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Efficient DBU accelerated synthesis of ^{18}F-labelled trifluoroacetamides†

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Nucleophilic ^{18}F-fluorination of bromodifluoromethyl derivatives was performed using [^{18}F]Bu$_4$NF in the presence of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene). This novel procedure provided a diverse set of [^{18}F]trifluoroacetamides in good to excellent radiochemical conversions. A mechanism where DBU acts as organomediator in this transformation is proposed.

Due to the favourable properties of fluorine, approximately one fifth of newly registered small drug molecules are organofluorine compounds.[1] Moreover, the artificial isotope ^{18}F ($t_{1/2}$ 109.8 min) has suitable nuclear properties for *in vivo* imaging in human subjects using positron emission tomography (PET).[2] Hence, there is a large demand for efficient fluorination methodologies in both medicinal[3] and radiosynthetic chemistry.[4]

Despite the remarkable developments in PET radiochemistry during the past decade,[4] lack of efficient radiochemical methodology may still be a bottleneck in drug discovery and development. It is particularly rate-limiting for microdosing studies, in which the distribution of the radiolabeled drug molecule, previously developed without the intent to be radiolabeled, is studied during the PET measurement.[5] In view of our long-term objective to facilitate PET studies during drug discovery and development, we turned our attention to the development of a new method for introducing fluorine-18 into trifluoroacetamide (–NCOCF$_3$) groups. Although these groups are important motifs in medicinal chemistry,[6] their radiolabelling has so far been remarkably neglected in the literature. On the other hand, more attention has been directed to the development of methods for the installation of [^{18}F]CF$_3$ groups into other type of motifs and two distinct approaches have been taken for this purpose. The first proceeds *via* direct substitution of a leaving group in the appropriate difluoromethyl analog with ^{18}F-fluoride (Scheme 1).[7–12] Traditionally, these transformations have been thermally activated, but more recently metal salts were successfully used as activators.[11] The second approach comprises a two-step procedure in which the [^{18}F]CF$_3$ functionality is incorporated into aromatic substrates *via* [^{18}F]CuCF$_3$ species.[8–10,13]

Scheme 1 General synthesis of ^{18}F-CF$_3$ moieties by displacement of a leaving group.

We started investigating the transformation of difluorobromoacetamide **1a** into the corresponding ^{18}F-trifluoromethyl analog [^{18}F]**2a** using [^{18}F]Bu$_4$NF in a set of solvents with varying temperatures (Table 1, entries 1–5). The reaction proceeded with low to modest radiochemical conversion (RCC; the fraction of radioactivity incorporated into the desired product) in all examined solvents, including DCE (entry 1) acetonitrile (entry 2) and DMSO (entry 3). The highest RCC (35%) was observed in DMF. There was no obvious difference between kryptofix/K^{18}F and [^{18}F]Bu$_4$NF as the fluorinating species (entries 5 *vs.* 4). Interestingly, the use of metal salts as additives did not lead to improvements in the RCC either (entries 6–8). In light of these results where reported methods failed, we turned our attention to nitrogen based nucleophilic organic activators for the ^{18}F-fluorination.[14] Thus, the transformation of **1a** into [^{18}F]**2a** was investigated in DMF at 100 °C using 1 equiv. of activator. Though DABCO and DBN did not provide an improvement in RCC (entries 9 and 12 *vs.* 4), gratifyingly, DMAP and pyridine increased the RCC to 59% and 68%, respectively (entries 10 and 11). A further increase in RCC to 71%, twice compared to control conditions without activator (*cf.* entries 4 and 13), was obtained using DBU. When two further guanidine derivatives were used, TBD and MTBD, an even higher RCC was observed (entries 15 and 16, respectively). However, when

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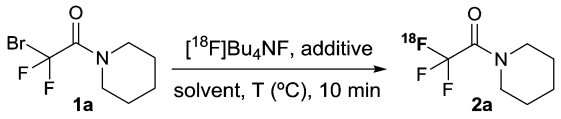
Table 1 ^{18}F-labelling of **2a** under various conditions[a]

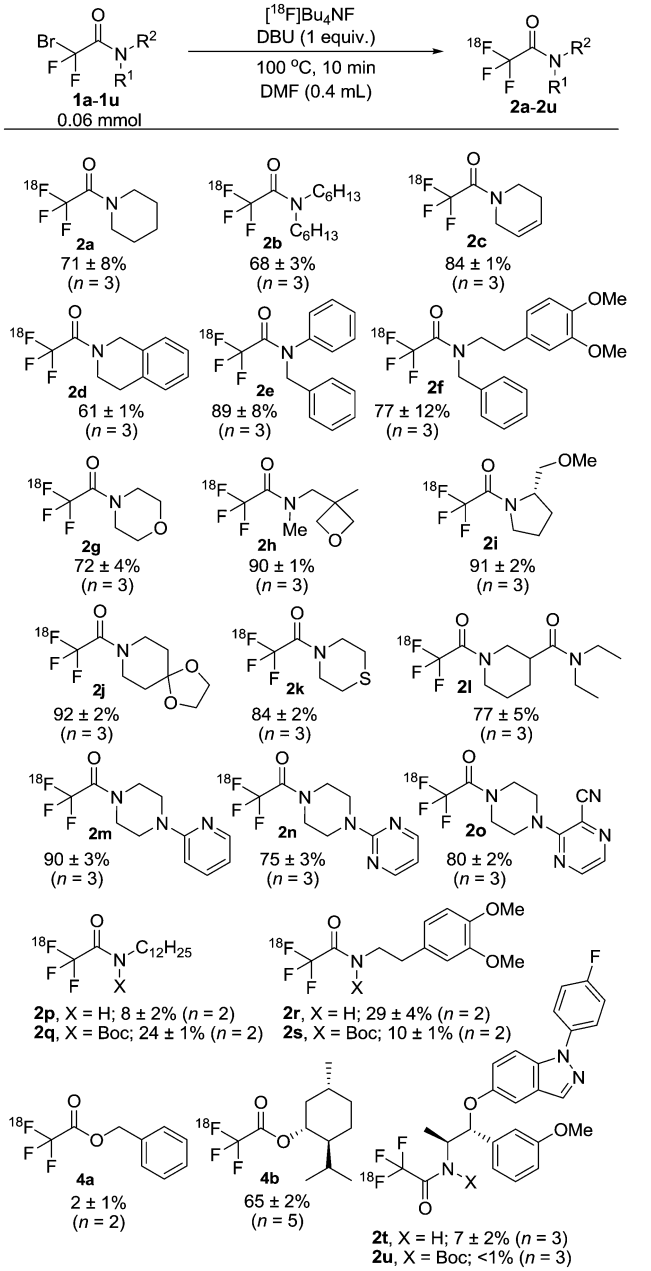


Entry	Solvent[b]	Temp. (°C)	Additive[c]	RCC[d] (%)
1	DCE	85	—	3 ± 2 (n = 2)
2	CH_3CN	60	—	29 ± 5 (n = 2)
3	DMSO	170	—	3 ± 1 (n = 2)
4	DMF	100	—	35 ± 13 (n = 3)
5	DMF	100	—[e]	22 ± 6 (n = 3)
6	DMF	100	$(PPh_3)_3CuOAc$	<1 (n = 2)
7	DCM	RT	AgOTf	2 ± 0 (n = 2)
8	DCE	80	AgOTf[f]	4 ± 1 (n = 2)
9	DMF	100	DABCO	41 ± 7 (n = 3)
10	DMF	100	DMAP	59 ± 16 (n = 3)
11	DMF	100	Pyridine	68 ± 9 (n = 3)
12	DMF	100	DBN	40 ± 7 (n = 3)
13	DMF	100	DBU	71 ± 8 (n = 3)
14	DMF	100	DBU[e]	65 ± 13 (n = 2)
15	DMF	100	TBD	81 ± 8 (n = 3)
16	DMF	100	MTBD	76 ± 12 (n = 3)

[a] Unless otherwise noted: **1a** (0.06 mmol, 19 mg), solvent 0.4 mL, additive 0.06 mmol (1 equiv.). [b] DMF = *N*,*N*-dimethylformamide; DCM = dichloromethane; DCE = 1,2-dichloroethane. [c] DMAP = 4-dimethylaminopyridine; DABCO = (1,4-diazabicyclo[2.2.2]octane); DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD = 1,5,7-triazabicyclo-[4.4.0]dec-5-ene; MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. [d] Estimated by radio-HPLC. [e] Using KF[^{18}F]/$K_{2.2.2}$. [f] 2 equiv.

the reactions with TBD and MTBD were repeated in the cold lab (using ^{19}F-containing TBAF) extensive hydrodebromination of the starting material **1a** was also detected. Because formation of this by-product would complicate the purification and isolation of [^{18}F]**2a** and since the reaction with DBU proceeded with a high RCC without hydrodebromination (or other side reactions), DBU was selected as the activator in the further studies.

With the improved conditions in hand, we explored the scope of the DBU-mediated reaction with different tertiary (**1a–1o**) and secondary (**1p** and **1r**) bromodifluoroacetamides (Scheme 2). Substrates with cyclic or linear alkyl chains (**1a–1b**), or including alkene functionalities (**1c**), gave the labelled amides [^{18}F]**2a–2c** in good to excellent RCC (71, 68 and 84%, respectively). The benzylic derivatives **1d–1f** and the morpholine, oxetane, proline and ketal derivatives **1g–1j** could also be conveniently transformed with [^{18}F]TBAF in the presence of DBU to [^{18}F]**2d–2j** (61–92% RCC). In metal catalyzed/mediated reactions, sulfur has a tendency to coordinate to the metal atom and thus inhibit the reaction. With the current methodology, thioether derivative [^{18}F]**2k** was obtained in excellent RCC (84%), thus suggesting an apparent insensitivity of the protocol to thiol functionalities. Next, substrate **1l**, with an additional amide function, and **1m–1o**, with some important nitrogen containing heterocycles commonly used in medicinal chemistry, were converted smoothly into trifluoromethyl derivatives [^{18}F]**2l–2o** in excellent RCCs (77, 90, 75 and 80%, respectively). Finally, we focused our attention to the more challenging secondary bromodifluoroacetamide substrates **1p** and **1r**. As expected, [^{18}F]**2p** and [^{18}F]**2r** were obtained in substantially lower RCCs than the tertiary amide derivatives using direct DBU-mediated fluorination. Considering that the



Scheme 2 Substrate scope in the ^{18}F-labelling mediated by DBU. **1a–1u**: bromodifluoroacetamides, **2a–2u**: trifluoroacetamides. RCCs estimated by radio-HPLC. Boc = *tert*-butoxycarbonyl.

introduction of a benzyl group into **1r** provided a threefold increase in RCC (*cf.* [^{18}F]**2f** *vs.* [^{18}F]**2r**) we decided to explore a protecting group strategy for the secondary amide substrates. However, much to our disappointment, *N*-Boc (*tert*-butoxycarbonyl) protection was not a viable solution for this purpose as it provided only marginal improvement, or even a reduction, in the RCC for [^{18}F]**2q** and [^{18}F]**2s**.

In an effort to improve the yields for this important class of compounds, the protocol was modified to include an ^{18}F-labelled ester as intermediate (Scheme 3).[15] Because of the basic radiofluorination reaction media, extensive hydrolysis was observed during the synthesis of ester [^{18}F]**4a** and the resulting RCC

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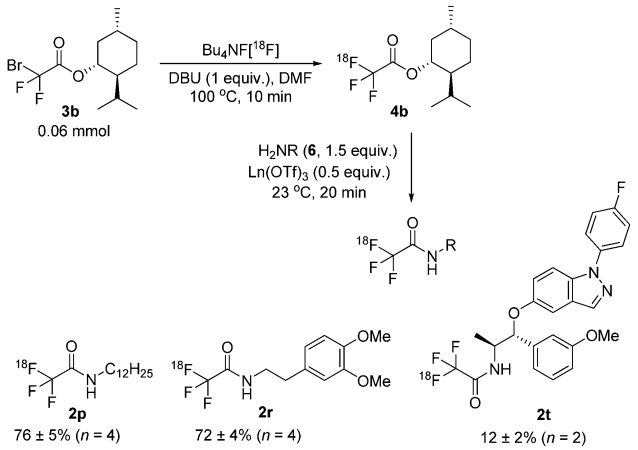
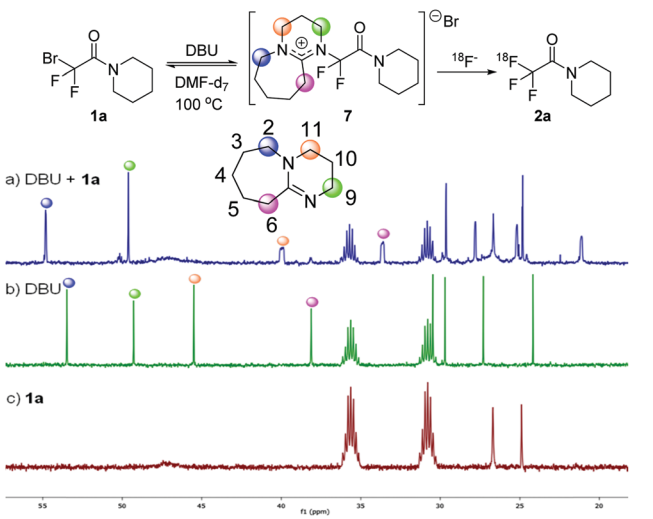


Scheme 3 Radiolabelling of [^{18}F]**4b** and derivatization to secondary amides. RCCs were estimated by radio-HPLC.

was only 2%. Gratifyingly, however, the more stable menthol ester [^{18}F]**4b** could be obtained in a 64% RCC and further converted, without intermediate purification, into the desired secondary amides [^{18}F]**2p** and [^{18}F]**2r** with high RCCs (76% and 72% respectively). To evaluate the utility of the current methodology for the labelling of druglike molecules it was applied to the ^{18}F-labelling of [^{18}F]**2t** (AZD5423), a nonsteroidal glucocorticoid agonist developed for the treatment of respiratory diseases.[12,16] Because [^{18}F]**2t** is a secondary amide, direct labelling in the presence of DBU proceeded with only a modest RCC (7%, Scheme 2) and starting from the *N*-Boc protected derivative **1u** failed. However, when using the above sequence (Scheme 3), with [^{18}F]**4b** as a key intermediate, we obtained the target molecule in a 12% RCC under non-optimized conditions.

In a preparative run, starting from 762 MBq of [^{18}F]Bu_4NF, [^{18}F]**2a** was isolated by semi-preparative HPLC in a 44% radiochemical yield (RCY, not corrected for decay) with a specific activity (S.A. = radioactivity per molar amount of product) of 0.10 GBq μmol^{-1}. Although an S.A. of 0.1 GBq μmol^{-1} is useful for PET microdosing studies, it is insufficient for examining drug-target engagement.[17] Accordingly, a more general application of the methodology for PET studies require an increase of the S.A of the product. In control experiments when [^{18}F]Bu_4NF was omitted from the reaction mixture, it was found that the formation of [^{19}F]**2a** was largely dependent on the amount of **1a** used in the reaction.[9] This indicates that ^{19}F from the CF_2Br group of **1a** assists in the formation of [^{19}F]**2a**, which lowers the S.A. of the product. This problem can be circumvented by lowering the concentration of **1a** in the reaction mixture. Indeed, by a 100-fold reduction in the amount of **1a** (from 60 to 0.6 μmol, see ESI†) and starting from 7.16 GBq of [^{18}F]Bu_4NF, [^{18}F]**2a** (284 MBq, 4% RCY) was obtained with an 84-fold improved specific radioactivity (8.4 GBq μmol^{-1}). Compared to literature examples,[7,11] this is a decent level of S.A. for a [^{18}F]CF_3 species, which inherently suffers from low S.A. Furthermore, since we observed that the formation of cold **2a** was unaffected by the radioactivity used in the reaction, the S.A. of [^{18}F]**2a** is expected to be proportional also to the starting radioactivity. Thus, we envisage that the S.A. could be easily increased further under automated conditions when a full cyclotron production may be used for the radiofluorination.[18] This would provide a product with a S.A. useful also for drug-target engagement studies. According to our studies neither the RCY nor the S.A. can be increased by increasing the amount of DBU (1 equiv.) in the reaction mixture.

A very interesting feature of the above study is the acceleration effect of DBU in the bromide-^{18}F exchange process (*cf.* Table 1 entries 4 and 13). In order to rationalize this effect, we monitored the reaction of **1a** with DBU using ^{13}C NMR spectroscopy (Scheme 4). The ^{13}C NMR spectra of DBU and isolated **1a** are given in Scheme 4b and c. When **1a** and DBU was mixed in DMF-d_7 and heated at 100 °C (simulating the reaction conditions according to Table 1, entry 4), the ^{13}C NMR signals of DBU underwent systematic changes (Scheme 4a). The signal at 46.5 ppm (assigned to C11) was shifted to 40.5 ppm and substantially broadened. The ^{13}C signal at 38.1 ppm (assigned to C6) also underwent a similar change shifting to 33.6 ppm. The shift of the ^{13}C NMR signals clearly shows that chemical environment of the above carbon atoms in DBU is significantly changed on addition of **1a**. Most probably DBU displaces the bromide of **1a** to form intermediate **7** (Scheme 4). The broadening of the shifts at 40.0 and 33.6 ppm may indicate C–F coupling and/or hindered rotation along the $C(F_2)$–N bond in **7**. The ^{13}C NMR spectrum of the mixture of DBU + **1a** (Scheme 4a) remained unchanged in the temperature range of 85–100 °C. When the reaction mixture of DBU + **1a** was cooled to room temperature intermediate **7** decomposed to DBU and **1a**. This indicates that formation of **7** is reversible[14] and its formation requires heating to at least to 85 °C. Based on the above, we suggest that DBU and CF_2Br precursors **1** form intermediates such as **7** prior to the reaction with [^{18}F]TBAF. In **7** two quaternary centers forms a strained $C(F_2)$–N bond, which is probably easier to cleave than the $C(F_2)$–Br bond. The behaviour of DBU as a nucleophilic catalyst is known in the literature.[14] However, this is the first study, when DBU is applied for mediating



Scheme 4 ^{13}C NMR studies for monitoring the formation of intermediate **7**. ^{13}C NMR spectra (125 MHz) at 100 °C in DMF-d_7. (a) DBU + **1a**. (b) DBU. (c) **1a**.

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the displacement of bromide from CF_2Br group and application for ^{18}F labelling.

In summary, we have shown for the first time that ^{18}F-labelled trifluoroacetamides can be efficiently synthesized from easily accessible CF_2Br derivatives and [^{18}F]TBAF in the presence of DBU (or analogues). The ^{18}F-labelled tertiary trifluoroacetamide products are typically formed with high RCC. For ^{18}F-labelling of secondary trifluoroacetamides, we propose a modified work-flow *via* synthesis of an ^{18}F-labelled ester reagent, which undergo transesterification with the corresponding amine. The radiosynthetic utility of the method was demonstrated by ^{18}F-labelling of the druglike substance [^{18}F]**2t** (AZD5423). The preparative scale experiments show that this method is suitable to produce ^{18}F-labelled trifluoroacetamides with sufficiently high specific activity for PET microdosing studies and with slight modification even for drug-target engagement studies (8.4 GBq μmol^{-1} for [^{18}F]**2a**). Mechanistic studies suggest that DBU has an activating effect on the displacement of bromide from the CF_2Br group of the precursor **1**. This study broadens the radiosynthetic scope of [^{18}F]CF_3 derivatives and assists in the development of new bromide to ^{18}F exchange methods where thermal activation or metal mediated transformations are unsuccessful.

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Notes and references

1 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (*c*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422; (*d*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637; (*e*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (*f*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422; (*g*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637.
2 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, 2008, **47**, 8998.
3 (*a*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (*b*) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (*c*) W. Kong, E. Merino and C. Nevado, *Chimia*, 2014, **68**, 430; (*d*) J. R. Wolstenhulme and V. Gouverneur, *Acc. Chem. Res.*, 2014, **47**, 3560; (*e*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214.
4 (*a*) K. Chansaenpak, B. Vabre and F. P. Gabbai, *Chem. Soc. Rev.*, 2016, **45**, 954; (*b*) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719; (*c*) C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3216.
5 M. Schou, K. Varnäs, S. Lundquist, R. Nakao, N. Amini, A. Takano, S. J. Finnema, C. Halldin and L. Farde, *Int. J. Neuropsychopharmacol.*, 2015, **18**, 10.
6 (*a*) K. Edman, R. Ahlgren, M. Bengtsson, H. Bladh, S. Bäckström, J. Dahmén, K. Henriksson, P. Hillertz, V. Hulikal, A. Jerre, L. Kinchin, C. Kåse, M. Lepistö, I. Mile, S. Nilsson, A. Smailagic, J. Taylor, A. Tjörnebo, L. Wissler and T. Hansson, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2571; (*b*) G. M. Gauvreau, L.-P. Boulet, R. Leigh, D. W. Cockcroft, K. J. Killian, B. E. Davis, F. Deschesnes, R. M. Watson, V. Swystun, C. K. Mårdh, P. Wessman, C. Jorup, M. Aurivillius and P. M. O'Byrne, *Am. J. Respir. Crit. Care Med.*, 2015, **191**, 161.
7 V. T. Lien and P. J. Riss, *BioMed Res. Int.*, 2014, **2014**, 10.
8 T. Rühl, W. Rafique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056.
9 M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941.
10 D. van der Born, C. Sewing, J. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru and D. J. Vugts, *Angew. Chem., Int. Ed.*, 2014, **53**, 11046.
11 (*a*) T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. Lee Collier and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2015, **54**, 9991; (*b*) S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell and V. Gouverneur, *Synlett*, 2016, 25.
12 P. Johnstrom and S. Stone-Elanderl, *J. Labelled Compd. Radiopharm.*, 1995, **36**, 537.
13 P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. – Eur. J.*, 2014, **20**, 9514.
14 J. E. Taylor, S. D. Bull and J. M. J. Williams, *Chem. Soc. Rev.*, 2012, **41**, 2109.
15 (*a*) H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki and T. Ohshima, *Org. Lett.*, 2014, **16**, 2018; (*b*) L. Wang, X.-J. Wei, W.-L. Jia, J.-J. Zhong, L.-Z. Wu and Q. Liu, *Org. Lett.*, 2014, **16**, 5842.
16 (*a*) M. Berger, D. Jan, A. Eriksson, B. Gabos, T. Hanson, M. Hemmerling, K. Henriksson, S. Ivanova, M. Lepisto, D. McKerrecher, M. Munck af Rosenschold, S. Nilsson, H. Rehwinkel and C. Taflin, WO2008/076048, 2008; (*b*) T. Eriksson and T. Hansson, WO2010/008341A1, 2010.
17 S. E. Lapi and M. J. Welch, *Nucl. Med. Biol.*, 2013, **40**, 314.
18 H. Shi, A. Braun, L. Wang, S. H. Liang, N. Vasdev and T. Ritter, *Angew. Chem., Int. Ed.*, 2016, **55**, 10786.

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