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Pd-Catalyzed Difluoromethylations of Aryl Boronic Acids, Halides, and Pseudohalides with ICF$_2$H Generated ex Situ

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Abstract: An expedient ex-situ generation of difluoroiodomethane (DFIM) and its immediate use in a Pd-catalyzed difluoromethylation of aryl boronic acids and ester derivatives in a two-chamber reactor is reported. Heating a solution of bromodifluoroacetic acid with sodium iodide in sulfolane proved to be effective for the generation of near stoichiometric amounts of DFIM for the ensuing catalytic coupling step. A two-step difluoromethylation of aryl (pseudo)halides with tetrahydroxydiboron as a low-cost reducing agent, both promoted by Pd catalysis, proved effective to install this fluorine-containing C$_1$ group onto several pharmaceutically relevant molecules. Finally, the method proved adaptable to deuterium incorporation by simply adding D$_2$O to the DFIM-generating chamber.

Exchanging hydrogen with fluorine in compounds of pharmaceutical interest can, in certain cases, improve their bioavailability and half-lives, as exemplified by enhanced cell-membrane permeation and metabolic stability.[1] The difluoromethyl group is one such fluorine-containing motif, capable of acting as a metabolic blocker when installed instead of a methyl group.[2] Furthermore, its polarized C–H bond can operate as a hydrogen bond donor rendering this motif a bioisostere to alcohols, amines, and thiols.[3] This fragment is displayed in several bioactive structures, some of which are commercial pharmaceutical and agrochemical products (Figure 1).[4]

In particular, aryl and heteroaryl structures exhibiting difluoromethyl appendages are of great interest, and thus several synthetic methods have emerged, including the transformation of a pre-existing functionality, or the direct installation of this fluorine-containing motif onto an aromatic core (Scheme 1a). The deoxygenative fluorination of aldehydes is the most commonly employed method relying on reagents, such as sulfur tetrafluoride or DAST, even though hydrogen fluoride is released as a byproduct.[5] Several elegant Pd-catalyzed cross-coupling procedures have been established by Zhang and others, involving the use of difluorocarbene precursors (BrCF$_2$CO$_2$Et, BrCF$_2$PO(OEt)$_2$, Ph$_3$P$^+$CF$_2$CO$_2^-$, ClCF$_2$H) and aryl boronic acid derivatives.[6] A recent report from the Sanford group demonstrated the worth of a Pd-catalyzed decarbon-
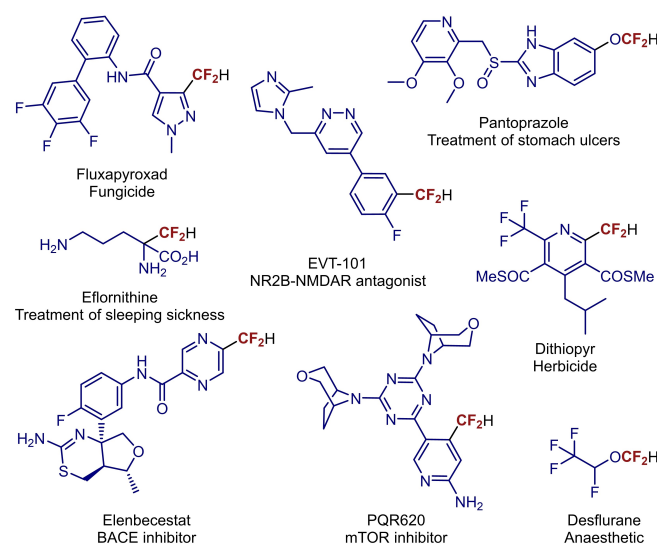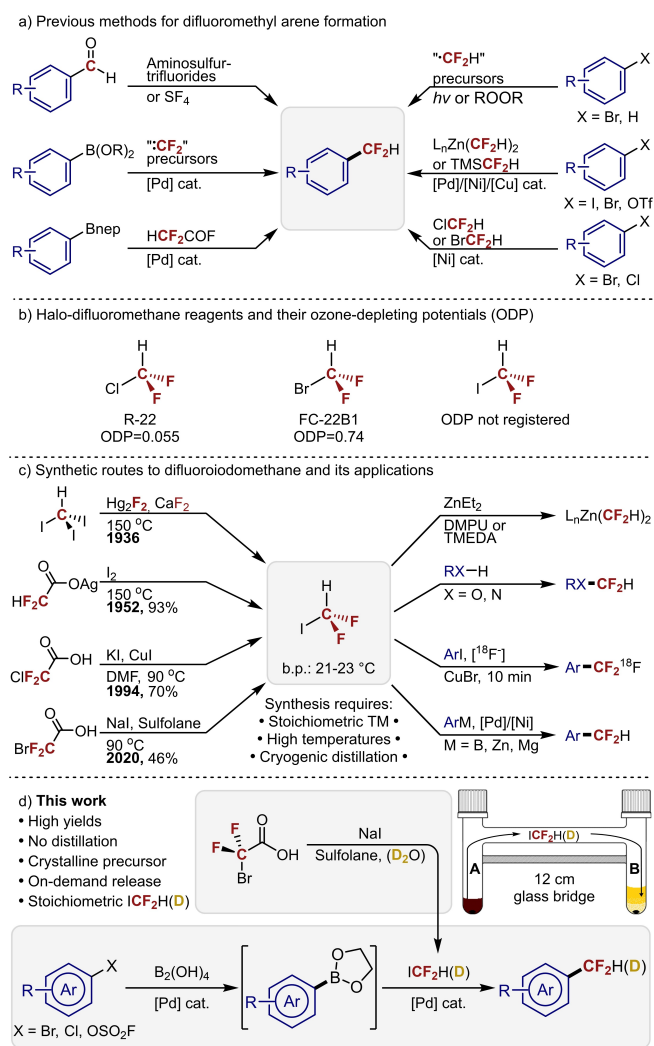

Figure 1. Examples of pharmaceuticals and agrochemicals containing a difluoromethyl group.

ylative Suzuki coupling between difluoroacetyl fluoride and aryl neopentylglycol boronate esters.[7] Several methods for radical-based difluoromethylations depending on peroxides or light and photocatalysts as activators have been developed.[8] Transition metal catalyzed cross-couplings of aryl (pseudo)halides and nucleophilic difluoromethyl sources, including TMSCF$_2$H,[9] ligated Zn(CF$_2$H)$_2$[10] and more[11] have also been reported, but display limited substrate scopes. Lastly, two Ni-catalyzed cross-electrophile couplings for the synthesis of difluoromethyl arenes have recently been published. The first relies on the use of a large excess of chlorodifluoromethane,[12] whereas in the other procedure, bromodifluoromethane[13] was exploited as the limiting reagent implying that an excess of the aryl halide is necessary. Interestingly, the use of both gaseous reagents is being phased out according to the Montreal Protocol due to their ozone-depleting potentials (ODPs;

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Scheme 1. Previous methods for the difluoromethylation of arenes. Synthetic routes to DFIM and applications.

Scheme 1b). Despite the ODPs of these halo-difluoromethane gases, they are handled and stored as stock solutions prepared by wastefully passing the gas through the solvent over several hours.[6b,12,13]

Difluoroiodomethane (DFIM) represents an alternative electrophilic difluoromethyl reagent, not being registered as toxic or ozone-depleting. However, the disadvantage of this reagent remains its low boiling point (21–23 °C) rendering it difficult to handle in stoichiometric amounts.[14] Different approaches for the synthesis and isolation of DFIM have been proposed throughout the last century as depicted in Scheme 1c.[15–18] Most methods rely on high reaction temperatures and the need for stoichiometric amounts of metal complexes. In 2020, researchers from Pfizer reported a metal free process,[18] demonstrating that bromodifluoroacetic acid in the presence of NaI in sulfolane at 90 °C generated efficiently DFIM with only small amounts of bromodifluoromethane.

Various synthetic applications of this low-boiling fluorine-containing reagent have been reported. One example involves
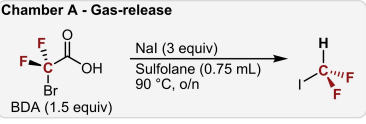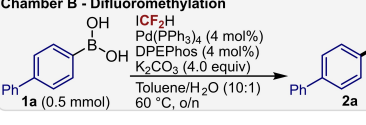
the conversion of DFIM into the aforementioned ligated bis(difluoromethyl)zinc reagent.[10,18] DFIM has also been successfully exploited for difluoromethylations of nitrogen- and oxygen-based nucleophiles.[19] Alternatively, the preparation of ^{18}F-labeled trifluoromethyl arenes for subsequent PET applications could be achieved starting from this fluorinated reagent.[20] Finally, DFIM was employed as the electrophilic coupling partner in various transition metal catalyzed cross-couplings with aryl boronic acids, zinc, and magnesium reagents as the nucleophilic coupling partner.[21]

In our efforts to develop chemical techniques for the safe handling of gaseous compounds, and to demonstrate their successful use as stoichiometric reagents, we have earlier reported the application of a two-chamber reactor in combination with easy-to-handle gas surrogates.[22–29] Others have reported its use for the expedient preparation of SO_2F_2.[30] Here, we report on a set-up for the simple synthesis of DFIM and its stoichiometric use in the Suzuki coupling with aryl boronic acids and derivatives thereof. We also demonstrate the usefulness of this reagent in an expedient two-step Pd-catalyzed difluoromethylation of aryl (pseudo)halides via the intermediate aryl boronic ethylene glycol ester using tetrahydroxydiboron as the reducing agent. Finally, the suitability of this synthetic methodology for the rapid installation of a deuterated difluoromethyl group onto an aromatic core was demonstrated, simply by the addition of D_2O in the DFIM releasing chamber (Scheme 1d).

In order to investigate the efficiency of the DFIM releasing chamber, a suitable and high yielding DFIM consuming reaction was necessary. Fortunately, Mikami et al. reported the Pd-catalyzed cross-coupling of aryl boronic acids and DFIM,[21a] thus demonstrating that the addition of a stock solution of DFIM in THF (1.5 equiv, 1.0–1.5 M) to a reaction mixture of 4-biphenyl-boronic acid (1 equiv), $Pd(PPh_3)_4$ (10 mol%), DPEPhos (10 mol%), and K_3PO_4 (2 equiv) in a toluene/H_2O (10:1) biphasic system stirred at 60 °C overnight provided the desired difluoromethylarene in an 89% yield. However, DFIM was only produced in a low 15% yield adapting a previous method starting from $ClCF_2CO_2H$ and with stoichiometric copper iodide.[17] To circumvent the low yielding DFIM protocol, we set-up a two-chamber reaction for this cross coupling event, resorting to the transition metal free conditions for DFIM production reported by Monfette et al., in Chamber A,[18] and the Mikami coupling conditions for difluoromethylation of aryl boronic derivatives in chamber B.

The results for the optimization are depicted in Table 1. Gratifyingly, we achieved a successful conversion of 4-biphenyl-boronic acid into 4-difluoromethylbiphenyl (**2a**) with an isolated yield of 89% after a thorough optimization of the reaction parameters. The conditions used consisted of stirring $Pd(PPh_3)_4$ (4 mol%), DPEPhos (4 mol%), and K_2CO_3 (4 equiv) in toluene/H_2O (10:1) in chamber B of the two-chamber system at 60 °C overnight. The best conditions for the gas release comprised of the solid DFIM precursor BDA (1.5 equiv) with NaI (3 equiv) and sulfolane (1 M) at 90 °C in chamber A (Table 1, entry 1). Exchanging the solvent in chamber A for DMF instead of sulfolane decreased the conversion to the desired product

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Table 1. Optimization of the reaction conditions.

	Deviation	Yield [%][a]
1	none	90 [89][b]
2	DMF i.o. sulfolane	41
3	without NaI	0
4	BDA (1.1 equiv) and NaI (2.2 equiv)	76
5	without DPEPhos	35
6	XantPhos i.o. DPEPhos	41
7	Pd(PPh₃)₄ (1 mol%) and DPEPhos (1 mol%)	38
8	Pd₂(dba)₃ (2 mol%) i.o. Pd(PPh₃)₄ (4 mol%)	21
9	K₃PO₄ (4 equiv) i.o. K₂CO₃ (4 equiv)	90
10	Et₃N (4 equiv) i.o. K₂CO₃ (4 equiv)	36
11	K₂CO₃ (3 equiv) i.o. K₂CO₃ (4 equiv)	83
12	70 °C i.o. 60 °C	88
13	THF i.o. toluene	46
14	without water	28
15	2 days and 70 °C	[95][b]

i.o. = instead of. [a] ^{1}H NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield as an average of two runs.

chromatography using normal phase silica gel. On the other hand, successful separation was achieved using C_{18} reversed-phase silica gel on preparative HPLC. Secondly, the corresponding difluoroacetophenone was often observed in the crude reaction mixture. This side product has previously been shown to originate from the hydrolysis of a difluorocarbene-palladium intermediate to form a carbonyl-palladium species followed by reaction with another equivalent of DFIM.[6c] These difluoroacetophenones could easily be separated from the desired product.

With the optimized conditions in hand, the applicability of the reaction conditions was tested on readily available aryl boronic acids (Scheme 2). The dimethoxyphenyl and N-Boc-indole derivatives afforded the difluoromethylated products in good yields with a reaction temperature of 60 °C (**2b** and **2c**). Most other substrates led to higher yields at a reaction temperature of 70 °C (conditions A). Simple arenes substituted with a phenoxy, tert-butyl, cyano- and methoxy groups resulted in good yields of **2d**–**f**. Unfortunately, the 2-substituted thiophene derivative proved challenging leading to **2g** in only a 23% yield with a high degree of biaryl formation. Lastly, good conversion to the dibenzofuran heterocyclic compound **2h** could be achieved in a satisfactory yield of 86%.

The esters of 4-biphenylboronic acid from ethylene glycol and diethanolamine were also converted to the desired difluoromethylated arenes in excellent yields (94 and 97%,

from 89 to 41% (entry 2). Omitting NaI with the potential of generating BrCF₂H instead resulted in no conversion to the desired product (entry 3). Interestingly, by lowering the amount of the gas precursor from 1.5 to 1.1 equivalents and accordingly NaI from 3.0 to 2.2 equivalents a conversion of 76% to the product was achieved (entry 4), implying that 69% of the fluorinated C1-fragment was successfully transferred from the solid precursor to the product.
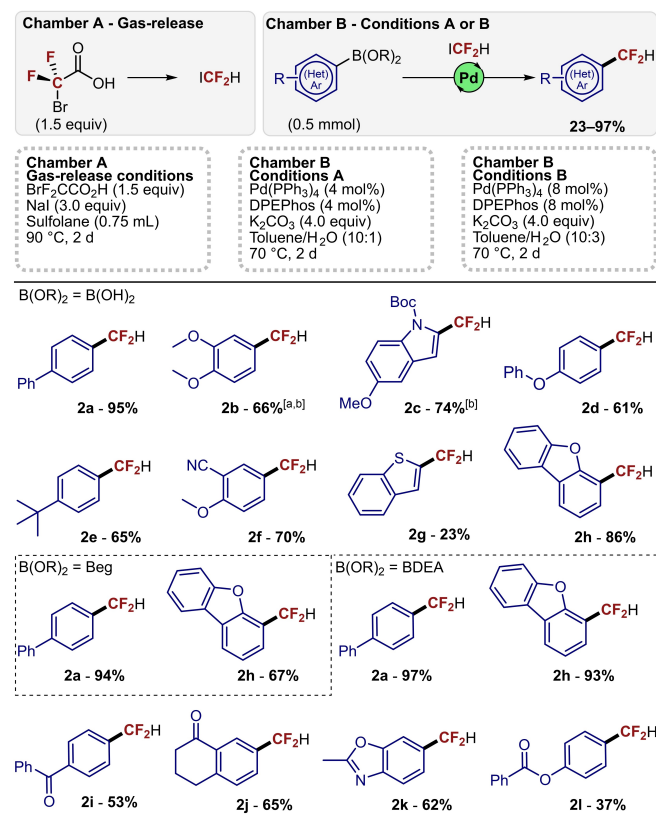
The conditions in the consuming chamber were also investigated by omitting DPEPhos and by exchanging DPEPhos for XantPhos both resulting in lower conversions (entries 5 and 6). Deterioration of the conversions was observed by lowering the amount of the catalyst system, and by substitution of the Pd^0 source with Pd₂(dba)₃ (entries 7 and 8). Resorting to the less expensive base K₂CO₃ (4 equiv) led to the same product yield as with K₃PO₄ and was superior to Et₃N or K₂CO₃ (3 equiv; entries 9–11). Elevating the reaction temperature of chamber B to 70 °C revealed no change in the conversion efficiency (entry 12). Replacing toluene with THF, and removal of water from chamber B provided poorer conversions (entries 13 and 14). Finally, we found the optimized conditions, by extending the reaction time to 2 days and elevating the temperature in chamber B to 70 °C we achieved an excellent product yield of 95% (entry 15).

Two side products were generally observed in the reaction mixture. Firstly, the product from undesired protodeboronation of the starting material was noted, a common side reaction in Suzuki–Miyaura cross-couplings. This side product proved difficult to separate from the desired product by column

Scheme 2. Scope of the Pd-catalyzed difluoromethylation of arylboronic acids and derivatives. Isolated yields are presented as an average of two runs. [a] 24 h. [b] 60 °C.

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respectively) applying the standard conditions B. Here, the catalyst loading was elevated from 4 to 8 mol%, and the water content was increased from a toluene/H_2O ratio of 10:1 to 10:3.

The more common pinacol and neopentylglycol esters[31] were not successful in this this set-up, but aryl trifluoroborate salts showed some conversion. A small investigation into the suitability of the catalytic difluoromethylation for these aryl boronic esters is shown in Scheme 2. Functionalization in the 4-position of dibenzofuran to **2h** could be achieved in good yields from both boronic esters. Substrates bearing an acyl group in either the *meta* or *para* position proved successful to generate **2i** and **2j**. The difluoromethylated benzoxazole **2k** (Scheme 2) could also be secured in 62% yield. More challenging was the arene containing a benzoate ester, which provided the desired product **2l** in 37% yield. The possibility of ester cleavage through hydrolysis is the most likely explanation of this modest yield.

Next, we set out to investigate the efficiency of this chemistry on more elaborate and bioactive structures. It is well established that aryl boronic acids and derivatives can be synthesized from the corresponding aryl (pseudo)halides,[32] but their isolation can be tedious. As such, it was desirable to develop a two-step protocol from aryl (pseudo)halides to access the corresponding difluoromethylated arenes. After considerable experimentation, we finally relied on a procedure, whereby the starting (pseudo)halides were efficiently converted under catalytic conditions to the corresponding boronate ester applying tetrahydroxydiboron and ethylene glycol.[32c] After a simple filtration and removal of solvent, further conversion to the difluoromethyl adducts could be achieved by employing the optimized conditions B.

A scope was undertaken to demonstrate the reliability of this protocol for aryl bromides, chlorides, and a fluorosulfate (Scheme 3). The model substrate 4-bromobiphenyl provided the desired product **2a** in a good yield of 82%, which is only slightly lower than the yield obtained from the corresponding aryl boronic acid. The TIPS-protected 4-bromophenol could be transformed smoothly into the difluoromethylated product **2m**. Oddly, when *N*-(4-bromophenyl)acetamide (analog of para-cetamol) was employed as the starting material, we observed a low conversion to the product. But upon methylation of the nitrogen, difluoromethylation was achievable to **2n** in an 85% yield. Two other aryl bromides displaying either an Fmoc- or Boc-protected amine, both led to high product yields (**2o** and **2p**). Substrates containing a secondary amide and two *meta* fluorides, or an *ortho*-methoxy group were also viable for this two-step protocol (**2q** and **2r**). An aryl bromide displaying a β-lactam could be transformed to **2s** with this protocol in a good yield. The difluoromethyl analogs of Boc-protected serotonin **2t** and fluoxetine (Prozac) **2u** were synthesized in 69 and 83%, respectively.

Examining the aryl chlorides, 2-chloronaphthalene was successfully difluoromethylated to **2v** in a yield of 61%, whereas a 51% yield of the difluoromethyl analog **2w** of triflupromazine (Vesprin®) could be secured. In a final example, a three-step sequence was adapted for the preparation of the
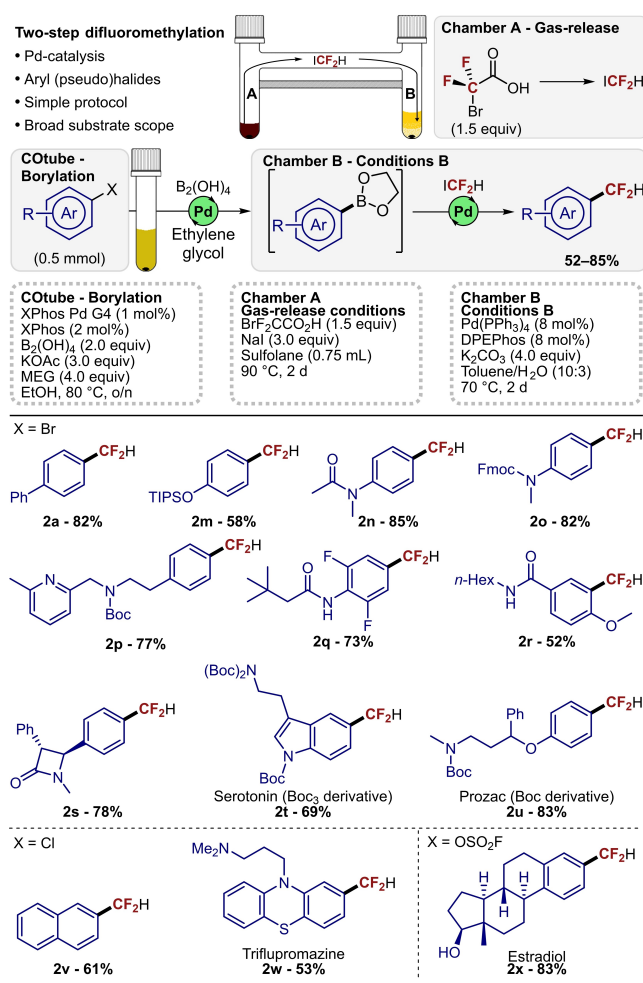
Scheme 3. Scope of the two-step Pd-catalyzed difluoromethylation of aryl (pseudo)halides. Isolated yields are presented as an average of two runs.

estradiol derivative **2x**, involving fluorosulfation,[29] borylation and difluoromethylation with a yield of 80% over three steps. This example illustrated the potential of bioactive phenols to be transformed into difluoromethyl bioisosteres in just three high yielding steps with minimal purification.

In a final demonstration, the protocol for DFIM generated ex situ could be further modified to prepare the corresponding deuterated analog, ICF_2D. To our delight, this was realized by simply adding D_2O to the standard conditions for the gas-release (Table 2) as illustrated with the [D_1]difluoromethylation of 4-biphenylboronic acid to **3a**. We found the optimized conditions for achieving the highest product yield and deuterium incorporation (93%) could be obtained by varying the amount of D_2O added to chamber A from 100–300 μL (entries 1–3). Interestingly, if water is exchanged for D_2O in the gas-consuming chamber, in the absence of D_2O in the gas release chamber, a 36% insertion of deuterium was observed in the formation of **3a** (entry 4). On the other hand, no significant increase in the degree of deuteration was noted when adding D_2O to both chambers (entry 5). These results suggest that hydrogen–deuterium exchange may take place through a
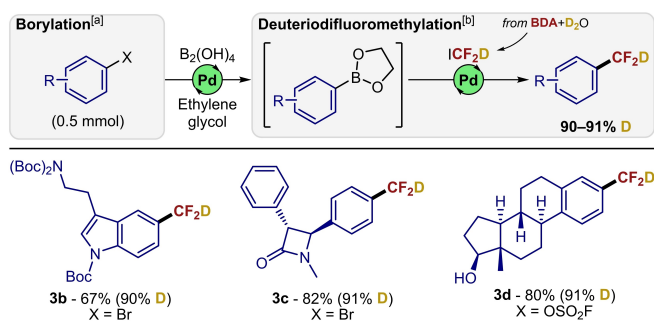
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Table 2. Direct synthesis and application of deuteriodifluoroiodomethane.

	Chamber A	Chamber B	Yield [%][b]
1	D$_2$O (100 μL)	toluene/H$_2$O (10:1)	90 (87% D)
2	D$_2$O (200 μL)	toluene/H$_2$O (10:1)	[88] (93% D)
3	D$_2$O (300 μL)	toluene/H$_2$O (10:1)	74 (93% D)
4	–	toluene/D$_2$O (10:1)	86 (36% D)
5	D$_2$O (100 μL)	toluene/D$_2$O (10:1)	89 (89% D)

[a] Pd(PPh$_3$)$_4$ (4 mol%), DPEPhos (4 mol%), K$_2$CO$_3$ (4 equiv), and toluene (1.8 mL) with H$_2$O or D$_2$O (180 μL) was used in chamber B. [b] Yields are presented as ^{19}F NMR yields and calculated using α,α,α-trifluorotoluene as internal standard. Yields in square brackets are isolated yields and yields in parentheses are percentage deuterium incorporation determined by ^{19}F NMR.

reactive intermediate, such as the difluorocarbene. Previously, the Zhang group reported that addition of excess D$_2$O to their cross coupling conditions with ClCF$_2$H provided up to 60% deuterium incorporation.[6b]

The deuteriodifluoromethylation protocol was further tested on two aryl bromides and a fluorosulfate (Scheme 4). A deuterated difluoromethyl analog of triple Boc-protected serotonin **3b** was achieved with a high yield of 67% and a deuterium incorporation of 90%. The β-lactam containing product **3c** was synthesized in a yield of 82% with an isotope incorporation of 91%. Likewise, a CF$_2$D analog of estradiol **3d** was synthesized starting from the fluorosulfate activated phenol (80% yield, 91% D incorporation).

In conclusion, we have developed a method for the ex-situ generation of difluoroiodomethane and its immediate use in a Pd-catalyzed difluoromethylation of aryl boronic acids and derivatives. We have demonstrated the utility of this method by establishing a two-step difluoromethylation of aryl (pseudo)halides employing tetrahydroxydiboron as a low-cost reducing agent. The atom efficiency for incorporation of the difluoromethyl fragment was displayed by applying only 1.1 equivalents of the gas precursor and still achieving 76% of the desired difluoromethylated product. We also discovered a simple method for the synthesis of novel deuteriodifluoroiodo-methane with D$_2$O serving as the deuterium source. This new reagent has been demonstrated to be a convenient source for the installation of deuteriodifluoromethyl groups.

Acknowledgements

Conflict of Interest

T.S. is co-owner of Sytracks a/s, which commercializes the two-chamber system (COware®).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Scheme 4. Scope of the two-step deuteriodifluoromethylation. Yields are of isolated products and yields in parentheses are percentage deuterium incorporation determined by ^{19}F NMR. [a] Aryl (pseudo)halide (0.5 mmol), XPhos Pd G4 (1 mol%), XPhos (2 mol%), B$_2$(OH)$_4$ (2 equiv), KOAc (3 equiv), ethylene glycol (4 equiv), EtOH, 80 °C, o/n. [b] Chamber A: BDA (1.5 equiv), NaI (3 equiv), dry sulfolane (0.75 mL), D$_2$O (200 μL), 90 °C, 2 days. Chamber B: Pd(PPh$_3$)$_4$ (8 mol%), DPEPhos (8 mol%), K$_2$CO$_3$ (4 equiv), toluene/H$_2$O (10:3), 70 °C, 2 days.

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