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Enantiodivergent Approach to Trifluoromethylated Amines: A Concise Route to Both Enantiomeric Analogues of Calcimimetic NPS R-568

Inmaculada Fernández,*[a] Victoria Valdivia,[b] Ana Alcudia,[a] Ahmed Chelouan,[a] and Noureddine Khiar*[b]

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Reported herein is a straightforward and enantiodivergent synthesis of both enantiomers of trifluoromethylated analogues of calcimimetic NPS R-569 in a highly estereoselective manner. The synthesis features a diastereoselective synthesis of the *N*-(isopropylsulfinyl)imine unit by the "DAG methodology" and a diastereoselective addition of Ruppert–Prakash's reagent to the imine as the key steps. No protecting groups were necessary, permitting an atom economic synthesis in only six steps. Further addition reactions of the CF_3 anion to different *N*-(isopropylsulfinyl)imines were performed to demonstrate the suitability of the sulfinyl substituent to balance perfectly reactivity and diastereoselectivity.

Introduction

In the last decade fluorinated drugs have gained increasing significance in medical applications, including finding use in central nervous system, anticancer, antibacterial, cardiovascular, and antiviral therapies as well as in in vivo nuclear medical tomography (PET).[1] Since the first fluorinated drug, 5-fluorouracil, was synthesized in 1957 as a potent antineoplasic agent inhibiting the enzyme thymidylate synthetase, several key drugs with great structural diversity have been launched on the market and account currently for almost 25% of drugs in the pharmaceutical development.[2] It has become evident that fluorinated compounds have a critical role and impact in drug potency, constructively altering pharmacological properties.[3] Accordingly, amides derived from trifluoromethylamines are generally more resistant to enzymatic hydrolysis, have different solubilities and present different desolvation capacities.[4] Because of their importance, the preparation of chiral trifluoromethylated amines is a current area of interest.[5] Even though the enantioselective trifluoromethylation of carbonyl compounds has recently been studied in some depth, there is no enantioselective approach as yet to the enantioselective trifluoromethylation of imines.[6] The best way to synthesise chiral trifluoromethylated amines is by the addition of a trifluoromethyl anion to an imine bearing a chiral auxiliary.

The gold standard of this approach is that reported by Prakash et al. using *N*-(*tert*-butylsulfinyl)imine,[7] developed by Ellman et al.,[8] as the activated imine and Ruppert–Prakash's reagent (CF_3SiMe_3) as the trifluoromethylating agent. The exceptional behaviour of the chiral sulfinyl group in *N*-sulfinylimines as activator, chiral controller and finally as a useful protecting group makes the sulfinamides of type **I** an extremely versatile chiral intermediate in the construction of chiral trifluoromethylated amines (Figure 1).[9] Although the addition of Ruppert–Prakash's reagent to *N*-(*p*-tolylsulfinyl)imines, pioneered by Davis,[10] has been reported to add only with moderate selectivity,[11] recently Kawano and Mukayama reported that the use of ammonium salts nBu$_4$NOAc or nBu$_4$NOPh as catalyst allows the formation of trifluoromethylated amine **II** with high diastereoselectivity.[12] On the other hand, as the addition of the methyl Grignard reagent to *N*-(*tert*-butylsulfinyl)imine takes place through a coordinated Zimmerman–Traxler-like transition state, the major isomer is the *syn*-sulfinamide.[13] In contrast, it has been shown that the addition of the trifluoromethyl group takes place through the Cram open transition state, affording the *anti*-sulfinamide as the main isomer.[7] Consequently, the methyl- and trifluoromethylamine obtained using either *tert*-butyl- or *p*-tolylsulfinylimines as chiral intermediate have the opposite configuration. Taking into account that in a medicinal chemistry program, the desired trifluoromethylated analogue of a chiral drug should have the same absolute configuration as the corresponding biologically active amine, both enantiomers of the sulfinylimine intermediate should be accessible, preferably at no additional cost. In this regard it is worth mentioning that none of the methods described for the synthesis of the *tert*-butyl- or *p*-tolylsulfinylimines is able to give both enantiomers in an enantiodivergent way. In this paper we

[a] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla,
c/. Profesor García González, 2, 41012 Sevilla, Spain
[b] Instituto de Investigaciones Químicas, C.S.I.C. – Universidad de Sevilla,
c/. Américo Vespucio, 49, Isla de la Cartuja, 41092 Sevilla, Spain

report the use of a single chiral auxiliary in a highly diastereoselective approach to the synthesis of sulfinamides **III**, important intermediates in the synthesis of both enantiomers of trifluoromethylated amines.

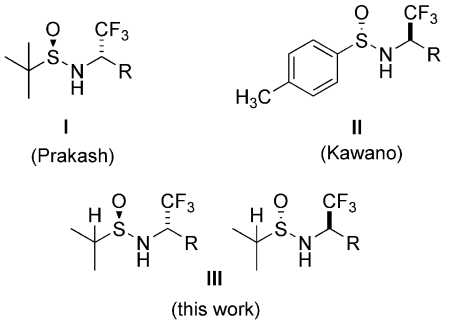


Figure 1. Trifluoromethylated sulfinamides **I**–**III**.

Within our research program directed towards the development of new asymmetric methodologies promoted by sulfur-based auxiliaries or ligands,[14] we have recently introduced *N*-(isopropylsulfinyl)imine as an alternative intermediate to the widely used (*tert*-butylsulfinyl)imine and (*p*-tolylsulfinyl)imine.[15a]

Besides the advantage of a lower molecular weight, in previous investigations we have highlighted the role of the isopropylsulfinyl group in conferring better enantiomeric discrimination than the *p*-tolylsulfinyl group and higher chemical reactivity with equal or even better enantiomeric discrimination than the most popular *tert*-butylsulfinyl group in the Corey–Chaykovsky reaction of chiral sulfinylimine,[15a] in the organocatalytic allylation of acyl hydrazones with ferrocenylsulfinyl derivatives[15b] and in the synthesis of enantiopure α-arylamines.[15c] In this paper we report a highly diastereoselective addition of Ruppert–Prakash's reagent to *N*-(isopropylsulfinyl)imines for the synthesis of various enantiomerically pure trifluoromethylated amines. The synthetic value of this approach is further demonstrated by the enantiodivergent synthesis of both enantiomers of trifluoromethylated analogues of a potent calcimimetic drug employing a single chiral auxiliary (dicyclohexylidene-D-glucose, DCGOH).

Results and Discussion

NPS R-568 (**1**; Figure 2) is a member of a new family of drugs named calcimimetics, recently launched onto the market for the treatment of hyperparathyroidism in patients with chronic kidney disease who are on dialysis and for the treatment of hypercalcemia in patients with parathyroid carcinoma.[16] Clinical studies with the calcimimetic NPS R-568 (**1**) have shown that its biological activity is closely related to the configuration of the chiral centre.[17] Accordingly, (*R*)-(+)-NPS R-568, the eutomer, is 10–100 times more potent than the (*S*)-(–) enantiomer, the distomer. We have recently disclosed an enantioselective synthesis of calcimimetic (*R*)-(+)-NPS R-568 (**1**) in six high-yielding steps starting from (*S*)-(isopropylsulfinyl)imine.[15c]

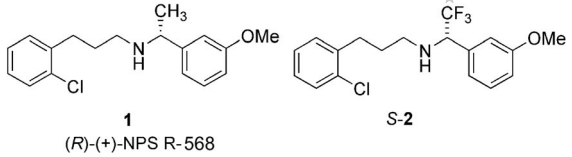
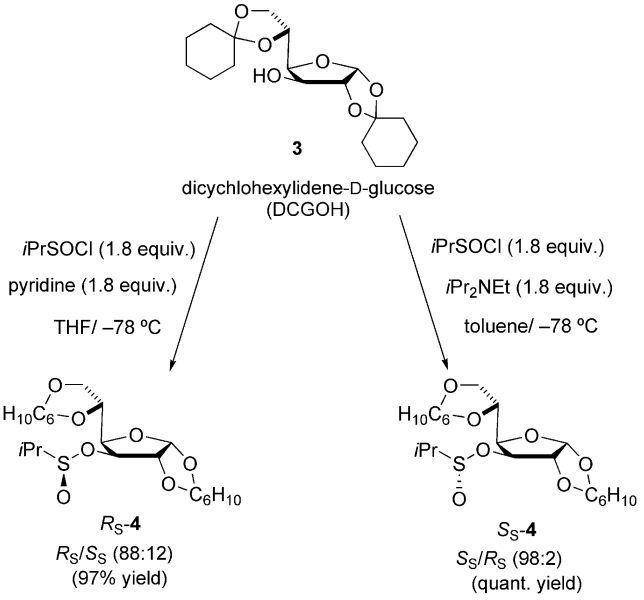


Figure 2. Chemical structure of (*R*)-(+)-NPS R-568 (**1**) and its trifluoromethylated analogue *S*-**2**.

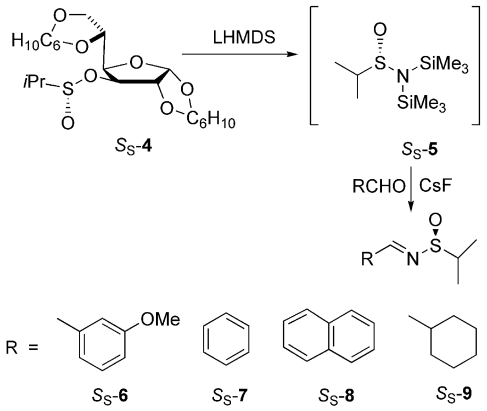
The spatially related trifluoromethylated analogue *S*-**2** should be accessible using the same route but by the addition of a trifluoromethyl group instead of a methyl Grignard as long as the stereochemical outcome of the reaction is the desired one. To determine the degree and sense of the stereocontrol exerted by the isopropylsulfinyl group, we have synthesized a number of *N*-(isopropylsulfinyl)imines and studied their reaction with Ruppert–Prakash's reagent. The asymmetric synthesis of both enantiomers of *N*,*N*-bis(trimethylsilyl)-2-propanesulfinamide (**5**) (see Scheme 2) has been achieved in an enantiodivergent manner using sugar-based sufinates *R*-**4** and *S*-**4** as sulfinylating agents, prepared by our DAG methodology (Scheme 1).[18]



Scheme 1. Enantiodivergent approach to the synthesis of S_S-**4** and R_S-**4** DCG 2-propanesulfinates.

The condensation of 1 mol-equiv. of the secondary carbinol **3** with 1.8 mol-equiv. of racemic *i*PrSOCl in THF using pyridine as base afforded the 2-propanesulfinate R_S-**4** in 97% chemical yield and 76% *de* (Scheme 1). As expected, by employing toluene as the solvent and by using exactly the same conditions as before but changing the base from pyridine to iPr_2NEt, 2-propanesulfinate S_S-**4** was obtained diastereoselectively in quantitative yield and 96% *de* (Scheme 1). In addition, the DCG 2-propanesulfinates **4** were stable as no decomposition of these sulfinates was detected after storage for several months at 4 °C.

The preparation of *N*-sulfinylimines **6**–**9** required a two-step one-pot synthesis that involved the condensation of LHMDS with sulfinate S_S-**4** leading to the sulfinamide **5** followed by condensation with a suspension of CsF and the aldehyde in THF (Scheme 2).



Scheme 2. Synthesis of *N*-(isopropylsulfinyl)imines **6**–**9**.

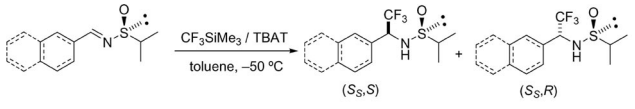
Note that the synthesis of *N*-sulfinylimines **6**–**9** using sulfinate S_S-**4** as the sulfinylating agent takes place efficiently under very mild reaction conditions as compared with the procedures reported before for the synthesis of the 2-methyl-2-propanesulfinamides **I** and *p*-toluenesulfinamides **II**. Accordingly, the complete transformation of sulfinate S_S-**4** to the silylated sulfinamide derivative **5** takes place at 0 °C in only 5 min and by condensation with the aldehyde, the final sulfinylimine is generally obtained in high chemical yield within one hour.

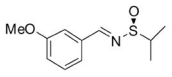
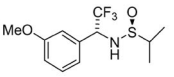
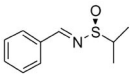
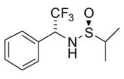
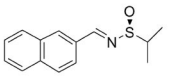
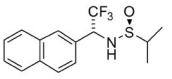
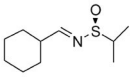
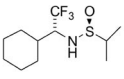
The condensation of Ruppert–Prakash's reagent with the *N*-sulfinylimines **6**–**9** using difluorotriphenylsilicate (TBAT)[19] as a soluble fluoride source in toluene at –50 °C afforded the corresponding trifluoromethylated sulfinamides in good-to-excellent yields. The results are compiled in Table 1.

The diastereomeric excesses of the products were measured by ^{1}H and ^{19}F NMR analysis of the crude mixtures. As can be observed from Table 1, the trifluoromethylated compounds **10**–**13** were obtained in excellent yields and in short reaction times. Note that both *N*-(arylsulfinyl)- and *N*-(alkylsulfinyl)imines are equally reactive towards Ruppert–Prakash's reagent and afforded the corresponding sulfinamides with excellent diastereoselectivities (up to 92% *de*, Table 1, entries 1 and 4), which is indicative of the highly stereochemical control exerted by the isopropylsulfinyl group. On the other hand, in all cases, the diastereomeric trifluoromethylated sulfinamides can be easily separated, which allows their preparation in optically pure form by flash chromatography.

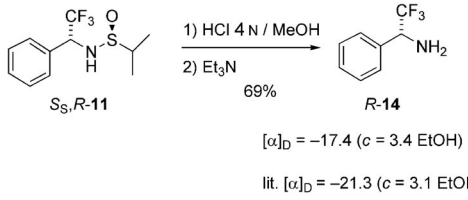
To determine the absolute configurations of the amides obtained and thus the sense of asymmetric induction, the synthesis of a known trifluoromethylamine was sought. Desulfinylation of *N*-sulfinamide (S_S,*R*)-**11** with 4 N HCl in methanol at 0 °C for 2 h provided, after addition of Et_3N and stirring overnight, the free amine *R*-**14** in good yield and with the *R* absolute configuration (Scheme 3).[20]

Table 1. Nucleophilic trifluoromethylation of *N*-sulfinylimines **6**–**9**.[a]



Entry	*N*-Sulfinylimine	Sulfinamide[b]	Yield (%)[c]	$S_S,R/S_S,S$
1	 S_S-**6**	 S_S,R-**10**	96	96:04
2	 S_S-**7**	 S_S,R-**11**	98	85:15
3	 S_S-**8**	 S_S,R-**12**	72	93:07
4	 S_S-**9**	 S_S,R-**13**	86	96:04

[a] All reactions were conducted in toluene as solvent at –50 °C. [b] Major diastereoisomer. [c] Isolated yield. [d] Determined by NMR analysis of the crude.



Scheme 3. Determination of the absolute configuration of trifluoromethylated amines: synthesis of *R*-**14**.

The stereochemical outcome of the addition of the trifluoromethyl group can be rationalized by a non-chelated Cram model in which the approach of the bulky trifluoromethylating complex takes place on the less hindered *Si* face of the double bond (Figure 3).

With these results in hand we synthesized the calcimimetic analogues. First, (S_S,*R*)-**10** was desulfinylated to yield *R*-**15**, which was treated with 3-(2-chlorophenyl)-2-propenyl chloride (**16**) in the presence of sodium carbonate to afford amide *R*-**17** in excellent yield (Scheme 4). In contrast to the corresponding methylated amide, which can be easily hydrogenated, the α,β-unsaturated trifluoromethylated amide *R*-**17** was inactive towards palladium-catalysed hydrogenation in all the solvents and hydrogen pressures assayed. This

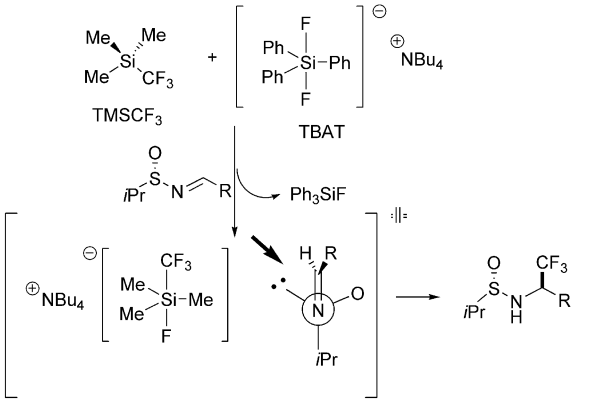
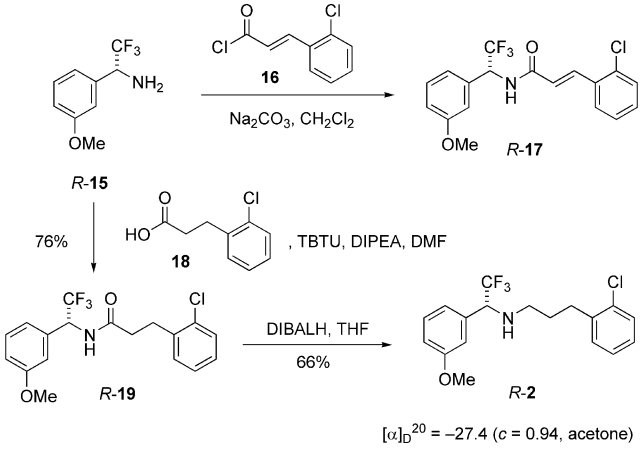
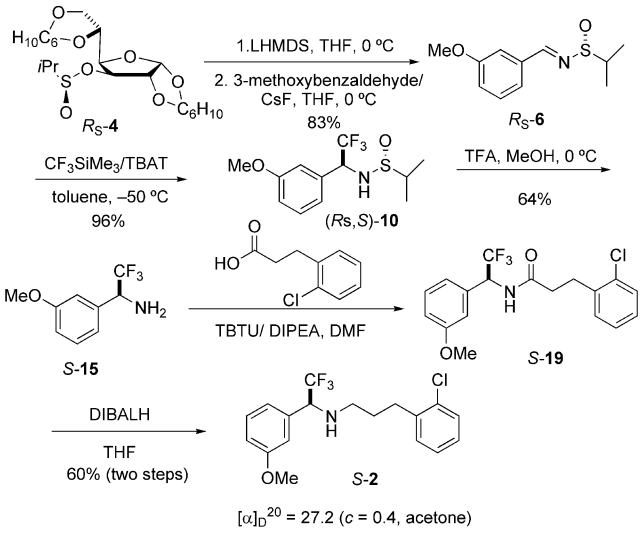


Figure 3. Model explaining the stereochemical outcome of the trifluoromethylation of the (isopropylsulfinyl)imines.

problem was solved by using the commercially available 3-(2-chlorophenyl)-2-propionic acid (**18**) as the starting material, which afforded the amide *R*-**19** in good yield in the presence of TBTU in DMF. Finally, the treatment of *R*-**19** with DIBALH in THF afforded the desired trifluoromethylated analogue of NPS R-568 in good yield (Scheme 4).



Scheme 4. Enantioselective synthesis of trifluoromethylated analogue of NPS R-568 (*R*-**2**).



Scheme 5. Enantioselective synthesis of the trifluoromethylated analogue of NPS R-568 (*S*-**2**).

Then, starting from sufinate R_S-**4** and following the same synthetic route we were able to obtain the other enantiomer with the same absolute configuration as the biologically active calcimimetic NPS R-568 (*S*-**2**) in 30% overall yield (Scheme 5).

Conclusions

The results presented in this work show that besides the advantage of lower molecular weight, the isopropylsulfinyl group confers high chemical reactivity and excellent stereocontrol. The usefulness of this new chiral controller has been demonstrated by a highly enantioselective synthesis of trifluoromethyl-arylamines. Both enantiomers of the calcimimetic drug *R*-(+)-NPS R-568 have been efficiently obtained by the use of the "DAG methodology", which allows the synthesis of both sulfinylating agents in an enantiodivergent and economic manner using DCGOH as the sole chiral auxiliary in the whole process. The results reported in this work demonstrate that the "DAG methodology" is the method of choice for the synthesis of a trifluoromethylated analogue of a biologically active amine as both enantiomers of the sulfinylimine intermediate are easily prepared in an enantiodivergent way.

Experimental Section

General Methods: Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. All reactions were performed under dry argon using oven-dried glassware and freshly distilled and dried solvents. THF and dichloromethane were dried with molecular sieves. Isopropylsulfinyl chloride[18a] and TBAT[19] were prepared according to previously reported procedures. The reactions were monitored by thin-layer chromatography (TLC) using silica gel GF254 (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, 230–400 mesh silica gel (Merck) was used. Columns were eluted with a positive air pressure. Chromatographic eluents are given as volume-to-volume ratios (v/v). NMR spectra were recorded with Bruker AMX_{500} (^{1}H, 500 MHz) and Bruker Avance DRX_{500} (^{1}H, 500 MHz) spectrometers. Chemical shifts are reported in ppm and coupling constants are reported in Hz. Routine ^{1}H and ^{13}C NMR spectra were referenced to the residual proton or carbon signals of the solvent, respectively. ^{19}F NMR spectra were referenced to $CFCl_3$ as the internal standard. High-resolution mass spectra were recorded with a Kratos MS-80RFA 241-MC spectrometer. Optical rotations were determined with a Perkin–Elmer 341 polarimeter.

(*S*)-(1,2:5,6-Di-*O*-Cyclohexylidene-α-D-glucofuranosyl) 2-Propanesulfinate (*S*-4): Diisopropylethylamine (DIPEA) (4.8 mL, 27.5 mmol) was added to a solution of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (DCG, **3**; 5 g, 15.27 mmol) in a mixture of toluene (210 mL) and dichloromethane (20 mL). The solution was stirred at –78 °C for 20 min before adding isopropylsulfinyl chloride (2.5 mL, 27.5 mmol).[2] After 1 h at –78 °C, the reaction mixture was hydrolysed with 10% aqueous HCl (100 mL), and the aqueous

phase was extracted with dichloromethane (3 × 60 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and then dried with Na_2SO_4. After removing the solvent under vacuum, sulfinate *S*-**4** was obtained (6.5 g, quantitative yield) as an oil in 96% *de*; $[\alpha]_D^{20}$ = –52 (*c* = 0.6, acetone). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.87 (d, *J* = 3.5 Hz, 1 H, 1-H), 4.70 (d, *J* = 2.5 Hz, 1 H, 3-H), 4.56 (d, *J* = 3.5 Hz, 1 H, 2-H), 4.29–4.22 (m, 2 H, 4-H and 5-H), 4.16–3.92 (m, 2 H, 6-H and 6′-H), 2.77 [m, *J* = 7.0 Hz, 1 H, SOC*H*$(CH_3)_2$], 1.72–1.25 (m, 20 H, Cy), 1.22 [d, *J* = 7.0 Hz, 6 H, SOCH(C*H*$_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.1, 109.7, 104.6, 84.2, 80.7, 79.9, 72.0, 66.5, 60.4, 55.6, 36.4, 35.7, 34.6, 25.2, 24.8, 24.0, 23.8, 23.7, 23.5, 13.9 ppm. HRMS: calcd. for $C_{21}H_{34}O_7S$ $[M]^+$ 430.2025; found 430.2016 (δ = 2.0 ppm).

(*R*)-(1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranosyl) 2-Propanesulfinate (*R*-4): Pyridine (3.3 mL, 27.5 mmol) was added to a solution of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (DCG, **3**; 5 g, 15.27 mmol) in THF (200 mL). The solution was stirred at –78 °C for 20 min before adding isopropylsulfinyl chloride (3.7 mL, 27.5 mmol). After 1 h at –78 °C, the reaction mixture was hydrolysed with 10% aqueous HCl (100 mL), and the aqueous phase was extracted with dichloromethane (3 × 60 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and then dried with Na_2SO_4. After removing the solvent under vacuum, sulfinate *R*-**4** was obtained (6.4 g, quantitative yield) as an oil in 80% *de*. The resulting mixture of diastereomers can be separated by silica gel column chromatography (AcOEt/hexane, 1:7); $[\alpha]_D^{20}$ = +15 (*c* = 0.8, acetone). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.87 (d, *J* = 3.5 Hz, 1 H, 1-H), 4.73 (d, *J* = 3.5 Hz, 1 H, 2-H), 4.69 (d, *J* = 1.3 Hz, 1 H, 3-H), 4.23–4.04 (m, 3 H, 4-H, 5-H, 6-H), 3.94–3.90 (m, 1 H, 6′-H) 2.79 [m, *J* = 7.0 Hz, 1 H, SOC*H*$(CH_3)_2$], 1.82–1.34 (m, 20 H, Cy), 1.24 [d, *J* = 7.0 Hz, 3 H, SOCH(C*H*$_3)_2$], 1.23 [d, *J* = 7.0 Hz, 3 H, SOCH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 113.0, 110.0, 105.0, 83.3, 83.1, 81.2, 71.7, 67.5, 56.0, 36.6, 36.4, 35.6, 34.8, 25.1, 24.8, 24.0, 23.9, 23.8, 23.5, 13.8, 13.7 ppm. HRMS: calcd. for $C_{21}H_{34}O_7S$ $[M]^+$ 430.2025; found 430.2020 (δ = 1.2 ppm).

(*R*)-*N*-[(*E*)-3-Methoxybenzylidene]-2-propanesulfinamide (*R*-6): 1 M LHMDS in THF (10.45 mL, 10.45 mmol, 1.5 equiv.) was added to a solution of sulfinate *R*-**4** (3 g, 6.97 mmol, 1 equiv.) in THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then transferred through a cannula to a second flask containing 3-methoxybenzaldehyde (1.7 mL, 13.94 mmol, 2 equiv.) and CsF (1.05 g, 6.97 mmol, 1 equiv.) in THF (15 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 × 35 mL), and the aqueous layer was extracted with AcOEt (4 × 35 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and finally dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (AcOEt/hexanes, 1:9), to give R_s-**6** (1.3 g, 83% yield) as a white solid; m.p. 50–51 °C; $[\alpha]_D^{20}$ = –74.8 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.55 (s, 1 H, N=C*H*Ar), 7.40–7.38 (m, 3 H, Ar), 7.06 (d, *J* = 7 Hz, 1 H, Ar), 3.86 (s, 3 H, OCH_3), 2.98 [m, *J* = 6.90 Hz, 1 H, C*H*$(CH_3)_2$], 1.32 [d, *J* = 6.95 Hz, 3 H, CH(C*H*$_3)_2$], 1.20 [d, *J* = 6.85 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.24, 154.80, 130.06, 124.8, 117.44, 113.87, 107.73, 50.22, 48.66, 9.64, 8.28 ppm. HRMS: calcd. for $C_{11}H_{15}NO_2S$ $[M]^+$ 225.0823; found 225.0823.

(*S*)-*N*-[(*E*)-3-Methoxybenzylidene]-2-propanesulfinamide (*S*-6): 1 M LHMDS in THF (17.6 mL, 17.64 mmol, 1.2 equiv.) was added to a solution of sulfinate *S*-**4** (6.7 g, 14.7 mmol, 1 equiv.) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and transferred through a cannula to a second flask containing 3-methoxybenzaldehyde (3.36 mL, 22.05 mmol, 1.5 equiv.) and CsF (2.7 g, 17.64 mmol, 1.2 equiv.) in THF (15 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 × 35 mL), and the aqueous layer was extracted with AcOEt (4 × 35 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and then dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (AcOEt/CH_2Cl_2, 1:30) to give *S*-**6** (2.68 g, 81% yield) as a white solid; m.p. 54 °C; $[\alpha]_D^{20}$ = +77 (*c* = 0.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.58 (s, 1 H, N=C*H*Ar), 7.49–7.43 (m, 3 H, Ar), 7.11–7.09 (m, 1 H, Ar), 3.89 (s, 3 H, OCH_3), 3.00 [m, *J* = 6.90 Hz, 1 H, C*H*$(CH_3)_2$], 1.35 [d, *J* = 6.95 Hz, 3 H, CH(C*H*$_3)_2$], 1.25 [d, *J* = 6.85 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.59 160.0, 135.3, 130.0, 122.6, 119.0, 113.0, 55.4, 53.9, 14.8, 13.50 ppm. HRMS: calcd. for $C_{11}H_{16}NO_2S$ $[M]^+$ 226.0901; found 226.0895.

(*S*)-*N*-[(*E*)-Benzylidene]-2-propanesulfinamide (*S*-7): 1 M LHMDS in THF (19 mL, 19 mmol, 1.5 equiv.) was added to a solution of sulfinate *S*-**4** (5.45 g, 12.6 mmol, 1 equiv.) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and transferred through a cannula to a second flask containing benzaldehyde (2 equiv.) and CsF (1 equiv.) in THF (19 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 × 35 mL), and the aqueous layer was extracted with AcOEt (4 × 35 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and finally dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (AcOEt/CH_2Cl_2, 1:30) to give *S*-**7** (1.84 g, 75% yield) as a white solid; m.p. 37–39 °C; $[\alpha]_D^{20}$ = +54 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.60 (s, 1 H, N=C*H*Ph), 7.83 (d, *J* = 7 Hz, 2 H, Ph), 7.50–7.43 (m, 3 H, Ph), 2.95 [m, *J* = 6.8 Hz, 1 H, C*H*$(CH_3)_2$], 1.33 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3)_2$], 1.25 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.6, 134.0, 132.5, 129.4, 128.9, 53.9, 14.8, 13.6 ppm. HRMS: calcd. for $C_{10}H_{13}NOS$ $[M]^+$ 196.0796; found 196.0797.

(*S*)-*N*-[(*E*)-Naphthalen-2-ylmethylene]-2-propanesulfinamide (*S*-8): 1 M LHMDS in THF (6.96 mL, 6.96 mmol, 1.5 equiv.) was added to a solution of sulfinate *S*-**4** (2 g, 4.64 mmol, 1 equiv.) in THF (8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and transferred through a cannula to a second flask containing 2-naphthaldehyde (1.26 mL, 9.30 mmol, 2 equiv.) and CsF (705 mg, 4.64 mmol, 1 equiv.) in THF (15 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 × 25 mL), and the aqueous layer was extracted with AcOEt (4 × 25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and with saturated aqueous NaCl and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (AcOEt/hexanes, 1:9), to give *S*-**8** (0.93 g, 82% yield) as a yellow oil; $[\alpha]_D^{20}$ = +22.5 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.16 (s, 1 H, N=C*H*Ar), 9.02 (d, *J* = 8.55 Hz, 1 H, Ar), 8.05–8.03 (m, 2 H, Ar), 7.92 (d, *J* = 8.10 Hz, 1 H, Ar), 7.64 (t, *J* = 7.05 Hz, 1 H, Ar), 7.57 (t, *J* = 7.55 Hz, 2 H, Ar), 3.05 [m, *J* = 6.85 Hz, 1 H, C*H*$(CH_3)_2$], 1.35 [d, *J* = 6.90 Hz, 3 H, CH(C*H*$_3)_2$], 1.29 [d, *J* = 6.85 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.31, 128.71, 128.15, 126.69, 126.04, 124.14, 123.67, 122.85, 121.34, 120.04, 119.15, 48.81, 9.57, 8.39 ppm. HRMS: calcd. for $C_{14}H_{15}NOS$ $[M]^+$ 245.0874; found 245.0881.

(*S*)-*N*-[(*E*)-Cyclohexylmethylene]-2-propanesulfinamide (*S*-9): 1 M LHMDS in THF (7.31 mL, 7.31 mmol, 1.5 equiv.) was added to a solution of sulfinate *S*-**4** (2.1 g, 4.87 mmol, 1 equiv.) in THF (8 mL) at 0 °C. The reaction mixture was stirred at –78 °C for 1 h and then transferred through a cannula to a second flask containing cyclohexanecarbaldehyde (1.18 mL, 9.74 mmol, 2 equiv.) and CsF (739 mg, 4.87 mmol, 1 equiv.) in THF (20 mL). After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 × 30 mL), and the aqueous layer was extracted with AcOEt (4 × 30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and with saturated aqueous NaCl and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (AcOEt/hexanes, 1:9) to give *S*-**9** (0.98 g, 75% yield) as a yellow oil; $[\alpha]_D^{20}$ = +48 (*c* = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.98 (d, *J* = 4.60 Hz, 1 H, N=C*H*Cy), 2.85 [m, *J* = 6.90 Hz, 1 H, C*H*$(CH_3)_2$], 2.51–2.44 (m, 1 H, Cy), 1.94–1.87 (m, 2 H, Cy), 1.84–1.77 (m, 2 H, Cy), 1.74–1.66 (m, 2 H, Cy), 1.39–1.34 (m, 4 H, Cy), 1.26 [d, *J* = 6.95 Hz, 3 H, CH(C*H*$_3)_2$] 1.17 [d, *J* = 6.85 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.47, 53.08, 43.96, 29.32, 25.87, 25.34, 14.54, 13.11 ppm. HRMS: calcd. for $C_{10}H_{20}NOS$ [M + H]$^+$ 202.1266; found 202.1260.

General Method for the Addition of the Trifluoromethyl Anion to *N*-Sulfinylimines: CF_3SiMe_3 (4.58 mmol, 4.5 equiv.) was added through a syringe to a suspension of the corresponding imine (1.01 mmol, 1 equiv.) and TBAT (1.11 mmol, 1.1 equiv.) in toluene (33 mL) under argon at –50 °C. After stirring overnight, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with AcOEt (3 × 20 mL). Finally, the organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue obtained was purified by flash chromatography (AcOEt/hexanes, 2:3) to give the corresponding trifluoromethyl-substituted amine.

(R_S,*S*)-*N*-[2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl]-2-propanesulfinamide [(R_S,*S*)-10]: The title compound was obtained starting from imine R_S-**6** and following the general procedure as a 96:4 mixture of diastereoisomers in 96% yield as a slightly yellow oil; $[\alpha]_D^{20}$ = –52.1 (*c* = 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.28 (t, *J* = 8 Hz, 1 H, Ar), 7.01–6.98 (m, 2 H, Ar), 6.91 (dd, *J* = 8 and 2 Hz, 1 H, Ar), 4.82 (q, *J* = 7 Hz, 1 H, C*H*CF_3), 4.53 (d, *J* = 6.5 Hz, 1 H, N*H*), 3.78 (s, 3 H, OCH_3), 2.77 [hept, *J* = 7 Hz, 1 H, C*H*$(CH_3)_2$], 1.24 [d, *J* = 7 Hz, 3 H, CH(C*H*$_3)_2$], 1.21 [d, *J* = 7 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.84, 135.13, 130.09, 124.63 (q, *J* = 280 Hz), 121.33, 114.67, 114.05, 60.13 (q, *J* = 31 Hz), 55.22, 54.91, 15.65, 15.08 ppm. ^{19}F NMR ($CDCl_3$, 400 MHz): δ = –74.70 ppm. HRMS: calcd. for $C_{12}H_{16}NO_2F_3S$ [M + H]$^+$ 296.0932; found 296.0928.

(S_S,*R*)-*N*-[2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl]-2-propanesulfinamide [(S_S,*R*)-10]: The title compound was obtained starting from imine *S*-**6** and following the general procedure as a unique diastereoisomer in 95.4% yield as a slightly yellow oil; $[\alpha]_D^{20}$ = +50.7 (*c* = 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.9 Hz, 1 H, Ar), 7.01–6.91 (m, 3 H, Ar), 4.83–4.80 (m, 1 H, C*H*CF_3), 4.00 (d, *J* = 5.8 Hz, 1 H, NH), 3.81 (s, 3 H, OCH_3), 2.77 [hept, *J* = 6.9 Hz, 1 H, C*H*$(CH_3)_2$], 1.26 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3)_2$], 1.25 [d, *J* = 6.7 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 135.0, 130.3, 126.7 (q, *J* = 281 Hz), 120.10, 114.9, 114.0, 60.3 (q, *J* = 31 Hz), 55.3, 55.1, 15.5, 14.9 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –74.57 ppm. HRMS: calcd. for $C_{12}H_{17}NO_2F_3S$ [M + H]$^+$ 296.0932; found 296.0937.

(S_S,*R*)-*N*-(2,2,2-Trifluoro-1-phenylethyl)-2-propanesulfinamide [(S_S,*R*)-11]: The title compound was obtained starting from imine **7*S*** and following the general procedure as a unique diastereoisomer in 86% yield; m.p. 80–83 °C; $[\alpha]_D^{20}$ = +24.2 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.45–7.43 (m, 5 H, Ar), 4.93–4.87 (m, 1 H, C*H*CF_3), 4.10 (d, *J* = 5.9 Hz, 1 H, N*H*), 2.88–2.78 [m, 1 H, C*H*$(CH_3)_2$], 1.31 [d, *J* = 6.95 Hz, 3 H, CH(C*H*$_3)_2$], 1.29 [d, *J* = 6.95 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 133.7, 129.6, 128.9, 128.0, 124.6 (q, *J* = 281.5 Hz), 60.34 (q, *J* = 30.8 Hz), 55.11, 15.49, 15.32 ppm. HRMS: calcd. for $C_{11}H_{15}NOF_3S$ [M + H]$^+$ 266.0826; found 266.0830.

(S_S,*R*)-*N*-[2,2,2-Trifluoro-1-(naphthalen-2-yl)ethyl]-2-propanesulfinamide [(S_S,*R*)-12]: The title compound was obtained starting from imine *S*-**8** and following the general procedure as a 85:15 mixture of diastereomers in 85% yield as a white solid; m.p. 112–114 °C; $[\alpha]_D^{20}$ = +131 (*c* = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (d, *J* = 8.5 Hz, 1 H, Ar), 7.93 (dd, *J* = 8 and 3.5 Hz, 2 H, Ar), 7.72 (d, *J* = 7.5 Hz, 1 H, Ar), 7.65 (td, *J* = 7 and 1 Hz, 1 H, Ar), 7.57 (t, *J* = 7 Hz, 1 H, Ar), 7.52 (t, *J* = 7.7 Hz, 1 H, Ar), 5.81 (q, *J* = 6 Hz, 1 H, C*H*CF_3), 4.32 (d, *J* = 5 Hz, 1 H, N*H*), 2.74 [sept, *J* = 7 Hz, 1 H, C*H*$(CH_3)_2$], 1.27 [d, *J* = 7 Hz, 3 H, CH(C*H*$_3)_2$], 1.24 [d, *J* = 7 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 133.94, 130.86, 130.37, 129.72, 129.17, 127.38, 126.32, 125.79, 125.10, 122.54, 55.06, 15.55, 14.98 ppm. ^{19}F NMR ($CDCl_3$, 400 MHz): δ = –73.43 ppm. HRMS: calcd. for $C_{15}H_{17}F_3NOS$ [M + H]$^+$ 316.0983; found 316.0976.

(S_S,*R*)-*N*-(1-Cyclohexyl-2,2,2-trifluoroethyl)-2-propanesulfinamide [(S_S,*R*)-13]: The title compound was obtained starting from imine *S*-**9** and following the general procedure as a 93:7 mixture of diastereomers in 72% yield as a white solid; m.p. 98–100 °C; $[\alpha]_D^{20}$ = +70.8 (*c* = 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.65 (d, *J* = 8.5 Hz, 1 H, NH), 3.55–3.51 (m, 1 H, C*H*CF_3), 2.84–2.79 [m, 1 H, C*H*$(CH_3)_2$], 1.86–1.82 (m, 5 H, Cy), 1.70–1.68 (m, 3 H, Cy), 1.46 (dq, *J* = 5 and 10 Hz, 1 H, Cy), 1.30 [d, *J* = 3.5 Hz, 3 H, CH(C*H*$_3)_2$], 1.29 [d, *J* = 3.5 Hz, 3 H, CH(C*H*$_3)_2$], 1.08 (dq, *J* = 12.4 and 3 Hz, 1 H, Cy) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 125.45 (q, *J* = 280 Hz), 63.31 (q, *J* = 28 Hz), 55.61, 37.74, 29.94, 27.34, 26.05, 25.86, 25.67, 21.12, 15.60, 14.85 ppm. ^{19}F NMR ($CDCl_3$, 400 MHz): δ = –73.10 ppm.

(*R*)-2,2,2-Trifluoro-1-phenylethylamine (*R*-14): 4 N HCl (0.7 mL, 2.71 mmol, 2 equiv.) was added to a solution of (S_S,*R*)-**11** (200 mg, 0.76 mmol, 1 equiv.) in MeOH (5 mL), under argon. After stirring for 1 h 30 min, the MeOH solvent was evaporated under reduced pressure to afford compound (*R*)-2,2,2-trifluoro-1-phenylethylamine hydrochloride (150 mg, 93.5%) as a white solid; m.p. 235–237 °C; $[\alpha]_D^{20}$ = –6.67 (*c* = 0.6, MeOH). ^1H NMR (CD_3OD, 500 MHz): δ = 7.63–7.55 (m, 5 H, Ar), 5.4 (q, *J* = 7.5 Hz, 1 H, C*H*CF_3), 4.87 (s, 3 H, N$H_3^+Cl^-$) ppm. ^{13}C NMR (CD_3OD, 125 MHz): δ = 134.6, 133.1, 132.2, 132.0, 127.4 (q, *J* = 280.3 Hz), 59.3 (q, *J* = 32.6 Hz) ppm. HRMS: calcd. for: $C_8H_9NF_3Cl$ [M + H]$^+$ 176.0687; found 176.0676.

Et_3N (0.19 mL, 1.34 mmol) was added to a suspension of this product (125 mg, 0.67 mmol) in diethyl ether (2 mL) under argon. After stirring overnight, the slurry was filtered and the liquid portion evaporated to afford *R*-**14** (85 mg, 72%) as a yellow oil; $[\alpha]_D^{20}$ = –17.44 (*c* = 3.4, EtOH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.43–7.38 (m, 5 H, Ar), 4.40 (q, *J* = 7.5 Hz, 1 H, C*H*CF_3), 1.80 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 135.4, 128.9, 128.6, 127.8, 125.7 (q, *J* = 275 Hz), 57.9 (q, *J* = 25 Hz) ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –73.48 ppm. HRMS: calcd. for: $C_8H_9NF_3$ [M – H]$^+$ 174.0530; found 174.0529.

(*R*)-2,2,2-Trifluoro-1-(3-methoxyphenyl)ethylamine (*R*-15): CF_3CO_2H (0.36 mL, 4.75 mmol) was added to a solution of sulfinamide (S_S,*R*)-**10** (124 mg, 0.42 mmol) in MeOH (5 mL) at 0 °C, and

the reaction mixture was stirred overnight. The solvent was removed under reduced pressure to give the corresponding ammonium trifluoroacetate. The residue was passed through a cation-exchange column (Isolute SPE SCX-2) to give the amine *R*-**15** (59 mg, 69%) as a yellow oil; $[\alpha]_D^{20}$ = –108 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 1 H, Ar), 7.05–7.02 (m, 2 H, Ar), 6.95–6.94 (m, 1 H, Ar), 4.35 (q, *J* = 7.4 Hz, 1 H, C*H*CF_3), 3.81 (s, 3 H, OCH_3), 1.78 (s, 2 H, NH_2) ppm. ^{13}C NMR (125 MHz): δ = 159.8, 137.0, 129.7, 125.7 (q, *J* = 280 Hz), 121.5, 114.3, 113.6, 57.9 (q, *J* = 29.5 Hz), 55.2 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –77.2 ppm. HRMS: calcd. for: $C_9H_{11}NOF_3$ $[M + H]^+$ 206.0802; found 206.0793.

(*S*)-2,2,2-Trifluoro-1-(3-methoxyphenyl)ethylamine (*S*-15): Starting from amine (R_S,*S*)-**10** and following the same experimental procedure as described above, the title compound was obtained in 64% yield with identical physical data to those of its enantiomer *R*-**15**; $[\alpha]_D^{20}$ = +95 (*c* = 0.6, $CHCl_3$).

(*R*)-3-(2-Chlorophenyl)-*N*-[2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl]-propanamide (*R*-19): A solution of amine *R*-**15** (15 mg, 0.073 mmol) and DIPEA (0.038 mL, 0.220 mmol) in DMF (1 mL) was added through a cannula to a stirred solution of 3-(2-chlorophenyl)propanoic acid (**18**; 13.43 mg, 0.073 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU; 23.44 mg, 0.073 mmol) in DMF (0.5 mL) at room temperature. After stirring for 10 min, DMF was removed in vacuo, CH_2Cl_2 (15 mL) was added and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (AcOEt/hexane, 1:5) gave the amide *R*-**19** (59.3 mg, 76%) as a white solid; m.p. 98–100 °C; $[\alpha]_D^{20}$ = –13.6 (*c* = 0.5, acetone). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H, Ar), 7.19–7.11 (m, 3 H, Ar), 6.94–6.88 (m, 3 H, Ar), 6.40 (d, *J* = 9.3 Hz, 1 H, N*H*), 5.74–5.66 (m, 1 H, C*H*CF_3), 3.80 (s, 3 H, OCH_3), 3.12–3.05 (m, 2 H, CH_2), 2.66–2.58 (m, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 159.9, 137.7, 134.2, 133.7, 130.7, 129.5, 127.9, 127.0, 124.4 (q, *J* = 281 Hz), 120.0, 114.5, 113.9, 55.3, 54.1 (q, *J* = 31 Hz), 36.0, 29.3 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –74.3 ppm. HRMS: calcd. for $C_{18}H_{18}NO_2F_3Cl$ $[M + H]^+$ 372.0978; found 372.0970. $C_{18}H_{17}NO_2F_3Cl$: C 58.15, H 4.61, N 3.77; found C 57.97, H, 5.05, N 3.63.

(*S*)-3-(2-Chlorophenyl)-*N*-[2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl]-propanamide (*S*-19): Starting from amine *S*-**15** and following the same experimental procedure as described above, the title compound was obtained in 87% yield; $[\alpha]_D^{20}$ = +13.3 (*c* = 0.6, $CDCl_3$).

(*R*)-*N*-[2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl]-3-(2-chlorophenyl)-1-propylamine (*R*-2): 1 M DIBALH in THF (0.53 mL, 0.53 mmol) was added to a stirred solution of amide *R*-**19** (50 mg, 0.133 mmol) in CH_2Cl_2 (2 mL) at room temperature. After stirring overnight, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The mixture was filtered through a Celite pad, adding CH_2Cl_2 (3 × 10 mL), and the filtrate was concentrated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/hexanes, 1:2) gave amine *R*-**2** (10 mg, 66%), as a pale-yellow oil; $[\alpha]_D^{20}$ = –27.37 (*c* = 0.94, acetone). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 3 H, Ar), 7.15–7.11 (m, 3 H, Ar), 6.98–6.89 (m, 3 H, Ar), 4.08 (q, *J* = 7.4 Hz, 1 H, C*H*CF_3), 3.82 (s, 3 H, OCH_3), 2.79–2.71 (m, 2 H, CH_2), 2.63 (t, *J* = 7.0 Hz, 2 H, CH_2), 1.86–1.79 (m, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8, 139.4, 133.9, 130.4, 129.7, 129.5, 125.4 (q, *J* = 28 Hz), 127.4, 126.8, 120.8, 114.3, 114.1, 64.6 (q, *J* = 28 Hz), 55.3, 47.1, 31.0, 29.8, 29.7 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –74.4 ppm. HRMS: calcd. for $C_{18}H_2ClF_3NO$ $[M + H]^+$ 358.1185; found 358.1184.

(*S*)-*N*-[2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl]-3-(2-chlorophenyl)-1-propylamine (*S*-2): Starting from amine *S*-**19** and following the same experimental procedure as described above, the title compound was obtained in 63% yield; $[\alpha]_D^{20}$ = +27.4 (*c* = 0.4, acetone).

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[1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) H.-J. Böhm, D. Banner, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637; c) P. Jeschke, *ChemBioChem* **2004**, *5*, 570; d) B. D. Roth, in: *Progress in Medicinal Chemistry*, vol. 40 (Eds.: F. D. King, A. W. Oxford), Elsevier, Amsterdam, **2002**; e) K. Drlica, M. Malik, *Curr. Top. Med. Chem.* **2003**, *3*, 249; f) D. T. Wong, F. P. Baymaster, E. A. Engleman, *Life Sci.* **1995**, *57*, 411.
[2] a) J. P. Begué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992; b) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303; c) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013.
[3] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.
[4] a) I. Ojima, K. Kato, F. A. Jameison, J. Conway, K. Nakahashi, M. Hagiawara, T. Miyamae, H. E. Radunz, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 219; b) D. Schirlin, C. Tarnus, S. Baltzer, J. M. Rémy, *Bioorg. Chem. Lett.* **1992**, *2*, 651.
[5] a) W. H. Pirkle, K. A. Simmons, *J. Org. Chem.* **1981**, *46*, 3239; b) Y. Wang, H. S. Mosher, *Tetrahedron Lett.* **1991**, *32*, 987; c) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119; d) J. Gawronski, N. Wascinska, J. Gajewy, *Chem. Rev.* **2008**, *108*, 5227.
[6] a) T. Billard, B. R. Langlois, *Eur. J. Org. Chem.* **2007**, 891; b) N. Shibata, S. Mizuta, H. Kawai, *Tetrahedron: Asymmetry* **2008**, *19*, 2633.
[7] G. K. S. Prakash, M. Mandal, G. A. Olah, *Angew. Chem. Int. Ed.* **2001**, *40*, 589.
[8] J. A. Ellman, T.-D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 985.
[9] a) G. K. S. Prakash, M. Mandal, G. A. Olah, *Org. Lett.* **2001**, *3*, 2847; b) G. K. S. Prakash, M. Mandal, *J. Am. Chem. Soc.* **2002**, *124*, 6538.
[10] F. A. Davis, *J. Org. Chem.* **2006**, *71*, 8993.
[11] G. K. S. Prakash, M. Mandal, G. A. Olah, *Synlett* **2001**, 77.
[12] Y. Kawano, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 894.
[13] a) G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913; b) D. Morton, R. Stockman, *Tetrahedron* **2006**, *62*, 8869.
[14] a) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; b) N. Khiar, B. Suárez, B. V. Valdivia, I. Fernández, *Synlett* **2005**, 2963; c) N. Khiar, R. Navas, B. Suárez, E. Álvarez, I. Fernández, *Org. Lett.* **2008**, *10*, 3697.
[15] a) I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Alvarez, N. Khiar, *Org. Lett.* **2005**, *7*, 1307; b) I. Fernández, V. Valdivia, M. Pernía, N. Khiar, *Org. Lett.* **2007**, *9*, 2215; c) I. Fernández, V. Valdivia, N. Khiar, *J. Org. Chem.* **2008**, *73*, 745.
[16] a) N. Nagano, *Pharmacol. Ther.* **2006**, *109*, 339; b) S. J. Stedon, J. Cunningham, *Lancet* **2005**, *365*, 2237; c) E. F. Nemeth, *Curr. Pharm. Des.* **2002**, *8*, 2077; d) M. E. Steffey, J. Fox, B. C. Van Wagenen, E. G. Delmar, M. F. Balandrin, E. F. Nemeth, *J. Bone Miner. Res.* **1993**, *8*, S175; e) S. J. Silverberg, H. G.

Bone, T. B. Marriott, F. G. Locker, S. Thys-Jacobs, G. Dziem, E. L. Kaatz, E. L. Sanguinetti, J. P. Bilezikian, *New Engl. J. Med.* **1997**, *337*, 1506.
[17] E. F. Nemeth, M. E. Steffey, L. G. Hammerland, B. C. P. Hung, B. C. Van Wagenen, E. G. DelMar, M. Balandrin, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 440.
[18] a) I. Fernández, N. Khiar, J. M. Llera, F. Alcudia, *J. Org. Chem.* **1992**, *57*, 6789; b) N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1994**, *35*, 5719; c) N. Khiar, C. S. Araujo, F. Alcudia, I. Fernández, *J. Org. Chem.* **2002**, *67*, 345; d) N. Khiar, F. Alcudia, J. L. Espartero, L. Rodríguez, I. Fernández, *J. Am. Chem. Soc.* **2000**, *122*, 7598.
[19] A. S. Pilcher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166.
[20] F. Gosselin, A. Roy, P. D. O'Shea, C.-Y. Chen, R. P. Volante, *Org. Lett.* **2004**, *6*, 641.

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