

# Virtually Instantaneous, Room-Temperature [<sup>11</sup>C]-Cyanation Using Biaryl Phosphine Pd(0) Complexes

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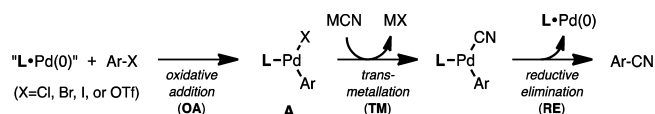
## S Supporting Information

**ABSTRACT:** A new radiosynthetic protocol for the preparation of [<sup>11</sup>C]aryl nitriles has been developed. This process is based on the direct reaction of *in situ* prepared L-Pd(Ar)X complexes (L = biaryl phosphine) with [<sup>11</sup>C]HCN. The strategy is operationally simple, exhibits a remarkably wide substrate scope with short reaction times, and demonstrates superior reactivity compared to previously reported systems. With this procedure, a variety of [<sup>11</sup>C]nitrile-containing pharmaceuticals were prepared with high radiochemical efficiency.

Incorporation of short-lived radioisotopes such as <sup>11</sup>C (*t*<sub>1/2</sub> = 20.4 min) into organic molecules for application in positron emission tomography (PET)<sup>1</sup> presents unique synthetic challenges.<sup>2</sup> The short half-life of <sup>11</sup>C necessitates reaction times on the order of seconds/minutes with clean reaction profiles to facilitate rapid purification. Additionally, the radiochemical reaction must outcompete all possible side reactions, which can be a challenge because there is a large stoichiometry bias between the radionuclide and all other species present in the reaction mixture (including the carrier gas), and submicromolar concentrations of radionuclides are typically employed. Lastly, the reaction conditions should be mild (i.e., rt under neutral conditions) to minimize decomposition of the radiotracer that is formed. Due to these restrictions, many high-yielding catalytic and even stoichiometric reactions cannot be applied to the synthesis of radiolabeled compounds.

A promising method to introduce a radioactive carbon unit into organic molecules is the Pd-mediated cyanation of aryl (pseudo)halides (Scheme 1).<sup>3,4</sup> This transformation is based on oxidative addition (OA) of the aryl (pseudo)halide to an “L-Pd(0)” intermediate to form complex A, transmetalation (TM) to form complex B, and reductive elimination (RE) to form the desired aryl nitrile product.

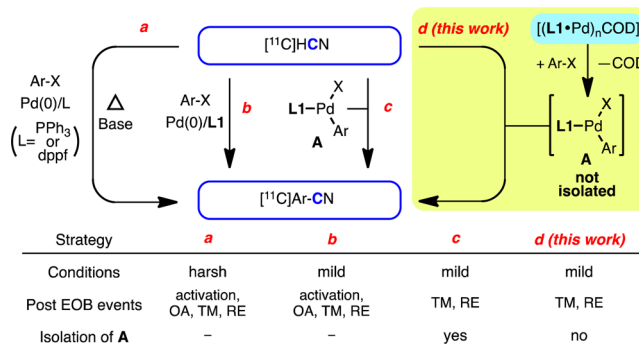
## Scheme 1. Mechanism of Pd-Mediated Cyanation of Aryl (Pseudo)halides



with cyanide, and reductive elimination (RE) to form the desired aryl nitrile product.

However, extension of this strategy to the radiosynthetic setting does not necessarily meet the challenges discussed above.<sup>2</sup> The use of traditional ligands (e.g., PPh<sub>3</sub> or 1,1'-bis(diphenylphosphino)ferrocene (dppf)) requires harsh reaction conditions, such as high temperatures, relatively long reaction times, and the use of base (e.g., K<sub>2</sub>CO<sub>3</sub>) to capture [<sup>11</sup>C]HCN in the gas phase, which diminishes the substrate scope (Scheme 2, a).<sup>5</sup> In addition, these reactions are typically

## Scheme 2. Synthetic Strategies for [<sup>11</sup>C]Aryl Nitriles



carried out in DMF or DMSO, which can hamper purification or multistep syntheses involving reactions incompatible with these solvents. On the other hand, we have recently demonstrated that biaryl phosphine ligands, specifically L1 (Figure 1), facilitate stoichiometric transmetalation with cyanide and reductive elimination of aryl nitriles at ambient temperature in under 5

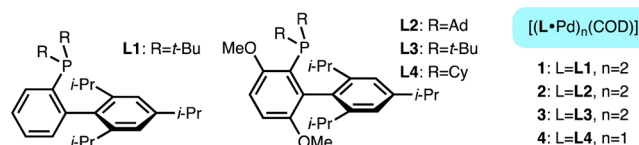


Figure 1. Structure of ligands L1–L4 and complexes 1–4.

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min.<sup>6</sup> Thus, we hypothesized that [<sup>11</sup>C]cyanation of aryl (pseudo)halides, even with an extremely low concentration of [<sup>11</sup>C]HCN, could be achieved under mild conditions using biaryl phosphines instead of traditional ligands (Scheme 2, b).

Even with this strategy, reagent activation (i.e., generation of “L-Pd(0)” from the Pd source) and oxidative addition, steps that do not involve the radionuclide, still take place *after* the end of bombardment (EOB), when [<sup>11</sup>C]HCN addition is complete, resulting in an unnecessary loss of radioactivity. Ideally, a preformed oxidative addition complex A, with L1, could be used directly (Scheme 2, c)<sup>7</sup> to avoid this loss of radioactivity. However, the independent synthesis and purification of A, which can be a challenging task for nonexperts, would limit the applicability of this strategy to radiotracer synthesis for PET imaging. Recently, we introduced a new class of biaryl phosphine (L1–L4)-bound Pd(0) complexes 1–4, which are functionally equivalent to “L-Pd(0)” at ambient temperature (Figure 1).<sup>8</sup> We envisioned that utilizing complexes 1–4, along with the desired aryl (pseudo)halide, should allow for the convenient generation of A *in situ* to set the stage for the formation of the aryl-<sup>11</sup>C bond (Scheme 2, d). This setup should allow us to take full advantage of the established system to prepare [<sup>11</sup>C]aryl nitriles in a mild and expeditious manner.

To test this hypothesis, a synthesis of [<sup>11</sup>C]3-aminobenzonitrile was attempted using 3-bromoaniline as a substrate (Table 1). In these experiments, the Pd source and the aryl halide were

**Table 1. Pd Source and Ligand Effect in the Synthesis of [<sup>11</sup>C]3-Aminobenzonitrile<sup>a</sup>**

Entry	Pd/L	Temp. (°C)	Time	RCC (%)
1	1	23	1 min	81
2	1	23	10 s	73
3	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	50	5 min	0
4	Pd <sub>2</sub> (dba) <sub>3</sub> /dppf	50	5 min	0
5	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ] <sup>b</sup>	100	5 min	30
6	Pd <sub>2</sub> (dba) <sub>3</sub> /L1	23	1 min	57
7	5	23	1 min	27
8	5, K <sub>2</sub> CO <sub>3</sub> , K <sub>3</sub> PO <sub>4</sub> or KOt-Bu	23	1 min	18-25

<sup>a</sup>Reaction conditions: Pd/L (0.004 mmol), 3-bromoaniline (0.008 mmol), toluene (0.1 mL), rt, 30 min; then [<sup>11</sup>C]HCN (1–5 mCi), THF (0.1 mL), rt, 1 min. <sup>b</sup>[Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.004 mmol), 3-bromoaniline (0.008 mmol), K<sub>2</sub>CO<sub>3</sub> (0.008 mmol), DMF (0.1 mL); then [<sup>11</sup>C]HCN (1–5 mCi), DMF (0.1 mL), 100 °C, 5 min.

mixed and allowed to stand for 30 min to generate A *in situ* (Table 1, a). Then, [<sup>11</sup>C]HCN in THF<sup>9</sup> was introduced into the reaction vial and allowed to react for 1 min (Table 1, b), and the reaction mixture was analyzed by radio TLC. The desired product was successfully formed with 81% radiochemical conversion (RCC) in the presence of 1 (entry 1).<sup>10</sup> In fact, nearly the same RCC was observed after only 10 s of reaction time (entry 2), though subsequent reactions were conducted for

1 min for consistency. In contrast, conventionally used Pd(0) sources, including [Pd(PPh<sub>3</sub>)<sub>4</sub>] (entry 3) and a combination of Pd<sub>2</sub>(dba)<sub>3</sub>/dppf (entry 4) did not produce any product at either rt or after heating the reaction mixture at 50 °C for 5 min. Only when the reaction with [Pd(PPh<sub>3</sub>)<sub>4</sub>] was carried out under much harsher conditions (DMF, 100 °C, 5 min) was the desired product formed, and then only in low yield (entry 5). Notably, Pd<sub>2</sub>(dba)<sub>3</sub>/L1 (entry 6) and L1-bound palladacycle 5,<sup>6</sup> alone (entry 7) or with an activating base (entry 8), could also be used to furnish the product, though both were less efficient than 1. Therefore, 1 is uniquely effective at forming A at rt in high yield, allowing for the effective [<sup>11</sup>C]cyanation of 3-bromoaniline under extremely mild conditions.

Under demonstration of the viability of this strategy, we next applied it to the syntheses of a variety of functionalized [<sup>11</sup>C](hetero)aryl nitriles (Table 2). Although 1 showed the

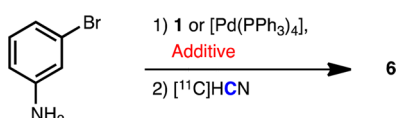
**Table 2. Radiosyntheses of [<sup>11</sup>C]Aryl Nitriles<sup>a</sup>**

Product	Ligand	X	RCC (%)
6 <sup>b</sup>	L=L1	X=Br	81 ± 1% (n=3)
7 <sup>b</sup>	L=L1	X=Cl	27 ± 7% (n=3)
	L=L1	X=Br	63 ± 2% (n=3)
	L=L1	X=I	> 95% (n=3)
8 <sup>b</sup>	L=L4	X=Br	89 ± 1% (n=3)
9 <sup>b</sup>	L=L4	X=Br	79 ± 7% (n=3)
10 <sup>b</sup>	L=L4	X=Br	89 ± 2% (n=3)
11 <sup>b</sup>	L=L1	X=Br	68 ± 3% (n=3)
12 <sup>b</sup>	L=L1	X=Br	46 ± 1% (n=3)
13 <sup>b</sup>	L=L2	X=Br	92 ± 1% (n=3)
14 <sup>b</sup>	L=L4	X=Br	18 ± 5% (n=3)
15 <sup>c</sup>	L=L4	X=OTf	64 ± 3% (n=3)

<sup>a</sup>Reported values indicate radiochemical conversion. Reaction conditions: [(L-Pd)<sub>2</sub>(COD)] (0.004 mmol in Pd), ArX (0.008 mmol), solvent (0.1 mL), rt, 30 min; then [<sup>11</sup>C]HCN (1–5 mCi), THF (0.1 mL) rt, 1 min. <sup>b</sup>Toluene as solvent. <sup>c</sup>THF as solvent.

most general reactivity, the ease of setting up these reactions with a stock solution of [<sup>11</sup>C]HCN in THF allowed for the quick determination of the ideal solvent and reagent (1–4) for each substrate. The reaction tolerates nucleophilic amine (6) and hydroxyl (7) groups, as well as a formyl group (8), which is susceptible to benzoin condensation at elevated temperatures.<sup>6</sup> Both aryl iodides and bromides can be used to furnish [<sup>11</sup>C]aryl nitriles in high yield, with aryl chlorides providing lower but still radiosynthetically useful yields (7).<sup>11</sup> The electronic nature of the arene did not bias the outcome of the reaction: highly electron-rich (7, 9) and -deficient (8, 10) [<sup>11</sup>C]nitriles were prepared with comparable efficiency. Heterocyclic compounds, such as quinoxaline (11), quinoline (12), thiazole (13), and pyrazole (14), were also viable substrates for this reaction. To our knowledge, these are the first examples of the [<sup>11</sup>C]-cyanation of 5-membered heteroaryl halides. Finally, a [<sup>11</sup>C]CN-labeled derivative of estrone was successfully synthesized from the corresponding triflate with high radiochemical yield (15). In all cases, the same straightforward setup as described above was used, and the results proved to be highly reproducible.

The susceptibility of the [<sup>11</sup>C]-cyanation of 3-bromoaniline with 1 or [Pd(PPh<sub>3</sub>)<sub>4</sub>] to inhibition by common contaminants and functional groups was also evaluated (Table 3).<sup>12</sup> Potential

**Table 3. Robustness Screen of the Radiosynthesis of [<sup>11</sup>C]-3-Aminobenzonitrile with **1** (a) and [Pd(PPh<sub>3</sub>)<sub>4</sub>] (b)<sup>a</sup>**


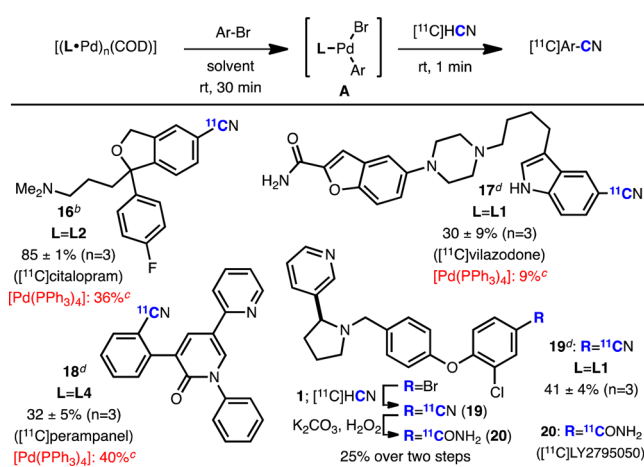
entry	additive	RCC (%) w/ 1 <sup>a</sup> (a)	RCC (%) w/ [Pd(PPh <sub>3</sub> ) <sub>4</sub> ] <sup>b</sup> (b)
1	none	81	30
2	water	80	n.d.
3	phenol	94	25
4	4-methoxybenzamide	88	9
5	pyridine	90	14
6	imidazole	92	0
7	5-fluoroindole	80	n.d.

<sup>a</sup>Reaction conditions: **1** (0.002 mmol), additive (0.008 mmol), 3-bromoaniline (0.008 mmol), toluene (0.1 mL), rt, 30 min; then [<sup>11</sup>C]HCN (1–2 mCi), THF (0.1 mL) rt, 1 min. <sup>b</sup>[Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.004 mmol), additive (0.008 mmol), 3-bromoaniline (0.008 mmol), K<sub>2</sub>CO<sub>3</sub> (0.008 mmol), DMF (0.1 mL); then [<sup>11</sup>C]HCN (1–5 mCi), DMF (0.1 mL), 100 °C, 5 min. n.d. = not determined.

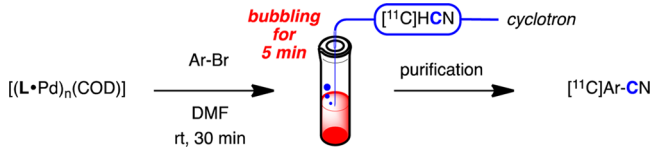
inhibitors were placed in the reaction vessel together with the aryl halide before carrying out oxidative addition to form **A**. The presence of common acidic compounds, such as water, phenol, or an amide did not significantly affect the outcome of the reaction with **1** (entries 2–4a). N-containing heterocycles that can impede metal-catalyzed cross-couplings, such as pyridine (entry 5a), imidazole (entry 6a), and indole (entry 7a), also did not show any inhibitory effects when using **1**. In contrast, while the reaction with [Pd(PPh<sub>3</sub>)<sub>4</sub>] could tolerate phenol (entry 3b), the presence of a free amide (entry 4b) or pyridine (entry 5b) diminished the yield, and imidazole completely inhibited the desired reaction (entry 6b). Thus, reactions carried out with **1** at rt are more robust than those carried out with [Pd(PPh<sub>3</sub>)<sub>4</sub>] at 100 °C

Another motivation in the development of our [<sup>11</sup>C]cyanation protocol is the abundance of cyano groups in pharmaceutically important small molecules,<sup>13</sup> as well as their ability to be readily transformed into other common functional groups such as carboxylic acids, amides,<sup>14</sup> amidines,<sup>15</sup> and tetrazoles.<sup>16</sup> Therefore, the syntheses of complex drug-based radiotracers using the corresponding aryl bromides as precursors were carried out (Table 4). All compounds were prepared using the same simple procedure presented above with no need to isolate the oxidative addition complexes. [<sup>11</sup>C]Citalopram (**16**, antidepressant),<sup>17</sup> [<sup>11</sup>C]vilazodone (**17**, antidepressant),<sup>18</sup> and [<sup>11</sup>C]perampanel (**18**, antiepileptic)<sup>19</sup> could be formed with high efficiency. The nitrile precursor to [<sup>11</sup>C]LY2795050 (**19**) was also easily prepared. Notably, [<sup>11</sup>C]LY2795050 itself (**20**, κ-opioid receptor antagonist) was also effectively prepared with 25% RCC from the corresponding bromide, demonstrating the potential utility of our protocol in multistep radiosyntheses. It is important to note that, to the best of our knowledge, this is the first preparation of [<sup>11</sup>C]vilazodone and [<sup>11</sup>C]perampanel. Although **18** could be prepared using [Pd(PPh<sub>3</sub>)<sub>4</sub>] with comparable yield as with **1** (albeit with a less clean reaction profile), both **16** and **17** were formed in significantly higher yields with **1** at rt than with [Pd(PPh<sub>3</sub>)<sub>4</sub>] at 100 °C (Table 4).

Finally, high-radioactivity syntheses of compounds **17–19** were carried out to assess applicability of this method for *in vivo* imaging (Table 5). To avoid loss of activity during transfer,

**Table 4. Syntheses of [<sup>11</sup>C]-Labeled Drugs<sup>a</sup>**

<sup>a</sup>Reported values indicate radiochemical conversion. Reaction conditions: [(L·Pd)<sub>n</sub>(COD)] (0.004 mmol in Pd), ArBr (0.008 mmol), solvent (0.1 mL), rt, 30 min; then [<sup>11</sup>C]HCN (1–5 mCi), THF (0.1 mL) rt, 1 min. <sup>b</sup>Toluene/acetone (5:1) was used as solvent. <sup>c</sup>[Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.004 mmol), ArBr (0.008 mmol), K<sub>2</sub>CO<sub>3</sub> (0.008 mmol), DMF (0.1 mL); then [<sup>11</sup>C]HCN (1–5 mCi), DMF (0.1 mL), 100 °C, 5 min. <sup>d</sup>DMF as solvent.

**Table 5. High-Radioactivity Synthesis of [<sup>11</sup>C]-Labeled Drugs**


[ <sup>11</sup> C]Ar-CN	17	18	19
starting / final activity (mCi)	188 / 35.3	156 / 15.1	70.0 / 14.5
RCY (%) <sup>a</sup>	18.8	9.7	20.7
total synthesis time (min) <sup>b</sup>	16.5	22.5	12.4
specific activity (Ci/μmol)	3.97	1.34	2.69

<sup>a</sup>Decay-uncorrected isolated radiochemical yield at end of synthesis. <sup>b</sup>Calculated after [<sup>11</sup>C]HCN delivery peaked to product isolation after HPLC purification.

[<sup>11</sup>C]HCN was captured from the carrier gas into the reaction mixture (*vide supra*). After achieving maximum radioactivity in the reaction mixture, HPLC eluent was added and the product was purified by reversed-phase HPLC. The absolute (decay uncorrected) radioactivity of the purified product ranged from 15 to 35 mCi,<sup>21</sup> and the whole process including chromatography took only 12–23 min after the solution capture of [<sup>11</sup>C]HCN, which is only 0.61–1.1 half-lives of <sup>11</sup>C. In addition, the specific activities of the products were all sufficiently high and reproducible. This is especially important in the preparation of high specific activity [<sup>11</sup>C]radiotracers. For comparison, the previous report of the synthesis of [<sup>11</sup>C]LY2795050 provided the final product with a specific activity of 0.64 Ci/μmol.<sup>20</sup> It should also be mentioned that the protocol is suitable for automation and remote control due to the ease of setup and purification of the product. This permits translation to human PET studies, which require strict validation.<sup>22</sup>

In conclusion, we have demonstrated the capability of new Pd complexes **1–4** to promote the nearly instantaneous [<sup>11</sup>C]-cyanation of (hetero)aryl halides and triflates at rt, an otherwise difficult transformation. The remarkable reactivity stems from

the capability of **1–4** to produce oxidative addition complex **A** *in situ*. As a consequence of the mild reaction conditions and robustness of this methodology, it exhibits wide functional group tolerance and is highly amenable for high-activity synthesis, even of densely functionalized molecules.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Author Contributions

||H.G.L. and P.J.M. contributed equally.

### Notes

The authors declare the following competing financial interest: MIT has obtained or has filed patents on some of the ligands/ precatalysts used in this work from which S.L.B. and former/current co-workers receive royalty payments.

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(10) A variety of solvents, including Et<sub>2</sub>O, DMSO, acetone, and *tert*-amyl alcohol, could be used to furnish the product in good RCC (see Supporting Information Table S1).

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(21) PET radiotracer administered doses vary but are generally 0.1–0.3 mCi/kg (human), 0.1–0.5 mCi/kg (nonhuman primates), 1–5 mCi/kg (rodent) for <sup>11</sup>C.

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