

Supporting Information

Regioselective heterohalogenation of 4-halo-anisoles via a series of sequential *ortho*-aluminations and electrophilic halogenations

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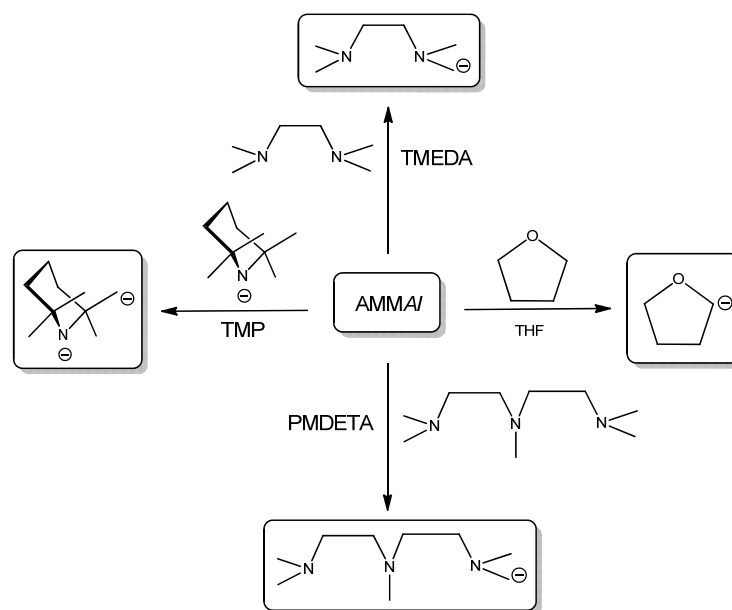
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General Methods

All reactions and manipulations were carried out under a protective argon atmosphere using either standard Schlenk techniques or a glove box. All solvents were dried over Na/benzophenone and freshly distilled prior to use. $[\text{LiAl}(\text{TMP})_2(i\text{Bu})_2]$ was prepared *in situ* by the literature method.¹ 4-iodoanisole, 4-bromoanisole, 4-chloroanisole, sulfonyl chloride, *N*-chlorosuccinimide, *N*-bromosuccinimide, hexachloroethane, 1,2-dibromotetrachloroethane, bromine and iodine were purchased from Aldrich and used as received. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV400 MHz spectrometer (operating at 400.03 MHz for ^1H and 100.58 MHz for ^{13}C). All ^{13}C NMR spectra were proton decoupled. Elemental analyses were performed by Denise Gilmour, University of Strathclyde Elemental Analysis Service, using Perkin Elmer 2400 Series II CHN/S Analyser. Gas chromatography-mass spectrometry was performed by Patricia Keating, University of Strathclyde, using Thermo Finnigan Polaris Q GCMS (ion trap).

¹ R. E. Mulvey, D. R. Armstrong, B. Conway, E. Crosbie, A. R. Kennedy, S. D. Robertson, *Inorg. Chem.* 2011, **50**, 12241-12251.



Scheme S1 Deprotonation sites of neutral TMEDA, PMDETA and THF and anionic TMP^- manifested through alkali-metal-mediated aluminations.

Synthesis of $[(\text{THF})\text{Li}(\mu\text{-TMP})\{1\text{-OMe-2-Al}(i\text{Bu})_2\text{-4-I-C}_6\text{H}_3\}]$ (2-int)

Hexane (10 mL) was added to an oven-dried Schlenk tube. Next, 1.6M $n\text{BuLi}$ (2.8 mL, 4.5 mmol) was added, followed by TMP(H) (0.77 mL, 4.5 mmol) at room temperature. The reaction mixture was left to stir for 10 min and then $i\text{Bu}_2\text{AlCl}$ (0.86 mL, 4.5 mmol) was injected into the Schlenk tube, producing a white suspension almost immediately. The reaction was left to stir for 1 hour and was then filtered through Celite and glass wool, which was then washed with more hexane (10 mL). To a separate Schlenk tube containing a solution of freshly prepared LiTMP in hexane (10 mL) [from a mixture of $n\text{BuLi}$ (2.8 mL, 4.5 mmol) and TMP(H) (0.77 mL, 4.5 mmol)], the solution was added through cannula to give a colourless solution. Finally, THF (0.36 mL, 4.5 mmol) and 4-iodoanisole (0.70 g, 3 mmol) were injected and the reaction mixture was left to stir overnight. A white suspension formed which dissolved on addition of 25 mL of toluene. The Schlenk tube was left in the freezer at -30°C . A crop (1.27 g, 71%) of colourless crystals formed in solution that were suitable for X-ray crystallographic analysis.

^1H NMR (400.13 MHz, 298 K, C_6D_{12}): δ = 0.54-0.75 [4H, m, 2 x CH_2 of $i\text{Bu}$], 0.85 [2H, m, 1 x βCH_2 of TMP], 1.06 [4H, m, 2 x βCH_2 of THF], 1.15 [6H, d, $^3J(\text{H,H})$ = 6.48 Hz, 2 x CH_3 of $i\text{Bu}$], 1.24 [6H, s, 2 x CH_3 of TMP], 1.35 [6H, d, $^3J(\text{H,H})$ = 6.47 Hz, 2 x CH_3 of $i\text{Bu}$], 1.36 [1H, m, 1 x γCH of TMP], 1.50 [2H, m, 1 x βCH_2 of TMP], 1.58 [6H, s, 2 x CH_3 of TMP],

1.86 [1H, m, 1 x γ CH of TMP], 2.29 [2H, m, 2 x CH of *i*Bu], 2.94 [4H, m, 2 x α CH₂ of THF], 3.19 [3H, s, CH₃O of 4-iodoanisole], 6.11 [1H, d, $^3J(\text{H,H}) = 8.53$ Hz, 1 x aromatic CH], 7.50 [1H, dd, $^3J(\text{H,H}) = 8.49$ Hz, $^4J(\text{H,H}) = 2.30$ Hz, 1 x aromatic CH], 8.49 ppm [1H, d, $^4J(\text{H,H}) = 2.30$ Hz, 1 x aromatic CH].

¹³C {¹H} (100.62 MHz, 298 K, C₆D₁₂): $\delta = 18.7$ [γ CH₂ of TMP], 25.0 [2 x β CH₂ of THF], 27.5 [2 x CH of *i*Bu], 28.0 [2 x CH₃ of *i*Bu], 28.5 [2 x CH₂ of *i*Bu], 30.2 [2 x CH₃ of TMP], 30.8 [2 x CH₃ of *i*Bu], 37.4 [2 x CH₃ of TMP], 44.2 [2 x β CH₂ of TMP], 53.2 [2 x quaternary C of TMP], 55.6 [CH₃O of 4-iodoanisole], 68.5 [2 x α CH₂ of THF], 90.6 [1 x quaternary C-I of 4-iodoanisole], 112.6 [1 x aromatic CH], 136.2 [1 x aromatic CH], 149.2 [1 x aromatic CH], 162.5 ppm [1 x quaternary C-OMe of 4-iodoanisole].

El. Analysis calc. for C₂₈H₅₀AlLiO₂IN (M_r = 593.54) C, 56.66; H, 8.49; N, 2.36; found: C, 55.22; H, 8.02; N, 1.95.

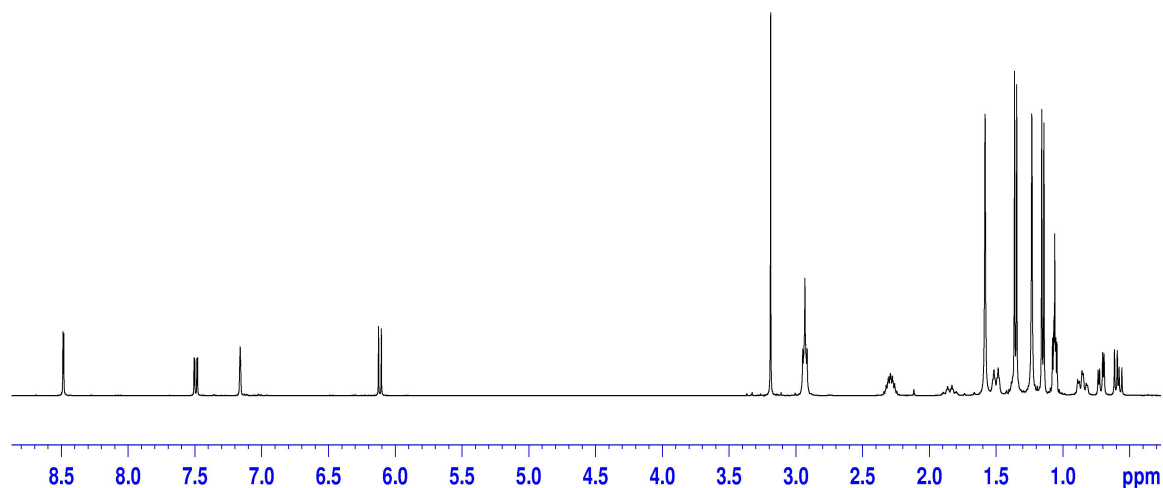


Figure S1 - ¹H NMR spectrum in C₆D₁₂ of aluminated 4-iodoanisole compound **2-int**

The molecular structure of **2-int** features a 6-atom, 5-element LiNAICCO ring, with TMP and deprotonated 4-iodoanisole making up a mixed bridging ligand set. The structure is completed by two terminal *i*Bu ligands on Al and a chelating THF ligand on Li. The Al centre displays a distorted tetrahedral geometry (subtending bond angles from {N(1)-Al(1)-C(2)} 107.03(6)^o to 116.50(7)^o {N(1)-Al(1)-C(4)} made up of three C atoms, from two terminal *i*Bu ligands (Al(1)-C(3) 2.0253(18) Å, Al(1)-C(4) 2.0195(18) Å) and one deprotonated 4-iodoanisole molecule (Al(1)-C(2) 2.0499(15) Å), with the fourth atom the N of the amido TMP (Al(1)-N(1) 1.9675(14) Å). Contact from Al to the Li atom is through one amido (TMP) N atom (Li(1)-N(1) 2.021(3) Å) and one metallated 4-iodoanisole molecule where coordination occurs

through the O atom of the methoxy group (Li(1)-O(2) 1.917(3) Å). Li is also coordinated to the O atom of a donor THF molecule (Li(1)-O(1) 1.904(3) Å) to complete a distorted trigonal planar geometry (subtending bond angles from 103.04(15)° {O(1)-Li(1)-O(2)} to 142.35(18)° {N(1)-Li(1)-O(1)}).

Crystal data for **2-int**: C₂₈H₅₀AlLiO₂IN, M_r = 593.54, triclinic, space group P-1, *a* = 11.2262(10), *b* = 11.3662(9), *c* = 13.7161(12) Å, α = 83.989(7)°, β = 79.243(8)°, γ = 62.826(2)°, *V* = 1529.2(2) Å³, *Z* = 2, λ = 0.71073 Å, μ = 1.098 mm⁻¹, *T* = 123(2) K; 16 599 reflections, 8298 unique, *R*_{int} = 0.0241; final refinement to convergence on *F*² gave *R* = 0.0267 (*F*, 7159 obs. data only) and *R*_w = 0.0666 (*F*², all data), GOF = 1.035.

Synthesis of 2-bromo-4-iodoanisole (3a)

10 mL of THF was added to dissolve the white precipitate (**2-int**) and an excess of *N*-bromosuccinimide (~3.2 g) was added to the reaction mixture at 0°C and stirred overnight. The mixture was diluted with saturated aq. NaHS₂O₃ (40 mL) and saturated aq. NH₄Cl (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-bromo-4-iodoanisole (0.87 g, 93%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.88 [3H, s, OCH₃], 6.66 [1H, d, ³*J*(H,H) = 8.65 Hz, 1 x aromatic C-H], 7.55 [1H, d, ³*J*(H,H) = 8.61 Hz, 1 x aromatic C-H], 7.83 ppm [1H, s, 1 x aromatic C-H].

¹³C {¹H} (100.62 MHz, 298 K, CDCl₃): δ = 56.3 [OCH₃], 82.4 [1 x aromatic C-I], 113.0 [1 x aromatic C-Br], 113.8 [1 x aromatic C-H], 137.3 [1 x aromatic C-H], 141.0 [1 x aromatic C-H], 156.0 ppm [1 x aromatic C-OCH₃].

El. Analysis calc. for C₇H₆OBrI (M_r = 312.93) C, 26.87; H, 1.93; found: C, 27.86; H, 1.97.

Synthesis of [(THF)Li(μ-TMP){1-OMe-2-Al(*i*Bu)₂-4-I-6-Br-C₆H₂}] (3-int)

Same procedure as **2-int** except this time **1** was prepared on a 3 mmol scale. THF (0.24 mL, 3 mmol) and 2-bromo-4-iodoanisole (0.63 g, 2 mmol) were injected and the reaction mixture was left to stir overnight. A white solid formed which was dissolved on addition of 25 mL of toluene. The solution was filtered and the Schlenk tube placed in the freezer at -30°C. A crop

(0.44 g, 33%) of colourless crystals formed in solution that were suitable for X-ray crystallographic analysis.

^1H NMR (400.13 MHz, 298 K, C_6D_6): δ = 0.58 [2H, m, 1 x CH_2 of *i*Bu], 0.69 [2H, m, 1 x CH_2 of *i*Bu], 0.84 [2H, m, 1 x βCH_2 of TMP], 1.04 [6H, s, 2 x CH_3 of TMP], 1.15 [6H, m, 2 x CH_3 of *i*Bu], 1.23 [4H, m, 2 x βCH_2 of THF], 1.32 [1H, m, 1 x γCH of TMP], 1.40 [6H, m, 2 x CH_3 of *i*Bu], 1.44 [2H, m, 1 x βCH_2 of TMP], 1.52 [6H, s, 2 x CH_3 of TMP], 1.79 [1H, m, 1 x γCH of TMP], 2.35 [2H, m, 2 x CH of *i*Bu], 3.23 [4H, m, 2 x αCH_2 of THF], 3.76 [3H, s, OMe], 7.72 [1H, s, 1 x aromatic C-H], 8.43 ppm [1H, s, 1 x aromatic C-H].

^{13}C $\{^1\text{H}\}$ (100.62 MHz, 298 K, C_6D_6): δ = 18.5 [1 x γCH_2 of TMP], 25.2 [2 x βCH_2 of THF], 27.3 [2 x CH_3 of *i*Bu], 27.4 [2 x CH of *i*Bu], 29.8 [2 x CH_3 of TMP], 31.3 [2 x CH_3 of *i*Bu], 37.7 [2 x CH_3 of TMP], 43.9 [2 x βCH_2 of TMP], 62.0 [OCH_3], 68.7 [2 x αCH_2 of THF], 93.3 [1 x aromatic C-I], 115.1 [1 x aromatic C-Br], 139.5 [1 x aromatic C-H], 147.5 [1 x aromatic C-H], 157.8 ppm [1 x aromatic C- OCH_3].

El. Analysis calc. for $\text{C}_{28}\text{H}_{49}\text{AlLiO}_2\text{NIBr}$ (M_r = 672.43) C, 50.01; H, 7.35; N, 2.08; found: C, 49.23; H, 7.15; N, 1.98.

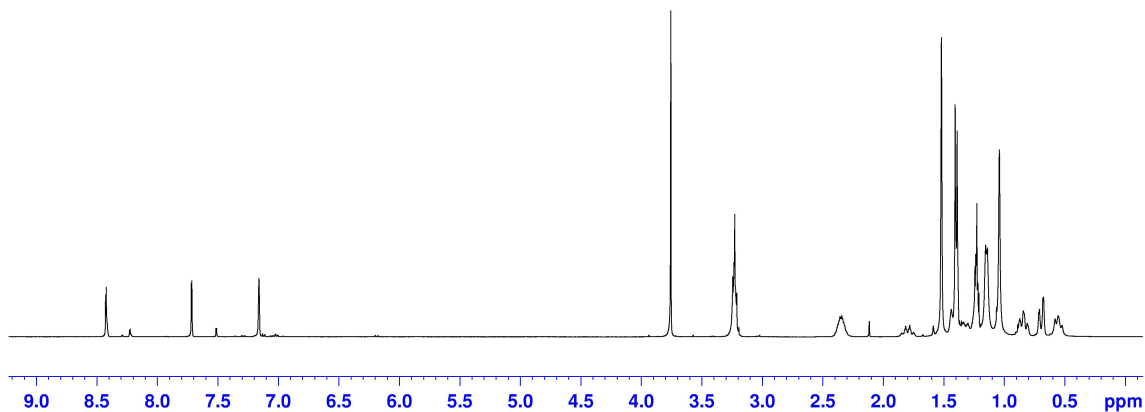


Figure S2 – ^1H NMR spectrum in C_6D_6 of aluminated 2-bromo-4-iodoanisole compound **3-int**

The molecular structure of **3-int** features a 6-atom, 5-element LiAlCCO ring, with TMP and deprotonated 2-bromo-4-iodoanisole making up a mixed bridging ligand set. The structure is completed by two terminal *i*Bu ligands on Al and a chelating THF ligand on Li. The Al centre displays a distorted tetrahedral geometry (subtending bond angles from $\{\text{C}(2)\text{-Al}(1)\text{-C}(4)\}$ $103.08(11)^\circ$ to $116.85(11)^\circ$ $\{\text{N}(1)\text{-Al}(1)\text{-C}(4)\}$ made up of three C atoms, from two terminal *i*Bu ligands (Al(1)-C(3) 2.024(3) Å, Al(1)-C(4) 2.027(3) Å) and one deprotonated 2-bromo-4-

iodoanisole molecule (Al(1)-C(2) 2.061(2) Å), with the fourth atom the N of the amido TMP (Al(1)-N(1) 1.978(2) Å). Contact from Al to the Li atom is through one amido (TMP) N atom (Li(1)-N(1) 2.019(5) Å) and one metallated 2-bromo-4-iodoanisole molecule where coordination occurs through the O atom of the methoxy group (Li(1)-O(2) 1.917(5) Å). Li is also coordinated to the O atom of a donor THF molecule (Li(1)-O(1) 1.908(5) Å) to complete a distorted trigonal planar geometry (subtending bond angles from 103.4(2)° {O(1)-Li(1)-O(2)} to 141.9(3)° {N(1)-Li(1)-O(1)}).

Crystal data for **3-int**: C₂₈H₄₉AlLiO₂NiBr, M_r = 672.43, triclinic, space group P-1, *a* = 11.9465(4), *b* = 14.3366(6), *c* = 19.2013(6) Å, α = 98.480(3)°, β = 101.603(3)°, γ = 96.384(3)°, *V* = 3152.4(2) Å³, *Z* = 4, λ = 0.71073 Å, μ = 2.335 mm⁻¹, *T* = 123(2) K; 33 478 reflections, 15 453 unique, *R*_{int} = 0.0225; final refinement to convergence on *F*² gave *R* = 0.0342 (*F*, 12556 obs. data only) and *R*_w = 0.0846 (*F*², all data), GOF = 1.039.

Synthesis of 2-bromo-4-iodo-6-chloroanisole (4a)

10 mL of THF was added to dissolve the white precipitate (**3-int**) and an excess of sulfonyl chloride (~1 mL) was added to the reaction mixture at 0°C and stirred overnight. The mixture was diluted with saturated aq. NaHSO₃ (40 mL) and saturated aq. NH₄Cl (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-bromo-4-iodo-6-chloroanisole (0.62 g, 90%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.89 [3H, s, OCH₃], 7.67 [1H, d, ⁴*J*(H,H) = 2.04 Hz, 1 x aromatic C-H], 7.79 ppm [1H, d, ⁴*J*(H,H) = 2.02 Hz, 1 x aromatic C-H].

¹³C {¹H} (100.62 MHz, 298 K, CDCl₃): δ = 60.7 [OCH₃], 86.9 [1 x aromatic C-I], 119.5 [1 x aromatic C-Br], 130.2 [1 x aromatic C-Cl], 138.0 [1 x aromatic C-H], 139.9 [1 x aromatic C-H], 153.5 ppm [1 x aromatic C-OCH₃].

El. Analysis calc. for C₇H₅OIBrCl (M_r = 347.38) C, 24.20; H, 1.45; found: C, 24.49; H, 1.38.

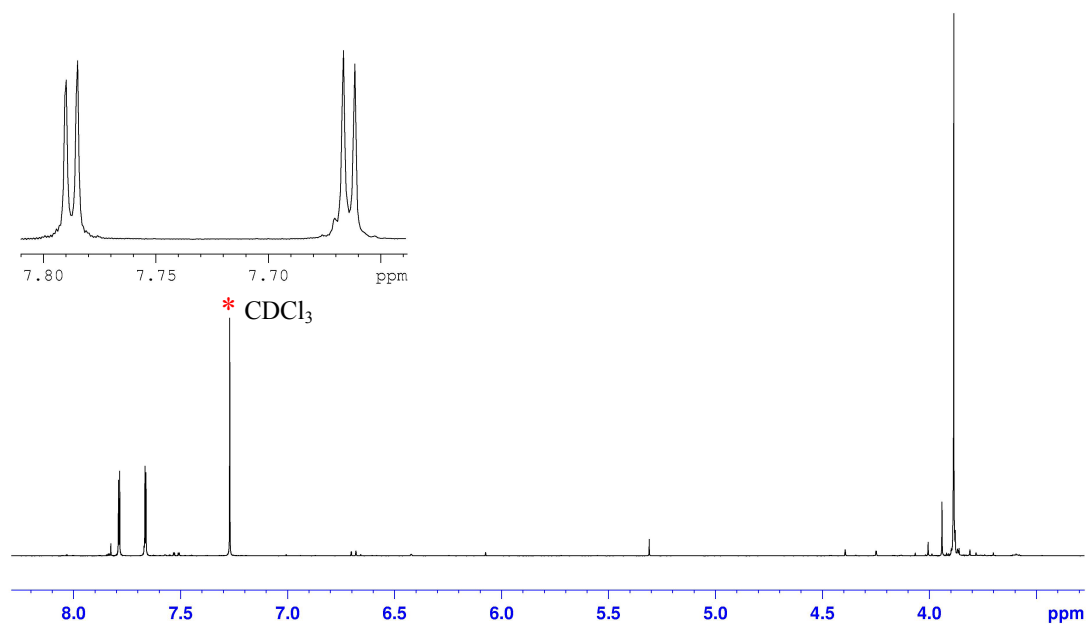


Figure S3 – ^1H NMR spectrum in CDCl_3 of 2-bromo-4-iodo-6-chloroanisole compound **4a**

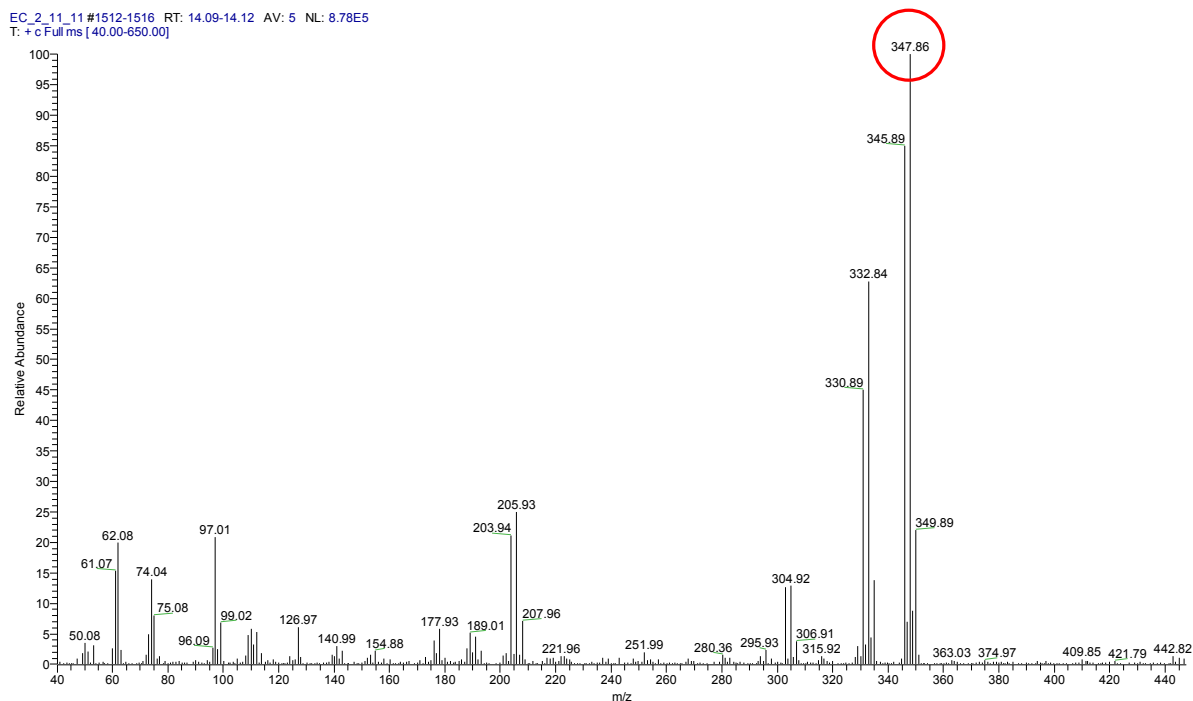


Figure S4 – Mass spectrum of compound **4a** highlighting parent ion peak at 347 m/z

Synthesis of 2-iodo-4-bromo-6-chloroanisole (**4b**)

Same procedure as **2-int** for the preparation of **1**. THF (0.36 mL, 4.5 mmol) and 4-bromoanisole (0.38 mL, 3 mmol) were injected and the reaction mixture was left to stir overnight. A white precipitate formed which dissolved on addition of 10 mL of THF. I₂ (18 mL of a 1M solution, 18 mmol) was added and the reaction was left to stir overnight. The mixture was diluted with saturated aq. NaHS₂O₃ (40 mL) and saturated aq. NH₄Cl (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-iodo-4-bromoanisole **3b** (0.81 g, 86%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.87 [3H, s, OCH₃], 6.69 [1H, d, ³J(H,H) = 8.78 Hz, 1 x aromatic C-H], 7.42 [1H, d, ³J(H,H) = 8.88 Hz, 1 x aromatic C-H], 7.89 ppm [1H, s, 1 x aromatic C-H].

3 mmol of **1** was prepared as described and 2-iodo-4-bromoanisole (0.63 g, 2 mmol) was added and left to stir overnight. Sulfuryl chloride (~1 mL) was added to the resulting solution at 0°C and left to stir overnight. The reaction mixture was worked-up as described above. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-iodo-4-bromo-6-chloroanisole **4b** (0.62 g, 89%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.87 [3H, s, OCH₃], 7.52 [1H, d, ⁴J(H,H) = 2.27 Hz, 1 x aromatic C-H], 7.82 ppm [1H, d, ⁴J(H,H) = 2.29 Hz, 1 x aromatic C-H].

¹³C {¹H} (100.62 MHz, 298 K, CDCl₃): δ = 60.6 [OCH₃], 93.1 [1 x aromatic C-I], 117.6 [1 x aromatic C-Br], 128.4 [1 x aromatic C-Cl], 133.3 [1 x aromatic C-H], 139.8 [1 x aromatic C-H], 155.2 ppm [1 x aromatic C-OCH₃].

El. Analysis calc. for C₇H₅OIBrCl (M_r = 347.38) C, 24.20; H, 1.45; found: C, 24.45; H, 1.37.

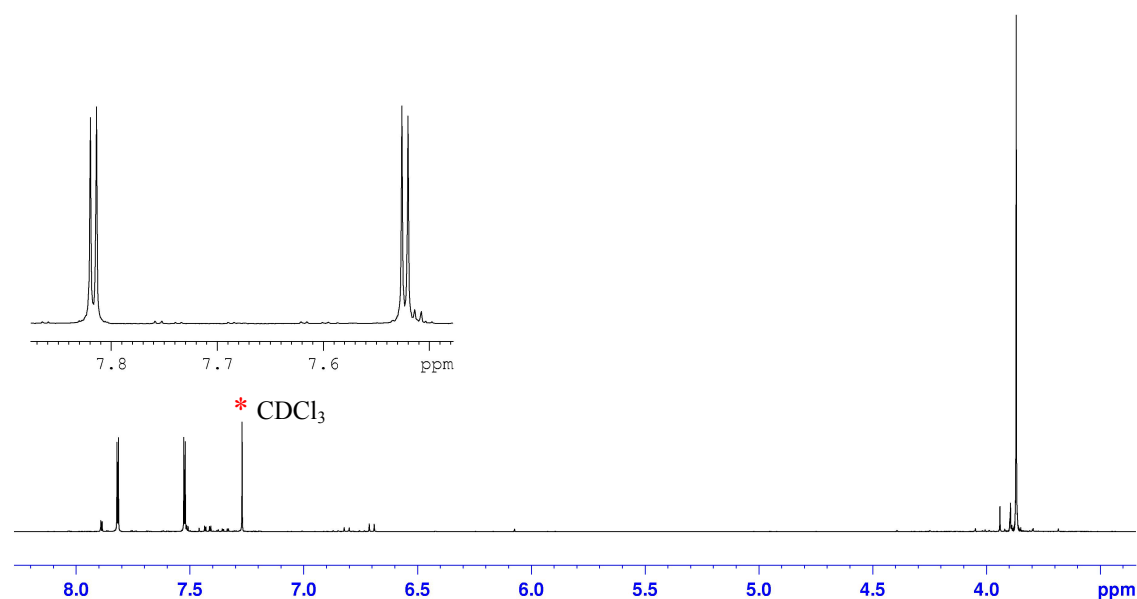


Figure S5 – ¹H NMR spectrum in CDCl₃ of 2-iodo-4-bromo-6-chloroanisole product **4b**

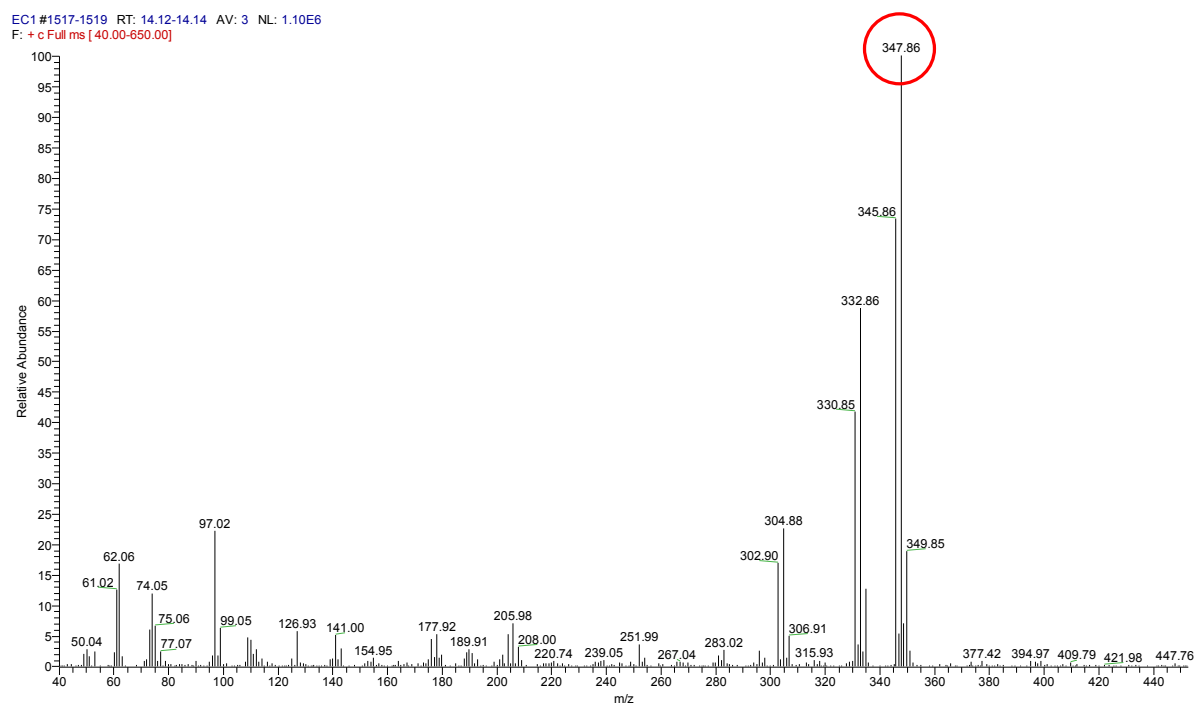


Figure S6 – Mass spectrum of compound **4b** highlighting parent ion peak at 347 m/z

Synthesis of 2-iodo-4-chloro-6-bromoanisole (**4c**)

Same procedure as **2-int** for the preparation of **1**. THF (0.36 mL, 4.5 mmol) and 4-chloroanisole (0.37 mL, 3 mmol) were injected and the reaction mixture was left to stir overnight. A white precipitate formed in solution which was dissolved on addition of 10 mL of THF. I₂ (18 mL of a 1M solution, 18 mmol) was added and the reaction was left to stir overnight. The mixture was diluted with saturated aq. NaHS₂O₃ (40 mL) and saturated aq. NH₄Cl (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-iodo-4-chloroanisole **3c** (0.72 g, 89%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.87 [3H, s, OCH₃], 6.74 [1H, d, ³J(H,H) = 8.75 Hz, 1 x aromatic C-H], 7.29 [1H, d, ³J(H,H) = 8.67 Hz, 1 x aromatic C-H], 7.75 ppm [1H, s, 1 x aromatic C-H].

3 mmol of **1** was prepared as described and 2-iodo-4-chloroanisole (0.54 g, 2 mmol) was added to the mixture and it was left to stir overnight. *N*-bromosuccinimide (~3.2 g) was added to the resulting solution at 0°C and it was left to stir overnight. The reaction mixture was worked-up as described above. The residue was purified by SiO₂ column chromatography using hexane as an eluent to give 2-iodo-4-chloro-6-bromoanisole **4c** (0.60 g, 86%).

¹H NMR (400.13 MHz, 298 K, CDCl₃): δ = 3.86 [3H, s, OCH₃], 7.55 [1H, d, ⁴J(H,H) = 2.46 Hz, 1 x aromatic C-H], 7.72 ppm [1H, d, ⁴J(H,H) = 2.45 Hz, 1 x aromatic C-H].

¹³C {¹H} (100.62 MHz, 298 K, CDCl₃): δ = 60.7 [OCH₃], 92.1 [1 x aromatic C-I], 116.6 [1 x aromatic C-Br], 130.7 [1 x aromatic C-Cl], 133.3 [1 x aromatic C-H], 137.9 [1 x aromatic C-H], 155.6 ppm [1 x aromatic C-OCH₃].

El. Analysis calc. for C₇H₅OIBrCl (M_r = 347.38) C, 24.20; H, 1.45; found: C, 24.55; H, 1.43.

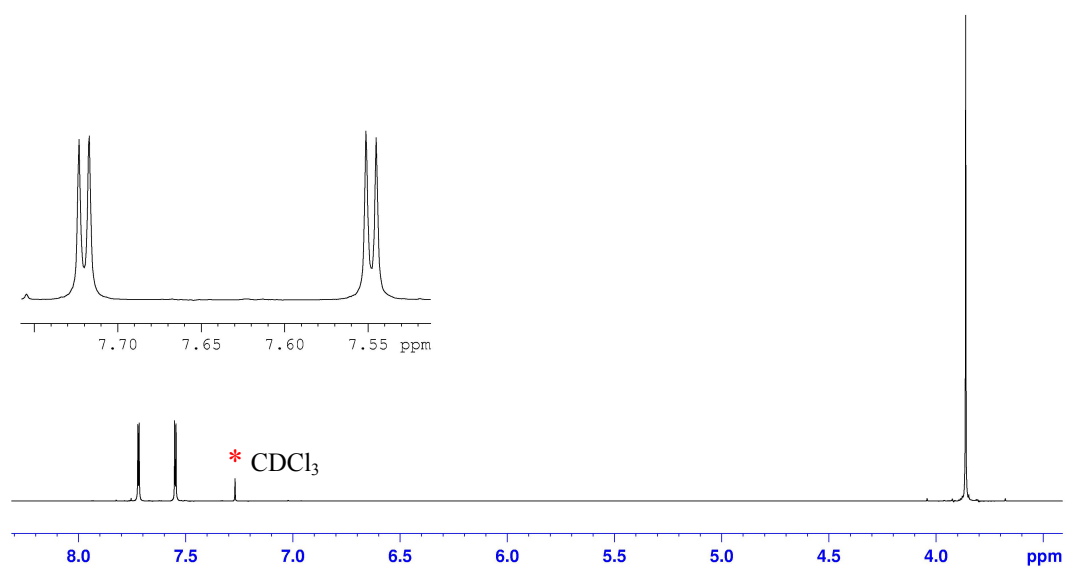


Figure S7 - ^1H NMR spectrum in CDCl_3 of 2-iodo-4-chloro-6-bromoanisole product **4c**

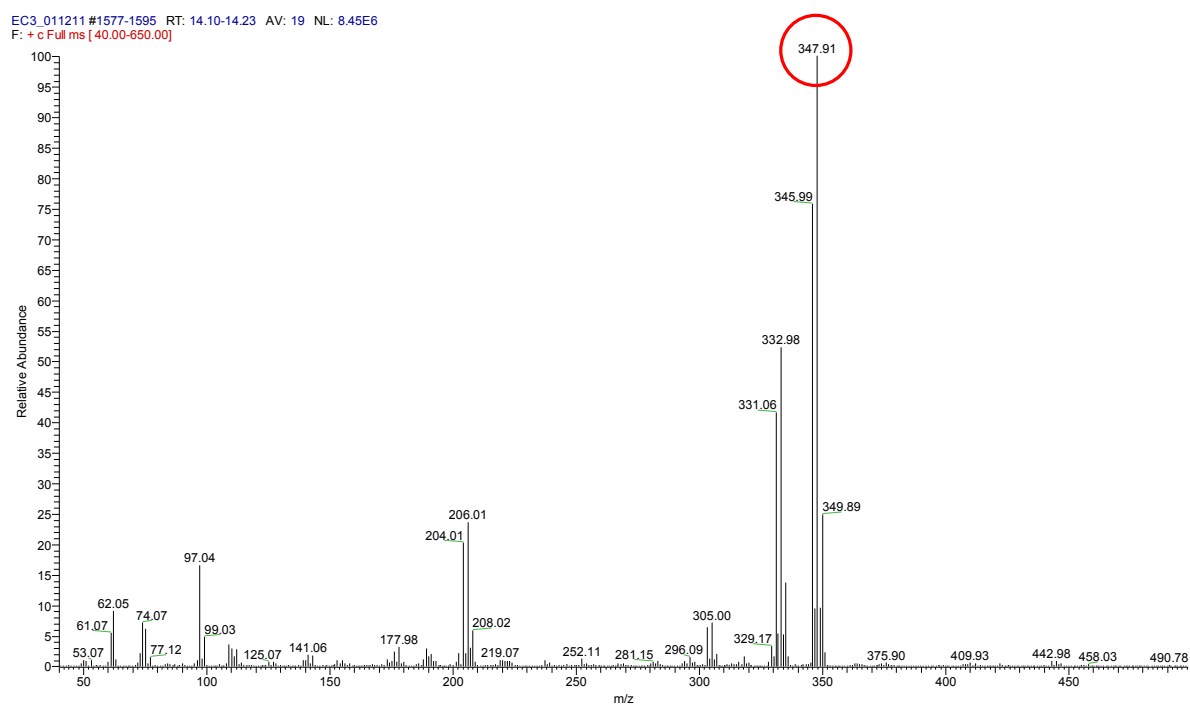
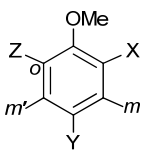


Figure S8 – Mass spectrum of compound **4c** highlighting parent ion peak at 347 m/z

Table S1 ¹H NMR data in CDCl₃ including coupling constants for multi-heterohalogenated compounds **3a-c** and **4a-c**.

	3a	3b	3c	4a	4b	4c	
X	Br	I	I	Br	I	I	
Y	I	Br	Cl	I	Br	Cl	
Z	H	H	H	Cl	Cl	Br	
OMe	3.88	3.87	3.87	3.89	3.86	3.87	
<i>o</i>	6.66, d, 8.65 Hz	6.69, d, 8.78 Hz	6.74, d, 8.75 Hz	-	-	-	
<i>m</i>	7.83	7.89	7.75	7.67, d, 2.04 Hz	7.52, d, 2.27 Hz	7.55, d, 2.46 Hz	
<i>m'</i>	7.55, d, 8.61 Hz	7.42, d, 8.88 Hz	7.29, d, 8.67 Hz	7.79, d, 2.02 Hz	7.82, d, 2.29 Hz	7.72, d, 2.45 Hz	