Reaction of ^{11}C-benzoyl chlorides with metalloid reagents: ^{11}C-labeling of benzyl alcohols, benzaldehydes and phenyl ketones from [^{11}C]CO

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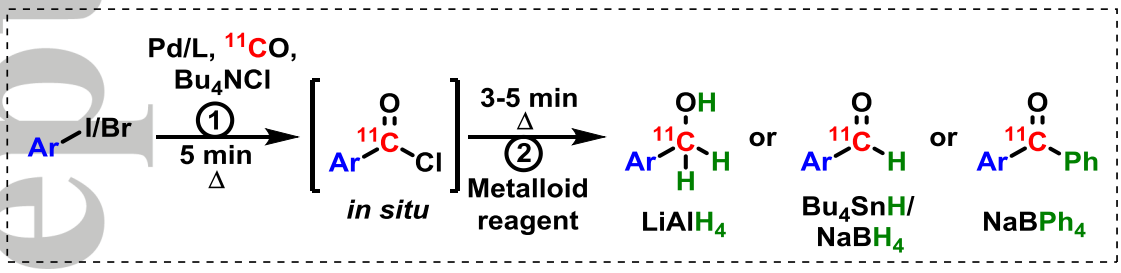
ABSTRACT

In this article we describe the carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) labeling of benzyl alcohols, benzaldehydes and ketones using an efficient two-step synthesis in which ^{11}C-carbon monoxide is used in an initial palladium-mediated reaction to produce ^{11}C-benzoyl chloride as a key intermediate. In the second step, the obtained ^{11}C-benzoyl chloride is further treated with a metalloid reagent to furnish the final ^{11}C-labeled product. Benzyl alcohols were obtained in moderated to high non-isolated radiochemical yields (RCY, 35-90%) with lithium aluminium hydride or lithium aluminium deuteride as metalloid reagent. Changing the metalloid reagent to either tributyltin hydride or sodium borohydride, allowed for the reliable syntheses of ^{11}C-benzaldehydes in RCYs ranging from 58-95%. Finally, sodium tetraphenylborate were utilized to obtain ^{11}C-phenyl ketones in high RCYs (77-95%). The developed method provides a new and efficient route to three different classes of compounds starting from aryl iodides or aryl bromides.

GRAPHICAL ABSTRACT



KEYWORDS

carbon-11, carbonylation, carbon monoxide, benzyl alcohols, benzaldehydes, phenyl ketones

1. INTRODUCTION

Short-lived positron-emitting radionuclides are utilized in different molecular imaging applications including positron emission tomography (PET). PET is a non-invasive imaging modality in which physiological and biochemical processes can be studied *in vivo* following the intravenous administration of a radiolabeled bioactive compound called radiotracer.[1,2] PET is frequently being used in cardiology,[3] neurology[4] as well as oncology[5], and more recently has proven to be a valuable technique in drug discovery.[6,7]

The abundance of carbon in organic molecules makes carbon-11 ($t_{1/2}$ = 20.4 min) an appealing isotope for PET radiotracer development. Carbon-11 is obtained as either [^{11}C]carbon dioxide ([^{11}C]CO_2) or [^{11}C]methane from the cyclotron, from which a number of secondary precursors can be obtained by well-established on-line procedures.[9] The secondary precursor [^{11}C]carbon monoxide ([^{11}C]CO), commonly prepared via metal-mediated reduction of in-target produced [^{11}C]CO_2, has been increasingly recognized as an ^{11}C-synthon for PET radiotracer production. Various ^{11}C-labeled functional groups can be prepared from [^{11}C]CO, including, ^{11}C-amides,[12] ^{11}C-esters,[13] ^{11}C-carboxylic acids[14] and ^{11}C-ketones[15]. We have previously reported the preparation of ^{11}C-labeled acid chlorides via a novel palladium-mediated carbonylation of aryl iodides with [^{11}C]CO and tetrabutylammonium chloride.[16] The *in situ* generated ^{11}C-benzoyl chloride derivative was then utilized to produce a series of ^{11}C-labeled amides, esters and aldehydes in high radiochemical yields (Scheme 1, route A). The method circumvented the need for corrosive chlorinating reagents, such as, $SOCl_2$ or phthaloyl dichloride, which previously have been used in the syntheses of ^{11}C-labeled acid chlorides via chlorination of the intermediary ^{11}C-labeled carboxylic acid/carboxylate.[17–19] In the present study, the above described reaction is extended to include aryl bromides as substrates for the initial ^{11}C-acid chloride formation, as well as metalloid reagents for the

subsequent reduction/nucleophilic reaction, thus enable the formation of ^{11}C-labeled benzyl alcohols, benzaldehydes and phenyl ketones (Scheme 1, route B).

<SCHEME 1>

2. EXPERIMENTAL

2.1 General information

All the precursors and references were bought from commercial vendors and used as per received. Analytical radio-HPLC was performed using a VWR LaChrom ELITE system (L-2450, L-2300, L-2200) with a Merck Chromolith Performance RP-18e column (4.6×100mm) using MeCN in 0.09% aqueous TFA. A diode-array detector (L-2450) and a Bioscan Flow-Count PMT radioactivity detector was used. Method 1: 1-20% MeCN for 7 min and then 20-90% MeCN for 5 min (12 min total) using a flow of 2 mL/min. Method 2: 5-50% MeCN for 7 min then 50-90% MeCN for 5 min (12 min total) using a flow of 2 mL/min. Method 3: 10-90% MeCN for 10 min, then 90% for two min (12 min total) using a flow of 2 mL/min. For the preparative run, the crude mixture was diluted with 1 mL of a mixture of MeCN and 0.9% aqueous TFA (1:1) and then injected on the preparative HPLC (a VWR LaPrep HPLC system (P110, P311) with an ACE-5 HL column (10×250mm) using MeCN in 0.09% aqueous TFA (30-90% over 10 min, then 90% for 5 min, 15 min total), UV detector (P311) and Bioscan Flow-Count PMT radioactivity detector. The radiochemical purity (RCP) and the molar activity (determined using a calibration curve) for the isolated product were determined by analytical radio-HPLC.

2.2 General procedure for the two-step reaction

[^{11}C]CO_2 was produced by 17 MeV proton bombardment of nitrogen gas (AGA, Nitrogen 6.0) containing 0.05% oxygen (AGA, Oxygen 4.6) through the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a Scanditronix MC-17 cyclotron and transferred to the hot cell using helium as a carrier gas. A carbon monoxide apparatus[19] was used to trap, concentrate and reduce [^{11}C]CO_2 to [^{11}C]CO and subsequently perform the initial carbonylative reaction. For the second reaction step, two 0.8 mL pear shaped oven dried vials were used. In the first vial, $Pd(dba)_2$ (2.3 mg, 4 µmol) and P(*t*-Bu)$_3$HBF$_4$ (4.7 mg, 16 µmol) was added and then capped and flushed with N_2 for 1 min. 400 µL DMF was added, the vial was vortexed (10 seconds) and then heated at 120 °C (30 seconds) during which the color went from red to light brown. The Pd/ligand mixture was added to a second capped and N_2-flushed vial containing tetrabutylammonium chloride (10 mg, 92 µmol) and the corresponding aryl halide (20 µmol). The vial was vortexed after which the mixture was added to the carbonylation apparatus (340 µL loop) just prior to [^{11}C]CO_2 delivery. When the reaction was finished the crude mixture was released from the reaction chamber into a capped 2 mL vial containing the metalloid reagent (50 µL 0.2 M LAH or 30 µmol $NaBH_4$/$NaBPh_4$) and then heated in a heating block for 3 to 5 min. The vial was allowed to cool for 1 min before piercing of the septa to release and determine any loss of gaseous radioactivity. In all reactions, >99% of the radioactivity was retained in the reaction vial after completed reaction, concluding that the [^{11}C]CO trapping efficiency (TE) was greater than 99% in all experiments.[20] An aliquot was drawn from the crude reaction mixture and analyzed with radio-HPLC to determine the non-isolated radiochemical yield (RCY).

3. RESULTS AND DISCUSSION

3.1 ^{11}C-Labeling of benzyl alcohols

The radiosynthesis of carbon-11 benzyl alcohol ([^{11}C]**2a**) was selected as a test reaction for the initial condition screening (Table 1), with iodobenzene (**1a**) as substrate for the initial carbonylation reaction, as previously described,[16] and lithium aluminium hydride (LAH, 0.2 M in THF) for the subsequent reduction. The reduction reaction outcome was studied in regards to reduction agent amount, reaction time and temperature as shown in Table 1. Using 100 µL of LAH and heating the reaction to 110 °C for 5 min gave the desired compound [^{11}C]**2a** in 84% RCY (Table 1, entry 1). Similar RCYs were observed at decreased reaction time (3 min, Table 1, entry 2), lower temperature (90 °C, Table 1, entry 3), and with a two-fold lower LAH amount (50 µL, Table 1, entry 4). However, a further reduction of LAH amount (20 µL) resulted in a reduced RCY (Table 1, entry 5). A slight improvement in RCY was observed at 100 °C with 50 µL of LAH (90%, Table 1, entry 6). When the aryl halide was changed to bromobenzene (**1b**) a RCY of 87% was obtained (Table 1, entry 7). In these experiments the temperature for the initial carbonylation reaction was increased to 140 °C.

<TABLE 1>

The best conditions (Table 1, entry 6) were next used to synthesize a series of ^{11}C-benzyl alcohols starting from the corresponding aryl halides. The results from these experiments are presented in Table 2. Using methyl 4-iodobenzoate (**1c**) as substrate a RCY of 86% of [^{11}C]**2b** was obtained (Table 2, entry 1). The short reaction time might circumvent the reduction of the methyl ester by LAH. 4-Iodoanisole (**1d**) produced [^{11}C]**2c** in 74% RCY (Table 2, entry 2), while the corresponding brominated starting material **1e** furnished the same product in 80% RCY (Table 2, entry 3). The meta-substituted precursor 3-methoxy-

iodobenzene (**1f**) and para-substituted 4-fluoro-iodobenzene (**1g**), provided their corresponding benzyl alcohols [^{11}C]**2d** and [^{11}C]**2e** in comparable RCYs (76-77%, Table 2, entries 4-5). However, only a moderated RCY (35%) of [^{11}C]**2f** was obtained with 3-bromoiodobenzene (**1h**) as substrate (Table 2, entry 6). The competing aryl bromide caused the RCY to be drop as the dehalogenated product (giving the product [^{11}C]**2a**) was identified with radio-HPLC (see supporting information). An attempt to circumvent this problem by lowering the carbonylative reaction temperature to 90 °C, resulted in a decreased RCY (24%, Table 2, entry 7) due to an incomplete carbonylative reaction.

<TABLE 2>

Next, we utilized lithium aluminum deuteride as the reducing agent to produce dual labeled benzyl alcohols. The incorporation of deuterium is well explored in pharmaceutical development and discovery, where it can offer mechanistic insights for example.[22] The labeling with deuterium has also been explored in studies with ^{11}C-labeled radiotracers, where the incorporation of deuterium changed the pharmacokinetic properties of the radiotracers.[23,24] Three different compounds were labeled with both carbon-11 and deuterium. The labeling of these three compounds proceeded in a similar manner as for their non-deuterated counterparts, yielding the corresponding benzyl alcohols [^{11}C]**2g-i** in high RCYs (74-86%, Table 2, entries 8-10).

In a final experiment to label benzyl alcohols, [^{11}C]**2a** was prepared on a semi-preparative scale in order to establish the molar activity. Starting from 10 GBq of [^{11}C]CO_2, 2.2 GBq (60% RCY) of radiochemically pure (RCP >99%) [^{11}C]**2a** was obtained 29 min after end-of-bombardment (EOB) (see supporting information for further details). The molar activity at

end-of-synthesis (EOS) was 266 GBq/μmol. The higher molar activity obtained with the method presented herein are in line with other ^{11}C-carbonylations reported in the literature.[25-27]

3.2 ^{11}C-Labeling of benzaldehydes

The use of aldehydes in drugs is restricted because of their reactivity. However, this reactivity, has been exploited in development of selective inhibitors of Hepatitis C NS3 protease and serine protease plasmin.[28,29] There are also examples of aldehydes as pathophysiological biomarkers, which are formed by lipid peroxidation when cells in the body are subjected to oxidative stress.[30] Aldehydes could also be used in the preparation of alkenes in the Wittig reaction.

In our initial report on ^{11}C-acid chlorides, we described the synthesis of an ^{11}C-benzaldehyde in 49% and 55% RCY using sodium hydride or triethylsilane, respectively.[16] However, the two-step procedure allows the use of any hydride source since it is separated from the initial carbonylation reaction. Thus, to further broaden the scope of possible hydride sources, and more importantly, improve the RCY of the ^{11}C-labeled benzaldehydes, tributyltin and sodium borohydride were evaluated. Initial experiments with tributyltin hydride as the hydride source provided the desired product [^{11}C]**3a** in 37% RCY (Table 3, entry 1) with the benzyl alcohol as the main by-product. When the reaction time was prolonged to 5 min the RCY increased marginally (43%, Table 3, entry 2). Surprisingly, no product was formed with heating at either 55 °C or 130 °C (55 °C was too low for the reaction to proceed and at 130 °C there were several unidentified byproducts formed). However, by carefully adjusting the temperature to 90 °C, the desired aldehyde [^{11}C]**3a** was obtained in excellent RCY (86%, Table 3, entry 3). Furthermore, doubling the amount of hydride source (30 μmol) returned a

near quantitative RCY (91%, Table 3, entry 4). Bromobenzene (**1b**) did not perform equally well under these conditions (RCY = 59%, Table 3, entry 5).

<TABLE 3>

One unfortunate drawback with this approach is, however, the inherent toxicity of the organotin reagent. Hence, the less toxic hydride source, sodium borohydride, where therefore evaluated. To our delight, with sodium borohydride as reducing reagent and heating for 3 min at 90 °C, [^{11}C]**3a** was again obtained in near quantitative RCY (91%, Table 3, entry 6). In addition, no change in RCY was observed at longer reaction time (Table 3, entry 7). It is noteworthy that almost no further reduction of the ^{11}C-labeled aldehyde to the corresponding ^{11}C-labeled benzyl alcohol [^{11}C]**2a** occurred under these reaction conditions (Figure 1). Moreover, RCY (90%, Table 3, entry 8) on a similar magnitude was observed with bromobenzene as substrate.

<FIGUE 1>

To investigate the scope of the reaction, a set of substituted ^{11}C-labeled aldehydes were synthesized from different aryl iodides and bromides (Table 4). Utilizing sodium borohydride as the hydride source, the methyl ester [^{11}C]**3b** was obtained in 58% RCY from **1c** (Table 4, entry 1). High RCYs were obtained (82-84%, Table 4, entries 2-3) for the para-substituted 4-methoxy benzaldehyde ([^{11}C]**3c**) with either the corresponding iodo- and bromo-precursor (**1d**, **1e**), whereas the 3-methoxy substituted benzaldehyde [^{11}C]**3d**, was obtained in 65% RCY from **1f** (Table 4, entry 4). The electron deficient substrates, **1i** and **1j**, yielded the

desired 4-cyano substituted [^{11}C]**3e** in good RCYs, 77% and 66%, respectively (Table 4, entries 5-6). Compound [^{11}C]**3f** was produced in an excellent RCY (95%, Table 1, entry 7) starting from 4-iodotoluene (**1k**). In the last experiment of this set, with 4-fluoroiodobenzene **1l** as precursor the desired product ([^{11}C]**3g**) was obtained in 81% RCY (Table 4, entry 8).

<TABLE 4>

3.3 ^{11}C-Labeling of ketones

Ketones are a common structural element found in a wide range of bioactive natural products as well as pharmaceuticals. Using the conditions developed for the labeling of aldehydes with sodium borohydride, we envisioned that phenyl ketones could be labeled using a similar strategy with the commensally available metalloid reagent, sodium tetraphenylborate. To test this hypothesis, precursor **1a** was subjected to the carbonylative reaction and subsequent addition of sodium tetraphenylborate (30 μmol), which resulted in a RCY of 90% of [^{11}C]**4a** (Table 5, entry 1). Comparable RCY (86%, Table 5, entry 2) was also obtained when the substrate was changed to the corresponding aryl bromide (**1b**) using 140 °C reaction temperature in the carbonylative reaction.

Next, we proceeded to evaluate the ^{11}C-labeling of different phenyl ketones with sodium tetraphenylborate as metalloid reagent. Using the present conditions, [^{11}C]**4b** was labeled in 88% RCY from 4-iodoanisole **1d** (Table 5, entry 3). When the precursor was changed to the corresponding bromine **1e**, a RCY of 93% (Table 5, entry 4) was achieved. A similar RCY was obtained when 4-fluoroiodobenzene (**1g)** was used substrate (95%, Table 5, entry 5). The 4-chloroiodobenzene **1l** provided the labeled phenyl ketone [^{11}C]**4d** in 77% RCY (Table 5, entry 6).

<TABLE 5>

4. CONCLUSIONS

In conclusion, we have described the ^{11}C-radiolabeling of benzyl alcohols, benzaldehydes and phenyl ketones using a two-step synthesis procedure. The methodology uses [^{11}C]CO in a palladium-mediated reaction to produce a ^{11}C-benzoyl chloride as a key intermediate, which in turn is treated with different metalloid reagents in a second step to yield the final ^{11}C-labeled product. Using lithium aluminiumhydride, sodium borohydride or sodium tetraphenylborate, ^{11}C-labeled benzyl alcohols, aldehydes or phenyl ketones could be obtained, respectively. The method could be used with either aryl iodides (120 °C carbonylative reaction temperature) or aryl bromides (140 °C carbonylative reaction temperature) with comparable results. The two-step reaction procedure is essential for the labeling method since these metalloid reagents obstruct the initial carbonylative process. Using the developed method it was possible to obtain a diverse set of carbon-11 labeled benzyl alcohols, benzaldehydes and phenyl ketones in RCYs ranging between 35-95%.

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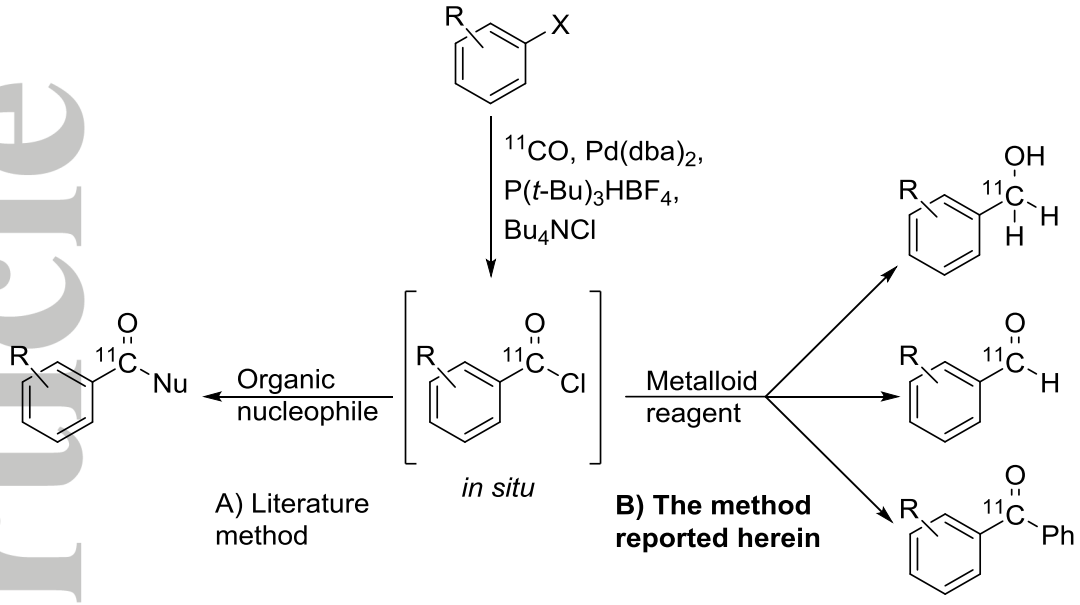
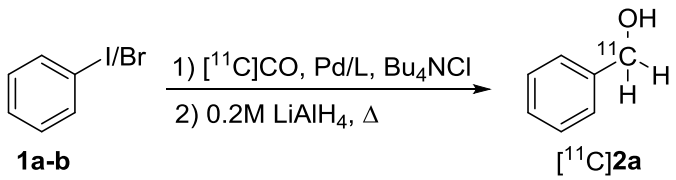


SCHEME 1 Palladium-mediated ^{11}C-carbonylations using organic nucleophiles (A, literature method) and metalloid reagents (B, the work presented herein)

TABLE 1 Optimization of the reaction conditions for the synthesis of ^{11}C-labeled benzyl alcohol [^{11}C]**2a**

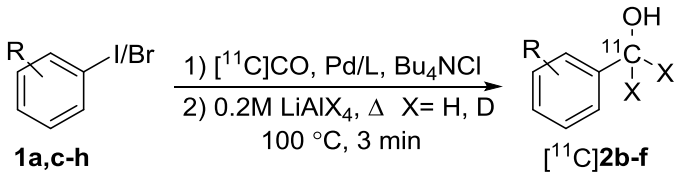


1a-b [^{11}C]**2a**

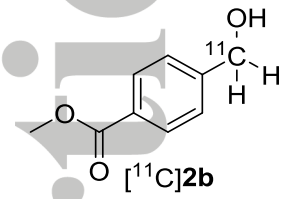
Entry	PhI/Br	LAH[a] amount (µL)	Temp/time (°C/min)	RCY (%)[b]
1	**1a** (X=I)	100	110 / 5	84
2	**1a**	100	110 / 3	85
3	**1a**	100	90 / 3	83
4	**1a**	50	90 / 3	86
5	**1a**	20	90 / 3	46
6	**1a**	50	100 / 3	90
7[c]	**1b** (X=Br)	50	100 / 3	87

[a]Lithium aluminium hydride. [b]Average of two reactions. RCY: Non-isolated radiochemical yield determined by radio-HPLC from an aliquot of the reaction mixture. The trapping of [^{11}C]CO in the carbonylation reaction was >99% for all experiments. [c]140 °C carbonylation temperature. Pd=$Pd(dba)_2$, L=P(*t*-Bu)$_3$HBF$_4$.

TABLE 2 Scope of ^{11}C-labeled benzyl alcohols



1a,c-h [^{11}C]**2b-f**



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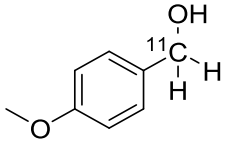
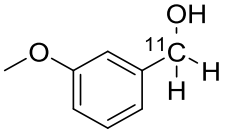
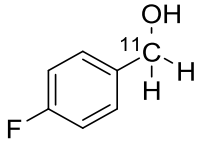


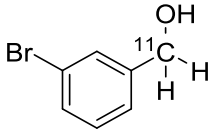
[^{11}C]**2c**



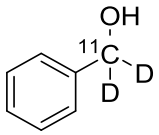
[^{11}C]**2d**



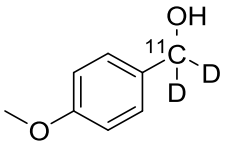
[^{11}C]**2e**



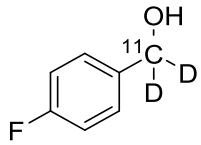
[^{11}C]**2f**



[^{11}C]**2g**



[^{11}C]**2h**



[^{11}C]**2i**

Entry	PhI/Br	Product	RCY (%)[a]
1	4-MeCOO-Ph-I (**1c**)	[^{11}C]**2b**	86
2	4-OMe-Ph-I (**1d**)	[^{11}C]**2c**	74
3[b]	4-OMe-Ph-Br (**1e**)	[^{11}C]**2c**	80
4	3-OMe-Ph-I (**1f**)	[^{11}C]**2d**	76
5	4-F-Ph-I (**1g**)	[^{11}C]**2e**	77
6	3-Br-Ph-I (**1h**)	[^{11}C]**2f**	35
7[c]	**1h**	[^{11}C]**2f**	24
8	**1a**	[^{11}C]**2g**	81
9	**1d**	[^{11}C]**2h**	86
10	**1g**	[^{11}C]**2i**	74

[a]Average of two reactions. RCY: Non-isolated radiochemical yield determined by radio-HPLC from an aliquot of the reaction mixture. The trapping of [^{11}C]CO in the carbonylation reaction was >99% for all experiments. [b]140 °C carbonylation temp. [c]90 °C carbonylation temp. Pd=$Pd(dba)_2$, L=$P(t\text{-}Bu)_3HBF_4$.

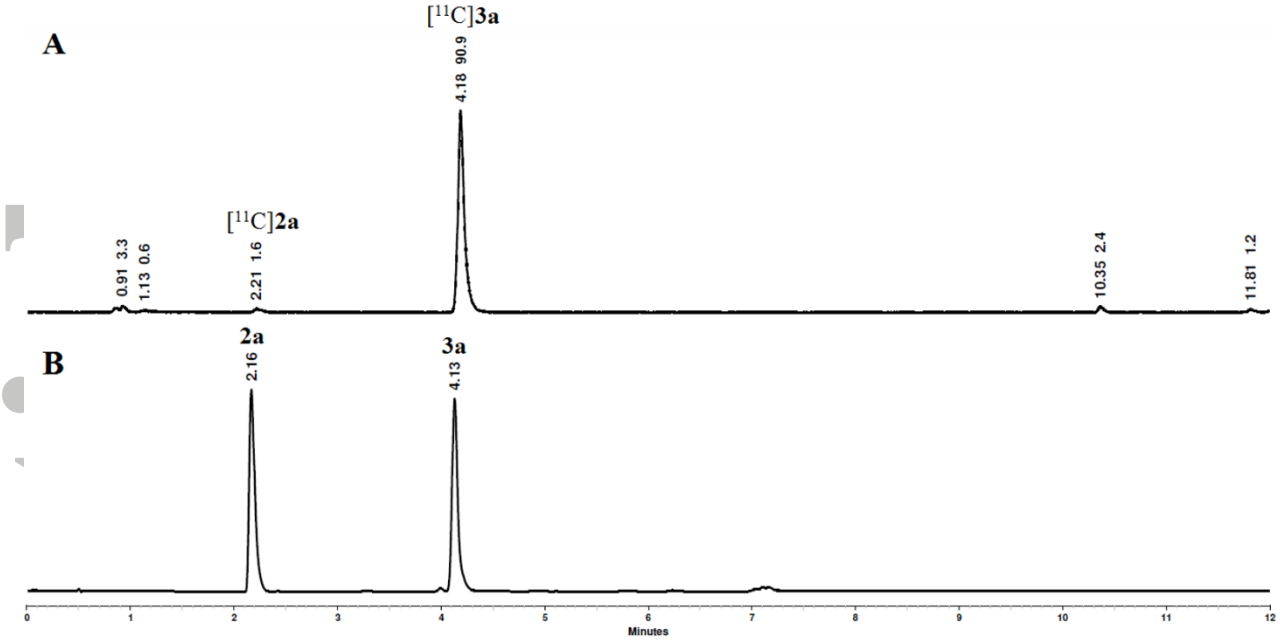
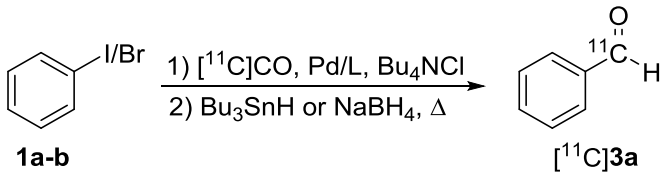


FIGURE 1 Aliquot of reaction mixture of **1a** and $NaBH_4$ (from Table 3, entry 9). A: Radio-chromatogram of [^{11}C]**3a** (4.18 min, 90.9%) and byproduct [^{11}C]**2a** (2.21 min, 1.6%) B: Spectrum max chromatogram of reference **3a** (4.13 min) with added **2a** (2.16 min). See supporting information for more information.

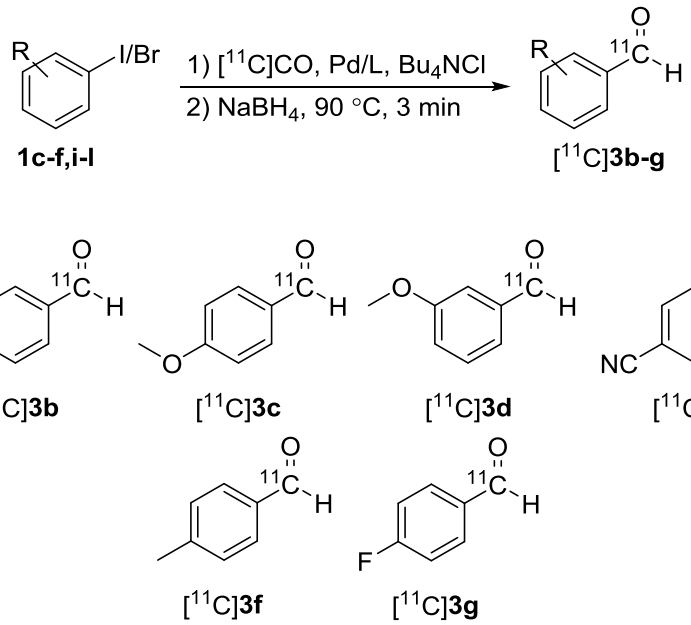
TABLE 3 Optimization of the reaction conditions in the synthesis of ^{11}C-labeled benzaldehyde [^{11}C]**3a**



Entry	PhI/Br	Reagent / µmol	Time / temp (°C / min)	Product	RCY (%)[a]
1	**1a**	Bu_3SnH / 15	110 / 3	[^{11}C]**3a**	37
2	**1a**	Bu_3SnH / 15	110 / 5	[^{11}C]**3a**	43
3	**1a**	Bu_3SnH / 15	90 / 5	[^{11}C]**3a**	86
4	**1a**	Bu_3SnH / 30	90 / 5	[^{11}C]**3a**	91
5[b]	**1b**	Bu_3SnH / 30	90 / 5	[^{11}C]**3a**	59
6	**1a**	$NaBH_4$ / 30	90 / 3	[^{11}C]**3a**	91
7	**1a**	$NaBH_4$ / 30	90 / 5	[^{11}C]**3a**	90
8[b]	**1b**	$NaBH_4$ / 30	90 / 3	[^{11}C]**3a**	90

[a]Average of two reactions. RCY: Non-isolated radiochemical yield determined by radio-HPLC from an aliquot of the reaction mixture. The trapping of [^{11}C]CO in the carbonylation reaction was >99% for all experiments. [b]140 °C carbonylation temp. Pd=$Pd(dba)_2$, L=P(*t*-Bu)$_3$HBF$_4$.

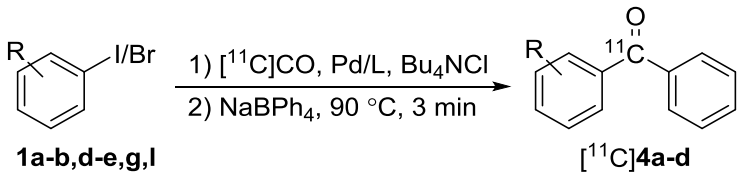
TABLE 4 Scope of ^{11}C-labeled benzaldehydes from sodium borohydride



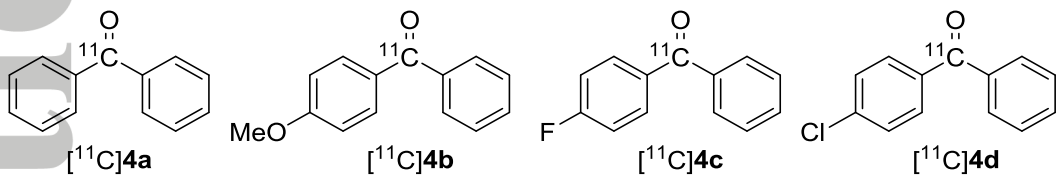
Entry	PhI/Br	Reagent (30 µmol)	Product	RCY (%)[a]
1	**1c**	$NaBH_4$	[^{11}C]**3b**	58
2	**1d**	$NaBH_4$	[^{11}C]**3c**	82
3[b]	**1e**	$NaBH_4$	[^{11}C]**3c**	84
4	**1f**	$NaBH_4$	[^{11}C]**3d**	65
5	4-CN-Ph-I (**1i**)	$NaBH_4$	[^{11}C]**3e**	77
6[b]	4-CN-Ph-Br (**1j**)	$NaBH_4$	[^{11}C]**3e**	66
7	4-Me-Ph-I (**1k**)	$NaBH_4$	[^{11}C]**3f**	95
8	4-F-Ph-I (**1l**)	$NaBH_4$	[^{11}C]**3g**	81

[a]Average of two reactions. RCY: Non-isolated radiochemical yield determined by radio-HPLC from an aliquot of the reaction mixture. The trapping of [^{11}C]CO in the carbonylation reaction was >99% for all experiments. [b]140 °C carbonylation temp. Pd=$Pd(dba)_2$, L=P(*t*-Bu)$_3$HBF$_4$.

TABLE 5 Scope of ^{11}C-labeled phenyl ketones from sodium tetraphenylborate



1a-b,d-e,g,l [^{11}C]**4a-d**



[^{11}C]**4a** [^{11}C]**4b** [^{11}C]**4c** [^{11}C]**4d**

Entry	PhI/Br	Reagent (30 µmol)	Product	RCY (%)[a]
1	**1a**	$NaBPh_4$	[^{11}C]**4a**	90
2[b]	**1b**	$NaBPh_4$	[^{11}C]**4a**	86
3	**1d**	$NaBPh_4$	[^{11}C]**4b**	88
4[b]	**1e**	$NaBPh_4$	[^{11}C]**4b**	93
5	**1g**	$NaBPh_4$	[^{11}C]**4c**	95
6	4-Cl-Ph-I (**1l**)	$NaBPh_4$	[^{11}C]**4d**	77

[a]Average of two reactions. RCY: Non-isolated radiochemical yield determined by radio-HPLC from an aliquot of the reaction mixture. The trapping of [^{11}C]CO in the carbonylation reaction was >99% for all experiments. [b]140 °C carbonylation temp. Pd=$Pd(dba)_2$, L=P(*t*-Bu)$_3$HBF$_4$.