Organocatalyzed Fluoride Metathesis

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Abstract: A new organocatalyzed fluoride metathesis reaction between fluoroarenes and carbonyl derivatives is reported. The reaction exchanges fluoride (F^-) and alternate nucleophiles (OAc^-, CO_2R^-, SR^-, Cl^-, CN^-, NCS^-). The approach provides a conceptually novel route to manipulate the fluorine content of organic molecules. By combining fluorination and defluorination steps into a single catalytic cycle, a byproduct free and 100% atom-efficient reaction can be achieved.

Fluorine is ubiquitous in organic synthesis. From modulating the bioavailability of agrochemicals and pharmaceuticals, to improving the chemical stability of refrigerants and polymers, fluorine plays a key role in chemical manufacturing.[1-4] Despite their importance, our current approach to the synthesis of fluorochemicals is not sustainable. Inorganic fluoride (fluorspar, CaF_2) is converted into HF which is ultimately used as the fluorine source for nearly all synthetic organofluorine compounds. Current estimates suggest that viable sources of fluorspar will sustain the fluorocarbons industry for less than 100 years.[5] Others have begun to question the long-term strategy behind the use of this finite resource.[6] Fluorine containing molecules are often treated as single use and can result in environmental contamination, leading to significant issues such as ozone depletion, global warming, and water contamination. Further to these concerns our current approaches to install and remove fluorine atoms into organic molecules are wasteful. Fluorination reagents such as tetrabutylammonium fluoride (TBAF), diethylaminosulfur trifluoride (DAST), and 1-chloromethyl-4-fluoro-1,4-diazonoabicyclo[2.2.2]octane bis(tetrafluoroborate) (selectfluor®), have low atom-efficiency, while defluorination methods often rely on stoichiometric main group reagents such as silanes or boranes to provide a thermodynamic driving force for breaking strong carbon–fluorine bonds.[7-9]

In this paper we describe an alternative approach to manipulate the fluorine content of molecules. We report an organocatalyzed fluoride metathesis reaction which involves the exchange of F^- with a wide variety of functional groups including acetate, carboxylate, thiol, chloride, cyanide and isothiocyanate (eq. 1). The reaction transfers the fluoride group between organic fragments.

$$R^1{-}F + R^2{-}X \rightleftharpoons R^1{-}X + R^2{-}F \quad \text{(eq. 1)}$$

Very recently Saunders and co-workers reported a stoichiometric fluoride metathesis reaction promoted by a Rh complex[10] The finding builds upon the pioneering work of Yamaguchi and co-workers who used $[RhH(PPh_3)_3]$ to establish exchange equilibria between fluoroarenes and esters or thioesters to form functionalised arenes and carbonyl fluorides.[11,12] These papers suggest a general approach to catalytic fluoride metathesis should be viable, but the current systems are constrained to stoichiometric or expensive metals and are limited in scope.

We became interested in the idea of using simple nucleophilic catalysts to achieve fluoride metathesis. In 2005, Sandford and co-workers reported the S_NAr reaction of 4-dimethylaminopyridine (DMAP) and pentafluoropyridine to form a pyridinium fluoride salt (Figure 1a).[13] This salt could be isolated and used as a nucleophilic source of F^- for the fluorination of a limited scope of organohalides. The studies form part of a broader set of work which targets the generation of anhydrous F^- by the combination of two organic components.[14-18] Interestingly, Schmidt and co-workers reported that the same pyridinium fluoride salt served as an electrophile in reactions with external nucleophiles.[19] We envisaged that these two modes of reactivity could be combined to create a catalytic method for fluoride metathesis (Figure 1b).

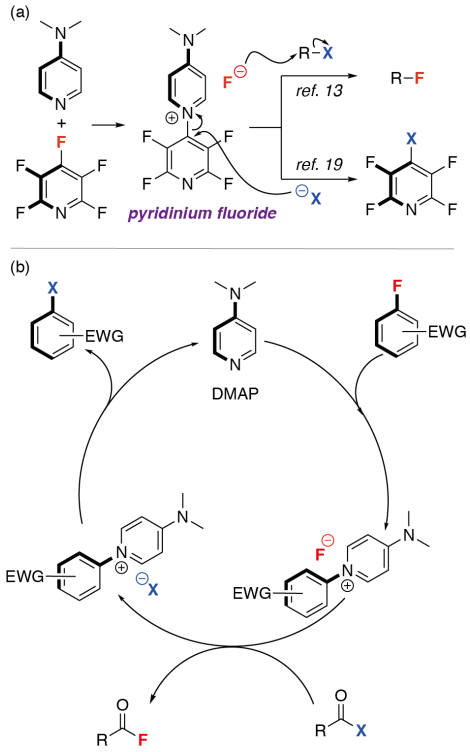
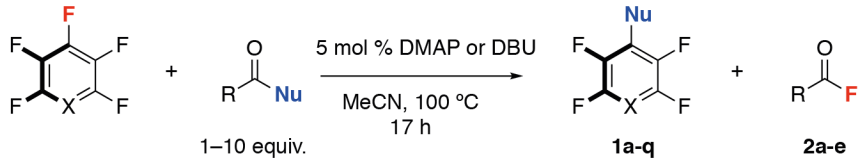


Figure 1. (a) A pyridinium salt from S_NAr addition of DMAP to pentafluoropyridine and its established reactivity. (b) A proposed catalytic cycle for fluoride metathesis.

In a series of experiments, we established the metathesis reaction between pefluoroarenes and suitable partners (acid anhydrides, dimethyl dicarbonate, s-phenyl thioacetate, benzoyl chloride, benzoyl cyanide, benzoyl isothiocyanate). Reactions were conducted with pentafluoropyridine as the fluoroarene of choice, due to it being activated towards reactions with nucleophiles by S_NAr. Following an initial screening of conditions and substrates, a reaction scope was developed in which pentafluoropyridine was reacted with a series of functional groups in the presence of 5 mol% DMAP catalyst in acetonitrile at 100 °C. The fluoride metathesis reaction creates two products, a new functionalisation fluoroarene (**1a-q**) and an acyl fluoride (**2a-e**), both of which contain usable fluorine content. Formation of the acyl fluoride provides a thermodynamic driving force for the forward reaction. In all cases, yields were recorded for both fluoride metathesis products and there is a clear and expected correlation between the yields of **1** and **2**. The reaction scope includes a variety of metathesis partners meaning it can be used as a general approach to create C–O, C–Cl, C–C, C–N and C–S bonds from high fluorine content arenes (Table 1).



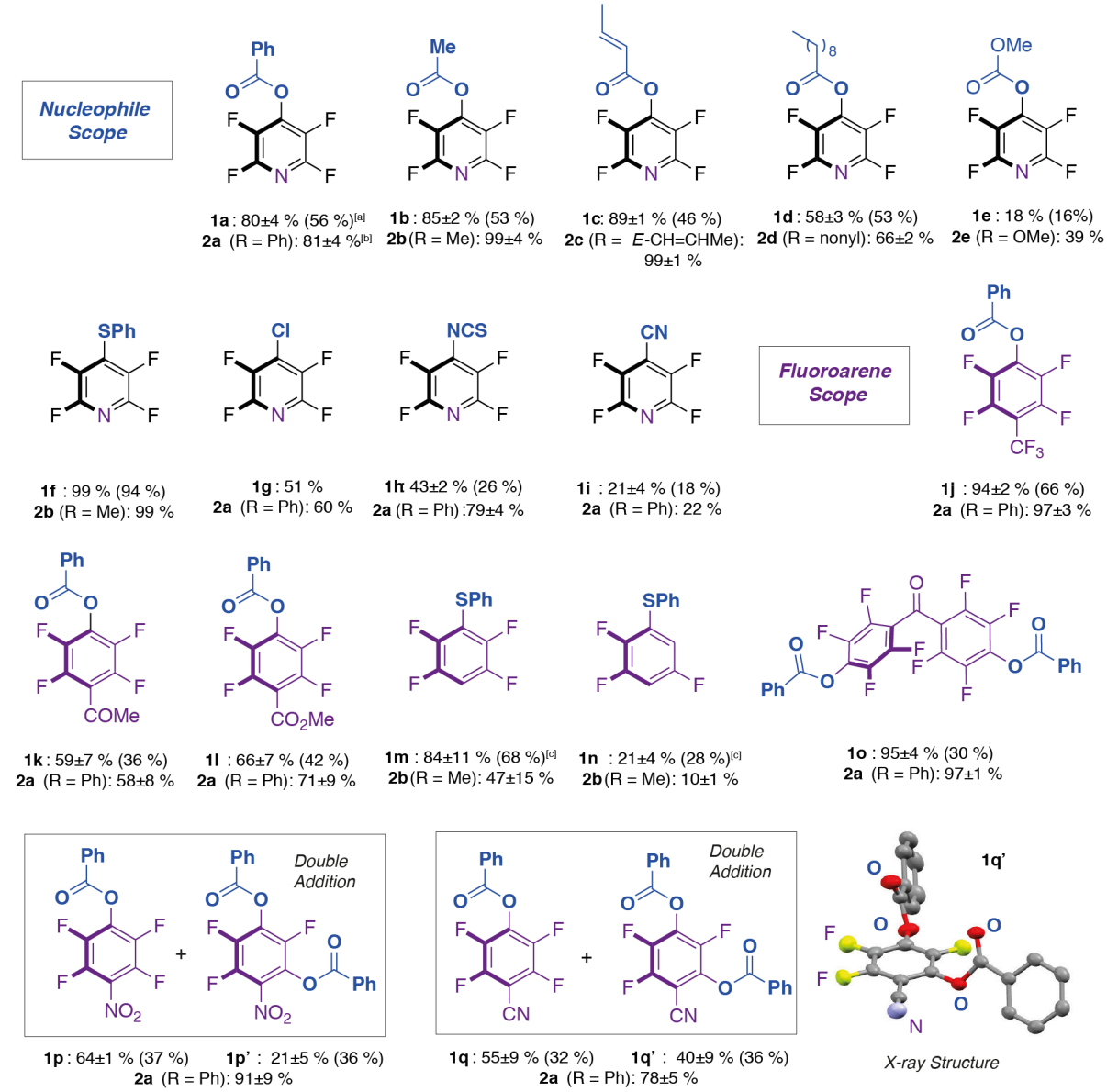


Table 1. Fluoride metathesis reaction of fluoroarenes with a range of different carbonyl derived functional groups. [a] Internal NMR yield of tetr fluoropyridine product using ^{19}F NMR (isolated yield after workup in parenthesis). [b] Internal NMR yield of the corresponding carbonyl fluoride using ^{19}F NMR. Standard deviation calculated from three repeats at a 99.9% confidence. [c] DBU was used as a catalyst.

The observed regioselectivity is consistent with that expected from a concerted or stepwise S_NAr mechanism. Yields of the reaction decreased for less stable nucleophiles such as carboxylates (prone to eliminate CO_2) and lower fluorine content arenes. For the highly reactive substrates pentafluorobenzonitrile and pentafluoronitrobenzene, a mixture of mono and disubstituted products were observed. In most cases, the disubstituted species was the minor product. Use of *S*-phenyl thioacetate to generate the highly nucleophilic benzenethiolate anion enabled expansion of the scope and fluoride metathesis of the less activated fluoroarenes pentafluorobenzene and 1,2,3,5-tetrafluorobenzene (**1m** and **1n**, Table 1). Interestingly, these reactions required the presence of 5 mol % of DBU to proceed and no conversion was observed when DMAP was used as a catalyst.[20] DBU proved a poorer catalyst for other reactions in the series and no product was observed for fluoride metathesis of pentafluorobenzene with benzoic anhydride using this catalyst.

Both the reaction products of fluoride metathesis are useful chemical intermediates. Substituted polyfluoroarenes are featured in liquid-crystal displays[21,22] and conjugated polymers for organic light-emitting diodes.[23,24] They are also useful building blocks for the synthesis of partially fluorinated arenes relevant to drug discovery through a further hydrodefluorination step.[25-27] Acyl fluorides are versatile fluorinating agents for a variety of reactions including: oxidative addition to transition metals;[27,28] the enantioselective ring-opening fluorination of epoxides,[29] and the hydrofluorination of alkynes.[30]

A series of experiments and calculations were undertaken to interrogate the proposed mechanism of fluoride metathesis. Monitoring the reaction of pentafluoropyridine with benzoic anhydride catalyzed by 5 mol % DMAP by ^{19}F NMR spectroscopy shows that **1a** and **2a** are formed at the same rate (supporting information). In further experiments, the direct reaction of DMAP with both pentafluoropyridine and acetyl anhydride could be observed. Hence, the stoichiometric reaction of DMAP with pentafluoropyridine forms the salt **3** through nucleophilic displacement of a fluoride group from the arene. Experimentally, this salt was found to be catalytically competent for the fluoride metathesis of pentafluoropyridine and benzoic anhydride to form **1a** and **2a**. Similarly, the stoichiometric reaction of DMAP with benzoic anhydride forms the salt **4** which was again catalytically competent (Figure 2a).

Kinetic analysis reveals the reaction to be 1st order in fluoroarene, 1st order in acid anhydride, and 2nd order in DMAP. These findings were verified by both initial rates and graphical analysis (VTNA, supporting info). The second order behaviour of catalyst in the empirical rate-law is notable as it implies a turnover-limiting sequence involving two equiv. of DMAP. The most sensible interpretation of this finding is that the catalyst plays a dual role in activating *both* components of the fluoride metathesis reaction and turnover occurs by two intersecting catalytic cycles each of which relies on DMAP as a catalyst (Figure 2b).

DFT calculations were undertaken to gain a greater appreciation of the key steps involved in substrate activation in each of these intersecting cycles. The B3LYP functional and a hybrid basis set were employed. Solvent (MeCN) and dispersion corrections were considered during the optimisation of stationary points. This computational approach has been used previously to model acetylisation reactions catalysed by DMAP.[31,32]

The overall reaction of pentafluoropyridine and acetic anhydride is calculated to be exergonic by –5.8 kcal mol^{-1}. The key steps of two intersecting catalytic cycles were calculated. One involving the activation of the anhydride by DMAP and the other the activation of the fluoroarene by DMAP. The transition states associated with both intersecting pathways occur by either a concerted S_NAr or a concerted nucleophilic addition-elimination step. Catalyst activation of *both* substrates is calculated to be facile under the reaction conditions. Hence reaction of DMAP with both pentafluoropyridine (**TS-1**, $\Delta G^{\ddagger}$ = 18.0 kcal mol^{-1}) and acetic anhydride (**TS-2**, $\Delta G^{\ddagger}$ = 14.1 kcal mol^{-1}) occur by low energy barriers. The calculations also show that DMAP activated substrates are more susceptible to nucleophilic attack by F^- or OAc^- than the parent reagents (supporting information).

Based on the analysis, the turnover limiting step is predicted to be associated with **TS-3** and the nucleophilic attack of the liberated fluoride anion on the acetylated DMAP fragment of **Int-2**. While the complexity of modelling explicit solvation in this system means that this conclusion should be treated with care, if this step is turnover limiting it would be consistent with the empirical rate law and 2nd order dependence on the catalyst.

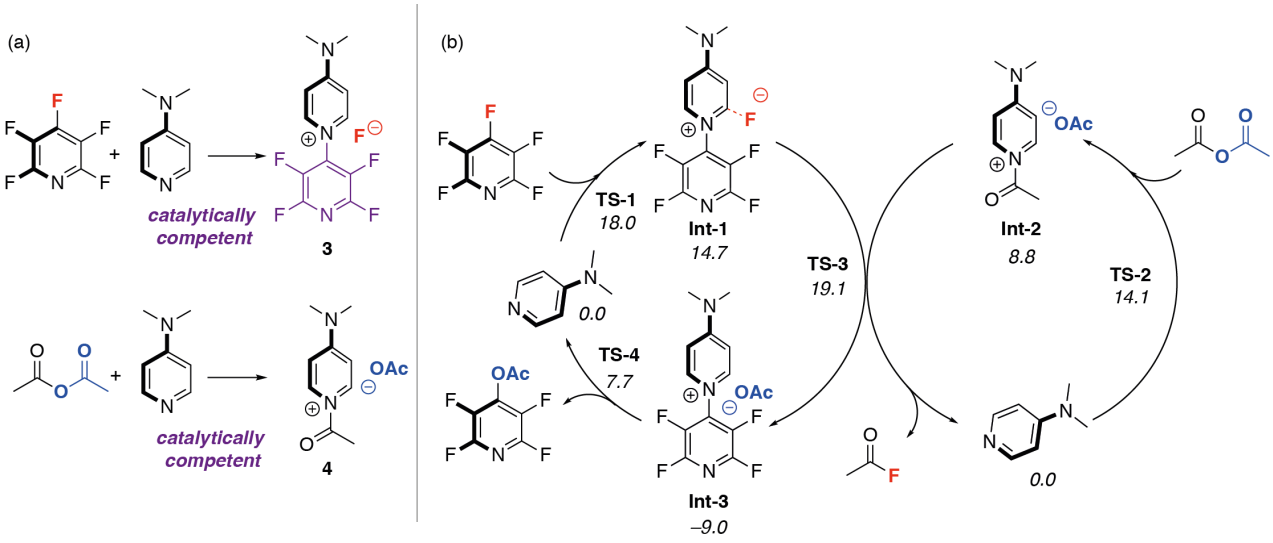


Figure 2. (a) Generation and catalytic competence of proposed intermediates **3** and **4**. (b) Proposed reaction pathway for the reaction of DMAP, C_5F_4N and acetic anhydride.

In summary, we have developed the first organocatalysed fluoride metathesis reaction. This approach is complementary to more established and less efficient methods for the fluorination and defluorination of organic molecules. By combining the two steps in a single catalytic cycle a conceptually new approach to manipulating the fluorine content of organic molecules has been achieved. This approach is 100 % atom-efficient and avoids the use of highly acidic or toxic fluorinating agents. While the reaction is currently limited to activated fluoroarenes, in the longer term the development more active catalysts or alternative strategies, such as π-activation of the arene, may allow fluoride metathesis to be established as a broad approach in the sustainable chemistry of fluorocarbons.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. X-ray crystallographic data for **1k** and **1q'** are available from the Cambridge Crystallographic Data Centre (CCDC 2021812-2021813) and as a .cif file, full details of the experiments and calculations are available as a .pdf.

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