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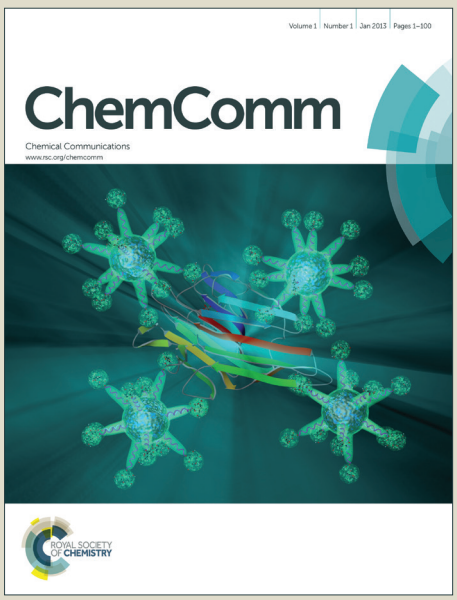

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ARTICLE TYPE

Cu(I)-mediated ^{18}F-trifluoromethylation of arenes: Rapid synthesis of ^{18}F-labeled trifluoromethyl arenes

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This report is concerned with an efficient, Cu^{I}–mediated method for the radiosynthesis of [^{18}F]trifluoromethyl arenes, an abundant motif in small molecule drug candidates and potential radiotracers for positron emission tomography. Three ^{18}F-labelled radiotracer candidates were synthesised from [^{18}F]fluoride ion as proof of principle. The new protocol is widely applicable for the synthesis of novel radiotracers in high radiochemical yields.

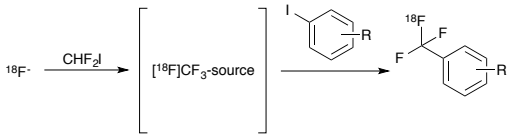
Molecular imaging with positron emission tomography (PET) allows for non-invasive, quantitative studies of radiotracer distribution in living subjects. In consequence of its maturation, PET is increasingly used in routine clinical diagnosis, commercial drug development, and in biomedical research. Novel radiotracers for imaging a variety of biological targets are continually needed to fully exploit the potential of PET. ^{18}F is the most frequently employed PET nuclide, owed to the extensive use of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) for clinical diagnosis.[2,3] The relevance of ^{18}F is based on its expedient half-life (109.7 min) rendering it suitable for multi-step reactions, transport of radiotracers over moderate distances, convenient handling of the tracer in imaging studies and high-yield cyclotron production of no-carrier-added (n.c.a) [^{18}F]fluoride ion. The ability to form stable C-F bonds promotes the straight introduction of F atoms into most small organic molecules.

Despite the strong demand for novel radiotracers for a variety of disease related biological mechanisms, radiotracer development is a complex process. Researchers and clinicians often struggle to obtain a desired radiotracer within a reasonable time frame because discovery of suitable molecular structures that can be labelled by established procedures often require time-consuming iterative cycles of candidate synthesis and biological evaluation.

Due to its properties, a wide portfolio of synthetic drug molecules and derivatives contain the metabolically stable CF_3 group, and consequently operationally simple, direct arene-trifluoromethylation methodology has become a key focus in current organic chemistry.[4] Radiolabelling these CF_3 groups is attractive to reposition known drug molecules for PET.[5]

We, hence, sought an efficient method for producing [^{18}F]trifluoromethyl arenes starting from [^{18}F]fluoride ion within our radiotracer development program. Radiosynthesis of the ^{18}F-labelled aryl trifluoromethane scaffold has been reported, however, mostly through the use of rare and unavailable electrophilic fluorinating agents or harsh conditions.[5] A more recent breakthrough employed Cu^{I} in combination with aryl iodides.[5a] We have explored a new route inspired by a recent report of [^{18}F]fluoroform by Vugts et al.[6]

For successful outcomes, reactions involving [^{18}F]fluoroform require diligent control of the gaseous intermediate, including low temperature distillation and trapping of the product at -80 °C in a secondary reaction vessel. These conditions and technical requirements are limiting factors with respect to the automated synthesis of high activity batches using automated synthesiser systems. Few commercially available systems provide more than one reactor and generally disfavour low temperature processes. We surmised that widespread adoption of trifluoromethylation reactions would strongly benefit from a straightforward nucleophilic one-pot method generally applicable to latest generation synthetic hardware. Such methodology would, furthermore, feature direct installation of nucleophilic [^{18}F]fluoride ion into candidate radiotracers to avoid losses of radioactivity, conserve specific radioactivity and achieve rapid and operationally simple radiosyntheses.[6] To achieve this we focused our effort on the in-situ formation of a suitable ^{18}F-trifluoromethylating reagent from an appropriate precursor and its direct conversion into the title compounds in the same reaction vessel (Scheme 1).



Scheme 1. Strategy for the radiosynthesis of [^{18}F]trifluoromethyl arenes

Difluoroiodomethane (CHF_2I) was selected as the starting material to provide a convenient source of Cu[^{18}F]CF_3. Our choice of Cu[^{18}F]CF_3 was encouraged by the work of Grushin et al.,[7a,b] who provided comprehensive insights into the formation and use of $CuCF_3$ for trifluoromethylation reactions using fluoroform, which we attempted to implement at first, albeit without success.[†]

To our dismay, the published reaction conditions translated poorly into radiochemistry.[7a†] This is most likely owed to the crucial presence of phase transfer catalysts in the radiofluorination reaction mixture to activate the [^{18}F]fluoride ion. Such reagents are known to increase basicity and reactivity when combined with strong, anionic bases like KOtBu in dipolar aprotic solvents.[7d-f] Although such strong bases were deemed crucial to deprotonate fluoroform (pk_a = 27 in DMSO) in previous reports,[7] only rapid discoloration alongside low yields was observed in our radiochemical experiments. Grushin and co-workers described that the use of KOtBu in excess would even permit omission of a supporting ligand and added triethylamine HF-complex to stabilise the Cu-CF_3 reagent. Addition of non-radioactive fluoride ion to the labelling reaction is prohibitive in the context of the tracer principle, a prerequisite for PET imaging. A second issue may be the fact that CuF is only stable as a complex in solution and otherwise disproportionates to Cu^0 and CuF_2. Since the development

of a one-pot method would require both species, n.c.a. [^{18}F]fluoride ion and Cu^{+}, to coexist this mechanism may deprive the reaction mixture of ^{18}F, which is only present in very low concentration (μM). Hence, obtaining the short-lived [^{18}F]CF_3-source *in situ* prior to trifluoromethylation in the same reaction vessel is rather challenging and, unfortunately, the Grushin method did not furnish the desired labelled products in useful radiochemical yields. Given this apparent incompatibility of reagents a methodological optimisation of various parameters became inevitable.

This prompted us to our working hypothesis. We surmised that KOtBu may not be required since the formation of difluorocarbene via α-elimination of HI from CHF_2I in the presence of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo [8.8.8]hexacosan (crypt-222), K_2CO_3, and $^{18}F^{-}$ facilitates the formation of Cu-[^{18}F]CF_3. In addition we considered that a supporting ligand may be beneficial to address the sensibility of the reaction to Cu-disproportionation and potentially stabilise a Cu-difluorocarbene complex.[7g†] Consequently, we chose the screening for the most efficient Cu-ligand system in combination with the most frequently used source of reactive ^{18}F-fluoride; crypt-222, K_2CO_3, and $^{18}F^{-}$ as starting point for our investigations, as we now report here.

Table 1. Effect of base/ligand on RCY of [^{18}F]**1b**. The concentration of ligand in the reaction mixture was 200 mM.

Entry	Ligand[a]	RCY (%)[b,c] [^{18}F]**1b**
1	None	0
2	tBuOK	2
3	triphenylphosphine	1
4	pyridine	2
5	DMAP	9
6	2,2'-bipyridine	8
7	phenanthroline	5
8	IPr·$CuBF_4$	2
9	TMEDA	19
10	DBU	3
11	NEt_3	28
12	DIPEA	42

[a] Abbreviations: DBU = 1,8-diazabicyclo[5.4.0]undecene; IPr·$CuBF_4$ = bis(1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene)copper(I) tetrafluoroborate; DMAP = 4-(dimethylamino)pyridine; TMEDA = *N,N,N',N'*-tetramethyl ethylenediamine; NEt_3 = triethylamine; DIPEA = *N,N*-diisopropyl-N-ethylamine [b] decay-corrected radiochemical yield in % of dispensed ^{18}F determined by radioHPLC or radioTLC.

We initially aimed to discover a simple CuI-ligand system capable of mediating the trifluoromethylation reaction without impeding the nucleophilic radiofluorination with [^{18}F]fluoride ion. As a model reaction, we chose to use a 1:1:1 molar ratio of CHF_2I, CuI, ligand (see table 1) and a model substrate, the iodoarene 4-iodo benzonitrile **1a** (~ 40 μmol) in DMF (0.3 mL). In preliminary experiments (not shown) we had found that a temperature of 145°C was necessary to achieve rapid conversion. Attempts to substitute the low boiling starting material CHF_2I (b.p. 22 °C) by a higher boiling difluoromethyl sulfonate in order to permit better control of the reaction stoichiometry and ease handling of the reagent were not successful. Neither difluoromethyl tosylate nor difluoromethyl triflate were found to react to the desired product under a variety of conditions. Consequently, we resorted to using CHF_2I for all further experiments. Despite this minor inconvenience, an activity balance of the reaction did not reveal any losses of gaseous radioactive material. In control experiments omitting either ligand, or CHF_2I no ^{18}F-labelled product was obtained (Table 1, entry 1-2), likewise, the use of triphenylphosphine gave only traces of product (Table 1, entry 3). Surprisingly, neither pyridine derivative screened gave significant yields of [^{18}F]**1b** (Table 1, entries 4−7). When the commercially available Cu-NHC complex bis(1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)copper tetrafluoroborate was used, [^{18}F]**1b** was formed in about 2% yield (Table 1, entry 8). At this point we deducted that a slightly more basic ligand would be required in dipolar aprotic media and turned our attention to aliphatic, tertiary amines. This hypothesis was rewarded with the first double-figured yield when tetramethylethylenediamine (TMEDA), a ligand that had proved its value previously, was used.[8] Under these conditions (Table 1, entry 9) [^{18}F]**1b** was obtained in 19 % radiochemical yield after 10 min at 145 °C. Encouraged by these positive findings we briefly considered DBU (3%, Table 1, entry 10) which turned out to be inferior to TMEDA. Further improved, albeit not yet satisfactory yield (28%, Table 1, entry 11) was achieved through the use of NEt_3 in combination with **1a**. Further screening of ligand-catalyst combinations (Table 1, entry 12) revealed *N,N*-diisopropyl-N-ethylamine (DIPEA) to be very effective with regard to the formation of [^{18}F]**1b**; without further optimisation a radiochemical yield of 42% was achieved. We hence refrained from further ligand screening and focussed further efforts on the CuI-DIPEA system. Although the majority of [^{18}F]fluoride ion had been consumed within 10 minutes of reaction time, a considerable amount of residual [^{18}F]fluoride ion left in the reaction mixture indicated further potential for improvement. In order to boost the conversion of [^{18}F]fluoride which we surmised would lead to further improvements in RCY we considered that alternative sources of naked [^{18}F]fluoride ion might prove beneficial. Sources of [^{18}F]fluoride ion were obtained by trapping [^{18}F]fluoride ion on a strong anion exchange resin followed by elution of the trapped radioactive material using an appropriate base in aqueous acetonitrile (MeCN-H_2O, 9:1). Through this protocol, reactive [^{18}F]fluoride ion complexes are obtained that have found widespread application in PET chemistry. In the context of our one-pot approach we conducted control experiments with DBU and TMEDA alongside DIPEA to avoid overlooking synergies in between the ^{18}F-complex, ligand and Cu^{I}. However, under the screened conditions, DIPEA was found to generally be superior to TMEDA and DBU. Substitution of the cryptand crypt-222 (Table 2, entry 1) by the corresponding crown ether 18-crown-6 (Table 2, entry 2) led to a slightly improved radiochemical yield of about 49%. Whereas the use of tetrabutylammonium hydroxide (TBAOH) to form tetrabutylammonium fluoride (TBA[^{18}F]F) (Table 2, entry 3) did not have any value, tetraethylammonium carbonate ($TEAHCO_3$) to essentially obtain tetraethylammonium fluoride (TEA[^{18}F]F) (Table 2, entry 4) had a remarkable impact (56%). The use of Cs_2CO_3 as a base, led to a significant increase in radiochemical yield in the formation of [^{18}F]**1b** (up to 83%, Table 2, entry 5). In the end, these conditions were equivalent to the combination of $KHCO_3$, crypt-222 and DIPEA which resulted up to 83 % RCY after 10 min at 145 °C (Table 2, entry 6).

Table 2. Effects of fluoride ion source on the RCY of [^{18}F]**1b**[a].

Entry	Base	Ligand	[^{18}F]**1b** (%)[a]
1	K_2CO_3/crypt-222	DIPEA	42
		TMEDA	19
2	K_2CO_3/18-crown-6	DIPEA	49
3	TBAOH	DIPEA	2
		TMEDA	18
4	$TEAHCO_3$	DIPEA	56
5	Cs_2CO_3	DIPEA	83
		TMEDA	38
		DBU	27
6	$KHCO_3$/crypt-222	DIPEA	83
		TMEDA	48
		DBU	47

[a] Abbreviations: TBAOH = tetrabutylammonium hydroxide; $TEAHCO_3$ = tetraethylammonium bicarbonate

Notably, screening of various combinations of inorganic base and phase transfer catalysts used to activate the [^{18}F]fluoride ion in

the next step indeed facilitated a duplication of the radiochemical yield when an even milder base was used, highlighting the strong influence of these reagents under our conditions. These conditions were used in all further experiments. In order to further optimise the reaction outcome, we focussed our attention on the contribution of the reaction time. Increasing the reaction time beyond 10 minutes did not improve the yield, instead it became apparent, that the bulk of the [^{18}F]fluoride ion had already been consumed within 10minutes of reaction time under our optimised conditions and the yield did not improve but only degrade further from this point. Substitution of DMF with DMSO or THF were detrimental (Table 3, entries 2 and 4) both of these solvents were ineffective. However, substitution of DMF for MeCN provided a viable alternative and similar yields were obtained. The main culprit of using MeCN under these conditions is the fairly pronounced pressure build up in the reactor, which may result in difficulties during automation. Moreover, a loss of activity was observed using acetonitrile as solvent.

Table 3. Effects of reaction time, and solvent on RCY of [^{18}F]**1b**

Entry	solvent	time / minutes	RCY (%)
1	DMF	10	83
2	DMSO	10	0
3	MeCN	10	78
4	THF	10	8
5	DMF	20	82

Variation of copper catalyst source. We tested whether CuI was the preferred source of copper catalyst by changing the copper salt in the promising reaction example that used DIPEA-CuI (Table 4, entry 1). Reaction did not occur when CuI was omitted (Table 4, entry 2). Equimolar replacement of CuI with CuCl, CuOAc, CuCN, or fluorotristriphenylphosphine Cu^{I} led to diminished radiochemical yield (Table 4, entries 3−7). Also arene complexes of CuOTf (Table 4, entry 8-10) were not effective in the absence of DIPEA or gave only trace ^{18}F-labelled product (Table 4, entry 8). Tetrakis acetonitrile CuOTf and CuBr provided the highest yields (table 3, entry 4). In our case CuBr was established as the preferred copper source.

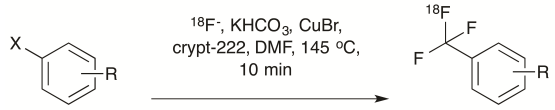
Table 4. Effects of copper source on RCY of [^{18}F]**1b**

Entry	Catalyst[a]	RCY (%)[b]
1	CuI	83
2	None	0
3	CuCl	40
4	CuBr	89
5	CuCN	60
6	CuOAc	10
7	CuF x PPh_3	0[b]
8	CuOTf x $(MeCN)_4$	5[b]
9	CuOTf x benzene	0[b]
10	CuOTf x toluene	0[b]
11	CuOTf x $(MeCN)_4$	93

[a] Abbreviations: CuOTf x $(MeCN)_4$ = tetrakisacetonitrile copper(I) triflate; CuOTf x benzene = Copper(I) trifluoromethane sulfonate benzene complex; CuOTf x toluene = Copper(I) trifluoromethane sulfonate toluene complex; CuF x PPh_3 = Fluorotris (triphenylphosphine)copper(I).

General conditions, as optimised above were used to investigate the substrate scope of the ^{18}F-trifluoromethylation. A variety of commercially available aryl halides were screened (Table 5). In essence, aryl iodides were confirmed to be the most appropriate halides for our purpose (Table 5, entry 1), a steep decline in radiochemical yield occurred when switching to the corresponding bromide **3a** or chloride **4a** (Table 5, entry 3-4). Most assayed functional groups were found to be compatible with the reaction conditions. Potentially sensitive substrates such as 4-cyano or 4-methoxycarbonylbenzenes, which may be sensitive to exposure to carbanionic forms of trifluoromethylating reagents, gave the desired radioactive products in high to excellent yields. Even **12a** containing a protic hydroxyl group was tolerated to some extent. The protic carboxamide **10a** gave low yield and two unidentified by-products were observed. Electron deficient substrates globally resulted in slightly higher radiochemical yields compared to electron-rich arenes.

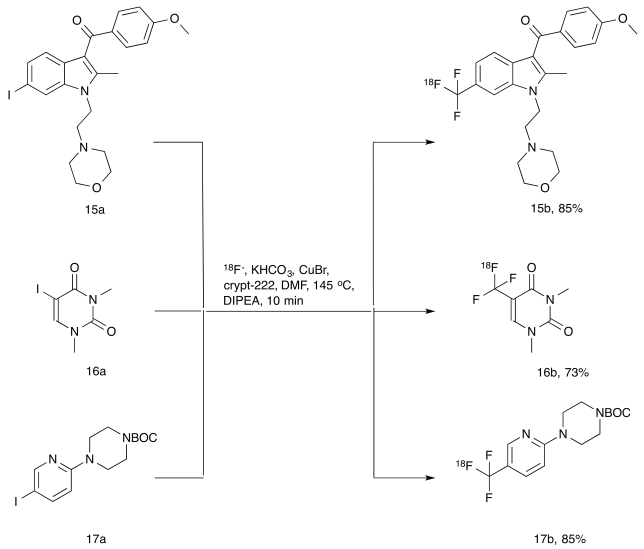
Table 5. Substrate scope of the ^{18}F-trifluoromethylation reaction.



Substrate	R	X	Product	RCY (%)[a]
1a	4-cyano	I	[^{18}F]**1b**	93±3
2a	4-t.butyl	I	[^{18}F]**2b**	69±8
3a	4-t.butyl	Br	[^{18}F]**2b**	1
4a	4-t.butyl	Cl	[^{18}F]**2b**	1
5a	4-methoxycarbonyl	I	[^{18}F]**5b**	86±7
6a	4-nitro	I	[^{18}F]**6b**	89±4
7a	4-pyridinyl	I	[^{18}F]**7b**	58±17
8a	3-methoxycarbonyl	I	[^{18}F]**8b**	86±8
9a	4-phenyl	I	[^{18}F]**9b**	84±2
10a	4-carboxamido	I	[^{18}F]**10b**	44±14
11a	4-benzyloxy	I	[^{18}F]**11b**	85±6
12a	4-hydroxy	I	[^{18}F]**12b**	12±1
13a	3,5-dimethyl	I	[^{18}F]**13b**	63±6
14a	2,6-dimethyl	I	[^{18}F]**14b**	75±6

[a] Screening conditions: 100 MBq scale, CuBr (58 µmol), CHF_2I (169 µmol), $KHCO_3$ (13 µM), crypt-222 (35 µmol), aryl halide (41 µmol), DIPEA (59 µmol), 145 °C, 10 min, DMF (300 µL); [b] RCY values are mean ± S.D.

Translation of the method: Radiotracer synthesis. Having confirmed that we were able to prepare a variety of [^{18}F]trifluoromethyl arenes efficiently within only 10 min, we investigated the feasibility of synthesising prospective radiotracer candidates bearing molecular structures common for small molecule drugs (Scheme 2).



Scheme 2. Direct radiosynthesis of [^{18}F]trifluoromethyl arenes

Treatment of the precursor **15a** ,with ^{18}F under our standard conditions afforded the potential subtype selective cannabinoid receptor agonist [^{18}F]**15b** in 85% RCY. Likewise, we investigated the direct radiosynthesis of trifluorothymine **16b** from the corresponding iodide precursor **16a** in order to provide this compound for our ongoing cancer imaging efforts in rodent models of peripheral tumours. [^{18}F]**16b** was obtained in a radiochemical yield of 73%. In an extension of our concept the BOC-protected piperazine **17a** was converted into the ^{18}F-trifluoromethylated BOC-protected piperazine

17b in 85% yield and deprotected with TFA in a second step to obtain the prospective 5-HT receptor radiotracer **17c**.

In this report, we have shown that Cu^{I} mediated ^{18}F-trifluoromethylation reactions are highly efficient in the presence of a simple combination of DIPEA, CuBr and iodo arene. We extended this methodology to three examples of a single-pot synthesis of candidate radioligands for PET imaging (Scheme 2). The resulting [^{18}F]trifluoromethyl arenes are obtained in sufficient yield in an operationally convenient protocol, suitable for straightforward automation. This direct and rapid conversion of iodoarenes is tolerant to diverse functional groups and consequently provides convenient access to a variety of drug molecules containing the CF_3-group. Given the high prevalence of the CF_3-group and its prominent role in drug development, paired with the availability of ^{18}F at most PET centres, we expect this novel methodology to be widely adapted for the development of PET radiotracers in particular from known, well characterised drug molecules.

Notes and references

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1 L. Cai, S. Lu, V. W. Pike *Eur. J. Org. Chem*. 2008, 2853−2873.

2 a) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee. *Angew. Chem. Int. Ed.* 2008, **47**, 8998-9033; b) P. J. H. Scott *Angew. Chem. Int. Ed.* 2009, **48**, 6001−6004.

3 G. J. Meyer, S. L. Waters, H. H. Coenen, A. Luxen, B. Mazière, B. Långström *Eur. J. Nucl. Med.* 1995, **22**, 1420−1432.

4 a) D. A. Nagib, D. W. C. MacMillan. *Nature* 2011, **480**, 224-228, b) A. Deb, S. Manna, A. Modak, T. Patra, S. Maity, D. Maiti. *Angew. Chem Int Ed* 2013, **52**, 9747–9750; c) S. Mizuta, K. M. Engle, S. Verhoog, O. Galicia-Lopez, M. O'Duill, M. Medebielle, K. Wheelhouse, G. Rassias, A. Thompson, V. Gouverneur *Org Lett.* 2013, **15**, 1250-1253; d) T. Furuya, A. S. Kamlet, T. Ritter *Nature* 2011, **473**, 470–477; e) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana M. O'Duill, K. Wheelhouse, G. Rassias, M. Medebielle, V. Gouverneur *J. Am. Chem. Soc.* 2013, **135**, 2505-2508.

5 a) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier *Nature Chem.* 2013, **5**, 941–944; b) L. Zhu, K. Ploessl, H. F. Kung *Science* 2013, **342**, 429-430. c) S. Mizuta, I. Stenhagen, M. O'Duill, J. Wolstenhulme, A. Kirjavainen, S. Forsback, M. Tredwell, G. Sandford, P. Moore, M. Huiban, S. Luthra, J. Passchier, O. Solin, V. Gouverneur *Org Lett.* 2013, **15**, 2648-2651; d) M. Tredwell, V. Gouverneur *Angew. Chem. Int. Ed.* 2012, **51**, 11426-11437; e) P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith, F. I. Aigbirhio *Org. Biomol. Chem.* 2012, **10**, 6980-6986; f) P. J. Riss, F. I. Aigbirhio *Chem. Commun.* 2011, **47**, 11873-11875; g) M. R. Kilbourn, M. R. Pavia, V. E. Gregor *Int. J. Rad. Appl. Instrum. A.* 1990, **41**, 823-828*; h)* O. Josse, D. Labar, B. Georges, V. Grégoire, J. Marchand-Brynaert *Bioorg. Med. Chem.* 2001, **9**, 665-675; i) W. R. Dolbier Jr, A.-R. Li, C. J. Koch, C.-Y. Shiue, A. V. Kachur *Appl. Radiat. Isotopes* 2001, **54**, 73-80.

6 D. van der Born, J. D. M. Herscheid, R. V. A. Orru, D. J. Vugts *Chem. Commun.* 2013, **49**, 4018-4020

7 a) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin *J. Org. Chem.* 2013, **78**, 11126-11146; b) O. A. Tomashenko,.V. V. Grushin *Chem. Rev.* 2011, **111**, 4475; c) E. A. Symons, M. J. Clermont *J Am Chem Soc* 1981, **103**, 3127-30; d) Marc Halpern "Phase-Transfer Catalysis" in Ullmann's Encyclopedia of Industrial Chemistry 2002, Wiley-VCH, Weinheim; e) E. V. Dehmlow, S. S. Dehmlow in Phase Transfer Catalysis, 3rd edn. 1993 VCH, Weinheim; f) C. M. Starks, C. L. Liotta, M. E. Halpern, in Phase-Transfer Catalysis 1994, Chapman & Hall, New York; g), W. Kirmse, Carbene Chemistry, Volume 1, Academic Press, Inc. LTD., New York-London 1971, 2. Edition.

8 P. J. Riss, S. Lu, S. Telu, F. I. Aigbirhio, V. W. Pike *Angew. Chem. Intl. Ed*. 2012, **51**, 2698–2702.

9 K. Virdee, P. Cumming, D. Caprioli, B. Jupp, A. Rominger, F. I. Aigbirhio, T. D. Fryer, P. J. Riss, J. W. Dalley *Neurosci Biobehav Rev.* 2012, **36**, 1188-1216.