Alkali halides as nucleophilic reagent source for \( N \)-directed palladium-catalysed \( \text{ortho-} \text{C–H} \) halogenation of \( s \)-tetrazines and other heteroaromatics

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Optimization studies for \( \text{ortho-selective} \) \text{C–H} \) bromination

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Copy of NMR spectrum
**General Conditions**

All reagents were purchased from commercial suppliers and used without purifications. All experiments were carried out under air using a microwave reaction vessel. Microwave heating was carried out using a CEM Discover microwave reactor. The microwave reactions were run in closed reaction vessels with magnetic stirring and with the temperature controlled via IR detection. Flash chromatography was performed on silica gel (40-63 μm). The identity and purity of the products were established at the “Chemical Analysis Platform and Molecular Synthesis University of Burgundy” (PACSMUB Platform – SATT SAYENS) using high-resolution mass spectrometry, elemental analysis and multinuclear NMR. $^1$H (500, 400 or 300 MHz), $^{13}$C (125 or 101 MHz), $^{19}$F (470 or 282 MHz) spectra were recorded on Bruker AVANCE III instruments in CDCl$_3$ or CD$_2$Cl$_2$ solution. Chemical shifts are reported in ppm relative to CDCl$_3$ ($^1$H: 7.26 and $^{13}$C: 77.16) or CD$_2$Cl$_2$ ($^1$H: 5.32 and $^{13}$C: 54.00) and coupling constants J are given in Hz. High resolution mass spectra (HRMS) were obtained on a Thermo LTQ-Orbitrap XL with ESI source.

**Optimization studies**

**Optimization studies for ortho-selective C–H iodination**

Table S1: Screening reaction conditions for mono-iodination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1).\[^{[a]}\]

| Entry | [Pd] (5 mol%) | Oxidant (equiv.) | [I\(^{-}\)] (equiv.) | Solvent [0.125 M] | T (°C) | Time (min) | Conv. (%) | 1a (%) | 1a' (%) | 1b (%) |
|-------|---------------|------------------|----------------------|-------------------|-------|------------|----------|--------|---------|---------|
| 1     | -             | PIDA (1.2)       | -                    | HOAc              | 110   | 30         | 0        | 0      | 0       | 0       |
| 2     | Pd(OAc)$_2$   | -                | Nal (1.2)            | HOAc              | 110   | 30         | 0        | 0      | 0       | 0       |
| 3     | Pd(OAc)$_2$   | PIDA (1.2)       | -                    | HOAc              | 110   | 30         | 57       | 0      | 0       | 50$^{[b]}$ |
| 4     | Pd(OAc)$_2$   | PIDA (2.0)       | Nal (2.0)            | HOAc              | 110   | 30         | 98       | 63     | 35      | 0       |
| 5     | Pd(OAc)$_2$   | PIDA (1.2)       | Nal (1.2)            | HOAc              | 110   | 30         | 38       | 26     | 12      | 0       |
| 6     | Pd(OAc)$_2$   | K$_2$S$_2$O$_8$ (1.2) | Nal (1.2)            | HOAc              | 110   | 30         | 0        | 0      | 0       | 0       |
| 7     | Pd(OAc)$_2$   | PIDA (1.2)       | Nal (1.2)            | CH$_3$NO$_2$      | 110   | 30         | 0        | 0      | 0       | 0       |
| 8     | Pd(OAc)$_2$   | PIDA (1.2)       | Nal (1.2)            | DCE               | 90    | 30         | 0        | 0      | 0       | 0       |
| 9     | Pd(OAc)$_2$   | PIDA (1.2)       | Nal (1.2)            | PhCF$_3$          | 110   | 30         | 0        | 0      | 0       | 0       |
| 10    | Pd(dba)$_2$   | PIDA (1.2)       | Nal (1.2)            | HOAc              | 110   | 30         | 46       | 43     | 3       | 0       |
| 11    | Pd(OIv)$_2$   | PIDA (1.2)       | Nal (1.2)            | HOAc              | 110   | 30         | 79       | 68     | 11      | 0       |
| 12    | Pd(OAc)$_2$   | PIDA (1.2)       | Nal (1.2)            | HOAc              | 110   | 30         | 86       | 67 (55)| 19 (9)  | 0       |
| 13    | Pd(OAc)$_2$   | PIDA (1.2)       | Li (1.2)             | HOAc              | 110   | 30         | 82       | 70     | 12      | 0       |
| 14    | Pd(OAc)$_2$   | PIDA (1.2)       | KI (1.2)             | HOAc              | 110   | 30         | 84       | 72 (68)| 12      | 0       |
| 15    | Pd(OAc)$_2$   | PIDA (1.2)       | N(Bu)$_4$I (1.2)     | HOAc              | 110   | 30         | 79       | 70     | 9       | 0       |

\[^{[a]}\] Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1, 0.25 mmol, 1 equiv.), [Pd] (5 mol%), [I\(^{-}\)] (1.2-2.0 equiv.), oxidant (1.2-2.0 equiv.), solvent [0.125 M], 90-110 °C, 30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on 1 by $^1$H and $^{19}$F NMR analysis. Isolated yield are given under bracket. PIDA: Phenylidine diacetate [PhI(OAc)$_2$]. PIFA: Bis(trifluoroacetoxy)iodobenzene [PhI(OCOCF$_3$)$_2$]. DCE: Dichloroethane. \(^{[b]}\) 7% of diacetoxylated product was observed.
**Optimization studies for ortho-selective C–H bromination**

**Table S2:** Screening reaction conditions for mono-bromination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1).

| Entry | Oxidant (equiv.) | [Br⁻] (equiv.) | Solvent [0.125 M] | T (°C) | Time (min) | Conv. (%) | 1c (%) | 1c' (%) | 1b (%) |
|-------|------------------|----------------|-------------------|--------|------------|-----------|--------|---------|--------|
| 1     | PIDA (3.2)       | NaBr (3.2)     | CH₃NO₂            | 110    | 45         | 5         | 0      | 0       | 0      |
| 2     | PIDA (1.2)       | NaBr (3.2)     | HOAc              | 110    | 45         | 47        | 47     | 0       | 0      |
| 3     | PIDA (1.2)       | NaBr (1.2)     | HOAc              | 110    | 30         | 88        | 71 (60)| 11      | 3[^b] |
| 4     | PIDA (1.2)       | KBr (1.2)      | HOAc              | 110    | 30         | 86        | 73 (60)| 13      | 9      |

[^a]: Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1, 0.25 mmol, 1 equiv.), [Pd(OAc)₂] (5 mol%), [Br⁻] (1.2-3.2 equiv.), PIDA (1.2-3.2 equiv.), solvent [0.125 M], 110 °C, 30-45 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on 1 by ^1H and ^19F NMR analysis. Isolated yield are given under bracket. PIDA: Phenyliodine diacetate [PhI(OAc)₂].[^b] 3% of diacetoxylated product was observed.

**Optimization studies for ortho-selective C–H chlorination**

**Table S3:** Screening reaction conditions for mono-chlorination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1).

| Entry | [Cl⁻] (equiv.) | Solvent [0.125 M] | T (°C) | Time (min) | Conv. (%) | 1d (%) | 1d' (%) | 1b (%) |
|-------|----------------|-------------------|--------|------------|-----------|--------|---------|--------|
| 1     | NaCl (1.2)     | HOAc              | 110    | 30         | 87        | 61     | 12      | 10[^b] |
| 2     | KCl (1.2)      | HOAc              | 120    | 30         | 83        | 67     | 12      | 6[^c]  |
| 3     | KCl (1.2)      | HOAc              | 110    | 30         | 89 (55%)  | 62 (11%)| 17      | 8[^c]  |

[^a]: Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1, 0.25 mmol, 1 equiv.), [Pd(OAc)₂] (5 mol%), [Cl⁻] (1.2 equiv.), PIDA (1.2 equiv.), HOAc [0.125 M], 110 °C, 30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on 1 by ^1H and ^19F NMR analysis. PIDA: Phenyliodine diacetate [PhI(OAc)₂].[^b] 4% of diacetoxylated product was observed.[^c] 2% of diacetoxylated product was observed.
Optimization studies for ortho-selective C–H acetoxylation

Table S4: Screening reaction conditions for mono-acetoxylation of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1).\(^a\)

| Entry | [Pd(OAc)\(_2\)] (mol%) | Oxidant (equiv.) | Additive (equiv.) | Solvent [0.125 M] | T (°C) | Time (min) | Conv. (%) | 1b (%) | 1b’ (%) |
|-------|------------------------|-----------------|-----------------|-------------------|--------|------------|-----------|--------|---------|
| 1     | 10                     | PIDA (1.2)      | -               | HOAc              | 110    | 10         | 59        | 52     | 7       |
| 2     | 5                      | PIDA (1.2)      | -               | HOAc              | 110    | 30         | 57        | 52     | 5       |
| 3     | 5                      | PIDA (1.2)      | -               | HOAc              | 110    | 30         | 57        | 50     | Trace   |
| 4     | 5                      | PIDA (1.2)      | KOAc (1.2)      | HOAc              | 110    | 30         | 50        | 50     | 6       |
| 5     | 10                     | PIDA (1.2)      | -               | HOAc              | 120    | 65         | 56        | 56     | 9       |
| 6     | 10                     | PIDA (1.2)      | -               | HOAc              | 110    | 30         | 60        | 54 (40)| 6       |
| 7     | 10                     | PIDA (3.0)      | -               | HOAc              | 110    | 10         | 77        | 53     | 24      |
| 8     | 10                     | K\(_2\)S\(_2\)O\(_8\) (3.0) | - | HOAc | 110 | 10 | 21 | 21 | 0 |
| 9     | 10                     | PIDA (6.0)      | -               | HOAc              | 110    | 30         | 56        | 51     | 5       |

\(^a\) Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1, 0.25 mmol, 1 equiv.), [Pd(OAc)\(_2\)] (5-10 mol%), oxidant (1.2-6.0 equiv.), additive (0-1.2 equiv.), HOAc [0.125 M], 110-120 °C, 10-30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on 1 by \(^1\)H and \(^19\)F NMR analysis. PIDA: Phenyliodine diacetate [PhI(OAc)\(_2\)].

General procedures

General procedure for the halogenation of heteroaryl derivatives

As a typical experiment, in a microwave reaction vessel equipped with a magnetic stirring bar was charged with heteroaryls (1 equiv., 0.25 mmol), [Pd(OAc)\(_2\)] (5 mol%), PIDA (1.2 equiv., 0.3 mmol) and KX (1.2 equiv., 0.3 mmol) in acetic acid [0.125 M] under air. The mixture was heated at 110 °C during the corresponding time under microwaves irradiations (200 Watts). After cooling down to room temperature, the solvent was removed under vacuum and the residue was analysed by \(^1\)H and \(^19\)F NMR spectroscopy to determine the conversion and selectivity of the halogenation reaction. The crude mixture was purified by silica gel column chromatography using an appropriate ratio of eluent (Dichloromethane or Ethyl Acetate/Heptane or Pentane) to afford the targeted product.

3-(2-Fluoro-6-iodophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1a)

Isolated yield: 68% (67 mg, as a purple solid). Rf = 0.51 (Dichloromethane/Heptane: 7/3).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.46–8.40 (m, 1H), 7.88–7.84 (m, 1H), 7.71–7.63 (m, 1H), 7.46–7.30 (m, 4H).

\(^19\)F{\(^1\)H} NMR (282 MHz, CDCl\(_3\)): \(\delta\) (ppm) = –108.8 (1F), –111.0 (1F).

3-(2-Bromo-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1c)

Isolated yield: 60% (52 mg, as a purple solid). Rf = 0.52 (Dichloromethane/Heptane: 7/3).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.42 (td, \(J = 7.6\) and \(1.8\) Hz, 1H), 7.69–7.65 (m, 1H), 7.62 (dt, \(J = 8.2\) and \(1.0\) Hz, 1H), 7.48 (td, \(J = 8.3\) and \(5.8\) Hz, 1H), 7.43 (td, \(J = 7.6\) and \(1.1\) Hz, 1H), 7.36 (ddd, \(J = 10.9, 8.4\) and \(1.1\) Hz, 1H), 7.30 (td, \(J = 8.9\) and \(1.0\) Hz, 1H).

\(^19\)F{\(^1\)H} NMR (470 MHz, CDCl\(_3\)): \(\delta\) (ppm) = –110.0 (1F), –111.0 (1F).
3-(2-Chloro-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1d)\(^1\)
Isolated yield: 55% (42 mg, as a purple solid). Rf = 0.55 (Dichloromethane/Heptane: 7/3).
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.42 (td, \(J = 7.6\) and 1.8 Hz, 1H), 7.70–7.63 (m, 1H), 7.55 (td, \(J = 8.3\) and 5.8 Hz, 1H), 7.46–7.43 (m, 2H), 7.41–7.33 (m, 1H), 7.29–7.23 (m, 1H).
\(^1^9\)F\(^{1}\)H NMR (282 MHz, CDCl\(_3\)): \(\delta\) (ppm) = −111.1 (1F), −111.1 (1F).

3-(2-Iodophenyl)-6-phenyl-1,2,4,5-tetrazine (2a)\(^1\)
Isolated yield: 61% (55 mg, as a purple solid). Rf = 0.44 (Dichloromethane/Heptane: 1/1).
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.73–8.71 (m, 2H), 8.12 (dd, \(J = 8.0\) and 1.0 Hz, 1H), 7.99 (dd, \(J = 7.7\) and 1.6 Hz, 1H), 7.70–7.58 (m, 4H), 7.31–7.26 (m, 1H).

3-(2-Bromophenyl)-6-phenyl-1,2,4,5-tetrazine (2c)\(^2\)
Isolated yield: 48% (37 mg, as a purple solid). Rf = 0.34 (Dichloromethane/Heptane: 1/1).
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.72–8.70 (m, 2H), 8.02 (dd, \(J = 7.7\) and 1.7 Hz, 1H), 7.83 (dd, \(J = 8.0\) and 1.1 Hz, 1H), 7.69–7.62 (m, 3H), 7.57 (td, \(J = 7.6\) and 1.2 Hz, 1H), 7.49 (td, \(J = 7.8\) and 1.7 Hz, 1H).

3-(2-Chlorophenyl)-6-phenyl-1,2,4,5-tetrazine (2d)\(^2\)
Isolated yield: 35% (23 mg, as a purple solid). Rf = 0.45 (Dichloromethane/Heptane: 1/1).
\(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) (ppm) = 8.69–8.67 (m, 2H), 8.05 (dd, \(J = 7.4\) and 2.0 Hz, 1H), 7.71–7.64 (m, 4H), 7.61–7.54 (m, 2H).

3-(4-Fluoro-6-Iodophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3a)
Isolated yield: 51% (50 mg, as a purple solid). Rf = 0.36 (Dichloromethane/Heptane: 1/1).
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.74–8.71 (m, 2H), 8.03 (dd, \(J = 8.7\) and 5.7 Hz, 1H), 7.85 (dd, \(J = 8.0\) and 2.6 Hz, 1H), 7.35–7.30 (m, 3H).
\(^1^9\)F\(^{1}\)H NMR (470 MHz, CDCl\(_3\)): \(\delta\) (ppm) = −105.3 (1F), −107.3 (1F).
\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 167.6 (d, \(J = 254.1\) Hz), 167.1, 164.9 (d, \(J = 256.7\) Hz), 163.0, 134.0 (d, \(J = 3.5\) Hz), 133.4 (d, \(J = 9.1\) Hz), 131.3 (d, \(J = 9.2\) Hz), 128.9 (d, \(J = 24.3\) Hz), 128.4 (d, \(J = 3.2\) Hz), 117.2 (d, \(J = 22.3\) Hz), 116.7 (d, \(J = 21.5\) Hz), 95.8 (d, \(J = 8.4\) Hz).
HRMS + p ESI (m/z) [M+H]\(^{+}\) calcd for C\(_{14}\)H\(_8\)F\(_3\)IN\(_2\): 396.97562; Found: 396.97519.

3-(4-Fluoro-6-bromophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3c)
Isolated yield: 50% (43 mg, as a purple solid). Rf = 0.36 (Dichloromethane/Heptane: 2/3).
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.74–8.71 (m, 2H), 8.06 (dd, \(J = 8.7\) and 5.9 Hz, 1H), 7.58 (dd, \(J = 8.2\) and 2.5 Hz, 1H), 7.35–7.27 (m, 3H).
\(^1^9\)F\(^{1}\)H NMR (470 MHz, CDCl\(_3\)): \(\delta\) (ppm) = −105.3 (1F), −106.3 (1F).
\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 167.2 (d, \(J = 255.2\) Hz), 165.8, 165.1 (d, \(J = 256.9\) Hz), 162.5, 133.7 (d, \(J = 9.2\) Hz), 130.9 (d, \(J = 9.0\) Hz), 130.0 (d, \(J = 3.5\) Hz), 127.7 (d, \(J = 3.0\) Hz), 123.3 (d, \(J = 9.9\) Hz), 122.2 (d, \(J = 24.8\) Hz), 116.9 (d, \(J = 22.1\) Hz), 115.7 (d, \(J = 21.5\) Hz).
HRMS + p ESI (m/z) [M+H]\(^{+}\) calcd for C\(_{14}\)H\(_8\)BrF\(_2\)N\(_2\): 348.98949; Found: 348.98915.

3-(4-Fluoro-6-chlorophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3d)
Isolated yield: 45% (34 mg, as a purple solid). Rf = 0.33 (Dichloromethane/Heptane: 2/3).
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.74–8.70 (m, 2H), 8.10 (dd, \(J = 8.7\) and 5.9 Hz, 1H), 7.39 (dd, \(J = 8.4\) and 2.5 Hz, 1H), 7.34–7.30 (m, 2H), 7.28–7.23 (m, 1H).
\(^1^9\)F\(^{1}\)H NMR (470 MHz, CDCl\(_3\)): \(\delta\) (ppm) = −105.3 (1F), −106.0 (1F).
\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 167.2 (d, \(J = 255.0\) Hz), 165.3 (d, \(J = 256.2\) Hz), 165.1, 162.5, 135.3 (d, \(J = 10.7\) Hz), 133.8 (d, \(J = 9.6\) Hz), 130.9 (d, \(J = 9.2\) Hz), 128.1 (d, \(J = 3.7\) Hz), 127.7 (d, \(J = 3.2\) Hz), 119.0 (d, \(J = 25.0\) Hz), 116.9 (d, \(J = 22.2\) Hz), 115.2 (d, \(J = 21.6\) Hz).
HRMS + p ESI (m/z) [M+H]^+ calcd for C_{14}H_{8}ClF_{2}N_4: 305.04001; Found: 305.03974.

3-(3-Fluoro-6-iodophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4a)
Isolated yield: 35% (35 mg, as a purple solid). Rf = 0.2 (Dichloromethane/Pentane: 3/7).

1H NMR (400 MHz, CDCl_3): δ (ppm) = 8.52 (ddd, J = 7.8, 1.6 and 1.0 Hz, 1H), 8.41 (ddd, J = 9.7, 2.6 and 1.5 Hz, 1H), 8.08 (dd, J = 8.8 and 5.3 Hz, 1H), 7.78 (dd, J = 8.9 and 3.0 Hz, 1H), 7.62 (td, J = 8.1 and 5.7 Hz, 1H), 7.38 (tdd, J = 8.3, 2.7 and 1.0 Hz, 1H), 7.07 (ddd, J = 8.7, 7.8 and 3.0 Hz, 1H).

3F(^1H) NMR (470 MHz, CDCl_3): δ (ppm) = -110.7 (1F), -112.4 (1F).

13C NMR (101 MHz, CDCl_3): δ (ppm) = 166.8 (d, J = 2.4 Hz), 164.7 (d, J = 247.7 Hz), 164.3 (d, J = 250.1 Hz), 162.7 (d, J = 3.2 Hz), 142.8 (d, J = 7.6 Hz), 138.5 (d, J = 7.7 Hz), 133.7 (d, J = 8.2 Hz), 131.2 (d, J = 8.0 Hz), 124.4 (d, J = 3.1 Hz), 120.5 (d, J = 21.3 Hz), 120.2 (d, J = 21.6 Hz), 119.2 (d, J = 24.3 Hz), 115.6 (d, J = 24.0 Hz), 88.7 (d, J = 3.7 Hz).

HRMS + p ESI (m/z) [M+H]^+ calcd for C_{14}H_{8}F_{2}N_4: 396.97562; Found: 396.97516.

3-(3-Fluoro-6-bromophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4c)
Isolated yield: 35% (30 mg, as a purple solid). Rf = 0.35 (Dichloromethane/Pentane: 3/7).

1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.52 (d, J = 7.8 Hz, 1H), 8.41 (d, J = 9.5 Hz, 1H), 7.81–7.78 (m, 2H), 7.62 (td, J = 8.0 and 5.6 Hz, 1H), 7.38 (td, J = 8.3 and 2.7 Hz, 1H), 7.22 (td, J = 8.2 and 3.1 Hz, 1H).

3F(^1H) NMR (470 MHz, CDCl_3): δ (ppm) = -110.7 (1F), -113.1 (1F).

13C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 166.5 (d, J = 2.3 Hz), 164.9 (d, J = 246.8 Hz), 163.5 (d, J = 248.6 Hz), 163.2 (d, J = 3.2 Hz), 136.6 (d, J = 7.8 Hz), 135.6 (d, J = 8.2 Hz), 134.2 (d, J = 8.3 Hz), 131.8 (d, J = 7.9 Hz), 124.7 (d, J = 3.0 Hz), 120.7 (d, J = 21.5 Hz), 120.5 (d, J = 22.2 Hz), 119.8 (d, J = 25.1 Hz), 117.2 (d, J = 3.4 Hz), 115.7 (d, J = 24.0 Hz).

HRMS + p ESI (m/z) [M+H]^+ calcd for C_{14}H_{8}BrF_{2}N_4: 348.98949; Found: 348.98911.

3-(3-Fluoro-6-chlorophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4d)
Isolated yield: 28% (21 mg, as a purple solid). Rf = 0.4 (Dichloromethane/Pentane: 3/7).

1H NMR (400 MHz, CDCl_3): δ (ppm) = 8.51 (d, J = 7.9 Hz, 1H), 8.40 (dt, J = 9.6 and 2.0 Hz, 1H), 7.83 (dd, J = 8.5 and 3.1 Hz, 1H), 7.65–7.59 (m, 2H), 7.38 (td, J = 8.0 and 2.5 Hz, 1H), 7.31–7.26 (m, 1H).

3F(^1H) NMR (470 MHz, CDCl_3): δ (ppm) = -110.7 (1F), -113.6 (1F).

13C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 165.8 (d, J = 2.2 Hz), 164.9 (d, J = 254.4 Hz), 163.2 (d, J = 3.2 Hz), 162.9 (d, J = 255.6 Hz), 134.2 (d, J = 8.3 Hz), 133.6 (d, J = 8.2 Hz), 133.4 (d, J = 8.2 Hz), 131.8 (d, J = 8.1 Hz), 129.3 (d, J = 3.5 Hz), 124.7 (d, J = 3.0 Hz), 120.7 (d, J = 21.4 Hz), 120.4 (d, J = 22.8 Hz), 119.5 (d, J = 25.3 Hz), 115.7 (d, J = 24.1 Hz).

HRMS + p ESI (m/z) [M+H]^+ calcd for C_{14}H_{8}ClF_{2}N_4: 305.04001; Found: 305.03989.

1-(1-Iodophenyl)-2-phenyl-diazone (5a)
Isolated yield: 39% (46 mg, as an orange solid). Rf = 0.4 (Dichloromethane/Heptane: 2/3).

1H NMR (400 MHz, CDCl_3): δ (ppm) = 8.04 (dd, J = 7.9 and 1.3 Hz, 1H), 8.02–7.99 (m, 2H), 7.64 (dd, J = 8.0 and 1.6 Hz, 1H), 7.57–7.50 (m, 3H), 7.45–7.41 (m, 1H), 7.19–7.15 (m, 1H).

1-(2-Bromophenyl)-2-phenyl-diazone (5c)
Isolated yield: 60% (39 mg, as an orange solid). Rf = 0.4 (Dichloromethane/Heptane: 2/3).

1H NMR (400 MHz, CDCl_3): δ (ppm) = 7.99 (dd, J = 8.1 and 1.7 Hz, 2H), 7.76 (dd, J = 7.9 and 1.4 Hz, 1H), 7.68 (dd, J = 8.0 and 1.7 Hz, 1H), 7.56–7.50 (m, 3H), 7.40 (td, J = 7.6 and 1.4 Hz, 1H), 7.32 (td, J = 7.5 and 1.7 Hz, 1H).

2-(1-Iodo-6-methylphenyl)-pyrimidine (6a)
Isolated yield: 65% (48 mg, as a colourless oil). Rf = 0.3 (Dichloromethane/Heptane: 3/7).

1H NMR (400 MHz, CDCl_3): δ (ppm) = 8.90 (d, J = 4.9 Hz, 2H), 7.76 (dd, J = 7.9 and 0.4 Hz, 1H), 7.32 (t, J = 4.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 2.12 (s, 3H).
Isolated yield: 61% (38 mg, as a colourless oil). Rf = 0.3 (Dichloromethane/Heptane: 1/1).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 8.90 (d, $J = 4.9$ Hz, 2H), 7.49 (dd, $J = 7.7$ and 0.6 Hz, 1H), 7.32 (t, $J = 4.9$ Hz, 1H), 7.24–7.21 (m, 1H), 7.17 (t, $J = 7.7$ Hz, 1H), 2.11 (s, 3H).

9-Iodo-2-methyl-napthtol[1,2-d]thiazole (7a)
Isolated yield: 56% (45 mg, as a white solid). Rf = 0.33 (Ethyl acetate/Heptane: 1.5/8.5).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 8.40 (d, $J = 7.4$ Hz, 1H), 7.92 (dd, $J = 8.3$ and 5.6 Hz, 2H), 7.75 (d, $J = 8.7$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H), 2.97 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) = 163.0, 147.0, 141.9, 134.9, 133.3, 129.4, 128.6, 126.5, 126.1, 119.7, 88.7, 20.5.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{12}$H$_9$IINS: 325.94949; Found: 325.94913.

9-Chloro-2-methyl-napthtol[1,2-d]thiazole (7d)
Isolated yield: 53% (31 mg, as a yellow solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.93 (d, $J = 8.7$ Hz, 1H), 7.86 (dd, $J = 8.1$ and 1.0 Hz, 1H), 7.79 (d, $J = 8.7$ Hz, 1H), 7.74 (dd, $J = 7.5$ and 1.2 Hz, 1H), 7.45 (t, $J = 7.8$ Hz, 1H), 2.99 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) = 164.3, 147.6, 135.5, 134.4, 130.3, 129.7, 127.8, 126.1, 125.8, 125.7, 120.0, 20.7.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{12}$H$_9$ClNS: 234.01387; Found: 234.01377.

1-(2-Iodophenyl)-4-nitro-1H-pyrazole (8a)
Isolated yield: 62% (49 mg, as a white solid). Rf = 0.25 (Dichloromethane/Heptane: 3/7).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 8.45 (d, $J = 0.5$ Hz, 1H), 8.27 (s, 1H), 8.03 (dd, $J = 8.0$ and 1.3 Hz, 1H), 7.54 (td, $J = 7.6$ and 1.4 Hz, 1H), 7.46 (dd, $J = 7.9$ and 1.7 Hz, 1H), 7.28 (t, $J = 8.0$ and 1.7 Hz, 1H).

$^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 142.4, 140.9, 140.5, 136.9, 132.1, 131.0, 130.0, 128.4, 94.3.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{10}$H$_7$NClO$_2$: 315.95775; Found: 315.95757.

1-(2-Iodophenyl)-4-bromo-1H-pyrazole (9a)
Isolated yield: 80% (76 mg, as a white solid). Rf = 0.25 (Ethyl acetate/Heptane: 1/9).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 7.86 (dd, $J = 8.0$ and 1.3 Hz, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.51 (dd, $J = 8.1$ and 1.3 Hz, 1H), 7.13 (t, $J = 8.0$ Hz, 1H).

$^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 141.8, 140.5, 138.3, 133.6, 132.1, 131.2, 130.4, 98.5, 95.0.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{10}$H$_6$BrClN$_2$: 382.84421; Found: 382.84384.

1-(2-Bromo-6-iodophenyl)-4-bromo-1H-pyrazole (10a)
Isolated yield: 70% (75 mg, as a white solid). Rf = 0.4 (Dichloromethane/Heptane: 1/9).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 7.90 (dd, $J = 8.0$ and 1.3 Hz, 1H), 7.75 (s, 1H), 7.68 (dd, $J = 8.1$ and 1.3 Hz, 1H), 7.55 (d, $J = 0.5$ Hz, 1H), 7.05 (t, $J = 8.0$ Hz, 1H).

$^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 141.8, 141.7, 139.0, 133.6, 132.4, 131.0, 122.9, 98.4, 95.0.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{10}$H$_6$Br$_2$I$_2$N$_2$: 426.79369. Found 426.79311.

4-Bromo-1-[[2-ido-6-methylphenyl)methyl]-1H-pyrazole (11a)
Isolated yield: 51% (48 mg, as a white solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 7.78 (d, $J = 7.6$ Hz, 1H), 7.47 (s, 1H), 7.25 (s, 1H), 7.20 (d, $J = 7.7$ Hz, 1H), 6.97 (t, $J = 7.7$ Hz, 1H), 5.5 (s, 2H), 2.37 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 140.4, 139.8, 138.2, 135.6, 131.4, 130.8, 129.0, 103.0, 93.2, 59.0, 20.9.

HRMS + p ESI (m/z) [M+H]$^+$ calcld for C$_{14}$H$_{12}$BrI$_2$N$_2$: 376.91448. Found: 376.91405.

3-(2-Bromophenylmethyl)-6-(phenylmethyl)-1,2,4,5-tetrazine (12c)
Isolated yield: 54% (46 mg, as a purple solid). Rf = 0.35 (Ethyl acetate/Heptane: 1/9).
1H NMR (400 MHz, CDCl3): δ (ppm) = 7.58 (dd, J = 8.0 and 1.2 Hz, 1H), 7.42–7.38 (m, 3H), 7.34–7.29 (m, 3H), 7.28–7.25 (m, 1H), 7.16 (td, J = 7.7 and 1.7 Hz, 1H), 4.79 (s, 2H), 4.62 (s, 2H).

13C NMR (101 MHz, CDCl3): δ (ppm) = 169.2, 168.7, 135.9, 135.6, 133.2, 132.0, 129.4, 129.3, 129.0, 127.9, 127.5, 125.1, 41.4, 41.3.

HRMS + p ESI (m/z) [M+H]+ calcd for C16H14BrN4: 341.03964; Found: 341.03923.

2-(2,4-Difluorophenyl)-6-bromo-pyridine (13c)
Isolated yield: 51% (34 mg, as a colourless oil). Rf = 0.35 (Ethyl acetate/Heptane: 3/7).
1H NMR (500 MHz, CDCl3): δ (ppm) = 8.75 (dd, J = 4.8 and 0.6 Hz, 1H), 7.80 (td, J = 7.7 and 1.8 Hz, 1H), 7.38–7.33 (m, 2H), 7.26 (dt, J = 8.0 and 2.2 Hz, 1H), 6.92 (td, J = 8.9 and 2.5 Hz, 1H).
19F(1H) NMR (470 MHz, CDCl3): δ (ppm) = -107.7 (d, J = 7.3 Hz, 1F), -108.6 (d, J = 7.3 Hz, 1F).
13C NMR (125 MHz, CDCl3): δ (ppm) = 163.4 (dd, J = 252.9 and 13.4 Hz), 161.7 (dd, J = 252.5 and 13.1 Hz), 152.9, 149.8, 136.5, 126.8 (dd, J = 18.7 and 4.4 Hz), 125.8, 124.1 (dd, J = 11.7 and 5.4 Hz), 123.3, 116.6 (dd, J = 24.3 and 3.9 Hz), 104.1 (dd, J = 26.8 and 25.1 Hz).

HRMS + p ESI (m/z) [M+H]+ calcd for C13H8BrF2N: 269.97244; Found: 269.97211.

2-(2,4-Difluorophenyl)-6-chloro-pyridine (13d)
Isolated yield: 70% (39 mg, as a colourless oil). Rf = 0.03 (Ethyl acetate/Heptane: 3/7).
1H NMR (400 MHz, CDCl3): δ (ppm) = 8.75 (d, J = 4.4 Hz, 1H), 7.80 (td, J = 7.7 and 1.8 Hz, 1H), 7.39 (dd, J = 7.8 and 1.0 Hz, 1H), 7.34 (ddd, J = 7.6, 4.9 and 1.2 Hz, 1H), 7.08 (dt, J = 8.3, 2.4, 1H), 6.87 (td, J = 8.9 and 2.5 Hz, 1H).
19F(1H) NMR (470 MHz, CD2Cl2): δ (ppm) = -109.4 (d, J = 7.0 Hz, 1F), -109.5 (d, J = 7.0 Hz, 1F).
13C NMR (101 MHz, CDCl3): δ (ppm) = 163.5 (dd, J = 252.1 and 14.4 Hz), 162.2 (dd, J = 249.2 and 11.17 Hz), 151.5, 149.8, 136.5, 135.3 (dd, J = 12.7 and 6.6 Hz), 125.9, 125.0 (dd, J = 19.0 and 4.2 Hz), 123.3, 113.6 (dd, J = 24.7 and 4.0 Hz), 103.6 (dd, J = 26.8 and 25.2 Hz).

HRMS + p ESI (m/z) [M+H]+ calcd for C13H7F2ClN: 226.02296. Found: 226.02279.

1-(2-Bromophenyl)-4-chloro-1H-pyrazole (15)
Isolated yield: 46% (29 mg, as a white solid). Rf = 0.35 (Ethyl acetate/Heptane: 1.5/8.5).
1H NMR (400 MHz, CDCl3): δ (ppm) = 7.82 (s, 1H), 7.71 (dd, J = 8.0 and 1.4 Hz, 1H), 7.67 (s, 1H), 7.49 (dd, J = 7.9 and 1.8 Hz, 1H), 7.43 (td, J = 7.6 and 1.4 Hz, 1H), 7.30 (td, J = 7.8 and 1.8 Hz, 1H).

1-(2-Bromo-5-iodophenyl)-4-chloro-1H-pyrazole (16)
Isolated yield: 90% (86 mg, as a white solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).
1H NMR (400 MHz, CDCl3): δ (ppm) = 7.86 (dd, J = 8.0 and 1.3 Hz, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.51 (dd, J = 8.1 and 1.3 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H).
13C NMR (101 MHz, CDCl3): δ (ppm) = 141.8, 140.5, 138.3, 133.6, 132.1, 131.2, 130.4, 98.5, 95.0.

HRMS + p ESI (m/z) [M+H]+ calcd for C16H6BrClIN2: 382.84421; Found: 382.84380.

General procedure for the acetoxylation
As a typical experiment, in a microwave reaction vessel equipped with a magnetic stirring bar was charged with 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1 equiv., 0.25 mmol), [Pd(OAc)2] (5 mol%), and PIDA (1.2 equiv., 0.3 mmol) in acetic acid [0.125 M] under air. The mixture was heated at 110 °C during 30 min under microwaves irradiations (200 Watts). After cooling down at room temperature, the solvent was removed in vacuum and the residue was analysed by 1H and 19F NMR to determine the conversion and the selectivity of the acetoxylation reaction. The crude mixture was purified by silica gel column chromatography using an appropriate ratio of eluent (Dichloromethane/Heptane) to afford the desired product.
3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b)
Isolated yield: 40% (33 mg, as a purple solid). Rf = 0.3 (Dichloromethane/Heptane: 3/1).

$^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 8.36 (td, $J$ = 7.7 and 1.7 Hz, 1H), 7.72–7.63 (m, 2H), 7.46 (td, $J$ = 7.8 and 0.9 Hz, 1H), 7.37 (dd, $J$ = 11.0 and 8.4 Hz, 1H), 7.28 (t, $J$ = 8.7 Hz, 1H), 7.20 (d, $J$ = 8.3 Hz, 1H), 2.18 (s, 3H).

$^{19}$F{$^1$H} NMR (470 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = –112.7 (1F), –113.8 (1F).

$^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 169.5, 164.0 (d, $J$ = 5.7 Hz), 162.2 (d, $J$ = 259.3 Hz), 162.8 (d, $J$ = 255.7 Hz), 162.2 (d, $J$ = 3.9 Hz), 150.7 (d, $J$ = 4.3 Hz), 135.1 (d, $J$ = 8.8 Hz), 133.7 (d, $J$ = 10.2 Hz), 132.2 (d, $J$ = 0.7 Hz), 125.6 (d, $J$ = 3.9 Hz), 121.0 (d, $J$ = 9.9 Hz), 120.5 (d, $J$ = 23.6 Hz), 118.0 (d, $J$ = 21.6 Hz), 116.4 (d, $J$ = 14.9 Hz), 114.8 (d, $J$ = 21.5 Hz), 21.0.

HRMS + p ESI (m/z) [M+Na]$^+$ calcd for C$_{16}$H$_{10}$F$_2$N$_4$O$_2$Na: 351.06640; Found: 351.06613.

3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b’)
Isolated yield: 40% (39 mg, as a purple solid). Rf = 0.20 (Dichloromethane/Heptane: 3/1).

$^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 7.70–7.65 (m, 2H), 7.29 (t, $J$ = 9.0 Hz, 2H), 7.21 (d, $J$ = 8.3 Hz, 2H), 2.17 (s, 6H).

$^{19}$F{$^1$H} NMR (470 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = –113.8 (2F).

$^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ (ppm) = 169.4, 162.8 (d, $J$ = 255.9 Hz), 162.4 (d, $J$ = 3.1 Hz), 150.7 (d, $J$ = 4.3 Hz), 133.9 (d, $J$ = 10.3 Hz), 120.5 (d, $J$ = 3.5 Hz), 116.2 (d, $J$ = 14.8 Hz), 114.8 (d, $J$ = 21.4 Hz), 21.0.

HRMS + p ESI (m/z) [M+Na]$^+$ calcd for C$_{18}$H$_{12}$F$_2$N$_4$O$_4$Na: 409.07188; Found: 409.07130.

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Copy of NMR spectrum

3-(2-Fluoro-6-iodophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1a)

1H NMR, 300 MHz, CDCl3

19F NMR, 282 MHz, CDCl3
3-(2-Bromo-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1c)

$^{1}H$ NMR, 500 MHz, CDCl$_3$

$^{19}F$ NMR, 470 MHz, CDCl$_3$
3-(2-Chloro-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1d)

1H NMR, 300 MHz, CDCl3

19F NMR, 282 MHz, CDCl3

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3-(2-Iodophenyl)-6-phenyl-1,2,4,5-tetrazine (2a)

1H NMR, 500 MHz, CDCl3

3-(2-Bromophenyl)-6-phenyl-1,2,4,5-tetrazine (2c)

1H NMR, 500 MHz, CDCl3
3-(2-Chlorophenyl)-6-phenyl-1,2,4,5-tetrazine (2d)

3-(4-Fluoro-6-iodophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3a)
3-(4-Fluoro-6-bromophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3c)

1H NMR, 400 MHz, CDCl3

19F NMR, 470 MHz, CDCl3
3-(4-Fluoro-6-chlorophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3d)

1H NMR, 400 MHz, CDCl3

13C NMR, 125 MHz, CDCl3
3-(3-Fluoro-6-iodophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4a)

$^{1}H$ NMR, 400 MHz, CDCl$_3$
3-(3-Fluoro-6-bromophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4c)

$^{13}$C NMR, 101 MHz, CDCl$3$

$^1$H NMR, 500 MHz, CDCl$3$
3-(3-Fluoro-6-chlorophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4d)

1H NMR, 400 MHz, CDCl3

19F NMR, 470 MHz, CDCl3
1-(2-Iodophenyl)-2-phenyl-diazene (5a)

$1^H$ NMR, 400 MHz, CDC$_2Cl_2$
1-(2-Bromophenyl)-2-phenyl-diazene (5c)

1H NMR, 400 MHz, CDCl3

2-(2-Iodo-6-methylphenyl)-pyrimidine (6a)

1H NMR, 400 MHz, CDCl3
2-(2-Bromo-6-methylphenyl)-pyrimidine (6c)

1H NMR, 400 MHz, CDCl3

9-Iodo-2-methyl-naphtol[1,2-d]thiazole (7a)

1H NMR, 500 MHz, CDCl3
9-Chloro-2-methyl-napthtol[1,2-d]thiazole (7d)

1H NMR, 400 MHz, CDCl₃
1-(2-Iodophenyl)-4-nitro-1H-pyrazole (8a)

1H NMR, 400 MHz, CD2Cl2
1-(2-chloro-6-iodophenyl)-4-bromo-1H-pyrazole (9a)

1H NMR, 400 MHz, CDCl3
1-(2-Bromo-6-iodophenyl)-4-bromo-1H-pyrazole (10a)

1H NMR, 400 MHz, CDCl3

13C NMR, 101 MHz, CDCl3
4-Bromo-1-[[2-methyl-6-iodophenyl]methyl]-1H-pyrazole (11a)

1H NMR, 400 MHz, CDCl3

13C NMR, 101 MHz, CDCl3
$^{13}$C NMR, 101 MHz, CDCl$_3$

3-(2-Bromophenylmethyl)-6-(phenylmethyl)-1,2,4,5-tetrazine (12c)

$^1$H NMR, 400 MHz, CDCl$_3$
2-(2,4-Difluorophenyl)-6-bromo-pyridine (13c)

1H NMR, 500 MHz, CDCl3

13C NMR, 101 MHz, CDCl3

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2-(2,4-Difluorophenyl)-6-chloro-pyridine (13d)

1H NMR, 400 MHz, CDCl3

19F NMR, 470 MHz, CD2Cl2
1-(2-Bromophenyl)-4-chloro-1H-pyrazole (15)

1H NMR, 400 MHz, CDCl₃

13C NMR, 101 MHz, CDCl₃
1-(2-Bromo-5-iodophenyl)-4-chloro-1H-pyrazole (16)

$^1$H NMR, 500 MHz, CDCl$_3$

$^{13}$C NMR, 125 MHz, CDCl$_3$
3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b)

1H NMR, 500 MHz, CD2Cl2

19F NMR, 470 MHz, CD2Cl2
3,6-bis(2-Fluoro-6-acetylphenyl)-1,2,4,5-tetrazine (1b')

1H NMR, 500 MHz, CD2Cl2

13C NMR, 125 MHz, CD2Cl2
