A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Site-selective Late-Stage Aromatic 18F-Fluorination via Aryl Sulfonium Salts

Authors: Tobias Ritter, Peng Xu, Da Zhao, Florian Berger, Aboubakr Hamad, Jens Rickmeier, Roland Petzold, Mykhailo Kondratiuk, and Kostiantyn Bohdan

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201912567
Angew. Chem. 10.1002/ange.201912567

Link to VoR: http://dx.doi.org/10.1002/anie.201912567
http://dx.doi.org/10.1002/ange.201912567

WILEY-VCH

10.1002/anie.201912567

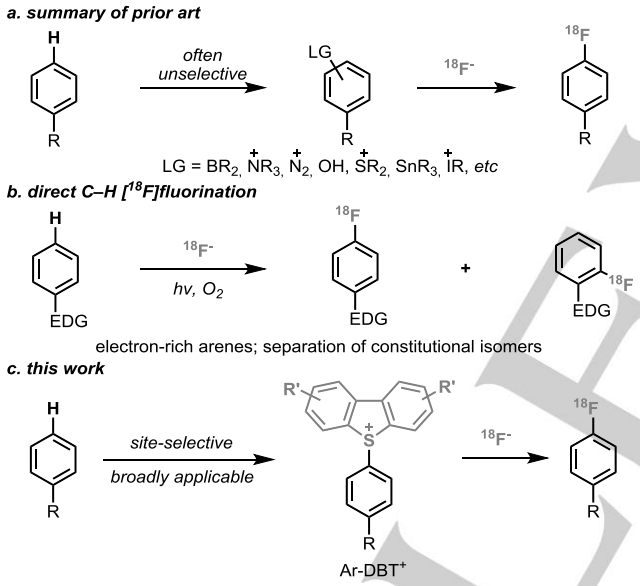
WILEY-VCH

Site-selective Late-Stage Aromatic ^{18}F-Fluorination via Aryl Sulfonium Salts

Peng Xu‡, Da Zhao‡, Florian Berger, Aboubakr Hamad, Jens Rickmeier, Roland Petzold, Mykhailo Kondratiuk, Kostiantyn Bohdan, and Tobias Ritter*

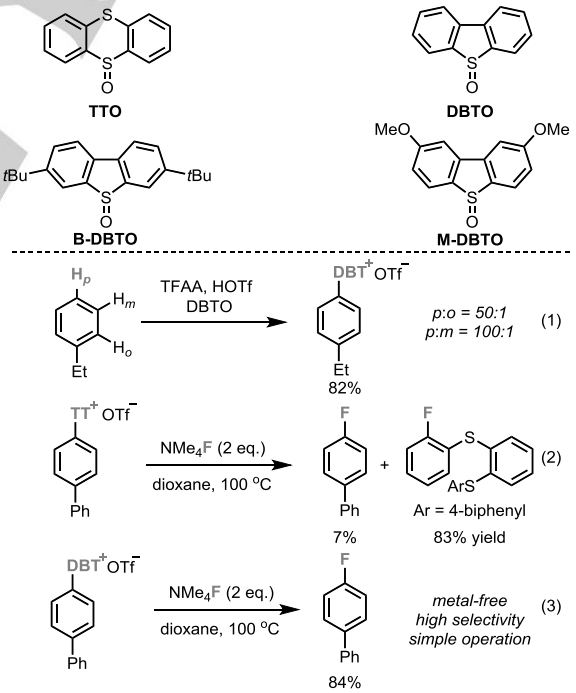
Abstract: Site-selective functionalization of C–H bonds in small complex molecules is a long-standing challenge in organic chemistry. Herein, we report a broadly-applicable and site-selective aromatic C–H dibenzothiophenylation reaction. The conceptual advantage of this transformation is further demonstrated through the two-step C–H ^{18}F-fluorination of a series of marketed small-molecule drugs.

Over the past ten years, several promising new methods for the introduction of the ^{18}F nucleus into small molecules have been disclosed, with the aim of impacting clinical care and drug discovery through ^{18}F positron-emission tomography (PET).[1,2]



Scheme 1. Strategies for aromatic C–^{18}F bond formation.

Yet, the implementation and translation to hospital settings is challenging, if the fluorination reactions are operationally complex.[3,4] Unfortunately, introduction of conventional leaving groups that can directly provide aryl fluorides upon reaction with fluoride cannot currently be accomplished at a late-stage, so the requirement of *de-novo* syntheses slows down PET tracer development (Scheme 1a). Direct C–H fluorination in this regard is promising but selectivity becomes a substantial concern in every direct C–H functionalization reaction, especially for PET tracer synthesis because even small quantities of constitutional isomers must be separated (Scheme 1b).[5] There are only few highly regioselective arene C–H functionalization reactions, and all of them either require suitable substitution patterns,[6a,d] directing groups,[6b,c] or afford functional groups that are not suitable for ^{18}F fluorination.[6e] Here we report a highly selective and late-stage C–H functionalization to afford aryl dibenzothiophenium salts, which can be converted to [^{18}F]Ar–F in a straightforward nucleophilic aromatic substitution reaction simply by adding fluoride (Scheme 1c). The C–H dibenzothiophenylation reaction developed herein can proceed in high selectivity for both small complex molecules and simple monosubstituted arenes to afford aryl dibenzothiophenium salts. Given the high selectivity and the operational simplicity, the two-step protocol to quickly access [^{18}F]Ar–F by arene C–H functionalization bodes well to accelerate ^{18}F PET development.



Scheme 2. Synthesis and fluorination of aryl sulfonium salts (TTO = thianthrene *S*-oxide; DBTO = dibenzothiophene *S*-oxide; B-DBTO = 3,7-di-*tert*-butyldibenzothiophene *S*-oxide; M-DBTO = 2,8-dimethoxydibenzothiophene *S*-oxide).

Some of the modern ^{18}F fluorination reactions are starting to have an impact on the synthesis of structurally complex ^{18}F-labeled small molecules that cannot be made by conventional nucleophilic aromatic substitution.[7] Most notably, practical ^{18}F-fluorodemetallation reactions mediated by copper that proceed on a large variety of small molecules have been developed by

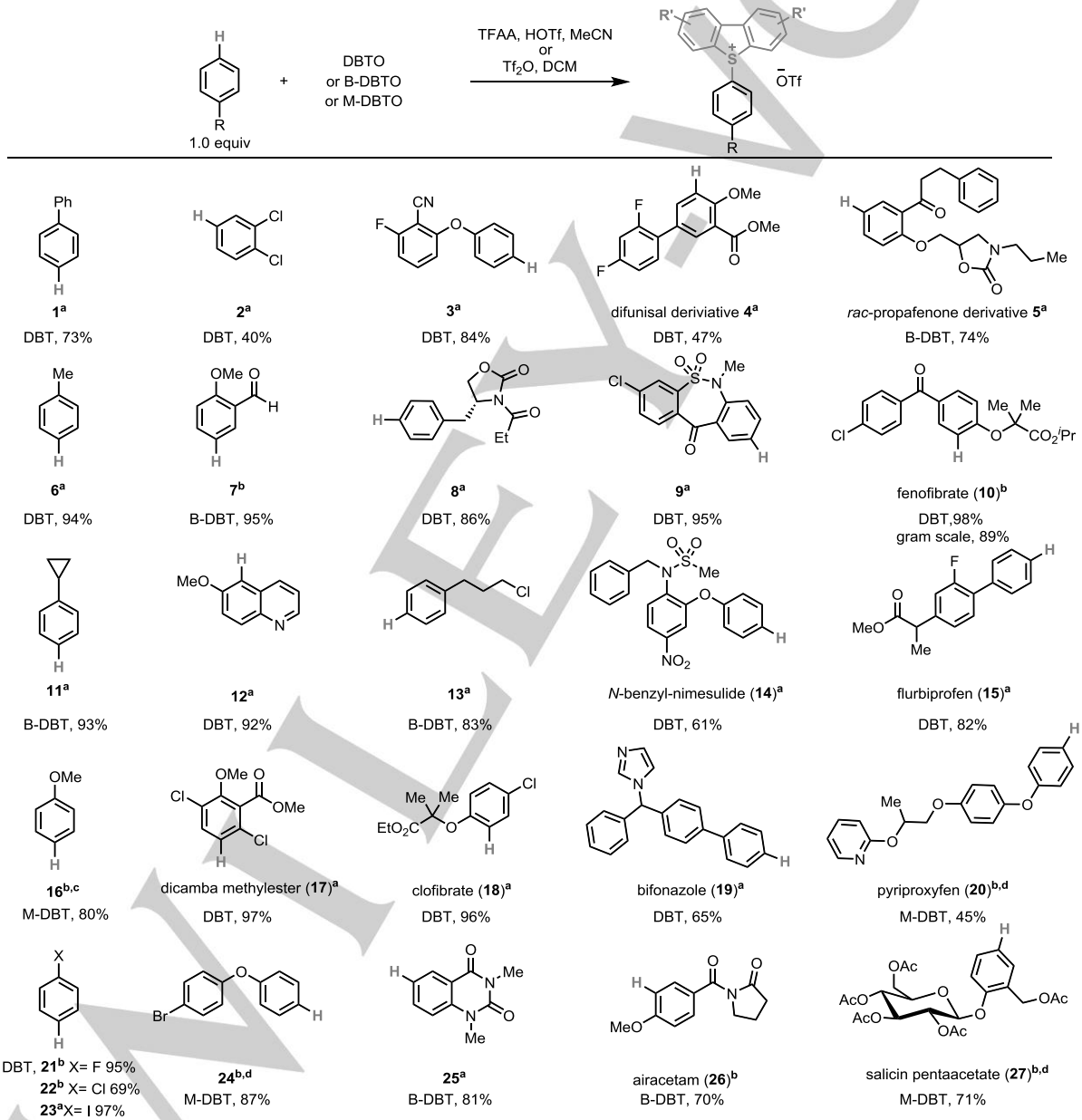
[a] Dr. P. Xu, Dr. D. Zhao, Dr. F. Berger, A. Hamad, Dr. J. Rickmeier, R. Petzold, M. Kondratiuk, K. Bohdan, and Prof. Dr. T. Ritter.
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: ritter@mpi-muelheim.mpg.de
[‡] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

Gouverneur[7c] as well as Sanford and Scott[7f,h], and Neumaier[7d]. Our group reported deoxyfluorination reactions[7g,i] that in addition can also functionalize small peptides.[7l] Sanford and Scott described a Cu-mediated, two-step ^{18}F-fluorination of electron-rich arenes via hypervalent iodine compounds.[7j] Nicewicz and Li have developed a promising C–H to C–^{18}F fluorination reaction that does not require coordination directing groups, enabled by laser-photoredox catalysis.[5d] None of the useful functional groups for F-18 introduction can currently be introduced selectively in a late-stage in a general sense. Direct ^{18}F-fluorination is desirable, but control of regioselectivity is challenging.

Aryl sulfonium salts are good precursors for ^{18}F-labeling of arenes.[8] Årstad demonstrated that dibenzothiophene sulfonium salts can be efficiently converted to ^{18}F-labeled arenes for electron-poor and -neutral substrates including several valuable PET tracers.[8d] However, previous methods for the preparation of aryl sulfonium salts often require aryl Grignard reagents, multiple step syntheses from aryl halides or strong acids as co-solvents, none of which are suitable for site-selective late-stage

Table 1. Site-selective aromatic C–H dibenzothiophenylation.



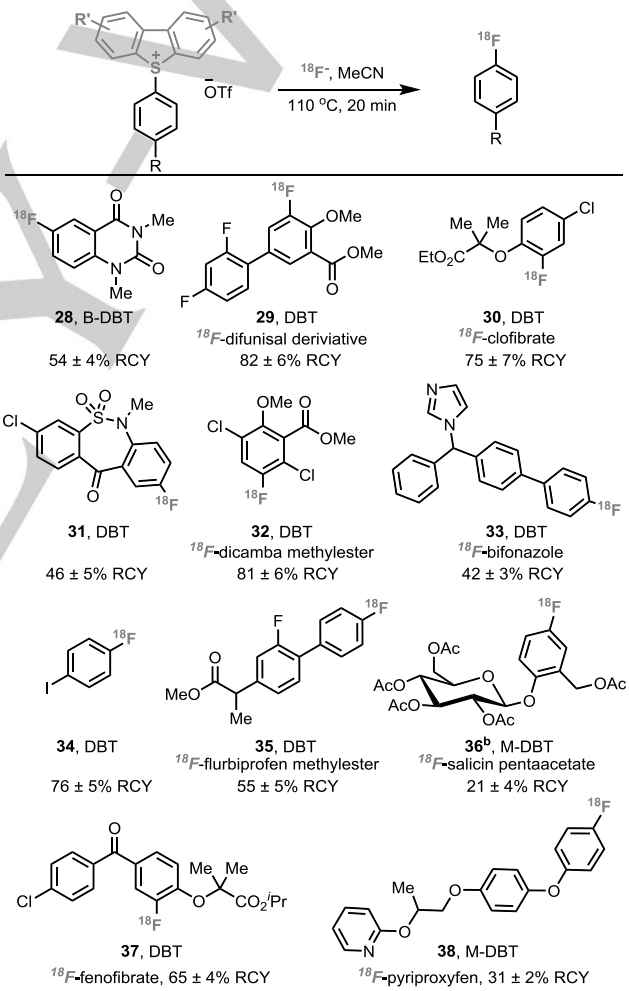
(a) Reaction condition A: 0.500 mmol arene, 2.00 to 4.00 equiv. triflic acid (HOTf), 3.00 equiv. trifluoroacetic anhydride (TFAA) and 1.50 to 2.00 equiv. DBTO or B-DBTO in MeCN (2.0 mL, c = 0.25 M), –40 °C to 25 °C. (b) Reaction condition B: 0.500 mmol arene, 1.50 to 2.00 equiv. DBTO, B-DBTO or M-DBTO in DCM (2.0 mL, c = 0.25 M), 1.50 to 2.00 equiv. triflic anhydride (Tf_2O), –40 °C to 25 °C. (c) 3.00 equiv. methanesulfonic anhydride instead of Tf_2O, and reaction performed at 0 °C to 25 °C. (d) 2.00 equiv. K_2CO_3 was added, and reaction performed at –78 °C to 25 °C.

incorporation.[8,9] Our previous approach via selective C–H thianthrenation[10] can also access aryl fluorides but requires an iridium-catalyzed photoredox protocol,[11] which adds additional challenges for implementation at good manufacturing practice (GMP) production facilities in radiopharmacies. Here we report a second highly selective arene C–H functionalization reaction, which differs conceptually from thianthrenation in that it can provide aryl sulfonium salts that can engage directly in C–F bond formation, simply by addition of fluoride. Furthermore, we show how a group of three electronically different dibenzothiophenes designed for ^{18}F fluorination can markedly expand the substrate scope compared to previous reported ^{18}F-fluorination of arylsulfoniums.[8]

Essential for the success of a site-selective late-stage ^{18}F-labeling method is the availability of a practical and general protocol to produce the precursors from readily available starting materials. We found that, in the presence of acid anhydrides as activators,[12] reaction of bench-stable dibenzothiophene *S*-oxide with ethylbenzene afforded the corresponding dibenzothiophenium salt with high positional selectivity (*p*:*o* = 50:1; *p*:*m* = 100:1; Scheme 2). In contrast to previously reported arylthianthrenium salts, aryl dibenzothiophenium salts can provide aryl fluoride directly. For example, treatment of biphenyl-derived dibenzothiophenium salt with fluoride afforded the aryl fluoride in 84% isolated yield, yet the corresponding thianthrenium salt gave the desired product in only 7% yield with the wrong C–S cleavage product as the major side-product (Scheme 2). The site-selective C–H functionalization reaction developed herein exhibits broad substrate scope (Table 1). Both electron-poor (**2**, **21**-**23**) and electron-rich arenes (**16**, **24**, **27**) proceed efficiently with high regioselectivity. Various functional groups are well tolerated, including halides (**2**, **21**-**24**), nitriles (**3**), ethers (**4**-**5**, **20**), esters (**4**, **10**, **15**), ketones (**5**), aldehydes (**7**), amides (**5**, **8**, **25**) and sulfonamides (**9**, **14**). Heterocycles such as quinolines (**12**), imidazoles (**19**), and pyridines (**20**) are also compatible. Arenes that are more electron-deficient than 1,2-dichlorobenzene are too electron-poor to react. The utility of our method for site-selective late-stage aromatic C–H functionalization is further demonstrated by the reactions of small complex substrates, drugs, agrochemicals and natural products. For example, the dibenzothiophenium salt of fenofibrate (**10**) was obtained in 89% isolated yield on gram scale. For all the substrates shown in Table 1, analytically pure compounds can be obtained by simple chromatography on silica gel.

As depicted in Scheme 1, three differently substituted dibenzothiophene *S*-oxides display similar high site-selectivity under otherwise identical reaction conditions. For unsymmetrical triaryl sulfonium salts, the S_NAr reaction occurs preferentially at the most electron-deficient arene.[8,13], As such, an electron-rich dibenzothiophen such as M-DBT should provide high selectivity for the desired arene fluorination. However, M-DBT is less reactive than more electron-deficient dibenzothiophenes such as DBT, and cannot be used to efficiently C-H functionalize less electron-rich arenes. Thus, the dibenzothiophene *S*-oxide selected for each arene should be electron-deficient enough to functionalize the arene, and electron-rich enough to provide high selectivity in fluorination. For example, both DBT and B-DBT salts of compound **25** could be synthesized in good yields. However, fluorination of the B-DBT salt affords 94% yield of desired fluorination product while DBT salt gives only 55% yield of desired product with 42% yield of the undesired side-product (see Supporting Information). By use of electron-rich M-DBT, ^{18}F-fluorination with aryl sulfoniums can now proceed on otherwise challenging electron-rich complex substrates (**36**, **38**) (Table 2).[8] Moreover, a range of small-molecule drugs were successfully ^{18}F-labeled. Halides (**30**-**32**, **34**, **35**, **37**), amides (**28**), sulfonamides (**31**), heterocycles (**33**, **38**) were well tolerated. Substrates bearing *ortho*-substituents proceeded efficiently to afford the desired ^{18}F-labeled products (**29**, **30**, **32**, **37**).

Table 2. Aromatic ^{18}F-fluorination.



(a) Reaction conditions: aryl dibenzothiophenium precursor (9.0 µmol) in 500 µL MeCN at 110 °C for 20 min. RCY: decay-corrected radiochemical yield. (b) Kryptofix 222 and K_2CO_3 were added, and reaction performed in 500 µL DMSO.

Elution of the ^{18}F-fluoride from the anion exchange cartridge is commonly achieved with an aqueous solution of a base.[14] Aryldibenzothiophenium salts can be used directly for elution of ^{18}F-fluoride, which avoids the addition of bases or kryptofix.[7g,i,l] No special care is required to exclude air or moisture at any

stage of the radio-synthesis, and the radiolabeled product can be readily separated from the starting material due to the pronounced polarity difference owing to the cationic sulfonium salt. No carrier-added ^{18}F-fluorination enabled the automated synthesis of ^{18}F-labeled compound **32** in high molar activity (1.4 Ci·μmol^{-1}). A Hammett analysis of the ^{19}F-fluorination with aryl dimethoxyldibenzothiophenium salts (Hammett-slope ρ = +3.4) is consistent with a mechanism proceeding via C–F bond reductive elimination from hypervalent sulfurane as previously suggested.[8d,15]

In conclusion, we developed a site-selective late-stage aromatic ^{18}F-fluorination, enabled by a selective C–H dibenzothiophenylation reaction. We show for the first time how a collection of three electronically different dibenzothiophenes appropriately matched to the electronic requirements of the arene can expand the substrate scope compared to prior art. Beyond the immediate practicality of our method, the new procedure developed herein may inspire the development of diverse site-selective carbon–heteroatom bond formation.

Acknowledgements

We thank the Max-Planck-Institut für Kohlenforschung for funding. We thank the HPLC and MS departments of the Max-Planck-Institut für Kohlenforschung for technical assistance. We thank Jonas Börgel and Matthew B. Plutschack (all from Max-Planck-Institut für Kohlenforschung) for helpful discussions.

Keywords: C–F bond formation • site-selectivity • ^{18}F-labeling • radiochemistry • late-stage C–H functionalization

[1] (a) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci*. **2014**, *5*, 4545−4553. (b) K. Chansaenpak, B. Vabre, F. P. Gabbai, *Chem. Soc. Rev*. **2016**, *45*, 954−971. (c) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719−766. (d) X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson, S. H. Liang, *Angew. Chem., Int. Ed.* **2019**, *58*, 2580−2605.

[2] (a) R. Chakravarty, H. Hong, W. Cai, *Mol. Pharmaceutics* **2014**, *11*, 3777−3797. (b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem*. **2015**, *58*, 8315−8359. (c) D. A. Mankoff, M. D. Farwell, A. S. Clark, D. A. Pryma, *JAMA Oncol*. **2017**, *3*, 695−701. (d) H. H. Coenen, J. Ermert, *Clin. Transl. Imaging* **2018**, *6*, 169−193.

[3] M. G. Campbell, J. Mercier, C. Genicot, V. Gouverneur, J. M. Hooker, T. Ritter, *Nat. Chem.* **2017**, *9*, 1–3.

[4] (a) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639−642. (b) E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456−17458. (c) H. Ren, H.-Y. Wey, M. Strebl, R. Neelamegam, T. Ritter, J. M. Hooker, *ACS Chem. Neurosci*. **2014**, *5*, 611−615. (d) H. Lee, J. Börgel, T. Ritter, *Angew. Chem., Int. Ed.* **2017**, *56*, 6966−6969.

[5] (a) F. Cacace, A. P. Wolf, *J. Am. Chem. Soc.* **1978**, *100*, 3639−3641. (b) G. Firnau, R. Chirakal, E. S. Garnett, *J. Nucl. Med.* **1984**, *25*, 1228−1233. (c) K. Yamamoto, J. Li, J. Garber, A. O. J. D. Rolfes, G. B. Boursalian, J. C. Borghs, C. Genicot, J. Jacq, M. van Gastel, F. Neese, T. Ritter, *Nature* **2018**, *554*, 511−514. (d) W. Chen, Z. Huang, N. E. S. Tay, B. Giglio, M. Wang, H. Wang, Z. Wu, D. A. Nicewicz, Z. Li, *Science* **2019**, *364*, 1170−1174.

[6] (a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931. (b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169. (c) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522. (d) C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853–857. (e) G. B. Boursalian, W. S. Ham, A. R Mazzotti, T. Ritter, *Nat. Chem.* **2016**, *8*, 810–815.

[7] For selected examples, see: (a) Y. Ye, S. D. Schimler, P. S. Hanley, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 16292–16295. (b) X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842−6845. (c) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, V. Gouverneur, *Angew. Chem., Int. Ed.* **2014**, *53*, 7751−7755. (d) B. D. Zlatopolskiy, J. Zischler, P. Krapf, F. Zarrad, E. A. Urusova, E. Kordys, H. Endepols, B. Neumaier, *Chem. Eur. J.* **2015**, *21*, 5972−5979. (e) X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angew. Chem., Int. Ed.* **2015**, *54*, 5241−5245. (f) A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2015**, *17*, 5780−5783. (g) C. N. Neumann, J. M. Hooker, T. Ritter, *Nature* **2016**, *534*, 369−373. (h) K. J. Makaravage, A. F. Brooks, A. V. Mossine, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2016**, *18*, 5440−5443. (i) M. H. Beyzavi, D. Mandal, M. G. Strebl, C. N. Neumann, E. M. D'Amato, J. Chen, J. M. Hooker, T. Ritter, *ACS Cent. Sci*. **2017**, 3, 944−948. (j) M. S. McCammant, S. Thompson, A. F. Brooks, S. W. Krska, P. J. H. Scott, M. S. Sanford, *Org. Lett.* **2017**, *19*, 3939−3942. (k) N. J. Taylor, E. Emer, S. Preshlock, M. Schedler, M. Tredwell, S. Verhoog, J. Mercier, C. Genicot, V. Gouverneur, *J. Am. Chem. Soc.* **2017**, *139*, 8267−8276. (l) J. Rickmeier, T. Ritter, *Angew. Chem., Int. Ed.* **2018**, *57*, 14207−14211.

[8] (a) L. Mu, C. R. Fischer, J. P. Holland, J. Becaud, P. A. Schubiger, R. Schibli, S. M. Ametamey, K. Graham, T. Stellfeld, L. M. Dinkelborg, L. Lehmann, *Eur. J. Org. Chem.* **2012**, *2012*, 889−892. (b) K. Sander, T. Gendron, E. Yiannaki, K. Cybulska, T. L. Kalber, M. F. Lythgoe, E. Årstad, *Sci. Rep.* **2015**, *5*, 9941. (c) K. Sander, E. Galante, T. Gendron, E. Yiannaki, N. Patel, T. L. Kalber, A. Badar, M. Robson, S. P. Johnson, F. Bauer, S. Mairinger, J. Stanek, T. Wanek, C. Kuntner, T. Kottke, L. Weizel, D. Dickens, K. Erlandsson, B. F. Hutton, M. F. Lythgoe, H. Stark, O. Langer, M. Koepp, E. Årstad, *J. Med. Chem*. **2015**, *58*, 6058−6080. (d) T. Gendron, K. Sander, K. Cybulska, L. Benhamou, P. K. B. Sin, A. Khan, M. Wood, M. J. Porter, E. Årstad, *J. Am. Chem. Soc*. **2018**, *140*, 11125−11132.

[9] (a) M. Hori, T. Kataoka, H. Shimizu, *Yakugaku-Zasshi*, **1973**, *93*, 476–482. (b) M. Date, H. Kimura, J. Yamamoto, EP 1350789 B1, **2001**.

[10] (a) F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223–228. (b) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, *Angew. Chem., Int. Ed.* **2019**, *58*, 14615–14619. (c) P. S. Engl, A. P. Häring, F. Berger, G. Berger, A. Pérez-Bitrián, T. Ritter, *J. Am. Chem. Soc.* **2019**, 141, 13346–13351. (d) R. Sang, S. E. Korkis, W. Su, F. Ye, P. S. Engl, F. Berger, T. Ritter, *Angew. Chem., Int. Ed.* **2019**, *58*, 16161–16166.

[11] J. Li, J. Chen, R. Sang, W.-S. Ham, M. B. Plutschack, F. Berger, S. Chabbra, A. Schnegg, C. Genicot, T. Ritter, *Nat. Chem.* **2019**, *accepted*.

[12] For selected examples on aromatic C−H functionalization with activated sulfoxide, see: (a) I. L. Baraznenok, V. G. Nenajdenko, E. S. Balenkova, *Tetrahedron*, **2000**, *56*, 3077−3119. (b) J. A. Fernández-Salas, A. P. Pulis, D. J. Procter, *Chem. Commun.* **2016**, *52*, 12364–12367.

[13] (a) J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier: New York, **1968**. (b) F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH 2013, e-book ISBN: 9783527656141.

[14] M.-C. Lasne, C. Perrio, J. Rouden, L. Barré, D. Roeda, F. Dolle, C. Crouzel, *Top. Curr. Chem.* **2002**, *222*, 201–258.

[15] D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701−8780.

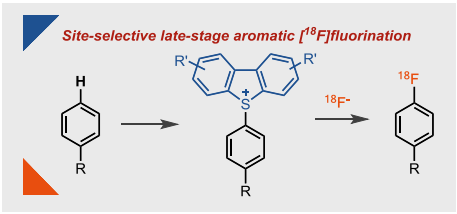
10.1002/anie.201912567

WILEY-VCH

Entry for the Table of Contents

Layout 2:

COMMUNICATION



A site-selective late-stage aromatic ^{18}F-fluorination is reported. The collection of three electronically different dibenzothiophenes enables ^{18}F-labeling of a series of small complex molecules.

*Peng Xu‡, Da Zhao‡, Florian Berger, Aboubakr Hamad, Jens Rickmeier, Roland Petzold, Mykhailo Kondratiuk, Kostiantyn Bohdan, and Tobias Ritter **

Page No. – Page No.

Site-selective Late-Stage Aromatic ^{18}F-Fluorination via Aryl Sulfonium Salts