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Research Article

Synthesis of ^{18}F-labelled biphenyls via SUZUKI cross-coupling with 4-[^{18}F]fluoroiodobenzene

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Summary

The SUZUKI reaction of organoboron compounds with 4-[^{18}F]fluoroiodobenzene has been developed as a novel radiolabelling technique in ^{18}F chemistry. The cross-coupling reaction of *p*-tolylboronic acid with 4-[^{18}F]fluoroiodobenzene was used to screen different palladium complexes, bases and solvents. Optimized reaction conditions ($Pd_2(dba)_3$, Cs_2CO_3, acetonitrile, 60°C for 5 min) were further applied to the synthesis of various ^{18}F-labelled biphenyls bearing different functional groups. The reaction proceeded in excellent radiochemical yields of up to 94% within 5 min while showing good compatibility to many functional groups. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: SUZUKI cross-coupling; 4-[^{18}F]fluoroiodobenzene; ^{18}F-labelled biphenyls

Introduction

The 4-fluorophenyl group is a common structural motif found in many fluorinated drugs, and the beneficial effect of a fluoroaryl group in drug design and development with regard to drug metabolism, *in vivo* activity and stability has been reviewed recently.[1] The mild and efficient introduction of a 4-[^{18}F]fluorophenyl group into a distinct position of a given molecule would lead to potential PET radiotracers. In this line, the use of palladium-mediated C–C and C–N bond forming reactions with ^{18}F-labelled aryl halides can be regarded as a general method for the versatile synthesis of a wide variety of ^{18}F-labelled radiotracers.

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Various palladium-mediated C–C and C–N cross-coupling reactions with 4-[^{18}F]fluoroiodobenzene and 4-[^{18}F]bromofluorobenzene have been reported in the literature for the synthesis of ^{18}F-labelled compounds. The most commonly employed reaction is the STILLE cross-coupling utilizing several organostannane derivatives as the organometallic component.[2–6] Other methods make use of the SONOGASHIRA reaction[7] and the BUCHWALD *N*-arylation reaction.[8,9]

However, within the class of palladium-mediated cross-coupling reactions the organoboron compound-based SUZUKI reaction has not been used for the synthesis of ^{18}F-labelled radiotracers yet. The mild reaction conditions, the extensive functional group compatibility and the circumvention of toxic tin by-products would make the SUZUKI reaction an attractive alternative to the frequently employed STILLE reaction. Moreover, the SUZUKI reaction has already proved to be a reliable and robust synthetic method in the synthesis of several ^{11}C-labelled compounds.[10,11]

In this report, we describe the synthesis of various ^{18}F-labelled biphenyls via Suzuki cross-coupling reaction with 4[^{18}F]fluoroiodobenzene. The reaction conditions were optimized by screening various palladium complexes, bases and solvents. Optimized reaction conditions were used to synthesize several ^{18}F-labelled biphenyls to study the functional group compatibility of the reaction.

Results and discussion

The SUZUKI reaction follows the typical catalytic cycle proposed for palladium-mediated carbon–carbon bond forming reactions. Several different palladium complexes, bases and solvents have been utilized to give the desired cross-coupled products in high yields.[12,13] However, to use the SUZUKI cross-coupling reaction in radiosyntheses with the short-lived positron emitter ^{18}F one has to adapt the reaction conditions to the short physical half-life ($t_{1/2} = 109.6$ min) of ^{18}F and the extraordinary stoichiometrical relation typically found in syntheses using tracer amounts. For this purpose we set up the reaction of commercially available *p*-tolyl boronic acid with 4-[^{18}F]fluoroiodobenzene to give 4′-[^{18}F]fluoro-4-methyl biphenyl as a model reaction to explore optimized reaction conditions by screening different palladium complexes, bases and solvents (Figure 1).

The radiochemical yield of 4′-[^{18}F]fluoro-4-methyl biphenyl was determined by radio-TLC referring to the percentage of the radioactivity area of the desired cross-coupled product related to the total radioactivity area. The results are summarized in Table 1.

In a first set of reactions (entry 1–10) the influence of different palladium complexes and bases on the radiochemical yield was studied when acetonitrile as the solvent was used. A wide variety of palladium complexes can be used for SUZUKI cross-coupling reactions. Palladium(0) complexes $Pd(PPh_3)_4$ and

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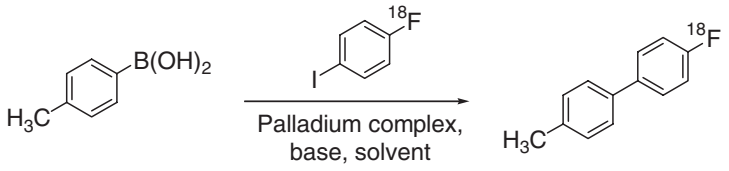

Figure 1. SUZUKI cross-coupling of *p*-tolyl boronic acid with 4-[^{18}F]fluoroiodobenzene

Table 1. Optimization of SUZUKI reaction with 4-[^{18}F]fluoroiodobenzene

Entry	Palladium complex[a]	Base	Solvent	Radiochemical yield (%)[b]
1	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	90
2	$Pd(PPh_3)_4$	K_3PO_4	CH_3CN	55(87)[f]
3	$Pd(PPh_3)_4$	KOAc	CH_3CN	86(95)[f]
4	$Pd_2(dba)_3$	Cs_2CO_3	CH_3CN	89
5	$Pd_2(dba)_3$	K_3PO_4	CH_3CN	91
6	$Pd_2(dba)_3$	KOAc	CH_3CN	90
7	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	CH_3CN	54(76)[f]
8	$Pd(PPh_3)_2Cl_2$	K_3PO_4	CH_3CN	82
9	$Pd(PPh_3)_2Cl_2$	KOAc	CH_3CN	88
10	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	CH_3CN	88
11	$Pd_2(dba)_3$	Cs_2CO_3	DMF	88
12	$Pd_2(dba)_3$	Cs_2CO_3	DMF	91[c]
13	$Pd_2(dba)_3$	K_3PO_4	DMF	85[c]
14	$Pd(PPh_3)_4$	K_3PO_4	DMF	90[c]
15	$Pd(PPh_3)_2Cl_2$	K_3PO_4	toluene	68[c]
16	$Pd_2(dba)_3$	Cs_2CO_3	toluene	32[c]
17	$Pd_2(dba)_3$	Cs_2CO_3	CH_3CN	74[d]
18	$Pd_2(dba)_3$	Cs_2CO_3	CH_3CN	27[e]
19	$Pd_2(dba)_3$	Cs_2CO_3	DMF	28[e]

[a]Molar ratio of *p*-tolyl boronic acid/Pd-complex/base:10/1/25.
[b]All reactions were carried out at 60°C for 5 min.
[c]Reaction was carried out at 80°C for 5 min.
[d]Reaction was carried out at 40°C for 5 min.
[e]4-[^{18}F]Fluoroidodobenzene was added to the solution containing the base and the palladium complex prior to the addition of *p*-tolyl boronic acid.
[f]In parenthesis: reaction time of 20 min.

$Pd_2(dba)_3$ are frequently used, but $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ plus PPh_3 are also known to be efficient.

When $Pd(PPh_3)_4$ as the palladium complex is used high radiochemical (90 and 86%) yields are obtained when Cs_2CO_3 or KOAc as the base are used (entry 1 and 3), whereas only a moderate radiochemical yield of 55% is achieved when K_3PO_4 is used (entry 2). Prolongation of the reaction time from 5 to 20 min increased the radiochemical yield to 87%. Comparable high radiochemical yields of 89–91% are obtained independently from the used base with $Pd_2(dba)_3$ as the palladium(0) complex (entries 4–6).

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The use of $Pd(PPh_3)_2Cl_2$ as palladium(II) complex gave radiochemical yields of 82 and 88%, when K_3PO_4 or KOAc was used (entries 8 and 9). Lower radiochemical yields (54%) are observed when Cs_2CO_3 is used as the base (entry 7). However, prolongation of the reaction time to 20 min increased the radiochemical yield to 76%. Palladium(II) complex $Pd(OAc)_2$ plus PPh_3 as co-ligand (ratio 1:2) afforded high radiochemical yield of 88% with Cs_2CO_3 as the base (entry 10).

In a second set of reactions the effect of DMF as the solvent was tested (entries 11–14). High radiochemical yields of 88 and 91%, respectively, were obtained with $Pd_2(dba)_3$ and Cs_2CO_3 at 60°C (entry 11) and 80°C (entry 12). Thus, increase of the reaction temperature did not further improve the radiochemical yield. No significant differences in the radiochemical yields (85 and 90%) were observed for palladium(0) complexes $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ when K_3PO_4 as the base was used and the reaction was carried out at 80°C (entries 13 and 14).

In entries 15 and 16 lower radiochemical yields of 68 and 32% were achieved when toluene as the solvent was used. Thus, toluene seems to be a less suitable solvent for SUZUKI reactions with 4-[^{18}F]Fluoroidodobenzene when compared with acetonitrile or DMF.

Lowering the reaction temperature from 60 to 40°C resulted in a decrease of the radiochemical yield from 89 to 74% (entries 4 and 17).

In all reactions (entries 1–17) a polar by-product could be detected at the start of the TLC plates. We assume that the by-product consists of a complex between the palladium complex and 4-[^{18}F]fluoroiodobenzene.

In a last set of reactions (entries 18 and 19) we studied the influence of the order of reagent addition. Examples in the literature describing SUZUKI and SONOGASHIRA cross-coupling reactions with $^{11}CH_3I$ report on the importance of the order of reagent addition to provide reasonable and reproducible radiochemical yields.[11,14] However, in our case addition of *p*-tolyl boronic acid to a pre-formed solution consisting of palladium complex, 4-[^{18}F]fluoroiodobenzene and base gave significantly lower radiochemical yields of 28 and 27%, respectively (entries 18 and 19) while forming several unspecified side-products.

The data summarized in Table 1 clearly demonstrate the favourable characteristics of the SUZUKI reaction involving 4-[^{18}F]fluoroiodobenzene as a coupling partner. The reaction proceeds very fast (5 min) under mild conditions (60°C), and the reaction seems to be quite tolerable to different palladium complexes and bases when polar solvents like acetonitrile or DMF are used. However, the reaction proceeds in much lower radiochemical yields when an non-polar solvent like toluene is used. Thus, we chose $Pd_2(dba)_3$ as the palladium complex, Cs_2CO_3 as the base and acetonitrile as the solvent in the following experiments to test the functional group compatibility of the SUZUKI reaction with 4-[^{18}F]fluoroiodobenzene.

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For this purpose we subjected various functionalized organoboron compounds to a cross-coupling reaction with 4-[^{18}F]fluoroiodobenzene to give the corresponding ^{18}F-labelled biphenyls **[^{18}F]15-[^{18}F]28** (Figure 2).

The results are summarized in Table 2.

We were very pleased to find that application of the found optimized SUZUKI reaction conditions with 4-[^{18}F]fluoroiodobenzene gave in most cases high radiochemical yields of 77–94% within the array of different functionalized organoboron compounds. The reaction tolerates ester groups (entry 8), OMe and SMe groups (entries 10 and 11), methanesulfonyl groups (entry 12), hydroxy groups (entry 13) and nitro groups (entry 14). This observation is in agreement with the known functional group compatibility of the SUZUKI reaction.[12,13] Most compounds tested were boronic acids (entries 1–13). However, the reaction is not limited to boronic acids. As exemplified in entry 14, boronic acid esters gave comparable radiochemical yields, hence offering an even broader range of starting materials.

For most reactions a reaction time of 5 min at 60°C gave sufficient radiochemical yields. Prolongation of the reaction time to 20 min did not significantly improve the radiochemical yields (entries 10 and 14).

The influence of sterically more hindered aryl boronic acids was tested by using 2-methyl-phenyl boronic acid **2** and 3-methyl-phenyl boronic acid **3** in the cross-coupling reaction with 4-[^{18}F]fluoroiodobenzene (entries 2 and 3). The obtained high radiochemical yields of 91 and 90%, respectively, for both reactions confirm the suitability of the SUZUKI reaction to form sterically hindered biaryls.[13]

In contrast to carboxylic acid esters (entry 8), carboxylic acids seem to be not tolerated very well (entry 9), and reaction of carboxylic acid-containing boronic acid **9** with 4-[^{18}F]fluoroiodobenzene gave only low to moderate radiochemical yields of 37% after 5 min and 45% after 20 min.

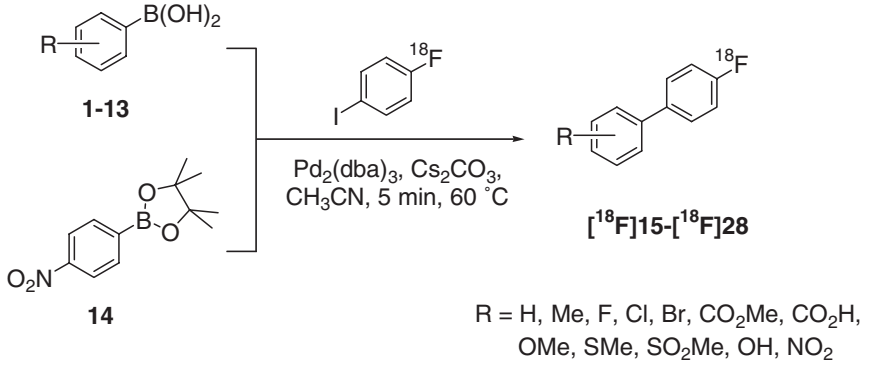

Figure 2. SUZUKI cross-coupling of several organoboron compounds 1–14 with 4-[^{18}F]fluoroiodobenzene to give ^{18}F-labelled biphenyls [^{18}F]15-[^{18}F]28

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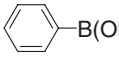
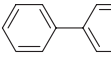
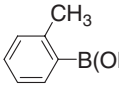
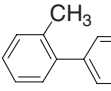
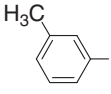
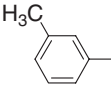
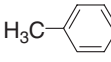
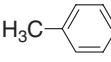
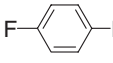
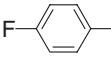
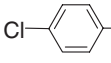
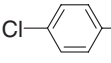
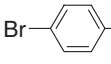
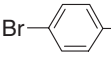
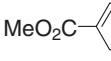
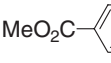
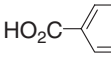
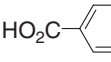
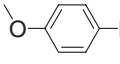
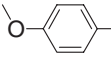
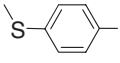
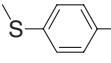
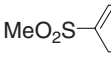
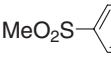
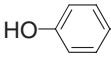
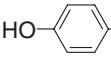
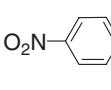
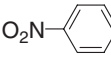
Table 2. SUZUKI reaction of several organoboron compounds with 4-[^{18}F]fluoro-iodobenzene

Entry	Organoboron compound	Product	Radio-chemical yield (%)[a,b]
1	 **1**	 **[^{18}F]15**	90
2	 **2**	 **[^{18}F]16**	91
3	 **3**	 **[^{18}F]17**	90
4	 **4**	 **[^{18}F]18**	90
5	 **5**	 **[^{18}F]19**	82
6	 **6**	 **[^{18}F]20**	77
7	 **7**	 **[^{18}F]21**	30(34)[c]
8	 **8**	 **[^{18}F]22**	89
9	 **9**	 **[^{18}F]23**	37(45)[c]
10	 **10**	 **[^{18}F]24**	82(85)[c]
11	 **11**	 **[^{18}F]25**	94
12	 **12**	 **[^{18}F]26**	84
13	 **13**	 **[^{18}F]27**	93
14	 **14**	 **[^{18}F]28**	88(90)[c]

[a]The radiochemical yields were determined by radio-TLC referring to the percentage of the radioactivity area of the ^{18}F-labelled biphenyl related to the total radioactivity area.
[b]All reactions were carried out at 60°C for 5 min.
[c]In parenthesis: reaction time of 20 min.

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An interesting trend is notable within the reaction of halogen-substituted boronic acids with 4-[^{18}F]fluoroiodobenzene (entries 5–7). Fluorine- and chlorine-containing boronic acids **5** and **6** afforded high radiochemical yields of 82 and 77%, respectively (entries 5 and 6), whereas bromine-containing compound **7** gave the corresponding biphenyl compound **[^{18}F]21** in only 30% radiochemical yield after 5 min and 34% after 20 min. This low radiochemical yield might be explained by a competing homo-coupling reaction of 4-bromo-phenyl boronic acid **7** according to a SUZUKI reaction. The tendency of an increasing rate of competitive homo-coupling correlates with the increasing susceptibility of aryl halides to undergo an oxidative addition to the reactive palladium(0) species, being Br > Cl > F. Thus, 4-bromo-phenyl boronic acid **7** successfully competes with 4-[^{18}F]fluoroiodobenzene to undergo the oxidative addition leading to substantial amounts of homo-coupled product rather than to form the desired cross-coupled product **[^{18}F]21** in high radiochemical yields.

In summary, we have developed a novel radiolabelling method for the synthesis of 4-[^{18}F]fluorophenyl-substituted biaryls via the SUZUKI cross-coupling reaction between organoboron compounds with 4-[^{18}F]fluoroiodobenzene. Optimized reaction conditions ($Pd_2(dba)_3$, Cs_2CO_3, acetonitrile, 60°C) usually afforded the desired ^{18}F-labelled biphenyls in excellent radiochemical yields (> 80%) within 5 min. The found broad tolerance towards various functional groups along with the mild and efficient reaction conditions make the SUZUKI a promising novel radiolabelling technique for the convenient synthesis of ^{18}F-labelled radiotracers.

Experimental

General

^{1}H-NMR spectra were recorded on a Varian Inova-400 at 400 MHz. Chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale. Melting points were determined on a Galen III melting point apparatus (Cambridge Instruments) and are uncorrected. Flash-chromatography was conducted according to Still *et al.*[15] Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plastic plates, with visualization under UV (254 nm). Compounds **1–14** were purchased from Aldrich.

Chemical syntheses

General procedure for the synthesis of biphenyls **15−28**. To a solution containing the aryl boronic acid (0.74 mmol) in DMF (5 ml) was added 4-fluoro-iodobenzene (0.57 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol) and caesium carbonate (1.13 mmol). The mixture was stirred at 60°C until TLC analysis showed consumption of fluoroiodobenzene. Then, ethyl acetate (50 ml) was

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added and the solution was filtered through Celite. Evaporation of the solvent gave the crude product, which was purified by flash-chromatography (EtOAc/petroleum ether 40–60).

*4-fluoro-biphenyl (***15***)*. Yield: 99%. ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 1H; Ar-H), 7.41 (m, 2H, Ar-H), 7.48–7.53 (m, 2H, Ar-H), 7.58–7.62 (m, 4H, Ar-H). Melting point 71–74°C.

*4′-fluoro-2-methyl-biphenyl (***16***)*. Instead of $Pd(PPh_3)_2Cl_2$ $Pd_2(dba)_3$ was used as catalyst. Yield: 99%. ^{1}H-NMR ($CDCl_3$) δ 2.27 (s, 3H; CH_3), 7.08–7.14 (m, 2H; Ar-H), 7.20–7.25 (m, 2H; Ar-H), 7.27–7.32 (m, 4H; Ar-H).

*4′-fluoro-3-methyl-biphenyl (***17***)*. Yield: 64%. ^{1}H-NMR ($CDCl_3$) δ 2,44 (s, 3H; CH_3), 7.14–7.20 (m, 3H; Ar-H), 7.33–7.62 (m, 5H; Ar-H).

*4′-fluoro-4-methyl-biphenyl (***18***)*. Yield: 70%. ^{1}H-NMR ($CDCl_3$) δ 2.44 (s, 3H; CH_3), 7.15 (m, 2H; Ar-H), 7.28 (m, 2H, Ar-H), 7.46–7.60 (m, 4H; Ar-H). Melting point 73–76°C.

*4,4′-difluoro-biphenyl (***19***)*. Yield: 91%. ^{1}H-NMR ($CDCl_3$) δ 7.12 (m, 4H; Ar-H), 7.46–7.52 (m, 4H; Ar-H). Melting point 67–68°C.

*4-chloro-4′-fluoro-biphenyl (***20***)*. Yield: 91%. ^{1}H-NMR ($CDCl_3$) δ 7.11–7.17 (m, 2H; Ar-H), 7.39–7.44 (m, 2H; Ar-H), 7.45–7.54 (m, 4H; Ar-H). Melting point 83–88 °C.

*4-bromo-4′-fluoro-biphenyl (***21***)*. Yield: 58%. ^{1}H-NMR ($CDCl_3$) δ 7.10–7.16 (m, 2H; Ar-H), 7.39–7.53 (m, 4H; Ar-H), 7.54–7.58 (m, 2H; Ar-H). Melting point 86–91°C.

*4′-fluoro-4-biphenyl-carboxylic acid methyl ester (***22***)*. Yield: 79%. ^{1}H-NMR ($CDCl_3$) δ 3,94 (s, 3H; CH_3), 7.13–7.18 (m, 2H; Ar-H), 7.57–7.62 (m, 4H; Ar-H), 8.08–8.11 (m, 2H; Ar-H). Melting point 99–100°C.

*4′-fluoro-biphenyl-4-carboxylic acid (***23***)*. Yield: 64%. ^{1}H-NMR (DMSO) δ 7.32 (m, 2H; Ar-H), 7.77–7.80 (m, 4H; Ar-H), 8.01 (m, 2H; Ar-H), 12.88 (b, 1H, COOH). Melting point 234–236°C.

*4′-fluoro-4-methoxy-biphenyl (***24***)*. Yield: 86%. ^{1}H-NMR ($CDCl_3$) δ 3.85 (s, 3H; CH_3), 6.98 (m, 2H; Ar-H), 7.10 (m, 2H; Ar-H), 7.46–7.51 (m, 4H; Ar-H). Melting point 83–85°C.

*4′-fluoro-4-methylsulfanyl-biphenyl (***25***)*. Yield: 73%. ^{1}H-NMR ($CDCl_3$) δ 2.53 (s, 3H; CH_3), 7.09–7.15 (m, 2H; Ar-H), 7.31–7.34 (m, 2H; Ar-H), 7.42–7.54 (m, 4H; Ar-H). Melting point 122–123°C.

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4′-fluoro-4-(methanesulfonyl)-biphenyl (**26**). Yield: 80%. ^{1}H-NMR ($CDCl_3$) δ 3.10 (s, 3H; CH_3), 7.18 (m, 2H; Ar-H), 7.59 (m, 2H; Ar-H), 7.73 (m, 2H; Ar-H), 8.01 (m, 2H; Ar-H). Melting point 144–146°C.

4′-fluoro-biphenyl-4-ol (**27**). Yield: 54%. ^{1}H-NMR (DMSO) δ 6.83 (m, 2H; Ar-H), 7.22 (m, 2H; Ar-H), 7.46 (m, 2H; Ar-H), 7.59 (m, 2H; Ar-H), 9.55 (s, 1H; OH). Melting point 143–150°C.

4′-fluoro-4-nitro-biphenyl (**28**). Yield: 61%. ^{1}H-NMR ($CDCl_3$) δ 7.16-7.22 (m, 2H; Ar-H), 7.57–7.62 (m, 2H; Ar-H), 7.67–7.71 (m, 2H; Ar-H), 8.28 (m, 2H; Ar-H). Melting point 122–125°C.

Radiochemical syntheses

No-carrier-added aqueous [^{18}F]fluoride ion was produced in a IBA CYCLONE 18/9 cyclotron by irradiation of [^{18}O]H_2O via the ^{18}O(p,n)^{18}F nuclear reaction. Synthesis of 4-[^{18}F]fluoroiodobenzene was performed in an automated nucleophilic fluorination module (Nuclear Interface, Münster) as described by Wuest *et al.*[5,9] Purified 4-[^{18}F]fluoroiodobenzene was eluted from the RP18 cartridge (Merck LiChrolut) with acetonitrile, DMF or toluene. Radio-TLC analysis was performed on Merck silica gel F-254 plastic plates using petroleum ether (b.p. 40–60°C) or mixtures of petroleum ether/ethyl acetate as eluent. For reading the radio-TLC plates a Bas2000 scanner (Fujix) was used.

General procedure for the SUZUKI reaction with 4-[^{18}F]fluoroiodobenzene

To an Eppendorf plastic vial containing the boronic acid (18 μmol), the palladium complex (1.8 μmol) and the base (45 μmol) in 300 μl of solvent (acetonitrile, DMF or toluene) was added 10 μl of 4-[^{18}F]fluoroiodobenzene (0.8–2.0 MBq) in acetonitrile, DMF or toluene. The sealed vial was heated and vortexed in a Thermocycler comfort (Eppendorf) at the indicated temperature. Progress of the reaction was monitored by analysing aliquots (1.5 μl) on TLC plates after 5 and 20 min.

4-[^{18}f]fluoroiodobenzene. Radio-TLC: $R_f = 0.53$, petroleum ether; $R_f = 0.64$, 10% EtOAc/petroleum ether; $R_f = 0.69$, 30% EtOAc/petroleum ether; $R_f = 0.75$, 50% EtOAc/petroleum ether.

4-[^{18}f]fluoro-biphenyl ([**^{18}F**]**15**). Radio-TLC: $R_f = 0.29$, petroleum ether.

4′-[^{18}f]fluoro-2-methyl-biphenyl ([**^{18}F**]**16**). Radio-TLC: $R_f = 0.30$, petroleum ether.

4′-[^{18}f]fluoro-3-methyl-biphenyl ([**^{18}F**]**17**). Radio-TLC: $R_f = 0.24$, petroleum ether.

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4′-[^{18}f]fluoro-4-methyl-biphenyl ([**^{18}F]18**). Radio-TLC: $R_f = 0.26$, petroleum ether.

4,4′-[^{18}f]difluoro-biphenyl ([**^{18}F]19**). Radio-TLC: $R_f = 0.29$, petroleum ether.

4-chloro-4′-[^{18}f]fluoro-biphenyl ([**^{18}F]20**). Radio-TLC: $R_f = 0.28$, petroleum ether.

4-bromo-4′-[^{18}f]fluoro-biphenyl ([**^{18}F]21**). Radio-TLC: $R_f = 0.30$, petroleum ether.

4′-[^{18}f]fluoro-4-biphenyl-carboxylic acid methyl ester ([**^{18}F]22**). Radio-TLC: $R_f = 0.22$, 10% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-biphenyl-4-carboxylic acid ([**^{18}F]23**). Radio-TLC: $R_f = 0.19$, 50% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-4-methoxy-biphenyl ([**^{18}F]24**). Radio-TLC: $R_f = 0.35$, 10% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-4-methylsulfanyl-biphenyl ([**^{18}F]25**). Radio-TLC: $R_f = 0.42$, 10% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-4-(methanesulfonyl)-biphenyl ([**^{18}F]26**). Radio-TLC: $R_f = 0.18$, 30% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-biphenyl-4-ol ([**^{18}F]27**). Radio-TLC: $R_f = 0.35$, 30% EtOAc/petroleum ether.

4′-[^{18}f]fluoro-4-nitro-biphenyl ([**^{18}F]28**). Radio-TLC: $R_f = 0.33$, 10% EtOAc/petroleum ether.

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