Efficient, recoverable, copper-free Sonogashira reaction under FBS and thermomorphic mode

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ABSTRACT

The solubility property of high fluorine content ligands allows us to report in this article the accomplishment under the fluorous biphasic system (FBS) the Pd-catalyzed Sonogashira reactions using novel recyclable Pd catalysts with fluorous-ponytails in the structure of 2,2′-bpy ligands that are only soluble in perfluorinated solvents at room temperature. Alternatively, without using any fluorous solvent but under the thermomorphic mode, the same Pd catalysts proceed with the Cu-free Sonogashira reactions homogeneously in DMF at 135 ± 5 °C, whereas the product mixtures after reaction remain in solution and the Pd catalysts precipitate from DMF at low temperature.

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1. Introduction

The concept of fluorous biphasic catalysis (FBC) was first introduced by Horváth and Rábai in 1994 [1]. This field has evolved rapidly since then [2]. FBC has already been applied to a variety of common organic reactions, e.g., hydroboration of alkenes [3,4], hydroformylation of alkenes [1,5], epoxidation of alkenes [6–8], Wacker oxidation of alkenes [9], palladium allylic alkylation [10], and oxidation of alcohols [11]. Although FBC combines the advantages of homogeneous catalysis and heterogeneous catalysis [12,13], the large-scale usage of perfluorocarbon solvents has suffered from high cost and environmental pollutions. In response to these limitations, new methodologies have been introduced [14–19], one of which is based on the thermomorphic property [14,15] of catalysts in organic solvent. For example, a number of fluorous bipyridine ligands have been successfully synthesized to replace fluorinated phosphines and used in the Pd-catalyzed Heck reaction [18,20] as well as in the Cu-catalyzed the aerobic oxidation of alcohols [19]. These novel fluorous bipyridine ligands are also useful in the Sonogashira reaction described below.

The Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides provides a powerful tool for carbon–carbon bond formation, which has been widely applied in areas such as natural product synthesis, pharmaceutical industry and material science

[21–23]. The reaction usually proceeds in the presence of homogeneous Pd catalyst and Cu salt. As the most widely employed co-catalysts, the Cu salts also mediate the homocoupling of terminal alkynes and usually may result in a high Cu contamination (of the product) [24]. The homocoupled side product of terminal alkynes is problematic when terminal alkynes are difficult to obtain. In view of all these factors, reported here are the uses of novel Pd complexes with fluorous bipyridyl ponytails as catalysts in the copper-free Sonogashira reaction under the fluorous biphasic system (FBS) and separately under the thermomorphic mode.

2. Results and discussion

2.1. Catalyst synthesis

As shown in Scheme 1, the reaction of [Pd(CH₃CN)₂Cl₂] or [Pd(PhCN)₂Cl₂] with three highly fluorinated bipyridine derivatives, 4,4′-bis(R_fCH₂OCH₂)-2,2′-bpy (**1a–c**) [19], resulted in the Pd complexes, [PdCl₂(4,4′-bis-(R_fCH₂OCH₂)-2,2′-bpy)] (**2a–c**), as pale yellow solids, where $R_f = n\text{-}C_9F_{19}$ (**a**), $n\text{-}C_{10}F_{21}$ (**b**), $n\text{-}C_{11}F_{23}$ (**c**), respectively. The fluorine contents of **1a–c** are 61.2%, 62.3% and 63.3%, respectively. The partition ratios of **1a–c** in CH₂Cl₂/FC77 system are 1.04:1, 1:42 and 1:70, respectively. On the other hand, the partition ratios of **1b–c** in DMF/FC77 system are very small (*ca.* 1:1000). The distribution results of **1a–c** in two different solvent systems are shown in Table 1. Because of good partition ratios of the ligands **1b–c** in DMF/FC 77 system, the Pd complexes **2b–c**

Scheme 1.
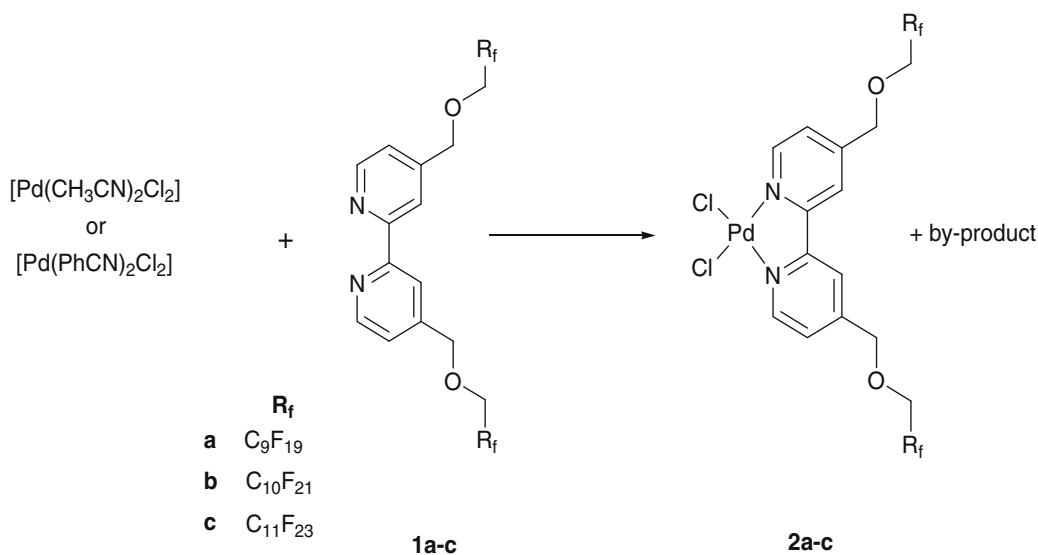
Table 1
Distribution partition of ligands **1a–c** in two biphasic systems.

Ligand (F%)	CH$_2$Cl$_2$:FC 77	DMF:FC 77
1a: 61.2	1.04:1	1:6.9
1b: 62.3	1:42	1:1000
1c: 63.3	1:70	1:>1000

were selected as the catalysts for the C–C bond forming Sonogashira reaction under FBS.

2.2. Sonogashira reaction with Pd complex **2b** as catalyst under FBS

As shown in Scheme 2, in the presence of **2b** (1 mol%) and 1,4-diazabicyclo[2.2.2]octane (DABCO) base, aryl iodide and phenylacytelene can be smoothly coupled to afford the corresponding arylacetylenes in moderate to excellent yields at the temperature of 135 ± 5 °C. Tables 2 and 3 list the results of Sonogashira reaction under FBS with and without the addition of CuI, respectively. The Pd complex **2b** is an effective catalyst in the recycling runs of Sonogashira reaction of iodo-4-nitrobenzene (**3b**) and phenylacytelene (**4a**), apparently.

The recycling usage of **2b**-catalyst with CuI co-catalyst in Sonogashira reaction, shown in Table 2, gave an average yield of >99% 4-nitrophenylacetylene. The similar **2b**-catalyzed Sonogashira reaction under a Cu-free condition gave also good results of recovery and reusage. The yield slightly dropped after the 7th run as shown in Table 3 with the average yield of 98% over 8 runs, only a few percents lower than that in Table 2. An averaged yield of 96% and a good recyclability up to 8 times were also demonstrated

Table 2
Recycling results of **2b**-catalyzed Sonogashira reaction of **3b** and **4a** with CuI under FBS.

Cycle no.	Time (h)	Temperature (°C)	Yield[a] (%)
1	4	135	100 (96)
2	4	135	100
3	4	135	100 (94)
4	4	135	100
5	4	135	100 (95)
6	4	135	100
7	4	135	100
8	6	135	>99

Conditions: DMF/FC 77 1:1 (3 mL each); CuI 10 mol% (0.0275 mmol, 5.3 mg), iodo-4-nitrobenzene (**3b**: 0.275 mmol, 68.5 mg), phenylacetylene (**4a**: 0.33 mmol, 33.7 mg), DABCO: 1.5 equivalents (0.413 mmol, 46.2 mg), 1 mol% Pd complex **2b** (4 mg). After each cycle, the DMF and FC 77 layers were separated at 0 °C using a separatory funnel. The FC 77 layer was washed with 2 mL DMF (or CH$_2$Cl$_2$) before proceeding to the next cycle.
[a] Based on GC yield (internal standard is NMP); isolated yields are given in parentheses.

for the **2b**-catalyzed Sonogashira reaction of **4a** with unactivated iodobenzene, **3a**, under FBS (see Table A in Supplementary material). There was almost no homocoupled dimer formation under FBS with or without CuI.

2.3. Sonogashira reaction with Pd complex **2a–c** as catalyst under the thermomorphic mode

In addition to reactions under FBS, the same Pd-catalyzed Sonogashira reactions was also successfully carried out employing the
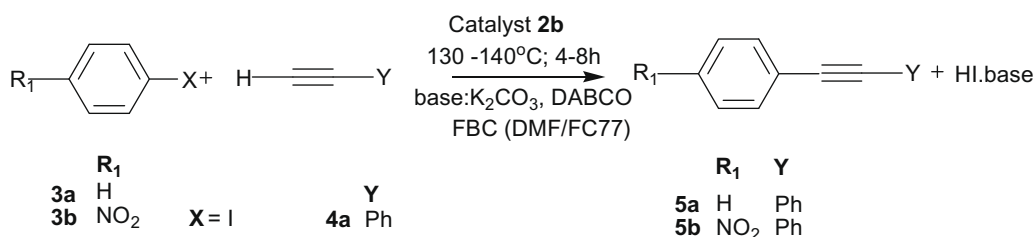

Scheme 2.

Table 3
Recycling results of **2b**-catalyzed Sonogashira reaction of **3b** and **4a** without CuI under FBS.

Cycle no.	Time (h)	Temperature (°C)	Yield[a] (%)
1	4	135	100
2	4	135	100 (96)
3	4	135	100
4	4	135	100 (96)
5	4	135	97
6	4	135	97
7	8	135	98 (95)
8	8	135	92

Reaction conditions: 1 mol% Pd complex **2b** (4 mg); DMF/FC 77 (3 mL each); CuI-free; **3b** (0.275 mmol, 68.5 mg); **4a** (0.33 mmol, 33.7 mg); DABCO (0.413 mmol, 46.2 mg).
[a] Based on GC yield; isolated yields are given in parentheses.

thermomorphic mode. Shown in Scheme 3, the Pd-catalyzed Sonogashira reactions of aryl halide (**3a–f**) with alkyne (**4a–b**) demonstrated the recycling usage with **2a–c** as the catalysts in DMF under the thermomorphic mode, at 135 ± 5 °C varying between 2 and 8 h in each run. At the end of each cycle, the product mixtures were cooled to −10 °C then centrifuged, followed by decantation for recovery of catalysts. The collected **2a–c** was added again with fresh DMF, substrates, and base to proceed to the next cycle. The products were quantified by GC analysis with an internal standard (NMP) or alternatively by isolated weights. The results showed that the Sonogashira coupling at this setting is clean and efficient. One example is shown in Table 4, in which the **2b**-catalyzed Sonogashira reaction of **3b** and **4a** with 10% CuI gave rise to excellent yields and a good recycling capability for 14 times under the thermomorphic mode.

Both **2a** and **2b**-catalyzed Sonogashira reactions of **3a** with 1-hexyne, **4b**, was tested under the thermomorphic mode with the results shown in Table 5. Almost quantitative yields were obtained for the first 3 runs each with time between 4 and 6 h. Afterwards, the yield dropped greatly as expected because of the lower reactivity of **4b** relative to that of **4a**.

The Cu-free condition was successful in **2b**-catalyzed Sonogashira reaction of **3b** with **4a** under the thermomorphic mode. As shown in Table 6, very high yields have been easily achieved for 8 cycles. Judged between the results in Table 3 and in Table 6, one can conclude that in the same Sonogashira reaction catalyzed by **2b**, the recycling results with the thermomorphic mode were better than with FBS. With the thermomorphic mode, the dependence of the solubility of fluorous catalysts in organic solvent on temperature only is important for recovery of catalysts. However, with FBS the solubility of fluorous catalysts in organic solvent and in fluorous solvent are both important. Apparently in this case, the single phase formation during catalysis and the phase separa-

tion during recovery of catalysts are more efficient under the thermomorphic mode.

Shown in Fig. 1 are the pictures of the 3 stages of **2b**-catalyzed Cu-free Sonogashira reaction of **3b** and **4a** under the thermomorphic mode. Before the start of the reaction, both reactants **3b** and **4a** and DABCO base were soluble in DMF, yet complex **2b** was not. During the catalysis, the DMF solution became monophasic when the temperature was raised to *ca.* 135 °C; the picture shown at this stage being at the 5th run. At the end of the reaction, the product mixtures were cooled to room temperature with concurrent catalyst precipitation out of DMF. By decantation the solid catalyst was readily recovered by for reuse.

Both **2a** and **2c** were also good catalysts for Pd-catalyzed Sonogashira reactions. The catalytic abilities in the decreasing order are **2a** > **2b** > **2c** (see Table B in Supplementary material) parallel to the fluorous chain length [19]. Although **2a** was the best catalyst among the three used in Sonogashira reaction under the thermomorphic mode, its operating temperature range [18] between −10 and 140 °C was less convenient. Thus, **2b** whose operating temperature range was between 25 and 140 °C was chosen to demonstrate most reactions. A variety of bases including DABCO, K_2CO_3, NEt_3, and piperidine had been used (see Table C in Supplementary material), and it was found that K_2CO_3 and DABCO generally worked better than remaining organic bases used. Furthermore, because K_2CO_3 was not totally soluble in DMF, it may also precipitate out along with the recovered catalyst. The slight insolubility of K_2CO_3 could occasionally result in the separation and recovery problems. DABCO, on the other hand, was chosen as a better base because of high b.p. and good solubility in DMF. The expected substituent electronic influence was also observed [25], with electron-withdrawing group speeding up and the electron-releasing group slowing down the reaction, respectively. Consistently, the rate of the catalyzed Sonogashira reaction with R_1-C_6H_4-I [R_1 = H (**3a**), NO_2 (**3b**), and CH_3 (**3c**)] decreased with substituent NO_2 > H > CH_3 (see Table D in Supplementary material).

Low Pd catalyst loadings had also been tested. Instead of 1 mol%, reactions with 0.1, 0.02 and 0.001 mol% of Pd catalyst **2b** were also successfully carried out. The results were shown in Table 7.

In a polymer supported, heterogeneous, Pd-catalyzed Sonogashira reaction, the turnover number (TON) is usually around 1000 at the high end in a single batch mode [26]. Interestingly, the effective Pd-catalyzed Sonogashira reaction of aryl iodide and phenylacetylene by **2b** shows a very high TON. The TON of 82 000 (entry 3 in Table 7) from the Cu-free Sonogashira reaction of this type was easily achieved at 140 °C under the thermomorphic conditions. It seems that the present Sonogashira reaction under the thermomorphic mode may have overcome the difficult separation and low efficiency problems at the same time.

Catalyst **2a-c**
130 -140°C; 2-8 h
base:K₂CO₃, DABCO, etc.
FBC (DMF/FC77)

R_1—⟨ ⟩—X + H—≡≡—Y → R_1—⟨ ⟩—≡≡—Y + HX·base

	R_1	X			Y
3a	H	I	**4a**		Ph
3b	NO₂	I	**4b**		C₄H₉
3c	Me	I			
3d	NO₂	Br			
3e	CN	Br			
3f	CH₃CO	Br			

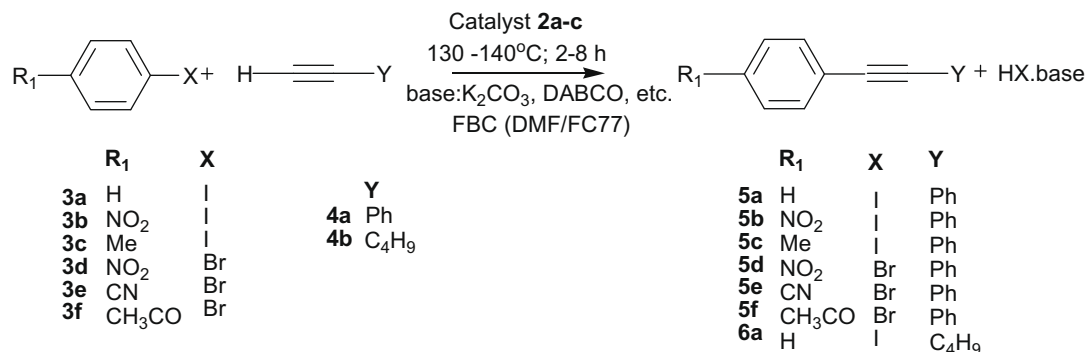|	R_1	X	Y
5a	H	I	Ph
5b	NO₂	I	Ph
5c	Me	I	Ph
5d	NO₂	Br	Ph
5e	CN	Br	Ph
5f	CH₃CO	Br	Ph
6a	H	I	C₄H₉

Scheme 3.

Table 4
Recycling results of **2b**-catalyzed Sonogashira reaction of **3b** and **4a** under the thermomorphic mode.

Cycle no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Yield (%)	100	100	100	100	100	100	100	100	100	100	100	74	82	91

Conditions: reaction time = 4 h; 1 mol% Pd complex **2b** (4 mg); DMF (5 mL); CuI 10 mol% (0.0275 mmol, 5.3 mg); **3b** (0.275 mmol, 68.5 mg); **4a** (0.33 mmol, 33.7 mg); DABCO: 1.5 equivalents (0.413 mmol, 46.2 mg).

Table 5
Recycling results of **2a**- and **2b**-catalyzed Sonogashira reactions of **3a** and **4b** under the thermomorphic mode.

Catalyst	Loading (%)	Temperature (°C)	Base	Yield[a]
2a	1	135	K_2CO_3	99, 99, 99, 30
2b	1	135	K_2CO_3	99, 99, 99, 28

Conditions: 1 mol% Pd complex [**2a** (3.7 mg), **2b** (4 mg)]; DMF (5 mL); CuI 10 mol% (0.0275 mmol, 5.3 mg); **3a** (0.275 mmol, 56.1 mg); **4b** (0.33 mmol, 33.7 mg); K_2CO_3: 1.5 equivalents (0.413 mmol, 57.1 mg).
[a] Based on GC yield.

Table 6
Recycling results of **2b**-catalyzed CuI-free Sonogashira reaction of **3b** and **4a** under the thermomorphic mode.

Cycle no.	Time (h)	Temperature (°C)	Yield[a] (%)
1	2	135	100 (98)
2	2	135	100
3	4	135	100
4	4	135	100 (97)
5	4	135	100
6	4	135	100 (97)
7	4	135	100
8	4	135	100 (96)

Reaction condition: 1 mol% Pd catalyst **2b** (4.0 mg); DMF (5 ml); CuI-free; **3b** (0.275 mmol, 68.5 mg), **4a** (0.33 mmol, 33.7 mg), DABCO (0.412 mmol, 46.2 mg).
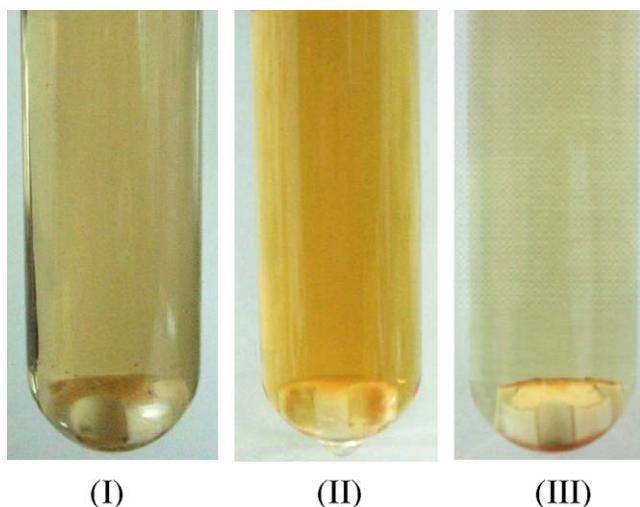[a] Based on GC yield; isolated yields are given in parentheses.

Fig. 1. Photographs of **2b**-catalyzed Sonogashira reaction (I) reactant mixture (**3b** + **4a**) plus DABCO in DMF and the insoluble Pd catalyst, (II) homogeneous DMF solution at 135 °C from 5th run, and (III) product mixture in DMF and the precipitation of catalyst **2b** at 25 °C.

*2.4. The **2b**-catalyzed Sonogashira reaction of activated bromobenzene under thermomorphic mode*

The activated bromobenzenes, R_1-C_6H_4-Br [R_1 = NO_2 (**3d**), CN (**3e**), and CH_3CO (**3f**)], were also tested in the Sonogashira reactions under the thermomorphic mode. A much longer time, *ca.* 14 h, was needed for the reaction to complete; and the recycling results were

Table 7
Different loadings of catalyst in **2b**-catalyzed Cu-free Sonogashira reaction under the thermomorphic mode.

	2b loading (%)	Reactant	Time (h)	Yield[a] (%)	TON
1	0.1	**3b**, **4a**	3	100 (100)	1000
				99[b]	990
				99[b]	990
2	0.02	**3b**, **4a**	6	100	5000
				99[b]	4950
3	0.001	**3b**, **4a**	7	82 (82)	82 000

[a] Based on GC yield (internal standard is NMP); isolated yields are given in parentheses.
[b] In order to show the recoverability, **2b** in entry 1 and entry 2 was recycled and reused for twice and once, respectively.

Table 8
Recycling results of **2b**-catalyzed Sonogashira reaction of activated bromobenzenes, **3d–f**, and **4a** under the thermomorphic mode.

Substrate	Loading (%)	Temperature (°C)	Base	Yield[a]
3d	1	135	DABCO	98, 97 (96), 92, 90 (88), 89
			K_2CO_3	98, 98 (97), 93, 92 (91), 90
3e	1	135	DABCO	96, 96 (94), 82, 66 (65)
			K_2CO_3	97, 96 (95), 89, 56 (56)
3f	1	135	DABCO	50, trace
			K_2CO_3	51, trace

Reaction condition: 1 mol% Pd catalyst **2b** (4.0 mg); DMF (5 ml); 10% CuI; **3d–f** (0.275 mmol), **4a** (0.33 mmol, 33.7 mg), DABCO: 1.5 equivalents (0.412 mmol, 46.2 mg); reaction time = 14 h.
[a] Based on GC yield (internal standard is NMP); isolated yields are given in parentheses.

3d better than **3e** better than **3f**, parallel to the substituent electronic effects for bromobenzenes. Because the acetyl group was not electron-withdrawing enough, the relevant second cycle data gave already a poor yield. The strong electron-withdrawing nitro group gave the best results. The results of Sonogashira reaction using three different activated bromobenzens were shown in Table 8, using either DABCO or K_2CO_3 as a base.

3. Conclusions

To our knowledge, this is the first example of Pd-catalyzed Sonogashira reaction of aryl halide with alkynes, with the same Pd catalysts running under either FBS or the thermomorphic mode. If taking advantage of the thermomorphic property, the use of expensive fluorinated solvents can be avoided. We have also demonstrated that the good TON of Cu-free Sonogashira catalysis is achieved, with both aryl iodides and aryl bromides as the substrate, and the Pd catalysts easily recovered and reused (up to 14 cycles in one of the examples).

4. Experimental

4.1. General procedures

Gas chromatographic/mass spectrometric data were obtained using an Agilent 6890 Series gas chromatograph with a series

5973 mass selective detector. The reaction was monitored with a HP 6890 GC using a 30 m × 0.250 mm HP-1 capillary column with a 0.25 μm stationary phase film thickness. The flow rate was 1 mL/min and splitless. Samples analyzed by fast atom bombardment (FAB) mass spectroscopy were done by the staff of the National Central University (Taiwan) mass spectrometry laboratory. Infrared spectra were obtained on a Perkin–Elmer RX I FT-IR Spectrometer. NMR spectra were recorded on Bruker AM 500 and Joel AM 200 using 5 mm sample tubes. CD_3OD, CD_2Cl_2, $CDCl_3$, deuterated DMF and deuterated Me_2SO were the references for both ^1H and ^{13}C NMR spectra; and Freon® 11 ($CFCl_3$) was the reference for ^{19}F NMR spectra.

4.1.1. Starting materials

Chemicals, reagents, and solvents employed were commercially available and used as received. $C_9F_{19}CH_2OH$, $C_{10}F_{21}CH_2OH$ and $C_{10}F_{23}CH_2OH$ were purchased from Aldrich and SynQuest.

4.2. Preparation of Pd complexes 2a–c where R_f = n-C_9F_{19} (a), n-$C_{10}F_{21}$ (b), and n-$C_{11}F_{23}$ (c)

Equal molar [$PdCl_2(CH_3CN)_2$] (134.9 mg, 0.52 mmol) and respective ligands 1a–c (0.52 mmol) [19] in different reactions were charged into a round bottomed flask, and CH_2Cl_2 (3 mL) added as solvent. The solution color changed from red to yellow after the mixing for several min. The solution was further stirred at 60 °C for 24 h before the solvents and volatiles were removed under vacuum. The resulting yellow solids were collected as spectroscopically pure products.

4.2.1. Analytical data of 2a

(NMR data collected in *d*-DMF at 90 °C because of poor solubility): yield 96%; ^1H NMR (500 MHz, DMF-d_6, δ ppm, J Hz) 9.29 (d, 2H, $^3J_{HH}$ = 5.8, H_6), 8.47 (s, 2H, H_3), 7.81 (d, 2H, $^3J_{HH}$ = 5.8, H_5), 5.08 (s, 4H, bpy-CH_2), 4.47 (t, 4H, $^3J_{HF}$ = 14.6, $C_{10}F_{21}$-CH_2); ^{19}F NMR (470.5 MHz, DMF-d_6, δ ppm, J Hz) −80.9 (t, 6F, $^3J_{FF}$ = 7.52, −CF_3), −119.3 (4F), −121.2 (16F), −122.2 (4F), −122.8 (4F), −125.6 (4F); ^{13}C NMR (126 MHz, DMF-d_6, δ ppm) 72.4 (bpy-CH_2), 68.2 (CH_2CF_2), 121.5, 125.0, 150.5, 153.0, 157.0 (bpy), 105.0–116.0 ($C_{10}F_{21}$); FT-IR (KBr pellets, v_{max}/cm^{-1}): 1624, 1561 (m, *v*bpy) 1207, 1148 (vs, *v*CF_2); HR-MS (FAB): (M^+; m/z=) $C_{32}N_2H_{14}F_{38}O_2Pd^{35}Cl_2$ calcd. 1355.8860, found 1355.8823; $C_{32}N_2H_{14}F_{38}O_2Pd^{37}Cl^{35}Cl$ calcd. 1357.8864, found 1357.8848; $C_{32}N_2H_{14}F_{38}O_2Pd^{37}Cl_2$ calcd. 1359.8835, found 1359.8792.

4.2.2. Analytical data of 2b

(NMR data collected in *d*-DMF at 90 °C because of poor solubility): yield 96%; ^1H NMR (500 MHz, DMF-d_6, δ ppm, J Hz) 9.29 (d, 2H, $^3J_{HH}$ = 5.8, H_6), 8.47 (s, 2H, H_3), 7.81 (d, 2H, $^3J_{HH}$ = 5.8, H_5), 5.08 (s, 4H, bpy-CH_2), 4.47 (t, 4H, $^3J_{HF}$ = 14.6, $C_{10}F_{21}$-CH_2); ^{19}F NMR (470.5 MHz, DMF-d_6, δ ppm, J Hz) −80.9 (t, 6F, $^3J_{FF}$ = 7.52, −CF_3), −121.0 (4F), −121.3 (20F), −122.1 (4F), −122.7 (4F), −125.5 (4F); ^{13}C NMR (126 MHz, DMF-d_6, δ ppm) 74.2 (bpy-CH_2), 68.2 (CH_2CF_2), 120.3, 124.5, 140.9, 151.8, 157.3 (bpy), 105.0–116.0 ($C_{10}F_{21}$); FT-IR (KBr pellets, v_{max}/cm^{-1}): 1623, 1558 (m, *v*bpy) 1208, 1151 (vs, *v*CF_2); HR-MS (FAB): (M^+; m/z=) $C_{34}N_2H_{14}F_{42}O_2Pd^{35}Cl_2$ calcd. 1455.8869, found 1455.8842; $C_{34}N_2H_{14}F_{42}O_2Pd^{35}Cl^{37}Cl$ calcd. 1457.8767, found 1457.8741; $C_{34}N_2H_{14}F_{42}O_2Pd^{37}Cl_2$ calcd. 1459.8737, found 1459.8734.

4.2.3. Analytical data of 2c

(NMR data collected in *d*-DMF at 90 °C because of very poor solubility): yield 90.4%; ^1H NMR (500 MHz, DMF-d_6, δ ppm, J Hz) 9.29 (d, 2H, $^3J_{HH}$ = 5.8, H_6), 8.47 (s, 2H, H_3), 7.81 (d, 2H, $^3J_{HH}$ = 6.0, H_5), 5.09 (4H, s, bpy-CH_2), 4.48 (t, 4H, $^3J_{HF}$ = 14.29, $C_{10}F_{23}$-CH_2); ^{19}F NMR (470.5 MHz, DMF-d_6, δ ppm, J Hz) −81.0 (t, 6F, $^3J_{FF}$ = 7.5,

−CF_3), −119.3 (4F), −121.3 (24F), −122.2 (4F), −122.9 (4F), −125.7 (4F); ^{13}C NMR (126 MHz, DMF-d_6, δ ppm): ^{13}C NMR spectrum was not obtained due to the extremely weak signal at 90 °C; FT-IR (KBr pellets, v_{max}/cm^{-1}): 1602, 1558 (m, *v*bpy), 1207, 1152 (vs, *v*CF_2); HR-MS (FAB): (M^+; m/z=) $C_{36}N_2H_{14}F_{46}O_2Pd^{35}Cl_2$ calcd. 1555.8732, found 1555.8721; $C_{36}N_2H_{14}F_{46}O_2Pd^{37}Cl^{35}Cl$ calcd. 1557.8679, found 1557.8656; $C_{36}N_2H_{14}F_{46}O_2Pd^{37}Cl_2$ calcd. 1559.8674, found 1559.8662.

4.2.4. Recycling studies

All the Pd-catalyzed Sonogashira reaction products are known products. The products (5a–f and 6a) have been checked by GC/MS, NMR spectrometer and m.p. if the product is a solid. These data are listed below.

(5a) PhC≡CPh: white solid, m.p.: 60–61 °C. ^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): d 7.56–7.51 (m, 4H), 7.38–7.31 (m, 6H). GC/MS (m/z; EI): 178 (M^+), 89 (M^+−C_7H_7), 76 ($C_6H_4^+$).

(5b = 5d) 4-$O_2NC_6H_4CCPh$: yellow solid, m.p.: 119–120 °C. ^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): 8.20 (d, J = 8.6, 2H), 7.65 (d, J = 8.6, 2H), 7.57–7.52 (m, 2H), 7.38–7.36 (m, 3H). GC/MS (m/z; EI): 223 (M^+), 193 (M^+−NO), 177 (M^+−NO_2), 165 (M^+−CNO_2), 151 (M^+−$C_2H_2NO_2$).

(5c) 4-$CH_3C_6H_4C$≡CPh: white solid, m.p.: 73–74 °C. ^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): d 7.54–7.50 (m, 2H), 7.42 (d, J = 8.0, 2H), 7.37–7.26 (m, 3H), 7.14 (d, J = 8.0, 2H), 2.36 (s, 3H). GC/MS (m/z; EI): 192 (M^+), 165 (M^+−C_2H_3), 115 (M^+−C_6H_5), 96 (M^{2+}).

(5e) 4-NCC_6H_4C≡CPh: yellow solid, mp.: 91–92. ^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): 7.63 (q, J = 8.5, 4H), 7.55–7.56 (m, 2H), 7.40 (d, J = 2.1, 2H), 7.39 (d, J = 1.65, 1H). GC/MS (m/z; EI): 203 (M^+), 176 (M^+−CHN), 150 (M^+−C_3H_3N), 101 (M^+−C_7H_4N), 88 (M^+−C_8H_5N), 75 (M^+−C_9H_6N).

(5f) 4-$CH_3COC_6H_4C$≡CPh: white solid, m.p.: 98–99 °C.
^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): d 7.95 (d, J = 8.0, 2H), 7.61 (d, J = 8.0, 2H), 7.55 (d, J = 2.4, 2H), 7.39–7.35 (m, 3H), 2.62 (s, 3H).
GC/MS (m/z; EI): 220 (M^+), 205 (M^+−CH_3), 176 (M^+−C_2H_4O), 151 (M^+−C_4H_5O), 88 (M^+−C_9H_8O).

(6a) PhC≡C(CH_2)$_3CH_3$: colorless liquid. ^1H NMR (500 MHz, CDCl$_3$, δ ppm, J Hz): d 7.41–7.37 (m, 2H), 7.29–7.25 (m, 3H), 2.41 (t, J = 7.2, 2H), 1.63–1.56 (m, 2H), 1.54–1.47 (m, 2H), 0.95 (t, J = 7.2, 3H). GC/MS (m/z; EI): 158 (M^+), 143 (M^+−CH_3), 129 (M^+−CH_3CH_2), 115 (M^+−$CH_3CH_2CH_2$), 102 (M^+−C_4H_8), 89 (M^+−C_5H_9), 77 ($C_6H_5^+$).

4.3. Recycling studies of the Sonogashira reaction with Pd complex 2b as catalyst under FBS

4.3.1. With the addition of 10% CuI

4.3.1.1. Sonogashira reaction with C_6H_5I, 3a, as the substrate.
Under the fluorous biphasic system, the vessel was charged with DMF (3 mL), FC77 (3 mL), 3a (0.275 mmol, 56.1 mg), phenylacetylene (4a: 0.33 mmol, 33.7 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex 2b (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg). The reaction mixture was refluxed at 135 °C for 4–6 h before the reaction was stopped and the 2 layers separated using a separatory funnel at 0 °C. The FC77 fraction was retained for recycling experiments.

4.3.1.2. Sonogashira reaction with p-$IC_6H_4NO_2$, 3b, as the substrate.
Under the fluorous biphasic system, the vessel was charged with DMF (3 mL), FC77 (3 mL), 3b (0.275 mmol, 68.5 mg), 4a (0.33 mmol, 33.7 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex 2b (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg).

The reaction mixture was refluxed at 135 °C for several hours before the reaction was stopped and the 2 layers separated using a separatory funnel at 0 °C. The FC77 fraction was retained for recycling experiments.

4.3.2. Without CuI addition
4.3.2.1. Sonogashira reaction with p-IC₆H₄NO₂, 3b, as the substrate. Except for no CuI addition, the procedures of this section are almost the same as those of Section 4.3.1.2.

4.4. Recycling studies of the Sonogashira reaction with Pd complex 2a–c as catalyst under thermomorphic mode (aryl iodides as substrates)

4.4.1. Sonogashira reaction of 1-hexyne and C₆H₅I
In a typical run, the reaction vessel was charged with DMF (5 mL), **3a** (0.275 mmol, 56.1 mg), **4b** (0.412 mmol, 33.2 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex **2a–c** (about 4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg). Then the reaction mixture was set to react at *ca.* 135 °C for 4h before GC analysis. After the reaction, the product mixtures were centrifuged and the precipitated catalyst was recovered by decantation at room temperature after each run. The recovered Pd catalyst was washed with 2 mL DMF (or CH₂Cl₂) before proceeding to the next cycle.

4.4.2. Sonogashira reaction with C₆H₅I as the substrate
In a typical run, the reaction vessel was charged with DMF (5 mL), **3a** (0.275 mmol, 56.1 mg), **4a** (0.33 mmol, 33.7 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex (about 4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg). Then the reaction mixture was set to react at *ca.* 135 °C for a period of time before GC analysis. After the reaction, the product mixtures were centrifuged and the precipitated Pd catalyst was recovered by decantation at room temperature after each run. The recovered Pd catalyst was washed with 2 mL DMF (or CH₂Cl₂) before proceeding to the next cycle.

4.4.3. Sonogashira reaction with p-IC₆H₄NO₂ as the substrate
In a typical run, the reaction vessel was charged with DMF (5 mL), **3b** (0.275 mmol, 68.5 mg), **4a** (0.33 mmol, 33.7 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg). Then the reaction mixture was set to react at *ca.* 135 °C for a period of time before GC analysis. After the reaction, the product mixtures were centrifuged and the precipitated Pd catalyst was recovered by decantation at room temperature after each run. The recovered Pd catalyst was washed with 2 mL DMF (or CH₂Cl₂) before proceeding to the next cycle.

4.4.4. Sonogashira reaction with p-IC₆H₄Me as the substrate
In a typical run, the reaction vessel was charged with DMF (5 mL), **3c** (0.275 mmol, 60.0 mg), **4a** (0.33 mmol, 33.7 mg), DABCO (0.825 mmol, 92.4 mg), the 1 mol% Pd complex **2b** (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg). Then the reaction mixture was set to react at *ca.* 135 °C for a period of time before GC analysis. After the reaction, the product mixtures were centrifuged and the precipitated **2b** was recovered by decantation at room temperature after each run. The recovered **2b** was washed with 2 mL DMF (or CH₂Cl₂) before proceeding to the next cycle.

4.5. Recycling studies of the Sonogashira reaction with Pd complex 2b as catalyst using different loadings under thermomorphic mode

4.5.1. General procedures
In a typical run, the reaction vessel was charged with 0.1, 0.02 or 0.001 mol% of Pd catalyst **2b**, {[0.1%: **2b** (4 mg), **3b** (2.75 mmol, 685 mg), **4a** (3.3 mmol, 337.1 mg), DABCO (4.13 mmol, 462 mg)], [0.02%: **2b** (4 mg), **3b** (13.75 mmol, 3426.5 mg), **4a** (16.5 mmol, 1685.5 mg), DABCO (20.65 mmol, 2310 mg)] and [0.001%: **2b** (1 mg), **3b** (69 mmol, 14.2 g), **4a** (82.5 mmol, 8.57 g), DABCO (100 mmol, 11.5 g)]}. Then the reaction mixture was set to react in DMF, at 140 °C for a period of time before GC analysis. After the reaction, the product mixtures were centrifuged and the precipitated **2b** was recovered by decantation at room temperature. And the products were analyzed by GC/MS and NMR spectrometer.

4.6. Aryl bromides as substrates

The procedures of Sections 4.6.1–4.6.3 are almost the same as those of Section 4.4.1 except that the reaction time was 14 h and the bromobenzene derivatives were used instead of aryl iodides. Below, only the amounts of chemicals used were given.

4.6.1. Sonogashira reaction with p-BrC₆H₄NO₂, 3d, as the substrate
DMF (5 mL), 4-NO₂C₆H₄Br (**3d**: 0.275 mmol, 55.6 mg), **4a** (0.33 mmol, 33.7 mg), DABCO or K₂CO₃ (0.825 mmol), the 1 mol% Pd complex **2b** (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg).

4.6.2. Sonogashira reaction with p-BrC₆H₄CN, 3e, as the substrate
DMF (5 mL), *p*-BrC₆H₄CN (**3e**: 0.275 mmol, 50.1 mg), **4a** (0.33 mmol, 33.7 mg), DABCO or K₂CO₃ (0.825 mmol), the 1 mol% **2b** (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg).

4.6.3. Sonogashira reaction with p-BrC₆H₄C(O)CH₃, 3f, as the substrate
DMF (5 mL), 4-CH₃C(O)C₆H₄Br (**3f**: 0.275 mmol, 54.7 mg), **4a** (0.33 mmol, 33.7 mg), DABCO or K₂CO₃ (0.825 mmol), the 1 mol% **2b** (4 mg), and 10 mol% CuI (0.0275 mmol, 5.3 mg).

Acknowledgment

Appendix A. Supplementary material

The data for other Tables (A–D) as supplementary materials can be found in the online version. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.10.042.

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