Supplementary information for:

Micromolding of solvent resistant microfluidic devices

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1. Fabrication recipe for hybrid SIFEL-PDMS devices.

1. Fabricate a master of SU-8 on a 4-inch silicon wafer using soft lithography.
2. Place the master in a desiccator together with an open vial (2mL) containing 1H,1H,2H,2H-perfluoroctyltrichlorosilane, depressurize the desiccator to a pressure of *p*~0.3mbar, and let the vapor react with the surface of the master for 2 hours.
3. Remove the master from the desiccator, put it in an oven and bake it for two hours at 120 ℃. This step is essential to avoid the SIFEL layer getting damaged upon demolding (step 9) as unbaked SIFEL bonds to SU-8 (see Fig. S1).
4. Let the master cool down to room temperature, pour 5-10g of SIFEL (2610 grade, Shin Etsu) onto the center of the master, place the master in the desiccator, and depressurize the desiccator (*p*~0.3mbar) to remove air from SIFEL by degassing for half an hour.
5. Place the partially-covered master on a spin-coater, and spin successively at 250 rpm for 5 s and at 500 rpm for 40 s to obtain a homogeneous coating.
6. Bake the coated master in an oven at 68 ºC for ~1hour to cure the layer of SIFEL. The resulting thickness is approximately 175 µm, see Fig. S3.
7. (optional) To obtain thicker layers, repeat steps 4-6 as desired. We recommend this approach rather than creating the thicker layer in one go by spinning at speeds lower than those indicated in step 4, because this leads to wrinkling as shown in Fig. S2. Wrinkling not only makes the layer less transparent, it also makes the material less facile to handle.
8. Mix 60g of PDMS (base) with 6g of curing agent (Sylgard 184, Dow Corning), degass the mixture in the desiccator (*p*~0.3mbar) for 30 minutes, pour it on top of the SIFEL-coated master placed in a 13 cm wide petridish, and cure the layer of PDMS at 68 ºC for at least 2 hours.
9. After cooling down, carefully detach the SIFEL-PDMS layer from the master. Punch holes in the layer to be able to connect the channels engraved in this layer to feed lines after bonding (step 13). In case one intends to inject fluids that swell PDMS, we recommend the use of at least three layers of SIFEL (steps 4-7) to ensure the fluid flows from the feed line inserted in the holes into the SIFEL channels without contacting the PDMS layer.
10. To seal the microchannels engraved in the layer of SIFEL (step 12), coat a microscope glass slide (26 mm x 76 mm) by a thin layer of SIFEL. This is done as follows: prepare a 0.45µm filtered 30wt % solution of SIFEL in 1,3-bis(trifluormethyl)benzene, dispense a few mL on the slide to cover most of its surface, wait 30 minutes to evaporate most of the solvent from the solution, and subsequently spin-coat the solution on the slide successively at 500 rpm for 30s and at 4000 rpm for 30s to obtain a homogeneously coated glass slide.
11. Bake the spincoated filtered SIFEL in the oven at 68 ºC for 18 minutes.
12. Press the patterned layer of SIFEL obtained in step 9 onto the pre-cured SIFEL layer obtained in step 11 at a pressure of approximately 500 N/m^2 for 2 hours at 68 ºC. Cure overnight at 68 ºC.
13. Tubing can be attached to the sealed microchannels by coating the outside of the bottom end of the tubing with 75 wt% SIFEL in 1,3-bis(trifluormethyl)benzene and inserting the tubes into the punched holes. Cure at 68 ºC for at least two hours.
14. (optional) apply epoxy resin to the fluidic connections to improve the mechanical stability.

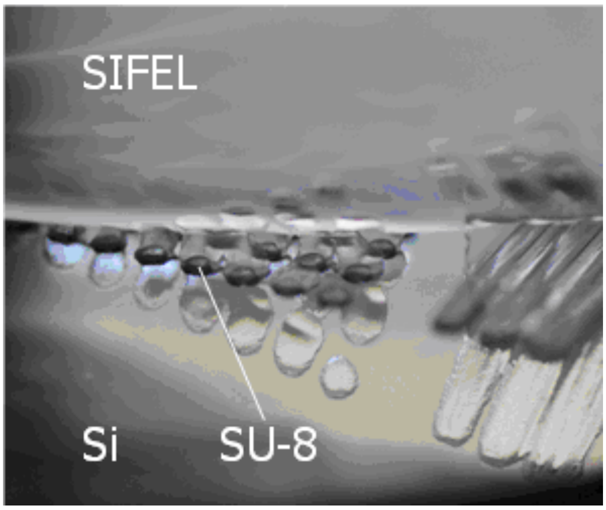


Fig. S1 SIFEL is demolded from an unbaked SU-8/Si mold. Adhesion to SU-8 is such that the SIFEL tears upon demolding.

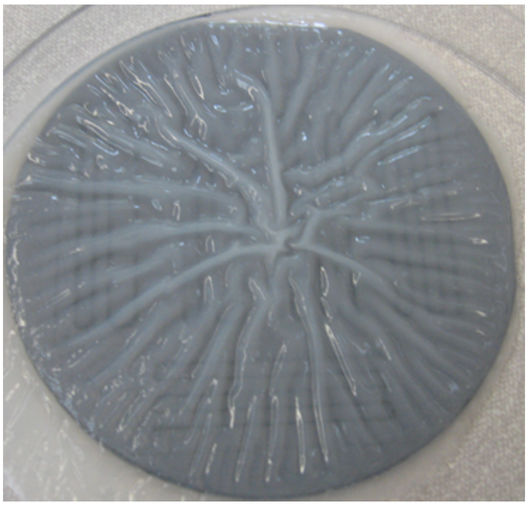


Fig. S2 SIFEL cured as a thick layer. The top surface is wrinkled with a thickness varying up to an order of magnitude.

Ad 5:
At 68 ºC the SIFEL curing process is limited by the evaporation of solvent, because we observe different curing times for different thicknesses.
The thickness of the cured layer T (in micrometer) depends on the spin speed S (in rpm) according to the fit

$$\text{Log}(T) = -0.9314 \cdot \log(S) + 4.6707$$

Spinning at 250 rpm before going to 500 rpm helps even out the deposited SIFEL and results in reduced 'streaking' (V-shaped uncoated sections near the edge of the wafer).

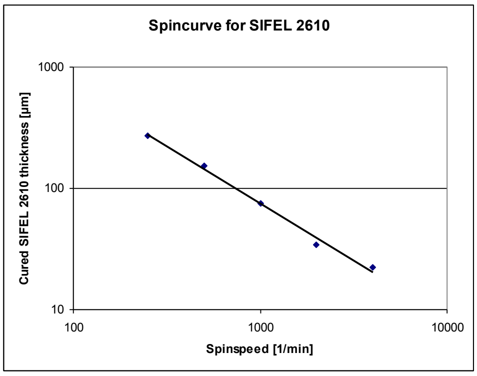


Fig. S3 Spincurve for SIFEL 2610. The black line is the spincurve fitted.

Ad 6:
Curing of SIFEL starts at the edge and works its way to the centre – this can be observed by eye. In case wrinkling occurs, the use of thinner layers is recommended.

Ad 7:
We recommend to cast subsequent layers of SIFEL within four hours after curing the previous layer as we observed a reduced adherence between the layers with longer waiting times.

Ad 8:
The PDMS layer is introduced for several reasons. Firstly, it serves as a more rigid backbone that provides mechanical support to tubing. Secondly, using only a limited number of SIFEL coatings means that the device is still transparent. Thirdly, PDMS costs roughly 1/10th of SIFEL, so the dual layer approach has a definite cost advantage. Lastly, it makes sense from a practical point of view as the PDMS layer can be cast as a single layer as opposed to the stepwise spincoating and curing of SIFEL.

Ad 10:
SIFEL is used in solution, because it is easier to remove particulate matter from the commercial product in solution. As the solvent is highly hydrophobic, it is necessary to remove it after dispensing the solution on the glass slide to form a homogeneous coating after spinning. The coating is uniform in thickness, except close to the edges of the slide (edge-beat). To avoid improper bonding, cut the microchannel structures in the layer of SIFEL-PDMS obtained in step 9 such that they easily fit on top of a microscope.

Ad 11:
Baking the SIFEL coating for 18 minutes ensures the coating retains shape, without being fully cured. Please note that it is essential that the coating is partially-cured to be able to form an adhesive bond when pressed against the patterned SIFEL layer in step 12.

Ad 12:
Pressure during clamping can be easily regulated by making a clamp with a flat top plate and using weights to control the pressure. The optimum pressure we found is 500 N/m^2; both the use of a lower pressure of 250 N/m^2 as well as a higher pressure of 1000 N/m^2 resulted in improperly bonded devices. We did not optimize for curing time. To prevent PDMS from sticking to the clamp, put Scotch tape on the surface of the clamp.

For easy evaluation of micromolded SIFEL as a possible platform, we have compared information on attainable geometries, temperature of operation and the delamination pressures for SIFEL and PDMS in Table S1. Most properties shown are similar for PDMS and SIFEL. While SIFEL-PDMS devices delaminate at lower pressure than PDMS, SIFEL-PDMS devices are sufficiently robust to allow successful application.

2. PDMS and SIFEL comparison of material and devices properties

Below is a summary of material properties of PDMS and SIFEL that are relevant in device fabrication and operation, and properties of the devices made from those materials in Table S1.

Table S1 Selected properties of PDMS and SIFEL

	PDMS	SIFEL
O_2 permeation	$8\cdot10^2$ barrer [1]	$8\cdot10^2$ barrer
Tensile strength	2.24 MPa	0.8 MPa [2]
Shore A hardness	50 [3]	35 [2]
Temperature of operation	-45 to 200 ºC [3]	-50 to 200 ºC [2]
Feature aspect ratio attained	1:17 [4]	1:2.5
Device delamination overpressure	PDMS-glass: 5 bar [5]	SIFEL-SIFEL: 2.5 bar

The feature aspect ratio is limited by lift-off of molded material from the water. Even with similarly silanized masters, SIFEL is more prone to stick to the master. The indicated feature aspect ratio is for features as depicted in Fig. 1b of the main text. Other device properties are in the same range.

Delamination pressure was determined by increasing gas pressure using a gas filled syringe with the outlet of the channel closed and recording the maximum pressure attainable until device failure.

To investigate gas permeation, a pressure differential was applied over a thin SIFEL membrane and the amount of gas flowing through the membrane was determined. A 53 micron SIFEL film with $1\cdot10^{-4}$ m^2 surface area was cured inside a metal ring and supported on fine gauze (~0.4 mm opening). Pure O_2 was permeated with a 2.59 bar pressure differential at room temperature. The flow of permeating gas was measured using a soap film meter.

3. Compatibility with fluids: wetting, swelling, acid/base resistance

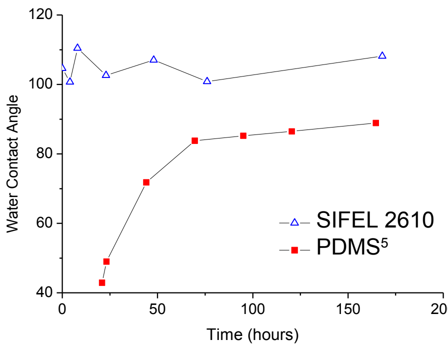


Fig. S4 The SIFEL-water contact angle is stable in time, unlike the water-PDMS contact angle. At t=0, PDMS is plasma exposed and SIFEL is demolded.

PDMS has the unwelcome property that its surface energy changes reversibly after air/oxygen plasma bonding[6]. Because the rate and extent of this surface modification, the contact angle depends on many factors including age, exposure to solvents, etc.[7,8], and the variable partial wetting that results from it renders multiphase hydrodynamics[9] inside a PDMS device difficult. As we do not need a plasma for bonding, our SIFEL devices exhibited stable contact angles (See for water Fig.S4).

To further characterize the material for use with different solvents, the contact angle of several liquids on SIFEL was measured (see Table S2). Droplets for measurements of contact angles were dispensed manually on flat SIFEL. Images were obtained using an EasyDrop (Krüss) and analyzed using the accompanying Drop Shape Analysis program, using horizontal baselines.

Table S2. Static contact angles for representative liquids on SIFEL show mostly wetting behavior with one case of near perfect wetting

Compound	SIFEL Contant Angle (θ)	Compound	SIFEL Contant Angle (θ)
Methanol	40	Dimethylformamide	78
Ethanol	53	Water	104
Dichloromethane	48	1H,1H,2H,2H-perfluoroctanol	<<10
Cyclohexane	45	Perfluorodecane	swell
Hexadecane	53	Wacker Oil AK5	39
Toluene	55	Wacker Oil AK1	24
Tetrahydrofuran	60.4		

Swelling ratios and material leaching were determined similar to Lee[7]. We submerged pieces of SIFEL of approximately 50x10x1 mm in representative solvents for 24h. A slide ruler was used for length measurements. The data, shown in Figure 3 of the main text, is also shown below in Table S3.

Resistance to acids and bases commonly used in organic synthesis was determined by submerging cured SIFEL into a solution for 24 hours. The SIFEL samples (size ~3x3x0.2mm, weight ~20 mg) were checked for color and weight changes.

Table S3 Swelling and weight change of SIFEL exposed to common solvents for organic synthesis.

Solvent	Swelling [m/m]	Weight change [%]
Water	1	-0.05
Dimethylsulfoxide	1.01	-0.04
Diisopropylamine	1.01	-0.36
Dimethylformamide	1.02	-0.11
Ethanol	1.02	-0.06
Toluene	1.04	-0.16
Hexadecane	1.04	-0.08
Dichloromethane	1.05	-0.32
Tetrahydrofuran	1.05	-0.24
Ethanol	1.06	-0.05
Chloroform	1.07	-0.23
Pentane	1.08	-0.18
Diethylether	1.09	-0.47
Cyclohexane	1.44	-0.38

5. Cleavage of N-Boc from Boc-L-phenylalanine methyl ester

The reference reaction was performed in a flask. 500 mg of Boc-L-phenylalanine methyl ester was dissolved in 20vol% of trifluoroacetic acid in chloroform (5 ml) The mixture was allowed to react for 2 hours under vigorous stirring at room temperature. Afterwards, the reaction was quenched with 5 ml of TEA and poured in 10 ml of water. The organic layer was separated and washed with additional 10 ml of water. The layers were separated again and the organic layer was dried on anhydrous sodium sulphate, filtered and evaporated. The remaining oil was analyzed by HPLC.

LC-MS was performed on a SHIMADZU Liquid Chromatograph Mass Spectrometer, LCMS-2010, LC-8A pump with a diode-array detector SPD-M20. The column used here was the Xbridge Shield RP 18.5μm (4.6x150mm) with 1/1 v/v MeOH-H_2O and 0.1 volume percent of formic acid mixture as an eluent.

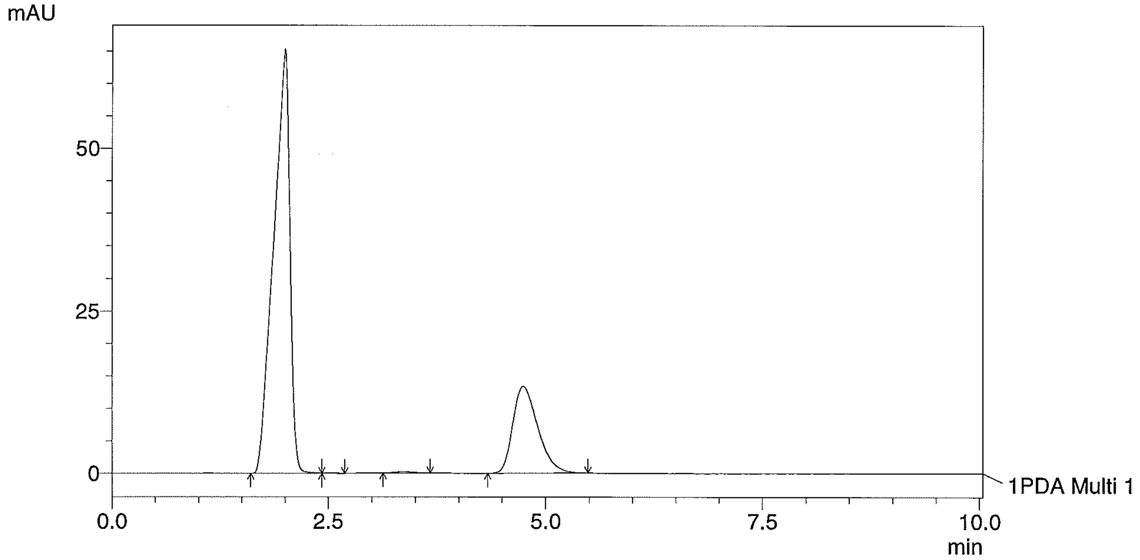
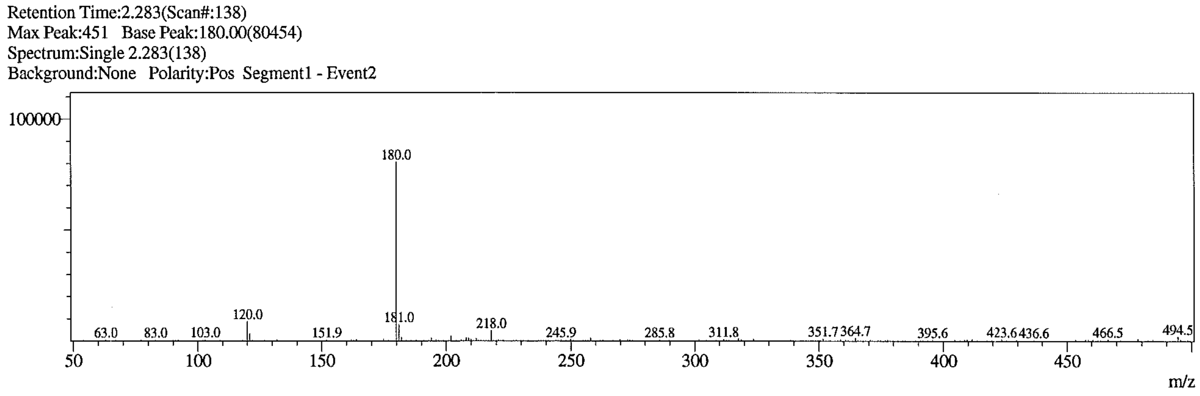
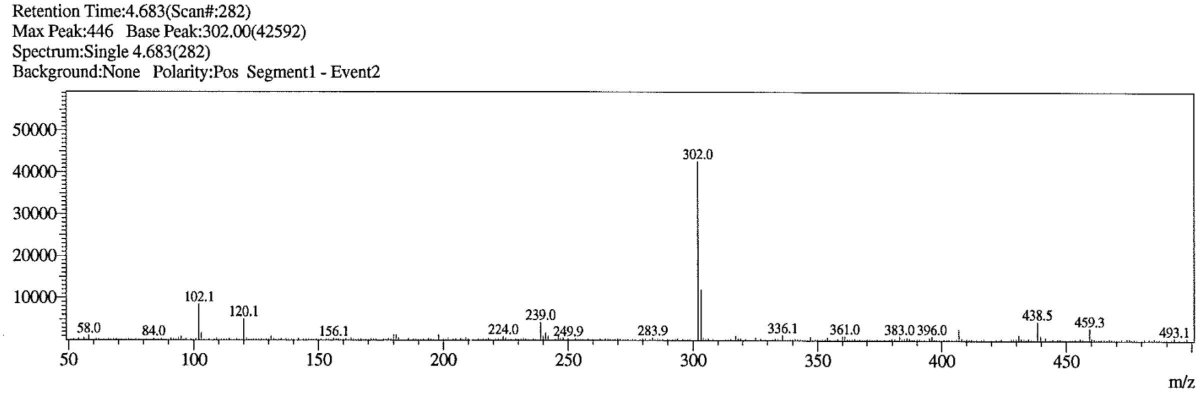


Fig. S5 HPLC analysis of product mixture, analyzed at 253nm to show only phenyl rings from protected and unprotected phenylalanine methyl ester. Conversion can be directly obtained from peak area and is 76%.

Peak with a retention time of 2.238min corresponds to L-phenylalanine methyl ester.
MS found: 180.0 L-phenylalanine methyl ester


Retention Time:2.283(Scan#:138)
Max Peak:451 Base Peak:180.00(80454)
Spectrum:Single 2.283(138)
Background:None Polarity:Pos Segment1 - Event2

Peak with a retention time of 4.683min corresponds to Boc-L-phenylalanine methyl ester.
MS found: 302.10 Boc-L-phenylalanine methyl ester + Na


Retention Time:4.683(Scan#:282)
Max Peak:446 Base Peak:302.00(42592)
Spectrum:Single 4.683(282)
Background:None Polarity:Pos Segment1 - Event2

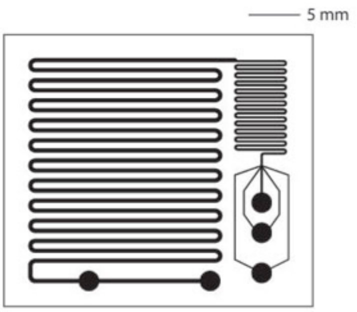


Figure S6 Schematic representation of the microreactor used in this work.

For the microfluidic reaction experiment, three 5 ml syringes (Hamilton, 1000 series) were charged with reactant solution and loaded onto Harvard PhD series syringe pump. The reactor used was the same design as shown in Figure 1, and is shown schematically in Figure S6. The internal volume of the reactor was 16 µL. Boc-L-phenylalanine methyl ester (0.8M in chloroform) and trifluoroacetic acid (TFA; 40vol% in chloroform) were introduced in the inlet sections, and triethylamine (TEA; undiluted) was introduced in the quench port. Because PEEK tubing and connectors dissolved in the TFA solution, only PTFE tubing and connectors were used. Unused channels were capped off by placing teflon tape in between the ferrule and the PEEK union. Flow rates for the two syringes at the inlet and the syringe at the quench port were all 4 µL/hr so that residence time was 2 hours. After reaction, TEA and TFA were extracted using water and the sample was dried under vacuum.

LC-MS was performed on a SHIMADZU Liquid Chromatograph Mass Spectrometer, LCMS-2010, LC-8A pump with a diode-array detector SPD-M20. The column used here was the Xbridge Shield RP 18.5µm (4.6x150mm) with 1/1 v/v MeOH-H_2O and 0.1 volume percent of formic acid mixture as an eluent.

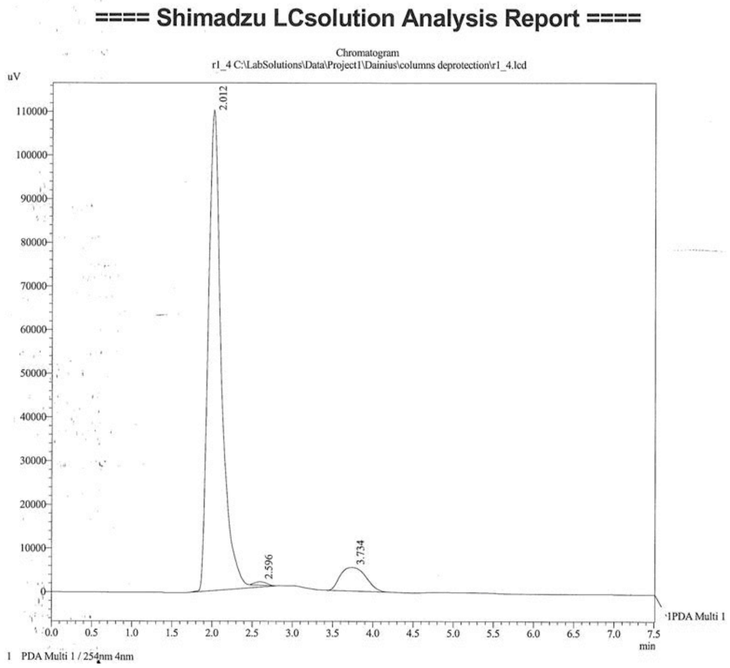
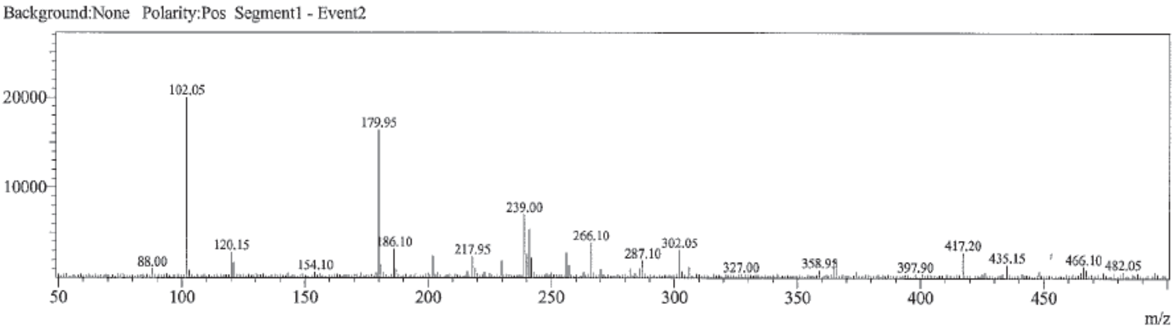


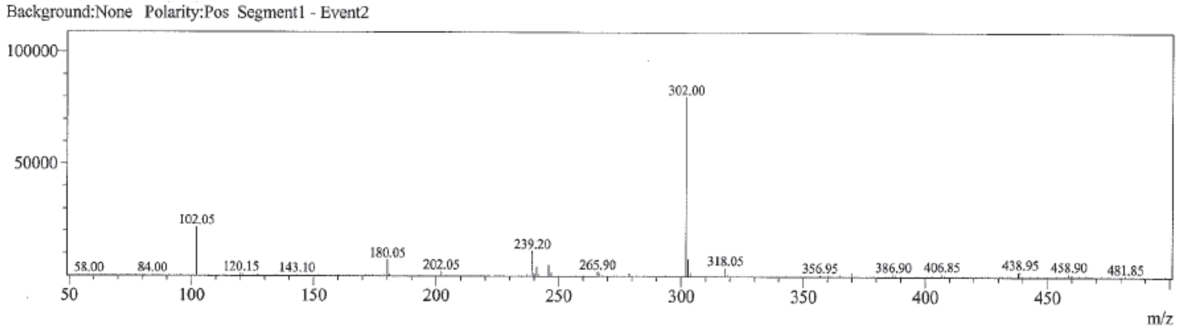
Fig. S7 HPLC analysis of product mixture, analyzed at 253nm to show only phenyl rings from protected and un-protected phenylalanine methyl ester. Conversion can be directly obtained from peak area and is 91%.

Peak with a retention time of 2.012min corresponds to L-phenylalanine methyl ester.
MS found: 102.05 tirethylamine
179.95 L-phenylalanine methyl ester
239.00 triethylamine + TFA + Na



Peak with a retention time of 3.734min corresponds to Boc-L-phenylalanine methyl ester.

MS found: 102.05 tirethylamine
302.10 Boc-L-phenylalanine methyl ester + Na



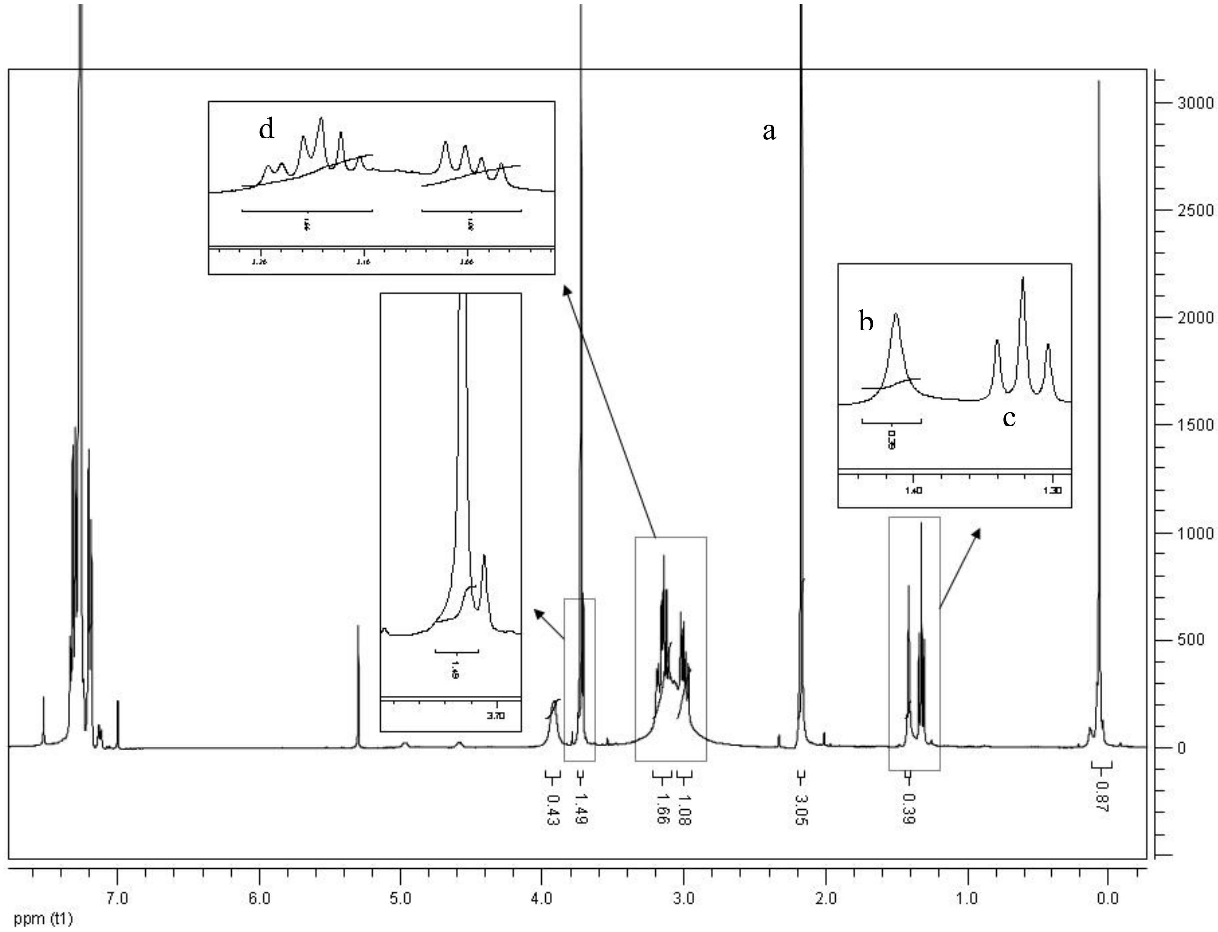


Fig. S8 ^{1}H NMR spectrum of product mixture obtained from deprotection of Boc-L-phenylalanine methyl ester. Besides from Boc-L-phenylalanine methyl ester and L-phenylalanine methyl ester, triethylamine and leached PDMS can be observed.

^{1}H NMR revealed the presence both Boc-L-phenylalanine methyl ester and L-phenylalanine methyl ester, as well as triethylamine. Singlet a corresponds to 3 protons of ester group. Singlet b corresponds to protons of Boc- group. The starting compound should have Boc-L-phenylalanine methyl ester 3 protons of ester group and 9 protons of Boc-group. That is different in presented spectra. Instead of 9 Boc- protons, only 0.39 is revealed, indicating a conversion of around 95%. This agrees with the result found in LC-MS.

Triplet c and multiplet d proves the presence of triethylamine in the sample. The presence of this base makes L-phenylalanine methyl ester soluble in $CDCl_3$ and prevents Boc-group cleavage outside the reactor.

In the product NMR, we also observe PDMS at 0.05 ppm. The PDMS was most likely extracted due to the highly aggressive nature of TFA. The amount of PDMS corresponds to 0.17 monomer units per molecule of phenylanaline methyl ester. Because flow of reactant is 3.2 μmol/hr, this corresponds to a leaching of 0.54 μmol PDMS monomer every hour.

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