Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Combining Radial and Continuous Flow Synthesis to Optimize and Scale-up the Production of Medicines

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Supply chains of generic drugs revealed their vulnerability during the COVID-19 pandemic as in many markets essential medicines were not available in sufficient amounts due restrictions on international trade. Currently, drug production in batch cannot adapt rapidly to market demands. Flow chemistry is a valuable tool for on-demand production of active pharmaceutical ingredients (APIs). Here, we reveal a new concept to develop and produce APIs, where an automated synthesizer that works with discrete volumes of solutions is employed at the discovery stage to identify the optimal synthetic route and conditions before a commercially available continuous flow system is used for scale-up. This concept is illustrated by the synthesis of nifedipine and paracetamol, in short supply in Germany during the COVID-19 pandemic, and the local anesthetic lidocaine.

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List of medications in short supply in European countries due to the COVID-19 pandemic:

Shortage of paracetamol were reported in Germany,[1] Sweden,[2] Spain,[3] Romania,[4] Latvia,[5] Ireland,[6] Czech Republic,[7] and Belgium.[8]

Shortages of nifedipine were reported in Germany,[1] Sweden,[2] Romania[4] and Italy.[9]

Shortages of Lidocaine were reported in Sweden.[2]

Materials and methods:

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Varian 400 MHz, Bruker 400 MHz, Varian, 600 MHz or Bruker 700 MHz spectrometer. Chemical shifts were referenced using the residual solvent peak as an internal reference with the exception of nifedipne where the residual peak of chloroform was overlapping with the compound signals ($CDCl_3$: 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; DMSO d_6: 2.50 ppm ^{1}H NMR, 39.52 ppm ^{13}C NMR; CD_3OD 3.31 ppm ^{1}H NMR, 49.00 ppm ^{13}C NMR). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), tt (triplet of triplets).

For continuous flow processes a Vapourtec R2 pump module and R4 heating modules were used, together with an HPLC pump (KNAUER, Azura P 4.1S).

The same Vapourtec R4 heating module is used as heated reactor in the radial synthesizer.

A scheme of the radial synthesizer and its components is given in Figure S1 and Figure S2. For detailed information about the radial synthesizer see reference 7 of the manuscript.[10]

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[1] List of medications in short supply in Germany during the COVID-19 pandemic: https://www.gelbe-liste.de/lieferengpaesse/lieferengpaesse-medikamente

[2] List of medications in short supply in Sweden during the COVID-19 pandemic: https://docetp.mpa.se/LMF/Reports/Restnoteringar.xlsx

[3] List of medications in short supply in Spain during the COVID-19 pandemic: https://www.google.com/search?client=firefox-b-e&q=listadesabastecimiento

[4] List of medications in short supply in Romania during the COVID-19 pandemic: https://www.anm.ro/_/DISCONTINUITATE%20MEDICAMENTE/30.10.2020%20Notificari%20Sunset%20pt.postat%20incepand%20cu%20luna%20IUNIE%202016.pdf

[5] List of medications in short supply in Latvia during the COVID-19 pandemic: https://www.zva.gov.lv/lv/zalu-piegades-partraukumu-parvaldiba-latvija?lang=lv&q=nifed

[6] List of medications in short supply in Ireland during the COVID-19 pandemic: https://www.hpra.ie/homepage/medicines/medicines-information/medicines-shortages

[7] List of medications in short supply in Czech republic during the COVID-19 pandemic: http://www.sukl.cz/modules/marketreport/index.php?h=index&a=search&data%5BNAME%5D=parace&data%5Bcode%5D=&data%5Breport_type%5D=&data%5Breport_reimb%5D=&data%5Breport_from%5D=&data%5Breport_to%5D=&data%5Bdate_from%5D=&data%5Bdate_to%5D=&sort=date_report&order=DESC&x=0&y=0

[8] List of medications in short supply in Belgium during the COVID-19 pandemic: https://pharmastatus.be/

[9] List of medications in short supply in Italy during the COVID-19 pandemic: https://www.aifa.gov.it/documents/20142/847339/elenco_medicinali_carenti.csv/34b6d134-14b5-ac8c-c147-b94d4ff7701a

[10] S. Chatterjee, M. Guidi, P. H. Seeberger, K. Gilmore *Nature* **2020**, 579, 379-384.

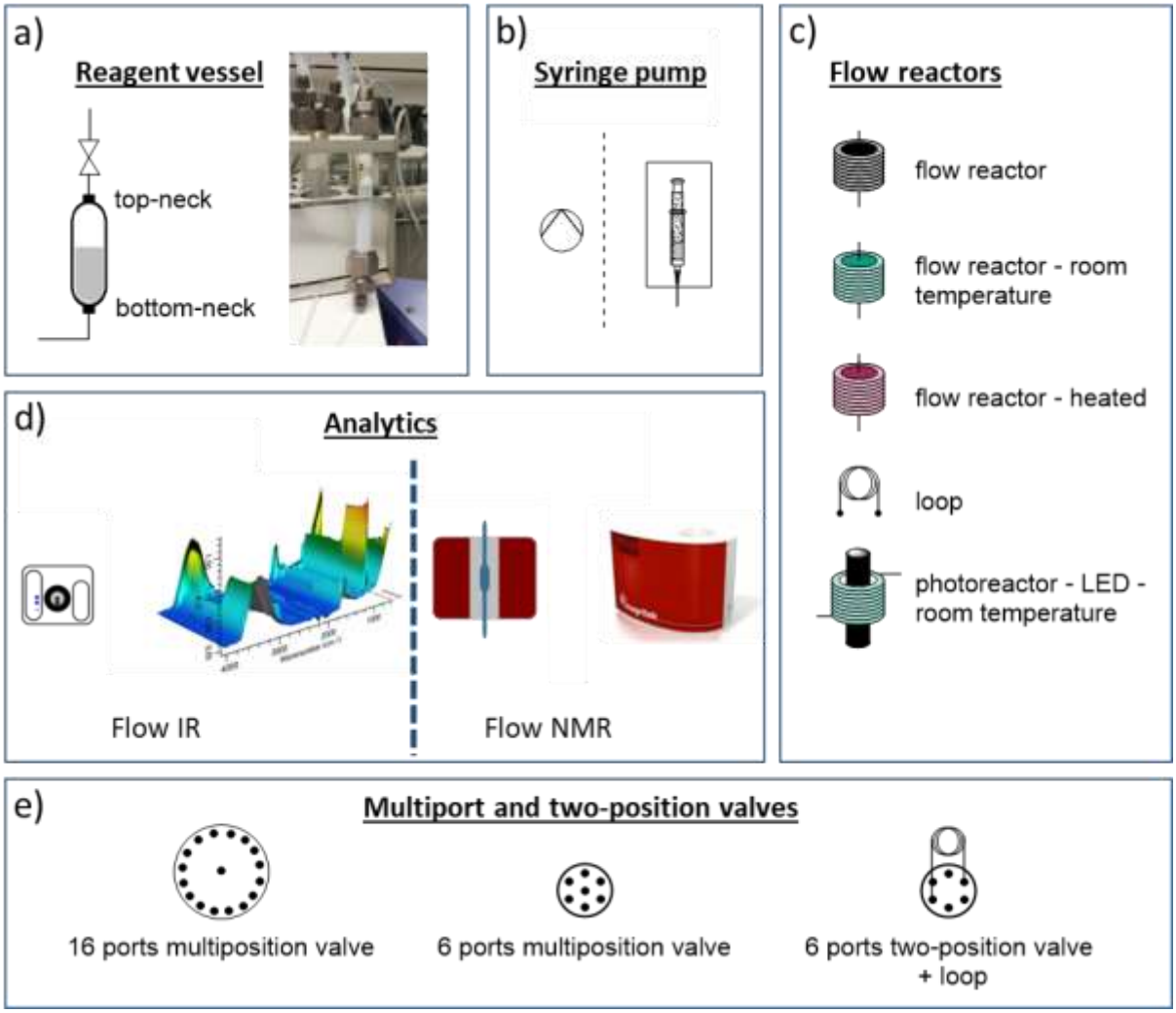


Figure S1: Components of the radial synthesizer.

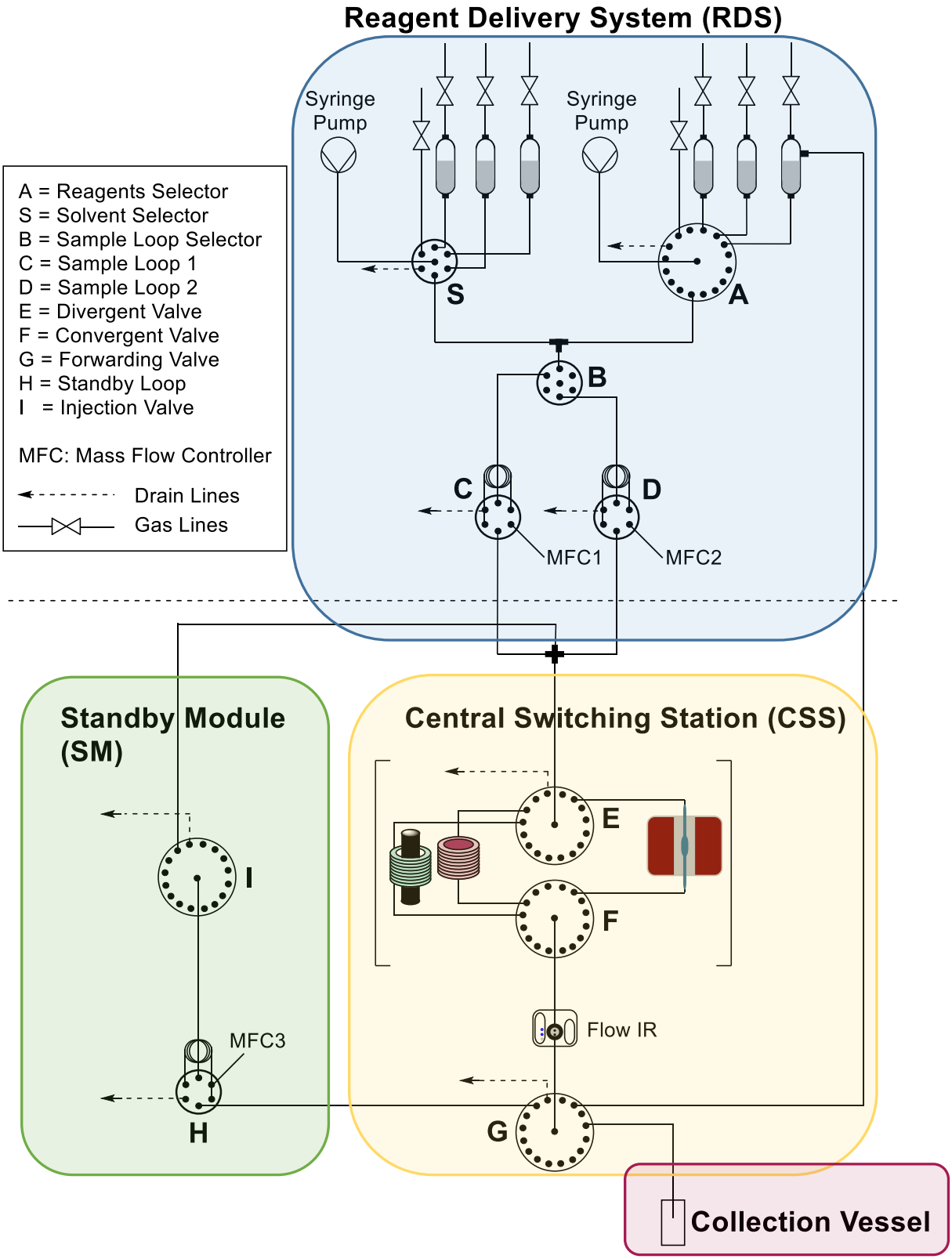


Figure S2: The Radial Synthesizer is composed of three main blocks: the reagents delivery system (RDS), the central switching station (CCS) and the standby module (SM).

Reagent solutions are stored in pressurized vessels within the reagent delivery system (RDS). All the tests are preformed using 0.5 mL sample loops (on valve C and D) and 0.5 mL standby loop (on valve H). The reactor is a 10 mL coil heated by a Vapourtec R4 heating module. Intermediates are stored either in a 0.5 mL loop within the standby module (valve H) or in pressurized vessels within the reagents delivery system (RDS). Final products are collected in either pressurized or unpressurized vessels (Figure S2).

Six pathways of solution flow through the instrument were identified, defined by the starting location of the reagents and their destination (Figure S3). **R-R** (reagent delivery system – reagent delivery system), **R-S** (reagent delivery system – standby module), **R-C** (reagent delivery system - collection), **S-R** (standby module – reagent delivery system), **S-S** (standby module – standby module) and **S-C** (standby module – collection).

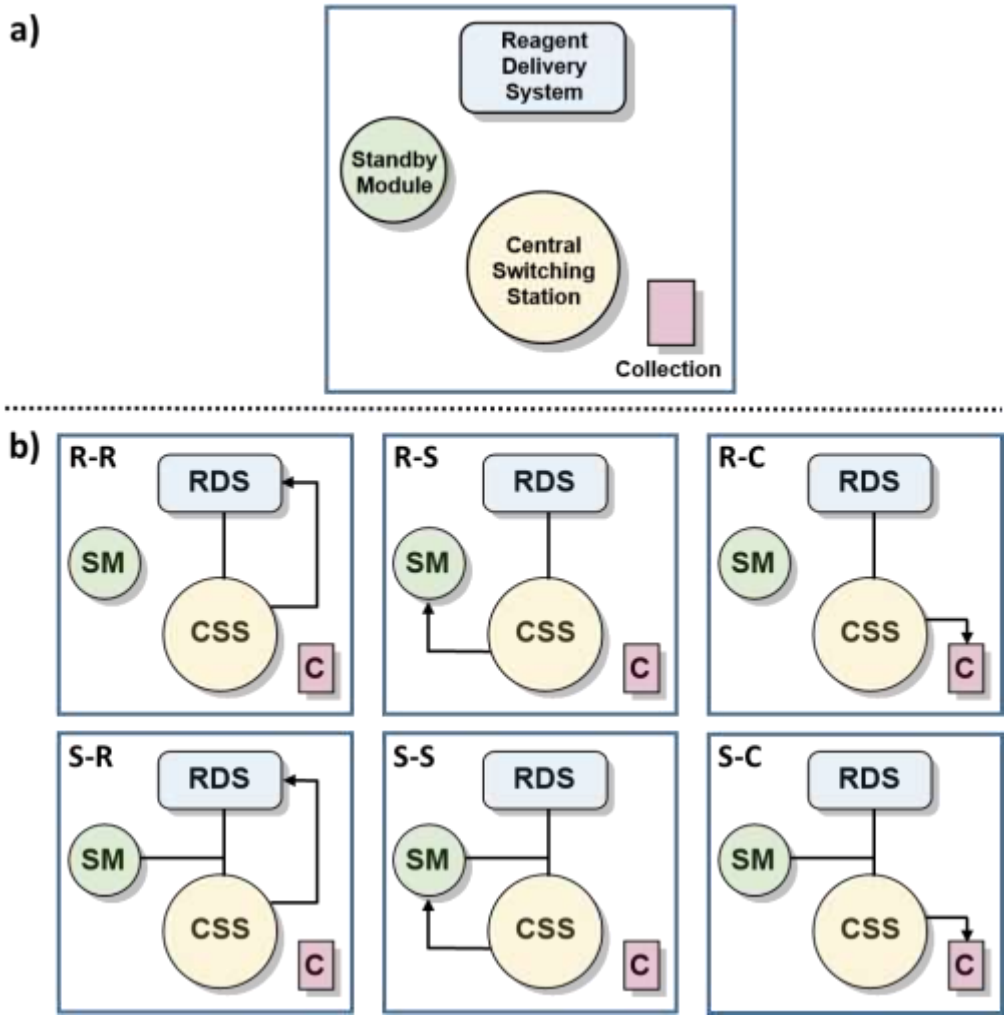
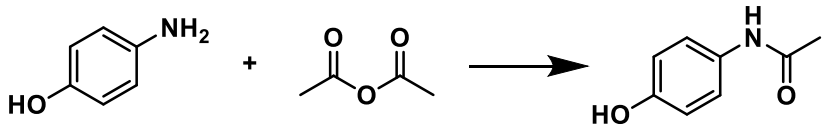


Figure S3: a) The radial synthesizer´s main sections: reagent delivery system (RDS), central switching station (CSS), standby module (SM) and collection vessels (C). b) Six pathways of solution flow through the instrument are described by the starting location of the reagents and their destination. For example, **R–C** refers to a solution starting in the **R**DS and ending in the **C**ollection vessel.

Radial synthesis of paracetamol

The one-step synthesis of paracetamol (Scheme S1) was optimized using the **R-C** pathway in the radial synthesizer (Figure S4).



4 **5** **1**

Scheme S1: Synthesis of paracetamol **1** via acetylation of 4-aminophenol **4**

Solutions of para-aminophenol **4** and acetic anhydride **5** in different solvents (or as neat reagents) were prepared and loaded into the reagent delivery system of the radial synthesizer and different temperatures and residence times were screened for each combination (Table S1).

The greenest process for the acetylation of para-aminophenol uses water as a solvent. However, para-aminophenol (**4**) has a very poor solubility in water, preventing the use of this solvent for the flow process. On the contrary, **4** is solubilized instantly when acetic anhydride (**5**) is added to the mixture. After screening different solvents we found that acetic acid is also a good solvent for **4**. Attempting to keep water as the main solvent, we investigated the solubility of **4** in a mixture of water/acetic acid and we found that one millimole of **4** is soluble in a 0.5 mL mixture of water and acetic acid 4:1. Acetic anhydride (**5**), on the other hand, is a liquid reagent immiscible with water, we then decided to use it neat.

Screening of different solvents and residence times revealed that full conversion of **4** to **1** is achieved in just five minutes at room temperature with no precipitation observed when using neat acetic anhydride (**5**) (Table S1 entry 9). A rapid screening of the reaction stoichiometry revealed that this reaction works at the same rate when fewer equivalents of acetic anhydride (**5**) are employed. Reducing the amount of **5**, that is a good solvent for paracetamol (**1**), results in direct crystallization of the product. Crystallization starts after ten minutes from addition when working with three equivalents of **5** (Table S1 entry 4).

Table S1: Conditions screening for acetylation of para-aminophenol (**4**)

Entry	Conc. **4** (M)	Solvent of **4**	Equiv. **5**	Solvent of **5**	T (° C)	t (min)	Yield. %
1	2	H_2O	3	-	60	5	93 [a]
2	2	H_2O	3	-	R.T.	5	94 [a]
3	2	H_2O	3	H_2O	-	-	- [a]
4	2	H_2O/AcOH 4:1	3	-	R.T.	5	95 [b]
5	2	H_2O/AcOH 4:1	3	DMF	60	5	(50) [c]
6	2	H_2O/AcOH 4:1	3	*i*PrOH	60	30	(>99) [c]
7	2	H_2O/AcOH 4:1	3	*i*PrOH	R.T.	30	(62) [c]
8	2	H_2O/AcOH 4:1	5 (neat)	-	60	5	(>99) [c]
9	2	H_2O/AcOH 4:1	5 (neat)	-	R.T.	5	>99 [c]

[a] Results for batch test, due to poor solubility of **4** in H_2O and/or lack of miscibility of **5** with H_2O, this test couldn´t be carried out in the radial synthesizer. **4** is promptly solubilized upon addition of **5** and the product **1** precipitates after less than 10 minutes after reaction completion. The reported yield is the crystallized yield after 1 h stirring at room T. [b] Test in radial synthesizer. The product **1** precipitates after less than 10 minutes from collection. The reported yield is the crystallized yield after 1 h stirring at room temperature upon collection in unpressurized vessel. [c] Test in radial synthesizer. The product **1** does not precipitate. The results are reported as conversion (in parenthesis) calculated from the ^{1}H NMR of the crude, by the ratio of the integrated area of the aromatic peaks of **4** to the total area of aromatic peaks of **4** + **1**.

Radial synthesizer pathway for synthesis of paracetamol 1

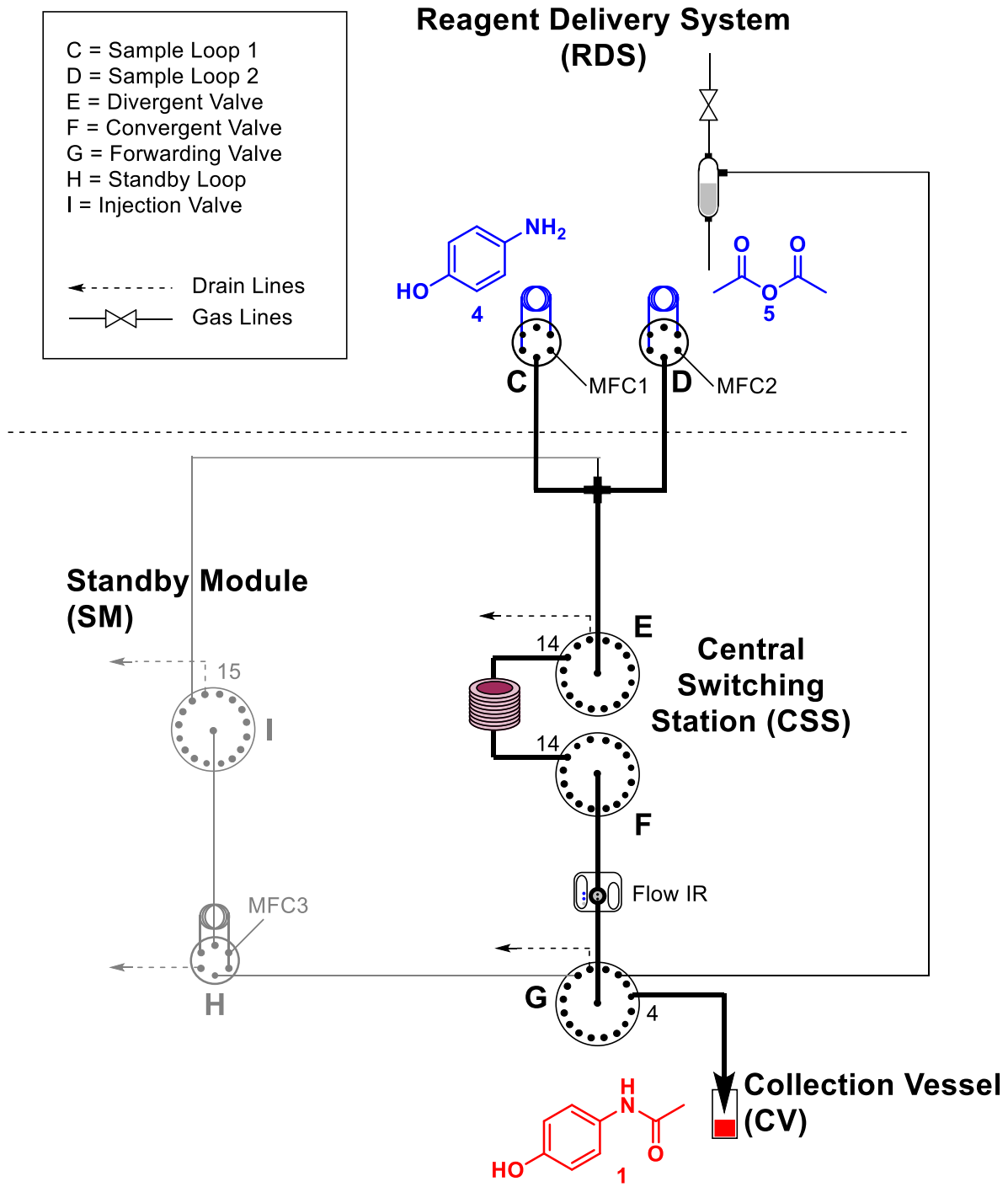


Figure S4: The synthesis of paracetamol was optimized using the **R-C** pathway in the radial synthesizer. Reagents are delivered by the RDS, pass through a heated or room temperature coil and the product is collected in a non-pressurized collection vessel (CV).

Scale-up of synthesis of paracetamol

Scale-up of this process was performed under continuous flow conditions using a Vapourtec R2 pump module, feeding a 2 M solution of **4** in water/acetic acid 4:1 from pump A and neat acetic anhydride (**5**) from pump B (Figure S5). When a 10 mL coil reactor was used, the two feeds were set respectively at 1.5 and 0.45 mL/min and the resulting solution was collected upon reaction in a flask and stirred at room temperature for 1 h. After running the system for 15 minutes we achieved 6.36 g of crystallized **1** (94% crystallization yield).

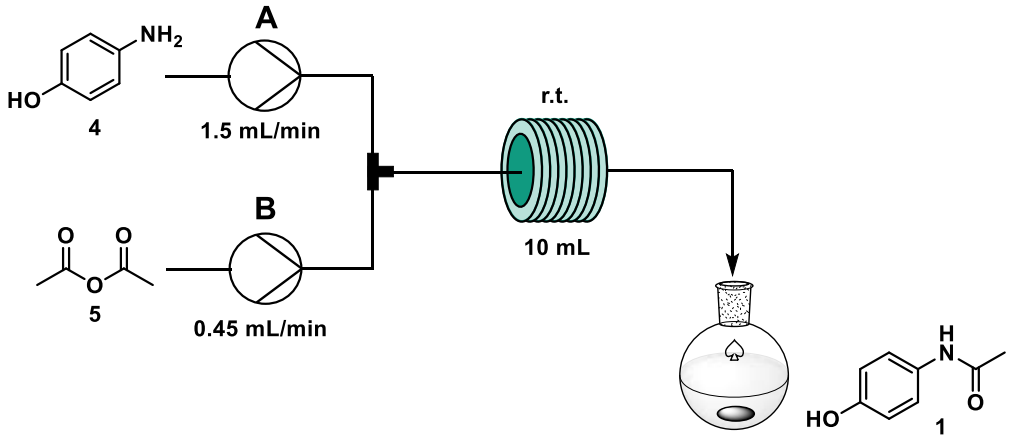


Figure S5: Continuous flow synthesis of paracetamol followed by batch crystallization.

Since crystallization happens spontaneously after reaction completion, without the need for any antisolvent addition and/or heating/cooling operations, we envisioned the possibility of telescoping an in-line flow-crystallization module. This module was based on the SMBR (serial micro-batch reactors) technique[11] that generates a segmented flow, spaced by nitrogen, which can carry slurries minimizing clogging phenomena that generally affect solid-liquid systems in flow.

The flow crystallization module was built by wrapping a 20 mL PFA coil (i.d. 1.6 mm) around a 1 L glass bottle which can be used to control the temperature by filling it with an appropriate liquid/mixture and heating it up or cooling it down. Connection of one end of the crystallization coil with the outlet of our reactor and a nitrogen gas feed through a Tee junction generated the segmented flow (Figure S6).

In order to allow longer residence times in the crystallization module the 10 mL coil reactor was replaced with a 1.5 mL one and flow rates were dropped at 0.25 mL/min and 0.075 mL/min respectively for pump A and pump B. N_2 flow rate was set at 0.5 mL/min. Crystallization occurs in droplets and the slurry exiting the telescoped process is directly filtered to give pure crystals of paracetamol. Collecting for 15 minutes on the filter we achieved 634 mg of paracetamol (56%) after a 30 minutes residence time in the crystallization module at 25 °C.

Attempts to increase the crystallization yield were made. Using a lower flow rate to achieve a longer residence time in the 20 mL crystallization module was not possible due to the limits of the Vapourtec pumps (minimum flow rate is 0.05 mL/min).

Resizing the crystallization module from 20 to 40 mL in order to achieve a residence time of 1 h (comparable to batch crystallization process) raised the crystallization yield to 93%, although after 3 minutes of collection a destabilization of the segmented flow, due to reactor fouling, was observed.

Lowering the temperature from 25 to 5 °C by filling the glass bottle with water and ice did not lead to a significant increase in the yield.

[11] B. Pieber, M. Shalom, M. Antonietti, P. H. Seeberger, K. Gilmore *Angew. Chem. Int. Ed.* **2018**, 57, 9976 –9979.

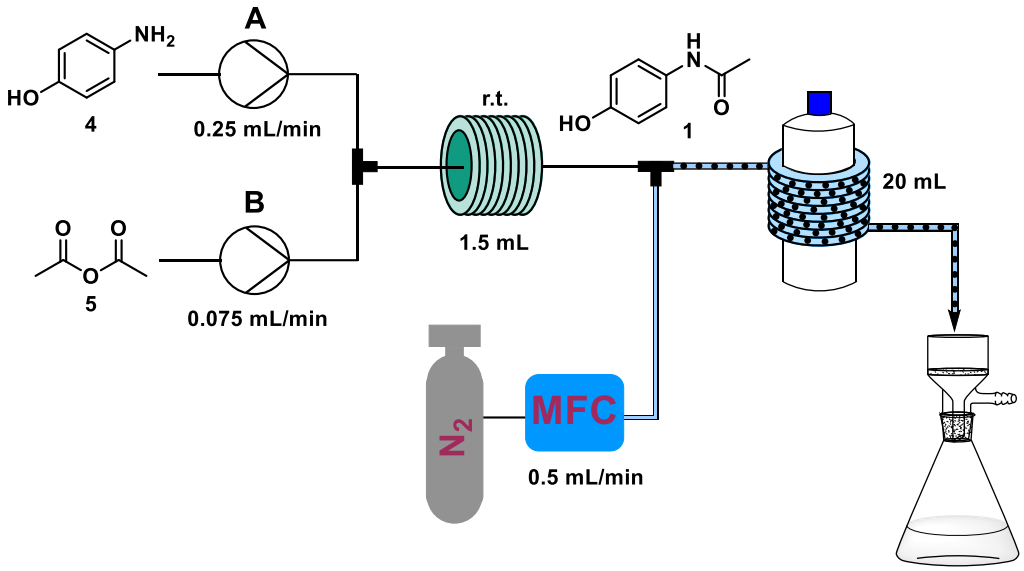


Figure S6: Continuous flow synthesis of paracetamol followed by flow crystallization and filtration.

Considering that the productivity of a process is dependent on the flow rate applied, the flow synthesis followed by batch crystallization (Figure S5) was more efficient, as it allows for the preparation of 25.6 g/h of paracetamol (1229 doses/day). At its best (not considering clogging issues), the flow crystallization could yield 4 g/h of paracetamol, due to the lower flow rate necessary to reach the 1 hour residence time in the crystallization module. For the scale up of the synthesis of paracetamol, we therefore opted for the setup described in Figure S5.

Calculation for productivity:

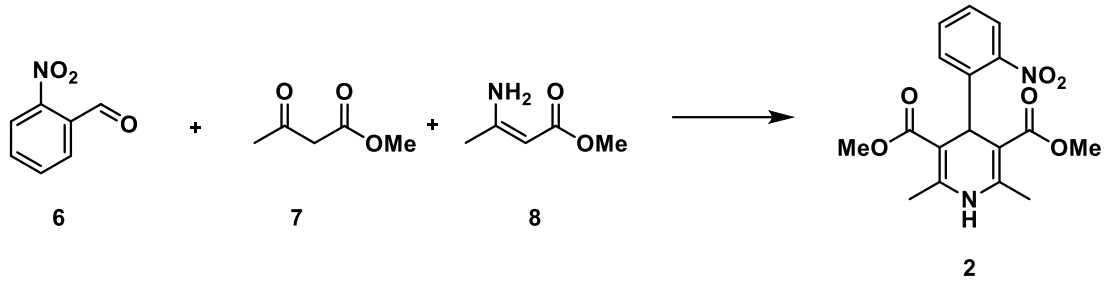
[**4**] (mmol mL^{-1}) * flow rate A (mL min^{-1}) * MM **1** (mg $mmol^{-1}$) * yield (%) * 60 min =

= 2 * 1.5 * 151.163 * 0.94 * 60 = 25.6 g/h

Dose of **1** = 500 mg/tablet[1]

25.6 g/h * 24 h / 0.5 g = 1229 doses/day

Radial synthesis of nifedipine



Scheme S2: Synthesis of nifedipine (**2**) from 2-nitrobenzaldehyde (**6**), methyl acetoacetate (**7**) and methyl 3-aminocrotonate (**8**).

Solutions of 2-nitrobenzaldehyde **6** (0.5 M) and a solution of methyl acetoacetate **7** (1.1 equiv.) and methyl 3-aminocrotonate **8** (1 equiv.) in alcohol solvents were prepared and loaded into the reagent delivery system of the radial synthesizer. The effects of temperature, and residence time on the conversion of **6** were screened using the pathway **R-C** in the synthesizer[10].

This reaction is generally carried out overnight in batch, and the temperature is limited by the boiling point of the solvent in use (ethanol or methanol). Aiming at accelerating the reaction, temperatures from 90 °C to 150 °C and a residence time range between 5 minutes and 3 hours were screened. Stop flow conditions were applied for the longer residence times (stop flow conditions were applied for the longer residence times).

Reaction time decreased as expected with increasing temperature and the best conversion was found employing ethanol as solvent (60 minutes residence time at 140 °C). However, a high amount of side product was generated at this temperature, probably due to transesterification of **2** by ethanol and only a 30% yield of the desired product was obtained (Table S2 entry 2). This issue was solved by changing the solvent from ethanol to methanol (entry 6). After collection, the solvent was evaporated, and the crude was analyzed via ^{1}H NMR. NMR yield (68%) was determined for this product via ^{1}H NMR vs 2,2,6,6-tetramethylpiperidine.

Table S2: Conditions screening for synthesis of nifedipine **2**.[a]

Entry	Conc. **6** (M)	Solvent	T (°C)	t (min)	Conversion of **6**	Yield %[b]
1	0.5	EtOH	140	5	45	<5
2	0.5	EtOH	140	60	>95	30
3	0.5	MeOH	90	60	71	20
4	0.5	MeOH	110	60	74	35
5	0.5	MeOH	130	60	95	55
6	0.5	MeOH	140	60	96	66
7	0.5	MeOH	150	60	97	68

[a] Conditions screened using the pathway **R-C** pathway on the synthesizer; The reaction was monitored via ^{1}H NMR. [b] Yield determined by ^{1}H NMR using 2,2,6,6-tetramethylpiperidine as internal standard.

Radial synthesizer pathway for synthesis of nifedipine 2

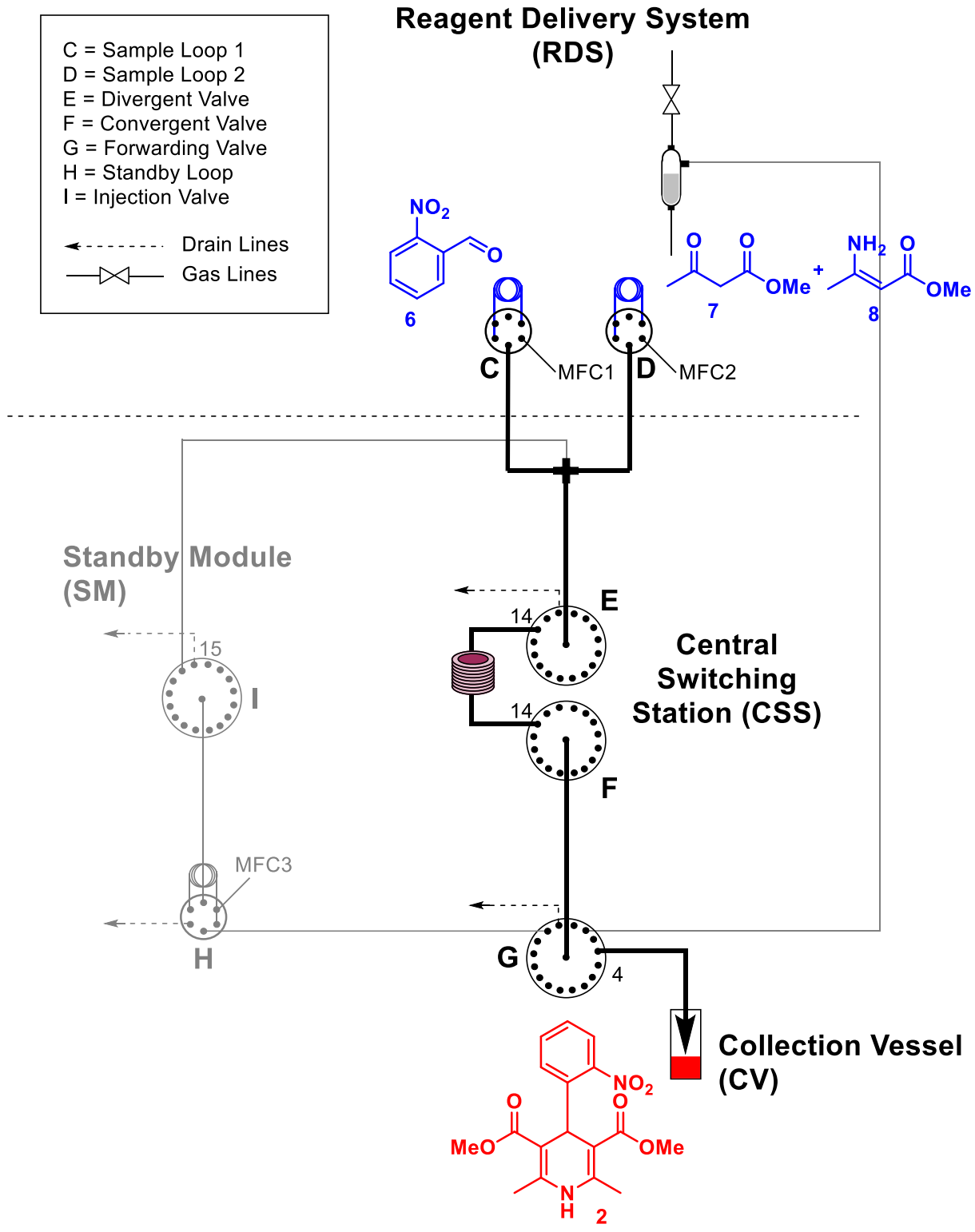


Figure S7: Radial synthesis of nifedipine (**R-C** pathway).

Scale-up of synthesis of nifedipine:

For the scale up of this process a Vapourtec R2 pump module was used to feed a 0.5 M solution (25 mL, 12.5 mmol) of **6, 7** (1 equiv.), and **8** (1.1 equiv.) in methanol in a 10 mL heated coil reactor (150°C) at 0.167 mL/min (heating module: Vapourtec R4) (Figure S8**Error! Reference source not found.**). The starting material was fully consumed and crude NMR showed clean formation of the desired product **2** within 60 minutes. The system was run for 150 minutes, collecting 25 mL of crude solution. The volume of the crude solution was reduced by evaporation to 10~15 mL and crystallization of nifedipine was achieved by slowly adding 15 mL of H_2O to the crude mixture and stirring for 1 hour. We isolated 3.06 g of crystallized nifedipine (**2**) (71% yield).

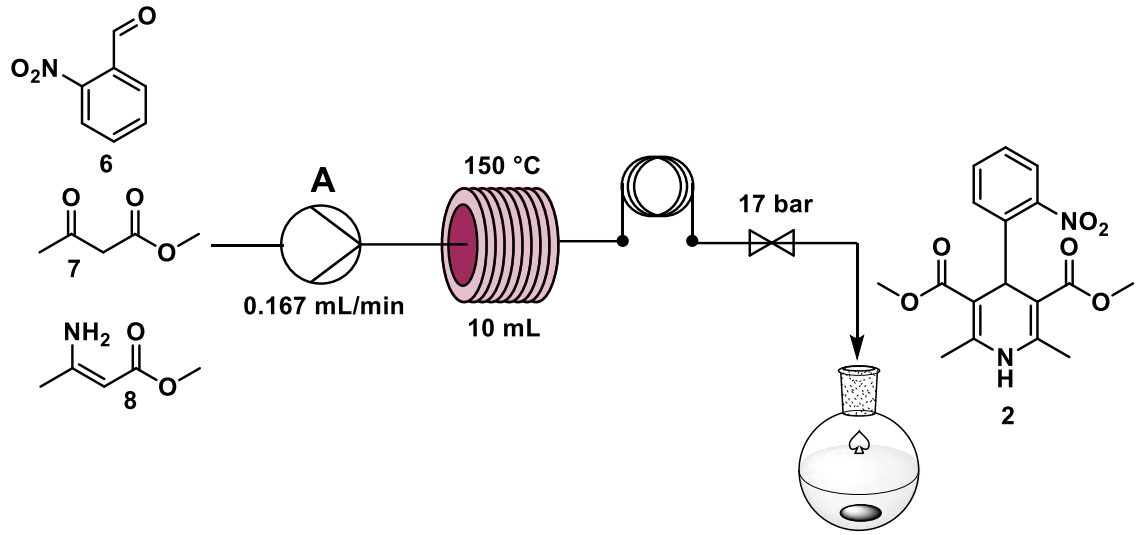


Figure S8: Continuous flow synthesis of nifedipine.

Higher temperatures were screened for this continuous flow process, but despite full conversion of the starting material was shown, the yield of nifedipine **3** dropped when increasing temperature over 150 °C (Table **S3** and Figure S9).

This confirmed that optimal conditions were those of Table S2, entry 7 found with the radial synthesizer.

Calculation for productivity:

[**6**] (mmol mL^{-1}) * flow rate A (mL min^{-1}) * MM **2** (mg $mmol^{-1}$) * yield (%) * 60 min =

= 0.5 * 0.167 * 346.335 * 0.71 * 60 = 1.2 g/h

Dosage of **2** = 10 mg/tablet [1]

1.2 g/h * 24 h / 0.010 g = 2880 doses/day

Table S3: Temperature screening for the synthesis of nifedipine **2**.

Entry	Conc. **6** (M)	Solvent	T (°C)	t (min)	Conversion of **6**	Yield %[b]
1	0.5	EtOH	140	5	45	<5
2	0.5	EtOH	140	60	>95	30
3	0.5	MeOH	90	60	71	20
4[a]	0.5	MeOH	100	60	71	23
5	0.5	MeOH	110	60	74	35
6[a]	0.5	MeOH	120	60	90	43
7	0.5	MeOH	130	60	95	55
8	0.5	MeOH	140	60	96	66
9	0.5	MeOH	150	60	97	68
10[a]	0.5	MeOH	170	60	98	55

11[a]	0.5	MeOH	190	60	99	38
12[a]	0.3	MeOH	140	90	95	57
13[a]	0.3	MeOH	150	90	94	61

[a] New conditions, tested only under continuous flow conditions. Screening includes new temperature values and longer residence times. The reaction was monitored via ^{1}H NMR. [b] Yield determined by ^{1}H NMR using 2,2,6,6-tetramethylpiperidine as internal standard.

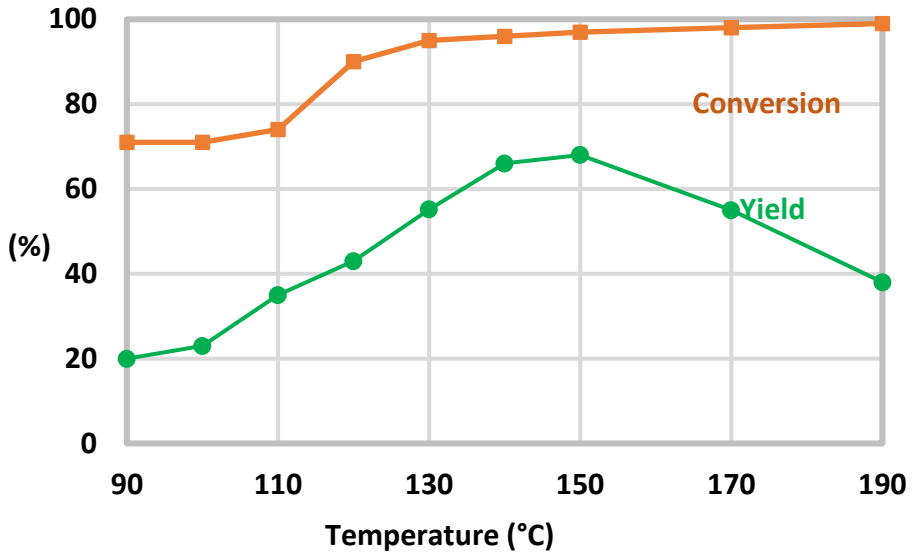
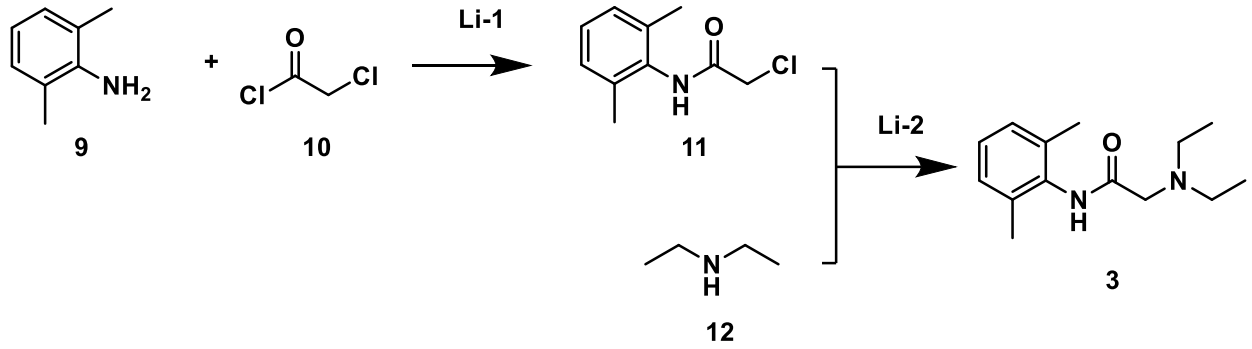


Figure S9: Reaction results by temperature change at 0.5M in Methanol, nifedipine (●, green), conversion (■, orange).

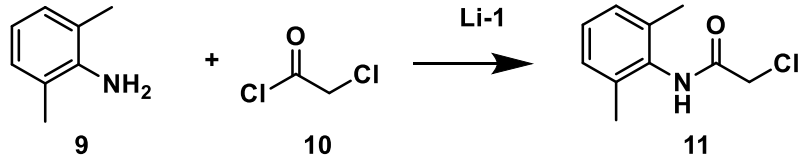
Radial Synthesis of Lidocaine:

Each step was individually optimized and then linked with the others for the final process optimization. The following acronyms are used to refer to the individual reactions in the process: Step 1 = Li-1, Step 2 = Li-2 (Scheme S3).



Scheme S3: Synthesis of Lidocaine **3** (Li-1 + Li-2).

Optimization of Li-1:



Scheme S4: Synthesis of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide **11** (Li-1) from 2,6-dimethylaniline **9** and 2-chloroacetyl chloride **10**.

Solutions of 2,6-dimethylaniline **9** and chloroacetyl chloride **10** in different solvents were prepared and loaded into the reagent delivery system of the radial synthesizer (Table S4). A quick screening of conditions was performed using the **R-C** pathway, and we could assess that Li-1 is highly reproducible in short reaction times at room temperature (Table S4, entry 3).

Table S4: Screening of conditions for step Li-1.

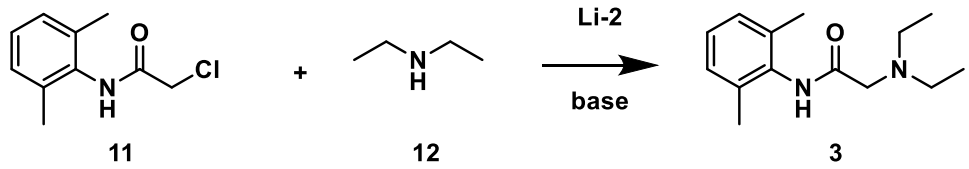
Entry	Conc. **9** (M)	Solvent	Equiv. **10**	T (° C)	t (min)	Yield %[a]
1[b]	1	NMP	1.15	120	20	-[c]
2	1	NMP	1.15	R.T	20	95
3	1	NMP	1.15	R.T.	10	95

[a] Yield determined by weighting the solid intermediate **11**, crystallized upon addition of H_2O to the crude mixture leaving the synthesizer (1 mL of H_2O in 1 mL sample of reaction mixture). [b] Conditions reproduced from literature[12,13]. [c] No crystallization occurred.

[12] C. W. Coley, A.; D. A. Thomas III, J. A. M. Lummiss, J. N. Jaworski, C. P. Breen, V. Schultz, et al. *Science* **2019** 365, 6453, DOI: 10.1126/science.aax1566.

[13] A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J-C. M. Monbaliu, et al. *Science* **2016**, 352, 6281, 61-67.

Optimization of Li-2:



11 12 3

Scheme S5: Synthesis of Lidocaine **3** via substitution of diethylamine **12** on 2-chloro-N-(2,6-dimethylphenyl)acetamide **11**.

The optimization of Li-2 was performed by generating intermediate **11** as reported in Table S4 entry 5, using the **R-S** pathway (Figure S10). Solutions of diethylamine **12** and KOH dissolved in H_2O and methanol (1:1) were loaded in the RDS of the radial synthesizer. Conditions for Li-2 were screened (Table S5) using the **S-C** pathway in the radial synthesizer (Figure S11) and best results were achieved at 130 °C for 20 minutes.

Crude reaction mixture was extracted with hexane and NH_4Cl/NaCl (1:1) and the residue, after evaporation of the solvent, was dissolved in $CDCl_3$ and analyzed via ^1H NMR.

Crystallization via formation of lidocaine HCl salt: After extraction with NH_4Cl/NaCl (1:1), the organic layers were evaporated and the residue was re-dissolved in 5 mL of n-hexane. 0.2 mL of HCl solution in Et_2O 2 N (2 equiv.) were slowly added. The slurry generated was stirred for 1 h and then filtered and washed with n-hexane, achieving 42.0 mg of Lidocaine HCl (yield: 62%). Crystals of Lidocaine HCl were dissolved in $CDCl_3$ and analyzed via ^1H NMR.

Table S5: Screening of conditions for step Li-2

Entry	Conc. **11** (M)[a]	Equiv. **12**[b]	Equiv. of KOH	T (°C)	t	Conv. (%)[c]	Yield (%)
1e	0.5	3	1.2	60	20 h	97	81[d]
2	0.5	3	1.2	60	3.5 h	85	71[d]
3	0.5	3	1.2	60	20 min	-	
4	0.5	Neat (15)	1.2	60	20 min	-	
5	0.5	3	1.2	130	5 min	79	52[d]
6	0.5	3	1.2	130	20 min	93	62[f]

[a] The concentration of **11** is calculated assuming a 100 % yield in step Li-1, since the second step Li-2 is performed directly from the crude mixture of Li-1. [b] KOH and **12** were both dissolved in H_2O/MeOH 1:1, then added simultaneously to the crude mixture of Li-1 using the **S-C** path. [c] Conversion was estimated via ^1H NMR by the ratio between the integrated area of the CH_2 peak of **3** (3.29 ppm) and the total area of CH_2 peaks of **3** + **11** (4.25 ppm) [d] Isolated yield after extraction with hexane and evaporation. Yield is calculated from the weight of the residue and the conversion. [e] Test performed in batch. [f] Yield calculated on the weight of the crystallized product as lidocaine hydrochloride salt.

Radial synthesizer pathways for synthesis of lidocaine 3

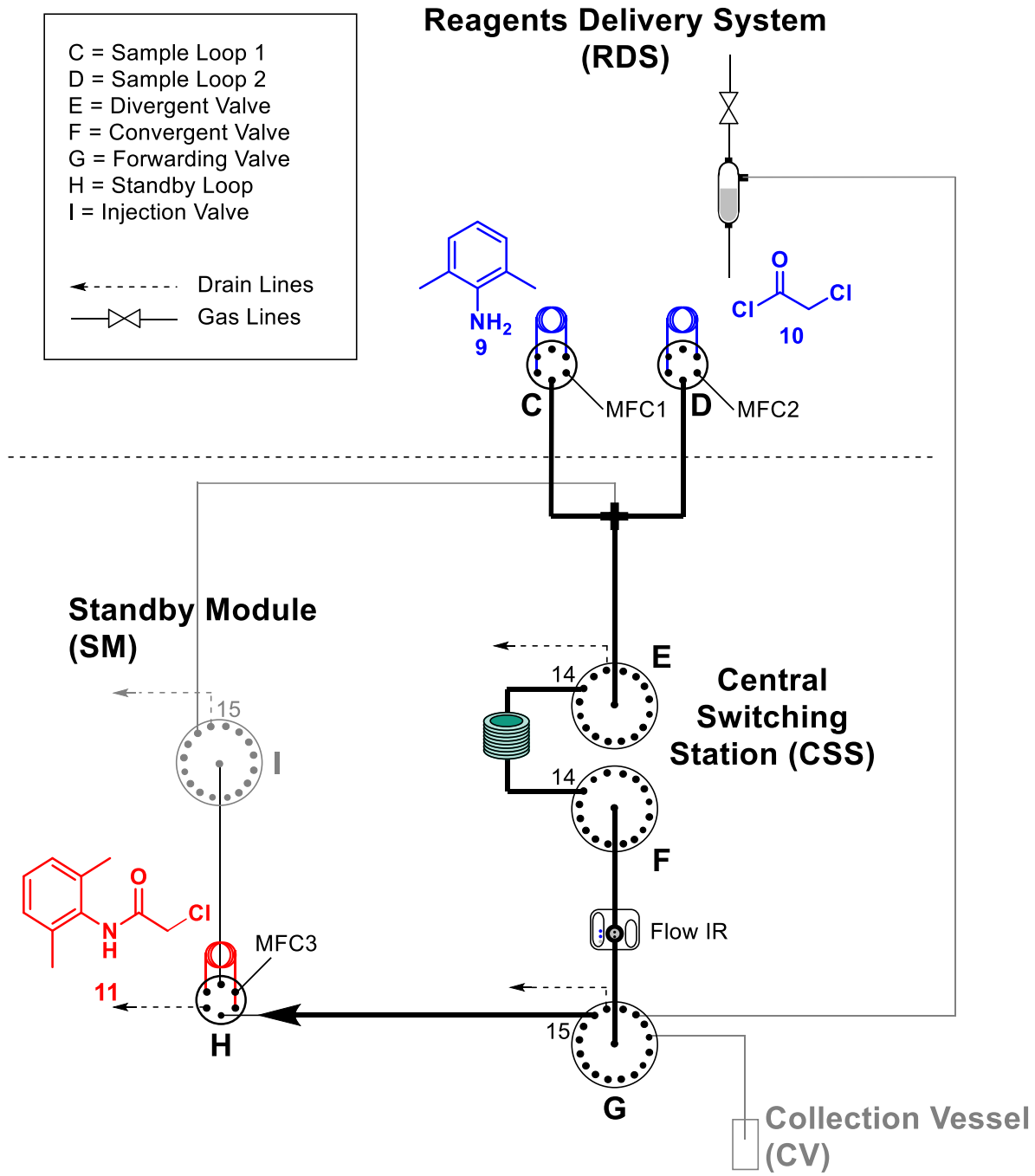


Figure S10: First step of the radial synthesis of Lidocaine (Li-1) performed using the **R-S** pathway.

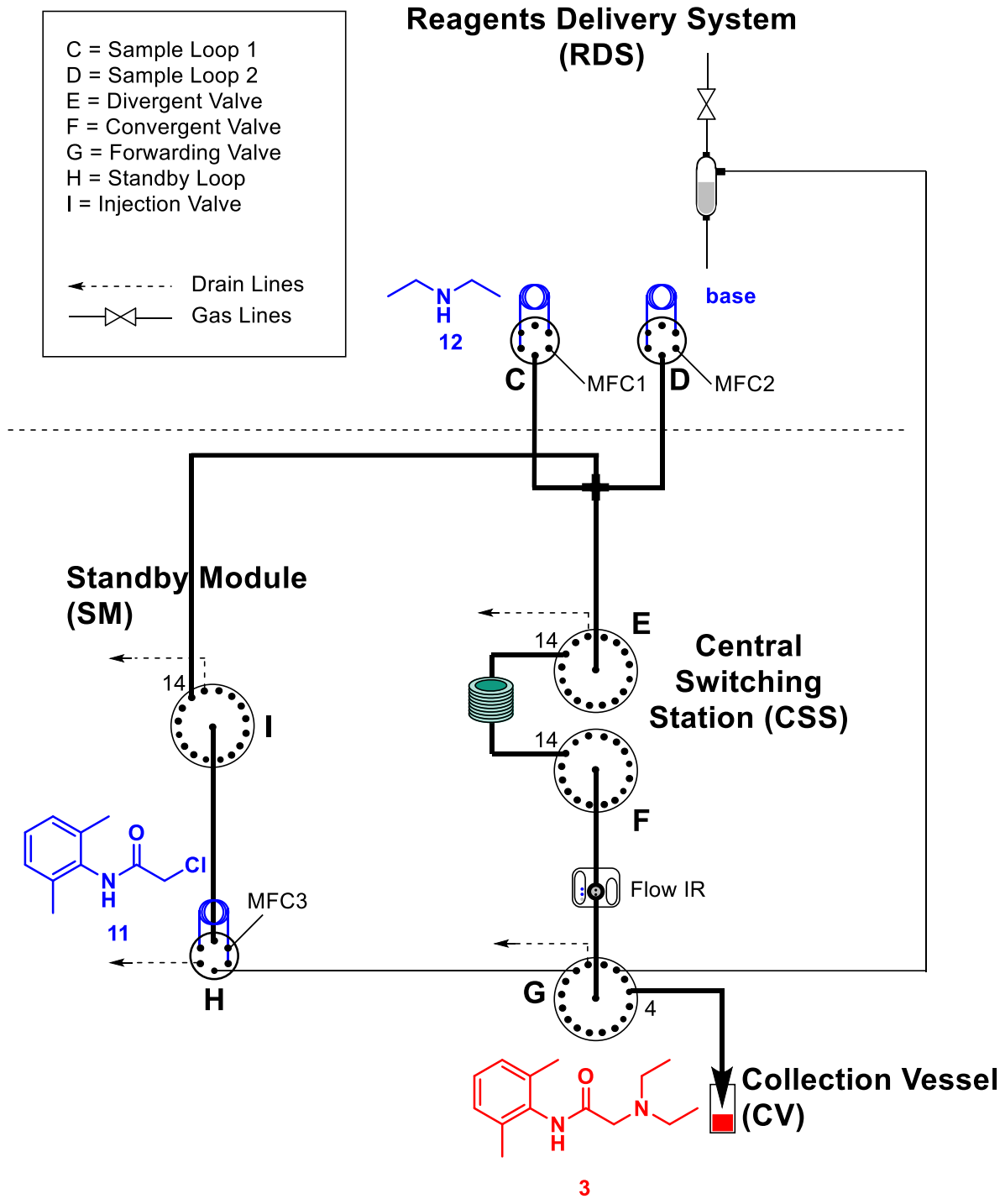


Figure S11: Second step of the radial synthesis of Lidocaine (Li-2) performed using the **S-C** pathway.

Scale-up of synthesis of lidocaine

The flow synthesis of lidocaine was scaled up using a Vapourtec R2 pump module and a 1.6 mL room temperature coil for the first step. Solutions of **9** (1 M in NMP) and **10** (1.15 M in NMP) were pumped at 0.08 mL/min each to achieve a 10-minute residence time. The second step was telescoped pumping a solution of diethylamine **12** (0.75 M) and KOH (0.3 M) in methanol/water 1:1 at 0.34 mL/min (total flow rate 0.5 mL/min) through a 10 mL coil heated at 130 °C by a Vapourtec R4 module (20 min residence time) (Figure S12).

The crude reaction mixture exiting the system was collected for 90 minutes (45 mL) and was extracted with hexane and NH_4Cl/NaCl (1:1). The organic layers were evaporated and the residue re-dissolved in 10 mL of hexane. 7.2 mL of HCl solution in Et_2O 2 N (2 equiv.) were slowly added. The slurry generated was stirred for 1 h and then filtered and washed with n-hexane, achieving 1.15 g of lidocaine HCl (yield: 59%). Crystals of lidocaine HCl were dissolved in $CDCl_3$ and analyzed via ^1H NMR.

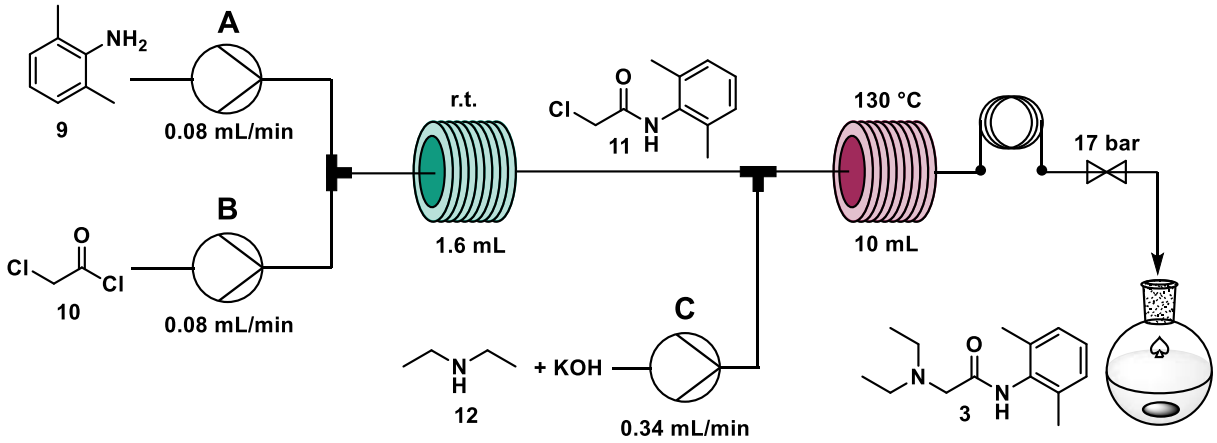


Figure S12: Continuous flow synthesis of lidocaine (Li-1 + Li-2)

Calculation for productivity: [14]

[**9**] (mmol mL^{-1}) * flow rate A (mL min^{-1}) * MM **3** (mg $mmol^{-1}$) * yield (%) * 60 min =

= 1 * 0.08 * 234.34 * 0.59 * 60 = 0.8 g/h

0.8 g/h * 24 h = 19.2 g/day

[14] The dosage of lidocaine varies from case to case, we therefore found appropriate to report the productivity as g/day instead of doses/day.

Characterization:

N-acetyl-para-aminophenol (paracetamol **1**)

^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.16 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 1.97 (s, 3H). These data are in accordance with those previously published.[15]

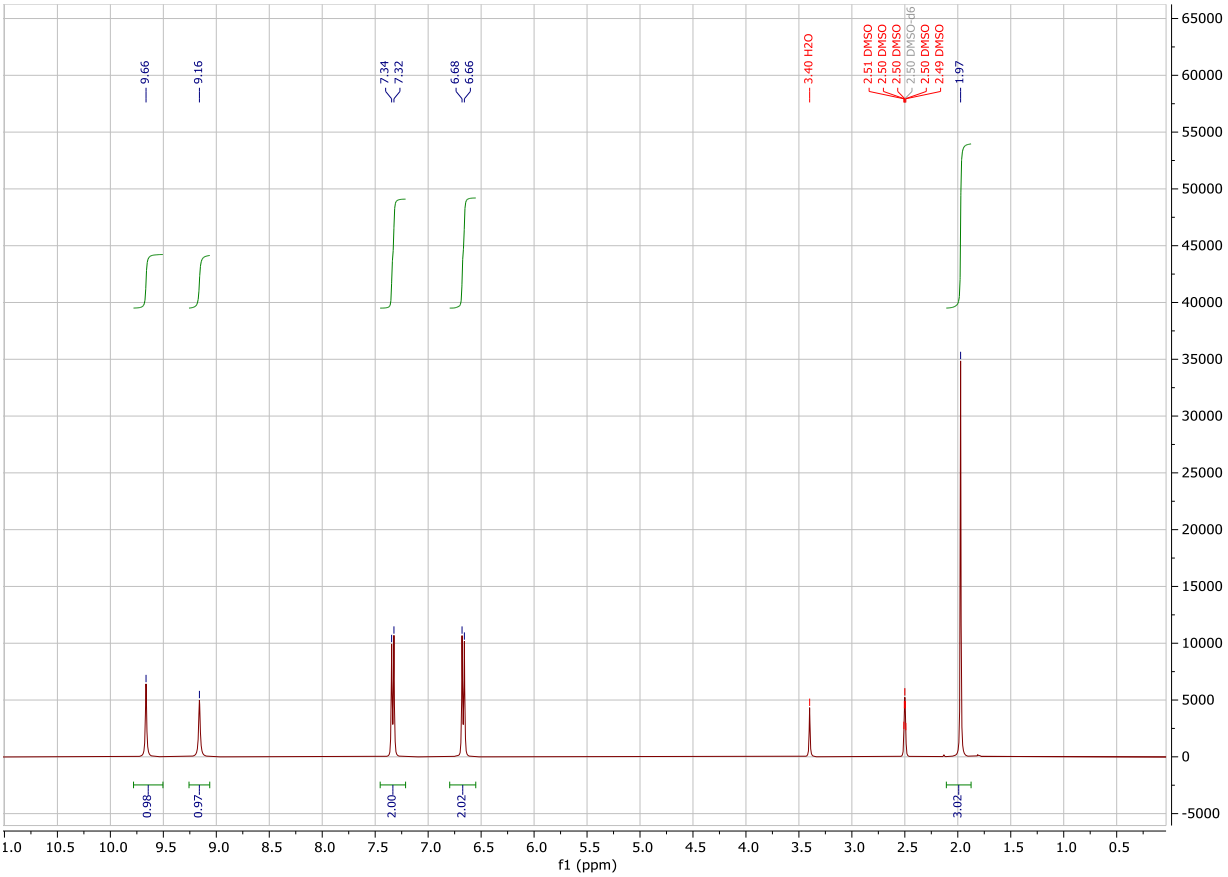


Figure S13: ^{1}H NMR spectrum of paracetamol **1**

[15] N. Drillaud, E. Banaszak-Léonard, I. Pezron, C. Len J. Org. Chem. **2012**, 77, 21, 9553 – 9561.

Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nifedipine **2**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.21 – 7.15 (m, 1H), 5.85 (s, 1H), 5.65 (s, 1H), 3.52 (s, 6H), 2.26 (s, 6H). These data are in accordance with those previously published.[16]

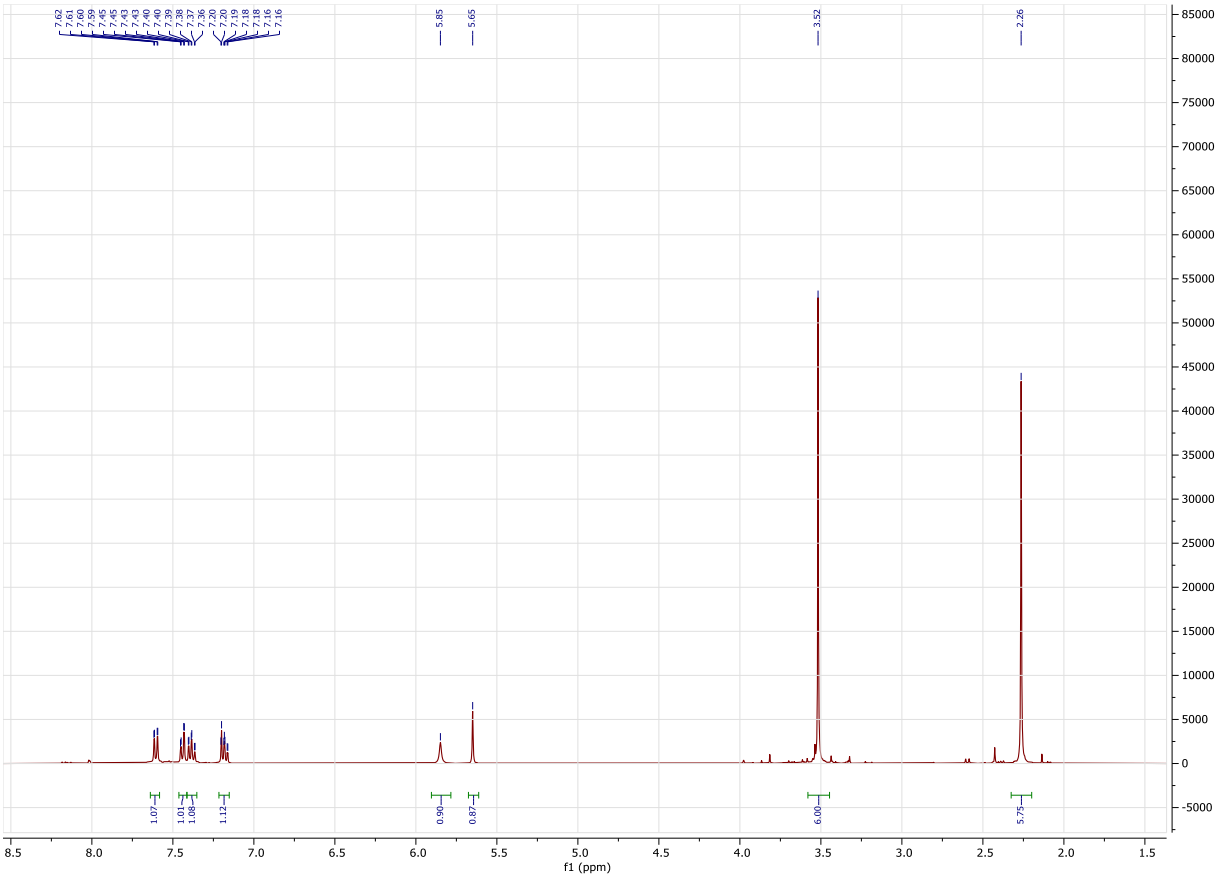


Figure S14: ^{1}H NMR spectrum of nifedipine **2**

[16] K. L. Bridgwood, G. E. Veitch, S. V. Ley *Org. Lett*. **2008**, 10, 16, 3627–3629.

N-(2,6-dimethylphenyl)-N^2,N^2-diethylglycinamide (lidocaine **3**) hydrochloride

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 7.00 (m, 3H), 4.32 (s, 2H), 3.62 – 3.34 (m, 4H), 2.27 (s, 6H), 1.54 (t, *J* = 7.3 Hz, 6H). These data are in accordance with those previously published.[12,13]

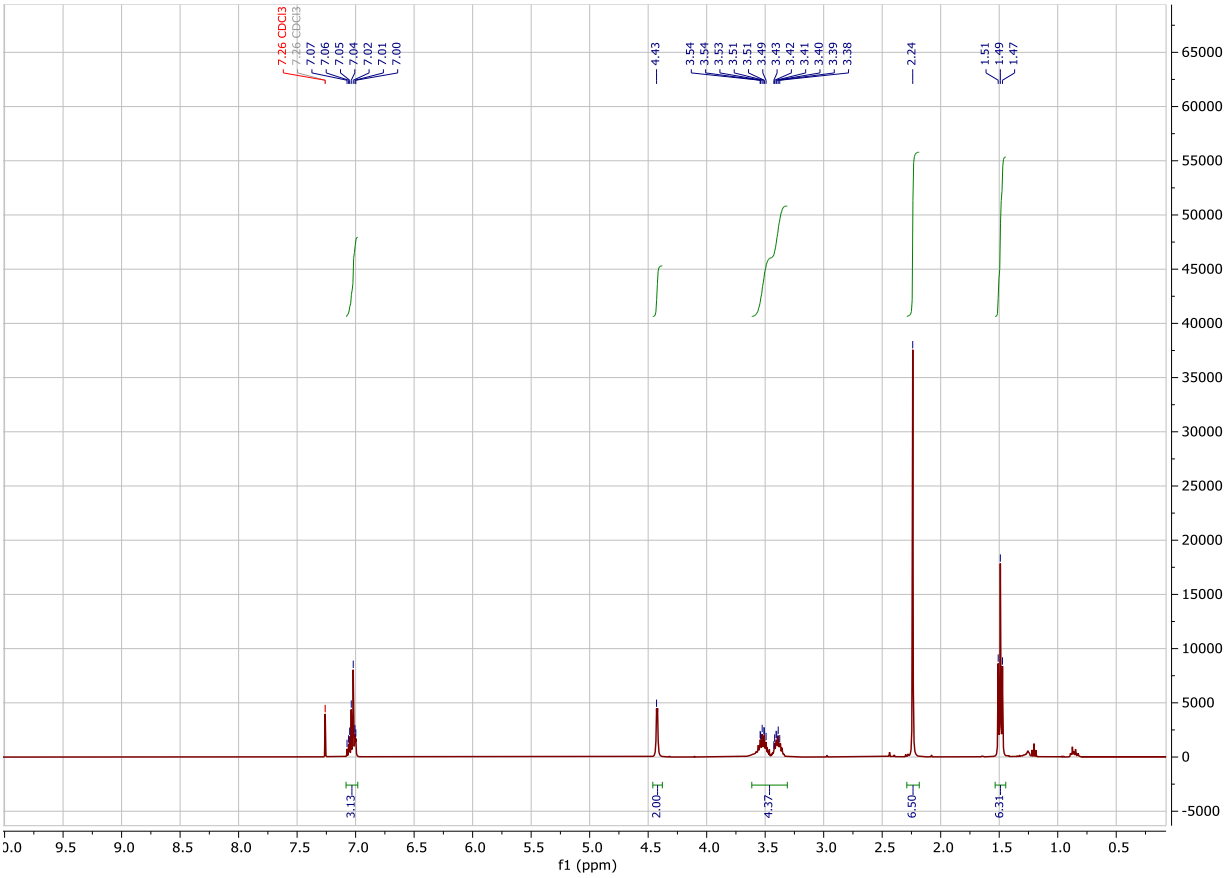


Figure S15: ^{1}H NMR spectrum of lidocaine hydrochloride

2-chloro-*N*-(2,6-dimethylphenyl)acetamide **11**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.20 – 7.04 (m, 3H), 4.25 (s, 2H), 2.24 (s, 6H). These data are in accordance with those previously published[17]

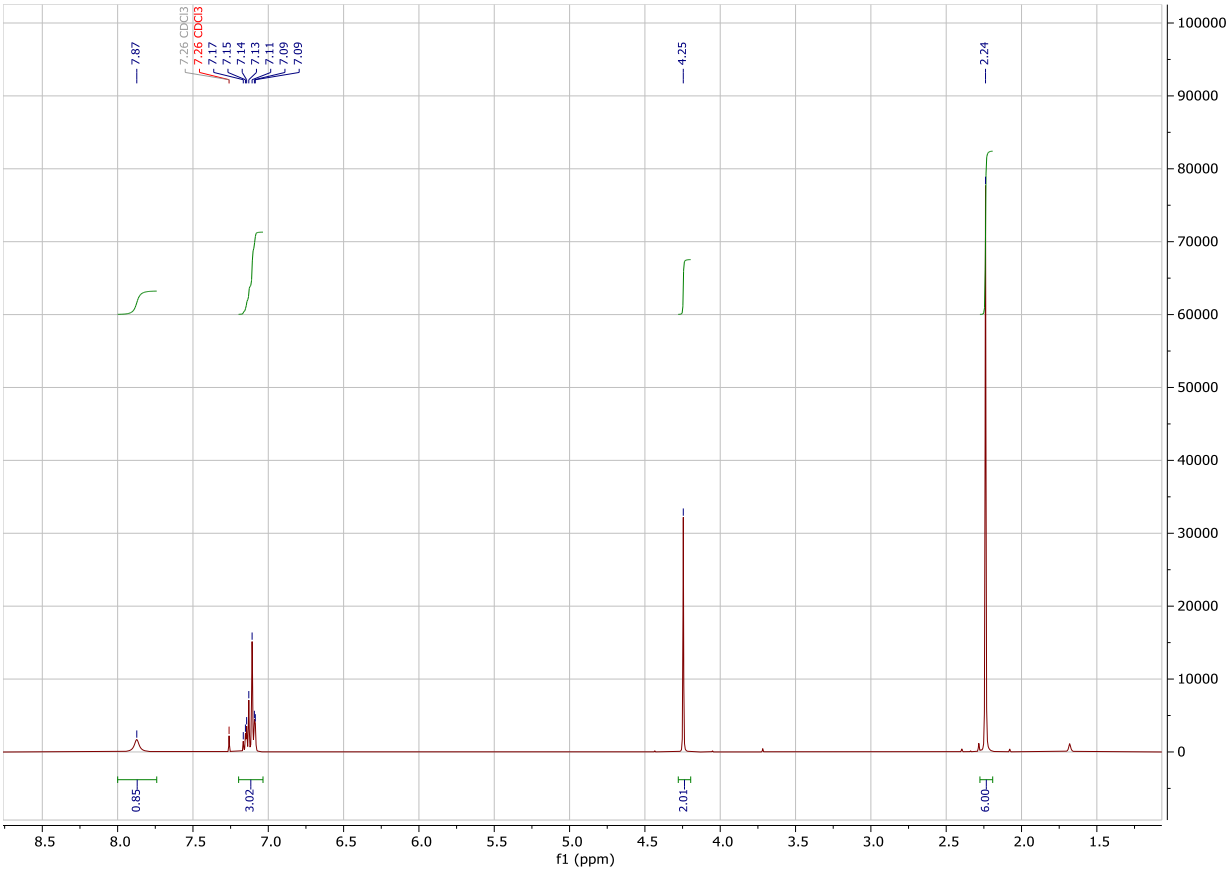


Figure S16: ^{1}H NMR spectrum of intermediate **11** (2-chloro-*N*-(2,6-dimethylphenyl)acetamide)

[17] D. E. Fitzpatrick, T. Maujean, A. C. Evans, S. V. Ley, *Angew. Chem. Int. Ed.* **2018**, 57, 15128-15132.

N-(2,6-dimethylphenyl)-N^2,N^2-diethylglycinamide (Lidocaine **3**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.10 – 7.08 (m, 3H), 3.23 (s, 2H), 2.70 (q, *J* = 7.1 Hz, 4H), 2.23 (s, 6H), 1.14 (t, *J* = 7.1 Hz, 6H). These data are in accordance with those previously published[13].

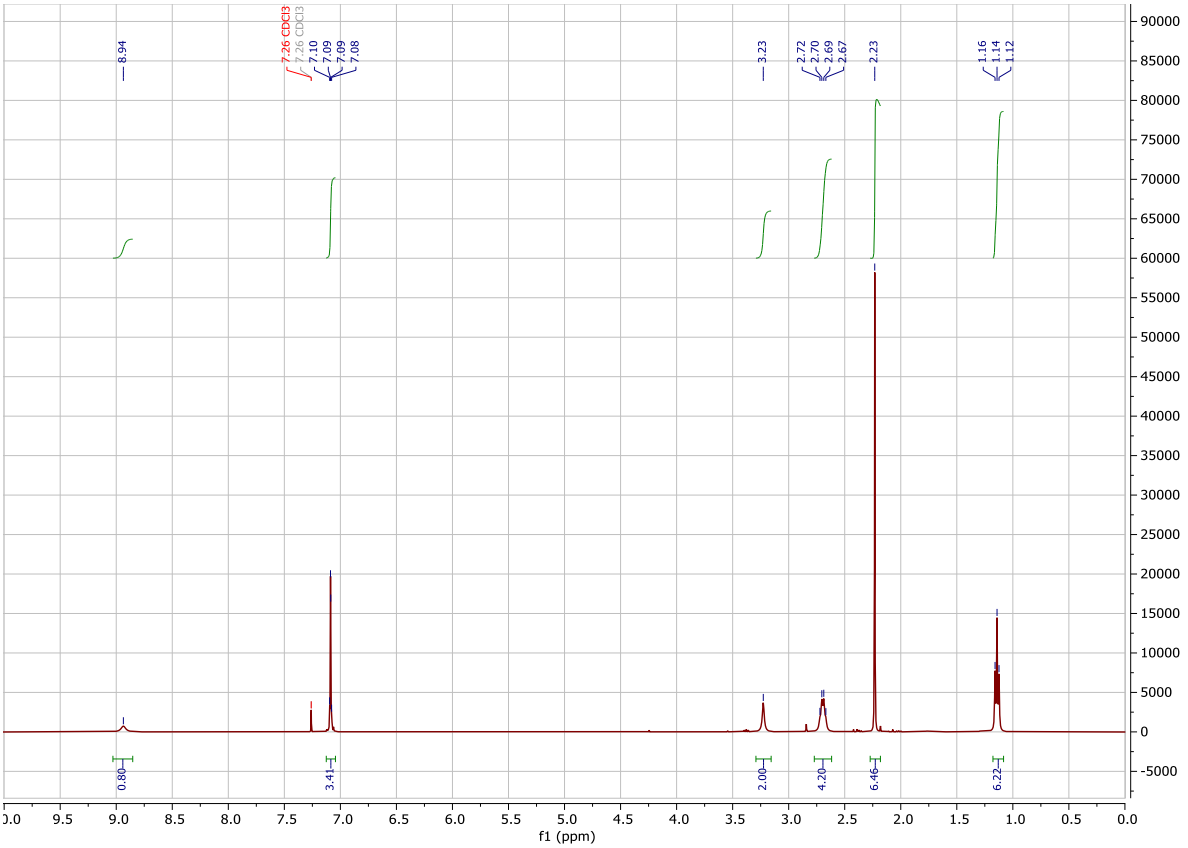


Figure S17: ^{1}H NMR spectrum of lidocaine (**3**)