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Regioselective synthesis and metallation of fluoroiodopyrazines. Application to the synthesis of aryl and alkylbenzylpyrazines. Diazines. Part 31

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Abstract—The regioselective metallation of 2-fluoropyrazine allowed the synthesis of various 5- and 6-iodofluoropyrazines. Use of cross-coupling reactions with iodofluoropyrazines under Suzuki or Negishi conditions led to aryl and alkylfluoropyrazines. The benzylfluoropyrazines have been used as building block to synthesize a wide range of arylbenzylfluoropyrazines which could exhibit mesomorphic properties. © 2002 Elsevier Science Ltd. All rights reserved.

The presence of a fluorine atom into a molecule is of particular interest because it makes considerable changes in its physical and chemical behavior. Thus, this access to fluorinated compounds is of special interest for applications as pharmaceuticals[1] or highly polarizable materials.[2] The fluorodiazines could be used as building blocks to synthesize such molecules. It has been recently reported that the two-ring architecture of phenylpyrimidines have interesting properties as liquid crystal devices.[3] Furthermore the introduction of fluorine atoms as lateral substituents improves the polarizability of the materials and ensures a low viscosity.[4]

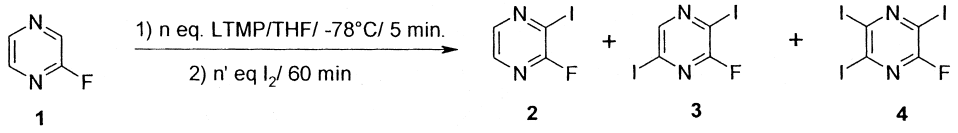
The fluorine atom has been previously used as an *ortho*-directing group in the metallation reaction of various π-deficient heterocycles such as pyridine,[5] quinoline,[6] pyrimidine[7] and more recently with pyrazine.[8] We report here the regioselective synthesis of various iodofluoropyrazines.

The introduction of a second halogen atom such as iodine is of a great synthetic interest because it allows, using the palladium-catalyzed cross-coupling reactions, the synthesis of aryl or alkylpyrazines.

Previously the lithiation of fluoropyrazine **1** with stoichiometric amounts of LTMP and iodine used as the electrophile has been described[8] affording the 2-fluoro-3-iodopyrazine **2** as sole product. The lithiation of fluoropyrazine **1** has been reinvestigated using various equivalents of metallating agent and iodine (Scheme 1, Table 1).

With 1.1 equiv. of LTMP and 2 equiv. of iodine (entry 1), the 2-fluoro-3-iodopyrazine **2** was the major product. With 2.1 equiv. of LTMP and iodine a mixture of the three mono, di and triiodo derivatives **2**, **3**, **4** was obtained (entry 2). When LTMP and iodine were in large excess the triiodo compound **4** was obtained as the sole product (entry 3).

The structure of the diodo compound **3** could be assigned



Scheme 1.

Table 1. Lithiation and iodation of **1**

Entry	*n*	*n'*	**2** (%)	**3** (%)	**4** (%)
1	1.1	2	50	6	6
2	2.1	2	11	35	15
3	4	4	–	–	65

Keywords: metallation; fluoropyrazines; cross-coupling reactions.

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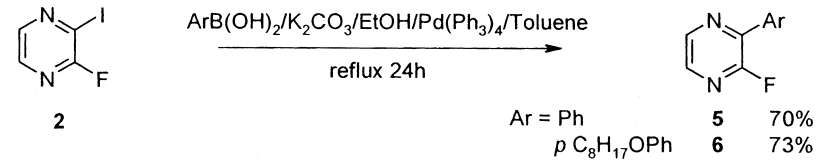
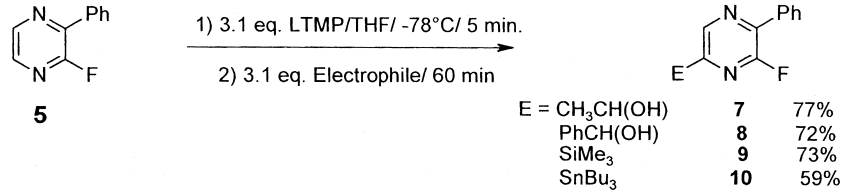


Scheme 2.



Scheme 3.

unambiguously thanks to the observed long-range hydrogen-fluorine constant (3.5 Hz).This value is in agreement with this previously given for fluoropyrazine by Jovanic,[9] who indicated a higher value for $^5J_{F-H5}$ (4.7 Hz) than $^4J_{F-H6}$ (1.4 Hz). This result allowed us to highlight that under these conditions the iodine atoms were at C_3 and C_6 position.

The palladium-catalyzed coupling reaction has been tested with **2** and phenylboronic acids under the Suzuki conditions (Scheme 2).

A further lithiation of compound **5** was achieved with 3 equiv. of LTMP followed by reaction with various electrophiles leading to trisubstituted pyrazines **7**–**10** (Scheme 3).

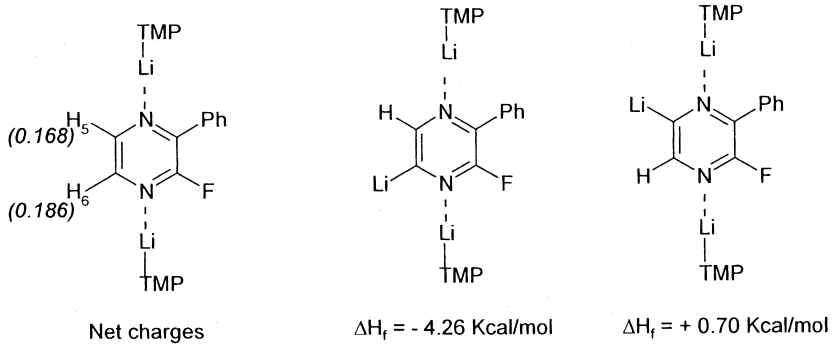
The structures of the compounds **7**–**10** have been assigned thanks to long-range hydrogen–fluorine coupling constant $^5J_{F-H5}$ (4.0–5.6 Hz) highlighting that the functionalization occurred exclusively at C_6 position.

It would be interesting to explain the regioselectivity of the metallation which occurred *ortho* to a nitrogen atom without assistance of an *ortho*-directed group. So some theoretical calculations using the Li/PM3 semi-empirical method have been performed.

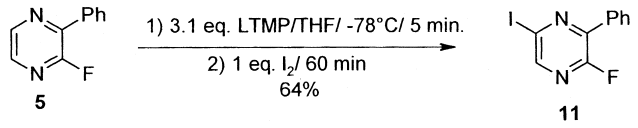
It could be assumed that first a complexation occurred between the lithium of the metallating agent (LTMP) and the two nitrogen atoms of the diazine moiety which behaves as a chelating agent through its nitrogen atoms. The site of deprotonation could be determined by the net charge of the two hydrogen atoms (Scheme 4). The net charges determined with PM3 for H_5 (0.168) and H_6 (0.186) indicated that this latter one was the more acidic, so the deprotonation could, under kinetic conditions, occur at this position. When the metallation is performed with alkylamides, the deprotonation is considered as thermodynamically controlled, then it could be assumed that the heats of formation of the lithio compounds could be examined in a simple approach for the regioselectivity. The heats of formation of the two lithio derivatives were determined with PM3; the 6-lithio derivative was found as the most stable (Scheme 4). This result could explain the total regioselectivity of the functionnalization at C_6.

However, when compound **5** is reacted with 3 equiv. of LTMP at −78°C for 5 min followed by reaction with 1 equiv. of iodine, a monoiodo derivative **11** was obtained in 64% yield beside traces of diiododerivative (Scheme 5).

The ^{1}H NMR spectrum of **11** showed a signal at 8.15 ppm with a coupling constant of 1.7 Hz which could be assigned to a $^4J_{F-H6}$ and so indicated a iodation at C_5. However, in order to determine unambiguously the site of iodation, a structure elucidation of compound **11** has been carried out



Scheme 4.



Scheme 5.

applying gradient enhancement HMBC sequence, using long-range $^{1}H-^{15}N$ heteronuclear coupling at natural abundance. This method has been previously used to determine the structure of quinazoline[10] derivatives and thiocarboxamidepyrazines.[11] The unequivocal ^{15}N assignment of compounds **1** and **5** was based on $^{2}J(^{1}H-^{15}N)$ interaction in proton-coupled nitrogen which was given in a range from 9.8 to 14.4 Hz in diazine series.[12] The ^{15}N spectrum of **1** (Scheme 6) exhibited two signals: a doublet at 290 ppm (^{2}J=10 Hz) assigned to N_1 and a triplet at 350 ppm with the same coupling constant for N_4. The ^{1}H NMR spectrum of **1** showed three signals at 8.09, 8.32 and 8.37 ppm, which have been allocated by applying a gradient HMBC pulse sequence with a long-range delay optimized for a coupling constant of 10 Hz. Correlations were observed between N_1 at 290 ppm and H_6 (8.09 ppm) and N_4 at 350 Hz and H_3 and H_5 (8.32 and 8.37 ppm). The ^{15}N spectrum of 2-fluoro-3-phenylpyrazine **5** presented two signals at 290 and 345 ppm assigned, respectively, to N_1 and N_4. The ^{1}H spectrum presented two signals at 8.16 and 8.60 ppm. The $^{1}H-^{15}N$ gradient HMBC spectrum showed correlation between N_1 at 290 and H_6 (8.16) and N_4 at 345 and H_5 (8.60). For the compound **11** the ^{15}N spectrum showed two signals at 300 and 322 ppm. The $^{1}H-^{15}N$ gradient HMBC spectrum exhibited a correlation between N_1 at 300 ppm and H_6 at 8.15. These results allowed us to determine unambiguously the structure of **11** as the 2-fluoro-3-phenyl-5-iodopyrazine (Scheme 6).

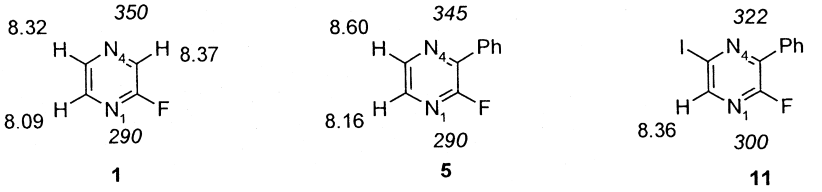
The unexpected iodination occurring at C_5, whereas the other electrophiles take place at C_6 urged us to reinvestigate the lithiation of **5** followed by reaction with iodine as the electrophile under various experimental conditions (Scheme 7, Table 2).

These results require some comments: with 1.1 equiv. of metallating agent and an excess of iodine, the 6-iodo derivative **12** was obtained in good yield (entry 1). An excess of LTMP and of iodine gave the diiodo derivative **13** as sole product in good yield (entries 3, 5). When the metallating agent was in excess in relation to iodine the 5-iodo derivative **11** was obtained as sole product (entries 2, 4 and 6).

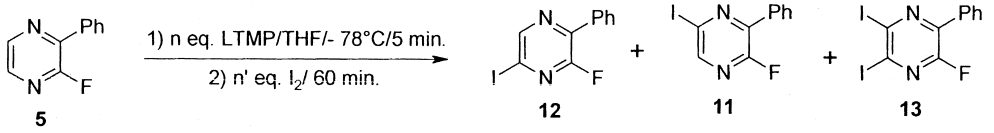
It could be assumed that the reaction of **5** with 1–4 equiv. of LTMP at −78°C led first to the 6-lithio derivative which reacted with iodine to give the 6-iodo derivative **12**. This compound underwent a further isomerization involving an iodine atom migration leading to the 5-iodo derivative **11**. Such isomerizations resulting from an halogen migration has been previously described with bromopyridines,[5f] iodopyridines[13] and iodopyrimidines,[14] it is known as a 'halogen-dance' mechanism which implies a halogen–lithium exchange.

To determine if such an exchange occurred, we have reacted the 6-iodo derivative **12** with 3.1 equiv. of LTMP at −78°C for 30 min followed by a reaction of hydrolysis with HCl in ethanol. Under theses conditions, the 5-iodo derivative **11** was obtained in 89% (Scheme 8).

When the diiodo derivative **13** was submitted to reaction with LTMP under similar conditions, followed by reaction either with HCl or with acetaldehyde, the compound **11** or



Scheme 6.



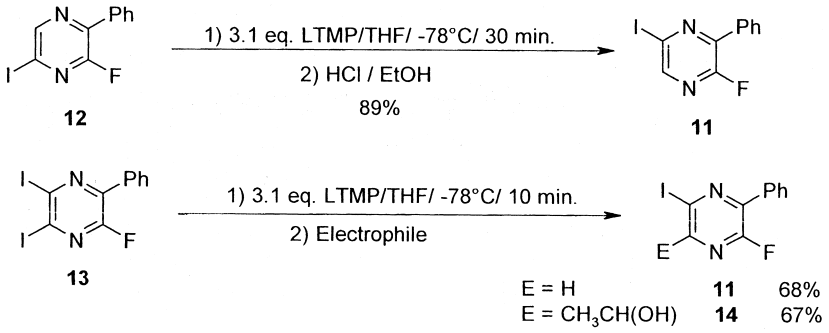
Scheme 7.

Table 2. Lithiation and iodation of **5**

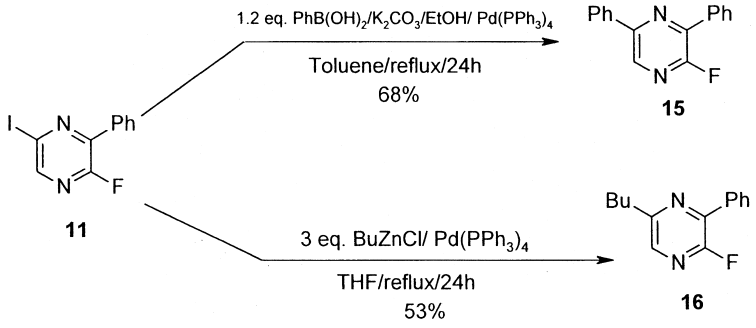
Entry	n	n'	**12** (%)	**11** (%)	**13** (%)
1	1.1	2.0	73	–	–
2	2.1	1.0	–	59	–
3	2.1	2.0	–	–	80
4	3.1	1.0	–	64	–
5	3.1	3	–	–	68
6	4.1	1.0	–	57	–

the secondary alcohol **14** were obtained in 67% yield. These results highlighted that the iodine–lithium exchange occurred exclusively at the C_6 position.

The compound **11** has been submitted to palladium-catalysed cross-coupling reaction with phenyl boronic acid under the Suzuki conditions and the butylzinc chloride under the Negishi conditions (Scheme 9).



Scheme 8.



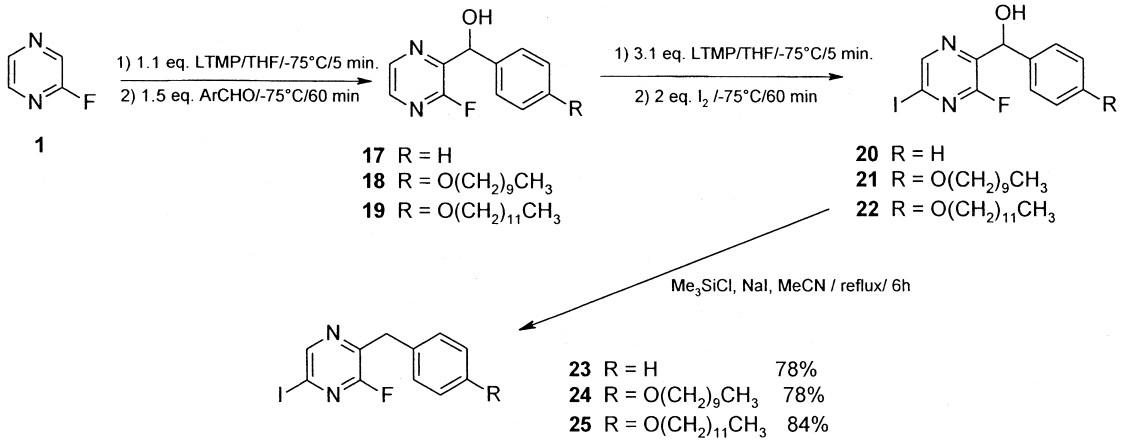
Scheme 9.

In a previous paper[8] we have reported that treatment of 2-fluoro-3-(phenylhydroxymethyl)pyrazine with LTMP at −78°C for a short reaction time (5 min), followed by reaction with iodine as the electrophile allowed the regioselective iodation at C_6 leading to 2-fluoro-6-iodo-3-(phenylhydroxymethyl)pyrazine.

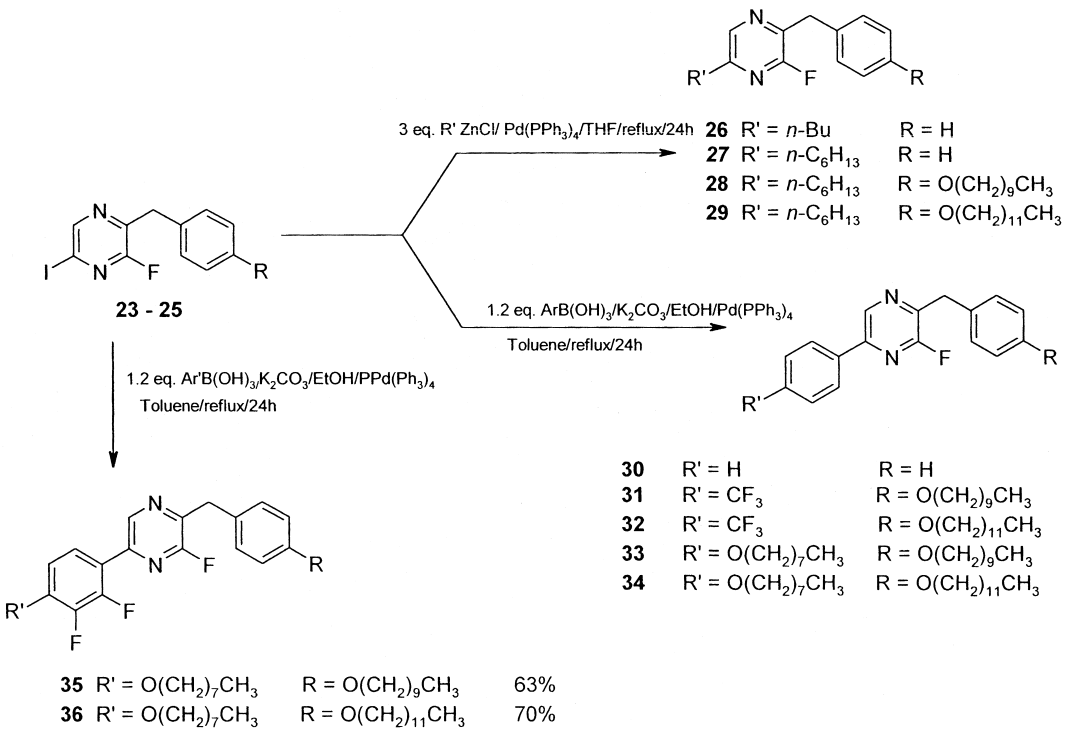
Using the fluoropyrazine as building block, we report here the synthesis of a range of 6-iodo-3-benzylpyrazines by the strategic use of metallation (Scheme 10).

Compounds, having conjugate aromatic units leading long terminal alkoxy chains are known to present optical anisotropy and so are used as liquid crystal devices. The main structural factors, which improve the mesomorphic properties have been recently reported. So it has been highlighted that the necessary polarity for molecular tilting is provided by an ether oxygen and by the heterocyclic nitrogens, so phenylpyrimidines have been described as efficient moieties. It has been hightlighted that use of lateral fluoro substituents provides the polarity for molecular tilting,[4,15] moreover two lateral fluoro substituents *ortho* to each other give better mesomorphic and physical properties.[16]

So we have developed a flexible route (Scheme 11) that allowed the synthesis of a wide structural range of compounds utilizing the 2-fluoro-6-iodo-3-benzylpyrazines **23**–**25** as starting materials. Introduction of alkyl group at the C_6 position was performed by a cross coupling reaction with alkylzinc chlorides under Negishi conditions leading to compounds **26**–**29** in good yields. Various arylboronics acids were reacted with the compounds **23**–**25** under Suzuki



Scheme 10.



Scheme 11.

conditions allowing synthesis of a wide range of 2-fluoro-3-benzyl-6-arylpyrazines **30**–**36**. Structural variations could be obtained by the choice of suitable arylboronic acids bearing alkoxy ether with terminal chains from different length or with trifluoromethyl group. Lithiation *ortho* to 1,2-difluoroaromatic unit has provided the route to 2,3-difluoroarylboronic acids which are implied in palladium-catalyzed cross-coupling reaction to give compounds **35** and **36** with two fluorine atoms as lateral substituents. The compounds **32**, **34** and **36** have been tested for mesomorphic properties.

Only the compound **36** with low melting point (60°C) has highlighted a mesophase at 65°C and an isotropic liquid at 70°C.

The skilled regioselective metallation of 2-fluoropyrazines allowed us to synthesize 5-and 6-iodo-2-fluoropyrazines which opened the route to a wide range of materials with lateral fluoro substituents, one of them have exhibited mesomorphic properties. The synthesis of various compounds with arylfluorodiazines as central building block and multiple lateral fluoro substituents to generate new liquid crystal materials with low melting points is in progress.

1. Experimental

Melting points were determined on a Kofler hot-stage. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in deuteriochloroform on Bruker instruments (AC 200 and Avance 300). Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin–Elmer FTIR 1650 spectrophotometer.

All reagents were of commercial quality and were purchased from Aldrich Chemical or Acros. Pd-catalysis $Pd(PPh_3)_4$ was prepared according to the literature.[17] 4-Trifluoromethyl- and 4-alcoxyphenylboronic acids were synthesized by halogen-metal exchange followed by reaction with trimethoxyborane from the commercially available 1-bromo-4-trifluoromethylbenzene or 1-bromo-4-methoxybenzene. The 2,3-difluoro-4-alcoxyphenylboronic acids were synthesized by *ortho*-lithiation of corresponding 1-alcoxy-2,3-difluorobenzenes with *n*-butyllithium followed by reaction with trimethoxyborane.

Fluoropyrazine **1** and 2-fluoro-3-iodopyrazine **2** were synthesized according the procedure described in the litterature.[4]

1.1. Procedure A for direct lithiation by lithium 2,2,6,6-tetramethylpiperidide

A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−50°C), stirred and anhydrous THF (15 mL) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (TMPH) was added. The mixture was warmed to 0°C. After 20 min, the mixture temperature was then carried to the temperature θ_1 and the pyrazine dissolved in 5 mL of THF added. After a time t_1 at θ_1, the electrophile was introduced and stirring was continued for a time t_2 at θ_2. Hydrolysis was then carried out at θ_2 using a solution of 35% aqueous hydrochloric acid, ethanol and THF (1/4/5) for θ_2=−78°C. At room temperature, the mixture was made slightly basic with saturated sodium hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorized with sodium thiosulphate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3×20 mL), the

combined organic extracts were then dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

1.2. Procedure B for cross-coupling of arylboronic acids with halodiazines under Suzuki conditions

A mixture of the halodiazine, the arylboronic acid (*n* equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aqueous 2 M potassium carbonate (2 equiv.) and ethanol (1 mL) in degassed toluene (15 mL) was heated under reflux under nitrogen for a time *t*. The reaction mixture was cooled, diluted with 20 mL of water and dichloromethane (1/1) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3×20 mL), the combined organic extracts were dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

1.3. Procedure C for cross-coupling of organozincic with idoopyrazines under Negishi conditions

A solution of alkyllithium in hexane was added to cold (−78°C), stirred and anhydrous THF (20 mL) under an atmosphere of dry argon. Then a solution of dry zinc chloride (9 equiv.) in dry THF (5 mL) was added. The mixture was warmed to room temperature, then $Pd(PPh_3)_4$ (5 mol%) and a solution of substituted iodopyrazine (1 equiv.) in THF (5 mL) were introduced. The mixture was heated under reflux under nitrogen for a time *t*. After cooling, an aqueous solution of EDTA (9 equiv.) was added, the solution mixture was made slightly basic with saturated sodium hydrogen carbonate solution. The reaction mixture was diluted with 20 mL of water and dichloromethane (1/1). The aqueous layer was extracted with dichloromethane (3×20 mL), the combined organic extracts were dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

1.4. Procedure D for reduction of the phenylcarbinol group into benzyl group

A mixture of trimethylsilyl chloride (6 equiv.) and sodium iodide (6 equiv.) in dry acetonitrile (10 mL) were stirred at room temperature for 5 min. Then a solution of phenylpyrazine carbinol (1 equiv.) in acetonitrile (5 mL) was introduced, the mixture was heated under reflux for a time *t*. The reaction mixture was cooled, diluted with 60 mL of water and dichloromethane (1/2), then the solution mixture was made slightly basic with saturated sodium hydrogen carbonate solution. The mixture was decolorized by treatment with sodium thiosulphate to eliminate excess of iodine. The aqueous layer was extracted with dichloromethane (3×20 mL), and the organic layer washed with water (20 mL).The combined organic extracts were dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

1.4.1. 2-Fluoro-3,6-diiodopyrazine (3). Metallation of **1** (200 mg, 2.04 mmol) according procedure A with *n*-BuLi 1.6 M (2.1 equiv., 2.66 mL), TMPH (2.2 equiv., 0.76 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 1.036 g), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/2)) 250 mg (35%) of **3** as a yellow solid, mp=148°C, ^{1}H NMR ($CDCl_3$): δ 8.58 (d, 1H, J_{H5-F}=3.7 Hz, H_5); ^{19}F NMR ($CDCl_3$): δ −72.38. Anal. calcd for $C_4HFI_2N_2$ (349.86): C, 13.73; H, 0.29; N, 8.01. Found: C, 13.5; H, 0.4; N, 8.2.

1.4.2. 2-Fluoro-3,5,6-triiodopyrazine (4). Metallation of **1** (200 mg, 2.04 mmol) according procedure A with *n*-BuLi 1.6 M (4.0 equiv., 5.10 mL), TMPH (4.1 equiv., 1.41 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (4 equiv., 2.072 g), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/2)) 631 mg (65%) of **4** as a yellow solid, mp=138–139°C, ^{19}F NMR ($CDCl_3$): δ −67.62. Anal. calcd for $C_4FI_3N_2$ (475.76): C, 10.10; N, 5.89. Found: C, 10.4; N, 5.8.

1.4.3. 2-Fluoro-3-phenylpyrazine (5). Coupling of phenylboronic acid (1.2 equiv.) with **2** (494 mg, 2.2 mmol) according to the general procedure B, *t*=24 h gave after purification by column chromatography (silica, eluent: petroleum ether/dichloromethane (1/1)) 276 mg (72%) of **5** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.60 (q, 1H, J_{H5-F}=4.6 Hz; J_{H5-H6}=2.4 Hz H_5); 8.16 (m, 1H, H_6); 8.08 (m, 2H, $2H_{Ph}$); 7.53 (m, 3H, $3H_{Ph}$); ^{13}C NMR ($CDCl_3$) δ 156.8 (d, J_{C2-F}=257.2 Hz, C_2); 141.4 (d, J_{C3-F}=24.0 Hz, C_3); 140.7 (C_5 or C_6); 138.5 (C_5 or C_6); 132.3 (C_{Ph}); 129.3 (CH_{Ph}); 127.7 (CH_{Ph}); ^{19}F NMR ($CDCl_3$): δ −74.66. Anal. calcd for $C_{10}H_7FN_2$ (174.11): C, 68.98; H, 4.05; N, 16.09. Found: C, 68.82; H, 4.08; N, 16.29.

1.4.4. 2-Fluoro-3-(4-*n*-octyloxy)phenylpyrazine (6). Coupling of **4** octyloxyphenylboronic acid (970 mg, 1.5 equiv.) with **2** (400 mg, 1.79 mmol) according to the general procedure B, *t*=24 h gave after purification by column chromatography (silica, eluent: petroleum ether/dichloromethane (1/1)) 395 mg (73%) of **6** as a white solid, mp=32–34°C; ^{1}H NMR ($CDCl_3$): δ 8.45 (dd, 1H, J_{H5-F}=4.9 Hz, J_{H5-H6}=2.6 Hz, H_5); 7.96 (m, 3H, H_6+$2H_{Ph}$); 6.95 (d, 1H, *J*=9.0 Hz, $2H_{Ph}$); 3.95 (t, 2H, CH_2); 1.73 (m, 2H, CH_2); 1.52–1.22 (massif, 10H, $5CH_2$); 0.82 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 161.3 (C_{Ph}); 157.9 (d, J_{C2-F}=256.5 Hz, C_2); 142.6 (d, J_{C3-F}=24.0 Hz, C_3); 141.9 (C_5 or C_6); 138.8 (C_5 or C_6); 130.7 (CH_{Ph}); 126.0 (C_{Ph}); 115.0 (CH_{Ph}); 68.5 (CH_2); 32.2–23.1 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.46. Anal. calcd for $C_{18}H_{23}F_3N_2$ (302.39): C, 71.50; H, 7.67; N, 9.26 Found: C, 71.67; H,7.72; N, 9.46.

1.4.5. 2-Fluoro-6-(1-hydroxyethyl)-3-phenylpyrazine (7). Metallation of **5** (80 mg, 0.46 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 0.89 mL), TMPH (3.2 equiv., 0.25 mL), t_1=5 min, θ_1=−78°C, followed by reaction with acetaldehyde in excess, t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 77 mg (77%) of **7** as a yellow oil, ^{1}H NMR ($CDCl_3$): δ 8.67 (d, 1H, J_{H5-F}=4.7 Hz, H_5); 8.03 (m, 2H, $2H_{Ph}$); 7.51 (m, 3H, $3H_{Ph}$); 5.00 (q, 1H, J_{CH-CH3}=6.6 Hz, CH); 3.00 (s broad, 1H, OH); 1.61 (d, 3H, J_{CH3-CH}=6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 157.2 (d, J_{C2-F}=259.4 Hz, C_2); 155.4

(C_6); 140.9 (d, J_{C3-F}=24.0 Hz, C_3); 38.8 (C_5); 133.6 (C_{Ph}); 130.5 (CH_{Ph}); 129.1 (CH_{Ph}); 68.2 (CH); 24.0 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.54. Anal. calcd for $C_{12}H_{11}FN_2O$ (218.34): C, 66.01; H, 5.08; N, 12.83. Found: C, 65.92; H, 5.12; N, 12.76.

1.4.6. 2-Fluoro-6-(1-phenylhydroxymethyl)-3-phenylpyrazine (8). Metallation of **5** (104 mg, 0.60 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.16 mL), TMPH (3.2 equiv., 0.32 mL), θ=−78°C, followed by reaction with benzaldehyde (3.1 equiv., 0.18 mL), t_2=60 min, gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 110 mg (72%) of **7** as a beige solid, mp=97–98°C; ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H, J_{H5-F}=4.0 Hz, H_5); 8.02 (m, 2H, $2H_{Ph}$); 7.43 (m, 8H, $8H_{Ph}$); 5.90 (d, 1H, J_{CH-OH}=5.0 Hz, CH); 5.30 (s broad, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 157.0 (d, J_{C2-F}=259.4 Hz, C_2); 153.7 (C_6); 141.7 (C_{Ph}); 140.9 (d, J_{C3-F}=23.3 Hz, C_3); 139.5 (C_5); 133.5 (C_{Ph}); 130.6–127.2 (CH_{Ph}); 74.4 (CH); ^{19}F NMR ($CDCl_3$): δ −76.15. Anal. calcd for $C_{17}H_{13}FN_2O$ (280.30): C, 72.84; H, 4.67; N, 9.99. Found: C, 72.79; H, 5.03; N, 9.68.

1.4.7. 2-Fluoro-3-phenyl-6-(trimethylsilyl)pyrazine (9). Metallation of **5** (103 mg, 0.59 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.14 mL), TMPH (3.2 equiv., 0.32 mL), θ=−78°C, followed by reaction with trimethylsilyl chloride (3.1 equiv., 0.22 mL), t_2=60 min gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 105 mg (73%) of **9** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, J_{H5-F}=5.5 Hz, H_5); 8.08 (m, 2H, $2H_{Ph}$); 7.50 (m, 3H, $3H_{Ph}$); 0.31 (m, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ 160.8 (C_6); 160.2 (d, J_{C2-F}=255.8 Hz, C_2); 147.9 (C_5); 143.3 (d, J_{C3-F}=24.7 Hz, C_3); 135.8 (C_{Ph}); 132.2 (CH_{Ph}); 130.8 (CH_{Ph}); 0.0 (CH_3); ^{19}F NMR ($CDCl_3$): δ −77.74. Anal. calcd for $C_{13}H_{15}FN_2Si$ (246.36): C, 63.38; H, 6.14; N, 11.37. Found: C, 63.81; H, 6.32; N, 11.34.

1.4.8. 2-Fluoro-3-phenyl-6-(tributylstannyl)pyrazine (10). Metallation of **5** (75 mg, 0.43 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 0.83 mL), TMPH (3.2 equiv., 0.23 mL), t_1=5 min, θ_1=−78°C, followed by reaction with tributyltin chloride (3 equiv., 0.35 mL), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 117 mg (59%) of **10** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, J_{H5-F}=5.6 Hz, H_5); 7.98 (m, 2H, $2H_{Ph}$); 7.39 (m, 3H, $3H_{Ph}$); 1.60–0.79 (massif, 27H, *n*-Bu); ^{13}C NMR ($CDCl_3$): δ 165.3 (C_6); 158.9 (d, J_{C2-F}=255.7 Hz, C_2); 148.9 (C_5); 140.4 (d, J_{C3-F}=24.7 Hz, C_3); 134.3 (C_{Ph}); 130.3 (CH_{Ph}); 129.1 (CH_{Ph}); 29.4 (CH_2); 27.7 (CH_2); 14.1 (CH_3); 10.5 (CH_2); ^{19}F NMR ($CDCl_3$): δ −73.93; LRMS(IC) [M+H]: 464 for $C_{22}H_{33}FN_2Sn$ (463.22).

1.4.9. 2-Fluoro-5-iodo-3-phenylpyrazine (11). Metallation of **5** (168 mg, 0.97 mmol) according with procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.87 mL), TMPH (3.2 equiv., 0.52 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 245 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/4)) 165 mg (64%) of **11** as a white solid, mp<50°C; ^{1}H NMR ($CDCl_3$): δ 8.36 (d, 1H, J_{H6-F}=1.7 Hz, H_6); 8.06 (m, 2H $2H_{Ph}$); 7.52 (m, 3H, $3H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 158.5 (d, J_{C2-F}=257.2 Hz, C_2); 147.7 (C_6); 144.3 (d, J_{C3-F}=24.7 Hz, C_3); 132.6 (C_{Ph}); 131.3 (CH_{Ph}); 129.2 (CH_{Ph}); 110.6 (C_5); ^{19}F NMR ($CDCl_3$): δ −79.76. Anal. calcd for $C_{10}H_6FIN_2$ (300.00): C, 40.03; H, 2.02; N, 9.30. Found: C, 40.16; H, 1.98; N, 9.48

1.4.10. 2-Fluoro-6-iodo-3-phenylpyrazine (12). Metallation of **5** (150 mg, 0.86 mmol) according procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.59 mL), TMPH (1.2 equiv., 0.17 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 438 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/4)) 188 mg (73%) of **12** as a white solid, mp=97°C; ^{1}H NMR ($CDCl_3$): δ 8.52 (d, 1H, J_{H5-F}=4.3 Hz, H_5); 8.04 (m, 2H, $2H_{Ph}$); 7.51 (m, 3H, $3H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 156.2 (d, J_{C2-F}=265.9 Hz, C_2); 150.1 (C_5); 140.9 (d, J_{C3-F}=21.8 Hz, C_3); 132.8 (C_{Ph}); 131.0 (CH_{Ph}); 129.0 (CH_{Ph}); 109.1 (C_6); ^{19}F NMR ($CDCl_3$): δ −71.17. Anal. calcd for $C_{10}H_6FIN_2$ (300.00): C, 40.03; H, 2.02; N, 9.30. Found: C, 39.95; H, 2.09; N, 8.96.

1.4.11. 3.5-Diodo-2-fluoro-3-phenylpyrazine (13). Metallation of **5** (73 mg, 0.42 mmol) according procedure A with *n*-BuLi 1.6 M (2.1 equiv., 0.55 mL), TMPH (2.2 equiv., 0.16 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 213 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 148 mg (83%) of **13** as a white solid, mp=115–116°C; ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 2H, $2H_{Ph}$); 7.51 (m, 3H, $3H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 155.0 (d, J_{C2-F}=264.5 Hz, C_2); 141.2 (d, J_{C3-F}=23.3 Hz, C_3); 131.8 (C_{Ph}); 131.5 (CH_{Ph}); 129.1 (CH_{Ph}); 124.1 (C_5 or C_6); 122.5 (C_5 or C_6); ^{19}F NMR ($CDCl_3$): δ −76.55. Anal. calcd for $C_{10}H_5FI_2N_2$ (425.90): C, 28.20; H, 1.42; N, 6.58. Found: C, 28.33; H, 1.30; N, 6.28.

1.4.12. 2-Fluoro-6-(1-hydoxyethyl)-5-iodo-3-phenylpyrazine (14). Metallation of **13** (200 mg, 0.47 mmol) according to procedure A with *n*-BuLi 1.6 M (3.1 equiv., 0.91 mL), TMPH (3.2 equiv., 0.25 mL), t_1=5 min, θ_1=−78°C, followed by reaction with acetaldehyde in excess, t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 108 mg (67%) of **14** as a white solid, mp=104–105°C; ^{1}H NMR ($CDCl_3$): δ 7.94 (m, 2H, $2H_{Ph}$); 7.39 (m, 3H, $3H_{Ph}$); 5.03 (q, 1H, J_{CH-CH3}=6.4 Hz, CH); 3.15 (s large, 1H, OH); 1.45 (d, 3H, J_{CH3-CH}=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 157.8 (d, J_{C2-F}=260.1 Hz, C_2); 157.0 (C_6); 142.4 (d, J_{C3-F}=24.7 Hz, C_3); 132.3 (C_{Ph}); 131.1 (CH_{Ph}); 139.2 (CH_{Ph}); 110.0 (C_5); 69.8 (CH); 23.6 (CH_3). Anal. calcd for $C_{12}H_{10}FIN_2O$ (344.12): C, 41.88; H, 2.93; N, 8.14. Found: C, 41.93; H, 2.98; N, 8.16.

1.4.13. 3.5-Diphenyl-2-fluoropyrazine (15). Coupling of phenylboronic acid (98 mg, 1.2 equiv.) with **11** (200 mg, 0.67 mmol) according to the procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (2/1)) 113 mg (68%) of **15** as a white solid, mp=69–70°C; ^{1}H

NMR ($CDCl_3$): δ 8.38 (d, 1H, J_{H6-F}=1.9 Hz, H_6); 8.07 (m, 2H, $2H_{Ph}$); 7.93 (m, 2H, $2H_{Ph}$); 7.39 (m, 6H, $6H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 157.4 (d, J_{C2-F}=256.5 Hz, C_2); 150.3 (C_5); 140.39 (d, J_{C3-F}=24.0 Hz, C_3); 136.6 (C_6); 135.9 (C_{Ph}); 134.0 (C_{Ph}); 130.8–127.2 (CH_{Ph}); ^{19}F NMR ($CDCl_3$): −79.57. Anal. calcd for $C_{16}H_{11}N_2F$ (250.26): C, 76.78; H, 4.43; N, 11.19. Found: C, 76.66; H, 4.45; N, 11.32.

1.4.14. 5-Butyl-2-fluoro-3-phenylpyrazine (16). Cross-coupling reaction of butylzinc chloride (obtained by reaction of zinc chloride (676 mg, 9 equiv.) and *n*-BuLi 1.6 M (3 equiv., 1.03 mL)) and **11** (165 mg, 0.55 mmol) with 32 mg of $Pd(PPh_3)_4$ according procedure C for a time of 24 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/2)) 68 mg (53%) of **16** as a colorless oil; ^1H NMR ($CDCl_3$): δ 7.98 (m, 2H, $2H_{Ph}$); 7.85 (d, 1H, J_{H6-F}=1.5 Hz, H_6); 7.39 (m, 3H, $3H_{Ph}$); 2.78 (t, 2H, CH_2); 1.69 (m, 2H, CH_2); 1.33 (m, 2H, CH_2); 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.9 (d, J_{C2-F}=260.1 Hz, C_2); 155.1 (C_5); 140.9 (d, J_{C3-F}=24.0 Hz, C_3); 138.7 (C_6); 134.1 (C_{Ph}); 130.4 (CH_{Ph}); 129.1 (CH_{Ph}); 34.6 (CH_2); 31.0 (CH_2); 22.7 (CH_2); 14.3 (CH_3); ^{19}F NMR ($CDCl_3$): δ −81.52. Anal. calcd for $C_{14}H_{15}N_2F$ (230.28): C, 73.02; H, 6.57; N, 12.16. Found: C, 72.80; H, 6.64; N, 12.28.

1.4.15. 2-Fluoro-3-(1-phenylhydroxymethyl)pyrazine (17). Metallation of **1** (200 mg, 2.04 mmol) according procedure A with *n*-BuLi 1.6 M (1.1 equiv., 1.40 mL), TMPH (1.2 equiv., 0.41 mL), t_1=5 min, θ_1=−78°C, followed by reaction with benzaldehyde (1.5 equiv., 0.31 mL), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (3/8)) 296 mg (71%) of **17** as a white solid, mp=81–82°C; ^1H NMR ($CDCl_3$): δ 8.46 (dd, 1H, J_{H5-H6}=2.7 Hz, J_{5-F}=3.9 Hz, H_5), 8.14 (m, 1H, H_6), 7.30 (m, 5H, phenyl), 5.97 (d, 1H, J_{CH-OH}=5.6 Hz, CH), 4.64 (d, 1H, OH); ^{19}F NMR ($CDCl_3$): δ −77.58. Anal. calcd for $C_{11}H_9FN_2O$ (204.20): C, 64.70; H, 4.44; N, 13.70. Found: C, 64.6; H, 4.3; N, 13.9.

1.4.16. 2-Fluoro-3-[1-(4-*n*-decyloxyphenyl)hydroxymethyl]pyrazine (18). Metallation of **1** (200 mg, 2.04 mmol) according procedure A with *n*-BuLi 1.6 M (1.1 equiv., 1.40 mL), TMPH (1.2 equiv., 0.41 mL), t_1=5 min, θ_1=−78°C, followed by reaction with 4-*n*-decyloxybenzaldehyde (1.5 equiv., 0.84 mL), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (3/8)) 518 mg (71%) of **18** as a white solid, mp=62–63°C; ^1H NMR ($CDCl_3$): δ 8.36 (d, 1H, J_{H5-F}=3 Hz, H_5); 8.05 (s, 1H, H_6); 7.18 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 6.77 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 5.85 (d, 1H, J_{CH-OH}=6.4 Hz, CH); 4.53 (d, 1H, J_{OH-CH}=6.4 Hz, OH); 3.83 (t, 2H, CH_2); 1.66 (m, 2H, CH_2); 1.36–1.18 (m, 14H, $7CH_2$); 0.79 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.6 (C_{Ph}); 157.6 (d, J_{C2-F}=254.5 Hz, C_2); 146.4 (d, J_{C3-F}=29.0 Hz, C_3); 140.7 (C_5, C_6) 132.8 (C_{Ph}); 128.5 ($2CH_{Ph}$); 115.1 ($2CH_{Ph}$); 70.7 (CH); 68.4 (CH_2); 32.3–23.1 (CH_2); 12.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −76.77. Anal. calcd for $C_{21}H_{29}FN_2O_2$ (360.42): C, 69.97; H, 8.11; N, 7.77. Found: C, 69.80; H, 8.52; N, 7.97.

1.4.17. 2-Fluoro-3-[1-(4-*n*-dodecyloxyphenyl)hydroxymethyl]pyrazine (19). Metallation of **1** (200 mg, 2.04 mmol) according procedure A with *n*-BuLi 1.6 M (1.1 equiv., 1.40 mL), TMPH (1.2 equiv., 0.41 mL), t_1=5 min, θ_1=−78°C, followed by reaction with 4-*n*-dodecyloxybenzaldehyde (1.5 equiv., 0.84 mL), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (3/8)) 523 mg (66%) of **19** as a white solid, mp=64–65°C; ^1H NMR ($CDCl_3$): δ 8.34 (m, 1H, H_5) 8.02 (s, 1H, H_6); 7.17 (d, 2H, J=8.4 Hz, $2H_{Ph}$); 6.75 (d, 2H, J=8.4 Hz, $2H_{Ph}$); 5.83 (d, 1H, CH); 4.58 (s, 1H, OH); 3.82 (t, 2H, CH_2); 1.65 (m, 2H, CH_2); 1.33–1.17 (m, 18H, $9CH_2$); 0.78 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.6 (C_{Ph}); 157.6 (d, J_{C2-F}=254.8 Hz, C_2); 146.8 (d, J_{C3-F}=28.9 Hz, C_3); 140.7 (C_5, C_6) 138.0 (C_{Ph}); 128.1 ($2CH_{Ph}$); 115.0 ($2CH_{Ph}$), 70.7 (CH); 68.4 (CH_2); 32.3–23.1 (CH_2); 14.53 (CH_3); ^{19}F NMR ($CDCl_3$): δ −76.81. Anal. calcd for $C_{25}H_{33}FN_2O_2$ (388.53): C, 71.10; H, 9.86; N, 7.21. Found: C, 71.22; H, 9.77; N, 7.26.

1.4.18. 2-Fluoro-3-(phenylhydroxymethyl)-6-iodopyrazine (20). Metallation of **17** (500 mg, 2.45 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 4.75 mL), TMPH (3.1 equiv., 3.1 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2.0 equiv., 1.25 g), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (1/4)) 679 mg (84%) of **20** as a colorless liquid; ^1H NMR ($CDCl_3$): δ 8.70 (d, 1H, J_{H5-F}=3.7 Hz, H_5), 7.31 (m, 5H, phenyl), 5.90 (d, 1H, J_{CH-OH}=7.0 Hz, CH), 4.32 (d, 1H, J_{OH-CH}=7.0 Hz, OH); ^{19}F NMR ($CDCl_3$): δ −74.41. Anal. calcd for $C_{11}H_8FIN_2O$ (330.10): C, 40.02; H, 2.44; N, 8.48. Found: C, 39.90; H, 2.41; N, 8.62.

1.4.19. 2-Fluoro-3-[1-(4-*n*-decyloxyphenyl)hydroxymethyl)]-6-iodopyrazine (21). Metallation of **8** (200 mg, 0.56 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.07 mL), TMPH (3.2 equiv., 0.30 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 282 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (1/4)) 162 mg (60%) of **21** as a white solid, mp=46–47°C; ^1H NMR ($CDCl_3$): δ 8.63 (d, 1H, J_{H5-F}=3.8 Hz, H_5); 7.16 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 6.76 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 5.78 (s, 1H, CH); 4.14 (s. large, 1H, OH); 3.83 (t, 2H, CH_2); 1.67 (m, 2H, CH_2); 1.36–1.18 (massif, 14H, $7CH_2$); 0.77 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.7 (C_{Ph}); 155.6 (d, J_{C2-F}=262.9 Hz, C_2); 149.0 (C_5); 145.0 (d, J_{C3-F}=27.1 Hz, C_3); 132.2 (C_{Ph}); 128.4 ($2CH_{Ph}$); 115.2 ($2CH_{Ph}$); 109.9 (C_6); 70.5 (CH); 68.4 (CH_2); 32.3–23.1 (CH_2); 13.53 (CH_3); ^{19}F NMR ($CDCl_3$): δ −73.52. Anal. calcd for $C_{21}H_{28}FIN_2O_2$ (486.62): C, 51.83; H, 5.80; N, 5.76. Found: C, 51.88; H, 5.86; N, 5.74.

1.4.20. 2-Fluoro-3-[1-(4-*n*-dodecyloxyphenyl)hydroxymethyl)]-6-iodopyrazine (22). Metallation of **19** (300 mg, 0.77 mmol) according procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.50 mL), TMPH (3.2 equiv., 0.42 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 392 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica, eluent: ethylacetate/cyclohexane (1/4)) 233 mg (59%) of **22** as a yellow solid, mp=51–52°C; ^1H NMR ($CDCl_3$): δ 8.72 (d,1H, J_{H5-F}=3.5 Hz, H_5); 7.25 (d, 2H, J=8.3 Hz, $2H_{Ph}$) 6.65 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 5.87 (d, 1H, J_{CH-OH}=6.0 Hz,

CH); 4.27 (d, 1H, J_{OH-CH}=6.0 Hz, OH); 3.92 (t, 2H, CH_2) 1.76 (m, 2H, CH_2); 1.27 (massif, 18H, $9CH_2$) 0.89 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.7 (C_{Ph}); 155.6 (d, J_{C2-F}=262.6 Hz, C_2); 148.9 (C_5); 132.2 (C_{Ph}); 128.4 ($2CH_{Ph}$); 115.1 ($2CH_{Ph}$); 109.9 (C_6); 70.5 (CH); 68.4 (CH_2); 32.3–23.1 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −73.53. Anal. calcd for $C_{23}H_{32}FIN_2O_2$ (514.43): C, 53.69; H, 6.29; N, 5.45. Found: C, 53.76; H, 6.68; N, 5.27.

1.4.21. 2-Fluoro-3-benzyl 6-iodopyrazine (23). Reduction of **20** (686 mg, 2.08 mmol) according procedure D with heating for 6 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 450 mg (69%) of **23** as a white solid, mp=51–52°C; ^1H NMR ($CDCl_3$): δ 8.68 (d, 1H, J_{H5-F}=3.8 Hz, H_5), 7.30 (m,5H, $5H_{Ph}$), 4.16 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 157.1 (d, J_{C2-F}=263.3 Hz, C_2); 149.9 (C_5); 144.0 (d, J_{C3-F}=27.1 Hz, C_3); 136.7 (C_{Ph}); 129.2 (CH_{Ph}); 127.5 (CH_{Ph}); 109.1 (C_6); 38.0 (CH_2); ^{19}F NMR ($CDCl_3$): δ −74.59. Anal. calcd for $C_{11}H_8FIN_2$ (314.10): C, 42.06; H, 2.56; N, 8.92. Found: C, 42.02; H, 2.42; N, 9.06.

1.4.22. 2-Fluoro-3-(4-*n*-decyloxybenzyl)-6-iodopyrazine (24). Reduction of **21** (400 mg, 0.82 mmol) according procedure D with heating for 6 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 300 mg (78%) of **24** as a white solid, mp=42–43°C; ^1H NMR ($CDCl_3$): δ 8.66 (d, 1H, J_{H5-F}=3.8 Hz, H_5); 7.20 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 6.84 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 4.08 (s, 2H, CH_2); 3.92 (t, 2H, CH_2); 1.77 (m, 2H, CH_2); 1.44–1.28 (massif, 12H, $6CH_2$); 0.90 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.7(C_{Ph}); 157.1 (d, J_{C2-F}=263.0 Hz, C_2); 149.9 (C_5); 144.4 (d, J_{C3-F}=26.9 Hz, C_3); 130.4 ($2CH_{Ph}$); 128.4 (C_{Ph}); 115.2 ($2CH_{Ph}$); 108.7 (C_6); 68.4 (CH_2); 37.2–23.1 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.92. Anal. calcd for $C_{21}H_{28}FION_2$ (470.36): C, 53.62; H, 6.00; N, 5.96. Found: C, 53.70; H, 6.39; N, 5.96.

1.4.23. 2-Fluoro-3-(4-*n*-dodecyloxybenzyl)-6-iodopyrazine (25). Reduction of **22** (218 mg, 0.42 mmol) according procedure D with heating for 2 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 176 mg (84%) of **25** as a white solid, mp=49–50°C; ^1H NMR ($CDCl_3$): δ 8.57 (d, 1H, J_{H5-F}=3.8 Hz, H_5); 7.10 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 6.75 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 3.99 (s, 2H, CH_2); 3.83 (t, 2H, CH_2); 1.67 (m, 2H, CH_2); 1.38–1.19 (massif, 18H, $9CH_2$); 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 157.2 (C_{Ph}); 155.6 (d, J_{C2-F}=262.8 Hz, C_2); 148.4 (C_5); 143.0 (d, J_{C3-F}=26.9 Hz, C_3); 128.9 ($2CH_{Ph}$); 126.9 (C_{Ph}); 113.7 ($2CH_{Ph}$); 107.3 (C_6); 66.9 (CH_2); 35.7–21.7 (CH_2); 13.1 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.92. Anal. calcd for $C_{23}H_{32}FION_2$ (498.43): C, 55.42; H, 6.47; N, 5.62. Found: C, 55.64; H, 6.73; N, 5.78.

1.4.24. 2-Fluoro-3-benzyl-6-butylpyrazine (26). Cross-coupling reaction of butylzinc chloride (obtained by reaction of zinc chloride (1.13 g, 9 equiv.) and *n*-BuLi 1.6 M (3 equiv., 1.72 mL)) and **23** (290 mg, 0.92 mmol) with 53 mg of $Pd(PPh_3)_4$ according procedure C for a time of 24 h gave after purification by column chromatography (silica, eluent: ethylacetate/petroleum ether (1/4)) 161 mg (72%) of **26** as a yellow oil; ^1H NMR ($CDCl_3$): δ 8.27 (d, 1H, J_{H5-F}=4.1 Hz, H_5), 7.29 (m, 5H, $5H_{Ph}$), 4.14 (s, 2H, CH_2), 2.73 (t, 2H, CH_2) 1.69 (qt, 2H, CH_2), 1.37 (qt, 2H, CH_2), 0.95 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.4 (d, J_{C2-F}=253.5 Hz, C_2); 154.8 (C_6); 142.0 (d, J_{C3-F}=29.1 Hz, C_3); 140.5 (C_5); 137.7 (C_{Ph}); 129.2 (CH_{Ph}); 126.1 (CH_{Ph}); 38.2–22.7 (CH_2); 14.2 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.94. Anal. calcd for $C_{15}H_{17}FN_2$ (244.32): C, 73.74; H, 7.01; N, 11.47. Found: C, 73.31; H, 7.03; N, 11.78.

1.4.25. 2-Fluoro-3-benzyl-6-hexylpyrazine (27). Cross-coupling reaction of hexylzinc chloride (obtained by reaction of zinc chloride (82 mg, 9 equiv.) and *n*-HexLi 33 wt% (3 equiv., 0.81 mL)) and **23** (210 mg, 0.67 mmol) with 39 mg of $Pd(PPh_3)_4$ according procedure C for a time of 24 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 164 mg (90%) of **27** as an orange oil; ^1H NMR ($CDCl_3$): δ 8.26 (d, 1H, J_{H5-F}=4.4 Hz, H5); 7.25 (m, 5H, $5H_{Ph}$); 4.19 (s, 2H, CH_2); 2.72 (t, 2H, CH_2); 1.69 (m, 2H, CH_2); 1.32 (m, 6H, $3CH_2$); 0.89 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.4 (d, J_{C2-F}=253.4 Hz, C_2); 154.3 (C_6); 142.0 (d, J_{C3-F}=29.1 Hz, C_3); 140.8 (C_5); 137.7 (C_{Ph}); 129.0 (CH_{Ph}); 127.2 (CH_{Ph}); 38.2–20.0 (CH_2); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.84. Anal. calcd for $C_{17}H_{21}FN_2$ (272.36): C, 77.96; H, 7.77; N, 10.29. Found: C, 74.92; H, 7.66; N, 10.28.

1.4.26. 2-Fluoro-3-(4-*n*-decyloxybenzyl)-6-hexylpyrazine (28). Cross-coupling reaction of hexylzinc chloride (obtained by reaction of zinc chloride (419 mg, 9 equiv.) and *n*-HexLi 33 wt% (3 equiv., 0.42 mL)) and **24** (160 mg, 0.84 mmol) with 20 mg of $Pd(PPh_3)_4$ according procedure C for a time of 24 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 69 mg (47%) of **28** as a white solid, mp=22–23°C; ^1H NMR ($CDCl_3$): δ 8.16 (d, 1H, J_{H5-F}=4.1 Hz, H_5); 7.14 (d, 2H, J=8.3 Hz, H_{Ph}); 6.74 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 4.02 (s, 2H CH_2); 3.83 (t, 2H, CH_2); 2.63 (t, 2H, CH_2); 1.66 (m, 4H, $2CH_2$); 1.35–1.19 (massif, 20H, $10CH_2$); 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.4 (C_{Ph}); 158.3 (d, J_{C2-F}=253.5 Hz, C_2); 154.1 (C_6); 142.4 (d, J_{C3-F}=28.9 Hz, C_3); 140.7 (C_5); 130.3 ($2CH_{Ph}$); 129.5 (C_{Ph}); 115.0 ($2CH_{Ph}$); 68.3 (CH_2); 37.4–26.4 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.93. Anal. calcd for $C_{28}H_{41}FN_2$ (428.57): C, 75.67; H, 9.64; N, 6.54. Found: C, 75.45; H, 9.73; N, 6.65.

1.4.27. 2-Fluoro-3-(4-*n*-dodecyloxybenzyl)-6-hexylpyrazine (29). Cross-coupling reaction of hexylzinc chloride (obtained by reaction of zinc chloride (433 mg, 9 equiv.) and *n*-HexLi 33 wt% (3 equiv., 0.43 mL)) and **25** (176 mg, 3.5 mmol) with 20 mg of $Pd(PPh_3)_4$ according procedure C for a time of 24 h gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1/1)) 126 mg (79%) of **29** as a white solid, mp=37–38°C; ^1H NMR ($CDCl_3$): δ 8.15 (d, 1H, J_{H5-F}=4.1 Hz, H_5); 7.12 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 6.73 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 4.00 (s, 2H, CH_2); 3.81 (t, 2H, CH_2); 2.61 (t, 2H, CH_2); 1.63 (m, 4H, $2CH_2$); 1.33–1.17 (massif, 24H, $12CH_2$); 0.79 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 158.4 (C_{Ph}); 158.3 (d, J_{C2-F}=253.6 Hz, C_3); 154.1 (C_6); 142.4 (d, J_{C3-F}=29.0 Hz, C_3); 140.7 (C_5); 130.3 ($2CH_{Ph}$);

129.5 (C_{Ph}); 115.0 ($2CH_{Ph}$); 68.3 (CH_2); 37.4–22.9 (CH_2); 14.4 (CH_3). Anal. calcd for $C_{29}H_{45}FN_2$ (456.68): C, 76.27; H, 9.93; N, 6.13. Found: C, 76.35; H, 9.91; N, 6.04.

1.4.28. 2-Fluoro-3-benzyl-6-phenylpyrazine (30). Coupling of phenylboronic acid (96 mg, 1.2 equiv.) with **23** (206 mg, 0.66 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (2/1)) 148 mg (85%) of **30** as a white solid, mp=95–96°C; ^{1}H NMR ($CDCl_3$): δ 8.86 (d, 1H, J_{H5-F}=4.8 Hz, H_5); 7.99 (m, 2H, $2H_{Ph}$); 7.50 (m, 3H, 3 H_{Ph}); 7.36 (m, 5H, 5 H_{Ph}); 4.27 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 156.9 (d, J_{C2-F}=254.3 Hz, C_2); 147.6 (C_6); 141.7 (d, J_{C3-F}=29.8 Hz, C_3); 136.7 (C_5); 136.1 (C_{Ph}); 133.6 (C_{Ph}); 129.1 (CH_{Ph}); 127.9 (CH_{Ph}); 127.7 (CH_{Ph}); 125.4 (CH_{Ph}); 36.8 (CH_2); ^{19}F NMR ($CDCl_3$): δ −79.16. Anal. calcd for $C_{17}H_{13}FN_2$ (264.31): C, 77.24; H, 4.95; N, 10.60. Found: C, 77.38; H, 4.98; N, 10.68.

1.4.29. 2-Fluoro-3-(4-*n*-decyloxybenzyl)-6-(4-trifluoromethylphenyl)pyrazine (31). Coupling of 4-trifluoromethylphenylboronic acid (90 mg, 1.5 equiv.) with **24** (150 mg, 0.32 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (2/1)) 125 mg (80%) of **31** as a white solid, mp=76–77°C; ^{1}H NMR ($CDCl_3$): δ 8.88 (d, 1H, J_{H5-F}=4.4 Hz, H_5); 8.10 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 7.75 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 6.86 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 4.21 (s, 2H, CH_2); 3.92 (t, 2H, CH_2); 1.75 (m, 2H, CH_2); 1.44–1.27 (m, 12H, $6CH_2$); 0.86 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.6 (C_{Ph}); 158.2 (d, J_{C2-F}=255.8 Hz, C_2); 147.2 (C_6); 145.1 (d, J_{C3-F}=29.1 Hz, C_3); 138.4 (C_{Ph}); 138.4 (C_5); 132.2 (q, J_{C-F}=32.7 Hz, C_{Ph}); 125.9 ($2CH_{Ph}$); 126.5 (C_{Ph}); 126.4 ($2CH_{Ph}$); 126.3 ($2CH_{Ph}$); 124.3 (q, J_{C-F}=272.5 Hz, CF_3); 115.1 ($2CH_{Ph}$); 68.4 (CH_2); 37.6–23.1 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.39. Anal. calcd for $C_{28}H_{32}F_4N_2$ (488.56): C, 68.84; H, 6.60; N, 5.73. Found: C, 68.69; H, 6.89; N, 5.58.

1.4.30. 2-Fluoro-3-(4-*n*-dodecyloxybenzyl)-6-(4-trifluoromethylphenyl)pyrazine (32). Coupling of 4-trifluoromethylphenylboronic acid (90 mg, 1.5 equiv.) with **25** (157 mg, 0.82 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (2/1)) 104 mg (86%) of **32** as a white solid, mp=78–79°C; ^{1}H NMR ($CDCl_3$): δ 8.88 (d, 1H, J_{H5-F}=4.4 Hz, H_5); 8.10 (d, 2H, J=8.2 Hz, $2H_{Ph}$); 7.75 (d, 2H, J=8.2 Hz, $2H_{Ph}$); 7.27 (d, 2H, J=8.5 Hz, $2H_{Ph}$); 6.86 (d, 2H, J=8.5 Hz, $2H_{Ph}$); 4.21 (s, 2H, CH_2); 3.93 (t, 2H, CH_2); 1.72 (m, 2H, CH_2); 1.43–1.27 (m, 18H, $9CH_2$); 0.89 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.6 (C_{Ph}): 158.2 (d, J_{C2-F}=255.7 Hz, C_2); 147.2 (C_6); 145.1 (d, J_{C3-F}=29.1 Hz, C_3); 135.4 (C_{Ph}): 138.3 (C_5); 131.8 (q, J_{C-F}=32.7 Hz, C_{Ph}); 130.4 ($2CH_{Ph}$); 128.9 (C_{Ph}); 127.5 ($2CH_{Ph}$); 126.4 ($2CH_{Ph}$); 124.3 (q, J_{C-F}=271.6 Hz, CF_3); 115.1 ($2CH_{Ph}$); 68.4 (CH_2); 37.6–23.1 (CH_2); 14.50 (CH_3); ^{19}F NMR ($CDCl_3$): δ −78.47. Anal. calcd for $C_{30}H_{36}F_4N_2$ (516.62): C, 69.75; H, 7.02; N, 5.42. Found: C, 69.62; H, 7.42; N, 5.59.

1.4.31. 2-Fluoro-3-(4-*n*-decyloxybenzyl)-6-(4-*n*-octyloxyphenyl)pyrazine (33). Coupling of 4-*n*-octyloxyphenylboronic acid (71 mg, 1.2 equiv.) with **25** (89 mg, 0.19 mmol) according to the general procedure **B** (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (1/1)) 85 mg (82%) of **33** as a white solid, mp=70–71°C; ^{1}H NMR ($CDCl_3$): δ 8.77 (d, 1H, J_{H5-F}=4.5 Hz, H_5); 7.92 (d, 2H, J=8.5 Hz, $2H_{Ph}$); 7.25 (d, 2H, J=8.1 Hz, $2H_{Ph}$); 6.99 (d, 2H, J=8.5 Hz, $2H_{Ph}$); 6.84 (d, 2H, J=8.1 Hz, $2H_{Ph}$); 4.16 (s, 2H, CH_2); 4.01 (t, 2H, CH_2); 3.92 (t, 2H, CH_2); 1.72 (m, 4H, $2CH_2$); 1.44–1.28 (m, 24H, $12CH_2$); 0.90 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 161.3 (C_{Ph}); 158.4 (C_{Ph}); 158.0 (d, J_{C2-F}=252.9 Hz, C_2); 148.9 (C_6); 142.2 (d, J_{C3-F}=29.8 Hz, C_3); 137.5 (C_5); 130.3 ($2CH_{Ph}$): 129.6 (C_{Ph}); 128.6 ($2CH_{Ph}$); 127.4 (C_{Ph}); 115.4 ($2CH_{Ph}$); 115.1 ($2CH_{Ph}$); 68.4 (CH_2); 37.4–23.1 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.63. Anal. calcd for $C_{35}H_{49}FN_2$ (548.78): C, 76.60; H, 9.00; N, 5.10. Found: C, 76.85; H, 9.18; N, 5.36.

1.4.32. 2-Fluoro-3-(4-*n*-dodecyloxybenzyl)-6-(4-*n*-octyloxyphenyl)pyrazine (34). Coupling of 4-*n*-octyloxyphenylboronic acid (104 mg, 1.2 equiv.) with **25** (173 mg, 0.35 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (1/1)) 143 mg (71%) of **34** as a white solid mp=80–81°C; ^{1}H NMR ($CDCl_3$): δ 8.67 (d, 1H, J_{H5-F}=4.5 Hz, H_5); 7.82 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 7.15 (d, 2H, J=8.1 Hz, $2H_{Ph}$); 6.88 (d, 2H, J=8.7 Hz, $2H_{Ph}$); 6.74 (d, 2H, J=8.1 Hz); 4.05 (s, 2H, CH_2); 3.90 (t, 2H, CH_2); 3.81 (t, 2H, CH_2); 1.68 (m, 4H, $2CH_2$); 1.33–1.00 (m, 28H, $14CH_2$); 0.80 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 161.3 (C_{Ph}); 158.4 (C_{Ph}); 158.3 (d, J_{C2-F}=253.8 Hz, C_2); 148.9 (C_6); 142.2 (d, J_{C3-F}=29.1 Hz, C_3); 137.5 (C_5); 130.4 ($2CH_{Ph}$); 129.6 (C_{Ph}); 128.6 ($2CH_{Ph}$); 127.4 (C_{Ph}); 115.4 ($2CH_{Ph}$); 115.1 ($2CH_{Ph}$); 68.4 ($2CH_2$); 37.4–23.0 (CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −79.62. Anal. calcd for $C_{37}H_{53}FN_2$ (576.34): C, 77.04; H, 9.26; N, 4.86. Found: C, 77.12; H, 9.38; N, 5.02.

1.4.33. 2-Fluoro-3-(4-*n*-decyloxybenzyl)-6-(2,3-difluoro-4-*n*-octyloxyphenyl)pyrazine (35). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (73 mg, 1.2 equiv.) with **24** (100 mg, 0.21 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (1/1)) 78 mg (63%) of **35** as a white solid mp=70–71°C; ^{1}H NMR ($CDCl_3$): δ 8.80 (dd, 1H, J_{H5-F}=4.5 Hz, J_{H5-F}=2.2 Hz, H_5); 7.63 (m, 1H, H_{Ph}); 7.16 (d, 1H, J=8.3 Hz, $2H_{Ph}$); 6.75 (m, 3H, $3H_{Ph}$); 4.09 (s, 2H, CH_2); 4.01 (t, 2H, CH_2); 3.83 (t, 2H, CH_2); 1.75 (m, 2H, CH_2); 1.66 (m, 2H, CH_2); 1.42–1.18 (massif, 24H, $12CH_2$); 0.79 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 157.1 (C_{Ph}); 156.6 (d, J_{C2-F}=255.0 Hz, C_2); 149.0 (C_{Ph}); 148.8 (dd, J_{C-F}=252.5 Hz, J_{C-F}=11.6 Hz, C_{Ph}–F); 142.7 (C_6); 142.4 (d, J_{C3-F}=29.8 Hz, C_3); 140.4 (dd, J_{C-F}=247.0 Hz, J_{C-F}=14.5 Hz, C_{Ph}–F); 139.6 (C_5); 129.0 ($2CH_{Ph}$); 127.7 (C_{Ph}); 123.0 (CH_{Ph}); 115.2 (C_{Ph}); 113.6 ($2CH_{Ph}$); 108.5 (CH_{Ph}); 68.8 (CH_2); 66.9 (CH_2); 36.1–21.6 (CH_2); 13.1 (CH_3); ^{19}F NMR ($CDCl_3$): δ −78.68 (Fpyr); −138.38 (FPh); −158.82 (FPh). Anal.

calcd for $C_{35}H_{47}F_3N_2O_2$ (584.76): C, 71.89; H, 8.10; N, 4.79. Found: C, 71.97; H, 8.28; N, 4.74.

1.4.34. 2-Fluoro-3-(4-*n*-dodecyloxybenzyl)-6-(2,3-difluoro-4-*n*-octyloxyphenyl)pyrazine (36). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (106 mg, 1.2 equiv.) with **25** (155 mg, 0.31 mmol) according to the general procedure B (toluene, t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/dichloromethane (1/1)) 132 mg (70%) of **36** as a white solid mp=70–71°C; ^{1}H NMR ($CDCl_3$): δ 8.78 (dd, 1H, J_{H5-F}=4.5 Hz, J_{H5-F}=1.9 Hz, H_5); 7.61 (m, 1H, H_{Ph}); 7.15 (d, 1H, J=8.3 Hz, $2H_{Ph}$); 6.73 (m, 3H, $3H_{Ph}$); 4.07 (s, 2H, CH_2); 3.99 (t, 2H, CH_2); 3.81 (t, 2H, CH_2); 1.70 (m, 4H, $2CH_2$); 1.38–1.16 (m, 28H, $14CH_2$); 0.78 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 158.5 (C_{Ph}); 158.1 (d, J_{C2-F}=254.3 Hz, C_2); 150.4 (C_{Ph}); 150.3 (dd, J_{C-F}=252.8 Hz, J_{C-F}=12.3 Hz, C_{Ph}–F); 144.2 (C_6); 143.8 (d, J_{C3-F}=29.1 Hz, C_3); 141.8 (dd, J_{C-F}=247.0 Hz, J_{C-F}=14.5 Hz, C_{Ph}–F); 130.4 ($2CH_{Ph}$); 129.1 (C_{Ph}); 124.4 (CH_{Ph}); 116.6 (C_{Ph}); 115.1 ($2CH_{Ph}$); 110.0 (CH_{Ph}); 70.2 (CH_2); 68.3 (CH_2); 37.5–23.0 (CH_2); 14.5 (CH_3). Anal. calcd for $C_{37}H_{51}F_3N_2O_2$ (612.81): C, 72.52; H, 8.39; N, 4.57. Found: C, 72.49; H, 8.29; N, 4.48.

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