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Regioselective synthesis and metallation of tributylstannylfluoropyrazines. Application to the synthesis of some new fluorinated liquid crystals diazines. Part 34

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Abstract—Starting from fluoropyrazine, a general synthetic route including metallation and palladium-catalyzed cross-coupling reactions is described to access to rod-like alkylaryl or diarylpyrazines. Among them, some have liquid crystalline properties.

According to its high electron-withdrawing effect and its small size the fluorine atom makes considerable changes in physical and chemical behaviors of fluorinated compounds which have special interest for applications as pharmaceuticals[1] or highly polarizable materials.[2]

Previously the fluorine atom has been used to induce the *ortho*-metallation reaction in π-deficient heterocycles such as pyridine,[3] quinoline,[4] pyrimidine[5] series and more recently with pyrazine.[6] Using the fluoropyrazine **1** as starting material, we report here the controlled regioselective synthesis of 3- or 6-tributylstannyl-2-fluoropyrazines via the metallation reaction. Introduction of a tributylstannyl group or an iodine atom allows further cross-coupling reactions which provide an highly efficient and flexible method to synthesize various alkyl or aryl pyrazines.

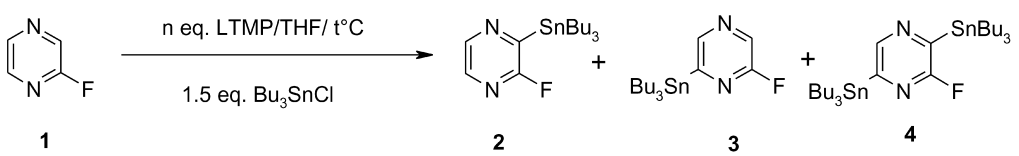
Recently some papers dealing with the synthesis and the mesomorphic properties of terphenyls with lateral fluoro substituents and alkyl or alkoxy substituents in the 4 and 4′ positions have been published.[7–9] The presence of a fluoro-substituent in terphenyls offers advantages for devising ferroelectric host materials with the reduction of the melting point and a tendency to form tilted smectic phases.[9] It has also been mentioned that the two-ring architecture of phenylpyrimidines ensures a low viscosity and makes them well suited for ferroelectric mixtures for displays.[9b]

The aim of this work was to use the fluoropyrazine as building block to synthesize various alkylaryl and diarylpyrazines which are aza-analogues of terphenyls which could provide rod-like molecules with potential liquid crystals applications.

1. Results

Recently, we have reported that the reaction of fluoropyrazine **1** with an excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP) and tributyltin chloride using the in situ trapping method at low temperature (−100°C) led to 2-fluoro-3,6-bistributylstannylpyrazine in good yield.[6a] We have reinvestigated this reaction under various experimental conditions to control the synthesis of monostannylated compounds (Scheme 1, Table 1).

With 1.1 equiv. of LTMP at −78°C a mixture of monostannylpyrazines **2** and **3** was observed (entry 1) whereas at −100°C the 3-stannyl compound **2** was obtained as the sole



1 2 3 4

Scheme 1.

Keywords: metallation; fluoropyrazines; cross-coupling reactions; liquid crystals.
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Table 1. Result of lithiation of **1** with in situ trapping method with Bu_3SnCl as the electrophile

Entry	*n* (equiv.)	*t* (°C)	**2** (%)	**2** (%)	**4** (%)
1	1.1	−78	11	26	–
2	1.1	−100	54	–	–
3	2.1	−100	15	10	52
4	4.0	−100	–	20	63

product (entry 2). When an excess of metallating agent was used the distannyl compound **4** was obtained as the major compound (entries 3 and 4).

In a previous paper[6a] it has been established that metallation of fluoropyrazine **1** at −78°C with 1.1 equiv. of LTMP and a short reaction time (5 min) led to the intermediate 2-fluoro-3-lithiopyrazine **1a**. So, in order to improve the yield of **2**, the lithio derivative **1a** was obtained at −78°C, then the temperature was lowered at −100°C and Bu_3SnCl was added at this temperature, under these experimental conditions **2** has been obtained as the sole product in a better yield (74%) (Scheme 2). When **1** reacted with 2.1 equiv. of LTMP and with 2.2 equiv. of Bu_3SnCl under the in situ trapping method at −100°C the 2-fluoro-3,6-bistributylstannylpyrazine **4** was obtained in high yield (Scheme 2).

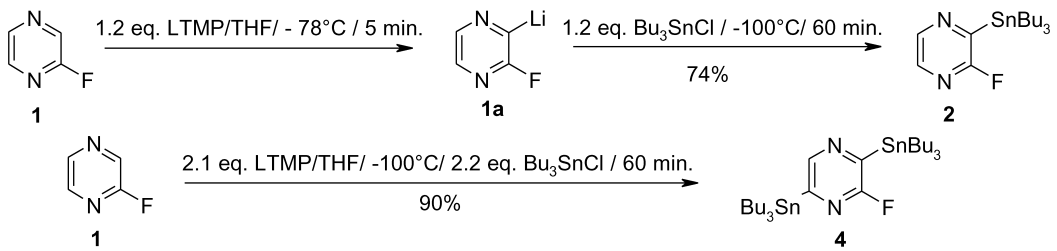
When compound **2** was submitted to a further metallation with 2.1 equiv. of LTMP at −78°C following by reaction with acetaldehyde as electrophile, the compound **5** with a tributylstannyl group at C_6 and a secondary alcohol at C_3 was obtained in 40–44% yield beside the distannylated compound **4** in 20–25% yield (Scheme 3).

This unexpected result requires some comments: (a) The distannylated compound **4** was obtained without addition of tributyltin chloride, that implies a further metallation at C_6 and that the tributylstannyl group was supplied either from **2** or from another stannylated intermediate. (b) The presence of a secondary alcohol at C_3 could result from an intermediate 3-lithio derivative resulting from a tin–lithium exchange, whereas the stannyl group at C_6 could result as for **4** from a further metallation.

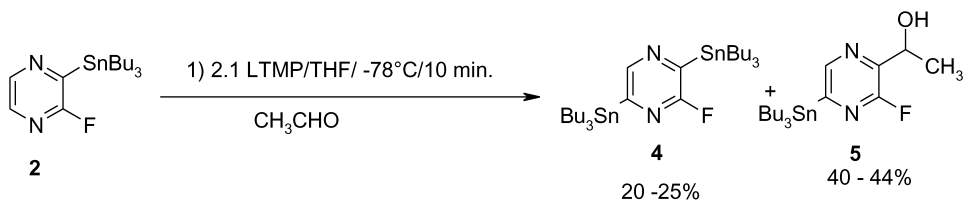
In another way, the secondary alcohol **5** could be obtained by direct metallation of **3** with 2.1 equiv. of LTMP at −78°C, followed by reaction with acetaldehyde as an electrophile. Under these conditions **5** has been obtained in high yield (97%) (Scheme 4).

This last result could allow us to propose an original synthesis of the 2-fluoro-6-tributylstannylpyrazine **3**. When metallation of **2** was performed with 2.1 equiv. of LTMP at −78°C with a short reaction time and was followed by protonation of the lithio derivative at this temperature, compound **3** was obtained in 63% yield. So starting from fluoropyrazine **1**, compound **3** was obtained in a global yield of 46% in two steps. The compound **3** has also been obtained in better yields (72%) by metallation of **1** under the in situ trapping method (Scheme 5).

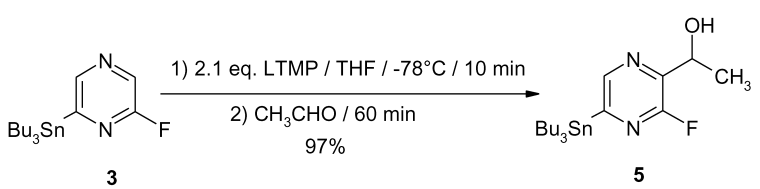
The aim of this work is the synthesis of rod-like molecules like phenylalkyl or diarylpyrazines with one or three lateral fluoro substituents, which implies that two consecutive cross-coupling reactions must be achieved. The first one at the C_6 position could be performed under the Stille conditions between the 2-fluoro-6-tributylstannylpyrazine



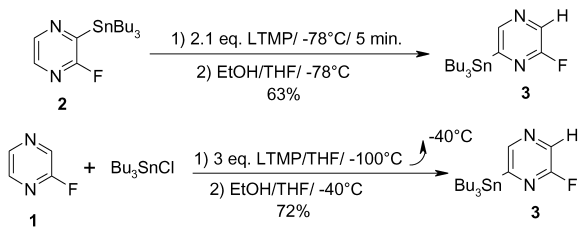
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

3 and various aryl- iodides or bromides. The second one at C_3 could involve the reaction of a 2-fluoro-3-iodo-6-arylpyrazines with arylboronic acids leading to diarylpyrazines. Reaction of 2-fluoro-3-iodo-6 arylpyrazines with alkylzinc chlorides under the Negishi conditions or with alkylacetylenes according to the Sonogashira coupling reaction could afford the expected alkylphenylpyrazines.

First, we have tested the cross-coupling reaction between the 2-fluoro-6-tributylstannylpyrazine **3** and various aryl-iodides or bromides under the Stille conditions. Under these conditions, the 2-fluoro-6-arylpyrazines **6**–**9** have been obtained with moderate yields.

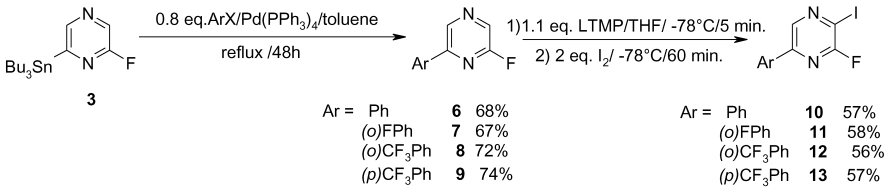
Then, the fluorine atom at C_2 has been used as *ortho*-directing group to induce a lithiation at C_3. So, treatment of compounds **6**–**9** with 1.1 equiv. of LTMP at −78°C for 5 min, followed by reaction with 2 equiv. of iodine at this temperature for 60 min afforded the expected 3-iodo derivatives **10**–**13** (Scheme 6).

Starting from the iodo compounds **10**–**13** various kinds of cross-coupling reactions have been achieved to access to various diaryl and alkylarylpyrazines **14**–**20** (Scheme 7).

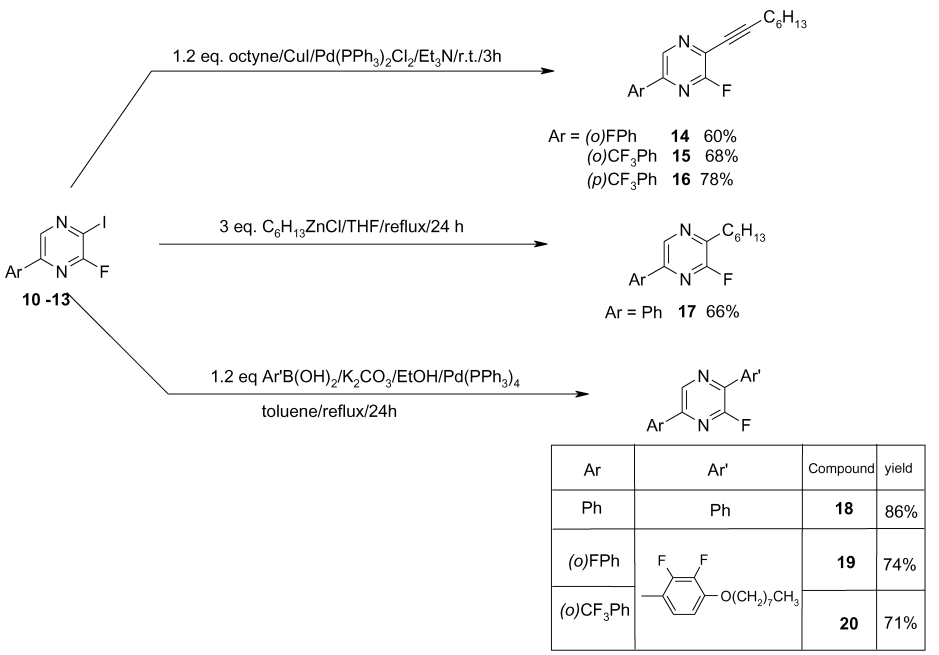
Compounds **14**–**17** are arylpyrazines with a terminal long alkyl chain and lateral fluoro substituents, whereas compounds **18**–**20** are linear terphenyl aza-analogues with for **19** and **20** three lateral fluoro substituents in close proximity to each other. These compounds such as fluoro substituted terphenyl previously described[9] have low melting points but unfortunately do not exhibit mesomorphic properties.

In the aim to generate liquid crystalline compounds, synthesis of a series of rod-like diarylpyrazines with two terminal alkyl chains and lateral fluorosubstituents has been achieved using the 2-fluoro-3-iodopyrazine as starting material and cross-coupling reactions under Suzuki conditions (Scheme 8).

To check the influence of number of aromatic rings, we have also synthesized using cross-coupling reaction under Stille conditions a tetraaromatic compound **32** with a bipyrazine as central moiety, six lateral fluoro substituents and two terminal alkoxy chains on the phenyl rings (Scheme 9).

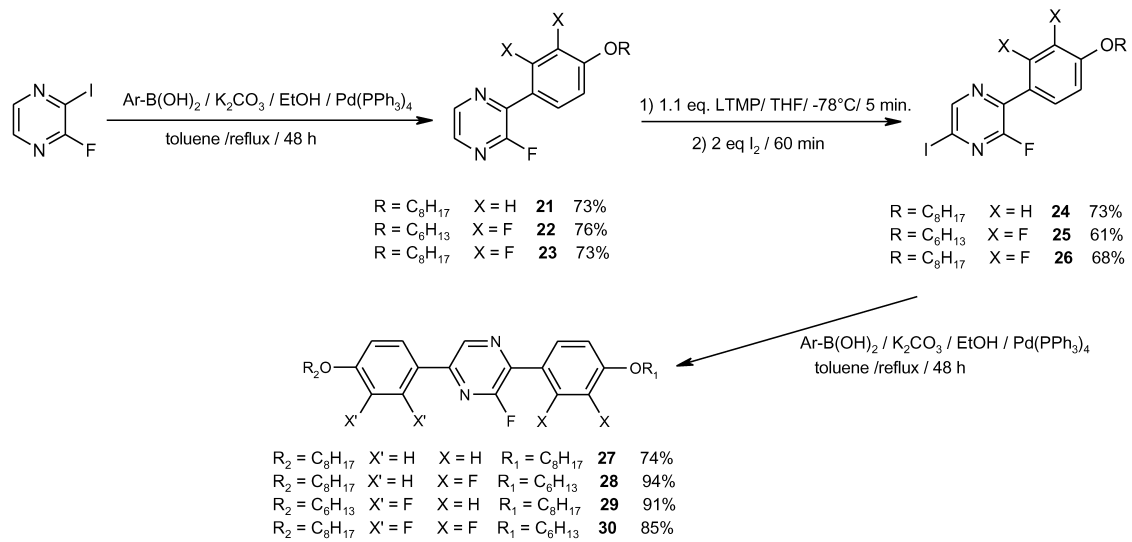


Scheme 6.

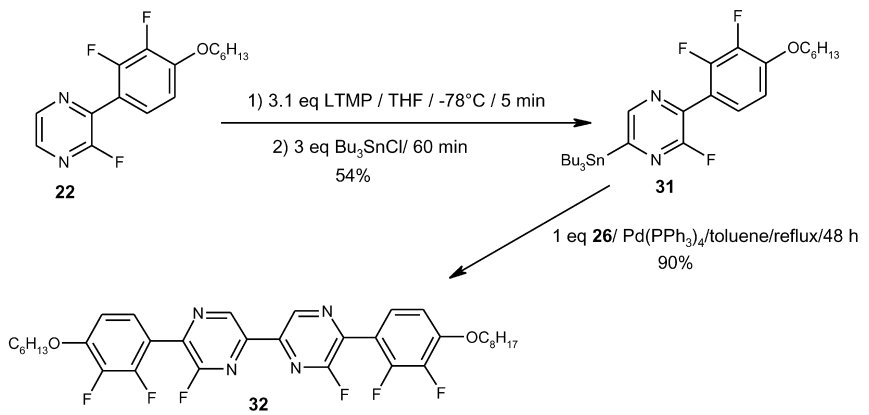


Ar	Ar'	Compound	yield
Ph	Ph	**18**	86%
(o)FPh		**19**	74%
(o)CF_3Ph		**20**	71%

Scheme 7.



Scheme 8.



Scheme 9.

Compounds with one, three or six lateral fluoro substituents and alkoxy substituents on the end positions exhibit mesophases. The transition temperatures given in Table 2 have been measured with a polarizing microscope and were confirmed using differential scanning calorimetry (DSC) at the IPCMS (Institut de Physique et de Chimie des Martériaux de Strasbourg) in the laboratory of the Professor J. F. Nicoud.

The presence of one or three lateral fluoro substituents on the diarylpyrazines **27**–**29** generates low-melting liquid crystals with wide-range smectic C phases (29 to 67.8°C). The trifluoro compounds have lower melting points with a decreasing of the smectic phase stability. For the penta-fluoro compounds we observe the lost of mesophases in the triaryl compound **30** while the tetraaromatic compound **32** have mesophases with higher transition temperatures.

Table 2. Transition temperatures and mesophases

Compound	Mesophases
27	C 89.7 S_C 157.5 N 179.1 I
28	C 66.5 S_C 114.0 N 134.5 I
29	C 82.5 S_C 111.0 N 149.0 I
30	C 128.9 I
32	C 145.0 S_C 164.0 N 196.0 I

2. Conclusion

Starting from fluoropyrazine as building block, we have described a general synthetic route to access to various alkylaryl or diaryl pyrazines with multiple fluoro-substituents in strategic lateral position to generate a wide range of molecules. Some diarylpyrazines with lateral fluoro substituents and alkoxy groups in end positions are low-melting liquid crystals. The general synthetic routes involved the selective metallation at low temperature of fluoropyrazine and various palladium-catalyzed cross coupling reactions to introduce selectively linear alkyl or substituted phenyl groups.

3. Experimental

3.1. General

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 Co. or Acros. Pd-catalysis $Pd(PPh_3)_4$ was prepared according to the literature.[10] The 2- or 4-trifluoromethyl- and 4-alcoxyphenylboronic acids were synthesized by halogen-metal exchange followed by reaction with trimethoxyborane from the commercially available 1-bromo-2- or -4-trifluoromethylbenzenes and 1-bromo-4-methoxybenzene according to the literature.[8d] 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.[8a]

Fluoropyrazine **1** was synthesized according the procedure described in the literature.[6a]

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.

Procedure B for 'in situ' trapping metallation by lithium 2,2,6,6-*tetramethylpiperidide*. The fluoropyrazine dissolved in 10 mL THF and tri-*n*-butyltin chloride were simultaneously introduced at −100°C into the solution containing metallating agent (LTMP) prepared according to procedure A. The mixture was then stirred for a time *t*, during this time, temperature was slowly increase from θ_1 to θ_2. The following steps are similar to procedure A.

Procedure C for cross-coupling of aryl halides with tributylstannylpyrazine under Stille conditions. A solution of 2-fluoro-6-tributylstannylpyrazine, arylhalide (0.8 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in degassed toluene (15 mL) was heated under reflux under nitrogen atmosphere for a time *t*. After cooling, a mixture of water (10 mL) and dichloromethane (10 mL) was added. The organic phase 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.

Procedure D 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 (1 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.

Procedure E for cross-coupling of alkylacetylenes with iodopyrazines under Sonogashira conditions. A mixture of 1-octyne, CuI (0.035 equiv. per coupling), $PdCl_2(PPh_3)_2$ (0.02 equiv. per coupling) was added to dry triethylamine (15 mL) previously flushed with nitrogen. The mixture was stirred for 30 min at room temperature before introduction of 6-aryl-2-fluoro-3-iodopyrazine then kept at this temperature for 3 h. After elimination of triethylamine iodide by filtration, the solution was dried over magnesium sulfate. The solvent was removed and the reaction mixture was purified by column chromatography on silica gel.

3.1.1. 2-Fluoro-3-tributylstannylpyrazine (2). Metallation of **1** (200 mg, 2.04 mmol) according to the procedure A with *n*-BuLi 2.5 M (1.1 equiv., 0.9 mL), TMPH (1.2 equiv., 0.41 mL), t_1=5 min, θ_1=−100°C, followed by reaction of tributyltin chloride (1.2 equiv., 0.66 mL) in THF (5 mL), t_2=60 min, θ_2=−100°C gave after purification by column chromatography (silica, eluent: dichloromethane/cyclohexane (1:1)) 584 mg (74%) of **2** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.59 (dd, 1H, J_{6-5}=2.5 Hz, J_{H5-F}=5.7 Hz, H_5); 7.97 (m, 1H, H_6); 1.8–0.53 (m, 27H, Bu); ^{19}F NMR ($CDCl_3$): δ −69.4. Anal. calcd for $C_{16}H_{29}FN_2Sn$ (387.13): C, 49.64; H, 7.55; N, 7.23. Found: C, 49.5; H, 7.6; N, 7.2.

3.1.2. 2-Fluoro-6-tributylstannylpyrazine (3). Metallation of **1** (200 mg, 2.04 mmol) according to the procedure B with *n*-BuLi 1.6 M (3.1 equiv., 2.95 mL), TMPH (3.15 equiv., 1.08 mL), and tri-*n*-butyltin chloride (1 equiv., 0.58 mL), *t*=2.5 h, θ_1=−100°C, θ_2=−40°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/cyclohexane (1:1)) 501 mg (54%) of **3** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 1H, J_{H5-F}=5.5 Hz, H_5); 8.17 (d, 1H, J_{H3-F}=8.3 Hz, H_3); 1.8–0.53 (m, 27H, Bu); ^{19}F NMR ($CDCl_3$): δ −79.11. Anal. calcd for $C_{16}H_{29}FN_2Sn$ (387.13): C, 49.64; H, 7.55; N, 7.23. Found: C, 49.5; H, 7.4; N, 7.1.

3.1.3. 2-Fluoro-3,6-bis(tributylstannyl)pyrazine (4). Metallation of **1** (300 mg, 3.06 mmol) according to the general procedure B with *n*-BuLi 1.6 M (4.1 mL, 2.1 equiv.), TMPH (1.1 mL, 2.15 equiv.), *t*=60 min, θ=−100°C and tri-*n*-butyltin chloride (2.0 g, 6.27 mmol) afforded after purification by column chromatography (silica gel, eluent: dichloromethane/cyclohexane (3:2)) 1.86 g (90%) of **4** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 1H, $J_{5,F}$=6.8 Hz, $J_{5,Sn}$=3.8 Hz, H_5); 1.8–0.53 (m, 54H, Bu); ^{19}F NMR ($CDCl_3$): δ −67.89. Anal. calcd for $C_{28}H_{55}FN_2Sn_2$ (676.17): C, 49.73; H, 8.20; N, 4.14. Found: C, 49.9; H, 8.5; N, 4.3.

3.1.4. 2-Fluoro-3-(1-hydroxyethyl)-6-(tributylstannyl)-pyrazine (5). Metallation of **4** (790 mg, 2.04 mmol) according to the procedure A with *n*-BuLi 2.5 M (2.1 equiv., 1.8 mL), TMPH (2.2 equiv., 0.80 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 gel, eluent: dichloromethane/ethylacetate (10:1)) 853 mg (97%) of **5** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.39 (d, 1H, J_{H5-F}=5.2 Hz, H_5); 5.04 (m, 1H, CH); 4 (m, 1H, OH); 1.8–0.85 (m, 30H, Bu, Me); ^{19}F NMR ($CDCl_3$): δ −69.4. Anal. calcd for $C_{18}H_{23}FON_2Sn$ (431.18): C, 50.14; H, 7.71; N, 6.49. Found: C, 50.5; H, 8.0; N, 6.8.

3.1.5. 2-Fluoro-6-phenylpyrazine (6). Coupling of iodobenzene (0.05 mL, 0.8 equiv.) with **3** (200 g, 0.52 mmol) according to the procedure C (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/ether petroleum (1:1)) 49 mg (68%) of **6** as a white solid, mp 59–60°C. ^{1}H NMR ($CDCl_3$): δ 8.97 (d, 1H, J_{H5-F}=4.7 Hz, H_5); 8.51 (d, 1H, J_{H3-F}=8.5 Hz, H_3); 8.05 (m, 2H, Ph); 7.53 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$): δ 160.2 (d, J_{C2-F}=253.6 Hz, C_2); 150.8 (C_6); 138.7 (C_5); 134.9 (C_{Ph}); 131.4 (d, J_{C3-F}=37.8 Hz, C_3); 130.9 (CH_{Ph}); 129.5 (CH_{Ph}); 127.5 (CH_{Ph}); ^{19}F NMR ($CDCl_3$): δ −80.07. Anal. calcd for $C_{10}H_7FN_2$ (174.11): C, 68.98; H, 4.05; N, 16.09. Found: C, 69.11; H, 4.18; N, 16.12.

3.1.6. 2-Fluoro-6-(2-fluorophenyl)pyrazine (7). Coupling of 1-fluoro-2-iodobenzene (0.1 mL, 0.8 equiv.) with **3** (400 mg, 1.03 mmol) according to the procedure C (t=48 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/ether petroleum (1:2)) 107 mg (67%) of **7** as a colorless solid, mp <50°C. ^{1}H NMR ($CDCl_3$): δ 8.87 (dd, 1H, $J_{H5-Fpyr}$=4.9 Hz, J_{H5-FPh}=1.9 Hz, H_5); 8.36 (d, 1H, J_{H3-F}=8.6 Hz, H_3); 8.01 (t, 1H, Ph); 7.5–7.14 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$): δ 160.1 (d, J_{C-F}=252.1 Hz, C_2 or C_{Ph}–F); 160.0 (d, J_{C-F}=253.6 Hz, C_2 or C_{Ph}–F); 146.3 (C_6); 142.3 (C_5); 132.5 (CH_{Ph}); 131.8 (d, J_{C3-F}=37.1 Hz, C_3); 131.2 (CH_{Ph}); 125.2 (CH_{Ph}); 122.8 (C_{Ph}); 116.8 (d, J_{C-F}=22.5 Hz, CH_{Ph}); ^{19}F NMR ($CDCl_3$): δ −79.66 (F_{pyr}); −114.18.(F_{Ph}). Anal. calcd for $C_{10}H_6F_2N_2$ (192.17): C, 62.50; H, 3.15; N, 14.58. Found: C, 62.62; H, 3.04; N, 14.49.

3.1.7. 2-Fluoro-6-(2-trifluoromethylphenyl)pyrazine (8). Coupling of 1-bromo-2-trifluoromethylbenzene (0.56 mL, 0.8 equiv.) with **3** (2 g, 5.16 mmol) according to the procedure C (t=48 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/ether petroleum (1:2)) 724 mg (72%) of **8** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, J_{H5-F}=4.3 Hz, H_5); 8.49 (d, 1H, J_{H3-F}=8.3 Hz, H_3); 7.85–7.51 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$): δ 159.5 (d, J_{C2-F}=255.8 Hz, C_2); 151.0 (C_6); 141.8 (C_5); 134.8 (C_{Ph}); 132.6 (d, J_{C3-F}=36.3 Hz, C_3); 132.3 (CH_{Ph}); 132.1 (CH_{Ph}); 130.1 (CH_{Ph}); 128.7 (q, J_{C-F}=31.2 Hz, C_{Ph}); 127.1 (CH_{Ph}); 124.1 (q, J_{C-F}=273.9 Hz, CF_3); ^{19}F NMR ($CDCl_3$): δ −57.13 (CF_3); −79.66 (F_{pyr}). Anal. calcd for $C_{11}H_6F_4N_2$ (242.18): C, 55.56; H, 2.50; N, 11.57. Found: C, 54.33; H, 2.42; N, 11.85.

3.1.8. 2-Fluoro-6-(4-trifluoromethylphenyl)pyrazine (9). Coupling of 1-bromo-4-trifluoromethylbenzene (0.52 mL, 0.8 equiv.) with **3** (1.78 g, 4.59 mmol) according to the procedure C (t=48 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/ether petroleum (1:2)) 655 mg (74%) of **9** as a yellow solid mp 83–84°C. ^{1}H NMR ($CDCl_3$): δ 8.99 (d, 1H, J_{H5-F}=4.6 Hz, H_5); 8.44 (d, 1H, J_{H3-F}=8.3 Hz, H_3); 8.15 (d, 2H, J=8.2 Hz, $2H_{Ph}$); 7.77 (d, J=8.2 Hz, $2H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 160.1 (d, J_{C2-F}=254.2 Hz, C_2); 149.2 (C_6); 139.0 (C_5); 138.9 (C_{Ph}); 132.7 (d, J_{C3-F}=37.3 Hz, C_3); 132.3 (q, J_{C-F}=32.5 Hz, C_{Ph}); 127.8 ($2CH_{Ph}$); 126.5 ($2CH_{Ph}$); 124.2 (q, J_{C-F}=272.4 Hz, CF_3). ^{19}F NMR ($CDCl_3$): δ −63.22 (CF_3); −78.83 (F_{pyr}). Anal. calcd for $C_{11}H_6F_4N_2$ (242.18): C, 54.56; H, 2.50; N, 11.57. Found: C, 54.49; H, 2.61; N, 11.46.

3.1.9. 2-Fluoro-3-iodo-6-phenylpyrazine (10). Metallation of **6** (295 mg, 1.69 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 1.16 mL), TMPH (1.2 equiv., 0.34 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 858 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 289 mg (57%) of **10** as a colorless solid, mp 105–106°C; H NMR ($CDCl_3$): δ 8.75 (d, 1H, J_{H5-F}=4.0 Hz, H_3); 8.01 (m, 2H, H_{Ph}); 7.32 (m, 3H, H_{Ph}); ^{13}C NMR ($CDCl_3$): δ 159.3 (d, J_{C2-F}=251.4 Hz, C_2); 150.1 (C_6); 139.6 (C_5); 133.9 (C_{Ph}); 131.4 (CH_{Ph}); 129.7 (CH_{Ph}); 127.4 (CH_{Ph}); 100.0 (d, J_{C3-F}=45.8 Hz, C_3); ^{19}F NMR ($CDCl_3$): δ −65.00. Anal. calcd for $C_{10}H_6FIN_2$ (300.00): C, 40.03; H, 2.02; N, 9.30. Found: C, 40.29; H, 2.06; N, 9.24.

3.1.10. 2-Fluoro-6-(2-fluorophenyl)-3-iodopyrazine (11). Metallation of **7** (226 mg, 1.17 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.81 mL), TMPH (1.2 equiv., 0.24 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 597 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 218 mg (58%) of **11** as a brown solid, mp <50°C. ^{1}H NMR ($CDCl_3$): δ 8.80 (dd, 1H, $J_{H5-Fpyr}$=4.4 Hz, J_{H5-FPh}=1.8 Hz, H_5); 8.00 (t, 1H, H_{Ph}); 7.47–7.13 (m, 3H, $3H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 161.2 (d, J_{C-F}=252.1 Hz, C_2 or C_{Ph}–F); 159.1 (J_{C-F}=252.1 Hz, C_2 or C_{Ph}–F); 146.0 (C_6); 143.1 (C_5); 132.9 (CH_{Ph}); 131.1 (CH_{Ph}); 125.4 (CH_{Ph}); 121.9 (C_{Ph}); 117.0 (d, J_{C-F}=22.5 Hz, CH_{Ph}); 100.8 (d, J_{C3-F}=45.0 Hz, C_3); ^{19}F NMR ($CDCl_3$): δ −64.50 (F_{Pyr}); −113.2 (F_{Ph}). Anal. calcd for $C_{10}H_5F_2IN_2$ (318.06): C, 37.76; H, 1.58; N, 8.81. Found: C, 37.97; H, 1.79; N, 8.46.

3.1.11. 2-Fluoro-3-iodo-6-(2-trifluoromethylplenyl)pyrazine (12). Metallation of **8** (300 mg, 1.24 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.85 mL), TMPH (1.2 equiv., 0.25 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 629 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 255 mg (56%) of **12** as a beige solid, mp 96–97°C. ^{1}H NMR ($CDCl_3$): δ 8.44 (d, 1H, J_{H5-F}=4.0 Hz, H_5); 7.84–7.50 (m, 4H, $4H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 158.7 (d, J_{C2-F}=253.6 Hz, C_2); 150.1 (C_6); 142.7 (C_5); 133.7 (C_{Ph}); 132.4 (CH_{Ph}); 132.1 (CH_{Ph}); 130.4 (CH_{Ph}); 129.1 (q, J_{C-F}=31.2 Hz, C_{Ph}); 127.3 (CH_{Ph}); 124.0

(q, J_{C-F}=273.9 Hz, CF_3); 101.13 (d, J_{C3-F}=44.3 Hz, C_3); ^{19}F NMR ($CDCl_3$): δ −56.31 (CF_3); −64.50 (F_{Pyr}). Anal. calcd for $C_{11}H_5F_4IN_2$ (368.07): C, 35.90; H, 1.37; N, 7.61. Found: C, 35.97; H, 1.45; N, 7.63.

3.1.12. 2-Fluoro-3-iodo-6-(4-trifluoromethylplenyl)pyrazine (13). Metallation of **9** (400 mg, 1.65 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 1.14 mL), TMPH (1.2 equiv., 0.33 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 838 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 345 mg (57%) of **13** as a colorless solid, mp 126–125°C. ^{1}H NMR ($CDCl_3$): δ 8.76 (d, 1H, J_{H5-F}=4.2 Hz, H_5); 8.13 (d, 2H, J=8.2 Hz, $2H_{Ph}$); 7.76 (d, 2H, J=8.2 Hz, $2H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 159.3 (d, J_{C2-F}=253.9 Hz, C_2); 148.3 (C_6); 139.7 (C_5); 137.2 (C_{Ph}); 132.5 (q, J_{C-F}=33.0 Hz, C_{Ph}); 127.7 ($2CH_{Ph}$); 126.6 ($2CH_{Ph}$); 124.1 (q, J_{C-F}=272.5 Hz, CF_3); 101.9 (d, J_{C3-F}=45.0 Hz, C_3); ^{19}F NMR ($CDCl_3$): δ −63.36 (CF_3); −64.28 (F_{Pyr}). Anal. calcd for $C_{11}H_5F_4IN_2$ (368.07): C, 35.90; H, 1.37; N, 7.61. Found: C, 35.97; H, 1.36; N, 7.52.

3.1.13. 2-Fluoro-6-(2-fluorophenyl)-3-(oct-1-ynyl)pyrazine (14). Coupling reaction of **11** (121 mg, 0.38 mmol) according to the procedure E with CuI (3 mg, 0.035 equiv.), $PdCl_2(PPh_3)_2$ (5 mg, 0.018 equiv.) and 1-octyne (0.07 mL, 1.2 equiv.) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 69 mg (60%) of **14** as a colorless solid, mp <50°C. ^{1}H NMR ($CDCl_3$): δ 8.90 (dd, 1H, $J_{H5-FPyr}$=4.5 Hz, J_{H5-FPh}=1.9 Hz, H_5); 7.97 (m, 1H, H_{Ph}); 7.38–7.08 (m, 3H, $3H_{Ph}$); 2.46 (t, 2H, J=7.1 Hz, CH_2); 1.61 (qt, J=7.1 Hz, CH_2); 1.41 (m, 2H, CH_2); 1.24 (m, 4H, $2CH_2$); 0.83 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 161.0 (d, J_{C-F}=252.1 Hz, C_2 or C_{Ph}–F); 159.7 (d, J_{C-F}=255.7 Hz, C_2 or C_{Ph}–F); 144.6 (C_6); 142.0 (C_5); 132.5 (CH_{Ph}); 131.2 (CH_{Ph}); 127.6 (d, J_{C3-F}=31.9 Hz, C_3); 125.3 (CH_{Ph}); 122.7 (C_{Ph}); 116.9 (d, J_{C-F}=22.5 Hz, CH_{Ph}); 101.0 (C_{sp1}); 74.3 (C_{sp1}); 31.7 (CH_2); 29.0 (CH_2); 28.4 (CH_2); 22.9 (CH_2); 20.1 (CH_2); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −73.31 (F_{Pyr}); −113.59 (F_{Ph}). Anal. calcd for $C_{18}H_{18}F_2N_2$ (300.35): C, 71.98; H, 6.04; N, 9.33. Found: C, 71.92; H, 6.12; N, 9.42.

3.1.14. 2-Fluoro-3-(oct-1-ynyl)-6-(2-trifluoromethylphenyl)pyrazine (15). Coupling reaction of **12** (150 mg, 0.41 mmol) according to the procedure E with CuI (3 mg, 0.036 equiv.), $PdCl_2(PPh_3)_2$ (6 mg, 0.019 equiv.) and 1-octyne (0.07 mL, 1.2 equiv.) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 97 mg (68%) of **15** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, 1H, J_{H5-F}=4.1 Hz, H_5); 7.72 (d, 1H, J=7.2 Hz, H_{Ph}); 7.58 (t, 1H, J=7.2 Hz, H_{Ph}); 7.53 (t, 1H, J=7.2 Hz, H_{Ph}); 7.43 (d, 1H, J=7.2 Hz, H_{Ph}); 2.46 (t, 2H, J=7.1 Hz, CH_2); 1.62 (q, 2H, J=7.1 Hz, CH_2); 1.41 (m, 2H, CH_2); 1.25 (m, 4H, $2CH_2$); 0.81 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 157.8 (d, J_{C2-F}=257.9 Hz, C_2); 147.2 (C_6); 139.9 (C_5); 133.3 (C_{Ph}); 130.9 (CH_{Ph}); 130.7 (CH_{Ph}); 128.7 (CH_{Ph}); 127.7 (q, J_{C-F}=31.2 Hz, C_{Ph}); 127.1 (d, J_{C3-F}=29.8 Hz, C_3); 125.8 (CH_{Ph}); 122.7 (q, J_{C-F}=273.9 Hz, CF_3); 99.9 (C_{sp1}); 72.7 (C_{sp1}); 30.3 (CH_2); 27.5 (CH_2); 27.0 (CH_2); 21.5 (CH_2); 18.7 (CH_2); 13.0 (CH_3); ^{19}F NMR ($CDCl_3$): δ −57.11 (CF_3); −73.91 (F_{Pyr}); Anal. calcd for $C_{19}H_{18}F_4N_2$ (350.36): C, 65.14; H, 5.18; N, 8.00. Found: C, 65.11; H, 5.53; N, 7.76.

3.1.15. 2-Fluoro-3-(oct-1-ynyl)-6-(4-trifluoromethylphenyl)pyrazine (16). Coupling reaction of **13** (250 mg, 0.68 mmol) according to the procedure F with CuI (5 mg, 0.036 equiv.), $PdCl_2(PPh_3)_2$ (10 mg, 0.020 equiv.) and 1-octyne (0.12 mL, 1.2 equiv.) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 186 mg (78%) of **16** as a colorless solid, mp 84–85°C. ^{1}H NMR ($CDCl_3$): δ 8.82 (d, 1H, J_{H5-F}=4.1 Hz, H_5); 8.05 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 7.67 (d, 2H, J=8.3 Hz, $2H_{Ph}$); 2.46 (t, 2H, CH_2); 1.60 (m, 2H, CH_2); 1.40 (m, 2H, CH_2); 1.24 (m, 4H, $2CH_2$); 0.83 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.8 (d, J_{C2-F}=257.2 Hz, C_2); 146.7 (C_6); 138.4 (C_5); 137.9 (C_{Ph}); 132.6 (q, J_{C-F}=32.7 Hz, C_{Ph}); 128.5 (d, J_{C3-F}=30.5 Hz, C_3); 127.7 ($2CH_{Ph}$); 126.5 ($2CH_{Ph}$); 124.2 (q, J_{C-F}=272.5 Hz, CF_3); 101.7 (C_{sp1}); 74.1 (C_{sp1}); 31.6 (CH_2); 29.0 (CH_2); 28.8 (CH_2); 22.9 (CH_2) 20.1 (CH_2); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −63.37 (CF_3); −73.14 (F_{Pyr}). Anal. calcd for $C_{19}H_{18}F_4N_2$ (350.36): C, 65.14; H, 5.18; N, 8.00. Found: C, 65.24; H, 5.32; N, 7.96.

3.1.16. 2-Fluoro-3-hexyl-6-phenylpyrazine (17). A solution of *n*-hexyllithium in hexane (0.81 mL, 3 equiv.) was added to cold (−78°C), stirred and anhydrous THF (30 mL) under an atmosphere of dry argon. Then a solution of dry zinc chloride (82 mg, 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 **10** (200 mg, 0.67 mmol) in THF (5 mL) were introduced. The mixture was heated under reflux under nitrogen for 24 h. 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 (eluent dichloromethane/petroleum ether (1:2) to give 114 mg (66%) of **17** as a orange liquid. ^{1}H NMR ($CDCl_3$): δ 8.74 (d, 1H, J_{H5-F}=4.5 Hz, H_5); 7.89 (m, 2H, $2H_{Ph}$); 7.38 (m, 3H, $3H_{Ph}$); 2.84 (t, 2H, CH_2); 1.69 (m, 2H, CH_2); 1.36–1.21 (m, 6H, $3CH_2$); 0.81 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.4 (d, J_{C2-F}=253.6 Hz, C_2); 148.3 (C_6); 145.0 (d, J_{C3-F}=29.8 Hz, C_3); 137.9 (C_5); 135.2 (C_{Ph}); 130.3 (CH_{Ph}); 129.4 (CH_{Ph}); 127.2 (CH_{Ph}); 32.0–22.9 ($5CH_2$); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −80.08. Anal. calcd for $C_{16}H_{19}FN_2$ (258.34): C, 74.39; H, 7.41; N, 10.84. Found: C, 74.32; H, 7.64; N, 10.86.

3.1.17. 3,6-Diphenyl-2-fluoropyrazine (18). Coupling of phenylboronic acid (45 mg, 1.2 equiv.) with **10** (92 mg, 031 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 66 mg (86%) of **18** as a colorless solid, mp 113–114°C. ^{1}H NMR ($CDCl_3$): δ 8.89 (d, 1H, J_{H5-F}=5.3 Hz, H_5); 8.02–7.94 (m, 4H, $4H_{Ph}$); 7.40 (m, 6H, $6H_{Ph}$); ^{13}C NMR ($CDCl_3$): δ 156.0 (d, J_{C2-F}=256.5 Hz, C_2); 147.5 (C_6); 138.5 (d, J_{C3-F}=24.0 Hz, C_3); 137.0 (C_5); 133.4 (C_{Ph}); 132.4 (C_{Ph});

129.3–125.9 (10CH_{Ph}); ^{19}F NMR ($CDCl_3$): δ −75.15). Anal. calcd for $C_{16}H_{11}FN_2$ (250.27): C, 76.79; H, 4.43; N, 11.19. Found: C, 76.71; H, 4.89; N, 10.73.

3.1.18. 3-(2,3-Difluoro-4-*n*-octyloxyphenyl)-2-fluoro-6-(2-fluorophenyl)pyrazine (19). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (108 mg, 1.2 equiv.) with **11** (100 mg, 0.31 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: ethylacetate/petroleum ether (1:4)) 100 mg (74%) of **19** as a colorless solid, mp <50°C. ^1H NMR ($CDCl_3$): δ 9.06 (dd, 1H, $J_{H5-Fpyr}$=4.5 Hz, J_{H5-FPh}=2.1 Hz, H_5); 8.04 (m, 1H, H_{Ph}); 7.43–7.11 (m, 4H, 4H_{Ph}); 6.82 (m, 1H, H_{Ph}); 4.04 (t, 2H, J=6.6 Hz, OCH_2); 1.77 (q, 2H, J=6.6 Hz, CH_2); 1.41–1.17 (m, 10H, 5CH_2); 0.80 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 161.1 (d, J_{C-F}=252.1 Hz, C_2 or C_{Ph}–F); 157.3 (d, J_{C-F}=256.5 Hz, C_2 or C_{Ph}–F); 150.7 (C_{Ph}); 149.9 (dd, J_{C-F}=253.6, 11.6 Hz, C_{Ph}–F); 146.0 (C_6); 142.1 (C_5); 141.8 (dd, J_{C-F}=247.7, 14.2 Hz, C_{Ph}–F); 136.5 (d, J_{C3-F}=31.2 Hz, C_3); 132.5 (CH_{Ph}); 131.3 (CH_{Ph}); 125.4 (2CH_{Ph}); 122.8 (C_{Ph}); 116.9 (d, J_{C-F}=23.2, CH_{Ph}); 115.9 (C_{Ph}); 109.9 (CH_{Ph}); 70.3 (OCH_2); 32.2–23.04 (6CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.60 (F_{Pyr}); −113.71 (F_{Ph}); −136.99 (F_{Ph}); −158.64 (F_{Ph}). Anal. calcd for $C_{24}H_{24}F_4N_2O$ (432.47): C, 66.66; H, 5.59; N, 6.48. Found: C, 66.61; H, 5.63; N, 6.47.

3.1.19. 3-(2,3-Difluoro-4-*n*-octyloxyphenyl)-2-fluoro-6-(2-trifluoromethylphenyl)pyrazine (20). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (166 mg, 1.2 equiv.) with **12** (179 mg, 0.49 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:41)) 166 mg (71%) of **20** as a colorless solid, mp 72–73°C. ^1H NMR ($CDCl_3$): δ 8.60 (d, 1H, J_{H5-F}=4.5 Hz, H_5); 7.72–7.46 (m, 4H, 4H_{Ph}); 7.31 (m, 1H, H_{Ph}); 6.80 (m, 1H, H_{Ph}); 4.00 (t, 2H, OCH_2); 1.75 (m, 2H, CH_2); 1.40–1.18 (m, 10H, 5CH_2); 0.77 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.4 (d, J_{C2-F}=257.9 Hz, C_2); 149.4 (C_{Ph}); 148.6 (C_6); 148.5 (dd, J_{C-F}=253.9, 11.8 Hz, C_{Ph}–F); 140.3 (dd, J_{C-F}=248.2, 14.2 Hz, C_{Ph}–F); 140.2 (C_5); 135.8 (d, J_{C3-F}=29.0 Hz, C_3); 133.3 (C_{Ph}); 130.9 (2CH_{Ph}); 128.7 (CH_{Ph}); 127.7 (q, J_{C-F}=31.2 Hz, C_{Ph}); 125.7 (CH_{Ph}); 124.1 (CH_{Ph}); 122.8 (q, J_{C-F}=273.9 Hz, CF_3); 114.1 (C_{Ph}); 108.4 (CH_{Ph}); 68.8 (OCH_2); 30.8–21.6 (6CH_2); 13.0 (CH_3); ^{19}F NMR ($CDCl_3$): δ −56.74 (CF_3); −75.15 (F_{Pyr}); −136.83 (F_{Ph}); −158.68 (F_{Ph}). Anal. calcd for $C_{25}H_{24}F_6N_2O$ (482.47): C, 62.24; H, 5.01; N, 5.81. Found: C, 62.28; H, 4.97; N, 5.78.

3.1.20. 2-Fluoro-3-(4-*n*-octyloxyphenyl)pyrazine (21). Coupling of 4-*n*-octyloxyphenylboronic acid (670 mg, 1.5 equiv.) with 2-fluoro-3-iodopyrazine (400 mg, 1.79 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 393 mg (73%) of **21** as a colorless solid, mp 34–35°C. ^1H 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, OCH_2); 1.73 (m, 2H, CH_2); 1.52–1.22 (m, 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 (2CH_{Ph}); 126.0 (C_{Ph}); 115.0 (2CH_{Ph}); 68.5 (OCH_2); 32.2–23.1 (6CH_2); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.46. Anal. calcd for $C_{18}H_{23}FN_2O$ (302.39): C, 71.50; H, 7.67; N, 9.26. Found: C, 71.67; H, 7.72; N, 9.46.

3.1.21. 3-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-2-fluoropyrazine (22). Coupling of 2,3-difluoro-4-*n*-hexyloxyphenylboronic acid (432 mg, 1.5 equiv.) with 2-fluoro-3-iodopyrazine (250 mg, 1.12 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 264 mg (76%) of **22** as a white solid, mp 29–30°C. ^1H NMR ($CDCl_3$): δ 8.49 (dd, 1H, J_{H5-F}=4.5 Hz, J_{H5-H6}=1.9 Hz, H_5); 8.13 (m, 1H, H_6); 7.25 (m, 1H, H_{Ph}); 6.80 (m, 1H, H_{Ph}); 4.02 (t, 2H, OCH_2); 1.76 (m, 2H, CH_2); 1.43–1.23 (m, 6H, 3CH_2); 0.81 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.8 (d, J_{C2-F}=253.5 Hz, C_2); 149.3 (C_{Ph}); 148.4 (dd, J_{C-F}=253.6, 11.6 Hz, C_{Ph}–F); 140.7 (C_5 or C_6); 140.3 (dd, J_{C-F}=248.5, 14.2 Hz, C_{Ph}–F); 139.5 (C_5 or C_6); 137.4 (d, J_{C3-F}=29.1 Hz, C_3); 123.9 (CH_{Ph}); 114.4 (C_{Ph}); 107.4 (CH_{Ph}); 68.8 (OCH_2); 30.4–21.5 (4CH_2); 12.9 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.60 (Fpyr); −137.45 (FPh); −158.76 (FPh). Anal. calcd for $C_{16}H_{17}F_3N_2O$ (310.32): C, 61.93; H, 5.52; N, 9.03. Found: C, 61.92; H, 5.59; N, 9.02.

3.1.22. 3-(2,3-Difluoro-4-*n*-octyloxyphenyl)-2-fluoropyrazine (23). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (1.34 g, 1.5 equiv.) with 2-fluoro-3-iodopyrazine (700 mg, 3.13 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 775 mg (73%) of **23** as a colorless solid, mp 41–42°C. ^1H NMR ($CDCl_3$): δ 8.48 (dd, 1H, J_{H5-F}=4.5 Hz, J_{H5-H6}=2.6 Hz, H_5); 8.11 (m, 1H, H_6); 7.23 (m, 1H, H_{Ph}); 6.78 (m, 1H, H_{Ph}); 4.00 (t, 2H, OCH_2); 1.75 (m, 2H, CH_2); 1.42–1.18 (m, 10H, 5CH_2); 0.79 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.2 (d, J_{C2-F}=255.7 Hz, C_2); 150.7 (C_{Ph}); 149.8 (dd, J_{C-F}=253.6, 11.6 Hz, C_{Ph}-F); 142.1 (C_5 or C_6); 141.7 (dd, J_{C-F}=248.1 Hz, J_{C-F}=14.1 Hz, C_{Ph}–F); 140.9 (C_5 or C_6); 138.8 (d, J_{C3-F}=29.1 Hz, C_3); 125.3 (CH_{Ph}); 115.7 (C_{Ph}); 109.8 (CH_{Ph}) 70.2 (OCH_2); 32.1–23.0 (6CH_2); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −74.51 (Fpyr); −137.34 (FPh); −158.63 (FPh). Anal. calcd for $C_{18}H_{21}F_3N_2O$ (338.37): C, 63.89; H, 6.26; N, 8.28. Found: C, 63.93; H, 6.38; N, 8.34.

3.1.23. 2-Fluoro-6-iodo-3-(4-*n*-octyloxyphenyl)pyrazine (24). Metallation of **21** (95 mg, 0.32 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.22 mL), TMPH (1.2 equiv., 0.06 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 160 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 99 mg (73%) of **24** as a pale yellow solid, mp 58–59°C. ^1H NMR ($CDCl_3$): δ 8.67 (d, 1H, J_{H5-F}=4.5 Hz, H_5); 7.94 (d, 2H, J=9.0 Hz, 2H_{Ph}); 6.91 (d, 2H, J=9.0 Hz, 2H_{Ph}); 3.93 (t, 2H, OCH_2); 1.73 (m, 2H, CH_2); 1.40–1.21 (m, 10H, 5CH_2); 0.82 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 161.6 (C_{Ph}); 155.8 (d, J_{C2-F}=265.2 Hz, C_2); 149.9 (C_5); 140.8 (d, J_{C3-F}=21.8 Hz, C_3); 130.6 (2CH_{Ph}); 124.9 (C_{Ph}); 115.2 (2CH_{Ph}); 107.2 (C_6); 68.6 (OCH_2); 32.2–23.1 (6CH_2); 14.5 (CH_3); ^{19}F NMR

($CDCl_3$): δ −70.96. Anal. calcd for $C_{18}H_{22}FIN_2O$ (428.28): C, 50.48; H, 5.17; N, 6.54. Found: C, 50.81; H, 5.36; N, 6.55.

3.1.24. 3-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-2-fluoro-6-iodopyrazine (25). Metallation of **22** (200 mg, 0.64 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.44 mL), TMPH (1.2 equiv., 0.13 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 326 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 191 mg (68%) of **25** as a colorless solid, mp 53–54°C. ^{1}H NMR ($CDCl_3$): δ 8.75 (d, 1H, J_{H5-F}=3.8 Hz, H_5); 7.23 (m, 1H, H_{Ph}); 6.80 (m, 1H, H_{Ph}); 4.03 (t, 2H, OCH_2); 1.78 (m, 2H, CH_2); 1.43–1.24 (m, 6H, $3CH_2$); 0.81 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.1 (d, J_{C2-F}=265.2 Hz, C_2); 151.0 (C_{Ph}); 150.2 (C_5); 149.7 (dd, J_{C-F}=254.3, 11.6 Hz, C_{Ph}–F); 141.7 (dd, J_{C-F}=248.8, 14.2 Hz, C_{Ph}–F); 137.0 (d, J_{C3-F}=27.6 Hz, C_3); 125.2 (CH_{Ph}); 114.7 (C_{Ph}); 110.6 (C_6); 109.9 (CH_{Ph}); 70.3 (OCH_2); 31.9–22.9 ($4CH_2$); 14.4 (CH_3); ^{19}F NMR ($CDCl_3$): δ −76.76 (Fpyr); −136.44 (FPh); −158.52 (FPh). Anal. calcd for $C_{16}H_{16}F_3IN_2O$ (436.21): C, 44.06; H, 3.70; N, 6.42. Found: C, 44.19; H, 3.82; N, 6.48.

3.1.25. 3-(2,3-Difluoro-4-*n*-octyloxyphenyl)-2-fluoro-6-iodopyrazine (26). Metallation of **23** (151 mg, 0.44 mmol) according to the procedure A with *n*-BuLi 1.6 M (1.1 equiv., 0.31 mL), TMPH (1.2 equiv., 0.09 mL), t_1=5 min, θ_1=−78°C, followed by reaction with iodine (2 equiv., 226 mg), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:4)) 126 mg (61%) of **26** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.74 (d, 1H, J_{H5-F}=3.8 Hz, H_5); 7.23 (m, 1H, H_{Ph}); 6.79 (m, 1H, H_{Ph}); 4.02 (t, 2H, OCH_2); 1.77 (m, 2H, CH_2); 1.44–1.17 (m, 10H, $5CH_2$); 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.1 (d, J_{C2-F}=265.2 Hz, C_2); 151.0 (C_{Ph}); 150.2 (C_5); 149.7 (dd, J_{C-F}=254.3, 11.6 Hz, C_{Ph}–F); 141.7 (dd, J_{C-F}=248.5, 14.5 Hz, C_{Ph}–F); 137.0 (d, J_{C3-F}=27.6 Hz, C_3); 125.2 (CH_{Ph}); 114.7 (C_{Ph}); 110.6 (C_6); 109.9 (CH_{Ph}); 70.3 (OCH_2); 32.3–23.0 ($6CH_2$); 14.5 (CH_3); ^{19}F NMR ($CDCl_3$): δ −70.95 (Fpyr); −136.77 (FPh); −158.31 (FPh). Anal. calcd for $C_{18}H_{20}F_3IN_2O$ (464.26): C, 46.57; H, 4.34; N, 6.03. Found: C, 46.34; H, 4.25; N, 6.26.

3.1.26. 3,6-Di(4-*n*-octyloxyphenyl)-2-fluoropyrazine (27). Coupling of 4-*n*-octyloxyphenylboronic acid (118 mg, 1.5 equiv.) with **24** (134 mg, 0.31 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:1)) 117 mg (73%) of **27** as a colorless solid, transitions (°C) C 89.7 S_C 157.5 N 179.1 I. ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 1H, J_{H5-F}=5.3 Hz, H_5); 7.95 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 7.89 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 6.92 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 6.90 (d, 2H, J=8.6 Hz, $2H_{Ph}$); 3.91 (m, 4H, $2OCH_2$); 1.71 (m, 4H, $2CH_2$); 1.39–1.21 (m, 20H, $10CH_2$); 0.81 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 161.3 (C_{Ph}); 161.0 (C_{Ph}); 157.1 (d, J_{C2-F}=255.8 Hz, C_2); 147.8 (C_6); 138.6 (d, J_{C3-F}=24.7 Hz, C_3); 137.5 (C_5); 130.3 ($2CH_{Ph}$); 128.6 ($2CH_{Ph}$); 127.3 (C_{Ph}); 126.3 (C_{Ph}); 115.4 ($2CH_{Ph}$); 115.0 ($2CH_{Ph}$); 68.5 ($2OCH_2$); 32.2–23.1 ($12CH_2$); 14.5 ($2CH_3$); ^{19}F NMR ($CDCl_3$): δ −75.41. Anal. calcd for $C_{32}H_{43}FN_2O_2$ (506.70): C, 75.85; H, 8.55; N, 5.53. Found: C, 75.77; H, 8.72; N, 5.45.

3.1.27. 3-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-2-fluoro-6-(4-*n*-octloxyphenyl)pyrazine (28). Coupling of 4-*n*-octyloxyphenylboronic acid (87 mg, 1.5 equiv.) with 3-(2,3-difluoro-4-*n*hexyloxyphenyl)-2-fluoro-6-iodopyrazine (101 mg, 0.23 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 112 mg (94%) of **28** as a colorless solid, transitions (°C) C 66.5 S_C 114.0 N 134.5 I. ^{1}H NMR ($CDCl_3$): δ 8.88 (d, J_{H5-F}=4.9 Hz, H_5); 7.95 (d, 2H, J=9.0 Hz, 2HPh); 7.29 (m, 1H, H_{Ph}); 6.95 (d, 2H, J=9.0 Hz, $2H_{Ph}$); 6.80 (m, 1H, H_{Ph}); 4.04 (t, 2H, OCH_2); 3.96 (t, 2H, OCH_2); 1.75 (m, 4H, $2CH_2$); 1.52–1.18 (m, 16H, $8CH_2$); 0.80 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 161.7 (C_{Ph}); 157.5 (d, J_{C2-F}=255.0 Hz, C_2); 150.3 (C_{Ph}); 150.0 (C_6); 149.8 (dd, J_{C-F}=253.6, 11.6 Hz, C_{Ph}–F); 141.8 (dd, J_{C-F}=247.8, 14.5 Hz, C_{Ph}–F); 137.8 (C_5); 134.7 (d, J_{C3-F}=30.5 Hz, C_3); 128.9 ($2CH_{Ph}$); 126.9 (C_{Ph}); 125.1 (CH_{Ph}); 116.1 (C_{Ph}); 115.5 ($2CH_{Ph}$); 109.8 (CH_{Ph}); 70.3 (OCH_2); 68.6 (OCH_2); 32.2–22.9 ($10CH_2$); 14.5 ($2CH_3$); ^{19}F NMR ($CDCl_3$): δ −75.69 (Fpyr); −137.21 (FPh); −158.76 (FPh). Anal. calcd for $C_{30}H_{37}F_3N_2O_2$ (514.63): C, 70.02; H, 7.25; N, 5.44. Found: C, 69.89; H, 7.14; N, 5.34.

3.1.28. 6-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-2-fluoro-3-(4−octyloxyphenyl)pyrazine (29). Coupling of 2,3-difluoro-4-*n*-hexyloxyphenylboronic acid (82 mg, 1.5 equiv.) with 2-fluoro-6-iodo-3-(4-*n*-octyloxyphenyl)-pyrazine (90 mg, 0.21 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 99 mg (91%) of **29** as a colorless solid, transitions (°C); C 82.0 S_C 111.0 N 149.0 I. ^{1}H NMR ($CDCl_3$): δ 8.93 (dd, 1H, $J_{H5-Fpyr}$=5.3 Hz, J_{H5-FPh}=2.3 Hz, H_5); 8.02 (d, 2H, J=9.0 Hz, $2H_{Ph}$); 7.71 (m, 1H, H_{Ph}); 6.94 (d, 2H, J=9.0 Hz, $2H_{Ph}$); 6.78 (m, 1H, H_{Ph}); 4.02 (t, 2H, OCH_2); 3.95 (t, 2H, OCH_2); 1.74 (m, 4H, $2CH_2$); 1.44–1.16 (m, 16H, $8CH_2$); 0.82 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 159.8 (C_{Ph}); 155.4 (d, J_{C2-F}=257.2 Hz, C_2); 149.0 (C_{Ph}); 149.0 (dd, J_{C-F}=252.5, 11.8 Hz, C_{Ph}–F); 141.6 (C_6); 140.4 (dd, J_{C-F}=247.8, 14.5 Hz, C_{Ph}–F); 139.6 (C_5); 138.4 (d, J_{C3-F}=23.3 Hz, C_3); 129.1 ($2CH_{Ph}$); 124.5 (C_{Ph}); 122.9 (CH_{Ph}); 115.2 (C_{Ph}); 113.6 ($2CH_{Ph}$); 108.5 (CH_{Ph}); 68.8 (OCH_2); 67.1 (OCH_2); 30.8–21.5 ($10CH_2$); 13.0 ($2CH_3$); ^{19}F NMR ($CDCl_3$): δ −74.39 (Fpyr); −137.97 (FPh); −158.86 (FPh). Anal. calcd for $C_{30}H_{37}F_3N_2O_2$ (514.63): C, 70.02; H, 7.25; N, 5.44. Found: C, 70.03; H, 7.34; N, 5.43.

3.1.29. 3-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-6-(2,3-difluoro-4-*n*-octyloxyphenyl)-2-fluoropyrazine (30). Coupling of 2,3-difluoro-4-*n*-octyloxyphenylboronic acid (88 mg, 1.5 equiv.) with **26** (90 mg, 0.21 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:2)) 96 mg (85%) of **30** as a colorless solid, mp 127–128°C. ^{1}H NMR ($CDCl_3$): δ 8.99 (m, 1H, J_{H5-F}=4.5 Hz, H_5); 7.76 (m, 1H, H_{Ph}); 7.32 (m, 1H, H_{Ph}); 6.81 (m, 2H, $2H_{Ph}$); 4.04 (t, 4H, $2OCH_2$); 1.78 (m, 4H, $2CH_2$); 1.44–1.18 (m, 16H, $8CH_2$); 0.79 (m, 6H, $2CH_3$); ^{13}C

NMR ($CDCl_3$): δ 155.8 (d, J_{C2-F}=256.5 Hz, C_2); 149.3 (m, $2C_{Ph}$); 149.0 (dd, J_{C-F}=252.4, 12.3 Hz, C_{Ph}–F); 148.5 (dd, J_{C-F}=253.3, 11.6 Hz, C_{Ph}–F); 143.9 (C_6); 140.4 (dd, J_{C-F}=247.8, 15.2 Hz, C_{Ph}–F); 140.3 (dd, J_{C-F}=247.8, 14.5 Hz, C_{Ph}–F); 139.8 (C_5); 134.6 (d, J_{C3-F}=30.5 Hz, C_3); 123.9 (CH_{Ph}); 123.3 (CH_{Ph}); 114.8 (m, C_{Ph}); 114.4 (m, C_{Ph}); 108.6 (CH_{Ph}); 108.4 (CH_{Ph}); 68.8 ($2OCH_2$); 30.8–21.5 ($10CH_2$); 13.0 ($2CH_3$); ^{19}F NMR ($CDCl_3$): δ −74.66 (Fpyr); −137.02 (FPh); −137.74 (Fph); −158.65 (2FPh). Anal. calcd for $C_{30}H_{35}F_5N_2O_2$ (550.61): C, 65.44; H, 6.41; N, 5.09. Found: C, 65.38; H, 6.64; N, 4.99.

3.1.30. 3-(2,3-Difluoro-4-*n*-hexyloxyphenyl)-2-fluoro-6-tributylstannylpyrazine (31). Metallation of **22** (192 mg, 0.62 mmol) according to the procedure A with *n*-BuLi 1.6 M (3.1 equiv., 1.20 mL), TMPH (3.2 equiv., 0.33 mL), t_1=5 min, θ_1=−78°C, followed by reaction with tributyltin chloride (3 equiv., 0.52 mL), t_2=60 min, θ_2=−78°C gave after purification by column chromatography (silica gel, eluent: dichloromethane/petroleum ether (1:4)) 199 mg (54%) of **31** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, J_{H5-F}=5.6 Hz, H_5); 7.24 (m, 1H, H_{Ph}); 6.78 (m, 1H, H_{Ph}); 4.01 (t, 2H, OCH_2); 1.76 (m, 2H, CH_2); 1.62–1.00 (m, 24H, $12CH_2$); 0.81 (t, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$): δ 166.7 (C_6); 158.7 (d, J_{C2-F}=255.0 Hz, C_2); 150.4 (C_{Ph}); 149.8 (dd, J_{C-F}=253.6, 11.6 Hz, C_{Ph}–F); 148.8 (C_5); 141.8 (dd, J_{C-F}=248.1, 14.2 Hz, C_{Ph}–F); 136.4 (d, J_{C3-F}=30.5 Hz, C_3); 125.2 (CH_{Ph}); 116.3 (C_{Ph}); 109.8 (CH_{Ph}); 70.2 (OCH_2); 31.9–22.9 ($11CH_2$); 14.4 (CH_3); 13.9 ($3CH_3$); 10.5 ($3CH_2$); ^{19}F NMR ($CDCl_3$): δ −74.08 (Fpyr); −137.3 (FPh); −158.8 (FPh). $C_{28}H_{43}F_3N_2OSn$ (M=599.36) MS (m+1/z) 601.

3.1.31. 6,6′-Difluoro-5-(2,3-difluoro-4-*n*-hexyloxyphenyl)-5′-(2,3-difluoro-4-*n*-octylphenyl)-2,2′-bipyrazine (32). Coupling of **31** (140 mg, 1.2 equiv.) with **26** (90 mg, 0.19 mmol) according to the general procedure C (t=48 h) gave after purification by column chromatography (silica, eluent: dichloromethane/petroleum ether (1:2)) 114 mg (90%) of **32** as a colorless solid, transitions (°C) C 145.0 S_C 164.0 N 196.0 I. ^{1}H NMR ($CDCl_3$): δ 9.43 (d, 2H, J_{H5-F}=4.1 Hz, $2H_5$); 7.88 (m, 2H, $2H_{Ph}$); 6.84 (m, 2H, $2H_{Ph}$); 4.05 (t, 4H, J=6.6 Hz, $2OCH_2$); 1.79 (m, 2H, $2CH_2$); 1.42–1.17 (m, 16H, $8CH_2$); 0.93 (m, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 157.0 (d, J_{C2-F}=259.4 Hz, $2C_2$); 151.1 ($2C_{Ph}$); 150.0 (dd, J_{C-F}=254.3, 11.6 Hz, $2C_{Ph}$-F); 146.5 ($2C_6$); 141.8 (dd, J_{C-F}=235.4, 14.2 Hz, $2C_{Ph}$-F); 140.4 ($2C_5$); 139.6 (d, J_{C3-F}=32.0 Hz, $2C_3$); 125.5 ($2CH_{Ph}$); 115.5 ($2C_{Ph}$); 110.0 ($2CH_{Ph}$); 70.3 ($2OCH_2$); 32.1–23.0 ($10CH_2$); 14.4 ($2CH_3$); ^{19}F NMR ($CDCl_3$): δ −74.73 (Fpyr); −136.44 (2FPh); −158.54 (2FPh). Anal. calcd for $C_{34}H_{36}F_6N_4O_2$ (646.68): C, 63.15; H, 5.61; N, 8.66. Found: C, 63.19; H, 5.67; N, 8.53.

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