EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Multifunctional 2- and 3-fluoropyrroles

Authors: Darren Heeran and Graham Sandford

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900185

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900185

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201900185

Multifunctional 2- and 3-fluoropyrroles

Darren Heeran and Graham Sandford*

Dr Darren Heeran and Prof. Graham Sandford
Department of Chemistry
Durham University
South Road, Durham, DH1 3LE, U.K.
E-mail: Graham.Sandford@durham.ac.uk

https://www.dur.ac.uk/chemistry/staff/profile/?id=199

Supporting information for this article is given via a link at the end of the document. CCDC 1879860-1879866 contain the supplementary crystallographic data for this paper.

Abstract: Sequential reaction cascades for the synthesis of polysubstituted 2- and 3-fluoropyrrole derivatives from common polybromopyrrole precursors have been developed. A strategic variation of a combination of regioselective debromolithiation followed by trapping of the corresponding carbanions by electrophilic fluorination and Pd catalysed cross coupling reactions allows access to polyfunctional fluoropyrrole products by methodology applicable to drug discovery programs, extending the range of five-membered fluoroazaheteroaromatic derivatives potentially available for incorporation into screening libraries.

Introduction

Since the seminal work by Fried and Sabo concerning the enhanced biological activity of Fludrocortisone,[1] the introduction of fluorine into organic systems has been shown to effectively modulate lipophilicity, metabolic stability and pH profiles of many classes of organic systems.[2–6] These factors underpin the strategic use of fluorine within drug design and many commercially successful life science products contain fluorinated groups within their structures.[7–9]

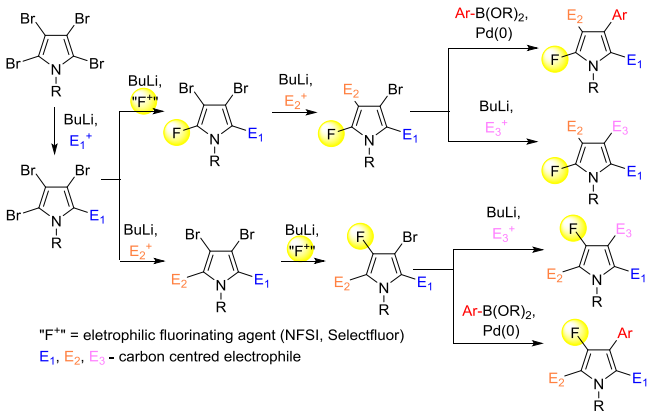
In particular, fluorinated six-membered heterocycles are structural units found within a number of commercially important life science products. Fluoro-pyridine or –pyrimidine motifs have well-established synthetic protocols at both discovery and industrial scales[10–17] and, as a result, life science products containing six-membered fluoroheteroaromatic units such as Voriconazole (antifungal, Pfizer), Capecitabine (anticancer, Roche) and Diclosulam (herbicide, Dow) have now reached the commercial market[18–20] with many others such as Abemaciclib (anticancer, Eli Lilly), Riociguat (heart failure, Bayer) and Verubecestat (Alzheimers, Merck) in clinical trials.[21] In contrast, while functionalised five-membered heterocycles such as pyrroles, thiophenes and furans are prevalent structural units within life science products and many biologically active compounds,[22] corresponding occurences of fluorinated five-membered heteroaromatic in life science products are very rare. This is primarily due to the lack of readily available, convenient, efficient and regioselective synthetic methodologies for the synthesis of wide ranges of, for example, fluoropyrrole analogues at the drug discovery stage.

The most direct method for the synthesis of fluoropyrroles is the transformation of C-H to C-F bonds by reaction of the parent pyrrole with an electrophilic fluorinating agent. Whilst electrophilic bromination and chlorination reactions of pyrroles using halogenating agents such as NBS, NCS, Br_2 or Cl_2 are well established,[23] related fluorination reactions utilising XeF_2[24,25] or Selectfluor™[26,27] often proceed in low yields. For example, we reported a systematic study on the effect of various substituents on the fluorination of pyrrole derivatives using Selectfluor™[28] and, although these procedures provided access to several novel fluoropyrroles bearing electron withdrawing groups on the pyrrole ring, in general, competing oxidation and subsequent polymerisation of the pyrrole substrate limits the scope of this strategy.

Other approaches to the synthesis of fluoroyrrole derivatives are restricted to very few examples of processes such as photochemical modification of the Balz-Schiemann reaction,[29] fluorodecarboxylation of highly substituted derivatives using Selectfluor[30] and reaction of Grignard[31] or lithiated[32] derivatives with N-fluorobenzene sulfonamide (NFSI). Additionally, the lack of commercially available multifunctional pyrroles to act as substrates in fluorination reactions limits the range of fluoropyrrole products accessible by this approach.

In general, therefore, current methodologies for the preparation of fluoropyrrole derivatives are inefficient, have a very limited substrate scope and the synthesis of diverse libraries of fluoropyrroles for drug discovery programmes has not been achieved.[33] Thus, there is not only a requirement for the development of effective fluorination methods applicable to a range of substrates but also for the synthesis of multifunctional pyrroles in general.

We envisioned that polybromopyrrole derivatives could act as appropriate substrates where several bromine atoms could be used as functional groups for fluorination reactions in conjunction with sequences of cross coupling and debromolithiation/trapping chemistries. By varying the order in which functionalisations are sequentially applied, access to a diverse library of highly functionalised pyrrole products, including fluoropyrroles, could be possible (Scheme 1).



Scheme 1. Concept sequential reaction cascades for fluoropyrrole synthesis.

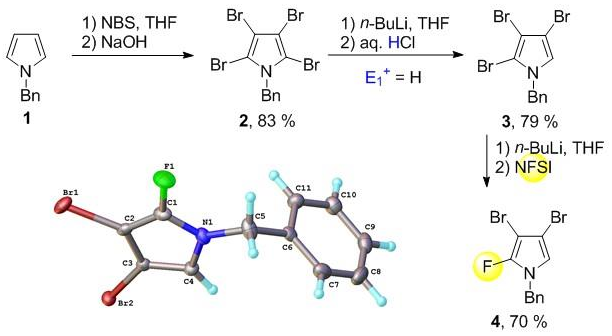
However, despite the potential utility of polybrominated pyrroles, tetra- and tri-brominated pyrroles have been scarcely utilised in synthesis, with only a limited number of reactions reported, largely concerning Suzuki,[34–39] Sonogashira,[40] Heck,[41] and more recently, Stille[42] processes for the synthesis of polymeric systems from 2,5-dibromopyrrole derivatives. Metal halogen exchange reactions of tetra- and tri-

brominated pyrrole substrates have received even less attention and, until very recently, metal-halogen exchange of a tetrabrominated pyrrole substrate had not been reported. In the only example, *N*-phenyl-2,3,4,5-tetrabromopyrrole could be selectively lithiated at the 2-position before addition of benzophenone and acidic work up gave a 2-diphenylmethylene product.[43] Tribrominated pyrrole derivatives, such as *N*-TIPS-2,3,4-tribromopyrrole, have also been utilised in a limited number of metal halogen exchange reactions[44,45] whereby lithiation occurs selectivity at the 2-position to yield 2-substituted-3,4-dibromopyrrole products.

Here, we describe proof-of-concept syntheses of multi-substituted fluoropyrrole derivatives by fluorination, debromolithiathion/trapping and Pd catalysed coupling cascades.

Results and Discussion

We began our studies with the perbromination of *N*-benzylpyrrole (**1**) using NBS following a literature procedure.[34] (Scheme 2).



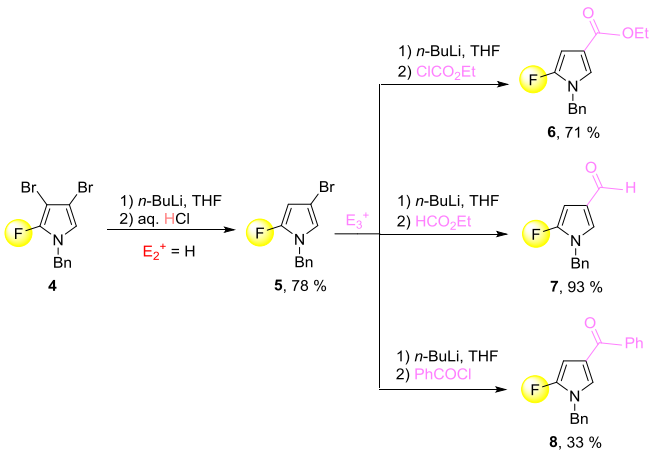
Scheme 2. Synthesis and molecular structure of 2-fluoro-3,4-dibromopyrrole **4**.

Tetrabromo-*N*-benzylpyrrole (**2**) reacted with *n*-BuLi in THF and, following quenching with dilute HCl, gave 2,3,4-tribromo-*N*-benzylpyrrole (**3**) as the only product (Scheme 2). The regioselectivity follows related results established by Schlosser which indicate that the bromine atom occupying the most acidic site selectively undergoes debromolithiation.[47]

Unfortunately, analogous reactions involving quenching the lithiated intermediate formed from **2** with a solution of electrophilic fluorinating agent NFSI in THF gave a complex mixture of products, including appreciable quantities of difluorinated products, as observed by GC-MS analysis, despite using only 1 eq. of *n*-BuLi. This is likely a result of 'halogen dance' type processes previously reported for similar halogenated heterocyclic systems and facilitated by a slow fluorination reaction step.[48]

In contrast, however, fluorination of tribromopyrrole derivative **3** using NFSI under similar conditions, gave desired 2-fluoro-3,4-dibromopyrrole (**4**) which was purified by column chromatography (Scheme 2). Storage of pure **4** at -18 ºC led to the isolation of crystals of suitable quality for x-ray crystallography confirming the structure (Scheme 2) and, hence, the regioselectivity of fluorination at the most acidic site consistent with observations discussed above.

Dibromofluoropyrrole **4** is a potentially useful fluorinated building block and so we assessed the regioselectivity of further debronolithiation reactions (Scheme 3). Hydrodebromination using *n*-BuLi followed by quenching with aq. HCl was performed and gave a single product **5**. Analysis of the ^{1}H NMR spectrum of **5** shows a proton-proton coupling of *J*=2.2 Hz which is consistent with four-bond coupling[49] for related *N*-substituted 2,3- and 2,4-dibromopyrrole derivatives. The observed regioselectivity reflects the ability of the fluorine substituent to increase acidity of *ortho*-sites.



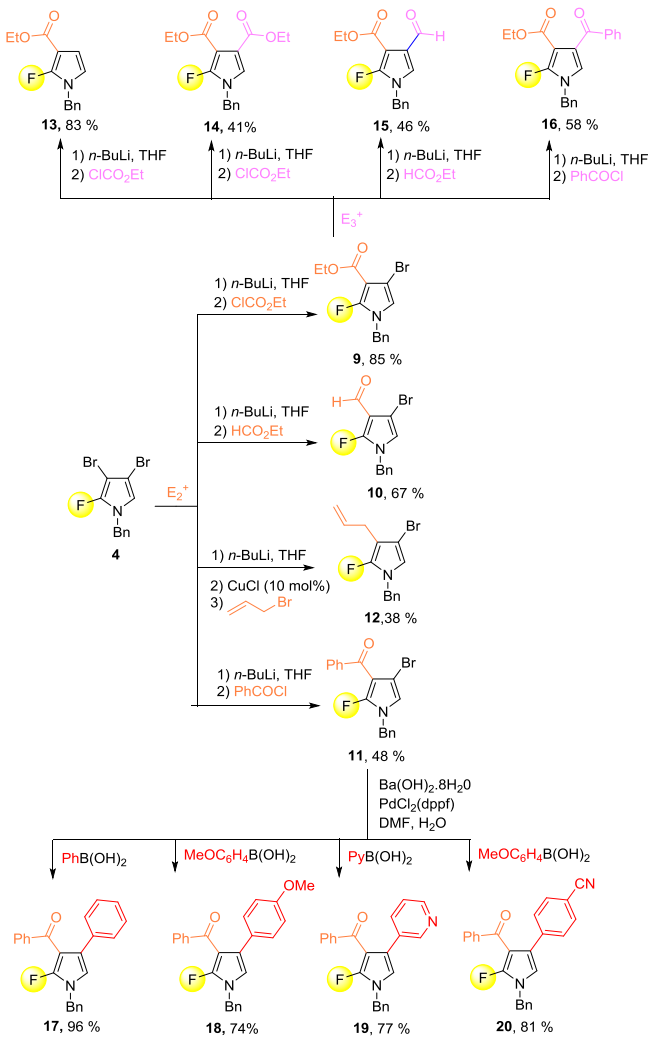
Scheme 3. Synthesis of 2-fluoro-4-substituted pyrrole derivatives from **5**.

Ready access to fluorobromopyrrole **5** allowed us to synthesise a range of 2-fluoropyrrole systems by trapping corresponding carbanions with a short series of electrophiles. Fluoropyrrole systems bearing ester (**6**), aldehyde (**7**) and ketone (**8**) functional groups at the 4-position were formed by reaction with ethyl chloroformate, ethyl formate and benzoyl chloride respectively providing a small series of model 2-fluoro-4-substituted pyrrole systems (Scheme 3). ^{19}F NMR data of 2-fluoropyrrole derivative **6** (δ_F -140.04 ppm in $CDCl_3$), was in excellent agreement with that previously reported in the literature (δ_F -140.07 ppm) and distinct from the shift of regioisomer ethyl 2-fluoro-*N*-benzylpyrrole-3-carboxylate (δ_F -129.22 ppm).[27]

Fluorination of **5** was also attempted to give access to 2,4-difluoro-*N*-benzylpyrrole but, when using NFSI in THF as the electrophile source, the major component of the crude reaction mixture was the hydrodebrominated product alongside only trace amounts of the desired 2,4-difluoropyrrole derivative. Competing electron transfer reactions between the intermediate lithiate and NFSI, in agreement with observations previously reported in the synthesis of 3-fluoro-*N*-TIPS-pyrrole using NFSI[32] and in reactions of a range of organometallic nucleophiles with N-F electrophilic fluorinating agents,[50,51] is suggested as a possible mechanism for this process.

The range of fluoropyrrole products accessible from dibromofluoropyrrole **4** could also be expanded by varying the substituent at the 3-position. Excellent regioselectivity upon debromolithiation/trapping occurs and a small range of electrophiles was again used to give the corresponding 3-substituted 2-fluoropyrroles **9-12** in good to excellent yields (Scheme 4). The structure of **11** was confirmed by x-ray crystallography (Figure 1).

10.1002/ejoc.201900185



Scheme 4. Synthesis of 2-fluoro-3,4-disubstituted pyrrole derivatives from **4**.

Using similar reaction conditions with allyl bromide as the quenching electrophile, no alkylation occurs upon lithiation of **4**. However, addition of a Cu^{I} salt to the reaction mixture prior to the addition of the electrophile, forming a much softer organocopper nucleophile,[53] led to the isolation of allylated product **12** (Scheme 4).

Additionally, hydrodebromination reactions of 2-fluoro-3-substituted-4-bromopyrrole compounds provided access to regioisomeric fluoropyrrole products. Using fluoropyrrole **9** as a model substrate, reaction with *n*-BuLi followed by quenching with aq. HCl gave **13** (Scheme 4). Synthesis of a mixture of compounds **6** and **13** has previously been reported.[27]

Additonally, fluoropyrrole derivative **9** was used as the substrate that enabled the synthesis of further 3,4-disubstituted 2-fluoropyrrole products. Fluoropyrrole derivatives **14**, **15** and **16** were obtained in moderate yields by applying analogous lithiation/trapping protocols (Scheme 4) extending the range of fluoropyrrole systems available.

Furthermore, we used Pd catalysed cross coupling chemistry to diversify the range of fluoropyrrole products obtainable by this general strategy. Suzuki-type cross coupling conditions adapted from those reported by Ghosez[54] allowed us to synthesise a range of aryl substituted products (**17 – 20**) with the conditions tolerating substituted arylboronic acids bearing both electron-donating and electron-

withdrawing substituents as well as heteroaromatic boronic acids in good to excellent yields (Scheme 4). The structures of **16** and **19** were confirmed by x-ray crystallography (Figure 1).

Having demonstrated the synthesis of a diverse range of 2-fluoro-*N*-benzylpyrrole derivatives by sequential processes, we sought to expand the methodology to provide access to corresponding 3-fluoropyrrole derivatives and envisioned that this could be achieved by simply delaying the fluorination step in the reaction sequence (Scheme 1).

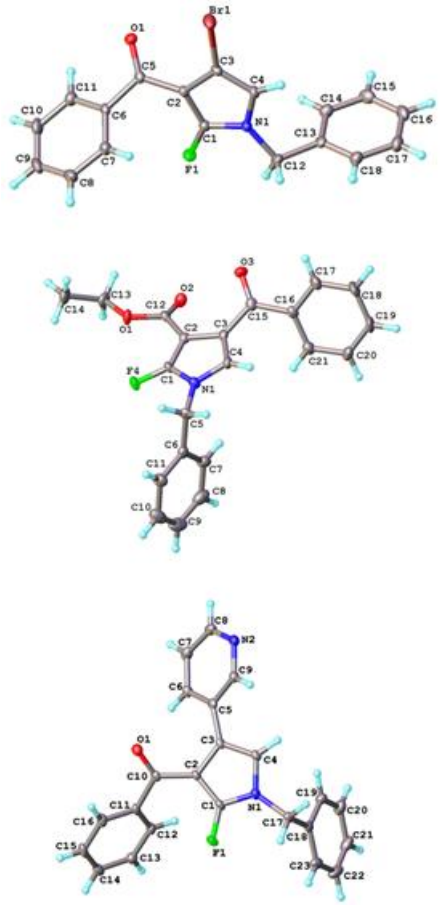
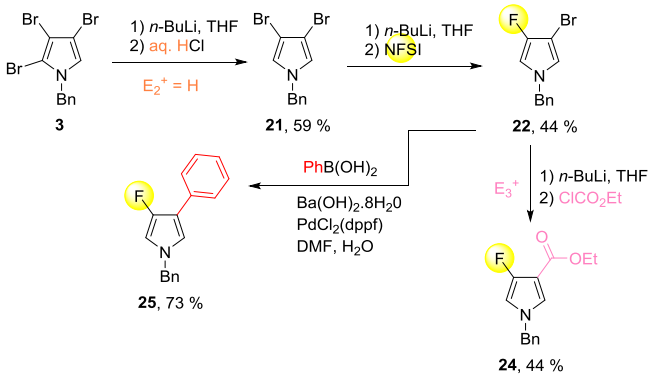


Figure 1. Molecular structures of **11, 16** and **19**.

Hydrodebromination of tribromopyrrole **3** (Scheme 5) gave **21** and subsequent fluorination of **21** gave 3-fluoro-4-bromopyrrole derivative **22** in moderate yield. The yield of this reaction was limited by the formation of debrominated product **23**, formed by competing electron transfer reactions discussed above. Optimisation attempts using excess or sub-stoichiometric amounts of NFSI had no desirable effect on the yield, whilst the addition of Selectfluor™, a more powerful oxidant, in a THF/MeCN mixture gave exclusively **23**. The ^{19}F NMR spectrum of isolated 3-fluoro-4-bromopyrrole derivative **22**, however, corresponded well with that reported previously for 3-fluoropyrrole derivatives[32] and the structure of **22** was confirmed by x-ray crystallography.



Scheme 5. Synthesis of 3-fluoro-pyrrole derivatives

Using 3-fluorinated building block **22** we synthesised a representative 3-fluoropyrrole derivative by metal-halogen exchange using *n*-BuLi and quenching the intermediate carbanion with ethyl chloroformate to give the ester substituted 3-fluoropyrrole derivative **24** in moderate yield. Finally, we carried out a Suzuki cross coupling reaction of **22** under similar conditions to those described above and obtained 3-fluoropyrrole derivative **25** in good yield.

Conclusions

An efficient sequential polybromination-derivatisation strategy for the synthesis of a variety of 2- and 3-fluoropyrrole derivatives by strategically varying the order in which debromolithiation/trapping/fluorination and Pd catalyzed cross coupling are applied has been developed (Scheme 1). Clearly, this proof-of-concept methodology could be expanded to reactions involving many other electrophiles, Pd catalyzed processes, other 5-membered heterocyclic core scaffolds and different sequential processes. This strategy, therefore, provides methodology for the synthesis multifunctional fluoropyrrole derivatives bearing multiple reaction handles for further diversification and expedient access to a diverse array of polyfunctional fluoropyrrole products that can, in principle, be incorporated into life science screening libraries.

Acknowledgements

We thank EPSRC (Durham University DTA) for a studentship to D.H. and Dr. D. S. Yufit for X-ray crystallographic analysis.

Keywords: fluoroheterocycle • selective fluorination • fluoropyrrole • electrophilic fluorination • nitrogen heterocycle

[1] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455–1456.

[2] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[3] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[4] C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319.

[5] K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029.

[6] I. Ojima, Ed. , *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Oxford, **2009**.

[7] D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081.

[8] P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.

[9] P. Jeschke, *Pest Manag. Sci.* **2010**, *66*, 10–27.

[10] A. Shestopalov, L. Rodinovskaya, V. Mortikov, A. Fedorov, in *Fluor. Heterocycl. Chem. Vol. 2 6-Membered Heterocycles* (Ed.: V. Nenajdenko), Springer International Publishing, **2014**, pp. 1–58.

[11] A. M. Shestopalov, A. A. Shestopalov, L. A. Rodinovskaya, A. V Gromova, in *Fluorinated Heterocycl. Compd. Synth. Chem. Appl.* (Ed.: V.A. Petrov), John Wiley & Sons, Inc., **2009**, pp. 243–271.

[12] A. Gakh, in *Halogenated Heterocycles Synth. Appl. Environ.* (Ed.: J. Iskra), Springer Berlin Heidelberg, **2012**, pp. 33–63.

[13] T. Kosjek, E. Heath, in *Halogenated Heterocycles Synth. Appl. Environ.* (Ed.: J. Iskra), Springer Berlin Heidelberg, **2012**, pp. 219–246.

[14] P. D. Schuman, P. Tarrant, D. A. Warner, G. Westmoreland, *US 3954758*, **1976**.

[15] A. Yamazaki, H. Morisawa, Y. Oda, K. Uchida, *US 4186266*, **1980**.

[16] B. Baasner, E. Klauke, *US 4703121*, **1987**.

[17] A. Harsanyi, A. Conte, L. Pichon, A. Rabion, S. Grenier, G. Sandford, *Org. Process Res. Dev.* **2017**, *21*, 273–276.

[18] E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842.

[19] B. R. Smith, C. M. Eastman, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 9764–9773.

[20] "FDA Approved Drug Products," can be found under http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu, **2018**.

[21] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[22] V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233–15266.

[23] W. Ando, D. Bellus, U. Bergsträßer, D. Black, H. Heydt, B. König, G. Maas, F. Mathey, M. Regitz, J. Schatz, *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations Vol. 9: Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom*, Thieme, **2014**.

[24] J. Wang, A. I. Scott, *Tetrahedron Lett.* **1994**, *35*, 3679–3682.

[25] J. Wang, A. I. Scott, *Tetrahedron* **1994**, *50*, 6181–6192.

[26] B. Troegel, T. Lindel, *Org. Lett.* **2012**, *14*, 468–71.

[27] K. Hiramatsu, H. Tamamura, *Eur. J. Org. Chem.* **2016**, 3491–3494.

[28] D. Heeran, G. Sandford, *Tetrahedron* **2016**, *72*, 2456–2463.

[29] H. Onda, H. Toi, Y. Aoyama, H. Ogoshi, *Tetrahedron Lett.* **1985**, *26*, 4221–4224.

[30] J. Wang, A. I. Scott, *J. Chem. Soc., Chem. Commun.* **1995**, 2399–2400.

[31] S. Yamada, A. Gavryushin, P. Knochel, *Angew. Chemie Int. Ed.* **2010**, *49*, 2215–2218.

[32] K. D. Barnes, Y. Hu, D. A. Hunt, *Synth. Commun.* **1994**, *24*, 1749–1755.

[33] O. V. Serdyuk, V. M. Muzalevskiy, V. G. Nenajdenko, *Synthesis* **2012**, *44*, 2115–2137.

[34] T. T. Dang, R. Ahmad, T. T. Dang, H. Reinke, P. Langer, *Tetrahedron Lett.* **2008**, *49*, 1698–1700.

[35] A. Wakamiya, N. Sugita, S. Yamaguchi, *Chem. Lett.* **2008**, *37*, 1094–1095.

[36] S.-M. T. Toguem, O. Fatunsin, A. Villinger, P. Langer, *Tetrahedron Lett.* **2011**, *52*, 3732–3735.

[37] S.-M. Toguem, P. Langer, *Synlett* **2011**, 513–516.

[38] S. Schröter, T. Bach, *Synlett* **2005**, 1957–1959.

[39] T. Bach, S. Schröter, *Heterocycles* **2007**, *74*, 569.

[40] F. Ullah, T. Dang, J. Heinicke, A. Villinger, P. Langer, *Synlett* **2009**, 838–842.

[41] S.-M. T. Toguem, I. Knepper, P. Ehlers, T. T. Dang, T. Patonay, P. Langer, *Adv. Synth. Catal.* **2012**, *354*, 1819–1826.

[42] J. Shi, I. Murtaza, S. Shao, X. Zhu, Y. Zhao, M. Zhu, O. Goto, H. Meng, *Sci. China Chem.* **2017**, *60*, 90–98.

[43] F. Faigl, S. Deák, Z. Mucsi, T. Hergert, L. Balázs, B. Sándor, B. Balázs, T. Holczbauer, M. Nyerges, B. Mátravölgyi, *Tetrahedron* **2016**, *72*, 5444–5455.

[44] M. G. Banwell, B. L. Flynn, E. Hamel, D. C. R. Hockless, *Chem. Commun.* **1997**, *2*, 207–208.

[45] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, J. M. Muchowski, *J. Org. Chem.* **1990**, *55*, 6317–6328.

[46] H. M. Gilow, D. E. Burton, *J. Org. Chem.* **1981**, *46*, 2221–2225.

[47] M. Schlosser, *Organometallics in Synthesis: A Manual*, Wiley, **1996**.

[48] M. Schnürch, M. Spina, A. F. Khan, M. D. Mihovilovic, P. Stanetty, *Chem. Soc. Rev.* **2007**, *36*, 1046–1057.

[49] T. Fukuda, T. Ohta, E. Sudo, M. Iwao, *Org. Lett.* **2010**, *12*, 2734–2737.

[50] E. Differding, G. M. Rüegg, *Tetrahedron Lett.* **1991**, *32*, 3815–3818.

[51] E. Differding, M. Wehrli, *Tetrahedron Lett.* **1991**, *32*, 3819–3822.

[52] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

[53] B. H. Lipshutz, S. Sengupta, in *Org. React.*, John Wiley & Sons, Inc., **2004**.

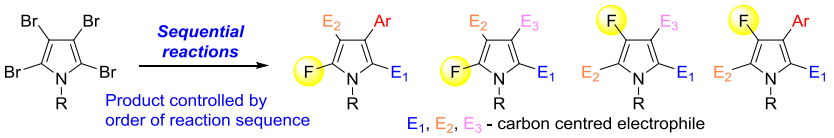
[54] L. Ghosez, C. Franc, F. Denonne, C. Cuisinier, R. Touillaux, *Can. J. Chem.* **2001**, *79*, 1827–1839.

10.1002/ejoc.201900185

*Darren Heeran, Graham Sandford**

Page No. – Page No.

Multifunctional 2- and 3-fluoropyrroles



Displacement of bromine atoms from tetrabromopyrrole by strategically varying the order in which debromolithiation/trapping/fluorination and Pd catalyzed cross coupling are applied, provides methodology for the synthesis of multifunctional of 2- and 3-fluoropyrrole derivatives bearing multiple reaction handles for further diversification.

Key Topic : Organofluorine Chemistry