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Efficient synthesis of fluorinated biphenyl derivatives via Pd-catalyzed Suzuki coupling reactions in aqueous solvents at room temperature

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Abstract

A variety of fluorinated biphenyl derivatives were obtained in good yields in aqueous solvents at room temperature by Suzuki coupling reaction of aryl bromides and aryl boronic acid in the presence of high activity catalyst—some air-stable hemilabile P–O coordinated cyclopalladated complexes. The structures of above catalysts were characterized by element analyses, IR, ^{1}H NMR, ^{13}C NMR and ^{31}P NMR.

Keywords: Cyclopalladated catalyst; Suzuki coupling reaction; Fluorinated biphenyl derivatives

1. Introduction

Fluorinated biphenyl derivatives are fundamental building blocks in fluorinated liquid crystals. The fluoro-substitution of benzene rings in mesomorphic molecules may lead to some changes in the melting point, viscosity, birefringence, dielectric anisotropy and other physical properties. The liquid crystalline materials containing monofluoro-, difluoro- or trifluoro-substituted phenyls [1–3] are the most prominent for application in thin-film transistor liquid crystal displays (TFT-LCD$_S$). The long, lath-like molecular structure of most fluorinated liquid crystalline compounds demanded by thin-film transistor liquid crystal displays makes cross-coupling reactions very important in synthesis. Suzuki cross-coupling reaction is one of the most efficient methods for the construction of C_{aryl}–C_{aryl} bonds [4–6] and should be a powerful method for the synthesis of such compounds. The most frequently used catalyst for the Suzuki reaction is $Pd(PPh_3)_4$, but often a number of by-products are formed in the reaction and usually require elevated reaction temperatures (usually 50–100 °C) to function efficiently [7]. There has recently been considerable interest in the synthesis of new, high activity, air-stable palladium-based catalyst that can be used in room temperature and in aqueous solvents in the Suzuki reaction since such catalysts have the potential to be used in industrial systems [8]. Therefore the development of more efficient catalysts, which can easily be prepared and modified on a larger scale, is still an important topic in this area. In order to efficiently synthesize some fluorinated liquid crystals in industry goal, we have developed a new, air-stable and high active P–O coordinated palladium-catalysts. These complexes are ideal catalysts for the coupling of deactivated aryl bromides as they are comparatively inexpensive, very easily synthesized and can be used to give conversions at low concentrations. While the reactions of fluorinated liquid crystal materials proceed with these catalysts at room temperature in aqueous solvents, the best results were obtained. In this paper, we wish to report a general and efficient method for the synthesis of fluorinated biphenyl derivatives via Suzuki coupling reactions catalyzed by air-stable hemilabile P–O coordinated cyclopalladated complexes in aqueous solvents at room temperature.

2. Results and discussion

2.1. Structure of complexes 1–3

The reaction of sodium diphenyl phosphine carboxylate with Na_2PdCl_4 as mole ratio 2:1 gives the complexes **1–3** in almost quantitative yield (>98%). (Scheme 1).

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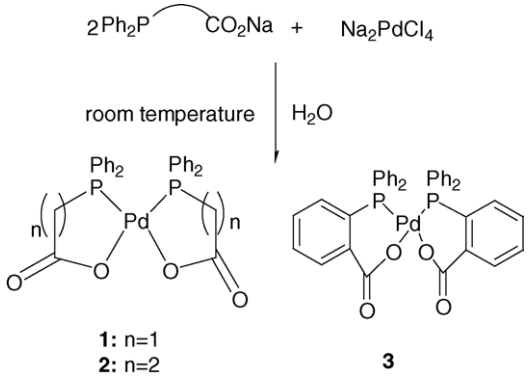


Scheme 1. Synthesis of Pd(II) chelate complexes **1**–**3**.

Single crystal crystallographic analysis of complex **1** revealed the expected Pd(II) square planar geometry with P, O chelation of the diphenyl phosphine acetate ligands. The unit cell of complex **1** is built up of mononuclear $[(Ph_2PCH_2COO)_2Pd]$ units and dichloromethane molecules in a 1:1 ratio. The molecular structure of the complex **1** is shown in Fig. 1. Fig. 2 shows a perspective view of the crystal packing in the unit cell. Selected bond distances and angles of the complex **1** with their estimated standard deviations are listed in Table 1. In the complex **1**, the Pd atom is chelated by two diphenyl phosphine acetate ligands in a *cis* arrangement. The Pd(II) ion has an square planar coordination geometry. The two diphenyl phosphine acetate ligands are each bonded to palladium in bidentate mode, forming five-membered chelated rings. The Pd–O bond distances of 2.076(3) and 2.082(3) Å are slightly longer than those found in other O-coordinated Pd(11) complexes [9–12]. The Pd–P bond distances of 2.214(1) and 2.216(1) Å are in accordance with the values usually encountered in related compounds [13–15].

There are some potential intermolecular interactions (C–H···Y hydrogen bonds, Y=O, N) in the crystal lattice [16,17]. O_2 atom forms potential weak C–H···O interaction with the C_{16} atom, with the donor and the acceptor distance of $C_{16}\cdots O_2 = 3.2694$ Å, C_{16}–$H_{16}A\cdots O_2 = 144.48^\circ$ (symmetry code; $1-x, 1-y, -z$). The O_1 atom also forms weak C–H···O interaction with the C_{27} atom in phenyl ring and C_{29} atom in dichloromethane group. The distances between the donor and the acceptor are $C_{27}\cdots O_1 = 3.2415$ Å, C_{27}–$H_{27}A\cdots O_1 = 126.28^\circ$ (symmetry code $2-x, -1/2+y, 1/2-z$), and $C_{29}\cdots O_1 = 3.1852$ Å, C_{29}–$H_{29}A\cdots O_1 = 164.92^\circ$ (symmetry code $1-x, -1/2+y, 1/2-z$), respectively. In the solid state, all above extensive hydrogen bonds connecting $[(Ph_2PCH_2COO)_2Pd]$ and dichloromethane solvent molecules together form network structure to stabilize the crystal structure.

The element analysis, IR, ^{1}H NMR and ^{31}P NMR of complexes **1**–**3** are also examined. These experiment data are in agreement with the crystal structural.

2.2. Efficiency and advantages of catalysts

Complexes **1**–**3** are highly active catalyst for the synthesis of fluorinated biphenyl derivatives via Suzuki coupling reactions in aqueous solvents at room temperature (Table 2). For example, While we have applied traditional catalyst $Pd(PPh_3)_4$ to synthesize 3,4-difluoro-4′-(4′-pentyl-bicyclohexyl-4-yl)-biphenyl by Suzuki cross-coupling of 3,4-difluorophenyl-boronic acid with 4-(4′-pentyl-bicyclohexyl-4-yl)-bromobenzene upon $Pd(PPh_3)_4$ catalysis at any loading at room temperature, we cannot get the goal production. We cloud get 3,4-difluoro-4′-(4′-pentyl-bicyclohexyl-4-yl)-biphenyl only in the presence of 1.0 mol% catalyst loading of $Pd(PPh_3)_4$ and obtained 70–80% yield based on 4-(4′-pentyl-bicyclohexyl-4-yl)-iodobenzene after 6 h at refluxing temperature. Using complexes **1**–**3** as catalysts, we can get compound 3,4-difluoro-4′-(4′-pentyl-bicyclohexyl-4-yl)-biphenyl in nearly quantitative yield based on 4-(4′-pentyl-bicyclohexyl-4-yl)-bromobenzene even at catalyst loadings as low as 0.01 mol% at room temperature. When we change palladacycle structure from complex **1** to **3**, no discernible influence was observed. No inconspicuousness difference was observed in yield and in the reaction time, while the effect of varying the fluorinated aryl boronic acids in the Suzuki cross-coupling reactions was investigated (entry 1–5, Table 2). Complexes **1**–**3** are all

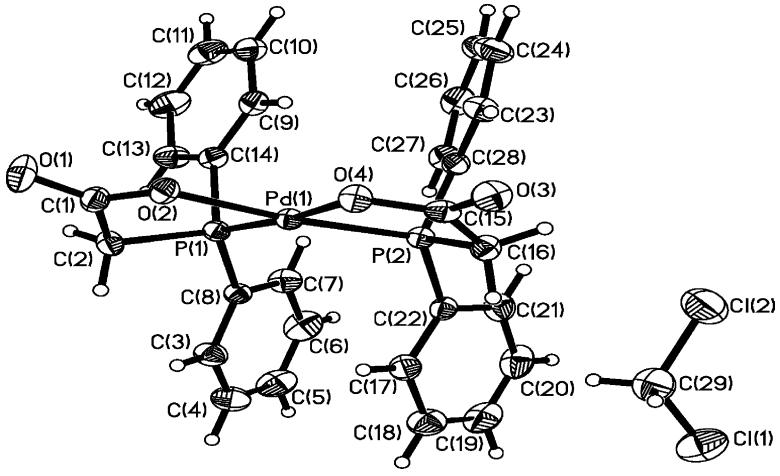


Fig. 1. Molecular structure of $[(Ph_2PCH_2COO)_2Pd]\cdot CH_2Cl_2$ with the atomic numbering scheme.

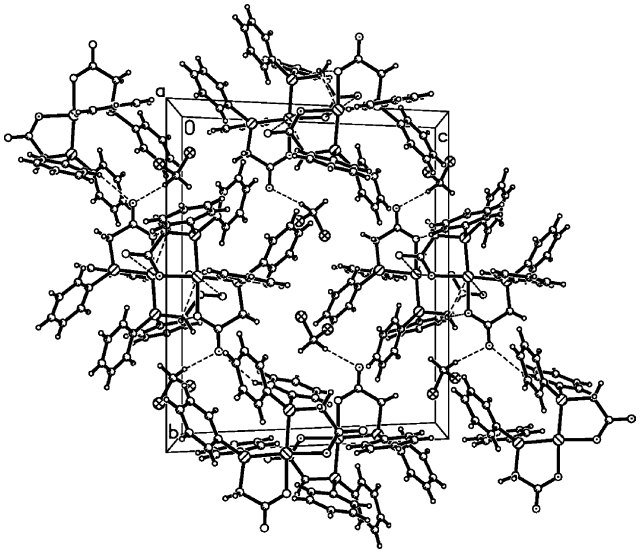


Fig. 2. A view of the crystal packing down the *a*-axis for the complex **1**.

Table 1
Selected bond lengths (Å) and angles (°) of the complex **1**

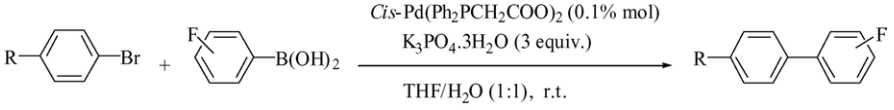
Pd(1)–O(4)	2.076(3)	P(1)–C(14)	1.808(4)
Pd(1)–O(2)	2.082(3)	P(1)–C(2)	1.814(4)
Pd(1)–P(1)	2.2141(14)	P(1)–C(8)	1.815(4)
Pd(1)–P(2)	2.2161(11)	P(2)–C(28)	1.813(4)
O(4)–Pd(1)–O(2)	92.18(10)	O(2)–Pd(1)–P(2)	174.11(8)
O(4)–Pd(1)–P(1)	174.15(8)	P(1)–Pd(1)–P(2)	100.61(4)
O(2)–Pd(1)–P(1)	82.74(8)	C(15)–O(4)–Pd(1)	121.9(2)
O(4)–Pd(1)–P(2)	84.20(8)	C(16)–P(2)–Pd(1)	99.72(13)

effective towards both electron-rich and electron-deficient aryl bromides under mild condition (entry 6–8). Comparing to $Pd(PPh_3)_4$ catalysis, complexes **1–3** all show remarkable stability to air and moisture—in solution they show no sign of decomposition after 3 months, whilst solid samples can be kept in air for at least 1 year. No decomposition is observed when complexes **1–3** are heated at 140 °C in air, demonstrating that the catalysts also show good thermal stability. All features of synthesis method of complexes **1–3**, such as mild reaction conditions, high yield, simple separation, short reaction period and good stability of production would make the synthesis of above catalysts become a promising method in industry applications.

2.3. Catalytic load and recyclability

It is known that it is important to achieve good yields using minimum catalysts in mild reaction condition. We also examined the effect of catalyst loading on a convenient coupling between 4-bromoacetophenone and 4-fluorophenylboronic acid. High yields (>93%) and a TON of 9300 were obtained even at catalyst loadings as low as 0.01 mol%. These

Table 2
Synthesis of fluorinated biphenyl derivatives[a]



Entry	R–Br	F, B(OH)$_2$	R, F	Time[b] (h)	Yield[c]
1	C_3H_7–Br	F, B(OH)$_2$	C_3H_7, F	5	92
2	C_3H_7–Br	F, F, B(OH)$_2$	C_3H_7, F, F	5	91
3	C_3H_7–Br	F, F, F, B(OH)$_2$	C_3H_7, F, F, F	6	89
4	C_5H_{11}–Br	F, B(OH)$_2$	C_5H_{11}, F	5	94
5	C_5H_{11}–Br	F, F, B(OH)$_2$	C_5H_{11}, F, F	5	95
6	F, B(OH)$_2$	F, B(OH)$_2$	H_3COC, F	6	99
7	H_3C–Br	F, B(OH)$_2$	H_3C, F	6	88
8	F, B(OH)$_2$	F, B(OH)$_2$	H_3CO, F	8	92
9	C_5H_{11}–I	F, F, B(OH)$_2$	C_5H_{11}, F, F	6	79[d]

[a] Aryl bromide (1mmol), fluorinated phenylboronic acid (1.5 mmol), $K_3PO_4 \cdot 3H_2O$ (3 mmol), **1** (0.001 mmol), THF = 2 ml. The reaction was performed at room temperature, THF + H_2O = 4 ml (1:1).
[b] Reaction time not optimised.
[c] Isolated yield was based on the aryl bromide.
[d] The reaction was performed at refluxing temperature with 1 mol% $Pd(PPh_3)_4$.

are indications of an effective catalytic system that has commercial and industrial potential.

An advantage of this method is its simple experimental procedure, the ease of product isolation and recycle of catalyst. A dark red solution was always observed during the processes of the reactions. Upon completion of the reactions, extraction with Et_2O drove the catalyst to partition predominately in the aqueous phase of the reaction mixture. The organic product could be conveniently isolation from Et_2O. The aqueous phase showed dark red. Therefore, it was possible to recycle the dark red species. For example, the product resulting from the coupling of 4-bromoacetophenone and 4-fluorophenylboronic acid in the presence of 1.0 mol% catalyst was obtained in 99% yield after 6 h in aqueous solvents at room temperature for the first cycle, 93% yield after 4 h for the second cycle, and 90% yield after 4 h for the third cycle. Soon afterwards, deposition of palladium black was observed. This indicated that the dark red species is likely active species here. This water-soluble active species is likely formed based on the hemilabile behaviour of P–O coordinated palladium complexes, the opening of Pd–O bond may be initiated under catalytic conditions, thus generating water-soluble active species and free coordination sites using for catalysis [18]. Further investigations of the mechanism of this catalyst are underway in our lab.

3. Conclusions

The synthesis of various fluorinated biphenyl derivatives was readily achieved via well-defined hemilabile P–O coordinated palladium complexes-catalyzed Suzuki coupling of aryl bromides and fluorinated phenylboronic acids in aqueous-phase at room temperature. This approach with high activity, good selectivity, mild reaction condition and aqueous-phase reaction, as well as potential recycling of the catalytic species develops environmentally sustainable chemical processes and provides a practical procedure for the synthesis of fluorinated liquid crystals in industry applications.

4. Experiment

All reactions were carried out using the Schlenk techniques. Elemental analyses were measured with a Perkin-Elmer 1400C analyzer. NMR spectra were recorded on Varian INOVADLG400 (^{1}H, ^{13}C) NMR spectrometers. In all case $CDCl_3$ was used as solvent. The ^{1}H and ^{13}C chemical shifts are expressed as δ-values relative to TMS. Silica gel 60 GF254 was used for analytical TLC.

4.1. General procedure for the synthesis of fluorinated biphenyl derivatives

In a 25.0 ml two-neck flask were placed 1.0 mmol of 4-bromoacetophenone, 1.5 mmol of fluorinated phenylboronic acid, 3.0 mmol of $K_3PO_4{\cdot}3H_2O$, 0.001 mmol of **1** and 4 ml of THF + H_2O (1:1). The mixture in flask was allowed to stir at room temperature (25–27 °C) for 6 h. Reaction progress was monitored by TLC and when the reaction was completed, 5 ml of water were added and extracted by 3 × 5 ml of ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of crude product by flash chromatography on silica gel.

4.1.1. 4-Fluoro-4′-(4-propyl-cyclohexyl)-bipheny

Anal. Found: C, 85.21; H, 7.49%; $C_{21}H_{23}F$ Calcd.: C, 85.67; H, 7.87%; ^{1}H NMR ($CDCl_3$): δ 0.91(t, J = 7.2 Hz, 3H), 1.02–1.11(m, 2 H), 1.20–1.39 (m, 5 H), 1.44–1.50 (m, 2 H), 1.90 (t, J = 6.4, 4 H), 2.47–2.53 (m, 1 H), 7.07–7.12 (m, 2 H), 7.27 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 7.50–7.54 (m, 2H). ^{13}C NMR: δ 14.61, 20.23, 33.77, 34.54, 37.23, 39.91, 44.47, 115.59, 115.80, 127.07, 127.49, 128.63, 137.47, 137.95, 147.26, 161.23, 163.68.

4.1.2. 3,4-Difluoro-4′-(4-propyl-cyclohexyl)-biphenyl

Anal. Found: C, 80.35; H, 6.65%; $C_{21}H_{22}F_2$ Calcd.: C, 80.74; H, 7.10%; ^{1}H NMR ($CDCl_3$): δ 0.91(t, J = 7.2 Hz, 3 H), 1.05–1.11 (m, 2 H), 1.20–1.52 (m, 7 H), 1.89 (t, J = 12.4 Hz, 4 H), 2.43–2.47 (m, 1 H), 7.14–7.21 (m, 1 H), 7.26–7.28 (m, 3 H), 7.33 (m, 1 H), 7.43 (d, J = 7.6 Hz, 2 H).

4.1.3. 3,4,5-Trifluoro-4′-(4-propyl-cyclohexyl)-biphenyl

Anal. Found: C, 76.04; H, 6.21%; $C_{21}H_{21}F_3$ Calcd.: C, 76.34; H, 6.41%; ^{1}H NMR ($CDCl_3$): δ 1.03–1.08 (m, 3 H), 1.14–1.23 (m, 2 H), 1.36–1.63 (m, 7 H), 1.96–2.02 (m, 4 H), 2.48–2.64 (m, 1 H), 7.11–7.16 (m, 1 H), 7.21–7.24 (m, 1 H), 7.36 (d, J = 8 Hz, 2 H), 7.48 (d, J = 8 Hz, 2 H).

4.1.4. 4-Fluoro-4″-(4′-pentyl-bicyclohexyl-4-yl)-biphenyl

Anal. Found: C, 86.41; H, 8.53%; $C_{29}H_{35}F$ Calcd.: C, 86.52; H, 8.76%; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 6.4 Hz, 3 H), 0.97–1.33 (m, 18 H), 1.73–1.96 (m, 9 H), 2.49 (m, 1 H), 7.08–7.12 (m, 2 H), 7.27 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 7.50–7.54 (m, 2 H). ^{13}C NMR: 14.33, 22.93, 26.88, 30.30, 30.54, 32.45, 33.84, 34.80, 37.68, 38.12, 43.11, 43.62, 44.50, 115.59, 115.81, 127.06, 127.48, 128.63, 137.48, 137.93, 147.28, 161.23, 163.68.

4.1.5. 3,4-Difluoro-4′-(4′-pentyl-bicyclohexyl-4-yl)-biphenyl

Anal. Found: C, 82.64; H, 8.09%; $C_{29}H_{34}F_2$ Calcd.: C, 82.82; H, 8.15%; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 6.4 Hz, 3 H), 0.97–1.33 (m, 18 H), 1.73–1.96 (m, 9 H), 2.49 (m, 1 H), 7.17–7.22 (m, 1 H), 7.25–7.28 (m, 3 H), 7.33–7.39 (m, 1 H), 7.43 (d, J = 6.4 Hz, 2 H).

4.1.6. 4-Acetyl-4′-fluorobiphenyl

Anal. Found: C, 78.28; H, 5.17%; $C_{14}H_{11}OF$ Calcd.: C, 78.46; H, 5.21%; ^{1}H NMR ($CDCl_3$): δ 7.14–7.18 (m, 2 H), 7.58–7.65 (m, 4 H), 8.02 (d, J = 8.0 Hz, 2 H), 2.64 (s, 3 H).

4.1.7. 4-Fluoro-4′-methyl-biphenyl

Anal. Found: C, 83.65; H, 5.76%; $C_{13}H_{11}F$ Calcd.: C, 83.81; H, 5.99%; ^{1}H NMR ($CDCl_3$): δ 7.54–7.50 (m, 2 H), 7.43 (d, J = 8.0 Hz, 2 H),7.24 (d, J = 8.0 Hz, 2 H), 7.14–7.08 (m, 2 H), 2.39 (s, 3 H).

4.1.8. 4-Methoxy-4′-fluoro-biphenyl

Anal. Found: C, 77.08; H, 5.21; $C_{13}H_{11}OF$ Calcd.: C, 77.21; H, 5.48%; ^1H NMR ($CDCI_3$): δ 7.51–7.46 (m, 4H), 7.10 (t, J = 8.8 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 3.84 (s, 3H).

4.2. Structure determinations

Single-crystals of **1** suitable for X-ray were obtained by slow evaporation of a CH_2CI_2 solution of **1** at room temperature. The data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Crystal data: $C_{29}H_{26}CI_2O_4P_2Pd$, M = 677.74, monoclinic, $P2_1/C$, T = 293(2), a = 10.658(2) Å, b = 17.943(4) Å, c = 16.618(6) Å, β = 116.72(2)°, Z = 4, Dc = 1.586 Mg m^{-3}. Of 14,955 data collected ($2\theta_{max}$ = 25.23°). 5119 were independent (R_{int} = 0.0300). Final refinement converged at R_1 = 0.0483, wR_2 = 0.0943, respectively. Intensities were corrected for Lorentz and polarization effects and empirical absorption, and the data reduction was carried out using SADABS program [19]. The structure was solved by direct methods using SHELXS-97 [20]. All the non-hydrogen atoms were refined on F^2 anisotropically by full-matrix least squares method. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent carbon atoms. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography [21].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2005.09.003.

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