Published in final edited form as:

Angew Chem Int Ed Engl. 2012 March 12; 51(11): 2698–2702. doi:10.1002/anie.201107263.

Cu(I)-catalyzed ^{11}C -carboxylation of boronic acid esters: a rapid and convenient entry to ^{11}C -labeled carboxylic acids, esters and amides

Patrick J. Riss*,

Wolfson Brain Imaging Centre, University of Cambridge Box 65 Addenbrooke's Hospital, CB2 0QQ, Cambridge, UK

Molecular Imaging Branch, National Institute of Mental Health, Bldg 10 Room B3C346A, 10 Center Drive, Bethesda, MD 20892-1003, USA

Shuiyu Lu,

Molecular Imaging Branch, National Institute of Mental Health, Bldg 10 Room B3C346A, 10 Center Drive, Bethesda, MD 20892-1003, USA

Sanjay Telu,

Molecular Imaging Branch, National Institute of Mental Health, Bldg 10 Room B3C346A, 10 Center Drive, Bethesda, MD 20892-1003, USA

Franklin I. Aigbirhio, and

Wolfson Brain Imaging Centre, University of Cambridge Box 65 Addenbrooke's Hospital, CB2 0QQ, Cambridge, UK

Victor W. Pike

Molecular Imaging Branch, National Institute of Mental Health, Bldg 10 Room B3C346A, 10 Center Drive, Bethesda, MD 20892-1003, USA

Keywords

carbon-11; PET; radiochemistry; carboxylation; boronic acid ester; radiotracer

Non-invasive 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 in biomedical research. Novel radiotracers for imaging a variety of biological targets are continually needed to fully exploit the potential of PET. Consequently, the generation of reliable chemical methodology for labeling organic molecules with short-lived positron-emitters is key to the production of novel radiotracers intended for complex imaging studies in human subjects.^[1,2]

Carbon-11, 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 carbon-12 with carbon-11 represents an often elegant and desirable approach in radiotracer development. Carbon-11 is readily obtained in high activity and in high specific radioactivity from moderate energy cyclotrons via the $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ nuclear

*pr340@wbic.cam.ac.uk.

**Supporting information for this article is available on the WWW under <http://www.angewandte.org>.

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}C]CH₃I or [^{11}C]CH₃OTf.^[2]

Direct applications of [^{11}C]CO₂ in radiotracer synthesis are mostly ^{11}C -carboxylations of Grignard and organolithium reagents to produce ^{11}C -labeled carboxylic acids (Scheme 1).^[4] For successful outcomes, these reactions require great care, including diligent control of reagent stoichiometry, and the exclusion of moisture and atmospheric CO₂. 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}C]CO₂ 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 installation of carbon-11 into candidate radiotracers is attractive with regard to avoiding losses of radioactivity, conserving specific radioactivity and achieving rapid and simple radiosyntheses.

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 in molecules devoid of reactive electrophilic functional groups, whereas boronic acid esters can be readily introduced into highly functionalised molecules.^[6] In view of these considerations and of recent developments in transition metal mediated carboxylation reactions,^[7-9] in particular with Cu-*bis*-oxazoline^[8] and Cu-*N*-heterocyclic carbene (Cu-NHC)^[9] type catalysts, we succeeded in devising a new catalytic methodology for C- ^{11}C bond formation direct from [^{11}C]CO₂ using boronic acid esters, as we now report here.

1. Optimization of trapping agent/complex ligand

In non-radioactive chemistry, carboxylation reactions are generally carried out with super-stoichiometric amounts of CO₂ at atmospheric pressure where low solubility of CO₂ in liquid reaction media is not an obstacle, since the dissolved CO₂ is in continuous equilibrium with that in the gas phase. We hypothesised that the diffusion of CO₂ into the liquid phase is often the rate-limiting step because long reaction times at atmospheric pressure 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 ^{11}C -radiochemistry, only a trace amount (<1 μmol) of [$^{11}\text{C}/^{12}\text{C}$]CO₂ is present in the stream of inert carrier gas and hence the partial pressure of [^{11}C]CO₂ is very low. Consequently, the amount of $^{11}\text{CO}_2$ dissolved in solution is also very low in accord with Henry's law, even within a pressurised reaction vessel. To overcome this issue, the [^{11}C]CO₂ needs to be held in solution whilst preserving its reactivity. Earlier studies have used strongly basic imines, such as DBU or phosphazene bases to retain [^{11}C]CO₂ in solution.^[5] We turned our attention to similar compounds which in addition to being basic might also chelate metals 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}C]CO₂ in solution. As a model reaction, we chose to use a 1: 1: 3 molar ratio of phenylboronic acid 1,3-propanediol ester (**1a**; ~ 60–70 μmol), CuI catalyst and CsF in DMF (0.4 mL).

In a control experiment omitting base/ligand, [^{11}C]CO₂ trapping efficiency was low and no [^{11}C]**1b** was obtained (Table 1, entry 1). Other bases improved 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 the [^{11}C]CO₂ exceedingly well. However, negligible [^{11}C]**1b** was formed (Table 1, entry 9), presumably because radioactivity became trapped as unreactive *t*-BuO¹¹CO₂K.

Bis-oxazolines 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}C]CO₂ 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 *bis*-oxazoline ligand (Table 1, entry 12). This gave an increased yield of [^{11}C]**1b**, but with sub-optimal trapping efficiency. Further screening of ligand-catalyst combinations (Table 1, entries 13–14) revealed TMEDA to be outstandingly effective with regard to [^{11}C]CO₂ trapping efficiency.

2. Variation of copper catalyst source

We tested whether CuI was the preferred source of copper catalyst 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 radiochemical yield (Table 2, entries 3–6). Also Cu(0) (Table 2, entry 7) was less effective than CuI. Attempted generation of Cu(I) in situ from CuF₂ and ascorbic acid gave only trace [^{11}C]**1b** (Table 2, entry 8), probably due to the low stability of CuF which disproportionates immediately to yield Cu(0) and CuF₂.^[11] Therefore CuI was established as the preferred copper source.

3. Effect of fluoride ion source and solvent

We observed that omission of CsF from reactions 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 TBAF (Table 3, entry 2) or 18-crown-6 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 K 2.2.2 in conjunction with KF under homogeneous conditions led to remarkable improvements in carboxylation yields (Table 3, entries 5–9). Thus, the combination of CuI, KF, K 2.2.2 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 comparable RCY (57%) after only 7 min (Table 3, entry 6). Reaction at 100 °C for 5 min gave [^{11}C]**1b** in 81% RCY (Table 3, entry 7). However, 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-K 2.2.2 and CuI to 3: 1 gave almost quantitative incorporation of the trapped [^{11}C]CO₂ into [^{11}C]**1b** (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 Cu-organyl intermediate thus hampering reaction with n.c.a. [^{11}C]CO₂. Equally good results were obtained irrespective of the purity of CuI being used.

Replacements of DMF with alternative reaction media were detrimental, except for DMA. Unlike DMF and DMA, dioxane and DME were ineffective in combination with TMEDA for [^{11}C]CO₂ trapping. Reactants degraded rapidly in HMPA or MeCN. Neat TMEDA gave low yield.

4. Investigation of substrate scope

Established effective conditions (Table 3, entries 8–9) were used to investigate the substrate scope of the ^{11}C -carboxylation reaction. A variety of commercially available boronic acid esters were screened (Table 4).

Many functional groups were found to be compatible with the ^{11}C -carboxylation reaction. Sensitive substrates such as 4-bromo, 4-cyano or 4-formylbenzenes, 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 hydroxyl 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 high yield. Unlike alkylboronic acid ester **17a**, examples of a vinyl (**18a**) and an alkynylboronic acid ester (**19a**) gave high yields.

5. Conversion of the ^{11}C -labeled acids into derivatives

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 . 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 e.g., ^{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 pre-charged 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 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 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 were used with ^{11}C **6b** to synthesise ^{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 methodology to an example of a single-pot synthesis of a candidate radioligand for PET imaging (Scheme 3), based on a known oxytocin receptor ligand, **9d**.^[14] Thus, **9a** was reacted with ^{11}C CO_2 as described previously. Solvent, TMEDA and unreacted ^{11}C CO_2 were removed by evaporation in vacuo. The residue containing ^{11}C **9b** was re-dissolved in DMF, mixed with SOCl_2 (50 mM) and heated to 100 °C for 2 min. Due to the absence of TMEDA, 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 . Product identity was confirmed with HPLC and LC-MS.

Summary

CuI-mediated carboxylations of boronic acid esters are rapid under sub-atmospheric partial pressures of [^{11}C]CO₂ in an inert atmosphere in the presence of a simple combination of TMEDA, KF and K 2.2.2. The resulting [^{11}C]carboxylic acids are obtained in high specific radioactivity. [^{11}C]Carboxylic acids 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 carboxyl groups and their derivatives in PET radiotracers, paired with the availability of [^{11}C]CO₂ at most PET centres, we expect this novel methodology to be widely adapted for PET radioligand development.

Experimental Section

Typical ^{11}C -carboxylation reaction

Cyclotron-produced [^{11}C]CO₂, trapped on a column of molecular sieves (13X), was released by purging the heated column (330 °C) with He gas at 15 mL/min and directed into a reaction vial containing boronic acid ester (60 μmol) and TMEDA (60 mg, 0.5 mmol) plus CuI: K 2.2.2: KF (0.3: 1: 1 μmol) in DMF (400 μL). The reaction vessel was sealed when radioactivity content reached a maximum (after ~ 2 min), heated at 90 °C for 5 min, and then rapidly cooled to RT. The reaction mixture was quenched with aqueous formic acid (0.1 M, 10 mL) and passed through a C18 plus 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

SOCl₂ (25 mmol) in DMF (0.5 mL) was added to [^{11}C]9b. This mixture was heated to 100 °C for 2 min before the amine 20 (20 mg, 130 μmol) was added. The mixture was then kept at 50 °C for 5 min, quenched with water and injected onto a Luna RP18(2) column (10 μm , 250 mm $\times$ 10 mm, Phenomenex) eluted with MeCN-25 mM HCOONH₄ (6: 4 v/v) at 4.75 mL/min. [^{11}C]9d (t_{R} = 14.5 min) was obtained in 20% RCY.

For details of other syntheses see supporting information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

PJR was supported by a Medical Research Council (UK) postdoctoral fellowship as a visiting volunteer worker at the NIH. ST, SL and VWP were supported by the Intramural Research Program of the NIH (NIMH). We thank Mr. Jinsoo Hong (NIMH) for technical assistance and the NIH Clinical PET department (Chief, Dr. P. Herscovitch) for carbon-11 production.

References

1. Cai L, Lu S, Pike VW. Eur. J. Org. Chem. 2008;2853–2873.
2. a) Antoni, G.; Kihlberg, T.; Långström, B. Handbook of Nuclear Chemistry. Vértes, A.; Nagy, S.; Klencsár, Z., editors. Vol. 4. Amsterdam: Kluwer Academic Publishers; 2003. p. 119-157. b) Miller PW, Long NJ, Vilar R, Gee AD. Angew. Chem. Int. Ed. 2008; 47:8998–9033. c) Allard M, Fouquet E, James D, Szlosek-Pinaud M. Curr. Med. Chem. 2008; 15:235–277. [PubMed: 18288983] d) Scott PJH. Angew. Chem. Int. Ed. 2009; 48:6001–6004.

3. Meyer GJ, Waters SL, Coenen HH, Luxen A, Mazière B, Långström B. *Eur. J. Nucl. Med.* 1995; 22:1420–1432. [PubMed: 8586089]
4. a) Pike VW, Eakins MN, Allan RM, Selwyn AP. *J Radioanal. Chem.* 1981; 64:291–297. b) Pike VW, Eakins MN, Allan RM, Selwyn AP. *Int. J. Appl. Radiat. Isot.* 1982; 33:505–512. [PubMed: 6981606] c) Livni E, Elmaleh DR, Levy S, Brownell GL, Strauss WH. *J. Nucl. Med.* 1982; 23:169–175. [PubMed: 6977020] d) van der Meij M, Carruthers NI, Herschied JDM, Jablonowski JA, Leysen JE, Windhorst AD. *J. Label. Compd. Radiopharm.* 2003; 46:1075–1086.
5. a) Hooker JM, Schönberger M, Schieferstein H, Fowler JS. *Angew. Chem. Int. Ed.* 2008; 47:5989–5992. b) Hooker JM, Reibel AT, Hill SM, Schueller MJ, Fowler JS. *Angew. Chem. Int. Ed.* 2009; 48:3482–3485. c) Wilson AA, Garcia A, Houle S, Sadovski O, Vasdev N. *Chem. Eur. J.* 2011; 17:259–264. [PubMed: 21207622]
6. Kleeberg C, Dang L, Lin Z, Merder TB. *Angew. Chem. Int. Ed.* 2009; 48:5350–5354.
7. a) Ukai K, Aoki M, Takaya J, Iwasawa N. *J. Am. Chem. Soc.* 2006; 128:8706–8707. [PubMed: 16819845] b) Riduan SN, Zhang Y. *Dalton Trans.* 2010; 39:3347–3357. [PubMed: 20379526] c) Correa A, Martin R. *Angew. Chem. Int. Ed.* 2009; 48:6201–6204.
8. Takaya J, Tadami S, Ukai K, Iwasawa N. *Org. Lett.* 2008; 10:2697–2700. [PubMed: 18507391]
9. a) Ohishi T, Nishiura M, Hou Z. *Angew. Chem. Int. Ed.* 2008; 47:5792–5795. b) Ohishi T, Zhang L, Nishiura M, Hou Z. *Angew. Chem. Int. Ed.* 2011; 50:8114–8117.
10. a) Kolbe H. *Annal. Chem. Pharm.* 1860; 113:125–127. b) Schmitt R. *J. Prakt. Chem.* 1885; 31:397–411. c) Lindsey AS, Jeskey H. *Chem. Rev.* 1957; 57:583–620.
11. Gulliver DJ, Levason W, Webster M. *Inorg. Chim. Acta.* 1981; 52:153–159.
12. Shah F, Hume SP, Pike VW, Ashworth S, McDermott J. *Nucl. Med. Biol.* 1994; 21:573–581. [PubMed: 9234314]
13. a) Vaidyanathan G, Zalutsky MR. *Nucl. Med. Biol.* 1992; 19:275–281. b) Wester HJ, Hamacher K, Stocklin G. *Nucl. Med. Biol.* 1996; 23:365–372. [PubMed: 8782249]
14. Bellenie BR, Barton NP, Emmons AJ, Heer JP, Salvagno C. *Bioorg. Med. Chem. Lett.* 2009; 19:990–994. [PubMed: 19095447]

Scheme 1.

Radiosynthesis of [^{11}C]carboxylic acids from classical organometallic reagents or novel reactions of boronic acid esters with [^{11}C]CO₂.

Scheme 2.

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

Scheme 3. Synthesis of ^{11}C -labeled oxytocin receptor ligand, $[^{11}\text{C}]\mathbf{9d}$.

Table 1Effect of base/ligand on [^{11}C]CO $_2$ trapping efficiency and RCY of [^{11}C]1b.

Entry	Base/ligand ^a	[^{11}C]CO $_2$ trapped ^b (%)	RCY ^c (%)
1	none	20	0
2	pyridine	24	nd ^d
3	1,3-imidazole	35	nd
4	K 2.2.2	46	3
5	DMAP	51	nd
6	DABCO	82	19
7	PMEDA	99	trace
8	DBU	97	7
9	IPr-HCl/ <i>t</i> -BuOK	99	trace
10	(4 <i>S</i> ,4' <i>S</i>)-PBIPO	85	9
11	(4 <i>R</i> ,4' <i>R</i>)-PBIPO	83	7
12	DBU-(4 <i>S</i> ,4' <i>S</i>)-PBIPO	85	57
13	DMEDA	99	40
14	TMEDA	97	49

[a] Abbreviations: DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undecene; DMAP = 4-(dimethylamino)pyridine; DMEDA = *N,N'*-dimethylethylenediamine; IPr-HCl = 1,3-*bis*-(2,6-diisopropylphenyl)imidazolium chloride; K 2.2.2 = 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-isopropylloxazoline); (4*R*,4'*R*)-PBIPO = (4*R*,4'*R*)-(+)-2,2'-(3-isopropylidene)*bis*(4-benzylloxazoline); PMEDA = *N,N,N',N''*-pentamethyldiethylenetriamine; TMEDA = *N,N,N',N''*-tetramethylethylenediamine.

[b] Trapping efficiency represents decay-corrected trapped radioactivity as a % of dispensed radioactivity.

[c] Decay-corrected radiochemical yields (RCYs) are estimated from dispensed [^{11}C]CO $_2$.

[d] nd = not determined.

Table 2Effects of copper catalyst and MF on 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] Copper salt catalyst screening conditions: 400 μL DMF, 50 μmol **1a**, 100 mM TMEDA, 2 μmol catalyst, 150 μmol CsF, 90 $^{\circ}\text{C}$, 10 min.

[b] Fine ground copper powder.

[c] In presence of 100 mM ascorbic acid.

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

Entry	MF	Temp (°C)	Time (min)	RCY (%)
1	CsF	90	10	49
2	TBAF	90	10	trace
3	KF-18-C-6	90	10	38
4	CsF-18-C-6	90	10	44
5	KF-K 2.2.2	90	10	54
6	KF-K 2.2.2	95	7	57
7	KF-K 2.2.2	100	5	81
^{8b}	KF-K 2.2.2	80	5	99
^{9b}	KF-K 2.2.2	95	5	99

^[a] Screening conditions: 400 μL DMF, 50 μmol **1a**, 100 mM TMEDA, 2 μmol CuI, 150 μmol fluoride salt,^[b] 0.3 μmol CuI, 0.9 μmol KF and K 2.2.2.

Table 4Substrate scope of the ^{11}C -carboxylation reaction.

Substrate	R	Product	RCY (%) ^a
1a	phenyl	$[^{11}\text{C}]\text{1b}$	99 ± 1
2a	4-methylphenyl	$[^{11}\text{C}]\text{2b}$	99 ± 1
3a	4-formylphenyl	$[^{11}\text{C}]\text{3b}$	99 ± 1
4a	4-bromophenyl	$[^{11}\text{C}]\text{4b}$	77 ± 7
5a	4-chlorophenyl	$[^{11}\text{C}]\text{5b}$	71 ± 5
6a	4-fluorophenyl	$[^{11}\text{C}]\text{6b}$	77 ± 6
7a	4-cyanophenyl	$[^{11}\text{C}]\text{7b}$	78 ± 27
8a	4-nitrophenyl	$[^{11}\text{C}]\text{8b}$	85 ± 3
9a	4-biphenyl	$[^{11}\text{C}]\text{9b}$	59 ± 24
10a	4-hydroxyphenyl	$[^{11}\text{C}]\text{10b}$	20 ± 5
11a	2-aminophenyl	$[^{11}\text{C}]\text{11b}$	7 ± 3
12a	3-aminopyridin-5-yl	$[^{11}\text{C}]\text{12b}$	3 ± 1
13a	2-acetamido pyridin-5-yl	$[^{11}\text{C}]\text{13b}$	18 ± 5
14a	4,6-dimethoxy pyrimidin-2-yl	$[^{11}\text{C}]\text{14b}$	3 ± 2
15a	6-chloropyrazin-2-yl	$[^{11}\text{C}]\text{15b}$	5 ± 1
16a	3-methylthiophen-2-yl	$[^{11}\text{C}]\text{16b}$	69 ± 1
17a	but-1-yl	$[^{11}\text{C}]\text{17b}$	8 ± 3
18a	<i>E</i> -2-(4-chlorophenyl)vin-1-yl	$[^{11}\text{C}]\text{18b}$	91 ± 5
19a	5-chlorobut-1-yn-1-yl	$[^{11}\text{C}]\text{19b}$	70 ± 1

^[a] RCY values are mean $\pm$ S.D. ($n = 3$).