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Supporting Information

Palladium-Catalyzed Cross-Dehydrogenative Coupling of *o*-Xylene: Evidence of a New Rate-Limiting Step in the Search for Industrially Relevant Conditions

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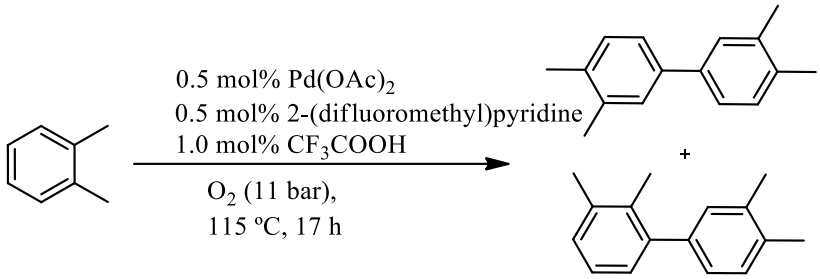
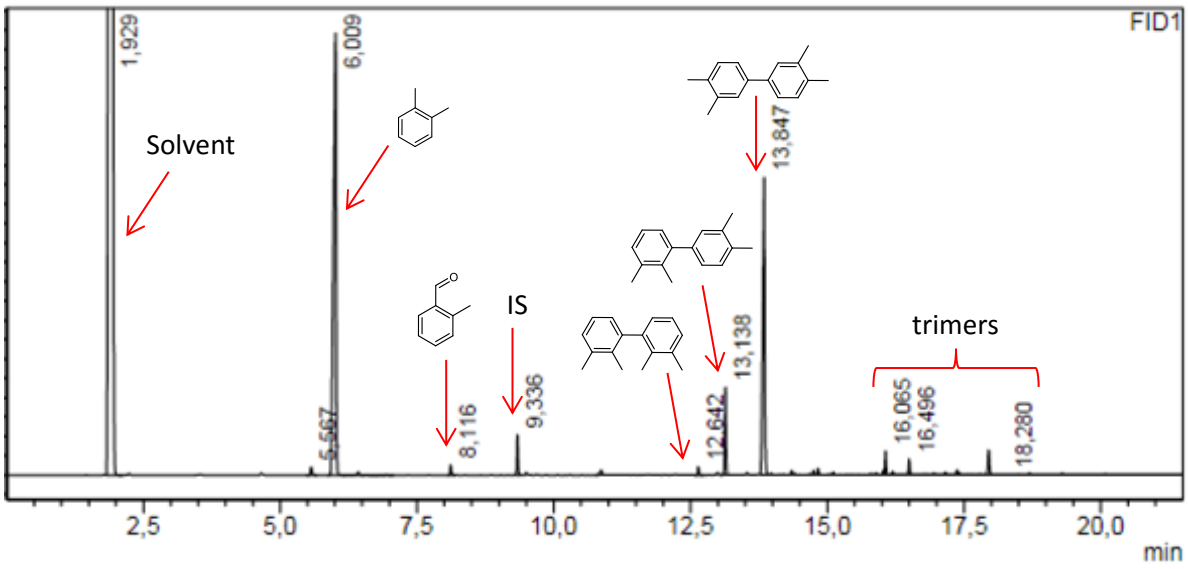
1. General considerations

NMR spectra were recorded on a Bruker AMX 400 spectrometer at r.t. Chemical shifts are given in ppm relative to $CDCl_3$ (^1H, 7.26 ppm). GC measurements were performed on a Shimadzu GC-2010 Plus Gas Chromatograph using a SH-Rxi-5HT column. All reactions were carried out without taking precautions to exclude de air and moisture. Yields of crude reaction were determined by calibrated GC analysis after addition of *n*-dodecane as the GC internal standard. All commercial reagents and solvents were used without further purification. Palladium acetate was purchased from Strem.

2. Representative procedure for aerobic oxidative coupling of *o*-xylene



In a vial, palladium acetate (0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (0.041 mmol, 0.5 mol%), trifluoroacetic acid (0.082 mmol, 1 mol%) and *o*-xylene (1 mL) were combined. The reaction tube was placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reaction was stirred at 115 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis. GC method: 50 °C, 4 min; 20 °C/min to 300 ° C; 300 °C, 5 min. When indicated, the crude was purified by flash chromatography using Pe:AcOEt (99:1) as eluent, affording 3,3',4,4'-tetramethyl-1,1'-biphenyl as a colourless solid. ^1H NMR data of the isolated material matched the spectroscopic data reported in the literature for this compound. ^1H-NMR: δ 7.40 – 7.37 (m, 2H), 7.36 – 7.32 (m, 2H), 7.23 – 7.18 (m, 2H), 2.35 (s, 6H), 2.32 (s, 6H).[1]



3. Additional reaction optimization data

3.1. Initial optimization experiments

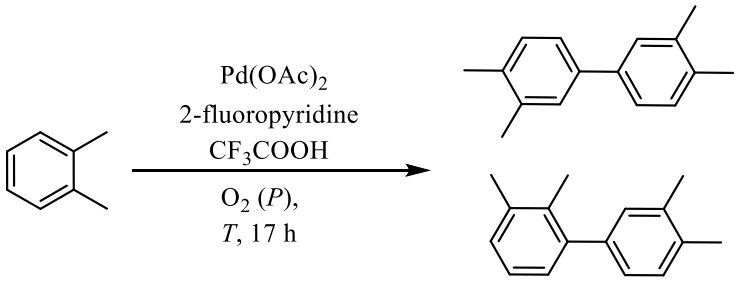


Table S1. Initial optimization experiments.

Entry	*T* (°C), P (bar)	ArAr yield (%)[a),b)]	Regio (%)[a),c)]	Chemo (%)[a),d)]
1	80 °C / 1	8,0	88	94
2	80 °C / 1	0,9	67	74
3	80 °C / 1	0,9	70	76
4	95 °C / 11	12,6	89	83
5	95 °C / 11	11,.9	62	46
6	95 °C / 11	17,6	83	79

[a)] Determined by GC analysis, internal standard = *n*-dodecane. [b)] Collective biaryl yield. [c)] % of 3,3‘,4,4‘-tetramethylbiphenyl *vs* all dimers. [d)] % of dimers *vs* side products (oxidation and trimers).

Entry 1: Stahl`s conditions[2]

Entry 2: In a microwave tube, palladium acetate (1.8 mg, 8.2 µmol, 0.1 mol%), 2-fluoropyridine (1.6 mg, 0.016 mmol, 0.2 mol%), trifluoroacetic acid (1.1 mg, 9.8 µmol, 0.12 mol%), copper (II) triflate (3.0 mg, 8.2 µmol, 0.1 mol%) and *o*-xylene (1 mL) were added. The microwave tube was sealed, then purged with oxygen and a balloon filled with oxygen was attached. The reaction was introduced in a preheated oil bath and stirred at 80 ºC for 17 h. After that time, the balloon was removed, the reaction was allowed to reach room temperature and *n*-dodecane (20 µL) was added as internal standard. The mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Entry 3: In a microwave tube, palladium acetate (1.8 mg, 8.2 µmol, 0.1 mol%), 2-fluoropyridine (1.6 mg, 0.016 mmol, 0.2 mol%), trifluoroacetic acid (1.1 mg, 9.8 µmol, 0.12 mol%) and *o*-xylene (1 mL) were added. The microwave tube was sealed, then purged with oxygen and a balloon filled with oxygen was attached. The reaction was introduced in a preheated oil bath and stirred at 80 ºC for 17 h. After that time, the balloon was removed, the reaction was allowed to reach room temperature and *n*-dodecane (20 µL) was added as internal standard. The mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Entry 4: In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-fluoropyridine (8.0 mg, 0.082 mmol, 1.0 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%), and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminium block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated alluminium block and the reactions were stirred at 95 °C for 17 h. After that time, the autoclave was removed from the alluminium block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Entry 5: In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tube was placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reaction was stirred at 95 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as

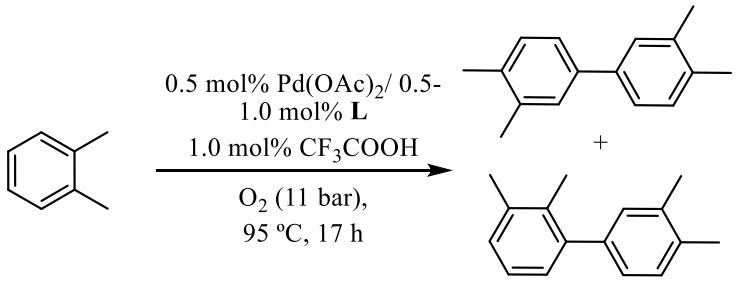
internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Entry 6: In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-fluoropyridine (4.0 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tube was placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reaction was stirred at 95 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

3.2. Screening of ligands

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), the corresponding pyridine ligand (0.041 mmol or 0.082 mmol), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 95 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Regioselectivities are expressed as the "regioratio", *i.e.*, yield(3344)/yield(2334+2233), with 3344 being the desired 3,3',4,4'-tetramethyl-1,1'-biphenyl product, and 2334/2233 being the regiomeric 2,3,3',4'/2,2',3,3'-tetramethyl-1,1'-biphenyl byproducts. Chemoselectivities are expressed as the "chemoratio", *i.e.*, yield(3344+2334+2233)/ yield(Balc+Bald+Bza+trimers), with Balc being 2-methylbenzyl alcohol, Bald being 2-methylbenzaldehyde, Bza being 2-methylbenzoic acid, and trimers being all isomers with a molecular weight corresponding to hexamethylterphenyl. The percentage of benzylic oxygenation or trimeric byproducts are relative to the total amount of products (*i.e.*, biaryls plus byproducts).



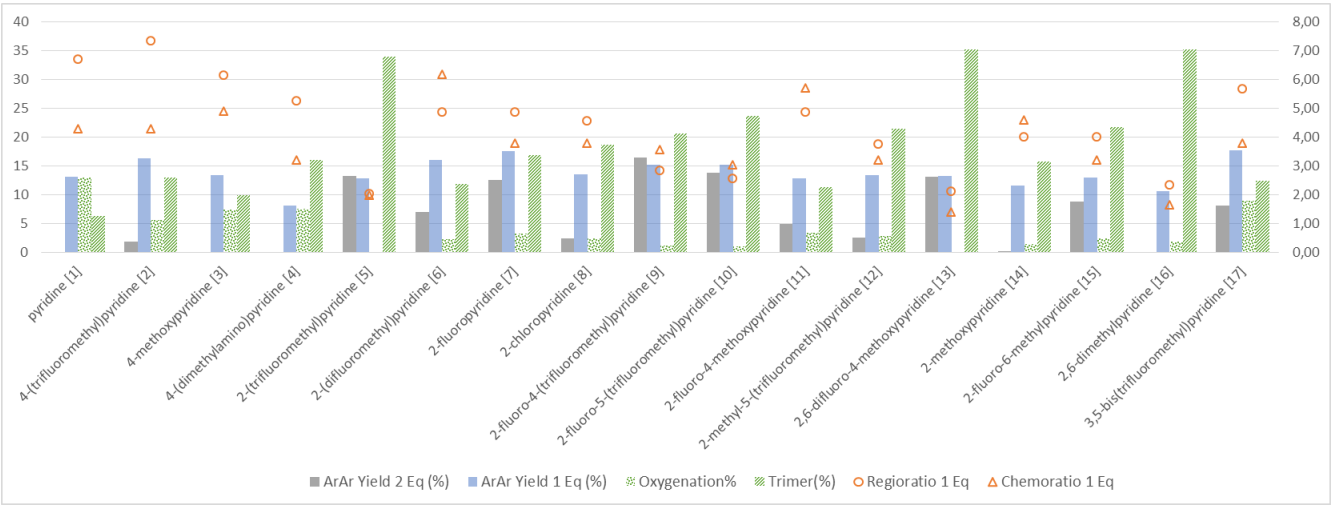


Table S2. Screening of pyridine ligands [a)]

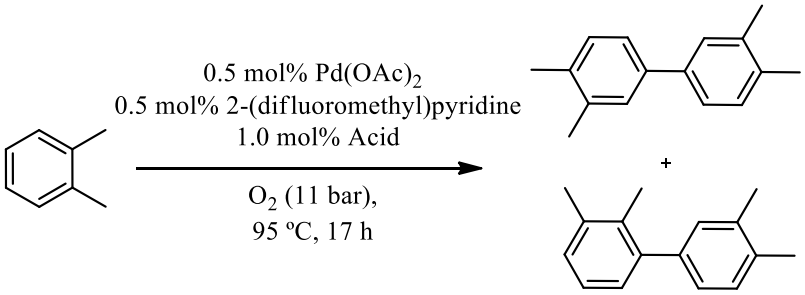
Entry	Ligand	eq	ArAr yield (%)[b), c)]	Regio [b)]	Chemo [b)]	Oxid (%) [b)]	Trim (%) [b)]
1	pyridine	1	13,1	6,7	4,3	13,0	6,2
2		2	0,1	2,2	0,3	41,2	52,9
3	4-CF_3-pyridine	1	16,4	7,3	4,3	5,5	12,9
4		2	1,9	10,1	1,8	27,6	6,9
5	4-OMe-pyridine	1	13,5	6,1	4,9	7,4	9,8
6		2	0,1	7,3	0,1	66,7	16,7
7	4-Me_2N-pyridine	1	8,2	5,2	3,2	7,5	15,9
8		2	0,4	4,6	2,3	0,0	33,3
9	2-CF_3-pyridine	1	12,9	2,0	1,5	0,0	33,8
10		2	13,3	2,4	1,5	0,0	10,1

11	2-CHF_2-pyridine	1	16,4	4,8	6.1	2,1	11,8
12		2	7,0	11,5	3,3	19,8	3,3
13	2-F-pyridine	1	17,6	4,9	3,8	3,2	16,8
14		2	12,6	8,1	4,9	10,7	5,3
15	2-Cl-pyridine	1	13,6	4,6	3,8	2,3	18,6
16		2	2,5	5,2	1,3	40,0	4,4
17	2-F-4-CF_3-pyridine	1	15,3	2,8	3,5	1,0	20,5
18		2	16,5	4,0	4,9	2,0	14,6
19	2-F-5-CF_3-pyridine	1	15,3	2,6	3,0	1,0	23,6
20		2	2,6	7,3	1,8	30,0	5,0
21	2-F-4-OMe-pyridine	1	12,9	4,9	5,7	3,3	11,3
22		2	5,0	9,0	1,6	12,2	26,8
23	2-Me-5-CF_3-pyridine	1	13,5	3,8	3,2	2,8	21,3
24		2	2,6	7,3	1,8	30,0	5,0
25	2,6-F_2-4-OMe-pyridine	1	13,3	2,1	1,8	0,0	35,1
26		2	13,1	2,4	1,5	0,0	35,5
27	2-OMe-pyridine	1	11,6	4,0	4,2	1,4	15,7
28		2	0,2	5,7	1,2	0,0	33,3
29	2-F-6-Me-pyridine	1	13,0	4,0	3,2	2,3	21,6
30		2	8,9	7,3	2,5	20,0	8,8
31	2,6-Me_2-pyridine	1	10,6	2,3	1,6	1,8	35,1
32		2	0,1	3,2	0,1	66,7	0,0
33	3,5-$(CF_3)_2$-pyridine	1	17,8	5,7	3,8	8,8	12,4
34		2	8,1	7,3	3,0	18,7	5,6

[a)] Conditions: $Pd(OAc)_2$ (0.5 mol%), ligand (0.5 or 1.0 mol%), CF_3CO_2H (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 95 °C/11 bar O_2. [b)] Determined by GC analysis, internal standard = *n*-dodecane. [c)] Collective biaryl yield.

3.3. Screening of acids

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), the corresponding acid (0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 95 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



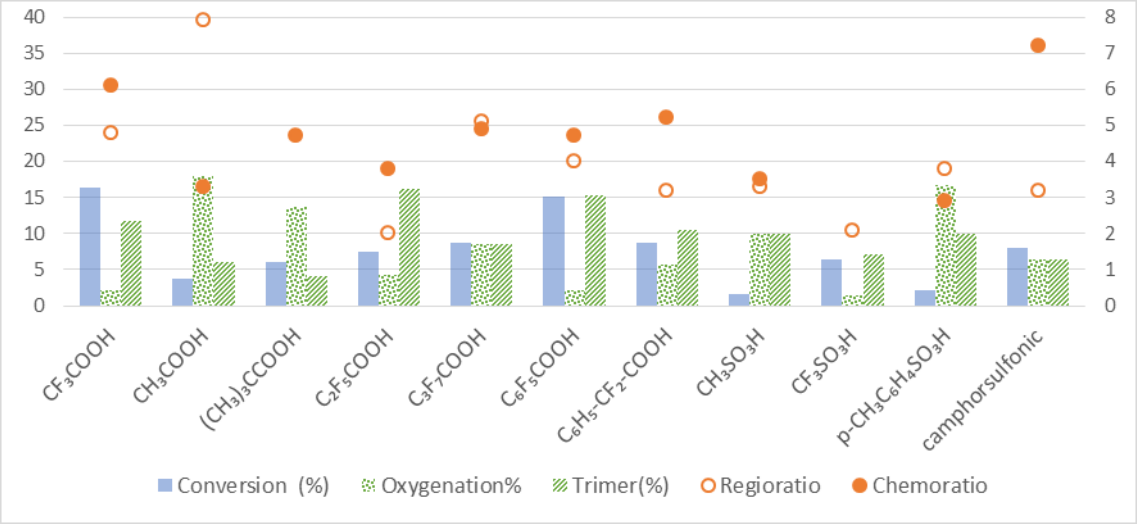


Table S3. Screening of acids [a)]

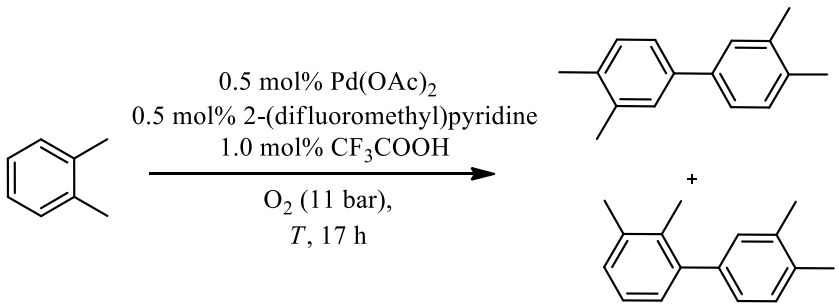
Entry	Acid	ArAr yield (%)[b), c)]	Regio[b)]	Chemo[b)]	Oxid (%)[b)]	Trim(%)[b)]
1	CF_3COOH	16,4	4,8	6,1	2,1	11,8
2	CH_3COOH	3,8	7,9	3,3	18,0	6,0
3	$(CH_3)_3CCOOH$	6,0	10,0	4,7	13,7	4,1

4	C_2F_5COOH	7,4	2,0	3,8	4,3	16,1
5	C_3F_7COOH	8,8	5,1	4,9	8,5	8,5
6	C_6F_5COOH	15,1	4,0	4,7	2,5	15,3
7	C_6H_5-CF_2-COOH	8,7	3,2	5,2	5,8	10,6
8	CH_3SO_3H	1,6	3,3	3,5	10,0	10,0
9	CF_3SO_3H	6,4	2,1	10,2	1,4	7,1
10	*p*-$CH_3C_6H_4SO_3H$	2,2	3,8	2,9	16,7	10,0
11	camphorsulfonic	8,1	3,2	7,2	6,4	6,4

[a] Conditions: $Pd(OAc)_2$ (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), acid (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 95 °C /11 bar O_2. [b] Determined by GC analysis, internal standard = *n*-dodecane. [c] Collective biaryl yield.

3.4. Temperature optimization

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tube was placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reaction was stirred at the indicated temperature for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



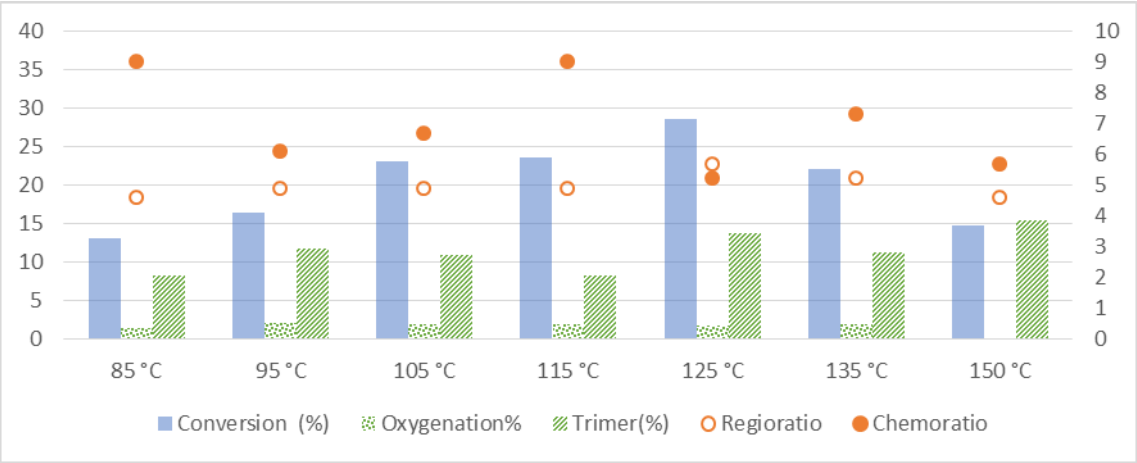


Table S4. Temperature optimization [a)]

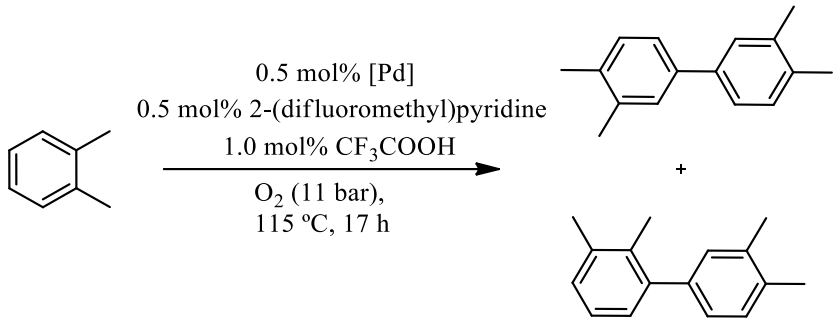
Entry	T (° C)	ArAr yield (%)[b), c)]	Regio[c)]	Chemo[c)]	Oxid (%) [c)]	Trim (%) [c)]
1	85	13,1	4,6	9,0	1,4	8,3
2	95	16,4	4,8	6,1	2,1	11,8
3	105	23,1 (24,3)	4,9	6,7	1,9	10,9
4	115	23,7 (23,1)	4,9	9,0	1,9	8,3
5	125	28,6 (26,1)	5,7	5,2	1,87	13,9
6	135	22,1(21,9)	5,2	7,3	1,9	11,4
7	150	14,8	4,6	5,7	0,0	15,4

[a)] Conditions: $Pd(OAc)_2$ (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), CF_3CO_2H (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 11 bar O_2. [b)] Determined by GC analysis, internal standard = *n*-dodecane. [c)] Collective biaryl yield. Numbers in brackets are isolated yield of the mixture of biaryls.

3.5. Screening of palladium sources

In a vial, the corresponding palladium source (0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as

internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



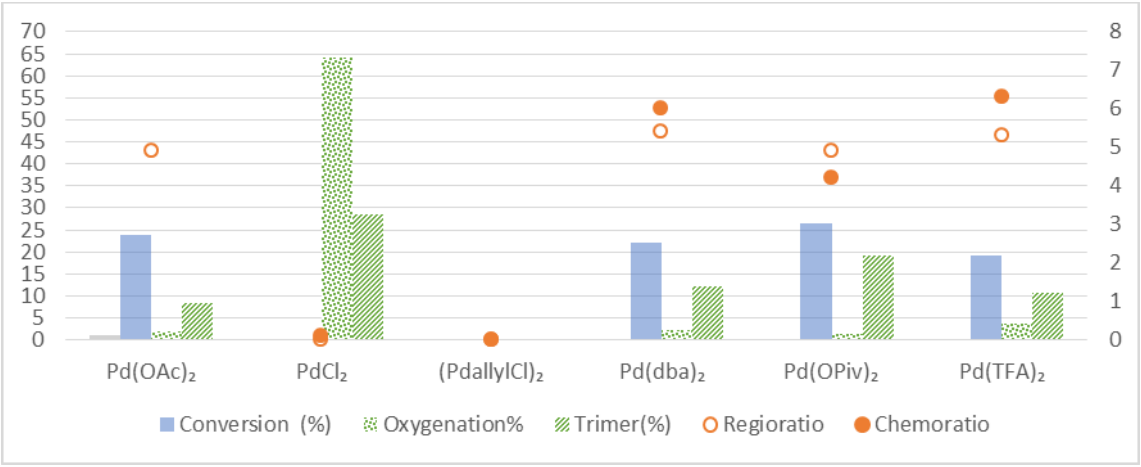


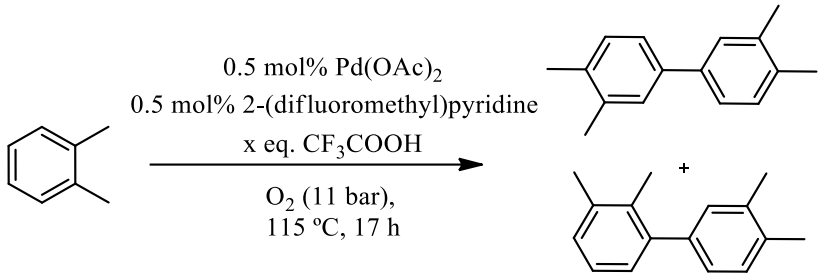
Table S5. Screening of palladium sources [a)]

Entry	Pd source	ArAr yield (%)[b), c)]	Regio[b)]	Chemo[b)]	Oxid (%) [b)]	Trim (%) [b)]
1	$Pd(OAc)_2$	23,7	4,9	9,0	1,9	8,3
2	$PdCl_2$	0,1	n.d.	0,1	64,3	28,6
3	$(PdallylCl)_2$	n.r.	n.d.	n.d.	n.d.	n.d.
4	$Pd(dba)_2$	22,0	5,4	6,0	2,3	12,1
5	$Pd(OPiv)_2$	26,5	4,9	4,2	1,5	19,2
6	$Pd(TFA)_2$	19,1	5,3	6,3	3,6	10,8

[a)] Conditions: Pd source (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), CF_3CO_2H (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 115 °C/11 bar O_2. [b)] Determined by GC analysis, internal standard = *n*-dodecane. [c)] Collective biaryl yield. Numbers in brackets are isolated yield of the mixture of biaryls.

3.6. Optimization of the amount of CF_3COOH

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (the amount indicated in each case) and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowedto reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



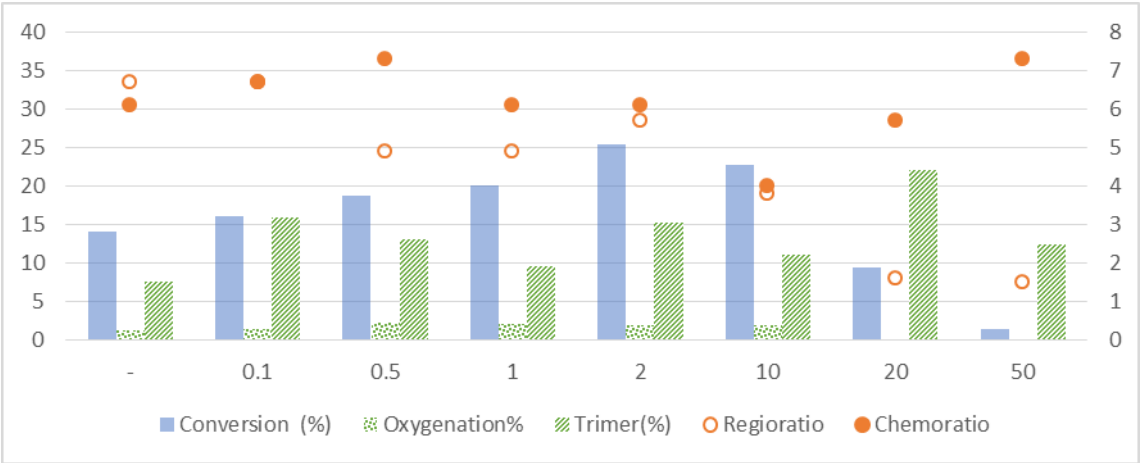


Table S6. Optimization of the amount of CF_3COOH [a)]

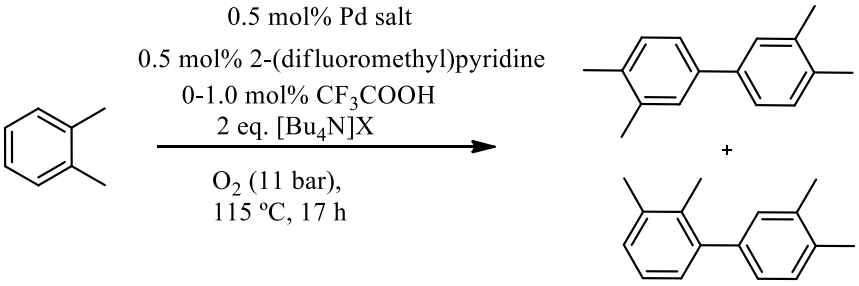
Entry	Eq CF_3COOH[b)]	ArAr yield (%)[c), d)]	Regio[c)]	Chemo[c)]	Oxid (%) [c)]	Trim (%) [c)]
1	-	14,2	6,7	6,1	1,3	7,7
2	0.1	16,1	6,7	6,7	1,5	15,9
3	0.5	18,8	4,9	7,3	2,3	13,1
4	1	20,1	4,9	6,1	2,2	9,6
5	2	25,5	5,7	6,1	1,9	15,3

6	10	22,8	3,8	4,0	1,9	11,1
7	20	9,5	1,6	5,7	0,0	22,1
8	50	1,4	1,5	7,3	0,0	12,5

[a] Conditions: $Pd(OAc)_2$ (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), CF_3CO_2H in *o*-xylene (1 mL) were stirred for 17 h at 115 °C/11 bar O_2. [b] Equivalents of CF_3COOH respect to $Pd(OAc)_2$. [c] Determined by GC analysis, internal standard = *n*-dodecane. [d] Collective biaryl yield.

4. Effect of tetrabutylammonium salts on the CDC of *o*-xylene

In a vial, palladium source (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), optionally trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%), tetrabutylammonium salt (0.082 mmol, 1.0 mol%) and *o*-xylene (1 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



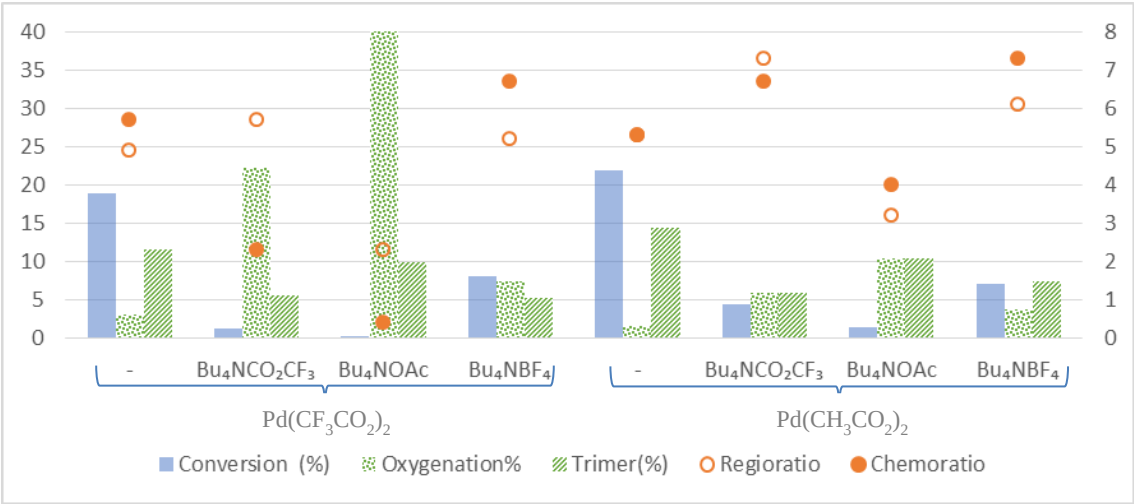
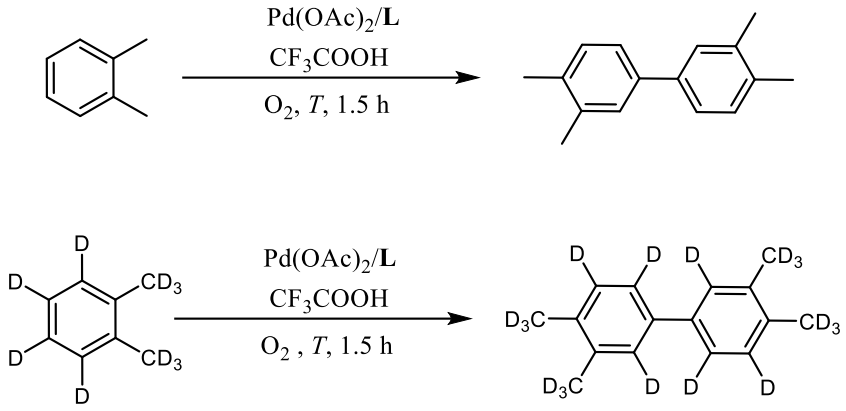


Table S7. Effect of the tetrabutyl ammonium salts [a)]

Entry	Pd source[b)]	Additive	ArAr yield (%)[c), d)]	Regio[c)]	Chemo[c)]	Oxid (%)[c)]	Trim (%)[c)]
1	$Pd(CF_3CO_2)_2$	-	18,9	4,9	5,7	3,2	11,7
2	$Pd(CF_3CO_2)_2$	$Bu_4NCO_2CF_3$	1,3	5,7	2,3	22,2	5,6
3	$Pd(CF_3CO_2)_2$	Bu_4NOAc	0,3	2,3	0,4	60,0	10,0
4	$Pd(CF_3CO_2)_2$	Bu_4NBF_4	8,2	5,2	6,7	7,4	5,3
5	$Pd(OAc)_2$	-	22,0	5,3	5,3	1,5	14,5
6	$Pd(OAc)_2$	$Bu_4NCO_2CF_3$	4,4	7,3	6,7	6,0	6,0
7	$Pd(OAc)_2$	Bu_4NOAc	1,5	3,2	4,0	10,5	10,5
8	$Pd(OAc)_2$	Bu_4NBF_4	7,2	6,1	7,3	3,7	7,4

[a)] Conditions: Pd source (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), $[Bu_4N]X$ (1.0 mol%), and optionally CF_3CO_2H (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 115 °C/11 bar O_2. [b)] When $Pd(TFA)_2$ was used, no CF_3CO_2H was added. [c)] Determined by GC analysis, internal standard = *n*-dodecane. [d)] Collective biaryl yield.

5. Determination of the Kinetic Isotopic Effect.



Experiments using 2-(difluoromethyl)pyridine at 11 bar of O_2 pressure:

Table 2, entry 1

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene or *o*-xylene-d_{10} (1.0 mL) were combined. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Table 2, entry 2

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg, 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene or *o*-xylene-d_{10} (500 µL) were combined. This solution was used as a catalyst stock solution. In a vial, 100 µL of the corresponding catalyst stock solution was placed and *o*-xylene or *o*-xylene-d_{10} was added (900 µL) to reach 1.0 mL volume. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and

the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Table 2, entries 3-5

In a vial, palladium acetate (9.0 mg, 0.041 mmol, 0.5 mol%), 2-(difluoromethyl)pyridine (5.3 mg , 0.041 mmol, 0.5 mol%), trifluoroacetic acid (6.0 µL, 0.082 mmol, 1.0 mol%) and *o*-xylene or *o*-xylene-d_{10} (1.0 mL) were combined. This solution was used as a catalyst stock solution. In a vial, 500 µL of the corresponding catalyst stock solution and 500 µL the solvent indicated in each case were added. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Experiments using 2-fluoropyridine in AcOH:

Table 2, entry 6

In a vial, palladium acetate (4.5 mg, 0.02 mmol, 0.1 mol%), 2-fluoropyridine (4.0 mg, 0.04 mmol, 0.2 mol%), trifluoroacetic acid (2.7 mg, 0.024 mmol, 0.12 mol%) and acetic acid (2.0 mL) were combined and stirred at room temperature for 30 min. The resulting bright-yellow solution was used as a catalyst stock solution. In a microwave tube, the catalyst stock solution (400 µL) and *o*-xylene or *o*-xylene-d_{10} (480 µL) were added. The microwave tubes were sealed, then purged with oxygen and a balloon filled with oxygen was attached. The reactions were introduced in a preheated oil bath and stirred at 80 ºC for 1.5 h. After cooling down, *n*-dodecane (20 µL) was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Table 2, entry7

In a vial, palladium acetate (4.5 mg, 0.02 mmol, 0.1 mol%), 2-fluoropyridine (4.0 mg, 0.04 mmol, 0.2 mol%), trifluoroacetic acid (2.7 mg, 0.024 mmol, 0.12 mol%) and acetic acid (2.0 mL) were combined and stirred at room temperature for 30 min. The resulting bright-yellow solution was used as a catalyst stock solution. In a vial, the catalyst stock solution (400 µL) and *o*-xylene or *o*-xylene-d_{10} (480 µL) were added. The reaction tubes were placed in a 7-well aluminum block

which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the valves were closed to keep 1 bar of oxygen inside of the autoclave. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 80 °C for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

Table 2, entries 8-9

In a vial, palladium acetate (4.5 mg, 0.02 mmol, 0.1 mol%), 2-fluoropyridine (4 mg, 0.04 mmol, 0.2 mol%), trifluoroacetic acid (2.7 mg, 0.024 mmol, 0.12 mol%) and acetic acid (2.0 mL) were combined and stirred at room temperature for 30 min. The resulting bright-yellow solution was used as a catalyst stock solution. In a vial, the catalyst stock solution (400 µL) and *o*-xylene or *o*-xylene-d_{10} (480 µL) were added. The reaction tubes were placed in a 7-well aluminum block which wa introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at the temperature indicated for each reaction for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

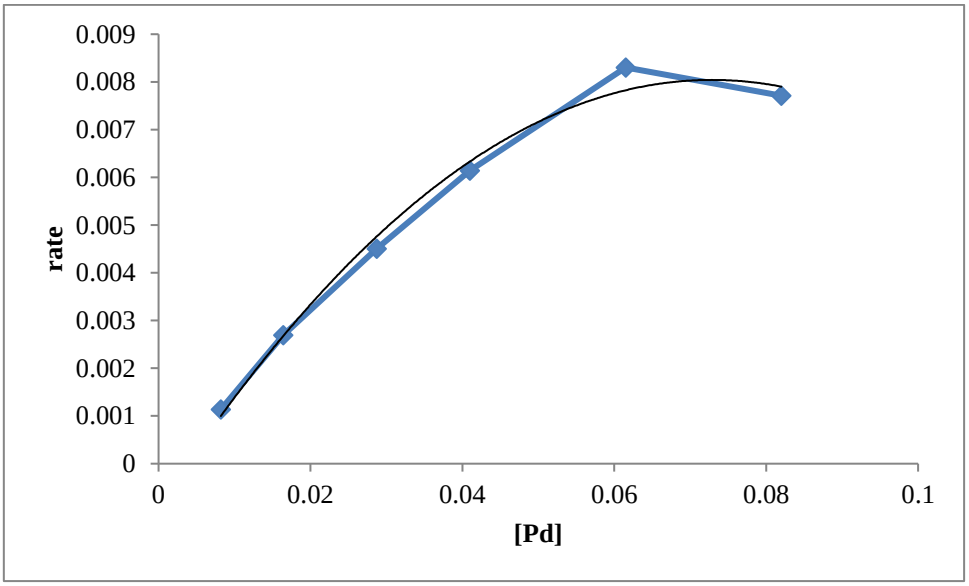
Table 2, entry10

In a vial, palladium acetate (4.5 mg, 0.02 mmol, 0.1 mol%), 2-fluoropyridine (4.0 mg, 0.04 mmol, 0.2 mol%), trifluoroacetic acid (2.7 mg, 0.024 mmol, 0.12 mol%) and acetic acid (2.0 mL) were combined and stirred at room temperature for 30 min. The resulting bright-yellow solution was used as a catalyst stock solution. In a vial, the catalyst stock solution (400 µL) and *o*-xylene or *o*-xylene-d_{10} (480 µL) were added. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the valves were closed to keep 1 bar of oxygen inside of the autoclave. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 1.5 h. After that time, the autoclave was removed from the aluminum block and allowe to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.

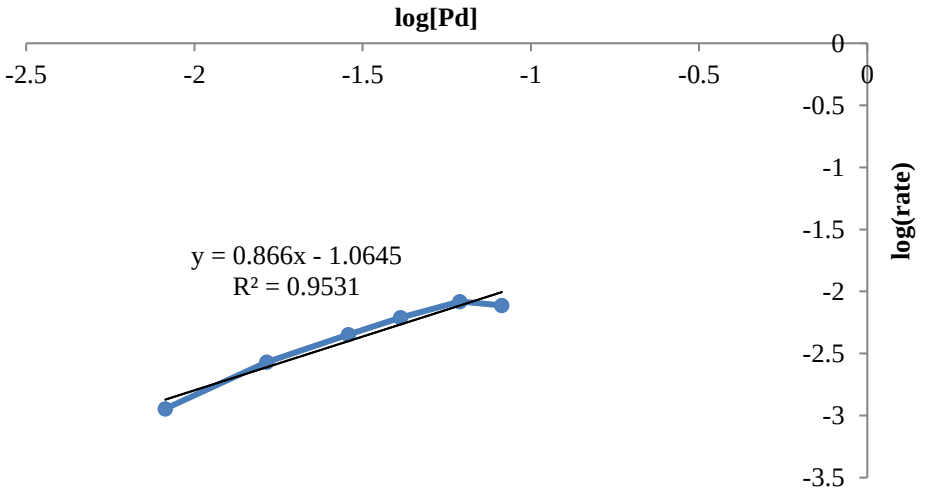
6. Determination of the order of the reaction respect to Pd.

Catalyst loading 0.1-1.0 mol% of palladium acetate

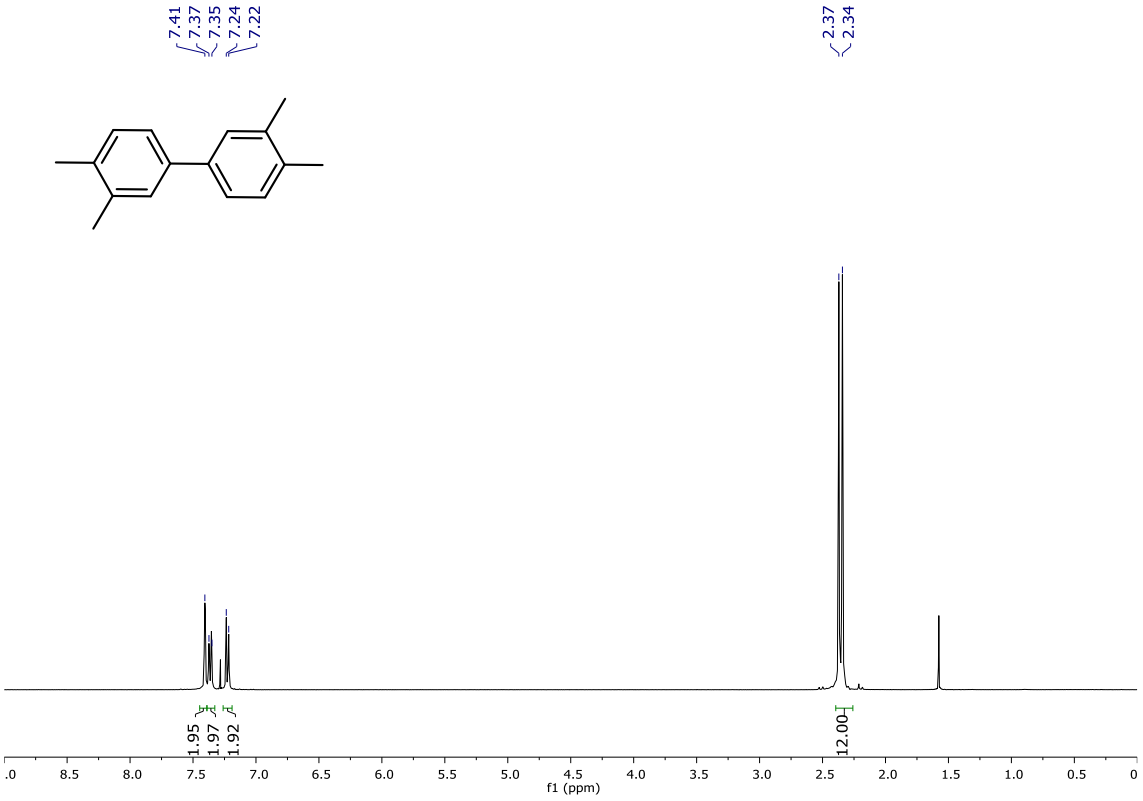
In a vial, 100 µL (0.008 mmol, 0.1 mol% of palladium acetate), 200 µL (0.016 mmol, 0.2 mol% of palladium acetate), 350 µL (0.029 mmol, 0.35 mol% of palladium acetate), 500 µL (0.041 mmol, 0.5 mol% of palladium acetate), 750 µL (0.061 mmol, 0.75 mol% of palladium acetate), 900 µL (0.074 mmol, 0.9 mol% of palladium acetate) and 1.0 mL (0.082 mmol, 1.0 mol% of palladium acetate) of a catalyst stock solution (36.0 mg, 0.16 mmol of palladium acetate, 21.2 mg, 0.16 mmol of 2-(difluoromethyl)pyridine and 24 µL, 0.32 mmol of trifluoroacetic acid in 2 mL of *o*-xylene) was charged and different amount of *o*-xylene was added in each case to complete the volume to 1 mL. The reaction tubes were placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 11 bar of oxygen. The autoclave was placed inside a preheated aluminum block and the reactions were stirred at 115 °C for 40 min. After that time, the autoclave was removed from the aluminum block and allowed to reach room temperature, then the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard and the mixture was filtered through a celite plug and rinsed with AcOEt. Samples were evaluated by GC analysis.



The plot of the logarithms of the reaction rate against the concentration of palladium acetate provides a straight line with slope of 0.9, revealing that the reaction is first order respect to palladium.


log[Pd]
-2.5
-2
-1.5
-1
-0.5
0
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
log(rate)
y = 0.866x - 1.0645
R² = 0.9531

7. ^{1}H-NMR chromatogram



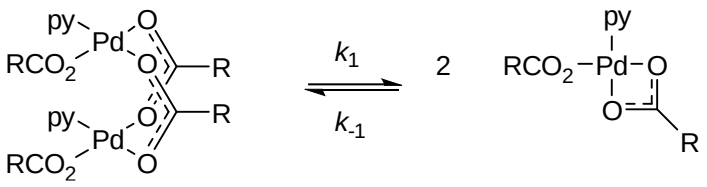
8. Derivation of the reaction rate law

Scheme S1 presents an elementary reaction step sequence involving dissociation of pyridine ligand containing (Pd/N = 1/1), dimeric carboxylate-bridged Pd(II) species into monometallic species that enter into the catalytic cycle, [3] which follows Stahl's transmetalation mechanism and similarly assumes the product-forming reductive elimination step to be fast relative to the other steps under low steady-state conditions for the intermediate Pd species.[4] Solvent molecules that may occupy vacant coordination sites are not included in the equations.

(1) $[Pd(RCO_2)_2py]_2 \leftrightarrows 2\ [Pd(RCO_2)_2py]$ defined by rate constants k_1 and k_{-1}

abbreviated as: $Pd_2X_4 \leftrightarrows 2\ PdX_2$

or displayed graphically (generating a monometallic κ^2-(O,O) bound Pd(II) carboxylate):



(2) $[Pd(RCO_2)_2py] + ArH \leftrightarrows PdAr(RCO_2)py + RCO_2H$ defined by rate constants k_2 and k_{-2}

abbreviated as: $PdX_2 + ArH \leftrightarrows PdArX + HX$

(3) $2\ PdAr(RCO_2)py \rightarrow Pd(RCO_2)_2py + PdAr_2py$ defined by rate constant k_3

abbreviated as: $2\ PdArX \rightarrow PdX_2 + PdAr_2$

(4) $PdAr_2py \rightarrow Pd^0py + ArAr$ (fast) defined by rate constant k_4

abbreviated as: $PdAr_2 \rightarrow Pd^0 + ArAr$

When applying the steady-state approximation to the intermediate Pd species, then:

$$rate = \frac{d[\mathrm{ArAr}]}{d\mathrm{t}} = -0.5\frac{d[\mathrm{ArH}]_{\mathrm{ArAr}}}{d\mathrm{t}} = 0.5(k_2[\mathrm{PdX_2}][\mathrm{ArH}] - k_{-2}[\mathrm{PdArX}][\mathrm{HX}]) \quad \text{(S1)}$$

where $d[\mathrm{ArH}]_{\mathrm{ArAr}}$ denotes the change in concentration of ArH consumed for ArAr formation only (*i.e.*, not for side-reactions such as *e.g.* benzylic oxidation). In addition:

$$\frac{d[\mathrm{PdX_2}]}{d\mathrm{t}} = 0 = 2k_1[\mathrm{Pd_2X_4}] - 2k_{-1}[\mathrm{PdX_2}]^2 - k_2[\mathrm{PdX_2}][\mathrm{ArH}] + k_{-2}[\mathrm{PdArX}][\mathrm{HX}] + k_3[\mathrm{PdArX}]^2 \quad \text{(S2)}$$

which can be rewritten as the square equation:

$$0 = 2k_{-1}[\mathbf{PdX_2}]^2 + k_2[\mathrm{ArH}][\mathbf{PdX_2}] - 2k_1[\mathrm{Pd_2X_4}] - k_{-2}[\mathrm{PdArX}][\mathrm{HX}] - k_3[\mathrm{PdArX}]^2 \quad \text{(S3)}$$

Solving this square equation using the Citardauq variant of the abc-formula yields:

$$[\mathrm{PdX_2}] = \frac{-4k_1[\mathrm{Pd_2X_4}] - 2k_{-2}[\mathrm{PdArX}][\mathrm{HX}] - 2k_3[\mathrm{PdArX}]^2}{-k_2[\mathrm{ArH}] - \sqrt{k_2^2[\mathrm{ArH}]^2 + 8k_{-1}(2k_1[\mathrm{Pd_2X_4}] + k_{-2}[\mathrm{PdArX}][\mathrm{HX}] + k_3[\mathrm{PdArX}]^2)}} \quad \text{(S4)}$$

In neat ArH with the Pd catalyst loaded at ~0.5 mol% (default conditions), and with $[Pd(RCO_2)_2py]_2$ (= Pd_2X_4) as the stable resting state of the catalyst,[3] the following relationships hold under conditions of rate-limiting dimer dissociation and low steady-states for the intermediate Pd species:

$$[\mathrm{ArH}] >> [\mathrm{Pd_2X_4}] \quad \text{(S5)}$$

$$[\mathrm{ArH}] >> [\mathrm{PdArX}] \quad \text{(S6)}$$

$$[\mathrm{ArH}] >> [\mathrm{HX}] \quad \text{(S7)}$$

$$[\mathrm{ArH}]^2 >>> [\mathrm{PdArX}][\mathrm{HX}] \quad \text{(S8)}$$

$$[\mathrm{ArH}]^2 >>> [\mathrm{PdArX}]^2 \quad \text{(S9)}$$

$$[\mathrm{Pd_2X_4}] >> [\mathrm{HX}] \quad \text{(S10)}$$

$$k_{-1} << k_2 \quad \text{(S11)}$$

In addition, the reverse reaction in equilibrium (2), *i.e.*, the protolysis of PdArX, may be expected to proceed at very low rate under neat conditions ([ArH] >> [HX]) compared to biaryl formation in AcOH as solvent ([ArH] ≈ [HX]) with Stahl's $Pd(MeCO_2)(CF_3CO_2)$ + 2 equiv 2-F-py catalyst (*i.e.*, Pd/N = 1/2).[4] That is, k_{-2}[PdArX][HX] can be ignored under neat conditions, and in fact has also been ignored — even in the presence of AcOH as solvent — in a kinetic study of arene acetoxylation involving the $[Pd(MeCO_2)_2py]_2$ (*i.e.*, Pd/N = 1/1) catalyst supposed to enter into the catalytic cycle by dissociation to a monometallic species that subsequently induces rate-limiting arene palladation.[3] The foregoing allows equations S1 and S4 to be simplified to:[5]

$$rate = \frac{d[\mathrm{ArAr}]}{d\mathrm{t}} = -0.5\frac{d[\mathrm{ArH}]_{\mathrm{ArAr}}}{d\mathrm{t}} \approx 0.5k_2[\mathrm{PdX_2}][\mathrm{ArH}] \quad \text{(S12)}$$

$$[\mathrm{PdX_2}] \approx \frac{2k_1[\mathrm{Pd_2X_4}] + k_3[\mathrm{PdArX}]^2}{k_2[\mathrm{ArH}]} \quad \text{(S13)}$$

Applying steady-state conditions to PdArX yields (again ignoring k_{-2}[PdArX][HX]):

$$\frac{d[\mathrm{PdArX}]}{d\mathrm{t}} = 0 \approx k_2[\mathrm{PdX_2}][\mathrm{ArH}] - 2k_3[\mathrm{PdArX}]^2 \quad \text{(S14)}$$

Inserting S13 into S14 yields:

$$\frac{d[\mathrm{PdArX}]}{d\mathrm{t}} = 0 = 2k_1[\mathrm{Pd_2X_4}] + k_3[\mathrm{PdArX}]^2 - 2k_3[\mathrm{PdArX}]^2 \quad \text{(S15)}$$

which equals:

$$[\mathrm{PdArX}]^2 = \frac{2k_1[\mathrm{Pd_2X_4}]}{k_3} \quad \text{(S16)}$$

Inserting S13 into the S12 rate equation yields:

$$rate = \frac{d[\mathrm{ArAr}]}{d\mathrm{t}} = -0.5\frac{d[\mathrm{ArH}]_{\mathrm{ArAr}}}{d\mathrm{t}} \approx 0.5k_2[\mathrm{ArH}]\frac{2k_1[\mathrm{Pd_2X_4}] + k_3[\mathrm{PdArX}]^2}{k_2[\mathrm{ArH}]}$$

$$= k_1[\mathrm{Pd_2X_4}] + 0.5k_3[\mathrm{PdArX}]^2 \quad \text{(S17)}$$

Inserting S16 into the S17 rate equation yields:

$$rate = \frac{d[\mathrm{ArAr}]}{d\mathrm{t}} = -0.5\frac{d[\mathrm{ArH}]_{\mathrm{ArAr}}}{d\mathrm{t}} \approx 2k_1[\mathrm{Pd_2X_4}] \quad \text{(S18)}$$

Under low steady-state conditions for the intermediate Pd species and with Pd_2X_4 as the stable resting state of the catalyst that is generated quantitatively in neat arene medium from $Pd(RCO_2)_2$ + 1 equiv py,[3] S18 translates into the experimentally observed first order in Pd rate equation:

$$rate = \frac{d[\mathrm{ArAr}]}{d\mathrm{t}} = -0.5\frac{d[\mathrm{ArH}]_{\mathrm{ArAr}}}{d\mathrm{t}} \approx k_{\mathrm{obs}}[\mathrm{Pd}]_{\mathrm{tot}} \quad \text{(S19)}$$

where k_{obs} denotes the experimentally observed rate constant, and $[Pd]_{tot}$ denotes the total amount of palladium charged into the reactor. According to S18, k_{obs} is proportional to k_1 and not dependent on other rate constants that respond to the isotopic nature of the arene (*i.e.*, regular *o*-

xylene or *o*-xylene-d_{10}). Therefore, S19 also explains the lack of a KIE under neat arene conditions, besides the experimentally observed first order in Pd. The outcome is as expected for this sequence of reactions when the first step is rate-determining.[6]

9. References

[1] P. Puthiaraj, P. Suresh, K. Pitchumani, *Green Chem.* **2014**, *16*, 2865-2875.

[2] Y. Izawa, S. S. Stahl, *Adv. Synth. Catal.* **2010**, *352*, 3223-3229.

[3] A. K. Cook, M. S. Sanford, *J. Am. Chem. Soc*. **2015**, *137*, 3109-3118.

[4] D. Wang, Y. Izawa, S. S. Stahl, *J. Am. Chem. Soc*. **2014**, *136*, 9914-9917.

[5] To provide a numerical illustration of S9, *i.e.*, $[ArH]^2 >>> [PdArX]^2$, note that at the default Pd catalyst loading of 0.5 mol%, with a low steady-state that equals 0.01*catalyst loading, $[ArH]^2 = 1.7*10^7 [PdArX]^2$.

[6] J. R. Murdoch, *J. Chem. Educ*. **1981**, *58*, 32-36.