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# [$^{18}$F]Fluorophenyl organometallics as intermediates of no-carrier-added $^{18}$F-fluoroarylation reactions

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**Abstract**

Based on the recent availability of no-carrier-added (n.c.a.) 1-bromo-4-[$^{18}$F]fluorobenzene with high radiochemical yield, the 4-[$^{18}$F]fluorophenyl compounds of lithium, sodium and magnesium can now also effectively be prepared. Thus, [$^{18}$F]fluoroarene reagents with a nucleophilic reaction centre are available and suitable among others for the formation of [$^{18}$F]fluorophenyl compounds with electron donating substituents in the radiosynthesis of $^{18}$F-labelled complex organic structures. For these arylation reactions, however, the presence of macroscopic amounts of a haloarene as co-reactant is necessary with all n.c.a. [$^{18}$F]fluorophenyl metallics. The $^{18}$F-fluoroarylation was verified for examples of aryl-carbon, -silicon, -sulphur, and -nitrogen bond formation with radiochemical yields of 20–25% related to the starting radioactivity of [$^{18}$F]fluoride.


*Keywords:* $^{18}$F-Fluoroarylation; Organometallic compounds; Iodonium salts; Fluorine-18; 1-Bromo-4-[$^{18}$F]fluorobenzene

## 1. Introduction

The radionuclide fluorine-18 is the most frequently used positron emitter ($t_{1/2} = 109.7$ min) in positron emission tomography (PET), which is an imaging technique for the absolute measurement of radiotracers labelled with positron emitters, enabling the elucidation of their in vivo pharmacokinetics and biodistribution by non-invasive means [1]. Until now the practical synthesis of radiotracers labelled with fluorine-18 without addition of fluorine-19 carrier (i.e. macroscopic amounts) is limited to nucleophilic reactions using no-carrier-added (n.c.a.) [$^{18}$F]fluoride, i.e. amounts in the range of pmol to nmol while other reagents normally used in μmol to mmol amounts. If a direct nucleophilic $^{18}$F-fluorination of a more complex compound is not achievable, e.g. with arenes of high electron density or with temperature and base sensitive precursors, there are two alternative possibilities for $^{18}$F-labelling: via $^{18}$F-labelled intermediates (synthons) or via prosthetic groups, respectively. $^{18}$F-labelling via prosthetic groups can be divided in $^{18}$F-fluoroalkylation [2–4], $^{18}$F-fluoroacylation [5–8] or $^{18}$F-fluoroamidation [9,10] syntheses based on preceding aliphatic, *homo* aromatic and more recently *hetero* aromatic [11] substitution reactions. Synthons for built-up reactions are often fluorine-18 labelled arenes with substituents for further derivatization. Using this strategy the introduction of [$^{18}$F]fluoride is performed via "small" arene molecules activated for nucleophilic aromatic substitution reactions by electron withdrawing groups. After introduction of the $^{18}$F-label more complex structures are obtained by a following built-up synthesis in several steps. The starting $^{18}$F-labelled intermediates are mostly simple structures such as substituted benzonitriles, benzaldehydes, benzophenones, benzoic acid derivatives or nitrobenzene with a nitro or trimethylammonium moiety as leaving group (for review see [12]). The $^{18}$F-fluorination step of these molecules normally leads to radiochemical yields (RCYs) of more than 70%. Due to the electronic structure of their activating group all these intermediates react as electrophiles in

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subsequent reactions [12,13]. Thus, there is a lack of n.c.a. $^{18}$F-labelling intermediates including an aromatic ring which may react as a nucleophile.

In organic syntheses Grignard or organolithium compounds play an important role in order to achieve carbon-carbon bond formation. In those cases the organometallic compound serves as carbanion in nucleophilic reactions. Another possibility for an aryl-C or aryl-N connection is the transition metal mediated cross-coupling reaction with an arylhalide as comprehensively discussed in a recent review [14]. For all kinds of reactions the n.c.a. starting intermediates 1-bromo-4-[$^{18}$F]fluorobenzene or 1-[$^{18}$F]fluoro-4-iodobenzene have been made readily available by efficient one-step synthesis procedures via corresponding bis-(halophenyl)iodonium precursors [15,16]. Therefore, it seemed promising to investigate possibilities of converting n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzenes into 4-[$^{18}$F]fluorophenyl-organometallics in order to obtain a nucleophilic intermediate for the formation of $^{18}$F-fluorinated arenes with electron-donating substitutents.

## 2. Results and discussion

Organometallic reactions using no-carrier-added $^{18}$F-labelled benzene derivatives differ from the classic organic chemistry in two critical points. First of all the short half life of fluorine-18 requires a fast and efficient synthesis of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene ([**$^{18}$F**]**1**) via nucleophilic pathways, which has to be freshly prepared and separated before starting the subsequent formation of organometallics. Second, the low mass of n.c.a. [**$^{18}$F**]**1** may cause problems during the formation of organometallics and subsequent reactions thereof due to conditions far from stoichiometry by orders of magnitude.

### 2.1. Synthesis of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene

Several methods were described for the synthesis of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene [17,15]. The easiest way is the $^{18}$F-labelling of symmetrically substituted bis(4-bromodiphenyl)iodonium salts, which yields n.c.a. [**$^{18}$F**]**1** in one step and in high radiochemical yields and was used here. The preparation of the iodonium salt precursor is described elsewhere [15].

### 2.2. Work up procedure of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene

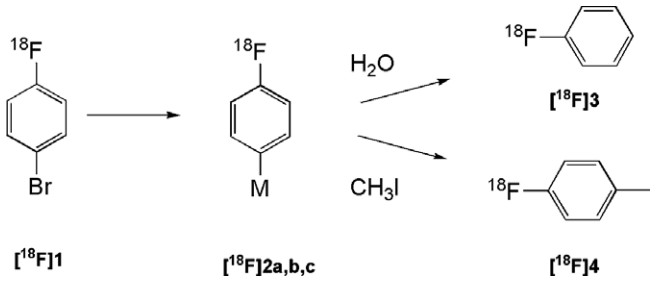
Like in organometallic synthesis on a macroscopic scale the n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene isolated from the labelling solution has to be absolutely free of moisture for further reactions; this is true for metal–halogen exchange reactions and in situ syntheses with metals. In a first attempt the separation of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene from the reaction mixture was performed by a two-step procedure including a gas chromatographic separation step, which required about 80 min work up time and lead to only about 15% RCY of [**$^{18}$F**]**1**. The advantage of this procedure is that 1-bromo-4-iodobenzene can be completely isolated in dry form from reagents, precursor and side products.

An improvement in the preparative yields of radioactive products could, however, be achieved by replacing the gas chromatographic work up procedure by a semi-preparative liquid chromatography. This was performed on a small glass column with a stationary phase consisting of silica Si-60 conditioned by dry diethyl ether. Thereby the whole reaction mixture of the radiofluorination step could be separated within 10 min. Elution of the column with a total volume of 5.5 mL of diethyl ether lead to a recovery of about 95% of n.c.a. [**$^{18}$F**]**1** in a total volume of 3 mL while discarding the first fraction of about 2.5 mL eluate. Via this new work up procedure the total time of synthesis could be halved to 40 min and a yield of 28% of radioactivity (RCY = 36%) of n.c.a. [**$^{18}$F**]**1** was obtained. The major disadvantage of this liquid isolation procedure is the incomplete separation of the side product 1-bromo-4-iodobenzene.

### 2.3. Preparation of 4-[$^{18}$F]fluorophenylorganometallics [$^{18}$F]2a,b,c

The following examinations were made using n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene separated by the above-mentioned GC-separation. Because of the high reactivity and the small masses of the 4-[$^{18}$F]fluorophenylorganometallics of lithium, magnesium and sodium ([**$^{18}$F**]**2a**,**b**,**c**) it is not possible to analyze the formation of these compounds directly. Therefore, the hydrolysis to [$^{18}$F]fluorobenzene [**$^{18}$F**]**3** and/or the formation of 4-[$^{18}$F]fluorotoluene [**$^{18}$F**]**4** with methyl iodide were used as monitor reactions because of their fast and easy performance and product detection (see Scheme 1). Thus, it was possible to indirectly prove the intermediate formation of the 4-[$^{18}$F]fluorophenylorganometallics [**$^{18}$F**]**2a**,**b**,**c** and to optimize the reaction conditions of their formation.

At first, the metal–halogen exchange with *n*-butyllithium or phenyllithium were selected for the conversion of n.c.a. [**$^{18}$F**]**1** to 4-[$^{18}$F]fluorophenyllithium ([**$^{18}$F**]**2a**). However, only 1% RCY of [$^{18}$F]fluorobenzene ([**$^{18}$F**]**3**) could be obtained via the metal–halogen exchange reaction in the absence of macroscopic amounts of haloarenes, like the




Scheme 1. Synthesis and monitor reactions of 4-[$^{18}$F]fluorophenylorganometallics; M = Li, Na, MgBr.

isotopic carrier 1-bromo-4-fluorobenzene (**1**), and subsequent hydrolysis of the organometallic intermediate (cf. Table 1).

This low radiochemical yield may be explained by multiple lithiation reactions at the aromatic ring leading to aryne intermediates which tend to stabilize by reactions with aromatic compounds [18] (cf. Scheme 2). However, it was possible to overcome this problem by adding macroscopic amounts of a co-reacting haloarene (co-reactant) to the reaction mixture. Using for example 1-bromo-4-fluorobenzene as isotopic co-reactant a RCY of 72% of [$^{18}$F]fluorobenzene could be observed (see Table 1).

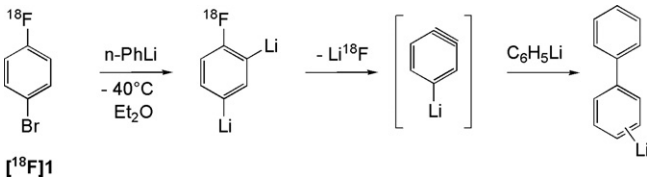
The results of the syntheses of 4-[$^{18}$F]fluorophenylorganometallics are summarized in Table 1. The yields were determined by hydrolysis of [**$^{18}$F**]**2a**,**b**,**c** to [$^{18}$F]fluorobenzene as monitor reaction.

It is known from the literature that tetramethylethylenediamine (TMEDA) acts as an activator on *n*-butyllithium by monomerization of the reagent [19] and should therefore increase the RCY of the $^{18}$F-labelled model compounds. Metal–halogen exchange reactions with *n*-butyllithium and TMEDA, however, proved to be too reactive and lead only to a RCY of 18% in presence of 1-bromo-4-fluorobenzene as co-reactant. The same yields were observed in the case of phenyllithium as metal–halogen exchange agent (without TMEDA) and 1-bromo-4-fluorobenzene as co-reactant at room temperature. At 0 °C no reaction of phenyllithium with 1-bromo-4-[$^{18}$F]fluorobenzene was observed (see Table 1).

Table 1
Synthesis of 4-[$^{18}$F]fluorophenyl metallics from 1-bromo-4-[$^{18}$F]fluorobenzene as monitored by hydrolysis to [$^{18}$F]fluorobenzene

| Metallation reagent | [$^{18}$F]fluorobenzene | [$^{18}$F]fluoride | Reaction temperature |
|---|---|---|---|
| *n*-BuLi[a] | 1 ± 1 (no co) | 93 ± 5 | −40 °C |
| *n*-BuLi[b] | 72 ± 4 (co) | 20 ± 2 | −40 °C |
| *n*-BuLi + TMEDA[c] | 18 ± 2 (co) | 75 ± 2 | −40 °C |
| PhLi[d] | 17 ± 3 (co) | 72 ± 4 | RT |
| Mg[e] | 95 ± 4 (co) | 0 | 0 °C |
| Li[f] | 46 ± 3 (co) | 45 ± 3 | Reflux (5 min) |
| Li[g] | 90 ± 5 (co) | 1 ± 0.5 | RT |
| Na[h] | 69 ± 3 (co) | 22 ± 2 | 0 °C |

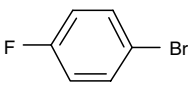
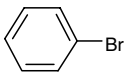
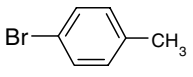
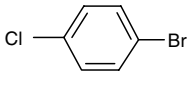
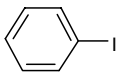
(no co) = no addition of co-reactant; (co) = addition of co-reactant.
[a] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 1 mL of diethyl ether, [*n*-BuLi] = 400 mmol/L, 15 min.
[b] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 1 mL of diethyl ether, [*n*-BuLi] = 400 mmol/L, 15 min, [1-bromo-4-fluorobenzene] = 1.6 mmol/L.
[c] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 1 mL of diethyl ether, [*n*-BuLi] = 400 mmol/L, [TMEDA] = 400 mmol/L, 15 min, [1-bromo-4-fluorobenzene] = 1.6 mmol/L.
[d] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 1 mL diethyl ether, [PhLi] = 400 mmol/L, 30 min, [1-bromo-4-fluorobenzene] = 1.6 mmol/L.
[e] [Mg] = 4 mol/L, n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 5 mL of diethyl ether, [1,2-dibromoethane] = 320 mmol/L, 10 min.
[f] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 5 mL of diethyl ether, [lithium] = 2.4 mol/L, [bromobenzene] = 96 mmol/L, RT (15 min).
[g] N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 5 mL of diethyl ether, [lithium] = 2.4 mol/L, [bromobenzene] = 96 mmol/L, ultra sound, 5 min.
[h] 1 mL of solution (f); [sodium *tert*-butylate] = 0.4 mol/L, 5 min.




Scheme 2. Defluorination of 1-bromo-4-[$^{18}$F]fluorobenzene ([**$^{18}$F**]**1**) via formation of [$^{18}$F]LiF and arynelithium exemplified for the reaction with phenyllithium.

Considering the dependence of the metallation reactions from the presence of a co-reactant, studies were performed for improving the radiochemical yields with respect to their nature and concentration. Again, those focussed on the metal–halogen exchange with *n*-butyllithium. By successive addition of 1-bromo-4-fluorobenzene as carrier in amounts of up to 3.25 mmol/L the radiochemical yield of [$^{18}$F]fluorobenzene (after hydrolysis) could be increased to a maximum value of 72 ± 4% at 1.6 mmol/L (Table 1). Application of these improved conditions in the $^{18}$F-fluoroarylation reaction of 4-[$^{18}$F]fluorophenyllithium with methyl iodide lead to 4-[$^{18}$F]fluorotoluene with a RCY of 50% (based on trapped 1-bromo-4-[$^{18}$F]fluorobenzene) as listed in Table 2. These results prove that although n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene can be prepared in good radiochemical yields and easily be isolated, it is not possible

Table 2
Effect of co-reactant compounds on the radiochemical yields of 4-[$^{18}$F]fluorophenyllithium as monitored by methylation and subsequent hydrolysis

| Co-reactant | 4-[$^{18}$F]fluorotoluene [**$^{18}$F**]**4** | [$^{18}$F]fluorobenzene [**$^{18}$F**]**3** | [$^{18}$F]fluoride |
|---|---|---|---|
|  | 50 ± 3 | 12 ± 2 | 18 ± 2 |
|  | 32 ± 2 | 13 ± 2 | 18 ± 2 |
|  | 4.5 ± 1 | 0.5 ± 0.5 | 77 ± 4 |
|  | 3.5 ± 1 | 1 ± 1 | 81 ± 4 |
|  | 1.5 ± 1 | 1 ± 1 | 89 ± 4 |

*Reaction conditions*: n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 1 mL of diethyl ether, [co-reactant] = 1.6 mmol/L, [*n*-BuLi] = 0.4 mol/L, −40 °C, 15 min; [$CH_3I$] = 0.8 mol/L, room temperature, 30 min.

to prepare n.c.a. 4-[$^{18}$F]fluorophenyllithium without addition of macroscopic amounts of a haloarene as co-reactant.

In order to avoid the addition of 1-bromo-4-fluorobenzene as authentic carrier and for maintaining n.c.a. conditions, different haloarenes were tested as co-reactant. For this purpose, bromobenzene, bromotoluene, bromochlorobenzene and iodobenzene were examined with respect to their effect on the formation of 4-[$^{18}$F]fluorophenyllithium. These experiments were conducted using 1.6 mmol/L of the respective co-reactant in the metallation step, followed by conversion with methyliodide and subsequent hydrolysis in order to destroy any remaining metal intermediate. Thus, these reactions served again as monitor processes. Here, the formation of 4-[$^{18}$F]fluorotoluene was stopped by alcoholysis where [$^{18}$F]fluorobenzene was formed by the reaction of 4-[$^{18}$F]fluorophenyllithium with methanol (cf. above). The results obtained are summarized in Table 2.

It can be concluded that only bromobenzene offers itself as an appropiate co-reactant for the synthesis of n.c.a. 4-[$^{18}$F]fluorophenyllithium via metal–halogen exchange reaction with BuLi yielding a maximum radiochemical yield of about 45 ± 4% (sum of 4-[$^{18}$F]fluorotoluene and [$^{18}$F]fluorobenzene). Furthermore, these results demonstrate that n.c.a. 4-[$^{18}$F]fluorophenyllithium can successfully be prepared in presence of bromobenzene. Without a co-reactant the formation of n.c.a. 4-[$^{18}$F]fluorophenyllithium is not possible. This is due to the unavoidable addition of a large excess of lithiation agents compared to the small amount of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene which leads to multiple side reactions. These side reactions can obviously be reduced by a co-reacting compound which may serve as "catcher" of excess lithium. However, due to the aromatic co-reactant it will lead to a mixture of the n.c.a. labelled product with a large amount of a non-$^{18}$F-substituted aromatic side product. Using n-BuLi for the metallation reaction, an extensive $^{18}$F-defluorination of the 1-bromo-4-[$^{18}$F]fluorobenzene obviously occurs yielding free [$^{18}$F]fluoride with more than 20% RCY. The various reactivities of the co-reactants, due to their different mesomeric and inductive effects, are probably responsible for the formation of free [$^{18}$F]fluoride. Thus, the use of iodobenzene as co-reactant led to 90% of free [$^{18}$F]fluoride instead of [$^{18}$F]fluoroarenes. Bromobenzene has obviously the most compatible reactivity to 1-bromo-4-[$^{18}$F]fluorobenzene.

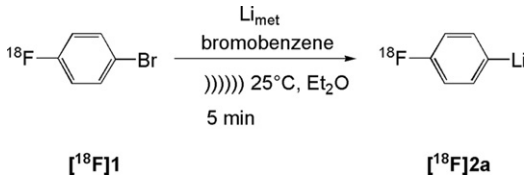
With respect to the relatively low yields of the metal–halogen exchange reactions further optimization experiments focused on the preparation of the labelled aryllithium compound with elemental lithium. In classic metallation procedures the alkyl or aryl halide is refluxed over the alkali metal in ether in presence of a starter, most often methyl iodide, upon which the organometallic compound is formed within a few minutes. This methodology was adapted to the small reaction volumes used with n.c.a. reagents and indeed led to a radiochemical yield of about 46 ± 3% of 4-[$^{18}$F]fluorophenyllithium in the presence of bromobenzene used as co-reactant and as starter (see Table 1). Although the carrier 1-bromo-4-fluorobenzene was replaced by bromobenzene, what could be expected to reduce the maximum RCY (cf. Table 2), the same radiochemical yield of 45 ± 4% was obtained as for the metal–halogen exchange using *n*-BuLi (cf. Table 1).

Encouraged by this improvement a further modification was introduced. Instead of thermal activation of the reaction mixture ultrasound was used as a mild and effective alternative [20]. Thereby, it was possible to raise the RCY of n.c.a. 4-[$^{18}$F]fluorophenyllithium up to 90% in presence of bromobenzene as co-reactant (cf. Table 1) and [$^{18}$F]fluorobenzene could almost quantitatively be obtained upon hydrolysis of the intermediate. Here, by ultrasonic activation a breakthrough was achieved for the in situ synthesis with the free metal in $Et_2O$ at 25 °C (see Scheme 3). Thus, it appears possible to prepare the $^{18}$F-fluoroarylation agent in radiochemical yields suitable for use in routine labelling syntheses.

For comparison, optimization studies of preparing n.c.a. 4-[$^{18}$F]fluorophenyllithium were also performed with n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene which was isolated by the semi-preparative silica gel column method (see Section 4). As described above, the eluted 1-bromo-4-[$^{18}$F]-fluorobenzene is accompanied by unknown amounts of 1-bromo-4-iodobenzene. Since a co-reactant is always necessary for the consecutive reaction with 4-[$^{18}$F]fluorophenyllithium, the concentration of bromobenzene was also optimized in this case for the lithiation reaction via elemental lithium and ultrasonic activation. The amount of elemental lithium was enlarged from 2.4 mol/L to 3.3 mol/L because a part of the lithium metal reacts with the more reactive 1-bromo-4-iodobenzene, originating from the decomposition of the precursor iodonium salt.

As shown in Fig. 1 a minimum concentration of 80 mmol/L of bromobenzene in the reaction mixture was found necessary in order to convert 1-bromo-4-[$^{18}$F]fluorobenzene into 4-[$^{18}$F]fluorophenyllithium quantitatively. This indicates again that bromobenzene is necessary as co-reactant and probably also as starter for the activation of the elemental lithium.

The following studies were performed using n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene isolated by GC-separation, i.e. free of 1-bromo-4-iodobenzene. Based on the experience of the improved preparation of 4-[$^{18}$F]fluorophenyllithium it was also attempted to prepare the corresponding n.c.a. 4-[$^{18}$F]fluorophenylsodium ([**$^{18}$F**]**2c**) via transmetalla-




Scheme 3. Optimized in situ synthesis of 4-[$^{18}$F]fluorophenyllithium ([**$^{18}$F**]**2a**) without formation of [$^{18}$F]LiF.

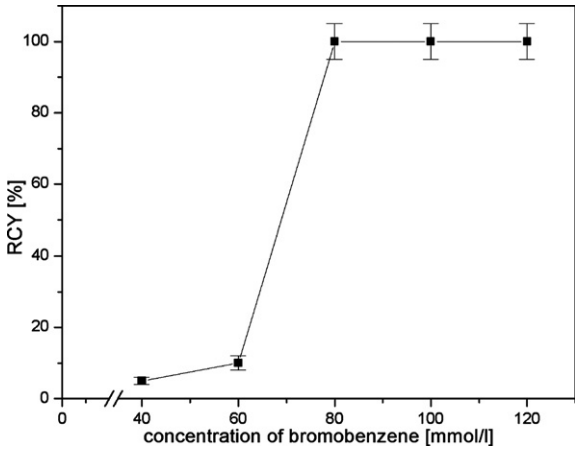



Fig. 1. Dependence of the formation of 4-[$^{18}$F]fluorophenyllithium ([**$^{18}$F**]**2a**) on the concentration of co-reactant bromobenzene added; reaction conditions: n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene in 3 mL of diethyl ether, [**$^{18}$F**]**1**, [lithium] = 3.3 mol/L, ultra sound, 10 min, bromobenzene, RT.

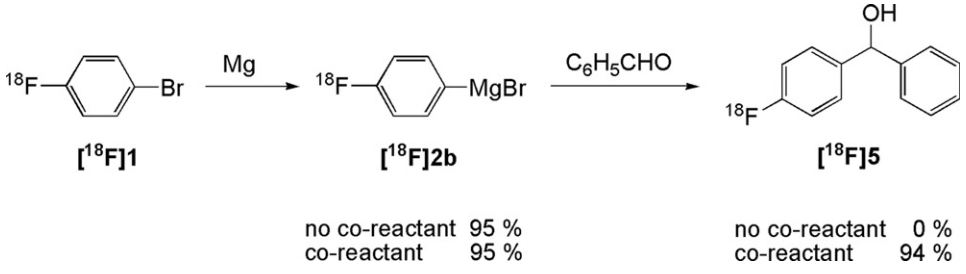
tion starting from the lithium compound [**$^{18}$F**]**2a** and sodium *tert*-butylate. This led to a 69% RCY of 4-[$^{18}$F]fluorophenylsodium in presence of bromobenzene. In the experiments on the formation of 4-[$^{18}$F]fluorophenylsodium a loss of organic bound radioactivity of about 20–25% was observed, probably caused by the formation of [$^{18}$F]LiF. Nevertheless, the sodium analogue of 4-[$^{18}$F]fluorophenyllithium is especially interesting due to its higher reactivity in organometallic reactions which will broaden the variability of n.c.a. $^{18}$F-labelled compounds achievable. However, due to the necessary detour via [$^{18}$F]fluorophenyllithium and the lower RCY of 4-[$^{18}$F]fluorophenylsodium this advantage counts only in cases of very unreactive compounds to be $^{18}$F-fluoroarylated. The failure of an in situ synthesis of 4-[$^{18}$F]fluorophenylsodium from 1-bromo-4-[$^{18}$F]fluorobenzene is not comprehensible.

In contrast to the lithiation reactions the Grignard compound, 4-[$^{18}$F]fluorophenylmagnesium bromide ([**$^{18}$F**]**2b**), was formed nearly quantitatively by starting from n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene and by activation of the magnesium turnings with 1,2-dibromoethane. For this no haloarene co-reactant was necessary and [$^{18}$F]fluorobenzene ([**$^{18}$F**]**3**) was obtained after hydrolysis with a RCY of 95%.

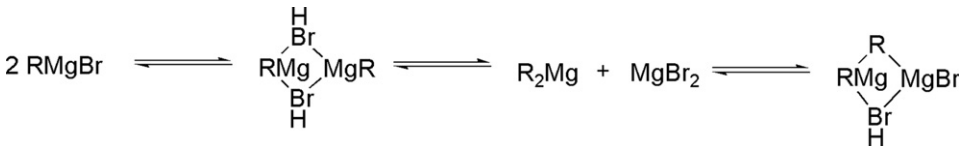
### *2.4. Fluoroarylation reactions using the organometallics [$^{18}$F]2a,b,c as intermediates*

The unexpected results of the formation of 4-[$^{18}$F]fluorophenylmagnesium bromide ([**$^{18}$F**]**2b**) initiated examinations of its possible n.c.a. reactions with benzaldehyde in order to form 4-[$^{18}$F]fluorobenzhydrol ([**$^{18}$F**]**5**). Unfortunately, a reaction of n.c.a. 4-[$^{18}$F]fluorophenylmagnesium bromide with the carbonyl moiety did not take place without a co-reactant. It succeeded, however, again in presence of bromobenzene as co-reactant and led to a RCY of 94% of [**$^{18}$F**]**5** (see Scheme 4).

Obviously, for stoichiometric reasons the organometallic reactions of n.c.a. $^{18}$F-labelled Grignard-reagents like 4-[$^{18}$F]fluorophenylmagnesium bromide are strongly hampered by the impossibility of forming a Schlenk-equilibrium (see Scheme 5) in contrast to macroscopic organometallic syntheses. Therefore, the addition of a co-reactant is necessary to increase the concentration of halo compounds until the requirement of a Schlenk-equilibirium is fulfilled which is necessary to enable a consecutive reaction of the organometallic reagent. Thus, the formation of 4-[$^{18}$F]fluorophenylmagnesium bromide is possible without a co-reactant because of the lesser reactivity of magnesium. But further reactions cannot be performed without a co-reactant because of the low concentration of n.c.a. Grignard compounds which are not able to form a Schlenk-equilibirium due to stoichiometric reasons.




Scheme 4. Synthesis of 4-[$^{18}$F]fluorobenzhydrol ([**$^{18}$F**]**5**) via 4-[$^{18}$F]fluorophenylmagnesium bromide ([**$^{18}$F**]**2b**).




Scheme 5. Schlenk-equilibrium in organometallic reactions.

Analogously, the application of n.c.a. 4-[$^{18}$F]fluorophenyllithium for $^{18}$F-fluoroarylation was examined in presence of a co-reactant with simple model compounds for the purpose of preparation of [$^{18}$F]fluoroarenes which are not available via direct n.c.a. nucleophilic $^{18}$F-labelling methods due to their lack of activating groups.

In contrast to the synthesis of n.c.a. (4-[$^{18}$F]fluorophenyl)phenylmethanol [21] that of the tertiary alcohol (4-[$^{18}$F]fluorophenyl)diphenylmethanol [**$^{18}$F]6** is not described in the literature. Therefore, the synthesis of [**$^{18}$F]6** (cf. Scheme 6) appeared as an attractive model reaction for the $^{18}$F-fluoroarylation of benzophenones.

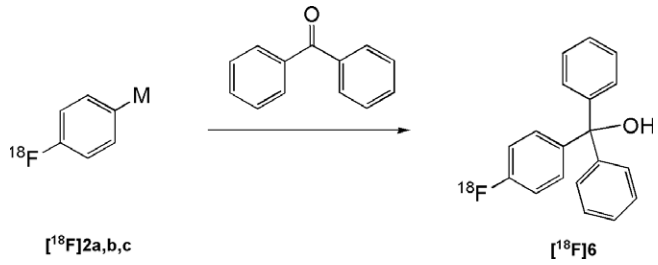
Table 3 summarizes the RCY of n.c.a. (4-[$^{18}$F]fluorophenyl)diphenylmethanol synthesized with the three different 4-[$^{18}$F]fluorophenylorganometallics prepared here. 4-[$^{18}$F]Fluorophenyllithium and 4-[$^{18}$F]fluorophenylsodium gave similar and highest RCY of about 48–50%, relative to the radioactivity of the 4-[$^{18}$F]fluorophenylorganometallic. With 4-[$^{18}$F]fluorophenylsodium, however, this result is already obtained at room temperature whereas the lithium derivative needed reflux conditions, which demonstrates the higher reactivity of 4-[$^{18}$F]fluorophenylsodium. The reactivity of 4-[$^{18}$F]fluorophenylmagnesium appears somewhat lower as indicated by a RCY of 43%, which was also obtained under reflux conditions.

The results with four different model compounds which were prepared from 4-[$^{18}$F]fluorophenyllithium are summarized in Table 4. All compounds are not available by direct nucleophilic substitution reactions with n.c.a. [$^{18}$F]fluoride. These studies were performed using 1-bromo-4-[$^{18}$F]fluorobenzene isolated by the column separation method, i.e. with traces of 1-bromo-4-iodobenzene present.

N.c.a. 4-(4-[$^{18}$F]fluorophenyl)-1-methylpiperidin-4-ol ([**$^{18}$F]7**) is another example of the synthesis of $^{18}$F-labelled tertiary [$^{18}$F]fluorophenyl alcohols. The (4-phenyl)-piperidin-4-ol unit is found as a building block in some pharmaceuticals and is therefore of general interest. The optimized conversion of 4-[$^{18}$F]fluorophenyllithium into [**$^{18}$F]7** via 4-methylpiperidinone is accomplished within 20 min at room temperature with a total radiochemical yield of 25 ± 5% related to the starting radioactivity of [$^{18}$F]fluoride.

Disulfides can be converted for the preparation of thioether derivatives by lithiumorganic compounds via nucleophilic substitution at a sulphur atom under cleavage of the S–S bond [22]. A transfer of this reaction type to n.c.a. conditions was exemplified by the synthesis of 4-[$^{18}$F]fluorothioanisole ([**$^{18}$F]8**) with a total RCY of 20 ± 3% after 15 min reaction time at RT.

The synthesis of silyl-containing compounds directly via n.c.a. [$^{18}$F]fluoride is limited because of the high affinity of




Scheme 6. Synthesis of n.c.a. (4-[$^{18}$F]fluorophenyl)diphenylmethanol ([**$^{18}$F]6**) via 4-[$^{18}$F]fluorophenylorganometallics [**$^{18}$F]2a,b,c**.

Table 3
Radiochemical yield of (4-[$^{18}$F]fluorophenyl)diphenylmethanol via n.c.a. 4-[$^{18}$F]fluorophenylorganometallics (RCY are related to radioactivity of 4-[$^{18}$F]fluorophenylorganometallics)

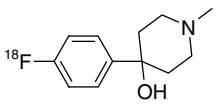
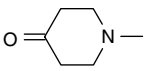
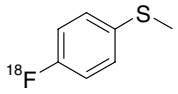
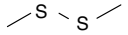
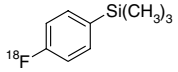
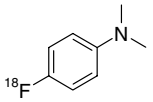
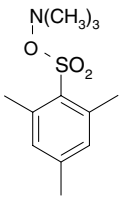
| Organometallic compound [**$^{18}$F]2a,b,c** | RCY (%) |
|---|---|
| 4-[$^{18}$F]fluorophenylmagnesium bromide[a] | 43 ± 3 |
| 4-[$^{18}$F]fluorophenyllithium[b] | 48 ± 4 |
| 4-[$^{18}$F]fluorophenylsodium[c] | 50 ± 4 |

[a] N.c.a. 4-[$^{18}$F]fluorophenylmagnesium bromide in 3 mL of diethyl ether, [bromobenzene] = 60 mmol/L, [benzophenone] = 260 mmol/L, 15 min, reflux.

[b] N.c.a. 4-[$^{18}$F]fluorophenyllithium in 3 mL diethyl ether, [bromobenzene] = 60 mmol/L, [benzophenone] = 260 mmol/L, 15 min, reflux.

[c] N.c.a. 4-[$^{18}$F]fluorophenylsodium in 1 mL of diethyl ether and 2 mL of *n*-hexane, [bromobenzene] = 60 mmol/L, [benzophenone] = 260 mmol/L, 15 min, RT.

Table 4
Radiochemical yields of model [$^{18}$F]fluoroarenes with high electron density prepared via n.c.a. 4-[$^{18}$F]fluorophenyllithium (RCY are related to starting 4-[$^{18}$F]fluoride)

| Product | Educt | Temperature | Time (min) | RCY (%) |
|---|---|---|---|---|
|  [**$^{18}$F]7** |  | RT | 20 | 25 ± 5 |
|  [**$^{18}$F]8** |  | RT | 15 | 20 ± 3 |
|  [**$^{18}$F]9** | $(CH_3)_3SiCl$ | RT | 30 | 26 ± 4 |
|  [**$^{18}$F]10** |  | −25 °C to RT | 30 | 19 ± 3 |

*Reaction conditions*: n.c.a. 4-[$^{18}$F]fluorophenyllithium in 1 mL diethyl ether, [bromobenzene] = 80 mmol/L, [educt] = 0.5–0.8 mmol/mL in 0.5 mL of diethyl ether.

fluoride to silicon which is normally exploited for the cleavage of silyl-containing protecting groups. N.c.a. 4-[$^{18}$F]-fluorophenyltrimethylsilane ([**$^{18}$F**]**9**) was available using 4-[$^{18}$F]fluorophenyllithium in a RCY of $26 \pm 4\%$ within 30 min at RT.

As a further example, the synthesis of tertiary amines via electrophilic amination was achieved via the reaction of [$^{18}$F]fluorophenyllithium with *N*,*N*-dimethyl-*O*-mesitylsulfonylhydroxylamine with a RCY of $19 \pm 3\%$ starting at −25 °C and warming the reaction solution up to RT within 30 min.

## 3. Conclusion

The small amount of substance using no-carrier-added $^{18}$F-labelled compounds is the main restriction of the presented metal organic reactions. Without a haloarene as co-reactant (isotopic or non-isotopic) radiosyntheses of n.c.a. 4-[$^{18}$F]fluorophenylorganometallics of lithium, magnesium or sodium, respectively, their further reactions are not feasible. In the case of lithiation reactions this is due to unavoidable addition of large excess of lithiation agents compared to the small amounts of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene which lead to multiple side reactions. These side reactions can be diminished by a co-reactant compound which probably serves as ''catcher'' for excess lithium. In the case of the formation of the Grignard compound using less reactive magnesium a co-reactand as ''catcher'' compound is not necessary but for the further $^{18}$F-fluoroarylation reaction a Schlenk-equilibirium cannot be formed without a co-reactant. Compared to the palladium-mediated cross-coupling reactions, the addition of a co-reactant is certainly the major disadvantage of the radiosyntheses using n.c.a. 4-[$^{18}$F]fluorophenylorganometallics of lithium, magnesium or sodium. Nevertheless, reactions using n.c.a. 4-[$^{18}$F]fluorophenyllithium, magnesium bromide or sodium offer the possibility of a three-step synthesis of $^{18}$F-labelled aromatic compounds like tertiary [$^{18}$F]fluorophenyl alcohols, silylethers and thioanisol for which $^{18}$F-labelling via direct methods or via the palladium-mediated cross-coupling reaction are not possible. Thus, 4-[$^{18}$F]fluorophenylmetallics prove to be useful reagents for arylation reactions with electrophilic centres. They widely enlarge the variety of syntheses of n.c.a. $^{18}$F-labelled complex organic structures containing a [$^{18}$F]fluorophenyl moiety.

## 4. Experimental

### 4.1. Materials

Reagents and anhydrous solvents were purchased from Sigma–Aldrich (Steinheim, Germany) or Merck (Darmstadt, Germany). They were used without further purification. Oxygen-18 enriched water (>95% enriched) was supplied by Rotem GmbH (Leipzig, Germany). Sep-Pak™ C-18 plus-cartridges were purchased from Waters (Eschborn, Germany), EN-cartridges, LiChrolut™ (65 × 10 mm) and LiChrolut™ RP-18 from Merck (Darmstadt, Germany).

The syntheses of (4-fluoro-phenyl)trimethylsilane [23], (4-fluorophenyl)-diphenylmethanol [24], (4-fluorophenyl)-phenylmethanol [25] and *N*,*N*-dimethyl-*O*-mesitylsulfonyl-hydroxylamine [26] were performed as described in the literature and the identity was confirmed by comparison of NMR-data.

Thin layer chromatography (TLC) was performed on precoated plates of silica gel $60_{F254}$ (Merck). The compounds were detected by UV at 254 nm. Analytical HPLC was performed on the following systems: HPLC Sykam (S1000) pump, Knauer UV/VIS-detector (type 97) with a constant wavelength of 254 nm and an EG&G ACE Mate™ radioactivity detector. Gas chromatography was performed on a Hewlett–Packard HP 5890 Series II equipped with a TCD.

### 4.2. Synthesis of 1-bromo-4-[$^{18}$F]fluorobenzene ([**$^{18}$F**]**1**)

For all substitution experiments [$^{18}$F]fluoride was produced by the $^{18}$O(p,n)$^{18}$F nuclear reaction via bombardment of an isotopically enriched [$^{18}$O]water (1.3 mL) target with a 17 MeV proton beam at the BC 1710 Baby Cyclotron, FZ Jülich. The [$^{18}$F]fluoride (148–222 MBq) in 10–20 μL water, 10 mg (26.5 μmol) Kryptofix® 2.2.2 and 13.25 μL of a 1 M $K_2CO_3$ solution were dried two times by azeotropic evaporation with 1 mL anhydrous acetonitrile at 80 °C in a 5 mL Wheaton glass vial.

The closed reaction vial containing dry [$^{18}$F]fluoride was heated to 130 °C in an oil bath and a solution of the bis(4-bromophenyl)iodonium bromide dissolved in 0.8 mL DMF (90 mmol/L) was added [15]. For quality control, aliquots of the reaction mixture (20 μL) were quenched in 300 μL acetonitrile at the appropriate time (10 min) and analyzed by reversed phase HPLC using acetonitrile/water (60/40, v/v) on a Nucleosil 100-5 C-18 column (250 × 4.6 mm) at 254 nm.

| | |
|---|---|
| *k* (1-bromo-4-fluorobenzene) | 3.96 |
| *k* (1-bromo-4-iodobenzene) | 7.92 |

### 4.3. Gas chromatographic isolation of [**$^{18}$F**]**1**

The organic components of the reaction mixture were separated from the solvent and the salts by a solid phase extraction on a Sep-Pak$^{TM}$ C-18 cartridge. Then, the cartridge was washed with 10 mL of water and afterwards dried by a stream of air. By rinsing the cartridge with 2 mL of diethylether [**$^{18}$F**]**1** was coeluted with 1-bromo-4-iodobenzene. The whole eluate was passed through a cartridge filled with anhydrous $MgSO_4$ for drying. The volume of the solution was then reduced to about 1 mL at 0 °C by using a stream of argon. The solution (800–1000 μL) was injected by a 1-mL GC syringe into a gas chromatographic

system and separated as described below. N.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene was trapped in dry form in a glass trap cooled by liquid nitrogen. From there the product was taken up in 1–5 mL of dry diethyl ether for further reactions.

Gas chromatographic separation was performed on Chromosorb W-AW-DMCS (60–80 mesh) with 6% bentone and 20% DC 200 in a glass column (4 m × 8 mm) and with a helium gas flow of 150 mL/min. The injector was heated to 240 °C. A TCD detector was used for the detection of the reference compounds. At the outlet of the GC, a heated 1/16″ stainless steel line lead to a Valco valve oven (HVEC-220V, heated to 200 °C) with a heated three-way valve after the outlet. One exit of the valve was connected to a trap cooled by liquid nitrogen and the other to a heated 1/16″ stainless steel line to collect the labelled product. The parameters of the temperature program of the column oven were:

| | |
|---|---|
| Starting temperature (°C) | 140 |
| Start of heating (min) | 5 |
| Heating rate (°C/min) | 15 |
| Reset (min) | 50 |
| *k* (1-bromo-4-fluorobenzene) | 4.53 |
| *k* (1-bromo-4-iodobenzene) | 8.53 |

### 4.4. Column chromatographic isolation of [$^{18}$F]1

Alternatively, after finishing the $^{18}$F-labelling reaction the whole reaction mixture was given on a small glass column (120 × 10 mm) for column chromatography. The stationary phase consisted of silica Si-60 (0.063–0.200 mm) conditioned by dry diethyl ether. The whole reaction mixture (0.5 mL DMF) was separated within 10 min whereby the first 2.5 mL eluate was discarded (diethyl ether). The following 3 mL contained about 95% of total n.c.a. [$^{18}$F]**1**. Due to the strong adsorption of DMF on silica the separation of the aromatic compounds from the dipolar aprotic solvent succeeded easily.

### 4.5. Metallorganic reactions

In the following, general descriptions of radioorganometallic reactions performed are given. More detailed experimental conditions for specific reactions are discussed and mentioned with figures and tables.

The organometallic reactions using n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene (approximately 135–370 MBq) were performed using 3- or 5-mL reactivials or 5-mL double necked flasks which were initially heated for removing traces of water and flushed with inert argon gas. Disposable syringes, cannulae and Hamilton-syringes for adding solutions and solvents were also flushed and stored under argon gas before use. Because the metal organic intermediates are not stable and not directly analyzable, they were hydrolyzed by addition of 300 μL of water to the reaction solution.

### 4.6. Synthesis of 4-[$^{18}$F]fluorophenyllithium ([$^{18}$F]2a) via n-butyllithium

At −40 °C 0.4 mmol (250 μL) *n*-butyllithium in hexane (1.6 M) was added to a solution of 4-bromo-[$^{18}$F]fluorobenzene and 1.6 μmol of 4-bromofluorobenzene dissolved in 1 mL of dry diethyl ether in a 5-mL Wheaton glass vial. The reaction mixture was stirred for 15 min at −40 °C and then heated to the temperature required for the following reaction step.

### 4.7. In situ synthesis of [$^{18}$F]2a

*(a) Thermic activation*: Lithium metal (0.08 g/11.5 mmol) was stored under an argon atmosphere in a two necked round bottom flask equipped with a reflux condenser. An ether solution (5 mL) of n.c.a. 4-bromo-[$^{18}$F]fluorobenzene and a selected amount of bromobenzene was added under stirring during 15 min. Afterwards, the reaction mixture was refluxed for another 5 min.

*(b) Ultrasonic activation*: Lithium metal (0.08 g/11.5 mmol) was stored under an argon atmosphere in a two necked round bottom flask equipped with a reflux condenser. An ether solution (5 mL) of n.c.a. 1-bromo-4-[$^{18}$F]fluorobenzene ([$^{18}$F]**1**) and bromobenzene (0.48 mmol) were added dropwise under stirring. The formation of [$^{18}$F]**2a** was effectively supported by treating the reaction mixture in the water bath of an ultrasound laboratory cleaner (60 W, 45 kHz) and complete within 5 min. The reaction was performed while keeping room temperature.

### 4.8. Synthesis of 4-[$^{18}$F]fluorophenylmagnesium bromide ([$^{18}$F]2b)

Magnesium (0.1 g/4.1 mmol) suspended in a solution of n.c.a. 4-bromo-[$^{18}$F]fluorobenzene in 3 mL of ether was stirred under an argon atmosphere in a two necked round bottom flask equipped with a reflux condenser. 1,2-Dibromomethane (0.2 mL, 2.3 mmol) was added dropwise under stirring at 25 °C to start the reaction. The in situ formation of [$^{18}$F]**2b** started 2–3 min after the addition and was complete within 8–12 min. The exothermic reaction was controlled by cooling with an ice bath (0 °C).

### 4.9. Synthesis of 4-[$^{18}$F]fluorophenylsodium ([$^{18}$F]2c)

To a solution of 4-[$^{18}$F]fluorophenyllithium in 1 mL of diethyl ether stored in a Wheaton glass vial, a suspension of 77 mg (0.8 mmol) sodium *tert*-butylate in 2 mL of *n*-hexane was added at 0 °C. After stirring the reaction mixture for 5 min the reaction was completed and the reagent of the following reaction step could be added.

### 4.10. Arylation reactions with [$^{18}$F]2a, [$^{18}$F]2b or [$^{18}$F]2c

In general, the corresponding amount of precursor to be $^{18}$F-fluoroarylated (cf. Tables 3 and 4) dissolved in 0.5 mL of diethyl ether was placed either in a 3- or 5-mL reactivial under stirring at RT or with heating at reflux in a two necked round bottom flask equipped with a reflux condenser. From the etheric solution of [$^{18}$F]**2a**, [$^{18}$F]**2b** or [$^{18}$F]**2c** as obtained (see above) 1 mL was added to the precursor solution. All equipment was previously flushed with argon gas. The reaction was stopped with 0.5 mL of methanol and analyzed by HPLC on a Nucleosil 100-5 C-18 column (250 × 4.6 mm) using acetonitrile/water (70/30, v/v, solvent A or 60/40, v/v, solvent B) or on a Superspher Si 60 column using ethanol with 0.1% triethylamine (solvent C) at 254 nm.

| | |
|---|---|
| *k* (4-fluorotoluene) | 3.44 (solvent A) |
| *k* ((4-fluorophenyl)diphenylmethanol) | 3.92 (solvent A) |
| *k* ((4-fluorophenyl)phenylmethanol) | 2.55 (solvent A) |
| *k* ((4-fluoro-phenyl)trimethylsilane) | 5.10 (solvent B) |
| *k* (4-fluorodimethylaniline) | 3.20 (solvent B) |
| *k* (4-fluorothioanisole) | 4.50 (solvent B) |
| *k* (4-(4-fluorophenyl)-1-methylpiperidin-4-ol) | 3.80 (solvent C) |

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