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Deprotonative Functionalization of the Difluoromethyl Group

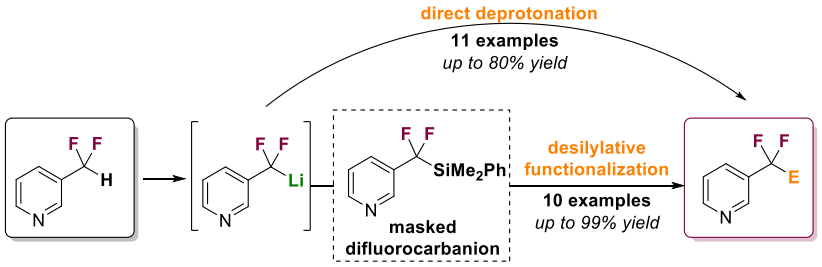
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Supporting Information Placeholder



ABSTRACT: The functionalization of 3-(difluoromethyl)pyridine has been developed *via* direct deprotonation of -CHF_2 with a lithiated base and subsequent trapping with various electrophiles in THF. *In situ* quench gives access to 3-pyridyl-CF_2-$SiMe_2Ph$ as a new silylated compound, which can be post-functionalized with a fluoride source to obtain a larger library of 3-(difluoroalkyl)pyridines that were not accessible via direct deprotonation.

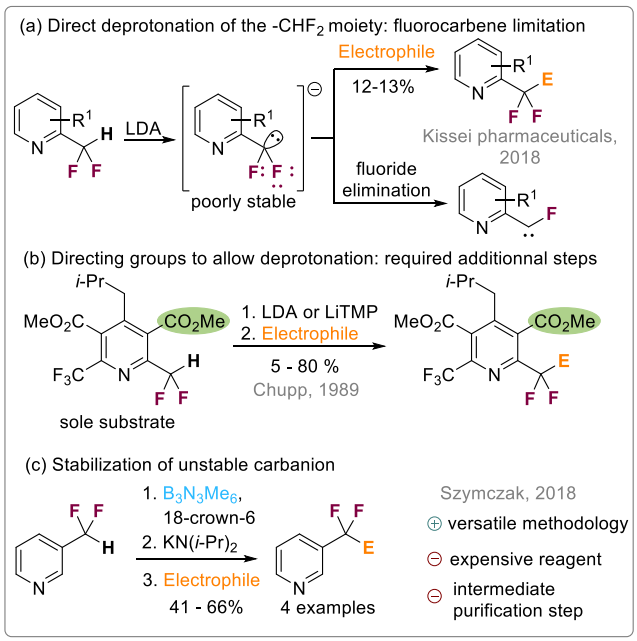
It is nowadays well-established that the introduction of fluorine atoms or fluorinated functional groups can have a profound impact on the physical, chemical and biological properties of molecules.[1–7]

The -CHF_2 group has been increasingly studied over the past few years as its interesting properties are essential for the development of new bioactive molecules. Aside from usual characteristics shared with other fluorinated substituents, the -CHF_2 moiety is a lipophilic bioisostere of hydroxy, sulfanyl and amino groups and its action has been demonstrated as an unusual hydrogen bond donor that can influence intramolecular interactions and conformational preference.[8–14] The potential of this group led to a plethora of syntheses to introduce the -CHF_2 moiety as a terminal group in heteroaromatic molecules.[15,16]

The parent difluoromethylene linkage is an attractive structural motif in drug design and agrochemistry due to its bioisosteric relationship with carbonyl or oxygen atom.[8] Unfortunately, in contrast to the -CHF_2 group, its synthetic access remains underdeveloped and relies on the use of toxic, explosive reagents prohibited for an industrial application (e.g. DAST).[17] An attractive approach is the late-stage functionalization of the -CHF_2 moiety, and, more precisely, its deprotonation followed by electrophilic trapping (Scheme 1). In the case of pyridines, frequently encountered core in agrochemical research,[18,19] only one example of direct deprotonation of 2-(difluoromethyl)pyridine has been reported without success.[20] The functionalization of difluoromethyl heteroarenes has been scarcely reported, presumably because of the poor stability of the generated difluoromethyl carbanion leading to the corresponding fluorocarbene.[21,22] In the presence of a lateral directing group, the deprotonation of 2-(difluoromethyl)pyridine succeeded with better yields (b);[23] However, highly functionalized starting materials were employed which limited the scope of the reaction. Additionally, this strategy requires further steps for the installation and the removal of the directing groups. In 2018, a breakthrough was achieved by Szymczak *et al.*, by employing hexamethylborazine ($B_3N_3Me_6$) as Lewis acid for the stabilization of the difluoromethyl carbanion, before electrophilic trapping (c).[24] Although this versatile methodology was applied to 3-(difluoromethyl)pyridine, a drawback for large scale application is the use of the high-cost Lewis acid and the purification step of the compound bearing the borazine.

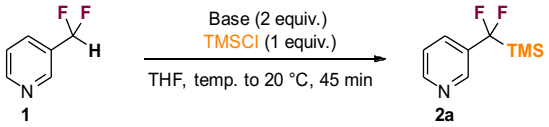
Related to our ongoing work in developing industrially viable approaches to emergent fluorinated substituents, we were also interested in functionalizing the difluoromethyl group by deprotonation, relying on cheap, easy to handle organometallic bases such as LDA. However, the instability of the generated CF_2^- intermediate would be an issue, as mentioned earlier. Therefore, we decided to study first the reaction under kinetic control using *in situ*-trapping conditions in order to avoid *α*-

Scheme 1. Functionalization of *gem*-difluorinated heterocycles through deprotonation of $-CHF_2$



elimination of fluoride,[21,22] with commonly used TMSCl (Table 1). In addition, this would lead to difluoromethyl surrogates, namely (Het)ArCF_2SiMe_3, poorly available so far, which are an economic alternative to borazines. Those ideal masked (Het)ArCF_2^- anions could be used for further transformations in analogy to the Ruppert-Prakash reagent.[25–28] We focused our studies on 3-(difluoromethyl)pyridine, which have hitherto been poorly described. When the substrate was added to a mixture of 2 equivalents of LDA and 1 equivalent of TMSCl as electrophile at -78 °C, 77% of silylated **2a** were obtained, whereas a reverse or equimolar ratio of base and electrophile led to lower yields (Table 1, entries 1–3). We were quite satisfied with these results, compared to Szymczak's observation that the use of LDA on $PhCF_2$-H afforded low yields and mainly *α*-defluorination.[24] When temperature was increased (entries 5–6), the yield dropped drastically certainly due to rapid degradation of the difluoromethyl carbanion above -78 °C.[21] When the bulkier LiTMP was used, only 10% of **2a** were produced albeit with 19% of recovered starting material as well as numerous side-products. We inverstigated also other bases like the mixed base LDA/*t*-BuOK (entry 9) and KHMDS (entry 10), which revealed inefficient. On the other hand, we also considered the non-ionic Schwesinger superbase P_4-*t*-Bu, described to successfully generate fluorinated carbanions, thanks to the strong destabilization of the $[P_4$-*t*-Bu/H$]^+$,F^- ion pair disfavoring *α*-elimination of fluoride.[29,30] In our hands, the yield was moderate in comparison to that obtained with LDA (33%, entry 11). The amount of recovered **1** could arise from the demonstrated activation of organosilicons by P_4-*t*-Bu.[31,32] Two other silylated electrophiles were assessed with LDA. $Me_2PhSiCl$ gave a comparable yield in contrast to *t*-BuMe_2SiCl which afforded 23% of **2c** in accordance with literature.[33]

Table 1. Optimization of the reaction conditions of *in situ* quench[a]



1 **2a**

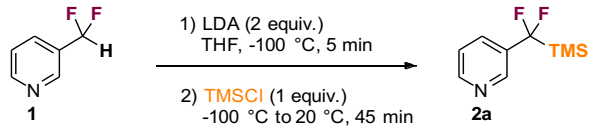
entry	base	temp. (°C)	yield of **2a** (%)	recov. **1** (%)
1[b]	LDA	- 78	61	25
2	LDA	- 78	77	0
3[c]	LDA	- 78	55	52
4[d]	LDA	- 78	74	0
5	LDA	- 50	16	31
6	LDA	- 30	0	36
7	LDA	-100	54	0
8	LiTMP	- 78	10	19
9	LDA/*t*-BuOK	- 78	NR	99
10	KHMDS	- 78	NR	100
11	P_4-*t*-Bu	- 78	33	60
12[e]	LDA	-78	76 (**2b**)	0
13[f]	LDA	-78	23 (**2c**)	0

[a] Reaction conditions: **1** (1.92 mmol) in THF (14 mL) under Ar. Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. [b] 1 equiv. of LDA was used. [c] 2 equiv. of TMSCl were used. [d] Temperature: -78 °C for 2 h. [e] $Me_2PhSiCl$ was used as electrophile. [f] *t*-BuMe_2SiCl was used as electrophile.

Although these results were quite gratifying, the *in situ* trapping strategy is expected to have a limited scope as used electrophiles have to be compatible with the lithiated base.[34,35] We therefore decided to perform the reaction under sequential trapping conditions (Scheme 2).

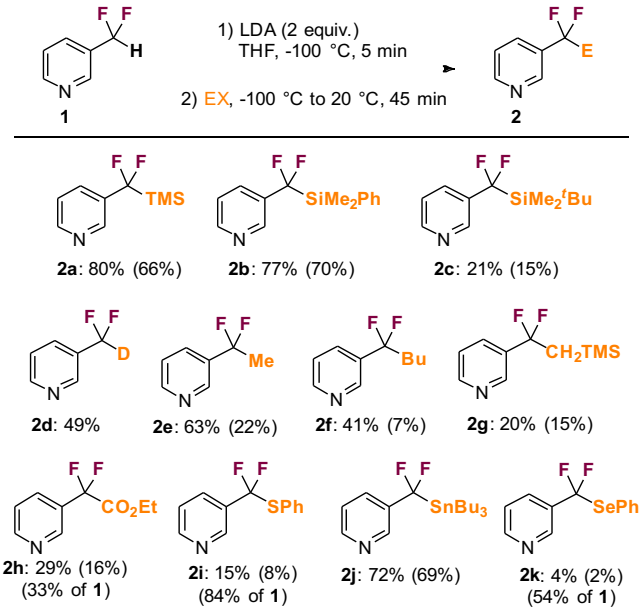
When once again LDA was used as base and TMSCl as electrophile at -78 °C, the desired product **2a** was obtained with a low yield of 35%. By decreasing the temperature to -100 °C, it was possible to obtain **2a** in 80% yield, thus with the same efficiency as under the best *in situ* quench conditions. Regarding other lithium bases, no formation of **2a** was observed with PhLi, *n*-BuLi, *s*-BuLi or *t*-BuLi. When assessing again mixed bases, such as LDA/*t*-BuOK or TMPMgCl•LiCl, a complex mixture of fluorinated compounds was obtained (see Supporting Information for details).

Scheme 2. Approach to a sequential quench



With these optimized conditions, using LDA as base, we studied the scope of the reaction with various electrophiles (Scheme 3). Analogously to the *in situ* quench strategy TMSCl and $Me_2PhSiCl$ gave high yields (up to 80% NMR yield for **2a**, Scheme 3) compared to *t*-$BuMe_2SiCl$ which afforded 21% of **2c**. The (deuterodifluoromethyl)pyridine **2d** was obtained in 49% yield when using *in situ* formed DCl as the electrophile. MeI gave a satisfactory 63% yield of **2e**. Alkyl halide electrophiles such as BuI or $TMSCH_2Cl$ provided full conversion but with low to moderate yields of the desired compounds **2f** and **2g**, respectively. Ethyl chloroformate, which allowed the introduction of a carboxylic moiety, gave a yield of 29% of **2h**. Although frequently employed in polar organometallic chemistry, diphenyl disulfide gave only a very poor yield of **2i** (15%). In a similar manner phenylselenyl chloride afforded 4% of **2k**. Conversely, stannane **2j** was obtained in good yield after trapping with tributyltin chloride, and would prove highly useful for further transformation by Stille cross-coupling to afford new Het-CF_2-Ar derivatives.[36]

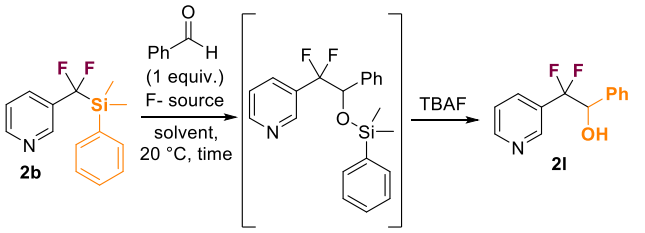
Scheme 3. Scope of electrophiles for sequential quench[a]



[a] ^{19}F NMR yields were calculated with fluorobenzene as an internal standard. Isolated yields are in parentheses.

Complementary to the scope of the sequential trapping conditions, we then focused on a third strategy, in which difluorosilylated products were used as masked difluoromethyl carbanions. Relieved from the concern of potential α-defluorination of the carbanion, higher temperatures can be used in order to increase the scope and yields. As a proof of concept, we investigated the reaction of **2b** with benzaldehyde, an electrophile which proved unsuccessful under lithiation conditions (Table 2).

Table 2. Optimization of reaction conditions for the formation of difluoromethylalcohol 2l[a]

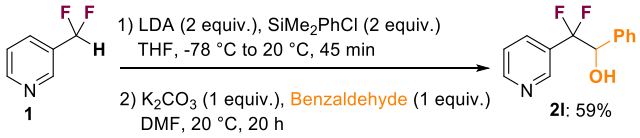


entry	F^- source (nb. equiv.)	solvent	time (h)	yield of **2l** (%)
1	TBAT (1)	THF	1	57 (52)
2	TMAF (1)	THF	1	59 (43)
3	KF (1)	THF	18	NR
4	TBAT (0.1)	THF	14	71 (56)
5	TMAF (0.1)	THF	48	54 (47)
6	KF (0.1)	DMF	3	64 (53)
7	-	DMF	24	traces
8[b]	-	DMF	18	23
9	TBAT (0.1)	DMF	0.5	99 (81)
10	TMAF (0.1)	DMF	0.5	51 (39)

[a] Reaction conditions: **2b** (0.5 mmol), benzaldehyde (0.5 mmol) in solvent (9 mL) at 20 °C under Ar. Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. Isolated yields are in parentheses. [b] Reaction mixture was heated to 90 °C. TBAT stands for [*n*-Bu_4N^+,$F_2Ph_3Si^-$], TBAF for [*n*-Bu_4N^+,F^-], TMAF for [Me_4N^+,F^-].

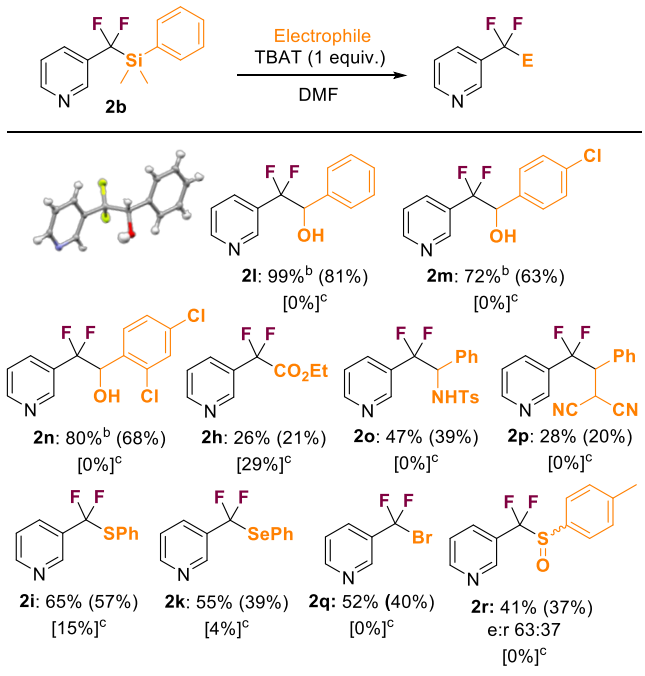
To our delight, **2l** was obtained using stoichiometric amounts of fluoride —either TBAT or TMAF— with a moderate yield (Table 2, entries 1–2). By decreasing the amount of TBAT or TMAF in THF, the reaction slowed down (entries 4–5). KF as fluoride source revealed inefficient in THF due to solubility problems (entry 3). However, when DMF was used as a solvent, higher yield and faster reaction was observed with catalytic amount of KF (entry 6). In fact, the Lewis basic activation of silicon by the solvent for fluoroalkyl transfer has already been reported by Amii *et al*. in the absence of any fluoride source.[37] Accordingly, when the mixture of **2l** and benzaldehyde was heated to 90 °C in absence of fluoride, full conversion was obtained, with formation of 23% of product **2l** (entry 8). When DMF was used as solvent in the presence of TBAT or TMAF as fluoride sources (entries 9–10), the reaction was complete after 30 min at 20 °C affording an excellent yield of 99% with TBAT (entry 9). The structure of the newly prepared (3-pyridyl)difluoromethyl carbinol was confirmed by single crystal X-Ray diffraction. We next investigated a one-pot strategy, in order to avoid the purification step of the silylated species **2b** (Scheme 4). The direct functionalization of the 3-difluoromethyl pyridine **1** with benzaldehyde was achieved using K_2CO_3 in DMF affording **2l** in a gratifying yield of 59% (see Supporting Information for details).

Scheme 4. One-pot strategy



Next, we studied the use of other electrophiles as a proof of concept of this strategy.

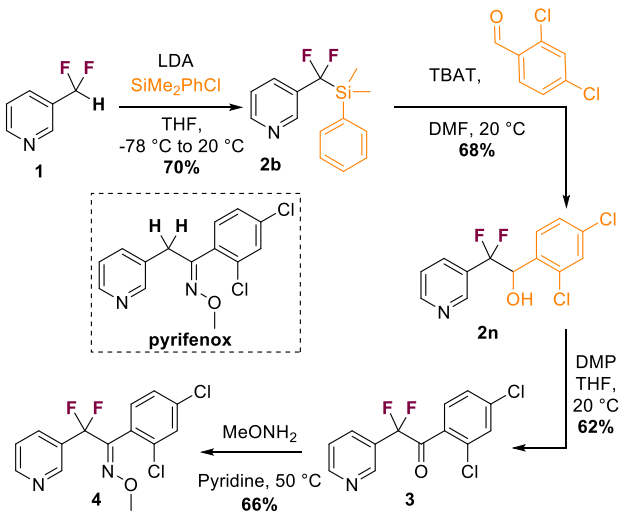
Scheme 5. Scope of the desilylative functionalization of difluoro(3-pyridyl)methane[a]



[a] Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. Isolated yields are in parentheses. [b] 0.1 equiv. of TBAT was used. [c] Yields obtained from sequential trapping.

With the best conditions for benzaldehyde (Table 2, entry 9), other electrophiles that showed inefficient towards metalation with lithiated bases, finally afforded good to moderate results, namely 4-chlorobenzaldehyde (**2m**: 72% NMR yield), 2,4-dichlorobenzaldehyde (**2n**: 80% NMR yield), tosylated aldimine (**2o**: 47% NMR yield), benzylidenemalononitrile, (**2p**: 28% NMR yield), diphenyl disulfide (**2i**: 65% NMR yield), phenylselenyl chloride (**2k**: 55% NMR yield), cyanogen bromide (**2q**: 52% NMR yield) and menthyl sulfinate (**2r**: 41% NMR yield). Only ethyl chloroformate (**2h**: 26% NMR yield) gave a similar yield as under sequential deprotonation (Scheme 5). Using the silicon-based strategy, the difluoro derivative of pyrifenox, a fungicide inhibiting ergosterol biosynthesis, was easily obtained for the first time in 4 steps with an overall unoptimized yield of 19%.

Scheme 6. Synthesis of difluoro derivative of pyrifenox



In conclusion, direct deprotonation of 3-(difluoromethyl)pyridine was developed for the first time *via* either *in situ* trapping with chlorosilanes or sequential trapping with various electrophiles after metalation of the difluoromethyl group with LDA. The newly created difluoro(3-pyridyl)methylsilanes can then react as masked difluorocarbanions and add to C=O, C=C, S–S, S-O, Se–Cl, and C=N bonds. This methodology was successfully adapted to a one-pot procedure affording novel HetAryl-CF_2-R building-blocks based on an operationally simple and cheap methodology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Optimization of sequential trapping, X-ray data, experimental procedures, and characterization data (PDF).

Accession Codes

CCDC 2017677 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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