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Nucleophilic Fluorination Facilitated by a CsF-CaF_2 Packed Bed Reactor in Continuous Flow.

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A simple to prepare, dry and handle packed bed reactor carrying CsF on CaF_2, towards nucleophilc fluorinations in continuous flow, is reported. The reactor also proved adaptable for silyl-ether deprotection and trifluoromethylations with Ruppert's reagent. The study includes reactor stability and scale-up investigations.

The substitution of hydrogen with fluorine during the design of pharmaceuticals and agrochemicals, has become a well-established method, towards alteration of a compounds metabolic stability and bioavailability.[1] Given the success of fluorinated structures several methods for fluorine introduction have been developed. These methods are divided into four categories, named accordingly to the character of the fluorine being installed; being radical, electrophilic, nucleophilic, and metal mediated.[2] Nucleophilic fluorination often occurs through S_N2-type displacement of leaving groups, at sp^3-hybridized carbon centres. Similar leaving groups, bound directly to an electron deficient aromatic core (sp^2-carbon) can also be displaced through S_NAr reactions.[3] Despite their simple appearance, nucleophilic fluorinations are hampered by the low solubility of metal fluorides, such as CsF, and the need for perfectly dry reaction conditions. These drawbacks are normally addressed by superstoichiometric amounts of metal fluoride, addition of phase transfer catalysts, elevated temperatures and long reaction times. Drying, handling and storage of anhydrous metal fluorides is problematic and requires the use of a glovebox.[4] Furthermore, drying of the soluble fluoride source tetrabutylammonium fluoride (TBAF), is hampered by the Hofmann elimination, leading to its decomposition. This was circumvented by the group of DiMagno who reported on the *in situ* formation of anhydrous TBAF by reacting hexafluorobenzene with tetrabutylammonium cyanide.[5] Later, the groups of Melanie Sanford and Yossi Zafrani have reported on soluble quaternary ammonium fluorides that tolerates drying.[6] In 2011, Noël *et. al.* reported on the palladium catalysed fluorination of aryl triflates in continuous flow, using pre-dried CsF packed in a bed reactor.[7] To obtain high reactivity and to avoid obstruction of flow, Noël used CsF particles obtained by two-fold sieving of CsF-powder through different mesh-nets inside a glovebox.

During our research into fluorination reactions, and inspired by the work of Noël *et. al.,* we became interested in the potential benefits of adapting nucleophilic fluorinations into a continuous flow setup.[8] Besides acting as a static mixer and heat exchanger, a packed bed reactor (PBR) will enhance the mass transport of otherwise insoluble fluoride anions by its inherent large surface-to-volume ratio of loaded reagents. Importantly, a PBR loaded with a metal-fluoride will push any halide exchange equilibriums in favour of the fluorinated product (See Figure 1).[9] This effect arises as the reactor simulates a setup in which expelled CsCl is removed continuously from the reaction while being replenished with

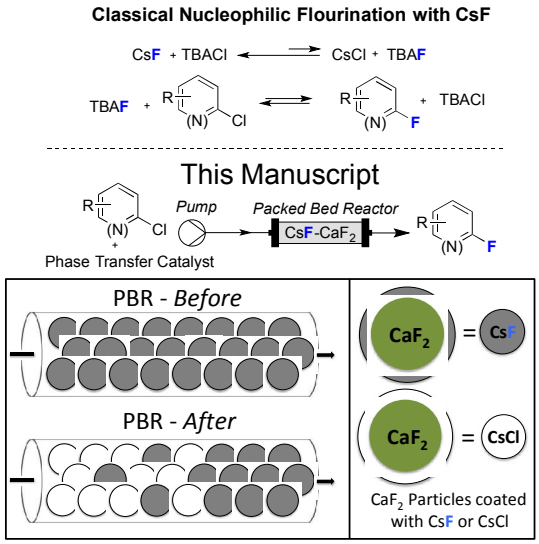

Figure 1. Nucleophilic Fluorination using CsF and the CsF-CaF_2 Packed Bed Reactor.

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Electronic Supplementary Information (ESI) available: Experimental methods, flow reactor design including ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR of all reported compounds . See DOI: 10.1039/x0xx00000x

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fresh CsF, as the reaction mixture moves through the column (Figure 1).[10] Finally, as the encaged metal-fluoride is sealed from its surroundings, extractive in-line drying, by flushing of the PBR with superheated solvents, will remove any CsF-bound water, thereby setting the stage for nucleophilic fluorinations.

In this manuscript we wish to report on the development of an efficient CsF-CaF_2 packed bed reactor towards nucleophilic fluorinations. The reactor material was obtained by evaporation of dissolved CsF onto correctly sized CaF_2 particles. Efficient in-line drying was achieved by passing superheated acetonitrile or toluene through the reactor bed. This *"simple to handle and dry"* flow setup provided reactive CsF applied in nucleophilic halo-substitution reactions of both benzylic bromides and chloro-(hetero)aromatic derivatives. Reactor stability and accessibility tests proved that a total loading of *only 2 equivalents* of CsF was sufficient in these transformations. Finally, the continuous flow setup also proved reactive in fluoride-mediated removal of silyl-based protection groups and trifluoromethylations of aldehydes and ketones with excellent isolated yields and residence times down to 2 minutes.

Initial experiments using a packed bed reactor loaded with commercial available CsF (directly from the bottle, ball-milled or grinded in a mortar) failed. This failure can be ascribed to the presence of small CsF particles that leads to high pressure drops and clogging of the PBR. In order to circumvent sorting of hygroscopic metal fluoride particles, focus was instead turned towards the identification of a solid support upon which CsF could be loaded. Silica gel and alumina oxide failed as solid supports, due to the Lewis basic nature of fluoride (Figure 2).[11] Next, the reactor was loaded with fluoride ion exchanged Amberlyst IRA-900 polymer beads. This amberlyst system provided a reactor with apparent good conversion into the desired nucleophilic substituted 2-fluoropyridine. However, the mass balance was poor with the majority of injected material being retained inside the polymeric matrix. After significant experimentation, attention was finally turned towards fluorospar (CaF_2) as a solid support. Early reports by the group of Clark, indicated that KF or CsF loaded onto CaF_2 did not impede the fluoride nucleophilicity in batch reactions.[12] Commercially available CaF_2 with 98% of all particles ranging in size from 0.1 µm – 60 µm was chosen for further testing.[13] The support was prepared by addition of

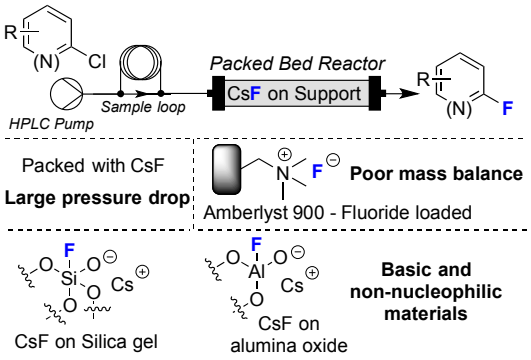


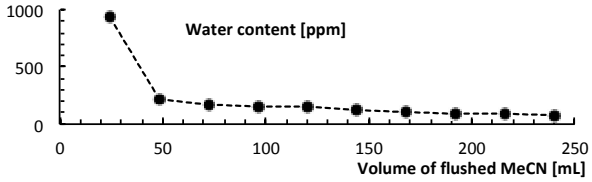
Figure 2. Failed Solid Supports for CsF-Loaded Reactor.

CaF_2 to the metal fluoride dissolved in MeOH followed by slow evaporation of the solvent (see electronic supplementary information (ESI) for details). Gentle grinding of the material provided a MF-CaF_2 support that, when loaded into the PBR, did not lead to the obstruction of flow or resulted in large pressure drops. Prior to the first application of each MF-CaF_2 packed bed reactor simple in-line drying was preformed by passing acetonitrile or toluene through the column at 180 °C until no more water was expelled (Table 1 A, see ESI for details). The initial experiments were centred on the nucleophilic fluorination of benzyl bromides and chlorides in continuous flow (Table 1). CsF-CaF_2 proved more reactive than its corresponding KF-CaF_2, and hence, CsF was chosen as the fluoride source (see ESI for reactions with KF-CaF_2).

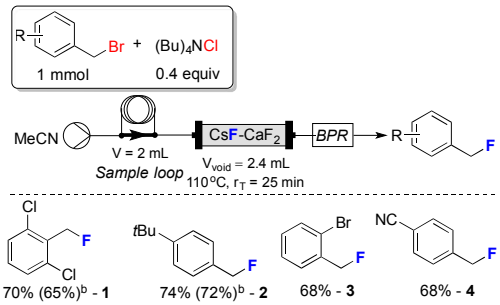
The benzyl halide (0.5 M) and tetrabutylammonium chloride (TBACl – 40 mol %) were dissolved in MeCN and passed through the PBR with a residence time of 25 minutes at 110 °C (See ESI for reactor setup). This setup afforded the desired benzyl fluorides in isolated yields ranging

Table 1. In-Line Drying and Nucleophilic Fluorinations[a]

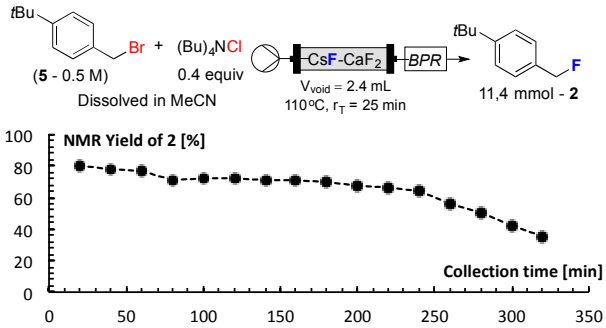
A) In-Line Drying of CsF-CaF_2 Reactor



B) Nucleophillic Fluorination of Benzylic Bromides and Chlorides



C) CsF Accessibility Test by Scale-out Synthesis of **2**.



[a]See ESI for specific reaction details for each entry. [b] The corresponding benzyl chloride was used instead.

from 65 – 74% (Table 1 – B, Compounds **1** – **4**).[14,15] Aliphatic halides did only provide trace fluorination, along with

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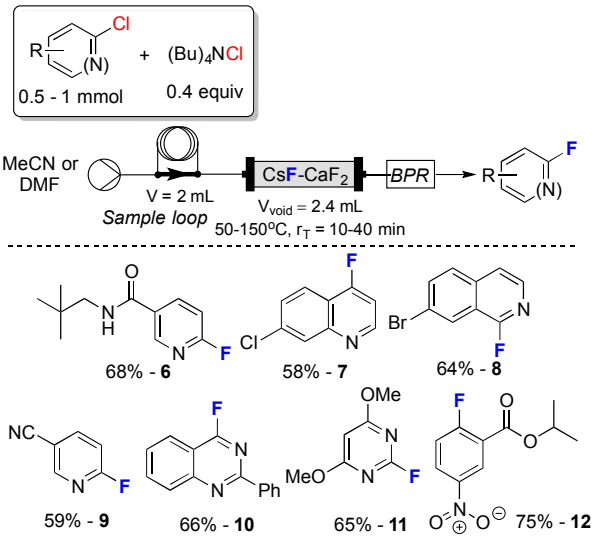
elimination products, when subjected to the flow-setup.[16] In order to test the fluoride accessibility of the CsF-CaF_2 material a scale-out experiment was performed with 1-bromomethyl-4-*tert*butylbenzene (**5**) (Table 1 – C). **5** (0.5 M) was pumped through the PBR, under identical conditions as above, and samples were collected in 20-minute intervals. The ^{1}H-NMR yield of **2** was determined for all samples using dimethyl terephthalate as internal standard. The yield of **2** slowly decreased from 80 % – 66 % over the first 240 minutes after which it quickly deteriorated. The combined yield of the first 240 minutes corresponds to the formation of 11.4 mmol of **2**. 21 mmol of CsF loaded onto CaF_2 was packed on the reactor, corresponding to more than 50 % of loaded CsF being accessible, or a loading of *only 2 equivalents of CsF!*[17]

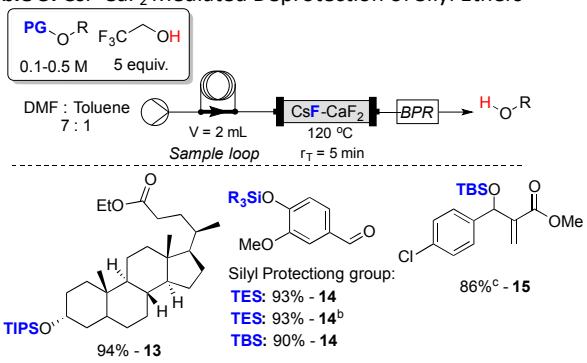
Next, attention was turned towards the nucleophilic substitution of chlorinated heteroaromatics, the results of which are depicted in Table 2. 2-Chloropyridine carrying either a 5-neopentyl amide or a 5-cyano as substituent afforded the fluorinated compounds **6** and **9** in 68% and 59% isolated yields, respectively. 4,7-Dichloroquinoline afforded mono 4-fluorinated **7** in 58% isolated yield and 64% of **8** was secured after column chromatography. Next, two pyrimidine analogues were tested affording the desired products in 66% and 65% isolated yields (compunds **10** and **11**, respectively). Finally, nucleophilic displacement of chloride on isopropyl 2-chloro-5-nitrobnzoate afforded **12** in a good 75% isolated yield. Full conversion was obtained for all entries in Table 2, and besides the fluorinated products, side-products resulting from heteroaromatic dimerization or hydrolysis were identified. Having established the nucleophilicity of the in-line dried CsF-CaF_2 support, it was next decided to investigate its utility in fluoride-mediated reactions. Three alcohols, the ethyl ester of lithocholic acid, vaniline and the Morita-Baylis-Hillman alcohol, prepared from 4-chlorobenzaldehyde with methyl acrylate,

Table 2. Nucleophilic Aromatic Fluorinations in Flow.



[a]See ESI for specific reaction details for each entry.

Table 3. CsF-CaF_2 Mediated Deprotection of Silyl Ethers[a]



[a]The silylether (0.1 M) and trifluoroethanol (0.5 M) in DMF:toluene (7:1) at 120 °C with r_T = 5 min. [b] TES-protected vaniline (0.5 M) with trifluoroethanol (2.5 M). [c] Trifluoroethanol (0.12 M) at room temp. with r_T = 20 min.

where all protected as their corresponding TES, TIPS, and TBS silyl ethers (See Table 3). Full conversion to the alcohols were obtained by passing the silylethers dissolved DMF:toluene (7:1) through the CsF-CaF_2 PBR at 120 °C with a residence time of 5 minutes.[18,19] Trifluoroethanol functioned as the proton source for the deprotection. TIPS removal from **13** afforded alcohol in a near quantitative 94% isolated yield. The TES-ether, and the more stable TBS ether, was cleaved from vaniline in isolated yields of 93% and 90%, respectively. Increasing the concentration to 0.5 M of **14** did not affect the reaction and afforded the free alcohol in an identical 93% isolated yield. Finally, TBS-ether removal from **15** at room temperature with a residence time of 20 minutes afforded the free alcohol in a good 86% isolated yield.

As the last part of this study the trifluoromethylation of aldehydes and ketones using Ruppert's reagent was investigated.[16a,20] With a residence time of only 5 minutes, at room temperature, full trifluoromethylation was accomplished using the CsF-CaF_2 reactor (See Table 4). The crude reactions were obtained as a mixture of the alcohol and the corresponding TMS-protected ethers, the latter that was cleaved during acidic workup. Four aldehydes were tested, carrying both electron donating and electron withdrawing groups, and afforded isolated yields ranging from 70% – 83% (compounds **16**, **17**, **19** and **20**). One heteroaromatic aldehyde was tested, 1-methyl-1*H*-pyrrole-2-carbaldehyde, and afforded **18** in 84% isolated yield. 4-Cyanoacetophenone (**22**) proved highly reactive, affording **21** in an excellent 94 % isolated yield. Finally, compound **22** was selected for a scale-out experiment. Additional optimization revealed that the residence time needed to convert **22** to **21** was less than 60 seconds, even at an increased concentration of 0.75 M for **22**. However, the reaction exotherm caused the PBR to overheat. This heat was dissipated by cooling the CSF-CaF_2 PBR in a water bath at room temperature combined with an increase in r_T to 120 seconds. This setup afforded a stable system and the scale-out reaction was run for 42 minutes resulting in the isolation of 34 mmol of **21** (7.4 grams). Interestingly, catalytic behaviour of fluoride was observed as 34 mmol of **21** was secured with only 21 mmol of CsF loaded onto the onto the packed bed reactor.

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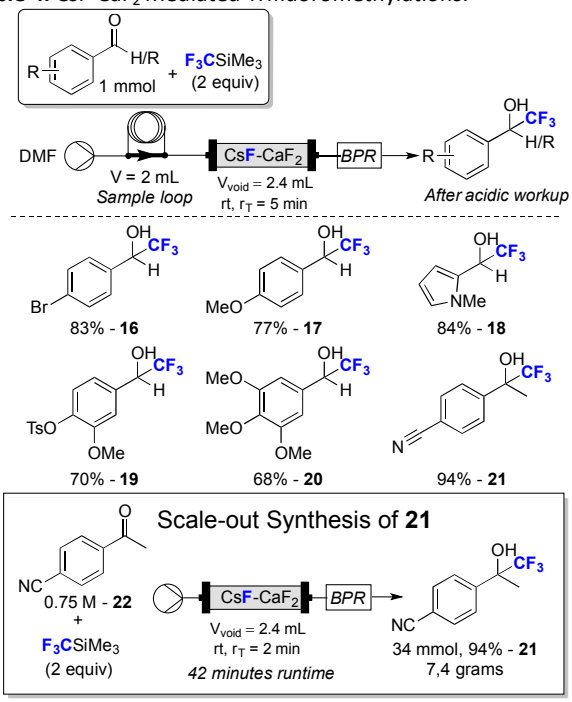
Table 4. CsF-CaF_2 Mediated Trifluoromethylations.[a]



[a]See ESI for specific reaction details for each entry.

In conclusion, a simple to prepare, store and handle continuous flow packed bed reactor carrying cesium fluoride loaded onto a calcium fluoride support has been developed. Efficient in-line water removal from the CsF-CaF_2 support was accomplished by passing superheated solvents through the reactor, thereby avoiding the need for glovebox handling of hygroscopic metal fluoride salts. As the reaction mixture is continuously passed on to sections with higher fluoride concentrations any unfavourable halide exchange equilibriums are eliminated. The reactor was applied in nucleophilic fluoride substitution reactions of benzylic bromides and the more challenging nucleophilic aromatic substitution of chloro(hetero)aromates. Fluoride accessibility was determined by a scale-out experiment and only a loading of 2 equivalents of CsF is required. The CsF-CaF_2 packed bed reactor also proved highly adaptable towards classical deprotection of silyl ethers with residence times down to 5 minutes. Finally, CsF-CaF_2 mediated trifluoromethylation of aldehydes and ketones were performed with excellent isolated yields. Scale-out of the trifluoromethylation of 4-cyanoacetophenone, with a residence time of 2 minutes at room temperature, afforded more than 7 grams of the desired product in only 42 minutes.

Conflicts of interest

There are no conflicts to declare.

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