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Solvent-Free, Uncatalyzed Asymmetric "Ene" Reactions of *N-tert*-Butylsulfinyl-3,3,3-trifluoroacetaldimines: General Approach to Enantiomerically Pure α-(Trifluoromethyl)tryptamines

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A novel approach to regioselectively substituted and stereoselectively α-trifluoromethylated tryptamines is reported based on the ene reaction of Boc-protected 3-methyleneindolines with optically pure (*R*)- or (*S*)-*tert*-butanesulfinyltrifluoroacetaldimine. Boc- and sulfinylamido-protected α-trifluoromethyltryptamines are obtained in 60-70% yield and 85/15 dr by just heating equimolar amounts of the two reaction partners at 80–90 °C for 2-3 h without solvent. The absolute configuration of the amino α-carbon has been assigned based on the vibrational circular dichroism (VCD) spectral analysis. The two protecting group can be chemoselectively removed allowing further regio- and stereoselective elaboration of the ene products to various biologically interesting compounds. .

Introduction

Indole nucleus constitutes one of the most important scaffolds of naturally occurring biologically active compounds. Indole-derived molecules are being involved in numerous biological processes controlling essential functions in virtually all living organisms.[1] Since the early days of medicine, indole structure has inspired design and synthesis of a countless number of indole-based pharmaceutical products.[2]

Although many methods have been developed to synthesize indole derivatives,[3] biologically active fluorinated analogues are much less common. However, the established ability of fluorine to increase lipophilicity, its high electronegativity and relatively small van der Waals radius, render fluorine-containing indole derivatives of high pharmaceutical potential.[4,5] In particular, the introduction of a CF_3, into a structure of potentially bio-active compound, is an established paradigm in the modern medicinal chemistry and drug-design.[4-6] Over the past decades highly efficient methods have been developed for asymmetric synthesis of trifluoromethylated amines and their derivatives based on the use of very effective synthetic building blocks.[7] In the area of CF_3-containing indoles, Han and Soloshonok reported a reliable and generalized access to biologically interesting derivatives possessing the $CF_3CH(NH_2)$-pharmacophoric group.[8] Their approach is based on the reaction of (*S*)- and (*R*)-*N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine with a number of substituted indoles under Lewis acid-catalysed Friedel–Crafts approach.

The high reaction rates together with excellent yields and stereoselectivities observed in these reactions, underscored the remarkable potential of the chiral sulfinyltrifluoroacetaldimine as a valuable alternative to the several other reagents developed over the last two decades for the synthesis of optically active trifluoromethylated amines.[9]

Among the indole-derived biologically significant amines, tryptamine is a very important alkaloid found in animals, fungi, and plants[10] and is structurally similar to the amino acid tryptophan, from which it derives its name. Due to the pharmacological activity, tryptamine derivatives have attracted considerable synthetic interest throughout the years.[11]

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Among them, α-trifluormethyltryptamine, obtained by the vinylnitrosoindole cycloaddition strategy of Zimmer and Reissig,[12] has received a particular attention.[13]

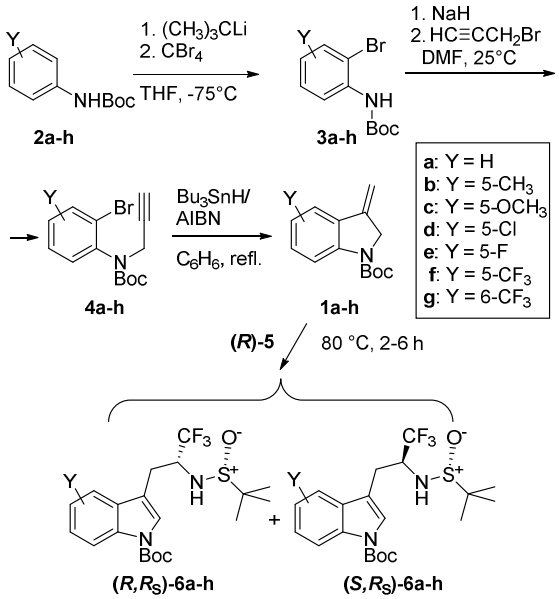
More recently, Hanamoto and coworkers developed an original approach to racemic β-trifluormethyltryptamines based on the reaction of regioselectively substituted indoles with 1-tosyl-2-(trifluoromethyl)aziridine in toluene at 100 °C, in the presence of diethylzinc as a base.[14] After the $Ti(OiPr)_4$-catalyzed deprotection of the amino group with Me_3SiCl in THF, quantitative yields of the expected product were obtained (Scheme 3).

Taking into account that the chemistry of trifluoroacetaldimines is rather well-studied,[7] it is very surprising that only a single example of the corresponding ene-type reactions has been reported so far.[15] Thus, regardless the apparent synthetic opportunities for the preparation of polyfunctional biologically relevant compounds, ene reactivity remains virtually unexplored area of the N-sulfinyl imines.[7,16] Therefore, we were very excited to face this challenge, especially in its the most difficult, uncatalyzed and solvent-free mode. We assumed that insufficient reactivity of the C=N bond can be counterbalanced by electron rich carbon-carbon double bond of the corresponding reaction partner. For example, few years ago we showed that properly substituted 3-methyleneindolines constitute valuable building blocks for the synthesis of highly functionalized 3-alkylsubstituted indoles, by simply heating them with the equimolar amount of strong electrophilic carbonyl compounds such as glyoxylic esters, dialkyl 2-oxomalonates or ethyl trifluoropyruvate.[17] While the electrophilicity of the C=N bond in *N*-sulfinyltrifluoroacetaldimines is obviously lower, as compared with the above mentioned carbonyl compounds, we thought that the exceptional reactivity of the 3-methyleneindolines might be sufficient for the ene reaction to take place. In this work, we report that simple heating of *N*-Boc-protected 3-methyleneindolines with (*S*)- and (*R*)-*N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine, under solvent-free conditions, leads to the corresponding ene reaction, thus allowing for the efficient asymmetric synthesis of α-(trifluoromethyl)tryptamines of high pharmaceutical interest.

Result and Discussion

Substituted 3-methyleneindolines **1a-h** were prepared according to the four-step protocol, involving *ortho*-metalation/bromination of starting anilines **2**, *N*-propargylation of the resulting *tert*-butyl *N*-(2-bromoaryl)carbamates **3** and tributyltin hydride/AIBN-promoted reductive radical cyclization of the *N*-propargylcarbamate **4** (Scheme 1).[18]

As was anticipated, mixing of 3-methyleneindolines **1** with imine **5** at ambient temperature, did not lead to any reaction products. Gradual increase of the temperature to 50 °C did not result in any noticeable reaction, indicating that rather harsh conditions might be needed to observe the desired reactivity. Finally, we found that the target ene reaction takes place at about 80 °C, proceeding rather smoothly with appreciable yield and stereochemical outcome of the corresponding addition products **6** (Scheme 1). In a typical experiment, the equimolar amounts of the substituted 3-methyleneindolines **1a-h** and (*R*)- or (*S*)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine **5** were mixed in a sealed 5 mL glass tube and the resulting mixture was heated for 2–6 h at 80° C.



Scheme 1

Upon cooling, silica gel column chromatography of the resulting crude product allowed isolation of mixtures of **(*R*,*R*$_s$)-6** and **(*S*,*R*$_s$)-6** with yields and diastereomeric ratios presented in the Table. In some cases the separation of both diastereomers was possible. The diastereomeric ratios were determined by integration of the doublets (J ~ 7 Hz) attributed to the trifluoromethyl groups at δ ~75-–76 ppm in the ^{19}F NMR spectrum of the crude mixture.

Table. 1-*tert*-Butoxycarbonyl-*N*-*tert*-butanesulfynyl-α-trifluoromethyltryptamines from the reaction of 1-*tert*-butoxycarbonyl-3-methyleneindolines and (*R*)-*N*-*tert*-butanesulfinyltrifluoro-acetaldimine at 80 °C without solvent.

3-Methylene-indoline (Y)	Adduct	Yield, % [a] ((*R*,*R*$_s$)/(*S*,*R*$_s$))[b]
5-H	**6a**	62 (83:17)
5-CH_3	**6b**	71 (86:14)
5-OCH_3	**6c**	68 (85:15)
5-Cl	**6d**	55 (88:12)
5-F	**6e**	64 (86:14)
5-CF_3	**6f**	69 (84:16)
6-CF_3	**6g**	47 (85:15)

[a] Yield of the diastereomeric mixture. [b] Determined by the integration of the CF_3 doublets at δ –75.05 - –75.29 (major diastereomer) and δ –75.35 - –75.75 (minor diastereomer) in the ^{19}F NMR spectrum of the crude reaction mixture.

The absolute configuration (AC) at the newly created -HC*(CF_3)NH- carbon of the major diastereomer **6e** obtained from

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the reaction of 1-*tert*-butoxycarbonyl-5-fluoro-3-methyleneindoline (**1e**) with (R_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine (*R*)-**5** has been assigned by comparing the experimental vibrational circular dichroism (VCD) and infrared (IR) spectra with the data computed by means of Density Functional Theory (DFT): this approach proved to be quite powerful and robust for AC assignment of various organic molecules, especially for non-solid samples.[18-20] In setting up the calculation protocol, (*S*) AC (see SI) was fixed on the sulfur atom. In order to find all possible conformations, a conformational search was employed for the two diastereomeric form (R,S_S)-**6e** and (S,S_S)-**6e**. All conformers were fully optimized and then VCD and IR spectra were calculated at different DFT levels of theory.[21-22] The final computed spectra were obtained as averages over the conformers Boltzmann's populations (see Supporting Information for protocol details). In Fig. 1a experimental VCD and IR spectra of the two major diastereomers obtained from the reaction of 3-methyleneindoline **1e** with (*R*)- and (*S*)-*N*-*tert*-butanesulfinyltrifluoroacetaldimine, respectively, are reported. For consistency with the previous results, the comparison with the calculated spectra of diastereomers (S,R_S)-**6e** and (R,R_S)-**6e** is shown in Fig. 1b

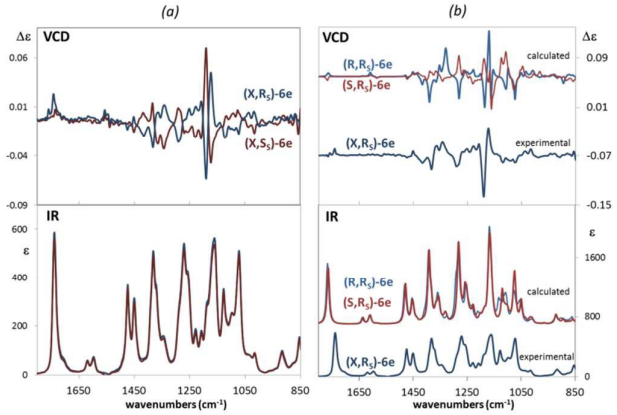

Fig 1. *(a)*: experimental VCD (top panel) and IR (bottom panel) spectra of the two enantiomers of major diastereomer **6e** recorded in CCl_4 (see Supporting Information for experimental details); *(b)* comparison of VCD (top panel) and IR (bottom panel) spectra between experimental (R_S) enantiomer and calculated VCD and IR spectra for diastereomers (R,R_S)-**6e** and (S,R_S)-**6e** at DFT/PBE0/TZVP level of theory. Experimental VCD spectrum is reported as semi-difference of VCD spectra on the left.

VCD spectra, in the range of 1050-1450 cm^{-1}, are in good enantiomeric relationship. Calculated VCD and IR spectra of the two possible diastereomers (R,R_S)-**6e** and (S,R_S)-**6e** are compared with the experimental spectra for (X,R_S)-**6e** (Fig. 1b). The calculated VCD curve, which better qualitatively predicts experimental spectrum, is, without any doubt, the one of the corresponding (R,R_S)-**6e** diastereomer. Indeed, the intense experimental doublet centered at ca. 1180 cm^{-1} is well predicted in signs by calculated (R,R_S)-**6e** VCD curve, while for (S,R_S)-**6e**, smaller VCD features with opposite behavior are calculated. The vibrational normal modes in correspondence of the calculated doublet are comprised of C*-H bending modes coupled with some other C-H bending and C-F stretching (see SI for details). The C*-H bending mode has already been found as a good probe for central carbon chirality discrimination in a number of VCD spectra.[23-24] The double check, effected with the enantiomer **(*S*,*S*$_S$)-6e**, obtained as the major diastereomer from the reactions of the methyleneindoline **1e** with the aldimines **(*S*)-5** confirmed the previous assignment.

Calculated IR spectra are less informative about diastereomeric discrimination but it is also worth noting that they nicely predict the experimental one.

Considering the stereochemical outcome obtained in these reactions, we were rather satisfied with the chemical yields and the diastereoselctivity averaging 60% and 85/15 ratio. One may agree that for the reactions conducted at 80 °C without a solvent, these values are quite appreciable. Furthermore, the diastereomeric ratio in these *ene* reactions is not noticeably influenced by the nature of substituents on the aromatic ring of starting 3-methylene-indolines **1a**-**h**. Thus, in the case of substrates bearing electron-withdrawing and –donating, as well as sterically bulky substituents, the diastereomeric ratios were ranging between 88/12 and 84/16.

From a mechanistic point of view, the observed mode of stereoselectivity could be explained by considering the *ene* reaction like a [4+2] pericyclic reaction running across a unique transition state so that the stereoselectivity could derive from the different activation energy of the two possible transition states. As shown in Fig. 2 (*a*), attack of the exocyclic methylene of indoline occurs preferentially at the *re* face of C=N double bond leading to the adduct (R,R_S)-**6** as the main diastereomer. Presumably, the activated complex assumes a distorted skew-boat conformation with the bulky trifluoromethyl group occupying an equatorial position.

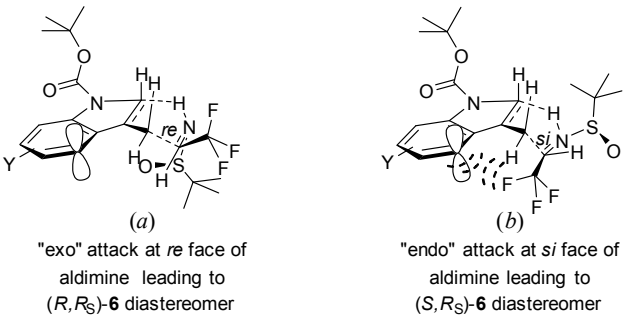

Fig 2. Plausible TS configurations of the "ene" reaction of 3-methyl-eneindolines and (R_S)-*tert*-butanesulfinyltrifluoroacetaldimine

As a final goal of this study, we decided to demonstrate some useful transformations of products **6**. *tert*-Butanesulfinyl group in **6**, besides being a valuable chiral auxiliary, can be treated merely as an amine protecting group. However, in products **6**, both *tert*-butanesulfinyl and Boc protective groups are liable towards acidic conditions. Nevertheless, in the case of the di-protected indoles **6**, the different nature of the two nitrogen protecting-groups could be synthetically exploited by a selective removal under appropriate hydrolytic conditions. Thus, when a solution of the di-protected indole **6f** was refluxed (48 h) in a 1:9 dioxane-water mixture,[25] Boc was selectively removed rendering the remaining sulfinyl group on the amino nitrogen (**7f**) useful for further stereoselective transformations (Scheme 2).

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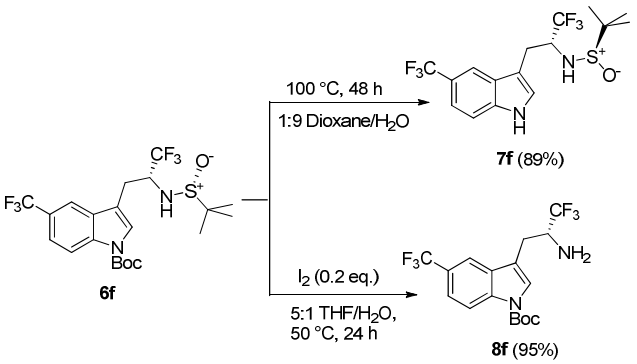
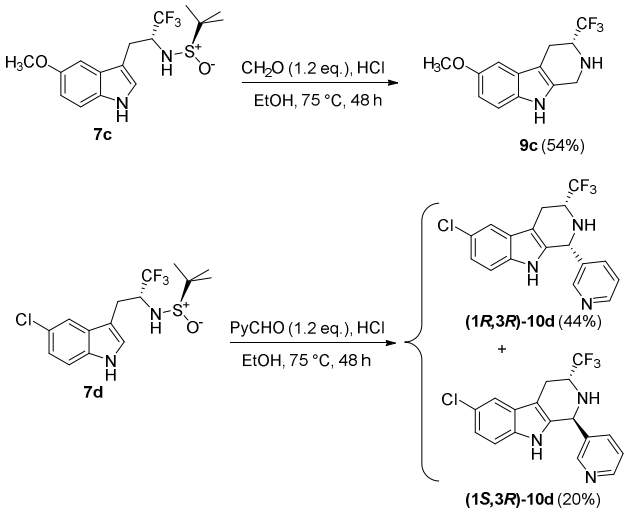


Scheme 2

Alternatively, sulfinyl group can be selectively removed in nearly quantitative yield by heating at 50 °C a solution **6** in 5:1 THF/H_2O mixture in the presence of iodine (20%),[26] making the Boc protection at the heterocyclic nitrogen (**8f**) a potential *ortho*-directing group to be exploited for possible further functionalization with polar organometallic reagents. Under more forcing conditions both Boc and sulfinyl groups are completely removed in few minutes. Under such conditions, in the presence of aldehydes, the one-pot synthesis of diastereomeric 1-alkyl(aryl)-substituted 3-trifluoromethyltetrahydrocarbolines could be easily realized (see for example Scheme 3).



Scheme 3

Chemistry and synthetic transformations of this new type enantiomerically pure α-(trifluoromethyl)tryptamines are currently under investigation and will be reported in a due course.

Conclusions

In conclusion, we have successfully realized the first example of ene reaction between 1-*tert*-butoxycarbonyl-3-methylene-indolines and (*R*)-*N*-*tert*-butanesulfinyltrifluoroacetaldimine allowing simple and straightforward preparation of pharmaceutically important α-(trifluoromethyl)tryptamines. The reactions are conducted under green chemistry conditions, without a solvent, at 80 °C giving rise to the target products with appreciable chemical yields and diastereoselectivity. The absolute configuration of the obtained product in one case has been determined by VCD spectra and DFT calculations. The different protective (Boc and -S*O^{t}Bu) groups at the two nitrogen atoms of the resulting tryptamines, can be chemoselectively removed, under different reaction conditions, allowing the remaining protective group to carry on its specific regio- (Boc) or stereoselective (-S*O^{t}Bu) orientation in further synthetic transformations.

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Experimental

If not specified otherwise, ^{1}H NMR and ^{1}H-decoupled ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution using tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded at 376 MHz in $CDCl_3$ solution using $CFCl_3$ as a reference standard. *J* values are expressed in Hz. Mass spectra were obtained by electron impact fragmentation at 70 eV ionization potential. The purity of all final products was testified by elemental analyses of the diastereomeric mixtures performed on Carlo Erba Elemental Analyzer Mod. 1106. VCD experiments were performed with a Jasco FVS6000 spectrometer on 0.1 M/$CDCl_3$ solutions in 0.200 mm BaF_2 cells. DFT calculations were carried out by the use of Gaussian09 set of programs[20] (for further details see SI). Further information about working routine and technical details can be found in previous publications from this laboratory. The starting fluoro-, trifluoromethyl- and trifluoromethoxy substituted anilines and 2-bromo-5-fluoroaniline were commercial products and were used without further purification.

New starting material used in this work:

tert-Butyl N-(2-bromo-4-methoxyphenyl)-N-(prop-2-yn-1-yl)carbamate. It was obtained in 75% of yield from *p*-anisidine following the same protocol previously reported.[17] Chromatography of the crude on silica gel (eluent 9:1 v/v petroleum ether/diethyl ether) allowed to recover a colorless oil consisting of a 3:1 mixture of two conformers exhibiting the following spectral characteristics. Major conformer: ^{1}H NMR δ 7.28 (d, *J* = 8.6 Hz, 1 H), 7.14 (d, *J* = 2.7 Hz, 1 H), 6.84 (dd, *J* = 8.6 and 2.7, 1 H), 4.76 (dd, *J* = 17.6 and 2.3 Hz, 1 H), 3.91 (dd, *J* = 17.6 and 2.3 Hz, 1 H), 3.81 (s, 3 H), 2.20 (bs, 1 H), 1.36 (s, 9 H); ^{13}C NMR δ 159.1, 154.0, 132.9, 131.0, 123.8, 117.8, 113.5, 80.7, 72.2, 55.6, 38.2, 28.1. Minor conformer, typical absorptions: ^{1}H NMR δ 7.35 (d, *J* = 8.6 Hz, 1 H), 7.15 (b, 1 H), 4.61 (d, *J* = 17 Hz, 1 H), 3.79 (s, 3 H), 2.22 (bs, 1 H), 1.52 (s, 9 H) ^{13}C NMR δ 156.7, 154.3, 133.2, 131.3, 118.2, 114.0, 81.3, 71.9, 39.5. Anal.: calcd for $C_{15}H_{18}BrNO_3$ (340.22) C, 52.96; H, 5.33; N, 4.12. Found C, 53.13; H, 5.36; N, 4.17.

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1-tert-Butoxycarbonyl-5-metoxy-3-methyleneindoline. It was prepared in 53% yield by tributyltin hydride-promoted radical cyclization of the above 2-bromoarylcarbamate as previously reported.[17] Chromatography of the crude product on silica gel, eluent, 9:1 petroleum ether/diethyl ether mixture, allowed to get a pale yellow solid exhibiting the following spectroscopic and analytical characteristics. Mp 40-42 °C; ^{1}H NMR δ 7.86 (d, *J* = 8.4 Hz, 1 H), 6.95 (s, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 5.43 (bs, 1 H), 5.03 (bs, 1 H), 4.56 (bs, 2 H), 3.81 (s, 3 H), 1.55 (s, 9 H). ^{13}C NMR δ 155.5, 151.5, 141.1, 130.0, 116.1, 116.0, 105.2, 101.6, 101.2, 80.5, 55.7, 53.6, 28.4. Anal.: calcd for $C_{15}H_{19}NO_3$ (261.32) C, 68.94; H, 7.33; N, 5.36. Found C, 68.67; H, 7.45; N, 5.41.

General Procedure for the synthesis of (R)-1-tert-butoxycarbonyl-3-[2-((R)-tert-butanesulfin-ylamido)-3,3,3-trifluoropropyl]indoles.

3-methyleneindoline **1a-f** (1.0 mmol) and (*R*)- or (*S*)-*tert*-butanesulfinyltrifluoacetaldimine were mixed in a sealed vial without solvent and heated at 70-80°C in a oil bath for the time reported in the Table. After cooling, the diastereomeric ratio was determined by ^{19}F NMR analysis before the crude mixture was take up with dichloromethane (1 mL) and chromatographed on silica gel using 65:35 petroleum ether-ethyl acetate mixture as the eluent. Yields are reported in the Table. For irresolvable diastereomeric mixture, the structure of each diastereomer was inferred from the specific ^{1}H, ^{13}C and ^{19}F NMR signals in the spectrum of the diastereomeric mixture.

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]indole (**6a**$_{(R)}$).* Slight yellow very viscous oil. ^{1}H NMR δ 8.14 (bd, *J* = 7.6 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.50 (s, 1 H), 7.35 (t, *J* = 8.5 Hz, 1 H), 7.28 (t, *J* = 8.5 Hz, 1 H) 4.05 (m, 1 H), 3.74 (d, *J* = 9.6 Hz, 1 H), 3.26 (dd, *J* = 15 and 4.0 Hz, 1 H), 3.03 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.68 (s, 9 H), 1.01 (s, 9 H); ^{13}C NMR δ 148.9, 134.9, 129.4, 124.6 (q, *J* = 281 Hz), 124.3, 124.2, 123.2, 117.9, 114.9, 113.8, 83.3, 57.6 (q, *J* = 29 Hz), 56.6, 27.6, 24.8, 21.6; ^{19}F NMR δ −75.33 (d, *J* = 7.1 Hz, 3 F).

*(S,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]indole (**6a**$_{(S)}$).* Slight yellow very viscous oil; ^{1}H NMR δ 7.91 (m, 1 H), 7.55 (s, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.5 Hz, 1 H), 7.19 (t, *J* = 8.5 Hz, 1 H), 4.05 (quint, *J* = 6.8 Hz, 1H), 3.53 (d, *J* = 9.6 Hz, 1 H), 3.24 (dd, *J* = 15 and 6.0 Hz, 1 H), 3.10 (dd, *J* = 15 and 6.4 Hz, 1 H), 1.59 (s, 9 H), 0.93 (s, 9 H); ^{19}F NMR δ −75.52 (d, *J* = 7.1 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{20}H_{27}F_3N_2O_3S$ (432.50) C, 55.54; H, 6.29; N, 6.48. Found C, 55.41; H, 6.34; N, 6.51.

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methylindole (**6b**$_{(R)}$).* White solid, mp 77-79 °C; ^{1}H NMR δ 8.00 (bd, *J* = 8.3 Hz, 1 H), 7.44 (s, 1 H), 7.27 (s, 1 H), 7.16 (d, *J* = 8.3 Hz, 1 H), 4.04 (m, 1 H), 3.58 (d, *J* = 9.6 Hz, 1 H), 3.24 (dd, *J* = 15 and 3.9 Hz, 1 H), 2.98 (dd, *J* = 15 and 9.6 Hz, 1 H), 2.47 (s, 3 H), 1.67 (s, 9 H), 1.01 (s, 9 H); ^{13}C NMR δ 149.4, 133.7, 132.3, 130.0 (d, *J* = 9.5 Hz), 126.0, 125.1 (q, *J* = 282 Hz), 124.5, 118.3, 115.0, 114.0, 83.6, 58.2 (q, *J* = 29 Hz), 57.1, 28.1 (3 C), 25.3, 22.1 (3 C), 21.3; ^{19}F NMR δ −75.34 (d, *J* = 7.0 Hz, 3 F).

*(S,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methylindole (**6b**$_{(S)}$).* Yellow Viscous oil ^{1}H NMR in the mixture δ 7.92 (bs, 1 H), 7.52 (s, 1 H), 7.20 (s, 1 H), 7.09 (d, *J* = 8.3 Hz, 1 H), 4.06 (quint, *J* = 5.8 Hz, 1 H), 3.54 (d, *J* = 6.0 Hz, 1 H), 3.21 (dd, *J* = 15 and 5.8 Hz, 1 H), 3.07 (dd, *J* = 15 and 6.8 Hz, 1 H), 2.39 (s, 3 H), 1.59 (s, 9 H), 0.93 (s, 9 H); ^{13}C NMR δ 149.4, 133.6, 132.3, 130.6, 126.5, 125.1 (q, *J* = 282 Hz), 124.8, 118.3, 115.0, 114.0, 83.6, 58.2 (q, J = 29 Hz), 57.1, 28.1 (3 C), 25.3, 22.3 (3 C), 21.3; ^{19}F NMR δ −75.47 (d, *J* = 7.0 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{21}H_{29}F_3N_2O_3S$ (446.53) C, 56.49; H, 6.55; N, 6.27. Found C, 56.47; H, 6.60; N, 6.37.

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methoxyindole (**6c**).* Whit solid, mp 113-115 °C; ^{1}H NMR δ 7.94 (bd, 8.0 Hz, 1 H), 7.39 (s, 1 H), 6.88 (s, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 3.96 (m, 1 H), 3.81 (s, 3 H), 3.72 (d, *J* = 9.4 Hz, 1 H), 3.15 (dd, *J* = 15 and 4.3 Hz, 1 H), 2.92 (dd, *J* = 15 and 9.1 Hz, 1 H), 1.59 (s, 9 H), 0.96 (s, 9 H); ^{13}C NMR δ 155.5, 148.9, 130.2, 129.5, 124,9, 124.6 (q, *J* = 282 Hz), 115.7, 113.5, 112.7, 100.7, 83.1, 57.3 (q, *J* = 29 Hz), 56.7, 55.2, 27.6 (3 C), 25.0, 21.6 (3 C); ^{19}F NMR δ −75.25 (d, *J* = 7.1 Hz, 3 F). Analysis: calcd for $C_{21}H_{29}F_3N_2O_4S$ (462.53) C, 54.53; H, 6.32; N, 6.06. Found C, 55.40; H, 6.41; N, 6.12.

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-chloroindole (**6d**).* White solid, mp 72–74 °C; ^{1}H NMR δ 8.07 (d, *J* = 8.4 Hz, 1 H), 7.53 (s, 1 H), 7.49 (d, *J* = 1.5 Hz, 1 H), 7.30 (dd, *J* = 9.0 and 1.9 H, 1 H), 4.01 (m, 1 H), 3.85 (d, *J* = 9.4 Hz, 1 H), 3.21 (dd, *J* = 15 and 3.5 Hz, 1 H), 3.02 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.68 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR δ 149.0, 133.7, 131.2, 128.5, 126.1, 125.0 (q, *J* = 282 Hz), 124.8, 118.2, 116.4, 113.7, 84.3, 58.1 (q, *J* = 29 Hz), 57.1, 28.1 (3 C), 25.1, 22.2 (3 C); ^{19}F NMR δ, −75.18 (d, *J* = 6.3 Hz, 3 F). Analysis: calcd for $C_{20}H_{26}ClF_3N_2O_3S$ (466.94) C, 51.44; H, 5.61; N, 6.00. Found C, 51.54; H, 5.71; N, 6.09.

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-((R)-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-fluoroindole (**6e**$_{(R)}$).* Pale yellow viscous oil; ^{1}H NMR δ 8.03 (bs, 1 H), 7.49 (s, 1 H), 7.14 (dd, *J* = 8.4 and 2.4 Hz, 1 H), 7.06 (td, *J* = 9.2 and 2.8 Hz, 1 H), 4.16 (m, 1 H), 3.71 (d, *J* = 9.6 Hz, 1 H), 3.39 (dd, *J* = 15 and 4.0 Hz, 1 H), 3.19 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.93 (s, 9 H), 1.34 (s, 9 H); ^{13}C NMR δ 159.3 (d, *J* = 240 Hz), 149.2, 131.8, 130.9 (d, *J* = 9.5 Hz), 126.4, 125.1 (q, *J* = 282 Hz), 116.5 (d, *J* = 9.1 Hz), 113.9 (d, *J* = 4.0 Hz), 112.6 (d, *J* = 25 Hz), 104.2 (d, *J* = 24 Hz), 84.2, 57.9 (q, *J* = 29 Hz), 57.1, 28.2 (3 C), 25.5 (q, *J* = 1.9 Hz), 22.2 (3 C); ^{19}F NMR δ −75.72 (d, *J* = 7.0 Hz, 3 F), −120.01 (s, 1 F).

*(S,R_S)-1-tert-butoxycarbonyl-3-[2-((R)-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-fluoroindole (**6e**$_{(S)}$).* Pale yellow oil; ^{1}H NMR δ 8.10 (bs, 1 H), 7.55 (s, 1 H), 7.18 (dd, *J* = 8.7 and 2.5 Hz, 1 H), 7.08 (td, *J* = 9.1 and 2.6 Hz, 1 H), 4.03 (m, 1 H), 3.55 (d, *J* = 7.4 Hz, 1 H), 3.22 (dd, *J* = 15 and 5.6 Hz, 1 H), 3.02 (dd, *J* = 15 and 6.8 Hz, 1 H), 1.68 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR δ 159.3 (d, *J* = 239 Hz), 149.2, 131.8, 130.9 (d, *J* = 9.5 Hz), 126.4, 125.1 (q, *J* = 281 Hz), 116.5 (d, *J* = 9.1 Hz), 114.0 (d, *J* = 4.0 Hz), 112.6 (d, *J* = 25 Hz), 104.2 (d, *J* = 24 Hz), 84.2, 57.9 (q, *J* = 29 Hz), 57.1, 28.2 (3 C), 25.5 (q, *J* = 1.9 Hz), 22.2 (3 C); ^{19}F NMR δ −74.71 (d, *J* = 6.7 Hz, 3 F), −120.01 (s, 1 F). Analysis of the diastereomeric mixture: calcd for $C_{20}H_{26}F_4N_2O_3S$ (450.49) C, 53.32; H, 5.82; N, 6.22. Found C, 53.21; H, 5.90; N, 6.37.

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*(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-(trifluoromethyl)indole (**6f**).* Pale yellow oil; ^{1}H NMR δ 8.25 (d, *J* = 8.6 Hz, 1 H), 7.79 (s, 1 H), 7.61 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 4.02 (m, 1 H), 3.77 (d, *J* = 9.5 Hz, 1 H), 3.26 (dd, *J* = 15 and 4.3 Hz, 1 H), 3.09 (dd, *J* = 15 and 9.1 Hz, 1 H), 1.68 (s, 9 H), 1.03 (s, 9 H); ^{13}C NMR δ 148.4, 136.4, 129.3, 125.9, 124.8 (q, *J* = 280 Hz), 124.6 (q, *J* = 32 Hz), 124.1 (q, *J* = 270 Hz), 121.0, 115.3, 115.2, 114.0, 84.2, 57.7 (q, *J* = 29 Hz), 56.6, 27.5 (3 C), 24.6, 21.5 (3 C); ^{19}F NMR δ −61.48 (3 F), −75.12 (d, *J* = 6.8 Hz, 3 F). Analysis: calcd for $C_{21}H_{26}F_6N_2O_3S$ (500.50) C, 50.39; H, 5.24; N, 5.60. Found C, 50.31; H, 5.28; N, 5.69.

*(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-6-(trifluoromethyl)indole (**6g$_{(R)}$**).* Viscous yellow oil; ^{1}H NMR δ 8.87 (bs, 1 H), 7.57 (s, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 3.98 (m, 1 H), 3.66 (d, *J* = 9.7 Hz, 1 H), 3.20 (dd, *J* = 15 and 4.2 Hz, 1 H), 3.01 (dd, *J* = 15 and 8.9, 1 H), 1.62 (s, 9 H), 0.97 (s, 9 H); ^{13}C NMR δ 148.4, 134.0, 131.8, 126.8, 126.2 (q, *J* = 32 Hz), 124.6 (q, *J* = 282 Hz), 124.2 (q, *J* = 270 Hz), 119.0 (q, *J* = 3.0 Hz), 118.4, 113.7, 112.5 (q, *J* = 4.1 Hz), 84.3, 57.6 (q, *J* = 29 Hz), 56.7, 27.5 (3 C), 24.6, 21.6 (3 C); ^{19}F NMR δ −61.56 (3 F), −75.12 (d, *J* = 7.1 Hz, 3 F).

*(S,R$_S$)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-6-(trifluoromethyl)indole (**6g$_{(S)}$**).* Viscous yellow oil; ^{1}H NMR δ 8.41 (bs, 1 H), 7.73 (s, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.45 (d, *J* = 8.3 Hz, 1 H), 4.06 (quint, *J* = 5.9 Hz, 1 H), 3.71 (d, *J* = 7.7 Hz, 1 H), 3.26 (dd, *J* = 15 and 5.4 Hz, 1 H), 3.13 (dd, *J* = 15 and 6.4 Hz, 1 H), 1.63 (s, 9 H), 1.15 (s, 9 H); ^{13}C NMR δ 148.5, 134.2, 132.0, 127.4, 126.2 (q, *J* = 32 Hz), 124.6 (q, *J* = 282 Hz), 124.2 (q, *J* = 270 Hz), 119.1, 118.8112.6, 112.5, 84.3, 57.0 (q, *J* = 29 Hz), 56.4, 27.6 (3 C), 25.0, 21.9 (3 C); ^{19}F NMR δ −61.6 (3 F), −75.52 (d, *J* = 7.1 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{21}H_{26}F_6N_2O_3S$ (500.50) C, 50.39; H, 5.24; N, 5.60. Found C, 50.24; H, 5.31; N, 5.72.

*Selective deprotection of the adducts **6c** and **6f** by removal of tert-butoxycarbonyl (Boc) group.*[25]

Adduct **6c** (or **6f**) (0.50 mmol) was added to a 1:9 dioxane/H_2O mixture (20 mL)and the resulting suspension was refluxed until the starting material was completely disappeared (48 h, *tlc*, SiO_2, eluent, 1:1 petroleum ether/ethyl acetate). After cooling, the reaction mixture was poured into water (30 mL), extracted with dichloromethane (3 × 50 mL) and the collected organic phases were dried with Na_2SO_4. After the solvent evaporation at reduced pressure, chromatography of the crude product on silica gel (eluent, 1:1 petroleum ether/ethyl acetate) allowed to get pure indole.

*(R,R$_S$)-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methoxyindole (**7c**, 96%).* White solid, mp 92-94 °C; ^{1}H NMR δ 8.13 (bs, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.11 (s, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.87 (dd, *J* = 8.8 and 2.4 Hz, 1 H), 4.02 (m, 1 H), 3.88 (s, 3 H), 3.60 (d, *J* = 9.1 Hz, 1 H), 3.30 (dd, *J* = 15 and 3.4 Hz, 1 H), 3.09 (dd, *J* = 15 and 9.1 Hz, 1 H), 0.98 (s, 9 H); ^{13}C NMR δ 154.2, 131.2, 127.6, 125.3 (q, *J* = 281 Hz), 124.4, 123.9, 112.4, 112.1, 108.9, 57.9 (q, *J* = 29 Hz), 56.9, 55.8, 25.4, 22.0 (3 C); ^{19}F NMR δ −75.00 (d, *J* = 7.5 Hz, 3 F); MS (70 eV) m/z (%) 304 (M^+–C_4H_{10}, 20), 160 (100), 145 (21), 117 (14). Analysis: calcd for $C_{16}H_{21}F_3N_2O_2S$ (362,41) C, 53.03; H, 5.84; N, 7.73. Found C, 53.17; H, 5.91; N, 7.66.

*(R,R$_S$)-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-trifluoromethylindole (**7f**, 94%).* White solid, mp 83-85 °C; ^{1}H NMR (acetone-d_6) δ 10.1 (s, 1 H), 8.16 (s, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.56 (s, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 4.19 (m, 1 H), 3.39 (dd, *J* = 14 and 3.4 Hz, 1 H), 3.26 (dd, *J* = 14 and 11 Hz, 1 H), 2.1 (bs, 1 H), 0.83 (s, 9 H); ^{13}C NMR (acetone-d_6) δ 137.9, 130.1, 127.3, 126.5, 125.8 (q, *J* = 282 Hz), 120.6, 117.7, 116.2, 111.9, 110.7, 59.5 (q, *J* = 28 Hz), 56.3, 24.3, 21.3 (3 C); ^{19}F NMR (acetone-d_6) δ −60.66 (s, 3 F), −75.93 (d, *J* = 7.3 Hz, 3 F); MS (70 eV) m/z (%) 342 (M^+–C_4H_{10}, 10), 198 (100), 178 (6), 151 (8). Analysis: calcd for $C_{16}H_{18}F_6N_2OS$ (400.38) C, 48.00; H, 4.53; N, 7.00. Found C, 48.17; H, 4.62; N, 6.93.

*Selective deprotection of the adduct **6f** by removal of tert-butanesulfinyl group*.[26]

Iodine (25 mg, 0.05 mmol) was added to a solution of the adduct **6f** (0.25 g, 0.50 mmol) in 5:1 THF/H_2O (15 mL) and the mixture was stirred at 50 °C until the complete disappearance of the starting material was observed (24 h, *tlc*, SiO_2, eluent, 1:1 petroleum ether/ethyl acetate). After cooling, 1 M aqueous NaOH (1 mL) was added and the mixture was poured into water (20 mL), extracted with dichloromethane (3 × 25 mL) and the collected organic phases were dried with Na_2SO_4. After the solvent was evaporated at reduced pressure, chromatography of the residue on silica gel (eluent, 6:4 petroleum ether/ethyl acetate) allowed to collect pure indole **8f**.

*(R,R$_S$)-1-(tert-butoxycarbonyl)-3-(2-amino-3,3,3-trifluoropropyl)-5-(trifluoromethyl)-1H-indole (**8f**)* as a pale yellow oil (0.19 g, 95%). ^{1}H NMR δ 8.25 (d, *J* = 8.7 Hz, 1 H), 7.81 (s, 1 H), 7.66 (s, 1 H), 7.59 (d, *J* 8.7 Hz, 1 H), 3.56 (m, 1 H), 3.20 (dd, *J* = 15 and 2.3 Hz, 1 H), 2.80 (dd, *J* = 15 and 10 Hz, 1 H), 1.70 (s, 9 H), 1.43 (bs, 2 H); ^{13}C NMR δ 148.6, 136.6, 129.3, 125.8 (q, *J* = 280 Hz), 125.5, 124.5 (q, *J* = 32 Hz), 124.2 (q, *J* = 270 Hz), 120.9, 115.5, 115.2, 115.1, 84.0, 53.1 (q, *J* = 29 Hz), 27.6 (3C), 25.1; ^{19}F NMR δ –61.45 (s, 3 F), –79.06 (d, *J* = 7.1 Hz, 3 F). Analysis: calcd for $C_{17}H_{18}F_6N_2O_2$ (396.33) C, 51.52; H, 4.58; N, 7.07. Found C, 51.38; H, 4.65; N, 7.12.

*General procedure for the synthesis of tetrahydrocarbolines **9c** and **10d***

Conc. HCl (0.5 mL) was cautiously added to a solution of the indole derivative **6** (0.50 mmol) and the aldehyde (1.2 equiv.) and the mixture was made to react at 75 °C until the starting indole was disappeared (48 h, by tlc, SiO_2, 1:3 petroleum ether/ethyl acetate). After cooling at room temperature, aqueous 1 M KOH was added until the pH 11-12 was reached, the mixture was extracted with dichloromethane (3 × 20 mL) and the collected organic phases were dried with Na_2SO_4. Alter the solvent was evaporated at reduced pressure, chromatography of the residue on silica gel (eluent, petroleum ether/ethyl acetate 1:3) allowed to get the expected product which was characterized as follows:

*(R)-6-methoxy-3-(trifluoromethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**9c**).* (54%) From **7c** (0.23 g, 0.50 mmol) and

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formaldehyde (37% in H_2O, 50 μL, 18 mg, 0.6 mmol); White solid, mp 60-62 °C; ^{1}H NMR (DMSO-d_6) δ 7.18 (d, *J* = 8.6 Hz, 1 H), 6.93 (d, *J* = 1.7 Hz, 1 H), 6.67 (d, *J* = 8.6 and 1.7 Hz, 1 H), 3.94 (s, 2 H), 3.74 (s, 3 H), 3.6 (m, 1 H), 2.86 (dd, *J* = 3.2 and 14.0 Hz 1 H), 2.66 (dd, *J* =10.6 and 14.0 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 153.5, 134.8, 131.2, 127.6, 127.0 (q, *J* = 278 Hz), 111.9, 110.6, 104.9, 100.0, 55.7, 55.2 (q, *J* = 28 Hz), 42.3, 21.8; ^{19}F NMR (DMSO-d_6) δ −75.16 (t, *J* = 3.5 Hz, 3 F). MS (70 eV) *m/z* (%) 270 (M^+, 81), 199 (15)173 (100), 158 (77), 130 (11). Analysis: calcd for $C_{13}H_{13}F_3N_2O$ (270,26) C, 57.78; H, 4.85; N, 10.37. Found C, 57.59; H, 5.00; N, 10.22.

(1*R*,3*R*)- and (1*S*,3*R*)-*(R)-6-chloro-3-(trifluoromethyl)-2,3,4,9-tetrahydro-1-(pyrid-3-yl)-1H-pyrido[3,4-b]indole (**10d**)* (63%). From **7d** (0.23 g, 0.5 mmol) and 3-pyridinecarbaldehyde (65 mg, 0.61 mmol). Diastereomeric mixture of (1*R*,3*R*)-**10d** and (1*S*,3*R*)-**10d**, dr = 2.2 (from the integral of the signals at δ −74.98 and −74.63, respectively, in the ^{19}F NMR spectrum of the crude reaction mixture). white solid, mp > 300 °C. (1*R*,3*R*)-**10d**: ^{1}H NMR (DMSO-d_6) δ 10.74 (s, 1 H), 8.63 (s, 1 H), 8.55 (d, *J* = 4,4 Hz, 1 H), 8.51 (s, 1 H), 7.74 (d, *J* = 7.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz), 7.42 (dd, *J* = 8.1 and 4.4 Hz, 1 H), 7.23(d, *J* = 8.5 Hz, 1 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 5.31 (s, 1 H), 3.87 (m, 1 H), 3.5 (bs, 1 H), 2.9 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 150.4, 149.5, 137.0, 136.9, 136.8, 135.2, 128.0, 126.6 (q, *J* = 276 Hz), 124.1, 123.7, 121.4, 117.6, 113.1, 106.7, 55.5 (q, *J* = 23 Hz), 55.3, 21.7; ^{19}F NMR (DMSO-d_6) δ −74.98 (d, *J* = 7.8 Hz). (1*S*,3*R*)-**10d**: ^{1}H NMR δ 11.14 (s, 1 H), 8.6 (s, 1 H), 8.55 (d, *J* = 4,4 Hz, 1 H), 8.50 (s, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.37 (dd, *J* = 8.1 and 4.4 Hz, 1 H), 7.33(d, *J* = 8.5 Hz, 1 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 5.33 (s, 1 H), 3.72 (m, 1 H), 3.5 (bs, 1 H),), 3.03 (dd, *J* = 16 and 5.3 Hz, 1 H), 2.76 (dd, *J* = 16 and 10 Hz, 1 H); ^{13}C NMR δ 149.9, 148.9, 137.6, 137.0, 136.1, 135.6, 134.9, 127.0 (q, *J* = 276 Hz), 123.9, 123.7, 121.6, 117.7, 113.1, 107.0, 52.0, 50.8 (q, *J* = 28 Hz), 21.4; ^{19}F NMR δ −74.63 (d, *J* = 7.8 Hz). Analysis of the diastereomeric mixture: calcd for $C_{17}H_{13}ClF_3N_3$ (351.76) C, 58.05; H, 3.73; N, 11.95. Found C, 58.13; H, 3.82; N, 12.10.

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