CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201806272

Link to VoR: http://dx.doi.org/10.1002/chem.201806272

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Nucleophilic substitution of aliphatic fluorides via pseudohalide intermediates

Amit K. Jaiswal, Pragati Kishore and Rowan D. Young*

Abstract: *We report a method for aliphatic fluoride functionalisation with a variety of nucleophiles. Carbon-fluoride bond cleavage is thermodynamically driven by the use of silylated pseudohalides TMS-OMs or TMS-NTf$_2$, resulting in the formation of TMS-F and a trapped aliphatic pseudohalide intermediate. The rate of fluoride/pseudohalide exchange and the stability of this intermediate are such that little rearrangement is observed for terminal fluoride positions in linear aliphatic fluorides. The ability to convert organofluoride positions into pseudohalide groups allows facile nucleophilic attack by a wide range of nucleophiles. The late introduction of the nucleophiles also allows for a wide range of functional group tolerance in the coupling partners. Selective alkyl fluoride mesylation is observed in the presence of other alkyl halides, allowing for orthogonal synthetic strategies.*

Carbon-fluorine bonds are becoming ever more accessible and abundant in organic compounds.[1] Their incorporation into a variety of molecules is attractive due to their lipophilicity, spectral properties, and their chemical inertness. Indeed, the high strength of a carbon-fluorine single bond renders them difficult to chemically transform.

Despite their stability, recent advances have been made in the catalytic functionalisation of sp^3 carbon-fluorine bonds. Notably so for Lewis acid catalyzed C-F bond functionalisation,[2] but also in the domains of transition metal catalyzed C-F bond functionalisation, electron-transfer induced C-F bond functionalisation and hydrogen-bond activated C-F bond functionalisation.[3]

Generally, Lewis acid catalyzed C-F bond functionalisation requires highly reactive and fluorophillic Lewis acid centres. Such catalysts have low functional group tolerance, with their reactivity either arrested or hindered in the presence of alcohol, amine, ester, carboxylic acid, carbonyl, ether, and nitrile groups *(inter alia*). Furthermore, Lewis acid catalyst strategies that proceed via carbocation pathways are prone to rearrangement and elimination reactions, and Friedel-Crafts reactivity, resulting in poor tolerance of arene solvents.[2c,d,i,j,m,o,p] Indeed, C-F functionalisation exploiting Friedel-Crafts reactivity also suffers from poor selectivity and low reactivity with arenes deactivated with electron withdrawing groups.[2i,j,m,o,p]

A strategy that has recently been exploited to overcome poor reactivity and/or improve selectivity, has been to pre-install silyl groups on coupling partners prior to C-F functionalisation.[2c,d,g,h,k,q] During the functional defluorination reaction, silyl fluoride by-products act as thermodynamic sinks, driving reactivity. Such a strategy requires extra synthetic steps in preparing the silylated reagent, and can reduce the reactivity of the reagent (for example, silyl ethers are poorer nucleophiles compared to alcohols). Alternatively, hydrosilanes have been employed as co-reagents in reactions that utilize protons as a leaving group.[2i,p] The hydrosilane acts to sequester HF by-products that would otherwise deactivate the Lewis acid catalyst, however, it is well known that hydrosilanes can act as hydride sources, competing with nucleophiles intended to be installed at the C-F position.[2b,o]

The above strategies have been utilized for the incorporation of a relatively limited number of nucleophilic groups into C-F positions, and are generally restricted to stable carbocation C-F positions (e.g. tertiary, benzylic). Non-stabilised positions lead to elimination and rearrangement reactions.

A large degree of the constraint placed on nucleophiles in Lewis or Brønsted acid catalyzed reactions lies in the ability of highly basic nucleophiles to sequester the acid catalyst. This generally restricts coupling nucleophiles to less basic molecules, or reduces the reaction rate and yield of C-F couplings employing more basic nucleophiles (for example, very few examples of aliphatic C-F nucleophilic substitution exist for Lewis acid catalyzed reactions, and those that do generally use less nucleophilic nitrogen donors such as amides).[2q]

To address this issue, we sought to develop a reaction protocol that i) allows the incorporation of a wide variety of carbon and heteroatom based nucleophilic coupling partners, ii) avoids the need to generate silyl functionalized nucleophiles, iii) allows high functional tolerance in the nucleophilic coupling partner, iv) provides high regioselectivity and avoids elimination/rearrangement reactions, and v) results in a higher rate of C-F bond activation.

To accomplish these benefits, we sought to deconvolute the process of functional defluorination chemistry into two distinct steps; i) defluorination, and ii) functionalisation. Defluorination involves the breaking of inert C-F bonds, and this step requires extremely reactive catalysts that do not tolerate nucleophilic functionalities. We reasoned that the generation of a metastable carbon electrophilic intermediate would facilitate complete C-F bond activation in the absence of sensitive coupling partners. After catalytic C-F activation was complete, the functionalisation step could then be achieved by the introduction of a nucleophilic

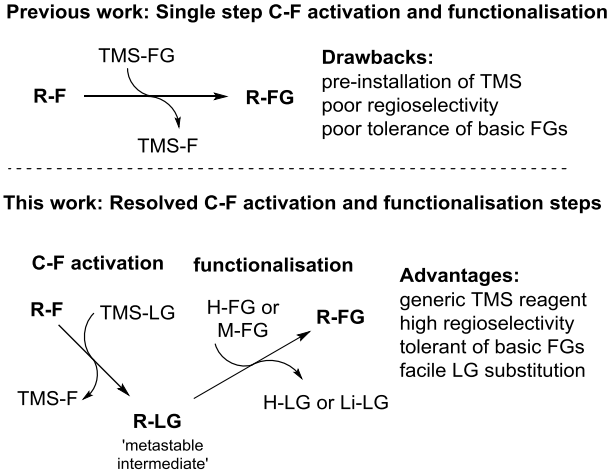

Figure 1. By resolving C-F activation and functionalisation into separate steps, we are able to introduce more nucleophilic coupling partners with a large range of functional group tolerance, achieve better regioselectivity and avoid extra synthetic steps required when using specific silylated coupling partners. FG = Functional Group; LG = Leaving Group.

10.1002/chem.201806272
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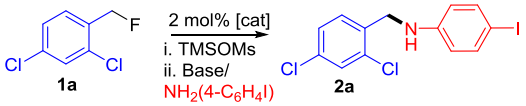
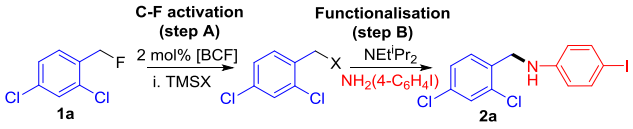
Table 1. Optimisation of C-F functionalisation via mesylate intermediate.



entry	solvent	catalyst	TMSOMs (equiv.)	base	yield (%)[a]
1	DCE	BCF	1.2	NEt^{i}Pr$_2$	74
2	DCE	BCF	1.4	NEt^{i}Pr$_2$	80
3	DCE	BCF	1.6	NEt^{i}Pr$_2$	93
4	DCE	BCF	1.6	K_2CO_3	86
5	DCE	BCF	1.6	TEA	79
6	DCE	BCF	1.6	DBU	45
7	DCE	ACF	1.6	NEt^{i}Pr$_2$	88
8	DCE	$AlMe_3$	1.6	NEt^{i}Pr$_2$	60
9	DCE	-	1.6	NEt^{i}Pr$_2$	0
10	DCM	BCF	1.6	NEt^{i}Pr$_2$	46
11	DCB	BCF	1.6	NEt^{i}Pr$_2$	<5
12	Toluene	BCF	1.6	NEt^{i}Pr$_2$	0

Conditions: i. 0.4 mmol **1a**, 0.6 mmol TMSOMs in 0.8 mL solvent, r.t. 5 min; ii. 1.6 mmol *p*-iodoaniline, 1.6 mmol base, r.t. 12 h.
[a] Yield determined by GC-MS. DCE – 1,2-dichloroethane, DCM – dichloromethane, DCB – 1,2-dichlorobenzene, BCF – $B(C_6F_5)_3$, ACF – $Al(C_6F_5)_3.C_6H_5CH_3$, TEA – triethylamine, DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2. C-F functionalisation tested with various pseudo-halides.



entry	X	step **A**[a]		step **B** (**3a**)[a]	
		time	yield (%)	time	yield (%)
1	OMs	5 min	97	12 h	93
2	OTf	5 min	N.D.	12 h	0
3	NTf_2	3 h	93	12 h	89
4	I	12 h	95	24 h	92

[a] Yield determined by GC-MS. Conditions used identical to Table 1, entry 3 with exception to (pseudo)halide reagent.

functional group to react with the metastable carbon electrophile (Figure 1).

To facilitate this strategy, we focused our attention on aliphatic pseudo-halides as metastable carbon electrophiles. Alkyl pseudo-halides, such as triflates, mesylates and triflimides, are known to react with a variety of nucleophiles, and even partake in metal catalysed cross-coupling chemistry.[4] They are stable in respect to elimination and rearrangement reactions under mild conditions, and tolerant of highly Lewis acidic conditions. And importantly, TMSOTf, TMSOMs and $TMSNTf_2$ are widely available and affordable.

Although TMSOTf is a widely employed Lewis acid catalyst, it has been shown that TMSOTf is not sufficiently Lewis acidic to activate strong C-F bonds independently.[2r]

To optimize the C-F activation step, 2,4-dichlorobenzyl fluoride (**1a**) was employed as an aliphatic fluoride substrate, TMSOMs was employed as the pseudo-halide source and *p*-iodoaniline was used as a nucleophilic coupling partner.

An initial assay of the quantity of TMSOMs to use for optimum product yield revealed that 1.6 equiv. of TMSOMs resulted in the best yield of **2a** with lower concentrations providing inferior yields,

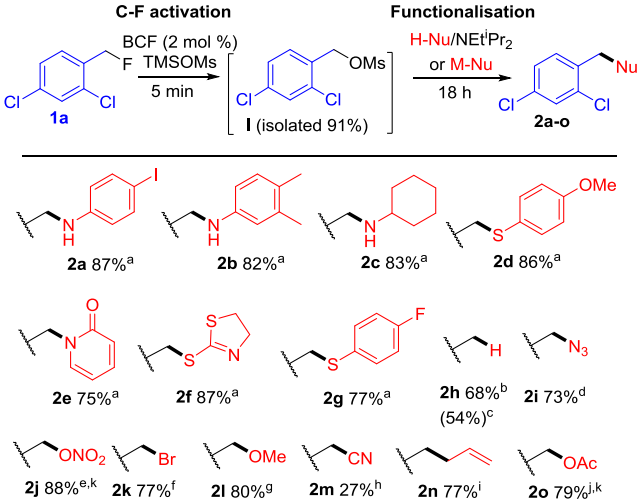


Figure 2. Reaction scope of nucleophiles used in functionalisation of intermediate **I**. Conditions: step i. 0.4 mmol **1a**, 0.002 mmol BCF, 0.6 mmol TMSOMs, 0.8 mL DCE, r.t. 5 min; step ii. 1.6 mmol Nu, r.t. 18 h, 1.6 mmol NEt^{i}Pr$_2$ used with protio nucleophiles, nucleophilic alkali salts dissolved in DMF without base. Isolated yields reported. [a] H-Nu used. [b] $Na[BH_4]$ used. [c] $SiHEt_3$ used. [d] NaN_3 used. [e] $NaNO_3$ used. [f] $[NBu_4]Br$ used dissolved in CH_2Br_2. [g] LiOMe used dissolved in MeOH. [h] NaCN used. [i] $MgBr(C_3H_5)$ used. [j] NaOAc used. [k] GC-MS yield.

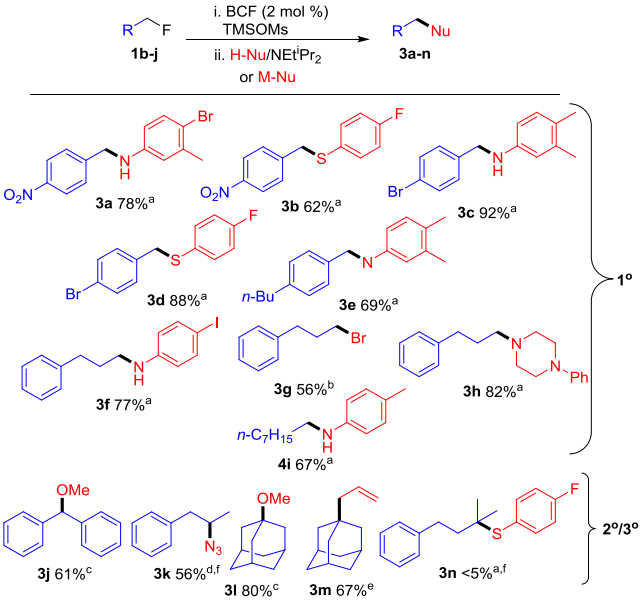


Figure 3. Scope of alphatic fluorides for one-pot C-F functionalisation via mesylate intermediates. Conditions step i. 0.4 mmol **1**, 0.002 mmol BCF, 0.6 mmol TMSOMs, 0.8 mL DCE, r.t. 5 min; step ii. 1.6 mmol Nu, r.t. 18 h, 1.6 mmol NEt^{i}Pr$_2$ used with protio nucleophiles, nucleophilic alkali salts dissolved in DMF without base. Isoltated yields reported. [a] H-Nu used. [b] $[NBu_4]Br$ used dissolved in CH_2Br_2. [c] LiOMe used dissolved in MeOH. [d] NaN_3 used. $MgBr(C_3H_5)$ used. [e] GC yield.

and high concentrations failing to improve the reaction yield significantly (Table 1, entries 1-3).

Screening of organic and inorganic base partners required for the second step revealed the sterically demanding Hunig's base (NEt^{i}Pr$_2$) to be most effective (Table 1, entries 3-6), delivering a

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high yield of **2a** in 1,2-dichloroethane (DCE). Inorganic bases such as potassium carbonate also promoted the reaction.

$[B(C_6F_5)_3]$ (BCF) was found to perform well as a catalyst at low loading. Aluminium based catalysts were also found to enable the reaction (Table 1, entries 7-8). The use of $AlMe_3$ as a catalyst resulted in lower yields in part due to partial conversion of **1a** to 1,3-dichloro-4-ethyl benzene but $[Al(C_6F_5)_3.C_7H_8]$ (ACF) was found to perform almost as well as BCF for the conversion of **1a**

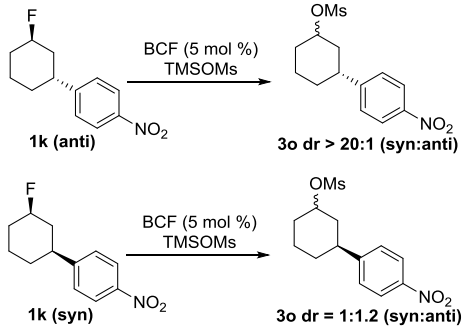
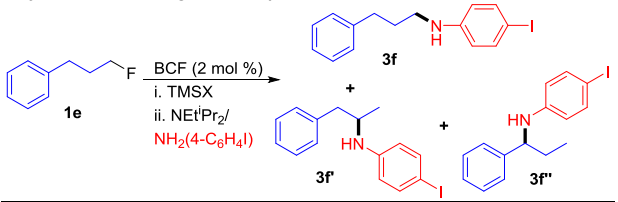


Figure 4. Study on stereo retention/inversion for fluoride/mesylate exchange.

Table 3. Regioselectivity for C-F functionalisation of primary alkyl fluorides using various pseudo-halides/iodide.



entry	X	yield **3f** (%)[a]	yield **3f'+3f''** (%)
1	OMs	83(77)	0
2	OTf	0	0
3	NTf_2	0	0
4	I	28	13

[a] Yield determined by GC-MS, isolated yield in parentheses.

to **2a**, however, ACF is less solvent tolerant than BCF and is more dangerous to handle (ACF is shock and thermal sensitive).[5] In the absence of any catalyst, no conversion of **1a** was observed (Table 1, entry 9). A simple solvent screen showed that other non-coordinating solvents DCM and 1,2-dichlorobenzene (DCB) were inferior to DCE (Table 1, entries 10-11). Electron rich arenes, such as toluene, resulted in Friedel-Crafts alkylation as opposed to generation of the mesylate intermediate (Table 1, entry 12). Hydrogen bond facilitated benzylic fluoride substitution with amines has reported in protic solvents, such as iso-propanol and water, but such solvents were not tolerated under our conditions.[6] Monitoring of the reaction listed in entry 3 Table 1 revealed that **1a** was completely consumed after 5 minutes, producing the mesylate intermediate **I** almost quantitatively. S_N2 substitution with *p*-iodoaniline then proceeded to generate **2a** in 93% based on **1a** as determined by GC-MS (Table 2, entry 1). Employing the more weakly coordinating triflate pseudo-halide resulted in fast consumption of **1a** (<5 min), but no detectable trace of the triflate intermediate (Table 2, entry 2). Addition of *p*-iodoaniline to this mixture failed to generate any of **2a**, confirming that the triflate intermediate was not formed or decomposed quickly in solution, rendering triflate as unsuitable for this reaction. Triflimide was found to work well in the reaction, generating the triflimide intermediate in 93% yield, albeit in a longer time of 3 hours. Reaction with *p*-iodoaniline was also found to proceed at room temperature overnight to give the product **2a** in high yield (Table 2, entry 3). Finally, iodide was employed to benchmark the reaction to previously reported halodefluorination reactions.[2c,7] The substitution of fluoride for iodide occurred much slower using TMSI than the pseudo-halides, taking place over 12 hours to give a high yield of an iodide intermediate. Further reaction with *p*-iodoaniline proceeded to generate **2a**, but it was found that this reaction also took place at a much slower rate than in the mesylate and triflimide cases (Table 2, entry 4). It may be that the relative faster reaction rates that are observed with TMSOMs and TMSOTf (compared to $TMSNTf_2$ and TMSI) are a result of an S_E2' reaction pathway.[2a,2g] Accordingly, conditions as listed in Table 1 entry 3 were employed in subsequent C-F functionalisation reactions.

Using fluoride **1a**, the scope of nucleophilic coupling partners for the one-pot reaction was explored (Figure 2). However, the mesylate intermediate **I** (Figure 2) could also be isolated in 91% yield. The reaction performed well employing protic nucleophiles in conjunction with Hunig's base, generating products **2a-g**, or with metalated nucleophiles in the absence of added base, generating products **2h-o**. For solubility purposes, inorganic salt coupling partners generally needed to be dissolved in polar solvents (e.g. DMF, DMSO) before addition to the reaction. A range of amino and thiol nucleophiles worked well under the ascribed conditions, all providing excellent isolated yields of >75% (**2a-g**). However, the introduction of oxygen nucleophiles, through the formation of ether (**2l**) or ester (**2o**) products was found to be

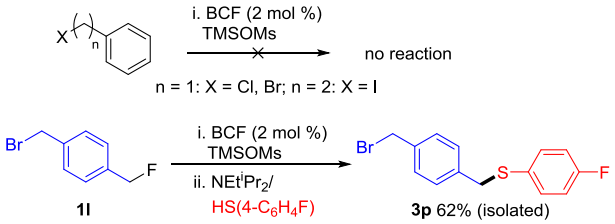


Figure 5. Selective C-F functionalisation in the presence of other alkyl halide groups. Conditions: i. 0.4 mmol **1l** or alkyl halide, 0.6 mmol TMSOMs in 0.8 mL solvent, r.t. 5 min; ii. 1.6 mmol *p*-fluorothiocresol, 1.6 mmol NEt^iPr_2, r.t. 12 h.

more efficient with the use of the inorganic salts NaOMe and NaOAc respectively.

Formal hydrodefluorination could be effected to generate 1,3-dichloro-4-methyl benzene (**2h**) through the use of either hydrosilane or borohydride hydrido sources, with sodium borohydride providing superior results in this reaction (68% yield). The reaction of the mesylate intermediate **1a** with group 1 and 2 salts NaN_3, $NaNO_3$, [TBA]Br, LiOMe, NaCN, $MgBr(C_3H_5)$ and NaOAc gave access to the products **2i-2o** in moderate to excellent yields. Such nucleophiles react directly with BCF to form borate salts and would hinder catalysis if used in direct substitution reactions.[8]

The reaction was then extended to other fluoride substrates (Figure 3). It was found that both electron withdrawing (**3a-d**) and electron donating (**3e**) substituents in benzylic fluorides tolerated the reaction conditions. Aliphatic primary fluorides (**3f-i**), secondary fluorides (**3j-k**) and tertiary fluorides (**3l-m**) were all

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found to be competent in the reaction. However, in the case of 2-flouro-2-methyl-4-phenyl butane (**1j**), product **3n** could not be detected and instead only intramolecular cyclisation products were observed. This stands in contrast to reactions carried out using 1-fluoro-3-phenyl propane (**1e**), which is also capable of intramolecular cyclisation but gave **3f-h** in moderate to high yields, suggesting that substitution of fluoride by mesylate may occur more slowly in tertiary positions. Intramolecular Friedel-Crafts cyclisation observed in the reaction of **1j** suggests an S_N1 mechanistic pathway, however, such a pathway would be considered 'high-energy' for primary and secondary alkyl fluoride position (such as in **1e**), and an S_N2 pathway may be possible in these instances.[9] To shed more light onto the mechanism of the fluoride/mesylate exchange, an enantio-enriched secondary fluoride (**1k**) was subject to catalytic mesylation conditions (Figure 4). Mesylation of **1k** (anti) gave almost exclusively the syn mesylate isomer (**3o**), however, mesylation of the syn isomer of **1k** gave a mixture of syn and anti **3o** (syn:anti = 1:1.2). These data suggest that the syn isomer of **3o** is thermodynamically preferred over the anti isomer, and that a predominantly S_N1 pathway operates, where a degree of 'ion-pairing' between the carbocation and fluoroboronate anion may contribute to observed anti **3o** product in the reaction using syn **1k**. Both S_N1 and S_N2 pathways have been reported for related halodefluorination reactions.[7b,7c]

Retention of regiochemistry for primary positions (**3f-i**) in Lewis acid catalyzed fluoride substitution reactions is challenging in S_N1 type substitutions.[2c,2d] As such, we decided to benchmark the above descried reactions with other halide and pseudo-halide sources to determine the origin of the high regioselectivity.

The reaction products were surveyed for the reaction between 1-fluoro-3-phenyl propane (**1e**) and *p*-iodoaniline using TMSOMs, TMSOTf, $TMSNTf_2$ and TMSI intermediates (Table 3). In S_N1 substitution of primary alkyl fluorides, rearrangement of 1° carbocation intermediates to generate 2° and 3° carbocations may occur faster than alkyl pseudo-halide formation. Thus, the regioselectivity of the C-F functionalisation step is indicative of the rate of pseudo-halide attack of the intermediate carbocation. The fast reaction rate of TMSOMs (see above) was confirmed, with full retention of regioselectivity. Indeed, the terminal product **3f** was observed exclusively, and obtained in high yield (Table 3, entry 1). The slower reacting TMSI generated a mixture of primary and secondary products (**3f**, **3f'** and **3f''**), indicating that rearrangement occurred at a comparative rate to iodide attack of the intermediate carbocation (Table 3, entry 4), and further supporting an S_N1 pathway for BCF catalysed substitution of primary alkyl fluorides. The relative proportion of primary to secondary products could not be evaluated for TMSOTf and $TMSNTf_2$, due to the total lack of any observable products **3f**, **3f'** and **3f''** (Table 3, entries 2-3), however, inspection of the reaction mixture that employed $TMSNTf_2$ before addition of *p*-iodoaniline revealed both primary and secondary aliphatic NTf_2 intermediates.

Finally, the relative reactivity of alkyl fluoride to other alkyl halide positions was tested. In a set of control reactions, benzyl chloride, benzyl bromide and 1-iodo-2-phenyl ethane were subject to catalytic mesylation reaction conditions (Figure 5). Under these conditions, no consumption of starting materials or generation of mesylate products was observed. Thus, 1-bromomethyl-4-fluoromethylbenzene (**1l**), containing both benzylic bromide and fluoride positions, was subject to the conditions of Table 1, entry 3 employing *para*-fluorothiophenol as a nucleophile. Under these conditions, exclusive functionalisation of the benzyl-fluoro position in **1l** was observed to generate **3p** in 62% isolated yield (Figure 5).[10] Similar reactivity preference has been observed in hydrogen-bonding activated Friedel-Crafts alkylations using benzylic fluorides and aluminium catalyzed alkynyl couplings with benzylic fluorides.[2d,2m] The ability to selectively target fluoride positions in the presence of alkyl chloro, bromo and iodo motifs represents a distinct advantage of this methodology over previously reported halodefluorination approaches,[2c,5] and provides the possibility of orthogonal synthetic strategies.

In conclusion, we have developed a widely applicable methodology for the nucleophilic substitution of aliphatic C-F positions. The method is based on activating C-F positions by their conversion to pseudo-halide groups (namely OMs, NTf_2). The deconvolution of nucleophilic C-F substitution into two distinct activation and functionalisation steps allows the incorporation of a wider range of nucleophilic coupling partners. The fast reaction of TMSOMs with aliphatic C-F bonds in the presence of BCF catalyst also allows for high regiochemistry retention in primary aliphatic fluorides. Lastly, the reaction is found to be highly selective for C-F positions over other aliphatic halide groups, allowing selective C-F functionalisation in the presence of higher aliphatic halides.

General experimental procedure for synthesis of compounds 2a-o (Figure 2)

To an oven dried reaction vessel in a glove box was added 1,2-dichloroethane (0.8 mL), 2,4-dichlorobenzylfluoride (**1a**) (0.4 mmol) and trimethylsilyl mesylate (0.6 mmol). BCF catalyst (2 mol %) was then added to the reaction vessel and the reaction was left to stand at room temperature for 5 minutes. To the reaction was then added either a protio nucleophile (1.6 mmol) with Hunig's base (1.6 mmol), or an alkali salt of the corresponding nucleophile's conjugate base dissolved in DMF solvent (2 mL). The reaction was left to stir at room temperature for 18 hours. After the completion of the reaction, dichloroethane (DCE) solvent was removed under reduced pressure and the residue extracted into ethyl acetate followed by washing with water once and brine three times. The organic extract was dried over sodium sulfate and reduced in volume. Target compounds were isolated via silica gel chromatography using hexane/EtOAc eluent.

Acknowledgements

We thank the National University of Singapore and the Singapore Ministry of Education for financial support (WBS R-143-000-586-112 and R-143-000-666-114).

Keywords: defluorination • carbon-fluorine activation • Lewis acid • catalysis • boron

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10.1002/chem.201806272

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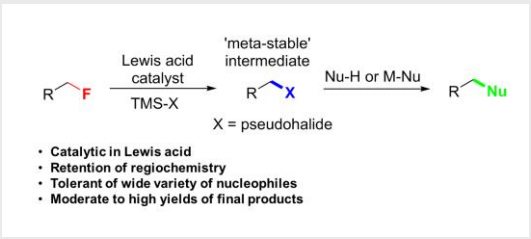

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