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# Diastereoselective Synthesis of 2-Phenyl-3-(trifluoromethyl)piperazines as Building Blocks for Drug Discovery

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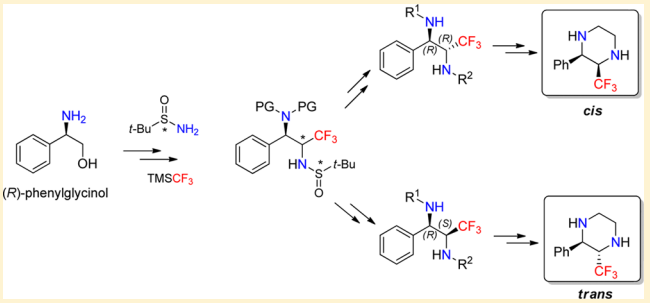
Supporting Information

**ABSTRACT:** The synthesis of enantiomerically pure *cis*- and *trans*-2-phenyl-3-(trifluoromethyl)piperazines is described. It involved, as the key step, a diastereoselective nucleophilic addition of the Ruppert–Prakash reagent ($TMSCF_3$) to α-amino sulfinylimines bearing Ellman's auxiliary. This methodology allows an entry into hitherto unknown trifluoromethylated and stereochemically defined piperazines, key scaffold components in medicinal chemistry.




The piperazine ring is present in a great variety of molecules involved in the regulation of many biological processes, therefore being classified as a privileged structural element for the construction of drug-like molecules.[1] Substituted piperazines are frequently embedded in the molecular architecture of therapeutically valuable compounds,[2] including antifungals, antidepressants, antivirals and antibiotics, among others.[3] Some examples of marketed drugs that contain the piperazine motif are shown in Figure 1.

Piperazines are small alicyclic platforms that allow for the differential derivatization of their opposing nitrogens in a well-defined linear fashion. Additionally, the nitrogen atoms, whose basicity can be modulated to a certain extent depending on the nature of the attached substituents, can establish important hydrogen bond interactions with the target protein, and often play a role in increasing the water solubility of lipophilic compounds.

Although most pharmaceutically relevant compounds bearing the piperazine scaffold only have substituents on the nitrogen atoms, carbon-substituted piperazines have also been reported and evaluated for their pharmacological properties.[4] Several synthetic strategies have been employed for the preparation of *C*-substituted piperazines, namely, reductive cyclocondensations,[5] alkylation and reduction of 2-methylpyrazines,[6] reduction of the corresponding (di)ketopiperazines,[7] α-lithiation and alkylation of *N*-*t*-butyloxycarbonyl (Boc) protected piperazines,[8] and several intramolecular metal-mediated ring closure strategies.[9]

The incorporation of fluorinated groups into the carbon skeleton of piperazines has not been extensively explored to date.[10] It is well-known that selective introduction of fluorine atoms into organic molecules has become a powerful strategy to modulate their biological properties.[11] Specifically, the replacement of one or more hydrogen atoms by fluorine in

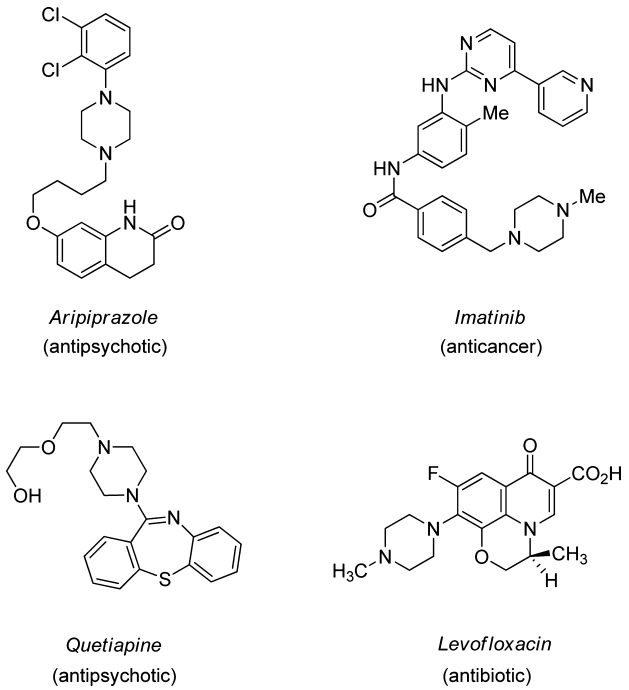



**Figure 1.** Marketed drugs containing the piperazine motif.

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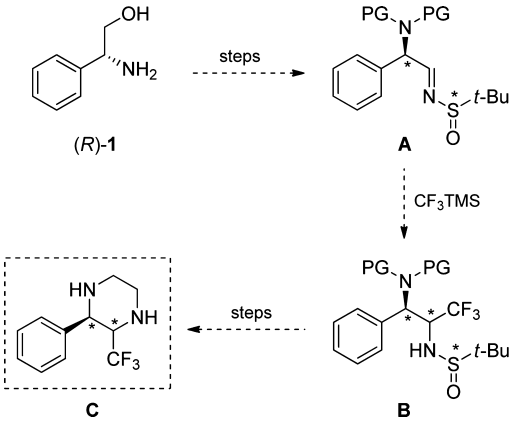
the vicinity of an amine function often results in a lower basicity, a higher metabolic stability and a decrease in acute toxicity.[12] In the past decades, $CF_3$ containing compounds have attracted considerable synthetic interest[13] mainly due to the effect that this particular fluorinated group can have on the physicochemical and pharmacokinetic/pharmacodynamic properties of organic molecules. For this reason, its introduction into potential drug candidates is a commonly employed approach in drug discovery programs.

Given the importance of piperazines in medicinal chemistry, 3-trifluoromethyl-2-arylpiperazines (**C**) could constitute attractive building blocks for drug discovery.[14] This novel molecular template presents a pair of lipophilic functional groups (Ph and $CF_3$) in a well-defined spatial organization (*cis* or *trans*) enabling unprecedented hydrophobic interactions with biological targets. Despite the relatively simple approach, and to the best of our knowledge, the synthesis of **C** has not yet been described, triggering concerns about the chemical and configurational stability of this type of diamines. Instead of commencing the synthesis from a commercially available fluorinated building block, a potentially stereoselective strategy that could use simple $\alpha$-amino acid derivatives as starting materials was envisaged (Scheme 1). The nucleophilic addition of the Ruppert–Prakash reagent ($TMSCF_3$)[15] to preformed $\alpha$-amino imines (**A**) represents a straightforward route to obtain trifluoromethylated vicinal diamines (**B**).[16] Ellman's *N*-(*tert*-butanesulfinyl)imines have been successfully employed in this context.[17] Having access to an orthogonally protected diamine building block (**B**) was deemed essential.

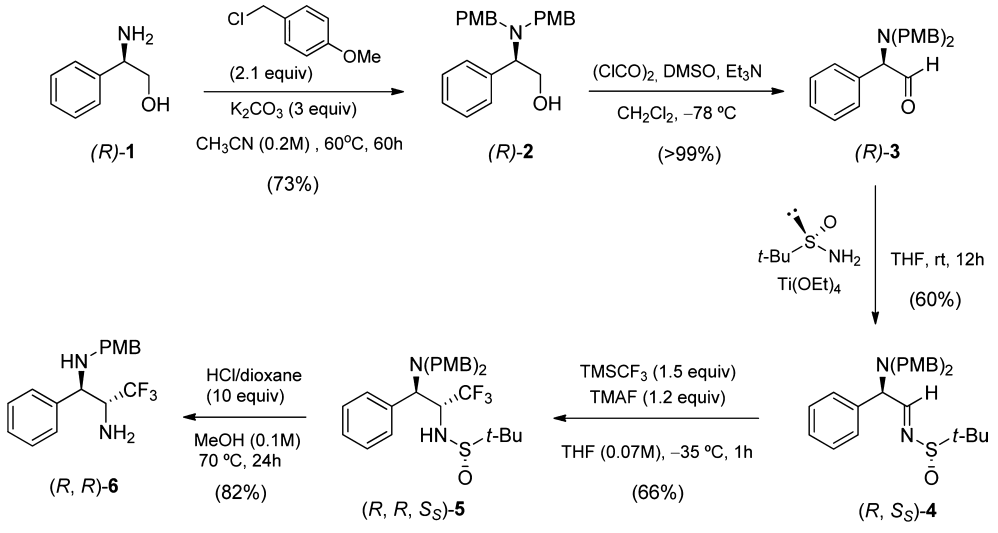
**Scheme 1. Synthetic Strategy for the Synthesis of Fluorinated Piperazines**




As shown in Scheme 2, our synthesis began with the protection of (*R*)-phenylglycinol as the corresponding bis-*p*-methoxybenzyl (PMB) derivative (*R*)-**2** in good yield (73%). Swern oxidation followed by condensation of the resulting $\alpha$-amino aldehyde with (*S*)-(−)-2-methyl-2-propanesulfinamide, in the presence of titanium(IV) ethoxide as dehydrating agent, yielded *tert*-butylsulfinimine ($R,S_S$)-**4** in enantiomerically pure form (60% yield). With compound ($R,S_S$)-**4** in hand, we tested different conditions in order to carry out the key diastereoselective nucleophilic trifluoromethylation.[18] After a careful optimization, it was found that the best conditions involved the dropwise addition of $TMSCF_3$ to a solution of the Ellman's imine and finely ground tetramethylammonium fluoride (TMAF), as activator of the Ruppert–Prakash reagent, at −35 °C. Following this protocol, the protected diamine ($R,R,S_S$)-**5** was obtained in 66% yield as a single diastereoisomer. According to previous reports,[17a] imine **4** exists in the (*E*) configuration, and the diastereoselectivity observed is due to the *si* face attack prompted by both chiral centers present in the molecule. Then, the *tert*-butanesulfinyl group was removed upon exposure to hydrochloric acid in refluxing methanol in a sealed tube, yielding the monoprotected diamine ($R,R$)-**6**.[19] The use of a closed reaction vessel proved essential for the partial unmasking of the benzylic amine, a prerequisite for the subsequent enclosure of both nitrogens into a piperazine ring.

We then decided to explore the formation of the required 6-membered heterocycles. Thus, treatment of ($R,R$)-**6** with 1,2-dibromoethane led to the formation of complex mixture of products. In order to have a more predictable reactivity profile, 2-chloroacetyl chloride was chosen as electrophile. This strategy divides the overall heterocycle formation process in two trivial chemical reactions: (a) an amide bond formation reaction; followed by (b) a 6-*exo* trig cyclization of the resulting chloroderivative ($R,R$)-**7**. As expected, the initial amide coupling took place exclusively via the primary amine in

**Scheme 2. Synthesis of Enantiomerically Pure Monoprotected Diamine ($R,R$)-6**





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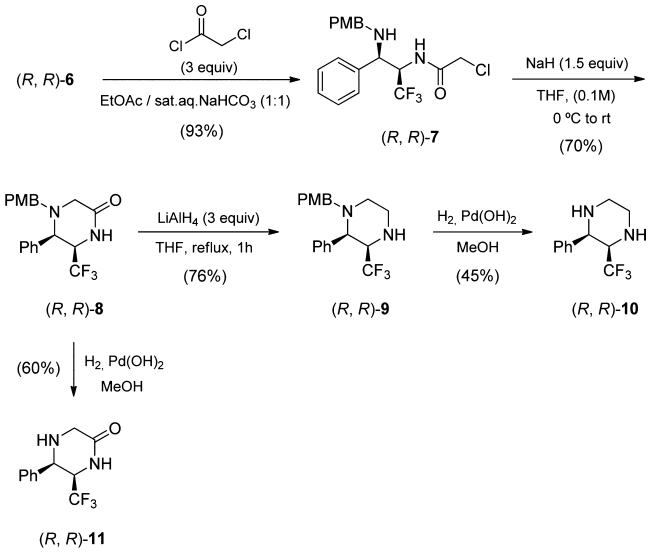
compound **6**, despite the strong electron withdrawing effect of the contiguous trifluoromethyl group. α-Chloroamide (*R*,*R*)-**7** was isolated in excellent yield (93%) after flash column chromatography. The cyclization to the oxopiperazine (*R*,*R*)-**8** proceeded in good yield (70%) upon treatment of (*R*,*R*)-**7** with sodium hydride (Scheme 3). Reduction of the keto group with

**Scheme 3. Synthesis of *cis*-2-Phenyl-3-(trifluoromethyl)piperazine Derivatives**



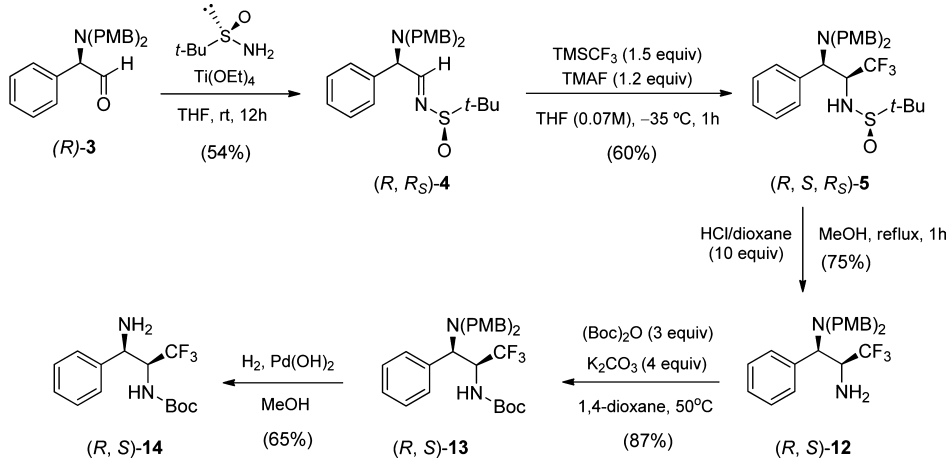

lithium aluminum hydride afforded the *N*-PMB protected piperazine (*R*,*R*)-**9** in 76% yield. After several unsuccessful attempts to remove the remaining PMB group under oxidative conditions (DDQ, CAN), this was finally achieved by hydrogenolysis in the presence of catalytic amounts of $Pd(OH)_2$. These optimized conditions could be also applied to piperazinone (*R*,*R*)-**8**, obtaining the attractive fluorinated building block (*R*,*R*)-**11** in enantiopure form.

Access to the *trans* diastereoisomers was secured by a modified synthetic route that again started from (*R*)-phenylglycinol but used the opposite enantiomer of Ellman's auxiliary (Scheme 4). On the basis of synthetic precedence, it was anticipated that the chiral auxiliary would neglect any potential influence of the aminoalcohol chirality on the stereochemical outcome of the 1,2-addition reaction. Thus, condensation of aldehyde (*R*)-**3** with commercially available (*R*)-*N*-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ yielded sulfinylimine ($R,R_S$)-**4** (54% yield). Subsequent nucleophilic addition with the Ruppert−Prakash reagent gave the corresponding protected vicinal diamine in moderate yield (60%) and complete diastereocontrol. The stereochemical outcome indicates that the chiral auxiliary is able to overturn any intrinsic substrate selectivity. Unfortunately, attempts to deprotect ($R,S,R_S$)-**5** under the conditions used for the *cis* diastereoisomer (HCl in MeOH, 70 °C in a sealed tube) led to an unseparable mixture of mono- and bis-PMB diamino derivatives. Selective removal of the chiral auxiliary in compound ($R,S,R_S$)-**5** could be achieved in 75% yield after treatment with hydrochloric acid in refluxing methanol for 1 h. Boc-protection of the free amine followed by hydrogenolysis with Pearlman's catalyst afforded amino carbamate (*R*,*S*)-**14** in 57% yield (two steps). Monoprotected diamine (*R*,*S*)-**14** constitutes an interesting fluorinated scaffold for further derivatization.

Following our cyclization strategy for the *cis* diastereoisomeric series, compound (*R*,*S*)-**14** underwent smooth *N*-acylation to give the corresponding chloroacetamide (*R*,*S*)-**15** in quantitative yield. Attempts to cleave the Boc protecting group at this stage ($TFA/CH_2Cl_2$, rt, 20 h) resulted in the epimerization of the trifluoromethylated carbinamine as detected by $^{19}F$ NMR. This undesired event could be avoided when the ring closing alkylation was carried out with *N*-Boc derivative (*R*,*S*)-**15**. Upon addition of NaH and tetrabutylammonium iodide (TBAI) to a diluted solution of (*R*,*S*)-**15** in a mixture of THF and DMF, the corresponding Boc-protected piperazinone was obtained in high yield (90%) as a single diastereoisomer. TFA-mediated deprotection of (*R*,*S*)-**16** could be carried out at this stage avoiding the undesired acid-catalyzed epimerization observed in the acyclic derivative. In this manner, ketopiperazine (*R*,*S*)-**17** was obtained in very good yield (90%) (Scheme 5).

In order to complete the synthesis of the *trans* piperazine (*R*,*S*)-**20**, the amide group in (*R*,*S*)-**16** was efficiently converted into the corresponding thioamide (*R*,*S*)-**18** in 72% yield. Subsequent reduction with Ni-Raney under hydrogen atmosphere allowed the isolation of the Boc-protected piperazine (*R*,*S*)-**19** in acceptable yield (69%). For the cleavage of the Boc

**Scheme 4. Synthesis of Enantiomerically Pure Boc-Protected Diamine (*R*,*S*)-14**





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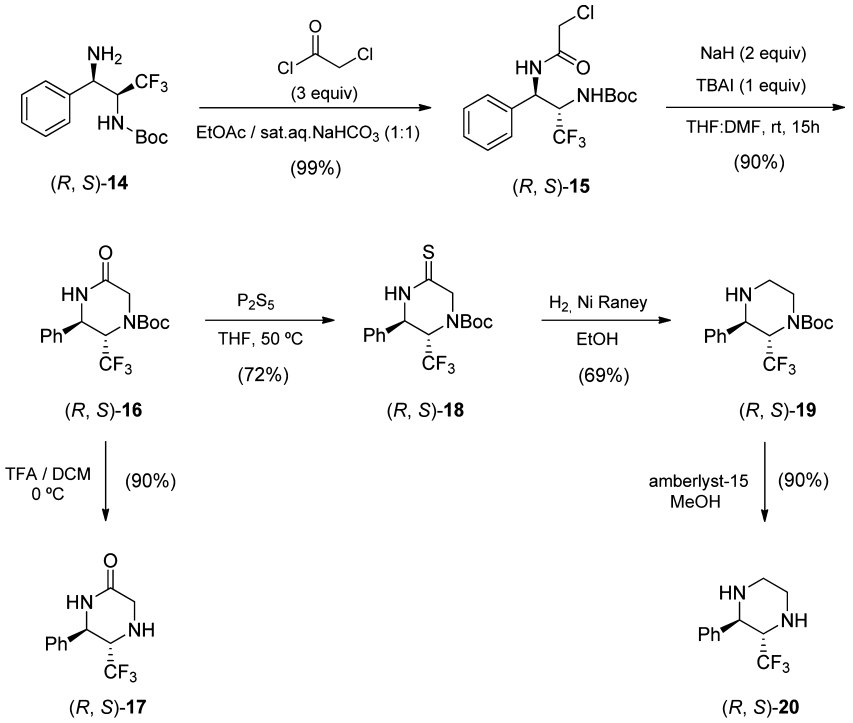
**Scheme 5. Synthesis of *trans*-2-Phenyl-3-(trifluoromethyl)piperazine Derivatives**




group, it was found that best results (90% yield) were obtained with solid phase supported reagent amberlyst-15 (Scheme 5).

The relative stereochemistry for the compounds of each series (*cis* and *trans*) was proven by analyzing the corresponding vicinal proton−proton coupling constants on the chair conformations of compounds (*R*,*R*)-**10** and (*R*,*S*)-**20**. According to the Karpluss equation, value for $^3J_{HH}$ in the *cis*-disubstituted piperazine (*R*,*R*)-**10** was 4.0 Hz, while in the *trans*-substituted counterpart (*R*,*S*)-**20** $^3J_{HH}$ was found to be 9.0 Hz. These values are consistent with the axial−equatorial and the axial−axial relationship between vicinal protons $H_a$ and $H_b$, respectively (Figure 2). The same stereochemistry was assumed for previous compounds within each series.

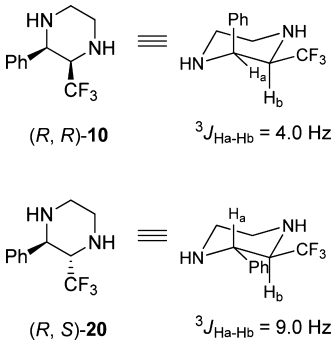



**Figure 2.** Relative stereochemistry for the *cis*- and *trans*-diastereoisomers.

Summarizing, we have developed practical synthetic strategies to the *cis* and *trans* diastereoisomers of 3-trifluoromethyl-2-arylpiperazines derivatives starting from enantiomerically pure phenylglycinol. The introduction of the $CF_3$ relies on the nucleophilic 1,2-addition of $TMSCF_3$ to *t*-butanesulfinyl imines. While this study focused exclusively on the preparation of piperazines, the intermediate 1-trifluoromethyl-2-phenyldiamines could serve as valid synthetic intermediates for other interesting scaffolds. The presence of the $CF_3$ at the piperazine core should have a noticeable effect on its metabolic stability, basicity and lipophilicity.

## EXPERIMENTAL SECTION

**General Methods.** All reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere. The following solvents were purified prior to use: THF was distilled from sodium/benzophenone, $CH_2Cl_2$ was distilled from calcium hydride. All other solvents and reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and phosphomolybdic acid solution or potassium permanganate stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). $^1H$ and $^{13}C$ NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm ($\delta$), referenced to the residual proton resonances of the solvents. Coupling constants ($J$) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad. Melting points were determined in open capillary tubes with a temperature gradient of 10 °C/min. They were read from a digital display and are uncorrected. High resolution mass spectra were recorded on a QToF mass spectrometer configured with an electrospray ionization source, maintained at 140 °C, using nitrogen as the nebulizer gas, argon as collision gas and Lockmass device for mass calibration using Leucine-Enkephaline as standard substance. Spectra were acquired either in positive or in negative ionization mode, by scanning from 50 to 1200 Da in 0.1 s. In positive mode the capillary needle voltage was either 0.5 or 2.0 kV. In negative mode the capillary needle voltage was 2.0 kV. Cone voltage was 25 V in both ionization modes.

*Synthesis of (R)-2-[Bis(4-methoxybenzyl)amino]-2-phenylethanol (**2**).* A mixture of (*R*)-phenylglycinol (**1**, 3 g, 21.87 mmol), 4-methoxybenzyl chloride (6.2 mL, 45.93 mmol) and potassium carbonate (9 g, 65.61 mmol) in acetonitrile (109 mL) was stirred at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60 °C for 60 h. The resulting yellow suspension was filtered to separate solids, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel employing a mixture of hexane/EtOAc (5:1) as eluent. Compound (*R*)-**2** was obtained as a thick colorless oil (6.03 g, 73% yield): $[\alpha]^{25}_{D}$ −119.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.34 (d, *J* = 11.1 Hz, 2H), 3.77 (dd, *J* = 8.8, 4.3 Hz, 1H), 3.94 (s, 6H), 3.99 (d, *J* = 11.1 Hz, 2H), 4.06 (dd, *J* = 8.8, 4.2 Hz, 1H), 4.22 (t, *J* = 8.8 Hz, 1H), 6.50−6.54 (m, 4H), 6.81−6.84 (m, 6H), 6.92−6.97 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 52.6 ($CH_2$), 55.2 ($CH_3$), 60.3 ($CH_2$), 62.6 (CH), 113.9 (CH), 127.9 (CH), 128.3 (CH), 129.2 (CH), 130.0 (CH), 131.1 (C), 135.2 (C), 158.8 (C); HRMS (EI) calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$ 378.2069, found 378.2066.

**General Procedure for the Synthesis of Sulfinylimines 4.** To a stirred solution of oxalyl chloride (0.86 mL, 9.86 mmol) in dry $CH_2Cl_2$ (17 mL) at −78 °C under $N_2$ atmosphere, dimethyl sulfoxide (1.47 mL, 20.67 mmol) was added. After 15 min, a solution of (*R*)-**2** (3 g, 7.95 mmol) in $CH_2Cl_2$ (17 mL) was added dropwise. After 30 min, $NEt_3$ (3 mL, 21.47 mmol) was added, and the resulting mixture was stirred at −78 °C for 40 min, when the cooling bath was removed and, 10 min later, TLC revealed the total disappearance of the starting material. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous phase extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to yield compound (*R*)-**3** as a thick colorless oil (quantitative yield), which was used without further purification in the next step.

α-Amino aldehyde (*R*)-**3** (2.99 g, 7.95 mmol) and (*S*)- or (*R*)-2-methyl-2-propanesulfinamide (964 mg, 7.95 mmol) were dissolved in dry THF (40 mL) into a flame-dried flask under $N_2$ atmosphere. The reaction flask was cooled to 0 °C, and a solution of titanium tetraethoxide (7.25 g, 31.80 mmol) in THF (20 mL) was slowly added from an addition funnel. The reaction mixture was allowed to stir overnight, and then it was carefully poured into an ice-cooled solution of brine. The resulting suspension was filtered through a pad of Celite, rinsing it with EtOAc. The filtrate was taken to a separating funnel, and the aqueous layer was extracted with EtOAc (3 × 20 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to yield imine **4**.

*(S,E)-N-{(R)-2-[Bis(4-methoxybenzyl)amino]-2-phenylethylidene}-2-methylpropane-2-sulfinamide [(R,S$_S$)-**4**].* The title compound was obtained according to the general procedure described above starting from aldehyde (*R*)-**3** and (*S*)-(−)-2-methyl-2-propanesulfinamide. Purification by flash chromatography (silica gel; hexane/EtOAc, gradient from 4:1 to 2:1) gave 2.28 g of imine (*R*,*S*$_S$)-**4** (60% yield) as a yellow oil: $[\alpha]^{25}_{D}$ +121.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (s, 9H), 3.47 (d, *J* = 13.8 Hz, 2H), 3.69 (d, *J* = 14.4 Hz, 2H), 3.72 (s, 6H), 4.64 (d, *J* = 5.9 Hz, 1H), 6.81−6.85 (m, 4H), 7.23−7.26 (m, 5H), 7.32−7.36 (m, 4H), 8.21 (d, *J* = 5.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.2 ($CH_3$), 53.2 ($CH_2$), 54.9 ($CH_3$), 57.1 (C), 68.1 (CH), 113.5 (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 129.9 (CH), 130.3 (C), 137.1 (C), 158.6 (C), 169.3 (CH); HRMS (EI) calcd for $C_{28}H_{35}N_2O_3S$ $[M + H]^+$ 479.2363, found 479.2368.

*(R,E)-N-{(R)-2-[Bis(4-methoxybenzyl)amino]-2-phenylethylidene}-2-methylpropane-2-sulfinamide [(R,R$_S$)-**4**].* The title compound was obtained according to the general procedure described above starting from aldehyde (*R*)-**3** and (*R*)-(+)-2-methyl-2-propanesulfinamide. Purification by flash chromatography (silica gel; hexane/EtOAc, 5:1) gave 2.05 g of imine (*R*,*R*$_S$)-**4** (54% yield) as a yellow oil: $[\alpha]^{25}_{D}$ −81.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.18 (s, 9H), 4.11 (d, *J* = 11.4 Hz, 2H), 4.21 (d, *J* = 11.4 Hz, 2H), 4.26 (s, 6H), 5.08 (d, *J* = 4.5 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 4H), 7.16−7.24 (m, 5H), 7.26−7.27 (m, 4H), 8.11 (d, *J* = 4.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.6 ($CH_3$), 52.8 ($CH_2$), 55.1 ($CH_3$), 56.7 (C), 66.3 (CH), 113.6 (CH), 127.8 (CH), 128.5 (CH), 128.95 (CH), 129.8 (CH), 130.6 (C), 136.8 (C), 158.6 (C), 169.3 (CH); HRMS (EI) calcd for $C_{28}H_{35}N_2O_3S$ $[M + H]^+$ 479.2363, found 479.2354.

**General Procedure for the Synthesis of Protected Diamines 5.** The corresponding *N*-sulfinyl imine **4** (500 mg, 1.04 mmol) was dissolved in dry THF (8 mL) into a flame-dried flask. To this solution tetramethylammonium fluoride (116 mg, 1.25 mmol) was added, and the mixture was cooled to −35 °C. A solution of Ruppert−Prakash reagent, $TMSCF_3$, (0.23 mL, 1.56 mmol) in THF (7 mL) was then added dropwise from an addition funnel, and the mixture was stirred at that temperature until TLC revealed the disappearance of the starting material (1 h). At that moment, the cooling bath was removed, and the reaction mixture was quenched with saturated aqueous $NH_4Cl$, extracted with ethyl acetate (3 × 15 mL), dried ($Na_2SO_4$), filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to afford diamine **5**.

*(S)-N-{(2R,3R)-3-[Bis(4-methoxybenzyl)amino]-1,1,1-trifluoro-3-phenylpropan-2-yl)-2-methylpropane-2-sulfinamide [(R,R,S$_S$)-**5**].* The title compound was obtained according to the general procedure described above starting from imine (*R*,*S*$_S$)-**4**. Purification by flash chromatography (silica gel; hexane/EtOAc, 4:1) gave 377 mg of (*R*,*R*,*S*)-**5** (66% yield) as a white solid: mp 108−109 °C; $[\alpha]^{25}_{D}$ −37.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.97 (s, 9H), 3.00−3.04 (m, 3H), 3.80 (s, 6H), 3.94 (d, *J* = 13.5 Hz, 2H), 4.15 (d, *J* = 8.8 Hz, 1H), 4.49−4.56 (m, 1H), 6.85−6.90 (m, 4H), 7.26−7.326 (m, 6H), 7.41−7.50 (m, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −71.05 (d, $J_{HF}$ = 6.7 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.9 ($CH_3$), 53.5 ($CH_2$), 55.2 ($CH_3$), 55.6 (q, $^2J_{CF}$ = 27.1 Hz, CH), 56.3 (C), 62.6 (CH), 113.7 (CH), 125.33 (q, $^1J_{CF}$ = 282.1 Hz, $CF_3$), 128.5 (CH), 128.8 (CH), 130.00 (CH), 130.4 (C), 130.5 (C), 130.8 (CH), 158.7 (C); HRMS (EI) calcd for $C_{29}H_{36}F_3N_2O_3S$ $[M + H]^+$ 549.2393, found 549.2415.

*(R)-N-{(2S,3R)-3-[Bis(4-methoxybenzyl)amino]-1,1,1-trifluoro-3-phenylpropan-2-yl)-2-methylpropane-2-sulfinamide [(R,S,R$_S$)-**5**].* The title compound was obtained according to the general procedure described above starting from imine (*R*,*R*$_S$)-**4**. Purification by flash chromatography (silica gel; hexane/EtOAc, 4:1) gave 342 mg of (*R*,*S*,*R*$_S$)-**5** (60% yield) as a white solid: mp 152−153 °C; $[\alpha]^{25}_{D}$ −86.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.32 (s, 9H), 2.89 (d, *J* = 12.9 Hz, 2H), 3.80 (s, 6H), 3.80−3.83 (m, 2H), 3.90 (d, *J* = 10.8 Hz, 1H), 4.45−4.54 (m, 1H), 5.27 (s, 1H), 6.84−6.89 (m, 4H), 7.26−7.32 (m, 6H), 7.41−7.49 (m, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −71.09 (d, $J_{HF}$ = 5.9 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.5 ($CH_3$), 51.0 ($CH_2$), 55.01 (q, $^2J_{CF}$ = 26.6 Hz, CH), 55.2 ($CH_3$), 56.4 (C), 59.7 (CH), 113.8 (CH), 125.1 (q, $^1J_{CF}$ = 282.2 Hz, $CF_3$), 128.2 (CH), 128.3 (CH), 130.0 (CH), 130.1 (C), 130.8 (CH), 131.9 (C), 158.9 (C); HRMS (EI) calcd for $C_{29}H_{36}F_3N_2O_3S$ $[M + H]^+$ 549.2399, found 549.2397.

*Synthesis of (1R,2R)-3,3,3-Trifluoro N-(4-methoxybenzyl)-1-phenylpropane-1,2-diamine (**6**).* HCl (4 M solution in dioxane; 1.4 mL, 5.5 mmol) was dropwise added to a solution of diamine (*R*,*R*,*S*)-**5** (300 mg, 0.55 mmol) in MeOH (5.5 mL), and the mixture was stirred at 70 °C in a sealed tube overnight. Then, solvents were removed under reduced pressure, and the residue was quenched with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 15 mL). Organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated in a vacuum. Crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, gradient from 4:1 to 2:1) to yield compound (*R*,*R*)-**6** as a light yellow oil (146 mg, 82% yield): $[\alpha]^{25}_{D}$ −33.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.64 (br s, 2H), 3.47 (d, *J* = 12.9 Hz, 1H), 3.53−3.62 (m, 1H), 3.62 (d, *J* = 12.9 Hz, 1H), 3.80 (s, 3H), 4.00 (d, *J* = 4.6 Hz, 1H), 6.83−6.88 (m, 2H), 7.15−7.20 (m, 2H), 7.32−7.41 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −73.49 (d, $J_{HF}$ = 7.6 Hz, 3F); $^{13}$C NMR (75 MHz, CDCl3) $\delta$ 50.3 ($CH_2$), 55.2 ($CH_3$), 57.9 (q, $^2J_{CF}$ = 27.0 Hz, CH), 60.6 (q, $^3J_{CF}$ = 1.5 Hz, CH), 113.78 (CH), 125.97 (q, $^1J_{CF}$ = 282.4 Hz, $CF_3$), 127.96 (CH), 128.34 (CH), 128.47 (CH), 129.31 (CH), 131.9 (C), 137.9 (C), 158.7 (C); HRMS (EI) calcd for $C_{17}H_{20}F_3N_2O$ $[M + H]^+$ 325.1522, found 325.1524.

*Synthesis of 2-Chloro-N-[(2R,3R)-1,1,1-trifluoro-3-[(4-methoxybenzyl)amino]-3-phenylpropan-2-yl]acetamide (**7**).* To a suspension of PMB-protected diamine (*R*,*R*)-**6** (400 mg, 1.23 mmol) in a mixture of EtOAc and saturated aqueous $NaHCO_3$ (1:1, 24 mL) at 0 °C, 2-chloroacetyl chloride was added (0.3 mL, 3.69 mmol), and the mixture was stirred for 1.5 h, when TLC revealed the


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disappearance of the starting material. Layers were separated, and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$) and filtered. After evaporation of solvents, the crude product was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to yield compound (*R*,*R*)-**7** as a white solid (458 mg, 93% yield): mp 84−85 °C; $[\alpha]^{25}_D$ −63.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.98 (br s, 1H), 3.53 (d, *J* = 12.9 Hz, 1H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.81 (s, 3H), 4.06 (dd, *J* = 7.2, 15.3 Hz, 2H), 4.10 (d, *J* = 4.5 Hz, 1H), 4.87−4.97 (m, 1H), 6.83−6.86 (m, 2H), 7.08 (d, *J* = 9.8 Hz, 1H), 7.17−7.20 (m, 2H), 7.31−7.441 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −70.00 (d, $J_{HF}$ = 7.8 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 42.4 ($CH_2$), 50.4 ($CH_2$), 54.03 (q, $^2J_{CF}$ = 28.4 Hz, CH), 55.24 ($CH_3$), 60.0 (CH), 113.87 (CH), 124.4 (d, $^1J_{CF}$ = 283.0 Hz, $CF_3$), 127.7 (CH), 128.5 (CH), 128.8 (CH), 129.5 (CH), 131.1 (C), 136.6 (C), 158.9 (C), 166.0 (C); HRMS (EI) calcd for $C_{19}H_{21}ClF_3N_2O_2$ [M + H]$^+$ 401.1238, found 401.1250.

*Synthesis of (5R,6R)-4-(4-Methoxybenzyl)-5-phenyl-6-(trifluoromethyl)piperazin-2-one (**8**).* To a solution of (*R*,*R*)-**7** (300 mg, 0.75 mmol) in dry THF, NaH (60% in mineral oil; 45 mg, 1.13 mmol) was added portionwise at 0 °C. The resulting suspension was stirred overnight and then, the reaction mixture was quenched with saturated aqueous $NH_4Cl$. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated in a vacuum. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, gradient from 5:1 to 2:1) to yield 191 mg of keto piperazine (*R*,*R*)-**8** as a white solid (70% yield): mp 91−92 °C; $[\alpha]^{25}_D$ −34.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.29 (d, *J* = 13.4 Hz, 1H), 3.33 (dd, *J* = 4.0, 17.8 Hz, 2H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.81 (s, 3H), 4.16 (d, *J* = 4.6 Hz, 1H), 4.46−4.55 (m, 1H), 6.85−6.90 (m, 2H), 6.96 (br s, 1H), 7.16−7.21 (m, 2H), 7.25−7.28 (m, 2H), 7.35−7.38 (m, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −71.40 (d, $J_{HF}$ = 7.4 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 52.5 ($CH_2$), 55.3 ($CH_3$), 57.2 ($CH_2$), 58.3 (q, $^2J_{CF}$ = 29.7 Hz, CH), 59.2 (CH), 114.02 (CH), 123.31 (d, $^1J_{CF}$ = 281.9 Hz, $CF_3$), 128.3 (CH), 128.6 (CH), 128.7 (C), 129.8 (CH), 130.0 (CH), 131.4 (C), 159.1 (C), 170.0 (C); HRMS (EI) calcd for $C_{19}H_{19}F_3N_2O_2Na$ [M + Na]$^+$ 387.1291, found 387.1291.

*Synthesis of (2R,3R)-1-(4-Methoxybenzyl)-2-phenyl-3-(trifluoromethyl)piperazine (**9**).* $LiAlH_4$ (63 mg, 1.65 mmol) was added portionwise to a solution of keto piperazine **8** (200 mg, 0.55 mmol) in dry THF (5.5 mL) at 0 °C. The resulting suspension was heated at reflux for 1 h, when TLC revealed the disappearance of the starting material. The reaction mixture was quenched at 0 °C with $Na_2SO_4{\cdot}10H_2O$, stirring until aluminum salts turned white (1 h approx.). Then, it was filtered through a pad of Celite and washed with $CH_2Cl_2$. The filtrate was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica; hexane/EtOAc, 5:1) to give PMB-protected piperazine (*R*,*R*)-**9** as a colorless oil (147 mg, 76% yield): $[\alpha]^{25}_D$ −8.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.21 (dt, *J* = 9.6, 3.3 Hz, 1H), 3.61−3.75 (m, 2H), 3.90−3.99 (m, 3H), 4.31−4.38 (m, 1H), 4.38 (s, 3H), 4.47 (d, *J* = 3.2 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.31−7.34 (m, 3H), 7.49−7.51 (m, 2H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −69.58 (s, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.8 ($CH_2$), 46.9 ($CH_2$), 55.2 ($CH_3$), 58.4 ($CH_2$), 61.6 (d, $^2J_{CF}$ = 26.9 Hz, CH), 61.9 (CH, 113.66 (CH), 125.2 (d, $^1J_{CF}$ = 282.6 Hz, $CF_3$), 127.7 (2CH), 129.7 (CH), 130.5 (C), 130.7 (CH), 135.9 (C), 158.7 (C); HRMS (EI) calcd for $C_{19}H_{22}F_3N_2O$ [M + H]$^+$ 351.1679, found 351.1685.

*Synthesis of (2R,3R)-2-Phenyl-3-(trifluoromethyl)piperazine (**10**).* To a solution of piperazine (*R*,*R*)-**9** (70 mg, 0.20 mmol) in MeOH (2 mL), $Pd(OH)_2$ on carbon (20% in Pd; 140 mg, 0.20 mmol) was added portionwise. A balloon filled with hydrogen was then connected, and the resulting black suspension was stirred overnight. The reaction mixture was filtered through a pad of Celite, rinsing it with EtOAc, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica; hexane/EtOAc, gradient from 1:1 to 1:2) yielded unprotected piperazine (*R*,*R*)-**10** as a colorless oil (21 mg, 45% yield): $[\alpha]^{25}_D$ −45.7 (*c* 0.4, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.02 (br s, 2H), 2.81−2.86 (m, 1H), 3.00−3.16 (m, 2H), 3.20−3.27 (m, 1H), 3.54 (qd, *J* = 9.3, 4.0 Hz, 1H), 4.36 (dq, *J* = 4.0, 2.0 Hz, 1H), 7.26−7.43 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −64.15 (d, $J_{HF}$ = 8.4 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 41.6 ($CH_2$), 45.9 ($CH_2$), 58.7 (q, $^2J_{CF}$ = 24.2 Hz, CH), 59.5 (CH), 122.3 (q, $^1J_{CF}$ = 288.7 Hz, $CF_3$), 126.9 (q, $^5J_{CF}$ = 0.9 Hz, CH), 127.5 (CH), 128.2 (CH), 139.4 (C); HRMS (EI) calcd for $C_{11}H_{14}F_3N_2$ [M + H]$^+$ 231.1109, found 231.1117.

*Synthesis of (5R,6R)-5-Phenyl-6-(trifluoromethyl)piperazin-2-one (**11**).* $Pd(OH)_2$ on carbon (20% in Pd; 190 mg, 0.27 mmol) was added portionwise to a solution of (*R*,*R*)-**8** (100 mg, 0.27 mmol) in MeOH (3 mL). A balloon filled with hydrogen was then connected, and the resulting black suspension was stirred overnight. The reaction mixture was filtered through a pad of Celite, rinsing it with EtOAc, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica; hexane/EtOAc, gradient from 1:1 to 1:2) yielded unprotected keto piperazine (*R*,*R*)-**11** as a white solid (40 mg, 60% yield): mp 95−97 °C; $[\alpha]^{25}_D$ −154.4 (*c* 1.0, MeOH); $^1$H NMR (300 MHz, MeOD) $\delta$ 3.54−3.68 (m, 2H), 4.20 (qd, *J* = 7.6, 4.3 Hz, 1H), 4.52−4.54 (m, 1H), 7.23−7.39 (m, 5H). $^{19}$F NMR (282 MHz, MeOD) $\delta$ −70.63 (dd, $J_{HF}$ = 7.6, 2.2 Hz, 3F); $^{13}$C NMR (75 MHz, MeOD) $\delta$ 48.5 ($CH_2$), 55.7 (CH), 56.4 (q, $^2J_{CF}$ = 26.5 Hz, CH), 124.6 (q, $^1J_{CF}$ = 284.3 Hz, $CF_3$), 126.4 (CH), 127.5 (CH), 127.9 (CH), 136.8 (C), 171.2 (C); HRMS (EI) calcd for $C_{11}H_{12}F_3N_2O$ [M + H]$^+$ 245.0896, found 245.0900.

*Synthesis of (1R,2S)-3,3,3-Trifluoro-N,N-bis(4-methoxybenzyl)-1-phenylpropane-1,2-diamine (**12**).* HCl (4 M solution in dioxane; 3.7 mL, 14.6 mmol) was dropwise added to a solution of diamine (*R*,*S*,*R*$_S$)-**5** (800 mg, 1.46 mmol) in MeOH (15 mL), and the mixture was heated at reflux for 1 h. Then, solvents were removed under reduced pressure, and the residue was quenched with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 15 mL). Organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated in vacuo. Crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, gradient from 8:1 to 5:1) to yield 486 mg of compound (*R*,*S*)-**12** as a white solid (75% yield): mp 51−52 °C; $[\alpha]^{25}_D$ −74.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.15 (br s, 2H), 3.01 (d, *J* = 13.4 Hz, 2H), 3.78−3.84 (m, 1H), 3.81 (s, 6H), 3.85 (d, *J* = 13.8 Hz, 2H), 4.00−4.11 (m, 1H), 6.88−6.93 (m, 4H), 7.20−7.28 (m, 6H), 7.38−7.44 (m, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −73.03 (d, $J_{HF}$ = 6.1 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 52.8 ($CH_2$), 53.5 (q, $^2J_{CF}$ = 26.6 Hz, CH), 55.2 ($CH_3$), 61.5 (CH), 114.0 (CH), 126.07 (q, $^1J_{CF}$ = 280.2 Hz, $CF_3$), 127.9 (CH), 127.9 (CH), 129.7 (CH), 129.9 (CH), 130.6 (C), 133.2 (C), 158.8 (C); HRMS (EI) calcd for $C_{25}H_{28}F_3N_2O_2$ [M + H]$^+$ 445.2103, found 445.2103.

*Synthesis of tert-Butyl {[(2S,3R)-3-bis(4-methoxybenzyl)amino]-1,1,1-trifluoro-3-phenylpropan-2-yl}carbamate (**13**).* A solution of di-*tert*-butyl dicarbonate (661 mg, 3.03 mmol) in 1,4-dioxane (4 mL) was added to a solution of (*R*,*S*)-**12** (450 mg, 1.01 mmol) and $K_2CO_3$ (558 mg, 4.04 mmol) in 1,4-dioxane (4 mL). The resulting colorless solution was stirred at 50 °C in a sealed tube for 15 h. After cooling, the reaction mixture was quenched with sat. aq. $NH_4Cl$, and the aqueous layer extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated at reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to afford 479 mg of (*R*,*S*)-**13** as a white solid (87% yield): mp 70−72 °C; $[\alpha]^{25}_D$ +12.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.49 (s, 9H), 2.91 (d, *J* = 13.3 Hz, 2H), 3.70 (d, *J* = 13.3 Hz, 2H), 3.81 (s, 6H), 3.91 (d, *J* = 11.8 Hz, 1H), 4.86 (br s, 1H), 5.24 (br s, 1H), 6.87−6.90 (m, 4H), 7.23−7.27 (m, 6H), 7.39−7.45 (m, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −72.65 (s, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.2 ($CH_3$), 52.5 ($CH_2$), 52.8 (q, $^2J_{CF}$ = 26.0 Hz, CH), 55.0 ($CH_3$), 59.2 (CH), 80.6 (C), 113.9 (CH), 125.2 (q, $^1J_{CF}$ = 282.9 Hz, $CF_3$), 128.1 (CH), 128.1 (CH), 129.4 (CH), 129.8 (CH), 130.5 (C), 132.9 (C), 155.6 (C), 158.8 (C); HRMS (EI) calcd for $C_{30}H_{36}F_3N_2O_4$ [M + H]$^+$ 545.2627, found 545.2642.

*Synthesis of tert-Butyl [(2S,3R)-3-amino-1,1,1-trifluoro-3-phenylpropan-2-yl]carbamate (**14**).* $Pd(OH)_2$ on carbon (20% in Pd; 583 mg, 0.83 mmol) was added portionwise to a solution of (*R*,*S*)-**13** (450


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mg, 0.83 mmol) in MeOH (8 mL). A balloon filled with hydrogen was then connected, and the resulting black suspension was stirred overnight. The reaction mixture was filtered through a pad of Celite, rinsing it with EtOAc, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica; hexane/EtOAc, 4:1) yielded Boc-protected diamine (*R*,*S*)-**14** as a white solid (164 mg, 65% yield): mp 69−70 °C; $[\alpha]^{25}_{D}$ −13.5 (*c* 1.0, $CHCl_3$); This compound was obtained as a mixture of rotamers; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.19 (s, 2H), 1.35 (s, 7H), 1.53 (s, 2H), 4.17−4.28 (m, 1H), 4.58 (s, 1H), 5.89 (d, *J* = 8.8 Hz, 1H), 7.28−7.38 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −73.91 (d, $J_{HF}$ = 8.5 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.2 ($CH_3$), 52.5 (CH), 56.5 (q, $^2J_{CF}$ = 28.8 Hz, CH), 80.2 (C), 125.3 (q, $^1J_{CF}$ = 283.5 Hz, $CF_3$), 126.3 (CH), 128.1 (CH), 128.7 (CH), 141.0 (C), 155.3 (C); HRMS (EI) calcd for $C_{10}H_{12}F_3N_2O_2$ [M + H (− *t*-Bu)]$^+$ 249.0851, found 249.0861.

*Synthesis of (2S,3R)-tert-Butyl 5-oxo-3-phenyl 2-(trifluoromethyl)piperazine-1-carboxylate (**16**).* To a suspension of (*R*,*S*)-**14** (100 mg, 0.33 mmol) in a mixture of EtOAc and saturated aqueous $NaHCO_3$ (1:1, 6 mL) at 0 °C, 2-chloroacetyl chloride was added (0.08 mL, 0.99 mmol), and the mixture was stirred for 1.5 h, when TLC revealed the disappearance of the starting material. Layers were separated, and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to yield compound (*R*,*S*)-**15** as a white solid (quantitative yield), which was used without further purification in the next step.

Crude chloroacetamide (*R*,*S*)-**15** (126 mg, 0.33 mmol) was dissolved in a 10:1 mixture of THF/DMF (0.2M) unser $N_2$ atmosphere. To this solution NaH (60% in mineral oil; 26 mg, 0.66 mmol) and TBAI (122 mg, 0.33 mmol) were successively added, and the resulting yellow suspension was stirred at room temperature overnight. Then, $H_2O$ was added, and the aqueous layer was extracted with EtOAc, dried ($Na_2SO_4$), filtered and concentrated at reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc, gradient from 4:1 to 2:1) to give (*R*,*S*)-**16** as a white solid (102 mg, 90% yield): mp 141−142 °C; $[\alpha]^{25}_{D}$ +38.9 (*c* 1.0, $CHCl_3$); This compound was obtained as a mixture of rotamers; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, 5H), 1.36 (s, 4H), 3.84 (d, *J* = 28.2, 0.5H), 3.92 (d, *J* = 27.9, 0.5H), 4.47 (d, *J* = 18.9 Hz, 0.5H), 4.65 (d, *J* = 19.2 Hz, 0.5H), 4.73 (dd, *J* = 17.4, 9.3 Hz, 0.5H), 4.92 (d, *J* = 4.65 Hz, 1H), 4.97 (dd, *J* = 17.1, 8.7 Hz, 0.5H), 7.20−7.22 (m, 2H), 7.33−7.42 (m, 3H), 7.48 (br s, 1H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −72.15 (t, *J* = 8.0 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.7 ($CH_3$), 27.9 ($CH_3$), 44.4 ($CH_2$), 45.5 ($CH_2$), 53.2 (CH), 53.4 (CH), 54.4 (q, $^2J_{CF}$ = 31.2 Hz, CH), 56.6 (q, $^2J_{CF}$ = 30.7 Hz, CH), 82.1 (C), 82.4 (C), 124.2 (q, $^1J_{CF}$ = 283.8 Hz, $CF_3$), 124.30 (q, $^1J_{CF}$ = 284.2 Hz, $CF_3$), 125.7 (CH), 125.6 (CH), 128.7 (CH), 128.7 (CH), 129.1 (CH), 129.1 (CH), 138.6 (C), 138.9 (C), 152.9 (C), 153.5 (C), 167.0 (C), 167.3 (C); HRMS (EI) calcd for $C_{16}H_{18}F_3N_2O_3$ [M − H]$^-$ 343.1269, found 343.1269.

*Synthesis of (5S,6R)-6-Phenyl-5-(trifluoromethyl)piperazin-2-one (**17**).* TFA (1 mL) was added to a stirred solution of (*R*,*S*)-**16** (75 mg, 0.22 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C, and the mixture was stirred for 2 h at that temperature, when TLC revealed the disappearance of the starting material. Then, it was quenched with sat. aq. $Na_2CO_3$, and the aqueous layer was extracted with $CH_2Cl_2$. The organic phase was then dried ($Na_2SO_4$), filtered and concentrated at reduced pressure to yield 48 mg of (*R*,*S*)-**17** as a colorless oil (90% yield): $[\alpha]^{25}_{D}$ −12.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.08 (br s, 1H), 3.39−3.49 (m, 1H), 3.61 (q, *J* = 18.4 Hz, 2H), 4.73 (dd, *J* = 4.7, 2.0 Hz, 1H), 6.92 (s, 1H), 7.29−7.41 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −72.39 (d, $J_{HF}$ = 7.9 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 46.2 ($CH_2$), 55.5 (CH), 58.9 (q, $^2J_{CF}$ = 28.0 Hz, CH), 125.0 (q, $^1J_{CF}$ = 284.6 Hz, $CF_3$), 126.7 (CH), 128.8 (CH), 128.9 (CH), 139.1 (C), 168.9 (C); HRMS (EI) calcd for $C_{11}H_{12}F_3N_2O$ [M + H]$^+$ 245.0902, found 245.0904.

*Synthesis of (2S,3R)-tert-Butyl-3-phenyl-5-thioxo-2-(trifluoromethyl)piperazine-1-carboxylate (**18**).* $P_2S_5$ (51 mg, 0.23 mmol) was added to a solution of (*R*,*S*)-**16** (100 mg, 0.29 mmol) in THF (3 mL) under $N_2$ atmosphere, and the resulting yellow suspension was heated at 50 °C for 30 min, when TLC revealed the disappearance of the starting material. The reaction mixture was filtered and solvents were removed in a vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc, 4:1) to give (*R*,*S*)-**18** as a light yellow solid (75 mg, 72% yield): mp 137−138 °C; $[\alpha]^{25}_{D}$ −14.5 (*c* 1.0, $CHCl_3$); This compound was obtained as a mixture of rotamers; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.16 (s, 4H), 1.39 (s, 5H), 4.24 (d, *J* = 20.6 Hz, 0.5H), 4.35 (d, *J* = 20.4 Hz, 0.5H), 4.78 (dd, *J* = 15.8, 7.7 Hz, 0.5H), 4.90−5.09 (m, 2H), 5.21 (d, *J* = 20.8 Hz, 0.5H), 7.17−7.19 (m, 2H), 7.37−7.39 (m, 3H), 8.81 (s, 0.5H), 8.91 (s, 0.5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −72.46 (d, $J_{HF}$ = 8.1 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.7 ($CH_3$), 28.0 ($CH_3$), 50.1 ($CH_2$), 51.4 ($CH_2$), 53.8 (q, $^2J_{CF}$ = 31.6 Hz, CH), 55.4 (CH), 55.5 (CH), 82.3 (C), 82.8 (C), 125.8 (CH), 125.9 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 136.9 (C), 137.4 (C), 152.3 (C), 153.2 (C), 196.0 (C), 196.6 (C); HRMS (EI) calcd for $C_{16}H_{18}F_3N_2O_2S$ [M − H]$^-$ 359.1041, found 359.1041.

*Synthesis of (2S,3R)-tert-Butyl-3-phenyl-2-(trifluoromethyl)-piperazine-1-carboxylate (**19**).* To a solution of thioamide (*R*,*S*)-**18** (75 mg, 0.21 mmol) in EtOH (2 mL) Raney Ni was added, and the mixture was stirred under $H_2$ atmosphere (balloon) at room temperature for 30 min. The reaction mixture was filtered through a pad of Celite, rinsing it with EtOAc, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica; hexane/EtOAc, 4:1) yielded Boc-protected piperazine (*R*,*S*)-**19** as a colorless oil (48 mg, 69% yield): $[\alpha]^{25}_{D}$ +74.8 (*c* 1.0, $CHCl_3$); This compound was obtained as a mixture of rotamers; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.50 (s, 9H), 1.98 (s, 1H), 2.73 (br s, 2H), 3.10 (br s, 1H), 3.87−4.00 (m, 1H), 4.37 (s, 1H), 5.02 (br s, 0.5H), 5.22 (br s, 0.5H), 7.29−7.45 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −70.18 (s, 1.5F), −70.38 (s, 1.5F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.2 ($CH_3$), 30.9 ($CH_3$), 38.4 ($CH_2$), 39.6 ($CH_2$), 41.1 ($CH_2$), 51.9 (CH), 53.2 (q, *J* = 26.4 Hz, CH), 81.3 (C), 125.9 (q, $^1J_{CF}$ = 287.0 Hz, $CF_3$), 127.4 (CH), 127.5 (CH), 128.6 (CH), 139.8 (C), 154.4 (C), 155.0 (C); HRMS (EI) calcd for $C_{12}H_{14}F_3N_2O_2$ [M + H (− *t*-Bu)]$^+$ 275.1007, found 275.1009.

*Synthesis of (2S,3R)-2-Phenyl-3-(trifluoromethyl)piperazine (**20**).* Amberlyst-15 (310 mg, 4.1 mmol/g, 1.27 mmol) was added to a solution of Boc-protected piperazine (*R*,*S*)-**19** (42 mg, 0.13 mmol) in MeOH (2 mL) in a solid phase reactor. The resulting mixture was shaken at room temperature for 18 h. The resin was then filtered and washed with MeOH. Then 7 N $NH_3$ in MeOH (5 mL) was added to the solid phase reactor, and the resulting mixture was shaken at room temperature for 5 h. The resin was filtered and washed with 7 N $NH_3$ in MeOH. The combined organic extracts were concentrated in a vacuum yielding piperazine (*R*,*S*)-**20** as a colorless oil (26 mg, 90% yield): $[\alpha]^{25}_{D}$ −64.9 (*c* 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.18 (s, 2H), 2.04−3.14 (m, 4H), 3.41 (dq, *J* = 9.0, 6.8 Hz, 1H), 3.77 (d, *J* = 9.0 Hz, 1H), 7.30−7.42 (m, 5H). $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −72.18 (d, $J_{HF}$ = 6.9 Hz, 3F); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 45.2 ($CH_2$), 46.3 ($CH_2$), 61.7 (q, $^3J_{CF}$ = 1.3 Hz, CH), 62.6 (q, $^2J_{CF}$ = 25.4 Hz, CH), 124.7 (d, $^1J_{CF}$ = 281.1 Hz, $CF_3$), 128.1 (CH), 128.3 (CH), 128.4 (CH), 139.6 (C); HRMS (EI) calcd for $C_{11}H_{14}F_3N_2$ [M + H]$^+$ 231.1109, found 231.1109.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1$H, $^{13}$C, and $^{19}$F NMR spectra for all new compounds are provided. 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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