2,2-Difluoroethylation of heteroatom nucleophiles via a hypervalent iodine strategy

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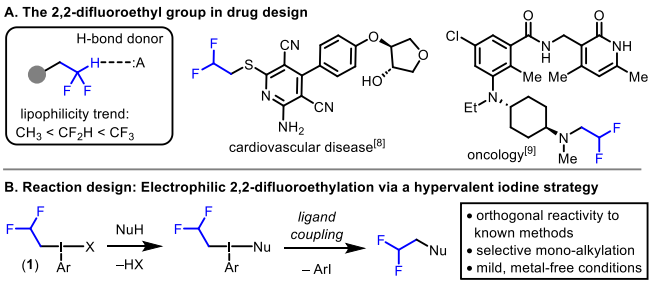
Abstract: The 2,2-difluoroethyl group is an important lipophilic hydrogen bond donor in medicinal chemistry, but its incorporation into small molecules is often challenging. Herein, we demonstrate electrophilic 2,2-difluoroethylation of thiol, amine and alcohol nucleophiles with a hypervalent iodine reagent, (2,2-difluoroethyl)(aryl)iodonium triflate, via a proposed ligand coupling mechanism. This transformation offers a complementary strategy to existing 2,2-difluoroethylation methods and allows access to a wide range of 2,2-difluoroethylated nucleophiles, including the drugs Captopril, Normorphine and Mefloquine.

The importance of fluorinated compounds in materials science, agrochemistry and pharmaceuticals is undisputed.[1–4] In medicinal chemistry, in particular, fluorinated functional groups can be used as a design strategy to create properties that are not found in biologically available molecules and to improve the physicochemical properties of drug compounds.[5,6] The development of innovative synthetic methods for the introduction of fluorinated groups into small molecules is thus an important research area. The difluoroethyl group (-CH_2CF_2H) has recently become popular as a lipophilic hydrogen bond donor (Scheme 1A).[7–10] Incorporation of electronegative fluorine atoms allows for lipophilicity modulation and increases the acidity of the α-proton, tuning drug target affinity and specificity.[11–13] Furthermore, the C–F bonds can impart metabolic stability, making the difluoroethyl group a stable bioisostere for alcohol, ether, thiol, amine and amide pharmacophores. Despite its utility in drug design, selective 2,2-difluoroethylation is relatively under-developed.[14] Existing methods are often substrate-specific and rely mainly on radical fluoroalkylation of unsaturated systems,[15–21] transition-metal catalysed cross-coupling approaches,[22–27] and electrophilic 2,2-difluoroethylation via an S_N2 mechanism.[28–34] The latter can frequently suffer from low conversions for sterically encumbered nucleophiles and over-alkylation of primary amines, while the former two require the use of expensive transition metals. A complementary, metal-free method for the selective 2,2-difluoroethylation of a wide range of structurally diverse nucleophiles would be a valuable driver for the design and synthesis of new drug targets.

Hypervalent iodine reagents are known to possess great mechanistic flexibility in their reaction with nucleophiles,[35–37] enabling access to motifs that are difficult to synthesise using traditional approaches. Inspired by the success of hypervalent iodine chemistry for the installation of fluoroalkyl groups,[38–43] we postulated that the design of a 2,2-difluoroethyl(aryl)iodonium reagent (**1**) would allow for efficient transfer of the CH_2CF_2H motif to a wide variety of nucleophiles (Scheme 1B). As these reactions likely occur via a ligand coupling mechanism, they offer a complementary strategy to existing methods, enabling access to new 2,2-difluoroethylated motifs.

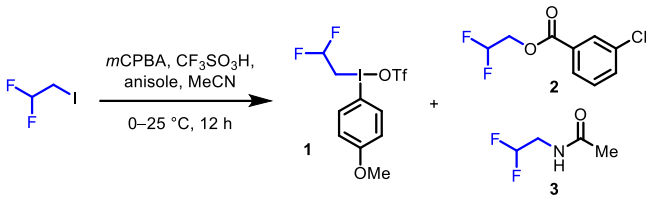


Scheme 1. 2,2-Difluoroethylation of drug targets. (A = hydrogen bond acceptor, NuH = nucleophile.)

(2,2-Difluoroethyl)(4-methoxyphenyl)iodonium triflate **1** was successfully synthesised from commercially available 1,1-difluoro-2-iodoethane (Table 1), as confirmed by ^1H and ^{19}F NMR analysis of the crude reaction mixture (see ESI). Optimisation showed that the choice of oxidant was pivotal for the successful formation of iodane **1** (Table 1, entries 1 and 5–6), and that electron-rich aromatic ligands (*e.g.* 4-methoxyphenyl) helped stabilise this species in solution (entry 3). Electron-poor aromatic ligands made the iodane highly susceptible to nucleophilic attack by the reduced oxidant, 3-chlorobenzoic acid, leading to the formation of difluoroethylbenzoate **2** (entry 4). Crucially, water was detrimental to the reaction outcome, as it enabled the formation of difluoroethylacetamide **3** via a Ritter-like reaction of the hypervalent iodine intermediate with MeCN (entry 7).[44,45] Rapid decomposition of 2,2-difluoroethyl(aryl)iodonium triflate **1** to iodoanisole was observed upon isolation (see ESI). However,

we were optimistic that we could trap the hypervalent iodine intermediate **1** with nucleophiles *in situ*, thereby generating an efficient platform for 2,2-difluoroethylation.

Table 1. *In situ* formation of (2,2-difluoroethyl)(aryl)iodonium triflate **1**

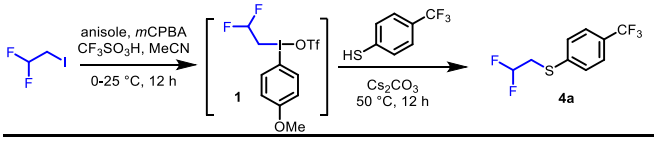


Entry	Deviation from standard conditions[a]	**1** [%][b]	**2** [%][b]	**3** [%][b]
1	**None**	**59**	**1**	**0**
2	Solvent = DCM	77	0	0
3	ArH = benzene	33	0	0
4	ArH = nitrobenzene	23	55	0
5	Oxidant = Selectfluor	6	0	0
6	Oxidant = Urea.H_2O_2	<1	<1	0
7	1 equiv. H_2O	51	0	33

[a] Standard conditions (i) 1,1-difluoro-2-iodoethane (1.04 mmol), anisole = methoxybenzene (1.14 mmol), *m*CPBA (2.5 mmol), CF_3SO_3H (1.2 equiv), MeCN (5 mL, 0.2 M), 0–25 °C, 12 h, Ar, exclusion of light. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. Unreacted 1,1-difluoro-2-iodoethane accounted for the remaining mass balance.

Indeed, using 4-(trifluoromethyl)benzenethiol as a model nucleophile, we were able to trap the fluoroalkyl(aryl)iodonium intermediate *in situ* and detect the desired 2,2-difluoroethylated thiophenol **4a** in 78% yield by ^{19}F NMR spectroscopy (Table 2). Unreacted 1,1-difluoro-2-iodoethane and small amounts of difluoroethylbenzoate **2** accounted for the remainder of the mass balance. A range of oxidants were screened to improve the oxidation of 1,1-difluoro-2-iodoethane and avoid the formation of **2**, however no competent alternative to *meta*-chloroperbenzoic acid (*m*CPBA) was identified (see ESI). The sensitivity of the reaction to water precluded the use of aqueous oxidants (Table 2, entry 2). While DCM showed successful formation of the hypervalent iodine intermediate **1** (Table 1, entry 2), coordinating solvents such as MeCN[46,47] gave a higher yield of fluoroalkylated product **4a** in the trapping experiments (Table 2, entry 1 vs. 3). Addition of hexafluoroisopropanol (HFIP) as a co-solvent, which has previously been shown to have a beneficial effect on the synthesis and stabilisation of iodine(III) species,[48–50] did not improve our results (entry 4). Attempts to reduce the reaction time and temperature led to diminished difluoroethylation yields (entries 5-7). Our optimised one-pot conditions were thus as follows: Oxidation of 1,1-difluoro-2-iodoethane with 2.5 equiv. *m*CPBA in the presence of trifluoromethanesulfonic acid (1.2 equiv) and anisole (1.1 equiv.) in MeCN for 12 hours, followed by reaction with the nucleophile (1.1 equiv.) and Cs_2CO_3 (2.0 equiv.) at 50° C for a further 12 hours afforded the desired 2,2-difluoroethylated thiophenol **4a** in 71% isolated yield.

Table 2. Reaction optimisation: 2,2-difluoroethylation of thiol nucleophiles[a]

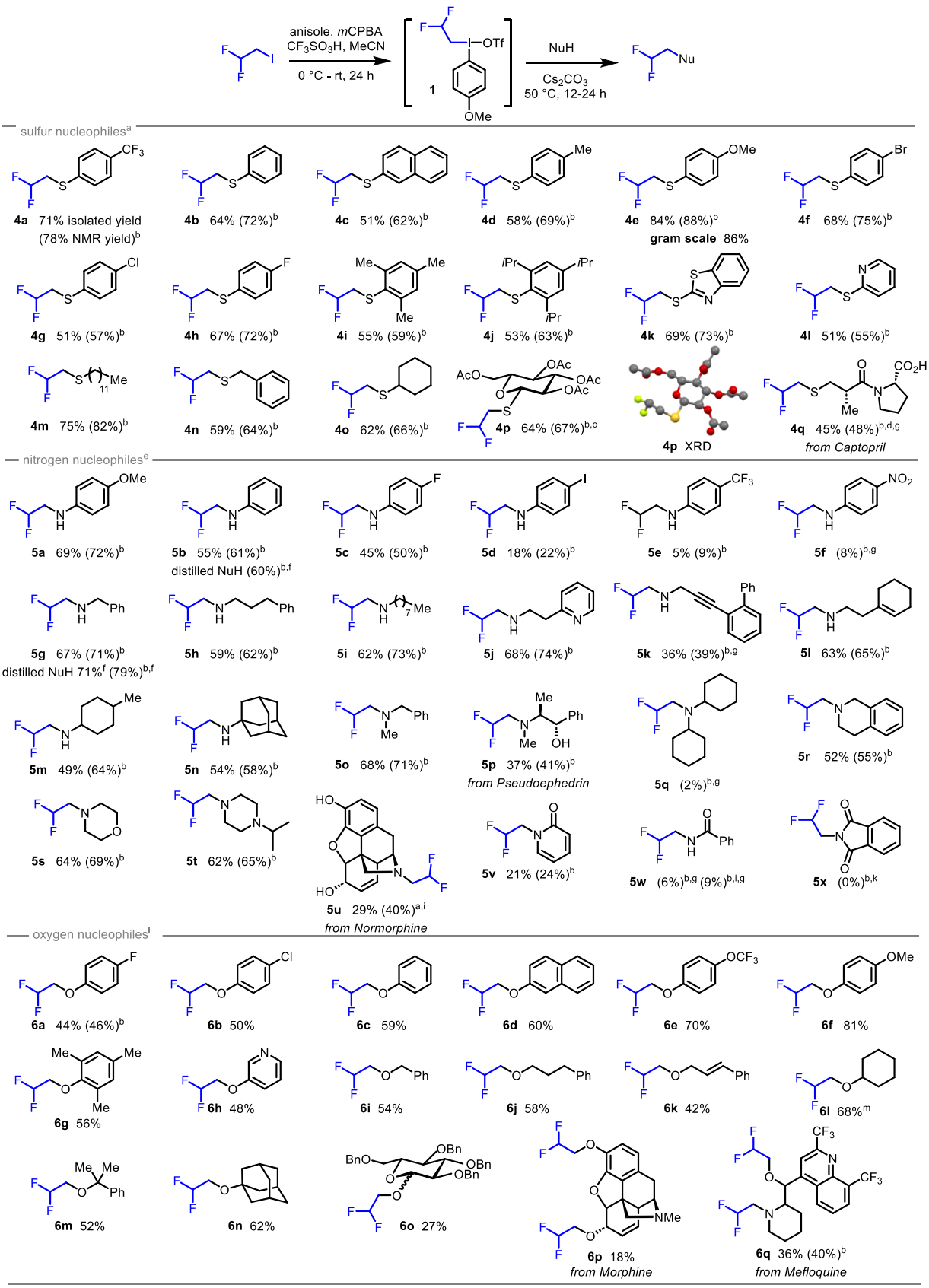


Entry	Deviation from standard conditions	**4a** [%][b]
1	**None**	**78 (71)**
2	Oxidant = H_2O_2 (30% in H_2O)	2
3	Solvent = DCM	58
4	solvent = MeCN:HFIP (5:1, 6 mL)	70
5	t (step 1) = 3 h	66
6	t (step 1) = 3 h, t (step 2) = 1 h	53
7	T (step 2) = r.t.	61

[a] Standard conditions: (i) 1,1-difluoro-2-iodoethane (1.04 mmol), anisole (1.14 mmol), *m*CPBA (2.5 mmol), CF_3SO_3H (1.2 equiv), MeCN (5 mL, 0.2 M), 0–25 °C, 10 h; (ii) 4-(trifluoromethyl)benzenethiol (1.1 mmol), Cs_2CO_3 (2.0 mmol), 50 °C, 12 h. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. Unreacted 1,1-difluoro-2-iodoethane and small amounts of difluoroethylbenzoate **2** accounted for the remainder of the mass balance. Yields of the isolated product are given in brackets.

With optimised conditions in hand, we investigated the scope and generality of our method (Scheme 2). The method proved to be very robust for thiol nucleophiles. Aromatic and aliphatic 2,2-difluoroethylthiols were obtained in good yields for electron-rich and electron-poor thiols (**4a**–**o**: 51-84%), while steric bulk on the nucleophile led to a slight reduction in yield (**4i–j**: 53–55%). Scale-up to gram scale was successful without a reduction in yield (**4e** was obtained in 84% isolated yield on a 1 mmol scale, and 86% isolated yield (1.06 g) on a 6 mmol scale). Pleasingly, heteroaromatics such as benzothiazole (**4k**) and pyridine (**4l**) were stable to the oxidising conditions, affording 2,2-difluoroethylated products in 69% and 51% respectively. 2-Mercaptopyridine (**4l**) was selectively functionalised on sulfur, as confirmed by NOESY, ^{13}C and ^{19}F NMR spectroscopy.

Next, we demonstrated the application of this methodology to more complex targets: 2,2-difluoroethylation of 1-thio-β-D-glucose tetraacetate proceeded in 64% yield, and the structure of the product **4p** was confirmed by X-ray crystallography.[51] Finally, late-stage functionalisation of a drug target was demonstrated by 2,2-difluoroethylation of the hypertenstion drug Captopril in 45% yield (**4q**). The 2,2-difluoroethylation of these targets has not previously been reported.



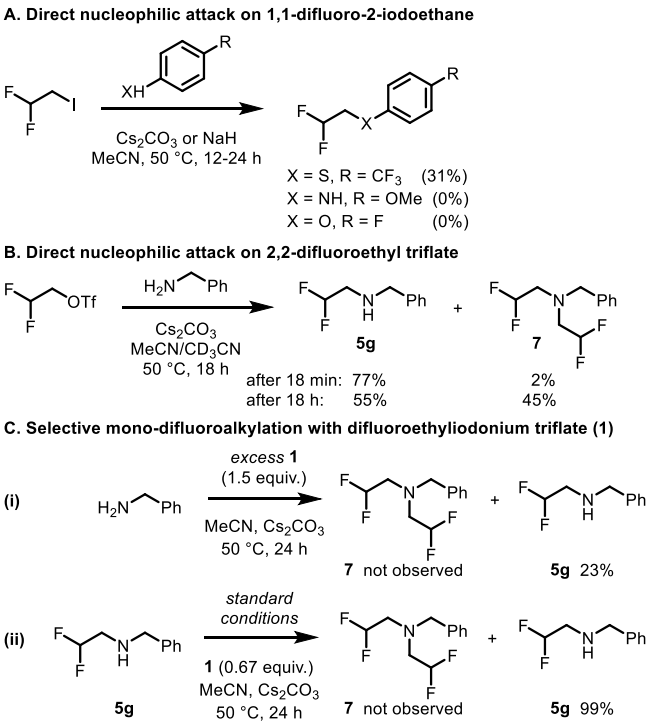
Scheme 2. 2,2-Difluoroethylation Scope. Yields are of isolated products. [a] Conditions: (i) 1,1-difluoro-2-iodoethane (1.04 mmol), anisole (1.1 equiv), *m*CPBA (2.5 equiv), CF_3SO_3H (1.2 equiv.), MeCN (5 mL, 0.2 M), 0–25 °C, 12 h; (ii) thiol (1.1 equiv.), Cs_2CO_3 (2.0 equiv.), 50 °C, 12 h. [b] Crude yield in parentheses, determined by ^{19}F NMR spectroscopy. [c] Structure confirmed by XRD. [d] Reaction time (step 2) = 36 h. [e] Conditions: (i) 1,1-difluoro-2-iodoethane (1.04 mmol), anisole (1.1 equiv.), *m*CPBA (2.1 equiv.), CF_3SO_3H (1.2 equiv.), MeCN (5 mL, 0.2 M), 0–25 °C, 24 h; (ii) amine (1.5 equiv.), Cs_2CO_3 (2.0 equiv.), 50 °C, 24 h. [f] Amine was distilled before use. [g] NaH (3.5 equiv.) was used as the base in step 2. [k] No reaction with phthalimide or potassium phthalimide; reaction time (step 2) = 3 days. [l] Conditions: (i) as [e]; (ii) alcohol (1.5 equiv.), NaH (3.5 equiv.), 50 °C, 24 h. [m] Reaction time (step 2) = 16 h.

Nitrogen-containing functional groups are one of the most significant motifs in medicinal chemistry[52,53] and the fluoroalkylation of amines has recently received much interest.[15,54,55] However, amine nucleophiles often show reduced reactivity towards hypervalent iodine compounds, requiring high reaction temperatures of up to 110 °C.[56] Indeed, when we submitted 4-methoxyaniline to our reaction conditions, we observed a lower yield of the desired 2,2-difluoroethylated product along with significant amounts of difluoroethylbenzoate **2** and Ritter product **3**. After slight re-optimisation (see ESI), increasing the amount of amine nucleophile (to 1.5 equiv.) and the reaction time in step 2, we were delighted to find 2,2-difluoroethylation conditions that afforded *N*-(2,2-difluoroethyl)-4-methoxyaniline **5a** in 69% yield upon isolation (Scheme 2B). Other electron-neutral and electron-rich aromatic and aliphatic amines also afforded synthetically useful yields of the corresponding 2,2-difluoroethylated products (**5a**–**c**: 48–69%, **5g–p**: 37–71%). A strong correlation was observed between amine nucleophilicity and difluoroethylation yields, with decreased reactivity observed for electron-deficient anilines (**5c**–**f**) and sterically encumbered secondary amines (**5o–q**, **5u**). Similarly, 2-pyridone (**5w**), amides and amide salts (**5x**–**y**) were not competent nucleophiles under these conditions.
However, we were pleased to demonstrate the applicability of our method to the late-stage difluoroethylation of pharmaceutically relevant nitrogen-containing molecules such as Pseudoephedrin (**5p**: 37%), morpholine (**5s**: 64%) and Normorphine (**5u**: 29%).

Continuing our investigation of pharmaceutically relevant motifs, our attention next turned to fluoroalkyl ethers. After slight re-optimisation (see ESI), 2,2-difluoroethyl(aryl)iodonium triflate **1** was successfully reacted with alcohol nucleophiles, allowing access to 2,2-difluoroethyl ethers (Scheme 2C). Reactivity trends largely matched those observed for amine nucleophiles. We were delighted to find that in addition to electron-neutral and -rich phenols (**6c**–**f**) and sterically unencumbered aliphatic substrates (**6i**–**k**), halogenated phenols (**6a**–**b**) and sterically hindered secondary and tertiary aliphatic alcohols (**6l**–**n**) were also difluoroethylated in good yields. It should be noted here that fluorinated molecules of low molecular weight are relatively volatile. To account for potential loss of volatile products upon isolation, ^{19}F NMR yields are reported in addition to isolated yields for difluoroethylsulfanes **4** and -amines **5** (Scheme 2). This was not possible for difluoroethyl ether products **6**, as they were indistinguishable from difluoroethylbenzoate **2** by ^{19}F NMR spectroscopy.
2,2-Difluoroethylation of complex alcohols was demonstrated with the functionalisation of D-glucose tetraacetate (**6o**: 27%) and drug compounds Morphine (**6p**: 18%) and Mefloquine (**6q**: 36%).

2-Hydroxypyridine was selectively 2,2-difluoromethylated on nitrogen (**5v**), while functionalisation of 3-hydroxypyridine (**6g**) occurred selectively on oxygen. Mefloquine, which contains secondary aliphatic amine and alcohol functional groups, predominantly showed unselective *N*- and *O*-difluoroethylation (**6q**), with small amounts (6%) of the *N*-fluoroalkylated product (without functionalisation of the alcohol) detected by ^{19}F NMR spectroscopy. Normorphine, by contrast, which contains a secondary amine and two (allylic and phenolic) alcohol functional groups, gave selective *N*-difluoroethylation (**5u**), with no *O*-difluoroethylation observed. When the amine group is protected, as is the case in Morphine, the two hydroxyl groups were difluoroethylated indiscriminately (**6p**).

The generally accepted mechanism for the reaction of iodonium salts with nucleophiles proceeds through nucleophilic attack on the hypervalent iodine centre followed by ligand coupling (Scheme 4A).[36,57–60] Our substrate scope shows a clear correlation between nucleophilicity and difluoroethylation yields, which supports this mechanistic proposal. Direct reaction of nucleophiles with 1,1-difluoro-2-iodoethane gave significantly reduced yields of the corresponding product (thiol: 31%, amine or alcohol: 0%), demonstrating that formation of the hypervalent iodine intermediate is critical for the reaction to proceed efficiently (Scheme 4A).



Scheme 4. Control reactions: **A.** Direct nucleophilic attack on 1,1-difluoro-2-iodoethane. **B.** Direct nucleophilic attack on 2,2-difluoroethyl triflate. **C.** Selective mono-difluoroalkylation with (2,2-difluoroethyl)(aryl)iodonium triflate (**1**). Yields and conversions were determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard.

To further determine the contribution of this background reaction and to investigate the potential formation of 2,2-difluoroethyl triflate under the reaction conditions, the reaction of benzylamine with (a) 1,1-difluoro-2-iodoethane, (b) the *in situ* generated (2,2-difluoroethyl)(4-methoxyphenyl)iodonium triflate **1**, and (c) 2,2-difluoroethyl triflate were followed by ^{19}F NMR spectroscopy (see ESI). The reaction with 1,1-difluoro-2-iodoethane is sluggish, and its contribution to the overall reaction of benzylamine with (2,2-difluoroethyl)(4-methoxyphenyl)-iodonium triflate **1** remains at <10% after 24 hours. Difluoroethylation with 2,2-difluoroethyl triflate is very fast (indeed, it is faster than the reaction with **1** by a factor of ca. 10), but a significant amount (45%) of over-alkylation to bis-difllluoroethylbenzylamine **7** occurs within the time frame of the reaction (Scheme 4B). Importantly, our method was

highly selective for mono-alkylation of primary amines (Scheme 4C). When benzylamine was reacted with an excess of the hypervalent iodine reagent, no over-alkylation to bis-difluoroethylbenzamine **7** was detected (Scheme 4Ci). Instead, mono-difluoroethylbenzamine **5g** was formed selectively. Similarly, when **5g** was isolated and re-submitted to our standard fluoroalkylation conditions, it was recovered without undergoing any further difluoroethylation (Scheme 4Cii).

In conclusion, we have demonstrated an electrophilic 2,2-difluoroethylation strategy for thiol, amine and alcohol nucleophiles with a 2,2-difluoroethyl(aryl)iodonium salt. This methodology allows for selective, metal-free incorporation of the lipophilic hydrogen bond donor CH_2CF_2H into pharmaceutically relevant targets, providing a handle for the modulation of pharmacokinetic properties during drug design and optimisation. From a more fundamental point of view, this manuscript demonstrates the first successful synthesis and application of a hypervalent iodine(III) complex bearing the difluoroethyl group. This work is part of ongoing efforts within our group to design and synthesise hypervalent iodine complexes bearing non-stabilised functional groups.

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Keywords: Alkylation • Fluorine • Medicinal Chemistry • Hypervalent compounds • Synthetic methods

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