Non-Classical Amide Bond Formation: Transamidation and Amidation of Activated Amides and Esters by Selective N–C/O–C Cleavage

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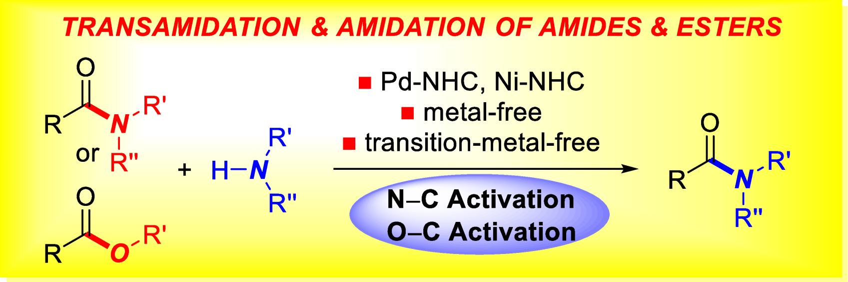

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Abstract In the past several years, tremendous advances have been made in non-classical routes for amide bond formation that involve transamidation and amidation reactions of activated amides and esters. These new methods enable the formation of extremely valuable amide bonds via transition-metal-catalyzed, transition-metal-free or metal-free pathways by exploiting chemoselective acyl C–X (X = N, O) cleavage under mild conditions. In a broadest sense, these reactions overcome the formidable challenge of activating C–N/C–O bonds of amides or esters by rationally tackling $n_N \rightarrow \pi^*_{C=O}$ delocalization in amides and $n_O \rightarrow \pi^*_{C=O}$ donation in esters. In this account, we summarize the recent remarkable advances in the development of new methods for the synthesis of amides with a focus on (1) transition-metal/NHC-catalyzed C–N/C–O bond activation, (2) transition-metal-free highly selective cleavage of C–N/C–O bonds, (3) the development of new acyl-transfer reagents, and (4) other emerging methods.

Key words amides; transamidation; N–C activation; esters; amidation; O–C activation; catalysis; transition-metal-free; NHCs; palladium; nickel

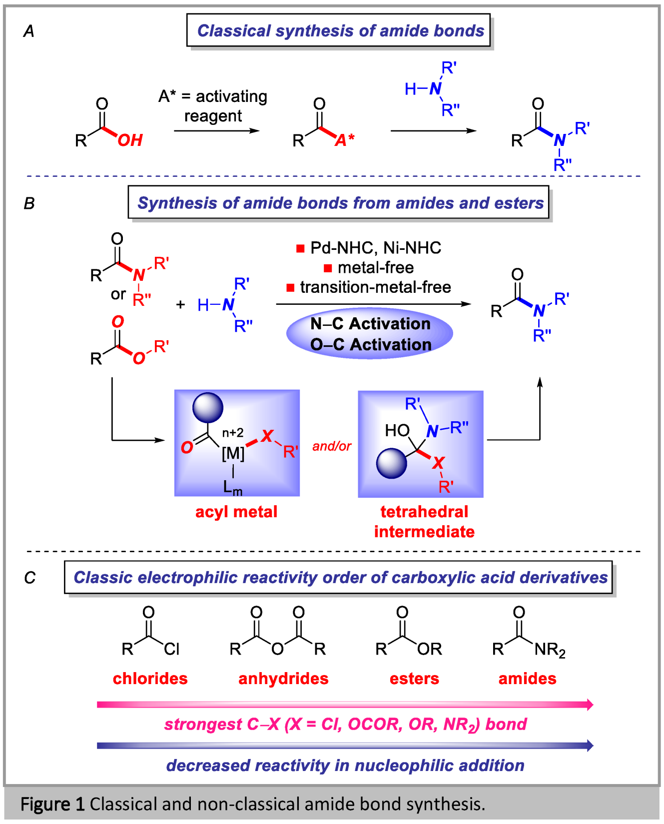


Figure 1 Classical and non-classical amide bond synthesis.

1. Introduction

The amide bond is an essential motif in chemistry and biology.[1] Amides form key linkages in natural products, pharmaceuticals and polymers, but perhaps most importantly, amides play an indispensable role as linkers in biomacromolecules, such as peptides and proteins.[1–3] Due to the importance of amides, amide bond forming reactions occupy an eminent position in organic synthesis.[4] The importance of developing new methods for amide bond synthesis is highlighted by the overwhelming fact that the amide bond forming reactions represent *the* most common reaction executed by medicinal chemists,[5] while amide bonds are present in *more than 75%* of prospective drug candidates.[6]

Traditional methods of forming amide bonds involve the use of stoichiometric coupling reagents and carboxylic acids as carbonyl electrophiles (Figure 1A).[3,4] Transamidation of amides and amidation of esters have emerged to be among the most powerful methods for the formation of amide bonds (Figure 1B).[7,8] The surge of recent studies amply demonstrate that the formidable challenge of selectively cleaving the amide N–C(O) and ester C–O(O) bonds can be successfully addressed in a very general and synthetically useful manner.

Most crucially, the recent studies show that in contrast to the textbook knowledge on the order of electrophilic reactivity of carboxylic acid derivatives (Figure 1C),[9] both amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ delocalization, RE = 15-20 kcal/mol in planar amides, RE = resonance energy)[10,11] and $n_O \rightarrow \pi^*_{C=O}$ isomerization in esters follow a broad continuum of electrophilic reactivity spectrum that (1) can be easily modulated by rational modification of stereo-electronic properties of the amide and ester bond, and (2) this mechanism can be effectively exploited for the formation of amide bonds by non-classical reaction pathways. In general, "activated amide bonds" are defined as any amide bonds in which Nlp delocalization decreasing amidic resonance is feasible.[7e] An important consideration in the synthesis of activated amides is the choice of precursors; ideally, activated amides are prepared either from unactivated 1° or 2° amides or from carboxylic acid derivatives by complementary reaction pathways.[7e]

In this personal account, we summarize our work together with the recent remarkable advances in the development of new non-classical amide bond forming reactions by transamidation of amides and amidation of esters. The account focuses on the following methods: (1) ground-state-destabilization of amide C–N bonds, which enables formation of acyl-metals; (2) transition-metal-catalyzed activation of ester C–O bonds to furnish an alternative means of accessing acyl-metals; (3) transition-metal-free direct nucleophilic addition to amide or ester X–C=O bonds to form tetrahedral intermediates with exceptional selectivity; (4) other mechanisms. Broadly, this area has emerged from acyl substitution reactions, including intramolecular lactamizations via tetrahedral intermediates and amidations with preformed metal amides.[2,4i]

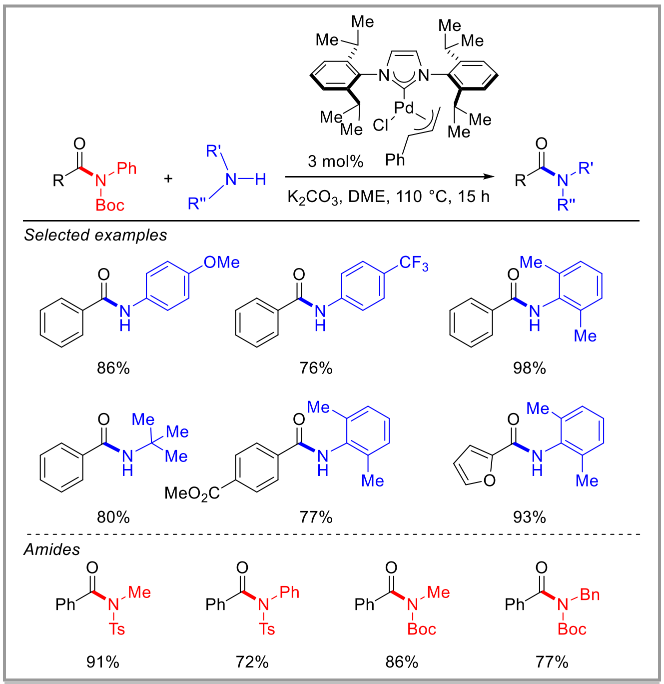
This novel reactivity manifold has great implications on the general reactivity of common amide and ester bonds that extends far beyond the topic of this review.[1–11] We hope that the review will stimulate further progress in the field by a range of interested chemists.

2. Transamidation of Amides

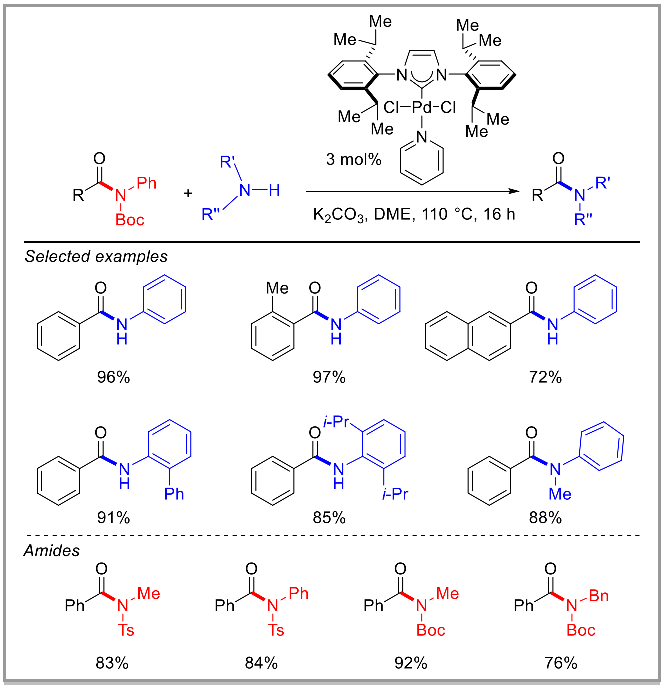
2.1 Transamidation by Metal–NHC Catalysis (Pd–NHC, Ni–NHC)

Pd–NHC (NHC = N-heterocyclic carbene) complexes have emerged as versatile catalysts for transamidation of amides, enabling for the first time to achieve acyl-Buchwald-Hartwig type cross-coupling of amides. In 2017, our group reported the first method for transamidation of N-activated 2° carboxamides using Pd–NHCs (Scheme 1).[12] The high chemoselectivity of this method relies on N-site-selective activation of a 2° amide bond to furnish ground-state-destabilized N-Boc or N-Ts amide,[11b] followed by chemoselective oxidative addition of the N–C(O) bond to give acyl-palladium intermediate, which is converted to the amide product via ligand exchange and reductive elimination. These reactions proceed smoothly in the presence of [Pd(NHC)(cin)Cl] as catalyst (3 mol%), K_2CO_3 as base and DME as solvent at 110 °C. Transamidation of N-activated 2° amides gives amide products in good to excellent yields. The method features broad substrate scope, including sterically-hindered anilines and aliphatic amides. Importantly, even in this early report, various N-substituted amides, such as N-Ph/Ts and N-Me/Boc amides that can be prepared from common 2° amides in a single, operationally straightforward step, were also compatible.

In the same year, we expanded the direct transamidation of amides by acyl-metal intermediates to the use of Pd–PEPPSI type precatalysts (Scheme 2).[13] Notably, the ease of preparation,



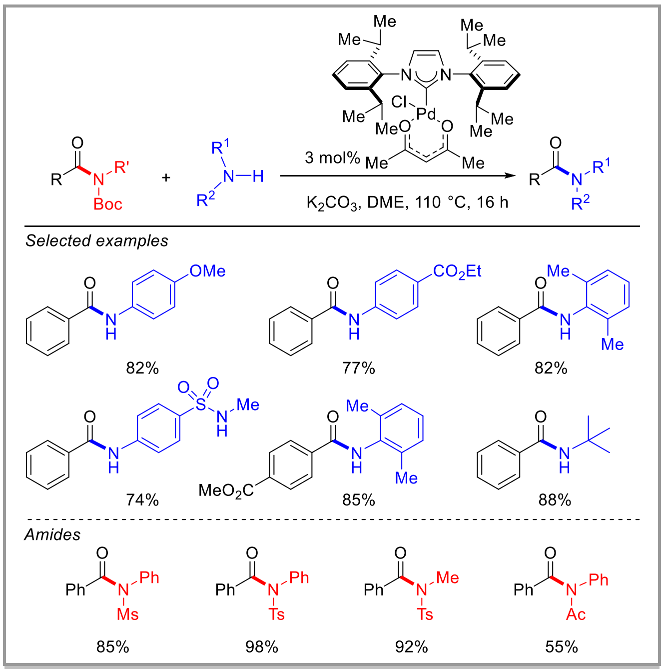
Scheme 1 [Pd(NHC)(cin)Cl]-catalyzed transamidation of N-activated secondary amides (amide Buchwald-Hartwig reaction).



Scheme 2 [Pd–PEPPSI]-catalyzed amide Buchwald–Hartwig cross-coupling (transamidation).

moisture- and air-stability, and a plethora of Pd–PEPPSI-type complexes available offer a clear advantage of this protocol.

Later, in 2019, we reported another class of Pd(II)–NHC precatalysts, namely [Pd(NHC)(acac)Cl] complexes, for the direct transamidation of N-activated amides (Scheme 3).[14] This method affords amide products in good to excellent yields and features a broad scope with respect to the reaction components, including those with electrophilic groups owing to the high activity of the precatalysts. Various N-substituted secondary amide derivatives, such as N-Ts, N-Ms and N-Ac, worked smoothly under standard reaction conditions. Recognizing the main advantage of [Pd(NHC)(acac)Cl] complexes in the ease of preparation from $Pd(acac)_2$ and NHC salts, we presented an assay for *in situ* screening of NHC salts in this transamidation owing to the facile *in situ* synthesis of [Pd(NHC)(acac)Cl] catalysts.[14]

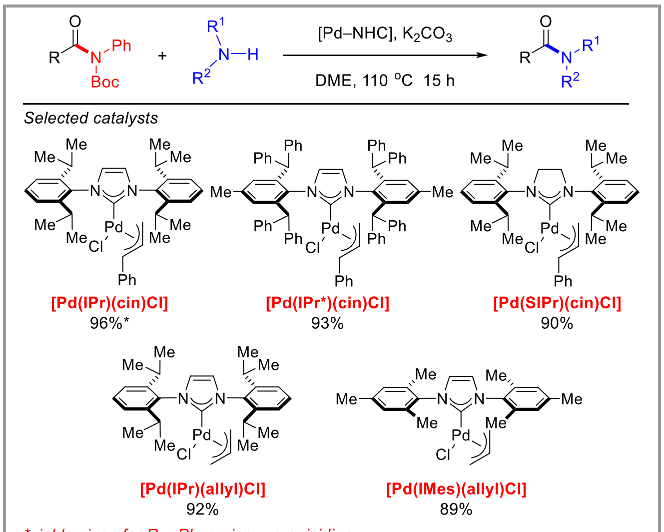


Scheme 3 [Pd(NHC)(acac)Cl]-catalyzed Buchwald–Hartwig cross-coupling (transamidation).

In 2020, we reported a study on the effect of various [Pd(NHC)(allyl)Cl] precatalysts in the acyl-Buchwald-Hartwig transamidation of amides (Scheme 4).[15] Importantly, these Pd–NHC-catalyzed conditions permit for the synthesis of functionalized amides from substrates that are not compatible with transition-metal-free or Ni–NHC-catalyzed transamidation methods. In evaluation of 7 well-defined, air- and moisture-stable [Pd(NHC)(allyl)Cl] precatalysts, we found that [Pd(IPr)(cin)Cl], [Pd(SIPr)(cin)Cl] and [Pd(IPr)(ally)Cl] complexes were the most efficient precatalysts in the acyl Buchwald-Hartwig cross-coupling of N-Ph/Boc amides.

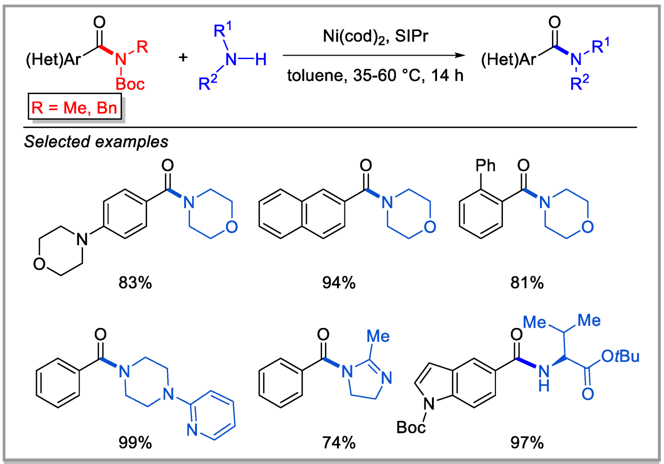
To provide information on the reaction mechanism, we reported examination of the full catalytic cycle by DFT calculations.[15] The results suggested that oxidative addition of the N–C(O) bond was the rate determining step. The viability of the formation of acyl-Pd(II)(NHC)(amido) intermediates suggests considerable opportunities for the design and development of new cross-coupling methods involving amide electrophiles.[16]

The use of Ni–NHC catalysts in the transamidation of amides has been elegantly pioneered by Garg and co-workers. In their seminal 2016 report, they accomplished a two-step method for N-activation of 2° amides with the Boc group, followed by Ni–NHC-catalyzed transamidation (Scheme 5).[17] Their strategy involves site-selective N-Boc activation to afford twisted, ground-state-destabilized amides.[11b] The Ni–NHC-catalyzed N–C bond activation affords acyl-nickel intermediate, which is converted to the desired amide products in the presence of an appropriate amine. The method features broad substrate scope, including basic heteroatoms, heterocyclic amines and amino acid derived nucleophiles. The advantage of this method involves the use of a 3d transitional metal, low temperature and non-basic conditions. However, the use of air-sensitive $Ni(cod)_2$ limits this approach to a glove-box set-up. It general, it is worthwhile to note that Ni and Pd catalysis should be regarded as complementary methods of activation of amide bonds.[7d] While Ni is cheaper and more sustainable, the reactions catalyzed by Pd are typically characterized by a broader scope. Furthermore, low catalyst loading is more easily achieved with Pd, which is particularly important when using expensive ancillary ligands. It could also be noted on the basis of the reported examples that Pd catalysis appears to be significantly more promising as a synthetic tool in this area than Ni catalysis.



*yields given for R = Ph, amine = p-anisidine

Scheme 4 [Pd(NHC)(allyl)Cl] catalysts in amide Buchwald–Hartwig cross-coupling (transamidation).

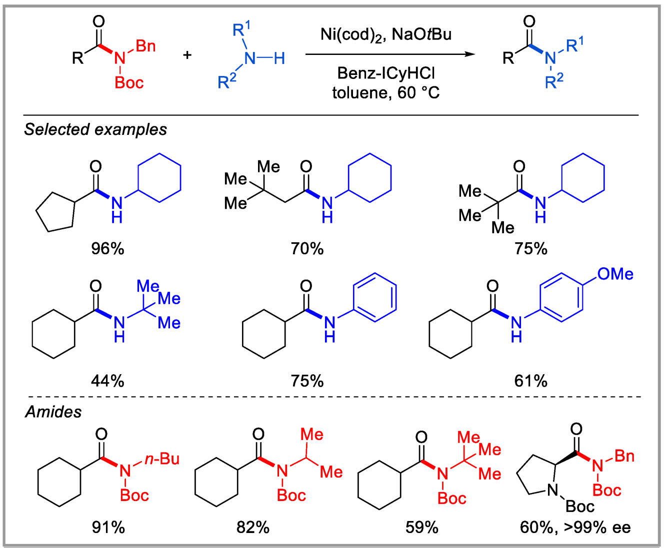


Scheme 5 [Ni–NHC]-catalyzed transamidation of N-activated secondary amides.

Later, the authors have presented a practical solution in the form of Ni(cod)$_2$ paraffin capsules.[18] On the other hand, Pd(II)–NHC catalysts are well-defined, air- and moisture-stable, while the activation to Pd(0) proceeds under the reaction conditions, which heavily contributes to the current broad use of Pd(II)–NHC complexes in organic synthesis and catalysis.[12–16]

In 2017, Garg and co-workers reported Ni–NHC-catalyzed transamidation of aliphatic amides with amines via a similar two-step approach (Scheme 6).[19] In this method they used Ni(cod)$_2$ as catalyst and benzimidazolylidene NHC, Benz-ICy, as ligand. The amide products were obtained in good to excellent yields and with very good tolerance to steric hindrance at the α-carbon of the aliphatic amide substrates. Notably, chiral amino acid derived electrophiles underwent the cross-coupling with full retention of configuration under standard reaction conditions.

They proposed that the more electron-rich nature of Benz-ICy facilitates oxidative addition of the aliphatic amide N–C(O) bond. Indeed, a recent study on σ-donating properties of NHC ligands suggests that benzimidazolylidenes such as Benz-ICy are more σ-donating than their imidazolylidene analogues, such as ICy, as measured by the $^1J_{CH}$ coupling constant (ICy: 220.3 Hz; Benz-IPr: 217.6 Hz).[20]



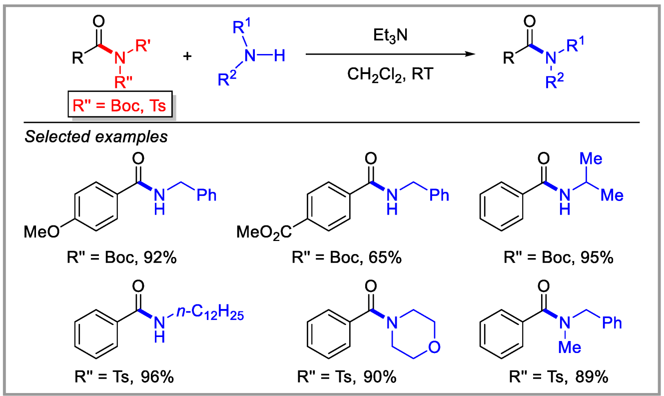
Scheme 6 [Ni–NHC]-catalyzed transamidation of N-activated aliphatic secondary amides.

2.2 Transition-Metal-Free Transamidation via Tetrahedral Intermediates

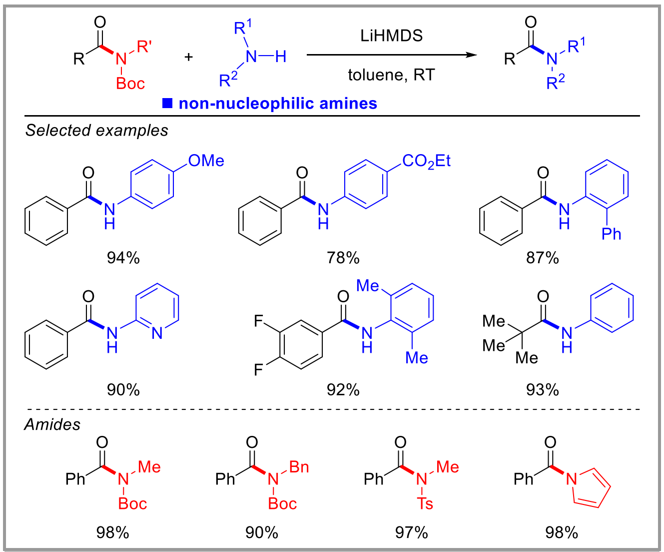
Nucleophilic acyl substitution reactions represent a fundamental reaction in the organic chemistry toolbox that is taught to all undergraduate chemistry students.[9] The main challenge in exploiting amides as electrophiles in acyl substitution reactions is amidic resonance, $n_N \rightarrow \pi^*_{C=O}$ delocalization (RE = 15-20 kcal/mol in planar amides).[10,11]

Following our mechanistic studies on ground-state-destabilization of amides,[11] and the introduction of this concept to cross-coupling reactions of amides,[7a] in 2017, we reported metal-free transamidation of N-activated 2° amides under mild conditions (Scheme 7).[21] The method involves two steps: (1) site-selective N-Boc or N-Ts activation of 2° amides to weaken amidic resonance by affording non-planar, electronically-destabilized amides, and (2) nucleophilic addition of amines to furnish tetrahedral intermediates, which thermodynamically collapse to give the desired amide transamidation products. In this design, electronic properties of the leaving group facilitate the collapse of the tetrahedral intermediate. The method is characterized by metal-free, operationally-simple conditions, and works smoothly with a wide range of amides and nucleophilic amines. We also achieved a direct conversion of 2° amides via one-pot N-activation/transamidation.

In 2018, we reported a highly selective, transition-metal-free method for transamidation of N-activated primary or secondary amides with *non-nucleophilic* amines (Scheme 8).[22] In this approach, we demonstrated that the use of LiHMDS as base and toluene as solvent enables for the first time to afford transamidation products under mild, room temperature conditions. The method is compatible with a broad substrate scope, including electron-deficient, sterically-hindered, heterocyclic as well as anilines featuring sensitive functional groups, such as halides or esters. Notably, different N-activated 1° and 2° amides, including N,N-Boc$_2$, N-Ts, N-Ms amides and N-acyl-pyrroles worked well under standard reaction conditions. The practical value of this method was highlighted in the synthesis of



Scheme 7 Metal-free transamidation of N-activated secondary amides.

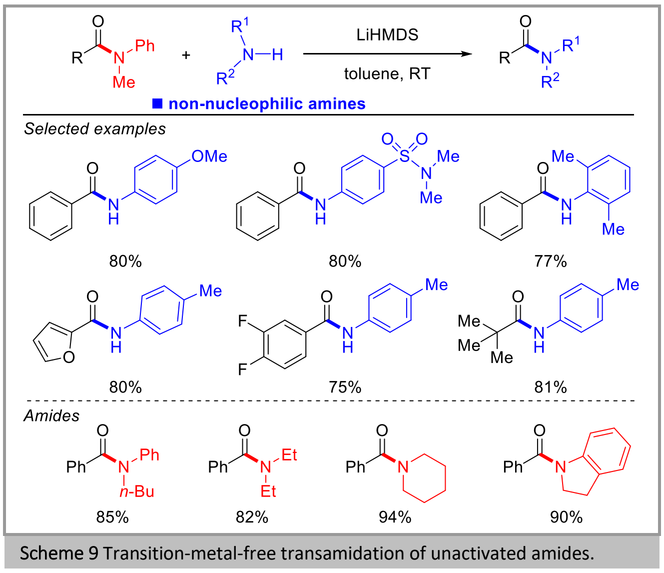


Scheme 8 Transition-metal-free transamidation of N-activated primary and secondary amides.

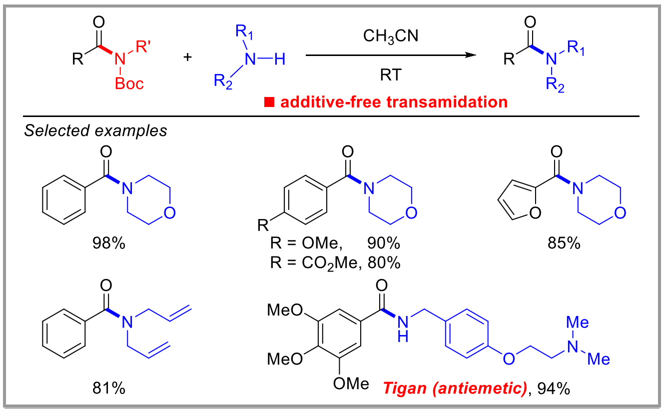
pharmaceuticals, such as moclobemide (MAO inhibitor) and lidocaine (local anesthetic).

In 2019, encouraged by the success of transition-metal-free transamidation reactions of N-activated amides, we reported the first general method for transition-metal-free, highly chemoselective transamidation of *unactivated* N,N-dialkyl and N,N-aryl-alkyl tertiary amides under mild conditions (Scheme 9).[23] This method relies on aniline deprotonation with LiHMDS, and features mild conditions, operational-simplicity and broad scope. This transition-metal-free transamidation was explored by DFT calculations, and the results indicated that the rate-determining step is LiHMDS-mediated nucleophilic addition. The practical utility of this new transamidation method was further showcased in the synthesis of bioactive agents and late stage diversification.

It is further noteworthy that this transamidation method showed excellent chemoselectivity in two directions: (1) with respect to different functional groups, and (2) between different amide and ester electrophiles, which allows to distinguish amide electrophiles along the continuum spectrum of the electrophilic reactivity of amides. *In some cases, amides are more reactive than acyl halides, which defies the traditional trend in nucleophilic acyl substitution (Figure 1C)*[9] *and calls for revisiting the common perception of the electrophilic properties of amide bonds.*



Scheme 9 Transition-metal-free transamidation of unactivated amides.

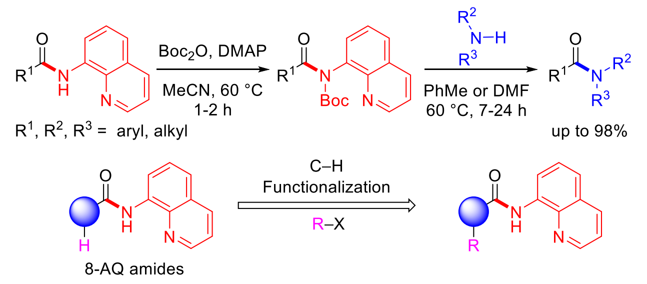


Scheme 10 Metal- and additive-free transamidation of N-activated secondary amides.

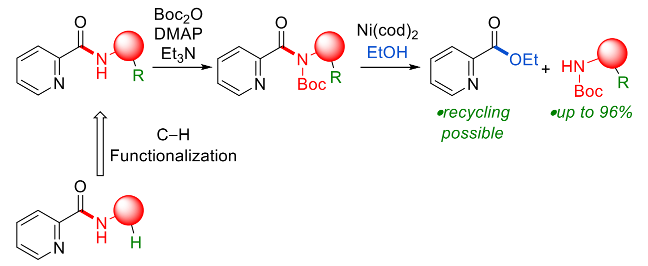
In 2019, we have further extended transamidation reactions with nucleophilic amines, and reported a metal-free, highly chemoselective method for transamidation of N-Boc activated 2° amides under mild conditions in the absence of any additives (Scheme 10).[24] The method demonstrated excellent functional group tolerance by matching polar properties of the solvent with the stability of ground-state-activated amides. The method is beneficial in terms of decreased waste generation and atom economy. The method was showcased to furnish a best-selling drug, Tigan (antiemetic).[25] In general, transition-metal-free transamidations and metal-catalyzed Buchwald-Hartwig reactions should be regarded as complementary in analogy to transition-metal-free and metal-catalyzed amidation of esters (see Section 3.1.1 for guidelines on the scope and utility of these reactions).

Following our initial reports on metal-free transamidation of ground-state-destabilized amides, several groups have published excellent studies demonstrating the utility of this emerging transamidation manifold in C–H functionalization, synthesis of unnatural amino acids and polymer synthesis.

In 2018, Verho and co-workers reported a practical, metal-free transamidation of 8-aminoquinoline amides via a two-step strategy (Scheme 11).[26] The authors first activated secondary 8-aminoquinoline amides with N-Boc to give ground-state-destabilized amides, followed by treatment with amines in toluene or DMF at 60 °C. The reaction is compatible with various alkyl amines, less nucleophilic amines and sensitive functional groups. It is worth noting that this strategy significantly expands the potential of 8-aminoquinoline amides as substrates for C–H functionalization,[27] which was elegantly demonstrated by the authors to afford functionalized amide products in good to excellent yields.



Scheme 11 Metal-free transamidation of N-8-aminoquinoline amides.

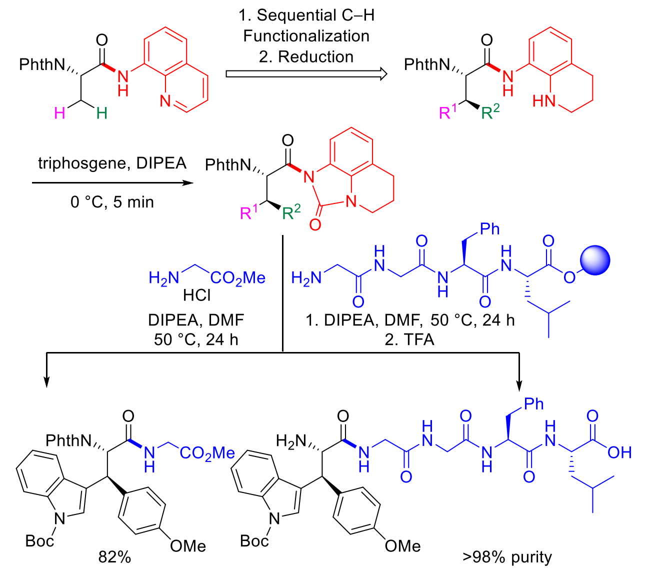


Scheme 12 Ni-catalyzed C–N bond cleavage in picolinamides.

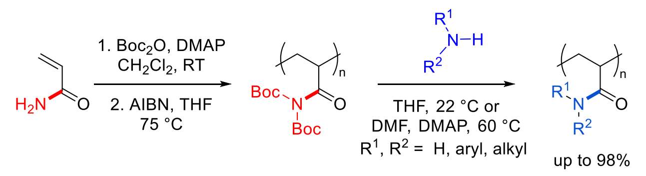
In 2019, Maes and co-workers reported Ni-catalyzed cleavage of N–C(O) bond of picolinamides after N-Boc activation (Scheme 12).[28] In this strategy, secondary picolinamide group directs the C–H functionalization step on the aliphatic amide chain, followed by N-Boc activation to afford ground-state-destabilized amide, which was treated with Ni(cod)$_2$ in ethanol to furnish the desired N-Boc protected amines and ester byproduct. The ester byproduct was recycled by treatment with amines and La(OTf)$_3$ to re-form secondary picolinamides. The authors demonstrated broad functional group tolerance of this approach.

In 2019, Geyer and co-workers reported transition-metal-free transamidation of N-acyl ureas with protected amino acids and peptides (Scheme 13).[29] Notably, they performed sequential C–H arylation using 8-aminoquinoline amide as a directing group. N-acyl urea activated amides were then prepared in two steps involving pyridine reduction and cyclization. This ground-state-destabilized amide was treated with protected amino acid or peptide in DMF at 50 °C in the presence of DIPEA to afford amide products in good yields. Impressively, this transamidation approach was demonstrated on a gram-scale to provide sterically congested β-branched α-amino acids.

In 2018, Hillmyer and co-workers developed metal-free transamidation of poly-di-(Boc)-acrylamide [poly(DBAm)] to afford poly(acrylamides), showcasing the power of new transamidation methods (Scheme 14).[30] In this approach, the authors first activated 1° amide by site-selective introduction of two Boc groups, followed by radical polymerization in the presence of AIBN at 75 °C. Poly(DBAm) was next treated with various amines in the presence of DMAP in THF or DMF to furnish poly(acrylamides) in good to excellent yields. Notably, this transamidation could tolerate various amines, including primary, α-branched, sterically-hindered secondary amines and anilines. The utility of this method was demonstrated in the synthesis of block polymers and on-demand gelation process.



Scheme 13 Sequential C(sp^3)–H arylation of tryptophan/metal-free transamidation.



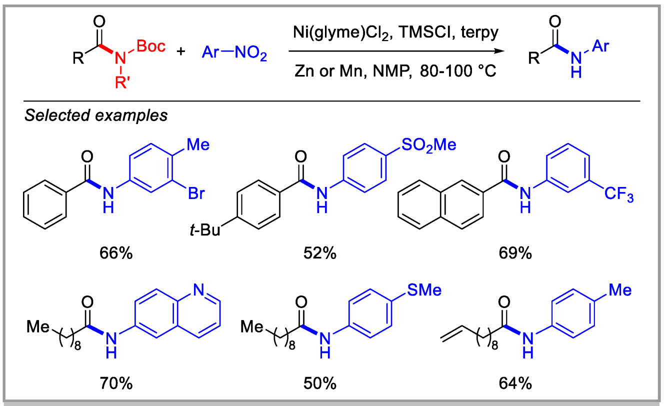
Scheme 14 Metal-free transamidation of N-Boc-activated polyacrylamides.

2.3 Reductive Transamidation

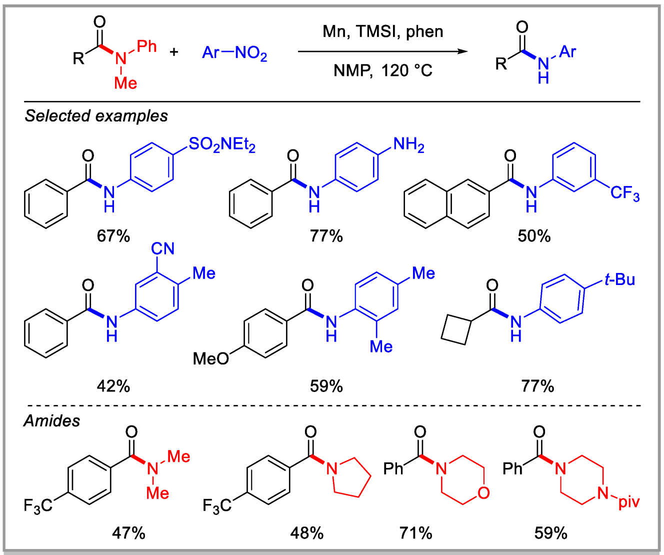
Nitroarenes have recently stimulated renewed interest as the cheap, readily available and orthogonal source of nucleophilic nitrogen under reductive conditions.[31] Transamidations with nitroarenes under reductive conditions have been spearheaded by Hu and co-workers.

In 2017, the Hu group reported a reductive transamidation of N-Boc-activated 2° alkyl and aryl amides with nitroarenes to furnish amide products (Scheme 15).[32] The reaction was performed in the presence of Ni(glyme)Cl$_2$ as catalyst, Zn or Mn as reductant, 1,10-phenanthroline or 6',2''-terpyridine as ligand, and chlorotrimethylsilane or iodotrimethylsilane as additive in NMP at 80-100 °C to afford amide products in good yields. This method is characterized by a broad substrate scope and excellent functional group tolerance. The authors proposed nitrosobenzene, N-phenyl hydroxylamine and azobenzene as potential nitrogen-containing intermediates, which are formed in the reduction of nitroarenes. Mechanistic studies with isolated intermediates suggested that azobenzene might be a potential intermediate in these reductive transamidations.

In 2018, Hu and co-workers developed a manganese-mediated reductive transamidation of unactivated tertiary amides deploying nitroarenes as nitrogen source (Scheme 16).[33] It is particularly noteworthy that this transamidation reaction is mediated solely by an inexpensive manganese metal without additional metal catalysts to afford amide products in high yields. This reductive transamidation also demonstrated excellent functional group compatibility, including various electronically-differentiated, sterically-hindered and sensitive functional groups on both the amide and nitroarene coupling partners. The synthetic utility was neatly demonstrated by rapid derivatization of bioactive tertiary amides. Control reactions suggested that azoarene is the active intermediate in this transamidation rather than nitrosobenzene, N-phenyl hydroxylamine or aniline.



Scheme 15 Nickel-catalyzed reductive transamidation of N-Boc-activated secondary amides.



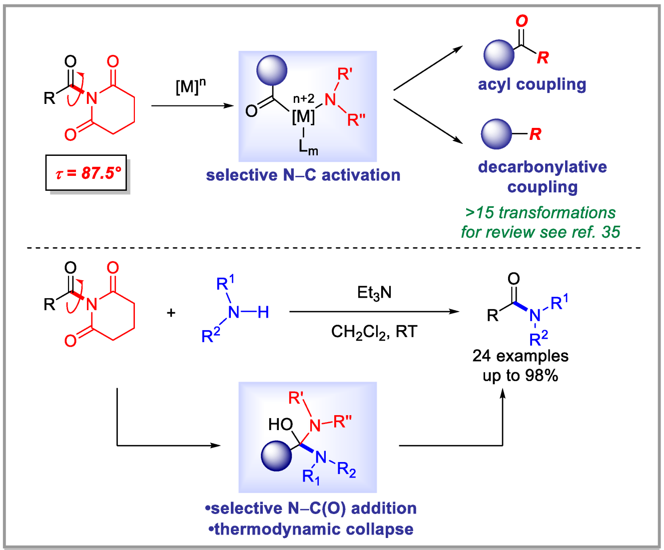
Scheme 16 Manganese-mediated reductive transamidation of tertiary amides.

Overall, it is notable that the authors demonstrated that the direct use of nitroarenes as nitrogen source instead of anilines leads to efficient transamidation processes. As already illustrated in several impressive examples by Hu and co-workers, the use of orthogonal nitroarene coupling partners is likely to have a broadly beneficial impact on the synthesis of amide bonds by this unconventional disconnection.

2.4 New Acyl-Transfer Reagents

Another dominant direction in the evolution of new transamidation reactions is the development of new acyl-transfer reagents.

In 2015, our group introduced N-acyl-glutarimides as fully twisted, ground-state-destabilized amides for Suzuki-Miyaura cross-coupling of amides (Scheme 17A).[34a] Subsequently, we demonstrated that N-acyl-glutarimides are privileged electrophiles for decarbonylative amide cross-couplings, thus launching the decarbonylative amide cross-coupling manifold.[34b] At present, N-acyl-glutarimides are the go-to-amides in the development of new cross-coupling reactions by N–C(O) activation, including Pd, Ni, Rh and Co catalysis.[35] In 2018, we reported metal-free transamidation of N-acyl-glutarimides with aliphatic amines under mild room temperature conditions.[36] These bench-stable reagents selectively afford transamidation products by the cleavage of the exocyclic amide bond in good to excellent yields via tetrahedral intermediates. The excellent performance of N-acyl-glutarimides in N–C(O) bond activation hinges on 3 factors: (1) almost perpendicularly twisted amide bond ($\tau = 87.5°$); (2) unusually high stability of the twisted amide linkage under various reaction conditions; and (3) high selectivity for the exocyclic N–C(O) bond cleavage owing to the weakened amidic resonance (ER = 0 kcal/mol).[37]



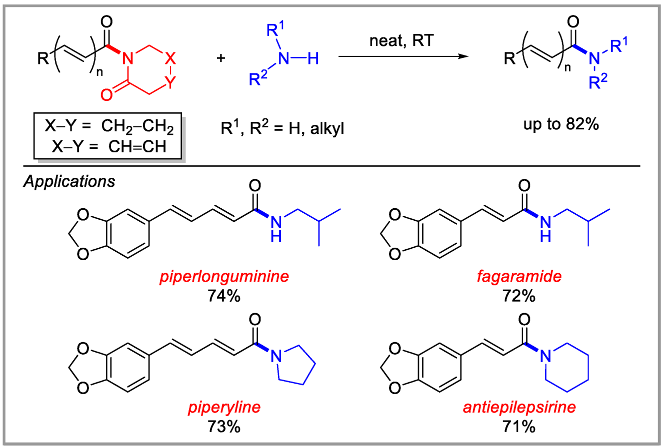
Scheme 17 Fully twisted N-acyl-glutarimides: metal-catalyzed N–C activation and metal-free transamidation of N-acyl-glutarimides.

The concept of using N-acyl-imides is not limited to N-acyl-glutarimides; for example, related N-acyl-succinimides[38] and N-acyl-saccharins[39] have been deemed most useful for select applications when (1) more stable amides, and/or (2) better leaving groups are required for a synthetic process.

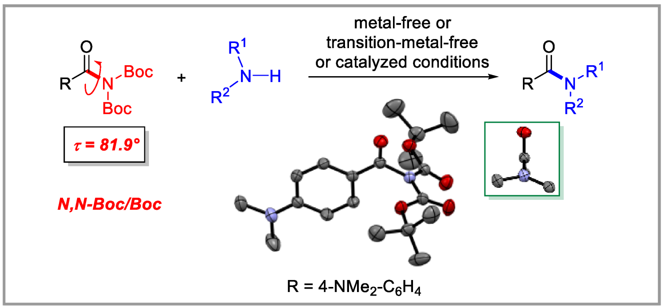
In a related avenue, in 2019, Rajendran and co-workers developed N-acyl-2-piperidones for metal-free transamidation with nucleophilic amines under solvent-free, room temperature conditions (Scheme 18).[40] The X-ray structure of a vinyl derivative was solved and indicated a moderately twisted amide bond ($\tau = 20.4°$, $\chi_N = 11.7°$). Notably, the method tolerates various functionalized amines, including amino acids and amino alcohols. The synthetic utility of this new acylation reagent was demonstrated in the synthesis of bioactive nature products, antiepilepsirine, piperlonguminine, piperyline and fagaramide.

To expand the available amide precursors for transition-metal-catalyzed and metal-free reactions, our group has pioneered several classes of novel acylic twisted amides (Schemes 19-20).

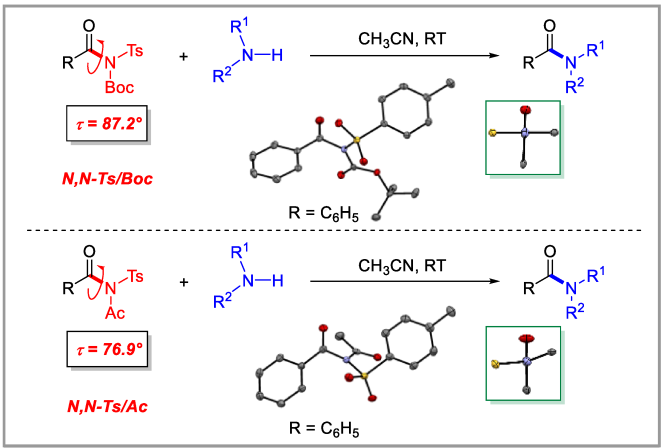
In 2018, we reported structural study of N,N-di-Boc amides as the first example of “reversibly twisted” common acyclic amides (Scheme 19).[41] Importantly, these amides feature almost perpendicular twist (up to τ = 81.9°) and could be directly derivatized in transamidation reactions by engaging primary amides via site-selective N,N-di-Boc activation in excellent yield. In the past years, several groups have reported the utility of N,N-di-Boc amides in N–C(O) bond activation under transition-metal-catalyzed or transition-metal-free conditions.[7f,g] The high reactivity and excellent selectivity for the acyl-amide bond cleavage indicates that N,N-di-Boc amides have high value in organic synthesis. Crucially, these amides are routinely prepared from 1° benzamides, which makes them orthogonal to other precursors for N–C(O) and O–C(O) activation.



Scheme 18 Metal-free transamidation of N-acyl-2-piperidones.

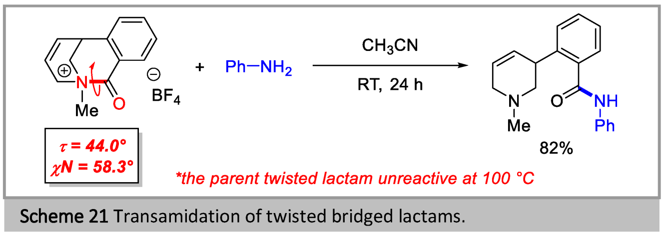


Scheme 19 Synthesis and transamidation of twisted di-Boc-amides.



Scheme 20 Transamidation of twisted acyclic amides.

In 2018, our laboratory further expanded the twist limit available in acyclic amide bonds by reporting the most twisted acyclic amides prepared to date (Scheme 20).[42] We found that N,N-Ts/Boc (τ = 87.2°) and N,N-Ts/Ac (τ = 76.9°) amides feature practically perpendicular amide bonds. In these amides, the classical overlap between N_{lp} and CO π* orbital is disrupted due to (1) strained and twisted geometrical structure; (2) electronic activation. It is particularly noteworthy that 87.2° twist angle of N,N-Ts/Boc amide for the first time matches perpendicular and thus far only examples of isolated fully twisted amides in bridged lactam scaffolds, 1-aza-2-adamantanone by Kirby,[10e] and 2-quinuclidonium by Stoltz.[10f]



Scheme 21 Transamidation of twisted bridged lactams.

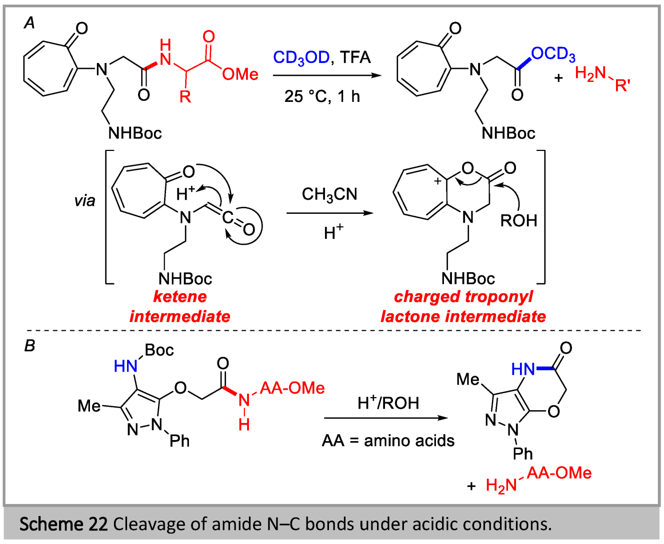
As expected on the basis of twist, N,N-Ts/Boc and N,N-Ts/Ac amides readily react with $BnNH_2$ at room temperature to afford transamidation products without any additives (Scheme 20). The excellent performance and high twist suggest a considerable potential of these amides in acylation reactions. In general, these twisted amides feature close to non-existent resonance energy.[37] The reactivity of such twisted amides in transamidation reactions depends on amide bond distortion, steric hindrance and the leaving group ability.[36]

We have also made progress in transamidation reactions of classic bridged lactams (Scheme 21).[43,44] During the studies on N-alkylation of 1-azabicyclo[3.3.1]nonan-2-one bridged lactams, we found that N-alkyl salts undergo rapid opening with non-nucleophilic anilines at room temperature. In contrast the parent bridged lactam was completely unreactive under the same reaction conditions. Since bridged lactams have provided key information of the structure/activity relationship on non-planar amides, it could be expected that a similar activation pathway would operate in acyclic twisted amide analogues. On the other hand, given the facile synthesis by the intramolecular Heck reaction, N-activated bridged lactams have a significant potential in the synthesis of N-containing heterocycles by a sew/cut approach.[44] Recently, several intriguing reactions of these bridged amides have been discovered, including hydrogenolysis,[45a] σ N–C scission,[45b] Ru-catalyzed twisted amide cross-metathesis,[45c] and polymerization,[45d,e] which in theory could be coupled with transamidation reactions.

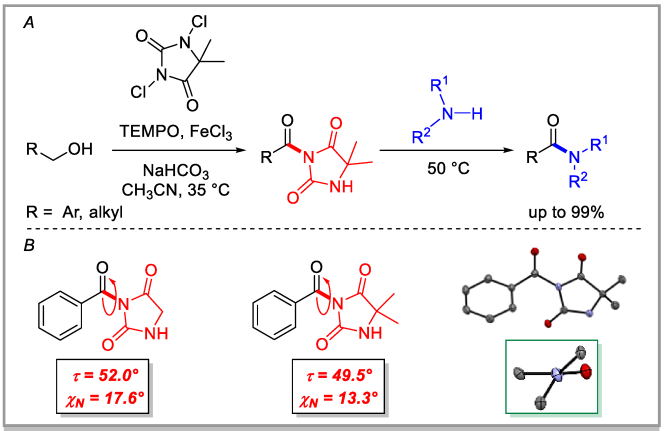
Activation of amides has also been proposed to proceed via the formation of ketene intermediates. In 2015, Sharma and co-workers developed hydrolysis of a hybrid peptide derived from N-troponylaminoethylglycine (Traeg) and α-amino acids under mild conditions (Scheme 22-A).[46] They proposed a pathway involving protonation of the troponyl carbonyl group to enhance the reactivity of amide, and subsequent N–C(O) bond cleavage to afford ketene intermediate, which was converted to a positively charged troponyl lactone via intramolecular cyclization.

In 2019, the same group reported intramolecular transamidation of 4-aminopyrazolyloxy acetamide peptide analogues under mild acidic conditions (Scheme 22-B).[47] The key step involves transamidation after Boc deprotection under acidic conditions, and intramolecular nucleophilic addition/elimination.

Several other transamidations of acyclic twisted amides have been reported (Schemes 23-26). In 2018, Bjørsvik and co-workers reported domino oxidative amidation/telescoped transamidation for the synthesis of amides from alcohols and amines (Scheme 23A).[48] The key step involves formation of twisted N-acyl-5,5-dimethylimidazolidine-2,4-diones. We found that such twisted N-acyl-hydantoins feature higher amide bond distortion that the related N-acyl-succinimides due to increased nitrogen pyramidalization (Scheme 23B).[49] In particular, 5,5-dimethyl-hydantoins appear to be promising twisted amides for cross-coupling and metal-free amidations. In the reaction reported by the Bjørsvik group, the first step involves oxidative amidation of alcohols using TEMPO as terminal oxidant. The authors proposed that the mechanism could involve the formation of iron complex (R-CHO-Fe^{III}), followed by amidation with 1-chloro-5,5-dimethylimidazolidine-2,4-dione, and transamidation of N-acyl-5,5-dimethylhydantoins with amines to furnish final amide products in good overall yields. The practical utility of this domino process was highlighted in the synthesis of an insect repellent, N,N-diethyl-*m*-toluamide, in continuous flow.



Scheme 22 Cleavage of amide N–C bonds under acidic conditions.

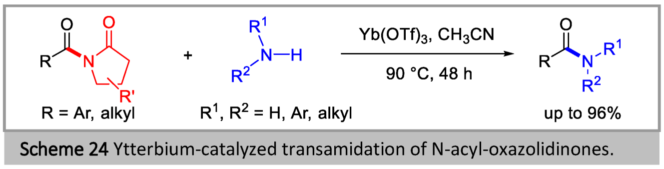


Scheme 23 Domino oxidative amidation and transamidation via twisted N-acyl-hydantoins.

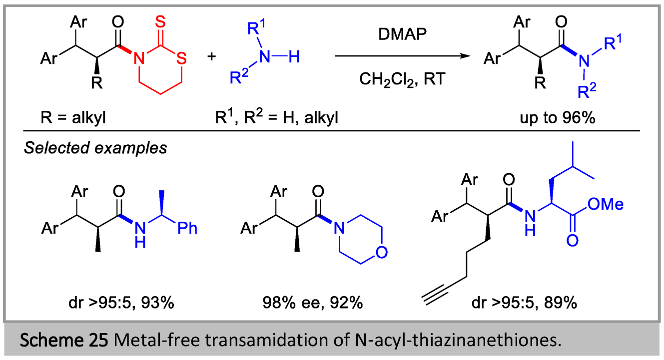
In 2018, Evano and co-workers reported ytterbium-catalyzed transamidation of N-acyl-oxazolidinones (Scheme 24).[50] In this method they used $Yb(OTf)_3$ as catalyst and acetonitrile as solvent at 90 °C to achieve transamidation in high yields. The reaction was applied to transamidation of asymmetric Evans' aldol and alkylation products without loss of stereochemistry.

In 2019, Urpi and co-workers reported transamidation of N-acyl thiazinanethiones with amines in the presence of DMAP under metal-free conditions in excellent yields (Scheme 25).[51] Notably, various enantiopure N-acyl thiazinanethiones, prepared by enantioselective benzylation catalyzed by Ni(II) complexes, underwent transamidation in good yields without epimerization.

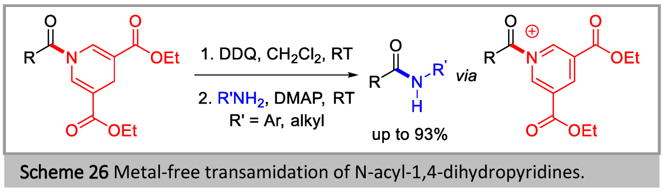
In 2015, Gothelf and co-workers reported transamidation of N-acyl-1,4-dihydropyridines via oxidation to N-acyl-pyridinium (Scheme 26).[52] Mechanistically, the reaction is related to our N-alkylation of bridged lactams (Scheme 21)[43] in that the neutral amide is unreactive. In their strategy, oxidation of N-acyl-1,4-dihydropyridines with DDQ affords activated pyridinium intermediates, which then react with amines in the presence of DMAP to furnish the desired transamidation products. This study might open the door to off-on switchable acylation reagents for various acylation reactions of the amide bond.



Scheme 24 Ytterbium-catalyzed transamidation of N-acyl-oxazolidinones.



Scheme 25 Metal-free transamidation of N-acyl-thiazinanethiones.

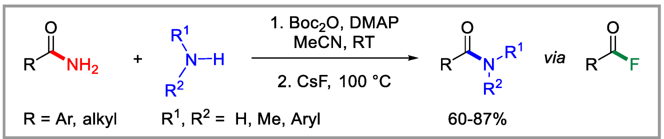


Scheme 26 Metal-free transamidation of N-acyl-1,4-dihydropyridines.

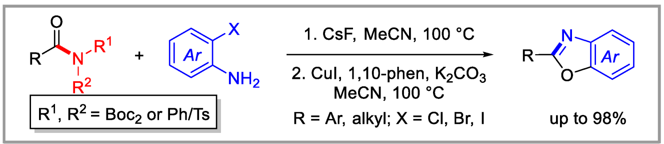
2.5 Tandem Transamidations

Recently, major progress has been made in transamidation by a tandem mechanism, i.e. reactions where activated amides are first converted to more reactive acyl intermediates. Arguably, the first example of such cooperative mechanism has been reported by our group in the Suzuki acyl cross-coupling of N,N-di-Boc amides catalyzed by a combined action of Pd and Lewis base, where amide is first converted to acyl-ammonium, which then undergoes oxidative addition to Pd(0).[53]

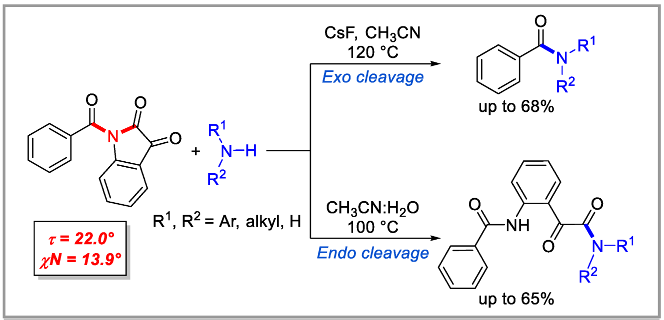
The Zeng group uncovered an intriguing mechanism of activating destabilized amide bonds by nucleophilic addition of fluoride to form acyl fluorides. The authors have confirmed that the acyl fluoride is the reactive intermediate and that CsF is acting as a nucleophilic catalyst. In 2018, they reported an impressive one-pot, transition-metal-free transamidation of primary amides via cesium fluoride-catalyzed pathway (Scheme 27).[54] In this protocol, the primary amide is first converted via the site-selective N-*tert*-butoxycarbonylation to twisted N,N-di-Boc amides (see also Scheme 19), followed by CsF-catalyzed transamidation to form the amide products in excellent yields. Notably, the method is compatible with various functional groups and steric hindrance owing to the mild conditions for amide formation. The proposed mechanism involves the formation of acyl fluoride by the reaction of CsF with N,N-di-Boc-amides, followed by nucleophilic addition of amines to afford the amide product and regenerate CsF. The formation of intermediate acyl fluoride was observed by several methods, including ^{19}F NMR, GC-FID and mass spectrometry, further supporting the proposed mechanism.



Scheme 27 Transition-metal-free transamidation of primary amides via tandem di-Boc activation/catalytic transacylation.



Scheme 28 Synthesis of benzoxazoles via tandem metal-free transamidation of N-Boc activated secondary amides/cross-coupling.



Scheme 29 Transition-metal-free selective exo/endo N–C bond cleavage in N-acyl-isatins.

In 2018, Zeng and co-workers applied their CsF-catalyzed transamidation to the synthesis of benzoxazoles via one-pot, two step tandem process involving CsF-catalyzed site-selective N–C(O) bond cleavage and Cu-catalyzed intramolecular cyclization (Scheme 28).[55] In this method, N,N-di-Boc activated 1° amides or N-Ts activated 2° amides were treated with CsF and 2-halo-anilines to afford transamidation products, which were then converted to benzoxazoles via intramolecular cyclization in the presence of Cu(I)-catalysis. This method tolerates various amide and aniline substrates, affording benzoxazoles in good to excellent yields.

Crucially, CsF is the key component in this methodology; the desired benzoxazole product was not formed when CsF was replaced with benzoyl fluoride. CsF is proposed to have a dual role: (1) Cs$^+$ enhances the electrophilicity of the carbonyl group by coordination to the carbonyl oxygen; (2) CsF acts as a good fluoride source due to low lattice energy.

In 2019, Zeng and co-workers reported a divergent transamidation of N-acyl-isatins controlled by the reaction conditions (Scheme 29).[56] N-acyl-isatins represent another class of attractive acyclic twisted amides ($\tau = 22.0°$, $\chi_N = 13.9°$). The Zeng group discovered that treatment of N-acyl-isatins under their CsF-catalyzed conditions in acetonitrile at 120 °C afforded the exo-transamidation products, while the traditional conditions in acetonitrile:water at 100 °C in absence of any additives resulted in the endo N–C(O) bond cleavage, further highlighting the advantages gained by developing new reagent systems for transformations of amides.

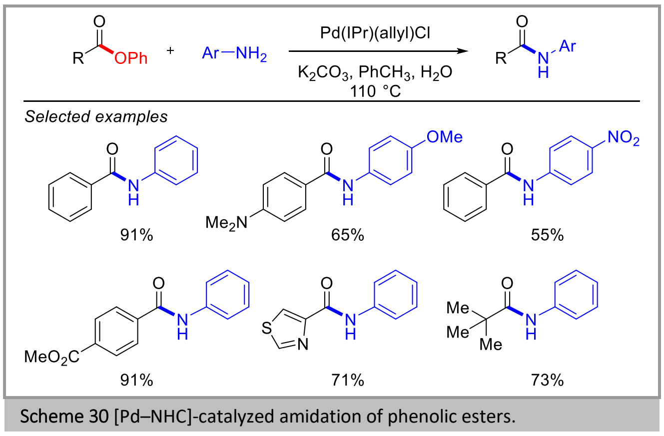
Overall, the elegant tandem nucleophilic substitution process developed by the Zeng group offers significant opportunities for efficient transamidation of less reactive amide bonds by this novel mechanism.

3. Amidation of Esters

3.1 Amidation of Esters by Metal–NHC Catalysis (Pd–NHC, Ni–NHC)

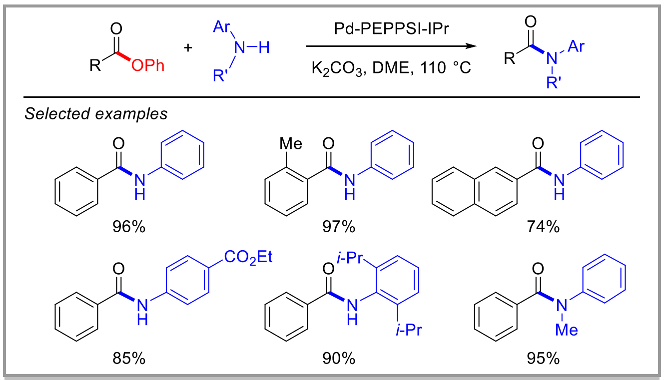
In the classic trend of relative reactivity toward nucleophilic acyl addition, esters are more reactive than amides (Figure 1C),[9] however, esters are still stabilized by a significant $n_O \rightarrow \pi^*_{C=O}$ resonance stabilization, resulting in their high bench-stability.[57] Since the seminal studies of Yamaguchi and Itami in 2011,[7c] aromatic esters have been established as an attractive class of aryl electrophiles for cross-coupling. These reactions typically involve Ni/phosphine catalysis to effect C–O oxidative addition and decarbonylation, however, several examples of Pd/phosphine systems have been reported. The broad interest of esters as novel acyl electrophiles in cross-coupling reactions results from (1) the inherent presence of esters in organic synthesis, (2) the potential synthetic advantages of exploring an alternative class of bench-stable electrophiles for organic synthesis, and (3) the ease of synthesis often under orthogonal conditions to other classes of bench-stable electrophiles.

In 2017, Newman and co-workers reported the first method for Pd–NHC-catalyzed cross-coupling of aryl esters with anilines to furnish a series of amide products in good to excellent yields via C–O bond activation (Scheme 30).[58] Importantly, the reaction is compatible with a wide range of non-nucleophilic anilines and phenolic esters, including electron-deficient aminopyridines, bifunctional aminophenols and chiral proline esters, which were shown to retain stereochemical information. The authors proposed a possible mechanism for this direct amidation process, involving oxidative addition of the ester C–O bond to Pd(0)–NHC to afford acyl-metal intermediate, followed by ligand exchange with aniline. Crucially, in this early study, the authors have already demonstrated that the reactivity of esters in this direct amidation can be correlated with the relative activation of the C–O bond in that typical aromatic esters require Pd–NHC catalysis to achieve high yields in the process.

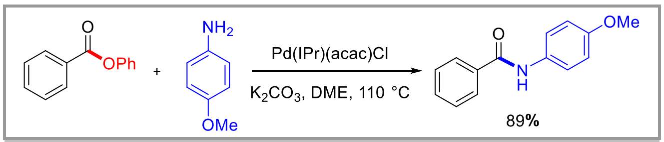


Scheme 30 [Pd–NHC]-catalyzed amidation of phenolic esters.

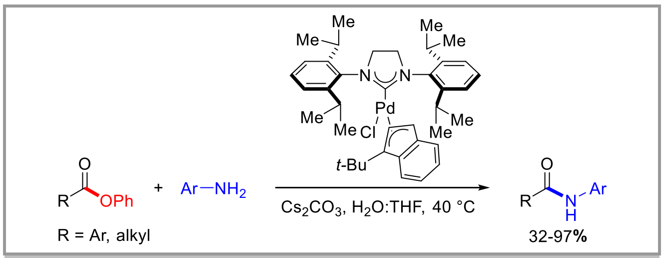
In 2017, our group reported the direct Buchwald-Hartwig acyl cross-coupling of phenolic esters with anilines catalyzed by practical Pd–PEPPSI precatalysts (Scheme 31).[13] It is worth noting that (1) the reaction exploits commercially-available, moisture- and air-stable, and easily prepared in a single, operationally-simple step Pd–PEPPSI catalysts, (2) our approach demonstrated a common manifold for the transamidation of amides (cf. Scheme 2) and amidation of esters (Scheme 31) under the same reaction conditions by complementary N–C/O–C bond cleavage, (3) the method using Pd–PEPPSI affords amide products in good to excellent yields. The reaction showed a broad substrate scope with respect to both reaction components. Mechanistically, an induction period was observed in kinetic experiments, and the reaction was showed to follow similar kinetics to [Pd(NHC)(allyl)Cl] catalysts.



Scheme 31 [Pd–PEPPSI]-catalyzed acyl Buchwald–Hartwig cross-coupling of phenolic esters.



Scheme 32 [Pd(IPr)(acac)Cl]-catalyzed acyl Buchwald–Hartwig cross-coupling of phenolic esters.

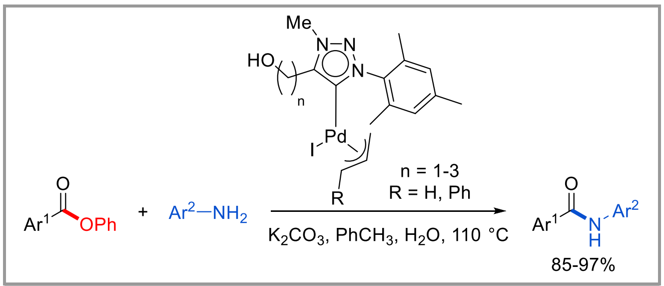


Scheme 33 [Pd(NHC)(1-t-Bu-ind)Cl]-catalyzed acyl Buchwald–Hartwig cross-coupling of phenolic esters.

Later, in 2019, our group developed acyl Buchwald-Hartwig cross-coupling of esters catalyzed by [Pd(IPr)(acac)Cl] (Scheme 32).[14] This study indicated that [Pd(NHC)(acac)Cl] complexes, which are easily synthesized from Pd(acac)$_2$ and NHC salts, feature high activity and significant potential in the development of new cross coupling methods by acyl C–O activation.

In 2018, Hazari and co-workers reported acyl Buchwald-Hartwig cross-coupling of phenolic esters with anilines[59] catalyzed by their [Pd(NHC)(1-*t*-Bu-ind)(Cl)] precatalysts[60] (Scheme 33). They found that the imidazolidinylidene ligand, SIPr, showed the highest reactivity under their conditions. Thus, the amidation reaction proceeded very smoothly using [Pd(SIPr)(1-*t*-Bu-ind)(Cl)] as catalyst and CsCO$_3$ as base in THF/H$_2$O at 40 °C to afford amide products in good to excellent yields. Notably, water as co-solvent facilitated the amidation by increasing the rate of catalyst activation. The authors proposed that the reaction is triggered under mild conditions due to the rapid activation of [Pd(SIPr)(1-*t*-Bu-ind)(Cl)] precatalysts, indicating an important direction in the development of future amidation catalysts.

In 2019, Mendoza-Espinosa and co-workers reported an important study on the development of novel classes of Pd–NHC catalysts for acyl Buchwald-Hartwig cross-coupling of phenolic esters (Scheme 34).[61] They found that a series of new mesoionic aNHC (aNHC = abnormal NHC) Pd complexes developed in their group bearing allyl (R = H) and cinnamyl (R = Ph) throw-away ligands and triazolylidene scaffold show excellent reactivity in the direct amidation of aryl esters with anilines. Their showed that the cinnamyl-type triazolylidene Pd precatalysts (n = 1 or 2) featured the best reactivity in the amidation process. These two Pd(II)–NHC catalysts can tolerate various substituents, steric-hindrance, electron-rich and electron-withdrawing esters and anilines. This study sets the stage for the use of novel classes of Pd–NHC catalysts for acyl cross-coupling reactions of esters and amides, including transamidation and amidation reactions.



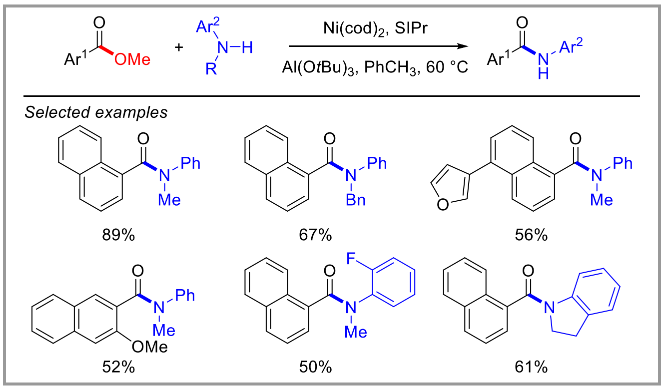
Scheme 34 [Pd–aNHC]-catalyzed acyl Buchwald–Hartwig cross-coupling of phenolic esters.

In 2016, Garg and co-workers reported the first nickel–NHC-catalyzed amidation of methyl esters via direct oxidative addition (Scheme 35).[62] The method uses Ni(cod)$_2$ as catalyst, imidazolidinylidene ligand, SIPr, and Al(O*t*-Bu)$_3$ as stoichiometric additive. The authors proposed that the reaction involves Ni-catalyzed oxidative addition of acyl C–O bond, ligand exchange, and reductive elimination to furnish amides products. This mechanism was supported by DFT computations.

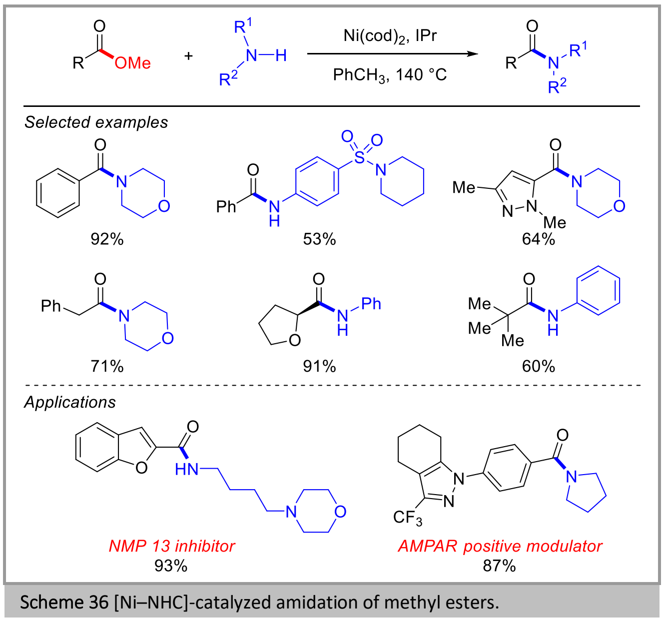
Furthermore, DFT studies revealed that the key role of Al(O*t*-Bu)$_3$ could involve lowering the kinetic and thermodynamic barriers of the amidation process. Although this method is limited to conjugated esters, the authors have set an important precedent for the development of future amidation reactions of unactivated esters.

In 2018, Newman and co-workers reported Ni–NHC-catalyzed amidation of methyl esters via direct oxidative addition (Scheme 36).[63] In their approach, the Newman group enlisted Ni(cod)$_2$ as catalyst and imidazolylidene ligand, IPr, in toluene at 140 °C. The advantages of this method include (1) sustainable approach to amide bond formation, (2) capacity for orthogonal synthetic applications, and (3) direct amidation of esters for the synthesis of biomolecules. The reaction affords various amide products in good to excellent yields. A particularly impressive range of amines smoothly underwent the amidation process in high yields, while epimerization was not observed when enantiopure esters and amines substrates were used. Control experiments indicated that this amidation is thermodynamically controlled by removing methanol from the reaction at high temperature, thus driving the process forward for the formation of amides.

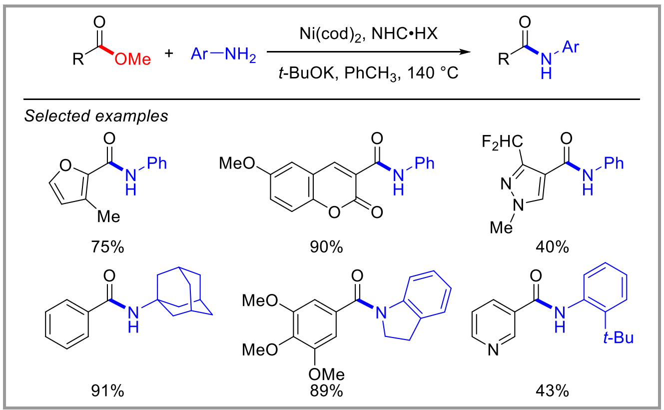
Later, in 2019, Newman and co-workers examined a series of NHC ligands to further expand the scope of the direct amidation of methyl esters under Ni–NHC catalysis conditions (Scheme 37).[64] In the evaluation of 60 NHC, phosphine and pyridine ligands, they identified 9 ligands, including NHCs, phosphines, and phenanthrolines, that can efficiently catalyze the direct amidation of methyl esters using Ni(cod)$_2$. These improved conditions enable the amidation of challenging substrates, such as sterically-hindered methyl esters, cyclic amines, bulky primary and secondary amines.



Scheme 35 [Ni–NHC]-catalyzed amidation of methyl esters.

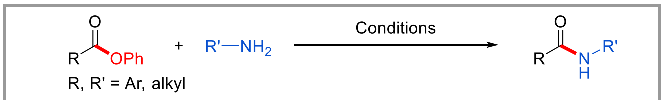


Scheme 36 [Ni–NHC]-catalyzed amidation of methyl esters.



Scheme 37 [Ni–NHC]-catalyzed amidation of methyl esters.

In 2019, during the development of new conditions for Pd–NHC-catalyzed direct amidation of phenolic esters with anilines, Nechaev, Asachenko and co-workers reported transition-metal-free amidation, and compared their method with the previous results on Pd–NHC-catalyzed methods (Scheme 38).[65] In their method, they use NaH as base at 130 °C in the absence of solvents to achieve the amidation of esters in typically good to excellent yields. A broad range of both ester and aniline coupling partners works under these conditions, however, the reaction is not compatible with sensitive carbonyl functional groups.



Conditions 1: NaH, 130 °C, 20 h	up to 97%
Conditions 2: Pd-PEPPSI-IPr, K$_2$CO$_3$, DME, 110 °C, 16 h	up to 96%
Conditions 3: Pd(IPr)(allyl)Cl, K$_2$CO$_3$, H$_2$O, PhCH$_3$, 110 °C, 16 h	up to 98%
Conditions 4: Pd(SIPr)(*t*-Bu-ind)Cl, Cs$_2$CO$_3$, H$_2$O, THF, 40 °C, 4 h	up to 96%

Scheme 38 Transition-metal-free vs. [Pd–NHC]-catalyzed amidation of phenolic esters.

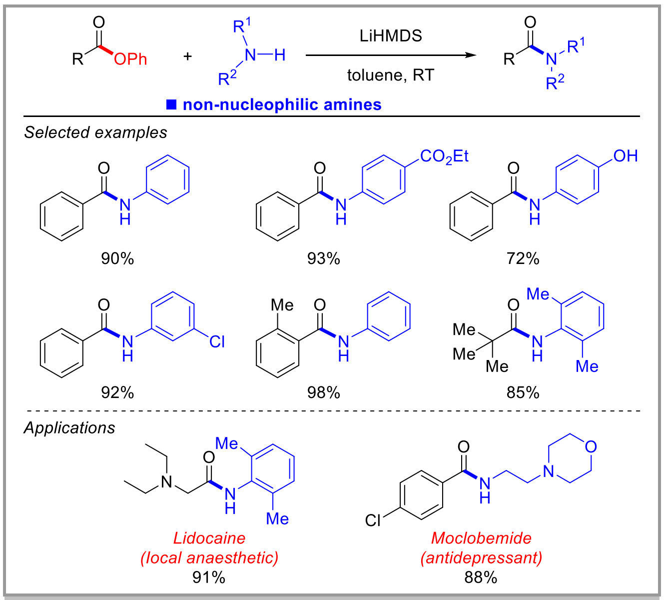
3.1.1 Guidelines for Transition-Metal-Catalyzed and Transition-Metal-Free Reactions

Nota bene, activation of phenolic esters can proceed via oxidative addition of the C–O bond to Pd(0) or Ni(0) (Section 3.1) or by the direct nucleophilic addition to yield a tetrahedral intermediate (Section 3.2). The same divergent pathway is true for transamidation of amide bonds (acyl-metals vs. tetrahedral intermediates) (Section 2.1 vs. Section 2.2). In some cases, especially with more reactive electrophiles or nucleophiles, both pathways can overlap. Recognizing an inherent reactivity of the reaction components in the amidation and transamidation reactions of activated esters and amides is an important consideration for the future development of improved amide bond forming methods.

From the scope and utility perspective, it is important to realize that transition-metal-free and metal-catalyzed amidation reactions of both amides and esters are complementary to each other. Among the advantages of transition-metal-free methods are avoidance of toxic metals, mild reaction conditions and broad functional group tolerance with respect to non-electrophilic or less electrophilic groups. Note, however, that the use of non-nucleophilic amines still requires strong bases, which might not be compatible with certain functional groups. On the other hand, transition-metal-catalysis offers the use of mild bases, or in some cases even avoidance of bases altogether, in combination with non-nucleophilic amines, which permits to tolerate electrophilic functional groups. Furthermore, transition-metal-catalysis expands functional group tolerance to other groups, including enolizable protons, which are often problematic using stronger metal bases. Our recommendation is that the users test both transition-metal-free and metal-catalyzed conditions to gauge the best results. When aliphatic nucleophilic amines are used, we recommend to test transition-metal-free methods first (Section 2.2., Schemes 7, 10-14). For non-nuclophilic amines, we recommend the use of catalytic conditions, preferably bench-stable Pd(II)–NHCs (Sections 2.1 and 3.1, Schemes 1-4, 30-34) or LiHMDs-mediated conditions (Sections 2.2 and 3.2, Schemes 8-9 and 39-40).

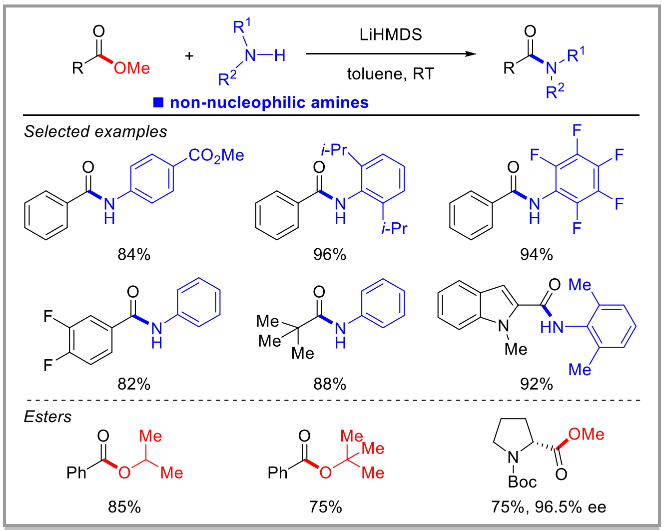
3.2 Transition-Metal-Free Amidation of Esters by Tetrahedral Intermediates

Recognizing the inherent reactivity of *activated* esters, in 2018, we reported a highly selective direct amidation of phenolic esters at room temperature by tetrahedral intermediates (Scheme 39).[22] This method uses LiHMDS as base under mild conditions. This operationally-simple protocol features a very broad substrate scope with respect to both esters and amines, including electron-deficient anilines, sterically-hindered substrates, sensitive functional groups, such as halides and esters. It is further noteworthy that the direct amidation of chiral proline derivatives proceeds without racemization under these mild reaction conditions. The synthetic value of this protocol was showcased in the rapid synthesis of pharmaceuticals, such as moclobemide (MAO inhibitor) and lidocaine (local anesthetic), directly exploiting the non-conventional amide bond formation from aryl esters.



Scheme 39 Transition-metal-free amidation of phenolic esters under mild conditions.

In 2019, we significantly expanded the transition-metal-free direct amidation of esters via tetrahedral intermediates under very mild conditions to *unactivated* esters (Scheme 40).[23] As is well-known, the direct amidation of alkyl esters with non-nucleophilic amines has been a major challenge due to higher $n_O \rightarrow \pi^*_{C=O}$ isomerization. As an example, the recent major advance featured Ni(cod)$_2$ catalysis and required temperatures as high as 140 °C (cf. Scheme 37).[63] In our design, LiHMDS-mediated direct amidation of alkyl esters with non-nucleophilic amines proceeds under mild and chemoselective reaction conditions. This method is characterized by a very broad substrate scope, including electronically-deactivated, sterically-hindered, and electrophilic functional groups. Another advantage of this method is that these sustainable transition-metal-free conditions are compatible with a series of ester precursors, including OBn, *i*-Pr and *t*-Bu esters that are beyond the scope of related transition-metal-catalyzed methods.[63] DFT calculations indicated that the rate-determining step of this amidation involves nucleophilic addition to the C=O ester bond.

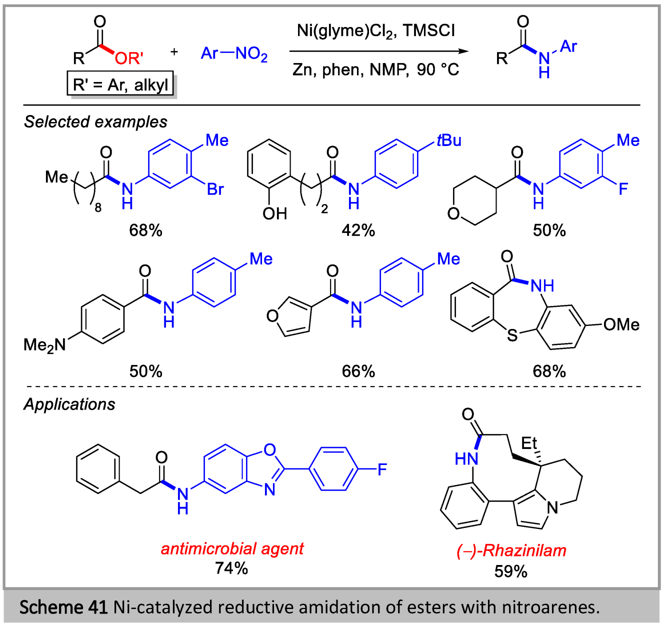


Scheme 40 Transition-metal-free amidation of alkyl esters under mild conditions.

3.3 Reductive Amidation of Esters

As outlined in Section 2.3, nitroarenes represent an attractive alternative source of nitrogen precursors for the formation of amides by non-classical reaction mechanisms.

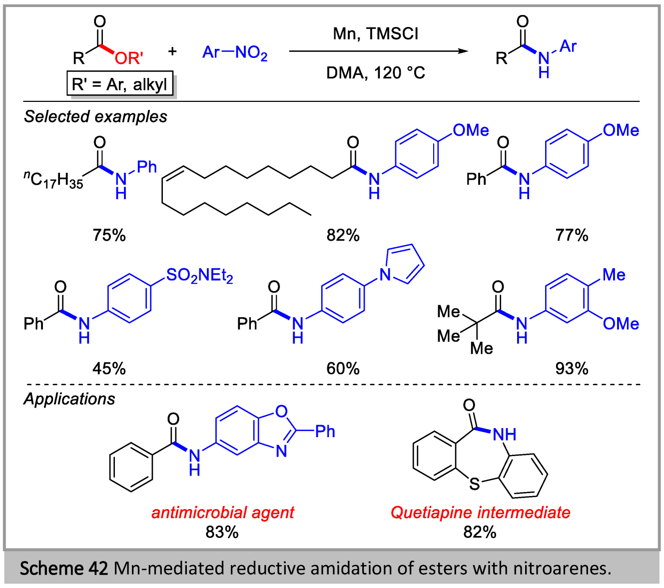
In 2017, Hu and co-workers developed a Ni-catalyzed reductive amidation of esters with nitroarenes (Scheme 41).[66] The method affords amides from various alkyl and aryl esters and nitroarenes in the presence of Ni(glyme)Cl$_2$ as catalyst, Zn as reductant, 1,10-phenanthroline as ligand and TMSCl as additive in NMP at 90 °C.



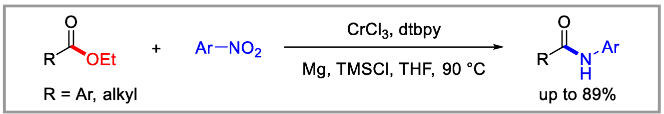
Scheme 41 Ni-catalyzed reductive amidation of esters with nitroarenes.

As the key advantage, nitroarenes are stable, cost-economic and orthogonal to anilines as nitrogen precursors. For example, the use of nitroarenes allows one to readily tolerate alkyl halides and ketones in the amidation process. This reductive amidation by Hu and co-workers features a very broad scope of esters and nitroarenes. Mechanistically, the authors proposed two possible pathways: (1) oxidative addition of the C–O bond to Ni(0), and (2) the reaction of Ni(0) with azobenzene to form a Ni(II) nitrene intermediate. Based on the studies with isolated intermediates, including nitrosobenzene, phenylhydroxyamine, aniline, azoxybenzene and azobenzene that could be formed in situ by reduction of nitrobenzene with Zn, azobenzene is the most likely intermediate in this process. The synthetic value of the method was illustrated in the rapid synthesis of several bioactive molecules and the total synthesis of (–)-rhazinilam.

In 2019, Cheung, Ma and co-workers reported Mn-mediated reductive amidation of alkyl and aryl esters with nitroarenes in the absence of additional catalysts or ligands (Scheme 42).[67] In this approach, they only need TMSCl as additive to reductively couple nitroarenes using Mn as reductant in DMA at 120 °C. This reductive amidation is characterized by a broad substrate scope with respect to both ester and nitroarene partners. Based on the stoichiometric studies with isolated intermediates, the authors proposed that nitrosobenzene is the major reaction intermediate. The synthetic value of this reaction was demonstrated by the preparation of several bioactive amides in high yields.



Scheme 42 Mn-mediated reductive amidation of esters with nitroarenes.



Scheme 43 Cr-catalyzed amidation of alkyl esters with nitroarenes.

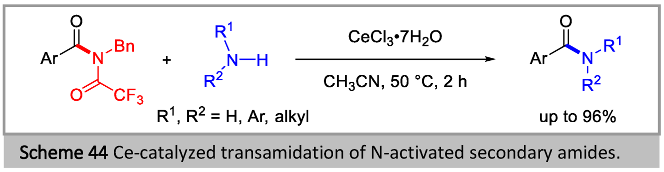
In 2019, Zeng and co-workers reported a Cr-catalyzed reductive amidation of alkyl esters with nitroarenes (Scheme 43).[68] This method employs cost-economic, air-stable $CrCl_3$ as precatalyst, 4,4'-di-*tert*-butyl-2,2'-bipyridine as ligand, Mg as reductant and TMSCl as additive in THF at 90 °C. The reaction affords amide products in good to excellent yields. As an important advantage, the method avoids polar and toxic solvents, such as NMP or DMA. Mechanistically, the authors proposed that the ester C–O bond is activated by a reactive, low-valent Cr species in the presence of Mg to afford acyl–Cr intermediate, which then gives imido–Cr intermediate by the reaction with the reduced nitroarene possibly via diazene or diazene 1-oxide intermediates, followed by hydrolysis. This impressive reaction demonstrates the benefits of non-conventional amidation reactions mediated by unexplored metals in organic synthesis.

4. Transamidation of Amides by Other Mechanisms

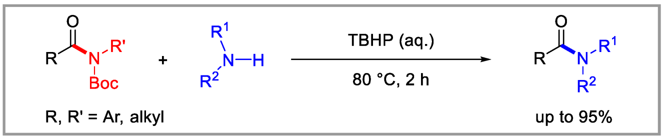
In addition to the amide bond forming reactions by well-defined, non-conventional mechanisms from amides and esters, recently significant progress has been recorded in the development of transamidations by other mechanisms. In this section, we briefly summarize these recent developments to allow comparison with the main topic of the review, and highlight areas for future progress. Reactions of amides that proceed by unknown mechanisms or have been demonstrated only for a single class of substrates by acyl substitution are also included in this section.

In 2018, Srivastava and co-workers reported cerium-catalyzed transamidation of N-activated 2° amides under ultrasonic irradiation (Scheme 44).[69] In this intriguing method, they first activate 2° amides by introducing electron-withdrawing trifluoroacetyl (TFA) group at the nitrogen atom. Treatment of N-TFA activated amides with amines and $CeCl_3 \cdot 7H_2O$ in acetonitrile under ultrasonic irradiation affords amide products in good to excellent yields. The reaction features a broad scope of amides and amines. Several advantages of this method include (1) cheap and sustainable cerium catalyst, (2) mild reaction conditions, (3) short reaction time. The reaction represents the first example of ultrasonic irradiation to enhance transamidation of amides.

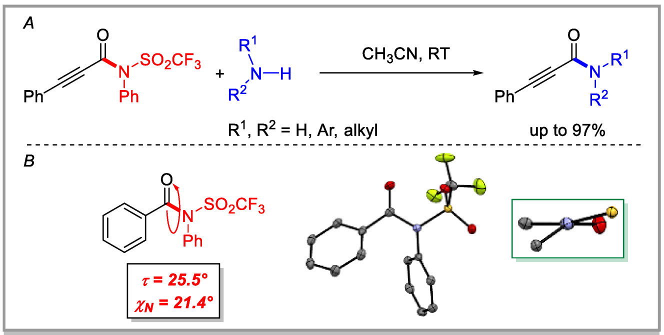
In 2019, Srivastava and co-workers reported TBHP-mediated transamidation of N-Boc activated 2° amides under aqueous conditions (Scheme 45).[70] The method involves the two step N-activation/transamidation protocol. Interestingly, the authors found that TBHP is the key promoter to facilitate the transamidation reaction. The method tolerates a wide range of amides and amines, including aromatic and aliphatic amides as



Scheme 44 Ce-catalyzed transamidation of N-activated secondary amides.



Scheme 45 TBHP-initiated transamidation of N-activated secondary amides.



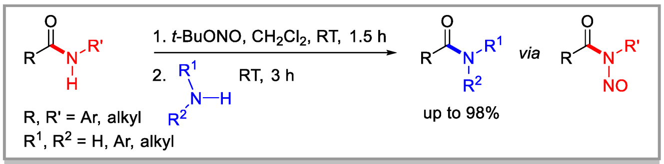
Scheme 46 Metal-free transamidation of N-triflyl-propiolamides via twisted N-Tf amides.

well as amines in water at 80 °C. The authors proposed that this transamidation follows a radical mechanism; in support of this hypothesis the reaction was inhibited by radical scavengers, such as TEMPO and BHT.

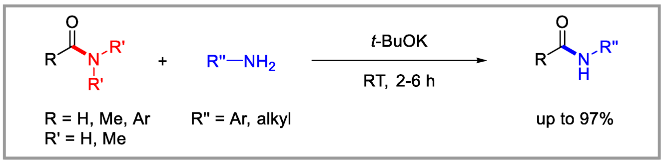
In 2019, Maas and co-workers reported metal-free transamidation of N-Tf-propiolamides (Tf = triflyl) with various aromatic and aliphatic amines under mild conditions in good to excellent yields (Scheme 46A).[71] Notably, the required N-Tf-propiolamides could be readily prepared from terminal alkynes, isocyanates and Tf_2O in a one-pot process. N-Tf-propiolamides are bench-stable solids that show a high potential as N-acylation precursors. This reaction is likely mechanistically related to acyl-substitution, however, the presence of ketene-type intermediates cannot be excluded. More generally, we showed that N-Tf activation leads to very attractive, twisted, electronically-activated amides that are significantly more reactive than N-Ts amides owing to the activating effect of triflimide (Scheme 46B).[72]

In 2019, Kandasamy and co-workers reported *tert*-butyl nitrite mediated, one-pot, metal-free transamidation of 2° amides via N-nitrosamide intermediates (Scheme 47).[73] In this method 2° amides are first activated to afford N-nitrosamide intermediates, which are next treated with amines to afford amide products via nucleophilic addition. This excellent approach can tolerate various amides and amines, furnishing amides in good to excellent yields. This study provides an alternative to N–Boc or N–tosyl activated 2° amides, however, the lower stability of the N–NO linkage is the main limitation of this method.

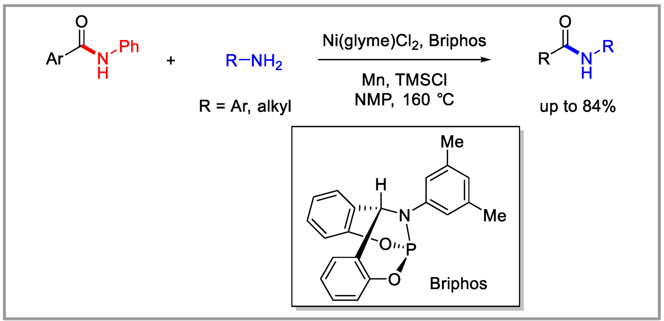
In 2019, Dash and co-workers reported a KO*t*-Bu-promoted transamidation of 1° and 3° amides at room temperature (Scheme 48).[74] Intriguingly, the authors proposed a radical pathway. The reaction tolerates various functional groups on amines. The amide scope was mostly probed with DMF and DMAC, however, benzamides were also shown to be compatible under the reaction conditions. Furthermore, cyclopropylamines afford enamides after ring opening in good yields.



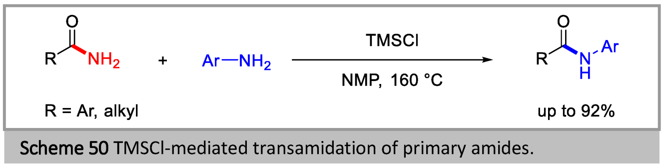
Scheme 47 Metal-free transamidation of N-nitroso-activated secondary amides.



Scheme 48 KO*t*-Bu-promoted transition-metal-free transamidation of amides.



Scheme 49 Ni-catalyzed direct transamidation of secondary amides.

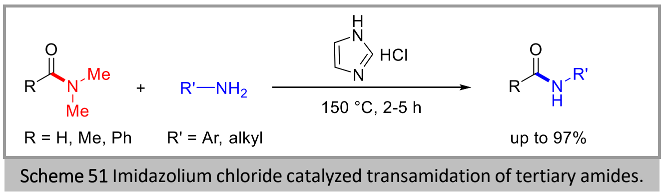


Scheme 50 TMSCl-mediated transamidation of primary amides.

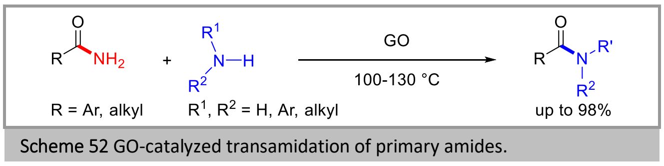
In 2018, Lee and co-workers reported Ni-catalyzed direct transamidation of unactivated 2° amides (Scheme 49).[75] The method uses $Ni(glyme)Cl_2$ as catalyst, Briphos as ligand, Mn and TMSCl as additives in NMP at 160 °C. The yields are typically good, while the substrate scope includes several examples of reactive functional groups. Notably, this method avoids preactivation of 2° amides. Although the mechanism is not clear at present, the authors proposed oxidative addition of the N–C bond to Ni(0), which could be facilitated by the formation of N-TMS activated anilines and/or amides in the presence of TMSCl.

In 2019, Lee and co-workers reported metal-free transamidation of 1° amides in the presence of TMSCl in NMP at 160 °C (Scheme 50).[76] This reaction is notable because unactivated 1° amides are readily engaged in the direct nucleophilic addition to afford transamidation products with a satisfactory scope. Although the mechanism is not clear, several experiments suggested that N,N-di-silylated anilines might not be the reactive species in this process. However, it is likely that N-activation of the amide bond takes place as a part of the mechanism.

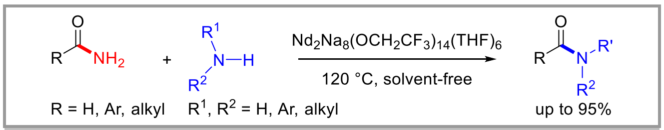
In another approach to amide bond transamidation, in 2018, Yuan and co-workers reported transamidation of 3° amides catalyzed by imidazolium chloride (Scheme 51).[77] The reaction proceeds at 150 °C using excess of DMF, DMAC or DMBA. The authors proposed that the reaction involves activation of the amide carbonyl by H⁺, nucleophilic addition of imidazole, and amine elimination to give the key N-acyl-imidazole intermediate; however, at this stage only few amides have been demonstrated to be suitable substrates for this process.



Scheme 51 Imidazolium chloride catalyzed transamidation of tertiary amides.



Scheme 52 GO-catalyzed transamidation of primary amides.



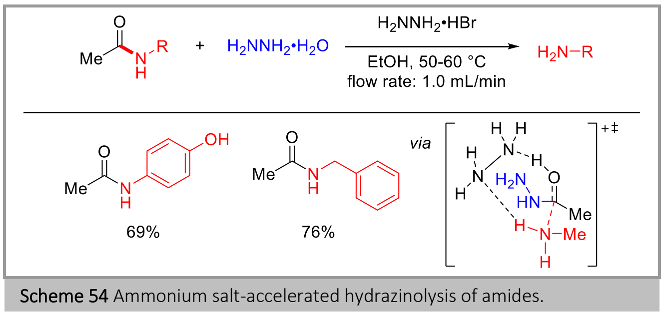
Scheme 53 Transamidation of primary amides catalyzed by heterobimetallic lanthanide alkoxides.

Impressively, the reaction was successfully performed on 50 g scale, demonstrating the utility in the synthesis of amides.

In 2018, Shankarling and co-workers reported graphene oxide (GO) catalyzed transamidation of 1° amides in good to excellent yields (Scheme 52).[78] GO was prepared by an improved Hummers' method.[79] The reaction features very broad scope of amines, including aliphatic, cyclic, and aromatic amines. In addition, various amides are tolerated including aliphatic and aromatic amides, imides and ureas. GO carbocatalyst has several advantages from the environmental point of view, and could be recycled up to 5 times. The proposed mechanism involves amide activation by H-bonding, followed by nucleophilic addition, and elimination by an overall surface isomerization mechanism.[80] Basu and co-workers reported a related GO-catalyzed transamidation of amides (not shown).[81]

In 2017, Sheng and co-workers reported transamidation of amides catalyzed by heterobimetallic lanthanide alkoxide catalysts (Scheme 53).[82] They found that neodymium-based catalyst, $Nd_2Na_8(OCH_2CF_3)_{14}(THF)_6$, showed the highest activity. This method works well with 1° amides, DMF and DMAC as well as various aliphatic and aromatic amines to give the desired amide products in good to excellent yields. The proposed mechanism involves dual activation of the amide bond and amine by $Nd_2Na_8(OCH_2CF_3)_{14}(THF)_6$. In this mechanism, the lanthanide Lewis acid activates the amide bond oxygen, while the metal alkoxide Brønsted base activates the amine. Several related methods on the direct amidation of esters catalyzed by metal alkoxides have been reported.[83]

In 2019, Ohshima and co-workers reported mechanistic investigation and application to a microwave flow process of hydrazinolysis of unactivated amides[84] reported earlier by their group[85] (Scheme 54). On the basis of kinetic and DFT studies they found that the presence of both the hydrazinium salt and hydrazine is critical for efficient transamidation. Hydrazinium salt activates the amide carbonyl and facilitates amine elimination during the hydrazinolysis process. As such, much higher activation energies were required for nucleophilic addition and elimination in the absence of hydrazinium salt (ΔG‡ = 27.7, 29.9 kcal/mol cf. ΔG‡ = 44.4, 43.2 kcal/mol, respectively).



Scheme 54 Ammonium salt-accelerated hydrazinolysis of amides.

The methodology was also applied to a microwave flow process to afford amines on multigram scale in good yields.

5. Conclusions and Outlook

In summary, tremendous progress has been made in the synthesis of amides by non-conventional methods involving transamidation of amides and amidation reactions of esters. These methods enable the synthesis of valuable new amide bonds by chemoselective C–N/C–O cleavage. As highlighted in this account, the major progress has been achieved in the thriving disconnection by oxidative addition of bench-stable acyl C–X (X = N, O) bonds. These reactions, in particular, with well-defined air- and moisture-stable Pd(II)–NHC catalysts, intercept the traditional manifold of Buchwald-Hartwig cross-coupling and apply this versatile platform to the synthesis of amides. From a practical standpoint, the use of mild bases and robust, bench-stable catalysts deliver a new, practical way of constructing broadly useful amides for various applications.

As an alternative, key advances have been made in Ni–NHC catalysis for the synthesis of amides by transamidation and amidation reactions. However, while this manifold is certainly promising, it is important to note that the use of $Ni(cod)_2$ severely limits the potential uses of this approach, inviting progress in the use of bench-stable Ni precursors.

Another class of reactions involve highly chemoselective nucleophilic addition to amides and esters to afford tetrahedral intermediates. Although these reactions require stronger bases, remarkable chemoselectivity has been demonstrated on multiple occasions. More broadly, this manifold defies the traditional conceptual view of the reactivity of bench-stable amides (cf. Figure 1C) and shows that practical manipulation of even well-resonance stabilized ($n_N \rightarrow \pi^*_{C=O}$) N,N-dialkyl amides is feasible under mild reaction conditions. For practitioners, the tetrahedral addition manifold should always be considered together with Pd–NHC catalysis since both methods are complementary in scope and functional group tolerance.

With respect to the reductive methods, exciting progress has been made using Ni, Mn and Cr. Because of the orthogonal nature of nitroarenes, this class of transamidations can accelerate the synthesis of amides taking full advantage of these substrates.

Finally, several crucial transamidation methods that are either in their early stage of development or have not been clearly understood mechanistically have been reported.

We anticipate that future progress in this area will be closely tied to mechanistic studies.[86–88] Ultimately, this non-conventional approach will provide a greatly enriched toolbox for the synthesis of amides, featuring mild conditions, orthogonal substrates and operational-simplicity available to all practicing chemists.

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