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Recent Developments in Amide Synthesis Using Nonactivated Starting Materials

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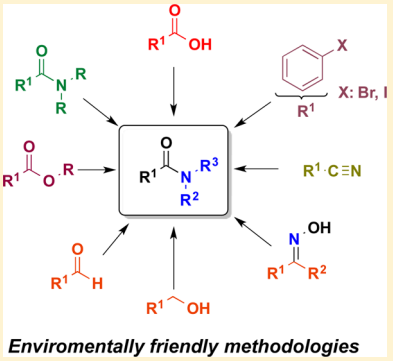
ABSTRACT: Amides are unquestionably one of the most important functional groups in organic chemistry because of their presence in numerous interesting molecules such as peptides, pharmaceutical agents, naturally occurring molecules, proteins and alkaloids, among others. This synopsis surveys the diverse recent approaches to amide synthesis from nonactivated carboxylic acids and derivatives as well as noncarboxylic compounds, highlighting the most innovative methodologies and those that are more eco-friendly compared to traditional methods while focusing on recent developments during the past two years.



The importance of amide formation is shown by the presence of the amide group in agrochemicals, insecticides, polymers, pharmaceutical agents, and a vast number of naturally occurring molecules with biological activity,[1] including about 25% of commercially available drugs;[2] as a consequence, amide bond formation is one of the most important transformations in current organic synthesis.

Traditional methods for amide synthesis include the use of activated carboxylic acid derivatives,[3] such as acyl chlorides or anhydrides, as well as the use of stoichiometric amounts of coupling agents,[4] which are generally toxic and/or expensive and generate waste. Usually, all of these methodologies are associated with significant drawbacks such as long reaction times, harsh reaction conditions, and low to moderate yields, as in the case of hindered or less reactive reagents, not to mention the moderate reactivity associated with peptide synthesis. Furthermore, all of the described methodologies result in large amounts of byproducts leading to poor overall atom-economy and difficult purification procedures, which implies a negative environmental impact due to the generation of large quantities of waste material. Hence, in the past few years, a new brand of catalytic strategies has been developed to provide efficient, cheap, and environmentally friendly sustainable approaches toward amide synthesis under mild conditions and with a broad synthetic scope.

This synopsis highlights the most recent advances for amide synthesis since the last reviews in this area were published.[2a,5] Thus, emphasizing the most innovative methods with a wide scope. Coupling reactions and noncatalytic methodologies are beyond the scope of this revision. First, direct amidation of carboxylic acid is considered, followed by the transamidation reaction. Subsequently, the use of small esters as starting materials is discussed. Finally, some alternative substrates such as aldehydes, alcohols, azides, aldoximes, nitriles, and halide compounds, among others, are exemplified.

Direct amidation between carboxylic acids and amines without the use of coupling reagents is the ideal transformation for amide synthesis because water is the only obtained byproduct. In the past few years, several catalysts have been tested in order to explore the transformation, and boric acid and its derivatives are the most studied.

In 1970, Nelson et al.[6] reported the use of boron reagents to promote amide synthesis for the first time; however, it was not until 1996 that Yamamoto's group was able to develop an efficient catalytic method involving a boron derivative.[7] Since then, a great array of boron catalysts have been synthesized, and a recent efficient example is the (2-(thiophen-2-ylmethyl)phenyl) boronic acid **1**.[8] According to Blanchet's research, this catalyst was successfully applied to the direct amidation of aliphatic, α-hydroxyl, aromatic, heteroaromatic acids, and *N*-Boc-protected amino acids as well as primary, secondary, and heterocyclic amines. It was hypothesized that the sulfur atom in the catalyst plays a double role by facilitating the formation of the acyloxyboron intermediate **2** and promoting the collapse of **3** (Scheme 1).

Furthermore, Blanchet[9] has expanded his work by reporting a new chlorinated boronic acid **6** for catalytic peptide synthesis from *N*-Boc-protected α-amino acids and α-aminoesters without racemization, which enhanced the scope of this methodology (Scheme 2). In this case, the chlorine atom acts similarly to the sulfur atom in **1**.

In the case of less nucleophilic and less reactive aryl amines, Ishihara et al.[10] reported a cooperative catalysis between the boronic acid **12** and 4-(dimethylamino)pyridine-*N*-oxide **13**, giving excellent yields with a large variety of carboxylic acids. The

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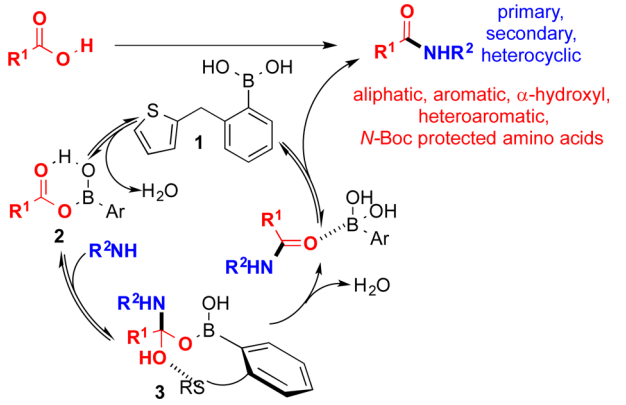
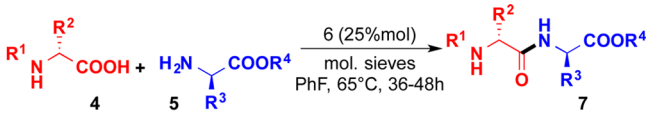
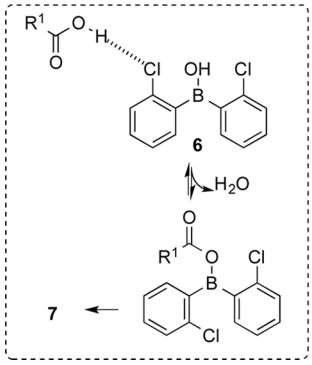
Scheme 1. Proposed Catalytic Cycle for the Direct Amidation of Carboxylic Acids Catalyzed by 1[8]



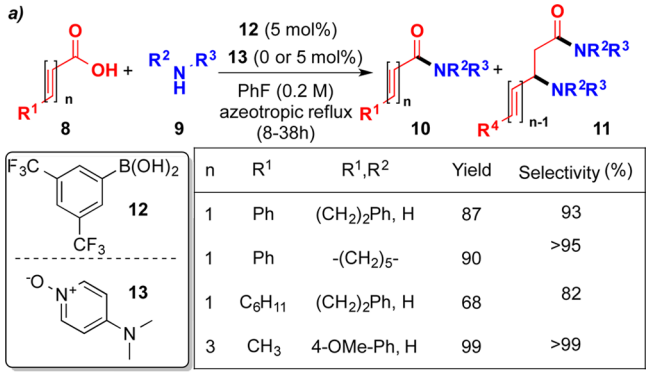
Scheme 2. Selected Examples of Peptide Synthesis Catalyzed by Boronic Acid 6[9]



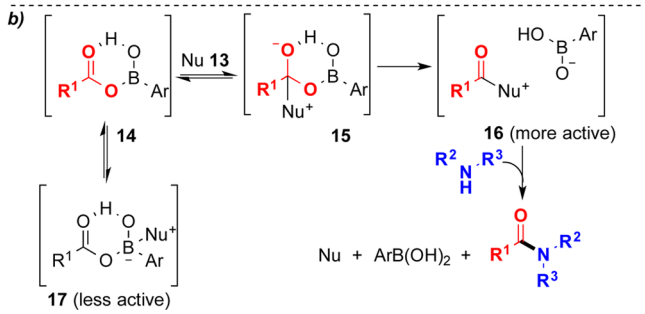


Dipeptide	Yield (%)
Boc-Phe-Val-OMe	51
Boc-Phe-Gly-OMe	55
Z-Pro-Phe-OMe	60
Z-Pro-Gly-OEt	73
Boc-Gly-Gly-OBn	80
Boc-Gly-Phe-OMe	72

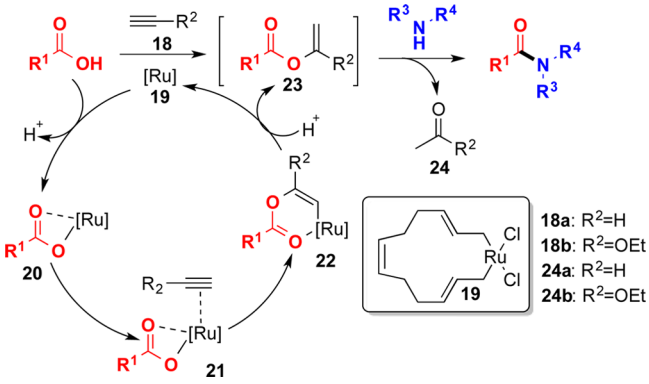
Scheme 3. (a) Cooperative Catalysis of Boronic Acid–DMAPO and (b) Proposed Mechanism[10]



n	R^1	R^1,R^2	Yield	Selectivity (%)
1	Ph	$(CH_2)_2$Ph, H	87	93
1	Ph	$-(CH_2)_5-$	90	>95
1	C_6H_{11}	$(CH_2)_2$Ph, H	68	82
3	CH_3	4-OMe-Ph, H	99	>99



Scheme 4. Catalytic Ruthenium Direct Amidation via Enol Esters[14]



author argued that the use of this Lewis base catalyst generated intermediate **15** and then intermediate **16**, which is a more reactive intermediate (Scheme 3), which extended the substrate scope to more hindered acids and amines as well as conjugated and polyconjugated acids where the selectivity of the aza-Michael addition product **11** was about 82%.

Some other boron derivatives have been successfully applied to different pharmaceutical and biologically active compounds.[11] Additionally, the use of commercially available aryl boronic acids[12] and (mesocellular siliceous foam) MCF-supported catalysts[13] has been recently investigated.

On the other hand, while boron-based catalysts are currently perhaps the most used compounds in amidation reactions, transition metals have also been of great interest in this area. For example, Goossen et al.[14] reported a novel methodology for the direct amidation of carboxylic acids via acetylene **18a** or ethoxyacetylene **18b** activation and catalyzed by the ruthenium complex **19**. In this case, after the initial coordination of the acetylene and the carboxylate to the ruthenium atom, the formed enol ester **23** acts as the acylating agent for the amine. The desired amide is obtained with excellent yields, along with the volatile acetaldehyde **24a** or ethyl acetate **24b** as the only byproducts (Scheme 4). This methodology provides excellent yields when tested with aromatic, heteroaromatic, and aliphatic carboxylic acids as well as primary and secondary amines; however, in the case of aromatic amines, low yields were observed. The functional group tolerance for the method is great, and aldehydes, amides, esters, and free hydroxyl groups may be present without any loss of activity. Like ruthenium, some other transition metals such as niobium[15] and hafnium[16] have also been explored with less significant results.

Solid supports such as chromatographic silica gel have also been considered. One example worth noting is our own work on the direct condensation of carboxylic acids and amines under microwave irradiation.[17] A large number of amides can be easily synthesized with excellent yields using primary or secondary aliphatic amines. This methodology can also be applied to aromatic amines with moderate yields. Aliphatic, aromatic, and unsaturated carboxylic acids can be successfully employed. As a result, a rapid, clean, efficient, low-cost, and green methodology was developed (Scheme 5). Mesoporous silica SBA-15[18] and S-triazine[19]-based compounds can also catalyze this transformation but with a wider substrate scope.

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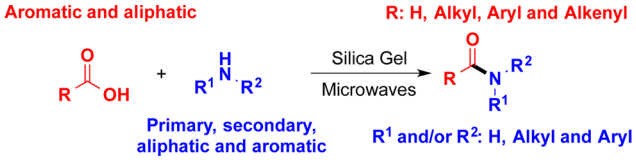
Scheme 5. Direct Amidation under Microwave Irradiation Using Silica Gel as a Solid Support[17]



In the majority of the examples presented above, the carboxylic acid is the one which undergoes the activation process. Despite amine activation being recently studied,[20] these methodologies do not have a good atom-economy and thus are not presented in detail in this review.

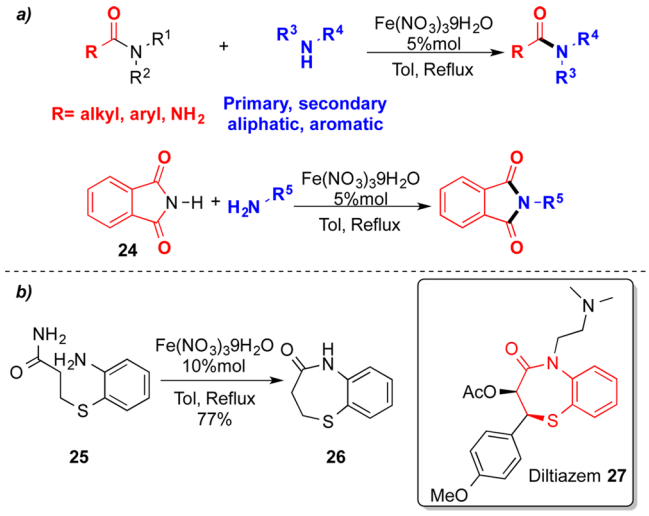
The transamidation reaction is the second most desired transformation in amide synthesis after direct amidation of carboxylic acids. The recent interest resides not only in the high atom-economy involved when ammonia is exchanged but also in the interesting implied chemistry. Using amines and amides as the starting materials, this reaction allows for the exchange of substituents of the amide group due to the cleavage of the C−N bond present in the initial amide and the formation of a new and different C−N bond. However, long reaction times as well as the use of strong reaction conditions such as high temperatures and the need for sealed systems or an inert atmosphere are some of the main drawbacks for this reaction. Recently, several methodologies have been developed to overcome the unfavorable thermodynamic and kinetic factors associated with this transformation.

Transition metals and nonprecious metal reagents have been the most successful reagents and catalysts for this transformation. Iron magnetic nanoparticles[21] and MnO_2[22] are some of the newly reported catalysts for the transamidation reaction of primary amines. Nevertheless, the increasing need for a more rapid, efficient, and general methodology applicable to secondary amines and secondary amides is what encouraged us to develop our own transamidation methodology catalyzed by Fe(III) and water.[23] Using 5 mol % of simple iron salts as a catalyst, we were able to achieve a transamidation reaction between alkyl and aryl amides and urea with aromatic and aliphatic (primary and secondary) amines using toluene as the solvent (Scheme 6). Additionally, we were able to apply this strategy for the protection of primary amines with phthalimide **24** and also in the synthesis of **26**, which is a molecule with the structural core of diltiazem **27** and related drugs.

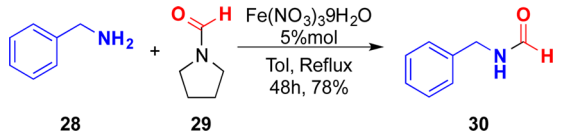
As mentioned before, one of the greatest weaknesses of transamidation reactions is the relatively reduced scope when referring to secondary amides. Unlike primary and secondary small amides where volatile amines are released, thus driving the equilibrium, a competition reaction between the two amines present in the reaction medium may occur when employing larger secondary or tertiary amides. Only a few examples of these substrates have been described. In our specific case, we isolated **30** after transamidation of an excess (1.7 equiv) of benzylamine **28** and formylpyrrolidine **29** with a good yield (Scheme 7).

Concerning the transamidation reaction of secondary amides, Garg et al.[24] recently developed a two-step approach assisted by a nickel catalyst. Unfortunately, this methodology required 3 equiv of Boc_2O and generated a significant amount of waste. Despite this, the novelty and extensive applications make it worth mentioning. As shown in Scheme 8, the authors proposed the *N*-Boc functionalization of amide **31**, generating the active substrate **36**. The acyl metal complex intermediate **37** can be obtained via

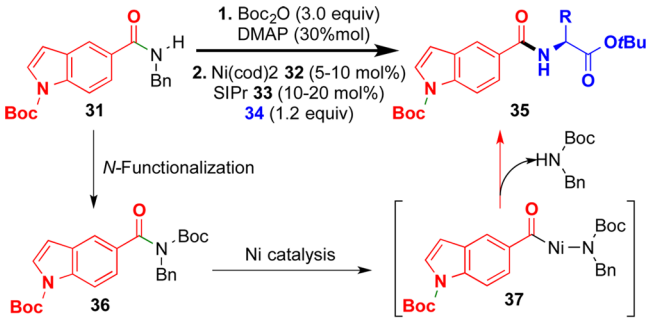
Scheme 6. (a) Scope of the Transamidation Reaction Catalyzed by Fe(III) and (b) Intramolecular Transamidation To Obtain 26[23]



Scheme 7. Transamidation of Tertiary Amide 29[23]



Scheme 8. Two-Step Approach for Transamidation of Secondary Amide 31 with Amine−Acid Derivatives[24]



Product	R	Yield
35a	Me	99%
35b	CH_2Ph	99%
35c	$CH(CH_3)_2$	97%
35d	$CH_2CH(CH_3)_2$	99%
35e		95%

the oxidative addition of **36** over the nickel catalyst. Primary or secondary amines can be used to trap **37**, producing the desired amide **35** (Scheme 8). This methodology could be applied to secondary amino acid derivatives (**34a−e**) and the secondary amide **31** to obtain the desired products (**35a−e**) with good to excellent yields.

In the case of solid supports, zeolites[25] and silica gel[26] have also been of great interest due to the possibility of reusing the catalyst without a significant decrease in activity. Remarkably, the use of

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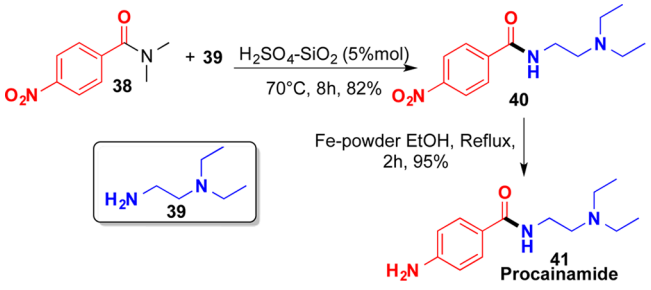
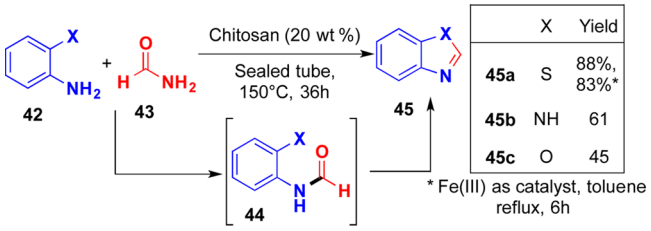
catalytic amounts of H_2SO_4–SiO_2[26a] allowed the synthesis of procainamide **41** via a transamidation reaction between **38** and **39**, followed by the reduction of the nitro group (Scheme 9). Procainamide is a commercially available anti-arrhythmic drug.

Scheme 9. Synthesis of Procainamide[26a]



Different transition-metal-free approaches such as potassium persulfate[27] and boronic acid derivatives[28] have also been employed. Some other reusable catalysts such as ionic liquids,[29] chitosan,[30] and even Ce(III) immobilized on agarose[31] were recently explored for this transformation. The use of chitosan[30] under solvent-free conditions afforded the synthesis of benzo[*d*]heterocycles **45** via a transamidation reaction followed by the dehydration of amide **44** (Scheme 10). Compound **45a** was also obtained by employing Fe(III) as a catalyst in a similar one-pot transamidation–dehydration reaction.[23]

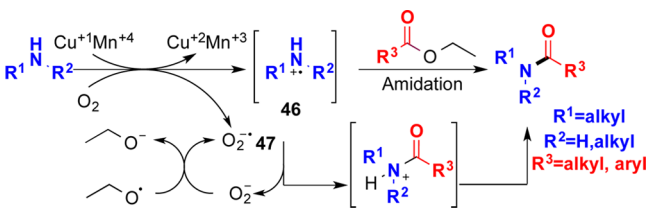
Scheme 10. Synthesis of Benzo[*d*]heterocycles via a Transamidation Reaction[30]



Esters are one of the most common synthetic intermediates in organic chemistry, not only as intermediates in the synthesis of structurally complicated target molecules but also as a starting material in the synthesis of simple structures similar to the amide bond formation. In fact, in vivo protein synthesis by ribosomes is known to employ this route.[32] However, synthetic approaches toward the transformation of esters to amides still has significant drawbacks such as a limited scope (usually the preferred substrates are primarily amines and benzoates), the need for harsh reaction conditions, low yields, and long reaction times.

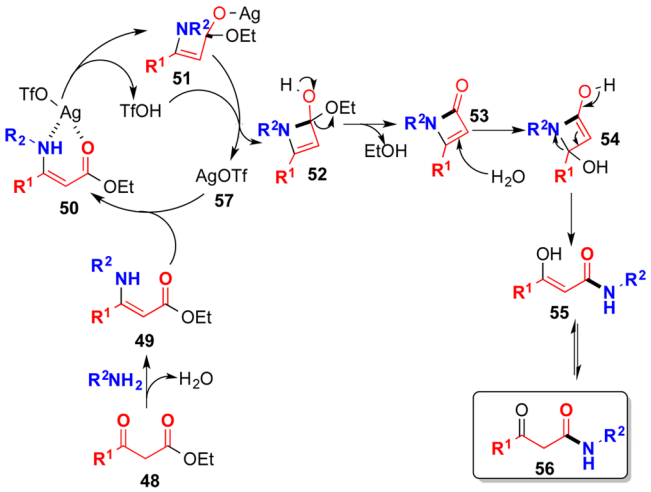
As in the two aforementioned methodologies, transition metals such as zirconium,[33] niobium,[34] silver,[35] and copper–manganese spinel oxide[36] also play an important role in the synthesis of amides from esters. Shah and co-workers[36] recently reported a brand new methodology for the synthesis of amides via aminyl radical cation **46**. This intermediate can be obtained due to the switch in the oxidation state between $Cu^{1+/2+}$ and $Mn^{3+/4+}$ and the generation of the oxygen radical anion **47**, which is responsible for the formation of **46**. The described methodology can be applied to primary and secondary amides including heterocyclic amines (e.g., pyrrolidine or morpholine) as well as aliphatic esters and ethyl benzoates (Scheme 11).

Scheme 11. Copper–Manganese Spinel Oxide Catalyzed Synthesis of Amides from Esters[36]



β-Oxo amides have been of great interest in recent years due to their applicability for the synthesis of several heterocyclic compounds.[37] In 2015, Wang's research group[35] reported the synthesis of these target molecules via the amidation of *β*-oxo esters catalyzed by silver(I). Several clever control experiments allowed for the conclusion that the reaction does not follow a condensation process, but instead an enamine is formed followed by a Michael-type reaction (Scheme 12). According to the

Scheme 12. Mechanism of the Synthesis of *β*-Oxo Amides from *β*-Oxo Esters[35]



author's proposed mechanism, once the enamine **49** is formed, it can be coordinated by the silver(I) ion in order to obtain **51** via the six-membered intermediate **50**. Intermediate **52** and catalyst **57** regeneration is possible due to the protolysis of **51**. Elimination of ethanol in **52** and a Michael addition of water on **53** followed by the ring opening sequence of **54** and a tautomerization process resulted in the desired *β*-oxo amide **56** with moderate to good yields when employing primary and secondary aliphatic amines. The availability of the starting materials as well as the air-stable reaction conditions are the greatest advantages of this methodology.

Simple salts and hydroxides of metals for groups I and II have also been explored for this transformation. As shown in Scheme 13, calcium iodide[38] has recently been employed in the development of a new approach for the synthesis of alfuzosin **61** (used in the treatment of prostatic hyperplasia). On the other hand, lithium hydroxide[39] was reported as a catalyst in a solvent-free methodology for the amide synthesis from esters that could be applied to the ring opening of lactones such as **62**.

In addition to the examples cited before, other inorganic compounds have also been successfully employed for the synthesis of amides from esters. In 2014, Caldwell and co-workers[40] reported the amidation of esters with amino alcohols

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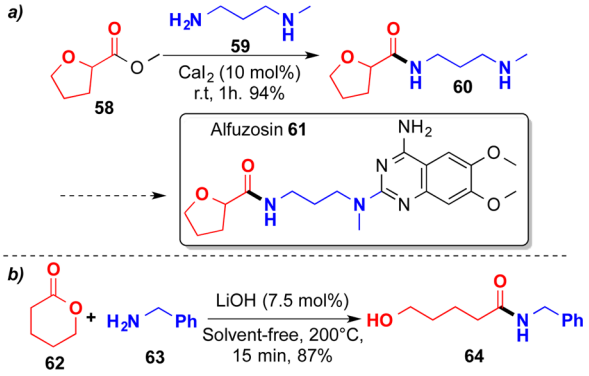
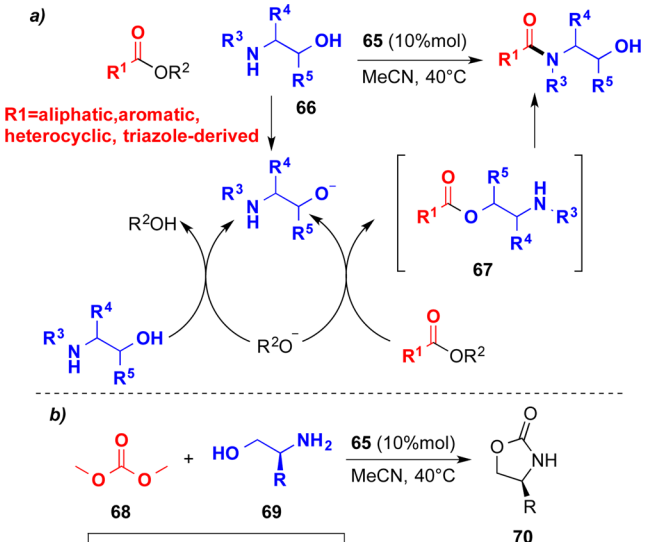
Scheme 13. (a) Calcium-Catalyzed Amidation of Esters Applied to Alfuzosin Synthesis[38] and (b) Ring Opening of δ-Valerolactone Catalyzed by LiOH[39]



66 catalyzed by BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) **65**, which is a strong organic base that removes the acidic proton of the alcohol. Interestingly, this methodology can be applied to aliphatic ester derivatives as well as aromatic, heterocyclic, and triazole-derived motifs. A mechanistic study suggested a transesterification process followed by an intramolecular rearrangement of **67** (Scheme 14). The generality of this method allows the synthesis

Scheme 14. (a) Mechanisms for Ester Amidation of Amino Alcohols and (b) Synthesis of Oxazolidinones Using an Organobase Catalyst[40]



Product	R	Yield
70a	CH_2Ph	68%
70b	Ph	66%
70c	$CH(CH_3)_2$	84%
70d	H	51%
70e	CH_2OH	87%

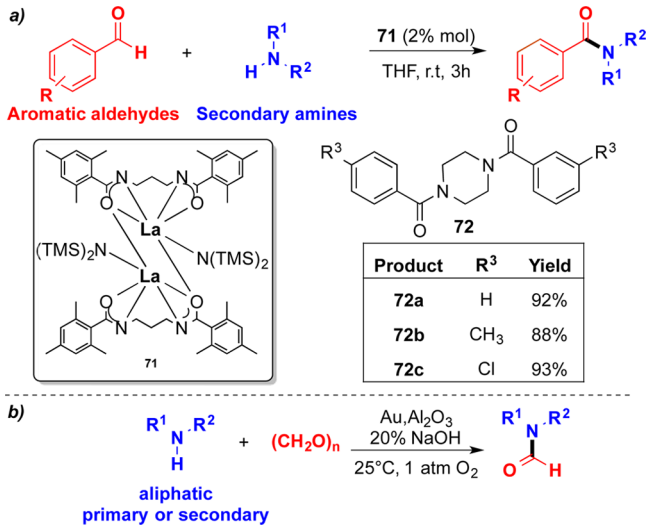
of oxazolidinone systems **70** employing dimethyl carbonate **68** as the starting material when using proteinogenic amino acid alcohol derivatives (**70a**–**70c**), ethanolamine (**70d**), and even amino diols (**70e**). Some other recent methodologies include microwave irradiation under base-free conditions,[41] *N*-heterocyclic carbenes,[42] mesoporous silica,[26b] ionic liquids,[43] and trifluoroethanol.[44]

There have also been recent advances in amide synthesis from different reagents such as aldehydes, alcohols, aldoximes, and nitriles, among others. In this section, we present some selected examples of those reagents to extend the scope of the article and to provide the reader with a complete overview of current amide synthesis.

Direct amidation of aldehydes with amines has also been of great interest due to the availability of the starting material as well as the atom-economy associated with this transformation. However, the use of stoichiometric or pseudostoichiometric amounts of oxidizing agents such as TBHP (*tert*-butyl hydroperoxide)[45] or iodine[46] is a serious drawback for those methods.

Yao and co-workers[47] recently studied the direct amidation of aldehydes under mild conditions employing rare-earth metal complexes while avoiding the need for additional oxidant. In their last report,[47b] several aromatic aldehydes and secondary amines were employed to obtain the desired amides with good to excellent yields when the lanthanum complex **71** was used as a catalyst (Scheme 15a). It has to be noted that a big excess of

Scheme 15. (a) Lanthanum Complex Application in the Amide Bond Formation[47b] and (b) N-Formylation of the Amine Catalyzed by Au[48]



Product	R^3	Yield
72a	H	92%
72b	CH_3	88%
72c	Cl	93%

aldehyde is needed; in fact, the catalyst also accelerates the disproportionation reaction, generating the acid, the alcohol, and the corresponding ester as a byproduct. Three different bis-amidation products (**72a**–**c**) were also obtained. Alternatively, Shi and co-workers[48] reported a new *N*-formylation methodology with a supported nanogold catalyst with paraformaldehyde being applied to the primary and secondary amines and where the catalyst can be reused at least five times without having a considerable decrease in reaction yields (Scheme 15b).

Even though several aldehydes are commercially available, alcohols are still preferred as the starting material due to the greater stability. As a consequence, the aerobic oxidative coupling of alcohols and amines to generate amides has raised great interest in the past few years.[49] Such methodologies propose a hemiaminal **73** intermediate and must avoid the formation of undesired secondary products, as illustrated in Scheme 16a (imines, iminium ions, enamines, or nitriles). One of the most remarkable results obtained in this field is the copper/ABNO-catalyzed amide synthesis reported by Stahl and co-workers.[49a] In this case, both the primary and secondary amines work smoothly

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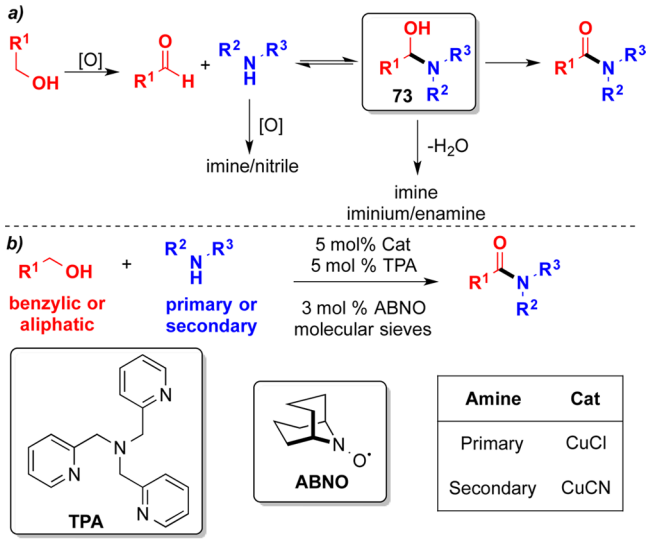
J. Org. Chem. 2016, 81, 11548−11555

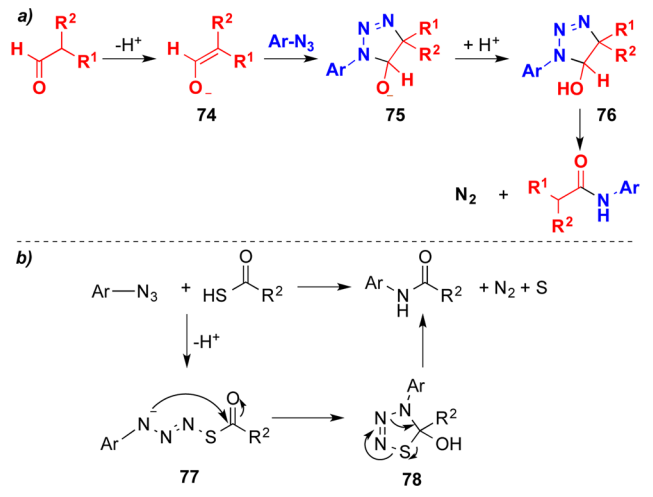
Scheme 16. (a) Oxidative Coupling of Alcohols and Amines and (b) Aerobic Amide Synthesis Catalyzed by Cu/ABNO[49a]



by employing different copper salts (CuCl and CuCN, respectively) when reacting with benzylic and other aliphatic alcohols (Scheme 16b).

On the other hand, aldehydes can also react with more reactive azides to produce the desired amides releasing N_2 as the only byproduct. The use of a basic catalyst, such as KOH,[50] K_2CO_3,[50] or basic ionic liquids,[51] allows for the reaction of aromatic azides with aliphatic primary and secondary aldehydes. The proposed mechanism includes the formation of a triazoline intermediate **76** after a 1,3-dipolar cycloaddition between the azide and the enolate **74** generated from the aldehyde (Scheme 17a). In addition, *N*,*N*-diethyl urea[52] has also been employed as a catalyst.

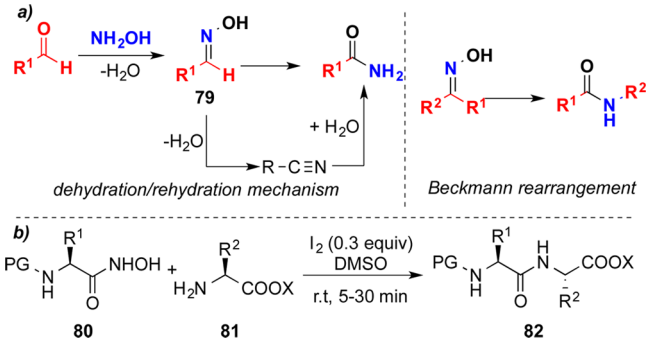
Scheme 17. Proposed Mechanism for (a) Base-Catalyzed Amidation of Azides[50] and (b) Anilide Formation from Thioacids[53]



Alternatively, Yan and co-workers[53] recently reported the synthesis of amides from azides and thioacids via intermediate **77**. Cyclization of **77** to thiotriazoline **78** followed by the elimination of N_2 and S generates amides with excellent yields when using thioacetic acid and perfluoroaryl azides as the starting materials (Scheme 17b). However, the main disadvantages of this methodology compared to the methodology presented above are the difficulty in the synthesis of thioacids as well as their lower stability. It is worth mentioning that all of these methods are limited to the use of electron-deficient aryl azides as well as enolizable aldehydes.

Furthermore, aldehydes can be transformed into aldoximes **79** by reacting with hydroxylamine.[54] These aldoximes can be converted into primary or secondary amides via a dehydration/rehydration mechanism or via the Beckman rearrangement, respectively (Scheme 18a). Rearrangement of aldoximes to

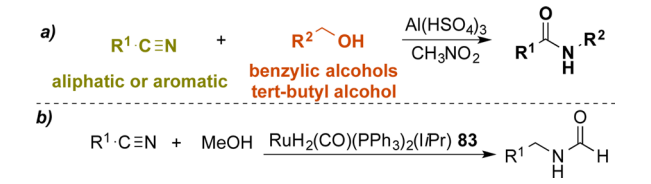
Scheme 18. (a) Amide Synthesis from Aldoximes[54] and (b) Synthesis of Dipeptide Esters from Hydroxamic Acids[56]



primary amides involves a nitrile intermediate and is usually catalyzed by ruthenium complexes.[55] Moreover, Sureshbabu and co-workers[56] recently reported the synthesis of dipeptide esters **82** by coupling *N*-protected hydroxamic acids **80** with esterified amino acids **81** in the presence of catalytic amounts of iodine (Scheme 18b).

Nitriles have been commonly used in the Ritter reaction to obtain amides from alcohols. Recently, aluminum hydrogen sulfate[57] has been employed in the reaction between aliphatic and aromatic nitriles with benzylic alcohols and *tert*-butyl alcohol (Scheme 19a). Despite the advantages of employing this catalyst

Scheme 19. (a) N-Substituted Amide Synthesis from Nitriles[57] and (b) N-Formylation of Nitriles Catalyzed by Ru[58]



(recyclability, short reaction times, and easy product isolation, among others), it cannot be applied in the synthesis of formamides. However, Hong and co-workers[58] recently reported the first synthesis of formamides from aromatic and aliphatic nitriles and methanol where a ruthenium complex **83** is used as the catalyst (Scheme 19b). Thermal amidation from nitriles and amines[59] as well as primary amide synthesis catalyzed by gold nanoparticles[60] have also been explored.

Aryl halides have also been employed in amide synthesis when reacting with amines. Despite aryl iodides being the preferred substrates for this transformation, bromine compounds have also been explored.[61] One of the most remarkable examples is the work developed by Seayad and co-workers,[62] where different aryl bromides **84** were transformed to Weinreb amides **87** by reacting

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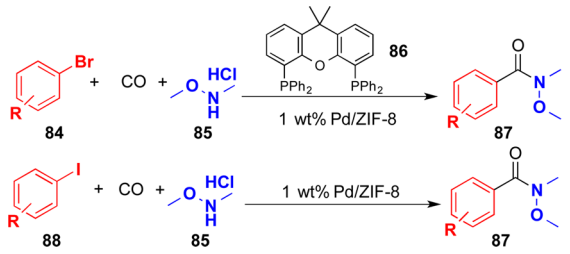
J. Org. Chem. 2016, 81, 11548−11555

with *N*,*O*-dimethylhydroxyamine hydrochloride **85** and employing palladium as a catalyst and Xantphos **86** as an organic ligand. As shown in Scheme 20, the use of **86** can be avoided when using

Scheme 20. Weinreb Amide Synthesis from Aryl Halides[62]



iodinated compounds **88**. Palladium acetate as a catalyst[63] and photoinduced[64] aminocarbonylation of aryl iodides as well as the direct synthesis of cyclic imides from carboxylic anhydrides have also been reported.[65]

In summary, although amides are undeniably one of the most important functional groups in organic, pharmaceutical, and biological chemistry, there are still major challenges to generating this type of compounds. In this synopsis, we survey different synthetic methodologies focused on amide synthesis enclosed within the principles of green chemistry. Recent advances in the direct amidation of carboxylic acids and esters as well as transamidation reactions and other approaches where several reagents can be employed are covered. It is noteworthy that there is not a general synthetic pathway for peptide bond formation and that various methodologies must be applied according to specific substrates.

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Notes

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Biographies

Andrea Ojeda-Porras received her bachelor's degrees in Chemistry and Chemical Engineering in 2014 from Universidad de los Andes. In the same year, she started her M.Sc. under the supervision of Dr. Diego Gamba-Sánchez and obtained her degree in 2016. Her research in Gamba's group was focused on the development of new synthetic methodologies for amides and thioamides with high atom-economy as well as the study of the Pummerer reaction toward the synthesis of heterocyclic compounds.

Diego Gamba-Sánchez was born in Bogotá, Colombia. He received his B.Sc. in Chemistry from the Universidad Nacional de Colombia (Bogotá) in 2004 and his M.Sc. degree in Biomolecules and Organic Synthesis from the Université de Poiters, France, in 2006; then, he moved to École Polytechnique, Palaiseau, where he worked under the guidance of Dr. Joëlle Prunet, and he received his Ph.D. in the field of diastereoselective synthesis of 1,3-diols. Later, Diego joined the group of Prof. Thorsten Bach at Technische Universität München, Germany, where he spent one year working on total synthesis of natural products. Then, he moved back to Colombia and started his independent career at the Universidad de los Andes, Bogotá, where he was promoted to Associate Professor in June 2014. The research in his group focused on the development of new synthetic strategies for amide synthesis, the use of whole cells as biocatalysts, the synthesis of antibiotics, and the application of abundant natural products as the source for chemical complexity or as chiral protonating agents.

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