Supplementary Informations

Rapid Suzuki-Miyaura Couplings with ppm Level of Palladium Catalyst in a High-Pressure and High-Temperature Water System

Ikuhiro Nagao, Maya Chatterjee and Hajime Kawanami *

National Institute of Advanced Industrial Science and Technology, 4-2-1 Nigatake, Miyagino-ku, Sendai, Miyagi 983-8551, Japan; inagao2018@gmail.com (I.N.); c-maya@aist.go.jp (M.C.)

* Correspondence: h-kawanami@aist.go.jp; Tel.: +81-22-237-2097

Received: 21 September 2018; Accepted: 9 October 2018; Published: date

For all the experiments, total flow rates of water and substrates solution from liquid pumps were kept constant at 4.8 mL/min under ambient conditions. Under the working conditions, Reynolds number and residence time of the fluid in the microreactor at various temperature and pressure were estimated as described below:

Density and viscosity data from "NIST Chemistry Webbook" were utilized for the calculations.

Residence time (t) in the reaction tube was calculated using equation (1).

$$t = \pi \left(\frac{r}{20}\right)^2 \times L \times \rho_w \times \left(\frac{60}{F_{total}}\right) \qquad (1)$$

where t: residence time (s), r: inner diameter of microreactor SUS316 tube (= 0.5 mm), L: length of SUS316 microreactor tube (cm), ρ_w: density of water at certain temperature/pressure (g/cm^3), F_{total}: total flow rate of pumps (g/min).

Graphical representation of residence time using reactor of 450 cm length (0.88 cm^3) at various temperatures/pressures is shown in **Figure S1**.

On the other hand, Reynolds number (Re) was calculated based on equation (2).

$$Re = Du\rho_w/\mu_w \qquad (2)$$

where D: inner diameter (5.0×10^{-4} m), u: velocity of the object relative to the fluid (m/s), ρ_w: density of water (kg.m^{-3}), μ_ω: dynamic viscosity of water (kg/(m.s)).

Graphical representation of Reynolds number at various temperatures/pressures is shown in **Figure S2**. Applied conditions in this investigation (pressure = 30~45 MPa; temperature = 350~445 ºC) correspond to the estimated Reynolds number of approximately >3.0×10^3.

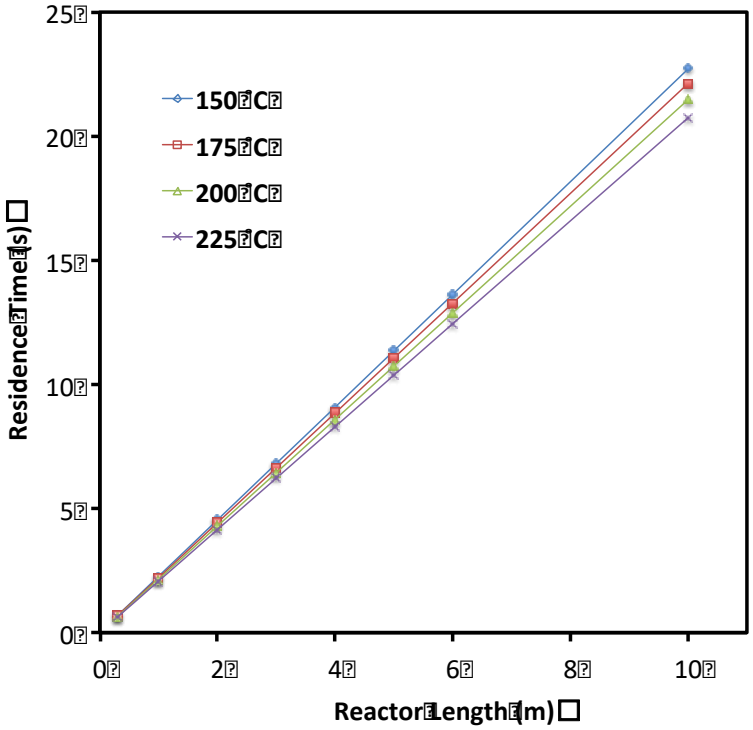


Figure S1. Residence time vs reactor length of reactor system.

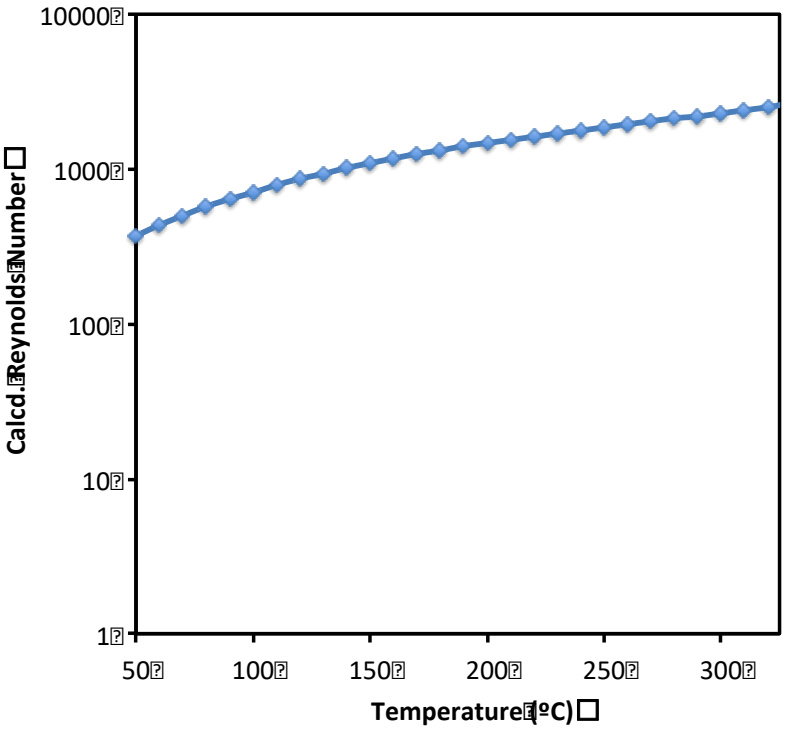
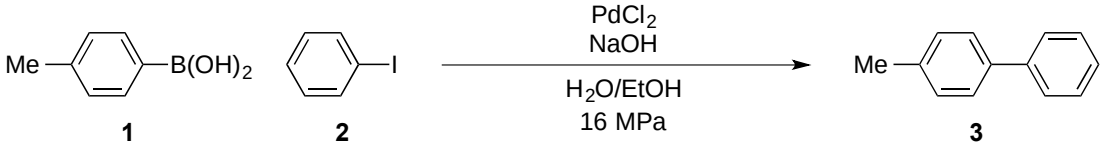


Figure S2. Reynolds Number at each temperature.

Table S1.

References					Process conditions														
Manuscript			SI		Water	Aqueous Solution of Catalyst/Base			EtOH Solution of Substrate		Equivalence		Coil Reactor		Reactor Conditions		Extraction	Theoretical Production Efficiency	
Tables	Entries	Figures	Tables	Entries	Feeding Rate from Pump1	PdCl2 Conc	NaOH Conc	Feeding Rate from Pump2	Substrates Conc (1/2)	Feeding Rate from Pump3	PdCl2	NaOH	Diameter/Length	Volume (mL)	Pressure	Temperature	Feeding Rate from Pump4	4-Methylbiphenyl	
					(mL/min)	(mM)	(M)	(mL/min)	(M)	(mL/min)	(mol%)	(mol%)	(mm/m)		MPa	degC	(mL/min)	(mmol/min)	(mg/min)
Table 1	1	Figure 2	Table S2	1	4.24	1.0	1.0	0.40	0.50/0.50	0.16	0.5	500	0.5/10	1.96	16	50	4.80	0.080	13.46
	2			2												100			
	3			3												125			
	4			4												175			
	5			5												200			
				6												225			
				7												250			
				8												275			
				9												300			
				10												325			
Table 1	6					0.50					0.25					200			
		Figure 2	Table S2	11	4.44	1.0		0.20				250				50			
				12												100			
				13												125			
				14												150			
				15												175			
Table 1	7			16												200			
				17												225			
				18												250			
Table 1	8					0.50					0.125					200			
		Figure 3	Table S3	1,8,15,22		0.010					0.0025		0.5/6	1.18		see Table S3			
				2,9,16,23									0.5/5	0.98					
				3,10,17,24									0.5/4	0.79					
				4,11,18,25									0.5/3	0.59					
				5,12,19,26									0.5/2	0.39					
				6,13,20,27									0.5/1	0.20					
				7,14,21,28									0.5/0.3	0.059					
Table 1	9	Figure 4	Table S4	1		0.10					0.025		0.5/10	1.96		200			
				2	4.48			0.16			0.02	200							
				3	4.52			0.12			0.015	150							
				4	4.56			0.08			0.01	100							
				5	4.60			0.04			0.005	50							
				6	4.64			0			0	0							
Table 1	10			7	4.44	0.010		0.20			0.0025	250				225			
				8	4.52			0.12			0.0015	150							
				9	4.55			0.09			0.001125	112.5							
				10	4.56			0.08			0.001	100							
				11	4.57			0.07			0.000875	87.5							
				12	4.58			0.06			0.00075	75							
				13	4.6			0.04			0.0005	50							
				14	4.64			0			0	0							
		Figure 5	Table S5	1	4.26			0.30		0.24	0.0025	250				200		0.12	20.19
				2	4.08			0.40		0.32								0.16	26.92
				3	3.90			0.50		0.40								0.20	33.65
				4	3.72			0.60		0.48								0.24	40.38
				5	4.04			0.60	1.5/1.5	0.16								0.24	40.38
				6	3.66			0.90		0.24								0.36	60.57
				7	3.28			1.20		0.32								0.48	80.76
				8	2.90			1.50		0.40								0.60	100.95
				9	2.52			1.80		0.48								0.72	121.14
		Figure 6			4.44			0.20	0.50/0.50	0.16								0.080	13.46

Table S2. Screening of Process Temperatures



1 **2** **3**

Entry	$PdCl_2$ (mol%)	NaOH (eq)	Temp (˚C)	Residence time (s)	Yield of **3** (%)
1	5.0×10^{-1}	5.0	50	24.4	38
2			100	24.0	78
3			125	23.7	82
4			175	22.7	84
5			200	21.5	98
6			225	20.7	97
7			250	19.9	67
8			275	19.0	62
9			300	17.8	53
10			325	16.4	39
11	2.5×10^{-1}	2.5	50	24.4	5
12			100	23.7	33
13			125	23.2	64
14			150	22.7	79
15			175	22.1	90
16			200	21.5	99
17			225	20.7	99
18			250	19.9	77

a) Process conditions: refer to Figure S1.; b) The yields were determined by ^{1}H-NMR using tridecane as an internal standard.

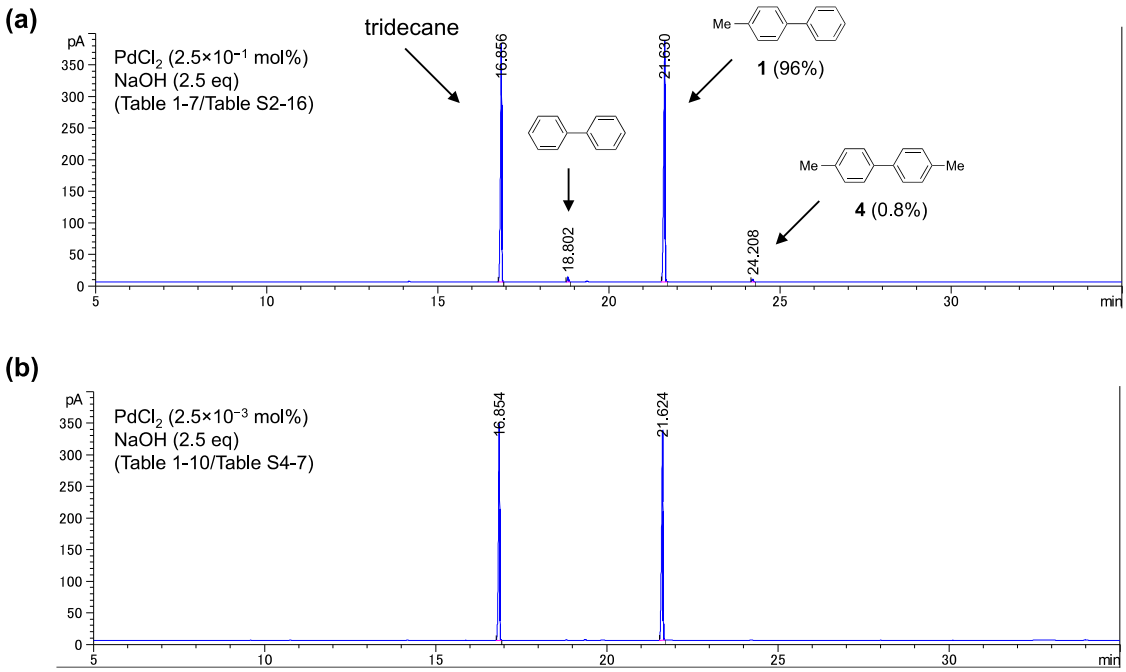


Figure S3. GC Charts of the reaction products without purifications.

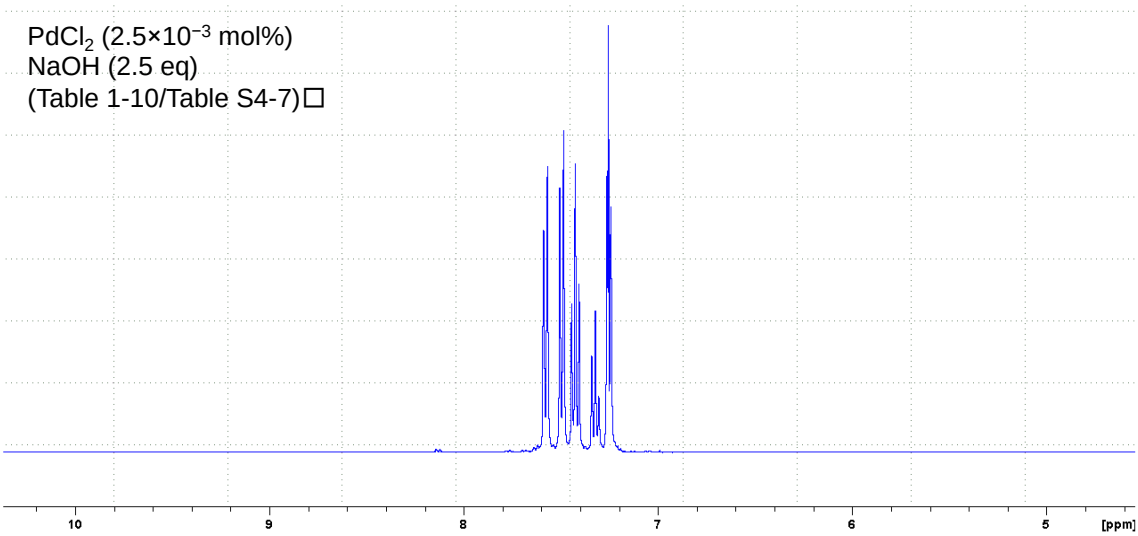
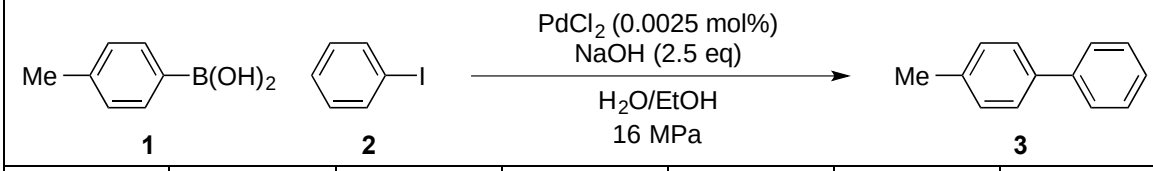


Figure S4. NMR Chart of the reaction product without purifications.

Table S3. Effects of Residence Time.



1 **2** **3**

Entry	Temp (˚C)	Reactor Vol. (mL)	Residence Time (s)	Yield of **3** (%)	TON	TOF (s^{-1})
1	225	1.18	12.4	99	3.96×10^4	3.19×10^3
2		0.98	10.4	98	3.94×10^4	3.78×10^3
3		0.79	8.3	97	3.87×10^4	4.67×10^3
4		0.59	6.2	95	3.79×10^4	6.12×10^3
5		0.39	4.1	95	3.78×10^4	9.22×10^3
6		0.20	2.1	90	3.61×10^4	1.72×10^3
7		0.059	0.62	61	2.45×10^4	3.95×10^3
8	200	1.18	12.9	99	3.94×10^4	3.05×10^3
9		0.98	10.7	96	3.86×10^4	3.61×10^3
10		0.79	8.6	92	3.69×10^4	4.30×10^3
11		0.59	6.4	91	3.63×10^4	5.67×10^3
12		0.39	4.3	83	3.33×10^4	7.77×10^3
13		0.20	2.1	64	2.56×10^4	1.22×10^4
14		0.059	0.64	53	2.12×10^4	3.31×10^4
15	175	1.18	13.3	98	3.93×10^4	2.96×10^3
16		0.98	11.1	97	3.87×10^4	3.49×10^3
17		0.79	8.8	93	3.72×10^4	4.23×10^3
18		0.59	6.6	73	2.91×10^4	4.41×10^3
19		0.39	4.4	62	2.49×10^4	5.66×10^3
20		0.20	2.2	39	1.55×10^4	7.05×10^3
21		0.059	0.66	41	1.64×10^4	2.48×10^4
22	150	1.18	13.6	77	3.06×10^4	2.25×10^3
23		0.98	11.4	70	2.79×10^4	2.45×10^3
24		0.79	9.1	60	2.38×10^4	2.62×10^3
25		0.59	6.8	36	1.43×10^4	2.10×10^3

26		0.39	4.5	25	1.01×10^4	2.25×10^3
27		0.20	2.3	12	4.84×10^3	2.10×10^3
28		0.059	0.68	9	3.69×10^3	5.42×10^3
a) Process conditions: refer to Figure S1.; b) The yields were determined by ^{1}H-NMR using tridecane as an internal standard.						

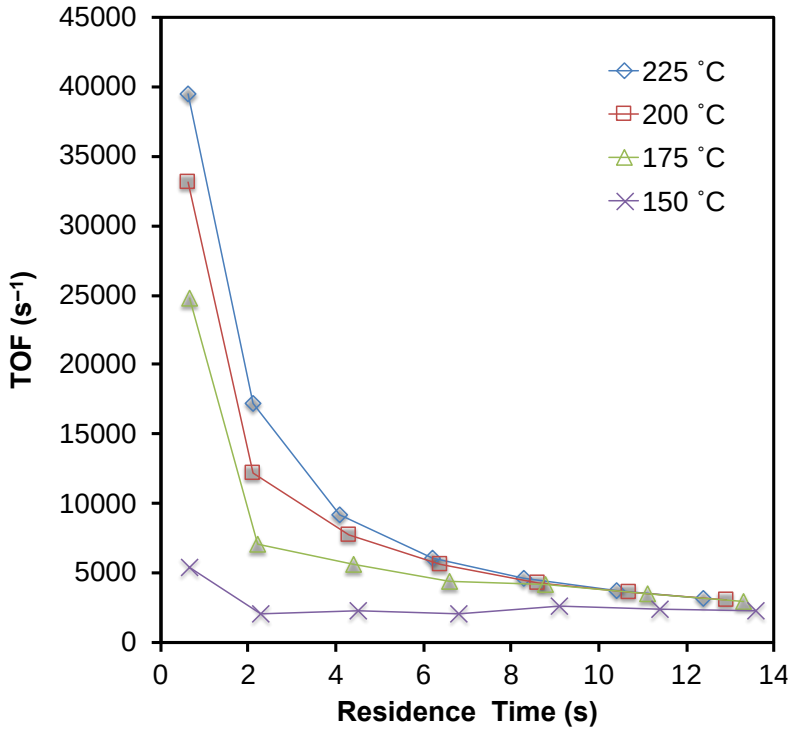
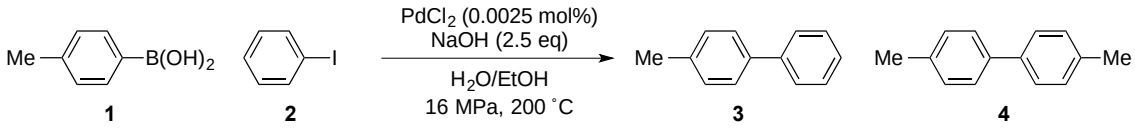


Figure S5 The residence time effects on turn over frequency (TOFs); ◆: 225ºC, ■: 200ºC, ▲: 175ºC, ×: 150ºC.

Table S4. Effect of Substrate Concentration.



1 2 3 4

Entry	Total Concentration of Substrates (M)	Yield (%)	
		3	**4**
1	0.025	>96%	0.14
2	0.033		0.22
3	0.042		0.24
4	0.050		0.29
5	0.050		0.22
6	0.075		0.23
7	0.10		0.29
8	0.125		0.68
9	0.15		0.79

a) Process conditions: refer to Figure S1.; b) The yields were determined by ^{1}H-NMR using tridecane as an internal standard.

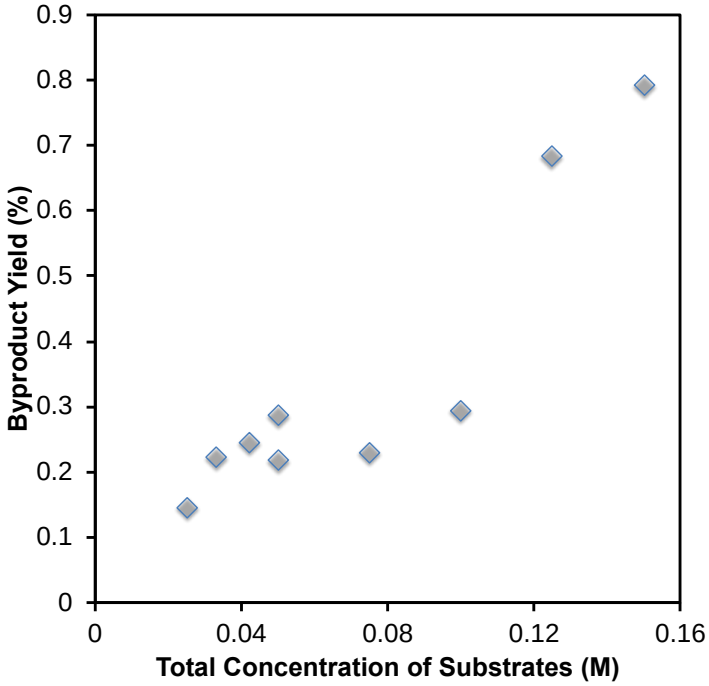


Figure S6 Production ratio of by-products (1,1'-biphenyl and 4,4'-dimethyl-1,1'-biphenyl) in the concentration of substrate (**1** + **2**).