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Copper(II)-Mediated [^{11}C]Cyanation of Arylboronic Acids and Arylstannanes

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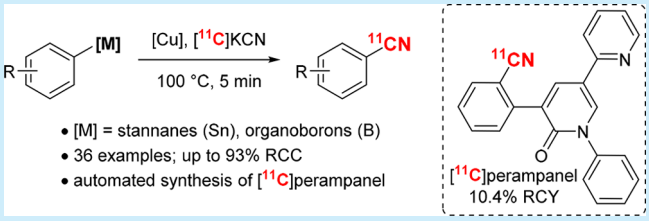
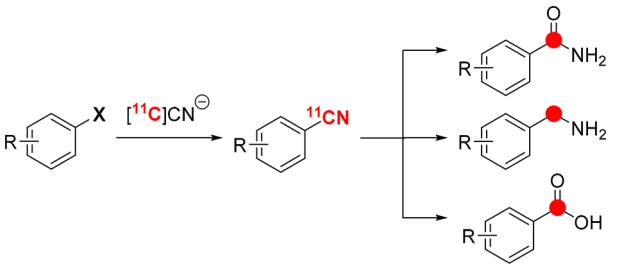
Supporting Information

ABSTRACT: A copper-mediated method for the transformation of diverse arylboron compounds and arylstannanes to aryl-[^{11}C]-nitriles is reported. This method is operationally simple, uses commercially available reagents, and is compatible with a wide variety of substituted aryl- and heteroaryl substrates. This method is applied to the automated synthesis of high specific activity [^{11}C]perampanel in 10% nondecay-corrected radiochemical yield (RCY).



Carbon-11 is a radioisotope that is commonly used for positron emission tomography (PET) imaging.[1] The introduction of carbon-11 into PET radiotracers is particularly challenging due to its very short half-life ($t_{1/2}$ = 20 min).[2] A number of methods have been developed for [^{11}C]-radiolabeling, and some of the most attractive involve the late-stage introduction of a [^{11}C]CN substituent (Scheme 1).[3] [^{11}C]-Cyanide offers an advantage because it can be readily generated from [^{11}C]CO_2.[1,2] Additionally, the nitrile functionality is common in bioactive molecules[4] and can also be rapidly transformed into other important functional groups, including amides, carboxylic acids, and amines (Scheme 1).

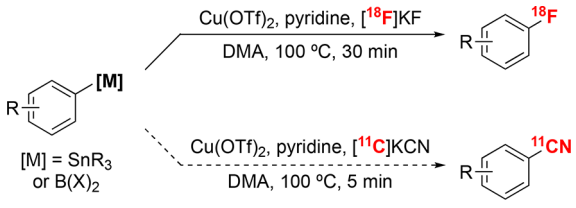
Scheme 1. Diversification of [^{11}C]Nitrile Substrates



There are currently two major methods for the [^{11}C]-cyanation of aromatic and heteroaromatic substrates. The first uses aryl halide precursors in combination with a Pd catalyst to engage [^{11}C]cyanide in aryl−CN cross coupling.[5−8] These reactions often provide high yields, exhibit broad scope, and proceed under mild conditions. However, Pd is relatively toxic;[9] furthermore, the Pd-aryl intermediates and phosphine ligands required for these reactions can be challenging to handle, particularly in the context of automated radiochemical synthesis.[10]

A second [^{11}C]radiocyanation method involves the reaction of aryl halides with [^{11}C]CuCN (i.e., the Rosenmund−von Braun reaction).[11−13] This transformation offers the advantages of operational simplicity (i.e., no phosphine ligands, no requirement to preform organometallic intermediates, no need to remove palladium) and the relatively low toxicity of Cu.[9] However, it suffers from low yields, modest scope, and forcing reaction conditions (often requiring temperatures of 150−250 °C).[2] We sought to develop an alternative Cu-mediated [^{11}C]radiocyanation that would leverage the advantages while addressing the limitations of the existing Cu method. Our laboratory has recently reported that arylboron compounds and arylstannanes undergo Cu-mediated [^{18}F]-radiofluorination with [^{18}F]KF.[14−17] We hypothesized that changing the nucleophile from fluoride to cyanide under similar reaction conditions might enable a mechanistically analogous [^{11}C]radiocyanation reaction (Scheme 2).[18] We demonstrate

Scheme 2. Inspiration from Cu-Mediated [^{18}F]Fluorination of Arylorganometallics



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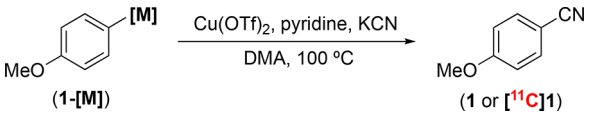
here that the combination of $Cu(OTf)_2$, pyridine, and [^{11}C]KCN effectively promotes the [^{11}C]radiocyanation of diverse aryl boronic acids, aryl boronate esters, aryl trifluoroborates, and arylstannanes under relatively mild conditions. We show that this transformation is compatible with a wide variety of functional groups and of aryl/heteroaryl substrates. Furthermore, it is readily translated to the automated synthesis of the radiotracer [^{11}C]perampanel.[19] Notably, while this work was underway, the team of Hooker, Vasdev, and Liang published a related method for the Cu-mediated [^{11}C]cyanation of arylboronic acids.[20]

Our initial studies focused on establishing the feasibility of the Cu-mediated cyanation of aryl organometallic reagents under conditions analogous to those for our [^{18}F]-radiofluorination reactions.[15] Using $Cu(OTf)_2$ and pyridine in DMA at 100 °C, the reaction of 4-methoxyphenyl tributylstannane (**1-SnBu$_3$**) with KCN afforded 4-methoxybenzonitrile (**1**) in 28% yield in 1 h, as determined by ^{1}H NMR spectroscopy (Table 1, entry 1). Comparable results were

Table 1. Initial Results with KCN and Optimization with [^{11}C]KCN[a]



(**1-[M]**) (**1** or [^{11}C]**1**)

entry	[M]	changes from standard	product (yield or RCC, %)
Results with KCN[b]			
1	**1-SnBu$_3$**	none	**1** (28)
2	**1-B(OH)$_2$**	none	**1** (32)
3	**1-BF$_3$K**	none	**1** (26)
4	**1-Bpin**	none	**1** (6)
5	**1-Bpin**	KF (1.2 equiv)	**1** (21)
Results with [^{11}C]KCN[c]			
6	**1-SnBu$_3$**	[^{11}C]KCN in DMA	[^{11}C]**1** (42)
7	**1-SnBu$_3$**	DMA prep, H_2O[d]	[^{11}C]**1** (41)
8	**1-SnBu$_3$**	none	[^{11}C]**1** (66)
9	**1-B(OH)$_2$**	none	[^{11}C]**1** (79)
10	**1-BF$_3$K**	none	[^{11}C]**1** (93)
11	**1-Bpin**	none	[^{11}C]**1** (76)

[a]Standard conditions: substrate (10 μmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), DMA (1 mL, 10 mM). [b]KCN (2 equiv), 100 °C, 1 h. Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trifluorobenzene as an internal standard. [c][^{11}C]KCN in H_2O, 100 °C, 5 min. Reported values indicate radiochemical conversion (RCC) of determined by radio-TLC ($n \geq 2$). [d]H_2O (0.2 mL, 17% v/v).

obtained with the corresponding boronic acid (**1-B(OH)$_2$**) and trifluoroborate (**1-BF$_3$K**) substrates (32% and 26% yields, respectively), while the boronate ester afforded a lower yield (6%). However, the yield with the boronate ester could be increased to 21% by the addition of 1.2 equiv of KF. This additive likely promotes transmetalation via the formation of a borate intermediate. Notably, no fluorinated product was observed upon the addition of KF.

We next translated this method to [^{11}C]radiocyanation using anhydrous [^{11}C]KCN. Gratifyingly, the product ([^{11}C]**1**) was formed in 42% RCC, as determined by radio-TLC with identity confirmed by radio-HPLC (entry 6). Subsequent studies revealed that anhydrous conditions (which were essential for the analogous [^{18}F]radiofluorination with [^{18}F]KF) are not required for [^{11}C]radiocyanation. For example, a comparable 41% RCC was obtained upon the addition of exogenous water (0.2 mL, 17% v/v) to the anhydrously prepared [^{11}C]KCN reaction mixture. Furthermore, an even higher yield (66% RCC, entry 8) was observed when the [^{11}C]KCN was prepared and used directly as an aqueous solution. This modification decreased the overall synthesis time by 4 min (approximately 20% of the ^{11}C half-life). The improved RCC under these conditions is likely due to increased solubility of [^{11}C]KCN.

Using this aqueous [^{11}C]KCN preparation, we next evaluated the [^{11}C]radiocyanation of other aryl organometallic substrates. As summarized in Table 1, entries 8−11, various arylboron compounds afforded comparable and/or improved RCCs relative to their stannane counterpart, with the trifluoroborate (**1-BF$_3$K**) giving the best result (93% RCC). Notably, KF was not required for the [^{11}C]radiocyanation of arylboronate ester (**1-Bpin**), likely due to the decreased amount of KCN available in the reactions.

The scope of this transformation was further evaluated using a variety of organoboron and organostannane substrates (denoted by the footnotes in Figure 1). These studies showed that electron-donating ([^{11}C]**1**−**4**), -neutral ([^{11}C]**5**), and -withdrawing ([^{11}C]**6**−**7**) substituents on the aromatic ring are all well-tolerated. *Ortho*-substituted substrates underwent [^{11}C]radiocyanation in comparable yields to their unsubstituted counterparts ([^{11}C]**8**−**10**).[20] In addition, carbonyl groups ([^{11}C]**11**−**14**) were compatible with the reaction conditions.[19] Significantly, precursors containing unprotected benzoic acid ([^{11}C]**12**) and phenol ([^{11}C]**4**) substituents also afforded modest to excellent yields. Aryl bromides were tolerated at various sites around the phenyl ring ([^{11}C]**16**−**18**), and could serve as handles for further elaboration of the products. Pyridine derivatives and related nitrogen heterocycles also underwent [^{11}C]radiocyanation in moderate to high yields ([^{11}C]**19**−**25**).

Overall, the scope of this transformation is broader, and many of the RCCs are higher than those of previously reported methods for the [^{11}C]radiocyanation of aromatic substrates.[8,20] As an example, our method affords quinoline product [^{11}C]**20** in 71% RCC from **20-B(OH)$_2$**. For comparison, recently reported Cu-mediated [^{11}C]radiocyanation conditions provide 18% RCC for the same substrate,[20] while a Pd-mediated method affords 46% RCC from the analogous aryl bromide.[8] Notably, subjecting **20-B(OH)$_2$** to our related Cu-mediated fluorination affords only trace amounts of product (<10% ^{19}F NMR yield),[21] demonstrating that this cyanation reaction also has improved scope relative to fluorination. Finally, it is noteworthy that a number of the products in Figure 1 have not been labeled with [^{11}C]nitrile before, including [^{11}C]**3**−**4**, **6**, **8**−**9**, **12**, **14**−**15**, **17**−**19**, **22**, **25**, and **27**.

As a final demonstration of this method, we pursued the automated, clinical-scale synthesis of [^{11}C]perampanel. Perampanel, an FDA-approved drug for epilepsy, has been [^{11}C]radiolabeled once before using a Pd-mediated method with an aryl bromide precursor to afford [^{11}C]**26** in 40% RCC (manual, radio-TLC) and 9.7% RCY (isolated, nondecay corrected).[8] Our manual method provided 90 ± 2% RCC of [^{11}C]**26** from the arylboronate ester using approximately 1 mCi of [^{11}C]KCN per reaction. The synthesis was scaled to 450 mCi of [^{11}C]KCN, and the [^{11}C]radiocyanation and subsequent HPLC purification of [^{11}C]**26** were conducted using an automated radiosynthesis module. Without further optimization, this procedure afforded [^{11}C]**26** in 10.4 ± 0.4% nondecay corrected radiochemical yield (RCY; Scheme 3). The

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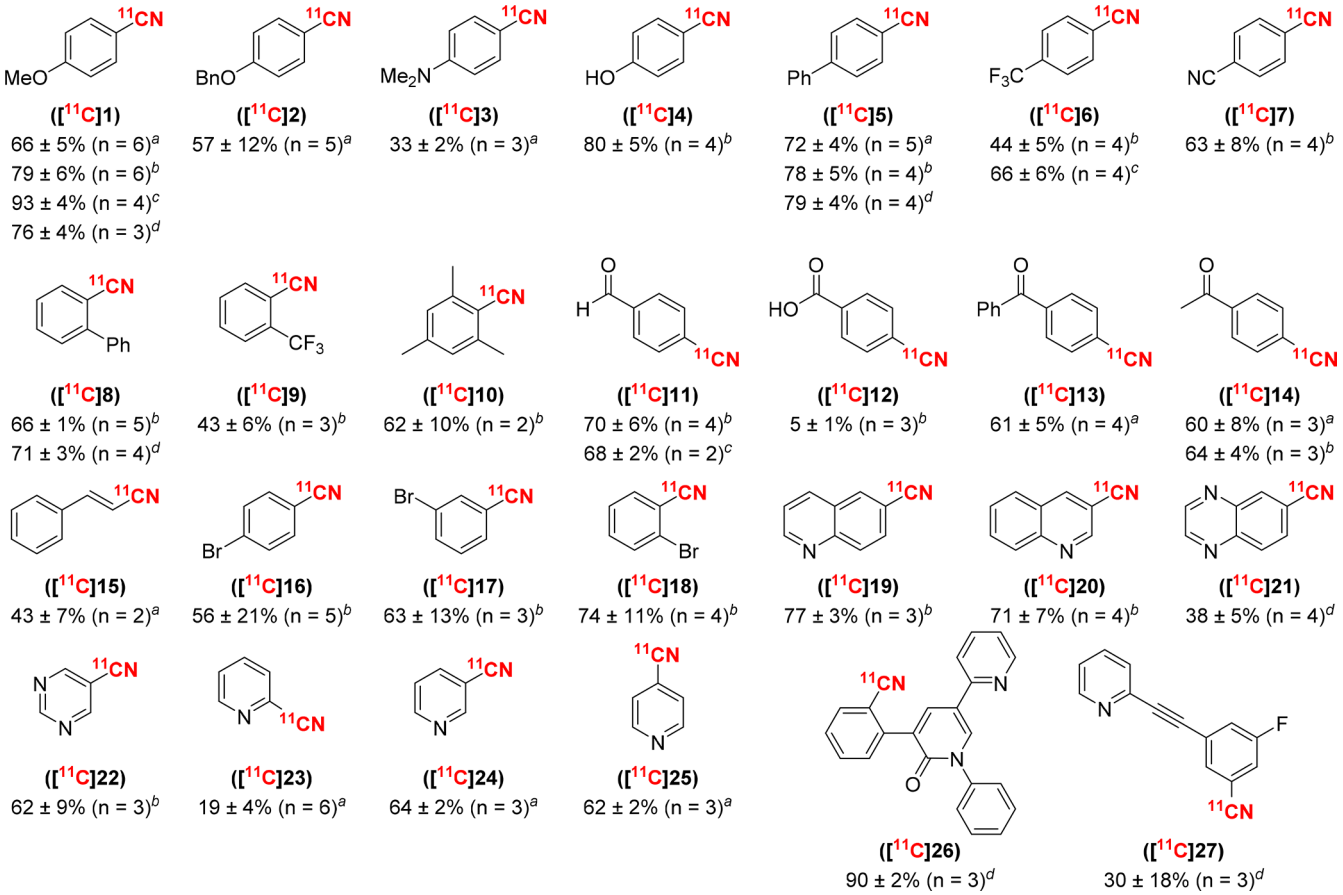
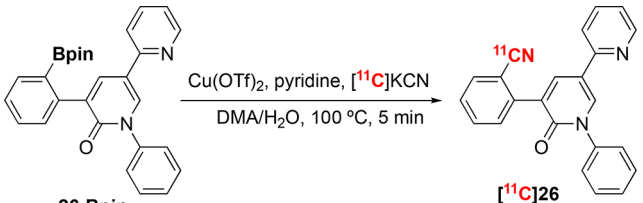


Figure 1. Substrate scope. Reported values indicate radiochemical conversion (RCC) of determined by radio-TLC ($n \geq 2$). General conditions: substrate (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), [^{11}C]KCN in H_2O (0.1 mL), DMA (10 mM), 100 °C, 5 min. [M] = (a) $SnBu_3$, (b) $B(OH)_2$, (c) BF_3K, (d) Bpin.

fully automated synthesis lasted approximately 32 min from the end of bombardment.

Scheme 3. Automation of [^{11}C]Perampanel[a]



[a]General conditions: **26-Bpin** (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), [^{11}C]KCN, DMA, 100 °C, 5 min. Radiochemical yield (RCY) determined by isolated material after preparative-HPLC ($n = 2$). QC was performed to confirm the correct product was formed and purify was >95%. NDC = nondecay corrected. DC = decay corrected. SA = specific activity.

In conclusion, this paper describes a Cu-mediated [^{11}C]-radiocyanation of diverse aryl organometallic reagents. This method is compatible with a wide range of substrates, including those containing carboxylic acids, phenols, aldehydes, and heterocycles. This method is also amenable to automation on a clinically relevant scale, as demonstrated in the synthesis of [^{11}C]perampanel.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00242.

Optimization details, experimental procedures, radio-HPLC/TLC traces, and complete characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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