Supporting Information

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Kinetics Studies on a Multicomponent Knoevenagel–Michael Domino Reaction by an Automated Flow Reactor

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Hierarchical silica monoliths as high-performance supports

Hierarchically structured, macro–mesoporous silica monoliths of the type illustrated by Figure S1 are attractive as supports for chemical separations and heterogeneous catalysis. Their hierarchical pore space architecture is realized through a continuous silica block that is perforated by intersecting networks of macropores and mesopores. The macropores (>50 nm) allow fast, advection-dominated transport through the material; the mesopores (2–50 nm), accessible only by diffusion, generate a large surface area for adsorption and chemical reaction. Silica-based monolithic columns applied in this work are prepared by Merck (Darmstadt, Germany) with tetramethoxysilane and polyethylene oxide as reactants in a sol–gel process accompanied by phase separation. The interskeleton macropores and a meso–microporous silica skeleton are formed during the sol–gel transition that accompanies spinodal decomposition of the reactants. In a second step, the intraskeleton micropores are widened into mesopores by hydrothermal treatment, resulting in hierarchical macro–mesoporous monoliths with interskeleton macropores and intraskeleton mesopores, without micropores (as highlighted in Figure S1).

For the studies reported in this work, we used aminopropylated silica monoliths from Merck KGaA (Darmstadt, Germany) in an analytical column format (4.6 mm inner diameter), with bed lengths of 50 mm and 5 mm, clad in polyether ether ketone (Chromolith® HighResolution). These silica monoliths are a benchmark with conservative morphological properties. The most
relevant morphological parameters of the employed silica monoliths are summarized in Table S1. Here, \( d \), \( V \), and \( \varepsilon \) denote the mean pore size, pore volume, and porosity of the macropore space or mesopore space. Further, the tortuosity \( \tau \) and specific surface area \( S_{\text{BET}} \) are specified for the mesopore space. The coverage with aminopropyl groups is \( \sim 2.8 \, \mu\text{mol/m}^2 \), as determined by elemental analysis.

| Table S1. Typical properties of the benchmarked hierarchical (macro–mesoporous) silica monoliths. |
|------------------------------------------------------------|
| **Macropore space**                                      | **Mesopore space**                          |
| \( d_{\text{macro}} \) (\( \mu \text{m} \)) | \( V_{\text{macro}} \) (ml g\(^{-1}\)) | \( \varepsilon_{\text{macro}} \) ( – ) | \( d_{\text{meso}} \) (\( \AA \)) | \( V_{\text{meso}} \) (ml g\(^{-1}\)) | \( \varepsilon_{\text{meso}} \) ( – ) | \( \tau_{\text{meso}} \) ( – ) | \( S_{\text{BET}} \) (m\(^2\) g\(^{-1}\)) |
| 1.15 | 1.95 | 0.57 | 150 | 1.0 | 0.68 | 1.25 | 250 |

Macro- and mesoporosity can be related to the total porosity of the monoliths \( (\varepsilon_{\text{tot}}) \) by \( \varepsilon_{\text{tot}} = (1 - \varepsilon_{\text{macro}})\varepsilon_{\text{macro}} + \varepsilon_{\text{meso}} \), because the interskeleton macroporosity \( \varepsilon_{\text{macro}} \) is discussed with respect to the total column volume, while intraskeleton mesoporosity \( \varepsilon_{\text{meso}} \) is referenced to the skeleton volume. Using the data from Table S1, these silica monoliths are recognized as highly porous, hierarchical structures with a total porosity \( \varepsilon_{\text{tot}} \) of \( \sim 86\% \).

Decreasing macropore size and skeleton thickness of silica monoliths towards sub-micrometer dimensions, as in these Chromolith\textsuperscript{\textregistered} HighResolution monoliths, increases the external surface area of the silica skeleton, reduces resistance to diffusion in the mesopores, and also minimizes backmixing in the macropores.\textsuperscript{[S7,S11]} Therefore, these morphological features lead to extremely narrow residence-time distributions on the catalytic support and guarantee strong driving forces for mass and heat transfer as well as reaction. Consequently, plug-flow conditions are realized in the microreactor (on a macroscopic scale) and diffusive transport limitations are eliminated. Thereby, microreactor operation is shifted from diffusion to reaction control, providing direct access to the intrinsic reaction kinetics, e.g., of the Knoevenagel condensation.\textsuperscript{[S11,S12]}

For a detailed analysis of the macropore space morphology of these silica monoliths, the reader is referred to Hormann et al.\textsuperscript{[S13]} and Hormann and Tallarek\textsuperscript{[S14]}; for a detailed analysis of flow and transport in the macropore space, the reader is referred to Hlushkou et al.\textsuperscript{[S15]}; for a detailed analysis of the mesopore space morphology and hindered diffusion in the mesopores, the reader is referred to Reich et al.\textsuperscript{[S2]}; and for a detailed analysis of microreactor plug-flow behavior and catalyst effectiveness, the reader is referred to Haas et al.\textsuperscript{[S11]}. 
S2) General experimental setup and devices

Kinetics studies were conducted with an automated flow reactor assembled from commercially available HPLC instrumentation. Figure S2 shows a photo of the employed system. On the left side, the substrate solutions are mixed, diluted with ethanol, and pumped to the microreactor, which is placed in a thermostatted device programmed to pre-heat the substrate solutions and keeping the temperature of the microreactor constant (±1 °C). The reaction solutions leaving the microreactor first flow through the injection loop of the injection valve (usually kept in the load-position). Behind the injection valve, an inline diode array detector (DAD) is positioned to monitor the reaction processes with high temporal resolution and determine when the reactor achieves steady-state operation. When the injection valve switches to the inject-position, the volume of the injection loop is transferred as discrete plug to an online coupled HPLC setup (Fig. S2, right side).

![Figure S2. Flow setup of the automated flow reactor with an integrated microreactor (left) and the HPLC system (right), which are online coupled through an injection valve.](image)

The flow apparatus was assembled from of the following devices:

1. Automated flow reactor (Fig. S2, left)
   - Agilent 1260 Infinity Quaternary Pump
   - Agilent 1290 Infinity Thermostatted Column Compartment
   - Agilent 1100 Diode Array Detector
   - Agilent 1290 Infinity Binary Pump (only for the setup with two reactors)
2. Injection valves (Fig. S2, middle)
   - Agilent 1290 Infinity Valve Drive with a 2-position/6-port valve head (~1.3 μl injection volume)
- Agilent 1100 2-position/6-port valve (~1.75 μl injection volume, only for the setup with two reactors)

3. HPLC (Fig. S2, right)
- Agilent 1290 Infinity Binary Pump
- Agilent 1290 Infinity Thermostatted Column Compartment
- Agilent 1290 Infinity Diode Array Detector

For the kinetics studies on the multicomponent reactions, an aminopropylated silica monolith was mounted in the automated flow reactor. The flow chart is illustrated by Fig. S3.

**Figure S3.** Flow chart for the automated flow reactor combined with an aminopropylated silica monolith (4.6 mm inner diameter × 5 mm length) as microreactor for kinetics studies on the multicomponent reactions.
S3) Kinetics studies on the Michael addition

To obtain the reaction rate constants \( k \) for the Michael addition, the recorded data were plotted corresponding to the integrated rate law of the reaction, where \( t \) is the reaction time, \([\text{BMN}]\) is the benzylidenemalononitrile concentration in the reaction solution, and \([\text{BMN}]_0\) is its starting concentration:

\[
\frac{1}{[\text{BMN}]} = k_2 \cdot t + \frac{1}{[\text{BMN}]_0} \tag{S1}
\]

According to equation S1 the recorded data of the kinetics studies on the Michael addition were plotted as illustrated in Fig. S4A and B. Rate constants resulting from the measurements with increasing benzaldehyde \([\text{BA}]_0\) and malononitrile \([\text{MN}]_0\) starting concentrations in the Michael addition system are presented and discussed in the main text around Fig. 2. It should be noted that the quality of the linear fit is much better for the Michael addition with added malononitrile (Fig. S4B) than with the added benzaldehyde (Fig. S4A), because benzaldehyde and dimedone form a side product via Knoevenagel condensation and therefore disturb the pure second-order reaction kinetics. This is also discussed in the main text (Fig. 2).

**Figure S4.** Recorded data of the kinetics studies on the Michael addition with \([\text{BMN}]_0 = [\text{DD}]_0 = 10 \text{ mmol l}^{-1}\). **A** Inverse benzaldimine concentration \([\text{BMN}]^{-1}\) in the reaction solution as a function of reaction time for increasing benzaldehyde starting concentration \([\text{BA}]_0\). The slopes of the linear fits correspond to the rate constants \( k \) of the Michael addition. **B** Same plot as in **A** but with increasing malononitrile starting concentration \([\text{MN}]_0\).
Here, we also visualize benzylidenemalononitrile and dimedone concentrations as a function of the reaction time for the situation with added malononitrile and compare this with the data for the case of the added benzaldehyde (Fig. S5A). It can be clearly seen that the concentration difference between both Michael addition substrates is significantly lower when malononitrile is added. Therefore, side product formation can be excluded when the benzaldehyde is absent. Furthermore, plotting the logarithmic benzaldehyde concentration $\ln[BA]$ as a function of the reaction time provides a rate constant of $0.006 \text{ s}^{-1}$ for the formation of side product, which is discussed in the main text.

**Figure S5.** A Plot of the substrate concentrations as a function of reaction time, comparing the Michael reactions with added malononitrile and added benzaldehyde under conditions of equated equivalents ([BMN]/[DD]/[MN], 3:3:3 and [BMN]/[DD]/[BA], 3:3:3, respectively). B Plot of the logarithmic benzaldehyde concentration $\ln[BA]$ as a function of reaction time. The slope of the linear fit corresponds to the rate constant ($0.006 \text{ s}^{-1}$) characterizing the formation of side product.
S4) Modeling of a consecutive first order–second order reaction kinetics

Below, we develop the kinetics model of an ideal multicomponent domino reaction with a first-order reaction as first elementary reaction and a second-order reaction as second one, for which one substrate is given with defined starting concentration and another one is generated through the first reaction. Both elementary reactions are considered to proceed completely independent from each other, ignoring all effects that have been presented in the main text.

Description of the process and basic differential rate laws

For the following study, we consider all reactions to proceed irreversibly and with a selectivity of unity. In the equations, squared brackets are used to denote concentrations of the abbreviated molecules: BA for benzaldehyde, DD for dimedone, BMN for benzylidenemalononitrile, and THC for the tetrahydrochromene derivative as domino reaction product. Further, we introduce reaction time \( t \) and the reaction rate constants \( k_1 \) and \( k_2 \) for the Knoevenagel condensation and the Michael addition, respectively.

The differential rate law for the Knoevenagel reaction was experimentally verified to be

\[
\frac{d[B\text{A}]}{dt} = -k_1 [B\text{A}] \tag{S2}
\]

For the second step including the Michael addition, the rate law was determined as

\[
\frac{d[\text{THC}]}{dt} = -\frac{d[\text{DD}]}{dt} = k_2 [\text{BMN}][\text{DD}] \tag{S3}
\]

For the product of the Knoevenagel condensation, the change of the concentration with time is therefore given as

\[
\frac{d[\text{BMN}]}{dt} = k_1 [\text{BA}] - k_2 [\text{BMN}][\text{DD}] \tag{S4}
\]

Integrated rate laws

Only the differential rate law for the first elementary reaction can be classically integrated with limits from \( t_0 = 0 \) to \( t \) and from the starting concentration \([\text{BA}]_0\) to \([\text{BA}]\)

\[
\int_{[\text{BA}]_0}^{[\text{BA}]} \frac{d[\text{BA}]}{[\text{BA}]} = -\int_{t_0}^{t} k_1 \, dt, \tag{S5}
\]
resulting in the integrated form of first-order reactions (found in standard textbooks):

\[ [BA] = [BA]_0 e^{-k_1 t} \quad (S6) \]

On the other hand, integrated rate laws for consecutive first order–second order reactions are not available in textbooks or from publications (to the best of our knowledge). To integrate the differential rate law for the overall process, assumptions of mass conservation and a selectivity of unity lead to the following equations:

\[ [DD] = [DD]_0 - [THC] \quad (S7) \]
\[ [BMN] = [BA]_0 - [BA] - [THC] \quad (S8) \]

Using now equations S6–S8 in the differential rate law for the product of the domino reaction (equation S3) results in

\[ \frac{d[THC]}{dt} = k_2 ([BA]_0 - [BA]_0 e^{-k_1 t} - [THC]) ([DD]_0 - [THC]) \quad (S9) \]

or (writing out the final equation S9 in full)

\[ \frac{d[THC]}{dt} = k_2 [THC]^2 + k_2 [BA]_0 [THC] e^{-k_1 t} - k_2 ([BA]_0 + [DD]_0) [THC] - k_2 [BA]_0 [DD]_0 e^{-k_1 t} + k_2 [BA]_0 [DD]_0 \quad (S10) \]

This differential equation is a Riccati-type equation that does not have an obvious possibility for simplification towards an analytical solution. We therefore used an R-script, which provides numerical solutions by using the fourth-order Runge–Kutta method. As input parameters, the experimentally determined rate constants \( k_1 \) and \( k_2 \) for the exclusive Knoevenagel reaction and the exclusive Michael addition, respectively, were employed. In Fig. S6, the numerical solution is plotted as a function of the reaction time (solid lines) and the experimental results of the multicomponent domino reaction with equated starting concentrations are included as the solid circles.
Figure S6. Comparison of the experimentally investigated multicomponent domino reaction (solid circles) with a modeled reaction process assuming two independent consecutive reactions (solid lines).

This plot clearly supports the effects reported in the main text. First, the Knoevenagel reaction (represented by the decay of the benzaldehyde concentration [BA]) shows a lower reaction rate in the experiment than in the model due to a competition between benzaldehyde and dimedone for active sites on the reactor surface. Second, the Michael addition, represented by the decay of the dimedone concentration [DD], shows a higher reaction rate in the experiment than in the model. This can be explained, on the one hand, by the added malononitrile, which accelerates the reaction drastically (as shown in the main text). On the other hand, the adverse effect of the benzaldehyde on the Michael addition can be neglected since the benzaldimine species, which is responsible for this effect, cannot enrich on the active sites when malononitrile is present (as discussed in the main text). Finally, water is produced through the Knoevenagel condensation, which could provide another proton source, as discussed for malononitrile in the main text, and could therefore also increase the reaction rate. Altogether, these effects explain the much lower benzylidenemalononitrile concentrations [BMN] in the experiment compared with the model (Fig. S6), because the first (producing) reaction is slower and the second (consuming) reaction is faster in reality than in the model.
S5) Comparison between one-pot and sequential experimental designs

The comparison between the classical one-pot design and sequential operation was made for a little substrate scope of para-substituted benzaldehydes 1a–d, as indicated in Scheme 1 in the main text, with the intention to adjust the overall reaction rates. The anticipated influence of the substituents on the reactivity of the substituted benzaldehyde could be estimated from the Hammett equation (equation S11):

$$\log \frac{k}{k_0} = \sigma_{para} \rho$$  \hspace{1cm} (S11)

Here, $k$ denotes rate constants of the Knoevenagel reactions of para-substituted benzaldehydes 1b–1c and $k_0$ is the rate constant of the reference system, i.e., the Knoevenagel reaction of the unsubstituted benzaldehyde 1a with malononitrile (2). $\sigma_{para}$ represents the substituent constant of specific functional groups in para-position to the aldol group and $\rho$ is the reaction constant. Unsubstituted benzaldehyde 1a serves as reference system with a substituent constant of $\sigma_{para} = 0$. The substituent constants of all functional groups employed in this work are summarized in Table S2.

| Molecule | Substituent | $\sigma_{para}$ (–) |
|----------|-------------|------------------|
| 1a       | --H         | 0                |
| 1b       | --OMe       | $-0.27$          |
| 1c       | --N(Me)$_2$ | $-0.83$          |
| 1d       | --CF$_3$    | $+0.54$          |

Since the Knoevenagel reaction relies on a nucleophilic attack on the aldehydes 1a–d, the reaction rate constant $k$ is expected to be lower for decreasing substituent constant $\sigma_{para}$, which results in a Hammett plot ($\sigma_{para}$ vs. log $k/k_0$) with a positive slope $\rho$. The UV-Vis spectra should support this trend, since an electron-releasing effect (methoxy and dimethylamino group, 1b and 1c), visualized by a bathochromic shift in the spectra, decreases the nucleophilicity of the aldehyde and should lower the reaction rate. Functional groups with a hypsochromic shift (trifluoromethyl, 1d) are regarded as electron-withdrawing, which should favor a nucleophilic attack on the aldehyde.
The UV-Vis spectra of the four aldehydes (1a–d), the four Knoevenagel products (5a–d), and the four tetrahydrochromene derivatives (4a–d) are shown in Fig. S7. For the aldehydes 1a–d (Fig. S7A), all UV-Vis spectra were recorded during the calibration measurements for the same concentration (3 mmol l⁻¹), so that bathochromic and hypsochromic shifts can be recognized directly as shifts of the absorption maximum and molar extinction coefficients at the absorption maximum; the UV-Vis spectra recorded for the Knoevenagel products 5a–d (Fig. S7B) and for the domino reaction products 4a–d (Fig. S7C), on the other hand, have been normalized to the respective absorption maxima.

**Figure S7.** UV-Vis spectra of the aromatic aldehydes 1a–d, the products of their Knoevenagel condensation with malononitrile (2) 5a–d, and the tetrahydrochromene derivatives 4a–d (panels A, B, and C, respectively), reflecting the multicomponent domino reaction illustrated by Scheme 1 in the main text.
The Hammett relationship remains valid also for the Michael addition step, as indicated by the UV-Vis spectra of 5a–d. However, with the here employed setup it was not possible to record the undistorted kinetics of the Michael addition due to the multicomponent design on the main reactor. In contrast, valve 1 (behind the smaller pre-reactor) allowed to extract experimentally determined Knoevenagel reaction rates from the data recorded with the sequential experiment design. The resulting Hammett plot is illustrated in Figure S8.

Figure S8. Hammett plot for the Knoevenagel condensation of the para-substituted benzaldehydes 1a–d with malononitrile (2), resulting in a slope as reaction constant of \( \rho = 1.02 \).

The obtained results are in good agreement with data from the literature \(^{[S17,S18]}\). The outlying point for the trifluoromethyl substituted benzaldehyde (1d) was observed similarly before \(^{[S17]}\) and could be explained by the increasingly relevant reverse-Knoevenagel reaction of the benzylidenemalononitrile derivative 5d, which is very prone to hydrolysis.

Figure S9 shows how the adjustments of the overall reaction rate were received experimentally. Comparing one-pot and sequential experimental designs, the concentrations of the aldehydes 1a–d and of dimedone (3) are depicted for three system flow rates. The general trend, which is discussed in the main text, becomes also visible in this data presentation: Not only the product areas for reactions conducted in the sequential design are larger than in the one-pot design (see Fig. 4 in the main text), but also the conversions of the substrates are higher. When comparing the four starting aldehydes of the substrate scope, the bathochromic shift in a UV-Vis spectrum seems to correlate with the expected lower reactivity. Since reaction rates for the Knoevenagel condensation and the Michael addition are lower, higher substrate concentrations are found in the reaction solution (corresponding to the lower turnover frequencies from Table 1 in the main
text). The hypsochromic shift characterizing the trifluoromethyl group, however, is associated only with a little change in the reactivity.

**Figure S9.** Aiming at the four tetrahydrochromene derivatives 4a–d of the substrate scope (Fig. 4, main text), the concentrations of the aldehydes 1a–d and of dimedone (3) in the reaction solutions are plotted for three different system flow rates to compare one-pot and sequential experimental designs.
S6) Additional details to the experimental section

Kinetics studies
Figure S10 illustrates the experimental details of the first conducted flow experiment to study the reaction kinetics of the Knoevenagel reaction between benzaldehyde (1a) and malononitrile (2) to yield benzyldenemalononitrile (5a). The first 62.5 min serve for the determination of the reaction order through the variation of the starting concentrations of benzaldehyde [BA], (1a) and malononitrile [MN], (2). Therefore, the quaternary pump was programmed to adjust the mixing proportions of the substrate solutions according to Fig. S10D. For each combination of mixing proportions, five volumetric flow rates (0.2, 0.3, 0.5, 0.75, and 1.0 ml min⁻¹) were investigated (Fig. S10C) to allow extraction of reaction rates. Afterwards, a control experiment was conducted (62.5–75 min) to verify that the reaction rate of the exclusive Knoevenagel reaction is not affected by catalyst poisoning over the experiment time.

Then (75–112.5 min), the concentration of dimedone (3) was stepwise increased to investigate its influence on the Knoevenagel reaction rate. Throughout the complete flow experiment, the temperature of the thermostatted column compartment with embedded microreactor is recorded (Figure S10E) as well as the system backpressure measured by the quaternary pump (Figure S10B). The dotted lines in Figure S10 indicate the times when the injection valve switched to start a new HPLC cycle, lasting only 2.5 min, with all UV-Vis active substances (1a, 3, 5a, 4a) baseline-separated. Online HPLC analysis was run isocratically with water/ethanol 67:33 (v/v) at 40 °C with a volumetric flow rate of 2 ml min⁻¹. The chromatograms of the online analysis of the flow experiment are illustrated in Figure S10A, with the dotted lines as the points of injection.

The structure of Figures S11 and S12 is similar and the HPLC conditions were not changed, so that only the goals of the experiments will be discussed below.
Figure S10. Experimental details to the kinetics studies on the Knoevenagel condensation. A Series of HPLC chromatograms recorded at a wavelength of 282 nm as online analysis of the flow experiment. B Real-time recorded system backpressure. C Programmed system flow rates as input parameter. D Programmed mixing proportions of the substrate solutions as input parameter. E Real-time recorded temperature of the thermostatted column compartment containing the microreactor.
Figure S11 illustrates the experimental details on the kinetics studies on the Michael addition of dimeredone (3) and benzylidene malononitrile (5a) to yield the tetrahydrochromene derivative 4a. Analogous to Fig. S10, the reaction order was determined first, then a control experiment was conducted to exclude catalyst poisoning on relevant timescales, and finally the influence of malononitrile (2) on the Michael addition was investigated.

**Figure S11.** Experimental details to the kinetics studies on the Michael condensation. A HPLC chromatograms recorded at a wavelength of 282 nm as online analysis of the flow experiment. B Real-time recorded system backpressure. C Programmed system flow rates as input parameter. D Programmed mixing proportions of the substrate solutions as input parameter. E Real-time recorded temperature of the thermostatted column compartment containing the microreactor.
As follow-up to Fig. S11, Figure S12 illustrates the experimental details corresponding to the investigation of the influence of benzaldehyde (1a) on the Michael addition between dimedone (3) and benzylidenemalononitrile (5a).

Figure S12. Experimental details to the influence of benzaldehyde (1a) on the Michael addition. A HPLC chromatograms recorded at a wavelength of 282 nm as online analysis of the flow experiment. B Real-time recorded system backpressure. C Programmed system flow rates as input parameter. D Programmed mixing proportions of the substrate solutions as input parameter. E Real-time recorded temperature of the thermostatted column compartment containing the microreactor.
Substrate scope and experimental design studies

When the automated flow reactor was changed over from one substrate to another, the general workflow using a new substrate followed four distinct steps:

1. Initial assessment: A test method was run in the sequential design under reaction conditions where all four UV-Vis active substances (aldehyde, dimedone, Knoevenagel product, Michael product) were present. Through injection by the valve behind reactor 2 (valve 2), HPLC conditions were found to obtain chromatograms with all signals baseline-separated. Switching of the valve behind reactor 1 (valve 1) allows to correlate the signals in the chromatogram (with corresponding UV-Vis spectra of the DAD) with the respective substances.

2. Calibration: The adapted HPLC conditions were used for calibration of the connected aldehyde (1a–d) and dimedone. Therefore, bottle concentrations of ~30 mmol l\(^{-1}\) were used and the system was programmed to change the mixing proportion from this bottle to pure ethanol from 0–50% in 10%-steps. For every concentration both valves were switched to obtain two calibration curves – one for each valve. Figure S13 illustrates an example from calibration of benzaldehyde (1a) with two calibration curves for the two valves; the calibration curve with the greater slope corresponds to valve 1 due to the larger injection volume.

![Figure S13. Calibration curves for benzaldehyde (1a). For valve 1, a calibration factor of 1.267 \(\cdot\) 10\(^5\) (\(R^2 = 0.99998\)) is obtained and for valve 2 a factor of 0.957 \(\cdot\) 10\(^5\) (\(R^2 = 0.99993\)).](image)

3. Run experiments in one-pot and sequential experimental designs: In both designs, the same method is performed by the automated system. After an introduction period at 1.00 ml min\(^{-1}\) to reach steady-state operation on the microreactors, chromatograms were recorded using both valves for three different total flow rates (1.00, 0.45, and 0.30 ml min\(^{-1}\)). The flow rates are
changed directly after injection from valve 2 to use the HPLC cycle to re-establish steady-state conditions on the reactors.

4. Collect fractions for offline analysis: After finishing the method, fractions were collected for the Knoevenagel condensation yielding 5a–d as well as for the domino reaction yielding 4a–d under conditions of almost complete conversion, respectively. Afterwards, the fractions were immediately dried under reduced pressure for nuclear magnetic resonance (NMR) and mass spectrometry (MS) offline analysis. The purity of the residue after evaporation of the solvents was high enough to collect data without further purification.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a).

H NMR (500 MHz, DMSO-d$_6$): $\delta$ = 7.31–7.26 (m, 2H), 7.21–7.16 (m, 1H), 7.16–7.11 (m, 2H), 6.97 (br, 2H), 4.17 (s, 1H), 2.53–2.50 (m, 2H), 2.25 (d, $J$ = 16 Hz, 1H), 2.10 (d, $J$ = 16 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H) ppm. $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ = 195.6, 162.4, 158.5, 144.7, 128.3, 127.1, 126.5, 119.6, 112.7, 58.3, 49.9, 39.5, 35.5, 31.8, 28.3, 26.8 ppm. HRMS (ESI) m/z calculated for C$_{19}$H$_{16}$N$_3$O$_3$Na [M+Na]$: 317.1260; m/z found: 317.1259.

2-Amino-7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b).

H NMR (500 MHz, DMSO-d$_6$): $\delta$ = 7.07–7.02 (m, 2H), 6.92 (br, 2H), 6.86–6.81 (m, 2H), 4.12 (s, 1H), 3.71 (s, 3H), 2.56–2.45 (m, 2H), 2.24 (d, $J$ = 16 Hz, 1H), 2.09 (d, $J$ = 16 Hz, 1H), 1.03 (s, 3H), 0.95 (s, 1H) ppm. $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ = 195.6, 162.1, 158.4, 157.9, 136.8, 128.2, 119.7, 113.6, 113.0, 58.6, 55.0, 50.0, 39.7, 34.7, 31.7, 28.4, 26.7 ppm. HRMS (ESI) m/z calculated for C$_{22}$H$_{21}$N$_3$O$_4$Na [M+Na]$: 347.1366; m/z found: 347.1364.

2-Amino-7,7-dimethyl-5-oxo-4-(4(dimethylamino)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c).

H NMR (500 MHz, DMSO-d$_6$): $\delta$ = 6.95–6.91 (m, 2H), 6.90 (br, 2H), 6.65–6.60 (m, 2H), 4.04 (s, 1H), 2.84 (br, 6H), 2.53–2.43 (m, 2H), 2.24 (d, $J$ = 16 Hz, 1H), 2.07 (d, $J$ = 16 Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H) ppm.

$^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ = 195.7, 161.9, 158.4, 149.2, 132.6, 127.9, 120.0, 113.4, 112.4, 58.9, 50.1, 40.3, 39.7, 34.6, 31.8, 28.5, 27.0 ppm.

HRMS (ESI) m/z calculated for C$_{22}$H$_{21}$N$_3$O$_4$Na [M+Na]$: 360.1682; m/z found: 360.1684.

2-Amino-7,7-dimethyl-5-oxo-4-(4(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d).

H NMR (500 MHz, DMSO-d$_6$): $\delta$ = 7.66 (d, $J$ = 8.2 Hz, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 7.13 (br, 2H), 4.29 (s, 1H), 2.56–2.52 (m, 2H), 2.26 (d, $J$ = 16 Hz, 1H), 2.11 (d, $J$ = 16 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H) ppm. $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ = 195.8, 163.0, 158.5, 149.4, 128.1, 127.3 (q, $J$ = 32 Hz), 125.4 (q, $J$ = 3.8 Hz), 123.2, 119.5, 112.0, 57.4, 49.9, 39.8, 35.6, 31.9, 28.3, 26.9 ppm. $^1$H NMR (250 MHz, DMSO-d$_6$): $\delta$ = –62.9 ppm. HRMS (ESI) m/z calculated for C$_{22}$H$_{18}$F$_3$N$_3$O$_3$Na [M+Na]$: 385.1134; m/z found: 385.1137.
2-Benzylidenemalononitrile (5a).
\( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)): \( \delta = 8.55 \) (s, 1H), 7.98–7.92 (m, 2H), 7.72–7.67 (m, 1H), 7.65–7.59 (m, 2H) ppm. \( ^{13}C \) NMR (125 MHz, DMSO-\( d_6 \)): \( \delta = 161.5, 134.3, 131.3, 130.5, 129.5, 114.2, 113.2, 81.6 \) ppm. HRMS (ESI+) m/z calculated for C\( _{10} \)H\( _{10} \)N\( _3 \) \([\text{M+NH}_4]^+\): 172.0869; m/z found: 172.0869.

2-(4-Methoxybenzylidene)malononitrile (5b).
\( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)): \( \delta = 8.39 \) (s, 1H), 8.00–7.95 (m, 2H), 7.21–7.15 (m, 2H), 3.89 (s, 3H) ppm. \( ^{13}C \) NMR (125 MHz, DMSO-\( d_6 \)): \( \delta = 164.3, 160.4, 133.3, 124.1, 115.2, 114.8, 113.9, 76.9, 55.9 \) ppm. HRMS (ESI+) m/z calculated for C\( _{11} \)H\( _8 \)N\( _2 \)ONa\( ^+ \) \([\text{M+Na}]^+\): 207.0529; m/z found: 207.0529.

2-(4-(Dimethylamino)benzylidene)malononitrile (5c).
\( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)): \( \delta = 8.05 \) (s, 1H), 7.87–7.82 (m, 2H), 6.88–6.84 (m, 2H), 3.11 (s, 6H) ppm. \( ^{13}C \) NMR (125 MHz, DMSO-\( d_6 \)): \( \delta = 158.8, 154.3, 133.6, 118.7, 116.2, 115.5, 115.2, 111.8, 39.4 \) ppm. HRMS (ESI+) m/z calculated for C\( _{12} \)H\( _{11} \)N\( _3 \)Na\( ^+ \) \([\text{M+Na}]^+\): 220.0845; m/z found: 220.0846.

2-(4-(Trifluoromethyl)benzylidene)malononitrile (5d).
\( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)): \( \delta = 8.69 \) (s, 1H), 8.14–8.08 (m, 2H), 8.04–8.00 (m, 2H) ppm. \( ^{13}C \) NMR (125 MHz, DMSO-\( d_6 \)): \( \delta = 160.1, 134.9, 132.7 \) (q, \( J = 32 \) Hz), 132.6, 132.4, 131.0, 126.4 (q, \( J = 3.7 \) Hz), 113.8, 112.7 ppm. \( ^{19}F \) NMR (250 MHz, DMSO-\( d_6 \)): \( \delta = -63.9 \) ppm.

The following Figures S14–S21 illustrate experimental details to the measurements performed to compare one-pot and sequential experimental designs for the four different benzaldehydes 1a–d. As described in the main text, HPLC cycles were run with an isocratic period (2.25 min), where for aldehydes 1a–c the same eluent was used as above (67:33 v/v water/ethanol), whilst for 1d a composition of 60:40 v/v water/ethanol was used; the subsequent gradient was run over 2.25 min to 0:100 v/v water/ethanol for all aldehydes. Afterwards, the HPLC column was equilibrated again on the composition of the isocratic period for 0.5 min before a new injection took place.

All experiments were performed for three flow rates. When reactors operated in steady-state, first valve 1 (behind reactor 1) was switched. During the online analysis cycle of 5 min the reactors were kept in steady-state. Then, valve 2 was switched and parameters were changed. In all following chromatograms (Figures S14–S21, panels A), injections can be alternatingly correlated to valve 1 (dotted lines) and valve 2 (dashed lines).
Figure S14. Experimental details to the multicomponent domino reaction of benzaldehyde (1a), malononitrile (2), and dmedone (3) to yield the tetrahydrochromene derivative 4a in the one-pot experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 265 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% dmedone ethanolic solution (30 mmol l⁻¹). E Real-time recorded system backpressure.
Figure S15. Experimental details to the multicomponent domino reaction of benzaldehyde (1a), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4a in the sequential experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 265 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
Figure S16. Experimental details to the multicomponent domino reaction of 4-methoxybenzaldehyde (1b), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4b in the one-pot experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 283 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-methoxybenzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
Figure S17. Experimental details to the multicomponent domino reaction of 4-methoxybenzaldehyde (1b), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4b in the sequential experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 283 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-methoxybenzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
Figure S18. Experimental details to the multicomponent domino reaction of 4-(dimethylamino)benzaldehyde (1c), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4c in the one-pot experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 244 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-(dimethylamino)benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
Figure S19. Experimental details to the multicomponent domino reaction of 4-(dimethylamino)benzaldehyde (1c), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4c in the sequential experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 244 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-(dimethylamino)benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
**Figure S20.** Experimental details to the multicomponent domino reaction of 4-(trifluoromethyl)benzaldehyde (1d), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4d in the one-pot experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 241 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-(trifluoromethyl)benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
Figure S21. Experimental details to the multicomponent domino reaction of 4-(trifluoromethyl)benzaldehyde (1d), malononitrile (2), and dimedone (3) to yield the tetrahydrochromene derivative 4d in the sequential experiment design. Dotted lines indicate injection via valve 1 and dashed lines injection via valve 2. A HPLC chromatogram recorded at a wavelength of 241 nm as online analysis of the flow experiment. B Programmed HPLC cycles. C Programmed flow rate of the quaternary pump, pumping with mixing proportions of 50% ethanolic 4-(trifluoromethyl)benzaldehyde solution (30 mmol l⁻¹) and 50% ethanolic malononitrile solution (30 mmol l⁻¹). D Programmed flow rate of the binary pump, pumping 100% ethanolic dimedone solution. E Real-time recorded system backpressure.
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