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Supplementary Information

Investigation of Petasis and Ugi Reactions in Series in an Automated Microreactor System

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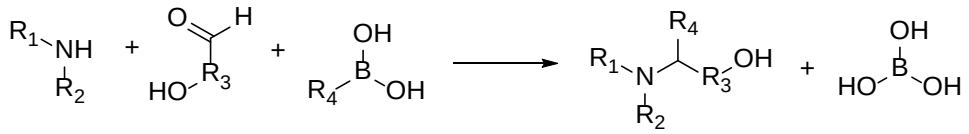
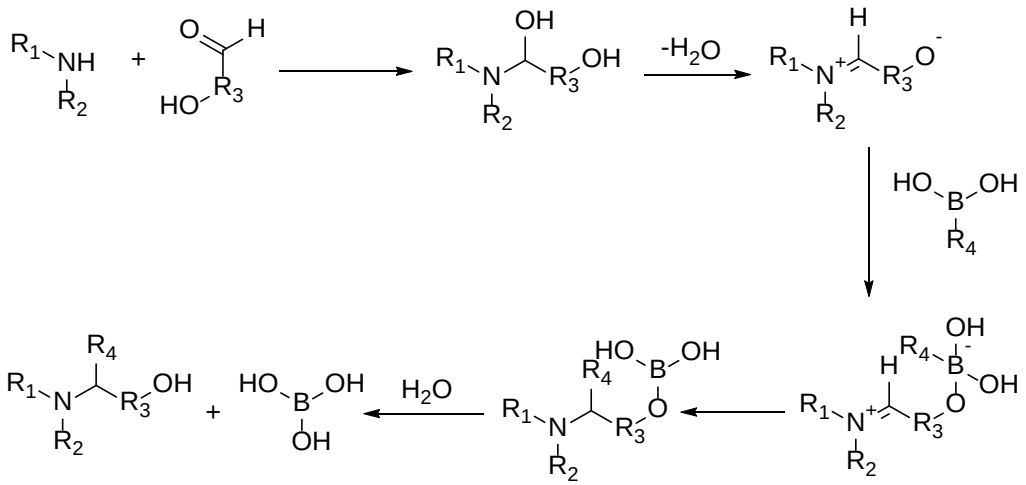
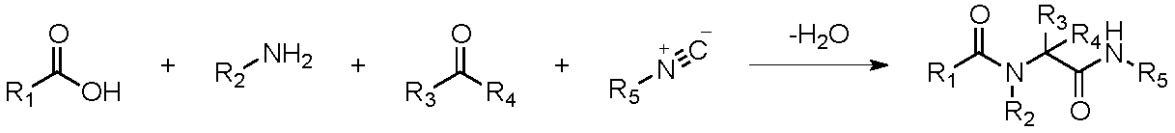


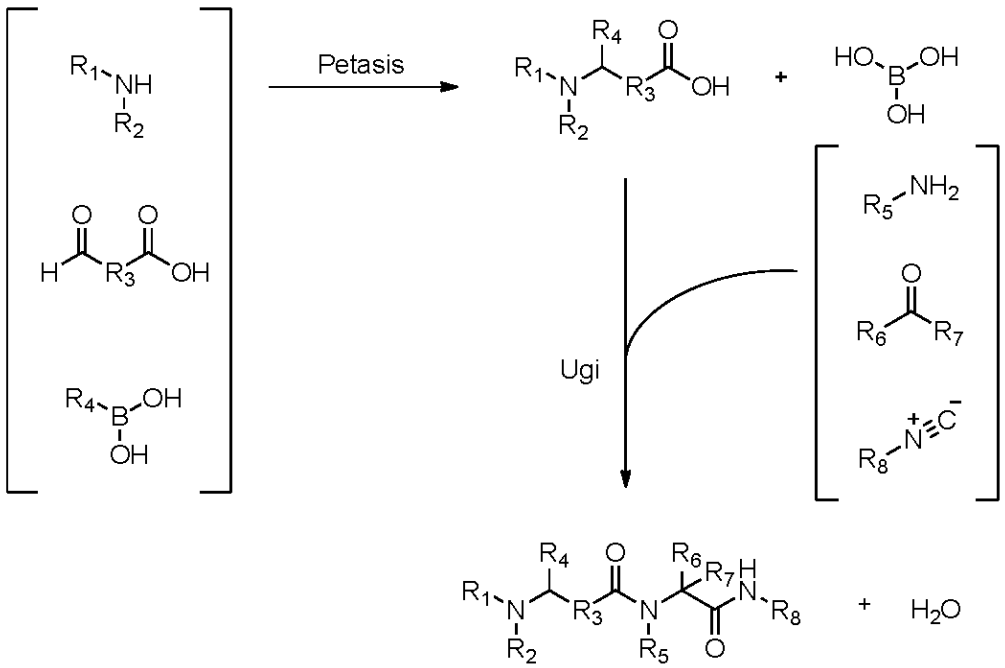
Scheme S1. General form of the Petasis reaction.[4]



Scheme S2. Proposed mechanism of the Petasis reaction.[14]



Scheme S3. General form of the Ugi reaction.[20]



Scheme S4. Petasis-Ugi tandem reaction.[19]

As a first step, the reactions were conducted at several concentrations in a variety of different solvents. To avoid clogging the microreactors used in subsequent experiments, solvents were tested to keep all reagents, the desired product, and eventual side-products in solution. The pure reagents, as well as the resulting raw product solution, were analyzed by Ultra Performance Liquid Chromatography (UPLC) equipped with a UV/Vis spectrometer and Gas Chromatography-Mass Spectrometry (GC-MS) to identify a suitable method to monitor yield and conversion of the reactions. UPLC-UV/Vis was found to be the superior technique to monitor the reagent and product concentrations. The experimental results presented were obtained using a Water Acquity UPLC with a Mercury Luna 3µ C18(2) column. The elution was carried out at a flow rate of 0.3 mL/min using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. After steps of isolation and purification, the pure product was analyzed by Nuclear Magnetic Resonance (NMR) spectroscopy to verify its structure.

The reactions were conducted in a microreactor with a volume of 232 µL. The layout of the employed microreactor is illustrated in Figure S1. Besides two inlets and an outlet, an additional inlet channel joins the reaction channel near the outlet to quench the reaction.

The microreactor was mounted in two separate stainless steel compression chucks. One chuck was placed on the area that is marked by a blue background in Figure S1 and equipped with ports for the inlets and outlet of the reactor as well as for cooling water. The second chuck was mounted on the area of the reactor that is marked red in Figure S1 and served to heat the reaction zone of the microreactor with an integrated Omega (CSS-01235/120V) heating cartridge.

To achieve a precisely controlled and uniform flow rate of the reagents, the prepared solutions were loaded in 8-mL Harvard Apparatus stainless steel syringes and infused by Harvard Apparatus PHD 2000 pumps.

A constant pressure during the reactions was accomplished by connecting a 100-psi backpressure regulator to the outlet of the microreactor. The temperature of the reactor was maintained by an Omega (CN9311) temperature controller. The cooling water was taken from a reservoir at room temperature by a recirculating pump.

The set point of the temperature controllers and syringe pumps were set by an automated Labview (version 8.5.1) program. Additionally, this platform controlled a Rheodyne six-way valve with a 2-µL sample loop after the reactor outlet to allow automated injection into the UPLC for analysis after steady state had been reached. In this way, several sets of reaction conditions were run and analyzed with minimal input required from the experimenter or downtime between reactions.

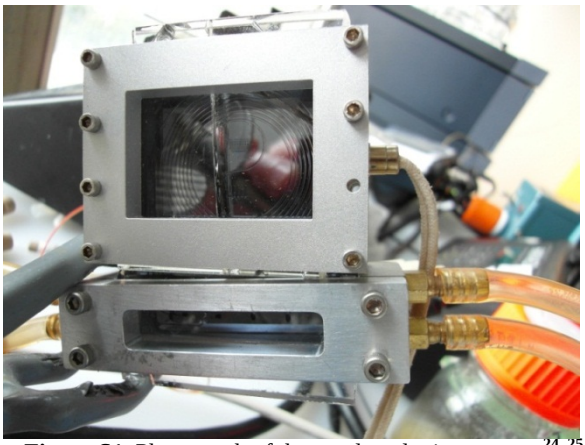
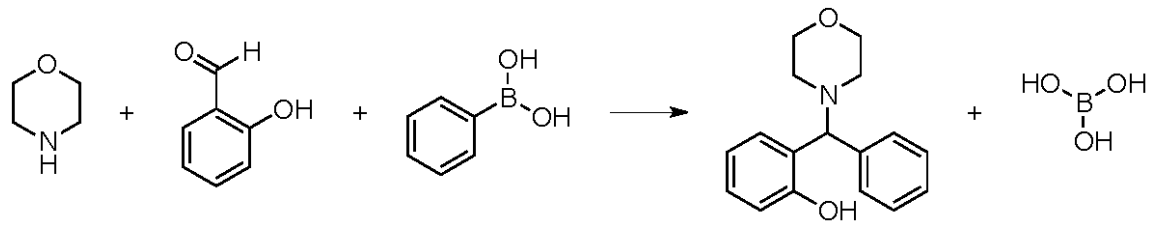
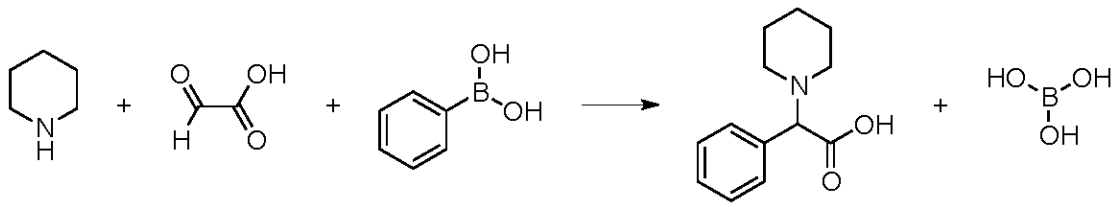


Figure S1. Photograph of the employed microreactor.[24, 25]



Scheme S5. Petasis reaction of morpholine, salicylaldehyde, and PBA.



Scheme S6. Petasis reaction of piperidine, glyoxylic acid, and PBA.

In order to identify suitable solvents and to isolate and purify the desired product, the two Petasis reactions were first conducted in batch reactors.

Morpholine, salicylaldehyde, and phenylboronic acid 871.2 mg (10 mmol) morpholine, 1221.2 mg (10 mmol) salicylaldehyde, and 1219.3 mg (10 mmol) PBA were dissolved in 10 mL acetonitrile. The reaction was conducted in a stirred 20-mL vial at 90 ˚C for 16 h. During the reaction, the solution developed a dark yellow color and white solid particles formed. Successive solubility studies showed that the particles were boric acid. The isolation of the pure product was accomplished by an aqueous workup to remove the water-soluble boric acid. After evaporation of the acetonitrile, pure product remained as an orange solid.

Piperidine, glyoxylic acid, and phenylboronic acid 851.5 mg (10 mmol) piperidine, 920.5 mg (10 mmol) glyoxylic acid, and 1219.3 mg (10 mmol) PBA were dissolved in 10 mL methanol. The equimolar reaction was conducted in a stirred 20-mL vial at 60 ˚C for 16 h. During the reaction, the solution assumed a dark yellow color. The isolation of the pure product was accomplished by flash chromatography using silica gel as the stationary phase. First, a 9:1 mixture of chloroform and methanol was used to elute unreacted PBA from the crude product. In a second step, the eluent was changed to an 8:2:2 mixture of 2-butanol, acetic acid, and water to isolate the desired product. After removal of the solvent, a sticky, slightly yellow solid was obtained. For the final purification, this solid was dissolved in isopropanol. The pure product could be precipitated by addition of n-hexane. After filtration and drying, the pure product was obtained as a white powder.

The employed experimental flow setup for the Petasis reaction is illustrated in Figure S2. As the employed microreactor has only two inlets, two of the three reagents were mixed in one syringe. To avoid the preliminary reaction of the aldehyde and the amine to the imine, these two compounds were kept in separate syringes. In order to ease the dissolution of the solid PBA, it was chosen to add the liquid amine. 1,2-Dimethoxybenzene was used as internal standard added to the aldehyde solution.

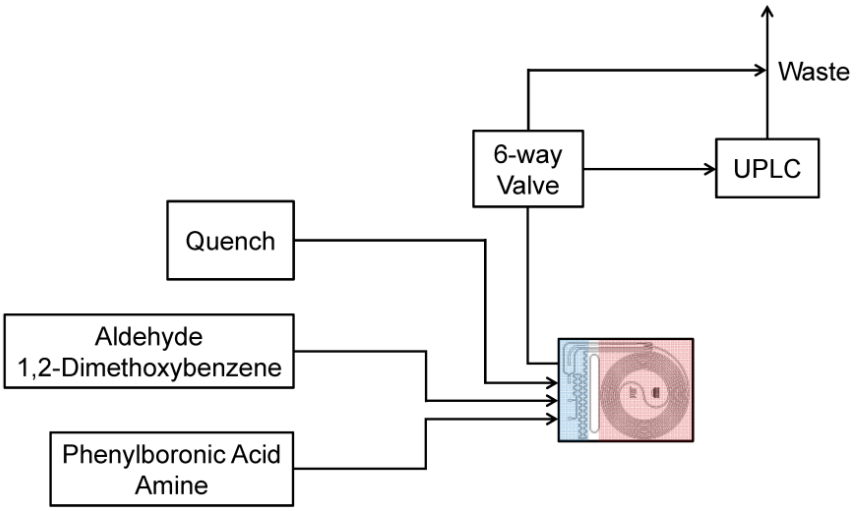


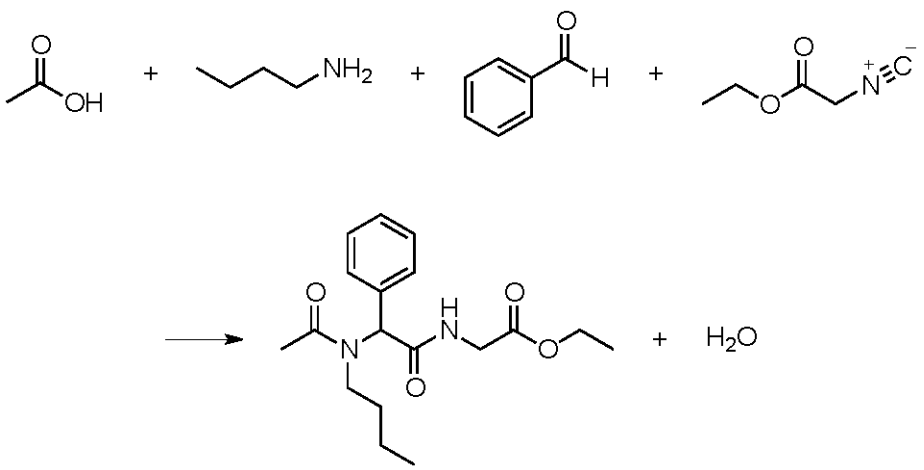
Figure S2. Setup of the microreactor system employed to study the Petasis reaction.

Morpholine, salicylaldehyde, and phenylboronic acid One of the 8-mL Harvard Apparatus stainless steel syringes was filled with an equimolar 0.1 M solution of salicylaldehyde and 1,2-dimethoxybenzene (DMB); 122.12 mg salicylaldehyde and 138.16 mg DMB were dissolved in N,N-dimethylformamide (DMF) using a 10-mL volumetric flask. The other 8-mL syringe was filled with a solution of PBA and 3 equivalents of morpholine; 121.93 mg PBA and 261.36 mg morpholine were dissolved in DMF using a 10-mL volumetric flask. As quench, pure DMF was flowed from a 10-mL S.G.E. glass syringe. All three syringes were driven at equal flow rates.

Piperidine, glyoxylic acid, and phenylboronic acid One of the 8-mL Harvard Apparatus stainless steel syringes was filled with a solution of 1.5 M glyoxylic acid and 0.2 M DMB, which served as an internal standard; 1380.75 mg glyoxylic acid and 276.32 mg DMB were dissolved in dimethylsulfoxide (DMSO) using a 10-mL volumetric flask.

The second 8-mL syringe was filled with a solution of 1 M PBA and 1.5 M piperidine. First, 1219.3 mg PBA were dissolved in 5 mL DMSO. The addition of 1277.25 mg piperidine caused the PBA to precipitate, but the addition of 1 mL trifluoroacetic acid (TFA) redissolved the solid. The 10-mL volumetric flask was then filled with DMSO. As quench, pure DMSO was flowed from a 10-mL S.G.E. glass syringe. All three syringes were driven at equal flow rates.

To begin the examination of the Petasis-Ugi tandem reaction, an individual Ugi reaction was conducted in a batch reactor. The established exemplary reaction involving acetic acid, n-butylamine, benzaldehyde, and ethylisocyanoacetate is shown in Scheme S7. This individual Ugi reaction was only conducted in batch and not in the microreactor setup.



Scheme S7. Ugi reaction of acetic acid, n-butylamine, benzaldehyde, and ethylisocyanoacetate.

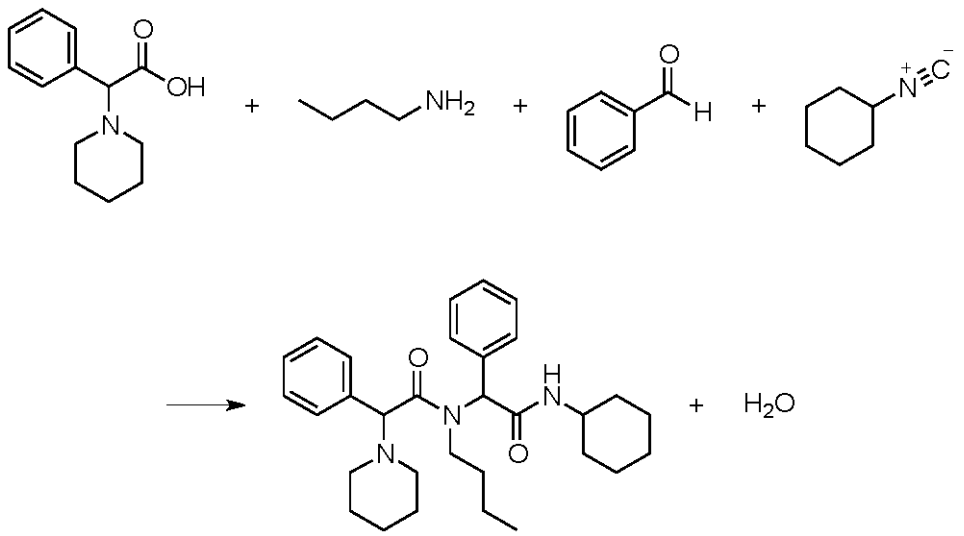
The Ugi reactions in batch were conducted following published experimental guidelines.[21] As recommended in the literature, benzaldehyde and n-butylamine were joined first for about 30 minutes in order to form the intermediate imine before the rest of the reagents were added.

Acetic acid, n-butylamine, benzaldehyde, and ethylisocyanoacetate 106.12 mg (1 mmol) benzaldehyde and 73.14 mg (1 mmol) n-butylamine were reacted in 1 mL methanol at room temperature. After 30 minutes, 60.05 mg (1 mmol) acetic acid and 113.11 mg (1 mmol) ethylisocyanoacetate were added and the solution left at room temperature for 18 hours. In the next step, the Ugi reaction was conducted employing the isolated and purified aminoacid formed by the Petasis reaction, n-butylamine, benzaldehyde, and

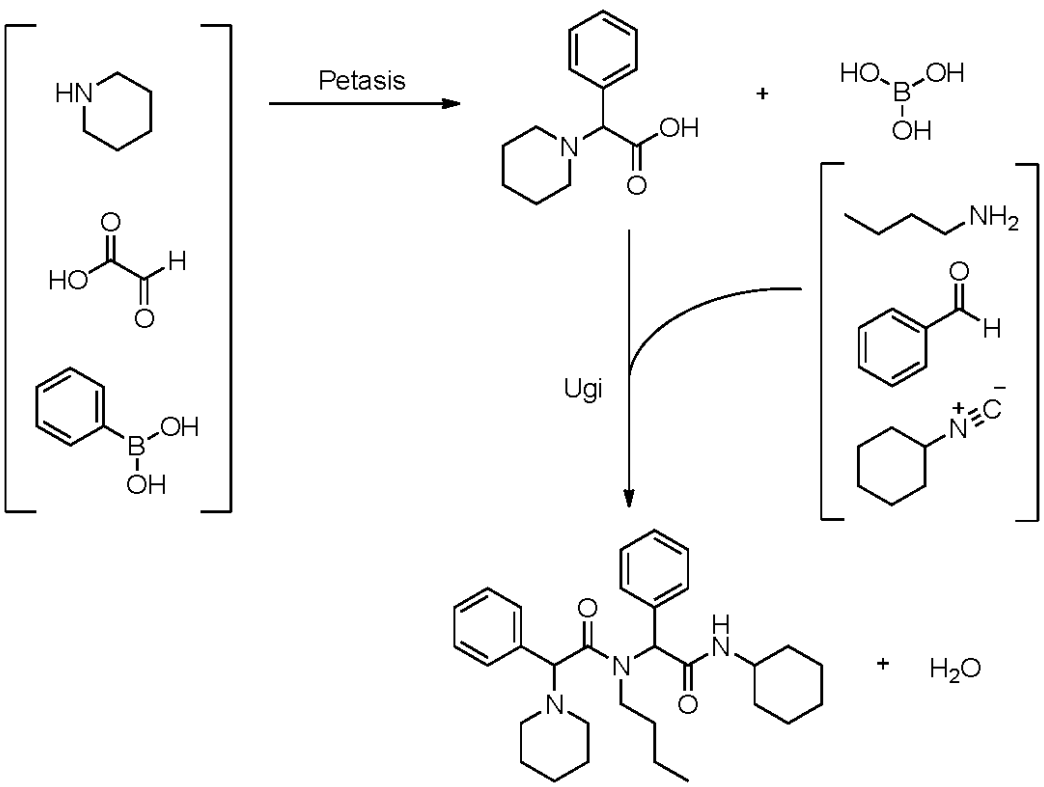
cyclohexylisocyanide. Employing the purified Petasis product, this reaction (Scheme S8) can be seen as an individual Ugi reaction.

Petasis product, n-butylamine, benzaldehyde, and cyclohexylisocyanide 146.28 mg (2 mmol) n-butylamine and 203.3 µL (2 mmol) benzaldehyde were brought to reaction in 2 mL methanol for 30 min at room temperature to form the intermediate imine. Then 249.2 µL (2 mmol) cyclohexylisocyanide and 219.8 mg (1 mmol) of the Petasis product were added. The reaction was conducted in a stirred 20-mL vial at room temperature for 16 h.

The isolation of the final product was accomplished by flash chromatography with silica gel as the stationary phase. A 3:1 mixture of n-hexane and ethylacetate with 1.5% triethylamine was used as eluent. After removal of the solvent, a sticky white solid remained.



Scheme S8. Ugi reaction of the Petasis product, n-butylamine, benzaldehyde, and cyclohexylisocyanide.



Scheme S9. Examined Petasis-Ugi tandem reaction.

The Petasis reaction was conducted as described, but instead of pure DMSO, the Ugi reactants were fed into the quench inlet of the first reactor. The outlet of the first reactor was connected to the second inlet of the second reactor. The first inlet of the second reactor was closed and pure DMSO fed into the quench inlet of the second reactor. This setup (Figure S3) was chosen to avoid dilution of the reactants by a DMSO quench of the first reactor and fluctuations of the product stream composition that would be caused by closing the quench inlet of the first reactor. Both syringes for the Petasis reaction were flowed at the same rate. The Ugi components were flowed at a rate equal to the total flow rate in the first reactor. The chromatogram in Figure S4 was recorded by UPLC-UV/Vis and shows the peaks of the reagents, the desired product, and the two internal standards, 1,2-dimethoxybenzene and naphthalene.

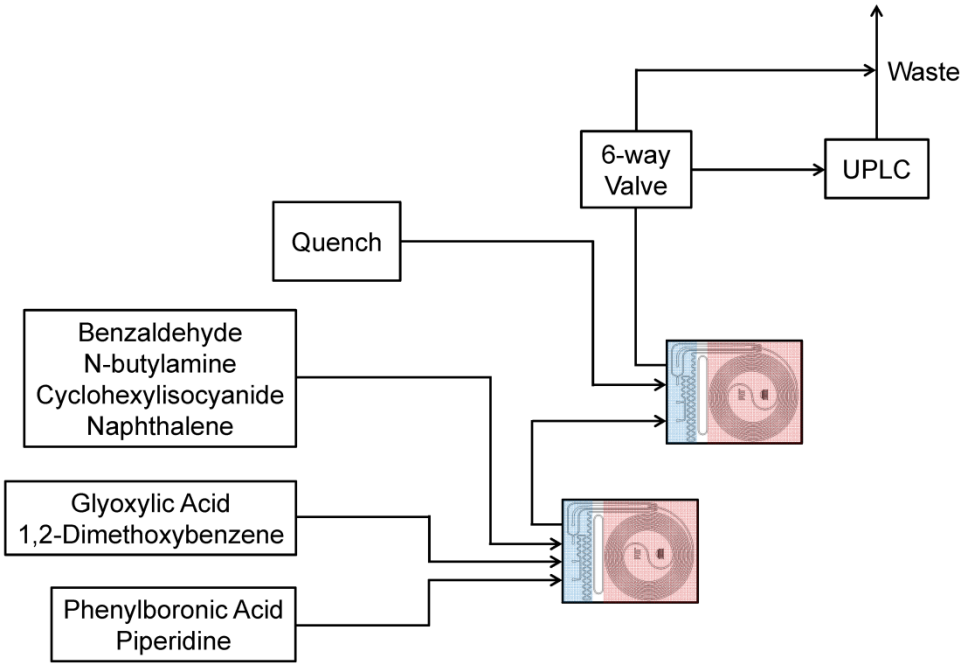


Figure S3. Setup of the microreactor system employed to study the Petasis-Ugi tandem reaction.

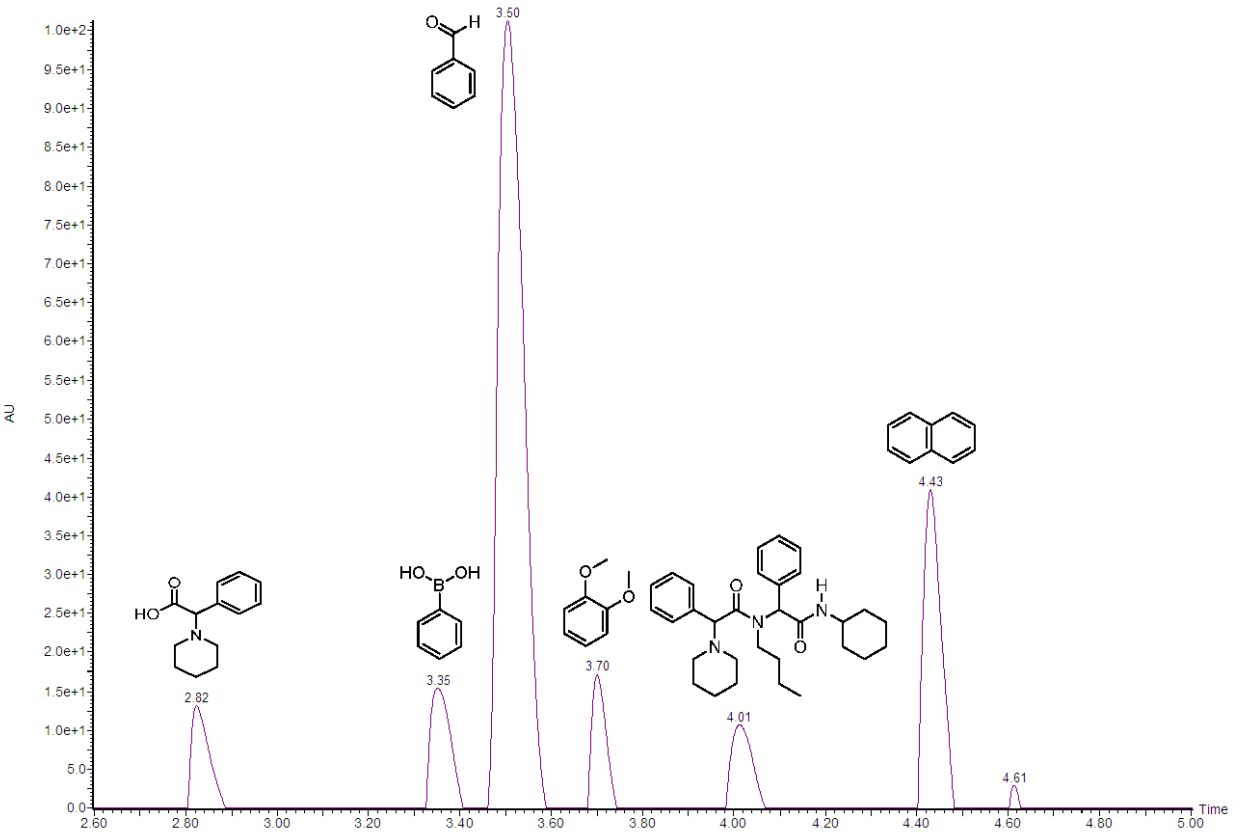


Figure S4. Example UPLC-UV/Vis spectrum of the Petasis-Ugi tandem reaction.

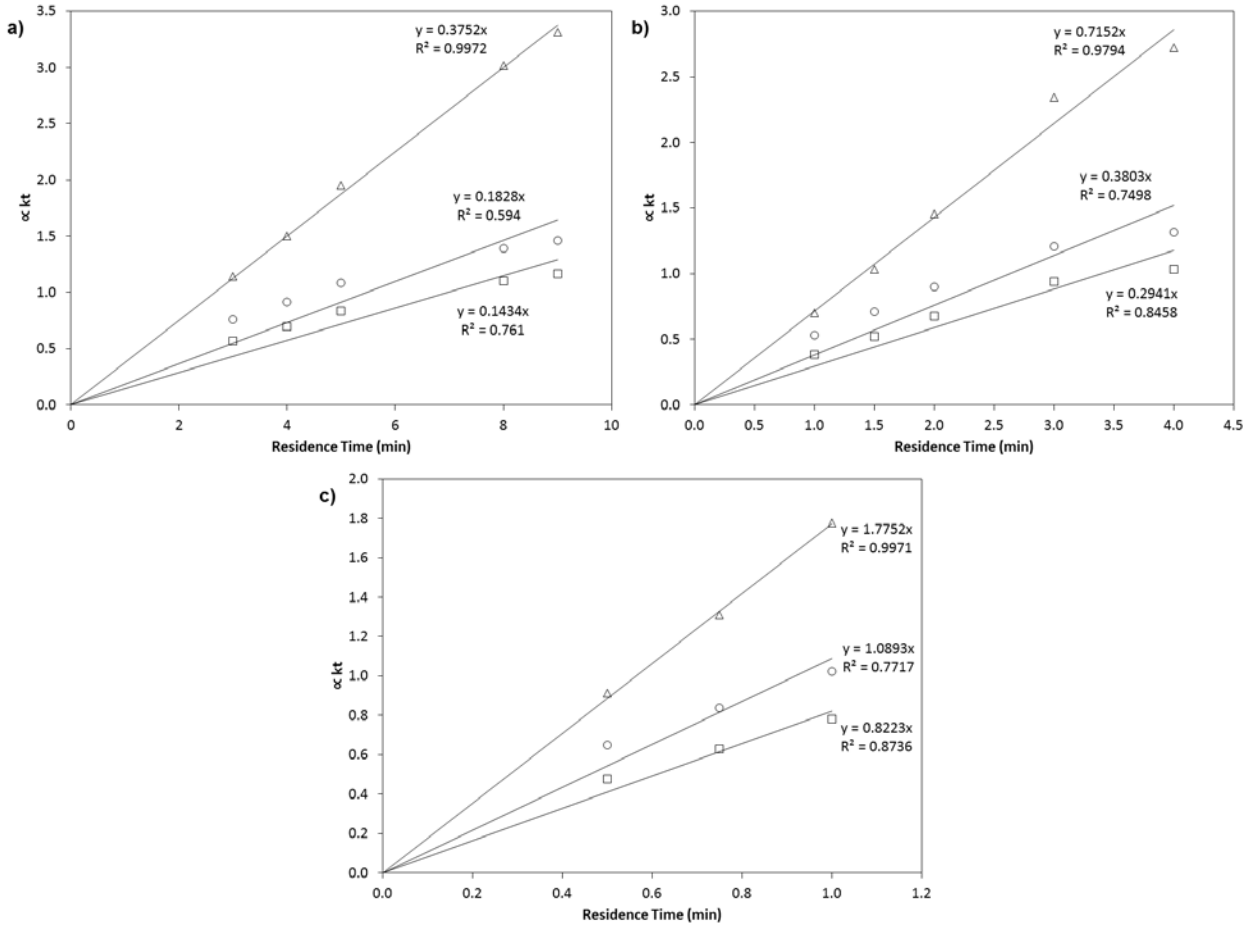


Figure S5. Application of different kinetic models to the experimental data of the Petasis reaction of salicylaldehyde at a) 160 ˚C, b) 180 ˚C, and c) 200 ˚C. Y-axis is proportional to kt resulting from each kinetic model: first-order (O), second-order non-equimolar (□), second-order equimolar (△) rate-limiting step.

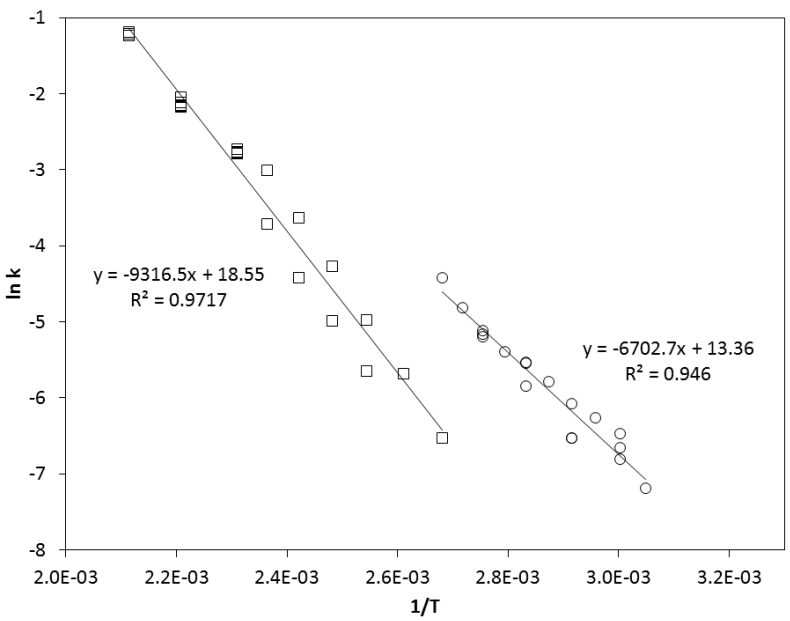


Figure S6. Arrhenius plot of ln k (L/mol·s) versus 1/T (K^{-1}) used to determine the activation energy of the Petasis reaction of salicylaldehyde (□) and the Petasis reaction of glyoxylic acid (O).

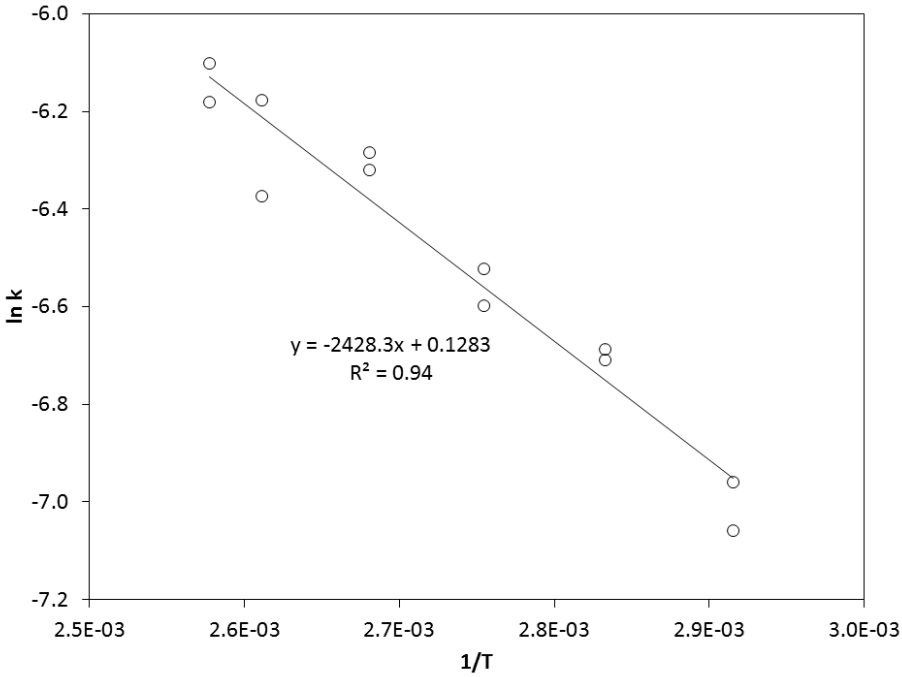


Figure S7. Arrhenius plot of ln k (L/mol·s) versus 1/T (K-1) for the Ugi reaction employing the Petasis product as a reactant.

Table S1. Salicylaldehyde Petasis yield vs. temperature.

Temperature (°C)	Residence Time (min)	Yield	Side Product
90	10	0.000	0
100	10	0.081	0
110	10	0.169	0
120	10	0.294	0
130	10	0.458	0
140	10	0.612	0
150	10	0.748	0
160	10	0.787	0
170	10	0.787	0.08
180	10	0.672	0.102
190	10	0.607	0.149
200	10	0.516	0.187
210	10	0.405	0.235
100	5	0.000	0
110	5	0.000	0
120	5	0.095	0
130	5	0.171	0
140	5	0.264	0
150	5	0.422	0
160	5	0.554	0
165	5	0.578	0
170	5	0.599	0
175	5	0.616	0
180	5	0.685	0.028
185	5	0.649	0.043
190	5	0.678	0.056
195	5	0.694	0.072
200	5	0.678	0.095
210	5	0.629	0.133
220	5	0.483	0.124

Table S2. Salicylaldehyde Petasis yield vs. residence time.

Temperature (°C)	Residence Time (min)	Yield
160	3	0.533
160	4	0.600
160	5	0.661
160	8	0.751
160	9	0.768
160	10	0.764
160	11	0.710
160	12	0.733
160	14	0.545
180	1	0.413
180	1.5	0.508
180	2	0.592
180	3	0.701
180	4	0.731
180	5	0.707
180	6	0.709
200	0.5	0.477
200	0.75	0.567
200	1	0.640
200	1.5	0.678
200	2	0.713
200	2.5	0.739
200	3	0.688
200	3.5	0.686
200	4	0.694
200	4.5	0.665
200	5	0.689
200	6	0.680
200	7	0.672
200	8	0.651
200	10	0.547

Table S3. Petasis reaction of 0.6 M glyoxylic acid, 0.6 M piperidine, and 0.5 M PBA.

Temperature (°C)	Residence Time (min)	Yield	Conversion	Side Product
60	10	0.480	0.683	0.000
70	10	0.579	0.751	0.000
80	10	0.635	0.818	0.000
90	10	0.774	0.879	0.004
100	10	0.879	0.899	0.041
110	10	0.758	0.846	0.080
120	10	0.734	0.816	0.093

Table S4. Petasis reaction of 0.75 M glyoxylic acid, 0.75 M piperidine, and 0.5 M PBA.

Temperature (°C)	Residence Time (min)	Yield	Conversion
35	3.5	0.000	0.550
35	3.5	0.000	0.569
40	3.5	0.000	0.561
45	3.5	0.000	0.567
50	3.5	0.090	0.554
50	3.5	0.000	0.578
55	3.5	0.137	0.577
60	3.5	0.189	0.586
60	3.5	0.212	0.588
65	3.5	0.286	0.616
70	3.5	0.235	0.610
70	3.5	0.235	0.687
75	3.5	0.392	0.653
80	3.5	0.451	0.669
80	3.5	0.454	0.647
85	3.5	0.488	0.712
90	3.5	0.558	0.705
90	3.5	0.538	0.727
95	3.5	0.631	0.732

Table S5. Petasis-Ugi tandem reaction.

Petasis Temperature (°C)	Petasis Residence Time (min)	Ugi Temperature (°C)	Ugi Residence Time (min)	Yield	Conversion	Side Product 1	Side Product 2
100	10	60	6.66	0.140	0.298	0.000	0.000
100	10	60	6.66	0.144	0.303	0.000	0.000
100	10	70	6.66	0.256	0.353	0.000	0.000
100	10	70	6.66	0.275	0.333	0.000	0.000
100	10	80	6.66	0.333	0.331	0.000	0.000
100	10	80	6.66	0.327	0.367	0.000	0.000
100	10	90	6.66	0.353	0.357	0.000	0.000
100	10	90	6.66	0.370	0.355	0.000	0.000
100	10	100	6.66	0.418	0.450	0.000	0.000
100	10	100	6.66	0.427	0.451	0.000	0.000
100	10	110	6.66	0.405	0.482	0.000	0.000
100	10	110	6.66	0.453	0.449	0.000	0.000
100	10	115	6.66	0.472	0.452	0.000	0.000
100	10	115	6.66	0.452	0.467	0.000	0.000
100	10	120	6.66	0.480	0.448	0.153	0.000
100	10	125	6.66	0.450	0.504	0.174	0.000
100	10	125	6.66	0.438	0.510	0.113	0.000
100	10	130	6.66	0.457	0.480	0.181	0.000
100	10	130	6.66	0.449	0.492	0.173	0.000
100	10	135	6.66	0.410	0.559	0.188	0.000
100	10	135	6.66	0.382	0.574	0.167	0.000
100	10	140	6.66	0.409	0.588	0.211	0.159
100	10	140	6.66	0.397	0.599	0.205	0.153
100	10	145	6.66	0.337	0.733	0.121	0.228
100	10	145	6.66	0.312	0.761	0.108	0.204

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