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Carbenes in Microreactors |*Hot Paper*|

Continuous-Flow N-Heterocyclic Carbene Generation and Organocatalysis

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Abstract: Two methods were assessed for the generation of common N-heterocyclic carbenes (NHCs) from stable imidazol(in)ium precursors using convenient and straightforward continuous-flow setups with either a heterogeneous inorganic base (Cs_2CO_3 or K_3PO_4) or a homogeneous organic base ($KN(SiMe_3)_2$). In-line quenching with carbon disulfide revealed that the homogeneous strategy was most efficient for the preparation of a small library of NHCs. The generation of free nucleophilic carbenes was next telescoped with two benchmark NHC-catalyzed reactions; namely, the transesterification of vinyl acetate with benzyl alcohol and the amidation of *N*-Boc-glycine methyl ester with ethanolamine. Both organocatalytic transformations proceeded with total conversion and excellent yields were achieved after extraction, showcasing the first examples of continuous-flow organocatalysis with NHCs.

Introduction

Numerous studies revolving around the properties and reactivity of N-heterocyclic carbenes (NHCs) have flourished since Arduengo's seminal report on the isolation and full characterization of 1,3-diadamantylimidazol-2-ylidene in 1991.[1] NHCs are nowadays recognized as powerful nucleophiles[2] and strong neutral Brønsted/Lewis bases,[3] in which the steric and electronic environments can be easily tuned by changing the nitrogen substituents and/or the nature of the central heterocycle.[4] In coordination chemistry, NHCs behave as powerful σ-donor and moderate π-acceptor ligands for the whole gamut of metals, whether they belong to the main group, the d-block elements, or the lanthanides and actinides.[5] Consequently, metal–NHC complexes are significantly more stable than their metal–phosphine analogues and are generally endowed with a superior catalytic activity.[6] For instance, Houk and Gard recently reported the conversion of amides into esters by using Ni–NHC catalysts to activate and cleave the amide bond.[7] Following the pioneering work of Ukai et al.[8] and Breslow[9] on the benzoin condensation catalyzed by thiazol-2-ylidenes generated in situ, the synthetic utility of NHCs was further broadened to organocatalysis. Indeed, several classes of organic substrates can be activated through the formation of various well-established reactive intermediates, for example, acyl anions, acylazoliums, azolium enolates, azolium homoenolates, or acid-base complexes.[10] Spectacular developments have been reported in this field over the past few years, with a particular emphasis on the design of enantiopure NHCs for stereoselective organocatalysis.[11]

For all their synthetic versatility and vast range of application, NHCs are oxygen- and moisture-sensitive species that demand strictly controlled reaction conditions. Thus, their handling and storage usually require an inert atmosphere, sophisticated glassware and procedures, and costly equipment such as glove-boxes.[12] To alleviate these experimental issues and to avoid their isolation, free carbenes are usually generated in situ from stable precursors.[13] In this respect, the most common and convenient access to NHCs consists of the deprotonation of an azol(in)ium salt with a strong base.[14]

Over the last decade, microreaction technology and continuous-flow chemistry have emerged as powerful tools to improve chemical manufacturing.[15] The inherent properties of microfluidic reactors in terms of fast mixing, efficient heat transfer, and accurate control over the local stoichiometry contribute to the development of more efficient, reliable, and safer chemical processes.[16] Previous reports have illustrated the successful implementation of transient,[17] moisture/oxygen-sensitive,[18] and dangerous species[19] within micro- and mesoreactors, even under intensified conditions.[20] Reaction telescoping is a common strategy in continuous-flow chemistry that aims to perform consecutive reactions continuously within the same uninterrupted reactor network.[21] Multistep sequences involving hazardous, toxic, and transient species benefit from process telescoping because it suppresses manual intervention and stockpiling of chemical intermediates. Instead, the troublesome species are immediately reacted inside the microreactor network, thereby avoiding degradation, decreasing chemical risk, and improving overall efficiency.[22]

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Given that NHCs are highly reactive, oxygen- and moisture-sensitive species, telescoping their preparation and their use in the controlled and confined environment of a microreactor could simplify their manipulation. In 2013, McQuade et al. reported a continuous-flow setup for the preparation and catalytic use of [Cu(NHC)Cl] complexes.[23] The copper(I)-carbene active species were obtained by oxidative addition of azolium salts onto Cu_2O, rather than by generation of free NHCs and coordination to the metal. More recently, Brown and co-workers reported the NHC-mediated oxidative esterification of various aldehydes by telescoping the formation of Breslow's intermediates from aldehydes and a thiazolium salt in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), their anodic oxidation into the corresponding acylazolium derivatives, and a final esterification reaction in an uninterrupted microreactor network.[24]

In this contribution, we report on the design of a convenient and straightforward continuous-flow setup for the generation of free NHC species, and their use as organocatalysts in two benchmark NHC-promoted reactions; namely, a transesterification and an amidation reaction. The implementation of in-line IR monitoring and continuous extraction/separation is also showcased for one example.

Results and Discussion

Continuous-flow NHC generation

Two distinct strategies were investigated for converting stable imidazol(in)ium salts into NHCs by using a continuous-flow setup. The first strategy used heterogeneous inorganic bases to deprotonate the azolium precursors, whereas the second approach relied on homogeneous organic bases. The batch analogues of these two approaches are both very common for the generation of NHCs in situ, either with heterogeneous inorganic bases, such as cesium carbonate[25] or with homogeneous organic bases, such as potassium bis(trimethylsilyl)amide (KHMDS).[26] We first sought a suitable method to assess the efficiency of the NHC generation in flow. Imidazol(in)ylidenes are known to form stable and isolable zwitterionic adducts with a variety of allenes[27] and heteroallenes including CO_2,[27] COS,[28] CS_2,[27] diimides,[27,29] ketenes,[30] and iso(thio)cyanates.[27] Among these various electrophiles, we selected carbon disulfide because this simple, widely available, liquid reagent instantaneously forms highly colored, shelf-stable zwitterions with nucleophilic carbenes (Scheme 1).[31]

The first NHC generation method involved a thermostated packed-bed reactor filled with an anhydrous inorganic base (Figure 1a). Anhydrous and degassed solvents [tetrahydrofuran (THF), MeCN, or *N*,*N*-dimethylformamide (DMF)] were employed to prepare feed solutions of imidazolium precursor **1a**, which served as a model substrate. They were conveyed to the packed-bed reactor through a syringe pump set at 0.25 mL min^{-1} to get a 10 min residence time. The reactor effluent was mixed with a large excess of carbon disulfide (0.25 mL min^{-1}) through a T-mixer located immediately after the outlet of the packed-bed reactor. A short perfluoroalkoxy

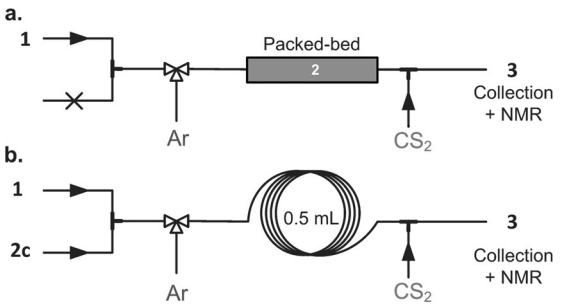
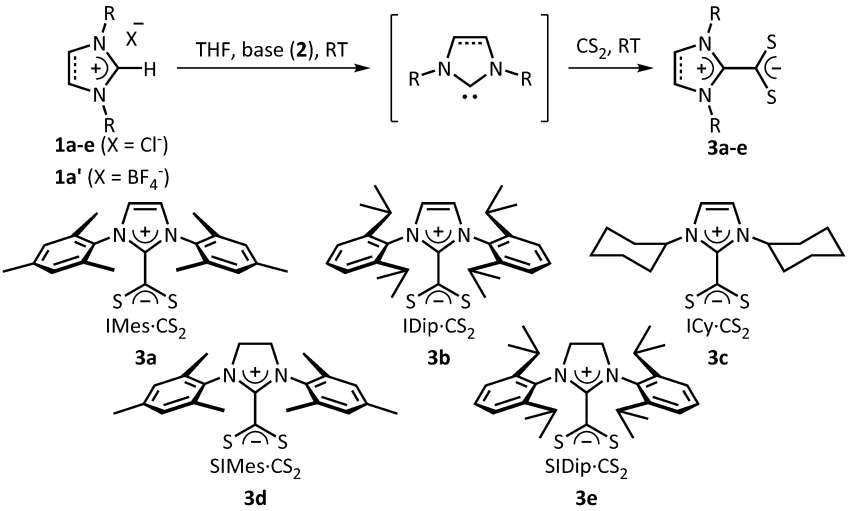


Figure 1. a) Heterogeneous and b) homogeneous strategies for the continuous-flow generation and quenching of NHCs. Both setups include an anhydrous argon inlet to flush the system via a three-way valve prior to utilization.



Scheme 1. Typical procedure for the transformation of imidazol(in)ium salts **1** into their stable zwitterionic NHC·CS_2 adducts **3**. The bases used were Cs_2CO_3 (**2a**), K_3PO_4 (**2b**), or $KN(SiMe_3)_2$ (**2c**).

alkane (PFA) capillary loop (0.25 mL internal volume) further increased the residence time to complete the formation of IMes·CS_2 (**3a**). The formation of this zwitterion could be visualized through the appearance of an intense red coloration in the PFA capillary loop. Samples were collected periodically and analyzed by ^{1}H NMR spectroscopy. Conversions were calculated by comparing the characteristic signals of the imidazolium precursor **1a** and the corresponding NHC·CS_2 zwitterionic adduct **3a** (Figure 2).[27,31]

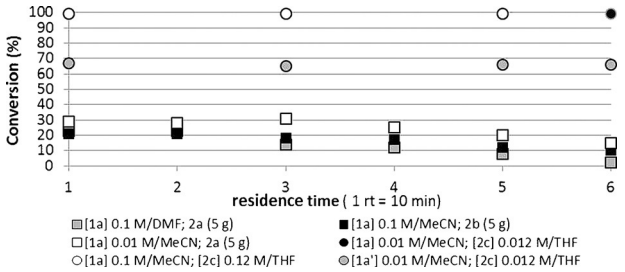


Figure 2. Representative conversions of imidazolium precursors **1a** and **1a′** using the heterogeneous (squares) and homogeneous (circles) strategies (see Figure 1).

Reactive packed-bed reactors are very convenient for performing continuous-flow processes, but they inherently suffer from the progressive disappearance of the packed reagent, and their performance is dramatically affected over the course of a reaction.[23] This phenomenon was clearly identified in our experiments as the conversion toward zwitterionic adduct **3a** usually dropped after 20 min of operation (Figure 2). The first set of results with the heterogeneous setup was collected with Cs_2CO_3 (**2a**) as the inorganic base (5 g) at 25 °C and a 0.1 M solution of **1a** in DMF. A mere 23% conversion was obtained at steady state (after 20 min). The conversion then began to decrease and was limited to 5% after 60 min of operation. Even lower conversions were obtained in MeCN or THF. Potassium phosphate (**2b**) performed similarly to Cs_2CO_3, with 21% conversion over 20 min of operation, which then dropped to 10% after 60 min. A 10-fold decrease in concentration helped to sustain a constant conversion of ca. 30% over 30 min, but did not prevent it from dropping when the run was further extended. The conversion of imidazolium precursor IDip·HCl (**1b**) did not exceed 5% under these conditions. IMes·HBF_4 (**1a′**) failed to react under these conditions, and the starting material **1a′** was recovered unchanged.

The continuous-flow setup was adapted for the second NHC generation method (Figure 1b). The packed-bed reactor was replaced by a PFA capillary loop (0.50 mL internal volume) and a second inlet was connected upstream to inject a solution of KHMDS (**2c**). Mixing of both reagent feeds was achieved through a polyether ether ketone (PEEK) T-mixer. The PFA capillary loop was thermostated at 25 °C and the quench with CS_2 was implemented as described above for the heterogeneous procedure.

A 0.01 M solution of **1a** in MeCN was pumped at a flow rate of 25 μL min^{-1} and reacted with a 0.02 M solution of KHMDS in MeCN (25 μL min^{-1}). After a residence time of 10 min in the PFA loop, the reactor effluent was quenched with a large excess of CS_2 (0.125 mL min^{-1}) and analyzed by ^{1}H and ^{13}C NMR spectroscopies. Under these conditions, a 51% conversion was reached. Samples were collected periodically over 2 h of operation and consistently gave the same conversion. An important solvent effect was noted when KHMDS was dissolved in THF, in which case the conversion of **1a** was complete. Total conversion was preserved when working with a reduced excess of KHMDS (1.2 equiv, 0.012 M in THF, 25 μL min^{-1}). The best combination of solvents involved MeCN to dissolve **1a**, and THF to dissolve KHMDS, ensuring total conversion and preventing the precipitation of KCl in the reactor. A 10-fold increase in concentration also led to complete conversion, although the zwitterionic NHC·CS_2 product **3a** accumulated in the second PFA loop. The immersion of the reactor in an ultrasonic bath prevented clogging and ensured a steady operation of the system for more than 2 h with consistent output.

In view of the good results obtained with **1a**, the homogeneous method was extended to the generation and quenching of NHCs derived from imidazolium salts **1b,c** and imidazolinium salts **1d,e** (Figure 1). In some instances, the excess of KHMDS was increased to 1.5 equiv to ensure complete conversion into zwitterionic adducts **3b–e**. A significant loss of efficiency was observed when IMes·HBF_4 (**1a′**) was used as carbene precursor instead of IMes·HCl (**1a**). This observation is in line with our failed attempts to deprotonate **1a′** by using a packed-bed column of Cs_2CO_3. It can be correlated with a previous study on the deprotonation rate of various imidazolium salts, which showed that the rate of C2-deprotonation increased with the basicity of the associated counteranion.[32] Indeed, the more basic chloride anion led to a significantly higher rate of carbene formation than its tetrafluoroborate counterpart. Despite some practical preparative assets over their chloride analogues,[33] the slower C2-deprotonation rates of imidazolium tetrafluoroborates may therefore hamper their use as efficient NHC precursors for continuous-flow applications. McQuade et al.[23] solved this issue by using a packed-bed column filled with an ion-exchange resin that allowed the in situ conversion of imidazol(in)ium tetrafluoroborates into more reactive imidazol(in)ium chlorides. Similarly, a packed-bed column filled with Dowex® 1X2 ion exchange resin (200–400 mesh, Cl^- form) was successfully adapted to our microfluidic setup to enable the use of **1a′** as an efficient NHC precursor (see the Supporting Information for details).

Organocatalytic applications

Having optimized the generation of NHCs under continuous-flow conditions, we devised a straightforward microfluidic setup to investigate two benchmark NHC-catalyzed reactions; namely, the transesterification and the amidation of esters. In 2002, Nolan[34] and Hedrick[35] independently reported the transesterification of esters with alcohols in the presence of preformed or in situ generated NHCs. The procedure was subsequently extended to other substrates such as phospho-

nates[36] and an asymmetric version was developed by Suzuki[37] and Maruoka.[38] In this study, the NHC-catalyzed transesterification of vinyl acetate with benzyl alcohol to afford benzyl acetate was selected as a model reaction and implemented in a continuous-flow setup (Figure 3). The upstream section of the microfluidic network consisted of the assembly designed for generating NHCs under homogeneous conditions (cf. Figure 1 b). The CS_2 quench line was removed and replaced by a premixing unit for benzyl alcohol (**4**; 1 M in THF or toluene) and vinyl acetate (**5**; 1 M in THF or toluene). The premixing unit consisted of a PFA capillary loop (0.25 mL internal volume) connected via a T-mixer to two syringe pumps set at 25 μL min^{-1} each. The stoichiometric mixture of **4** and **5** was then conveyed in a 1 mL PFA capillary loop together with the NHC catalyst. The outlet of the reactor was connected to an IR cell for in-line reaction monitoring.

The transesterification reached completion after a residence time of 10 min (total flow rate: 0.1 mL min^{-1}) at room temperature with **1a** as NHC precursor (0.01 M in MeCN) and KHMDS as base (0.012 M in THF). The flow rate and reagent ratios were adapted to have 1 mol% of NHC in the presence of substrates **4** and **5**. The choice of solvents, reagents, and products enabled the course of the reaction to be conveniently monitored by using in-line IR spectroscopy (Figure 4). The disappearance of **4** ($\tilde{\nu}_{OH}$ at 3438 cm^{-1}) and **5** ($\tilde{\nu}_{C=O}$ at 1764 cm^{-1} and $\tilde{\nu}_{C=C}$ at 1648 cm^{-1}), as well as the appearance of benzyl acetate **6** ($\tilde{\nu}_{C=O}$ at 1743 cm^{-1}) and acetaldehyde **7** ($\tilde{\nu}_{C=O}$ at 1730 cm^{-1}) were deduced from the evolution of characteristic vibration bands. Samples were collected, processed, and analyzed by NMR spectroscopy. The system was operated over 6 h with consistent results and high operational stability.

The model transesterification of vinyl acetate (**5**) with benzyl alcohol (**4**) was then carried out in THF with various NHC precursors and the conversions were determined by ^{1}H NMR spectroscopic analysis (Table 1). The nature of the *N*-substituents and of the central heterocyclic core (imidazolium or imidazolinium) markedly affected the catalytic activity. Similar trends were reported in batch by Nolan,[34] Hedrick,[35] and others.[39] Aryl-substituted imidazol-2-ylidenes IMes and IDip (Table 1, entries 1 and 2) afforded benzyl acetate in higher yield than the corresponding aryl-substituted imidazolin-2-ylidenes SIMes and SIDip (Table 1, entries 3 and 4). The highest conversion was obtained with NHC precursor **1a**, which led to a 96% yield of benzyl acetate (**6**) after work-up. The lower activity displayed by **1b** can be attributed to the steric congestion induced by its *ortho*-*i*Pr substituents. Similar results were obtained by using 1 M solutions of **4** and **5** in toluene instead of THF. This enabled the implementation of a simple yet efficient in-line quench/liquid–liquid extraction/separation system. The outlet

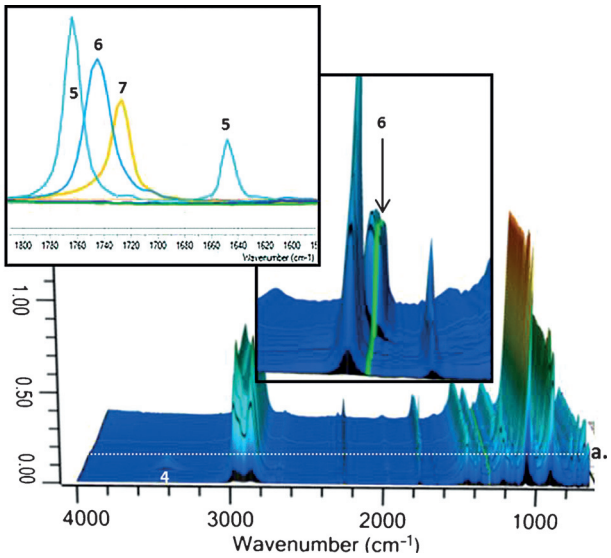


Figure 4. In-line IR monitoring of the NHC-organocatalyzed transesterification of vinyl acetate with benzyl alcohol. The upper insert summarizes the typical peaks for compounds **5**–**7** in the 1600–1800 cm^{-1} region. The dotted line (**a.**) marks the disappearance of reagents **4** and **5** and the appearance of products **6** and **7** approximately 10 min after injecting the catalyst.

Table 1. NHC-catalyzed transesterification of vinyl acetate (**5**) with benzyl alcohol (**4**) in THF.

Entry	NHC precursor[a]	Carbene	Conversion [%][b]
1	**1a**	IMes	>99[c]
2	**1b**	IDip	63[d]
3	**1d**	SIMes	10[d]
4	**1e**	SIDip	6[d]

[a] 1 mol%. [b] Determined from the ^{1}H NMR signal integral ratio of the benzylic protons in **4** and **6**. [c] KHMDS 0.012 M in THF. [d] KHMDS 0.015 M in THF.

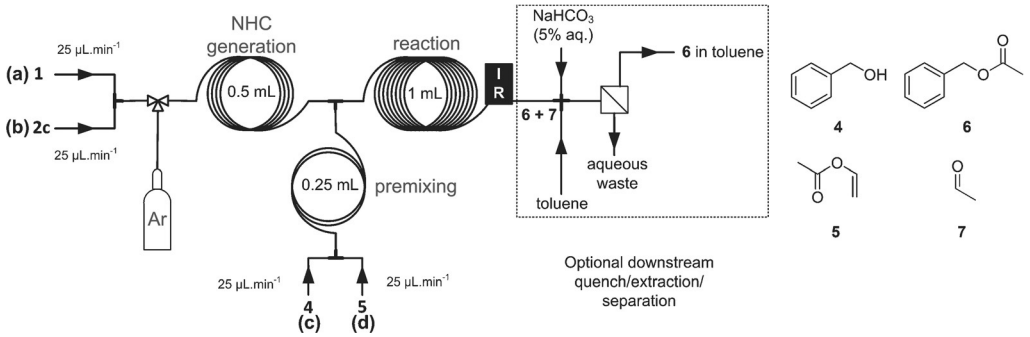


Figure 3. Continuous-flow setup for the preparation and use of NHCs as organocatalysts for a transesterification reaction.

of the reactor was connected to a cross junction for the concomitant injection of toluene (0.5 mL min^{-1}) and an aqueous solution of sodium bicarbonate (5%-wt, 0.5 mL min^{-1}). The resulting segments were then conveyed through a short PFA capillary section to a continuous liquid–liquid membrane separator.[40] The extraction/separation sequence afforded essentially pure **6** in 92% yield.

The scope of our continuous-flow methodology for the preparation and organocatalytic application of free NHCs was further extended to another benchmark NHC-promoted reaction; namely, the amidation of an unactivated ester.[41] In 2005, Movassaghi et al. reported a catalytic, one-pot, two-step amidation of unactivated esters using IMes as an organocatalyst.[41a] The reaction proceeded with the initial transesterification of a methyl ester with an amino alcohol. The intermediate amino ester then underwent an intramolecular O-to-N acyl shift,[41a,42] leading to the formation of an amide bond. The microfluidic setup devised for transesterification (cf. Figure 3) was easily modified to telescope the NHC generation sequence with an amidation reaction instead. Thus, the reaction loop was replaced by a 1.5 mL internal volume PFA capillary to increase the residence time to 15 min (Figure 5). Feeds **c** and **d**

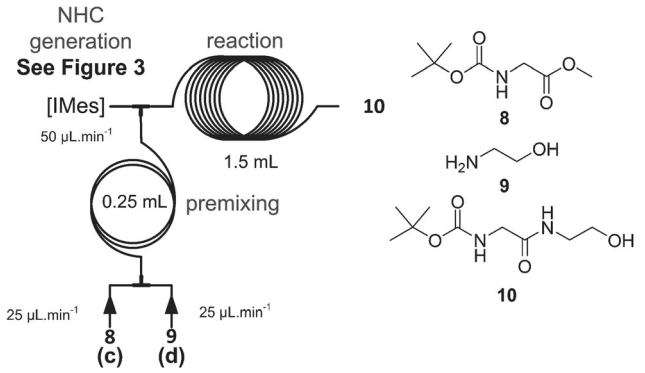


Figure 5. Continuous-flow setup for the preparation and use of IMes as an organocatalyst in the amidation of *N*-Boc-glycine methyl ester with ethanolamine.

were loaded with stock solutions of *N*-Boc-glycine methyl ester (**8**; 2 M in THF) and ethanolamine (**9**; 2 M in THF), respectively. Imidazolium salt **1a** (0.1 M in MeCN) served as a catalyst precursor along with KHMDS (0.12 M in THF). The flow rate and reagent ratios were adapted to attain a 5 mol% proportion of NHC vs. substrates **8** and **9**. Under these experimental conditions, full conversion was achieved as determined by ^{1}H NMR spectroscopic analysis of the crude mixture, and glycine derivative **10** was isolated in 70% yield after purification by column chromatography.

Conclusion

We have developed a convenient, straightforward, and versatile methodology for the continuous-flow generation of NHCs in the sealed and confined environment of a microfluidic reactor. The procedure was first optimized by using the instantaneous formation of stable, highly colored NHC·CS_2 zwitterions to trap the free carbenes. It was successfully extended to allow NHC-catalyzed reactions. In a first example, the NHC generation sequence was telescoped with the organocatalytic transesterification of vinyl acetate and benzyl alcohol. The microfluidic setup enabled the fast scouting of reaction parameters and screening of various NHC precursors to determine structure-activity relationships. In-line reaction monitoring, downstream quench, and liquid–liquid extraction/separation techniques were implemented. A similar strategy was applied to carry out an amidation reaction catalyzed by IMes. This second example showcased the formal direct telescoping of three chemical events including i) the generation of a free carbene, ii) the transesterification of *N*-Boc-glycine methyl ester with ethanolamine, and iii) a subsequent intramolecular O-to-N acyl shift leading to *tert*-butyl (2-hydroxyethylcarbamoyl)methylcarbamate within an uninterrupted reactor network.

Experimental Section

General information

^{1}H NMR spectra were recorded at 250 or 400 MHz and ^{13}C NMR spectra were recorded at 62.8 or 100.6 MHz with Bruker Avance spectrometers. The chemical shifts are reported in ppm relative to TMS as internal standard or to solvent residual peak. HRMS spectra were recorded with a FTMS (ESI) apparatus (Thermo Scientific Q Exactive). Solvents purchased from Labotec were dried according to standard procedures and deoxygenated prior to use (15 min Ar flow). Commercially available chemicals (Sigma-Aldrich or TCI) were used as received, except for benzyl alcohol, vinyl acetate, and amino ethanol, which were distilled and degassed prior to use. Potassium phosphate (K_3PO_4) and cesium carbonate (Cs_2CO_3) were stored in an oven at 80 °C. Potassium bis(trimethylsilyl)amide (KHMDS) was stored under a dry and inert atmosphere. Ion exchange resin Dowex® 1X2 200–400 mesh (Cl^- form) was rinsed with absolute ethanol and dried under high vacuum for 72 h prior to use. It was stored in a dessicator. Imidazolium and imidazolinium salts **1a**–**e** and **1a**′ were prepared according to reported procedures[43] and stored in a dessicator. *N*-(*tert*-Butoxycarbonyl)glycine methyl ester **8** was prepared according to standard procedures[44] and purified by column chromatography on silica gel 60 (230–400 mesh, Biosolve).

Experimental setup

The microfluidic device was constructed with high purity PFA coils (0.25, 0.5, 1.0, and 1.5 mL internal volume) and straight sections (1/16″ o.d., 0.03″ i.d.), Upchurch Scientific Super Flangeless nuts (natural PEEK, 1/4–28 thread for 1/16″ o.d. tubing), Upchurch Scientific Super Flangeless ferrules (yellow ETFE for 1/16″ o.d. tubing), Upchurch Scientific T-mixers (natural PEEK for 1/16″ tubing, 0.5 mm through hole), and Upchurch Scientific cross junctions (natural PEEK for 1/16″ tubing, 0.5 mm through hole). Dry argon (Air Liquide) was used for flushing the microfluidic device through a four-port bulkhead switching valve (Upchurch Scientific 1/4–28 ports for 1/16″ o.d. tubing). The feed solutions were conveyed to the reactor using Chemyx Nexus 3000 and/or Nexus 6000 syringe pumps. A continuous-flow liquid–liquid membrane separator (Zaiput Flow Technologies®) with a PTFE membrane (0.5 µm pores) was used for the continuous liquid–liquid extraction/separation ex-

periments. In-line, real-time IR monitoring was carried out with a FlowIR™ from Mettler-Toledo with a DTGS detector using Happ-Genzel apodization, equipped with a SiComp (Silicon) probe connected via a FlowIR™ sensor. Sampling was performed from 4000 to 650 cm^{-1} at 8 wavenumber resolution with 208 scans.

General procedure for the continuous-flow transformation of imidazol(in)ium salts into NHC·CS_2 zwitterions using the homogeneous strategy

The syringe pump used to deliver the 0.1 M solution of imidazol(in)ium precursor (**1**) in MeCN was set to 25 $\mu L\,min^{-1}$ and the syringe pump used to deliver the solution of KHMDS in THF was set to 25 $\mu L\,min^{-1}$. Depending on the nature of the precursor, the ratio [KHMDS]/[**1**] was adapted from 1.2 (**1a**) to 1.5 (**1b**–**e**). For precursor **1a′**, a packed-bed column filled with Dowex® 1X2 200–400 mesh (Cl^- form) was inserted before the first PFA loop. Both streams came in contact through a PEEK T-mixer using Super Flangeless nuts and ferrules. They were reacted in a PFA capillary loop (0.5 mL internal volume, 10 min residence time). The outlet of the first PFA loop was attached to a PEEK T-mixer with Super Flangeless nuts and ferrules. CS_2 was delivered by a third syringe pump, set to 0.125 $mL\,min^{-1}$ and the mixture was redirected to a second PFA capillary loop (0.25 mL internal volume). The outlet of the second PFA loop was connected to a collection vial. The critical section of the setup, i.e., the sequence (0.5 mL PFA loop — T-mixer — 0.25 mL PFA loop), was immerged in an ultrasonic bath to avoid reactor clogging. The solvents were removed under reduced pressure and the red solid residues were analyzed by ^1H and ^{13}C NMR spectroscopies. Experimental data matched those reported previously.[31]

General procedure for the continuous-flow NHC-organocatalyzed transesterification of vinyl acetate with benzyl alcohol

The syringe pumps delivering the solution of **1a** (0.01 M in MeCN) and the solution of KHMDS (0.012 M in THF) were set to 25 $\mu L\,min^{-1}$ (feeds **a** and **b**). Both streams came in contact through a PEEK T-mixer using Super Flangeless nuts and ferrules. They were reacted in a PFA capillary loop (0.5 mL internal volume, 10 min residence time). The outlet of the first PFA loop was attached to a PEEK T-mixer with Super Flangeless nuts and ferrules. The PEEK T-mixer was connected to a premixing unit for benzyl alcohol (**4**; 1 M in THF) and vinyl acetate (**5**; 1 M in THF) consisting of a PFA capillary loop (0.25 mL internal volume) connected via a PEEK T-mixer to two syringe pumps set to 25 $\mu L\,min^{-1}$ each (feeds **c** and **d**). The stoichiometric mixture of **4** and **5** was then conveyed in the presence of the NHC catalyst in a third PFA capillary loop (1 mL internal volume, 10 min residence time). The outlet of the reactor was connected to an IR cell for in-line reaction monitoring. The flow rate and reagent ratio were adjusted to 1 mol% NHC in the presence of substrates **4** and **5**. Evaporation of the solvents and filtration of the crude material on a short silica gel pad afforded essentially pure benzyl acetate (**6**) in 96% yield. ^1H and ^{13}C NMR data matched those reported previously.[34]

Start-up procedure: The entire microfluidic setup was flushed with dry argon. The reactor was operated with feed **a** = MeCN and feeds **b**,**c**,**d** = THF for 10 min. Feeds **c**,**d** were then switched to benzyl alcohol (**4**; 1 M in THF or toluene) and vinyl acetate (**5**; 1 M in THF or toluene), and the reactor was equilibrated for 20 min at 25 °C. Feeds **a** and **b** were then switched to the solution of **1a** (0.01 M in MeCN) and the solution of KHMDS (0.012 M in THF), respectively. The reactor was equilibrated for another 20 min.

Liquid–liquid extraction and separation: A PEEK cross junction was inserted after the IR cell for the consecutive injection of toluene (0.5 $mL\,min^{-1}$) and an aqueous solution of sodium bicarbonate (5%-wt, 0.5 $mL\,min^{-1}$). The fluids were then conveyed to a liquid–liquid PTFE membrane separator after a short PFA loop (0.25 mL internal volume). The aqueous stream was redirected to a waste tank, and the organic stream (toluene) was collected and concentrated under reduced pressure. The extraction/separation sequence afforded essentially pure **6** in 92% yield.

General procedure for the continuous-flow NHC organocatalyzed amidation of *N*-Boc-glycine methyl ester with ethanolamine

The syringe pumps delivering the solution of **1a** (0.1 M in MeCN) and the solution of KHMDS (0.12 M in THF) were set to 25 $\mu L\,min^{-1}$ (feeds **a** and **b**). Both streams came in contact through a PEEK T-mixer using Super Flangeless nuts and ferrules. They were reacted in a PFA capillary loop (0.5 mL internal volume, 10 min residence time). The outlet of the first PFA loop was attached to a PEEK T-mixer with Super Flangeless nuts and ferrules, and connected to a premixing unit (0.25 mL internal volume) for feeds **c** and **d** (2 M *N*-Boc-glycine methyl ester **8** in THF and 2 M ethanolamine **9** in THF, respectively). The two corresponding syringe pumps were set to 25 $\mu L\,min^{-1}$ each. The stoichiometric mixture of **8** and **9** was then conveyed in the presence of the NHC catalyst in a third PFA capillary loop (1.5 mL internal volume, 15 min residence time). The flow rates and reagents ratio were adjusted to 5 mol% of NHC in the presence of substrates **8** and **9**. The conversion of substrates **8** and **9** was complete, leading to glycine derivative **10** in 70% yield after purification by chromatography on silica gel.

Start-up procedure: The entire microfluidic setup was flushed with dry argon. The reactor was operated with feed **a** = MeCN, and feeds **b**,**c**,**d** = THF for 10 min. Feeds **c**,**d** were then switched to *N*-Boc-glycine methyl ester **8** (2 M in THF) and ethanolamine **9** (2 M in THF), and the reactor was equilibrated for 30 min at 25 °C. Feeds **a**,**b** were then switched to the solution of **1a** (0.1 M in MeCN) and the solution of KHMDS (0.12 M in THF), respectively. The reactor was equilibrated for another 30 min.

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