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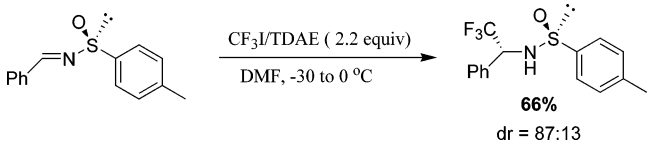
Nucleophilic Trifluoromethylation of Imines Using the CF_3I/TDAE Reagent

Wei Xu and William R. Dolbier, Jr.*

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

wrd@chem.ufl.edu

Received March 10, 2005



The nucleophilic trifluoromethylation reagent derived from CF_3I 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 coworkers have delved into its reactions with imine derivatives with the idea of developing methods for preparing trifluoromethylamines[10] 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 CF_3TMS 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 trifluoromethyliodide by tetrakis-(dimethylamino)ethylene (TDAE).[22] The chemical reactivity of the CF_3I/TDAE reagent bears some similarities to that of CF_3TMS, but, in part because it does not involve the necessity for TMS

(1) Bhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Mller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643.
(2) Jeschke, P. *ChemBioChem* **2004**, *5*, 570−589.
(3) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.
(4) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786.
(5) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123−131.
(6) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7632.
(7) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189−275.
(8) Prakash, G. K. S.; Krishnamurthy, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393−395.
(9) Dolbier, W. R., Jr. *Chim. Oggi* **2003**, *21*, 66−69.
(10) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett.* **2001**, 77−78.
(11) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589−590.
(12) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538−6539.
(13) Pirkle, W. H.; Hanske, J. R. *J. Org. Chem.* **1977**, *42*, 2436−2439.
(14) Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**, *32*, 987−990.
(15) Soloshonok, V. A.; Ono, T. *J. Org. Chem.* **1997**, *62*, 3030−3031.
(16) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron Lett.* **1997**, *38*, 5965−5966.
(17) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572−2582.
(18) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2002**, *116*, 103−107.
(19) Yong, K. H.; Chong, J. M. *Org. Lett.* **2002**, *4*, 4139−4142.
(20) Spanedda, M. V.; Ourevitch, M.; Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2004**, *45*, 5023−5025.
(21) Kochi, T.; Mukade, T.; Ellman, J. A. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 128−139.
(22) At-Mohand, S.; Takechi, N.; Mdebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2001**, *3*, 4271−4273.

10.1021/jo050483v CCC: $30.25
Published on Web 05/07/2005

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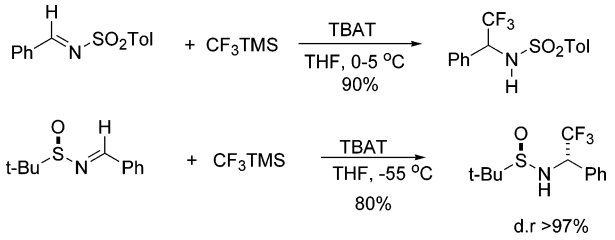

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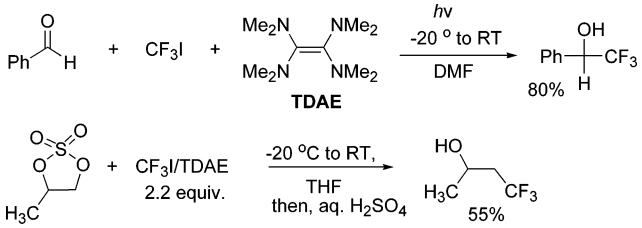

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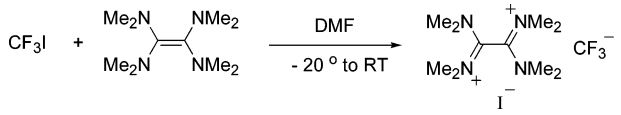


transfer as part of the mechanism, it also exhibits significant differences such as in its ability to open cyclic sulfates to produce β-trifluoromethyl alcohols.[23] On the other hand, CF_3TMS appears to be more suitable for reactions with substrates that bear readily enolizable hydrogens (such as aliphatic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

In our efforts to fully explore the scope and limitations of the CF_3I/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.

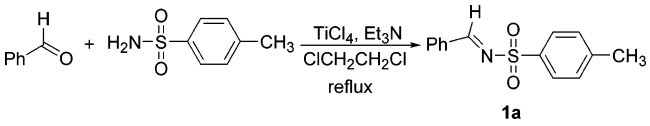
Results and Discussion

Nucleophilic trifluoromethylation using the CF_3I/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 °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



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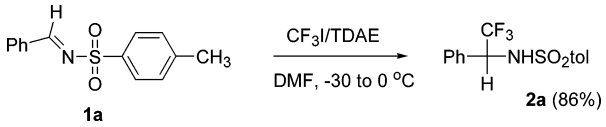


TABLE 1. Trifluoromethylation of *N*-Tosylimines

	$R_1R_2C{=}NSO_2Tol$		**2**, yield (%)
compd	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 CF_3I/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]

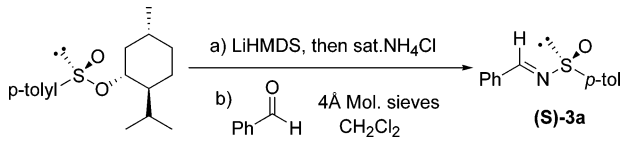
Enantiopure sulfinimines have been demonstrated to be versatile chiral imine building blocks for the asymmetric synthesis of amines.[11] There are a number of reasons for this, including the ability of the sulfinyl group to enhance nucleophilic addition to the C=N double bond, its ability to provide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

(23) Takechi, N.; Ait-Mohand, S.; Medebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2002**, *4*, 4671−4672.

(24) Blazejewski, J. C.; Anselmi, E.; Wilmshurst, M. P. *Tetrahedron Lett.* **1999**, *40*, 5475−5478.

(25) Ram, R. N.; Khan, A. A. *Synth. Commun.* **2001**, 841−846.

SCHEME 6



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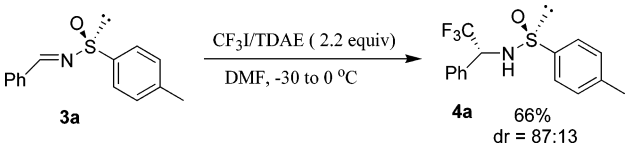


TABLE 2. Trifluoromethylation of *N*-Tolylsulfinimines

$R_1C_2H{=}NSO_2Tol$			
compd	R	dr	**4**, yield (%)
3a	Ph	87:13	66
3b	4-CH_3Ph	86:14	73
3c	4-CH_3OPh	82:18	71
3d	4-FPh	85:15	69
3e	4-CF_3Ph	88:12	74
3f	*n*-C_6H_{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*-Tolylsulfinylimines 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 CF_3^- reagent derived from CF_3I/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]

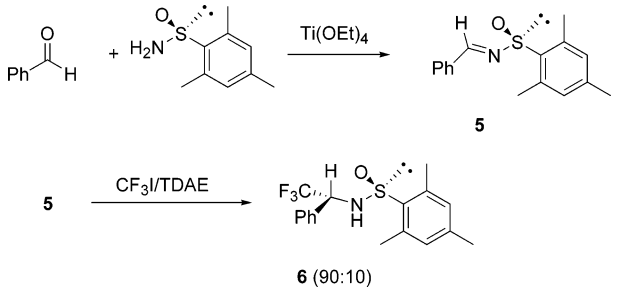
Unfortunately, only a modest increase in diastereoselectivity was observed as a result of using the mesityl rather than the tosyl derivative.

In an attempt to compare the diastereoselectivity of our reagent directly with that of CF_3TMS, the (2-methyl-2-propane)sulfinimine derivative of benzaldehyde was examined using our CF_3I/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 CF_3I/TDAE has proved to be effective for addition to both *N*-tosyl- and *N*-tolylsulfinaldimines and thus provides a viable synthetic alternative to the use of CF_3TMS 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 CF_3TMS-derived trifluoromethylation of (2-methyl-2-propane)sulfinaldimines.

SCHEME 8



Experimental Section

^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ using tetramethylsilane (TMS) and $CFCl_3$ 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 sulfinamide was prepared following Senannayake'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, CF_3I (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 hydrochloride acid solution. The resulting aqueous mixture was extracted with dichloromethane (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. 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; ^{1}H 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); ^{19}F NMR δ −74.3 (d, J = 6.5 Hz, 3F); MS (EI) *m*/*z* 329 (M^+), 328 (M^+ − H), 260 (M^+ − CF_3), 174 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − $C_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{15}H_{14}F_3NO_2S$: 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; ^{1}H 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); ^{19}F NMR δ −74.4 (d, J = 6.5 Hz, 3F); MS (EI) *m*/*z* 342 (M^+ − H), 274 (M^+ −

(26) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403−1406.
(27) Han, Z. X.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880−7881.
(28) Davis, F. A.; Ramachandar, T.; Wu, Y. Z. *J. Org. Chem.* **2003**, *68*, 6894−6898.
(29) Pruett, R. L.; Barr, J. T.; Rapp, K. E.; Bahner, C. T.; Gibson, J. D.; Lafferty, H. L. *J. Am. Chem. Soc.* **1950**, *72*, 3646−3650.
(30) Ruano, J. L. G.; Aleman, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677−680.

CF_3), 188 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-$CH_3C_6H_5$-$CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{16}H_{16}F_3NO_2S$: 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; ^{1}H 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); ^{19}F NMR δ −74.6 (d, J = 6.2 Hz, 3F); MS (EI) *m/z* 359 (M^+), 290 ($M^+ - CF_3$), 204 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-CH_3O-$C_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$); Anal. Calcd for $C_{16}H_{16}F_3NO_3S$: 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; ^{1}H NMR δ2.38 (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); ^{19}F NMR δ −74.5 (d, J = 6.4 Hz, 3F), −111.8 (s, 1F); MS (EI) *m/z* 347 (M^+), 346 (M^+ − H), 278 ($M^+ - CF_3$), 192 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-$FC_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{15}H_{13}F_4NO_2S$: 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; ^{1}H 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); ^{19}F NMR δ − 74.4 (d, J = 6.5 Hz, 3F); MS (EI) *m/z* 365 (M^+ + 2), 363 (M^+), 362 (M^+ − H), 294 ($M^+ - CF_3$), 208 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-$ClC_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{15}H_{13}ClF_3NO_2S$: 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; ^{1}H 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); ^{19}F NMR δ −73.9 (d, J = 6.5 Hz, 3F); MS (EI) *m/z* 374 (M^+), 373 (M^+ − H), 305 ($M^+ - CF_3$), 219 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-$NO_2C_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{15}H_{13}F_3N_2O_4S$: 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; ^{1}H 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 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); ^{19}F NMR δ −75.8 (d, J = 6.5 Hz, 3F); MS (EI) *m/z* 355 (M^+), 354 (M^+ − H), 286 ($M^+ - CF_3$), 200 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 (M^+ − 4-$FC_6H_5CHCF_3NH$), 91 ($C_6H_5CH_2^+$). Anal. Calcd for $C_{17}H_{16}F_3NO_2S$: 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; ^{1}H NMR δ 2.37 (s, 3H), 5.72 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.23−7.34 (m, 12H); ^{19}F NMR δ −69.9 (s, 3F); MS (EI) *m/z* 405 (M^+), 404 (M^+ − H), 336 ($M^+ - CF_3$), 250 (M^+ − 4-CH_3-$C_6H_4SO_2$), 155 ($M^+ - (C_6H_5)_2CCF_3NH$), 91 (C_6H_5-CH_2^+). Anal. Calcd for $C_{21}H_{18}F_3NO_2S$: 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*-(+)-sulfinimine (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, CF_3I (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 Na_2SO_4. 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; ^{1}H 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); ^{19}F 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^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3), 91 ($C_6H_5CH_2^+$), 77 ($C_6H_5^+$); HRMS (EI) calcd for $C_{15}H_{14}F_3NOS$ (M^+) 313.0748, found 313.0748. Anal. Calcd for $C_{15}H_{14}F_3$-NOS: 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; ^{1}H 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); ^{19}F 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^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3), 91 ($C_6H_5CH_2^+$); HRMS (EI) calcd for $C_{16}H_{16}F_3$-NOS (M^+) 327.0905, found 327.0891. Anal. Calcd for $C_{16}H_{16}F_3$-NOS: 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; ^{1}H 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); ^{19}F 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 $C_{16}H_{16}F_3$-NOS (M^+ + Na) 366.0751, found 366.0744. Anal. Calcd for $C_{16}H_{16}F_3NO_2S$: 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; ^{1}H 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); ^{19}F 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^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3), 91 ($C_6H_5CH_2^+$); HRMS (EI) calcd for $C_{15}H_{13}F_4$-NOS (M^+) 331.0654, found 331.0650. Anal. Calcd for $C_{15}H_{13}F_4$-NOS: 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; ^{1}H 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); ^{19}F 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^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3), 91 ($C_6H_5CH_2^+$); HRMS (EI) calcd for $C_{16}H_{13}F_6NOS$ (M^+) 381.0622, found 327.0624. Anal. Calcd for $C_{16}H_{13}F_6NOS$: 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; ^{1}H NMR ($CDCl_3$) 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 × 3F), −76.8 (d, J = 6.5 Hz, 0.72 × 3F); MS (EI) *m/z* 322 (M^+ + H), 321 (M^+), 273 (M^+ − SO), 182 (M^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3); HRMS (EI) calcd for $C_{15}H_{23}F_3NOS$ (M^+ + H) 322.1452, found 322.1461.

4g: pale white solid, yield 67%; mp 90−91 °C; ^{1}H NMR δ 2.36 (s, 0.88 × 3H), 2.43 (s, 0.12 × 3H), 4.56 (d, J = 6.9 Hz, 0.88 × 1H), 4.74 (t, J = 6.9 Hz, 0.12 × 1H), 4.86 (q, J = 7.5 Hz, 0.88 × 1H), 4.99 (d, J = 7.2 Hz, 0.88 ×1H), 7.15−7.59 (m, 8H); ^{19}F NMR δ −74.1 (d, J = 8.5 Hz, 0.12 × 3F), −74.3 (d, J = 9.0 Hz, 0.88 × 3F); MS (EI) *m/z* 347 (M^+), 299 (M^+ − SO), 208 (M^+ − SOC_6H_4-4-CH_3), 139 ($^+SOC_6H_4$-4-CH_3), 91 ($C_6H_5CH_2^+$); HRMS (EI) calcd for $C_{15}H_{13}ClF_3NOS$ (M^+) 347.0358, found 347.0350. Anal. Calcd for $C_{15}H_{13}ClF_3NOS$: 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; ^{1}H 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 × 3F), −73.9 (d, J = 7.1 Hz, 0.06 × 3F); HRMS (ESI) calcd for $C_{19}H_{16}F_3NOS$ (M^+ + Na) 386.0802, found 386.0744.

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

Acknowledgment. Support of this work in part by the National Science Foundation is acknowledged with thanks.

JO050483V