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Fluorinated 1-Phenyl-1*H*-tetrazol-5-yl Sulfone Derivatives as General Reagents for Fluoroalkylidene Synthesis

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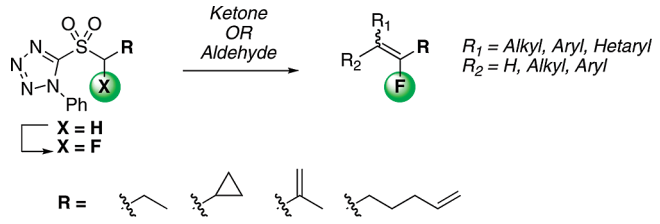

Julia−Kocienski olefination reagents 1-fluoropropyl, (cyclopropyl)fluoromethyl, 1-fluoro-2-methyl-2-propenyl, and 1-fluoro-5-hexenyl 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones were prepared by metalation followed by electrophilic fluorination. Although metalation−fluorination of *n*-propyl, 5-hexenyl, and (cyclopropyl)methyl PT-sulfones proceeded under homogeneous conditions, fluorination of 2-methyl-2-propenyl PT-sulfone required heterogeneous fluorination conditions. Condensation reactions of fluoro PT-sulfones with aldehydes resulted in fluoroalkylidenes in high yields. Screening of olefination conditions showed that stereoselectivity depended on reagent and carbonyl structure and can in many cases be tuned either toward *E*- or *Z*-selectivity. For example, LHMDS-mediated condensations of 1-fluoropropyl PT-sulfone in the presence of $MgBr_2 \cdot OEt_2$ were *Z*-selective with electron-rich aromatic aldehydes, a hindered aromatic aldehyde, and cinnamaldehyde. Low-temperature KHMDS-mediated condensations were *E*-selective with electron-rich and electron-deficient aromatic aldehydes and *Z*-selective with *n*-octanal. Dialkyl, aryl alkyl, and diaryl ketones reacted as well to give fluoro olefin products in 71−99% yields.

Introduction

Introduction of fluorine is known to alter physical, biological, and chemical properties of organic compounds.[1] Access to regiospecifically fluorinated compounds[2] continues to be of interest in many areas, such as pharmaceuticals,[3a] materials,[3b] and agrochemistry.[3c] There are principally two synthetic strategies for the synthesis of fluoroorganics, either via introduction of fluorine atom into specific molecules[2] or development of molecules via a building block assembly using fluorinated precursors.[4] As synthetic intermediates, fluoroolefins are pivotal compounds, and several methods have been developed for their synthesis,[5a] including Wittig and Horner−Wittig like reactions.[5]

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(5) For recent reviews, see: (a) van Steenis, J. H.; van der Gen, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2117–2133. (b) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1716. (c) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868–3935. For examples on the reactions of fluoroalkylphosphonium salt and fluoroalkylphosphonate, see: (d) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 886–888. (e) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1425–1430. (f) El-Khoury, M.; Wang, Q.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 9047–9048.

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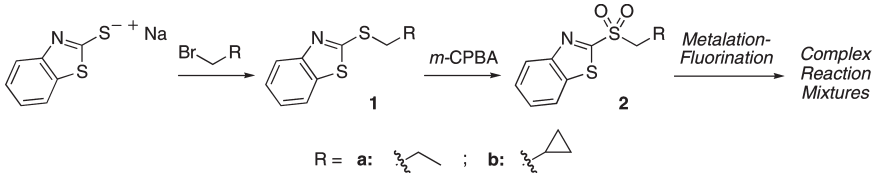
SCHEME 1. Attempts at Synthesis of Fluoroalkyl Benzothiazolyl Sulfones via Metalation−Fluorination

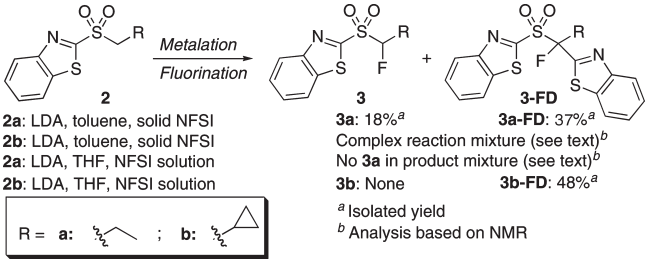


Since the original report on the one-pot Julia olefination,[6] this and its Kocienski variation have found wide use in synthetic organic chemistry for olefin synthesis via condensation reactions of heteroarylsulfonyl- or arylsulfonyl-substituted carbanions with aldehydes or ketones.[7] Despite this, such a method has not received much attention for the synthesis of vinyl fluorides until recently. Synthesis of variously functionalized fluoroolefins has been since reported by us and others, i.e., α-fluoro-α-methylvinyl derivatives,[8] stilbene- and styrene-like fluoroolefins,[9] fluoroacrylates,[10] fluoroacrylonitriles,[11] α-fluorovinyl phenyl sulfones,[12] α-fluorovinyl Weinreb amides,[10c,13] and enones.[13] Several approaches have been undertaken for the synthesis of fluorinated Julia−Kocienski reagents. These range from synthesis utilizing commercial fluorinated precursors[8,10b,10d,11] to halogen exchange reaction of the appropriate chloro derivative[8] to metalation−electrophilic fluorination.[9,10a,10c,11−13] Among these, we have extensively investigated the metalation−fluorination approach[9,10a,11−13] since it offers the most general access to fluorinated Julia−Kocienski reagents. During these investigations, we discovered that although benzylic fluorination of 1,3-benzothiazol-2-yl benzyl sulfones could be successfully conducted under heterogeneous metalation−electrophilic fluorination conditions,[9] reactivity of comparable 1,3-benzothiazol-2-yl alkyl sulfones was much more complex. On the basis of these observations, synthesis of the more stable Kocienski reagents 1-phenyl-1*H*-tetrazol-5-yl fluoroalkyl sulfones was considered appropriate. Herein, we report our results on the generality of the metalation-fluorination of 1,3-benzothiazol-2-yl and 1-phenyl-1*H*-tetrazol-5-yl alkyl sulfones and the generally efficient condensation reactions of the resulting 1-phenyl-1*H*-tetrazol-5-yl fluoroalkyl sulfones with aldehydes and ketones.

Results and Discussion

Our first goal was synthesis of appropriate fluoroalkyl derived heteroaryl sulfones for the Julia−Kocienski olefination. In our previous studies, we have developed a general method for the synthesis of Julia olefination reagents via heterogeneous metalation-fluorination of appropriate precursors, specifically 1,3-benzothiazol-2-ylsulfonyl (BT-sulfonyl) derivatives.[9,10a,11−13] Further, to date the only reported Julia olefination reagent for the synthesis of fluoroalkylidene derivatives was the benzothiazolyl-based α-fluoroethyl BT-sulfone.[8] Since its preparation via fluorination of ethyl BT-sulfide with F-TEDA-BF_4 (Selectfluor) gave only 30−35% of the α-fluoro sulfide precursor, α-fluoroethyl BT-sulfone reagent was synthesized from either commercially available 1-bromo-1-fluoroethane or from the α-chloroethyl sulfide via chlorine−fluorine substitution.[8] While this work was in progress, decarbethoxylation of appropriate BT-sulfone derivatives was reported to yield 1-fluoroethyl and 1-fluoropropyl BT-sulfones in 51% and 33% yield, respectively.[10d] On the basis of our earlier work, our initial attempts were therefore directed toward the synthesis of fluorinated BT-sulfone derivatives, specifically propyl and cyclopropyl BT-derivatives (Scheme 1).

SCHEME 2. Details of Metalation−Fluorination of Benzothiazolyl Sulfone Derivatives



Reaction of the sodium salt of 2-mercapto-1,3-benzothiazole with *n*-bromopropane or (bromomethyl)cyclopropane gave the sulfides **1a**[14] and **1b**[15a] that were subjected to *m*-CPBA oxidation to give the corresponding sulfones **2a**[14] and **2b**.[15] Both sulfones were subjected to metalation-fluorination using our heterogeneous conditions.[9] Typically, metalations were performed in toluene at −78 °C using LDA, followed by quenching of the carbanion with solid *N*-fluorodibenzenesulfonimide (NFSI). In the case of **2a**, the highest isolated yield of the desired monofluoro derivative 2-[(1-fluoropropyl)sulfonyl]-1,3-benzothiazole[10d] (**3a**, Scheme 2) was 18%. In addition, a product resulting from self-condensation (**3a-FD**, Scheme 2) was also isolated in 37% yield. Metalation-fluorination of **2b** gave a complex reaction mixture. The ^{1}H and/or ^{19}F NMR spectra showed the presence of about 30% of starting material **2b**, 3% of the

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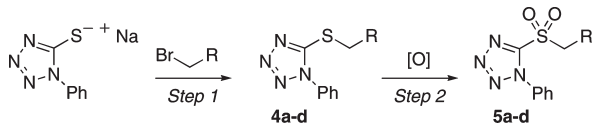
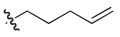
TABLE 1. Synthesis of Alkyl 1-Phenyl-1*H*-tetrazol-5-yl Sulfones



entry	R =	step 1 conditions	yield step 1	step 2 conditions	yield step 2
1		DMF, rt, 4.5 h	**4a:**[19] 98%	*m*-CPBA, $CHCl_3$, rt, overnight	**5a:**[19] 93%
2		DMF, rt, 5 h	**4b:** 98%	*m*-CPBA, $CHCl_3$, rt, overnight	**5b:** 89%
3		DMF, rt, 5 h	**4c:**[20] 97%	$Mo_7O_{24}(NH_4)_6.4H_2O$, EtOH, rt, overnight	**5c:** 65%
4		DMF, rt, 5.5 h	**4d:** 99%	$Mo_7O_{24}(NH_4)_6.4H_2O$, EtOH, rt, overnight	**5d:**[21] 90%

desired monofluoro product **3b**, and 8% of the fluorinated dimer (**3b-FD**, Scheme 2), in addition to other unidentified products. In either case, variation of reaction conditions, i.e., base (NaHMDS, *t*-BuLi), as well as stoichiometry of reagents led to little improvement. For example, deprotonation of **2b** with *t*-BuLi at −78 °C in toluene followed by addition of solid NFSI resulted in a complex reaction mixture that showed the desired monofluoro derivative and starting **2b** in a 43%:57% ratio, in addition to other unidentified byproducts (^{1}H NMR). Attempted metalation−fluorination of **2a** using NaH/F-TEDA-BF_4 (THF, 0 °C to rt) led to recovered starting material only. Next, we decided to perform the reaction under homogeneous fluorination conditions using THF as solvent. Metalation of **2a** in THF at −78 °C using LDA, followed by addition of a THF solution of NFSI, resulted in a mixture that showed the presence of sulfone **2a** and product **3a-FD** in a ratio of 73%:27%, but no monofluoro derivative **3a**, as assessed by ^{1}H NMR. Metalation−fluorination of **2b** under homogeneous conditions resulted in a mixture that contained sulfone **2b** and the self-condensation product in ∼30%:70% ratio, respectively (**3b-FD**, 48% isolated yield, Scheme 2). It has been reported[7,16] that 1,3-benzothiazol-2-yl sulfone derivatives containing sterically unencumbered substituents tend to undergo self-condensations even at low temperatures.

Metalated 1-phenyl-1*H*-tetrazol-5-yl sulfones have been found to be more stable compared to benzothiazolyl sulfones,[17] and the stability of 1-*tert*-butyl-1*H*-tetrazol-5-yl sulfones has been reported to be even greater.[16] Among the tetrazolyl derivatives, 1-phenyl-1*H*-tetrazol-5-yl *n*-alkyl sulfones have shown higher *E*-selectivity in condensation reactions compared to the *tert*-butyl analogues.[7,16] Further, synthesis of α-bromo and α-chloromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfones and condensation reactions with aldehydes have recently been reported.[18] These results led us to pursue the synthesis and fluorination of alkyl 1-phenyl-1*H*-tetrazol-5-yl sulfones. A series of 1-phenyl-1*H*-tetrazol-5-yl sulfones was synthesized in a simple two-step procedure (**5a**−**d**, Table 1).

Next, fluorination of sulfones **5a**−**d** was undertaken. Various reaction conditions were tested, and the results are displayed in Table 2. In all cases studied, a slight excess of LDA was added to a solution of sulfone **5a**−**d** at −78 °C in the solvent indicated, and after 15 min, a slight excess of NFSI was added either as solid or as a solution (Table 2). After completion of reaction and workup, the crude reaction mixture was analyzed by NMR spectroscopy. The ratios of starting sulfone **5a**−**d** to monofluoro product **6a**−**d** were determined by ^{1}H NMR. The ratios of fluorinated compounds, i.e., monofluoro product **6a**−**d**, the difluoro derivative (**diF**) and fluorinated dimer (**6-FD**, if present), were assessed by ^{19}F NMR (Table 2).

The results in Table 2 reveal that the reaction is sensitive to both reaction conditions as well as the structure of the sulfone. Initially, the reaction was performed with *n*-propyl derivative **5a** under our heterogeneous fluorination conditions, where LDA was added to solution of sulfone in toluene, followed by addition of solid NFSI (entry 1, Table 2).[9] The crude reaction mixture showed a ratio of 79%:21% of monofluoro derivative **6a** and starting sulfone **5a**, with trace amounts of the difluoro byproduct. In order to assess the influence of solvent, THF was used instead of toluene, and NFSI was added as solid (entry 2, Table 2). The resulting product mixture showed a similar composition, with a decrease in product yield. When the reaction was performed in THF under homogeneous metalation−fluorination conditions (addition of NFSI in solution), little change in product composition was again observed, with the yield of **6a** similar to that obtained under heterogeneous conditions (entry 3, Table 2). Metalation−fluorination of cyclopropyl derivative **5b** under heterogeneous conditions resulted in a more complex reaction mixture that contained monofluoro derivative **6b** and starting compound **5b** (56%:44%, entry 4, Table 2), along with a fluorinated dimer (**6b**:**6b-FD** 68%:32%). Minor dimer formation was observed when the reaction was performed under homogeneous metalation−fluorination conditions, and monofluoro product **6b** was isolated in 58% yield (entry 5, Table 2). This contrasts substantially to metalation−fluorination of benzothiazolyl

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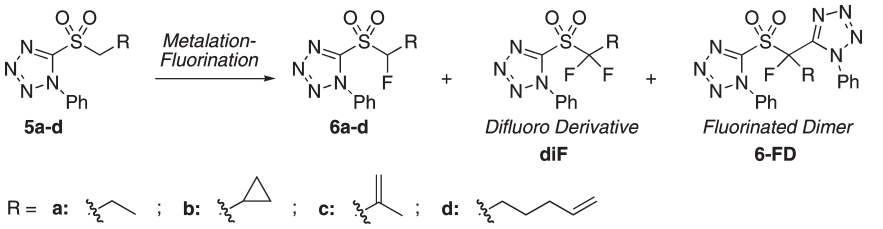
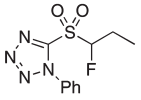
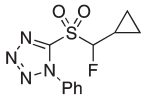
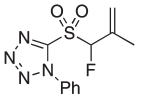
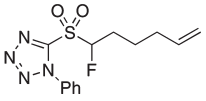
TABLE 2. Fluorination of Alkyl 1-Phenyl-1*H*-tetrazol-5-yl Sulfones



entry	fluorinated product	solvent	NFSI added as	ratios **6**:**5**; **6**:F-byproducts[a]	yield[b] (%)
1[c]		toluene	solid	79:21; trace **diF**	**6a**: 71
2[c]		THF	solid	75:25; no **diF**	**6a**: 58
3[c]		THF	THF solution	80:20; **6a**:**diF** 92:8	**6a**: 67
4		toluene	solid	56:44; trace **diF**; **6b**:**6b-FD** 68:32	**6b**: 22
5		THF	THF solution	74:26; **6b**:**6b-FD**:**diF** 95:3:2	**6b**: 58
6[c]		toluene	solid	86:14; **6c**:**diF** 97:3	**6c**: 53
7		THF	THF solution	--[d]	**6c**: NA[d]
8[c]		THF	THF solution	76:24; **6d**:**diF** 98:2	**6d:** 65

[a]Fluorinated byproducts: difluoro derivative (**diF**) and fluorinated dimer (**6-FD**). [b]Yields of isolated, purified products. [c]No fluorinated dimer (**6-FD**) observed by ^{19}F NMR. [d]Complex reaction mixture. No desired product **6c** was observed by ^{19}F NMR; **6c** was isolated in 59% yield when reaction was performed on a 100 mg scale but could not be repeated on larger scales.

sulfone analogue **2b**, where fluorinated dimer **3b-FD** was the *only* product formed under homogeneous reaction conditions (Scheme 2) and formation of only minor amounts of **3b-FD** was observed under heterogeneous fluorination conditions. In the fluorination of 2-propenyl derivative **5c** under heterogeneous conditions, fluorinated product **6c** was isolated in 53% yield (Table 2, entry 6). Under homogeneous conditions, fluorination of **5c** worked well on a small scale, but could not be repeated on a larger scale and resulted in complex reaction mixtures. Finally, fluorination of 5-hexenyl sulfone **5d** under homogeneous conditions resulted in the monofluoro derivative **6d** as the major fluorinated product, along with small amount of difluoro derivative (entry 8, Table 2).

In metalation−fluorination reactions, an electron-transfer (ET) mechanism has been suggested as a competing path to the S_N2 fluorination.[22] We have shown in the past that metalation−fluorination of 1,3-benzothiazol-2-yl arylmethyl sulfones proceeded well under heterogeneous conditions (formation of carbanion in toluene, followed by addition of solid NFSI). In these cases, no product, or a low amount of product, was isolated when the reaction was performed under homogeneous conditions, along with large amounts of recovered starting material. ET was suggested to compete with the fluorination.[9] This was also shown to occur in metalation−fluorination of nucleosides using NFSI,[23] where ET prevailed under homogeneous fluorination conditions,[23a] but under heterogeneous conditions fluorinated products were isolated.[23b] We were therefore surprised to find that metalation−fluorination of 1-phenyl-1*H*-tetrazol-5-yl sulfone derivatives could be performed under homogeneous conditions to yield the fluorinated products. Importantly, only the desired fluorinated **6d** was observed in the case of 5-hexenyl sulfone **5d**, with no detectable formation of cyclized or olefin migration products (entry 8, Table 2). Thus, it appears that the ET process is substantially lower in the case of PT-sulfones. Further, in the fluorination of 1,3-benzothiazolyl sulfone **2b** under homogeneous conditions, a self-condensation resulting in **3b-FD** was the major process (Scheme 2). This was not the case with its phenyltetrazolyl sulfone analogue **5b**, where only a minor amount of dimer formation was detected in the reaction mixture (entry 5, Table 2). Moreover, formation of fluorinated dimers was not observed for other substrates, when reactions were performed in THF.

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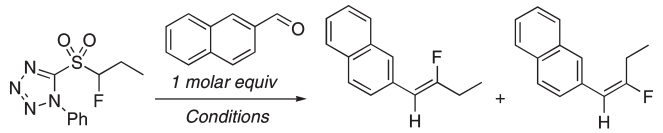
TABLE 3. Effect of Reaction Conditions on Stereoselectivity and Yield of Condensations of 6a with 2-Naphthaldehyde



6a **7: *Z*-isomer** **7: *E*-isomer**

entry	base (molar equiv)	solvent	additive (molar equiv)	T (°C), reaction time (h)	(%) E/Z ratio;[a] yield[b] (%)
1	LHMDS (1.3)	THF		0, 2	59/41; 90
2	LHMDS (2.4)	THF		0, 2	58/42; 92
3	LHMDS (1.1)	THF		−78 to −65, 3; −45−0, 1.5; rt, 1	59/41; 90
4	LHMDS (2.5)	DMF		−55 to +15, 4	43/57; 84
5	LHMDS (1.3)	DMF	DMPU[c]	−70, 1; −45, 0.5; rt, overnight	37/63; 34
6	LHMDS (2.5)	DMF	DMPU[c]	−70, 1; −45, 0.5; rt, overnight	37/63; 82
7	LHMDS (2.5)	DMF	HMPA[d]	−44 to +15, 4	37/63; 98
8	LHMDS (2.5)	HMPA		0 to +15, 4	30/70; 74
9	LHMDS (2.5)	DMPU		−20 to +15; 4	25/75; 78
10	LHMDS (2.5)	THF	$BF_3\cdot OEt_2$	0, 2; rt, 1	48/52; 78
11	LHMDS (3.0)	THF	$MgBr_2$ (anh)	rt, 4.5	17/83; 86
12	LHMDS (3.0)	THF	$MgBr_2\cdot OEt_2$	rt, 4.5	14/86; 94
13	LHMDS (3.0)	THF	$MgBr_2\cdot OEt_2$	0, 2	34/66; 78
14	phosphazene base-P_2-Et (1.4)	THF		0, 2	42/58; 55
15	phosphazene base-P_4-*t*-Bu (1.4)	THF		0, 2	24/76; 70
16	phosphazene base-P_4-*t*-Bu (1.4)	THF		−82, 2	29/71; 97
17	KHMDS (1.3)	DME		−55, 2.5; rt, overnight	58/42; 39
18	NaHMDS (1.3)	DME		−55, 2.5; rt, overnight	58/42; 39
19	KHMDS (1.3)	THF		0, 2	60/40; 75
20	KHMDS (1.1)	THF		−78, 2	73/27; 64

[a]Relative ratio of diastereomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation. No change in ratio was observed after purification. [b]Yields of isolated, purified products. [c]Cosolvent, ratio of DMF/DMPU 1:1 (v/v). [d]Cosolvent, ratio of DMF/HMPA 3:1 (v/v).

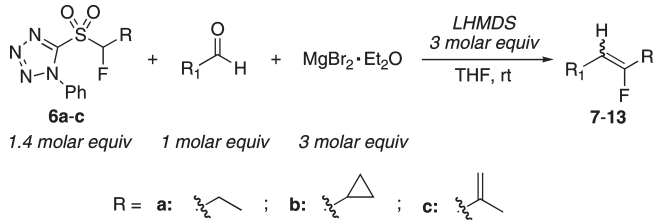
With the desired reagents in hand, we decided to test the olefination and the associated stereoselectivity under various reaction conditions. Effect of base counterion and solvent on the olefination stereoselectivity using unfluorinated PT-sulfones has originally been reported by Blakemore et al.[17] Effect of additives on olefinations using a PT-sulfone has subsequently been screened.[24] Recently, condensation reactions of α-chloromethyl PT-sulfones have been studied: room-temperature LHMDS-mediated condensations with electron-rich aromatic aldehydes were *E*-selective in the presence of $MgBr_2\cdot OEt_2$, whereas *Z*-stereoselectivity was observed in condensation with a series of aldehydes in the presence of HMPA.[18] Stereoselectivity and olefination yields under various reaction conditions was therefore assessed using 1-fluoropropyl sulfone **6a** and 2-naphthaldehyde. The results are displayed in Table 3. All reactions were performed under Barbier conditions;[7] i.e., base was added to a solution of 1 molar equiv of aldehyde and 1.2−1.5 molar equiv of sulfone (and additive, when used).

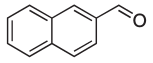
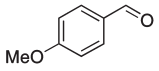
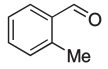
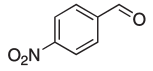
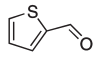
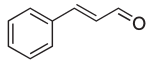
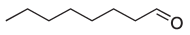
Use of LHMDS as base in THF at 0 °C gave the condensation product in a high 90% yield with an E/Z ratio of 59/41 (entry 1, Table 3). Increasing the amount of base (entry 2) or decreasing reaction temperature (entry 3) had no effect on either the E/Z ratio or the yield. The change of solvent to the more polar DMF reversed the E/Z ratio (43/57, entry 4). Addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) increased the *Z*-selectivity (entry 5, 34% yield), and the yield improved upon increasing the amount of base (entry 6, 82%). A similar result was obtained when HMPA was used as additive (entry 7). An additional increase in *Z*-selectivity was observed upon use of HMPA or DMPU alone as solvent (entries 8 and 9). Condensation in the presence of $BF_3\cdot OEt_2$ produced no stereoselection. High *Z*-selectivity was observed in THF at rt in the presence of anhydrous $MgBr_2$ (entry 11) or $MgBr_2\cdot OEt_2$ (entry 12), and this decreased with a decrease in temperature (entry 13). Next, the effect of various bases on selectivity and yield of condensations was tested. Marginal *Z*-selectivity was observed with phosphazene base P_2-Et (entry 14), and this selectivity increased to 24/76 when the phosphazene base P_4-*t*-Bu was used (entries 15 and 16).

The role of counterion on stereoselectivity has been demonstrated in LHMDS, KHMDS, and NaHMDS mediated condensations of unfluorinated *n*-alkyl PT-sulfones with *n*-alkanals.[17] An increase in *E*-selectivity was observed in solvents of higher polarity/coordinating capability. High *E*-selectivity was obtained when KHMDS/THF was used, and this improved in DME;[17] similar high trans selectivity was also observed in the reaction of unfluorinated *n*-alkyl PT-sulfone with benzaldehyde.[16] In the present case, the use of KHMDS or NaHMDS in DME showed modest *E*-selectivity (cis arrangement of alkyl and aryl moieties) similar to that obtained when LHMDS/THF was used (entries 17 and 18, compare to entries 1 and 2), and gave the product in a poor 39% yield. The use of KHMDS/THF instead improved the yield to 75% (entry 19). A further increase in *E*-selectivity was achieved by lowering the reaction temperature (73/27, entry 20). From the results in Table 3 it can be concluded that the use of polar solvents or additives (DMPU, HMPA, $MgBr_2$) favors *Z*-selectivity. Lower temperature and KHMDS as base gave highest *E*-selectivity (cis arrangement of the alkyl and aryl groups), opposite to what was observed

(24) (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773. (b) Albrecht, B. K.; Williams, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11949–11954.

TABLE 4. Study of *E*/*Z*-Stereoselectivity in the Condensations of 6a−c with Various Aldehydes



entry	R_1CHO	sulfone	time (h)	product: (%) *E*/*Z* ratio[a]	yield (%)[b]
1		**6a**	4.5	**7a**: 14/86	94
2		**6b**	2.5	**7b**: 38/62	70
3		**6c**	3	**7c**: 16/84	78
4		**6a**	3	**8a**: 3/97	87
5		**6b**	2	**8b**: 5/95	57
6		**6c**	2	**8c**: < 1/99	60
7		**6a**	4	**9a**: 18/82	77
8		**6b**	2	**9b**: 50/50	72
9		**6c**	3	**9c**: 28/72	77
10		**6a**	3	**10a**: 50/50	66
11		**6b**	2.5	**10b**: 73/27	45
12		**6c**	3	**10c**: 73/27	61
13		**6a**	4	**11a**: 1/99	75
14		**6b**	2	**11b**: 9/91	60
15		**6c**	3.5	**11c**: *Z* only	78
16		**6a**	4	**12a**: 19/81	72
17		**6b**	1.5	**12b**: 49/51	53
18		**6c**	2.5	**12c**: 38/62[c]	NA[c]
19		**6a**	2	**13a**: 44/56	71
20		**6b**	2.5	**13b**: 42/58	63
21		**6c**	2	**13c**: 80/20	63

[a]Relative ratio of diastereomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation. [b]Yields of isolated, purified products. [c]Ratio of isomers determined by ratio of *E*/*Z* doublets in ^{19}F NMR; pure product could not be isolated due to decomposition upon chromatography on both SiO_2 and Al_2O_3.

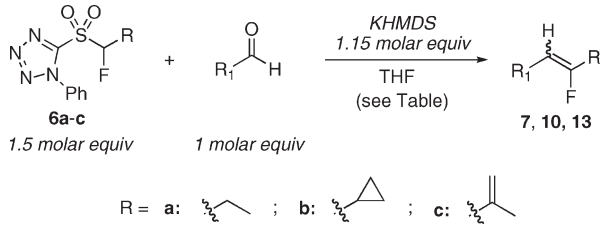
in reaction of unfluorinated *n*-alkyl PT-sulfone with benzaldehyde (trans disposition of alkyl and phenyl groups).[16]

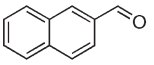
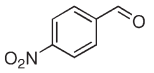
Next, the generality of the *Z*-stereoselective condensation of **6a** with 2-naphthaldehyde observed in the presence of $MgBr_2 \cdot OEt_2$ (Table 3, entry 12) was tested with a series of aldehydes. Condensations of (cyclopropyl)fluoromethyl PT-sulfone **6b** and of 1-fluoro-2-methyl-2-propenyl PT-sulfone **6c** with various aldehydes were performed as well. The results of the condensations are shown in Table 4. Similarly, the generality of *E*-selective condensation of 2-naphthaldehyde (KHMDS/THF, −78 °C, entry 20, Table 1) was also tested in reactions of **6a**−**c** with a series of aldehydes (Table 5).

From the results in Tables 4 and 5 it is observed that the stereoselectivity depends highly on the reagent, as well as the aldehyde. The following conclusions can be drawn from the two tables.

LHMDS/$MgBr_2 \cdot OEt_2$-Mediated Condensations. With the *n*-propyl olefination substrate **6a**, reactions are *Z*-selective under these conditions (Table 4) for electron-rich (entries 1, 4, 13) and hindered aromatic aldehydes (entry 7) as well as cinnamaldehyde (entry 16). For the electron-poor aromatic aldehyde and *n*-octanal (entries 10 and 19), condensations are not stereoselective. Reactions of cyclopropyl derivative **6b** show moderate to good *Z*-selectivity with electron-rich aromatic aldehydes (entries 2, 5, and 14), *E*-selectivity in the case of *p*-nitrobenzaldehyde (entry 11), and no stereoselectivity for the hindered *o*-methylbenzaldehyde, cinnamaldehyde, and *n*-octanal (entries 8, 17, and 20,

TABLE 5. Low-Temperature Condensations of 6a−c Using KHMDS/THF[a]



entry	R_1CHO	sulfone	T (°C), time (h)	product: (%) *E*/*Z* ratio[b]	yield (%)[c]
1		**6a**	–78-(–60), 2	**7a**: 73/27	64
2		**6b**	–78-(–60), 2	**7b**: 50/50	83
3		**6c**	–78-(–60), 2	**7c**: 46/54	73
4		**6a**	–78-(–60), 3.5	**10a**: 67/33	90
5		**6b**	–78-(–60), 2.5	**10b**: 67/33	71
6		**6a**	–78-(–60), 2.5	**13a**: 27/73	74
7		**6b**	–78-(–60), 2.5	**13b**: 36/64	72
8		**6c**	–78-(–60), 2.5	**13c**: 50/50	83

[a]Reactions were performed under Barbier conditions (ref 7). [b]Relative ratio of diastereomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation. [c]Yields of isolated, purified products.

respectively). With the 2-methyl-2-propenyl derivative **6c**, good to excellent *Z*-stereoselectivity was observed under the LHMDS/$MgBr_2 \cdot OEt_2$-mediated conditions with electron-rich aromatic systems and the sterically hindered *o*-methylbenzaldehyde (entries 3, 6, 9, and 15), whereas moderate *Z*-selectivity was observed with cinnamaldehyde (entry 18). In contrast, reactions with *p*-nitrobenzaldehyde and *n*-octanal were *E*-selective (Table 4, entries 12 and 21).

KHMDS-Mediated Condensations. Condensations of **6a** mediated by KHMDS at low temperature (Table 5) are *E*-selective with electron-rich and electron-poor aromatic aldehydes (entries 1 and 4) and *Z*-selective with *n*-octanal (entry 6). The selectivity with *n*-octanal parallels that observed by Blakemore et al. in reactions of unfluorinated PT-sulfones (trans disposition of alkyl chains).[17] Condensations of **6b** showed no stereoselectivity in the reaction of 2-naphthaldehyde, moderate *E*-selectivity with *p*-nitrobenzaldehyde, and moderate *Z*-selectivity with *n*-octanal (entries 2, 5, 7). The two KHMDS-mediated low-temperature condensations of **6c** with 2-naphthaldehyde and *n*-octanal were not stereoselective (Table 5, entries 3, 8).

No further attempts were made to optimize condensation conditions for each specific reagent. However, there is the possibility of tuning the condensation toward *E*- or *Z*-stereoselectivity by modulation of reaction conditions in several cases.

Finally, reactivity of ketones with **6a** and **6b** was tested. Condensation reactions proceeded with dialkyl, alkyl aryl, as well as diaryl ketones. The yield strongly depended on stoichiometry of reagents, and typically, best yields were obtained when the molar equivalence of ketone/sulfone/LHMDS was 1:2:3 (compare entries 1 and 2, 3 and 4, 5 and 6, and 7 and 8). For unsymmetrical ketones acetophenone and 1-indanone, stereochemistry of the major isomer formed in the condensations with **6a** was determined by NOESY. In both cases, condensations were *E*-selective.

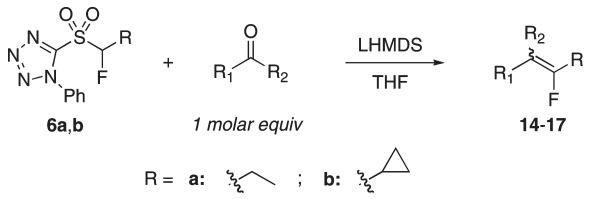
Conclusions

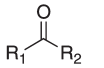
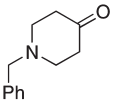
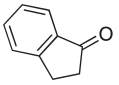
In conclusion, a series of phenyltetrazolyl fluoroalkyl sulfones has been prepared via metalation−fluorination. Successful fluorination of the structurally different *n*-propyl, (cyclopropyl)methyl, 2-methyl-2-propenyl, and 5-hexenyl 1-phenyl-1*H*-tetrazol-5-yl sulfones demonstrates generality of the approach. Metalation−fluorination of *n*-alkyl and (cyclopropyl)methyl sulfones proceeds under homogeneous conditions, whereas fluorination of 2-methyl-2-propenyl PT-sulfone requires heterogeneous fluorination conditions. The fluorinated PT-sulfones undergo condensation reactions with aldehydes to give α-fluoroalkylidenes in high yields. Screening of olefinations with a series of aldehydes showed that stereoselectivity depended on both, the structure of PT-sulfone as well as the aldehyde. Reaction conditions can in many cases be modulated toward *E*- or *Z*-selectivity. Condensations also proceeded with dialkyl, aryl alkyl, and diaryl ketones, and the products were isolated in yields ranging from 71 to 99%.

Experimental Section

5-{[(Cyclopropyl)methyl]sulfanyl}-1-phenyl-1*H*-tetrazole (4b). (Bromomethyl)cyclopropane: 2.11 g (15.6 mmol); DMF: 78 mL; sodium salt of 1-phenyl-1*H*-tetrazol-5-thiol (4.07 g, 20.3 mmol); reaction time 5 h; extraction: EtOAc (3 × 150 mL). Yield: 3.55 g (98%) of white solid **4b**. Mp (recrystallized from 50% CH_2Cl_2 in

TABLE 6. Reactivity of 6a and 6b with Ketones[a]



entry	 limiting	sulfone: molar equiv	LHMDS: molar equiv	T (°C), time (h)	product: yield (%)[b]	(%) isomer ratio[c]
1		**6a**: 1.2	1.3	0, 2	**14a**: 39	NA
2		**6a**: 2	3	0, 2	**14a**: 77	NA
3		**6b**: 1.2	1.3	0, 2	**14b**: 40	NA
4		**6b**: 2	3	0, 1.5	**14b**: 71	NA
5		**6a**: 1.2	1.3	0, 1.5; rt, 1	**15a**: 64	NA
6		**6a**: 2	3	0, 2	**15a**: 99	NA
7		**6b**: 1.2	1.3	0, 2.5	**15b**: 23	NA
8		**6b**: 2	3	0, 2	**15b**: 91	NA
9		**6a**: 1.2	2.4	0, 2	**16a**: 88	26/74[d]
10		**6b**: 1.2	2.4	0, 3	**16b**: 96	25/75
11		**6a**: 1.2	2.4	0, 2	**17a**: 77	78/22[e]
12		**6b**: 1.2	2.4	0, 3	**17b**: 88	78/22

[a]Reactions were performed under Barbier conditions (ref 7). [b]Yields of isolated, purified products. [c]Relative ratio of isomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation (more downfield: more upfield resonance). [d]Stereochemistry of major isomer was determined by NOESY; *E*/*Z* 74/26. [e]Stereochemistry of major isomer was determined by NOESY; *E*/*Z* 78/22.

hexanes): 53−54 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.60−7.52 (m, 5H, Ar-H), 3.35 (d, 2H, J = 7.3), 1.30−1.22 (m, 1H), 0.71−0.61 (m, 2H), 0.42−0.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 133.9, 130.2, 129.9, 124.0, 39.7, 10.6, 6.4. HRMS (APCI): calcd for $C_{11}H_{13}N_4S$ $[M + H]^+$ 233.0855, found 233.0859.

5-[(5-Hexenyl)sulfanyl]-1-phenyl-1*H*-tetrazole (4d). 6-Bromo-1-hexene: 1.00 g (6.13 mmol); DMF: 30.6 mL; sodium salt of 1-phenyl-1*H*-tetrazol-5-thiol (1.60 g, 7.97 mmol); reaction time 5.5 h; extraction: EtOAc (3 × 100 mL). Yield: 1.58 g (99%) of colorless oily **4d**. ^1H NMR (500 MHz, $CDCl_3$): δ 7.59−7.52 (m, 5H, Ar-H), 5.78 (ddt, 1H, J=17.0, 10.1, 6.9), 5.01 (dd, 1H, J = 17.0, 1.4), 4.96 (br d, 1H, J = 10.1), 3.40 (t, 2H, J = 7.4), 2.10 (q, 2H, J = 7.2), 1.84 (quint, 2H, J = 7.4), 1.55 (quint, 2H, J = 7.4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 138.1, 133.8, 130.2, 129.9, 123.9, 115.1, 33.2, 33.1, 28.6, 27.8. HRMS (APCI): calcd for $C_{13}H_{17}N_4S$ $[M + H]^+$ 261.1168, found 261.1171.

5-{[(Cyclopropyl)methyl]sulfonyl}-1-phenyl-1*H*-tetrazole (5b). Sulfide **4b**: 3.55 g (15.3 mmol) in $CHCl_3$ (45.2 mL); *m*-CPBA: 7.91 g (45.9 mmol, 3.0 molar equiv) in $CHCl_3$ (106 mL); extraction: CH_2Cl_2 (3 × 50 mL). Yield of **5b**: 3.59 g (89%) of a white solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 54−55 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.70−7.68 (m, 2H, Ar-H), 7.65−7.59 (m, 3H, Ar-H), 3.67 (d, 2H, J = 6.9), 1.31−1.24 (m, 1H), 0.79−0.69 (m, 2H), 0.53−0.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 133.3, 131.7, 129.9, 125.5, 61.6, 4.8, 3.8. HRMS (APCI): calcd for $C_{11}H_{13}N_4O_2S$ $[M + H]^+$ 265.0754, found 265.0758.

5-[(2-Methyl-2-propenyl)sulfonyl]-1-phenyl-1*H*-tetrazole (5c). Sulfide **4c**: 1.50 g (6.47 mmol, 1.0 molar equiv); $Mo_{27}O_{24}(NH_4)_6.4H_2O$: 0.652 g (0.527 mmol); EtOH: 130 mL; H_2O_2 (50% in water): 3.63 mL (64.6 mmol, 10 molar equiv); extraction: EtOAc (3 × 150 mL). Yield of **5c**: 1.14 g (66%) of white solid. Mp: (recrystallized from 50% CH_2Cl_2 in hexanes) 72−73 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64−7.58 (m, 5H, Ar-H), 5.27 (d, 1H, J = 1.0), 5.15 (d, 1H, J = 1.0), 4.40 (s, 2H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 133.2, 131.7, 130.7, 129.8, 125.5, 123.7, 63.8, 23.2. HRMS (APCI): calcd for $C_{11}H_{13}N_4O_2S$ $[M + H]^+$ 265.0754, found 265.0758.

General Procedure for Fluorination of Alkyl 1-Phenyl-1*H*-tetrazol-5-yl Sulfones 5a−d. Method A. A solution of sulfone **5a−c** (1 molar equiv) in dry toluene was cooled to −78 °C (dry ice/*i*-PrOH) under nitrogen. LDA (2 M solution in heptane/THF/EtPh, 1.05 molar equiv for **5a** and **5b**, 1.1 molar equiv for **5c**) was added to the reaction mixture. After 12 min, solid NFSI (1.25 molar equiv) was added, the mixture was allowed to stir at −78 °C for 50 min and warmed to rt, and stirring was continued for an additional 50 min. Saturated aq NH_4Cl was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3×), and the combined organic layer was washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixtures were

purified by column chromatography on silica gel, and the product was eluted by 10% EtOAc in hexanes (**5a** and **5b**) or CH_2Cl_2 (**5c**).

Method B. A solution of sulfone **5a**, **5b**, or **5d** (1 molar equiv) in dry THF was cooled to −78 °C (dry ice/*i*-PrOH) under nitrogen. LDA (1.10 molar equiv, 2 M solution in heptane/THF/EtPh) was added to the reaction mixture. After 15 min, a solution of NFSI (1.25 molar equiv) in dry THF (1.3 mL per mmol of sulfone) was added, the mixture was allowed to stir at −78 °C for 50 min and then warmed to rt, and stirring was continued for an additional 50 min. Saturated aq NH_4Cl was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3×), and the combined organic layer was washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixtures were purified by column chromatography on silica gel with 10% EtOAc in hexanes as eluting solvent. For each substrate, the amount of substrate, reagents, and solvent and product yield are given under the specific compound heading below.

5-[(1-Fluoropropyl)sulfonyl]-1-phenyl-1*H*-tetrazole (6a). (Method A) Sulfone **5a**: 1.00 g (3.97 mmol, 1 molar equiv); toluene: 12 mL; LDA: 2.08 mL (4.17 mmol, 1.05 molar equiv, 2 M solution in heptane/THF/EtPh); NFSI: 1.56 g (4.94 mmol, 1.25 molar equiv); extraction: EtOAc (3 × 50 mL). Yield of **6a**:[10d] 760 mg (71%) of a white solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 77−78 °C. (Method B) Sulfone **5a**: 1.00 g (3.97 mmol, 1 molar equiv) in THF (8 mL); NFSI: 1.56 g (4.94 mmol, 1.25 molar equiv) in THF (5 mL). Yield of **6a**:[10d] 722 mg (67%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67−7.60 (m, 5H, Ar-H), 5.81 (ddd, 1H, J = 47.9, 9.2, 3.7), 2.37−2.11 (m, 2H), 1.23 (t, 3H, J = 7.6). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8, 133.0, 131.9, 129.8, 125.8, 104.2 (d, J_{CF} = 224.7), 20.3 (d, J_{CF} = 19.2), 8.71 (d, J_{CF} = 3.2). ^{19}F NMR ($CDCl_3$): δ −178.8 (ddd, J_{FH} = 48.8, 33.6, 15.3). HRMS (APCI): calcd for $C_{10}H_{12}FN_4O_2S$ $[M + H]^+$ 271.0660, found 271.0656.

5-{[(Cyclopropyl)fluoromethyl]sulfonyl}-1-phenyl-1*H*-tetrazole (6b). (Method B) Sulfone **5b**: 1.00 g (3.79 mmol, 1 molar equiv) in dry THF (7 mL); NFSI: 1.49 g (4.73 mmol, 1.25 molar equiv) in THF (5 mL); LDA: 2.08 mL (4.17 mmol, 1.10 molar equiv); extraction: EtOAc (3 × 50 mL). Yield of **6b**: 616 mg (58%) of a white solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 72−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67−7.60 (m, 5H, Ar-H), 5.28 (dd, 1H, J = 47.2, 8.5), 1.57−1.48 (m, 1H), 1.04−0.85 (m, 3H), 0.79−0.74 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.0, 133.1, 131.8, 129.8, 125.8, 106.4 (d, J_{CF} = 225.2), 7.1 (d, J_{CF} = 23.8), 3.7, 3.4 (d, J_{CF} = 7.3). ^{19}F NMR ($CDCl_3$): δ −169.8 (dd, J_{FH} = 47.3, 10.7). HRMS (APCI): calcd for $C_{11}H_{12}FN_4O_2S$ $[M + H]^+$ 283.0660, found 283.0664. For fluorination of **5b** using method A and spectral data of **6b-FD**, see the Supporting Information.

5-[(1-Fluoro-2-methyl-2-propenyl)sulfonyl]-1-phenyl-1*H*-tetrazole (6c). (Method A) Sulfone **5a**: 1.00 g (4.02 mmol, 1 molar equiv); toluene: 24.7 mL; LDA: 2.08 mL (4.17 mmol, 1.1 molar equiv); NFSI: 1.58 g (5.02 mmol, 1.25 molar equiv); extraction: EtOAc (3 × 50 mL). Yield of **6c**: 600 mg (53%) of a white solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 80−81 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67−7.60 (m, 5H, Ar-H), 6.26 (d, 1H, J_{HF} = 46.2), 5.59 (narrow m, 1H), 5.54 (narrow m, 1H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 133.0, 131.9, 131.2 (d, J_{CF} = 17.8), 129.8, 125.8, 124.5 (d, J_{CF} = 8.7) 104.1 (d, J_{CF} = 226.6), 18.6 (d, J_{CF} = 3.2). ^{19}F NMR ($CDCl_3$): δ −172.2 (d, J_{FH} = 48.8). HRMS (APCI): calcd for $C_{11}H_{12}FN_4O_2S$ $[M + H]^+$ 283.0660, found 283.0660.

5-[(1-Fluoro-5-hexenyl)sulfonyl]-1-phenyl-1*H*-tetrazole (6d). (Method B) Sulfone **5d**: 300 mg (1.03 mmol, 1 molar equiv) in THF (1.63 mL); NFSI: 405 mg (1.28 mmol, 1.25 molar equiv) in THF (1.35 mL); LDA: 0.565 mL (1.13 mmol, 1.10 molar equiv); extraction: EtOAc (3 × 30 mL). Yield of **6d**: 208 mg (65%) of a white solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 42−43 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66−7.59 (m, 5H, Ar-H), 5.86 (ddd, 1H, J = 48.3, 9.7, 3.2), 5.76 (ddt, 1H, J = 17.0, 10.1, 6.7), 5.07−5.02 (m, 2H), 2.30−2.06 (m, 4H), 1.81−1.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8, 136.9, 133.0, 131.9, 129.8, 125.8, 116.4, 103.3 (d, J_{CF} = 224.3), 32.9, 25.7 (d, J_{CF} = 19.2), 23.4 (d, J_{CF} = 1.8). ^{19}F NMR ($CDCl_3$): δ −177.5 (ddd, J_{FH} = 48.8, 33.6, 15.3). HRMS (APCI): calcd for $C_{13}H_{16}FN_4O_2S$ $[M + H]^+$ 311.0973, found 311.0972.

Representative Procedure for Condensations of 6a−c Using LHMDS/$MgBr_2\cdot OEt_2$. Condensations with 2-Thiophenecarboxaldehyde. Reaction with 6c. A mixture of 2-thiophenecarboxaldehyde (112 mg, 1 mmol), sulfone **6c** (395 mg, 1.4 mmol, 1.4 molar equiv), and $MgBr_2\cdot OEt_2$ (77.5 mg, 3 mmol, 3 molar equiv) in dry THF (12.5 mL) was allowed to stir at rt for 10 min. LHMDS (3.00 mL, 1 M solution in THF, 3.00 mmol, 3 molar equiv) was added dropwise, and stirring was continued at rt for 3 h (until complete consumption of starting material was observed by TLC). Saturated aq NH_4Cl was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure at rt. Analysis of the crude reaction mixture by ^{19}F NMR showed the presence of *Z* isomer only. The crude product was purified by column chromatography (CH_2Cl_2) to yield 131 mg (78%) of **11c** as a pale yellow oil (due to product volatility, solvent was carefully evaporated under a stream of nitrogen gas).

2-[(1*Z*)-2-Fluoro-3-methyl-1,3-butadienyl]thiophene (11c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, 1H, Ar-H, J = 5.2), 7.14 (d, 1H, Ar-H, J = 3.0), 7.03−7.02 (m, 1H, Ar-H), 6.14 (d, 1H, J_{HF} = 38.1), 5.52 (br s, 1H), 5.13−5.12 (narrow m, 1H), 1.96 (narrow m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9 (d, J_{CF} = 258.2), 136.4 (d, J_{CF} = 3.7), 134.5 (d, J_{CF} = 21.5), 127.6 (d, J_{CF} = 3.7), 127.1, 126.6 (d, J_{CF} = 9.6), 114.3 (d, J_{CF} = 6.4), 101.7 (d, J_{CF} = 14.7), 18.9 (d, J_{CF} = 3.7). ^{19}F NMR ($CDCl_3$): δ −112.7 (d, J_{FH} = 36.6). HRMS (CI): calcd for C_9H_9FS $[M]^+$ 168.0409, found 168.0421.

The crude reaction mixture obtained in reaction of **6a** and thiophene-2-carboxaldehyde showed an *E*/*Z* product ratio 1:99 that was purified by column chromatography (SiO_2, CH_2Cl_2, 75% of *E*/*Z*-**11a** as a pale yellow oil). HRMS (APPI): calcd for $C_8H_{10}FS$ $[M + H]^+$ 157.0482, found 157.0478. **2-[(*Z*)-2-Fluoro-1-butenyl]thiophene (11a).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 1H, Ar-H, J = 4.9), 7.00 (d, 1H, Ar-H, J = 3.0), 6.98−6.96 (m, 1H, Ar-H), 5.80 (d, 1H, J_{HF} = 38.5), 2.38 (dq, 2H, J = 14.8, 7.5), 1.18 (t, 3H, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4 (d, J_{CF} = 265.5), 136.3 (d, J_{CF} = 3.7), 126.7, 125.7 (d, J_{CF} = 3.7), 125.0 (d, J_{CF} = 9.2), 99.7 (d, J_{CF} = 12.8), 25.8 (d, J_{CF} = 26.6), 10.9 (d, J_{CF} = 3.7). ^{19}F NMR ($CDCl_3$): δ −97.8 (app dt, J_{FH} = 41.0, 13.5).

The crude reaction mixture obtained in reaction of **6b** and thiophene-2-carboxaldehyde showed an *E*/*Z* product ratio 9:91, that was purified by column chromatography (SiO_2, CH_2Cl_2, 60% of *E*/*Z*-**11b** as a pale yellow oil). HRMS (APPI): calcd for $C_9H_{10}FS$ $[M + H]^+$ 169.0482, found 169.0483. NMR data are reported only for the major isomer. **2-[(*Z*)-2-Fluoro-2-cyclopropyl-1-ethenyl]thiophene (11b).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20−7.18 (m, 1H, Ar-H), 6.97−6.96 (m, 2H, Ar-H), 5.88 (d, 1H, J_{HF} = 38.2), 1.67−1.57 (m, 2H), 0.87−0.79 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9 (d, J_{CF} = 260.9), 136.5 (d, J_{CF} = 4.1), 126.8, 125.3 (d, J_{CF} = 3.7), 124.7 (d, J_{CF} = 9.2), 99.2 (d, J_{CF} = 14.6), 12.7 (d, J_{CF} = 29.3), 5.4 (d, J_{CF} = 1.8). ^{19}F NMR ($CDCl_3$): δ −110.2 (dd, J_{FH} = 36.6, 18.3).

Representative Procedure for Condensations Using KHMDS/THF at Low Temperature. Condensation of 6a with 2-Naphthaldehyde. To a stirring solution of 2-naphthaldehyde (156 mg, 1 mmol) and sulfone **6a** (405 mg, 1.5 mmol) in dry THF (15.5 mL) at −78 °C was added KHMDS (2.30 mL, 0.5 M solution in

toluene, 1.15 mmol, 1.15 molar equiv) dropwise. Under stirring, the reaction temperature was allowed to increase from −78 to −60 °C over 2.0 h. The reaction was quenched with saturated aq NH_4Cl, diluted with water, and extracted with Et_2O (3 × 50 mL). The combined organic layer was thoroughly washed with water and then with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. Analysis of the crude reaction mixture by ^{19}F NMR showed the *E*/*Z* product in a 75:25 ratio. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to afford (*E*/*Z*)-**7a** as a white solid (128 mg, 64%). HRMS (APPI): calcd for $C_{14}H_{13}F$ $[M]^+$ 200.0996, found 200.0996. For ^1H NMR analysis, a small amount of the *E* and *Z* isomers was separated by column chromatography (SiO_2, hexanes). ***E*-7a.** White solid. Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 40−41 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82−7.79 (m, 3H, Ar-H), 7.63 (s, 1H, Ar-H) 7.49−7.44 (m, 2H, Ar-H), 7.32 (d, 1H, J = 8.4), 6.31 (d, 1H, J_{HF} = 21.7), 2.55 (dq, 2H, J = 23.2, 7.4), 1.24 (t, 3H, J = 7.4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2 (d, J_{CF} = 254.0), 133.6, 132.3, 132.1 (d, J_{CF} = 14.2), 128.2, 127.9, 127.8, 127.2 (d, J_{CF} = 3.2), 127.0 (d, J_{CF} = 2.3), 126.5, 126.0, 107.8 (d, J_{CF} = 28.8), 22.8 (d, J_{CF} = 27.9), 11.3. ^{19}F NMR ($CDCl_3$): δ −100.4 (app q, J_{FH} = 22.4). ***Z*-7a.** White solid. mp (recrystallized from 50% CH_2Cl_2 in hexanes) 53−54 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H, Ar-H), 7.80−7.77 (m, 3H, Ar-H), 7.65 (d, 1H, J = 8.4), 7.46−7.41 (m, 2H, Ar-H), 5.62 (d, 1H, J_{HF} = 39.5), 2.42 (dq, 2H, J = 15.1, 7.5), 1.23 (t, 3H, J = 7.6). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1 (d, J_{CF} = 266.4), 133.8, 132.4 (d, J_{CF} = 1.9), 131.7 (d, J_{CF} = 2.8), 128.2, 128.1, 127.7, 127.2 (d, J_{CF} = 7.3), 126.8 (d, J_{CF} = 7.8), 126.2, 125.8, 105.0 (d, J_{CF} = 8.7), 26.6 (d, J_{CF} = 27.5), 11.2 (d, J_{CF} = 3.2). ^{19}F NMR ($CDCl_3$): δ −100.6 (dt, J_{FH} = 39.7, 15.3).

Representative Procedure for Condensations of 6a and 6b with Ketones. Condensations with Benzophenone: Reaction with 6b. A stirring solution of benzophenone (91.0 mg, 0.50 mmol) and sulfone **6b** (282 mg, 1.00 mmol, 2 molar equiv) in dry THF (9.1 mL) was cooled to 0 °C under nitrogen gas. LHMDS (1.5 mL, 1.5 mmol, 3.0 molar equiv of 1 M solution in THF) was added, and the reaction mixture was allowed to stir at 0 °C until complete consumption of benzophenone was observed by TLC (2.0 h). The reaction was quenched with saturated aq NH_4Cl at rt, diluted with water, and extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to yield **15b** as a white solid (109 mg, 91%). Mp (recrystallized from 50% CH_2Cl_2 in hexanes): 43−44 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38−7.23 (m, 9H, Ar-H), 7.20−7.18 (m, 1H, Ar-H), 1.69 (dm, 1H, J_{HF} = 27.6), 0.98−0.89 (m, 2H), 0.75−0.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1 (d, J_{CF} = 255.9), 139.2 (d, J_{CF} = 8.2), 138.3, 131.1 (d, J_{CF} = 2.8), 129.7 (d, J_{CF} = 5.0), 128.5, 128.1, 127.2, 126.7, 119.1 (d, J_{CF} = 16.9), 11.4 (d, J_{CF} = 27.0), 5.7 (d, J_{CF} = 2.3). ^{19}F NMR ($CDCl_3$): δ −125.4 (d, J_{FH} = 27.5). HRMS (APPI): calcd for $C_{17}H_{15}F$ $[M]^+$ 238.1152, found 238.1148.

Reaction with 6a. The crude reaction mixture obtained in the reaction of **6a** and benzophenone was purified by column chromatography (SiO_2, CH_2Cl_2) to yield 75% of **15a** as a clear thick liquid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, 2H, Ar-H, J = 7.1), 7.30−7.25 (m, 5H, Ar-H), 7.21−7.18 (m, 3H, Ar-H), 2.32 (dq, 2H, J = 23.0, 7.4), 1.15 (t, 3H, J = 7.4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (d, J_{CF} = 261.4), 139.4 (d, J_{CF} = 8.2), 137.9, 130.4 (d, J_{CF} = 2.7), 129.8 (d, J_{CF} = 5.0), 128.6, 128.1, 127.4, 126.9, 119.9 (d, J_{CF} = 15.1), 24.2 (d, J_{CF} = 27.9), 11.7. ^{19}F NMR ($CDCl_3$): δ −108.44 (d, J_{FH} = 24.4). HRMS (APPI): calcd for $C_{16}H_{15}F$ $[M]^+$ 226.1152, found 226.1155.

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Supporting Information Available: Synthetic procedures for **1** and **2**; fluorination of **2a**,**b**; general synthetic procedures for **4a**−**d** and **5a**−**d**; fluorination of **5b** using method A; spectral data for **1**, **2**, **3a**, **3a-FD**, **3b-FD**, **4a**,**c**, **5a**,**d**, and **6b-FD**; ^{19}F and HRMS data of **7**−**17**; ^{13}C data of *Z*-**8** and **14**; copies of ^1H and ^{13}C spectra of **3a**, **3a-FD**, **3b-FD**, **4b**,**d**, **5b**,**c**, **6**, and **6b-FD**; *E*- and *Z*-**7a**, *Z*-**11a**, *Z*-**11c**, **14**, and **15**; and copies of ^1H NMR spectra of **1**, **2**, **4a**,**c**, **5a**,**d**, **7**−**11**, **12a**,**b**, and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.