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Green synthesis of fluorinated biaryl derivatives via thermoregulated ligand/palladium-catalyzed Suzuki reaction

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ABSTRACT

Fluorinated compounds have attracted considerable attention in pharmaceuticals, agrochemicals and material science due to their unique physical properties. This paper reports an efficient and environmentally benign protocol for the Suzuki reaction of aryl halides with fluorinated arylboronic acids over a thermoregulated ligand/palladium catalyst using water as sole medium, affording a variety of fluorinated biaryls, including fluorinated liquid crystals, in excellent yields. The catalyst could be recycled four times with high activity. The active catalyst was proved to be a palladium/ligand complex via a mercury-poisoning test.

1. Introduction

Fluorinated compounds find diverse applications in pharmaceuticals, agrochemicals and material science [1–3]. In recent years, fluorinated compounds have attracted attention from many researchers due to the anomalous physical properties and physiological activity. For example, the fluorinated graphene films exhibited significant changes on the optical, structural and transport properties [4]. Li et al. reported an efficient protocol for the synthesis of 2-fluoromethylated quinolines, which are of significant pharmacological interest for their use as potent antimalarial agents [5]. A series of fluorinated benzyloxyphenyl piperidine-4-carboxamides were synthesized and proved to be potent antithrombotic drugs [6]. Generally, synthetic methods for fluorinated biaryls are classified into two types: carbon-fluorine bond-forming reactions and carbon–carbon bond-forming reactions [1,2]. In the synthesis of fluorinated biaryls via the carbon–carbon bond-forming reactions, the cross-couplings involving organochlorosilanes [7,8], potassium aryltrifluoroborates [9–11], Grignard reagents [12,13] or organolithium reagents [14], have been developed, respectively. However, these methods require the use of highly specialized reagents.

The palladium-catalyzed cross-coupling reaction of arylboronic acid with aryl halide, known as the Suzuki cross-coupling reaction, is one of the exceedingly important methodologies for the construction of carbon–carbon bond in the synthesis of biaryls [15–22], in particular for the preparation of the fluorinated biaryls. Recently, the synthesis of fluorinated liquid crystals via the palladium-catalyzed Suzuki reaction of fluorinated arylboronic acids with aryl bromides containing cyclohexyl moiety in ethanol has been reported [23,24].

Recovery and recycling of catalysts poses a serious problem for industrial applications of homogeneous catalysis. So far, intensive work has been focused on developing efficient catalytic systems to solve this problem. Thermomorphic systems offer an alternative approach to facilitate the catalyst separation and preserve the benefits of homogeneous catalysis [25–31]. We have a long-standing interest in developing efficient aqueous/organic biphasic catalytic system for solving such a problem and a concept of the thermoregulated phase-transfer catalysis (TRPTC) has been reported [32–35]. In the traditional TRPTC system, a suitable organic solvent is necessary as a co-solvent for the efficient aqueous/organic biphasic catalysis.

Water is a desirable medium for chemical reactions for reasons of low cost, safety, and environmental concerns [36–43]. Recently, we reported an environmentally benign thermoregulated system using water as sole solvent for the Suzuki reaction [44]. In the present paper, this thermoregulated system is applied for the construction of fluorinated biaryls, providing a green and efficient protocol for the Suzuki cross-coupling of aryl bromides with fluorinated aryl boronic acids. To the best of our knowledge, the

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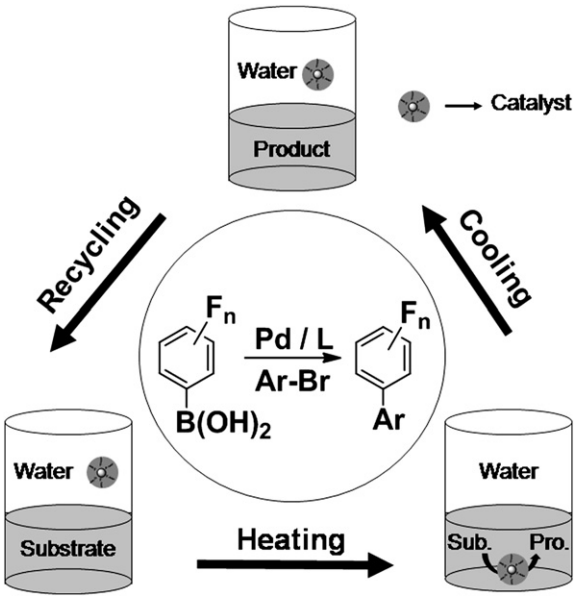


Fig. 1. Thermoregulated ligand/palladium-catalyzed Suzuki reaction in water.

synthesis of fluorinated biaryls in a thermoregulated system using water as sole medium has not been described in the literature. The key to the efficient protocol is the use of a polyethylene glycol modified phosphine ligand, which possesses a phase-transfer property due to the cloud point (*C*p) like a non-ionic surfactant. As shown in Fig. 1, the thermoregulated catalyst is able to transfer into the substrate phase (organic phase) to catalyze reaction at the temperature higher than its *C*p, thus allowing the reaction to take place in the substrate phase, and the recovery of the catalyst in the water phase upon cooling to room temperature (<*C*p).

2. Results and discussion

2.1. Optimization of reaction conditions

As known, an efficient palladium-catalyzed cross-coupling reaction is regulated by a number of factors, such as reaction temperature, palladium source, base and molar ratio of ligand-to-metal. Initially, the cross-coupling of 0.5 mmol 4-bromoanisole with 0.75 mmol 4-fluorophenylboronic acid using palladium/**L** as catalyst in 1 mL H_2O is chosen as a model reaction for screening the reaction temperature. The reaction conditions and the results are shown in Fig. 2. It is clear that the reaction temperature is crucial to the catalytic efficiency. The cross-coupling reaction was difficult to proceed at 60 °C. When increasing the reaction temperature from 60 °C to 66 °C, the isolated yield of the desired product was slowly increased from 6% to 13%. In contrast, the coupling reaction was sharply accelerated at 67 °C, affording 38% yield. Furthermore, 45% of the product yield was obtained when the reaction temperature increasing to 70 °C. These results indicate that the palladium catalyst stays in the aqueous phase at a lower temperature (<67 °C) and transfers into the substrate phase at a higher temperature (>67 °C).

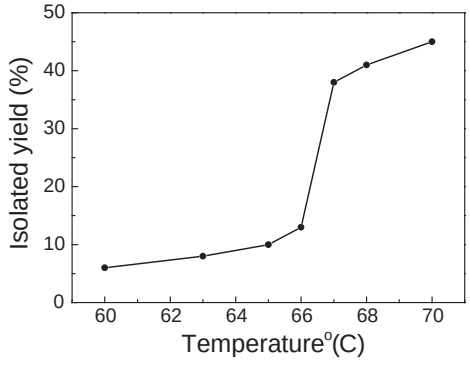


Fig. 2. The effect of temperature on the Suzuki reaction. Reaction conditions: 0.5 mmol of 4-bromoanisole, 0.75 mmol of 4-fluorophenylboronic acid, 1 mmol of Et_3N, 0.1 mol % $PdCl_2$, L/Pd = 2: 1 (molar ratio), 1 h, 1 mL H_2O.

The palladium source and base employed in the Suzuki reaction are also important to the catalytic efficiency. As shown in Table 1, the palladium sources have dramatic effects on the reaction activity. It is clear that palladium(II) salts such as $Pd(OAc)_2$ or $PdCl_2$ exhibited high catalytic activity (Table 1, entries 3 and 4), respectively. Using 0.1 mol% $PdCl_2$ as catalyst, 79% yield of the product could be obtained in 30 min (Table 1, entry 4). However, the catalytic activity of zero-valent palladium sources such as $Pd_2(dba)_3$ or Pd/C, was relatively low (Table 1, entries 1 and 2). The results showed that the use of $PdCl_2$ gave the best results.

Subsequently, the impact of various bases on the reaction was evaluated. As described in Table 1, the reaction rate is greatly affected by the base used. For instance, the coupling reactions using $K_3PO_4 \cdot 7H_2O$ or CH_3ONa (Table 1, entries 5 and 6) as base were less effective than those using K_2CO_3, NaOH or Na_2CO_3 (Table 1, entries 7, 8 and 9). It is noteworthy that the weak base Na_2CO_3 achieved the best yield among the inorganic bases, which is consistent with what Leadbeater reported [45]. Furthermore, the effect of an organic base Et_3N in the Suzuki reaction is evaluated. Interestingly, the yield was greatly improved when Et_3N was used (Table 1, entry 4). In addition, decreasing the palladium loading to 0.05 mol% for the cross-coupling of 4-bromoanisole with 4-fluorophenylboronic acid resulted in only 39% product yield (Table 1, entry 10).

To establish the best molar ratio of ligand-to-palladium, the Suzuki reaction of 4-bromoanisole and 4-fluorophenylboronic acid was carried out under various **L**/Pd molar ratio. The best result was obtained with **L**/Pd molar ratio of 2:1 (Table 2, entry 3). The yield was noticeably low when the **L**/Pd molar ratio increased to 8:1 (Table 2, entry 5). The reason for this might be that excess ligands led to an over-coordinated palladium complex, which could diminish the catalytic activity [46,47]. However, the blank experiment without ligand did not show competitive result under the same reaction conditions, only an 8% isolated yield was obtained (Table 2, entry 1).

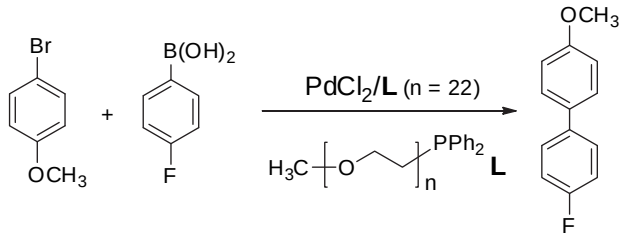
2.2. Mercury poisoning test

To determine whether the active catalytic species was a palladium/**L** complex or palladium particles, a mercury-poisoning test was performed accordingly. The coupling of 4-bromoanisole and 4-fluorophenylboronic acid under the conditions listed in Table 1 in the presence or absence of mercury was investigated. The reaction was allowed to proceed for 30 min (79% yield) before the mercury was added in a molar ratio of 300 equivalents to the palladium. Then the reaction was continued to proceed for another 30 min, a 98% product yield was obtained. The result verifies that the palladium/**L** complex is the true catalyst in the reaction.

2.3. Scope and limitations of substrates

The scope of the reaction system was explored with a range of aryl bromides and fluorinated arylboronic acids under the optimized conditions. As shown in Table 3, all reactions of fluorinated arylboronic acids provided the biaryl derivatives in good to

Table 1
The optimization of reaction conditions for the Suzuki reaction.



Entry	Pd source	Base	Yield [%][a]
1	$Pd_2(dba)_3$	Et_3N	16
2	Pd/C	Et_3N	27
3	$Pd(OAc)_2$	Et_3N	76
4	**$PdCl_2$**	**Et_3N**	**79**
5	$PdCl_2$	$K_3PO_4 \cdot 7H_2O$	51
6	$PdCl_2$	CH_3ONa	38
7	$PdCl_2$	K_2CO_3	65
8	$PdCl_2$	NaOH	63
9	$PdCl_2$	Na_2CO_3	68
10	$PdCl_2$	Et_3N	39[b]

Reaction conditions: 0.5 mmol of 4-bromoanisole, 0.75 mmol of 4-fluorophenylboronic acid, 1 mmol of base, 0.1 mol % Pd catalyst, **L**/Pd = 2: 1 (molar ratio), 80 °C, 30 min, 1 mL H_2O.
[a] Isolated yield.
[b] 0.05 mol % $PdCl_2$.

excellent yields. Various *para*-substituted aryl bromides bearing either electron-donating groups or electron-withdrawing groups such as methyl, methoxy, cyano and acetyl, afforded the corresponding products in excellent yields in 1 h (Table 3, entries 1, 2, 3 and 4). To our delight, sterically hindered aryl bromides were also highly reactive in this reaction system, giving the desired cross-coupling products in high yields (Table 3, entries 5 and 6). The present protocol obtains similar results with that catalyzed by the polyethylene-supported FibreCat Pd catalysts [48]. Recently, Scheuermann and co-workers developed a palladium nanoparticle catalyst on graphite oxide, which showed excellent catalytic activity in the Suzuki reaction of 4-bromo-1,2-difluorobenzene with arylboronic acids [49]. However, the coupling reaction of 3,4-difluorophenylboronic acid with aryl bromide is rarely reported [23,24]. Therefore, the Suzuki reaction of 3,4-difluorophenylboronic acid was also investigated in this thermoregulated system. As shown in Table 3, electron-deficient, electron-rich or sterically hindered aryl bromide substrates could be coupled with 3,4-difluorophenylboronic acids in excellent yields (Table 3, entries 7–10). The effect of the fluorine-substituents in different positions of the arylboronic acid on the Suzuki coupling reaction was studied further. As shown in Table 3, the reactivity of 2,3-difluorophenylboronic acid (Table 3, entries 11 and 12) was less active than that of 3,4-difluorophenylboronic acid (Table 3, entries 7, 8 and 9). 3,4,5-Trifluorophenylboronic acid is an inactive substrate in the presence of 0.1 mol% palladium, probably because the transmetalation of the highly electron-deficient 3,4,5-trifluorophenyl group to the Pd centre proceeds difficultly. The moderate to good yields could be obtained when palladium loading up to 0.5 mol% and prolonging the reaction time to 4 h (Table 3, entries 13 and 14). As aryl-substituted pyridines are the most common *N*-heteroaryl units in pharmaceutically active compounds [50], we further investigated the Suzuki reaction of *N*-heteroaryl bromides with 4-fluorophenylboronic acid. In the presence of 0.5 mol % $PdCl_2$, the Suzuki reaction of 3-bromopyridine with 4-fluorophenylboronic acid afforded excellent yields (Table 3, entries 15 and 16). For example, a 95% isolated yield was reached between 2-methoxy-5-bromopyridine and 4-fluoro-phenylboronic acid in 2 h (Table 3, entry 16). In addition, the reaction of 3-bromoquinoline with 4-fluorophenylboronic acid provided 92% yield after 2 h (Table 3, entry 17).

Table 2
The effect of **L**/Pd on the Suzuki reaction.

Entry	**L**/Pd	Yield [%][a]
1	0:1	8
2	1:1	52
3	**2:1**	**79**
4	4:1	65
5	8:1	27

Reaction conditions: 0.5 mmol of 4-bromoanisole, 0.75 mmol of 4-fluorophenylboronic acid, 1 mmol of Et_3N, 0.1 mol % $PdCl_2$, 80 °C, 30 min, 1 mL H_2O.
[a] Isolated yield.

2.4. Application in synthesis of fluorinated liquid crystals

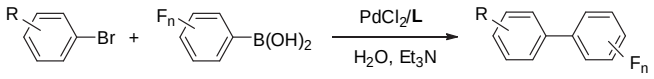
Fluorinated biphenyl derivatives are fundamental building blocks for synthesis of fluorinated liquid crystals, such as thin-film transistor liquid crystal displays (TFT-LCDs) [51]. The Suzuki reaction is one of the most powerful methods for the construction of fluorinated biaryls through two alternative cross-coupling paths (Scheme 1). The synthetic path **I** employing cyclohexylphenylboronic acids and aryl bromides has been reported for the construction of liquid crystals material units [52,53]. However, this method is limited in applications due to harsh reaction conditions and low product yield. Recently, the synthesis of TFT-LCDs in organic solvent via path **II** was emerged [23,24]. However, to the best of our knowledge, there is no previous report of the efficient synthesis of fluorinated liquid crystals using the commercially available arylboronic acids in water.

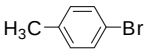
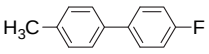
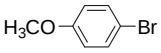
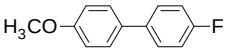
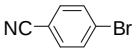
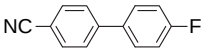
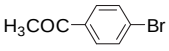
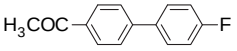
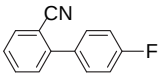
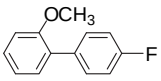
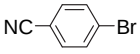
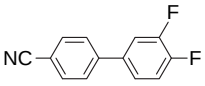
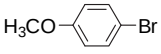
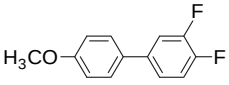
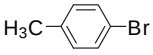
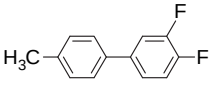
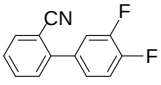
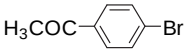
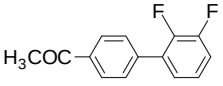
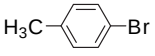
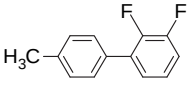
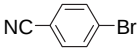
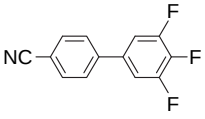
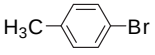
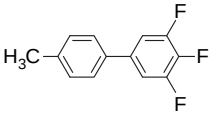
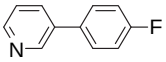
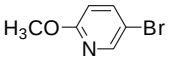
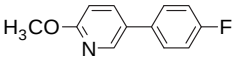
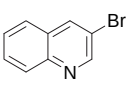
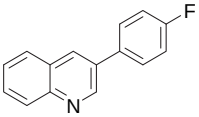
Therefore, the scope of substrates for the Suzuki reaction over the thermoregulated **L**/palladium catalyst for the synthesis of TFT-LCDs was investigated. The reaction was carried out with 0.5 mmol of aryl bromides, 0.75 mmol of fluorinated arylboronic acids with 0.1 mol % $PdCl_2$. As shown in Table 4, monofluoro, difluoro, trifluoro, or trifluoromethyl substituted arylboronic acids could be coupled in excellent yields in this thermoregulated system. For instance, the coupling reaction of inactive 3,4,5-trifluorophenylboronic acid also achieved good results by prolonging the reaction time (Table 4, entries 4 and 10).

2.5. Recycling of the catalyst

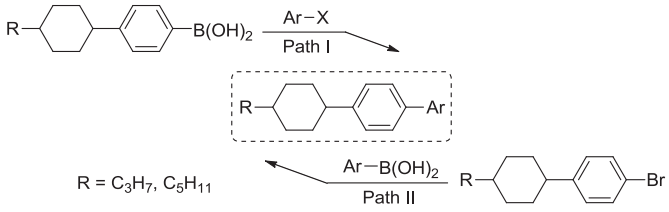
To test the reusability of the thermoregulated catalyst, we chose the Suzuki reaction of 4-(4-propyl-cyclohexyl)-bromobenzene with 4-fluorophenylboronic acid as a model reaction (Table 5). The reaction was performed under organic solvent-free conditions, in which water was the sole medium. When the reaction was completed, the reaction mixture was cooled down to room temperature. The catalyst could be recovered in water phase, and the organic phase gave 4-fluoro-4′-(4-propyl-cyclohexyl)-biphenyl as white solid product. The catalyst could be recycled at least four consecutive cycles. To further ascertain whether the recovered catalyst is a palladium/**L** complex or palladium particles, a mercury-poisoning test was designed for the reuse of the catalyst in the second run of the coupling of 4-(4-propyl-cyclohexyl)-bromobenzene with 4-fluorophenylboronic acid under the reaction conditions in Table 5. The reaction was allowed to proceed for 10 min before the mercury was added in a molar ratio of 300 equivalents to the palladium. The coupling reaction was quantitatively completed after another 50 min. The result indicates that the recovered catalyst is a palladium/**L** complex.

Table 3
The synthesis of fluorinated biphenyl derivatives.



Entry	Aryl bromides	Product	Time [h]	Yield [%][a]
1			1	98
2			1	98
3			1	98
4			1	97
5			2	93
6			2	91
7			1	96
8			2	98
9			2	93
10			2	95
11			4	76
12			4	68
13			4	65[b]
14			4	68[b]
15			2	94[b]
16			2	95[b]
17			2	92[b]

Reaction conditions: 0.5 mmol of aryl bromides, 0.75 mmol of arylboronic acids, 1 mmol of Et_3N, 0.1 mol % $PdCl_2$, **L**/Pd = 2: 1 (molar ratio), 80 °C, 1 mL H_2O.
[a] Isolated yield.
[b] 0.5 mol % $PdCl_2$.

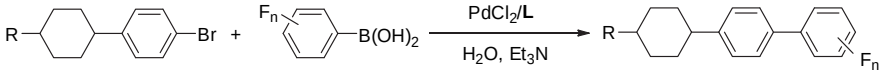


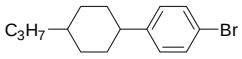
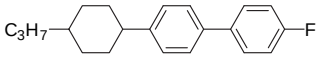
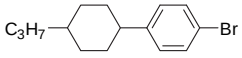
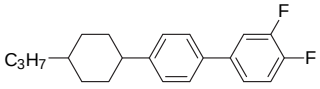
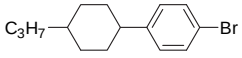
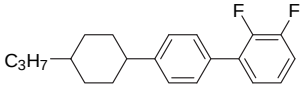
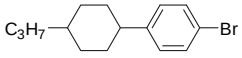
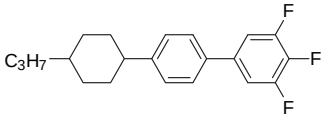
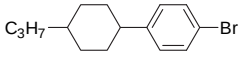
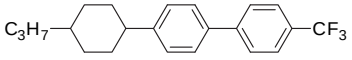
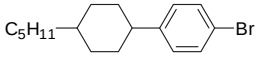
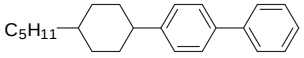
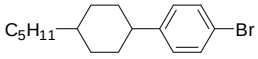
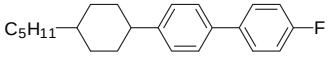
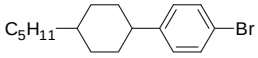
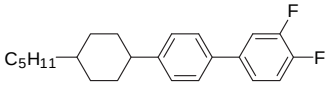
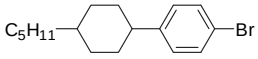
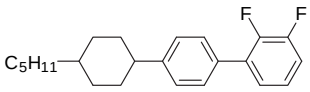
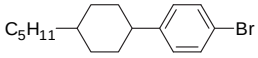
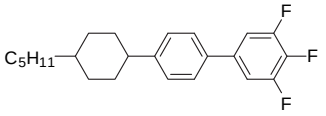
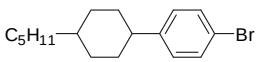
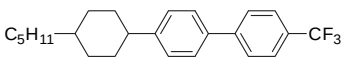
Scheme 1. Alternative synthetic paths for fluorinated liquid crystals.

3. Conclusion

In summary, we have developed an environmentally benign thermoregulated system using water as sole medium for the Suzuki reaction of aryl bromides with a range of fluorinated arylboronic acids in excellent yields, which offers an alternative approach to facilitate the separation and recycling of the catalyst. The mercury poisoning tests demonstrate that the Suzuki reaction is catalyzed by a palladium/**L** complex. Efforts including the application of the thermoregulated ligand/palladium system to other transformations and the development of more efficient thermoregulated ligands

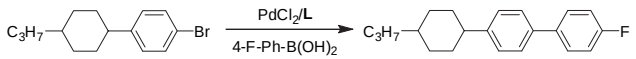
Table 4
The synthesis of fluorinated liquid crystals.



Entry	Aryl bromides	Product	Time [h]	Yield [%][a]
1			1	95
2			1	98
3			2	93
4			4	91
5			3	89
6			1	98
7			1	96
8			1	97
9			2	90
10			4	88
11			3	92

Reaction conditions: 0.5 mmol of aryl bromides, 0.75 mmol of arylboronic acids, 1 mmol of Et_3N, 0.1 mol % $PdCl_2$, **L**/Pd = 2: 1 (molar ratio), 80 °C, 1 mL H_2O.
[a] Isolated yield.

Table 5
Reusability of the catalyst in the synthesis of fluorinated liquid crystals.



Run	1st	2nd	3rd	4th	5th
Time [h]	1	1	1	1	2
Yield [%][a]	95	92	94	87	74

Reaction conditions: 0.5 mmol of 4-(4-propylcyclohexyl)-bromobenzene, 0.75 mmol of 4-fluorophenylboronic acid, 1 mmol of Et_3N, 0.1 mol % $PdCl_2$, **L**/Pd = 2: 1 (molar ratio), 80 °C, 1 mL H_2O.
[a] Isolated yield.

capable of activating aryl chlorides are currently under investigations in our laboratory.

4. Experimental

4.1. General remarks

All the reactions were carried out in nitrogen. All aryl halides and arylboronic acids were purchased from Alfa Aesar, or Avocado. Other chemicals were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Brucker Advance II 400 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. Mass spectroscopy data of the products were collected on an MS-EI instrument. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by ^{1}H NMR spectra to reported data.

4.2. Synthesis of $Ph_2P(CH_2CH_2O)_nCH_3$ (n = 22) (**L**)

The ligand $Ph_2P(CH_2CH_2O)_nCH_3$ (n = 22) (**L**, *C*p: 93 °C) was prepared according to the reported method [54]. ^{1}H NMR (400 MHz, D_2O): δ 2.39 (t, 2H), 3.37 (s, 3H), 3.55–3.65 (m, 95H), 7.31–7.50 (m, 10H) ppm. ^{13}C NMR (100 MHz, D_2O): δ 28.64 (d), 58.75 (s), 68.16 (d), 69.88–71.70 (m), 128.17 (s), 128.30 (d), 132.40 (d), 138.08 (d) ppm. ^{31}P NMR (400 MHz, D_2O): δ −22.70 ppm.

4.3. General procedure for the Suzuki reaction

A solution of $PdCl_2$ (0.09 mg, 0.0005 mmol) and ligand **L** (1.2 mg, 0.001 mmol) in deoxygenated H_2O (1 mL) was stirred at room temperature for 30 min under nitrogen. Et_3N (1 mmol, 101 mg), aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol) were then successively added. The reaction mixture was heated in oil bath under nitrogen with magnetic stirring. After cooling to room temperature, the reaction mixture was added to brine (15 mL) and extracted three times with diethyl ether (3 × 15 mL). The solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel (200–300 mesh) column.

4.4. Catalyst recycling for the Suzuki reaction

When the reaction was completed, the reaction mixture was cooled to room temperature and extracted with 2 mL ethyl ether. Et_3N (1 mmol, 101 mg), aryl bromide (0.5 mmol) and phenylboronic acid (0.75 mmol) were added to the aqueous phase separated from the previous catalytic run under nitrogen and reacted at 80 °C.

4.5. Characterization of the coupling products

4.5.1. 5-(4-Fluorophenyl)-2-methoxylpyridine
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.33 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 8.4, 2.4 Hz, 1H), 7.49–7.45 (m, 2H), 7.15–7.11 (m, 2H), 6.81 (d, J = 8.4, 1H), 3.98 (s, 3H), ppm; ^{13}C NMR δ 163.6, 162.5, 144.8, 137.4, 134.1, 129.2, 128.3, 115.9, 110.9, 53.57, ppm; MS (EI) m/z 203 (M^+, 100%): 203, 175, 172, 146, 133, 132, 107, 83, 63. Melting Point: 75 °C.

4.5.2. 3′,4′-difluoro-[1,1′-biphenyl]-4-carbonitrile
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.74 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.37–7.43 (m, 1H), 7.28–7.33 (m, 2H), ppm; ^{13}C NMR δ 151.9, 149.5, 143.5, 136.2, 132.8, 127.6, 123.4, 118.6, 118.1, 117.9, 116.4, 116.2, 111.6, ppm; MS (EI) m/z 215 (M^+, 100%): 215, 195, 164, 151, 123, 94, 87, 75, 51. Melting Point: 109–110 °C.

4.5.3. 3′,4′-difluoro-[1,1′-biphenyl]-2-carbonitrile
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.77–7.79 (m, 1H), 7.64–7.68 (m, 1H), 7.47–7.50 (m, 2H), 7.35–7.39 (m, 1H), 7.28–7.31 (m, 2H), ppm; ^{13}C NMR δ 152.0, 151.5, 149.5, 149.0, 143.3, 135.0, 133.4, 129.9, 128.2, 125.2, 118.1, 118.0, 111.3, ppm; MS (EI) m/z 215 (M^+, 100%): 215, 195, 188, 168, 138, 121, 94, 88, 75, 39. Melting Point: 102–103 °C.

4.5.4. 3′,4′,5′-trifluoro-[1,1′-biphenyl]-4-carbonitrile
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 7.2 Hz, 2H), ppm. ^{13}C NMR δ 152.8, 150.4, 142.5, 141.3, 138.8, 135.2, 132.9, 127.6, 118.4, 112.3, 111.6, 111.4, ppm. MS (EI) m/z 233 (M+, 100%): 233, 213, 206, 182, 156, 111, 75, 63. Melting Point: 104–105 °C.

4.5.5. 2′,3′-difluoro-4-(4-propylcyclohexyl)-1,1′-biphenyl
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.46 (d, J = 6.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.16–7.20 (m, 1H), 7.09–7.13 (m, 2H), 2.48–2.55 (m, 1H), 1.91 (t, J = 16 Hz, 4H), 1.44–1.54 (m, 2H), 1.31–1.39 (m, 3H), 1.20–1.28 (m, 2H), 1.02–1.11 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H), ppm; ^{13}C NMR δ 152.5, 150.1, 148.2, 146.9, 132.3, 131.5, 129.0, 127.3, 125.4, 124.2, 115.8, 44.6, 39.9, 37.2, 34.5, 33.7, 20.2, 14.6, ppm; MS (EI) m/z 314 (M^+, 100%): 314, 271, 229, 216, 203, 149, 121, 91, 81, 55. Melting Point: 76–77 °C.

4.5.6. 2′,3′-difluoro-4-(4-pentylcyclohexyl)-1,1′-biphenyl
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.46–7.48 (m, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.14–7.20 (m, 1H), 7.09–7.13 (m, 2H), 2.48–2.55 (m, 1H), 1.93 (t, J = 12 Hz, 4H), 1.44–1.54 (m, 2H), 1.20–1.35 (m, 9H), 1.02–1.11 (m, 2H), 0.90 (t, J = 8.0 Hz, 3H), ppm; ^{13}C NMR δ 152.5, 150.0, 148.2, 146.9, 132.3, 131.5, 129.0, 127.3, 125.4, 124.1, 115.8, 44.6, 37.6, 34.5, 33.8, 32.4, 26.9, 22.9, 20.2, 14.3, ppm; MS (EI) m/z 342 (M^+, 100%): 342, 314, 271, 229, 216, 203, 175, 151, 123, 87, 53. Melting Point: 52–53 °C.

Acknowledgments

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2011.04.007.

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