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ARTICLE

Formamide Catalyzed Activation of Carboxylic Acids – Versatile and Cost-Efficient Amidations and Esterifications

Peter H. Huy,*[a] and Christelle Mbouhom[b]

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A novel, broadly applicable method for the amide C-N and ester C-O bond formation is presented based on formylpyrrolidine (FPyr) as Lewis base catalyst. Thereby, trichlorotriazine (TCT), which is the most cost-efficient reagent for OH-group activations, was employed in amounts of ≤40 mol% with respect to the starting material (100 mol%). The new approach is distinguished by an excellent cost-efficiency, waste-balance (E-factor down to 3) and scalability (up to >80 g). Moreover, high levels of functional group combatibility, which includes acid-labile acetals and silyl ethers, are demonstrated and even peptide C-N bonds can be formed. In comparison to reported amidation procedures using TCT yields are considerably improved (for instance from 26 to 91%) and esterifications are facilitated for the first time in synthetically useful yields. These significant enhancements are rationalized by the activation by means of acid chlorides instead of less electrophilic acid anhydride intermediates.

Introduction

Amide and ester C-N and C-O bond formations account to the most important and frequently performed transformations in chemistry.[1-2] Both functional groups are ubiquitous as in peptides and proteins, synthetic polymers and pharmaceuticals, for instance. The majority of all amides **2** and esters **3** are synthesized by the straightforward condensation of carboxylic acids **1** with *N*- and *O*-nucleophiles (Scheme 1 **A**), which is referred to as amidation and esterification, respectively.[1-2] Thereby, conventionally reagents are employed to convert the hydroxy group of **1** into a decent leaving group, which facilitates subsequent nucleophilic substitution. As the consequence, waste by-products are formed, which typically results in a poor sustainability and cost-efficiency.[3]

Intriguing protocols for amidations without the necessity of reagents have been recently established based on boron,[4-7] Hafnium and Zirconium[8] Lewis acid catalysts, for example.[2e,g-k,m] The latest generation of catalyst such as the remarkable dioxoazatriborinane of Shibasaki and Kumagai, which is prepared in five steps, allow even for the synthesis of amides derived from challenging aromatic and sterically encumbered aliphatic carboxylic acids.[6,7]

Despite the significant progress accomplished in regard to catalytic C-N and C-O[2e,g] bond formation, not all esters and amides are accessible by means of catalysis in high levels of efficiency. In fact, a united appeal of several leading pharmaceutical companies evidences a highly urgent demand for the development of novel methods for amidations.[9] A comparison of some of the most common reagents for stoichiometric OH group activation of carboxylic acids and

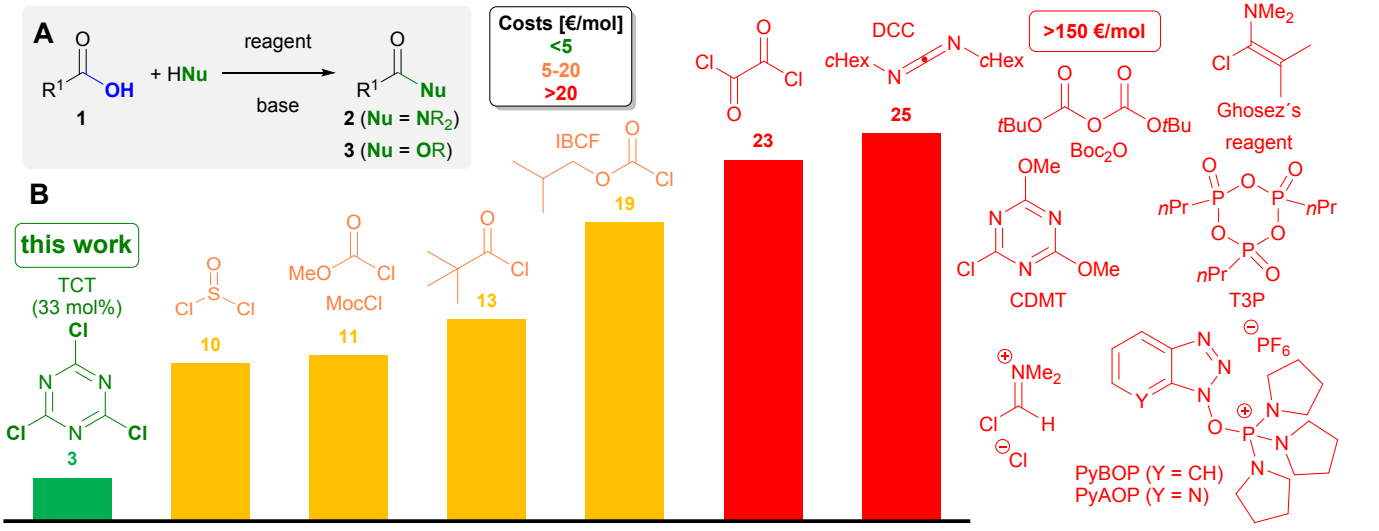

Figure 1 A Amidations and esterifications of carboxylic acids and **B** comparison of costs for various reagents for this transformation in respect to converted substrate (prices were obtained from Sigma Aldrich, see chapter 1.2 in the ESI for more details.

[a] Saarland University, Institute of Organic Chemistry, P. O. Box 151150, D-66041 Saarbruecken; homepage: peterhuylab.de; email: peter.huy@uni-saarland.de.
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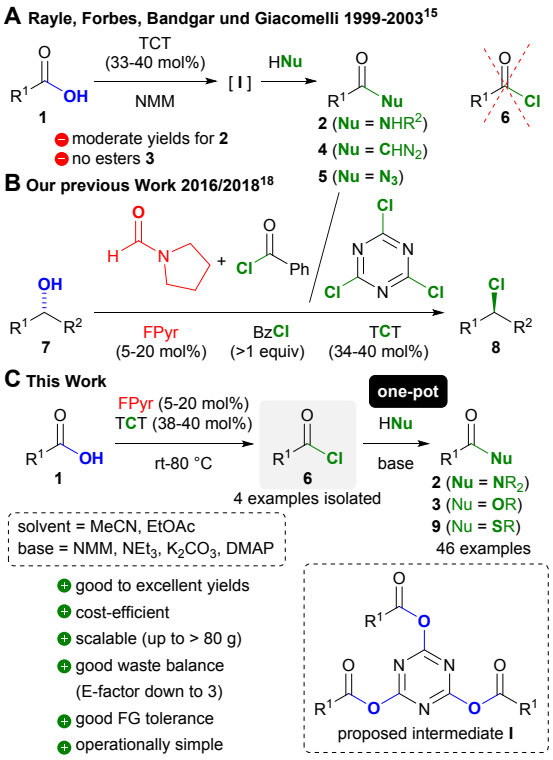
alcohols, for instance, is compiled in Scheme 1 **B.**[10] Indeed, trichlorotriazine (TCT),[11] which is also called cyanuric chloride, emerges as the least expensive reagent besides phosgene ($COCl_2$).[12] When a 3:1 stoichiometry of the hydroxy group bearing starting material in regard to TCT is anticipated, levels of costs are even lower than with common coupling reagents such as thionyl chloride ($SOCl_2$), *iso*-butyl chloroformate (IBCF), oxalyl chloride ($C_2O_2Cl_2$) and dicyclohexylcarbodiimide (DCC). Other frequently used coupling reagents like Ghosez´s chloro enamine[13] and T3P[14] are associated unavoidably with significantly higher costs. In contrast to oxalyl and thionyl chloride and phosgene, application of TCT in addition prevents formation of HCl as by-product, which should enable an enhanced functional group compatibility.

In fact, TCT (33-40 mol%) in conjunction with NMM (*N*-methylmorpholine) has been exploited for the synthesis of secondary amides **2**, diazoketones **4**, acyl azides **5**, and hydroxamic acids **2** (R^2 = OH, Scheme 1 **A**).[15,16] However, yields are often moderate (e.g. for secondary amides 65-75%)[15a] and esterifications have rarely been reported.[16] Thereby, activation of **1** is not realized through conversion to acid chlorides **6**,[15a,c] which could also be confirmed by own experiments (*vide infra*). Instead, mixed anhydrides of type **I** have been proposed as intermediates.[15]

Recently, we discovered that *N*-formylpyrrolidine (FPyr) is a potent Lewis base catalyst[17] for the transformation of alcohols **7** into alkyl chlorides **8**, which are mediated by either benzoyl chloride or TCT (Scheme 1 **B**).[18,19]



Scheme 1 Preceding and own work.

Furthermore, a substituted cyclopropenone and tropone, the latter of which even in catalytic quantities, have been employed as Lewis bases by the groups of Lambert and Nguyen in the production of acid chlorides, amides and esters with $C_2O_2Cl_2$.[20]

Against this background considering the excellent cost-efficiency of TCT, we envisioned the opportunity to develop a novel method for the synthesis of esters and amides via formamide catalyzed acid chloride generation (Scheme 1 **C**). Since chlorides of type **6** are more reactive towards nucleophiles than anhydrides such as **I**, we expected a much broader applicability and significantly enhanced yields. Herein, a novel method for the low-cost chlorination, amidation and esterification of carboxylic acids based on FPyr and TCT is disclosed.

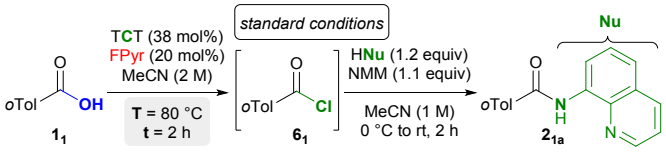
Results and discussion

Optimization of Reaction Conditions

While the full details of the optimization of the reaction conditions are enclosed in the ESI (chapter 3), only the essential findings are discussed in the following based on the synthesis of model amide $\mathbf{2_{1a}}$ (Table 1), which is a frequently engaged test substrate for CH-activations.[21] In terms of solvent, MeCN was identified as optimal (entry 1). Nevertheless, utilization of more environmental-friendly EtOAc rendered amide $\mathbf{2_{1a}}$ in a similar yield (entry 2). With respect of the transformation of **1→6**, heating to 80 °C effects conveniently short reaction durations ≤4 h (entries 1+2). However, the reaction temperature can be decreased to 40 °C, when 20 mol% of FPyr are employed instead of 10 (entry 3).

As an important finding, activation of aromatic acids **1** can also be achieved at room temperature, when MeCN is harnessed as solvent (entry 4). Moreover, the catalyst loading can be minimized to 5 mol% and instead of FPyr a two-fold amount of DMF is also feasible (entries 5+6).

Table 1 Optimization of reaction conditions for the preparation of amide $\mathbf{2_{1a}}$.



Entry	Deviation from standard conditions[a]	yield $\mathbf{2_{1a}}$[b] (%)
1	/	90
2	in **EtOAc** instead of MeCN	85
3[d]	**T = 40 °C, 20 mol%** FPyr in EtOAc	84
4[d]	**T = rt**, 20 mol% FPyr	78
5[d]	5 mol% **FPyr**	90
6[d]	**T** = 40 °C, 40 mol% DMF in EtOAc	83
7[e]	**K_2CO_3** instead of NMM in EtOAc	88
8	**NEt_3** instead of NMM	91
9	no catalyst	11[c]

a. For detailed reaction conditions see Table S12, ESI. b. Yields refer to isolated material after chromatography if not otherwise mentioned. c. **t** = 8-10 h. d. Yield determined by means of an internal NMR standard. e. Substrate concentration $\mathbf{6_1}$ 0.5 M).

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In general, aliphatic acids are more reactive than aromatic, which enables lower reaction temperatures in the former case (rt to 40 °C). Indeed, a low TCT amount around 40 mol% is pivotal for one-pot condensations in high yield. For instance, an increase to 60 mol% resulted in a depletion of the yield in the preparation of 2-naphthyl phenyl acetate from 93 to 68%.

A screening of manifold Lewis bases for the transformation of acids **1** into acid chlorides **6** including $OPPh_3$, DMSO, tropone and cyclopropenone derivatives revealed FPyr as by far most effective catalyst (Table S5, ESI). This is surprising, because some of the probed Lewis bases have been employed in related chlorinations of carboxylic acids with oxalyl chloride.[20] In comparison to alcohols,[18b] the conversion of carboxylic acids requires higher TCT amounts and increased reaction times. This is rationalized probably by a lower thermodynamic driving force, because the conjugation energy between the hydroxyl substituent and the carbonyl group in **1** is lost.

Pleasingly, for the formation of amides **2** and esters **3** from acid chloride intermediates **6** one equivalent of base is adequate, albeit in some cases yields are improved by using two. Even inexpensive K_2CO_3 is suitable for the synthesis of amides (entry 7), although utilization of NMM or NEt_3 sometimes causes enhanced yields (entries 1+8). For the synthesis of esters **3** derived from aromatic alcohols the aforementioned amine bases are recommended (Table S13 to 16, ESI). For condensation of weakly nucleophilic aliphatic alcohols with substrates **1** in good yields, addition of catalytic amounts of DMAP[22] proved to be crucial (4-dimethylaminopyridine, Table S17 to 18, ESI). Finally, in the absence of FPyr the product $\mathbf{2_{1a}}$ was obtained in a very low yield of 11%, which proves the crucial role of FPyr as catalyst (entry 9).

In fact, the solvent volume has a major impact on both, scalability and sustainability.[3] Fortunately, chlorinations **1→6** can be performed utilizing very low solvent amounts ([**1**] = 2-4 M), which also procures shorter reaction durations. Due to the successive addition of nucleophile and base, the solvent amount has to be increased. However, in most cases a concentration of 1 M with respect to the starting material **1** is sufficient to ensure stir-ability. Recommendations for reaction conditions in dependence on the starting materials are concluded in Scheme 3 **A** for the chlorination step **1→6** and in Scheme 5 **A** for the subsequent condensation **6→2/3**. As a support for the practitioner, we also included a more detailed reaction conditions guide in chapter 5.2 in the ESI.

Synthesis of Acid Chlorides

In clear contrast to preceding literature protocols,[15] carboxylic acid chlorides of type **6** are generated as intermediates, which can be monitored by NMR spectroscopy (chapter 3.1.6, ESI). Simultaneously, reversible formation of the respective acid anhydride was observed. In order to unambiguously verify that activation of **1** is accomplished by means of chlorination, four different acid chlorides were synthesized on a multigram scale and isolated after distillation in 79-90% yield (Scheme 2).

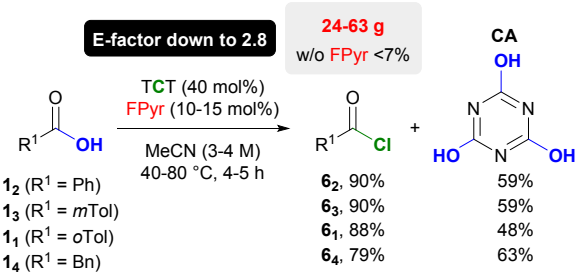
Thereby, it is important to heat the reaction mixture to 80 °C in order to decompose FPyr entirely, which prevents codistillation with the product. During the reactions a solid precipitates. Isolation through filtration and drying delivered a residue with the mass of ca. 80% of the theoretical yield of cyanuric acid (**CA**). Indeed, ^{13}C-NMR confirmed **CA** as the major component, which proves its role as main by-product. In Scheme 2 yields for **CA** are stated after purification by means of precipitation with hydrochloric acid from a basic solution.

As an important aspect, a good waste balance is attested through E-factors as low as 2.8, which is the ratio of mass of waste with respect to the mass of isolated products according to Sheldon.[3] Remarkably, this beneficial E-factor is in a range typical for the production of bulk chemicals (1.5-5),[3] which is explained through the low solvent and reagent amounts necessary. Noteworthy, in the absence of FPyr even heating to 80 °C did basically not effect formation of acid chlorides, which emphasises the importance of formamide catalysis. The addition of Brønsted bases has a deteriorative impact on the yield, in particular when acids bearing α-H-atoms are engaged (see Table S7, ESI.)

Synthesis of Amides

Initially, we investigated the substrate scope in terms of the synthesis of amides **2** (Scheme 3). A variety of aliphatic carboxylic acids bearing a primary (1°), secondary (2°) and tertiary (3°) α-carbon atom were transformed into the respective amides (Scheme 3 **B**). Among them even dimethylmalonic acid could be coupled with two equivalents of phenyl glycinol to afford diamide $\mathbf{2_{9i}}$. In addition, amides deduced from electron-rich and poor (hetero)aromatic carboxylic acids are accessible in good to excellent yields (Scheme 3 **C**). The method is also applicable to α,β-unsaturated substrates, whereby in example $\mathbf{2_{16b}}$ only little isomerisation occurred (*dr* = 97:3, Scheme 3 **D**). In cases, where the nucleophile is considered as the more valuable building block, the carboxylic acid **1** can be applied in excess. For instance, the amide $\mathbf{2_{16b}}$ was synthesized from 1.3 equiv of crotonic acid and 1.0 equiv of ephedrine.

Of particular significance is the functional group compatibility in the initiating transformation of acids **1** into chlorides **6** (Scheme 3 **F**). Since HCl in not released in stoichiometric quantities, even acid sensitive cyclic acetal and silyl ether functions are tolerated (examples $\mathbf{2_{20t}}$ and $\mathbf{2_{21f}}$). Moreover, cyano and ester groups, ketones, aldehydes and chloro alkanes (example $\mathbf{2_{10j}}$) are compatible. Examples for the production of esters also include carbamates (Scheme 5 **D**).



Scheme 2 Synthesis of carboxylic acid chlorides **6**.

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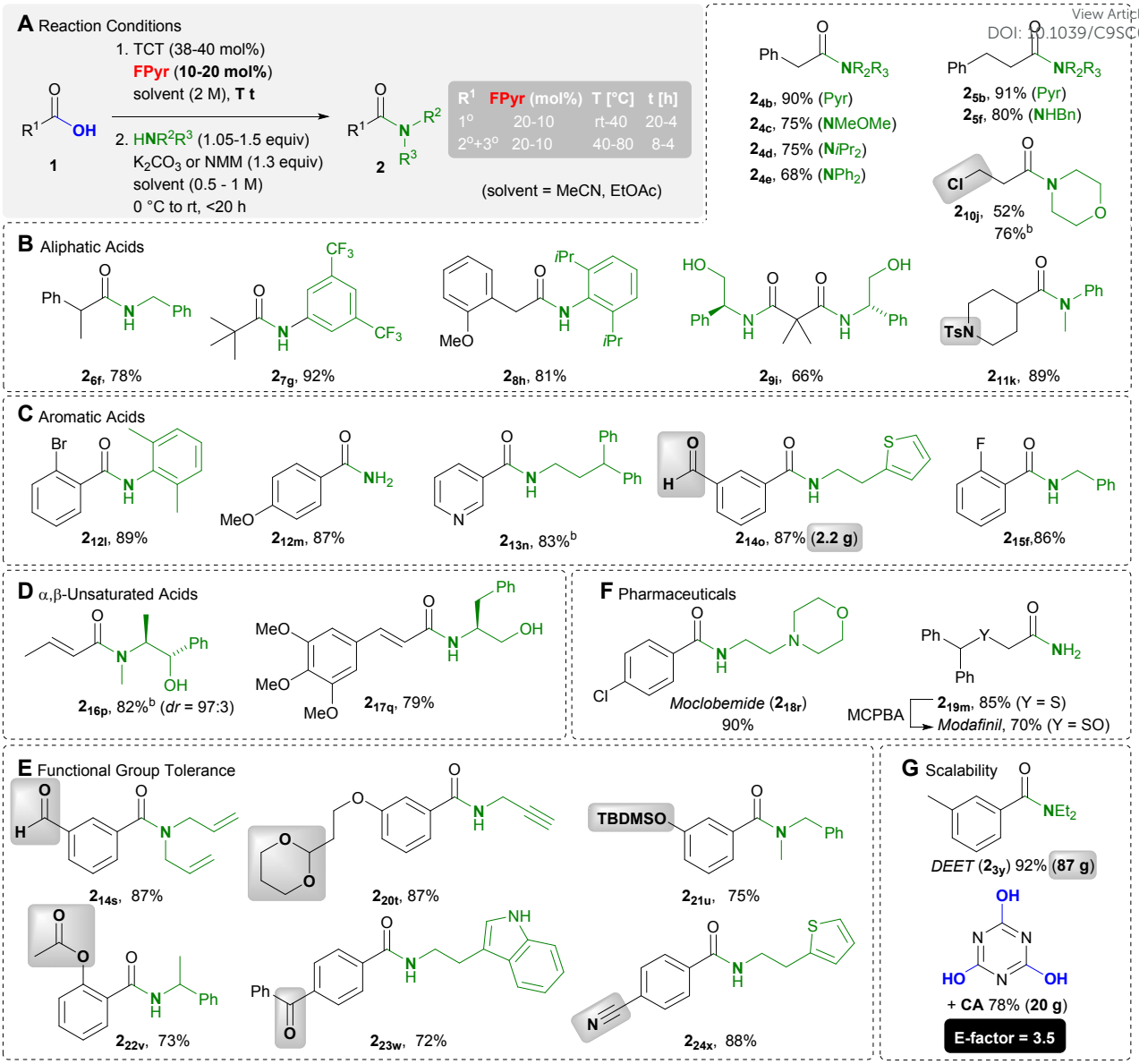

Scheme 3 Synthesis of amides of type 2. a. Isolated yield after chromatography or distillation if not otherwise mentioned. b. Yield determined by means of an internal NMR-Standard. c. With 1.3 equiv **1**, 49 mol% TCT, 1.7 equiv NMM and 1.0 equiv nucleophile. Pyr = *N*-pyrrolidyl, Ts = *para*-tolylsulfonyl, TBDMS = *tert*-butyldimethylsilyl.

To point out the synthetic value of our approach, the drugs Moclobemide and Modafinil have been prepared (Scheme 3 **F**). Eventually, significant scalability is proven by the synthesis of the insect repellent DEET on a 500 mmol scale, for which standard glass ware ≤1 L is sufficient (Scheme 3 **G**). An E-factor of 3.5 showcases a reasonable waste balance, in the determination of which also isolated cyanuric acid was considered. In fact, in all other examples ($\mathbf{2}_{14a}$, $\mathbf{3}_{30c}$ and $\mathbf{3}_{31d}$) prepared on a multigram scale, environmentally benign EtOAc was employed as solvent, too.

The scope with respect to the amine nucleophile is divers, as well. Scheme 3 includes examples derived from various primary and secondary amines, electron poor and sterically encumbered, weakly nucleophilic aniline derivatives (examples $\mathbf{2}_{7g}$ and $\mathbf{2}_{8h}$). In addition, application of plain aqueous ammonia solution enabled the synthesis of primary amides (examples $\mathbf{2}_{12m}$ and $\mathbf{2}_{19m}$). As documented by the synthesis of Weinreb amide $\mathbf{2}_{4c}$, hydrochloride salts of amines can be engaged as nucleophiles, which requires one additional equivalent of base.

Although β-amino acids are suitable starting materials (Scheme 5 **D**, example $\mathbf{3}_{24j}$), reaction of carbamate protected α-amino acid derivative $\mathbf{1}_{25}$ with TCT in the presence of FPyr yielded carboxamide $\mathbf{10}_{25}$ (Scheme 4 **A**). This outcome is most likely reasoned by formation of the cyclic intermediate $\mathbf{II}_{25}$ after activation of the acid function and subsequent nucleophilic substitution in benzylic position through the chloride counterion.

An amide protected alanine derivative was converted into the dipeptide $\mathbf{2}_{26z}$ in moderate yield and under epimerization (Scheme 4 **B**). Variation of the reaction conditions could neither enhance the yield nor the *dr* to a significant extent (see ESI). Gratifyingly, the dipeptide $\mathbf{2}_{27z}$ emerged from condensation with phthaloyl protected alanine $\mathbf{1}_{26}$ in an excellent yield as a virtually pure diastereomer.

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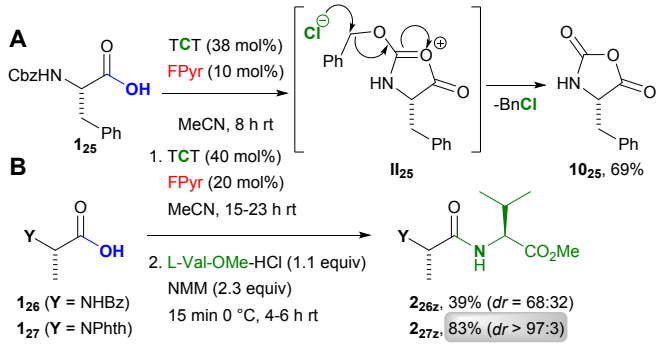


Scheme 4 α-Amino acid derivatives. Phth = Phthaloyl

Thus, the present protocol even allows for peptide C-N bond formation, when phthaloyl protected amino acids are employed. In comparison to other amino acid chlorides,[1] the phthaloyl protected analogues are less prone towards racemisation.[24] Against this background, we would also like to highlight recent contributions about the boron Lewis acid catalyzed synthesis of peptides.[5-7]

Synthesis of Esters

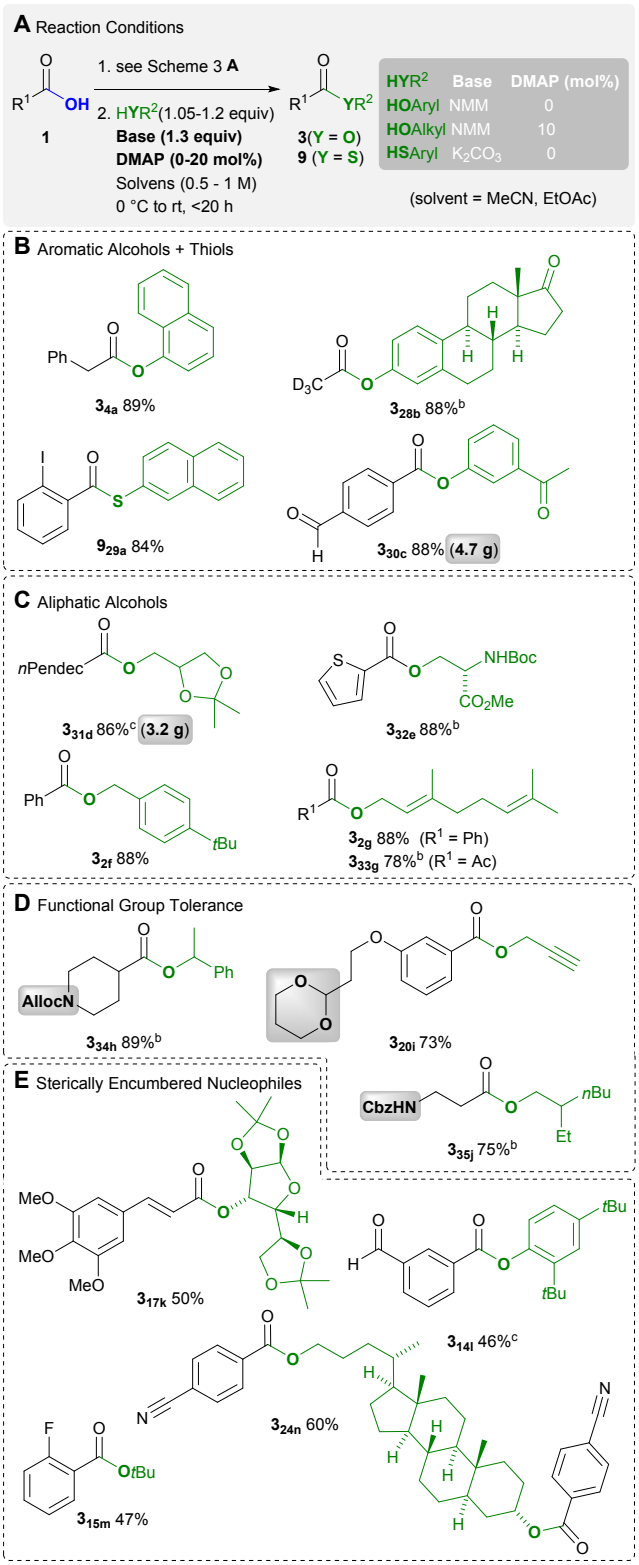
Due to the lower nucleophilicity of alcohols, the synthesis of esters of type **3** is more challenging. This is most probably also the reason, why esters have been rarely prepared by means of TCT.[16] Fortunately, the present catalytic method facilitates the synthesis of esters derived from both, aromatic and aliphatic alcohols, in yields of 73-89% yield (Scheme 5 **B** to **D**).

This also includes two examples on a 3-5 g scale, which certifies a high degree of practicability (examples $\mathbf{3_{30c}}$ and $\mathbf{3_{31d}}$). Since acid chlorides are not isolated, estrone derivative $\mathbf{3_{28b}}$ could be accessed via volatile trideutero acetoyl chloride. Reasoned by a higher nucleophilicity, 2-naphthalene thiol could be condensed with 2-iodobenzoic acid using K_2CO_3 instead of NMM (example $\mathbf{9_{29a}}$). Esterifications of sterically demanding alcohols with acid chlorides are usually accomplished using strong bases such as *n*BuLi.[25] Hence, the current method provides esters derived from sterically encumbered alcohols in moderate yields of 47-60% (Scheme 5 **D**).

Comparison Experiments

In order to compare our approach with a literature protocol harnessing TCT and NMM (Scheme 1 **A**),[15a] several amides and esters were prepared accordingly (see also chapter 4, ESI). Remarkably, in the event of four exemplary amides the differences in terms of yield between the reported protocol and the current catalytic method are in the range of 21 and 65% (Scheme 6 **A**). When K_2CO_3 was applied as base instead of NMM, the amides $\mathbf{2_{4b}}$ and $\mathbf{2_{1a}}$ were obtained in even more deteriorated yields ≤17% (this method 88-90%).

The yields for the preparation of esters of 8-58% according to ordinary TCT/NMM-activation[15a] must be classified as synthetically non-useful (current method 86-89%, Scheme 6 **B**). Utilization of DMAP, which has not been described in the literature, allows to improve the yield of ester $\mathbf{3_{31d}}$ (8→50%), whereas in example $\mathbf{3_{30c}}$ a slightly depleted yield was attained (42→36%). It should be emphasized that we optimized the literature conditions thoroughly in order to allow a meaningful comparison (see Table S19 to S22, ESI). The significantly improved yields testify our concept that acid chloride activation is superior to anhydride formation.



Scheme 5 Synthesis of Esters. a. isolated yield after chromatography. b. With 1.3 equiv **1**, 49 mol% TCT, 1.7 equiv NMM and 1.0 equiv nucleophile. c. With 1.1 equiv **1**, 44 mol% TCT, 2.3 equiv NMM and 1.0 equiv nucleophile.

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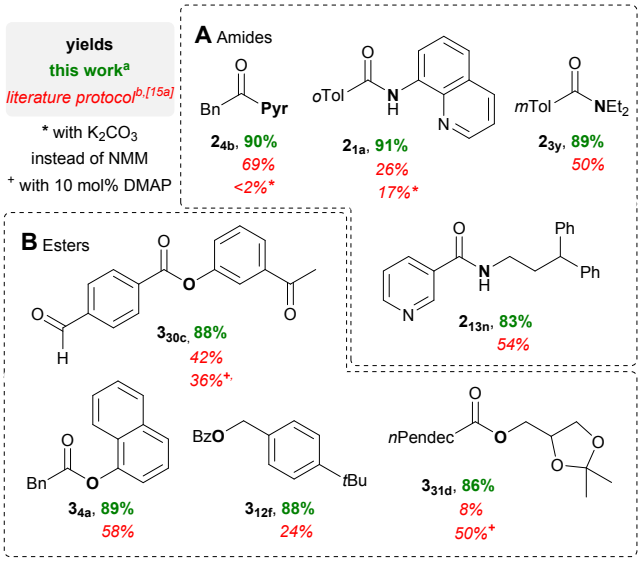


Scheme 6 Comparison of the present with the literature method[16a] employing TCT and NMM. a. For reaction conditions see Scheme 3 and Scheme 5; yields refer to isolated material after chromatographic purification or distillation. b. For reaction conditions see Scheme 1 **A** and chapter 4, ESI; yield determined with internal NMR-standard.

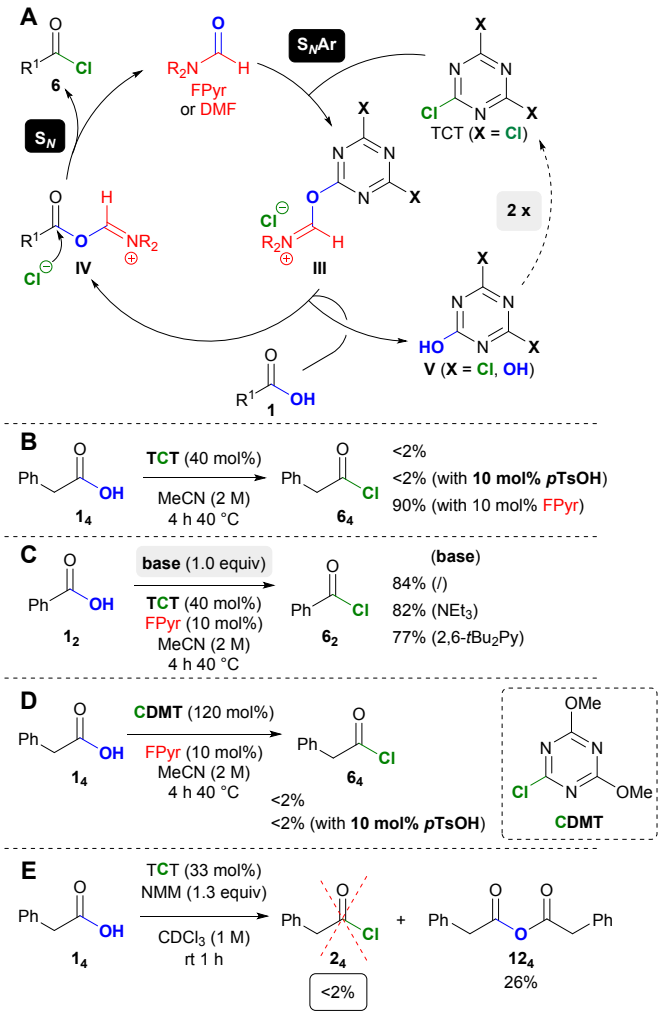
Proposed Mechanism

In alignment to our previous work on the catalytic chlorination of alcohols,[18] the related transformation of carboxylic acids **1** into acid chlorides **6** is most likely commenced by nucleophilic aromatic substitution (S_NAr) engaging TCT and FPyr (Scheme 7 **A**). That chloride substitution on a triazine scaffold proceeds via a stepwise S_NAr mechanism has been demonstrated previously.[26,27] Next, the plausible intermediate **III**, which shows structurally similarities to the Vilsmeier Haack reagent, should undergo replacement of the triazine moiety through the substrate **1**. In the following, the resulting Intermediate **IV** would surpass substitution with the chloride counter ion to afford the product **6** and regenerate FPyr. Dichlorohydroxy-triazine (**V** with **X** = Cl) results from the conversion of **III** with **1** to **IV**. As verified through the formation of **CA** and the low stoichiometry of TCT (40 mol% → 1.2 equiv, *vide supra*), **V** (**X** = Cl) undergoes two consecutive reactions with FPyr until all chlorine atoms are replaced.

Alkoxy iminium salts derived from alcohols, have been previously proven by us,[18a] which supports carboxyl iminium salts of type **IV** as key intermediates. Preliminary mechanistic elucidations according to the normalized time scale method of Burés,[28] revealed a reaction order of 1 in FPyr (chp. 3.1.6, ESI), which is in agreement with the proposed mechanism.

Remarkably, in the absence of FPyr no phenylacetoyl chloride ($\mathbf{6_4}$) is formed at all (Scheme 7 **B**). As an important finding, *para*-tolylsulfonic acid (*p*TsOH) does not promote production of $\mathbf{6_4}$, which rules out Brønsted acid catalysis. Furthermore, also Brønsted acid cocatalysis can be excluded, since the conversion of benzoic acid into benzoyl chloride is virtually not inhibited by bases such as NEt_3 and 2,6-bis-*tert*-butylpyridine (Scheme 7 **C**, Table S7, ESI).

Reaction of phenyl acetic acid ($\mathbf{1_4}$) with CDMT, which is closely related to intermediate **V**, does not give rise of the respective acid chloride $\mathbf{6_4}$ (Scheme 7 **C**, see also Table S8, ESI). Thus, the reason for the replacement of the chlorine atom in **V** is currently unclear (Scheme 7 **D**).



Scheme 7 A Proposed mechanism and **B-E** comparison experiments. Yields were determined by internal NMR standard.

That activation of carboxylic acids with NMM and TCT does not yield acid chlorides of type **6**[15a,c] was confirmed experimentally (Scheme 7 **E**, see Table S23, ESI). The proposed intermediate **I** (see Scheme 1), which might be insoluble in $CDCl_3$, was also not observed. Instead anhydride $\mathbf{12_4}$ was encountered in 26% yield, which provides an additional explanation for the low yields in the comparison experiments (*vide supra*).

Conclusions

In summary, a versatile formamide catalyzed method for the transformation of carboxylic acids into acid chlorides, amides, esters and thioesters has been developed. Thereby, cyanuric chloride (TCT), which is the cheapest reagent for OH group activation (alongside phosgene), is engaged as promotor in quantities ≤40 mol%. As the consequence, the presented protocol exhibits (1) an exceptional cost-efficiency. Additional important features are high levels of (2) scalability (>80 g) and

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(3) functional group compatibility including acid labile acetals and silyl ethers; (4) a reasonable waste-balance (E-factor down to 3) and (5) operational simplicity, since non-dry reaction conditions are viable. Remarkably, the formation of peptidic C-N bonds is possible, when phthaloyl protected amino acids are employed.

In comparison to ordinary protocols using TCT, not only the yields of amidations are significantly improved (e.g. 91% instead of 26%), but also esterifications are enabled in synthetically useful yields for the first time. The significant advancements are explained by the formation of carboxylic acid chlorides as intermediates instead of less electrophilic anhydrides. Finally, high levels of applicability were testified by the preparation of the pharmaceuticals Moclobemide and Modafinil and the insecticide DEET. Under consideration of the manifold enhancements a rapid application of the current method in academic and industrial laboratories is to be expected.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 Reviews on amidations: (a) T. Ziegler in *Science of Synthesis*, Vol. 21 (Ed. S. M. Weinreb), Georg Thieme: Stuttgart, **2005**, pp. 43-77; (b) E. Haslam, *Tetrahedron*, 1980, **36**, 2409; (c) C. A. G. N. Montalbetti and V. Falque *Tetrahedron*, 2005, **61**, 10827; (d) E. Valeur and Mark Bradley, *Chem. Soc. Rev*., 2009, **38**, 606; (e) K. Ishihara, *Tetrahedron*, 2009, **65**, 1085; (f) A. El-Faham and F. Albericio, *Chem. Rev.* 2011, **111**, 6557; (g) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471; (h) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.* 2013, 7453; (i) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714; (j) R. M. de Figueiredo, J.-S. Suppo and J. M. Campagne, *Chem. Rev.*, 2016, **116**, 12029; (k) A. Ojeda-Porras and D. Gamba-Sanchez, *J. Org. Chem.*, 2016, **81**, 11548; (l) J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140; (m) M.T. Sabatini, L. T. Boulton, H. F. Sneddon and T. D. Sheppard, *Nature Catal.*, 2019, **2**, 10.

2 Reviews about esterifications: (a) E. Haslam, *Tetrahedron*, 1980, **36**, 2409; (b) R. C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, New York, 2nd edn, 1999, p. 1932; (c) A. C. Spivey and S. Arseniyadis *Angew. Chem. Int. Ed.*, 2004, **43**, 5436; (d) R. Shelkov, M. Nahmany and A. Melman, *Org. Biomol. Chem.*, 2004, **2**, 397; (e) N. F. Jain and C. E. Masse in *Science of Synthesis*, Vol. 20b (Ed. J. S. Panek), Georg Thieme: Stuttgart, **2006**, pp. 711-715.

3 Selected reviews regarding sustainability: (a) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273; (b) C. J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. U.S.A.*, 2008, **105**, 13197; (c) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (d) P. Anastas and N. Eghbali, *Chem. Soc. Rev.* 2010, **39**, 301; (e) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437; (f) P. J. Dunn, *Chem. Soc. Rev.*, 2012, **41**, 1452; (g) R. A. Sheldon, *Green Chem.* 2017, **19**, 18.

4 Reviews on boron Lewis acid catalysis: (a) H. Charville, D. Jackson, G. Hodgesc, A. Whiting, *Chem. Commun.*, 2010, **46**, 1813; (b) H. Zheng and D. G. Hall, *Aldrichim. Acta*, 2014, **47**, 41; (c) P. Huy and B. Zoller, *Nachr. Chem.* 2019, **67**, 51.

5 Seminal Publications: (a) K. Ishihara, S. Ohara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196; (b) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813; (c) R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed.*, 2008, **47**, 2876; (d) N. Gernigon, R. M. Al-Zoubi and D. G. Hall, *J. Org. Chem.*, 2012, **77**, 8386; (e) M. T. Sabatini, L. T. Boulton and T. D. Sheppard, *Sci. Adv.*, 2017, **3**, e1701028; (f) S. Arkhipenko, M. T. Sabatini, A. S. Batsanov, V. Karaluka, T. D. Sheppard, H. S. Rzepa and A. Whiting, *Chem. Sci.*, 2018, **9**, 1058.

6 (a) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki and N. Kumagai, *Nature Chem.*, 2017, **9**, 471; (b) Z. Liu, H. Noda, M. Shibasaki and N. Kumagai, *Org. Lett*., 2018, **20**, 612; (c) H. Noda, Y. Asada, M. Shibasaki and N. Kumagai, *J. Am. Chem. Soc.* 2019, **141**, 1546; (d) C. R. Opie, H. Noda, M. Shibasaki, and N. Kumagai, *Chem. Eur. J.*, 2019, **25**, 4648.

7 For other leading boron Lewis acid catalyzed methods for the synthesis of challenging amides see: (a) K. Ishihara and Y. Lu, *Chem. Sci.*, 2016, **7**, 1276; (b) K. Wang, Y. Lu and K. Ishihara, *Chem. Commun.*, 2018, **54**, 5410; (c) D. N. Sawant, D. B. Bagal, S. Ogawa, K. Selvam and S. Saito, *Org. Lett.*, 2018, **20**, 4397.

8 For example see: (a) H. Lundberg, F. Tinnis, H. Adolfsson, *Chem. Eur. J.* 2012, **18**, 3822; (b) H. Lundberg, H. Adolfsson, *ACS Catal.* 2015, **5**, 3271, (c) H. Lundberg, F. Tinnis, J. Zhang, A. G. Algarra, F. Himo, H. Adolfsson, *J. Am. Chem. Soc.* 2017, **139**, 2286.

9 A round-table of representatives of several pharmaceuticals companies repeatedly requested more efficient methods for amidations as primary target: (a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411; (b) M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weibert, *Green Chem.*, 2018, **20**, 5082.

10 For the cost assessment for each reagent the lowest price at Sigma-Aldrich was selected. We are fully aware that the costs would drop significantly on an industrial scale. Nevertheless, we are convinced that current study allows for a relative ranking with respect to cost-efficiency. For more details, see chapter 1.2 in the ESI.

11 Reviews on TCT: (a) S. S. Voyutskii, V. L. Vakula, *Russ. Chem. Rev.* **1964**, 92-103; (b) N. Kriebitzsch and H. Klenk in *Ullmann´s Encyclopedia of Industrial Chemistry*, vol. **A8** (Eds. W. Gerhartz et al.), VCH, Weinheim, 1987, pp. 191-200; (c) Z. J. Kaminsky, *Biopolymers*, 2000, **55**, 140; (d) G. Blotny, *Tetrahedron*, 2006, **62**, 9507.

12 At Sigma-Aldrich phosgene is only available as a relatively costly solution and is therefore not included in Figure 1. As carbonyl dichloride is readily prepared from CO and Cl_2, the real costs are likely to be significantly lower.

13 (a) A. Devos, J. Remion, A. M. Frisque-Hesbain, A. Colens, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1979, 1180; (b) B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, L. Ghosez, M. Murakami, M. Yoshioka and W. Nagata, *Org. Synth.*, 1979, **59**, 26.

14 (a) H. Wissmann and H.-J. Kleiner, *Angew. Chem., Int. Ed.*

Engl., 1980, **19**, 133; (b) R. Escher und P. Bünning, *Angew. Chem., Int. Ed. Engl.* 1986, *25*, 277.
15 (a) H. L. Rayle and L. Fellmeth, *Org. Process Res. Dev.*, 1999, **3**, 172; (b) D. C. Forbes, E. J. Barrett, D. L. Lewis and M. C. Smith, *Tetrahedron Lett.*, 2000, **41**, 9943; (c) B. P. Bandgar and S. S. Pandit, *Tetrahedron Lett.*, 2002, **43**, 3413; (d) G. Giacomelli, A. Porcheddu and M. Salaris, *Org. Lett.*, 2003, **5**, 2715.
16 Acid chlorides, amides and esters have been prepared using TCT (50 mol%) and NEt_3: K. Venkataraman, D. R. Wagle, *Tetrahedron Lett.*, 1979, *20*, 3037. Therein, the preparation of two acid chlorides (aromatic) and two esters (with MeOH) has been described. Own comparison experiments showed that aromatic benzoyl chloride can be accessed in poorly reproducible yields of 63-78%, while aliphatic phenylacetyl chloride was mainly converted into the respective anhydride (yield phenyl ethanoyl chloride 6-10%; see chapter 4.2, ESI).
17 Reviews on Lewis base catalysis in nucleophilic substitutions: (a) J. An, R. M. Denton, T. H. Lambert and E. D. Nacsa, *Org. Biomol. Chem.*, 2014, *12*, 2993; (b) P. H. Huy, T. Hauch and I. Filbrich, *Synlett*, 2016, **27**, 2631.
18 (a) P. H. Huy, S. Motsch and S. M. Kappler, *Angew. Chem. Int. Ed.*, 2016, **55**, 10145; *Angew. Chem.*, 2016, **128**, 10300; (b) P. H. Huy and I. Filbrich, *Chem. Eur. J.*, 2018, **24**, 7410.
19 In addition, formamides such as dimethylformamide (DMF) are known to catalyse the chlorination of carboxylic acids using thionyl and oxalyl chloride, respectively: (a) R. Richter and B. Tucker, *Helv. Chim. Acta*, 1959, 1653; (b) H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, 1960, **72**, 836.
20 (a) D. J. Hardee, L. Kovalchuke and T. H. Lambert, *J. Am. Chem. Soc.*, 2010, **132**, 5002; (b) T. V. Nguyen and A. Bekensir, *Org. Lett.*, 2014, **16**, 1720; (c) T. V. Nguyen, D. J. M. Lyons, *Chem. Commun.*, 2015, **51**, 3131.
21 See for instance: (a) Y. Ano, M. Tobisu and N. Chatani, *Org. Lett.*, 2012, **14**, 354; (b) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (c) Y. Aihara and N Chatani, *Chem. Sci.*, 2013, **4**, 664.
22 For DMAP catalyzed amidations and esterifications using DCC and Boc_2O, respectively, see: (a) B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522; (b) D. K. Mohapatra and A. Datta, *J. Org. Chem.*, 1999, **64**, 6879; (c) K. Takeda, A. Akiyama, H. Nakamura, S.-i. Takizawa, Y. Mizuno, H. Takayanagi and Y. Harigaya, *Synthesis*, 1994, 1063; (d) L. J. Gooßen, A. Döhring, *Synlett*, 2004, 263; (e) S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich and H. Zipse, *Chem. Eur. J.*, 2005, **11**, 4751; (f) I. Held, P. von den Hoff, D. S. Stephenson, H. Zipse, *Adv. Synth. Catal.*, 2008, **350**, 1891.
23 *N*-Boc- amino acids have been converted to carboxamides upon activation of the C-Terminus: (a) S. Mobashery, M. Johnston, *J. Org. Chem.* 1985, **50**, 2200; (b) R. Wilder, S. Mobashery, *J. Org. Chem.* 1992, **57**, 2755.
24 J. C. Sheehan, D. W. Chapman, R. W. Roth, *J. Am. Chem. Soc.* **1952**, *71*, 3823.
25 (a) E. M. Kaiser, R. A. Woodruff, *J. Org. Chem*., 1970, **35**, 1198; (b) G. P. Crowther, E. M. Kaiser, R. A. Woodruff, C. R. Hauser, A. Brossi, R. A. LeMahieu and P. LaSalle, *Org. Synth.*, 1971, **51**, 96.
26 Z. J. Kamiki, P. Paneth, J. Rudzinski, *J. Org. Chem.* **1998**, 63, 4248.
27 For the substitution of all chlorine atoms on the triazine core of TCT through *O*- and *N*-nucleophiles, respectively, the reaction temperature has to be gradually raised from 0 to 60 °C (see ref. 11). This experimental observation is most probably rationalized by a decreasing reaction rate for the consecutive S_NAr-substitutions in the order $1^{st} > 2^{nd} > 3^{rd}$ Cl-atom. since each replacement introduces a new electron donating substituent. In contrast, the present method allows quantitative conversion of sterically unbiased acids such as dodecanoic acid already at room temperature (see Table S3, entries 1+2+12, ESI). Since 40 mol% of TCT (= 1.2 equiv) have been applied, even the 3rd chlorine atom of TCT must have been partially replaced.
28 J. Burés, *Angew. Chem. Int. Ed.* 2016, **55**, 2028.

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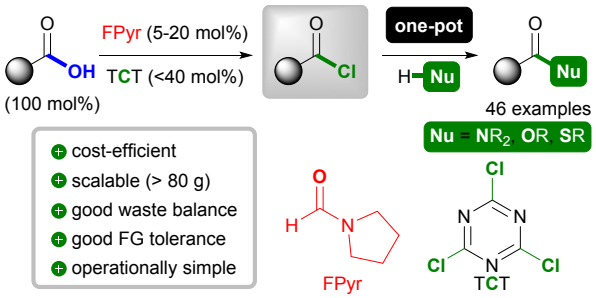

Formamide catalysis enables highly cost-efficient amide C-N and ester C-O bond formation through carboxylic acid chlorides as essential intermediates.