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Conversion of methyl ketones and methyl sulfones into α-deutero-α,α-difluoromethyl ketones and α-deutero-α,α-difluoromethyl sulfones in three synthetic steps

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ABSTRACT

Deuterodifluoromethyl ketones and sulfones were assembled in three synthetic steps from methyl ketones and sulfones, respectively. The key synthetic transformation is the deuteration of the difluorocarbanion generated by the release of trifluoroacetate from highly α-fluorinated gem-diols. High levels of deuterium on the "CF_2D" group were routinely observed. This strategy is mild and versatile and it can be applied to both ketones and sulfones without additional concerns of over- or under-fluorination. Additional examples address issues of over-deuteration when compounds with other acidic protons are subjected to the reaction conditions. This process not only demonstrates a new method to install a "CF_2D" group but also extends the scope of trifluoroacetate release to sulfones.

Fluorinated organic compounds are particularly attractive to the pharmaceutical industry, because fluorination may increase potency, modulate basicity, or enhance resistance to metabolic transformations.[1,2] Accordingly, an increasing number of newly approved pharmaceuticals display a fluorine on their structure. Another more recent strategy to address drug metabolism is the incorporation of deuterium in the place of hydrogen atom.[3,4] Although this process is substantially less explored compared to fluorination in medicinal chemistry, deuteration is commonly used in organic chemistry to label compounds for mechanistic or kinetic studies. The convergence of these two fields has yielded some examples of organic molecules that display both fluorine and deuterium[5–7]; however, this area is widely under-developed and there are few synthetic methods to access these unique structures.[8]

The two existing "CF_2D" reagents have been derived from trifluoromethylation reagents, however a deuterium replaces a fluorine atom. The most recognizable example is trimethyl(deuterodifluoromethyl)silane **1**, derived from the Ruppert-Prakash reagent, but the reagent **1** has only been reported to transfer deuterium and not the "CF_2D" group (Scheme 1).[9] The other reagent, sulfoximine **2,** has been prepared twice, but the levels of deuterium incorporation on the "CF_2D" group too low to enable its use.[10] The other published compounds arise from quenching difluorinated anions with D_2O or CD_3OD, yet none of these reports are primarily directed to the synthesis of deuterofluorocarbons.[11–19] The only exception is the synthesis of 19-deutero-19,19-difluoroandrost-4-3,17-dione (**3**) which was conducted to study the mechanism of inactivation of aromatase.[5] Herein, we report that deuterodifluoromethyl ketones and sulfones can be readily accessed via deuteration of the difluoroenolate generated from highly α-fluorinated gem-diols.

In 2011, we reported that the base-mediated fragmentation of highly α-fluorinated gem-diols produces difluoroenolates that readily participate in aldol reactions (Scheme 2).[20] This mild yet powerful process releases trifluoroacetate and has enabled the reaction of difluoroenolates with halogenation reagents,[21,22] imines,[23] trifluoromethyl ketones,[24] and disulfides.[25] Also, the difluoroenolates can be treated with water to produce difluoromethyl ketones without concerns of over- or under-fluorinated by-products.[26] Based on these prior data, we hypothesized that a difluoroenolate, formed following the release of trifluoroacetate, could

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[3] Present address: DSM Chemicals, Frankfort, IN 46401, USA.

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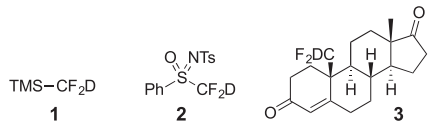
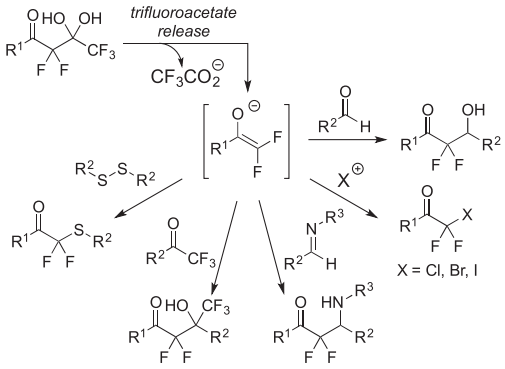
0040-4039/



Scheme 1. Notable compounds displaying a "CF_2D" group.

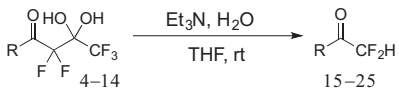


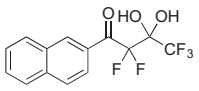
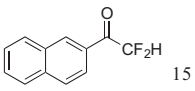
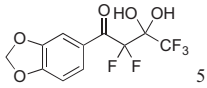
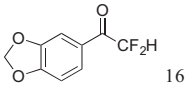
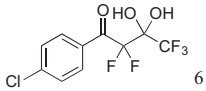
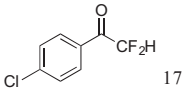
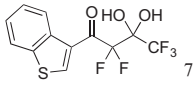
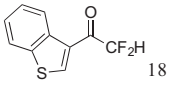
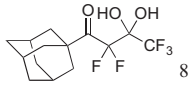
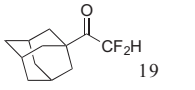
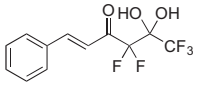
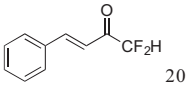
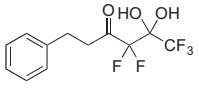
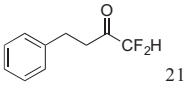
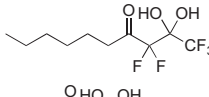
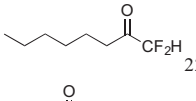
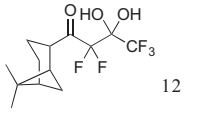
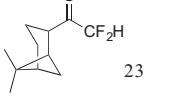
Scheme 2. Reactions of difluoroenolates formed by the release of trifluoroacetate from highly α-fluorinated gem-diols.

be effectively trapped with deuterium. We envisioned that this method could assemble "CF_2D" groups adjacent to ketones with high levels of deuterium incorporation and furthermore, we aimed to conduct side-by-side comparisons between the pronated and deuterated products (see below).

The requisite highly α-fluorinated gem-diols **4**–**14** were synthesized as described in the literature (Table 1).[20–22] Specifically, this class of compound can be accessed from methyl ketones by trifluoroacetylation followed by difluorination. Next, we treated substrates **4**–**14** in a 3:1 mixture of H_2O and THF with Et_3N (4 equiv.) and received the difluoromethyl ketones **15**–**25** in good to excellent yields (i.e. 71–99%). Phenyl- and heteroaromatic substituted ketones are compatible with the process, but LiBr was added to the reaction mixture in the case of the thiophene **7**. Alkyl substituted and α,β-unsaturated ketones participate in the process as well. Also, these data correlate well with similar studies conducted by Pattison and coworkers using CH_3CN as solvent,[26] however, the mixture of THF and water are more adaptable to the subsequent deuteration studies. Notable, examples of complex difluoromethyl ketones are the steroid- and glucose-derived compounds **24** and **25**, respectively. Although no epimerization of the α-stereogenic center of the steroid derivative **24** was observed, the basic conditions did promote epimerization of the α-benzyloxy substituent on **25**. Clearly, the center on the latter compound is more acidic

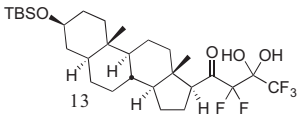
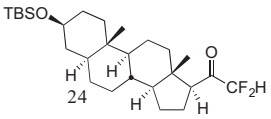
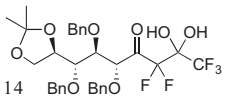
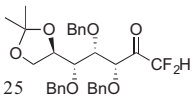
Table 1
Preparation of difluoromethyl ketones **15**–**25**.



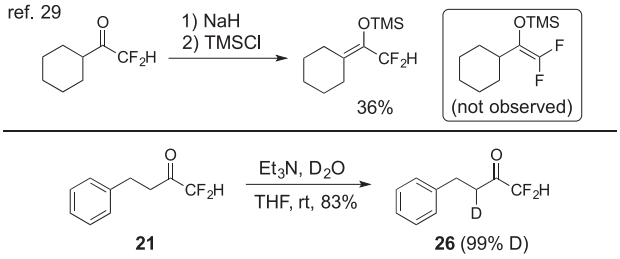
Entry	Substrate	Major product	Yield[a]
1	 4	 15	96%
2	 5	 16	88%
3	 6	 17	71%
4	 7	 18	92%[b]
5	 8	 19	96%
6	 9	 20	78%[b]
7	 10	 21	99%
8	 11	 22	88%
9	 12	 23	94%

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Major product	Yield[a]
10	 13	 24	94%
11	 14	 25	74%

[a] Isolated yields.
[b] LiBr was added.

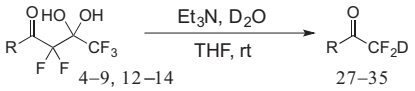


Scheme 3. Examples of deactivated carbanion formation from α-fluorosubstituents.

than the former; however, the subtle differences among the fluorinated ketones **21**–**25** will play a more prominent role in creating deuterated analogues. Specifically, processes to prevent over-deuteration as well as under deuteration must be identified.

The deactivation of carbanion formation from α-fluoro substituents was shown in 1976 by Hine.[27] Specifically, the rate of deuterium exchange was considerably slower in methyl difluoroacetate than methyl acetate when compared in methanol-d with sodium methoxide. Subsequent computation studies[28] and synthetic studies[29] have further supported that fluorine substitution can have a dramatic effect on acidity of neighboring protons. For example, NaH-mediated deprotonation of 1-cyclohexyl-2,2-diflu-

Table 2
Preparation of deuterodifluoromethyl ketones **27**–**35**.



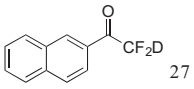
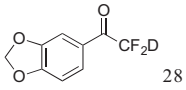
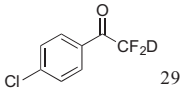
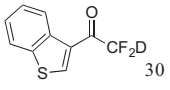
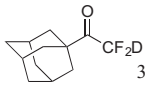
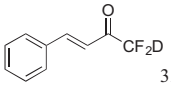
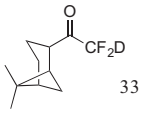
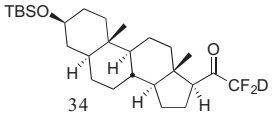
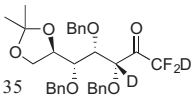
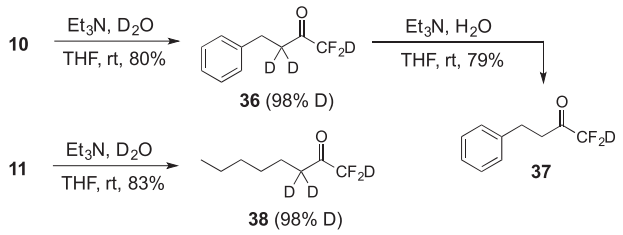
Entry	Substrate	Major product	Yield[a]	% D[b]
1	**4**	 27	89%	98%
2	**5**	 28	86%	98%
3	**6**	 29	47%	96%
4	**7**	 30	89%	97%
5	**8**	 31	90%	98%
6	**9**	 32	26%[c]	99%
7	**12**	 33	90%	99%
8	**13**	 34	81%	99%

Table 2 (*continued*)

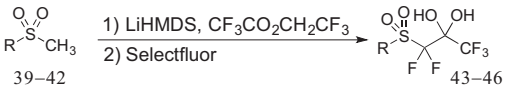
Entry	Substrate	Major product	Yield[a]	% D[b]
9	**14**	 35	76%	98%

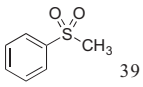
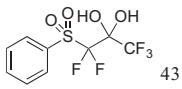
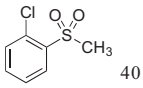
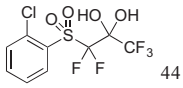
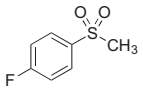
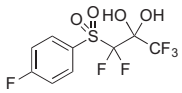
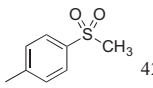
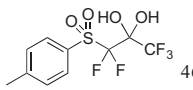
[a] Isolated yields.
[b] Percent deuterium incorporation were determined by ^{19}F NMR, see Supporting Information for details.
[c] The major product was the dimer and it was isolated in 69% yield, see Supporting Information for details.



Scheme 4. Additional deuterium incorporation studies on **10** and **11**.

Table 3
Preparation of fluorosulfone-based gem-diols **43**–**46**.



Entry	Substrate	Major product	Yield[a]
1	 39	 43	87%
2	 40	 44	93%
3	 41	 45	82%
4	 42	 46	71%

[a] Isolated yields.

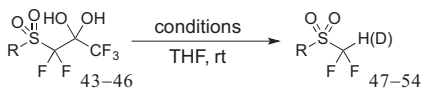
oro-1-ethanone followed by trapping with TMSCl fails to generate the difluoroenolate as reported by Liu and Zhou (Scheme 3).[29] To demonstrate that difluoromethyl ketones cannot be used to assemble the "CF_2D" group, difluoromethyl ketone **21** was treated with Et_3N in a mixture of 3:1 D_2O and THF. Across 24 h, deuteration occurred slowly at the CH_2 group adjacent to ketone, but the "CF_2-H" group was untouched as observed by ^{19}F NMR. The undesired deuterated product **26** was isolated in 83% yield.

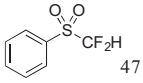
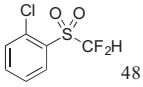
Treatment of the pentafluorinated gem-diols with D_2O in the place of water in the presence of base provided the desired deuterodifluoromethyl ketones **27**–**35** (Table 2). Levels of deuterium incorporation were typically 96–99% as determined by ^{19}F NMR. This method is a powerful process to access the "CF_2D" groups which is devoid of under- or over-fluorination as well as low levels of deuteration. It is fully compatible with aryl, heteroaryl, alkenyl, and alkyl substituted ketones. The case of the steroid-based derivative **34** shows that the "CF_2D" group can be installed on complex structures; however, the formation of glucose derivative **35** demonstrates that the other α-position is subjected to deuteration under these conditions. Specifically, analyses of HRMS, ^1H, ^{13}C, and ^{19}F NMR confirmed that no additional deuterium atoms were present on steroid **34**, yet the presence of the additional deuterium was readily observed for glucose **35**. These data prompted additional studies to address the potential of over-deuteration.

Over-deuteration of difluoromethyl ketones can be readily addressed due to the differences in acidity of the two α-carbons. For example, treatment of the gem-diol **10** with D_2O and Et_3N provides the product **36** with complete deuteration of all three α-protons (Scheme 4). Subsequently, if the trideuterated compound **36** is subjected to Et_3N and H_2O, only two of the deuteriums are exchanged and the "CF_2D" remains intact on **37**. A similar result occurred during the deuteration of **11** to give **38**.

Difluoromethyl sulfones are an important class of fluorinated building blocks that have been championed by Prakash.[30,31] Despite the widespread use of these reagents, the deuterated ana-

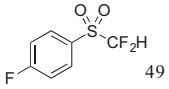
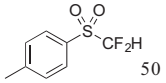
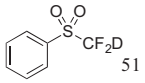
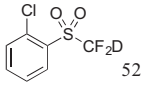
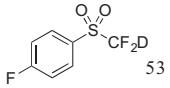
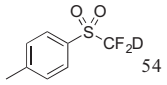
Table 4
Preparation of difluoromethyl sulfones **47**–**50** and deuterodifluoromethyl sulfones **51**–**54**.



Entry	Substrate	Conditions	Major product	Yield[a]	% D[b]
1	**43**	Et_3N, H_2O	 47	87%	na
2	**44**	Et_3N, H_2O	 48	quant.	na

(*continued on next page*)

Table 4 (*continued*)

Entry	Substrate	Conditions	Major product	Yield[a]	% D[b]
3	**45**	Et_3N, H_2O	 49	89%	na
4	**46**	Et_3N, H_2O	 50	85%	na
5	**43**	Et_3N, D_2O	 51	74%	97%
6	**44**	Et_3N, D_2O	 52	96%	96%
7	**45**	Et_3N, D_2O	 53	80%	98%
8	**46**	Et_3N, D_2O	 54	91%	98%

[a] Isolated yields.
[b] Percent deuterium incorporation were determined by ^{19}F NMR, see Supporting Information for details.

logues have not been established. In order to extend the scope of this strategy and produce another group of "CF_2D" compounds, we synthesized the requisite highly α-fluorinated gem-diols from the methylphenylsulfones **39**–**42** (Table 3). The two-step trifluoroacetylation and difluorination protocol[20] provided the gem-diols **43**–**46**.

The base-promoted release of trifluoroacetate in the presence of H_2O or D_2O provided the difluoromethyl sulfones **47**–**50** or deuterodifluoromethyl sulfones **51**–**54**, respectively (Table 4). Again, deuteration occurred in very high levels (i.e., >95% by ^{19}F NMR) and yields were very good. Also, trifluoroacetate release still occurs exclusively, regardless of the exchange of the ketone group with a sulfone group.

In conclusion, deuterodifluoromethyl ketones and sulfones were assembled with high levels of deuterium on the "CF_2D" group. This strategy is mild and versatile as it can be applied to both ketones and sulfones without concerns of over- or under-fluorination. Additional examples were provided to address issues of over-deuteration when compounds with other acidic protons are subjected to the reaction conditions. This process not only demonstrates a new method to install a "CF_2D" group but also extends the scope of trifluoroacetate release to sulfones.

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.12.018.

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