Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2018, **9**, 1168

Site-selective ^{18}F fluorination of unactivated C–H bonds mediated by a manganese porphyrin†

Wei Liu,[a] Xiongyi Huang,[a] Michael S. Placzek,[bc] Shane W. Krska,[d] Paul McQuade,[e] Jacob M. Hooker*[bc] and John T. Groves *[a]

Received 19th October 2017
Accepted 2nd December 2017

DOI: 10.1039/c7sc04545j

rsc.li/chemical-science

The first direct C–H ^{18}F fluorination reaction of unactivated aliphatic sites using no-carrier-added [^{18}F] fluoride is reported. Under the influence of a manganese porphyrin/iodosylbenzene system, a variety of unactivated aliphatic C–H bonds can be selectively converted to C–^{18}F bonds. The mild conditions, broad substrate scope and generally inaccessible regiochemistry make this radio-fluorination a powerful alternate to established nucleophilic substitution for the preparation of ^{18}F labeled radio tracers.

Introduction

Positron emission tomography (PET) is a noninvasive nuclear medicine imaging technique with clinical and research applications in diverse areas of medicine, notably in oncology, cardiology, neuroscience and in drug development.[1] Following administration of a radiolabeled bioactive molecule into a patient or research subject, PET can provide a quantitative time course of three-dimensional images stemming from molecular interactions *in vivo*. Among the commonly used PET radioisotopes, ^{18}F is the preferred radionuclide largely due to its suitable half-life (110 min) for synthesis and imaging.[2] Because of the importance of ^{18}F-containing radiotracers in clinical and research domains, much effort has been devoted to developing new strategies to introduce ^{18}F substituents into complex bioactive molecules.[3]

Despite the recent advances, current methods for incorporating an ^{18}F atom at C sp^3 positions are still dominated by traditional nucleophilic substitution of no-carrier-added ^{18}F fluoride with a precursor molecule, typically bearing a suitable leaving group such as an alkyl halide or sulfonate at the labeling site (Fig. 1a).[1b] One major drawback of this displacement approach is that the preparation of the precursor molecules usually requires multistep synthesis and the highly activated precursor are prone to degradation, for example through elimination of the leaving group. Accessibility of precursors, in fact, often hinders the development of a radiotracer in PET imaging for research applications.

A potential solution to issues related to pre-functionalization of labeling precursors would be to develop methods to directly and selectively convert C–H bonds to C–^{18}F bonds, thus obviating the complex precursor synthesis. This is feasible given the rapid growth of direct aliphatic C–H ^{19}F fluorination over the past three years (Fig. 1b). In 2012, Lectka *et al.* and our group independently developed methods that can directly convert

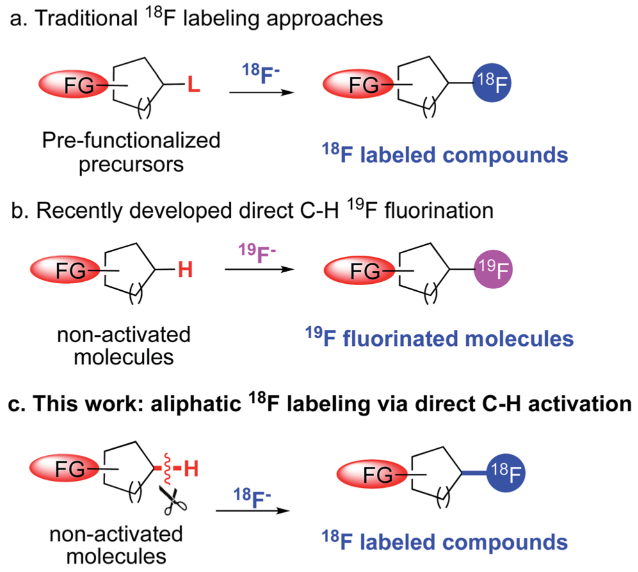


Fig. 1 (a) Traditional ^{18}F labeling methods rely on nucleophilic substitution of pre-functionalized precursors with ^{18}F fluorides. (b) Recent studies allow direct conversion of aliphatic C–H bonds to C–F with nucleophilic fluoride sources. (c) Current work enables ^{18}F labeling of aliphatic sites by direct C–H activation.

---

[a] *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, USA. E-mail: jtgroves@princeton.edu*

[b] *Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, USA. E-mail: hooker@nmr.mgh.harvard.edu*

[c] *Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA*

[d] *Department of Process Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, USA*

[e] *Imaging Research, Merck Research Laboratories, West Point, Pennsylvania 19486, USA*

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/c7sc04545j

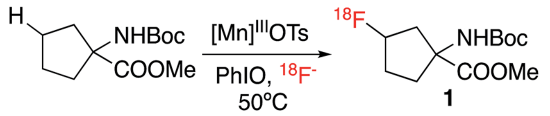
unactivated aliphatic C–H bonds to C–F bonds.[4] Whereas Lectka's system relies on radical-based chemistry between a copper(I) promoter and an electrophilic fluorination reagent, Selectfluor,[5] our method utilizes nucleophilic fluorides from AgF/TBAF as the sole fluorine source, in conjunction with a manganese porphyrin catalyst. Since then, a number of other elegant protocols have been reported that can selectively construct C sp^3–F bonds by means of C–H activation.[6] Whereas most of these newly developed fluorination methods utilize an electrophilic fluorine source, such as Selectfluor or NFSI, our Mn-based chemistry appears to be the only method that currently employs the fluoride ion, making it particularly suitable for ^{18}F labeling methods.

The transition from ^{19}F to ^{18}F chemistry is always challenging, due largely to the short half-life of ^{18}F, the requirement for short reaction time, the sub-stoichiometric concentrations of ^{18}F fluoride and the unique ^{18}F labeling conditions. As a result, the translation of promising fluorination reactions to radio-fluorination is often problematic. We have recently explored the value of a manganese salen catalyst for direct C–H ^{18}F labeling at benzylic positions,[7] which represents the first direct C sp^3–H bond ^{18}F labeling with no-carrier-added [^{18}F] fluoride. Despite this success, direct labeling of unactivated aliphatic sites with stronger C–H bonds remained a challenge. In addition, there were no general methods that can incorporate ^{18}F at tertiary carbon positions, since the traditional displacement approach usually leads to significant desaturation side reactions.[8] Given these limitations, we sought to develop a more general method that can directly label unactivated aliphatic C–H bonds with [^{18}F]fluoride. Radiolabeled alkyl fluorides are ubiquitous as PET tracers and incorporation of ^{18}F at these positions hold promise to increase the metabolic stability of the target molecules, as the labeling positions are likely the sites of phase I metabolism by cytochrome P450 enzymes. In this context, we report herein a manganese porphyrin mediated ^{18}F labeling strategy that can selectively replace an unactivated aliphatic sp^3 hydrogen with an ^{18}F atom. The resulting products can be used for the synthesis of labeled molecules suitable for PET imaging.

Results and discussion

We chose Boc-protected 1-amino-cyclopentane-carboxylic acid methyl ester (Boc-ACPC-OMe) as a lead substrate for direct C–H ^{18}F labeling. Fluorinated derivatives of this unnatural amino acid, 3- and 2-FACPC, target amino acid transporters and have shown uptake into brain tumors, but their preparation requires multi-step syntheses.[9] After extensive screening, we found that a manganese(III)pentafluorophenyl porphyrin coordinated with a tosyl ligand, Mn(TPFPP)OTs, was the optimal catalyst. With Mn(TPFPP)OTs in conjunction with iodosylbenzene as the terminal oxidant, Boc-ACPC-OMe could be labeled efficiently with ^{18}F to form 3-fluoro-Boc-ACPC-OMe (**1**) exclusively. As is illustrated in Table 1, various tosyl coordinated manganese(III) porphyrins and salen complexes were evaluated. Employment of the manganese salen complex, which effects selective benzylic C–H ^{18}F labeling,[7] afforded only trace amounts of aliphatic labeling product **1**. Apparently, the intermediate O=Mn^V (salen) species is either not reactive enough or too fleeting to abstract strong aliphatic C–H bonds effectively. We then turned our attention to different manganese porphyrin complexes, as they are efficient catalysts for aliphatic C–H halogenations.[4b,10] Although Mn(TMP)OTs afforded only moderate radiochemical conversions, introducing electron-withdrawing *meso*-substituents into the porphyrin ring significantly increased the labeling efficiency, with Mn(TPFPP)OTs affording an RCC of 32%. After optimizing the solvent and oxidant loading, we found that protected 3-[^{18}F]-FACPC could be prepared in an acetone/acetonitrile solution with radiochemical conversions up to 48% within only 10 minutes.

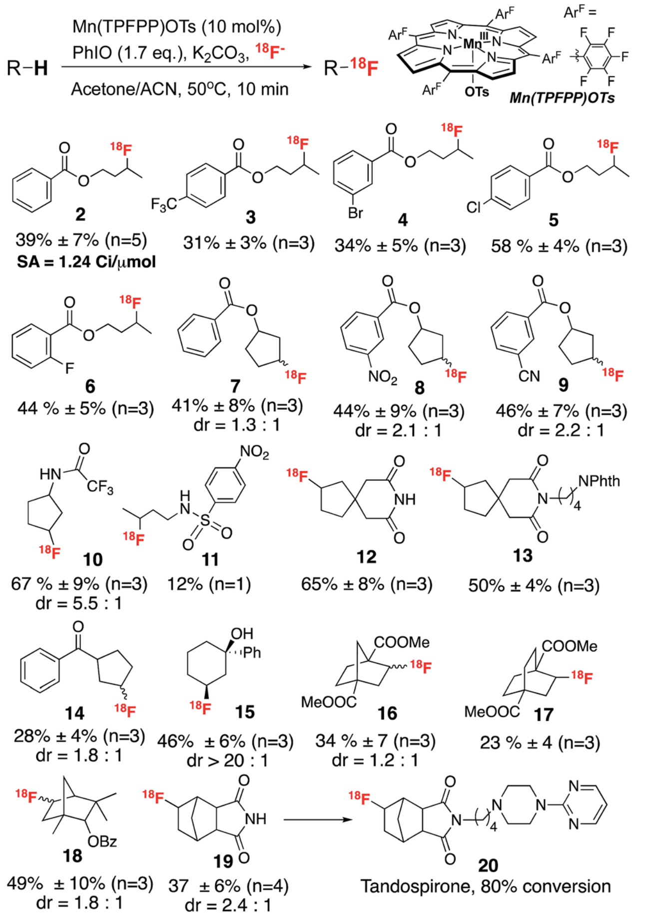
Table 1 Reaction optimizations of direct aliphatic C–H ^{18}F fluorination of Boc-ACPC-OMe[a]



L[b]	Solvents	PhIO	RCC[c] %
Salen	Acetone	1.1 eq.	Trace
TMP	Acetone	1.1 eq.	6 ± 2
TDClP	Acetone	1.1 eq.	24 ± 4
TDFPP	Acetone	1.1 eq.	31 ± 2
TPFPP	Acetone	1.1 eq.	32 ± 5
TPFPP	CH_3CN	1.1 eq.	36 ± 4
TPFPP	2 : 1 CH_3CN/acetone	1.1 eq.	38 ± 2
TPFPP	2 : 1 CH_3CN/acetone	1.7 eq.	48 ± 3

[a] Reactions were run with ~200 μCi ^{18}F fluoride. [b] Salen = Jacobsen's catalyst, TMP = tetramesitylporphyrin, TDClP = tetrakis(2,6-dichlorophenyl)porphyrin, TDFPP = tetrakis(2,6-difluorophenyl) porphyrin, TPFPP = tetrakis(pentafluorophenyl)porphyrin. [c] The radiochemical conversion (RCC%) is calculated by integration of radio-peaks from TLC and HPLC analysis of reaction mixtures; average of at least three experiments.

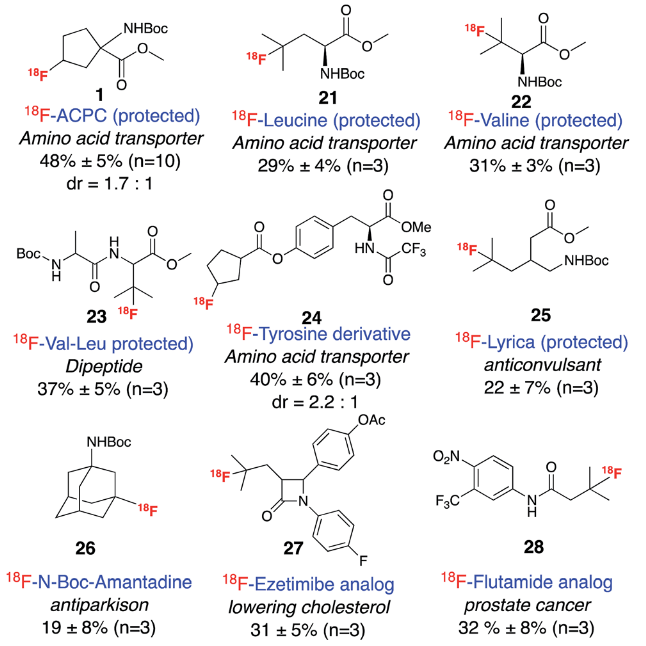
Using the optimized conditions, we then investigated the substrate scope of this direct aliphatic ^{18}F labeling reaction. A variety of small molecules bearing multiple unactivated C sp^3–H bonds were efficiently labeled with radiochemical conversions ranging from 12% to 67% (Scheme 1). Common functional groups, such as esters, amides and alcohols were well tolerated in this initial assessment. The labeling usually occurs at the least sterically hindered and most electron rich methylene or methine positions. For example, labeling of a series of substituted butyl benzoates (**2–6**) occurred mainly at the methylene positions remote from the electron-withdrawing benzoate group. In addition, substituted five-membered ring compounds (**7–10**, **12–14**) afforded C3 labeled fluoride as the major products, probably due to a stereoelectronic effect. Notably, labeling of 1-phenylcyclohexanol (**15**) resulted in ^{18}F incorporation exclusively at the positions *cis* to the hydroxyl group, suggesting the involvement of a directive effect in the fluorine transfer step, similar to that observed in the analogous Mn–^{19}F fluorination reaction.[4b] Moreover, this labeling protocol can be used to prepare radiolabeled drug precursors, which can



Scheme 1 Substrate scope of the Mn-mediated aliphatic C–H ^{18}F fluorination. Reactions were run with ~400 μCi ^{18}F fluoride.

then be converted to the ^{18}F labeled drug analog. For example, [^{18}F]fluorotandospirone (**20**), which targets the 5-HT neurotransmitter system,[11] was prepared *via* a two-step protocol in an overall 30% RCC. The specific activity of compound **2** was calculated to be 1.24 Ci μmol^{-1} (end of bombardment), which meets the imaging requirements for fluorine-18 labeling reactions.

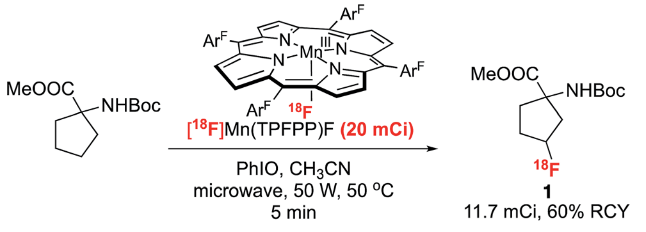
In order to demonstrate the utility of this method for late-stage radio-fluorination, we applied the reaction conditions to a variety of bioactive molecules (Scheme 2). ^{18}F-labeled natural and unnatural amino acids are an important class of imaging agents for PET that target the increased rates of amino acid transport by many tumor cells.[12] We anticipated that a direct fluorination method could significantly accelerate the development of amino acid based PET tracers. Although direct fluorination of leucine and valine have recently been achieved using electrophilic fluorine sources, Selectfluor or NFSI,[13] we were surprised to find that ^{18}F labeled leucine or valine analogs have never been reported, apparently due to the synthetic inaccessibility of their corresponding precursors. Gratifyingly, subjection of the protected analogues of these two amino acids to our standard labeling conditions afforded exclusively tertiary carbon-labeled compounds **21** and **22** with RCCs of 29% and 31%, respectively. Tertiary selectively was also observed for the labeling of a leucine containing dipeptide complex, Boc-Val-Leu-OMe, **23**. In addition, ^{18}F labeled tyrosine analogs, such as 2-[^{18}F]-fluoro-L-tyrosine (FTYR) and *O*-(2′-[^{18}F]fluoroethyl)-L-tyrosine (FET), are also promising tracers for brain imaging.[14] Under our standard labeling reaction, a cyclopentane carboxylic ester derivative of tyrosine afforded the aliphatic ring labeled product **24** with an RCC of 40%. We anticipate that these compounds could have potential as tracers for amino acid transporter imaging.



Scheme 2 Selective radio-fluorination of bioactive molecules. Reactions were run with ~400 μCi ^{18}F fluoride.

Another important application of PET imaging is in the area of pharmacokinetics as a noninvasive method for determining drug distribution and action.[15] Thus, an efficient method for introducing ^{18}F on a pre-existing drug motif may prove very useful in medicinal chemistry. In this context, several important drug molecules have been subjected to our standard labeling conditions. Radiolabeling of pregabalin, an anticonvulsant drug that has been commercialized by Pfizer under the trade name Lyrica,[16] afforded mainly tertiary-labeled product **25**. Analogs of flutamide,[17] a prostate cancer drug, and ezetimibe, a cholesterol lowering drug, were both labeled efficiently at the tertiary positions, producing **27** and **28**. Radio-fluorination of amantadine, an antiviral and anti-Parkinson disease drug, afforded mostly the tertiary product **26** with secondary labeled compounds as minor side products, which were easily separated by semi-preparative HPLC. The separation of these regioisomers offers the potential for rapid testing of imaging properties of labeled analogs from a single late-stage synthetic product.

Finally, we have successfully translated this ^{18}F-labeling reaction into a reliable and reproducible protocol that can afford radiolabeled molecules on a scale suitable for animal studies. The scale up of the labeling reaction was achieved by



Scheme 3 Scale-up synthesis of 3-[^{18}F]-FACPC.

using a microwave-assisted "dry-down free" process. In this protocol, [^{18}F]fluoride captured on an anion exchange cartridge was eluted using an acetone/acetonitrile solution of Mn^{III}(TPFPP)OTs with over 90% elution efficiency of the ^{18}F fluoride. Radiolabeling of protected FACPC to afford 3-[^{18}F]-FACPC was accomplished within 10 min using the eluted Mn(TPFPP)^{18}F solution in conjunction with the terminal oxidant, PhIO, with microwave irradiation. Starting with 20 mCi ^{18}F^{-}, we were able to complete the synthesis within 45 min and isolate 11.7 mCi 3-[^{18}F]-FACPC as the final labeling product, with an overall 60% non-decay-corrected radio chemical yield (Scheme 3 and ESI† for details).

Conclusions

We have developed a direct aliphatic C–H ^{18}F labeling method using non-carrier-added [^{18}F]fluoride that is suitable for inaccessible and unreactive sites. The value of this transformation has been highlighted *via* the radio-fluorination of biologically active molecules without the need for pre-activation. Our future investigation will focus on developing PET tracers using this methodology and applying them for animal and human studies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the US National Science Foundation award CHE-1464578 (J. T. G.) and in part by the Center for Catalytic Hydrocarbon Functionalization, an Energy Frontier Research Center, U.S. Department of Energy, Office of Science, Basic Energy Sciences, under Award No. DE SC0001298 (J. T. G.). Portions of this research were carried out by W. L. and X.H. at the Merck Research Laboratories, Rahway, NJ and the Martinos Center for Biomedical Imaging using resources provided by the Center for Functional Neuroimaging Technologies, P41EB015896, and shared instrumentation grants S10RR017208 and S10RR023452. We also thank Dr Hong Ren for assistance on the radiochemistry.

Notes and references

1 (*a*) M. E. Phelps, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 9226–9233; (*b*) S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501–1516.

2 M. Tredwell and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2012, **51**, 11426–11437.

3 (*a*) T. L. Ross, J. Ermert, C. Hocke and H. H. Coenen, *J. Am. Chem. Soc.*, 2007, **129**, 8018–8025; (*b*) C. Hollingworth, A. Hazari, M. N. Hopkinson, M. Tredwell, E. Benedetto, M. Huiban, A. D. Gee, J. M. Brown and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2011, **50**, 2613–2617; (*c*) Z. H. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2012, **51**, 6733–6737; (*d*) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, **334**, 639–642; (*e*) E. Lee, J. M. Hooker and T. Ritter, *J. Am. Chem. Soc.*, 2012, **134**, 17456–17458; (*f*) M. Huiban, M. Tredwell, S. Mizuta, Z. H. Wan, X. M. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941–944; (*g*) T. J. A. Graham, R. F. Lambert, K. Ploessl, H. F. Kung and A. G. Doyle, *J. Am. Chem. Soc.*, 2014, **136**, 5291–5294; (*h*) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766; (*i*) F. Buckingham and V. Gouverneur, *Chem. Sci.*, 2016, **7**, 1645–1652; (*j*) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2014, **16**, 3224–3227; (*k*) S. H. Liang and N. Vasdev, *Angew. Chem., Int. Ed.*, 2014, **53**, 11416–11418; (*l*) G. Tarantino, L. Botti, N. Dimitratos and C. Hammond, *RSC Adv.*, 2017, **7**, 30185–30190; (*m*) M. S. McCammant, S. Thompson, A. F. Brooks, S. W. Krska, P. J. H. Scott and M. S. Sanford, *Org. Lett.*, 2017, **19**, 3939–3942; (*n*) M. D. Levin, T. Q. Chen, M. E. Neubig, C. M. Hong, C. A. Theulier, I. J. Kobylianskii, M. Janabi, J. P. O'Neil and F. D. Toste, *Science*, 2017, **356**, 1272–1275; (*o*) M. G. Campbell, J. Mercier, C. Genicot, V. Gouverneur, J. M. Hooker and T. Ritter, *Nat. Chem.*, 2017, **9**, 1–3; (*p*) M. S. Sanford and P. J. H. Scott, *ACS Cent. Sci.*, 2016, **2**, 128–130; (*q*) C. N. N. Eumann, J. M. Hooker and T. Ritter, *Nature*, 2016, **534**, 369–373; (*r*) M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612–633.

4 (*a*) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim and T. Lectka, *Angew. Chem., Int. Ed.*, 2012, **51**, 10580–10583; (*b*) W. Liu, X. Y. Huang, M. J. Cheng, R. J. Nielsen, W. A. Goddard and J. T. Groves, *Science*, 2012, **337**, 1322–1325; (*c*) X. Huang and J. T. Groves, *J. Biol. Inorg Chem.*, 2017, **22**, 185–207; (*d*) W. Liu and J. T. Groves, *Acc. Chem. Res.*, 2015, **48**, 1727–1735; (*e*) C. R. Pitts, D. D. Bume, S. A. Harry, M. A. Siegler and T. Lectka, *J. Am. Chem. Soc.*, 2017, **139**, 2208–2211.

5 C. R. Pitts, S. Bloom, R. Woltornist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler and T. Lectka, *J. Am. Chem. Soc.*, 2014, **136**, 9780–9791.

6 (*a*) Y. Amaoka, M. Nagatomo and M. Inoue, *Org. Lett.*, 2013, **15**, 2160–2163; (*b*) S. Bloom, C. R. Pitts, R. Woltornist, A. Griswold, M. G. Holl and T. Lectka, *Org. Lett.*, 2013, **15**, 1722–1724; (*c*) S. Bloom, S. A. Sharber, M. G. Holl, J. L. Knippel and T. Lectka, *J. Org. Chem.*, 2013, **78**, 11082–11086; (*d*) M. G. Braun and A. G. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 12990–12993; (*e*) W. Liu and J. T. Groves, *Angew. Chem., Int. Ed.*, 2013, **52**, 6024–6027; (*f*) W. Liu, X. Y. Huang and J. T. Groves, *Nat. Protoc.*, 2013, **8**, 2348–2354; (*g*) J. B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494–17500; (*h*) S. Bloom, J. L. Knippel and T. Lectka, *Chem. Sci.*, 2014, **5**, 1175–1178; (*i*) S. Bloom, M. McCann and T. Lectka, *Org. Lett.*, 2014, **16**, 6338–6341; (*j*) C. W. Kee, K. F. Chin, M. W. Wong and C. H. Tan, *Chem. Commun.*, 2014, **50**, 8211–8214; (*k*) J. B. Xia, Y. Ma and C. Chen, *Org. Chem. Front.*, 2014, **1**, 468–472; (*l*) P. Xu, S. Guo, L. Y. Wang and P. P. Tang, *Angew. Chem., Int. Ed.*, 2014, **53**, 5955–5958; (*m*) J. M. Miao, K. Yang, M. Kurek and H. B. Ge, *Org. Lett.*, 2015, **17**, 3738–3741; (*n*) Q. Zhang, X. S. Yin, K. Chen, S. Q. Zhang and B. F. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 8219–8226; (*o*) R. Y. Zhu, K. Tanaka, G. C. Li, J. He, H. Y. Fu, S. H. Li and J. Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 7067–7070; (*p*) X. Y. Huang, W. Liu, J. M. Hooker and J. T. Groves, *Angew. Chem., Int. Ed.*, 2015, **54**, 5241–5245.

7 X. Y. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker and J. T. Groves, *J. Am. Chem. Soc.*, 2014, **136**, 6842–6845.

8 T. Nishikata, S. Ishida and R. Fujimoto, *Angew. Chem., Int. Ed.*, 2016, **55**, 10008–10012.

9 N. Jarkas, R. J. Voll, L. Williams, V. M. Camp and M. M. Goodman, *J. Med. Chem.*, 2010, **53**, 6603–6607.

10 W. Liu and J. T. Groves, *J. Am. Chem. Soc.*, 2010, **132**, 12847–12849.

11 S. Endo, *CNS Drugs*, 1996, **5**, 154.

12 (*a*) J. McConathy, L. Martarello, E. J. Malveaux, V. M. Camp, N. E. Simpson, C. P. Simpson, G. D. Bowers, J. J. Olson and M. M. Goodman, *J. Med. Chem.*, 2002, **45**, 2240–2249; (*b*) N. Galldiks and K. J. Langen, *The quarterly journal of nuclear medicine and molecular imaging: official publication of the Italian Association of Nuclear Medicine*, 2014.

13 S. D. Halperin, D. Kwon, M. Holmes, E. L. Regalado, L. C. Campeau, D. A. DiRocco and R. Britton, *Org. Lett.*, 2015, **17**, 5200–5203.

14 L. M. Wang, W. C. Qu, B. Lieberman, K. Ploessl and H. F. Kung, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3482–3485.

15 A. J. Fischman, N. M. Alpert and R. H. Rubin, *Clin. Pharmacokinet.*, 2002, **41**, 581–602.

16 R. H. Dworkin and P. Kirkpatrick, *Nat. Rev. Drug Discovery*, 2005, **4**, 455–456.

17 J. W. Baker, G. L. Bachman, I. Schumach, D. P. Roman and A. L. Tharp, *J. Med. Chem.*, 1967, **10**, 93–95.