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Pd⁰–Mediated Rapid C–[¹¹C]Methylation and C–[¹⁸F]Fluoromethylation: Revolutionary Advanced Methods for General Incorporation of Short–Lived Positron–Emitting ¹¹C and ¹⁸F Radionuclides in an Organic Framework

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1. Introduction

The study of *in vivo* bioscience and medical treatment from molecular point of view requires the precise evaluation of molecule behavior in living systems, especially involving the human body. Positron emission tomography (PET) is a non-invasive imaging technology with a good resolution, high sensitivity, and accurate quantification, which makes it possible to timely and spatially analyze the dynamic behavior of molecules in *in vivo* systems using a specific molecular probe labeled with positron-emitting radionuclides such as ¹¹C, ¹³N, ¹⁸F, and ⁷⁶Br (Phelps, 2004). PET has been extensively used for the diagnosis of diseases such as cancers, cerebral dysfunction, and etc., and recently, in medical checkups as an early detection approach. In the current paradigm shift to drug discovery, PET molecular imaging will provide an important new scientific platform to execute human microdosing trials during the early stage of drug development, especially from the viewpoint of promoting evidence-based medicine (Lappin & Garner, 2003; Bergström et al., 2003). A core concept and the driving force of molecular imaging would truly be “Seeing is Believing”. It is of significant value to unveil the vital functions and phenomena of living systems by molecular imaging the *in vivo* behavior of a ligand and the localization of a biologically significant target molecule. The potential of PET molecular imaging in an interdisciplinary scientific area strongly depends on the availability of suitable radioactive molecular probes with specific biological functions. The development of biologically significant novel PET probes will be accomplished by the combination of an efficient synthetic strategy for designed molecules and new advances in the field of labeling chemistry (Schubiger et al., 2007).

Among the short-lived positron-emitting radionuclides, ¹¹C and ¹⁸F with a half-life of 20.4 and 109.8 min, respectively, have often been used for radiolabeling as the most significant radionuclides from both a chemical and biological perspective as well as from the viewpoint

of radiation exposure safety. With respect to the ^{11}C -incorporation on organic carbon frameworks, we have been developing multiple-type Pd^0 -mediated rapid $[^{11}\text{C}]$ methyations onto an arene including a heteroaromatic compound, and alkene, alkyne and alkane structures by $[^{11}\text{C}]$ carbon-carbon bond forming reactions (rapid C- $[^{11}\text{C}]$ methyations) using $[^{11}\text{C}]$ methyl iodide and an excess amount of an organostannane or organoboron within a very short time span (5 min) (Suzuki et al., 1997; Hosoya et al., 2004; Hosoya et al., 2006; Doi et al., 2009; Suzuki et al., 2009). These labeling reactions provide a high generality and practicability as groundbreaking methods for introducing the $[^{11}\text{C}]$ methyl group into almost any organic framework. Regarding the ^{18}F radionuclide, a rather longer half-lived positron emitter than ^{11}C , the ^{18}F -labeling can be mainly accomplished by ordinary methods involving nucleophile substitution with the ^{18}F anion, as exemplified by the synthesis of 2- $[^{18}\text{F}]$ fluoro-2-deoxy-D-glucose ($[^{18}\text{F}]$ FDG) (Ido et al., 1978) and 3'- $[^{18}\text{F}]$ fluoro-3'-deoxythymidine ($[^{18}\text{F}]$ FLT) (Grierson et al, 1997, as cited in Bading & Shields, 2008). In this chapter, newly advanced methodologies for introducing the short-lived ^{11}C radionuclide into various carbon frameworks (rapid C- $[^{11}\text{C}]$ methyations) and the rather longer half-lived ^{18}F radionuclide into a benzene framework (C- $[^{18}\text{F}]$ fluoromethylation) are described in detail in addition to their applications for radiolabeling biologically and clinically significant organic molecules.

2. PET molecular imaging technology–principle, properties, and benefits

The short-lived positron emitting radionuclide ^{11}C was first produced by Crane and Lauritsen in 1934 (Lauritsen et al., 1934, as cited in Allard et al., 2008). They investigated the physical properties of this radionuclide and demonstrated that ^{11}C undergoes β^+ decay with a half-life of 20.4 min, yielding ^{11}B as the stable nuclide (Figure 1). A positron (positively charged electron, e^+) ejected by this process collides with a nearby electron within a few millimeters in tissue to produce two high-energy γ -ray photons of 511 keV each. These photons travel in opposite directions at 180 degrees, penetrating the body, and can be detected by a pair of opposing scintillation detectors. If the two opposite detectors are simultaneously hit, it is assumed that the photons come from the same decay event. The data are fed to a computer system that can reconstruct the three-dimensional tomographic imaging and provide a highly accurate quantitative analysis of a radiolabeled drug in a body over time, measured as becquerel (Bq) per pixel. Because of the really high specific radioactivity of positron-emitter labeled compounds, PET enables *in vivo* imaging using an extremely small mass of the compound (sub-femtomole), namely, at extremely low concentrations (sub-picomolar) far below the critical concentration of pharmacological effects. The other typical positron-emitting radionuclides for PET studies, along with their half-lives ($t_{1/2}$) are: ^{15}O ($t_{1/2} = 2.07$ min); ^{13}N ($t_{1/2} = 9.96$ min); ^{68}Ga ($t_{1/2} = 67.6$ min); ^{18}F ($t_{1/2} = 109.7$ min); ^{64}Cu ($t_{1/2} = 12.7$ h). The benefits of the use of PET technology in scientific research areas are as follows: (1) O, N, and C are included as ubiquitous elements constituting a biologically active compound in nature, providing the diversity of the labeled compounds without modifying the properties (or functions) of the molecule; (2) the molecule including the positron emitting radionuclide can be externally and quantitatively measured using a PET camera with a high resolution and sensitivity; (3) a short half-life is very relevant to human PET studies in terms of the high required safety for radiation exposure.

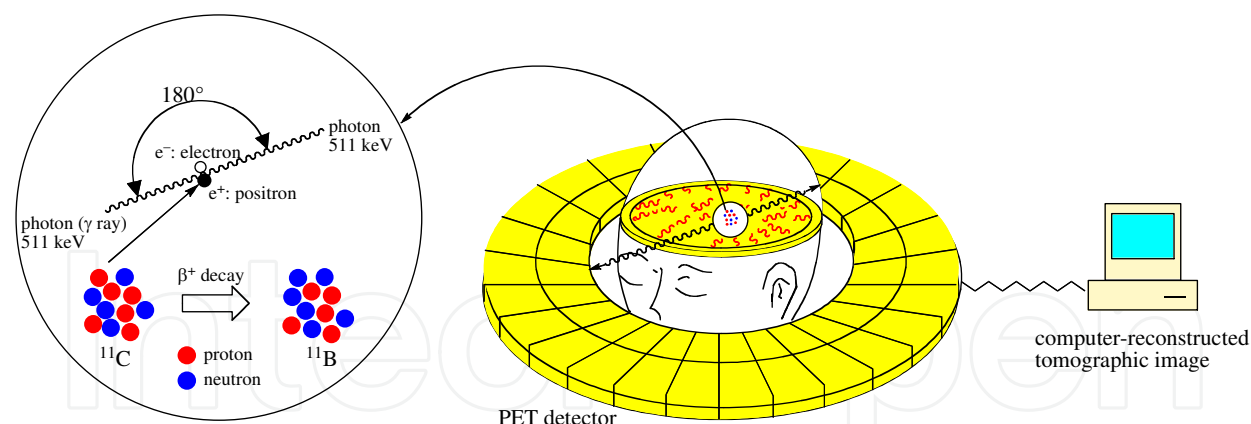


Fig. 1. Principle of the brain imaging by PET as shown by ¹¹C to ¹¹B decay.

3. Rapid chemistry needed for ¹¹C-labeling—working against time

The special aspects of PET radiochemistry such as short half-lives, extremely small amounts of available radionuclides, and relatively high-energy radiation impose severe restrictions on the synthesis of PET probes. In general, the synthesis of a pure, injectable ¹¹C-labeled probe must be accomplished within 2-half lives of ca. 40 min due to the quick decay of the radioactivity. The synthesis process for the pharmaceutical formulation includes the following steps: (1) derivatives of a ¹¹C isotope produced by a cyclotron to an appropriate labeling precursor such as ¹¹CH₄, ¹¹CH₃I, ¹¹CH₃OTf, ¹¹CO, and ¹¹CO₂; (2) evaluation of the reaction efficiency (radiochemical yield) by analytical high performance liquid chromatography (HPLC) after the ¹¹C-labeling of the target probe; (3) work-up and chromatographic purification of the desired ¹¹C-labeled probe; and (4) preparation of an injectable solution for an animal/human PET study (pharmaceutical formulation). Therefore, the time allowed for a ¹¹C-labeling reaction should be less than 5 min, inevitably necessitating a rapid chemical reaction. Another difficulty encountered in the synthesis of a ¹¹C-labeled PET probe is the availability of an extremely small amount (nano-mol level) of the ¹¹C-labeling precursor such as [¹¹C]CH₃I. Therefore, the labeling reaction is usually carried out with a large amount (milli-gram level) of the reacting substrate to promote the reaction. In addition, the efficient and secure purification of a small amount of the synthesized ¹¹C-labeled probe from a large amount of the remaining substrate must be considered since a PET probe is usually intravenously injected into both living animals and humans.

4. Attractive features of rapid C-[¹¹C]methylation—four kinds of rapid C-[¹¹C]methylations

Thus far, in the field of PET chemistry, the [¹¹C]methylation of the hetero atoms of N, O, and S has mainly been explored and utilized because of its simple reaction conditions namely, only by mixing ¹¹CH₃I and a large amount of the substrate (Allard et al., 2008). However, a carbon-hetero atom bond tends to be readily metabolized to produce ¹¹CH₃OH, ¹¹CH₂O and H¹¹COOH, which are dispersed in whole organs, thus decreasing the credibility of a PET image. It could be said that “the facts are the enemy of the truth.” We here considered that the [¹¹C]methylation by [¹¹C]C-C bond formation (referred to as C-[¹¹C]methylation)

(Suzuki et al., 1997) will have a number of benefits because of the following reasons: (1) The ^{11}C methyl group introduced into a carbon will be metabolically stable, and therefore, such a ^{11}C -labeled probe will provide a highly credible PET image; (2) the methyl group is the smallest nonpolar functional group, and therefore, the introduction of a methyl group has the least influence on the biological activity of the parent compound; furthermore, the methyl group is rather positively used in drug design as magic methyl to control the lipophilicity as well as the fixation of the conformation of a molecule; (3) a short half-life of the ^{11}C -incorporated probe is favorable for the rapid screening involving optimization of reaction conditions and the evaluation of the *in vivo* behavior, thus allowing several trials per day. Accordingly, we have devised a plan to realize four types of rapid C- ^{11}C methylations for arene, alkene, alkyne, and alkane frameworks (Figure 2), which allow the ^{11}C -labeling of almost any organic compound. The following pharmacokinetic (PK)/pharmacodynamic (PD) studies in *in vivo* systems by PET provide a key methodology to eventually promote “evidence-based medicine” at the molecular level. With regard to such a ^{11}C -C-C bond forming reaction, organometallic compounds comprised of the group IA and IIA metals were previously used. For example, [methyl- ^{11}C]thymidine was prepared in a radiochemical yield of 20% with radiochemical purities >99% by the reaction of ^{11}C CH₃I with the lithiated derivative obtained from the bromo precursor (Sundoro-Wu et al., 1984). In such a reaction, however, the use of a moisture-sensitive organolithium compound is difficult to justify the stoichiometry for an extremely small amount of ^{11}C CH₃I, resulting in the inevitable production of a large amount of an undesired demethylated derivative due to the use of an excess amount of the lithiated substrate. Furthermore, the undesired side reaction such as the rearrangement of the lithiation position occurs under such drastic conditions. Consequently, the tedious separation of demethylated side products and regioisomers is inevitably needed to purify the desired compound. Thus, the reaction based on the use of “soft metalloids” as nucleophilic substrates was ideal for this requirement, if realized, as described in detail in section 5.

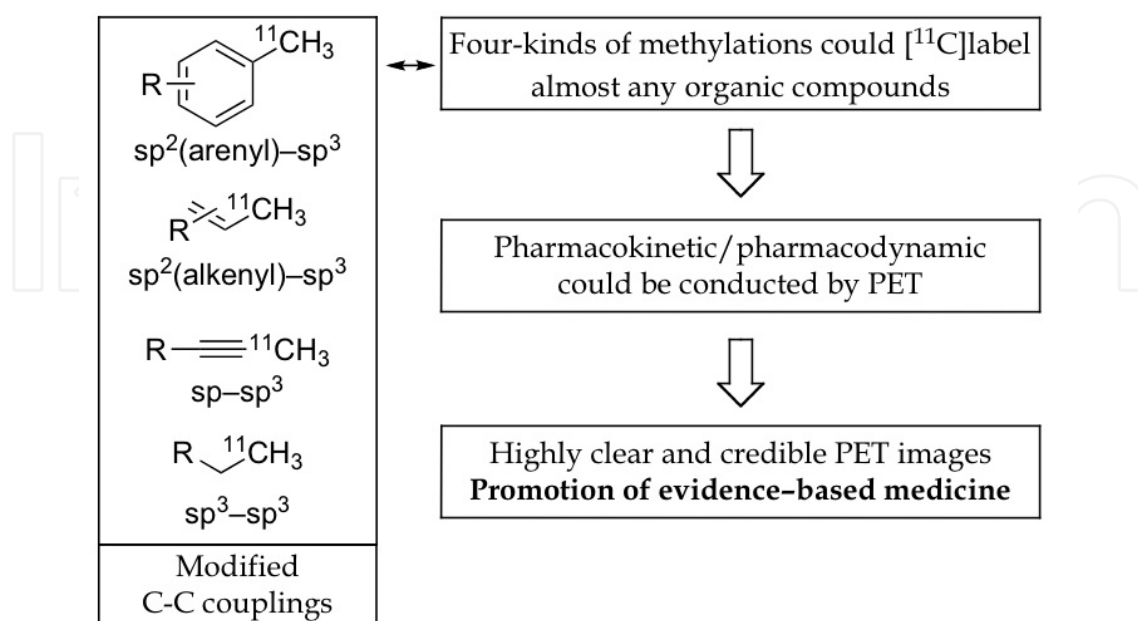


Fig. 2. Attractive features of rapid C- ^{11}C methylations.

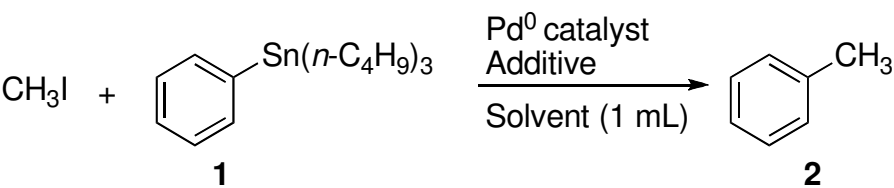
5. Benefits of using of an organostannane as a trapping substrate for [¹¹C]methyl iodide

A general protocol for the rapid C-methylation was established for the first time based on a Stille-type reaction using phenyltributylstannane and CH₃I, then [¹¹C]CH₃I, a frequently-used ¹¹C-labeling precursor (Suzuki et al., 1997). The Stille reaction is among the most generally used C-C bond forming reactions in organic synthesis as a reaction of an organometallic (-metalloid) reagent with an organic electrophile (Stille, 1986). The organotin compounds can be prepared by a number of routes even if containing a variety of reactive functional groups. Moreover, the reagent is not particularly oxygen or moisture sensitive. In the palladium(0)-catalyzed coupling of an organic electrophile with an organotin reagent, essentially only one of the groups on the tin atom selectively enters into the coupling reaction, namely an unsymmetrical organotin reagent comprised of three simple alkyl (except methyl) groups, and the fourth group, such as the arenyl, alkenyl, or alkynyl group. The latter fourth group can selectively transfer. The Stille reaction was thought to be useful for our purpose because of its favorable properties of the triorganostannane compounds, such as (1) their high tolerance to various chemical reactions and chromatographic purification conditions, enabling the incorporation of a radioisotope as the final step of the PET-probe synthesis; and (2) the extremely low polarity of a trialkyltin(IV) derivative, enabling an easy separation of the desired product from a large amount of the remaining tin substrate. However, to the best of our knowledge, at that time, there was little information on the Stille reaction using methyl iodide as an sp³-hybridized carbon partner in comparison to its wide applicability to sp²-hybridized arenyl or sp³-hybridized allylic halides; it seemed rather difficult to realize the methylation in high yield due to the unavoidable scrambling between the methyl group in methyl iodide and phenyl groups in the triphenylphosphine ligand, P(C₆H₅)₃, by the reaction of methyl iodide with the less reactive phenyltributylstannane in the presence of Pd{P(C₆H₅)₃}₄ (Morita et al., 1995). The use of the higher reactive phenyltrimethylstannane as a substrate also induces the competition between ¹¹CH₃ in [¹¹C]CH₃I and CH₃ groups in the stannane to produce [¹¹C]ethane as a byproduct (Suzuki et al., 1997, also see section 6). Furthermore, the labeled-compound obtained from the trimethyltin derivative resulted in a much lower specific activity than the tributyltin derivative (Samuelsson & Långström, 2003; Madsen et al., 2003). It should be added that tributyltin derivative is practically non-toxic, while the trimethyl- and triethyltins have a significant acute toxicity (Smith, 1998; Buck et al., 2003). Consequently, we have been obliged to devise new reaction conditions capable of promoting a rapid cross-coupling reaction using the less reactive tributyltin derivative as a substrate for trapping [¹¹C]CH₃I.

6. Realization of Pd⁰-mediated rapid C-methylations by the reaction of methyl iodide with an excess amount of arenyltributylstannanes (rapid coupling between sp²(arenyl)- and sp³-hybridized carbons)

Keeping the ¹¹C radiolabeling conditions of a PET-probe synthesis in mind, we set up a model reaction using methyl iodide and an excess amount of phenyltributylstannane (**1**) (CH₃I/**1** = 1:40 in molar ratio) to possibly restrict the reaction time to less than 5 min (Table 1) (Suzuki et al., 1997). The yield of the methylated product, toluene (**2**), was determined on the basis of the CH₃I consumption. As anticipated, the conventional Stille-reaction

conditions with a reaction time of 30 min did not give the desired product at all (Table 1, Entry 1), leading us to introduce the concept of coordinative unsaturation to activate the palladium catalyst. Thus, we found that the use of a coordinatively unsaturated Pd⁰ complex, Pd{P(*o*-CH₃C₆H₄)₃}₂ (Paul et al., 1995), generated in situ by mixing Pd₂(dba)₃ (dba: dibenzylideneacetone) and the sterically bulky tri-*o*-tolylphosphine (P(*o*-CH₃C₆H₄)₃; cone angle, 194°) (Tolman, 1977) instead of triphenylphosphine (P(C₆H₅)₃; cone angle 145°) (Tolman, 1977), significantly increased the coupling efficiency (76%, Table 1, Entry 2). Next, we introduced an additional concept to shorten the reaction time (from 30 min to 5 min); the simple heating (80 °C) was less effective for lowering the yield, but the stabilization of the transiently formed palladium catalyst, strongly solvated by *N,N*-dimethylformamide (DMF), effectively suppressed the decrease in the yield to a considerable extent. Furthermore, we intended to enhance the reactivity by adding a Cu^I salt with the expectation of Sn to Cu transmetallation, and K₂CO₃ in order to react with the (*n*-C₄H₉)₃SnX (X = I and/or Cl) generated during the reaction to neutralize the reaction system. Thus, the reaction using the CH₃I/**1**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ system (1:40:0.5:2:2:2) in DMF at 60 °C for 5 min gave the desired product in 91% yield (Table 1, Entry 6) (Suzuki et al., 1997). It should be noted that when phenyltrimethylstannane was used instead of phenyltributylstannane, the reaction produced toluene (**2**) in >100% yield (122–129%) together with ethane, indicating the unexpected cross-coupling reactions (scrambling) between the methyl in methyl iodide and the methyl on the tin atom. The reaction between the phenyl and methyl on the tin atom was also contaminated to yield toluene (undesired product in actual PET probe synthesis) to a significant extent (Suzuki et al., 1997), thereby decreasing the yield of the desired [¹¹C]toluene. The specific radioactivity of desired [¹¹C]toluene would also be deduced by the contamination of [¹²C]toluene formed by the reaction between the methyl



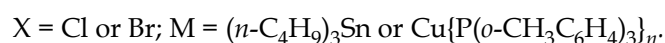
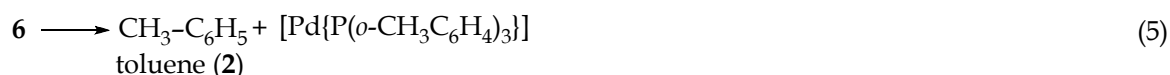
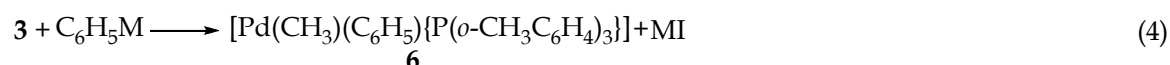
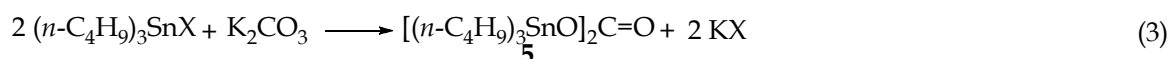
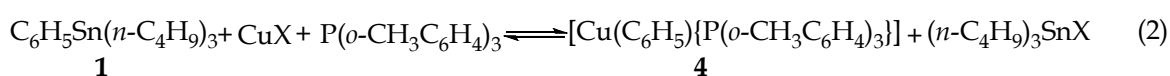
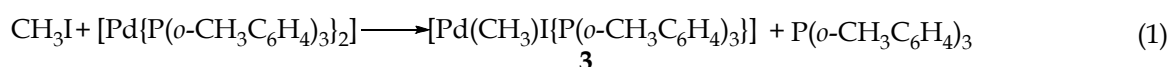
Entry ^a	Pd ⁰ comlex (μmol)	Ligand (L) and/or additive (μmol)	Pd ⁰ :L (mol ratio)	Solvent	Temp. (°C)	Time (min)	Yield of 2 (%) ^a
1	Pd{P(C ₆ H ₅) ₃ } ₄ (10)	—	—	DMSO	40	30	0
2	Pd ₂ (dba) ₃ (5)	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃ (20)	1:2	DME	40	30	76
3	Pd ₂ (dba) ₃ (5)	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃ (20)	1:2	DME	80	5	41
4	Pd ₂ (dba) ₃ (5)	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃ (20)	1:2	DMF	80	5	63
5	Pd ₂ (dba) ₃ (5)	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃ (20), CuI (20)	1:2	DMF	60	5	3
6	Pd ₂ (dba) ₃ (5)	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃ (20), CuCl (20), K ₂ CO ₃ (20)	1:2	DMF	60	5	91

^aReaction was carried out with CH₃I (10 μmol), stannane **1** (400 μmol), and Pd⁰ (10 μmol). ^bYield was determiend by GLC analysis based on CH₃I consumption. dba: dibenzylideneacetone; DMSO: dimethyl sulfoxide; DME: 1,2-dimethoxyethane; DMF: *N,N*-dimethylformamide.

Table 1. Rapid cross-coupling of methyl iodide and phenyltributylstannane (**1**).

groups and phenyl groups on the tin atom (Madsen et al., 2003). It was assumed from these results that the reaction of [¹¹C]CH₃I and phenyltrimethylstannane under PET radiolabeling conditions would produce the undesired radioactive and volatile [¹¹C]ethane. As described later (see the section 8.2), these phenomena were observed during the palladium-mediated reaction of 1-(2'-Deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-(trimethylstannyl)uracil to synthesize 1-(2'-Deoxy-2'-fluoro-β-D-arabinofuranosyl)-[methyl-¹¹C]thymidine (Samuelsson & Långström, 2003). Therefore, we concluded that the arenyltributylstannane, though less reactive, would be a much more suitable coupling partner than the arenyltrimethylstannane in view of the increased efficiency of the reaction, relatively low toxicity, and the safety of the radiation exposure.

The conditions of the reaction are significantly different from those of the originally reported Stille coupling reaction. Thus, the coupling of methyl iodide and phenyltributylstannane probably proceeds by the mechanism proposed in Equations 1-5 (Suzuki et al., 1997). In the first step, methyl iodide undergoes oxidative addition with



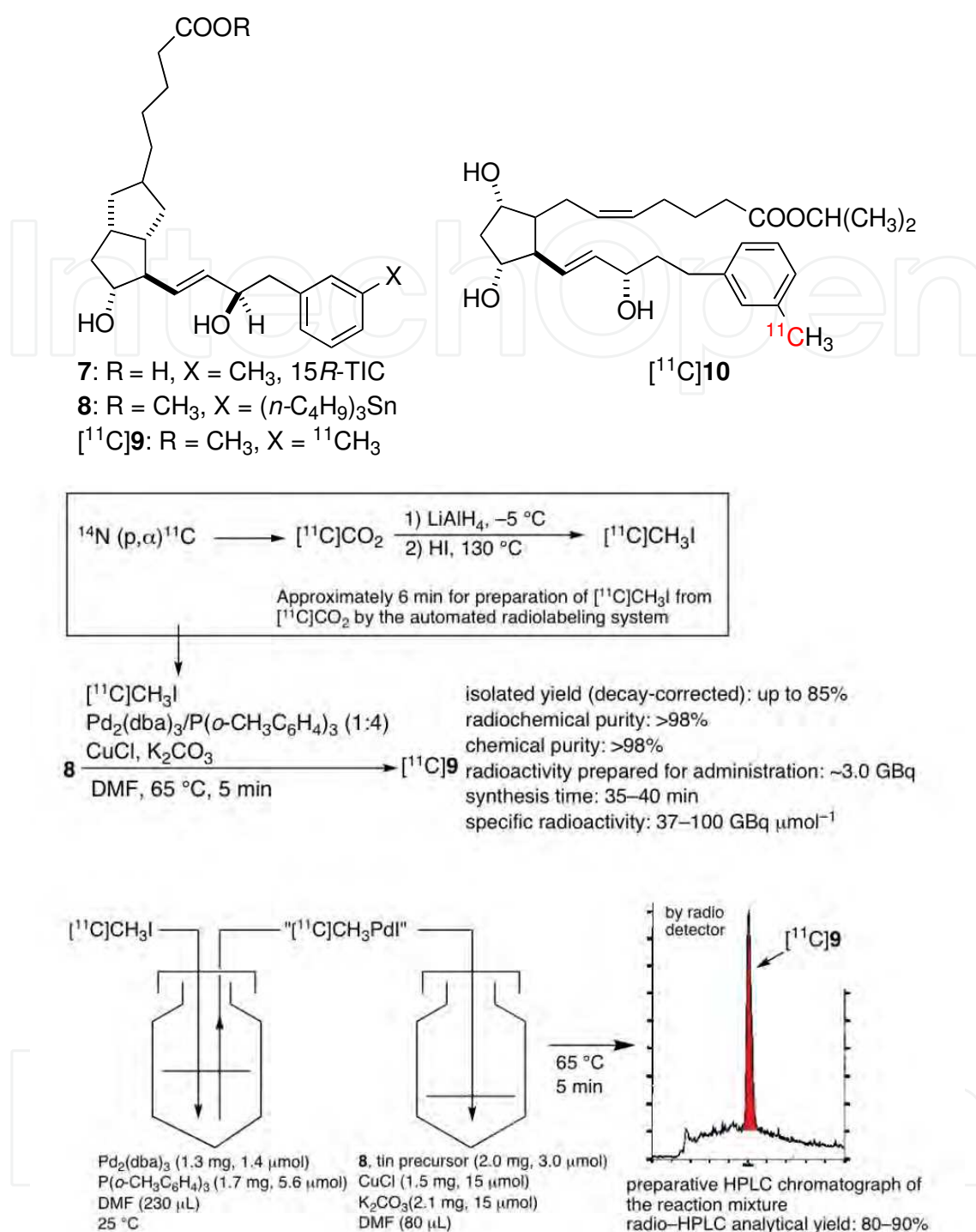
a Pd⁰ species to generate methyl-Pd^{II} iodide **3** (oxidative addition, Eq. (1)). The Pd^{II} complex **3** may directly react with the phenylstannane **1** to afford the (methyl)(phenyl)Pd^{II} complex **6** (substitution, Eq. (4)); however, the formation of the latter would be facilitated by the phenyl-copper compound **4** formed by the preceding Sn/Cu transmetalation (Eq. (2)). The effect of K₂CO₃ would be explained by the neutralization of (n-C₄H₉)₃SnX to form the stable bis(tributylstannyl)carbonate **5** (Eq. (3)). At the same time, K₂CO₃ serves to synergically work with a Cu^I salt to promote the Sn/Cu transmetalation (Eqs. (2) and (3)) (Hosoya et al., 2006). Finally, toluene is formed by reductive elimination from the Pd^{II} complex **6** (reductive elimination, Eq. (5)). The significant ligand effect of tri-*o*-tolylphosphine is attributed to its considerable bulkiness (cone angle = 194°, which is greater than that in tri-*tert*-butylphosphine (182°)) (Tolman, 1997), which facilitates the generation of the coordinatively unsaturated Pd⁰ and Pd^{II} intermediates (Louie & Hartwig, 1995). Transmetalation to give **6** and/or the reductive elimination of toluene requires the formation of the tricoordinate Pd^{II} complex. DMF may stabilize such Pd intermediates even at high temperatures. It should be noted that J. K. Stille *et al.* previously reported the reaction of methyl iodide and *p*-methoxyphenyltributylstannane in the presence of Pd{P(C₆H₅)₃}₄ at 50 °C for 24 h, in which the scrambling reaction between the methyl and the phenyl groups in the methyl iodide and triphenylphosphines, respectively, preferably occurred to give the desired *p*-methoxytoluene in only 3% together with 1-methoxy-4-phenylbenzene as the major

byproduct in 8% yield, suggesting that the promotion of the Stille reaction using methyl iodide as an sp^3 -carbon partner could be difficult (Morita et al., 1995) until our successful result was demonstrated (Suzuki et al., 1997).

7. Application for the synthesis of 15*R*-[^{11}C]TIC methyl ester as specific probe for prostaglandin receptor (IP_2) in the central nervous system

In a preceding study of prostaglandin (PG), we succeeded in developing (15*R*)-16-*m*-tolyl-17,18,19,20-tetranorisocarbacyclin (15*R*-TIC, **7**), which was selectively responsive to a novel prostacyclin receptor (IP_2) in the central nervous system (Suzuki et al., 1996; Suzuki et al., 2000b). The tolyl group in **7** was intended as a trigger component to create a PET molecular probe. Therefore, we planned to apply the rapid C-methylation conditions to the synthesis of a PET molecular probe, the 15*R*-[^{11}C]TIC methyl ester using [^{11}C]CH₃I, prepared from [^{11}C]CO₂ according to an established method (Fowler & Wolf, 1997), and the stannane **8** (Suzuki et al., 2000a). However, we found that the C-[^{11}C]methylation under radiolabeling conditions, even after using an excess amount of a Cu^I salt, lacked reproducibility for some unknown reasons. During the course to overcome this difficulty along with the actual PET-probe synthesis, we encountered some valuable information that led to a solution of the problem by using CuI instead of CuCl that severely retarded the methylation of the phenyltributylstannane (Table 1, Entry 5). In order to minimize this inhibitory effect of CuI, we changed the one-pot operation to a two-pot stepwise procedure during the actual PET-probe synthesis (Figure 3) (Suzuki et al., 2004). This procedure consists of independent syntheses of a methylpalladium complex and a phenyl copper complex at room temperature (25 °C), and then the mixing of these species in one portion at a higher temperature (65 °C, 5 min). As expected, the highly qualified PET probe, the 15*R*-TIC methyl ester ([^{11}C]**9**), was obtained by thus C-[^{11}C]methylation procedure from **8** in an 85% isolated yield (decay-corrected, based on the radioactivity of [^{11}C]CH₃I trapped in the Pd solution; it indicates the production efficiency) with a purity of greater than 98%, which was applicable for a human PET study with a sufficient radioactivity of 2–3 GBq and high reproducibility (Figure 3). The specific radioactivity was 37–100 GBq μmol^{-1} . The total synthesis time was 35–40 min.

After the ethical committee gave its official approval for a human PET study, the principal author, M. Suzuki, was nominated to be the first volunteer. Thus, the 15*R*-[^{11}C]TIC methyl ester ([^{11}C]**9**) was injected into his right arm and it passed through the blood-brain barrier. It was then hydrolyzed in the brain to a free carboxylic acid, which was eventually bound to the IP_2 receptor. PET images of horizontal slices indicated that a new receptor, IP_2 , was distributed throughout various structures in the human brain (Figure 4) (Suzuki et al., 2004). A PET study of the middle cerebral artery occlusion using a monkey model demonstrated that 15*R*-TIC revealed a potent neuroprotective effect against focal cerebral ischemia as judged by the [^{15}O]O₂ consumption and the uptake of [^{18}F]FDG (Cui et al., 2006). Recently, rat PET studies using the 15*R*-[^{11}C]TIC methyl ester ([^{11}C]**9**) showed that [^{11}C]**9** could be useful for the *in vivo* analyses of the mrp2-mediated hepatobiliary transport (Takashima et al., 2010). Furthermore, the PK/PD studies of [^{11}C]**9** in humans (submitted for publication) as well as a translational study of Alzheimer's disease patients to evaluate the progress of such neurodegenerative diseases are now in progress. A PET probe of the 17-(3-[^{11}C]methylphenyl)-18,19,20-trinor-prostaglandin $\text{F}_{2\alpha}$ isopropyl ester ([^{11}C]**10**) (Björkman et al., 2000) targeting the receptor of prostaglandin $\text{F}_{2\alpha}$ ($\text{PGF}_{2\alpha}$) was also synthesized using a procedure similar to [^{11}C]**9**.



[¹¹C]CH₃I, formed from [¹¹C]CO₂ according to the established method, was trapped in a solution of Pd₂(dba)₃ (1.3 mg, 1.4 μmol) and P(*o*-CH₃C₆H₄)₃ (1.7 mg, 5.6 μmol) in DMF (230 μL) at room temperature. The solution was transferred to a vial containing stannyl precursor **8** (2.0 mg, 3.0 μmol), CuCl (1.5 mg, 15 μmol), and K₂CO₃ (2.1 mg, 15 μmol) in DMF (80 μL), and the resulting mixture was heated at 65 °C for 5 min. Prior to the preparative HPLC, a solid phase extraction column was used to remove the salts and palladium residue from the reaction mixture. The desired product, 15*R*-[¹¹C]TIC methyl ester [¹¹C]**9**, after HPLC separation and intravenous formulation usually had a isolated radioactivity of approximately 2.5 GBq, sufficient for an *in vivo* human PET study.

Fig. 3. Synthesis of 15*R*-[¹¹C]TIC methyl ester ([¹¹C]**9**) under PET radiolabeling conditions.

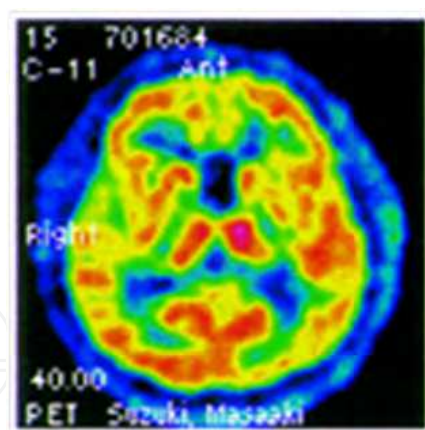
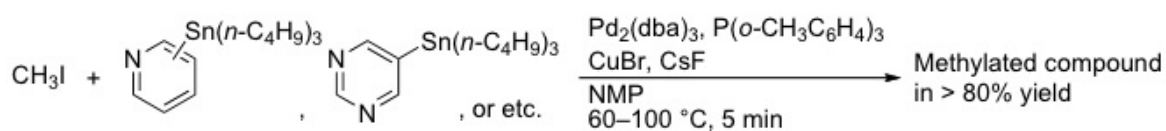


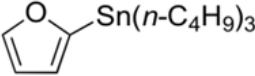
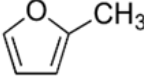
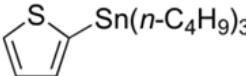
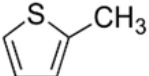
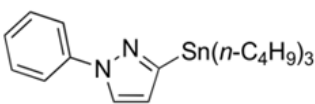
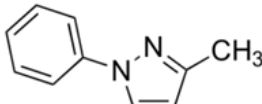
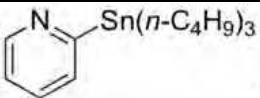
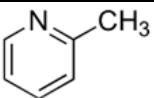
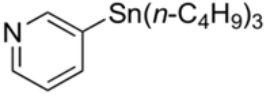
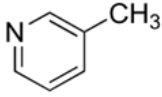
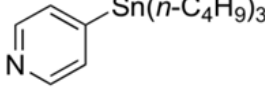
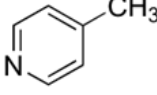
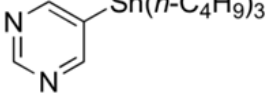
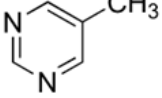
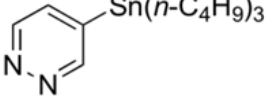
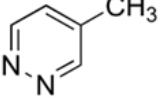
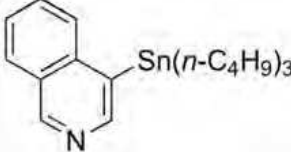
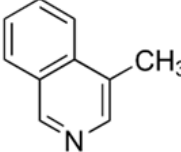
Fig. 4. PET imaging in human brain using $[^{11}\text{C}]9$.

8. Rapid C- $[^{11}\text{C}]$ methylation of heteroaromatic compounds: importance of using a large amount of bulky arenylphosphine, $\text{Cu}^{\text{I}}/\text{F}^-$ or $\text{Cu}^{\text{I}}/\text{K}_2\text{CO}_3$ synergic effect, and the selection of an amide solvent

8.1 Pd^0 -mediated rapid coupling of methyl iodide and heteroarenylstannanes applicable to 2- and 3- $[^{11}\text{C}]$ methylpyridines

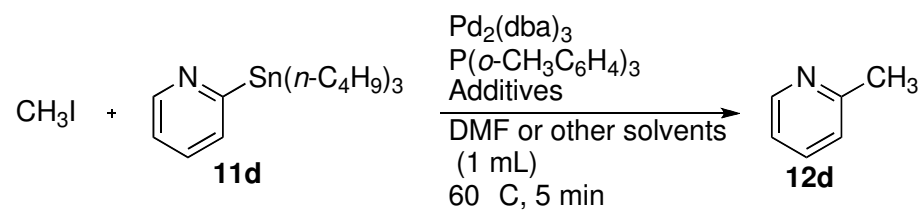
There is a strong demand for the incorporation of a short-lived ^{11}C -labeled methyl group into the heteroaromatic carbon frameworks, because such structures often appear in major drugs and their promising candidates. The Pd^0 -mediated rapid trapping of methyl iodide with an excess amount of a hetero-aromatic ring-substituted tributylstannane **11a-i** was done (Suzuki et al., 2009) by first using our previously developed $\text{CH}_3\text{I}/\mathbf{11a-i}/\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuCl}/\text{K}_2\text{CO}_3$ (1:40:0.5:2:2:2) combination system in DMF at 60 °C for 5 min (conditions A; Suzuki et al., 1997), but the reaction produced low yields of the various kinds of heteroaromatic compounds (Table 2, Entries 1–9). An increase in the phosphine ligand (conditions B) significantly improved the yield for the heteroarenylstannanes, **11b**, **11c**, and **11i**, but the conditions were still insufficient in terms of the range of adaptable heteroaromatic structures. Another CuBr/CsF combination system (conditions C) also provided a result similar to conditions B using an increased amount of the phosphine. Thus, pyridine and the related heteroaromatic compounds still remained as less reactive substrates. Consequently, the problem was overcome by replacing the DMF solvent with *N*-methyl-2-pyrrolidinone (NMP). It is of interest that such a solvent effect was not observed for the $\text{CuCl}/\text{K}_2\text{CO}_3$ combination system, but appeared for the CuBr/CsF reaction system (Table 3, Entry 2), giving 2-methylpyridine (2-picoline, **12d**) in 81% yield. The other solvents, except for the amide-type solvent and amine additives, were not effective (Table 3, Entries 4–11). Thus, the reaction in NMP at 60–100 °C for 5 min using the $\text{CH}_3\text{I}/\mathbf{11a-i}/\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuBr}/\text{CsF}$ (1:40:0.5:16:2:5) combination (conditions D) gave the methylated products **12a-i** in >80% yields (based on the reaction of CH_3I) for all of the heteroaromatic compounds listed in this study (Table 2, Entries 1–9). Thus the combined use of NMP and increased amount of the bulky arenylphosphine is important to efficiently promote the reaction. The conditions using a $\text{Pd}\{\text{P}(\text{tert-C}_4\text{H}_9)_3\}_2/\text{CsF}$ system in NMP reported by G. C. Fu *et al.* (Littke et al., 2002) were not effective by producing only a poor yield (21%, Table 3, Entry 2) as judged by the methylation of 2-pyridyltributylstannane (**11d**). The addition of CuBr to this system improved the yield to only a small extent (39%).



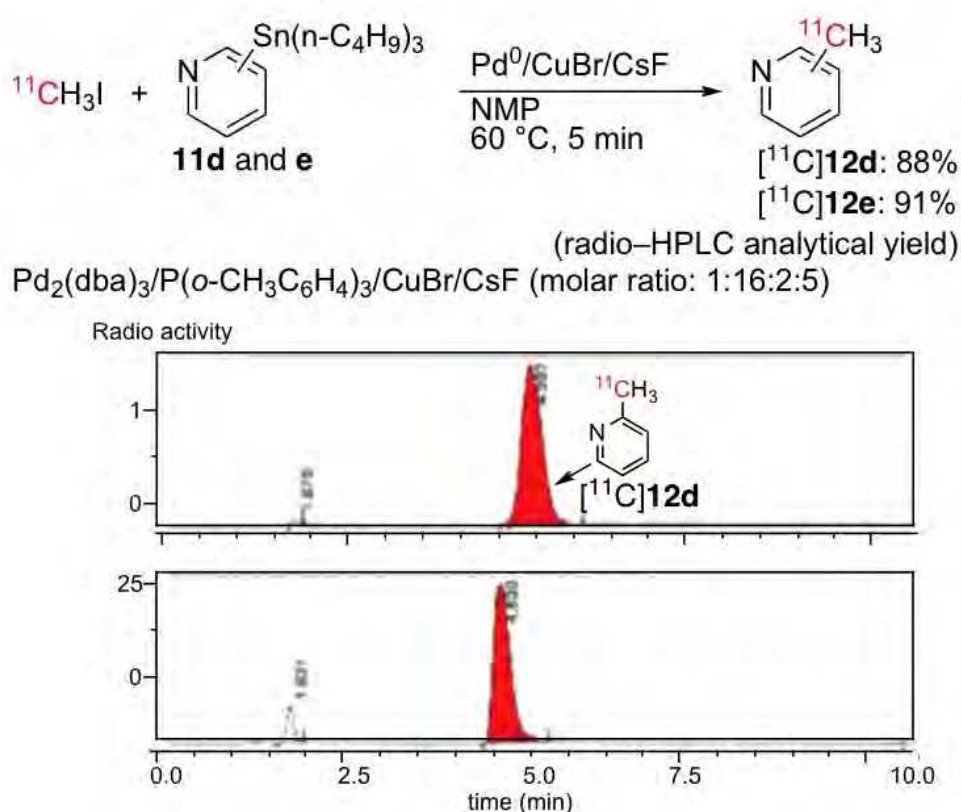
Entry ^a	Heteroarenyl stannane	Methylated product	Yield (%) ^b			
			A ^c	B ^c	C ^c	D ^c
1	 11a	 12a	28	75	73	80
2	 11b	 12b	57	87	91	94
3	 11c	 12c	52	88	90	94
4	 11d	 12d	16 (14) ^d	67	63	81
5	 11e	 12e	25 (53) ^e	61	66	80
6	 11f	 12f	79	60	68	87
7	 11g	 12g	3	50	48	62 (87) ^f
8	 11h	 12h	25	72	70	90
9	 11i	 12i	12	83	75	83

^aReaction was carried out with CH₃I (10 μmol), stannane **11** (400 μmol), and Pd⁰ (10 μmol). ^bThe products were identified by GLC analyses and comparison with authentic samples. Yields were determined by GLC based on CH₃I consumption using *n*-nonane and *n*-heptane as internal standards, and are the average of 2 or 3 runs. ^cReaction conditions (molar ratio): A: CH₃I/**11**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ (1:40:0.5:2:2:2) in DMF at 60 °C for 5 min; B: CH₃I/**11**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ (1:40:0.5:16:2:5) in DMF at 60 °C for 5 min; C: CH₃I/**11**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuBr/CsF (1:40:0.5:16:2:5) in DMF at 60 °C for 5 min; D: CH₃I/**11**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuBr/CsF (1:40:0.5:16:2:5) in NMP at 60 °C for 5 min. ^dCH₃I/**11d**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃ (1:40:0.5:2) in DMF at 120 °C for 5 min (stepwise procedure) (Iida et al, 2004). ^eCH₃I/**11e**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ (1:40:0.5:2:2:2) in DMF at 80 °C for 3 min (Prabhakaran et al, 2005). ^fThe reaction was conducted at 100 °C.

Table 2. General rapid C-methylation on various neutral and basic heteroaromatic rings.



performed using Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuBr/CsF (1:16:2:5 in molar ratio) in NMP at 80 °C for 5 min and the deprotection of TFA proceeded using 2 M NaOH at 25–50 °C for 1 min, giving [¹¹C]H-1152 ([¹¹C]**13**) with 86 ± 4% (*n* = 3) radio-HPLC analytical yield. The isolated total radioactivity was 3.8 ± 1.2 GBq (*n* = 3) with the radiochemical yield of 63 ± 14% (*n* = 3) (decay-corrected, based on [¹¹C]CH₃I). Both chemical and radiochemical purities were >99%. The total synthesis time was 38 min. The specific radioactivity at the end of the formation was 97 ± 10 GBq μmol⁻¹ (*n* = 3). The use of [¹¹C]**13** for molecular imaging studies of cardiovascular diseases is now in progress.



Red carbon in the structure means a radionuclide.

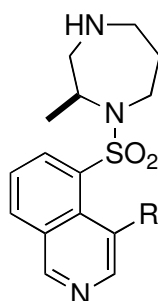
Fig. 5. Syntheses of 2- and 3-[¹¹C]methylpyridines ([¹¹C]**12d, e**).

8.2 Efficient syntheses of [methyl-¹¹C]thymidine and 4'-[methyl-¹¹C]thiothymidine

[¹⁸F]FLT has been developed as a more specific tumor imaging agent than [¹⁸F]FDG (Grierson et al., 1997, as cited in Bading & Shields, 2008). This pyrimidine analogue lacking a hydroxy group at C-3' is phosphorylated by thymidine kinase 1 (TK₁) and trapped in cancer cell. The TK₁ activity increases almost 10-fold during the DNA synthesis, and thus, the imaging reflects the cell proliferation differentiating tumor from inflammation (Lee et al., 2009). The first human imaging study was conducted with 1-(2'-deoxy-2'-[¹⁸F]fluoro-1-β-D-arabinofuranosyl)thymine ([¹⁸F]FMAU) (Sun et al., 2005, as cited in Bading & Shields, 2008), showing that the tumors in the brain, prostate, thorax, and bone could be clearly visualized. However, there is the primary limitation in the use of [¹¹C]- or [¹⁸F]FMAU which is being a relatively poor substrate for TK₁ and a relatively good substrate for TK₂, probably

accounting for its localization in the mitochondrion-rich human myocardium. On the other hand, 4'-thiothymine (**15b**), which resembles the biological properties of thymidine (**15a**) with a higher stability for the phosphorylase cleavage, underwent the $^{11}\text{CH}_3$ -labeling for the tumor imaging using a rat, exhibited a higher potential as an attractive PET probe than [^{18}F]FLT (Toyohara et al., 2008). Although the PET imaging studies using various kinds of ^{11}C - and ^{18}F -labeled thymidine analogues have been extensively continued, it is still difficult to synthesize the labeled compounds.

Thus, we applied the rapid C- ^{11}C methylation of a heteroarenylstannane (see the section 8.1) to the synthesis of the ^{11}C -labeled thymidine and its thio-analogue (Koyama et al., 2011). 1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-[methyl- ^{11}C]thymine ([^{11}C]FMAU) and 4'-[methyl- ^{11}C]thiothymine ([^{11}C]**15b**) have so far been labeled by ^{11}C using 5-trimethyl and/or tributylstannyl precursors via the Stille-type cross-coupling reaction with [^{11}C]methyl iodide (Samuelsson & Långström, 2003; Toyohara et al., 2008). However, as anticipated, the previously reported conditions had fewer effects on the syntheses of 5-tributylstannyl-2'-deoxyuridine (**14a**) and 4'-thio-2'-deoxyuridine (**14b**) using $\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3$ (1:4 in molar ratio) at 130 °C for 5 min in DMF, giving the desired products **15a** and **b** in only 32 and 30% yields, respectively (Table 4, Entries 1 and 4). Therefore, we tried to adapt the current reaction conditions, including the synergic systems developed in our laboratory, for such heteroaromatic compounds. First, the reaction using $\text{CH}_3\text{I}/\textbf{14a}/\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuCl}/\text{K}_2\text{CO}_3$ (1:25:1:32:2:5) at 80 °C gave thymidine (**15a**) in 85% yield (Entry 2). Whereas, $\text{CH}_3\text{I}/\textbf{14a}/\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuBr}/\text{CsF}$ (1:25:1:32:2:5) including another CuBr/CsF system promoted the reaction at a milder temperature (60 °C), giving **15a** in quantitative yield (Entry 3). The chemo-response of the thiothymidine-precursor **14b** was different from the thymidine system **14a**. The optimized conditions obtained for **14a** including the CuBr/CsF system gave 4'-thiothymidine (**15b**) in only 40% yield (Table 4, Entry 5). The reaction using 5-fold amounts of CuBr/CsF at 80 °C gave **15b** in a much higher yield (83%, Entry 6), but unexpectedly, the reaction was accompanied by a large amount of an undesired destannylated product. It was considered that the destannylated product **17** would have been produced by proton transfer to the transmetallated Cu intermediate **16** from **14b**_{Cu2} with the enhanced acidity by Cu^I coordination of a sulfur atom in the thiothymidine structure (Figure 6). As expected, such a destannylation was significantly suppressed by changing the medium to a much more basic system, in which the stannyl substrate **14b** would be changed to the deprotonated **18**. Thus, the conditions $\text{CH}_3\text{I}/\textbf{14b}/\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuCl}/\text{K}_2\text{CO}_3$ (1:25:1:32:2:5) at 80 °C gave **15b** in nearly quantitative yield (98%, Table 4, Entry 7).



13: R = CH₃, H-1152

[^{11}C]**13**: R = [^{11}C]CH₃, [^{11}C]H-1152

conducted under slightly improved conditions using a half-amount of phosphine (16 equiv) to give 45 and 42–59% isolated yields (decay-corrected, based on the radioactivity of $[^{11}\text{C}]\text{CH}_3\text{I}$ trapped in the Pd solution). The total synthesis time was 42 min in each case until the radiopharmaceutical formulation, exhibiting the isolated radioactivity of 3.7–3.8 GBq and the specific radioactivity of 89–200 GBq μmol^{-1} with both a chemical purity of $\geq 98\%$ and radiochemical purity of $\geq 99.5\%$ sufficient for both of animal and human PET studies (Koyama et al., 2011). We are currently in the process of applying these synthetic procedures to the PET probe syntheses according to the Guideline of Good Manufacturing Practice (GMP).

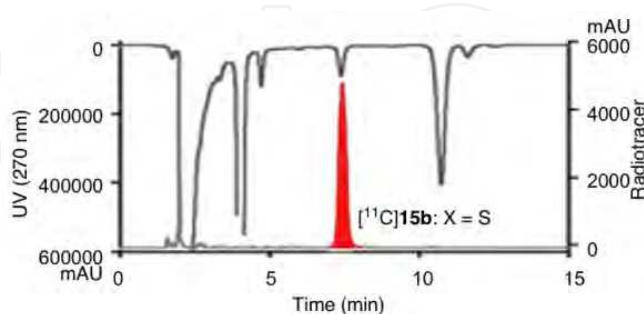
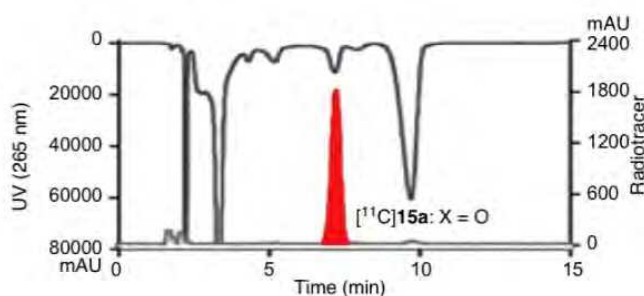
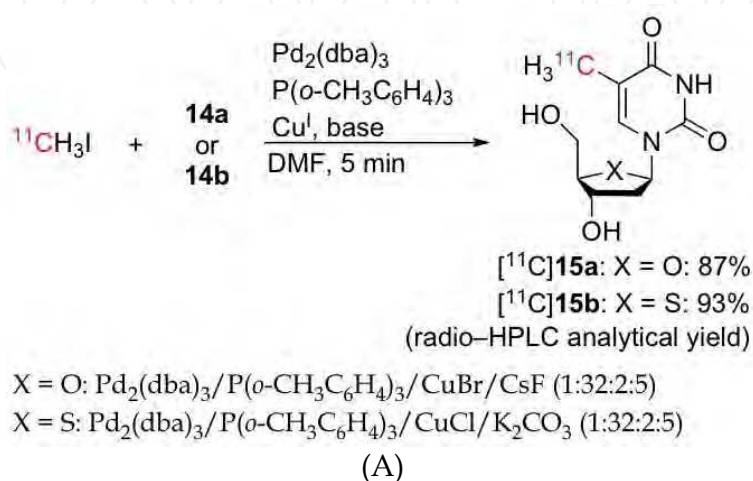
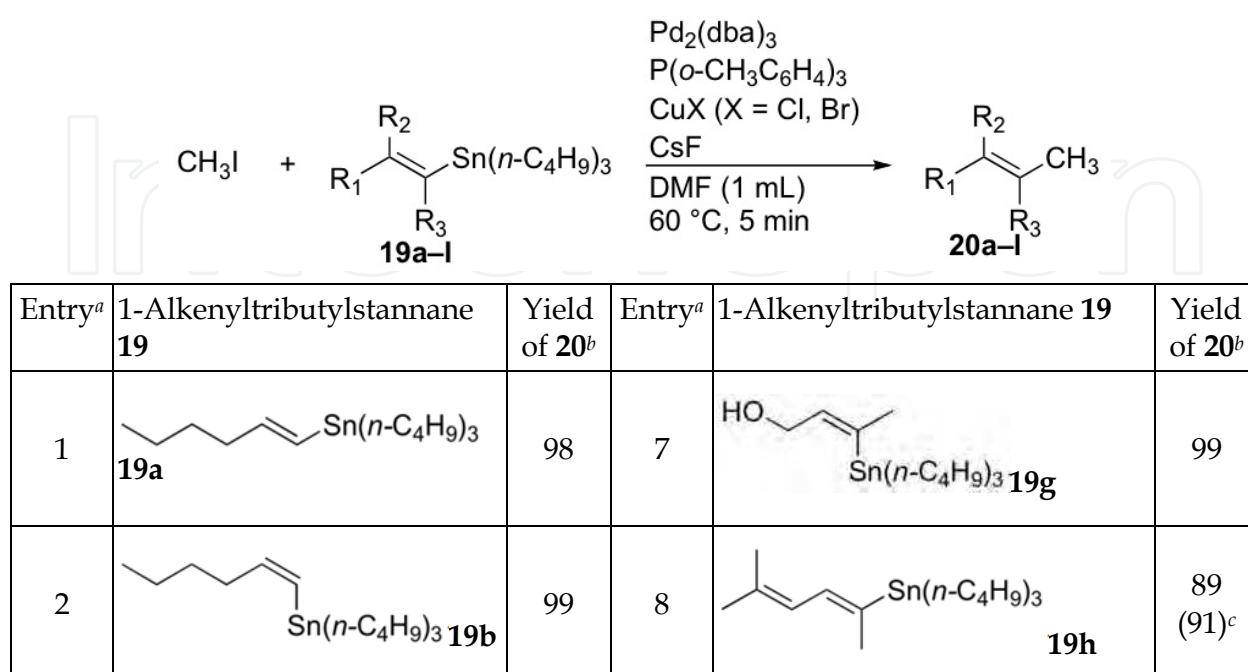
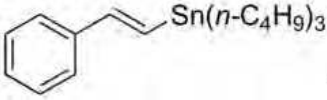
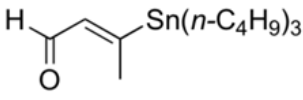
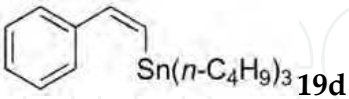
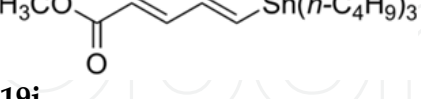
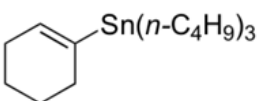

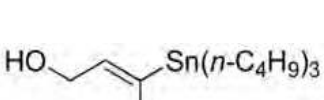
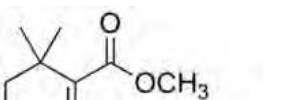


Fig. 7. Synthetic scheme of [methyl- ^{11}C]thymidine ($[^{11}\text{C}]\text{15a}$) and 4'-[methyl- ^{11}C]thiothymidine ($[^{11}\text{C}]\text{15b}$) for a PET study (A), and the HPLC chart for the analysis of $[^{11}\text{C}]\text{15a}$, **b** (B and C, respectively, radioactivity and UV vs. time). The peaks at the retention times of 7.6 and 7.4 min labeled B and C are $[^{11}\text{C}]\text{15a}$ and **b**, respectively. For the HPLC chart after the isolation of $[^{11}\text{C}]\text{15a}$ and **b**, see supporting information in the ref. Koyama et al., 2011.

9. Rapid C-[¹¹C]methylation of alkenes: Rapid C-methylation of alkenes (rapid coupling between sp²(alkenyl)–sp³ hybridized carbons)

The rapid C-[¹¹C]methylation of stannyl alkene structures provides methylalkene structures, which are frequently observed in various biologically significant compounds such as retinoids, vitamin K₂, squalene, and other isoprenoids, which are important for cancer chemotherapy. In the process of optimizing the rapid C-methylation conditions using twelve types of non-functional and functional 1-alkenyltributylstannanes as model compounds **19a–l** (él), we developed four types of reaction conditions, A–D, that proceeded in DMF at 60 °C for 5 min (Table 5) (Hosoya et al., 2006). Among these, reaction conditions B: CH₃I/**19a–l**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuX (X = Br or Cl)/K₂CO₃ (molar ratio, 1:40:0.5:4:2:5) worked well on various alkenyl stannanes rather than the previously developed conditions A: CH₃I/**19a–l**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ (molar ratio, 1:40:0.5:2:2:2). In addition, conditions D consisting of CH₃I/**19a–l**/Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuX (X = Br, Cl, or I)/CsF (molar ratio, 1:40:0.5:2:2:5) showed the best results from the viewpoint of general applicability, affording the corresponding methylated compounds **20a–l** in 90% or greater yields (for the consumption of methyl iodide) (Hosoya et al., 2006). The high efficiency of the reaction is presumably due to the synergic effect of the Cu^I salt and the fluoride anion to promote the Sn to Cu transmetallation and the formation of coordinatively unsaturated Pd complexes formed by a bulky arenylphosphine. Under conditions C using P(*tert*-C₄H₉)₂(CH₃), the yield was lower than that for conditions D using P(*o*-CH₃C₆H₄)₃, particularly against α,β-unsaturated carbonyl substrates (alkenyltributylstannanes **19i–l** in Table 5, Entries 9–12). In this context, the reactions using the Pd⁰ complex, {(π-allyl)PdCl}₂/3P(*tert*-C₄H₉)₂(CH₃), (CH₃)₄NF, 3-Å molecular sieves (Menzel & Fu, 2003), PdCl₂/2P(*tert*-C₄H₉)₃, CuI, and CsF (Mee et al., 2004) gave the desired compound in only the same 2% yields, as judged by the reaction of 1-cyclohexenyltributylstannane (**19e**). Furthermore, the stereo isomerization of a double bond under our conditions did not occur at all under these reaction conditions.

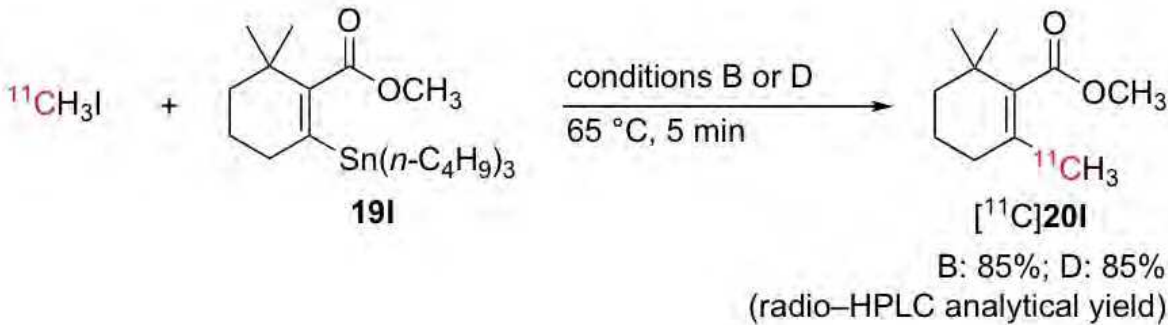


Entry ^a	1-Alkenyltributylstannane 19	Yield of 20 ^b	Entry ^a	1-Alkenyltributylstannane 19	Yield of 20 ^b
3	 19c	83 (88) ^c	9	 19i	85 (96) ^c
4	 19d	84 (89) ^c	10	 19j	86 (93) ^c
5	 19e	99	11	 19k	95
6	 19f	99	12 ^d	 19l	84 (91) ^c

^aReactions were carried out under conditions D using CH₃I (10 μmol), stannane **19a–l** (400 μmol), Pd₂(dba)₃ (5 μmol), P(*o*-CH₃C₆H₄)₃ (20 μmol), CuBr (20 μmol), and CsF (50 μmol). For the results under conditions A, B, and C, see ref. Hosoya et al., 2006. ^bThe products were identified by GLC analyses and comparison to authentic samples. The yields were determined by GLC based on CH₃I. ^cModified conditions: Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuBr/CsF (1:8:4:10 in molar ratio). ^dThe reaction using the conditions B: Pd₂(dba)₃/P(*o*-CH₃C₆H₄)₃/CuCl/K₂CO₃ (1:8:4:10 in molar ratio) gave **20l** in 71% yield.

Table 5. Rapid C-methylation on alkenyl structures.

The utility of the rapid methylation of an alkene was well demonstrated by the synthesis of a ¹¹C-labeled partial retinoid derivative [¹¹C]**20l** using reaction conditions B or D (X = Br), to produce in the high yield of 85% (radio-HPLC analytical yield) for both conditions (Figure 8) (Hosoya et al., 2006, see also section 11.4).



(A)

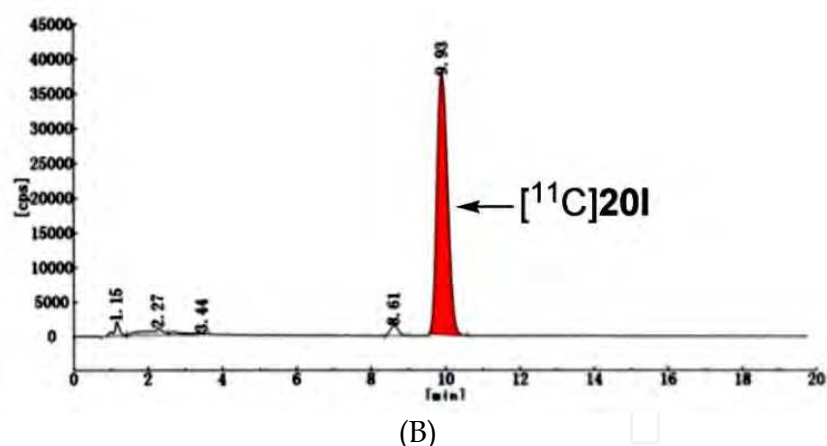


Fig. 8. Synthetic scheme of ¹¹C-labeled retinoid derivative [¹¹C]20I (A), and radio-HPLC chart in the analysis of the reaction mixture (B).

10. Rapid C-[¹¹C]methylation of alkynes

10.1 Rapid C-methylation of alkynes (rapid coupling between sp-sp³ hybridized carbons)

We set up a model reaction using methyl iodide and an excess amount of 1-hexynyltributylstannane (**21**) ($\text{CH}_3\text{I}/\mathbf{21} = 1:40$) with the reaction time fixed at 5 min (Figure 9) (Hosoya et al., 2004). The reaction with $\text{Pd}\{\text{P}(\text{C}_6\text{H}_5)_3\}_4$ gave the desired 2-heptyne (**22**) in a poor yield. The previous conditions, $\text{Pd}_2(\text{dba})_3/\text{P}(o\text{-CH}_3\text{C}_6\text{H}_4)_3/\text{CuCl}/\text{K}_2\text{CO}_3$, established for the sp²(arenyl)-sp³ rapid methylation, were also not applicable for this reaction. Based on the screenings of the phosphine ligand and additives, we found that the bulky and strong σ -electron-donating ligand, $\text{P}(\text{tert-C}_4\text{H}_9)_3$, facilitates the methylation (Hosoya et al., 2004). The combinations with fluoride ions, such as CsF or KF, were extremely efficient in promoting the reaction in a high yield. As a consequence, the reaction in the presence of bis(tri-*tert*-butylphosphine)palladium(0) ($\text{Pd}\{\text{P}(\text{tert-C}_4\text{H}_9)_3\}_2$) and KF in DMF at 60 °C for 5 min resulted in forming **22** in 95% yield (Hosoya et al., 2004).

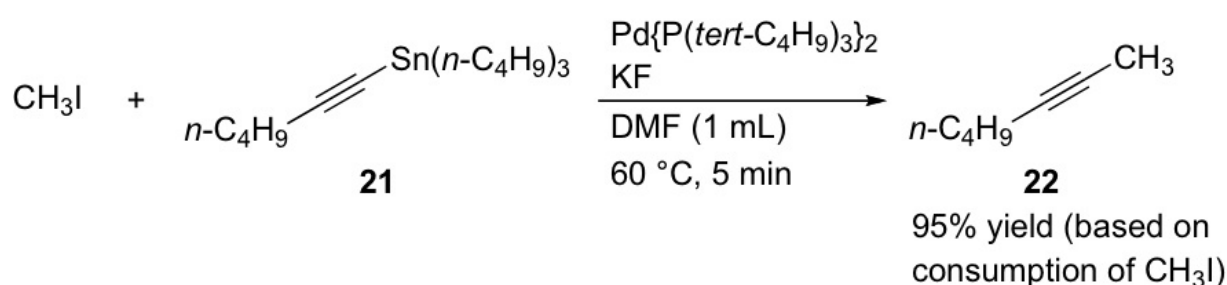


Fig. 9. Rapid coupling of methyl iodide with 1-hexynyltributylstannane (**21**).

The reaction was applicable to various kinds of functionalized alkynylstannanes including the stannyl precursors **23** and **24**, which are the substrates with steroid and deoxyribonucleoside frameworks, giving methylated compounds **25** and **26** in 87 and 74% yields, respectively (Hosoya et al., 2004).

10.2 Synthesis of [^{11}C]iloprost methyl ester

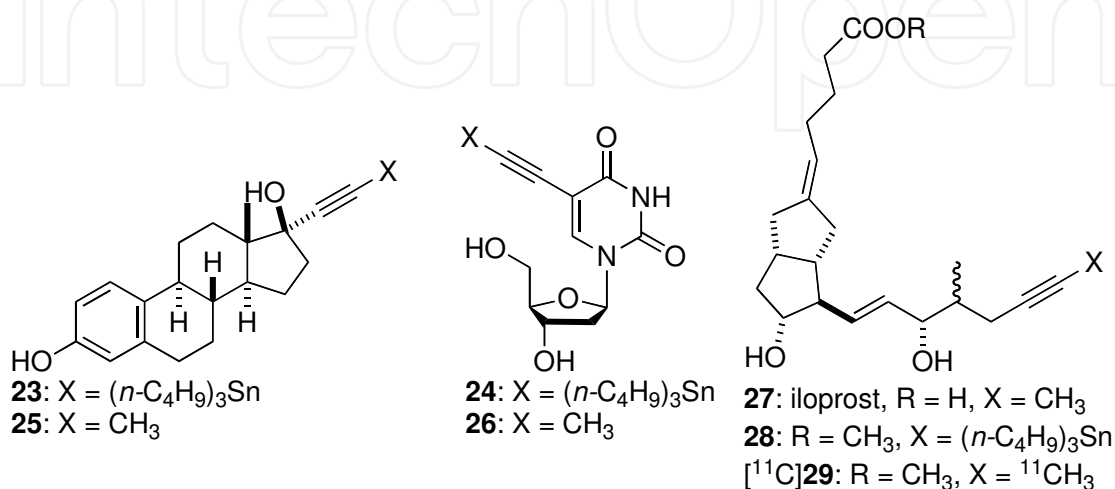
Iloprost (**27**) is a stable prostacyclin (PGI_2) analogue specific for the PGI_2 receptor, IP_1 , in peripheral systems used as a potential therapeutic agent (Skuballa & Vorbrüggen, 1981), having the structure of 1-propynyl on the ω -side chain. According to the method established in the previous section, the ^{11}C -labeled iloprost methyl ester ([^{11}C]**29**) was synthesized using [^{11}C] CH_3I and a stannyl precursor **28** in up to 72% radio-HPLC analytical yield. The optimization of the synthesis of [^{11}C]**29** is currently in progress.

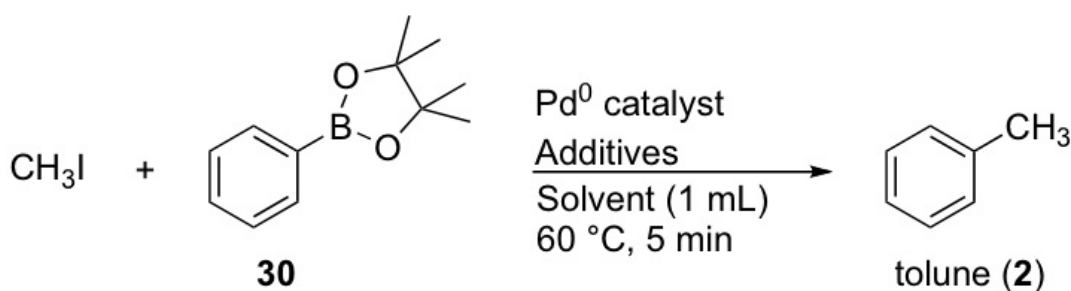
11. Rapid C-methylations using organoborons as trapping nucleophiles

In general, organoboron compounds are less toxic than organostannanes. Therefore, we intended to elaborate the rapid C-methylation based on the Suzuki-Miyaura coupling reaction (Miyaura & Suzuki, 1995) as a complementary method to the Stille-type rapid C-methylation. In this context, the Merck group reported the syntheses of [^{11}C]toluene derivatives by the reaction using [^{11}C]methyl iodide and an excess amount of arenylboron in the presence of $\text{PdCl}_2(\text{dppf})$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) and K_3PO_4 in DMF under microwave heating at high temperature (Hostetler et al., 2005). In contrast, we intended to establish a more efficient method by moderate thermal conditions based on the use of a Pd^0 complex without using microwaves in view of the careful treatment of a radiolabeled compound, and eventually, succeeded in developing very mild practical reaction conditions thus able to avoid the fear of an accidental radiation exposure (Doi et al., 2009).

11.1 Pd^0 -mediated rapid C-methylations by coupling reaction of methyl iodide and a large excess arenyl- or alkenyl boronic acid ester

By keeping an actual PET-probe synthesis in mind, we set up the model reaction using methyl iodide and an excess amount of phenylboronic acid pinacol ester (**30**) ($\text{CH}_3\text{I}/\text{30} = 1:40$) with the short reaction time fixed at 5 min (Doi et al., 2009). The results are summarized in Table 6. We first attempted the known conditions frequently used for a





Entry ^a	Pd ⁰ complex	Ligand (L)	Pd:L (mol ratio)	Additives ^b	Solvent	Yield of 2 (%) ^c
1	Pd{P(C ₆ H ₅) ₃ } ₄	—	—	K ₂ CO ₃	1,4-dioxane	39
2	PdCl ₂ {P(C ₆ H ₅) ₃ } ₂	—	—	K ₃ PO ₄	DME/H ₂ O (9:1)	24
3	PdCl ₂ (dppf) · CH ₂ Cl ₂	—	—	K ₃ PO ₄	DME/H ₂ O (9:1)	28
4	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	K ₂ CO ₃	DMF	91
5	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	K ₂ CO ₃	DMF/H ₂ O (9:1)	94
6	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	Cs ₂ CO ₃	DMF	92
7	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	K ₃ PO ₄	DMF	87
8	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	CuCl/K ₂ CO ₃	DMF	81
9	Pd ₂ (dba) ₃	P(<i>o</i> -CH ₃ C ₆ H ₄) ₃	1:2	KF	DMF	81

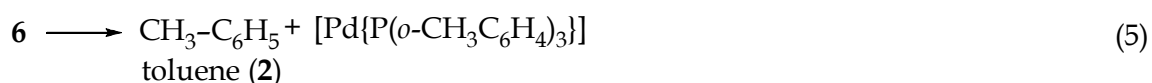
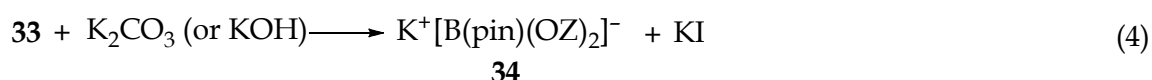
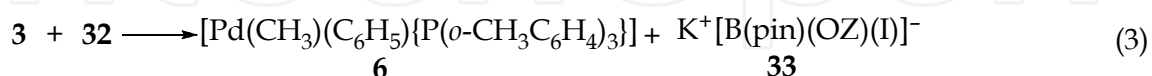
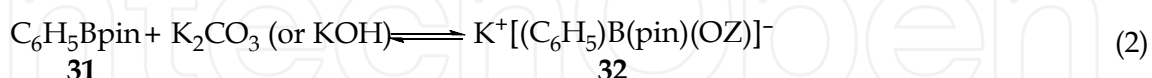
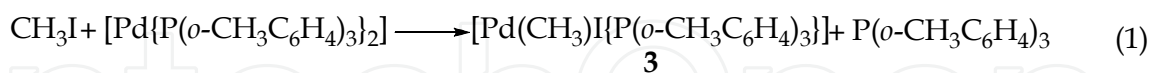
^aReaction was carried out with CH₃I (10 μmol) and **30** (400 μmol), Pd⁰ (10 μmol). ^b20 μmol of the additive was used. ^cThe yield was determined by GLC based on CH₃I. dppf: 1,1'-bis(diphenylphosphino)ferrocene.

Table 6. Rapid cross-coupling of methyl iodide with phenylboronic acid pinacol ester (**30**).

Suzuki–Miyaura coupling reaction (Miyaura & Suzuki, 1995), but such conditions did not give any satisfactory results (24–39% yields; Table 6, Entries 1–3). Therefore, we attempted the use of a Pd⁰ complex coordinated with the bulky phosphine in a non-volatile solvent with a high polarity inspired by our successful studies on the Pd⁰-mediated rapid C-[¹¹C]methylations using organostannanes (Suzuki et al., 1997; Hosoya et al., 2004; Hosoya et al., 2006; Suzuki et al., 2009). As expected, the reaction was dramatically accelerated by the

use of the tri-*o*-tolylphosphine complex in DMF in the presence of K_2CO_3 , K_2CO_3/H_2O , Cs_2CO_3 , or K_3PO_4 to give the desired toluene in 87–94% yields (Table 6, Entries 4–7).

The rapid coupling reaction of methyl iodide and **30** probably proceeded via several steps (Eqs. (1)–(5); Doi et al., 2009) as exemplified by the presence of K_2CO_3 or K_2CO_3/H_2O ;



Z = COOK or H

the oxidative addition of methyl iodide to the Pd^0 species to generate the methyl- Pd^{II} iodide **3** (Eq. (1)); the formation of a boronate complex **32** with a high polarity boron-carbon bond by the coordination of a base, such as KCO_3^- or OH^- , in a mixed system of K_2CO_3/H_2O (Eq. (2)); and the substitution of **3** with **32** to afford the $[Pd^{III}(\text{methyl})(\text{phenyl})]$ complex **6** and the unstable borate $K^+[B(\text{pin})(OZ)(I)]^-$ (**33**; Z = COOK or H) (Eq. (3)). The latter would be further converted to the more stable borate, $K^+[B(\text{pin})(OZ)_2]^-$ (**34**), and KI (Eq. (4)). Finally, the reductive elimination from **6** gives the desired toluene (**2**) (Eq. (5)).

The conditions were found to be versatile for various arenyl, alkenyl, and hetero-aromatic ring substituted borons (Doi et al., 2009). Thus, the reactions with of both arenylborons with both electron-donating and electron-withdrawing groups on their aromatic rings and hetero-aromatic, ring-substituted boron compounds smoothly proceeded under the conditions of $CH_3I/\text{boron}/Pd_2(dba)_3/P(o-CH_3C_6H_4)_3/K_2CO_3$ (1:40:0.5:2:2) in DMF at 60 °C for 5 min, gave the corresponding methylation products in 80–99% yields. The conditions were also applied to the rapid C-methylation of various types of alkenyl compounds, giving the corresponding methylalkenes in 86–99% yields. The *E* and *Z* stereoisomers gave the corresponding methylated products with the retention of stereochemistry, which confirmed that the reaction proceeded in a completely stereocontrolled manner.

Boronic acid and the more lipophilic esters showed the same reactivity as the pinacol boronate, making the labeled probe purification easier (Doi et al., 2009).

The actual $[^{11}C]$ methylation using the above-mentioned conditions (Table 6, Entry 4) was well demonstrated in the synthesis of the $[^{11}C]p$ -xylene (Figure 10). Thus, the reaction of the $[^{11}C]$ methyl iodide with pinacol tolylboronate **35** gave the $[^{11}C]p$ -xylene ($[^{11}C]\mathbf{36}$) in 96% radio-HPLC analytical yield. For the rapid C- $[^{11}C]$ methylation, K_2CO_3 was more effective than KF or CsF.

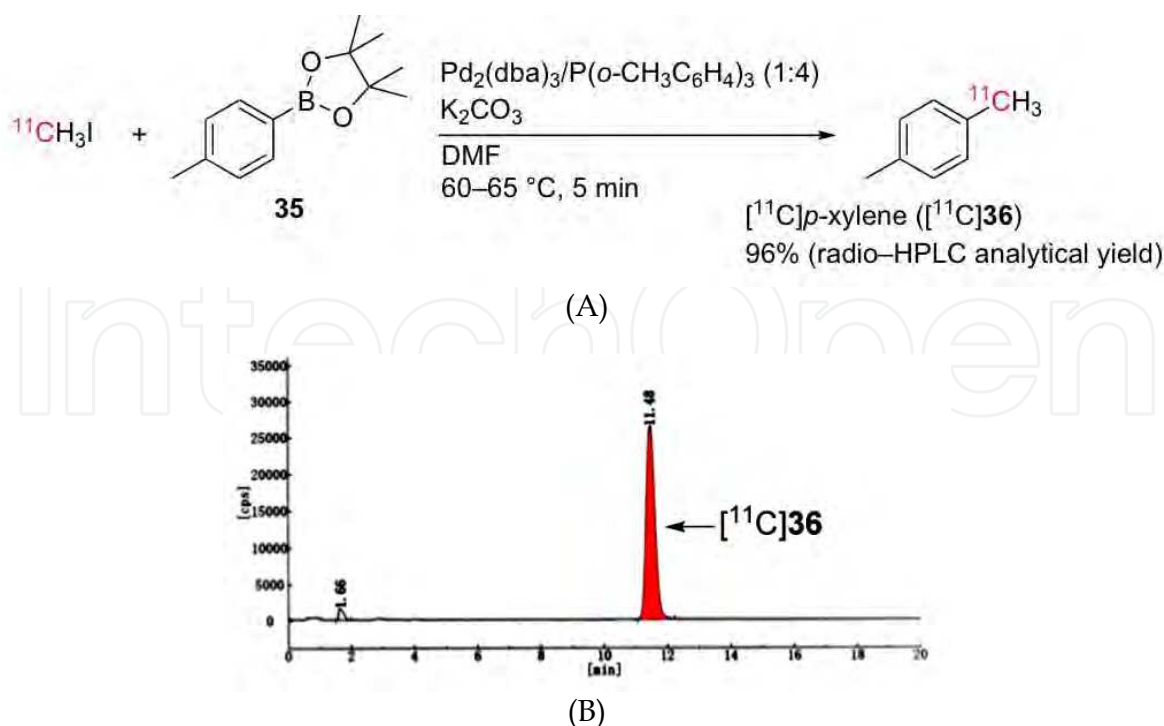


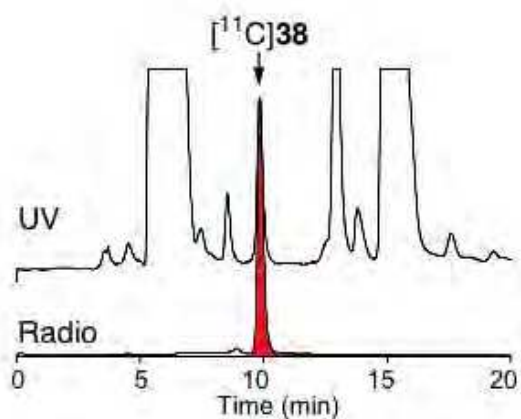
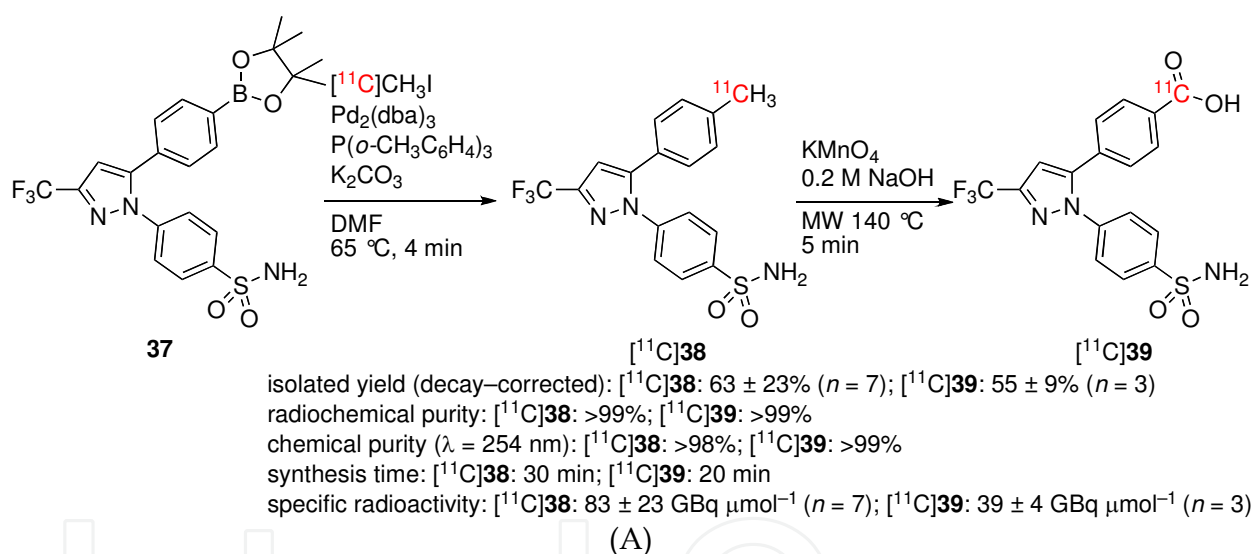
Fig. 10. Synthetic scheme of ¹¹C-labeled *p*-xylene ([¹¹C]36) by rapid C-[¹¹C]methylation using pinacol tolylboronate (35) (A), and radio-HPLC chart in the analysis of the reaction mixture (B).

11.2 Efficient synthesis of [¹¹C]celecoxib and its metabolites, [¹¹C]SC-62807

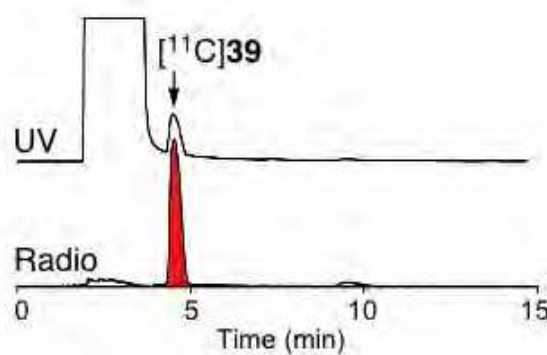
Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazole-1-yl]benzenesulfonamide, 38) is a selective cyclooxygenase (COX)-2 inhibitor that has analgesic and anti-inflammatory effects in patients with rheumatoid arthritis, but has no effect on the COX-1 activity at therapeutic plasma concentrations. In humans, celecoxib is extensively metabolized in the liver via sequential two-step oxidative pathways, initially to a hydroxymethyl metabolite (SC-60613), and upon subsequent further oxidation to a carboxylic acid metabolite (SC-62807, 39). The majority of celecoxib is excreted into the bile as SC-62807. In this context, Wu et al. reported that SC-62807 is a substrate of drug transporters, such as OATP1B1 and BCRP, which presumably mediate its hepatobiliary transport. Therefore, celecoxib or SC-62807 radiolabeled with a short-lived positron-emitting radionuclide could be a potential PET probe for evaluating the function of these drug transporters in hepatobiliary excretion (Takashima-Hirano et al., 2011).

The synthesis of [¹¹C]celecoxib ([¹¹C]38) was achieved in one-pot by reacting [¹¹C]methyl iodide with an excess amount of the corresponding pinacol borate precursor 37 using Pd₂(dba)₃/P(o-CH₃C₆H₄)₃/K₂CO₃ (1:4:9 in molar ratio) at 65 °C for 4 min in DMF (Figures 11A and B) according to the method established in a previous section in 55 ± 30% (*n* = 5) radio-HPLC analytical yield. The isolated radiochemical yield of [¹¹C]38 was 63 ± 23% (*n* = 7) (decay-corrected, based on [¹¹C]CH₃I) with a specific radioactivity of 83 ± 23 GBq μmol⁻¹ (*n* = 7) (Takashima-Hirano et al., 2011). The average synthesis time including formulation was 30 min with >99% and >98% radiochemical and chemical purities, respectively. [¹¹C]SC-62807 ([¹¹C]39) was also synthesized from the purified [¹¹C]38 by

further rapid oxidation in the presence of an excess amount of KMnO_4 under microwave irradiation (Figures 11A and C) with an $87 \pm 5\%$ ($n = 3$) radio-HPLC analytical yield. The isolated radiochemical yield of $[^{11}\text{C}]\mathbf{39}$ was $55 \pm 9\%$ ($n = 3$) (decay-corrected, based on $[^{11}\text{C}]\mathbf{38}$) and a specific radioactivity of $39 \pm 4 \text{ GBq } \mu\text{mol}^{-1}$ ($n = 3$). The average time of synthesis including formulation was 20 min and produced a $>99\%$ radiochemically pure product. Now, the synthesis of $[^{11}\text{C}]\mathbf{39}$ was conducted using an automated sequential radiolabeling system equipped with microwave irradiation from the boron precursor $\mathbf{37}$. There, nine operations from the $[^{11}\text{C}]\text{CH}_3\text{I}$ production to the formation of $[^{11}\text{C}]\mathbf{39}$ were smoothly done automatically. PET studies in rats and the metabolite analyses of $[^{11}\text{C}]\text{celecoxib}$ and $[^{11}\text{C}]\text{SC-62807}$ showed mostly different excretion processes between these compounds, and consequently, $[^{11}\text{C}]\text{SC-62807}$ was rapidly excreted via hepatobiliary excretion without further metabolism (Figure 11D), and therefore evaluated that it has a high potential as a PET probe suitable to investigate the hepatobiliary transport (Takashima-Hirano et al., 2011).



(B)



(C)

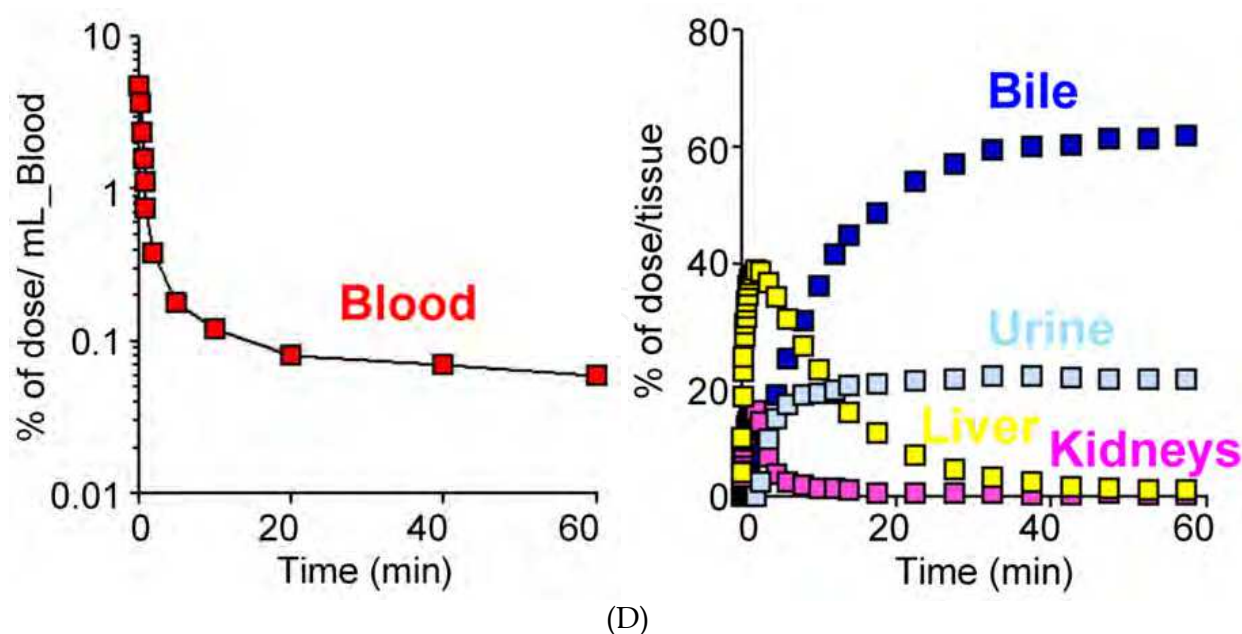


Fig. 11. Synthetic scheme of [¹¹C]celecoxib ([¹¹C]38) and [¹¹C]SC-62807 ([¹¹C]39) (A), the HPLC chart for the analysis of [¹¹C]38 (B) and [¹¹C]39 (C), and the time profiles of activity in the blood (red point), liver (yellow point), kidney (pink point), bile (blue point), and urinary bladder (light blue point) determined by PET imaging and blood sampling over 60-min period after administration of [¹¹C]SC-62807 ([¹¹C]39) to male Sprague-Dawley rats (D). The peak at a retention time of 9.6 min labeled B is [¹¹C]38 and the peak at a retention time of 4.4 min labeled C is [¹¹C]39. UV absorbance: 254 nm.

11.3 Efficient synthesis of ¹¹C-incorporated acromelic acid analogue

Acromelic acid A (Figure 12), a minor constituent isolated from *Clitocybe acromelalga*, induces allodynia in mice by intrathecal (i.t.) administration. If we can identify the receptor involved in the induction of allodynia, it may provide a trigger to develop novel analgesic drugs for use in the treatment of neuropathic pain. In this context, we have synthesized a novel ¹¹C-labeled PET probe [¹¹C]41, which was designed based on the (phenylthio)pyrrolidine derivative 41 that can competitively block the acromelic acid-induced allodynia (Kanazawa et al., 2011). A protocol in which the Pd⁰-mediated rapid methylation of the pinacol borate precursor 40 with [¹¹C]CH₃I using Pd₂(dba)₃, P(o-CH₃C₆H₄)₃, and K₂CO₃ in DMF and the following deprotection of the TFA-protected amino acid moiety and hydrolysis of methyl esters were successively performed in one-pot within 5 min (4 and 1 min each) was established for the synthesis of a PET probe [¹¹C]41 with > 99% of both radiochemical and chemical purities (Kanazawa et al., 2011). The isolated yield was 34–43% (decay-corrected, based on trapped [¹¹C]CH₃I). The obtained radioactivity of [¹¹C]41 after an injectable formulation under the normal conditions was 5.0–6.0 GBq and the specific radioactivity was 70–100 GBq μmol⁻¹ (Figure 12). The total synthesis time of [¹¹C]41 was within 30 min (Figure 12).

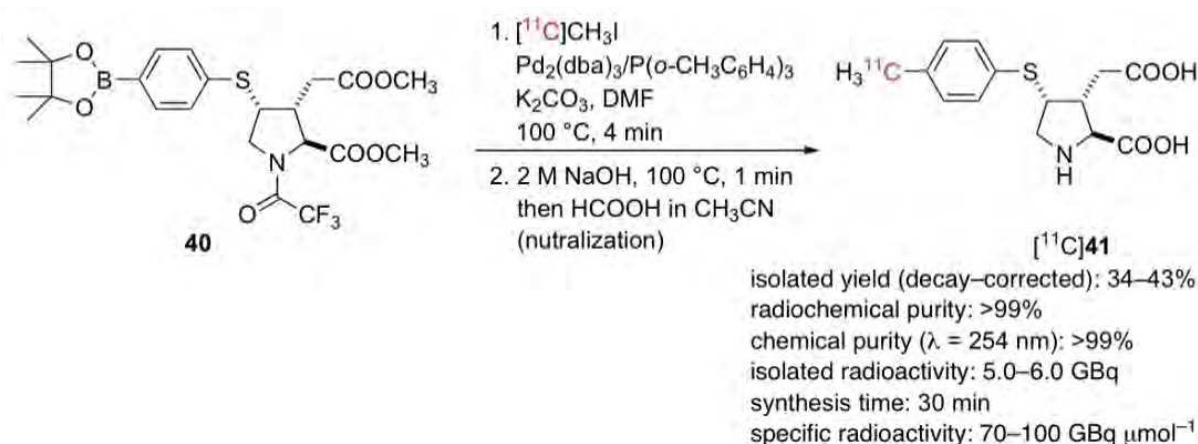


Fig. 12. Efficient synthesis of ^{11}C -labeled acromelic acid analogue $[^{11}\text{C}]\text{41}$.

11.4 Synthesis of $[^{11}\text{C}]\text{all-trans-retinoic acid}$

Retinoids are a class of chemical compounds including both naturally dietary vitamin A (retinol) metabolites and active synthetic analogs (Germain et al., 2006). Both experimental and clinical studies have revealed that retinoids regulate a wide variety of essential biological processes, such as vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, differentiation, apoptosis, and homeostasis, as well as their disorders. The all-*trans*-retinoic acid (ATRA), the most potent biologically active metabolite of retinol, has been used in the treatment of acute promyelocytic leukemia. In this context, we focused on the ^{11}C -labeling of ATRA. The Pd^0 -mediated rapid C- $[^{11}\text{C}]$ methylation using pinacol borate precursor **42** was successfully applied to the synthesis of $[^{11}\text{C}]\text{ATRA}$ ($[^{11}\text{C}]\text{43}$) (Suzuki et al., 2011b). The labeling reaction was conducted using $[^{11}\text{C}]\text{CH}_3\text{I}$ in the presence of $\text{Pd}_2(\text{dba})_3$, $\text{P}(\text{o}-\text{CH}_3\text{C}_6\text{H}_4)_3$, and Na ascorbate (1:4:9) in DMF- H_2O at 65°C for 4 min followed by basic hydrolysis of the methyl (at 65°C) and ethyl ester (at 100°C) for 2 min, to afford the desired $[^{11}\text{C}]\text{43}$ in 36% radio-HPLC analytical yield (Figure 13). The isolated radioactivity was 1.5 GBq with >99% and 97% radiochemical and chemical purities, respectively. The isolated radiochemical yield was 25% (decay-corrected, based on $[^{11}\text{C}]\text{CH}_3\text{I}$). Total synthesis time

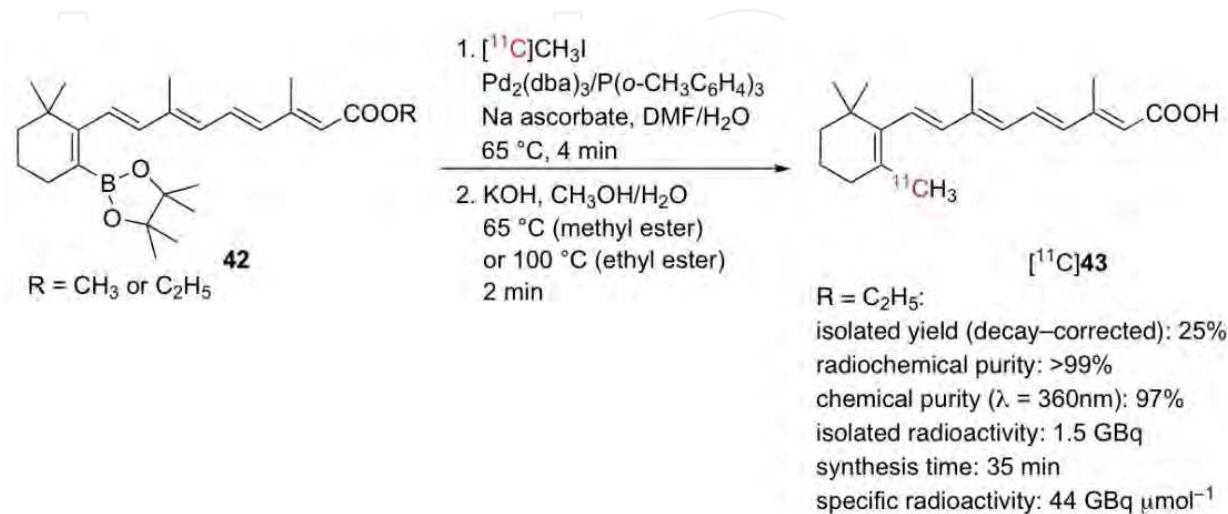


Fig. 13. Synthesis of ^{11}C -labeled all-*trans*-retinoic acid ($[^{11}\text{C}]\text{ATRA}$, $[^{11}\text{C}]\text{43}$).

including HPLC purification and formulation was 35 min. The decomposition of the product has not been observed at 90 min after the end of the synthesis in the presence of sodium ascorbate as judged by the conservation of radiochemical purity >99%.

12. Rapid C-[¹¹C]methylation of alkanes

12.1 Rapid C-[¹¹C]methylation (rapid coupling sp³-sp³ hybridized carbons)

The development of the fourth target of the rapid C-[¹¹C]methylations (rapid methylation of an alkane framework) (see Figure 2) by the coupling between sp³-sp³ carbons using ¹¹CH₃I and organoborons is also currently underway using a similar procedure in our group.

12.2 Another rapid coupling between sp³-sp³ hybridized carbons: Efficient synthesis of [¹¹C]NSAIDs and these esters

In order to perform the *in vivo* molecular imaging of cyclooxygenases (COXs), well-known as key enzymes in prostaglandin biosynthesis, we intended to develop a novel method to rapidly incorporate a ¹¹C radionuclide into various 2-arenylpropionic acids that have a common methylated structure, particularly abundant among nonsteroidal anti-inflammatory drugs (NSAIDs). Consequently, we elaborated the rapid ¹¹C-labeling using the reaction of [¹¹C]CH₃I and an enolate intermediate generated from the corresponding ester under basic conditions, followed by the one-pot hydrolysis to convert it into the ¹¹C-incorporated acid as [¹¹C]NSAID (Figure 14A) (Takashima-Hirano et al., 2010b). Methoxy 2-arenylpropionate is much less polar due to the increase in hydrophobicity of an introduced methyl group and the less hyperconjugation between the C-H σ bond of the benzylic position and C=O π*, which is also possible for the LUMO (π*) of a phenyl moiety, allowing easy separation of the desired ¹¹C-labeled product from the demethylated compound. This method is quite general and utilized for the syntheses of the following six PET probes of NSAIDs: [¹¹C]ibuprofen ([¹¹C]50), [¹¹C]naproxen ([¹¹C]51), [¹¹C]flurbiprofen ([¹¹C]52), [¹¹C]fenoprofen ([¹¹C]53), [¹¹C]ketoprofen ([¹¹C]54), [¹¹C]loxoprofen ([¹¹C]55), and their corresponding esters as racemates ([¹¹C]44-49), with sufficient radioactivity (1.7-5.5 GBq) for animal and human PET studies. The isolated radiochemical yields (decay-corrected) based on [¹¹C]CH₃I of [¹¹C]44-55 were 26-76%. Notably, we found that methyl esters were particularly useful as pro-radioprobes for the study of neuroinflammation in the brain. The microPET studies of rats with lipopolysaccharide (LPS)-induced brain inflammation clearly showed that the radioactivity of the PET probes, [¹¹C]ketoprofen methyl ester ([¹¹C]48) and [¹¹C]ketoprofen ([¹¹C]54) specifically accumulated in the inflamed region (Figure 14B), giving the first successful example of the *in vivo* molecular imaging of neuroinflammation by the noninvasive PET technology. A metabolite analysis in the rat brain revealed that the intravenously administrated methyl ester was initially taken up in the brain and then underwent hydrolysis to form a pharmacologically active form of the corresponding acids. Hence, we succeeded in the general ¹¹C-labeling of 2-arenylpropionic acids and their methyl esters as PET probes of NSAIDs to construct a potentially useful PET-probe library for the *in vivo* imaging of inflammation involved in the COX expression (Shukuri et al., 2011). The above racemic NSADs are readily separated by a chiral column to give an optically pure compound. Tetrabutylammonium fluoride (TBAF) was also effective to promote the rapid [¹¹C]methylation of the enolate in THF as found in our (Takashima-Hirano et al., 2010a) and other group (Kato et al., 2010). The [¹¹C]methylation of an analogous enolate has been

applied to the synthesis of ^{11}C -labeled α -aminoisobutyric acid as a PET probe for cancer imaging (Kato et al., 2011).

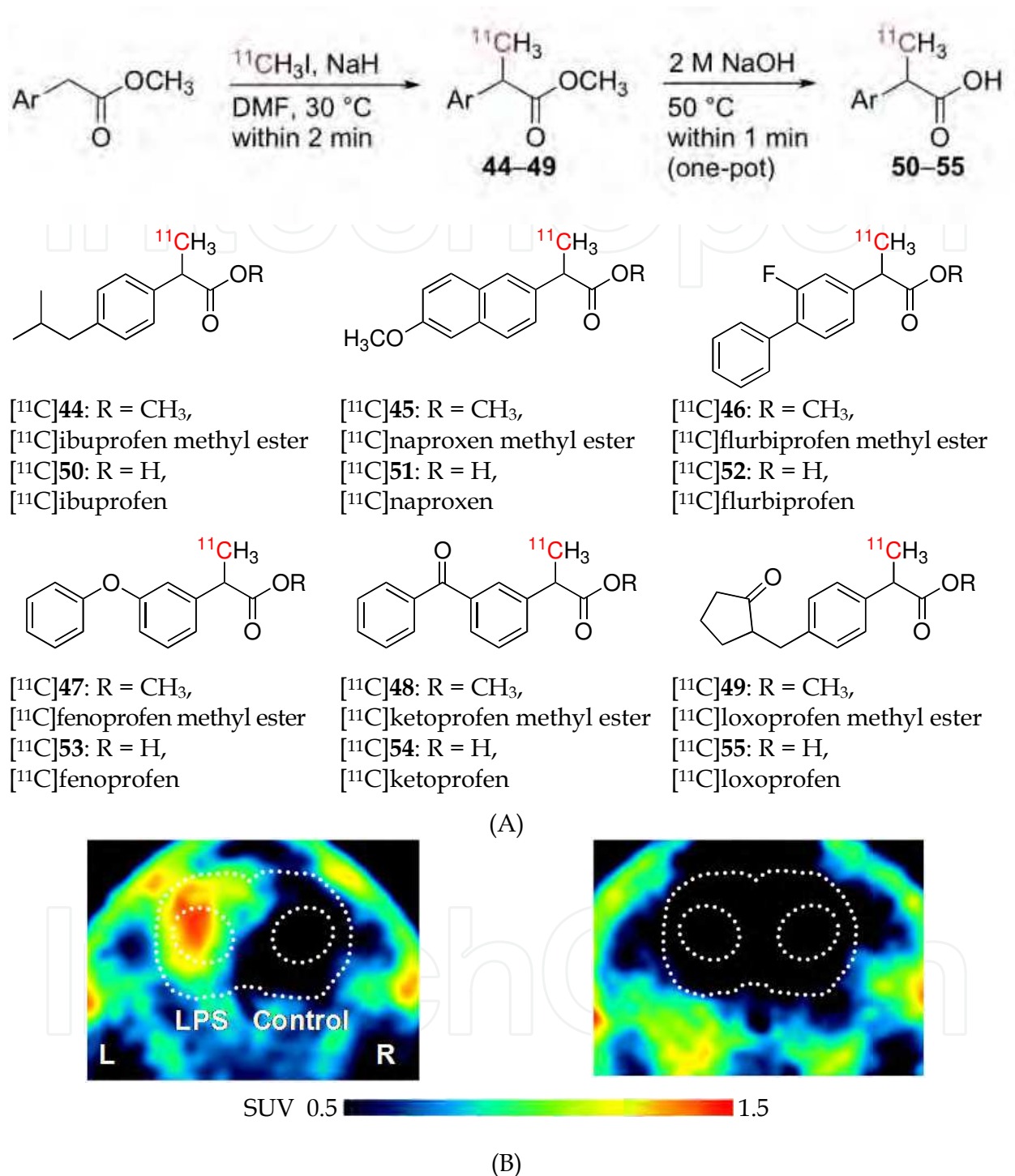


Fig. 14. Synthesis of ^{11}C -labeled 2-arylpropionoc acids and their esters (A), and PET images of ^{11}C ketopropfen methyl ester (^{11}C 48, left panel) and ^{11}C ketopropfen (^{11}C 54, right panel) in rat brain inflammation induced by lipopolysaccharide injection into the left striatum (B). Left PET image showed high accumulation in the area of inflammation, indicating that the methyl ester penetrated the blood-brain barrier and underwent hydrolysis in the brain to produce carboxylic acid as a pharmacologically active form, accumulating the inflammation area.

13. Opportunity for the rapid C-[¹⁸F]fluoromethylation (rapid ¹⁸F-incorporation into an organic framework through the carbon-carbon bond forming reaction)

13.1 Rapid C-fluoromethylations

The C-[¹¹C]methylation is associated with C-[¹⁸F]fluoromethylation by a similar coupling methodology using [¹⁸F]fluoromethyl bromide ([¹⁸F]FCH₂Br) and [¹⁸F]fluoromethyl iodide ([¹⁸F]FCH₂I) as the available ¹⁸F-labeling precursor for the synthesis of various types of PET tracers by N- or O-[¹⁸F]fluoromethylation (Zhang & Suzuki, 2007). There are many benefits based on the success of the ¹⁸F-labeling by rapid C-[¹⁸F]fluoromethylation: (1) capability of a relatively long *in vivo* study complementary to ¹¹C, (2) feasible delivery of ¹⁸F-labeled probes to distant PET centers and clinics, (3) insertion of multi-reactions after labeling, and (4) the use as a prosthetic group in click chemistry for the labeling of peptides, nucleic acids, sugars, etc. The application of rapid ¹⁸F-labeling to biologically significant organic compounds will be reported in due course.

Initially, we investigated the Pd⁰-mediated rapid cross-coupling using non-radioactive fluoromethyl iodide and phenyltributylstannane or a boron compound prior to the actual C-[¹⁸F]fluoromethylation (Doi et al., 2009). The conditions for rapid C-methylation using an organoboron in Table 6, Entry 4, were efficient for the synthesis of the fluoromethyl arene. Furthermore, a slightly improved condition using the 1:3 ratio of Pd⁰/P(*o*-CH₃C₆H₄)₃ was found to be the most effective for promoting the fluoromethylation with pinacol phenylboronate **30**, giving the desired benzyl fluoride in 57% yield (Doi et al., 2009). Thus, the conditions using FCH₂I for the synthesis of an [¹⁸F]fluoromethyl-labeled PET probe was established.

13.2 Rapid C-[¹⁸F]fluoromethylation

We set up the reaction using ca. 0.5 GBq of [¹⁸F]FCH₂X (X = Br or I) and a 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid methyl ester (**56**) (Figure 15). First, we found that the labeling reaction using [¹⁸F]FCH₂I and **56** for 5 min at 65 °C gave the desired *p*-([¹⁸F]fluoromethyl)benzoic acid methyl ester ([¹⁸F]**57**) using Pd₂(dba)₃/P(*o*-CH₃C₆H₅)₃ (1:6) and K₂CO₃ in DMF. The radio-HPLC analytical yield of [¹⁸F]**57** was 23 %, but a considerable amount of side products with a high polarity appeared, which might be the [¹⁸F]fluoride ion derived from the decomposition of [¹⁸F]FCH₂I. However, to the best of our knowledge, this result was the first evidence for the Pd⁰-mediated rapid C-[¹⁸F]fluoromethylation. After a broader investigation of not only labeling chemistry, but also the mechanical operations of our radiolabeling system, we concluded that the C-[¹⁸F]fluoromethylation with [¹⁸F]FCH₂Br will be more practical than that with [¹⁸F]FCH₂I. Actually, [¹⁸F]FCH₂I was essentially more reactive to the Pd⁰ complex, but [¹⁸F]FCH₂I was not stable and gradually decomposed in the light-exposed solution. For these reasons, we then focused on developing the C-[¹⁸F]fluoromethylation using [¹⁸F]FCH₂Br. The reaction was dramatically promoted under the conditions of 120 °C for 5 and 15 min in DMPU/H₂O (9:1) to give [¹⁸F]**57** in 48 and 64% yields, respectively. HPLC analyses showed that the reaction for 5 min resulted in the unreacted [¹⁸F]FCH₂Br remaining to a considerable extent, but the reaction for 15 min produced a remarkably sharp peak of [¹⁸F]**57** as the main product. The C-[¹⁸F]fluoromethylation would be completed within 15 min because the reaction for 30 min

did not produce a further increase in the yield. The 15-min reaction thus obtained matches well with the ^{18}F -incorporated PET-probe synthesis because of the longer half-life (110 min) of the ^{18}F radionuclide compared to ^{11}C (20.4 min) (Doi et al., 2010).

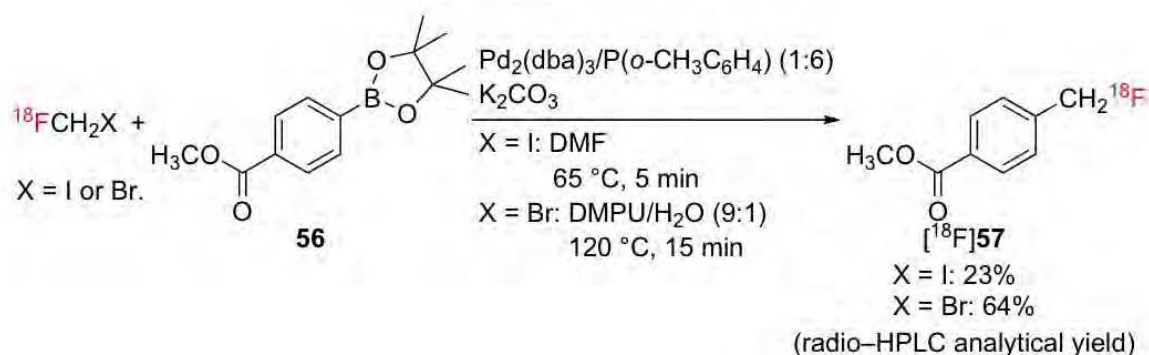


Fig. 15. Rapid C-[^{18}F]fluoromethylation using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid methyl ester (56) under PET radiolabeling conditions.

14. Conclusions

In this chapter, a ground-breaking methodology based on the use of cutting-edge chemistry was introduced for the synthesis of a short-lived ^{11}C -incorporated PET tracer. First, a general method for the rapid reaction of methyl iodide with an arenyltributylstannane (excess amount) (the Stille-type reaction) was established, producing a methylarene in the presence of the bulky tri-*o*-tolylphosphine-bound coordinatively unsaturated Pd^0 complex, a Cu^{I} salt, and K_2CO_3 based on a synergic effect to promote the reaction. The reaction was used for the synthesis of the 15R-[^{11}C]TIC methyl ester as an actual PET probe. The rapid C-methylation was expanded to other types of rapid methylations including the methylation on heteroaromatic frameworks by adding another Cu^{I} /CsF synergy and choosing the bulky trialkylphosphine for the alkene and alkyne, thus allowing the radio synthesis of various biologically and clinically important molecules. To meet the further demands of an efficient labeling method in PET, we established a rapid methylation using methyl iodide and an organoboron compound (Suzuki-Miyaura type coupling) as a complementary trapping substrate to an organostannane in the presence of Pd^0 , tri-*o*-tolylphosphine, and K_2CO_3 or $\text{K}_2\text{CO}_3/\text{H}_2\text{O}$ in high yield. The reaction conditions were also applied to the C-fluoromethylation, and, after slight modifications, we realized the incorporation of the rather longer half-lived ^{18}F radionuclide into organic frameworks (rapid C-[^{18}F]fluoromethylation). Our five original papers (Suzuki et al., 2009; Doi et al., 2009; Hosoya et al., 2006; Koyama et al., 2011; Hosoya et al., 2004, in order for ranking) were ranked Nos. 1–5 among the top 10 articles published in the same domain in BioMedLib (search engine for the 20 million articles of MEDLINE, April 2009–June 2011). Accordingly, a “Bible” on the syntheses of ^{11}C - and ^{18}F -labeled compounds has been continuously updated to provide valuable information required for a PET chemist.

As shown in Figure 16, RIKEN CMIS has utilized three types of remote-controlled synthesizers for ^{11}C - and ^{18}F -labeling, which originally developed with the focus on synthetic organic chemistry.

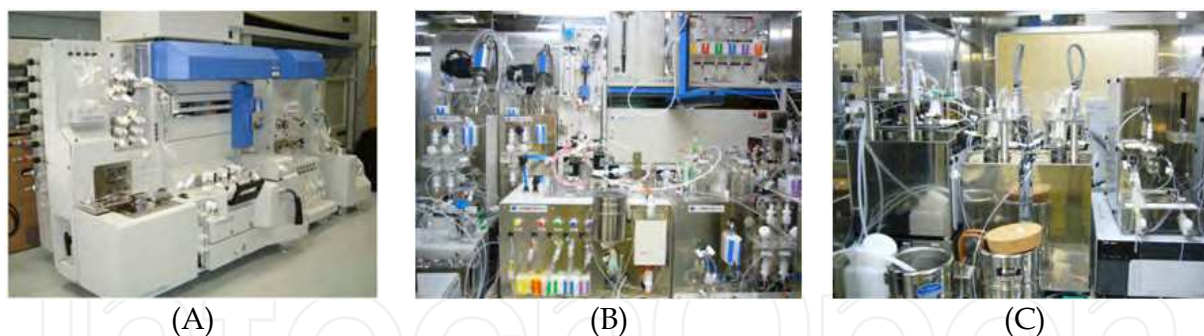


Fig. 16. Our original remote-controlled synthesizer for ¹¹C- and ¹⁸F-labeling; H19D: an early type system hybridized by septum-cannula and robot-arm method for the solution transfer (A), H20S: the improved model for step-wise labeling operations (B), and H20J: standard model focused on the simplicity and operational stability of the remote controlled synthetic procedures (C).

The next step is the application of the described synthetic procedure for the synthesis along with the Guidance of Good Manufacturing Practice (GMP) regulation. We also consider that the rapid reactions using a microfluidic system (microreactor) will be important in order to reduce the amount of a substrate (if scarce or very expensive) without lengthening the reaction time.

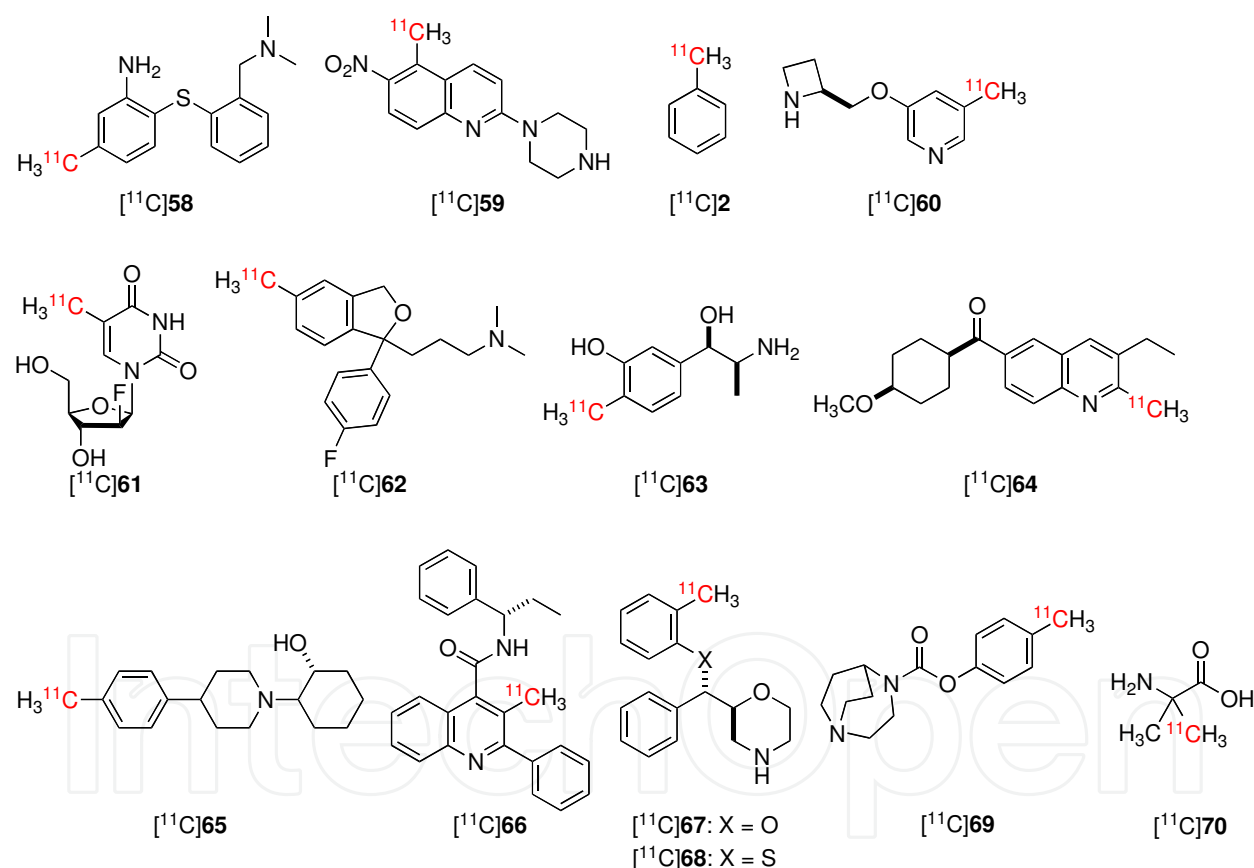
The methods thus described have widely been applied by other groups to synthesize ¹¹C-labeled PET probes, such as *N,N*-dimethyl-2-(2-amino-4-[¹¹C]methylphenylthio)benzylamine (MADAM, [¹¹C]58, Tarkiainen et al., 2001), the serotonin transporter inhibitor, 5-[¹¹C]methyl-6-nitroquipazine ([¹¹C]59, Sandell et al., 2002), [¹¹C]toluene ([¹¹C]2, Gerasimov et al., 2002), the central nicotinic acetylcholine inhibitor, 3-[(2S)-azetidin-2-ylmethoxy]-5-[¹¹C]methylpyridine ([¹¹C]60, Karimi & Långström, 2002; Iida et al., 2004), [¹¹C]FMAU ([¹¹C]61, Samuelsson & Långström, 2003), the serotonin reuptake inhibitor, citalopram analogue, [5-methyl-¹¹C]{3-[1-(4-fluorophenyl)-5-methyl-1,3-dihydroisobenzofuran-1-yl]-propyl}-dimethylamine ([¹¹C]62, Madsen et al., 2003), the adrenergic neurotransmitter, 4-[¹¹C]methylmetaraminol ([¹¹C]63, Langer et al., 2003), the metabotropic glutamate 1 antagonist, (3-ethyl-2-[¹¹C]methyl-6-quinolinyl)-(cis-4-methoxycyclohexyl)methanone ([¹¹C]64, Huang et al., 2005), the COX-2 selective inhibitor and prescription drug, [¹¹C]celecoxib ([¹¹C]38, Prabhakaran et al., 2005), (+)-*p*-[¹¹C]methylvesamicol for mapping sigma₁ receptors ([¹¹C]65, Ishiwata et al., 2006), the NK-3 receptor antagonist, [¹¹C]SB 222200 ([¹¹C]66, Bennacef et al., 2007), the reboxetin analogues ([¹¹C]67 and [¹¹C]68, Zeng et al., 2009), the derivative of the selective α7 nicotinic acetylcholine receptor partial agonist, 4-[¹¹C]methylphenyl 2,5-diazabicyclo[3.2.2]nonane-2-carboxylate ([¹¹C]CHIBA-1001, [¹¹C]69, Toyohara et al., 2009), [¹¹C]α-aminoisobutyric acid for cancer imaging ([¹¹C]70), etc.

15. Perspectives

Molecular imaging with PET is the only method for elucidating the whole-body pharmacokinetics of molecules in humans. This technique could be adapted for the efficient screening of drug candidates in humans during the early stage of the drug development process (phase 0 as a pre-clinical trial), and accelerating the path leading to clinical trials,

resulting in revolutionizing drug development. The chemistry covering a broad range of designs, syntheses, and labelings is expected to play a central role in this interdisciplinary scientific field.

The objective of the study was to develop a novel chemical methodology for *in vivo* molecular imaging adaptable from animals to humans. As already described, we developed various types of rapid C-[^{11}C]methylations and C-[^{18}F]fluoromethylations by the Pd^0 -mediated cross-coupling reactions between [^{11}C]methyl iodide or [^{18}F]fluoromethyl iodide (or bromide) and organostannanes or organoborons, respectively, for the synthesis of short-lived PET molecular probes. The synthesis method would also be applicable for the incorporation of other carbon isotope units, such as CH_2^{18}F , $^{13}\text{CH}_3$, $^{14}\text{CH}_3$, CD_3 , and CH_2^{19}F , allowing the application to accelerator mass spectrometry (AMS) and MRI. In particular, PET and AMS using ^{11}C and ^{14}C (use of 10^{-20} M), respectively, are two methods capable of promoting a human microdose study under political regulations (Europe, 2004; U.S., 2006; Japan, 2008).



We intend to further expand the rapid C-[^{11}C]methylations and [^{18}F]fluoromethylations and their applications in order to construct a library of ^{11}C - and ^{18}F -incorporated biologically significant molecules involved in various diseases important for medical treatment, such as cerebral diseases (Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), etc.), cardiovascular diseases (hypertention, stroke, glaucoma, etc.), cancer, diabetes, infection (human immunodeficiency virus (HIV), hepatitis C virus (HCV), influenza, prion, etc.), inflammation, neuropathic pain, and transporter dysfunction, as a frontier research to promote *in vivo* molecular science.

In an advanced medical field, tailor-made medicine, personalized medicine based on single nucleotide polymorphism, and evidence-based medicine based on PK/PD studies in humans are emphasized by the rapid progress of genome science. We believe that the advancement of “*in vivo* molecular science in humans” is strongly required in order to achieve the medical objectives. The progress of *in vivo* human molecular science will serve to overcome the “Death Valley” existing between a preclinical study and the clinical trials in the drug development process in order to revolutionize disease diagnosis and the drug discovery process.

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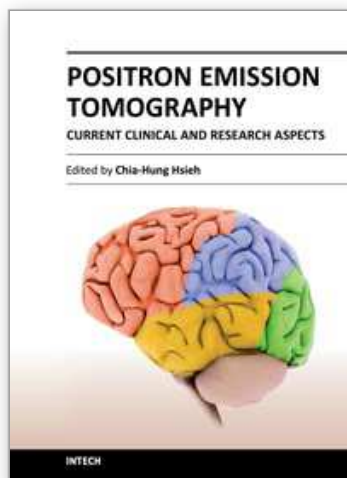
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