nevertheless, these bench-stable reagents can be selectively cleaved at the exocyclic amide bond using Pd(II)–NHC precatalysts. As expected from bond distortion, high temperature (110 °C) is required for N–C(O) bond activation.

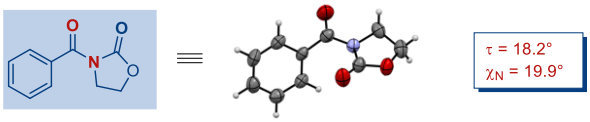


Figure 7. Structures of *N*-acyl-oxazolidinone (CCDC 287740).

2.1.7. *N*-Acyl-Isatins. In 2019, the Zeng group reported *N*-acyl-isatins as novel amide-based electrophilic reagents for N–C(O) bond activation.[64] *N*-Acyl-isatins feature two adjacent carbonyl groups on the same side of the five-membered ring and are thus analogous to *N*-acyl-α-ketoamides. Crystallographic analysis indicated that the parent compound in this class contains distorted amide bond (τ = 21.95°, χ_N = 13.87°, N–C(O) = 1.412 Å) (Figure 8). These reagents are unique in that selective cleavage of the exo- or endocyclic amide bond can be achieved under different reaction conditions resulting in acylation, arylation or transamidation reactions.

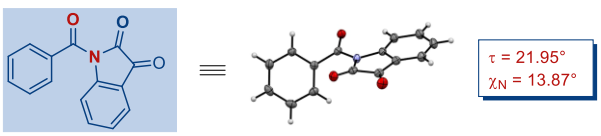


Figure 8. Structure of *N*-acyl-isatin (CCDC 1815157).

2.1.8. *N*-Acyl-Lactams. In 2021, our group expanded the range of amide bond cross-coupling reagents to *N*-acyl-δ-valerolactams as highly efficient mono-*N*-acyl-activated amides for cross-coupling.[65] These reagents combine the

reactive features of *N*-acyl-glutarimides with acyclic *N*-acyl-amides. The exocyclic amide bond of the parent *N*-benzoyl-*δ*-valerolactam showed higher amide bond distortion (τ = 33.2°, χ_N = 20.8°, N–C(O) = 1.408 Å) than the endocyclic amide bond (τ = 13.1°, χ_N = 22.2°, N–C(O) = 1.396 Å) (Figure 9). Resonance energy of the exocyclic amide bond (E_R = 5.6 kcal/mol) is significantly lower than that of the endocyclic bond (E_R = 9.2 kcal/mol), indicating the structural and energetic preference for N–C(O) bond cleavage. In addition, ΔPA revealed that the amide bond strongly favors protonation at the amide oxygen atom (ΔPA = 12.0 kcal/mol) of the endocyclic amide bond.

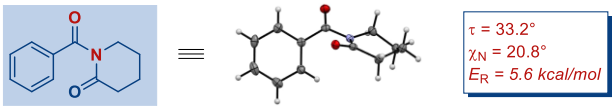


Figure 9. Structure of *N*-acyl-*δ*-valerolactam (CCDC 2082397).

2.2. *N*-Acyl-Sulfonylamides

2.2.1. *N*-Ts-Amides. In 2015, Garg and Zou groups reported *N*-acyl-sulfonamides as reagents in Ni-catalyzed esterification of amides and Pd-catalyzed acylative Suzuki cross-coupling.[44,45,66] In 2016, our group elucidated structural and energetic parameters of these *N*-sulfonyl cross-coupling reagents.[67] Crystallographic analysis of the parent *N*-benzoyl-tosylamide showed that this compound contains a significantly distorted amide bond (τ = 18.8°, χ_N = 19.9°, N–C(O) = 1.410 Å) (Figure 10). Resonance energy and rotational barrier were determined as 9.7 kcal/mol and 7.01 kcal/mol, indicating ground-state-destabilization and electronic activation of the N–C(O) bond. Moreover, calculation of proton affinities indicated that *N*-benzoyl-tosylamide favors protonation at the amide oxygen atom (ΔPA = 9.3 kcal/mol). *N*-Acyl-sulfonamides are among the most reactive acyclic amide bond cross-coupling reagents, however, a notable disadvantage is that the synthesis by sulfonylation of 2° amides with *p*-toluenesulfonyl chloride is often problematic. Most commonly, *N*-acyl-tosylamides are synthesized from acyl chlorides and *p*-toluenesulfonamides, which does not represent a synthetic advantage over *N*-cyclic amide-based reagents.

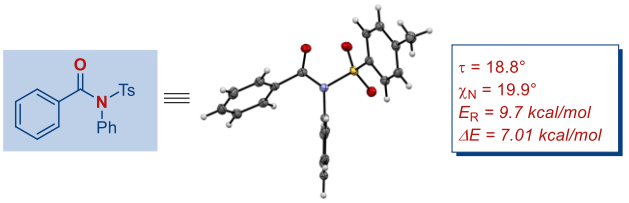


Figure 10. Structure of *N*-acyl-tosylamide (CCDC 1486094).

2.2.2. *N*-Ms-Amides. In 2017, our group reported *N*-mesylamides as amide-based N–C(O) reagents for cross-coupling.[68] The concept behind –NRMs activation is analogous to –OMs activation of phenols. The benefits of *N*-Ms activation include higher atom economy, and, more importantly, low steric hindrance around the N–C(O) bond, which permits for cross-coupling of sterically-hindered nucleophiles. The X-ray structure of the parent *N*,*N*-Ms,Ph amide showed moderate steric activation of the amide bond (τ = 6.8°, χ_N = 17.2°, N–C(O) = 1.398 Å) (Figure 11). Rotational barrier and resonance energy were determined as 5.5 kcal/mol and 10.3 kcal/mol, indicating ground-state-destabilization and electronic activation. Protonation is favored at the amide oxygen (ΔPA = 10.3 kcal/mol). Evaluation of amide activating groups showed the following order of reactivity: *N*-acyl-glutarimide ≫ *N*,*N*-Ms/Ph ≈ *N*,*N*-Ts/Ph ≫ *N*,*N*-Ar/Me (anilide).

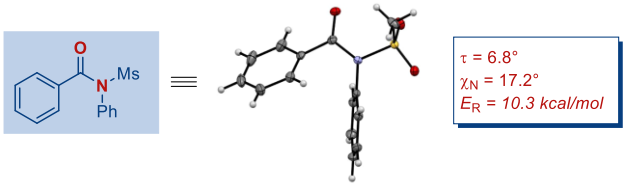


Figure 11. Structure of *N*-acyl-mesylamide (CCDC 1525510).

2.2.3. *N*,*N*-Ms$_2$-Amides and *N*,*N*-Ts$_2$-Amides. In 2018, Rhee and co-workers reported *N*,*N*-Ms$_2$ and *N*,*N*-Ts$_2$ amides as N–C(O) cross-coupling reagents.[69] The X-ray structures confirmed highly distorted amide bonds in the parent amides of *N*,*N*-Ts$_2$: τ = 81.0°, χ_N = 1.7° and *N*,*N*-Ms$_2$: τ = 63.2°, χ_N = 27.1° (Figure 12). Interestingly, the sum of distortion parameters, the additive Winkler-Dunitz parameter,[41] is higher for *N*,*N*-Ms$_2$ than *N*,*N*-Ts$_2$ amide, $\Sigma_{(\tau + \chi N)}$ = 90.3°. In addition, DFT studies indicated that *N*,*N*-Ms$_2$ amide is characterized by a lower free energy of oxidative addition intermediate in Pd-catalyzed Suzuki–Miyaura cross-coupling (ΔG = 66.64 kcal/mol) than *N*,*N*-Ts$_2$ amide (ΔG = 83.52 kcal/mol). Overall, this suggests that *N*,*N*-Ms$_2$ are preferred electrophilic reagents for N–C(O) activation than *N*,*N*-Ts$_2$ amides.

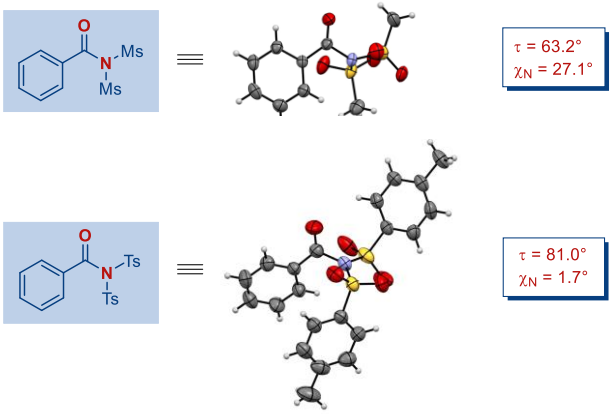


Figure 12. Structures of *N*,*N*-Ms$_2$-amide and *N*,*N*-Ts$_2$-amide (CCDC 1822719, 1822720).

2.2.4. *N*,*N*-Ts,Ac-Amides and *N*,*N*-Ts,Boc-Amides. In 2018, our group reported mixed doubly-activated *N*-sulfonyl amides, *N*,*N*-Ts,Ac and *N*,*N*-Ts,Boc amides.[70] The combination of *N*,*N*-Ts/Ac and in particular *N*,*N*-Ts/Boc substituents at nitrogen atom results in almost perpendicular twist in *N*-acyclic amides. Crystallographic studies

demonstrated that both *N*,*N*-Ts,Ac (τ = 76.9°, χ_N = 15.9°, N–C(O) = 1.481 Å) and *N*,*N*-Ts,Boc amide bonds (τ = 87.2°, χ_N = 1.4°, N–C(O) = 1.486 Å) are extremely twisted (Figure 13). Notably, the amide bond in *N*,*N*-Ts,Boc represented the most twisted acyclic amide reported. Interestingly, the *N*-Ac group in *N*,*N*-Ts,Ac amide is practically planar (τ = 4.6°, χ_N =16.4°, N–C(O) = 1.406 Å), and thus unreactive. These amides showed high reactivity in metal-free transamidation and Pd-catalyzed acylative Suzuki–Miyaura cross-coupling.

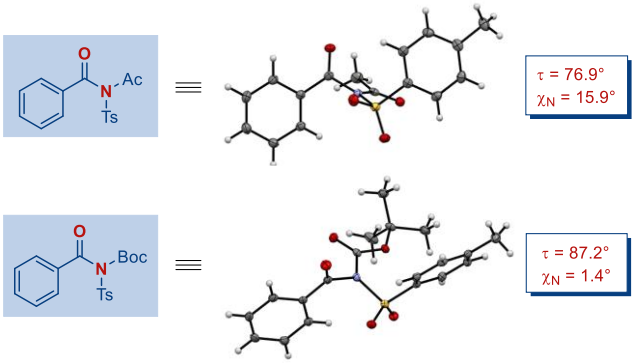


Figure 13. Structures of *N*,*N*-Ts/Ac and *N*,*N*-Ts/Boc amides (CCDC 1870944, 1870945).

2.2.5. *N*-Tf-Amides. In 2019, our group reported trifluoromethanesulfonamides (triflamides) for selective N–C(O) bond cleavage.[71] These amides can be regarded as more reactive analogues of *N*-Ts and *N*-Ms activation of the amide bond, in analogy to OTf activation of phenols. The X-ray structure of the parent *N*,*N*-Tf,Ph amide showed twisted amide bond (τ = 25.5°, χ_N = 21.4°, N–C(O) = 1.425 Å) (Figure 14). Resonance energy is lower than *N*-Ts amides (E_R = 8.3 kcal/mol), indicating a decrease in $n_N \rightarrow \pi^*_{C=O}$ conjugation resulting from delocalization of nitrogen lone pair into the *N*-Tf group. Protonation affinity studies showed that *N*-Tf amides strongly favor protonation at the amide oxygen atom (ΔPA = 12.4 kcal/mol). As expected, *N*-Tf amides showed much higher reactivity than *N*-Ts and *N*-Ms amides in acyl Suzuki–Miyaura cross-coupling.

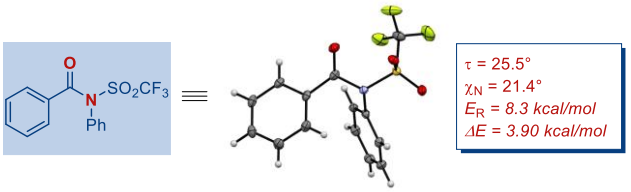


Figure 14. Structure of *N*-Tf-amide (CCDC 1882900).

2.3. *N*-Boc-Amides

In 2015, the Garg group first applied *N*,*N*-Boc/alkyl amides in Ni(0)/NHC-catalyzed acyl N–C(O) bond activation, resulting in esterification.[44] Later, they demonstrated that *N*,*N*-Boc/alkyl amides can be activated by Ni(cod)$_2$/SIPr system in Suzuki-Miyaura cross-coupling.[72-73] In 2016, our group systematically investigated a series of *N*-Boc/R activated amides by a combination of crystallographic and computational methods.[67] We found that the parent *N*,*N*-Boc/Ph amide features a significant distortion of the amide bond (τ = 29.1°, χ_N = 8.4°, N–C(O) = 1.406 Å) (Figure 15). Resonance energy and rotational barrier were determined as 7.2 kcal/mol and 3.62 kcal/mol, confirming the significantly lowered $n_N \rightarrow \pi^*_{C=O}$ delocalization and the potential of these amide precursors in N–C(O) bond activation. Proton affinity revealed that protonation of the amide oxygen is favored over amide nitrogen (ΔPA = 12.1 kcal/mol) and carbamate oxygen (ΔPA = 6.2 kcal/mol). Importantly, *N*,*N*-Boc/R amides are readily accessible from 2° amides, which provides a general method of activation of common amide bonds.

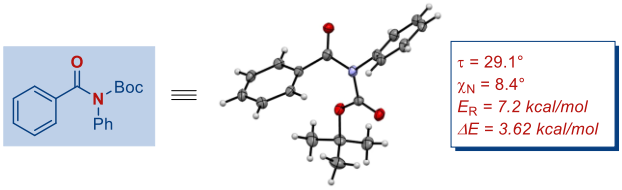


Figure 15. Structure of *N*-Boc-amide (CCDC 1882900).

2.4. *N*,*N*-Boc$_2$-Amides

In 2016, our group reported *N*,*N*-Boc$_2$ amides as readily prepared substrates from common 1° amides for cooperative catalysis using a combination of Pd and a Lewis base in acyl Suzuki–Miyaura cross-coupling.[74] Later, we applied *N*,*N*-Boc$_2$ amides as acyl and aryl electrophiles in Ni-catalyzed Negishi cross-coupling and Rh-catalyzed decarbonylative C–H arylation.[75-76] Detailed structural and computational studies revealed that these amides belong to the most twisted amides reported, with the parent *N*,*N*-Boc$_2$ benzamide characterized by τ = 72.5°, χ_N = 3.6°, N–C(O) = 1.467 Å (Figure 16).[77] Interestingly, we found that electron-donating groups at para-position of the aromatic ring of *N*,*N*-Boc$_2$ benzamides result in an enhancement of the N–C(O) bond rotation by reinforcing Ar to $\pi^*_{C=O}$ conjugation. We also established that *N*,*N*-Boc$_2$ benzamides can revert to benzamides under thermal and acid-mediated conditions, which represents the first example of reversible bond twisting of acyclic amides. Resonance energy and rotational barrier were determined as 6.3 kcal/mol and 3.33 kcal/mol, indicating highly reactive amide bonds. Moreover, *N*,*N*-Boc$_2$ amides strongly favor protonation at the amide oxygen atom (ΔPA = 17.4 kcal/mol). The key synthetic advantage of *N*,*N*-Boc$_2$ amides is that they can be directly prepared from 1° amides.

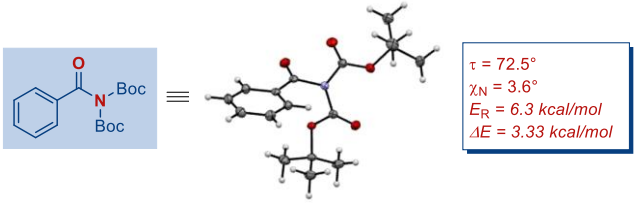


Figure 16. Structure of *N*,*N*-Boc$_2$-amide (CCDC 1552721).

2.5. *N*-Acyl-Amides

In 2018, our group reported *N*-Ac-amides as "ring deconstructed" analogues of *N*-acyl-glutarimides that can be

synthesized form 2° and 1° amides in Pd-catalyzed acyl and Ni-catalyzed decarbonylative Suzuki-Miyaura cross-coupling.[78] The internal N–C(O) bond in *N*-acetyl-amide shows approximately half-twisted amide bond (τ = 43.0°, χ_N = 10.9°, N–C(O) = 1.422 Å), while the *N*-Ac bond is practically planar (τ = 5.1°, χ_N = 10.9°, N–C(O) = 1.395 Å) (Figure 17). Resonance energy of the twisted amide bond was determined as 8.4 kcal/mol, which was lower than that of exocyclic *N*-Ac bond (10.7 kcal/mol). Interestingly, protonation of *N*-Ac oxygen was found to be strongly favored over protonation of twisted amide bond (ΔPA = 10.9 kcal/mol). These structural and energetic features indicate significant ground-state-destabilization of mono-*N*-Ac activated amide bonds. Subsequently, Stanley group developed related *N*-benzoyl-activated amides and applied these precursors in Ni-catalyzed alkene/alkyne carboacylations.[79-80]

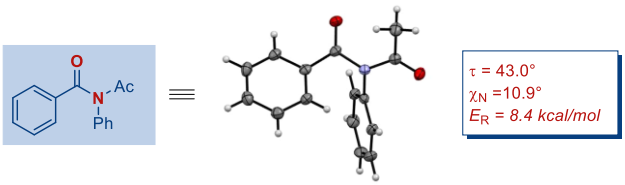


Figure 17. Structure of *N*-acetyl-amide (CCDC 1855917).

2.6. *N*-Ar-Amides (Anilides)

After the Garg group reported Ni-catalyzed conversion of *N*-acyl-anilines (anilides) to esters in 2015,[44] our group conducted comprehensive computational studies on resonance destabilization of anilides.[81] These anilides are quite unique from other classes of activated amides in that the main N_{lp} delocalization is to the *N*-Ar ring rather than *N*-sulfonyl or *N*-acyl group, which results in much higher stability of the *N*-activating group substitution; however, at the expense of lower activation of the N–C(O) amide bond. Resonance energy of the parent *N*,*N*-Ph/Me anilide is 13.5 kcal/mol, which indicates a lower degree of amide bond destabilization compared with other classes of activated amides (Figure 18). Interestingly, we found that by changing a single substituent on the aromatic rings of anilides, the resonance energy can be varied by 10 kcal/mol. Anilides favor protonation at the oxygen atom (ΔPA = 11.0 kcal/mol). These amides are particularly effective in cross-coupling using Ni-catalysis.

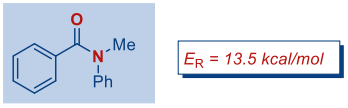


Figure 18. Structure of *N*-aryl-amide (anilide).

2.7. *N*-Heterocyclic Amides

2.7.1. *N*-Acyl-Pyrroles and *N*-Acyl-Pyrazoles. In 2017, our group demonstrated that *N*-acyl-pyrroles and *N*-acyl-pyrazoles can be applied in Pd-catalyzed acyl cross-coupling by selective N–C(O) cleavage.[82] Notably, although the amide bond is planar in these systems, electronic activation of the nitrogen atom through delocalization of N_{lp} into the heterocyclic π-system is sufficient for activation of the amide N–C(O) bond. Resonance energy (7.8-9.3 kcal/mol) and rotational barrier (7.5-8.0 kcal/mol) confirmed a significant decrease of $n_N \rightarrow \pi^*_{C=O}$ conjugation (Figure 19). Kinetic studies showed that planar *N*-acyl-pyrrole is more effective than twisted *N*-acyl-2,5-Me_2-pyrrole due to higher stability. Moreover, protonation of the amide bond oxygen is highly favored over nitrogen (ΔPA = 11.0 kcal/mol). Later, Maiti and Tobisu reported decarbonylative reactions of *N*-acylated heterocyclic amides.[83-84] From the synthetic standpoint, *N*-acyl-pyrroles can be readily prepared from 1° amides by Paal–Knorr synthesis, providing another general method of activation of common amide bonds.

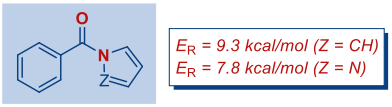


Figure 19. Structures of *N*-acyl-pyrrole and *N*-acyl-pyrazole.

2.7.2. *N*-Acyl-Carbazoles and *N*-Acyl-Indoles. In 2020, our group introduced *N*-acyl-indoles and *N*-acyl-carbazoles as highly reactive electrophiles in selective activation of amide bonds.[85] In particular, the amide bond in *N*-benzoyl-carbazole is relatively planar (τ = 25.1°, χ_N = 3.2°, N–C(O) = 1.400 Å), however, the key destabilization originates from N_{lp} to Ar conjugation in planar carbazole ring (Figure 20). Calculations showed that resonance energy and rotational barrier in *N*-benzoyl-carbazole (7.8 kcal/mol, 5.42 kcal/mol) are significantly lower than in *N*-benzoyl-indole (10.5 kcal/mol, 8.12 kcal/mol) and *N*-benzoyl-pyrrole (9.3 kcal/mol, 7.78 kcal/mol), which is consistent with N_{lp} to Ar conjugation on the conjugated carbazole ring. Furthermore, protonation of the amide oxygen is favored over the amide nitrogen (ΔPA = 10.7 kcal/mol). Importantly, *N*-acyl-carbazoles can be readily prepared from 1° amides by acid-catalyzed condensation or Pd-catalyzed *N*-arylation.

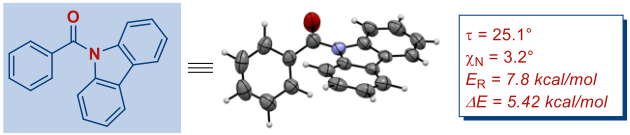


Figure 20. Structure of *N*-acyl-carbazole (CCDC 149367).

2.7.3. *N*-Acyl-Imidazoles. In 2019, the Miller group reported the synthesis and characterization of several new twisted amides based on substituted *N*-acyl-imidazole scaffold.[86] These *N*-acyl-imidazoles were fully investigated by crystallographic, spectroscopic and computational methods, which revealed some of the most twisted acyclic amide bonds discovered (τ = 88.6°, χ_N = 21.6°, N–C(O) = 1.469 Å) (Figure 21). Rotational barrier (9.7 kcal/mol), high C=O infrared stretching frequency (1713 cm^{-1}) and downfield C=O ^{13}C NMR shift (169.6 ppm) are in agreement with highly twisted amide bond. Preliminary reac-

tivity and stability studies indicated that these *N*-acyl-imidazole amides can be used as mild acylating reagents in metal-free transamidation and transesterification reactions.

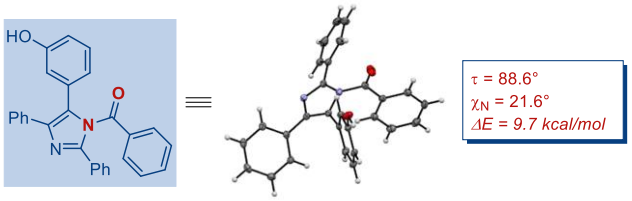


Figure 21. Structure of *N*-acyl-imidazole (CCDC 1895221).

2.7.4. *N*-Pyrimidines (MAPA). In 2017, our group reported *N*-methylamino-*N*-2-pyrimidyl amides (MAPA) with increased $n_N \rightarrow \pi_{Ar}$ conjugation.[87] These amides have been designed as significantly more reactive, yet stable, analogues of anilides, where the *N*-Me-*N*-2-pyrimidyl amide contains relatively planar amide bond (τ = 20.9°, χ_N = 5.2°, N-C(O) = 1.378 Å), while the $n_N \rightarrow \pi_{Ar}$ delocalization is the major driving force enabling selective N–C(O) activation (Figure 22). These amides overcome the main limitation of anilides, which is low reactivity in Pd-catalysis. Resonance energy of the parent MAPA amide is 6.7 kcal/mol, which indicates highly activated amide bond, and can be compared with less activated analogues, such as *N*-Me-*N*-2-pyridyl (8.8 kcal/mol) and *N*-Me-*N*-4-pyridyl (10.7 kcal/mol). Furthermore, MAPA can be readily prepared from unactivated 1° or 2° amides by standard alkylation, S_NAr and cross-coupling, thus providing another method to accessing acyl-metals from common amides.

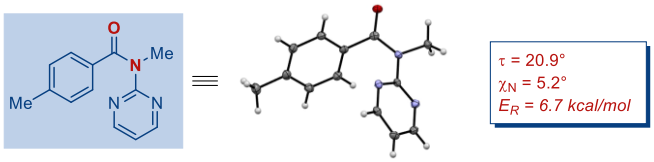


Figure 22. Structure of *N*-Me-*N*-pyrimidyl-amide (CCDC 1563403).

In 2022, we further extended the utility of MAPA amides by designing doubly-activated *N*,*N*-pym/Boc amides.[88] These amides represent the first class of acyclic α-alkyl amides that have been successfully used in Pd-catalyzed cross-coupling of 3°, 2° and 1° aliphatic amides. Selective N–C(O) bond activation in these amides is achieved by a combination of twist and external $n_N \rightarrow \pi^*_{C=O/Ar}$ delocalization. Structural studies showed a moderately twisted amide bond (τ = 28.7°, χ_N = 9.3°, N–C(O) = 1.404 Å) (Figure 23). Resonance energy (6.4 kcal/mol) is consistent with the external $n_N \rightarrow \pi^*_{C=O/Ar}$ delocalization, activating the N–C(O) amide bond. Determination of proton affinities (ΔPA = 12 kcal/mol) confirmed that these amides favor protonation at the oxygen atom.

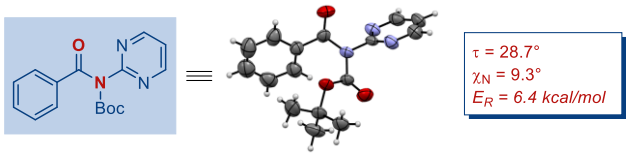


Figure 23. Structure of *N*-Boc-*N*-pyrimidyl-amide (CCDC 2114044).

In 2020, the Zhou group reported a related class of *N*-2-pyrimidyl and *N*-2-pyridyl amides for Rh-catalyzed transarylation of benzamides.[89] In this amide bond design, *N*-heterocyclic group serves as a directing group for $C_{(aryl)}$–C(O) bond insertion. The bulky *N*-di-isopropyl-phenyl group is essential to provide the required syn configuration of the heterocyclic nitrogen directing group (Figure 24). This class of amides represents an attractive entry to the alternative C–C(O) bond activation of the amide bond by a formal aryl exchange of benzamides.

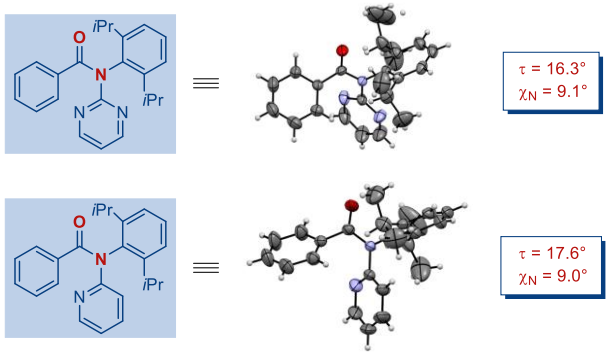


Figure 24. Structures of *N*-pyrimidyl-*N*-Ar and *N*-pyridyl-*N*-Ar amides (CCDC 1944055, 1944056).

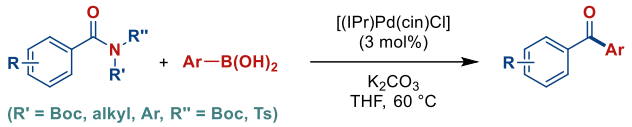
3. Amide N–C Bond Activation: Abundance of Manifolds Enabled by Ground-State-Destabilization

The emergence of ground-state-destabilization has enabled activation of the N–C(O) amide bond by several previously unknown reaction manifolds. In general, activation of amide bonds can be classified into the following reaction classes: (1) acyl coupling; (2) decarbonylative coupling; (3) radical coupling; and (4) transition-metal-free coupling. The common feature of these reactions is weakening of the $n_N \rightarrow \pi^*_{C=O}$ resonance, which enables selective oxidative addition of the N–C(O) bond to a transition metal, decarbonylation, formation of acyl radicals or mild nucleophilic addition to the N–C(O) bond. In this section, we highlight key reactions with a focus on amide bond class primed for the N–C(O) activation reactions.

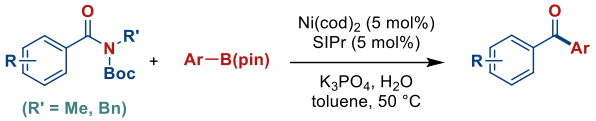
3.1. Acyl Cross-Coupling

Since 2017, our group have developed Pd(II)–NHC complexes for acyl Suzuki-Miyaura cross-coupling of amides with high efficiency (Scheme 5).[90-98] Compared to the originally reported Pd/PR_3 systems, the use of Pd(II)–NHC catalysis provides major advantages in this cross-coupling manifold, such as (1) broad generality in N–C(O) bond activation in that even less reactive amides can

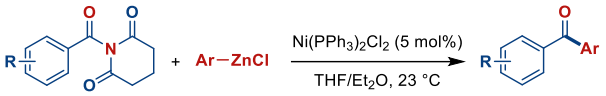
Scheme 5. Suzuki–Miyaura Cross-Coupling of Amides by Pd(II)–NHC Catalysis



Scheme 6. Suzuki–Miyaura Cross-Coupling of *N*-Boc Activated Amides by Ni(0)–NHC Catalysis



Scheme 7. Ni-Catalyzed Negishi Cross-Coupling of *N*-acyl-glutarimides



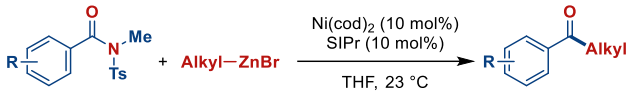
undergo efficient C–N activation; (2) high turnover numbers for different classes of amides; (3) dramatically faster reaction rates than with Pd/PR_3 catalysis; (4) low reaction temperatures, where cross-couplings can often be conducted at ambient conditions.

Among NHC ligands tested, IPr typically shows the best catalytic efficiency. Furthermore, different ancillary ligands and precatalysts, such as Pd(IPr)(allyl)Cl, Pd(IPr)(cin)Cl, Pd-PEPPSI-IPr, Pd(IPr)(1-*t*-Bu-ind)Cl, Pd(IPr)(acac)Cl, Pd(IPr)(aniline)Cl, $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ are compatible with amide Suzuki-Miyaura cross-coupling reactions. While all of these precatalysts show high efficiency, $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ has been identified as the most reactive Pd(II)–NHC precatalyst thus far.[95] To date, Pd(II)–NHCs are the most reactive and general Pd system for the cross-coupling of a wide range of amides.

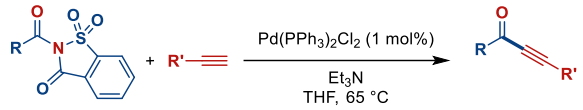
In 2016, the Garg group reported Ni(0)–NHC-catalyzed Suzuki–Miyaura cross-coupling of amides by N–C(O) activation (Scheme 6).[72] This catalytic system permits the formation of C–C bonds from *N*-Boc-activated amides using non-precious Ni catalysis. The combination of 5 mol% $Ni(cod)_2$ and 5 mol% SIPr as a catalytic system tolerates a variety of functional groups such as ketones, amines, and heterocycles to generate the desired ketone products. Furthermore, the authors demonstrated the use of amides as synthons for the synthesis of bioactive molecules by sequential cross-couplings. However, this Ni(0)-catalytic system requires the use of organoboranes and suffers from the air-sensitive nature of Ni(0). Despite significant potential, this Ni(0) system is still awaiting broad applications in acyl C–C coupling of amides.

In 2016, our group reported the first Negishi cross-coupling of *N*-acyl-glutarimides with arylzinc reagents (Scheme 7).[99] This cross-coupling proceeds under exceedingly mild room temperature conditions using 5 mol% of

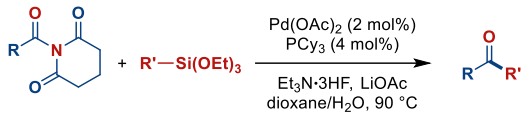
Scheme 8. Ni-Catalyzed Negishi Cross-Coupling of *N*-Ts Activated Amides



Scheme 9. Pd-Catalyzed Sonogashira Cross-Coupling of *N*-acyl-saccharins



Scheme 10. Pd-Catalyzed Hiyama Cross-Coupling of *N*-acyl-glutarimides



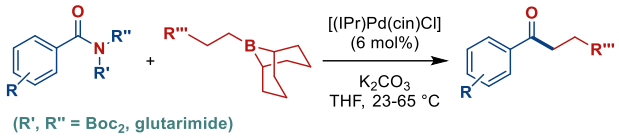
bench-stable $Ni(PPh_3)Cl_2$ as precatalyst. The most interesting feature of this cross-coupling is high reaction rate at room temperature, with the reactions being complete in < 10 min. Interestingly, this system is fully selective for acyl cross-coupling in that decarbonylative coupling products are not formed. These Negishi cross-couplings are compatible with various activated amides, such as *N*-acyl-glutarimides, *N*-acyl-succinimides and *N*,*N*-Boc_2 amides.

In the same year, the Garg group reported alkyl Negishi cross-coupling of *N*-Ts-activated amides with alkyl organozinc reagents using 10 mol% $Ni(cod)_2$/SIPr as catalytic system (Scheme 8).[100] This reaction provides an attractive entry to aryl/alkyl ketones by amide N–C(O) bond activation. *N*-Boc activated amides are also compatible, but in general, were found to be less reactive. Notably, the authors applied this cross-coupling to the synthesis of a glucagon receptor modulator, showcasing the utility of aryl/alkyl ketone products.

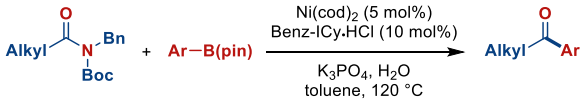
In 2016, the Zeng group reported the first example of acyl Sonogashira cross-coupling of amides (Scheme 9).[101] This reaction is unique for *N*-acyl-saccharins in that other amides were found ineffective. Using 1 mol% $Pd(PPh_3)_3Cl_2$ as catalyst in the presence of Et_3N, which may act as a Lewis base to active the amide, a broad range of ynones could be prepared in high selectivity and good yields, including aryl, alkenyl and alkyl *N*-acyl-saccharins. Notably, this Sonogashira coupling was achieved under Cu-free conditions. Due to the strongly electron-withdrawing nature of saccharin, *N*-acyl-saccharins often show unique reactivity in N–C(O) bond activation.

In 2020, the Lee group reported the first Hiyama cross-coupling of amides (Scheme 10).[102] The reaction was developed using *N*-acyl-glutarimides and arylsiloxanes in the presence of $Pd(OAc)_2/PCy_3$ catalytic system.[102] Various *N*-acyl-glutarimides, such as aryl, vinyl, and alkyl showed good activity in this cross-coupling. Furthermore, this

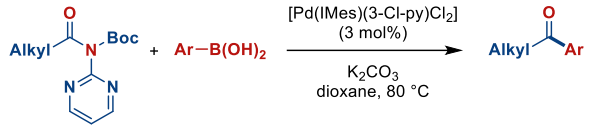
Scheme 11. Pd-Catalyzed B-Alkyl Suzuki Cross-Coupling of *N*-acyl-glutarimides and *N*-Boc$_2$ Amides



Scheme 12. Ni-Catalyzed Suzuki–Miyaura Cross-Coupling of α-Alkyl *N*-Boc Activated Amides



Scheme 13. Pd-Catalyzed Suzuki–Miyaura Cross-Coupling of α-Alkyl *N*,*N*-Boc/pym Amides



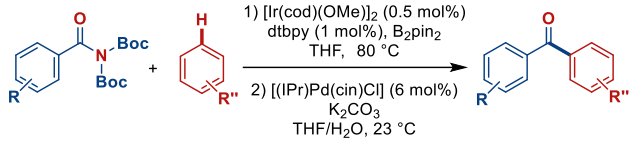
reaction is compatible with *N*-acyl-succinimides and *N*-Ts-activated amides. Interestingly, the products of esterification of the amide bond have not been observed using the developed catalyst system.

In 2018, our group and Rueping group independently reported Pd and Ni-catalyzed B-alkyl Suzuki cross-coupling of amides.[103-104] We found that using 6 mol% (IPr)Pd(cin)Cl, various amides, including *N*-acyl-glutarimides and challenging *N*,*N*-Boc$_2$ amides prepared directly by activation of 1° amides are competent substrates for this alkylation (Scheme 11). On the other hand, the Rueping group demonstrated Ni(0)–NHC-catalyzed alkylation of amides using 10 mol% Ni(cod)$_2$/IPr·HCl as catalytic system (not shown). Different from Pd catalysis, only anilides are compatible with this Ni catalytic system. In this case, higher nucleophilicity of Ni–NHCs enable oxidative addition of the less reactive N–C(O) bonds. This is another instance where Pd and Ni catalysis offer complementary reactivity in N–C(O) bond activation, where Pd catalysis is compatible with highly distorted amides and electronically-activated amides as electrophiles.

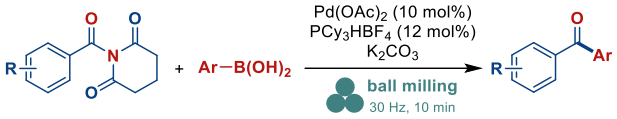
Cross-coupling of α-alkyl amides is more challenging than *N*-activated benzamides due to higher activation energy for N–C oxidative addition. In 2018, the Garg group reported an efficient protocol for Suzuki–Miyaura cross-coupling of α-alkyl amides using Ni–NHC catalysis (Scheme 12).[105] Interestingly, the key for successful cross-coupling is to use benimidazol-2-ylidene Benz-ICy·HCl as a ligand. This reaction works well with *N*-Boc activated amides and aryl organoboronate esters as the coupling reagents. The authors demonstrated the utility of alkyl/aryl products in sequential Suzuki-Miyaura cross-coupling and Fischer indole synthesis.

In 2022, our group addressed the challenge of N–C(O) activation of α-alkyl amides in Pd catalysis by developing *N*,*N*-Boc/pym amides as electrophiles for user-friendly Pd–NHC-catalyzed Suzuki–Miyaura cross-coupling of

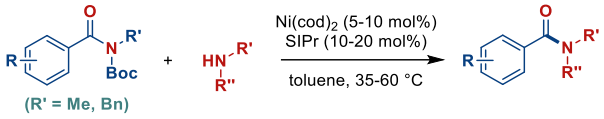
Scheme 14. Ir/Pd-Catalyzed C–H Acylation of Arenes with *N*,*N*-Boc$_2$ Amides



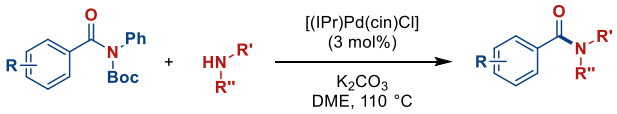
Scheme 15. Mechanochemical Suzuki–Miyaura Cross-Coupling of *N*-acyl-glutarimides



Scheme 16. Ni-Catalyzed Transamidation of *N*-Boc Activated Amides



Scheme 17. Pd-Catalyzed Acyl Buchwald–Hartwig Cross-Coupling of *N*-Boc and *N*-Ts Activated Amides



aliphatic amides (Scheme 13).[88] This protocol was shown to be effective for various 3°, 2° and 1° aliphatic amide derivatives. The success of this approach hinges upon (1) highly reactive, doubly-activated amide precursors, and (2) steric impact of NHC ancillary ligands; interestingly, less demanding [Pd(IMes)(3-Cl-py)Cl$_2$] was found favored for 3° and 2° amides, while [Pd(IPr)(3-Cl-py)Cl$_2$] was preferred for less sterically-hindered 1° aliphatic amides. Furthermore, aromatic amides are also compatible substrates for the cross-coupling using this approach with *N*,*N*-pym/Boc amides. The design of new activated amides is expected to facilitate the development of cross-coupling reactions of challenging amide electrophiles.

Another burgeoning area of amide N–C bond activation is the development of tandem processes. In 2020, our group demonstrated that Ir-catalyzed meta-selective C–H borylation can be successfully coupled with N–C bond activation of *N*,*N*-Boc$_2$ activated amides (Scheme 14).[106] This sequential protocol permits to couple unactivated arenes with common 1° amides and is compatible with a broad substrate scope of substituted amides and arenes, including natural products and pharmaceuticals. Furthermore, decarbonylative Suzuki–Miyaura C–C coupling between the *N*-acyl-glutarimides and nonactivated arenes is feasible by this sequential protocol. This reaction pro-

vides facile access to meta-acylated biaryl ketones and biaryls by combining C–H and N–C activation pathways.

In 2022, we reported the first mechanochemical activation of amides by developing Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-acyl-glutarimides driven by mechanical force (Scheme 15).[107] Using 10 mol% $Pd(OAc)_2$ and 12 mol% $PCy_3{\cdot}HBF_4$ as catalytic system, this method showed excellent functional group tolerance and could be applied in late-stage modification of pharmaceuticals. The reaction was conducted for short reaction time under heating-free, solvent-free ball-milling conditions. Using *N*-acyl-glutarimides as electrophilic amide precursors was the key to high yield and N–C cross-coupling selectivity.

Following their previous reports on Ni-catalyzed esterification of amides,[44,108] in 2016, the Garg group reported a two-step approach to achieve net transamidation of 2° amides (Scheme 16).[109] In this study, the secondary amide bond can be activated by *N*-Boc protection, followed by amination using $Ni(cod)_2$/SIPr catalytic system. In 2017, the Garg group achieved Ni-catalyzed transamidation of aliphatic amides (not shown).[110] This reaction works well using Benz-ICy·HCl as NHC ligand and *N*-Boc activated amide bonds. A wide variety of *N*-R amides are compatible, including *N*-Bn, *N*-Me, *N*-*i*-Pr and *N*-*t*-Bu.

In 2017, our group reported Pd(II)–NHC-catalyzed transamidation of *N*-Boc and *N*-Ts activated amides (Scheme 17).[111-112] This acyl Buchwald-Hartwig cross-coupling is conducted using air- and moisture-stable (IPr)Pd(cin)Cl catalyst, showing excellent tolerance to a broad range of amide and amine coupling partners. Subsequently, we demonstrated Pd–PEPPSI-catalyzed Buchwald–Hartwig cross-coupling of *N*-Boc and *N*-Ts activated amides (not shown).[112] Notably, the developed catalytic system is reactive for both activated amides and phenolic esters with high selectivity for the acyl bond cleavage.

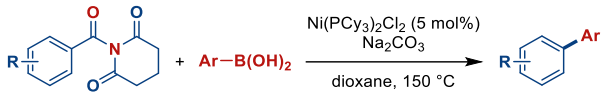
Well-defined Pd(II)–NHC catalytic systems, including different NHC ligands have been developed for acyl C–C and C–N cross-couplings of activated amides.[113-128]

3.2. Decarbonylative Cross-Coupling

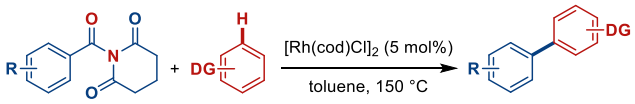
Following the establishment of decarbonylative Heck reaction using amides as electrophiles by our group in 2015,[48,17] all major classes of decarbonylative cross-couplings of amides by N–C bond activation have been developed. The present challenge in decarbonylative N–C(O) cross-couplings is to expand the scope of amides beyond *N*-acyl-glutarimides, which are by far the most reactive amides in this cross-coupling manifold; however, these precursors are usually synthesized from carboxylic acids cf. common 1° or 2° amides.

In 2016, our group reported the first biaryl Suzuki–Miyaura cross-coupling of amides (Scheme 18).[130] This reaction uses *N*-acyl-glutarimides and boronic acids with well-defined, air-stable $Ni(PCy_3)_2Cl_2$ as catalyst. The reaction tolerates a broad range of electron-deficient, electron-neutral and electron-rich substituents on both coupling partners. This study represented the first decarbonylative biaryl cross-coupling transform of amides and

Scheme 18. Ni-Catalyzed Biaryl Suzuki–Miyaura Cross-Coupling of *N*-acyl-glutarimides



Scheme 19. Rh-Catalyzed Decarbonylative C–H Arylation of *N*-acyl-glutarimides



opened the door N–C(O) decarbonylative cross-coupling with various nucleophiles. In 2019, as an important advancement to improve functional group tolerance, our group[131] and the Zeng group[132] independently reported the first Pd-catalyzed decarbonylative biaryl Suzuki-Miyaura cross-coupling using *N*-acyl-glutarimides, *N*-Ac-amides and *N*-acyl-saccharins (not shown).

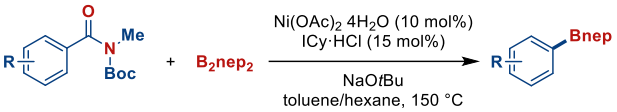
In 2016, our group reported Rh(I)-catalyzed C–H arylation of *N*-coordinating arenes using *N*-acyl-glutarimides as electrophiles (Scheme 19).[133] This reaction works well with benzo[*h*]quinolines and arenes bearing *N*-directing groups, such as pyridines, pyrimidines, pyrazoles and imines to provide functionalized biaryl products in good yields. ESI-MS studies indicated the presence of Rh-aryl intermediates, consistent with amide activation by Rh(I). This study merged *N*-directed C–H activation with selective amide N–C(O) activation using *N*-acyl-glutarimides.

In 2016, the Shi group reported nickel–NHC catalyzed decarbonylative borylation of amides with B_2nep_2 by selective N–C(O) activation (Scheme 20).[134] Using $Ni(OAc)_2{\cdot}4H_2O$ and ICy·HCl as a catalytic system, this reaction showed good functional group tolerance and was applied in late-stage borylation. The reaction represents a rare example of decarbonylative amide cross-coupling of *N*-Boc activated amides. Crystallographic studies provided insight into the key Ni-acyl and Ni-aryl intermediates; however, the pathway involving esterification and C–O activation has not been excluded. In view of the versatile utility of arylboronates, this protocol advanced decarbonylative manifold of amides to C–heteroatom bond formation, offering access to important building blocks.

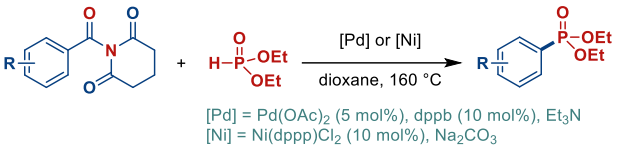
In 2017, our group reported Pd- or Ni-catalyzed decarbonylative phosphorylation of amides (Scheme 21).[135] This new Hirao cross-coupling for C–P bond formation tolerates a wide range of functional groups and gives aryl phosphonates in good to excellent yields. The reaction works well with *N*-acyl-glutarimides as well as *N*-Ts activated amides and atom-economic *N*-Ms amides, which can be prepared from common 2° amides. In terms of catalyst development, it is important to note the complementary nature of Pd and Ni catalyst systems, which show

broad complementarity in decarbonylative N–C bond activation reactions of amide bonds.

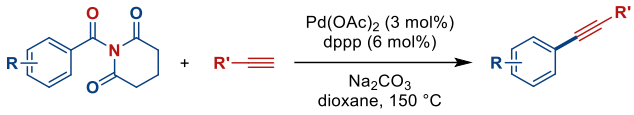
Scheme 20. Ni-Catalyzed Decarbonylative Borylation of *N*-Boc Activated Amides



Scheme 21. Pd- or Ni-Catalyzed Decarbonylative Phosphorylation of N-acyl-glutarimides



Scheme 22. Pd-Catalyzed Decarbonylative Alkynylation of N-acyl-glutarimides



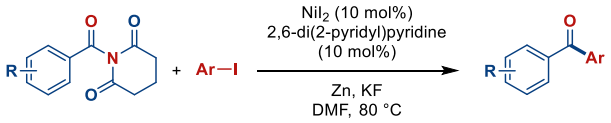
In 2018, the Chen group reported Pd-catalyzed decarbonylative alkynylation of amides using *N*-acyl-glutarimides as electrophiles (Scheme 22).[136] This transformation could be applied to aliphatic and aromatic terminal alkynes, providing a Sonogashira transform from amides. Decarbonylative cross-couplings of activated amides have been reported, including Pd and Rh-catalyzed decarbonylative borylation, Pd-catalyzed decarbonylative thiolation and Pd-catalyzed cyanation.[137-140] Furthermore, important advances have been made in Ni-catalyzed decarbonylative amination, deamidative cross-coupling, thiolation, cyanation, and silylation.[141-146] These reactions preferably use *N*-acyl-glutarimides as activated N–C electrophiles.

3.3. Radical Cross-Coupling

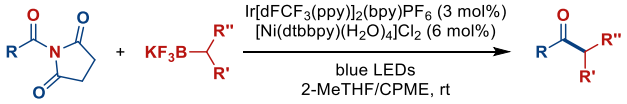
Since the discovery of N–C(O) activation in 2015, activated amides have emerged as attractive precursors in cross-coupling by single-electron mechanisms. In general, two pathways are predominant: (1) oxidative addition of the N–C bond, followed by single-electron oxidation/reduction; (2) direct single-electron transfer to generate acyl radicals. The most successful activated amide bond precursors in this reactivity manifold are *N*-cyclic imides, such as *N*-acyl-glutarimides, *N*-acyl-succinimides, *N*-acyl-saccharins, as well as *N*-acyl-imidazoles.

In 2017, the Han group reported Ni-catalyzed reductive cross-coupling reaction between *N*-acyl-glutarimides and aryl iodides (Scheme 23).[147] This important study established the use of amide N–C activation in the cross-coupling of two electrophiles. Mechanistically, the reaction relies on the selective insertion into the amide bond to furnish the acyl metal intermediate, which is oxidatively added to aryl radical from aryl iodides. NiI_2 and Zn have been identified as the best Ni precursor and reductant.

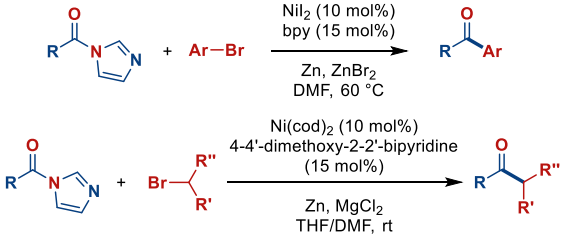
Scheme 23. Ni-Catalyzed Reductive Cross-Coupling of *N*-acyl-glutarimides with Aryl Iodides



Scheme 24. Ni-Catalyzed Cross-Coupling of *N*-acyl-succinimides and Alkyltrifluoroborates



Scheme 25. Ni-Catalyzed Reductive Cross-Coupling of *N*-acyl-imidazoles with Aryl and Alkyl Bromides



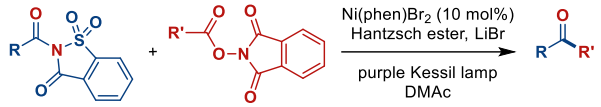
The key consideration is to apply terpyridine as a tridentate ligand. This reaction tolerates broad substrate scope of the amide and aryl iodide components, providing biaryl ketones in good to excellent yields. The work highlighted the unique combination of radical reductive cross-coupling with amide bond activation.

In 2017, the Molander group reported visible-light Ir-photoredox/Ni-catalyzed acyl cross-coupling of *N*-acyl-succinimides and alkyltrifluoroborates (Scheme 24).[148] In analogy to the related cross-coupling of aryl halides with alkyltrifluoroborates, the reaction proceeds via a radical coupling mechanism. The key intermediate is acyl-Ni generated by selective oxidative addition of the N–C bond, which is oxidatively added to an alkyl radical generated in the photoredox cycle. Interestingly, this reaction works well only with *N*-acyl-glutarimides and *N*-acyl succinimides, which presumably is due to higher stability of the *N*-activated amide bond to the reaction conditions.

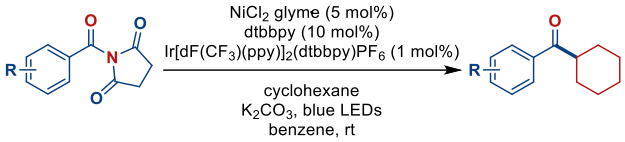
In 2017, the Li group reported Ni-catalyzed direct acylation of aryl and alkyl bromides with *N*-acyl-imidazoles (Scheme 25).[149] Mechanistic studies revealed two complementary pathways: (1) single-electron-reduction of the amide bond; and (2) oxidative addition of the amide bond. This study presented the first example of using planar, electronically-activated *N*-acyl-imidazoles in radical cross-coupling. The method is notable for its very broad scope and application to complex natural products and pharmaceuticals. More generally, these methods should

be considered in the context of acylations of carboxylic acid derivatives owing to the ease of synthesis of activated amide precursors from abundant carboxylic acids.

Scheme 26. Ni-Catalyzed Decarboxylative Cross-Coupling of *N*-acyl-saccharins with *N*-hydroxy-phthalimide Esters



Scheme 27. Ni-Catalyzed Cross-Coupling of *N*-acyl-succinimides with Aliphatic Hydrocarbons



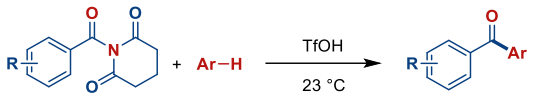
In 2021, the Opatz group reported Ni-catalyzed photoreductive cross-coupling between *N*-acyl-saccharins and *N*-hydroxy-phthalimide esters (Scheme 26).[150] The key step involves oxidative addition of the N–C bond of the activated amide to Ni, followed by radical trapping to produce Ni(III) intermediate. Interestingly, only *N*-acyl-saccharins showed high reactivity as amide bond precursors in this transformation. Furthermore, the protocol avoids expensive iridium photocatalysts and employs Hantzsch ester as a benign photoreductant. This reaction is notable in that both coupling partners *N*-acyl-saccharins and *N*-hydroxy-phthalimide esters can be directly prepared from abundant carboxylic acids.

In 2020, Hong and Baik reported the cross-coupling of amides with aliphatic hydrocarbons via dual Ni/Ir metallaphotoredox catalysis (Scheme 27).[151] This reaction achieves synergistic activation of N–C amide acyl bond and aliphatic C(sp^3)–H bond. This acylation of aliphatic hydrocarbons proceeds in the absence of directing groups and was proposed to involve C(sp^3)–H activation prior to the N–C amide bond oxidative addition. Interestingly, only *N*-acyl-succinimides gave good yields of the ketone products, while other activated amides as well as carboxylic acid derivatives, such as acid chlorides and anhydrides, showed significantly lower reactivity.

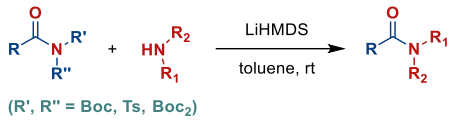
3.4. Transition-Metal-Free Coupling

Direct nucleophilic addition to the amide bond to generate tetrahedral intermediates is another area that has greatly benefited from the discovery of ground-state-destabilized amides. These reactions are enabled by high selectivity in the nucleophilic addition, where the tuning of $n_N \rightarrow \pi^*_{C=O}$ resonance and sterics around the amide bond permits to achieve unprecedented selectivity using electrophilic amides. From the synthetic standpoint, these transition-metal-free additions are particularly valuable if activated amides can be readily prepared from common 1° and 2° amides. This manifold complements cross-couplings or radical couplings, where activated amides often offer advantages over other carboxylic acid derivatives in terms of stability and efficiency.

Scheme 28. Friedel-Crafts Acylation of Arenes with *N*-acyl-glutarimides



Scheme 29. LiHMDS-Mediated Transamidation of Twisted Amides



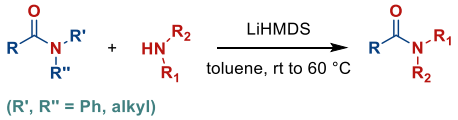
In 2016, our group reported Friedel-Crafts acylation of *N*-acyl-glutarimides with aromatic hydrocarbons under mild, metal-free conditions (Scheme 28).[152] This Friedel-Crafts acylation is broad in scope of both coupling partners. Only *N*-cyclic imides, such as *N*-acyl-glutarimides and *N*-acyl-succinimides are compatible due to the competing cleavage of the *N*-activating group in other activated amide precursors. Following this study, various C–C and C–N bond forming reactions were achieved using activated amides as electrophiles under transition-metal-free conditions.[153-156]

In 2018, inspired by the success of Pd and Ni-catalyzed transamidation reactions of activated amides, we reported a transition-metal-free transamidation under exceedingly mild conditions (Scheme 29).[157] Using LiHMDS as base, transamidation of a series of activated amides that could be readily prepared from common 1° and 2° amides, such as *N*-Boc, *N*-Boc_2, *N*-Ts, *N*-acyl-pyrroles, with non-nucleophilic amines proceeds with very broad substrate scope at operationally-simple, room temperature conditions. This transamidation features deprotonation/nucleophilic addition pathway, which is distinct from the more traditional addition/deprotonation mechanism. The success of this reaction depends on high electrophilicity of the amide bond enabling direct nucleophilic addition.

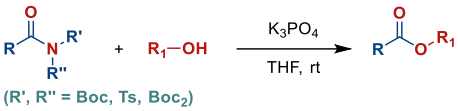
In 2019, we have expanded transition-metal-free transamidation to unactivated amides (Scheme 30).[158-159] We found that LiHMDS mediates highly chemoselective transamidation of anilides as well as *N*,*N*-dialkyl amides with non-nucleophilic amines at room temperature. This method showed excellent functional group tolerance. The utility was highlighted in late-stage modification and synthesis of pharmaceuticals. Furthermore, we observed high chemoselectivity between different classes of amides, which could be selectively reacted depending on amide bond resonance. This reaction provided a method for rarely reported highly chemoselective nucleophilic addition to unactivated amide bonds.

In 2018, we reported transition-metal-free esterification of activated amides under mild conditions (Scheme 31).[160] Using K_3PO_4 as base, the reaction demonstrated excellent functional group tolerance and broad substrate scope, which compared favorably with the original Ni-catalyzed

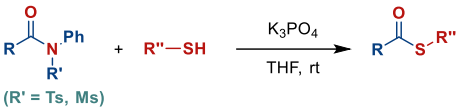
Scheme 30. LiHMDS-Mediated Transamidation of Anilides and Planar Amides



Scheme 31. Transition-Metal-Free Esterification of *N*-Boc and *N*-Ts Activated Amides



Scheme 32. Transition-Metal-Free Thioesterification of *N*-Ts Activated Amides



protocol.[44] This esterification protocol was readily applied to the late-stage diversification of pharmaceuticals and natural products. A broad range of activated amides including *N*-Boc, *N*-Ts and *N*-acyl-glutarimides were compatible with metal-free conditions.

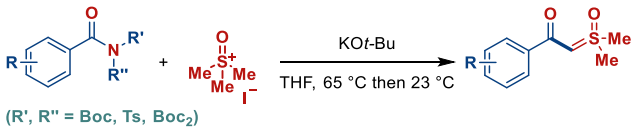
In a broader sense, the use of transition-metal-catalyzed and transition-metal-free protocols has already been demonstrated for acyl C–O, C–N and C–C bond formation from activated amides. These methods should be considered complementary owing to different reaction mechanisms (acyl-metal vs. tetrahedral intermediates), divergent scope and different reagent systems.

In 2020, we reported direct thioesterification and selenoesterification of activated amides under transition-metal-free conditions (Scheme 32).[161-162] This reaction is compatible with *N*-Ts and *N*-Ms amides, while *N*-Boc amides undergo scission of the *N*-activating group. The reaction works well with both aryl and aliphatic amides. Interestingly, these mild conditions are also compatible with the preparation of less stable selenoesters.

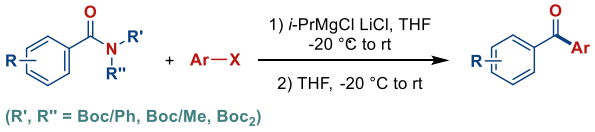
In 2018, the Zeng group reported another mechanism for direct nucleophilic addition to amides by trapping the amide bonds as acyl fluoride intermediates.[163]

In 2021, our group reported direct synthesis of sulfoxonium ylides from amides (Scheme 33).[164] This reaction involves nucleophilic addition of dimethyloxosulfonium methylide, Corey-Chaykovsky reagent, which is generated in situ from KO*t*-Bu/trimethylsulfoxonium iodide. This protocol permits the synthesis of versatile sulfoxonium ylides from amides by C–C bond formation. The utility of this method was demonstrated in late-stage modification of pharmaceuticals. Various activated amides are compatible, including *N*-Boc, *N*-Ts and *N,N*-Boc$_2$, which is a general trend observed for transition-metal-free reactions by acyl addition to the activated amide bond.

Scheme 33. Transition-Metal-Free Synthesis of Sulfoxonium Ylides from N-Boc Activated Amides



Scheme 34. Transition-Metal-Free Ketone Synthesis by Acylation of Grignard Reagents with *N*-Boc Amides



In 2020, we reported transition-metal-free acylation of activated amides by using functionalized Knochel-type Grignard reagents (Scheme 34).[165-166] This method outcompetes transition-metal-catalyzed protocols in terms of substrate scope owing to the fact that many functionalized Grignard reagents are readily accessed in situ by operationally-simple halogen-magnesium exchange with *i*-PrMgCl·LiCl. Furthermore, the method compares very favorably with the traditional Weinreb amides owing to the fact that both *N,N*-Boc$_2$ and *N*-Boc amides prepared from common 1° and 2° amides are compatible. The utility of this method was highlighted in the synthesis of bioactive products.

Recently, methods on transition-metal-free N–C bond cleavage of activated amides have been reported.[167-173]

4. Future Directions

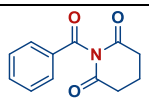
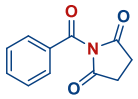
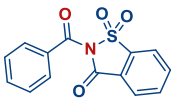
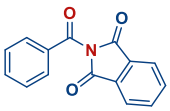
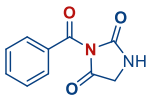
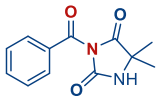
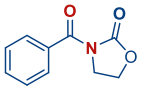
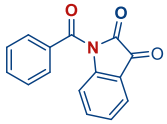
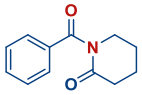
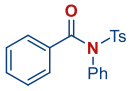
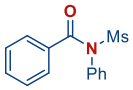
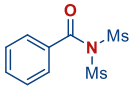
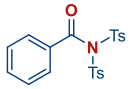
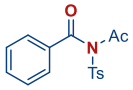
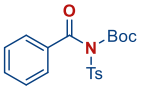
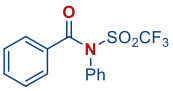
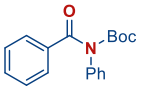
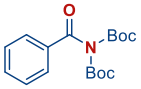
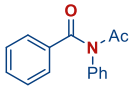
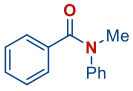
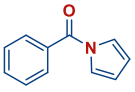
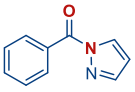
Since 2015, remarkable progresses in activation of the N–C amide bond has been achieved. The amide bond once considered "inert" should now be regarded as a "readily modifiable" functional group, where the reactivity is readily tuned by $n_N \rightarrow \pi^*_{C=O}$ conjugation. This progress has been made possible by the discovery of new classes of activated amides and the concept of ground-state-destabilization. It is critical that future studies focus on the discovery of new classes of activated amides and detailed structure-activity relationship pertaining to amide bond geometry and electronic destabilization.

Although the field of amide N–C bond activation has exploded in recent years, there are many challenges and opportunities: (1) the development of sterically and electronically-altered amide bonds is required for tuning the entire range of N–C amide bond activation and unlocking new reactivity patterns; in particular, examples of amides that are readily prepared from common primary and secondary amides are scarce. (2) the field is dominated by Pd

and Ni catalysis, and the use of non-precious metals, such as Fe, Co, Cu is highly encouraged to break amide bonds; (3) tandem reactions and multicomponent reactions for complex organic synthesis by N–C activation are rarely reported;[174-175] in particular, considering that general mechanisms for the oxidative addition of the N–C(O) bond and selective formation of tetrahedral intermediates have been established, this reactivity manifold is now available for the development of reactions that involve elementary N–C oxidative addition as well as the plethora of known reactions of carboxylic acid derivatives. (4) mechanistic studies, including experimental and computational approaches, are crucial for developing new activation modes of amide bonds;[176-177] In this respect, the Reader is encouraged to consult excellent already published reviews and perspectives on mechanisms of amide bond activation.[37-39] (5) activation of inert and planar amide bonds will be highly useful for direct late-stage modification of bioactive molecules; in this context, a particularly sought after property of activated amides is the ability to twist α-alkyl amides, which so far have proved to be significantly more challenging than their aryl counterparts. (6) the advancement of amide N–C activation reactions to industrial settings should be considered;[178-179] (7) the development of N–C bond activation reactions of amide bond isosteres, including thioamides, will open vistas in synthetic transforms;[180-181] (8) amide bond re-routing through more reactive intermediates is underdeveloped and will open new reactivity patterns of amide bonds;[182] (9) amide bond exchange reactions represent another highly attractive area that might find applications in diversification of biomolecules provided that this manifold can be expanded to alkyl derivatives.[183]

Seven years after the initial discoveries, it is abundantly clear that re-positioning of the reactivity scale of amide bond will have a transformative impact on organic synthesis. Tables 1 and 2 present summaries of parameters of activated amides and the reactions developed to date.

Table 1. Summary of Distortion Parameters of Twisted and Activated Amides (structural parameters are given in deg, resonance energy is given in kcal/mol)

entry	amide	τ	χ_N	E_R	reference
1		88.6	6.6	-1.49	46
2		46.1	9.5	-0.64	53
3		23.0	12.5	2.0	56
4		55.0	8.4	-1.83	50
5		52.0	17.6°	-0.1	60
6		49.5	13.3	0.0	60
7		18.2	19.9	-	63
8		22.0	13.9	-	64
9		33.2	20.8	5.6	65
10		18.8	19.9	9.7	67
11		6.8	17.2	10.3	68
12		63.2	27.1	-	69
13		81.0	1.7	-	69
14		76.9	15.9	-	70
15		87.2	1.4	-	70
16		25.5	21.4	8.3	71
17		29.1	8.4	7.2	67
18		72.5	3.6	6.3	77
19		43.0	10.9	8.4	78
20		-	-	13.5	81
21		-	-	9.3	82
22		-	-	7.8	82

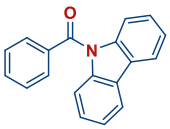
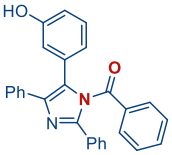
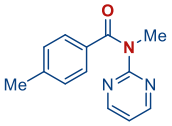
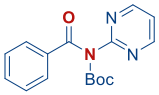
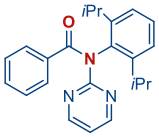
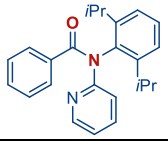
23		25.1	3.2	7.8	85
24		88.6	21.6	-	86
25		20.9	5.2	6.7	87
26		28.7	9.3	6.4	88
27		16.3	9.1	-	89
28		17.6	9.0	-	89

Table 2. Summary of Reactions of Twisted and Activated Amides

entry	reaction	catalyst	reference
1	Acyl Suzuki-Miyaura Cross-Coupling	Pd-NHC	46
2	Acyl Suzuki-Miyaura Cross-Coupling	Ni-NHC	72
3	Acyl Suzuki-Miyaura Cross-Coupling	Pd-Phosphine	45
4	Esterification	Ni-NHC	44
5	Acyl Negishi Cross-Coupling	Ni-Phosphine	99
6	Acyl Negishi Cross-Coupling	Ni-NHC	100
7	Acyl Sonogashira Cross-Coupling	Pd-Phosphine	101
8	Acyl Hiyama Cross-Coupling	Pd-Phosphine	102
9	Acyl B-Alkyl Suzuki-Miyaura Cross-Coupling	Pd-NHC	103
10	Acyl B-Alkyl Suzuki-Miyaura Cross-Coupling	Ni-NHC	104
11	Acyl Suzuki-Miyaura Cross-Coupling, α-Alkyl Amides	Ni-NHC	105
12	Acyl Suzuki-Miyaura Cross-Coupling, α-Alkyl Amides	Pd-NHC	88
13	C–H Acylation	Ir/Pd-NHC	106
14	Transamidation	Ni-NHC	109
15	Transamidation	Pd-NHC	111
16	Decarbonylative Heck Cross-Coupling	Pd	47
17	Decarbonylative Suzuki-Miyaura Cross-Coupling	Ni-Phosphine	130
18	Decarbonylative C–H arylation	Rh	133
19	Decarbonylative C–H arylation	Lewis base/Rh	76
20	Decarbonylative Borylation	Ni-NHC	134
21	Decarbonylative Phosphorylation	Pd-Phosphine Ni-Phosphine	135
22	Decarbonylative Sonogashira Cross-Coupling	Pd-Phosphine	136
23	Decarbonylative Thioetherification	Pd-Phosphine	140
24	Decarbonylative Amination	Ni-Phosphine	141
25	Decarbonylative Reduction	Ni-Phosphine	142
26	Decarbonylative Cyanation	Ni-Phosphine	144
27	Decarbonylative Silylation	Ni-Phosphine	145
28	Decarbonylative Thioetherification	Ni-Phosphine	146
29	Radical Reductive Cross-Coupling	Ni-bpy	149
30	Radical Photoreductive Cross-Coupling	Ni-Phen	150
31	Ring-Opening Olefin Metathesis	Ru-NHC	178
32	Friedel-Crafts Acylation	Metal-free	152
33	Amide Transamidation	Metal-free	157
34	Amide Esterification	Metal-free	160
35	Amide Thioesterification	Metal-free	161
36	Sulfoxonium Ylide Synthesis	Metal-free	164
37	Kumada-type Cross-Coupling	Metal-free	165

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Notes

The authors declare no competing financial interest.

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Jessica Feliciano is a recent graduate from Rutgers University who received a Bachelor's Degree in Neuroscience and a Minor in Chemistry. She is currently working at Princeton University CLIA COVID Laboratory where she is conducting research and constantly striving to learn and enjoy learning new techniques and methods.

Michal Szostak received his Ph.D. from the University of Kansas in 2009. He carried out postdoctoral research at Princeton University and University of Manchester. In 2014, he joined the faculty at Rutgers University, where he is currently Professor of Chemistry. His research group is focused on the development of new synthetic methodology based on transition-metal-catalysis, amide bond activation, inert bond activation, NHC ligands, and application to the synthesis of biologically active molecules.

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ABBREVIATIONS

Ac: acetyl
Acac: acetylacetone
Ar: aryl
Boc: *tert*-butyloxycarbonyl
Bn: benzyl
Bpy: 2,2'-bipyridyl
Cin: cinnamyl
Cy: cyclohexyl
DFT: density functional theory
DG: directing group
E_R: resonance energy
HMDS: hexamethyldisilazide
Ms: methanesulfonyl
NHC: N-heterocyclic carbene
PA: proton affinity
Phen: 1,10-phenanthroline
χ_N: N-pyramidalization
τ: twist angle
Tf: triflate
Ts: toluenesulfonyl

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ABSTRACT

Amide N–C(O) Bond Activation: Emergence of Ground-State-Destabilization