Transition Metal-mediated Reactions using [^{11}C]Cyanide in Synthesis of ^{11}C-labelled Aromatic Compounds

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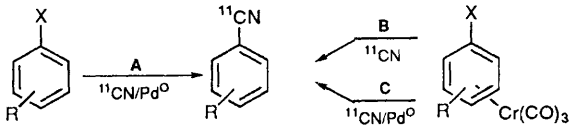
Aromatic and heteroaromatic nitriles, labelled with carbon-11 in the cyano group, have been synthesized by rapid palladium- and chromium-mediated reactions using hydrogen [^{11}C]cyanide. The ^{11}C-cyanation on aryl iodides, bromides, and triflate, or on heteroaromatic bromides, in the presence of tetrakis(triphenylphosphine)palladium, afforded 54–99% radiochemical yield in 5 min. The Pd^0-promoted ^{11}C-cyanation was performed with varying concentrations of substrate, down to the sub-micro molar scale (>0.1 μmol). The decay-corrected radiochemical yields of [*cyano*-^{11}C]benzonitriles after purification by semi-preparative HPLC were 50–90%, based on hydrogen [^{11}C]cyanide, with a total synthesis time of 20–25 min and a radiochemical purity >98%. Nucleophilic aromatic substitution with ^{11}C-cyanide on tricarbonylchromium complexes of some fluoroarenes resulted in radiochemical yields of 46–74%. In a combined synthetic sequence, Pd^0-assisted ^{11}C-cyanation on chloroarene(tricarbonyl)chromium complexes, the radiochemical yields were 95%. By mono-^{11}C-cyanation on 1,4-dibromobenzene, the difunctional precursor 4-bromo[*cyano*-^{11}C]benzonitrile was obtained. Subsequent cross-coupling with phenyl(trimethyl)tin in the presence of tetrakis(triphenylphosphine)palladium afforded 4-[*cyano*-^{11}C]biphenylcarbonitrile in 60% radiochemical yield. The synthesis time before purification was 15 min counted from end of bombardment.

The advancement of positron emission tomography (PET) as an important technique in basic science and clinical research has increased the demand for compounds labelled with short-lived positron emitters. Among the radionuclides available, ^{11}C and ^{18}F with half-lives of 20.3 and 110 min, respectively, are the most common nuclides used in the labelling of biologically interesting compounds.[1] In evaluation of the synthetic procedure, one aspect to consider is that the labelled precursors obtained by the appropriate nuclear reaction using an accelerator are of high specific radioactivity (typically 1–6 Ci μmol^{-1}). Because of the short half-lives, the time available for incorporation of the radionuclide into the target molecule is a critical parameter.[2] An extended arsenal of methods, suitable for rapid, small-scale syntheses in which low amounts of labelled precursors are used is, therefore, essential for improvement in production of radiochemicals and for further progress in the field of positron emission tomography.[3]

During the last few decades, the development of organo-transition metal chemistry has provided an increased range of synthetic strategies. A wide variety of reactions employing transition metals such as palladium or chromium, both as stoichiometric reagents and as catalysts have been described.[4] The objective of this study was to explore the usefulness of some of these metal-mediated reactions in rapid synthesis of compounds labelled with short-lived β^+-emitting radionuclides. As a model system the nucleophilic displacement reaction on aromatic compounds was chosen.

In many syntheses of radiopharmaceuticals, the labelled reagents used are of electrophilic character.[1,5] At present, the number of nucleophilic precursors labelled with positron emitters is limited to [^{11}C]cyanide, [^{11}C]nitroalkanes, [^{18}F]-fluoride and [^{13}N]ammonia (half-life 10.0 min). Other ^{11}C-reagents with nucleophilic character are [^{11}C]methyllithium[6] and [^{11}C]methyl cuprate,[7] both of which can be obtained from [^{11}C]methyl iodide.

In this paper, the transition metal-mediated ^{11}C-cyanation of a number of aromatic model compounds including furan and pyridine is reported (Scheme 1). The ^{11}C-labelled nitriles

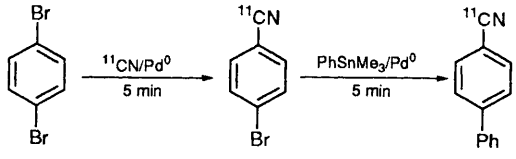


X = I, Br, OTf, (**A**); F, Cl (**B**); Cl (**C**)

Scheme 1

have been synthesized employing either a palladium-assisted coupling reaction on aromatic halides and triflate (route **A**), or a nucleophilic substitution on tricarbonylchromium complexes of arenes (route **B**). A combined palladium and chromium tricarbonyl assisted preparation of ^{11}C-labelled aromatic nitriles (route **C**), has also been studied.

Investigation of the impact of different parameters, *i.e.* substrate concentration, solvent, reaction time and reaction temperature, is presented. Preliminary results on the use of [^{18}F]fluoride and [^{11}C]methyllithium as nucleophiles in similar procedures are also discussed. Furthermore, the possibility of using synthetic strategies involving serial carbon–carbon coupling reactions in preparation of radiochemicals is described (Scheme 2).



Scheme 2

Results and Discussion

In labelling synthesis, as well as in conventional organic synthesis, nitriles are versatile intermediates due to their facile transformation to compounds with other functional groups, *e.g.* acids, aldehydes, amines and amides. Palladium-catalysed cyanation of aromatic triflates[8] and halides,[8,9] using reagents

Table 1 Palladium(0)-assisted cyanation of aromatic compounds using [^{11}C]cyanide[a]

Entry	R	X	Labelled product	Radiochemical yield (%)[b]
1	H	I	[*cyano*-^{11}C]Benzonitrile	95 ± 5* (90)
2	H	Br		90
3	H	Cl		45
4	H	F		0
5	Br	4-Br	4-Bromo[*cyano*-^{11}C]benzonitrile	88 (62)
6	CH_3	4-Br	4-[*cyano*-^{11}C]Toluonitrile	90
7	CH_3	4-Cl		12
8	CH_3	4-F		0
9	NH_2	3-I	3-[*cyano*-^{11}C]Cyanoaniline	> 99
10	NH_2	3-Br		54
11	NO_2	2-I	2-Nitro[*cyano*-^{11}C]benzonitrile	72
12	OCH_3	3-I	3-[*cyano*-^{11}C]Cyanoanisole	> 99 (64)
13	OCH_3	3-Br		85
14	OH	3-Br	3-[*cyano*-^{11}C]Cyanophenol	81
15	H	OTf	[*cyano*-^{11}C]Benzonitrile	62

[a] Substrate (50–90 μmol) and Pd^0 (2 μmol) in THF (1 cm^3). Reaction time 5 min and reaction temp. 90 °C. [b] Determined by analytical HPLC as the percentage of the total amount of radioactivity in a sample withdrawn from the reaction mixture. Values given within parentheses are decay-corrected radiochemical yields, obtained after purification on semi-preparative HPLC, based on hydrogen [^{11}C]cyanide trapped. The radiochemical purity was higher than 98%. * Example given for $n = 10$, mean value ± range. For the other experiments $n \geqslant 2$.

such as potassium cyanide or trimethylsilyl cyanide, is a convenient method for synthesis of arenenitriles. As previously reported, the reaction of halogenobenzene derivatives with [^{11}C]cyanide is assisted by tetrakis(triphenylphosphine)palladium.[10] In the present investigation, several aromatic and heteroaromatic nitriles, labelled with carbon-11 in the cyano group, have been synthesized from the corresponding halides or triflate using this palladium-promoted carbon–carbon bond-forming reaction.

Pd^0-Mediated ^{11}C-Cyanation.—Of the different aryl halides employed in this reaction, the iodo compounds afforded the highest radiochemical yields (72–99%), as determined by analytical HPLC (Table 1). Good results were also achieved uisng the bromo substrates. The chlorobenzene derivatives were found to be less reactive, and, as expected, no product was obtained using the fluoro substrates. The decay-corrected radiochemical yields of the [*cyano*-^{11}C]benzonitriles after purification by semi-preparative HPLC was 62–90%, based on hydrogen [^{11}C]cyanide (entries 1, 5 and 12). The total synthesis time was 20–25 min counted from end of bombardment. When the tetrakis(triphenylphosphine)palladium was omitted, no labelled product was obtained.

In the synthesis of the heteroaromatic nitriles 3-[*cyano*-^{11}C]cyanofuran and 3-[*cyano*-^{11}C]cyanopyridine radiochemical yields between 70 and 80% were obtained using the corresponding bromo substrates. The reaction with phenyl triflate (entry 15) resulted in a 62% yield of [*cyano*-^{11}C]benzonitrile. The conversion of a phenolic compound into an aryl triflate can easily be performed,[11] and this synthesis of ^{11}C-labelled aromatic nitriles might, therefore, be a useful alternative to the reaction with aryl halides.

The reaction time for the palladium-promoted ^{11}C-cyanation was standardised to 5 min, although the coupling reaction was complete in 2 min when the aryl iodides were used. A reaction time longer than 5 min for the less reactive substrates had no beneficial effect on the radiochemical yield. As illustrated in Table 1, the presence of different substituents on the aromatic halide, *e.g.* amino, hydroxy, methoxy or nitro, had no pronounced effect on the reaction, and moderate to high radiochemical yields were achieved.

The possibility of performing the above reaction in different media was investigated. The highest radiochemical yield (> 99%), was obtained when the cyanation was carried out in THF at 90 °C. It was observed that a higher reaction temperature increased the amount of side products, while a lower temperature resulted in a decreased yield. The radiochemical yield was high (70–99%) for acetonitrile, dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) as solvents.

To preserve the activity of the palladium(0) complex, it was added to the reaction mixture in its solid state as late as possible in the synthetic procedure. A decreased radiochemical yield was observed in some experiments where a solution of the metal complex, prepared in advance was used. This is probably a result of the rapid oxidation, by molecular oxygen, of the palladium triphenylphosphine complex in solution.[4c] The problem was eliminated when all the reaction steps were conducted under an argon atmosphere, using carefully degassed solvents. However, for the model reactions presented here this procedure was not considered to be necessary.

The rapidly achieved conversion of ^{11}C-cyanide into labelled product, and the compatibility with various functional groups as well as different solvents, indicates the usefulness of these palladium-promoted reactions in radiolabelling synthesis.

Pd^0-Mediated ^{11}C-Cyanation in Sub-micromolar Scale.—In performing the palladium-promoted cyanation, standard conditions for catalytic reactions[9a] were employed, *i.e.* a molar ratio of aryl halide and tetrakis(triphenylphosphine)-palladium(0) in the range of 50 : 1. Approximately 2 μmol of Pd^0 were used in the labelling procedure. However, the organo-palladium complex generated was in large excess as compared to the amount of cyanide used in the reaction.[1a] Considering the fact that a stoichiometric ratio of aryl halide to Pd^0 would be sufficient, and taking into account the advantage of using small amounts of substrate and reagents in radiolabelling synthesis, an investigation of the influence of these parameters on the radiochemical yield was conducted.

In order to obtain efficient and reproducible trapping of hydrogen [^{11}C]cyanide in organic solvents, a frequently used procedure is to add Kryptofix® and a base, *e.g.* potassium hydroxide, to the trap solution. In the sub-micromolar experiments, these reagents were excluded since the hydrogen [^{11}C]cyanide was effectively trapped in a mixture of [$Pd(PPh_3)_4$] and substrate in THF at room temperature.

Reducing the amount of iodobenzene to a molar excess of 10 : 1 with respect to palladium and employing 2 μmol of Pd^0, did not affect the radiochemical yield of the reaction. The radiochemical yield was maintained at 80% (crude product)

Table 2 Cyanation on tricarbonylchromium complexes of arenes using [^{11}C]cyanide[a]

Entry	R	X	Labelled product	Radiochemical yield (%)[b]
1	H	F	[*cyano*-^{11}C]Benzonitrile	74
2	H	Cl		30
3	Me	4-F	4-[*cyano*-^{11}C]Toluonitrile	69
4	Me	4-Cl		50
5	Me	4-Br		0
6	Me	3-F	3-[*cyano*-^{11}C]Cyanoanisole	46
7*	H	Cl	[*cyano*-^{11}C]Benzonitrile	95
8*	Me	4-Cl	4-[*cyano*-^{11}C]Toluonitrile	95

[a] Substrate (15–40 μmol) in DMSO (0.5–1.0 cm^3). Reaction temp. 135 °C and reaction time 10 min. [b] Determined as the percentage of the total amount of radioactivity in an aliquot taken from the reaction mixture. * In the presence of Pd^0 (1–2 μmol), reaction time 5 min.

even for reactions using a 1 : 1 molar ratio of iodobenzene to palladium(0) and with a decrease in the amount of substrate to 100 μg (0.5 μmol). A 50% decay-corrected radiochemical yield, based on [^{11}C]cyanide, was obtained after purification by semi-preparative HPLC. It was observed that a further reduction of the substrate–palladium complex resulted in a decreased yield. A 23% decay-corrected yield of purified [*cyano*-^{11}C]benzonitrile was obtained in a reaction employing 20 μg (0.1 μmol) of iodobenzene and 1 equiv. of palladium(0) compound.

The specific radioactivity of [^{11}C]cyanide produced in the system used is in the order of 5 Ci μmol^{-1}.* The quantity of cyanide in a reaction where 100 mCi is employed is thus approximately 20 nmol. Generally, all substrates and reagents are in large excess as compared to the labelled precursor and the reactions are of pseudo-first order kinetics.[2] In the experiments described above, the molar ratio is altered in such a way that the reaction order is changed, and this will slow down the product formation, thereby decreasing the absolute radiochemical yield. This is, of course, an essential point to consider in development of radiotracer synthesis where submicromolar amounts of unlabelled precursors are used.

The volumes of solvent and of reaction vessels were not changed during the investigation and, consequently, a lower concentration of reactants was obtained when the molar amounts were reduced. In order to generate the small quantity of [$Pd(PPh_3)_4$] employed, a solution of the palladium compound was prepared prior to use. This may also have influenced the amount of product obtained, *vide supra*.

Arene(tricarbonyl)chromium Complexes in ^{11}C-*Cyanation Reactions.*—In this study, different routes to ^{11}C-labelled aromatic nitriles were investigated as illustrated in Scheme 1. Employing tricarbonylchromium complexes of arenes, route **B**, the nucleophilic substitution by [^{11}C]cyanide were readily achieved on the fluoroarene complexes. The chloroarene complexes were less reactive and the bromo substrate showed no reactivity towards the ^{11}C-labelled cyanide (Table 2, entries 1–6).

In this route to aromatic nitriles, DMSO was the solvent affording the highest radiochemical yields of labelled benzonitriles (70% entries 1 and 3). In DMF moderate yields (50%) were obtained using the same substrates. By changing the solvent employed in the trapping of [^{11}C]cyanide from water, earlier reported in the ^{11}C-cyanation of tricarbonyl(fluorobenzene)chromium,[12] to DMSO, the reaction sequence could be simplified and the radiochemical yield was increased. The 35% yield of ^{11}C-labelled benzonitrile obtained by Balatoni *et al.*,[12] was thus improved significantly in the present investigation to 74% of the crude product.

Decomplexation of the chromium unit is usually achieved by displacement of the arene by other donor ligands, or by oxidative methods.[4b,d,e] Under the labelling conditions employed here, decomplexation steps to remove the tricarbonylchromium were not necessary, since the displacement of the arene ligand occurred during the reaction. Generally, arene(tricarbonyl)chromium complexes are stable in crystalline form, but quite unstable in solution. Presumably, the small quantities of complex used in this investigation were oxidised by trace amounts of oxygen in the solvent and reaction vessel. Careful measures taken to exclude oxygen during this cyanation reaction may increase the yield, but the time necessary for conventional decomplexation of the labelled product then has to be considered. The radiochemical yield of final product obtained might, therefore, not be significantly improved by such measures.

Oxidative addition of palladium(0) to aryl halide is facilitated when the π-electron density of the arene is reduced, and a convenient method to accomplish this reduced electron density is to use arene(tricarbonyl)chromium complexes.[13] As illustrated in Table 2 (entries 7–8) the palladium-promoted cyanation of the tricarbonyl(chlorobenzene)chromium complexes afforded high radiochemical yields. The yields were increased, from < 50%, obtained using either the chromium- or palladium-mediated route, to 95%, when the combined sequence was employed. Considering the wide availability of aryl chlorides, and with their high stability as compared to aryl iodides, this route to produce ^{11}C-labelled aromatic compounds in high yields may be of general interest.

The enhanced reactivity towards nucleophiles provided by the electron-withdrawing tricarbonylchromium moiety has thus proven to be valuable in radiolabelling synthesis. Still, there are other aspects on the altered reactivity in tricarbonylchromium complexes which might be of interest in future labelling procedures. The enhanced acidity of benzylic hydrogens facilitates generation of benzylic anions, which may then be treated with electrophilic reagents like [^{11}C]methyl iodide. Since the bulky tricarbonylchromium group blocks one of the faces of the arene and thus controls the orientation of the approaching reactants, this may be a method applicable to stereoselective synthesis of radiopharmaceuticals.[14]

Pd^0-*Mediated* ^{11}*C-Cyanation and subsequent Cross-coupling.*—Transition metal-catalysed reactions of organic halides with organometallic compounds, *e.g.* Grignard, zinc or aluminum reagents, provides an efficient method for carbon–carbon bond formation.[15] Because of its tolerance of a variety of reactive functional groups, the cross-coupling of organic halides with tin reagents, commonly referred to as the Stille-coupling,[16a] is one of the most versatile of reactions.[16b]

In this investigation, mono-^{11}C-cyanation on dibromo-

* Calculated from the specific radioactivity of ^{11}C-labelled benzamide[19] (2–3 Ci μmol^{-1} at end of synthesis), corrected to end of bombardment.

benzene was achieved employing the palladium-promoted reaction (Table 1, entry 5). To explore the prospect of introducing a labelled aromatic structure into more complex molecules, the 4-bromo[*cyano*-^{11}C]benzonitrile was further functionalised by a subsequent reaction with trimethyl(phenyl)-tin (Scheme 2).

The synthesis of 4-[*cyano*-^{11}C]biphenylcarbonitrile was performed using a one-pot procedure. After the incorporation of ^{11}C-cyanide, the cross-coupling was carried out by adding [$Pd(PPh_3)_4$], the organotin reagent and the solvent. The reaction sequence could be performed using THF both in the cyanation reaction and in the subsequent coupling. Even better results were achieved when the second reaction step was conducted in a mixture of THF and another solvent, *e.g.* toluene, DMF or 1-methyl-2-pyrrolidone. A 60% radiochemical yield of 4-[*cyano*-^{11}C]biphenylcarbonitrile (crude product) was obtained in THF/toluene at 120 °C, as compared to 25% yield when THF alone was used. The synthesis time was approximately 15 min counted from end of bombardment.

The strategy of rapid, palladium-assisted cross-couplings is of considerable interest in the preparation of radiopharmaceuticals. Further investigation on the application of this procedure in the synthesis of labelled compounds, *e.g.* reagents suitable for labelling of macromolecules, is now in progress.

Reactions using Other β^+*-Labelled Nucleophilic Precursors.*—Throughout the present work the nucleophile employed has been ^{11}C-labelled cyanide. Two other positron-emitting reagents acting as nucleophiles, [^{11}C]methyllithium and hydrogen [^{18}F]fluoride, have also been investigated. The ^{11}C-labelled methyllithium was prepared from [^{11}C]carbon dioxide by a synthetic sequence including conversion into [^{11}C]methyl iodide[17] followed by an exchange reaction with butyllithium.[6] The [^{11}C]methyllithium could then be treated with aryl iodides in presence of Pd^0 to give, for example, ^{11}C-labelled toluene.* The radiochemical yields in these reactions were low (< 10%), and no effort was made further to develop the procedure.

Attempts to use [^{18}F]fluoride as the labelled nucleophile were not successful in the palladium-promoted reactions, nor in the substitution on arene(tricarbonyl)chromium complexes. The cyanation of aryl halides has been proposed to proceed through oxidative addition of Pd^0 to the halide, followed by replacement of the halogen on palladium by cyanide. The organo-palladium species formed then undergoes reductive elimination, leading to carbon–carbon bond formation between the cyanide and the aryl group.[4c] A similar reaction mechanism, employing [^{18}F]fluoride instead of [^{11}C]cyanide, is probably not involved. Fluoro complexes of transition metals are, in many instances, more stable than the corresponding heavier halogen analogues,[18] and the strong coordination of fluoride to palladium(II) may prevent the formation of a carbon–fluorine bond in the reductive elimination process. In nucleophilic substitution on arene(tricarbonyl)chromium complexes, it is possible that the [^{18}F]fluoride, instead of attacking the activated site of the arene, to a large extent is coordinated to the metal centre.

Characterisation of Products.—The identity of the ^{11}C-labelled compounds was assessed by reversed-phase analytical HPLC of products before and after addition of unlabelled reference substances, using two different analytical HPLC systems. To ensure that all of the radioactive substances injected into the HPLC columns were eluted, a comparison of the radioactivity in the injected volume and in the collected fractions was made.

The position of the radionuclide was verified by conducting a combined ^{11}C/^{13}C-synthesis of 3-methoxy[*cyano*-^{11}C/^{13}C]-benzonitrile. After conversion of the nitrile into 3-methoxy-[*cyano*-^{11}C/^{13}C]benzamide,[19] the purified product was analysed by GC–MS, ^{1}H and ^{13}C NMR spectroscopy. The data obtained were compared to spectroscopic data for the unlabelled reference substance. The result confirmed the proposed position of the radiolabel, and also verified the product identity.†

Conclusions.—The transition metal-mediated reactions reported herein provide versatile methods for rapid incorporation of [^{11}C]cyanide into aromatic and heteroaromatic compounds. Palladium-promoted ^{11}C-cyanations on halides or triflate, nucleophilic substitution by ^{11}C-labelled cyanide on tricarbonyl chromium complexes of arenes, or a combined palladium- and chromium-assisted synthesis, enables efficient conversion of aromatic or heteroaromatic fluoro-, chloro-, bromo-, iodo- or triflates into the corresponding ^{11}C-nitriles. The possibility of conducting the cyanation on a submicromolar scale with regard to the unlabelled precursors enhances the versatility of these reactions in radiolabelling syntheses.

Cross-coupling of a difunctional ^{11}C-precursor with organotin reagents, in the presence of a Pd^0 complex, further extends the range of compounds that may be labelled with carbon-11 using this approach. Taking into account the facile transformation of nitriles to other functionalities, these transition metal-mediated reactions provide a new and useful route to a wide variety of labelled aromatic compounds.

Experimental

General.—[^{11}C]Carbon dioxide was prepared by the ^{14}N(p,α)^{11}C nuclear reaction using a nitrogen (AGA® Nitrogen 6.0) gas target (containing 0.1% oxygen, AGA® Oxygen 6.0) and 17 MeV protons produced by the Scanditronix MC-17 Cyclotron at the Uppsala University PET Centre. The [^{11}C]carbon dioxide was converted into hydrogen [^{11}C]cyanide, according to published procedures,[20] by use of the Scanditronix RNP-17 radionuclide production system. [^{18}F]Fluoride was prepared by the ^{18}O(p,n)^{18}F nuclear reaction using an isotopically enriched [^{18}O]water (1.0 cm^3) target and 17 MeV protons produced by the Scanditronix MC-17 Cyclotron. The conversion into a reactive [^{18}F]fluoride labelling system was carried out similar to a method described in literature.[21] ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. The GC–MS analyses were performed on a Varian 3400 Capillary GC connected to a Finnigan Incos 50 Mass Spectrometer, using a 30 m × 0.32 mm column, liquid phase DB-5 0.25 μm.

Analytical HPLC was performed using one of the two following systems; either a Hewlett & Packard 1084 equipped with a UV-detector in series with a β^+-flow detector, and a

* To [^{11}C]methyllithium, generated in THF at −72 °C, was added aryl halide (80 μmol) and Pd^0 (2 μmol) dissolved in THF or benzene. The reaction was carried out at different temperatures (0–100 °C) in less than 5 min.

† 3-Methoxybenzamide δ_H(300 MHz, [$^2H_6$]-DMSO, Me_4Si) 3.81 (3 H, s, OCH_3), 7.09 (1 H, dd, 4-H), 7.34 (1 H, dd, 5-H), 7.42 and 8.01 (2 H, NH_2), 7.45 (1 H, dd, 2-H) and 7.48 (1 H, dd, 6-H); δ_C(75.4 MHz, [$^2H_6$]-DMSO, Me_4Si) 55.11 (OCH_3), 112.54 (2-C), 116.97 (4-C), 119.60 (6-C), 129.24 (5-C), 135.62 (1-C), 159.04 (3-C) and 167.60 ($CONH_2$); *m/z* 151 (M^+). 3-Methoxy[*carboxy*-^{11}C/^{13}C]benzamide δ_H(300 MHz, [$^2H_6$]-DMSO, Me_4Si) 3.80 (3 H, s, OCH_3), 7.09 (1 H, dd, 4-H), 7.36 (1 H, dd, 5-H), 7.39–7.47 (4 H, m) and 7.98 (1 H, $CONH_2$); δ_C(75.4 MHz, [$^2H_6$]-DMSO, Me_4Si) 167.49 ($CONH_2$, major peak); *m/z* 152 (M^+).

C-18 Nucleosil 10 μm column, 250 × 4.6 mm (i.d.), or a Hewlett & Packard 1090 liquid chromatograph equipped with a UV-diode array detector in series with a β^+-flow detector, and a C-18 Spherisorb ODS 1 10 μm column or a Hamilton PRP-1 column, 250 × 4.6 mm (i.d.).

Semi-preparative HPLC was performed using a Beckman 126 pump and a Beckman Ultrashere C-18 5 μm, 250 × 10 mm (i.d.) column connected to a Beckman 166 UV-detector in series with a β^+-flow detector. A modified Gilson 231 Autosampler was used for injection and fraction collection.

Mobile phases were 0.05 mol dm^{-3} ammonium formate pH 3.5 (A), 0.01 mol dm^{-3} potassium dihydrogen phosphate with 0.01% sodium azide pH 5.6 (B), methanol (C) and acetonitrile–water (500/70 v/v) (D).

Phenyl triflate was prepared using a literature procedure.[11] Tricarbonylchromium complexes of arenes were synthesized according to a general procedure.[22] 3-Cyanofuran was synthesised from 3-bromofuran employing a method described for cyanation on aryl iodides.[9d] 3-Cyanophenol was synthesized from 3-cyanoanisole by reaction with BBr_3.[23] The products were characterised by spectroscopic methods (^1H and ^{13}C NMR, IR, GC–MS).

All other reference substances, reagents and solvents were of commercial grade and used as supplied, with the following exceptions: arenes were distilled or recrystallised before use, ethers were distilled from sodium or sodium benzophenone ketyl prior to use and dimethyl sulfoxide was dried over activated 4 Å molecular sieves.

Synthesis of [cyano-^{11}C]*Aryl Nitriles from Aryl Halides.*—In a 4 cm^3 septum-equipped glass vessel, Kryptofix® 2.2.2 (3.0 mg, 8.0 μmol) and 5 mol dm^{-3} aqueous potassium hydroxide (1.5 mm^3, 7.5 μmol)* was dissolved in THF (1 cm^3). The vessel was immersed in an ethanol–solid CO_2 bath for 5 min after which the cold bath was removed. Hydrogen [^{11}C]cyanide was passed through Sicapent® (100 × 10 mm), to reduce the amount of ammonia from the hydrogen [^{11}C]cyanide production, and trapped in the base solution. The potassium [^{11}C]cyanide solution obtained was transferred to a 1.5 cm^3 glass vial containing the aryl halide (50–90 μmol). [$Pd(PPh_3)_4$] (2–2.5 mg, 1.7–2.2 μmol) was added and the reaction mixture was heated at 90 °C for 5 min.

The identity and radiochemical purity of the products were determined by HPLC analyses of an aliquot withdrawn from the reaction mixture, using the following conditions: solvent B:D 65:35 isocratic elution 0–2 min, linear gradient to 10:90 2–10 min, flow 2 cm^3 min^{-1}, column temperature 40 °C, wavelength 230 nm. The retention times were 3 to 9 min for the ^{11}C-labelled nitriles (Table 1) employing the Spherisorb ODS 1 column. The Hamilton PRP-1 column generally gave longer retention time for the same product.

In some experiments the reaction mixture was purified by semi-preparative HPLC employing the following conditions: solvent A:C 60:40 isocratic elution 0–5 min, linear gradient to 10:90 2–10 min, flow 5 cm^3 min^{-1}, column temperature 20 °C, wavelength 254 nm. The product fraction was collected, the radioactivity measured and the radiochemical purity determined by analytical HPLC using the conditions described above. The retention times were approximately 10, 12 and 13 min for [*cyano*-^{11}C]benzonitrile, 4-bromo-[*cyano*-^{11}C]benzonitrile and 3-[*cyano*-^{11}C]cyanoanisole, respectively.

Synthesis of [cyano-^{11}C]*Nitriles from Aryl Triflate and Heteroaromatic Bromides.*—These reactions were performed according to the general procedure given for the aryl halides.

* 1 mm^3 = 1 μl.

Synthesis of [cyano-^{11}C]*Benzonitrile on a Sub-micromolar Scale.*—In a 4-cm^3 septum-equipped glass vessel was placed [$Pd(PPh_3)_4$] (0.5 mg, 0.4 μmol). THF (0.5 cm^3) and iodobenzene (50 mm^3 10 mmol dm^{-3} in THF, 0.5 μmol) were then added to the vessel 10 s before trapping of hydrogen [^{11}C]cyanide. In reactions using 0.1 μmol, a solution of [$Pd(PPh_3)_4$] in THF (95 mmol dm^{-3}) was used. The Pd solution (100 mm^3, 0.095 μmol) was transferred to a reaction vessel containing THF (0.4 cm^3) and iodobenzene (10 mmol dm^{-3}; 10 mm^3, 0.1 μmol) immediately before trapping of hydrogen[^{11}C]-cyanide. The cyanation reaction was carried out for 5 min at 90 °C.

The reaction mixture was purified by semi-preparative HPLC employing the conditions described above, and the radiochemical yield and radiochemical purity were determined according to the same procedure.

Synthesis of [cyano-^{11}C]*Aryl Nitriles from Arene(tricarbonyl)chromium.*—In a 2-cm^3 septum-equipped glass vessel Kryptofix® 2.2.2. (4–6 mg, 11–16 μmol) and aqueous potassium hydroxide (5 mol dm^{-3}; 1–2.5 mm^3, 5–13 μmol) were dissolved in DMSO (0.5–1 cm^3). Hydrogen [^{11}C]cyanide was trapped in the solution at room temperature. The potassium [^{11}C]cyanide solution obtained was transferred to a 1.5 cm^3 glass vial containing the arene(tricarbonyl)chromium (5–10 mg, 15–40 μmol). Alternatively, the potassium [^{11}C]cyanide solution was transferred to a 1.5-cm^3 glass vessel containing the same amount of arene(tricarbonyl)chromium and [$Pd(PPh_3)_4$] (1–3 mg, 0.8–2.6 μmol).

The reaction mixture was agitated and heated at 135 °C for 10 min (or for 5 min when the palladium compound was used). Aliquots were withdrawn from the reaction mixture and the identity and radiochemical purity of the products were determined by analytical HPLC (HP 1084) employing the following conditions: solvent A:C 65:35 isocratic elution 0–2 min, linear gradient to 10:90 2–10 min, flow 2 cm^3 min^{-1}, column temperature 40 °C, wavelength 254 nm. The retention times were 5 to 8 min for the different ^{11}C-labelled benzonitriles (Table 2). Analyses were also performed using the HP 1090 instrument and conditions given above.

Synthesis of 4-[cyano-^{11}C]*Biphenylcarbonitrile.*—Kryptofix® 2.2.2 (2.5 mg, 6.6 μmol), 1,4-dibromobenzene (2 mg, 8.5 μmol) and [$Pd(PPh_3)_4$] (2.0 mg, 1.7 μmol) were placed in a 4-cm^3 septum-equipped glass vessel. THF (0.5 cm^3) and aqueous potassium hydroxide (5 mol dm^{-3}; 1.5 mm^3, 7.5 μmol) were added to the vessel immediately before the trapping of hydrogen [^{11}C]cyanide. The cyanation reaction was conducted at 90 °C for 5 min. After addition of toluene (0.5 cm^3) and [$Pd(PPh_3)_4$] (2 mg, 1.7 μmol) the mixture was agitated for 20 s, before phenyl trimethyltin (5 mm^3, 27 μmol) was introduced. The cross-coupling reaction was carried out during 5 min at 120 °C.

The reaction mixture was purified by semi-preparative HPLC employing the following conditions: solvent A:D 40:60 isocratic elution 0–5 min, linear gradient to 10:90 2–10 min, flow 5 cm^3 min^{-1}, column temperature 20 °C, wavelength 254 nm. The product fraction was collected at a retention time of *ca.* 12 min, and the decay-corrected radiochemical yield was in the range of 40%.

The identity and radiochemical purity of the product, purified, or in an aliquot withdrawn from the reaction mixture, was determined by analytical HPLC employing the following conditions: solvent A:D 60:40 (Spherisorb column) or 50:50 (Hamilton column) isocratic elution 0–2 min, linear gradient to 10:90 2–10 min, flow 2 cm^3 min^{-1}, column temperature 40 °C, wavelength 254 nm. The retention time for 4-[*cyano*-^{11}C]biphenylcarbonitrile was 9.9 min (Hamilton).

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