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Pd(0)-mediated [^{11}C]carbonylation of aryl and heteroaryl boronic acid pinacol esters with [^{11}C]carbon monoxide under ambient conditions and a facile process for the conversion of [*carbonyl*-^{11}C] esters to [*carbonyl*-^{11}C]amides

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ABSTRACT

A new method has been developed for the Pd(0)-mediated [^{11}C]carbonylation of aryl/heteroaryl boronic acid pinacol esters with [^{11}C]carbon monoxide in the presence of *p*-benzoquinone and triphenylphosphine in a mixture of *N*,*N*-dimethylformamide (DMF) and methanol (MeOH) or just MeOH under ambient pressure at 65 °C. This method was used to convert a variety of different aryl/heteroaryl boronates to the corresponding [*carbonyl*-^{11}C]esters with decay-corrected radiochemical yields in the range of 6–80%. Furthermore, some of these [*carbonyl*-^{11}C]esters were treated with sodium hydroxide or aqueous ammonium to give the corresponding [*carbonyl*-^{11}C]carboxylic acids and amides, respectively. This new method was also used to achieve the direct syntheses of [^{11}C]aspirin using water or tetramethylammonium hydroxide as the nucleophile instead of MeOH in DMF.

1. Introduction

Synthetic methods for incorporating a carbonyl moiety into an aryl or heteroaryl group are powerful processes for the construction of valuable synthetic intermediates and interesting pharmacological compounds. A wide variety of different metal-catalyzed carbonylation reactions have been reported in the literature to date, including the reactions of aryl and heteroaryl halides, triflates and boronates with carbon monoxide, which have been used extensively.[1–4] The application of these reactions to the synthesis of positron emission tomography (PET) probes has attracted considerable attention from researchers because of their tolerance towards a wide variety of functional groups, which has resulted in the synthesis of several useful diagnostic probes.[5,6] PET probes are generally synthesized using short-lived isotopes such as ^{11}C and ^{18}F ($t_{1/2}$=20.4 and 119 min, respectively), and the synthetic processes used to construct these probes are therefore required to progress much more rapidly than conventional reactions, especially for ^{11}C-labeled PET probes. However, a typical carbonylation reaction using CO generally requires excess amount of CO, and long reaction times, and high pressure (if necessary) and high temperature (if necessary) conditions, because CO is poorly soluble in most common solvents[7,8] and not very reactive.[9] Several interesting pieces of equipment and useful methods, however, have been developed to overcome these issues and allow for the successful synthesis of [*carbonyl*-^{11}C]compounds including high-pressure vessels,[10] recirculation systems,[11] microfluidic reactor systems,[12] chemical [^{11}C]O-fixation techniques,[13,14] microwave systems[15] and Xe-gas carrier systems.[16] Several Pd-mediated rapid [^{11}C]carbonylation reactions have recently been reported that can be conducted without the need for specialist equipment, except for the [^{11}C]O generation system. For example, Dahl et al.[17] reported the palladium-mediated [^{11}C]carbonylation of aryl halide and triflates under atmospheric conditions using xantphos as a supporting ligand to give [^{11}C]amides, [^{11}C]esters, [^{11}C]carboxylic acids, [^{11}C]aldehydes and [^{11}C]ketones in good to excellent yields. Vilar et al.[14] also succeeded in the synthesis of [^{11}C]amides from aryl halides under atmospheric conditions using a combination of a palladium(II) dimer and a hindered phosphine. In a separate study, Suzuki and co-workers[18] reported the palladium-mediated oxidative [^{11}C]carbonylation of aryl boronates under atmospheric conditions to produce [^{11}C]esters in low to moderate yields. As part of the same study, the authors also reported the successful synthesis of [^{11}C]tamibarotene (Scheme 1).

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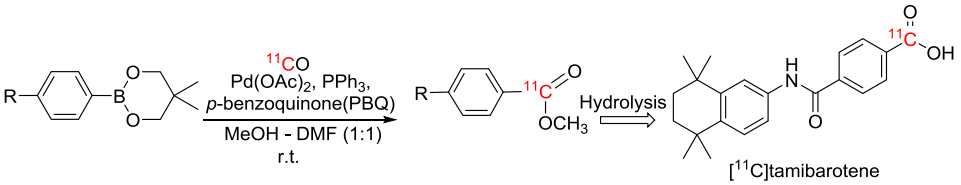
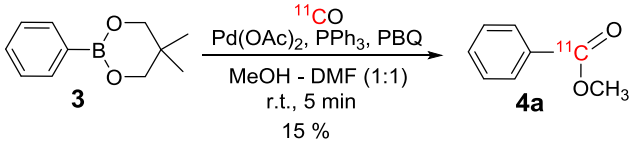
0040-4020/



Scheme 1. [^{11}C]Carbomethoxylation of aryl boronic acid neopentyl glycol esters.

Among these methods, the process reported by Suzuki appears to be suitable for the synthesis of [*carbonyl*-^{11}C] containing PET probes because it can be applied to boronate ester precursors, which are much more stable and less toxic than the corresponding aryl halides/triflates. Although Suzuki's method was used to complete the synthesis of [^{11}C]tamibarotene, it has subsequently only been applied to the synthesis of several *p*-substituted methyl benzoate derivatives (Scheme 1). With this in mind, we decided to study the scope and limitation of this [^{11}C]carbonylation reaction using a variety of aryl/heteroaryl boronates. We also investigated the application of this process to the synthesis of [^{11}C-*carbonyl*] aspirin and [^{11}C-*carbonyl*]salicylic acid, as well as several related derivatives.

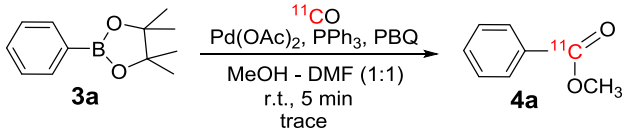
Aspirin is one of the oldest drugs, and is still used today to provide pain relief and alleviate the symptoms of a fever. Interestingly, however, this drug has recently attracted considerable attention for its role in preventing the risk of several types of cancer,[19] Alzheimer's disease (AD)[20] and heart attacks.[21] Sasaki et al.[22] reported the synthesis of [^{11}C]salicylic acid (**1**) and [^{11}C]aspirin (**2**) via the Grignard reaction of 2-bromomagnesiumanisole with [^{11}C]O_2 as part of their work towards investigating the role of hydroxyl radicals in the brains of mice (Scheme 2). The biodistribution results of this particular study revealed that compound **1** showed better uptake into the mouse brain than **2**. Furthermore, Brune et al.[23] reported the accumulation of [^{14}C]aspirin in the inflamed tissues of rats. These results prompted us to investigate the synthesis of [^{11}C]salicylic acid (**1**) and [^{11}C]aspirin (**2**), as well as their [^{11}C]derivatives, to develop a simpler and more efficient method for their production.



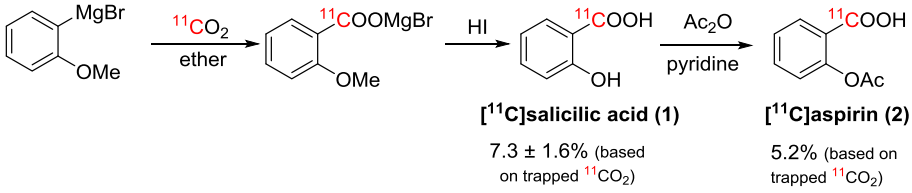
Scheme 3. [^{11}C]carbomethoxylation of boronic acid neopentyl ester (**3**).

radioactivity of the vessel was measured. The vessel was then held at ambient temperature for 5 min. As shown in Scheme 3, the reaction proceeded smoothly to give the desired product **4a** in 15% decay-corrected radiochemical yield (RCY).

The [^{11}C]carbomethoxylation reaction was also conducted using phenyl boronic acid pinacol ester (**3a**), as shown in Scheme 4. The same reaction was conducted using phenylboronic acid pinacol ester (**3a**) because more boronic acid pinacol esters are commercially available than the corresponding neopentyl esters. Unfortunately, however, this reaction only afforded a trace amount of **4a** (Scheme 4). Furthermore, it was not possible to increase the yield of this reaction by simply extending the reaction time (1%, after



Scheme 4. [^{11}C]carbomethoxylation of phenyl boronic acid pinacol ester (**3a**).



Scheme 2. Synthesis of [^{11}C]salicylic acid (**1**) and [^{11}C]aspirin (**2**).

2. Results and discussion

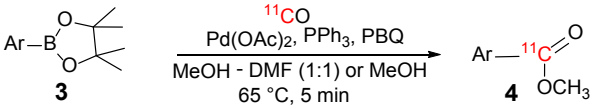
2.1. Synthesis of methyl-[^{11}C]esters

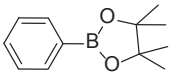
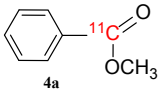
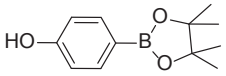
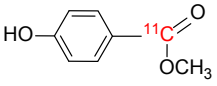
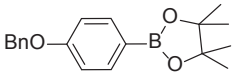
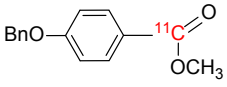
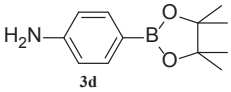
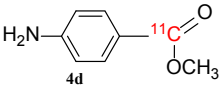
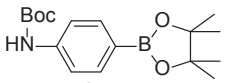
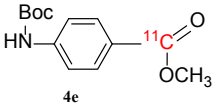
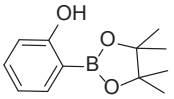
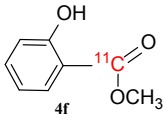
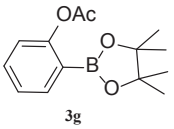
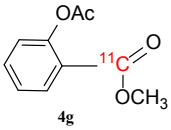
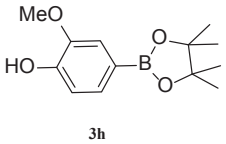
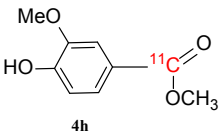
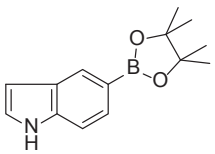
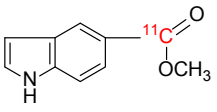
This [^{11}C]O generating system was initially applied to the synthesis of methyl [^{11}C]benzoate **4a** using a previously published method from the literature.[18] Briefly, the freshly generated [^{11}C]O gas was bubbled into a reaction vessel containing a mixture of palladium(II) acetate [Pd(OAc)$_2$], triphenylphosphine (PPh_3), *p*-benzoquinone (PBQ) and phenyl boronic acid neopentyl ester (**3**) in a 1:1 (v/v) mixture of *N*,*N*-dimethylformamide (DMF) and methanol (MeOH) at ambient temperature. After all of the freshly generated [^{11}C]O gas had passed through the reaction vessel, the 10 min). Although it has been reported that boronic acid neopentyl esters are much more reactive than the corresponding pinacol esters,[24] we did not expect such a disappointing result. To increase the reactivity of **3a**, it was therefore decided that the reaction would be conducted at an elevated temperature of 65 °C for 5 min.

Pleasingly, the heated reaction proceeded efficiently to give methyl [^{11}C]benzoate (**4a**) in 46±4% RCY (Table 1, entry 1). Furthermore, the [^{11}C]carbonylation of **3a** proceeded much more efficiently when it was conducted at the higher temperature of 65 °C using only MeOH as the solvent, with **3a** being isolated in a RCY of 65±2%. The higher temperature conditions were therefore applied to a variety of different aryl boronic acid pinacol esters using the two different solvent conditions (i.e., a 1:1 mixture of MeOH and

DMF [1:1] or MeOH). As shown in Table 1, all of the pinacol esters tested successfully underwent the [^{11}C]carbonylation reaction at the higher temperature to give the corresponding [^{11}C]esters. Notably, the presence of a *p*-hydroxyl group on the phenyl rings of substrates **3b** and **3h** was well tolerated under these conditions, with the corresponding [^{11}C]ester **4b** and **4h** being formed in good yields in both solvent systems (Table 1, entries 2 and 9). The benzyl protected substrate **3c** gave a slightly lower yield than **3b** (Table 1, entry 3). The presence of a hydroxyl group at the *ortho*-position of the phenyl ring of the substrate was also well tolerated, with the corresponding methyl [^{11}C]salicylate **4f** being formed in good yield in MeOH (Table 1, entry 6). Interestingly, the corresponding *O*-acetyl substrate **3g** decomposed under these reaction conditions to give the de-acetylated analog **4f** as the major product in good RCY in both solvent systems (Table 1, entry 7). The presence of a free amino group on the phenyl ring of the substrate had an adverse impact on the reaction, with the desired product being formed in a very low yield (Table 1, entry 4). However, Boc-protection of the

Table 1
[^{11}C]Carbomethoxylation of aryl boronic acid pinacol esters



Entry	Compound	Product	Solvent	Yield %[a]
1	 **3a**	 **4a**	MeOH—DMF MeOH	46±4 65±2
2	 **3b**	 **4b**	MeOH—DMF MeOH	68±19 80±13
3	 **3c**	 **4c**	MeOH—DMF MeOH	53±6 46±6
4	 **3d**	 **4d**	MeOH—DMF MeOH	12±2 6±2
5	 **3e**	 **4e**	MeOH—DMF MeOH	72±7 56±15
6	 **3f**	 **4f**	MeOH—DMF MeOH	19±5 64±4
7	 **3g**	 **4g**	MeOH—DMF MeOH	21±4 (**4g**), 60±5 (**4f**) 20±14 (**4g**), 73±10 (**4f**)
8	 **3h**	 **4h**	MeOH—DMF MeOH	53±15 80±10
9	 **3i**	 **4i**	MeOH—DMF MeOH	60±9 16±6

[a] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.

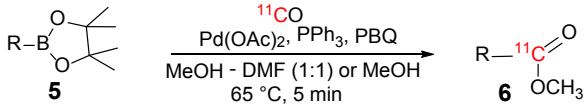
amino group led to a much higher yield of the [^{11}C]ester (Table 1, entry 5). The presence of a nitrogen atom was also well tolerated in substrate **3i** bearing an indole ring, where the corresponding [^{11}C] ester **4i** was produced in good RCY using a mixture of MeOH and DMF as the solvent (Table 1, entry 10).

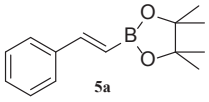
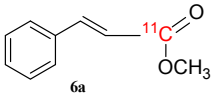
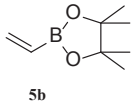
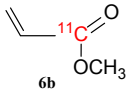
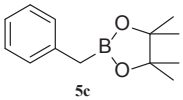
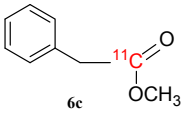
This result prompted us to investigate the application of this reaction to several alkenyl- and alkyl-based boronic acid pinacol esters, including 2-phenylvinyl boronic acid pinacol ester (**5a**), vinyl boronic acid pinacol ester (**5b**) and benzyl boronic acid pinacol ester (**5c**). As shown in Table 2, alkenyl compounds **5a** and **5b** gave the corresponding [^{11}C]esters **6a** and **6b** in moderate RCYs using a mixture of MeOH and DMF (Table 2, Entry 1). In contrast, benzyl boronic acid pinacol ester (**5c**) only afforded a low yield of the [^{11}C] ester **6c**.

results of this comparison revealed that there was no discernible difference in the yields between the boronic acids and the corresponding pinacol esters. These results therefore demonstrated that these [^{11}C]carbonylation conditions could also be applied to boronic acid derivatives.

The alkoxy-[^{11}C]carbonylation of heteroaryl boronic acid pinacol esters was also investigated using a variety of different alcohols, including benzyl alcohol, ethanol and *tert*-butyl alcohol (Table 5). The results of these experiments revealed that benzyloxy and ethoxy groups could be efficiently introduced to the [^{11}C]carbonyl group using our newly developed conditions to give the corresponding esters **11a** and **11b** in moderate RCYs. However, the attempted alkoxy-[^{11}C]carbonylation of 3-quinolineboronic acid pinacol ester (**7b**) using *tert*-butyl alcohol was unsuccessful (Table 5, entry 3).

Table 2
[^{11}C]Carbomethoxylation of allyl and alkyl boronic acid pinacol esters



Entry	Compound	Product	Solvent	Yield %[a]
1	 5a	 6a	MeOH—DMF MeOH	29±15 10±9
2	 5b	 6b	MeOH—DMF MeOH	34±16 27±13
3	 5c	 6c	MeOH—DMF MeOH	4±1 nd[b]

[a] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.
[b] nd: Not detected.

In most cases, the reaction mixtures existed as brown suspensions when before they were heated in MeOH, whereas the use of a mixture of MeOH and DMF as the solvent afforded clear brown solutions. However, black solutions were observed in both solvent systems after the reaction mixtures had been heated at 65 °C for 5 min. Given that Suzuki and co-workers[18] reported a very low RCY (2%) for the [^{11}C]carbonylation of **3** in MeOH at ambient temperature, it is highly likely that the solubility of the substrate could have a significant impact on the success of the [^{11}C]carbonylation reaction, although further studies would be needed to develop a detailed understanding of the effects of the solvent system on the reaction.

We also investigated the application of our newly developed reaction conditions to a series of heteroaryl boronic acid pinacol esters. As expected, all of the pyridine-, quinoline- and isoquinoline-bearing pinacol boronic esters tested in the current study reacted smoothly under the optimized conditions to give the desired [^{11}C]esters **8a**, **8b** and **8c** in good to moderate RCYs (Table 3, entries 1–3). Pinacol boronic acid esters bearing thiophene (**7d**) and furan-(**7e**) ring systems also reacted to give the corresponding [^{11}C]esters **8d** and **8e**, although the RCYs were much lower (Table 3, entries 4 and 5).

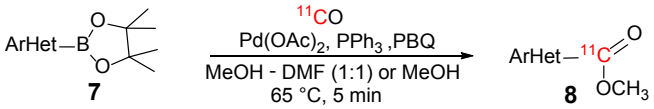
Several boronic acid derivatives were also investigated to provide an effective comparison with the pinacol esters (Table 4). The

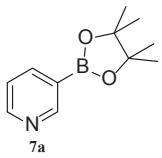
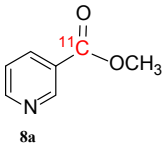
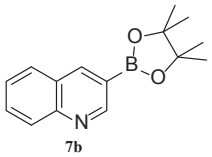
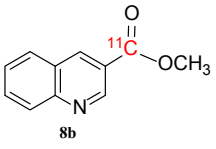
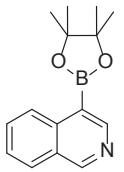
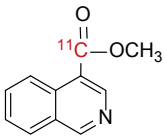
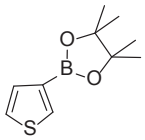
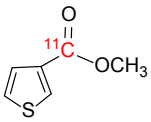
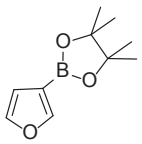
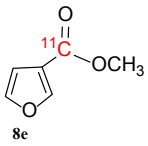
2.2. Synthesis of [^{11}C]salicylic acid (1), [^{11}C]nicotinic acid (12) and [^{11}C]aspirin (2)

According to the literature,[18] [^{11}C]esters can be readily hydrolyzed to give the corresponding [^{11}C]acids. As shown in Table 6 esters **3f** and **7e** were successfully hydrolyzed with aqueous sodium hydroxide to give the [^{11}C]carboxylic acids **1** and **12**, respectively, in good to excellent yields (Table 6, entries 1 and 2). Unfortunately, however, this method could not be applied to the synthesis of [^{11}C]aspirin (**2**) because it contains a readily hydrolyzable *O*-acetyl group. For this reason, we also investigated the direct [^{11}C]carboxylation of boronic ester **3g**. Although Långström et al.[25] recommended the use of a 6 M aqueous solution of tetramethylammonium hydroxide (TBAOH) as the hydroxyl source, the application of these conditions to the palladium-mediated [^{11}C]carboxylation of **3g** failed to provide a better yield than that obtained using only water, with [^{11}C]aspirin (**2**) being formed in a low RCY of 15±2% (Scheme 5). Notably, this reaction did not lead to the formation of any [^{11}C] salicylic acid (**1**).

Compared with the other [^{11}C]carbonylation reactions, the direct synthesis of [^{11}C]aspirin (**2**) was inefficient, but this simple and direct strategy for the synthesis of **2** could be useful for generating a [^{11}C]aspirin PET probe.

Table 3
[^{11}C]Carbomethoxylation of heteroaryl boronic acid pinacol esters



Entry	Compound	Product	Solvent	Yield %[a]
1	 7a	 8a	MeOH—DMF MeOH	52±2 64±26
2	 7b	 8b	MeOH—DMF MeOH	22±11 46±8
3	 7c	 8c	MeOH—DMF MeOH	75±17 60±9
4	 7d	 8d	MeOH—DMF MeOH	29±11 11±3
5	 7e	 8e	MeOH—DMF MeOH	17±6 10±4

[a] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.

2.3. Amidation of methyl-[^{11}C]esters

We also investigated the amidation of several [^{11}C]ester, including compounds **4b**,**f**,**g** and **8a**–**c**, by treating them with aqueous ammonia. Thus, [^{11}C]esters **4f** and **8a** were smoothly converted to the corresponding amides [^{11}C]salicylamide (**13a**) and [^{11}C]nicotinamide (**13b**) in moderate RCYs by treatment with a 25% aqueous ammonia solution (Table 7, entries 3 and 4). Pleasingly, the application of the amidation conditions to the 4-hydroxyphenyl derivative **4b** afforded the corresponding [^{11}C]amide **13c** in good RCY (Table 7, entry 1). Disappointingly, however, the benzyloxy derivative **4c** did not react with the ammonia solution, even when the reaction time was extended considerably (Table 7, entry 4). In contrast, the quinoline and isoquinoline [^{11}C]esters **8b** and **8c** reacted successfully with ammonia to afford the corresponding amides **13e** and **13f** in moderate RCYs (Table 7, entries 5 and 6).

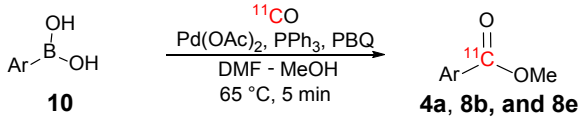
2.4. An attempt on the synthesis of [^{11}C]aldehyde 14

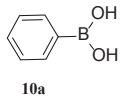
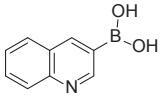
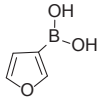
Last, we also investigated the synthesis of the [^{11}C]aldehyde **14** from **3h** using a series of appropriate hydrogen sources such as trimethylsilyl hydride (Et_3SiH) and tributyltin hydride (Bu_3SnH) (Scheme 6). Unfortunately, we could not detect any of the desired [^{11}C]aldehyde **14**. Therefore, here we provided the [^{11}C]carbonylation method seemed undesirable for the synthesis of [^{11}C]aldehyde compounds.

3. Conclusion

The palladium-mediated [^{11}C]carbonylation of aryl/heteroaryl, alkenyl and alkyl boronic acid pinacol esters with [^{11}C]O in the presence of PBQ and PPh_3 in DMF-MeOH or just MeOH has been extensively studied. A number of substituents and/or the existence of heteroaromatic systems have been found to tolerate the reaction conditions to give the corresponding [*carbonyl*-^{11}C]esters with RCYs in the range of 6–80%. Several of these [*carbonyl*-^{11}C]esters were converted to the corresponding [*carbonyl*-^{11}C]carboxylic acids and amides following their treatment with aqueous sodium hydroxide and ammonium solutions, respectively. This new method was also successfully used for the direct synthesis of [^{11}C]aspirin (**2**), with water or TBAOH being used as the nucleophile instead of MeOH. It is noteworthy that aspirin has recently been reported to

Table 4
[^{11}C]carbomethoxylation of aryl boronic acid



Entry	Compound	Product	Solvent	Yield %[a]
1	 10a	**4a**	MeOH—DMF MeOH	54±3 19±12
2	 10b	**8b**	MeOH—DMF MeOH	50±14 82±12
3	 10c	**8e**	MeOH—DMF MeOH	16±5 10±4

[a] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.

synthesis of **2** could therefore help to analyze the mechanism of action of these anti-inflammatory drugs.

4. Experimental

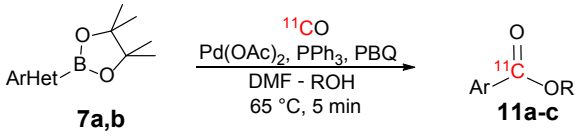
4.1. General

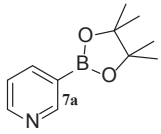
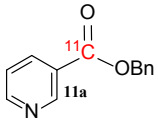
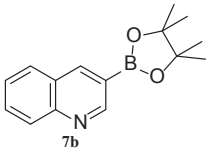
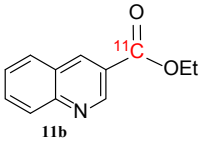
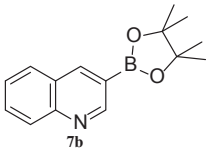
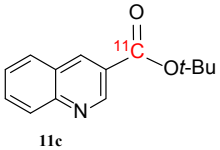
All commercially available reagents and solvents were used without further purification. The radioactivity in all the experiments were determined by a dose calibrator (IGC-3R Curiemeter; Aloka, Tokyo, Japan). High-performance liquid chromatography (HPLC) was conducted using a JASCO HPLC system with a NaI(Tl) scintillation detector system. ^{11}C-labeled products were identified by the comparison of the retention time of those ^{12}C-authentic samples, which were purchased or synthesized by known chemical procedures. Flush column chromatography was performed using silica gel Wakogel C-200. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 (0.25 mm layer thickness) plates and visualized with UV light.

4.2. Preparation of [^{11}C]O and the labeling reaction

[^{11}C]O_2 was produced by a ^{14}N(p,α)^{11}C reaction in a N_2 gas target on a CYPRIS HM-18 cyclotron (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan), and the resulting [^{11}C]O_2 gas was concentrated by solidification onto a stainless steel coil at −145 to −155 °C. The stainless steel coil was then heated to −70 °C, and the [^{11}C]O_2 gas was reduced to [^{11}C]O by passing it through a Mo column at 850 °C. Following the removal of any unreduced [^{11}C]O_2 from the gas stream using an ascarite column, the resultant [^{11}C]O/He stream was concentrated on another stainless coil, which filled with

Table 5
Alkoxy-[^{11}C]carbonylation of heteroaryl boronic acid pinacol esters

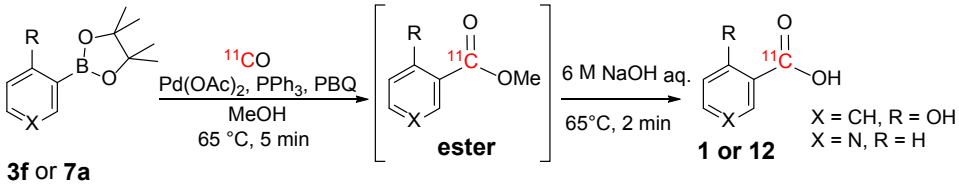


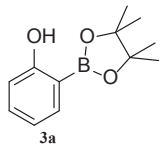
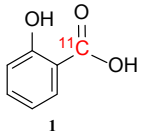
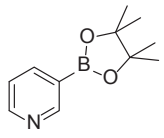
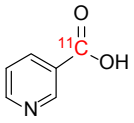
Entry	Compound	Product	Alcohol ratio (DMF/ROH)	Yield %[a]
1	 7a	 11a	BnOH (3/1)	52±11 (n=3)
2	 7b	 11b	EtOH (1/1)	34
3	 7b	 11c	t-BuOH (1/1)	nd[b]

[a] Decay-corrected radiochemical yield based on trapped [^{11}C]carbon monoxide.
[b] nd: Not detected.

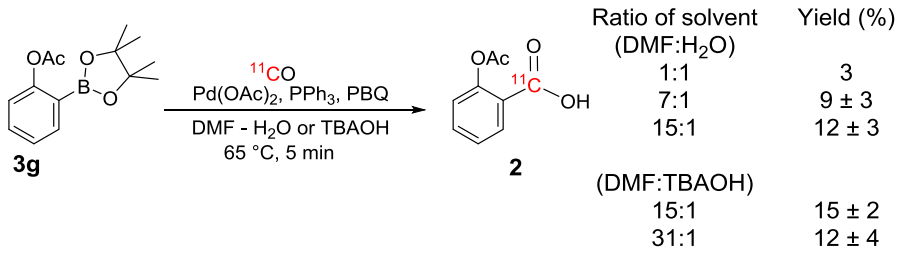
directly activate the adenosine monophosphate-activated protein kinase (AMPK) and reduce the risk of cancer.[26] The development of new methods for the synthesis of radiochemical probes such as **2** is therefore of critical importance to develop a deeper understanding of the relationship between AMPK activation and the novel effect of salicylic acid compounds, such as reducing the risk of cancer, Alzheimer's disease and heart attack. This new approach for the direct

Table 6
Synthesis of [^{11}C]salicylic acid (**1**) and [^{11}C]nicotinic acid (**12**)



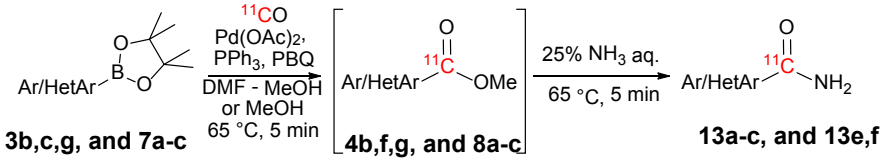
Entry	Compound	Product	Solvent	Yield %[a]
1	 3a	 1	MeOH	58±5
2	 7a	 12	MeOH	76±14

[a] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.



Scheme 5. Direct synthesis of [^{11}C]aspirin (**2**).

Table 7
Synthesis of aryl [*carbonyl*-^{11}C]amide



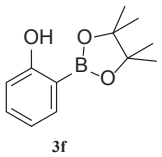
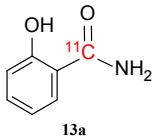
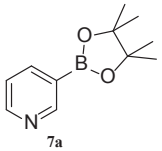
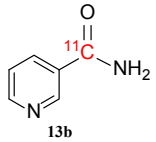
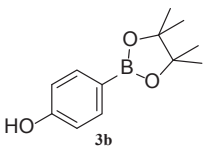
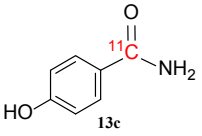
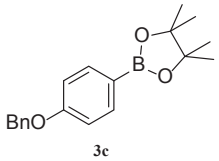
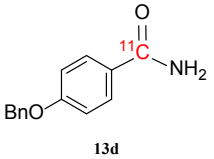
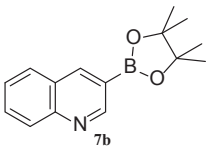
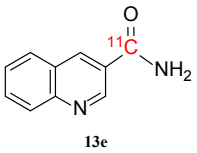
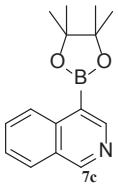
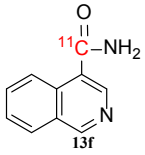
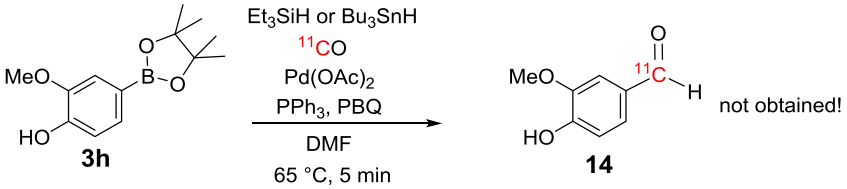
Entry	Compound	[^{11}C]ester	Product	Yield %[c]
1[a]	 3f	4f	 13a	46±7
2[b]	 7a	8a	 13b	35±24
3[a]	 3b	4b	 13c	78±14

Table 7 (*continued*)

Entry	Compound	[^{11}C]ester	Product	Yield %[c]
4[a]	 **3c**	4c	 **13d**	nd.[d]
5[a]	 **7b**	8b	 **13e**	23±7
6[a]	 **7c**	8c	 **13f**	18±3

[a] In MeOH.
[b] In DMF—MeOH (1:1).
[c] Average radiochemical yield (n=3)±standard deviation was determined by radiochromatogram of analytical HPLC based on the starting radioactivity of the reaction vessel after decay correction.
[d] nd: Not detected.



Scheme 6. Synthesis of the [^{11}C]aldehyde **14**.

molecular sieves at −70 to −80 °C. The concentrated [^{11}C]O gas was then released by heating with He carrier gas (flow rate 2.0 mL/min), and the resulting mixture was bubbled into a reaction vessel (5 mL volume) containing the reaction mixture via a needle at ambient temperature. After all of the radioactive gas had passed through the vessel, the needles were removed. The radioactivity of the vessel was then measured and the mixture was heated at 65 °C for 5 min. The progress of the reaction was monitored by HPLC analysis and the radiochemical yield was calculated based on the amount of trapped [^{11}C]O in the vessel (Fig. 1).

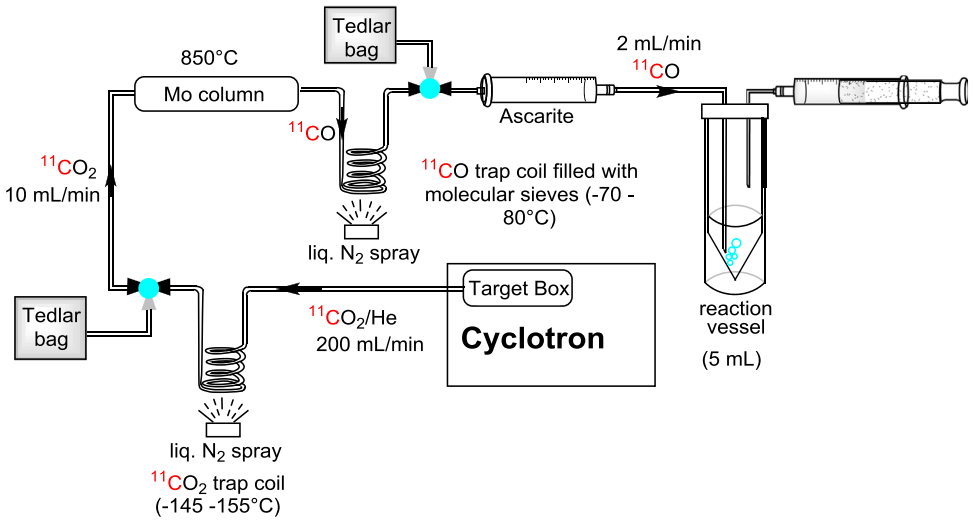


Fig. 1. Schematic drawing of the [^{11}C]carbonylation reaction system.

4.3. Typical procedure for the synthesis of [^{11}C]esters

A mixture of **3g** (5.0 mg, 19 μmol), $Pd(OAc)_2$ (4.2 mg, 19 μmol), PPh_3 (10 mg, 38 μmol), and *p*-benzoquinone (2.0 mg, 19 μmol) was placed in 5.0 mL vial and dissolved in DMF (400 μL)—MeOH (400 μL) or MeOH (800 μL). Then [^{11}C]O gas was passed through the vial with a stream of helium (2 mL/min) and the mixture was heated at 65 °C for 5 min. Part of the resulting mixture was purified by high-performance liquid chromatography (HPLC) and the RCY of the fraction was determined by a NaI(Tl) well-type scintillation detector system. Products were identified by comparison their retention times with those of the authentic samples. The detail HPLC conditions of each compound were provided in the supplemental materials.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.01.008.

References and notes

1. Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum. Press: New York, NY, 1991.
2. Maitlis, P.; Haynes, A. *Metal-catalysis in Industrial Organic Processes*; RSC: Cambridge, UK, 2006.
3. Kollåar, L. *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, Germany, 2008.
4. Beller, M.; Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C-X Bonds*; Springer: Heidelberg, 2013.
5. Långström, B.; Itsenko, O.; Rahman, O. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 794.
6. Kealey, S.; Gee, A.; Miller, P. *J. Labelled Compd. Radiopharm.* **2014**, *57*, 195.
7. Fogg, P. G. T.; Gerrard, W. *Solubility of Gases in Liquids: a Critical Evaluation of Gas/Liquid Systems in Theory and Practice*; J. Wiley: Chichester, UK; New York, NY, 1991.
8. Recently, Skrydstrup and coworkers have developed the simpler and safer in-site CO-precursor 'COgen', which are now commercially available. By the use of COgen is possible to do stoichiometric carbonylation: Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
9. Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Jorn Wiley & Sons: Chichester, UK, 2000; pp 85–92.
10. Itsenko, O.; Kihlberg, T.; Långström, B. *Nat. Protoc.* **2006**, *1*, 798.
11. Lidström, P.; Kihlberg, T.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2701.
12. Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Audrain, H.; Bender, D.; Passchier, J.; Gee, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2875.
13. Kealey, S.; Plisson, C.; Collier, T. L.; Long Nicholas, J.; Husbands Stephen, M.; Martarello, L.; Gee Antony, D. *Org. Biomol. Chem.* **2011**, *9*, 3313.
14. Buscemi, G.; Miller, P. W.; Kealey, S.; Gee, A. D.; Long, N. J.; Passchierb, J.; Vilar, R. *Org. Biomol. Chem.* **2011**, *9*, 3499.
15. Dahl, K.; Schou, M.; Rahman, O.; Halldin, C. *Eur. J. Org. Chem.* **2014**, 307.
16. Eriksson, J.; Johan, H.; Windhorst, A. D. *J. Labelled Compd. Radiopharm.* **2012**, *55*, 223.
17. Dahl, K.; Schou, M.; Amini, N.; Halldin, C. *Eur. J. Org. Chem.* **2013**, 1228.
18. Takashima-Hirano, M.; Ishii, H.; Suzuki, M. *ACS Med. Chem. Lett.* **2012**, *3*, 804.
19. Cuzick, J.; Thorat, M. A.; Bosetti, C.; Brown, P. H.; Burn, J.; Cook, N. R.; Ford, L. G.; Jacobs, E. J.; Jankowski, J. A.; La Vecchia, C.; Law, M.; Meyskens, F.; Rothwell, P. M.; Senn, H. J.; Umar, A. *Ann. Oncol.* **2014**, *25*, 2065.
20. Pomponi, M. F. L.; Gambassi, G.; Pomponi, M.; Masullo, C. *Aging Dis.* **2010**, *1*, 37.
21. Fuster, V.; Dyken, M. L.; Vokonas, P. S.; Hennekens, C. *Circulation* **1993**, *87*, 659.
22. Sasaki, T.; Ogawa, K.; Ishii, S.; Senda, M. *Appl. Radiat. Isot.* **1999**, *50*, 905.
23. Brune, K.; Rainsford, K. D.; Schweitzer, A. *Br. J. Clin. Pharmacol.* **1980**, *10*, 279S.
24. Zhang, N.; Hoffman, D.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956.
25. Karimi, F.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2256.
26. Hawley, S. A.; Fullerton, M. D.; Ross, F. A.; Schertzer, J. D.; Chevtzoff, C.; Walker, K. J.; Peggie, M. W.; Zibrova, D.; Green, K. A.; Mustard, K. J.; Kemp, B. E.; Sakamoto, K.; Steinberg, G. R.; Hardie, D. G. *Science* **2012**, *336*, 918.