

Nordeman, P., Chow, S. Y., Odell, Adam

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# Palladium-Mediated $^{11}\text{C}$ -Carbonylations Using Aryl Halides and Cyanamide

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P. Nordeman,<sup>a</sup> S. Y. Chow,<sup>b</sup> A. F. Odell,<sup>c</sup> G. Antoni,<sup>a</sup> and L. R. Odell<sup>b\*</sup>

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A robust and high-yielding radiochemical synthesis of  $^{11}\text{C}$ -*N*-cyanobenzamides using a palladium-mediated aminocarbonylation with  $^{11}\text{C}$ -CO, aryl halides and cyanamide is described. The bidentate ligand 1,1'-bis(diphenylphosphino)ferrocene provided  $^{11}\text{C}$ -*N*-cyanobenzamides from aryl-iodides, bromides, triflates and even chlorides in 28–79% radiochemical yield after semi-preparative HPLC. To further highlight the utility of this method, novel  $^{11}\text{C}$ -*N*-cyanobenzamide analogs of flufenamic acid, meflenamic acid, dazoxiben and tamibarotene were synthesized in 34–71% radiochemical yields.

## Introduction

Positron emission tomography (PET) is a powerful noninvasive modality for the visualization of biological functions, in real time, using a positron emitting nuclide incorporated into a bioactive molecule (tracer).<sup>1,2</sup> PET is an important clinical diagnostic tool and has found extensive use in the monitoring of disease progression and treatment response in cancer patients.<sup>2–4</sup> PET has also emerged as an enabling tool to study the underlying biological processes in many neurological disorders and in the development of drugs targeting the CNS.<sup>5</sup>

One of the most important nuclides used in PET is the cyclotron-produced carbon-11 ( $^{11}\text{C}$ ) with a half-life of 20.4 min.<sup>6</sup> This is mainly due to the potential introduction of the carbon nuclide into various positions in a molecule of interest without disturbing its biological activity.  $^{11}\text{C}$  is typically produced in the form of  $^{11}\text{C}$ -carbon dioxide ( $^{11}\text{CO}_2$ ) and can be readily transformed into a number of key building blocks including  $^{11}\text{C}$ -carbon monoxide ( $^{11}\text{CO}$ ).<sup>7,8</sup> The synthetic versatility of  $^{11}\text{CO}$  is well-known and it can be utilized in various metal-mediated reactions yielding a host of different carbonyl and carboxylic acid derivatives including amides, acids, esters and ketones.<sup>9–13</sup>

Despite these advances, there are a multitude of biologically important functional groups and scaffolds that cannot be prepared using existing  $^{11}\text{CO}$  technology. This highlights one of the major limitations of PET, namely the lack of generally applicable methods for the incorporation of the radionuclide into a target molecule. This has created a situation where tracer synthesis is dominated by a handful of

synthetic methods (e.g. methylation) and potential tracers are invariably designed to conform within the narrow confines of existing chemistry, rather being naturally guided by target biology. To overcome these issues, there is an increasing demand for the development of new radiochemical methods that are suitable for the labelling of complex biologically active molecules. The use of  $^{11}\text{C}$ , however, poses a number of additional challenges as the short half-life of  $^{11}\text{C}$  demands the development of fast and efficient reactions.

Bioisosteric replacement has played a vital role in drug discovery and development since the term was first coined in the 1950's by Harris Friedman.<sup>14,15</sup> The concept is based upon the assumption that atoms or functional groups with comparably shapes and/or physicochemical properties will interact similarly with a biological target and elicit analogous biological effects.<sup>15</sup> Thus, bioisosteres have been employed to improve potency and selectivity, alter physical properties, modulate metabolism, increase permeability and adsorption and reduce the toxicity of a biologically active compound.<sup>16</sup> However, despite the widespread use of bioisosteres to optimize these properties in drug discovery and development, this strategy remains largely unexplored in the field of PET tracer development.

The carboxylic acid is an important functional group capable of interacting with a biological target through both hydrogen bonding and electrostatic interactions. Carboxylic acids can also increase aqueous solubility and influence pharmacokinetics and are found in a wide range of drug and biologically active molecules. This has led to the development of several bioisosteres for this moiety.<sup>15–20</sup>

*N*-Cyanobenzamides (Scheme 1) are an interesting, yet relatively unexplored, class of carbonyl derivatives.<sup>21,22</sup> They have been employed as intermediates in the synthesis of diverse heterocyclic scaffolds and they have also found utility as carboxylic acid bioisosteres in a number of biologically active molecules.<sup>20,23,24</sup> Recently, we reported the

<sup>a</sup> Preclinical PET Platform Chemistry, Department of Medicinal Chemistry, Uppsala University.

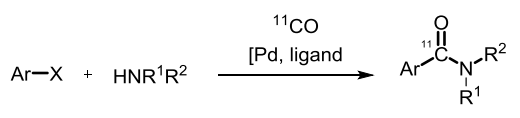
<sup>b</sup> Division of Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala University, Box 574, 75123, Uppsala, Sweden.

<sup>c</sup> School of Medicine, St. James' University Hospital, University of Leeds, LS9 7TF, Leeds, UK.

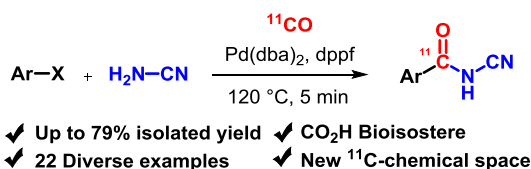
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carbonylative synthesis of this functional group, under palladium(0) catalysis, starting from an aryl halide, cyanamide and carbon monoxide using a bridged two compartment setup.<sup>25,26</sup> Realizing that this provided an excellent starting point for the development of  $^{11}\text{C}$ -carbonylation chemistry we sought to develop the first synthetic procedure for the preparation of  $^{11}\text{C}$ -labelled *N*-cyanobenzamides.<sup>6,27</sup> This would make a valuable addition to the radiochemistry toolbox, opening up a new area of  $^{11}\text{C}$ -chemical space, that can be exploited in the design and synthesis of novel PET tracers. Herein, we describe a rapid, robust and high yielding method for the preparation of  $^{11}\text{C}$ -*N*-cyanobenzamides via a palladium mediated carbonylation using an aryl halide, cyanamide and  $^{11}\text{C}$  (Scheme 1).

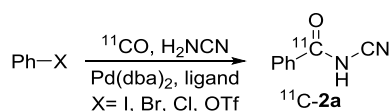
#### Previous work: $^{11}\text{C}$ -Benzamides



#### This work: $^{11}\text{C}$ -*N*-Cyanobenzamides



detected using this ligand. The lower RCP was due to the formation of a highly lipophilic impurity, possibly the  $^{11}\text{C}$ -Pd-Xantphos intermediate prior to nucleophilic attack by cyanamide.<sup>29</sup> We continued our ligand screening by using the less strained oxydi-2,1-phenylenebis(diphenylphosphine) (DPEphos), however full trapping of  $^{11}\text{C}$  was not achieved in the range 90–150 °C and no improvement in RCP was observed (entry 5–7). To our delight, the bidentate ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf) gave complete trapping of  $^{11}\text{C}$  (RTE >99%) and the desired product in high RCP (94±2%, entry 8). This may be attributed to the flexible ligand backbone, allowing it to stabilize the electronically and structurally disparate intermediates (i.e. Pd(0) and Pd(II)) formed during the reaction.<sup>32–34</sup> When the temperature was increased to 150 °C, small amounts of unknown side-products were detected in the reaction mixture (entry 9). Using lower temperature gave lower RTE (84%) indicating that higher temperatures were essential for the effective conversion of iodobenzene to the corresponding  $^{11}\text{C}$ -*N*-cyanobenzamide **11C-2a**.



Scheme 1. Pd-mediated synthesis of  $^{11}\text{C}$ -*N*-cyanobenzamides and  $^{11}\text{C}$ -benzamides

## Results and discussion

### Method development

We initiated our search for suitable reaction conditions using iodobenzene and cyanamide as model substrates, with bis(dibenzylidene-acetone)palladium(0) as the palladium source. THF has previously been successfully used as a solvent for  $^{11}\text{C}$ -carbonylations,<sup>28</sup> however, the more polar DMF readily dissolved all components and was therefore chosen for further evaluation. The radiotrapping efficiency (RTE, defined here as the fraction of immobilized  $^{11}\text{C}$  at the end of synthesis [EOS]) was determined by removal of non-reacted  $^{11}\text{C}$  by flushing the crude reaction mixture with helium for 1 min.

The ligand-free carbonylation resulted in a RTE of 85% and gave conversion of trapped  $^{11}\text{C}$  to product (RCP) of 88% (Table 1, entry 1) as measured by radio-HPLC. We continued by evaluating the monodentate ligand triphenylphosphine, which gave the desired product in the same quantity (RTE 95%, RCP 75%, entry 2). Analysis of the crude reaction mixture suggested the presence of a side-product, which was identified as  $^{11}\text{C}$ -benzoic acid by co-elution using analytical radio-HPLC. The bidentate ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) has previously been successfully in both  $^{11}\text{C}$  and CO carbonylations.<sup>9,29–31</sup> In our setup complete consumption of  $^{11}\text{C}$  (RTE >99%) was achieved with this ligand at 120 °C and 150 °C but with lower RCP (61% and 72%, entry 3–4). Interestingly, no formation of acid was

Table 1. Optimization of Reaction Conditions<sup>a</sup>

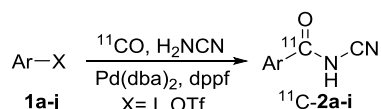
n	Ligand	Temp (°C)	RTE (%) <sup>b</sup>	RCP (%) <sup>c</sup>
1	-	120	85	88
2	PPh <sub>3</sub>	120	95	75
3	Xantphos	120	>99	61
4	Xantphos	150	>99	72
5	DPEPhos	90	85	88
6	DPEPhos	120	76	79
7	DPEPhos	150	82	86
8	dppf	120	>99	94±2 <sup>d</sup>
9	dppf	150	>99	87
10	dppf	90	84	86
11 <sup>e</sup>	dppf	120	84	87
12 <sup>e</sup>	dppf	140	96±2	93±3 <sup>d</sup>
13 <sup>e</sup>	dppf	150	93	90
14 <sup>f</sup>	dppf	170	63	74
15 <sup>g</sup>	dppf	120	89	88

<sup>a</sup>Reaction conditions: Ph-I (20 μmol), H<sub>2</sub>N-CN (400 μmol), Pd(dba)<sub>2</sub> (8 μmol), Ligand (monodentate 20 μmol, bidentate 10 μmol), DMF (400 μL), temp, 5 min. <sup>b</sup>The fraction of immobilized  $^{11}\text{C}$  after purging with N<sub>2</sub>. <sup>c</sup>Determined by analytical radio-HPLC. <sup>d</sup>Average of three experiments. <sup>e</sup>Ph-Br was used. <sup>f</sup>Ph-Cl was used. <sup>g</sup>Ph-OTf was used.

Encouraged by the promising result obtained with iodobenzene, the best conditions (entry 8) were used for the reaction of cyanamide with bromobenzene. This gave a RTE of 84% and RCP of 87%. When the temperature was increased to 140 °C, the product was formed in a high RCP of 89±3% with almost quantitative RTE (96±2%, Table 1, entry 12). Increasing the temperature to 150 °C again resulted in an erosion of the yield due to the formation of unknown side-products (entry

13). Next, we proceeded by evaluating the less reactive chlorobenzene in the carbonylative reaction. At 170 °C the RTE was 63% and the RCP 74% (entry 14). The pseudo-halide phenyl triflate was reacted under similar conditions as iodobenzene and was found to smoothly undergo carbonylation at 120 °C with RTE of 89% and RCP of 88% (entry 15).

With a suitable carbonylative protocol in hand, we continued by exploring the generality of the method using aryl iodides with different electronic properties (Table 2). Here the RTE and RCP for each reaction was determined as well as the isolated radiochemical yield (RCY) following semi-preparative HPLC. From iodobenzene and phenyl triflate  $^{11}\text{C}$ -*N*-cyanobenzamide  $^{11}\text{C}$ -**2a** was isolated in 79% and 72% RCY, respectively. Substrates bearing electron withdrawing (EWG) and electron donating (EDG) groups in the 4-position performed well affording the desired products in moderate to high isolated radiochemical yield ( $^{11}\text{C}$ -**2b-f**, 41–73%). A good yield was also obtained when the methoxy group was moved to the 3-position furnishing 64% RCY of  $^{11}\text{C}$ -**2g**. Notably, full chemoselectivity was achieved in the reaction with 1-chloro-4-iodobenzene and 57% of the 4-chloro substituted product  $^{11}\text{C}$ -**2e** was obtained. Finally, the *ortho*-CF<sub>3</sub> containing substrate (entry 9) gave a lower RCY (28%) of the corresponding  $^{11}\text{C}$ -*N*-cyanobenzamide  $^{11}\text{C}$ -**2h** presumably due to a combination of unfavorable steric and electronic effects.

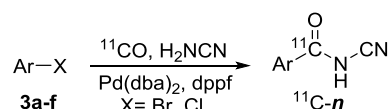


**Table 2.** Reaction Scope Using Aryl Iodides<sup>a</sup>

n	Ar-X	Prod. $^{11}\text{C}$ - <b>2n</b>	RTE (%) <sup>b</sup>	RCY (%) <sup>c</sup>
1	Ph	a	>99	79
2	Ph <sup>d</sup>	a	89	72
3	4-OMe-Ph	b	95±3	73
4	4-CN-Ph	c	92±2	62
5	4-C <sub>6</sub> H <sub>5</sub> -Ph	d	94±3	68
6	4-Cl-Ph	e	85±3	57
7	4-COH-Ph	f	72	41
8	3-OMe-Ph	g	82	64
9	2-CF <sub>3</sub> -Ph	h	64	28

<sup>a</sup>Reaction conditions: Ar-I (20 μmol), H<sub>2</sub>NCN (400 μmol), Pd(dba)<sub>2</sub> (8 μmol), dppf (10 μmol), DMF (400 μL), 120 °C, 5 min. Values with ± indicate the average of three experiments. <sup>b</sup>The fraction of immobilized  $^{11}\text{C}$  after purging with N<sub>2</sub>. <sup>c</sup>After semi-preparative HPLC (decay corrected from EOB). RCP of the isolated products were >95%. <sup>d</sup>Ph-OTf.

To further extend the utility of the reaction, the scope was expanded to include aryl- and heteroaromatic bromides (Table 3). By using the protocol from entry 12 in Table 1 (i.e. increasing the temperature to 140 °C),  $^{11}\text{C}$ -*N*-cyanobenzamide  $^{11}\text{C}$ -**2a** was synthesized in 72% RCY. Using chlorobenzene at 170 °C furnished the same product in reduced 34% RCY (entry 2). Both the electron rich (entry 3) and electron deficient



**Table 3.** Reaction Scope Using Aryl Bromides<sup>a</sup>

n	Ar-X	Temp	Prod. $^{11}\text{C}$ - <b>n</b>	RTE (%) <sup>b</sup>	RCY (%) <sup>c</sup>
1	Ph	140	2a	96±2	72
2	Ph <sup>d</sup>	170	2a	63	34
3	4-OMe-Ph	140	2b	90	68
4	4-CN-Ph	140	2c	91±4	67
5	2-naphthalene	140	4a	94	51
6	2-benzofuran	140	4b	88±1	48
7	2-thiophene	140	4c	88±3	59
8	3-thiophene	140	4d	84±1	64
9	3-pyridine	140	4e	78	55

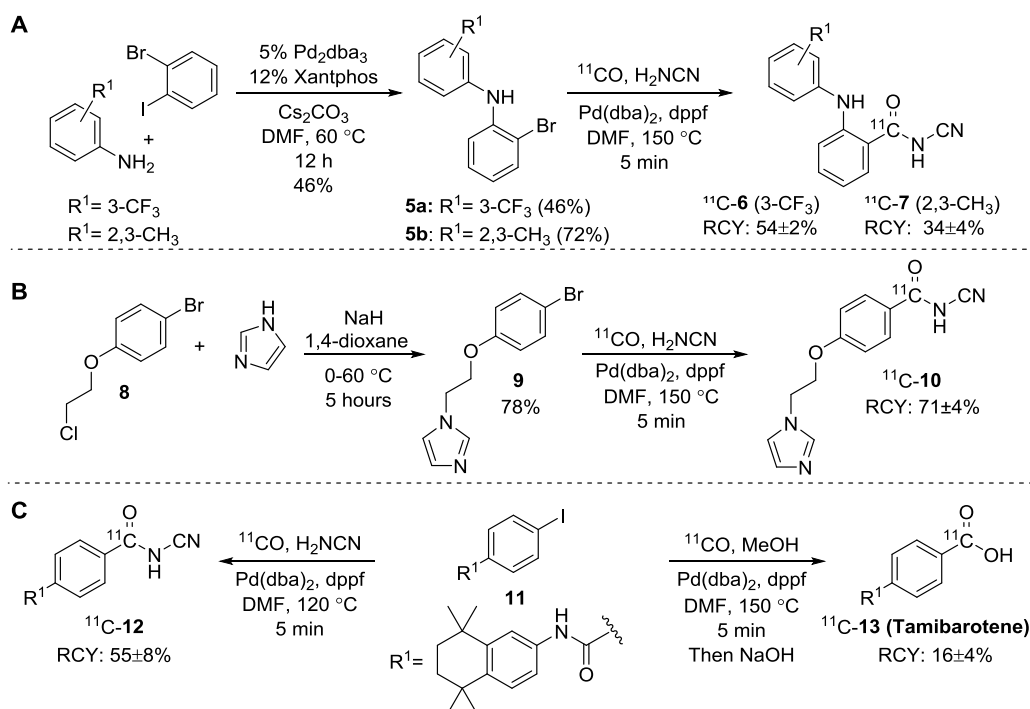
<sup>a</sup>Reaction conditions: Ar-Br (20 μmol), H<sub>2</sub>NCN (400 μmol), Pd(dba)<sub>2</sub> (8 μmol), dppf (10 μmol), DMF (400 μL), 140 or 170 °C, 5 min. Values with ± indicate the average of three experiments. <sup>b</sup>The fraction of immobilized  $^{11}\text{C}$  after purging with N<sub>2</sub>. <sup>c</sup>After semi-preparative HPLC. RCP of the isolated products were >95%. <sup>d</sup>Ph-Cl.

substrates (entry 4) gave corresponding products  $^{11}\text{C}$ -**2b** and  $^{11}\text{C}$ -**2c** in similar RCY whereas 2-bromonaphthalene **3e** yielded labelled  $^{11}\text{C}$ -**4a** in 51% RCY.

A number of electron-rich heterocycles were also effectively transformed into the corresponding  $^{11}\text{C}$ -*N*-cyanamide products. 2-Bromobenzofurane afforded  $^{11}\text{C}$ -*N*-cyanobenzofuran-2-carboxamide ( $^{11}\text{C}$ -**4b**) in 48% RCY while 2- and 3-bromothiophene gave products  $^{11}\text{C}$ -**4c** and  $^{11}\text{C}$ -**4d** in 59% and 64% isolated RCY, respectively. Notably, 3-bromopyridine was transformed into  $^{11}\text{C}$ -*N*-cyanonicotinamide ( $^{11}\text{C}$ -**4e**) in 55% RCY.

### Synthesis of $^{11}\text{C}$ -cyanobenzamide analogs of various bioactive molecules

To further exemplify our developed methodology, we explored the labeling with  $^{11}\text{C}$  of *N*-cyanobenzamide analogs of a variety of bioactive molecules (Scheme 2). Firstly, we prepared the *N*-cyanobenzamide derivatives of flufenamic acid ( $^{11}\text{C}$ -**6**) and mefenamic acid ( $^{11}\text{C}$ -**7**), two nonsteroidal anti-inflammatory and antipyretic drugs (NSAID) used to treat muscle and menstrual pain, respectively.<sup>35–37</sup> This required access to the *ortho*-bromoaniline precursors **5a** and **5b**, which were synthesized via a palladium-catalyzed amination using 5% tris(dibenzylidene-acetone)dipalladium(0) and 12% Xantphos as the ligand in 46% and 72% yield, respectively (Scheme 2A).<sup>38</sup> Despite the potentially palladium-coordinating amino moiety in close vicinity to the bromide, the reactions performed well at 140 °C yielding  $^{11}\text{C}$ -**6** in 54±2% RCY and  $^{11}\text{C}$ -**7** in 34±4% RCY. The precursor of the thromboxane synthase inhibitor dazoxiben was synthesized from 1-bromo-4-(2-chloroethoxy)benzene (**8**) and imidazole in 78% yield (Scheme 2B). Using the optimized conditions for aryl bromides, the radiolabelled  $^{11}\text{C}$ -**10** was isolated using semi-preparative HPLC in 71±4%.



**Scheme 2A.** Precursor synthesis and radiolabeling of  $^{11}\text{C}$ -6 and  $^{11}\text{C}$ -7, analogs of flufenamic acid and mefenamic acid, respectively; **2B.** Synthesis of  $^{11}\text{C}$ -N-cyanobenzamide analog of dazoxiben  $^{11}\text{C}$ -10. **2C.** Radiosynthesis of  $^{11}\text{C}$ -N-cyanobenzamide  $^{11}\text{C}$ -12 and  $^{11}\text{C}$ -tamibarotene ( $^{11}\text{C}$ -13)

Finally, we synthesized compound **11** a precursor for the labelling of tamibarotene, a synthetic retinoic acid receptor agonist.<sup>39,40</sup> Tamibarotene is approved in Japan for use against all-*trans*-retinoic acid refractive acute promyelocytic leukemia<sup>41</sup> and is currently being investigated for the treatment of insulin resistance,<sup>42</sup> vasculitis<sup>43</sup> intracerebral hemorrhage<sup>44</sup> and Alzheimer's disease.<sup>45,46</sup>  $^{11}\text{C}$ -Tamibarotene ( $^{11}\text{C}$ -13) was prepared from the iodo-precursor **11** via an alkoxycarbonylation using the conditions from Table 3 at 150 °C using methanol as the nucleophile (Scheme 2C). Subsequent hydrolysis of the methyl ester intermediate using sodium hydroxide the afforded  $^{11}\text{C}$ -13 in 16% RCY and a specific activity of 205 GBq/ $\mu\text{mol}$ . Notably, our method gave a similar yield with a 5-fold improvement in specific activity compared to the oxidative alkoxylation procedure reported by Suzuki and co-workers (44 GBq/ $\mu\text{mol}$  and RCY 26±13%).<sup>47</sup> Importantly, the corresponding  $^{11}\text{C}$ -N-cyanobenzamide analogue was synthesized using the optimized conditions for aryl iodides yielding  $^{11}\text{C}$ -12 in 55±8% RCY and a specific activity of 291 GBq/ $\mu\text{mol}$  after semi-preparative-HPLC. The radiochemical purity in both syntheses was in excess of 99%. Thus, both the  $^{11}\text{C}$ -labelled parent molecule and its corresponding  $^{11}\text{C}$ -cyanobenzamide bioisostere were efficiently prepared from a common precursor, using similar reaction conditions, further highlighting the utility of the method developed herein.

## Conclusions

In conclusion, a palladium mediated  $^{11}\text{C}$ -carbonylative methodology yielding  $^{11}\text{C}$ -N-cyanobenzamides from aryl halides has been described. The substrate scope was found to be excellent and electron rich as well as electron deficient aryl iodides and bromides all performed well. The method was also extended to include the carbonylation of challenging heteroaryl bromides, phenyl triflate and even chlorobenzene. Notably, good to high isolated radiochemical yields were obtained ranging from 28-79% after semi-preparative HPLC. Moreover, the developed method was exemplified by synthesizing novel  $^{11}\text{C}$ -N-cyanobenzamide analogs of the NSAID's flufenamic acid and mefenamic acid as well as dazoxiben and tamibarotene in 34-71% decay corrected RCY. This method allows rapid and robust access to new  $^{11}\text{C}$ -chemical space and exploration of cyanobenzamide bioisosteres of the ubiquitous carboxylic acid group.

## Experimental

### General Chemical Information

Chemicals were purchased from commercial suppliers and were used without further purification. NMR spectra were recorded on a Varian Mercury plus spectrometer ( $^1\text{H}$  at 400 MHz and  $^{13}\text{C}$  at 101 MHz) at ambient temperature. Chemical shifts ( $\delta$ ) are reported in ppm referenced to methanol, chloroform or DMSO. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with silica gel 60

F254 (0.2 mm, Merck) and visualized by UV-light (254 nm). Flash column chromatography (FCC) was performed using silica gel 60 (40–63  $\mu$ m, Merck). Analytical UHPLC-MS was performed with an ion-trap mass spectrometer and UV-DAD detection using a C18 (50 $\times$ 3 mm) column using a gradient of 10–90 (1.5 mL/min, 2 min) and MeCN (0.05% HCOOH) in H<sub>2</sub>O (0.05% HCOOH) as the eluent.

<sup>11</sup>CO<sub>2</sub> was created through the <sup>14</sup>N(p,n)<sup>11</sup>C nuclear reaction at the Uppsala University Hospital by a Scandtronix MX17 cyclotron and transferred to the hotlab where it was reduced over a bead of zinc (400 °C) and then used in the carbonylation reaction which was remotely controlled.<sup>48</sup> Semi-preparative radio-HPLC was performed using a VWR LaPrep HPLC system (P110, P311) with a Beckman Coulter™ Ultrapshere™ ODS column (10 $\times$ 250mm) with a gradient of 10–90 % (6 mL/min, 10 min) of MeCN in H<sub>2</sub>O. Analytical radio-HPLC was performed using a VWR LaChrom ELITE system (L-2130, L-2200, L-2400) with a Merck Chromolith Performance RP-18e column (4.6 $\times$ 100mm) and a gradient of 10–90 (*method 1*: 4 mL/min, 10 min. *Method 2*: 4 mL/min, 5 min. *Method 3*: 4 mL/min, 7 min) MeCN in H<sub>2</sub>O. Both HPLC-systems were buffered with 0.09% TFA (for purification of <sup>11</sup>C-**6**, 0.1% HCOOH was used), used 254 nm UV-detection and were equipped with a Bioscan Flow-Count PMT radioactivity detector. See supporting information for further information.

#### Synthesis and characterization of precursors and references

Compounds **2a–e**, **4a** and **4e** are known and were synthesized according to reference 24. Compounds **2f**, **2g**, **4b**, **4d**, **6**, **7**, **10**, **12** were synthesized in a peptide coupling reaction from the corresponding carboxylic acid. The carboxylic acid (0.5 mmol), PyBOP (260 mg, 0.5 mmol), Et<sub>3</sub>N (436  $\mu$ L, 2.5 mmol), cyanamide (32 mg, 0.75 mmol) were dissolved in 1,4-dioxane (2 mL) and the reaction was stirred for 12 hours at ambient temperature. The crude mixture was concentrated and purified by FCC (Acetone/MeOH [99:1] containing 2% Et<sub>3</sub>N). Compounds **2h** and **4c** were synthesized from the corresponding acid chloride. The acid chloride (0.5 mmol), cyanamide (32 mg, 0.75 mmol), Et<sub>3</sub>N (174  $\mu$ L, 1 mmol) were dissolved in 1,4-dioxane (2 mL) and stirred at 50 °C for 12 hours. The mixture was concentrated and purified by FCC (Acetone/MeOH [99:1] containing 2% Et<sub>3</sub>N). This yielded 40–70% of the corresponding *N*-acyl cyanamides as the Et<sub>3</sub>N-salt.

***N*-Cyano-4-formylbenzamide (2f).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  10.04 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.3 Hz, 2H), 3.22 (q, *J* = 7.3 Hz, 6H), 1.31 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR (100 MHz, MeOD)  $\delta$  193.8, 178.2, 143.6, 139.6, 130.2, 130.1, 122.6, 47.9, 9.2. HRMS calcd for C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 175.0508, found *m/z* 175.0509.

***N*-Cyano-3-methoxybenzamide (2g).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  7.55–7.52 (m, 2H), 7.30–7.26 (m, 1H), 7.04–7.01 (m, 1H), 3.81 (s, 3H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3, 9H). <sup>13</sup>C NMR (100 MHz, MeOD)  $\delta$  178.8, 160.9, 139.0, 130.0, 121.9, 118.4, 114.4, 55.7, 47.9, 9.2. HRMS calcd for C<sub>10</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 177.0664, found *m/z* 177.0660.

***N*-Cyano-2-(trifluoromethyl)benzamide (2h).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  7.71–7.68 (m, 1H), 7.64–7.52 (m, 3H), 3.21 (q, *J*

= 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR (100 MHz, MeOD)  $\delta$  179.1, 138.6 (d, *J* = 2.3 Hz), 131.6 (q, *J*<sub>C-F</sub> = 1.1 Hz), 128.8, 128.2, 126.5 (q, *J*<sub>C-F</sub> = 31.8 Hz), 125.8 (q, *J* = 5.1 Hz), 124.0 (q, *J* = 272.9 Hz), 119.4, 46.5, 7.8. HRMS calcd for C<sub>9</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>O [M+H]<sup>+</sup> *m/z* 215.0432, found *m/z* 215.0429.

***N*-Cyanobenzofuran-2-carboxamide (4b).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  7.66 (d, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.43–7.36 (m, 2H), 7.29–7.24 (m, 1H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.29 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR  $\delta$  170.8, 156.6, 153.1, 129.1, 127.6, 124.5, 123.4, 121.3, 112.7, 111.2, 47.9, 9.2. HRMS calcd for C<sub>10</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 187.0508, found *m/z* 187.0509.

***N*-Cyanothiophene-2-carboxamide (4c).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  7.64–7.61 (m, 1H), 7.53–7.50 (m, 1H), 7.15–6.91 (m, 1H), 3.20 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR (100 MHz, MeOD)  $\delta$  173.9, 142.9, 131.4, 131.3, 128.5, 121.8, 47.9, 9.2. HRMS calcd for C<sub>6</sub>H<sub>4</sub>N<sub>2</sub>OS [M+H]<sup>+</sup> *m/z* 153.0123, found *m/z* 153.0129.

***N*-Cyanonicotinamide (4e).** <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  9.14–9.07 (m, 1H), 8.62 (dd, *J* = 5.1, 1.7 Hz, 1H), 8.41 (ddd, *J* = 8.0, 2.2, 1.7 Hz, 1H), 7.51 (ddd, *J* = 8.0, 5.1, 0.9 Hz, 1H), 3.22 (q, *J* = 7.3 Hz, 6H), 1.32 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR (100 MHz, MeOD)  $\delta$  176.5, 151.4, 149.9, 138.6, 134.5, 124.9, 122.1, 47.9, 9.2. HRMS calcd for C<sub>7</sub>H<sub>5</sub>N<sub>3</sub>O [M+H]<sup>+</sup> *m/z* 148.0511, found *m/z* 148.0514.

**2-Bromo-*N*-(3-(trifluoromethyl)phenyl)aniline (5a).** 3-(trifluoromethyl)aniline (80 mg, 0.5 mmol), 1-bromo-2-iodobenzene (141 mg, 0.5 mmol), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 5 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35 mg, 12 mol%), cesium carbonate (488 mg, 1.5 mmol) was added to DMF (5 mL), capped and stirred at 60 °C for 12 hours. After cooling, the mixture was filtered, concentrated and purified by FCC (pentane:EtOAc [7:1] yielding 73 mg (46%) of **5**. <sup>1</sup>H NMR  $\delta$  7.61 (ddd, *J* = 8.0, 1.3, 0.5 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.32–7.24 (m, 2H), 7.24–7.18 (m, 2H), 7.14–7.10 (m, 1H), 6.93 (ddd, *J* = 8.0, 6.4, 2.5 Hz, 1H). <sup>13</sup>C NMR  $\delta$  146.0, 142.0, 134.6, 132.6 (q, *J*<sub>C-F</sub> = 31.8 Hz), 131.0, 129.4, 125.7 (d, *J*<sub>C-F</sub> = 271.4 Hz), 124.9, 122.1, 121.4, 117.6 (q, *J*<sub>C-F</sub> = 4.0 Hz), 117.1, 114.5 (q, *J*<sub>C-F</sub> = 4.0 Hz). HRMS calcd for C<sub>13</sub>H<sub>9</sub>NBrF<sub>3</sub> [M+H]<sup>+</sup> *m/z* 315.9949, found *m/z* 315.9944.

***N*-(2-bromophenyl)-2,3-dimethylaniline (5b).** Synthesized as per **5a** from 2,3-dimethylaniline. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41 (s, 1H), 7.28–7.21 (m, 3H), 7.17–7.15 (m, 1H), 6.87 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.81 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 2.49 (s, 3H), 2.32 (s, 3H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)  $\delta$  143.04, 139.38, 138.24, 132.68, 131.25, 128.15, 126.39, 126.12, 121.72, 119.56, 110.82, 20.67, 13.89. HRMS: *m/z* = 276.0395 [M + H]<sup>+</sup>, calculated for C<sub>14</sub>H<sub>15</sub>NBr: 276.0388

***N*-Cyano-2-((3-(trifluoromethyl)phenyl)amino)benzamide (6).** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.01 (d, *J* = 7.9 Hz, 1H), 7.48–7.37 (m, 3H), 7.29 (d, *J* = 3.1 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.86–6.77 (m, 1H), 3.18 (q, *J* = 7.3 Hz, 6H), 1.28 (t, *J* = 7.3 Hz, 9H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  180.6, 145.6, 144.6, 132.9, 132.7, 132.6 (q, <sup>2</sup>*J*<sub>CF</sub> = 32.0 Hz), 131.2, 125.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 271.4 Hz), 123.5 (q, <sup>4</sup>*J*<sub>CF</sub> = 1.5 Hz), 123.0, 122.4, 119.8, 118.6 (q,

$^3J_{\text{CF}} = 4.0$  Hz), 116.24 (d,  $^3J_{\text{CF}} = 4.0$  Hz), 116.18, 47.9, 9.2. HRMS calcd for  $\text{C}_{15}\text{H}_{10}\text{F}_3\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$   $m/z$  306.0854, found  $m/z$  306.0859.

**N-Cyano-2-((2,3-dimethylphenyl)amino)benzamide (7).**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.01 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.49 – 7.35 (m, 3H), 7.28 – 7.18 (m, 2H), 6.26 (dd,  $J = 8.4, 0.9$  Hz, 1H), 2.36 (s, 3H), 1.90 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  167.2, 155.2, 141.4, 139.6, 135.3, 133.8, 133.0, 131.6, 127.9, 126.9, 126.6, 123.3, 117.9, 114.6, 20.0, 13.3. HRMS calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}$   $[\text{M} + \text{H}]^+$ , 266.1293, found 266.1301.

**1-(2-(4-Bromophenoxy)ethyl)-1H-imidazole (9).**  $^1\text{H}$  NMR (400 MHz, MeOD)  $\delta$  7.71 (t,  $J = 1.1$  Hz, 1H), 7.41–7.33 (m, 2H), 7.21 (t,  $J = 1.3$  Hz, 1H), 6.97 (t,  $J = 1.2$  Hz, 1H), 6.86–6.81 (m, 2H), 4.40 (dd,  $J = 5.5, 4.5$  Hz, 2H), 4.23 (dd,  $J = 5.5, 4.5$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  159.0, 138.9, 133.4, 129.0, 121.0, 117.6, 114.3, 68.8, 47.5. ESI-HRMS calcd for  $\text{C}_{11}\text{H}_{12}\text{BrN}_2\text{O}$   $[\text{M}+\text{H}]^+$   $m/z$  267.0133, found  $m/z$  267.0133.

**4-(2-(1H-Imidazol-1-yl)ethoxy)-N-cyanobenzamide (10).**  $^1\text{H}$  NMR (400 MHz, MeOD)  $\delta$  7.91 (d,  $J = 9.0$  Hz, 2H), 7.77 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.89 (d,  $J = 9.0$  Hz, 1H), 4.47 – 4.39 (m, 2H), 4.34 – 4.27 (m, 2H), 3.20 (q,  $J = 7.3$  Hz, 6H), 1.30 (t,  $J = 7.3$  Hz, 12H).  $^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  179.4, 162.3, 138.8, 131.6, 131.1, 128.7, 123.3, 121.2, 114.7, 68.5, 47.9, 29.9, 9.3. ESI-HRMS calcd for  $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2$   $[\text{M}+\text{H}]^+$   $m/z$  257.1039, found  $m/z$  257.1037.

**4-Iodo-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (11).** The compound was synthesized according to reference 49 using 4-iodobenzoic acid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}$ )  $\delta$  10.12 (s, 1H), 7.91 (d,  $J = 8.2$  Hz, 2H), 7.74 (d,  $J = 8.2$  Hz, 2H), 7.65 (d,  $J = 1.8$  Hz, 2H), 7.55 (d,  $J = 8.7$  Hz, 1H), 7.27 (d,  $J = 8.6$  Hz, 1H), 1.64 (s, 4H), 1.23 (d,  $J = 4.7$  Hz, 12H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  164.5, 144.5, 140.0, 137.2, 136.4, 134.4, 129.5, 126.4, 118.3, 118.1, 99.1, 34.6, 34.6, 34.0, 33.6, 31.6, 31.6. ESI-HRMS calcd for  $\text{C}_{21}\text{H}_{25}\text{INO}$   $[\text{M}+\text{H}]^+$   $m/z$  434.0981, found  $m/z$  434.0982.

**N1-Cyano-N4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide (12).**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}$ )  $\delta$  10.27 (s, 1H), 8.09 (d,  $J = 8.6$  Hz, 2H), 8.03 (d,  $J = 8.6$  Hz, 2H), 7.73 – 7.64 (m, 1H), 7.64 – 7.53 (m, 1H), 7.29 (d,  $J = 8.6$  Hz, 1H), 1.65 (s, 6H), 1.24 (d,  $J = 5.2$  Hz, 12H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  167.0, 164.2, 144.6, 140.2, 139.2, 136.3, 134.1, 128.3, 128.0, 126.5, 118.3, 118.1, 109.6, 34.6, 34.6, 34.0, 33.6, 31.7, 31.6. ESI-HRMS calcd for  $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$   $m/z$  376.2025, found  $m/z$  376.2037.

**4-((5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)benzoic acid (13).**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}$ )  $\delta$  10.24 (s, 1H), 8.13 – 7.93 (m, 4H), 7.67 (s, 1H), 7.58 (d,  $J = 10.9$  Hz, 1H), 7.29 (d,  $J = 8.6$  Hz, 1H), 1.64 (s, 4H), 1.24 (d,  $J = 5.0$  Hz, 12H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  167.2, 165.0, 145.0, 140.5, 139.2, 136.8, 133.8, 129.7, 128.2, 126.9, 118.8, 118.6, 35.0, 34.4, 34.0, 32.1, 32.1. ESI-HRMS calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$   $m/z$  352.1913, found  $m/z$  352.1913.

#### Radiochemistry

The aryl halide (20  $\mu\text{mol}$ ) and cyanamide (16.8 mg, 400  $\mu\text{mol}$ ) were added to an oven dried 2 mL vial, capped and flushed for 2 min with argon. To a second oven dried 2 mL vial was added

bis(dibenzylideneacetone)-palladium(0) (2.3 mg, 8  $\mu\text{mol}$ ) and 1,1'-bis(diphenyl-phosphino)ferrocene (4.8 mg, 10  $\mu\text{mol}$ ) which was then capped and flushed with argon for 2 min before dry DMF (400  $\mu\text{L}$ ) was added. After a second flush with argon (2 min) the DMF/ $\text{Pd}(\text{dba})_2/\text{dppf}$  solution was heated at 90 °C for 1 min, creating a homogenous solution. The mixture was added to the first vial and subsequently added to the injection loop (200  $\mu\text{L}$  capacity) of the  $^{11}\text{C}$ -carbon monoxide system.<sup>47</sup> After the reaction was finished, the radioactivity was measured. After flushing with nitrogen for 1 min, the activity was measured again yielding the RTE. An aliquot was taken for the determination of RCP. The crude mixture was diluted with 50% aqueous MeCN (total volume 500  $\mu\text{L}$ ) and purified by semi-preparative radio-HPLC. After collecting the product, RCP was determined for the pure product. The identity was determined by co-elution of the corresponding non-isotopically labeled *N*-cyanobenzamide. For the molar activity of  $^{11}\text{C}$ -12 and  $^{11}\text{C}$ -13, a calibration curve with five points using the corresponding reference. The total mass and the concentration of the purified product was then determined. The amount of activity was calculated back to the end of synthesis to get comparable data, expressed in GBq/ $\mu\text{mol}$ . The molar activity was determined to be 291 GBq/ $\mu\text{mol}$  for  $^{11}\text{C}$ -12 and 205 GBq/ $\mu\text{mol}$  for  $^{11}\text{C}$ -13.

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