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Palladium-catalysed and phosphine-promoted synthesis of diaryl ethers through self-coupling

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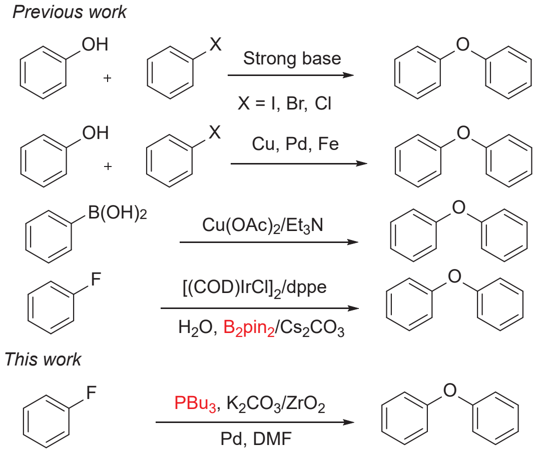
An efficient, palladium acetate-catalysed, tributylphosphine-promoted direct synthesis of symmetrical diaryl ethers through the self-coupling of aryl fluorides has been developed with K_2CO_3/ZrO_2 as a base. This provides an alternative method to prepare aromatic polymers, important synthetic intermediates and natural products for use in the field of pharmaceuticals and industrial materials.

Keywords: self-coupling, phosphine, symmetrical diaryl ethers, aryl fluorides

Over several decades, aromatic polyimides have been generally recognised to possess excellent mechanical properties and outstanding thermal stability. A variety of symmetrical diaryl ether compounds have been used as the precursor of aromatic polyimides and widely applied to the pesticide, medicine and material fields.[1] In addition, symmetrical diaryl ethers have been applied in the microelectronic and aerospace industries on account of their high thermal stability, chemical resistance and electronic properties.[2] Therefore, the synthesis of symmetrical diaryl ether derivatives is still of interest today.

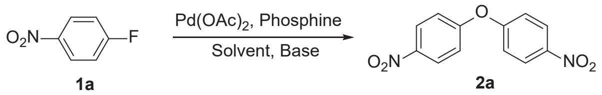
The classical method for the synthesis of diaryl ether derivatives is a C–O coupling reaction of phenolic derivatives with a C–X bond.[3–6] In most cases, transition metals have played a key role in this transformation. Many transition metals, such as Fe, Ir, Rh, Pd and Cu, have shown excellent catalytic activity in this area.[7,8] For example, a versatile sol-gel immobilised copper catalyst for the Ullmann arylation of phenols has been shown to be effective by Monnier, Taillefer and others.[9–14] Magnetic copper ferrite nanoparticles have also been used as catalysts for this transformation.[15–17] Other syntheses of diaryl ether derivatives have been reported.[18–26] Recently, we developed iridium-catalysed C–F activation of fluoroarenes with the use of bis(pinacolato)diboron (B_2pin_2) as an additive for a B–F bond activation.[27] This provides a convenient method to convert fluoride aromatic compounds into symmetrical diaryl ethers. However, we found that iridium catalysts, ligands and B_2pin_2 reagent are all expensive for this transformation (Scheme 1). Herein, we describe a palladium acetate-catalysed and tributylphosphine-promoted synthesis of diaryl ether derivatives by the self-coupling of aryl fluorides in moderate to high yields in the presence of the basic K_2CO_3/ZrO_2 conditions.

In the start of the investigation, the reaction of *p*-fluoronitrobenzene (**1a**) was used to establish the reaction by using a phosphine as an additive[28] with palladium acetate as a catalyst. Interestingly, the self-coupling product was obtained, although in a low yield. Next, the reaction conditions were modified to obtain a better yield (Table 1). Only a low yield was obtained, even by changing the solvents, phosphine and metals. Interestingly, quite a good yield was obtained when a supported solid base was used for this reaction. We examined several supported solid bases under different reaction conditions, including K_2CO_3/ZrO_2, K_2CO_3/Al_2O_3 and Cs_2CO_3/ZrO_2. These are easily prepared following known methods.[29–32] As listed in Table 1, the results showed that the simple K_2CO_3/ZrO_2 could promote this reaction with good yield, although K_2CO_3/Al_2O_3 gave disappointing results. A blank experiment showed that the reaction did not occur without a phosphine or base.



Scheme 1 Synthesis of diaryl ether derivatives promoted by boron and phosphine.

Table 1 Screening of reaction conditions[a]



1a **2a**

Entry	Phosphine	Base	Solvent	Yield/%[b]
1	PPh_3	Cs_2CO_3	DMF	13
2	PPh_3	K_2CO_3	DMF	<5
3	PPh_3	K_3PO_4	DMF	<5
4	PPh_3	Cs_2CO_3	DCE	<5
5	PPh_3	Cs_2CO_3	THF	<5
6	PPh_3	Cs_2CO_3	Toluene	16
7	PPh_3	Cs_2CO_3	Xylene	15
8	PPh_3	K_2CO_3/ZrO_2	Toluene	73
9	PPh_3	K_2CO_3/Al_2O_3	Toluene	27
10	PPh_3	Cs_2CO_3/ZrO_2	Toluene	<5
11	PPh_3	K_2CO_3/ZrO_2	Xylene	77
12	PBu_3	K_2CO_3/ZrO_2	Xylene	82
13	$P(OMe)_3$	K_2CO_3/ZrO_2	Xylene	<5

[a] Reaction conditions: **1a** (1.0 mmol), $Pd(OAc)_2$ (2 mol%), phosphine (2.0 equiv.), base (1.5 equiv.), 24 h, 110 °C or reflux.

[b] Isolated yields based on **1a**.

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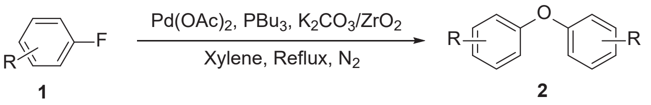
Table 2 Substrate expansion of aryl fluorides[a]



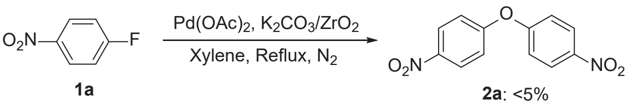
Entry	R	Yield/%[b]	Melting point/°C Measured	Reported	Ref.
1	*p*-NO_2	82 (**2a**)	141–142	143	33
2	*o*-NO_2	77 (**2b**)	113	114	34
3	*p*-CN	71 (**2c**)	177–178	179–181	35
4	*o*-CN	68 (**2d**)	–[c]	none[d]	none
5	*o*-CN–*p*-NO_2	85 (**2e**)	103	103–104	36
6	*o*-NO_2–*p*-F	76 (**2f**)	97–99	none[d]	none
7	*o*-Cl–*p*-NO_2	74 (**2g**)	153	154–156	37
8	*o*-NO_2–*p*-Cl	65 (**2h**)	150–152	154	38
9	*o*-NO_2–*p*-NO_2	83 (**2i**)	136–137	138	39
10	*o*-Br–*p*-NO_2	69 (**2j**)	158–159	none[d]	none

[a] Reaction conditions: **1** (1.0 mmol), $Pd(OAc)_2$ (2 mol%), $P(nBu)_3$ (2.0 equiv.), base (1.5 equiv.), 24 h, reflux.

[b] Isolated yields based on **1**.

[c] Oil was obtained.

[d] M.p. was not in the literature.



Scheme 2 Control experiment.

Encouraged by such promising results, we applied this methodology to a variety of substrates to determine the scope and limitations of the method. Almost all the substrates reacted smoothly and produced the corresponding products with moderate to good yields. As expected, when the substrate with a Br group was used to test this reaction, the self-coupling reaction took place successfully, providing the desired product in 69% yield (Table 2).

To reveal the possible reaction mechanism, a control experiment involving no phosphine was tested for this reaction. The result showed that the reaction did not happen without a phosphine reagent (Scheme 2).

In summary, we have developed a palladium acetate-catalysed and tributylphosphine-promoted diaryl ether synthesis in moderate to high yields using K_2CO_3/ZrO_2 as a base. The reaction involves oxygen insertion and then self-coupling of aryl fluorides. This provides an alternative method to prepare some aromatic polymers, important synthetic intermediates and natural products for use in the field of pharmaceuticals and industrial materials.

Experimental

All solvents were dried and purified by known procedures and freshly distilled under nitrogen from appropriate drying agents before use. The products were isolated by column chromatography on silica gel (200–300 mesh or 100–200 mesh) using petroleum ether (60–90 °C) and ethyl acetate as eluents. Silica gel for column chromatography was purchased from Qingdao Haiyang Chemical Co. Ltd. All yields described herein are the isolated yields after column chromatography. Reaction progress and product mixtures were routinely monitored by TLC using TLC SiO_2 sheets, and compounds were visualised under ultraviolet light. Melting points were determined using a WRS-1B digital melting point apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 or 600 NMR spectrometer. ^1H NMR chemical shifts are referenced to tetramethylsilane (TMS) (0 ppm). Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t) and multiplet (m).

Preparation of diaryl ethers; general procedure

A mixture of fluorobenzene (1.0 mmol), PBu_3 (2.0 mmol), $Pd(OAc)_2$ (2 mol%), K_2CO_3/ZrO_2 (1.5 equiv., based on K_2CO_3, 2.070 g) in xylene (10 mL) was stirred at reflux under nitrogen for 24 h or according to the TLC. On completion, the resulting mixture was filtered and washed with DCM. The combined organic solvent layers were separated, the solvent evaporated and the product purified by column chromatography with dichloromethane/*n*-hexane (1:1–1:2) as the eluent to provide the corresponding product **2**.

4,4′-oxybis(nitrobenzene) (**2a**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.19 (m, *J* = 9.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.7 (s), 144.2 (s), 126.2 (s), 119.3 (s).

2,2′-oxybis(nitrobenzene) (**2b**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.2 (s), 141.2 (s), 134.6 (s), 126.2 (s), 124.7 (s), 120.9 (s).

4,4′-oxydibenzonitrile (**2c**): ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.6 Hz, 4H), 7.70 (d, *J* = 8.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 108.0 (s), 118.3 (s), 119.7 (s), 134.5 (s), 159.2 (s).

2,2′-oxydibenzonitrile (**2d**); ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4 (s), 134.6 (s), 134.2 (s), 124.9 (s), 118.8 (s), 115.0 (s), 105.3 (s). HRMS calcd for $C_{14}H_9N_2O$ $[M + H]^+$: 221.0715; found: 221.0712.

4,4′-oxybis(3-fluoro-1-nitrobenzene) (**2e**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.8 Hz, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 113.6 (s), 113.8 (s), 119.9 (s), 120.8 (s), 120.8 (s), 144.5 (s), 144.5 (s), 148.1 (s), 148.2 (s), 151.1 (s), 153.6 (s).

4,4′-oxybis(1-fluoro-3-nitrobenzene) (**2f**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 2H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 113.4 (s), 113.6 (s), 121.8 (s), 122.0 (s), 122.2 (s), 122.3 (s), 141.1 (s), 141.2 (s), 145.5 (s), 145.5 (s), 156.7 (s), 159.2 (s). HRMS calcd for $C_{12}H_7F_2N_2O_5$ $[M + H]^+$: 297.0323; found: 297.0324.

4,4′-oxybis(3-chloro-1-nitrobenzene) (**2g**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 119.3 (s), 123.9 (s), 126.3 (s), 127.0 (s), 144.6 (s), 155.9 (s).

4,4′-oxybis(1-chloro-3-nitrobenzene) (**2h**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 2H), 8.19 (d, 2H, *J* = 8.6 Hz), 7.07 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 113.4 (s), 113.6 (s), 121.8 (s), 122.0 (s), 122.2 (s), 122.3 (s), 141.1 (s), 141.2 (s), 145.5 (s), 145.5 (s), 156.78 (s), 159.2 (s).

4,4′-oxybis(1,3-dinitrobenzene) (**2i**): ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J* = 8.0 Hz), 7.35 (t, 2H, *J* = 8.0 Hz), 6.99 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 115.3 (s), 117.9 (s), 120.7 (s), 135.7 (s), 139.0 (s), 159.0 (s).

4,4′-oxybis(3-bromo-1-nitrobenzene) (**2j**): ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 2H), 8.24 (d, 2H, *J* = 8.6 Hz), 7.02 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 105.3 (s), 115.0 (s), 118.8 (s), 124.9 (s), 134.2 (s), 134.6 (s), 157.4 (s). HRMS calcd for $C_{12}H_7Br_2N_2O_5$ $[M + H]^+$: 416.8722; found: 416.8717.

Electronic Supplementary Information

Detailed experimental procedures and ^1H NMR and ^{13}C NMR data for compounds **2** are available in the ESI through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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