Julia Olefination as a General Route to Phenyl (α-Fluoro)vinyl Sulfones

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Abstract: Mild and efficient synthesis of phenyl (α-fluoro)vinyl sulfones via condensation of aldehydes and a ketone with a novel benzothiazolyl based bis-sulfone reagent is reported and this proceeds with moderate to good *Z*-stereoselectivity.

Key words: fluorination, olefination, Julia, fluorovinyl sulfones, benzothiazole

Herein we report the development and application of a novel reagent for the preparation of phenyl (α-fluoro)vinyl sulfones. Sulfones in general are important synthetic intermediates, leading to a variety of compounds.[2] Specifically, (α-fluoro)vinyl sulfones have been subjected to a range of transformations, such as desulfonylation leading to vinyl fluorides,[3] stannyldesulfonylation,[4] or silyl and germyldesulfonylation,[5] and thus they serve as versatile synthetic intermediates to a variety of fluoroolefins. Also, vinyl sulfones can be used for cycloadditions and are Michael acceptors.[3b,6] (α-Fluoro)vinyl sulfones can be prepared by various approaches, such as: addition of fluoromethyl phenyl sulfone anion to carbonyl compounds,[3a] Horner–Wadsworth–Emmons[3–5] or Peterson's olefination,[7] *syn* elimination of sulfoxides,[8] or via electrochemical method.[9] Synthesis of vinyl fluorides using fluorobis(phenylsulfonyl)methane has also been shown.[10] An attractive method for the synthesis of carbon–carbon double bonds is the modified or one-pot Julia–Kocienski olefination.[11] The use of Julia reaction for the synthesis of vinyl fluorides has recently begun to receive attention.[12,13] In this context, our synthesis of vinyl fluorides hinges on development of general routes to fluorinated 1,3-benzothiazolyl sulfones via metalation–electrophilic fluorination.[13] The α-fluoro 1,3-benzothiazol-2-yl sulfones so derived were subjected to condensations with a series of aldehydes and ketones to afford high yields of regiospecifically fluorinated 1,2-diaryl olefins[13a] as well as α-fluoro acrylates.[13b] Encouraged by these results, we decided to explore the utility of Julia olefination for the synthesis of phenyl (α-fluoro)vinyl sulfones.

Briefly, our synthesis of the desired reagent for the preparation of phenyl (α-fluoro)vinyl sulfones via modified Julia olefination initially commenced from the commercially available chloromethyl phenyl sulfone. Displacement of chloride with the sodium salt of 2-mercapto-1,3-benzothiazole provided the mono sulfone **1**, however the conversion proceeded only at high temperatures. In order to increase the reactivity of the halomethyl phenyl sulfone, the iodo derivative was synthesized (sodium benzenesulfinate and CH_2I_2).[14] As anticipated, reaction of the iodomethyl sulfone derivative proceeded at the milder 70 °C to give **1** in 83% isolated yield, that was subjected to oxidation to bis-sulfone **2** using catalytic ammonium molybdate $[(NH_4)_6Mo_7O_{24}\cdot 4H_2O]$ and H_2O_2[15] (75%, Scheme 1). Subsequent fluorination of **2** using NaH and Selectfluor in THF resulted in a mixture of starting **2**, monofluoro **3** and difluoro **4** derivatives (39:55:6) and upon chromatographic purification, the monofluoro derivative was isolated in 40% yield. The use of KO*t*-Bu and Selectfluor in DMF reported for the fluorination of bis(benzenesulfonyl)methane[16] resulted in a mixture of **2**:**3**:**4** in approximately 1:1:1 ratio. Much better results were obtained when **1** was first subjected to deprotonation using LDA in toluene, followed by electrophilic fluorination with NFSi. This resulted in a mixture of **1**, monofluoro and difluoro derivatives in a ratio (%) of 23:69:8, respectively. Since separation of the mono and difluoro derivatives proved to be problematic, **1** was initially separated from the products. The mixture of mono and difluoro derivatives was then oxidized to bis-sulfones **3** and **4** using H_5IO_6 and catalytic CrO_3.[17] At this stage, **3** could be easily separated from the difluoro byproduct **4**, to give the monofluoro bis-sulfone **3** in 49% yield (over two steps).

With the desired reagent **3** in hand, condensation reactions with carbonyl compounds were tested. The use of Julia reaction for the synthesis of acrylates[18] and α-fluoro acrylates[12b,13b] under mild, DBU-mediated conditions has been reported. Aldehydes were therefore subjected to condensation reactions under similar mild conditions. In a typical experiment, aldehyde (1 mol equiv) and bis-sulfone **3** (1.3 mol equiv) were dissolved in freshly distilled CH_2Cl_2 at room temperature, and DBU (1.5 or 4.0 mol equiv, entry 1, Table 1) in CH_2Cl_2 was added to the reaction mixture. The progress of the reaction was monitored by TLC for the disappearance of the aldehyde and the reactions were typically complete within 35–120 minutes. The reaction mixtures were partially concentrated and then directly loaded onto a dry silica gel column. The combined *E*/*Z*-product mixture was eluted and the *E*/*Z* ratio was analyzed by ^{19}F NMR spectroscopy.

In the case of alkanals that could potentially lead to volatile products, an internal standard was added to the *E*/*Z*-fluoroalkene mixtures eluted from the column, and the yield was assessed by ^{19}F NMR spectroscopy, prior to complete solvent removal. The yields and stereochemical

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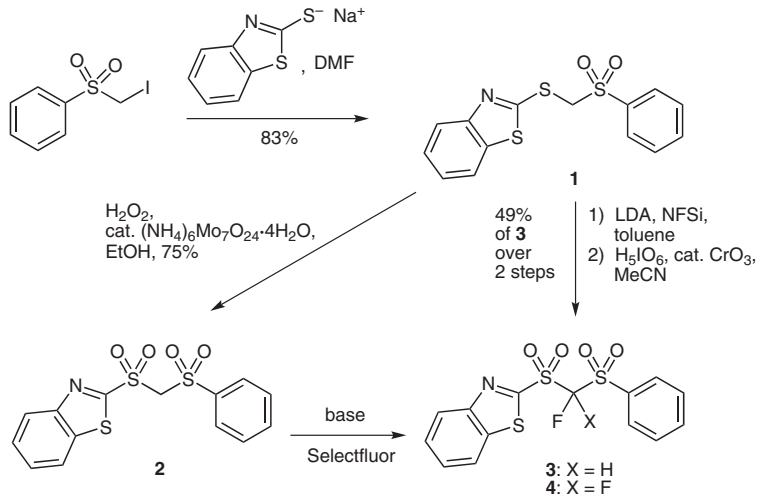


Scheme 1 Synthesis of the fluorinated bis-sulfone

outcomes of the reactions are shown in Table 1 and comparison to some alternative synthetic routes in the literature is included.

All aldehydes tested gave high to excellent yields of fluorovinyl sulfones. The use of 4.0 mol equivalents of DBU instead of 1.5 mol equivalents did not change the yield or *E*/*Z* ratio (entry 1). It should also be noted that the *E*/*Z* ratio did not change significantly upon purification of the products, except in the case of **13** (entry 9, unstable product, *E*/*Z* ratio 22:78 after purification). In all cases studied, the major isomer formed was *Z*. The observed stereoselectivities in these cases can be rationalized on the same principles as described in our synthesis of α-fluoroacrylates.[13b] The stereochemical outcome in reactions with aldehydes using our methodology is complementary to other known methods, where the major or exclusive isomer formed was *E*.[3,7,19] In the case of aromatic aldehydes stereoselectivity decreased with the bulk of the aldehyde (entries 6, 8), however, branching of the aldehyde did not appear to have any influence on the *E*/*Z* ratio in the case of aliphatic aldehydes (entries 10–12).

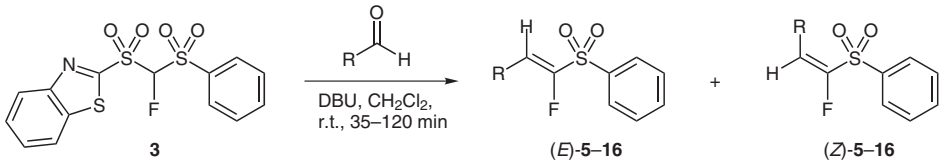
Since $MgBr_2$ has been shown to alter the *E*/*Z* ratio,[12b,20] some experiments were conducted in its presence.[21] Wherever tested, these data are also presented in Table 1. In the case of aromatic aldehydes, stereoselectivity depended on the aldehyde: it decreased for 4-nitrobenzaldehyde (entry 3), remained the same for thiophene-2-carboxaldehyde (entry 7), and improved for 2-methoxybenzaldehyde (entry 6). A substantial improvement in stereoselectivity was observed for octanal (entry 10). Similar (entry 3) or somewhat better yields (entries 6, 7, and 10) were obtained in the presence of $MgBr_2$.

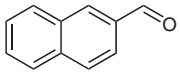
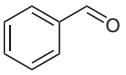
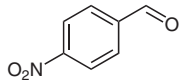
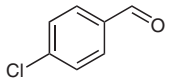
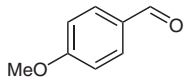
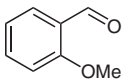
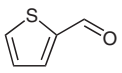
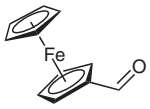
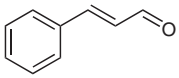
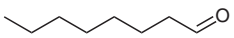
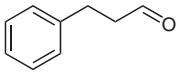
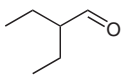
We were further interested in the reactivity of bis-sulfone **3** with ethyl 2-formyl-1-cyclopropanecarboxylate, in order to assess the applicability of the method to the synthesis of fluorinated compounds with the pyrethrin structural motif,[22] that are of interest in agricultural chemistry. Since the commercial cyclopropyl carboxaldehyde was a mixture of *trans* and *cis* isomers in a 9:1 ratio, four isomeric products were expected and were formed in the reaction. These were isolated in 80% yield by column chromatography (SiO_2, CH_2Cl_2). For characterization purposes the isomers from one reaction were partially separated by preparative TLC (SiO_2, 25% EtOAc in hexanes) to give *Z-trans*, *Z-cis* and a mixture of *E-trans* and *E-cis* isomers. Products formed in the reaction and their ratios, along with chemical shifts of the vinylic F and H atoms that are most diagnostic in isomer assignments, are shown in Scheme 2.

As a test substrate for reactivity of ketones, *N*-benzylpiperidone was subjected to olefination. Under the conditions used for olefination of aldehydes (DBU, CH_2Cl_2), a sluggish reaction was observed, with 47% conversion after 24 hours. Upon changing the reaction solvent to THF, the reaction was complete in 6 hours and the condensation product was isolated in 65% yield.[23] A comparable 70% yield was obtained in the reaction of *N*-benzylpiperidone (1 mol equiv) with **3** (2.4 mol equiv) in the presence of LHMDS (2.4 mol equiv, 0 °C), after standard aqueous workup and purification by chromatography. On the other hand, olefination of acetophenone and 1-indanone with **3** in the presence of LHMDS was inefficient. No further attempts were made to optimize reactivity of ketones with **3** at this time.

We were curious to compare the reactivity of the Horner–Wadsworth–Emmons (HWE) reagent to that of the bis-sulfone **3** for the synthesis of fluorovinyl sulfones under these mild condensation conditions, using DBU. For this, reactions of 2-naphthaldehyde and 1-octanal were chosen. Indeed, $PhSO_2CHFP(O)(OEt)_2$ (1.3 mol equiv) underwent reaction with 2-naphthaldehyde (1 mol equiv) in the presence of DBU (4.0 mol equiv) in CH_2Cl_2 at room temperature to give the condensation products in 80% yield and a 40:60 *E*/*Z* ratio. Reaction with 1-octanal (1.5 mol equiv of DBU) resulted in 48:52 *E*/*Z* product mixture in 65% yield. In this comparison substantially higher stereoselectivities were obtained in condensation reactions of **3** with 2-naphthaldehyde (Table 1, entry 1, 4.0 mol equiv of

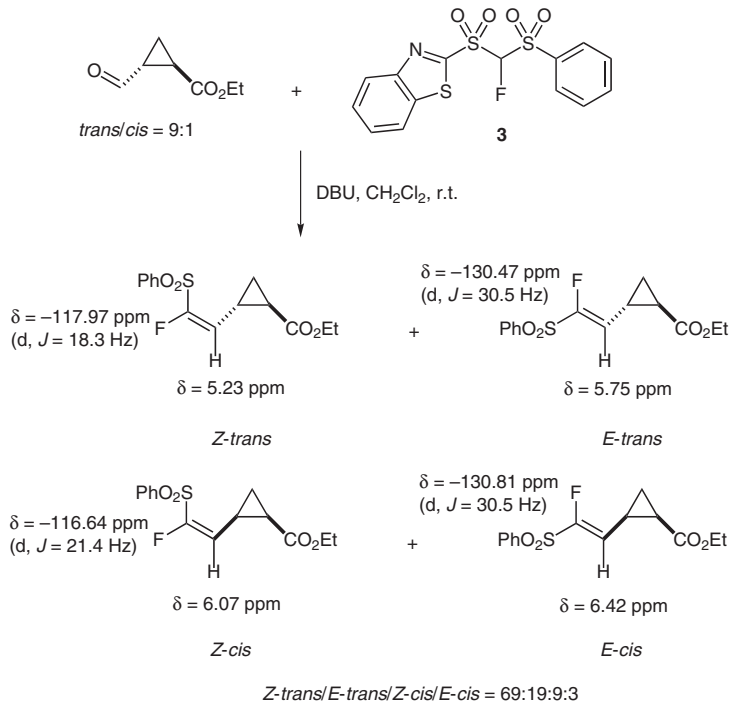
Table 1 Mild Synthesis of (α-Fluoro)vinyl Sulfones via the Julia Olefination



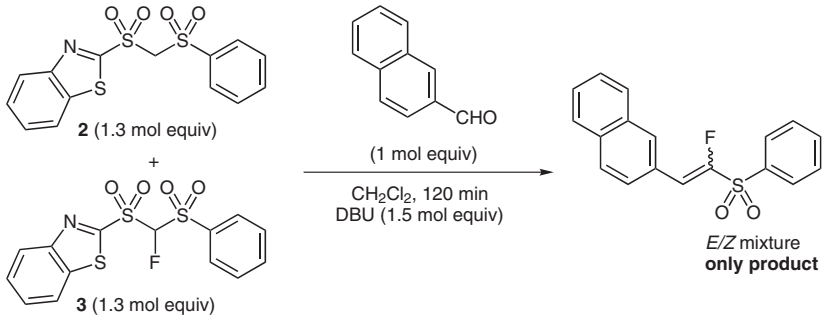
Entry	Aldehyde	Time (min)[a]	Products **5**–**16** Yield,[b] *E*/*Z* ratio[c] (lit.)[d]	^{19}F NMR: δ (ppm)[e], *J* (Hz)
1		120	**5**: 94%, 16:84 Using 4.0 mol equiv of DBU: 93%, 17:83	–111.64 (d, *J* = 21.4) –125.20 (d, *J* = 33.6)
2		80	**6**: 90%, 16:84 (85%, 95:5),[19] (52%, 77:23),[7] (85%, *E* only),[3b] (67%, *E* only)[3a]	–112.16 (d, *J* = 21.4) –125.12 (d, *J* = 36.6)
3		90	**7**: 85%, 22:78 With $MgBr_2$: 84%, 29:71 (95%, 93:7)[3b]	–108.08 (d, *J* = 18.3) –119.46 (d, *J* = 33.6)
4		70	**8**: 89%, 17:83 (85%, 81:19),[3c] (80%, *E* only)[3a]	–111.06 (d, *J* = 21.4) –124.23 (d, *J* = 36.6)
5		90	**9**: 90%, 12:88 (81%, 98:2)[3b]	–114.09 (d, *J* = 24.4) –128.86 (d, *J* = 33.6)
6		120	**10**: 75%, 48:52 With $MgBr_2$: 91%, 36:64	–112.93 (d, *J* = 21.4) –126.96 (d, *J* = 36.6)
7		90	**11**: 82%, 11:89 With $MgBr_2$: 96%, 9:91	–116.85 (d, *J* = 21.4) –124.46 (d, *J* = 36.6)
8		80	**12**: 72%, 44:56	–117.25 (d, *J* = 24.4) –130.52 (d, *J* = 33.6)
9		40	**13**:[f] 87%, 13:87 (72%, *E* only)[3b]	–120.01 (d, *J* = 21.4) –127.87 (d, *J* = 30.5)
10		90	**14**: 85% (91%),[g] 22:78 With $MgBr_2$: 95%, 4:96 (44%, 83:17)[7]	–117.19 (d, *J* = 21.4) –129.43 (d, *J* = 33.6)
11		35	**15**: 66%, 23:77 (90%, 68:32),[19] (52%, 90:10)[7]	–116.21 (d, *J* = 21.4) –128.08 (d, *J* = 33.6)
12		90	**16**: 59% (71%),[g] 23:77	–116.09 (d, *J* = 24.4) –129.60 (d, *J* = 33.6)

[a] Time at isolation.
[b] Yields of isolated, purified products (reactions were performed under similar conditions but were not optimized for individual cases).
[c] Relative ratio of isomers determined by ^{19}F NMR of the crude reaction mixture.
[d] Where applicable, literature data and references are provided for comparison.
[e] Referenced to $CFCl_3$ as internal standard.
[f] The product is unstable and undergoes decomposition.
[g] Yield determined by addition of internal standard octafluoronaphthalene to the *E*/*Z* mixture eluted from the column, prior to complete solvent evaporation.

DBU, 17:83 *E*/*Z*) and 1-octanal (Table 1, entry 10, 22:78 *E*/*Z*). Finally, in order to compare the reactivity of **3** and $PhSO_2CHFP(O)(OEt)_2$, a reaction of each with 2-naphthaldehyde was monitored by ^{19}F NMR in the presence of octafluoronaphthalene as an internal standard. Reaction of **3** (1.3 mol equiv) with 2-naphthaldehyde (1 mol equiv) in



Scheme 2 Condensation of **3** with ethyl 2-formyl-1-cyclopropane carboxylate



Scheme 3 Comparative reactivity of **2** and **3** with 2-naphthaldehyde

the presence of DBU (1.5 mol equiv) showed 60% conversion to products after 15 minutes. In contrast, in the reaction of the HWE reagent under identical conditions, only about 8% conversion to products occurred in 15 minutes, indicating a higher reactivity of **3** under these mild condensation conditions.

We then assessed the influence of fluorine atom substitution on the reactivity of the bis-sulfone reagent. For this a competitive experiment was conducted, where the non-fluorinated bis-sulfone **2** (1.3 mol equiv) and its fluorinated analogue **3** (1.3 mol equiv) were allowed to react with 2-naphthaldehyde (1 mol equiv) in CH_2Cl_2 using DBU (1.5 mol equiv). After 120 minutes, the reaction was diluted with CH_2Cl_2 and washed with aqueous NH_4Cl. The organic layer was washed with water, dried with anhydrous Na_2SO_4, and analyzed by TLC (SiO_2, 15% EtOAc in hexanes) and by ^1H NMR. The only product obtained was fluorinated alkene **5**. This was also confirmed by comparison to the independently synthesized 1-phenylsulfonyl-2-(2-naphthyl)ethene (Scheme 3).

In summary, we have developed an efficient synthesis of a novel benzothiazolyl-based bis-sulfone reagent for the preparation of fluorovinyl phenyl sulfones via a one-pot Julia olefination. Condensation reactions with aldehydes are high yielding and proceed under mild conditions to give fluoroolefins with moderate to good *Z*-selectivity. The bis-sulfone reagent also showed a greater reactivity as compared to the HWE reagent $PhSO_2CHFP(O)(OEt)_2$. As originally reported by us in the synthesis of α-fluoro acrylates,[13b] in this case as well fluorine substitution increases the reactivity of the bis-sulfone reagent.

Synthesis of (1,3-Benzothiazol-2-ylsulfanyl)methyl Phenyl Sulfone (1)

A solution of iodomethyl phenyl sulfone (3.00 g, 10.6 mmol, 1 mol equiv) and the sodium salt of 2-mercapto-1,3-benzothiazole (6.04 g, 31.9 mmol, 3 mol equiv) in DMF (90.0 mL) was heated at 70 °C for 18 h. The reaction mixture was cooled to r.t., diluted with H_2O and extracted three times with EtOAc (300 mL). The organic layer was thoroughly washed with H_2O, aq NaOH (1 M), H_2O, aq NH_4Cl and

finally with brine, and dried over anhyd Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 0.1% acetone in CH_2Cl_2) to give 2.82 g (83%) of **1** as an ivory solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, 2 H, ArH, *J* = 7.5 Hz), 7.72 (d, 1 H, ArH, *J* = 7.9 Hz), 7.68 (d, 1 H, ArH, *J* = 7.9 Hz), 7.42–7.32 (m, 4 H, ArH), 7.30 (t, 1 H, ArH, *J* = 7.9 Hz), 5.03 (s, 2 H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 151.9, 137.0, 135.5, 133.9, 129.2, 128.7, 126.2, 124.9, 121.8, 121.0, 54.9. HRMS: *m*/*z* calcd for $C_{14}H_{11}NO_2S_3Na$ [M^+ + Na]: 343.9844; found: 343.9837.

Synthesis of (1,3-Benzothiazol-2-ylsulfonyl)fluoromethyl Phenyl Sulfone (3)

Step 1: Fluorination

A stirring solution of (1,3-benzothiazol-2-ylsulfanyl)methyl phenyl sulfone **1** (2.00 g, 6.22 mmol, 1 mol equiv) in dry toluene (95 mL), was cooled to –80 °C (dry ice/*i*-PrOH) under nitrogen gas. Lithium diisopropylamide (3.58 mL, 7.16 mmol, 1.15 mol equiv of a 2.0 M solution in heptane–THF–EtPh) was added to the reaction mixture with stirring. After 15 min solid NFSi (2.45 g, 7.79 mmol, 1.25 mol equiv) was added. The mixture was allowed to stir at –80 °C for 50 min, then warmed to r.t., and the stirring was continued for an additional 50 min. Then, sat. aq NH_4Cl (80 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted three times with EtOAc (200 mL), and the combined organic layer was washed with H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The ^{1}H NMR and ^{19}F NMR spectra of the crude reaction mixture showed the presence of **1**, monofluoro and difluoro derivatives in a ratio (%) of 23:69:8, respectively. Purification by column chromatography (SiO_2, CH_2Cl_2) afforded 1.55 g of a mixture of mono and difluoro derivatives that were subjected to oxidation.

Step 2: Oxidation

To a solution of H_5IO_6 (4.68 g, 20.5 mmol) in MeCN (100 mL) was added CrO_3 (22.8 mg, 0.228 mmol), and after stirring at r.t. for 5 min a solution of the mono and difluoro derivatives (1.55 g, obtained in step 1) in MeCN (15.0 mL) was added. The reaction mixture was allowed to stir at r.t. for 39 h and the conversion was checked by ^{19}F NMR and TLC (SiO_2, CH_2Cl_2). Since a small amount of unoxidized difluoro derivative was still present, H_5IO_6 (0.520 mg, 2.28 mmol) was added, and the reaction was allowed to proceed for another 5 h, when ^{19}F NMR and TLC showed complete conversion of the monosulfones to the bis-sulfones. The reaction mixture was filtered and the solid residue was washed with MeCN. The filtrate was concentrated under reduced pressure, H_2O was added, and the mixture was extracted with EtOAc (3×). The combined EtOAc layers were thoroughly washed with H_2O and finally with brine, and dried over anhyd Na_2SO_4. The crude product mixture was separated by column chromatography (SiO_2, CH_2Cl_2) to give 1.13 g (49% yield over two steps) of **3** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (br d, 1 H, ArH, *J* = 8.3 Hz), 8.07 (d, 2 H, ArH, *J* = 7.4 Hz), 8.04 (br d, 1 H, ArH, *J* = 8.3 Hz), 7.80 (br t, 1 H, ArH, *J* = 7.6 Hz), 7.71–7.63 (m, 4 H, ArH), 6.37 (d, 1 H, $^2J_{FH}$ = 45.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 152.6, 137.6, 136.0, 134.8, 130.5, 129.5, 129.0, 128.2, 126.1, 122.4, 105.0 (d, $^1J_{CF}$ = 268.2 Hz). ^{19}F NMR (470 MHz): δ = –169.95 (d, $^2J_{FH}$ = 45.8 Hz). HRMS: *m*/*z* calcd for $C_{14}H_{10}FNO_4S_3Na$ [M^+ + Na] 393.9648; found: 393.9643.

Condensation of 4-Chlorobenzaldehyde with 3

To a stirring solution of 4-chlorobenzaldehyde (100 mg, 0.711 mmol, 1 mol equiv) and **3** (344 mg, 0.926 mmol, 1.3 mol equiv) in freshly distilled CH_2Cl_2 (4.4 mL) was added DBU (163 mg, 1.07 mmol, 1.5 mol equiv) in CH_2Cl_2 (4.4 mL) at r.t. Upon addition of DBU, the reaction mixture immediately turned yellow. The stirring was continued at r.t. until complete consumption of the aldehyde was observed by TLC (SiO_2, CH_2Cl_2, 70 min). The reaction mixture was directly loaded onto a dry silica gel column (200–300 mesh) and the product **8** was eluted with CH_2Cl_2 as an *E*/*Z* mixture. Upon removal of solvent under reduced pressure, 187 mg (89%) of **8** was isolated and *E*/*Z* ratio was determined by ^{19}F NMR (Table 1, entry 4). HRMS: *m*/*z* calcd for $C_{14}H_{10}ClFO_2SNa$ [M^+ + Na]: 318.9966; found: 318.9960. For ^{1}H NMR analysis, a small amount of the *E*- and *Z*-isomers was separated by TLC (SiO_2, 20% acetone in hexane). *E*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, 2 H, ArH, *J* = 7.8 Hz), 7.71 (t, 1 H, ArH, *J* = 7.7 Hz), 7.61 (t, 2 H, ArH, *J* = 7.8 Hz), 7.51 (d, 2 H, ArH, *J* = 8.7 Hz), 7.37 (d, 2 H, ArH, *J* = 8.7 Hz), 7.02 (d, 1 H, $^2J_{FH}$ = 34.5 Hz). *Z*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, 2 H, ArH, *J* = 7.8 Hz), 7.69 (t, 1 H, ArH, *J* = 7.4 Hz), 7.56 (t, 2 H, ArH, *J* = 7.6 Hz), 7.38 (ABq, 4 H, ArH, *J* = 8.5 Hz), 6.84 (d, 1 H, $^2J_{FH}$ = 21.2 Hz).

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References and Notes

(1) Undergraduate research participant.
(2) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.
(3) (a) Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; LeTourneau, M. E. *J. Chem. Soc., Chem. Commun.* **1985**, 678. (b) Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3959. (c) McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T. *Tetrahedron Lett.* **1990**, *31*, 5449.
(4) (a) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439. (b) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45. (c) Berkowitz, D. B.; de la Salud-Bea, R.; Jahng, W.-J. *Org. Lett.* **2004**, *6*, 1821.
(5) Wnuk, S. F.; Garcia, P. I. Jr.; Wang, Z. *Org. Lett.* **2004**, *6*, 2047.
(6) Uno, H.; Sakamoto, K.; Tominaga, T.; Ono, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1441.
(7) Asakura, N.; Usuki, Y.; Iio, H. *J. Fluorine Chem.* **2003**, *124*, 81.
(8) Nakamura, T.; Guha, S. K.; Ohta, Y.; Abe, D.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2031.
(9) Kunugi, A.; Yamane, K.; Yasuzawa, M.; Matsui, H.; Uno, H.; Sakamoto, K. *Electrochim. Acta* **1993**, *38*, 1037.
(10) Prakash, G. K. S.; Chacko, S.; Olah, G. A. *Abstracts of Papers*; 234th National Meeting of the American Chemical Society, Boston MA, American Chemical Society: Washington (DC), **2007**, ORGN 846.
(11) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163.
(12) (a) Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S. *Tetrahedron Lett.* **2003**, *44*, 8127. (b) Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T. *J. Org. Chem.* **2007**, *72*, 7871.

(13) (a) Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553. (b) Zajc, B.; Kake, S. *Org. Lett.* **2006**, *8*, 4457.
(14) Bordwell, F. G.; Clemens, A. H.; Smith, D. E.; Begemann, J. *J. Org. Chem.* **1985**, *50*, 1151.
(15) Ono, K.; Yoshida, A.; Saito, N.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H.; Kittaka, A. *J. Org. Chem.* **2003**, *68*, 7407.
(16) Ni, C.; Li, Y.; Hu, J. *J. Org. Chem.* **2006**, *71*, 6829.
(17) Xu, L.; Cheng, J.; Trudell, M. L. *J. Org. Chem.* **2003**, *68*, 5388.
(18) Blakemore, P. R.; Ho, D. K. H.; Nap, W. M. *Org. Biomol. Chem.* **2005**, *3*, 1365.
(19) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405.
(20) Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* **2006**, *71*, 2009.
(21) In a typical experiment, to a mixture of aldehyde (1 mol equiv), bis-sulfone **3** (1.3 mol equiv) and anhyd $MgBr_2$ (1.8 mol equiv) in anhyd THF (5 mL per mmol of aldehyde), a solution of DBU (3.9 mol equiv) in anhyd THF (5 mL per mmol of aldehyde) was added. The mixture was stirred at r.t., until the disappearance of the aldehyde was observed by TLC. Aqueous NH_4Cl was added and the mixture was extracted with EtOAc (3×). The organic layer was washed with H_2O and brine, dried over anhyd Na_2SO_4 and the solvent was evaporated.
(22) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (b) Liu, W.; Qin, S.; Gan, J. *J. Agric. Food Chem.* **2005**, *53*, 3814.
(23) Conditions as reported in ref. 12b were used (*N*-benzylpiperidone: 1.2 mol equiv; **3**: 1 mol equiv; DBU: 1.4 mol equiv; THF: 5 mL per mmol of **3**; r.t., 6 h).