Difluoromethylenation

Difluoromethyl Phenyl Sulfone as a Selective Difluoromethylene Dianion Equivalent: One-Pot Stereoselective Synthesis of *anti*-2,2-Difluoropropane-1,3-diols**

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That more and more organofluorine compounds have been found to display biological effects such as mimicry, blocking, polarity, and lipophilicity is attributed to the unique properties of the fluorine atom.[1] For instance, the C–F bond mimics the C–H bond because of its similar bond length, and the difluoromethylene group is isosteric and isopolar to an ethereal oxygen atom.[2] Hence, the synthesis of fluorine-containing analogues of bioactive natural products is of great interest because of their potential applications in the pharmaceutical industry.[3] Since *anti*-1,3-diol functionality is a fundamental unit in many naturally occurring compounds, its stereoselective preparation is attractive to synthetic organic chemists.[4] *anti*-2,2-Difluoropropane-1,3-diols **3** are a group of interesting compounds, but not much is known about their synthesis. To the best of our knowledge, the only reported method to synthesize these compounds is by diasteroselective Meerwein–Pondorff–Verley reduction of α,α-difluoro-β-hydroxy ketones.[5] The disadvantage of this approach is the need to prepare the α,α-difluoro-β-hydroxy ketone precursors.

In 1997, we reported the preparation of difluorobis(trimethylsilyl)methane ($TMSCF_2TMS$) as a potential difluoromethylene dianion ("$^{-}CF_2^{-}$") equivalent.[2] However, $TMSCF_2TMS$ was found only to couple with one equivalent of an aldehyde, for example, with benzaldehyde to give 2,2-difluoro-1-phenylethanol (after acid hydrolysis).[2]

We recently disclosed alkoxide- and hydroxide-induced nucleophilic trifluoromethylation of nonenolizable carbonyl compounds and disulfides by using trifluoromethyl sulfone or sulfoxide.[6] The chemistry is based on the nucleophilic attack by alkoxide (commonly potassium *tert*-butoxide) or hydroxide on the sulfur center of trifluoromethyl phenyl sulfone (**4a**) or sulfoxide (**4b**) to release a trifluoromethyl anion [Scheme 1, Eq. (1)]. We assumed that a similar type of S–C bond cleavage could occur with difluoromethyl phenyl

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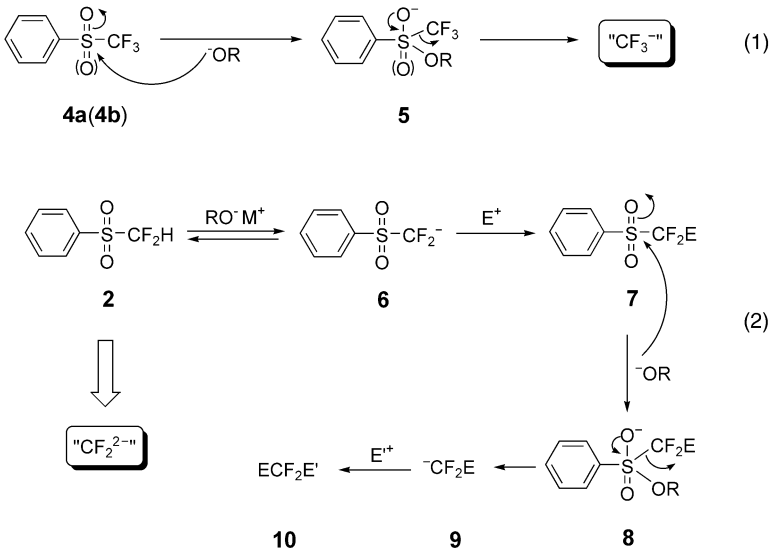


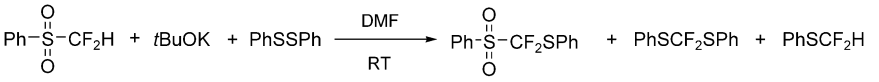
Scheme 1. Mechanistic considerations. R = H, alkyl group. E, E′ = electrophiles, such as disulfides and aldehydes.

sulfone **2** ($PhSO_2CF_2H$). The chemistry of **2** is even more interesting than that of **4a** [Scheme 1, Eq. (2)]. It is known that the hydrogen atom of the CF_2H group in compound **2** is rather acidic, and a common base such as sodium methoxide or even aqueous sodium hydroxide can deprotonate it in an equilibrium mode to generate $PhSO_2CF_2^-$ (**6**).[7,8] In 1989, Stahly showed that anion **6**, generated in situ, can react with aldehydes to give difluoromethylated carbinols in aqueous NaOH in the presence of a phase-transfer agent.[8] However, he did not observe any S–C bond cleavage in aqueous NaOH (RT, 4 h). Obviously, aqueous NaOH is not nucleophilic enough to activate the S–C bond scission, and with hydroxide or alkoxide the deprotonation of difluoromethyl sulfone **2** is much faster than S–C bond cleavage. Thus, by use of an appropriate alkoxide such as *t*BuOK that acts both as a base and a nucleophile, sulfone **2** might react stepwise with two electrophiles to give new difluoromethylene-containing products [Scheme 1, Eq. (2)]. Thus, difluoromethyl phenyl sulfone **2** can be regarded as a selective difluoromethylene dianion ("CF_2^{2-}") synthon.

With the above considerations in mind, we first treated the $PhSO_2CF_2H$/*t*BuOK system with diphenyl disulfide (PhSSPh) as an electrophile. The results are shown in Table 1. By using different reactant ratios, both monosubstitution product **12** and disubstitution product **13** can be obtained at room temperature with high selectivity (Table 1, entries b and g). This result confirms our previous assumption that the reactivities of deprotonation and S–C bond cleavage are different, and that these two steps can be controlled selectively (see Scheme 2). An excess of *t*BuOK facilitates completion of S–C bond-cleavage process, which is similar to our previous observations with the trifluoromethyl sulfone system.[6] Furthermore, the formation and consumption of $PhSCF_2H$ (**14**) with time (Table 1, entries e and f) indicate that there is an equilibrium between anionic species **16** and **14** with protonation/deprotonation by *t*BuOH/*t*BuOK.

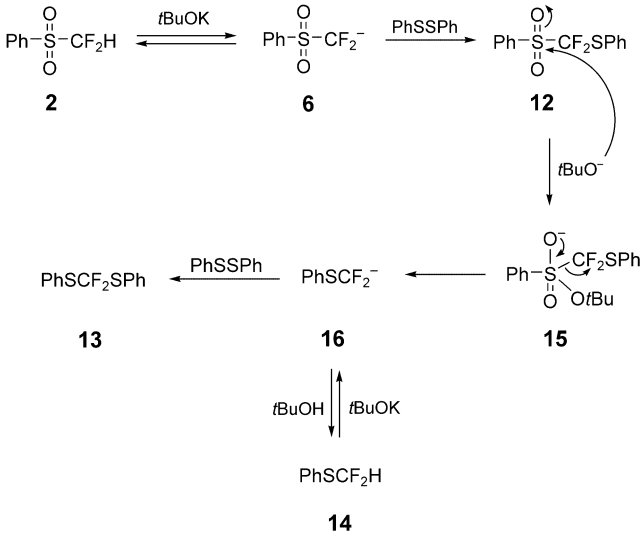
Reaction of benzaldehyde (**1a**) and sulfone **2**/*t*BuOK in DMF is much more intriguing and rewarding (see Scheme 3). Similar to the reaction with diphenyl disulfide, $PhSO_2CF_2H$ (1.0 equiv)/*t*BuOK (3.0 equiv) reacts with **1a** (2.0 equiv) at −50 °C→RT over 90 min to generate monosubstituted product **17** (^{19}F NMR: 41 % yield), as earlier shown by Stahly in aqueous NaOH,[8] and disubstituted product **3a** (^{19}F NMR: 58 % yield, *anti*/*syn* = 98/1). When **2** (1.0 equiv)/*t*BuOK (4.0 equiv) reacted with PhCHO (3.0 equiv) at −50 °C→RT for 8 h with

Table 1: Difluoromethylenation of PhSSPh with **2**.

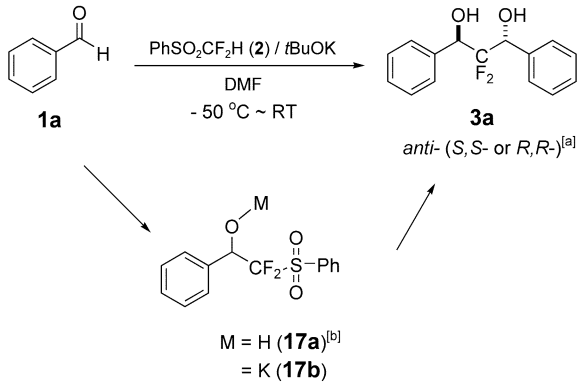


Entry	Reactant ratio [equiv]			Reaction time	Product yield [%][a]		
	2	*t*BuOK	**11**		**12**	**13**	**14**
a	1	1.0	1.0	30 min	76	0	5
b	1	1.5	1.0	50 min	91	3	6
c	1	2.5	2.0	14 h	64	22	14
d	1	3.0	2.0	4 h	41	44	14
e	1	3.5	2.0	4 h	0	84	16
f	1	3.5	2.0	15 h	0	97	3
g	1	4.0	2.0	4 h	0	99	0

[a] Yields were determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as the internal standard.



Scheme 2. Stepwise formation of **12** and **13**.



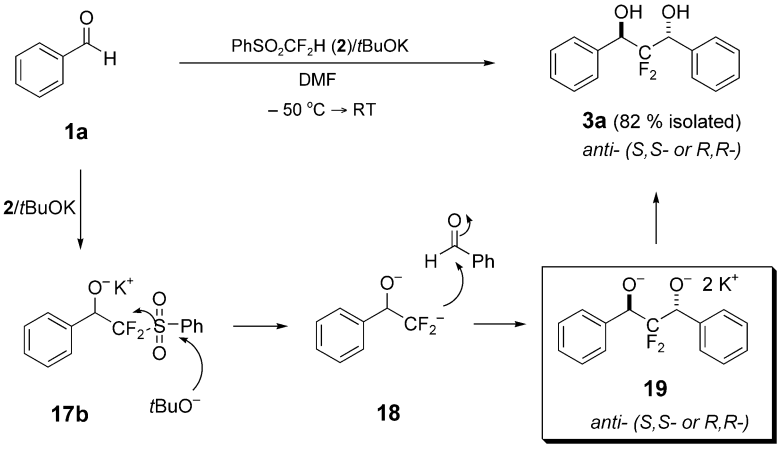
Scheme 3. Reaction of PhCHO (excess) and **2**/*t*BuOK. [a] ^{19}F NMR for *anti* isomer: $\delta = -120.9$ ppm (pseudo t, $^{3}J(F,H) = 11.4$ Hz, 2F). [b] ^{19}F NMR: $\delta = -104.4$ ppm (dd, $J = 238.0$, 2.8 Hz, 1F); $\delta = -119.8$ ppm (dd, $J = 238.0$, 21 Hz, 1F).

activation by *t*BuOK, alkoxide **17b** is formed in situ and undergoes S–C bond fission to generate dianionic intermediate **18**, which can react with a further equivalent of benzaldehyde to form disubstituted *anti*-diol **3a** in excellent yield (^{19}F NMR: 92%, isolated product: 82%) and high diastereoselectivity (*anti*/*syn* = 97/3, *de* = 94%). The observed high diastereoselectivity can be interpreted by a charge–charge repulsion effect during the second addition (Scheme 4). To the best of our knowledge, this may be the first time that high diastereoselectivity has been achieved in the reaction of a dianion with another, neutral electrophile under the influence of an intramolecular charge–charge repulsion effect (during product formation) rather than the traditional steric control (based on Cram's rule).[9,10]

Table 2 demonstrates the application of this methodology to the synthesis of various 2,2-difluoropropane-1,3-diols with high stereoselectivity from nonenolizable aldehydes.[11] The yields of diols are a bit lower for electron-rich aldehydes (entries d and g), probably due to the relative instability of the corresponding dianion intermediates.

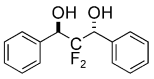
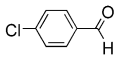
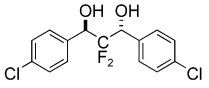
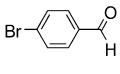
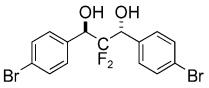
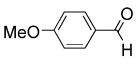
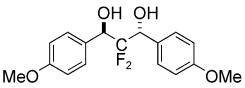
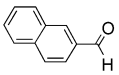
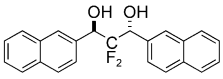
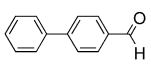
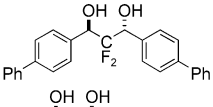
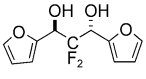
Besides symmetrical *anti*-2,2-difluoropropane-1,3-diols, this new methodology can also be used to synthesize unsymmetrical *anti*-2,2-difluoropropane-1,3-diols. Scheme 5 shows an example of this type of synthesis. Difluoro(phenylsulfonyl)methyl-substituted alcohol **17a** can be easily obtained and isolated by Stahly's approach in high yield.[8] Activation of **17a** with *t*BuOK generates the dianion intermediate **18**, which further reacts with *p*-chlorobenzaldehyde **1b** to give unsymmetrical *anti*-2,2-difluoropropane-1,3-diol **20** (after hydrolysis) with high diastereoselectivity.

In conclusion, potassium *tert*-butoxide-induced difluoromethylenation with difluoromethyl phenyl sulfone enables us to synthesize both symmetrical and unsymmetrical *anti*-2,2-difluoropropane-1,3-diols with high diastereoselectivity (up to 94% *de*). This unusual type of high diastereoselectivity was obtained by means of an intramolecular charge–charge repulsion effect rather than the traditional steric control (based on Cram's rule). Difluoromethyl phenyl sulfone can be used as a selective synthon for the difluoromethylene dianion ($^{-}CF_2^{-}$), which can couple with two electrophiles (e.g., diphenyl disulfide or nonenolizable aldehydes) to give new difluorinated products. Since difluoromethyl phenyl sulfone can be readily prepared from inexpensive chemicals such as

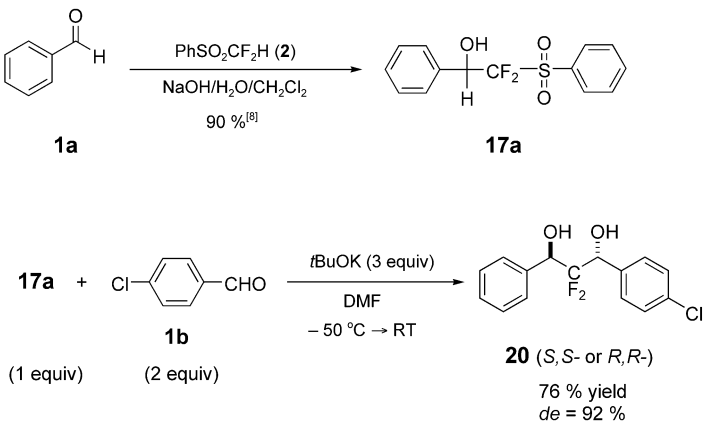


Scheme 4. Proposed mechanism of diastereoselective formation of **3a** from PhCHO and **2**/*t*BuOK.

Table 2: Preparation of 2,2-difluoropropane-1,3-diols **3** from aldehydes **1** (3 equiv) and difluoromethyl phenyl sulfone **2** (1 equiv) with *t*BuOK (4 equiv) in DMF at −50 °C → RT.

Entry	Substrate **1**	Product **3**	Yield [%][a]	*anti*/*syn*[b]	*de* [%]
a			82	97:3	94
b			78	94:6	88
c			70	96:4	92
d			52	94:6	88
e			69	97:3	94
f			75	96:4	92
g			63	93:7	86

[a] Yields of isolated product. [b] *anti*/*syn* ratios were determined by ^{19}F NMR spectroscopy.



Scheme 5. Synthesis of unsymmetrical *anti*-2,2-difluoropropane-1,3-diol **20**.

CF_2ClH or CF_2Br_2,[12,13] this new methodology provides a convenient and efficient synthetic tool for many potential applications.

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[10] DFT calculations (B3LYP6-31G**//B3LYP6-31G* + ZPE level) on 3,3-difluoro-2,4-pentanediolate dianion as a model showed the *anti* structure to be 5.5 kcal mol^{-1} more stable than the corresponding *syn* structure. Furthermore, the absence of changes in the *anti*/*syn* diol ratios on prolonged treatment with base indicate lack of product reversibility.
[11] Typical procedure for *t*BuOK-induced difluoromethylenation: The reaction was commonly carried out in a Schlenk flask under an argon atmosphere. A solution of *t*BuOK (1.12 g, 10 mmol) in DMF (5 mL) was added to solution of difluoromethyl phenyl sulfone (**2**, 480 mg, 2.5 mmol) and benzaldehyde (800 mg, 7.5 mmol) in DMF (5 mL) at −50 °C. The reaction flask was then sealed, and the reaction mixture was then stirred at −50 °C for 1 h, followed by stirring at −50 °C→RT overnight. The reaction mixture was quenched with ice water (20 mL), and extracted with diethyl ether (3 × 20 mL). The combined ethereal phase was washed with a saturated aqueous solution of NH_4Cl, and then with water. After drying over $MgSO_4$, the diethyl ether solvent was removed under vacuum. The crude product was further purified by chromatography on a silica gel column (hexanes/ethyl acetate 9/1, then 1/1) to give 2,2-difluoro-1,3-diphenyl-1,3-propanediol as a white crystalline solid, (541 mg, 82 % yield, *anti*/*syn* = 97/3, determined by ^{19}F NMR). *anti* isomer: ^1H NMR ([D$_6$]actone): $\delta = 5.27$ (m, 4H), 7.28–7.50 ppm (m, 10H); ^{19}F ([D$_6$]acetone): $\delta = -120.9$ ppm (dd, $J = 11$ Hz, $J = 11$ Hz, 2F); HRMS (DCI/NH_3): *m*/*z* calcd for $C_{15}H_{18}F_2NO_2$ [M+NH_4^+]: 282.1305, found: 282.1304.
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