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Highly Efficient and Stereoselective Julia–Kocienski Protocol for the Synthesis of α-Fluoro-α,β-unsaturated Esters and Weinreb Amides Employing 3,5-Bis(trifluoromethyl)phenyl (BTFP) Sulfones

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Abstract: α-Fluoroacetates **3** and Weinreb amide **4**, bearing a α-[3,5-bis(trifluoromethyl)phenyl]sulfonyl (BTFP-sulfonyl) group at the α-position, are employed in the highly stereoselective synthesis of α-fluoro-α,β-unsaturated alkenoates and Weinreb amides, respectively. Aromatic and aliphatic aldehydes are condensed under extremely mild and simple reaction conditions using potassium carbonate in dimethylformamide at room temperature under solid-liquid phase-transfer catalysis conditions in good yields and high *Z*-diastereoselectivities, specially in the case of the fluorinated Weinreb amides. A detailed computational mechanistic study suggests a final non-concerted elimination of sulfur dioxide and 3,5-bis(trifluoromethyl)phenoxide and explains the observed high stereoselectivities for the reaction on the basis of thermodynamic and kinetic considerations.

Keywords: alkenes; esters; Julia–Kocienski olefination; sulfones; Weinreb amides

Introduction

Fluorine plays a very important role in the design of new compounds since it is well-established that it strongly modifies their chemical, physical, and biological properties. However, fluorinated compounds are the least abundant natural organohalides.[1] Therefore, fluorinated analogues of natural products, building blocks, or simple fluorine-containing organic molecules have become highly desirable compounds.[2] In this context, structures with the fluoro olefin moiety are gaining importance due to their interesting biological properties.[1,3] Different approaches have been developed for the synthesis of fluorine-containing olefins such as the electrophilic fluorination of vinyllithiums[4] or stannanes,[5] fluorodesilylation of vinylsilanes,[6] the Horner–Wadsworth–Emmons reaction of α-fluorophosphonates with carbonyls,[7] the Peterson olefination,[8] and the palladium-catalyzed reductive defluorination of allylic *gem*-difluorides.[9] Very recently, the Julia–Kocienski olefination[10] has been succesfully used for the synthesis of fluoro olefins such as vinyl fluorides[11] and α-fluoroacrylates[12] employing fluorinated 1,3-benzothiazol-2-yl (BT) sulfones **1** (Figure 1).

We have recently demonstrated that the 3,5-bis(trifluoromethyl)phenyl (BTFP)-sulfonyl group is an excellent nucleofuge in base-promoted β-elimination processes.[13] On the other hand, BTFP sulfones (**2**, Figure 1) are excellent partners for the stereoselective synthesis of di-, tri- and tetrasubstituted olefins through the Julia–Kocienski olefination of carbonyl compounds under simple reaction conditions using KOH and phosphazenes as bases.[14] Very recently, BTFP sulfones have also been successfully used for the stereoselective synthesis of α,β-unsaturated esters and Weinreb amides under solid-liquid PTC conditions.[15,16] Herein we report the synthesis of α-(BTFP

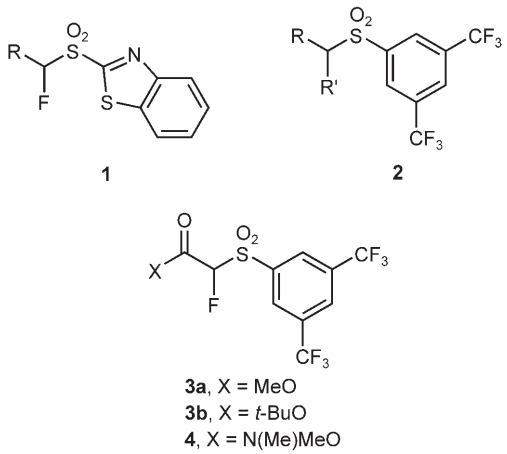


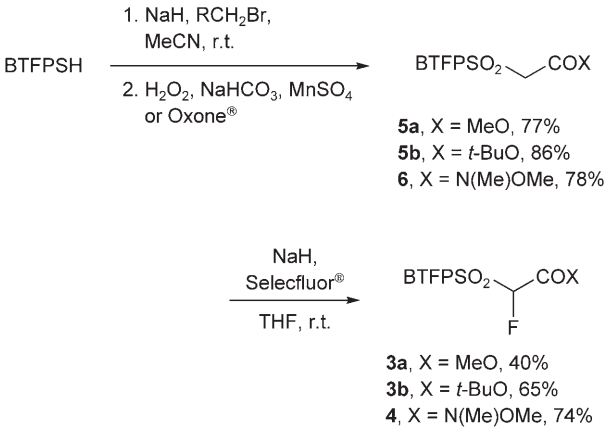
Figure 1. BT and BTFP sulfones **1**–**4**.

sulfonyl)-α-fluoroacetates **3** and Weinreb amide **4** and their use as efficient reagents for a highly stereoselective synthesis of α-fluoro-α,β-unsaturated esters and Weinreb amides, respectively.

Results and Discussion

Synthesis of Fluorinated Sulfones

Fluorinated BTFP sulfones **3a**, **3b**, and **4** were prepared in good yields from commercially available 3,5-bis(trifluoromethyl)benzenethiol[17] by NaH mediated *S*-alkylation with methyl bromoacetate, *tert*-butyl bromoacetate, and 2-bromo-*N*-methoxy-*N*-methylacetamide,[18] respectively. Oxidation with either 30% H_2O_2/$NaHCO_3$/$MnSO_4 \cdot H_2O$[19] or oxone®,[20] of the corresponding sulfanes and final electrophilic fluorination of **5** and **6** with NaH/Selectfluor® afforded the desired sulfones (Scheme 1). Significant quantities of unreacted non-fluorinated starting material (~20%) were recovered from all the fluorination reactions.



Scheme 1. Synthesis of fluorinated BTFP sulfones **3** and **4**.

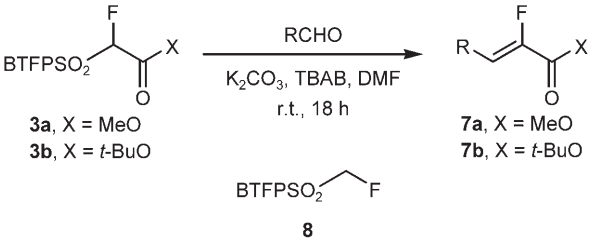
This could be the reason for the moderate yields observed in the fluorination process. Compound **6** afforded the best yield, probably due to the higher stability of the corresponding enolate intermediate.

Synthesis of α-Fluoro-α,β-Unsaturated Esters

With the fluorinated sulfones prepared, different reaction conditions were first assayed for the synthesis of fluorinated acrylate **7aa** *via* one-pot Julia olefination of benzaldehyde with BTFP sulfone **3a**. Since previously studies with unfluorinated BTFP sulfones **5b** and **6**[15] had shown K_2CO_3 (9 equiv.) and TBAB (0.1 equiv.) in DMF under Barbier conditions (addition of the base over the solution of the sulfone and the aldehyde) as the most efficient olefination methodology, the optimization experiments with **3a** and benzaldehyde were carried out under these solid-liquid PTC conditions at room temperature. The obtained yields and *Z*/*E* ratios are displayed in Table 1, entries 1–4. Under the typical reaction conditions, a 66% conversion of the desired olefin **7aa** was obtained with an excellent *Z* stereoselectivity (*Z*/*E*: 92/8) [^{19}F NMR: $J_{F,H}$ = 35.3 Hz (*Z*-**7aa**), $J_{F,H}$ = 27.3 Hz (*E*-**7aa**)] along with considerable amounts of decarboxylated 3,5-[bis(trifluoromethyl)phenyl] fluoromethyl sulfone (**8**) (Table 1, entry 1). Under anhydrous conditions, the yield was fairly improved but still giving substantial amounts of the decarboxylated sulfone **8** (Table 1, entry 2). Finally, the yield of the olefination was found to be very high when working under non-Barbier conditions (Table 1, entry 3) and especially if the sulfone was used in two-fold excess, conditions which afforded the desired (*Z*)-**7aa** in 95% yield with no traces of decarboxylated product **8** in the crude reaction mixture (Table 1, entry 4).

Under the optimized reaction conditions, the synthesis of α-fluoroacrylates through the modified Julia olefination with methyl and *tert*-butyl esters **3a** and **3b** was next investigated (Table 1, entries 5–19). As shown, the fluorinated BTFP sulfone reagents **3** were significantly more reactive than the non-fluorinated congeners **5**[15] probably due to the alpha effect of the fluorine atom. Condensation of BTFP sulfones **3a** and **3b** with selected aldehydes gave, in general, good yields of the corresponding α-fluoro-α,β-unsaturated esters **7a** and **7b**, respectively. *Z*-configurated olefins were mainly obtained from aromatic aldehydes (Table 1, entries 4–13), the selectivity being lower for *t*-Bu ester **3b** (compare entries 4, 6, 8, and 11 with 5, 7, 9, and 12) and for electron-rich aldehydes such as 4-methoxybenzaldehyde (Table 1, entry 10). The stereoselectivity but not the yield was independent of the steric demands of the electrophile as demonstrated in the olefination of 2-chlorobenzaldehyde (Table 1, entry 13).

Table 1. Synthesis of α-fluoro-α,β-unsaturated esters.



Entry	X	RCHO	No.	Yield (%)[a]	Z/E[b]
1	Me	PhCHO	**7aa**	63 [34][c]	92/8
2	Me	PhCHO	**7aa**	85 [6][c,d]	92/8
3	Me	PhCHO	**7aa**	95 [5][d]	93/7
4	Me	PhCHO	**7aa**	>95 [0][d,e]	93/7
5	*t*-Bu	PhCHO	**7ba**	75[d,e]	82/18
6	Me	4-$CF_3C_6H_4CHO$	**7ab**	50[d,e]	94/6
7	*t*-Bu	4-$CF_3C_6H_4CHO$	**7bb**	42[d,e]	88/12
8	Me	4-ClC_6H_4CHO	**7ac**	60[d,e]	92/8
9	*t*-Bu	4-ClC_6H_4CHO	**7bc**	68[d,e]	83/17
10	*t*-Bu	4-$MeOC_6H_4CHO$	**7bd**	94[d,e]	61/39
11	Me	2-naphthaldehyde	**7ae**	47[d,e]	91/9
12	*t*-Bu	2-naphthaldehyde	**7be**	72[d,e]	79/21
13	Me	2-ClC_6H_4CHO	**7af**	68[d,e]	90/10
14	Me	$Ph(CH_2)_2CHO$	**7ag**	66[d,e]	48/52
15	*t*-Bu	$Ph(CH_2)_2CHO$	**7bg**	92[d,e]	23/77
16	Me	Citronellal	**7ah**	61[d,e]	43/57
17	*t*-Bu	Citronellal	**7bh**	75[d,e]	19/81
18	Me	*c*-$C_6H_{11}CHO$	**7ai**	71[d,e]	93/7
19	*t*-Bu	*c*-$C_6H_{11}CHO$	**7bi**	91[d,e]	85/15

[a] Isolated yield after flash chromatography. In brackets isolated yield for decarboxylated compound **8**.
[b] Relative ratio determined by ^{1}HNMR over the crude reaction mixture.
[c] Barbier-type conditions were used.
[d] The reaction was performed under anhydrous conditions.
[e] 2 Equivalents of sulfone were used.

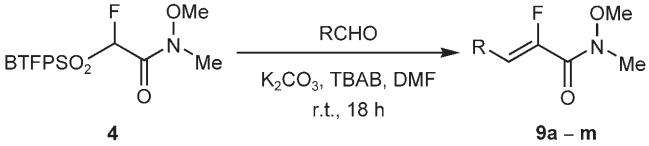
The reaction of BTFP sulfones **3** with aliphatic aldehydes such as 3-phenylpropanal afforded better yields and *E*-selectivities for *tert*-butyl ester **3b** than for methyl ester **3a** (Table 1, entries 14 and 15). The change in stereoselectivity with respect to aromatic aldehydes was confirmed in the reaction of the β-branched aldehyde citronellal which gave, especially in the case of sulfone **3b**, a significantly increased *E*-selectivity (Table 1, entry 17). Finally, the reaction with cyclohexanecarbaldehyde, an α-branched substrate, reversed the stereochemistry in favor of the *Z*-fluoro-α,β-unsaturated esters **7ai** and **7bi** (Table 1, entries 18 and 19). In general, all the studied examples showed an increased *E*-selectivity for *t*-Bu ester **3b** with respect to the results observed for **3a**.

The results obtained with BTFP sulfones **3a** and **3b** in the one-pot Julia olefination of aromatic and aliphatic aldehydes emphasize the ability of these derivatives to generate in very good yields and selectivities (*Z*)-α-fluoro-α,β-unsaturated alkenoates under very mild reaction conditions. This is an important result since the previously employed BT sulfone **1** (Figure 1, R = *t*-BuO,[12a]) affords (*E*)-α-fluoro-α,β-unsaturated alkenoates in the presence of DBU as base in CH_2Cl_2 at room temperature. On the other hand, (*Z*)-α-fluoro-α,β-unsaturated alkenoates can be obtained with BT sulfone **1** (Figure 1, R = Et,[12b]) employing DBU as base but in the presence of stoichiometric amounts of $MgBr_2$.

Synthesis of α-Fluoro-α,β-Unsaturated Weinreb Amides

The synthesis of α-fluoro-α,β-unsaturated Weinreb amides with BTFP sulfone **4** was next investigated under the optimized reaction conditions. Sulfone **4** reacted with aryl and alkyl aldehydes in good yields to afford the corresponding diastereomerically pure (*Z*/*E* > 99/1) *Z*-unsaturated Weinreb amides (Table 2). The stereochemistry was independent of the electronic character or the steric demands of the aldehyde (Table 2, entries 1–7). However, the yield of the reaction was lower for electron-rich aldehydes such as, 4-methoxybenzaldehyde and 6-methoxy-2-naphthaldehyde (Table 2, entries 4 and 6). With respect to aliphatic aldehydes, branching at the α- or β-position did not affect the reaction yield or the stereoselectivity (Table 2, entries 8–13).

Table 2. Synthesis of (*Z*)-α-fluoro-α,β-unsaturated Weinreb amides.



Entry	RCHO	No.	Yield (%)[a]
1	PhCHO	**9a**	83
2	4-$CF_3C_6H_4CHO$	**9b**	63
3	4-ClC_6H_4CHO	**9c**	62
4	4-$MeOC_6H_4CHO$	**9d**	45
5	2-naphthaldehyde	**9e**	81
6	6-MeO-2-naphthaldehyde	**9f**	55
7	2-ClC_6H_4CHO	**9g**	99
8	*n*-$C_9H_{19}CHO$	**9h**	56
9	$Ph(CH_2)_2CHO$	**9i**	57
10	PhCH(Me)CHO	**9j**	46
11	*c*-C_5H_9CHO	**9k**	51
12	*c*-$C_6H_{11}CHO$	**9l**	65
13	citronellal	**9m**	63

[a] Isolated yield after flash chromatography.

The *Z* configurations of compounds **9** were assigned by ^{19}F NMR spectroscopy (see Supporting Information) and confirmed by X-ray analysis for (*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacrylamide[21] (**9a**, Figure 2).

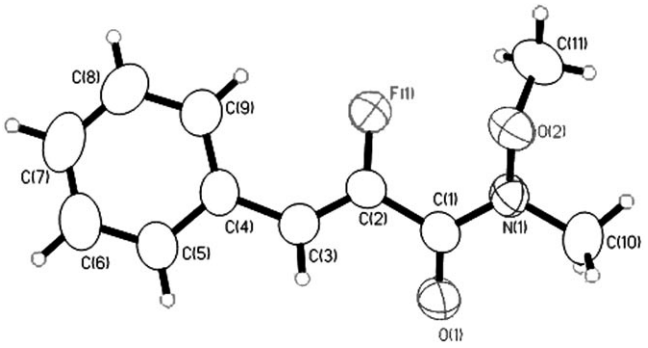
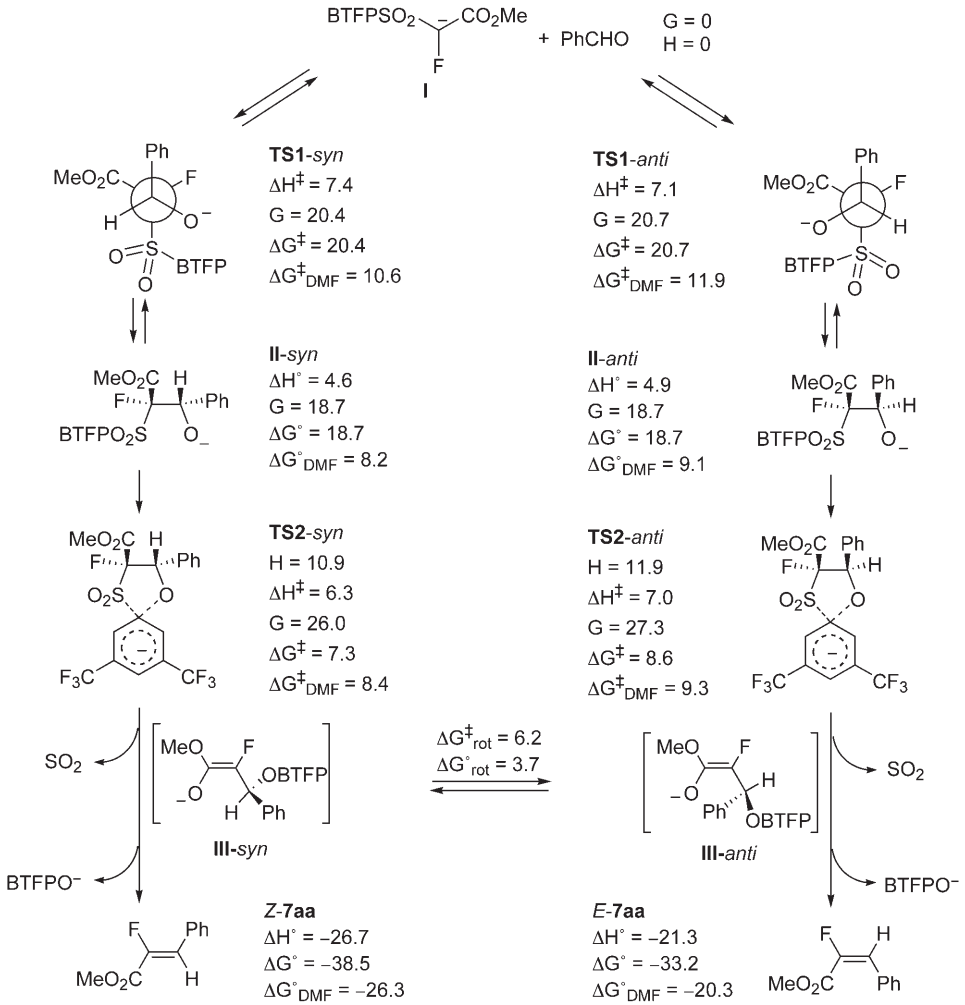


Figure 2. X-ray structure of **9a**.

Computational Mechanistic Studies

Computational studies were performed for the olefination of benzaldehyde with sulfone **3a** using the functional B3LYP and the 6-311++G** basis set as implemented in Gaussian 03.[22] As we have previously shown for the olefination of aromatic aldehydes with non-fluorinated sulfones **5** and **6**,[15] the reaction proceeds through a two-step mechanism (Scheme 2). The first one (**TS1**) corresponds to the nucleophilic addition of enolate I to benzaldehyde and generating a high-in-energy alkoxy intermediate (**II**-type). The second step involves the nucleophilic aromatic substitution of the sulfonyl group by the formed alkoxide (**TS2**)[23] and lies at the highest point along the reaction coordinate. Introduction of solvent effects does not significantly alter the results. In DMF the energy of **II**-type intermediates decreases, increasing the activation barrier for the second step. IRC calculation undoubtedly connects **TS2** with the final alkene **7aa** through an asynchronous elimination of SO_2 and



Scheme 2. Proposed mechanism for the fluoro-Julia–Kocienski olefination of aldehydes with BTFP sulfones.

BTF-phenoxide. No intermediates could be detected during the elimination process that leads to the irreversible formation of the final products.

Comparison of the energies at **TS1** and **II**-type structures reveals the existence of a *ca.* 1:1 equilibrium between the diastereomeric *syn* and *anti* intermediates, which would not lead to any selectivity. In contrast, the data show that **TS2**-*syn* is kinetically favored over **TS2**-*anti* by 1.3 kcal mol^{-1} due to the minor steric interactions between the phenyl and ester moieties, predicting the formation of the experimentally encountered *Z*-isomer. These data indicate that **TS2** might be the selectivity-determining step.

Alternatively, the rotation around the C–C bond after elimination of SO_2 and prior to the elimination of ArO^- would eventually lead to the thermodynamic convergence of both pathways to the more stable *Z*-isomer through **III**-*syn via* an E1cB-type elimination. The rotation barrier is low (6.2 kcal mol^{-1}),[24] suggesting that the rotation might indeed be important. Nonetheless, both kinetic considerations at **TS2** and thermodynamic factors during elimination after **TS2**, merge at the formation of the same isomer (*Z*-**7aa**) and account for the high *Z*-diastereoselectivity observed in the process.

The energies for the rotation process after elimination of SO_2 and prior to the elimination of ArO^- for *tert*-butyl ester **3b** and Weinreb amide **4** were also calculated in order to explain the lower selectivity observed in the olefination of aldehydes with **3b** and the exclusive formation of *Z*-amides from **4** (Figure 3). With respect to the rotation barrier ($\Delta G^{\neq}_{rot}$), the highest value was obtained for the *tert*-butyl ester **3b** (7.6 kcal/mol), while methyl ester **3a** (6.2 kcal/mol) and Weinreb amide **4** (6.5 kcal mol^{-1}) showed very similar energies (Figure 3). However, calculated ΔG^0_{rot} for *tert*-butyl ester **3b** and Weinreb amide **4** were 2.3 kcal/mol and 6.3 cal/mol, respectively, which would account for the exclusive formation of the *Z*-amides **9** and the lower selectivity observed (see Table 1) for **3b** when compared with the methyl derivative **3a** ($\Delta G^0_{rot} = 3.7$ Kcal/mol). Then, according to the calculation studies, the rotation process in intermediate **III** is more favored for **3a** and **4**, which in concert with the biggest energy gap between the **III**-*syn* and **III**-*anti* intermediates for the Weinreb amide would explain the higher Z-selectivity obtained when BTFP sulfone **4** is employed in the olefination reaction. Cartesian coordinates for transition states and reactant complexes are included in the Supporting Information

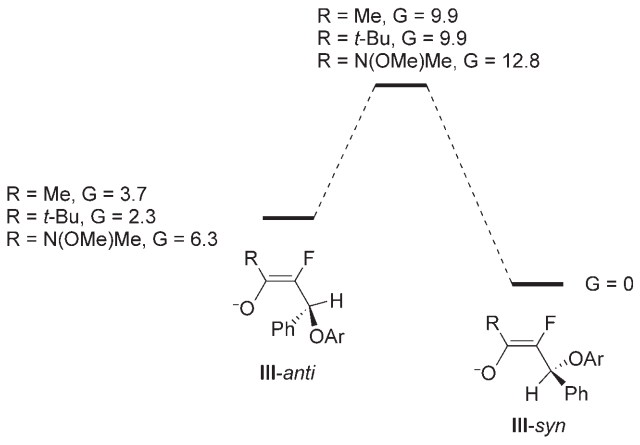


Figure 3. Rotation energies (kcal mol^{-1}) for intermediates **III** for BTFP sulfones **3** and **4**.

Conclusions

In summary, we have shown that the Julia–Kocienski olefination is an efficient strategy for the selective preparation of (*Z*)-α-fluoro-α,β-unsaturated esters and Weinreb amides employing BTFP sulfones under solid-liquid PTC conditions at room temperature. The reaction is highly diastereoselective, particularly in the case of Weinreb amides, allowing the olefination of both aromatic and aliphatic aldehydes. According to computational studies, the reaction mechanism involves a non-concerted elimination of SO_2 and 3,5-bis(trifluoromethyl)phenoxide. Furthermore, both kinetic and thermodinamic considerations point to spirocyclic **TS2**, which is closely related to the Smiles rearrangement, being responsible for the high *Z*-diastereoselectivity of the reaction.

Experimental Section

General Procedure for the Synthesis of Sulfones 5a, 5b, and 6

To a room temperature stirred solution of NaH (95%, 150 mg, 6 mmol) in MeCN (15 mL), was dropwise added 3,5-bis(trifluoromethyl)benzenethiol (835 μL, 5 mmol) under an argon atmosphere. After stirring of the reaction mixture for 15 min, the corresponding alkyl bromide (5.5 mmol) was added at the same temperature and the stirring was continued for 1 d. The reaction was quenched with H_2O (20 mL) and the mixture was extracted with EtOAc (2×20 mL). The combined organic layers were dried ($MgSO_4$), and evaporated to afford the corresponding 3,5-bis(trifluoromethyl)phenyl sulfanes, which were used in the next step without further purification.

To a 0 °C stirred solution of the corresponding sulfane (5 mmol) in a 1/1 mixture of MeOH/H_2O (44 mL), was slowly added oxone® (50 mmol, 31 g). The reaction mixture was then stirred at room temperature for 1 d. After MeOH had been evaporated, the residue was dissolved in CH_2Cl_2 (50 mL) and filtered through celite. After quenched with water (50 mL), the mixture was extracted with CH_2Cl_2 (2× 25 mL), washed with a saturated solution of NaCl (3× 50 mL), and dried with anhydrous $MgSO_4$. Evaporation of

the solvent afforded the corresponding pure crude sulfones **5a**, **5b**, and **6** which were recrystallized in ether/hexane or purified by flash chromatography (hexane/EtOAc). Products **5b**[15] and **6**[15] have been previously described and gave satisfactory spectroscopic and physical data. For compound **5a** see Supporting Information.

General Procedure for the Preparation of Sulfones 3a, 3b, and 4

To a 0 °C stirred slurry of NaH (95%, 140 mg, 5.5 mmol) in THF (20 mL), a solution of the corresponding sulfone (5 mmol) in THF (10 mL) was added under an argon atmosphere. After stirring for 30 min at the same temperature, selecfluor® (1.99 g, 5.5 mmol) was added. The resulting mixture was stirred overnight at the same temperature and then quenched with a saturated aqueous solution of NH_4Cl (20 mL). The mixture was then extracted with EtOAc (2× 20 mL) and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), NaCl (15 mL), and finally with H_2O (15 mL). The organic phase was then dried ($MgSO_4$). Evaporation of the solvent afforded the corresponding crude sulfones **3a**, **3b**, and **4**, which were purified by flash chromatography (hexane/EtOAc). See Supporting Information for physical and spectrosocpic data.

General Procedure for Condensation of Aldehydes with Fluorinated Sulfones 3a, 3b, and 4

Under an argon atmosphere, a DMF (3 mL) solution of fluorinated BTFP sulfone (0.3 mmol), K_2CO_3 (2.7 mmol) and TBAB (0.03 mmol) was stirred at room temperature for 15 min. Then, neat aldehyde (0.15 mmol) was added and the resulting reaction mixture was stirred at room temperature for 18 h. After this time, the reaction was hydrolyzed with saturated aqueous solution of NH_4Cl (10 mmol) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with H_2O (3×10 mL), dried ($MgSO_4$) and evaporated to afford the crude reaction mixture which was purified by flash chromatography to yield the corresponding α-fluoro esters and α-fluoro Weinreb amides **7** and **9**. See Supporting Information for physical and spectrosocpic data.

Compounds **7aa**,[25] **7ab**,[26] **7ac**,[27] **7ae**,[26] **7ag**,[28] **7ai**,[28] **7ba**,[12a] **7bc**,[29] **7bd**,[12a] and **7be**[12a] have been previously described and gave satisfactory spectroscopic and physical data.

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