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Room temperature deoxofluorination of aromatic aldehydes with XtalFluor-E under highly concentrated conditions†

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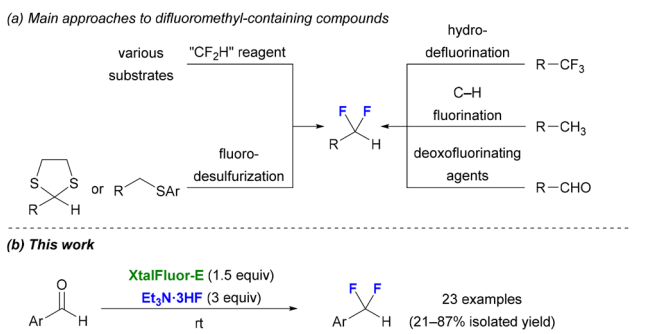
The synthesis of difluoromethyl-containing compounds exploiting the deoxofluorination reaction of aromatic aldehydes using XtalFluor-E is described. This transformation occurs at room temperature under highly concentrated conditions, *i.e.*, with no added solvent. A wide range of difluoromethyl-containing compounds was obtained in 21 to 87% isolated yields.

The impact of fluorine and fluorinated substituents in medicinal chemistry and agrochemistry is evident by an increased number of fluorinated compounds in these fields.[1] Amongst the various fluorinated substituents, the difluoromethylene group (CF_2H) has seen growing interest in recent years. This is due, in part, to its distinct properties, which makes it a "lipophilic hydrogen bond donor" moiety, *i.e.*, a somewhat lipophilic group with the ability to act as a hydrogen bond donor.[2] Recently, difluoromethylene-containing molecules have also been used as synthetic intermediates given that the CF_2H moiety can be deprotonated.[3]

A number of approaches for the preparation of difluoromethylene-containing molecules have been explored over the years (Scheme 1a), with the main ones being the direct introduction of the CF_2H group,[4] the fluorodesulfurization of 1,3-dithiolanes[5] or alkyl aryl thioethers,[6] the hydrodefluorination of trifluoromethylated compounds,[7] the fluorination of C–H bonds[8] or the deoxofluorination of aldehydes. Among these, the latter remains the most straightforward method and it can be achieved using DAST (diethylaminosulfur trifluoride, Et_2NSF_3),[9a] Deoxo-Fluor (bis(2-methoxyethyl)aminosulfur trifluoride, $(MeOCH_2CH_2)_2NSF_3$)[9b] as well as Fluolead (4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride).[10] The use of a combination of tetramethylammonium fluoride (Me_4NF) with sulfuryl fluoride (SO_2F_2),[11a] perfluorobutanesulfonyl fluoride (PBSF),[11b] or trifluoromethanesulfonic anhydride (Tf_2O)[11b] or a Ph_2S/Selectfluor combination have also been documented.[12] While most of these approaches allow the preparation of difluoromethyl-containing compounds in good yields, there is still room for improvement and the development of complementary methods.[13]

Diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalFluor-E, has been developed as a practical substitute to the main deoxofluorinating agents, *i.e.*, DAST and Deoxo-Fluor, in deoxofluorination reactions due to its crystallinity and increased thermal stability.[14–16] In a single example, the potential for XtalFluor-E to promote the deoxofluorination of an aldehyde was demonstrated in the initial report.[15b,17] Herein, we report new reaction conditions and an improved scope for the synthesis of difluoromethylene-containing compounds from aromatic aldehydes using XtalFluor-E (Scheme 1b). A variety of difluoromethylene-containing compounds was obtained in moderate to good isolated yields. Notably, optimization of the reaction conditions showed that the reaction was best run at room temperature under highly concentrated conditions.[18]

The first task at hand was to optimize the reaction conditions. Given the predominance of aromatic compounds bearing a difluoromethylene group in medicinal chemistry



Scheme 1 The difluoromethyl group: previous approaches and current work.

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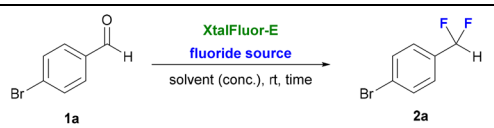
and agrochemistry,[2] we selected 4-bromobenzaldehyde (**1a**) as the model substrate and optimization results are shown in Table 1. Under the initial conditions reported (Table 1, entry 1),[15b] the corresponding product **2a** was observed in 83% NMR yield. We then explored the choice of the solvent. Of the solvents tested (Table 1, entries 2–9), only cyclohexane provided a similar NMR yield (85%). Given that all other solvents provided <51% yield, the optimization was pursued with cyclohexane. We next turned our attention to the fluoride source (Table 1, entries 10–12). Unfortunately, all the fluoride sources tested (TBAF, DMPU·13HF[19] or Olah's reagent,[20] *i.e.*, 70% HF/pyridine) provided at best trace amounts of **2a**. The use of DBU as an additive was also explored as it was shown to trigger the release of fluoride ion from XtalFluor-E.[15b,21] However, the product was only obtained in 12% yield (Table 1, entry 13), so $Et_3N{\cdot}3HF$ was kept as the fluoride source. An increase in concentration from 0.33 M (Table 1, entry 9) to 1 M (Table 1, entry 14) had a limited impact on the yield. Surprisingly, removing the solvent altogether provided **2a** in an almost similar yield (Table 1, entry 15). Given that neither CH_2Cl_2 or cyclohexane (the best results obtained thus far) were green solvents,[22] the apparent absence of a specific role for the solvent, and the general interest for solvent-free reaction as a step towards sustainability,[23] we decided to pursue the optimization without any added solvents. The NMR yield could be increased to 77% by running the reaction for 18 h (Table 1, entry 16) instead of 4 h (Table 1, entry 15). Increasing the amount of $Et_3N{\cdot}3HF$ to 3 equivalents provided **2a** in 85% NMR yield with an isolated yield of 78% for this somewhat volatile compound (Table 1, entry 17). Further increase in the amount of $Et_3N{\cdot}3HF$ had no impact on the yield (Table 1, entry 18). Only lower yields were observed when modifying the nucleophilicity of the fluoride reagent (Table 1, entries 19–22).[24] Finally, reducing the number of equivalents of XtalFluor-E to 1.1 (Table 1, entry 23) or using XtalFluor-M instead (Table 1, entry 24) led to lower yields. Ultimately, the reaction conditions reported in entry 17 were determined to be optimal and thus used for the rest of the study.

We initially realized a robustness screen[25] with different additives bearing functional groups that have been shown to react with XtalFluor-E, such as a carboxylic acid,[26] a primary alcohol,[15a,b,27] a ketone,[15a,b,28] an amide[29] and a formamide.[30] As shown in Scheme 2, a considerable drop in yield was observed for all the additive expect with acetophenone. For benzoic acid and benzyl alcohol, the corresponding fluorinated products (*i.e.*, benzoyl fluoride and benzyl fluoride) were detected in low yields in the crude reaction mixture. Overall, those results indicate that all those functional groups, aside from ketones, should be avoided on a substrate.

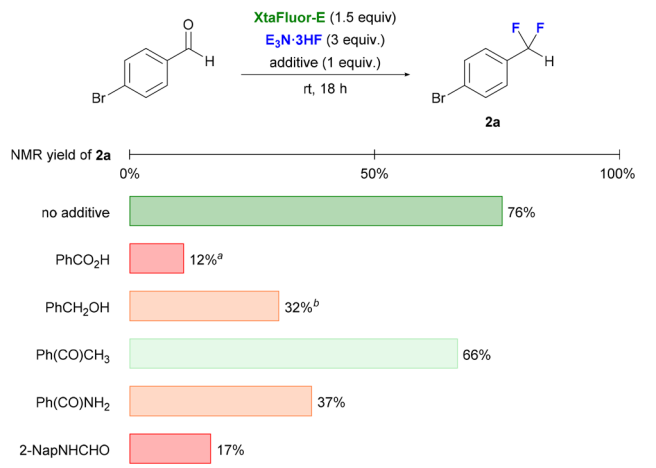
The scope of the transformation was next examined and the results are shown in Scheme 3. The NMR yields are provided alongside the isolated yields (after purification by flash chromatography) as in a few cases, the latter is moderate due to the volatility of the fluorinated products. Overall, a wide range of aromatic and heteroaromatic aldehydes could be used and

Table 1 Selected optimization results for the deoxofluorination of 4-bromobenzaldehyde (**1a**) using XtalFluor-E[a]

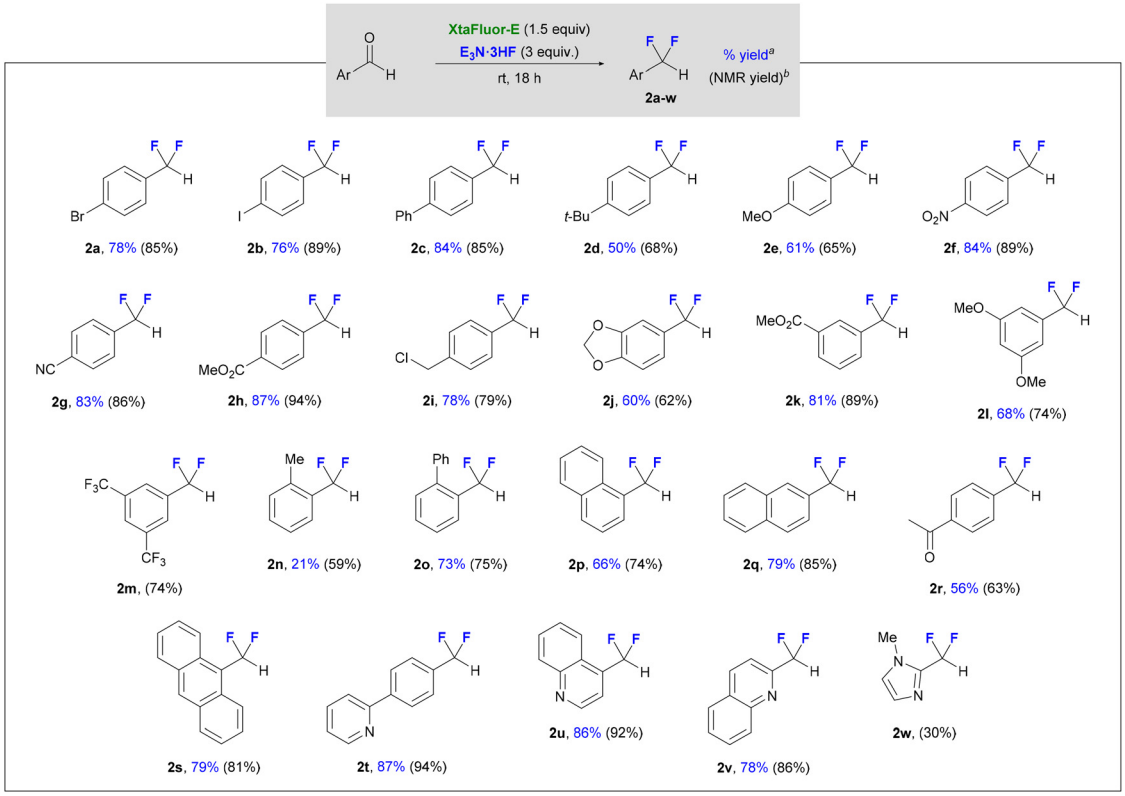


Entry[b]	F^- source (equiv.)	Solvent	Time (h)	Yield[c] (%)
1	$Et_3N{\cdot}3HF$ (2)	CH_2Cl_2	4	83
2	$Et_3N{\cdot}3HF$ (2)	EtOAc	4	38
3	$Et_3N{\cdot}3HF$ (2)	CH_3CN	4	32
4	$Et_3N{\cdot}3HF$ (2)	Toluene	4	68
7	$Et_3N{\cdot}3HF$ (2)	2-MeTHF	4	20
8	$Et_3N{\cdot}3HF$ (2)	MTBE	4	51
9	$Et_3N{\cdot}3HF$ (2)	Cyclohexane	4	85
10[d]	TBAF (2)	Cyclohexane	4	0
11	DMPU·13HF	Cyclohexane	4	Traces
12	Olah's reagent	Cyclohexane	4	Traces
13	DBU	Cyclohexane	4	12
14[e]	$Et_3N{\cdot}3HF$ (2)	Cyclohexane	4	75
15	$Et_3N{\cdot}3HF$ (2)	—	4	69
16	$Et_3N{\cdot}3HF$ (2)	—	18	77
17	**$Et_3N{\cdot}3HF$ (3)**	**—**	**18**	**85 (78)[f]**
18	$Et_3N{\cdot}3HF$ (4)	—	18	85
19	$Et_3N{\cdot}3HF$ (3) + Et_3N (1)	—	18	66
20	$Et_3N{\cdot}3HF$ (3) + Et_3N (2)	—	18	51
21	$Et_3N{\cdot}3HF$ (2) + Et_3N (1)	—	18	74
22	$Et_3N{\cdot}3HF$ (2) + Et_3N (2)	—	18	73
23[g]	$Et_3N{\cdot}3HF$ (3)	—	18	61
24[h]	$Et_3N{\cdot}3HF$ (3)	—	18	34

[a] The reaction were performed on a 0.5 mmol scale. [b] Concentration was 0.33 M when a solvent was used except entry 14. [c] Yield estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as the internal standard. [d] TBAF = tetrabutylammonium fluoride; a 1 M solution of TBAF in THF was used. [e] Concentration was 1 M. [f] Yield of **2a** after purification by silica gel flash chromatography. [g] XtalFluor-E (1.1 equiv.) was used. [h] XtalFluor-M (1.5 equiv.) was used.

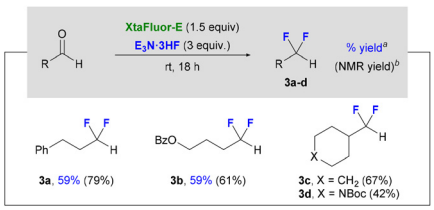


Scheme 2 Deoxofluorination of 4-bromobenzaldehyde in presence of additives. All reactions were performed on a 0.5 mmol scale. Yield estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as the internal standard. [a] 16% of PhCOF was also observed by ^{19}F NMR in the crude reaction mixture. [b] 16% of $PhCH_2F$ was also observed by ^{19}F NMR in the crude reaction mixture.



Scheme 3 Deoxofluorination of aromatic aldehydes using XtalFluor-E. All reactions were performed on a 1.0 mmol scale. [a] Yield after purification by flash chromatography on silica gel. [b] Yield estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene or 1-bromo-4-(trifluoromethyl)benzene as the internal standard.

provided the corresponding difluoromethyl-containing compounds in moderate to good isolated yields (21–87%). The reaction works well with both electron-rich and electron-poor compounds. Various functional groups including ether, ester, nitro, cyano and halogens were tolerated. Interestingly, 4-(chloromethyl)benzaldehyde provided **2i** in 78% yield with no evidence of displacement of the chloride by a fluoride. A chemoselective reaction on 4-acetylbenzaldehyde was also possible with the formation of **2r** in 56% yield. Heteroaromatic compounds such as pyridines and quinolines worked well, though the imidazole-derivative provided only a low NMR yield of the corresponding product.



Scheme 4 Preliminary results for the deoxofluorination of aliphatic aldehydes using XtalFluor-E. All reactions were performed on a 1.0 mmol scale except for **3b** (0.76 mmol scale). [a] Yield after purification by flash chromatography on silica gel. [b] Yield estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as the internal standard.

Finally, we also tested a few aliphatic aldehydes (Scheme 4) using the optimized conditions. The corresponding difluoromethyl-containing compounds (**3a–d**) were obtained in moderate yields (59% isolated yields; 42–79% NMR yields) suggesting that further optimization would probably be required to increase the yields for this class of aldehydes.

In conclusion, we have described new reaction conditions and an improved scope for the synthesis of difluoromethylene-containing compounds from aromatic aldehydes using XtalFluor-E. A variety of difluoromethylene-containing compounds were obtained in low to good isolated yields. Notably, optimization of the reaction conditions showed that the reaction was best run at room temperature under highly concentrated conditions without the need for an added solvent.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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