

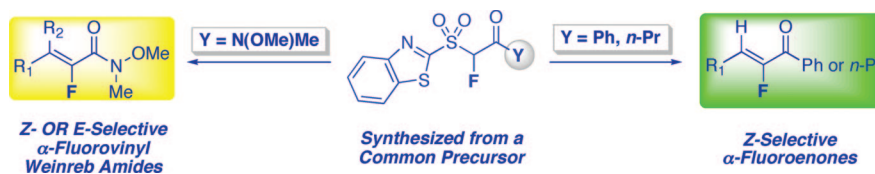
α -Fluorovinyl Weinreb Amides and α -Fluoroenones from a Common Fluorinated Building Block

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Synthesis and reactivity of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfonyl)fluoroacetamide, a building block for Julia olefination, is reported. This reagent undergoes condensation reactions with aldehydes and cyclic ketones to give α -fluorovinyl Weinreb amides. Olefination reactions proceed under mild, DBU-mediated conditions, or in the presence of NaH. DBU-mediated condensations proceed with either *E*- or *Z*-selectivity, depending upon reaction conditions, whereas NaH-mediated reactions are $\geq 98\%$ *Z*-stereoselective. Conversion of the Weinreb amide moiety in *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide to ketones, followed by oxidation, resulted in another set of olefination reagents, namely (1,3-benzothiazol-2-ylsulfonyl)fluoromethyl phenyl and propyl ketones. In the presence of DBU, these compounds react with aldehydes tested to give α -fluoroenones with high *Z*-selectivity. The use of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide as a common fluorinated intermediate in the synthesis of α -fluorovinyl Weinreb amides and α -fluoroenones has been demonstrated. Application of the Weinreb amide to α -fluoro allyl amine synthesis is also shown.

Introduction

Fluorine-containing organic molecules are of high interest, due to altered physical, biological, and chemical properties caused by fluorine atom introduction.¹ One of the approaches for the synthesis of fluorinated compounds is via the use of appropriate fluorinated building blocks.² Among various fluoroorganics, functionalized fluoroolefins have been the subject of many investigations, either as end products or as synthetic intermediates. A convenient route for olefination is via the

modified Julia reaction.^{3,4} However, this method has not received much attention for the synthesis of vinyl fluorides until recently. Application of this reaction for the preparation of fluoroalkylidenes was initially demonstrated by using a single olefination precursor.⁵ We were the first to utilize metalation–fluorination as a general approach for the preparation of novel Julia reagents for the synthesis of functionalized fluoroolefins.^{6–9} Various functionalized fluoroolefins are now conveniently accessible by the Julia–Kocienski olefination.^{6–11} In our work,

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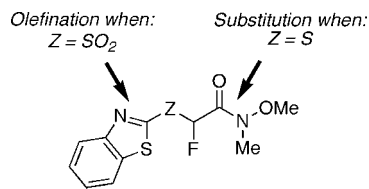


FIGURE 1. Fluorinated Julia–Weinreb Amide Building Block

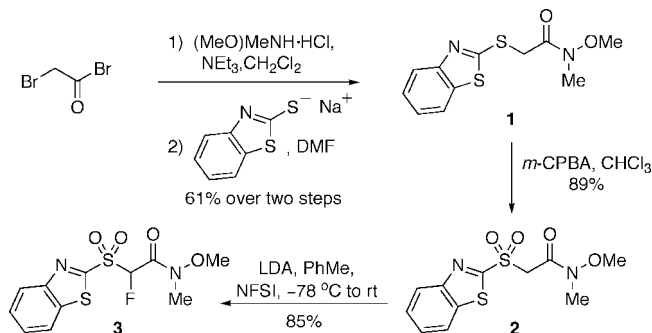
we have developed a series of isolable and stable fluorinated reagents that have yielded facile access to α -fluorostilbene and styrene derivatives,⁶ α -fluoroacrylates,⁷ α -fluorovinyl sulfones,⁸ and α -fluoroacrylonitriles.⁹

On the basis of our previous results, we became interested in the development and use of functionalized fluorinated building blocks that would allow synthesis of various Julia olefination reagents from common precursors. Among the various functional groups, the (*N*-methoxy-*N*-methyl) amide moiety can be easily converted to α -fluoro ketones and α -fluoro aldehydes, and is a useful synthetic intermediate in organic synthesis.¹² An appropriate heteroaryl derivative, such as *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfonyl)fluoroacetamide, or its precursor *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide would therefore offer two potential sites for modification (Figure 1). The benzothiazolyl sulfone moiety would provide one point of diversity, namely olefination,^{3,4} and the amide part would provide the second point of diversity by virtue of its reactivity toward metal alkyls and hydride reducing agents.¹² A two-step synthesis of a fluorovinyl Weinreb amide has been reported from tetrafluoroethane (HFC-134a), albeit in a low 30% yield.¹³ An example of the Weinreb–Wittig–Horner reagent (EtO)₂P(O)CHFC(O)NMe(OMe) has been reported as well; however, no details on its synthesis, characterization, and reactivity were provided.¹⁴

Recently, Aidhen et al. reported synthesis and NaH-mediated condensation reactions of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfonyl)acetamide with aldehydes, leading to vinyl Weinreb amides via Julia olefination.¹⁵ While this work was in progress, syntheses of α,β -unsaturated Weinreb amides¹⁶ and the α -fluoro analogues¹¹ were reported with use of 3,5-bis(trifluoromethyl)phenyl sulfones.

Herein, we present our synthesis of the benzothiazolyl-based fluoro Julia–Weinreb amide reagent and study of its reactions at both reactive centers. Specifically, reactions at the amide functionality of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide, followed by oxidation, led to a second set of Julia olefination reagents that were also subjected to condensation reactions to give α -fluoroenones. The effect of reaction conditions on olefination selectivity under mild, DBU-mediated conditions as well as with NaH is presented. Finally, the utility of the fluoro Julia–Weinreb amide building block for the synthesis of fluoroallyl amines, a class of dipeptide

SCHEME 1. Synthesis of Fluoro Julia–Weinreb Reagent



isosteres,¹ is demonstrated by a concise synthesis of a known dipeptidyl peptidase II inhibitor.¹⁷

Results and Discussion

At the outset, synthesis of a suitable reagent for Julia–Kocienski olefination^{3,4} was undertaken. Stabilized carbanions derived from 1,3-benzothiazol-2-yl (BT) sulfone derivatives have been successfully used by us in fluoro Julia olefination reactions.^{7–9} Thus, we sought the synthesis of a Weinreb amide derivative based on the benzothiazolyl moiety.

As shown in Scheme 1, the known BT-sulfide **1**¹⁵ was prepared by reaction of the sodium salt of 2-mercapto-1,3-benzothiazole with 2-bromo-*N*-methoxy-*N*-methylacetamide¹⁸ (prepared from bromoacetyl bromide and (MeO)MeNH·HCl). Oxidation of BT-sulfide **1** with *m*-CPBA yielded the known sulfone **2**¹⁵ (Scheme 1). Metalation–fluorination of sulfone **2** with LDA and *N*-fluorodibenzene-sulfonimide (NFSI) in toluene resulted in the monofluoro derivative **3** in 85% yield.

With the desired fluoro Julia–Weinreb reagent **3** in hand, we screened the reactivity of the reagent. Various reaction conditions and additives were tested in condensation reactions of 2-naphthaldehyde (Table 1). All DBU-mediated reactions were performed under Barbier conditions,⁴ whereas when NaH was used as base, 2-naphthaldehyde was added to a mixture of sulfone and NaH.

Wide changes in stereoselectivity were observed depending upon reaction solvent, reaction temperature, and the additive. Good yield and moderate *Z*-selectivity was observed in the DBU-mediated condensation in CH₂Cl₂ at room temperature, but there was no selectivity when the reaction was performed at -78 °C (entries 1 and 2). Higher *Z*-selectivity was obtained in THF at room temperature (entry 3) and this increased at -78 °C (entry 4), and products were isolated in good yields in both cases. Room temperature olefination in toluene resulted in a marginal increase in *Z*-selectivity (entry 5) compared to the room temperature reaction in THF (entry 3); however, the reaction was much slower, with approximately 95% conversion after 48 h. Changing the reaction solvent to DMF resulted in a reversal of selectivity with the *E*-isomer predominating, but the *E/Z* ratio was unaffected by a change in the reactant stoichiometry (entries 6 and 7). Highest *E*-selectivity was obtained in DMPU, and the *E/Z* product mixture was isolated in a high 93% yield (entry 8). Lowering of reaction temperature to -78 °C in a 1:1 mixture of DMF and DMPU (to prevent freezing) again

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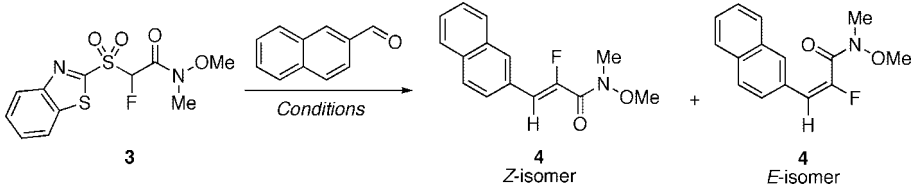
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TABLE 1. Effect of Reaction Conditions on Condensation Reactions of **3** with 2-Naphthaldehyde


entry	base	solvent	aldehyde:sulfone: base (molar equiv)	additive (molar equiv)	<i>T</i> , rxn time (h)	(%) <i>E/Z</i> ratio; ^a yield ^b
1	DBU	CH ₂ Cl ₂	1.0:1.2:4.0		rt, 2	33/67; 90%
2	DBU	CH ₂ Cl ₂	1.0:1.2:4.0		−78 °C, 3.5	50/50; 96%
3	DBU	THF	1.0:1.2:4.0		rt, 2	19/81; 84%
4	DBU	THF	1.0:1.2:4.0		−78 °C, 4	4/96; 84%
5	DBU	PhMe	1.0:1.2:4.0		rt, 48	16/84; NA ^c
6	DBU	DMF	1.0:1.3:2.6		rt, 20	74/26; NA ^c
7	DBU	DMF	1.3:1.0:2.0		rt, 15	74/26; NA ^c
8	DBU	DMPU	1.3:1.0:2.0		rt, 17	78/22; 93%
9	DBU	DMF-DMPU ^d	1.3:1.0:2.0		−78 °C, 3.5	25/75; NA ^c
10	DBU	DMPU	1.3:1.0:2.0		75 °C, 2.5	78/22; NA ^c
11	DBU	THF	1.0:1.3:3.9	MgBr ₂ (1.8)	rt, 48	10/90; 78%
12	DBU	THF	1.2:1.0:3.0	MgBr ₂ (1.4)	rt, 48	7/93; 78%
13	DBU	THF	1.2:1.0:3.0	ZnBr ₂ (1.4)	rt, 48	15/85; 74%
14	NaH	THF	1.0:1.3:2.6		rt, 20; 70 °C, 2	Only Z, 84%
15	NaH	THF	1.0:2.0:4.0		rt, 1	Only Z, 90%
16	NaH	THF	1.0:2.0:4.0	18-Crown-6 (6.0)	rt, 1.5	40/60; NA ^c
17	NaH	THF	1.0:2.0:4.0	15-Crown-5 (6.0)	rt, 1.5	12/88; NA ^c
18 ^e	K ₂ CO ₃	DMF	1.0: 2.0:18.0	TBAB (0.2)	rt, 18	55/45; NA ^c

^a Relative ratio of diastereomers in the crude reaction mixture determined by ¹⁹F NMR prior to isolation. No change in ratio was observed after purification. ^b Yields of isolated, purified products. ^c Product not isolated from reaction mixture. ^d A 1:1 mixture of DMF and DMPU was used to prevent freezing at −78 °C. ^e Reaction conditions were identical with those described in ref 11.

avored formation of the *Z*-isomer (entry 9). An increase in reaction temperature from room temperature to 75 °C did not affect the olefination selectivity in DMPU (compare entries 8 and 10).

Next, reactions were performed in the presence of salt additives. The role of MgBr₂ additive on the stereochemical outcome of Julia olefination with benzothiazolyl derived reagents has recently been demonstrated in the synthesis of α -fluoroacrylates.¹⁰ In the present case, a room temperature reaction in THF, in the presence of MgBr₂ resulted in an increased *Z*-selectivity, whereas a change in the reactant stoichiometry had little effect on olefination selectivity and yield (entries 11 and 12). Addition of ZnBr₂ showed only a marginal increase in selectivity (compare entries 3 and 13). Finally, the use of NaH as base in THF resulted in the exclusive formation of the *Z*-isomer (entries 14 and 15). Under these conditions the rate of the reaction and yield increased with higher molar excess of sulfone and NaH (entry 15). To assess whether there was any influence of the cation on the stereoselectivity, condensations were performed in the presence of an excess of 18-Crown-6 and 15-Crown-5, using NaH. In both cases, a decrease of stereoselectivity was observed, which was more pronounced for 18-Crown-6 (entries 16 and 17). This indicates that the counterion likely also plays a role in the stereoselection. The DBU/MgBr₂/THF result (entries 11 and 12) is also consistent with this observation. Finally, in order to compare the condensation reactivity of **3** with 2-naphthaldehyde to that of the recently described 3,5-bis(trifluoromethyl)phenyl sulfone based reagent,¹¹ a reaction was performed under the reported conditions¹¹ (entry 18). Under these conditions, no stereoselectivity was obtained in the reaction with **3**, likely indicating a link between aryl or heteroarylsulfonyl moiety and the mechanistic path, leading to markedly different stereochemical results.

Although we identified reaction conditions that gave exclusive *Z*-selectivity, we wanted to assess whether the mild DBU-mediated olefinations, which gave condition dependent complementary olefination products with 2-naphthaldehyde, would be applicable to other substrates as well. Table 2 shows condensation reactions of a range of aldehydes using either method A (DBU, THF, −78 °C, molar ratio of aldehyde:sulfone:DBU = 1:1.4:4, Barbier conditions⁴) or method B (DBU, DMPU, room temperature, molar ratio of aldehyde:sulfone:DBU = 1.3:1.0:2, Barbier conditions⁴).

As can be seen from Table 2, using method A, high *Z*-selectivity was observed for aromatic aldehydes (entries 1 and 3). The trend reversed in the case of thiophene, where the *E* isomer predominated (entry 5). No selectivity was observed in the case of *n*-octanal (entry 7). Condensations using method B were *E*-selective in all cases. Selectivity was moderate in the case of electron-poor aromatic and aliphatic aldehydes (entries 4 and 8). For the substrates studied, product yields were in the range of 69–93%.

We next explored the scope of the *Z*-selective olefinations using method C (NaH, THF, room temperature, molar ratio of carbonyl compound:**3**:NaH = 1:2:4, aldehyde added to sulfone/NaH mixture). Table 3 shows a series of carbonyl compounds that were subjected to condensation reactions.

With all aldehydes studied, high *Z*-stereoselectivity was observed (*Z/E* \geq 99), except in the case of thiophene-2-carboxaldehyde, where 2% of the *E* isomer was formed (Table 3, entry 6). The yields were in the range of 71% to quantitative. The reactivity of ketones with **3** using NaH was tested as well. *N*-Benzylpiperidone gave a product in 57% yield, but reaction with acetophenone resulted in a complex mixture.

Next, we wanted to test whether the second point of diversity, i.e., the amide in the Julia–Weinreb reagent **3**, could be

TABLE 2. DBU-Mediated Condensation Reactions of **3**

entry	RCHO	conditions, rxn time (h)	products 4-7 : (%) <i>E/Z</i> ratio, ^a yield ^b	δ (ppm); mult, <i>J</i> (Hz)
1		Method A, 4	4 : 6/94; ^c 86% ^c	<i>E</i> -isomer: -110.5; d, 21.3
2		Method B, 17	4 : 78/22; 93%	<i>Z</i> -isomer: -120.5; d, 36.6
3		Method A, 2.5	5 : 3/97; 92%	<i>E</i> -isomer: -104.8; d, 21.3
4		Method B, 16	5 : 67/33; 83%	<i>Z</i> -isomer: -115.0; d, 33.6
5		Method A, 4	6 : 74/26; 78%	<i>E</i> -isomer: -115.7; broad s
6		Method B, 17	6 : 86/14; 81%	<i>Z</i> -isomer: -119.7; d, 33.6
7		Method A, 2.5	7 : 54/46; 74%	<i>E</i> -isomer: -117.5; broad s
8		Method B, 16	7 : 67/33; 69%	<i>Z</i> -isomer: -125.7; d, 36.6

^a Relative ratio of diastereomers in the crude reaction mixture determined by ¹⁹F NMR prior to isolation. No change in olefin ratio was observed after purification. ^b Yields of isolated, purified products (reactions were performed under similar conditions with either method A or method B, but were not optimized for individual cases). ^c Practically no change in *E/Z* ratio and yield was observed upon increasing the sulfone from 1.2 to 1.4 molar equiv (compare entry 4, Table 1).

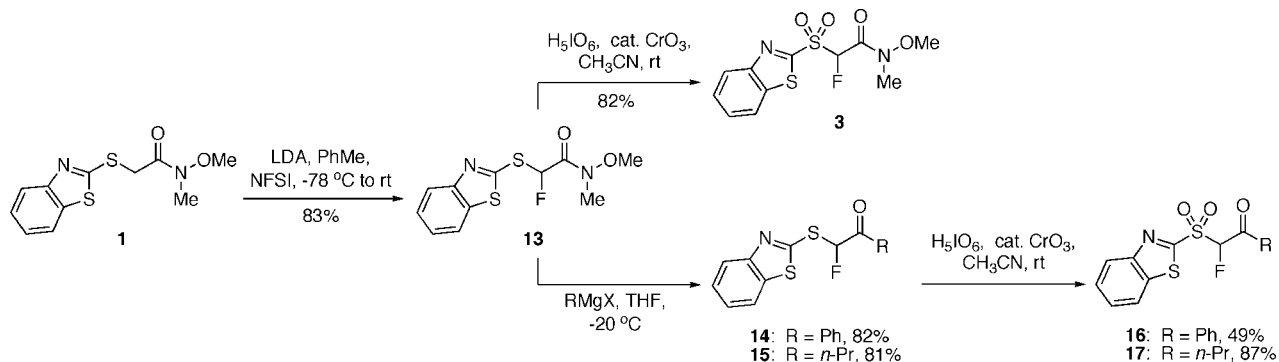
TABLE 3. Condensation Reactions of **3** with Carbonyl Compounds Using NaH

entry	R ₁ CHO or R ₁ C(O)R ₂	conditions, rxn time	products 4-12 : (%) <i>E/Z</i> ratio, ^a yield ^b	<i>Z</i> -isomer: δ (ppm); mult, <i>J</i> (Hz)
1		Method C, 1 h	4 : <i>Z</i> -isomer only, 90%	-120.5; d, 36.6
2		Method C, 1.5 h	8 : 1/99, 89%	-124.0; d, 36.6
3		Method C, 1.5 h	5 : <i>Z</i> -isomer > 99; 85%	-115.0; d, 33.6
4		Method C, 1.5 h	9 : <i>Z</i> -isomer > 99; 80%	-122.0; d, 36.6
5		Method C, 1.5 h	10 : <i>Z</i> -isomer only; quantitative	-125.1; d, 36.6
6		Method C, 1.5 h	6 : 2/98; 99%	-119.7; d, 33.6
7		Method C, 1.5 h	7 : <i>Z</i> -isomer > 99; 83%	-125.7; d, 36.6
8		Method C, 1.5 h	11 : <i>Z</i> -isomer only; 71%	-124.7; d, 36.6
9		Method C, ^c 45 min	12 : NA; 57%	-126.3 (s)
10		Method C, rt–heating, 8 h	Complex rxn mixture – products not identified	--

^a Relative ratio of diastereomers in the crude reaction mixture determined by ¹⁹F NMR prior to isolation. ^b Yields of isolated, purified products. ^c The ratio of *N*-benzylpiperidone:3:NaH = 2.5:1:2.

modified prior to the olefination reaction. This would allow for the synthesis of a *second set of Julia reagents from a common precursor*. Specifically, we were interested in the synthesis of keto derivatives. Upon the basis of our previous results demonstrating the higher reactivity of aldehydes with fluoro Julia

reagents,^{7–9} we reasoned that keto derivatives of BT-sulfone would undergo selective reactions with aldehydes under mild conditions, without participation of the keto moiety. Since BT-sulfone derivatives are labile under basic conditions, we decided that rather than the reaction of **3** with organometallics, the

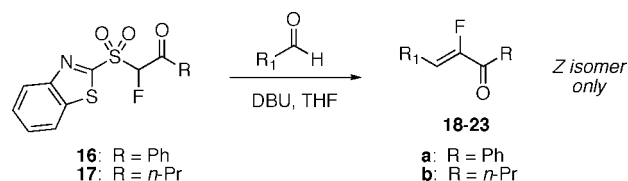
SCHEME 2. Conversion of **1** to a Second Set of Fluoro Julia Olefination Reagents and to **3** via a Common Intermediate

fluorinated sulfide precursor would be a better substrate for this modification. BT-sulfide **1** was therefore subjected to metalation–fluorination with LDA and NFSI in toluene, to give fluoro BT-sulfide derivative **13** in 83% yield.

Reaction of **13** with 2.25 molar equiv of PhLi ($-78\text{ }^{\circ}\text{C}$ to room temperature) gave a complex reaction mixture. Upon reaction of **13** with 2.5 molar equiv of PhMgBr at room temperature, some desired product formation was observed in an otherwise complex reaction mixture. Lowering the temperature to $-20\text{ }^{\circ}\text{C}$ and use of 6 molar equiv of the Grignard reagent resulted in successful formation of the desired (1,3-benzothiazol-2-ylsulfanyl)fluoromethyl phenyl ketone **14** that was isolated in 82% yield (Scheme 2). Oxidation of **14** with H_5IO_6 in the presence of catalytic CrO_3 in CH_3CN ¹⁹ gave sulfone **16** in 49% isolated yield. To test generality, **13** was also reacted with *n*-propylmagnesium bromide at $-20\text{ }^{\circ}\text{C}$, to give the *n*-propyl derivative **15** that was isolated in 81% yield. Oxidation of **15** with H_5IO_6 and catalytic CrO_3 in CH_3CN ¹⁹ was fast and smooth at rt to give sulfone **17** in 87% isolated yield (Scheme 2). Since **13** can be potentially converted to **3**, we also explored this route (Scheme 2). In fact, **3** can be smoothly prepared from **1** in 68% overall yield, in comparison to the 76% overall yield via Scheme 1. Therefore, **13** serves as a *key common intermediate* to both types of Julia olefination reagents.

Although α -fluoro- α,β -enones are versatile synthetic intermediates, methods for their synthesis are sparse.^{13,20} With the two reagents (1,3-benzothiazol-2-ylsulfanyl)fluoromethyl phenyl (**16**) and *n*-propyl ketone (**17**) in hand, we tested their reactivity for the synthesis of α -fluoro- α,β -enones. Reagent **16** was subjected to DBU-mediated olefination with *p*-methoxybenzaldehyde. A room temperature reaction of **16** in either CH_2Cl_2 or THF showed very little conversion to product in 24 h. However, use of refluxing THF resulted in complete conversion to products. In contrast, condensation reactions of **17** led to complex reaction mixtures at higher temperatures. Lowering the reaction temperature to $0\text{ }^{\circ}\text{C}$ resulted in good yields of the α -fluoroenone. Due to lower solubility of **17** in THF, a mixture of CH_2Cl_2 and THF was used as reaction solvent. In both cases, the reactions were monitored by TLC (after ca. 15 min in the case of **16** and after 2 h in the case of **17**) and if starting aldehyde

TABLE 4. Condensation Reactions of Fluoro Julia Reagents **16** and **17**



rxn	substrate	sulfone: molar equiv; ^a DBU: molar equiv ^a	rxn time, T	products 18-23 , yield ^b
1		16 : 3; DBU: 4	0.5 h, reflux	R = Ph: 18a , 61%
2		17 : 3; DBU: 6	16 h, $0-5\text{ }^{\circ}\text{C}$	R = <i>n</i> -Pr: 18b , 89%
3		16 : 4; DBU: 6	0.5 h, reflux	R = Ph: 19a , 64%
4		16 : 2; DBU: 4	0.5 h, reflux	R = Ph: 20a , 81%
5		17 : 2; DBU: 6	8 h, $0\text{ }^{\circ}\text{C}$ - rt	R = <i>n</i> -Pr: 20b , 86%
6		16 : 4; DBU: 3	40 min, reflux	R = Ph: 21a , 71%
7		17 : 3; DBU: 6	8 h, $0-5\text{ }^{\circ}\text{C}$	R = <i>n</i> -Pr: 22b , 90%
8		17 : 1.5; DBU: 6	3 h, $0-5\text{ }^{\circ}\text{C}$	R = <i>n</i> -Pr: 23b , 73%

^aTotal amount of sulfone and DBU used for complete aldehyde consumption. For good conversions, sequential addition of sulfone and DBU was required (please see the Experimental Section and the Supporting Information for details). ^bYields of isolated, purified products.

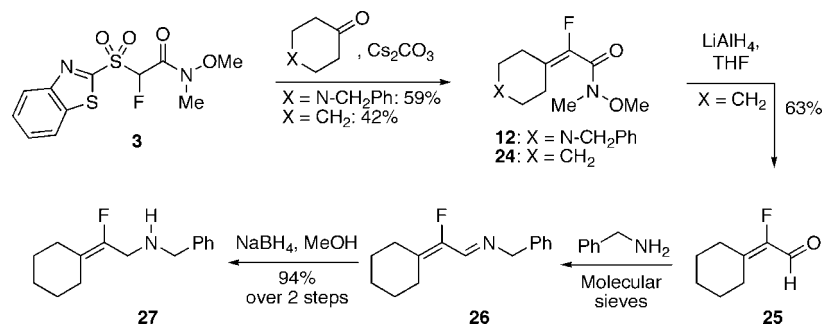
was still present, additional sulfone and DBU were added (please see the Experimental Section for details). Condensation reactions of **16** and **17** with some representative aldehydes are displayed in Table 4. In all cases studied, only the *Z*-isomer was observed. No attempts were made to further optimize the reaction conditions.

We were next interested in the application of the methodology to the synthesis of α -fluoro allyl amines. The biological relevance of the α -fluoro allyl amine motif is well documented.¹ α -Fluoro- α,β -unsaturated Weinreb amides can be convenient intermediates in α -fluoro allyl amine synthesis (Scheme 3). To explore this application, α -fluoro allyl amine **27** (Scheme 3) was chosen as a target, due to its reported inhibitory activity toward dipeptidyl peptidase II.¹⁷ Although we have shown that NaH-mediated condensation of *N*-benzylpiperidone and **3** led to product **12**, we were curious whether the condensation would occur under milder conditions. Successful use of Cs_2CO_3 as a base has been demonstrated in other Julia–Kocienski olefinations, e.g., in condensations of *p*-nitrophenyl sulfones²¹ or in

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SCHEME 3. Synthesis of α -Fluoro Allyl Amine with Fluoro Julia–Weinreb Reagent 3

methylations with *tert*-butyltetrazolyl sulfones.²² In the present case, Cs_2CO_3 -mediated condensation of **3** with *N*-benzylpiperidone resulted in a 59% yield of **12** (comparable to the NaH -mediated condensation). In comparison, cyclohexanone gave a 42% yield of condensation product **24** (perhaps due to product volatility). Condensation product **24** was subsequently converted to aldehyde **25** (63%) that was then subjected to imine formation with benzylamine to give **26**. Reduction of **26** yielded the desired **27** in 94% yield over two steps.

Conclusions

In conclusion, we have synthesized a benzothiazolyl sulfone derived reagent for the synthesis of α -fluorovinyl Weinreb amides via Julia olefination. The reactivity of the reagent was studied under mild, DBU-mediated conditions as well as with NaH . Lower temperatures and relatively nonpolar solvents favor formation of the *Z*-isomer, whereas polar solvents and higher temperatures favor formation of the *E*-isomer. Formation of the *Z*-isomer strongly predominated ($\geq 98\%$) when NaH was used as base. This is to our knowledge the first example showing tunability of reaction condensations leading to the α -fluorovinyl Weinreb amide derivatives. Further, conversion of the amide moiety to a keto functionality in benzothiazolylsulfanyl fluoroacetamide derivative yielded another set of Julia reagents for the synthesis of α -fluoroenones. The methodology presented offers access to two different sets of Julia olefination reagents via a common fluorinated precursor. A series of α -fluoroenones was prepared under mild conditions with DBU as base, with complete *Z*-stereoselectivity. We have also demonstrated the utility of the reagent for synthesis of α -fluoro allyl amines via Weinreb amides, by preparation of a biologically relevant dipeptidyl peptidase inhibitor.

Experimental Section

***N*-Methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide (3) via Fluorination of 2.** A solution of sulfone **2** (1.00 g, 3.33 mmol, 1 molar equiv) in dry toluene (185 mL) was cooled to -78°C under nitrogen gas. LDA (3.50 mmol, 1.75 mL, 1.05 molar equiv of a 2 M solution in heptane/THF/EtPh) was added to the reaction mixture. After 15 min solid NFSI (1.31 g, 4.17 mmol, 1.25 molar equiv) was added. The mixture was allowed to stir at -78°C for 50 min, then warmed to rt and stirred for an additional 50 min. Saturated aq NH_4Cl was added and the mixture was extracted with EtOAc (3 \times), 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 mixture was purified by column chromatography (SiO_2 , 40% EtOAc in hexanes) to yield **3** (0.905 g, 85%)

as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 8.29 (d, 1H, Ar–H, $J = 8.2$ Hz), 8.04 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.69–7.62 (m, 2H, Ar–H), 6.58 (d, 1H, $^2J_{\text{HF}} = 47.6$ Hz), 3.90 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 161.7, 159.7 (d, $^2J_{\text{CF}} = 22.4$ Hz), 152.7, 138.0, 128.8, 128.1, 126.1, 122.5, 94.9 (d, $^1J_{\text{CF}} = 226.1$ Hz), 62.2, 32.9. ^{19}F NMR (282 MHz, CDCl_3): δ -181.5 (d, $^2J_{\text{FH}} = 48.8$ Hz). HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{11}\text{FN}_2\text{O}_4\text{S}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 341.0036, found 341.0028.

***N*-Methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide (13).** A solution of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)acetamide **1** (2.02 g, 7.51 mmol, 1 molar equiv) in dry toluene (50 mL) was cooled to -78°C under nitrogen gas. LDA (9.60 mmol, 4.80 mL, 1.28 molar equiv of a 2 M solution in heptane/THF/EtPh) was added to the reaction mixture. After 20 min, solid NFSI (2.84 g, 9.01 mmol, 1.2 molar equiv) was added. The mixture was allowed to stir at -78°C for 50 min, then warmed to rt and stirred for an additional 50 min. Saturated aq NH_4Cl (30 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 \times 30 mL), and the combined organic layer was washed with saturated aq NaHCO_3 (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2 , 40% EtOAc in hexanes) to yield **13** (1.79 g, 83%) as a pale yellow liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.98 (d, 1H, Ar–H, $J = 8.3$ Hz), 7.82 (d, 1H, Ar–H, $J = 7.8$ Hz), 7.49–7.36 (m, 3H), 3.81 (s, 3H), 3.28 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -161.0 (d, $^2J_{\text{FH}} = 51.9$ Hz). HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{11}\text{FN}_2\text{O}_2\text{S}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 309.0138, found 309.0130.

***N*-Methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide (3) via Oxidation of 13.** H_5IO_6 (302 mg, 1.32 mmol) was dissolved in CH_3CN (20 mL) by vigorous stirring at rt for 30 min. CrO_3 (5.0 mg, 0.050 mmol, 15 mol %) was added and the reaction mixture was stirred for an additional 5 min to give an orange colored solution. A solution of fluoro sulfide **13** (95.1 mg, 0.332 mmol) in CH_3CN (5 mL) was added dropwise to this mixture, resulting in the formation of a green precipitate. After the addition was complete the reaction mixture was stirred at rt for 3 h at which time TLC (SiO_2 , 50% EtOAc in hexanes) showed a complete consumption of **13**. The reaction mixture was filtered through a Celite pad, the Celite was washed with EtOAc, and the solvent was evaporated under reduced pressure. Water was added to the residue (30 mL) and the mixture was extracted with EtOAc (3 \times 30 mL), then the combined organic layer was washed with saturated aq Na_2SO_3 (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4 . The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2 , 50% EtOAc in hexanes) to afford **3** as a white solid (87.0 mg, 82%).

(1,3-Benzothiazol-2-ylsulfanyl)fluoromethyl Phenyl Ketone (14). To a solution of fluoro sulfide **13** (1.01 g, 3.51 mmol) in dry THF (10.0 mL) was added PhMgBr (21.0 mL, 1 M solution in THF, 21.0 mmol) dropwise at -20°C . The reaction mixture was stirred at -20°C and after 1 h TLC (SiO_2 , 20% EtOAc in hexanes) showed the disappearance of **13**. The reaction was quenched with

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saturated aq NH₄Cl (30 mL), the aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with NaHCO₃ (30 mL) and brine (30 mL) and then dried over Na₂SO₄. The organic layer was concentrated in vacuo and the crude product was purified by column chromatography (SiO₂, 10% EtOAc in hexanes) to afford **14** as a colorless liquid (872 mg, 82%). ¹H NMR (500 MHz, CDCl₃): δ 8.10 (d, 1H, Ar-H, *J* = 7.8 Hz), 8.03 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.95 (d, 1H, ²*J*_{HF} = 51.6 Hz), 7.83 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.65 (t, 1H, Ar-H, *J* = 7.8 Hz), 7.52 (t, 2H, Ar-H, *J* = 7.4 Hz), 7.41 (t, 1H, Ar-H, *J* = 7.4 Hz), 7.31–7.28 (m, 1H, Ar-H), 7.18–7.17 (m, 1H, Ar-H). ¹⁹F NMR (CDCl₃): δ -162.1 (d, ²*J*_{FH} = 51.9 Hz). HRMS (ESI) calcd for C₁₅H₁₀FNOS₂Na [M + Na]⁺ 326.0080, observed 326.0076.

(1,3-Benzothiazol-2-ylsulfanyl)fluoromethyl *n*-Propyl Ketone (15). To a stirring solution of *n*-propylmagnesium bromide, prepared from *n*-propyl bromide (3.40 mL, 37.1 mmol) and Mg (891 mg, 37.1 mmol) in THF (60 mL), at -20 °C was added a solution of fluoro sulfide **13** (1.77 g, 6.19 mmol) in THF (30 mL) dropwise. After complete addition, the reaction mixture was stirred at -20 °C for 1 h, then warmed to 0 °C and quenched with saturated aq NH₄Cl. The reaction mixture was diluted with water and extracted with EtOAc (2 × 30 mL). The combined organic layer was thoroughly washed with water and with brine and dried over anhydrous Na₂SO₄, then the solvent was evaporated in vacuo. The crude product was purified by column chromatography (SiO₂, 5% EtOAc in hexanes) to afford ketone **15** as a yellow oil (1.35 g, 81%). ¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.81 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.47 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.37 (t, 1H, Ar-H, *J* = 7.6 Hz), 6.83 (d, 1H, ²*J*_{HF} = 51.0 Hz), 2.77 (t, 2H, *J* = 7.2 Hz), 1.71 (sext, 2H, *J* = 7.3 Hz), 0.97 (t, 3H, *J* = 7.4 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -163.6 (d, ²*J*_{FH} = 51.9 Hz). HRMS (ESI) calcd for C₁₂H₁₂FNOS₂Na [M + Na]⁺ 292.0237, found 292.0230.

(1,3-Benzothiazol-2-ylsulfanyl)fluoromethyl Phenyl Ketone (16). H₅IO₆ (2.62 g, 11.5 mmol) was dissolved in CH₃CN (50 mL) by vigorous stirring at rt for 30 min. CrO₃ (11.0 mg, 0.110 mmol, 4 mol %) was added and the reaction mixture was stirred for an additional 5 min to give an orange colored solution. A solution of fluoro sulfide **14** (872 mg, 2.87 mmol) in CH₃CN (10 mL) was added dropwise to this mixture, resulting in an exothermic reaction and formation of a yellowish precipitate. After the addition was complete the reaction mixture was stirred overnight at which time TLC (SiO₂, 25% EtOAc in hexanes) showed a complete consumption of **14**. The reaction mixture was filtered through a Celite pad, the Celite was washed with CH₃CN, and the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc (3 × 50 mL), then the combined organic layer was washed with saturated aq Na₂SO₃ (30 mL) and brine (30 mL) and dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO₂, 40% EtOAc in hexanes) to afford **16** as a colorless solid (472 mg, 49%). ¹H NMR (500 MHz, CDCl₃): δ 8.29 (d, 1H, Ar-H, *J* = 7.8 Hz), 8.12 (d, 2H, Ar-H, *J* = 8.3 Hz), 8.05 (d, 1H, Ar-H, *J* = 7.4 Hz), 7.71–7.64 (m, 3H, Ar-H), 7.55 (t, 2H, Ar-H, *J* = 7.8 Hz), 6.81 (d, 1H, ²*J*_{HF} = 47.9 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 185.3 (d, ²*J*_{CF} = 17.5 Hz), 161.6, 152.7, 137.8, 135.5, 134.0, 130.1, 129.1, 129.0, 128.2, 126.1, 122.6, 99.5 (d, ¹*J*_{CF} = 233.7 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -179.3 (d, ²*J*_{FH} = 48.8 Hz). HRMS (ESI) calcd for C₁₅H₁₀FNOS₂Na [M + Na]⁺ 357.9978, observed 357.9974.

(1,3-Benzothiazol-2-ylsulfanyl)fluoromethyl *n*-Propyl Ketone (17). H₅IO₆ (2.51 g, 11.0 mmol) was dissolved in CH₃CN (44 mL) by vigorous stirring at rt for 30 min. CrO₃ (5.5 mg, 0.055 mmol, 2 mol %) was added and the reaction mixture was stirred for an additional 5 min to give an orange colored solution. A solution of fluoro sulfide **15** (739 mg, 2.75 mmol) in CH₃CN (11 mL) was added dropwise to this mixture, resulting in an exothermic reaction and formation of a precipitate. The reaction mixture was stirred at

rt and TLC (SiO₂, 20% EtOAc in hexanes) showed a complete consumption of **15** after 30 min. The reaction mixture was filtered through a sintered glass funnel and then through a Celite pad, and the Celite was washed with CH₃CN (10 mL). The filtrate was concentrated under reduced pressure at rt, water was added to the residue, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated aq Na₂SO₃ and brine then dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂, 15% EtOAc in hexanes) to afford sulfone **17** as a white solid (720 mg, 87%). ¹H NMR (500 MHz, CDCl₃): δ 8.25 (d, 1H, Ar-H, *J* = 7.9 Hz), 8.04 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.69–7.63 (m, 2H, Ar-H), 5.97 (d, 1H, ²*J*_{HF} = 48.2 Hz), 2.88 (dtd, 1H, *J* = 18.7, 7.2, 2.7 Hz), 2.76 (dt, 1H, *J* = 18.9, 7.1 Hz), 1.71 (sext, 2H, *J* = 7.3 Hz), 0.96 (t, 3H, *J* = 7.3 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -182.3 (d, ²*J*_{FH} = 48.8 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 196.6 (d, ²*J*_{CF} = 19.7 Hz), 161.3, 152.4, 137.4, 128.8, 128.1, 125.7, 122.4, 100.6 (d, ¹*J*_{CF} = 237.1 Hz), 42.1, 16.0, 13.3. HRMS (ESI) calcd for C₁₂H₁₂FNOS₂Na [M + Na]⁺ 324.0135, found 324.0124.

Representative Procedures for Condensations of Aldehydes with *N*-Methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfanyl)fluoroacetamide (3), Using Methods A, B, and C. Method A: Synthesis of (*E/Z*)-2-Fluoro-*N*-methoxy-*N*-methyl-3-(4-nitrophenyl)propenamide (5). To a stirred solution of the *p*-nitrobenzaldehyde (151 mg, 1.00 mmol, 1 molar equiv) and sulfone **3** (445 mg, 1.4 molar equiv) in dry THF (7.8 mL) at -78 °C was added a cooled (-75 °C) solution of DBU (609 mg, 4.00 mmol, 4.0 molar equiv) in dry THF (7.8 mL). The reaction mixture was allowed to stir at -78 °C until complete consumption of aldehyde was observed by TLC (3 h), saturated aq NH₄Cl (15 mL) was added, the reaction mixture was brought to rt and extracted with Et₂O (3 × 50 mL). The combined organic layer was washed with 1 N NaOH (40 mL), water, and brine then dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. Analysis of the crude reaction mixture by ¹⁹F NMR showed the *E/Z* product ratio of 3:97. The crude product was purified by column chromatography (20% EtOAc in hexanes) to yield 233 mg (92%) of (*E/Z*)-**5** as a pale yellow solid. Although 3% of (*E*)-**5** was detected, NMR data are reported only for the major isomer. Major isomer (*Z*)-**5**: ¹H NMR (500 MHz, CDCl₃): δ 8.23 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.75 (d, 2H, Ar-H, *J* = 8.5 Hz), 6.73 (d, 1H, ³*J*_{HF} = 35.7 Hz), 3.81 (s, 3H), 3.30 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -115.0 (d, ³*J*_{FH} = 33.6 Hz). HRMS (ESI) calcd for C₁₁H₁₁FN₂O₄Na [M + Na]⁺ 277.0595, found 277.0593.

Method B: Synthesis of (*E/Z*)-2-Fluoro-*N*-methoxy-*N*-methyl-3-(2-thienyl)propenamide (6). To a stirred solution of thiophene-2-carboxaldehyde (45.8 mg, 0.409 mmol, 1.3 molar equiv) and **3** (100 mg, 0.314 mmol, 1.0 molar equiv) in DMPU (2.4 mL) at rt was added a solution of DBU (95.7 mg, 0.629 mmol, 2 molar equiv) in DMPU (2.4 mL) dropwise. The reaction mixture was allowed to stir for 18 h, at which time complete consumption of **3** was observed by TLC (SiO₂, 30% EtOAc in hexanes). The reaction was quenched with saturated aq NH₄Cl (5 mL), the aqueous layer was extracted with Et₂O (3 × 20 mL), the combined organic layer was washed with 1 N NaOH (20 mL), water, and brine then dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. Analysis of the crude reaction mixture by ¹⁹F NMR showed the *E/Z* product ratio of 86:14. The crude product was purified by column chromatography (SiO₂, 20% EtOAc in hexanes) to afford 55 mg (81%) of (*E/Z*)-**6** as a pale yellow viscous liquid. For the ¹H NMR data of (*Z*)-**6** (minor isomer in the present case), please see the Supporting Information. Major isomer (*E*)-**6**: ¹H NMR (500 MHz, CDCl₃): δ 7.29 (d, 1H, Ar-H, *J* = 4.3 Hz), 7.13 (d, 1H, Ar-H, *J* = 3.1 Hz), 6.98 (app t, 1H, Ar-H, *J* ≈ 4.3 Hz), 6.71 (d, 1H, ³*J*_{HF} = 22.0 Hz), 3.75 (s, 3H), 3.30 (s, 3H). (*E/Z*)-**6** HRMS (ESI) calcd for C₉H₁₀FN₂O₂Na [M + Na]⁺ 238.0308, observed 238.0301.

Method C: Synthesis of (Z)-2-Fluoro-N-methoxy-N-methyl-3-(4-methoxyphenyl)propenamide (8).¹¹ A suspension of NaH (70.5 mg, 2.94 mmol, 4 molar equiv) and **3** (467 mg, 1.47 mmol, 2 molar equiv) in dry THF (8.4 mL) was stirred at rt under a nitrogen atmosphere for 2 min. A solution of *p*-methoxybenzaldehyde (100 mg, 0.734 mmol, 1 molar equiv) in dry THF (3.4 mL) was added dropwise. The reaction mixture was allowed to stir at rt for 1.5 h and then quenched with saturated aq NH₄Cl (10 mL). The mixture was extracted with Et₂O (3 × 40 mL), then the combined organic layers were washed with 1 N NaOH (30 mL), water, and brine and dried over Na₂SO₄. Analysis of the crude reaction mixture by ¹⁹F NMR showed the *E/Z* product ratio of 1:99. The crude product was purified by column chromatography (SiO₂, 20% EtOAc in hexanes) to yield 156 mg (89%) of **8** as a light brown semisolid. (Z)-**8**: ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, 2H, Ar-H, *J* = 8.5 Hz), 6.90 (d, 2H, Ar-H, *J* = 8.8 Hz), 6.69 (d, 1H, ³*J*_{HF} = 37.5 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.27 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -124.0 (d, ³*J*_{FH} = 36.6 Hz). HRMS (ESI) calcd for C₁₂H₁₄FNO₃Na [M + Na]⁺ 262.0849, found 262.0844.

General Procedure for the Synthesis of 18a²³–21a via Condensations of Aldehydes with Fluoro Sulfone 16. To a refluxing solution of aldehyde (1 molar equiv) and DBU (3 molar equiv) in THF (28 mL/mmol of aldehyde) was added sulfone **16** (2 molar equiv) dissolved in THF (4.5 mL/mmol of **16**) dropwise. The reaction was stirred at reflux for ca. 15 min and the conversion was checked by TLC. If sulfone was consumed and unreacted starting aldehyde was observed, an additional 1 molar equiv of each of DBU in THF (2 mL/mmol of DBU) and solid **16** were added (in the case of *o*-methoxybenzaldehyde, 3 molar equiv of DBU and 2 molar equiv of **16** were added). If both sulfone and aldehyde were still present, an additional 1 molar equiv of DBU in THF (2 mL/mmol of DBU) was added. After heating under reflux for an additional 15 min, the conversion was again checked by TLC. If unreacted starting aldehyde was present, an additional 1 molar equiv of solid **16** was added. In all cases, consumption of starting aldehyde was observed after 30–40 min of reflux. The reaction was quenched with saturated aq NH₄Cl and the mixture was extracted with EtOAc (3×). The organic layer was washed with saturated aq NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated. The crude product was purified by column chromatography. As representative procedures, condensations of *p*-nitrobenzaldehyde and thiophene-2-carboxaldehyde with **16** are given in the Supporting Information. For other substrates, see Table 4 for details on reagent stoichiometry, reaction time, temperature, and yield. See the Supporting Information for additional details, such as TLC and column chromatographic conditions, spectroscopic data of products, as well as literature reference for known compounds.

General Procedure for Synthesis of 18b,^{20d} 20b, 22b, and 23b^{20d} via Condensations of Aldehydes with Fluoro Sulfone 17. A solution of aldehyde (1 molar equiv) and DBU (6 molar equiv) in THF (28.0 mL/mmol of aldehyde) was cooled to 0 °C. Sulfone **17** (2 molar equiv, except for 3-phenylpropanal, where 1.5 molar equiv was used) was dissolved in CH₂Cl₂ (30.0 mL/mmol of **17**) and was added *slowly, dropwise* to the reaction mixture over 2–3 h (1 h in the case of 3-phenylpropanal). Very slow addition of **17** is *critical*, since sulfone **17** is unstable under the reaction conditions, thus resulting in higher consumption of **17** upon faster additions. The reaction mixture was allowed to stir at 0 °C until complete disappearance of aldehyde was observed by TLC. If sulfone consumption was observed, an additional 1 molar equiv of **17** was added *slowly, dropwise over several hours*. Upon disappearance of the aldehyde, saturated aq NH₄Cl was added to the reaction mixture and the mixture was extracted with EtOAc (2×). The combined organic layer was washed with water and brine and dried over anhydrous Na₂SO₄, then the solvent was evaporated.

Condensations of **17** with *p*-nitrobenzaldehyde and 3-phenylpropanal are given in the Supporting Information as representative procedures. For other substrates, see Table 4 for details on reagent stoichiometry, reaction time, temperature, and yield. See the Supporting Information for additional details, such as TLC and column chromatographic conditions, spectroscopic data of products, as well as literature reference for known compounds.

Synthesis of 24 via Condensation of Cyclohexanone with Fluoro Sulfone 3. To a solution of sulfone **3** (251 mg, 0.788 mmol, 1 molar equiv) in dry DMF (10.0 mL) was added Cs₂CO₃ (1.03 g, 3.16 mmol, 4 molar equiv) and the color of the reaction mixture turned deep yellowish-orange. The suspension was stirred at rt for 30 min, and a solution of cyclohexanone (154 mg, 1.57 mmol, 2 molar equiv) in dry DMF (2.0 mL) was added. The reaction mixture was stirred at rt for 30 h, saturated aq NH₄Cl (30 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated aq NaHCO₃ (30 mL) and brine (30 mL) and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the crude product was purified by column chromatography (SiO₂, 20% EtOAc in hexanes) to give **24** as a clear liquid (66.6 mg, 42%). ¹H NMR (500 MHz, CDCl₃): δ 3.73 (s, 3H), 3.23 (s, 3H), 2.29–2.23 (m, 4H), 1.64–1.57 (m, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -127.0 (br s). HRMS (ESI) calcd for C₁₀H₁₆FNO₂Na [M + Na]⁺ 224.1057, observed 224.1055.

Reduction of 24. To a suspension of LiAlH₄ (18.0 mg, 0.474 mmol) in dry THF (5.0 mL) at 0 °C was added a solution of **24** (43.0 mg, 0.214 mmol) in dry THF (1.0 mL). The reaction mixture was stirred at 0 °C for 15 min and at rt for 1 h, then cooled to 0 °C and 0.1 N HCl (3 mL) was added to the mixture. The mixture was extracted with Et₂O (3 × 30 mL) and the combined organic layer was washed with saturated aq NaHCO₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography (SiO₂, CH₂Cl₂) to yield **25**²⁴ as a colorless liquid (18.0 mg, 63%). ¹H NMR (500 MHz, CDCl₃): δ 9.79 (d, 1H, ³*J*_{HF} = 18.0 Hz), 2.63–2.61 (m, 2H), 2.44–2.42 (m, 2H), 1.72–1.64 (m, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -137.6 (d, ³*J*_{FH} = 18.3 Hz).

Synthesis of 27 from 25. Step 1: Condensation of 25 with Benzylamine. To a mixture of benzylamine (16.0 mg, 0.149 mmol) and aldehyde **25** (17.0 mg, 0.120 mmol) in dry CH₂Cl₂ (10.0 mL) were added molecular sieves (4 Å, 200 mg) and the mixture was stirred overnight. After 22 h, TLC (SiO₂, 20% EtOAc in hexanes) showed complete consumption of **25**. The solvent was evaporated and the crude product **26** (33.0 mg) was subjected to reduction without further purification.

Step 2: Reduction of 26. To a solution of imine **26** (33.0 mg, crude product from step 1) in CH₃OH (10.0 mL) was added NaBH₄ (11.3 mg) at 0 °C. The reaction mixture was stirred for 1 h and after the starting material was fully consumed, the mixture was evaporated. Saturated aq NH₄Cl (20 mL) was added to the solid residue and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with NaHCO₃ (30 mL) and brine (30 mL) then dried over Na₂SO₄. The organic layer was concentrated and the crude product was purified by silica gel chromatography (20% EtOAc in hexanes) to afford **27**¹⁷ as a colorless liquid (26.0 mg, 94% yield over two steps). ¹H NMR (500 MHz, CDCl₃, NH exchanged): δ 7.34–7.31 (m, 3H, Ar-H), 7.27–7.25 (m, 2H, Ar-H), 3.78 (s, 2H), 3.41 (d, 2H, ³*J*_{HF} = 22.6 Hz), 2.24 (br s, 2H), 2.02–1.99 (br m, 2H), 1.64–1.52 (br m, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -121.8 (t, ³*J*_{FH} = 21.4 Hz). HRMS (ESI) calcd for C₁₅H₂₁FN [M + H]⁺ 234.1653, observed 234.1652.

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Supporting Information Available: General procedures with methods A, B, and C, representative procedures for condensations of **16** and **17**, synthetic details, ¹H NMR as well as HRMS

data, literature references (where applicable) for **1**, **2**, (*Z*)-**4**, (*Z*)-**6**, (*Z*)-**7**, (*Z*)-**9**–(*Z*)-**11**, **12**, (*Z*)-**18a**–(*Z*)-**21a**, (*Z*)-**18b**, (*Z*)-**20b**, (*Z*)-**22b**, and (*Z*)-**23b**, ¹H NMR spectra of **1**–**25** and **27**, as well as ¹³C NMR spectra of **3**, **16**, and **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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