Synthesis of Enantiomerically Pure (*R*,*R*)- and (*S*,*S*)-1,2-Bis(pentafluorophenyl)ethane-1,2-diamine and Evaluation of the pK_a Value by Ab Initio Calculations

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1,2-Bis(pentafluorophenyl)ethane-1,2-diamine (**1**) was synthesized by the imino pinacol coupling of 4-methoxy-*N*-(pentafluorobenzylidene)benzylamine using a Zn–Cu couple and *p*-TsOH·H_2O. The optical resolution of (±)-**1** by means of chiral HPLC gave enantiomerically pure (*R*,*R*)- and (*S*,*S*)-**1**. The pK_a value of **1** was estimated by a titration experiment and ab initio calculations, showing that **1** has a basicity comparable to aniline derivatives.

Introduction of a pentafluorophenyl (C_6F_5) group to functional compounds is now an attractive method to modulate the potential,[1] because the C_6F_5 group has the increased electron-withdrawing property and the interesting ability of stacking with an electron-rich aromatic ring.[2] Moreover, the C_6F_5–heteroatom (O, N, halogen) interaction is also under active discussion,[3] and we have recently explored a C_6F_5–oxygen interaction by X-ray analysis.[1d] In these respects, we have reported the preparation and structural properties of (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-bis(pentafluorophenyl)ethanol (**A**),[1a] (1*R*,2*S*)-2-amino-1-(pentafluorophenyl)-2-phenylethanol (**B**),[1d] and (1*R*,2*R*)- and (1*S*,2*S*)-bis(pentafluorophenyl)ethane-1,2-diol (**C**)[1c] in optically pure forms (Fig. 1). We focus here on the synthesis of (*S*,*S*)- and (*R*,*R*)-1,2-bis(pentafluorophenyl)-ethane-1,2-diamine [(*S*,*S*)-**1** and (*R*,*R*)-**1**] as the fluorinated analogs of 1,2-diphenylethane-1,2-diamine [(*S*,*S*)-**2** and (*R*,*R*)-**2**], which are widely used as excellent ligands for asymmetric catalysts.[4] The pK_a value of the diamine **1** is the important index for its practical application to asymmetric synthesis as a chiral ligand, and, therefore, it was evaluated both by a titration experiment in H_2O–EtOH and by using ab initio calculations.

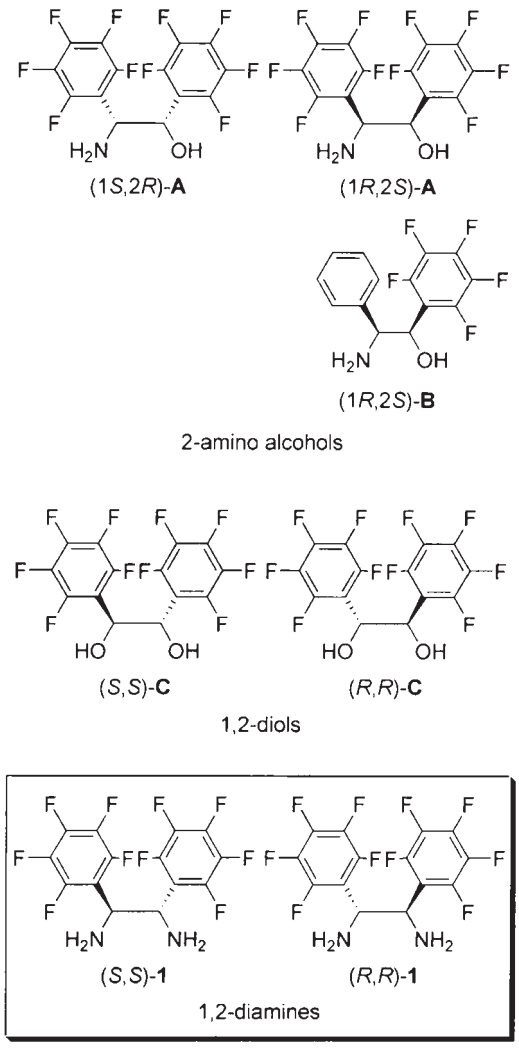

Fig. 1.

Results and Discussion

We planned that the compound (±)-**1** could be synthesized via the imino pinacol coupling of 4-methoxy-*N*-(pentafluorobenzylidene)aniline (**3a**)[5a] or 4-methoxy-*N*-(pentafluorobenzylidene)benzylamine (**3b**) according to the method for the non-fluorinated analog **2**[6] because Fujisawa and Shimizu had reported the enantioselective imino pinacol coupling of *N*-benzylidene-*p*-anisidine in the presence of a Zn–Cu couple and (+)-camphorsulfonic acid (CSA) leading to (*R*,*R*)-*N*,*N*-di-*p*-anisyl-1,2-diphenylethylenediamine with 97% ee as a mixture of *dl*:*meso* (81:19) isomers in 63% yield. Alterations in the reactivity and selectivity of the imines **3** by the influence of the C_6F_5 group would give us a useful measure for designing the reaction of a compound having a C_6F_5 group, and the novel coupling products may have attractive features. Many other cat-

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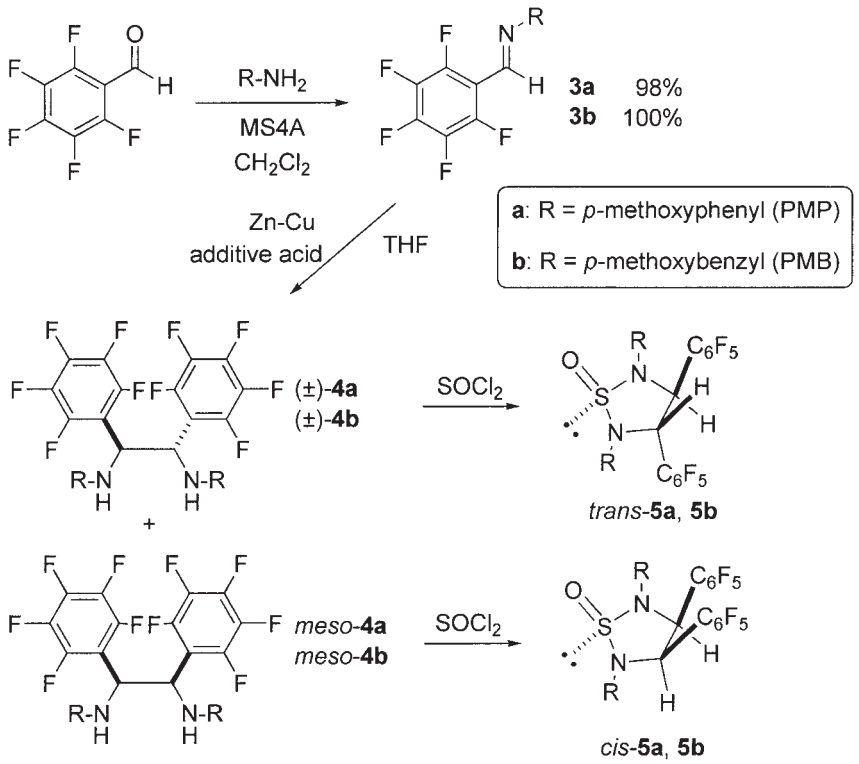


Scheme 1.

Table 1. Iminopinacol Coupling of Imine **3a**

Entry	Solvent	Acid	Time/h	*Racemic*:*Meso*[a]	**4a**/%[b]
1	DMF	(+)-CSA	30	—	complex mixture
2	CH_2Cl_2	(+)-CSA	6	44:56	trace
3	Et_2O	(+)-CSA	6	—	no reaction
4	THF	(+)-CSA	6	46:54	57

a) Determined by ^{19}F NMR analysis. b) Isolated yield.

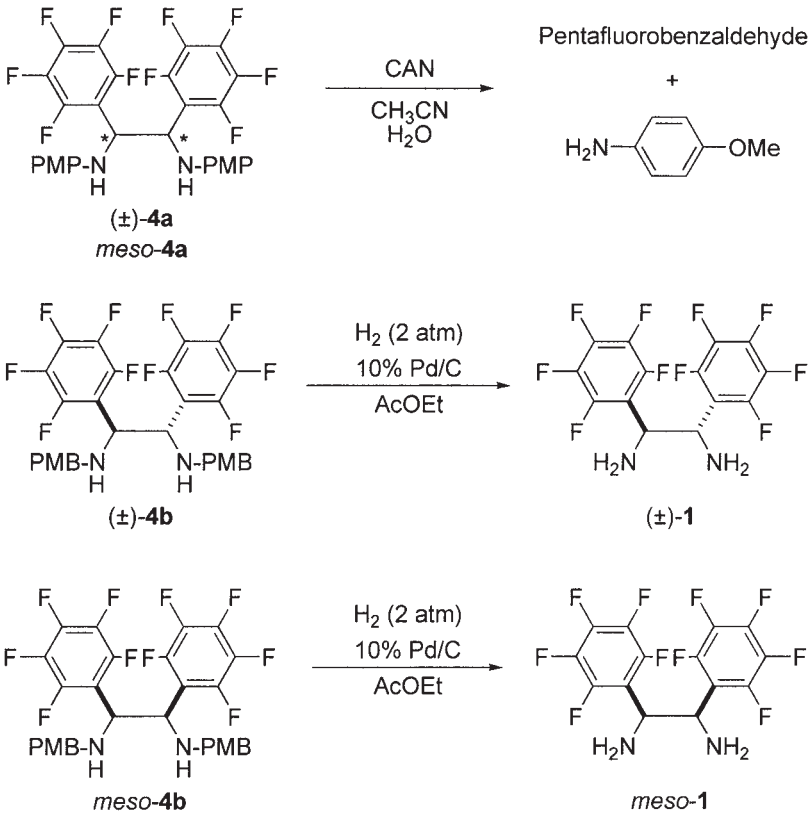
Table 2. Iminopinacol Coupling of Imine **3b**

Entry	Acid	Time/h	*Racemic*:*Meso*[a]	**4b**/%[b]
1	(+)-CSA	3.5	50:50	14
2	*p*-TsOH·H_2O	1.0	51:49	27

a) Determined by ^{19}F NMR analysis. b) Isolated yield.

alysts[7] might be available for this coupling reaction; however, we used only the Zn–Cu couple here because of its ease of handling and treatment.

Imines **3a** and **3b** were prepared by the reaction of pentafluorobenzaldehyde with *p*-anisidine and 4-methoxybenzylamine, respectively, in almost quantitative yields (Scheme 1)[8] as *E*-isomers exclusively.[5b] The imino pinacol coupling of **3a** was carried out by using the Zn–Cu couple and (+)-CSA at room temperature (Scheme 1),[6] giving *N*,*N*′-bis(4-methoxyphenyl)-1,2-bis(pentafluorophenyl)ethane-1,2-diamine (**4a**) (57% yield, *dl*:*meso* 46:54). The reaction was found to be highly sensitive to the solvent (Table 1), with THF being the most suitable among the examined solvents such as DMF, CH_2Cl_2, and Et_2O (Table 1, entries 1–3). The diastereomeric structures of the *dl*- and *meso*-forms of **4a** were determined by ^{1}H NMR after transformation into the corresponding thiadiazolidine oxide **5a** by treatment with $SOCl_2$ (Scheme 1).[9] In *trans*-**5a**, a couple of doublets (δ 5.92 and 6.35) due to the two non-equivalent methine protons were observed, suggesting the *dl*-form of **4a**. On the other hand, in *cis*-**5a**, a singlet (δ 6.29) for the equivalent methine protons appeared, indicating the *meso*-form of **4a**. Unfortunately, no chiral induction was observed despite the use of (+)-CSA. Fujisawa and Shimizu[6b] suggested that in their reaction with non-fluorinated imine, a sufficient basicity of the nitrogen atom is essential for the formation of a transient complex with (+)-CSA, which affects the reactivity as well as the diastereo- and enantioselectivity. In this aspect, imine **3a** with the electron-withdrawing C_6F_5 group is at a considerable disadvantage for this reaction. Therefore, the obtained yield of 57% seems to be rather valuable. The imino pinacol coupling of **3b** was then examined under similar conditions (Scheme 1, Table 2), giving *N*,*N*′-bis(4-methoxybenzyl)-1,2-bis(penta-



Scheme 2.

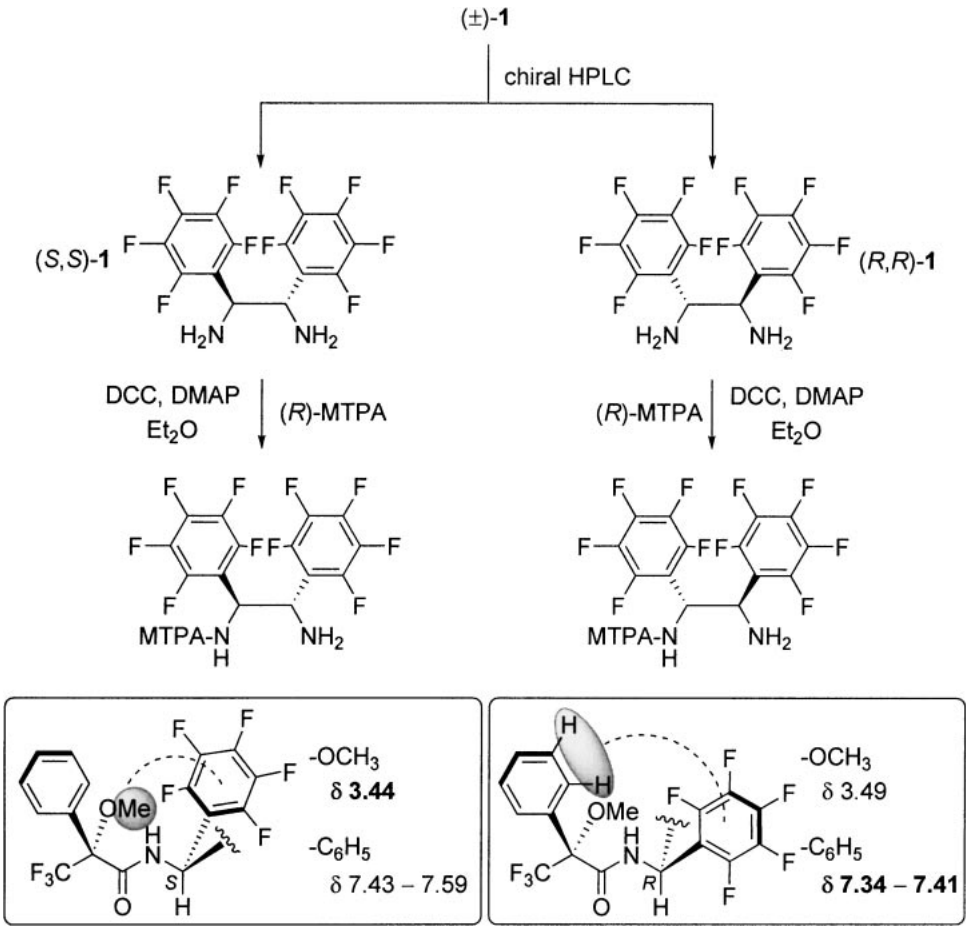
fluorophenyl)ethane-1,2-diamine (**4b**) in 14% yield as a mixture of *dl*- and *meso*-**4b** without diastereo- and enantioselectivity (Scheme 1 and Table 2). The structures of *dl*- and *meso*-**4b** were similarly determined by ^{1}H NMR after transformation into the corresponding *trans*-**5b** (δ 5.01 and 5.67) and *cis*-**5b** (δ 5.46). Replacement of the (+)-CSA additive with *p*-TsOH$\cdot$H$_2$O also gave a mixture of (±)-**4b** and *meso*-**4b** with a slightly improved yield of 27%. Despite much effort, the yield could not be improved, and unidentified by-products were always formed.

Attempts for the removal of *p*-methoxyphenyl (PMP) and *p*-methoxybenzyl (PMB) groups leading to compound **1** are shown in Scheme 2. Diamine (±)-**4a** was treated with 0.5 molar amounts of cerium(IV) ammonium nitrate (CAN), which gave the starting aldehyde and *p*-anisidine via oxidative decomposition. *meso*-**4a** also had similar results. In contrast, the removal of 4-methoxybenzyl groups from diamine (±)-**4b** was successfully accomplished with 10% Pd/C under 2 atm of H_2 to give (±)-**1** in 86% yield. A similar treatment of *meso*-**4b** also gave *meso*-**1** in 38% yield.

The optical resolution of (±)-**1** was then attempted using two methods: a) salt formation with chiral acids, and b) HPLC separation with a chiral column. The chiral acids used in the former method were (+)-mandelic acid, (+)-tartaric acid, (+)-CSA, (−)-*O*,*O*′-dibenzoyltartaric acid, (−)-menthoxyacetic acid, and (+)-naproxen.[10] Among them, three-times recrystallizations of the salts prepared from (±)-**1** and an equimolar amount of (+)-naproxen afforded (*S*,*S*)-**1** with 96% ee in 17% overall yield, although the additional recrystallizations of the (*S*,*S*)-**1** (96% ee) were useless for further improvement of the optical purity. At present, the HPLC resolution of (±)-**1** with a chiral column (CHIRALCEL OD-H, hexane:2-propanol:diethylamine = 70:20:0.1) is the better choice, giving (*R*,*R*)-**1** (99% ee) and (*S*,*S*)-**1** (>99% ee) in high optical purity. Interestingly, the HPLC resolution of (±)-**1** can be performed more effectively than that of non-fluorinated (±)-**2**, because a hundred mg of both enantiomers is obtainable in one charge using a 4.6 mm (d) × 25 cm (l) column. The absolute configurations of (*R*,*R*)-**1** and (*S*,*S*)-**1** were determined by ^{1}H NMR spectra after transformation into the corresponding mono MTPA (MTPA: α-methoxy-α-(trifluoromethyl)phenylacetic acid) amides, (*R*,*R*)-**6** and (*S*,*S*)-**6**,[11] in which the methyl group in the methoxy moiety of (*S*,*S*)-**6** is observed at upper field (δ 3.44) than that (δ 3.49) of (*R*,*R*)-**6** due to the ring current effect[12] of the pentafluorophenyl group located on the same side, as shown in Scheme 3.

The pK_a of the conjugate acid of **1** was estimated both by a titration experiment and a computational method, because information on the basicity is requisite for predicting the stability of the metal–amine complex[13] for asymmetric catalysis. As the pK_a values reported for amines are commonly measured in water, it is preferred that those of **1** and **2** are measured in water. However, the solubility of the amines **1** and **2** is low even in acidic water. This forced us to measure the pK_a values in a mixed solvent of H_2O–EtOH (1:2) to obtain referential information. Thus, these diamines were titrated with 0.5 M KOH in a mixed solvent of aqueous nitric acid and EtOH (1:2) using a potentiometric apparatus. The obtained pK_{a2} values of **1** and **2** in H_2O–EtOH (1:2) were 5.8 and 8.3 (2.5 p*K* unit difference), respectively.

For an estimate of the pK_a values of **1** and **2** in water, ab ini-



Scheme 3.

tio calculations[14] were carried out. A linear correlation between the molecular electrostatic potential (MEP) minima (V_{min}) in the vicinities of the amino groups and the pK_a values has proven to be effective for evaluating a wide range of pK_a values of amines,[15] although chiral amines and 1,2-diamines are not involved. For estimation of the pK_a values of the 1,2-diamines **1** and **2**, we revalued the linear correlation between the MEP and the authentic experimental pK_a values of the amines involving ethylenediamine,[16] (2*R*,3*R*)-2,3-diaminobutane,[16] and (*R*)-1-phenylethylamine. In particular, we employed the MEP at the nitrogen atom(s) of amines ($V_N^{RNH_2}$) rather than those in the vicinity of the amino group.[17] The values of the MEP at the nitrogen atom(s) ($V_N^{RNH_2}$) of primary amines (17 examples) and *p*-substituted anilines (5 examples)[18] were calculated at the B3LYP/6-311G** level after optimization of the geometry of amines at the B3LYP/6-311G** level[19] using the Gaussian 98W.[20] As a result, the calculated values were found to be sufficiently correlated with the experimental pK_a values (in water) for the corresponding conjugate acids of the amines[21] (best fit line: $(pK_a) = -145.498 \times (V_N^{RNH_2}) - 2671.12$ (Eq. 1), $r^2 = 0.9958$, RMS error = 0.16) (Table 3). The calculated pK_a (or pK_{a2}) values of ethylenediamine, (2*R*,3*R*)-2,3-diaminobutane, and (*R*)-1-phenylethylamine showed good accuracy, with the differences between the experimental and the theoretical values calculated from Eq. 1 being only 0.04, <0.01, and 0.18 p*K* units, respectively. These results show that this method is suitable for estimation of the pK_a of diamines **1** and **2**. The pK_{a2} values of **1** and **2** in water were thus estimated from Eq. 1 after calculation of the corresponding $V_N^{RNH_2}$ to give 6.1 ± 0.2 ($V_N^{RNH_2} = -18.4002$) and 8.9 ± 0.2 ($V_N^{RNH_2} = -18.4196$), respectively, which are similar to those determined by titrations. Noteworthy is that the pK_{a2} value of **1** was revealed to have a stronger basicity than those of aniline derivatives involving 2-naphthylamine, which is known to form stable metal complexes.[22]

Conclusion

Enantiomerically pure 1,2-diamines bearing two pentafluorophenyl groups, (*R*,*R*)-**1** and (*S*,*S*)-**1**, were synthesized for the first time by the imino pinacol coupling of the corresponding imine, and the pK_{a2} of **1** and the non-fluorinated analog **2** were estimated both by the titration experiments in H_2O–EtOH (1:2) and by using ab initio calculations. The linear correlation procedure in the calculation method afforded the pK_{a2} value (in water) of 6.1 for **1** and 8.9 for **2**. The difference of 2.8 p*K* units between them is significant in the application to organic reactions as a catalyst ligand. The catalytic abilities of (*R*,*R*)- and (*S*,*S*)-**1** as chiral ligands are now under examination.

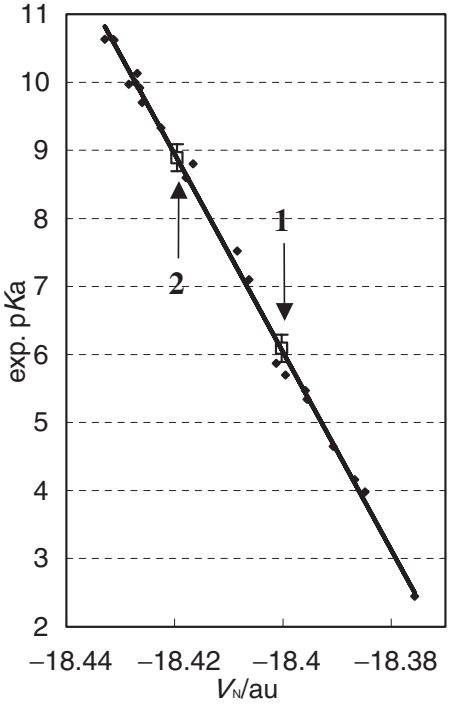
Experimental

General. All reactions were carried out under a nitrogen atmosphere with dry and freshly distilled solvents under anhydrous

Table 3. Correlation between Calculated $V_N^{RNH_2}$ and Experimental pK_a Values in Water

Amines	$V_N^{RNH_2}$ /au [a]	Exp. pK_a [c]	Calc. pK_a [k]
i-PrNH_2	−18.4329	10.63[d]	10.82
EtNH_2	−18.4314	10.63[e]	10.60
MeNH_2	−18.4312	10.62[e]	10.57
(*S*)-PhCH(NH_2)Me	−18.4269	10.13[f]	9.95
(2*S*,3*S*)-[MeCH(NH_2)-]$_2$ [b]	−18.4270	10.00[f]	10.00
meso-[MeCH(NH_2)-]$_2$ [b]	−18.4285	9.97[f]	10.20
$NH_2CH_2CH_2NH_2$ [b]	−18.4264	9.92[g]	9.88
CH_2=$CHNH_2$	−18.4260	9.7[h]	9.82
$PhCH_2NH_2$	−18.4225	9.33[h]	9.31
$BrCH_2CH_2CH_2NH_2$	−18.4200	8.93[i]	8.94
$Cl_2CFCH_2CH_2NH_2$	−18.4166	8.8[i]	8.44
$CF_3CH_2CH_2NH_2$	−18.4179	8.6[i]	8.64
$F_2CHCH_2NH_2$	−18.4084	7.52[i]	7.26
$CF_3CH(F)CH_2NH_2$	−18.4060	7.1[i]	6.94
$CF_3CH_2NH_2$	−18.4013	5.87[i]	6.22
$CF_3CF_2CH_2NH_2$	−18.3996	5.7[i]	5.97
$Cl_3CCH_2NH_2$	−18.3959	5.47[i]	5.43
p-MeO-$C_6H_4NH_2$	−18.3960	5.34[h]	5.40
p-F-$C_6H_4NH_2$	−18.3907	4.65[j]	4.69
2-NpNH_2	−18.3868	4.16[h]	4.11
p-Cl-$C_6H_4NH_2$	−18.3848	3.98[g]	3.83
p-CF_3-$C_6H_4NH_2$	−18.3757	2.45[j]	2.50

a) Calculation was performed at the B3LYP/6-311G ** level using Gaussian 98W. b) pK_{a2} (second dissociation constant) values were estimated in case of diamine. c) pK_a values of the conjugate acids. d) Ref. 19a. e) Ref. 19b. f) Ref. 19c. g) Ref. 19d. h) Ref. 19e. i) Ref. 19f. j) Ref. 19g. k) Calculation from Eq. 1.



Best fit line (Eq. 1):
(pK_a) = −145.498 × ($V_N^{RNH_2}$) − 2671.12,
r^2 = 0.9958, RMS error = 0.16.
1: $V_N^{RNH_2}$ (−18.4002), p$K_{a\ calc}$ (6.1 ± 0.2).
2: $V_N^{RNH_2}$ (−18.4196), p$K_{a\ calc}$ (8.9 ± 0.2).

conditions unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography with precoated silica-gel plates (Merck 60 F_{254}, plate length 40 mm). As a usual workup procedure, the reaction mixture was extracted with ethyl acetate (EtOAc). The organic layer was dried over $MgSO_4$, filtered with suction, and concentrated under reduced pressure. Preparative column chromatography was carried out using silica gel (Fuji Silysia BW-127 ZH, 100–270 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 200 MHz and 50 MHz, respectively, and chemical shifts are given relative to tetramethylsilane (TMS). ^{19}F NMR spectra were measured at 188 MHz, and chemical shifts are given relative to CCl_3F using C_6F_6 as secondary reference (−162.9 ppm).

(*E*)-4-Methoxy-*N*-(pentafluorobenzylidene)aniline (3a). To a solution of pentafluorobenzaldehyde (196 mg, 1.00 mmol) in dry CH_2Cl_2 (1.0 mL) was added *p*-anisidine (123 mg, 1.00 mmol) in the presence of molecular sieves 4A. After stirring at room temperature for 3 h, the mixture was filtered. The filtrate was concentrated to give a yellow solid. After purification by column chromatography (SiO_2, hexane/EtOAc (4:1)), compound **3a** (295 mg, 0.979 mmol) was obtained in 98% yield.

Yellow solid, mp 128–129 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.96 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 8.59 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 55.4, 114.4, 122.4, 144.0, 145.7, 159.4; ^{19}F NMR (188 MHz, $CDCl_3$) δ −163.1 to −162.9 (m, 2F), −151.7 (t, J = 21 Hz, 1F), −143.4 to −143.3 (m, 2F); IR (KBr) 835, 1036, 1251, 1494, 1651, 2844, 2972, 3026 cm^{-1}.

(*E*)-4-Methoxy-*N*-(pentafluorobenzylidene)benzylamine (3b). Compound **3b** was prepared from 4-methoxybenzylamine (137 mg, 1.00 mmol) and pentafluorobenzaldehyde (196 mg, 1.00 mmol) in 100% yield (315 mg, 1.00 mmol) by the procedure described for **3a**.

Yellow solid, mp 80–81 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.84 (s, 2H), 6.89 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 55.2, 65.8, 114.0, 129.1, 130.0, 149.8, 159.4; ^{19}F NMR (188 MHz, $CDCl_3$) δ −163.2 to −162.9 (m, 2F), −152.2 (t, J = 21 Hz, 1F), −143.9 to −143.8 (m, 2F); IR (KBr) 1032, 1169, 1228, 1497, 1612, 1652, 2844, 2899, 3009 cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_5NO$: C, 57.15; H, 3.20; N, 4.44%. Found: C, 57.00; H, 3.04; N, 4.52%.

***N*,*N*′-Bis(4-methoxyphenyl)-1,2-bis(pentafluorophenyl)ethane-1,2-diamine ((±)-4a and *meso*-4a).** A mixture of zinc powder (2.58 g, 37.9 mmol) and $Cu(OAc)_2 \cdot H_2O$ (141 mg, 0.710 mmol) in acetic acid (30 mL) was stirred at the reflux temperature for 5 min. The resulting precipitate was filtered, washed with acetic acid, and then with ether (×3). The obtained Zn–Cu couple was dried in vacuo and then 10 mL of THF was added. To the Zn–Cu suspension were added a solution of (+)-CSA (697 mg, 3.00 mmol) in THF (2.0 mL) and then a solution of **3a** (301 mg, 1.00 mmol) in dry THF (3.0 mL) subsequently at room temperature under a N_2 atmosphere. After stirring the mixture at room temperature for 6 h, saturated aqueous $NaHCO_3$ (10 mL) was added at 0 °C. The resulting mixture was filtered through a pad of Celite.

The filtrate was extracted with EtOAc (×3), and the combined extracts were washed with brine. The mixture was dried over anhydrous Na_2SO_4 and concentrated to give a crude product of a mixture of *meso*-**4a** and (±)-**4a**, which was found to be separable by the higher solubility of *meso*-**4a** in EtOH and by column chromatography. The crude product was washed with EtOH and filtered to give *meso*-**4a** (44 mg, 0.073 mmol, 15% yield) as a residue. Column chromatography (SiO_2, hexane/EtOAc (15:1)) of the filtrate afforded *meso*-**4a** (49 mg, 0.081 mmol, 16% yield) and a mixture of *meso*- and (±)-**4a**, the latter of which was washed with EtOH to give (±)-**4a** (79 mg, 0.13 mmol, 26% yield).

(±)-**4a**: white solid; mp 143–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 6H), 4.30 (br, 2H), 5.32 (s, 2H), 6.59 (d, J = 9.0 Hz, 4H), 6.77 (d, J = 9.0 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 53.9, 55.6, 115.0, 115.1, 139.6, 153.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ −161.5 to −161.3 (m, 4F), −153.4 (t, J = 21 Hz, 2F), −144.5 to −144.3 (m, 4F); IR (KBr) 822, 989, 1129, 1242, 1513, 1655, 2837, 2920, 2959, 3380, 3421 cm^{-1}. Anal. Calcd for $C_{28}H_{18}F_{10}N_2O_2$: C, 55.64; H, 3.00; N, 4.63%. Found: C, 55.59; H, 3.31; N, 4.47%.

meso-**4a**: white solid; mp 170–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.69 (s, 6H), 3.96 (br, 2H), 5.27 (s, 2H), 6.54 (d, J = 9.0 Hz, 4H), 6.70 (d, J = 9.0 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 53.9, 54.9, 114.3, 114.9, 138.3, 153.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.2 to −162.1 (m, 4F), −154.8 (t, J = 21 Hz, 2F), −147.7 to −147.5 (m, 2F), −144.3 to −144.0 (m, 2F); IR (KBr) 821, 982, 1038, 1116, 1248, 1412, 1523, 1655, 1744, 2843, 2915, 2961, 3015, 3368, 3413 cm^{-1}. Anal. Calcd for $C_{28}H_{18}F_{10}N_2O_2$: C, 55.64; H, 3.00; N, 4.63%. Found: C, 55.32; H, 3.13; N, 4.73%.

***N*,*N*′-Bis(4-methoxybenzyl)-1,2-bis(pentafluorophenyl)ethane-1,2-diamine ((±)-4b and *meso*-4b).** To a solution of $CuSO_4$ (1.50 g, 9.37 mmol) in water (10 mL) was added a solution of zinc powder (13.1 g, 200 mmol) in water (32 mL) at room temperature. After stirring at room temperature for 1 h, the resulting mixture was filtered and washed with acetone (×3) and then with Et_2O (×3). The Zn–Cu couple was dried in vacuo. To the Zn–Cu suspension in THF (90 mL) was added a solution of *p*-TsOH·H_2O (38.1 g, 200 mmol) in THF (70 mL) at room temperature under a N_2 atmosphere, and then a solution of **3b** (31.5 g, 100 mmol) in dry THF (90 mL) was added to the mixture at 0 °C over 15 min. After stirring at room temperature for 2 h, aqueous saturated $NaHCO_3$ (200 mL) and then aqueous NaOH were added to adjust the pH to 7–8 at 0 °C. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc (×3), and treated in the usual manner to give a crude product. EtOH (200 mL) was added, and the mixture was stirred for 1 h. Insoluble *meso*-**4b** (3.58 g, 5.66 mmol, 11% yield) was separated by filtration. After concentrating the filtrate, the residue was purified by column chromatography (SiO_2, hexane/EtOAc (15:1)) to give pure *meso*-**4b** (0.592 g, 0.936 mmol, 2% yield) and a mixture of *meso*-**4b** and (±)-**4b**. The latter mixture was washed with EtOH to obtain (±)-**4b** (4.42 g, 6.99 mmol, 14% yield).

(±)-**4b**: white solid; mp 140–141 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.43 (br, 2H), 3.61 (d, J = 13.8 Hz, 2H), 3.69 (d, J = 13.8 Hz, 2H), 3.78 (s, 6H), 4.52 (s, 2H), 6.80 (d, J = 8.7 Hz, 4H), 7.14 (d, J = 8.7 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 51.9, 55.3, 56.6, 113.7, 129.2, 131.2, 158.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.6 to −162.4 (m, 4F), −155.0 (t, J = 21 Hz, 2F), −143.2 to −143.1 (m, 4F); IR (KBr) 768, 985, 1112, 1244, 1524, 1613, 1656, 2842, 2941, 3039, 3292 cm^{-1}. Anal. Calcd for $C_{30}H_{22}F_{10}N_2O_2$: C, 56.97; H, 3.51; N, 4.43%. Found: C, 56.73; H, 3.48; N, 4.30%.

meso-**4b**: white solid; mp 159–161 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (br, 2H), 3.35 (d, J = 13.2 Hz, 2H), 3.61 (d, J = 13.2 Hz, 2H), 3.78 (s, 6H), 4.23 (s, 2H), 6.72 (d, J = 8.5 Hz, 4H), 6.84 (d, J = 8.7 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 51.0, 55.2, 55.9, 113.5, 129.2, 130.9, 158.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.3 to −162.0 (m, 4F), −157.1 (t, J = 20 Hz, 2F), −146.9 to −146.8 (m, 2F), −143.4 to −143.3 (m, 2F); IR (KBr) 853, 978, 1033, 1115, 1251, 1505, 1614, 2811, 2846, 2941, 3036, 3399 cm^{-1}. Anal. Calcd for $C_{30}H_{22}F_{10}N_2O_2$: C, 56.97; H, 3.51; N, 4.43%. Found: C, 56.97; H, 3.36; N, 4.52%.

2,5-Bis(4-methoxyphenyl)-*trans*-3,4-bis(pentafluorophenyl)-1,2,5-thiadiazolidine 1-Oxide (*trans*-5a). To a CH_2Cl_2 (3.0 mL) solution of (±)-**4a** (77 mg, 0.13 mmol) and triethylamine (71 μL, 0.51 mmol) was added a solution of distilled $SOCl_2$ (14 μL, 0.19 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under a N_2 atmosphere. After stirring the mixture at room temperature for 3 h, the reaction was quenched by the addition of brine. The organic layer was treated in the usual manner to give *trans*-**5a** (83 mg, 0.13 mmol) quantitatively.

White solid; mp 152–154 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.77 (s, 3H), 5.89 (d, J = 10.2 Hz, 1H), 6.36 (d, J = 10.2 Hz, 1H), 6.81–6.90 (m, 4H), 7.20–7.26 (m, 4H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −161.2 to −160.9 (m, 4F), −151.7 (t, J = 21 Hz, 1F), −151.0 (t, J = 21 Hz, 1F), −143.8 to −143.6 (m, 1F), −142.6 to −142.5 (m, 2F), −139.2 to −139.0 (m, 1F); IR (KBr) 669, 951, 998, 1155, 1249, 1509, 1655, 2840, 2917, 2964, 3385 cm^{-1}. Anal. Calcd for $C_{28}H_{16}F_{10}N_2O_3S$: C, 51.70; H, 2.48; N, 4.31%. Found: C, 52.04; H, 2.78; N, 4.36%.

2,5-Bis(4-methoxyphenyl)-*cis*-3,4-bis(pentafluorophenyl)-1,2,5-thiadiazolidine 1-Oxide (*cis*-5a). *cis*-**5a** was prepared from *meso*-**4a** (71 mg, 0.12 mmol) and $SOCl_2$ (13 μL, 0.18 mmol) in 81% yield (62 mg, 0.12 mmol) by a similar procedure to that described for *trans*-**5a**.

White solid; mp 192–194 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 6H), 6.26 (s, 2H), 6.84 (d, J = 8.9 Hz, 4H), 7.16 (d, J = 8.9 Hz, 4H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.0 to −161.7 (m, 2F), −161.0 to −160.8 (m, 2F), −151.7 (t, J = 21 Hz, 2F), −143.2 (d, J = 24 Hz, 2F), −139.8 (d, J = 21 Hz, 2F); IR (KBr) 985, 1254, 1360, 1505, 1609, 1654, 2841, 2922, 2968, 3364, 3507 cm^{-1}. Anal. Calcd for $C_{28}H_{16}F_{10}N_2O_3S$: C, 51.70; H, 2.48; N, 4.31%. Found: C, 51.97; H, 2.76; N, 4.14%.

2,5-Bis(4-methoxybenzyl)-*trans*-3,4-bis(pentafluorophenyl)-1,2,5-thiadiazolidine 1-Oxide (*trans*-5b). *trans*-**5b** was prepared from (±)-**4b** (10 mg, 0.010 mmol) and $SOCl_2$ (1.4 μL, 0.020 mmol) in 93% yield (10 mg, 0.093 mmol) by the procedure described above.

White solid; mp 172–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.65 (d, J = 13.2 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.16 (d, J = 13.2 Hz, 1H), 4.23 (d, J = 14.7 Hz, 1H), 4.35 (d, J = 14.7 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 5.67 (d, J = 10.5 Hz, 1H), 6.74 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.3 to −162.0 (m, 2F), −161.2 (m, 2F), −153.1 (t, J = 21 Hz, 1F), −151.9 (t, J = 21 Hz, 1F), −143.0 to −142.8 (m, 1F), −142.0 to −141.9 (m, 2F), −138.6 to −138.5 (m, 1F); IR (KBr) 819, 940, 982, 1057, 1116, 1251, 1506, 1613, 1654, 2847, 2918, 3015 cm^{-1}. Anal. Calcd for $C_{30}H_{20}F_{10}N_2O_3S$: C, 53.10; H, 2.97; N, 4.13%. Found: C, 53.34; H, 3.36; N, 3.88%.

2,5-Bis(4-methoxybenzyl)-*cis*-3,4-bis(pentafluorophenyl)-1,2,5-thiadiazolidine 1-Oxide (*cis*-5b). *cis*-**5b** was prepared from

meso-**4b** (10 mg, 0.010 mmol) and $SOCl_2$ (1.4 μL, 0.020 mmol) in 93% yield (10 mg, 0.093 mmol) by the procedure described above.

White solid; mp 157–158 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.78 (s, 6H), 4.04 (s, 4H), 5.46 (s, 2H), 6.81 (d, $J = 8.7$ Hz, 4H), 7.24 (d, $J = 8.7$ Hz, 4H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.2 to −162.0 (m, 2F), −161.5 to −161.2 (m, 2F), −152.5 (t, $J = 21$ Hz, 2F), −142.4 to −142.3 (m, 2F), −139.6 to −139.5 (m, 2F); IR (KBr) 818, 899, 986, 1089, 1256, 1306, 1360, 1505, 1614, 1657, 2840, 2914, 3008, 3064 cm^{-1}. Anal. Calcd for $C_{30}H_{20}F_{10}N_2O_3S$: C, 53.10; H, 2.97; N, 4.13%. Found: C, 53.05; H, 3.07; N, 4.16%.

(±)-1,2-Bis(pentafluorophenyl)ethane-1,2-diamine ((±)-1). A mixture of 10% Pd/C (170 mg, 0.160 mmol) and (±)-**4b** (1.00 g, 1.58 mmol) in EtOAc (7.0 mL) was stirred at room temperature for 8 h under 3 atm of H_2. The resulting mixture was filtered with Celite and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc (0.8:1)) to give (±)-**1** (530 mg, 1.35 mmol) in 86% yield.

White solid, mp 78–79 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.01 (br, 4H), 4.50 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 52.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.0 to −161.8 (m, 4F), −155.1 (t, $J = 21$ Hz, 2F), −143.9 to −143.8 (m, 4F); IR (KBr) 829, 984, 1128, 1502, 1655, 2922, 2962, 3310 cm^{-1}; Anal. Calcd for $C_{14}H_6F_{10}N_2$: C, 42.87; H, 1.54; N, 7.14%. Found: C, 43.21; H, 1.49; N, 7.09%.

Optical Resolution of (±)-1,2-Bis(pentafluorophenyl)ethane-1,2-diamine by Recrystallization with (*S*)-(+)-Naproxen. Racemic diamine (±)-**1** (100 mg, 0.25 mmol) and (*S*)-(+)-naproxen (59 mg, 0.26 mmol) in EtOH (0.8 mL) were stirred at the reflux temperature for 20 min. After cooling to room temperature, the salts were separated by decantation from the filtrate. Recystallizaiton (3 times) of the salts from EtOH (0.7 mL) gave white crystals. The crystals were treated with 1 M aqueous NaOH and extracted with Et_2O (3 times). The combined extracts were dried over anhydrous Na_2SO_4, and concentration under reduced pressure gave (*S*,*S*)-**1** (17 mg, 0.043 mmol, 96% ee) in 17% yield.

Optical Resolution of (±)-1,2-Bis(pentafluorophenyl)ethane-1,2-diamine by Chiral HPLC. Racemic diamine (±)-**1** (280 mg) was resolved by chiral HPLC into (*S*,*S*)-**1** (>99% ee, 107 mg) and (*R*,*R*)-**1** (99% ee, 110 mg).

The conditions of HPLC are as follows: column; Daicel CHIRALCEL OD-H, ϕ4.6 mm × 25 cm, hexane/*i*-PrOH/Et_2NH (70:30:0.1)), 0.5 mL min^{-1}, UV 254 nm; retention time = 15 and 22 min for (*S*,*S*)- and (*R*,*R*)-**1**. $[\alpha]_D^{26}$ for (*S*,*S*)-**1** = −51.4 (*c* 1.9, MeOH); $[\alpha]_D^{26}$ for (*R*,*R*)-**1** = +50.7 (*c* 1.9, MeOH).

***meso*-1,2-Bis(pentafluorophenyl)ethane-1,2-diamine (*meso*-1).** *meso*-**1** was prepared from *meso*-**4b** (683 mg, 1.08 mmol) under 2 atm of H_2 in 38% yield (159 mg, 0.405 mmol) following the procedure described for (±)-**1**.

White solid, mp 125–126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68 (br, 4H), 4.51 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$ (except for C_6F_5 carbon)) δ 53.2; ^{19}F NMR (188 MHz, $CDCl_3$) δ −162.4 to −162.2 (m, 4F), −156.0 (t, $J = 20$ Hz, 2F), −144.5 to −144.4 (m, 4F); IR (KBr) 841, 953, 979, 1082, 1120, 1247, 1318, 1414, 1501, 1525, 1658, 2973, 3333, 3365, 3425 cm^{-1}; Anal. Calcd for $C_{14}H_6F_{10}N_2$: C, 42.87; H, 1.54; N, 7.14%. Found: C, 43.20; H, 1.46; N, 7.12%.

Formation of (*R*)-MTPA Amide from (*R*,*R*)-1. To an ethereal solution of (*R*,*R*)-**1** (20.1 mg, 0.0510 mmol), DMAP (4.4 mg, 0.036 mmol), and DCC (21.6 mg, 0.105 mmol) was added an ethereal solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-MTPA) (20.6 mg, 0.0880 mmol) at 0 °C under a N_2 atmosphere. After stirring at room temperature for 3 h, the resulting mixture was diluted with water and extracted with Et_2O. The usual treatment of the mixture gave a colorless oil. After purification by column chromatography (SiO_2, hexane/EtOAc (2:1)), (*R*)-MTPA amide was obtained in 80% yield (24.7 mg, 0.0406 mmol): Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.14 (br, 2H), 3.49 (s, 1H), 4.70 (d, $J = 10.6$ Hz, 1H), 5.63 (dd, $J = 10.6$, 7.3 Hz, 1H), 7.34–7.41 (m, 5H), 7.91 (d, $J = 7.3$ Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −161.6 to −161.1 (m, 4F), −153.6 (t, $J = 21$ Hz, 1F), −153.3 (t, $J = 21$ Hz, 1F), −143.9 (d, $J = 22.4$ Hz, 2F), −143.4 (d, $J = 22.4$ Hz, 2F), −69.9 (s, 3F).

Formation of (*R*)-MTPA Amide from (*S*,*S*)-1. (*R*)-MTPA amide of (*S*,*S*)-**1** was prepared from (*S*,*S*)-**1** (23.5 mg, 0.0630 mmol) with (*R*)-MTPA (21.8 mg, 0.0930 mmol) in 67% yield (25.7 mg, 0.0422 mmol) by the procedure described above: Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (br, 2H), 3.44 (s, 1H), 4.70 (d, $J = 10.3$ Hz, 1H), 5.64 (dd, $J = 10.3$, 7.7 Hz, 1H), 7.43–7.59 (m, 5H), 7.89 (d, $J = 7.7$ Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −161.5 to −161.0 (m, 4F), −153.9 (t, $J = 21$ Hz, 1F), −153.6 (t, $J = 21$ Hz, 1F), −143.9 (d, $J = 22.1$ Hz, 2F), −143.6 (d, $J = 22.4$ Hz, 2F), −70.0 (s, 3F).

Titration Experiments. Solutions of diamines **1** and **2** (0.5 M) in aqueous nitric acid (pH 2.5) and ethanol (1:2) were titrated with aqueous 0.5 M KOH using a potentiometer. The isoelectric points were observed at pH 5.8 and 8.3, respectively.

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