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OPEN-SOURCE FRACTION COLLECTOR FOR FLASH COLUMN CHROMATOGRAPHY AND CONTINUOUS FLOW REACTIONS†

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ABSTRACT

The design and construction of an open-source fraction collector and its applications in flash column chromatography are described. With the collection vials arranged in a circular array, the outlet of the flash column is guided by an arm to stay above each vial over a defined interval of time, liberating the chemists from the manual labor of swapping vials in high frequency. The assembly is constructed with flow reactor components (plunger pump, tubing, and valves) and optional 3D printed parts (vial holders and arm). The applicability of such a device is demonstrated through relevant examples from the daily work of a chemist, including the purification of crude products, the separation of a reaction mixture, and the fractional collection of effluents from continuous flow reactors.

Introduction

Column chromatography is one of the most important methods of separation and purification of organic compounds. Since the first use of a packed column by Tswett,[1,2] the mobile phase has usually been driven by gravity, which works fairly well in purifying milligrams of compounds.[3] However, in gram-scale separations, the gravity- driven column is tediously slow and frequently gives poor recovery due to band tailing.[4] In the 1970s, flash chromatography was introduced in order to accelerate preparative chromatography.[4] The flow rate of the mobile phase is increased by exerting pressure at the top of the column[5] with pressurized gas,[6–8] especially with

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air from blood pressure bulbs[9] or aquarium pumps.[10] However, the operation of manual flash chromatography is still tedious and cumbersome: chemists must frequently swap the vials collecting the effluent fractions in very short intervals (typically 1–3 min, depending on the fraction volume) while periodically performing thin layer chromatography (TLC) to monitor the separation progress. When refilling the solvent vessel, the column is subjected to the expansion of the gas in the dead volumes during the depressurization, which promotes longitudinal mixing by creating flaws in the packed bed. Moreover, the standard equipment used for manual column chromatography typically consists of widely available and affordable glassware that cannot withstand pressure above a few bars. Operations under high pressure to achieve high flow rates must be avoided or transferred to commercial solutions, which are in turn costly.

The automatic equipment for column chromatography (Fig. 1A) often relies on plunger pumps to deliver solvents (Fig. 1a) continuously into a packed column (Fig. 1b). This operation (Fig. 1a and b) resembles a packed-bed continuous flow reactor (Fig. 9c). Over the past decade, micro- and mesofluidic technonogy[11] has been progressively integrated into the general tool box for synthetic chemists[12] due to its intensified transport processes, access to extreme conditions,[13] and straightforward scale up.[14] Parts to build up flow reactors (especially pumps, tubing, fittings, and column cartridges) are widely available from commercial sources, which enables the construction of a flash chromatographic system at the same time.

Connecting a solvent bottle, a plunger pump, and a packed column with tubing, a primitive flash system can be constructed easily (Fig. 1A). The pump delivers the solvent in stable high flow rates (>10 mL min^{-1}), which are often inaccessible with manual pressurization (Fig. 1a). As the mobile phase is pressurized at the pump head, the solvent reservoir at the pump inlet can be refilled without interrupting the separation process (Fig. 1a). The packed columns for commercial setups are cheap and readily available (Fig. 1b). The plastic cartridges could withstand pressures up to 10 bar; some brands of them can be reused. Although the use of plunger pumps and robust column cartridges could significantly increase the efficiency of flash chromatography, the high effluent flow rate drastically reduces the time to collect every fraction (<1 min) leaving no opportunity to perform TLC during the process. Therefore, an automated fraction collector is required to free the operator from this repetitive and labor intensive task (Fig. 1c). Pumps are often the most expensive component in a flow setup, especially high speed (>10 mL min^{-1}) plunger pumps employed for ultra-fast (flash chemistry) and large-scale reactions. Synthetic chemists may hesitate to purchase such costly devices for only a few reactions. An inexpensive fraction collector could support the routine use of high-speed pumps in column chromatography. This would enhance the efficiency of preparative separations without the need for commercial automated

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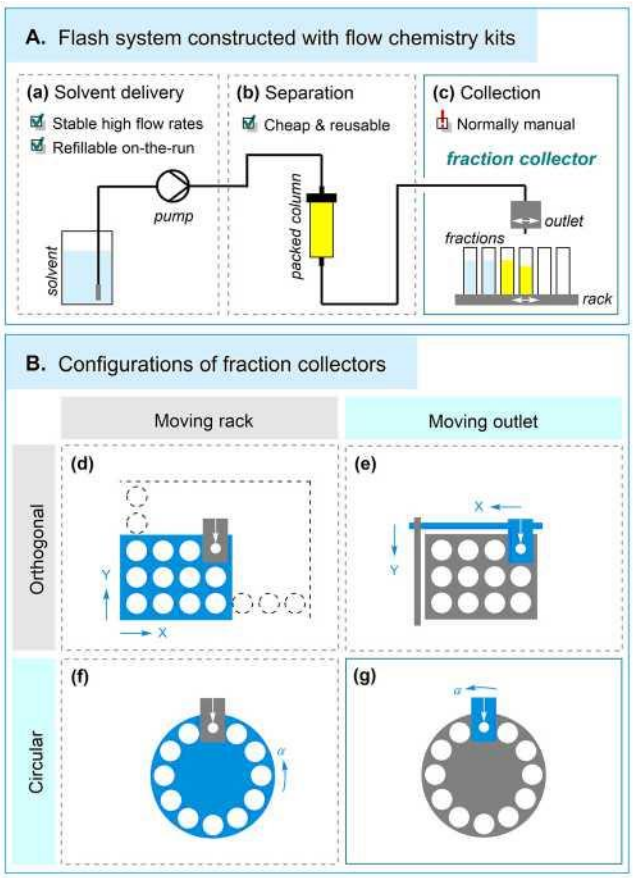
equipment.

Fig. 1 *The construction of a flash chromatography system with common parts and components of continuous flow setups.*



In manual column chromatography, chemists have designed various models of fraction collectors to facilitate the movement between the column outlet and the vials collecting the eluents.[15] Their configuration (Fig. 1B) can be either orthogonal (Fig. 1d and e) or circular (Fig. 1f and g) depending on the shape of the vial holder. The orthogonal configuration easily fits the rectangular test tube racks commonly used in daily lab practice and on commercial flash setups. However, moving such a rack beneath the outlet (Fig. 1d)[16,17] requires more space, as it needs a footprint with twice the length and width of the rack to access all the entries. Therefore, many commercial models (e.g. Advion-Interchim, Biotage, Teledyne) move the outlet nozzle above the vials (Fig. 1e),[18-21] so that the entire setup becomes more compact. Rotational fraction collectors require specially designed circular vial holders, and are less space-efficient if the collection vials do not populate the entire surface of the holder. However, a rotating rack (Fig. 1f)[22-26] can accommodate more fractions in only one dimension (α) and

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return to the starting position seamlessly; the rotational motion of the motors does not need to be converted to the linear motion in two dimensions (X and Y in Fig. 1d and e). Since a rack of vials containing hundreds of milliliters of liquid is quite heavy, moving the outlet (Fig. 1f)[27] is mechanically easier to realize.

In this article, we introduce an open-source fraction collector for chromatographic applications of high-speed plunger pumps. Adopting the circular moving-outlet configuration (Fig. 1f), the outlet of the flow system is guided by a mechanical arm to stay above each vial over equal intervals of time. The design and construction of mechanical components and vial holders are explained in a general approach, allowing modifications for different flow rates and vial arrangements. The required materials are commercially available with affordable prices. The entire assembly (including the pump) (Fig. 5) costs roughly 90%-less than commercial setups.

Results and discussion

DESIGN AND DEVELOPMENT

When the effluent from the column is collected in cylindrical vials in identical size (outer diameter d and height), the geometric design of the circular fraction collector determines the number of vials (N) the ring-shaped rack can hold. It also defines the radius of the rack (R), which equals the length of the arm moving the outlet. For the convenience of design and modification, formulas have been derived from an ideal case, in which N vials are arranged tightly with their centers located on the same circle (radius R) (Fig. 2A). As each vial is tangent to its neighbors, the distance of two adjacent vial centers is d. Using the law of cosines[28] (eqn (2)), the angular displacement from one vial to the next (⍁) can be calculated and related to the number of vials (N) (eqn (1)). Combining the triangular relations (eqn (1) and (2)), the design formulae for d, R, and N are derived (Fig. 2B). Considering that the vials are not always tightly packed in reality, the suffixes "min" and "max" are added to show the limits when selecting the two other parameters.

After selecting the geometric parameters (d, N, and R), the machinery to move the column outlet over the vials can be configured. A stepper motor can perform precise rotations with its shaft, where the angular displacement is ensured, a functional fraction collector can be built using readily available components.proportional to the number of pulses it receives from the driver module.[29,30] In response to the command from a microcontroller,[31] the driver module sends the pulses to move the arm by an angle (θ) after the time interval required to collect one fraction (*t*), guiding the outlet to the next vial.

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Fig. 2 *Geometric design of circular fraction collectors.*

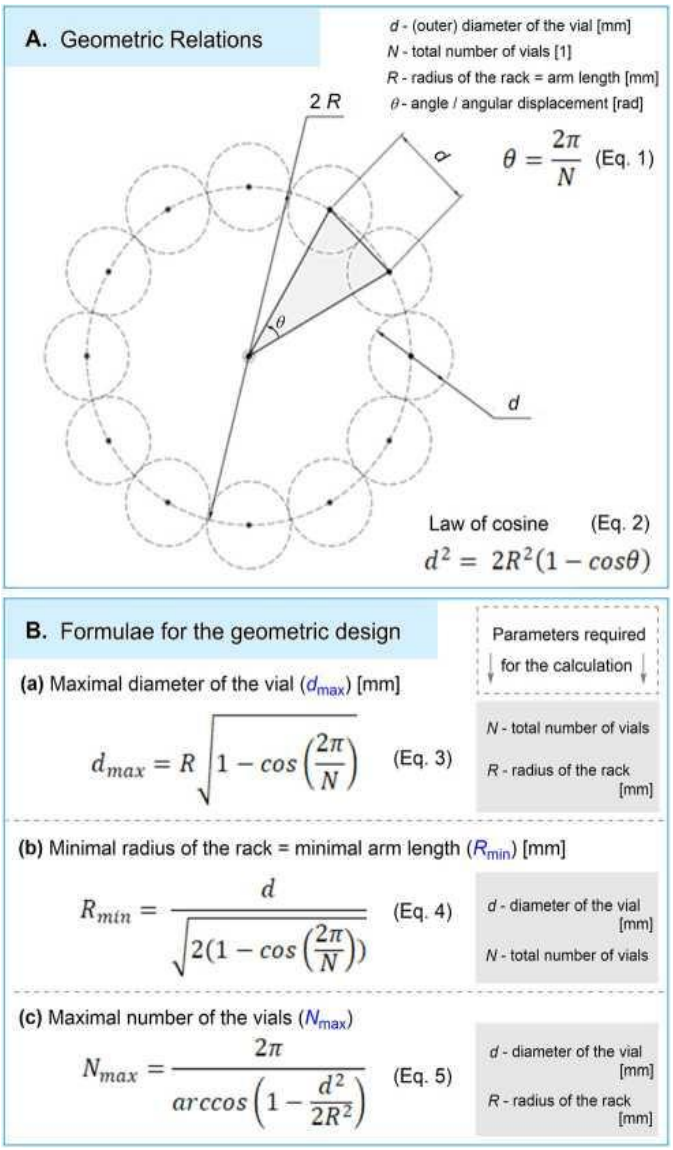

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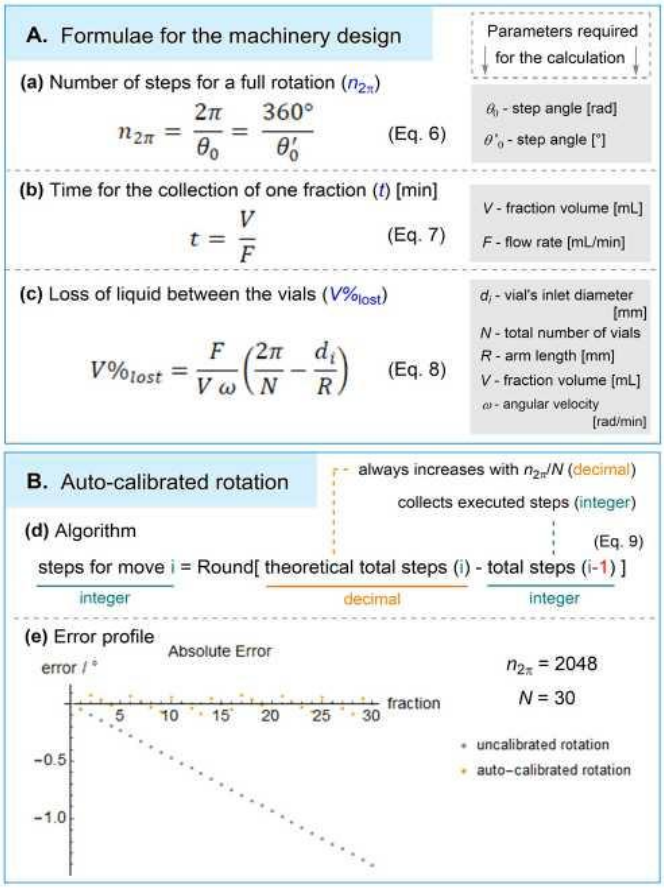
Fig. 3 *Machinery design of circular fraction collectors.*



To program the movement of a specific stepper motor, the number of steps for a complete revolution ($n_{2\pi}$) needs to be known, as well as the time interval between two successive movements (t) (Fig. 3A). As the number of steps in a full rotation cannot always be exactly divided by the number of vials (N), the stepper motor can only take integer steps, and the round-off errors accumulate as more fractions are collected. This can lead to significant misalignment of the outlet and the collection vial (Fig. 3e, blue points), causing the effluent to spill. To correct this, the number of steps for each move must be calculated using the theoretical value ($n_{2\pi}/N$, decimal number) as reference (auto-calibration) (Fig. 3d). This ensures that round-off errors cancel out over time, maintaining accurate arm movement (Fig. 3e, orange points), and preventing spills and loss of valuable material. Once the accuracy of the arm movement is

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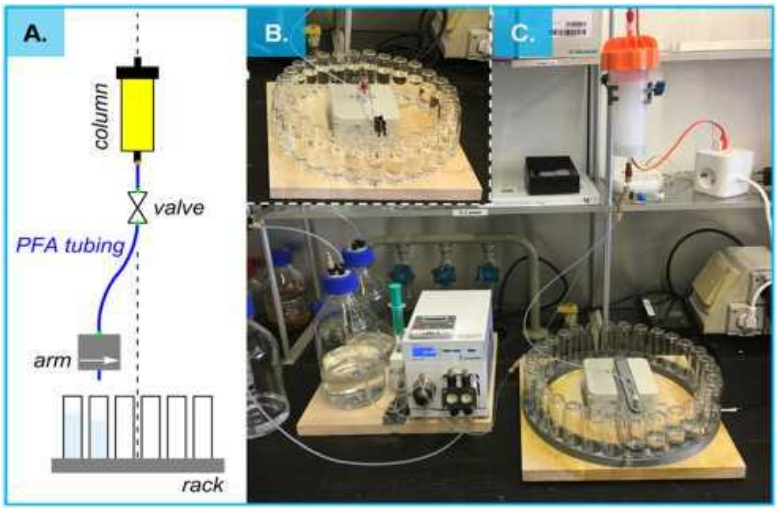
CONSTRUCTION OF FRACTION COLLECTORS

As wood is resistant to most of common organic solvents used in chromatography, we arranged a circular array of uniformed glass vials *(d* = 28 mm) on a square wooden board (300 mm × 300 mm, thickness 20 mm). This size is compact enough to fit into any fume hood or on a benchtop. Using eqn (5) with R = (300 - 28)/2 mm = 136 mm, the board can accommodate a maximum of 30 vials in a circle (N_{max} = 30.46). The minimal radius (R_{min}) to fit 30 vials in a circle was calculated with eqn (4) to be 133.93 mm. For the convenience of drawing, the arm length (R) was set to 134 mm. The vial positions were marked on the wooden board with a pencil.

To enable precise arm movement, a stepper motor (θ_0' = 5.625°/64, $n_{2\pi}$ = 2048 from eqn (6)) was mounted on the lid of a rectangular cable box containing the driver board and the microcontroller. The motor shaft was positioned vertically at the center and connected to a piece of stainless steel tubing (arm, o.d. 1/16 in) using aluminum coupling and plastic fittings. The outlet of the flash column was connected to a segment of PFA tubing (o.d. 1/16 in, i.d. 0.03 in; length 500 mm), with its other end clamped to the moving end of the arm. To prevent the interference between the tubing and the arm, the column was fixed vertically above the center of the wooden board (Fig. 4A).

Fig. 4 *Fraction collector with 30 vial positions: (A) position of the column; (B) version without 3D-printed parts; (C) version with a 3D- printed arm and vial holders.*



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The outlet of the PFA tubing was adjusted to be approximately 5 mm above the vial inlets by gently bending the arm. Once the circuit and power supply are connected, the automated fraction collector is ready for use (Fig. 4B) without human intervention during the collection of 30 fractions. However, the filled vials must be removed from the board before the arm completes a full revolution.

To simplify vial replacement, vial holders covering one third of the circle (10 vials) were designed and 3D-printed using poly lactic acid (PLA) filament (Fig. 4C). However, as PLA shrinks irreversibly when exposed to acetone and dichloromethane (DCM), it was later replaced with polypropylene (PP). Polypropylene can withstand several common solvents in flash chromatography, including petroleum ether (PE), ethyl acetate (EA), dichloromethane, and acetone.

CONFIGURATION FOR FLASH CHROMATOGRAPHY

For the daily purification of organic compounds, a flash chromatography system (Fig. 5) equipped with our fraction collector (Fig. 4C) was assembled. The mobile phase was delivered by a plunger pump (P1) with a maximal flow rate of 50 mL min^{-1}, a capacity rarely exploited in lab-scale synthesis. An L-valve (V1) at the pump inlet allows switching between two solvent bottles, which is convenient for adding and changing solvent. Fluid conduits use PFA tubing with an outer diameter: 1/8 inch for pump inlets and 1/16 inch for other connections commonly used in flow reactor assembly. Silica columns are packed in commercial cartridges (50 g size; column volume CV = 80 mL measured by barometric method) with Luer fitting. A ball valve (V2) at the column outlet interrupts solvent flow during the pauses, column packing (vide infra), or sample loading thus ensuring the silica bed does not drain.

Before performing column chromatography, thin layer chromatography (TLC) must be conducted on the crude mixture to determine the mobile phase compositions. The mobile phase should meet the following criteria: (a) all components are soluble, (b) the retention factor (R_f) of the target compound falls between 0.2–0.3, and (c) no impurities are nearby ($|\Delta R_f| \leq 0.2$).[4,32]

The packed column is primed with the less-polar ingredient of the mobile phase (weak solvent). Samples, either loaded on a porous material (e.g., silica or celite) or in the liquid form (concentrated solution in weak solvent or neat), are added to the top of the column. Once the flow rate is set on the pump (P1), the separation process begins by (1) opening the ball valve (V2), (2) activating the fraction collector, and (3) starting the pump. The effluent from the column is collected in equal-volume fractions (eqn (7) in Fig. 3b), mimicking the "collect all" mode on commercial devices.

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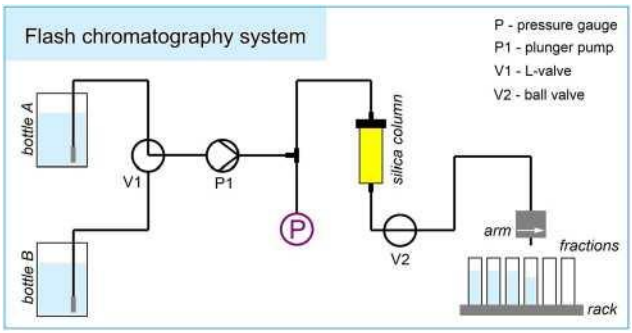
The pressure gauge (P) at the outlet of the pump (P1) is a useful tool to monitor the back pressure generated by the column (Fig. 5). A stable back pressure could indicate the end point of column priming. To visualize the stability of pressure, a gauge with ≤0.1 bar resolution is recommended. Clogging inside the column could invoke overpressure, which requires stopping the solvent supply immediately to avoid damage to the flow system. Some brands of pumps have integrated a pressure sensor to trigger an automatic shut-down when the pressure exceeds a set threshold.

Fig. 5 *Flash chromatography setup constructed with the components of flow reactors in organic chemistry labs.*



ISOCRATIC SEPARATION: PURIFICATION OF A BENZOTRIAZOLE DERIVATIVE

In established synthetic protocols of organic compounds, the target molecule is often isolated from mixtures containing small amounts of impurities under isocratic conditions, i. e., constant mobile phase composition. The flash system equipped with a fraction collector (Fig. 5) was used to purify the crude product from the nitrosative synthesis of N-phenyl benzotriazole (2b) (Fig. 6). Benzotriazole derivatives are useful synthetic building blocks for a wide range of applications.[33]

N-Phenyl-o-phenylenediamine 1b (0.325 M in the reaction mixture) was nitrosated by dinitrogen trioxide (N_2O_3) (Fig. 6a) in acetonitrile (MeCN) under both flow and batch conditions following established protocols.[34] Due to the strong exotherm[34] of the reaction (Fig. 6a), slow dissipation of reaction heat could lead to temperature overshooting, thus potentially forming by-products. The reaction was performed twice under identical conditions (solvent, concentration (c), temperature (T), and time (t)) in flow and batch reactors. As the flow reactor provides a significantly larger specific area for heat transfer than the batch reactor, fewer impurities were expected. For details on experimental procedures, see the ESI.†

The TLC analysis of the reaction mixture showed that a 90 : 10 (v/v) mixture of PE (solvent A) and EA (solvent B)

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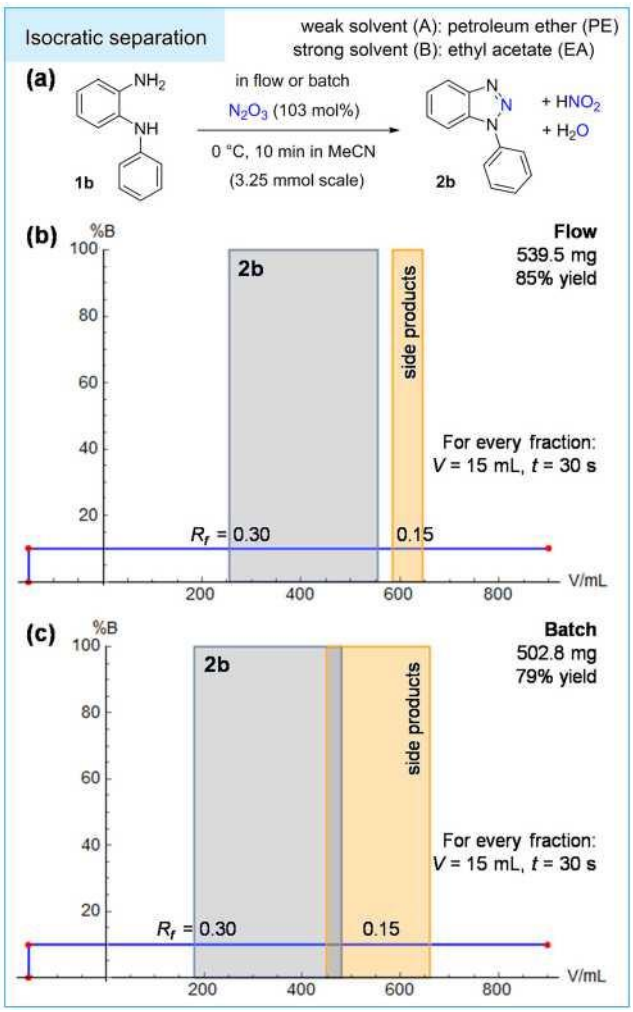
was a suitable mobile phase for the purification of 2b (R_f = 0.30). However, the R_f of the side products is quite close to that of 2b ($|\Delta R_f|$ = 0.15), requiring a larger column or reduced sample loading for a clear separation. With the mobile phase flow rate set to 30 mL min^{-1} ($V\%_{lost}$ = 0.27%, eqn (8)), a 15 mL fraction was collected in 30 s. The effluent before the fractional collection (forerun) was collected separately in a graduated cylinder, yielding a volume of approximately 150 mL, which was roughly half of the calculated value (CV/R_f = 267 mL).

Fig. 6 *Isocratic purification of the crude product (2b) from a nitrosative reaction (50 g silica column, 30 mL min^{-1}). (a) Synthesis of 2b; (b and c) distribution of compounds in collected fractions (identified by TLC) during the purification of samples from flow (b) and batch (c) reactions.*



A clear separation between 2b and the impurities was achieved from the sample generated under flow conditions (Fig. 6b), giving the pure product in 85% yield. When the crude product from the batch reaction was subjected to the same separation procedure (Fig. 6c), three fractions containing both 2b and the impurities were

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collected because of increased amount of impurities.

Isocratic methods are frequently used for isolating and purifying a single compound, while the collection of other components is usually not necessary. Conditions for isocratic separation (mobile phase and column) are often described in the preparative procedures of organic compounds. In the separation of compounds with small R_f difference ($|\Delta R_f| < 0.2$) and in the isolation of more than one ingredient, isocratic methods may not be sufficient.

STEP GRADIENT SEPARATION OF REACTION MIXTURES

In the development of a synthetic process, separating multiple components from a mixture is often necessary. Substrates and products (including side products) must be isolated in high purity to characterize the structures and to determine conversions and yields. Quantities based on isolated pure compounds provide the most reliable data, which serve as the benchmark for the instrumental methods (NMR, UV-vis, IR, HPLC, GC, etc.).

For separating complex mixtures, non-isocratic methods (such as linear and step gradient) often outperform isocratic methods. A linear variation of mobile phase composition (linear gradient) requires the collaboration of two pumps controlled by an external computer program, which is integrated into commercial chromatography setups. Using the simple setup (Fig. 5) with only one pump, a step gradient could be realized by switching the L-valve (V1) to a different solvent. Similar to isocratic separation (Fig. 6), the mobile phase compositions at each step were optimized by adjusting the volume ratio of weak (A) and strong (B) solvents on TLC until the R_f of the target compound fell between 0.2–0.3.

During the optimization of the *N*-nitrosation of *N*-methyl benzamide (3g) (Fig. 7a), the product *N*-nitrosamide (4g) was isolated under isocratic conditions (10% B) (Fig. 7b, entry 2). However, the unconverted starting material (3g) could not be effectively eluted from the column with the same mobile phase due to its low R_f (Fig. 7c, entry 7). To recover 3g, the volume fraction of the strong solvent (B) in the mobile phase was increased from 10% to 50% after 4g had been fully eluted (Fig. 7d). The output from the column was collected in 15 mL fractions using our fraction collector set to 30 s interval (eqn (7)), as in the isocratic experiments (Fig. 6). The separation began with 10% B; after confirming the absence of 3g in the 30th fraction (450 mL) via TLC, the pump inlet was switched to the next solvent composition (50% B) by turning the L-valve (V1). Switching the mobile phase without interrupting the separation process is not possible with manual flash columns.

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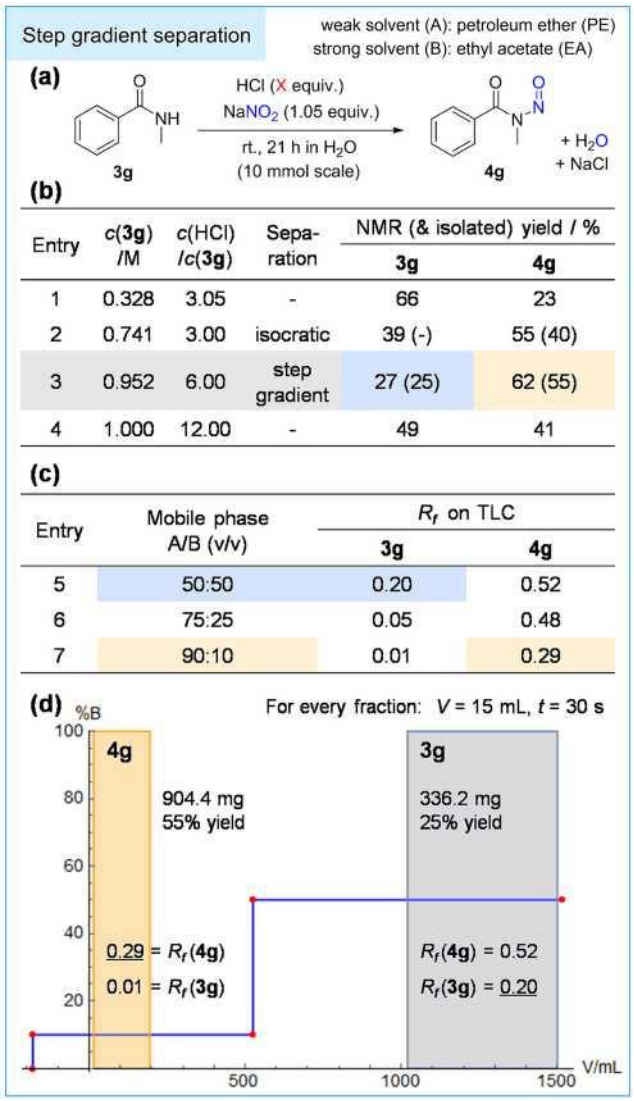
Fig. 7 *Step gradient separation of the amide (3g) and the nitrosamide (4g) (50 g silica column, 30 mL min^{-1}). (a) Synthesis of 4g; (b) optimization of reaction conditions; (c) TLC retention factors (Rf); (d) distribution of compounds in collected fractions (identified by TLC).*



TRACKING CONCENTRATION CHANGES OVER TIME

In a continuous flow system, changes in concentration over time can be monitored using the in-line analytical device at the outlet.[35] Commercial flash chromatographic setups often integrate in-line UV-vis and evaporative light scattering (ELS) detectors for monitoring the concentration. For stable compounds, fraction collection at constant time intervals provides an alternative approach to track concentrations across time segments using off-line analytical instruments.

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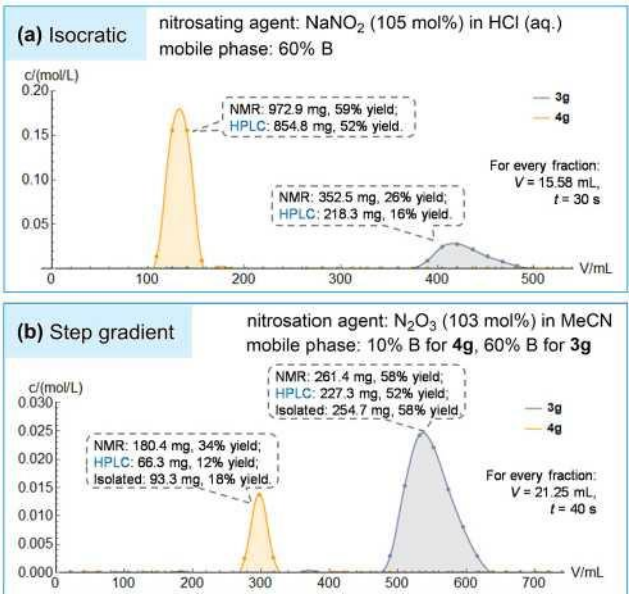
The column chromatographic setup (Fig. 5) operates as a continuous flow system where output composition changes over time. In the separation of reaction mixtures containing 3g and 4g (analyzed by ^{1}H NMR), the collected fractions were quantitatively diluted and analyzed by HPLC-UV (λ = 254 nm) to determine the concentration distribution profile (Fig. 8). Calibration of the pump (P1) ensures the accuracy of fraction volume (*V*), enabling the calculation of the total amount (n) of components in the collected fractions (HPLC yields in Fig. 8).

Fig. 8 *Elution curves obtained from fractional collection and off-line HPLC-UV analysis (50 g silica column; solvent: A = petroleum ether, B = ethyl acetate; internal standard: $PhCF_3$).*



The reaction mixture prepared under optimized conditions (Fig. 7b, entry 3) with $NaNO_2$ was separated under isocratic conditions (Fig. 8a). Compound 4g was collected in two fractions that form a sharp peak, whereas 3g spread across seven fractions despite its low yield. The broadening of the peak[36] with retention time, caused by diffusion and absorption kinetics, is a well-known phenomenon in absorptive chromatography.[37]

N-Methyl amide 3g can be quantitatively nitrosated by N_2O_3 in MeCN (*vide infra)*. The reaction mixture was quenched with MeOH, evaporated under reduced pressure, and separated with stepped gradient (Fig. 8b, cf. Fig. 7d). However, from the evaporated mixture, substrate 3g was recovered in >50% yield, whereas only a small amount of *N*-nitroamide 4g was isolated. This result (Fig. 8b) suggests that 4g decomposes into 3g during the evaporation of the reaction mixture containing nitrous acid (HNO_2), which releases reddish-brown fume under reduced pressure (see the ESI†). In this experiment, larger fractions (*V* ≈ 20 mL) were collected by adjusting the

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program to a longer time interval (t = 40 s).

In the purification of organic compounds, obtaining a detailed elution profile (Fig. 8) with accurate concentrations is not always necessary. The distribution of compounds in collected fractions can easily be visualized by TLC (Fig. 6b and c and 7d), which is sufficient to decide whether fractions should be combined or discarded. Nevertheless, the fraction collector proves to be a useful tool for quantitative experiments, especially in teaching activities with limited access to in-line analytical devices.

FRACTIONAL COLLECTION OF OUTPUT FROM FLOW REACTORS

Flow reactors resemble column chromatography in their continuous liquid output with variable composition. During the optimization of reactions in micro-/mesofluidic reactors, process parameters (c, T, p, flow rate, etc.) are measured under steady state, where these factors remain constant over time. As an alternative to in-line analysis, which can be a very costly option, fractional collection of the reactor output enables off-line measurement of concentrations in small time segments (Fig. 9), providing a comprehensive overview to the stability of the continuous flow process.

In the nitrosation of *N*-methyl amide 3g with N_2O_3 (Fig. 9a) using the same flow reactor for Fig. 6a,[34] the freshly generated N_2O_3 solution from reactor I and the substrate solution were mixed in equal flow rates (0.25 mL min^{-1}) in a T-mixer M2. The reaction proceeded quantitatively within 10 min in reactor II; the output from the flow system was collected in 0.5 mL fractions after the disappearance of the blue color at the outlet of reactor II. The concentrations of substrate 3g and product 4g in every fraction were determined by HPLC-UV and plotted in Fig. 9b. In all collected fractions, 3g was completely converted, and the concentration of 4g remained stable at 0.325 M for 14 min, which corresponds to a quantitative yield of 4g when the flow reactor is operating at the steady state.

In a published protocol for the synthesis of ketamine (6), the final step is the thermal rearrangement of imine (5) catalyzed by a solid acid, namely Montmorillonite K10.[38] The re-optimization of reaction conditions was carried out in the same packed bed flow reactor (Fig. 9c), which resembles the chromatographic setup in Fig. 5. A solution of 5 in degassed absolute ethanol (EtOH) was pumped through the bed of Montmorillonite granules (reactor III) packed in a stainless steel cartridge under high temperature and pressure conditions, and then collected in 20 fractions. The relative peak areas of 5, 6, and an impurity determined by HPLC-UV are plotted in Fig. 9d. Unlike the tubular reactor (Fig. 9A), a stable plateau of concentration did not appear, even though the volumes of the reaction mixture are the same (10 mL). The longitudinal diffusion[36] caused by the solid packing

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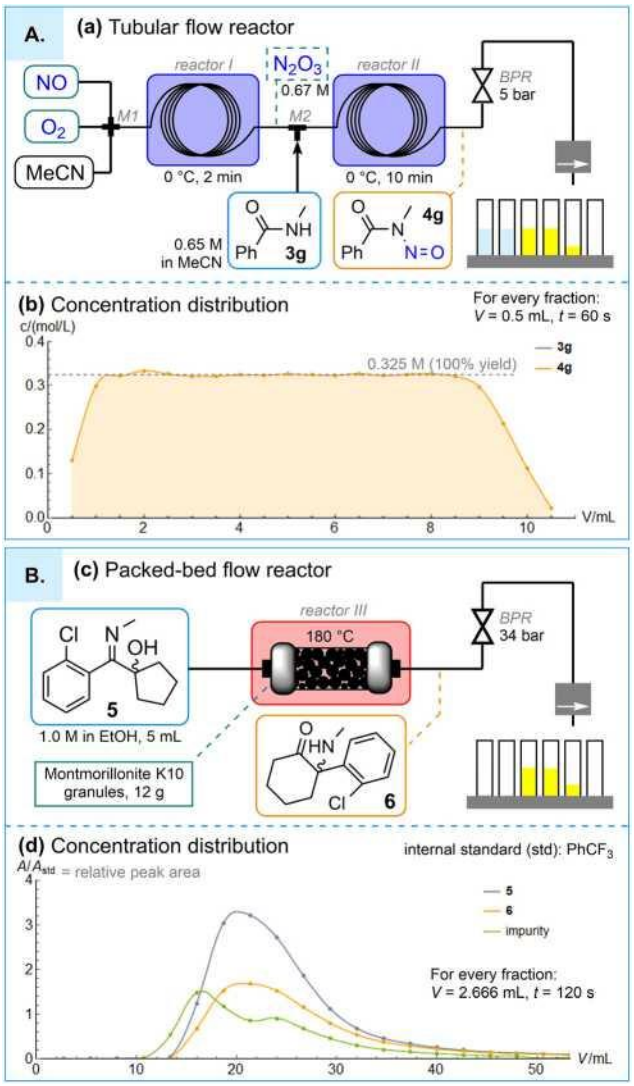
material required a longer time (therefore larger injection volume) for the output concentrations to stabilize.

Optimizing the residence time in flow often proceeds by varying the flow rates instead of adapting the internal reactor volume, provided that mixing efficiency is not affected. Increasing flow rates are associated with shorter residence times. Thus, in these experiments, the flow rate in every experiment is different. The frequent resetting of the time interval (*t* in eqn (7)) for the arm movement by editing and uploading the program between every experiment became quite laborious and cumbersome. To facilitate easy (re)setting of *t*, a potentiometer (R) is introduced in the upgraded version (Mk2).

Fig. 9 *Fractional collection of output from flow reactors operating under steady (A) and non-steady states (B).*



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The potentiometer's knob position is read by the microcontroller before executing every arm movement, allowing the real-time adjustment of the collection period (t). For the circuit and program, see the ESI.†

Conclusions

An open-source fraction collector was designed, constructed, and successfully applied in column chromatography in combination with a high speed (>10 mL min^{-1}) plunger pump. The setup is simple, cost effective, and easy to build, with all components available from commercial sources at reasonable prices. The underlying principles governing the structure and operation of the circular moving-arm fraction collector are explained and summarized, allowing widespread adoption and easy adaption for different vial numbers and sizes. Models for 3D printing of the arm and vial racks, the circuit and programs for the mechanics, as well as other construction details are provided for building the fraction collector that accommodates 30 vials (28 mm outer diameter).

Using this fraction collector, along with a single pump, tubing and valves from flow reactors, a simple chromatographic setup (Fig. 5) was assembled and used for diverse applications in organic synthesis. Examples of nitrosative reactions at the gram-scale have showcased the capability of this system to handle both isocratic and step gradient separations.

Additionally, as a standalone device, the fraction collector can be utilized in other types of continuous flow applications for off-line analysis of concentration change over time. To accommodate the frequent change in flow rate during the optimization of reaction time, real-time adjustment of the collection period is enabled with the integration of a potentiometer.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Dr. Yuesu Chen: conceptualization (lead); investigation (equal); writing – original draft preparation. Cassian Desmons: investigation (equal) – chemical experiments; data curation. Dr. Martin Cattoen: conceptualization – 3D model; investigation – 3D printing. Prof. Dr. Jean-Christophe M. Monbaliu: supervision; resources; writing – review and editing.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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