

Electronic Supplementary Information

Flash Carboxylation: Fast Lithiation - Carboxylation Sequence at Room Temperature in Continuous Flow

Bartholomäus Pieber, Toma Glasnov and C. O. Kappe*

Christian Doppler Laboratory for Flow Chemistry and Institute of Chemistry, University of Graz, Heinrichstrasse 28, 8010 Graz, Austria.

Fax: +43(316)3809840; E-mail: toma.glasnov@uni-graz.at; oliver.kappe@uni-graz.at

General Remarks. All substrates and reagents were purchased from Sigma-Aldrich and were used without further purification. THF (HPLC grade) was dried using molecular sieves (3Å) prior to use. ^1H -NMR and ^{13}C spectra were recorded on a Bruker 300 MHz instrument using DMSO_{d6} or CDCl_3 as solvent. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate a singlet, doublet, triplet, quadruplet, and multiplet respectively. Melting points were determined on a StuartTM SMP3 melting point apparatus. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 \times 4.6 mm, particle size 5 μm) at 25 $^\circ\text{C}$ using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 1.0 mL/min. The following gradient was applied: linear increase from solution 30% B to 100 % B in 8 min, hold at 100% solution B for 2 min. All synthesized compounds have been characterized by ^1H and ^{13}C NMR analysis as well as their melting points and identified by data reported in literature.

Continuous Flow Set up

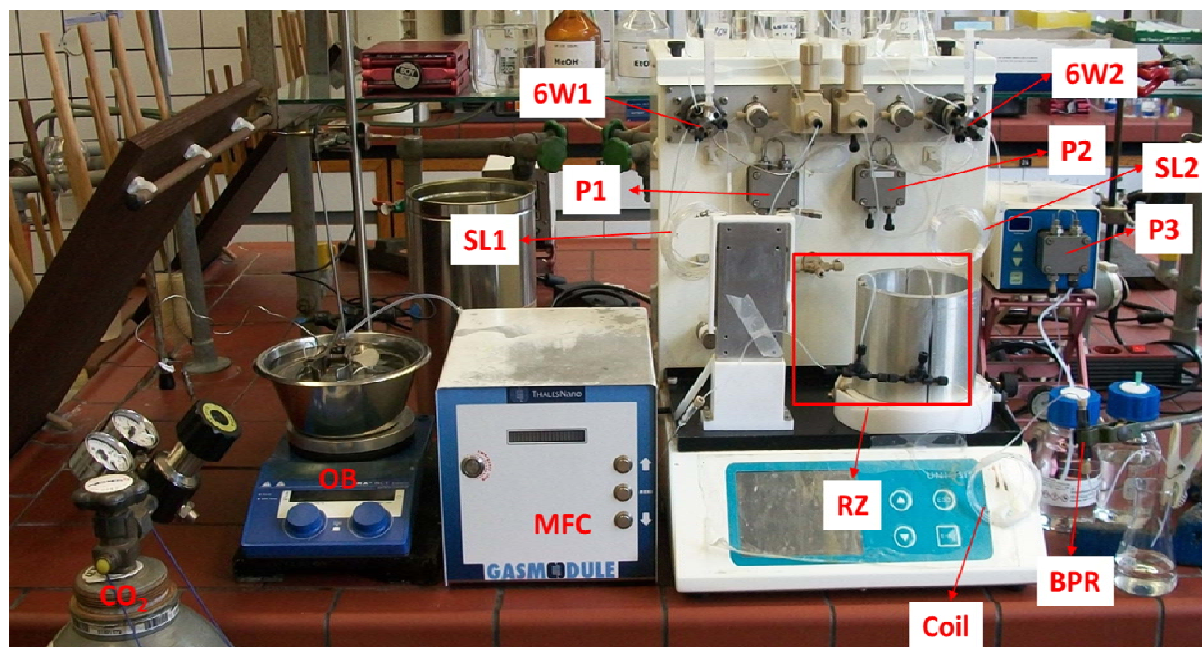


Figure S1. 4-Feed gas/liquid continuous flow reactor for carboxylation using CO_2 . Carbon dioxide is preheated using a stainless steel coil (~10 mL) in an oil bath (OB) set at 65°C before entering the mass flow controller (MFC).^{S1} The liquid flow rate of the organometallic base and the substrate in dry THF is controlled using HPLC pumps (P1,P2). The reagents are loaded in either a 4 mL (substrate, SL1) or a 3 mL (base, SL2) sample loop and can be introduced in the flow system by 6 way valves (6W1, 6W2).^{S2} The reaction zone (RZ) is explained in more detailed below (Figure S2). For adding the water quench a third HPLC pump (P3) is used. The reaction mixture and the quench solution pass a 1 mL coil (Coil) for dissolving any precipitates. Pressure regulation occurs in a static 10 bar back pressure regulator (BPR).

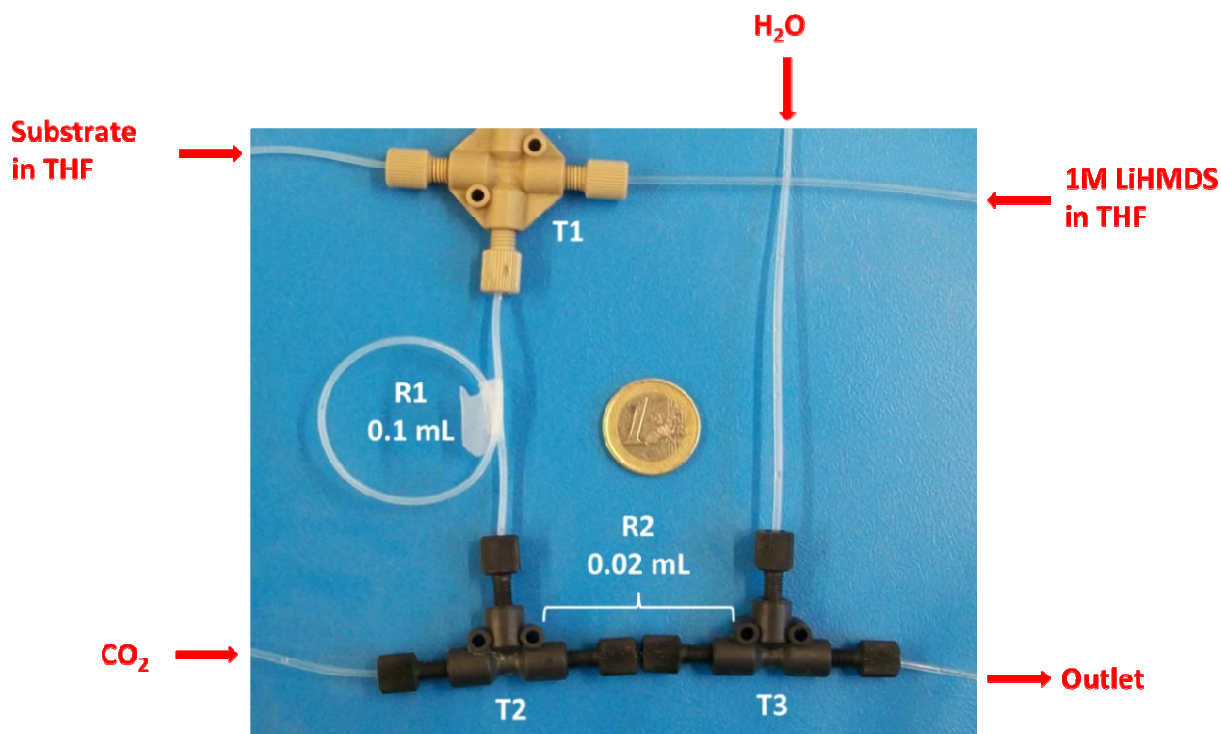


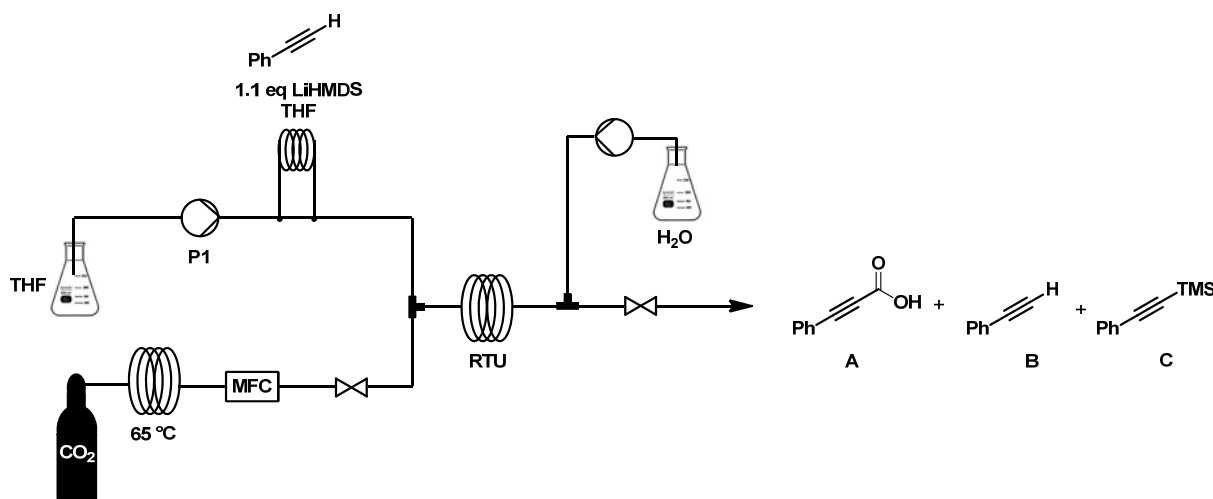
Figure S2. Reaction Zone. The substrate solution is mixed with the organometallic base in a T-mixing unit (**T1**, i.d. 0.5 mm). Metalation is carried out in a residence time unit made of PTFE (**R1**, i.d. 0.8 mm, 0.1 mL). The organometallic intermediate is mixed with CO_2 in a second T-mixer (**T2**, i.d. 0.5 mm) entering a second residence coil (**R2**, PTFE, i.d. 0.8 mm, 0.02 mL). The reaction is then quenched in a third mixing unit (**T3**, i.d. 0.5 mm) before reaching the back pressure regulator.

General Conditions for Using the Mass Flow Controller^{S1} with CO_2 . The pressure regulator of the gas cylinder was set at 30-40 bar and the system was first flushed with the maximum CO_2 flow rate (74 ml min^{-1}). As soon as the system pressure was reached (~ 10 bar) the liquid streams were activated. After 2-5 minutes additional flushing at the maximum gas the desired gas flow rate was chosen and experiments were started after the gas flow rate got stable.

Cleaning Procedure. In order to avoid clogging or other serious problems during the course of this research study the reactor was flushed with a cleaning solvent after use. The solvent mixture of choice for such efforts is $\text{AcOH}:\text{THF}:\text{H}_2\text{O}$ (1:1:1) which removes all impurities caused by the organometallic reagent/intermediate and traces of water within the reaction solvents. After washing, the reactor was additionally flushed/stored in *i*PrOH.

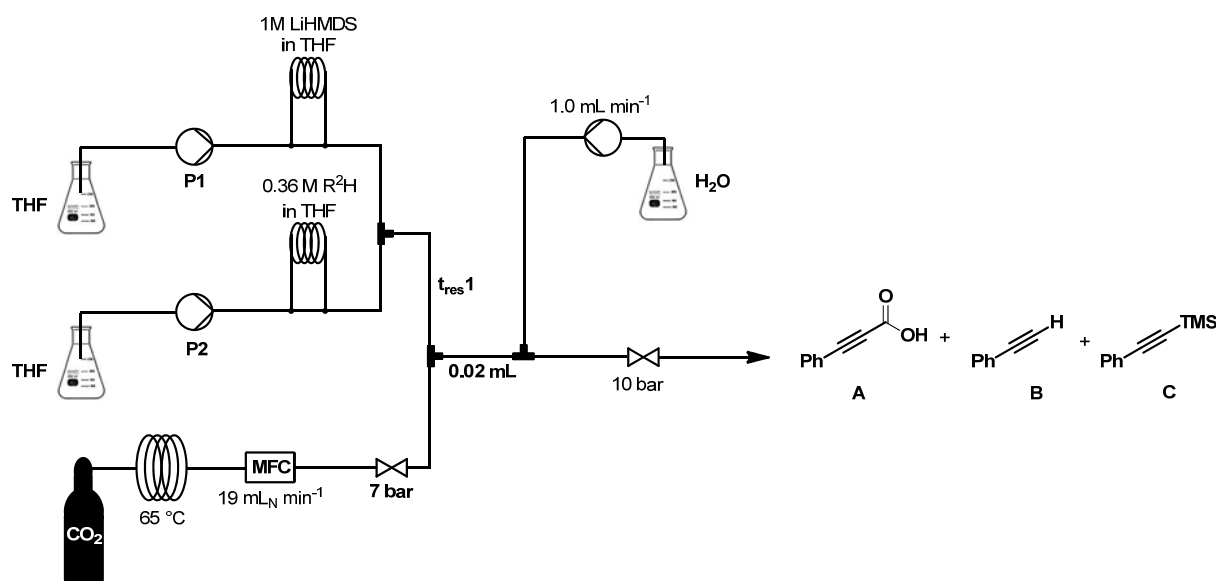
Optimization

Table S1. Optimization of the carboxylation parameters.^a



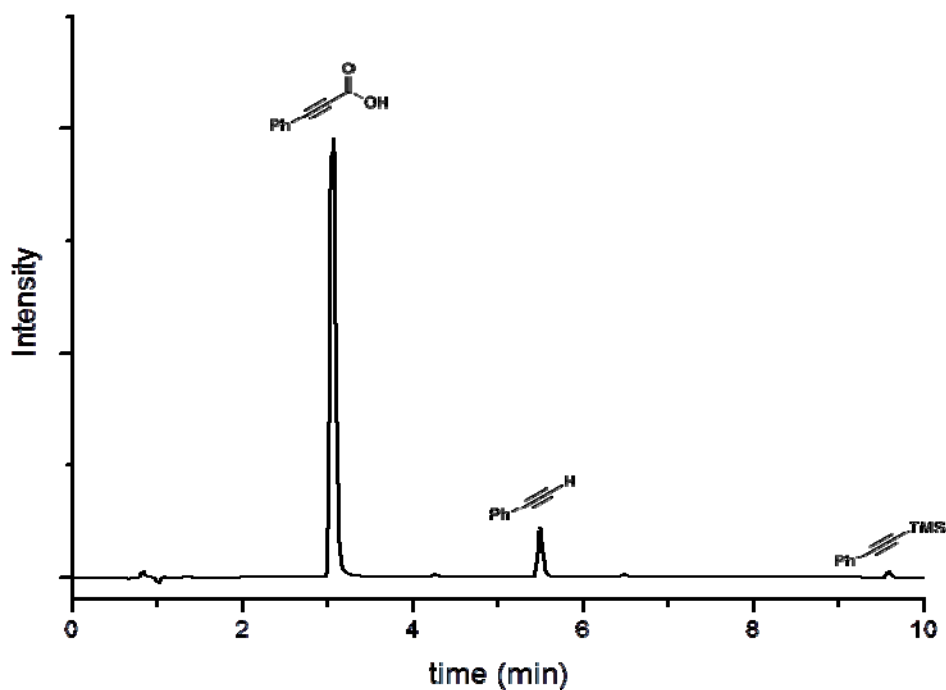
Entry	T (RTU) [°C]	RTU [V]	Liquid Flow (P1)[mL min ⁻¹]	Gas Flow [mL min ⁻¹]	BPR [bar]	A [%] ^c	B [%] ^c	C [%] ^c
1	100	10	0.8	45(9.0) ^b	17	93	7	<1
2	80	10	0.8	45(9.0)	17	96	4	<1
3	60	10	0.8	45(9.0)	17	95	5	<1
4	r.t.	10	0.8	45(9.0)	17	97	3	<1
5	r.t.	10	0.8	45(9.0)	10	97	3	<1
6	r.t.	10	1.5	45(4.8)	10	96	4	<1
7	r.t.	4.0	2	15(1.2)	10	90	5	4
8	r.t.	4.0	2.5	19(1.2)	10	94	5	1
9	r.t.	2.0	3	23(1.2)	10	88	6	6
10	r.t.	1.0	2.5	19(1.2)	10	91	7	1
11	r.t.	1.0	3	23(1.2)	10	93	4	3
12	r.t.	0.1	2.5	19(1.2)	10	92	3	5
13	r.t.	0.02	2.5	19(1.2)	10	92	5	3

^a Conditions: 1 mmol phenylacetylene and 1.1 mmol LiHMDS (1M in THF) were dissolved in 2 mL dry THF and injected via a sample loop. ^b CO₂ equivalents in parentheses. ^c Determined as HPLC-UV/VIS peak area percent at 215 nm.

Table S2. Implementation of the metalation step.^a

Entry	Coil 1 [V]	Liquid Flow (P1) [mL min ⁻¹]	Liquid Flow (P2) [mL min ⁻¹]	A [%] ^b	B [%] ^b	C [%] ^b
1	1	0.7	1.8	87	5	8
2	0.1	0.7	1.8	88	5	7
3	0.02	0.7	1.8	74	14	12

^a The reaction was carried out using 1.42 mmol phenylacetylene. ^c Determined as HPLC-UV/VIS peak area percent at 215 nm.

**Figure S3.** Representative HPLC-UV/VIS chromatogram (215 nm) for the carboxylation of phenylacetylene under the optimized conditions (Table S2, Entry 2)

General experimental procedure for the synthesis of carboxylic acids from alkynes and heterocycles (Table 1, Figure 3). The respective alkyne or heterocycle (1.42 mmol) in dry THF (4 mL) and 3 mL of either an 1 M solution of LiHMDS in THF (commercially available) or an 1M solution of LDA in THF/hexanes (commercially available) were loaded into individual sample loops. Pump 1 was set at 1.8 mL min⁻¹ and pump 2 at 0.7 mL min⁻¹. Sample loop 2 containing the base was switched 45 seconds prior to sample loop 1 to injecting mode in order to avoid diffusion phenomena and guarantee a proper stoichiometry. The 2 streams were combined in a T-mixing unit before passing a 0.1 mL residence time unit. Afterwards, the mixture entered a second T-mixer where CO₂ was introduced at 19 mL_N min⁻¹. Carboxylation occurs in a second residence time unit (0.02 mL) prior to a third mixer where, in case of LiHMDS a water quench (1 mL min⁻¹), or in case of LDA a water:AcOH quench (10:1, 1 mL min⁻¹) was added. The mixture was finally collected after passing a 10 bar static back pressure regulator.

Work up A. THF was removed under reduced pressure and the aqueous residue was extracted twice using Et₂O (15 mL). The organic layer was discarded and the aqueous phase was acidified using concentrated HCl until precipitation (pH ~1). The mixture was cooled in an ice bath, the solid collected by filtration and carefully washed with cold, aqueous HCl (1M) to furnish analytically pure carboxylic acids after drying in a desiccator under reduced pressure.

Work up B. THF was removed under reduced pressure and the aqueous residue was extracted twice using Et₂O (15 mL). The organic layer was discarded and the aqueous phase was acidified using HCl (pH ~1). Afterwards, Et₂O (20 mL) was added to extract the carboxylic acid. The organic phase was washed with brine and dried over Na₂SO₄. Evaporation of the organic solvent afforded the respective carboxylic acids which were finally dried in a desiccator under reduced pressure.

3-Phenylpropionic acid (Table 1, 2a). From phenylacetylene (145.1 mg, 1.42mmol) and LiHMDS. Work up A resulted in the title compound as white solid in 85% (177.2 mg, 1.21 mmol). m.p. 132-134°C ¹H NMR (300 MHz, DMSO) δ 13.81 (br, s, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H). ¹³C NMR (75 MHz, DMSO) δ 154.72, 133.04, 131.36, 129.48, 119.40, 84.84, 82.18.

3-(p-Tolyl)propionic acid (Table 1, 2b). From 4-ethynyltoluene (164.9 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as white solid in 81% (184.0 mg, 1.15 mmol). m.p. 143-144°C ¹H NMR (300 MHz, DMSO) δ 13.75 (br, s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 2H). ¹³C NMR (75 MHz, DMSO) δ 154.81, 141.62, 133.04, 130.11, 116.33, 85.31, 81.86, 21.66.

3-(4-Chlorophenyl)propionic acid (Table 1, 1c). From 1-chloro-4-ethynylbenzene (194.0 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as white solid in 78% (199.2 mg, 1.10 mmol). m.p. 184-186°C ¹H NMR (300 MHz, DMSO) δ 13.93 (br, s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (75 MHz, DMSO) δ 154.58, 136.28, 134.82, 129.71, 118.32, 83.55, 83.01.

3-(4-Methoxyphenyl)propionic acid (Table 1, 1d). From 4-ethynylanisole (187.5 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as off-white solid in 84% (211.1 mg, 1.20mmol). m.p. 139-140°C ¹H NMR (300 MHz, DMSO) δ 13.63 (br, s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 1H). ¹³C NMR (75 MHz, DMSO) δ 161.66, 154.96, 135.12, 115.19, 111.00, 85.75, 81.51, 55.94, 55.89.

3-(4-(Trifluoromethyl)phenyl)propionic acid (Table 1, 1f). From 4-ethynyl- α,α,α -trifluorotoluene (240.9 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as white solid in 89% (270.3 mg, 1.26mmol). m.p. 142-145°C ¹H NMR (300 MHz, DMSO) δ 14.11 (br, s, 1H), 7.92 – 7.79 (m, 4H). ¹³C NMR (75 MHz, DMSO) δ 154.36, 133.78, 131.11, 130.68, 126.36, 126.32, 126.27, 126.22, 125.94, 123.81, 123.79, 122.33, 83.91, 82.72.

3-(Thiophen-3-yl)propionic acid (Table 1, 1g). From 3-ethynylthiophene (153.2 mg, 1.42 mmol) and LiHMDS. Work up B resulted in the title compound as off-white solid in 81% (174.6 mg, 1.15mmol).m.p. 133-135°C ¹H NMR (300 MHz, DMSO) δ 13.76 (br, s, 1H), 8.20 (dd, *J* = 2.8, 1.0 Hz, 1H), 7.71 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.33 (dd, *J* = 5.0, 1.0 Hz, 1H). ¹³C NMR (75 MHz, DMSO) δ 154.84, 135.34, 130.38, 128.23, 118.35, 82.00, 80.77.

3-Cyclohexylpropionic acid (Table 1, 1i). From ethynylcyclohexane (153.6 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as yellow oil in 90% (193.6 mg, 1.27 mmol). ¹H NMR (300 MHz, DMSO) δ 13.38 (br, s, 1H), 2.68 – 2.55 (m, 1H), 1.77 (m, 2H), 1.63 (m, 2H), 1.53 – 1.21 (m, 6H). ¹³C NMR (75 MHz, DMSO) δ 154.82, 91.72, 74.61, 31.51, 28.21, 25.52, 24.53.

3-Cyclopentylpropionic acid (Table 1, 1j). From ethynylcyclopentene (133.6 mg, 1.42 mmol) and LiHMDS. Work up A resulted in the title compound as off-white solid in 66% (128.9 mg, 0.93mmol). m.p. 55-57°C ¹H NMR (300 MHz, DMSO) δ 13.33 (br, s, 1H), 2.93 – 2.68 (m, 1H), 2.07 – 1.78 (m, 2H), 1.77 – 1.42 (m, 6H). ¹³C NMR (75 MHz, DMSO) δ 154.80, 92.31, 74.15, 33.09, 29.27, 25.16.

Thiophene-2-carboxylic acid (Figure 3, 4a). From thiophene (119.3 mg, 1.42 mmol) and LDA. Work up B resulted in the title compound as white solid in 79% (143.8 mg, 1.12mmol). m.p. 125-127°C. ¹H NMR (300 MHz, DMSO) δ 13.02 (s, 1H), 7.88 (d, *J* = 4.9 Hz, 1H), 7.73 (d, *J* = 2.5 Hz, 1H), 7.18 (m, 1H). ¹³C NMR (75 MHz, DMSO) δ 163.37, 135.08, 133.73, 133.66, 128.68.

5-Methylthiophene-2-carboxylic acid (Figure 3, 4b). From 2-methylthiophene (138.9 mg, 1.42 mmol) and LDA. Work up A resulted in the title compound as off-white solid in 48% (95.6 mg, 0.67mmol). m.p. 132-134°C. ¹H NMR (300 MHz, CDCl₃) δ 10.41 (s, 1H), 7.73 (d, *J* = 3.7 Hz, 1H), 6.83 (d, *J* = 3.7 Hz, 1H), 2.57 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.60, 149.98, 135.60, 130.02, 126.79, 15.95.

4-Methylthiophene-2-carboxylic acid (Figure 3, 4c). From 3-methylthiophene (139.1 mg, 1.42 mmol) and LDA. Work up A resulted in the title compound as off-white solid in 43% (85.7 mg, 0.60 mmol). m.p. 118-120°C. ¹H NMR (300 MHz, DMSO) δ 12.96 (s, 1H), 7.56 – 7.53 (m, 1H), 7.47 (s, 1H), 2.23 (s, 3H). ¹³C NMR (75 MHz, DMSO) δ 163.38, 138.68, 135.42, 134.60, 129.07, 15.66.

5-Chlorothiophene-2-carboxylic acid (Figure 3, 4d). From 2-chlorothiophene (167.8 mg, 1.42 mmol) and LDA. Work up A resulted in the title compound as light brown solid in 72% (166.7 mg, 1.03 mmol). m.p. 149-151°C. ¹H NMR (300 MHz, DMSO) δ 13.45 (s, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.23 (d, *J* = 4.0 Hz, 1H). ¹³C NMR (75 MHz, DMSO) δ 162.25, 135.25, 133.88, 133.66, 128.96.

Benzo[*b*]thiophene-2-carboxylic acid (Figure 3, 4e). From benzo[*b*]thiophene (190.3 mg, 1.42 mmol) and LDA. Work up A resulted in the title compound as white solid in 70% (176.2 mg, 0.99 mmol). m.p. 238-240°C. ¹H NMR (300 MHz, DMSO) δ 13.47 (s, 1H), 8.12 (s, 1H), 8.08 – 7.98 (m, 2H), 7.56 – 7.42 (m, 2H). ¹³C NMR (75 MHz, DMSO) δ 163.99, 141.77, 139.18, 135.18, 130.72, 127.49, 126.20, 125.53, 123.44.

Benzofuran-2-carboxylic acid (Figure 3, 4f) From benzofuran (190.3 mg, 1.42 mmol) and LDA. Work up A resulted in the title compound as yellow solid in 46% (105.3 mg, 0.65 mmol). m.p. 190-192°C. ¹H NMR (300 MHz, DMSO) δ 13.58 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H). ¹³C NMR (75 MHz, DMSO) δ 160.54, 155.42, 146.60, 128.02, 127.29, 124.28, 123.55, 113.97, 112.53.

References

[S1] <http://www.thalesnano.com>

[S2] <http://www.uniqlsis.com>

