Radiochemistry

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Cu^{I}-Catalyzed ^{11}C Carboxylation of Boronic Acid Esters: A Rapid and Convenient Entry to ^{11}C-Labeled Carboxylic Acids, Esters, and Amides**

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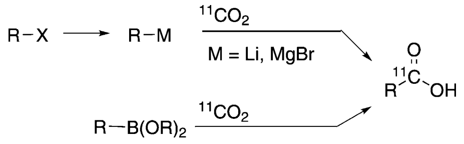
Noninvasive imaging with positron emission tomography (PET) allows for quantitative studies of radiotracer distribution in living subjects and is increasingly used in routine clinical diagnosis, preclinical and clinical-phase drug development, and biomedical research. Novel radiotracers for imaging a variety of biological targets are continually needed to fully exploit the potential of PET. Consequently, the existence of reliable chemical methods for labeling organic molecules with short-lived positron emitters is key to the production of novel radiotracers intended for complex imaging studies in humans.[1,2]

^{11}C, despite its short half-life ($t_{1/2} = 20.4$ min), is a valuable radiolabel for PET radiotracers because carbon is present in nearly all biochemicals and drug candidates.[2,3] Isotopic substitution of ^{12}C with ^{11}C represents an often elegant and desirable approach in radiotracer development. The isotope ^{11}C is readily obtained in high activity and high specific radioactivity from moderate-energy cyclotrons by the ^{14}N(p,α)^{11}C nuclear reaction.[2] Irradiation of nitrogen gas in the presence of oxygen produces [^{11}C]carbon dioxide, whereas irradiation in the presence of hydrogen produces [^{11}C]methane. The direct use of these two primary precursors for radiolabeling has, however, been quite limited. Instead, major effort has been expended on converting these precursors into ^{11}C-labeling agents with more versatile reactivity. For example, most ^{11}C-labeled radiotracers are obtained by alkylation of heteroatom nucleophiles with $^{11}CH_3I$ or $^{11}CH_3OTf$.[2]

Direct applications of $^{11}CO_2$ in radiotracer synthesis are mostly ^{11}C carboxylations of Grignard and organolithium reagents to produce ^{11}C-labeled carboxylic acids (Scheme 1, top).[4] For successful outcomes, these reactions require great care, including diligent control of reagent stoichiometry, and the exclusion of moisture and atmospheric CO_2. Moreover, these methods are limited with respect to the structural diversity of products that may be obtained. Recently, interest in the direct incorporation of $^{11}CO_2$ into radiotracers has been revived by Hooker et al. and Wilson et al. who elaborated novel carboxylation methods for the synthesis of ^{11}C-labeled carbamates and ureas.[5] Such direct incorporation of ^{11}C into candidate radiotracers is attractive with regard to avoiding losses of radioactivity, conserving specific radioactivity, and achieving rapid and simple radiosyntheses.



Scheme 1. Radiosynthesis of [^{11}C]carboxylic acids from $^{11}CO_2$ and classical organometallic reagents or boronic acid esters.

Within our radiotracer development programs, we sought an efficient method for producing [^{11}C]carboxylates that might display high functional-group tolerance. Unlike organolithium and Grignard reagents, boronic acid esters are quite stable to air and moisture and therefore are easily handled and stored. Moreover, organolithium and Grignard reagents can only be formed from molecules devoid of reactive electrophilic functional groups, whereas boronic acid esters can be readily introduced into highly functionalized molecules.[6] In view of these considerations and of recent developments in transition metal-mediated carboxylation reactions,[7–9] in particular with copper–bisoxazoline[8] and copper N-heterocyclic carbene (Cu-NHC)[9] type catalysts, we succeeded in devising a new catalytic method for C–^{11}C bond formation direct from $^{11}CO_2$ using boronic acid esters, as we now report herein (Scheme 1, bottom).

First, we tried to optimize the trapping agent/complex ligand. In non-radioactive chemistry, carboxylation reactions are generally carried out with super-stoichiometric amounts of CO_2 at atmospheric pressure where low solubility of CO_2 in liquid reaction media is not an obstacle, since the dissolved CO_2 is in continuous equilibrium with that in the gas phase. We hypothesized that the diffusion of CO_2 into the liquid phase is often the rate-limiting step because reaction times can be remarkably decreased when the reaction is conducted at elevated pressure, as for example in the Kolbe–Schmitt synthesis of salicylic acid.[10] However, in the case of no-carrier-added (n.c.a.) ^{11}C radiochemistry, only a trace amount

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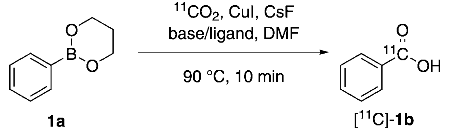
(<1 μmol) of [^{11}C/^{12}C]CO$_2$ is present in the stream of inert carrier gas and hence the partial pressure of ^{11}CO$_2$ is very low. Consequently, the amount of ^{11}CO$_2$ dissolved in solution is also very low in accord with Henry's law, even within a pressurized reaction vessel. To overcome this issue, the ^{11}CO$_2$ needs to be held in solution whilst preserving its reactivity. In earlier studies strongly basic imines, such as 1,8-diazabicyclo[5.4.0]undecene (DBU) or phosphazene bases, have been used to retain ^{11}CO$_2$ in solution.[5] We turned our attention to similar compounds which in addition to being basic might also chelate metal ions or act as complex ligands that can promote the carboxylation reaction.

We aimed initially to discover a simple metal salt–ligand system capable of mediating the carboxylation reaction while simultaneously retaining a high proportion of delivered ^{11}CO$_2$ in solution. As a model reaction, we chose to use phenylboronic acid 1,3-propanediol ester (**1a**; ca. 60–70 μmol), CuI catalyst, and CsF in a 1:1:3 molar ratio in dimethylformamide (DMF; 0.4 mL). In a control experiment omitting base/ligand, ^{11}CO$_2$ trapping efficiency was low and no [^{11}C]-**1b** was obtained (Table 1, entry 1). Other bases improved the trapping efficiency without giving useful yields of [^{11}C]-**1b** (Table 1, entries 2–9). As expected, the published catalytic Cu-NHC ligand mixture[9] also trapped ^{11}CO$_2$ exceedingly well. However, only trace amounts of [^{11}C]-**1b** were formed (Table 1, entry 9), presumably because radioactivity became trapped as unreactive *t*BuO^{11}CO$_2$K.

Table 1: Effect of the base/ligand on the ^{11}CO$_2$ trapping efficiency and the decay-corrected radiochemical yield of [^{11}C]-**1b**.



Entry	Base/ligand[a]	^{11}CO$_2$ trapped[b] [%]	RCY[c] [%]
1	none	20	0
2	pyridine	24	nd[d]
3	1,3-imidazole	35	nd
4	crypt-222	46	3
5	DMAP	51	nd
6	DABCO	82	19
7	PMEDA	99	trace
8	DBU	97	7
9	IPr·HCl/*t*BuOK	99	trace
10	(4*S*,4′*S*)-PBIPO	85	9
11	(4*R*,4′*R*)-PBIPO	83	7
12	DBU+(4*S*,4′*S*)-PBIPO	85	57
13	DMEDA	99	40
14	TMEDA	97	49

[a] Abbreviations: DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-(dimethylamino)pyridine; DMEDA = *N*,*N*′-dimethylethylenediamine; IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride; crypt-222 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane; (4*S*,4′*S*)-PBIPO = (4*S*,4′*S*)-(−)-2,2′-(3-pentylidene)bis(4-isopropyloxazoline); (4*R*,4′*R*)-PBIPO = (4*R*,4′*R*)-(+)-2,2′-(3-isopropylidene)bis(4-benzyloxazoline); PMEDA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [b] Trapping efficiency represents decay-corrected trapped radioactivity as percentage of dispensed radioactivity. [c] RCYs are estimated from dispensed ^{11}CO$_2$. [d] nd = not determined.

Bisoxazolines also gave efficient trapping, although only low yields of [^{11}C]-**1b** were obtained after 10 min at 90 °C (Table 1, entries 10 and 11).[8] The low yields were attributed to loss of ^{11}CO$_2$ from the reaction mixture at elevated temperature. Therefore, we turned our attention to using a combination of one of the efficient trapping agents, DBU, with a bisoxazoline ligand (Table 1, entry 12). This gave an increased yield of [^{11}C]-**1b**, but with suboptimal trapping efficiency. Further screening of ligand–catalyst combinations (Table 1, entries 13 and 14) revealed TMEDA to be outstandingly effective with regard to ^{11}CO$_2$ trapping efficiency.

The second step was to vary the copper catalyst source. We tested whether CuI was the preferred source by changing the copper salt in the promising reaction example that used TMEDA/CuI (Table 2, entry 1). Reaction did not occur when CuI was omitted (Table 2, entry 2). Equimolar replacement of CuI with CuCl, CuBr, CuCN, or CuOTf did not improve the radiochemical yield (Table 2, entries 3–6). Also Cu^0 (Table 2, entry 7) was less effective than CuI. Attempted generation of Cu$^{\mathrm{I}}$ in situ from CuF$_2$ and ascorbic acid gave only trace amounts of [^{11}C]-**1b** (Table 2, entry 8), probably due to the low stability of CuF which disproportionates immediately to yield Cu^0 and CuF$_2$.[11] Therefore CuI was established as the preferred copper source.

Table 2: Effects of the copper catalyst and MF on the RCY of [^{11}C]-**1b**.[a]

Entry	Catalyst	MF	RCY [%]
1	CuI	CsF	49
2	none	CsF	–
3	CuCl	CsF	13
4	CuBr	CsF	24
5	CuCN	CsF	36
6	CuOTf	CsF	9
7	Cu^{0}[b]	CsF	3
8	CuF$_2$[c]	CsF	trace
9	CuF$_2$	none	9
10	CuI	none	–

[a] Conditions: DMF (400 μL), **1a** (50 μmol), TMEDA (100 mm), catalyst (2 μmol), CsF (150 μmol), 90 °C, 10 min. [b] Finely ground copper powder. [c] In the presence of ascorbic acid (100 mm).

Third, we studied the effect of the fluoride ion source and the solvent. We observed that omission of CsF resulted in low or no yield of [^{11}C]-**1b** (Table 2, entries 9 and 10). We considered that higher concentrations of fluoride ion might prove beneficial. In order to circumvent the limited solubility of CsF in DMF, we turned our attention to more soluble sources of fluoride ion. The use of tetrabutylammmonium fluoride (TBAF; Table 3, entry 2) or [18]crown-6 (18C6) with either KF (Table 3, entry 3) or CsF (Table 3, entry 4) gave no improvement over the use of CsF alone (Table 3, entry 1). However, the use of crypt-222 in conjunction with KF under homogeneous conditions led to remarkable improvements in the carboxylation yields (Table 3, entries 5–9). Thus, the combination of CuI, KF, crypt-222, and TMEDA after 10 min at 90 °C gave [^{11}C]-**1b** in 54 % RCY (Table 3, entry 5). An increase of the reaction temperature to 95 °C gave a comparable RCY (57 %) after only 7 min (Table 3,

Table 3: Effects of the fluoride ion source on the RCY of [^{11}C]-**1b**.[a]

Entry	MF	T [°C]	t [min]	RCY [%]
1	CsF	90	10	49
2	TBAF	90	10	trace
3	KF+18C6	90	10	38
4	CsF+18C6	90	10	44
5	KF+crypt-222	90	10	54
6	KF+crypt-222	95	7	57
7	KF+crypt-222	100	5	81
8[b]	KF+crypt-222	80	5	99
9[b]	KF+crypt-222	95	5	99

[a] Screening conditions: DMF (400 μL), **1a** (50 μmol), TMEDA (100 mM), CuI (2 μmol), fluoride salt (150 μmol). [b] CuI (0.3 μmol), KF+crypt-222 (0.9 μmol).

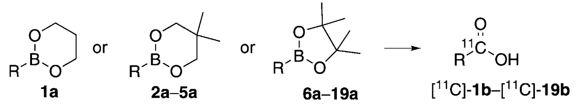
entry 6). Reaction at 100 °C for 5 min gave [^{11}C]-**1b** in 81 % RCY (Table 3, entry 7). However, the yield decreased at 110 °C due to rapid loss of activity from the reaction mixture.

Remarkably, decrease of the CuI catalyst load to 0.3 μmol and adjustment of the molar ratio of KF+crypt-222 and CuI to 3:1 gave almost quantitative incorporation of the trapped $^{11}CO_2$ (Table 3, entries 8 and 9). We attribute this finding to a stoichiometry effect and reason that a large excess of Cu^I shifts the equilibrium towards the organo–copper intermediate thus hampering reaction with n.c.a. $^{11}CO_2$. Equally good results were obtained irrespective of the purity of CuI being used.

Replacements of DMF with alternative reaction media were detrimental, except for dimethylacetamide (DMA). Unlike DMF and DMA, dioxane and 1,2-dimethoxyethane (DME) were ineffective in combination with TMEDA for $^{11}CO_2$ trapping. Reactants degraded rapidly in hexamethylphosphoramide (HMPA) or MeCN. Neat TMEDA gave low yield.

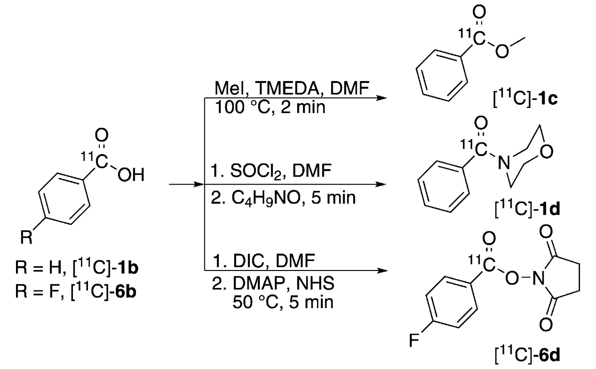
The most effective conditions (Table 3, entries 8 and 9) were used to study the substrate scope. A variety of commercially available boronic acid esters were screened (Table 4). Many functional groups were found to be compatible with this carboxylation reaction. Sensitive substrates such as 4-bromo-, 4-cyano- or 4-formylbenzene, which clearly would not survive exposure to Grignard or organolithium reagents, gave the desired radioactive products in high to excellent yields. Even **10a** containing a protic hydroxy group was tolerated to some extent. Amino groups, as in **11a** and **12a**, were however less tolerated. Electron-deficient heterocycles (**13a**–**15a**) generally gave low yields whereas electron-rich **16a** gave a high yield. Unlike alkyl boronic acid ester **17a**, examples of a vinyl (**18a**) and an alkynyl boronic acid ester (**19a**) gave high yields.

Table 4: Substrate scope of the ^{11}C carboxylation reaction.[a]



Substrate	R	Product	RCY [%][b]
1a	phenyl	[^{11}C]-**1b**	99±1
2a	4-methylphenyl	[^{11}C]-**2b**	99±1
3a	4-formylphenyl	[^{11}C]-**3b**	99±1
4a	4-bromophenyl	[^{11}C]-**4b**	77±7
5a	4-chlorophenyl	[^{11}C]-**5b**	71±5
6a	4-fluorophenyl	[^{11}C]-**6b**	77±6
7a	4-cyanophenyl	[^{11}C]-**7b**	78±27
8a	4-nitrophenyl	[^{11}C]-**8b**	85±3
9a	4-biphenyl	[^{11}C]-**9b**	59±24
10a	4-hydroxyphenyl	[^{11}C]-**10b**	20±5
11a	2-aminophenyl	[^{11}C]-**11b**	7±3
12a	3-aminopyrid-5-yl	[^{11}C]-**12b**	3±1
13a	2-acetamidopyrid-5-yl	[^{11}C]-**13b**	18±5
14a	4,6-dimethoxypyrimid-2-yl	[^{11}C]-**14b**	3±2
15a	6-chloropyraz-2-yl	[^{11}C]-**15b**	5±1
16a	3-methylthien-2-yl	[^{11}C]-**16b**	69±1
17a	but-1-yl	[^{11}C]-**17b**	8±3
18a	*E*-2-(4-chlorophenyl)vinyl	[^{11}C]-**18b**	91±5
19a	5-chlorobut-1-ynyl	[^{11}C]-**19b**	70±1

[a] Conditions: $^{11}CO_2$, CuI, TMEDA, crypt-222, KF, DMF, 100 °C, 5 min. [b] RCY values are mean ± (standard deviation) ($n=3$).

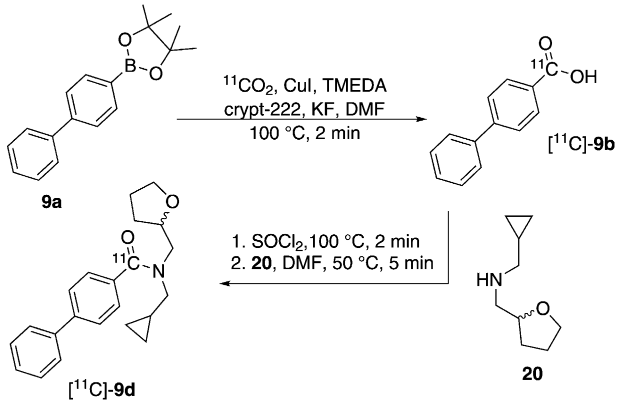


Scheme 2. Rapid conversion of ^{11}C-labeled carboxylic acids into ^{11}C-labeled esters and amides.

Having found that we were able to prepare a variety of [^{11}C]carboxylic acids efficiently within only 10 min from the end of radionuclide production, we investigated their further conversion into labeled derivatives (Scheme 2). Treatment of crude [^{11}C]-**1b** with methyl iodide (50 mM) at 100 °C for 2 min gave [^{11}C]benzoic acid methyl ester [^{11}C]-**1c** in 84 % RCY. The HPLC-purified product was obtained within 18 min from end of radionuclide production in a radiochemical purity of > 99 % and with a specific radioactivity of 3 Ci μmol^{-1}. No particular precautions in terms of exclusion of air, a source of carrier CO_2, were necessary to obtain the product with such high specific radioactivity.

Besides carboxylic acids and esters, carboxamides are among the most abundant functional groups in biomolecules and a variety of widely used radiotracers contain benzamide groups, for example [^{11}C]-(*R*)-PK 11195.[12] We therefore investigated the conversion of model compound [^{11}C]-**1b** into a reactive intermediate for amide formation (Scheme 2) as follows. Solid-phase extraction of the ^{11}C-labeled acid with a C18 SPE cartridge was used to remove TMEDA and other basic constituents from the reaction mixture. The cartridge was then dried in a stream of helium for 2 min before elution of [^{11}C]-**1b** with DMF into a reaction vessel precharged with $SOCl_2$ (50 mM final concentration). The mixture was heated to 100 °C for 2 min, morpholine (50 mM) was added, and the mixture was again heated for 2 min. HPLC and LC-MS analysis revealed clean conversion of [^{11}C]-**1b** into amide [^{11}C]-**1d** in 46% RCY with a specific radioactivity of 2.5 Ci µmol^{-1} at 23 min from radionuclide production. We also investigated the use of carbodiimide reagents for amide formation. As a proof of principle, diisopropylcarbodiimide (DIC), DMAP, and *N*-hydroxysuccinimide (NHS) were used with [^{11}C]-**6b** to synthesize [^{11}C]-**6d**, a ^{11}C-labeled analogue of the useful peptide- and protein-labeling agent [^{18}F]SFB in 49% RCY.[13]

We extended this method to an example of a one-pot synthesis of a candidate radioligand for PET imaging (Scheme 3), based on the known oxytocin receptor ligand **9d**.[14] Thus, **9a** was reacted with $^{11}CO_2$ as described previously. Solvent, TMEDA, and unreacted $^{11}CO_2$ were removed by evaporation in the vacuum. The residue containing [^{11}C]-**9b** was redissolved in DMF, mixed with $SOCl_2$ (50 mM), and heated to 100°C for 2 min. As no TMEDA was present, a homogeneous reaction mixture was obtained. Amine **20** was then added and the mixture kept at 50°C for 5 min. HPLC gave [^{11}C]-**9d** in 20% RCY at 43 min from radionuclide production with a radiochemical purity of >98% and a specific radioactivity of 1.5 Ci µmol^{-1}. Product identity was confirmed with HPLC and LC-MS.



Scheme 3. Synthesis of the ^{11}C-labeled oxytocin receptor ligand [^{11}C]-**9d**.

We showed herein that CuI-mediated carboxylations of boronic acid esters are rapid under subatmospheric partial pressures of $^{11}CO_2$ in an inert atmosphere in the presence of a simple combination of TMEDA, KF, and crypt-222. The resulting [^{11}C]carboxylic acids are obtained in high specific radioactivity, and they can be rapidly converted into ^{11}C-labeled esters and amides, thus enhancing the range of functional groups accessible for labeling. This conversion of boronates is significantly more tolerant to diverse functional groups (e.g., halo, nitro or carbonyl) than reactions with organolithium or organomagnesium reagents. Given the high prevalence of carboxy groups and their derivatives in PET radiotracers, paired with the availability of $^{11}CO_2$ at most PET centres, we expect this novel method to be widely adapted for PET radioligand development.

Experimental Section

^{11}C carboxylation: Cyclotron-produced $^{11}CO_2$, trapped on a column of molecular sieves (13X), was released by purging the heated column (330°C) with He gas at 15 mL min^{-1} and directed into a reaction vial containing boronic acid ester (60 µmol) and TMEDA (60 mg, 0.5 mmol) plus CuI:crypt-222:KF (0.3:1:1 µmol) in DMF (400 µL). The reaction vessel was sealed when the radioactivity content reached a maximum (after about 2 min), heated at 90°C for 5 min, and then rapidly cooled to room temperature. The reaction mixture was quenched with aqueous formic acid (0.1M, 10 mL) and passed through a C18 SPE cartridge (Waters). The cartridge was dried in a stream of He and the [^{11}C]carboxylic acid was eluted in high radiochemical purity with DMF.

Radiosynthesis of [^{11}C]-**9d**: $SOCl_2$ (25 mmol) in DMF (0.5 mL) was added to [^{11}C]-**9b**. This mixture was heated to 100°C for 2 min before amine **20** (20 mg, 130 µmol) was added. The mixture was then kept at 50°C for 5 min, quenched with water, injected onto a Luna RP18(2) column (10 µm, 250 mm × 10 mm, Phenomenex), and eluted with MeCN/25 mM $HCOONH_4$ (6:4, v/v) at 4.75 mL min^{-1}. [^{11}C]-**9d** ($t_R = 14.5$ min) was obtained in 20% RCY.

For details of the other syntheses see the Supporting Information.

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