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Functionalization by Metallation of Fluoropyrazine. Diazines XXI.

Nelly Plé, Alain Turck, Arnault Heynderickx and Guy Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique. UPRES-A 6014

IRCOF-INSA, B.P. 08, 76131 Mont-Saint-Aignan Cedex (France)

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Abstract: Lithiation of fluoropyrazine followed by quenching with various electrophiles was successfully achieved and was used to synthesize new pyrazine derivatives. A further lithiation of 2-fluoro-3-substituted pyrazines allowed access to 2,3,6-trisubstituted pyridazine derivatives. As an application, a one-pot synthesis of a quinuclidinylfluoropyrazine has been performed. When the 3-substituent bears a TMS protected alcohol, functionalization *via* metallation at C_5 position provides tetrasubstituted pyrazines in good yield . © 1998 Elsevier Science Ltd. All rights reserved.

Halogenopyrazines are an important class of compounds in pyrazine chemistry since they can undergo easy displacement of the halogen atom with nucleophiles affording numerous otherwise inaccessible pyrazines.[1,2] Furthermore, synthesis of new pyrazines can be achieved using halogen to induce *ortho*-directed metallation and functionalization of 2-halogenopyrazines. Some years ago the regioselective lithiation of chloropyrazine was performed providing a new synthetic route to 2,3-disubstituted pyrazines.[3] As a continuation of our studies on diazines, [4] we report the direct lithiation and functionalization of fluoropyrazine.

The introduction of fluorine into a molecule results in considerable changes in its physical and chemical behaviour, thus making fluorinated compounds of special interest to both the synthetic and medicinal chemist. The fluorine atom has been previously used as an *ortho*-directing group with pyridine,[5] quinoline [6] and more recently with pyrimidine.[4c]

Starting from chloropyrazine, syntheses of fluoropyrazine[7] have been previously described in the literature with good yields (57-93%).

Fluoropyrazine **2** has been obtained in 80% yield *via* substitution of chlorine by a fluorine atom according to the procedure described by Zergenyi.[7d] The conditions of metallation have been optimized using various reaction times with LDA or LTMP as the metallating agent and with acetaldehyde as the electrophile (Scheme 1, Table 1).

Fax +332(35)522962 E-mail : <Guy. Queguiner@insa-rouen.fr>

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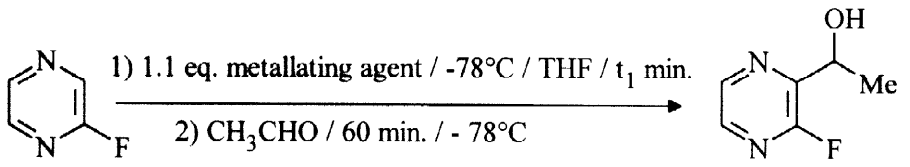
Scheme 1



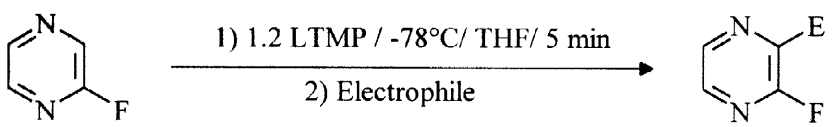
1 **2**

Table 1. Metallation of 2-fluoropyrazine **1** and reaction with acetaldehyde

Metallating agent	Reaction times t_1	Yield
LDA	5	52 %
"	10	65 %
"	15	42 %
LTMP	5	86 %
"	10	71 %
"	30	0%

The best result was obtained with LTMP as metallating agent and a short reaction time (5 min). These experimental conditions were chosen for the further reaction of **1** with other electrophiles (Scheme 2, Table 2).

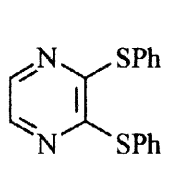
Scheme 2



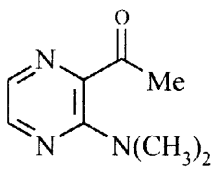
1 **2 - 13**

Table 2. Metallation of 2-fluoropyrazine **1** and reaction with electrophiles

Electrophile	E	Product	Yield
CH_3CHO	$CH_3CH(OH)$	**2**	86 %
PhCHO	PhCH(OH)	**3**	71 %
Ph_2CO	$Ph_2C(OH)$	**4**	45 %
Furfural	Furyl-2	**5**	69 %
p.(MeO)C_6H_4CHO	*p*.(MeO)$C_6H_4CH(OH)$	**6**	74 %
o.(MeO)C_6H_4CHO	*o*.(MeO)$C_6H_4CH(OH)$	**7**	75 %
HCOOEt	CHO	**8**	90 %
PhSSPh	SPh	**9**	30 %
I_2	I	**10**	54 %
BrCN	Br	**11**	28 %
$CH_3CON(CH_3)_2$	CH_3CO	**12**	34 %
$PhCON(CH_3)_2$	PhCO	**13**	68 %



14



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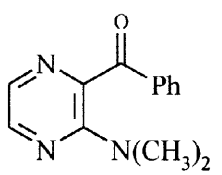
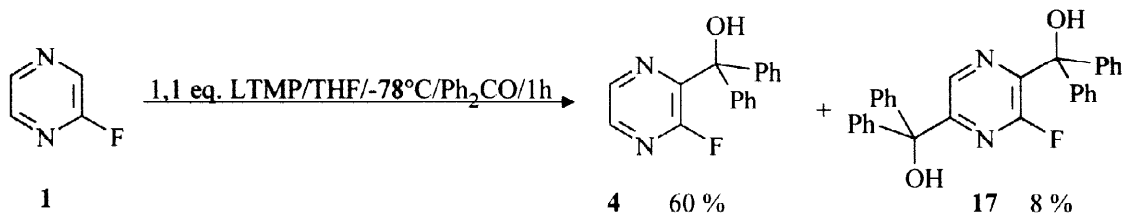


16

It was noticed that with diphenylsulfide as the electrophile, 2,3-diphenylthiopyrazine **14** was obtained in 12 % yield along with monosubstituted derivative **9**. Compound **14** results from a further nucleophilic substitution of fluorine atom by phenylthiolate ion. With N,N-dimethylacetamide or N,N-dimethylbenzamide as electrophile, substitution of fluorine by the N,N-dimethyl amino group was also observed leading to compounds **15** and **16** in 15 and 20 % yield respectively.

With the aim of improving the yield of the alcohol **4**, lithiation of **1** was performed under the experimental conditions of the *in situ* trapping method.[8] Compound **4** was obtained with a better yield (60%) along with dialcohol **17** in low yield (8%), which could result from a further lithation of **4** (Scheme 3).

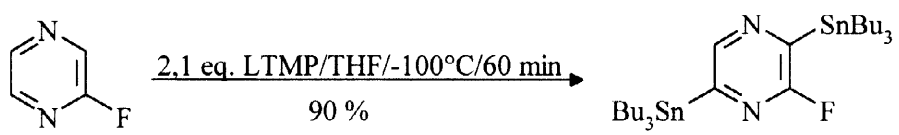
Scheme 3



1 **4** 60 % **17** 8 %

Moreover, when **1** was lithiated using the *in situ* trapping method with an excess of LTMP (2 equivalents) at low temperature (-100°C), and tributyltin chloride was used as the electrophile, 2-fluoro-3,6 tributylstanylpyrazine **18** was obtained in good yield, indicating that a further lithiation took place (Scheme 4).

Scheme 4



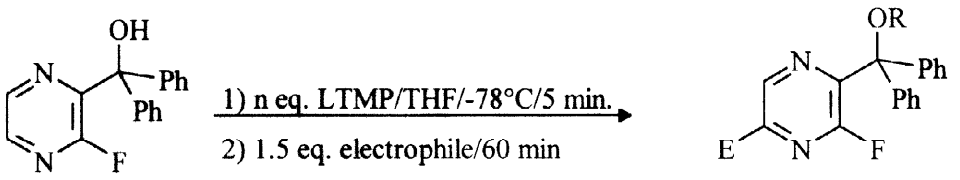
1 **18**

For compounds **17** and **18**, functionalization at the C_6 position has been unambiguously assigned thanks to long-range hydrogen-fluorine coupling constants. The remaining pyrazine hydrogen of **17** and **18** exhibited a high coupling constant (4.5 Hz for **17** and 6.0 Hz for **18**). These values are in agreement with those previously described for 2-fluoropyrazine by Jovanic,[9] which indicated a higher value for $^5J_{5,F}$ than $^4J_{6,F}$ ($^5J_{5,F}$ = 4.7 Hz , $^4J_{6,F}$ = 1.4 Hz).

This result urged us to check if an excess of metallating agent could induce a further lithiation at C_6 regardless of the structure of the 3-substituent.

Treatment of **4** with LTMP at -78°C for a short reaction time (5 min) followed by reaction with various electrophiles allowed functionalization at C_6 and afforded 2,3,6-trisubstitued pyrazines in good yields, (Scheme 5 Table 3).

Scheme 5



4 **17, 19 - 23**

Table 3. Metallation of **4** and reaction with various electrophiles

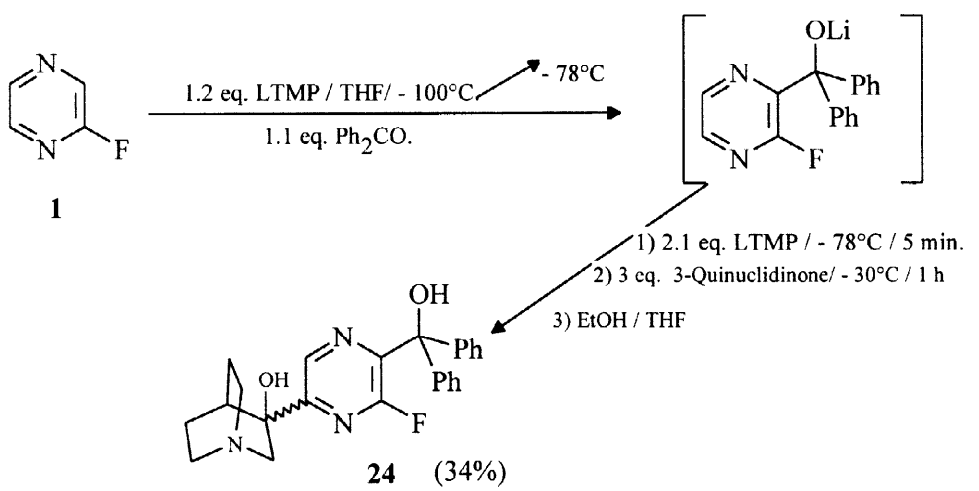
n eq.	Electrophile	E	R	Compound	Yield
2.1	Ph_2CO	$Ph_2C(OH)$	H	**17**	54 %
3.1	Ph_2CO	$Ph_2C(OH)$	H	**17**	90 %
3.1	CH_3CHO	$CH_3CH(OH)$	H	**19**	86 %
3.1	$ClSiMe_3$	Me_3Si	$SiMe_3$	**20**	95%
3,1	$ClSiMe_3$	Me_3Si	H	**21***	95 %
3.1	I_2	I	H	**22**	99 %
3.1	CCl_3CCl_3	Cl	H	**23**	76 %

- ** Compound 21 resulted from hydrolysis from 20*

As an application we have synthetised a quinuclidinylpyrazine. Similar structures previously described in the literature were found to possess muscarinic activity.[10,11]

The 3-hydroxyquinuclidinylpyrazine **24** was obtained "one pot" starting from 2-fluoropyrazine **1** (Scheme 6).

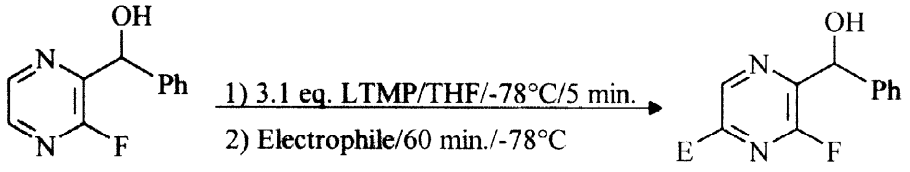
Scheme 6



1 **24** (34%)

Under similar experimental conditions, lithiation of the secondary alcohol **3** was achieved and the lithiated derivative reacted with acetaldehyde or iodine as the electrophile leading to compounds **25** and **26** in good yields (Scheme 7).

Scheme 7



3

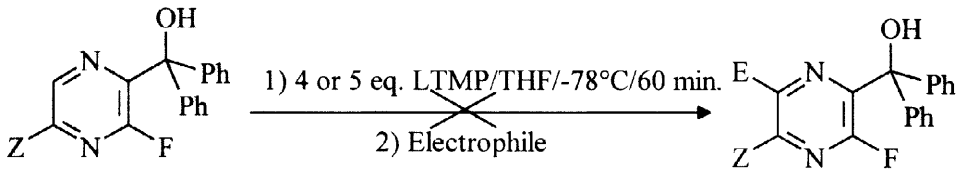
E = $CH_3CH(OH)$ **25** 90 %

E = I **26** 84 %

In view of the successful fontionalization at C_6, it was deciced to test the possibility of metallation at C_5 in order to gain access to tretrasubstituted pyrazines.

Attempts to metalate compounds **17,19-22** were performed with an excess of LTMP (4 or 5 equivalents) in THF at -78°C with various electrophiles (Scheme 8).

Scheme 8



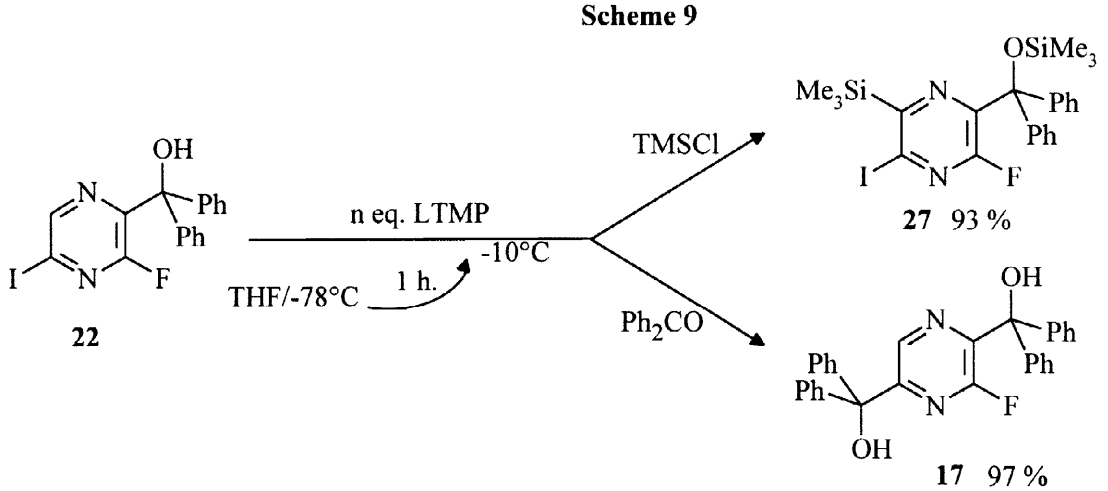
17, 19 - 22

Z : $Ph_2C(OH)$, $CH_3CH(OH)$, $SiMe_3$, I

Electrophile : PHCHO, TMSCl, CH_3CHO

In all cases the lithiation failed and the starting materials were recovered. It could be assumed that bulky substituents such as $Ph_2C(OH)$ or $SiMe_3$ could prevent approach of a hindered base such as LTMP at the C_5 position. Further attempts were performed with the iodo derivative **22** and LTMP as metallating agent according to the "*in situ* trapping" method, with a rise of temperature from -78°C to -10°C over one hour. The electrophile was TMSCl or benzophenone (Scheme 9, Table 4).

Scheme 9



22

27 93 %

17 97 %

Table 4. Metallation of **22** according *in situ* trapping method

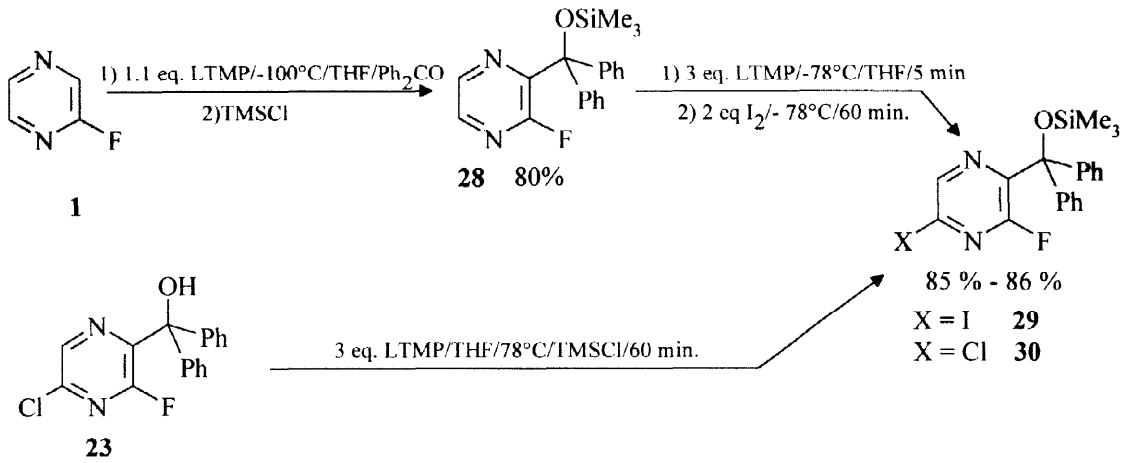
n eq.	Electrophile	Compound	Yield
6	TMSCl	**27**	93 %
5	Ph_2CO	**17**	97 %

With TMSCl as the electrophile the tetrasubstituted compound **27**, resulting from lithiation at the C_5 position was obtained in good yield, whereas with benzophenone the dialcohol **17**, resulting from an iodine-lithium exchange,[12] was obtained in high yield.

These results exhibited a considerable difference in the reactivity of **22** (metallation versus halogen-metal exchange), which could be due to the nature of the substituent at C_3 towards the two electrophiles. It must be noted that in the first case, TMSCl and LTMP were present in excess in the reaction mixture leading to protection of the alcohol as its trimethyl silyl ether, whereas in the second case the substituent at C_3 was a lithium alkoxide. To determine what kind of 3-substituent had a determining effect, the silylethers **29**, **30** were synthetized and then submitted to the metallation reaction.

The iodo compound **29** was obtained by metallation of silylether **28** with LTMP followed by reaction with iodine, whereas **30** was easily obtained starting from the corresponding tertiary alcohol **23** by treatment with LTMP followed by reaction with trimethylsilyl chloride (Scheme 10).

Scheme 10



Compounds **29** and **30** were then submitted to lithiation at -78°C with 2 equivalents of LTMP and reacted with various electrophiles leading to tetrasubstituted pyrazines (Scheme 11, Table 5).

Scheme 11

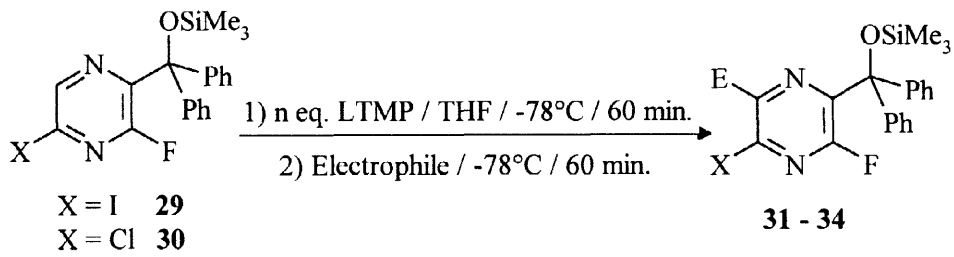


Table 5. Metallation of compounds **29** and **30** and reaction with various electrophiles

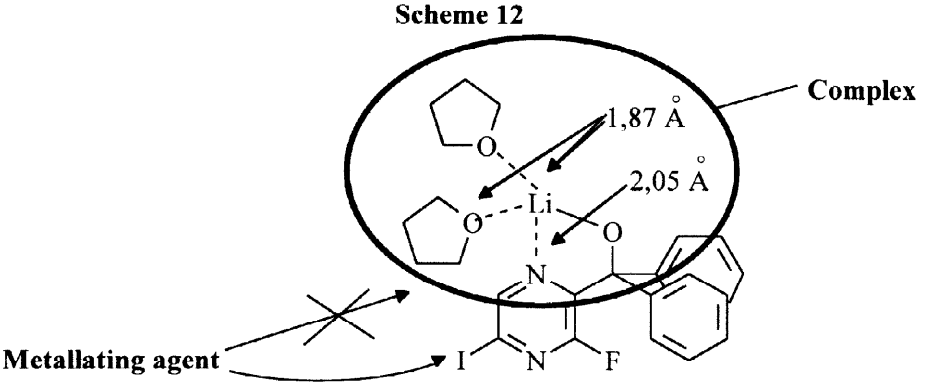
X	n eq.	Electrophile	Compound	Yield
I	2,1	Ph_2CO	**31**	70 %
I	2,1	CH_3CHO	**32**	81 %
I	2,1	CH_3I	**33**	60 %
Cl	3,1	$SiMe_3$	**34**	66 %
Cl	3,1	I	**35**	70 %

The difference in reactivity could be explained as follows:

It could be assumed that with an alkoxide group the lithium undergoes a complexation between the oxygen of the alkoxide and the nitrogen of the heterocycle ; lithium being generally tetracoordinated, it could be complexed with two supplementary solvent molecules, or included in a dimer structure with two pyrazines.

Such a complex has been modeled by computer-aided molecular modeling with the MMX method. The geometry of the mixed aggregate reveals a steric hindrance which could prevent approach of the bulky base, LTMP, thus inhibiting deprotonation at C_6 and allowing only a halogen-exchange at C_5. (Scheme 12). However, another plausible explanation may be the fact that built-in metal alkoxides tend to trigger single-electron transfer processes.

Scheme 12



We have highlighted the possibility of lithiating the 5 position when there is a silyl ether protecting group on the alcohol. These results provided a new synthetic route to tetrasubstituted pyrazines by reaction of 6-lithioderivatives with various electrophiles.

CONCLUSION

Ortho-directed metallation and functionalization of fluoropyrazine has been performed leading to various 2-fluoro-3-substituted pyrazines. The use of an excess of metallating agent with the *in situ* trapping method allowed funtionalization at the C_6 position. This result was developed with 2-fluoro-3-diphenylhydroxymethylpyrazine to synthesize various 2,3,6-trisubstituted pyrazines.

It was highlighted that the nature of the substituent at the C_3 position had an influence upon the reactivity of 6-fluoropyrazines, such that the presence of a lithium alkoxide induced an halogen-metal exchange whereas a protecting group such as trimethylsilyl ether allowed functionalization at the C_5 position affording tetrasubstituted pyrazines.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. Mass spectra were recorded at 70 eV (EI) on a JEOL JMS-AX 500 spectrometer.

Tetrahydrofuran was distilled from benzophenone/sodium and used immediatly. Water content of the solvent was estimated by the modified Karl Fischer method (THF less than 50 ppm water).[13]

Metallations were performed under an argon atmosphere. Reagents were handled with syringes through septa.

General procedure for metallation A.

A solution of *n*-butyllithium 1.6 or 2.5 M in hexane (n eq.) was added to cooled (-50°C), stirred, anhydrous tetrahydrofuran (20 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (n eq.) was added. The mixture was warmed to 0°C for 20 minutes. The mixture was then carried to θ_1. The pyrazine dissolved in 5 ml of tetrahydrofuran was added and the mixture was stirred for a time t_1 at θ_1. A solution of electrophile in 5 ml of tetrahydrofuran was introduced and stirring was continued for a time t_2 at q_2. Hydrolysis was then carried out at θ_2 using a solution of 35% aqueous hydrochloric acid (2ml), ethanol (2ml) and tetrahydrofuran (5ml) for θ_2= - 78°C. For a temperature eq.ual or higher than 0°C, the hydrolysis solution was a mixture of water (2 ml) and ethanol (8ml). The solution was warmed to room temperature, made slightly basic with a saturated sodium hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorised with sodium thiosulphate and evaporated nearly dryness. The residue was extracted with dichloromethane (3x20ml). The organic extract was dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel by sublimation, distillation or sublimation.

General procedure for metallation B : so called "in situ trapping technique"

A solution of *n*-butyllithium (1.6 M in hexane) was added to cold (-50°C), stirred, anhydrous tetrahydrofuran (15 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpyperidine was added. The mixture was warmed to 0°C and it was allowed to stand at 0°C for 20 minutes. The mixture temperature was then carried to θ. The pyrazine dissolved in 5 ml tetrahydrofuran and the electrophile were simultaneously introduced and the mixture was stirred for a time t. during this time temperature was slowly increase from θ_1 to θ_2. The following steps are similar to metallation A

2-Fluoropyrazine (1): Chloropyrazine (1.56 ml, 75 mmol) was introduced in a solution of anhydrous potassium fluoride (2.00 g, 135 mmol) in 50 ml *N*-methylpyrrolidinone. The mixture was refluxed for 2.5 h. A distillation at atmospheric pressure at 108°C gave 5.9g (80%) of **1** as a colorless liquid; ^{1}H NMR ($CDCl_3$): δ 8.37 (dd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{5,F}$ = 4.5 Hz, H_5); 8.32 (dd, 1H, $J_{3,6}$ = 1.2 Hz, $J_{3,F}$ = 8.3 Hz, H_3); 8.09 (m, 1H H_6); ^{13}C NMR ($CDCl_3$): δ. 160.1 (d, J = 252 Hz, C_2), 141.5, 141.5 (d, J = 20Hz, C_5 , C_6), 113.6 (d, J = 40 Hz, C_3); ^{19}F NMR ($CDCl_3$): δ - 80.37.Anal Calcd for $C_4H_3FN_2$ (98.08): C, 48.98, H, 3.08, N, 28.56. Found C, 48.6, H, 3.1, N, 28.8.

2-Fluoro-3-(1-hydroxyethyl)pyrazine (2): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with acetaldehyde (2ml, 37 eq.), t_2 = 60 min, θ_2= - 78°C afforded after purification by column chromatography (silica, eluent : dichloromethane/ethylacetate (10/1)) 250 mg (86%) of **2** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.42 (dd, 1H, $J_{5,6}$ = 2.5 Hz, $J_{5,F}$ = 6.8 Hz, H_5); 8.11 (m, 1H, H_6); 5.07 (m, 1H, J = 6.5 Hz, CH); 3.90 (d, 1H, J = 6.5 Hz, OH); 1.48 (dd, 3H, J = 6.5 Hz, $J_{Me,F}$ = 0.9 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ - 79.23. Anal Calcd for $C_6H_7FN_2O$ (142.13): C, 50.70; H, 4.96; N, 19.71. Found: C, 51.0; H, 4.7; N, 19.7.

2-Fluoro-3-(1-phenylhydroxymethyl)pyrazine (3): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C,

followed by reaction with benzaldehyde (325 mg, 3.06 mmol.) t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : cyclohexane/ethylacetate (3/8)) 295 mg (71%) of **3** as a white solid, mp 81-82°C; ^{1}H NMR ($CDCl_3$): δ 8.46 (dd, 1H, $J_{5,6}$ = 2.5 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 = 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.

2-Fluoro-3-(diphenylhydroxymethyl)pyrazine (4): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with benzophenone (390 mg, 2.1mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography silica, eluent : ether/cyclohexane (1/1)) 458 mg (80%) of **4** as a white solid, mp 54-55°C; ^{1}H NMR ($CDCl_3$): δ 8.46 (dd, 1H, $J_{5,6}$ = 2.6 Hz, $J_{5,F}$ = 4.3 Hz, H_5); 8.20 (m, 1H, H_6); 7.34 (m, 10H Phenyl); 6.00 (s,1H, OH).Anal Calcd for $C_{17}H_{13}FN_2O$ (280.30): C, 72.94; H, 4.67; N, 9.99. Found: C, 72.8; H, 4.9; N, 9.8.

2-Fluoro-3-[1-(2-furyl)hydroxymethyl]pyrazine (5) : Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with furfural (295 mg, 3.06mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane, 273 mg (69%) of **5** as a orange oil; ^{1}H NMR ($CDCl_3$): δ 8.47 (dd, 1H, $J_{5,6}$ = 2.6 Hz, $J_{5,F}$ = 3.9 Hz, H_5); 8.19 (m, 1H, H_6); 7.32 (d, 1H J = 1.1 Hz, $H_{5'}$); 6.28 (m,1H, $H_{4'}$); 6.25 (d, 1H, J = 3.2 Hz, $H_{3'}$); 6.00 (d, 1H, J = 7.5 Hz, CH); 4.56 (d, 1H, OH). ^{19}F NMR ($CDCl_3$): δ - 78.66 Anal Calcd for $C_9H_7FN_2O_2$ (194.16): C, 55.67; H, 3.63; N, 14.42. Found: C, 55.7; H, 3.8; N, 14.2.

2-Fluoro-3-[1-(4-methoxyphenyl)hydroxymethyl]pyrazine (6) : Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with *p*-anisaldehyde (415 mg, 3.06mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (3/8)), 353 mg (74%) of **6** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.37 (dd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{5,F}$ = 3.9 Hz, H_5); 8.04 (m, 1H, H_6); 7.23 (d, 2H J = 8.7 Hz, $H_{2'}$, $H_{6'}$); 6.78 (d, 2H, $H_{3'}$, $H_{5'}$); 5.88 (d, 1H, J = 5.6 Hz, CH); 4.81 (d, 1H, OH); 3.69 (s, 3H, OCH_3). ^{19}F NMR ($CDCl_3$): δ - 77.91. Anal Calcd for $C_{12}H_{11}FN_2O_2$ (234.23): C, 61.53; H, 4.73; N, 11.96. Found: C, 61.6; H, 4.7; N, 11.9.

2-Fluoro-3-[1-(2-methoxyphenyl)hydroxymethyl]pyrazine (7) : Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, $_1$= - 78°C, followed by reaction with *o*-anisaldehyde (416 mg, 3.06mmol.) afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (3/8)), 358 mg (75%) of 7 as a yellow solid, mp 90-91°C; ^{1}H NMR ($CDCl_3$): 8.47 (dd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{5,F}$ = 4 Hz, H_5); 8.12 (m, 1H, H_6); 7.24 (m, 2H); 6.78 (m, 2H); 6.26 (d, 1H, J = 8 Hz, CH); 4.34 (d, 1H, OH); 3.76 (s, 3H, OCH_3). ^{19}F NMR ($CDCl_3$): - 77.7. Anal Calcd for $C_{12}H_{11}FN_2O_2$ (234.23): C, 61.53; H, 4.73; N, 11.96. Found: C, 61.3; H, 4.9; N, 12.0.

2-Fluoro-3-formylpyrazine (8): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with ethylformiate (0.25 ml, 3.06 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane) 231 mg (90%) of **8** as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 10.16 (d, 1H, $J_{CHO,F}$= 0.4 Hz, CHO); 8.69 (dd,1H, $J_{5,6}$ = 2.4Hz, $J_{5,F}$= 3.8 Hz); 8.44 (d, 1H, $J_{6,F}$= 1.5 Hz); ^{19}F NMR ($CDCl_3$): δ - 76.22 .Anal Calcd for $C_5H_3FN_2O$ (126.09): C, 47.63; H, 2.39; N, 22.20. Found: C, 47.4; H, 2.7; N, 22.0.

2-Fluoro-3-phenylthiopyrazine (9): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with diphenyl sulfide (670 mg, 3.06 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ether/cyclohexane (1/2)) a mixture of **9** and **14**. Ratio and yields established by NMR spectra. gave (30%) of **9** (and 12% of **14**); ^{1}H NMR ($CDCl_3$): δ 8.14 (d,1H, $J_{5,6}$ = 2.7Hz; $J_{5,F}$ = 4.5Hz, H_5); 7.84 (m, 1H, H_6); 7.50 (m, 5H, Phenyl). $C_{10}H_7FN_2S$ (206.24). MS (EI): *m/z* = 206 (M^+).

2-Fluoro-3-iodopyrazine (10): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with iodine (1.0 g, 4 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography

(silica, eluent : dichloromethane/cyclohexane (1/1)) 247 mg (54%) of **10** as a white solid, mp 45-46°C; ^{1}H NMR ($CDCl_3$): δ 8.28 (dd, 1H, $J_{5,6}$= 2.5 Hz, $J_{5,F}$= 4 Hz, H_5); 8.09 (m, 1H, H_6); ^{19}F NMR ($CDCl_3$): δ - 64.4 . Anal Calcd for $C_4H_2FIN_2$ (223.97): C, 21.45; H, 0.90; N, 12.51. Found: C, 21.6; II, 0.6; N, 12.3.

2-Fluoro-3-bromopyrazine (11): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with cyanogen bromide (324 mg, 3.06 mmol.) afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (1/1)) 101 mg (28%) of **11** as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 8.27 (dd, 1H, $J_{5,6}$= 2.5 Hz, $J_{5,F}$= 4 Hz, H_5); 8.09 (m, 1H, H_6). Anal Calcd for $C_4H_2BrFN_2$ (176.97): C, 27.15; H, 1.14; N, 15.83. Found: C, 27.0; H, 1.0; N, 15.6.

2-Acetyl-3-fluoropyrazine (12): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with N,N-dimethylacetamide (266 mg, 3.06 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane) 114 mg (34%) of **12** as a white solid, mp 35-36°C; ^{1}H NMR ($CDCl_3$): δ 8.57 (d, 1H, $J_{5,6}$= 2.4 Hz, $J_{5,F}$= 3.9 Hz, H_5); 8.38 (dd, 1H, $J_{5,6}$= 2.4 Hz, $J_{6,F}$= 1.6 Hz, H_6); 2.7 (s, 3H, CH_3). Anal Calcd for $C_6H_5FN_2O$ (140.12): C, 51.43; H, 3.6; N, 19.99. Found: C, 51.6; H, 3.6; N, 19.7.

2-Benzoyl-3-fluoropyrazine (13): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with N,N-dimethylbenzamide (460 mg, 3.06 mmol.), t_2 = 60 min, θ= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/ethylacetate (18/1)) 280 mg (68%) of **13** as a white solid; mp 99-100°C. ^{1}H NMR ($CDCl_3$): δ 8.59 (dd, 1H, $J_{5,6}$= 2.6 Hz, $J_{5,F}$= 6.3 Hz, H_5); 8.39 (m, 1H, H_6); 7.9 (m, 2H, $H_{2'}$, $H_{6'}$); 7.55 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); ^{19}F NMR ($CDCl_3$): δ - 74.99. Anal Calcd for $C_{11}H_7FN_2O$ (202.19): C, 65.34; H, 3.50; N, 13.85. Found: C, 65.6; H, 3.4; N, 13.7.

2,3-Diphenylthiopyrazine (14): Metallation of **1** (200 mg, 2.04 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.9 ml, 1.1 eq.), TMPH (0.41 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with diphenyl sulfide (670 mg, 3.06 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ether/cyclohexane (1/2)) a mixture of **19** and **24**. Ratio and yields established by NMR spectra. gave 12% of **24** and (30% of **19**); ^{1}H NMR ($CDCl_3$): δ 7.96 (s, 2H, H_5, H_6); 7.50 (m, 10H, phenyl). $C_{16}H_{12}N_2S_2$ (296.41). MS (EI): *m/z* = 296 (M^+).

2-Acetyl-3-dimethylaminopyrazine (15): Purification of **15** was performed by column chomatography (silica , eluent dichloromethane) giving 51 mg (15%) of **15** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, $J_{5,6}$= 2.0 Hz, H_5); 7.84 (d, 1H, H_6); 2.97 (s, 6H, NMe_2); 2.67 (s, 3H, MeCO). Anal Calcd for $C_8H_{11}N_3O$ (165.19): C, 58.17; H, 6.70; N, 25.44. Found: C,58.5; H, 6.6; N, 25.1.

2-Benzoyl-3-dimethylaminopyrazine (16): Purification of **16** was performed by column chomatography (silica , eluent dichloromethane/ethylacetate (18/1)) giving 97 mg (21%) of **26** as a yellow solid, mp 104-105°C; ^{1}H NMR ($CDCl_3$): 8.14 (d, 1H, $J_{5,6}$= 2.6 Hz, H_5); 8.00 (m, 2H, $H_{2'}$, $H_{6'}$); 7.86 (d, 1H, H_6); 7.50 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 3.00 (s, 6H, NMe_2). Anal Calcd for $C_{12}H_{13}N_3O$ (227.26): C, 68.70; H, 5.76; N, 18.49. Found: C,68.5; H, 5.7; N, 18.8.

2-Fluoro-3,6-bis(diphenylhydroxymethyl)pyrazine (17):

Method A: metallation of **4** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.68 ml, 3.1 eq.),TMPH (0.72 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C and benzophenone (290 mg, 1.57 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ether/cyclohexane (1/1)) 595 mg (90%) of **17** as a yellow solid; mp 62-63°C.

Method B: metallation of **22** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (4.47 ml, 5.1 eq.),TMPH (1.21 ml, 5.15 eq.),t_1 = 60 min, θ_1= - 78°C and benzophenone as an electrophile (290mg, 1.57 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : cyclohexane/ether (1/1)) 641 mg (97%) of **27** as a yellow solid, mp 62-63°C. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 1H, $J_{5,F}$= 4.5 Hz, H_5); 7.35 (m, 20H, phenyl); 5.95 (s, 1H, OH); 4.54 (s, 1H, OH); ^{19}F NMR ($CDCl_3$): δ - 67.67. Anal Calcd for $C_{30}H_{23}FN_2O_2$ (462.52): C, 77.90; H, 5.01; N, 6.06. Found: C, 78.1; H, 5.2; N, 5.9.

2-Fluoro-3,6-bis(tributylstannyl)pyrazine (18): 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 eq.),TMPH (1.1 ml, 2.15 eq.),t = 60 min, θ= - 100°C and tri-n-butyltin chloride (2.0 g, 6.27 mmol.) afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (3/2)) **1.86 g (90%)** of **18** 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.

2-Fluoro-3-(diphenylhydroxymethyl)-6-(1-hydroxyethyl)pyrazine (19): Metallation of **4** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.76 ml, 3.1 eq.),TMPH (0.76 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with acetaldehyde (1.1 ml, 20 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (1/2)) 400 mg (86%) of **19** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 1H, $J_{5,F}$= 4.4 Hz, H_5); 7.29 (m, 10H, phenyl); 6.09 (s, 1H, OH); 4.88 (q,1H, *J* = 6.6 Hz, CH); 3.44 (m, 1H, OH); 1.51 (d, 3H, CH_3); ^{19}F NMR ($CDCl_3$): δ - 88.92. Anal Calcd for $C_{19}H_{17}FN_2O_2$ (324.35): C, 70.36; H, 5.28; N, 8.64. Found: C, 70.6; H, 5.3; N, 8.8.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-trimethylsilylpyrazine (20): Metallation of **4** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.76 ml, 3.1 eq.),TMPH (0.76 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with chlorotrimethylsilane (0.46 ml, 3.6 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (2/3)) 577 mg (95%) of **20** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.51 (d, 1H, $J_{5,F}$= 5.3 Hz, H_5); 7.27 (m, 10H, phenyl); 0.32 (s, 9H, Me_3); - 0.12 (s 9H, $OSiMe_3$); ^{19}F NMR ($CDCl_3$): δ- 65.58. Anal Calcd for $C_{23}H_{29}FN_2OSi_2$ (424.66): C, 65.05; H, 6.90; N, 6.59. Found: C, 65.1; H, 7.0; N, 6.6.

2-Fluoro-3-(diphenylhydroxymethyl)-6-trimethylsilylpyrazine (21): Hydrolysis of **20** (500 mg, 1.18 mmol) with a mixture of methanol (10 ml) and sulfuric acid 36N (1 ml) at room temperature for 15 minutes afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (2/3)) 395 mg (95%) of **21** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 1H, $J_{5,F}$= 5.3 Hz, H_5); 7.32 (m, 10H, phenyl); 6.15 (s, 1H, OH); 0.40 (s, 9H, Me_3); ^{19}F NMR ($CDCl_3$): δ - 66.49. Anal Calcd for $C_{20}H_{21}FN_2OSi$ (352.48): C, 68.15; H, 6.00; N, 7.95. Found: C, 67.9; H, 5.9; N, 7.9.

2-fluoro-3-(diphenylhydroxymethyl)-6-iodopyrazine (22): metallation of **4** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.76 ml, 3.1 eq.),TMPH (0.76 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with iodine (726mg, 2.86 mmol.), t_2 = 60 min,θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (2/8)) 575 mg (99%) of **22** as a white solid, mp 127-128°C. ^{1}H NMR ($CDCl_3$): δ 8.73 (d, 1H, $J_{5,F}$= 4.0 Hz, H_5); 7.30 (m, 10H, phenyl); 5.48 (s, 1H, OH); ^{19}F NMR ($CDCl_3$): δ - 63.49. Anal Calcd for $C_{17}H_{12}FIN_2O$ (406.20): C, 50.27; H, 2.98; N, 6.89. Found: C,50.0; H, 2.8; N, 6.7.

2-Fluoro-3-(diphenylhydroxymethyl)-6-chloropyrazine (23): Metallation of **4** (400 mg, 1.43 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.76 ml, 3.1 eq.),TMPH (0.76 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with hexachloroethane (508mg, 2.14 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/petroleum ether (2/1)) 342 mg (76%) of **23** as a white solid, mp 98-99°C. ^{1}H NMR ($CDCl_3$): δ8.48 (d, 1H, $J_{5,F}$= 3.6 Hz, H_5); 7.33 (m, 10H, phenyl); 5.46 (s, 1H, OH). Anal Calcd for $C_{17}H_{12}ClFN_2O$ (314.74): C, 64.87; H, 3.84; N, 8.90. Found: C, 65.1; H, 3.9; N, 9.0.

3-[2-(6-Fluoro-5-(diphenylhydroxymethyl)pyrazinyl)]-1-azabicyclo[2,2,2]octan-3-ol (24):

Metallation of **1** (200 mg, 2.04 mmol) according to general procedure B with *n*-BuLi 1.6M (1.34 ml, 1.05 eq.), TMPH (0.4 ml, 1.1 eq.) with benzophenone as electrophile (2.14 mmol), t = 30 min, θ = -100°C. temperature was then rised to - 78°C in 1 hour. Then a solution of LTMP (2.25 eq.) in THF (10 ml) previously prepared was added at this temperature. After 5 minutes a solution of quinuclidinone (0.77g, 6.011 mmol) in THF (5ml) was added and the solution was stirred at - 78°C for 1 hour. The solution was warmed to - 30°C and kept at this temperature for 1 hour. Hydrolysis was performed by a mixture THF/EtOH (1/1), neutralised with HCl (10N) and solvent was evaporated under reduce pressure. The residue was extracted by dichloromethane (3x20)ml, the organic extract dried over magnesium sulfate. Solvent removal afforded a

crude product which was purified by colum chromatography (silica, eluent: ethylacetate) 281 mg (34%) of **24** as a white solid, mp 60-61°C. ^{1}H NMR ($CDCl_3$): 8.75 (d, 1H, $J_{5,F}$= 4.7 Hz, H_5); 7.30 (m, 10H, phenyl); 3.65 (d, 1H, J = 16 Hz); 2.90 (d, 1H, J = 16 Hz); 2.8-2.7 (m, 4H) 2.70 (m, 5H); 2.20 (m, 1H); 2.05 (m, 1H); 1.95 (s, 1H); 1.2 (m, 4H) Anal Calcd for $C_{24}H_{24}FN_3O_2$ (405.47): C, 71.09; H, 5.96; N, 10.36. Found: C, 70.9; H, 5.9; N, 10.3.

2-Fluoro-3-(phenylhydroxymethyl)-6-(1-hydroxyethyl)pyrazine (25): Metallation of **3** (200 mg, 0.98 mmol) according to the general procedure A with *n*-BuLi 1.6 M (1.9 ml, 3.1 eq.),TMPH (0.52 ml, 3.15 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with acetaldehyde (0.54 ml, 10 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (1/1)) 219 mg (90%) of **25** as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 8.51 (d, 1H, $J_{5,F}$= 4.0 Hz, H_5); 7.27 (m, 5H, phenyl); 5.92 (s, 1H, CH); 3.50 (d, 1H, J = 6.4 Hz, OH); 1.43 (d, 3H, J = 6.4 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ - 79.44. Anal Calcd for $C_{13}H_{13}FN_2O_2$ (248.25): C, 62.89; H, 5.28; N, 11.28. Found: C, 63.0; H, 5.5; N, 11.4.

2-Fluoro-3-(phenylhydroxymethyl)-6-iodopyrazine (26): Metallation of **3** (500 mg, 2.45 mmol) according to the general procedure A with *n*-BuLi 1.6 M (4.75 ml, 3.1 eq.),TMPH (1.3 ml, 7.7 eq.),t_1 = 60 min, θ_1= - 78°C, followed by reaction with iodine (1.25 g, 4.9 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ethylacetate/cyclohexane (1/4)) 678 mg (84%) of **26** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 1H, $J_{5,F}$= 3.7 Hz, H_5); 7.31 (m, 5H, phenyl); 5.90 (d, 1H, J = 7.0 Hz, CH); 4.32 (d, 1H, J = 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, 39.9; H, 2.4; N, 8.6.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-iodo-5-trimethylsilylpyrazine(27):
Metallation of **22** (100 mg, 0.25 mmol) according to the general procedure B, with *n*-BuLi 1.6 M (0.9 ml, 6.1 eq.),TMPH (0.25 ml, 6.15 eq.), t = 60 min,θ = - 78°C and chlorotrimethylsilane as an electrophile (0.13 ml, 1.0 mmol.) θ_1 = - 78°C, θ_2 = - 10°C afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (1/3)) 128 mg (93%) of **27** as a white solid; mp 82-83°C. ^{1}H NMR ($CDCl_3$): δ 7.32 (s, 10H, phenyl); 0.48 (s , 9H, $SiMe_3$); -0.03 (s, 9H, $OSiMe_3$); ^{19}F NMR ($CDCl_3$): δ - 70.34. Anal Calcd for $C_{23}H_{28}FIOSi_2$ (550.56): C, 50.17; H, 5.12; N, 5.09. Found: C, 50.2; H, 4.9; N, 5.1.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]pyrazine (28): Metallation of **1** (200 mg, 2.04 mmol) was performed according procedure previously described to synthesize **4** with benzophenone as electrophile. Before hydrolysis, chlorotrimethylsilane was added at -78°C and mixture was stirred for 30 minutes. After hydrolysis and treatment of mixture reaction as previously, purification by column chromatography (silica, eluent : dichloromethane/petroleum ether (1/1)) afforded 676 mg (80%) of **28** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.46 (dd, 1H, $J_{5,6}$ = 2.6 Hz, $J_{5,F}$= 3.9 Hz, H_5); 8.20 (m, 1H, H_6, 7.34 (m, 10H, phenyl); -0.09 (s, 9H, OSi Me_3). Anal Calcd for $C_{20}H_{21}FIN_2OSi$ (352.48): C, 68.15; H, 6.00; N, 7.95. Found: C, 68.0 H, 5.9; N, 8.2.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-iodopyrazine (29): Metallation of **28** (236 mg mg, 0.67mmol) was performed according to the general procedure A with *n*-BuLi 1.6 M (1.30 ml, 3.1 eq.),TMPH (0.34 ml, 3.2 eq.), t_1 = 30 min, θ_1= - 78°C and iodine as an electrophile 340 mg,, 1.34 mmol.). afforded after purification by column chromatography silica, eluent : dichloromethane/cyclohexane (1/2)) 275 mg (86%) of **29** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 8.71 (d, 1H, $J_{5,F}$= 3.9 Hz, H_5); 7.30 (s, 10H, phenyl); -0.10 (s, 9H, OSi Me_3). Anal Calcd for $C_{20}H_{20}FIN_2OSi$ (478.38): C, 50.21; H, 4.21; N, 5.85. Found: C, 50.5 H, 4.3; N, 5.9.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-chloropyrazine (30): Metallation of **23** (94.5 mg, 0.3 mmol) according to the general procedure B with *n*-BuLi 2.5 M (0.9 ml, 1.1 eq.),TMPH (0.41 ml, 1.2 eq.), t = 65 min, θ= - 78°C and chlorotrimethylsilane as an electrophile (0.11 ml, 0.9 mmol.) afforded after purification by column chromatography (silica, eluent : dichloromethane/petroleum ether (1/1)) 99 mg (85%) of **30** as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 8.43 (d, 1H, $J_{5,F}$= 4.0 Hz, H_5); 7.20 (s, 10H, phenyl); -0.10 (s, 9H, $OSiMe_3$). Anal Calcd for $C_{20}H_{20}ClFN_2OSi$ (386.93): C, 62.08; H, 7.23; N, 5.21. Found: C, 62.0; H, 7.1; N, 5.1.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-iodo-5-(diphenylhydroxymethyl)pyrazine (31):
Metallation of **29** (104 mg, 0.22mmol) according to the general procedure A with *n*-BuLi 2.5 M (0.18 ml, 2 eq.),TMPH (0.08 ml, 2.1 eq.), t_1 = 60 min, θ_1 = - 78°C and benzophenone as an electrophile (0.43 ml, 0.24

mmol.) t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (1/1)) 102 mg (70%) of **31** as a white solid, mp 54-55°C. ^{1}H NMR ($CDCl_3$): δ 7.32 (s, 20H, phenyl); 4.78 (s 1H, OH); -0.07 (s, 9H, $OSiMe_3$); ^{19}F NMR ($CDCl_3$): δ - 70.85. Anal Calcd for $C_{33}H_{30}FIO_2Si$ (660.60): C, 60.00; H, 4.58; N, 4.24. Found: C, 60.2; H, 4.6; N, 4.0.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-iodo-5-(1-hydroxyethyl)pyrazine (32): Metallation of **29** (170 mg, 0.36mmol) according to the general procedure A with *n*-BuLi 2.5 M (0.30 ml, 2 eq.),TMPH (0.13 ml, 2.1 eq.), t_1 = 60 min, θ_1= - 78°C with acetaldehyde as an electrophile (1.0 ml, 18 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane) 148 mg (81%) of **32** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.29 (s, 10H, phenyl); 5.05 (m, 1H, CH); 2.93 (d, 1H, J = 9.0 Hz, OH); 1.49 (d, 3H, J = 6.5 Hz, CH_3); -0.10 (s, 9H, $OSiMe_3$); ^{19}F NMR ($CDCl_3$): δ - 70.91. Anal Calcd for $C_{22}H_{24}FIN_2O_2Si$ (506.43): C, 52.18; H, 4.77; N, 5.53. Found: C, 52.0; H, 4.5; N, 5.3.

2-fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-iodo-5-methylpyrazine (33): metallation of **29** (170 mg, 0.36mmol) according to the general procedure A with *n*-BuLi 2.5 M (0.30 ml, 2 eq.),TMPH (0.13 ml, 2.1 eq.), t_1 = 60 min, $_1$= - 78°C with iodomethane as an electrophile (70 l, 1.1 mmol.), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (1/1)) 106 mg (60%) of **33** as a white solid, mp 95-96°C. ^{1}H NMR ($CDCl_3$): δ 7.29 (s, 10H, phenyl); 2.63 (s 3H, CH_3); -0.05 (s, 9H, $OSiMe_3$); ^{19}F NMR ($CDCl_3$): δ - 71.48. Anal Calcd for $C_{21}H_{22}FIN_2OSi$ (492.41): C, 51.22; H, 4.50; N, 5.69. Found: C, 51.6; H, 4.4; N, 5.6.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-chloro-5-trimethylsilylpyrazine (34): Metallation of **30** (94.5 mg, 0.3 mmol) according to the general procedure B with *n*-BuLi 2.5 M (0.36 ml, 3.1 eq.),TMPH (0.52 ml, 3.1 eq.), t = 65 min, θ = - 78°C with chlorotrimethylsilane as an electrophile (0.13 ml, 1.0 mmol.) afforded after purification by column chromatography (silica, eluent : dichloromethane/ether petroleum (1/2)) 91 mg (66%) of **34** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.36-7.25 (m, 10H, phenyl); 0.31 (s , 9H, $SiMe_3$); -0.03 (s, 9H, $OSiMe_3$). Anal Calcd for $C_{23}H_{28}ClFN_2OSi_2$ (459.11): C, 60.17; H, 6.15; N, 6.10. Found: C, 60.4; H, 6.4; N, 6.3.

2-Fluoro-3-[diphenyl(trimethylsilyloxy)methyl]-6-chloro-5-iodopyrazine (35): Metallation of **30** (90 mg, 0.28 mmol) according to the general procedure A with *n*-BuLi 2.5 M (0.47 ml, 4.1 eq.),TMPH (0.20 ml,42.1 eq.), t_1 = 60 min, θ_1= - 78°C with iodine as an electrophile (102 mg, 0.40 mmol.),t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/cyclohexane (1/1)) 72 mg (70%) of **35** as a white solid, mp 114-115°C. ^{1}H NMR ($CDCl_3$): δ 7.29 (s, 10H, phenyl); -0.08 (s, 9H, $OSiMe_3$). Anal Calcd for $C_{20}H_{19}ClFIN_2Si$ (512.82): C, 46.84; H, 3.73; N, 5.46. Found: C, 46.8; H, 3.6; N, 5.3.

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