Supporting Information

Palladium-catalyzed aerobic oxidative coupling of *o*-xylene in flow:

a safe and scalable protocol for cross-dehydrogenative coupling

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1. General information

All components as well as reagents and solvents were used as received without further purification, unless stated otherwise. Reagents and solvent were bought from Sigma Aldrich and if required, kept under argon atmosphere. Technical solvents were bought from VWR International and used as received. $Pd(OAc)_2$ was bought from Fluorochem. It should be noted that the supplier for $Cu(OTf)_2$ is crucial as the reaction only worked with $Cu(OTf)_2$ bought from Sigma Aldrich. When the salt with the same specifications from ABCR was used, no conversion could be detected. However, we also observed that a good catalytic reaction could be obtained by freshly mixing Cu(OAc)2 and trifluoromethanesulfonic acid prior to start the reaction. The product isolation was performed using silica (60, F254, Merck™), and TLC analysis was performed using Silica on aluminum foils TLC plates (F254, Supelco Sigma-Aldrich™) with visualization under ultraviolet light (254 nm and 365 nm) or appropriate TLC staining. ^{1}H-NMR, ^{13}C-NMR spectra were recorded on ambient temperature using a Bruker-Avance 400 or Mercury 400. ^{1}H-NMR spectra are reported in parts per million (ppm). Known products were characterized by comparing to the corresponding ^{1}H-NMR and ^{13}C-NMR from literature. All reactions were monitored by GC using a calibration curve with 10% *n*-decane as internal standard accorded to the authentic samples on a GC-FID (Varian 430-GC) in combination with an auto sampler (Varian CP-8400).

2. Assembly of the capillary microreactor system

A schematic representation of the experimental setup and a picture of this setup are shown in Figure S1 and S2. All capillary tubing and microfluidic fittings were purchased from IDEX Health and Science. A six-way valve system was applied to feed pure solvent into the microreactor system with the help of a syringe and thus to save the reaction solution before running a reaction process (Figure S3). Before every run the pumped liquid was degassed. After switching the six-way valve, the reaction solution consisting of solvent, substrate, catalyst, internal standard was introduced into the reaction system by a HPLC pump (Shimadzu LC-20AD). In a metal T-micromixer the liquid was combined with pure oxygen regulated by a mass flow controller (MFC, Bronkhorst) to form slug flow. The reactor consisted of 29.4 m stainless steel capillary tubing (ID = 750 μm) with an inner volume of 13 mL, which was coiled and immersed in the oil bath for providing accurate temperature control. The temperature of the tubing after the oil bath was kept at 50°C by electric heating wires and the use of thermal insulation foam The pressure in the microreactor system was controlled by a back pressure regulator (BPR, Bronkhorst). A cool trap was placed before this BPR in order to capture the evaporated solvent and to protect the BPR. The reaction effluent from the capillary microreactor was first fed into a waste vessel. Then it was directed into a gas-liquid separator by switching a three-way valve after the running reached steady state. In the gas-liquid separator, the gas and liquid phases were separated and the liquid phase including products was further directed into a sample vessel and then into a sample collector. During a run, samples up to 200 μL were taken. The sample was extracted with ethyl acetate and then cleaned with saturated bicarbonate solution. The organic phase was purified over a short plug of silica (Celite) and analysed by GC-FID in order to obtain the product yield and conversion. Such a microreactor system could be operated safely under harsh conditions (e.g., high pressures and high temperatures).

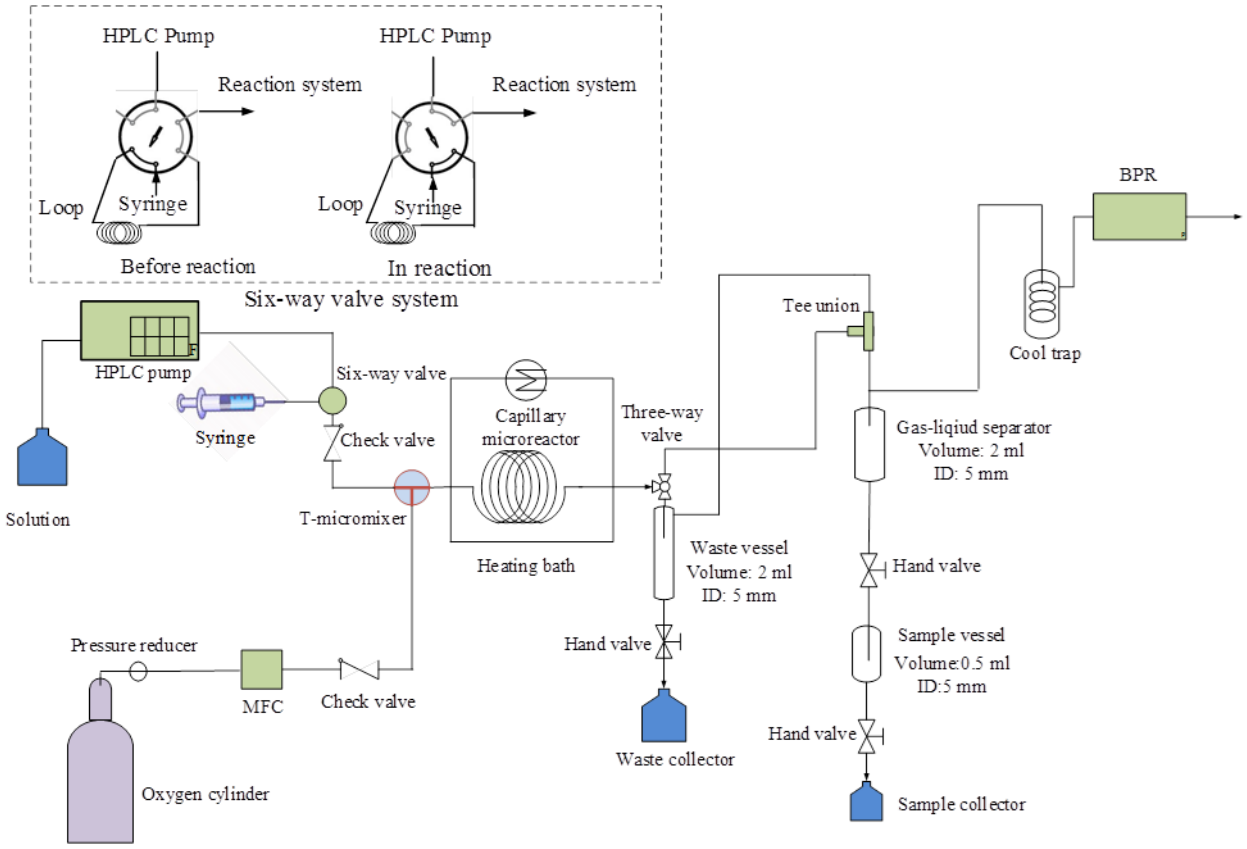


Figure S1. Schematic representation (process scheme) of the capillary microreactor setup for the aerobic cross-dehydrogenative coupling of *o*-xylene. This setup allows to safely employ harsch reaction conditions (up to 70 bar O_2 pressure and > 150 °C).

Figure S2. Picture of the capillary microreactor setup for the aerobic cross-dehydrogenative coupling of o-xylene.

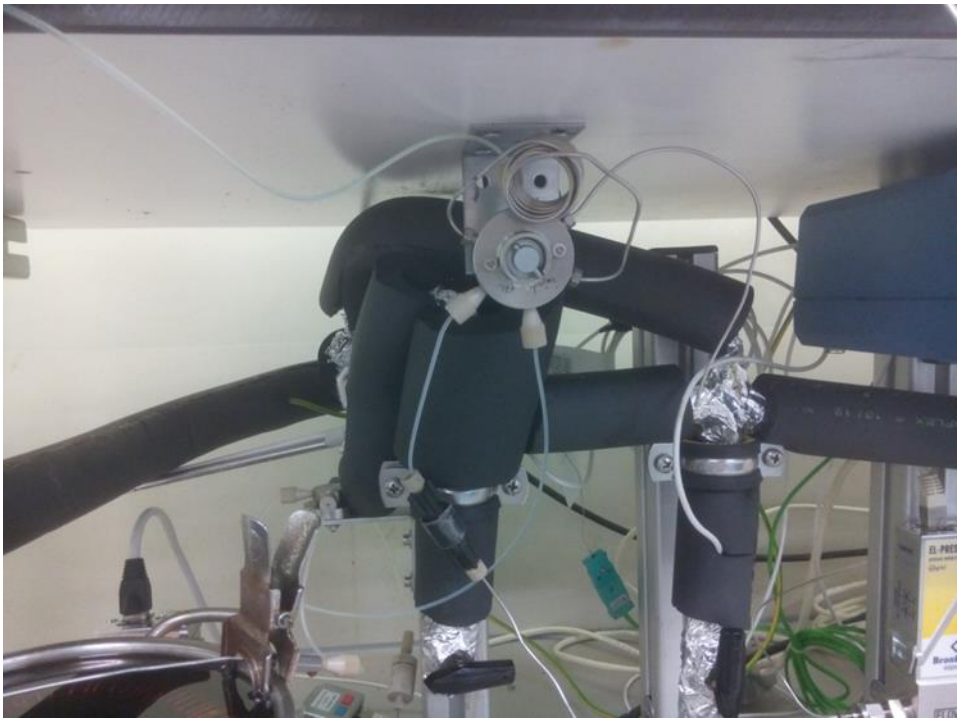
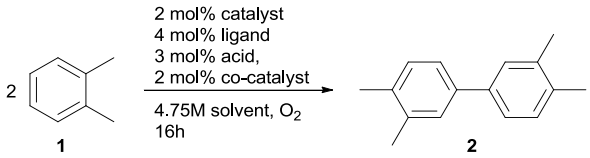


Figure S3. Zoomed-in picture of the six-way valve sampling loop, which allows to introduce reactant plugs into the reactor.

3. Control experiments and reaction conditions screening in batch

Table S1. Control experiments and reaction conditions screening in batch



1 2

Entry	Variation of the standard protocol[a]	Conversion (%)	Yield[b] (%)	Regioselectivity[c] (%)
1	none	86	28	95
	Catalyst:			
2	No catalyst	n.d.	0	n.d.
3	$Pd(ACN)_2Cl_2$	48	10	87
4	$Pd(TFA)_2$	69	0	n.d.
5	Pd/C	n.d.	0	n.d.
	Ligand:			
6	Ac-Gly-OH	69	11	62
7	2,6-difluoropyridine	89	11	84
	Co-catalyst:			
8	no co-catalyst	44	10	n.d.
9	$CuCl_2$	n.d.	0	n.d.
10	CuBr	n.d.	0	n.d.
11	DDQ	n.d.	0	n.d.
12	$CrCl_3$	n.d.	0	n.d.
13	V_2O_5	n.d.	<5	n.d.
14	$Co(NO_3)_2$	n.d.	0	n.d.
15	$Fe(NO_3)_3$	n.d.	0	n.d.
16	$FeCl_2$	n.d.	0	n.d.
17	$H_4PMo_{11}VO_{40}$	n.d.	0	n.d.
	Acid:			
18	TfOH	60	19	91
19	MsOH	86	15	94
	Solvent:			
20[d]	TFA	45	11	36
21	Dioxane	46	10	66
22	4.75M HCl/MeOH	0	0	n.d.
23	$EtCO_2H$	86	10	98
24	PivOH	n.d.	0	n.d.
25	1,4-Dioxane	46	10	66
26	neat	85	11	80
	Additives:			
27	HFIP	87	16	96
28	KI	n.d.	0	n.d.
29	benzoquinone	n.d.	0	n.d.
30	4Å mol sieves	n.d.	0	n.d.
31	$NaNO_2$	n.d.	0	n.d.

[a]STANDARD CONDITIONS: CATALYST: $Pd(OAc)_2$ LIGAND: 2-fluoropyridine, ACID: TFA, CO-CATALYST: $Cu(OTf)_2$, SOLVENT: AcOH. [b]GC-yield based on *n*-decane as internal standard. [c]Regioselectivity of 3,4,3',4'-tetramethyl-biphenyl vs 2,3,3',4'-tetramethyl-biphenyl. [d]T = 60°C. n.d. = not determined.

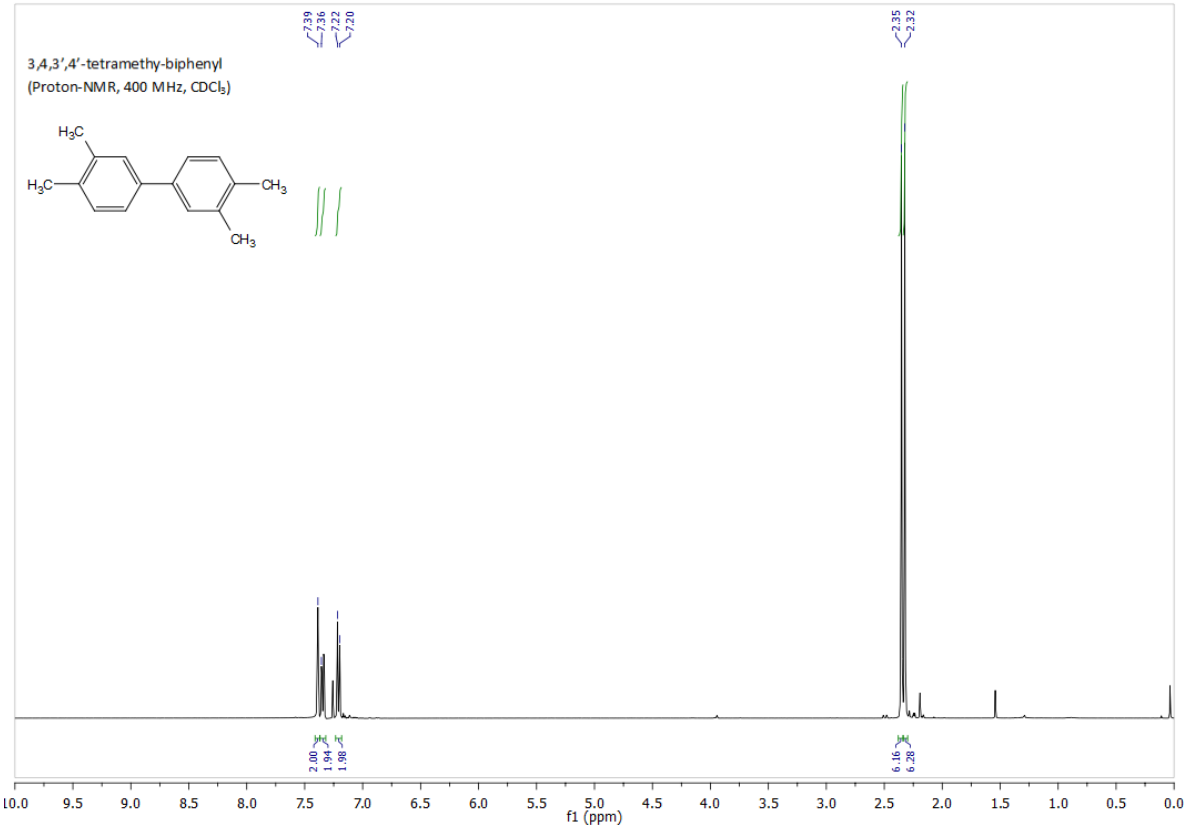
Exemplary procedure for the batch reaction (entry 1):

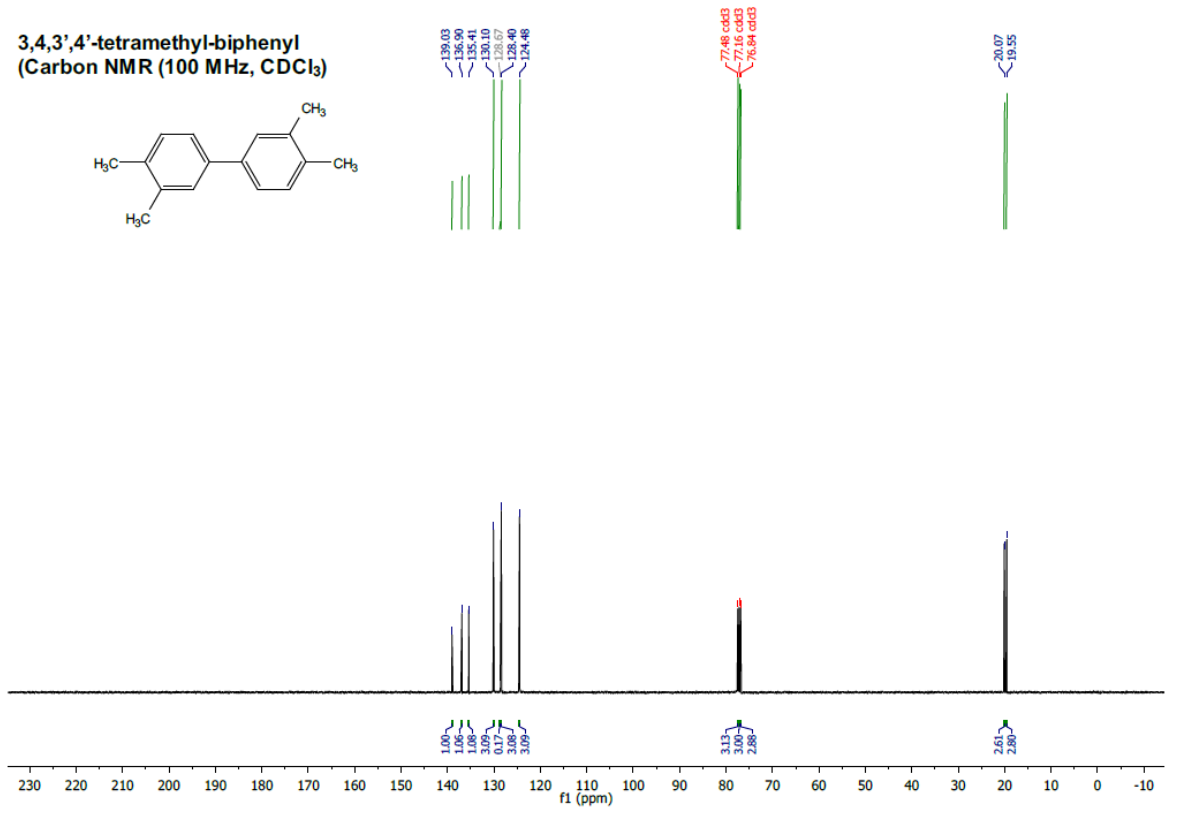
A 4 mL vial was charged with 13.5 mg (2.2 mol%, 0.04 mmol) $Cu(OTf)_2$.Under argon the $Cu(OTf)_2$.was suspended in 180 mg (1.70 mmol) o-xylene. 400 mg of a yellow stock solution were added. The stock solution was prepared by dissolving 88.8 mg (2.2 mol%, 0.39 mmol) $Pd(OAc)_2$ in 3.77 mL (4.75M) acetic acid and the consecutive addition of 36 µL (2.6 mol%, 53 mg, 0.47 mmol) trifluoroacetic acid and 65 µL (4.2 mol%, 0.75 mmol) 2-fluoropyridine. After each addition, the vial was sealed and sonicated for 1 min. The headspace of the vial was evacuated and filled with oxygen 3 times and a balloon with oxygen was attached on top before heating the reaction mixture to 110°C for 16h. After the reaction mixture cooled down an EtOAc solution containing 33 µL (10 mol%, 24.1 mg, 0.17 mmol) n-decane as internal standard was added prior to extraction with bicarb solution and EtOAc followed by filtration over a silica plug. The reaction was analyzed by GC-FID.

4. Literature

[1] W. Liu, A. Lei, *Tetrahedron Lett.* **2008**, *49*, 610-613.

5. Spectra


3,4,3',4'-tetramethy-biphenyl
(Proton-NMR, 400 MHz, CDCl3)
H3C
H3C
CH3
CH3
7.39
7.36
7.22
7.20
2.35
2.32
2.00
1.94
1.98
6.16
6.28
f1 (ppm)


3,4,3',4'-tetramethyl-biphenyl
(Carbon NMR (100 MHz, CDCl3)
CH3
H3C
CH3
H3C
139.03
136.90
135.41
130.10
128.67
128.40
124.48
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
20.07
19.55
1.00
1.06
1.08
3.09
0.17
3.08
3.09
3.13
3.00
2.88
2.61
2.80
f1 (ppm)