

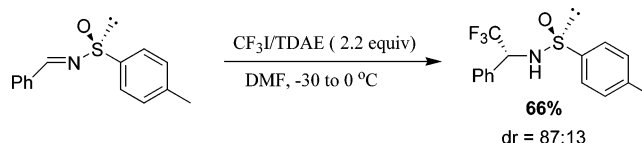
Nucleophilic Trifluoromethylation of Imines Using the CF₃I/TDAE Reagent

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The nucleophilic trifluoromethylation reagent derived from CF₃I and tetrakis(dimethylamino)-ethylene (TDAE) was found to be effective in addition to both *N*-tosyl aldimines and *N*-tolyl sulfinimines, the latter reaction exhibiting very good diastereoselectivity.

Introduction

The trifluoromethyl substituent has long been recognized for the beneficial impact that it can have upon the biological activity of molecules.^{1,2} Although there are many methods to directly or indirectly introduce a trifluoromethyl group into a molecule,³ over the past decade or so there has been an increase in the activity directed toward methods involving “nucleophilic trifluoromethylation”.^{4–6} Because of the instability of directly generated trifluoromethyl Grignards and lithium reagents,⁷ indirect methods utilizing in situ-generated trifluoromethyl anion were required. Beginning with Prakash’s report in 1989 of a very effective procedure using Ruppert’s reagent (trifluoromethyltrimethylsilane) to carry out nucleophilic trifluoromethylations,⁸ there has been considerable effort expended in the development of this and alternative methods for accomplishing such chemistry.⁹

There is a broad scope of substrates that have been shown to undergo nucleophilic trifluoromethylation using Ruppert’s reagent, and most recently Prakash and co-workers have delved into its reactions with imine deriva-

tives with the idea of developing methods for preparing trifluoromethylamines¹⁰ and, in particular, *chiral* trifluoromethylamines,^{11,12} which had previously only been synthesized from precursors (i.e., ketones) already bearing a trifluoromethyl group.^{13–21} Indeed, use of CF₃TMS proved to be very effective for nucleophilic trifluoromethylation of *N*-tosyl aldimines and *N*-(2-methyl-2-propane-sulfinyl)imines (Scheme 1), with the latter reactions exhibiting excellent diastereoselectivity.

An alternative approach to nucleophilic trifluoromethylation that was discovered in our laboratories in 2001 involves the generation of the required, sequestered trifluoromethylcarbanion by two-electron reduction of trifluoromethyl iodide by tetrakis-(dimethylamino)ethylene (TDAE).²² The chemical reactivity of the CF₃I/TDAE reagent bears some similarities to that of CF₃TMS, but, in part because it does not involve the necessity for TMS

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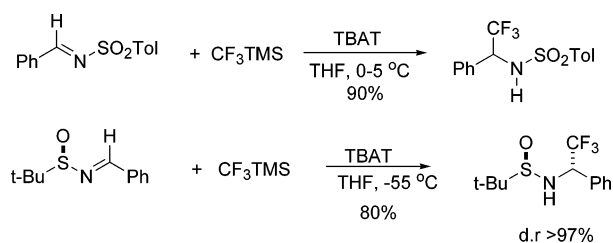
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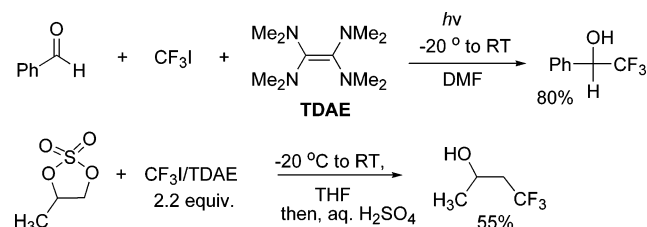
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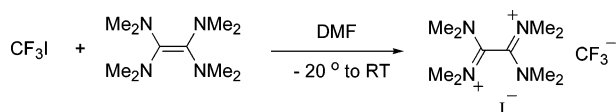
SCHEME 1



SCHEME 2



SCHEME 3



transfer as part of the mechanism, it also exhibits significant differences such as in its ability to open cyclic sulfates to produce β -trifluoromethyl alcohols.²³ On the other hand, CF_3TMS appears to be more suitable for reactions with substrates that bear readily enolizable hydrogens (such as aliphatic aldehydes).

In our efforts to fully explore the scope and limitations of the $\text{CF}_3\text{I}/\text{TDAE}$ reagent in nucleophilic trifluoromethylation chemistry, we considered it important to examine its reactivity with imines of the type studied by Prakash with CF_3TMS . In the event, the end results were quite similar, but some significant differences were also observed. We report the results of this study in this paper.

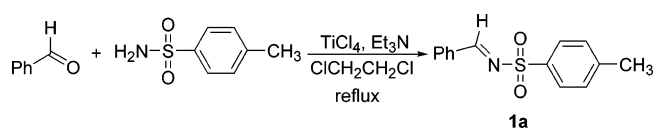
Results and Discussion

Nucleophilic trifluoromethylation using the $\text{CF}_3\text{I}/\text{TDAE}$ reagent is experimentally quite straightforward. Such chemistry is exemplified by the reactions of aldehydes and cyclic sulfates, where addition of 2.2 equiv of CF_3I to the appropriate dry solvent (i.e., DMF) containing the substrate at $-20\text{ }^\circ\text{C}$ is followed by slow addition of 2.2 equiv of TDAE and warming to room temperature to give products (Scheme 2). In the former example, irradiation by a sun lamp was shown to enhance yields.

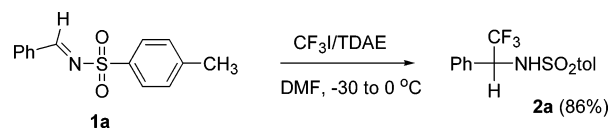
It has been demonstrated that, under such conditions, a stabilized TDAE dication/trifluoromethyl anion “complex” is generated by a two-electron transfer from TDAE to CF_3I (Scheme 3).²² This in situ reagent then can deliver a trifluoromethyl anion to appropriate electrophilic substrates.

Simple alkyl- or aryl-substituted imines are relatively unreactive toward nucleophilic trifluoromethylation, although Blazejewski and co-workers were able to obtain

SCHEME 4



SCHEME 5

TABLE 1. Trifluoromethylation of *N*-Tosylimines

compd	$\text{R}_1\text{R}_2\text{C}=\text{NSO}_2\text{Tol}$		2, yield (%)
	R_1	R_2	
1a	Ph	H	86
1b	4- CH_3Ph	H	84
1c	4- CH_3OPh	H	84
1d	4-FPh	H	81
1e	4-ClPh	H	78
1f ^a	4- NO_2Ph	H	76
1g	PhCH=CH	H	62
1h ^b	Ph	Ph	54

^a In this case, the substrate was added to the reaction mixture 30 min after the mixing of CF_3I and TDAE. ^b About 50% of starting material was recovered in this reaction.

modest to good yields for aryl systems by facilitating the reaction of CF_3TMS using TMS-imidazole.²⁴

As Prakash showed, the reactivity of imines toward nucleophilic trifluoromethylation can be significantly enhanced by using *N*-tosylimines, with the *p*-toluenesulfonyl group being removed from the adduct by its treatment with phenol and 48% HBr to give the respective primary amine products.¹⁰

Tosylimines are readily synthesized from the respective aldehydes or ketones by a procedure developed by Ram and Khan (Scheme 4).²⁵

When a series of *N*-tosylimines, 1a–h, was allowed to react with the trifluoromethyl anion reagent derived from $\text{CF}_3\text{I}/\text{TDAE}$ in the usual manner, very good yields of the trifluoromethylated adducts were obtained, as exemplified in Scheme 5. The results for the entire series are given in Table 1, and it can be seen that the reaction is quite effective for aromatic *N*-tosylaldimines and still satisfactory for the benzophenone *N*-tosylimine. In this case, irradiation by a sun lamp does not enhance the reaction. Unfortunately, the analogous reactions with imines bearing aliphatic substituents on the imine carbon did not produce the desired adducts. Such attempts included the *N*-tosylimines of acetophenone, *p*-chloroacetophenone, cyclohexanone, and hexanal. In contrast, aliphatic aldehydes had been reported to provide adducts using Prakash's CF_3TMS methodology.¹⁰

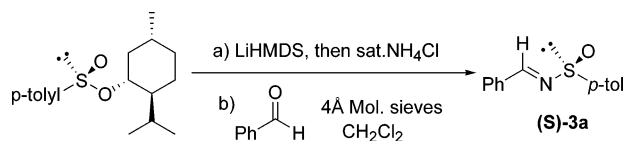
Enantiopure sulfinimines have been demonstrated to be versatile chiral imine building blocks for the asymmetric synthesis of amines.¹¹ There are a number of reasons for this, including the ability of the sulfinyl group to enhance nucleophilic addition to the $\text{C}=\text{N}$ double bond, its ability to provide superior stereocontrol, and not to

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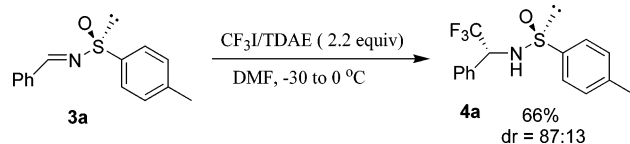
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SCHEME 6



SCHEME 7

TABLE 2. Trifluoromethylation of *N*-Tolylsulfinimines

R ₁ C ₂ H=NSO ₂ Tol			
compd	R	dr	4, yield (%)
3a	Ph	87:13	66
3b	4-CH ₃ Ph	86:14	73
3c	4-CH ₃ OPh	82:18	71
3d	4-FPh	85:15	69
3e	4-CF ₃ Ph	88:12	74
3f	<i>n</i> -C ₆ H ₁₃	72:28	48
3g	4-ClPh	88:12	67
3h	1-naphthyl	94:6	42
3i	C(CH ₃) ₃		no product

mention its easy removal under mild acid conditions. *N*-*p*-Tolylsulfinimines are easily prepared from the respective aldehydes or ketones and commercially available (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate by a procedure developed by Davis and co-workers (Scheme 6).²⁶ According to Davis, *p*-toluenesulfinimides are much more convenient chiral auxiliaries to make than are *N*-*tert*-butylsulfinimides.

Indeed, when nucleophilic trifluoromethylation of *p*-toluenesulfinimides 3a–f was carried out with the CF₃⁻ reagent derived from CF₃I/TDAE, very good yields and diastereoselectivities were observed for a wide variety of substrates (Scheme 7, Table 2), including, in this case, one derived from an aliphatic aldehyde (4f).

In hopes of increasing the diastereoselectivity of the reaction, the tolyl group was replaced by a mesityl group. This necessitated the use of an alternative procedure for the preparation of sulfinimine 5 from *S*-(+)-2,4,6-trimethylphenyl sulfonamide (Scheme 8).^{27,28}

Unfortunately, only a modest increase in diastereoselectivity was observed as a result of using the mesityl rather than the tolyl derivative.

In an attempt to compare the diastereoselectivity of our reagent directly with that of CF₃TMS, the (2-methyl-2-propane)sulfinimine derivative of benzaldehyde was examined using our CF₃I/TDAE reagent. Unfortunately, no significant amount of products deriving from nucleophilic trifluoromethylation was able to be detected in this reaction.

Conclusion

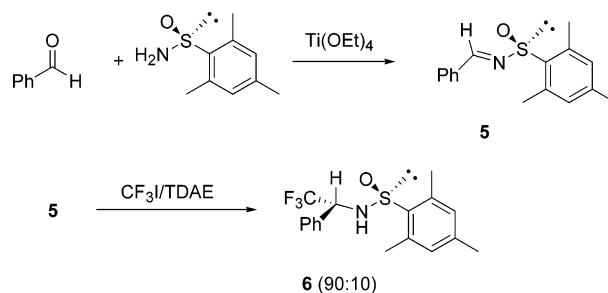
In conclusion, the nucleophilic trifluoromethylation reagent derived from CF₃I/TDAE has proved to be

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SCHEME 8



effective for addition to both *N*-tosyl- and *N*-tolylsulfinaldimines and thus provides a viable synthetic alternative to the use of CF₃TMS in the synthesis of trifluoromethylamines. The *N*-tosylimine reaction appears to be limited to use with nonenolizable aldimines, and the diastereoselectivities of the *N*-tolylsulfinimine reaction, while good, fall short of those observed by Prakash in the CF₃TMS-derived trifluoromethylation of (2-methyl-2-propane)sulfinaldimines.

Experimental Section

¹H and ¹⁹F NMR spectra were recorded in CDCl₃ using tetramethylsilane (TMS) and CFCl₃ as internal standards, respectively. TDAE was prepared by a published procedure (with some modification),²⁹ *N*-tosyl aldimines 1a–g were prepared according to the previous literature.²⁵ Sulfinimines 3a–e, 3g, and 3h were prepared according to Davis's method,²⁶ and 3f was prepared by Ruano's Procedure.³⁰ *S*-(+)-2,4,6-Trimethylphenyl sulfonamide was prepared following Senanayake's method,²⁷ and 5 was prepared by a published procedure.²⁸

General Procedure for Trifluoromethylation of *N*-Tosyl Aldimines. Into a three-necked flask equipped with a dry ice reflux condenser were added 10 mL of anhydrous DMF and the *N*-tosylimine (1 mmol). The system was degassed and filled with dry nitrogen under a balloon. The solution was cooled to -30 °C, and TDAE (2.2 mmol) was added. After stirring for 15 min, CF₃I (2.2 mmol) was bubbled into the mixture. The solution was vigorously stirred at -30 °C for 30 min and then allowed to warm slowly to room temperature. The mixture was stirred overnight, after which it was quenched with 2 N hydrochloric acid solution. The resulting aqueous mixture was extracted with dichloromethane (three times); the extract washed with brine (three times) and then dried over Na₂SO₄. The solvent was removed, and the crude product was purified by silica gel chromatography (ethyl acetate/hexane = 1:5) to give the trifluoromethylated product.

4-Methyl-*N*-(2,2,2-trifluoro-1-phenyl-ethyl)-benzenesulfonamide, 2a:¹⁰ pale white solid, yield 86%; mp 155–156 °C; ¹H NMR δ 2.37 (s, 3H), 4.92 (q, *J* = 7.5 Hz, 1H), 5.23 (d, *J* = 9.3 Hz, 1H), 7.15–7.18 (m, 4H), 7.28–7.33 (m, 3H), 7.60 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ -74.3 (d, *J* = 6.5 Hz, 3F); MS (EI) *m/z* 329 (M⁺), 328 (M⁺ - H), 260 (M⁺ - CF₃), 174 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - C₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₅H₁₄F₃NO₂S: C, 54.70; H, 4.28; N, 4.25. Found: C, 54.72; H, 4.21; N, 4.18.

4-Methyl-*N*-[2,2,2-trifluoro-1-(4-methyl-phenyl)-ethyl]-benzenesulfonamide, 2b: pale white solid, yield 84%; mp 181–182 °C; ¹H NMR δ 2.31 (s, 3H), 2.37 (s, 3H), 4.87 (q, *J* = 7.5 Hz, 1H), 5.21 (d, *J* = 9.0 Hz, 1H), 7.08 (s, 4H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ -74.4 (d, *J* = 6.5 Hz, 3F); MS (EI) *m/z* 342 (M⁺ - H), 274 (M⁺ -

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CF₃), 188 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - 4-CH₃C₆H₅-CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₆H₁₆F₃NO₂S: C, 55.97; H, 4.70; N, 4.08. Found: C, 55.49; H, 4.70; N, 4.07.

4-Methyl-N-[2,2,2-trifluoro-1-(4-methoxy-phenyl)-ethyl]-benzenesulfonamide, 2c:¹⁰ pale white solid, yield 84%; mp 152–153 °C; ¹H NMR δ 2.37 (s, 3H), 3.77 (s, 3H), 4.85 (q, *J* = 8.4 Hz, 1H), 5.31 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ -74.6 (d, *J* = 6.2 Hz, 3F); MS (EI) *m/z* 359 (M⁺), 290 (M⁺ - CF₃), 204 (M⁺ - 4-CH₃-C₆H₄-SO₂), 155 (M⁺ - 4-CH₃O-C₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺); Anal. Calcd for C₁₆H₁₆F₃NO₂S: C, 53.48; H, 4.49; N, 3.90. Found: C, 53.36; H, 4.48; N, 3.81

4-Methyl-N-[2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethyl]-benzenesulfonamide 2d: pale white solid, yield 81%; mp 182–183 °C; ¹H NMR δ 2.38 (s, 3H), 4.90 (q, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 6.92–6.99 (m, 2H), 7.17–7.20 (m, 4H), 7.60 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ -74.5 (d, *J* = 6.4 Hz, 3F), -111.8 (s, 1F); MS (EI) *m/z* 347 (M⁺), 346 (M⁺ - H), 278 (M⁺ - CF₃), 192 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - 4-FC₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₅H₁₃F₄NO₂S: C, 51.87; H, 3.77; N, 4.03. Found: C, 51.82; H, 3.73; N, 3.92.

4-Methyl-N-[2,2,2-trifluoro-1-(4-chloro-phenyl)-ethyl]-benzenesulfonamide, 2e:¹⁰ pale white solid, yield 78%; mp 202–203 °C; ¹H NMR δ 2.39 (s, 3H), 4.90 (q, *J* = 7.8 Hz, 1H), 5.43 (d, *J* = 7.2 Hz, 1H), 7.11–7.25 (m, 6H), 7.60 (d, *J* = 8.4 Hz, 2H); ¹⁹F NMR δ -74.4 (d, *J* = 6.5 Hz, 3F); MS (EI) *m/z* 365 (M⁺ + 2), 363 (M⁺), 362 (M⁺ - H), 294 (M⁺ - CF₃), 208 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - 4-ClC₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₅H₁₃ClF₃NO₂S: C, 49.52; H, 3.60; N, 3.85. Found: C, 49.36; H, 3.52; N, 3.76.

4-Methyl-N-[2,2,2-trifluoro-1-(4-nitro-phenyl)-ethyl]-benzenesulfonamide, 2f: yellow solid, yield 76%; mp 166–167 °C; ¹H NMR δ 2.38 (s, 3H), 5.05 (q, *J* = 8.7 Hz, 1H), 5.65 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 2H); ¹⁹F NMR δ -73.9 (d, *J* = 6.5 Hz, 3F); MS (EI) *m/z* 374 (M⁺), 373 (M⁺ - H), 305 (M⁺ - CF₃), 219 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - 4-NO₂C₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₅H₁₃F₃N₂O₄S: C, 48.13; H, 3.50; N, 7.48. Found: C, 47.74; H, 3.50; N, 7.16.

4-Methyl-N-(1,1,1-trifluoro-4-phenylbut-3-en-2-yl)-benzenesulfonamide, 2g:¹⁰ pale white solid, yield 62%; mp 119–120 °C; ¹H NMR δ 2.36 (s, 3H), 4.58 (q, *J* = 8.7 Hz, 1H), 4.96 (d, *J* = 9.3 Hz, 1H), 5.90 (d, *J* = 17.1, 8.1 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 7.21–7.33 (m, 7H), 7.75 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ -75.8 (d, *J* = 6.5 Hz, 3F); MS (EI) *m/z* 355 (M⁺), 354 (M⁺ - H), 286 (M⁺ - CF₃), 200 (M⁺ - 4-CH₃-C₆H₄-SO₂), 155 (M⁺ - 4-FC₆H₅CHCF₃NH), 91 (C₆H₅CH₂⁺). Anal. Calcd for C₁₇H₁₆F₃NO₂S: C, 57.46; H, 4.54; N, 3.94. Found: C, 57.59; H, 4.43; N, 3.88.

4-Methyl-N-(2,2,2-trifluoro-1,1-diphenyl-ethyl)-benzenesulfonamide, 2h: pale white solid, yield 54%; mp 184–185 °C; ¹H NMR δ 2.37 (s, 3H), 5.72 (s, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.23–7.34 (m, 12H); ¹⁹F NMR δ -69.9 (s, 3F); MS (EI) *m/z* 405 (M⁺), 404 (M⁺ - H), 336 (M⁺ - CF₃), 250 (M⁺ - 4-CH₃-C₆H₄SO₂), 155 (M⁺ - (C₆H₅)₂CCF₃NH), 91 (C₆H₅-CH₂⁺). Anal. Calcd for C₂₁H₁₈F₃NO₂S: C, 62.21; H, 4.47; N, 3.45. Found: C, 62.05; H, 4.44; N, 4.40.

General Procedure for Trifluoromethylation of Sulfinimines. Into a three-necked flask equipped with a dry ice reflux condenser were added 10 mL of anhydrous DMF and S-(+)-sulfonimine (1 mmol). The system was degassed and filled with dry nitrogen with a balloon. The solution was cooled to -30 °C, and TDAE (2.2 mmol) was added. After the reaction was stirred for 15 min, CF₃I (2.2 mmol) was bubbled into the mixture. The solution was vigorously stirred at -30 °C for 30 min and then warmed slowly to room temperature. The mixture was stirred overnight, and the reaction was quenched with saturated ammonia chloride solution. The resulting aqueous mixture was extracted with dichloromethane (three

times), and the extract was washed with brine (three times) and dried over Na₂SO₄. The solvent was removed, and the crude product was purified by silica gel chromatography (ethyl acetate/hexane = 1:5) to give the trifluoromethylated product as a mixture of diastereomers. There was no indication of a significant separation of the diastereomers during the chromatography.

4a: pale white solid, yield 66%; mp 107–108 °C; ¹H NMR δ 2.31 (s, 0.87 × 3H), 2.37 (0.13 × 3H), 4.57 (d, *J* = 6.6 Hz, 0.87 × 1H), 4.66–4.77 (m, 0.13 × 2H), 4.85 (q, *J* = 7.2 Hz, 0.87 × 1H), 7.15–7.25 (m, 0.87 × 7H), 7.36–7.40 (m, 0.13 × 7H), 7.47 (d, *J* = 8.1 Hz, 0.87 × 2H), 7.55 (d, *J* = 8.1 Hz, 0.13 × 2H); ¹⁹F NMR δ -74.2 (d, *J* = 6.2 Hz, 0.13 × 3F), -74.4 (d, *J* = 8.4 Hz, 0.87 × 3F); MS (EI) *m/z* 313 (M⁺), 265 (M⁺ - SO), 174 (M⁺ - SOC₆H₄-4-CH₃), 139 (+SOC₆H₄-4-CH₃), 91 (C₆H₅CH₂⁺), 77 (C₆H₅⁺); HRMS (EI) calcd for C₁₅H₁₄F₃NOS (M⁺) 313.0748, found 313.0748. Anal. Calcd for C₁₅H₁₄F₃NOS: C, 57.50; H, 4.50; N, 4.47. Found: C, 57.29; H, 4.51; N, 4.35.

4b: pale white solid, yield 73%; mp 102–103 °C; ¹H NMR δ 2.33 (s, 0.86 × 3H), 2.40 (s, 3H), 2.44 (s, 0.14 × 3H), 4.56 (d, *J* = 6.9 Hz, 0.86 × 1H), 4.69–4.72 (m, 0.14 × 1H), 4.78 (q, *J* = 7.2 Hz, 0.14 × 1H), 4.89 (q, *J* = 7.2 Hz, 0.86 × 1H), 7.12–7.20 (m, 0.86 × 4H), 7.25 (d, *J* = 6.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 0.14 × 4H), 7.61 (d, *J* = 8.4 Hz, 0.86 × 2H), 7.55 (d, *J* = 7.8 Hz, 0.14 × 2H); ¹⁹F NMR δ -74.3 (d, *J* = 8.5 Hz, 0.14 × 3F), -74.4 (d, *J* = 8.5 Hz, 0.86 × 3F); MS (EI) *m/z* 327 (M⁺), 278 (M⁺ - SO), 188 (M⁺ - SOC₆H₄-4-CH₃), 139 (+SOC₆H₄-4-CH₃), 91 (C₆H₅CH₂⁺); HRMS (EI) calcd for C₁₆H₁₆F₃NOS (M⁺) 327.0905, found 327.0891. Anal. Calcd for C₁₆H₁₆F₃NOS: C, 58.70; H, 4.93; N, 4.28. Found: C, 58.35; H, 4.88; N, 4.21.

4c: pale white solid, yield 71%; mp 87–88 °C; ¹H NMR δ 2.38 (s, 0.82 × 3H), 2.43 (s, 0.18 × 3H), 3.78 (s, 0.82 × 3H), 3.83 (s, 0.18 × 3H), 4.59 (d, *J* = 6.6 Hz, 0.82 × 1H), 4.70–4.80 (m, 0.18 × 2H), 4.87 (q, *J* = 7.5 Hz, 0.82 × 1H), 6.80–6.85 (m, 0.82 × 2H), 6.92–6.97 (m, 0.18 × 2H), 7.12–7.42 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 0.82 × 2H), 7.60 (d, *J* = 8.1 Hz, 0.18 × 2H); ¹⁹F NMR δ -74.47 (d, *J* = 8.5 Hz, 0.18 × 3F), -74.52 (d, *J* = 8.5 Hz, 0.82 × 3F); HRMS (ESI) calcd for C₁₆H₁₆F₃NOS (M⁺ + Na) 366.0751, found 366.0744. Anal. Calcd for C₁₆H₁₆F₃NO₂S: C, 55.97; H, 4.70; N, 4.08. Found: C, 55.65; H, 4.88; N, 4.41.

4d: pale white solid, yield 69%; mp 92–93 °C; ¹H NMR δ 2.37 (s, 0.85 × 3H), 2.43 (s, 0.15 × 3H), 4.62 (d, *J* = 6.6 Hz, 0.85 × 1H), 4.70–4.80 (m, 0.15 × 2H), 4.91 (q, *J* = 7.8 Hz, 0.85 × 1H), 6.95–7.01 (m, 0.85 × 2H), 7.09–7.15 (m, 0.85 × 2H), 7.20–7.36 (m, 4H), 7.49 (d, *J* = 8.1 Hz, 0.85 × 2H), 7.59 (d, *J* = 8.4 Hz, 0.15 × 2H); ¹⁹F NMR δ -74.3 (d, *J* = 8.5 Hz, 0.14 × 3F), -74.4 (d, *J* = 8.5 Hz, 0.86 × 3F); MS (EI) *m/z* 331 (M⁺), 283 (M⁺ - SO), 192 (M⁺ - SOC₆H₄-4-CH₃), 139 (+SOC₆H₄-4-CH₃), 91 (C₆H₅CH₂⁺); HRMS (EI) calcd for C₁₅H₁₃F₄NOS (M⁺) 331.0654, found 331.0650. Anal. Calcd for C₁₅H₁₃F₄NOS: C, 54.38; H, 3.95; N, 4.23. Found: C, 54.28; H, 3.83; N, 4.11.

4e: pale white solid, yield 74%; mp 96–97 °C; ¹H NMR δ 2.35 (s, 0.88 × 3H), 2.45 (s, 0.12 × 3H), 4.81 (d, *J* = 6.3 Hz, 1H), 5.00 (q, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.46 (m, 0.88 × 2H), 7.52 (d, *J* = 8.1 Hz, 0.88 × 2H), 7.62 (m, 0.12 × 2H), 7.71 (d, *J* = 7.8 Hz, 0.12 × 2H); ¹⁹F NMR δ -63.28 (s, 0.12 × 3F), -63.32 (s, 0.88 × 3F), -73.9 (d, *J* = 6.2 Hz, 0.12 × 3F), -74.0 (d, *J* = 6.9 Hz, 0.88 × 3F); MS (EI) *m/z* 381 (M⁺), 333 (M⁺ - SO), 245 (M⁺ - SOC₆H₄-4-CH₃), 139 (+SOC₆H₄-4-CH₃), 91 (C₆H₅CH₂⁺); HRMS (EI) calcd for C₁₆H₁₃F₆NOS (M⁺) 381.0622, found 381.0624. Anal. Calcd for C₁₆H₁₃F₆NOS: C, 50.39; H, 3.44; N, 3.67. Found: C, 50.12; H, 3.51; N, 3.50.

4f: pale yellow liquid that crystallizes upon standing, yield 48%; mp 66–67 °C; ¹H NMR (CDCl₃) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.28 (s, 6H), 1.45–1.87 (m, 4H), 2.41 (s, 3H), 2.44 (s, 0.14 × 3H), 3.58–3.66 (m, 0.28 × 1H), 3.76–3.83 (m, 0.72 × 1H), 4.02 (d, *J* = 7.8 Hz, 0.72 × 1H), 4.34 (d, *J* = 9.0 Hz, 0.28 ×

1H), 7.28–7.32 (m, 2H), 7.56–7.61 (m, 2H); ^{19}F NMR δ -75.4 (d, J = 6.2 Hz, 0.28 \times 3F), -76.8 (d, J = 6.5 Hz, 0.72 \times 3F); MS (EI) m/z 322 (M^+ + H), 321 (M^+), 273 (M^+ - SO), 182 (M^+ - SOC_6H_4 -4- CH_3), 139 ($^+\text{SOC}_6\text{H}_4$ -4- CH_3); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{23}\text{F}_3\text{NOS}$ (M^+ + H) 322.1452, found 322.1461.

4g: pale white solid, yield 67%; mp 90–91 °C; ^1H NMR δ 2.36 (s, 0.88 \times 3H), 2.43 (s, 0.12 \times 3H), 4.56 (d, J = 6.9 Hz, 0.88 \times 1H), 4.74 (t, J = 6.9 Hz, 0.12 \times 1H), 4.86 (q, J = 7.5 Hz, 0.88 \times 1H), 4.99 (d, J = 7.2 Hz, 0.88 \times 1H), 7.15–7.59 (m, 8H); ^{19}F NMR δ -74.1 (d, J = 8.5 Hz, 0.12 \times 3F), -74.3 (d, J = 9.0 Hz, 0.88 \times 3F); MS (EI) m/z 347 (M^+), 299 (M^+ - SO), 208 (M^+ - SOC_6H_4 -4- CH_3), 139 ($^+\text{SOC}_6\text{H}_4$ -4- CH_3), 91 ($\text{C}_6\text{H}_5\text{CH}_2^+$); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{ClF}_3\text{NOS}$ (M^+) 347.0358, found 347.0350. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{ClF}_3\text{NOS}$: C, 51.80; H, 3.77; N, 4.03. Found: C, 51.56; H, 3.66; N, 3.84.

4h: pale white solid, yield 42%; mp 109–110 °C; ^1H NMR δ 2.23 (s, 3H), 4.88 (d, J = 5.7 Hz, 1H), 5.80 (q, J = 7.2 Hz,

1H), 7.03 (d, J = 8.4 Hz, 2H), 7.40–7.60 (m, 8H), 7.82–7.92 (m, 4H); ^{19}F NMR δ -73.2 (d, J = 7.6 Hz, 0.94 \times 3F), -73.9 (d, J = 7.1 Hz, 0.06 \times 3F); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{-NOS}$ (M^+ + Na) 386.0802, found 386.0744.

6: pale white solid, yield 57%; ^1H NMR δ 2.29 (s, 3H), 2.51 (s, 6H), 4.68 (d, J = 9.0 Hz, 0.90 \times 1H), 4.82 (d, J = 8.7 Hz, 0.10 \times 1H), 4.94 (q, J = 6.3 Hz, 0.90 \times 1H), 4.97–5.04 (m, 0.10 \times 1H), 6.85 (s, 2H), 7.41–7.48 (m, 5H); ^{19}F NMR δ -74.3 (d, J = 6.2 Hz, 0.90 \times 3F), -74.5 (d, J = 6.2 Hz, 0.10 \times 3F).

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