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# Lewis Acid Promoted Diastereoselective Addition of TMSCN and $TMSCF_3$ to Isatin-Derived *N*-Sulfinyl Ketimines: Synthesis of Optically Active Tetrasubstituted 3-Aminooxindoles

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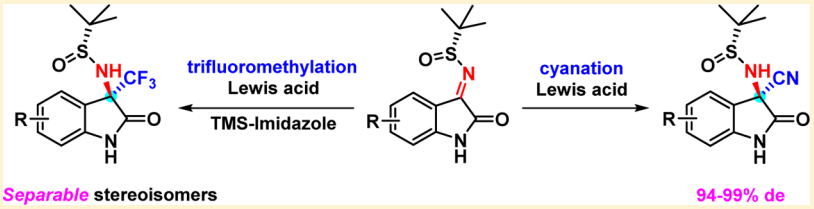
Supporting Information




**ABSTRACT:** A practical and efficient method for preparation of highly enantiomerically enriched 3-cyano-3-aminooxindoles and 3-trifluoromethyl-3-aminooxindoles with up to 99% optical purity by a Lewis acid promoted diastereoselective Strecker reaction and trifluoromethylation of isatin-derived *N-tert*-butanesulfinyl ketimines has been developed. This protocol allows direct use of N-free isatin substrates under mild conditions.

In past years, 3-aminooxindoles, particularly chiral quaternary 3-aminooxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position, have attracted considerable attention from synthetic chemists, as they are widely distributed in natural products, biologically active compounds, and drug candidates.[1] Therefore, many asymmetric methods have been developed to achieve these crucial compounds, which mainly follow two strategies.[2−4] One entails catalytic asymmetric amination of 3-substituted oxindoles;[2] the second is stereoselective nucleophilic addition of organometallic agents[3a−c,5g] or electron-rich reagents[3d,e,4] to isatin-derived ketimines. In contrast to the amination approach, the second one represents a more convenient and straightforward route as the starting materials could be easily prepared and the protecting group on 3-amino could be readily removed under mild conditions.

Among the chiral 3-aminooxindoles, 3-cyano-3-aminooxindoles are key intermediates for the synthesis of interesting oxindole-based quaternary $\alpha$-amino acids and the bioactive agent spirohydantoin[1d] developed by AstraZeneca as a TRPV1 antagonist for chronic pain control. Despite the great usefulness of cyano functionality, however, related methods for stereoselective access to enantiomerically enriched 3-cyano-3-aminooxindoles have received scant attention. To the best of our knowledge, only recently have several investigations on direct asymmetric cyanation of related ketimines been performed.[4] For instance, up to 74% ee was obtained for the first asymmetric Strecker reaction of isatin-derived ketimines using a cinchona alkaloid-based phosphinamide catalyst.[4a] Addition of TMSCN to chiral ketimines was achieved but gave much less satisfactory results (up to 48% de).[4b] Highly enantioselective Strecker reaction was newly developed for isatin-derived *N*-Boc-ketimines promoted by cinchona/quinine thiourea catalysts;[4c,d] however, these processes still suffer some limitations, as they generally require a long reaction time (1−5 days), a low reaction temperature (−25 to −75 °C), and the methyl as protecting group on isatin nitrogen is hard to remove.

We have been involved in developing asymmetric approaches for the generation of diverse structurally unique $\alpha$-amino acids such as unnatural $\alpha$-arylglycines,[5a,c] $\alpha$-allenylglycines,[5b] $\beta,\gamma$-unsaturated $\alpha$-amino acids,[5d] and $\alpha$-quaternary amino acids.[5e,f] More recently, we succeeded on a simple zinc-mediated diastereoselective allylation/propargylation of isatin-derived *N-tert*-butanesulfinyl ketimines to access highly enantiomerically enriched quaternary 3-aminooxindoles.[5g] Encouraged by these results, our interest was stimulated to build a 3-cyano-3-aminooxindole skeleton stereoselectively via asymmetric Strecker reaction of the corresponding *N*-sulfinyl imines. Herein, we wish to disclose results of our efforts on this subject.

Initially, the Strecker reaction of N-free isatin-derived *N*-sulfinyl imine **1a** with TMSCN in $CH_2Cl_2$ was investigated (Table 1). As we know, the reaction of *N*-unprotected isatin ketimines is more atom-economical but usually much more difficult to realize.[6] In the absence of any Lewis acid catalyst, the reaction did not proceed well at ambient temperature (entry 1). To promote the reaction, attempts to employ Lewis acid as additive were then carried out. While $In(OTf)_3$ gave poor results, the desired transformation occurred in the presence of 30 mol % of $Sc(OTf)_3$, and cyanide **2a** was formed in low yield with a promising diastereoselectivity (80% de)

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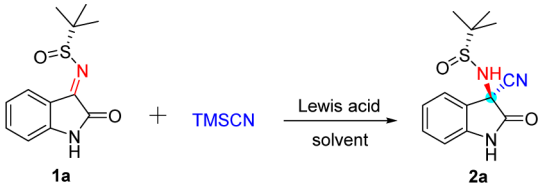
**Table 1. Screening of Conditions for Diastereoselective Strecker Reaction of *N*-Sulfinyl Imine 1a[a]**




1a 2a

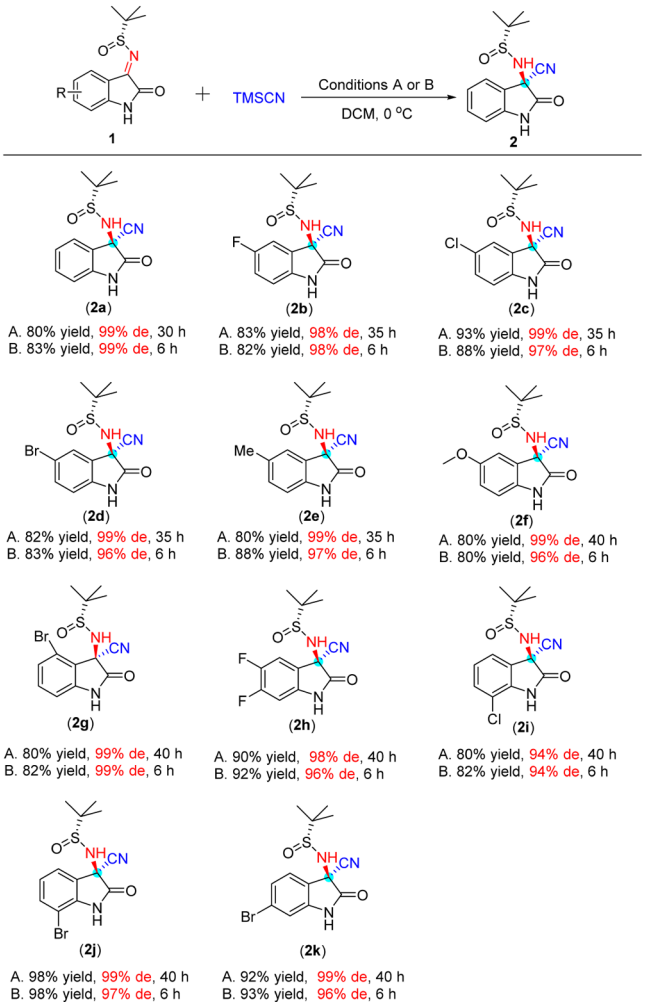
| entry | additive | mol (%) | temp (°C) | time (h) | yield[b] (%) | de[c] (%) |
|---|---|---|---|---|---|---|
| 1 | | | rt | 24 | trace | |
| 2 | $In(OTf)_3$ | 30 | rt | 24 | trace | |
| 3 | $Sc(OTf)_3$ | 30 | rt | 24 | 20 | 80 |
| 4 | $Yb(OTf)_3$ | 30 | rt | 24 | 64 | 96 |
| 5 | $Yb(OTf)_3$ | 30 | 40 | 10 | 96 | 94 |
| 6 | $MgBr_2{\cdot}Et_2O$ | 30 | rt | 7 | 92 | 92 |
| 7 | $MgBr_2{\cdot}Et_2O$ | 30 | 0 | 30 | 83 | 99 |
| 8 | $MgBr_2{\cdot}Et_2O$ | 10 | 0 | 30 | 80 | 99 |
| 9 | KF | 10 | rt | 6 | 95 | 10 |
| 10 | $MgBr_2{\cdot}Et_2O$/KF | 10/10 | 0 | 6 | 87 | 99 |
| 11[d] | $MgBr_2{\cdot}Et_2O$/KF | 10/10 | 0 | 6 | 83 | 99 |

[a]The reaction was performed with 0.12 mmol of **1a**, 3 equiv of TMSCN in DCM in the presence of additive. [b]Isolated yield. [c]Determined by HPLC analysis. [d]With 2 equiv of TMSCN employed.

(entries 2 and 3). To our delight, the use of $Yb(OTf)_3$ as catalyst dramatically improved both the yield and diastereoselectivity (entries 4 and 5). With strong Lewis acid $MgBr_2{\cdot}Et_2O$, the reaction went to completion in 7 h and afforded product **2a** in 92% yield and 92% de (entry 6). Notably, we observed a significant increase in the diastereoselectivity (99% de) when the reaction temperature was decreased to 0 °C, albeit a longer reaction time was required (entry 7). In addition, it was found that the employment of 10 mol % of $MgBr_2{\cdot}Et_2O$ was essential to achieve both good yield and excellent diastereoselectivity (80% yield, 99% de) (entry 8). On the other hand, the use of potassium fluoride as additive resulted in a rapid reaction, being complete within 6 h at room temperature (entry 9). It is considered that strong affinity of fluoride ion toward the silicon might indeed facilitate the polarization of the Si−CN bond of TMSCN.[7] Inspired by these results, we were pleased to discover that $MgBr_2{\cdot}Et_2O$/KF (10 mol %) was an ideal catalytic system which perfectly combines the advantages of two different classes of additives. It enabled the Strecker reaction of *N*-sulfinyl imine **1a** to proceed smoothly at 0 °C, leading to a diastereomerically pure (99% de) **2a** in 87% yield after 6 h (entry 10). The optimal ratio of TMSCN to imine **1a** was determined to be 2:1 in terms of atom economy and efficiency (entry 11).

Having identified the optimal reaction conditions, a wide range of unprotected isatin ketimines bearing different substituents were investigated. To our delight, the reaction was found to be quite general; isatin imines containing either electron-donating or electron-withdrawing groups on the phenyl ring could be successfully applied, affording the α-amino nitrile products **2a**−**k** in high yields (80−93% yield) and excellent diastereoselectivities (94−99% de) (Table 2). It is noteworthy that the reaction seems insensitive to the steric effects of the R group; the challenging 4-bromoisatin imine could also be used as a suitable substrate, giving **2g** with extremely high diastereoselectivity (99% de), as well. Using the procedure with only magnesium bromide diethyl ether as

**Table 2. Diastereoselective Cyanation of Ketimines[a,b,c,d]**




[a]The reaction was performed on 0.12 mmol scale, with 2 equiv of TMSCN and 0.1 equiv of $MgBr_2$ in 2 mL of DCM at 0 °C. [b]Isolated yields. [c]Diastereoselectivity was determined by HPLC analysis. [d]A was the outcome of the reaction without the addition of KF; B was the outcome of 0.1 equiv of KF as additive.

additive (condition A), the reaction slowly proceeded to completion in 30−45 h in all cases. As expected, when 10 mol % of KF was employed as cocatalyst (condition B), a fast conversion of the reaction (completion in 6 h) was observed, albeit with a slight decrease in diastereoselectivity in some cases. These results indicate that $MgBr_2{\cdot}Et_2O$ acts as a stereoselectivity controller in the reaction process, while KF serves as the reaction accelerator.

The absolute configuration of **2a** at the newly formed stereogenic carbon center was determined to be *S* by single-crystal X-ray analysis. Assuming an analogous reaction mechanism, the same stereochemistry of the obtained 3-cyano-3-aminooxindoles could be assigned. Following up our initial plan, removal of the *N*-sulfinyl group and conversion of the cyano functionality into ester was smoothly carried out under mild conditions within one step (Scheme 1). The corresponding N-free isatin-based α,α-disubstituted amino acid **3** was obtained without significant loss of optical purity (98% ee).

Encouraged by the above results, we turned our attention to the more challenging trifluoromethylation of those ketimines in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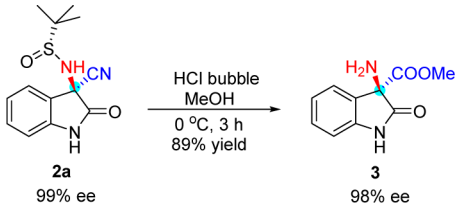
**Scheme 1. Synthesis of Isatin-Based α-Amino Acid**

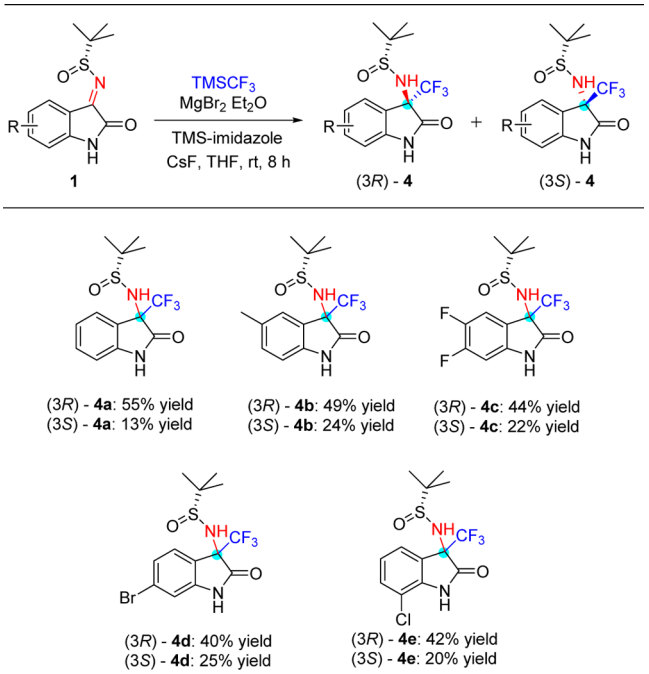



an attempt to generate optically active 3-trifluoromethyl-3-aminooxindoles. In contrast to the extensive studies of trifluoromethylation of carbonyl compounds,[8] reactions of imines with Ruppert's reagent, $TMSCF_3$, were limited.[9−11] In most examples, activated substrates such as nitrones,[9b] iminium ions,[9c−e] and azirines[10a] were employed. To our knowledge, there is no report on asymmetric trifluoromethylation of ketimines.[12]

While the above developed catalytic system has been shown to be effective for cyanation, the expected trifluoromethylation did not occur under identical conditions. Fortunately, after careful evaluation of conditions, we found that the reaction of isatin-derived *N*-sulfinyl imine **1a** with $TMSCF_3$ can be performed in the presence of TMS-imidazole and CsF in THF, giving two separable diastereoisomers (3*R*)-**4a** and (3*S*)-**4a** in 40 and 25% yield, respectively. When $MgBr_2{\cdot}Et_2O$ was added to the reaction system, the diastereoselectivity was improved to give a 4:1 ratio in favor of (3*R*)-**4a** product (55% yield). Further screening of other Lewis acid and solvent could not give better results. Compared to the excellent stereocontrol achieved in the asymmetric Strecker reaction, the decline of the diastereoselectivity in trifluoromethylation may be attributed to the unknown effect of TMS-imidazole.[13] However, attempts to replace TMS-imidazole by other reagents that can equally promote the reaction were unsuccessful at this time. Nevertheless, the current system allows concurrent accessing of various pharmaceutically interesting N-free 3-trifluoromethyl-3-aminooxindoles in both enantiomeric forms (Table 3). The structure of the minor isomer (3*S*)-**4e** was confirmed by single-crystal X-ray analysis, thus the main stereoisomer was determined to have *R* configuration for the newly formed C3 carbon center. Conversion of the trifluoromethylation products to the corresponding free amines has also been examined. As exemplified by (3*R*)-**4a**, highly enantioenriched amine **5** (98% ee) can be readily obtained by removal of the *N*-*tert*-butanesulfinyl group under acidic conditions (Scheme 2).

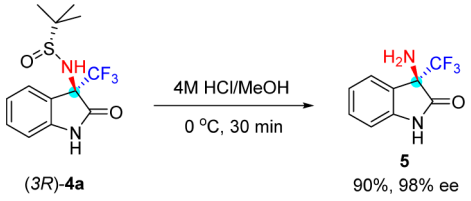
In summary, we have developed a highly diastereoselective Strecker reaction of *N*-*tert*-butanesulfinyl ketimines derived from N-unprotected isatins. The reaction could be accomplished with ease in the presence of a catalytic amount of magnesium bromide diethyl ether at 0 °C. Notably, the use of potassium fluoride as cocatalyst could accelerate the reaction dramatically. The method allows exceptionally mild, efficient, and ready access to a broad range of enantiomerically enriched 3-cyano-3-aminooxindoles (94−99% de). Moreover, we have achieved the first asymmetric trifluoromethylation of ketimines; various highly valuable 3-trifluoromethyl-3-aminooxindoles can be prepared in both enantiomeric forms under mild conditions. In contrast to the previous success,[4c,d] direct use of N-free isatin substrates constitutes an exceptionally remarkable advantage of this approach.

**Table 3. Trifluoromethylation of Ketimines[a,b]**




[a]The reaction was performed on 0.12 mmol scale, with 3 equiv of $TMSCF_3$, 0.1 equiv of $MgBr_2{\cdot}Et_2O$, 3 equiv of CsF, and 3 equiv of TMS-imidazole in 2 mL of dry THF at rt. [b]Isolated yields.

**Scheme 2. Removal of the *N*-Sulfinyl of Trifluoromethylation Product**




## EXPERIMENTAL SECTION

**General Information.** All reactions were carried out in dry glassware with magnetic stirring. Solvents were dried and distilled by standard procedures. NMR spectra were recorded on a spectrometer (300 MHz for $^1H$ and 100 MHz for $^{13}C$). Chemical shifts are reported in δ parts per million referenced to an internal $SiMe_4$ standard for $^1H$ NMR and chloroform-*d* (δ 77.16), DMSO-*d* (δ 39.52), or acetone-*d* (δ 29.84 and 202.26) for $^{13}C$ NMR. HPLC was performed by using C18 column (5 μm, 4.6 × 150 mm column) with acetonitrile/water as the eluent. The mass analyzer type used for the HRMS was Q-TOF for ESI and Magnetic Sector for EI.

**General Procedure for the Preparation of *N*-*tert*-Butanesulfinyl Ketimines.** To (*R*)-*tert*-butanesulfinamide (11 mmol, 1.3 g) mixed with isatin (10 mmol) dissolved in dry $CH_2Cl_2$ in a glass reaction vessel was added $Ti(OEt)_4$ successively. The mixture was refluxed until the starting materials disappeared. The reaction was then quenched with brine and filtered through a pad of Celite. The filtrate was extracted with ethyl acetate, and the combined organic phase was washed three times with brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel flash chromatography using ethyl acetate/petroleum ether as eluent to afford the corresponding imine **1**.

**General Procedure for the Strecker Reaction of Imines 1 with TMSCN.** The imine **1** (0.12 mmol) and the Lewis acid (0.012 mmol) were placed into a glass reaction vessel, and 2 mL of fresh DCM and TMSCN (0.24 mmol) was added sequentially. The mixture was stirred at room temperature and monitored by TLC. When the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reaction was over, brine was added and the mixture was extracted with EA. The combined organic phase was dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether as eluent to afford the corresponding 3-aminooxindole product **2**.

*(R)-N-((S)-3-Cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2a**):* colorless powder (26.6 mg, 80%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 80/20, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 8.71 min, $t$(minor) 9.63 min; $[\alpha]_D^{25}$ −58.50 ($c$ 0.2, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.21 (s, 9H), 4.79 (s, 1H), 7.01 (d, $J$ = 9.0 Hz, 1H), 7.10 (t, $J$ = 9.0 Hz, 1H), 7.33 (t, $J$ = 9.0 Hz, 1H), 7.52 (d, $J$ = 9.0 Hz, 1H), 9.55 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.6, 57.6, 58.0, 112.4, 115.6, 124.0, 124.1, 126.3, 132.3, 141.4, 170.5; ESI-MS ($m/z$, %) 278 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{15}N_3O_2SNa$ [M + Na$^+$] 300.0783, found 300.0783.

*(R)-N-((S)-3-Cyano-5-fluoro-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2b**):* colorless powder (29.4 mg, 83%); 98% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 70/30, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 10.12 min, $t$(minor) 11.39 min; $[\alpha]_D^{25}$ −52.77 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.12 (s, 9H), 6.95 (dd, $J_1$ = 3.0 Hz, $J_2$ = 9.0 Hz, 1H), 7.17 (s, 1H), 7.25 (dt, $J_1$ = 3.0 Hz, $J_2$ = 9.0 Hz, 1H), 7.45 (dd, $J_1$= 3.0 Hz, $J_2$ = 9.0 Hz, 1H), 11.26 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.3, 57.0, 58.3, 112.3 ($J_{C-F}$ = 6.0 Hz), 113.4 ($J_{C-F}$ = 20.0 Hz), 115.7, 118.3 ($J_{C-F}$ = 20.0 Hz), 126.6 ($J_{C-F}$ = 6.0 Hz), 137.8, 158.0 ($J_{C-F}$ = 190.0 Hz), 169.1; ESI-MS ($m/z$, %) 296 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SFNa$ [M + Na$^+$] 318.0688, found 318.0690.

*(R)-N-((S)-5-Chloro-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2c**):* colorless powder (34.7 mg, 93%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 75/25, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 9.45 min, $t$(minor) 10.53 min; $[\alpha]_D^{25}$ −21.92 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.12 (s, 9H), 6.96 (d, $J$ = 9.0 Hz, 1H), 7.18 (s, 1H), 7.44 (d, $J$ = 9.0 Hz, 1H), 7.60 (s, 1H), 11.37 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.3, 57.0, 58.1, 112.7, 115.6, 125.7, 126.9, 127.0, 131.6, 140.4, 168.8; ESI-MS ($m/z$, %) 312 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SClNa$ [M + Na$^+$] 334.0393, found 334.0394.

*(R)-N-((S)-5-Bromo-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2d**):* colorless powder (35.0 mg, 82%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 60/40, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 7.23 min, $t$(minor) 8.08 min; $[\alpha]_D^{25}$ −10.80 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.13 (s, 9H), 6.92 (d, $J$ = 5.0 Hz, 1H), 7.18 (s, 1H), 7.58 (d, $J$ = 5.0 Hz, 1H), 7.72 (s, 1H), 11.38 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.2, 57.0, 58.0, 113.1, 114.4, 115.6, 127.4, 128.3, 134.4, 140.8,168.6; ESI-MS ($m/z$, %) 357 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SBrNa$ [M + Na$^+$] 377.9888, found 377.9885.

*(R)-N-((S)-3-Cyano-5-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2e**):* colorless powder (27.9 mg, 80%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 75/25, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 7.59 min, $t$(minor) 8.32 min; $[\alpha]_D^{25}$ −28.09 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.12 (s, 9H), 2.28 (s, 3H), 6.83 (d, $J$ = 8.4 Hz, 1H), 7.09 (s, 1H), 7.18 (d, $J$ = 8.4 Hz, 1H), 7.33 (s, 1H), 11.08 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 20.6, 22.3, 56.8, 58.1, 110.8, 116.2, 125.1, 126.0, 132.0, 132.3, 139.0, 169.3; ESI-MS ($m/z$, %) 292 [M + H]$^+$; ESI-HRMS calcd for $C_{14}H_{17}N_3O_2SNa$ [M + Na$^+$] 314.0939, found 314.0939.

*(R)-N-((S)-3-Cyano-5-methoxy-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2f**):* colorless powder (29.4 mg, 80%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 70/30, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 8.61 min, $t$(minor) 9.60 min; $[\alpha]_D^{25}$ −28.00 ($c$ 0.3, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.14 (s, 9H), 3.74 (s, 3H), 6.88 (d, $J$ = 9.0 Hz, 1H), 6.98 (d, $J$ = 9.0 Hz, 1H), 7.13−7.15 (m, 2H), 11.04 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.3, 55.7, 56.9, 58.4, 111.7, 112.2, 116.1, 116.5, 126.3, 134.5, 155.5, 169.0; ESI-MS ($m/z$, %) 308 [M + H]$^+$; ESI-HRMS calcd for $C_{14}H_{17}N_3O_3SNa$ [M + Na$^+$] 330.0888, found 330.0887.

*(R)-N-((S)-4-Bromo-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2g**):* colorless powder (34.0 mg, 80%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 70/30, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 13.90 min, $t$(minor) 18.20 min; $[\alpha]_D^{25}$ +3.01 ($c$ 0.3, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.19 (s, 9H), 6.93−6.96 (m, 2H), 7.27−7.38 (m, 2H), 11.36 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.4, 57.1, 58.9, 110.3, 114.4, 119.9, 122.7, 126.6, 133.6, 144.2, 169.1; ESI-MS ($m/z$, %) 355 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SNaBr$ [M + Na$^+$] 377.9888, found 377.9887.

*(R)-N-((S)-3-Cyano-5,6-difluoro-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2h**):* colorless powder (33.7 mg, 90%); 98% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 75/25, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 8.71 min, $t$(minor) 9.72 min; $[\alpha]_D^{25}$ −44.04 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.11 (s, 9H), 7.02 (s, 1H), 7.12 (s, 1H), 7.70 (s, 1H), 11.37 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.2, 57.0, 57.9, 101.3 (d, $J_{C-F}$ = 23.0 Hz), 115.4 (d, $J_{C-F}$ = 5.0 Hz), 115.7, 121.0, 138.5 (d, $J_{C-F}$ = 8.0 Hz), 145.9 (dd, $J_{1C-F}$ = 13.0 Hz, $J_{2C-F}$ = 240.0 Hz), 151.5 (dd, $J_{1C-F}$ = 14.0 Hz, $J_{2C-F}$ = 248.0 Hz), 169.2; ESI-MS ($m/z$, %) 314 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{13}N_3O_2SNaF_2$ [M + Na$^+$] 336.0594, found 336.0593.

*(R)-N-((S)-7-Chloro-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2i**):* colorless powder (30.7 mg, 82%); 94% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 70/30, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 11.82 min, $t$(minor) 13.14 min; $[\alpha]_D^{25}$ −67.50 ($c$ 0.6, MeOH); $^1$H NMR (300 MHz, acetone) $\delta$ 1.21 (s, 9H), 5.90 (s, 1H), 7.22 (t, $J$ = 8.4 Hz, 1H), 7.49 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.4 Hz, 1H), 7.63 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.4 Hz, 1H), 10.43 (s, 1H); $^{13}$C NMR (100 MHz, acetone) $\delta$ 22.5, 57.9, 59.1, 116.1, 116.5, 125.3, 125.6, 127.4, 132.5, 140.3, 169.5; ESI-MS ($m/z$, %) 312 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SNaCl$ [M + Na$^+$] 334.0393, found 334.0394.

*(R)-N-((S)-7-Bromo-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2j**):* colorless powder (41.7 mg, 98%); 99% de, determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 70/30, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 14.72 min, $t$(minor) 16.11 min; $[\alpha]_D^{25}$ −81.28 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, DMSO) $\delta$ 1.14 (s, 9H), 7.09 (t, $J$ = 8.4 Hz, 1H), 7.22 (s, 1H), 7.55 (d, $J$ = 8.4 Hz, 1H), 7.61 (d, $J$ = 8.4 Hz, 1H), 11.56 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 22.3, 57.0, 58.9, 103.1, 115.6, 124.8, 126.7, 134.5, 141.1, 169.2; ESI-MS ($m/z$, %) 356 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SNaBr$ [M + Na$^+$] 377.9888, found 377.9885.

*(R)-N-((S)-6-Bromo-3-cyano-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2k**):* colorless powder (39.1 mg, 92%); determined by HPLC analysis, C18 column ($H_2O/CH_3CN$ = 75/25, 1.0 mL/min, $\lambda$ 254 nm), $t$(major) 10.50 min, $t$(minor) 11.50 min; $[\alpha]_D^{25}$ −30.64 ($c$ 0.5, MeOH); $^1$H NMR (300 MHz, acetone) $\delta$ 1.13 (s, 9H), 7.12 (d, $J$ = 1.2 Hz, 1H), 7.19 (s, 1H), 7.34 (dd, $J_1$ = 1.2 Hz, $J_1$ = 8.4 Hz, 1H), 7.49 (d, $J$ = 8.4 Hz, 1H), 11.38 (s, 1H); $^{13}$C NMR (100 MHz, acetone) $\delta$ 22.2, 57.0, 57.7, 113.9, 115.5, 124.3, 124.4, 125.9, 127.5, 143.1, 169.1; ESI-MS ($m/z$, %) 356 [M + H]$^+$; ESI-HRMS calcd for $C_{13}H_{14}N_3O_2SNaBr$ [M + Na$^+$] 377.9888, found 377.9881.

**Synthesis of 3.** **2a** (20 mg, 0.07 mmol) was dissolved in 5 mL of MeOH and cooled to 0 °C. HCl gas was bubbled 20 min. The resulting solution was then stirred for another 2 h at the same temperature, then quenched by saturated aqueous $NaHCO_3$, and the mixture was extracted with EA (10 mL × 3). The combined organic phase was washed three times with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether (1:1) to afford the corresponding product **3**.

*Methyl (R)-3-Amino-2-oxoindoline-3-carboxylate (**3**):*[4b] colorless oil (13.2 mg, 89%); 98% de, determined by HPLC analysis: Chiracel AD-H column ($n$-hexane/isopropyl alcohol = 80/20, 0.7 mL/min, $\lambda$ 254 nm), $t$(minor) 14.12 min, $t$(major) 15.45 min; $^1$H NMR (300 MHz, MeOH) $\delta$ 3.66 (s, 3H), 6.93 (d, $J$ = 9.0 Hz, 1H), 7.03 (t, $J$ = 9.0 Hz, 1H), 7.28−7.30 (m, 2H).

**General Procedure for the Trifluoromethylation Reaction of Imines 1 with $TMSCF_3$.** The imine **1** (0.12 mmol), CsF (0.36 mmol), and magnesium bromide diethyl ether (0.012 mmol) were mixed in an dried glass reaction vessel; dry THF (2 mL) was injected


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after the $TMSCF_3$ (0.36 mmol) and TMS-imidazole (0.36 mmol) were added. The mixture was stirred at room temperature and monitored by TLC. After the disappearance of the substrate, brine was added and the mixture was extracted with EA (10 mL × 3). The combined organic phase was washed three times with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether to afford the corresponding 3-trifluoromethyl-3-aminooxindole product **4**.

*(R)-2-Methyl-N-((R)-2-oxo-3-(trifluoromethyl)indolin-3-yl)-propane-2-sulfinamide ((3R)-**4a**):* colorless oil (21.2 mg, 55%); $[\alpha]_D^{25}$ −36.60 (*c* 0.5, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.12 (s, 9H), 4.51 (s, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 8.87 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.3, 57.5, 64.7 (d, $J_{C-F}$ = 50.0 Hz), 111.3, 122.0, 122.3, 122.7 (d, $J_{C-F}$ = 140.0 Hz), 127.3, 131.8, 141.9, 171.1; ESI-MS (*m*/*z*, %) 321 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{15}F_3N_2O_2SNa$ $[M + Na^+]$ 343.0704, found 343.0706.

*(R)-2-Methyl-N-((S)-2-oxo-3-(trifluoromethyl)indolin-3-yl)-propane-2-sulfinamide ((3S)-**4a**):* colorless oil (5.0 mg, 13%); $[\alpha]_D^{25}$ −104.33 (*c* 0.3, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 5.27 (s, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 9.82 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.8, 57.5, 64.0 (d, $J_{C-F}$ = 30.0 Hz), 111.6, 120.6, 123.0, 123.2 (d, $J_{C-F}$ = 280.0 Hz), 128.1, 131.7, 142.6, 171.2; ESI-MS (*m*/*z*, %) 321 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{15}F_3N_2O_2SNa$ $[M + Na^+]$ 343.0704, found 343.0707.

*(R)-2-Methyl-N-((R)-5-methyl-2-oxo-3-(trifluoromethyl)indolin-3-yl)propane-2-sulfinamide ((3R)-**4b**):* colorless oil (19.6 mg, 49%); $[\alpha]_D^{25}$ +15.00 (*c* 0.1, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.19 (s, 9H), 2.35 (s, 3H), 4.41 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 8.31 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.2, 22.4, 57.4, 64.9 (d, $J_{C-F}$ = 30.0 Hz), 110.9, 122.2, 128.0, 132.3, 133.3, 139.2, 171.0; ESI-MS (*m*/*z*, %) 335 $[M + H]^+$; ESI-HRMS calcd for $C_{14}H_{17}F_3N_2O_2SNa$ $[M + Na^+]$ 357.0861, found 357.0852.

*(R)-2-Methyl-N-((S)-5-methyl-2-oxo-3-(trifluoromethyl)indolin-3-yl)propane-2-sulfinamide ((3S)-**4b**):* colorless oil (9.6 mg, 24%); $[\alpha]_D^{25}$ −117.33 (*c* 0.2, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 2.38 (s, 3H), 5.25 (s, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 9.50 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.4, 22.9, 57.4, 63.8 (d, $J_{C-F}$ = 50.0 Hz), 111.3, 120.4, 128.7, 132.2, 132.7, 140.1, 171.4; ESI-MS (*m*/*z*, %) 335 $[M + H]^+$; ESI-HRMS calcd for $C_{14}H_{17}F_3N_2O_2SNa$ $[M + Na^+]$ 357.0861, found 357.0856.

*(R)-N-((R)-5,6-Difluoro-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3R)-**4c**):* colorless oil (16.5 mg, 44%); $[\alpha]_D^{25}$ −67.20 (*c* 0.3, MeOH); $^1$H NMR (300 MHz, acetone-*d*) $\delta$ 1.18 (s, 9H), 5.54 (s, 1H), 7.07 (t, *J* = 8.7 Hz, 1H), 7.61 (t, *J* = 8.7 Hz, 1H), 10.31 (s, 1H); $^{13}$C NMR (100 MHz, acetone-*d*) $\delta$ 22.5, 57.8, 66.1 (d, $J_{C-F}$ = 30.0 Hz), 101.8 (d, $J_{C-F}$ = 20.0 Hz), 117.7 (d, $J_{C-F}$ = 20.0 Hz), 120.1, 124.2 (d, $J_{C-F}$ = 230.0 Hz), 140.9 (d, $J_{C-F}$ = 10.0 Hz), 147.0 (dd, $J_{1C-F}$ = 10.0 Hz, $J_{2C-F}$ = 200.0 Hz), 153.0 (dd, $J_{1C-F}$ = 10.0 Hz, $J_{2C-F}$ = 200.0 Hz), 170.2; ESI-MS (*m*/*z*, %) 357 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{13}F_5N_2O_2SNa$ $[M + Na^+]$ 379.0516, found 379.0513.

*(R)-N-((S)-5,6-Difluoro-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3s)-**4c**):* colorless oil (8.3 mg, 22%); $[\alpha]_D^{25}$ −51.60 (*c* 0.3, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.36 (s, 9H), 5.20 (s, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 10.01 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.8, 57.6, 64.3 (d, $J_{C-F}$ = 30.0 Hz), 101.7 (d, $J_{C-F}$ = 20.0 Hz), 115.1, 118.0 (d, $J_{C-F}$ = 20.0 Hz), 122.9 (d, $J_{C-F}$ = 220.0 Hz), 139.6 (d, $J_{C-F}$ = 10.0 Hz), 146.5 (dd, $J_{1C-F}$ = 10.0 Hz, $J_{2C-F}$ = 200.0 Hz), 152.8 (dd, $J_{1C-F}$ = 10.0 Hz, $J_{2C-F}$ = 200.0 Hz), 171.3; ESI-MS (*m*/*z*, %) 357 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{13}F_5N_2O_2SNa$ $[M + Na^+]$ 379.0516, found 379.0526.

*(R)-N-((R)-6-Bromo-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3R)-**4d**):* colorless oil (19.0 mg, 40%); $[\alpha]_D^{25}$ −14.03 (*c* 0.2, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.20 (s, 9H), 4.44 (s, 1H), 7.12 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 8.69 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.4, 57.6, 64.8, 114.7, 121.1, 126.0, 126.6, 128.7, 142.9, 170.4; ESI-MS (*m*/*z*, %) 398 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{14}F_3N_2O_2SBrNa$ $[M + Na^+]$ 420.9809, found 420.9802.

*(R)-N-((S)-6-Bromo-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3S)-**4d**):* colorless oil (11.9 mg, 25%); $[\alpha]_D^{25}$ −73.53 (*c* 0.3, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 5.28 (s, 1H), 6.77 (s, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 10.13 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.8, 57.6, 63.8 (d, $J_{C-F}$ = 30.0 Hz), 114.9, 119.1, 123.0 (d, $J_{C-F}$ = 220.0 Hz), 126.3, 126.4, 129.4, 143.9, 171.0; ESI-MS (*m*/*z*, %) 398 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{14}F_3N_2O_2SBrNa$ $[M + Na^+]$ 420.9809, found 420.9810.

*(R)-N-((R)-7-Chloro-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3R)-**4e**):* colorless powder (17.9 mg, 42%); $[\alpha]_D^{25}$ −75.00 (*c* 0.3, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.20 (s, 9H), 4.41 (s, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.3, 57.6, 65.9 (d, $J_{C-F}$ = 20.0 Hz), 116.1, 123.3, 124.5, 125.6 (d, $J_{C-F}$ = 320.0 Hz), 126.1, 131.8, 139.2, 169.4; ESI-MS (*m*/*z*, %) 355 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{14}F_3N_2O_2SNaCl$ $[M + Na^+]$ 377.0314, found 377.0312.

*(R)-N-((S)-7-Chloro-2-oxo-3-(trifluoromethyl)indolin-3-yl)-2-methylpropane-2-sulfinamide ((3S)-**4e**):* colorless powder (8.5 mg, 20%); $[\alpha]_D^{25}$ −33.29 (*c* 0.7, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 5.52 (s, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 10.14 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.9, 57.7, 64.7 (d, $J_{C-F}$ = 30.0 Hz), 116.9, 122.0, 124.2, 125.6 (d, $J_{C-F}$ = 320.0 Hz), 126.6, 132.2, 140.3, 170.6; ESI-MS (*m*/*z*, %) 355 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_{14}F_3N_2O_2SNaCl$ $[M + Na^+]$ 377.0314, found 377.0315.

**Synthesis of 5.** **4a** (10 mg, 0.03 mmol) was cooled to 0 °C, and 4 M HCl/MeOH was added. The resulting solution was stirred for 30 min at the same temperature, then quenched by saturated aqueous $NaHCO_3$. The mixture was extracted with EA (10 mL × 3). The combined organic phase was washed three times with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether (2:1) as eluent to afford product **5**.

*(R)-2-Methyl-N-((R)-2-oxo-3-(trifluoromethyl)indolin-3-yl)-propane-2-sulfinamide (**5**):* colorless oil (6.8 mg, 90%); $[\alpha]_D^{25}$ +30.09 (*c* 0.2, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (s, 2H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.30−7.44 (m, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 8.38 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 62.9 (d, $J_{C-F}$ = 30.0 Hz), 110.78 (s), 122.59 (s), 123.66 (s), 124.82 (s), 125.89 (s), 131.28 (s), 141.36 (s), 174.78 (s); EI-MS (*m*/*z*, %) 216 $[M]^+$; EI-HRMS calcd for $C_9H_7F_3N_2O$ $[M]^+$ 216.0510, found 216.0509.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of NMR and HPLC spectra, and crystallographic data for **2a** and **4e** (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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