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# Catalytic and Sustainable Amide Bond Formation using a DABCO/Dichlorotriazine System

Pauline Adler,<sup>\*,[a]</sup> Marion Gras,<sup>[a]</sup> and Michael Smietana<sup>\*,[a]</sup>

Amides are one of the most important functional groups in organic chemistry and play essential roles in both the pharmaceutical industry and life sciences. However, due to the natural reactivity of carboxylic acids and amines, their direct coupling is challenging and often leads to reactions that are not atom-economic and produce large amounts of non-recoverable by-products. Despite the impressive number of coupling reagents available, sustainable methods for amide

bond formation are still needed. To address this challenge, a new catalytic approach for the direct preparation of amides from carboxylic acids and amines is reported here. This method combines organocatalysis with a substoichiometric amount of activating agent under mild conditions (open air, room temperature, green solvents). This method was applied with good efficiency on a wide range of substrates, without epimerization of chiral stereocenters and on SPPS.

## Introduction

The amide functional group is one of the most important in organic synthesis, with a wide range of applications in different fields. For example, therapeutic peptides have demonstrated their effectiveness in pharmaceutical chemistry,<sup>[1]</sup> and approximately 25% of marketed drugs and two-thirds of drug candidates contain at least one amide function.<sup>[2]</sup> Furthermore, the use of amides in material and polymer chemistry is of great importance, such as for OLED applications,<sup>[3]</sup> dentistry,<sup>[4]</sup> or nanocomposites.<sup>[5]</sup> In organic synthesis, amides are also significant, owing to their outstanding reactivity as nucleophiles. The Maulide group, in particular, has demonstrated their utility in recent years for structural modifications, including alpha-substitution,<sup>[6–8]</sup> desaturation<sup>[9]</sup> or synthesizing heterocycles.<sup>[10,11]</sup>

The interest in amides has been steadily increasing, as new methods for their preparation continue to emerge.<sup>[12]</sup> There are numerous ways to create an amide bond, including classical peptide synthesis methods, which are highly effective. However, these methods require the use of at least stoichiometric amounts of activating reagents and often involve hazardous solvents. This leads to the production of large quantities of waste, which is even more problematic for industrial scale-up.<sup>[13,14]</sup>

The development of environmentally-friendly methods for amide bond formation is crucial, as demonstrated by the

emergence of innovative techniques<sup>[15]</sup> that use non-activated starting materials,<sup>[16]</sup> solvent-free processes,<sup>[17–19]</sup> electrochemical reactions,<sup>[20,21]</sup> or catalysis.<sup>[22–27]</sup>

Two types of catalysts have been developed for amide synthesis: enzymes<sup>[28]</sup> and Lewis acids (boron-based<sup>[23,29–31]</sup> and metal-based catalysts<sup>[32,33]</sup>).<sup>[34]</sup> These methods have demonstrated cost-effectiveness and broad applicability. However, with the impressive number of recent reviews on sustainable amide synthesis progress,<sup>[35–49]</sup> it is clear that this topic is still of great importance, and there is an urgent need for new, environmentally-friendly approaches.

Chloro-triazine and in particular cyanuric chloride (2,4,6-trichloro-1,3,5-triazine or TCT) or 2-chloro-4,6-disubstituted-1,3,5-triazines are a family of condensing reagents having multiple activating sites.<sup>[50–54]</sup> They are among the most used to promote efficiently amide formation in substoichiometric quantities (Figure 1).<sup>[55–57]</sup> The group of Huy has recently developed an efficient method using TCT as activating agent.<sup>[58]</sup> The latter is activated with catalytic formamide to access acyl chloride intermediates, which further react with amines. While this method offers significant advantages in terms of efficiency and cost compared to classical amide formation methods, the toxicity and hazards of TCT remain a concern (Figure 1a).<sup>[59]</sup> Chloro-disubstituted triazines are safer reagents,<sup>[57,60,61]</sup> but require the use of a tertiary base, typically NMM (*N*-methylmorpholine), which leads to the formation of an ammonium chloride intermediate (Figure 1b). This intermediate, known as DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride), is an effective coupling agent that can be used in pure water or with a co-solvent.<sup>[62,63]</sup> DMTMM can be prepared or purchased<sup>[55,64,65]</sup> and has been used for late stage amide synthesis,<sup>[66,67]</sup> unfortunately with moderate yields on highly functionalized structures. The main drawback of the DMTMM reagent is the release of 1 equivalent of NMM. Numerous reports describe the use of other tertiary amines to replace NMM and compare the reactivity of the “DMTMM-like” reagents.<sup>[18,68–73]</sup> Kunishima *et al.* have reported an elegant catalytic system involving a tertiary amine-substituted cyclo-

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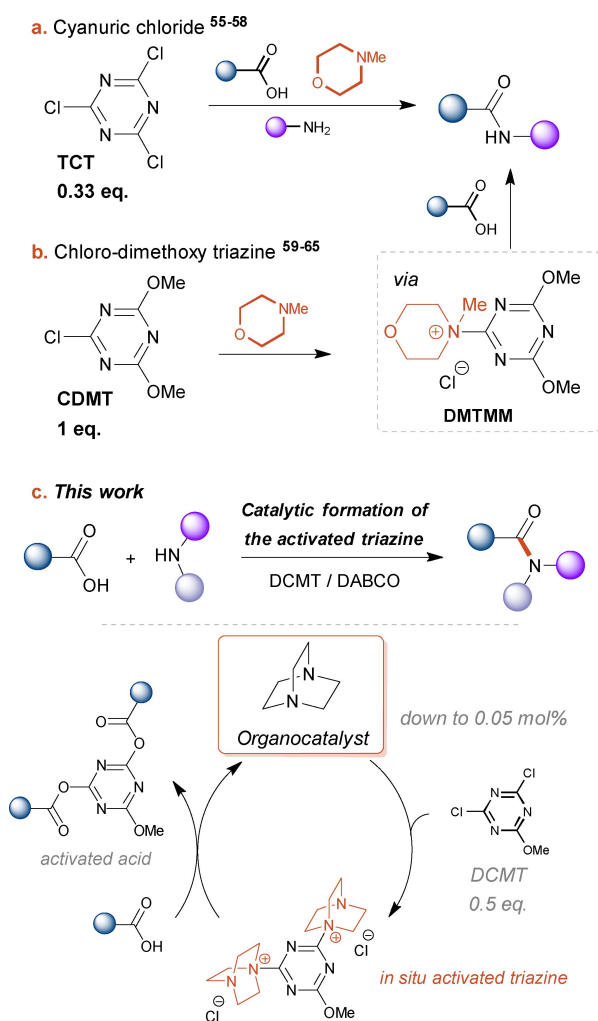


Figure 1. Triazine-based coupling reagents.

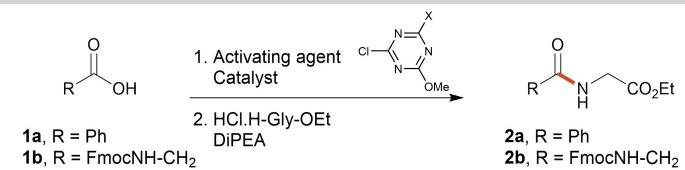
dextrin and CDMT for the direct synthesis of amide in an aqueous solvent.<sup>[74]</sup> Moreover, the group of Beghetto has shown that 1,4-dimethylpiperazine was more efficient than NMM for the activation and that 0.5 eq. of tertiary amine was sufficient to promote the reaction.<sup>[69]</sup>

However, their report did not explore a catalytic approach. More recently, the same group investigated the stoichiometric use of triazine reagents synthesized from 2,4-dichloro-6-methoxy-1,3,5-triazine and various tertiary amines to form amides derived from phenethylamine. However, the *in situ* formation and evaluation of these activating agents was not reported.<sup>[70]</sup> We report herein an operationally simple catalytic system that employs dichlorotriazine as an activating agent and a tertiary amine as the promoter for direct amidation from carboxylic acids and amines (Figure 1c). This activating agent was compared to other triazine reagents, or more common carboxylic acid activators.

## Results and Discussion

As a proof of concept, we desired to prepare DMTMM *in situ* with 10 mol% of *N*-methylmorpholine as a catalyst (Table 1, Entry 1), benzoic acid **1 a**, and glycine ethyl ester hydrochloride in the presence of 1.1 equiv. of 2-chloro-4,6-dimethoxy-1,3,5-triazine. The reaction was run in the eco-friendly solvent 2-MeTHF for 18 h. We were pleased to observe that the resulting amide was formed in a good 64% NMR yield. Different tertiary amines were then screened as catalyst (see the supporting information for fully detailed optimizations considering catalyst, solvent, temperature, time of activation, time of reaction, base, and stoichiometry) and DABCO turned out to be the most efficient (Table 1, Entry 2) with an excellent 93% yield. This result was particularly interesting knowing the reported degradation of the proposed intermediate (2,4-bis(DABCO + Cl<sup>-</sup>)-6-methoxy-1,3,5-triazine).<sup>[75]</sup> As a controlled experiment, the absence of catalyst failed to yield traces of product (Table 1, Entry 3). Our proof of concept achieved using 1.1 equivalent of 2-chloro-4,6-dimethoxy-1,3,5-triazine, we decided to lower the amount of activating agent by using 0.5 equivalent of 2,4-dichloro-6-methoxy-1,3,5-triazine. Using the same amount of DABCO (Table 1, Entry 4), the desired amide was formed in an excellent 96% NMR yield. Decreasing the catalyst loading to 1 mol%, 0.1 mol% and 0.05 mol% led to a slow decrease of the NMR yields (Table 1, Entries 5–7). Unfortunately, this coupling system was not suitable with aqueous media, as the NMR yield dropped to 37% in an acetonitrile/water solvent system, probably due to the instability of DCMT in water (Table 1, Entry 8). We finished our investigation using Fmoc-glycine **1 b** as carboxylic acid partner. Using the classical conditions, we encountered solubility issues that led to a poor 20% yield (Table 1, Entry 9). We thus decided to pursue our optimization efforts on this particular substrate. The substrate was not soluble in 2-MeTHF which was thus replaced with ethyl acetate and the dilution was increased by a factor of 4 to reach full solubilization. In these conditions, the yield increased to 53% (Table 1, Entry 10). We hypothesized that the modest yield could be explained by a lack of reactivity of the activated carboxylic acid. Inspired by the work of Baran on the total synthesis of vinigrol,<sup>[76]</sup> where DMAP (10 mol%) was added to a DMTMM-promoted amide synthesis, we decided to add 10 mol% of DMAP and to slowly introduce over 30 minutes the mixture of ammonium chloride, DiPEA and DMAP in the solvent system EtOAc:DCM (5:2), due to the poor solubility of the ammonium salt in ethyl acetate (Table 1, Entry 11). We were pleased to achieve an excellent 85% isolated yield in these conditions and kept the latter for the scope. For the study of the scope, a minimum amount of dichloromethane was used exclusively when the ammonium chloride was not soluble in ethyl acetate.

Table 1. Optimization of the reaction.



1. Activating agent  
Catalyst

2. HCl.H-Gly-OEt  
DiPEA

**1a**, R = Ph  
**1b**, R = FmocNH-CH<sub>2</sub>

**2a**, R = Ph  
**2b**, R = FmocNH-CH<sub>2</sub>

Entry <sup>[a]</sup>	Activating agent	R	Catalyst	Catalyst loading [mol%]	Solvent	Yield [%] <sup>[b]</sup>
1	X = OMe	Ph	NMM	10	2-MeTHF	64
2	X = OMe	Ph	DABCO	10	2-MeTHF	93
3	X = OMe	Ph	none	10	2-MeTHF	Traces
4 <sup>[c]</sup>	X = Cl	Ph	DABCO	10	2-MeTHF	96
5 <sup>[c]</sup>	X = Cl	Ph	DABCO	1	2-MeTHF	90
6 <sup>[c]</sup>	X = Cl	Ph	DABCO	0.1	2-MeTHF	85
7 <sup>[c]</sup>	X = Cl	Ph	DABCO	0.05	2-MeTHF	78
8 <sup>[c]</sup>	X = Cl	Ph	DABCO	0.1	ACN/H <sub>2</sub> O (1:1)	37
9 <sup>[c]</sup>	X = Cl	FmocNHCH <sub>2</sub>	DABCO	10	2-MeTHF	20 <sup>d</sup>
10 <sup>[c]</sup>	X = Cl	FmocNHCH <sub>2</sub>	DABCO	10	EtOAc (0.05 M)	53 <sup>d</sup>
11 <sup>[c]</sup>	X = Cl	FmocNHCH <sub>2</sub>	DABCO + DMAP	10 + 10	EtOAc (0.05 M) + min. DCM	85 <sup>d</sup>

[a] Reactions were run on 0.2 mmol scale. Benzoic acid (1 eq.), triazine (X = OMe, 1.1 eq. or X = Cl, 0.5 eq.) and catalyst were mixed in the solvent (0.2 M) and stirred 1 hour at room temperature. A solution of glycine ethyl ester hydrochloride and DiPEA in the solvent was added to the reaction mixture and let 18 hours under stirring at room temperature. [b] Yields refer to <sup>1</sup>H NMR yields on the crude residue using 1,3,5-trifluorobenzene as reference. [c] 30 minutes of activation and 1 hour of reaction. [d] Isolated yield. *Abbreviations:* DiPEA: di-isopropylethylamine; NMM: *N*-methylmorpholine; DMA: *N,N*-dimethylacetamide; ACN: acetonitrile; THF: tetrahydrofuran; DABCO: 1,4-diazabicyclo[2.2.2]octane.

## Study of the scope

With optimized conditions in hand, we then evaluated the scope of the reaction. We started our investigation by varying the nature of the carboxylic acid (Figure 2).

Both electron-rich and electron-poor benzoic acids yielded the corresponding amides **2c** and **2d** respectively in good yields. The method also proved its efficiency with aliphatic carboxylic acid to prepare **2e** in a good 84% yield. Turning our attention to the synthesis of dipeptides we have noticed a decrease in yield with the Boc protecting group on glycine (**2f**) compared to the Fmoc analogue (**2b**). However, using *N*-Boc protected benzylated glutamic acid (**2g**), the yield was slightly better.  $\alpha$ -Substituted amino-acids, such as *N*-Fmoc-*S*-trityl-protected cysteine (**2h**) and *N*-Fmoc-phenylalanine (**2i**) were excellent substrates for this coupling. For the latter, the enantiopure amide **2i** was prepared as the sole stereoisomer, proving the non-racemization of this stereogenic center during the reaction (see the supplementary materials for chiral HPLC details). Using Fmoc-valine, the yield decreased slightly to 64% (**2j**) probably due to steric hindrance. The bulky carboxyl **2k** was prepared in a moderate yield with this method, despite a longer activation time of 3 hours. Pleasingly our method showed good efficiency with heteroaromatic compounds, such as thiophene (**2l**, 84%) and furan (**2m**, 85%). However, the presence of pyridine core led to poor yield.

Concerning the scope of the amine we showed that primary amine hydrochlorides are good partners leading to the corresponding amides **2a** and **3a–3d** in good yields. Moreover, no racemization could be observed using enantiopure alanine ethyl ester (**3b**). Dibenzylated glutamic acid yielded very efficiently to the corresponding amide **3c** in an excellent 88% yield. The less nucleophilic aniline reacted as well leading to the

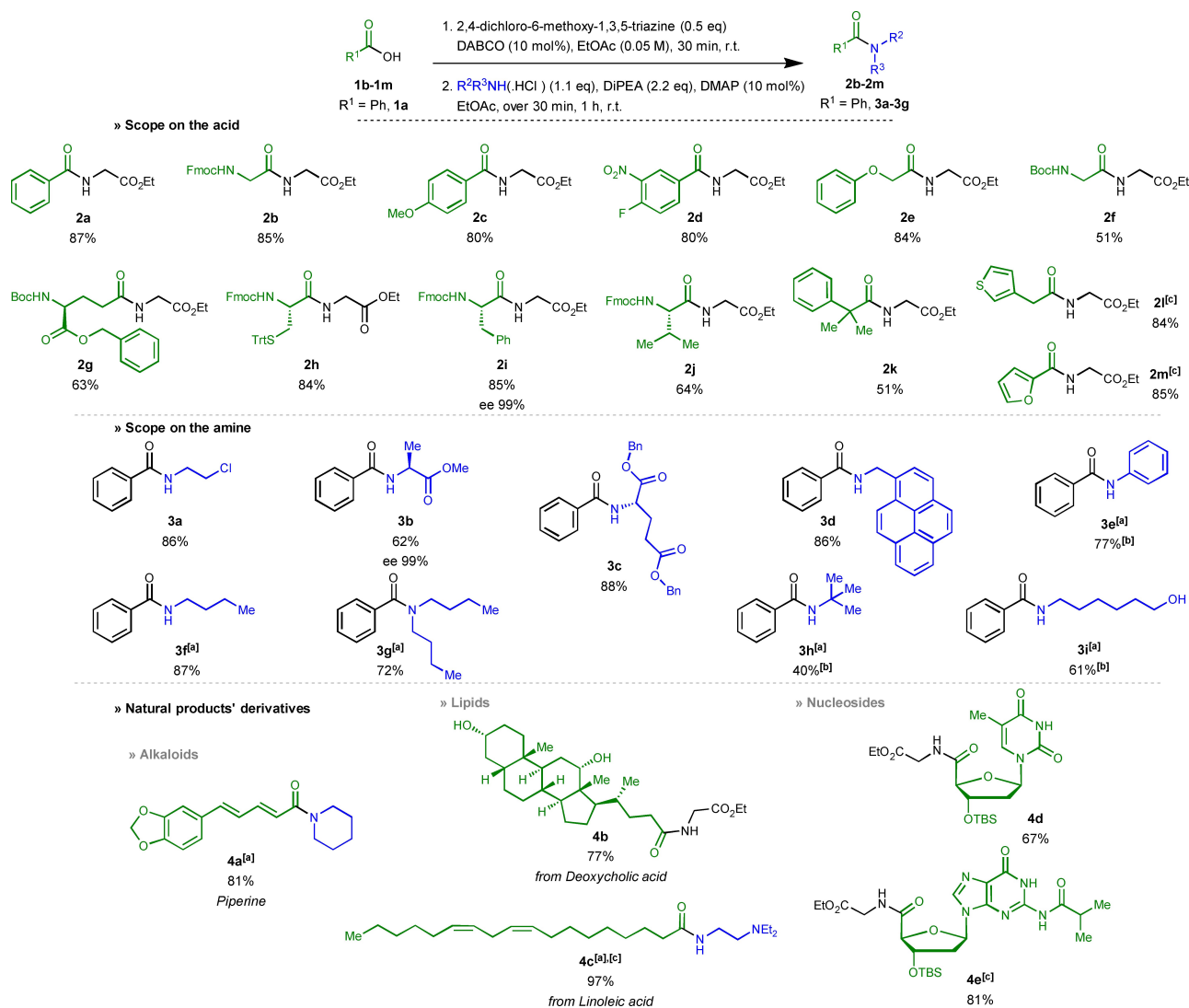
expected amide **3e** within 77% yield. In the case of aliphatic free amines *n*-butylamine was very efficient (**3f**, 87%) whereas a slight decrease in yield was observed using di-*n*-butylamine (**3g**, 72%). However, a significant drop of the yield was observed for the sterically hindered *tert*-butylamine (**3h**, 40%). The preparation of the amide **3i** from 6-aminohexan-1-ol showed the total chemoselectivity of this reaction for the amine towards unprotected alcohols.

For unclear reasons, it appeared that DMAP was detrimental to the reaction in some cases. The protocol was slightly modified to obtain a better yield for those compounds (**3e**, **3h** and **3i**). Finally, we applied our methodology to the synthesis of natural product and bioconjugates. We prepared in a good 81% yield the alkaloid piperine **4a**, a major bio-active component of pepper, that exhibits beneficial therapeutic properties.<sup>[77]</sup> Derivatives of biomolecules, such as lipids and nucleosides were also prepared. The deoxycholic acid, a complex lipid, led the corresponding amide (**4b**) in good 77% yield while the amide **4c** from linoleic acid was obtained in excellent 97% yield. It must be noted that the amine partner for the preparation of **4c**, as a diamine, was not detrimental to the efficiency of the reaction. Considering nucleotides analogues, we prepared **4d** in good yield starting from 5'-carboxylic acid 2'-deoxythymidine. Better yield was obtained from the analogous 5' oxidized 2'-deoxyguanosine (**4e**).

Scaling up the reaction of **1i** with glycine from 1 mmol to 10 mmol did not affect the yield of the reaction (86 vs 85%).

## Solid phase peptide synthesis

To showcase its efficiency and to demonstrate its utility, we applied our conditions to solid phase peptide synthesis (see



**Figure 2.** Scope of the reaction. [a] From free amine, no dichloromethane was necessary. [b] No DMAP, solvent was 2-MeTHF, addition of the amine in one time, [c] 0.5 eq of DCMT and 1 eq of amine were added after 1 hour of reaction to achieve full completion.

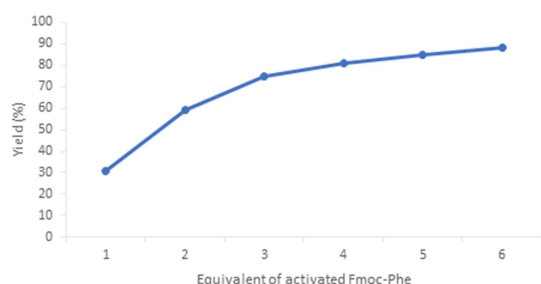
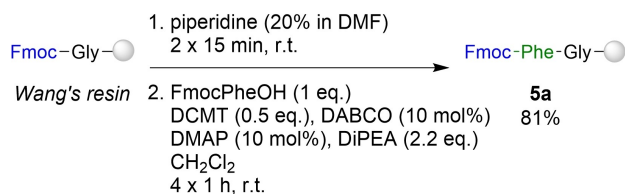
Supporting information for details). Yields were calculated by Fmoc titration and the absorption of dibenzofulvene at 301 nm. Optimization was performed adding one by one equivalent of activated Fmoc-phenylalanine to prepare the dipeptide **5a**. A plateau is reached with around 4 equivalents that we kept for the scope as a good compromise (Figure 3). We performed a short scope of this method with the synthesis of two tripeptides **5b** and **5c** and a tetrapeptide **5d**. Each step was done either with the DCMT/DABCO system or with HATU as comparison, followed by a capping with acetic anhydride. For both tripeptides **5b** and **5c** it is notable that the incorporation of the bulky trityl protected cysteine is as efficient with our method as with HATU. The next introduction of phenylalanine to access **5b** or of another bulky cysteine to form **5c** showed a small decrease in yield compared to HATU. For the preparation of the tetrapeptide **5d**, all incorporations with DCMT/DABCO were as efficient as the ones using HATU. This scope showed the

applicability of the developed method for the preparation of this family of biomolecules.

### Comparison to the literature – sustainability of the method

We then decided to compare the efficiency of our method to classical activating agents, such as HATU, PyBOP/HOBt, EDCl·HCl/HOBt and DMTMM. The synthesis of **2i** on a 1 mmol scale was chosen as model (Table 2). We reproduced conditions found in the literature to compare the efficiency on the same 1 mmol scale. HATU yielded to 80% yield for the formation of the dipeptide **2i** (Table 2, entry 2).<sup>[78]</sup> The system PyBOP/HOBt was the most efficient with an excellent 97% yield (Table 2, entry 3).<sup>[79]</sup> EDCl·HCl/HOBt led to a lower 76% yield (Table 2, entry 4),<sup>[80]</sup> comparable to the 73% yield obtained using DMTMM (Table 2, entry 5).<sup>[67]</sup> Compared to the literature, our method is favorably positioned in terms of yields (86%).

## » Optimization



## » Peptide synthesis

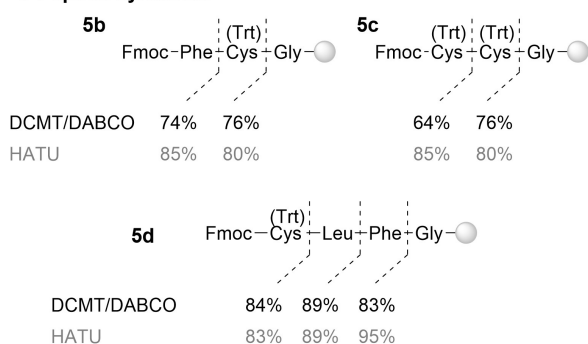


Figure 3. Solid phase peptide synthesis.

We then turned our attention to evaluating the green metrics of our conditions in comparison to those required with the well-known activating agents. Amide couplings are typically

considered poor atom economical reactions due to the use of stoichiometric amounts of activating agents and bases.<sup>[13,81]</sup> The classical methods showed an atom economy (AE) around 50% (Table 2, full description of experimental protocol and calculations can be found in the supplementary material). The catalytic system we developed allowed us to improve the AE of the reaction to 77%. However, the AE metric only considers the reactants and their stoichiometry, and not the use of potential bases, catalysts, or equivalents of reactants. To measure their impact more accurately, we used the reaction mass efficiency (RME). Our method showed the best RME compared to the methods in the literature, with an RME of 43%, while the other methods had an RME of around 30%. We attribute this result to the use of only 0.5 equivalent of triazine, which has two activating sites. Unfortunately, the use of 2.2 equivalents of the base remains a limitation.

If we consider the costs of the activating agents (found at the supplier Sigma-Aldrich) for the preparation of 1 mol of the final product **2i**, it clearly appears that this new DCMT/DABCO system is the most economical (3604 € per mol of final product) compared to the other system. This is mostly due to the 2 activating sites of the DCMT and the resulting 0.5 equivalent used in the reaction. Despite a slightly lower yield, the cost of our conditions are three times less compared to PyBOP/HOBt. Considering health and hazard issues (Table 2) DCMT is the less toxic system of all selected. Moreover, DCMT and HOBt are the only reagents that can be stored at room temperature while HATU and PyBOP need to be stored at 2–8 °C and DMTMM and EDCI·HCl at –20 °C.

Finally, in terms of thermal stability, explosivity and shock sensitivity, HOBt and PyBOP are known to be explosive, while EDCI or chlorinated agents such as chloro-dimethoxy-triazine were reported as most recommended,<sup>[82]</sup> highlighting even more the advantages of our method.

Table 2. Comparison to the literature.

Entry	Coupling agents	Yield [%]	AE [%]	RME [%]	Prices <sup>[a]</sup> [€/mol]	GHS
1	DCMT/DABCO	86	77	43	3 604	
2	HATU <sup>[78]</sup>	80	52	31	9 981	
3	PyBOP/HOBt <sup>[79]</sup>	97	40	30	11 907	
4	EDCI·HCl/HOBt <sup>[80]</sup>	76	55	27	6 196	
5	DMTMM <sup>[67]</sup>	73	59	29	24 450	

[a] Price of coupling agent for the synthesis of 1 mol of the final product following the reported procedures. Prices were found on the website of the supplier Sigma-Aldrich: <https://www.sigmaaldrich.com/FR/fr>.

## Conclusion

In conclusion, we have developed a sustainable method for amide bond formation that uses DABCO as an organic catalyst to activate the triazine activating reagent, which then activates the carboxylic acid. By lowering the catalyst loading to 0.05 mol%, we were able to achieve high yields without significant loss. Our method was shown to have a wide scope and did not result in epimerization during the reaction. Additionally, we demonstrated its efficiency compared to classical methods in batch and on SPPS. The *in-situ* formation of quaternary ammonium triazine prevents the usual degradation of the triazine by dealkylation of the ammonium, which is typically promoted by the chloride counter-anion. Our findings suggest that this method represents a major advance in sustainable reactions for amide formation from carboxylic acid and amine. We have proven its efficiency, atom economy, mass efficiency, cost-effectiveness, and health and hazard implications, as well as its storage conditions.

## Experimental Section

**General procedure for the formation of amides:** To a solution of carboxylic acid (1 mmol, 1 eq.) in ethyl acetate (20 mL) was added DABCO (10 mol%) and 2,4-dichloro-6-methoxy-1,3,5-triazine (0.5 eq.) at room temperature, under air. After 30 minutes of stirring at room temperature, the solution of amine (or ammonium chloride, 1.1 eq.), DiPEA (2.2 eq.) and DMAP (10 mol%) in AcOEt (5 mL and low amount of DCM for solubility, *eg* 2 mL) was added to the reaction mixture over 30 minutes with the syringe pump. After addition, the reaction was stirred for another 1 h at room temperature (monitored by TLC). After dilution in EtOAc and HCl (1 M), the organic phase was separated and washed with a saturated solution of NaHCO<sub>3</sub> then by water. After drying on sodium sulfate and evaporation, the crude residue was obtained and purified by automatic flash chromatography on silica.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** amide · catalysis · DABCO · triazine

[1] L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang, C. Fu, *Sig. Transduct. Target. Ther.* **2022**, *7*, 1–27.

- [2] X. Wang, *Nat. Catal.* **2019**, *2*, 98–102.  
 [3] Y. Qin, G. Li, T. Qi, H. Huang, *Mater. Chem. Front.* **2020**, *4*, 1554–1568.  
 [4] M. Vojdani, R. Giti, *J. Dent.* **2015**, *16*, 1–9.  
 [5] D. L. Francisco, L. B. Paiva, W. Aldeia, *Polym. Compos.* **2019**, *40*, 851–870.  
 [6] P. Adler, C. J. Teskey, D. Kaiser, M. Holy, H. H. Sitte, N. Maulide, *Nat. Chem.* **2019**, *11*, 329–334.  
 [7] D. Kaiser, C. J. Teskey, P. Adler, N. Maulide, *J. Am. Chem. Soc.* **2017**, *139*, 16040–16043.  
 [8] C. R. Gonçalves, M. Lemmerer, C. J. Teskey, P. Adler, D. Kaiser, B. Maryasin, L. González, N. Maulide, *J. Am. Chem. Soc.* **2019**, *141*, 18437–18443.  
 [9] C. J. Teskey, P. Adler, C. R. Gonçalves, N. Maulide, *Angew. Chem. Int. Ed.* **2019**, *58*, 447–451; *Angew. Chem.* **2019**, *131*, 456–460.  
 [10] T. Stopka, P. Adler, G. Hagn, H. Zhang, V. Tona, N. Maulide, *Synthesis* **2019**, *51*, 194–202.  
 [11] H. Zhang, M. Riomet, A. Roller, N. Maulide, *Org. Lett.* **2020**, *22*, 2376–2380.  
 [12] R. M. de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122.  
 [13] E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631.  
 [14] J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*, 140–177.  
 [15] M. T. Sabatini, L. T. Boulton, H. F. Sneddon, T. D. Sheppard, *Nat. Catal.* **2019**, *2*, 10–17.  
 [16] A. Ojeda-Porras, D. Gamba-Sánchez, *J. Org. Chem.* **2016**, *81*, 11548–11555.  
 [17] T. Lainer, F. Czerny, M. Haas, *Org. Biomol. Chem.* **2022**, *20*, 3717–3720.  
 [18] K. Yamada, M. Kota, K. Takahashi, H. Fujita, M. Kitamura, M. Kunishima, *J. Org. Chem.* **2019**, *84*, 15042–15051.  
 [19] W. I. Nicholson, F. Barreateau, J. A. Leitch, R. Payne, I. Priestley, E. Godineau, C. Battilocchio, D. L. Browne, *Angew. Chem. Int. Ed.* **2021**, *60*, 21868–21874; *Angew. Chem.* **2021**, *133*, 22039–22045.  
 [20] P. W. Seavill, J. D. Wilden, *Green Chem.* **2020**, *22*, 7737–7759.  
 [21] Y. He, L. Zeng, M. Li, L. Gu, S. Zhang, G. Li, *J. Org. Chem.* **2022**, *87*, 12622–12631.  
 [22] L. Bering, E. J. Craven, S. A. Sowerby Thomas, S. A. Shepherd, J. Micklefield, *Nat. Commun.* **2022**, *13*, 380.  
 [23] M. T. Sabatini, L. T. Boulton, T. D. Sheppard, *Sci. Adv.* **2017**, *3*, e1701028.  
 [24] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792.  
 [25] C. W. Cheung, M. L. Ploeger, X. Hu, *Nat. Commun.* **2017**, *8*, 14878.  
 [26] G. M. Torres, Y. Liu, B. A. Arndtsen, *Science* **2020**, *368*, 318–323.  
 [27] A. Umehara, S. Shimizu, M. Sasaki, *ChemCatChem* **2023**, *15*, e202201596.  
 [28] R. V. Ulijn, B. Baragaña, P. J. Halling, S. L. Flitsch, *J. Am. Chem. Soc.* **2002**, *124*, 10988–10989.  
 [29] S. Liu, Y. Yang, X. Liu, F. K. Ferdousi, A. S. Batsanov, A. Whiting, *Eur. J. Org. Chem.* **2013**, 5692–5700.  
 [30] P. Nelson, A. Pelter, *J. Chem. Soc.* **1965**, 5142–5144.  
 [31] J. Zhou, M. Paladino, D. G. Hall, *Eur. J. Org. Chem.* **2022**, e202201050.  
 [32] S. Ghosh, A. Bhaumik, J. Mondal, A. Mallik, S. Sengupta Bandyopadhyay, A. Mukhopadhyay, *Green Chem.* **2012**, *14*, 3220–3229.  
 [33] W. Muramatsu, H. Yamamoto, *Org. Lett.* **2022**, *24*, 7194–7199.  
 [34] H. Lundberg, F. Tinnis, N. Selander, H. Adolffson, *Chem. Soc. Rev.* **2014**, *43*, 2714–2742.  
 [35] P. Chandra, *ChemistrySelect* **2021**, *6*, 10274–10322.  
 [36] J. J. Davies, D. C. Braddock, P. D. Lickiss, *Org. Biomol. Chem.* **2021**, *19*, 6746–6760.  
 [37] S. Hazra, F. Gallou, S. Handa, *ACS Sustain. Chem. Eng.* **2022**, *10*, 5299–5306.  
 [38] G. Li, M. Szostak, *Synthesis* **2020**, *52*, 2579–2599.  
 [39] S. R. Manne, B. G. de la Torre, A. El-Faham, F. Albericio, *Synthesis* **2020**, *52*, 3189–3210.  
 [40] N. Martín, F. G. Cirujano, *Catal. Commun.* **2022**, *164*, 106420.  
 [41] E. Massolo, M. Pirola, M. Benaglia, *Eur. J. Org. Chem.* **2020**, 4641–4651.  
 [42] W. Muramatsu, T. Hattori, H. Yamamoto, *Chem. Commun.* **2021**, *57*, 6346–6359.  
 [43] K. Pedrood, S. Bahadorikhalili, V. Lotfi, B. Larijani, M. Mahdavi, *Mol. Divers.* **2022**, *26*, 1311–1344.  
 [44] D. Procopio, C. Siciliano, S. Trombino, D. E. Dumitrescu, F. Suci, M. L. D. Gioia, *Org. Biomol. Chem.* **2022**, *20*, 1137–1149.  
 [45] A. S. Santos, A. M. S. Silva, M. M. B. Marques, *Eur. J. Org. Chem.* **2020**, 2501–2516.  
 [46] J. Singh, A. Sharma, *New J. Chem.* **2022**, *46*, 16220–16242.  
 [47] M. Todorovic, D. M. Perrin, *Pept. Sci.* **2020**, *112*, e24210.  
 [48] A. Tortajada, M. Börjesson, R. Martín, *Acc. Chem. Res.* **2021**, *54*, 3941–3952.

- [49] R. Upadhyay, R. Rana, S. K. Maurya, *ChemCatChem* **2021**, *13*, 1867–1897.
- [50] G. Giacomelli, A. Porcheddu, in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 197–290.
- [51] G. Giacomelli, A. Porcheddu, L. D. Luca, *Curr. Org. Chem.* **2004**, *8*, 1497–1519.
- [52] G. Giacomelli, A. Porcheddu, M. Salaris, *Org. Lett.* **2003**, *5*, 2715–2717.
- [53] L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2001**, *66*, 7907–7909.
- [54] L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2002**, *67*, 6272–6274.
- [55] Z. J. Kamiński, *Pept. Sci.* **2000**, *55*, 140–164.
- [56] Z. J. Kamiński, *Tetrahedron Lett.* **1985**, *26*, 2901–2904.
- [57] H. L. Rayle, L. Fellmeth, *Org. Process Res. Dev.* **1999**, *3*, 172–176.
- [58] P. H. Huy, C. Mbouhom, *Chem. Sci.* **2019**, *10*, 7399–7406.
- [59] D. A. Probst, P. R. Hanson, D. A. Barda, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2004**.
- [60] C. E. Garrett, X. Jiang, K. Prasad, O. Repič, *Tetrahedron Lett.* **2002**, *43*, 4161–4165.
- [61] Z. J. Kamiński, B. Kolesińska, M. Małgorzata, *Synth. Commun.* **2004**, *34*, 3349–3358.
- [62] A. Falchi, G. Giacomelli, A. Porcheddu, M. Taddei, *Synlett* **2000**, *2000*, 275–277.
- [63] M. Kunishima, C. Kawachi, K. Hioki, K. Terao, S. Tani, *Tetrahedron* **2001**, *57*, 1551–1558.
- [64] A. Zivanovic, *Synlett* **2012**, *23*, 2426–2427.
- [65] S. A. Raw, *Tetrahedron Lett.* **2009**, *50*, 946–948.
- [66] K. Hattori, K. Koike, K. Okuda, T. Hirayama, M. Ebihara, M. Takenaka, H. Nagasawa, *Org. Biomol. Chem.* **2016**, *14*, 2090–2111.
- [67] N.-J. Kim, F.-N. Li, J. H. Lee, S. Park, K. Kim, C. Lim, Y. T. Han, H. Yun, J.-W. Jung, H. Park, H.-D. Kim, B. Y. Woo, S. S. Shin, S.-Y. Kim, J. K. Choi, Y.-S. Jeong, Y. Park, Y.-H. Park, D.-D. Kim, S. Choi, Y.-G. Suh, *Chem. Asian J.* **2013**, *8*, 400–409.
- [68] M. Kunishima, T. Ujigawa, Y. Nagaoka, C. Kawachi, K. Hioki, M. Shiro, *Chem. Eur. J.* **2012**, *18*, 15856–15867.
- [69] R. Sole, V. Gatto, S. Conca, N. Bardella, A. Morandini, V. Beghetto, *Molecules* **2021**, *26*, 191.
- [70] R. Sole, L. Agostinis, S. Conca, V. Gatto, N. Bardella, A. Morandini, C. Buranello, V. Beghetto, *Synthesis* **2021**, *53*, 1672–1682.
- [71] V. Gatto, S. Conca, N. Bardella, V. Beghetto, *Materials* **2021**, *14*, 3069.
- [72] J. Liu, H. Fujita, M. Kitamura, D. Shimada, M. Kunishima, *Org. Biomol. Chem.* **2021**, *19*, 4712–4719.
- [73] Z. J. Kamiński, B. Kolesińska, J. Kolesińska, G. Sabatino, M. Chelli, P. Rovero, M. Błaszczak, M. L. Głowska, A. M. Papini, *J. Am. Chem. Soc.* **2005**, *127*, 16912–16920.
- [74] M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao, S. Tani, *J. Am. Chem. Soc.* **2001**, *123*, 10760–10761.
- [75] B. Kolesińska, K. Barszcz, Z. J. Kamiński, D. Drozdowska, J. Wietrzyk, M. Switalska, *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 619–627.
- [76] T. J. Maimone, J. Shi, S. Ashida, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 17066–17067.
- [77] L. Gorgani, M. Mohammadi, G. D. Najafpour, M. Nikzad, *Compr. Rev. Food Sci. Food Saf.* **2017**, *16*, 124–140.
- [78] C. Jöst, C. Nitsche, T. Scholz, L. Roux, C. D. Klein, *J. Med. Chem.* **2014**, *57*, 7590–7599.
- [79] C. Kitada, T. Asami, N. Nishizawa, *Metastin Derivatives And Use Thereof*, **2006**, WO2006001499 A2.
- [80] I. Sharma, D. Crich, *J. Org. Chem.* **2011**, *76*, 6518–6524.
- [81] A. P. Dicks, A. Hent, in *Green Chemistry Metrics: A Guide to Determining and Evaluating Process Greenness* (Eds.: A. P. Dicks, A. Hent), Springer International Publishing, Cham, **2015**, pp. 17–44.
- [82] J. B. Sperry, C. J. Minter, J. Tao, R. Johnson, R. Duzguner, M. Hawksworth, S. Oke, P. F. Richardson, R. Barnhart, D. R. Bill, R. A. Giusto, J. D. I. Weaver, *Org. Process Res. Dev.* **2018**, *22*, 1262–1275.

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