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Asymmetric Friedel–Crafts Reactions of *N-tert*-Butylsulfinyl-3,3,3-trifluoroacetaldimines: General Access to Enantiomerically Pure Indoles Containing a 1-Amino-2,2,2-trifluoroethyl Group

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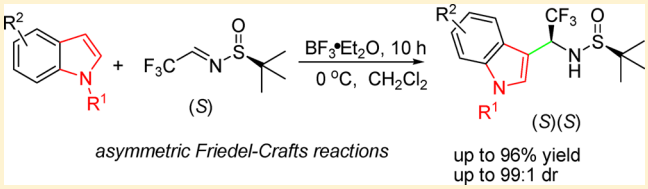
Supporting Information

ABSTRACT: We have demonstrated that 3,3,3-trifluoroacetaldimine (*S*)-**1** easily reacts with indole derivatives under Friedel–Crafts reactions to provide reliable and generalized access to biologically interesting compounds containing the $CF_3CH(NH_2)$– pharmacophoric group. The reactions proceed with high rates and generally excellent yields (>90%) and stereochemical outcomes (99:1 dr).



Indoles represent one of the most abundant classes of naturally occurring biologically active compounds. From the early days of pharmaceutical science, indole-derived drugs have played a pivotal role in modern medicine.[1] In view of the ever-increasing importance of fluorine in modern drug development,[2] the synthesis and medicinal chemistry of fluorine-containing indoles have received particular attention.[3] Consistent with our longstanding interest in the synthesis of biologically relevant fluorinated compounds,[4] we have been developing the chemistry of (*S*)- and (*R*)-*N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine [(*S*)-**1** and (*R*)-**1**, respectively] (Figure 1)[5] as distinctive reagents for wide-ranging preparation

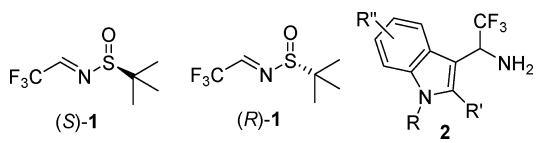
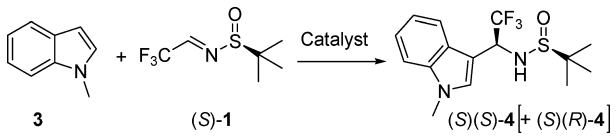


Figure 1. Chiral trifluoromethyl imines **1** and indole derivatives **2**.

of various classes of compounds containing the 2,2,2-trifluoro-1-aminoethyl [$CF_3CH(NH_2)$–] pharmacophoric group.[6] One of the still unexplored areas of the reactivity of imines **1** is Friedel–Crafts-type additions, which can provide direct access to trifluoromethyl-containing indoles **2** (Figure 1). Therefore, motivated by the novelty of both Friedel–Crafts reactions of imines **1** and the type of compounds **2**, we decided to investigate the Lewis acid-catalyzed reactions of (*S*)-**1** with various indoles. Our results suggest that this approach is exceptionally successful in granting generalized access to indoles bearing substituents on both the six- and five-membered rings.

To exclude the potential reactivity of the NH function of the parent indole, as a model compound we chose to study *N*-methylindole (**3**). Friedel–Crafts reactions of **3** with imine (*S*)-**1** are presented in Table 1. Attempts to use $AlCl_3$ as the catalyst led to complete decomposition of the starting compounds (entry 1). Instead, the application of a less strong Lewis acid, $Cu(OTf)_2$, allowed the preparation of the target products **4** in 60% yield, albeit with rather low diastereoselectivity (entry 2). We found that the stereochemical outcome could be

Table 1. Optimization of the Conditions for the Reaction of Indole 3 with Imine (*S*)-1[a]



entry	catalyst (mol %)	solvent	temp.	time (h)	yield (%)[b]	dr[c]
1	$AlCl_3$ (20)	CH_2Cl_2	rt	4	trace	–
2	$Cu(OTf)_2$ (20)	CH_2Cl_2	rt	4	60	70:30
3	$BF_3{\cdot}Et_2O$ (20)	CH_2Cl_2	rt	4	17	95:5
4	$BF_3{\cdot}Et_2O$ (100)	CH_2Cl_2	rt	4	87	93:7
5	BF_3 Et_2O (100)	toluene	rt	4	47	89:11
6	$BF_3{\cdot}Et_2O$ (100)	Et_2O	rt	4	50	94:6
7	$BF_3{\cdot}Et_2O$ (100)	*n*-hexane	rt	4	52	80:20
8	$BF_3{\cdot}Et_2O$ (100)	CH_2Cl_2	0 °C	10	90	98:2

[a]Reaction conditions: sulfinylimine **1** (1 mmol), indole **3** (1.2 mmol), catalyst, 5 mL of solvent. [b]Isolated yields of major diastereomers. [c]Determined by ^{19}F NMR analysis of the crude reaction mixtures.

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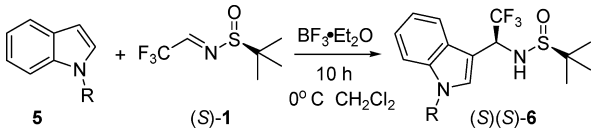
significantly improved to 95:5 with the application of $BF_3{\cdot}Et_2O$ (entry 3) as the catalyst for this reaction. Further optimization attempts led us to use a stoichiometric amount of $BF_3{\cdot}Et_2O$ (entry 4). The necessity to apply a rather large quantity of Lewis acid in these reactions can be rationalized by the fact that the sulfoxide oxygen in imine (*S*)-**1** can act as a Lewis base and thus neutralize the catalyst effect.[7] Attempts to use solvents other than CH_2Cl_2 were rather unsuccessful, resulting in both lower chemical yields and lower diastereoselectivity (entries 5–7). Finally, we found that lowering the reaction temperature from ambient to 0 °C afforded the target product in 90% yield with improved selectivity (entry 8), although the reaction was slower, taking about 10 h for its completion. These results clearly demonstrated that the Friedel–Crafts reaction of imine (*S*)-**1** with indole **3** can be conducted under very mild conditions and affords the target compounds in synthetically valuable yields and diastereoselectivity. The next goals of this study were to explore the structural generality of these reactions and elucidate a possible mechanistic rationale for the observed stereochemical outcome.

First, we investigated the effect of the substituent on the indole nitrogen, and the results are summarized in Table 2. In

Table 2. Reactions of *N*-Substituted Indoles 5 with Imine (*S*)-1[a]



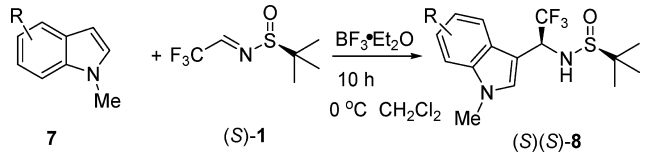
entry	R	product	yield (%)[b]	dr[c]
1	CH_3	**6a**	90	98:2
2	Et	**6b**	82	98:2
3	Bn	**6c**	85	96:4
4	Cbz	**6d**	NR	–
5	H	**6e**	36[d]	77:23

[a]Reaction conditions: sulfinylimine **1** (1 mmol), indole **5** (1.2 mmol), $BF_3{\cdot}Et_2O$ (1 mmol), CH_2Cl_2 (5 mL). [b]Isolated yields of major diastereomers; NR indicates no reaction. [c]Determined by ^{19}F NMR analysis of the crude reaction mixtures. [d]The reaction was run for 18 h.

the reactions of *N*-ethyl and *N*-benzyl derivatives **5** we observed reactivity similar to that of *N*-methylindole (entries 2 and 3 vs 1), and the corresponding products **6** were isolated in good yields and diastereomeric purity. In sharp contrast, indole **5** bearing a Cbz protecting group (entry 4) failed to react with imine (*S*)-**1**; not even a trace amount of the expected product **6** was observed in the reaction mixture. Of particular interest was the reaction of unprotected indole **5** (entry 5), which gave a rather poor outcome. While the reaction did take place, the product **6** was isolated in 36% yield with low diastereoselectivity. This brief screening allowed us to outline some general principles and limitations of these Friedel–Crafts reactions in terms of the electronic properties of the *N*-substituent as well as the possibility of using unsubstituted indole.

Next, we focused on exploring the generality of these reactions using *N*-methylindoles **7** (Table 3) bearing substituents in all possible positions of the indole framework. For the purpose of comparison, all of the reactions were conducted under the standard conditions: sulfinylimine **1** (1 mmol), indole **7** (1.2 mmol), and $BF_3{\cdot}Et_2O$ (1 mmol) in

Table 3. Reactions of Various Substituted *N*-Methylindoles 7 with Imine (*S*)-1[a]



entry	R	product	yield (%)[b]	dr[c]
1	2-CH_3	**8a**	87	96:4
2	2-CHO	**8b**	NR	–
3	4-CN	**8c**	60	99:1
4	4-MeO	**8d**	80	97:3
5	5-CN	**8e**	75	99:1
6	5-MeO	**8f**	92	99:1
7	5-$COOCH_3$	**8g**	96	97:3
8	5-COOH	**8h**	90[d]	77:23
9	6-Cl	**8i**	68	90:10
10	6-Br	**8j**	64	90:10
11	7-Br	**8k**	74	96:4
12	7-CH_3	**8l**	82	99:1
13	2-CH_3-5-MeO	**8m**	94	99:1

[a]Reaction conditions: sulfinylimine **1** (1 mmol), indole **7** (1.2 mmol), $BF_3{\cdot}Et_2O$ (1 mmol), CH_2Cl_2 (5 mL). [b]Isolated yields of major diastereomers; NR indicates no reaction. [c]Determined by ^{19}F NMR analysis of the crude reaction mixtures. [d]The yield of two diastereomers.

CH_2Cl_2 (5 mL) at 0 °C for 10 h. In the case of 2-substituted derivatives (entries 1 and 2), we again observed a dramatic effect of the substituent's electronic properties on the reaction outcome. Thus, while the 2-Me derivative **7** reacted efficiently with imine (*S*)-**1**, the 2-formyl-containing **7** failed completely to undergo the desired transformation, indicating a detrimental effect of its electron-withdrawing property on the reactivity. By contrast, the electronic properties of a substituent at the 4-position (on the phenyl ring) showed just a little effect the stereochemical outcome. For example, 4-CN and 4-MeO derivatives **7** (entries 3 and 4) cleanly reacted with imine (*S*)-**1** to afford the corresponding products **8** in 60 and 80% yield, respectively, both with excellent diastereoselectivity. A similar trend was observed also in the series of 5-substituted indoles **7**. The reactions of derivatives **7** bearing 5-CN and 5-MeO groups (entries 5 and 6) gave rise to the corresponding products **8** as single diastereomers in 75 and 92% yield, respectively. Unexpectedly, very interesting results were obtained in the case of derivatives **7** containing an ester (R = CO_2Me; entry 7) and a free carboxylic group (entry 8) at the 5-position. In both reactions we observed excellent reactivity, and the target products were isolated in high yields. However, while in the case of the 5-CO_2Me containing indole **7** we obtained virtually complete stereoselectivity (99:1), the 5-COOH-bearing substrate gave a rather poor stereochemical outcome (77:23). Also, lower than normal stereoselectivities and chemical yields were recorded for the reactions of 6-Cl- and 6-Br-substituted derivatives **7** (entries 9 and 10). The presence of a substituent in the last possible position on the indole framework (the 7-position) was quite consistent with the usually very good stereochemical outcome observed in these reactions. Thus, 7-Br- and 7-methyl-containing indoles **7** gave the corresponding products **8k** and **8l** in 74 and 82% yield with 96:4 and 99:1 diastereoselectivity, respectively (entries 11 and 12). Finally, to conclude this structural generality part of the study, we

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conducted the reaction of 2-methyl-5-methoxy-disubstituted indole **7** with imine (*S*)-**1**. As one can see from entry 13, the desired product **8** was obtained in high yield (94%) with an excellent stereochemical outcome (99:1 dr).

Taking advantage of the high crystallinity of product **8l** containing a methyl group at the 7-position, we conducted its crystallographic analysis to determine the absolute configuration of the newly created stereogenic carbon. According to the X-ray data, the configuration of **8l** is (*S*,*S*) (Figure 2). The absolute configurations of the other products **8** were assigned accordingly as (*S*,*S*) on the basis of the close similarity of their spectral and chiroptical properties.

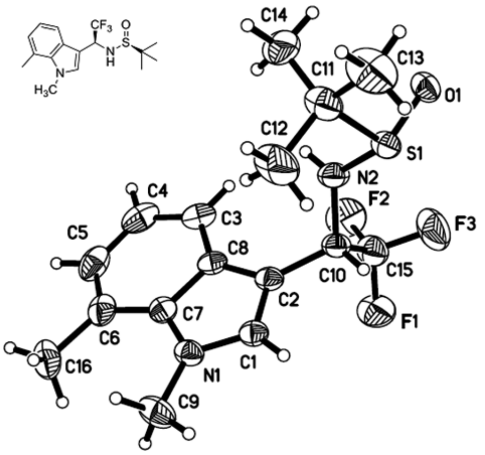


Figure 2. ORTEP structure of compound **8l**.

Taking into account the (*S*,*S*) absolute configuration of products **8**, we can discuss a plausible mechanistic rationale for the observed stereochemical outcome in the reactions under study. As shown in Figure 3, three possible transition states

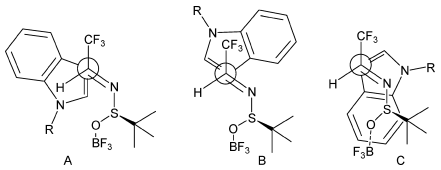


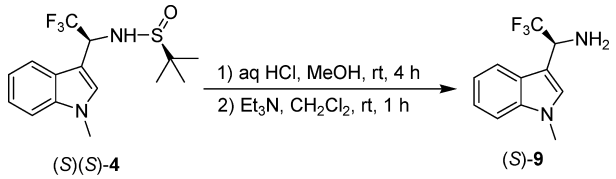
Figure 3. Possible transition states.

(TSs) **A**, **B**, and **C** can be constructed to account for the experimental results. Considering TSs **A**–**C**, one may agree that TS **A** seems less sterically crowded, but only TS **C** can account for the quite unexpected effect of the substituents at the 5- and 6-positions in the phenyl ring of the indole on the observed stereochemical outcome.

Finally, we believed that it would be desirable to demonstrate the deprotection of the products obtained to confirm the possibility of preparing free CF_3-containing amines by this new approach. To this end, we conducted the reaction of *N*-Me derivative (*S*,*S*)-**4** (Scheme 1). Under the standard conditions,[7] the deprotection step proceeded without any complications, and amine (*S*)-**9** was isolated in 92% yield. Also, the enantioselectivity of (*S*)-**9** was been examined, and the ee value was found to be 99.6%, indicating that no racemization happened during the deprotection process.

To conclude, we have demonstrated that 3,3,3-trifluoroacetaldimine (*S*)-**1** easily undergoes Friedel–Crafts reactions with

Scheme 1. Deprotection of Product 4



indole derivatives in the presence of stoichiometric amounts of $BF_3{\cdot}Et_2O$. The reactions feature a wide range of generality with good-to-excellent stereochemical outcomes. On the basis of the experimental data reported here, one may assume that the developed method is a highly synthetically valuable approach for the preparation of various novel biologically interesting indole derivatives containing the $CF_3CH(NH_2)$– pharmacophoric group.

EXPERIMENTAL SECTION

Typical Procedure for the Friedel–Crafts Reaction of *N*-Methylindoles and Sulfinylimine 1. To a solution of indole **7** (1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (130 μL, 1.0 mmol) dropwise. Then the solution of sulfinylimine **1** (201 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added in one portion. Stirring was continued at 0 °C for 10 h, and then the reaction was quenched with H_2O (10 mL). The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (2 × 30 mL) and brine solution (1× 30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude mixture was charged onto silica gel and purified through flash chromatography (eluent: 1:1 PE/EtOAc) to furnish the corresponding product **8**.

*(S)-2-Methyl-N-((S)-2,2,2-trifluoro-1-(1-methyl-1H-indol-3-yl)-ethyl)propane-2-sulfinamide (**6a**).* Colorless oil. Yield: 298 mg (90%). $[\alpha]_D^{25}$ = +101.12 (*c* = 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.16–7.12 (m, 1H), 5.13 (qd, *J* = 8.0, 4.0 Hz, 1H), 3.93 (br, 1H), 3.76 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.3, 130.5, 126.5, 125.3 (q, J_{FC} = 282.8 Hz), 122.4, 120.3, 120.0, 109.7, 104.1, 55.9, 54.7 (q, $^3J_{FC}$ = 32.3 Hz), 33.0, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.99. IR (cm^{-1}): 2959, 2927, 1552, 1475, 1364, 1336, 1267, 1170, 1133, 1118, 1072, 1014, 743. HRMS (TOF MS ESI): calcd for $C_{15}H_{19}F_3N_2OSNa$ $[M + Na]^+$ 355.1068, found 355.1068.

*(S)-N-((S)-1-(1-Ethyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**6b**).* Colorless oil. Yield: 285 mg (82%). $[\alpha]_D^{25}$ = +95.85 (*c* = 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.26–7.21 (m, 2H), 7.14–7.10 (m, 1H), 5.13 (qd, *J* = 8.0, 4.0 Hz, 1H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.94 (s, 1H), 1.46 (t, *J* = 8.0 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.4, 128.7, 126.7, 125.3 (q, J_{FC} = 282.8 Hz), 122.2, 120.4, 120.0, 109.8, 104.3, 55.9, 54.8 (q, $^3J_{FC}$ = 32.3 Hz), 41.2. 22.6, 15.3.^{19}F NMR (376 MHz, $CDCl_3$): δ −73.95. IR (cm^{-1}): 2979, 2960, 2927, 1471, 1464, 1363, 1267, 1170, 1134, 1118, 1076, 742. HRMS (TOF MS ESI): calcd for $C_{16}H_{21}F_3N_2OSNa$ $[M + Na]^+$ 369.1224, found 369.1221.

*(S)-N-((S)-1-(1-Benzyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**6c**).* Colorless oil. Yield: 348 mg (85%). $[\alpha]_D^{25}$ = +82.72 (*c* = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.31–7.23 (m, 5H), 7.21–7.17 (m, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.34–5.24 (m, 2H), 5.15 (qd, *J* = 8.0, 4.0 Hz, 1H), 3.97 (d, *J* = 4.0 Hz, 1H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 136.7, 129.9, 128.9, 128.9, 127.9, 126.8, 126.8, 125.2 (q, J_{FC} = 282.8 Hz), 122.6, 120.3, 110.2, 105.0, 56.0, 54.6 (q, $^3J_{FC}$ = 32.3 Hz), 50.3, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.03. IR (cm^{-1}): 3195, 3064, 2960, 2926, 1552, 1469, 1454, 1363, 1338, 1267, 1172, 1134, 1122, 1072, 742. HRMS (TOF

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MS ESI): calcd for $C_{21}H_{23}F_3N_2OSNa$ $[M + Na]^+$ 431.1381, found 431.1382.

*(S)-2-Methyl-N-((S)-2,2,2-trifluoro-1-(1H-indol-3-yl)ethyl)-propane-2-sulfinamide (**6e**).* Pale-yellow solid, mp 154−155 °C. Yield: 114 mg (36%). $[\alpha]_D^{25}$ = +109.17 (c = 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26−7.18 (m, 1H), 7.16−7.12 (m, 2H), 5.16 (qd, J = 8.0, 4.0 Hz, 1H), 4.12 (d, J = 4.0 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7, 126.7, 125.9, 125.3 (q, J_{FC} = 282.8 Hz), 122.5, 120.1, 119.9, 112.0, 104.9, 56.1, 54.9 (q, $^3J_{FC}$ = 32.3 Hz), 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.90. IR (cm^{-1}): 2957, 2923, 2852, 1462, 1266, 1254, 1174, 1118, 1068, 1032, 750. HRMS (TOF MS ESI): calcd for $C_{14}H_{17}F_3N_2OSNa$ $[M + Na]^+$ 341.0911, found 341.0911.

*(S)-N-((S)-1-(1,2-Dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8a**).* Yellow oil. Yield: 303 mg (87%). $[\alpha]_D^{25}$ = +157.80 (c = 0.53, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 1H), 7.24−7.21 (m, 1H), 7.18−7.14 (m, 1H), 7.09−7.05 (m, 1H), 5.13 (d, J = 8.0 Hz, 1H), 3.96 (br, 1H), 3.56 (s, 3H), 2.42 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.4, 137.1, 126.2, 125.7 (q, J_{FC} = 282.8 Hz), 121.3, 120.4, 119.8, 109.1, 99.9, 55.4, 54.1 (q, $^3J_{FC}$ = 32.3 Hz), 29.6, 22.6, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.38. IR (cm^{-1}): 2957, 1473, 1365, 1268, 1168, 1124, 1075, 744. HRMS (TOF MS ESI): calcd for $C_{16}H_{21}F_3N_2OSNa$ $[M + Na]^+$ 369.1224, found 369.1224.

*(S)-N-((S)-1-(4-Cyano-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8c**).* Pale-yellow solid, mp 167−168 °C. Yield: 210 mg (60%). $[\alpha]_D^{25}$ = −64.85 (c = 0.73, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.0, 4.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.29 (t, J = 4.0 Hz, 1H), 5.80 (s, 1H), 4.36 (s, 1H), 3.85 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6, 131.9, 126.9, 126.2, 125.0 (q, J_{FC} = 282.8 Hz), 121.9, 119.4, 115.0, 105.7, 101.7, 56.5, 52.4 (q, $^3J_{FC}$ = 31.3 Hz), 33.4, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.39. IR (cm^{-1}): 2960, 2927, 2220, 1460, 1365, 1347, 1265, 1172, 1126, 1067, 789. HRMS (TOF MS ESI): calcd for $C_{16}H_{18}F_3N_3OSNa$ $[M + Na]^+$ 380.1020, found 380.1021.

*(S)-2-Methyl-N-((S)-2,2,2-trifluoro-1-(4-methoxy-1-methyl-1H-indol-3-yl)ethyl)propane-2-sulfinamide (**8d**).* Pale-yellow solid, mp 148−149 °C. Yield: 292 mg (80%). $[\alpha]_D^{25}$ = −2.50 (c = 0.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, J = 8.0 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 5.46 (s, 1H), 4.93 (s, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 138.5, 127.5, 125.0 (q, J_{FC} = 282.8 Hz), 123.1, 116.6, 106.5 (d, J = 2.0 Hz), 103.3, 100.5, 56.5, 55.6 (q, $^3J_{FC}$ = 32.3 Hz), 55.4, 33.2, 22.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.28. IR (cm^{-1}): 2958, 1503, 1468, 1346, 1260, 1168, 1124, 1077, 734. HRMS (TOF MS ESI): calcd for $C_{16}H_{21}F_3N_2O_2SNa$ $[M + Na]^+$ 385.1174, found 385.1171.

*(S)-N-((S)-1-(5-Cyano-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8e**).* White solid, mp 173−174 °C. Yield: 270 mg (75%). $[\alpha]_D^{25}$ = +194.09 (c = 0.37, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.49 (dd, J = 8.0, 4.0 Hz, 1H), 7.41−7.38 (m, 2H), 5.11 (qd, J = 8.0, 4.0 Hz, 1H), 3.98 (d, J = 4.0 Hz, 1H), 3.84 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0, 133.2, 126.3, 126.2,, 126.1, 125.3, 124.9 (q, J_{FC} = 282.8 Hz), 120.4, 110.8, 105.2, 103.4, 56.0, 54.3 (q, $^3J_{FC}$ = 32.3 Hz), 33.4, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.15. IR (cm^{-1}): 2958, 2928, 2221, 1488, 1379, 1365, 1265, 1171, 1150, 1117, 1072, 804. HRMS (TOF MS ESI): calcd for $C_{16}H_{18}F_3N_3OSNa$ $[M + Na]^+$ 380.1020, found 380.1017.

*(S)-2-Methyl-N-((S)-2,2,2-trifluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)ethyl)propane-2-sulfinamide (**8f**).* Yellow oil. Yield: 330 mg (92%). $[\alpha]_D^{25}$ = +116.60 (c = 0.49, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 8.8, 2.4 Hz, 1H), 5.09 (qd, J = 8.0, 4.0 Hz, 1H), 3.91 (d, J = 4.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4, 132.6, 131.0, 126.9, 125.3 (q, J_{FC} = 282.8 Hz), 112.8, 110.5, 103.3, 101.9, 55.7, 55.7, 54.6 (q, $^3J_{FC}$ = 32.3 Hz), 33.2, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.00. IR (cm^{-1}): 3206, 2957, 2927, 2870, 2834, 1624, 1579, 1548, 1493, 1457, 1426, 1363, 1347, 1267, 1225, 1168, 1127, 1069, 1037, 797. HRMS (TOF MS ESI): calcd for $C_{16}H_{21}F_3N_2O_2SNa$ $[M + Na]^+$ 385.1174, found 385.1172.

*Methyl 3-((S)-1-((S)-1,1-Dimethylethylsulfinamido)-2,2,2-trifluoroethyl)-1-methyl-1H-indole-5-carboxylate (**8g**).* White solid, mp 75−76 °C. Yield: 372 mg (96%). $[\alpha]_D^{25}$ = +128.96 (c = 0.44, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.30−7.28 (m, 2H), 5.22−5.15 (m, 1H), 4.36 (s, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 139.6, 131.9, 126.0, 125.1 (q, J_{FC} = 282.8 Hz), 123.5, 123.2, 122.0, 109.5, 105.9, 56.1, 54.3 (q, $^3J_{FC}$ = 32.3 Hz), 51.8, 33.0, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.01. IR (cm^{-1}): 2953, 1715, 1457, 1289, 1266, 1252, 1170, 1115, 1075, 771. HRMS (TOF MS ESI): calcd for $C_{17}H_{21}F_3N_2O_3SNa$ $[M + Na]^+$ 413.1123, found 413.1120.

*3-((S)-1-((S)-1,1-Dimethylethylsulfinamido)-2,2,2-trifluoroethyl)-1-methyl-1H-indole-5-carboxylic Acid (**8h**).* White solid, mp 192−193 °C. Yield: 338 mg (90%). $[\alpha]_D^{25}$ = +117.25 (c = 0.86, $CHCl_3$).

Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.91 (dd, J = 8.0, 1.6 Hz, 1H), 7.34 (s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 5.27−5.20 (m, 2H), 3.84 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 139.8, 131.5, 126.1, 124.1 (q, J_{FC} = 278.8 Hz), 124.0, 123.7, 121.8, 109.4, 106.4, 56.6, 54.4 (q, $^3J_{FC}$ = 32.3 Hz), 33.3, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.62.

Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.79 (dd, J = 8.8, 1.2 Hz, 1H), 7.31 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 4.0 Hz, 1H), 4.70 (d, J = 4.0 Hz, 1H), 3.75 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 139.5, 130.0, 126.4, 125.0 (q, J_{FC} = 282.8 Hz), 124.1, 123.7, 121.9, 109.3, 108.5, 56.6, 55.2 (q, $^3J_{FC}$ = 32.3 Hz), 33.1, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.83.

IR (cm^{-1}): 3295, 3160, 2964, 2925, 2854, 2608, 1705, 1694, 1678, 1616, 1458, 1410, 1389, 1366, 1347, 1318, 1291, 1268, 1246, 1214, 1171, 1138, 1118, 1072, 1051, 1024, 1010, 916, 773, 750, 709. HRMS (TOF MS ESI): calcd for $C_{16}H_{19}F_3N_2O_3SNa$ $[M + Na]^+$ 399.0966, found 399.0966.

*(S)-N-((S)-1-(6-Chloro-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8i**).* Pale-yellow oil. Yield: 250 mg (68%). $[\alpha]_D^{25}$ = +110.92 (c = 0.57, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.22 (s, 1H), 7.09 (dd, J = 8.0, 1.6 Hz, 1H), 5.11 (qd, J = 8.0, 4.0 Hz, 1H), 4.11 (d, J = 3.6 Hz, 1H), 3.65 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.8, 131.4, 128.5, 125.1 (q, J_{FC} = 282.8 Hz), 125.0, 121.4, 120.8, 109.9, 104.3, 55.9, 54.5 (q, $^3J_{FC}$ = 32.3 Hz), 33.1, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.10. IR (cm^{-1}): 3207, 2960, 2928, 2871, 1614, 1549, 1491, 1475, 1458, 1423, 1365, 1330, 1267, 1170, 1146, 1118, 1070, 899, 863, 843, 805. HRMS (TOF MS ESI): calcd for $C_{15}H_{18}ClF_3N_2OSNa$ $[M + Na]^+$ 389.0678, found 389.0675.

*(S)-N-((S)-1-(6-Bromo-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8j**).* Yellow oil. Yield: 264 mg (64%). $[\alpha]_D^{25}$ = +91.75 (c = 0.61, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.0, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.23−7.20 (m, 2H), 5.10 (qd, J = 8.0, 4.0 Hz, 1H), 4.08 (s, 1H), 3.66 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 131.3, 125.3, 125.2 (q, J_{FC} = 282.8 Hz), 123.3, 121.7, 116.0, 112.9, 104.5, 55.9, 54.5 (q, $^3J_{FC}$ = 32.3 Hz), 33.0, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.11. IR (cm^{-1}): 2959, 2928, 1546, 1474, 1455, 1365, 1329, 1266, 1170, 1146, 1119, 1073, 854, 804. HRMS (TOF MS ESI): calcd for $C_{15}H_{18}BrF_3N_2OSNa$ $[M + Na]^+$ 433.0173, found 433.0159.

*(S)-N-((S)-1-(7-Bromo-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8k**).* Yellow solid, mp 55−56 °C. Yield: 301 mg (74%). $[\alpha]_D^{25}$ = +79.04 (c = 0.79, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.20 (s, 1H), 6.94 (t, J = 8.0 Hz, 1H), 5.13 (qd, J = 8.0, 4.0 Hz, 1H), 4.13 (s, 3H), 4.10 (s, 1H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.6, 133.4, 129.6, 127.5, 125.1 (q, J_{FC} = 282.8 Hz), 121.2, 119.5, 104.3, 104.2, 56.0, 54.3 (q, $^3J_{FC}$ = 32.3 Hz), 37.3, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.01. IR (cm^{-1}): 2958, 1566, 1471, 1456, 1411, 1365, 1266, 1171, 1113, 1074, 780, 737. HRMS (TOF MS ESI): calcd for $C_{15}H_{18}BrF_3N_2OSNa$ $[M + Na]^+$ 433.0173, found 433.0169.

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*(S)-N-((S)-1-(1,7-Dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (**8l**).* White solid, mp 127−128 °C. Yield: 284 mg (82%). $[\alpha]_D^{25}$ = +98.78 (*c* = 0.82, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.11 (qd, *J* = 8.0, 4.0 Hz, 1H), 4.06 (s, 3H), 3.91 (d, *J* = 4.0 Hz, 1H), 2.77 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.0, 132.0, 127.6, 125.2 (q, J_{FC} = 282.8 Hz), 125.1, 121.7, 120.3, 118.3, 103.8, 55.9, 54.6 (q, $^3J_{FC}$ = 32.3 Hz), 37.2, 22.6, 19.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.00. IR (cm^{-1}): 2962, 2930, 1459, 1365, 1267, 1168, 1114, 1073, 781, 746. HRMS (TOF MS ESI): calcd for $C_{16}H_{21}F_3N_2OSNa$ $[M + Na]^+$ 369.1224, found 369.1222.

*(S)-2-Methyl-N-((S)-2,2,2-trifluoro-1-(5-methoxy-1,2-dimethyl-1H-indol-3-yl)ethyl)propane-2-sulfinamide (**8m**).* White solid, mp 130−131 °C. Yield: 354 mg (94%). $[\alpha]_D^{25}$ = +232.8 (*c* = 0.51, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.0 Hz, 2H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.11 (d, *J* = 8.0 Hz, 1H), 3.97 (d, *J* = 4.0 Hz, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 2.40 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 138.8, 132.3, 126.5, 125.8 (q, J_{FC} = 282.8 Hz), 111.1, 109.7, 102.8, 99.3, 55.6, 55.2, 54.1 (q, $^3J_{FC}$ = 32.3 Hz), 29.7, 22.6, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.34. IR (cm^{-1}): 2956, 1489, 1456, 1264, 1230, 1166, 1124, 1074. HRMS (TOF MS ESI): calcd for $C_{17}H_{23}F_3N_2O_2SNa$ $[M + Na]^+$ 399.1330, found 399.1328.

Procedure for Deprotection of 4. Cleavage of the chiral *tert*-butylsulfinyl group was carried out in a 25 mL round-bottom flask, to which 0.5 mmol of **4** and 5 mL of MeOH were added. Then 1 mL of aqueous HCl (36%) was added dropwise with stirring at room temperature. After 4 h, when the reaction was complete as determined by TLC monitoring, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and Et_3N (15.0 mmol) was added. The mixture was stirred at rt for 1 h, and then H_2O (10 mL) was added. The organic layer was removed, washed with water and brine, and dried with anhydrous Na_2SO_4. The mixture was filtered and concentrated. The crude product was purified by layer chromatography to give product **9** in 92% yield.

*(S)-2,2,2-Trifluoro-1-(1-methyl-1H-indol-3-yl)ethanamine (**9**).* Pale-yellow solid, mp 52−53 °C. Yield: 106 mg (92%). $[\alpha]_D^{25}$ = +2.08 (*c* = 0.67, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.27−7.22 (m, 1H), 7.17−7.13 (m, 2H), 4.73 (q, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 1.80 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.0, 127.8, 126.7, 126.5 (q, J_{FC} = 282.8 Hz), 122.3, 119.9, 119.4, 109.7, 109.3 (d, *J* = 2.0 Hz), 51.4 (q, $^3J_{FC}$ = 31.3 Hz), 32.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.66. IR (cm^{-1}): 3376, 3283, 3188, 2919, 2855, 1616, 1553, 1477, 1468, 1399, 1277, 1243, 1179, 1160, 1151, 1118, 1090, 945, 809, 741, 712. HRMS (TOF MS EI$^+$) *m*/*z* calcd for $C_{11}H_{11}F_3N_2$ 228.0874, found 228.0870.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full spectroscopic data and copies of ^1H and ^{13}C NMR spectra for compounds **6**−**9**, HPLC spectra of compound **9**, and X-ray crystallographic data for **8l** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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