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Generation and Trapping of Ketenes in Flow

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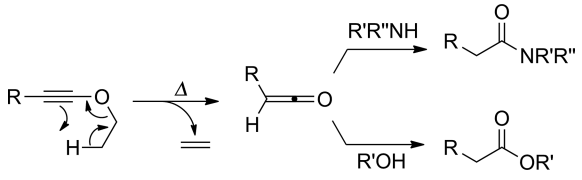
Ketenes were generated by the thermolysis of alkoxyalkynes under flow conditions, and then trapped with amines and alcohols to cleanly give amides and esters. For a 10 min reaction time, temperatures of 180, 160, and 140 °C were required for >95 % conversion of EtO, *i*PrO, and *t*BuO alkoxyalkynes, respectively. Variation of the temperature and flow rate with inline monitoring of the output by IR spectroscopy allowed the kinetic parameters for the conversion of 1-ethoxy-1-octyne to be easily estimated (E_a = 105.4 kJ/mol). Trapping of the in-situ-generated ketenes by alcohols to give esters required the addition of a tertiary amine catalyst to prevent competitive [2+2] addition of the ketene to the alkoxyalkyne precursor.

Introduction

Flow chemistry has traditionally been seen as a tool in process chemistry where the safety aspects and ease of scale-up outweigh the effort involved in the optimisation of a reaction to work well under flow conditions.[1] There is increasing recognition that the flow method also has an important role in discovery chemistry,[2] particularly where the formation of an intermediate may be optimised before it goes on to react with a wide variety of substrates to generate a library of compounds. Flow chemistry has the advantage that temperatures well above the normal boiling point of solvents can be used safely, due to its excellent high-pressure capability. This makes the thermal generation of reactive intermediates attractive. We are interested in the use of flow chemistry to rapidly carry out a number of reactions under precisely controlled conditions with inline monitoring of outcomes, to allow fast study[3] and optimisation of processes.

The reaction we chose to investigate was the generation of ketenes by thermal sigmatropic rearrangement of alkoxyalkynes,[4] and their trapping with amines[5] or alcohols[6] to provide amides and esters, respectively. Acylation, particularly of amines, is the most frequently used reaction in pharmaceutical discovery,[7] and one of the most used reactions in the synthesis of drug candidates.[8] It is still often carried out using acyl chlorides, but this approach has the disadvantages that moisture-sensitive precursors must be handled, and halide by-products are formed. Although a variety of other coupling reagents are used, most are very atom inefficient.[9] The generation and trapping of ketenes [Equation (1)] offers the prospect of a clean synthesis of amides and esters where the only by-product is a low molecular weight, volatile alkene. No work-up of the reaction should be needed apart from removal of the solvent, and the reaction would therefore also be suitable for incorporation into multistep flow-chemistry sequences. The precursor alkoxyalkynes are readily available.[10]



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Results and Discussion

The required alkoxyalkyne precursors were produced from readily available vinyl ethers in a two-pot sequence (Scheme 1). Addition of bromine to ethyl or *tert*-butyl vinyl ethers followed by in situ elimination of HBr using triethylamine and aqueous work-up gave (*Z*)-β-bromo-vinyl ethers

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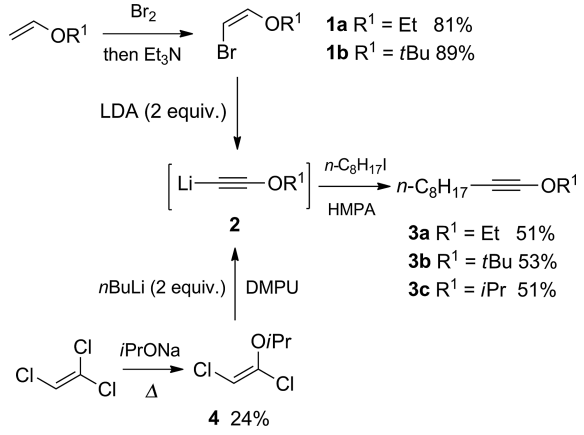
1 in reasonable yield.[11] Treatment of **1** with 2 equiv. of LDA gave lithiated alkynyl ether **2**, which was alkylated with iodooctane to give the required alkynyl ethers **3a** and **3b**. The corresponding isopropoxy alkyne **3c** was prepared from trichloroethylene by isopropoxide substitution to give **4**,[10a] followed by base-induced elimination to give lithiated alkoxyalkyne **2**, which was alkylated as before.[10a] It is worth noting that lithiated alkoxyalkynes **2** are poorly reactive towards alkylation.



Scheme 1. Synthesis of alkoxyalkynes **3**; HMPA = hexamethylphosphoramide, DMPU = *N*,*N*′-dimethylpropyleneurea, LDA = lithium diisopropylamide.

Thermolysis experiments under flow conditions were carried out using a Vapourtec R2+/R4 system with inline IR spectroscopic monitoring using a sodium chloride flow cell with 0.1 mm spacing in a Bruker alpha spectrometer.[12] The Vapourtec system provides two pumped channels, each of which could be switched between solvent and reagent, and which include a six-port two-position rheodyne valve allowing an injection loop to be switched into the flow. The reaction-coil temperature is controlled using circulated heated air. A liquid handler was used to collect samples for reaction analysis (Figure 1, single pumped channel A shown). Slugs of 2 mL volume containing alkoxyalkyne **3a**, **3b**, or **3c** (0.5 mmol) and benzylamine (0.5 mmol) premixed in toluene were introduced into a constant flow of toluene (1 mL/min) using the injection loop, and then passed

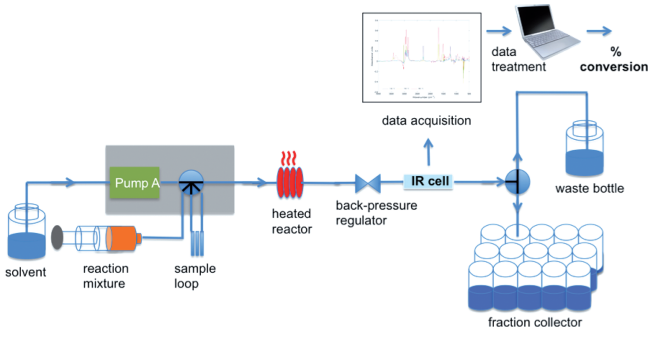
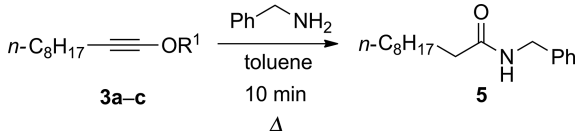


Figure 1. Schematic representation of the flow set-up for a single-channel sample-loop reaction with stainless steel reactor, inline IR spectroscopy, and fraction collector for offline validation by NMR spectroscopy.

through a heated 10 mL capacity stainless steel tube of 1 mm internal diameter providing a residence time of approximately[13] 10 min. A 250 psi back-pressure regulator was used to prevent boiling of the solvent. The ratios of the starting alkoxyalkyne (i.e., **3a**–**3c**) to the benzamide product (i.e., **5**) [Equation (2)] resulting from reaction at various temperatures were determined by ^{1}H NMR spectroscopy after removal of the solvent from collected samples in vacuo. The results are shown in Figure 2, and indicate a temperature-dependent half-life of 10 min at approximately 155, 132, and 109 °C, where the alkoxy group (R^1) is Et, *i*Pr, and *t*Bu, respectively. This reflects the known order of thermal instability of alkoxyalkanes **3a**–**3c**.[4f] The optimum temperatures for quantitative formation of **5** over 10 min, were found to be approximately 180 °C (R^1 = Et), 160 °C (R^1 = *i*Pr), and 140 °C (R^1 = *t*Bu).



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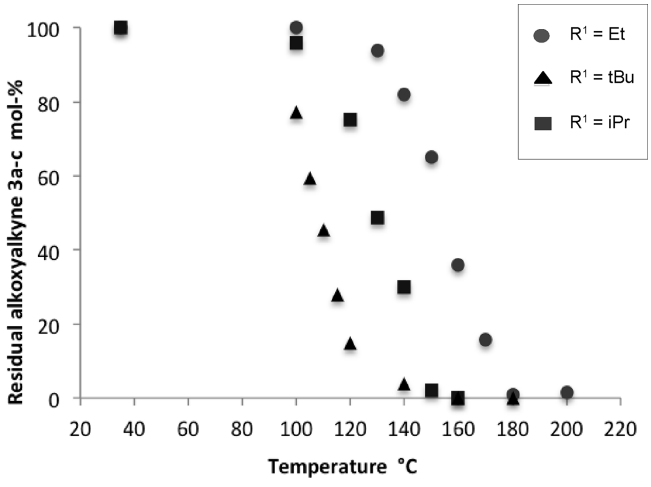

Figure 2. Thermolysis of alkoxyalkynes **3a** (R^1 = Et), **3b** (R^1 = *t*Bu), or **3c** (R^1 = *i*Pr) under 10 min flow with trapping by benzylamine (1 equiv.) in toluene.

A key advantage of flow systems is that both the reaction time and the temperature may be varied in a series of easily programmed automated experiments. Potentially, this allows the kinetics of reactions to be readily established. For the reaction of ethoxyalkyne **3a** with benzylamine, variation of the flow rate between 10 and 0.5 mL/min permitted residence times between 2 and 20 min, and we chose temperatures between 150 and 180 °C for kinetic studies. The residence times were corrected for thermal expansion of the solvent, and the precise control of the flow rate by the instrument was confirmed by independent volumetric measurement of the collected samples. For the measurement of temperature, we relied on a thermocouple in direct contact with the stainless steel column. In all cases, the only products observed were the starting materials and the amide

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product (i.e., **5**). In addition to ^{1}H NMR spectroscopy, we also used inline IR spectroscopy to monitor the conversion of the alkoxyalkyne to the amide. The peak heights of the respective calibrated absorption peaks at 2271 and 1683 cm^{-1} were used to calculate [**3a**]/[**3a**]$_0$ (see Supporting Information).

The expected first order kinetics were demonstrated (Figure 3), and the data from monitoring of the crude products by ^{1}H NMR spectroscopy and that obtained by inline monitoring by IR spectroscopy were found to correlate well. This confirms the validity of the latter method for quantifying conversion. Arrhenius plots of the first-order rate constants against the reciprocal of the temperature (Figure 3, inset) showed excellent linearity, and allowed the activation energy of the reaction to be estimated as 105.4 kJ/mol based on IR spectroscopic monitoring, and 108.9 kJ/mol based on offline NMR spectroscopy. The difference is probably due to a slight nonlinearity in the calibration of the IR spectroscopic data. Thermal transfer calculations (see Supporting Information) indicate that fluid in the stainless steel reactor tubing reaches the bath temperature very quickly (within the first 20 cm, i.e., within <2% of total length), and observation of the short cooling coil at the exit of the heated reactor demonstrates that cool-down is also rapid. However, it is uncertain whether the rate of heat transfer from the heated air to the coil is sufficient to prevent significant cooling of the initial part of the reactor by entering solvent, and, while the calculated E_a values are in reasonable agreement with the activation energy of 121 kJ/mol determined for the thermolysis of 1-ethoxyhept-1-yne in decalin by Olsman,[4e] this may explain the deviation in the kinetic plots observed at the fastest pumping speeds.

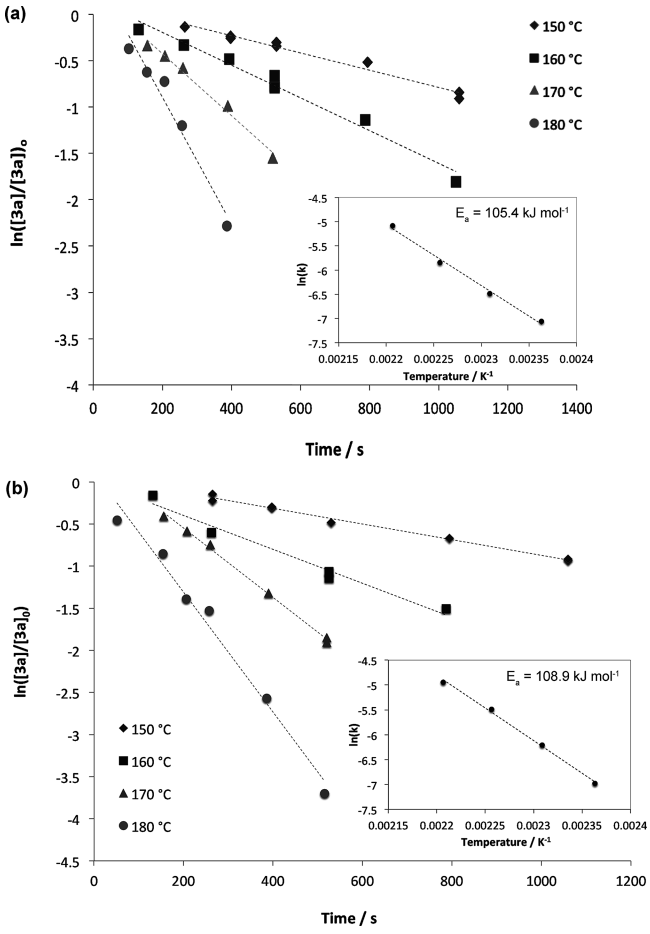

Figure 3. First order kinetics of the thermolysis of 1-ethoxydec-1-yne (**3a**) and (inset) Arrhenius plots obtained from (a) inline monitoring by IR spectroscopy, and (b) offline monitoring by ^{1}H NMR spectroscopy. Rate constants: at 150 °C, $k = 0.93 \times 10^{-3}$ (from IR and NMR); at 160 °C, $k = 1.77 \times 10^{-3}$ (IR) and 2.01×10^{-3} (NMR); at 170 °C, $k = 3.34 \times 10^{-3}$ (IR) and 4.12×10^{-3} (NMR); at 180 °C, $k = 6.84 \times 10^{-3}$ (IR) and 7.12×10^{-3} (NMR).

Having established optimum conditions for the formation of the ketene intermediate, we applied the in situ ketene trapping reaction to the acylation of a range of amines (Table 1). We chose to use 1-ethoxydec-1-yne (**3a**) and ethoxyethyne (**7**) as ketene precursors, but given the complete thermolysis of all the alkoxyalkyne precursors (i.e., **3a**–**3c**) shown in Figure 2, we suggest that isoproproxy- or *tert*-butylalkyne substrates could be similarly used. For these experiments, **3a** was premixed with **6** as described above, whereas **7** was delivered from a reagent bottle, and then combined (in a mixing T) with a solution of amine **6** delivered from an injection loop, before passage through the column at 180 °C (10 min residence time, vide supra).

To the best of our knowledge, the only reported examples of ketenes generated from alkoxyalkynes being trapped by alcohols are intramolecular.[6] Indeed, upon thermolysis of **3a** in the presence of 1 equiv. benzyl alcohol under flow conditions in toluene (180 °C, 10 min residence time), we obtained ester **10a** in only 28% yield, the major product (72%) being the cyclobutenone (i.e., **11**) resulting from [2+2] cycloaddition between the intermediate ketene and **3a** [Equation (3)]. Given the efficiency of the trapping of the ketene by amines, we sought to catalyse the reaction between the ketene and alcohols by using a tertiary amine.[14] We were pleased to find that thermolysis of **3a** in the presence of benzyl alcohol and pyridine (1 equiv. of each) gave the desired ester (i.e., **10a**) in an improved yield of 62%, although substantial amounts of **11** (38%) were also formed. Switching to the more nucleophilic 4-dimethylaminopyridine (DMAP) reduced the amount of adduct **11** to 2.5%, and with 2 equiv. DMAP, **11** was undetectable. Further investigation showed that 1 equiv. 1,4-diazabicyclo[2.2.2]octane (DABCO) gave only 0.5% of **11**, and catalytic quantities could be used with acceptable results (1.5 and 7% of **11** were formed with 0.5 and 0.1 equiv. DABCO, respectively) indicating a reasonably fast turnover of the amine. A reasonable catalytic cycle is shown in Scheme 2, although a base-catalysed mechanism cannot be ruled out.

It seemed possible that an intermediate of structure **12** would be stable enough to allow trapping with the alcohol after the thermolysis step was complete. Thus, to this end, 1-ethoxydec-1-yne (**3a**) and DMAP (1 or 2 equiv.) were subjected to our usual thermolysis conditions (10 min, 180 °C), and then the cooled flow was immediately combined with a solution of benzyl alcohol. However, these conditions gave mixtures of products **10a** and **11** in 60:40 and 80:20 ratios,

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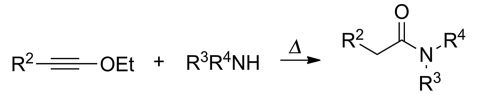
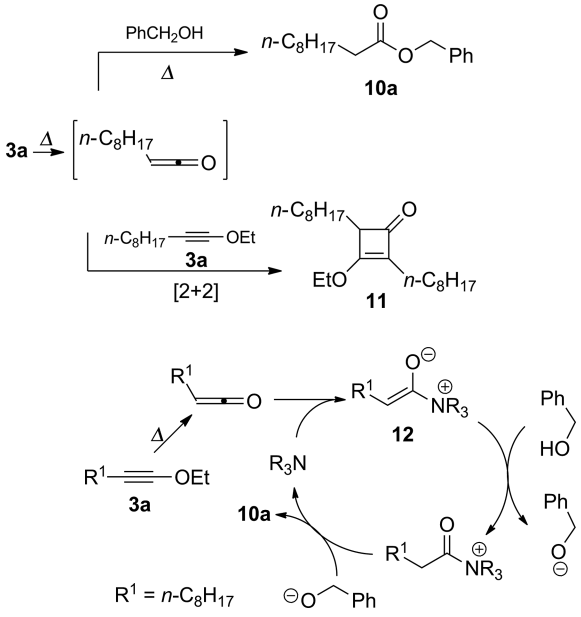
Table 1. Acylation of amines by in situ formation and trapping of ketenes under flow conditions.[a]



3a $R^2 = n\text{-}C_8H_{17}$ **6** **8** $R^2 = n\text{-}C_8H_{17}$
7 $R^2 = H$ **9** $R^2 = H$

R^3R^4NH **6**	Product of reaction of **6** with **3a** (yield [%])[b]		Product of reaction of **6** with **7** (yield [%])[b]	
$PhCH_2NH_2$	**5**	(92)	**9a**	(97)
$tBuNH_2$	**8b**	(96)	**9b**	(99)
iPr_2NH	**8c**	(80)	**9c**	(74)
Piperidine	**8d**	(87)	**9d**	(87)
Pyrrolidine	**8e**	(84)	**9e**	(88)
Morpholine	**8f**	(86)	**9f**	(93)
Cyclohexylamine	**8g**	(85)	**9g**	(97)
N-Methyl-*N*-cyclohexylamine	**8h**	(93)	**9h**	(92)
Dicyclohexylamine	–	–[c]	**9i**	(89)
1,2,3,4-Tetrahydroisoquinoline	–	–[d]	**9j**	(96)
$PhNH_2$	**8k**	(86)	–	–[d]
N-Allylaniline	**8l**	(92)	**9l**	(94)
Diallylamine	**8m**	(87)	**9m**	(89)
2-Aminopyridine	**8n**	(72)	**9n**	(82)

[a] For the synthesis of **5** and **8b**–**8n**, the reagents were premixed in the carrier solvent (toluene) before introduction into the solvent flow via a sample loop. For the synthesis of **9a**–**9n**, solutions of ethoxyethyne and the amine trap **6** in toluene were mixed on the flow system using a T-mixer. All reactions were conducted with a residence time of 10 min at 180 °C. [b] Isolated yield of product of >95% purity by ^1H NMR spectroscopy. [c] A mixture of **6**, **8i**, and the cyclobutenone product of [2+2] cycloaddition[4d] between **3a** and the ketene intermediate was recovered. [d] Not carried out.



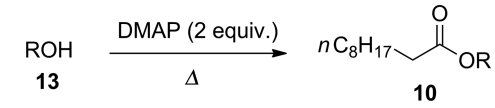
(3)

Scheme 2. Tertiary-amine-catalysed acylation of alcohols under flow conditions.

from 1 and 2 equiv. DMAP, respectively. Since DMAP is an efficient kinetic trap for the ketene, this result demonstrates the reversibility of trapping by the tertiary amine in the absence of protonation of **12** by alcohol.

We tested the acylation with a variety of alcohols, and we were pleased to obtain good isolated yields (Table 2), except in the case of trapping with *tert*-butanol, which did not give any of the ester product.

Table 2. Acylation of alcohols by in situ formation and trapping of ketenes under flow conditions.[a]



ROH **13**	Product	Yield [%][b]
$PhCH_2OH$	**10a**	71
Hexan-1-ol	**10b**	68
1-Geraniol	**10c**	77
2-Methylbutanol	**10d**	75
2-Propanol	**10e**	66

[a] Reagents were premixed in the carrier solvent (toluene) before introduction into the solvent flow via a sample loop. All reactions were conducted with a residence time of 10 min at 180 °C. [b] Isolated yield of product of >95% purity by ^1H NMR spectroscopy following aqueous work-up and solvent removal in vacuo.

Conclusions

Flow chemistry, particularly using inline IR spectroscopic monitoring, provides a fast platform for both optimising, and acquiring basic kinetic data on reactions. The in situ generation of ketenes by thermolysis of alkoxyalkynes provides a clean method for the acylation of amines, and, with the addition of a catalytic tertiary amine, also of alcohols. The process is suitable for direct input of the products into a subsequent flow reaction as the only by-product is a volatile alkene.

Experimental Section

General Methods: Batch synthesis reactions for the preparation of **3a**–**3c** were carried out under an argon atmosphere using standard Schlenk and syringe techniques. All glassware was dried at 160 °C overnight before cooling in a sealed desiccator over silica gel before use. CH_2Cl_2 was freshly distilled from CaH_2. THF was freshly distilled under argon from sodium and benzophenone. NMR spectra were recorded with a Bruker AV300 or DPX400 MHz spectrometer, as stated. ^1H chemical shifts are reported in ppm, referenced to residual solvent signals. The following abbreviations are used to designate multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C spectra are proton decoupled, and are referenced to solvent signals. ^{13}C resonances are reported as C, CH, CH_2, or CH_3 depending on the number of directly attached protons (0, 1, 2, or 3, respectively), as determined by DEPT experiments. Electron-impact-ionisation mass spectra (EI) and chemical-ionisation (CI) mass spectra were recorded with a ThermoQuest TraceMS GC–MS instrument. Electrospray mass spectra (ES) were recorded in CH_3CN or MeOH using a VG platform quadrupole spectrometer. Accurate-mass spectra were re-

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corded with a VG analytical 70–250-SE double-focussing mass spectrometer using electron-impact ionisation (EI) at 70 eV, or a Bruker Apex III instrument using electrospray ionisation. LCMS was carried out with a Waters ZQ machine, using an Acquity UPLC BEH C18 column (50 mm × 2.1 mm i.d., 1.7 µm packing diameter) at 40 °C. The UV detection was a summed signal from wavelengths of 210 nm to 350 nm and alternate-scan positive and negative electrospray was used. Scan range: 100–1000 Da, scan time: 0.27 s, and inter-scan delay: 0.10 s. Values of *m*/*z* are reported in atomic mass units (Da). Infrared spectra for compound characterisation were run as neat films with a Thermo Nicolet 380 FTIR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm^{-1}). Peaks are recorded as s (strong), m (medium), w (weak), sh (shoulder), and br (broad).

Continuous-Flow Methods: All reactions were carried out on a Vapourtec R2+/R4 system with a tubular stainless steel reactor of 1 mm internal diameter and 10 mL capacity using a 250 psi back-pressure regulator to prevent the boiling of solvents. In situ IR spectroscopic measurements were recorded with a Bruker ALPHA FTIR Universal Sampling Module at room temperature using a Harrick DLC 2™ Demountable Liquid Flow Cell with sodium chloride windows and 100 µm spacers. Full details of inline IR analysis are provided in the Supporting Information. A Gilson sample handler was used to collect fractions for offline analysis.

Continuous-Flow Procedure A: For the synthesis of decanamides **5** and **8b**–**8n**: 1-Ethoxydec-1-yne (**3a**) was premixed with an equivalent amount of amine **6** in toluene (2 mL) before insertion into a continuous flow of toluene (1 mL/min) via an injection loop. The mixture then passed through a stainless steel tube (10 mL; 1 mm i.d.) heated at 180 °C, after which it was collected. The solvent was removed to give the product. Where necessary (**8l** and **8n**), the product was purified by chromatography on silica gel using a gradient of ethyl acetate in cyclohexane.

Continuous-Flow Procedure B: For the synthesis of acetamides **9a**–**9n**: A solution of amine **6** (2.0 mmol) in toluene (2.5 mL) was used to fill a 2 mL injection loop (which thus contained a maximum of 1.6 mmol amine). The amine solution plug was inserted into a flow of toluene (0.5 mL/min), which was then combined with a bottle-fed plug of ethoxyacetylene (0.8 M solution in toluene; 2 mL, 1.6 mmol), also flowing at 0.5 mL/min, using a mixing T to give a combined flow rate of 1 mL/min. The solution was passed through a stainless steel tube (10 mL; 1 mm i.d.) heated at 180 °C, after which it was collected. The solvent was removed to give the product. The products were purified by chromatography on silica gel using a gradient of ethyl acetate in cyclohexane as eluent.

Continuous-Flow Procedure C: For the synthesis of esters **10a**–**10e**: 1-Ethoxydec-1-yne (**3a**; 0.5 mmol, 0.0911 g), alcohol **13** (0.5 mmol), and DMAP (1.0 mmol, 0.122 g) were dissolved in toluene (1.6 mL). This solution was inserted into a continuous flow of toluene (1 mL/min) via a sample loop, and then passed through a stainless steel tube (10 mL; 1 mm i.d.) heated at 180 °C. The solution containing the product was collected, washed with HCl (aq.), water, and brine, and dried ($MgSO_4$). The solvent was removed to give the product.

1-Ethoxydec-1-yne (3a): *n*BuLi (2.5 M solution in hexanes; 42 mL, 0.105 mol) was added to a solution of diisopropylamine (14.8 mL, 0.1 mol) in THF (8 mL) under argon at 0 °C. A solution of (*Z*)-1-bromo-2-ethoxyethene (7.55 g, 0.050 mol) in THF (58 mL) was added dropwise at –70 °C, and then the mixture was warmed to room temp. and stirred for 2 h. The solution was recooled to –70 °C, and HMPA (18.3 mL, 0.105 mol) was added dropwise. The solution was stirred for 30 min, then iodooctane (6.64 mL, 0.045 mol) was added, and the solution was warmed to room temp. and stirred for 30 h. The reaction mixture was quenched with water (200 mL), diethyl ether (100 mL) was added, and the organic phase was separated and dried with $MgSO_4$. Concentration under reduced pressure gave a dark oil (8.59 g), which was purified on basic alumina (grade III) with hexane elution to give compound **3a** (4.18 g, 51%) as a colourless oil. IR: $\tilde{\nu}$ = 2925 (m), 2271 (s), 1222 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.00 (q, J = 7.1 Hz, 2 H), 2.10 (t, J = 6.8 Hz, 2 H), 1.44 (quint, J = 6.8 Hz, 2 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.1–1.5 (m, 10 H), 0.88 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.26 (C), 73.72 (CH_2), 37.32 (C), 31.84 (CH_2), 29.24 (CH_2), 29.13 (CH_2), 28.81 (CH_2), 22.63 (CH_2), 17.18 (CH_2), 14.29 (CH_2), 14.07 (CH_3), 14.03 (CH_3) ppm.

1-*tert*-Butoxydec-1-yne (3b): *n*BuLi (2.5 M solution in hexanes; 39.3 mL, 0.098 mol) was added to THF (7.2 mL) and diisopropylamine (13.85 mL, 0.098 mL) at 0 °C under argon. A solution of 1-bromo-2-*tert*-butoxyethene (8.32 g, 0.047 mol) in THF (45 mL) was then added dropwise to the solution at –70 °C, and the resulting mixture was warmed to room temp. and stirred for 2 h. The solution was then recooled to –70 °C. HMPA (17.1 mL, 0.098 mol) was added, and the solution was stirred for 30 min. Iodooctane (6.21 mL, 0.042 mol) was then added, and the solution was stirred at room temp. for 30 h. The reaction was quenched with water (200 mL), and the mixture was extracted with diethyl ether (100 mL). The organic phase was dried over $MgSO_4$. Concentration under reduced pressure gave a dark oil (10.04 g). Purification on basic alumina (grade III) with hexane elution gave compound **3b** (5.20 g, 53%) as a colourless oil. IR: $\tilde{\nu}$ = 2925 (m), 2262 (m), 1159 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (t, J = 6.6 Hz, 2 H), 1.52–1.23 (m, 12 H), 1.35 (s, 9 H), 0.88 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.60 (C), 83.62 (C), 40.00 (C), 31.91 (CH_2), 29.98 (CH_2), 29.33 (CH_2), 29.20 (CH_2), 28.88 (CH_2), 26.83 (CH_2), 26.83 (CH_2), 22.67 (CH_3), 17.45 (CH_2), 13.98 (CH_3) ppm.

1-Isopropoxydec-1-yne (3c): *n*BuLi (1.6 M solution in hexanes; 10.25 mL, 16.14 mmol) was cooled to –30 °C, and THF (20 mL) was added. The mixture was cooled further to –70 °C, then a solution of 1,2-dichloro-2-isopropoxyethene (1.251 g, 8.07 mmol) in THF (40 mL) was added dropwise. The mixture was stirred for 15 min at –70 °C, then a solution of DMPU (1.946 mL, 16.14 mmol) in THF (10 mL) was added. The solution was stirred for a further 15 min, and then it was warmed to –10 °C and stirred for 10 min before recooling to –78 °C. A solution of 1-iodooctane (1.457 mL, 8.07 mmol) in THF (20 mL) was added dropwise. The resulting solution was stirred at room temperature for 3 d. The reaction was quenched with brine (20 mL), the layers were separated, and the organic phase washed with brine (20 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were dried with $MgSO_4$. The solvent was removed in vacuo to give a brown oil (3.068 g). Purification was carried out by flash-column chromatography (RediSep Alumina, Basic, 240 g, 100% cyclohexane) with a FlashMaster Personal purification platform to give compound **3c** (0.809 g, 51%) as a colourless oil. IR: $\tilde{\nu}$ = 2979 (s), 2268 (m), 1231 (s), 1143 (s), 1101 (m), 925 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (sept, J = 6.2 Hz, 1 H), 2.13 (t, J = 6.9 Hz, 2 H), 1.52–1.23 (m, 18 H), 0.89 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.93 (C), 80.51 (CH), 38.58 (C), 31.87 (CH_2), 29.86 (CH_2), 29.26 (CH_2), 29.16 (CH_2), 28.85 (CH_2), 22.66 (CH_2), 21.25 (CH_3), 17.34 (CH_2), 14.07 (CH_3) ppm.

***N*-Benzyldecanamide (5):**[15] According to continuous-flow procedure A, but dissolving the reagents in toluene (8 mL) and using a 10 mL injection loop, benzylamine (0.218 mL, 2 mmol) gave com-

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pound **5** (0.480 g, 92%) as a white solid, m.p. 74–75 °C. IR: $\tilde{\nu}$ = 3291 (m), 2916 (m), 1631 (s), 1554 (m), 694 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 5.77 (br. s, 1 H, NH), 4.44 (d, J = 5.5 Hz, 2 H), 2.21 (dd, J = 7.3, 7.3 Hz, 2 H), 1.66 (quint, J = 7.6 Hz, 2 H), 1.41–1.23 (m, 12 H), 0.89 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.95 (C), 138.42 (C), 128.67 (CH), 127.79 (CH), 127.45 (CH), 43.56 (CH_2), 36.63 (CH_2), 31.84 (CH_2), 29.43 (CH_2), 29.32 (CH_2), 29.30 (CH_2), 29.23 (CH_2), 25.76 (CH_2), 22.64 (CH_2), 14.08 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{28}NO$ [M + H]$^+$ 262.2165; found 262.2161.

***N*-(*tert*-Butyl)decanamide (8b):** According to continuous-flow procedure A, *tert*-butylamine (1.0 mmol, 105.1 µL) gave compound **8b** (0.218 g, 96%) as a white solid, m.p. 33–35 °C. IR: $\tilde{\nu}$ = 3307 (m), 2959 (m), 1644 (s), 732 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (br. s, 1 H, NH), 2.07 (t, J = 7.6 Hz, 2 H), 1.59 (quint, J = 7.1 Hz, 2 H), 1.34 (s, 9 H), 1.23–1.37 (m, 12 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.51 (C), 50.99 (C), 37.75 (CH_2), 31.83 (CH_2), 29.43 (CH_2), 29.35 (CH_2), 29.25 (CH_2), 29.21 (CH_2), 28.83 (CH_3), 25.78 (CH_2), 22.64 (CH_2), 14.07 (CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{30}NO$ [M + H]$^+$ 228.2322; found 228.2318.

***N*,*N*-Diisopropyldecanamide (8c):**[16] According to continuous-flow procedure A, diisopropylamine (1.0 mmol, 141.1 µL) gave compound **8c** (0.204 g, 80%) as a pale yellow oil. IR: $\tilde{\nu}$ = 2923 (m), 1638 (s), 1438 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (m, 1 H), 3.43 (m, 1 H), 2.22 (t, J = 8.1 Hz, 2 H), 1.56 (quint, J = 7.1 Hz, 2 H), 1.32 (d, J = 7.1 Hz, 6 H), 1.19–1.29 (m, 12 H), 1.15 (d, J = 6.6 Hz, 6 H), 0.83 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.95 (C), 48.12 (CH), 45.36 (CH), 35.31 (CH_2), 31.74 (CH_2), 29.37 (CH_3), 29.17 (CH_2), 25.36 (CH_2), 22.52 (CH_2), 20.90 (CH_2), 20.58 (CH_2), 13.95 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 278.3 (100) [M + Na]$^+$, 533.5 (35) [2M + Na]$^+$.

1-(Piperidin-1-yl)decan-1-one (8d):[17] According to continuous-flow procedure A, piperidine (1.0 mmol, 98.8 µL) gave compound **8d** (0.208 g, 87%) as a pale yellow oil. IR: $\tilde{\nu}$ = 2923 (s), 1635 (s), 1434 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (dd, J = 5.6, 5.6 Hz, 2 H), 3.38 (dd, J = 5.6, 5.6 Hz, 2 H), 2.30 (t, J = 7.7 Hz, 2 H), 1.19–1.36 (m, 8 H), 1.19–1.35 (m, 12 H), 0.87 (t, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.49 (C), 46.68 (CH_2), 42.54 (CH_2), 33.46 (CH_2), 31.83 (CH_2), 29.50 (CH_2), 29.42 (CH_2), 29.23 (CH_2), 26.55 (CH_2), 25.56 (CH_2), 25.47 (CH_2), 24.56 (CH_2), 22.61 (CH_2), 14.04 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 262.3 (100) [M + Na]$^+$, 502.5 (10) [2M + Na]$^+$.

1-(Pyrrolidin-1-yl)decan-1-one (8e): According to continuous-flow procedure A, pyrrolidine (0.5 mmol, 41.1 µL) gave compound **8e** (0.098 g, 86%) as a brown oil. IR: $\tilde{\nu}$ = 2922 (m), 1640 (s), 1425 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.39 (dt, J = 13.5, 6.8 Hz, 4 H), 2.21 (t, J = 7.5 Hz, 2 H), 1.74–1.98 (m, 4 H), 1.60 (quint, J = 7.3 Hz, 2 H), 1.13–1.34 (m, 12 H), 0.83 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.72 (C), 46.48 (CH_2), 45.43 (CH_2), 34.73 (CH_2), 31.74 (CH_2), 29.41 (CH_2), 29.35 (CH_2), 29.16 (CH_2), 26.01 (CH_2), 24.84 (CH_2), 24.30 (CH_2), 22.53 (CH_2), 13.97 (CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{27}NNaO$ [M + Na]$^+$ 248.1985; found 248.1986.

1-Morpholinodecan-1-one (8f):[18] According to continuous-flow procedure A, morpholine (0.5 mmol, 43.3 µL) gave compound **8f** (0.101 g, 84%) as a pale yellow oil. IR: $\tilde{\nu}$ = 2922 (m), 1645 (s), 1426 (m), 1115 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49–3.63 (m, 6 H), 3.36–3.44 (m, 2 H), 2.24 (t, J = 7.7 Hz, 2 H), 1.55 (quint, J = 7.2 Hz, 2 H), 1.12–1.32 (m, 12 H), 0.81 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.74 (C), 66.80 (CH_2), 66.53 (CH_2), 45.91 (CH_2), 41.70 (CH_2), 32.97 (CH_2), 31.71 (CH_2), 29.30 (CH_2), 29.12 (CH_2), 25.12 (CH_2), 22.49 (CH_2), 13.94 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 264.3 (100) [M + Na]$^+$, 296.3 (42) [M + Na + MeOH]$^+$.

***N*-Cyclohexyldecanamide (8g):** According to continuous-flow procedure A, cyclohexylamine (1.0 mmol, 114.7 µL) gave compound **8g** (0.215 g, 85%) as a white solid, m.p. 71–73 °C. IR: $\tilde{\nu}$ = 3297 (m), 2917 (m), 1637 (s), 1546 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.17 (br. s, 1 H, NH), 3.66 (m, 1 H), 2.05 (t, J = 8.0 Hz, 2 H), 1.76–1.90 (m, 2 H), 1.63 (dt, J = 14.0, 4.0 Hz, 2 H), 1.40–1.57 (m, 4 H), 0.93–1.38 (m, 16 H), 0.81 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.22 (C), 48.08 (CH), 37.24 (CH_2), 33.39 (CH_2), 31.95 (CH_2), 29.79 (CH_2), 29.54 (CH_2), 29.45 (CH_2), 29.36 (CH_2), 25.99 (CH_2), 25.66 (CH_2), 24.97 (CH_2), 22.75 (CH_2), 14.10 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 317.3 (100) [M + Na + MeCN]$^+$.

***N*-Cyclohexyl-*N*-methyldecanamide (8h):** According to continuous-flow procedure A, *N*-methyl-*N*-cyclohexylamine (0.5 mmol, 65.2 µL) gave compound **8h** (0.124 g, 93%) as a yellow oil. IR: $\tilde{\nu}$ = 2923 (s), 1640 (s), 1450 (m) cm^{-1}. A rotameric mixture was observed by NMR spectroscopy. Additional rotamer peaks are indicated *. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.42 (tt, J = 11.0, 3.0 Hz, 1 H), 3.51 (* tt, J = 11.5, 3.0 Hz, 1 H), 2.79 (s, 3 H), 2.76 (* s, 3 H), 2.29 (t, J = 7.5 Hz, 2 H), 2.25 (* t, J = 7.5 Hz, 2 H), 0.97–1.87 (m, 20 H), 0.85 (t, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.60 (C*), 172.56 (C), 56.55 (CH), 51.96 (CH*), 34.14 (CH_2), 33.53 (CH_2), 31.78 (CH_2), 30.91 (CH_2*), 29.82 (CH_2), 29.45 (CH_2), 29.37 (CH_2), 29.18 (CH_2), 26.94 (CH_3), 25.78 (CH_2), 25.57 (CH_2), 25.24 (CH_2*), 25.10 (CH_2), 22.56 (CH_2), 13.98 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{34}NO$ [M + H]$^+$ 268.2635; found 268.2629.

***N*-Phenyldecanamide (8k):**[15] According to continuous-flow procedure A, aniline (1.0 mmol, 91.2 µL) gave compound **8k** (0.212 g, 86%) as a white solid, m.p. 63–64 °C. IR: $\tilde{\nu}$ = 3313 (m), 2916 (m), 1655 (s), 1600 (s), 1538 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (br. s, 1 H, NH), 7.45 (d, J = 8.0 Hz, 2 H), 7.21 (t, J = 8.0 Hz, 2 H), 7.00 (t, J = 7.3 Hz, 1 H), 2.26 (t, J = 7.6 Hz, 2 H), 1.63 (quint, J = 7.3 Hz, 2 H), 1.11–1.32 (m, 12 H), 0.80 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.69 (C), 138.04 (C), 128.85 (CH), 124.06 (CH), 119.86 (CH), 37.73 (CH_2), 31.80 (CH_2), 29.41 (CH_2), 29.35 (2 CH_2), 29.24 (CH_2), 25.65 (CH_2), 22.61 (CH_2), 14.06 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 495.5 (20) [2M + Na]$^+$, 517.4 (4) [2M + Na]$^+$.

***N*-Allyl-*N*-phenyldecanamide (8l):** According to continuous-flow procedure A, *N*-allylaniline (0.5 mmol, 67.8 µL) gave, after purification on silica, compound **8l** (0.132 g, 92%) as a yellow oil. IR: $\tilde{\nu}$ = 2923 (m), 1657 (s), 699 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–6.93 (m, 5 H), 6.02–5.66 (m, 1 H), 5.26–4.87 (m, 2 H), 4.21 (d, J = 6.2 Hz, 2 H), 1.96 (t, J = 7.3 Hz, 2 H), 1.47 (m, 2 H), 0.95–1.38 (m, 12 H), 0.80 (t, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.19 (C), 143.17 (C), 133.77 (CH), 129.85 (CH), 128.72 (CH), 128.13 (CH), 117.92 (CH_2), 52.56 (CH_2), 34.74 (CH_2), 32.22 (CH_2), 29.75 (CH_2), 29.69 (CH_2), 29.64 (CH_2), 29.61 (CH_2), 25.87 (CH_2), 23.01 (CH_2), 14.75 (CH_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{30}NO$ [M + H]$^+$ 288.2322; found 288.2313.

***N*,*N*-Diallyldecanamide (8m):**[19] According to continuous-flow procedure A, diallylamine (0.5 mmol, 61.7 µL) gave compound **8m** (0.109 g, 87%) as a pale yellow oil. IR: $\tilde{\nu}$ = 3298 (br.), 2918 (s), 1641 (s), 1552 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65–5.81 (m, 2 H), 5.03–5.20 (m, 4 H), 3.95 (m, 2 H), 3.84 (m, 2 H), 2.27 (t, J = 7.7 Hz, 2 H), 1.61 (quint, J = 7.1 Hz, 2 H), 1.16–1.36 (m, 12 H), 0.84 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.00 (C), 133.36 (CH), 132.91 (CH), 116.87 (CH_2),

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116.31 (CH_2), 49.00 (CH_2), 47.65 (CH_2), 32.88 (CH_2), 31.73 (CH_2), 29.32 (3 CH_2), 29.13 (CH_2), 25.821 (CH_2), 22.51 (CH_2), 13.95 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{30}NO$ [M + H]$^+$ 252.2327; found 252.2316.

***N*-(Pyridin-2-yl)decanamide (8n):** According to continuous-flow procedure A, 2-aminopyridine (0.5 mmol, 0.047 g) gave, after purification on silica, compound **8n** (0.089 g, 72%) as a white solid, m.p. 38–40 °C. IR: $\tilde{\nu}$ = 3255 (m), 2923 (m), 1697 (m), 1431 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (br. s, 1 H, NH), 8.27 (m, 2 H), 7.71 (td, J = 8.0, 2.0 Hz, 1 H), 7.03 (td, J = 6.0, 1.5 Hz, 2 H), 2.39 (t, J = 7.76 Hz, 2 H), 1.72 (quint, J = 7.4 Hz, 2 H), 1.26 (m, 12 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.42 (C), 151.19 (C), 147.87 (CH), 138.82 (CH), 119.92 (CH), 114.71 (CH), 38.11 (CH_2), 32.22 (CH_2), 29.78 (CH_2), 29.71 (CH_2), 29.61 (CH_2), 29.60 (CH_2), 25.78 (CH_2), 23.02 (CH_2), 14.45 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{25}N_2O$ [M + H]$^+$ 249.1967; found 249.1961.

Benzylacetamide (9a):[20] According to continuous-flow procedure B, benzylamine gave compound **9a** (0.231 g, 97%) as a white solid, m.p. 54–56 °C. IR: $\tilde{\nu}$ = 3285 (br. s), 1636 (s), 1544 (s), 692 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 5 H), 7.08 (br. s, 1 H, NH), 4.31 (d, J = 5.8 Hz, 2 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.23 (C), 138.22 (C), 128.26 (CH), 127.37 (CH), 126.98 (CH), 43.20 (CH_2), 22.63 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 191.2 (100) [M + H + MeCN]$^+$.

***N*-(*tert*-Butyl)acetamide (9b):**[21] According to continuous-flow procedure B, *tert*-butylamine gave compound **9b** (0.183 g, 99%) as a white solid, m.p. 96–97 °C. IR: $\tilde{\nu}$ = 3284 (br. s), 1641 (m), 1555 (s), 1223 (s), 606 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (br. s, 1 H, NH), 1.85 (s, 3 H), 1.28 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.51 (C), 50.92 (C), 28.62 (CH_3), 24.27 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 157.2 (89) [M + H + MeCN]$^+$.

***N*,*N*-Diisopropylacetamide (9c):**[22] According to continuous-flow procedure B, diisopropylamine gave compound **9c** (0.187 g, 74%) as a yellow oil. IR: $\tilde{\nu}$ = 2967 (m), 1633 (s), 1442 (m), 1324 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (sept, J = 6.7 Hz, 1 H), 3.44 (m, 1 H), 1.98 (s, 3 H), 1.28 (d, J = 6.8 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.45 (C), 49.07 (CH), 45.24 (CH), 23.70 (CH_3), 20.74 (CH_3), 20.41 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 144.2 (43) [M + H]$^+$, 185.3 (29) [M + MeCN + H]$^+$, 207.3 (100) [M + Na + MeCN]$^+$, 208.3 (12) [M + Na + MeCN + H]$^+$, 309.3 (11) [2M + Na]$^+$.

1-(Piperidin-1-yl)ethanone (9d):[23] According to continuous-flow procedure B, piperidine gave compound **9d** (0.178 g, 87%) as a yellow oil. IR: $\tilde{\nu}$ = 2933 (m), 1627 (s), 1322 (s), 1264 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (t, J = 5.6 Hz, 2 H), 3.28 (t, J = 5.6 Hz, 2 H), 1.96 (s, 3 H), 1.53 (m, 2 H), 1.46 (m, 2 H), 1.41 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.42 (C), 47.16 (CH_2), 42.18 (CH_2), 26.15 (CH_2), 25.23 (CH_2), 24.20 (CH_2), 21.17 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 169.2 (100) [M + H + MeCN]$^+$, 191.3 (36) [M + Na + MeCN]$^+$, 192.2 (4) [M + H + Na + MeCN]$^+$, 255.3 (25) [2M + H]$^+$, 277.3 (5) [2M + Na]$^+$.

1-(Pyrrolidin-1-yl)ethanone (9e):[23] According to continuous-flow procedure B, pyrrolidine gave compound **9e** (0.159 g, 88%) as a yellow oil. IR: $\tilde{\nu}$ = 3455 (br. s), 1619 (s), 1422 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (t, J = 6.8 Hz, 4 H), 1.80 (s, 3 H), 1.73 (quint, J = 6.7 Hz, 2 H), 1.63 (quint, J = 6.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.48 (C), 46.61 (CH_2), 44.92 (CH_2), 25.55 (CH_2), 24.03 (CH_2), 21.91 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 155.2 (100) [M + H + MeCN]$^+$, 177.2 (50) [M + Na + MeCN]$^+$.

1-Morpholinoethanone (9f):[24] According to continuous-flow procedure B, morpholine gave compound **9f** (0.191 g, 93%) as a yellow oil. IR: $\tilde{\nu}$ = 3501 (br. s), 1629 (s), 1425 (s), 1248 (s), 1111 (s), 1021 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (t, J = 5.0 Hz, 2 H), 3.59 (t, J = 5.0 Hz, 2 H), 3.52 (t, J = 5.0 Hz, 2 H), 3.39 (t, J = 5.0 Hz, 2 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.90 (C), 66.61 (CH_2), 66.37 (CH_2), 46.46 (CH_2), 41.55 (CH_2), 20.94 (CH_3) ppm. LCMS (HpH): m/z (%) = 129.9 (100) [M + H]$^+$.

***N*-Cyclohexylacetamide (9g):**[25] According to continuous-flow procedure B, cyclohexylamine gave compound **9g** (0.218 g, 97%) as a white solid, m.p. 104–105 °C. IR: $\tilde{\nu}$ = 3220 (br. s), 1635 (s), 1399 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (br. s, 1 H), 3.63 (ttd, J = 11.5, 3.9, 7.3 Hz, 1 H), 1.86 (s, 3 H), 1.84–1.00 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.12 (C), 48.06 (CH), 32.86 (CH_2), 25.53 (CH_2), 24.74 (CH_2), 23.15 (CH_3) ppm. LCMS (HpH): m/z (%) = 142.1, 100 [M + H]$^+$.

***N*-Cyclohexyl-*N*-methylacetamide (9h):**[26] According to continuous-flow procedure B, *N*-methyl-*N*-cyclohexylamine gave compound **9h** (0.229 g, 92%) as a yellow oil. IR: $\tilde{\nu}$ = 2927 (m), 1632 (s), 1505 (m), 1021 (m) cm^{-1}. A rotameric mixture was observed by NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (tt, J = 11.5, 4.5 Hz, 0.5 H), 3.29 (tt, J = 11.5, 4.5 Hz, 0.5 H), 2.63 (s, 1.5 H), 2.58 (s, 1.5 H), 1.90 (s, 1.5 H), 1.86 (s, 1.5 H), 1.70–0.80 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.45 (C), 169.36 (C), 57.03 (CH), 51.43 (CH), 30.33 (CH_2), 29.69 (CH_3), 29.22 (CH_2), 26.34 (CH_3), 25.28 (CH_2), 25.13 (CH_2), 25.08 (CH_3), 24.78 (CH_3) ppm. MS (ESI$^+$): m/z (%) = 156.2 (42) [M + H]$^+$.

***N*,*N*-Dicyclohexylacetamide (9i):** According to continuous-flow procedure B, dicyclohexylamine gave compound **9i** (0.319 g, 89%) as a white solid, m.p. 101–103 °C. IR: $\tilde{\nu}$ = 12931 (m), 1624 (s), 1310 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 (t, J = 6.1 Hz, 1 H), 2.34 (m, 1 H), 1.80 (s, 3 H), 1.85–1.00 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.52 (C), 55.59 (CH), 31.31 (CH_2), 30.12 (CH_2), 26.55 (CH_2), 26.03 (CH_2), 25.31 (CH_2), 25.22 (CH_2), 24.04 (CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{26}NO$ [M + H]$^+$ 224.2009; found 224.2006.

1-[3,4-Dihydroisoquinolin-2(1*H*)-yl]ethanone (9j):[27] According to continuous-flow procedure B, 1,2,3,4-tetrahydroisoquinoline (1.0 mmol, 0.134 g) gave compound **9j** (0.168 g, 96%) as a white solid, m.p. 44–46 °C. IR: $\tilde{\nu}$ = 3019 (w), 1640 (m), 1426 (m), 727 (s) cm^{-1}. A rotameric mixture was observed by NMR spectroscopy. Additional rotamer peaks are indicated *. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.13 (m, 4 H), 7.28–7.13 (* m, 4 H), 4.78 (s, 2 H), 4.67 (* s, 2 H), 3.87 (* t, J = 5.9 Hz, 2 H), 3.73 (t, J = 5.9 Hz, 2 H), 2.96 (t, J = 5.9 Hz, 2 H), 2.90 (* t, J = 5.9 Hz, 2 H), 2.24 (s, 3 H), 2.23 (* s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.41 (C), 169.32 (C*), 135.01 (C*), 133.96 (C), 133.45 (C), 132.50 (C*), 128.86 (CH*), 128.21 (CH), 126.83 (CH), 126.58 (CH), 126.53 (CH*), 126.45 (CH*), 126.27 (CH), 125.95 (CH*), 48.01 (CH_2*), 44.01 (CH_2), 43.93 (CH_2*), 39.41 (CH_2*), 29.39 (CH_2), 28.45 (CH_2*), 21.87 (CH_3*), 21.61 (CH_3) ppm. LCMS: m/z (%) = 176.1 (100) [M + H]$^+$.

***N*-Allyl-*N*-phenylacetamide (9l):**[28] According to continuous-flow procedure B, *N*-allylaniline gave compound **9l** (0.264 g, 94%) as a pale brown solid, m.p. 41–43 °C. IR: $\tilde{\nu}$ = 1641 (s), 1392 (s), 1273 (s), 704 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.04 (m, 5 H), 5.75 (tdd, J = 6.4, 16.8, 10.2 Hz, 1 H), 4.97 (m, 2 H), 4.19 (d, J = 6.3 Hz, 2 H), 1.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.70 (C), 142.74 (C), 132.91 (CH), 128.29 (CH), 127.80 (CH), 127.59 (CH), 117.40 (CH_2), 51.70 (CH_2), 22.39 (CH_3)

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ppm. MS (ESI$^+$): *m/z* (%) = 176.2 (100) [M + H]$^+$, 198.2 (4) [M + Na]$^+$, 217.2 (54) [M + MeCN + H]$^+$.

***N,N*-Diallylacetamide (9m):**[29] According to continuous-flow procedure B, diallylamine gave compound **9m** (0.198 g, 89%) as a yellow oil. IR: $\tilde{\nu}$ = 3081 (w), 1636 (s), 1410 (m), 1245 (m), 920 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 (tdd, *J* = 6.4, 16.8, 10.2 Hz, 1 H), 5.64 (tdd, *J* = 6.4, 16.8, 10.2 Hz, 1 H), 5.05 (m, 4 H), 3.87 (d, *J* = 6.0 Hz, 2 H), 3.76 (m, 2 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.20 (C), 133.01 (CH), 132.45 (CH), 116.87 (CH), 116.23 (CH), 49.69 (CH_2), 47.45 (CH_2), 22.63 (CH_3) ppm. MS (ESI$^+$): *m/z* (%) = 181.3 (100) [M + H + MeCN]$^+$, 279.3 (8) [2M + H]$^+$.

***N*-(Pyridin-2-yl)acetamide (9n):**[30] According to continuous-flow procedure B, 2-aminopyridine gave compound **9n** (0.178 g, 81.7%) as a white solid, m.p. 62–64 °C. IR: $\tilde{\nu}$ = 3180 (w), 1687 (s), 1577 (s), 1528 (s), 1430 (s), 1298 (s), 774 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (br. s, 1 H, NH), 8.29 (d, *J* = 5.0 Hz, 1 H), 8.16 (d, *J* = 8.1 Hz, 1 H), 7.70 (t, *J* = 7.9 Hz, 1 H), 7.03 (t, *J* = 5.5 Hz, 1 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.00 (C), 151.82 (C), 147.35 (CH), 138.48 (CH), 119.58 (CH), 114.45 (CH), 24.50 (CH_3) ppm. LCMS: *m/z* (%) = 137.0 (100) [M + H]$^+$.

Benzyldecanoate (10a):[31] According to continuous-flow procedure C, benzylalcohol gave compound **10a** (0.093 g, 71%) as a pale yellow oil. IR: $\tilde{\nu}$ = 2923 (s), 1731 (s), 1151 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.31 (m, 5 H), 5.04 (s, 2 H), 2.28 (t, *J* = 7.7 Hz, 2 H), 1.50–1.63 (m, 2 H), 1.18 (m, 12 H), 0.80 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.10 (C), 136.12 (C), 128.51 (CH), 128.13 (2 CH), 66.03 (CH_2), 34.32 (CH_2), 29.38 (CH_2), 29.22 (3 CH_2), 29.10 (CH_2), 24.94 (CH_2), 22.64 (CH_2), 14.09 (CH_3) ppm. MS (CI): *m/z* (%) = 263.2 (2.5) [M + H]$^+$.

Octyldecanoate (10b):[32] According to continuous-flow procedure C, 1-hexanol gave compound **10b** (0.087 g, 68%) as a colourless oil. IR: $\tilde{\nu}$ = 2995 (m), 1734 (s), 1170 (m), 732 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.06 (t, *J* = 6.7 Hz, 2 H), 2.29 (t, *J* = 7.5 Hz, 2 H), 1.54–1.71 (m, 4 H), 1.18–1.47 (m, 18 H), 0.82–0.96 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.99 (C), 64.36 (CH_2), 34.39 (CH_2), 31.84 (CH_2), 31.42 (CH_2), 29.41 (CH_2), 29.25 (CH_2), 29.13 (CH_2), 28.61 (CH_2), 25.59 (CH_2), 25.02 (CH_2), 22.64 (CH_2), 22.53 (CH_2), 14.07 (CH_3), 13.97 (CH_3) ppm. MS (ESI$^-$): *m/z* (%) = 171.1 (100) [$C_{10}H_{19}O_2$]$^-$.

(*E*)-2,3,7-Trimethylocta-2,6-dien-1-yl Decanoate (10c): According to continuous-flow procedure C, 1-geraniol gave compound **10c** (0.119 g, 77%) as a pale yellow oil. IR: $\tilde{\nu}$ = 2923 (s), 1735 (s), 1161 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35 (t, *J* = 7.1 Hz, 1 H), 5.09 (t, *J* = 6.1 Hz, 1 H), 4.60 (d, *J* = 7.1 Hz, 2 H), 2.30 (t, *J* = 7.6 Hz, 2 H), 2.02–2.15 (m, 4 H), 1.71 (s, 3 H), 1.69 (s, 3 H), 1.58–1.66 (m, 5 H), 1.22–1.35 (m, 12 H), 0.89 (t, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.93 (C), 142.09 (C), 131.80 (C), 123.76 (CH), 118.43 (CH), 61.16 (CH_2), 39.53 (CH_2), 34.41 (CH_2), 31.86 (CH_2), 29.42 (CH_2), 29.26 (CH_2), 29.15 (CH_2), 26.30 (CH_2), 25.66 (CH_3), 25.02 (CH_2), 22.65 (CH_2), 17.68 (CH_3), 16.45 (CH_3), 14.08 (CH_3) ppm. HRMS (ES$^+$): calcd. for $C_{20}H_{36}NaO_2$ [M + Na]$^+$ 331.2608; found 331.2615.

2-Methylbutyl Decanoate (10d): According to continuous-flow procedure C, 2-methylbutanol gave compound **10d** (0.071 g, 75%) as a colourless oil. IR: $\tilde{\nu}$ = 2924 (s), 1736 (s), 1155 (s), 732 (m), 696 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (dd, *J* = 11.0, 6.2 Hz, 1 H), 3.69 (dd, *J* = 10.6, 7.0 Hz, 1 H), 2.23 (t, *J* = 7.5 Hz, 2 H), 1.46–1.72 (m, 3 H), 1.01–1.44 (m, 14 H), 0.74–0.92 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.05 (C), 68.87 (CH_2), 34.41 (CH), 34.12 (CH_2), 31.84 (CH_2), 29.41 (CH_2), 29.24 (CH_2), 29.15 (CH_2), 26.03 (CH_2), 25.03 (CH_2), 22.64 (CH_2), 16.37 (CH_3), 14.07 (CH_3), 11.19 (CH) ppm. HRMS (ES$^+$): calcd. for $C_{15}H_{30}NaO_2$ [M + Na]$^+$ 265.2138; found 265.2142.

Isopropyl Decanoate (10e):[33] According to continuous-flow procedure C, isopropanol gave compound **10e** (0.071 g, 66%) as a yellow oil. IR: $\tilde{\nu}$ = 2924 (s), 1732 (s), 1108 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.01 (sept, *J* = 6.3 Hz, 1 H), 2.26 (t, *J* = 7.5 Hz, 2 H), 1.54–1.69 (m, 2 H), 1.25–1.35 (m, 12 H), 1.23 (d, *J* = 6.2 Hz, 6 H), 0.88 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.46 (C), 67.29 (CH), 34.73 (CH_2), 31.84 (CH_2), 29.41 (CH_2), 29.24 (2 CH_2), 29.10 (CH_2), 25.03 (CH_2), 22.64 (CH_2), 21.84 (CH_3), 14.09 (CH_3) ppm. MS (CI): *m/z* (%) = 214.2 (2) [M], 215.2 (67) [M + H]$^+$, 232.3 (100) [M + NH_4]$^+$.

3-Ethoxy-2,4-dioctylcyclobut-2-enone (11): Using a 10 mL injection loop, a solution of 1-ethoxydec-1-yne (**3a**; 0.364 g, 2.0 mmol) in toluene (8 mL) was inserted into a continuous flow of toluene (1 mL/min), which then passed through a stainless steel tube (10 mL; 1 mm i.d.) heated at 180 °C, after which it was collected. The solvent was removed to give the crude product. Purification by column chromatography (basic alumina grade III eluting with hexane/diethyl ether, 3:1) gave compound **11** (0.320 g, 95%) as a colourless oil. IR: $\tilde{\nu}$ = 2929 (m), 1615 (s), 1323 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26–4.38 (m, 2 H), 3.35 (t, *J* = 5.8 Hz, 1 H), 2.05 (t, *J* = 7.1 Hz, 2 H), 1.60 (m, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 1.16–1.38 (m, 24 H), 0.87 (t, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.86 (C), 179.15 (C), 121.04 (C), 68.12 (CH), 58.85 (CH_2), 31.83 (2 CH_2), 29.72 (CH_2), 29.47 (CH_2), 29.40 (CH_2), 29.28 (CH_2), 29.22 (CH_2), 28.50 (CH_2), 28.23 (CH_2), 26.54 (CH_2), 22.63 (2 C), 15.16 (CH_3), 14.07 (CH_3) ppm. HRMS (ES$^+$): calcd. for $C_{22}H_{41}O_2$ [M + H]$^+$ 337.3101; found 337.3105. Compound **11** is a known compound that has previously been characterised by boiling point and refractive index.[4e]

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