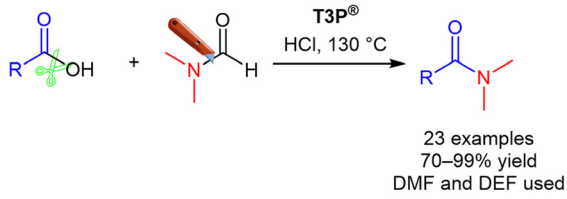
Synthesis L. Bannwart et al. Paper

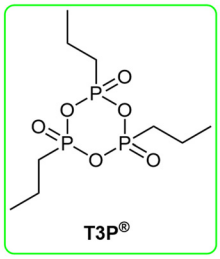
Metal-Free Amidation of Acids with Formamides and T3P®

Linda Bannwart
Stefan Abele
Simone Tortoioli*

Chemistry Process R&D, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, 4123 Allschwil, Switzerland
simone.tortoioli@actelion.com

This paper is dedicated to the memory of the inspirational late Professor Vincenzo Caia.





Received: 12.02.2016
Accepted after revision: 07.03.2016
Published online: 12.04.2016
DOI: 10.1055/s-0035-1561427; Art ID: ss-2016-t0107-op

Abstract A new, simple and metal-free method for the direct formation of dialkylamides from carboxylic acids employing *N*,*N*-dialkylformamides as amine source is described. The one-pot reaction is promoted by propylphosphonic anhydride (T3P®) in the presence of 0.5 equivalents of HCl.

Key words formamides, propylphosphonic anhydride, amidation, carboxylic acids, metal-free

Amides are recurring moieties in natural products, commercial drugs and agrochemicals, and they are routinely prepared from carboxylic acids by acid activation (e.g., acid chlorides) and coupling with amines.[1] This efficient and general approach suffers from being a multistep sequence involving relatively unstable intermediates; in addition, high pressures might be required for volatile amines. Small formamides such as *N*,*N*-dimethylformamide (DMF) are very attractive as alternative and cheap amine sources[2] especially when they can be employed in one pot at the acid activation step. The use of thionyl chloride, phosphorous pentoxide, and 1,1′-carbonyldimidazole as reagents for this purpose has been documented,[3] however with limited applications and scope or requiring extremely high temperatures. More recently, a radical copper-catalyzed oxidative coupling of acids that avoids pre-activation has been developed to prepare several types of simple amides.[4] Excess of oxidant [1.5–3 equiv of *t*-butyl hydroperoxide (TBHP) or di-*t*-butyl peroxide (TBP)] at elevated temperatures is required, which poses serious problems of process safety, particularly for large-scale applications, in addition to the production of metal wastes that are difficult to treat on scale.

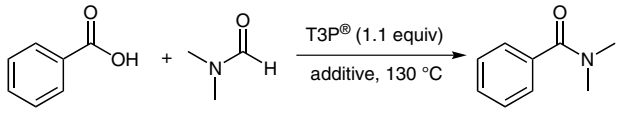
Alternative methods that are amenable for scale-up and that could take advantage of available formamides as amine surrogates without the need for potentially explosive reagents and metal promoters or without required handling of highly corrosive and irritating reagents would be desirable.

T3P® is the trade name of propylphosphonic anhydride, which is a stable, low-toxicity and convenient reagent that is mostly used for peptide couplings and amide formations in both academia and industrial settings.[5] In the course of our application of T3P® for ordinary amide couplings, we observed, besides the expected product, the formation of small amounts of *N*,*N*-dimethylamide impurity when DMF was used as solvent. With the aim to translate this finding into a productive transformation, we started a study with benzoic acid (**1**) as the model substrate (Table 1).

When only T3P® was employed, the desired *N*,*N*-dimethylbenzamide product **2** was observed after 22 hours at 130 °C, albeit with low conversion (47%; Table 1, entry 1), whereas in the absence of T3P® no reaction occurred and unreacted acid was recovered (entry 2). The effect of a series of additives was then studied. Bases such as Et_3N and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) did not significantly affect the reaction (entries 3 and 4), whereas conversion was enhanced in the presence of NH_4Cl along with the formation of the expected nitrile and benzamide derivatives (entry 5).[6] Full conversion was achieved with Et_4NCl (entry 7)[6d] and weak acids such as Et_3NHCl and pyridinium chloride could also be employed in sub-stoichiometric amounts (entries 8–10). When the amount of T3P® was lowered to 0.5 equivalents, a decrease in reaction conversion was observed (entries 11 vs. 8). HCl 4 M in dioxane was identified to be very effective, with full conversion being achieved after only 5 hours (entry 12). Other strong acids such as conc.

aqueous HBr, H_2SO_4, and TfOH, TsOH, and trifluoroacetic acid (TFA) were screened, but these conditions resulted in either lower conversions or in side-product formation.[7]

Table 1 Conditions Screening for the Amidation of Benzoic Acid (**1**) with DMF



1 **2**

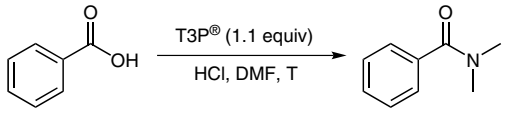
Entry	Additive (equiv)	Time (h)	Conv. (%)[a]
1	–	22	47
2[b]	NH_4Cl (1.1)	22	0
3	Et_3N (1.1)	20	23
4	DMAP (0.5)	22	68
5[c]	NH_4Cl (1.1)	22	56
6	$B(OH)_3$ (1.1)	48	6
7	Et_4NCl (1.1)	22	98
8	Et_3NHCl (0.5)	21	98
9	Et_3NHCl (0.2)	22	97
10	Py·HCl (0.5)	22	96
11[d]	Et_3NHCl (0.5)	29	83
12[e]	HCl (0.5)	5	99

[a] Conversion (% a/a) based on LC/MS analysis: [area% dimethylamide **2** / (area% acid **1** + area% T3P® adducts + amide **2**)] × 100 (see experimental section).
[b] No T3P® employed.
[c] 20% nitrile and 3% **2** formed (85% total conversion).
[d] 0.5 equiv of T3P® used.
[e] HCl (4 M in dioxane) used.

The superior effect of HCl in the reaction and its intrinsic simplicity, led us to focus our attention on this additive; a summary of the reaction optimization is reported in Table 2. An increased amount of acid did not reduce the reaction time (entry 2), whereas when it was used in catalytic amounts (10%) the reaction still proceeded to full conversion but with prolonged times (entry 3). Aqueous HCl resulted in lower conversion after 48 hours (entry 4), presumably because of the negative effect of water on the reaction. The temperature was also found to play a crucial role since at 110 °C the reaction was slower but reached full conversion, whereas the reactivity was considerably decreased when the reaction was conducted at 80 °C (entries 5 and 6).

Having identified the optimal operating conditions, we proceed to study the substrate scope of our amidation reaction (Scheme 1). Electron-withdrawing and electron-donating substituents on the benzene ring were well tolerated, although decreased reactivity was observed with the 3,4-dimethoxy derivative (substrate **3**).

Table 2 Reaction Optimization



1 **2**

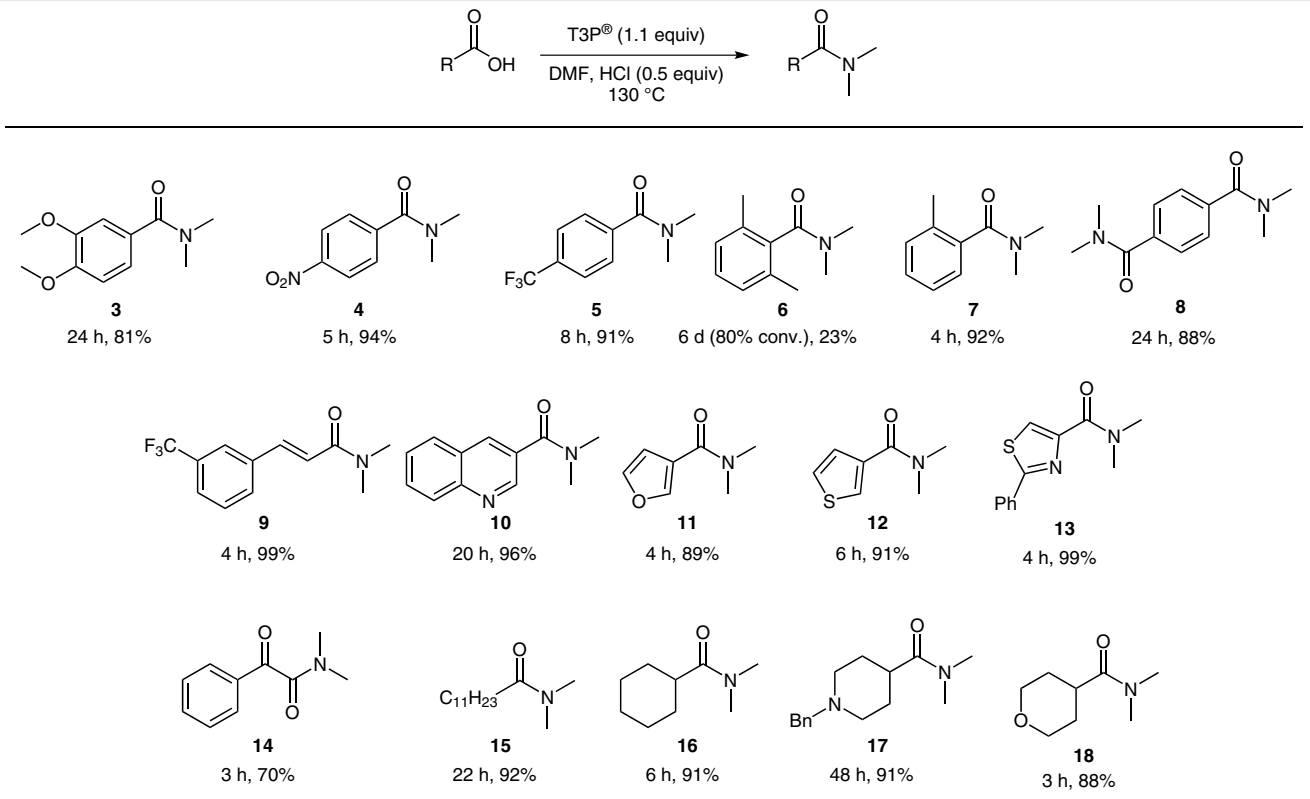
Entry	HCl (equiv)	Time (h)	Conv. (%)[a]	Yield (%)[b]
1	0.5	5	>99	89
2	1.0	5	>99	–
3	0.1	21	97	80
4	aq HCl (0.5)[c]	48	86	–
5	0.5[d]	22	>99	91
6	0.5[e]	22	58	–

[a] Conversion (% a/a) base on LC/MS analysis: [area% dimethyl amide **2** / (area% acid **1** + area% T3P® adducts + amide **2**)] × 100 (see experimental section).
[b] Yield of isolated product (see experimental section).
[c] Conc. HCl 32% in water used.
[d] Reaction temperature was 110 °C.
[e] Reaction temperature was 80 °C.

Steric effects also have an influence on the reaction, as observed with the 2,6-dimethyl derivative **6**, which required six days to reach 80% conversion but was recovered only in 23% yield, probably due to decomposition of both product and starting material after such prolonged heating.[8] In contrast, we were pleased to see that the *ortho*-methyl substituted derivative **7** performed well. Excellent yields were also obtained with terephthalic acid (compound **8**) and with cinnamic substrate **9**.

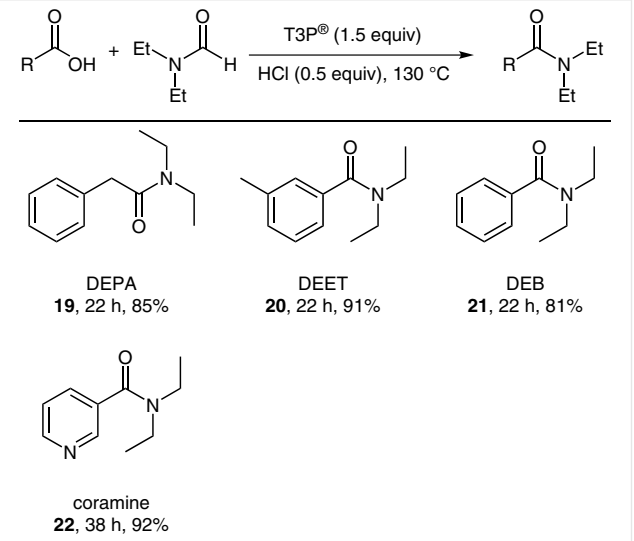
Amidation of heteroaryl carboxylic acids such as quinoline, furan, thiophene and thiazole derivatives was generally fast and high-yielding (substrates **10**–**13**). In the case of α-oxo-carboxylic acid, the expected product **14** was obtained in slightly lower yield because of the formation of dimethylamide **2** as side-product, resulting from the competing acid-catalyzed decarbonylation process occurring at this temperature. Aliphatic substrates also performed very well with both acyclic and cyclic derivatives, with **15** and **16** being obtained in high yields. In addition, dimethylamides from heterocyclic substrates such as *N*-benzylpiperidine and pyran **17** and **18** could be prepared in 91 and 88% yields, respectively, with the slow reacting piperidyl substrate requiring 48 hours for full conversion.

The study was then extended to the preparation of diethylamides by employing *N*,*N*-diethylformamide as diethylamine source; the results are shown in Scheme 2. Also in this case the reaction performed well, with 1.5 equivalents of T3P® needed for full conversion within 22 to 38 hours. This transformation is particularly useful because a series of compounds with important commercial applications could be conveniently prepared. Insect repellents DEPA (**19**),[9] DEB (**21**)[10] and well-known DEET (**20**)[11] were



Scheme 1 Scope of the amidation with DMF. Reaction time to reach conversion of ≥95% and yields of isolated products are reported; HCl 4 M in dioxane was used.

obtained in high yields (81–91%), whereas coramine **22**,[12] a stimulant that is widely employed in the mid-twentieth century, was prepared in 92% yield.

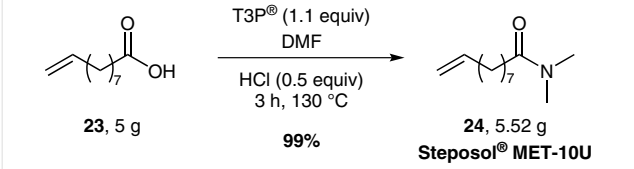


Scheme 2 Amidation with *N*,*N*-diethylformamide. Reaction time to reach conversion of ≥95% with yields of isolated products are reported; HCl 4 M in dioxane used.

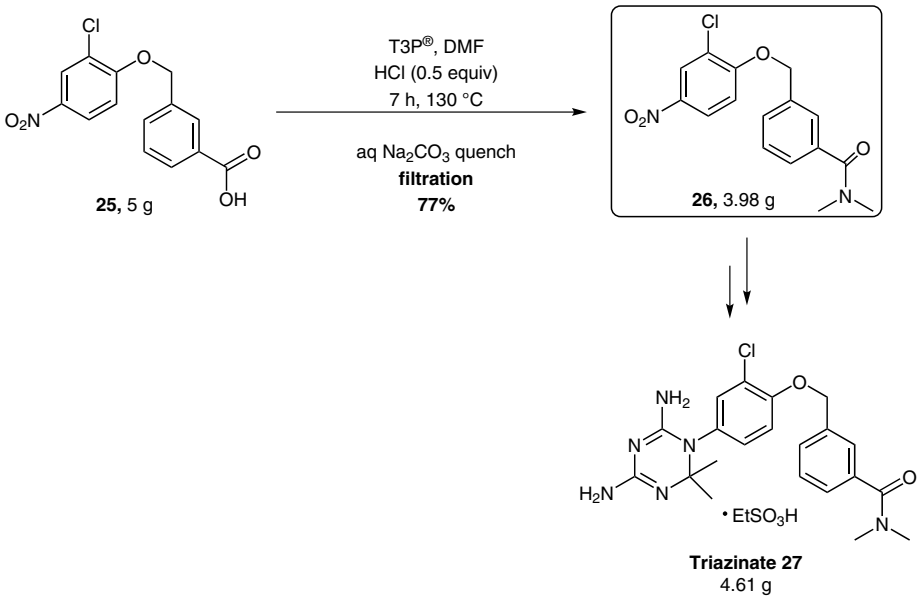
As limitations for this amidation protocol, less reactive *p*-toluenesulfonic acid did not convert into the corresponding sulfimide, and only unreacted starting material was recovered; with indole-3-carboxylic acid and N-Cbz-L-proline, degradation of the substrate or formation of side-products was observed. Amidation with *N*-methylformamide of **1** resulted in incomplete conversion and the formation of side-products besides the desired *N*-methylcarboxamide.

To demonstrate the synthetic utility of the reaction, we performed preparative-scale syntheses of industrially relevant compounds.

Steposol® MET-10U is the trade name of *N*,*N*-dimethyl-9-decenamide (**24**), a biodegradable product used as cleaning solvent with a huge range of applications in the field of surfactants for metal, paint, and adhesive cleaning.[13] This



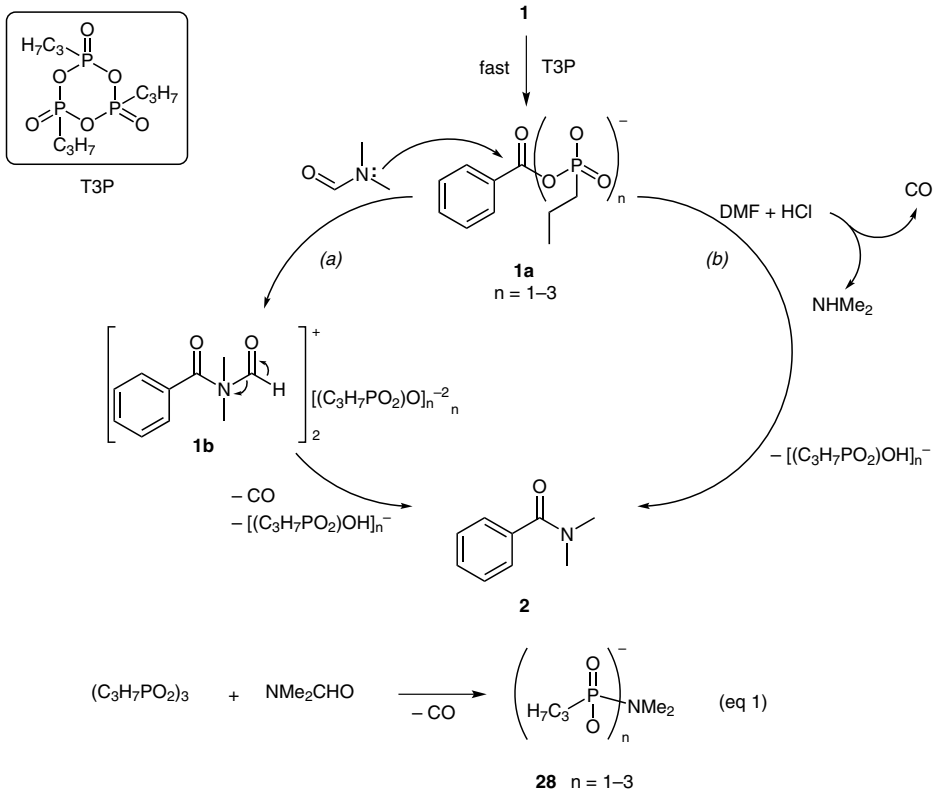
Scheme 3 Preparation of Steposol® MET-10U **24**



Scheme 4 Synthesis of triazinate **27**

amide was readily obtained on a 5 gram scale by using our method from the corresponding acid **23** after 3 hours in 99% yield (Scheme 3).

Triazinate **27** is a dihydrofolate reductase inhibitor that underwent clinical studies on combination therapies for the treatment of neoplastic disorders.[14] The synthesis in-



Scheme 5 Mechanistic hypothesis of the T3P®-mediated amidation with DMF

volves the formation of key dimethylamide intermediate **26** through classical acid activation with $SOCl_2$ of **25** followed by treatment with dimethylamine.[15] With our method, direct conversion of acid **25** into the dimethylamide was achieved within 7 hours and pure product was conveniently recovered by simple filtration in 77% yield after quenching the reaction with aqueous Na_2CO_3 (Scheme 4, see experimental section for details). The target product was then obtained as described in the original synthesis.[15]

Two different pathways are conceivable for this amidation reaction, as depicted in Scheme 5 (benzoic acid (**1**) is taken for simplicity). Mixed anhydrides of type **1a** formed by the reaction of acid **1** with T3P®,[16] could be attacked by the dimethylamine moiety of DMF to give product **2** and CO through intermediate **1b** (pathway *a*).[17] Alternatively, dimethylamine formed from DMF decomposition, could be trapped by anhydrides **1a** affording amide **2** after addition–elimination (pathway *b*).

DMF decomposition to CO and $NHMe_2$ in the presence of mineral acids and heating is well known[17] and also in our case CO was detected[18a] in the off-gas of a control experiment with DMF and HCl at 130 °C, indicating pathway (*b*) as mechanism and demonstrating that the formation of dimethylamine and CO are independent of the presence of intermediates **1a**. A radical cleavage of DMF can, in this case, be ruled out because the presence of styrene as a radical scavenger had no influence on the reaction. In addition, an experiment with DMF, HCl, and T3P® at 130 °C showed a larger evolution of CO than without T3P®, suggesting that phosphonic anhydride itself promotes the decomposition of DMF to generate dimethylamine and carbon monoxide (supporting pathway (*b*)). As a mechanism for the cleavage of DMF promoted by T3P®, it is tentatively proposed that phosphonoamidates of type **28** are formed, resulting from attack of the nitrogen of DMF to T3P® with the liberation of CO (Scheme 5, equation 1).[18b]

In conclusion, a new, operationally simple method for the synthesis of dialkylamides has been presented. The method is suitable for a large range of aromatic, heteroaromatic, and alkyl carboxylic acids and shows good functional group tolerance. The amine sources are commodity chemicals such as dimethyl- and diethylformamide, which are also easy to handle liquids. Compared with existing methods, the procedure reported herein does not require metal catalysts, stoichiometric oxidants, or highly corrosive reagents, which are important aspects especially for large-scale processes. Low toxic propylphosphonic anhydride (T3P®) is key for this transformation, which represents an additional application of this versatile reagent in organic synthesis.

All the chemicals employed are commercially available and were used as such with no further purification. Solution of T3P® in DMF was purchased from Euticals; T3P® in diethylformamide was prepared from a sample of neat T3P®.

Infrared spectra were recorded with a Perkin Elmer SPECTRUM ONE-Spectrophotometer and are reported as cm^{-1} (w = weak, m = medium, s = strong). High-resolution mass spectrometric measurements were performed with a SYNAPT G2 MS (Waters) Q-Tof instrument that can provide up to 40,000 FWHM resolution, data-acquisition rate of 20 spectra/second, exact mass (1 ppm RMS) information and a dynamic range of up to five orders of magnitude (conditions for analysis are provided below). LC/MS analyses were performed with a Dionex HPG-3200RS binary pump coupled with Thermo MSQ Plus MS (ionization: ESI+), Dionex DAD-3000RS and Column oven Dionex TCC-3200. Conditions for analysis are provided below. Melting points were measured with a Büchi B-540 melting point apparatus using open glass capillaries. ^1H and ^{13}C (proton decoupled) spectra were recorded with a Bruker NMR 500 MHz Avance HD spectrometer equipped with a DCH-Cryoprobe (500 and 125 MHz, respectively). ^{19}F spectra were recorded with a Bruker NMR 400 MHz Avance 2, spectrometer with 5 mm BBO Probehead at 375 MHz. Chemical shifts (δ) values are reported in parts per million (ppm) using residual solvent signal ($CHCl_3$ or DMSO) as reference and the coupling constants (*J*) are reported in Hz. Compounds **9**, **10**, **13**, **15**, **17**, and **18** are novel and were characterized by ^1H, ^{13}C NMR, IR and HRMS analyses.

T3P®-Mediated Amidation with DMF; General Procedure

A 20 mL Radleys Carousel screw-capped glass tube was charged with carboxylic acid (2 mmol, 1.0 equiv), DMF (1.2 mL), T3P® in DMF 50% (1.28 mL, 1.4 g, 1.1 equiv) and HCl (4 M in dioxane, 0.25 mL, 1.0 mmol, 0.5 equiv) at r.t. The mixture was heated to 130 °C (ca. 120 °C internal) and stirred until the conversion according to LC-MS or TLC was ≥95%. The solution was quenched at 10 °C with aq half-saturated Na_2CO_3 (5 mL; *caution*: gas evolution) and extracted with *i*-PrOAc (10 mL and 2 × 5 mL or until no product was present in the aqueous phase). Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel as described below.

T3P®-Mediated Amidation with *N*,*N*-Diethylformamide; General Procedure

The experimental protocol is similar to that with DMF with the difference that a 50% solution of T3P® in *N*,*N*-diethylformamide (1.91 g, 3 mmol, 1.5 equiv) and *N*,*N*-diethylformamide (1.2 mL) were employed. Upon reaching full conversion, the reaction mixture was treated as described for the work-up of the DMF protocol and the products purified as detailed below.

N,*N*-Dimethylbenzamide (2)[4a]

The reaction was performed according to the general procedure with benzoic acid (**1**) as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness, and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give a colorless oil that tended to crystallize upon standing.

Yield: 531 mg (89%); mp 42–44 °C (lit.[4j] 42–43 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (m, 5 H), 3.13 (s, 3 H), 2.99 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.64, 136.38, 129.52, 128.36, 127.07, 39.61, 35.37.

MS: m/z = 150.14 $[M + 1]^+$.

The analytical data are consistent with reported data.

3,4-Dimethoxy-*N*,*N*-dimethylbenzamide (3)[4i]

The reaction was performed according to the general procedure with 3,4-dimethoxybenzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:9) to give **3**.

Yield: 339 mg (81%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94–7.02 (m, 2 H), 6.80–6.90 (m, 1 H), 3.90 (d, *J* = 3.8 Hz, 6 H), 3.06 (br s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.45, 150.11, 148.81, 128.62, 120.20, 110.89, 110.36, 55.98, 39.88, 35.56.

MS: *m*/*z* = 210.17 $[M + 1]^+$.

The analytical data are consistent with reported data.

4-Nitro-*N*,*N*-dimethylbenzamide (4)[4h]

The reaction was performed according to the general procedure with 4-nitrobenzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:9) to give **4**.

Yield: 365 mg (94%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.2 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 3.16 (s, 3 H), 2.98 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.27, 148.29, 142.52, 128.09, 123.82, 39.35, 35.39.

MS: *m*/*z* = 195.19 $[M + 1]^+$.

The analytical data are consistent with reported data.

4-Trifluoromethyl-*N*,*N*-dimethylbenzamide (5)[4h]

The reaction was performed according to the general procedure with 4-trifluoromethylbenzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness, and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:4) to give **5**.

Yield: 395 mg (91%); white solid; mp 95–96 °C (lit.[19b] 96 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 3.14 (s, 3 H), 2.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.15, 139.93, 131.89, 131.63, 131.37, 131.11, 127.42, 125.55, 125.52, 125.49, 125.46, 39.43, 35.35.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –62.90.

MS: *m*/*z* = 218.13 $[M + 1]^+$.

The analytical data are consistent with reported data.

2,6-Dimethyl-*N*,*N*-dimethylbenzamide (6)[20]

The reaction was performed according to the general procedure with 2,6-dimethylbenzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give **6**.

Yield: 80 mg (23%); off-white solid; mp 63–64 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13–7.18 (m, 1 H), 7.03 (m, 2 H), 3.17 (s, 3 H), 2.81 (s, 3 H), 2.25 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.30, 136.71, 133.49, 128.25, 127.47, 37.44, 34.18, 18.98.

MS: *m*/*z* = 178.25 $[M + 1]^+$.

The analytical data are consistent with reported data.

2-Methyl-*N*,*N*-dimethylbenzamide(7)[4i]

The reaction was performed according to the general procedure with 2-methylbenzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give **7**.

Yield: 299 mg (92%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.27 (m, 1 H), 7.14–7.20 (m, 3 H), 3.12 (s, 3 H), 2.82 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.51, 136.75, 133.95, 130.32, 128.73, 125.91, 125.79, 38.39, 34.55, 18.92.

MS: *m*/*z* = 164.08 $[M + 1]^+$.

The analytical data are consistent with reported data.

***N*,*N*,*N*′,*N*′-Tetramethylterephthalamide (8)**[3d]

The reaction was performed according to the general procedure with terephtalic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (20 g Isolute SPE column, Flash Si II; CH_2Cl_2–MeOH, 10:0 to 96:4) to give **8**.

Yield: 387 mg (88%); white solid; mp 200–202 °C (lit.[21] 200–202 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.63 (m, 4 H), 3.13 (s, 6 H), 2.98 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.88, 137.51, 127.14, 39.53, 35.37.

MS: *m*/*z* = 221.15 $[M + 1]^+$.

The analytical data are consistent with reported data.

(*E*)-*N*,*N*-Dimethyl-3-[3-(trifluoromethyl)phenyl]acrylamide (9)

The reaction was performed according to the general procedure with (*E*)-3-[3-(trifluoromethyl)phenyl]acrylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:4) to give **9**.

Yield: 480 mg (99%); white solid; mp 107–110 °C (lit.[22] 82–84 °C).

IR: 2929 (m), 1957 (w), 1649 (s), 1610 (s), 1490 (m), 1395 (s), 1324 (s), 1163 (s), 1066 (s), 976 (m), 830 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.5 Hz, 1 H), 7.64 (s, 4 H), 6.99 (d, *J* = 15.5 Hz, 1 H), 3.21 (s, 3 H), 3.10 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.07, 140.61, 138.81, 131.49, 131.23, 130.97, 130.71, 127.92, 125.81, 125.78, 125.75, 125.72, 125.03, 122.87, 119.99, 37.49, 36.02.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –62.77.

MS: *m*/*z* = 244.17 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}NOF_3$: 244.0944; found: 244.0953.

***N*,*N*-Dimethylquinoline-3-carboxamide (10)**[23]

The reaction was performed according to the general procedure with 3-quinolinecarboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to only EtOAc) to give **10**.

Yield: 385 mg (96%); yellow solid; mp 63–64 °C.

IR: 2927 (m), 2159 (w), 1724 (m), 1612 (s), 1499 (m), 1392 (s), 1255 (m), 1075 (s), 932 (s), 858 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.00 (d, *J* = 2.1 Hz, 1 H), 8.28 (d, *J* = 1.9 Hz, 1 H), 8.15–8.16 (m, 1 H), 7.88 (dd, *J* = 1.1, 8.2 Hz, 1 H), 7.80 (m, 1 H), 7.63 (m, 1 H), 3.21 (s, 3 H), 3.03–3.10 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.13, 148.59, 148.26, 135.11, 130.69, 129.45, 129.23, 128.30, 127.44, 127.05, 39.73, 35.62.

MS: *m*/*z* = 201.18 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}N_2O$: 201.1023; found: 201.1025.

N,*N*-Dimethylfuro-3-carboxamide (11)[24]

The reaction was performed according to the general procedure with 3-furoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:1) to give **11**.

Yield: 248 mg (89%); off-white solid; mp 68–70 °C (lit.[24b] 70–71 °C).

^1H NMR (500 MHz, DMSO-d_6): δ = 8.07 (dd, *J* = 0.9, 1.4 Hz, 1 H), 7.73 (m, 1 H), 6.70 (dd, *J* = 0.8, 1.8 Hz, 1 H), 3.09 (br s, 3 H), 2.95 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.95, 144.49, 143.62, 121.72, 111.30, 38.88, 35.72.

MS *m*/*z* = 140.12 $[M + 1]^+$.

The analytical data are consistent with reported data.

N,*N*-Dimethylthiophene-3-carboxamide (12)[25]

The reaction was performed according to the general procedure with 3-thiophenecarboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give **12**.

Yield: 283 mg (91%); colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 1.2, 3.0 Hz, 1 H), 7.28 (dd, *J* = 3.0, 5.0 Hz, 1 H), 7.19 (dd, *J* = 1.2, 5.0 Hz, 1 H), 3.05 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.87, 136.80, 127.28, 126.42, 125.62, 39.37, 35.54.

MS: *m*/*z* = 156.09 $[M + 1]^+$.

The analytical data are consistent with reported data.

N,*N*-Dimethyl-2-phenylthiazole-4-carboxamide (13)

The reaction was performed according to the general procedure with 2-phenylthiazole-4-carboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4.5:0.5 to 3.5:1.5) to give **13**.

Yield: 461 mg (99%); low-melting yellow solid; mp 30–31 °C.

IR: 3488 (w), 2926 (m), 1975 (w), 1624 (s), 1504 (m), 1462 (s), 1388 (s), 1174 (s), 1077 (m), 993 (s), 826 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.96–7.98 (m, 2 H), 7.90 (s, 1 H), 7.44–7.47 (m, 3 H), 3.38 (s, 3 H), 3.16 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.15, 164.13, 151.75, 133.20, 130.43, 129.05, 126.63, 123.80, 39.20, 36.37.

MS: *m*/*z* = 233.20 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}N_2OS$: 233.0743; found: 233.0745.

N,*N*-Dimethyl-2-oxo-2-phenylacetamide (14)[4f]

The reaction was performed according to the general procedure with 2-oxo-2-phenylacetic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (20 g Isolute SPE column, Flash Si II; heptane–EtOAc, 8:1 to 1:1) to give **14**.

Yield: 248 mg (70%); colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 1.2, 7.2 Hz, 2 H), 7.61–7.64 (m, 1 H), 7.48–7.51 (m, 2 H), 3.05–3.10 (m, 3 H), 2.90–2.96 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.85, 167.06, 134.77, 133.04, 129.64, 129.04, 37.05, 33.99.

MS: *m*/*z* = 178.23 $[M + 1]^+$.

The analytical data are consistent with reported data.

N,*N*-Dimethyldodecanamide (15)

The reaction was performed according to the general procedure with lauric acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:1) to give **15**.

Yield: 419 mg (92%); colorless oil.

IR: 2922 (s), 2853 (s), 1648 (s), 1395 (s), 1266 (w), 1144 (m), 1060 (w), 721 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.02 (s, 3 H), 2.96 (s, 3 H), 2.32 (m, 2 H), 1.58–1.66 (m, 2 H), 1.23–1.36 (m, 16 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.27, 37.30, 35.34, 33.45, 31.93, 29.65, 29.64, 29.55, 29.50, 29.35, 25.22, 22.70, 14.14.

MS: *m*/*z* = 228.24 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{29}NO$: 228.2322; found: 228.2331.

N,*N*-Dimethylcyclohexanecarboxamide (16)[26]

The reaction was performed according to the general procedure with cyclohexane carboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:1) to give **16**.

Yield: 283 mg (91%); colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.02 (s, 3 H), 2.91 (s, 3 H), 2.47 (tt, *J* = 3.3, 11.6 Hz, 1 H), 1.77 (m, 2 H), 1.61–1.71 (m, 3 H), 1.48–1.51 (m, 2 H), 1.21–1.27 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.09, 40.67, 37.05, 35.49, 29.18, 25.89, 25.87.

MS: *m*/*z* = 156.19 $[M + 1]^+$.

The analytical data are consistent with reported data.

1-Benzyl-*N*,*N*-dimethylpiperidine-4-carboxamide (17)

The reaction was performed according to the general procedure with 1-benzylpiperidine-4-carboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (5 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:9) to give **17**.

Yield: 450 mg (91%) yellow solid; mp 83.5–84.5 °C.

IR: 2926 (m), 1730 (w), 1635 (s), 1493 (m), 1341 (m), 1266 (m), 1139 (m), 997 (m), 789 (w) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.35 (m, 4 H), 7.23–7.28 (m, 1 H), 3.53 (s, 2 H), 3.05 (s, 3 H), 2.95 (m, 5 H), 2.49 (tt, *J* = 3.7, 11.4 Hz, 1 H), 2.02 (t, *J* = 11.4 Hz, 2 H), 1.85–1.93 (m, 2 H), 1.68 (d, *J* = 12.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.09, 138.45, 129.09, 128.19, 126.96, 63.27, 53.21, 38.93, 37.06, 35.61, 28.53.

MS: *m*/*z* = 247.16 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{22}N_2O$: 247.1805; found: 247.1809.

N,*N*-Dimethyltetrahydro-2*H*-pyran-4-carboxamide (18)

The reaction was performed according to the general procedure with tetrahydro-2*H*-pyran-4-carboxylic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (10 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to only EtOAc) to give **18**.

Yield: 278 mg (88%); white solid; mp 65–67 °C.

IR: 2951 (s), 2829 (m), 2160 (w), 1673 (m), 1623 (s), 1498 (m), 1389 (s), 1246 (m), 1119 (s), 1036 (m), 882 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.01 (ddd, *J* = 2.1, 4.1, 11.3 Hz, 2 H), 3.44 (td, *J* = 2.2, 11.9 Hz, 2 H), 3.06 (s, 3 H), 2.95 (s, 3 H), 2.75 (tt, *J* = 3.8, 11.3 Hz, 1 H), 1.89 (m, 2 H), 1.60 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.24, 67.33, 37.80, 37.02, 35.67, 28.89.

MS: *m*/*z* = 158.13 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{15}NO_2$: 158.1176; found: 158.1175.

N,*N*-Diethyl-2-phenylacetamide (19)[27]

The reaction was performed according to the general procedure with *N*,*N*-diethylformamide using phenylacetic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (50 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give **19**.

Yield: 327 mg (85%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 2 H), 7.23–7.28 (m, 3 H), 3.72 (s, 2 H), 3.41 (q, *J* = 7.1 Hz, 2 H), 3.31 (q, *J* = 7.1 Hz, 2 H), 1.14 (t, *J* = 7.1 Hz, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.12, 135.56, 128.69, 128.64, 126.66, 42.38, 40.96, 40.16, 14.24, 12.98.

MS: *m*/*z* = 192.24 $[M + 1]^+$.

The analytical data are consistent with reported data.

N,*N*-Diethyl-3-methylbenzamide (20)[28]

The reaction was performed according to the general procedure with *N*,*N*-diethylformamide using *m*-toluic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (50 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 1:2) to give **20**.

Yield: 347 mg (91%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.29 (m, 1 H), 7.19 (m, 2 H), 7.14–7.16 (m, 1 H), 3.54 (br s, 2 H), 3.26 (br s, 2 H), 2.37 (s, 3 H), 1.25 (br s, 3 H), 1.11 (br s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.48, 138.23, 137.29, 129.78, 128.23, 126.94, 123.16, 43.28, 39.16, 21.42, 14.26, 12.96.

The analytical data are consistent with reported data.

N,*N*-Diethylbenzamide (21)[29]

The reaction was performed according to the general procedure with *N*,*N*-diethylformamide using benzoic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (25 g Isolute SPE column, Flash Si II; heptane–EtOAc, 1:2) to give **21**.

Yield: 286 mg (81%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.40 (m, 5 H), 3.56 (br s, 2 H), 3.27 (br s, 2 H), 1.26 (br s, 3 H), 1.13 (br s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.32, 137.31, 129.10, 128.41, 126.29, 43.31, 39.25, 14.26, 12.95.

MS: *m*/*z* = 178.27 $[M + 1]^+$.

The analytical data are consistent with reported data.

N,*N*-Diethylnicotinamide (22)[30]

The reaction was performed according to the general procedure with *N*,*N*-diethylformamide using nicotinic acid as starting material. After work-up, the crude material was absorbed on Celite, concentrated to dryness and purified by chromatography on silica gel (50 g Isolute SPE column, Flash Si II; heptane–EtOAc, 1:1 to only EtOAc) to give **22**.

Yield: 329 mg (92%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.63 (s, 2 H), 7.71 (dd, *J* = 1.7, 7.8 Hz, 1 H), 7.32–7.34 (m, 1 H), 3.55 (s, 2 H), 3.26 (s, 2 H), 1.25 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.56, 150.30, 147.22, 134.27, 133.01, 123.41, 43.45, 39.57, 14.34, 12.90.

MS: *m*/*z* = 179.25 $[M + 1]^+$.

The analytical data are consistent with reported data.

Large-Scale (5 g) Amidation of 9-Decenoic Acid (23) To Give *N*,*N*-Dimethyl-9-decenamide (24; Steposol® MET-10U)[31]

A mixture of 9-decenoic acid (**23**; 5.02 g, 28 mmol, 1 equiv), DMF (16.8 mL), 50% T3P® in DMF (18 mL, 19.6 g, 30.8 mmol, 1.1 equiv) and HCl (4 M in dioxane, 3.5 mL, 14 mmol, 0.5 equiv) was heated to 130 °C until TLC analysis revealed that no starting acid remained (3 h, $KMnO_4$ as staining agent). The mixture was quenched at 10 °C with aq. half-saturated Na_2CO_3 (70 mL, *caution*: gas evolution) and extracted with *i*-PrOAc (140 mL and 2 × 70 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was absorbed on Celite and purified by chromatography on silica gel (50 g Isolute SPE column, Flash Si II; heptane–EtOAc, 4:1 to 2:1) to give **24**.

Yield: 5.52 g (99%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.79–5.83 (m, 1 H), 4.92–5.02 (m, 2 H), 2.99 (s, 3 H), 2.92 (s, 3 H), 2.29–2.30 (m, 2 H), 2.03 (m, 2 H), 1.61–1.67 (m, 2 H), 1.32–1.41 (m, 8 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.20, 139.13, 114.15, 37.31, 35.35, 33.79, 33.41, 29.46, 29.31, 28.99, 28.89, 25.18.

MS: *m*/*z* = 198.26 $[M + 1]^+$.

The analytical data are consistent with reported data.

Large-Scale (5 g) Amidation of 3-[(2-Chloro-4-nitrophenoxy)methyl]benzoic Acid (25) To Give 3-[(2-Chloro-4-nitrophenoxy)methyl]-*N*,*N*-dimethylbenzamide (26)[15]

A mixture of benzoic acid **25** (5 g, 15.4 mmol, 1 equiv), DMF (8.9 mL), 50% T3P® in DMF (10.4 mL, 11.3 g, 17.8 mmol, 1.1 equiv) and HCl (4 M in dioxane, 2.03 mL, 8.12 mmol, 0.5 equiv) was heated to 130 °C for 7

h (conversion >95% a/a, LC/MS). The reaction mixture was quenched at 10 °C with aq. half-saturated Na_2CO_3 (50 mL, *caution*: foaming observed). The product precipitated during the quench and was recovered by filtration, washing with H_2O, to give pure amide **26**.

Yield: 3.98 g (77%); off-white solid; mp 116–117 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 2.8 Hz, 1 H), 8.26 (dd, *J* = 2.8, 9.2 Hz, 1 H), 7.48–7.57 (m, 4 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 5.44 (s, 2 H), 2.99 (s, 3 H), 2.90 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.18, 159.26, 141.37, 137.20, 136.24, 129.14, 129.03, 127.37, 126.67, 125.95, 125.09, 122.53, 114.38, 71.06, 39.51, 35.26.

MS: *m*/*z* = 335.04 [M + 1]$^+$.

Synthesis of Triazinate 27[15]

A mixture of amide **26** (3.9 g, 11.7 mmol, 1 equiv) and Raney/Ni (ca. 2.5 g) in EtOH (60 mL) was stirred at 30 °C under 10 bar of hydrogen until full conversion was observed (ca. 20 h). The suspension was filtered over Celite, washing with EtOH (ca. 30 mL) and the filtrate was concentrated under reduced pressure to dryness to provide the corresponding aniline.

Yield: 3.45 g (97%, >95% a/a); brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 2 H), 7.38–7.44 (m, 2 H), 6.73–6.85 (m, 2 H), 6.51 (dd, *J* = 2.5, 8.6 Hz, 1 H), 5.07 (s, 2 H), 3.13 (s, 3 H), 2.98 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.40, 146.89, 141.53, 137.41, 136.53, 128.64, 128.45, 126.66, 125.98, 124.50, 117.18, 117.08, 114.28, 71.86, 39.64, 35.42.

MS: *m*/*z* = 305.17 [M + 1]$^+$.

The amine was of sufficient purity to be used in the next step without any further purification.

To a solution of amine intermediate (3.38 g, 11.1 mmol, 1 equiv) in acetone (35 mL) was added ethylsulfonic acid (0.96 mL, 11.6 mmol, 1.05 equiv) and cyanoguanidine in one portion (1.03 g, 12.2 mmol, 1.1 equiv). The resulting mixture was heated to reflux and the formation of a precipitate was observed over the time. After reaching full conversion (6 h) the suspension was cooled to 0 °C, filtered, and the was solid washed with acetone (ca. 20 mL) to give triazinate **27**.

Yield: 4.61 g (77%); off-white solid; mp 212–213.5 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.86 (s, 1 H), 7.49–7.57 (m, 4 H), 7.37–7.41 (m, 3 H), 5.31 (m, 2 H), 3.00 (s, 3 H), 2.91 (s, 3 H), 2.47 (q, *J* = 7.4 Hz, 2 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.10 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.27, 157.89, 157.86, 154.90, 137.14, 136.94, 132.06, 130.74, 129.08, 128.93, 128.42, 127.17, 126.51, 122.71, 115.25, 70.43, 70.29, 45.69, 35.26, 27.68, 27.58, 10.33.

MS: *m*/*z* = 429.12 [M + 1]$^+$.

Acknowledgment

Dr. Hasim Ibrahim is thanked for discussions and encouragement. Dr. Peter Pojarliev from Euticals is thanked for generous gifts of T3P® samples. We would also like to thank François Le Goff and Jürgen Seifert for HRMS and IR analyses.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561427.

References

(1) For a review on amide bond formation, see: Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.
(2) Ding, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9226.
(3) (a) $SOCl_2$: Kumagai, T.; Anki, T.; Ebi, T.; Konishi, A.; Matsumoto, K.; Kurata, H.; Kubo, T.; Katsumoto, K.; Kitamura, C.; Kawase, T. *Tetrahedron* **2010**, *66*, 8968. (b) P_2O_5: Schindlbauer, H. *Monatsh. Chem.* **1968**, *99*, 1799. (c) P_2O_5: Ciszek, J. W.; Keane, Z. K.; Cheng, L.; Stewart, M. P.; Yu, L. H.; Natelson, D.; Tour, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3179. (d) 1,1-Carbonyldimidazole with *N*,*N*-dimethylacetamide: Aavula, S. K.; Chikkulapally, A.; Hanumanthappa, N.; Jyothi, I.; Kumar, C. H. V.; Manjunatha, S. G.; Sythana, S. K. *J. Chem. Res.* **2013**, 155.
(4) (a) Santhosh Kumar, P.; Sathish Kumar, G.; Arun Kumar, R.; Veera Reddy, N.; Rajender Reddy, K. *Eur. J. Org. Chem.* **2013**, 1218. (b) Priyadarshini, S.; Amal Joseph, P. J.; Lakshmi Kantam, M. *RSC Adv.* **2013**, *3*, 18283. (c) Xie, Y.-X.; Song, R.-J.; Yang, X.-H.; Xiang, J.-N.; Li, J.-H. *Eur. J. Org. Chem.* **2013**, 5737. (d) Liu, H. Q.; Liu, J.; Zhang, Y.-H.; Shao, C.-D.; Yu, J.-X. *Chin. Chem. Lett.* **2015**, *26*, 11. (e) From cinnamic acids: Yan, H.; Yang, H.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *Tetrahedron* **2013**, *69*, 7258. (f) From cinnamic acids: Li, H.; Pan, C.; Cheng, Y.; Zhu, C. *Tetrahedron Lett.* **2013**, *54*, 6679. (g) From α-oxocarboxylic acids: Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Biomol. Chem.* **2013**, *11*, 4573. (h) From α-oxocarboxylic acids: Li, D.; Wang, M.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640. (i) From aldehydes: Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 3231. (j) From alcohols: Xu, K.; Hu, Y.; Zhang, S.; Zha, Z.; Wang, Z. *Chem. Eur. J.* **2012**, *18*, 9793.
(5) (a) Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13*, 5048. (b) Millbanks, C. In *e-EROS Encyclopedia of Reagents for Organic Synthesis [Online]*; Wiley & Sons: New York, **2001**. (c) Koch, P.; Vedder, C.; Schaffer, T. *Chim. Oggi* **2008**, *26*, 6. For additional applications of T3P® see: (d) Review: Augustine, J. K.; Vairaperumal, V.; Narasimhan, S.; Alagarsamy, P.; Radharkrishnan, A. *Tetrahedron* **2009**, *65*, 9989. (e) Review: Vishwanatha, B. T. M.; Panguluri, N. R.; Sureshbabu, V. V. *Synthesis* **2013**, *45*, 1569. (f) Augustine, J. K.; Bombrun, A.; Mandal, A. B.; Alagarsamy, P.; Atta, R. N.; Selvam, P. *Synthesis* **2011**, 1477.
(6) T3P® is also used as dehydrating agent to form nitriles. For representative examples, see: (a) Herold, P.; Mah, R.; Tschinke, V.; Stajanovic, A.; Behnke, D.; Marti, C.; Stutz, S.; Jelakovic, S. EP1958634A2, **2008**. (b) Meudt, A.; Scherer, S.; Nerdinger, S. WO2005/070879A1, **2005**. (c) Augustine, J. K.; Atta, R. N.; Ramappa, B. K.; Boodappa, C. *Synlett* **2009**, 3378. (d) The exact role of Et_4NCl is unclear; however, it can be postulated that it acts as a weak acid that could enhance DMF cleavage, therefore promoting the reaction.
(7) Pure TfOH, TsOH, and TFA were employed; for HBr and H_2SO_4, aqueous concentrated solutions were used.
(8) An efficient method for the synthesis of sterically hindered secondary amides has been reported, see: Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9173.
(9) *N*,*N*-Diethyl-2-phenylacetamide (DEPA): (a) Martensson, O.; Nilsson, E. *Acta Chem. Scand.* **1960**, *14*, 1129. (b) Hougard, J.-M.; Pennetier, C. US2007/122437 A1, **2007**. (c) Von Deyn, W.;

Bastiaans, H. M. M.; Pohlman, M.; Rack, M.; Baumann, E.; Puhl, M.; Hofmann, M.; Tedeschi, L.; Kordes, M.; Koradin, C.; Anspaugh, D. D.; Culbertson, D. L.; Cotter, H. V. T.; Oloumi-Sadeghi, H. (BASF Aktiengesellschaft) WO2006/56433A2, **2006**.

(10) *N*,*N*-Diethylbenzamide (DEB): (a) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323. (b) Gruenewald, H.-W.; Axt, A. US2008/319015 A1, **2008**.

(11) *N*,*N*-Diethyl-3-methylbenzamide (DEET): (a) Fradin, M. S.; Day, J. F. *N. Engl. J. Med.* **2002**, *347*, 13. (b) http://www.deet.com/.

(12) *N*,*N*-Diethylnicotinamide (Coramine): (a) Fricker, K. DE653873C, **1934**. (b) *Martindale: The Extra Pharmacopoeia*, 30th ed.; Reynolds, J. E. F., Ed.; The Pharmaceutical Press: London, **1993**, 1229.

(13) http://www.stepan.com/products/Surfactants/STEPOSOL%C2%AE/STEPOSOL%C2%AE-MET-10U.aspx; accessed March 31, 2016.

(14) Manning, P. T.; Misko, T. P. WO2005/025620A2, **2005**.

(15) (a) Chang, P. *Drugs Future* **1989**, *14*, 138. (b) Baker, B. R.; Ashton, W. T. *J. Med. Chem.* **1973**, *16*, 209; and references cited therein.

(16) Intermediates **1a** (*n* = 1–3) have been observed (but not isolated) by LC/MS and the structure was assigned on the basis of *m*/*z* values.

(17) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

(18) (a) Carbon monoxide was observed in the off-gas during the course of the reaction by analysis with a Dräger Pac® 5500 gas detector. (b) The formation of this species was not proven, despite several measurements by ^{31}P NMR spectroscopy of control reaction mixtures.

(19) Baba, H.; Moriyama, K.; Togo, H. *Synlett* **2012**, *23*, 1175.

(20) (a) Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875. (b) Allais, A.; Meier, J.; Mathieu, J.; Nomine, G.; Peterfalvi, M.; Deraedt, R.; Chifflot, L.; Benzoni, J.; Fournex, R. *Eur. J. Med. Chem.* **1975**, *10*, 187.

(21) Schiemenz, G. P.; Stein, G. *Tetrahedron* **1970**, *26*, 2007.

(22) Houlihan, W. J.; Gogerty, J. H.; Ryan, E. A.; Schmitt, G. *J. Med. Chem.* **1985**, *28*, 28.

(23) Yamada, S.; Morita, C. *Chem. Lett.* **2001**, 1034.

(24) (a) Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; da Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. P. *Bioorg. Med. Chem.* **2007**, *15*, 1947. (b) Kinoshita, T.; Icbinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33*, 1313; (melting point).

(25) Tang, D.-T. D.; Collins, K. D.; Ernst, J. B.; Glorius, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 1809.

(26) Sunada, Y.; Kawakami, H.; Imaoka, T.; Motoyama, Y.; Nagashima, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 9511.

(27) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, *15*, 3370.

(28) http://www.sigmaaldrich.com/spectra/fnmr/FNMR009877.PDF; accessed March 31, 2016.

(29) Luo, Q.-L.; Lv, L.; Li, Y.; Tan, J.-P.; Nan, W.; Hui, Q. *Eur. J. Org. Chem.* **2011**, 6919.

(30) http://www.sigmaaldrich.com/spectra/fnmr/FNMR010347.PDF; accessed March 31, 2016.

(31) Yun, J. I.; Kim, H. R.; Kim, S. K.; Kim, D.; Lee, J. *Tetrahedron* **2012**, *68*, 1177.