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# Direct Catalytic Amidations from Carboxylic Acid and Ester Derivatives: A Review

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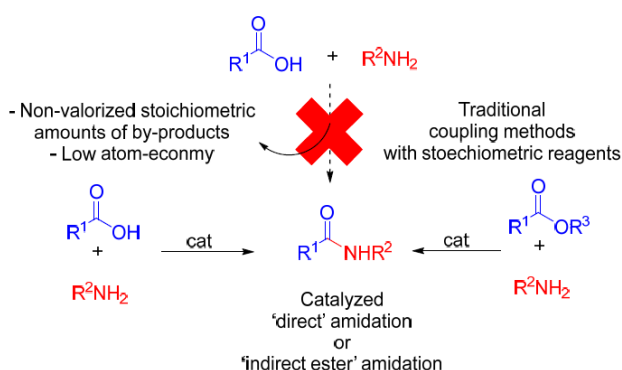
**Abstract:** The prevalence of amides in biological systems and chemical fields such as polymers, materials and natural products drives continuous research on novel procedures to obtain these ubiquitous functional groups. Currently, efforts to this purpose are mainly focused around the discovery of direct and catalytic methods that are more atom economic, safe and practical for diversified applications (e.g., organic, medicinal and peptide chemistries, material and polymer purposes, etc.), in accordance with green chemistry principles. The field of amide synthesis has attained such a level of significance that the number of reviews and articles addressing it grown exponentially in the last decade. Rather than providing a general overview of amidation methods, which have been described broadly and well in recent literature, the purpose of this review is to highlight recent efforts in the catalytic formation of amide bonds from amines and carboxylic acids or esters. The goal is to emphasize mechanistic and catalytic aspects, but also to discuss substrate tolerance and racemization issues (when applicable).

**Keywords:** amides; metal-transition catalysis; direct aminolysis; mechanistic insights; esters

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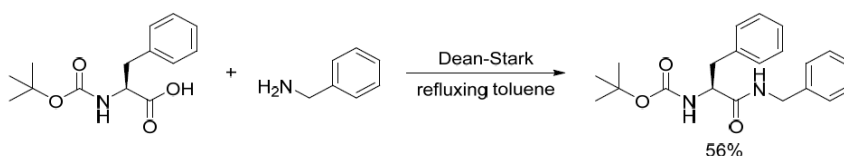
## 1. Introduction

The amide bond is of particular importance, not only for its key function in peptide/protein structures, but also its role in a large number of natural and synthetic small molecules and polymers [1,2]. Amide bond formation is traditionally achieved through the activation of the carboxylic acid partner using a greater-than-stoichiometric quantity of some complex activating agent (carbodiimides + additives (HOBT, HOAt or Oxyma), phosphonium or guanidinium salts, etc.), thus generating a large amount of unvalorized byproducts, whereas amide formation is 'just' about the elimination of one molecule of water. In 2006, a round table dedicated to the development of green chemistry research ranked "amide formation avoiding poor atom economy reagents" as a top priority [3]. This point is even more crucial, as the formation of amides from acids and amines is by far the most used reaction in medicinal chemistry [4]. This review intends to highlight more recent progress in catalytic formation of amide bonds from amines, carboxylic acids and esters (Scheme 1) [5–7]. These catalytic amidation strategies were recently covered by Sheppard, Wang and Perrin, who focused on green aspects, perspectives and peptide synthesis [8–10]. General reviews on amide bond formation that do not focus on catalytic direct approaches have also appeared [11,12]. Catalytic redox reactions starting from aldehydes or alcohols are beyond the scope of this review and, consequently, will not be reported herein [12]. C–H catalytic amidation reactions from nitrene precursors, which cannot be considered as direct amidation of amines, have been recently covered in comprehensive reviews and thus will not be addressed here [13]. This review aims to focus on mechanistic and practical aspects and to discuss substrate tolerance and racemization (whenever relevant).



**Scheme 1.** Catalytic amidation reactions from amines and acids (or esters).

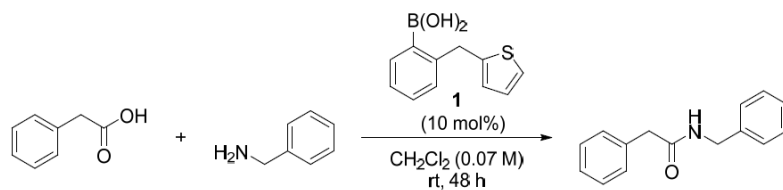
Before discussing catalyzed reactions, it is appropriate to comment on amidation reactions under thermal conditions in the absence of a catalyst. The direct thermal condensation of acids and amines is indeed possible, but usually requires high temperatures (>160 °C) to proceed and is thus generally limited to insensitive and poorly functionalized substrates [14,15]. The key issue is the formation of poorly reactive ammonium salts from the carboxylic and amine partners. Nevertheless, these statements must be tempered and depend largely on the reaction partners, in particular, the acidity of the carboxylic acid, and the reaction conditions [16]. Therefore, when a catalytic reaction is carried out under thermal conditions, it is necessary to conduct a control reaction without any catalyst to obtain the background uncatalyzed reaction. For example, the reaction of Boc-Phe-OH with benzylamine under refluxing toluene using a Dean–Stark apparatus allows the formation of the corresponding amide at a 56% yield (Scheme 2) [17]. Microwave-assisted solvent-free preparations have appeared in the literature and may be considered as practical and easy to handle conditions for undemanding substrates [18,19]



**Scheme 2.** Thermal amidation of Boc-Phe-OH with benzylamine.

In direct amidation reactions from amines and carboxylic acids, the only byproduct is water. Thus, the central question is how to trap/remove water to promote/favor amide formation. Either azeotropic removal of water (using a Dean–Stark apparatus or a Soxhlet extractor with a dehydrating agent) or excess molecular sieves have been used. While molecular sieves allow a reaction at lower temperature, they are incompatible with large-scale synthesis. Indeed, catalytic amidations have been used only marginally in the large-scale synthesis of amides [20].

The nature of the dehydrating agent and the method of activating it may also be crucial in these reactions, as illustrated by Blanchet in the boronic acid **1**-catalyzed amidation of phenylacetic acid with benzylamine (Scheme 3) Supplementary Information described in ref [21]. Both the type of drying agent (4 Å MS vs. 5 Å MS) and the activation method (microwaves vs. Kugelrohr) have a profound impact on the yield. Questions as to the actual role of molecular sieves in these reactions have thus arisen, and recent developments have shed light on the function of these agents beyond simple water traps (Scheme 3).



Drying agent (activation method):

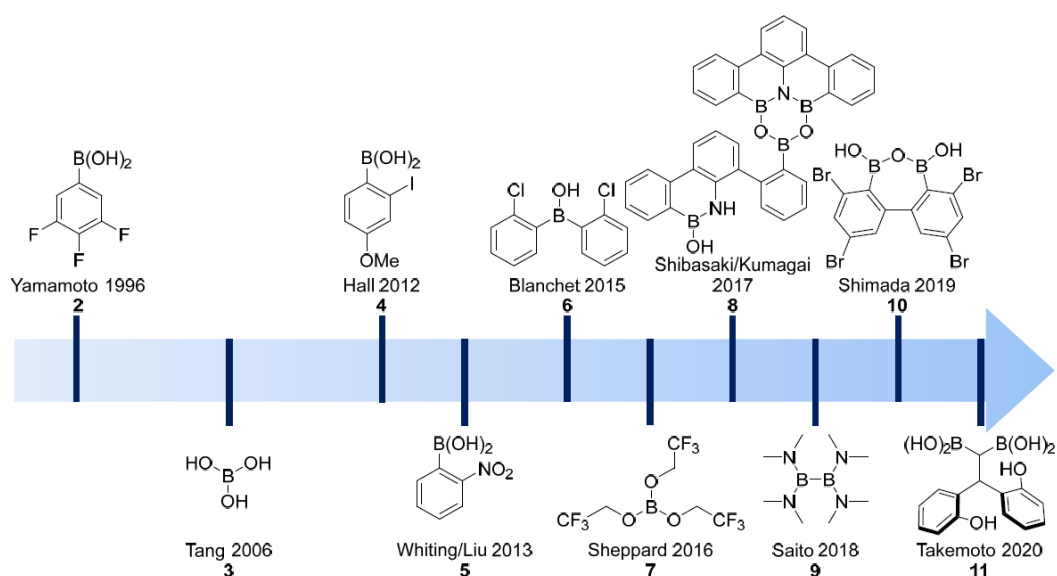
none	0%
pwd MgSO <sub>4</sub> (Kugelrhor, 250 °C)	<5%
pwd 4Å MS (μW, 30 min)	43%
pwd 4Å MS (Kugelrhor, 250 °C)	50%
pwd 5Å MS (μW, 30 min)	0%
pwd 5Å MS (Kugelrhor, 250 °C)	9%

**Scheme 3.** Influence of the nature and method of activation of the drying agent in an amidation reaction; μM = microwaves.

## 2. Direct Amidations of Carboxylic Acids with Amines

### 2.1. Boron-Derived Catalysts

From the seminal boronic acid catalysts described by Yamamoto in 1996 (structure **2**) to the much more elaborated bis-boronic acids (Figure 1, structures **3–11**), boron derivatives have emerged as an efficient class of catalysts that allow the formation of amides under milder conditions in the presence of sensitive and functionalized substrates. For a general review of boronic acid catalysis, see [22].

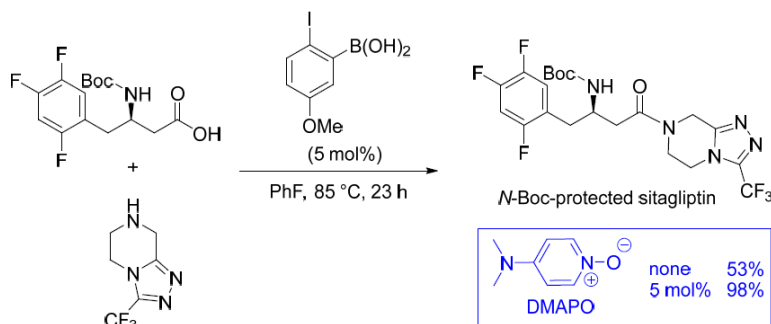


**Figure 1.** Evolution of boron-derived catalysts used in direct amidation reactions.

Since the publication of Ishihara and Yamamoto's seminal paper, more than 20 boron-derived catalysts were described in the literature in the 1996–2015 period (for a list of catalysts developed in this period, see [5]). Initially, in 1996, refluxing conditions were required (using toluene, xylene or mesitylene), and thus these reactions were restricted to rather non-functionalized substrates. In the following paragraphs, we would like to highlight how the evolution of the fine understanding of the mechanisms involved in these reactions has enabled the refinement of the structure of catalysts and for reactions to be achieved under mild conditions with more complex or sensitive substrates.

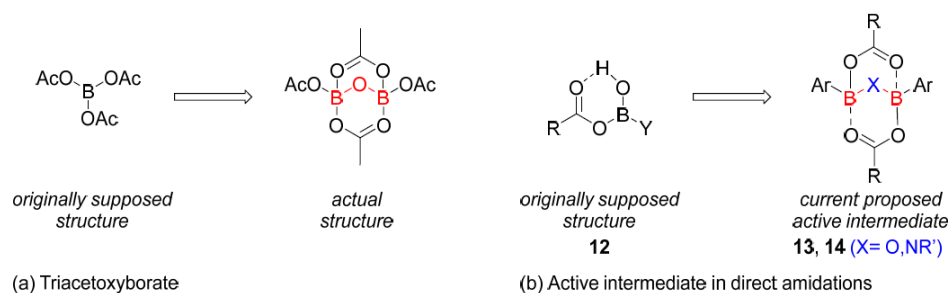
As illustrated in Figure 1, ortho-substituted derivatives (see structures **4–6**, Figure 1) have experimentally emerged as promising catalytic systems, allowing reactions at room temperature for less-demanding substrates and reactions around 60 °C for the synthesis

of dipeptides [21,23,24]. Ishihara also described the use of DMAPO as an efficient acyl-transfer co-catalyst in these reactions, as illustrated in the multigram-scale of *N*-Boc-protected sitagliptin [25,26] (Scheme 4). This co-catalyst was also used in the microwave-assisted synthesis of cinnamides using a PhB(OH)<sub>2</sub>/DMAPO catalytic system [27].



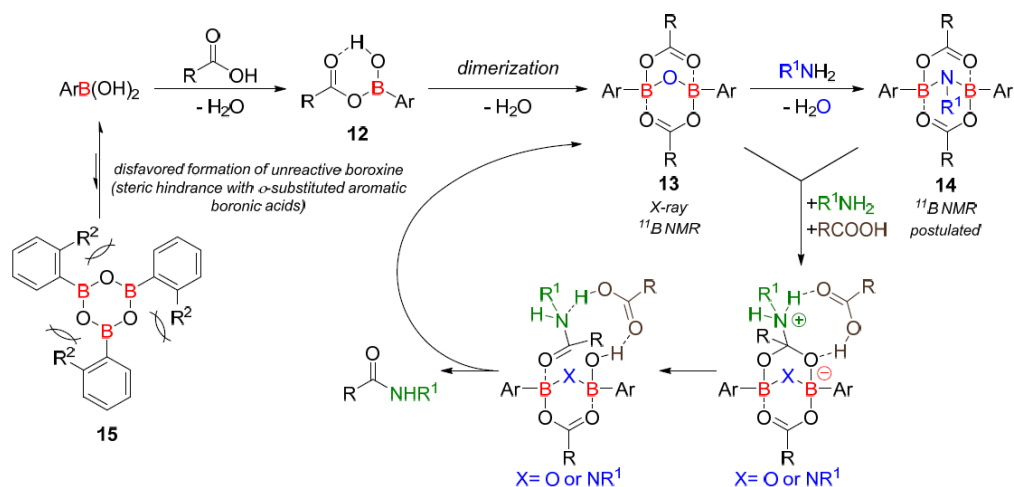
**Scheme 4.** DMAPO as a co-catalyst in boronic acid-catalyzed amidation reactions.

These ortho-substituted boronic acids have thus appeared experimentally as efficient catalysts, but their efficiency has not been directly correlated to the generally accepted mechanism for these reactions. A major breakthrough in this area was achieved in 2018 in an extensive mechanistic study by Sheppard and Whiting [28]. Supported by related analytical, experimental and theoretical studies, evidence has been found that the reaction does not proceed through a ‘monocyclic’ acyloxyboron **12** active intermediate, as was initially proposed and accepted, but through the formation of a bicyclic intermediate involving a 2:2 carboxylic acid/arylboronic complex **13** (or **14**) (Scheme 5b). Such intermediates embed a B-X-B (X = O or NR) connection, as previously observed by X-ray analysis in tetraacetyl diborate, which was originally assigned a triacetoxyborate structure (Scheme 5a).



**Scheme 5.** Mono- vs. bicyclic structures of boron derivatives. (a) Triacetoxyborate, (b) Active intermediate in direct amidations.

The isolated (and fully characterized) bicyclic derivative **13** is a key active intermediate in amide formation. In the presence of an amine, a new intermediate can be observed in <sup>11</sup>B NMR, which was tentatively attributed to the bicyclic compound **14** (Scheme 6). From the intermediates **13** or **14**, different mechanisms to explain the formation of the amide bond have been studied computationally, but no preferential pathway has been identified.



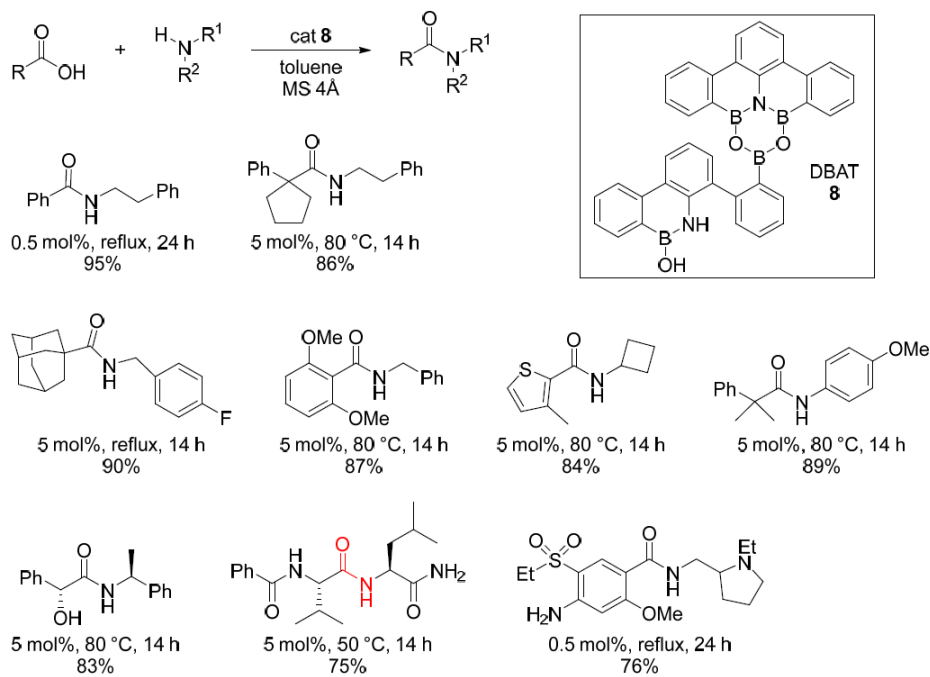
**Scheme 6.** Postulated (simplified) amidation mechanism.

The study by Sheppard and Whiting may also shed lights on some yet unexplained experimental observations:

- The formation of the bicyclic intermediate **13** is highly dependent of the quantity and nature of molecular sieves; a large quantity of 5 Å MS is required and less than 5% conversion was observed with 4 Å MS (see Scheme 3);
- Boroxine **15** could be considered as a poorly reactive 'resting state' intermediate. As determined by DFT, the use of *o*-substituted aromatic boronic acids destabilizes the formation of the corresponding boroxine **15** derivatives, thus explaining the efficiency and success of such ortho-substituted catalysts (see Figure 1);
- Finally, it should be noted that for borinic acid **6**, the actual catalyst can be determined to be ortho-chloro boronic acid (obtained by protodeborylation of borinic acid **6**).

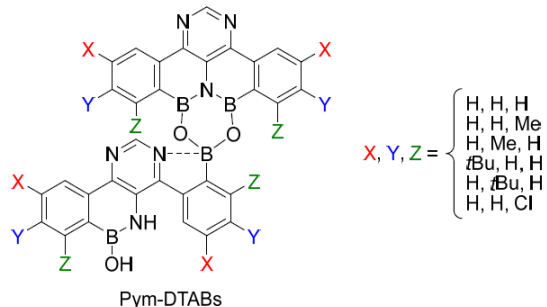
Moreover, this mechanistic study is in line with a work published in 2017 by Shibasaki and Kumagai describing the use of B-O-B heterocycles as efficient catalysts for direct amidation reactions [29], where 1,3-Dioxa-5-aza-2,4,6-triborinane (DATB) derivative **8** was found to be an efficient catalyst for the amidation of a wide range of carboxylic acids and amines. The scope of this catalyst includes undemanding substrates (for which catalytic loadings of 0.5 mol% can be used), highly epimerizable ones and hindered substrates or APIs, and the yields are high (Scheme 7).

This methodology has also been applied to the synthesis of peptides using Fmoc amino acids. This synthetic potential was illustrated in the synthesis of a pentapeptide (obtained by fragment coupling at the C-terminus of a glycine residue) [30].



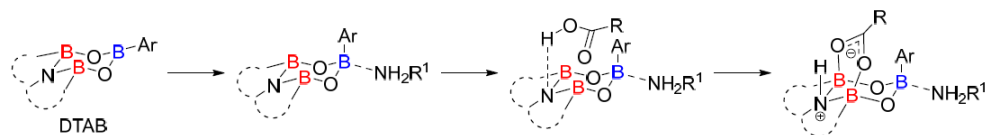
**Scheme 7.** DTAB 8 catalyzed reactions.

The major drawback of this methodology is the lengthy route to obtain such DTAB derivatives. Kumagai and Shibasaki then developed pyrimidine analogs—so-called Pym-DTABs (Figure 2). These compounds are more accessible and show rather similar catalytic performance (temperature, loading, scope) [31].



**Figure 2.** Pym-DTAB structure.

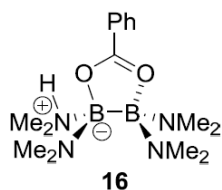
Mechanistic studies have highlighted the dual role of the two distinct classes of boron atoms [32]. The most Lewis acidic “O-B-O” boron atoms readily activate the amine via an adduct formation. The “B-N-B” moiety reacts as both a Brønsted base and a Lewis acid, allowing the formation of a “B-O=C-O-B” cyclic complex where the electrophilicity of the carboxylic function is activated (Scheme 8).



**Scheme 8.** Intermediates involved in the DTAB-catalyzed reactions.

Saito also described the use of simpler diboron structures—tetrahydroxy diboron and tetrakis(dimethylamino) diboron **9**—to enable the catalytic amidation of various (hetero)aromatic acids in refluxing toluene, with good yields with low catalytic loadings (2

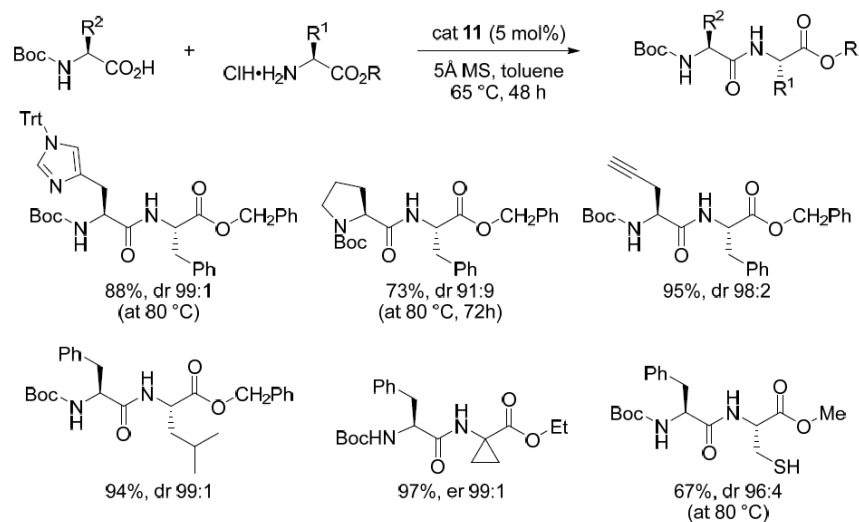
mol%) [33]. As illustrated in Figure 3, the cooperative role of the two boron centers in the amidation process is highlighted by structure **16**, detected by ESI-HRMS.



**Figure 3.** Mechanistic insights into the carboxylic acid activation with diboron catalyst **9**.

Shimada next developed diboronic acid anhydride **10** (Figure 1) with a B-O-B linkage. The catalyst **10** was shown to be effective in the amidation of alpha or beta hydroxy acids with a wide range of amines or anilines, but not in cases of ‘simple’ carboxylic acids (without OH groups). It also should be noted that these reactions were carried out in toluene (60 °C or reflux) in the absence a molecular sieve or Dean–Stark apparatus [34]. The reaction was next extended to  $\beta$ -hydroxy- $\alpha$ -amino acids (serine, threonine derivatives, etc.), to the formation of Weinreb amides and the synthesis of Garner’s aldehyde [35–37].

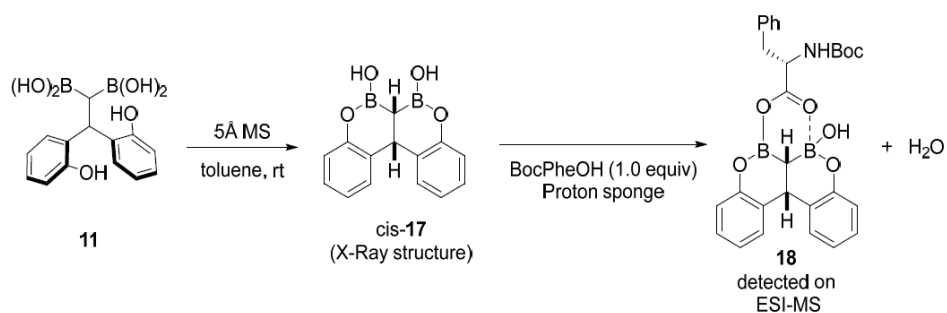
In 2020, Takemoto analyzed the catalytic performance of gem-diboronic acid **11**, incorporating a B-C-B linkage, in catalytic dehydrative peptide synthesis. As illustrated in Scheme 9, dipeptides were obtained in good yields in toluene at 65 °C in the presence of 5 Å MS. Epimerization-prone dipeptides were also synthesized, with only partial epimerization observed [38].



**Scheme 9.** Scope of dipeptide synthesis using cat **11**.

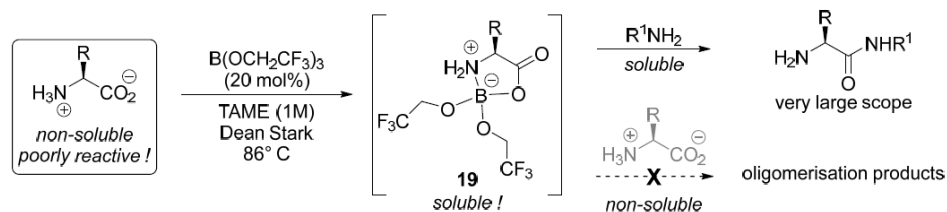
Preliminary mechanistic experiments were carried out. Cat **11** is not the actual catalyst and rapidly evolved in the presence of 5 Å MS to form of *cis*-**17** (determined by X-ray analysis). Addition of Boc-Phe-OH (in the presence of a proton sponge) led to the observation (by ESI-MS) of the dehydrated complex **18**, which embeds the two boron atoms and the carboxylic acid (Scheme 10).





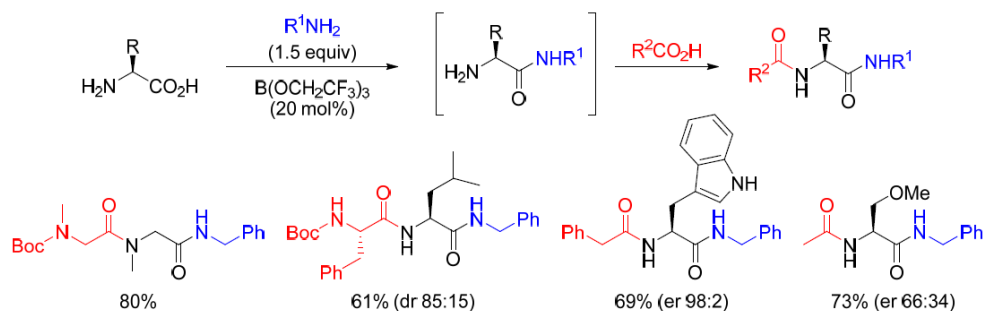
**Scheme 10.** Mechanistic insights into cat **11**-catalyzed reactions.

The fine comprehension of the reaction mechanisms and the search for gentle reaction conditions allowing the coupling of sensitive and/or functionalized substrates has led to the development of more and more structurally complex catalysts. More simple catalysts have also emerged, such as borate  $B(OCH_2CF_3)_3$  **7** developed by Sheppard [39,40]. In particular, Sheppard achieved an impressive selective catalytic amidation of unprotected amino acids. A large range of unprotected amino-acids and amines can be used in these reactions, with *tert*-amyl methyl ether (TAME) as solvent at 86 °C and a Dean–Stark apparatus [41]. As illustrated by the authors, the key point is the formation of soluble intermediate **19** in minute amounts from the insoluble zwitterionic amino acid (Scheme 11). This intermediate, in the presence of an apparent excess of amine, will smoothly yield the desired amide, while unwanted oligomerization is prevented. It should be emphasized that  $Ti(OiPr)_4$  could also be considered (at least in the most favorable cases) as a cheaper alternative in these reactions.



**Scheme 11.** Mechanistic insights into cat **7**-catalyzed reactions; TAME = *tert*-amyl methyl ether.

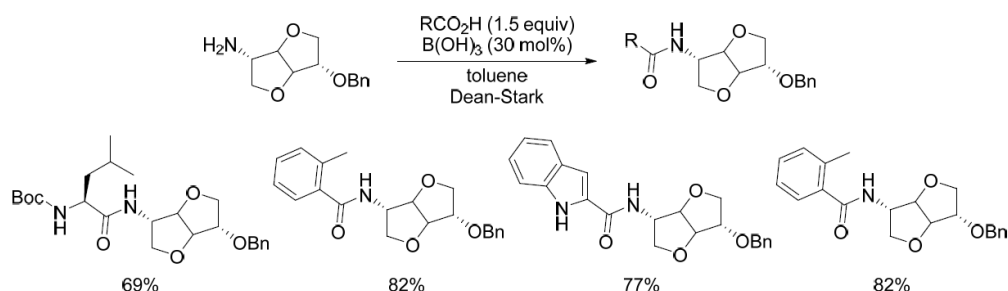
Sheppard and co-workers also developed a one-pot sequential double amidation process. As illustrated in Scheme 12, good yields were usually observed, but with significant enantiopurity erosion.



**Scheme 12.** Double amidation reactions.

More recently, the use of *tert*-butyl acetate as the solvent reaction was described by Sheppard. Beyond increased safety and durability, greater range was obtained using fewer nucleophilic anilines and polar substrates [42]. Interestingly, a large-scale procedure (100 mol) was described with no aqueous work-up or chromatography.

Nevertheless, it should be remembered that for undemanding substrates with low sensitivity, reactions can be carried out with simple and inexpensive boric acid [43–45], as recently illustrated by Popowycz for the synthesis of various amides from renewable isosorbide (Scheme 13) [46].

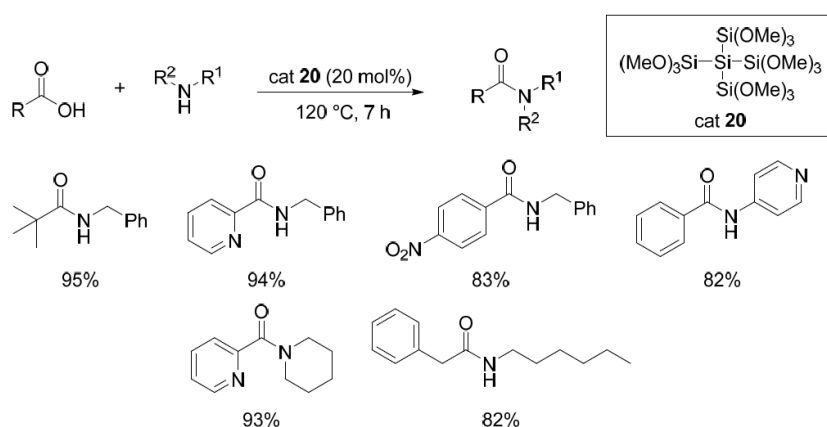


**Scheme 13.** Boric acid-catalyzed amidation of isosorbide.

Silica-supported and polymer-bound versions of these catalysts have been developed from appropriately derived aromatic boronic acids. Such immobilized catalysts have been proven to be easily recoverable, reusable and suitable in flow chemistry [47,48]. Taking a different approach, Ishihara used boronic acids bound to a cationic resin or complexed with DMAPO. In both cases, the boronic acid catalyst can be released to perform the reaction, while the poor solubility of the complexes allows undemanding work-up and high catalyst recovery [26].

## 2.2. Phosphorus- and Silicon-Derived Catalysts

Since the seminal work of Chan [49,50], the use of silicon reagents to perform amidation reactions has been well known, but even in modern developments, these reactions still require a stoichiometric amount of a silicon reagent, resulting in poor atom economy [51,52]. In 2022, Haas described a solvent-free procedure using 20 mol% of dodecamethoxyneopentasilane **20** as catalyst [53]. As illustrated in Scheme 14, relatively poorly functionalized amides were obtained in good to excellent yields (13 examples) in the absence of any external water trap. Neopentasilane **20** (20 mol%) fragments into five reactive silicons upon methanolysis. In this reaction, water is trapped by the formation of a polysiloxane byproduct.



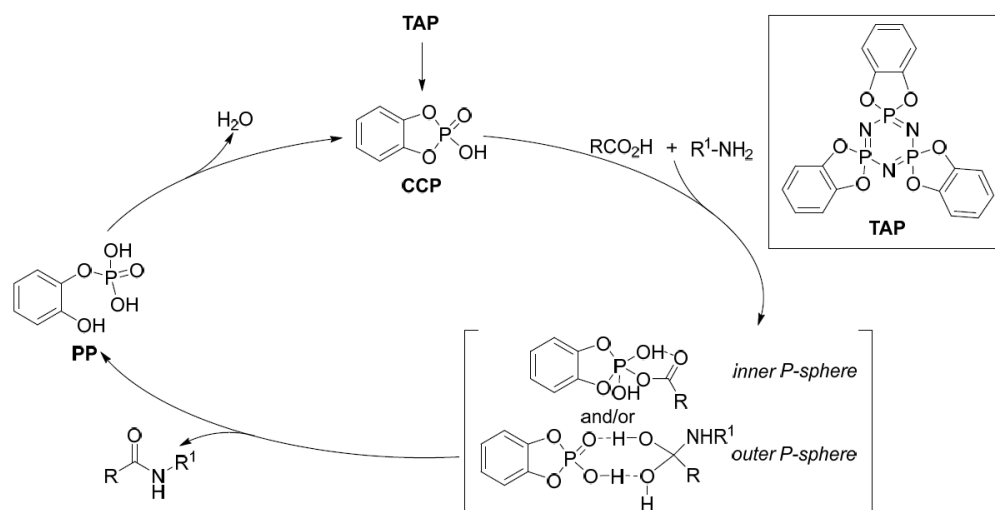
**Scheme 14.** Dodecamethoxyneopentasilane-catalyzed amidation reactions.

It should also be mentioned that the direct amidation of carboxylic acids can be performed under microwave irradiation using silica gel as a solid support and catalyst [54]. In a parallel study, the mechanism of this transformation was elucidated using IR and computational studies. This study highlights the role of some specific weakly interacting

SiOH pairs to organize/favor the co-existence of amine and carboxylic acid pairs in both their neutral and ionic forms [55].

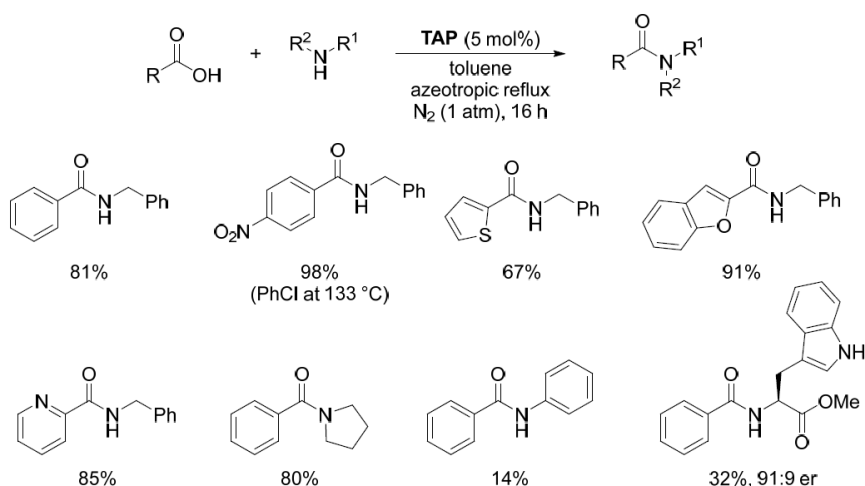
Phosphine and phosphine oxide (organo)catalysts have also been described as promoting direct amidation reactions. They are mainly based on a P(III)  $\leftrightarrow$  P(V) catalytic cycle, which requires a reductant (or an oxidant) in stoichiometric quantity to regenerate the catalytic species [56–58].

In 2020, Sato described the use of tris(*o*-phenylenedioxy)cyclotriphosphazene **TAP** as a pre-catalyst for the direct amidation of aromatic acids and amines [59]. On the basis of  $^{31}\text{P}$  NMR and ESI-MS experiments, different relevant catalytic intermediates were identified (Scheme 15). **TAP** acts as a pre-catalyst, generating the catechol cyclic phosphate **CCP** in situ. This catalytic species promotes amide formation while generating pyrocatechol phosphate (**PP**) as a byproduct. Next, dehydration of **PP** regenerates **CCP**, thus completing the catalytic cycle. Regarding the formation of the amide bond, two mechanisms were considered by the authors, involving either an inner *P*-sphere mechanism (direct attack of the carboxylic partner on the phosphorus atom of the **CCP**) or an outer *P*-sphere (with the phosphate of the **CCP** acting to stabilize a tetrahedral intermediate) mechanism. It should be stressed that **CCP** is a poorly stable compound, which is why pre-catalysts such as **TAP** are required and reactions must be carried out under an inert atmosphere.



**Scheme 15.** Mechanistic rationale in **TAP**-catalyzed amidation reactions.

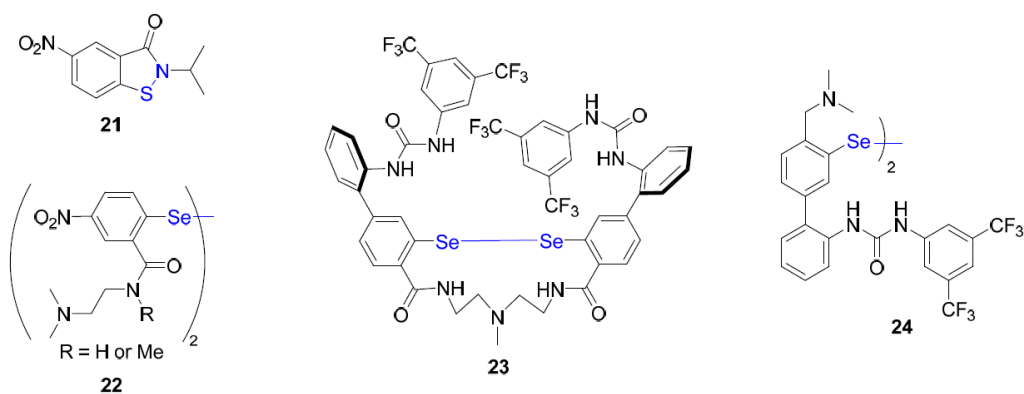
As illustrated in Scheme 16, a wide range (25 examples) of aromatic and heteroaromatic carboxylic acids have been efficiently coupled with mono- and di-substituted amines (Scheme 16). However, low yields were observed when aniline or H-Trp-OMe were used. Moreover, in the latter case, substantial erosion of the enantioselectivity (91:9 er) was also observed, probably due to the high temperature required in these reactions.



**Scheme 16.** TAP-catalyzed amidation reactions.

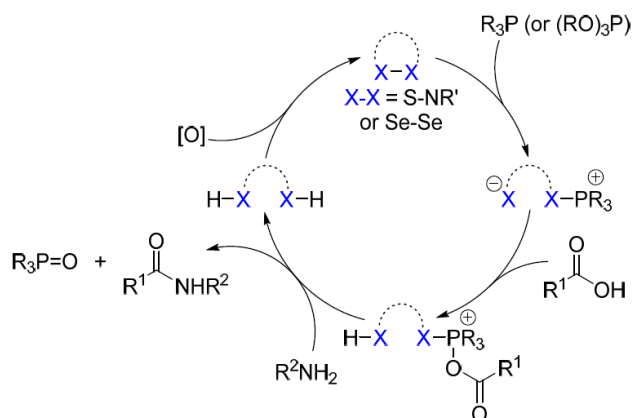
### 2.3. Organo-Catalyzed Reactions

Stoichiometric amounts of phosphines (or phosphites) have also been used in conceptually different organocatalyzed redox amidation reactions, playing on the cleavage of weak heteroatom–heteroatom bonds (S–N or Se–Se) of compounds **21–24** (Figure 4) [60–63].



**Figure 4.** S–N- and Se–Se-based organocatalysts.

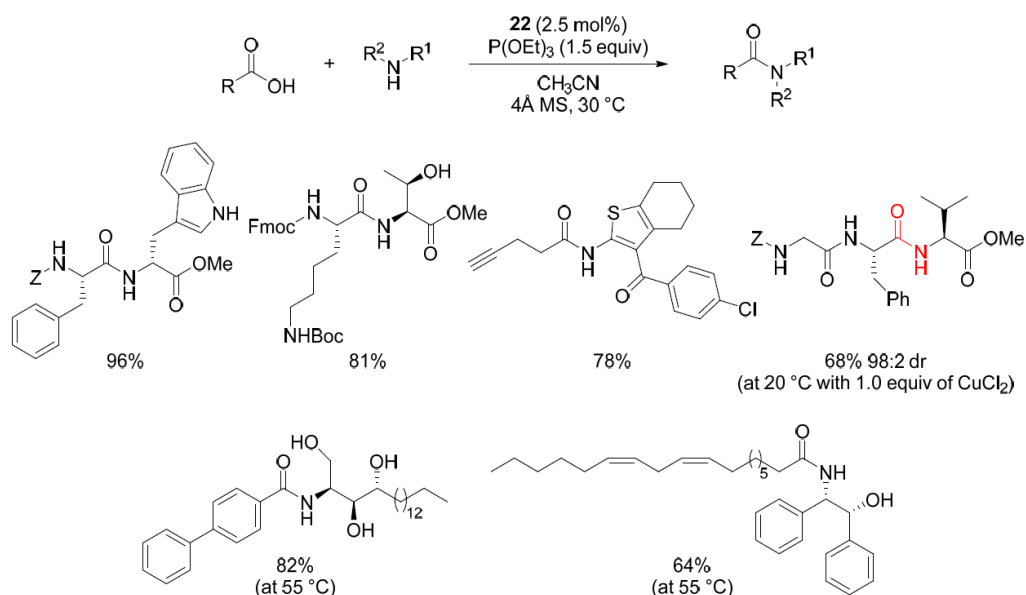
A general (and simplified) *modus operandi* is presented in Scheme 17. Cleavage of the weak heteroatom–heteroatom (S–N or Se–Se) bond by the nucleophilic phosphine enables the formation of an electrophilic phosphonium salt that can be trapped by the carboxylic acid. Such a generated activated acid can then react with the amine to generate the amide bond and phosphine oxide as a byproduct. Ultimately, the reduced organocatalyst is re-oxidized *in situ* to regenerate the catalyst and complete the catalytic cycle.



**Scheme 17.** General mechanism using S-N- and Se-Se-based organocatalysts.

S-acylthiosalicylamide **21** was first described by Liebeskind and notably allows the formation of various peptides and peptide derivatives under relatively mild conditions (20 mol% **21**, (EtO)<sub>3</sub>P (1.5 equiv.), MeCN, 50 °C, dry air, 4 Å MS) with high yields and in the absence of racemization [60]. In this case, dry air was used in the presence of a catalytic amount of a copper to promote the regeneration of the organocatalyst **21**.

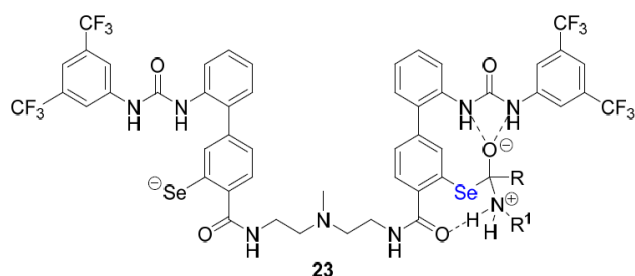
Liebeskind extended this dehydrative strategy to the use of diselenide derivative **22** (R = Me or H) [61]. The use of selenium instead of sulfur was chosen to enhance the re-oxidation of the reduced form of the organocatalyst and thus avoid the use of copper as a co-catalyst. Using diselenide **22**, catalyst loading can be reduced to 2.5 mol% and the reaction can be carried out in the absence of copper. It should be emphasized that the remote NMe<sub>2</sub> group in **22** also plays an important role in the oxidation step (re-formation of the Se-Se bond). As illustrated in Scheme 18, complex and highly functionalized amides have been obtained in high yields and in the absence of racemization for sensitive substrates.



**Scheme 18.** Organocatalyzed **22** amidation reactions.

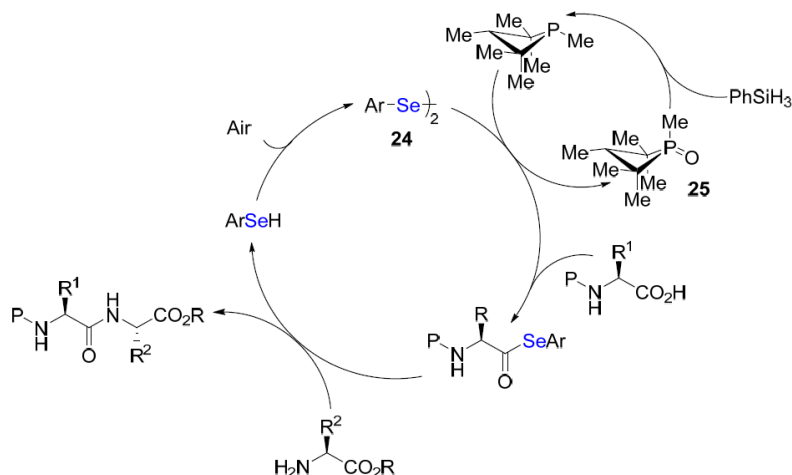
The design of the diselenide organocatalyst was next refined by Arora, introducing a urea in **23** to stabilize the tetrahedral intermediate in the amide bond formation (Figure 5), and a macrocycle to entropically favor the regeneration (oxidation) of the Se-Se bond [62]. This organocatalyst was used in the synthesis of various Fmoc-dipeptides under very mild conditions (**23** (5 mol%), PBu<sub>3</sub> (1.0 equiv.), 4 Å MS, MeCN, rt). This methodology was

ultimately used in solid phase peptide synthesis (SPPS) for the synthesis of the pentapeptide Fmoc-FEKAG-NH<sub>2</sub>.



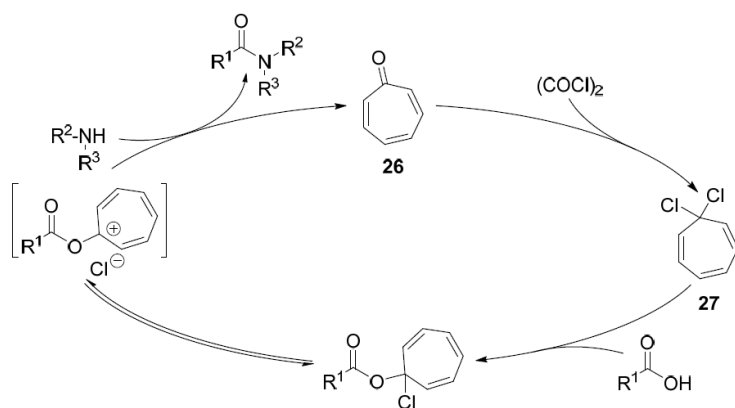
**Figure 5.** Urea-stabilized tetrahedral intermediate using organocatalyst **23**.

The major drawbacks of the diselenide catalyst **23** are its complexity and long/tedious synthesis (10 steps). In 2022, Arora developed a simpler ‘monomeric’ catalyst **24**, which still incorporates a urea moiety and a remote tertiary amine [63]. Regarding the nucleophilic phosphorus partner, phosphetane oxide **25** is used as a co-catalyst (10 mol%) and the phosphine is generated in situ in the presence of an excess of PhSiH<sub>3</sub> (2 equiv.) (Scheme 19). No dehydrating reagent (molecular sieves) is necessary under these conditions, which makes the procedure much easier, especially in SPPS.



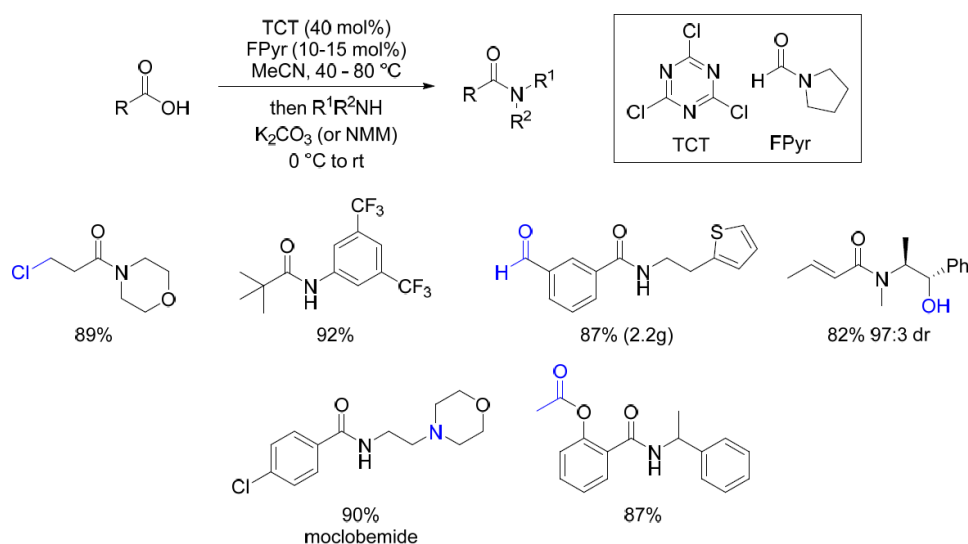
**Scheme 19.** The use of phosphetane oxide **25** as a phosphine precursor in **24**-catalyzed amidation reactions.

Taking a different approach, though one that still requires the presence of a stoichiometric oxidant, Nguyen described troponone organocatalyst **26** [64]. The troponone **26**, in the presence of oxalyl chloride (1.2 equiv.), generates 1,1-dichlorocycloheptatriene **27** and is able to react with and activate the carboxylic acid partner (Scheme 20). Such a compound can directly react with the amine to form the amide, or indirectly react through the transient formation of acyl chloride or anhydride. This strategy has been mainly used in the synthesis of esters (and lactones), but also in the synthesis of amides. The scope of this method nevertheless rather restricted (five examples in a 39–83% yield) when using dialkylamines.



**Scheme 20.** Tropone-organocatalyzed amidation reactions.

Huy used sub-stoichiometric amounts of trichlorotriazine (TCT) in amidation reactions [65]. TCT is a well-known peptide coupling reagent usually used in stoichiometric amounts. In the presence of a catalytic amount of *N*-formylpyrrolidine (FPyr), the amount of TCT could be reduced to 40 mol%. The scope of this method is quite large (27 examples) and it exhibits good tolerance of functional groups (Scheme 21). The use of the three chlorine atoms available in TCT allows good atom economy.

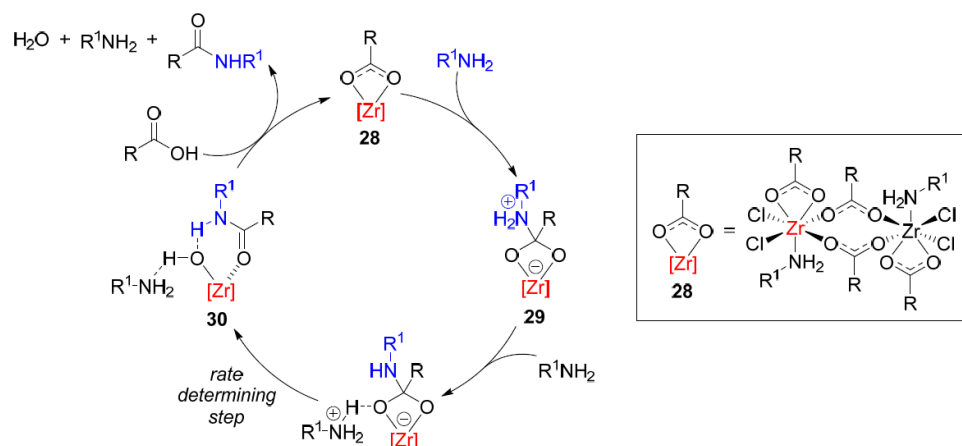


**Scheme 21.** Substoichiometric amounts of TCT in direct amidation reactions.

#### 2.4. Metal-Catalyzed Reactions

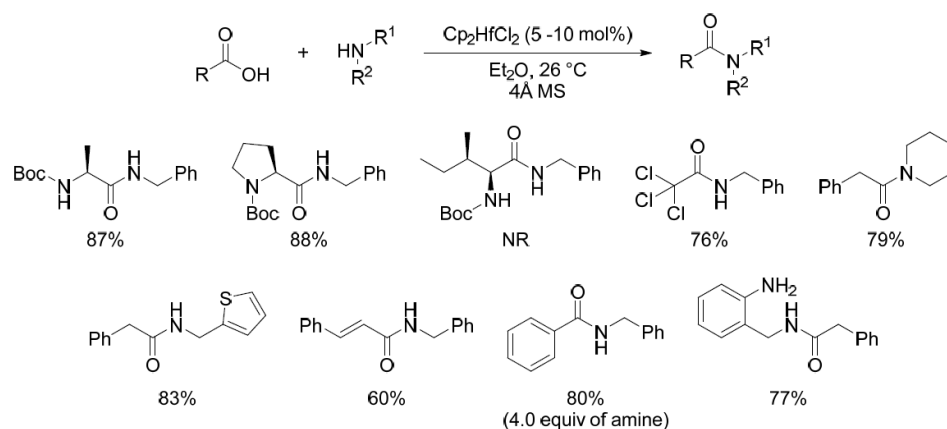
Although the use of metals (especially titanium salts) in direct amidation reactions has been known since the 1970s, these methodologies were limited by high temperatures, relatively high catalytic loadings and limited scope. In 2012, two groundbreaking papers independently published by the Aldolfsson and Williams groups described the use of group(IV) metal salts, using zirconium and titanium salts, respectively, to allow amidification under milder conditions and with greater scope [66,67]. The mechanism of the zirconium-catalyzed reactions was then studied in a work combining kinetics, NMR and DFT experiments (Scheme 22) [68]. The dinuclear zirconium complex **28** is the actual catalytic species that is able to react one carboxylate carbon with the amine to produce the tetrahedral intermediate **29**. After deprotonation (by the intervention of a second amine equivalent), the rate-determining step (with a barrier of 10.9 kcal/mol) is the cleavage of the C–O bond to produce **30**, which, in turn, releases the amide bond (accompanied by a water and amine molecule) and regenerates the catalytic species **28**. Interestingly, these studies also achieved improved reaction conditions (higher yields and lower catalytic

loadings). The need for molecular sieves to trap water can then be overcome by using the hydrolytically more stable  $\text{Cp}_2\text{Zr}(\text{OTf})_2 \cdot \text{THF}$  (2–10 mol%) (THF, 70 °C) [69,70].



**Scheme 22.** Mechanistic rationale in Zr-catalyzed amidations.

In 2015, Aldolfsson was also able to develop hafnium-catalyzed reactions using 10 mol% of  $\text{Cp}_2\text{HfCl}_2$ , enabling reactions at room temperature with short reaction times (90 min) [71]. This method showed great scope (>25 examples) and the yields were very good. However, the reaction is sensitive to steric hindrance at the carboxylic acid partner (no reaction with Boc-Ile-OH), and no reaction was observed with anilines (Scheme 23). CAN (ceric ammonium nitrate) was also reported to be an efficient catalyst (2 mol% loading) under microwave irradiation [19].



**Scheme 23.**  $\text{Cp}_2\text{HfCl}_2$ -catalyzed direct amidation reactions; NR = no reaction.

In 2019, Parac-Vogt described the use of Zr- and Hf-based Lewis-acid-PolyOxoMetallate (POM) complexes enabling amide formation in relatively mild conditions (1 mol% catalyst, DMSO, 70 °C) in the absence of molecular sieves and with a reusable catalyst [72,73]. The use of low catalytic loadings (1 mol%) and the stability of the catalyst can be rationalized by the nature of the POM framework, which prevents hydrolysis of the Lewis acid. More recently, the use of iron-based POMs has been described, though this requires higher temperatures (120 °C) and the use of a catalytic amount of  $\text{PhSiH}_3$  (30 mol%) [74]. The use of metal-organic frameworks (MOFs) that embed Zr-dicarboxylates as heterogeneous catalysts has also been reported [75]. Finally,  $\text{Nb}_2\text{O}_5$  was described as a heterogeneous and reusable Lewis acid for the direct amidation of carboxylic acids under refluxing toluene (or xylene), including examples with anilines and, with a carboxylic acid partner, unprotected alcohols, phenols and thiophenol [76].



## 2.5. Miscellaneous

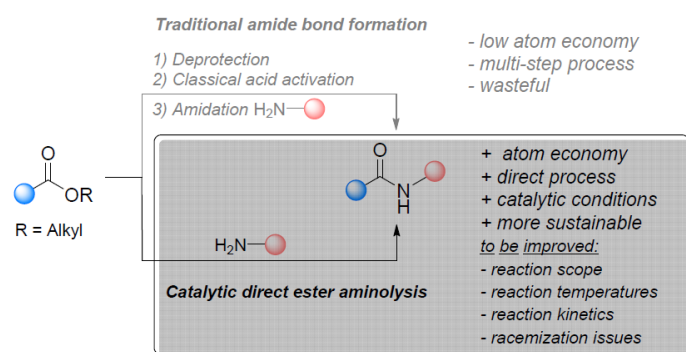
Kumar has described the use of substoichiometric (50 mol%) quantities of  $\text{KPF}_6$  in the amidation (and esterification) of carboxylic acids in the absence of solvent at 130 °C (14 examples) [77].

Electrochemical synthesis of amides and peptides was recently reported, but required a greater-than-stoichiometric quantity of phosphine to proceed [78,79].

Taking a completely different approach, the abiotic formation of amide bonds was described using adsorbed precursors on a Au(111) surface under ultrahigh vacuum conditions [80].

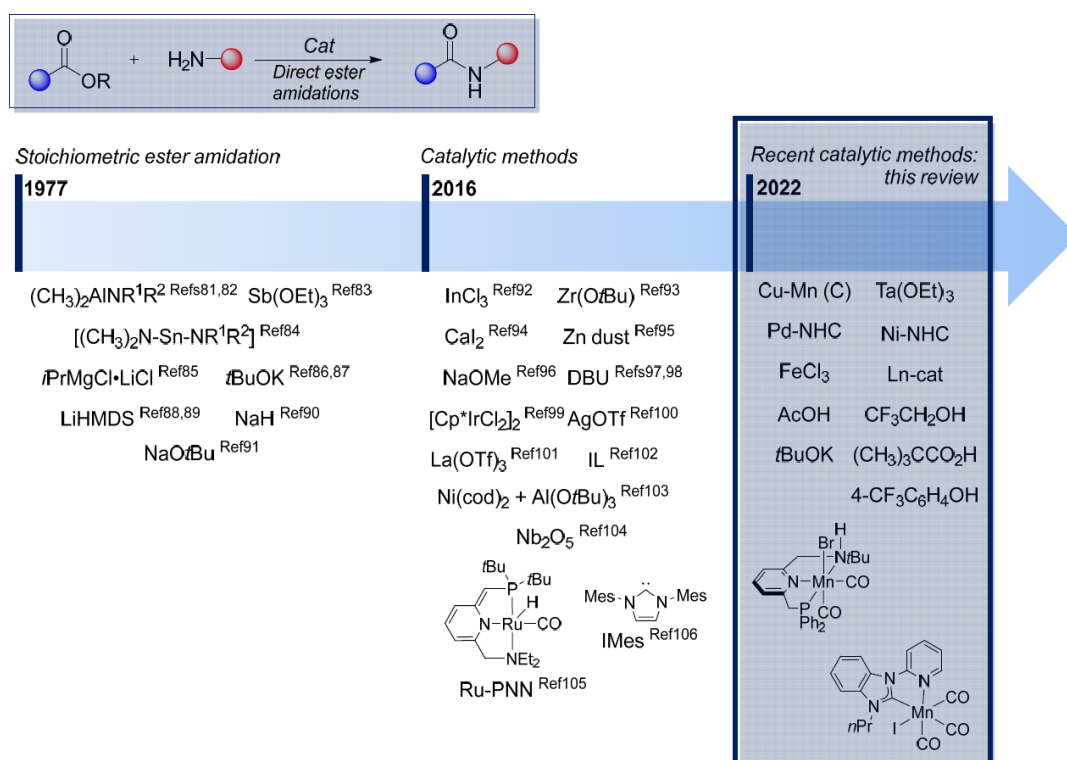
## 3. Direct Amidations of Carboxylic Esters with Amines

While the combination of carboxylic acids and amines is still the most widespread amidation method, either through activated carboxylic acids or direct amidation, further development of this field might involve the evaluation of other substrates to broaden applications and simplify reaction conditions (Scheme 24).



**Scheme 24.** Ester amidations: classical and direct strategies.

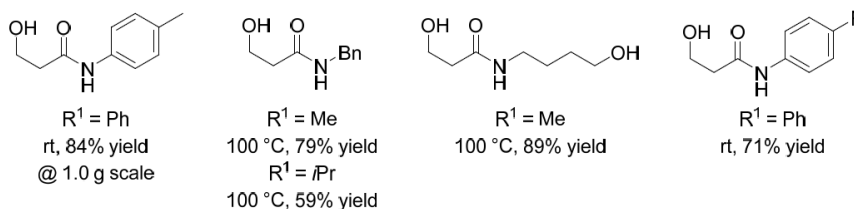
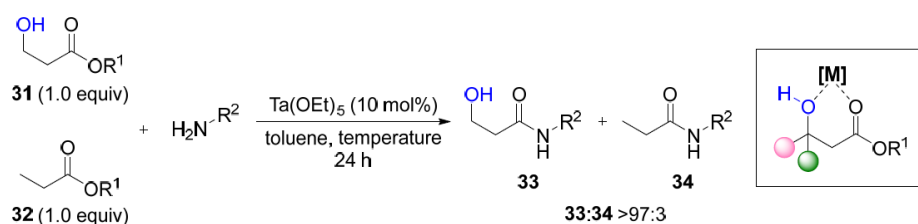
Direct amide synthesis from unactivated esters is a well-known method; however, it is rarely applied, as it often requires harsh reaction conditions (such as greater-than-stoichiometric quantities of strong bases or organometallic reagents to ensure amine deprotonation), even though esters afford a more electrophilic carbonyl site compared to free-carboxylic acids [81–106]. This method is also associated with excess reactants, the need for very nucleophilic amine substrates and long reaction times. Milder methods have been recently described [5,107–113]; however, narrow functional tolerance and racemization issues often prevent their generalization. While efforts have been made to develop more practical and milder conditions for direct amidation of esters with amines, there is still room for improvement by avoiding high temperatures and/or the need for noble metals or sensitive, complex and expensive catalytic systems. Moreover, kinetic issues and a broader substrate scope can also be considered. In this section, catalytic methods devised from 2016 to date are described, with attention to the discussion of mechanistic insights when relevant (Figure 6).



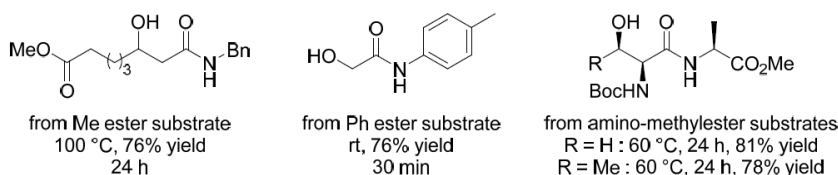
**Figure 6.** Direct ester amidations: overview of main methods since 1977 [81–106].

### 3.1. Transition Metal-Derived Catalysts

In 2016, Yamamoto and Tsuji explored the capacity of  $\beta$ -hydroxy esters to mediate metal-catalyzed hydroxy-directed amidation reactions [114]. Their idea was to use the  $\beta$ -hydroxyl group as a directing group for the activation of the carbonyl group through metal coordination to achieve the chemoselective aminolysis of esters. They identified tantalum(V) ethoxide (10 mol%) as the most efficient catalyst. In the presence of phenyl/methyl/isopropyl  $\beta$ -hydroxypropanoate **31** and equimolar amounts of competitive phenyl/methyl/isopropyl propanoate **32** (1.0 equiv. each) with amines (3.0 equiv.), more than 15 examples of amides were synthesized with remarkable chemoselectivities (**33:34** >97:3) (Scheme 25). Reactions with activated phenyl esters proceeded at room temperature, whereas higher temperatures (100 °C) are mandatory for unactivated methyl or isopropyl esters. The procedure was transposed to a large-scale synthesis and extended to a series of  $\beta$ -mono- and  $\beta$ -di-substituted  $\beta$ -hydroxy esters,  $\beta$ -hydroxy diesters,  $\alpha$ -hydroxy esters and aminoester substrates. In the latter case, dipeptide derivatives were synthesized in good yields in the absence of epimerization. The authors presumed that the observed racemization-free procedure is due to the use of methyl esters rather than activated carboxylic acids, even if aminolysis requires heating (60 °C to 100 °C). Interestingly, no amide formation was observed when *N*-Boc-cysteine methyl ester was used, showing no directing effect with a thiol group.

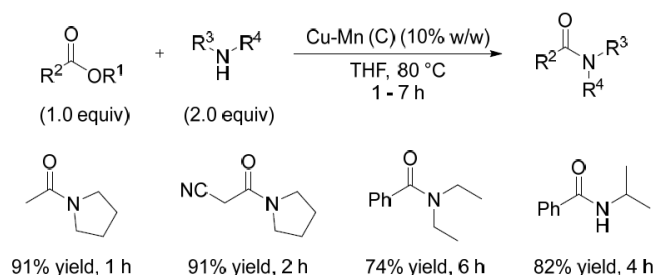


Extension of the method to other substrates:



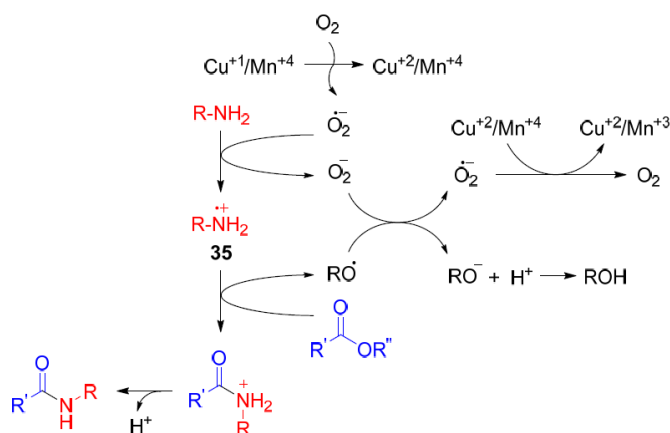
Scheme 25. Hydroxy-directed amidation of esters with  $\text{Ta(OEt)}_5$ .

In the same year, Shah proposed the use of Cu-Mn spinel oxide as an efficient catalyst for oxidative aminolysis of ethyl esters [115]. This bimetallic catalytic system can switch its state of oxidation between  $\text{Cu}^{+1/+2}$  and  $\text{Mn}^{+3/+4}$  and, consequently, participate in electron-transfer reactions through aminium radical cation formation. The reaction conditions were quite mild (THF, 80 °C, air, 1–7 h), and the primary and secondary amines were compatible, although the scope of this method was not very broad (Scheme 26).



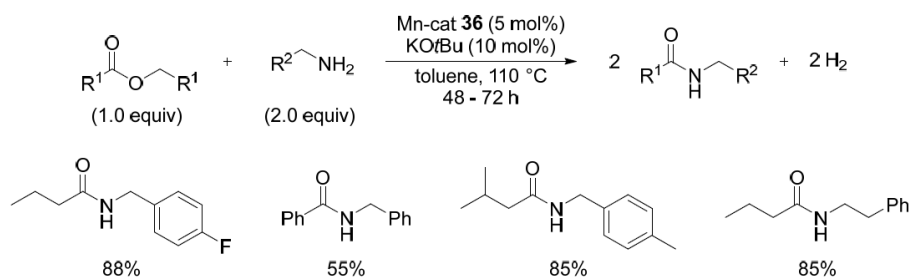
Scheme 26. Cu-Mn-spinel-oxide-catalyzed synthesis of amides.

Control experiments support a radical mechanism with the generation of a superoxide radical, which is responsible for the formation of the key aminium radical cation **35** for ester cleavage and amide formation. Indeed, no amide formation was detected when the reaction was run either under argon or in the presence of a radical scavenger (Scheme 27).



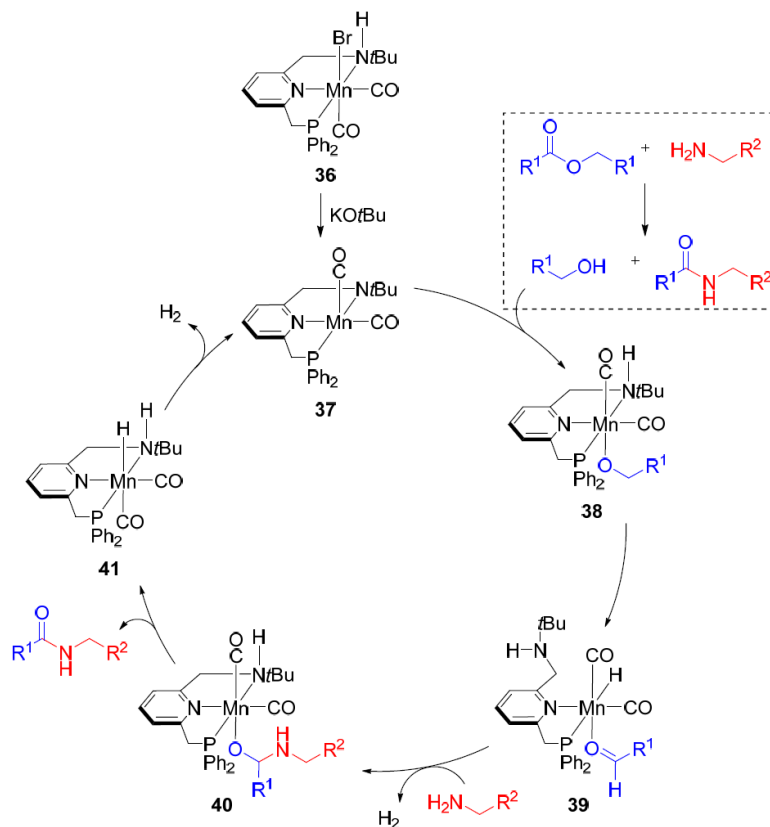
**Scheme 27.** Mechanistic insights into Cu-Mn-spinel-oxide-catalyzed synthesis of amides.

Manganese pincer complex **36** combined with a catalytic amount of *KOtBu* was employed in base-metal-catalyzed dehydrogenative amidations in the presence of amines with either alcohols or esters (Scheme 28) [116]. One remarkable advantage of the proposed strategy is that hydrogen gas is the only side compound formed. Nevertheless, the use of ‘symmetrical’ esters is necessary to ensure the formation of two equivalents of the same product. Indeed, the ‘alcohol’ moiety of the ester substrate (i.e.,  $R^1CH_2O-$ ) is also ‘recycled’ into amide through an oxidative process (Scheme 29). Concerning the reaction conditions, heating (toluene, 110 °C) as well as long reactions times (48–72 h) are necessary, with an ester–amine ratio of 1:2. Well they have narrow scope (10 amides), primary and secondary alkyl amines are compatible with the reaction conditions.



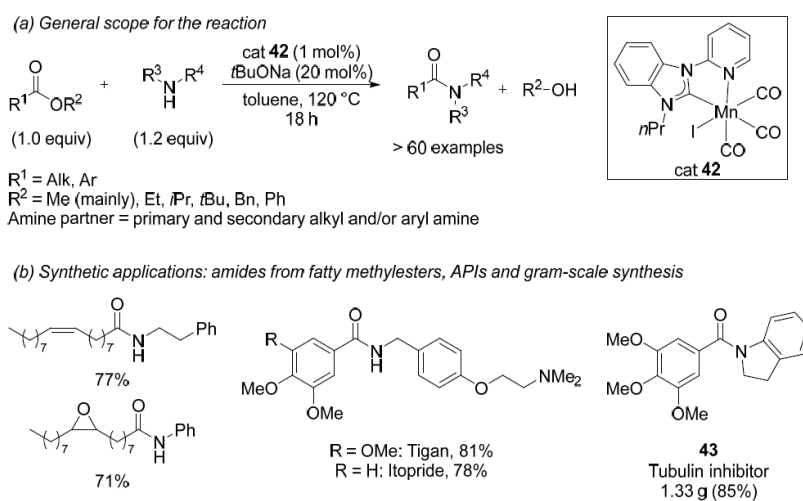
**Scheme 28.** Manganese-pincer-complex-catalyzed aminolysis of ester.

Based on experimental observations, a plausible mechanistic pathway has been proposed (Scheme 29). First, ester aminolysis takes place to form amide and alcohol. In parallel, intermediate **37** is formed through deprotonation of the N-H site in catalyst **36**. Thus, the obtained alcohol enters into the mechanistic cycle through reaction with **37**, producing a new intermediate **38**, which is prone to  $\beta$ -hydride elimination thanks to the opening of the hemilabile pincer arm, thereby forming **39**. Reaction of this intermediate with the amine engenders the formation of a manganese complex bound to the hemiaminal **40**, which, after  $\beta$ -hydride elimination, produces the amide and manganese hydride complex **41**. The latter is able to regenerate **37** via dehydrogenation.



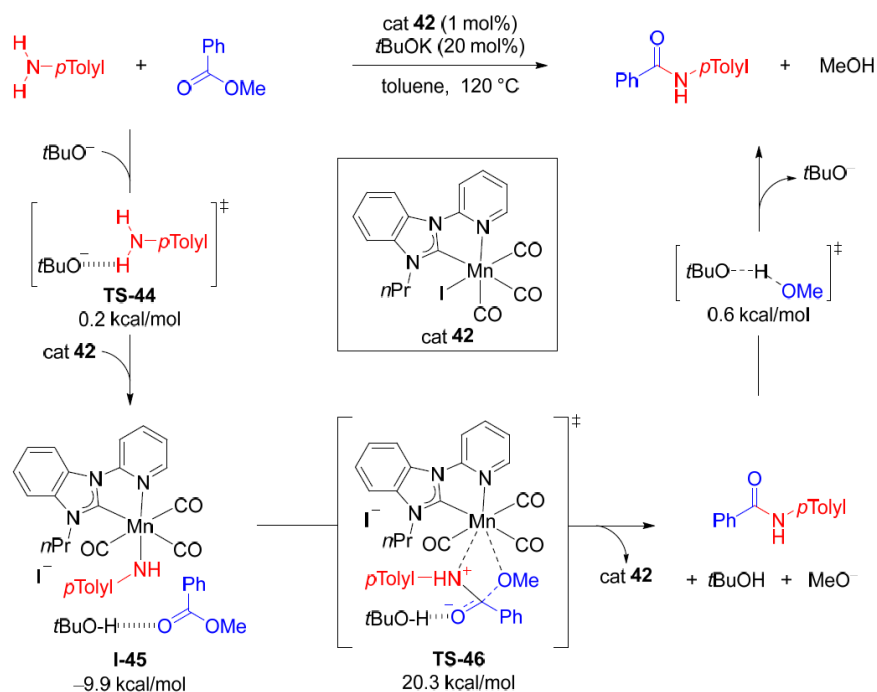
Scheme 29. Proposed mechanism for Mn-pincer-complex-36-catalyzed dehydrogenative amidation.

Taking a different approach, Wei and Liu described the synthesis and evaluation of air- and moisture-stable manganese pincer complexes on direct amidation of esters with amines [117]. Among the several complexes synthesized, the Mn(I)-pincer complex **42**, bearing a *N-n*-propyl benzimidazole and a pyridine ring, displayed better catalytic activity. With a low required catalyst loading (cat **42** (1 mol%), *t*BuONa (20 mol%), toluene, 120 °C, 18 h), the reaction is compatible with a broad scope of substrates concerning both ester and amine partners (around 60 aliphatic, aromatic and heteroaromatic amides) (Scheme 30a). This method has found interesting synthetic applications, such as the preparation of the amide-containing drugs tigan and itopride, the use of fatty acid esters as substrates and the gram-scale synthesis of **43** (Scheme 30b).



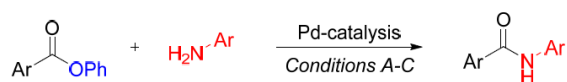
Scheme 30. Manganese(I)-pincer-complex-42-catalyzed aminolysis of ester. (a) General scope of the reaction, (b) Synthetic applications.

Based on DFT calculations, an acid–base mechanistic pathway seems more likely for this Mn(I)-catalyzed amidation than an oxidative addition–reductive elimination process. The transformation is believed to occur via three phases: (1) amine deprotonation (**TS-44**); (2) nucleophilic addition of the Mn-complex (**cat 42**) coordinated to the deprotonated amine (intermediate **I-45**) to the ester substrate associated with the dissociation of the amide through transition state **TS-46**; and (3) protonation of the methoxy ion by the in situ-generated *t*BuOH. The rate-determining step is the second step (C–N bond formation and amide dissociation; higher energy barrier of 30.2 kcal/mol) (Scheme 31).

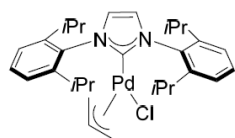


**Scheme 31.** Key intermediates (**I**) and transition states (**TS**) in DFT calculations for the acid–base mechanism of manganese-catalyzed aminolysis of ester.

Another trend in amide synthesis is the use of palladium-based catalysts for cross-coupling reactions between esters and amines. Since being first described in 2017 by Newman [118], other procedures have been proposed (Szostak in 2017 and Hazari in 2018) [119,120]. It is important to mention that, in all cases, activated aryl esters and aniline derivatives were used as substrates. In general, Pd-NHC complexes were used and reactions required high temperatures (110 °C) and excess of a base (Scheme 32). In the case of Hazari's work, amides could be formed in milder conditions by using both lower reaction temperatures (40 °C) and lower catalyst loading (1 mol%). These pioneering works on Pd-catalyzed cross-coupling of phenyl esters and anilines may offer a different reactivity towards aryl amides synthesis that cannot be achieved by other means. Despite some improvement towards more stable and easy-to-access catalytic systems (e.g., [Pd(NHC)(acac)Cl] pre-catalyst for phenolic esters cross-coupling (one example)) [121], mechanism elucidation for the use of unactivated esters with general amines (not only aromatic ones) is necessary to achieve more general amidation processes. To date, analogous to precedents in ketone synthesis from esters and biaryls [122–128], it is assumed that the Pd(0)-NHC active catalyst makes the oxidative addition into the ester C–O bond, followed by the reaction of the intermediate Pd(II) complex with the aniline partner.


**Conditions A (Newman 2017)**

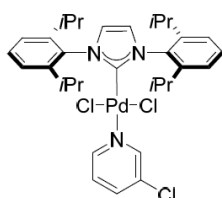
ester (1.0 equiv), amine (1.2 equiv)  
 Pd(IPr)(allyl)Cl (3 mol%)  
 K<sub>2</sub>CO<sub>3</sub> (1.5 equiv)  
 H<sub>2</sub>O (10 equiv)  
 Toluene, 110 °C, 16 h, argon  
 > 32 examples



Pd(IPr)(allyl)Cl

**Conditions B (Szostak 2017)**

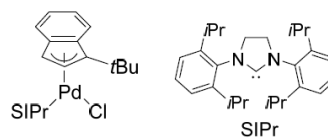
ester (1.0 equiv), amine (2.0 equiv)  
 Pd-PEPPSI (3 mol%)  
 K<sub>2</sub>CO<sub>3</sub> (3.0 equiv)  
 DME (0.25M)  
 110 °C, 16 h, argon  
 > 25 examples



Pd-PEPPSI

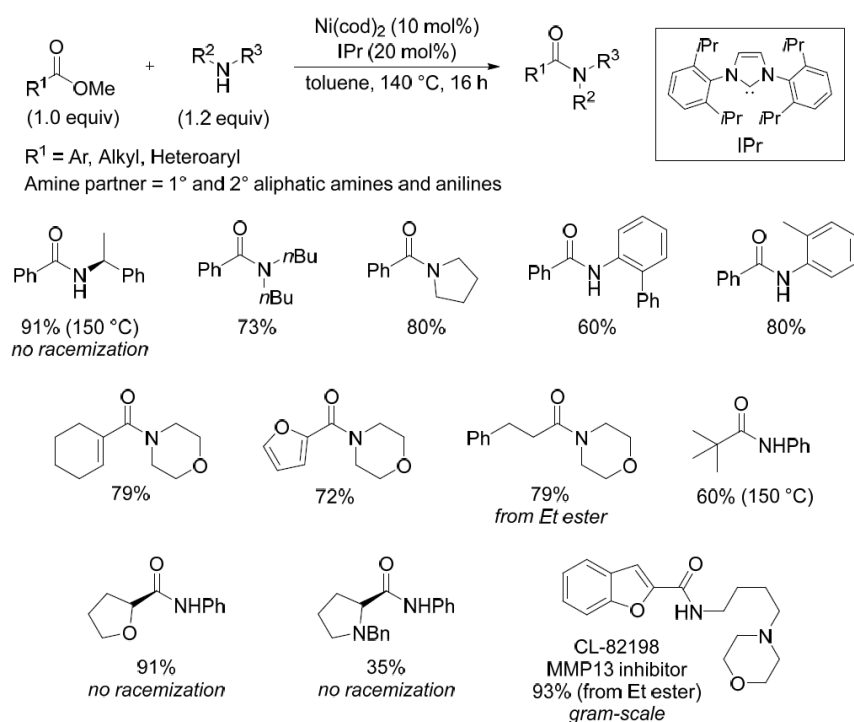
**Conditions C (Hazari 2018)**

ester (1.0 equiv), amine (1.2 equiv)  
 (η<sup>3</sup>-1-*t*-Bu-indenyl)Pd(SIPr)(Cl) (1 mol%)  
 Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv)  
 H<sub>2</sub>O/THF 4:1  
 40 °C, 4 h, N<sub>2</sub>  
 > 20 examples

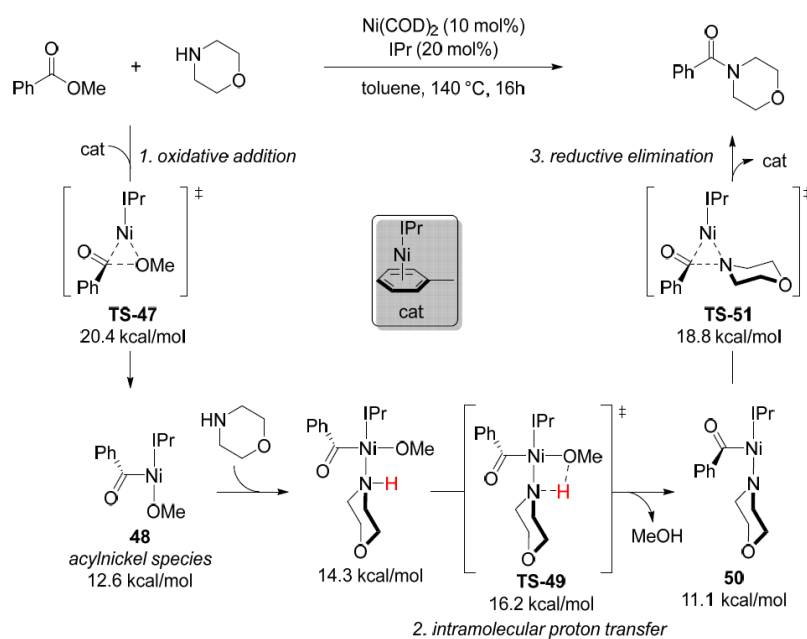

 (η<sup>3</sup>-1-*t*-Bu-indenyl)Pd(SIPr)(Cl)

**Scheme 32.** Palladium-catalyzed cross-coupling of aryl esters and anilines.

In 2018, Newman reported the merging of the Ni/NHC catalytic system for direct amidation of methyl esters in the absence of an external base (Scheme 33) [129]. This combination allows quite broad functional tolerance for methyl esters (aryl and alkyl substituted) and amines (primary and secondary aliphatic amines and aniline derivatives). Typically, the reaction conditions involve Ni(cod)<sub>2</sub> (10 mol%) and 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr) (20 mol%) as ligands in toluene at 140 °C for 16 h. The reaction has broad scope, obtaining around 50 amides in good yields. Although quite general, some improvements in terms of catalyst loading and temperature deserve to be considered. Soon after, the same group reported structures of many other ligands (NHC, phosphine, and nitrogen-containing ligands) compatible with this Ni-catalyzed coupling reaction and were able to improve on difficult transformations [130].


**Scheme 33.** Acid/base-free-Ni/IPr-catalyzed cross-coupling of methyl esters and amines.

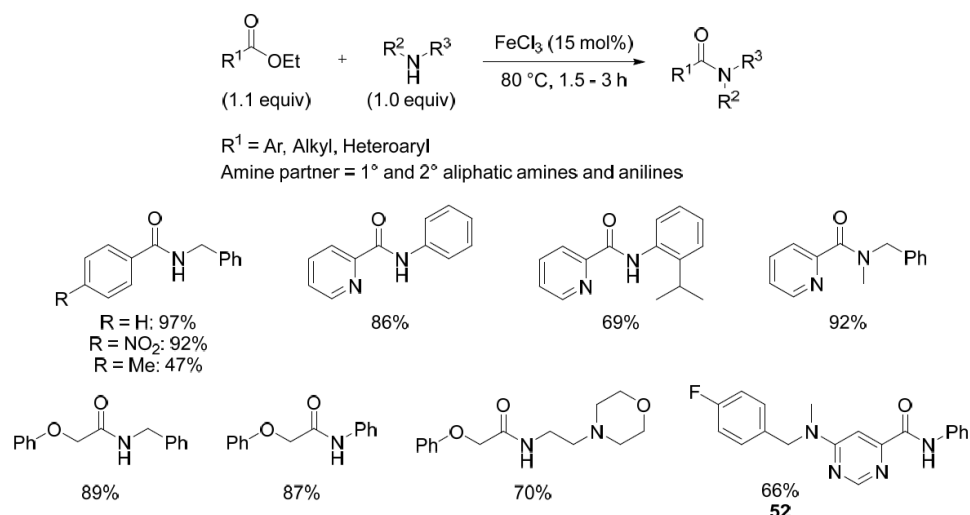
Concerning the reaction pathway, it has been argued that the reactions proceed through a neutral cross-coupling mechanism, which differs from classical acidic and basic activation of ester and amine substrates, respectively [123,124,131,132]. These assumptions are supported by DFT calculations by Hong (Scheme 34) [133]. The coupling reactions involve: (1) sequential oxidative addition of the catalyst into the C-O bond on the ester partner to obtain the acylnickel species **48** (via **TS-47**); (2) an intramolecular proton transfer (via **TS-49**) to form the Ni(II) amido complex **50**; and (3) reductive elimination via **TS-51** with concomitant product liberation and catalyst regeneration. As highlighted in Pd-catalyzed cross-couplings of esters and anilines, the bulky NHC ligand on the acylnickel species prevents decarbonylation.



**Scheme 34.** Key intermediates (**I**) and transition states (**TS**) in DFT calculations for Ni/IPr-catalyzed cross-coupling of aromatic methyl esters and amines.

In 2020, Moshapo reported the use of Fe(III) chloride salts as a low-priced and readily available Lewis acid catalyst to achieve direct amidation from esters [134]. The reaction conditions devised also have the advantage of being solvent-free and having lower temperatures requirements and shorter reactions times (80 °C at 1.5–3 h) (Scheme 35). The amidations were compatible with primary and secondary amines and with ethyl esters bearing aromatic and aliphatic functionalized backbones. Products were isolated in good yields and the procedure has found a synthetic application in the synthesis of the potential antitubercular pyrimidine carboxamide **52**. Furthermore, 2-pyridinecarboxamides were obtained using the devised conditions. For this class of compound, the authors ascribed the reactivity to iron coordination with the carbonyl oxygen and the pyridine nitrogen atoms, producing a stabilized intermediate complex prone to amidation. Indeed, 3-pyridinecarboxylate fails to produce the expected amide product.



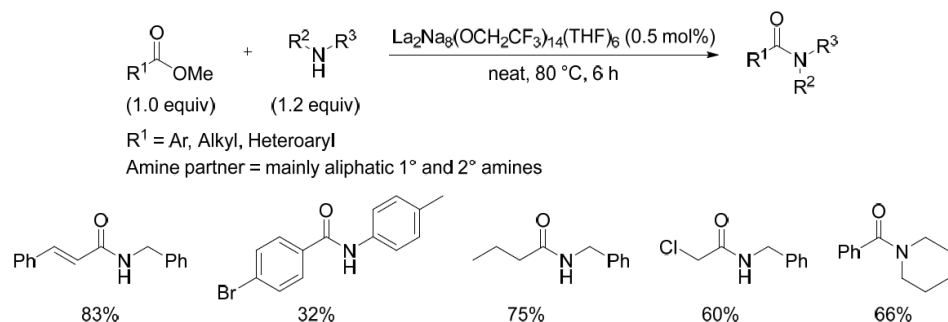


**Scheme 35.** FeCl<sub>3</sub> as Lewis acid catalyst for direct amidation from esters.

The amidation of unactivated methyl esters under continuous-flow conditions was recently achieved using a heterogeneous zirconium-oxide catalyst (amorphous zirconia) [135]. Although improvements are required in order to expand the scope of this reaction, to reduce reaction temperatures and to improve kinetics, this approach is very stimulating, as it breaks ground towards more sustainable alternative techniques and suggests future directions for direct amide synthesis from unactivated esters.

### 3.2. Lanthanide-Derived Catalysts

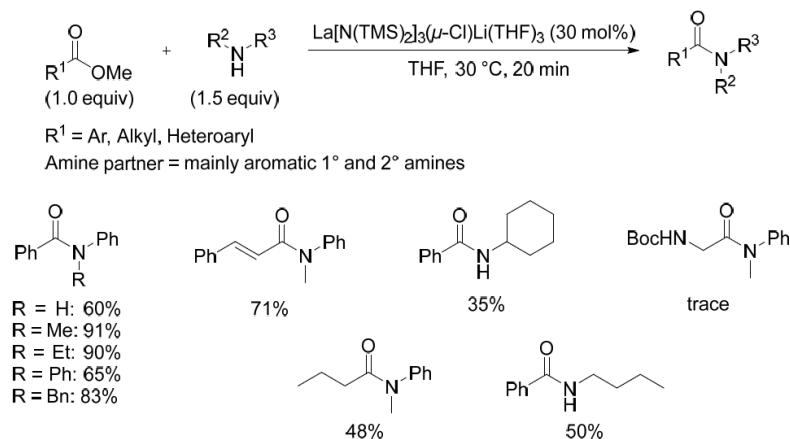
Along with examples in which transition metal-catalysis has been successfully used in the direct amidation of esters with amines, the use of rare-earth elements has emerged in recent years. In a seminal work by Yao and Yuan, published in 2018, a heterobimetallic lanthanum-sodium complex was used as an efficient catalyst for methyl ester amidation (Scheme 36) [136]. The reaction conditions were quite mild (ester:amine ratio 1:1.2, 80 °C, solvent-free, 6 h, with 0.5 mol% La<sub>2</sub>Na<sub>8</sub>(OCH<sub>2</sub>CF<sub>3</sub>)<sub>14</sub>(THF)<sub>6</sub>) and the scope was relatively broad (>35 amides). Nevertheless, yields for anilines as substrates were low, generally below 50%. The authors supposed that the heterobimetallic catalyst might simultaneously activate the ester and the amine substrates. Thus, an ‘intramolecular amidation’ might take place instead of the usually intermolecular reaction.



**Scheme 36.** Heterobimetallic La-Na complex for direct amidation from esters.

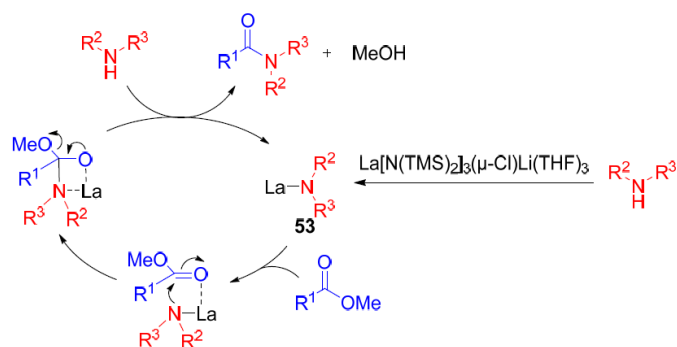
Soon after, the scope for primary or secondary reluctant anilines was improved by using the lanthanide tris(amide) complexes Ln[N(SiCH<sub>3</sub>)<sub>2</sub>](μ-Cl)Li(THF)<sub>3</sub>. In contrast with the use of the heterobimetallic lanthanum-sodium complex, 30 mol% of catalyst was necessary in this particular case to achieve good reaction outcomes [137]. Nevertheless, and quite remarkably, amidations (≈25 examples) took place at 30 °C in only 20 min in THF. Aromatic methyl esters were mainly used, but a few examples with aliphatic esters

were also reported. No reactivity was observed when Boc-protected glycine methyl esters were engaged in combination with secondary anilines (Scheme 37).



**Scheme 37.** La-complex for direct amidation from esters and anilines.

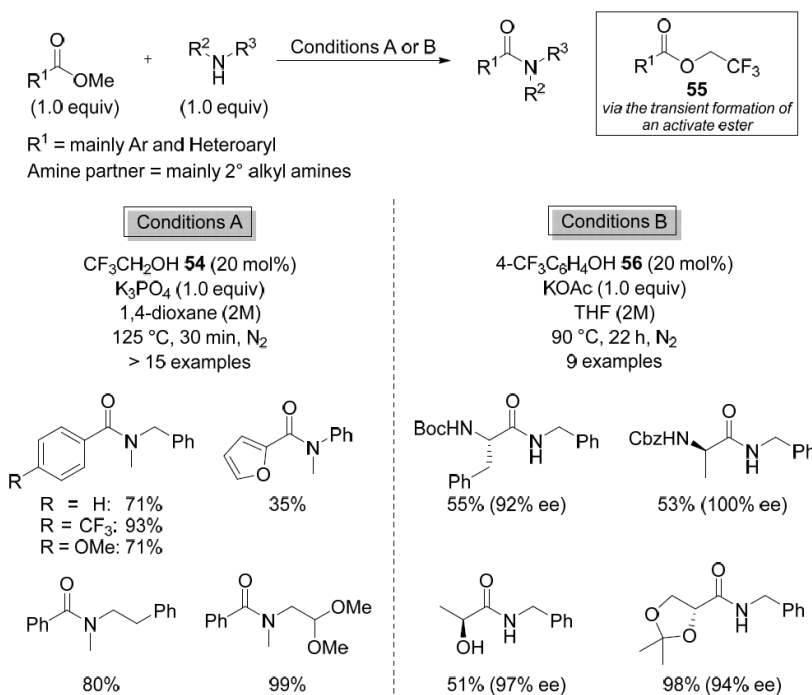
$^1\text{H}$  NMR monitoring combined with experimental controls suggests a mechanism that differs from classical processes, which mostly start from ester activation (Scheme 38). It is assumed that the first stage is amine deprotonation by the catalyst, producing intermediate **53**. After nucleophilic attack from **53** on the ester substrate, an amide and a lanthanide methoxide complex is formed, which, in turn, can deprotonate a second amine molecule to regenerate **53** and restart the catalytic cycle. It is believed that the MeOH side compound might react with **53** and produce some inactive species, explaining the need for such a high catalyst loading (30 mol%) in this particular case.



**Scheme 38.** Mechanism pathway for La-complex direct amidation from esters and anilines.

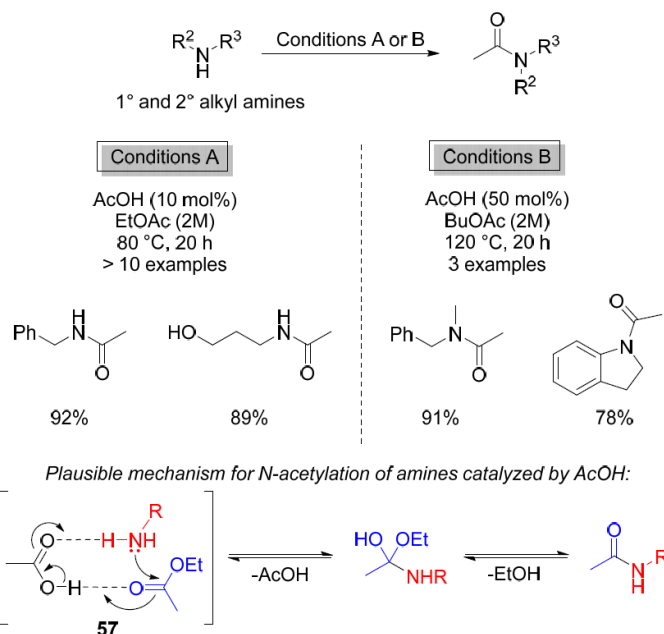
### 3.3. Miscellaneous

In 2017, Jamieson developed an organocatalyzed procedure for amidation of unactivated methyl esters through the use of trifluoroethanol (**54**, TFE; 20 mol%) [138]. The rationale behind using an alcohol as additive was to form the activated ester intermediate **55** via a preliminary transesterification. A notable advantage of this method is that the reaction conditions can be tuned to improve both the reaction scope and the stereoretention of chiral ester substrates. While the combination of TFE/ $\text{K}_3\text{PO}_4$  was effective for aminolysis of esters with primary and secondary alkyl amines, it was observed that such a mixture is incompatible with chiral esters (such as aminoester derivatives), for which complete epimerization was observed. The authors observed a strong relationship between the strength of the base and the epimerization levels. Thus, using 4-(trifluoromethyl)phenol (**56**) as the alcohol additive ( $\text{pK}_a$  9 vs. 12.5 for TFE) and replacing  $\text{K}_3\text{PO}_4$  for KOAc ( $\text{pK}_a$  values 12.3 and 6, respectively) allowed amidation processes in an epimerization-free manner from enantiopure esters (Scheme 39).



**Scheme 39.** Organocatalyzed approach for amide synthesis from esters and amines.

Furthermore, in 2017, Williams proposed acetic acid as an organocatalyst for the *N*-acetylation of primary and secondary alkyl amines, with either ethyl or butyl acetate as the acyl donor (Scheme 40) [139]. Due to the lower nucleophilicity of secondary amines, harsher reaction conditions were necessary to ensure good conversions. Based on experimental observations, the authors postulated that the transformation proceeds via a transition state involving acetic acid instead of a single proton (**57**). Such an approach was previously suggested by Whiting in 2011 [16]. Furthermore, peptide bond formation using pivalic acid as a Brønsted acid catalyst in a biomimetic manner was proposed by Yamamoto and Nakashima [140]. The method offers dipeptide production in a less costly and more environmentally-friendly manner, and could be transposed to flow chemistry. While the method required quite a high catalyst loading (50–100 mol%), the reaction conditions were mild (either 70 °C in THF for 72 h or room temperature in THF for 2–48 h) and compatible with classical *N*-urethane protecting groups in peptide chemistry (Boc, Cbz, Fmoc). It is important to mention that no notable racemization was detected when reactions were run at room temperature (up to 99:1 dr).



**Scheme 40.** Organocatalyzed approach for *N*-acetylation of amines using EtOAc or BuOAc.

In the field of direct *N*-acylation of amines by esters, plasma flow chemistry was used in 2022, obtaining amides from *tert*-butyl esters and primary and secondary aliphatic/cyclic amine and aniline derivatives [141].

Direct mechanochemical amidation of methyl and ethyl esters has been described [142]. The used strategy was applicable to a wide-ranging of substrates (ester and amines) and generated a large library of amides (>70 examples) under solvent-free conditions. While this emerging technic can also be successfully applied to the synthesis of APIs and agrochemicals, as well as transposed to the gram-scale synthesis of moclobemide, the procedure still requires substoichiometric amounts of *KOtBu* (85 mol%).

More recently, Lee and Maruoka identified a catalytic approach for *p*-hydroxyphenyl ester activation based on the combination of 4-iodoanisole (30 mol%)/*m*-chloroperoxybenzoic acid (MCPBA) (1.5–3.0 equiv.)/HF·pyridine (2.0 equiv.) for the in situ generation of a hypervalent iodine(III) [143]. The *p*-hydroxyphenyl group on the ester moiety acts as an activating group that combines with hypervalent iodine(III) species to produce a reactive acyl fluoride intermediate through oxidative dearomatization of phenols. The reaction conditions proposed were suited to amides (11 examples) and dipeptides (five examples). While the scope was somewhat narrow (only two amines were used: 1-phenylethylamine for 'general' amides and L-alanine methyl ester hydrochloride for dipeptides), it might be mentioned that the reluctant encumbered  $\alpha,\alpha$ -dialkyl- $\alpha$ -amino ester gave good yields (2 examples).

#### 4. Conclusions

Our motivation to write this review was to present a general overview of recent catalytic methods that enable amide bond formation from amines and carboxylic acids or esters. Rather than producing a novel review on amidation reactions, a subject that is covered widely and well in the literature, the idea here was to focus on direct carboxylic acid or ester aminolysis (without the need for an additional activation step). Though such topics have been partially covered in the literature, our goal was to emphasize the mechanistic aspects and comment, when possible, on novel technologies, limitations in substrate scope, racemization issues, practicability and scalability. Many amidation reactions can be efficiently catalyzed; however, difficult challenges remain. For example, simpler and more accessible catalytic systems associated with milder and more practical reaction conditions are crucial to promote novel methods to synthetic chemists in both academia and

industry. Thus, we have tried to show that, even though tremendous efforts led to quite elegant and efficient strategies, there is still room for further improvements. Due to the omnipresence of amides in biology and chemistry, amide bond formation is a constantly evolving research field. Future works should be directed towards more practical and milder reaction conditions in order to address the main gaps in this field (e.g., broader substrate tolerance, compatibility with organic, medicinal and peptide chemistry requirements, racemization issues, atom economy, etc.).

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