COMMUNICATION

Mn-Salen Catalysed Benzylic C-H Activation for the Synthesis of Aryl [^{18}F]CF $_3$ -containing PET probes

Cite this: DOI: 10.1039/x0xx00000x

L. Carroll,^a H. L. Evans,^a A. C. Spivey^b and E. O. Aboagye^a

Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The development of a Mn-salen complex catalysed oxidative benzylic fluorination of non-activated C-H bonds using [^{18}F]fluoride is described for installation of [^{18}F]CHRF, [^{18}F]CR $_2$ F and particularly [^{18}F]CF $_3$ containing groups in the presence of other functional groups.

PET is a non-invasive molecular imaging modality which allows the *in vivo* imaging of a variety of biological processes in patients. Of the leading PET radioisotopes currently available, fluorine-18 (^{18}F) is one of the most important, as evidenced by the numerous clinically-deployed ^{18}F radiotracers. These tracers include 2- [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), 3'-deoxy-3'- [^{18}F]fluorothymidine ([^{18}F]FLT) and [^{18}F]fluorodopa, which are widely used in the fields of oncology and neurology.^[1-4] While there has been an increase in the number of ^{18}F -containing pre-clinical radiotracers and new methods for the attachment of ^{18}F -containing prosthetic groups to target molecules, the initial incorporation of [^{18}F]fluoride is in most cases still achieved by classical nucleophilic substitution reactions (*i.e.*, via $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}\text{Ar}$ mechanisms). Recently however, protocols for the preparation of [^{18}F] aryl fluorides from aryl iodoniumsalts,^{[5],[6]} and by the use of Pd(IV) and Ni(II) complexes,^[7] [^{18}F]allylic fluorides by Pd-catalysed substitution, [^{18}F]4-fluorophenols by oxidative fluorination,^[8] and [^{18}F]trifluoromethyl aromatics catalysed by copper,^[9] have been described that bypass these traditional radiofluorination paradigms. Moreover, Groves *et al.* have very recently disclosed an appealing method for direct oxidative [^{18}F]fluorination at benzylic methylene C-H positions using [^{18}F]fluoride using a Mn(salen)OTs pre-catalyst.^[10-12] This report has prompted us to disclose a related procedure that we have developed and applied with particular success for the fluorination of aryl difluoromethyl compounds as an efficient approach to [^{18}F]labelled trifluoro aryl PET probes.

Selecting to work with Jacobsen-type pre-catalyst ($\pm$)-**1** and with iodosobenzene as stoichiometric oxidant due to their commercial availability, our initial objective was to define optimal conditions for the benzylic oxidative [^{18}F] fluorination of 1-ethylnaphthalene **2a** by [^{18}F] fluoride (Table 1).^[13]

Entry	Solvent	PhIO ^[c]	T/ $^{\circ}\text{C}$	Time	% RCI ^[d]
1	MeCN ^[a]	P	60	15	27
2	MeCN/MeOH ^[a]	P	60	30	trace
3	MeCN/ <i>t</i> -BuOH ^[a]	P	60	15	25
4	MeCN/DMF ^[a]	P	60	15	2
5	MeCN ^[b]	P	60	30	72
6	MeCN ^[b]	S	60	30	32
7	MeCN ^[b]	S	90	30	28
8 ^[c]	MeCN ^[b]	P	60	30	70

^[a][substrate] = 0.3 M; ^[b][substrate] = 0.1 M; ^[c]Method of PhIO addition, either P = in equal portions at 5 min intervals, N = None used or S = Single addition; ^[d]RCI = Radiochemical Incorporation, calculated from radio-HPLC analysis, n = 3 in each example; ^[e] Kryptofix 2.2.2. (K222) used instead of 18-c-6.

Table 1 – Optimisation of the oxidative [^{18}F] fluorination of 1-ethylnaphthalene **2a**.

A combination of different solvents, temperatures durations and protocols for addition of the PhIO were explored. Portion-wise addition of solid PhIO gave a promising radiochemical incorporation of 27% within 15 minutes (n = 3; entry 1). As PhIO is only sparingly soluble in most organic solvents, and full dissolution is critical for automated radiosynthesis, we explored the use of a co-solvent. Use of either MeOH or DMF as co-solvents (1:1 v/v) allowed complete dissolution of the

oxidant, but suppressed product formation (entries 2 and 4) whereas *t*-BuOH was ineffective as a co-solvent and gave identical levels of incorporation to when using MeCN alone (entry 3 *cf.* entry 1). Reverting to the use of just MeCN as solvent but with increased dilution (0.1 M *cf.* 0.3 M) we were pleased to observe that after a reaction time of 30 minutes 72% radiochemical incorporation could be achieved (entry 5). At this dilution, addition of the PhIO solution as a single portion gave 32% RCI after 30 min, which we considered adequate for compound labelling (entry 6). Increasing the temperature to 90 °C gave no discernible improvement in incorporation (entry 7) and replacement of 18-c-6 with Kryptofix® 2.2.2 (K222) had no significant influence on the level of RCI (entry 8).

Application of this reaction to several simple substrates was undertaken to delineate the scope of the method (Figure 1).

Figure 1 - Oxidative benzylic [^{18}F] fluorination of several different compounds using optimised labelling conditions, $n = 4$.

Successful labelling of compounds was achieved with moderate to good levels of incorporation in most cases. In general, secondary fluorides were introduced efficiently, whereas introduction at a primary position gave less than 5% RCI ([^{18}F]3c) and at a tertiary position gave a more promising 14% RCI ([^{18}F]3d). Site-selective labelling to give phenylalanine derivative [^{18}F]3e gave 49% RCI although no diastereoselectivity was observed.

Notwithstanding the attraction of installing a single fluorine atom site-selectively within a target molecule, labelling of CF_3 groups was of particular interest due to their occurrence in a number of pharmaceuticals and we anticipated that ^{18}F -labelling of a difluoromethyl group could be an attractive entry to labelled CF_3 units.¹⁴ The benzylic difluoromethyl containing precursors required for this approach are readily prepared by fluorodeoxygenation of benzaldehydes or by copper-catalysed difluoromethylation of aryl iodides using $\text{TMS-CF}_2\text{CO}_2\text{Et}$ (or $\text{TMS-CF}_2\text{H}$).^[15-17]

Ten benzylic difluoromethyl substrates also containing other potentially reactive functional groups (*i.e.* ether, aryl halide and carbamate groups) were investigated (Figure 2).

Figure 2 - ^{18}F Oxidative benzylic fluorination to give CF_3 - containing compounds, $n = 3$.

[^{18}F]Trifluoromethylbenzene ([^{18}F]3f) and its 4- and 2-brominated derivatives [^{18}F]3g and [^{18}F]3h were prepared in 27%, 44% and 54% RCYs respectively whereas the more electron deficient 4-nitro and 3-cyano derivatives [^{18}F]3i and [^{18}F]3j were much less efficiently labelled (1% and 8% RCI respectively). It appears therefore that although strongly electron withdrawing substituents deter [^{18}F]fluorine trapping of the presumed radical intermediate, bulky 2-substituents are tolerated. This is consistent with the successful formation of isomeric 2- and 4-substituted biaryls [^{18}F]3m and [^{18}F]3n and of 4- substituted biaryls [^{18}F]3k, [^{18}F]3l and [^{18}F]3o in 36%, 61%, 16%, 42% and 34% RCYs respectively.

Labelled bromophenyls [^{18}F]3g and [^{18}F]3h can also be deployed as prosthetic groups as illustrated by the preparation of biaryl [^{18}F]3k and [^{18}F]3j by Suzuki coupling (Scheme 1).

Scheme 1 – Synthesis of biaryls [^{18}F] 3k and 3o from [^{18}F]3g by Suzuki coupling, $n = 3$.

The specific radioactivity of a labelled probe, quantifies the amount of radioactivity relative to non-labelled material present, and constitutes an important property of the probe. For the synthesis of [^{18}F]3g, the specific activity was ~ 4 GBq/ μmol , starting from 190 MBq of starting [^{18}F]fluoride. This level of specific activity is ~ 10 fold greater than that reported by Huiban *et al.* for their [^{18}F]CF₃ labelling.^[9]

We also performed ICP-MS analysis on a purified sample of [^{18}F]3a which had been allowed to decay, and no manganese was detected (< 0.01 mg/l). Unlike Pd, which has a non-dietary limit of 100 $\mu\text{g/day}$ for a 50 Kg adult, Mn is essential for

various functions in the human body and a daily intake of 2.5 mg/day is recommended for a 50 Kg adult.^[18]

Mechanistically, we anticipate that the [¹⁸F]labelling reaction proceeds *via* essentially the same catalytic cycle as proposed by Liu and Groves for their ¹⁸F labelling using Mn(salen)OTs (Figure 5).^[11]

Figure 5 – Proposed catalytic cycle for the ¹⁸F-labelling reaction, and side-reaction to form alcohol by-products.

Thus, following initial Cl to OTf ligand exchange at Mn(III) effected by the AgOTf, [¹⁸F]fluoride is introduced *via* ligand exchange ($\rightarrow$ 4). Oxidation by PhIO then gives Mn(V) oxo species 5 which effects hydrogen atom abstraction from a benzylic position on the substrate concomitantly forming fluorohydroxy-manganese(IV) species 6 (X = ¹⁸F). This species then ‘rebounds’ the [¹⁸F]fluorine atom to the benzylic carbon centred radical to give the labelled product. Due to the low concentration of [¹⁸F]fluoride, hydroxide can presumably compete as a ligand at Mn giving *e.g.* the dihydroxymanganese(IV) intermediate 6 (X = OH), hydroxide radical ‘rebound’ from which would give alcohol side-products, as are observed in these reactions.

Conclusions

We have described a new method for radiolabelling *via* site-selective oxidative fluorination of benzylic difluoromethyl groups using [¹⁸F]fluoride to give aryl [¹⁸F]CF₃ compounds. The labelling reactions can be achieved without extensive investment in complex precursors and the straightforward experimental protocol holds promise for adaption to automated clinical PET probe production.

Acknowledgements

We thank Imanova Ltd. for [¹⁸F]fluoride and use of their radiochemistry facilities, Dr. Neil Bramall (University of Sheffield) for ICP analysis, and CRUK/EPSRC.MRC/DoH (England) for funding (grant C2536/A10337).

Notes and references

- ^a Comprehensive Cancer Imaging Centre, Department of Surgery and Cancer, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN; Email: l.carroll@imperial.ac.uk.
- ^b Department of Chemistry, Imperial College London, South Kensington Campus.
1. G. Smith, L. Carroll, and E. O. Aboagye, *Molecular Imaging and Biology*, 2012, **14**, 653-666.
2. P. W. Miller, N. L. Long, R. Vilar and A. D. Gee, *Angewandte Chemie International Edition*, 2008, **47**, 8998-9033.
3. E. O. Aboagye, *British Journal of Radiology*, 2010, **83**, 814-822.
4. S. Vallabhajosula, *Seminars in Nuclear Medicine*, 2007, 400-419.
5. V. W. Pike and F. I. Aigbirhio, *Journal of the Chemical Society, Chemical Communications* **1995**, 2215-2216.
6. T. L. Ross, J. Ermert, C. Hocke and H. H. Coenen, *Journal of the American Chemical Society* **2007**, **129**, 8018-8025.
7. C. Hollingworth, A. Hazari, M. N. Hopkinson, M. Tredwell, E. Benedetto, M. Huiban, A. D. Gee, J. M. Brown and V. Gouverneur, *Angewandte Chemie International Edition* **2011**, **50**, 2613-2617.
8. Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban and V. Gouverneur, *Angewandte Chemie International Edition* **2012**, **51**, 6733-6737.
9. M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nature Chemistry*, 2013, **5**, 941-944.
10. W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard and J. T. Groves, *Science*, 2012, **337**, 1322-1325.
11. W. Liu and J. T. Groves, *Angewandte Chemie International Edition*, 2013, **52**, 6024-6027.
12. X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker and J. T. Groves, *Journal of the American Chemical Society* **2014**, **136**, 6842-6845.
13. B. D. Brandes and E. N. Jacobsen, *The Journal of Organic Chemistry* **1994**, **59**, 4378-4380.
14. V. T. Lien and P. J. Riss, *BioMed Research International* **2014**, 2014.
15. L. N. Markovskij, V. E. Pashinnik and A. V. Kirsanov, *Synthesis* **1973**, 1973, 787-789.
16. Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *Journal of the American Chemical Society* **2012**, **134**, 1494-1497.
17. P. S. Fier and J. F. Hartwig, *Journal of the American Chemical Society* **2012**, **134**, 5524-5527.
18. EMA Guideline on the Specification Limits for Residues of Metal Catalysts EMEA/CHMP/SWP/4446/2000, 2008.