Amide bond formation strategies: latest advances on a dateless transformation

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Dedication ((optional))

Abstract: The synthesis of amides remains one of the most important transformations and it is one of the more frequently performed reactions. In the pharmaceutical industry, building of the amide group is pivotal and among the more important transformations in the design of the synthetic plan. This review presents an overview of only very recent contributions, published in the last three years, to highlight the latest progresses in this "dateless" reaction, with a special focus on metal-free methodologies. New, more efficient and/or greener stoichiometric methods as well as catalytic strategies have been discussed, either for the "classical" coupling approach between an amine and a carboxylic acid (or its activated equivalent), and for more innovative approaches, mainly involving oxidation procedures to generate amides starting from amines.

1. Introduction

The amide function is unarguably of primary importance, being the constituent of natural and synthetic polymers and found in a wide variety of bioactive small molecules prepared both by Nature and in the laboratory. In addition, amides have been employed as reaction partners in diverse transformations, representing the source for both the carbonyl and the amine group.[1] Amide bond formation is achieved by different biosynthetic routes,[2] including ribosomial synthesis,[3] ATP-dependent amide ligation mechanisms, and other enzymatic pathways based on hydrolases, proteases and acylases.[4]

In the pharmaceutical industry, building of the amide group is pivotal and among the more frequently performed reactions. As a consequence for its relevance, the investigation on "General methods for catalytic/sustainable (direct) amide or peptide formation" is included in the ten Key Green Chemistry Research Areas defined in 2018 by the ACS Green Chemistry Institute® Pharmaceutical Roundtable (GCIPR).[5]

Despite being energetically challenging, direct thermal amidation cannot be disregarded and, in our opinion, it should be kept as the landmark when developing a new strategy. In relatively recent times, studies were devoted to unveil further mechanistic details on the process,[6] which still finds applications at an industrial level.[7] On this backcloth, a wide plethora of methods has been devised, relying on mediators used either in catalytic or stoichiometric amount.[8] Through our analysis of the literature precedents, we considered the reported methodologies can be grouped in two classes, respectively aimed at building the C-N and the C-O bond. The former category encompasses the combination of diversified acyl and amine donor partners, and includes some rearrangements as the Schmidt,[9] the Beckmann and the Winstein reaction,[10] while the latter includes oxidation and hydration strategies.

The ideal strategy does not exist, the choice of the successful approach being strongly depending on the substrates; several issues need to be considered in the evaluation and selection of the methodology and represent in some cases still a challenge: the problem of chemoselectivity for the amidation in the presence of unprotected hydroxy or amino groups, or the issue of possible racemization when using chiral, not racemic, starting materials. Furthermore, additional considerations can be made in the analysis of the whole process, that takes in account also experimental factors, solvents, reaction temperature, work up and isolation procedures, which greatly influence the overall process mass intensification (PMI) of the process. [8a] Last, but not least, also the toxicity and the environmental impact of the synthetic approach are becoming more and more crucial aspects that need to be considered.[8b]

In the present review we will report on the very recent advances in the area; therefore, we have decided to discuss only contributions published in the last three years, specially focusing on metal-free strategies. Peptide synthesis will not be considered, as well as *N*-formylation reactions. In fact, the formation of amides entails the introduction of the CHO unit from different C1 sources; the various strategies developed are thus intrinsically dedicated to this specific N-C(O) bond formation.
Enzyme-catalyzed synthesis is an alternative method for amide bond formation, presenting the advantages of atom economy, environmentally benign reagents and conditions; however, since a very recent review was published on the topic,[4] it has not been included in the present review. On a side note, one should mention that acylation reactions have been exploited also in kinetic resolution and DKR.[11] It is worth mentioning that also some examples of photoredox catalysis involving the use of metal have recently been published.[12]
We have decided to discuss separately the "stoichiometric" methods first, and then the catalytic approaches, in both cases classifying the reactions in three subcategories: **C-N** bond formation strategies, **C-O** bond formation reaction and other methodologies.

2. Stoichiometric methods

In the present section we report those processes that rely on the use of a stoichiometric amount of a chemical species to allow the formation of the amide bond. Strategies designed to build the N-C(O) bond include the variously mediated condensations between carboxylic acids and amines, in some cases replaced

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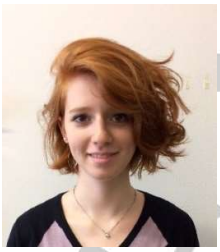
by precursors or surrogates, as well as reactions proceeding via a C-C bond breaking.

Elisabetta Massolo was born in Milano in 1988. After completing in 2012 her Master thesis in Chemistry with Prof. F. Sannicolò at Università degli Studi di Milano, she undertook the PhD program in the group of Prof. M. Benaglia working on organocatalytic methods; during this period she worked for six months on photoredox catalysis at Universität Regensburg in the group of Prof. B. König. As a postdoctoral fellow, in 2016 she joined the group of Prof. J. S. Johnson at University of North Carolina and in 2017 the group of Prof. Bo Li. In 2018 she continued her career in Università degli Studi di Milano in the group of Prof. M. Benaglia in the area of synthesis and catalysis. Since November 2019, she became part of the R&D Department of Flamma S.p.A

Margherita Pirola was born in Milan in 1992. After she took her master degree in chemical science at University of Milan in 2016, she won a six-month fellowship as a promising young researcher at the same University. She is currently doing her Ph.D. under the supervision of Prof. Maurizio Benaglia, working on the development of unconventional activation strategies and transformation of nitro derivatives and on the synthesis of chiral active pharmaceutical compounds



After completing his PhD with prof. M. Cinquini and F. Cozzi, in 1995 Maurizio Benaglia joined for two years prof. J. S. Siegel group at UCSD (USA); then he moved back to the University of Milan, where in 2015 he was appointed as Full Professor of Organic Chemistry. In 2000 he was awarded of the Giacomo Ciamician Medal and in 2019 of the Piero Pino Medal. His research activities focus on the development of novel synthetic methodologies, design of new chiral organocatalysts, study of stereoselective reactions in flow and with catalytic reactors, synthesis of pharmaceutical products, taking advantage also of 3D-printing technologies and alternative reaction media.

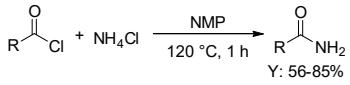
According to a recent survey in both Reaxys and GSK databases by the Sheppard group, most of the procedures for amide bond formation involve a nucleophilic acyl substitutions.[8a] These reactions typically imply activation of the carboxylic group either as acyl chlorides or reactive anhydrides and esters or, alternatively, the use of coupling reagents, that has been demonstrated can be used also above 100 mmol scale.[13]

Drawbacks associated with this kind of approaches are usually related to costs, toxicity, atom economy and by-products generation. Besides, limitations in scope are still observed, due to unsuitable sterics and electronics, and to products epimerization. Despite these issues, straightforward experimental procedures and high yields still make stoichiometric methods valuable and convenient strategies.

The bar has indeed been set pretty high in terms of effectiveness, but when it comes to purification as well as to economics and environmental concerns, there is still room for improvements. In fact, the newly proposed methods typically aim to offer advantages related to the ease in product isolation and to the greenness of the process, without giving up on yields and scalability. We would like to point out that a proper assessment of the process impact requires a comprehensive evaluation, taking into account reactants, reagents and solvents involved throughout all the phases, including work-up and purification. Often, eco-friendliness is claimed, based only on atom economy evaluations, which looks incorrect, especially if considering the condensing agent in the count; indeed, this species is not supposed to be incorporated in the final product.

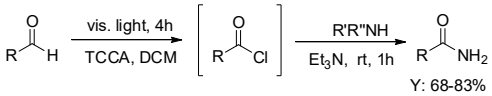
2.1. Strategies based on C-N bond formation

A variety of different acyl donors has been reported: replacing the carboxylic acid partner lays down directness while however allowing access to different activation modes. Even the more standard acyl chlorides keep being exploited in latest works: in 2018, Li and co-workers coupled these highly reactive acyl sources with ammonium salts as practical surrogates for gaseous or liquid ammonia.[14] NMP is used both as solvent and as base in the reaction, although it cannot be considered a solvent of choice based on green metrics (Scheme 1).



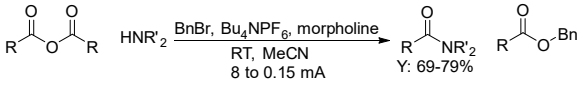
Scheme 1. Amidation with ammonium salt.

A radical, metal-free oxidative process has been recently applied to generate acyl chlorides, starting from aldehydes, in the presence of sunlight or artificial visible light as a blue LED source.[15] The *in situ* generated activated intermediate reacted with primary and secondary amines to afford the amides in good yields (Scheme 2).



Scheme 2. A two-step synthesis of amides starting from aldehydes.

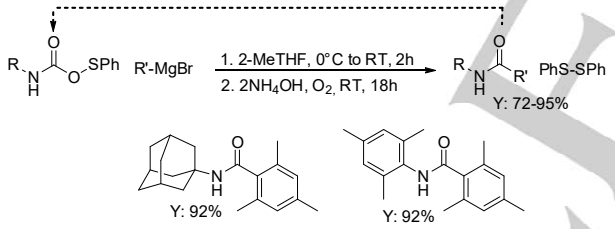
Innovation has been introduced also regarding the use of anhydrides, performing the reaction under electrosynthesis conditions (Scheme 3).[16]



Scheme 3. Electrochemical anion pool synthesis of amides.

A variety of amides were obtained in good yields with the worth noticing co-synthesis of benzoic esters; the procedure is implemented so that the unexploited carboxylate is turned into a valuable compound, this resulting in 82.7% atom economy. Besides the smart processing of the by-product, the method is made interesting by being base free, water tolerant and working at room temperature. PMI of the process was calculated to be about 30, when the PMI values for pharmaceutical products synthesis range between 26 and 100.

Thiocarbammates, easy to prepare and bench stable, proofed to be suitable partners for Grignard reagents in the synthesis of considerably hindered amides.[17] The method is remarkable also from the sustainability standpoint: besides being operational in 2-Me-THF, one of the recommended solvents according to the green solvent selection time, a basic work-up allows recovering the thiolate leaving group as diphenyl disulfide, which can be reused as reagent for the synthesis of thiocarbammates substrates (Scheme 4).



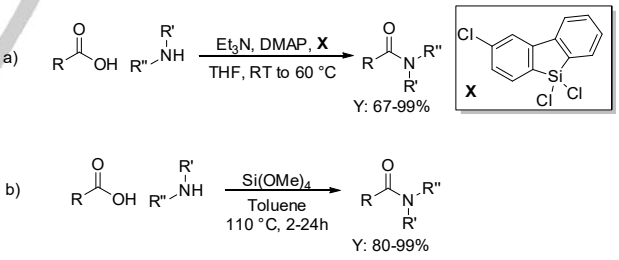
Scheme 4. Synthesis of amides from thiocarbammates.

In the context of direct amidations, new coupling agents keep being introduced. Rather recently, silicon based species started gaining attention in the field. The first study on the effectiveness of a silane in mediating the condensation between amines and carboxylic acids dates back to 1969, when tetrachlorosilane was employed by Chan and Wong to prepare anilines-derived amides, and, two years later, in peptide synthesis.[18] In the 2000s a few additional examples were sporadically published, where different classes of amides were prepared with high yield employing dimetylchlorosilane,[19] imidazoylsilanes, tetrakis(pyridine-2-yloxy)silane, and tetrakis (1,1,1,3,3,3-hexafluoro-2-propoxy)-silane,[20] and phenylsilane.[21]

Research activity on the topic somewhat intensified from 2016, when the Charette group reported on the use of 9-silafluorenyldichlorides as a custom-made coupling agents.[22] The new C-N bond forms intramolecularly via an intermediate where both the partners are coordinated to the silicon center (Scheme 5, eq.a). The rigid structure of the silicon mediator should allow access to hindered substrates, and the presence of a halogen on its ligand should provide for optimal electronic properties. The mechanistic hypothesis was supported by control experiments, which, however, cannot be considered sufficient to rule out the involvement of different intermediates. Various dipeptides were obtain in good yields and with minimal epimerization, but the addition of an excess of Et_3N and a catalytic amount of DMAP (4-*N,N*-dimethylamino pyridine) was needed. It should be noticed that the results achieved with simpler and commercially available silanes are somehow comparable to those obtained with these specially designed silafluorenil derivatives, which are strongly water sensitive and whose by-products need to be removed from the reaction mixture via column chromatography. While the extent of improvement with respect to previous works could be arguable, credit must be given for the establishment of this new class of reagents.

Recognizing the limitations of their own method, one year later the same group reported on the effectiveness of Ph_2SiH_2 as a coupling agent, serendipitously found to be active with no need for a metal catalyst; the longer reaction times needed were balanced out by a more beneficial stoichiometry.[23]

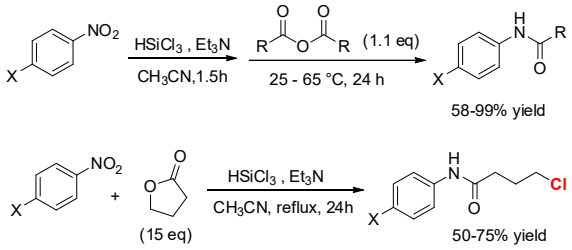
The organosilicon coupling agents brought some benefits in terms of applicability, but still require non-green conditions and generate by-products to be removed by chromatography. A meaningful step forward was taken by Bradock and co-workers, using tetramethyl orthosilicate to achieve quantitative yields for a wide range of amides, obtained pure products upon a simple aqueous work-up (Scheme 5, eq.b).[24]



Scheme 5. Silicon-based coupling agents in amides synthesis.

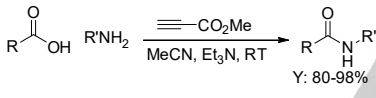
Recently our group has reported a two-step one pot, experimentally simple protocol to convert nitroarenes directly to *N*-aryl amides, without handling of the highly toxic and carcinogenic aniline derivatives (Scheme 6).[25] A metal-free reduction of the nitro group, mediated by trichlorosilane,[26] followed by the addition of an anhydride, afforded the corresponding *N*-aryl carboxyamide, that was isolated after a simple aqueous work up in good-excellent yields**.** When the metal-free methodology was applied to the reaction with γ–butyrolactone, the *N*-aryl butanamide was obtained,

featuring a chlorine atom at the γ–position, an advanced intermediate of a wide class of biologically active compounds.



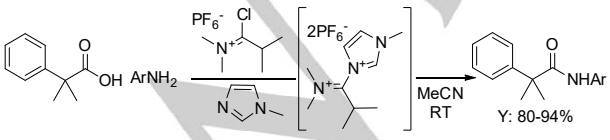
Scheme 6. One pot two-step synthesis of *N*-aryl amides from nitroarenes.

Considering the various active intermediates deriving from carboxylic acids, enol ester species have not been extensively exploited, the first example of a metal-free amide bond synthesis via this class of intermediates being reported by the Liu group in 2018. Previous examples relied either on Ru-based catalysts or on ynamides, which require a two-step synthesis. In Liu's work, instead, methyl propiolate is used in a one-pot reaction to get different amides in high yield via an α-acylenolester intermediate (Scheme 7). The mild conditions, short reaction times and low molecular weight of the reagent make this conceptually new method attractive also from a green chemistry perspective.[27]



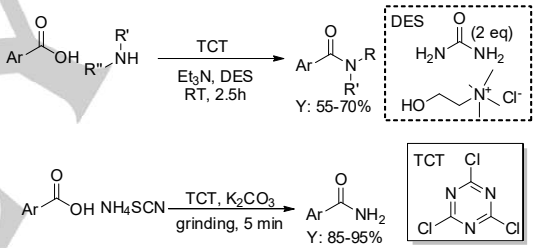
Scheme 7. Methyl propiolate-mediated condensation.

Advancements concern also the field of more classical condensing agents, as acyl imidazoliums. In 2018, it was showed that combining *N*-methylimidazole (NMI) with *N,N,N,N*-tetramethylchloroformamidinium hexafluorophosphate (TCFH) leads to the *in situ* generation of a powerful acyl transfer intermediate (Scheme 8). The TCFH:NMI system afforded amides from hindered acids and diverse anilines in yields generally above 90% and did not cause epimerization of the stereogenic centers at the α-position of the carboxy group.[28]



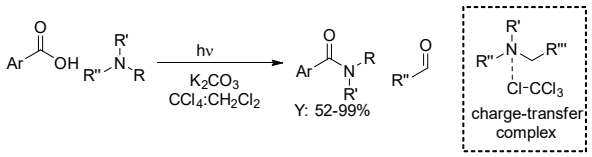
Scheme 8. Acyl imidazoliums as intermediate in amide synthesis.

To tackle sustainability challenges, Salimiyan and Saberi shifted the focus from the coupling mediator to the reaction media: they employed a classical yet convenient condensing agent, 2,4,6-trichloro-1,3,5-triazine (TCT), in a new generation solvent, a deep eutectic solvent (DES). DESs have been recently introduced as a green alternative to ionic liquids, sharing with them some chemico-physical properties but being inexpensive, non-toxic and biodegradable.[29] The employed DES consists in a mixture of urea and choline chloride and allows amides formation in good yields at room temperature, in relatively short time.[30] While the reaction is carried out in this environmentally beneficial medium, an organic solvent is still needed in the work-up phase for product extraction (Scheme 9); however, since ethyl acetate was used, one of the recommended solvents according to the Green Chemistry guidelines,[31] the overall greeness of the protocol could be still considered positively (Scheme 9). Alongside, the Pattarawarapan group applied the liquid-assisted grinding (LAG) technique to obtain primary amides in almost quantitative yields after 5 minutes reaction in the presence of TCT and potassium carbonate.[32] With respect to previously reported solvent-free approaches, this mechanochemical protocol[33] has the advantage of not requiring supported reagents



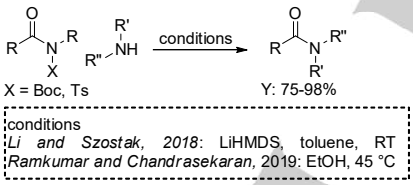
Scheme 9. Amide synthesis in alternative reaction media.

Alternatively to chemical activation, where the substrate is turned into a more reactive species by an additive, energy transfer can be exploited. Taking off from thermal amidation where heat simply allowed overcoming an energy barrier, a methodology has been developed by the Szpilman group based on the photochemical generation of highly reactive species. The key intermediate is the formation of an iminium ion deriving from an amine-CCl4 charge transfer complex upon irradiation. The scope proved broad and the method allowed a scale up over 10 grams with no need for the high dilution that characterizes photochemical reactions. While offering an interesting proof of concept encouraging the search for new reaction pathways and the exploitation of alternative energy forms and sources, the protocol relies on highly chlorinated solvents thus stepping away from Green Chemistry requirements (Scheme10).[34]



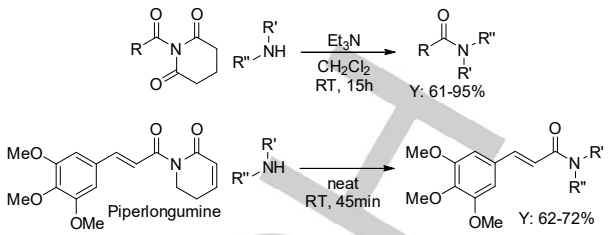
Scheme 10. Photochemical mediated amide synthesis.

Given the importance of the amide function, strategies are needed to enable its construction in different molecular frameworks and from different starting materials. Transamidation methodologies are of great interest, considering these could be applied for late stage functionalization of polymers and pharmaceuticals.[35] Primary amides should be the most easy to be transformed, although harsh conditions were needed in the protocol by the Lee group, employing trimethylsilyl chloride as the substrate activator.[36] The high stability of the N-C(O) bond, provided by nN→ π*C=O conjugation, makes amides poorly reactive electrophiles. Common workarounds imply the use of specific amide substrates, including gluataramides and *N*-tert-butyloxycarbonyl/tosyl amides, the more reactive nature of these substrates making the avoidance of metal catalysts possible. Since 2015, the Szostak group has actively investigating the stereoelectronic factors that affect resonance destabilization, and showed *N*-Boc amides smoothly may undergo base-promoted transamidation with alkyl- and arylamines (Scheme 11).[37] Shortly after, Ramkumar and Chandrasekaran extended the method to *N*-tosyl amides and provided a meaningful improvement to the procedure, which is now run in ethanol and water, with no additional base and with a lower excess of the amine nucleophile.[38]



Scheme 11. Transamidation reactions.

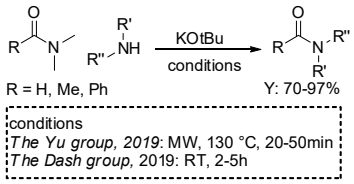
In *N*-acylglutarimides, the higher electrophilicity of the exocylic amide group derives from a lack of conjugation between the carbonyl and the nitrogen atom, that result as electronically disconnected.[39] Authors from the same group hence established glutarimides, easy to prepare and bench stable solids, as effectual acyl-transfer reagents (Scheme 12).[40] The method is metal free, mild and tolerant for a wide range of functional groups. However, although they are referred as easy to synthesize and bench stable, intermediate *N*-acylglutarimides still need to be prepared and isolated.



Scheme 12. *N*-acyl glutarimides as starting material in transamidations.

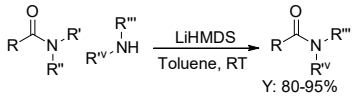
The translation of amide bond twist in the weakening of the amidic resonance was exploited by Subramani and Rajendran, who prepared a series of piperlongumine analogues. Distortion from planarity of the *N*-acyl pyperidone moiety is likely the factor which enables good yields with a variety of amines quickly and at room temperature. The practical significance of transamidation procedures was thus demonstrated in the preparation of bioactive products from naturally occurring substrates.[41]

Non-hindered amides also proved suitable substrates for transamidation reactions (Scheme 13). In 2019, independently, Dash.[42] and Yu.[43] successfully applied KOtBu in a transamidation starting from tertiary formamides, acetamides and even benzamides. Besides providing a mild and effective method, these works widened the plethora of mechanisms possibly operating within this context. In fact, control experiments and EPR analysis supported a radical pathway, where the amine nucleophile undergoes deprotonation followed by single-electron oxidation and the amide group on the reaction partner is reduced.



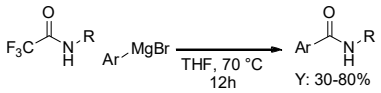
Scheme 13. Potassium *t*-butoxide-mediated transamidation reactions.

A major advancement was brought by a further contribution from the Szostak group, finding that tertiary amides could undergo the transamidation process with a variety of primary and secondary amines at room temperature; although in the presence of an excess of lithium hexamethyldisilazane (Scheme 14). Remarkably, the author provided an extensive selectivity study and a mechanistic investigation, building general guidelines for the use of unactivated amides (and esters) as electrophiles.[44]



Scheme 14. Lithium hexamethyldisilazane-mediated transamidation reactions.

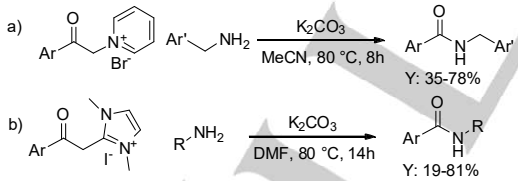
The possibility of the -CF3 group to act as a leaving one allowed for a different disconnection when using trifluoroacetyl amides as electrophiles in combination with Grignard reagents (scheme 15). In this conceptually interesting approach, trifluoroacetyl amides thus become the source for the *N*-acetyl portion of the final product.



Scheme 15. Synthesis of amides using trifluoroacetyl amides.

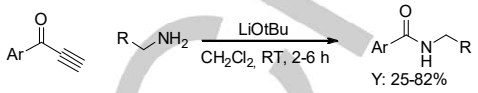
Those fluorinated amides are described as easy to isolate, stable, and react under fairly mild conditions to afford the products in good yields; however, the need for 3 equivalents of the Grignard nucleophile may undermine the synthetic practicality.[45]

Various other methods involving a C-C breaking in the acyl donor partner have been proposed (Scheme 16). Those methods, however, intrinsically suffer from the overall lengthening of the pathway towards the amide product, as the synthesis of the substrate has to be accounted for. In the works by Gandhi and Alvala, phenacylimidazolium and pyridinium salts, respectively, are employed in the presence of potassium carbonate: the benefit of using an inorganic base is counterbalanced with the need for organic solvents and high temperature.[46]



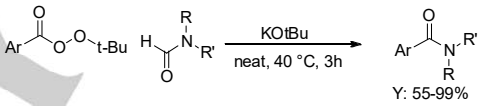
Scheme 16. Synthesis of amides from acylimidazolium and pyridinium salts.

α,β-Acetylenic ketones have been also employed as amide precursors. The method, reported by Cheng and co-workers in 2018, differs from the above mentioned ones, since it is meant to investigate the reactivity of ynones rather than proposing those as carboxylic acids surrogates. Optimized conditions are mild and, in short times, allow good yields for amides stating from differently substituted alkynes and primary and secondary amines, although steric hindrance is poorly tolerated.[47] Working under Glaser–Hay coupling reaction conditions, i.e. adding CuI to the mixture, the bisacetylene product formed, thus supporting the hypothesis that the mechanism proceeds via the formation of a terminal alkyne intermediate (Scheme 17).



Scheme 17. Synthesis of amides from acetylenic ketones.

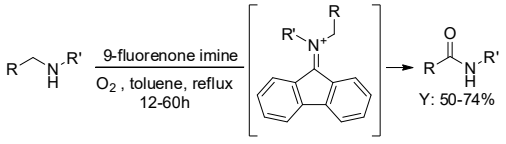
As nitrogen sources, alternatives to amines have been used, including hydroxylamines, azides, nitriles, isothiocyanates and formamides (Scheme 18). In particular, the latter have been employed in a recent contribution by Zhang and co-workers, in combination with benzoperoxoates under solvent free conditions. Analogous previously reported methods required a metal catalyst, harsh conditions and environmentally unfriendly reagents and solvents.[48]



Scheme 18. Synthesis of amides from formamides.

2.2. Strategies based on C-O bond formation

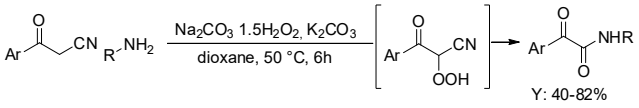
A distinct retrosynthetic approach involves the building of the amide C-O bond, achieved either via oxidation or hydration (Scheme 19). The former methods typically proceed via the in situ generation of an imine. In 2017, de Souza, von Zuben and Salles found optimized conditions to go from a benzylic amine to the corresponding unsymmetrical amide in the presence of NaOCl via attack by the oxygen donor partner.[49] Analogously, in the procedure by the Tan group, a tertiary amine served as the source for the carbon atoms in the (O)C-C skeleton, and *tert*-butylhydroperoxide worked both as C-N oxidant and as the amide oxygen donor.[50] Ghosh and Jana, instead, developed a methodology relying on the formation of the iminium ion from the amine substrate and fluorenone imine; a deprotonation leads to a zwitterionic species trapping molecular oxygen.[51]



Scheme 19. Synthesis of amides via oxidation of amines.

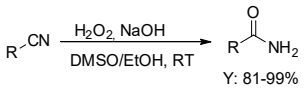
The procedure allowed for the preparation of a variety of amides, including 9-isoindolinone; its *N*-substituted derivatives are of growing pharmaceutical interest and a method dedicated to their preparation was introduced by the Foss group. This consisted in a radical reaction initiated by dioxane autooxidation under aerobic conditions, and remarkably offered selectivity and did not cause overoxidation.[52]

Targeting another relevant structural motif, i. e. α-ketoamides, Zhang and Wang developed a one-pot oxidation-amidation β-ketonitriles, using H_2O_2. The protocol is described as green procedure, although it requires dioxane as the solvent of choice (Scheme 20).[53]



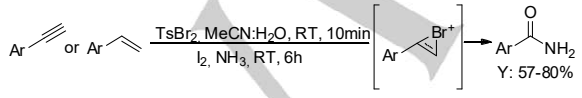
Scheme 20. Synthesis of α-ketoamides.

As for hydration reactions, those apply to unsaturated substrates of different nature (Scheme 21). For nitriles hydration, a recent technical advancement was brought by the Li group, who implemented a continuous-flow synthesis of primary amides with hydrogen peroxide, thus improving the safety of the process.[54]



Scheme 21. Continuous flow amide synthesis through nitriles hydration.

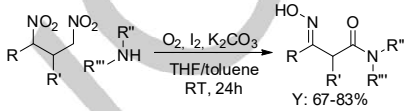
Slightly later, Loukrakpam and Phukan developed the metal-free hydration of alkenes and alkynes using liquid ammonia as nitrogen source (Scheme 22). The transformation relies on the use of *N,N*-dibromo-*p*-toluene sulfonamide and iodine, to allow addition of OH- and substitution by NH_3, respectively; it thus appears as suffering from poor atom economy and biocompatibility, although being working at room temperature.[55]



Scheme 22. Amide synthesis through alkenes and alkynes hydration.

2.3. Umpolung strategy

In a conceptually different setting, the amide bond can be formed relying on an umpolung amide synthesis (UmAS), that involves both C-N and C-O bond formation. Introduced by the Johnston group in 2010 and highlighted by Ke and Yeung in 2019, this method exploits α-halonitroalkanes to provide the skeleton of the carbonyl portion and in situ generated *N*-haloamines as electrophilic amine donors.[8c] This reactivity pattern was recently applied by the same group in the preparation of β 2,3-amino amides; 1,3-dinitroalkanes were turned into of γ-hydroxylamine-α-iodo nitroalkanes upon treatment with oxygen and iodine, responsible also for the amine partner transformation in the *N*-iodo derivative (Scheme 23). The transformation thus consists in a double umpolung process that, noteworthy, does not cause epimerization.[56]



Scheme 23. Umpolung strategy for the amide synthesis.

3. Catalytic methods

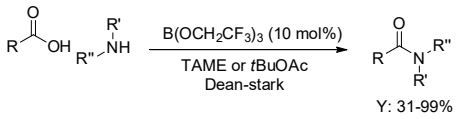
We named catalytic methods all the amidation examples relying on the use of substoichiometric amounts of a reagent. Direct amidation between carboxylic acids and amines is the most used strategy, as water is the only by-product, as in thermal synthesis of amides. Catalytic methods are not widely adopted often due to scarce efficacy, or the need of large quantities of solvents, also during the workup. Chemical yields and catalyst loading are frequent issues, along with limited substrate generality, especially for sterically demanding carboxylic acids.[8a] Water removal is often needed, performed by molecular sieves or azeotropic distillation, a high energy-requiring process. Of course, the main advantages are the production of less waste, along with a better e-factor. Metal-free methodologies may represent sometimes a greener alternative to metals-based methods, that offer encouraging results but are affected by metal separation, residual toxicity in the target compound and disposal of hazardous waste, which are all a matter of concern. Furthermore, other possible limits of their application are non-recyclability and inadequate substrate scope.

3.1. Strategies based on C-N bond formation

Among catalytic methods for direct amidation through the formation of a new C-N bond we can identify two main classes: the use of complexes of IV group metals, that will not be treated in this review, and boron containing Lewis Acids, meaning boronic acids derivatives. This second class was first reported in 1996 by Yamamoto and co-workers[57] and has been broadly studied and developed since then.

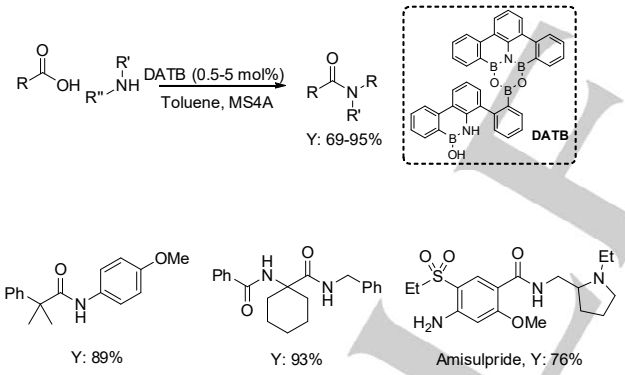
There are few examples of industrial scale application[58] of this kind of catalyst but there is still room for improvement. Recently, some contributions have been published by the Sheppard group: in 2017 the use of commercially available borate ester $B(OCH_2CF_3)_3$ as catalyst for direct amidation was reported.[59a] The authors optimized their protocol in the

perspective of applicability, focusing on operational simplicity, efficiency and PMI, both for reaction and work-up. In particular, they managed to reduce the amount of solvent, also during the work-up, avoiding column chromatography and preferring crystallization or the use of scavenger resins (Scheme 24). The methodology was applied also for unprotected aminoacids, demonstrating chemoselectivity and compatibility with pre-existing stereocenters.[59b] In 2019 the same procedure was studied in *t*-butyl acetate, considered a more sustainable and safer solvent.[59c] Due to the higher polarity of this solvent, polar substrates and less nucleophilic anilines could be successfully employed, leading to a very wide scope of reaction with generally high yields.



Scheme 24. Borate esters-mediated synthesis of amides

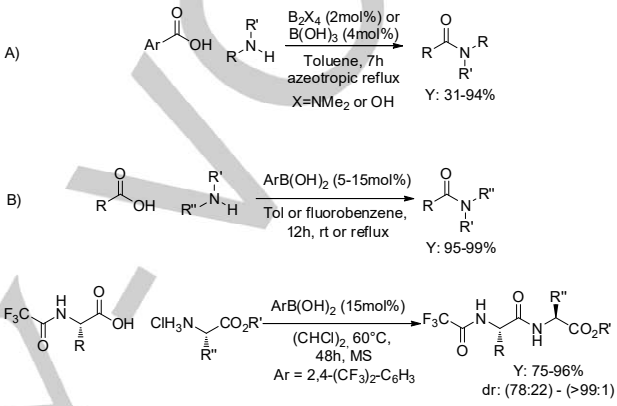
Another important contribution to the field came in 2017 from Kumagai's group, which reported the dehydrative amidation catalyzed by DATB ring system, characterized by the B_3NO_2 ring system (Scheme 25). [14c].



Scheme 25. Amidation reactions promoted by B_3NO_2 ring system.

The scope of the reaction is very broad, including sterically demanding acids and amines, and the yields are good. The typical loading of the catalyst is 5 mol%, which is quite low, but it should be noticed that still the catalyst is not commercially available and must be synthetized. In this case, molecular sieves were used, that are not well considered from a sustainability point of view, due to the high quantity of solvent needed during the workup in their presence. In this case, the author did not use azeotropic removal of water, preferring to work at lower temperatures than toluene reflux. Amino acids were suitable substrates and no epimerization was observed. The same authors later published a mechanistic investigation of their method in 2019.[60]

A different approach was proposed by Saito in 2018, in which commercially available catalysts, Tetrakis(dimethylamido)-diboron and tetrahydroxydiboron were used in 2 mol% loading for the synthesis of arylamides.[61a] The authors decided to go for a more sustainable azeotropic removal of water, working at reflux in toluene as solvent (Scheme 26, eq. A). The method works on aromatic carboxylic acids and with relatively inexpensive and commercially available catalysts.

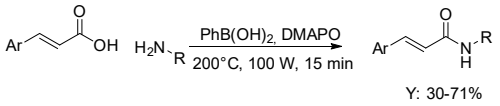


Scheme 26. Diboron complexes-catalyzed dehydrative amidation reactions.

In the same year the group of Ishihara proposed a procedure involving the use of ortho-susbstitued phenylboronic acids, and in particular 2,4-bis(trifluoromethyl)phenylboronic acid, as commercially available catalyst for direct dehydrative amidation (Scheme 26, eq. B). The yields are very high, and in some cases, the reaction works at room temperature, or in fluorobenzene at reflux (86°C). The synthesis of a key intermediate for the preparation of Bortezomib, an active pharmaceutical ingredient, was also achieved without any epimerization. The authors decided to focus also on α-dipeptides synthesis: the most common protecting groups (Fmoc, Boc or Cbz) are not compatible with this approach, so the authors decided to use *N*-trifluoroacetyl as convenient alternative, and managed to avoid almost completely epimerization in all cases. For α-dipeptides synthesis, the major drawbacks are long reaction times and the use of highly chlorinated solvents (1,2-dichloroethane).[61b]

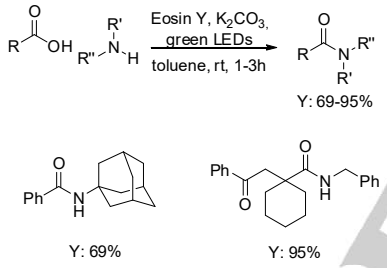
Carreaux and co-workers proposed a more peculiar example of boron based catalytic method for the synthesis of cinnamic amides. In their contribution the authors focused on the preparation of amides starting from conjugated carboxylic acids and various aliphatic and aromatic amines, in the presence of catalytic amounts of phenylboronic acid and DMAPO (4 *N,N* dimethylamino pyridine *N*-oxide), under solvent-free conditions and microwave assisted heating, at 200°C in only 15 minutes.[62] The reaction is quite clean and a simple work up with solvent extraction was needed to isolate the product. The reaction

proved to be chemoselective over the possible aza-Michael addition on the other electrophilic site of the acid, but unfortunately the yields are generally moderate and there is still room for improvement (Scheme 27).



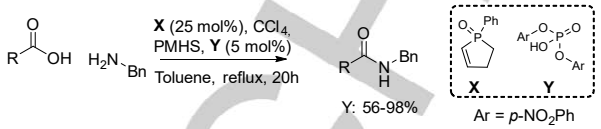
Scheme 27. Phenylboronic acid-catalyzed amidation reactions.

Along with boron-based catalysis, different catalytic methods were proposed in recent years, always aimed to realize a direct amidation reaction (Scheme 28). In 2019, the Singh group published a visible light-promoted photoredox catalyzed amidation, using Eosin Y as organic dye.[63] The reaction is interesting from the sustainability point of view, since an alternative form of energy is exploited, and no use of molecular sieves nor azeotropic distillation (requiring high temperatures) are needed. In short reaction times (1-3 h), good to excellent yields are obtained, also for sterically demanding substrates.



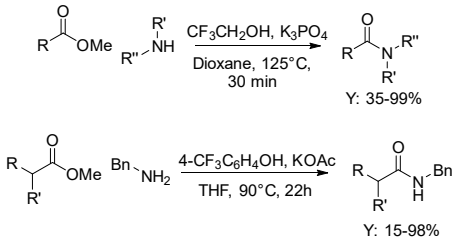
Scheme 28. A visible light-promoted photoredox catalyzed amidation.

In 2017 an example of phosphine catalyzed amidation was reported, in which the actual catalyst was formed in situ, starting from a commercially available pre-catalyst, 3-methyl-1-phenyl-2-phospholene oxide, by reduction in the presence of PMHS poly(methylhydroxysilane).[64a] This is actually presented as a "greener" version of a previous paper from the same authors, in which the reducing agent was $(EtO)_2MeSiH$, in combination with phosphate as precatalyst.[64b] Indeed, in the proposed modified protocol PMHS was employed as *in situ* reducing agent, a cheap and sustainable reagent, being a byproduct of the silicon industry. Although the reaction is promoted by catalytic amounts of phosphine, it requires the use of stoichiometric amounts of the silane and CCl_4. Unfortunately, due to its lower reactivity, an additional reduction step at the beginning of the catalytic cycle performed by bis(p-nitrophenyl) phosphate and a greater number of equivalents of PMHS were required. In some cases, a lower catalyst loading could be used, giving in most cases higher yields compared to the original paper. No racemization was observed in the case of enantiopure substrates, but still high temperature, long reaction times and the use of 2 equivalents of CCl_4 represent the major drawbacks of this reaction from the point of view of "green chemistry methodologies" (Scheme 29).



Scheme 29. A phosphine catalyzed amidation.

Considering different reaction partners, a direct amidation between unactivated esters and amines was proposed by Jamieson and co-workers in 2015,[65a] and more recently further improved. The idea was to form in situ a more activated ester using a catalytic amount of alcohol, to make it react with the amine. In the first paper, trifluoroethanol was used, in the presence of K_3PO_4, while in the second one, published in 2017, they focused on solvent and additives to enlarge reaction scope (Scheme 30). In order to include tertiary amides, they increased the temperature and switched from THF to dioxane as solvent, while to extend the method to esters bearing a stereocenter in alpha position they furtherly switched to 4-(trifluoromethyl)-phenol/KOAC as catalyst/base combination. The yields are still moderate in some cases, and high temperature (125°C) are often required.[65b]

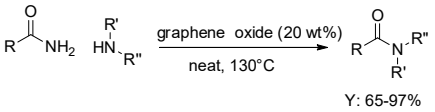


Scheme 30. Amidation between unactivated esters and amines.

Transamidation reactions require generally high temperatures and long reaction times, since breaking the inert amide bond is not an easy task. Many examples of metal catalyzed systems have been reported, but in an alternative metal-free approach, in 2019 the group of Shankarling published a transamidation reaction promoted by graphene oxide (GO).[66] The reaction is run under solvent-free conditions, with the heterogeneous catalyst, that can be recycled up to five times without any loss in the chemical activity (Scheme 31).

The reaction proved to be chemoselective, since substrates bearing free -OH group were well tolerated. No epimerization was observed for substrates containing a stereocenter, and transamidations of carboxamide, phtalimide,

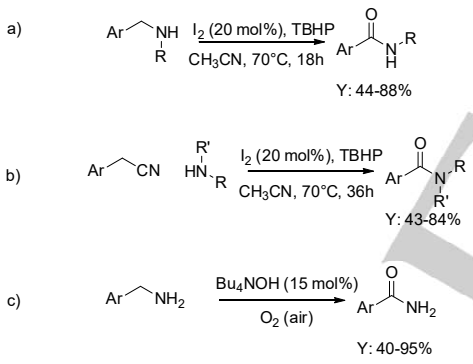
urea and thioamides with various amines were also successfully achieved.



Scheme 31. Graphene oxide-catalyzed amidation reactions.

3.2. Strategies based on C-O bond formation

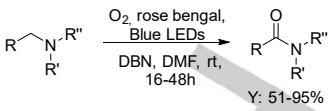
In recent years, some metal-free examples of amide synthesis made *via* CO bond formation have been reported, mainly by oxidation of amines (Scheme 32). One of the first report for this type of transformation was published in 2017 by Adimurthy and co-workers: a substoichiometric amount of iodine, in combination with 10 equivalents of TBHP (tertbutylhydroperoxyde) was used to oxidize benzylamines and arylacetonitriles to form benzamides. The protocol is efficient, with a high functional group tolerance, with more than 40 examples giving moderate to high yields.[67]



Scheme 32. Catalytic oxidation of amines to amides.

The same authors decided to further investigate the topic, trying to develop a greener and more sustainable version of this transformation, avoiding the use of a large excess of oxidizing agent, substituted by simple oxygen from air. In a 2019 paper a catalytic amount of tetrabutylammonium hydroxide ionic liquid was used to oxidize benzylamines to benzamides under solvent-free conditions.[68] From an environmental point of view, the use of oxygen from air as an oxidant is ideal, and the only byproduct of the reaction is water. Yields are generally higher than 80%, making this protocol very interesting, as the author already tested it on gram scale synthesis.

Among CO bond forming methods also some recent examples of photoredox catalysis have been reported (Scheme 33). In 2018 the Das' group has studied the photocatalyzed oxidation of tertiary amines, promoted by visible light in the presence of oxygen from air and Rose Bengal as organic dye.[69]



Scheme 33. Photoredox catalytic synthesis of amides.

The authors explored also the possibility of a one pot synthesis starting from secondary amines and a halide, to give directly the corresponding tertiary amide. The relevance of the method was proved also by the contributions of two other research groups: in 2019 the Singh group applied the method to tertiary amines conjugated with a pyridine moiety, obtaining higher yields in shorter reaction times, and high site- and chemoselectivity.[70] At the same time Lee and co-workers managed to obtain dihydroisoquinolones starting from *N*-substituted tetrahydroisoquinolines, using in this case Eosin Y and two equivalents of sodium azide as singlet oxygen quencher.[71]

4. Conclusion

The synthesis of amides remains one of the most important transformations and it is one of the more frequently performed reactions. Last year, the development of general, efficient, sustainable methods[72-73] for the amides formation was still included in the ten Key Green Chemistry Research Areas. Therefore, even if many high yielding strategies are available for the generation of the N-C=O group, the search for innovative, catalytic, inexpensive, not toxic methods continues today, more than ever, and interest numerous research groups, both in academia and in the industry.

This review has presented an overview of only very recent contributions, published in the last three years, to highlight the latest progresses in this "dateless" reaction. More efficient and/or greener stoichiometric methods as well as catalytic strategies have been discussed, either for the "classical" coupling approach between an amine and a carboxylic acid (or its activated equivalent), and for more innovative approaches, mainly involving oxidation procedures to generate amides starting from amines.

It is expected that numerous innovative and creative methodologies will be reported in the future, with the main aim to realize economically convenient and environmentally friendly procedures, able to dramatically reduce the waste generation. The use of efficient catalytic processes, either for the (photo)-oxidation of amines or for promoting the formation of the N-CO bond will be crucial towards the development of a new generation of amidation methods.

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Keywords: amides • C-N bond formation • amidation methods • coupling agents • C-O bond formation

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Entry for the Table of Contents

Layout 1:

MINIREVIEW

The amide function is unarguably of primary importance, being the constituent of natural and synthetic polymers and found in a wide variety of bioactive molecules. This review will discuss specifically the very recent advances in the area of amide synthesis, specially focusing on metal-free strategies, based either on stoichiometric and catalytic methods, published in the last three years.

Key Topic : Amide synthesis

*.E. Massolo, M. Pirola, M. Benaglia**

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Amide bond formation strategies: latest advances on a dateless transformation