Relative *Ortho*-Directing Power of Fluorine, Chlorine and Methoxy Group for the Metalation Reaction in the Diazine Series. Diazines XXXV

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The regioselectivity of the metalation of 2-chloro-6-methoxypyrazine, 2-fluoro-6-methoxypyrazine and 3-fluoro-6-chloropyridazine was studied; the relative *ortho*-directing power was F > OMe > Cl.

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Introduction.

Some years ago (1996) [1], we studied the relative *ortho*-directing power of the methoxy group and the chlorine atom for the metalation reaction in the diazine series. The substrate was 3-chloro-6-methoxypyridazine and various hindered alkylamides were used as metalating agents. In this paper we have extended the comparison to 2-chloro and -fluoro-6-methoxypyrazine and to 3-fluoro-6-chloropyridazine.

At first we shall recall the main results in the benzene and the pyridine series. The metalation of 4-fluoroanisole was studied by Gilman [2] as early as the forties', then Slocum [3], Kirk [4], Schlosser [5] and Bridges [6] studied again this metalation. In summary, when the metalating agent was an alkyllithium, its complexation with the *ortho*-directing group was the main parameter and the metalation took place mainly in *ortho*-position to the methoxy group. On the other hand, when a complexing agent was added or a weakly complexing metalating agent was used (LICKOR) [7], the acidity of the hydrogens became the main parameter and the metalation took place mainly in *ortho*-position to the fluorine atom.

The metalation of 4-chloroanisole with *n*-butyllithium [2,8] took place regioselectively in *ortho*-position to the methoxy group. However, Iwao [8] studied the metalation of 2-chloroanisole with *s*-butyllithium and observed a complete regiosepecificity in *ortho* to the chlorine atom and supposed that the steric hindrance of the chlorine atom on the methoxy group suppressed the complexing effect of this group.

The metalation of fluorochlorobenzenes [6,9] took place mainly in *ortho* position to the fluorine atom and in some cases highly regioselectively in this position.

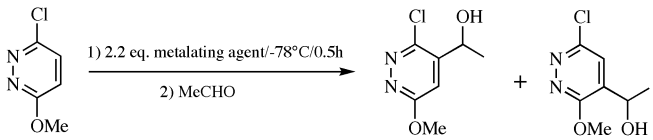
In the pyridine series there are few results dealing with the competition between a methoxy group and an halogen atom. M. Mallet [10] metalated 2-chloro-6-methoxypyridine with phenyllithium and diisopropylamine, the reaction was regioselective in *ortho*-position to the chlorine atom but Comins [11] observed a regioselective metalation in *ortho*-position to the methoxy group when using *t*-butyllithium as metalating agent.

The metalation of 2,6-dichloro-3-fluoropyridine [12] with *n*-butyl lithium was regioselective in *ortho* to the fluorine atom.

-Competition Cl-OMe.

As mentioned above, in the diazine series the competition between a chlorine atom and a methoxy group has been studied in our laboratory with 3-chloro-6-methoxypyridazine [1]. The main isomer had the substituent *ortho* to the methoxy group but the percentage of the two isomers was strongly dependent on the bulkiness of the alkylamide used as metalating agent, it varied between 60/40 and 97/3. The biggest base (LB_1) led to an highly regioselective metalation *ortho* to the methoxy group (Scheme 1, table 1)[1].

Scheme 1 [1]



1 **2a** **2b**

Table 1 [1]

entry	metalating agent	yield	% **2a**	% **2b**
1	LDA [a]	85	40	60
2	LTMP [b]	90	20	80
3	LB_1 [c]	89	3	97

[a] lithium diisopropylamide; [b] lithium 2,2,6,6-tetramethylpiperidide; [c] lithium *tert*-butyl-(1-isopropylpentyl)amide.

In the pyrazine series, 2-chloro-6-methoxy pyrazine **1** was metalated [13] and the main product had the substituent *ortho* to the methoxy group.

We have reinvestigated this reaction and varied some parameters using tetrahydrofuran as solvent (Scheme 2, Table 2).

Scheme 2

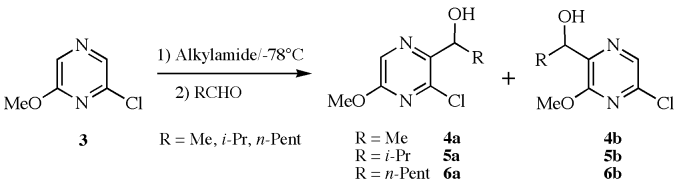


Table 2

Entry	Metalating Agent	n eq.	Metalation time min	Electrophile R =	Product	Yield	% **a**	% **b**
1*	LDA	2.2	120	*i*-Pr	**5**	90 %	13	87
2*	LTMP	2.2	120	*i*-Pr	**5**	57 %	15	85
3	LTMP	2.2	90	Me	**4**	73 %	20	80
4	LTMP	2.2	60	Me	**4**	80 %	32	68
5	LTMP	2.2	30	Me	**4**	66 %	29	71
6	LTMP	2.2	5	Me	**4**	60 %	30	70
7	LTMP	3.2	60	Me	**4**	73 %	33	67

* results previously described in ref [13].

The identification of the **a** and **b** isomers was performed by 2D NMR HMBC ^{1}H-^{13}C using ^{2}J CH correlation between the hydrogens of the methoxy group and C_6 then between C_6 and H_5 for isomers a.

The best yield was obtained with lithium diisopropylamide (entry 1). With lithium 2,2,6,6-tetramethylpiperidide, the yield decreased as the metalation time increased after 1 hour, (entries 2,3,4) but at the expense of isomer **4a**. It could be assumed that the lithio derivative in *ortho* to the chlorine atom may produce hetaryne which, in these series, are especially unstable.

In the pyridazine series (table 1) the percentage of isomers **a** and **b** was strongly dependent on the bulkiness of the base. A short study with the three bases previously used was performed, acetaldehyde and hexanal were used as electrophiles at –78 °C with 1 h metalation time and 2.2 equivalents of metalating agent (Table 3).

Table 3

Entry	Metalating Agent	Electrophile	Product	Yield	% Isomer **a**	% Isomer **b**
1	LDA	MeCHO	**4**	91	12	88
2	LDA	$C_5H_{11}CHO$	**6**	74	12	88
3	LTMP	MeCHO	**4**	80	32	68
4	LTMP	$C_5H_{11}CHO$	**6**	82	33	67
5	LB_1	MeCHO	**4**	71	38	62
6	LB_1	$C_5H_{11}CHO$	**6**	79	39	61

The percentage of the two isomers was not dependent on the aldehydes but as noted before, was dependent on the bulkiness of the base. The regioselectivity in *ortho* to the methoxy group lowered when the bulkiness of the base increased. This result is contrary to the one observed in the pyridazine series[1].

-Competition F-OMe.

In order to compare the methoxy group and the fluorine atom we studied the metalation of 2-fluoro-6-methoxy pyrazine **7**.

The metalation was first optimized with lithium 2,2,6,6-tetramethylpiperidide as metalating agent, acetaldehyde as electrophile, and tetrahydrofuran as solvent, then the metalating agent was varied, a short metalation time (5 minutes) gave the best results (Scheme 3, Table 4).

Scheme 3

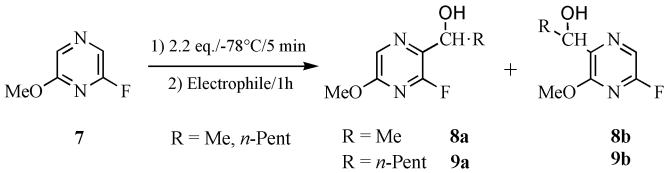


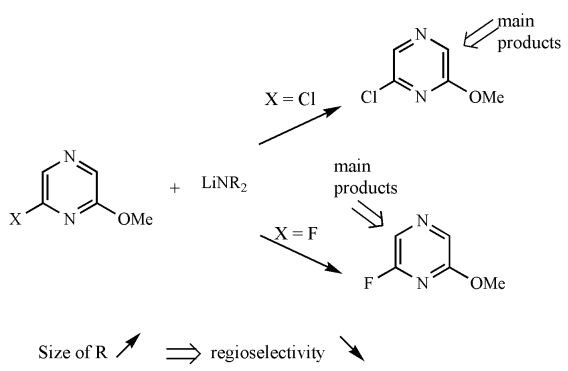
Table 4

Entry	Metalating Agent	Electrophile	Product	Yield	% Isomer **a**	% Isomer **b**
1	LDA	MeCHO	**8**	72	96	4
2	LDA	$C_5H_{11}CHO$	**9**	74	96	4
3	LTMP	MeCHO	**8**	78	88	12
4	LTMP	$C_5H_{11}CHO$	**9**	65	86	14
5	LB_1	MeCHO	**8**	71	88	12
6	LB_1	$C_5H_{11}CHO$	**9**	80	86	14

The main isomer had the substituent in the *ortho* position relative to the fluorine atom, contrary to what was observed with the chlorine atom. With lithium diisopropylamide the metalation was highly regioselective in the *ortho* position relative to the fluorine atom. The use of the two other more bulky bases decreased slightly the regioselectivity (Scheme 5).

The order of *ortho* directing power is F > OMe > Cl.

Scheme 4



-Competition F-Cl.

In order to compare directly the two halogens we planned to perform the metalation of fluoro-chloro-diazines.

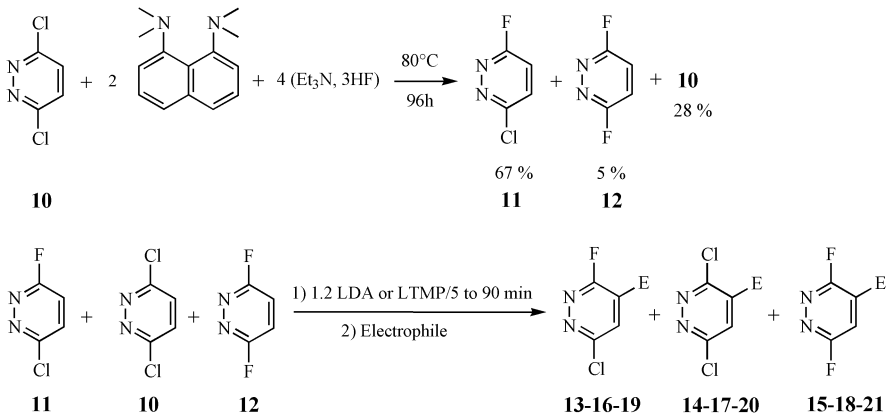
We have recently published the use of a mixture of proton sponge and the triethylamine fluorhydric acid complex to replace a chlorine atom by fluorine with 3,6-dichloropyridazine [14]. However the reaction gave an untractable mixture of products. The monofluoro compound **11** was the main product beside 28 % of starting material and a small amount (5 %) of difluoro derivative **12**. The metalation was performed on this mixture (Scheme 6).

metalation of a mixture richer in product **12** (15 %) led to difluorinated functionnalized products with the same percentage (15 %). This regioselective metalation *ortho* to the fluoro atom by comparison with the chlorine atom confirms the ordering preferentially obtained with halogeno methoxy diazines.

Conclusion.

In the diazine series, the methoxy group is a better *ortho* directing group than the chlorine atom for the metalation reaction. However, their relative *ortho* directing power can be dependent on the metalating agent.

Scheme 5



This metalation was performed with three electrophiles and the relative proportions of functionnalized compounds was determined by analysis of ^{1}H NMR spectra (Table 6).

The proportions of the functionalized products **13-21** were constant with the electrophiles, the metalating agent and the time and reflected the proportion of the starting material; this showed a similar behavior of the three compounds (**10-12**) with regard to the metalation reaction. The most important result was that the metalation of **11** was regioselective in *ortho* position relative to the fluorine atom, leading to the conclusion that the fluorine atom was a much better *ortho*-directing group than the chlorine atom in these series. We could not isolate products coming from the metalation of the difluoropyridazine **12**, however the

The fluorine atom is a better *ortho* directing atom than the methoxy group and consequently than the chlorine atom. This last effect has been verified with 3-fluoro-6-chloro pyridazine. The order of *ortho* directing efficiency in the diazine series is: F > OMe > Cl.

Although the metalations were performed with alkylamides, there must be a complexation of the metalating agent or/and of the lithio derivative with the *ortho* directing group to explain the better *ortho* directing power of the methoxy group than of the chlorine atom. In the case of the fluorine atom, its very strong electron-withdrawing effect makes the *ortho* hydrogens much more acidic, so there is no need for complexation to achieve the metalation.

Table 5

Entry	Metalating Agent	Metalating Time	Electrophile (%)	Yield	Product [a]	% [b]	Product	% [b]
1	LDA	5	MeCHO	46	**13 + 15**	77	**14**	23
2	LTMP	5	MeCHO	44	**13 + 15**	72	**14**	28
3	LTMP	20	MeCHO	48	**13 + 15**	74	**14**	26
4	LTMP	90	MeCHO	63	**13 + 15**	77	**14**	23
5	LTMP	90	PhCHO	55	**16 + 18**	72	**17**	28
6	LTMP	90	I_2	37	**19 +21**	77	**20**	23

[a] The amount of difluorocompounds **15**, **18**, **21** was too low to be quantified (< 5 %); [b] % determined by NMR.

EXPERIMENTAL

General Data.

Melting points were determined on Kofler apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 NMR spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield from an internal standard, tetramethylsilane in deuteriochloroform, or hexamethyldisiloxane in d_6-dimethylsulfoxide. Coupling constants (*J*) are given in hertz (Hz). Elemental analyses were performed on a Carlo-Erba CHN apparatus. Mass spectra were recorded on a JEOL JMS-AX500 mass spectrometer; samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Merck – Geduran SI60 (70-230 mesh).

General Procedure for Metalation.

A solution of *n*-butyllithium (1.6 *M* or 2.5 *M* in hexane) was added to cold (-50 °C), stirred and anhydrous tetrahydrofuran (15 mL) under an atmosphere of dry argon, then 2,2,6,6-tetramethylpiperidine or diisopropylamine was added and the mixture was warmed to 0 °C. After 20 min, the mixture temperature was then carried to the temperature θ_1 and the diazine dissolved in 5 mL of tetrahydrofuran. 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, tetrahydrofuran (1/4/5). At room temperature the mixture was made slightly basic with a saturated hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorized with a sodium thiosulfate solution. The solvent was removed under reduced pressure. The residue was extracted with dichloromethane (4 x 20 mL), the combined organic extracts were dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

2-Chloro-3-(1-hydroxyethyl)-6-methoxypyrazine (**4a**) and 2-Chloro-5-(1-hydroxyethyl)-6-methoxypyrazine (**4b**).

Metalation of **3** (150 mg, 1.04 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.43 mL), di*iso*propylamine (2.3 equiv., 0.33 mL), t_1 = 60 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: dichloromethane) 178 mg (91 %) of an unseparable mixture containing 12 % of **4a** and 88 % of **4b** as a pale yellow oil. ^{1}H NMR (deuteriochloroform, 300 MHz): **4a**, δ = 8.04 (s, 1H, H_5); 5.05 (qt, 1H, J = 6.4 Hz, CH); 3.87 (s, 3H, OCH_3); 3.69 (m, 1H, OH); 1.38 (d, 3H, J = 6.4 Hz, CH_3); ^{1}H NMR (deuteriochloroform, 300 MHz): **4b**, 8.00 (s, 1H, H_3); 4.92 (qt, 1H, J = 6.4 Hz, CH); 3.90 (s, 3H, OCH_3); 3.85 (m, 1H, OH); 1.36 (d, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): **4a**, δ = 159.3 (C_6); 147.0 (C_3); 144.4 (C_2); 132.3 (C_5); 66.3 (CH); 54.9 (O*C*H$_3$); 23.5 (CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): **4b**, δ = 156.4 (C_6); 146.6 (C_5); 144.4 (C_2); 133.6 (C_3); 65.6 (CH); 54.9 (OCH_3); 22.6 (CH_3). IR (KBr) for the mixture of **4a** and **4b** (cm^{-1}): 3412; 2978; 2953; 2932; 2869; 1734; 1542; 1463; 1419; 1369; 1291; 1222; 1175; 1140; 1082; 1053; 1010; 923.

Anal. Calcd. for the mixture of **4a** and **4b** $C_7H_9ClN_2O_2$ (188.61): C, 44.58; H, 4.81; N, 14.85. Found: C, 44.72; H, 5.02; N, 14.47.

2-Chloro-3-(1-hydroxyisopropyl)-6-methoxypyrazine (**5a**) and 2-Chloro-6-(1-hydroxyisopropyl)-6-methoxypyrazine (**5b**). See reference 13.

2-Chloro-3-(1-hydroxyhexyl)-6-methoxypyrazine (**6a**).

Metalation of **3** (141 mg, 0.98 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.34 mL), 2,2,6,6-tetramethylpiperidine (2.3 equiv., 0.38 mL), t_1 = 60 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: petroleum ether/ethylacetate (14/1)) 64 mg (27 %) of **6a** as colorless liquid and 131 mg (55 %) of **6b** as a colorless liquid.

Compound **6a** has ^{1}H NMR (deuteriochloroform, 300 MHz): δ = 8.04 (s, 1H, H_5); 4.90 (m, 1H, CH); 3.91 (s, 3H, OCH_3); 3.34 (br, 1H, OH); 1.71 (m, 2H, CH_2); 1.58-1.17 (m, 6H, $3CH_2$); 0.79 (m, 3H, CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): δ =159.1 (C_6); 146.6 (C_5); 142.6 (C_2); 132.3 (C_5); 69.8 (CH); 54.9 (O*C*H$_3$); 37.6 (CH_2); 31.9 (CH_2); 25.3 (CH_2); 22.9 (CH_2); 14.4 (CH_3); IR (KBr) (cm^{-1}): 3429; 2930; 2859; 1708; 1567; 1528; 1473; 1419; 1399; 1340; 1254; 1170; 1123; 1058; 1019; 916.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_2$ (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 53.87; H, 7.02; N, 11.15.

Compound **6b** has: ^{1}H NMR (deuteriochloroform, 300 MHz): δ = 8.00 (s, 1H, H_3); 4.80 (m, 1H, CH); 3.94 (s, 3H, OCH_3); 3.61 (d, 1H, J_{OH-CH} = 7.9 Hz, OH); 1.72 (m, 2H, CH_2); 1.53-1.19 (m, 6H, $3CH_2$); 0.79 (m, 3H, CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): δ = 155.1 (C_6); 144.7 (C_5); 142.9 (C_2); 132.3 (C_3); 67.8 (CH); 53.5 (OCH_3); 35.2 (CH_2); 30.6 (CH_2); 23.9 (CH_2); 22.5 (CH_2); 13.0 (CH_3). IR (KBr) (cm^{-1}): 3448; 2954; 2930; 2860; 1707; 1542; 1460; 1421; 1370; 1220; 1171; 1138, 1071; 1011; 927.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_2$ (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 54.03; H, 7.07; N, 11.52.

2-Fluoro-6-methoxypyrazine (**7**) [15].

A mixture of 2,6-difluoropyrazine (868 mg, 7.48 mmol) in methanol containing dissolved sodium metal (0.9 equiv., 0.158 g) was refluxed for 2 h. After cooling, the solvent was distilled at atmospheric pressure. The residue was washed with 10 mL of water and extracted with (3 x 20 mL). The combined organic extracts were dried over magnesium sulphate and evapored to afford 491 mg (51 %) of **7** as a colorless liquid; ^{1}H NMR (deuteriochloroform, 300 MHz): δ = 8.00 (d, 1H, J_{H5-F} = 4.1 Hz, H_5); 7.83 (d, 1H, J_{H3-F} = 7.9 Hz, H_3); 3.83 (s, 3H, OCH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): δ = 159.2 (d, J_{C6-F} = 7.2 Hz, C_6); 158.7 (d, J_{C2-F} = 255.8 Hz, C_2); 131.7 (d, J_{C5-F} = 4.3 Hz, C_5); 122.3 (d, J_{C3-F} = 34.9 Hz, C_3); 54.2 (O*C*H$_3$); ^{19}F NMR (deuteriochloroform, 200 MHz): δ = -85.11. IR (KBr) (cm^{-1}): 3079; 2995; 2948; 1592; 1537; 1480; 1435; 1405; 1329; 1252; 1201; 1180; 1140; 1046; 1009; 976; 854; 628; 488. LRMS (IE) [M$^+$]: 128 for $C_5H_5FN_2O$ (128.11).

2-Fluoro-3-(1-hydroxyethyl)-6-methoxypyrazine (**8a**).

Metalation of **7** (149 mg, 1.16 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.60 mL), diisopropylamine (2.3 equiv., 0.37 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: petroleum ether/dichloromethane (1/1)) 144 mg (72 %) of **8a** as a pale yellow oil; ^{1}H NMR

(deuteriochloroform, 300 MHz): δ = 8.01 d, 1H, J_{H5-F} = 3.8 Hz, H_5); 4.99 (m, 1H, CH); 3.89 (s, 3H, OCH_3); 3.63 (br, 1H, OH) ; 1.42 (d, 3H, J = 6.4 Hz, CH_3). ^{13}C NMR (deuteriochloroform, 300 MHz): δ = 158.9 (C_6); 155.0 (d, J_{C2-F} = 255.8 Hz, C_2); 135.9 (d, J_{C3-F} = 28.3 Hz, C_3); 130.3 (C_5); 64.7 (CH); 54.9 (OCH_3); 23.4 (CH_3); ^{19}F NMR (deuteriochloroform, 300 MHz): δ = -83.82. IR (KBr) (cm^{-1}): 3401; 2981; 2949; 1595; 1538; 1490; 1447; 1424; 1389; 1331; 1179; 1155; 1091; 1039; 1017; 978; 899.

Anal. Calcd. for $C_7H_9FN_2O_2$ (172.16): C, 48.84; H, 5.27; N, 16.27. Found: C, 48.67; H, 5.56; N, 16.06.

2-Fluoro-5-(1-hydroxyethyl)-6-methoxypyrazine (**8b**).

Metalation of **2** (156 mg, 1.22 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.67 mL), 2,2,6,6-tetramethylpiperidine (2.3 equiv., 0.47 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: petroleum ether/dichloromethane (1/1)) 167 mg (78 %) of a pale yellow oil containing 88 % of **8a** and 12 % of **8b**; ^{1}H NMR (deuteriochloroform, 300 MHz): **8b**, δ = 7.81 (d, 1H, J_{H3-F} = 8.3 Hz, H_3); 4.99 (m, 1H, CH); 3.93 (s, 3H, OCH_3); 3.63 (br, 1H, OH); 1.37 (d, 3H, J = 6.4 Hz, CH_3); ^{19}F NMR (deuteriochloroform, 300 MHz): **8b**, δ = -88.09. IR (KBr) for the mixture of **8a** and **8b** (cm^{-1}): 3400; 2981; 2949; 1682; 1594; 1538; 1489; 1446; 1424; 1391; 1331; 1179; 1155; 1091; 1039; 978.

Anal. Calcd. for the mixture of **8a** and **8b** $C_7H_9FN_2O_2$ (172.16): C, 48.84; H, 5.27; N, 16.27. Found: C, 48.89; H, 5.33; N, 16.55.

2-Fluoro-3-(1-hydroxyhexyl)-6-methoxypyrazine (**9a**).

Metalation of **7** (159 mg, 1.24 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.71 mL), di*iso*propylamine (2.3 equiv., 0.40 mL), t_1 = 5 min, θ_1 = -78 °C, followed by reaction with hexanal (2.2 equiv., 0.33 mL), t_2 = 60 min, θ_2 = -78 °C gave after purification by column chromatography (silica, eluent: petroleum ether/ethylacetate (14/1)) 210 mg (74 %) of **9a** as a colorless liquid; ^{1}H NMR (deuteriochloroform, 300 MHz): δ = 7.99 (d, 1H, J_{H5-F} = 3.4 Hz, H_5) 4.81 (t, 1H, J = 6.4 Hz, CH); 3.87 (s, 3H, OCH_3); 3.57 (br, 1H, OH); 1.66 (m, 2H, CH_2); 1.33-1.17 (m, 6H, $3CH_2$); 0.77 (m, 3H, CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): δ = 158.7 (C_6); 155.1 (d, J_{C2-F} = 255.8 Hz, C_2); 135.5 (d, J_{C3-F} = 28.3 Hz, C_3); 130.4 (C_5); 68.2 (CH); 54.7 (OCH_3); 37.4 (CH_2); 31.9 (CH_2); 25.2 (CH_2); 22.8 (CH_2); 14.2 (CH_3); ^{19}F NMR (deuteriochloroform, 300 MHz): δ = -84.33. IR (KBr) (cm^{-1}): 3411; 2932; 2860; 1595; 1540; 1488; 1459; 1425; 1389; 1331; 1177; 1150; 1113; 1039; 979.

Anal. Calcd. for $C_{11}H_{17}FN_2O_2$ (228.27): C, 57.88; H, 7.51; N, 12.27. Found: C, 57.87; H, 7.61; N, 12.36.

2-Fluoro-5-(1-hydroxyhexyl)-6-methoxypyrazine (**9b**).

Metalation of **7** (156 mg, 1.22 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (2.2 equiv., 1.67 mL), 2,2,6,6-tetramethylpiperidine (2.3 equiv., 0.47 mL), t_1 = 5 min, θ_1 = -78 °C, followed by reaction with hexanal (2.2 equiv., 0.32 mL), t_2 = 60 min, θ_2 = -78 °C gave after purification by column chromatography (silica, eluent: petroleum ether/ethylacetate (14/1)) 15 mg (5 %) of **9b** as a colorless liquid (besides 169 mg (60 %) of **9a**); ^{1}H NMR (deuteriochloroform, 300 MHz): δ = 7.82 (d, 1H, J_{H3-F} = 8.3 Hz, H_3); 4.82 (m, 1H, CH); 3.93 (s, 3H, OCH_3); 3.51 (br, 1H, OH) 1.66 (m, 2H, CH_2); 1.33-1.17 (m, 6H, $3CH_2$); 0.77 (m, 3H, CH_3); ^{19}F NMR (deuteriochloroform, 300 MHz): δ = -88.21.

Anal. Calcd. for $C_{11}H_{17}FN_2O_2$ (228.27): C, 57.88; H, 7.51; N, 12.27. Found: C, 58.20; H, 7.52; N, 12.16.

3-Chloro-6-fluoro-5-(1-hydroxyethyl)pyridazine (**13**) and 3,6-Dichloro-4-(1-hydroxyethyl)pyridazine (**14**).

Metalation of the mixture (160 mg, 1.18 mmol) of 3-chloro-6-fluoropyridazine (67 %, 0.81 mmol), 3,6-dichloropyridazine (28 %, 0.30 mmol) and 3,6-difluoropyridazine (5 %, 0.07 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (1.2 equiv., 0.89 mL), 2,2,6,6-tetramethylpiperidine (1.3 equiv., 0.26 mL), t_1 = 90 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: petroleum ether/ethylacetate (2/1)) 138 mg (63 %) of an untractable mixture containing 77 % of **13** + **15** and 23 % of **14**; ^{1}H NMR (deuteriochloroform, 300 MHz): **13**, δ = 7.85 (d, 1H, J_{H4-F} = 7.9 Hz, H_4); 5.07 (q, 1H, J_{CH-CH3} = 6.4 Hz, CH); 1.48 (d, 3H, J_{CH3-CH} = 6.4 Hz, CH_3); ^{1}H NMR (deuteriochloroform, 300 MHz): **14**, δ = 7.83 (s, 1H, H_5); 5.07 (q, 1H, J_{CH-CH3} = 6.4 Hz, CH); 1.48 (d, 3H, J_{CH3-CH} = 6.4 Hz, CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz) **13**: 163.8 (d, J_{C6-F} = 245.6 Hz, C_6); 155.9 (C_3); 139.3 (d, J_{C5-F} = 27.6 Hz, C_5); 130.3 (C_4); 63.4 (CH); 23.7 (CH_3); ^{13}C NMR (deuteriochloroform, 300 MHz): **14**, 157.2 (C_3 or C_6); 154.2 (C_3 or C_6); 149.2 (C_4); 127.8 (C_5); 65.9 (CH); 23.3 (CH_3); ^{19}F NMR (deuteriochloroform, 200 MHz): **13**, -87.05.

3-Chloro-6-fluoro-5-(1-hydroxyphenylmethyl)pyridazine (**16**) and 3,6-Dichloro-4-(1-hydroxyphenylmethyl)pyridazine (**17**).

Metalation of the mixture (152 mg, 1.12 mmol) of 3-chloro-6-fluoropyridazine (67 %, 0.77 mmol), 3,6-dichloropyridazine (28 %, 0.29 mmol) and 3,6-difluoropyridazine (5 %, 0.06 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (1.2 equiv., 0.84 mL), 2,2,6,6-tetramethylpiperidine (1.3 equiv., 0.25 mL), t_1 = 90 min, θ_1 = -78 °C, followed by reaction with benzaldehyde (1.5 equiv., 0.17 mL), t_2 = 60 min, θ_2 = -78 °C gave after purification by column chromatography (silica, eluent: petroleum ether/ethylacetate (2/1)) 150 mg (55 %) of an unseparable mixture containing 72 % of **16 + 18** and 28 % of **17**; ^{1}H NMR (deuteriochloroform, 300 MHz): **16**, 7.90 (d, 1H, J_{H4-F} = 7.7 Hz, H_4); 7.20 (m, 5H, $5H_{Ph}$); 5.85 (s, 1H, CH); 3.92 (br , 1H, OH); ^{1}H NMR (deuteriochloroform, 300 MHz): **17**, 7.92 (s, 1H, H_5); 7.20 (m, 5H, $5H_{Ph}$); 5.85 (s, 1H, CH); 3.92 (br, 1H, OH).

3-Chloro-6-Fluoro-5-iodopyridazine (**19**) and 3,6-Dichloro-4-iodopyridazine (**20**).

Metalation of the mixture (174 mg, 1.28 mmol) of 3-chloro-6-fluoropyridazine (67 %, 0.88 mmol), 3,6-dichloropyridazine (28 %, 0.33 mmol) and 3,6-difluoropyridazine (5 %, 0.07 mmol) was performed according to the general procedure with *n*-butyllithium 1.6 *M* (1.2 equiv., 0.96 mL), 2,2,6,6-tetramethylpiperidine (1.3 equiv., 0.28 mL), t_1 = 90 min, θ_1 = -78 °C, followed by reaction with iodine (1.1 equiv., 357 mg), t_2 = 60 min, θ_2 = -78 °C gave after purification by column chromatography (silica, eluent: petroleum ether/dichloromethane (2/1)) 123 mg (37 %) of an unseparable mixture containing 77 % of **19 + 21** and 23 % of **20**; ^{1}H NMR (deuteriochloroform, 300 MHz): **19**, 8.03 (d, 1H, J_{H4-F} = 6.6 Hz, H_4); ^{1}H NMR (deuteriochloroform, 300 MHz): **20**, 7.99 (s, 1H, H_5).

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