Amide Bond Activation: The Power of Resonance

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The amide bond represents the most fundamental functional group in numerous areas of chemistry, such as organic synthesis, drug discovery, polymers and biochemistry. Although typical amides are planar and the amide N–C(O) bond is notoriously difficult to break due to $n_N \rightarrow \pi^*_{C=O}$ resonance, over the past 5 years remarkable breakthroughs have been achieved in the activation of amides by complementary mechanisms that ultimately hinge on ground-state-destabilization of the amide linkage. In this review, we present an overview of the main reactivity manifolds employed in the activation of amides by selective N–C(O) cleavage pathways along with their main applications in catalytic as well as stoichiometric synthesis. This cutting-edge platform clearly demonstrates how to harness the power of amidic resonance to achieve a host of previously elusive transformations of amides and holds the promise to change the landscape of how chemists perceive the traditionally unreactive amide bonds into readily modifiable linchpin functional groups that can be readily triggered for the desired reactivity.

From Classical Bridged Lactams to Modern Twisted Amides

Amidic resonance, that is delocalization of the lone pair of electrons at nitrogen on the π^* system of the carbonyl group, is the central and fascinating feature of amide bond chemistry (Figure 1A) [1]. The resonance energy (15-20 kcal/mol in planar amides), and resulting stabilization and planarity of amides, was predicted in the classical studies by Pauling [2] and has tremendous consequences for the structure and reactivity of peptides and proteins, critical to all living organisms [3]. Likewise, the unreactivity of amide bonds is the hallmark property of this functional group that is broadly utilized in medicinal chemistry [4] and polymers [5]. Reactions

involving amides are the most common transformation executed daily in academic and commercial laboratories [4], while polyamides give raise to some of the most stable polymers created to date, such as Kevlar or Nylon66 [5]. The study of amidic resonance, including its aptitude to N-/O-protonation has drawn continued attention [6–8]. Interestingly, it is now recognized that amide bond twisting mechanism is widely present in biochemical activation of amides, including protein N-glycosylation [9], peptide hydrolysis [10] and cis-trans isomerization of proteins, among many other applications [11].

Although, as a direct consequence of resonance, amides are nucleophilic at the oxygen atom, rotation around the N–C(O) bond breaks $n_N \rightarrow \pi^*_{C=O}$ conjugation. This leads to several key structural and electronic changes within the amide bond, including rearrangement of the charge distribution, increased charge at the nitrogen atom, elongation of the N–C(O) bond, shortening of the C=O bond, and loss of coplanarity of the six atoms comprising the amide bond. The overall net effect is that such twisted amides are regarded as a new "amino-ketone" functional group rather than amides [1,6–8]. The key outcome is the capacity of such twisted amides to engender novel and unique properties of the traditionally unreactive amide bonds.

In this context, chemists have for years been fascinated by twisted amides. The first recorded prediction of a twisted amide (albeit not a successful synthetic effort) was in 1938 by Lukes, who foresaw twisted bridged lactams as "sterically impossible amides" [12]. Over the next decades, significant efforts have been dedicated to the invention of new bridged lactams, wherein the amide nitrogen is located at the ring fusion in a bridged bicyclic scaffold (Figure 1B). These efforts culminated in the extremely elegant examples of perfectly twisted orthogonal 3,5,7-trimethyl-1-aza-2-adamantanone and 2-quinuclidonium tetrafluoroborate reported by the groups led by Kirby [13] and Stoltz [14]. Simultaneously, the question of N-/O-protonation of twisted amides has attracted considerable interest with another very elegant example of 1-azabicyclo[3.3.1]nonan-2-one, which exists in N-/O- equilibrium upon protonation, reported by Greenberg and co-workers [15]. In sharp contrast to planar amides, which undergo hydrolysis reactions excruciatingly slowly ($t_{1/2}$ ca. 500 years), these perfectly twisted bridged lactams undergo instantaneous addition of nucleophiles to the acyl group, as expected from the extreme twist and "amino-ketone" character of the amide bond (Figure 1C). However, studies have also uncovered new reactivity, such as Pd-catalyzed σ N–C bond scission in a family of tricyclic

bridged lactams that curiously exist as in/out isomers [16] and recently was extended to more general N-alkylated bridged lactams [17].

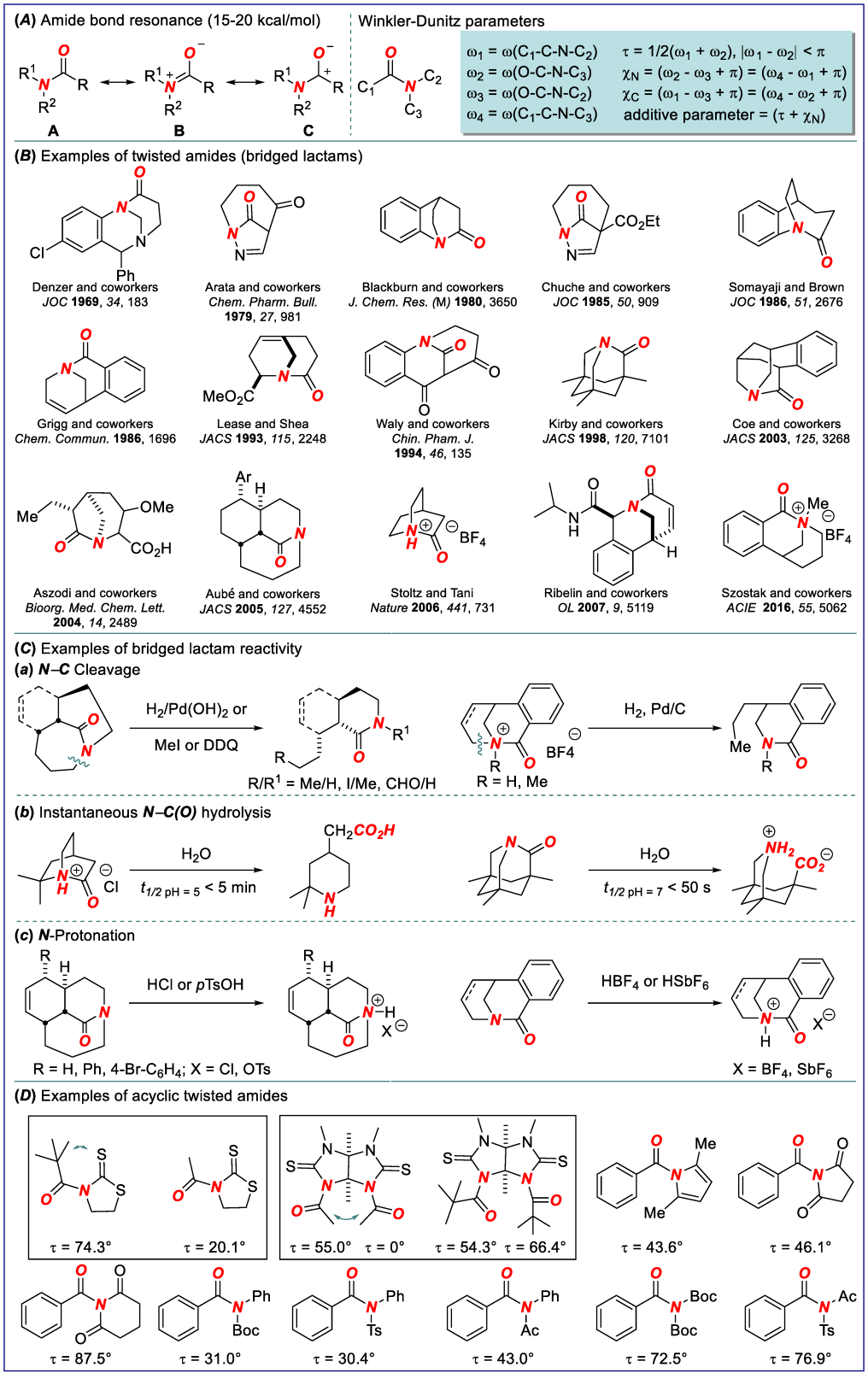

Figure 1. Amide bond and twisted amides: an overview.

(A) Amide bond resonance. (B) Examples of twisted bridged lactams. (C) Selected examples of reactivity. (D) Examples of acyclic twisted amides.

The geometric distortion of amides is described by Winkler-Dunitz parameters τ (twist angle), χ_N (N-pyramidalization) and χ_C (C-pyramidalization), including the additive Winkler-Dunitz parameter ($\tau + \chi_N$), which denote the magnitude of rotation around the N–C(O) bond, and pyramidalization [18]; τ is 0° for planar amide bonds and 90° for fully orthogonal bonds; χ_N and χ_C are 0° for planar bonds, and 60° for fully pyramidalized amide bonds [19] (Figure 1A, inset). Over the years bridged lactams spanning almost the entire range of Winkler-Dunitz scale have been prepared [18,19].

Building upon studies on bridged lactams, in the 1990s, the first examples describing activation of general acyclic twisted amides have been reported by Yamada (Figure 1D) [20]. In these amides, the amide bond distortion is achieved by steric hindrance around the N–C(O) axis, resulting in a handy activation mode of acyclic amides found across various facets of chemistry and biology. In contrast to bridged lactams, which by necessity are limited to bicyclic compounds, these acyclic twisted amides represent a modern and wide-ranging solution to rationally modulate amidic resonance by steric twisting and electronic ground-state-destabilization of the amide bond [21]. The capacity to twist secondary and even primary amides [21] and thus prime them towards the "amino-ketone" reactivity has led to remarkable breakthroughs in activation of amide N–C(O) bonds in the last 5 years. More than 20 previously elusive generic reaction types of amides have been discovered. New amide bonds have been identified. The connection between amide bond properties and ease of oxidative addition has been established. This burgeoning field has already found applications in the synthesis and modification of bioactive molecules. These studies have provided a very convincing argument that amide bonds should be considered as a readily modifiable and synthetically useful functional group rather than chemically unreactive carboxylic acid derivative as historically described in all undergraduate organic chemistry textbooks.

In this review, we present an overview of the main reactivity classes exploited in the activation of amides by selective N–C(O) cleavage pathways, with particular attention to amide

destabilization as the enabling feature for new reaction discovery of key relevance to all areas of chemistry utilizing amide bonds.

Evolution of Amide Bond Acyl Cross-Coupling Reactions

Acyl cross-coupling is one of the most frequently used catalytic methods for introducing the ubiquitous acyl group in organic synthesis. Amides have traditionally been unreactive as acyl-metal precursors due to the difficulty of N–C(O) oxidative addition as a result of $n_N \rightarrow \pi^*_{C=O}$ resonance. The discovery of ground-state-destabilized amides has allowed to establish acyl cross-coupling of amides as a versatile platform for transforming amides into a variety of valuable derivatives using mild transition-metal-catalyzed conditions (Figure 2).

Arguably, the most common and synthetically useful acyl bond cross-coupling reaction of amides is Suzuki–Miyaura cross-coupling (Figure 2A). In 2015, three reports by Szostak [22], Zou [23] and Garg [24] reported the first examples of the acyl cross-coupling of amides with organoboranes. In these reactions, oxidative addition was achieved by steric and electronic destabilization of the amide bond in N-acyl-glutarimides [22], N-acyl-tosylamides [23] and N-acyl-carbamates [24] using Pd/phosphine or Ni/NHC catalysis. The conversion of N-acyl-glutarimides was enhanced by the perfect twist of the amide bond ($\tau = 87.5°$) and promoted by the addition of acid to enable N-/O-switchable protonation further weakening the N–C(O) bond towards selective metal insertion [22]. The correlation of the amide bond reactivity with Winkler-Dunitz distortion parameters allowed to rationalize the facile activation of amides. In the Zou's study, it was notable that the authors could enhance the amide reactivity by attaching electron-withdrawing substituents to the nitrogen atom (e.g., $(3,5\text{-}CF_3)_2\text{-}C_6H_3$) to weaken resonance and achieve the cross-coupling of sterically-hindered amides [23]. On the other hand, Garg and co-workers demonstrated that $Ni(cod)_2$/SIPr system is efficient in the cross-coupling of N-Boc amides with boronic esters, including in the synthesis of bioactive agents and sequential cross-couplings of complex amides [24]. Overall, these reports demonstrated that C–C bond cross-coupling of amides is readily feasible under mild catalytic conditions that offer major improvements over the classic addition of hard organometallics to amides and set the stage for the recent impressive developments in C–C bond forming reactions of amides.

The literature on the Suzuki–Miyaura cross-coupling of amides focuses on several lines of research (Figure 2A). Given the tremendous impact of the classical Suzuki–Miyaura cross-

coupling, exemplified by the 2010 Nobel Prize, it is not surprising that the acyl Suzuki–Miyaura cross-coupling of amides has served as a testing ground for new concepts, amide electrophiles, catalytic systems and reagents in this emerging field.

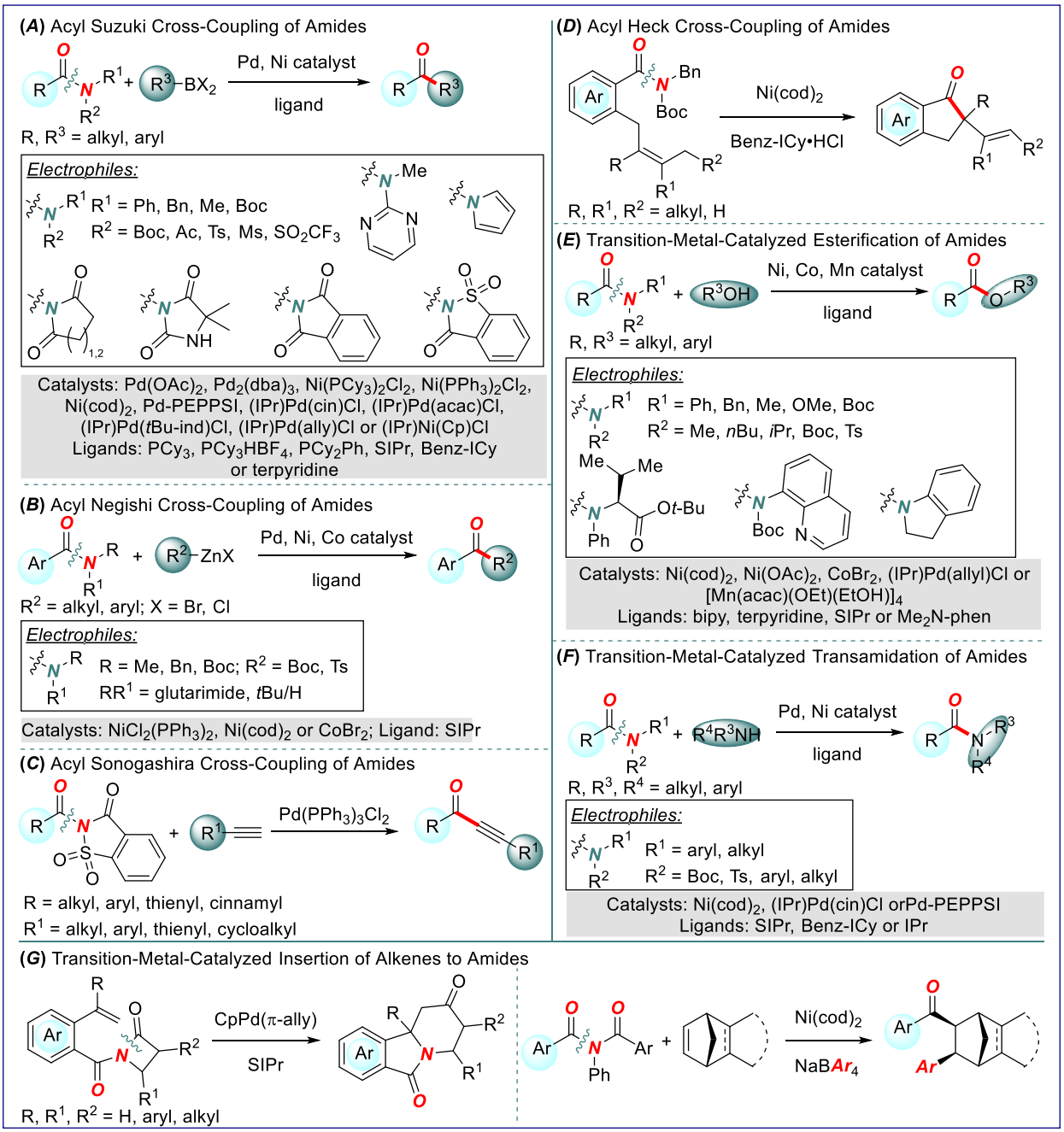

Figure 2. Acyl cross-coupling of amides.

(A) Suzuki cross-coupling. (B) Negishi cross-coupling. (C) Sonogashira cross-coupling. (D) Heck cross-coupling. (E) Esterification. (F) Transamidation. (G) Alkene insertion.

In 2016, Szostak has introduced the concept of cooperative catalysis in amide bond activation, wherein the activation of amides by a Lewis base (Et_3N) to give acyl-ammonium by transacylation is combined with Pd(0) catalysis to intercept this intermediate to give the acyl-Pd species; this permits utilization of versatile N,N-Boc_2 amides as electrophiles in the cross-coupling [25]. In another variant, Szostak introduced Pd–NHC catalysis to amide bond cross-coupling, finding that the commercially available [Pd(IPr)(cin)Cl] is an excellent catalyst for the cross-coupling [26]. This Pd(II)/NHC catalysis allows for the first time to achieve broad generality with respect to the amide bond in the cross-coupling.

On the other hand, the Garg group has pioneered Suzuki–Miyaura cross-coupling of alkyl amides enabled by the use of $Ni(cod)_2$ and the more strongly σ-donating Benz-ICy NHC ligand [27]. They have also cleverly addressed the issue of air-sensitivity of $Ni(cod)_2$ by developing $Ni(cod)_2$ paraffin capsules, which may well find application in Ni catalysis beyond amide cross-coupling [28]. Furthermore, Zou has demonstrated that borinic acids are suitable organoboron coupling partners, achieving in some cases higher reactivity than with boronic acids [29]. A variant of B-alkyl Suzuki cross-coupling of amides has also been reported [30]. However, perhaps the major surge of research has been realized by field testing various amide precursors in acyl Suzuki–Miyaura cross-coupling [31-36]. These amides include rotationally-inverted N-acyl-glutarimides [31], electronically-activated N-MAPA amides (MAPA = N-methyl-aminopyridine) [32], classic N-acyl-pyrroles [33], perfectly twisted N-Boc/Ts amides [34], intriguing mono-twisted N-Ac amides [35] or atom-economic N-Ms amides (Ms = mesyl) [36], among others. The real value of these different precursors is in distinct electronic and steric properties of the amide bond, including a gradual variation of resonance energy between 0 and 10 kcal/mol, which permits for selective cross-coupling and fine-tuning of new reactivity modes of amides by the combination of twist and nitrogen lone pair delocalization, not readily available using other acyl electrophiles. Furthermore, in many cases these twisted amide derivatives can be promptly prepared from common 1° or 2° amides, which attests to the generality of the amide cross-coupling concept and ensures broad applicability of this novel platform.

Recently, Amgoune and co-workers reported a very significant study on the mechanism of the Suzuki–Miyaura cross-coupling of N-acyl-glutarimides in the absence of external base ($Pd(OAc)_2$/PCy_3/Et_3N cat.) [37]. The reaction exploits PCy_3, which has emerged as a privileged phosphine ligand in the acyl Suzuki–Miyaura cross-coupling of amides [22,23]. The authors

have also applied this amide cross-coupling method in orthogonal functionalization in the presence of the twisted amide moiety under Ru-photoredox conditions, thus showcasing the potential of twisted amides as functional handles in organic synthesis.

Another class of novel reactions of amides are acyl Negishi cross-couplings (Figure 2B). In this case, both Pd- and Ni-based catalytic systems were initially developed by Szostak [38] and Garg and co-workers [39] for arylation and alkylation with aryl or alkyl organozinc reagents. These Negishi cross-couplings are particularly notable for their extraordinary mild room temperature conditions and full selectivity for N–C(O) acyl cleavage vs. N-activating group scission in N-Boc_2 [38] and N-Ts [39] precursors. A recent intriguing variation includes the use of first-row transition-metal Co catalysis by Danoun and co-workers with an in situ formation of organozinc reagents catalyzed by the same Co system [40]. In a related approach using Cr catalysis, Zeng and co-workers demonstrated the facility of the direct cross-coupling of 2° amides with organomagnesium reagents [41].

The first Sonogashira cross-coupling of amides was reported by Zeng and co-workers using N-acyl-saccharins developed earlier in their group (Figure 2B) [42]. This reaction is catalyzed by $Pd(PPh_3)_2Cl_2/Et_3N$ combination in the absence of Cu salts and established facile amide to ynone inter-conversion. In contrast, the Garg group developed the intramolecular Heck cross-coupling of amides to afford cyclic ketones bearing quaternary centers using $Ni(cod)_2$/Benz-ICy catalysis (Figure 2D) [43].

The acyl cross-coupling reactions of amides are not limited to C–C bond forming reactions, and include C–O (Figure 2E) and C–N cross-couplings (Figure 2F). The value of these processes is that they have allowed new methods for mild amide→ester and amide→amide inter-conversion, often with previously inaccessible functional group tolerance; however, care should be taken when developing these processes, in particular in light of facile transition-metal-free reactions of amides (see Figure 4).

One of the first examples was reported by the Garg group in 2015 (Figure 2E) [44]. This Ni-catalyzed esterification of amides has been conceptually very important in that it established that simple amide derivatives, such as N-Ts or N-Boc, undergo facile esterification in the presence of $Ni(cod)_2$/SIPr in the absence of external base. The Garg group has expanded this process to the esterification of alkyl amides by using $Ni(cod)_2$/terpy (terpy = terpyridine) system [45] as well as to kinetic profiling studies, which resulted in low catalyst loading (0.4 mol%,

$Ni(cod)_2$) [46], and the development of their paraffin capsules [47]. An alternative approach to amide esterification was reported by Danoun using $CoBr_2$/bipy/Mn (bipy = bipyridine) catalyst system, emphasizing the potential of first-row transition-metals in this catalysis platform [48], while Mashima developed manganese alkoxide complexes for esterification of dialkyl amides [49].

Akin to esterifications, transamidation reactions under mild transition-metal-catalyzed conditions have been developed (Figure 2F). Two main catalyst systems have been established for this class of reactions, Ni/NHC catalysis pioneered by Garg [50,51] and Pd/NHC catalysis developed by Szostak [52-54]. In general, these transamidations follow a two-step mechanism, in which 2° amide is first converted to an activated N-Boc or N-Ts derivative, followed by metal insertion to give acyl-metal species. An advantage is that these methods have allowed for the particularly difficult transamidation with non-nucleophilic anilines. Pd/NHC based systems leverage the use of highly reactive, air- and moisture-stable Pd(II)–NHC catalysts, including the commercially-available [Pd–PEPPSI] [53] and [Pd(IPr)(allyl)Cl] [54] classes of catalysts.

The metal insertion into the N–C(O) bond of strained amides has also been utilized to develop alkene insertion reactions with amides (Figure 2G). Murakami developed an intramolecular insertion of alkenes to N-acyl-β-lactams catalyzed by CpPd(allyl)/SIPr to afford tricyclic lactams [55], while the Stanley group reported intermolecular carboacylation of alkenes using $Ni(cod)_2$ as catalyst, N-benzoyl-benzamides as precursors and triarylboranes as transmetallating reagents [56].

Finally, it is important to note the ligand differences between the classic two-electron-type cross-coupling reactions (acyl coupling and decarbonylative coupling) and the radical-type cross-couplings via open-shell pathways. In general, strong σ-donating ligands, such as phosphines and NHCs are utilized in two-electron cross-couplings with the former being preferred for decarbonylative couplings and the latter for acyl couplings, while π-accepting ligands, such as bipyridines and related N-based ligands are preferred for radical cross-couplings.

Decarbonylative Manifold of Amides as a Gateway to Aryl Electrophiles

While acyl cross-coupling has been the major direction in the development of novel amide bond functionalization reactions, significant breakthroughs have been reported in the decarbonylative pathway (Figure 3). Principally, after metal insertion, the acyl-metal

intermediate can undergo decarbonylation (loss of CO) to generate a new aryl-metal intermediate. This process is formally equivalent to a metal insertion into a C–X halide or pseudohalide bond, however, involves amides as cross-coupling electrophiles. This means that (1) chemically orthogonal precursors can be exploited in the broadly useful cross-coupling manifolds; (2) biorelevant nature of the amide bond permits for the classical elementary reactions to be utilized in the functionalization of biomolecules and pharmaceuticals; (3) high stability of acyclic twisted amides and the range of resonance energies accessible by twisting and electronic destabilization (0-20 kcal/mol) translates into the cross-coupling selectivity that is inaccessible to other acyl electrophiles.

The key considerations in the development of new decarbonylative cross-couplings are (1) the stability of amides to the high temperatures required for CO de-insertion with N-acyl-glutarimides [31] being by far the privileged substrates for this class of reactions, and (2) the sequence of elementary steps with decarbonylation typically preferred prior to transmetalation using Pd catalysis, and facile oxidative addition, potentially involving C–C bond activation in some cases, using Ni catalysis.

In the last 5 years, the tantalizing potential of amides as aryl electrophiles has provided momentum to establish >10 novel catalytic decarbonylative processes using Pd, Ni and Rh catalysis (Figure 3). The most important is the biaryl Suzuki cross-coupling, drawing parallels to the classic Nobel Prize-winning biaryl Suzuki cross-coupling of aryl halides (Figure 3A). To date, two major catalytic systems have been developed, $Ni(PCy_3)_2Cl_2/Na_2CO_3$ [57,35] and $Pd(dppb)Cl_2/NaHCO_3$ [58]. It is also noteworthy that the Zeng group established $Pd(PPh_3)_2Cl_2/NaHCO_3$ for the Suzuki cross-coupling of N-acyl-saccharins [59], while the Rueping group showed the feasibility of decarbonylative B-alkyl coupling of N-anilides using $Ni(cod)_2$/dcype [60].

Another classes of decarbonylative reactions of amides involve Pd-catalyzed Heck coupling (Figure 3B) [61], Rh- [63] and Ni-catalyzed [64] C–H functionalizations (Figure 3C), Pd- [64] and Ni/Cu-cocatalyzed [65] Sonogashira cross-coupling, Ni- [66] and Pd-catalyzed [67] borylation, phosphorylation [68], Ni-catalyzed amidation, silylation [69] and thioesterification [70] (Scheme 3E) as well as Pd- [71] and Ni-catalyzed [72] cyanation (Scheme 3F). These reactions amply demonstrate the tremendous potential of amides as orthogonal cross-coupling partners that in many instances rival the traditional halides and pseudohalides.

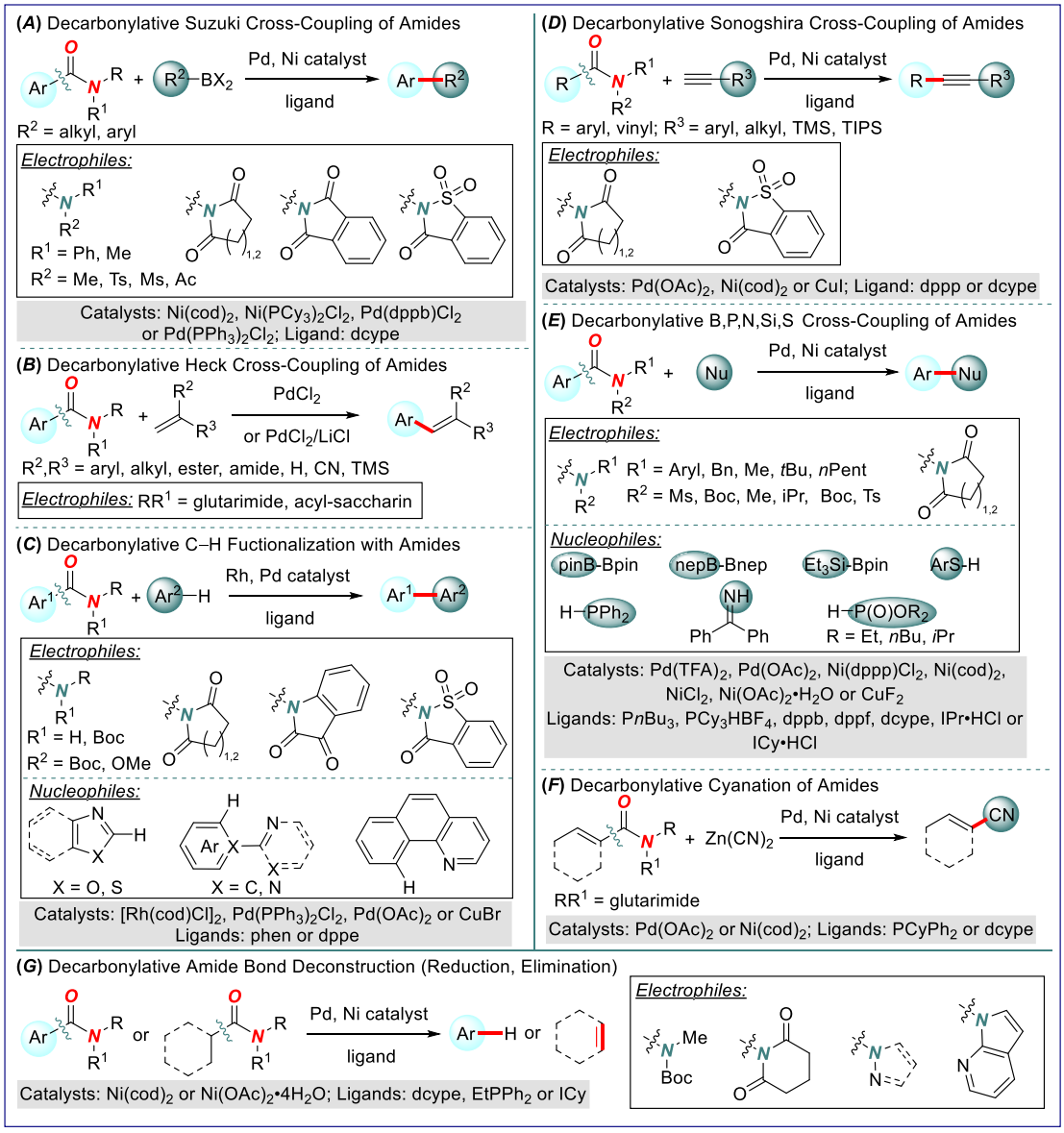

Figure 3. Decarbonylative cross-coupling of amides.

(A) Suzuki cross-coupling. (B) Heck cross-coupling. (C) C–H functionalization. (D) Sonogashira cross-coupling. (E) Heteroatom cross-coupling. (F) Cyanation. (G) Amide bond deconstruction.

Furthermore, the reduction [73,74] and Pd- [22] and Ni-catalyzed [75] decarbonylation of alkyl amides followed by β-hydride elimination have been developed as traceless deamidation protocols to afford arenes and olefins by amide bond de-construction (Figure 3G). These transformations cleave and transform ground-state-destabilized and twisted amides into a broad range of functional groups typically restricted to the traditional cross-coupling reactions.

The Merger of Amides with Radicals: Unique Opportunities for Catalysis

In this section, we will briefly highlight recent developments in the activation of amide N–C(O) bonds by open-shell pathways (Figure 4). As expected from the closed-shell mechanisms, activation of the amide bond by twisting offers new advantages to researchers engaged in radical chemistry.

In 2017, the Molander group accelerated progress in this area by developing acylation of N-acyl-succinimides with trifluoroborates by a combination of Ni and Ir-photoredox catalysis [76] (Scheme 4A). In this novel mechanism, Ni(0)-catalyst activates the N–C(O) amide bond to yield acyl-Ni(II) intermediate, which then undergoes single-electron transmetalation with the aid of oxidative Ir-photocatalysis. Conversely, the Han group showed that the same class of twisted amide substrates can be cleverly tuned to undergo the reductive cross-coupling with aryl iodides catalyzed by Ni/Zn system via the intermediacy of aryl radicals [77] (Scheme 4B). A recent exquisite advance of this work involves the use of classic N-acyl-imidazoles under reductive Ni/Zn catalysis conditions with aryl and alkyl bromides enabled through the generation of acyl radicals by the Li group [78]. The groups of Amgoune [79] and Matsuo [80] have developed improved methods for the cross-coupling of amides via silyl radicals and with 1° amines as Katritzky salt radical precursors (Scheme 4C).

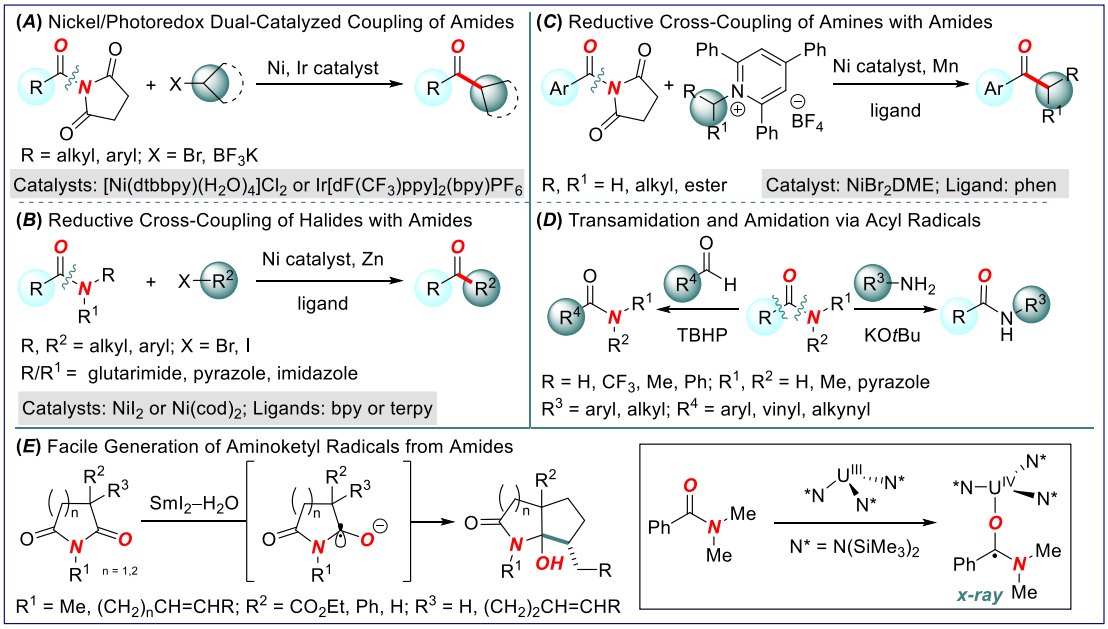

Figure 4. Activation of amides via radical mechanisms.

(A) Ni/photoredox catalysis. (B) Reductive coupling with halides. (C) Reductive coupling with amines. (D) Amidation and transamidation. (E) Generation of aminoketyl radicals.

It should also be pointed out that select transamidation reactions involve aminoacyl radicals as the key intermediates [81] (Scheme 4D). In a similar vein, the use of SmI_2 (Kagan's reagent) has recently emerged as a vehicle to generate unique aminoketyl radicals [82], and the X-ray structure of a stable amide radical anion has been recently solved [83] (Scheme 4D). Overall, these studies, coupled with an array of amides available, provide enticing opportunities to fully exploit amides in radical synthesis.

Advent of Mild Nucleophilic Acyl Addition Reactions to Amides

The final class of thriving amide bond activation reactions developed recently involve acyl addition reactions (Figure 5). These reactions benefit from two factors: (1) the emergence of a broad range of new classes of acyclic twisted amides; (2) the conceptualization that the amide bond activation reactions can proceed under extremely mild, synthetically valuable conditions, brought about by transition-metal-catalyzed cross-coupling technologies (see Figure 2).

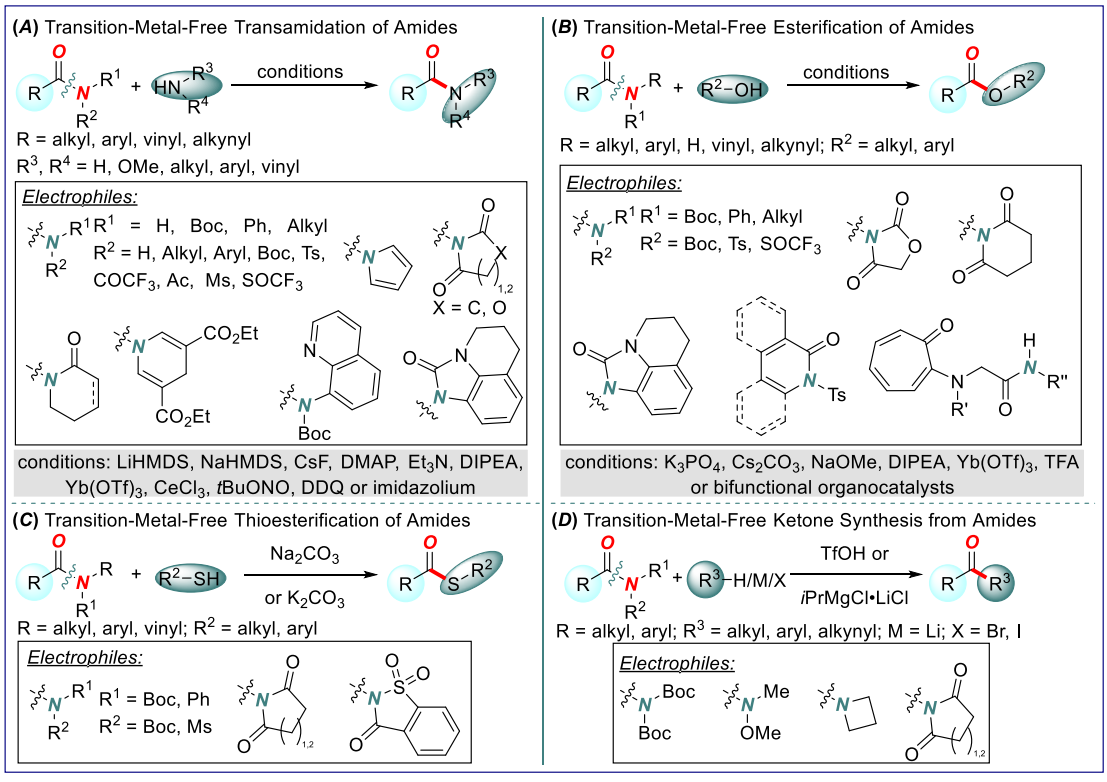

Figure 5. Activation of amides via transition-metal-free acylation.

(A) Transamidation. (B) Esterifcation. (C) Thioesterification. (D) Ketone synthesis.

One fundamental process includes transition-metal-free transamidation reactions of activated [84] and in some cases even unactivated dialkyl amides [85] promoted by LiHMDS (Figure 5A). These reactions proceed under extremely mild conditions and lead to amide bond exchange reactions by traditional nucleophilic addition to the amide bond. Noteworthy variants involve applications in C–H functionalization guided by the 8-aminoquinolyl moiety [86] and biomimetic transamidations catalyzed by $Zn(OAc)_2$ [87]. A similar sequence can be performed to effect transition-metal-free esterification of amides using K_3PO_4 or Cs_2CO_3 as a promoter [88,89] with further impressive examples of $ZnCl_2$-catalyzed biomimetic approach [90] and an intriguing nucleophilic fluoride catalysis [91] (Figure 5B). It is notable that some of these transition-metal-free esterifications appear to be more efficient than transition-metal-catalyzed variants.

Furthermore, these reactions have been recently extended to thioesterifications [92] (Figure 5C) and ketone synthesis from amides by Friedel-Crafts addition [94], or direct nucleophilic addition to pyramidalized N-acyl-azetidines [94], or electronically-activated N,N-Boc_2 amides [95] (Figure 5D). The latter class of substrates is particularly promising as amide-based ketone precursors owing to high twist [21] and ease of synthesis from common 1° or 2° amides. Overall, these transition-metal-free addition reactions demonstrate that in recent years our understanding of amides as electrophiles has increased dramatically and establish new valuable reactivity platform relying on the remarkably mild acyl additions to the amide bond.

Mechanistic Studies of Amide Bond Activation

The development of amide bond activation reactions has been closely connected to mechanistic studies on the properties of geometrically-distorted amide bonds and amidic resonance [1,6–8, 12–21]. Equally important have been studies elucidating the catalytic cycles in amide bond cross-coupling. The density functional theory (DFT) studies have been spearheaded by Hong and co-workers [96]. Due to space limitations, we will only highlight the key developments, and encourage the reader to consult the original literature.

In 2017, the Hong group established the catalytic cycle of Ni-catalyzed decarbonylative and acyl Suzuki cross-coupling of activated amides (Figure 6A-B) [97]. They found that both twist and coordination of N-substituents are critical for the high reactivity in the cross-coupling. The same group reported the mechanism of Pd-catalyzed decarbonylative Suzuki cross-coupling of amides, establishing decarbonylation prior to transmetalation as the chemoselectivity determining feature [58].

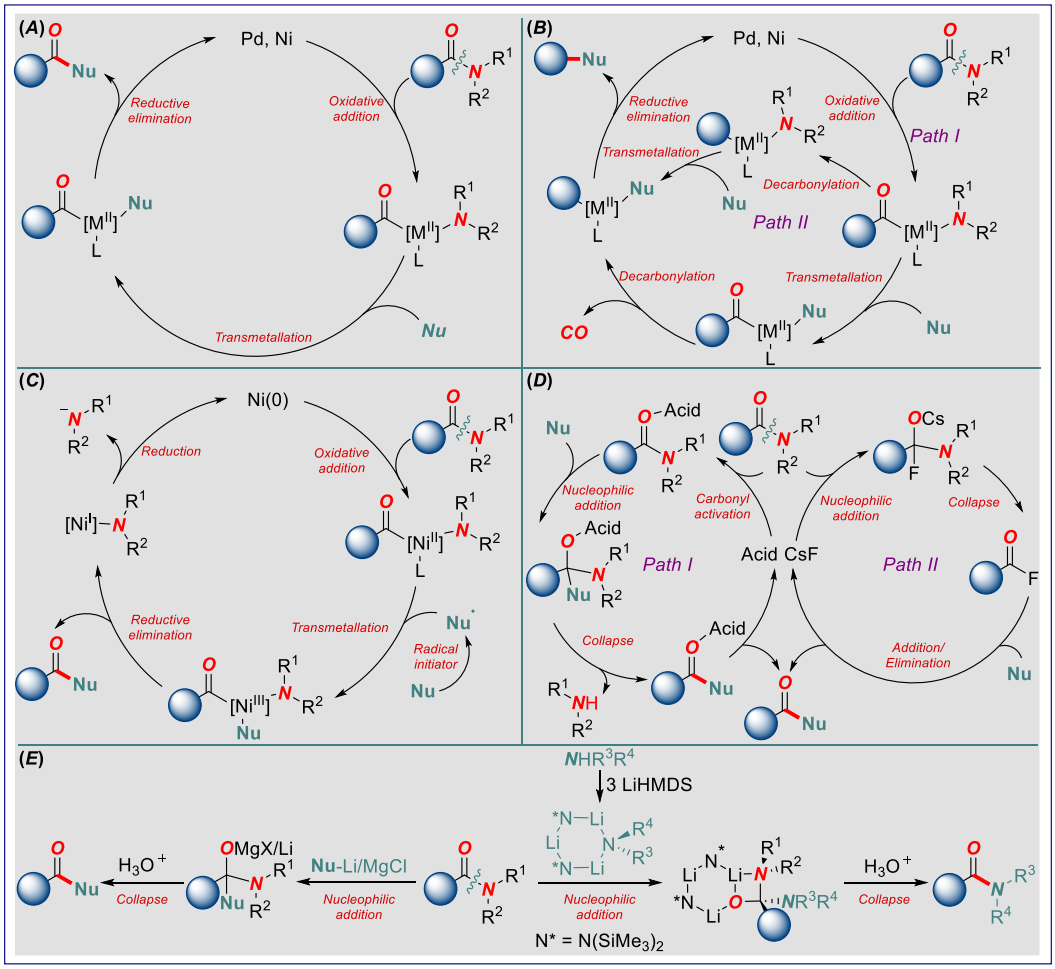

Figure 6. Mechanisms of amide bond activation.

(A) Acyl cross-coupling. (B) Decarbonylative cross-coupling. (C) Radical coupling. (D) Transition-metal-free acylation: path I (acid catalyzed), path II (fluoride catalyzed). (E) Transamidation and ketone synthesis.

The mechanism of Ni/NHC-catalyzed acyl Suzuki cross-coupling has been studied by Zhao and co-workers, finding that water facilitates transmetalation by protonating the basic N-

leaving group [98], while Poater and colleagues established transmetalation as the rate-determining-step in Pd/NHC-catalyzed Suzuki cross-coupling [99]. A recent study demonstrated the importance of proton transfer to the leaving group in the Pd-catalyzed Hirao cross-coupling [100]. Studies on the mechanism of radical coupling (Figure 6C) [78], fluoride-mediated esterification (Figure 6D) [91] and acyl addition (Figure 6E) [85] have been reported. We anticipate that the development of new twisted amides tied to the mechanistic studies will guide the design of modern amide bond activation reactions.

Concluding Remarks

The importance of amides in various areas of chemistry is undisputed. Historically, chemists perceive amide bonds as the most stable of carboxylic acid derivatives, and this fact is well-reflected in the undergraduate curriculum taught to every chemistry student. The recent major breakthroughs in activation of amide bonds call for changing this perception. As the recent studies clearly demonstrate, amides should be regarded as an easily modifiable functional group that can be subject to an array of new and generic reaction modes, including transition-metal-catalyzed acyl coupling, decarbonylative coupling, radical coupling or transition-metal-free acylation reactions.

While progress has been remarkable, it is important to outline several future challenges and opportunities in the synthetic space of amide bond activation and mechanistic understanding of amide twisting (see Outstanding Questions). One of the major issues that needs to be resolved is activation of fully unactivated acyclic amides. Related frontiers in the field include improved synthesis of acyclic twisted amides and elucidation of the precise role of N-substituents triggering amide bond twist and by extension high reactivity in N–C activation manifolds. An intriguing approach could involve the use of transition-metals by external coordination to N-remote substituents [101]. In this way, activation of even planar N,N-dialkyl amides could be potentially achieved by substrate or catalyst control. Further, it would be synthetically attractive to expand the approach to amide bond distortion by N-pyramidalization [102]. Several classes of N-pyramidalized amides have already been reported and future efforts directed towards the application of this activation framework could lead to the improved efficiency and selectivity in amide bond activation. Another manifold that will undoubtedly attract attention of chemists is the activation of amides by mechanical twisting [103]. This can be achieved by self-assembled

coordinating cages; however, it is worth noting that there are a plethora of simple amides that have been distorted to a similar extent by metal coordination. Furthermore, the amide bond activation manifold would benefit from the establishment of general reactivity principles and the discovery of improved catalyst systems that could be applied across various reaction classes in both the classical closed-shell mechanisms and radical open-shell pathways. The demonstration of acyl and decarbonylative amide bond activation in functionalization of complex biomolecules would further test the limits of this activation platform and provide a gateway to applications in medicinal chemistry and drug discovery.

Finally, it is now also clear that the recent leaps in amide bond activation have been enabled by the rational modification of amidic resonance and the development of new amide precursors. It appears that this approach of bond activation is highly general and can be applied to various, not necessarily related, reaction manifolds, thus attesting to the broad applicability of amide bond twisting. Given the tremendous importance of amides, we anticipate that this activation framework will thrive to enable exceedingly more efficient transformations of the amide bond.

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Declaration of Interests

The authors declare no competing interests.

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Glossary

Amides: carboxylic acid derivatives in which a nitrogen atom is attached to a carbonyl group.

Closed-shell pathway: a process describing heterolytic bond cleavage.

Cross-coupling reaction: a process that creates bonds between two different fragments using a metal catalyst.

Open-shell pathway: a process in which bonds are broken homolytically.

Transamidation: a process in which one amide bond is converted to another amide bond.

Twisted amide: an amide in which geometry of the six atoms comprising the amide bond is not planar.

Winkler-Dunitz parameters: a set of parameters used to describe geometric distortion of amide bonds.