EurJOC
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A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800378

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800378

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

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Synthesis of amides from alcohols and amines thru a domino oxidative amidation and telescoped transamidation process

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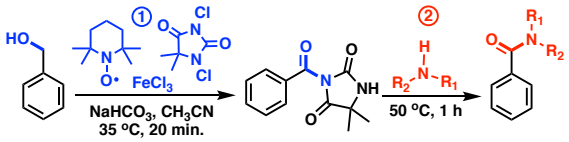
Graphical abstract



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Amides are synthesised from alcohols and amines by means of a domino oxidative amidation and transamidation process. The process is catalysed by TEMPO with iron ions as co-catalyst and 1,3-dichloro-5,5-dimethylhydantoin as the terminal oxidant. The process is conducted under benign reaction conditions using a multi-jet oscillating disk (MJOD) continuous flow reactor platform or using the classical batch approach. Target amides were achieved in yields of up to 90%. The method operates with both primary and secondary amines with benzyl and alkyl alcohols.

Key Topic

Synthetic method – amidation.

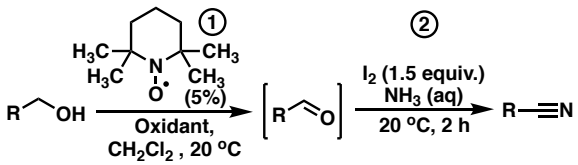
Abstract: The amide bond formation constitute a reaction of paramount importance in organic synthesis, both within academic research and industrial development and manufacturing of pharmaceutical chemicals and other biologically active compounds. Despite this fact, as well as the ever-increasing treatment costs of side streams and other environmental concerns regarding handling and transportation of hazardous reagents, contemporary synthesis has elicited few new reactions and methods for the preparation of amides. Herein, it is revealed a high yielding and expedite two-steps telescoped synthetic process that comprises a domino oxidative amidation and transamidation for the creation of amides. The process utilizes alcohols and amines as reaction pairs with TEMPO and Fe ions as catalytic system and 1,3-dichloro-5,5-dimethyl hydantoin as a terminal oxidant. The oxidative amidation and transamidation process is conducted under benign reaction conditions and short reaction time (≈30 min.) in a two-step telescoped fashion by means of a multi-jet oscillating disk (MJOD) continuous flow reactor platform. The disclosed process integrates alcohol oxidation and amide formation to afford target amide in yields up to 90%. The method operates with both primary and secondary amines together, but was hampered when bulky amine and/or alcohol were used as reagent/substrate.

Introduction

Numerous compounds and advanced materials comprise the amide group, whereof countless of pivotal importance in society and industry. Amides can be synthesized by means of a number of classical synthetic methods including the Schotten-Baumann reaction,[1] the Schmidt reaction,[2] the Beckmann rearrangement,[3] the Ritter reaction,[4] the Staudinger reaction,[5] the multi-component based Ugi reaction,[6] and some more contemporary methods including aminolysis of esters,[7] transamidation of primary amides,[8] amino carbonylation of haloarenes,[9] oxidative amidation of aldehydes,[10] oxidative amidation of alcohols,[11] and metal catalysed N-C bond formation.[12] Renewed interests were lately devoted towards the amide bond synthesis[13] due to steady emerging requirements and legislation for more environmentally benign production processes and cost control in the industry as well as necessities in de novo synthesis and modifications of highly complex proteins, peptides, and small molecules for pharmaceuticals and other fine chemical applications.

A long-standing project in our laboratory is devoted to the design, implementation, and development of new continuous flow processes. Within this research activity, we investigated the two-steps Togo nitrile synthesis[14] as a model system for continuous flow synthesis of benzonitriles from benzyl alcohols, Scheme 1.

The Togo nitrile synthesis might utilize 1,3-diiodo-5,5-dimethylhydantoin (DIH) as a terminal oxidant in a Montanari type oxidation (that is a catalytic oxidation process that involves TEMPO free radical and a terminal oxidant, which originally was sodium hypochlorite, see Scheme 5).[15] In a following step, oxidation with iodine or DIH in the presence of aqueous ammonia affords target nitrile.



Scheme 1. Togo two-step nitrile synthesis starting from alcohol.[14]

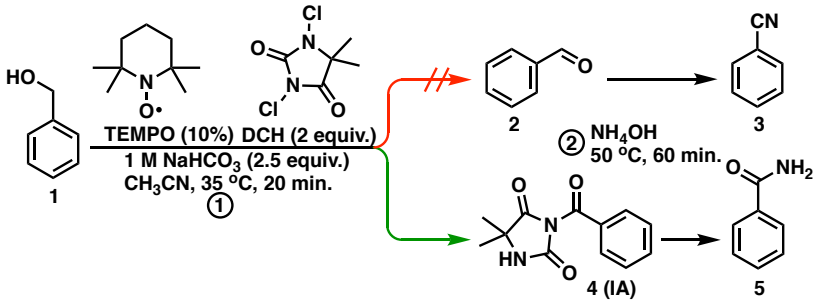
Results and Discussion

For our outlined continuous flow process, we wanted to examine whether the DIH oxidant could be replaced with the readily available and low-cost chlorinating / oxidising reagent 1,3-dichloro-5,5-dimethylhydantoin (DCH), and whether this oxidant could be utilized for both of the two steps of the process.

Our outline for a continuous flow process for the preparation of nitrile from its corresponding alcohol was constituted by a two-steps telescoped process (**1** → **2** → **3**): (i) oxidation of alcohol **1**

to aldehyde **2** by means of Montanari type oxidation,[15] and then (ii) an oxidative conversion of **2** to the target nitrile **3**, Scheme 2.

We started investigating each of the two distinct steps separately using a continuous flow multi-jet oscillating disk (MJOD) reactor platform previously designed and developed by our group.[16] The MJOD continuous flow reactor is realized in stainless steel and Teflon™ and operates with a total reactor volume on a multi-mL scale, although the MJOD reactor was designed to possess a favourable ratio between the reactor surface area (A) and the reactor volume (V) to achieve a ratio $\frac{A}{V} \approx 10$, when V=50 mL. The continuous flow reactor platform we used in this study is shown in Figure 1. Nevertheless, the expected product benzonitrile **3** was not obtained, but benzylamide **5** in good yield (66%). Samples collected during the course of the reaction revealed that the aldehyde **2** was absent, although 3-benzoyl-5,5-dimethylimidazolidine-2,4-dione **4** (that is the intermediate amide **IA**) was observed. In fact, after a reactor residence time of 20 min., a quantitative yield of **4** was observed, Scheme 2.



Scheme 2. Introductory experiment conducted on a MJOD flow reactor platform. Expected reaction path did not take place as anticipated (**1** → **2**) that comprise a Montanari oxidation that affords the intermediate aldehyde **2**. In subsequent step, an oxidative conversion (**2** → **3**) was expected to take place to afford the corresponding nitrile **3**. Altogether, a domino oxidative amidation and transamidation process (**1** → **4** → **5**) occured.

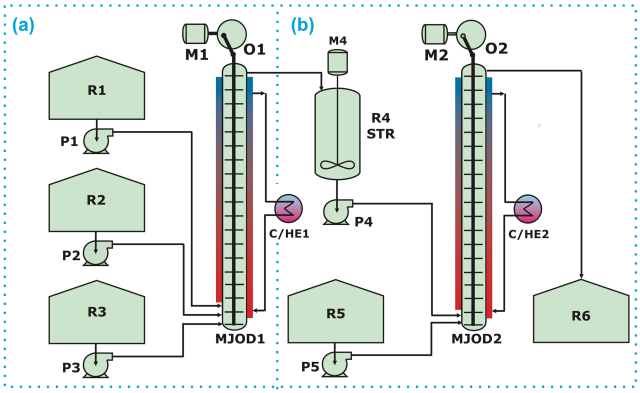
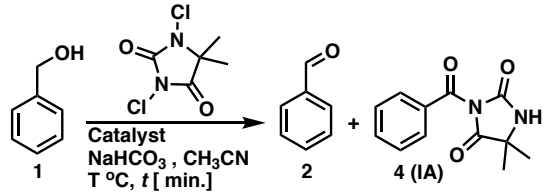


Figure 1. Process flow diagram for the MJOD flow reactor platform adapted and utilized for the continuous flow domino oxidative amidation and transamidation process. **R1-R3** and **R5** are reagent / substrate solution reservoirs, **R4-STR**: hold-up reservoir (stirred reactor), **R6**: post-reaction mixture reservoir **P1-P5**: pumps, **MJOD1-2**: multi-jet oscillating

disk (MJOD) reactor body, **M1-2**: electrical motor for oscillator (cam mechanism), **O1-2**: oscillator - cam mechanism, **M4**: electrical motor, **C/HE1-2**: Cooler/heater (heat exchanger).

These initial results spurred us to undertake further investigations of the influence of the various process variables on the outcome and course of the reaction. When one equivalent base was used, the aldehyde **2** was produced in excellent yield (entry #2, Table 1), which correspond to a quantity demanded for one cycle of the Montanari oxidation (Scheme 5).[15]

Table 1. Screening experiments



#	*t*	Catalyst		Oxidant		Base	y_2	y_4
	[min.]	Type	Qnty [%]	Type	[equiv.]	[equiv.]	[%]	[%]
1[a]	20	TEMPO	10	DCH	1.3	2.47	nd	66[b]
2[a]	20	TEMPO	10	DCH	1.3	1	>95	<5%
3	60	TEMPO	5	DCH	0.7	1	>98	0
4	60	TEMPO	5	DCH	1.4	1	>98	0
5	60	TEMPO	5	DCH	1.4	2	>98	0
6	60	TEMPO / $FeCl_3$	5 / 1	DCH	1.4	1	93	5
7	60	TEMPO / $FeCl_3$	5 / 1	DCH	1.4	2	52	44
8	60	TEMPO / $FeCl_3$	5 / 1	DCH	1.4	3	35	62
9	90	TEMPO / $FeCl_3$	5 / 1	DCH	1.4	3	nd	96
10[d]	90	TEMPO / $FeCl_3$	5 / 1	DCH	0.68	2	24[e]	70
11	150	TEMPO / $FeCl_3$	5 / 1	DCH	0.99	3	3	93
12[c]	90	TEMPO / $FeCl_3$	5 / 1	$Ca(OCl)_2$	2.0	3	>98	0
13	150	TEMPO / $FeCl_3$	5 / 1	DCH	1.4	2	nd	>96
14	90	TEMPO / $FeCl_2$	5 / 1	DCH	1.4	2	9	86
15[d]	90	$FeCl_3$	1	DCH	0.68	2	>96	0
16[d]	90	TEMPO	5	DCH	0.68	2	>98	0
17[d]	90	*t*-BuOOH / $FeCl_3$	75 / 1	DCH	0.68	2	93	5

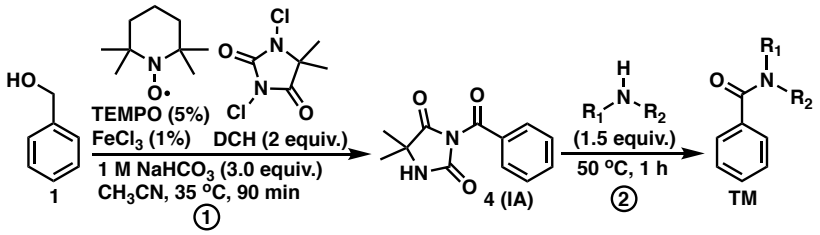
[a] Experiment was conducted in a MJOD reactor manufactured of Stainless steel. Iron ion thus present.

[b] Isolated yield of amide after transamidation (NH_4OH was added). The amide **4** was not isolated.

[c] 5,5-dimethylhydantoin was present i the reaction mixture (1 equivalent).

[d] Benzaldehyde was used as starting material.

[e] Aldehyde was not determined (nd). Another side product was observed in a quantity of ≈30% formed from oxidation of the aldehyde.



Scheme 3. Domino oxidative amidation of benzyl alcohol **1** and transamidation involving an amine NHR^1R^2 producing amide **TM**

When a base excess (≈2.5 equiv.) was used, the amide 3-benzoyl-5,5-dimethylimidazolidine-2,4-dione **4** was formed in good yield (entry #1, Table 1). Attempts to reproduce these experiments (entries #3–5) in a laboratory glass flask failed. It is known that transition metal ions might act as a co-catalyst with TEMPO in oxidation processes.[17] When our experiments were performed using our MJOD continuous flow reactor rig (Figure 1), the source for the metal ions (iron) could be the reactor body itself, as the reactor tube that is in direct contact with the reaction mixture is manufactured of stainless steel. Thus, it was reasonable to assume that iron ions operated as co-catalyst with TEMPO. Additional experiments performed in the laboratory glass flask were conducted with the presence of iron ions (entries #6-9), which resulted in outcomes in line with the results obtained using the continuous flow MJOD reactor. The telescoped domino oxidative amidation and transamidation process alongside the optimized reaction conditions is provided in Scheme 3.

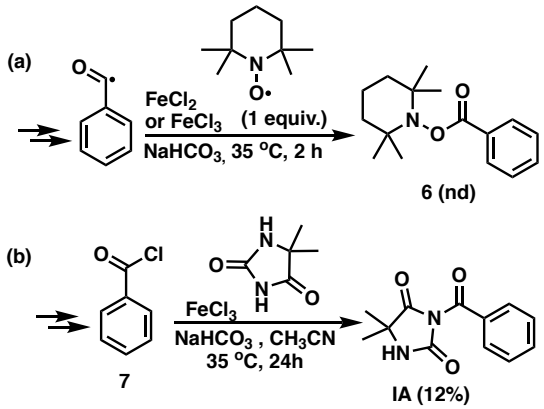
Reaction mechanism.

After a brief assessment of potential reaction pathways, we realized that a number of mechanistic reaction steps might be involved. Some might include radical reaction steps, since TEMPO free radical was imperative in order to operate the process. An intermediate amide (**IA**) and final product amid (**TM**) were observed, transformation that also might involve an in-situ formed acid chloride. A third possibility was a Montanari type oxidation (Scheme 5) as an integral part of the overall process.

Radical reaction steps. With the goal to elucidate whether radical reaction pathways were involved in the oxidative amidation, two distinct reaction experiments were carried out: (i) TEMPO free radical that might operate as an free radical initiator was replaced by an alternative radical species; *tert*-butyl hydroperoxide (entry #17, Table 1). The outcome of this experiment revealed trace amounts only of the intermediate amide (**IA**) **4**, which suggest that TEMPO is a key component, which do not operates as an radical initiator only. (ii) Attempts to trap an expected acyl radical did not afford the anticipated piperidin-1-yl benzoate product [Scheme 4(**a**)], which further on indicate

that free radicals are not involved in the reaction pathway[18] other that the oxidation of the TEMPO free radical.

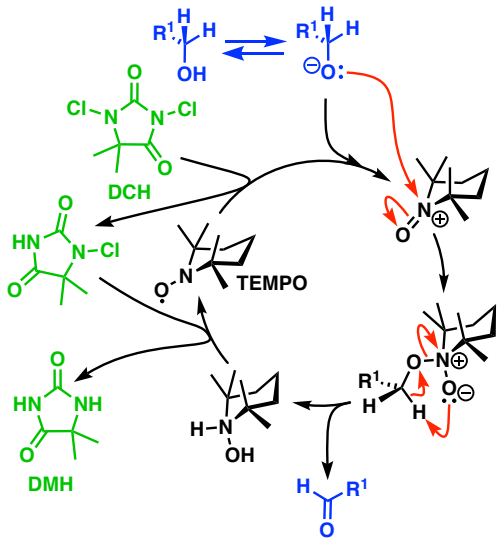
In-situ formation of an acid chloride. Another potential reaction pathway involves an acid chloride, which can be formed from aldehyde [18,19] by reaction with the *N*-formylformamide (N–Cl) moiety of 5,5-dimethyl-hydantoin. This hypothesis was verified by a reaction experiment involving benzoyl chloride **7** and 5,5-dimethylhydantoin (DMH), Scheme 4 (**b**). The expected product 3-benzoyl-5,5-dimethylhydantoin **4** was achieved in low yield only (12%), which suggest that the reaction essentially take place following some different mechanistic steps that not involves an acid chloride.



Scheme 4. (**a**) Attempts to trap a potential free radical (acyl). (**b**) Attempt to couple (thought produced *in-situ*) benzoic acid chloride **7** with 5,5-dimethylhydantion (**DMH**).

Selective oxidation of the alcohol into aldehyde. The Montanari type oxidation[15] of alcohols entails a mechanisms that involves TEMPO free radical as a pre-catalyst that together with a terminal oxidant, which here is 1,3-dichloro-5,5-hydantoin (DCH), can perform selective oxidation of the alcohol substrate to the corresponding carbonyl compound. As outlined in Scheme 5, the stoichiometry of this reaction request 1 mole of the oxidant (the N–Cl moieties are consumed in two steps) per mole of produced carbonyl compound (aldehyde). Since DCH is used as the terminal oxidant, one mole of 5,5-dimethylhydantoin (DMH) is produced as a by-product per mole of produced carbonyl compound, which also implies that both of the N–Cl moieties of DCH are involved in the catalytic cycle, see entries #1-5 of Table 1. Oxidation of alcohol was successfully completed following the stoichiometry proposed in Scheme 5.

Reaction pathways involving TEMPO with Fe ions as co-catalyst have previously been described,[20] but iron can also form complexes with aldehydes,[21] and amides,[22] which make the moiety more reactive.

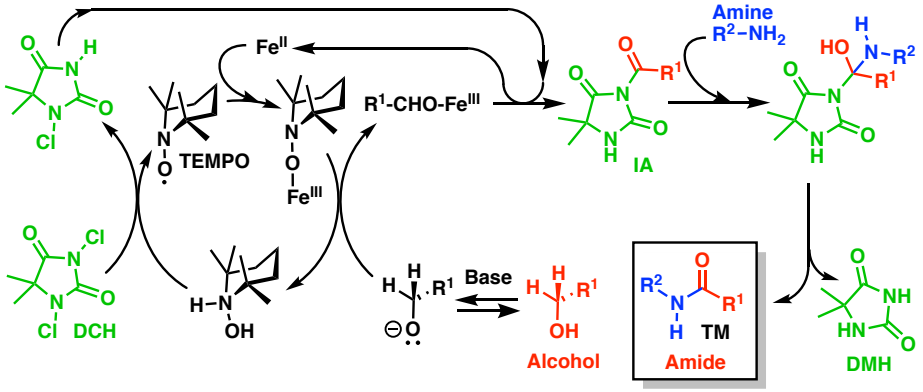


Scheme 5. Montanari type oxidation using 1,3-dichloro-5,5-dimethylhydantoin (DCH) as the terminal oxidant. The stoichiometry for the reaction is 1 mole terminal oxidant DCH (two N-Cl moieties) per 1 mole of alcohol substrate producing 1 mole of aldehyde and 1 mole of by-produduct DMH (5,5-dimeyhylhydantoin).

Our initial idea was evaluated by replacing the alcohol substrate with the corresponding aldehyde that subsequently reacted with Fe ions and further on attempted reacted with 5,5-dimethylhydantoin (DMH, the side product from the Monanari oxidation), however this experiment did not afford the amide intermediate **IA**. However, in an experiment (entry #10) using an increased quantity of DCH present, the intermediate amide **IA** was formed in a yield of 70%. This reaction suggest that the alcohol to carbonyl conversion is not an integral part of the overall process of the observed process.

An experiment (entry #11) using the alcohol as substrate with only one mole equivalent of the terminal oxidant DCH, revealed a quantitative yield of expected amide, from which we advise that the alcohol react with the iron/TEMPO complex[23] that acts as the catalyst for the generation of the proposed iron complex R^1–CHO-Fe.^{III} 2,2,6,6-tetramethylpiperidin-1-ol is then oxidized by DCH that produce **TEMPO** and finally the Iron/TEMPO complex.

In order to evaluate whether 1-chloro-5,5-dimethylimidazolidine-2,4-dione or 5,5-dimethyl-imidazolidine-2,4-dione (DMH) reacted with the Fe-complex (R^1–CHO-Fe^{III}), an experiment was conducted where DCH was replaced with $Ca(OCl)_2$ as the terminal oxidant (entry #12), but with the presence of 5,5-dimethylimidazolidine-2,4-dione. This experiment reveal that the Montanari oxidation type oxidation (Scheme 5) was the only operating one as no amide was produced. This suggests that the N–Cl moiety[24] react with the R^1-CHO-Fe^{III} complex. On the basis on this we suggest an reaction mechanism as outlined in Scheme 6.



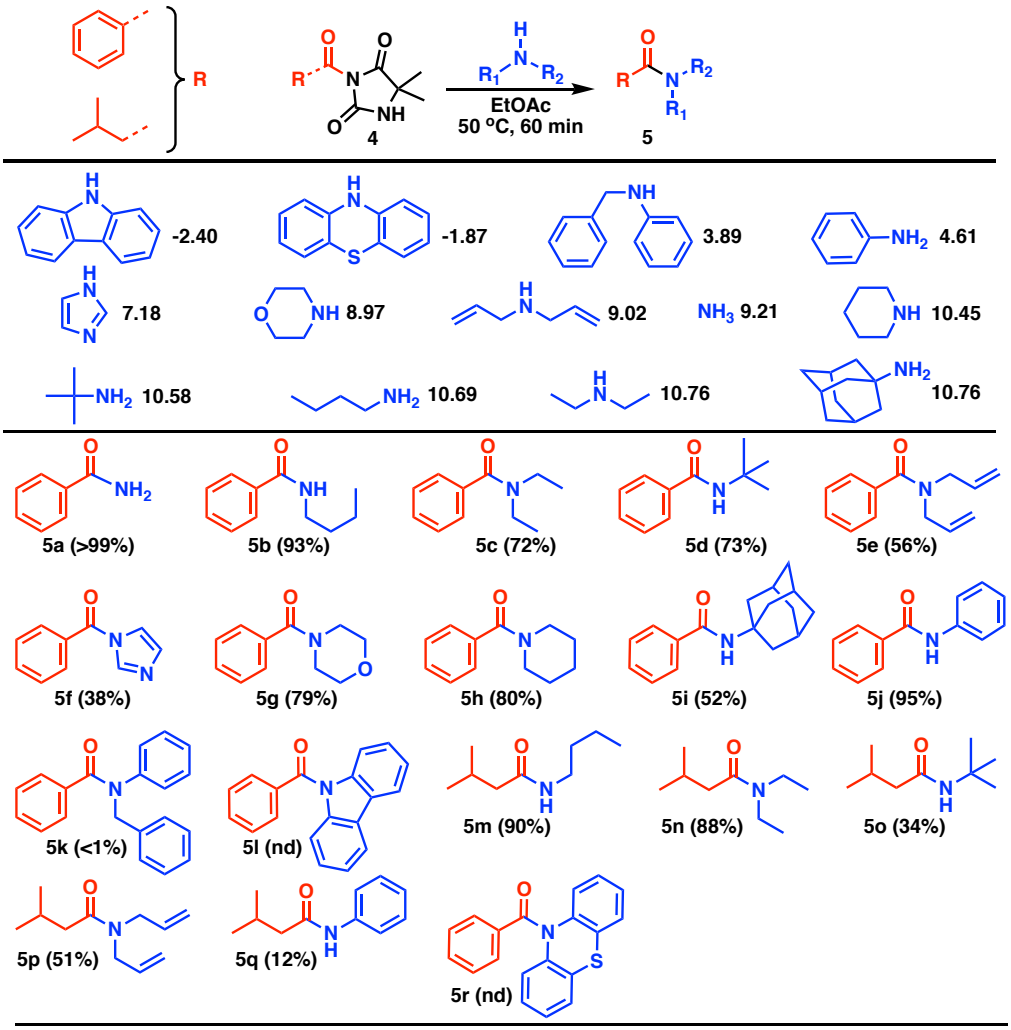
Scheme 6. Proposed reaction mechanisms for the TEMPO/Fe ion catalysed domino oxidative amidation (producing intermediate amide **IA**) followed by a transamidation reaction that produce target amide **TM**.

Some addition questions that were raised: (i) the importance of the quantity of base, and (ii) the redox state of the iron ions.[18] Experiments using reduced base quantity (entry #13) and replacing $FeCl_3$ with $FeCl_2$ (entry #14), respectively, afforded both similar high outcome of the amide.

The ultimate step of the process (frame **VI**) comprise a reaction between the amide intermediate **IA** and an amine under the formation of the target amide **TM**. The electron withdrawing carbonyls in the 5,5-dimethyl hydantoin moiety facilitate the reaction by weakening the amide C–N bond allowing the reaction to proceed under exceptionally benign reaction conditions and without the involvement of any transition metal catalyst.

Scope and limitation of the process. Variation of the amine in the trans amidation step was investigated by a series of assorted amines that were reacted with two various intermediate amides **IA**, Table 2.

Table 2. Scope of reaction – a selection of various primary and secondary amines that are reacted with benzyl alcohol and the aliphatic alcohol 2-methylpropan-1-ol.[a,b]

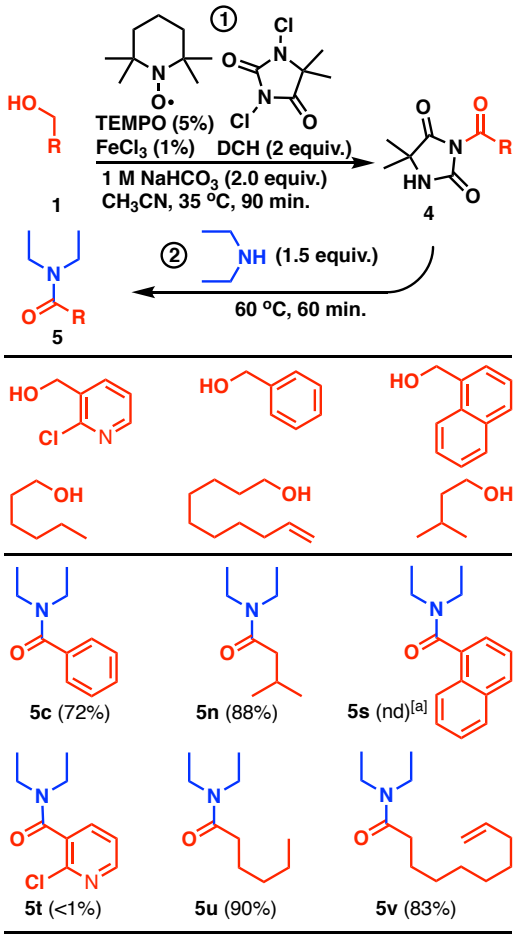


[a] The pK_a values given next to the amines were estimated by means of the Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2017 ACD/Labs). Data were retrived from SciFinder 12.12.2017.

[b] nd = not detected.

In addition, a series of alcohols were submitted for the domino oxidative amidation and trans amidation process using *N,N*-diethylamine in the transamidation step, Table 3. The expriments reveals that the reaction proceed to afford high yield of the target amide TM, when non bulky alcohols were used.

Table 3. Scope of reaction – a selection of various alcohols were submitted for the domino oxidative amidation and trans amidation process using the *N,N*-diethylamine in the trans amidation step.



[a] The substrate naphthalen-1-ylmethanol was oxidized selectively to 1-naphthaldehyde probably via Montanari type oxidation

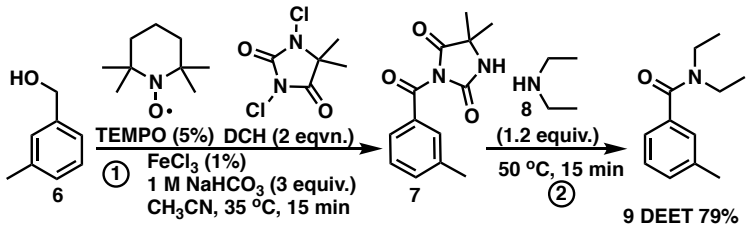
The results from the scope of the method suggest that steric effects and the basicity of the amine influence the reaction. In general, good to excellent yields were achieved when small primary and secondary amines were submitted for the process conditions. Amines with low pK_a values afforded low yields only or no product at all. Likewise, bulky amines resulted in lowered yields of target amides **5**.

A selection of amines were reacted with 3-methylbutanol in order to determine if the reaction operated with aliphatic alcohols, that all afforded expected amides **5m-q** (Table 2) in moderate to high yields. However, in the cases when 3-methylbutanol was used, the corresponding amide **4** was readily oxidised to the corresponding carboxylic acid, and was thus not isolated before the subsequent transamidation reaction. The achieved results from the scope and limitation study suggest that the reaction follows similar trends as benzyl alcohol.

An prospective industrial applications of the new amidation process.

N,N-diethyl-meta-toluamide (DEET) **9** is the active ingredient of more than 200 various commercially available insect repellent formulations for the application on the human body and clothing's. The insect repellents containing DEET **9** are used to control biting flies, mosquitoes, and numerous other insects.[25] DEET **9** is synthesised using a multistep synthesis, Scheme 7, whereof the last step involves the formation of the amide bond of the *N,N*-diethylamide moiety. Our new amidation method was tailored for a telescoped continuous flow process for the amidation step for the synthesis of DEET **9**. The two-steps telescoped process was implemented on a MJOD continuous flow reactor rig[16] that possessed a configuration as sketched in Figure 1. The reagents of the reservoirs **R1** (3-methylbenzyl alcohol, neat), **R2** (DCH, TEMPO and $FeCl_3$ dissolved in CH_3CN), and **R3** (aqueous $NaHCO_3$) were pumped into the input section of the **MJOD1** continuous flow reactor using the pumps **P1** (0.105 mL min.$^{-1}$), **P2** (1.74 mL min.$^{-1}$), and **P3** (2.36 mL min.$^{-1}$), Figure 1.

The post reaction mixture containing compound **7** was collected at the output section of the continuous flow reactor and transferred to a stirred hold-up tank (**R4-STR**). Reservoir **R5** was charged with diethylamine **8**. The intermediate **7** and the amine **8** were pumped (**P4** and **P5**) at adjusted rates and combined at the input section of the continuous flow reactor **MJOD2**. The overall telescoped continuous flow process afforded an isolated yield of 79% (2.11 g, 11 mmol, run time of ≈15 min.) of target *N,N*-diethyl-3-methylbenzamide **9** at an overall mass flow rate 11.2 g h^{-1} over the developed two-steps telescoped synthetic process.



Scheme 7. Oxidative amidation ① of 3-methylbenzyl alcohol **6** succeeded by transamidation ② of the amide intermediate 5,5-dimethyl-3-(3-methyl-benzoyl)imidazolidine-2,4-dione **7** with diethylamine **8** to achieve target product *N,N*-diethyl-3-methylbenzamide **9** (DEET).

Conclusions

In summary, we have developed a novel expedite two-step telescoped continuous flow process for the synthesis of amides using alcohols and amines as substrate and reagent pairs.

The unprecedented process emerges as a domino oxidative amidation followed by a transamidation. The established process was successfully used for the production of a series of amides and the commercial insect repellent DEET (*N,N*-diethyl-3-methylbenzamide) both on a

milli-gram scale batch approach and on a multi-gram scale continuous flow approach that was implemented on a MJOD continuous flow reactor platform.

Experimental Section

Chemical analysis. The GC–MS analyses were conducted using a capillary gas chromatograph furnished with a fused silica column (L 25 m, 0.20 mm i.d., 0.33 μm film thickness) with a helium pressure of 200 kPa, splitless /split injector and flame ionization detector. ^{1}H NMR spectra were recorded on a NMR spectrometer that operating at 500 MHz. ^{13}C NMR spectra were recorded with a NMR spectrometer operating at 125 MHz. Chemical shifts were referenced to the deuterated solvent used for the NMR experiment.

The continuous flow MJOD reactor. The Multi-Jet Oscillating Disk (MJOD) flow reactor platform have previously been described in detail.[16] A short account follows herein. The MJOD flow reactor platform configuration is outlined in Figure 1. The continuous flow MJOD reactor is a tubular reactor with an internal oscillating shaft. The internal shaft is fitted with multiple (N) multi-jet disks and the oscillating motion (*A, f*) is delivered by a electrical motor. Each multi-jet disk has four (4) jets and every disk is separated by a fixed length (h_{cavity}). The whole length of the reactor tube is encapsulated by a heating/cooling jacket. The reagents and substrate solutions are transferred to supply reservoirs that is connected to their corresponding pumps. The pump rate is adjusted to give the desired residence time and mole equivalents. Every reactor inlet is fatted with a one-way valve in order to prevent "kick-back" created by the oscillator (the multi headed piston shaft). The line connecting **P2** to **MJOD1** was fitted with an extra T-connector for the removal of build-up of precipitate in the inlet. Pressurised solvent was flushed through the line in order to remove precipitated and thus assure free tuning for accurate reagent supply to the flow reactor tube.

MJOD flow synthesis procedure to of benzylamide. A multi-jet oscillating disk flow reactor platform[16] **MJOD1** (V_{tot} 65 mL, L = 150 cm, r_{osc} = 1.5 s^{-1}) was pre-heated at heated at 35 °C. Benzyl alcohol (6.0 mL, 57.8 mmol) was transferred to the reagent reservoir **R1** (V_{tot} 6.0 mL). $NaHCO_3$ (12.034 g, 143 mmol) was dissolved in water (140 mL) and transferred to the reagent reservoir **R2** (V_{tot} 140 mL). 1,3-dichloro-5,5-hydantoin (22.00 g, 111 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.898 g, 5.75 mmol) were dissolved in acetonitrile (total volume 90 mL) and transferred to the reservoir **R3** (V_{tot} 90 mL). The reagents (**R1**–**R3**) were introduced into to the **MJOD1** reactor using pumps **P1** – **P3** at feeding rates that afforded a residence time of *t* = 20 min. The actual feeding rates were: **P1**: 0.083 mL min^{-1}, **P2**: 1.928 mL $min,^{-1}$ and **P3**: 1.239 mL $min.^{-1}$ The crude output product from **MJOD1** was collected in a stirred hold-up tank **HT1-R4** (V_{tot} 236 mL). NH_4OH (28%) was transferred to reservoir **R5** (V_{tot} 100 mL). The MJOD flow reactor **MJOD2** (V_{tot} 96 mL, L = 265 cm, r_{osc} = 1.5 s^{-1}) was cooled at 0 °C. The intermediate product of the hold-up tank **HT1** and NH_4OH

of reservoir **R5** were pumped into MJOD flow reactor **MJOD2** at rates (**P4**: 1.09 mL min^{-1}, **P5**: 0.46 mL min^{-1}) to afford a residence time of t = 60 min. The crude reaction mixture was collected in reservoir **R6** (V_{tot} 336 mL). The reaction mixture was extracted with ethyl acetate (5 × 30 mL). The organic layers were combined and washed with brine (3 × 15 mL), dried over anhydrous sodium sulfate, and filtrated. The solvent was removed under reduced pressure on a rotary evaporator to afford benzylamide in a yield of 66% (4.61 g, 38.14 mmol).

3-benzoyl-5,5-dimethylimidazolidine-2,4-dione. A magnet stirrer bar was placed in the reaction tube (10 mL) that was capped and flushed with argon. Benzyl alcohol (0.1 mL, 0.9 mmol), acetonitrile (1 mL) and 1 M $NaHCO_3$ (3 mL, 3 mmol) were transferred to the reaction tube and heated (35 ^oC) and stirred. An aqueous solution of $FeCl_3$ (8.1 mg mL^{-1}, 0.2 mL, 0.01 mmol) was then added to the reaction vial, whereupon a solution of 1,3-dichloro-5,5-hydantoin (0.394 g, 2.0 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0,007 g, 0.045 mmol) in acetonitrile (2 mL) was added over a period of 10 min. This reaction mixture was stirred for 80 min. The post reaction mixture was extracted with ethyl acetate (4 × 5 mL), washed with brine (3 × 3 mL), dried over anhydrous sodium sulfate, and then filtered. The solvents were removed under reduced pressure on a rotary evaporator. Crude yield of target product 3-benzoyl-5,5-dimethylimidazolidine-2,4-dione was determined to 96 % (GC). The post reaction mixture was purified by means of flash chromatography (EtOAc : Hx)(1 : 9 → 4 : 6) and analyzed by means of ^{1}H-NMR (500MHz, $CDCl_3$) δ: 8.15 (dd, 2H), 7.67 (t, 1H), 7.52 (t, 2H), 1.52 (s, 6H). ^{13}C-NMR (125 MHz) δ: 174.7, 166.1, 153.1, 134.7, 132.0, 130.4, 128.7, 59.2, 25.4. *m/z* HRMS (EI+): Found: [M]232.08433, Calculated: 232.08479.

General method, benzyl amide synthesis procedure: A magnet stirrer bar was transferred to a reaction vial (8 mL). 3-Benzoyl-5,5-dimethylimidazolidine-2,4-dione (0.194 g, 0.6 mmol) was transferred the reaction vial and dissolved in ethyl acetate (2 mL) and then sealed with a septum. The reaction vial was immersed into an oil bath an heated at 50 ^oC. Then *N*-butyl amine (0.12 mL, 1.2 mmol) was added and the reaction mixture was continuous stirred for another 60 min. The reaction mixture was filtered to remove precipitated the 5,5-dimethylhydantoine. The filtrate was the extracted with ethyl acetate (3 × 5 mL). The organic layers were combined and washed with brine (3 × 3 mL), dried over anhydrous sodium sulphate, and filtered. The organic solvents wre removed under reduced pressure on a rotary evaporator. The obtained solid crude was further purified by means of flash chromatography (EtOAc : Hx)(2 : 8) to afford *N*-butylbenzamide in a yield of 93 % (0.099 g, 0.56 mmol).

General method, alcohol screening. A magnetic stirrer bar was transferred to a reaction tube (10 mL), sealed with a septum and flushed with argon. Benzylalcohol (0.12 mL, 0.12 g, 0.99 mmol),

acetonitrile (1 mL) and 1M $NaHCO_3$ (2 mmol, 2 mL) were transferred to the reactor tube, which was then placed in an oil bath and warmed at 35 °C and stirred while solutions of $FeCl_3$ in H_2O (8.1 mg mL^{-1}, 0.2 mL, 0.01 mmol) and 1,3-dichloro-5,5-hydantoin (0.197 g, 1.0 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0,007 g, 0.045 mmol) in acetonitrile (2 mL) were added. The reaction mixture was stirred for 90 min., then the reaction temperature was increased to 60 °C and diethylamine (0.15 mL, 0.11 g, 15 mmol) was added. The reaction was left for another 60 min. under stirring. The post-reaction mixture was extracted with ethyl acetate (4 × 5 mL) and the organics was combined and washed with brine (3 × 5 mL) and dried over anhydrous sodium sulphate and filtered. Solvents were removed under reduced pressure on a rotary evaporator. The isolated crude prosuct was purified by means of flash chromatography (EtOAc : Hx)(2 : 8) affording *N,N*-diethyl-benzamide in a yield of 72%.

Radical trapping experiment.[18] A magnet stirrer bar was transferred to a reaction vial (8 mL), which then was capped and flushed with argon. Benzyl alcohol (0.1 mL, 0.9 mmol), acetonitrile (1 mL), and aqueous $NaHCO_3$ (1 M, 3 mL, 3 mmol) were transferred to the vial, whereupon the vial was immersed into an oil bath at a temperature of 35 °C under vigorous stirring. An aqueous solution of an iron salt ($FeCl_2$ 1%, $FeCl_3$ 1%, $FeCl_3$ 0.5 eqiuv.) was then added. Then a solution of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.9 mmol) in acetonitrile (2 mL) was added over a period of 10 min. The reaction mixture was leaved under stirring for 120 min. The reaction mixture was then extracted with ethyl acetate (4 × 5 mL). The crude isolated solid was analysed by means of a GC-MS. 2,2,6,6-Tetramethylpiperidin-1-yl benzoate was not observed, which demonstrate absence of free radicals in the reaction mixture.

Experiment: alternative radical initiator. A magnetic stirrer bar was transferred to a reaction vial (8 mL), which then was capped and flushed with argon. Benzaldehyde (0.1 mL, 0.9 mmol), acetonitrile (1 mL) and 1M $NaHCO_3$ (3 mL, 3 mmol) were then transferred to the vial, that was immersed into an oil bath (35 °C) under vigorous stirring. An aquatic solution of an iron salt ($FeCl_3$ 1%) and a solution of 1,3-dichloro-5,5-dimethylhydantoin (1.1 mmol) in acetonitrile (2 mL) were added, which was followed by a solution of *tert*-Butyl hydroperoxide (0.6 mmol in water, 0.072 mL). The reaction was then stirred for 90 min. The post reaction mixture was then extracted with ethyl acetate (4 × 5 mL), and the crude was analyzed on GC-MS, that revealed a **4** in low yield < 5%.

Experiment: investigate of the reaction mechanism that involves the formation and reaction with acid chloride. 5,5-dimethylhydantoin (0.2 mmol), $NaHCO_3$ (1 mmol), $FeCl_3$ (0.01 mmol), and a magnetic stirrer bar were transferred to a reactor vial (2 mL) that was sealed and flushed with argon. Acetonitrile-d_3 (0.7 mL) and benzoyl chloride (0.4 mmol) was added via syringe. The

reaction mixture was immersed in an oil bath (35 °C) and stirred vigorously for 24 h. The post reaction mixture was analyzed by ^{1}H NMR, which revealed a yield of 12% of **4**.

3-Methylbutanamide procedure: A magnetic stirrer bar was transferred to a reaction vial (8 mL), which was capped and flushed with argon. 3-Methylbutan-1-ol (0.1 mL, 0.081 g, 0.9 mmol), acetonitrile (1 mL) and 1 M $NaHCO_3$ (3 mL, 3 mmol) were transferred to the vial whereupon the vial was immersed into an oil bath (35 °C) under vigorous stirring. An aqueous solution of $FeCl_3$ (8.1 mg mL^{-1}, 0.2 mL, 0.01 mmol) was then added to the vial followed by a solution of 1,3-dichloro-5,5-hydantoin (0.394 g, 2.0 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0,007 g, 0.045 mmol) in acetonitrile (2 mL), which was added over a period of 10 min. The reaction was then stirred for 80 minutes. Reaction mixture was then extracted with ethyl acetate (4 × 5 mL) and washed with brine (3 × 3 mL). The organic phase was transferred to reaction flak together with a magnet. The flask was capped with a septum and heated to 50 °C. n-butylamine (0.12 mL, 0.089 g, 1.21 mmol) was added via syringe and reaction was stirred for 60 min. Reaction mixture was cooled to room temperature and extracted with Ethyl acetate (3 × 5 mL) organics was combined and washed with brine (3 × 3 mL) and dried over anhydrous sodium thiosulfate and filtered. Solvents were removed under reduced pressure on a rotary evaporator. Crude was further purified by means of flash chromatography (EtOAc : Hx)(2 : 8) affording N-butyl-3-methylbutanamide in a yield of 90 % (0.81 g, 0.127 mmol).

Syntheis of *N,N*-diethyl-3-methylbenzamide (DEET), one-pot batch procedure. A magnetic stirrer bar was transferred to a reaction vial (8 mL) and sealed with a septum. 3-Methylbenzylalcohol (0.12 mL, 0.12 g, 0.99 mmol), acetonitrile (1 mL) and 1M $NaHCO_3$ (3 mmol, 3 mL) was then added to the vial. The vial was head in an oil bath (35 °C) under vigorous stirring while An aquatic solution of $FeCl_3$ (8.1 mg mL^{-1}, 0.2 mL, 0.01 mmol) was then added, followed by a solution of 1,3-dichloro-5,5-hydantoin (0.394 g, 2.0 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0,007 g, 0.045 mmol) in acetonitrile (2 mL). The reaction mixture was stirred for 90 min, afterwards the temperature was increased to 50 °C and Diethylamine (0.12 mL, 0.088 g, 12 mmol) was added and stirred for 60 min. Reaction mixture was then extracted with Ethyl acetate (4 × 5 mL) and organics was combined and washed with brine (3 × 5 mL) and dried over anhydrous sodium thiosulfate and filtered. Solvents were removed under reduced pressure on a rotary evaporator. Crude was further purified by means of flash chromatography (EtOAc : Hx)(2 : 8) affording *N,N*-Diethyl-3-methylbenzamide in a yield of >95% (isolated yield of 0.18 g, 0.94 mmol).

Telescoped continuous flow synthesis leading to *N,N*-diethyl-3-methylbenzamide (DEET). The MJOD reactor (**MJOD1**) was prefilled with the reaction solvent (MeCN / H_2O). The heat-exchanger (**HE-1**) was adjusted at a temperature of 35 °C and the oscillator (**O1**) was adjusted to a

frequency *f*=2.5 Hz. The reservoir **R1** was filled with 3-methylbenzylalcohol (1.7 mL, 1.68 g, 14.0 mmol) (**R1,** V_{tot} =1.7 mL). Reservoir **R2** was filled with a solution of 1,3-dichloro-5,5-hydantoin (5.924 g, 30.0 mmol), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0,218 g, 1.40 mmol) and $FeCl_3$ (0.023 g, 0.14 mmol) in acetonitrile (**R2**, V_{tot} = 28 mL). Reservoir **R3** was filled with a solution of $NaHCO_3$ (3.444 g, 42 mmol, 38 mL, 1.1 M) (**R3**, V_{tot} = 38 mL). The reagents (**R1** – **R3**) were then pumped (using pumps **P1** – **P3**) into the MJOD flow reactor **MJOD1** at feeding rates to approach a residence time of *t* = 15 min. The feeding rates of the various pumps were: **P1**: 0.105 mL min^{-1}, **P2**: 1.74 mL min^{-1}, and **P3**: 2.36 mL $min.^{-1}$ Anti-clogging pulse in line 2 (between **P2** and **MJOD1**) was set to inject 0.2 mL acetonitrile every 5 min. The crude product from **MJOD1** was collected in a stirred hold-up tank (**HT1-R4**) (V_{tot} = 67.7 mL). The second MJOD reactor (**MJOD2**) was prefilled with solvent, heat-exchanger (**HE-2**) set to 50 °C and oscillation (**O2**) set to 2.0 Hz. Diethylamine (1.68 mL, 1.17 g, 16 mmol) was added to reservoir 5 (**R5**)(**R5**, V_{tot} = 1.68 mL). The contents of reservoir 4 and 5 was pumped (using **P4** and **P5**) into the MJOD reactor (**MJOD2**) at feeding rates to approach a residence time of 15 min. The utilized feeding rates were: **P4**: 6.0 mL min^{-1}, and **P5**: 0.15 mL min^{-1}. The crude product from **MJOD2** was collected in a hold-up tank (**HT2-R6**). Reaction mixture was then extracted with Ethyl acetate (4 × 20 mL) and organics was combined and washed with brine (3 × 15 mL) and dried over anhydrous sodium thiosulfate and filtered. Solvents were removed under reduced pressure on a rotary evaporator. Reaction gave *N,N*-Diethyl-3-methylbenzamide in a crude yield (2.11 g, 11.0 mmol) of 78 % determined by NMR.

***N*-butylbenzamide (5b).**[26] Yield 93 %, ^{1}H-NMR (500 MHz) *δ*: 7.73 - 7.72 (m, 2H), 7.45 - 7.42 (m, 1H), 7.38 - 7.35 (m, 2H), 6.33 (br, 1H), 3.42 - 3.38 (m, 2H), 1.40 - 1.32 (m, 2H), 0.90 (t, J = 7.26 Hz, 3H). ^{13}C-NMR (125 MHz) *δ*: 167.6, 134.9, 131.2, 128.5, 126.9, 39.8, 31.7, 20.2, 13.8. GC-MS (EI) m/z (%): 177.1 (5.5), 134 (16.7), 105.0 (100), 77.0 (46.2).

***N,N*-diethylbenzylamine (5c).**[27] Yield 72 %, ^{1}H-NMR (500 MHz) *δ*: 7.35 - 7.28 (m, 5H), 3.48 (br, 2H), 3.18 (br, 2H), 1.17 (br, 3H), 1.04 (br, 3H) ^{13}C-NMR (125 MHz) *δ*: 171.3, 137.3, 129.1, 128.4, 126.3, 43.3, 39.2, 14.2, 12.9. GC-MS (EI) m/z (%): 176.1 (25), 105.0 (100), 77.0 (41.8).

***N*-(*tert*-butyl)benzylamine (5d).**[28] Yield 73 %, ^{1}H-NMR (500 MHz) *δ*: 7.70 - 7.69 (m, 2H), 7.47 - 7.43 (m, 1H), 7.41 - 7.37 (m, 2H), 1.46 (s, 9H). ^{13}C-NMR (125 MHz) *δ*: 166.9, 136.0, 131.1, 128.5, 126.7, 51.6, 28.9. GC-MS (EI) m/z (%):177.1 (9.5), 162.0 (13.3), 105.0 (100), 77.0 (30.2).

***N,N*-diallylbenzylamine (5e).**[29] Yield 56 %, ^{1}H-NMR (500 MHz) *δ*: 7.42 - 7.34 (m, 5H), 5.86(m, 1H), 5.70 (m, 1H), 5.22 - 5.15 (m, 5H), 4.11 (m, 2H), 3.81 (m, 2H), ^{13}C-NMR (125 MHz) *δ*: 171.8, 136.3, 133.3, 133.2, 132.8, 130.1, 129.6, 128.4, 126.6, 117.6, 50.8, 47.0. GC-MS (EI) m/z (%): 200.1 (4.0), 160.1 (5.9), 113.0 (7.1), 105.0 (100), 77.0 (51.0).

(1*H*-imidazol-1-yl)(phenyl)methanone (5f).[30] Yield 38 %, ^{1}H-NMR (500 MHz) δ: 8.08 (m, 1H) 7.80 - 7.77 (m, 2H), 7.69 - 7-65 (m, 1H), 7.57 - 7.53 (m, 3H), 7.17 - 7.16 (m, 1 H) ^{13}C-NMR (125 MHz) δ: 166.2, 138.2, 133.6, 131.9, 130.9, 129.8, 129.0, 118.1. GC-MS (EI) m/z (%): 172.0 (3.8), 105,0 (100), 77.1 (88.9).

morpholino(phenyl)methanone (5g).[31] Yield 79 %, ^{1}H-NMR (500 MHz) δ: 7.43 - 7.34 (m, 5H), 3.85 - 3.35 (m, 8H), ^{13}C-NMR (125 MHz) δ: 170.5, 135.4, 129.9, 128.6, 127.1, 66.9. GC-MS (EI) *m/z* (%): 190.1 (18.0), 105.1 (100), 77.0 (48.9).

phenyl(piperidin-1-yl)methanone (5h).[32] Yield 80 %, ^{1}H-NMR (500 MHz) δ: 7.39 - 7.34 (m, 5H), 3.69 (m, 2H), 3.32 (m, 2H), 1.69 - 1.63 (m, 4H) 1.54 - 1.46 (m, 2H), ^{13}C-NMR (125 MHz) δ: 170.5, 136.5, 130.1, 129.4, 128.5, 128.4, 126.8, 30.9, 24.6. GC-MS (EI) *m/z* (%): 188.1 (48.4) 105.0 (100), 77.1 (70.6).

***N*-(adamantan-1-yl)benzamide (5i).**[33] Yield 52 %, ^{1}H-NMR (500 MHz) δ: 7.73 - 7.70 (m, 2H), 7.48 - 7.45 (m, 1H), 7.43 - 7.39 (m,2H), 2.13 (s, 9H), 1.77 - 1.70 (m, 6H) ^{13}C-NMR (125 MHz) δ: 166.6, 136.1 131.0, 128.5, 126.7, 52.3, 41.7, 36.4, 29.5. GC – MS (EI) *m/z* (%): 255.1 (13), 198.0 (38), 135.1 (5), 105.0 (100), 77.0 (67).

***N*-phenylbenzylamide (5j).**[32] Yield 95 %, ^{1}H-NMR (500 MHz) δ: 7.87 - 7.84 (m, 2H), 7.76 (br, 1H) 7.64 - 7.61 (m, 2H), 7.56 - 7.52 (m, 1H), 7.50 - 7.46 (m, 2H) 7.38 - 7.34 (m, 2H), 7.16 - 7.12 (m, 1H), ^{13}C-NMR (125 MHz). GC – MS (EI) *m/z* (%): 197.0 (11), 105.0 (100), 77.0 (81). GC-MS (EI) *m/z* (%): 197.0 (11.0), 105.0 (100), 77.0 (80.6).

***N*-butyl-3-methylbutanamide (5m).**[34] Yield 90 %, ^{1}H-NMR (500 MHz) δ: 5.53 - 5.35 (w, N-H) 3.30 - 3.24 (m, 2H) 2.07 - 2.01 (m, 3H) 1.53 - 1.46 (quintet, 2H) 1.41 - 1.31 (sextet, 2H) 0.99 - 0.91 (m, 9H), ^{13}C-NMR (125 MHz) δ: 172.4, 46.3, 39.1, 31.8, 30.9, 26.2, 22.5, 20.1, 13.7. GC-MS (EI) *m/z* (%): 157.1 (6.9), 142.0 (13.0), 115.1 (55.1), 73.0 (66.4) 57.1 (100).

***N,N*-diethyl-3-methylbutanamide (5n).** Yield 88 %, ^{1}H-NMR (500 MHz) δ: 3.38 - 3.33 (q, J = 7.12 Hz, 2H) 3.31 - 3.26 (q, J = 7.12 Hz, 2H) 2.16 - 2.13 (m, 3H) 1.16 - 1.12 (t, J = 7.16, 3H) 1.11 - 1.07 (t, J = 7.12 Hz) 0.95 - 0.92 (m, 6H), ^{13}C-NMR (125 MHz) δ: 171.2, 42.4, 42.0, 41.9, 40.1, 25.9, 22.7, 14.5, 13.2. GC-MS (EI) *m/z* (%): 157.1 (5.5), 142.1 (10.0), 115.1 (14.5), 100.1 (24.1), 72.1 (29.0), 58.1 (100).

***N*-(tert-butyl)-3-methylbutanamide (5o).** Yield 34 %, ^{1}H-NMR (500 MHz) δ: 5.34 - 5.10 (w, N-H) 2.09 - 2.01 (m, 1H) 1.91 - 1.89 (d, J = 7.21 Hz, 2H) 1.32 - 1.30 (s, 9H) 0.91 - 0.89 (m, 6H) ^{13}C-NMR (125 MHz) δ: 171.9, 51.06, 47.2, 28.8, 26.2, 22.4. FT-IR, ν (cm^{-1}): 3309, 3073, 2954, 2868, 1720, 1666, 1641, 1547, 1452, 1391, 1358, 1310, 1260, 1227, 1213, 1170, 931, 679, 603. GC-MS (EI) m/z (%): 157.1 (3.9), 115.1 (10.2), 58.1 (100).

***N,N*-diallyl-3-methylbutanamide (5p).** Yield 51 %, ^{1}H-NMR (500 MHz) δ: 5.78 - 5.70 (m, 2H) 5.20 - 5.07 (m, 4H) 3.98 -3.95 (m, 2H) 3.87 - 3.84 (m, 2H) 2.21 - 2.14 (m, 3H) 0.95 - 0.92 (m, 6H) ^{13}C-NMR (125 MHz) δ: 172.5, 133.6, 133.1, 117.0, 116.5, 49.2, 47.8, 41.8, 25.7, 22.7. GC-MS (EI) m/z (%): 181.1 (2.8), 166.0 (11.9), 124.0 (12.8), 82.4 (27.9),57.1 (74), 56.0 (100).

***N*-phenyl-3-methylbutanamide (5q).**[35] Yield 12 %, ^{1}H-NMR (500 MHz) δ: 7.52 - 7.48 (m, 2H) 7.32 - 7.28 (m, 2H) 7.10 - 7.05 (m, 1H) 2.23 - 2.18 (m, 3H) 1.03 - 0.97 (m, 6H). FT-IR, ν (cm^{-1}): 3282, 3243, 3192, 3131, 3073, 2964, 2964, 1655, 1596,1547, 1488, 1441, 1368, 1318, 1257, 1203, 964, 902, 758, 693, 557, 509. GC-MS (EI) m/z (%): 177.1 (6.6), 93.1 (100).

2-chloro-*N,N*-diethylnicotinamide (5t): Yield: <1%, GC-MS (EI) *m/z* (%): 213.9 (2.9), 212.0 (8.3), 196.9 (6.7), 183.0 (6.14), 177.1 (29.4), 141.9 (30.9), 140.0 (100), 114.0 (8.5), 111.9 (27.5).

***N,N*-diethylhexanamide (5u):** Yield 90 %, ^{1}H-NMR (500 MHz) δ: 3.40 – 3.35 (q, J = 7.09 Hz, 2H), 3.33 – 3.29 (q, J = 7.09 Hz, 2H), 2.31 – 2.28 (t, J = 7.64 Hz, 2H), 1.68 – 1.62 (m, 2H), 1.37 – 1.29 (m, 4H), 1.19 – 1.16 (t, J = 6.61 Hz, 3H), 1.12 – 1.09 (t, J = 7.04 Hz, 3H), 0.91 – 0.89 (t, J = 6.65 Hz, 3H). ^{13}C-NMR (125 MHz) δ: 172.4, 42.0, 40.1, 33.1, 31.7, 25.2, 22.5, 14.8, 13.9, 13.1. Cosy spectra in supporting information.

***N,N*-diethyldec-9-enamide (5v):** Yield 83 %, ^{1}H-NMR (500 MHz) δ: 5.86 – 5.76 (m, 1H), 5.04 – 4.91 (m, 2H), 3.39 – 3.27 (m, 4H), 2.36 – 2.27 (m, 2H), 2.08 – 2.00 (m, 2H), 1.44 – 1.26 (m, 10H), 1.20 – 1.08 (m, 6H). ^{13}C-NMR (125 MHz) δ: 172.6, 139.2, 114.2, 42.1, 40.2, 33.8, 33.2, 29.5, 29.3, 29.0, 28.9, 25.5, 24.9, 14.4, 13.1. Cosy spectra in supporting information. GC-MS (EI) *m/z* (%): 225.2 (7.4), 184.2 (10.3), 170.2 (4.7), 156.2 (2.8), 142.2 (9.4), 128.2 (58.3), 115.2 (100), 100.2 (64.2), 86.1 (14.1), 72.1 (34.3).

Acknowledgements

A. D. gratefully acknowledges the Department of Chemistry at University of Bergen for funding his research fellowships. Dr. Bjarte Holmelid is acknowledged for excellent technical assistance with the HRMS analyses.

Supporting information

Supplementary information and chemical compound information are available in the online version of the paper.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Oxidative amidation • transamidation • TEMPO • 1,3-dichloro-5,5-dimethylhydantoin • flow chemistry

[1] a) C. Schotten, *Ber.* **1884**, *17*, 2544-2547; b) E. Baumann, *Ber.* **1886**, *19*, 3218-3222.

[2] a) Schmidt, K. F. Über die Einwirkung von NH auf ordungen. *Angew. Chem.* **1923**, *36*, 511; b) Schmidt, K. F. Über den Imin-Rest. K. F. Schmidt. *Ber.* **1924**, *57B*, 704-706.

[3] Beckmann, E. Zur Kenntniss der Isonitrosoverbindungen. *Ber.* **1886**, *19*, 988-993.

[4] a) J. J. Ritter, P. P. Minieri, *J. Am. Chem. Soc.* **1948**, *70*, 4045-4048; b) J. J. Ritter, J. Kalish, *J. Am. Chem. Soc.* **1948**, *70*, 4048-4050.

[5] H. Staudinger, J. Meyer, *Helv. Chem. Acta.* **1919**, *2*, 635-646.

[6] a) I. Ugi, *Angew. Chem. Int. Ed.* **1962,** *1*, 8–21; b) I. Ugi, K. Offermann, G. Herlinger, D. Marquarding, *Ann.* **1967**, *709*, 1–10; c) I. Ugi, G. Kaufhold, *Ann.* **709**, 11–28 (1967). d) I. Ugi, S. Lohberger, R. Karl, In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, **1991**, *2*, 1083-1109; e) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210; f) I. Ugi, *Pure Appl. Chem.* **2001**, *73*, 187–191;

[7] a) B. C. Ranu, P. Dutta, *Synth. Commun.* **2003**, *33*, 297-302; b) R. Arora, S. Paul, R. Gupta, *Can. J. Chem.* **2005**, *83*, 1137-1140; c) C. Han, J. P. Lee, E. Lobkovsky, J. A. Porco, *J. Am. Chem. Soc.* **2005**, *127*, 10039-10044; d) B. Gnanaprakasam, D. Milstein, *J. Am. Chem. Soc.* **2011,** *133*, 1682-1685.;

[8] a) S. E. Eldred, D. A. Stone, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 3422-3423; b) C. L. Allen, B. N. Atkinson, J. M. J. Williams, *Angew. Chem., Int. Ed.* **2012**, *15*, 1383-1386; c) M. Tamura, T. Tonomura, K.-I. Shimizu, A. Satsuma, *Green Chem.* **2012**, *14*, 717-724; d) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2012**, *51*, 3905-3909; e) Y. Liu, M. Achtenhagen, R. Liu, M. Szostak. *Org. Biomol. Chem.* **2018**, *16*, 1322–1329.

[9] a) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2007**, *46*, 8460-8463; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2009**, *48*, 4114-4133; c) T. T. Dang, Y. Zhu, S. C. Ghosh, A. Chen, C. L. L. Chai, A. M. Seayad, *Chem. Commun.* **2012**, *48*, 1805-1807.

[10] a) J. J. Shie, J.-M. Fang, *J. Org. Chem.* **2003**, *68*, 1158–1160; b) I. E. Markó, A. Mekhalfia, *Tetrahedron Lett.* **1990**, *31*, 7237–7240; c) S. D. Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992–1995; d) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; e) S. C. Ghosh, J. S. Y. Ngiam, C. L. L. Chai, A. M. Seayad, T. T. Dang, A. Chen, *Adv. Synth. Catal.* **2012**, *354*, 1407–1412; f) B. Tan, N. Toda, C. F. Barbas III. *Angew. Chem. Int. Ed.* **2012**, *51*, 12538–12541.

[11] a) X.-F. Wu, M. Sharif, A. Pews-Davtyan, P. Langer, K. Ayub, M. Beller, *Eur. J. Org. Chem.* **2013**, *14*, 2783–2787; b) L. Zhang, W. Wang, A. Wang, Y. Cui, X. Yang, Y. Huang, X. Liu, J.-Y. Son, H.

Ojic, T. Zhang, *Green Chem.* **2013**, *15*, 2680–2684; c) Z. Wang, D. Zhu, L. Tang, S. Wang, S. Wang, *Angew. Chem., Int. Ed.* **2011**, *50*, 8917–8921; d) J. S. Foot, H. Kanno, G. M. P. Giblin, R. J. K. Taylor, *Synthesis* **2003**, 1055–1064; e) K. Xu, Y. Hu, S. Zhang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 9793–9797; f) R. Ohmura, M. Takahata, H. Togo, *Tetrahedron Lett.* **2010**, *51*, 4378–4381; g) M. Karimi, D. Saberi, K. Azizi, M. Arefi, A. Heydari, *Tetrahedron Lett.* **2014**, *55*, 5351–5353; h) X.-F. Wu, M. Sharif, J.-B. Feng, H. Neumann, A. Pews-Davtyan, P. Langer, M. A Beller, *Green Chem.* **2013**, *15*, 1956–1961; i) G. Meng, P. Lei, M. Szostak. *Org. Lett.* **2017**, *19*, 2158–2161; j) Y. Liu, S. Shi, M. Achtenhagen, R. Liu, M. Szostak, *Org. Lett.* **2017**, *19*, 1614–1617; k) S. Shi, M. Szostak. *Chem. Commun.,* **2017**, *53*, 10584–10587.

[12] a) L. U. Nordstrøm, H. Vogt, R. Madsen. *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673; b) Y. Zhang, C. Chen, S. C. Ghosh, Y. Li, S. H. Hong. *Organometallics* **2010**, *29*, 1374–1378. c) G. Meng, M. Szostak. *Eur. J. Org. Chem.* **2018**, 2352–2365.

[13] a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; b) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, 7453–7465.

[14] a) R. Ohmura, M. Takahata, H. Togo, H. *Tetrahedron Lett.* **2010**, *51*, 4378–4381; b) H. Shimojo, K. Moriyama, H. Togo, *Synthesis* **2013**, *45*, 2155–2164.

[15] a) P. L. Anelli, C.Biffi, F. Montanari, *J. Org. Chem.* **1987**, *52*, 2559-2562; b) P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970–2972; c) P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *Org. Synth.* **1990**, *69*, 212–219.

[16] L. Liguori, H.-R. Bjørsvik, *Org. Process Res. Dev.* **2011**, *15*, 997–1009.

[17] a) R. Das, D. Chakraborty, *Catal. Commun*. **2012**, *26*, 48–53; b) X. Jiang, J. Zhang, S. Ma. *J. Am. Chem. Soc.* **2016**, *138*, 8344–8347.

[18] J. Wang, C. Liu, J. Yuan, A. Lei, *Chem. Commun*. **2014**, *50*, 4736–4739.

[19] R. Yousefi, D. C. Whitehead, J. M. Mueller, R. J. Staples, B. Borhan, *Org. Lett*. **2011**, *13*, 608–611.

[20] C. Liu, D. Liu, A. Lei. *Acc. Chem. Res.* **2014**, *47*, 3459–3470.

[21] a) R. L. Cicero, J. D. Protasiewicz, *Organometallics* **1995**, *14,* 4792-4798; b) S. J. Mahmood, M. M. Hossain *J. Org. Chem.* **1998**, *63,* 3333–3336; c) S. J. Mahmood, A. K. Saha, M. M. Hossain. *Tetrahedron* **1998**, 54, 349–358.

[22] O. Clement, B. M. Rapko, B. P. Hay. *Coord. Chem. Rev.* **1998**, *170*, 203–243.

[23] a) R. A. Sheldon, I. W. C. E. Arends, G. –J. Ten Brink, A. Djiksman, *Acc. Chem. Res*. **2002**, *35*, 774–781; b) S. Ma, J. Liu, S. Li, B. Chen, J. Cheng, J. Kuang, Y. Liu, B. Wan, Y. Wang, J. Ye, Q. Yu,

W. Yuan W. S Yu, *Adv. Synth. Catal*., **2011**, *353*, 1005–1017; c) X. Jiang, J. Zhang S. Ma, *J. Am. Chem. Soc*. **2016**, *138*, 8344–8347.

[24] C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414–6417.

[25] *Reregistration Eligibility Decision facts sheet (R.E.D. FACTS) for the pesticide "DEET"*, US Environmental Protection Agency, EPA-738-F-95-010, April **1998**.

[26] N. Schröder, J. Wancel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, 134, 8298–8301

[27] L. Zhang, S. Su, H. Wu, S. Wang, *Tetrahedron*, **2009**, *65*, 10022–10024

[28] W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065.

[29] M. G. Voronkov, I. P. Tsyrendorzhieva, V. I. Rakhlin, *Russ. J. Org. Chem.* **2008**, *44*, 481–484.

[30] R. M. Claramunta, P.Cornagoa, D.Sanza, M. D. Santa-Maríaa, C.Foces-Focesb, I. Alkortac, J. Elguero, *J. Mol. Struct.* **2002**, *605*, 199–212.

[31] J. Gu. Z. Fang, C. Liu, Z. Yang, X. Li, P. Weia. K. Guo, *RSC Adv.* **2015**, *5*, 95014–95019.

[32] L. Zhang, S. Su, H. Wu, S. Wang, *Tetrahedron* **2009**, *65*, 10022–10024.

[33] R. G. Kalkhambkar, S. N. Waters, K. K. Laali, *Tetrahedron Lett.* **2011**, *52*, 867–871.

[34] P. Starkov, T. D. Sheppard, *Org. Biomol. Chem.*, **2011**, *9*, 1320–1323.

[35] K. D. Hesp, R. G. Bergman, J. A. Ellmanm, *J. Am. Chem. Soc.*, **2011**, *133*, 11430–11433.