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FULL PAPER

Expedited access to β-lactams *via* a telescoped three-component Staudinger reaction in flow

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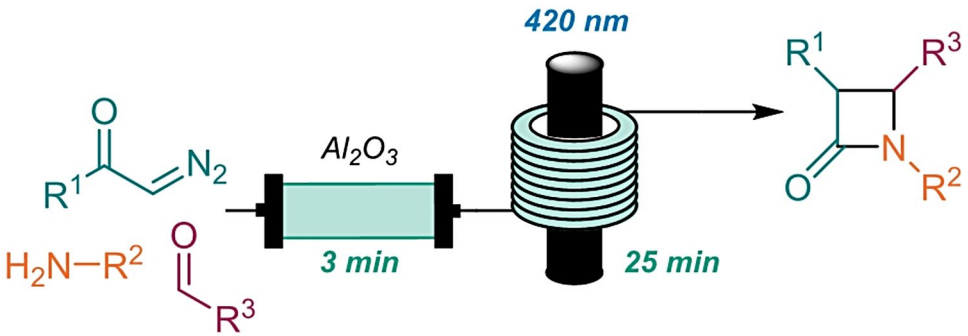
Abstract

The Staudinger reaction is widely used for the generation of β-lactams *via* the thermal cycloaddition of imines with ketenes. Traditionally, it cannot be performed as a multicomponent reaction between aldehydes, amines and ketenes, thus limiting its versatility. Recently we reported for the first time a three-component Staudinger reaction in batch, exploiting a photochemical Wolff rearrangement of diazoketones and an in situ generation of the imine. Here we report an expedited continuous flow approach that generates the crucial ketene intermediate prior to its telescoped reaction with an imine component at ambient temperatures. The imine is prepared by an in situ dehydration between amines and aldehydes in a packed bed reactor containing basic alumina as drying agent. The resulting telescoped flow approach features a fast dehydration reaction (t_{Res} ca. 3 min) as well as an efficient Wolff rearrangement using LEDs (420 nm) to afford the desired β-lactam products in less than 30 min which compares favorably with reaction times of several days in batch mode. Flow processing thereby affords a safe and streamlined entry to these important targets and allows their effective generation on gram scale. Moreover, this approach exploits several homogeneous and heterogeneous transformations under mild conditions that generate water and nitrogen gas as the only by-products.

Graphical abstract



Keywords Flow synthesis · Reaction telescoping · B-lactam · Ketene photocycloaddition · Staudinger reaction

Introduction

Multicomponent reactions (MCRs) are attractive means to generate molecular complexity by exploiting the sequenced union of several functionalized building blocks [1]. These popular reactions allow the rapid construction of heterocyclic scaffolds as well as entities based on amide bonds that can be assembled via Biginelli reactions [2], Ugi reactions [3] and other related MCRs [4]. MCRs have been exploited to construct drug-like libraries [5] as well as natural

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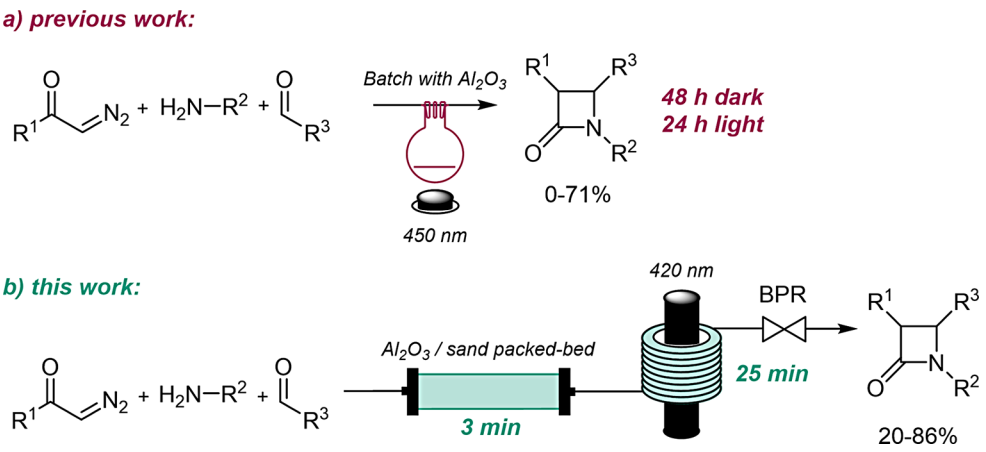
products and their analogues [6] and they typically do not require protecting group manipulations and generate benign by-products which adds to their value in the context of atom and step economy. Moreover, commercially available building blocks such as amines, carboxylic acids, isonitriles and aldehydes are frequently used starting materials adding to both the versatility and popularity of MCRs. While most MCRs exploit the thermal activation of substrates and the generation of related reactive intermediates that are formed and consumed in situ, there are some photochemical variants that are attractive additions to this field as photons are exploited as an energy source and traceless reagent equivalent [7]. In this field we have reported the use of ketenes, generated in situ through the photochemical Wolff rearrangement of diazoketones: these reactive intermediate react further with isocyanides and carboxylic acids or silanols, yielding respectively acrylamides (K-3CR) [8] and silyl enol ethers (SK-3CR) [9]. Recent studies have shown how this approach can be exploited using visible (blue) light instead of UV radiation, with benefits in terms of selectivity and efficiency [10].

The Staudinger reaction [11, 12] is a well-established method to assemble β-lactams *via* a cycloaddition between ketenes and imines. Although it could be potentially performed in a three-component fashion without preformation of the imines, by mixing ketene precursors with aldehydes and amines, this approach is hampered by the intrinsic reactivity of amines with acyl chlorides, the most common precursors of ketenes, and ketenes themselves. We have recently overcome this limitation by using the photochemical generation of ketenes and a light-off/light-on approach in which diazoketones, aldehydes and amines were mixed in the dark and only after imine formation the photochemical Wolff rearrangement was induced. This novel Ketene Three-Component Staudinger Reaction (K-3CSR) afforded a small library of β-lactams in moderate to good yields, but a drawback of this approach could be seen in the long reaction times for this batch process, indicating limited overall productivity (i.e., 48 h for imine formation and 24 h for Wolff rearrangement and cycloaddition) [13].

To improve on this, we set out to establish a continuous flow approach for the Staudinger multicomponent reaction that was anticipated to provide a faster and safer entry to β-lactam scaffolds. Crucially, these strained heterocyclic targets represent important scaffolds that often benefit from continuous flow processing [14]. Continuous flow technology is a powerful tool for improving known batch reactions and the discovery and subsequent exploitation of new reactivities [15]. Flow reactors exploit miniaturized set-ups that offer improved heat and mass transfer compared to alternative batch approaches [16]. This miniaturization leads to micro-mixing that can be enhanced by using static mixers, and the increased surface area to volume ratio leads to better dissipation of heat which allows using high temperatures as well as highly exothermic reactions in a safe manner. In addition to being able to telescope individual reactions into sequences [17], a further advantage of flow reactions is their inherent scalability by means scaling-out and scaling-up methods. This is important in the context of photochemical reactions which in traditional batch set-ups suffer from insufficient scalability due to the Beer-Lambert law. Using narrow diameter tubing thereby allows for full light penetration and uniform irradiation leading to simple scaling of flow approaches [18, 19]. Moreover, product degradation is minimized due to high spatiotemporal control, and longer operating times under steady state conditions allow for the preparation of larger product quantities. We envisioned that these advantages would offer a unique opportunity to streamline the Staudinger multicomponent reaction furnishing a scalable and efficacious entry to valuable β-lactam products (Scheme 1).



Scheme 1 Comparison between batch (**a**) and continuous flow (**b**) approach for the Staudinger MCR

Scheme 2 Staudinger reaction between phenyl diazoketone **1a** and imine **2a** to product **3a**

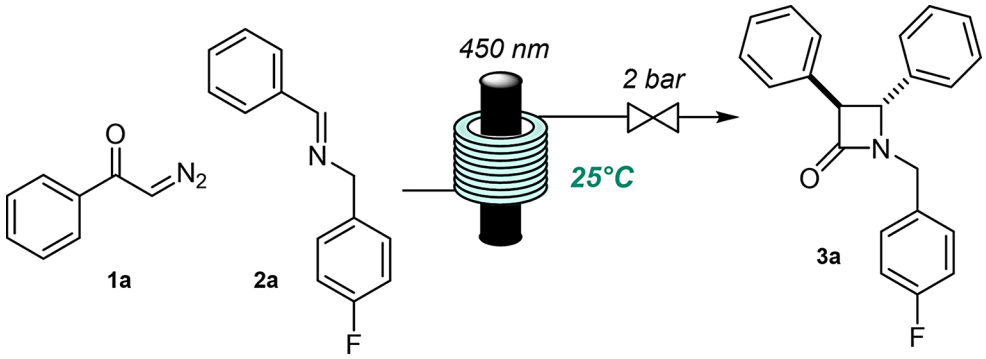


Table 1 Wolff rearrangement of diazoketone **1a** in flow during the Staudinger reaction with imine **2a**

Entry	Equivalent of 1a	Wavelength (nm)	LED intensity (W)	t_{Res}(min)	Φ (μL/min)	Solvent	Concentration (M)	Yield (%)
1	1	450	24	60	166	DCM	0.04	60[a]
2	1	450	24	60	166	DCM	0.1	59[a]
3	1	420	24	60	166	DCM	0.1	81[a]
4	1	420	60	60	166	DCM	0.1	87[b]
5	1	420	60	30	333	DCM	0.1	70[b]
6	1	420	60	25	400	DCM	0.1	74[b]
7	1.2	420	60	25	400	DCM	0.1	93[b]
8	1.2	420	60	25	400	MTBE	0.1	60[b]
9	1.2	420	60	25	400	MTBE: DCM 5:1	0.1	61[b]
10	1.2	420	60	25	400	MTBE: DCM 1:1	0.1	75[b]

[a] Presence of the diazoketone in the reaction mixture

[b] Complete consumption of the diazoketone

Material & methods

An Omnifit glass column (10 cm length, 6.6 mm inner diameter) was packed with a mixture of dried Al_2O_3 (grade I) and sand (ca. 1:2 by weight). The column was connected to a Vapourtec E-Series flow reactor equipped with peristaltic pumps. A solution of aldehyde, amine and diazoketone in dichloromethane (0.1 M) was prepared and pumped with a flow rate of 400 μL/min through the packed-bed cartridge followed by the photo-module equipped with high-intensity LEDs (rt, 60 W). The reaction yield was determined after purification by flash chromatography.

Results & discussion

The development of a three-component version of the Staudinger reaction in flow required optimization of three distinct processes: *i)* the condensation of both aldehyde and amine, *ii*) the Wolff rearrangement of the diazoketone induced by visible light, and *iii*) the cycloaddition of the resulting ketene with the imine to give the final β-lactam. Due to the elusive nature of ketenes, it was decided to investigate the last two processes together. Imine **2a** was prepared following a reported procedure [20] and in a preliminary experiment it was dissolved in DCM (0.04 M) together with diazoketone **1a** and pumped through a photochemical flow module irradiated with 450 nm LEDs (24 W, Scheme 2). Reaction concentration and wavelength were the same as previously employed by us in batch [13], while the retention time was set to 1 hour. Product **3a** was isolated as the *trans* isomer in 60% yield, although unreacted diazoketone and imine were still detected in the crude mixture by ^{1}H-NMR (Table 1, entry 1).

Increasing the concentration of the substrate solution was found to be beneficial if combined with the use of more energetic radiation (i.e., lower wavelength; Table 1, entries 2 and 3), affording **3a** in 81% yield, although unreacted starting materials were still detected. Finally, increasing the LED intensity resulted in complete consumption of the diazoketone (Table 1, entry 4). When a shorter residence time was tested, product **3a** was isolated with a moderate decrease in the yield (Table 1, entry 5).

Subsequently, with the latter conditions, we performed a switch-off experiment to determine the optimal irradiation time for this flow process [21]. We thus pumped the reagent solution through the photoreactor and switched the LEDs off after 30 min, thereby creating a gradient of effective exposure time. Quantitative ^{1}H-NMR analysis was employed as off-line technique to determine the reaction yield and the conversion of the photo-sensible starting material. Samples were collected every 5 min giving the data summarized in

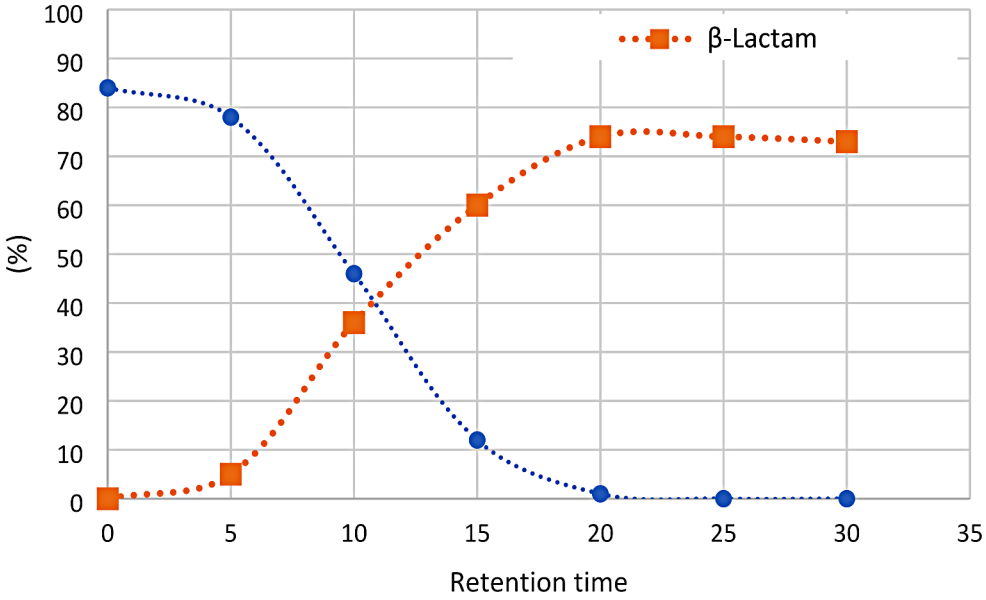
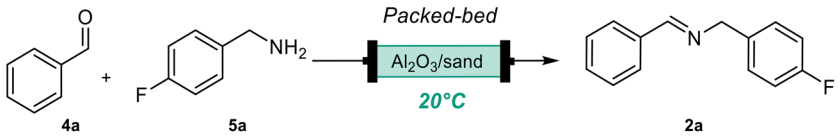


Fig. 1 Switch-off experiment performed using a solution (0.1 M in DCM) of diazoketone **1a** and imine **2a**, irradiating at 420 nm (60 W). Blue line: consumption of diazoketone, orange line: product formation



entry [a]	*4a*	t_{Res} *(min)*	*Φ (μL/min)*	*Yield (%)* [b]
1	1.2 equiv.	13	100	93
2	1.2 equiv.	3	400	100
3	1.1 equiv.	3	400	100
4	1 equiv.	3	400	97

[a] Reactions were performed in DCM (0.1 M), at the given flow rate at room temperature. The glass column was packed with a mixture of dried aluminum oxide and sand. [b] Reaction yield determined by ^{1}H-NMR using trichloroethylene as internal standard.

Table 2 Flow synthesis of imine **2a** using a packed column reactor

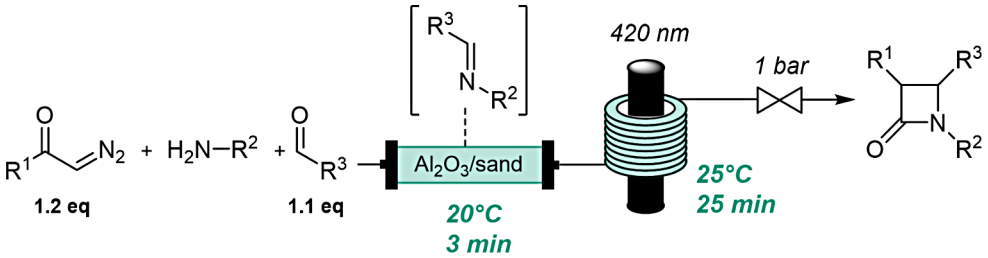
Fig. 1. This indicated that diazoketone **1a** was completely consumed after 25 min, giving a 74% yield of β-lactam **3a** (Table 1, Entry 6). Next, we tried to further improve the reaction yield by increasing the amount of diazoketone to 1.2 equivalents as unreacted imine was always detected in the crude. This afforded a significative improvement of the yield (93%, Table 1, entry 7).

To conclude the optimization of the continuous Staudinger reaction, we evaluated options to replace DCM with a greener solvent. Acetonitrile, ethyl acetate, 2-methyl tetrahydrofuran and methyl *tert*-butyl ether (MTBE) were tested, however, only the latter giving good results albeit with lower yields than DCM (Table 1, Entry 8). In addition, two mixtures of MTBE and DCM were tested (Table 1, Entries 9 and 10), affording **3a** in good yield (75%) when equal amounts of solvents were employed. Subsequent studies were conducted in DCM, although MTBE has the potential to be a greener alternative for this process.

Once the conditions for the Staudinger reaction were established, the imine forming step was optimized in flow using the same solvent and a similar flow rate (Scheme 3). This quickly confirmed Al_2O_3 as a suitable dehydrating agent allowing the imine to be isolated in quantitative yield when using the aldehyde in a small excess (Table 2, see Supporting Information for further details). In a control experiment an equimolar mixture of diazoketone, aldehyde and amine were passed through the packed bed reactor rendering the imine product quantitatively without degradation of the diazoketone.

Finally, both stages of the multicomponent process were combined as shown Scheme 3. Diazoketone, amine and aldehyde were dissolved in DCM (molar ratio 1.2: 1: 1.1) and pumped using a peristaltic pump of the Vapourtec flow reactor. The mixture initially passed through the packed bed column (t_{Res} ca. 3 min) generating the imine intermediate that then reacted with the in situ formed ketene in the

Scheme 3 General flow process of a ketene three-component Staudinger reaction (K-3CSR)



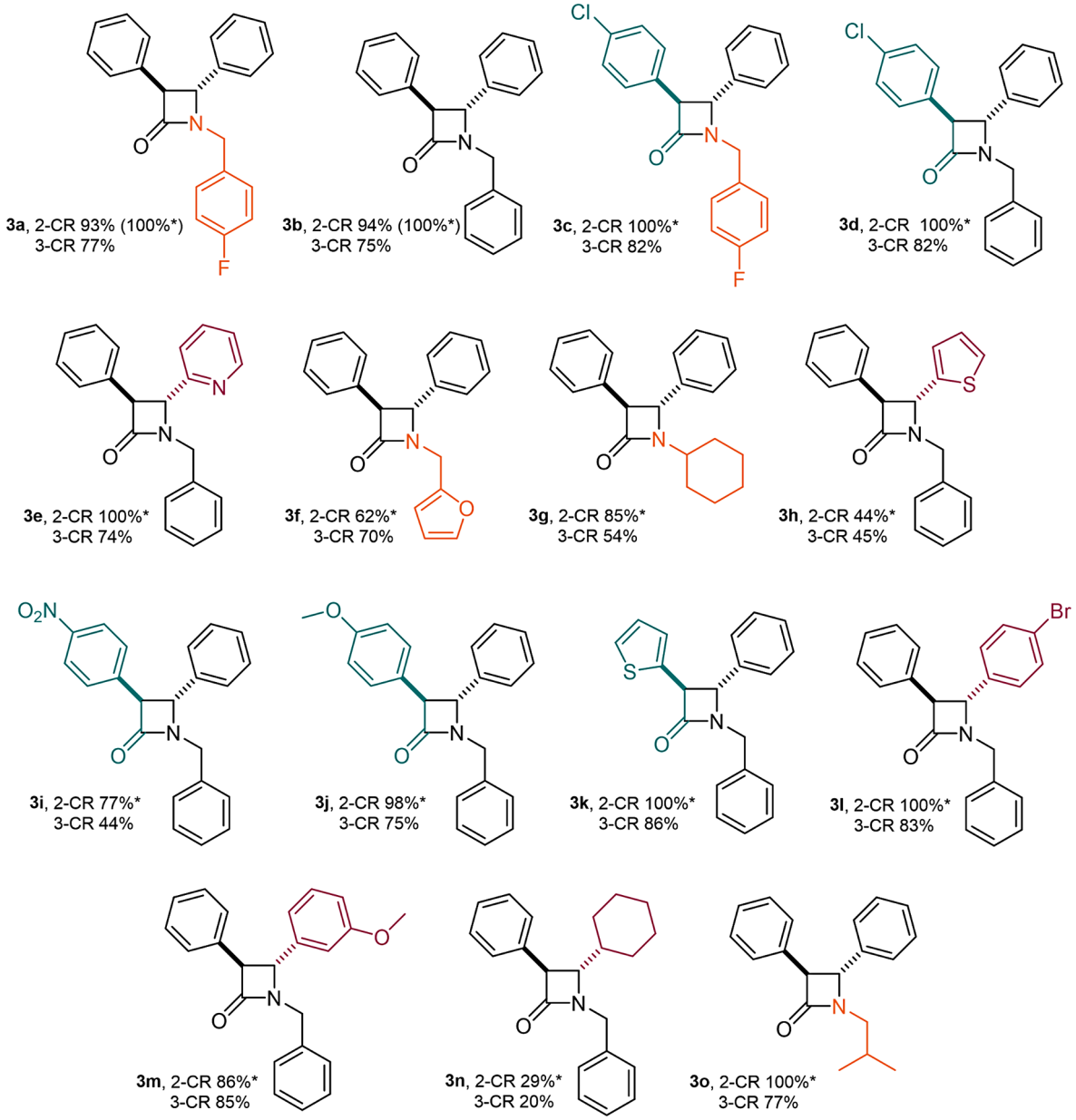


Fig. 2 Library of β-lactams generated *via* the flow Ketene Three-Component Reaction (* yield determined by ^{1}H-NMR using trichloroethylene as internal standard)

photo-module. The system was maintained at room temperature and a second peristaltic pump was used in reverse mode to act as a back-pressure regulator set to 1 bar.

Pleasingly, this approach proved general and allowed generating a small library of β-lactams that were typically obtained as single trans-isomers (Fig. 2). Each compound was synthesized both through the two- and three-component procedure allowing us to compare the overall efficiency of these strategies. The reactions proceeded with good to excellent yields except for aliphatic aldehydes (product **3n**), however, the resulting product, albeit isolated in low yield, could not be obtained in batch mode. Generally, the two-component reaction performed better with yields typically above 85%, however, the results of the three-component process are comparable when taking into account that in this case yields refer to two separate synthetic steps. Finally, a scale up for the synthesis of compound **3d** was conducted with the same performance as on small scale (83% yield, at 4 mmol scale) demonstrating the convenient preparation of this product on gram scale.

Conclusions & outlook

This work reports an efficient continuous flow version of the Ketene Three-Component Reaction towards a library of β-lactam products. This telescoped approach exploits a packed bed reactor filled with a mixture of Al_2O_3 and sand that affects the fast dehydration reaction between aldehydes and amines. The resulting imines then react with ketenes that are generated *via* a photochemical Wolff rearrangement in situ. Importantly, the dehydrating column can be used for up to 20 reactions at small scale (i.e., 0.3 mmol) making this strategy particularly attractive for library synthesis. Furthermore, the imine formation in flow required only three minutes compared to 48 h in batch mode, and the photochemical process can be performed in less than 30 min (instead of 24 h in batch) showcasing significant acceleration in flow due to better mass and photon transfer. Therefore, a significantly increased space time yield can be realized in flow mode (43.5 mmol L^{-1} h^{-1}, calculated for the flow synthesis of compound **3d**, vs. 0.36 mmol L^{-1} h^{-1} in batch), which together with the high atom economy of this multicomponent process makes this continuous approach highly desirable for the generation of libraries of these small-ring heterocycles.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41981-024-00333-0.

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References

1. Dömling A, Wang W, Wang K (2012) Chemistry and Biology of Multicomponent reactions. Chem Rev 112:3083–3135. https://doi.org/10.1021/cr100233r
2. Chandravarkar A, Aneeja T, Anilkumar G (2024) Advances in Biginelli reaction: a comprehensive review. J Heterocycl Chem 61:5–28. https://doi.org/10.1002/jhet.4742
3. Fouad MA, Abdel-Hamida H, Salah Ayoup M (2020) Two decades of recent advances of Ugi reactions: synthetic and pharmaceutical applications. RSC Adv 10:42644–42681. https://doi.org/10.1039/D0RA07501A
4. Banfi L, Basso A, Lambruschini C, Moni L, Riva R (2021) The 100 facets of the Passerini reaction. Chem Sci 12:15445–15472. https://doi.org/10.1039/D1SC03810A
5. Sunderhaus JD, Martin SF (2009) Applications of multicomponent reactions to the synthesis of Diverse Heterocyclic Scaffolds. Chem Eur J 15:1300–1308. https://doi.org/10.1002/chem.200802140
6. Arona ZD, Overman LE (2004) The tethered Biginelli condensation in natural product synthesis. Chem Commun 253–265. https://doi.org/10.1039/B309910E
7. Garbarino S, Ravelli D, Protti S, Basso A (2016) Photoinduced Multicomponent reactions. Angew Chem Int Ed 55:15476–15484. https://doi.org/10.1002/anie.201605288
8. Basso A, Banfi L, Garbarino S, Riva R (2013) Ketene three-component reaction: a metal-free Multicomponent Approach to Stereodefined Captodative olefins. Angew Chem Int Ed 52:2096–2099. https://doi.org/10.1002/anie.201209399
9. Ibba F, Capurro P, Garbarino S, Anselmo M, Moni L, Basso A (2018) Photoinduced Multicomponent synthesis of α-Silyloxy Acrylamides, an unexplored class of Silyl Enol Ethers. Org Lett 20:1098–1101. https://doi.org/10.1021/acs.orglett.8b00009
10. Capurro P, Lambruschini C, Lova P, Moni L, Basso A (2021) Into the Blue: Ketene Multicomponent reactions under visible light. J Org Chem 86:584515851. https://doi.org/10.1021/acs.joc.1c00278
11. Cossio FP, Arrieta A, Sierra MA (2008) The mechanism of the Ketene-Imine (Staudinger) reaction in its Centennial: still an Unsolved Problem? Acc Chem Res 41:925–936. https://doi.org/10.1021/ar800033j
12. For previous continuous flow methods for Staudinger reactions towards β-lactams, please see: (a) Hafez, AM, Taggi AE, Wack

H, Drury WJ, Lectka T (2000) Column Asymmetric Catalysis for β-Lactam Synthesis. Org Lett 2: 3963–3965. https://doi.org/10.1021/ol006659r (b) Hafner A, Ley SV (2015) Generation of Reactive Ketenes under Flow Conditions through Zinc-Mediated Dehalogenation. Synlett 26:1470–1474. https://doi.org/10.1055/s-0034-1380679

13. Minuto F, Lambruschini C, Basso A (2021) Ketene 3-Component staudinger reaction (K-3CSR) to β-Lactams: a New Entry in the class of Photoinduced Multicomponent reactions. Eur J Org Chem 2021:3270–3273. https://doi.org/10.1002/ejoc.202100577
14. For a recent review on the topic of strained ring synthesis in flow mode, please see: Donnelly K, Baumann M (2024) Advances in the Continuous Flow Synthesis of 3- and 4-Membered Ring Systems. Chem Eur J 30:e202400758. https://doi.org/10.1002/chem.202400758
15. Alfano AI, García-Lacuna J, Griffiths OM, Ley SV, Baumann M (2024) Continuous flow synthesis enabling reaction discovery. Chem Sci 15:4618–4630. https://doi.org/10.1039/d3sc06808k
16. Buglioni L, Raymenants F, Slattery A, Zondag SDA, Noël T (2022) Technological innovations in Photochemistry for Organic synthesis: Flow Chemistry, High-Throughput Experimentation, Scale-up, and Photoelectrochemistry. Chem Rev 122:2752–2906. https://doi.org/10.1021/acs.chemrev.1c00332
17. For selected recent examples, please see: (a) Maestro A, Nagy BS, Ötvös SB, Kappe CO (2023) A Telescoped Continuous Flow Enantioselective Process for Accessing Intermediates of 1-Aryl-1,3-diols as Chiral Building Blocks. J Org Chem 88:15523–15529. https://doi.org/10.1021/acs.joc.3c02040 (b) Capaldo L, Bonciolini S, Pulcinella A, Nuño M, Noël T (2022) Modular allylation of C(sp^3)–H bonds by combining decatungstate photocatalysis and HWE olefination in flow. Chem Sci 13:7325–7331. https://doi.org/10.1039/D2SC01581A (c) Martins GM, Magalhães MFA, Brocksom TJ, Bagnato VS, de Oliveira KT (2022) Scaled up and telescoped synthesis of propofol under continuous-flow conditions. J Flow Chem 12:371–379. https://doi.org/10.1007/s41981-022-00234-0
18. Donnelly K, Baumann M (2021) Scalability of photochemical reactions in continuous flow mode. J Flow Chem 11:223–241. https://doi.org/10.1007/s41981-021-00168-z
19. Zondag SDA, Mazzarella D, Noël T (2023) Scale-Up of photochemical reactions: transitioning from Lab Scale to Industrial Production. Annu Rev Chem Biomol Eng 8:283–300. https://doi.org/10.1146/annurev-chembioeng-101121-074313
20. Linder MR, Frey WU, Podlech J (2001) Diazoketones as precursors in β-lactam synthesis. New insights into the mechanism of the photochemically induced Staudinger reaction. J Chem Soc Perkin Trans 1:2566–2577. https://doi.org/10.1039/B105748K
21. Drelinkiewicz D, Alston ST, Durand T, Whitby RJ (2023) The switch-off method: rapid investigation of flow photochemical reactions. React Chem Eng 8:2134–2140. https://doi.org/10.1039/D3RE00261F

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