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Mechanochemical Difluoromethylations of Alcohols

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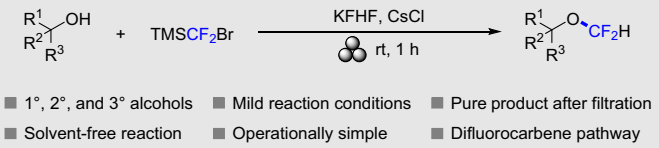
Difluoromethyl ethers are formed through mechanochemical reactions of alcohols with difluorocarbene in a mixer mill. The protocol could be applied to primary, secondary, and tertiary alcohols, yielding the corresponding products in excellent yields (up to 99%) after 1 h reaction time at room temperature. The transformations proceeded under solvent-free reaction conditions, followed by product purification by filtration, which drastically reduced the amount of waste generated during the process.



Keywords: **mechanochemistry, ball milling, solvent-free reaction, difluorocarbene, difluoromethyl ether**

Introduction

Due to its unique physiochemical properties, the difluoromethoxy group is an emerging structural motif in pharmaceutical and agrochemical research. Compared with a methoxy group, it induces a higher metabolic stability and lipophilicity, in contrast to a trifluoromethoxy moiety, it reveals hydrogen bond donor capabilities. As a result, the difluoromethoxy group has become a valuable structural component, allowing the fine-tuning of important properties.[1,2] Notable examples of marketed difluoromethyl ethers include the proton pump inhibitor Pantoprazole and the insecticide Flucythrinate.[3,4] In light of this background, the development of strategies to synthesize aryl and alkyl difluoromethyl ethers is of great interest.[5–7] Although recent approaches toward aryl difluoromethyl ethers involve C–H bond functionalizations of suitable arenes,[8–11] most methods start from phenols.[8,12–19] Deprotonations with bases lead to phenoxides which react with electrophilic difluorocarbene. For alcohols, this strategy is less effective due to their higher pK_a values. Initial attempts to apply difluorocarbene precursors in reactions with alcohols (HCF_2Cl,[20,21] $BrCF_2P(O)(EtO)_2$,[22] $TMSCF_2Br$,[16] CF_2N_2,[23] $ZnBrCF_3{\cdot}2CH_3CN$,[24] HFPO,[25] and $FSO_2CF_2CO_2H$[17]) showed the formation of the desired difluoromethyl ethers, but the protocols suffered from the requirement of an excess of alcohol, a poor reactivity, or a narrow substrate scope. Of particular interest is the study by Levchenko et al.,[26] who used $FSO_2CF_2CO_2H$ and copper catalyst to difluoromethylate primary and secondary alcohols. However, tertiary alcohols were not suitable and the air pollutant SO_2 is formed as a side product of the reaction (Scheme 1a). Shen and coworkers[27] reported a Lewis acid-activated difluoromethylated sulfonium ylide, which reacted by nucleophilic substitution of CF_2H^+ with various primary and secondary alcohols in dichloromethane (DCM). Due to increased steric hindrance, tertiary alcohols showed low conversions. Finally, Hu and coworkers[28] presented difluoromethylation of alcohols with $TMSCF_2Br$ as a difluorocarbene precursor (Scheme 1a). As mild activators, potassium acetate (KOAc) and potassium bifluoride (KFHF) were used. An extensive optimization revealed that the key to this transformation was a high concentration in a two-phase solvent system of DCM/water. Difluoromethyl ethers of primary, secondary, and tertiary alcohols were obtained after extraction of the reaction mixture with DCM and subsequent column chromatography. Secondary and

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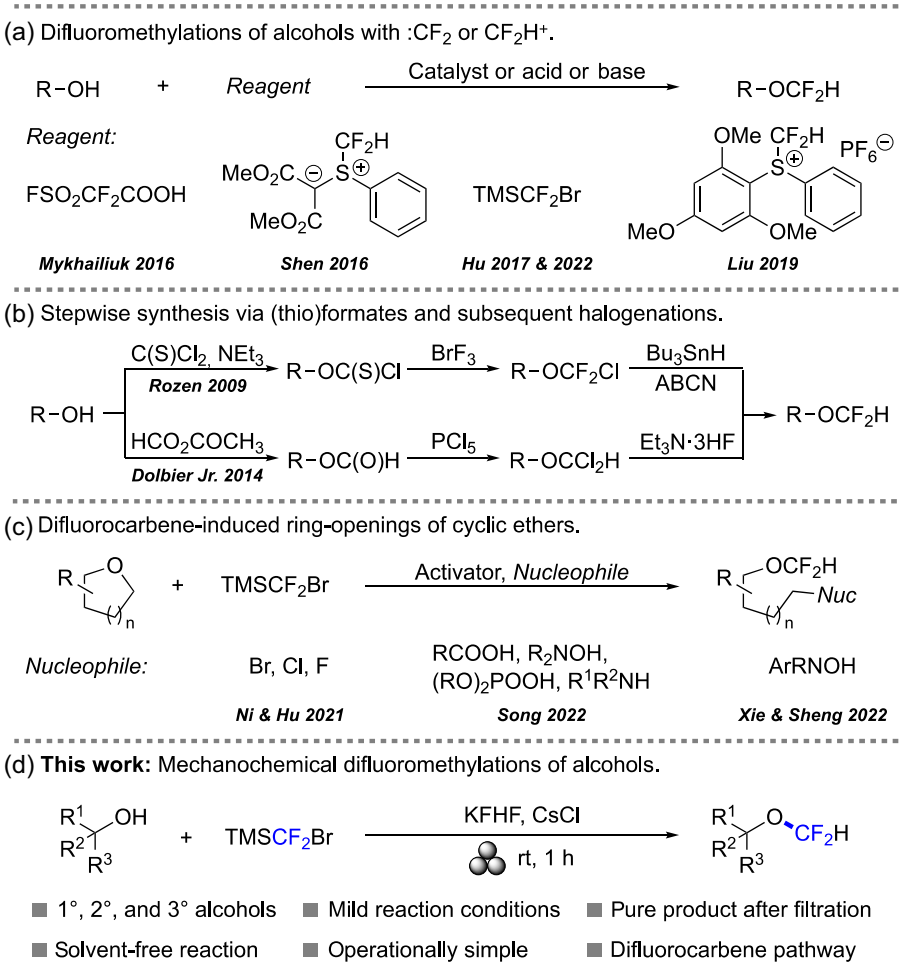

Scheme 1 | *Available strategies for synthesizing O-difluoromethylated alcohols.*

tertiary alcohols required more equivalents of both difluorocarbene precursor and activator. Recently, the same group reported an optimized protocol with water as a solvent.[29] Here also, DCM was used to extract the product from the reaction mixture, and modified conditions for secondary and tertiary alcohols were still required. Melting at elevated temperatures or solubilization with the addition of DCM was necessary to give satisfying yields for solid alcohols. In 2019, Liu and coworkers[30] developed difluoromethylations of alcohols with an *S*-(difluoro-methyl)sulfonium salt as a difluorocarbene precursor (Scheme 1a). Again, a two-phase solvent system and optimized conditions for secondary alcohols were required. Besides the synthesis of alkyl difluoromethyl ethers through the reaction of alcohol with difluorocarbene or CF_2H^+, stepwise approaches from alcohols via thioformates (Scheme 1b)[31,32] or more recently, difluorocarbene-induced ring-openings of cyclic ethers with various nucleophiles have been developed (Scheme 1c).[33–35] In general, however, the stepwise methods suffer from a rather small substrate scope and the requirement of multiple purifications, along with product structures of difluoromethyl ethers obtained by ring-opening of cyclic ethers being limited by ring size and nucleophile.

In the search for more environmentally benign reactions, ball milling has made a successful entry into various fields of chemistry.[36–54] Following a mechanochemical approach has often superseded the use of solvents, which are a major hazard and contribute greatly to the waste produced in a reaction. Furthermore, compared to analogous solvent-based syntheses the same or better results in yields and catalyst loadings have been achieved. Also, altered product selectivities, possible conversions of insoluble substrates, and shorter reaction times can be beneficial attributes of mechanochemical reactions.[48,55] In ball milling, the reactants, and reagents are simply added to a milling jar loaded with milling balls, the jar is sealed and placed inside a milling machine. When the machine is started, the jar is shaken or rotated, and the mixing of the reaction mixture, as well as energy transfer from the movement of the ball by shear and impact forces, can facilitate the reaction. In addition to batch processes in planetary and mixer mills, the use of

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continuously operated twin screw extruders[56–58] or resonant acoustic mixers[59–62] has recently shown promise for the scale-up in sustainable organic chemistry. Herein, we report mechanochemical difluoromethylations of primary, secondary, and tertiary alcohols yielding the corresponding difluoromethyl ethers after 1 h reaction time at room temperature (Scheme 1d). The reactions were carried out under solvent-free reaction conditions, allowing the isolation of the products by simple filtration, thereby reducing the amount of waste generated.

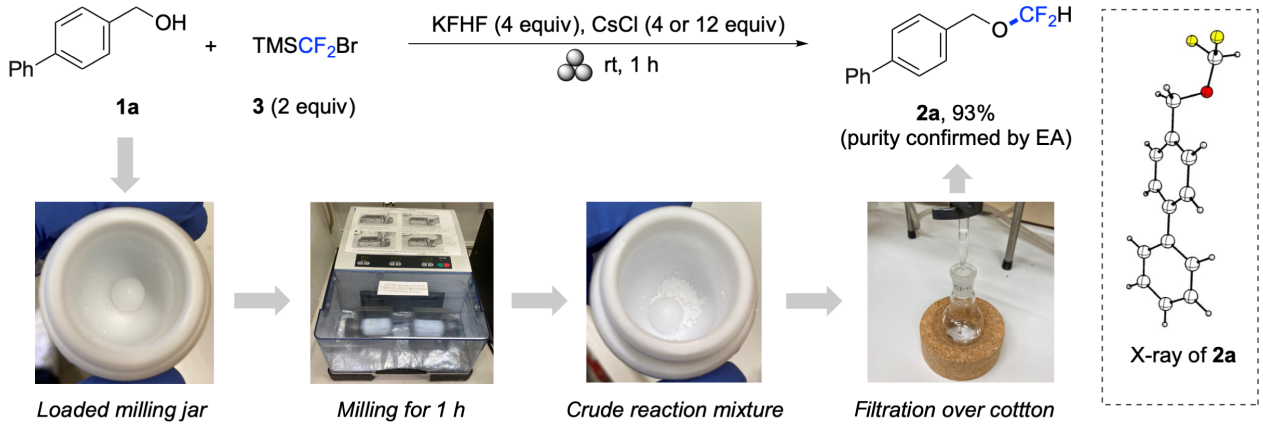
Results and Discussion

At the starting point of the investigation, various difluorocarbene precursors were screened in the reaction with a model substrate [1,1′-biphenyl]-4-ylmethanol (**1a**, see Supporting Information Table S1). Choices about activator and stoichiometry were made based on previously published solution-based protocols. The reactions were carried out for 1 h at room temperature in stainless steel (SS) milling equipment. Either difluoromethyl ether **2a** was either not formed at all or formed in a yield of up to 18% with a combination of $BrCF_2P(O)(OEt)_2$ and K_3PO_4. To our delight, the difluorocarbene precursor $TMSCF_2Br$ (**3**) developed by Hu and coworkers with KFHF as an activator yielded **2a** in 65% yield.[5,63,64] The high substrate density under mechanochemical conditions and the mild difluorocarbene generation with activator KFHF appeared to be beneficial in the direct reaction of alcohol as a nucleophile with difluorocarbene.[28] Furthermore, the identity of **2a** was confirmed by a single-crystal X-ray diffraction study (Scheme 2), which was solved in the $P2_1/n$ space group with six crystallographically independent molecules present in the asymmetric unit cell.

Optimization of the difluoromethylation reaction conditions

Based on the initial success with $TMSCF_2Br$ (**3**) as a difluorocarbene precursor, the reaction conditions were optimized. Varying the activator from KFHF to KF, CsF, NaI, KOAc, or TBAF), as well as liquid-assisted grinding (LAG) did not improve the yield of **2a** (see Supporting Information Table S2). Changing the milling equipment from SS to zirconium dioxide (ZrO_2) and polytetrafluoroethylene (PTFE) resulted in an increase in yield of **2a** from 65% to 70% and to 81%, respectively (Figure 1a). Since the weight of the balls was kept constant in the three performed reactions, we assumed that the increased yield was due to the high chemical inertness, a low surface adhesion, and likely, a more efficient mixing in the PTFE jars (for further details, see Supporting Information Table S3). Reducing the amount of KFHF in the PTFE jars lowered the yield of **2a** (Figure 1b, entry 2). To our delight, the use of alkali chloride salts as grinding auxiliaries in combination with 4 equiv of KFHF gave very positive results. Hence, the addition of either NaCl or CsCl to the reaction mixture led to **2a** in quantitative yield (entries 3–6). Lowering the amount of $TMSCF_2Br$ or KFHF resulted in a decreased yield of **2a** (entries 7 and 8). The same was observed when the milling frequency in the reaction with CsCl was reduced (entry 9). No product formation was observed with CsCl in the absence of KFHF or for a reaction under optimized conditions without milling (entries 10 and 11).

To our surprise, this very positive result was highly substrate specific. Thus, when the optimized conditions for solid alcohol **1a** (m.p. 100 °C) were transferred to liquid alcohol **1b** (m.p. –16 °C), difluoromethyl ether **2b** was obtained in only 22% yield (Figure 1b, entry 12). Further optimization of the amount of grinding auxiliary, as well as the type of ball, revealed that 12 equiv of CsCl with



Scheme 2 | *Optimized procedure for the mechanochemical difluoromethylation of alcohols. A crystallographic technique was used to determine the molecular structure, with anisotropic displacement parameters at a 50% probability level.*

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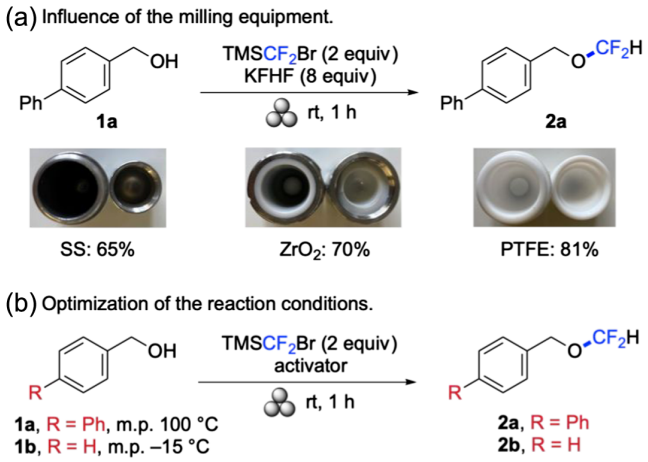

Entry	R	Activator (equiv)	Yield of **2** (%)[a]
1	Ph	KFHF (8.0)	81
2	Ph	KFHF (6.0)	57
3	Ph	KFHF (4.0), LiCl (4.0)	18
4	Ph	KFHF (4.0), NaCl (4.0)	quant.
5	Ph	KFHF (4.0), KCl (4.0)	87
6	Ph	KFHF (4.0), CsCl (4.0)	quant. (94)
7[b]	Ph	KFHF (4.0), CsCl (4.0)	75
8	Ph	KFHF (2.0), CsCl (6.0)	91
9[c]	Ph	KFHF (4.0), CsCl (4.0)	20
10	Ph	CsCl (8.0)	0
11[d]	Ph	KFHF (4.0), CsCl (4.0)	0
12	H	KFHF (4.0), CsCl (4.0)	22
13	H	KFHF (4.0), CsCl (8.0)	57
14[e]	H	KFHF (4.0), CsCl (8.0)	75
15[e]	H	KFHF (4.0), CsCl (12.0)	89
16[e]	H	KFHF (4.0), CsCl (16.0)	89
17[f]	H	KFHF (4.0), CsCl (4.0)	79
18[e,g]	H	KFHF (4.0), NaCl (18.7)	65%
19[e,g]	H	KFHF (4.0), KCl (13.4)	quant.

Figure 1 | *Standard conditions used in optimization of the reaction conditions: alcohol (0.2 mmol), activator, and $TMSCF_2Br$ (0.4 mmol, 2 equiv) in a PTFE milling jar (25 mL) with one PTFE milling ball (d = 12 mm; m = 3.45 g) at 25 Hz for 1 h. [a]Determined by ^1H or ^{19}F NMR spectroscopy; in parenthesis: yield after column chromatography. [b]With 1.5 equiv of $TMSCF_2Br$. [c]Milling at 20 Hz. [d]Without milling. [e]With another PTFE ball (d = 10 mm; m = 1.8 g). [f]With PhMe as LAG additive (0.25 μL·mg^{-1}). [g]The volume of the alkali chloride salt was equal to the volume of 12.0 equiv of CsCl.*

one PTFE ball (*d* = 10 mm) was superior to all other combinations in this case, yielding **2b** in 89% yield (entries 13–16). We attributed the requirement of a larger amount of CsCl, compared to the reaction with solid alcohol **1a** to an insufficient mixing as the combination of the liquid alcohol with the 4 equiv of CsCl led to a rather sticky reaction mixture (see Supporting Information Figure S1 and Table S4). A yield increase was also observed when toluene was used as a LAG additive (entry 17). Substitution of CsCl with NaCl was not possible, but cheaper KCl could replace CsCl (entries 18 and 19).

Until this stage, the product isolation involved extraction of the product from the jar with dichloromethane, followed by purification through a combination of aqueous work-up and column chromatography. In this manner, product **2a** was obtained in 94% yield (Figure 1b, entry 6). Considering the negative environmental impact of dichloromethane, this part of the process had to be changed. Pleasingly, less harmful ethyl acetate proved to be a suitable alternative for the extraction of the jar,[65] and the salts were removed by filtration over cotton. Following the new protocol, **2a** was obtained in 93% yield after solvent evaporation (Scheme 2).

Substrate scope

With the optimal conditions in hand, the applicability of the developed difluoromethylation procedure toward primary, secondary, and tertiary alcohols was explored (Scheme 3). 2-Phenyl benzyl alcohol (**1c**) and 1-naphthalenemethanol (**1d**) gave pure products **2c** and **2d** after filtration in yields of 85% and 91%, respectively. In the reaction with pyrene, purification by column chromatography was required due to an insufficient conversion and the formation of side products, obtaining **2e** in 44% yield. Benzyl alcohols **1f–j** with both electron-withdrawing and electron-donating substituents in the *para* position were smoothly converted to their difluoromethylated analogs **2f–j**; and in general, the yields were high (up to 99%). Changing the position of the methoxy substituent on benzyl alcohol from *para* (**1j**) to *meta* (**1k**) and *ortho* (**1l**) did not affect the reaction outcome. Starting from 3,4,5-trimethoxybenzyl alcohol, the yield of difluoromethyl ether **2m** was only 64%, and an additional purification to separate an undesired formate side product was required. 2-Phenyl ethanols bearing either a bromo (**1n**) or a methoxy (**1o**) substituent gave the corresponding products in excellent yields. Difluoromethylated glycol ether **2p** was obtained in 68% yield. Allyl and 3-thienyl alcohols **1q** and **1r** reacted well to provide the corresponding difluoromethyl ethers **2q** and **2r** in very good yields. Applying lignin model compound **1s** bearing a central carbonyl group and several ether moieties was less successful leading to difluoromethylated **2s** in only 19% yield after purification. Secondary alcohols with benzylic hydroxy groups gave [1-(difluoromethoxy)ethyl]arenes **2t**, **2u**, and **2v** in yields ranging from 96% to 99%. (–)-8-Phenylmenthol was successfully difluoromethylated to give pure **2w** in 47% yield. Difluoromethyl ether **2x** was obtained in 85% yield,

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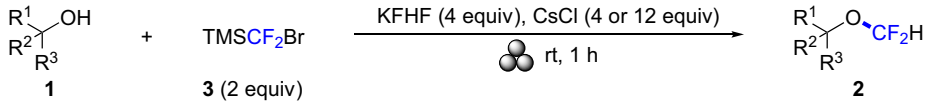
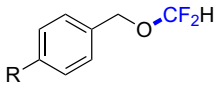
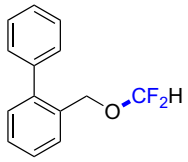


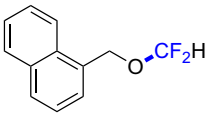
Primary alcohols



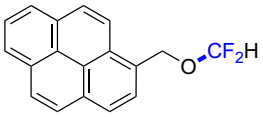
2a, R = Ph, 99% (93%)[a]
2b, R = H, 89%[b]



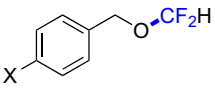
2c, 99% (85%)[a]



2d, 96% (91%)[a]

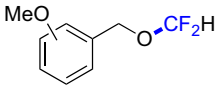


2e, 55% (44%)[a,c]

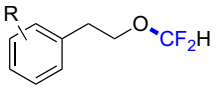


2f, X = CO_2Me, 99% (99%)[a]
2g, X = F, 94%[b]
2h, X = CN, 81% (39%)[a]

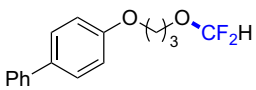
2i, X = Me, 81% (67%)[a]
2j, X = MeO, 74%[b]



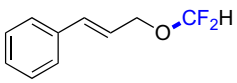
2k, 3-MeO, 99% (80%)[b]
2l, 2-MeO, 96%[b]
2m, 3,4,5-$(MeO)_3$, 64% (65%)[b,c]



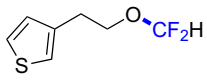
2n, R = 2-Br, 96% (75%)[b]
2o, R = 3,4-MeO, quant. (99%)[b]



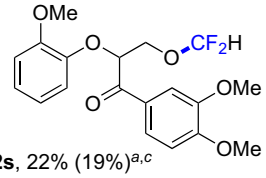
2p, 69% (68%)[a,c]



2q, 90% (88%)[a]

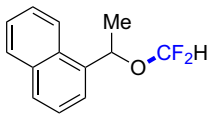


2r, quant.[b]

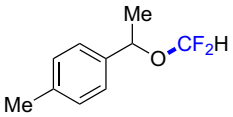


2s, 22% (19%)[a,c]

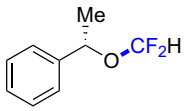
Secondary alcohols



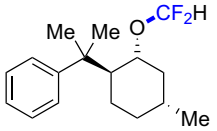
2t, 99% (99%)[a]



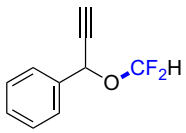
2u, 95% (61%)[b]



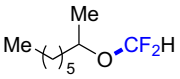
2v, 96% (26%)[b]



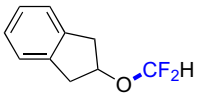
2w, 49% (47%)[b]



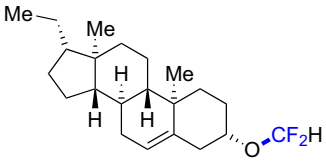
2x, 85%[b]



2y, 90%[b]

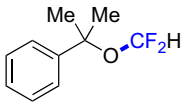


2z, 98% (87%)[a]

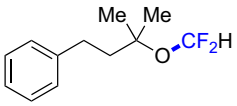


2aa, 91% (86%)[a,c]

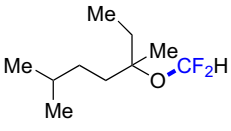
Tertiary alcohols



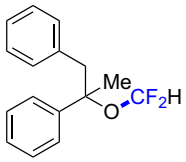
2ab, 90%[b]



2ac, 99% (97%)[b]



2ad, 28%[b]



2ae, 47% (42%)[b,c]

Scheme 3 | *Reaction conditions used to assess the scope of the alcohols: A mixture of alcohol (0.2 mmol), $TMSCF_2Br$ (0.4 mmol, 2 equiv), KFHF (0.8 mmol, 4 equiv), and CsCl ([a]0.8 mmol, 4 equiv or [b]2.4 mmol, 12 equiv) was milled at 25 Hz for 1 h. The yield was determined by ^1H NMR spectroscopy using dichloroethane as the internal standard. In parentheses: yield after filtration. [c]Purified by column chromatography.*

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demonstrating compatibility of the developed protocol with terminal alkynes. Octan-2-ol (**1y**) and indan-2-ol (**1z**) were smoothly converted leading to difluoromethyl ethers **2y** and **2z** in 90% and 98% yields, respectively. Furthermore, a derivative of the natural product pregnenolone was applied to this protocol affording the corresponding difluoromethyl ether **2aa** in 92% yield. For completion, the applicability of tertiary alcohols was investigated. Commonly, such compounds require optimized reaction conditions with an excess of the difluorocarbene precursor and prolonged reaction times. However, the standard reaction conditions worked well providing difluoromethyl ether **2ab** and **2ac** in 90% and 99% yields, respectively. Sterically, more hindered alcohol **1ad** gave product **2ad** in 28% yield. Difluoromethyl ether **2ae** was obtained in 47% yield from 1,2-diphenylpropane-2-ol (**1ae**). Attempts to difluoromethylated phenols, thiols, and imidazoles remained unsuccessful. *N*-Difluoromethylating 5-phenyltetrazole gave two regioisomers in 34% and 26% yields (for details, see Supporting Information Scheme S1).

To confirm the hypothesis that difluorocarbenes were involved under these solvent-free reactions with alcohols, the difluoromethylation of **1a** was performed under optimized conditions (Figure 1b, entry 6) in the presence of α-methyl styrene (for details, see Supporting Information Table S5). As suspected, the yield of **2a** dropped from quantitative to 43%, and with 1 equiv of α-methyl styrene, the corresponding difluorocyclopropane was formed in 61% yield. This trend was even more pronounced when 2 equiv of the olefine were added.

Conclusion

We have developed mechanochemical difluoromethylation reactions of primary, secondary, and tertiary alcohols. The mild, solvent-free reaction conditions tolerated various functional groups, and the products were obtained after milling for 1 h at room temperature in a mixer mill. $TMSCF_2Br$ served as a precursor of difluorocarbene, formed in situ, and smoothly reacted with the alcohol. The simplicity of the process and the possibility to purify the products by filtration highlights that these milling events offer opportunities for more environmentally benign reaction control.

The Cambridge Crystallographic Data Centre (CCDC) 2239503 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 sending an email to data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supporting Information

Supporting Information is available and includes additional optimizations of reaction conditions, detailed experimental procedures, and analytic data of the synthesized compounds.

Conflict of Interest

There is no conflict of interest to report.

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