

Electronic Supplementary Information

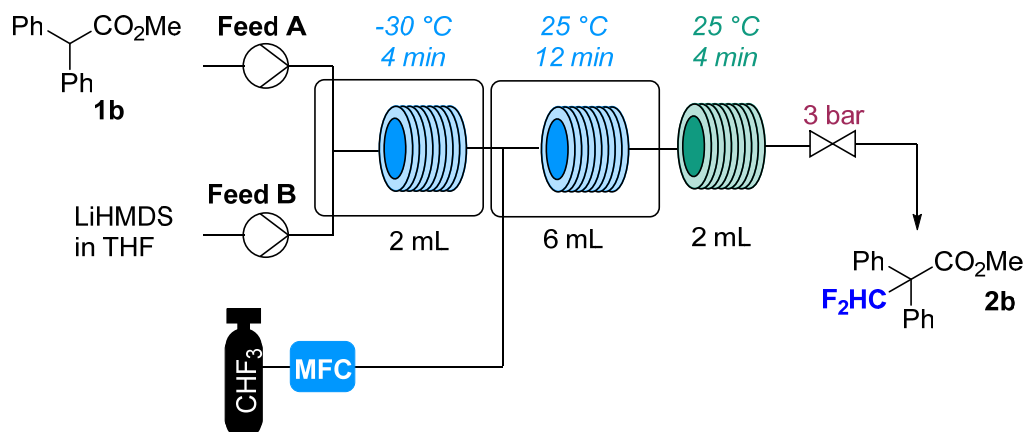
Utilization of fluoroform for difluoromethylation in continuous flow: a concise synthesis of α -difluoromethyl-amino acids

**Manuel Köckinger,^a Tania Ciaglia,^a Michael Bersier,^b Paul Hanselmann,^b Bernhard
Gutmann^{*ac} and C. Oliver Kappe^{*ac}**

^a *Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria.*

^b *Microreactor Technology, Lonza AG, CH-3930 Visp, Switzerland.*

^c *Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, 8010 Graz, Austria.*

Table S1 Difluoromethylation of methyl diphenylacetate **1b** under continuous flow conditions^a

	LiHMDS (equiv)	CHF ₃ (equiv)	conv (%) ^b	sel (%) ^b
1	1.3	3	30	53
2	2.0	3	43	74
3	3.0	3	34	62
4	4.0	3	35	71

^aConditions: Feed A: 0.5 M diethyl phenylmalonate **1b** in THF; Feed B: 1 M LiHMDS in THF; with flow rates for CHF₃ = 8.3 mL/min; flow rates of Feed A and Feed B were adjusted to yield the desired stoichiometry; the following conditions were obtained: LiHMDS (1.3-4.0 equiv); CHF₃ (3 equiv).

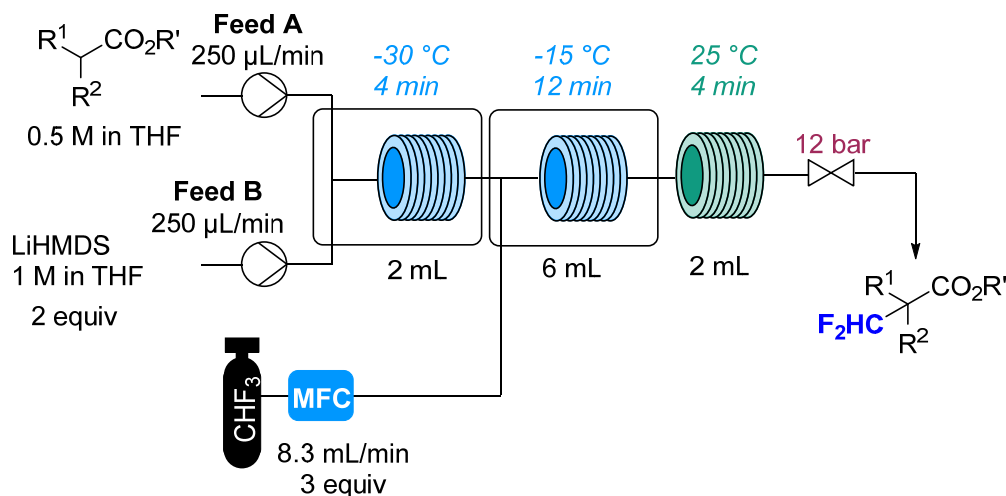
^banalyzed by GC-FID.

Experimental Section

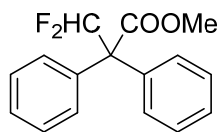
General

¹H and ¹³C NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Analytical HPLC analysis were carried out on a Shimadzu LC20-AD chromatograph equipped with a C18 reversed-phase (RP) analytical column (150 x 4.6mm, particle size 5 μm) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 3% B to 25% in 9 minutes, 25% B to 80% in 7 min hold at 80% B for 1 minute. Low resolution mass spectra were obtained on a LC-MS instrument using electrospray ionization (ESI) in positive or negative mode (Shimadzu LCMS-2020). All chemicals, solvents, catalysts, and ligands were obtained from known commercial suppliers and were used without any further purification. Microwave reactions were carried out in a Biotage Initiator+ single-mode microwave instrument. Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel. Thin-layer chromatography was performed on tlc silica gel 60 f254 20 x 20 cm. Trifluorotoluene was used as internal standard for ¹⁹F NMR.

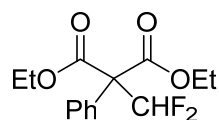
General procedure for continuous flow difluoromethylation



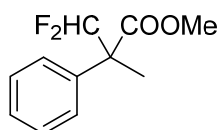
The flow setup consisted of two continuous syringe pumps (Asia Syrris) to introduce (i) a solution of substrate in THF (Feed A), and (ii) a commercial solution of LiHMDS (1.0 M in THF, Sigma-Aldrich); Feed B). Injection loops (perfluoroalkoxy alkanes (PFA), 0.8 mm i.d., 1.59 mm o.d.; internal volume: 2.0 mL (Feed A) and 2.5 mL (Feed B)) were used to deliver the two feeds. To start the experiment, the complete reactor setup was flushed by pumping dry THF with flow rates of Feed A = 250 $\mu\text{L}/\text{min}$ and Feed B = 250 $\mu\text{L}/\text{min}$. Fluoroform was introduced into the reactor with a flow rate of 8.3 mL/min using a calibrated Bronkhorst mass flow controller (MFC). The internal pressure of the reactor reached the target pressure of 12 bar after approximately 10 min. Substrate (1.00 mmol) was dissolved in neat THF and diluted to 2.00 mL in a volumetric flask with THF (Feed A). A LiHMDS solution (1.0 M, 2.5 mL) in THF was used as Feed B. Both solutions were loaded into their corresponding injection loops. Feed A and Feed B were pumped from the injection loops in a Y-shaped connector (Y Assembly PEEK 1/4-28 0.040in) in a cooling bath ($-30\text{ }^\circ\text{C}$). The combined mixture went through a first residence loop at $-30\text{ }^\circ\text{C}$ (1/16 in. o.d.; 0.8 mm i.d.; residence volume $V_1 = 2.0\text{ mL}$), before the mixture was combined with fluoroform in a second Y-shaped connector (Y Assembly PEEK 1/4-28 .040in) in a second cooling bath ($-15\text{ }^\circ\text{C}$). The combined mixture then went through a second residence loop (1/16 in. o.d.; 0.8 mm i.d.; residence volume $V_2 = 6.1\text{ mL}$) and left the flow system through a third residence loop at room temperature (1/8 in. o.d.; 1.6 mm i.d.; residence volume $V_3 = 2.0\text{ mL}$) and an adjustable back pressure regulator (Swagelok KCB1H0A2A5P60000, 0–26 bar).

Methyl 3,3-(difluoro)-2,2-diphenylpropanoate (2a)

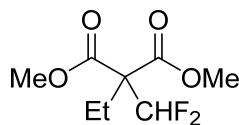
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/2 (v/v)). Yield: 173 mg (0.62 mmol, 62%); 93% by ^{19}F NMR ;light yellow viscous liquid. ^1H NMR (300 MHz, D_2O): δ = 7.45 – 7.19 (m, 10H), 6.90 (t, $^2J_{\text{HF}}$ = 55.0 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 171.1, 136.3, 129.8, 128.3, 128.2, 115.6 (t, $^1J_{\text{CF}}$ = 246.2 Hz), 64.7, 53.1. ^{19}F NMR (282 MHz, D_2O): δ = -123.0 (d, $^2J_{\text{HF}}$ = 55.0 Hz).

Diethyl 2-(difluoromethyl)-2-phenylmalonate (2b)

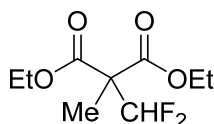
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/2 (v/v)). Yield: 21 mg (0.07 mmol, 7%); 7% by ^{19}F NMR ;light yellow viscous liquid. ^1H NMR (300 MHz, D_2O): δ = 7.45 – 7.31 (m, 5H), 6.56 (t, $^2J_{\text{HF}}$ = 54.9 Hz, 1H), 4.44 – 4.32 (m, 4H), 1.33 (t, $^3J_{\text{HH}}$ = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, D_2O): δ = 166.2, 129.5, 128.8, 128.3, 114.2 (t, $^1J_{\text{CF}}$ = 251.6 Hz), 62.8, 14.1. ^{19}F NMR (282 MHz, D_2O): δ = -123.57 (d, $^2J_{\text{HF}}$ = 55.0 Hz).

Diethyl 2-(difluoromethyl)-2-phenylmalonate (2c)

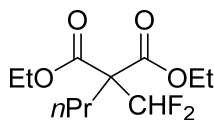
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/2 (v/v)). Yield: 39% by ^{19}F NMR. ^1H NMR (300 MHz, D_2O): δ = 7.42 – 7.31 (m, 5H), 6.38 (dd, $^2J_{\text{HF}}$ = 56.0, 55.4 Hz, 1H), 3.75 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 136.6, 129.0, 128.3, 126.7, 116.7 (dd, $^1J_{\text{CF}}$ = 247.1, 245.5 Hz), 54.8, 52.8, 14.7. ^{19}F NMR (282 MHz, D_2O): δ = -124.48 (dd, $^2J_{\text{FF}}$ = 277.0, $^2J_{\text{HF}}$ = 55.3 Hz), -129.91 (dd, $^2J_{\text{FF}}$ = 277.1, $^2J_{\text{HF}}$ = 56.1 Hz).

Dimethyl 2-(difluoromethyl)-2-ethylmalonate (2d)

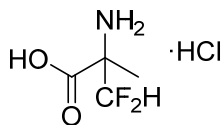
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/1 (v/v)). Yield: 172 mg (0.82 mmol, 82%); 93% by ^{19}F NMR; light yellow viscous liquid. ^1H NMR (300 MHz, D_2O): δ = 6.28 (t, $^2J_{\text{HF}}$ = 54.6 Hz, 1H), 3.79 (s, 6H), 2.14 (q, $^3J_{\text{HH}}$ = 7.5 Hz, 2H), 1.01 (t, $^3J_{\text{HH}}$ = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 167.3 (t, $^3J_{\text{CF}}$ = 4.4 Hz), 115.1 (t, $^1J_{\text{CF}}$ = 247.9 Hz), 62.0 (t, $^2J_{\text{CF}}$ = 21.2 Hz), 53.2, 23.0 (t, $^3J_{\text{CF}}$ = 2.9 Hz), 9.4 (t, $^3J_{\text{CF}}$ = 1.6 Hz). ^{19}F NMR (282 MHz, D_2O): δ = -126.18 (d, $^2J_{\text{HF}}$ = 54.6 Hz).

Diethyl 2-(difluoromethyl)-2-methylmalonate (2e)

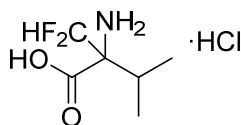
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/1 (v/v)). Yield: 82% by ^{19}F NMR; light yellow viscous liquid. ^1H NMR (300 MHz, D_2O): δ = 6.32 (t, $^2J_{\text{HF}}$ = 55.4 Hz, 1H), 4.21 (q, $^3J_{\text{HH}}$ = 7.1 Hz, 4H), 1.50 (s, 3H), 1.24 (t, $^3J_{\text{HH}}$ = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, D_2O): δ = 167.0 (t, $^3J_{\text{CF}}$ = 4.9 Hz), 114.6 (t, $^1J_{\text{CF}}$ = 246.2 Hz), 62.4, 58.3 (t, $^2J_{\text{CF}}$ = 22.7 Hz), 13.9, 12.1 (t, $^3J_{\text{CF}}$ = 4.0 Hz). ^{19}F NMR (282 MHz, D_2O): δ = -128.32 (d, $^2J_{\text{HF}}$ = 55.4 Hz).

Diethyl 2-(difluoromethyl)-2-propylmalonate (2f)

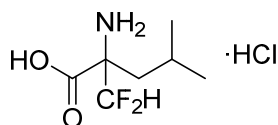
The product mixtures were collected and the solvent removed in vacuo. The products were isolated by thin layer chromatography (dichloromethane/hexane = 3/1 (v/v)). Yield: 80% by ^{19}F NMR; ^1H NMR (300 MHz, D_2O): δ = 6.27 (t, $^2J_{\text{HF}}$ = 54.7 Hz, 1H), 4.25 (q, $^3J_{\text{HH}}$ = 7.1 Hz, 4H), 2.07 – 1.98 (m, 2H), 1.49 – 1.33 (m, 2H), 1.27 (t, $^3J_{\text{HH}}$ = 7.1 Hz, 6H), 0.95 (t, $^3J_{\text{HH}}$ = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 166.8 (t, $^3J_{\text{CF}}$ = 4.5 Hz), 115.1 (t, $^1J_{\text{CF}}$ = 247.7 Hz), 62.0, 61.6, 31.4 (t, $^3J_{\text{CF}}$ = 2.4 Hz), 18.0, 14.6, 14.0. ^{19}F NMR (282 MHz, D_2O): δ = -126.10 (d, $^2J_{\text{HF}}$ = 54.7 Hz).

α -Difluoromethylalanine hydrochloride (2g)

The reaction mixture was concentrated in vacuo and diluted with 10 mL Et₂O. After filtration the filtrate was concentrated in vacuo and treated with 10 mL 6N HCl. The reaction mixture was heated to 150 °C for 45 min in a microwave reactor and washed with Et₂O (2x20 mL). The aqueous layer was mixed with activated carbon which was subsequently filtered off. After concentrating the crude product in vacuo it was recrystallized from MeOH/EtOH. Yield: 151 mg (0.86 mmol, 86%); colourless powder. mp 272 °C; ¹H NMR (300 MHz, D₂O): δ = 6.32 (t, ²J_{HF} = 53.1 Hz, 1H), 1.60 (s, 3H). ¹³C NMR (75 MHz, D₂O): δ = 169.2 (d, ³J_{CF} = 6.2 Hz), 114.3 (dd, ¹J_{CF} = 249.1 Hz, ¹J_{CF} = 246.0 Hz), 61.4 (dd, ²J_{CF} = 20.9 Hz, ²J_{CF} = 19.3 Hz), 16.8 (dd, ³J_{CF} = 4.6 Hz, ³J_{CF} = 2.1 Hz). ¹⁹F NMR (282 MHz, D₂O): δ = -126.77 (dd, ²J_{FF} = 281.4, ²J_{HF} = 52.7 Hz), -133.44 (dd, ²J_{FF} = 281.6, ²J_{HF} = 53.4 Hz).

 α -Difluoromethylvaline hydrochloride (2h)

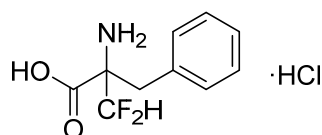
The reaction mixture was dried in vacuo and diluted with 10 mL Et₂O. After filtration the filtrate was concentrated in vacuo and treated with 10 mL 6N HCl. The reaction mixture was heated to 150 °C for 45 min in the microwave reactor and washed with Et₂O (2x20 mL). The aqueous layer was mixed with activated carbon which was subsequently filtered off. After concentrating the crude product in vacuo it was recrystallized from MeOH/EtOH. Yield: 155 mg (0.76 mmol, 76%); colourless powder. mp 272-282 °C; ¹H NMR (300 MHz, D₂O): δ = 6.47 (t, ²J_{HF} = 52.8 Hz, 1H), 2.33 (h, ³J_{HH} = 6.9 Hz, 1H), 1.07 (d, ³J_{HH} = 6.9 Hz, 3H), 1.02 (d, ³J_{HH} = 6.9 Hz, 3H). ¹³C NMR (75 MHz, D₂O): δ = 168.7, 114.8 (dd, ¹J_{CF} = 249.0 Hz, ²J_{CF} = 244.3 Hz), 68.5 (t, ²J_{CF} = 17.5 Hz), 30.30 (d, ³J_{CF} = 4.3 Hz), 16.6, 15.9. ¹⁹F NMR (282 MHz, D₂O): δ = -126.46 (dd, ²J_{FF} = 283.9, ²J_{HF} = 52.3 Hz), -130.72 (dd, ²J_{FF} = 281.6, ²J_{HF} = 53.3 Hz).

 α -Difluoromethylleucine hydrochloride (2i)

The reaction mixture was dried in vacuo and diluted with 10 mL Et₂O. After filtration the filtrate was concentrated in vacuo and treated with 10 mL 6N HCl. The reaction mixture was heated to 150 °C for 45 min in the microwave reactor and washed with Et₂O (2x20 mL). The

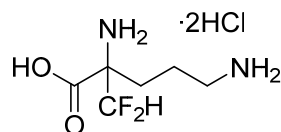
aqueous layer was mixed with activated carbon which was subsequently filtered off. After concentrating the crude product in vacuo it was recrystallized from MeOH/EtOH. Yield: 189 mg (0.87 mmol, 87%); colourless powder. mp 242-243 °C; ^1H NMR (300 MHz, D_2O): δ = 6.21 (t, $^2J_{\text{HF}}$ = 53.4 Hz, 1H), 1.97-1.84 (m, 1H), 1.07 (m, 2H), 0.93(d, $^3J_{\text{HH}}$ = 6.5 Hz, 3H), 0.89(d, $^3J_{\text{HH}}$ = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 170.0 (d, $^3J_{\text{CF}}$ = 5.0 Hz), 115.3 (dd, $^1J_{\text{CF}}$ = 249.1 Hz, $^1J_{\text{CF}}$ = 246.3 Hz), 65.3 (dd, $^2J_{\text{CF}}$ = 20.3 Hz, $^2J_{\text{CF}}$ = 16.2 Hz), 38.7 (d, $^3J_{\text{CF}}$ = 2.3 Hz), 23.5, 22.9, 21.4. ^{19}F NMR (282 MHz, D_2O): δ = -127.14 (dd, $^2J_{\text{FF}}$ = 277.9, $^2J_{\text{HF}}$ = 53.0 Hz), -132.73 (dd, $^2J_{\text{FF}}$ = 277.9, $^2J_{\text{HF}}$ = 53.9 Hz).

α -Difluoromethylphenylalaninehydrochloride (2j)



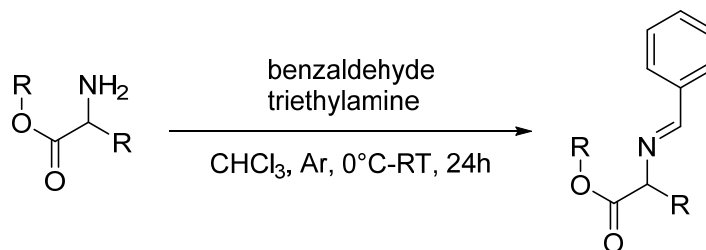
The reaction mixture was dried in vacuo and diluted with 10 mL Et_2O . After filtration the filtrate was concentrated in vacuo and treated with 10 mL 6N HCl. The reaction mixture was heated to 150 °C for 45 min in the microwave reactor and washed with Et_2O (2x20 mL). The aqueous layer was mixed with activated carbon which was subsequently filtered off. After concentrating the crude product in vacuo it was recrystallized from MeOH/EtOH. Yield: 216 mg (0.86 mmol, 86%); colourless powder. mp 245 °C; ^1H NMR (300.36 MHz, D_2O): δ = 7.40-7.32 (m, 3H), 7.26-7.20 (m, 2H), 6.39 (t, $^2J_{\text{HF}}$ = 53.1 Hz, 1H), 3.44 (d, $^2J_{\text{HH}}$ = 14.3 Hz, 1H), 3.06 (d, $^2J_{\text{HH}}$ = 14.3 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ = 168.6 (d, $^3J_{\text{CF}}$ = 5.9 Hz), 131.5, 130.1, 129.2, 128.4, 114.8 (dd, $^1J_{\text{CF}}$ = 249.0 Hz, $^1J_{\text{CF}}$ = 246.4 Hz), 66.5 (dd, $^2J_{\text{CF}}$ = 20.3 Hz, $^2J_{\text{CF}}$ = 16.9 Hz), 36.5 (d, $^3J_{\text{CF}}$ = 2.8 Hz). ^{19}F NMR (282 MHz, D_2O): δ = -127.01 (dd, $^2J_{\text{FF}}$ = 280.8, $^2J_{\text{HF}}$ = 52.6 Hz), -132.02 (dd, $^2J_{\text{FF}}$ = 280.8, $^2J_{\text{HF}}$ = 53.6 Hz).

α -Difluoromethylornithinedihydrochloride (2k)



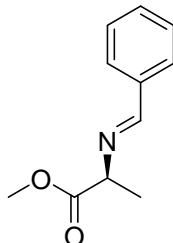
The reaction mixture was dried in vacuo and diluted with 10 mL Et_2O . After filtration the filtrate was concentrated in vacuo and treated with 10 mL 6N HCl. The reaction mixture was heated to 150 °C for 45 min in the microwave reactor and washed with Et_2O (2x20 mL). The aqueous layer was mixed with activated carbon which was subsequently filtered off. After concentrating the crude product in vacuo it was recrystallized from MeOH/EtOH. Yield: 194 mg (0.76 mmol, 76%) colourless powder. mp 228 °C; ^1H -NMR (300.36 MHz, D_2O): δ = 6.33 (t, $^2J_{\text{HF}}$ = 53.2 Hz, 1H), 3.02 (t, $^3J_{\text{HH}}$ = 7.6 Hz, 2H), 2.16-1.53 (m, 4H). ^{13}C NMR (75 MHz, D_2O): δ = 168.8 (d, $^3J_{\text{CF}}$ = 5.9 Hz), 114.9 (dd, $^1J_{\text{CF}}$ = 248.4 Hz, $^1J_{\text{CF}}$ = 246.0 Hz), 65.1 (dd, $^2J_{\text{CF}}$ = 21.3 Hz, $^2J_{\text{CF}}$ = 16.6 Hz), 38.7, 27.7 (d, $^3J_{\text{CF}}$ = 5.0 Hz), 20.9. ^{19}F NMR (282 MHz, D_2O): δ = 126.83 (dd, $^2J_{\text{FF}}$ = 281.6 Hz, $^2J_{\text{HF}}$ = 52.6 Hz), -132.39 (dd, $^2J_{\text{FF}}$ = 281.6 Hz, $^2J_{\text{HF}}$ = 53.8 Hz).

General procedure for the preparation of benzylidene-protected amino acid esters



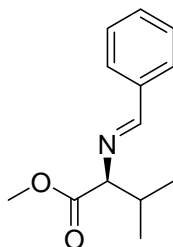
A dry 20 mL vessel with magnetic stirring bar was charged with 1 eq of amino acid ester hydrochloride (**1g** to **1k**), sealed and flushed with argon three times. CHCl_3 was added to afford a 1 M solution followed by the addition of 0.99 eq (1.99 eq in case of ornithine (**1k**)) of benzaldehyde. The resulting stirred solution was cooled to 0 °C. After adding 1.1 eq (2.2 eq in case of ornithine (**1k**)) of triethylamine over 10 min, the mixture was gradually warmed to room temperature and stirred for 24 h. The reaction mixture was filtered through Na_2SO_4 and the obtained light yellow filtrate was concentrated under vacuo and treated with Et_2O to precipitate $\text{Et}_3\text{N}\cdot\text{HCl}$. The formed colourless precipitate was filtered off and the obtained filtrate was concentrated in vacuo to give the benzylidene protected amino acid.

Methyl (S)-2-(benzylideneamino)propanoate (**1g**)

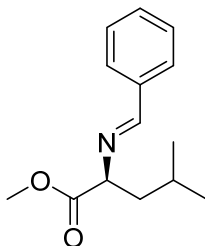


970 mg (6.95 mmol, 1.0 eq) L-Alanine methyl ester hydrochloride, 700 μL (6.88 mmol, 0.99 eq) benzaldehyde, 1.06 mL (7.65 mmol, 1.1 eq) triethylamine and 7 mL CHCl_3 . Yield: 1.289 g (6.74 mmol, 97%), yellow viscous oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 8.31 (s, 1H), 7.81-7.74 (m, 2H), 7.48-7.38 (m, 3H), 4.16 (q, $^3J_{\text{HH}}$ = 6.8 Hz, 1H), 3.75 (s, 3H), 1.53 (d, $^3J_{\text{HH}}$ = 6.8 Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 173.1, 163.1, 135.8, 131.3, 128.7, 128.6, 68.2, 52.4, 19.6.

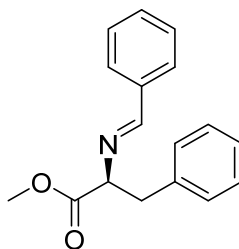
Methyl (S)-2-(benzylideneamino)-3-methylbutanoate (**1h**)



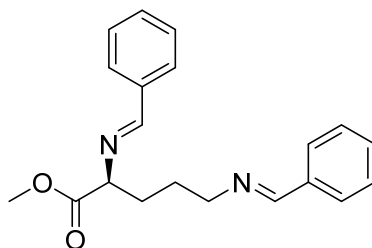
1.165 g (6.95 mmol, 1.0 eq) L-Valine methyl ester hydrochloride, 700 μL (6.88 mmol, 0.99 eq) benzaldehyde, 1.06 mL (7.65 mmol, 1.1 eq) triethylamine and 7 mL CHCl_3 . Yield: 1.4925 g (6.80 mmol, 98%), yellow viscous oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 8.24 (s, 1H), 7.83 – 7.74 (m, 2H), 7.46 – 7.36 (m, 3H), 3.75 (s, 3H), 3.67 (d, $^3J_{\text{HH}}$ = 7.3 Hz, 1H), 2.39 (dq, $^3J_{\text{HH}}$ = 13.7, $^3J_{\text{HH}}$ = 6.8 Hz, 1H), 0.95 (dd, $^3J_{\text{HH}}$ = 8.9, 6.8 Hz, 6H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 172.6, 163.4, 135.8, 131.2, 128.7, 128.7, 80.6, 52.1, 31.9, 19.6, 18.8.

Methyl (S)-2-(benzylideneamino)-4-methylpentanoate (1i)

1.271 g (7.00 mmol, 1.0 eq) L-Leucine methyl ester hydrochloride, 706 μ L (6.93 mmol, 0.99 eq) benzaldehyde, 1.07 mL (7.70 mmol, 1.2 eq) triethylamine and 7 mL CHCl_3 . Yield: 1.609 g (6.90 mmol, 99%), yellow viscous oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 8.23 (s, 1H), 7.76 – 7.70 (m, 2H), 7.36 – 7.29 (m, 3H), 4.05 (dd, $^3J_{\text{HH}}$ = 8.5, 5.9 Hz, 1H), 3.65 (s, 3H), 1.90 - 1.73 (m, 2H), 1.61 – 1.46 (m, 1H), 0.87 (dd, $^3J_{\text{HH}}$ = 14.1, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ = 172.5, 162.9, 135.5, 130.9, 128.4, 128.3, 71.3, 51.8, 41.9, 24.2, 23.0, 21.2.

Methyl (S)-2-(benzylideneamino)-3-phenylpropanoate (1j)

1.500 g (6.95 mmol, 1.0 eq) L-Phenylalanine methyl ester hydrochloride, 700 μ L (6.88 mmol, 0.99 eq) benzaldehyde, 1.06 mL (7.65 mmol, 1.1 eq) triethylamine and 7 mL CHCl_3 . Yield: 1.7831 g (6.67 mmol, 96%), yellow viscous oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 7.92 (s, 1H), 7.72-7.66 (m, 2H), 7.45-7.35 (m, 3H), 7.28-7.14 (m, 5H), 4.18 (dd, $^3J_{\text{HH}}$ = 8.8, 5.1 Hz, 1H), 3.75 (s, 3H), 3.39 (dd, $^2J_{\text{HH}}$ = 13.5, $^3J_{\text{HH}}$ = 5.1 Hz, 1H), 3.16 (dd, $^2J_{\text{HH}}$ = 13.5, $^3J_{\text{HH}}$ = 8.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 172.2, 163.9, 137.5, 135.6, 131.2, 129.9, 128.6, 128.6, 128.4, 126.7, 75.2, 52.4, 39.9.

Methyl (S)-2,5-bis((benzylidene)amino)pentanoate (1k)

1.530 g (7.00 mmol, 1.0 eq) L-Ornithine methyl ester dihydrochloride, 1.42 mL (13.93 mmol, 1.99 eq) benzaldehyde, 2.13 mL (15.4 mmol, 2.2 eq) triethylamine and 7 mL CHCl_3 . Yield: 2.2136 g (6.87 mmol, 98%), yellow viscous oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 7.68-7.56 (m, 4H), 7.47-7.29 (m, 12H), 7.20-7.08 (m, 4H), 4.10 (dd, $^3J_{\text{HH}}$ = 8.0 Hz, $^3J_{\text{HH}}$ = 5.2 Hz, 1H), 3.71 (s, 3H), 3.33 (t, $^3J_{\text{HH}}$ = 6.8 Hz, 2H), 2.07-1.88 (m, 2H), 1.79-1.54 (m, 2H).

