Synthetic Methods

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Direct Difluoromethylation of Alcohols with an Electrophilic Difluoromethylated Sulfonium Ylide

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Abstract: *A general method for the formation of alkyl difluoromethylethers under mild reaction conditions and with good functional-group tolerance was developed. The development of the method was based on the invention of a stable, electrophilic, difluoromethylating reagent, difluoromethyl-(4-nitrophenyl)-bis(carbomethoxy) methylide sulfonium ylide, which was synthesized by reaction of the easily available 4-nitrophenyl (difluoromethyl)thioether and dimethyl diazomalonate in the presence of a rhodium catalyst.*

Driven by their inherent and unique properties, fluorine and fluorinated groups have been increasingly employed by the medicinal chemists as key moieties to modulate the chemical, physical, and biological properties of drug and agrochemical candidates.[1] Consequently, the incorporation of either a fluorine atom or a fluorinated group into the target molecules has become routine practice at every stage of the development of preclinical drugs.[2] Among the many fluorinated groups, fluoroalkoxy groups such as OCF_3, OCF_2H, OCH_2F, and OCH_2CF_3 are rapidly gaining popularity.[3] In particular, the difluoromethoxy group (OCF_2H) is of great interest for the following reasons: 1) Like its bulkier analogue OCF_3, OCF_2H is a strong electron-withdrawing group which could decrease the electron density of the drug molecule to make it less likely to be oxidized by P450 and thus increase its lifetime in vivo;[4] 2) The proton in OCF_2H is capable of acting as a hydrogen-bond donor to improve the binding selectivity of the drug molecule.[5]

In light of the well-recognized biological potential of the difluoromethylether, in the past decades, a lot of effort has been focused on developing effective methods for the formation of difluoromethylether.[6] Interestingly, a majority of the reported difluoromethylether formation methods are related to the construction of aryl difluoromethylethers ($ArOCF_2H$) by a process involving the reaction of a phenoxide with an in situ generated difluorocarbene under basic conditions.[7] In contrast, methods for the formation of alkyl difluoromethylethers are far less documented. Application of the difluorocarbene strategy often results in low yields and formation of orthorfomate side products because of the strong basic nature of the alkoxide.[8] Although not explicitly stated in the literature, many common functional groups such as alkyl halide, alkene, and ester are not compatible with the reaction conditions. Reactions of a few simple alcohols with an in situ generated difluorocarbene under nonbasic conditions have also been reported by Chen and co-workers in 1989.[9] Yet, yields were moderate and alcohols with functional groups were not described. In the meanwhile, an indirect strategy for the formation of alkyl difluoromethylether by an oxidative desulfurization/fluorination process of the corresponding thionoesters has been explored.[10] However, this approach requires multiple steps and the overall efficiency remains to be improved before it becomes practical.

To develop a practical method for the formation of alkyl difluoromethylethers, a method which overcomes the drawbacks mentioned above, new strategies are clearly and urgently needed. Reaction of an alcohol with an electrophilic difluoromethylating reagent would provide a promising alternative. Pioneering work by Prakash and co-workers have demonstrated that the reaction of an alcohol with an in situ formed electrophilic difluoromethylating reagent, *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfonximinium tetrafluoroborate (**A**), generated the corresponding alkyl difluoromethylether in moderate yields, although the instability of the reagent, requirement of large excess of the alcohol (10 equivalents), and the formation of a methyl ether side product limited their widespread application.[11] Later on, the same group attempted to improve the reaction by employing a more stable electrophilic difluoromethylating reagent *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate (**B**).[12] Yet, this reagent is not reactive enough to give the desired difluoromethylether in high yield (Figure 1).

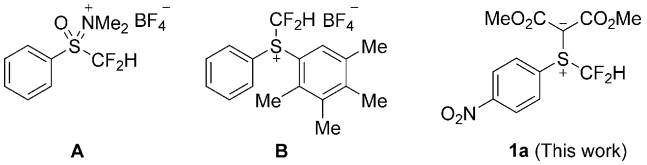

Figure 1. Electrophilic difluoromethylating reagents.

Thus, if an easily available and highly reactive electrophilic difluoromethylating reagent can be created, a general and practical method for the formation of alkyl difluoromethylethers would be possible. As part of our investigation of electrophilic fluoroalkyl reagents,[13] herein we report the invention of such an electrophilic difluoromethylating reagent, difluoromethyl-(4-nitrophenyl)-bis-(carbomethoxy)-methylide sulfonium ylide (**1a**). In the presence of a Lewis

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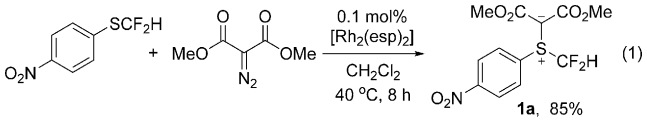
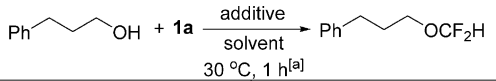
acid or Brønsted acid, a variety of alcohols reacted with **1a** to generate the corresponding alkyl difluoromethylethers in good yields.

The difluoromethyl-substituted sulfonium ylide **1a** could be easily and efficiently synthesized from the reaction of 4-nitrophenyl (difluoromethyl)thioether with dimethyl diazomalonate in the presence of 0.1 mol% $[Rh_2(esp)_2]$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) in dichloromethane in 85% yield after 8 hours at 40°C [Eq. (1)].[14] The reaction can be easily scaled up to 5.4 gram quantities with a 85% yield in the presence of 14 mg of $[Rh_2(esp)_2]$. The compound **1a** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis. The structure of **1a** was unambiguously confirmed by X-ray analysis of its single crystals (see the Supporting Information for details). The compound **1a** is a stable, crystalline, pale yellow solid. No detectable decomposition was observed after three days of storage on the shelf at ambient temperature and more than one month in the refrigerator.



(1)

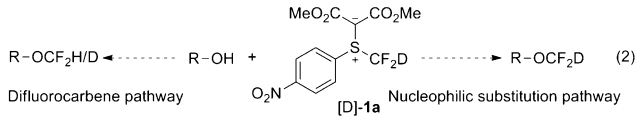
With this new reagent in hand, we then explored the reactivity of **1a** with alcohols. The reaction of 2.0 equivalents of 3-phenylpropan-1-ol with **1a** was initially chosen as the model reaction to optimize the reaction conditions. Surprisingly, reactions occurred in less than 49% yields when a base such as K_2CO_3, NaOH, LiO*t*Bu, or Cs_2CO_3 was added (Scheme 1, entries 1–7). Instead, by using 1.2 equivalents of the Lewis acid $LiBF_4$ as an additive, the difluoromethylation took place under very mild reaction conditions, thus giving the difluoromethylether in 85% yield as determined by ^{19}F NMR spectroscopy using an internal standard (entry 8). The choice of the solvent is crucial for the conversion of the reaction. Reactions conducted in toluene occurred in 74% yield while the yield decreased to 13% when THF was used as the solvent, and no desired difluoromethylether was formed if a polar solvent such as CH_3CN or DMF was used (entries 9–12). Further studies showed that the anion of $LiBF_4$ has a remarkable effect on the high efficiency of the reaction. Switching the anion from BF_4 to either PF_6, OTf, or NTf_2 led to the shut-down of the reaction (entries 13–15). Other Lewis acids such as $Zn(BF_4)_2$ or $TMSNTf_2$ were not as effective as $LiBF_4$ (entries 16 and 17). Further studies showed that the yield of the reaction decreased to 80 and 72% when 0.5 and 0.2 equivalents, respectively, of $LiBF_4$ were used (entries 18 and 19). Likewise, the yield of the reaction decreased to 49% yield when 1.0 equivalent of alcohol was used (entry 20).[15]



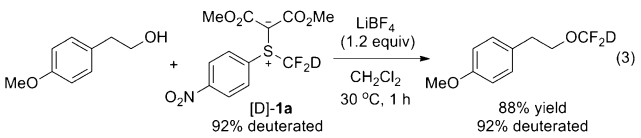
Entry	Additive	Solvent	Yield [%][b]	Entry	Additive	Solvent	Yield [%][b]
1	K_2CO_3	CH_2Cl_2	13	11	$LiBF_4$	MeCN	-
2	NaOH	CH_2Cl_2	6	12	$LiBF_4$	DMF	-
3	LiO*t*Bu	CH_2Cl_2	10	13	$LiPF_6$	CH_2Cl_2	-
4	Cs_2CO_3	CH_2Cl_2	14	14	$LiNTf_2$	CH_2Cl_2	-
5	Cs_2CO_3	toluene	49	15	LiOTf	CH_2Cl_2	-
6	Cs_2CO_3	THF	-	16	$Zn(BF_4)_2$	CH_2Cl_2	55
7	Cs_2CO_3	MeCN	-	17	$TMSNTf_2$	CH_2Cl_2	-
8	$LiBF_4$	CH_2Cl_2	85	18	$LiBF_4$	CH_2Cl_2	80[c]
9	$LiBF_4$	toluene	74	19	$LiBF_4$	CH_2Cl_2	72[d]
10	$LiBF_4$	THF	13	20	$LiBF_4$	CH_2Cl_2	49[e]

Scheme 1. Optimization of the reaction conditions for the reaction of 3-phenylpropan-1-ol with **1a**. [a] Reaction conditions: 3-phenylpropan-1-ol (0.20 mmol), reagent **1a** (0.10 mmol), additive (0.12 mmol) in solvent at 30°C for 1 h. [b] Yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard, and were calculated based on **1a**. [c] 50 mol% $LiBF_4$ was used; [d] 20 mol% $LiBF_4$ was used. [e] 1.0 equivalent of 3-phenylpropan-1-ol was used. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

Mechanistically, the Lewis acid mediated difluoromethylation of alcohols may proceed by a difluorocarbene pathway in which a spontaneous deprotonation of **1a** takes place to form a difluorocarbene, followed by the insertion of the difluorocarbene to the O–H bond of the alcohol. Alternatively, the reaction may undergo direct nucleophilic attack of the alcohol to the electrophilic difluoromethyl-substituted sulfonium ylide. To distinguish two likely pathways, we synthesized a deuterated difluoromethyl-substituted sulfonium ylide, [D]-**1a**, and subjected it to the Lewis acid mediated difluoromethylation reaction. Theoretically, a product derived from significant H–D exchange would be expected if the reaction proceeds by a difluorocarbene pathway. Otherwise, less of a H–D exchange would be observed for the direct nucleophilic substitution pathway [Eq. (2)].



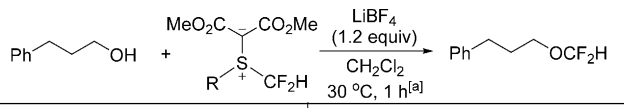
(2)



(3)

Experimentally, reaction of 2-(4-methoxyphenyl)ethanol with [D]-**1a** generated the deuterated difluomethylether, without deuterium scrambling, in 88% yield [Eq. (3)]. Since both [D]-**1a** and the deuterated difluomethylether did not undergo H–D exchange under the reaction conditions, these results clearly support a Lewis acid mediated difluoromethylether formation reaction proceeding by a simple nucleophilic substitution pathway. Since $LiBF_4$ is crucial for reactivity of the reagent, we speculate that $LiBF_4$ might interact with the two carbonyl groups of **1a** to form a lithium-enolate-type sulfonium salt intermediate, which is more electrophilic than the sulfonium ylide and will react with alcohol to give difluoromethylether.

To probe if the reaction could be further improved by the modification of the structure of the sulfonium ylide, next, we

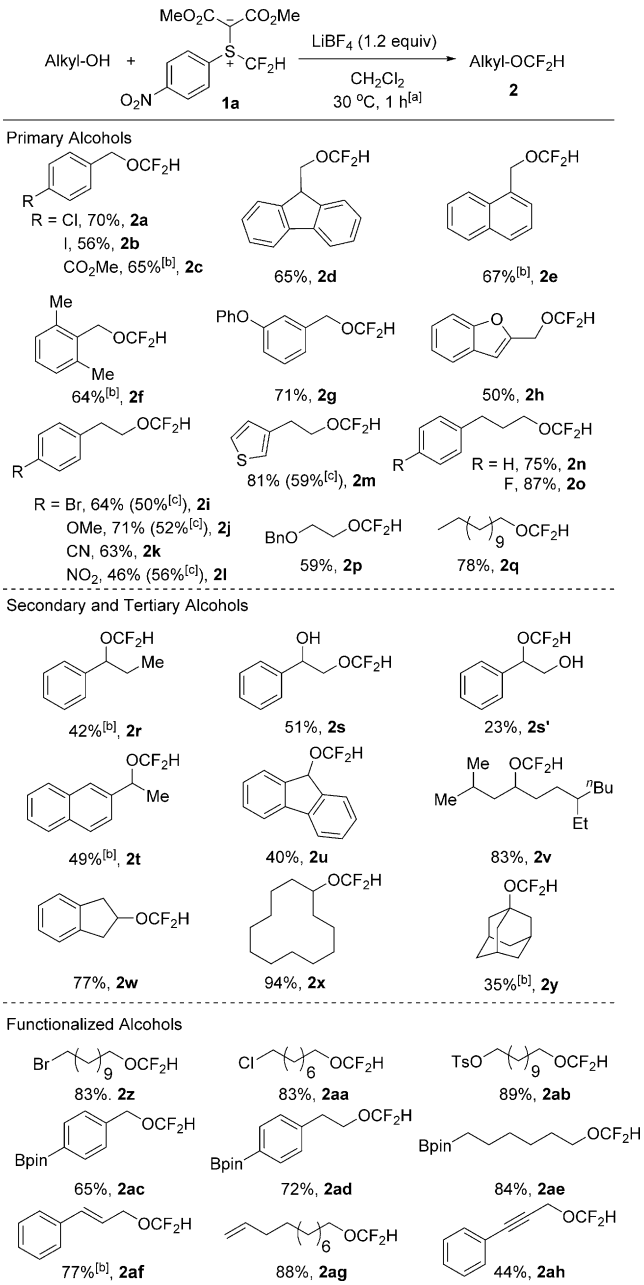


Entry	R	Ylide	Yield [%]	Entry	R	Ylide	Yield [%]
1	4-$NO_2C_6H_4$	**1a**	85	6	3-ClC_6H_4	**1f**	32
2	C_6H_4	**1b**	25	7	1-naphthyl	**1g**	41
3	4-MeC_6H_4	**1c**	20	8	2-pyridyl	**1h**	27
4	4-$MeOC_6H_4$	**1d**	3	9[b]	4-NO_2	**1i**	<2
5	4-FC_6H_4	**1e**	12	10	Bn	**1j**	<2

Scheme 2. The effect of the structure of the difluoromethyl-substituted sulfonium ylides on the reaction of difluoromethylation of alcohols. [a] Reaction conditions: 3-phenylpropan-1-ol (0.20 mmol), reagent **1a–j** (0.10 mmol), $LiBF_4$ (0.12 mmol) in CH_2Cl_2 at 30 °C for 1 h. Yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard, and were calculated based on reagent **1a**. [b] Difluoromethyl-(4-nitrophenyl) 2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-yl methylide sulfonium ylide was used.

synthesized various analogues (**1b–j**) of **1a** and studied the influence of the structure of the difluoromethyl-substituted sulfonium ylides. As shown in Scheme 2, in general, difluoromethyl-substituted sulfonium ylides with electron-poor arene moieties reacted in higher yields than those with electron-rich arene moieties. Difluoromethyl-substituted sulfonium ylides bearing a 4-nitrophenyl group (**1a**) gave the highest yield while reaction of an alcohol with either **1c** or **1d**, having an electron-rich 4-methyl or 4-methoxyphenyl group, respectively, occurred in the corresponding yields of 20 and 3%. Reactions of difluoromethyl-substituted sulfonium ylides with either a *para*-fluorophenyl group or a *meta*-chlorophenyl group also proceeded in lower yields. The observation of the higher reactivities of the reagents with electron-poor aryl groups also supported our assumption that lowering the electron density of the sulfonium ylides might increase the reactivity of the reagent. The difluoromethyl-substituted sulfonium ylide **1g**, with a bulkier naphthyl group, was much less effective than **1a**. Interestingly, the difluoromethyl-substituted sulfonium ylide **1h**, with an *ortho*-pyridyl group did not improve the reactivity of the reagent. Noticeably, locking the conformation of the two ester groups of the sulfonium ylide completely shut down the reactivity of the reagent, as indicated in the case of **1i**. This result suggests that the orientation of the two ester groups might make it less likely to generate an enolate-type intermediate when interacting with $LiBF_4$ and make it less reactive.

Having identified suitable conditions for the difluoromethylation of alcohols, we explored the applicability of these reaction conditions for the conversion of many alcohols into the corresponding difluoromethylethers. As summarized in Scheme 3, a variety of primary and secondary alcohols were difluoromethylated in moderate to high yields. Under the optimized reaction conditions, reactions of a tertiary alcohol occurred in low conversions. Nevertheless, it was found that moderate yield (35%) was observed when 5.0 equivalents of admantan-1-ol was reacted with **1a** in the presence of 2.0 mol% $HBF_4{\cdot}OEt_2$ (**2y**). Likewise, the yields of a few benzylic or allylic alcohols were improved significantly by emloying 5.0 equivalents of the corresponding alcohols using 2.0 mol% $HBF_4{\cdot}OEt_2$ as the catalyst (**2c**, **2e**, **2f**, **2r**, **2t**, **2af**).

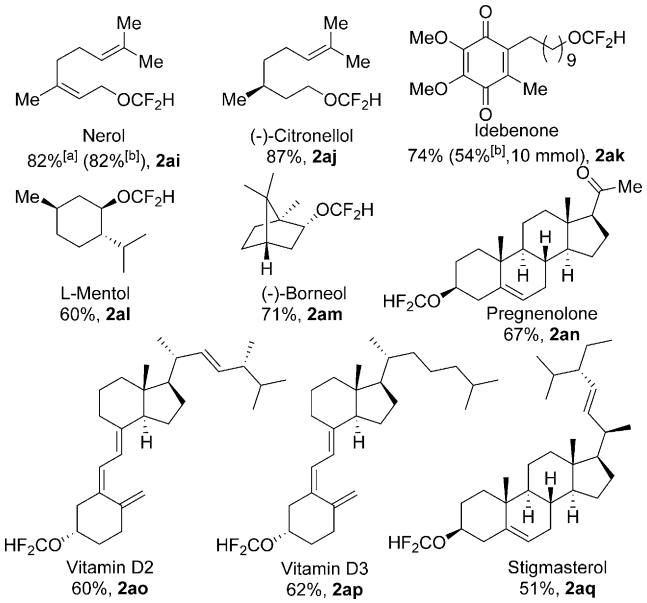


Scheme 3. Scope of the Lewis acid mediated Difluoromethylation of Alcohols. [a] Reaction conditions: alcohol (1.0 mmol), reagent **1a** (0.5 mmol), $LiBF_4$ (0.6 mmol) in CH_2Cl_2 (2.5 mL) at 30 °C for 1 h. Isolated yields that were calculated based on reagent **1a**; [b] Alcohol (2.5 mmol), reagent **1a** (0.50 mmol), $HBF_4{\cdot}OEt_2$ (2.0 mol%) in CH_2Cl_2 (2.5 mL) at room temperature for 1 h. Yield of isolated product was calculated based on **1a**. [c] Recovery of alcohol. Ts = 4-toluenesulfonyl.

Common functional groups such as aromatic fluoride, chloride, bromide, iodide, ester, cyano, and nitro groups, as well as heteroaryl groups such as benzofuran or thiophene were compatible (**2a–c**, **2h–m**, **2o**). Interestingly, reaction of 1-phenylethane-1,2-diol with **1a** gave two different products, **2s** and **2s′**, in 51% and 23% yield, respectively. In this case, the primary alcohol is slightly favored over the benzylic secondary hydroxy group.

Noticeably, alcohols bearing functional groups such as alkyl chloride, bromide, tosylate, or boryl groups which are sensitive to the basic conditions that are commonly used to generate the difluorocarbene could be efficiently converted into the corresponding difluoromethylethers in high yields (Scheme 3, **2z**–**ae**). Moreover, alcohols containing an alkene or alkyne group reacted efficiently with **1a** to give the difluoromethylethers in good yields (**2af**–**ah**). Previously, Hu and co-workers reported that the alkene group reacted preferentially over the hydroxy group for reaction of pent-4-en-1-ol with a difluorocarbene generated under neutral reaction conditions.[8d] Thus, the current method showcased some advantages over the tranditional difluorocarbene strategies.

To illustrate the advantage of the current difluoromethylation protocol, we selected several natural compounds and drug molecules that bear an alcohol group to investigate if the hydroxy group can be easily difluoromethylated. As shown in Scheme 4, difluoromethylated derivatives (**2ai**–**aq**) of a few



Scheme 4. Scope of the Lewis acid mediated Difluoromethylation of alcohols. Reaction conditions: alcohol (1.0 mmol), reagent **1a** (0.50 mmol), $LiBF_4$ (0.6 mmol) in CH_2Cl_2 (2.5 mL) at 30 °C for 1 h. Yield of isolated product was calculated based on **1a**. [a] Alcohol (2.5 mmol), reagent **1a** (0.50 mmol), $HBF_4{\cdot}OEt_2$ (2.0 mol %) in CH_2Cl_2 (2.5 mL) at room temperature for 1 h. Yield of isolated product was calculated based on **1a**. [b] Recovery of alcohol.

biologically active molecules such as nerol, (−)-citronellol, L-menthol, (−)-borneol, pregnenolone, stigmasterol, and vitamin D2/D3 can all be generated efficiently. Notably, the difluoromethylated derivative of Idebenone, a drug for treatment of Alzheimer's disease,[16] was scaled up to 10 mmol scale in 74 % yield (**2ak**). These results demonstrate the utility of the Lewis acid mediated difluoromethylation of alcohols to access compounds which are not easily accessible by other common methods.

In summary, a new and general method for the formation of alkyl difluoromethylethers was developed. A variety of functional groups are compatible, thus showing some advantages in comparison to the traditional methods. The development of such a method was based on the invention of an electrophilic difluoromethylating reagent, difluoromethyl-(4-nitrophenyl)-bis(carbomethoxy) methylide sulfonium ylide (**1a**), which was synthesized by reaction of easily available 4-nitrophenyl (difluoromethyl)thioether with dimethyl diazomalonate with 0.1 mol % $Rh_2(esp)_2$ catalyst. Further investigations of the reactivity of **1a** and its derivatives toward other nucleophiles are currently ongoing in our lab.

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[17] CCDC 1470492 (**1a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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