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Studies on the Synthesis of Specifically Fluorinated 4-Aminopyridine Derivatives by Regioselective Nucleophilic Aromatic Substitution and Catalytic Hydrodefluorination

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Dedicated to the memory of Prof. Manfred Schlosser.

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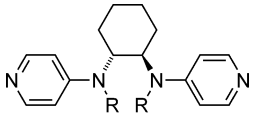
Abstract: The reactions of pentafluoropyridine and 2,4,6-trifluoropyridine with a series of primary and secondary amines were studied. Whereas the nucleophilic aromatic substitution of pentafluoropyridine occurs with high regioselectivity in all cases, providing the expected 4-aminopyridine derivatives in excellent yields, the regioselectivity of 2,4,6-trifluoropyridine is dependent on the steric hindrance of the attacking nucleophile. Small nucleophiles such as morpholine attack the 4-position of the pyridine ring with high preference, but more bulky diamines attack the 2- and 4-positions leading to the formation of three regioisomeric products. (*R,R*)-1,2-Diaminocyclohexane as moderately bulky diamine reacted with 2,4,6-trifluoropyridine to afford the desired bis(4-aminopyridinyl)cyclohexane derivative in 30% yield. For hydrodefluorination two methods were examined. A two-step procedure employing hydrazine and subsequently copper(II) sulfate removed just one fluorine substituent, but is not sufficiently high yielding for the reduction of more complex substrates. With the system titanocene difluoride as precatalyst and diphenylsilane as reducing agent we were able to selectively remove fluorine substituents at positions C-2 and C-4 of a variety of 4-aminopyridine derivatives. This protocol allows the synthesis of compounds such as the divalent chiral 4-(dimethylamino)pyridine (DMAP) analogue (*R,R*)-*trans*-*N,N′*-dimethyl-*N,N′*-bis(pyridin-4-yl)cyclohexane-1,2-diamine with fair overall yield.

Keywords: catalysis; fluorine; hydrodefluorination; nucleophilic aromatic substitution; pyridines

Introduction

Aminopyridine derivatives are important compounds in organic synthesis either as final targets, as reagents or as intermediates.[1] The most famous derivative of this class of heterocycles is 4-(dimethylamino)pyridine (DMAP),[2] very frequently employed as an efficient Brønsted base in stoichiometric or catalytic amounts.[3,4] This compound can also function as a powerful Lewis base, for example, in the stabilization of nanoparticles and nanotubes.[5] We were interested in the synthesis of the new divalent DMAP analogues **A** (Scheme 1) but could not access these new compounds by conventional substitution reactions starting from 4-halopyridines and *trans*-1,2-diaminocyclohexane or by other methods.[6] However, taking the detour *via* specifically fluorinated aminopyridine derivatives we could finally prepare these target compounds with reasonable efficacy.[7]

In this full report we want to disclose a detailed description of our approach to these compounds that involves the well known regioselective nucleophilic sub-



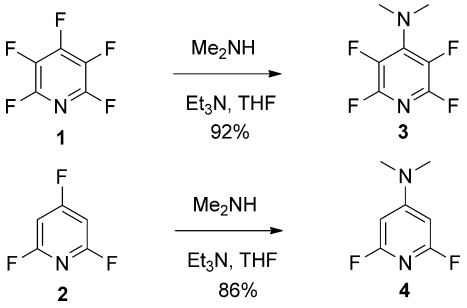
A

Scheme 1. Divalent 4-(dimethylamino)pyridine analogues **A**.

stitutions[8] of 2,4,6-trifluoropyridine or of pentafluoropyridine with the required amines. Subsequently, we describe the experiments to achieve partial or full catalytic hydrodefluorination (HDF)[9] with known or new catalytic systems to reach our final goal. A series of partially fluorinated aminopyridine derivatives was prepared that may also be of interest as building blocks in medicinal chemistry. It is well established that due to their high electronegativity fluorine atoms strongly alter the physical, chemical and biological properties of compounds[10] and a high percentage of newly registered drugs or crop protection products contain at least one fluorine atom.

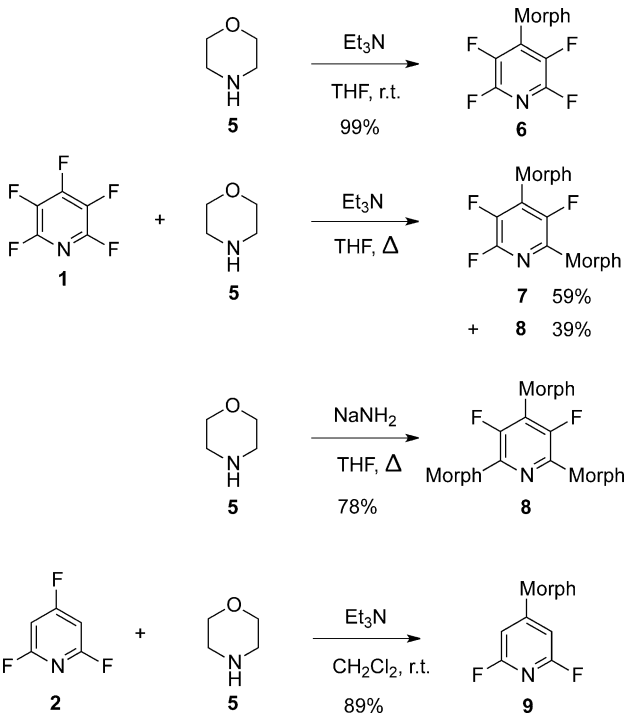
Results and Discussion

Nucleophilic displacement of fluorine in highly fluorinated pyridine derivatives and related heteroaromatic compounds occurs very readily since the heterocyclic system is strongly activated by the presence of the nitrogen atom and the electron-withdrawing fluorine substituents. The regioselectivity of the aromatic nucleophilic substitution processes has been carefully studied. The site-reactivity of pentafluoropyridine (**1**) follows the sequence 4-fluorine > 2-fluorine ⋙ 3-fluorine substituent. The reactions of **1** with various nucleophiles were summarized and discussed in detail.[8] 2,4,6-Trifluoropyridine (**2**) was also found to undergo nucleophilic substitution preferentially or exclusively at the 4-position.[8] Two typical examples[8i,e] are presented in Scheme 2 revealing the high regioselectivity and the efficacy of this process.



Scheme 2. Regioselective nucleophilic aromatic substitution of pentafluoropyridine (**1**) and 2,4,6-trifluoropyridine (**2**) leading to 4-dimethylaminopyridine derivatives **3** and **4**.[8i,e]

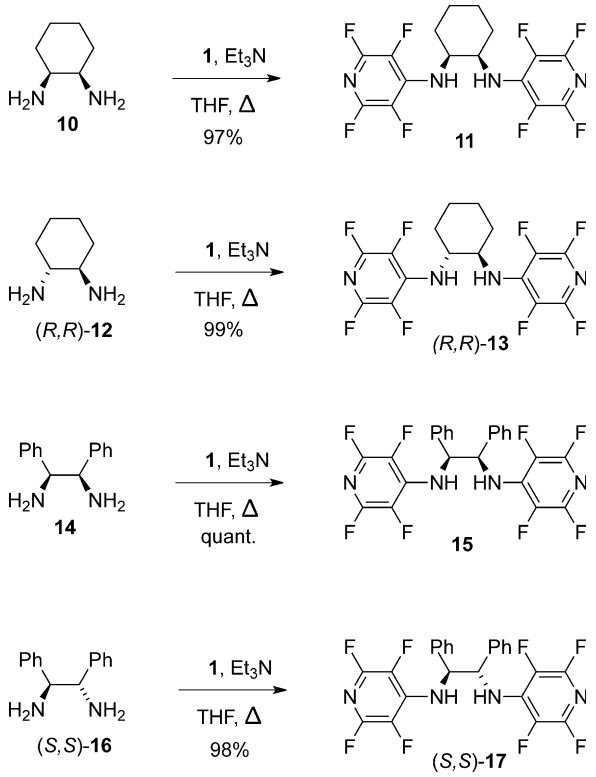
Starting with pyridine derivatives **1** and **2** and with morpholine **5** as model nucleophile we obtained the expected monosubstitution products **6**[8i] and **9**, when the reactions were performed at room temperature (Scheme 3). On the other hand, reaction of **1** with a large excess (46 equivalents) of morpholine furnished either a mixture of di- and trisubstituted products **7** and **8**, or with the assistance of sodium amide as stronger base the symmetrical trisubstituted compound **8**, exclusively. These transformations confirm the high regioselectivity in favor of the 4-substituted compounds. The subsequent substitution of primarily formed 4-aminopyridine derivative **6** requires an excess of the amine and harsher conditions and finally leads to 2,4,6-trismorpholino-substituted product **8**.



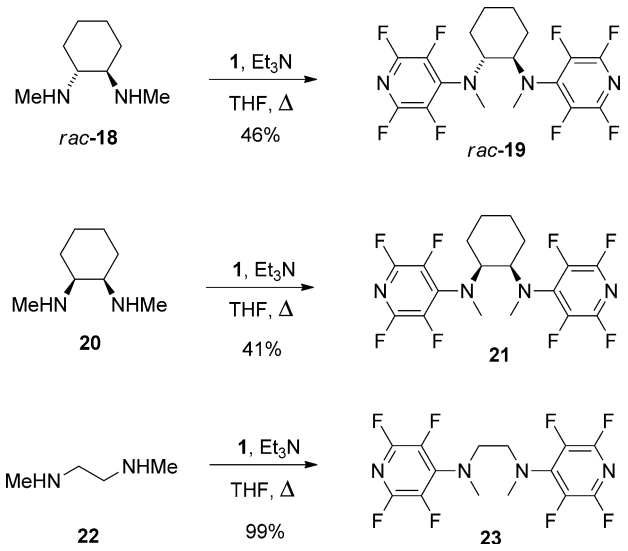
Scheme 3. Model reactions of pentafluoropyridine (**1**) and 2,4,6-trifluoropyridine (**2**) with morpholine leading to amino-substituted pyridines **6**–**9** (Morph = morpholinyl).

We then investigated the reactivity of vicinal diamines such as the stereoisomers of cyclohexane-1,2-diamine. The *cis*-compound **10** and four equivalents of electrophile **1** provided the expected divalent aminopyridine derivative **11** in excellent yield (Scheme 4). The corresponding (*R,R*)-stereoisomer **12** gave under similar conditions the enantiopure divalent compound (*R,R*)-**13** in 99% yield. Similar results were obtained with the 1,2-diamino-1,2-diphenylethane derivatives **14** and (*S,S*)-**16** which provided the *meso*-compound **15** and the (*S,S*)-configured product **17** with high efficacy. Although all transformations required heating to reflux in tetrahydrofuran to achieve these excellent yields, the examples of Scheme 4 confirm the high regioselectivity of nucleophilic substitution reactions of pentafluoropyridine (**1**).

Next we studied the substitutions employing *N*-methyl-substituted 1,2-diamines. Probably due to the higher steric hindrance the conversions of racemic precursor *rac*-**18** and of *meso*-compound **20** into compounds *rac*-**19** and **21**, respectively, were less efficient

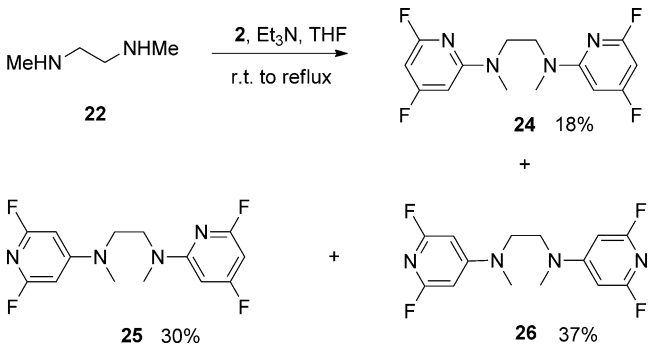


Scheme 4. Synthesis of divalent bis(tetrafluoropyridin-4-yl)-substituted 1,2-diamines **11**, (*R*,*R*)-**13**, **15**, and (*S*,*S*)-**17** by nucleophilic substitution of **1** with 1,2-diamines.



Scheme 5. Synthesis of divalent bis(tetrafluoropyridin-4-yl)-substituted 1,2-diamines *rac*-**19**, **21** and **23** by substitution of compound **1**.

(Scheme 5). In comparison, the acyclic *N,N'*-dimethyl-substituted diamine **22** furnished the expected product **23** almost quantitatively; this result is in accord-

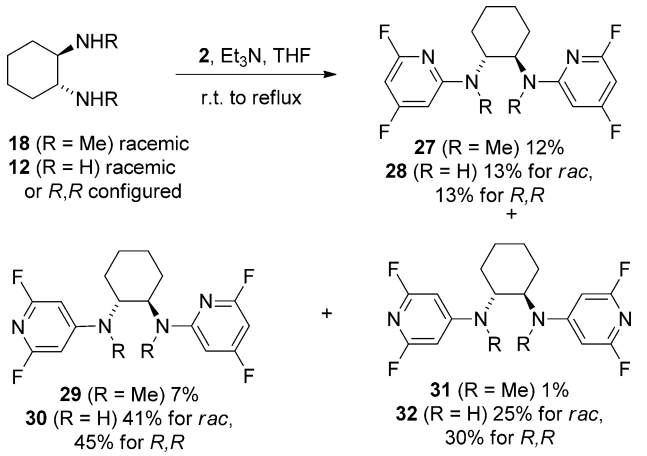


Scheme 6. Nucleophilic aromatic substitution of 2,4,6-trifluoropyridine (**2**) with 1,2-diamine **22** leading to regioisomeric compounds **24**, **25** and **26**.

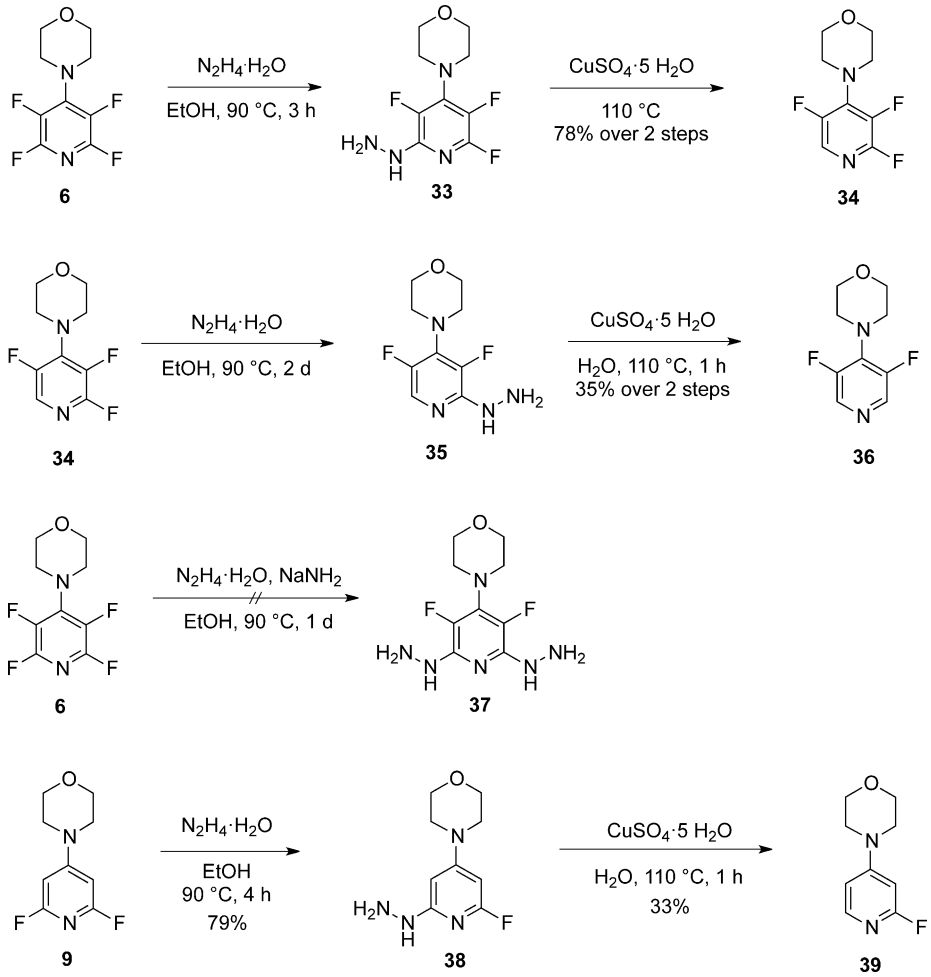
ance with the literature reporting a yield of 89% for this compound.[8i]

Whilst the substitutions employing **1** as strong electrophile occurred with very high regioselectivity even with the sterically more hindered secondary amines *rac*-**18**, **20** and **22**, this was no longer the case for the reactions of these nucleophiles with 2,4,6-trifluoropyridine (**2**). The reaction of four equivalents of this pyridine derivative with 1,2-diamine **22** furnished a mixture of the 2,2-, the 2,4-, and the 4,4-disubstituted products **24**–**26** in a good overall yield of 85% (Scheme 6). Although the three isomeric products were separable by column chromatography, the synthesis of the desired compound **26** was not very efficient.

The low regioselectivity became fatal when the sterically more hindered *N*-methylated 1,2-diaminocyclohexane derivative *rac*-**18** was employed (Scheme 7). The desired 4,4-disubstituted product *rac*-**31** was only obtained in 1% yield. The two other regioisomers *rac*-



Scheme 7. Nucleophilic aromatic substitutions of 2,4,6-trifluoropyridine (**2**) with *trans*-1,2-diaminocyclohexane derivatives **18** and **12**.



Scheme 8. Hydrodefluorination of 4-morpholinopyridines **6**, **34** and **9** by the two-step method employing hydrazine and copper sulfate.[11]

27 and *rac*-**29** were isolated in 12% and 7% yield, respectively, demonstrating that the substitution is not only unselective, but also quite inefficient. Gratifyingly, the sterically less hindered primary diamine **12** – studied as racemic compound and as enantiopure (*R,R*)-isomer – behaved much more productively, allowing a synthetically reasonable access to compounds *rac*-**32** and (*R,R*)-**32**. The process is still not regioselective and the undesired isomers **28** and **30** are formed in relatively high amounts, nevertheless, this route to the desired compound **32** is straightforward considering the simplicity of the method. Again, the three regioisomers were easily separated by column chromatography.

In summary, our results demonstrate an unexpectedly high effect of the steric hindrance of the attacking nucleophile on the regioselectivity of the nucleophilic aromatic substitution with compound **2**. To the best of our knowledge, results showing a similarly strong effect are not known. Apparently, the electronically favored attack at C-4 of 2,4,6-trifluoropyridine (**2**) becomes unfavorable when bulky secondary amines (such as **18**) are employed; in contrast, the reaction at C-2 (or C-6) is less hampered because the adjacent nitrogen atom is unsubstituted. When less bulky primary amines are used this effect could be partially overcome and the 4-substitution occurs in a higher percentage providing the expected products.

With the library of oligofluorinated aminopyridine derivatives in hand, we started to study the hydrodefluorination of these compounds. The final goal was the preparation of totally defluorinated compounds, either in one step or in a multi-step fashion, but we were also interested whether specifically fluorinated aminopyridines will be accessible by the applied methods. The first results with morpholino-substituted model compounds **6** and **9** as well as with intermediate **34** are collected in Scheme 8. The two-step method of Schlosser et al.[8e,11] consists in a regioselective nucleophilic substitution of fluoride by hydrazine delivering the 2-hydrazinopyridine derivatives. Subsequent treatment with copper sulfate at 110 °C replaces

the hydrazine moiety by a hydrogen atom. By this method trifluoro compound **34**, difluoro compound **36** and monofluoro compound **39** were obtained in moderate to good overall yields. An attempt to introduce two hydrazine substituents at C-2 and C-6 of compound **6** under forcing conditions to give **37** was not successful, thus precluding the direct two-fold defluorination of **6** to **36**.

After these encouraging first results we applied this method to divalent aminopyridines **23** and *rac*-**19**. In both cases, we observed a substitution with hydrazine at C-2 of both pyridine rings of the substrates, quantitatively leading to the desired intermediates **40** and **42**. Treatment of these compounds with copper sulfate provided the expected products **41** and **43** in moderate yields. Although the two examples demonstrate that the selective removal of one fluorine substituent per pyridine ring is also possible for divalent substrates, the results of Scheme 8 and Scheme 9 indicate that a complete removal by this two-step method would be laborious and probably inefficient.

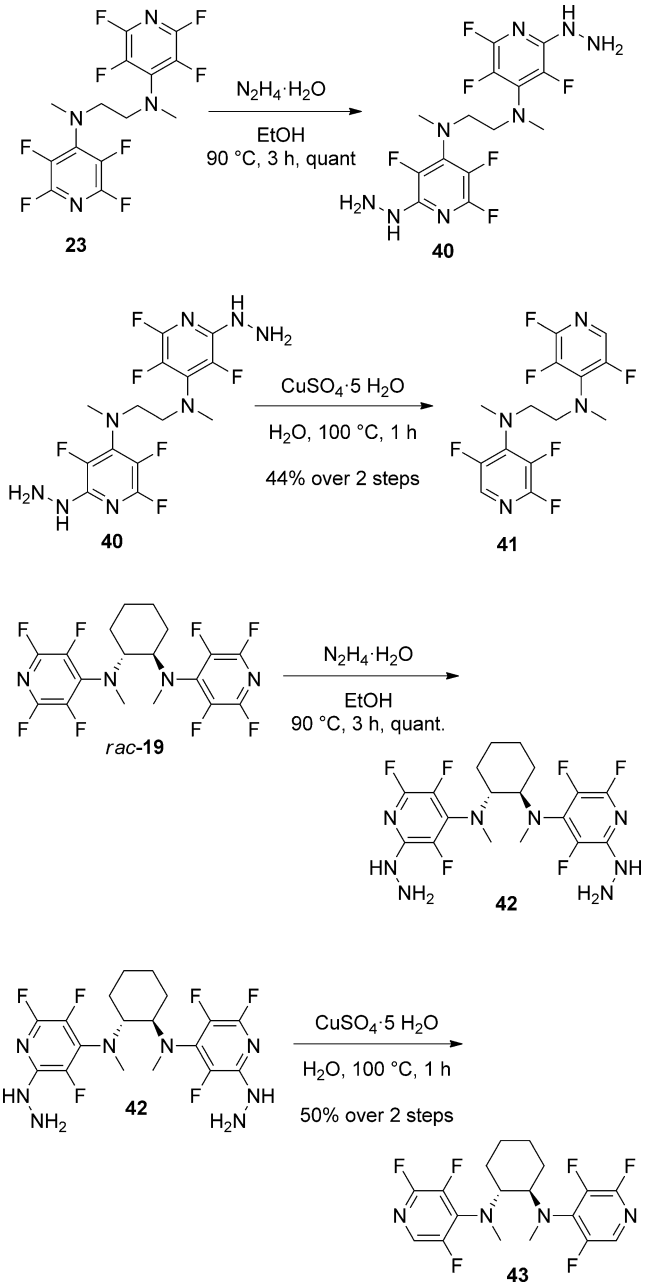
We also tried to reduce model compound **6** with an excess of samarium diiodide in tetrahydrofuran,[12] however, no conversion was observed up to temperatures of 70 °C. Next, we examined a catalytic hydrodefluorination method (HDF)[9] recently developed for fluoroalkenes[13] employing the pre-catalyst [Cp_2TiF_2] and diphenylsilane as reducing agent.[14] As test substrates we again used simple 4-morpholinopyridines **6** and **9** and identified 1,4-dioxane and 110 °C as optimal conditions. Under these conditions 15 mol% of the pre-catalyst were sufficient to convert both compounds into partially or completely defluorinated products **36** and **44** with excellent efficacy (Scheme 10).

Table 1 summarizes details of our optimization experiments. The use of 1,2-dimethoxyethane as solvent led to a considerable decrease of the reaction rate (entry 4). Full conversion of **6** into **36** was observed only after 96 h (92 % yield). The full defluorination of compound **6** to **44** could not be achieved by this method. Higher pre-catalyst loadings and longer reaction times caused decomposition of precursor **6** and/or the possible intermediates (entry 5).

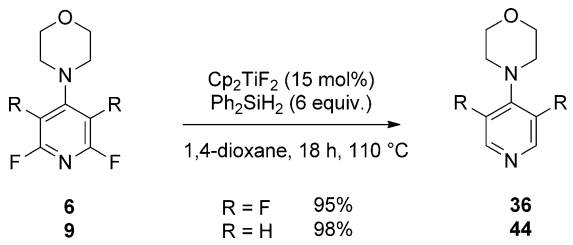
Table 1. Catalytic HDF of pyridine derivatives **6** and **9** according to Scheme 10.

Entry	Compound	*T* [°C]	*t* [h]	Cp_2TiF_2 [mol%]	Product, Yield
1	**6**	80	168	50	no reaction
2	**6**	90	120	24	**36**, 81%
3	**6**	110	24	15	**36**, 95%
4[a]	**6**	110	96	15	**36**, 92%
5	**6**	110	30	100	decomposition
6	**9**	110	24	15	**44**, 98%

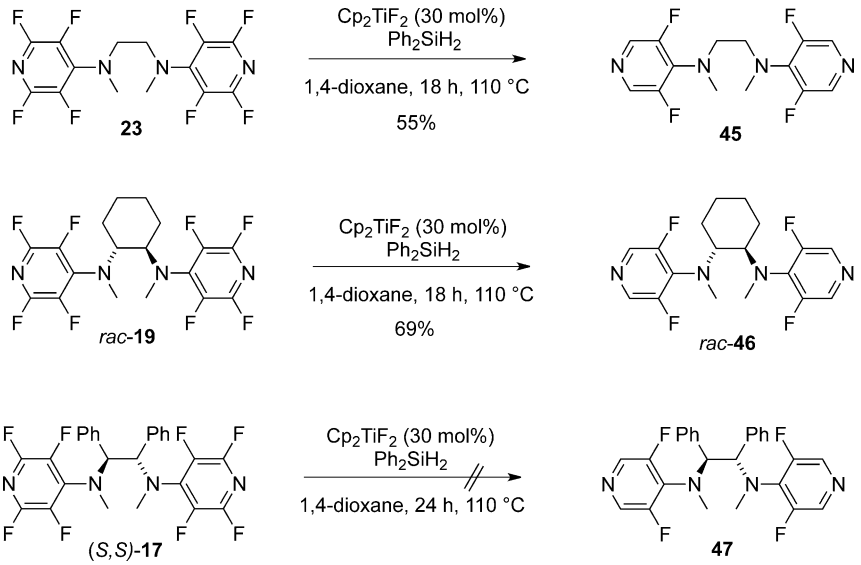
[a] 1,2-Dimethoxyethane as solvent.



Scheme 9. Two-step hydrodefluorinations of divalent aminopyridine derivatives **23** and *rac*-**19**.



Scheme 10. Catalytic hydrodefluorination of model substrates **6** and **9** under optimized conditions employing the [Cp_2TiF_2]/diphenylsilane system.

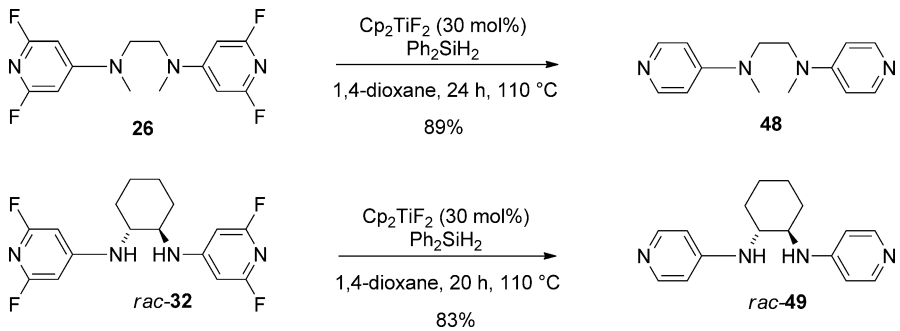


Scheme 11. Catalytic HDF of divalent octafluoro-substituted pyridines **23**, *rac*-**19** and (*S,S*)-**17**.

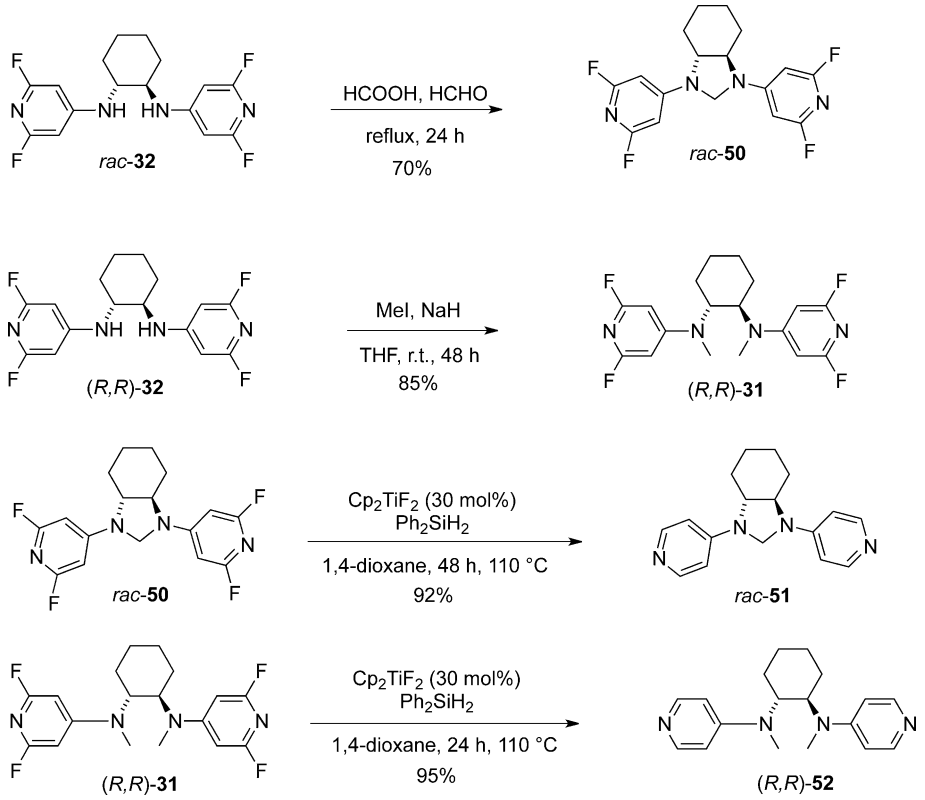
We then turned our attention to the divalent aminopyridine derivatives and applied the optimized conditions to compounds **23**, *rac*-**19** and (*S,S*)-**17** (Scheme 11). Gratifyingly, the method smoothly worked for the two octafluorinated substrates furnishing the expected tetrafluoro-substituted products **45** and *rac*-**46** in good yields. Surprisingly, substrate (*S,S*)-**17** with the 1,2-diphenylamino backbone did not afford product **47**, but it underwent complete decomposition. The benzylic positions in the backbone of this substrate possibly lead to side reactions and hence they are not compatible with the reaction conditions of this catalytic HDF method.

To our great pleasure 2,6-tetrafluorinated divalent pyridine derivatives **26** and **32** were very efficiently converted into the fully defluorinated target compounds **48** and **49** in excellent yields (Scheme 12). It should be noted that for the HDF reactions illustrated in Scheme 11 and Scheme 12 30 mol% of pre-catalyst Cp_2TiF_2 are used, in order to guarantee removal of four fluorine atoms from the precursors in reasonable reaction times.

Although the *N,N′*-dimethyl derivative **31** was directly available by the aromatic nucleophilic substitution (Scheme 7) the low yield of 1% strongly limits the access to this compound. We therefore tried a two-fold *N*-alkylation of *rac*-**32** in order to gain *rac*-**31**. Unexpectedly, the first attempt employing a reductive amination with formaldehyde and formic acid furnished the interesting bicyclic compound *rac*-**50** (Scheme 13). Gratifyingly, the direct *N*-methylation of (*R,R*)-**32** was very efficient, when sodium hydride and methyl iodide were employed. The *N*-alkylated compounds *rac*-**50** and (*R,R*)-**31** underwent the catalytic HDF with excellent efficacy affording the two new divalent DMAP-analogues **51** and (*R,R*)-**52** in more than 90% yield. An alkylation of (*R,R*)-**32** with 2-iodopropane in order to prepare an analogue of (*R,R*)-**52** with an altered conformation was not successful.



Scheme 12. Complete catalytic HDF of divalent tetrafluoro-substituted divalent pyridines **26** and *rac*-**32**.



Scheme 13. *N*-Alkylations of compounds *rac*-**32** and (*R*,*R*)-**32** and subsequent catalytic HDF affording divalent DMAP-analogues *rac*-**51** and (*R*,*R*)-**52**.

Conclusions

In this report we have demonstrated that pentafluoropyridine (**1**) and 2,4,6-trifluoropyridine (**2**) are suitable starting materials for the short, fairly efficient and versatile syntheses of a library of simple and complex fluorinated 4-aminopyridine derivatives. The removal of all or selected fluorine atoms of the resulting compounds by catalytic hydrodefluorination[15] or by processes activating the C–F bond leads to new 4-aminopyridine derivatives with unusual substitution patterns. The complete hydrodefluorination of compounds such as (*R*,*R*)-**31** led to the desired divalent analogue of 4-(dimethylamino)pyridine (*R*,*R*)-**52** that is of interest as a new enantiopure Lewis base and ligand.[16]

Experimental Section

General Methods

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Reagents were purchased and were used as received without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC). Products were purified by flash chromatography (FLC) on silica gel (32–63 μm). Unless otherwise stated, yields refer to chromatographically homogeneous and spectroscopically pure materials (^{1}H NMR spectroscopy). NMR spectra were recorded with JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm) and $CDCl_3$ (^{13}C: $\delta = 77.0$ ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. ^{13}C NMR spectra are ^{1}H-decoupled and in most cases ^{19}F-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet), dd (doublet of doublet), br s (broad singlet). MS and HR-MS analyses were performed with a Varian Ionspec QFT-7 instrument (ESI-FT ICR-MS). Elemental analyses were carried out with a Vario EL Elemental Analyzer. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

General Procedure 1 (GP1)

A solution of the amine with pentafluoropyridine (**1**) or 2,4,6-trifluoropyridine (**2**) in THF or in CH_2Cl_2 was stirred with Et_3N (4 equiv.) under an Ar atmosphere at room temperature or heated to 70 °C for a certain period of time. After cooling to room temperature the reaction was quenched by water addition. Extraction with Et_2O, solvent evaporation provided the crude product that was purified by flash chromatography (FLC).

General Procedure 2 (GP2)

4-Substituted tetrafluoropyridine and hydrazine monohydrate were dissolved in ethanol and stirred for the required time under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried and concentrated to give the crude hydrazine derivative. The crude product was suspended in water and the solution of $CuSO_4{\cdot}5H_2O$ in water was added drop-wise. The resulting mixture was refluxed for 1 h, after cooling down, ammonia solution (25%) was added until pH 9 was reached. Extraction with EtOAc, concentration and purification by FLC furnished the resulting pyridine derivative.

General Procedure 3 (GP3)

The substrate, titanocene difluoride, diphenylsilane and dry 1,4-dioxane were put into a Schlenk flask or a flask equipped with a J. Young PTFE valve and the resulting mixture was subsequently degassed by the freezing vacuum pump method. Subsequently, the mixture was shortly heated with a heat gun until the yellow color changed into dark-brown and the solution was then stirred at 110 °C for the required period (controlled by TLC). The reaction was quenched with MeOH and water was added. Extraction with Et_2O, drying with Na_2SO_4 and concentration furnished the crude product. Purification by FLC furnished the desired product.

2,3,5,6-Tetrafluoro-4-morpholinopyridine (6): According to **GP1**, morpholine (1.31 g, 15.0 mmol) was dissolved in THF (40 mL). A solution of **1** (2.54 g, 15.0 mmol) and Et_3N (5.25 mL, 37.5 mmol, 2.5 equiv.) in THF (4 mL) was added and the resulting mixture was stirred overnight at room temperature. Work-up and FLC (hexanes/EtOAc 5:1) afforded **6** as a colorless solid; yield: 3.49 g (99%, Lit[8i] 90%); mp 51–53 °C, Lit.[8i] 71–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 3.48 (m_c, 4H, CH_2N), 3.81 (m_c, 4H, CH_2O). The data agree with those of the literature.[17] ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 50.5$ (t, CH_2N), 67.0 (t, CH_2O), 135.1, 139.3, 144.9 (3 m_c, C-2, C-3, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -154.3$ (m_c, 2F, 3-F), −92.6 (m_c, 2F, 2-F).

3,5,6-Trifluoro-2,4-dimorpholinopyridine (7) and 3,5-Difluoro-2,4,6-trimorpholinopyridine (8): Morpholine (10.0 g, 115 mmol, 46 equiv.), **1** (0.420 g, 2.50 mmol) and Et_3N (2.08 mL, 15.0 mmol, 6 equiv.) were mixed and heated under reflux overnight. Work-up and FLC (hexanes/EtOAc 6:1) afforded **7** [yield: 0.45 g (59%)] and **8** [yield: 0.36 g (39%)] as colorless solids.

7: mp 94–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.31$ (m_c, 4H, CH_2N), 3.36 (m_c, 4H, CH_2N), 3.78 (m_c, 8H, CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 48.4$, 50.8 (2 t, CH_2N), 66.8, 67.3 (2 t, CH_2O), 132.7 (m_c, C-6), 138.6, 139.8, 143.3, 146.3 (4 m_c, C-2, C-3, C-4, C-5); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -161.2$, −143.1 (2 m_c, 2F, 3-F, 5-F), −92.7 (m_c, 1F, 6-F); IR (ATR): $\tilde{\nu} =$ 2985–2860 (C−H), 1620–1560 (C=C, C=N), 1470, 1190, 1110 (C−F) cm^{-1}; HR-MS (ESI-TOF): $m/z = 304.1258$, calcd. for $C_{13}H_{16}F_3N_3O_2$: 304.1267 $[M+H]^+$, $m/z = 326.1105$, calcd. for $[M+Na]^+$: 326.1087; anal. calcd. (%) for $C_{13}H_{16}F_3N_3O_2$ (303.3): C 51.48, H 5.32, N 13.86; found C 51.55, H 5.51, N 14.02.

8: mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.29$ (m_c, 12H, CH_2N), 3.78 (m_c, 12H, CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 48.7$, 51.1 (2 t, CH_2N), 67.0, 67.5 (2 t, CH_2O), 136.6 (m_c, C-4), 138.6 (m_c, C-3), 143.6 (m_c, C-2); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -148.8$ (m_c, 2F, 3-F); IR (ATR): $\tilde{\nu} =$ 2965–2825 (C−H), 1595, 1565 (C=C, C=N), 1485, 1185, 1110 (C−F) cm^{-1}; HR-MS (ESI-TOF): $m/z = 371.1897$, calcd. for $C_{17}H_{24}F_2N_4O_3$: 371.1889 $[M+H]^+$, $m/z = 393.1716$, calcd. for $[M+Na]^+$: 393.1709; anal. calcd. (%) for $C_{17}H_{24}F_2N_4O_3$ (370.4): C 55.13, H 6.53, N 15.13; found C 55.22, H 6.44, N 15.40.

Sodium amide (0.490 g, 12.5 mmol, 5 equiv.) was suspended in morpholine (10 mL, 115 mmol, 46 equiv.), pyridine derivative **1** (0.420 g, 2.50 mmol) was added and the resulting mixture was heated under reflux for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution, then extraction (EtOAc) and FLC (hexanes/EtOAc, 4:1) gave **8** as a colorless solid; yield: 717 mg (78%).

2,6-Difluoro-4-morpholinopyridine (9): According to **GP1**, morpholine (0.360 g, 4.00 mmol) and Et_3N (1.40 mL, 10.0 mmol, 2.5 equiv.) were dissolved in CH_2Cl_2 (9 mL). A solution of **2** (0.540 g, 4.00 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred overnight at room temperature. Work-up and FLC (hexanes/EtOAc 3:1) gave **9** as a colorless solid; yield: 0.711 g (89%); mp 201–202 °C; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 3.43$ (t, $J = 5.1$ Hz, 4H, CH_2N), 3.77 (t, $J = 5.1$ Hz, 4H, CH_2O), 6.37 (m_c, 2H, 3-H, 5-H); ^{13}C NMR (125 MHz, acetone-d_6): $\delta = 47.3$ (t, CH_2N), 66.7 (t, CH_2O), 89.5 (m_c, C-3), 163.2 (t, $J_{C,F} = 12.0$ Hz, C-4), 164.5 (dd, $J_{C,F} = 235$, 21.6 Hz, C-2); ^{19}F NMR (376 MHz, acetone-d_6): $\delta = -73.0$ (s, 2 F, 2-F); IR (ATR): $\tilde{\nu} =$ 3125 (=C−H), 2970–2865 (C−H), 1660–1530 (C=C, C=N), 1450, 1235, 1210, 1120 (C−F) cm^{-1}; HR-MS (ESI-TOF): $m/z =$ 201.0832, calcd. for $C_9H_{10}F_2N_2O$: 201.0834 $[M+H]^+$, $m/z =$ 223.0652, calcd. for $[M+Na]^+$: 223.0653; anal. calcd. (%) for $C_9H_{10}F_2N_2O$ (200.2): C 54.00, H 5.04, N 13.99; found C 54.19, H 5.19, N 14.08.

***cis-N,N′*-Bis(2,3,5,6-tetrafluoropyridin-4-yl)cyclohexane-1,2-diamine (11):** According to **GP1**, *cis*-cyclohexane-1,2-diamine (**10**) (0.100 g, 0.870 mmol) and Et_3N (0.490 mL, 3.48 mmol, 4 equiv.) were dissolved in THF (5 mL). A solution of **1** (0.565 g, 3.34 mmol, 4 equiv.) in THF (1 mL) was added and the mixture was stirred for 24 h under reflux. Work-up and FLC (hexanes/EtOAc 6:1) afforded **12** as a colorless solid; yield: 0.348 g (97%); mp 92–94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 1.56–1.74 (m, 6H, CH_2), 1.85–1.91 (m, 2H, CH_2), 4.26 (m_c, 2H, CH), 4.69 (m_c, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.3$ (t, CH_2), 29.2 (t, CH_2), 54.0 (dt, $J_{C,F} = 4.4$ Hz, CH), 131.7 (m_c, C-2/C-3), 136.7 (m_c, C-4), 144.3 (m_c, C-2/C-3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -162.3$ (m_c, 4F, 3-F), −93.1 (m_c, 4F, 2-F); HR-MS (ESI-TOF): $m/z = 413.1033$, calcd. for $C_{16}H_{12}F_8N_4$: 413.1012 $[M+H]^+$, $m/z = 435.0839$, calcd. for $[M+Na]^+$: 435.0832.

***(R,R)*-*N,N′*-Bis(2,3,5,6-tetrafluoropyridin-4-yl)cyclohexane-1,2-diamine (13):** According to **GP1**, (*R,R*)-cyclohexane-1,2-diamine (**12**) (0.100 g, 0.870 mmol) and Et_3N (0.490 mL, 3.48 mmol, 4 equiv.) were dissolved in THF (5 mL). A solution of **1** (0.565 g, 3.34 mmol, 4 equiv.) in THF (1 mL) was added and the mixture was stirred for 24 h under reflux. Work-up and FLC (hexanes/EtOAc 5:1) afforded **13** as a colorless solid; yield: 0.360 g (99%); mp 125–127 °C; $[\alpha]_D^{20}$: +103.4 ($c = 1.5$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 1.42 (m_c, 4H, CH_2), 1.89 (m_c, 2H, CH_2), 2.24 (m_c, 2H, CH_2), 3.77 (m_c, 2H, CH), 4.49 (m_c, 2H, NH);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6 (t, CH_2), 34.2 (t, CH_2), 59.4 (m_c, CH), 131.0 (m_c, C-2/C-3), 137.0 (m_c, C-4), 144.1 (m_c, C-2/C-3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −162.4 (m_c, 4F, 3-F), −93.2 (m_c, 4F, 2-F); HR-MS (ESI-TOF): *m/z* = 413.1002, calcd. for $C_{16}H_{12}F_8N_4$: 413.1012 $[M+H]^+$, *m/z* = 435.0836, calcd. for $[M+Na]^+$: 435.0832.

***meso*-*N,N′*-Bis(2,3,5,6-tetrafluoropyridin-4-yl)-1,2-diphenylethane-1,2-diamine (15):** According to **GP1**, *meso*-1,2-diphenylethane-1,2-diamine (**14**) (0.150 g, 0.710 mmol) and Et_3N (0.400 mL, 2.83 mmol, 4 equiv.) were dissolved in THF (5 mL). A solution of **1** (0.458 g, 2.72 mmol, 4 equiv.) in THF (1 mL) was added and the mixture was stirred for 24 h under reflux. Work-up and FLC (hexanes/EtOAc 6:1) afforded **15** as a slightly yellow solid; yield: 0.361 g (quant.); mp 176–178 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 5.78 (m_c, 2H, CH), 6.74 (m_c, 2H, NH), 7.24 (m_c, 2H, Ph), 7.34 (m_c, 4H, Ph), 7.72 (m_c, 4H, Ph); ^{13}C NMR (125 MHz, acetone-d_6): δ = 62.4 (dt, $J_{C,F}$ = 4.9 Hz, CH), 127.8 (d, Ph), 128.2 (d, Ph), 128.6 (d, Ph), 131.3 (m_c, C-2/C-3), 136.0 (m_c, C-4), 140.2 (s, Ph), 144.0 (m_c, C-2/C-3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −161.6 (m_c, 4F, 3-F), −96.8 (m_c, 4F, 2-F); HR-MS (ESI-TOF): *m/z* = 511.1170, calcd. for $C_{24}H_{14}F_8N_4$ $[M+H]^+$: 511.1169, *m/z* = 533.0991, calcd. for $[M+Na]^+$: 533.0988.

***(S,S)*-*N,N′*-Bis(2,3,5,6-tetrafluoropyridin-4-yl)-1,2-diphenylethane-1,2-diamine (17):** According to **GP1**, *(S,S)*-1,2-diphenylethane-1,2-diamine (**16**) (0.150 g, 0.710 mmol) and Et_3N (0.400 mL, 2.83 mmol, 4 equiv.) were dissolved in THF (5 mL). A solution of **1** (0.458 g, 2.72 mmol, 4 equiv.) in THF (1 mL) was added and the mixture was stirred for 24 h under reflux. Work-up and FLC (hexanes/EtOAc 5:1) afforded **17** as a colorless solid; yield: 0.355 g, (98%); 159–161 °C; $[\alpha]_D^{20}$: −62.1 (c = 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.14 (br s, 2H, NH), 5.28 (m_c, 2H, CH), 6.96 (m_c, 4H, Ph), 7.21–7.33 (m, 6H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 63.1 (dt, $J_{C,F}$ = 4.1 Hz, CH), 127.3 (d, Ph), 129.1 (d, Ph), 129.2 (d, Ph), 131.8 (m_c, C-2/C-3), 136.4 (m_c, C-4), 136.5 (s, Ph), 144.2 (m_c, C-2/C-3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −160.8 (m_c, 4F, 3-F), −92.5 (m_c, 4F, 2-F); HR-MS (ESI-TOF): *m/z* = 511.1171, calcd. for $C_{24}H_{14}F_8N_4$: 511.1169 $[M+H]^+$, *m/z* = 533.1001, calcd. for $[M+Na]^+$: 533.0988.

***rac-trans*-*N,N′*-Dimethyl-*N,N′*-bis(2,3,5,6-tetrafluoropyridin-4-yl)cyclohexane-1,2-diamine (19)**: According to **GP1**, *rac-trans-N,N′*-dimethylcyclohexane-1,2-diamine (**18**) (0.280 g, 1.97 mmol) and Et_3N (1.11 mL, 7.90 mmol, 4 equiv.) were dissolved in THF (20 mL). A solution of **1** (1.33 g, 7.87 mmol, 4 equiv.) in THF (5 mL) was added and the resulting mixture was stirred for 2 d under reflux. Work-up and FLC (hexanes/EtOAc 15:1) afforded **19** as a colorless solid; yield: 0.400 g (46%); mp 216–217 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (m_c, 2H, CH_2), 1.71–1.73 (m, 2H, CH_2), 1.82–1.94 (m, 2H, CH_2), 2.11–2.13 (m, 2H, CH_2), 2.76 (t, J_{HF} = 3.1 Hz, 6H, CH_3), 3.58–3.69 (m, 2H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1 (t, CH_2), 30.2 (t, CH_2), 33.5 (q, CH_3), 61.9 (d, CH), 134.6, 140.7, 145.2 (3 m_c, C-2, C-3, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −154.2 (m_c, 4F, 3-F), −92.7 (m_c, 4F, 2-F); IR (ATR): $\tilde{\nu}$ = 2955–2835 (C−H), 1635, 1525 (C=C, C=N), 1465, 1220, 1160, 1110 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 441.1315, calcd. for $C_{18}H_{16}F_8N_4$: 441.1320 $[M+H]^+$, *m/z* = 463.1136, calcd. for $[M+Na]^+$: 463.1139; anal. calcd. (%) for $C_{18}H_{16}F_8N_4$ (440.3): C 49.10, H 3.66, N 12.72; found: C 49.12, H 3.45, N 12.87.

***cis*-*N,N′*-Dimethyl-*N,N′*-bis(2,3,5,6-tetrafluoropyridin-4-yl)cyclohexane-1,2-diamine (21):** According to **GP1**, *cis-N,N′*-dimethylcyclohexane-1,2-diamine (**20**) (0.100 g, 0.70 mmol) and Et_3N (0.40 mL, 2.81 mmol, 4 equiv.) were dissolved in THF (5 mL). A solution of **1** (0.26 g, 1.54 mmol, 2.2 equiv.) in THF (2 mL) was added and the resulting mixture was stirred for 2 d under reflux. Work-up and FLC (hexanes/EtOAc 15:1) afforded **21** as a brownish foam; yield: 0.127 g (41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (m_c, 2H, CH_2), 1.77–1.81 (m, 4H, CH_2), 2.02–2.10 (m, 2H, CH_2), 2.76 (m_c, 6H, CH_3), 3.72–3.83 (m, 2H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9 (t, CH_2), 28.4 (t, CH_2), 38.9 (q, CH_3), 61.2 (d, CH), 134.2, 138.2, 145.4 (3 m_c, C-2, C-3, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −155.1 (m_c, 4F, 3-F), −95.8 (m_c, 4F, 2-F); HR-MS (ESI-TOF): *m/z* = 441.1324, calcd. for $C_{18}H_{16}F_8N_4$: 441.1320 $[M+H]^+$.

***N,N′*-Dimethyl-*N,N′*-bis(2,3,5,6-tetrafluoropyridin-4-yl)-ethane-1,2-diamine (23):** According to **GP1**, *N,N′*-dimethylethylene-1,2-diamine (**22**) (0.29 g, 3.30 mmol) and Et_3N (1.87 mL, 13.3 mmol, 4 equiv.) were dissolved in THF (20 mL). A solution of pentafluoropyridine (**1**) (1.13 g, 6.68 mmol, 2 equiv.) in THF (15 mL) was added and the resulting mixture was stirred overnight at room temperature. Work-up and following FLC (hexanes/ethyl acetate 6:1) afforded product **23** as a colorless solid; yield: 1.28 g (99%, lit.[8i] 90%); mp 140–141 °C (lit.[8i] 139–140 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.15 (t, J = 3.3 Hz, 6H, CH_3), 3.64 (s, 4H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 40.8 (q, CH_3), 52.7 (t, CH_2), 134.5, 139.8, 145.1 (3 s, C-2, C-3, C-4); ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −155.3 (m_c, 4F, 3-F), −92.7 (m_c, 4F, 2-F); IR (ATR): $\tilde{\nu}$ = 2990–2835 (C−H), 1630, 1530 (C=C, C=N), 1460, 1260, 1220, 1130, 1115 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 387.0826, calcd. for $C_{14}H_{10}F_8N_4$: 387.0850 $[M+H]^+$, *m/z* = 409.0649, calcd. for $[M+Na]^+$: 409.0670; anal. calcd. (%) for $C_{14}H_{10}F_8N_4$ (386.2): C 43.53, H 2.61, N 14.51; found: C 43.49, H 2.51, N 14.39.

***N,N′*-Dimethyl-*N,N′*-bis(4,6-difluoropyridin-2-yl)ethane-1,2-diamine (24), *N,N′*-dimethyl-*N*-(2,6-difluoropyridin-4-yl)-*N′*-(4,6-difluoropyridin-2-yl)ethane-1,2-diamine (25) and *N,N′*-dimethyl-*N,N′*-bis(2,6-difluoropyridin-4-yl)ethane-1,2-diamine (26):** According to **GP1**, *N,N′*-dimethylethylene-1,2-diamine (**22**) (0.220 g, 2.50 mmol) and Et_3N (1.40 mL, 10.0 mmol, 4 equiv.) were dissolved in THF (20 mL). A solution of **2** (0.670 g, 5.00 mmol, 2 equiv.) in THF (5 mL) was added and the mixture was stirred overnight under reflux. Work-up and FLC (hexanes/EtOAc 12:1, 8:1, 3:1) afforded **24** (yield: 0.143 g, 18%), **25** (yield: 0.235 g, 30%) and **26** (0.290 g, 37%) as a colorless solids.

24: mp 177–178 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 2.99 (s, 6H, CH_3), 3.71 (s, 4H, CH_2), 5.85 (m_c, 2H, 3-H/5-H), 5.96 (m_c, 2H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 37.2 (q, CH_3), 47.6 (t, CH_2), 84.6 (ddd, $J_{C,F}$ = 42.3, 24.8 Hz, C-3/C-5), 89.9 (ddd, $J_{C,F}$ = 23.8, 5.7 Hz, C-3/C-5), 158.4 (dd, $J_{C,F}$ = 20.1, 14.0 Hz, C-2), 163.7 (dd, $J_{C,F}$ = 233, 18.3 Hz, C-6), 172.9 (dd, $J_{C,F}$ = 254, 14.8 Hz, C-4); ^{19}F NMR (376 MHz, acetone-d_6): δ = −98.7 (m_c, 2F, 4-F), −65.5 (m_c, 2F, 6-F); IR (ATR): $\tilde{\nu}$ = 3120, 3100 (=C−H), 2925–2810 (C−H), 1710–1510 (C=C, C=N), 1455, 1260, 1180, 1110 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 315.1240, calcd. for $C_{14}H_{14}F_4N_4$: 315.1227 $[M+H]^+$, *m/z* = 337.1060, calcd. for

$[M+Na]^+$: 337.1047; anal. calcd. (%) for $C_{14}H_{14}F_4N_4$ (314.3): C 53.50, H 4.49, N 17.83; found: C 53.31, H 4.57, N 17.90.

25; mp 194–195 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 3.08 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.69 (m_c, 2H, CH_2), 3.81 (m_c, 2H, CH_2), 6.06 (m_c, 1H, 3′-H/5′-H), 6.19 (m_c, 1H, 3′-H/5′-H), 6.25 (br s, 2H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 37.5, 38.8 (2 q, CH_3), 47.6, 49.9 (2 t, CH_2), 84.6 (ddd, $J_{C,F}$ = 42.7, 25.1 Hz, C-3′/C-5′), 88.2 (m_c, C-3/C-5), 89.9 (ddd, $J_{C,F}$ = 23.9, 5.6 Hz, C-3′/C-5′), 159.7 (dd, $J_{C,F}$ = 20.3, 14.1 Hz, C-2′), 162.2 (dd, $J_{C,F}$ = 12.0 Hz, C-4), 164.1 (dd, $J_{C,F}$ = 232, 18.1 Hz, C-6′), 164.7 (dd, $J_{C,F}$ = 234, 22.2 Hz, C-2/C-6), 173.4 (dd, $J_{C,F}$ = 252, 14.6 Hz, C-4′); ^{19}F NMR (376 MHz, acetone-d_6): δ = −100.3 (m_c, 1F, 4′-F), −73.6 (s, 2F, 2-F), −66.6 (d, $J_{F,F}$ = 22.9 Hz, 1F, 6′-F); IR (ATR): $\tilde{\nu}$ = 3100 (=C−H), 2925–2815 (C−H), 1620–1510 (C=C, C=N), 1450, 1265, 1170, 1150, 1120 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 315.1239, calcd. for $C_{14}H_{14}F_4N_4$: 315.1227 $[M+H]^+$, m/z = 337.1061, calcd. for $[M+Na]^+$: 337.1047; anal. calcd. (%) for $C_{14}H_{14}F_4N_4$ (314.3): C 53.50, H 4.49, N 17.83; found: C 53.43, H 4.49, N 17.78.

26: mp 188–189 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 3.08 (s, 6H, CH_3), 3.82 (s, 4H, CH_2), 6.14 (m_c, 4H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 39.2 (q, CH_3), 49.8 (t, CH_2), 88.3 (dd, $J_{C,F}$ = 45.5 Hz, C-3/C-5), 161.5 (t, $J_{C,F}$ = 12.2 Hz, C-4), 164.4 (dd, $J_{C,F}$ = 234, 21.9 Hz, C-2); ^{19}F NMR (376 MHz, acetone-d_6): δ = −73.2 (s, 4F, 2-F); IR (ATR): $\tilde{\nu}$ = 3100 (=C−H), 2925–2855 (C−H), 1735–1520 (C=C, C=N), 1440, 1240, 1170 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 315.1201, calcd. for $C_{14}H_{14}F_4N_4$: 315.1227 $[M+H]^+$, m/z = 337.1023, calcd. for $[M+Na]^+$: 337.1047; calcd. (%) for $C_{14}H_{14}F_4N_4$ (314.3): C 53.50, H 4.49, N 17.83; found: C 53.31, H 4.49, N 17.60.

***rac-trans*-*N,N′*-Dimethyl-*N,N′*-bis(4,6-difluoropyridin-2-yl)cyclohexane-1,2-diamine (27), *rac-trans*-*N,N′*-dimethyl-*N*-(2,6-difluoropyridin-4-yl)-*N′*-(4,6-difluoropyridin-2-yl)cyclohexane-1,2-diamine (29) and *rac-trans*-*N,N′*-dimethyl-*N,N′*-bis(2,6-difluoropyridin-4-yl)cyclohexane-1,2-diamine (31):** According to **GP1**, *rac-trans*-**18** (1.12 g, 7.85 mmol) and Et_3N (4.41 mL, 31.4 mmol, 4 equiv.) were dissolved in THF (100 mL). A solution of **2** (4.18 g, 31.4 mmol, 4 equiv.) in THF (5 mL) was added and the mixture was refluxed for 72 h. Work-up and FLC (hexanes/EtOAc 15:1, 10:1, 5:1) afforded **27** (yield: 0.358 g, 12%), **29** (yield: 0.202 g, 7%) and **31** (0.026 g, 1%) as colorless solids.

27: mp 74–76 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.47 (m_c, 2H, CH_2), 1.77–1.83 (m, 6H, CH_2), 2.75 (s, 6H, CH_3), 4.81 (br s, 2H, CH), 5.97 (m_c, 2H, 3-H/5-H), 6.09 (m_c, 2H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 25.3 (t, CH_2), 30.0 (t, CH_2), 31.0 (q, CH_3), 56.0 (d, CH), 84.2 (ddd, $J_{C,F}$ = 43.9, 25.2 Hz, C-3/C-5), 89.0 (ddd, $J_{C,F}$ = 23.9, 5.5 Hz, C-3/C-5), 159.8 (dd, $J_{C,F}$ = 20.7, 14.4 Hz, C-2), 164.3 (dd, $J_{C,F}$ = 231, 18.0 Hz, C-6), 173.5 (dd, $J_{C,F}$ = 253, 14.1 Hz, C-4); ^{19}F NMR (376 MHz, acetone-d_6): δ = −100.5 (m_c, 2F, 4-F), −66.4 (d, $J_{F,F}$ = 23.2 Hz, 2F, 6-F); IR (ATR): $\tilde{\nu}$ = 3105 (=C−H), 2930, 2860, 2815 (C-H), 1625, 1565 (C=C, C=N), 1495, 1190, 1160, 1115 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 369.1699, calcd. for $C_{18}H_{20}F_4N_4$: 369.1697 $[M+H]^+$, m/z = 391.1516, calcd. for $[M+Na]^+$: 391.1516; anal. calcd. (%) for $C_{18}H_{20}F_4N_4$ (368.4): C 58.69, H 5.47, N 15.21; found: C 58.81, H 5.56, N 15.12.

29: mp 105–107 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.48–1.64 (m, 2H, CH_2), 1.74–1.90 (m, 6H, CH_2), 2.77, 2.79 (2 s, 3 H each, CH_3), 4.22, 4.87 (2 m_c, 1 H each, CH), 6.01 (m_c, 1H, 3′-H/5′-H), 6.15 (m_c, 1H, 3′-H/5′-H), 6.26 (br s, 2H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 25.4, 25.7, 29.7, 29.9 (4 t, CH_2), 32.3 (q, CH_3), 58.9 (d, CH), 84.5 (ddd, $J_{C,F}$ = 43.7, 25.2 Hz, C-3′/C-5′), 88.2 (m_c, C-3/C-5), 90.0 (ddd, $J_{C,F}$ = 24.0, 5.3 Hz, C-3′/C-5′), 159.6 (dd, $J_{C,F}$ = 20.7, 14.3 Hz, C-2′), 162.0 (t, $J_{C,F}$ = 12.2 Hz, C-4), 164.3 (dd, $J_{C,F}$ = 231, 17.9 Hz, C-6′), 164.5 (dd, $J_{C,F}$ = 233, 21.9 Hz, C-2/C-6), 173.5 (dd, $J_{C,F}$ = 253, 14.1 Hz, C-4′); ^{19}F NMR (376 MHz, acetone-d_6): δ = −100.3 (m_c, 1 F, 4′-F), −73.7 (m_c, 2F, 2-F), −66.4 (d, $J_{F,F}$ = 22.9 Hz, 1 F, 6′-F); IR (ATR): $\tilde{\nu}$ = 2935, 2860 (C−H), 1620, 1570, 1545 (C=C, C=N), 1495, 1240 1190, 1120 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 369.1699, calcd. for $C_{18}H_{20}F_4N_4$: 369.1697 $[M+H]^+$, m/z = 391.1524, calcd. for $[M+Na]^+$: 391.1516; anal. calcd. (%) for $C_{18}H_{20}F_4N_4$ (368.4): C 58.69, H 5.47, N 15.21; found: C 58.74, H 5.64, N 15.09.

31: mp 196–197 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.59–1.69 (m, 2H, CH_2), 1.82–1.87 (m, 6H, CH_2), 2.80 (s, 6H, CH_3), 4.27 (m_c, 2H, CH), 6.31 (s, 4H, 3-H/5-H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 25.2 (t, CH_2), 29.5 (t, CH_2), 32.1 (q, CH_3), 59.1 (d, CH), 88.3 (m_c, C-3/C-5), 161.9 (t, $J_{C,F}$ = 12.2 Hz, C-4), 164.5 (dd, $J_{C,F}$ = 233, 21.9 Hz, C-2); ^{19}F NMR (376 MHz, acetone-d_6): δ = −73.4 (s, 4F, 2-F); IR (ATR): $\tilde{\nu}$ = 3085 (=C−H), 2930, 2860 (C−H), 1635, 1545, 1510 (C=C, C=N), 1445, 1220, 1190, 1130 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 369.1699, calcd. for $C_{18}H_{20}F_4N_4$: 369.1697 $[M+H]^+$, m/z = 391.1521, calcd. for $[M+Na]^+$: 391.1516.

***rac-trans*- or (*R,R*)-*N,N′*-Bis(4,6-difluoropyridin-2-yl)cyclohexane-1,2-diamine (28), *rac-trans*- or (*R,R*)-*N*-(2,6-difluoropyridin-4-yl)-*N′*-(4,6-difluoropyridin-2-yl)cyclohexane-1,2-diamine (30) and *rac-trans*- or (*R,R*)-*N,N′*-bis(2,6-difluoro-pyridin-4-yl)cyclohexane-1,2-diamine (32):** According to **GP1**, *rac-trans*-**12** (0.500 g, 4.38 mmol) and Et_3N (2.45 mL, 17.5 mmol, 4 equiv.) were dissolved in THF (10 mL). A solution of **2** (2.33 g, 17.5 mmol, 4 equiv.) in THF (5 mL) was added and the resulting mixture was stirred for 36 h under reflux. Work-up and FLC (hexanes/EtOAc 6:1, 4:1, 1:1) afforded **28** (yield: 0.200 g, 13%), **30** (yield: 0.616 g, 41%) and **32** (yield: 0.370 g, 25%) as colorless solids.

The experiment was also performed with (*R,R*)-**12** to give the enantiopure products in almost identical yields: 13% for **28**, 45% for **30** and 30% for **32**.

28: mp 141–143 °C [147–149 °C for the *R,R*-isomer, $[\alpha]_D^{20}$: +68.5 (c = 1.04, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.35 (m, 2H, CH_2), 1.36–1.43 (m, 2H, CH_2), 1.77 (m_c, 2H, CH_2), 2.14 (m_c, 2H, CH_2), 3.55 (m_c, 2H, CH), 5.68 (m_c, 2H, 3-H/5-H), 5.81 (m_c, 2H, 3-H/5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6 (t, CH_2), 32.6 (t, CH_2), 55.7 (d, CH), 85.0 (ddd, $J_{C,F}$ = 41.7, 24.9 Hz, C-3/C-5), 90.1 (m_c, C-3/C-5), 158.6 (ddd, $J_{C,F}$ = 20.7, 14.2 Hz, C-2), 164.1 (ddd, $J_{C,F}$ = 235, 17.2 Hz, C-6), 172.2 (ddd, $J_{C,F}$ = 256, 14.0 Hz, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −98.7 (m_c, 2F, 4-F), −66.8 (m_c, 2F, 6-F); HR-MS (ESI-TOF): m/z = 341.1384, calcd. for $C_{16}H_{16}F_4N_4$: 341.1389 $[M+H]^+$.

30: mp 137–139 °C [131–133 °C for the *R,R*-isomer, $[\alpha]_D^{20}$: +135.4 (c = 1.04, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.47 (m, 4H, CH_2), 1.77–1.86 (m, 2H, CH_2), 2.08 (m_c, 1H, CH_2), 2.19 (m_c, 1H, CH_2), 3.12 (dt, J = 10.0, 8.6 Hz, 1H, CH), 3.89 (dt, J = 10.0, 8.9 Hz, 1H, CH), 4.75 (m_c, 1H, NH), 5.74 (s, 2H, 3-H/5-H), 5.91 (m_c, 2H, 3′-H/5′-H), 6.02 (m_c,

1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1 (t, CH_2), 24.9 (t, CH_2), 31.6 (t, CH_2), 32.9 (t, CH_2), 54.1 (d, CH), 59.6 (d, CH), 86.0 (ddd, $J_{C,F}$ = 41.7, 24.9 Hz, C-3′/C-5′), 87.8 (m_c, C-3/C-5), 91.7 (ddd, $J_{C,F}$ = 22.4, 5.6 Hz, C-3′/C-5′), 158.6 (ddd, $J_{C,F}$ = 19.9, 14.3 Hz, C-2′), 159.7 (ddd, $J_{C,F}$ = 11.9 Hz, C-4), 163.4 (ddd, $J_{C,F}$ = 237, 20.3 Hz, C-2/C-6), 164.1 (ddd, $J_{C,F}$ = 236, 17.1 Hz, C-6′), 172.1 (ddd, $J_{C,F}$ = 257, 13.9 Hz, C-4′); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −98.2 (m_c, 1F, 4′-F), −71.2 (s, 2F, 2-F), −66.8 (m_c, 1F, 6′-F); HR-MS (ESI-TOF): *m/z* = 341.1382, calcd. for $C_{16}H_{16}F_4N_4$: 341.1389 $[M+H]^+$.

32: mp 259–261 °C [250–252 °C for *R,R*-isomer, $[\alpha]_D^{20}$: +89.2 (*c* = 0.60, MeOH]; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.36–1.55 (m, 4H, CH_2), 1.76 (m_c, 2H, CH_2), 2.06–2.12 (m, 2H, CH_2), 3.54 (m_c, 2H, CH), 6.04 (s, 4H, 3-H/5-H), 6.56 (br s, 2H, NH); ^{13}C NMR (125 MHz, acetone-d_6): δ = 24.4 (t, CH_2), 32.1 (t, CH_2), 56.5 (d, CH), 87.4 (m_c, C-3/C-5), 160.9 (ddt, $J_{C,F}$ = 12.1 Hz, C-4), 163.3 (dd, $J_{C,F}$ = 233, 20.8 Hz, C-2); ^{19}F NMR (376 MHz, acetone-d_6): δ = −73.8 (s, 4F, 2-F); HR-MS (ESI-TOF): *m/z* = 341.1380, calcd. for $C_{16}H_{16}F_4N_4$: 341.1389 $[M+H]^+$.

2,3,5-Trifluoro-4-morpholinylpyridine (34): According to **GP2**, 2,3,5,6-tetrafluoro-4-morpholinylpyridine (**6**) (0.470 g, 2.00 mmol) and hydrazine monohydrate (2.00 g, 40.0 mmol, 20 equiv.) were dissolved in ethanol (12 mL) and stirred for 3 h under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (75 mL) and washed with water (2 × 50 mL). The organic phase was dried and concentrated to give crude **33** as a yellow solid; yield: 0.469 g (94%). The crude product **33** (0.124 g, 0.50 mmol) was suspended in water (1 mL) and a solution of $CuSO_4 \cdot 5H_2O$ (0.81 g, 3.25 mmol, 6.5 equiv.) in water (5 mL) was added drop-wise. The resulting mixture was heated to reflux for 1 h. Purification by FLC (hexanes/EtOAc 2:1) gave pyridine **34** as a colorless solid; yield: 90 mg (78% over 2 steps); mp 33–34 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.43 (m_c, 4H, CH_2N), 3.80 (m_c, 4H, CH_2O), 7.66 (m_c, 1H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.5 (t, CH_2N), 67.1 (t, CH_2O), 128.2 (d, C-6), 137.7 (s, C-4), 149.8, 150.0 (2 s, C-2, C-3), 150.6 (s, C-5); ^{19}F NMR (471 MHz, $CDCl_3$): δ = −150.7 (m_c, 1F, 3-F), −139.4 (m_c, 1F, 5-F), −89.9 (m_c, 1F, 2-F); IR (ATR): $\tilde{\nu}$ = 2965–2860 (C−H), 1615, 1565, 1510 (C=C, C=N), 1450, 1255, 1180, 1120, 1100 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 219.0749, calcd. for $C_9H_9F_3N_2O$: 219.0749 $[M+H]^+$, *m/z* = 241.0575, calcd. for $[M+Na]^+$: 241.0559; anal. calcd. (%) for $C_9H_9F_3N_2O$ (218.2): C 49.55, H 4.16, N 12.84; found: C 49.44, H 4.22, N 12.95.

3,5-Difluoro-4-morpholinylpyridine (36): According to **GP2**, 2,3,5-trifluoro-4-morpholinylpyridine (**34**) (0.110 g, 0.50 mmol) and hydrazine monohydrate (1.00 g, 20.0 mmol, 40 equiv.) were dissolved in ethanol (7 mL) and stirred for 48 h under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL). The organic phase was dried and concentrated to give **35** as a red solid (yield: 93 mg). The crude product was suspended in water (10 mL) and the solution of $CuSO_4 \cdot 5H_2O$ (0.66 g, 2.63 mmol, 6.5 equiv.) in water (10 mL) was added drop-wise. The resulting mixture was heated to reflux for 1 h. Purification by FLC (hexanes/EtOAc 10:1) gave pyridine **36** as a colorless solid; yield: 35 mg (35% over 2 steps); mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.39 (m_c, 4H, CH_2N), 3.81 (m_c, 4H, CH_2O), 8.15 (s, 2H, 2-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 50.6 (t, CH_2N), 67.2 (t, CH_2O), 134.4 (s, C-4), 135.1 (d, C-2), 136.2 (s, C-3); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −137.8 (s, 2F, 3-F); IR (ATR): $\tilde{\nu}$ = 3030 (=C−H), 2955, 2920, 2855 (C−H), 1600, 1550, 1505 (C=C, C=N), 1450, 1250, 1150, 1115 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 201.0839, calcd. for $C_9H_{10}F_2N_2O$: 201.0834 $[M+H]^+$.

2-Fluoro-4-morpholinylpyridine (39): According to **GP2**, 2,6-difluoro-4-morpholinylpyridine (**9**) (0.100 g, 0.50 mmol) and hydrazine monohydrate (0.500 g, 10.0 mmol, 20 equiv.) were dissolved in ethanol (7 mL) and stirred for 4 h under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL). The organic phase was dried and concentrated to give **38** as a yellow solid; yield: 84 mg (79%). The crude product **38** (53 mg, 0.25 mmol) was suspended in water (1 mL) and the solution of $CuSO_4 \cdot 5H_2O$ (0.41 g, 1.62 mmol, 6.5 equiv.) in water (10 mL) was added drop-wise. The resulting mixture was heated to reflux for 1 h. Purification by FLC (hexanes/EtOAc 2:1, 1:1) furnished pyridine **39** as a colorless solid; yield: 15 mg (33%, 26% over 2 steps); mp 153–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.29 (m_c, 4H, CH_2N), 3.82 (m_c, 4H, CH_2O), 6.18 (d, *J* = 1.4 Hz, 1H, 3-H), 6.54 (m_c, 1H, 5-H), 7.90 (d, *J* = 6.1 Hz, 1H, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.4 (t, CH_2N), 66.3 (t, CH_2O), 92.1 (d, C-3), 106.5 (d, C-5), 147.8 (d, C-6), 159.4 (s, C-4), 165.9 (s, C-2); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −68.9 (s, 1F, 2-F); IR (ATR): $\tilde{\nu}$ = 3110, 3020 (=C−H), 2975, 2960, 2925, 2860 (C−H), 1610, 1550, 1505 (C=C, C=N), 1450, 1195, 1120 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 183.0924, calcd. for $C_9H_{11}FN_2O$: 183.0928 $[M+H]^+$, *m/z* = 205.0741, calcd. for $[M+Na]^+$: 205.0748, *m/z* = 221.0491, calcd. for $[M+K]^+$: 221.0487, *m/z* = 387.1590, calcd. for $[2M+Na]^+$: 387.1603; anal. calcd. (%) for $C_9H_{11}FN_2O$ (182.2): C 59.33, H 6.09, N 15.38; found: C 59.34, H 5.92, N 15.22.

***N,N′*-Dimethyl-*N,N′*-bis(2,3,5-trifluoropyridine-4-yl)-ethane-1,2-diamine (41):** According to **GP2**, pyridine derivative **23** (0.193 g, 0.50 mmol) and hydrazine monohydrate (1.00 g, 20.0 mmol, 40 equiv.) were dissolved in ethanol (10 mL) and stirred for 3 h under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL). The organic phase was dried and concentrated to give **40** as a yellow solid; yield: 203 mg. The crude product **40** (0.183 g, 0.45 mmol) was suspended in water (1 mL) and a solution of $CuSO_4 \cdot 5H_2O$ (1.45 g, 5.80 mmol, 13 equiv.) in water (16 mL) was added drop-wise. The resulting mixture was refluxed for 1 h. Purification by FLC (hexanes/EtOAc 10:1) provided pyridine **41** as a yellow solid; yield: 68 mg (44% over 2 steps); mp 113–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.15 (t, *J* = 3.3 Hz, 6H, CH_3), 3.64 (s, 4H, CH_2), 7.61 (m_c, 2H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.8 (q, CH_3), 52.5 (t, CH_2), 128.1 (d, C-6), 137.1 (s, C-2), 137.3 (s, C-4), 150.0 (s, C-5), 169.4 (s, C-3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −153.5 (m_c, 2F, 3-F), −142.0 (m_c, 2F, 5-F), −92.3 (m_c, 2F, 2-F); IR (ATR): $\tilde{\nu}$ = 3015–2835 (C−H), 1610, 1560, 1525 (C=C, C=N), 1455, 1240, 1215, 1110 (C−F) cm^{-1}; HR-MS (ESI-TOF): *m/z* = 351.1046, calcd. for $C_{14}H_{12}F_6N_4$: 351.1039 $[M+H]^+$, *m/z* = 373.0866, calcd. for $[M+Na]^+$: 373.0858; anal. calcd. (%) for $C_{14}H_{12}F_6N_4$ (350.3): C 48.01, H 3.45, N 16.00; found: C 40.08, H 3.44, N 16.11.

***rac-trans*-*N,N′*-Dimethyl-*N,N′*-bis(2,3,5-trifluoropyridine-4-yl)cyclohexane-1,2-diamine (43):** According to **GP2**, pyri-

dine derivative *rac*-**19** (0.220 g, 0.50 mmol) and hydrazine monohydrate (1.00 g, 20.0 mmol, 40 equiv.) were dissolved in ethanol (10 mL) and stirred for 3 h under reflux. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (2×75 mL). The organic phase was dried and concentrated to give **42** as a yellow solid; yield: 230 mg. The crude product **42** (0.205 g, 0.44 mmol) was suspended in water (1 mL) and a solution of $CuSO_4{\cdot}5H_2O$ (1.43 g, 5.74 mmol, 13 equiv.) in water (20 mL) was added drop-wise. The resulting mixture was heated to reflux for 1 h. Purification by FLC (hexanes/EtOAc 15:1) provided pyridine **43** as a colorless solid; yield: 100 mg (50% over two steps); mp 118–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.35$ (m_c, 2H, CH_2), 1.65–1.74 (m, 2H, CH_2), 1.83–1.89 (m, 2H, CH_2), 2.08–2.11 (m, 2H, CH_2), 2.70 (t, J = 3.1 Hz, 6H, CH_3), 3.58–3.60 (m, 2H, CH), 7.64 (m_c, 2H, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.3$ (t, CH_2), 30.2 (t, CH_2), 33.3 (q, CH_3), 61.7 (d, CH), 128.3 (d, C-6), 136.9 (s, C-2), 138.5 (s, C-4), 150.1 (s, C-3), 151.1 (s, C-5); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -150.6$ (m_c, 2F, 3-F), −139.1 (m_c, 2F, 5-F), −90.5 (m_c, 2F, 2-F); IR (ATR): $\tilde{\nu}$ = 2940–2830 (C−H), 1610, 1515 (C=C, C=N), 1455, 1250, 1210, 1140 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 405.1523, calcd. for $C_{18}H_{18}F_6N_4$: 405.1508 $[M+H]^+$, m/z = 427.1347, calcd. for $[M+Na]^+$: 427.1328; anal. calcd. (%) for $C_{18}H_{18}F_6N_4$ (404.4): C 53.47, H 4.49, N 13.86; found: C 53.33, H 4.40, N 13.72.

3,5-Difluoro-4-morpholinopyridine (36): According to **GP3**, 2,3,5,6-tetrafluoro-4-morpholinopyridine (**6**) (50 mg, 0.21 mmol), titanocene difluoride (7 mg, 0.032 mmol, 15 mol%), diphenylsilane (0.235 mL, 1.27 mmol, 6 equiv.) and dry 1,4-dioxane (2 mL) were stirred for 18 h at 110 °C. The product was isolated after FLC (hexanes/ethyl acetate 4:1, 1:1) as a colorless solid; yield: 40 mg (95%); mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.39$ (m_c, 4H, CH_2N), 3.81 (m_c, 4H, CH_2O), 8.15 (s, 2H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 50.6$ (t, CH_2N), 67.2 (t, CH_2O), 134.4 (s, C-4), 135.1 (d, C-2), 136.2 (s, C-3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -137.8$ (s, 2F, 3-F); IR (ATR): $\tilde{\nu}$ = 3030 (=C−H), 2955, 2920, 2855 (C−H), 1600, 1550, 1505 (C=C, C=N), 1450, 1250, 1150, 1115 (C−F) cm^{-1}; MS (ESI-TOF): m/z = 201.0839, calcd. for $C_9H_{10}F_2N_2O$: 201.0834 $[M+H]^+$.

4-Morpholinopyridine (44): According to **GP3**, 2,6-difluoro-4-morpholinopyridine (**9**) (100 mg, 0.50 mmol), titanocene difluoride (16 mg, 0.08 mmol, 15 mol%), diphenylsilane (0.28 mL, 1.50 mmol, 3 equiv.) and dry 1,4-dioxane (2 mL) were stirred for 18 h at 110 °C. Product **44** was isolated after FLC (CH_2Cl_2/MeOH 95:5) as a colorless solid; yield: 80 mg (98%); mp 105–107 °C (lit.[18] 112–115 °C). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 3.30$ (t, J = 8.1 Hz, 4H, CH_2N), 3.77 (t, J = 8.1 Hz, 4H, CH_2O), 6.81 (d, $J \approx 6$ Hz, 2H, 3-H), 8.13 (d, $J \approx 6$ Hz, 2H, 2-H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 45.7$ (t, CH_2N), 66.1 (t, CH_2O), 108.1 (d, C-3), 148.8 (d, C-2), 155.9 (s, C-4); IR (ATR): $\tilde{\nu}$ = 3025 (=C−H), 2965–2880 (C−H), 1600–1535 (C=C, C=N), 1450, 1365, 1235, cm^{-1}; HR-MS (ESI-TOF): m/z = 165.1034, calcd. for $C_9H_{13}N_2O$: 165.1028 $[M+H]^+$.

***N,N′*-Dimethyl-*N,N′*-bis(3,5-difluoropyridin-4-yl)ethane-1,2-diamine (45):** According to **GP3**, *N,N′*-dimethyl-*N,N′*-bis(2,3,5,6-tetrafluoropyridin-4-yl)ethane-1,2-diamine (**23**) (250 mg, 0.65 mmol), titanocene difluoride (43 mg, 0.20 mmol, 30 mol%), diphenylsilane (0.73 mL, 3.90 mmol, 6 equiv.) and dry 1,4-dioxane (4 mL) were stirred for 18 h at 110 °C. Product **45** was isolated after FLC (hexanes/EtOAc 1:1) as a colorless solid; yield: 112 mg (55%); mp 146–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.04$ (t, J = 2.9 Hz, 6H, CH_3), 3.53 (s, 4H, CH_2), 8.04 (s, 4H, 2-H, 6-H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 40.8$ (q, CH_3), 52.5 (t, CH_2), 134.3 (s, C-4), 134.9 (d, C-2), 152.1 (s, C-3); ^{19}F NMR ($CDCl_3$, 376 MHz): $\delta = -138.3$ (s, 4F, 3-F); IR (ATR): $\tilde{\nu}$ = 3010 (=C−H), 2920, 2850 (C−H), 1600, 1525 (C=C, C=N), 1460, 1225, 1190, 1150 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 315.1226, calcd. for $C_{14}H_{14}F_4N_4$: 315.1227 $[M+H]^+$.

***rac-trans*-*N,N′*-Dimethyl-*N,N′*-bis(3,5-difluoropyridin-4-yl)cyclohexane-1,2-diamine (46):** According to **GP3**, *rac*-**19** (600 mg, 1.36 mmol), titanocene difluoride (88 mg, 0.41 mmol, 30 mol%), diphenylsilane (1.51 mL, 8.16 mmol, 6 equiv.) and dry 1,4-dioxane (6 mL) were stirred for 18 h at 110 °C. Product **46** was isolated after FLC (hexanes/EtOAc 4:1) as a colorless solid; yield: 345 mg (69%); mp 134–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.33$ (m_c, 2H, CH_2), 1.62–1.71 (m, 2H, CH_2), 1.83–1.86 (m, 2H, CH_2), 2.08–2.11 (m, 2H, CH_2), 2.66 (t, J = 2.7 Hz, 6H, CH_3), 3.55 (m_c, 2H, CH), 8.08 (br s, 4H, 2-H, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.4$ (t, CH_2), 30.2 (t, CH_2), 33.4 (q, CH_3), 61.5 (d, CH), 134.8 (d, C-2), 135.4 (s, C-4), 152.0 (s, C-3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -137.5$ (s, 4 F, 3-F); IR (ATR): $\tilde{\nu}$ = 3055 (=C−H), 2925–2855 (C−H), 1600, 1515 (C=C, C=N), 1425, 1200, 1145, 1150 (C−F) cm^{-1}; HR-MS (ESI-TOF): m/z = 369.1693, calcd. for $C_{18}H_{21}F_4N_4$: 369.1697 $[M+H]^+$.

***N,N′*-Dimethyl-*N,N′*-bis(pyridin-4-yl)ethane-1,2-diamine (48):** According to **GP3**, *N,N′*-dimethyl-*N,N′*-bis(2,6-difluoropyridine-4-yl)ethane-1,2-diamine (**26**) (145 mg, 0.46 mmol), titanocene difluoride (30 mg, 0.14 mmol, 30 mol%), diphenylsilane (0.51 mL, 2.76 mmol, 6 equiv.) and dry 1,4-dioxane (3 mL) were stirred for 24 h at 110 °C. Product **48** was isolated after FLC [CH_2Cl_2/MeOH/NH_3 in MeOH (7N), 95:5:2] as a colorless solid; yield: 99 mg (89%); mp 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (s, 6H, CH_3), 3.53 (s, 4H, CH_2), 6.43 (dd, J = 4.9, 1.6 Hz, 4H, 3-H), 8.21 (dd, J = 4.9, 1.6 Hz, 4H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 38.2$ (q, CH_3), 48.6 (t, CH_2), 106.5 (d, C-3), 150.3 (d, C-2), 153.1 (s, C-4); IR (ATR): $\tilde{\nu}$ = 3090–3030 (=C−H), 2990, 2805 (C−H), 1605, 1520 (C=C, C=N) cm^{-1}; HR-MS (ESI-TOF): m/z = 243.1604, calcd. for $C_{14}H_{18}N_4$: 243.1610 $[M+H]^+$; anal. calcd. (%) for $C_{14}H_{18}N_4$ (242.2): C 65.73, H 7.68, N 21.90; found: C 65.72, H 7.72, N 22.08.

***rac-trans*-*N,N′*-Bis(pyridin-4-yl)cyclohexane-1,2-diamine (49):** According to **GP3**, *rac-trans*-*N,N′*-bis(2,6-difluoropyridin-4-yl)cyclohexane-1,2-diamine (**32**) (50 mg, 0.15 mmol), titanocene difluoride (10 mg, 0.04 mmol, 30 mol%), diphenylsilane (0.163 mL, 0.88 mmol, 6 equiv.) and dry 1,4-dioxane (2 mL) were stirred for 20 h at 110 °C. Product **49** was isolated after FLC [EtOAc/MeOH/NH_3 in MeOH (7N), 95:5:2] and HPLC (RP, MeOH/H_2O, 70:30) as a colorless solid; yield: 33 mg (83%); mp 293–295 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.30–1.45 (m, 4H, CH_2), 1.79 (m_c, 2H, CH_2), 2.05 (m_c, 2H, CH_2), 3.34–3.41 (m, 2H, CH), 6.44 (d, J = 5.8 Hz, 4H, 3-H), 7.82 (d, J = 4.7 Hz, 4H, 2-H); ^{13}C NMR (101 MHz, CD_3OD): $\delta = 25.9$ (t, CH_2), 33.3 (t, CH_2), 57.1 (d, CH), 108.5 (d, C-3), 149.2 (d, C-2), 155.8 (s, C-4); HR-MS (ESI-TOF): m/z = 269.1770, calcd. for $C_{17}H_{21}N_4$: 269.1761 $[M+H]^+$.

3a,7a-*rac-trans*-1,3-Bis(2,6-difluoropyridin-4-yl)octahydro-1*H*-benzo[*d*]imidazole (*rac*-50): To a stirred solution of compound *rac*-**32** (70 mg, 0.206 mmol) in formaldehyde (1.8 mL of a 37% w/v solution in water, 20.6 mmol, 100 equiv.), formic acid (63 mg, 1.36 mmol, 6.7 equiv.) was added and the resulting mixture was heated to reflux for 24 h. The reaction was quenched by water (30 mL) and extracted with CH_2Cl_2 (3×50 mL). The product *rac*-**50** was obtained after FLC (hexanes/EtOAc 3:1) as a colorless solid; yield: 51 mg (70%); mp 192–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.67 (m, 4H, CH_2), 2.02 (m_c, 2H, CH_2), 2.64 (m_c, 2H, CH_2), 3.34 (m_c, 2H, CH), 4.75 (s, 2H, N-CH_2-N), 6.15 (s, 4H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.0 (t, CH_2), 30.0 (t, CH_2), 65.9 (d, CH), 70.7 (t, CH_2), 91.6 (m_c, C-3), 159.2 (dd, J = 11.1 Hz, C-4), 162.9 (dd, J = 240, 20.0 Hz, C-2); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −68.9 (s, 4F, 2-F); MS (ESI-TOF): m/z = 375.1208, calcd. for $C_{17}H_{16}F_4N_4Na$: 375.1209 $[M+Na]^+$.

(*R,R*)-*trans*-*N,N*′-Dimethyl-*N,N*′-bis(2,6-difluoropyridin-4-yl)cyclohexane-1,2-diamine (31): Enantiopure (*R,R*)-*trans*-*N,N*′-bis(2,6-difluoropyridin-4-yl)cyclohexane-1,2-diamine (**32**) (320 mg, 0.94 mmol) was dissolved in THF (10 mL) and NaH (228 mg, 6.65 mmol, 70% in mineral oil, 7 equiv.) was added at room temperature and the resulting mixture was stirred for 30 min. Then, methyl iodide (820 mg, 5.78 mmol, 6 equiv.) was added drop-wise and the resulting mixture was stirred for 48 h. The reaction was quenched by careful water addition and extraction (3×50 mL, CH_2Cl_2) and chromatographic purification (hexanes/EtOAc, 6:1) gave the product (*R,R*)-**31**; yield: 295 mg (85%); mp 201–203 °C; $[\alpha]_D^{20}$: +105.7 (c = 1.4, $CHCl_3$).

3a,7a-*rac-trans*-1,3-Bis(pyridin-4-yl)octahydro-1*H*-benzo-[*d*]imidazole (51): According to **GP3**, compound *rac*-**50** (30 mg, 0.085 mmol), titanocene difluoride (4 mg, 0.02 mmol, 20 mol%), diphenylsilane (0.094 mL, 0.51 mmol, 6 equiv.) and dry 1,4-dioxane (2 mL) were stirred for 48 h at 110 °C. Product **51** was isolated after FLC [EtOAc/NH_3 in MeOH (7N), 95:5] as a slightly yellow solid; yield: 22 mg (92%); mp 216–218 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.52 (m_c, 4H, CH_2), 1.97 (m_c, 2H, CH_2), 2.64 (m_c, 2H, CH_2), 3.25 (m_c, 2H, CH), 4.73 (s, 2H, N-CH_2-N), 6.66 (d, J = 4.6 Hz, 4H, 3-H), 8.33 (d, J = 4.4 Hz, 4H, 2-H); ^{13}C NMR (101 MHz, CD_3OD): δ = 24.3 (t, CH_2), 30.3 (t, CH_2), 65.6 (d, CH), 71.6 (t, CH_2), 101.8 (d, C-3), 150.2 (d, C-2), 153.2 (s, C-4); HR-MS (ESI-TOF): m/z = 281.1766, calcd. for $C_{17}H_{21}N_4$: 281.1761 $[M+H]^+$.

(*R,R*)-*trans*-*N,N*′-Dimethyl-*N,N*′-bis(pyridin-4-yl)cyclohexane-1,2-diamine (52): According to **GP3**, (*R,R*)-*N,N*′-dimethyl-*N,N*′-bis(2,6-difluoropyridin-4-yl)cyclohexane-1,2-diamine (**31**) (24 mg, 0.065 mmol), titanocene difluoride (5 mg, 0.02 mmol, 30 mol%), diphenylsilane (0.073 mL, 0.39 mmol, 6 equiv.) and dry 1,4-dioxane (2 mL) were stirred for 24 h at 110 °C. Product **52** was isolated after FLC [CH_2Cl_2/MeOH/NH_3 in MeOH (7N), 95:5:2] as a slightly yellow solid; yield: 18 mg (95%); mp 269–271 °C; $[\alpha]_D^{20}$: +157.3 (c = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42–1.48 (m, 2H, CH_2), 1.56–1.62 (m, 2H, CH_2), 1.89–1.94 (m, 4H, CH_2), 2.59 (s, 6H, CH_3), 3.83 (dd, J = 5.8, 3.1 Hz, 2H, CH), 6.49 (d, $J \approx 6$ Hz 4H, 3-H), 8.20 (d, $J \approx 6$ Hz, 4H, 2-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.2 (t, CH_2), 29.2 (t, CH_2), 30.5 (q, CH_3), 58.0 (d, CH), 106.7 (d, C-3), 150.1 (d, C-2), 153.7 (s, C-4); HR-MS (ESI-TOF): m/z = 297.2082, calcd. for $C_{18}H_{24}N_4$: 297.2079 $[M+H]^+$.

Copies of NMR spectra of all compounds can be found in the Supporting Information.

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