Supplementary Information

Enhanced Flow Synthesis of Small Molecules by In-Line Integration of Sequential Catalysis and Benchtop Twin-Column Continuous Chromatography

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EXPERIMENTAL DETAILS

Purifications. The table below reports the buffer concentration:

Phase	Buffer
Equilibration	40% CH_3CN, 60% 14 mM Na_2CO_3
Loading	40% CH_3CN, 60% 14 mM Na_2CO_3
Washing	100% 14 mM Na_2CO_3
Elution	100% CH_3CN
Storage	40% CH_3CN, 60% 14 mM Na_2CO_3

ADDITIONAL EXPERIMENTAL RESULTS

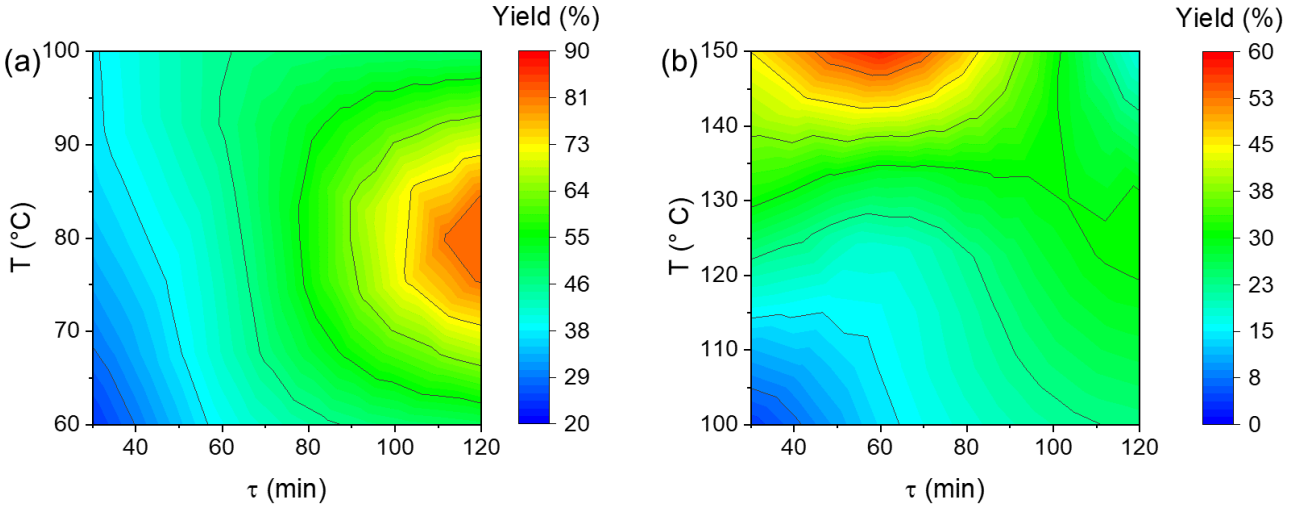

Figure S1. Contour plot showing the influence of temperature (T) and residence time (t) on the yield of phenylboronic acid (a) and biphenyl (b). As shown in this contour plot, several experiments were performed to optimize the two reactions under flow conditions. Analysis of the collected data allowed us to generate the contour map reported in this figure. In particular, the highest yields of phenylboronic acid **2** (**Figure S1a**) could be obtained at longer residence times (120 min) and at relatively low temperature (80 °C). In fact, increasing the temperature above this value, and reaching 100 °C, competitive formation of side products could be observed. The optimization of the Suzuki cross-coupling reaction has been conducted between 100 and 150 °C (**Figure S1b**), finding the optimum with a temperature of 150 °C and a residence time of 60 min. Lowering temperatures resulted in a substantial decrease of product yield. Moreover, increasing the residence time above 80 min provided biphenyl **3** in remarkable lower yield, probably due to concurrent degradation mechanisms.

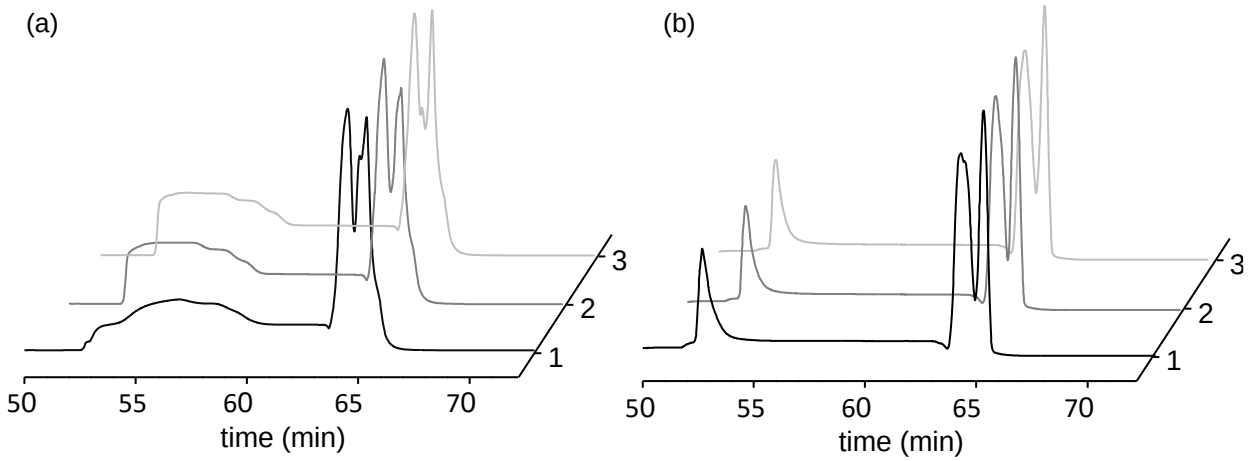

Figure S2. Superimposed wash and elution phases of the chromatograms obtained from the continuous-flow chromatography for aminoalcohol (a) and diphenylether (b). To show the broad applicability of the integrated synthesis-purification method, two additional small molecules, aminoalcohol and diphenylether, were synthesized and purified. In each batch purification, the breakthrough of the product was not observed during the load phase, which indicated the complete adsorption of the product. The wash phase was then operated with a step gradient of 50% acetonitrile to remove weakly bound impurities. Lastly, the elution phase with a step gradient of 100% acetonitrile desorbed the product completely, which was then analyzed with at-line HPLC on a C18 column (see Experimental Procedures section) to determine the purity and concentration. To assess the benefits introduced by a continuous process, the continuous-flow chromatographic process was applied to the two molecules. The process parameters implemented in the continuous process are reported above. Since, after completion, the columns are brought back to their initial states, multiple cycles can be performed consecutively to realize a periodically continuous process. The superimposed UV traces of the first column for three cycles in the wash and elution phases are shown here. Despite differences in the crude loaded, the elution profiles of the two molecules resembled each other in terms of the desorption of the weakly bound impurity at 54 min and that of the product at 70 min. Such good overlay of the product elution profile indicates that the continuous operation reached a steady state.

Table S1. Comparison between batch and continuous-flow purification processes (Product **4**).

	Solvent consumption ($L\ g^{-1}$)	Yield (%)	Productivity ($g\ h^{-1}\ L^{-1}$)	Purity (%)
Batch	3.1	64	5.6	92
Flow	2.4	68	7.5	92

Table S2. Comparison between batch and continuous-flow purification processes (Product **5**).

	Solvent consumption ($L\ g^{-1}$)	Yield (%)	Productivity ($g\ h^{-1}\ L^{-1}$)	Purity (%)
Batch	3.4	77	6.0	97
Flow	2.4	71	7.1	92

Table S3. Circularity analysis per 100 mg of purified biphenyl, obtained from different halobenzene derivatives. The process is analyzed for the three cases, which include both synthesis and purification in batch and/or flow. For each design, two scenarios are proposed, without (A) and with (B) reactant recycling.

Reagent: chlorobenzene

	batch synthesis + batch purification		flow synthesis + batch purification		flow synthesis + flow purification	
Scenario	A	B	A	B	A	B
M (mg) [a]	3071	3071	1463	1463	1323	1323
F_R [b]	0.00	0.17	0.52	0.75	0.68	0.81
V (mg) [c]	3071	2548	697	369	426	257
C_U [d]	0.00	0.17	0.52	0.75	0.68	0.81
E_F [e]	1.00	1.00	1.00	1.00	1.00	1.00
W (mg) [f]	2971	2449	597	269	326	157
LFI [g]	0.98	0.81	0.44	0.22	0.28	0.16
$F(X)$ [h]	0.9	0.9	0.9	0.9	0.9	0.9
MCI [i]	**0.115**	**0.268**	**0.602**	**0.804**	**0.744**	**0.859**

Reagent: bromobenzene

	batch synthesis + batch purification		flow synthesis + batch purification		flow synthesis + flow purification	
Scenario	A	B	A	B	A	B
M (mg) [a]	3326	3326	1661	1661	1447	1447
F_R [b]	0.00	0.18	0.46	0.68	0.62	0.75
V (mg) [c]	3326	2733	895	526	550	355
C_U [d]	0.00	0.18	0.46	0.68	0.62	0.75
E_F [e]	1.00	1.00	1.00	1.00	1.00	1.00
W (mg) [f]	3226	2633	795	425	450	255
LFI [g]	0.98	0.81	0.51	0.29	0.35	0.21
$F(X)$ [h]	0.9	0.9	0.9	0.9	0.9	0.9
MCI [i]	**0.114**	**0.274**	**0.542**	**0.742**	**0.689**	**0.810**

Reagent: iodobenzene

	batch synthesis + batch purification		flow synthesis + batch purification		flow synthesis + flow purification	
Scenario	A	B	A	B	A	B
M (mg) [a]	3586	3586	1863	1863	1574	1574
F_R [b]	0.00	0.19	0.41	0.63	0.57	0.71
V (mg) [c]	3586	2921	1097	685	677	455
C_U [d]	0.00	0.19	0.41	0.63	0.57	0.71
E_F [e]	1.00	1.00	1.00	1.00	1.00	1.00
W (mg) [f]	3491	2826	1000	588	580	358
LFI [g]	0.99	0.80	0.56	0.34	0.40	0.26
$F(X)$ [h]	0.9	0.9	0.9	0.9	0.9	0.9
MCI [i]	**0.112**	**0.279**	**0.493**	**0.693**	**0.641**	**0.768**

[a] M: mass load entering the process; [b] F_R: recycled/recyclable fraction; [c] V: amount of virgin materials; [d] C_U: reuse fraction; [e] E_F: extraction efficiency; [f] W: unrecoverable waste; [g] LFI: linear flow indicator; [h] $F(X)$: utility factor; [i] MCI: material circular index.

COMPOUNDS CHARACTERIZATION

Phenylboronic acid (2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.12 (d, 2H), 7.55 – 7.45 (t, 1H), 7.45 – 7.37 (t, 2H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.66, 133.48, 132.71, 131.23, 128.03.

Biphenyl (3)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.47 (d, 2H), 7.37 (t, 2H), 7.32 – 7.22 (t, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.31, 128.81, 127.30, 127.22.

1,3-bis[methyl(phenyl)amino]propan-2-ol (4)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 – 7.05 (t, 4H), 6.69 – 6.62 (d, 4H), 6.57 (t, 2H), 4.93 (d, 1H), 4.01 (m, 1H), 3.41 (dd, J = 14.8, 4.7 Hz, 2H), 3.22 (dd, J = 14.8, 7.5 Hz, 2H), 2.96 (s, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 149.33, 129.42, 129.40; 116.35, 112.41, 68.68, 65.19, 48.60.

Diphenyl ether (5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (t, 4H), 7.06 – 6.99 (t, 2H), 6.97 – 6.91 (d, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.01, 128.40, 121.82, 118.81.