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SHORT NOTE

A comparative study on Suzuki-type ^{11}C-methylation of aromatic organoboranes performed in two reaction media

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The Suzuki-type cross coupling reaction is a palladium-mediated multistep reaction that has been used to synthesize several ^{11}C-labeled tracers for PET. However, the impact of the selected organoborane reagent and reaction medium on the radiochemical yield (RCY) has not been thoroughly investigated. To bridge this gap, we studied the synthesis of 1-[^{11}C]methylnaphthalene using four different organoborane precursors in reactions performed in DMF/water and THF/water. In the synthesis of 1-[^{11}C]methylnaphthalene, the best radiochemical yields (RCYs), approximately 50%, were obtained with boronic acid and pinacol ester precursors, whereas less than 4% RCY was obtained when performing the reaction with the N-methylimidodiacetic acid boronic ester (MIDA ester) precursor. 1-[^{11}C]methylnaphthalene was obtained in higher yields in almost all syntheses performed in THF/water as compared to DMF/water. This observation was in line with previously reported results for [^{11}C]UCB-J, a tracer for the synaptic vesicle glycoprotein 2A (SV2A) receptor, that also was obtained in higher RCY when synthesized in THF/water. The same trend was observed with [^{11}C]cetrozole, where the RCY was more than doubled in THF/water compared to the previously published synthesis performed in DMF. These results suggest that THF/water could be the preferred reaction medium when producing PET tracers via the Suzuki-type coupling reaction.

KEYWORDS
[^{11}C]cetrozole, [^{11}C]UCB-J, 1-[^{11}C]methylnaphthalene, ^{11}C-methylation, organoborane compounds, positron emission tomography, Suzuki-type coupling

1 | INTRODUCTION

Suzuki-type cross coupling reactions utilizing a palladium catalyst at basic conditions is a mild and efficient way to form carbon-carbon bonds in organic synthesis. The method has been used in the production of PET tracers by incorporating carbon-11-labeled methyl groups at aromatic and aliphatic structures. A recently developed PET-tracer produced by the Suzuki-type cross coupling reaction is [^{11}C]UCB-J, a tracer that has been implemented at several PET-facilities to image the synaptic vesicle glycoprotein 2A (SV2A).1–5 The same methodology is also used to synthesize for example [^{11}C]ATRA, [^{11}C]cetrozole, [^{11}C]CIMBI-712, [^{11}C]dehydropravastatin,

17-[^{11}C]HAD, [^{11}C]MENET, [^{11}C]M-MTEB, N-(4-[^{11}C]ethylphenyl)propionamide, [^{11}C]palmitate, [^{11}C]PSPA-4, and [^{11}C]toluene derivatives (Figure 1A,B).[6–15]

Several organic chemistry publications have shown that Suzuki-type coupling reactions may benefit from the use of THF/water as reaction medium.[16–18] Still, most ^{11}C-labeled tracers have been synthesized from pinacol ester precursors in DMF or DMF/water medium while the use of THF solvent has only been reported for compounds labeled in aliphatic positions (Figure 1A,B). Recently, we showed that the radiochemical yield (RCY) of [^{11}C]UCB-J was improved by changing the reaction medium to THF/water. In the current work, we wanted to investigate if THF/water medium would improve the [^{11}C]methylation also for other aromatic structures. Several different organoborane precursors, for example, pinacol esters, trifluoroborates, and boronic acids, have been used in ^{11}C-methylation of tracers, but we found that the selection of organoborane species and their impact on the radiochemical yield (RCY) has not been investigated systematically.

The aim of the current study was to investigate how the organoborane precursor and reaction medium affect the RCY. For this, 1-[^{11}C]methylnaphthalene was selected as model compound and it was synthesized from commercially available organoborane precursors; naphthalene-1-boronic acid, 1-naphthylboronic acid *N*-methylimidodiacetic acid boronic ester (1-naphthylboronic acid MIDA ester), naphthalene-1-boronic acid pinacol ester, and potassium 1-naphthalenetrifluoroborate. The reactions were performed in DMF/water and in THF/water reaction media. We compared the results from 1-[^{11}C]methylnaphthalene synthesis to structurally complex compounds [^{11}C]UCB-J synthesized from trifluoroborate precursor and [^{11}C]cetrozole synthesized from pinacol precursor, to see if the trends observed for 1-[^{11}C]methylnaphthalene would have general implications (Figure 1C).

2 | EXPERIMENTAL

2.1 | Materials

Tris (dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$), tri(*o*-tolyl)-phosphine ($P(o\text{-tol})_3$), anhydrous potassium carbonate (K_2CO_3), *N,N*-dimethylformamide (DMF), acetonitrile (ACN), 37% ammonia solution, phosphorous pentoxide (Sicapent), Ascarite, hydroiodic acid (57%), trifluoroacetic acid (TFA) and tetrahydrofuran (THF, for DNA and peptide synthesis, max. 0.005% H_2O) were purchased from Sigma Aldrich (Stockholm, Sweden). Lithium aluminum hydride in THF (0.1 M, LAH) was purchased from ABX (Radeberg, Germany). THF was distilled from a mixture containing sodium and benzophenone just before use to remove water and peroxides. Aqueous solution of TFA (1%) was prepared by dilution with MilliQ water. Ammonium formate (AMF) buffer solution (50mM, pH 3.5) was purchased from Bio-Hospital (Kopparberg, Sweden). AMF buffer solution (pH 10) was prepared by mixing ammonia solution (40 ml, 37%) and AMF solution (2000 ml, 50mM, pH 3.5). The ^{11}C-methylation reactions were performed in disposable conical glass vials (crimp neck, 0.9 ml) with septa (11 mm aluminum crimp cap with 1.3 mm butyl/PTFE seal), purchased from VWR (Karlskoga, Sweden).

For the 1-[^{11}C]methylnaphthalene syntheses, naphthalene-1-boronic acid, 1-naphthylboronic acid MIDA ester, naphthalene-1-boronic acid pinacol ester and the reference 1-methylnaphthalene were bought from Sigma Aldrich (Stockholm, Sweden). Potassium 1-naphthalenetrifluoroborate was from Fisher Scientific (Göteborg, Sweden). For [^{11}C]UCB-J synthesis, the precursor (*R*)-3-(difluoroboranyl)-4-((2-oxo-4-(3,4,5-trifluorophenylpyrrolidin-1-yl)methyl)-pyridin-1-ium fluoride (BF_3-Dm-UCB-J) and the reference compound (4*R*)-1-[(3-methyl-4-pyridyl)methyl]-4-(3,4,5-trifluorophenyl) pyrrolidin-2-one (UCB-J), were purchased from Pharmasynth (Tartu, Estonia). For [^{11}C]cetrozole synthesis the precursor MD-298 and the cetrozole reference 4-((4-methylbenzyl)(4H-1,2,4-triazol-4-yl)amino) benzonitrile) were from RIKEN Center for Biosystems Dynamics Research (Kobe, Japan).

2.2 | Synthesis equipment

All syntheses were performed using the fully automated Tracer Production System (TPS) developed in-house (Uppsala University Hospital PET Centre, Sweden). The TPS device contains 10 modules, including a robotic liquid handler, a gripper with a shaker function, heating/cooling for reaction vials, injection port for semi-preparative HPLC, fraction collector, vortex evaporator, SPE reformulation system, sterile dispenser and a control software that allows independent tasks to run concurrently. Preparative HPLC purification were done using semi preparative HPLC (Agilent 1260 Infinity II). The effluent was monitored with a Bioscan Flow-Count PMT radioactivity detector and UV detector (Agilent 1260 Infinity II) set at 254 nm.

2.3 | Synthesis

Tris (dibenzylideneacetone)-dipalladium(0), tri(*o*-tolyl)-phosphine, potassium carbonate, and 1 mg organoborane

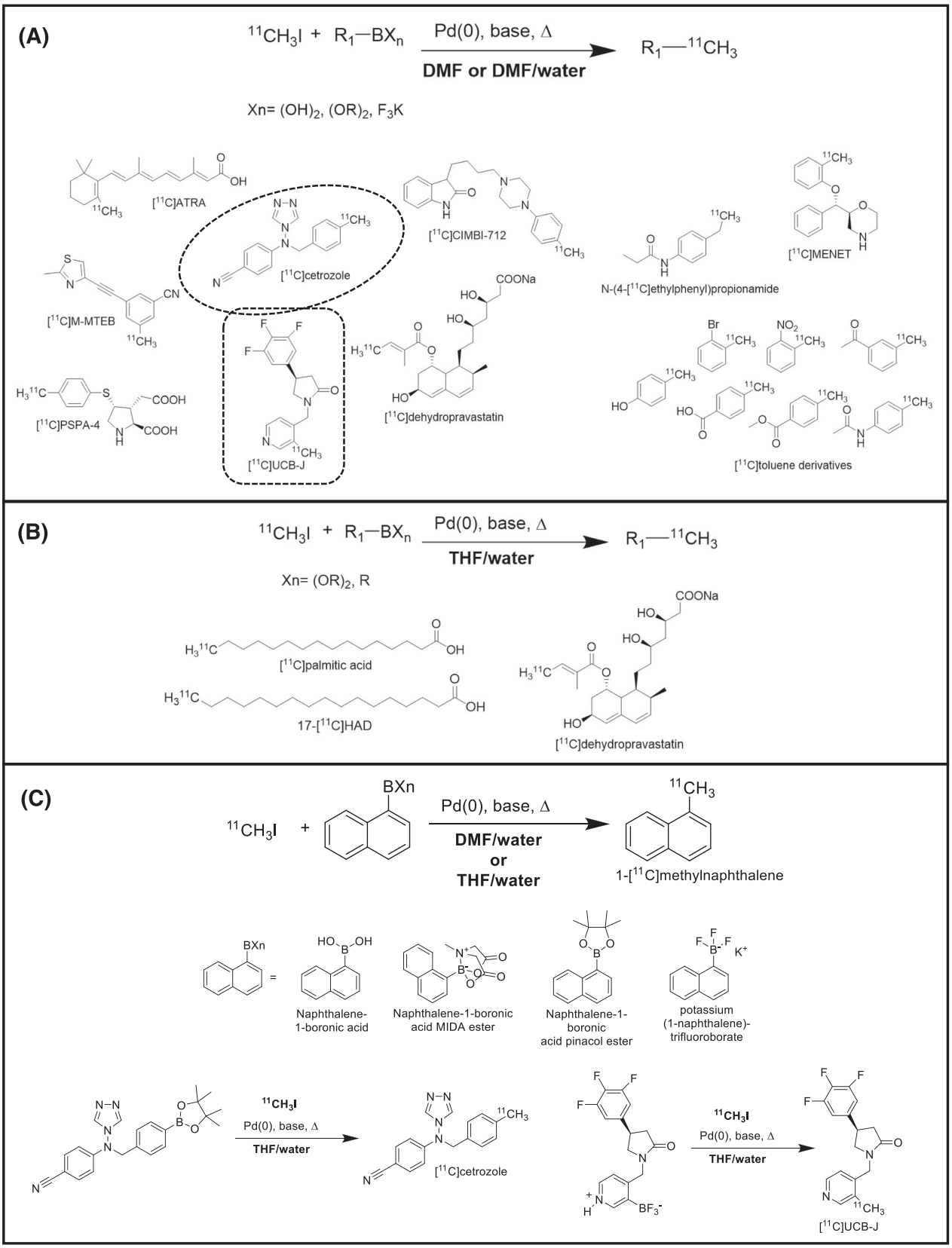

FIGURE 1 Suzuki-type coupling reaction schemes. (A) ^{11}C-labeled tracers synthesized using DMF or DMF/water as reaction medium. (B) ^{11}C-labeled tracers synthesized using THF or THF/water as reaction medium. (C) Reaction conditions investigated in current study, synthesizing 1-[^{11}C]methylnaphthalene, [^{11}C]cetrozole and [^{11}C]UCB-J. For references, see the text

precursor were weighed in a reaction vessel. Exact amounts of the compounds are listed Table S1. THF or DMF (350 μl) and MilliQ water (40 μl) was then added, the vessel was capped and the resulting solution was degassed with helium and vortexed. Immediately the THF reaction mixtures appeared homogenous with a clear dark red color that gradually turned yellowish. The DMF mixtures appeared as slightly pinkish black opalic solutions. In the synthesis of [^{11}C]cetrozole in DMF, all reagents were weighed in the same vessel, DMF was added, and reaction mixture was filtered and then degassed yielding a strong yellow solution.[19] All solutions were prepared approximately 30 min before addition of [^{11}C]methyl iodide.

Carbon-11 was obtained as [^{11}C]CO_2 was produced through the ^{14}N(p,α)^{11}C nuclear reaction by 17 MeV proton irradiation with the beam current 45 μA (Scanditronix MC-17 cyclotron) on nitrogen gas (AGA, Nitrogen 6.0) containing 0.05% oxygen (AGA, Oxygen 4.6). Typical irradiation time was 30 min, which gave approximately 30 GBq [^{11}C]CO_2 at the end of bombardment (EOB). The [^{11}C]CO_2 was converted to [^{11}C]methyl iodide by the "wet method" where first, [^{11}C]CO_2 was transferred to a reactor using helium gas (160 ml/min) and trapped in LAH (300 μl, 0.1 M in THF). The mixture was evaporated to dryness at 80°C under a stream of nitrogen gas (150 ml/min) during 2 min. Hydroiodic acid (600 μl, 57%) was added to the reactor and mixture was heated at 130°C for 70 s and then cooled to 80°C. The formed [^{11}C]methyl iodide was then transferred in a stream of nitrogen gas (10 ml/min) to the reaction vessel via a phosphorous pentoxide/ascarite column to remove moist and acidic vapors. [^{11}C]Methyl iodide was trapped in the reaction mixture at room temperature. After trapping, the reaction solution was mixed by a vigorous shake of the vial and then heated at 70°C for 4 min. The mixing was repeated after 1 min of heating.

The reaction mixture was diluted with 300 μl water and the ^{11}C-labeled product was purified by semi-preparative HPLC. 1-[^{11}C]methylnaphthalene and [^{11}C]cetrozole, synthesized in THF/water solutions, were purified using an ACE C18, 5 μm, 10 × 150 mm column. The eluent used for 1-[^{11}C]methylnaphthalene was acetonitrile in 50 mM AMF pH 3.5 (70/30). The eluent used for [^{11}C]cetrozole purification was acetonitrile in 50 mM AMF pH 3.5 (40/60). [^{11}C]Cetrozole synthesized in DMF solution was purified using ACE 5 SuperC18 5 μm (10 × 150 mm) with acetonitrile in 8.1 mM ammonium carbonate solution (40/60) as eluent.[19] [^{11}C]UCB-J was purified using a Phenomenex Gemini 5 μm NX-C18 (250 × 10 mm) column eluted with acetonitrile in AMF buffer (pH 10) (40/60). The preparative UV and radioactivity chromatograms of all the ^{11}C-labeled compounds are found in Figures S1–S6. In all syntheses, the radioactivity of the collected fraction was measured with a dose calibrator and then a sample was taken for analytical HPLC analysis.

2.4 | Radiochemical and chemical purity, identity, and molar activity

The radiochemical purity (RCP) and identity of the ^{11}C-labeled product was assessed by analytical HPLC (Agilent 1290 Infinity II pump) using a Phenomenex Kinetex 5 μm C18 100 Å (100 × 3.0 mm) column with an eluent flow of 0.7 ml/min. The effluent was monitored with a radioactivity detector (a Flow-Count PMT) and a UV detector set at 254 nm (Agilent 1290 Infinity II). The eluents used were acetonitrile in AMF buffer (pH 3.5) (50/50) for [^{11}C]methylnaphthalene, acetonitrile in AMF buffer (pH 3.5) (85/15) for [^{11}C]cetrozole and acetonitrile in AMF buffer (pH 3.5) (30/70) for [^{11}C]UCB-J. For [^{11}C]cetrozole synthesized in DMF, the eluents used were acetonitrile in 8.1mM ammonium carbonate (40/60) on a Gemini NX 5 μm C18 (100 × 4.6 mm) column. The analytical UV and radioactivity chromatograms of all the ^{11}C-labeled compounds are found in Figures S1–S6.

3 | RESULTS AND DISCUSSION

Three compounds, 1-[^{11}C]methylnaphthalene, [^{11}C]cetrozole, and [^{11}C]UCB-J were synthesized from [^{11}C]methyl iodide and organoborane precursors by the Suzuki type coupling reaction performed in THF/water, DMF or DMF/water (Figure 1C). The radioactivity yields for the isolated products in GBq (HPLC fraction), RCYs, RCPs and molar activities are listed in Table 1. The presented RCYs are decay corrected and based on the amount of trapped [^{11}C]methyl iodide in the reaction vial and the amount of radioactivity in the collected preparative HPLC fraction. By basing the RCYs on trapped amount of [^{11}C]methyl iodide in reaction vial, the events before the ^{11}C-methylation reaction were excluded. We did not observe any significant differences in the trapping efficiency of [^{11}C]methyl iodide depending on the solvents. For example, the trapped amount of [^{11}C]methyl iodide was 17.8 ± 4.5 GBq (n = 10) in the synthesis of 1-[^{11}C]methylnaphthalene performed in DMF/water, while when performed in THF/water the trapped activity was 19.6 ± 2.2 GBq (n = 10). Analysis of residual palladium in the isolated product was not performed but it can be noted that our previous studies have only showed extremely low amounts.[5,19]

TABLE 1 The radioactivity of the collected preparative HPLC fraction the RCY, concentration, molar activity (A_m), and radiochemical purity (%) of 1-[^{11}C]methylnaphthalene, [^{11}C]cetrozole, and [^{11}C]UCB-J. All RCYs are decay corrected and based on [^{11}C]methyl iodide. # Data from Rokka et al.[5]

	Medium	HPLC fraction (GBq)	RCY (%)	A_m (MBq/nmol)	RCP (%)	*n*
[^{11}C]Methylnaphthalene from boronic acid	THF/water	7.0 ± 0.4	54 ± 6	550 ± 50	>99.9	3
	DMF/water	6.2 ± 1.0	45 ± 2	410 ± 60	>99.9	3
[^{11}C]Methylnaphthalene from MIDA ester	THF/water	0.42	3,7	70	94.3	1
	DMF/water	0.30	2,8	50	89.6	1
[^{11}C]Methylnaphthalene from pinacol ester	THF/water	6.1 ± 1.3	49 ± 4	400 ± 300	>99.9	3
	DMF/water	6.5 ± 1.4	52 ± 4	360 ± 180	>99.9	3
[^{11}C]Methylnaphthalene from trifluoroborate	THF/water	3.8 ± 1.4	28 ± 10	550 ± 250	>99.4	3
	DMF/water	1.4 ± 0.3	16 ± 5	210 ± 70	>94.7	3
[^{11}C]Cetrozole from pinacol ester	THF/water	9.5 ± 1.5	82 ± 11	n/a	>99.9	5
	DMF	2.5; 3.9	31; 26	150	>95	2
[^{11}C]UCB-J from trifluoroborate	THF/water	2.7 ± 0.5	27 ± 8	420 ± 200	>99.8	3[#]
	DMF/water	0.2 ± 0.1	5.0 ± 3	n/a	>99.9	3[#]

The Suzuki-type coupling reaction with [^{11}C]methyl iodide is a multistep process where a ^{11}C-methyl palladium complex is formed by oxidative addition, the complex reacts with the organoborane precursor in a transmetalation step and finally the ^{11}C-labeled product is released by reductive elimination (Figure 2A).[18,20,21] The organoborane compound enters in transmetallic step in the form of a boronic acid. Organoboronates can be hydrolysed to the corresbonding boronic acid either in situ using base catalyzed hydrolysis or before the synthesis using either acid or base catalyzed hydrolysis. However, acidic or basic conditions can promote protodeboronation of boronic acid, which causes the precursor to lose its active site (Figure 2B).[18,22,23] Still, anhydrous conditions are not good either for boronic acids, because they may create trimeric anhydrides, so called boroxines. Boroxines are relatively stable at anhydrous conditions due to their partly aromatic moiety, which may inhibit the Suzuki-type coupling reaction. Optimal precursor hydrolysis into boronic acid form is needed when [^{11}C] methylations are performed, so that the hydrolysis do not limit the reaction rate.

The processes around transmetalation have been proposed as the reaction rate limiting step.[18,20,21,24] There are two main hypotheses how the organoborone species enters the catalytic cycle prior the transmetalation step (Figure 2C). According to computational studies, the lowest energy pathway is the so-called boronate pathway, where trihydroxyboronate is generated and then coupled to the palladium complex. However, experimental studies have indicated that the so-called oxo-palladium pathway is kinetically favored. Here the palladium halide reacts with a hydroxide ion and the formed oxo-palladium complex then reacts with the boronic acid. In case of ^{11}C-methylation [^{11}C]methyl iodide first has to couple with palladium complex before [^{11}C]methylation of organoborane precursor can happen In all experiments. the palladium–(o)tolylphosphine ratio was kept at a 1:2 (Table S1). Theoretically, this ratio of palladium and ligand can be considered optimal not to sterically hinder the transmetalation step involving the [^{11}C]methyl-palladium complex and the organoboronic compound.[25]

1-[^{11}C]Methylnaphthalene was first synthesized with standardized reaction conditions using four different types of organoborane precursors, performed in THF/water and DMF/water medium. The organoboranes were used as received and the purity may not be as high as precursor material manufactured specifically for PET-tracer synthesis. As the synthesis conditions were standardized to allow for direct comparison between the organoboranes, the RCY of 1-[^{11}C]methylnaphthalene could potentially be further improved but this was not the scope of this study. As Table 1 shows, the selection of the organoborane reagent had an impact on the RCY of 1-[^{11}C]methylnaphthalene. Highest RCYs were achieved using the boronic acid and the pinacol ester precursor while the trifluoroborate gave moderate yields and the MIDA ester gave the lowest yields.

Boronic esters are favorable as precursors, being relatively easy to synthesize and offer better stability during storage compared to boronic acids.[18,21,26] In the group of boronic esters, the pinacol ester has shown to be one of the most stable forms. In ^{11}C-methylations, pinacol esters have shown to react in mixtures where no water is

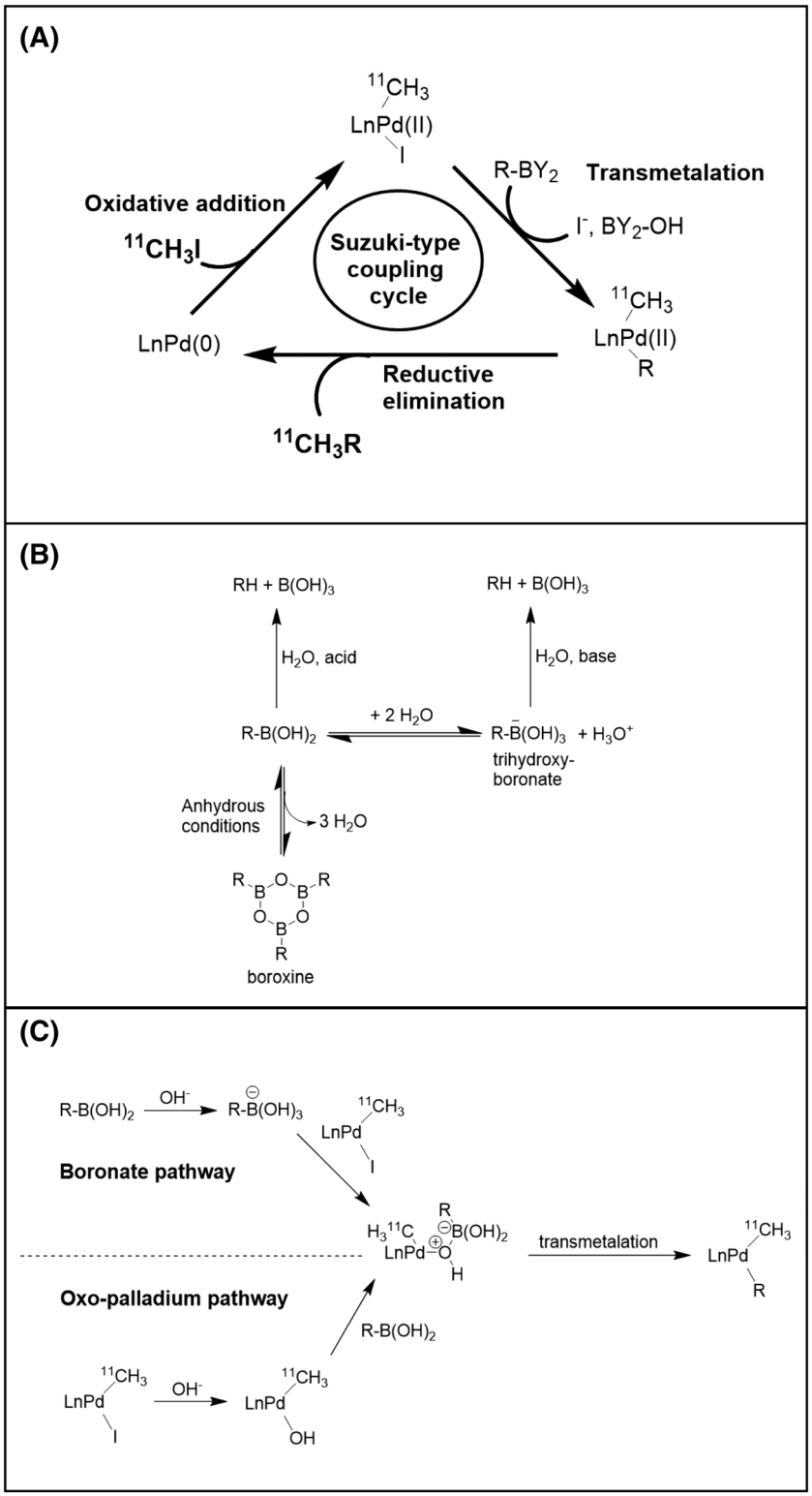

FIGURE 2 (A) The catalytic cycle of Suzuki-type reactions. (B) Boronic acids formed by hydrolysis are active species in Suzuki-type reaction but could be subjected to protodeboronation or transformation to boroxines. (C) The boronate and oxo-palladium pathways have been proposed to precede transmetalation of the boronic acid

added as is seen for example in the synthesis of [^{11}C] cetrozole, suggesting that pinacol esters may react directly with oxo-palladium complexes or exhibit favorable hydrolysis rate at semi-dry conditions to form suitable concentrations of boronic acid in situ.[8,13,15,19,27–29] This may explain why the RCY of 1-[^{11}C]methylnaphthalene was similar for the pinacol ester and the boronic acid (Table 1). Being stable in anhydrous conditions, the MIDA ester needs to hydrolyze to boronic acid before the Suzuki type coupling reaction can be performed.[26,27,30] The slow hydrolysis of MIDA esters are utilized in site specific conjugations, but as shown in our

study, this may not be beneficial for ^{11}C-chemistry that requires very short reaction times.

Potassium organotrifluoroborate salts are stable compounds with long shelf lives, and in synthesis they tolerate many common synthetic transformations. In aqueous and protic solutions, trifluoroborate hydrolyses to boronic acid. For Suzuki-type couplings, hydrolysis of trifluoroborate to boronic acid is essential for the coupling reaction as intact trifluoroborate cannot react with transmetalating species.[16–18] Hydrolysis of trifluoroborates is relatively slow which may be beneficial to avoid protodeboronation side reactions. Slow hydrolysis could also explain why the RCYs of 1-[^{11}C]methylnaphthalene were lower for the trifluoroborate precursor compared to boronic acid or pinacol ester precursor. In electron deficient aryl trifluoroborates, such as 1-naphthalenetrifluoroborate and the UCB-J precursor, the hydrolysis rate can be increased for example by performing the reaction in glass vessels and by using an aqueous biphasic reaction medium.[17] An enhanced hydrolysis rate of the organoborane precursors may explain the higher RCYs of 1-[^{11}C]methylnaphthalene and [^{11}C]UCB-J in THF/water reactions compared to the reactions performed in DMF/water.

Several publications are suggesting that aqueous biphasic conditions are important for Suzuki type coupling reactions. Although pure THF and water are miscible, addition of potassium carbonate makes water and THF less miscible, yielding a biphasic medium. A biphasic medium, like the THF/water reaction solution, could be beneficial as it may favor the oxo-palladium route that hinders the formation of trihydroxyboronate.[16,18,20,21,23] When reaction medium is changed to DMF/water basic homogenous medium is created which favors the formation of trihydroxyboronate and the boronate pathway. In our tests we observed a significant increase in the RCY for 1-[^{11}C]methylnaphthalene (starting with trifluoroborate precursor), [^{11}C]cetrozole, and [^{11}C]UCB-J, when the reaction medium was changed from DMF or DMF/water to THF/water (Table 1). Perhaps, this increase in RCY is due to enhanced precursor hydrolysis which could also imply that the oxo-palladium route is prominent in the ^{11}C-methylations of 1-[^{11}C]methylnaphthalene, [^{11}C]cetrozole, and [^{11}C]UCB-J.

We also noted in all tests that there were no visible particles in the THF/water solutions whereas in DMF/water solutions there were visible particles even after strong vortexing of the mixtures. Particles will sediment with time in the mixture, which decreases the availability of these components in reaction medium and may hinder the reaction. The second drawback of the visible particles is that they may clog the capillaries and columns when injected on the preparative HPLC. Thus, THF/water reaction mixture not only improves the RCYs, possibly by favoring the oxo-palladium route and improving the hydrolysis of the organoborane precursor, but it also dissolves the reaction components more efficiently and thus diminishes the mechanical problems which may occur with particulates. Because THF/water reaction mixtures do not contain visible particles, we assume that the vigorous shaking is not an important mediator for the reaction and the RCY would remain on the same level even if the reaction mixture is not shaken during the reaction, which may be case when commercial available synthesis devices are used.

Degassing of the reaction mixture is important for Suzuki type reactions because organoboranes as well as palladium(0) have tendency towards aerobic oxidation which decreases the coupling yield.[16,21] For that reason, all reaction mixtures used in this study were carefully degassed. To further minimize oxidative components in reaction mixtures, high-grade solvents were used; DMF was of anhydrous grade and THF was distilled fresh before use. Furthermore, all lines in the synthesis apparatus were flushed with nitrogen gas prior transfer of [^{11}C]methyl iodide to the reaction vessel to avoid bubbling air into the reaction mixture. The distillation of THF was not necessary, when high-grade THF is used from bottle which has been open less than 1 month as we have previously shown,[5] but these precautions are recommend, especially if the reagents and devices are not in daily use.

Prior this study we have produced [^{11}C]Cetrozole for clinical imaging studies and [^{11}C]UCB-J for preclinical imaging studies using published synthesis protocols.[5,19] As already shown, we could increase the RCY of [^{11}C]UCB-J when trifluoroborate precursor by changing the reaction medium from DMF/water to THF/water. Here, we demonstrate that THF/water can also increase the RCY of [^{11}C]cetrozole synthesized from pinacol ester precursor.

4 | CONCLUSIONS

The impact of organoboronate precursor and reaction medium selection on Suzuki-type ^{11}C-methylation coupling yields has been studied. For 1-[^{11}C]methylnaphthalene the highest RCY were achieved using boronic acid and pinacol ester precursors. The reaction media did not influence on RCY of 1-[^{11}C]methylnaphthalene when synthesized from pinacol ester precursor, but the aqueous biphasic conditions created using THF/water as reaction medium improved the RCY of 1-[^{11}C]methylnaphthalene synthesized from trifluoroborate and boronic acid precursor. In syntheses of [^{11}C]Cetrozole from pinacol precursor

and [^{11}C]UCB-J from trifluoroborate precursor, changing the reaction medium from DMF or DMF/water to THF/water gave a significant increase in the RCY. These results suggest that using a THF/water reaction medium should be considered when implementing synthesis protocols for Suzuki-type ^{11}C-methylations.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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