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Palladium-catalyzed direct arylation of polyfluoroarene and facile synthesis of liquid crystal compounds

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A convenient approach has been developed to prepare polyfluorobiphenyl by $Pd(OAc)_2/PCy_3$-catalyzed direct arylation of polyfluoroarenes with aromatic halides in the presence of Cs_2CO_3 as base and toluene as solvent. In most cases, the desired arylated products of aromatic bromides were obtained in good to excellent yield at 80°C, and aryl chlorides also gave modest to good yields of arylated products at 110°C. According to this efficient C—C bondforming method, polyfluorobiphenyl liquid crystal compounds were prepared by Pd-catalyzed direct arylation reactions of polyfluoroarenes with long alkyl chain substituted aryl bromides in 62–96% yield. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: palladium; arylation; polyfluoroarenes; C—H activation; liquid crystal compounds

Introduction

Polyfluorobiphenyl derivatives represent an important structural motif frequently found in medicinal chemistry,[1] electron transport devices,[2] organic light-emitting diodes,[3] sensitizers for the photo-splitting of water[4] and liquid crystals.[5] Among the myriad methods available for constructing polyfluorobiphenyl compounds, transition-metal catalyzed cross-coupling reaction of aryl metals reagent with aryl halide is one of the most commonly used approaches,[6] but classical methods have an intrinsic limitation in terms of atom and step economy (Scheme 1).[7] In this context, direct arylation of aryl halide via C—H functionalization of arene, which would avoid the use of a arylmetallic intermediate, would be an attractive alternative to the aforementioned traditional methods.[8] Recently, some significant progress has been made in the transition-metal catalyzed direct C—H activation of polyfluoroarenes with arylhalides.[9–11] For example, Fagnou *et al*. first proposed that $Pd(OAc)_2/P^tBu_2Me\text{-}HBF_4$ or S-Phos catalyzed the direct arylation of polyfluoroarenes with aryl halides.[9] Daugulis *et al*. reported CuI-catalyzed arylation of polyfluoroarene C—H bonds with aryl bromides or aryl iodides.[10] Furthermore, Zhang *et al*. illustrated Pd-catalyzed cross-coupling of polyfluoroarenes with aryl iodides in water.[11] Herein, we developed a new and simple catalysis system that Pd-catalyzed direct arylation of aryl bromides and even aryl chlorides via C—H functionalization of polyfluoroarenes, and which provided a concise and effective method for the synthesis of polyfluorobiphenyl structures of interest in liquid crystalline compounds.

Experimental

Materials and instruments

All the reactions were carried out under N_2 using magnetic stirring unless otherwise noted. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Varian Inova-400 spectrometer in $CDCl_3$, with tetramethylsilane as an internal standard and reported in ppm (δ). Electron ionization (EI) mass spectra were measured on a high-resolution mass spectrometer (Thermo Finnigan Trace GC/MAT95 XP, America). Toluene were dried over Na, distilled and stored under nitrogen. DMF, DMSO and 1,4-dioxane was distilled from calcium hydride and degassed with N_2. Column chromatography was performed with silica gel (300–400 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography (TLC) was carried out with GF254 plates from the same company. All other reagents were of analytical-grade quality purchased commercially and used as received.

Typical procedure for Pd-catalyzed arylation of fluoroarene with various aryl halides

The Schlenk tube (20 ml) equipped with a stir bar was charged with $Pd(OAc)_2$ (0.05 mmol, 10 mol%), PCy_3 (0.1 mmol, 20 mol%), and Cs_2CO_3 (1.2 equiv.). The reaction vessel was evacuated and backfilled with nitrogen three times. Aryl halide (0.5 mmol), fluoroarene (1.0 mmol) and solvent (1.0 ml) were added, and the mixture was stirred at 80 or 110°C under N_2 until the substrate was completely consumed. After cooling to room temperature,

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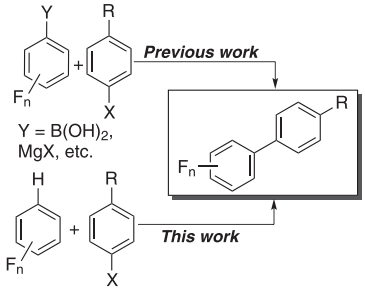


Scheme 1. Strategies toward synthesis of polyfluorobiphenyl derivatives.

the mixture was quenched with water and extracted with EtOAc (3×10 ml). The combined EtOAc extracts were dried with anhydrous Na_2SO_4, filtrated and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with petroleum ether (PE) or PE/EtOAc as the eluent to obtain the desired products. (Characterization data of compounds **3a–3p** can be found in the supporting information).

*2,3,4,5,6-Pentafluoro-4′-(4-propylcyclohexyl)-1,1′-biphenyl (**4a**)*

Yield 88%, 162.0 mg, white solid, m.p. 106–107°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4H, Ar—H), 2.53 (tt, J = 12.3, 3.2 Hz, 1H, H9), 2.02–1.81 (m, 4H, H10 and H10′), 1.54–1.44 and 1.11–1.02 (m, 4H, H11 and H11′), 1.41–1.27 (m, 3H, H12 and H13), 1.27–1.17 (m, 2H, —CH_2C**H$_2$**CH_3), 0.91 (t, J = 7.2 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C8), 144.2 (dm, J = 249.0 Hz, C3 and C3′), 140.1 (dm, J = 256.5 Hz, C1), 137.9 (dm, J = 264.5 Hz, C2 and C2′), 130.0 (C5), 127.2 (C7 and C7′), 123.6 (C6 and C6′), 115.9 (td, J = 17.4, 3.7 Hz, C4), 44.4 (C9), 39.7 (C13), 37.0 (C10 and C10′), 34.2 (C11 and C11′), 33.5 (C12), 20.0 (C14), 14.4 (C15). ^{19}F NMR (376 MHz, $CDCl_3$): δ −143.41 (dd, J = 23.1, 8.2 Hz, 2F, F2 and F2′), −156.23 (t, J = 21.0 Hz, 1F, F1), −162.50 (td, J = 22.9, 8.2 Hz, 2F, F3 and F3′). HRMS calcd for $C_{21}H_{21}F_5$ (M+): 368.1563; found: 368.1560. Anal. Calcd for $C_{21}H_{21}F_5$: C, 68.47; H, 5.75. Found: C, 68.25; H: 5.87.

*2,3,4,5,6-Pentafluoro-4′-(4-pentylcyclohexyl)-1,1′-biphenyl (**4b**)*

Yield 92%, white solid, m.p. 100–101°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 4H, Ar—H), 2.53 (tt, J = 12.4, 3.3 Hz, 1H, H9), 2.01–1.81 (m, 4H, H10 and H10′), 1.53–1.43 and 1.11–1.02 (m, 4H, H11 and H11′), 1.41–1.27 (m, 9H, H12, H13, H14, H15 and H16), 0.90 (t, J = 7.0 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C8), 144.3 (dm, J = 245.8 Hz, C3 and C3′), 140.0 (dm, J = 246.6 Hz, C1), 138.0 (dm, J = 251.5 Hz, C2 and C2′), 130.0 (C5), 127.2 (C7 and C7′), 123.7 (C6 and C6′), 116.0 (td, J = 17.6, 3.7 Hz, C4), 44.5 (C9), 37.4 (C13), 37.3 (C15), 34.2 (C10 and C10′), 33.6 (C11 and C11′), 32.2 (C12), 26.7 (C14), 22.8 (C16), 14.1 (C17). ^{19}F NMR (376 MHz, $CDCl_3$): δ −143.41 (dd, J = 23.1, 8.2 Hz, 2F, F2 and F2′), -156.23 (t, J = 21.0 Hz, 1F, F1), −162.50 (dt, J = 22.9, 8.2 Hz, 2F, F3 and F3′). HRMS calcd for $C_{23}H_{25}F_5$ (M+): 396.1876; found: 396.1879. Anal. Calcd for $C_{23}H_{25}F_5$: C, 69.68; H, 6.36. Found: C, 69.45; H: 6.63.

*2,3,4,5,6-Pentafluoro-4′-(4′-pentyl-[1,1′-bi(cyclohexan)]-4-yl)-1,1′-biphenyl (**4c**)*

Yield 96%, white solid, m.p. 141–142°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4H, Ar—H), 2.51 (tt, J = 11.6, 3.1 Hz, 1H, H9), 1.98–1.93 (m, 2H, H10 and H10′), 1.88–1.86 (m, 2H, H11 and H11′), 1.79–1.73 (m, 4H, H10 and H10′, H14 and H14′), 1.53–1.41 (m, 2H, H12 and H13), 1.31–1.21 (m, 6H, H15 and H15′, H18, H19), 1.20–1.12 (m, 6H, H11 and H11′, H14 and H14′, H15 and H15′), 1.10–0.96 (m, 3H, H16 and H17), 0.90–0.83 (m, 5H, H20 and H21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C8), 144.2 (dm, J = 246.1 Hz, C3 and C3′), 140.2 (dm, J = 251.8 Hz, C1), 137.8 (dm, J = 231.0 Hz, C2 and C2′), 130.0 (C5), 127.2 (C7 and C7′), 123.7 (C6 and C6′), 116.1 (td, J = 17.2, J = 4.2 Hz, C4), 44.6 (C9), 43.5 (C12), 43.0 (C13), 38.0 (C17), 37.5 (C19), 34.5 (C10 and C10′), 33.7 (C14 and C14′), 32.3 (C16), 30.4 (C18), 30.2 (C15 and C15′), 26.7 (C11 and C11′), 22.7 (C20), 14.1(C21). ^{19}F NMR (376 MHz, $CDCl_3$): δ −143.41 (dd, J = 23.1, 8.2 Hz, 2F, F2 and F2′), −156.24 (t, J = 21.0 Hz, 1F, F1), −162.51 (td, J = 22.9, 8.2 Hz, 2F, F3 and F3′). HRMS calcd for $C_{29}H_{35}F_5$ (M+) 478.2651; found: 478.2653. Anal. Calcd for $C_{29}H_{35}F_5$: C, 72.78; H, 7.37. Found: C, 72.54; H: 7.57.

*2,3,5,6-Tetrafluoro-4′-(4-propylcyclohexyl)-1,1′-biphenyl (**4d**)*

Yield 80%, white solid, m.p. 85–87°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.32 (m, 4H, Ar—H), 7.08–7.00 (m, 1H, Ar_F—H), 2.53 (tt, J = 12.3, 3.2 Hz, 1H, H9), 2.02–1.81 (m, 4H, H10 and H10′), 1.54–1.44 and 1.11–1.02 (m, 4H, H11 and H11′), 1.43–1.27 (m, 3H, H12 and H13), 1.27– 1.17 (m, 2H, —CH_2*CH_2*CH_3), 0.91 (t, J = 7.2 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (C8), 146.2 (dm, J = 258.3 Hz, C3 and C3′), 143.9 (dm, J = 255.8 Hz, C2 and C2′), 130.0 (t, J = 2.0 Hz, C5), 127.1 (C7 and C7′), 124.8 (t, J = 2.4 Hz, C6 and C6′), 121.6(C4), 104.5 (t, J = 22.7 Hz, C1), 44.5 (C9), 39.7 (C13), 37.0 (C10 and C10′), 34.2 (C11 and C11′), 33.5 (C12), 20.0 (C14), 14.1(C15). ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.42 (ddd, J = 22.5, 12.7, 9.8 Hz, 2F, F2 and F2′), −144.1 (ddd, J = 21.4, 12.8, 7.5 Hz, 2F, F3 and F3′). HRMS calcd for $C_{21}H_{22}F_4$ (M+) 350.1658; found: 350.1657. Anal. Calcd for $C_{21}H_{22}F_4$: C, 71.98; H, 6.33. Found: C, 71.71; H: 6.61.

*2,3,5,6-Tetrafluoro-4′-(4-pentylcyclohexyl)-1,1′-biphenyl (**4e**)*

Yield 78%, white solid, m.p. 89–91°C. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.36 (m, 4H, Ar—H), 7.08–7.00 (m, 1H, Ar_F—H), 2.53 (tt, J = 12.4, 3.3 Hz, 1H, H9), 1.96–1.87 (m, 4H, H10 and H10′), 1.54–1.44 and 1.12–1.02 (m, 4H, H11 and H11′), 1.35–1.22 (m, 9H, H12, H13, H14, H15 and H16), 0.90 (t, J = 7.0 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (C8), 146.1 (dm, J = 246.7 Hz, C3 and C3′), 143.9 (dm, J = 247.6 Hz, C2 and C2′), 130.0 (t, J = 2.0 Hz, C5), 127.1 (C7 and C7′), 124.8 (t, J = 2.0 Hz, C6 and C6′), 121.6 (C4), 104.5 (t, J = 22.7 Hz, C1), 44.5 (C9), 37.4 (C13), 37.3 (C10 and C10′), 34.2 (C11 and C11′), 33.6 (C12), 32.2 (C14), 26.7 (C15), 22.7 (C16), 14.1 (C17). ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.42 (ddd, J = 22.5, 12.7, 9.8 Hz, 2F, F2 and F2′), −144.1 (ddd, J = 21.1, 12.8, 7.5 Hz, 2F, F3 and F3′). HRMS calcd for $C_{23}H_{26}F_4$ (M+) 378.1968; found: 378.1965. Anal. Calcd for $C_{23}H_{26}F_4$: C, 72.99; H, 6.92. Found: C, 72.70; H: 7.21.

*2,3,5,6-Tetrafluoro-4′-(4′-pentyl-[1,1′-bi(cyclohexan)]-4-yl)-1,1′-biphenyl (**4f**)*

Yield 82%, white solid, m.p. 173–175°C. ^{1}H NMR (400 MHz, $CDCl_3$): 1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.31 (m, 4H, Ar—H), 7.08–7.00 (m, 1H, Ar_F—H), 2.51 (tt, J = 11.6, 3.1 Hz, 1H, H9), 1.97–1.93 (m, 2H, H10 and H10′), 1.88–1.84 (m, 2H, H11 and H11′), 1.78–1.73 (m, 4H, H10 and H10′, H14 and H14′), 1.54–1.43 (m, 2H, H12 and H13), 1.33–1.20 (m, 6H, H15 and H15′, H18, H19), 1.20–1.13 (m, 6H, H11 and H11′, H14 and H14′, H15 and H15′), 1.13–0.97 (m, 3H, H16 and H17), 0.92–0.85 (m, 5H, H20 and —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (C8), 146.1 (dm, J = 246.3 Hz, C3 and C3′), 143.9 (dm, J = 247.6 Hz, C2 and C2′), 130.0 (C5), 127.1 (C7 and C7′), 124.8 (C6 and C6′), 121.6 (t, J = 16.5 Hz, C4), 104.5 (t, J = 22.5 Hz, C1), 44.5 (C9), 43.4 (C12), 43.0 (C13), 38.0 (C17),

37.5 (C19), 34.5 (C10 and C10′), 33.7 (C14 and C14′), 32.3 (C16), 30.3 (C18), 30.2 (C15 and C15′), 26.7 (C11 and C11′), 22.8 (C20), 14.2 (C21). ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.4 (ddd, J = 22.5, 12.7, 9.8 Hz, 2F, F2 and F2′), −144.1 (ddd, J = 21.1, 12.8, 7.5 Hz, 2F, F3 and F3′). HRMS calcd for $C_{29}H_{36}F_4$ (M+) 460.2751; found: 460.2748. Anal. Calcd for $C_{29}H_{36}F_4$: C, 75.62; H, 7.88. Found: C, 75.33; H: 8.08.

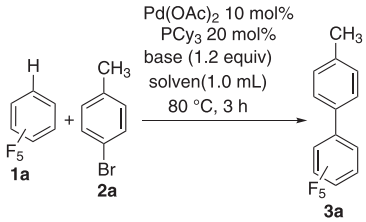
*2,3,4,6-Tetrafluoro-4′-(4-propylcyclohexyl)-1,1′-biphenyl (**4g**)*

Yield 71%, white solid, m.p. 71–72°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.26 (m, 4H, Ar—H), 6.89–6.82 (m, 1H, Ar_F—H), 2.52 (tt, J = 12.2, 3.3 Hz, 1H, H9), 1.96–1.86 (m, 4H, H10 and H10′), 1.53–1.44 and 1.12–1.01 (m, 4H, H11 and H11′), 1.41–1.27 (m, 3H, H12 and H13), 1.25–1.19 (m, 2H, —$CH_2CH_2CH_3$), 0.91 (t, J = 7.2 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4 (dm, J = 245.0 Hz, C3′), 149.7 (dm, J = 249.3 Hz, C1), 149.1 (dm, J = 248.8 Hz, C3), 148.7 (C8), 137.7 (dm, J = 246.9 Hz, C2), 130.0 (C5), 127.0 (C7 and C7′), 124.8 (C6 and C6′), 116.3–115.9 (m, C4), 101.1–100.6 (m, C2′), 44.5 (C9), 39.7 (C13), 37.0 (C10 and C10′), 34.2 (C11 and C11′), 33.5 (C12), 20.1 (C14), 14.4 (C15). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.22 (t, J = 10.1 Hz, 1F, F2), −134.01 (ddd, J = 21.4, 9.9, 5.1 Hz, 1F, F3), −135.59 (d, J = 21.6 Hz, 1F, F1), −165.00 (tdd, J = 21.6, 10.9, 6.1 Hz, 1F, F4). HRMS calcd for $C_{21}H_{22}F_4$ (M+) 350.1658; found: 350.1654. Anal. Calcd for $C_{21}H_{22}F_4$: C, 71.98; H, 6.33. Found: C, 71.73; H: 6.57.

*2,3,4,6-Tetrafluoro-4′-(4-pentylcyclohexyl)-1,1′-biphenyl (**4h**)*

Yield 75%, white solid, m.p. 54–56°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 4H, Ar—H), 6.89–6.81 (m, 1H, Ar_F—H), 2.52 (tt, J = 12.4, 3.3 Hz, 1H, H9), 1.96–1.84 (m, 4H, H10 and H10′), 1.53–1.44 and 1.11–1.02 (m, 4H, H11 and H11′), 1.39–1.20 (m, 9H, H12, H13, H14, H15 and H16), 0.90 (t, J = 7.0 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4 (dm, J = 244.9 Hz, C3′), 149.8 (dm, J = 249.0 Hz, C1), 149.1 (dm, J = 248.3 Hz, C3), 148.7 (C8), 137.7 (dm, J = 246.6 Hz, C2), 130.0 (C5), 127.0 (C7 and C7′), 124.8 (C6 and C6′), 116.3–115.9

Table 1. Optimization of reaction conditions[a]



Entry	[Pd] source	Ligand	Solvent	Base	Yield[b] (%)
1	$Pd(OAc)_2$	—	Toluene	Cs_2CO_3	Trace
2	$Pd(OAc)_2$	PPh_3	Toluene	Cs_2CO_3	95 (**3a**/**3a′** = 5/3)
3[c]	$Pd(OAc)_2$	PCy_3	Toluene	Cs_2CO_3	27
4	$Pd(OAc)_2$	PCy_3	Toluene	Cs_2CO_3	91
5	$PdCl_2(CH_3CN)_2$	PCy_3	Toluene	Cs_2CO_3	Trace
6	$Pd(OAc)_2$	PCy_3	DMF	Cs_2CO_3	Trace
7	$Pd(OAc)_2$	PCy_3	DMSO	Cs_2CO_3	Trace
8	$Pd(OAc)_2$	PCy_3	1,4-Dioxane	Cs_2CO_3	68
9	$Pd(OAc)_2$	PCy_3	Toluene	K_2CO_3	Trace
10	$Pd(OAc)_2$	PCy_3	Toluene	K_3PO_4	42
11	$Pd(OAc)_2$	PCy_3	Toluene	Na_2CO_3	Trace

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), [Pd] source 10 mol%, ligand 20 mol%.
[b]Isolated yields.
[c]5 mol% $Pd(OAc)_2$ and 10 mol% PCy_3 were used.

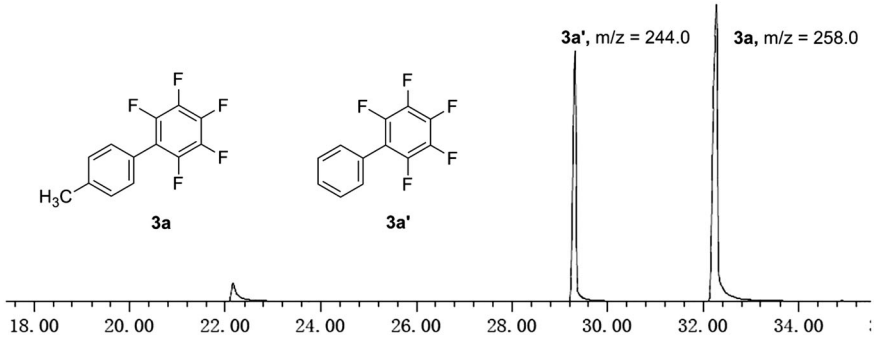


Figure 1. Partial GC mass spectrum of the reaction mixture catalyzed by $Pd(OAc)_2/PPh_3$.

(m, C4), 101.1–100.6 (m, C2′), 44.5 (C9), 44.1 (C13), 37.4 (C15), 34.3 (C10 and C10′), 33.5 (C11 and C11′), 32.2 (C12), 26.7 (C14), 22.7 (C16), 14.1 (C17). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.21 (t, J = 10.1 Hz, 1F, F2), −134.01 (ddd, J = 21.4, 9.9, 5.0 Hz, 1F, F3), −135.57 (d, J = 21.1 Hz, 1F, F1), −165.00 (tdd, J = 21.6, 10.9, 6.1 Hz, 1F, F4). HRMS calcd for $C_{23}H_{26}F_4$ (M+) 378.1968; found: 378.1965. Anal. Calcd for $C_{23}H_{26}F_4$: C, 72.99; H, 6.92. Found: C, 72.75; H: 7.15.

*2,3,4,6-Tetrafluoro-4′-(4′-pentyl-[1,1′-bi(cyclohexan)]-4-yl)-1,1′-biphenyl (**4i**)*

Yield 62%, white solid, m.p. 148–150°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (m, 4H, Ar—H), 6.90–6.80 (m, 1H, Ar_F—H), 2.50 (tt, J = 11.6, 3.1 Hz, 1H, H9), 1.98–1.93 (m, 2H, H10 and H10′), 1.89–1.84 (m, 2H, H11 and H11′), 1.79–1.73 (m, 4H, H10 and H10′, H14 and H14′), 1.55–1.42 (m, 2H, H12 and H13), 1.35–1.20 (m, 6H, H15 and H15′, H18, H19), 1.21–1.13 (m, 6H, H11 and H11′, H14 and H14′, H15 and H15′), 1.12–0.97 (m, 3H, H16 and H17), 0.93–0.85 (m, 5H, H20 and H21).^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4 (dm, J = 246.7 Hz, C3′), 149.6 (dm, J = 244.4 Hz, C1), 149.0 (dm, J = 243.1 Hz, C3), 148.7 (C8), 137.7 (dm, J = 245.8 Hz, C2), 130.0 (C5), 127.0 (C7 and C7′), 124.8 (C6 and C6′), 116.3–115.9 (m, C4), 101.1–100.6 (m, C2′), 44.5 (C9), 43.5 (C12), 42.9 (C13), 38.0 (C17), 37.5 (C19), 34.5 (C10 and C10′), 33.7 (C14 and C14′), 32.3 (C16), 30.3 (C18), 30.1 (C15 and C15′), 26.7 (C11 and C11′), 22.7 (C20), 14.1 (C21). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.21 (t, J = 10.1 Hz, 1F, F2), −134.01 (ddd, J = 21.5, 9.9, 5.0 Hz, 1F, F3), −135.58 (d, J = 21.6 Hz, 1F, F1), −165.00 (tdd, J = 21.6, 10.9, 6.1 Hz, 1F, F4). HRMS calcd for $C_{29}H_{36}F_4$ (M+) 460.2754; found: 460.2748. Anal. Calcd for $C_{29}H_{36}F_4$: C, 75.62; H, 7.88. Found: C, 75.45; H: 8.11.

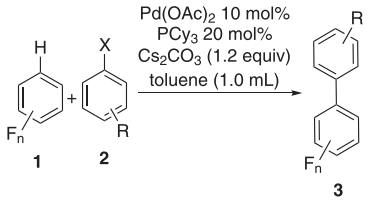
*2,3,5,6-Tetrafluoro-4-methoxy-4′-(4-propylcyclohexyl)-1,1′-biphenyl (**4j**)*

Yield 94%, white solid, m.p. 109–111°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 4H, Ar—H), 4.11 (t, J = 1.3 Hz, 3H, —OCH_3), 2.52 (tt, J = 12.3, 3.3 Hz, 1H, H9), 1.96–1.87 (m, 4H, H10 and H10′), 1.53–1.43 and 1.11–1.02 (m, 4H, H11 and H11′), 1.39–1.27 (m, 3H, H12 and H13), 1.25–1.19 (m, 2H, —$CH_2CH_2CH_3$), 0.91 (t, J = 7.2 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (C8), 144.3 (dm, J = 244.3 Hz, C3 and C3′), 141.2 (dm, J = 245.4 Hz, C2 and C2′), 137.3–137.0 (m, C1), 130.0 (C5), 127.1 (C7 and C7′), 124.6 (C6 and C6′), 114.3 (t, J = 17.0 Hz, C4), 62.2 (t, J = 3.6 Hz, C16), 44.5 (C9), 39.7 (C13), 37.0 (C10 and C10′), 34.2 (C11 and C11′), 33.5 (C12), 20.0 (C14), 14.4 (C15). ^{19}F NMR (376 MHz, $CDCl_3$): δ −144.5 (dd, J = 21.8, 8.6 Hz, 2F, F1), −157.7 (dd, J = 22.2, 8.7 Hz, 2F, F2). HRMS calcd for $C_{22}H_{24}OF_4$ (M+) 380.1756; found: 380.1758. Anal. Calcd for $C_{22}H_{24}F_4O$: C, 69.46; H, 6.36. Found: C, 69.17; H: 6.57.

*2,3,5,6-Tetrafluoro-4-methoxy-4′-(4-pentylcyclohexyl)-1,1′-biphenyl (**4k**)*

Yield 88%, white solid, m.p. 107–109°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 4H, Ar—H), 4.11 (t, J = 1.3 Hz, 3H, —OCH_3), 2.52

Table 2. $Pd(OAc)_2$-catalyzed arylation of polyfluoroarenes with aryl halides[a]



Entry	1	2/R, X	Product	T (°C)	t (h)	Yield[b] (%)
1	Pentafluorobenzene (**1a**)	4-OMe, Br (**2b**)	**3b**	80	3	90
2	**1a**	H, Br (**2c**)	**3c**	80	3	70
3	**1a**	2-Me, Br (**2d**)	**3d**	80	3	Trace
4	**1a**	4-F, Br (**2e**)	**3e**	80	10	90
5	**1a**	4-NO_2, Br (**2f**)	**3f**	80	12	85
6	**1a**	4-COMe, Br (**2g**)	**3g**	80	12	86
7	**1a**	4-COOMe, Br (**2h**)	**3h**	80	24	96
8	**1a**	4-ethenyl, Br (**2i**)	**3i**	80	10	72
9	**1a**	4-Ph-C_6H_4, Br (**2j**)	**3j**	80	10	85
10	**1a**	2-Bromonaphthalene (**2k**)	**3k**	80	8	98
11	**1a**	3-Bromopyridine (**2l**)	**3l**	80	24	55
12	1,2,4,5-Tetrafluoro-3-methoxybenzene (**1c**)	**2a**	**3m**	80	8	77
13[c]	1,2,4,5-Tetrafluorobenzene (**1b**)	**2b**	**3n**	80	4	63
14[c]	1,2,3,5-Tetrafluorobenzene (**1d**)	**2b**	**3o**	80	12	61
15	**1a**	4-Me, Cl (**2m**)	**3a**	110	4	73
16	**1a**	4-OMe, Cl (**2n**)	**3b**	110	4	84
17	**1a**	H, Cl (**2o**)	**3c**	110	8	60
18	**1a**	4-COMe, Cl (**2p**)	**3h**	110	12	86
19	**1b**	4-NO_2, Cl (**2q**)	**3p**	110	24	52
20	**1c**	**2m**	**3m**	110	5	81

[a]Reaction conditions: 1.0 mmol polyfluoroarenes, 0.5 mmol arylhalides.
[b]Isolated yields.
[c]Using 4.0 equiv. of polyfluoroarene.

(tt, J = 12.3, 3.2 Hz, 1H, H9), 1.96–1.87 (m, 4H, H10 and H10′), 1.53–1.43 and 1.12–1.02 (m, 4H, H11 and H11′), 1.35–1.21 (m, 9H, H12, H13, H14, H15 and H16), 0.90 (t, J = 7.0 Hz, 3H, —CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (C8), 144.3 (dm, J = 244.3 Hz, C3 and C3′), 141.2 (dm, J = 245.4 Hz, C2 and C2′), 137.3–137.0 (m, C1), 130.0 (C5), 127.1 (C7 and C7′), 124.6 (C6 and C6′), 114.3 (t, J = 17.0 Hz, C4), 62.2 (t, J = 3.6 Hz, C18), 44.5 (C9), 37.4 (C13), 37.3 (C15), 34.2 (C10 and C10′), 33.6 (C11 and C11′), 32.2 (C12), 26.7 (C14), 22.7 (C16), 14.1 (C17). ^{19}F NMR (376 MHz, $CDCl_3$): δ −144.5 (dd, J = 22.2, 8.6 Hz, 2F, F1), −157.7 (dd, J = 22.2, 8.6 Hz, 2F, F2). HRMS calcd for $C_{24}H_{28}OF_4$ (M+) 408.2075; found: 408.2071. Anal. Calcd for $C_{24}H_{28}F_4O$: C, 70.57; H, 6.91. Found: C, 70.42; H: 7.12.

*2,3,5,6-Tetrafluoro-4-methoxy-4′-(4′-pentyl-[1,1′-bi(cyclohexan)]-4-yl)-1,1′-biphenyl (**4l**)*

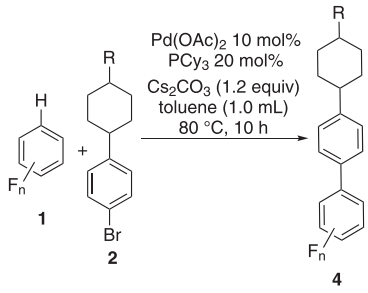
Yield 93%, white solid, m.p. 170–172°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 4H, Ar—H), 4.11 (t, J = 1.2 Hz, 3H, —OCH_3), 2.50 (tt, J = 11.9, 3.4 Hz, 1H, H9), 1.98–1.94 (m, 2H, H10 and H10′), 1.90–1.84 (m, 2H, H11 and H11′), 1.78–1.74 (m, 4H, H10 and H10′, H14 and H14′), 1.52–1.43 (m, 2H, H12 and H13), 1.32–1.20 (m, 6H, H15 and H15′, H18, H19), 1.21–1.13 (m, 6H, H11 and H11′, H14 and H14′, H15 and H15′), 1.12–0.97 (m, 3H, H16 and H17), 0.90–0.86 (m, 5H, H20 and H21).^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (C8), 144.3 (dm, J = 244.3 Hz, C3 and C3′), 141.2 (dm, J = 245.2 Hz, C2 and C2′), 137.2–137.0 (m, C1), 130.0 (C5), 127.1 (C7 and C7′), 124.5 (C6 and C6′), 114.3 (t, J = 17.2 Hz, C4), 62.2 (t, J = 3.6 Hz, C22), 44.5 (C9), 43.4 (C12), 42.9 (C13), 37.9 (C17), 37.5 (C19), 34.5 (C10 and C10′), 33.7 (C14 and C14′), 32.3 (C16), 30.3 (C18), 30.1 (C15 and C15′), 26.7 (C11 and C11′), 22.7 (C20), 14.1 (C21). ^{19}F NMR (376 MHz, $CDCl_3$): δ −144.4 (dd, J = 22.2, 9.0 Hz, 2F, F1), −157.5 (dd, J = 22.2, 8.6 Hz, 2F, F2). HRMS calcd for $C_{30}H_{38}OF_4$ (M+) 490.2855; found: 490.2853. Anal. Calcd for $C_{30}H_{38}F_4O$: C, 73.44; H, 7.81. Found: C, 73.30; H: 7.97.

Results and Discussion

Initially, the coupling reaction of pentafluorobenzene (**1a**), and 4-bromotoluene (**2a**) was selected as a model reaction to identify an effective catalytic system and optimize the reaction conditions (Table 1). Only $Pd(OAc)_2$ showed no catalytic activity toward the coupling reaction of **1a** and **2a** in the presence of Cs_2CO_3 as base in toluene at 80°C (Table 1, entry 1). When $Pd(OAc)_2$ and PPh_3 ligand were used, a moderate yield of coupling product **3a** with an undesirable 40% yield of byproduct **3a′** was obtained and confirmed by GC-MS analysis of the crude reaction mixture (Table 1, entry 2). The byproduct might be tentatively ascribed to P—C bond degradation of the ligand PPh_3 at high temperature (Fig. 1).[12] However, we were delighted to find that $Pd(OAc)_2/PCy_3$ as a highly active catalyst for this reaction selectively afforded a 91% yield of the only product **3a** (Table 1, entry 4). Compared with $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$ as palladium resource was inefficient in the arylated reaction (Table 1, entry 5). A significantly low yield was obtained with 5 mol% $Pd(OAc)_2$ (Table 1, entry 3). In addition, we screened several reaction conditions such as bases and solvents (Table 1, entries 6–11). Also, the $Pd(OAc)_2/PCy_3/Cs_2CO_3$ system in toluene at 80°C proved to be optimal for this reaction.

Under the optimal reaction conditions, we investigated the scope of Pd-catalyzed arylation of perfluorobenzene with various aryl bromides. As summarized in Table 2, all arylation reactions were very clean, and the corresponding polyfluoroarenes were

Table 3. Synthesis of fluorinated biphenyl compounds by Pd-catalyzed direct arylation of polyfluoroarenes[a]



Entry	Fluoroarene	R	Product	Yield[b] (%)
1	**1a**	4-(4-Propylcyclohexyl) **(2r)**	**4a**	88
2	**1a**	4-(4-Pentylcyclohexyl) **(2s)**	**4b**	92
3	**1a**	4-[4′-Pentyl-1,1′-bi(cyclohexyl)] **(2t)**	**4c**	96
4	**1b**	4-(4-Propylcyclohexyl) **(2r)**	**4d**	80
5	**1b**	4-(4-Pentylcyclohexyl) **(2s)**	**4e**	78
6	**1b**	4-[4′-Pentyl-1,1′-bi(cyclohexyl)] **(2t)**	**4f**	82
7	**1c**	4-(4-Propylcyclohexyl) **(2r)**	**4j**	94
8	**1c**	4-(4-Pentylcyclohexyl) **(2s)**	**4k**	88
9	**1c**	4-[4′-Pentyl-1,1′-bi(cyclohexyl)] **(2t)**	**4l**	93
10	**1d**	4-(4-Propylcyclohexyl) **(2r)**	**4g**	71
11	**1d**	4-(4-Pentylcyclohexyl) **(2s)**	**4h**	75
12	**1d**	4-[4′-Pentyl-1,1′-bi(cyclohexyl)] **(2t)**	**4i**	62

[a]Reaction conditions: 1.0 mmol polyfluoroarenes, 0.5 mmol arylbromides.
[b]Isolated yields.

obtained in moderate to good yield. The electronic effects of the substituents on the aromatic ring did not significantly affect the reaction (Table 2, entries 1, 2 and 4–8). We found that the catalyst system tolerated several reactive functional groups, such as —$COCH_3$, —COOMe, and —$CH=CH_2$. However, we failed to perform the arylation with 1-bromo-2-methylbenzene and pentafluorobenzene (Table 2, entry 3) for steric hindrance in the substrate. When pentafluorobenzene reacted with 4-bromobiphenyl, 2-bromonaphthalene and 3-bromopyridine, respectively, the corresponding arylated products were obtained in moderate to excellent yield (Table 2, entries 9–11). Tetrafluorobenzenes such as 1,2,4,5-tetrafluoro-3-methoxybenzene could also be arylated with 4-bromotoluene in satisfactory yield (Table 2, entry 12), and 1,2,4,5-tetrafluorobenzene and 1,2,3,5-tetrafluorobenzene also reacted selectively with 1-bromo-4-methoxybenzene to give the arylated products in 63% and 61% yield, respectively (Table 2, entries 13 and 14). Encouraged by this result, we investigated the arylation of perfluorobenzene and aryl chlorides. Initially, the attempt to obtain a satisfactory yield by reaction of pentafluorobenzene with chlorobenzene in toluene at 80°C failed, but we found that the reaction could be carried out smoothly at 110°C and provide 60% yield (Table 2, entry 17). The results showed that high reaction temperature was beneficial in improving the arylation of perfluorobenzene and aryl chlorides. The coupling reactions between aryl chlorides with an electron-withdrawing group, such as 4-$COCH_3$, and 4-NO_2 and pentafluorobenzene produced biaryls with good yields (76% and 86%, respectively, Table 2, entries 18 and 19). The electron-rich aryl chlorides reaction with perfluorobenzene, such as 1-chloro-4-methylbenzene, and 1-chloro-4-methoxybenzene also gave good yields (73%, 84% and 81%, respectively, Table 2, entries 15, 16 and 20) under the same conditions.

In addition, the liquid crystalline materials containing fluoro-substituted phenyls are the most prominent for application in thin-film transistor liquid crystal displays (TFT-LCDS). The long and lath-like molecular structure of most fluorinated liquid crystalline compounds required in TFT-LCDS makes the formation of C_{Aryl}—C_{Aryl} bonds very important in the synthesis reaction. In general, most fluorinated liquid crystalline compounds can be prepared through the Suzuki–Miyaura coupling reaction of arylboronic acid with aryl halide.[13] Our interest was focused on the concise preparation of polyfluorobiphenyl compounds with Pd-catalyzed direct arylation of polyfluoroarenes with aryl bromides. As expected, liquid crystal products **4a–4l** could be obtained through the treatment of aryl bromides with various polyfluoroarenes in the presence of $Pd(OAc)_2/PCy_3$ and Cs_2CO_3 in toluene at 80°C for 10 h and the yields of polyfluorobiphenyl compounds were 62–96% (Table 3). This procedure is a simple and efficient method for the preparation of polyfluorobiphenyl liquid crystal compounds at the laboratory scale.

Conclusions

In summary, we have described a simple and effective $Pd(OAc)_2/PCy_3$ catalyst system for the direct arylation of polyfluoroarenes with aryl bromides or even aryl chlorides in moderate to excellent yield under mild conditions. The simplicity of the reaction procedure coupled with the broad range of substrates renders this method particularly attractive for the efficient preparation of fluorinated liquid crystal compounds.

Acknowledgments

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