Electronic Supporting Information

Halogenase-mimicking Selective Chlorination of Unactivated C–H bonds by a Fe-complex

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EXPERIMENTAL DETAILS

1. Materials

$[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** was synthesized by standard reported protocol.[1] Sodium hypochlorite (NaOCl – 4% active chlorine) was purchased from Sigma-Aldrich. Bicyclo[4.1.0] heptane (norcarane) was prepared according to a literature method.[2] All the substrates were bought from TCI, and Sigma-Aldrich, and were passed through activated neutral alumina, silica, and $MgSO_4$ and distilled prior to use**.** All the solvents used were previously purified and dried by standard methods.[3]

2. Methods and Instrumentation

2.1 Ultraviolet-Visible Spectroscopy (UV-Vis)

UV-Vis data were measured using Agilent's Cary 8454 UV-Visible spectroscopy system equipped with 10 mm pathlength quartz cuvette with a volume of 0.6 mL/2 mL at room temperature and low temperature.

2.2 Electron Paramagnetic Resonance Spectroscopy (EPR)

EPR spectroscopic data was obtained by a Bruker spectrometer (Bruker, EMXmicro) operating at X-band frequency and magnetic field modulation of 100 kHz. All the experiments were conducted at 9.31 GHz microwave frequency and 10 G modulation amplitude at 85 K.

2.3 Gas Chromatography-Mass Spectrometry (GC-MS)

Gas Chromatography-Mass Spectrometry (GC-MS) was conducted on a Thermo Scientific ISQ QD Mass Spectrometer attached with a Thermo Scientific TRACE 1300 gas chromatograph using an HP-5 ms capillary column (30 m × 0.25 mm × 0.25 μm, J&W Scientific) with helium as the carrier gas. The method was set as: oven temperature program, 18 min; initial temperature, 60°C, hold for 2.00 min; ramp-1, 15°C min^{-1} to 180°C, hold for 1 min; ramp-2, 20°C to 280°C, hold for 1 min; injector temperature, 230°C; detector temperature, 280°C.

2.4 Mass Spectrometry

HRMS was performed in a Bruker mass spectrophotometer using an electrospray ionization source and acetonitrile-water as an eluent.

3. Experimental Procedures

3.1 UV-Vis Spectroscopic Studies of the Reaction Mixture

After adding 0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** and 4 mM (0.54 mg, 0.004 mmol) adamantane to 1 mL of acetonitrile, 200 μL of an aqueous solution of sodium hypochlorite solution (300 mM) was added. Immediately after half diluting the reaction mixture, it was subjected to the UV-Vis experiment. A characteristic peak at 547 nm was obtained for **2** (Figure 3A).

3.2 HRMS Analysis

After the addition of sodium hypochlorite solution to the reaction mixture, an aliquot was subjected immediately for direct injection in the detector (Figure S1).

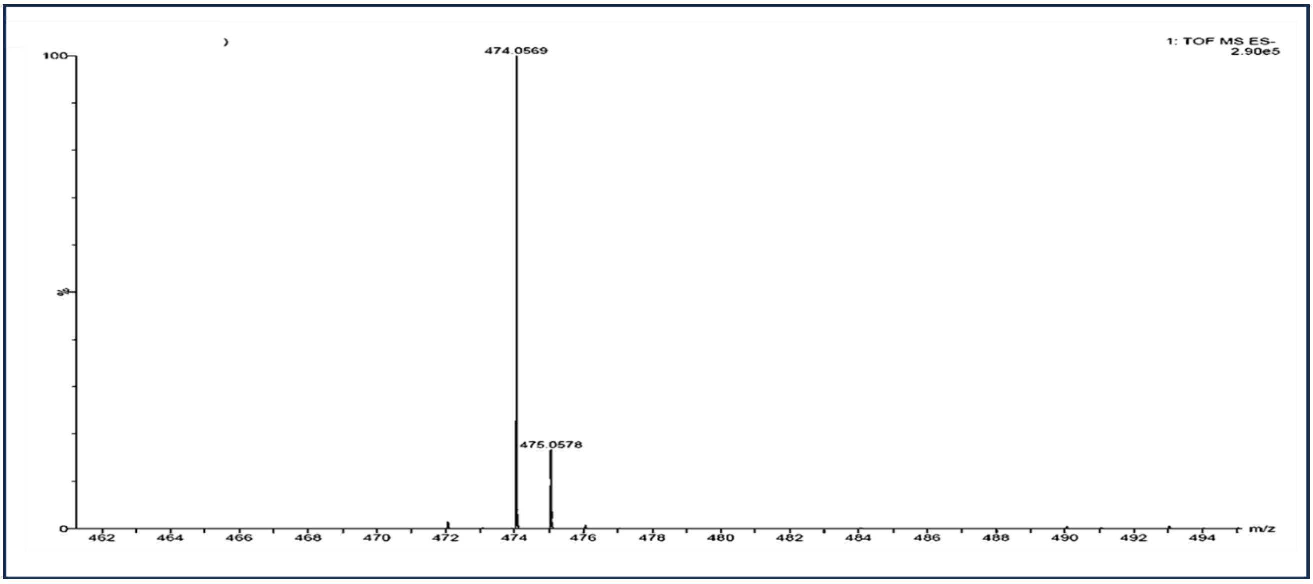


Figure S1. HRMS of **2**. Experimental m/z (M-) 474.0569(100%); Calculated m/z (M-) 474.0586 (100%)

3.3 EPR Spectroscopic Studies of the Reaction Mixture

After adding 0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** and 4 mM (0.54 mg, 0.004 mmol) adamantane to 1 mL of acetonitrile, 200 μL of an aqueous solution of sodium hypochlorite solution (300 mM) was added. Immediately, EPR spectroscopy was done at 85 K in an EPR tube loaded with the reaction mixture, followed by freezing in liquid nitrogen. The spectrum obtained shows an orthorhombic species with s = 1/2 and g values of 2.01, 1.98, and 1.79 (Figure 3B).

3.4 GC-MS Analysis of the Reaction Mixture

0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ (**1**) and 4 mM substrate were added to 1 mL of acetonitrile. To it, 200 μL of an aqueous sodium hypochlorite solution (12 eq. – 20 eq. with respect to substrate) was added iteratively over 1-2 h (40 μL in each iteration) under N_2 atmosphere at room temperature. After the reaction was over, the excess NaOCl was quenched by 1 mL aqueous saturated sodium thiosulphate solution and the products were extracted using 2 mL ethyl acetate/dichloromethane. The organic layer was passed through a basic alumina plug and dried over anhydrous Na_2SO_4, before being subjected to GC-MS analysis. The products were identified and quantified by GC-MS using bromobenzene as the internal standard. The yield and conversion were estimated using the response factor of authentic substrates and products.

3.5 Kinetic Measurements of the Chlorination Reaction of Cyclooctane:

To study the kinetics of the chlorination reaction by compound **2**, cyclooctane was chosen as the model substrate due to its good solubility in acetonitrile. Different concentrations of Cyclooctane (4 mM - 22 mM) were added to a 2 mL solution of **1** (0.2 mM) in CH_3CN. An aq. solution of NaOCl (300 mM, 400 µL) was added to it at room temperature under a dinitrogen atmosphere with constant stirring. Upon the addition of the oxidant, the colour of the reaction mixture changed to violet [an indication of the formation of the $Fe^V(O)$ reactive intermediate (**2**)]. 200 µL aliquot was withdrawn at regular time intervals. The excess NaOCl was quenched using $Na_2S_2O_3$ and the reaction mixture was extracted in ethyl acetate layer. The ethyl acetate layer was passed through a basic alumina plug and dried over anhydrous Na_2SO_4, before being subjected to GC-MS analysis for identification and quantification of the products using bromobenzene as the internal standard. Each kinetic measurement was done thrice. The initial rate is measure from the slope of the concentration of cyclooctane vs time plot (Section 6).

Also, we studied the kinetics of the chlorination reaction by **2** using UV-Vis spectroscopy. We selected cyclooctane as the substrate for this experiment. The iron(V)-oxo species was generated by adding 1.2 equ. of aq. NaOCl to complex **1**, and its decay was monitored in the UV-Vis following the addition of an excess concentration of the substrate. We observed that the absorbance of the characteristic peak of complex **2** at 547 nm decayed exponentially over time, which confirms the pseudo-first-order dependency of complex **1**/complex **2** to the reaction rate. We measured the observed reaction rates (k_{obs}) of cyclooctane oxidation at different substrate concentrations by the exponential fitting of the decay of complex **2** with time. From the linear plot of the k_{obs} vs [cyclooctane], we obtained a second-order rate constant value (k_2) of 0.26 M^{-1} s^{-1}. (for 0.1 mM of **2**) (Section 7).

3.6 Determination of the Kinetic Isotope Effect (KIE) under Catalytic Conditions

4 mM of both adamantane and adamantane-d_{16} were added to 2 mL of a solution of **1** (0.4 mM) in CH_3CN. An aq. solution of NaOCl (300 mM, 800 µL) was added to the solution at room temperature under a dinitrogen atmosphere. Upon the addition of the oxidant, the colour of the reaction mixture changed to violet. Then in order to identify and quantify the product in GC-MS, a 200 µL aliquot was extracted from the reaction mixture at intervals of 3 minutes for 21 minutes (Figure 2B). Then the initial concentration of the product formation for both substrates plotted against time. KIE of the reaction measured by the following equation:

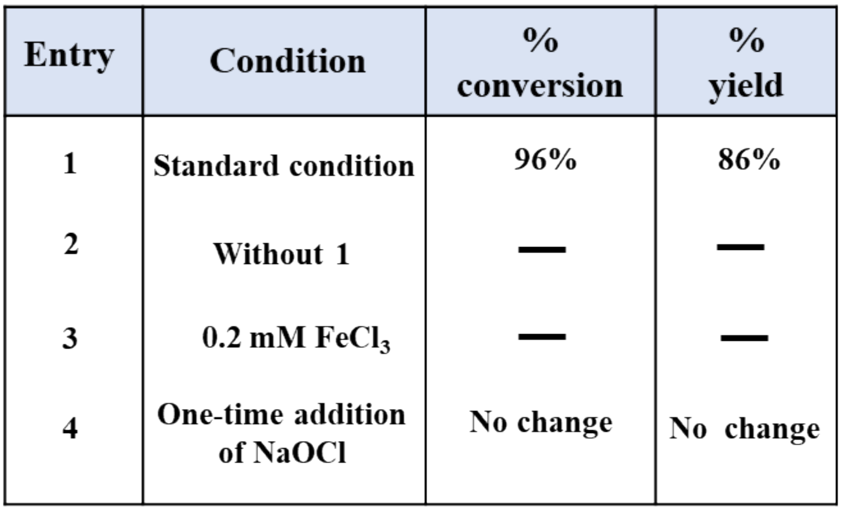
$$KIE = \frac{k_H}{k_D} = \frac{Slope\ of\ adamantane}{Slope\ of\ adamantane - D16} \qquad (1)$$

4. Reaction Conditions for the Chlorination of Organic Substrates

$$\textbf{R-H} \xrightarrow[\substack{\textbf{aq. NaOCl (60-80mM)} \\ \textbf{CH}_3\textbf{CN-H}_2\textbf{O, N}_2\textbf{, rt}}]{\textbf{5 mol\% 1 (0.2mM)}} \textbf{R-Cl}$$

Scheme 1. Standard reaction condition for chlorination

4.1 Optimization Table:



Entry	Condition	% conversion	% yield
1	Standard condition	96%	86%
2	Without 1	—	—
3	0.2 mM $FeCl_3$	—	—
4	One-time addition of NaOCl	No change	No change

Table S1. Optimization table; Standard Condition: Adamantane (4 mM), **1** (0.2 mM), aq. NaOCl (300 mM, 200 μL), CH_3CN (1 mL) under N_2 atmosphere.

4.2 Method for the Chlorination of Organic Substrates

0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** and 4 mM substrate were placed in a reaction tube under N_2 atmosphere. 1 mL acetonitrile was added to it and stirred for 10 min. Then 40 μL aq. NaOCl solution (300mM) (maintained under a N_2 atmosphere with continuous purging) was added to the solution in 15 min time intervals. All the reactions were completed within 2 h. After the end of the reaction, the solution became colourless. 1 mL saturated $Na_2S_2O_3$ solution was added to quench the extra NaOCl. The organic product was extracted with 2 mL EtOAc/DCM. The organic layer was filtered through a basic alumina plug and was subjected to GC-MS analysis for product identification and quantification. Bromobenzene was used as an internal standard. The yield and conversion were estimated using the response factor of authentic substrates and products.

4.3 Chlorination Reaction of cis-DMCH with 1:

0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** and 4 mM (0.6 μL, 0.004 mmol) cis-DMCH were placed in a reaction tube under N_2 atmosphere. 1 mL acetonitrile was added to it and stirred for 10 min. Then 40 μL aq. NaOCl solution (300 mM) (maintained under a N_2 atmosphere with continuous purging) was added to the solution in 15 min time intervals for 2 h. After the reaction, 1 mL of saturated $Na_2S_2O_3$ solution was added to quench the extra NaOCl. The product was extracted with 2 mL EtOAc, filtered through a basic alumina plug, and subjected to GC-MS analysis with bromobenzene as the internal standard.

4.4 Chlorination Reaction of Norcarane with 1:

0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)** and 4 mM (0.419 μL, 0.004 mmol) norcarane was placed in a reaction tube under N_2 atmosphere. 1 mL acetonitrile was added to it and stirred for 10 min. Then 40 μL aq. NaOCl solution (300 mM) (maintained under a N_2 atmosphere with continuous purging) was added to the solution in 15 min time intervals for 1 h. After the reaction, 1 mL of saturated $Na_2S_2O_3$ solution was added to quench the extra NaOCl. The product was extracted with 2 mL EtOAc, filtered through a basic alumina plug and subjected to GC-MS analysis with bromobenzene as the internal standard.

4.5 Chlorination Reaction of Adamantane in the presence of Imidazole:

0.2 mM $[Et_4N]_2[Fe^{III}(Cl)\text{-}(NO_2)bTAML]$ **(1)**, 4 mM (0.544 mg, 0.004 mmol) adamantane and 4 mM (0.27 mg, 0.004 mmol) imidazole were placed in a reaction tube under N_2 atmosphere. 1 mL acetonitrile was added to it and stirred for 10 min. Then 40 μL aq. NaOCl solution (300 mM) (maintained under a N_2 atmosphere with continuous purging) was added to the solution. After 10 min, 1 mL saturated $Na_2S_2O_3$ solution was added to quench the extra NaOCl. The organic product was extracted with 2 mL EtOAc, filtered through a basic alumina plug and subjected to GC-MS analysis with bromobenzene as the internal standard. The product analysis was compared to another reaction carried out under the same conditions, only without imidazole.

5. GC-MS traces for Product Quantification

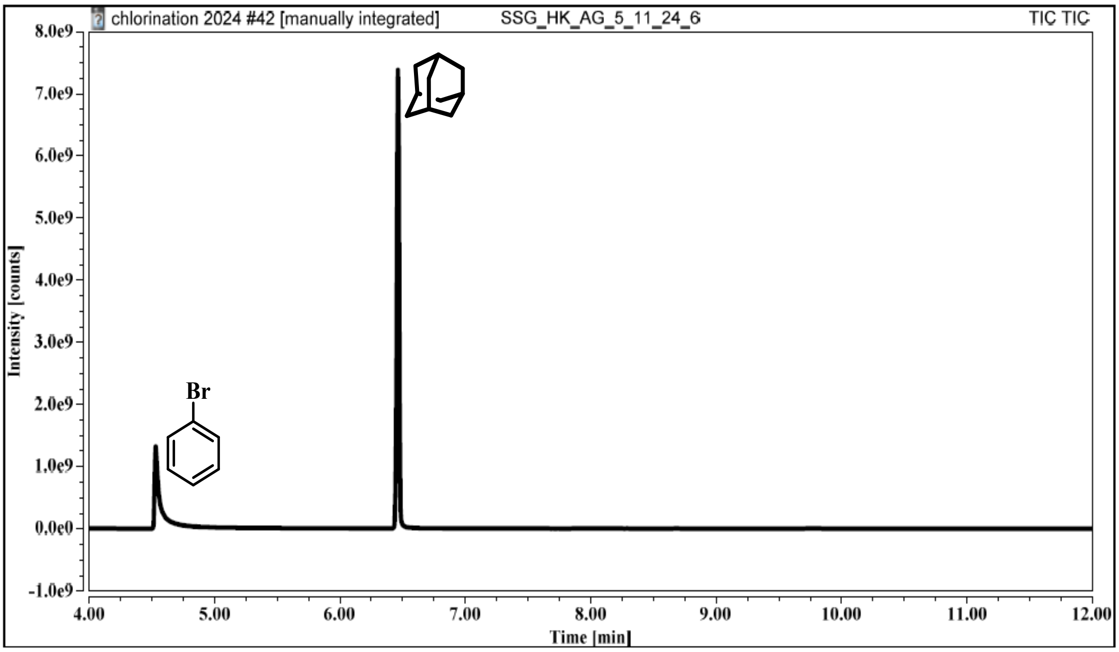


Figure S2. GC-MS trace for the chlorination reaction of Adamantane without catalyst

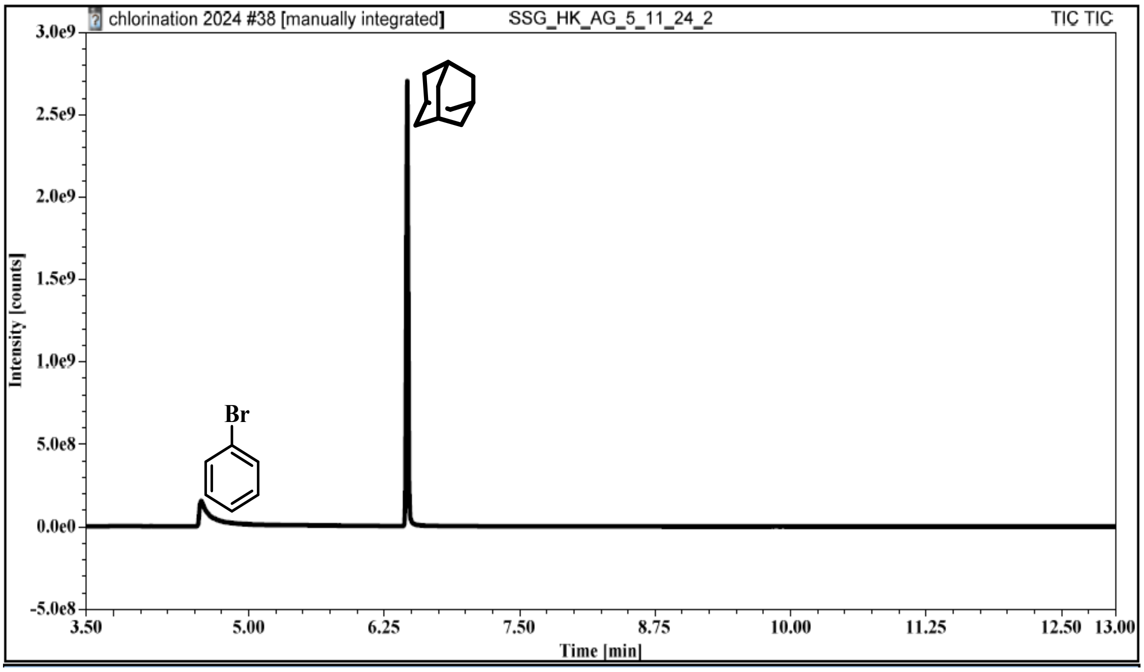


Figure S3. GC-MS trace for the chlorination reaction of Adamantane with $FeCl_3$

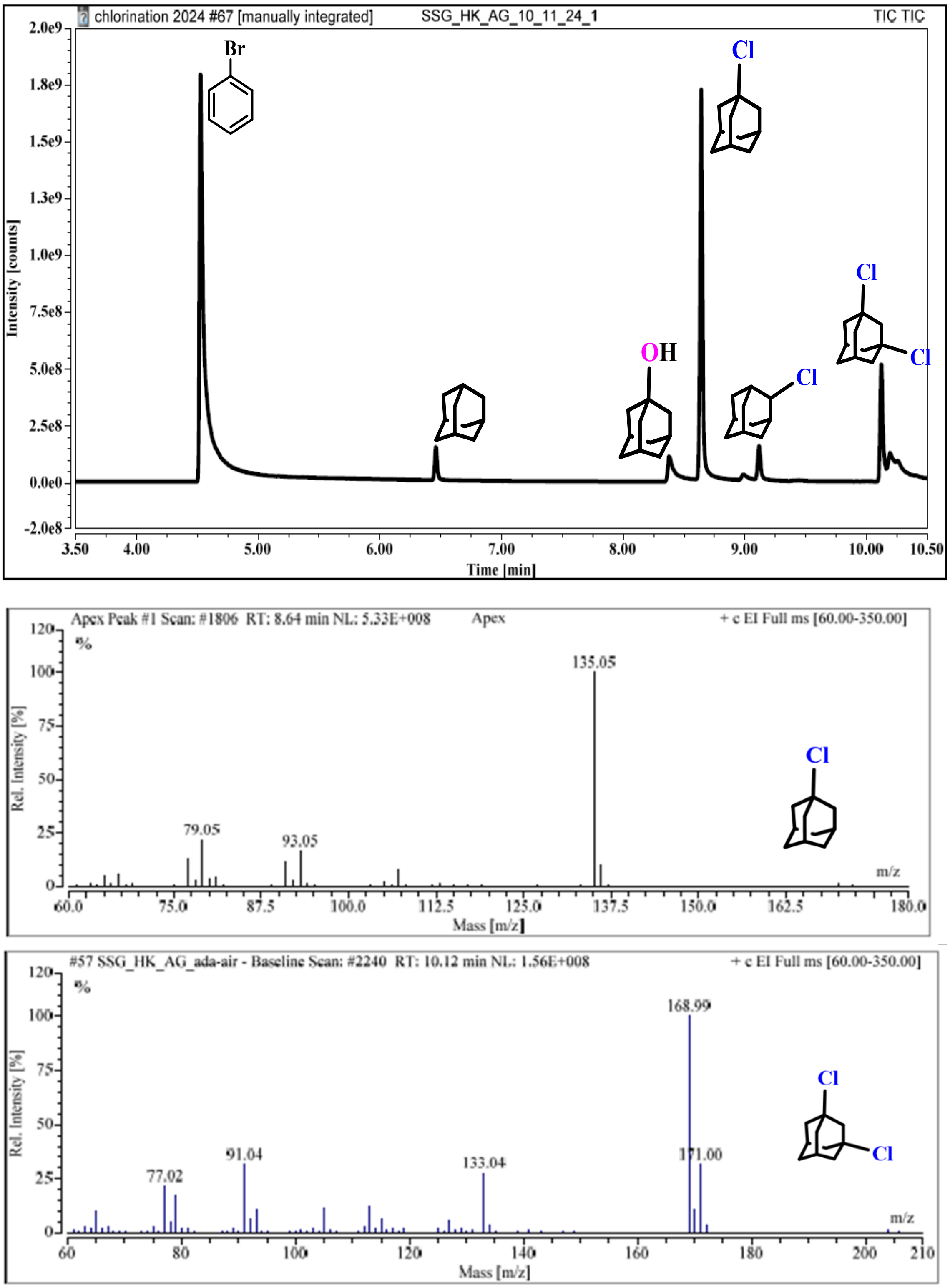


Figure S4. GC-MS trace for the chlorination reaction of Adamantane with one-time addition of NaOCl

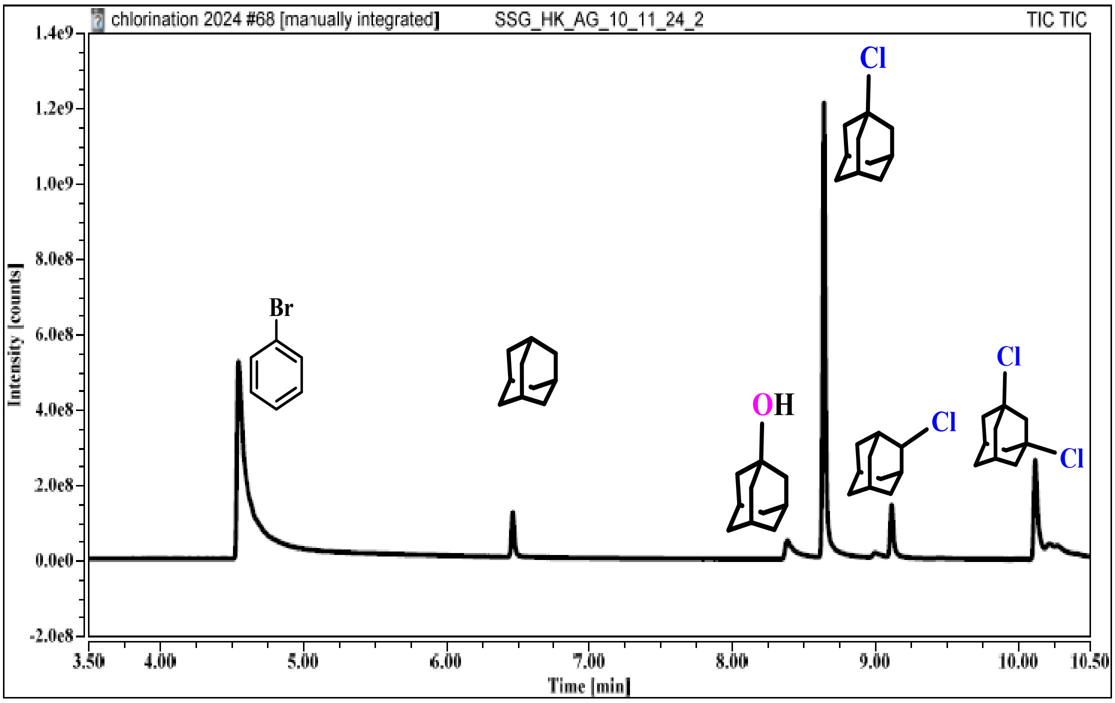


Figure S5. GC-MS trace for the chlorination reaction of Adamantane with iterative addition of

NaOCl

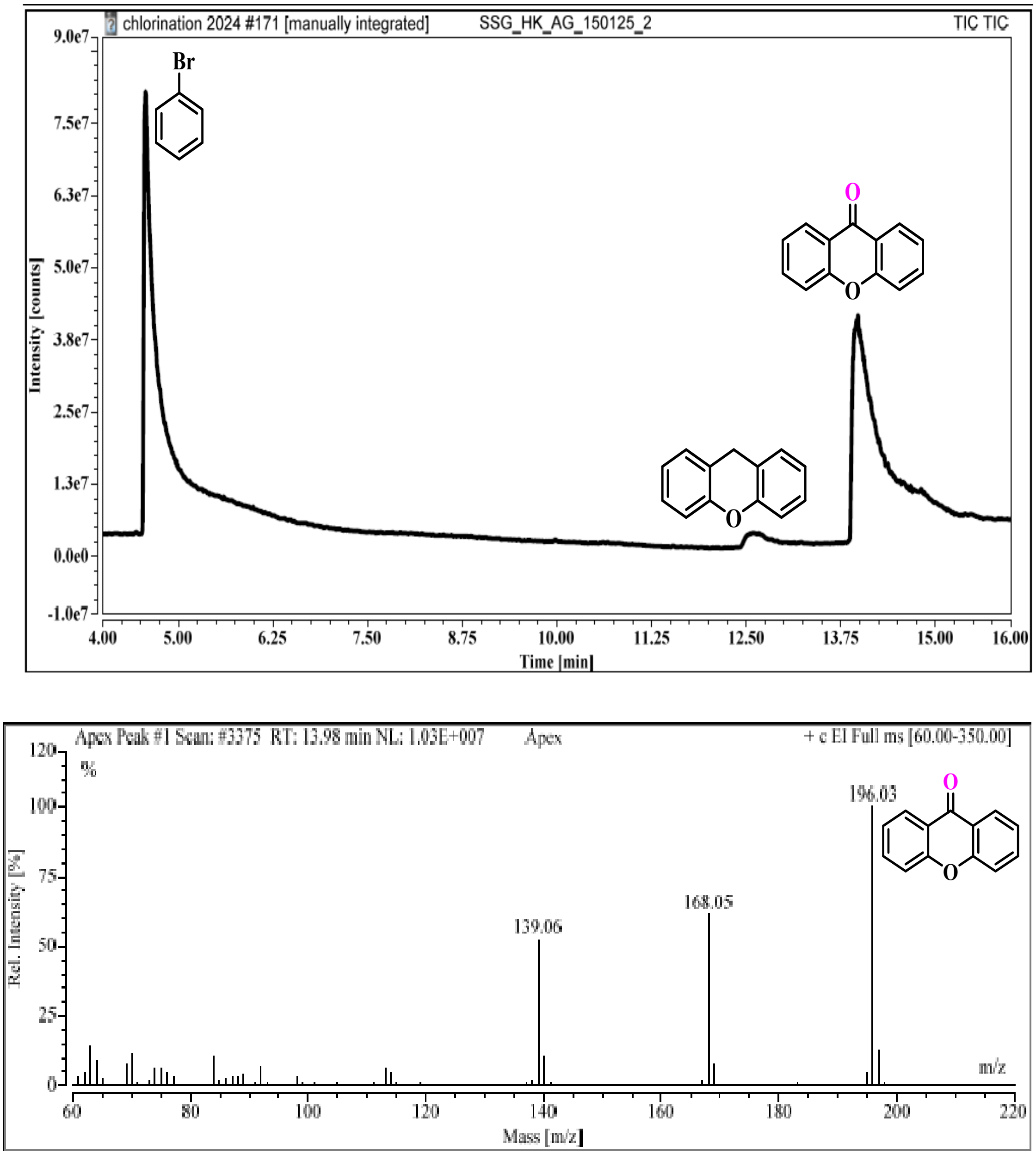


Figure S6. GC-MS trace for the chlorination reaction of Xanthene (Conversion: 95%, Yield: O = 87%)

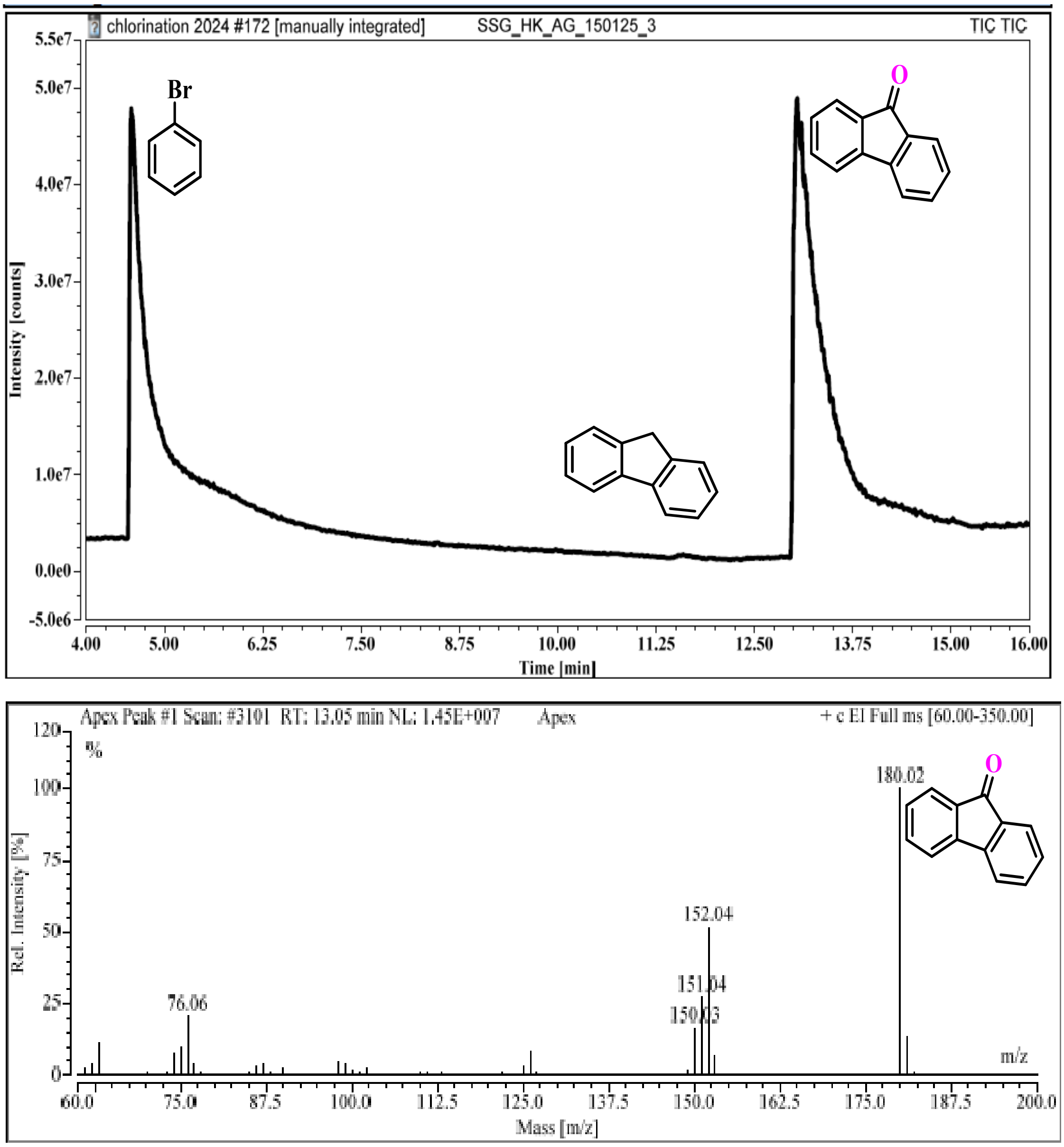


Figure S7. GC-MS trace for the chlorination reaction of Fluorene (Conversion: 98%, Yield: O = 93%)

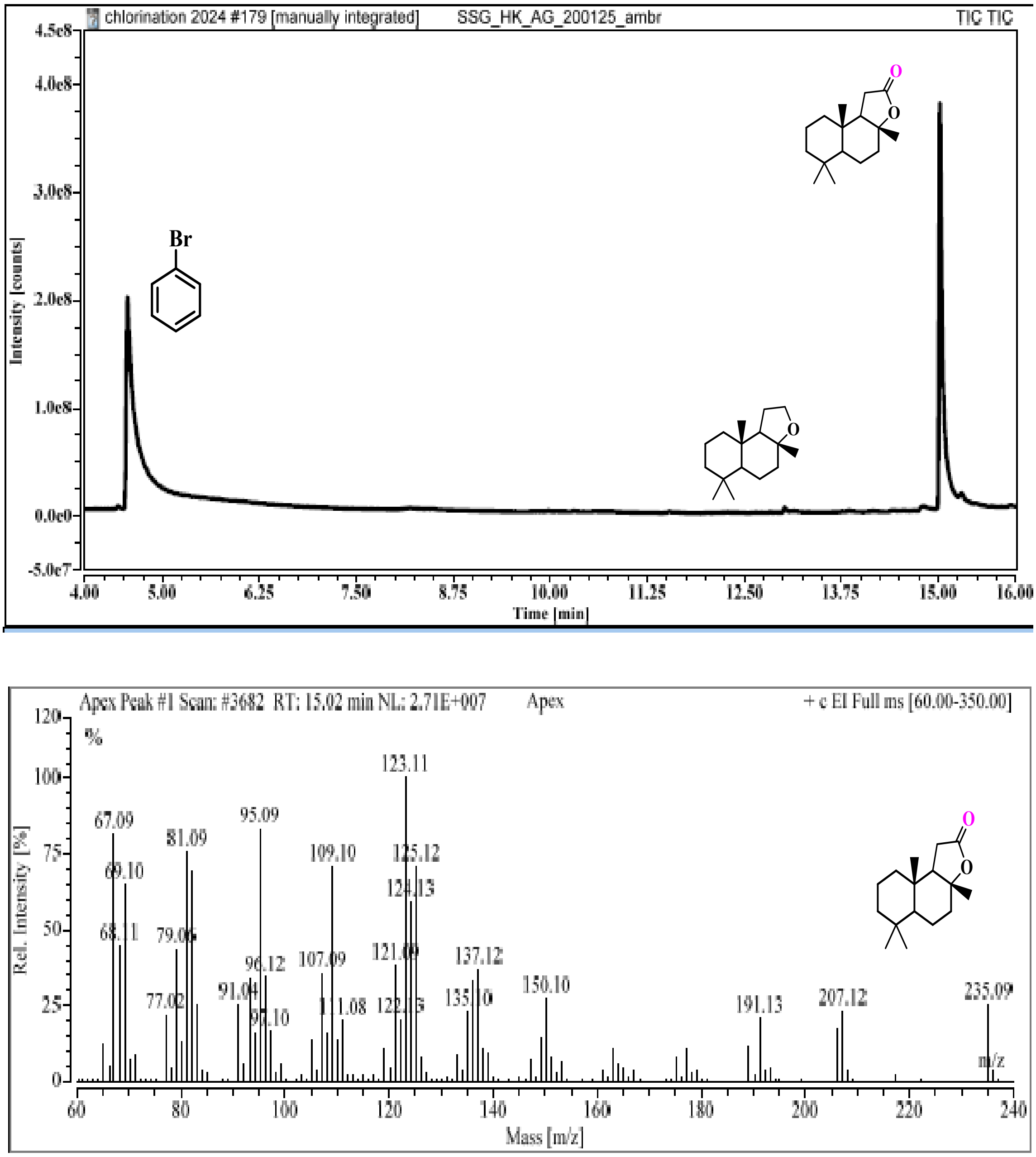


Figure S8. GC-MS trace for the chlorination reaction of Ambroxide (Conversion: 98%, Yield: O = 96%)

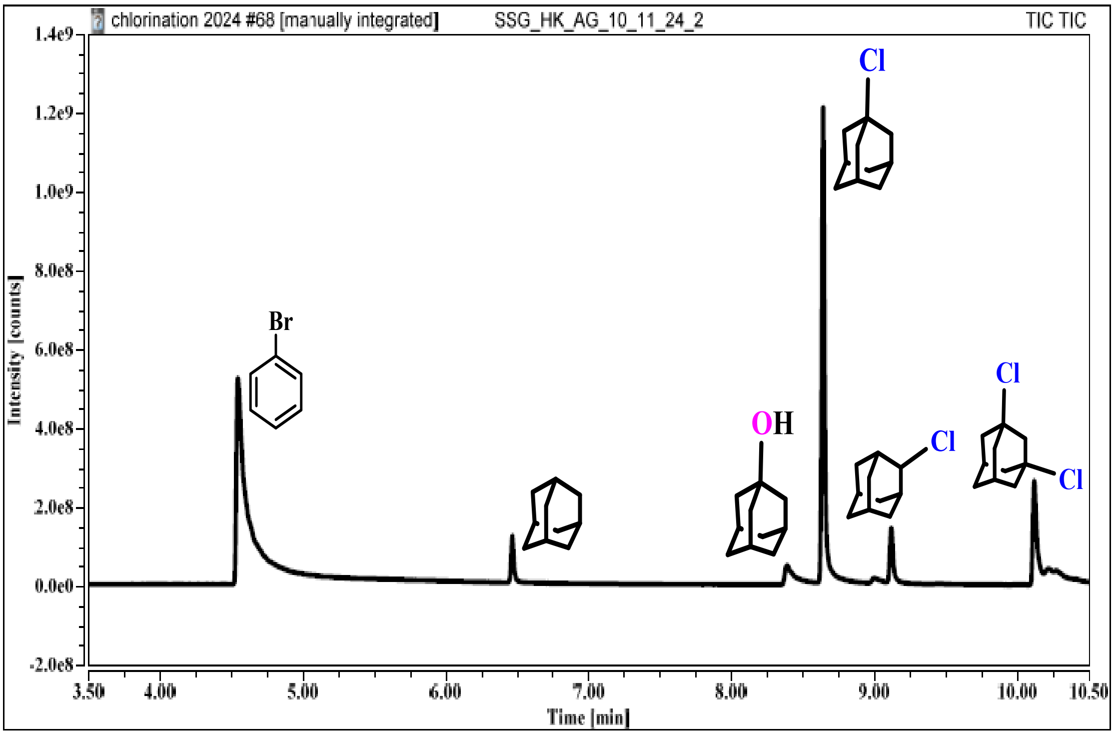
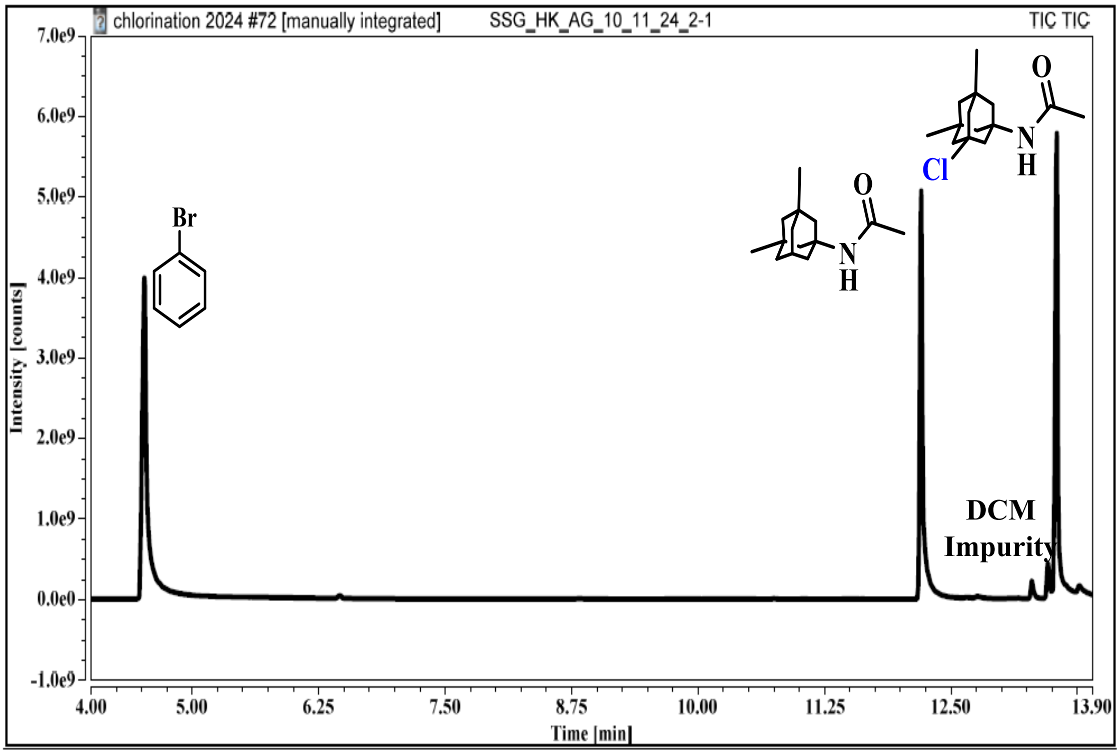


Figure S9. GC-MS trace of the chlorination reaction of Adamantane (Conversion: 92%, Yield: OH = 4%, Cl (monochloro) = 78%, Cl (dichloro) = 8%)



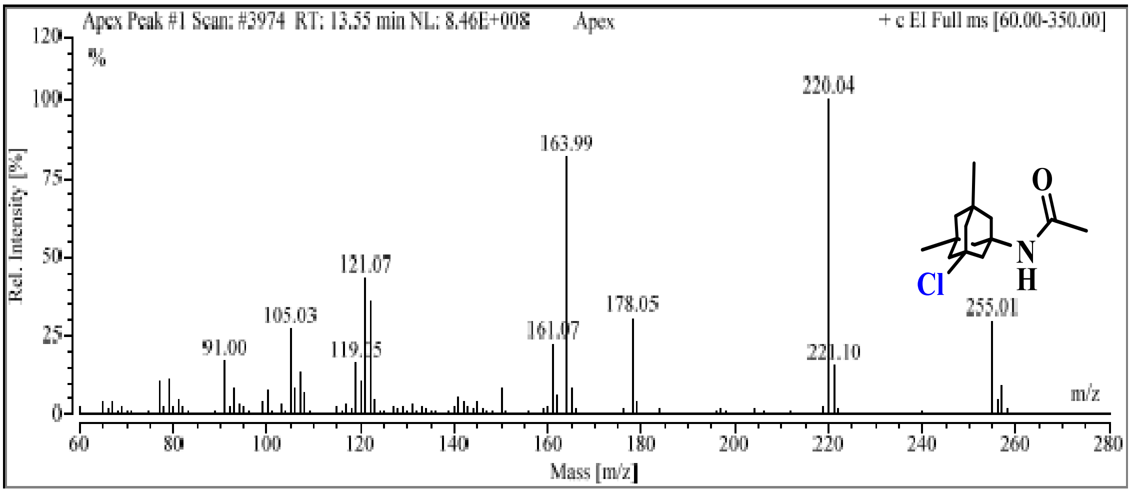


Figure S10. GC-MS trace of the chlorination reaction of N-acetyl-3,5-dimethyl-1-adamantanamine (Conversion: 68%, Yield: Cl = 61%)

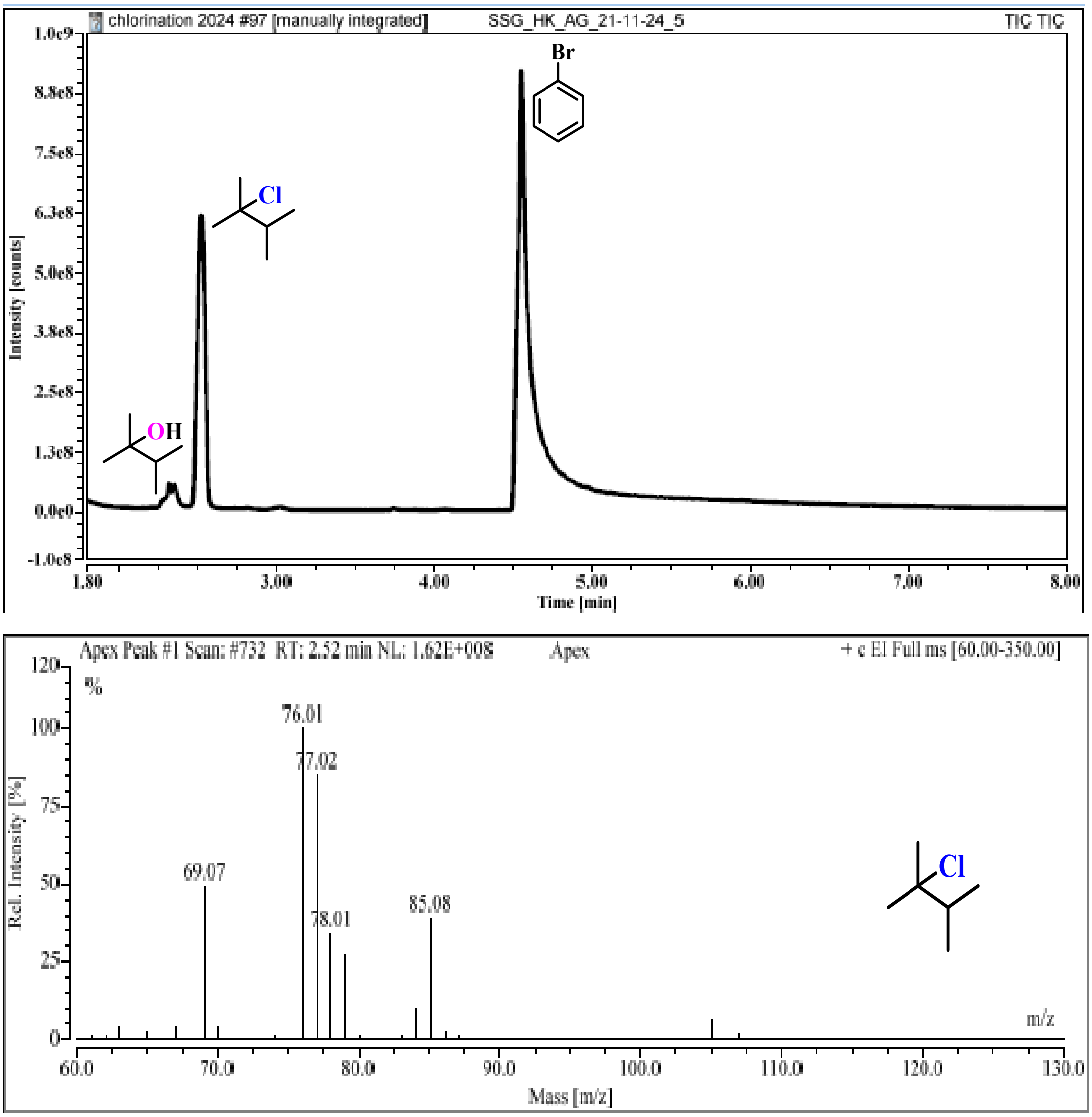


Figure S11. GC-MS trace of the chlorination reaction of 2,3-dimethyl butane (Conversion: 97%, Yield: OH = 15%, Cl = 80%)

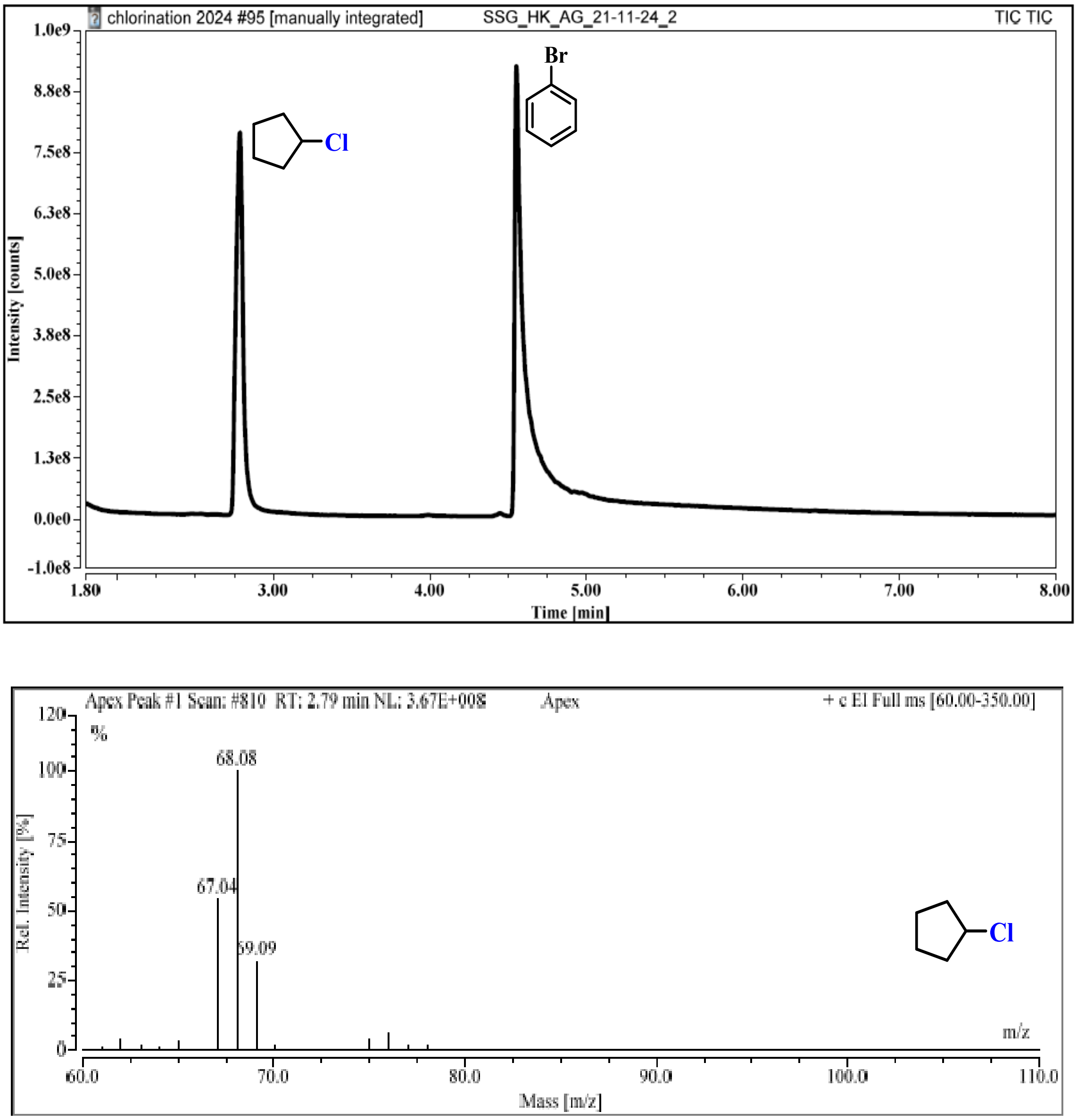


Figure S12. GC-MS trace of the chlorination reaction of Cyclopentane (Conversion: 98%, Yield: Cl = 94%)

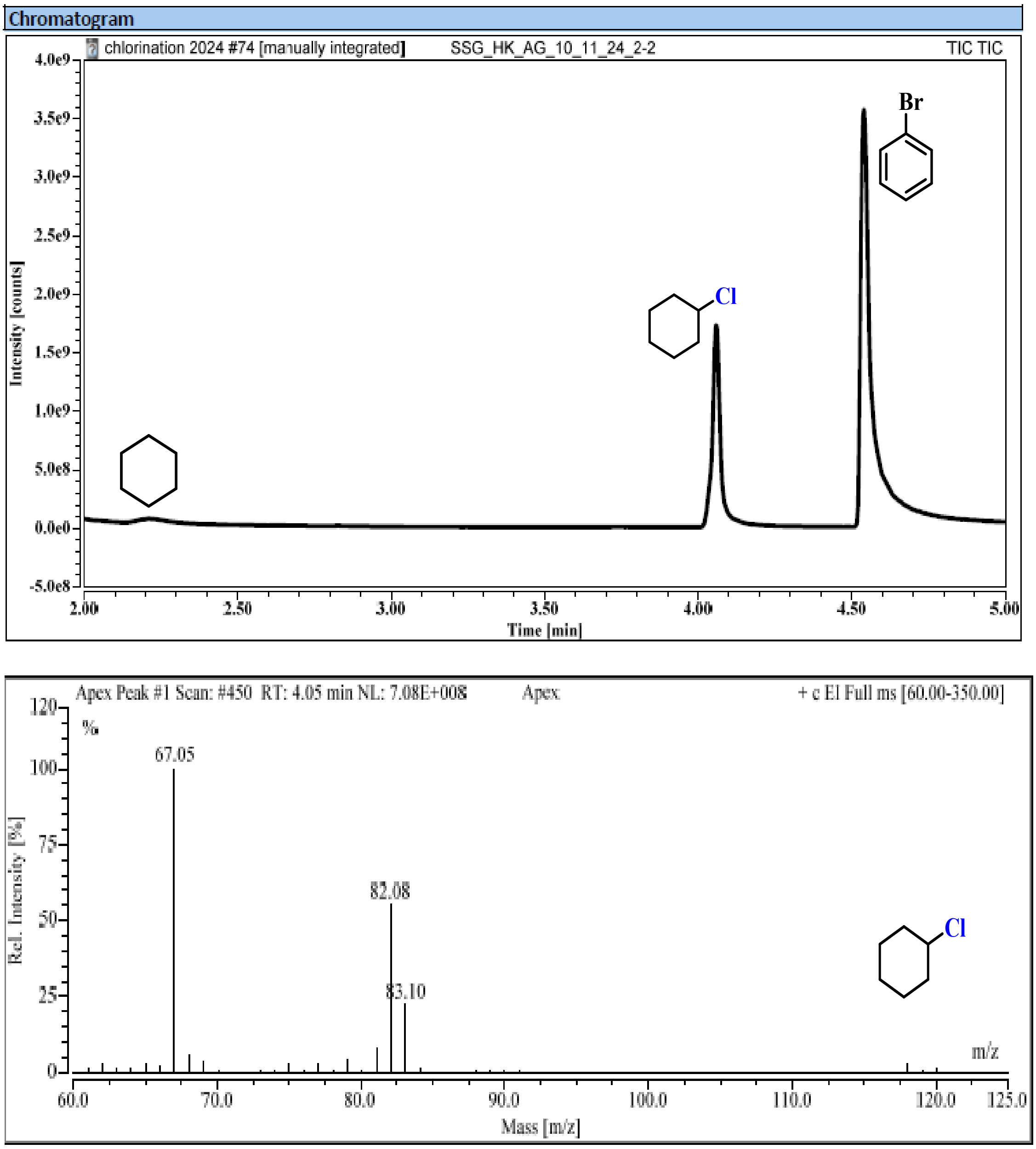


Figure S13. GC-MS trace of the chlorination reaction of Cyclohexane (Conversion: 95%, Yield: 92%)

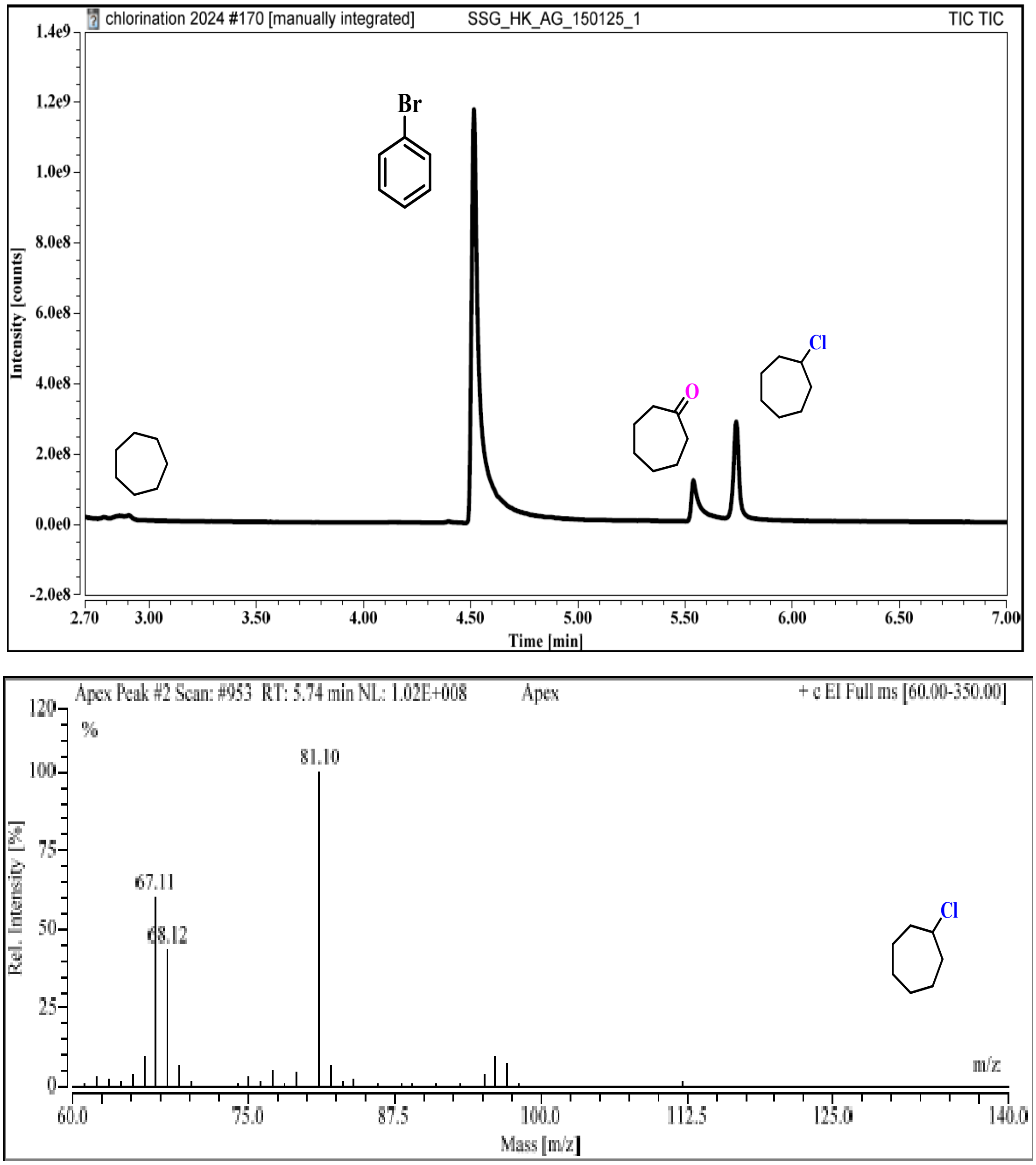


Figure S14. GC-MS trace of the chlorination reaction of Cycloheptane (Conversion: 93%, Yield: O = 26%, Cl = 65%)

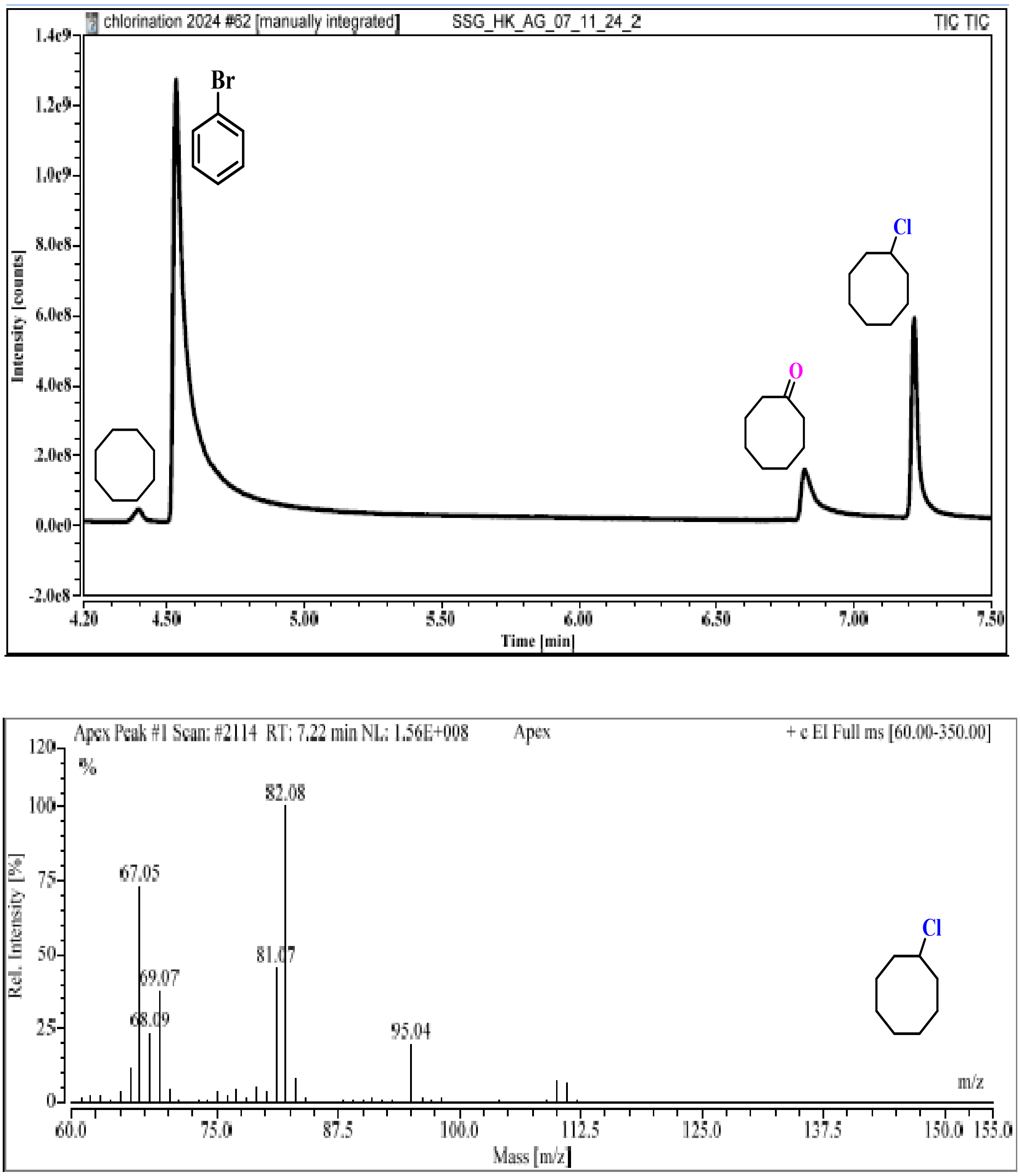


Figure S15. GC-MS trace of the chlorination reaction of Cyclooctane (Conversion: 88%, Yield: O = 19%, Cl = 68%)

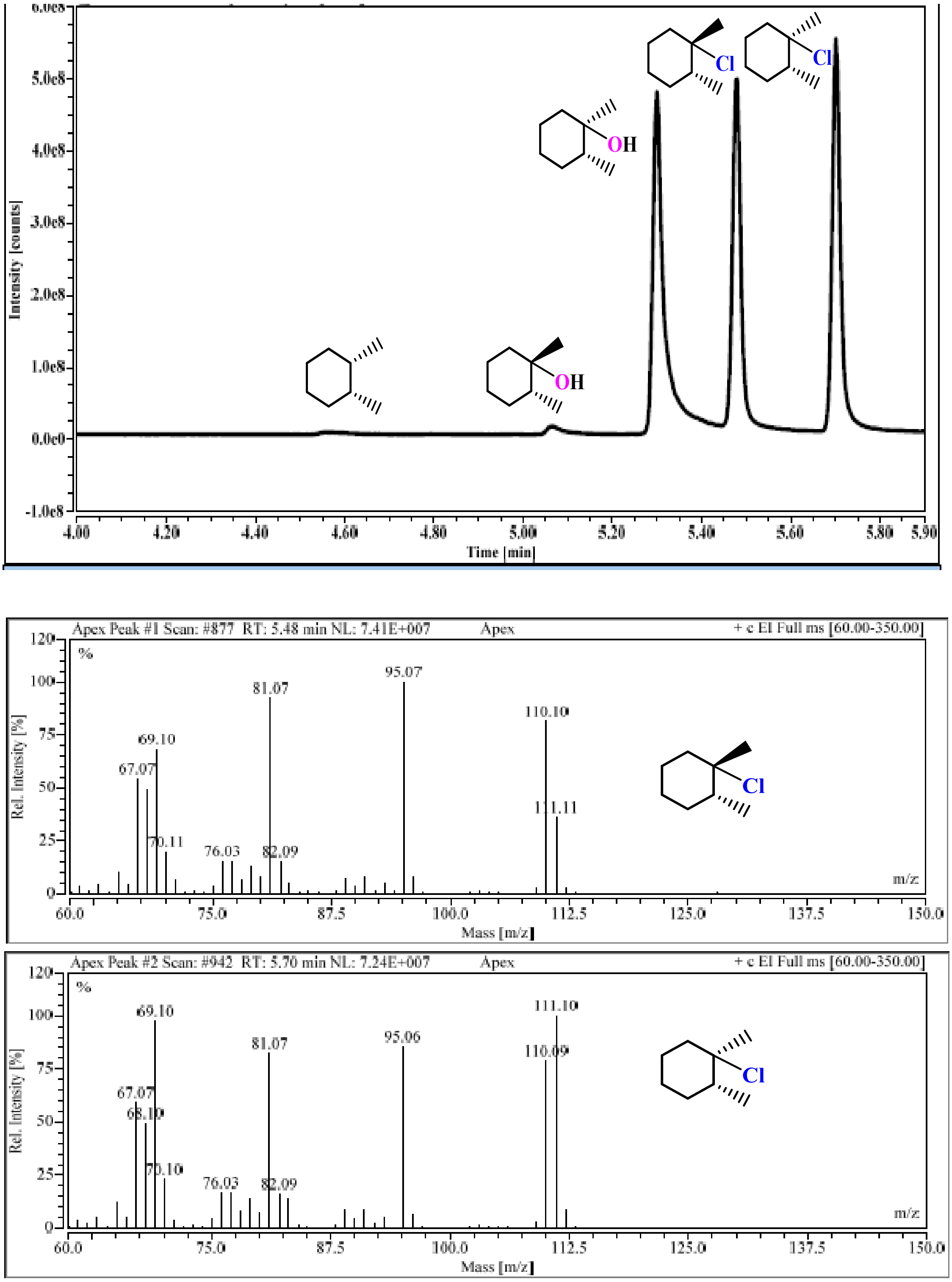


Figure S16. GC-MS for the chlorination reaction of cis-dimethyl cyclohexane (Conversion: 97%, Yield: OH (cis) = 30%, OH (trans) = 4%, Cl (cis) = 33%, Cl (trans) = 30%)

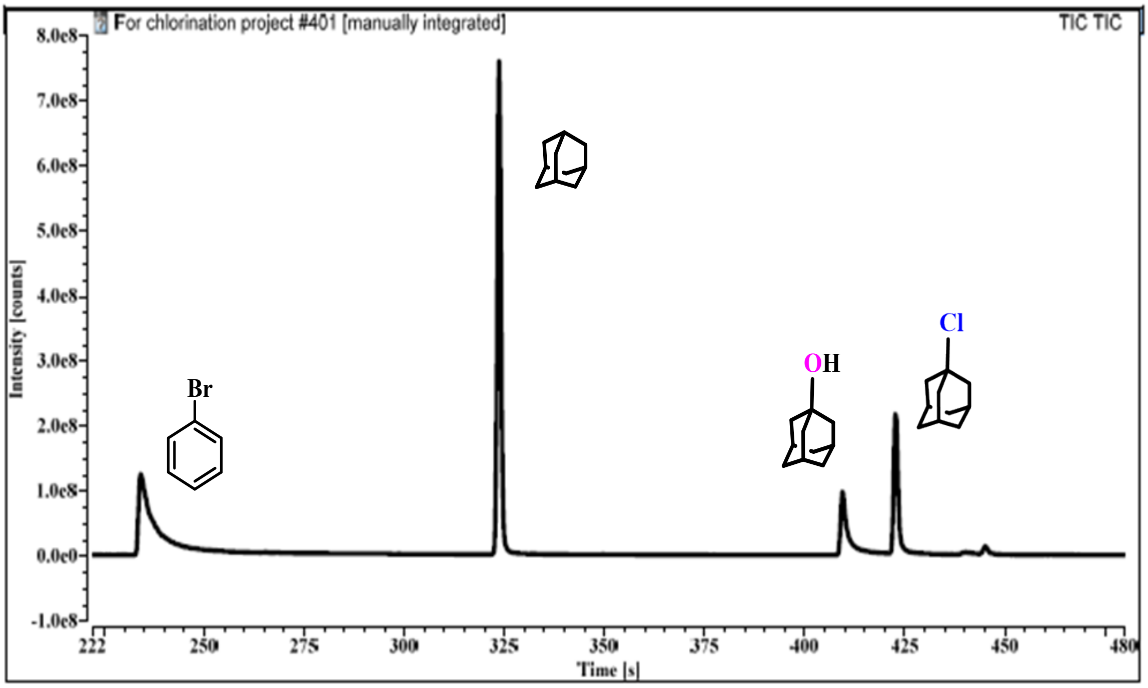


Figure S17. GC-MS trace for the chlorination reaction of Adamantane for 10 min without Imidazole (Conversion: 22%, Yield: OH = 7%, Cl = 15%)

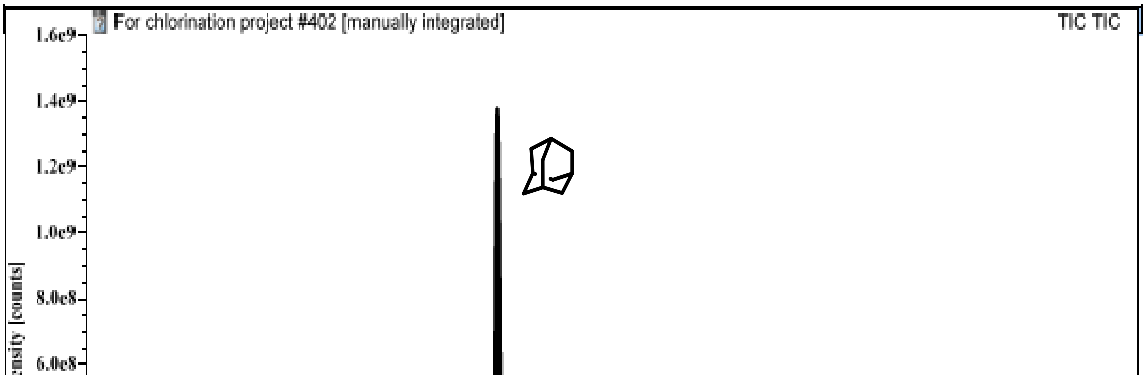


Figure S18. GC-MS trace for the chlorination reaction of Adamantane for 10 min in the presence of 1 eq. Imidazole (Conversion: 18%, Yield: OH = 13%, Cl = 5%)

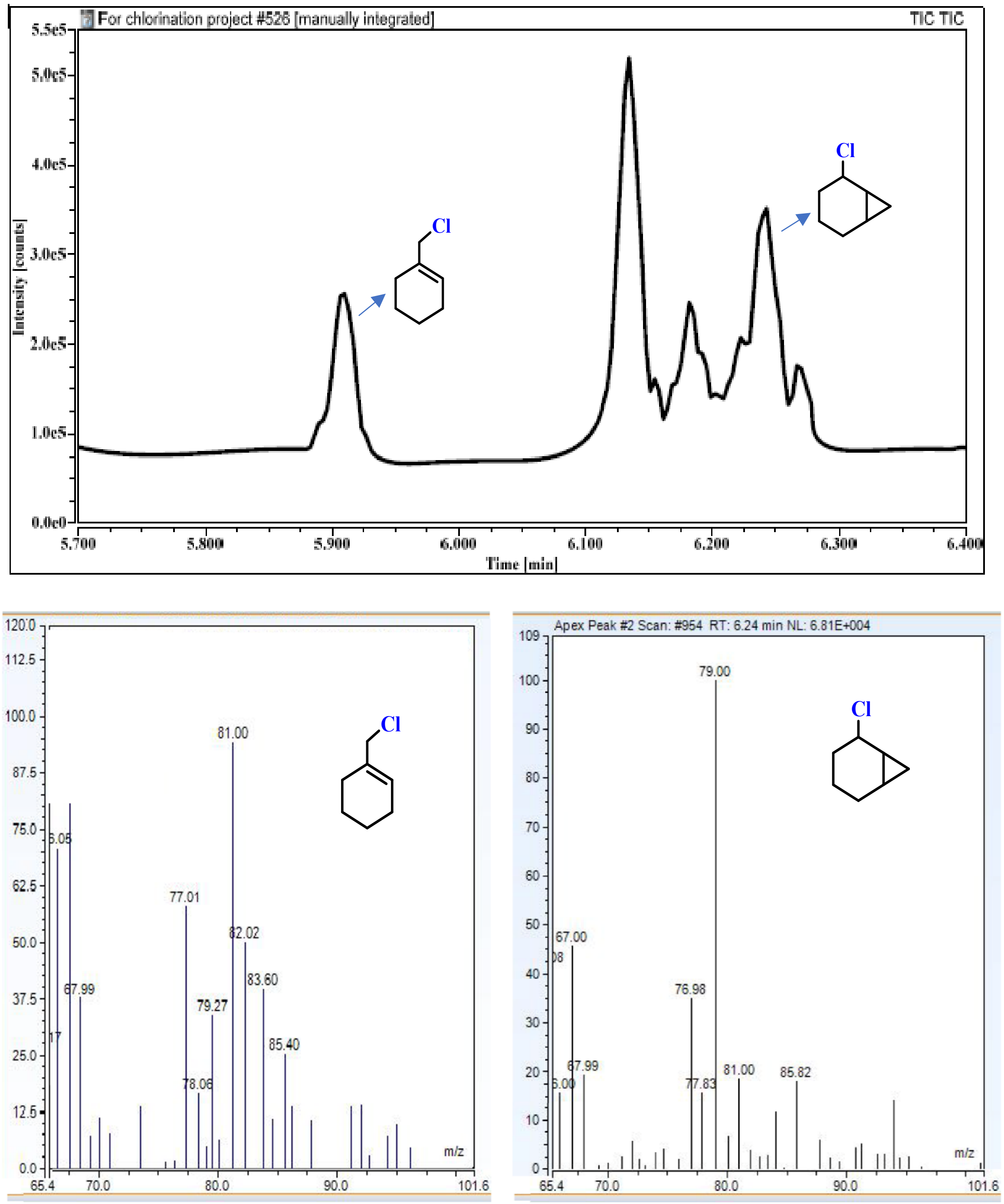
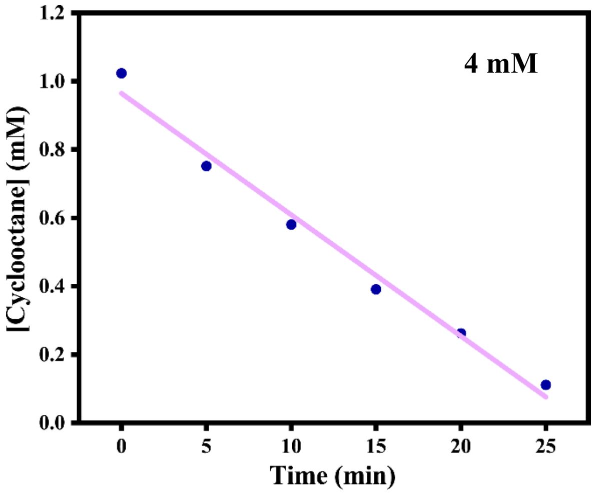
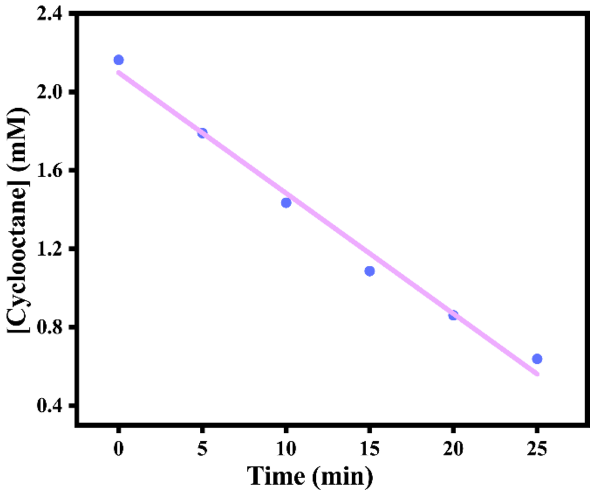
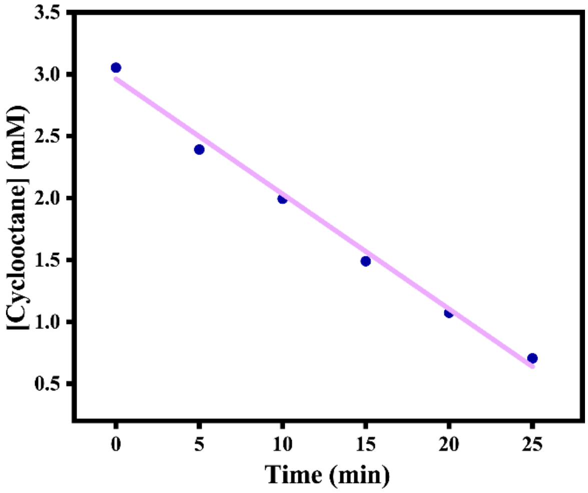


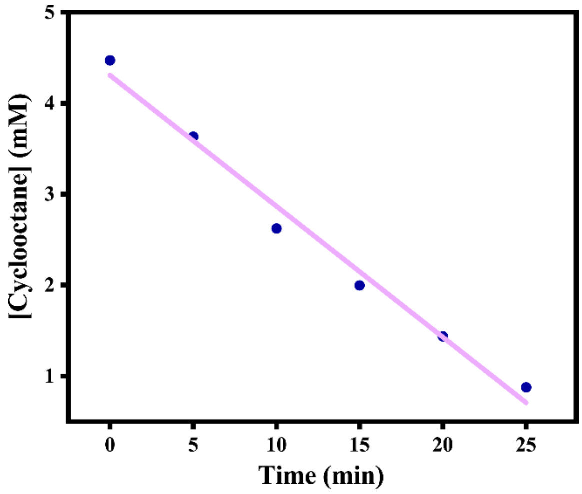
Figure S19. GC-MS trace for the chlorination reaction of Norcarane (rearrange: 4% & rebound: 4.3%)

6. Kinetic analysis of the reaction









10 mM

16 mM

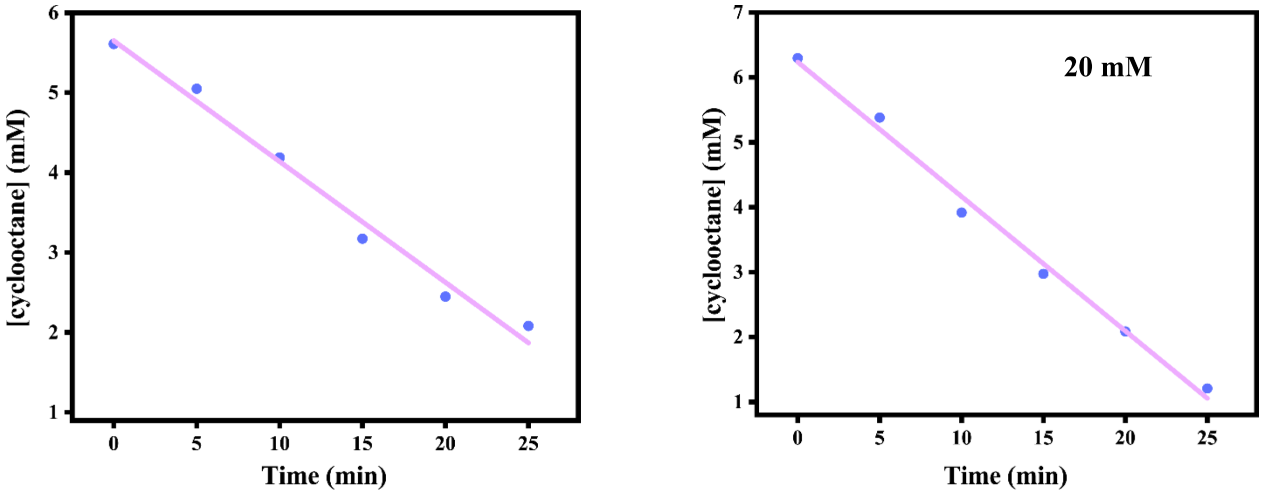


Figure S20. Initial rate measurement for [cyclooctane] variation (4 – 22 mM). [**1**] = 0.2 mM, [NaOCl] = 60 mM, Temperature: 25°C, $CH_3CN:H_2O$ (5:1 v/v) 2mL. During GC analysis, the reaction mixture was diluted 3.5 times. Each data point was the average of three reaction sets measured in GC. ($k_2 = 0.75\ M^{-1}\ s^{-1}$)

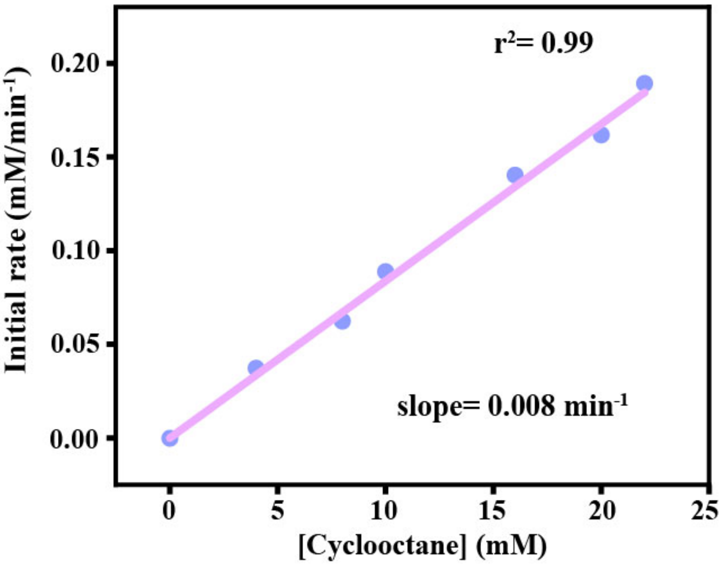


Figure S21. Initial rate vs. [Cyclooctane].

7. Kinetic analysis of the chlorination reaction by monitoring the decay of 2 in presence of the excess substrate concentration using UV-Vis spectroscopy:

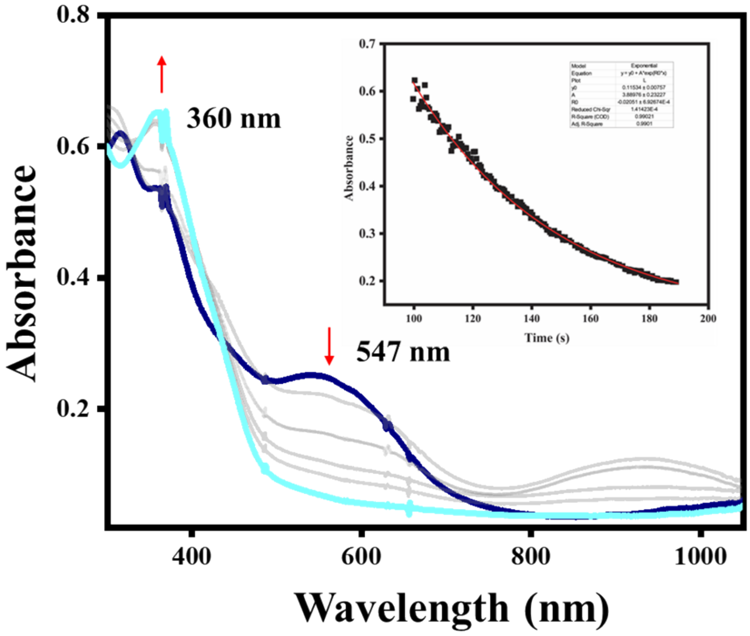


Figure S22: UV-Vis spectral changes upon reaction of **2** (1×10^{-4} M) with cyclooctane (0.075 M). (Inset) the absorbance vs time plot at 547 nm (■ indicates experimental data point; the red line is the exponential fit ($r^2 = 0.990$). Condition: **2** (0.1 mM), Cyclooctane (0.075 M), in CH_3CN-H_2O (5:1 v/v) 2 mL at 25° C in N_2 atm.

k_{obs}= 0.021 s^{-1}

k_{obs}= 0.025 s^{-1}

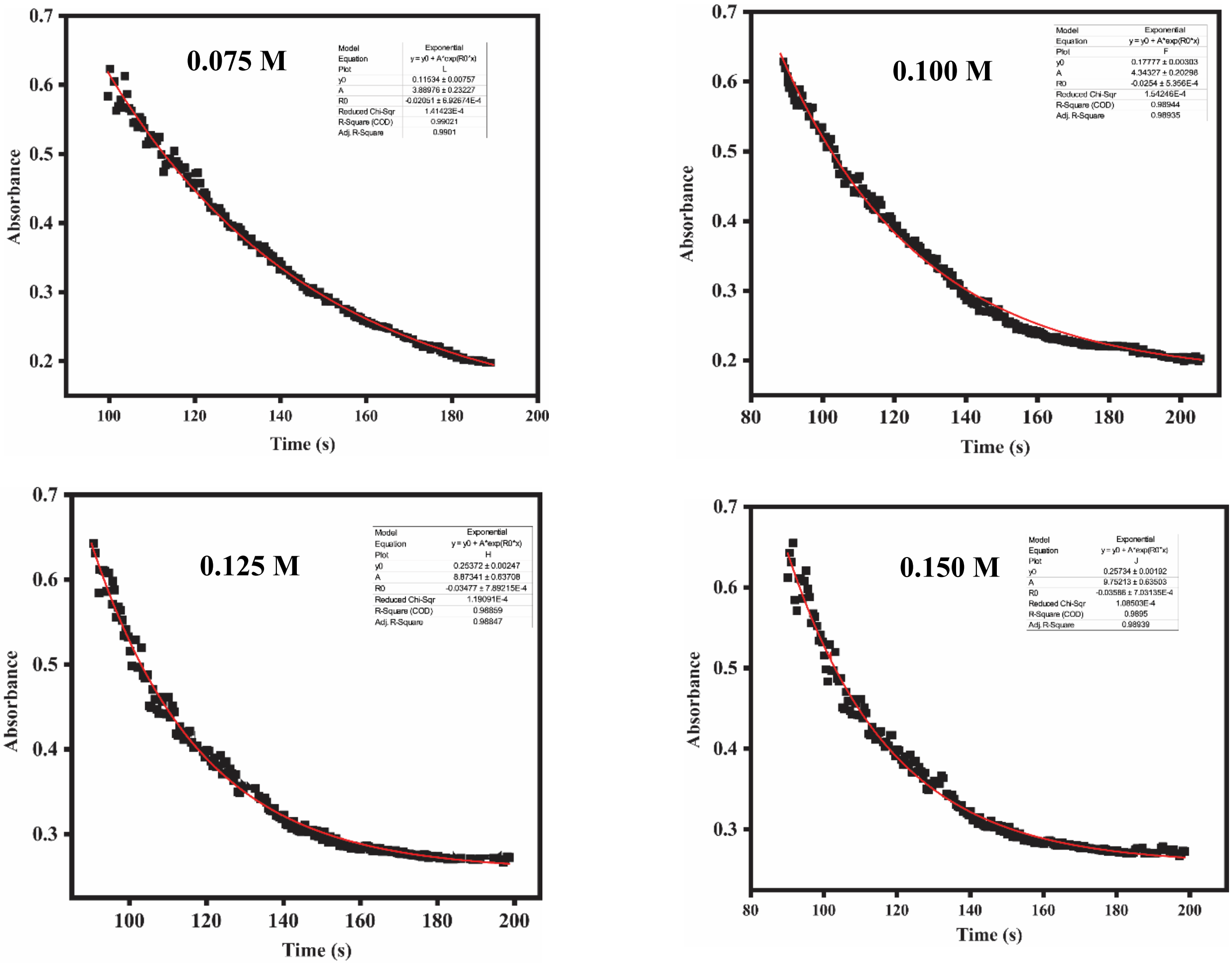


Figure S23. UV-Vis spectral decay of the peak at 547 nm (characteristic of complex **2**) with time for [cyclooctane] variation (0.075 – 0.150 M). [**1**] = 0.1 mM, [NaOCl] = 0.12 mM, Temperature: 25°C, $CH_3CN:H_2O$(5:1 v/v) 2mL, N_2 atmosphere.

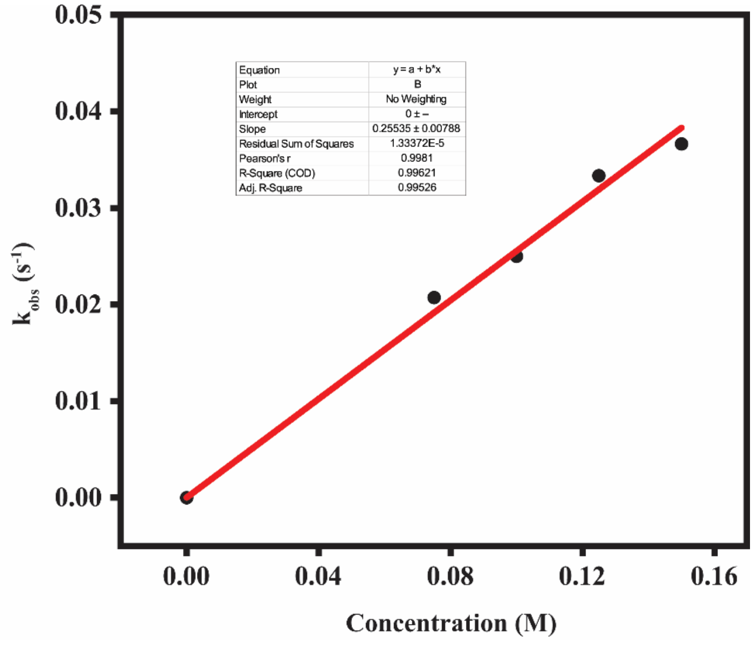
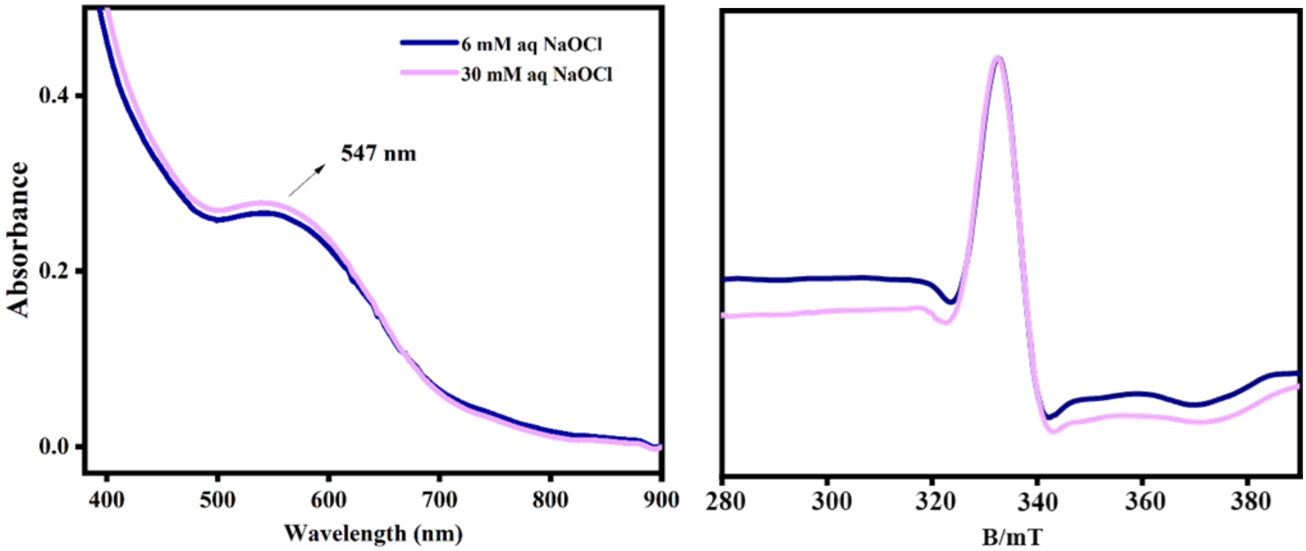


Figure S24: k_{obs} vs [cyclooctane] ($k_2 = 0.26$ M^{-1} s^{-1}, $r^2 = 0.995$)

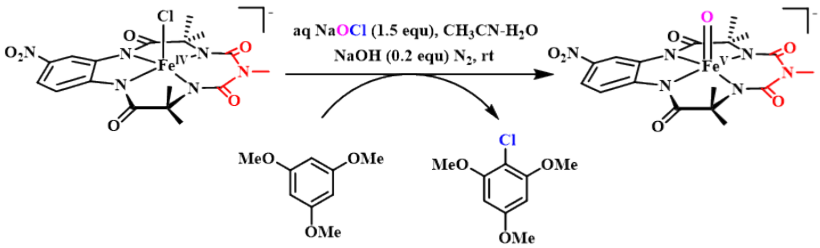
8. Formation of intermediate 2 under Hydroxylation and Chlorination conditions:



A. **B.**

Figure S25: (A) UV-Vis spectra of **2** under hydroxylation condition: **1** (0.1 mM), NaOCl (6 mM) in CH_3CN-H_2O at 25° C, and under chlorination condition: **1** (0.1 mM), NaOCl (30 mM) in CH_3CN-H_2O at 25° C, **(B)** EPR spectra of **2** in presence of 6 mM & 30 mM aq. NaOCl in CH_3CN-H_2O at 85 K

8. Detection of the $[Fe^{IV}(OCl)(Y)$-$(NO_2)bTAML]^{2-}$ intermediate using a chlorine radical trap:



Scheme 2: Trapping the chloride atom in the reaction between Fe(IV)Cl and NaOCl

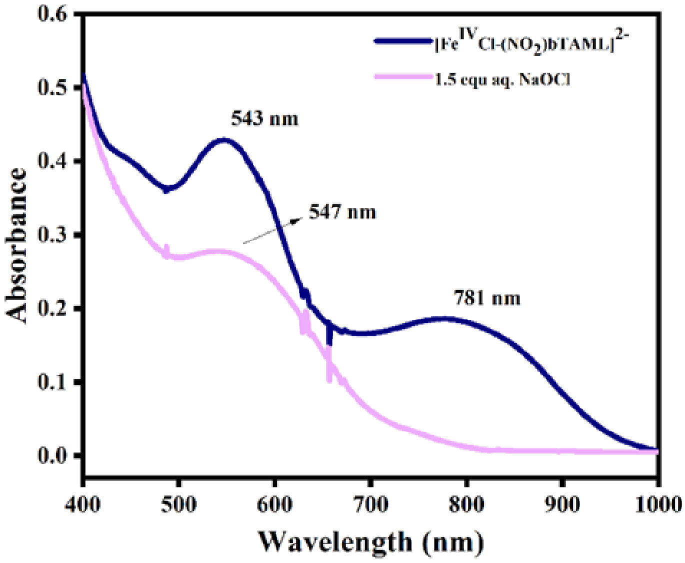


Figure S26*:* Addition of aq. NaOCl (0.3 mM) into $[Fe^{IV}Cl\text{-}(NO_2)bTAML]^-$ (0.2 mM) in presence of NaOH (0.4 mM) in $CH_3CN\text{-}H_2O$ (5:1) at rt.

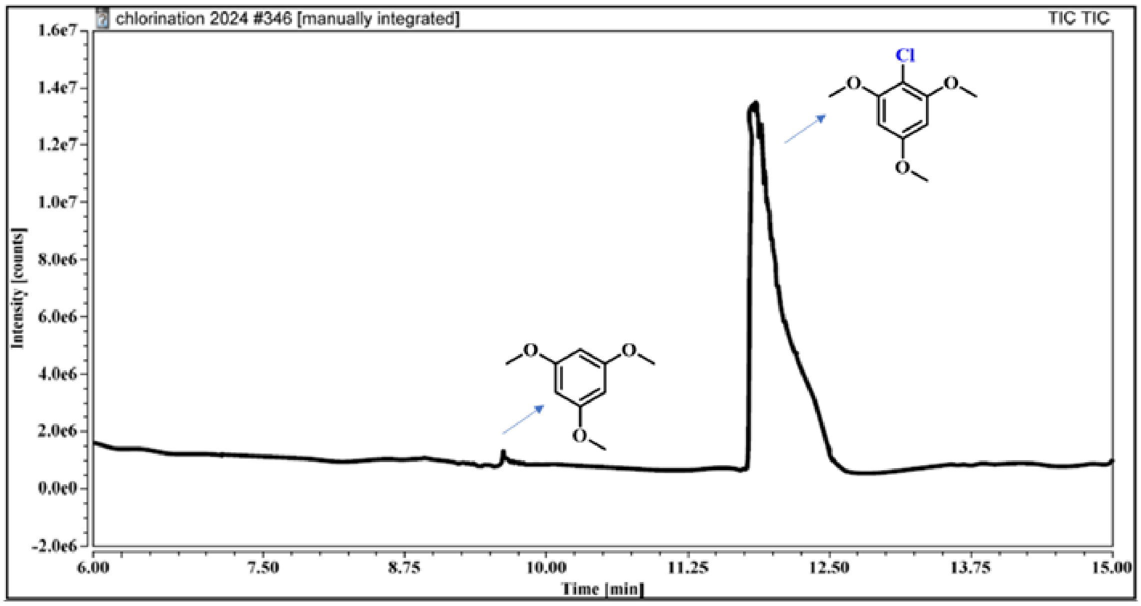


Figure S27: GC-MS trace for the reaction between 1,3,5-trimethoxybenzene (1.5 mM) and aq. NaOCl (3 mM) in presence of [Fe^{IV}(Cl)-(NO$_2$)bTAML]$^-$ (2 mM) and NaOH (0.4 mM) in CH_3CN-H_2O (5:1) at rt.

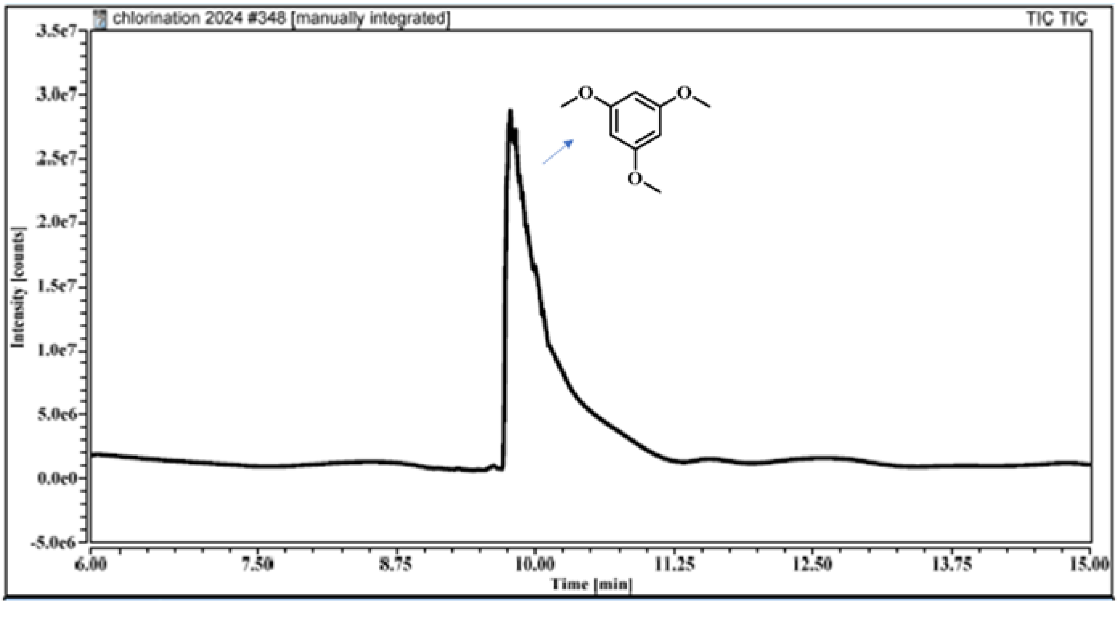


Figure S28: GC-MS trace for the reaction between 1,3,5-trimethoxybenzene (1.5 mM) and aq. NaOCl (3 mM) in presence of NaOH (0.4 mM) in CH_3CN-H_2O (5:1) at rt.

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