Electronic Supplementary Information

Direct Aerobic Oxidation of 2-Benzylpyridines in a Gas-Liquid Continuous-Flow Regime Using Propylene Carbonate as Solvent

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General Remarks. All chemicals were purchased from Sigma-Aldrich, or Alfa Aesar and were used without further purification. Reagents were weighed and handled in air at room temperature. ^{1}H-NMR and ^{13}C spectra were recorded on a Bruker 300 MHz instrument using $CDCl_3$ 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. Melting points were determined on a Stuart™ SMP3 melting point apparatus. GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector using a HP5 column (30 m×0.250 mm×0.025 μm). After 1 min at 50°C the temperature was increased in 25°C min^{-1} steps up to 300°C and kept at 300°C for 4 min. The detector gas for the flame ionization is H_2 and compressed air (5.0 quality).GC-MS analysis was performed on a Trace-GC Ultra – DSQ II-MS system (ThermoElectron, Waltham, MA, USA). The GC conditions were as follows: HP-5 MS column (30 m × 0.25 mm ID, 0.25 μm film, Agilent, Waldbronn, Germany); carrier gas helium 5.0, flow 1 mL min^{-1}, temperature gradient identical to GC-FID. The MS conditions were as follows: positive EI ionization, ionization energy 70 eV, ionization source temperature 280 °C, emission current 100 μA; full-scan-mode. Silica gel flash chromatography separations were performed on a Biotage SP1 instrument using petroleum ether/ethyl acetate mixtures as eluent.

Gas-Liquid continuous flow reactor

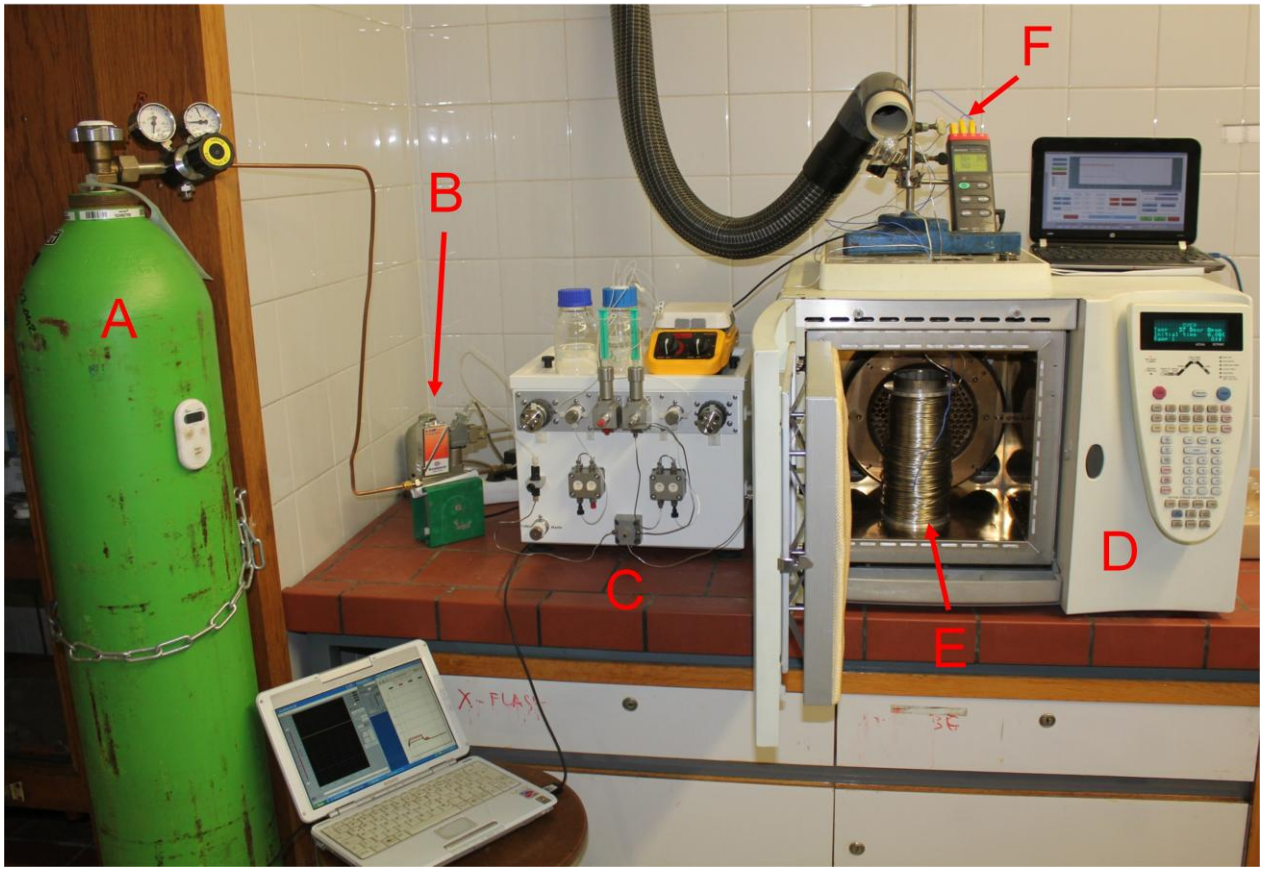


Fig. S1: Gas-liquid continuous flow reactor. The main parts of this custom-built device are a gas bottle (synthetic air, 5.0 quality) with a 50 bar pressure regulating valve (**A**), a mass flow controller (**B**),[S1] a binary pumping module (**C**),[S2] a GC oven (**D**) to heat the residence time unit (**E**) and a digital 4-channel-thermometer equipped with three thermocouples (**F**) to monitor the reaction temperature at different positions of the reaction coil.[S3]

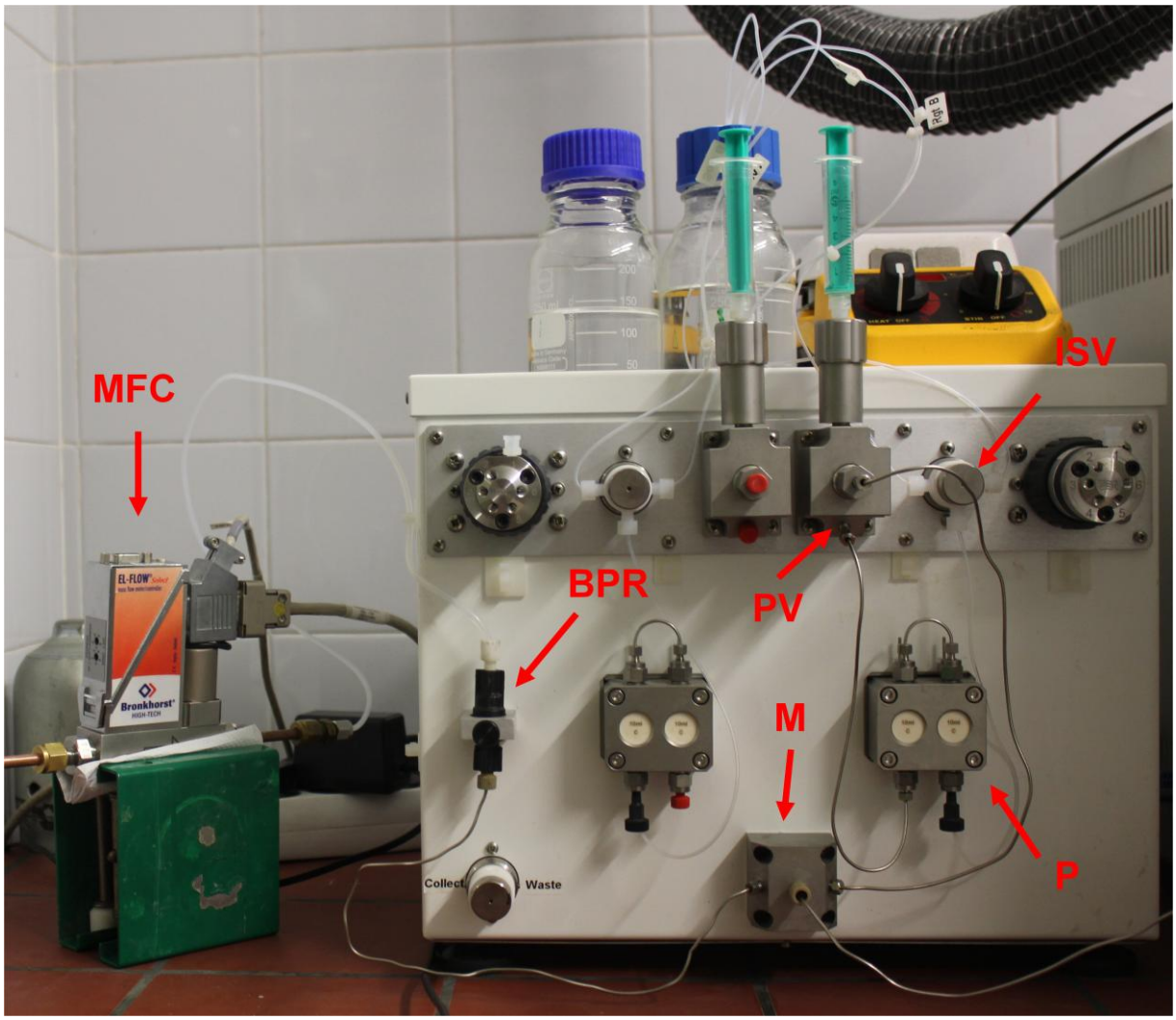


Fig. S2: Mass Flow controller (MFC, EL-FLOW Select F-201CV-5K0)[S1] and the Uniqsis Binary Pumping Module.[S2] The gaseous reagent (synthetic air) is controlled by the MFC and mixed with the liquid phase in a T-mixer (**M**) containing a pressure transducer after passing a 7 bar backpressure regulator (**BPR**). The liquid stream enters the binary pumping module through an inlet selection valve (**ISV**) which is used to control the liquid feed (*e.g.* either solvent or reagent). The flow rate is controlled by a HPLC pump (**P**) allowing flow rates from 0.01 to 10 mL min^{-1}. The priming valve (**PV**) equipped with another pressure transducer enables priming with solvent before performing a reaction. The system constantly monitors the pressure and will stop if the pressure either rises above or falls below the global limits. The maximum allowed pressure of this device is 100 bar.

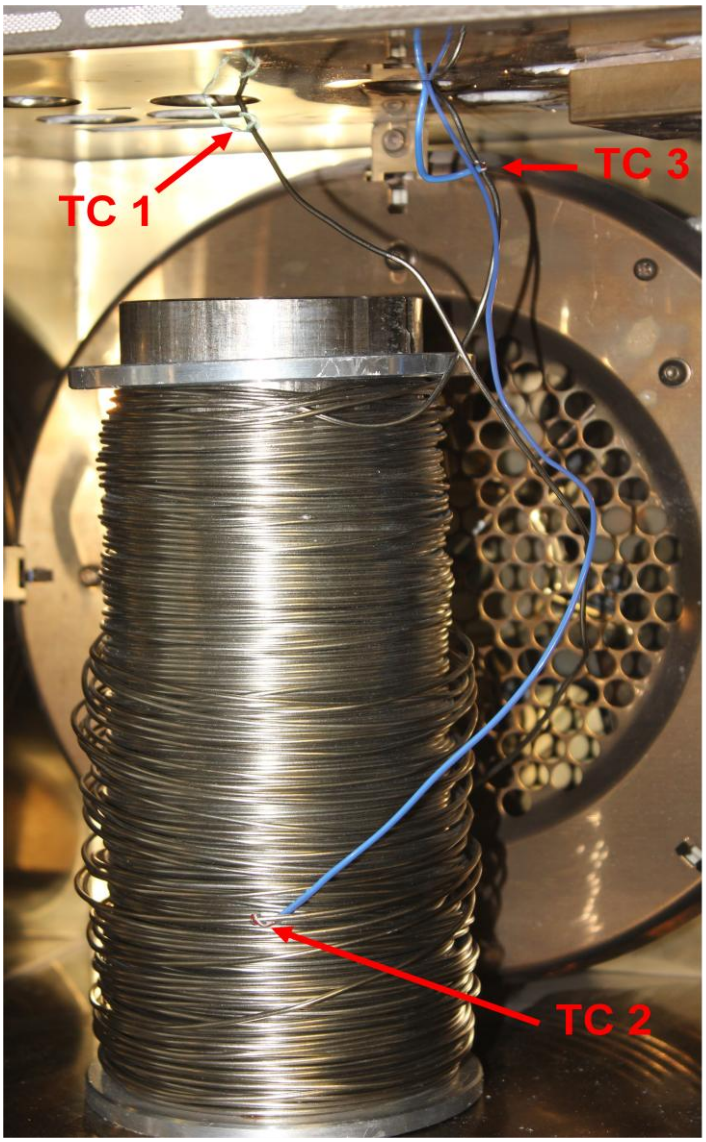


Fig. S3: Residence time unit (120 m stainless steel coil with an inner diameter of 0.8 mm) inside a GC-oven. To monitor the temperature at different positions thermocouples were installed at the entrance of the heated reaction zone (**TC 1**), after approximately 1 m of the coil (**TC 2**) and at the outlet of the oven (**TC 3**).

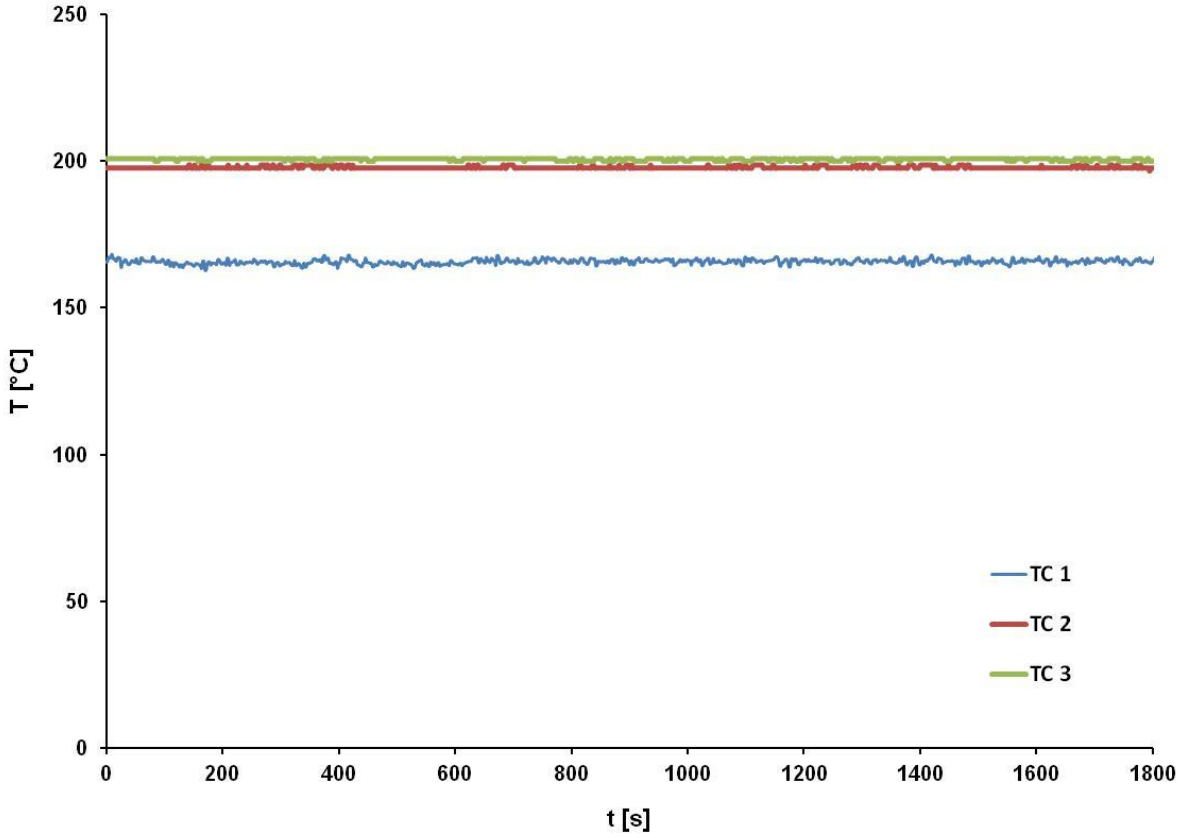
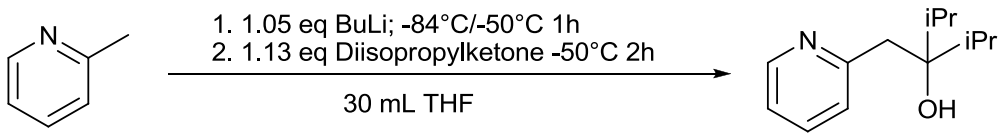


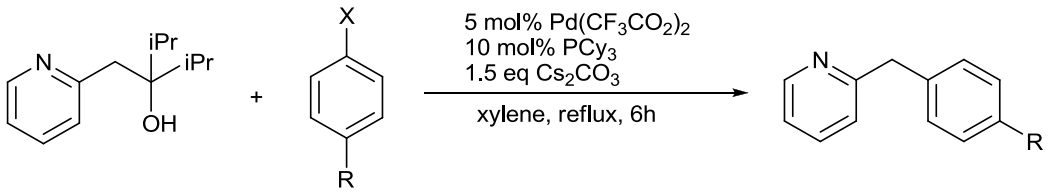
Fig. S3: Temperature profile of the temperature at the entrance of the heated reaction zone (**TC 1**), after approximately 1 m of the coil (**TC 2**) and at the outlet of the oven (**TC 3**) over 30 minutes using the optimized reaction conditions (liquid flow rate: 0.6 mL min^{-1}; air flow rate: 1.7 $_{N}L$ min^{-1}. At the beginning of the heated zone (TC 1) the temperature is significantly lower than the desired temperature (~ 165 °C), after 1 m of the stainless steel coil (TC 2, 198 °C) the temperature raised almost to the target temperature. The thermocouple at the end of the residence time unit (TC 3, 200 °C) shows exactly the reaction temperature.

Synthesis of 2,4-Dimethyl-3-(2-pyridinylmethyl)pentan-3-ol.[S4]



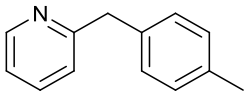
To a stirred solution of 2-methylpyridine (2 mL, 20.3 mmol) in dry THF (30 mL), under Ar-atmosphere was added BuLi (8.5 mL, 2.5 M in hexanes, 21.3 mmol) dropwise at -84 °C. After 30 min stirring at -84 °C the mixture was stirred for 30 min at 50 °C. Then diisopropylketone (3.3 mL, 22.9 mmol) was added and the mixture was stirred further at -50 °C for 2 h. The reaction was then quenched with water (25 mL) and extracted three times with ethyl acetate (25 mL). The combined organic fractions were washed with brine (25 mL), dried over MgSO4, filtered over a pad of Celite and concentrated. Column chromatography with an automated chromatography system using silica flash cartridges applying a heptane-ethyl acetate gradient resulted in 2,4-dimethyl-3-(2-pyridinylmethyl)pentan-3-ol (3.6 g, 86 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.1 Hz, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.23 – 7.07 (m, 2H), 6.33 (s, 1H), 2.91 (s, 2H), 2.01 – 1.82 (m, 2H), 0.89 (dd, *J* = 6.9, 4.8 Hz, 13H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.78, 147.83, 136.80, 124.55, 121.02, 78.11, 38.07, 35.18, 18.17, 17.92.

General procedure for the synthesis of 2-Benzylpyridines.[S4]



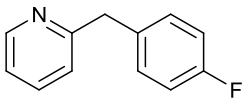
Palladium(II) trifluoroacetate (83 mg, 0.25 mmol), the aryl halide (5.0 mmol), 2,4-dimethyl-3-(2-pyridylmethyl)pentan-3-ol (1.25 g, 6.0 mmol), Cs_2CO_3 (2.45 g, 7.5 mmol), xylene (10 mL) and tricyclohexylphosphine (0.50 mmol) were subsequently transferred in an round bottomed flask. The resulting mixture was flushed with argon for 5 min and stirred at reflux under an argon-atmosphere for 6 h. After cooling to room temperature, the mixture was filtered over a pad of Celite (dichloromethane, 50 mL). The solvent was removed under reduced pressure and the crude residue was finally purified via column chromatography with an automated chromatography system using silica flash cartridges applying a heptane-ethyl acetate gradients.

2-(4-Methylbenzyl)pyridine (1b).



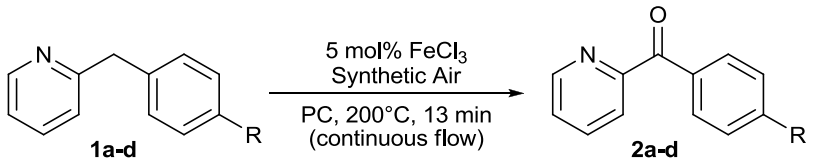
From 1-chloro-4-methylbenzene.Yield: 1.07 g (97 %). Isolated as yellow oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 3.7 Hz, 1H), 7.58 (td, *J* = 7.7, 1.8 Hz, 1H), 7.15 (dt, *J* = 7.7, 5.7 Hz, 6H), 4.14 (s, 2H), 2.34 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.29, 149.31, 136.49, 136.44, 135.88, 129.28, 128.99, 123.02, 121.15, 44.35, 21.03.

2-(4-Fluorobenzyl)pyridine (1d).



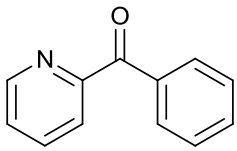
From 1-bromo-4-fluorobenzene. Yield: 843 mg (75 %). Isolated as yellow oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.2 Hz, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.24 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.13 (dd, *J* = 10.1, 6.9 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 4.14 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.21, 160.72, 159.97, 149.45, 136.60, 135.18 (d, *J* = 3.2 Hz) , 130.48 (d, *J* = 7.9 Hz), 123.00, 121.34, 115.34 (d, *J* = 21.2 Hz), 43.83.

General procedure for the direct aerobic oxidation of 2-benzylpyridines (1a-d) in continuous flow.



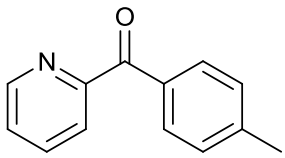
Feed A consisted of the respective 2-benzylpyridine 1 (2.3 mmol), $FeCl_3$ (19 mg; 0.12 mmol) dissolved in propylene carbonate (2 mL), whereas feed B was synthetic air (purity 5.0). The liquid stream (0.6 mL min^{-1}) and the gaseous stream (1.7 $_N$L min^{-1}) were mixed together in a T-shaped mixing device. The resulting biphasic stream was passed through a stainless steel reactor coil (0.8 mm inner diameter, 120 m length) at 200°C. The reaction mixture was collected at the outlet of the coil and isolated by filtration over a plug of silica (20 g) using copious amounts of petroleum ether/ ethyl acetate/ triethylamine (9:1:0.02).

Phenyl(pyridine-2-yl)methanone (2a).



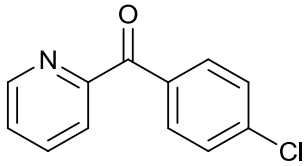
Compound **2a** was isolated in 81 % (338.3 mg) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.12 – 8.02 (m, 3H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.54 – 7.46 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 193.91, 155.10, 148.57, 137.07, 136.27, 132.94, 130.99, 128.17, 126.17, 124.63.

(4-Methylphenyl)(pyridine-2-yl)methanone (2b).



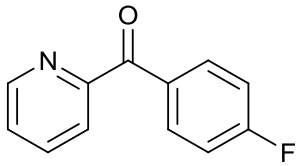
Compound **2b** was isolated in 69 % (321.6 mg) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (ddd, *J* = 4.7, 1.5, 0.8 Hz, 1H), 8.07 – 7.96 (m, 3H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.60, 155.41, 148.50, 143.80, 136.98, 133.63, 131.13, 128.90, 125.98, 124.53, 21.73.

(4-Chlorophenyl)(pyridine-2-yl)methanone (2c).



Compound **2c** was isolated in 81 % (411.4 mg) as white solid. m.p. 62-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 3H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 – 7.42 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 192.43, 154.68, 148.52, 139.41, 137.21, 134.58, 132.50, 128.47, 126.43, 124.69.

(4-Fluorophenyl)(pyridine-2-yl)methanone (2d).



Compound **2d** was isolated in 83 % (391,3 mg) as white solid. m. p. 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.7 Hz, 1H), 8.24 – 8.14 (m, 2H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.23 – 7.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.06, 165.70 (d_{CF}, *J* = 254.9 Hz), 154.90, 148.44, 137.18, 133.80 (d_{CF}, *J* = 9.3 Hz), 132.50 (d_{CF}, *J* = 3.0 Hz), 132.48, 126.29, 124.68, 115.45, 115.31 (d_{CF}, *J* = 21.8 Hz).

References

S1 www.bronkhorst.com

S2 www.uniqsis.com

S3 www.voltcraft.ch

S4 T. Niwa, H. Yorimutsu and K. Oshima, *Angew. Chem. Int. Ed.*, 2007, **46**, 2643-2645