Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2021, **12**, 6148

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th February 2021
Accepted 25th March 2021

DOI: 10.1039/d1sc01132d

rsc.li/chemical-science

Difluorination of α-(bromomethyl)styrenes *via* I(I)/I(III) catalysis: facile access to electrophilic linchpins for drug discovery†

Joel Häfliger, Keith Livingstone, Constantin G. Daniliuc and Ryan Gilmour *

Simple α-(bromomethyl)styrenes can be processed to a variety of 1,1-difluorinated electrophilic building blocks *via* I(I)/I(III) catalysis. This inexpensive main group catalysis strategy employs *p*-TolI as an effective organocatalyst when combined with Selectfluor® and simple amine·HF complexes. Modulating Brønsted acidity enables simultaneous *geminal* and *vicinal* difluorination to occur, thereby providing a platform to generate multiply fluorinated scaffolds for further downstream derivatization. The method facilitates access to a tetrafluorinated API candidate for the treatment of amyotrophic lateral sclerosis. Preliminary validation of an enantioselective process is disclosed to access α-phenyl-β-difluoro-γ-bromo/chloro esters.

Structural editing with fluorine enables geometric and electronic variation to be explored in functional small molecules whilst mitigating steric drawbacks.[1] This expansive approach to manipulate structure–function interplay continues to manifest itself in bio-organic and medicinal chemistry.[2] Of the plenum of fluorinated motifs commonly employed, the *geminal* difluoromethylene group[3] has a venerable history.[4] This is grounded in the structural as well as electronic ramifications of $CH_2 \rightarrow CF_2$ substitution, as is evident from a comparison of propane and 2,2-difluoropropane (Fig. 1, upper). Salient features include localized charge inversion ($C–H^{\delta+}$ to $C–F^{\delta-}$) and a widening of the internal angle from 112° to 115.4°.[5] Consequently, *geminal* difluoromethylene groups feature prominently in the drug discovery repertoire[6] to mitigate oxidation and modulate physicochemical parameters. Catalysis-based routes to generate electrophilic linchpins that contain the *geminal* difluoromethylene unit have thus been intensively pursued, particularly in the realm of main group catalysis.[7–9] Motivated by the potential of this motif in contemporary medicinal chemistry, it was envisaged that an I(I)/I(III) catalysis platform could be leveraged to convert simple α-(bromomethyl)styrenes to *gem*-difluorinated linchpins: the primary $C(sp^3)$–Br motif would facilitate downstream synthetic manipulations (Fig. 1, lower). To that end, *p*-TolI would function as a catalyst to generate *p*-TolIF_2 *in situ* in the presence of an external oxidant[10] and an amine·HF complex. Alkene activation (**I**) with subsequent bromonium ion formation (**II**)[11] would provide a pre-text for the first C–F bond forming process (**III**) with regeneration of the catalyst. A subsequent phenonium ion rearrangement[12]/fluorination sequence (**III** and **IV**) would furnish the *geminal* difluoromethylene group and liberate the desired electrophilic building block.

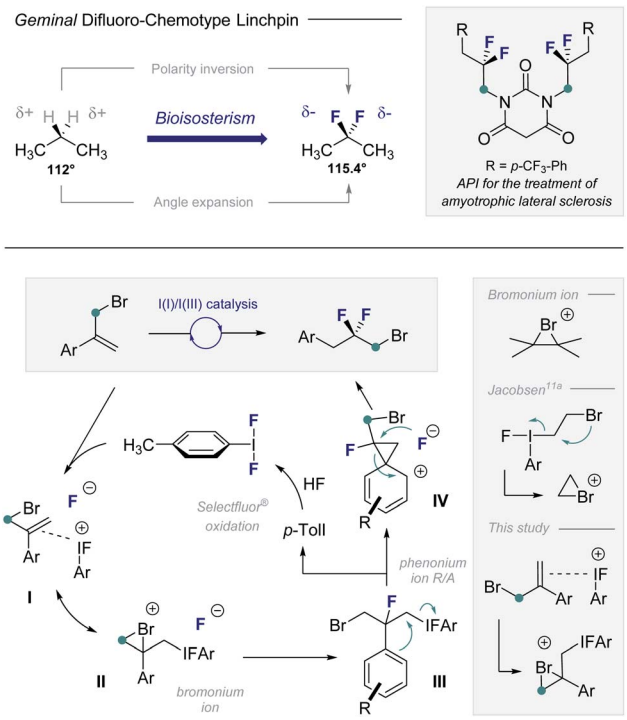


Fig. 1 The *geminal* difluoromethylene group: bioisosterism, and catalysis-based access from α-(bromomethyl)styrenes *via* I(I)/I(III) catalysis.

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 36, 48149 Münster, Germany. E-mail: ryan.gilmour@uni-muenster.de

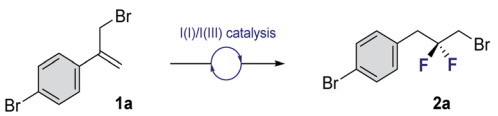
† Electronic supplementary information (ESI) available. CCDC 2055892. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01132d

To validate this conceptual framework, a short process of reaction optimization (**1a** → **2a**) was conducted to assess the influence of solvent, amine·HF ratio (Brønsted acidity)[13] and catalyst loading (Table 1). Initial reactions were performed with *p*-TolI (20 mol%), Selectfluor® (1.5 equiv.) as an oxidant, and $CHCl_3$ as the reaction medium. Variation of the amine : HF ratio was conducted to explore the influence of Brønsted acidity on catalysis efficiency (entries 1–4). An optimal ratio of 1 : 6 was observed enabling the product **2a** to be generated in >95% NMR-yield. Although reducing the catalyst loading to 10 and 5 mol% (entries 5 and 6, respectively) led to high levels of efficiency (79% yield with 5 mol%), the remainder of the study was performed with 20 mol% *p*-TolI. Notably, catalytic *vicinal* difluorination was not observed at any point during this optimization, in contrast with previous studies from our laboratory.[9d,i] A solvent screen revealed the importance of chlorinated solvents (entries 7 and 8): in contrast, performing the reaction in ethyl trifluoroacetate (ETFA) and acetonitrile resulted in a reduction in yield (9 and 10). Finally, a control reaction in the absence of *p*-TolI confirmed that an I(I)/I(III) manifold was operational (entry 11). An expanded optimization table is provided in the ESI.†

To explore the scope of this *geminal* difluorination, a series of α-(bromomethyl)styrenes were exposed to the standard reaction conditions (Fig. 2). Gratifyingly, product **2a** could be isolated in 80% yield after column chromatography on silica gel. The parent α-(bromomethyl)styrene was smoothly converted to species **2b**, as were the *p*-halogenated systems that furnished **2c** and **2d** (71 and 79%, respectively). The regioisomeric bromides **2e** and **2f** (70 and 62%, respectively) were also prepared for completeness to furnish a series of linchpins that can be functionalized at both termini by displacement and cross-coupling protocols (**2a**, **2e** and **2f**). Modifying the amine : HF ratio to 1 : 4.5 provided conditions to generate the ^{t}Bu derivative **2g** in 68% yield.[14] Electron deficient aryl derivatives were well tolerated as is demonstrated by the formation of compounds **2h**–**2k** (up to 91%). Disubstitution patterns (**2l**, 81%), sulfonamides (**2m**, 75%) and phthalimides (**2n**, 80%) were also compatible with the standard catalysis conditions. Gratifyingly, compound **2n** was crystalline and it was possible to unequivocally establish the structure by X-ray crystallography (Fig. 2, lower).[15] The C9–C8–C7 angle was measured to be 112.6° (*cf.* 115.4° for 2,2-difluoropropane).[5] Intriguingly, the C(sp^3)–Br bond eclipses the two C–F bonds rather than adopting a conformation in which dipole minimization is satisfied (F1–C8–C9–Br dihedral angle is 56.3°).

Cognizant of the influence of Brønsted acidity on the regioselectivity of I(I)/I(III) catalyzed alkene difluorination,[9d] the influence of the amine : HF ratio on the fluorination of

Table 1 Reaction optimization[a]



Entry	Solvent	Amine/HF	Catalyst loading [mol%]	Yield[b] [%]
1	$CHCl_3$	1 : 4.5	20	72
2	**$CHCl_3$**	**1 : 6.0**	**20**	**>95**
3	$CHCl_3$	1 : 7.5	20	94
4	$CHCl_3$	1 : 9.23	20	87
5	$CHCl_3$	1 : 6.0	10	87
6	$CHCl_3$	1 : 6.0	5	79
7	DCM	1 : 6.0	20	>95
8	DCE	1 : 6.0	20	93
9	ETFA	1 : 6.0	20	84
10	MeCN	1 : 6.0	20	50
11	$CHCl_3$	1 : 6.0	0	<5

[a] Standard reaction conditions: **1a** (0.2 mmol), Selectfluor® (1.5 equiv.), amine : HF source (0.5 mL), solvent (0.5 mL), *p*-TolI, 24 h, rt. [b] Determined by ^{19}F NMR using α,α,α-trifluorotoluene as internal standard.

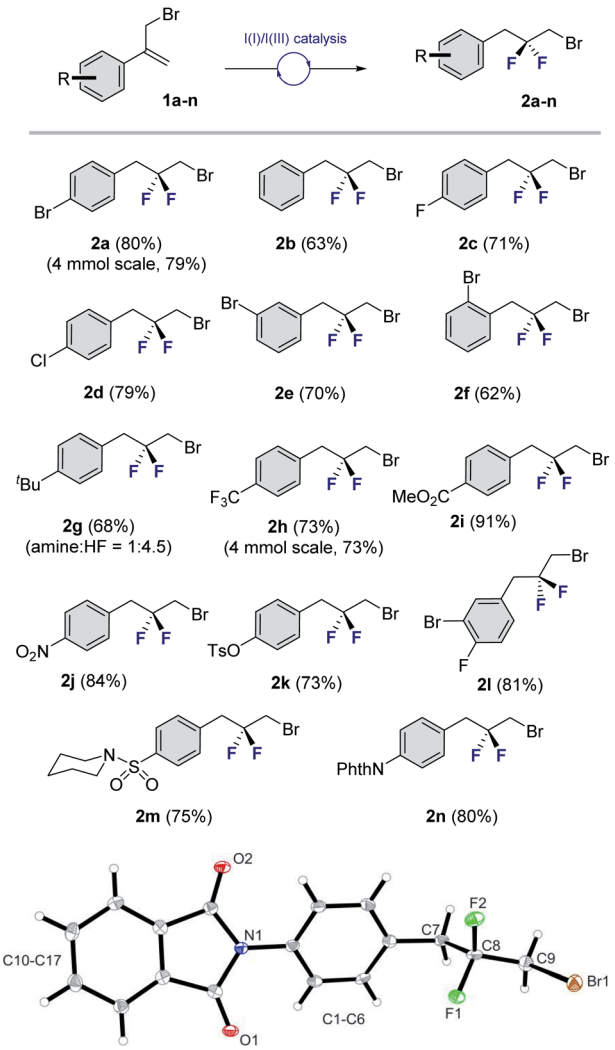


Fig. 2 Exploring the scope of the *geminal* difluorinative rearrangement of α-(bromomethyl)styrenes *via* I(I)/I(III) catalysis. Isolated yields after column chromatography on silica gel are reported. X-ray crystal structure of compound **2n** (CCDC 2055892†). Thermal ellipsoids shown at 50% probability.

electronically non-equivalent divinylbenzene derivatives was explored (Fig. 3, top). Initially, compound **3** bearing an α-(trifluoromethyl)styrene motif was exposed to the standard catalysis conditions with a 1 : 4.5 amine : HF ratio. Exclusive, chemoselective formation of **4** was observed in 79% yield. Simple alteration of the amine : HF ratio to 1 : 7.5 furnished the tetrafluorinated product **5** bearing both the *geminal* and *vicinal* difluoromethylene[16] groups (55% yield. 20% of the *geminal–geminal* product was also isolated. See ESI†). Relocating the electron-withdrawing group (α-CF_3 → β-CO_2Me) and repeating the reaction with 1 : 4.5 amine : HF generated the *geminal* CF_2 species **7** in analogy to compound **4**. However, increasing the amine : HF ratio to 1 : 6.0 led exclusively to double *geminal* difluorination (**8**, 55%).

Similarly, bidirectional *geminal* difluorination of the divinylbenzene derivatives **9** and **11** was efficient, enabling the synthesis of **10** (46%) and **12** (70%), respectively. This enables facile access to bis-electrophilic fluorinated linchpins for application in materials chemistry.

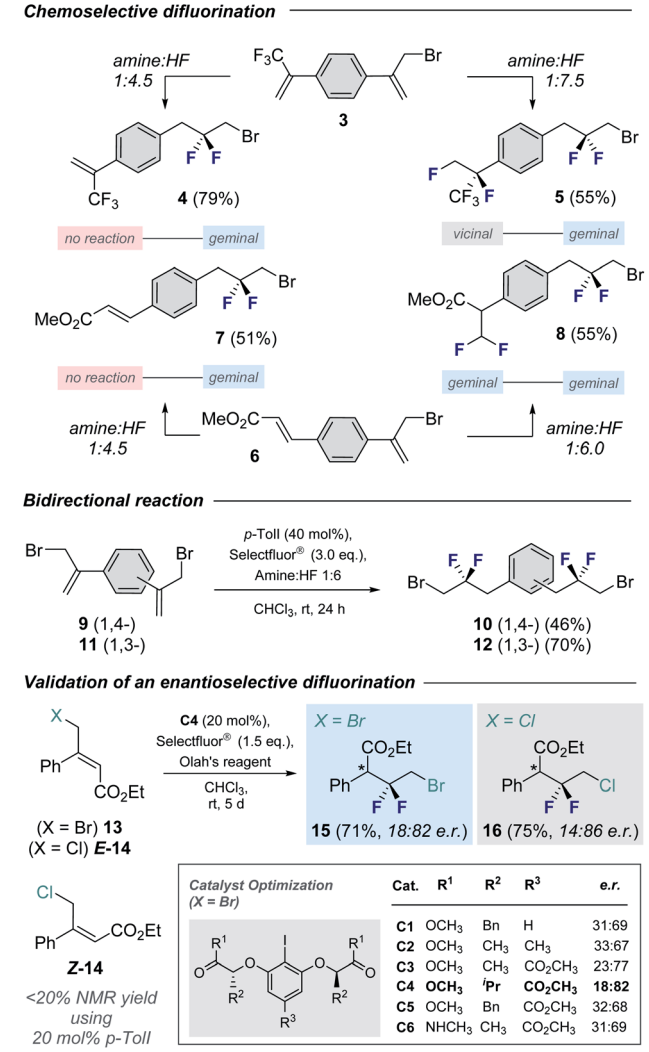


Fig. 3 Exploring the synthetic versatility of this platform. (Top) Leveraging Brønsted acidity to achieve chemoselective fluorination. (Centre) Bidirectional functionalization. (Bottom) Preliminary validation of an enantioselective variant.

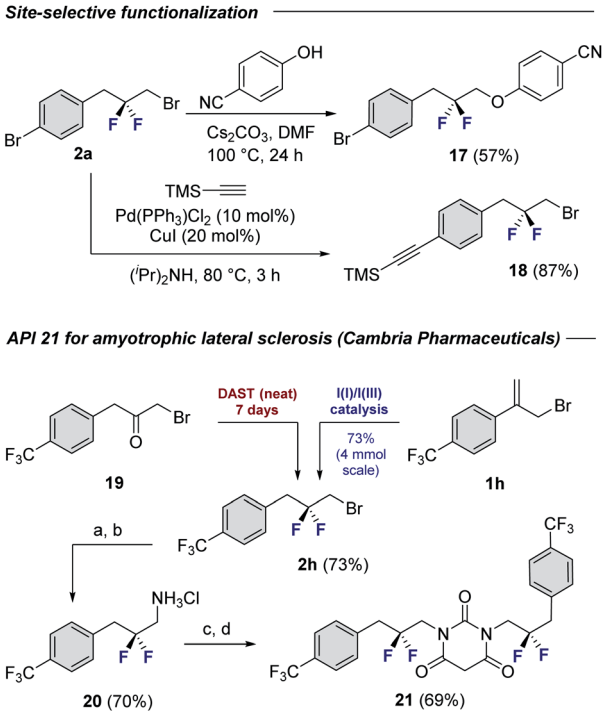


Fig. 4 Selected modification of building blocks **2a** and **2h**. Conditions: (a) NaN_3, DMF, 110 °C, 16 h. (b) $Pd(OH)_2/C$ (10 mol%), EtOH, 1 M HCl, rt, 24 h; (c) CDI, Et_3N, THF, 60 °C, 16 h; (d) malonyl chloride, DCM, 0 °C, 2 h.

Preliminary validation of an enantioselective variant[8d] was achieved using the trisubstituted alkene **13**. To that end, a series of C_2-symmetric resorcinol-based catalysts were explored (see Fig. 3, inset). This enabled the generation of product **15** in up to 18 : 82 e.r. and 71% isolated yield. It is interesting to note that this catalysis system was also compatible with the chlorinated substrate ***E*-14**. A comparison of geometric isomers revealed a matched-mismatched scenario: whilst ***E*-14** was efficiently converted to **16** (75%, 14 : 86 e.r.), ***Z*-14** was recalcitrant to rearrangement (<20%).

To demonstrate the synthetic utility of the products, chemoselective functionalization of linchpin **2a** was performed to generate **17** (57%) and **18** (87%), respectively (Fig. 4). Finally, this method was leveraged to generate an API for amyotrophic lateral sclerosis. Whereas the reported synthesis[17] requires the exposure of α-bromoketone **19** to neat DAST over 7 days,[18] compound **2h** can be generated using this protocol over a more practical timeframe (24 h) on a 4 mmol scale. This key building block was then processed, *via* the amine hydrochloride salt **20**, to API **21**.

Conclusions

In conclusion, an I(I)/I(III) catalysis manifold that facilitates the difluorinative rearrangement of α-(bromomethyl)styrenes is

disclosed. In addition to generating electrophiles with a single *geminal* difluoro motif, bidirectional processes are presented together with simultaneous *geminal* and *vicinal* difluorination. Preliminary validation of an enantioselective reaction is demonstrated, to enable the generation of versatile α-phenyl-β-difluoro-γ-bromo/chloro esters. Finally, the transformation has been leveraged to enable the synthesis of an amyotrophic lateral sclerosis drug: this provides an operationally simple alternative to common deoxyfluorinating reagents when preparing *gem*-difluoro linchpins for contemporary medicinal chemistry.

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 31st March 2021. The title contained a typesetting error. The oxidation state change in the title was incorrect and should read I(I)/I(III).

Acknowledgements

We acknowledge generous financial support from the WWU Münster and the European Commission (ERC Consolidator Grant, 818949 RECON).

Notes and references

1 (*a*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3; (*b*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*c*) L. Zimmer, C. Sparr and R. Gilmour, *Angew. Chem., Int. Ed.*, 2011, **50**, 11860; (*d*) M. Aufiero and R. Gilmour, *Acc. Chem. Res.*, 2018, **51**, 1701.

2 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

3 Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira and K. Müller, *J. Med. Chem.*, 2015, **58**, 9041.

4 (*a*) G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc., Perkin Trans. 1*, 1984, **1**, 1119; (*b*) G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Chem. Commun.*, 1981, 511.

5 D. O'Hagan, Y. Wang, M. Skibinski and A. M. Z. Slawin, *Pure Appl. Chem.*, 2012, **84**, 1587.

6 (*a*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (*b*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315; (*c*) I. G. Molnár, C. Thiehoff, M. C. Holland and R. Gilmour, *ACS Catal.*, 2018, **6**, 7167.

7 For selected reviews on I(III)-mediated fluorination of alkenes, see (*a*) S. V. Kohlhepp and T. Gulder, *Chem. Soc. Rev.*, 2016, **45**, 6270; (*b*) A. M. Arnold, A. Ulmer and T. Gulder, *Chem.–Eur. J.*, 2016, **22**, 8728; (*c*) S. Doobary and A. J. J. Lennox, *Synlett*, 2010, **31**, 1333.

8 For selected examples of 1,1-difluorination, see: (*a*) S. Hara, J. Nakahigashi, K. Ishi-I, T. Fukuhura and N. Yoneda, *Tetrahedron Lett.*, 1998, **39**, 2589; (*b*) N. O. Ilchenko, B. O. A. Tasch and K. J. Szabó, *Angew. Chem., Int. Ed.*, 2014, **53**, 12897; (*c*) T. Kitamura, K. Muta and J. Oyamada, *J. Org. Chem.*, 2015, **80**, 10431; (*d*) S. M. Banik, J. W. Medley and E. N. Jacobsen, *Science*, 2016, **353**, 51; (*e*) N. O. Ilchenko and K. J. Szabó, *J. Fluorine Chem.*, 2017, **203**, 104; (*f*) F. Scheidt, J. Neufeld, M. Schäfer, C. Thiehoff and R. Gilmour, *Org. Lett.*, 2018, **20**, 8073; (*g*) Z. Zhao, L. Racicot and G. K. Murphy, *Angew. Chem., Int. Ed.*, 2017, **56**, 11620; (*h*) T. Kitamura, K. Yoshida, S. Mizuno, A. Miyake and J. Oyamada, *J. Org. Chem.*, 2018, **83**, 14853; (*i*) W.-X. Lv, Q. Li, J.-L. Li, Z. Li, E. Lin, D.-H. Tan, Y.-H. Cai, W.-X. Fan and H. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 16544.

9 For selected examples of 1,2-difluorination, see (*a*) S. M. Banik, J. W. Medley and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2016, **138**, 5000; (*b*) I. G. Molnár and R. Gilmour, *J. Am. Chem. Soc.*, 2016, **138**, 5004; (*c*) M. K. Haj, S. M. Banik and E. N. Jacobsen, *Org. Lett.*, 2019, **21**, 4919; (*d*) F. Scheidt, M. Schäfer, J. C. Sarie, C. G. Daniliuc, J. J. Molloy and R. Gilmour, *Angew. Chem., Int. Ed.*, 2018, **57**, 16431; (*e*) N. Erdeljac, G. Kehr, M. Ahlqvist, L. Knerr and R. Gilmour, *Chem. Commun.*, 2018, **54**, 12002; (*f*) N. Erdeljac, K. Bussmann, A. Schöler, F. K. Hansen and R. Gilmour, *ACS Med. Chem. Lett.*, 2019, **10**, 1336; (*g*) S. Doobary, A. T. Sedikides, H. P. Caldora, D. L. Poole and A. J. J. Lennox, *Angew. Chem., Int. Ed.*, 2020, **59**, 1155; (*h*) N. Erdeljac, C. Thiehoff, R. Jumde, C. Daniliuc, S. Hoeppner, A. Faust, A. K. H. Hirsch and R. Gilmour, *J. Med. Chem.*, 2020, **63**, 6225; (*i*) S. Meyer, J. Häfliger, M. Schäfer, J. J. Molloy, C. G. Daniliuc and R. Gilmour, *Angew. Chem., Int. Ed.*, 2021, **60**, 6430.

10 (*a*) C. Ye, B. Twamley and J. M. Shreeve, *Org. Lett.*, 2005, **7**, 3961; (*b*) J. C. Sarie, C. Thiehoff, R. J. Mudd, C. Daniliuc, G. Kehr and R. Gilmour, *J. Org. Chem.*, 2017, **82**, 11792.

11 For an elegant example of harnessing bromonium ions in I(III)-mediated fluorination see: (*a*) M. D. Levin, J. M. Ovian, J. A. Read, M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2020, **142**, 14831For an example of the synthesis of β-difluoroalkyl azides *via* 1,2-azide migration, see: (*b*) Y. Ning, P. Sivaguru, G. Zanoni, E. A. Anderson and X. Bi, *Chem*, 2020, **6**, 486.

12 T. Bykova, N. Al-Maharik, A. M. Z. Slawin and D. O'Hagan, *J. Fluorine Chem.*, 2015, **179**, 188.

13 J. L. Cotter, L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, 1962, **84**, 793.

14 Highly electron rich substrates were avoided due to their known ability to undergo uncatalysed *vicinal* difluorination with HF and Selectfluor®: G. S. Lal, *J. Org. Chem.*, 1993, **58**, 2791.

15 CCDC 2055892 contains the ESI crystallographic data for compound **2n**.†

16 C. Thiehoff, Y. P. Rey and R. Gilmour, *Isr. J. Chem.*, 2017, **57**, 92.
17 (*a*) D. R. Kirsch, R. Benmohamed, A. C. Arvanites, R. I. Morimoto, G. Xia and R. B. Silverman, *WO Pat.*, 2010129665A2, 2010; (*b*) G. Xia, R. Benmohamed, R. I. Morimoto, D. R. Kirsch and R. B. Silverman, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5098.
18 P. A. Messina, K. C. Mange and W. J. Middleton, *J. Fluorine Chem.*, 1989, **42**, 137.