Supporting Information

Calibration-Free Quantification and Automated Data Analysis for High-Throughput Reaction Screening

Felix Katzenburg[1,†], Florian Boser[1,†], Felix R. Schäfer[1], Philipp M. Pflüger[1], Frank Glorius[1,*]

[1]Organisch-Chemisches Institut, Universität Münster, Corrensstraße 36, 48149 Münster, Germany.

[†]These authors contributed equally to this work.

*Email: glorius@uni-muenster.de (F.G.)

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S1. General Information

All reactions, except otherwise noted, were performed under argon in oven-dried glassware. Reaction temperatures are reported as the temperature of the medium surrounding the flask. The reactions were stirred using PTFE-coated magnetic stirring bars at roughly 700 rpm.

The solvents *n*-hexane, diethyl ether, *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), methanol (MeOH), methylene chloride (DCM), toluene and acetonitrile (MeCN) were obtained from a solvent purification system (HPLC grade, filtered through activated alumina/molecular sieves columns under positive argon pressure following a published procedure).[1] Other dry solvents were purchased from Acros Organics, Sigma Aldrich or Carl Roth, dried over activated 3 Å molecular sieves for a minimum of 48 h, and stored under argon. Deuterated solvents for NMR analysis were dried over activated 3 Å molecular sieves. Ethyl acetate (EtOAc) and *n*-pentane used for workup and flash column chromatography were of technical grade and purified prior to use by distillation.

Unless otherwise indicated, all chemicals were obtained from commercial sources such as Sigma-Aldrich, Acros Organics, Fluorochem, Alfa Aesar, TCI, and Fischer Scientific and were used without further purification. Compounds that decompose at room temperature were stored in the refrigerator or freezer. All thiols and heteroarenes acquired or synthesized within this project were stored in a refrigerator by default.

Analytical thin-layer chromatography plates from Merck (silica gel 60 F_{254}) were utilized for reaction control and purification. To visualise the spots, UV light (254 nm, 366 nm) and/or staining with basic $KMnO_4$ solution (1 g $KMnO_4$, 6 g K_2CO_3 and 0.1 g KOH in 100 mL deionised water) was used.

Flash column chromatography was carried out using Acros Organics silica for chromatography (0.035-0.070 mm, 60 Å) as a stationary phase under low positive pressure and the indicated solvent mixture as the mobile phase, according to a published procedure.[2] Automated flash column chromatography was carried out using a Biotage® Isolera One Flash Purification Chromatography equipped with a Biotage® Sfär Silica D - 60 µm column and the indicated solvent mixture as the mobile phase.

High-resolution mass spectra were obtained using a Bruker Daltonics microTOF or a Thermo Fisher Scientific LTQ Orbitrap XL spectrometer using Electron Spray Ionisation (ESI).

NMR spectra were recorded on Bruker NEO 400 MHz (^{1}H: 400.23 MHz, ^{13}C: 100.65 MHz), Bruker Avance II 400 MHz (^{1}H: 400.13 MHz, ^{13}C: 100.62 MHz), Varian 500 MHz INOVA (^{1}H: 499.83 MHz, ^{13}C: 125.70 MHz) or Varian Unity plus 600 (^{1}H: 599.31 MHz, ^{13}C: 150.71 MHz) spectrometer as solutions in appropriate deuterated solvent. All chemical shifts are reported as δ-values in parts per million (ppm) relative to residual solvent signals (*d*-chloroform: $\delta = 7.26$ ppm for ^{1}H NMR and $\delta = 77.2$ ppm for ^{13}C NMR at 25 °C, d_6-DMSO: $\delta = 2.50$ ppm for ^{1}H NMR and $\delta = 39.52$ ppm for ^{13}C NMR at 25 °C) or an internal reference (tetramethylsilane for ^{1}H and ^{13}C, $CFCl_3$ for ^{19}F and $MeNO_2$ for ^{15}N).[3] All coupling constants are reported in Hertz (Hz). For the characterization of the observed signal multiplicities, the following abbreviations (or combinations thereof) are used: s (singlet), d

(doublet), t (triplet), and m (multiplet). All spectra were analyzed with MestReNova (version 14.3.0-30573 by Mestrelab Research S.L.).

All photochemical reactions were performed in 10 mL Schlenk tubes (unless stated otherwise). The reactions were carried out in a commercial EvoluChem™ PhotoRedOx Duo photobox with irradiation by EvoluChem HCK1021-01-008 blue LEDs (30 W, λ_{max} = 450 nm). The reaction temperature in this set-up was approx. 30 °C.

S1.1. Setup for High-Throughput Experimentation in 96-Reaction Blocks

High-throughput experimentation (HTE) was performed in a semi-automated fashion utilizing an OT-2 liquid handler (Opentrons, SKU 999-00111) equipped with a P300 Single-Channel GEN2 and P300 8-Channel pipette. For all automated liquid transfers, 300 µL OT-2 Tips (Opentrons, SKU 999-00009) were used. Stock solutions were prepared manually in scintillation vials (20 mL, Thermo Fisher Scientific, FS7450420; 8 mL, Thermo Fisher Scientific, No. 10504463; 4 mL, Th. Geyer, No. 7613421). For the automated reaction setup, stock solutions were transferred into polypropylene (PP) reservoirs (Corning, single well, RES-SW96-HP-SI, 8 channel, RES-MW8-HP; 12 channel, RES-MW12-HP). For manual reaction setup, custom-made polytetrafluorethylene (PTFE) reservoirs (Figure S2) were used in combination with piston pipettes (Thermo Fisher Scientific, 1 channel, No. 11885762; 8 channel, No. 11825772; 12 channel, No. 11865772). Reaction arrays were conducted in 96-Well Block Assemblies (Analytical Sales and Services, Photoredox, SKU 96973; Parallel Synthesis, SKU 96960) equipped with glass shell vials (Analytical Sales and Services, SKU 84001-CASE). Oxygen-sensitive reactions were set up in a custom glove box (Figure S1). Photochemical reactions were irradiated with 445 nm Lumidox® II 96-Well LED Arrays (Analytical Sales and Services, SKU LUM296LS445) equipped with a custom water-cooled base. Additional cooling was provided by a cooling fan (Noctua NF-A14 industrialPPC-3000, No. 8590889) positioned in front of the reaction block. In all experiments, the Lumidox® II Controller (Analytical Sales and Services, SKU LUM2CON) was set to output stage 1 (80 mW per well). The assembly of LED array and 96-well block was placed on an orbital shaker (Grant-Bio, PMS-1000i) for mixing. If heating was required, the 96-well block was placed on a magnetic stirrer (IKA, RET basic, No. 0003622000). Reported temperatures refer to the temperature of the 96-well block. Crude reaction mixtures were filtered through 96 PTFE membrane filter plates (Macherey-Nagel, No. 738660.M) filled with approximately 125 mg silica per well. The filtrate was collected in 96 PP deep well plates (Starlab, No. S1896-1110). Samples for GC analysis were prepared in GC vials (Thermo Fisher Scientific, No.16318367) with micro inserts (VWR, No. 548-0006A).

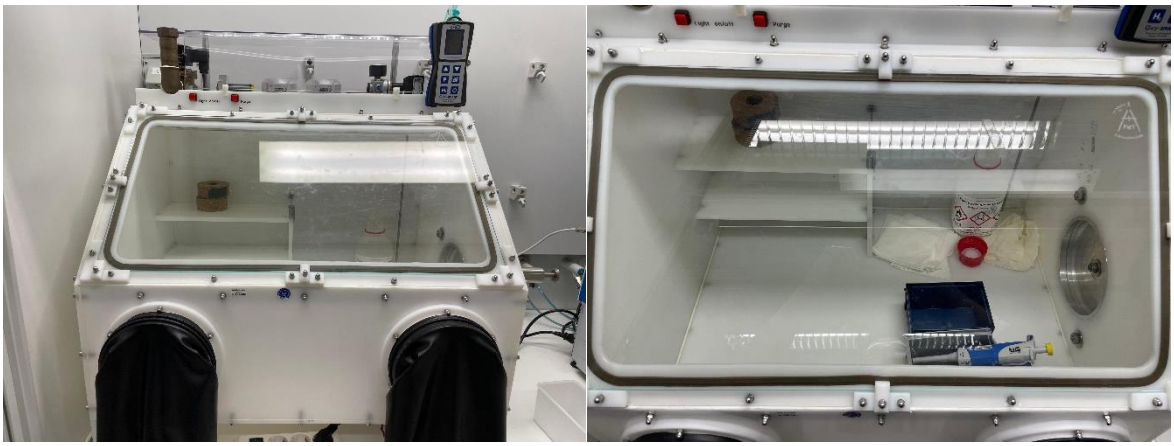


Figure S1. Custom glove box equipped with Orbitec OXY SMART Oxygen Analyser.

Figure S2. Custom-made polytetrafluorethylene (PTFE) reservoir.

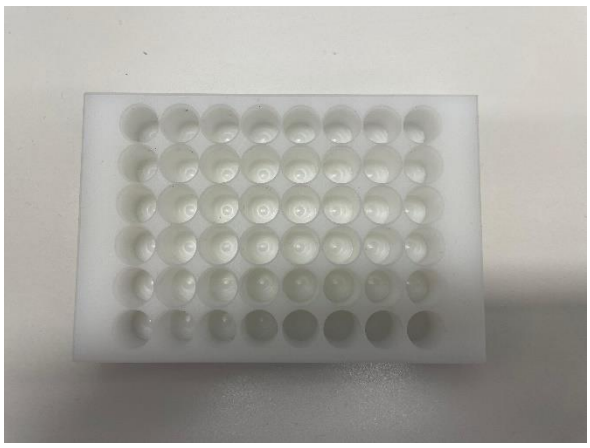


Figure S3. Custom-made 48-GC vial holders.

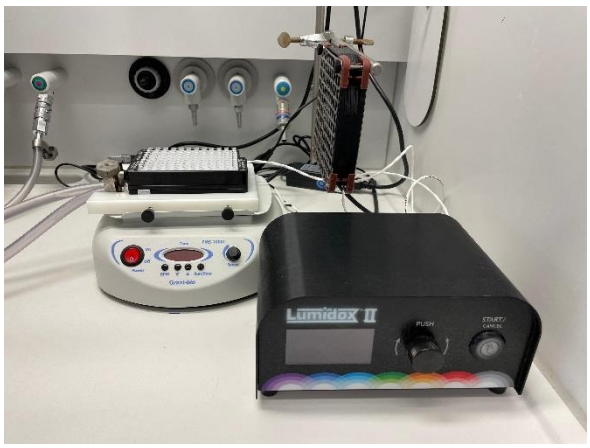


Figure S4. Photo setup for 96-well blocks with 445 nm Lumidox® II 96-Well LED Array equipped with a custom water-cooled base, a Noctua NF-A14 industrial PPC-3000 cooling fan and a Grant-Bio PMS-1000i orbital shaker.

S1.2. Protocols for OT-2 Liquid Handler

All Python protocols used to control the OT-2 Liquid Handler and custom labware definitions are available on zenodo (10.5281/zenodo.10407762).

S1.3. General Procedure for Automated Reaction Workup and Sample Preparation

Reaction workup and sample preparation were automated via Python scripts for the OT-2 liquid handler (scripts are available on zenodo at 10.5281/zenodo.10407762). In the workup protocol, a sample of each crude reaction mixture (30 µL – 60 µL) was aspirated from the 96-reaction block after mixing and transferred to a 96-filter plate on a deep well plate. Afterward, the filter was flushed four times with 250 µL EtOAc at intervals of 10 minutes. After removing the filter plate, the sample preparation script was run. In this protocol, each filtrate was mixed, and a sample of 120 µL was transferred into two GC vials with micro inserts positioned in custom 48-GC vial holders (Figure S3).

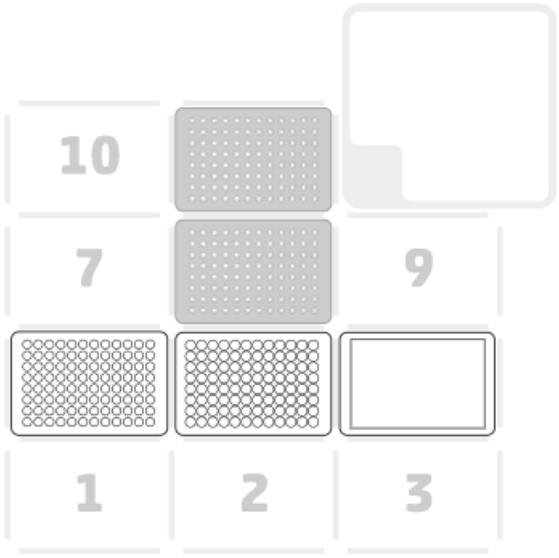


Figure S5. Deck view of OT-2 for the workup protocol. Labware: 300 µL tipracks (Pos. 11, 8), Paradox 96-Well Block Assembly (Pos. 4), 96-deep well plate with 96-filter plate (Pos. 5), single well reservoir (Pos. 6).

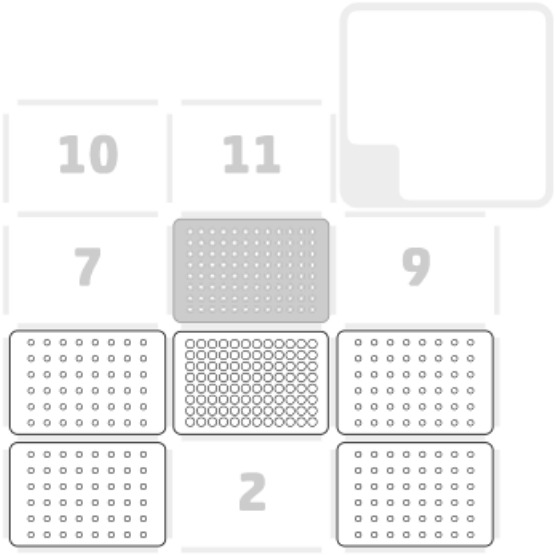


Figure S6. Deck view of OT-2 for the sample preparation protocol. Labware: 300 µL tipracks (Pos. 8), Paradox 96-Well Block Assembly (Pos. 5), 48 GC vial racks (Pos. 1, 3 ,4 , 6).

S1.4. Gas Chromatographic Analysis

Samples for GC were filtered over a pad of silica and eluted with EtOAc before analysis. GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system (HP-5MS column: 0.25 mm × 30 m, film: 0.25 µm) with an Agilent 5977B Mass Selective Detector (MSD). The applied methods are specified for each experiment, and method files are available on zenodo at 10.5281/zenodo.10407762.

GC-PA-FID measurements were performed on Agilent Technologies 7890A GC-system (HP-5MS column: 0.25 mm × 30 m, film: 0.25 µm) equipped with a Polyarc® system (connected to an Aux. EPC and a Thermal Aux. Zone) and a flame ionization detector (FID). The Polyarc® system was operated at 450 °C with an air flow rate of 7.5 mL/min and a hydrogen flow rate of 40 mL/min. The applied methods are specified for each experiment, and method files are available on zenodo at 10.5281/zenodo.10407762. Quantitative analysis was performed using dodecane as an internal standard. Reaction yields were calculated as the ratio of the carbon-normalized peak areas of an analyte (*a*) and the standard (*s*) (Equation 1).

$$Yield\ (\%) = \frac{Area_{\mathrm{a}}/Carbon\ Count_{\mathrm{a}}}{Area_{\mathrm{s}}/Carbon\ Count_{\mathrm{s}}} \cdot 100\% \qquad \textbf{Equation 1}$$

To match peaks in GC-MS and GC-PA-FID measurements of the same sample, retention indices (RI) were calculated for each peak in the chromatograms based on a calibration measurement with a C7 - C40 saturated alkanes standard (certified reference material, 1000 µg/mL each component in hexane, Merck, SKU 49452-U) using the formula defined by Kováts:[4]

$$RI_a = 100\left(\frac{t_{\mathrm{r,a}} - t_{\mathrm{r,n}}}{t_{\mathrm{r,n-1}} - t_{\mathrm{r,n}}} + n\right) \qquad \textbf{Equation 2}$$

Peaks were matched if their RI did not differ by more than 20. If several peaks met this criterion, the peaks with the smallest RI difference were matched. The calculation of RI values and the matching of peaks was performed autonomously using the pyGecko library.

S2. pyGecko Library

pyGecko is an open-source Python library for the processing, analysis and visualization of GC-MS and GC-FID data developed as part of this work (available on GitHub at https://github.com/FelixKatz77/pyGecko). pyGecko is implemented in Python3, building on the program packages SciPy,[5] RDKit,[6] ProteoWizard[7], pymzML[8], Pyteomics[9] and BRAIN.[10,11] The modular architecture and flexibility of pyGecko allow facile adaption to different screening, automation, and synthetic chemistry workflows.

S2.1. Overview

pyGecko is designed to perform automated data processing of GC measurements and is most powerful for the analysis of larger numbers of experiments measured under comparable chromatographic conditions (instrument, column, temperature program, detector). However, processing single injections is also possible, and most library functionalities can be used independently. Data analysis with pyGecko is typically initiated by parsing raw data from a machine into Python (Figure S7). Afterward, the data is processed, including smoothing, baseline correction, peak detection, and integration. Context information of the sample, like the retention time on an internal standard and a corresponding RI calibration, can be included to facilitate automatic information extraction. This also includes information about a reaction sample's starting materials and products to enable yield and conversion calculations. Following this contextualization, analytes can be assigned to peaks based on their molecular ion mass-to-charge ratio (m/z) and their isotopic distribution. Quantifications of analytes can be performed relative to an internal standard for FID measurements based on the carbon normalized peak area when a Polyarc® system is utilized or a previously recorded calibration curve is provided. Chromatograms, mass spectra and quantifications can be visualized and compared. Final results can be exported as CSV or PDF files. Measurements from reaction arrays can also be exported in the Open Reaction Database (ORD)[12] schema if the reaction metadata is provided in a JSON file.

Figure S7. Overview of pyGecko functionalities.

S2.2. Modules

Raw data parsing

pyGecko has parsing capabilities for different raw data file types (MS: D (Agilent), RAW (Thermo), mzML, mzXML; FID: CSV, .xy). Measurements can be parsed as injection (for single measurements) or sequence (for multiple related measurements). For measurements performed on Agilent GCs, metadata of injections and sequences is also parsed by reading the .acaml file (FID) or sequence.xml file (MS). After parsing, the individual measurements are stored in *Injection* objects that can be grouped in a *Sequence* object. For FID measurements, a solvent delay (a time point behind the solvent peak) has to be specified to enable accurate background subtraction.

Data Processing

GC-FID Measurements

For GC-FID measurements, smoothing of the signal is performed using the Savitzky-Golay algorithm[13] as implemented in SciPy. The optimal Savitzky-Golay window size for a chromatogram is identified using the Durbin-Watson statistic. Afterward, the baseline is estimated using the SNIP algorithm[14] and subtracted from the chromatogram. Peaks are detected using the find_peaks function implemented in SciPy with a prominence threshold (default: mean intensity of the chromatogram). Peak borders are estimated by a slope-based method evaluating the first derivative of the intensity to both sides of a peak. A border is set if the derivative falls below the gradient threshold (default: half of the absolute value of the first derivative of the chromatogram's intensities) within a window of 100 scans. Peak integration is performed within the borders using Simpson's rule as implemented in SciPy.

GC-MS measurements

Peaks are detected using the find_peaks function implemented in SciPy on the total ion chromatogram with a prominence threshold (default: median intensity of the chromatogram) and height threshold (default: fifty times the minimum intensity value). The thresholds were generally selected so that traces of substances (>1% relative to an internal standard) may not be detected to avoid misidentifications of compounds. The mass spectrum of a peak is extracted by searching for peaks on all mass traces within five scans of the peak in the total ion chromatogram.

For each peak in GC-FID and GC-MS chromatograms, a *Peak* object is initialized that wraps information like the retention time, height, area, width, mass spectrum, and assigned analytes.

Contextualization

Information about the experimental context can be included in the analysis to enable the automatic evaluation of experiments. An internal standard can be flagged by specifying the retention time and subsequently used to quantify analytes. To map substrates and potential products of a reaction array to the *Injections* of a *Sequence,* a CSV file containing the layout of the plate must be provided, and the sample names of the *Injections* must indicate the position of the corresponding well by the ending "-<row><column>" (e.g., "-A1" or "-D12"). The CSV file only needs to have two columns, 'x' and 'y',

specifying the substrates used in each row and column as a simplified molecular-input line-entry system (SMILES) string (example files can be found on zenodo at 10.5281/zenodo.10407762) (Table S1). The potential products can then be determined automatically if a reaction SMARTS mapping the substrates to the products is provided. Using this input, a *Reaction Array* object containing information about all substrates and targeted products in each well is initialized. *Injections* are mapped to a well based on the position specified by their sample name.

Table S1. Sample data (to be provided as CSV file) used to initialize a *Reaction Array* object. To map substrates to the corresponding products a reaction SMARTS (e.g., [c:1]1([a:2][a:3][a:4][a:5]1)[Cl,Br:6].[SH1:7][#6:8]>>[c:1]1([a:2][a:3][a:4][a:5]1)[S:7][#6:8]) has to be specified.

	A	B
1	x	y
2	Cn1c(Cl)c(Cl)nc1	COC(CCS)=O
3	BrC1=NC(C)=CN1C	SC1CCCCC1
4	CC1=NC=C(Br)N1C2=CC=C(OC)C=C2	SCC1=CC=CC=C1
5	COC1=CC=C(OC2=NC=C(Br)S2)C=C1	SC1=CC=C(Cl)C=C1
6	O=C(C1=C(Br)SC(C)=N1)OCC	SC1=CC=CC=C1Br
7	BrC1=CC=C(C2=CC=CC=C2)S1	SC1=CC=CC(OC)=C1
8	BrC1=C(CCCC)C=CS1	SC1=CC=C(N)C=C1
9	O=C(C1=CC=C(Br)O1)OC	SC1=CC=NC=C1
10		SC1=NC=CC=N1
11		SC1=CC=CC=N1
12		SC1=NC2=CC=CC=C2O1
13		SC1=NC2=CC=CC=C2S1

Additional information on reaction conditions, workup steps and analysis details can be specified in a JSON file and stored in a *Reaction Array* object. This file contains information about all added stock solutions and solids as well as the reaction conditions, workup and analysis (example files can be found on zenodo at 10.5281/zenodo.10407762). This information is required to automatically generate an ORD dataset after the analysis.

For each molecule assigned to a peak in a chromatogram, an *Analyte* object is initialized. From the *Analyte* object, information like the molecular mass or a molecule's carbon count can be accessed and used for downstream analysis.

RI calibration measurements for GC-FID and GC-MS measurements are parsed and processed as described above. In addition, the retention time and SMILES string of one alkane has to be specified to facilitate the automated assignment of the alkanes to the peaks in the chromatogram. Afterward, the *RI Calibration* can be used to calculate RI indices for all peaks in an *Injection* or *Sequence* employing Equation 2.

Information Extraction

Using the mapping of a *Reaction Array's* target products or substrates to the *Injections* of a *Sequence,* compounds are assigned to the corresponding *Peak* if it is present in the GC-MS chromatogram. This

assignment is performed by calculating the compound's molecular mass and searching for a signal with the corresponding m/z value in all *Peaks* of the *Injection*. To minimize false positive assignments, the intensity of the +1 or +2 isotope peak is calculated (using the BRAIN algorithm) and compared to the intensity of the signal in the chromatogram. The compound is assigned to the peak if the deviation between the calculated and measured intensity is below a threshold. If multiple peaks match these criteria, the compound is assigned to the peak with the smallest deviation from the calculated intensity.
For the quantification of analytes identified in the GC-MS chromatogram, the corresponding peak in a GC-FID measurement of the sample is mapped by comparing the RI values of the *Peaks*. *Peaks* are matched if the RI deviation is below 20. If multiple *Peaks* are found within this window, the *Peak* with the smaller deviation is matched. Afterward, the analyte is quantified relative to an internal standard using Equation 1 or a calibration curve.
MS spectra of *Peaks* can be compared by calculating their cosine similarity. If the similarity is above a user-specified threshold (default: 0.9), the spectra are considered to stem from the same analyte. The retention time difference can also be considered in the comparison.

Visualization

The following Visualizations are implemented in pyGecko:

- GC-MS and GC-FID chromatograms and stacked chromatograms

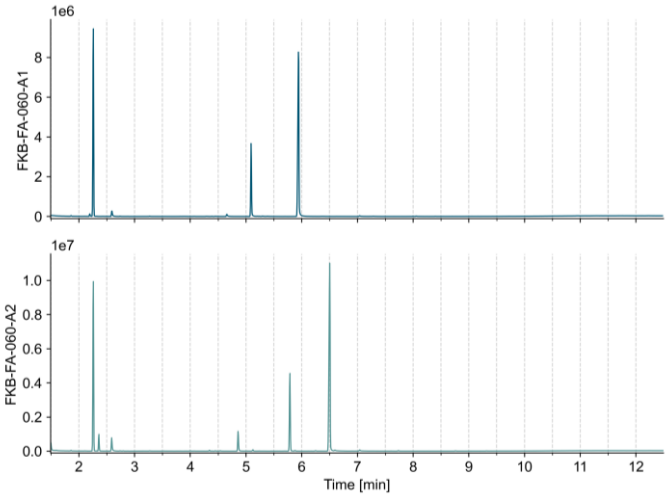


Figure S8. Stacked GC-MS chromatograms visualized by pyGecko.

- MS spectra and spectra comparisons

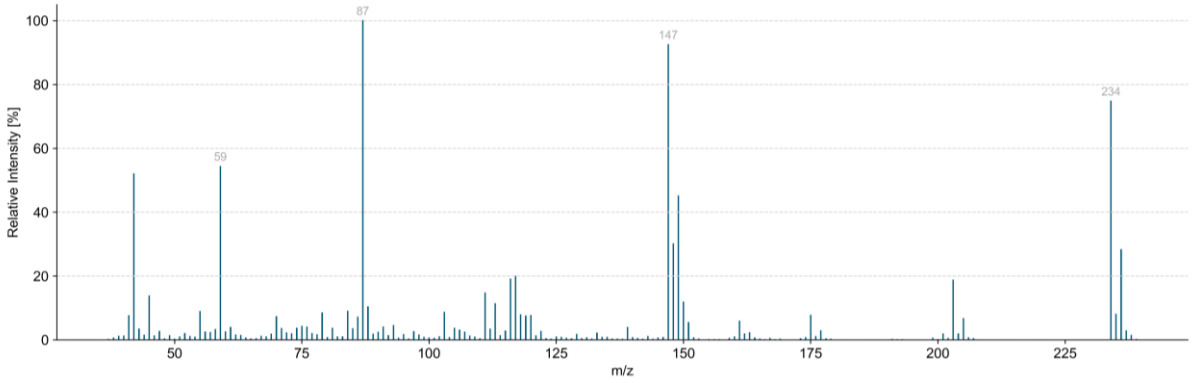


Figure S9. Mass spectrum visualized by pyGecko.

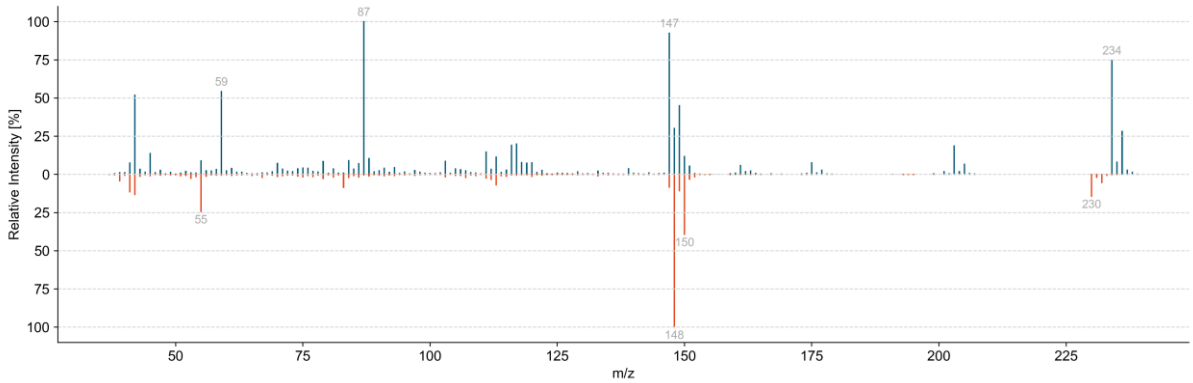


Figure S10. Comparison of mass spectra visualized by pyGecko.

- Heatmaps for yields and conversions of reaction arrays

Reporting

Reaction array reports can be automatically generated in CSV or PDF format. CSV reports contain the reaction yield or conversion as well as the retention time of the peaks identified for the compound in the GC-MS and GC-FID chromatograms. PDF reports contain the reaction yields or conversion, a heatmap, and the reaction components of the arrays, rows, and columns. If a JSON file specifying experimental metadata like concentration, labware, mixing, and analysis methods is specified upon initialization of the *Reaction Array* object, an ORD entry can be generated as a .pbtxt file.

S2.3. Best Practices for GC Measurements and Using pyGecko

pyGecko is a tool for processing and analyzing GC-MS and GC-FID measurements and was not developed to improve the quality of raw data or to compensate for technical or user-related artifacts. Therefore, the good condition and correct use of the GC should be guaranteed to achieve high-quality results. The development of suitable GC methods to ensure sufficient separation of all compounds of interest is of particular importance. An internal standard for quantification should not overlap with other compounds in a sample's chromatogram. RI calibrations must be performed under the same chromatographic conditions (instrument and method) using a suitable alkane standard. Methods for RI calculations should only have linear temperature ramps without an initial hold time when the formula defined by Kováts is applied (Equation 2). RIs can only be calculated reliably if a peak's retention time is between the retention times of the first and last alkane peaks in the calibration measurement. pyGecko was not developed to detect trace amounts of compounds. However, the sensitivity of the peak detection can be tuned by specifying the keyword arguments *prominence_ms*, *prominence_fid* and *trace_prominence* in the *pick_peaks* method. For details consult the pyGecko documentation at https://pygecko.readthedocs.io/en/latest/.

Prior to initiating a screening campaign, the suitability of target analytes for GC(-MS) analysis should be validated. This involves analyzing structurally similar model compounds to verify appropriate volatility and the presence of molecular ions in MS spectra. For compounds lacking molecular ion peaks, pyGecko facilitates identification through characteristic fragment patterns of compound classes.

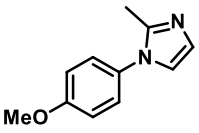
S2.4. Examples

Usage examples can be found at https://github.com/FelixKatz77/pyGecko/tree/main/examples.

S3. Site-Selective Thiolation of Halogenated Heteroarenes

S3.1. Starting Material Synthesis

Synthesis of 1-(4-Methoxyphenyl)-2-methyl-1*H*-imidazole (3')



According to a previously published literature procedure,[15] 2-methyl-1H-imidazole (648 mg, 7.90 mmol) and (4-methoxyphenyl)boronic acid (1.00 g, 6.58 mmol) were dissolved in MeOH (20 mL), and copper(I) oxide (73.0 mg, 0.51 mmol) was added. The red mixture was stirred for 16 h at room temperature while being open to air. The reaction progress was monitored by GC-MS. On completion, the suspension was filtered twice, and the filtrate was concentrated under reduced pressure. The crude mixture was purified by automated flash column chromatography with a gradient of EtOAc in pentane (50% - 100%). The product 1-(4-methoxyphenyl)-2-methyl-1*H*-imidazole (**3'**) (0.844 g, 4.48 mmol, 68%) was isolated as yellow-white crystals.

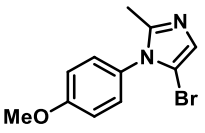
R_f (80% EtOAc in pentane) = 0.10.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 – 7.16 (m, 2H), 7.03 – 6.93 (m, 4H), 3.86 (s, 3H), 2.32 ppm(s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 159.4, 145.2, 131.1, 127.6, 127.0, 121.1, 114.7, 55.7, 13.8 ppm.

Analytical data in accordance with the literature.[15]

Synthesis of 5-Bromo-1-(4-methoxyphenyl)-2-methyl-1H-imidazole (3)



1-(4-Methoxyphenyl)-2-methyl-1*H*-imidazole (**3'**, 1.00 g, 5.31 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. 1-Bromopyrrolidine-2,5-dione (993 mg, 5.58 mmol) in DMF (10 mL) was added dropwise to the solution over 10 minutes at 0 °C. The mixture was stirred at 0 °C for 1 hour, then allowed to reach room temperature and stirred for further 23 h. The reaction progress was monitored by GC-MS. After full conversion, the mixture was diluted with DCM and water and quenched with a saturated solution of sodium hydrogen carbonate. The aqueous phase was extracted three times with DCM, and the combined organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography with a gradient of EtOAc in pentane (50% - 60%) to obtain 5-bromo-1-(4-methoxyphenyl)-2-methyl-1*H*-imidazole (**3**) (1.03 g, 3.85 mmol, 72%) as a brownish-white powder.

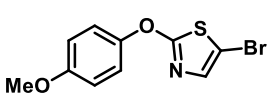
R_f (50% EtOAc in pentane) = 0.21.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (d, $J_{H\text{-}H}$ = 8.9 Hz, 2H), 7.01 (d, $J_{H\text{-}H}$ = 9.0 Hz, 2H), 6.98 (s, 1H), 3.88 (s, 3H), 2.24 ppm (s, 3H).

^{13}C{^{1}H} NMR (THF-*d*8, 101 MHz): δ 160.2, 146.9, 129.1, 128.6, 127.9, 114.8, 103.9, 55.7, 14.8 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 288.99525, measured: 288.99473.

Synthesis of 5-Bromo-2-(4-methoxyphenoxy)thiazole (4)



The procedure was adapted from two previously published procedures.[16,17] 2,5-dibromothiazole (1.00 g, 4.12 mmol), 4-methoxyphenol (511 mg, 4.12 mmol) and potassium carbonate (654 mg, 4.73 mmol) were stirred in dry dimethylformamide (10 mL) for 5 hours at 135 °C. The brown suspension was cooled to room temperature, and water was added. The aqueous phase was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by automated flash column chromatography with a gradient of EtOAc in pentane (0% - 10%), yielding the product 5-bromo-2-(4-methoxyphenoxy)thiazole (**4**) (1.00 g, 3.50 mmol, 85%) as colorless crystals.

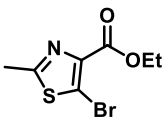
R_f (10% EtOAc in pentane) = 0.81.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 – 7.09 (m, 2H), 7.07 (s, 1H), 6.90 – 6.81 (m, 2H), 3.75 ppm (s, 3H).

^{13}C{^{1}H} NMR (THF-*d*8, 101 MHz): δ 174.4, 157.9, 148.5, 138.6, 121.8, 115.2, 100.7, 55.8 ppm.

Analytical data in accordance with the literature.[18]

Synthesis of Ethyl 5-bromo-2-methylthiazole-4-carboxylate (5)



The procedure was adapted from two previously published procedures.[19,20] Ethyl 2-methylthiazole-4-carboxylate (1.00 g, 5.84 mmol) was first dissolved in MeCN (20 mL). 1-Bromopyrrolidine-2,5-dione (2.08 g, 11.7 mmol) was added, and the mixture was heated to reflux at 85 °C for 24 hours. After letting the mixture cool down to room temperature, it was diluted with water, and a saturated solution of sodium hydrogen carbonate was slowly added. The solvent MeCN was removed under reduced pressure, DCM was added, and the aqueous layer was extracted with DCM three times. The combined organic layers were washed with water and brine, dried over MgSO4, filtered and then concentrated under reduced pressure to obtain a dark, viscous oil. The crude was purified by automated flush column chromatography with a gradient of EtOAc in pentane (0% - 40%), providing product 5-bromo-2-methylthiazole-4-carboxylate (**5**) (1.02 g, 4.06 mmol, 70%) as a pale-orange solid.

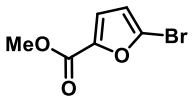
R_f (20% EtOAc in pentane) = 0.35.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.43 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H), 2.70 (s, 3H), 1.42 ppm (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 166.5, 161.1, 143.1, 116.2, 61.9, 19.9, 14.5 ppm.

Analytical data in accordance with the literature.[19,20]

Synthesis of Methyl 5-bromofuran-2-carboxylate (8)



The procedure was adapted from a previously published literature procedure.[21] 5-bromofuran-2-carboxylic acid (0.760 g, 3.98 mmol) was added to a Schlenk tube. The Schlenk tube was evacuated and backfilled with argon three times. Afterwards, the starting material was dissolved in MeOH (30.0 mL) and conc. H_2SO_4 (1.00 mL) was added dropwise. After stirring at 80 °C for 2 h and monitoring the reaction completion by TLC, the MeOH was removed under reduced pressure. The crude mixture was poured into water (300 mL), extracted with EtOAc four times and washed with brine. The combined organic phases were dried over magnesium sulfate, and volatile components were evaporated under reduced pressure. The crude was purified by flash column chromatography with EtOAc yielding the product methyl 5-bromofuran-2-carboxylate (**8**) (675 mg, 3.30 mmol, 83%) as a white crystalline solid.

R_f (10% EtOAc in penatane) = 0.38.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, $J_{H\text{-}H}$ = 3.5 Hz, 1H), 6.46 (d, $J_{H\text{-}H}$ = 3.5 Hz, 1H), 3.89 ppm (s, 3H).

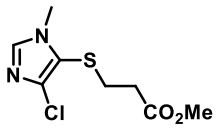
Analytical data in accordance with the literature.[21]

S3.2. Synthesis of Thiolated Heteroarenes

General Procedure:

The procedure was performed as previously published.[22] $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (0.012 mmol, 2 mol%), solid heteroarenes (0.6 mmol, 1.0 equiv) and solid thiols (0.9 mmol, 1.5 equiv) were added to a Schlenk tube. The Schlenk tube was evacuated and backfilled with argon three times. Afterward, dry dimethylacetamide and liquid heteroarenes and thiols were added. The reaction mixture was stirred at room temperature under irradiation from blue LEDs (30 W, λ_{max} = 450 nm) for 16 h. The reaction mixture was quenched with EtOAc and washed with a saturated solution of sodium hydrogen carbonate and water (two times). The organic phase was dried over $MgSO_4$. After the evaporation of volatile components, the crude product was purified.

Methyl 3-((4-chloro-1-methyl-1H-imidazol-5-yl)thio)propanoate (1a)



The title compound was prepared from 4,5-dichloro-1-methyl-1H-imidazole (90.6 mg, 0.60 mmol, 1.0 equiv) and methyl 3-mercaptopropanoate (108.2 mg, 0.90 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with EtOAc. The product (138.0 mg, 0.588 mmol, 98%) was isolated as a yellow oil.

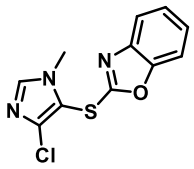
R_f (EtOAc) = 0.44.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.91 (t, $J_{H\text{-}H}$ = 7.0 Hz, 2H), 2.58 ppm (t, $J_{H\text{-}H}$ = 7.0 Hz, 2H).

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 257.01220, measured: 257.01190.

Analytical data in accordance with the literature.[22]

2-((4-Chloro-1-methyl-1H-imidazol-5-yl)thio)benzo[*d*]oxazole (1b)



The title compound was prepared from 4,5-dichloro-1-methyl-1H-imidazole (90.6 mg, 0.60 mmol, 1.0 equiv) and benzo[*d*]oxazole-2-thiol (136.1 mg, 0.90 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with a 1:1 mixture of pentane and EtOAc. The product (32.6 mg, 0.123 mmol, 21%) was isolated as an off-white solid.

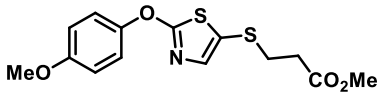
R_f (50% EtOAc in pentane) = 0.26.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (s, 1H), 7.62 – 7.57 (m, 1H), 7.46 – 7.42 (m, 1H), 7.33 – 7.27 (m, 2H), 3.75 ppm (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 160.38, 152.16, 141.84, 139.75, 139.73, 124.87, 124.86, 119.43, 110.42, 109.98, 33.45 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 287.99688, measured: 287.99679.

Methyl 3-((2-(4-methoxyphenoxy)thiazol-5-yl)thio)propanoate (4a)



The title compound was prepared from 5-bromo-2-(4-methoxyphenoxy)thiazole (**4**) (171.0 mg, 0.60 mmol, 1.0 equiv) and methyl 3-mercaptopropanoate (108.2 mg, 0.90 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with a 5:1 mixture of pentane and EtOAc. The product (130.7 mg, 0.402 mmol, 67%) was isolated as a yellow oil.

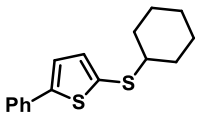
R_f (17% EtOAc in pentane) = 0.28.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 1H), 7.22 – 7.16 (m, 2H), 6.96 – 6.90 (m, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 2.92 (t, $J_{H\text{-}H}$ = 7.3 Hz, 2H), 2.62 ppm (t, $J_{H\text{-}H}$ = 7.3 Hz, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 177.13, 171.96, 157.88, 148.56, 145.05, 121.84, 121.45, 115.13, 55.79, 52.04, 34.31, 33.20 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 348.03347, measured: 348.03302.

2-(Cyclohexylthio)-5-phenylthiophene (6a)



The title compound was prepared from 2-bromo-5-phenylthiophene (143.5 mg, 0.60 mmol, 1.0 equiv) and cyclohexanethiol (**6**) (104.6 mg, 0.90 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with hexane. The product (36.1 mg, 0.132 mmol, 22%) was isolated as a yellow oil.

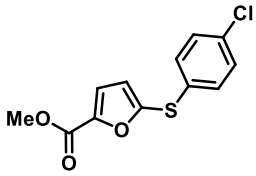
R_f (hexane) = 0.32.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 – 7.45 (m, 2H), 7.34 – 7.26 (m, 2H), 7.24 – 7.17 (m, 1H), 7.11 (d, $J_{H\text{-}H}$ = 3.7 Hz, 1H), 7.00 (d, $J_{H\text{-}H}$ = 3.7 Hz, 1H), 2.83 (tt, $J_{H\text{-}H}$ = 10.7, 3.7 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.71 (dt, $J_{H\text{-}H}$ = 12.4, 4.0 Hz, 2H), 1.58 – 1.47 (m, 1H), 1.38 – 1.07 ppm (m, 5H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 148.34, 136.17, 134.19, 132.45, 129.07, 127.88, 125.81, 123.38, 50.13, 33.35, 26.23, 25.74 ppm.

HR-MS (ESI): *m/z* calculated for $[M]^+$: 274.08444, measured: 274.08450.

Methyl 5-((4-chlorophenyl)thio)furan-2-carboxylate (8a)



The title compound was prepared from methyl 5-bromofuran-2-carboxylate (**8**) (123.0 mg, 0.60 mmol, 1.0 equiv) and 4-chlorobenzenethiol (130.2 mg, 0.90 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with a 20:1 mixture of pentane and EtOAc. The product (96.5 mg, 0.359 mmol, 60%) was isolated as an off-white solid.

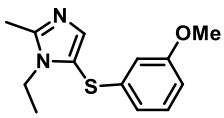
R_f (5% EtOAc in pentane) = 0.44.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 – 7.21 (m, 4H), 7.19 (d, $J_{H\text{-}H}$ = 3.4 Hz, 1H), 6.70 (d, $J_{H\text{-}H}$ = 3.5 Hz, 1H), 3.89 ppm (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 158.57, 149.05, 147.35, 133.79, 132.35, 130.95, 129.62, 119.48, 119.46, 52.29 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 290.98531, measured: 290.98531.

1-Ethyl-5-((3-methoxyphenyl)thio)-2-methyl-1H-imidazole (14a)



The title compound was prepared from 5-chloro-1-ethyl-2-methyl-1H-imidazole (43.4 mg, 0.30 mmol, 1.0 equiv) and 3-methoxybenzenethiol (63.1 mg, 0.45 mmol, 1.5 equiv). After following the general procedure, the crude mixture was purified by flash column chromatography with a 20:1 mixture of DCM and MeOH. The product (36.0 mg, 0.145 mmol, 48%) was isolated as a yellow oil.

R_f (5% MeOH in DCM) = 0.34.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (s, 1H), 7.14 (t, $J_{H\text{-}H}$ = 8.0 Hz, 1H), 6.70 – 6.58 (m, 3H), 3.90 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H), 3.73 (s, 3H), 2.45 (s, 3H), 1.13 ppm (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 160.23, 148.16, 139.03, 137.65, 130.01, 118.51, 117.08, 111.83, 111.54, 55.40, 38.85, 15.82, 14.36 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 271.08756, measured: 271.08734.

S3.3. Control Experiments

Polyarc Quantification Accuracy and Linearity

Before the analysis workflow was utilized on a reaction array, the quantification accuracy and linearity of the GC-Polyarc-FID were investigated by performing triplicate measurements of samples containing thiolation products **1a**, **1k**, **4a**, **6b**, **8d**, and **35f** in ratios of 1:3, 2:3 and 3:3 relative to dodecane as internal standard.

Preparation of stock solutions:

For the thiolation products, a sample of 0.05 mmol was transferred to a 2 mL volumetric flask and dissolved in EtOAc. Standard stock solutions of dodecane and decane were prepared by transferring 0.5 mmol of the alkanes to a 20 mL volumetric flask and dissolving the samples in EtOAc.

Sample preparation:

For each thiolation product, three samples were prepared by transferring 40 µL, 80 µL, and 120 µL of the stock solution into a GC vial. To each vial, 120 µL of the decane and dodecane standard stock solutions were added, and the sample was diluted by adding 1 mL EtOAc.

GC-PA-FID method:

All samples were measured in split mode (split ratio: 5:1, split flow 7.5 mL/min) with an injection volume of 1 µL at an inlet temperature of 280 °C and a septum purge flow of 3 mL/min. The column flow was set to 1.5 mL/min. The temperature program started at an initial oven temperature of 90 °C followed by a 2 min hold time and a 30 °C/min ramp until 280 °C. The final temperature was held for 3 min. The FID was operated at 320 °C with an air flow of 400 mL/min, a hydrogen flow of 2 mL/min and a makeup flow (N_2) of 25 mL/min (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

Data Processing:

All measurements were processed using the OpenLab software from Agilent. Ratios were calculated by dividing the carbon-normalized peak area of the thiolation products by the carbon-normalized peak area of dodecane.

Table S2. Normalized peak area ratios between thiolation products and dodecane were measured as triplicate measurements for thiolation product to dodecane ratios of 1:3, 2:3 and 1:1.

Compound	Ratio								
	1:3			2:3			1:1		
1a	0.31	0.31	0.31	0.64	0.64	0.64	1.00	1.00	1.00
1k	0.33	0.33	0.33	0.66	0.66	0.66	1.09	1.05	1.05
4a	0.27	0.29	0.29	0.61	0.61	0.58	0.98	0.96	0.93
6b	0.32	0.32	0.32	0.64	0.64	0.64	1.00	1.00	1.01
8d	0.33	0.33	0.33	0.65	0.65	0.65	1.04	1.05	1.04
14a	0.31	0.31	0.31	0.64	0.64	0.63	0.99	0.99	0.99

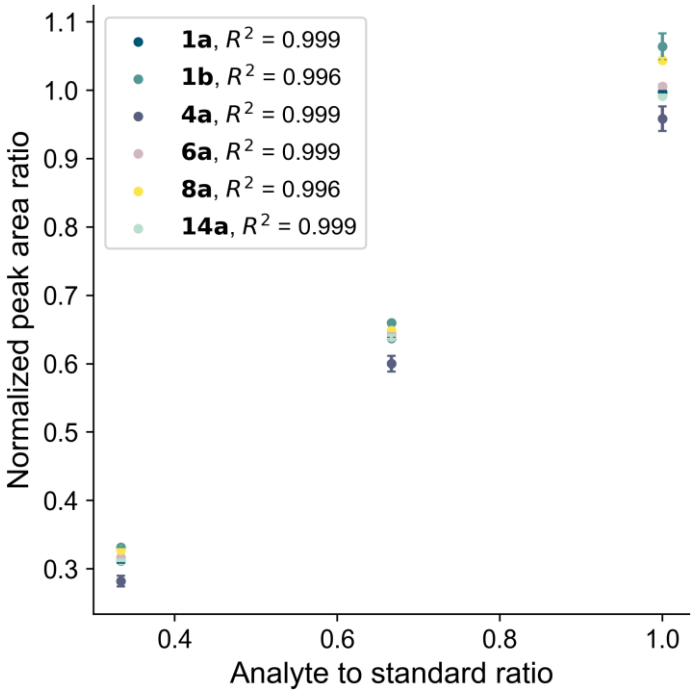


Figure S11. Scatterplot of the analyte to standard ratio against the average ratio of the normalized peak areas for the thiolation products.

Overall, an excellent average error of 2.2 % and a very good linearity were observed for the quantification using the GC-Polyarc-FID method.

Control Reaction Array

Before moving to a fully combinatorial 96-reaction array, the reproducibility of the reaction array setup and workup was validated by running the thiolation of **1** by **9** in all wells of a 96-reaction block.

The 4,5-dichloro-1-methyl-1H-imidazole (**1**) (366.9 mg, 2.43 mmol) and methyl 3-mercaptopropanoate (**9**) (459.7 mg, 3.83 mmol) were weighted into 20 mL scintillation vials and dissolved in 16.2 mL and 17.0 mL dimethylacetamide (DMA) respectively. $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (Ir-F) (39.3 mg, 0.0350 mmol) was weighted into 8 mL scintillation vial and dissolved in 5.80 mL DMA. Dodecane (510.99 mg, 3.00 mmol) was weighted into a 10 mL volumetric flask and dissolved in DMA. Afterward, 2 mL of the heteroarene stock solution was transferred to each well of an 8-channel PP reservoir, 1.4 mL of the thiol stock solution were transferred to each well of a 12-channel PP reservoir, and the Ir-F and dodecane stock solutions were transferred to the first and last reservoir of a 12-channel PP reservoir. Afterward, the stock solutions were dispensed into a Photoredox 96-Well Block Assemblie by executing a custom Python protocol on the OT-2 liquid handler (protocol can be found on zenodo at 10.5281/zenodo.10407762). Thereby, 100 µL of the heteroarene stock solution (0.015 mmol, 1.0 equiv), 100 µL of the thiol stock solution (0.0225 mmol, 1.5 equiv), 50 µL of the Ir-F stock solution (0.0003 mmol, 2 mol%) and 50 µL of the dodecane stock solution (0.015 mmol, 1.0 equiv) were dispensed into each well of the reaction array. The 96-well plate was then sealed and screwed tight and

placed on the Lumidox® II 96-well LED arrays at 445 nm with a custom water cooling and cooling fan for 24 hours under irradiation at 36 °C while shaking at 500 rpm (details in section S1.1). After 24 hours, the plate was unscrewed, the workup was conducted according to section S1.3, and GC analysis was conducted according to section S1.4. All samples were measured in split mode with an initial oven temperature of 110 °C followed by a 25 °C/min ramp until 280 °C. The final temperature was held for 3 min (GC method file can be found on zenodo at 10.5281/zenodo.10407762). Reaction yields are shown in Figure S13.

GC-PA-FID method:

All samples were measured in split mode (split ratio: 5:1, split flow 7.5 mL/min) with an injection volume of 1 µL at an inlet temperature of 280 °C and a septum purge flow of 3 mL/min. The column flow was set to 1.5 mL/min. The temperature program started at an initial oven temperature of 110 °C followed by a 25 °C/min ramp until 280 °C. The final temperature was held for 3 min. The FID was operated at 320 °C with an air flow of 400 mL/min, a hydrogen flow of 2 mL/min and a makeup flow (N_2) of 25 mL/min (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

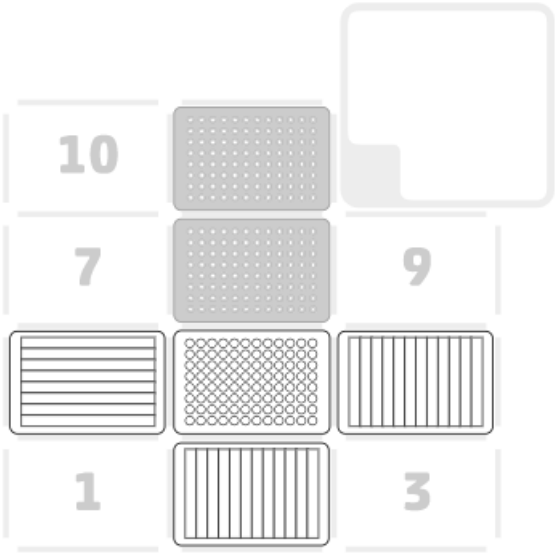


Figure S12. Deck view of OT-2 thiolation control protocol. Labware: 300 µL tipracks (Pos. 11, 8), Paradox 96-Well Block Assembly (Pos. 5), 8-channel (Pos. 4) and 12-channel reservoirs (Pos. 2, 6).

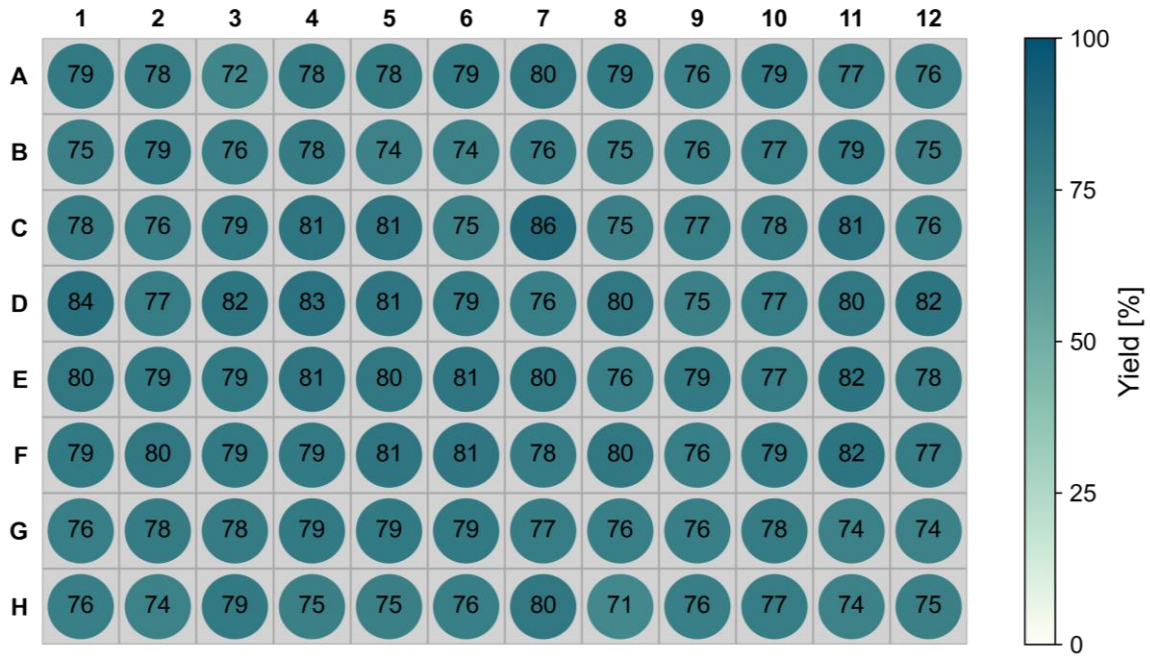


Figure S13. Heatmap illustrating the reaction yields for the thiolation of **1** with **9**.

With an average yield of 78% and a standard deviation of 2.6%, good reproducibility is shown for the proposed workflow.

Comparison with commercial software

To validate the developed data analysis pipeline results from pyGecko were compared them to those obtained using Agilent's OpenLab CDS software (the pmx file specifying the utilized data analysis method can be found on zenodo at 10.5281/zenodo.10407762).

Table S3. Comparison of quantification results obtained using pyGecko with results obtained using established Agilent's OpenLab CDS software for the control reaction array. The mean deviation between the calculated yields is 3.9%.

Well	pyGecko	Agilent	Well	pyGecko	Agilent	Well	pyGecko	Agilent
A1	79	79	**C9**	77	80	**F5**	81	85
A2	78	82	**C10**	78	77	**F6**	81	85
A3	72	73	**C11**	81	78	**F7**	78	82
A4	78	80	**C12**	76	81	**F8**	80	83
A5	78	80	**D1**	84	77	**F9**	76	79
A6	79	81	**D2**	77	69	**F10**	79	82
A7	80	82	**D3**	82	89	**F11**	82	85
A8	79	80	**D4**	83	90	**F12**	77	80
A9	76	77	**D5**	81	73	**G1**	76	79
A10	79	80	**D6**	79	70	**G2**	78	81
A11	77	79	**D7**	76	82	**G3**	78	81
A12	76	79	**D8**	80	84	**G4**	79	82
B1	75	76	**D9**	75	82	**G5**	79	82
B2	79	81	**D10**	77	81	**G6**	79	82
B3	76	79	**D11**	80	85	**G7**	77	80
B4	78	82	**D12**	82	89	**G8**	76	79
B5	74	79	**E1**	80	85	**G9**	76	79
B6	74	78	**E2**	79	83	**G10**	78	82
B7	76	68	**E3**	79	84	**G11**	74	77
B8	75	67	**E4**	81	85	**G12**	74	77
B9	76	81	**E5**	80	87	**H1**	76	79
B10	77	83	**E6**	81	87	**H2**	74	77
B11	79	85	**E7**	80	87	**H3**	79	81
B12	75	78	**E8**	76	80	**H4**	75	78
C1	78	81	**E9**	79	85	**H5**	75	78
C2	76	79	**E10**	77	81	**H6**	76	79
C3	79	82	**E11**	82	83	**H7**	80	83
C4	81	86	**E12**	78	81	**H8**	71	74
C5	81	85	**F1**	79	82	**H9**	76	79
C6	75	78	**F2**	80	83	**H10**	77	79
C7	86	98	**F3**	79	83	**H11**	74	76
C8	75	69	**F4**	79	82	**H12**	75	77

Table S4. Comparison of quantification results obtained using pyGecko with results obtained using established Agilent's OpenLab CDS software for the heteroarene thiolation array. The mean deviation between the calculated yields is 0.5%.

Well	pyGecko	Agilent	Well	pyGecko	Agilent
A1	75	74	**E4**	3	2
A2	76	77	**E5**	2	2
A3	19	21	**E8**	53	51
A4	57	57	**E11**	5	4
A5	58	58	**E12**	25	24
A6	56	55	**F1**	39	39
A8	31	31	**F2**	23	22
A11	13	12	**F4**	52	51
B1	7	6	**F5**	60	58
B2	23	23	**F6**	37	37
B3	7	7	**F7**	10	10
B4	36	36	**F8**	62	61
B5	40	40	**F9**	47	47
B6	29	29	**F10**	72	72
B10	11	11	**F11**	69	70
B11	4	3	**F12**	73	70
B12	14	14	**G1**	21	21
C1	24	24	**G2**	3	3
C2	55	54	**G4**	35	34
C3	16	15	**G5**	42	41
C4	31	31	**G6**	8	8
C5	38	37	**G8**	63	63
C6	24	24	**G9**	2	2
C8	14	14	**G10**	12	11
C9	7	7	**G11**	12	11
C10	15	15	**G12**	17	16
C11	19	19	**H1**	7	7
C12	28	28	**H4**	58	58
D1	21	22	**H5**	69	69
D2	31	31	**H6**	47	46
D4	35	33	**H8**	33	33
D5	54	54	**H9**	9	9
D6	33	33	**H10**	34	34
D10	8	8	**H11**	23	22
D11	4	4	**H12**	37	36

Comparison with manual analysis

To validate the developed data analysis pipeline results from pyGecko were compared them to those obtained by performing a manual analysis on 30 randomly selected wells from the heteroarene thiolation array using McLafferty's OpenChrom software. Prior to integration using the Trapezoid integrator, SNIP baseline detection was performed, and a Baseline Substract Filter was applied using the software's default settings (the ocb files can be found on zenodo at 10.5281/zenodo.10407762).

Table S5. Comparison of quantification results obtained using pyGecko with results obtained by performing a manual analysis using McLafferty's OpenChrom software for 30 randomly selected wells from the heteroarene thiolation array. The mean deviation between the calculated yields is 1.2%.

Well	pyGecko	Manual
A1	75	73
A10	0	0
A11	13	12
A5	58	55
B1	7	6
B11	4	4
B7	0	0
C10	15	15
C12	28	27
C3	16	13
C4	31	30
C8	14	14
D4	35	33
E12	25	25
E7	0	0
E8	53	52
E9	0	2
F1	39	40
F10	72	70
F12	73	70
F4	52	50
F6	37	36
F7	10	10
F8	62	60
G12	17	17
G2	3	3
G4	35	35
H2	0	0
H7	0	5
H8	33	32

S3.4. 96-Reaction Array of 12 Thiols and 8 Heteroarenes

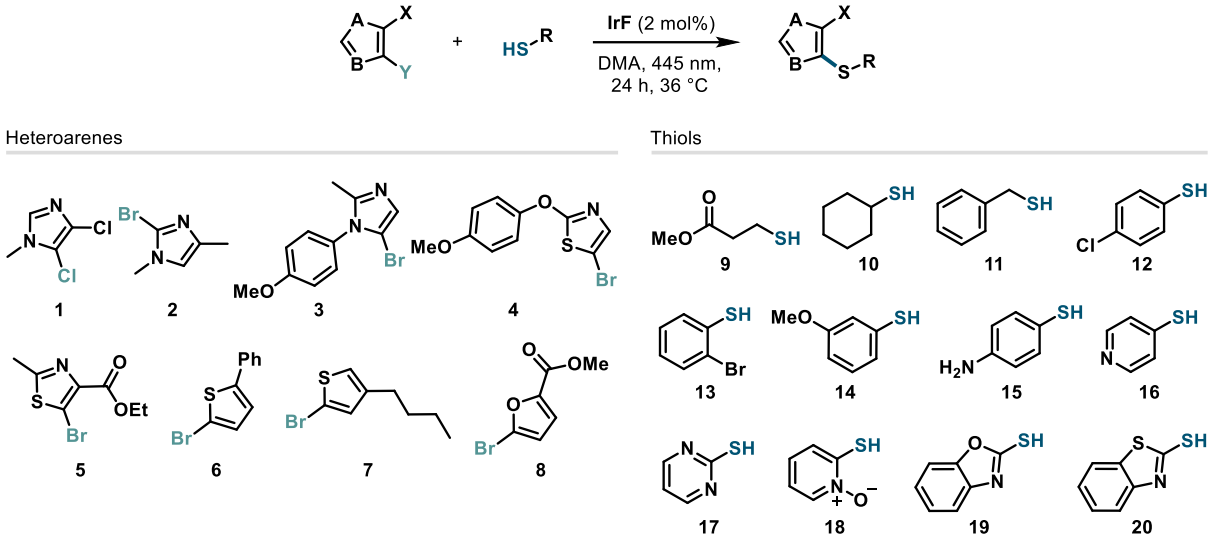


Figure S14. Evaluated scope for the site-selective thiolation of (multi)halogenated heteroarenes.

The heteroarenes **1-8** and thiols **9-20** were weighted into 20 mL scintillation vials and dissolved in 2.10 mL and 1.50 mL DMA, respectively (Table S6). Ir-F (39.3 mg, 0.0350 mmol) was weighted into an 8 mL scintillation vial and dissolved in 5.80 mL DMA. Dodecane (510.99 mg, 3.00 mmol) was weighted into a 10 mL volumetric flask and dissolved in DMA. Pyridine (266.97 mg, 3.375 mmol) was weighted into a 20 mL scintillation vial and dissolved in 3.00 mL DMA. Afterward, 2.00 mL of the 8 heteroarene stock solution was transferred to the wells of an 8-channel PP reservoir, 1.40 mL of the 12 thiol stock solution was transferred to the 12 wells of a 12-channel PP reservoir, and the Ir-F and dodecane stock solutions were transferred to the first and last reservoir of a 12-channel PP reservoir. 1.40 mL of the pyridine stock solution was transferred into the 10th and 11th wells of a 5-channel PP reservoir while the other wells were filled with 1.40 mL DMA. Afterward, the stock solutions were dispensed into a Photoredox 96-Well Block Assemblie by executing a custom Python protocol on the OT-2 liquid handler (protocol can be found on zenodo at 10.5281/zenodo.10407762). Thereby, 100 µL of the heteroarene stock solutions (0.015 mmol, 1.0 equiv), 100 µL of the thiol stock solutions (0.0225 mmol, 1.5 equiv), 20 µL of the pyridine stock solution (0.0225 mmol, 1.5 equiv) for rows F and G, 20 µL of DMA for rows A – E and H, 50 µL of the Ir-F stock solution (0.0003 mmol, 2 mol%) and 50 µL of the dodecane stock solution (0.015 mmol, 1.0 equiv) were dispensed into each well of the reaction array. The 96-well plate was then sealed and screwed tight and placed on the Lumidox® II 96-well LED arrays at 445 nm with a custom water cooling and cooling fan for 24 hours under irradiation at 36 °C while shaking at 500 rpm (details in section S1.1). After 24 hours, the plate was unscrewed, the workup was conducted according to section S1.3, and the GC analysis was conducted according to section S1.4. All samples were measured in split mode with an initial oven temperature of 110 °C followed by a 20 °C/min ramp until 320 °C. The final temperature was held for 2 min (GC method file can be found on zenodo at 10.5281/zenodo.10407762). Reaction yields are shown in Figure S16.

GC-PA-FID method:

All samples were measured in split mode (split ratio: 5:1, split flow 7.5 mL/min) with an injection volume of 1 µL at an inlet temperature of 280 °C and a septum purge flow of 3 mL/min. The column flow was set to 1.5 mL/min. The temperature program started at an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min. The FID was operated at 320 °C with an air flow of 400 mL/min, a hydrogen flow of 2 mL/min and a makeup flow (N_2) of 25 mL/min (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

GC-MS method:

All samples were measured in split mode (split ratio: 50:1, split flow 50 mL/min) with an injection volume of 2 µL at an inlet temperature of 300 °C and a septum purge flow of 3 mL/min. The column flow was set to 1 mL/min. The temperature program started at an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min. The MS detector was operated with a solvent delay of 1.75 min. (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

Table S6. Weighings and solvent volumes for stock solutions.

IUPAC Name	CAS Number	MW [g/mol]	*m* [mg]	*V* [mL]
4,5-Dichloro-1-methyl-1H-imidazole (**1**)	1192-53-6	150.99	47.6	2.10
2-Bromo-1,4-dimethyl-1H-imidazole (**2**)	235426-30-9	175.03	55.1	2.10
5-Bromo-1-(4-methoxyphenyl)-2-methyl-1H-imidazole (**3**)	2294948-68-6	267.13	84.2	2.10
5-Bromo-2-(4-methoxyphenoxy)thiazole (**4**)	1211531-96-2	286.14	90.1	2.10
Ethyl 5-bromo-2-methylthiazole-4-carboxylate (**5**)	1047675-70-6	250.11	78.8	2.10
2-Bromo-5-phenylthiophene (**6**)	29488-24-2	239.13	75.3	2.10
2-Bromo-4-butylthiophene (**7**)	350680-78-3	219.14	69.0	2.10
Methyl 5-bromofuran-2-carboxylate (**8**)	2527-99-3	205.01	64.6	2.10
Methyl 3-mercaptopropanoate (**9**)	2935-90-2	120.17	40.6	1.50
Cyclohexanethiol (**10**)	1569-69-3	116.22	39.2	1.50
Phenylmethanethiol (**11**)	100-53-8	124.20	41.9	1.50
4-Chlorobenzenethiol (**12**)	106-54-7	144.62	48.8	1.50
2-Bromobenzenethiol (**13**)	6320-02-1	189.07	63.8	1.50
3-Methoxybenzenethiol (**14**)	15570-12-4	140.20	47.3	1.50
4-Aminobenzenethiol (**15**)	1193-02-8	125.19	42.3	1.50
Pyridine-4-thiol (**16**)	4556-23-4	111.16	37.5	1.50
Pyrimidine-2-thiol (**17**)	1450-85-7	112.15	37.9	1.50
2-Mercaptopyridine 1-oxide (**18**)	1121-31-9	127.16	42.9	1.50
Benzo[*d*]oxazole-2-thiol (**19**)	2382-96-9	151.18	51.0	1.50
Benzo[*d*]thiazole-2-thiol (**20**)	149-30-4	167.24	56.4	1.50

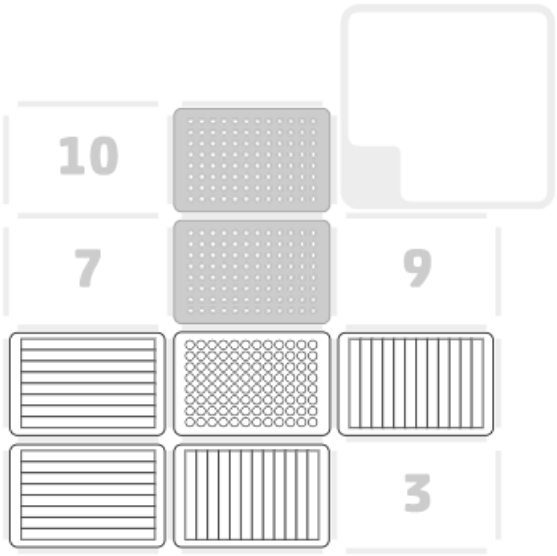


Figure S15. Deck view of OT-2 thiolation protocol. Labware: 300 µL tipracks (Pos. 11, 8), Paradox 96-Well Block Assembly (Pos. 5), 8-channel reservoirs (Pos. 1, 4), 12-channel reservoirs (Pos. 2, 6).

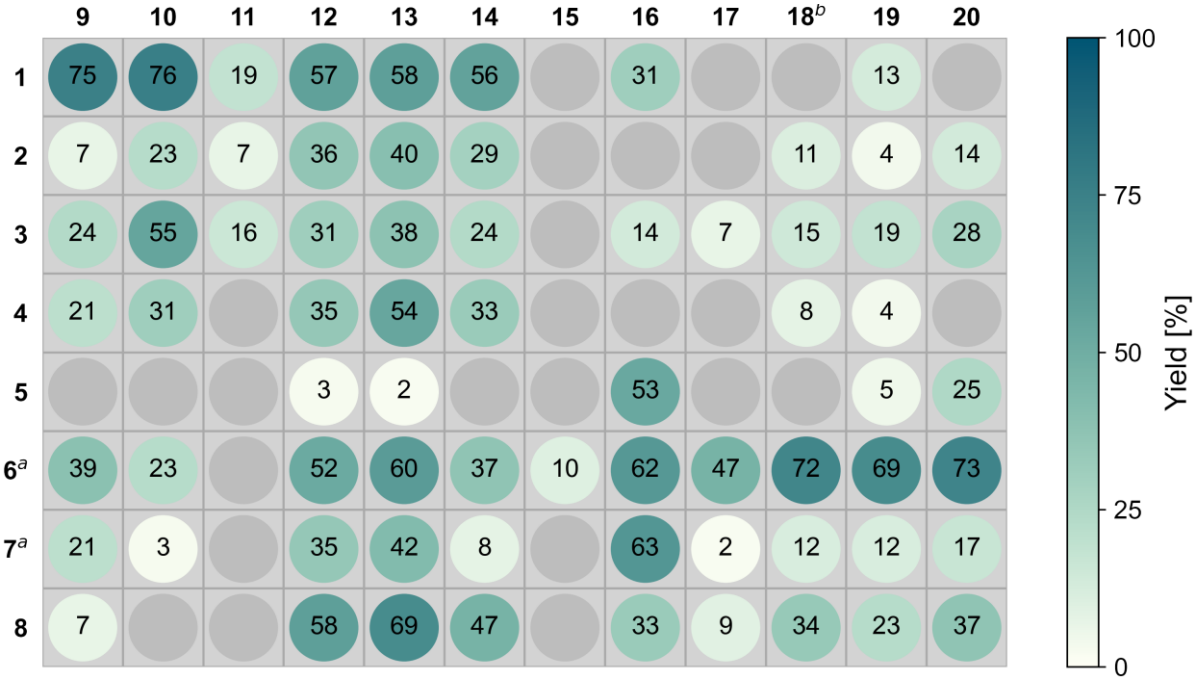
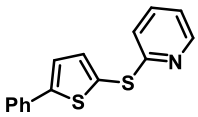


Figure S16. Heatmap illustrating the reaction yields of the heteroarene thiolation. [a]Pyridine (1.5 equiv) added. [b]Yields are given for the corresponding pyridine reduction product.

S3.5. Isolation of Reduction Product

To validate the structure of the pyridine reduction product **6b,** the compound was synthesized in batch and isolated. The characterization of the compound was performed by ^{1}H NMR, ^{13}C NMR, HR-MS and X-ray diffraction (Figure S23).

Synthesis of 2-((5-Phenylthiophen-2-yl)thio)pyridine (6b)



[Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ (13.4 mg, 0.006 mmol, 2 mol%), 2-bromo-5-phenylthiophene (71.7 mg, 0.30 mmol, 1.0 equiv) and 2-mercaptopyridine 1-oxide (57.2 mg, 0.45 mmol, 1.5 equiv) were added to a Schlenk tube. The Schlenk tube was evacuated and backfilled with argon three times. Afterward, dry DMA was added. The reaction mixture was stirred at room temperature under irradiation from blue LEDs (30 W, λ_{max} = 450 nm) for 16 h. The reaction mixture was quenched with EtOAc and washed with a saturated solution of sodium hydrogen carbonate and water (two times). The organic phase was dried over $MgSO_4$. After the evaporation of volatile components, the crude product was purified by flash column chromatography (8% EtOAc in pentane). The product 2-((5-phenylthiophen-2-yl)thio)pyridine (**6b**) (46.5 mg, 0.173 mmol, 56%) was obtained as a crystalline yellow solid.

R$_f$ (10% EtOAc in pentane) = 0.43.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (ddd, $J_{H\text{-}H}$ = 4.9, 1.9, 0.9 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.50 (ddd, $J_{H\text{-}H}$ = 8.1, 7.5, 1.9 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.36 – 7.30 (m, 3H), 7.05 – 6.98 ppm (m, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 162.19, 151.19, 149.55, 138.47, 137.14, 133.88, 129.19, 128.42, 127.55, 126.06, 124.10, 120.26, 120.22 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 292.02251, measured: 292.02242.

X-ray (single crystal): A colorless, plate-like specimen of **6b** (X-ray diffraction quality) was obtained by liquid/liquid diffusion with chloroform and pentane (CCDC Nr.: 2327437).

S4. C–N Cross-couplings

For the evaluation of palladium-catalyzed and nickel Adaptive Dynamic Homogeneous Catalysis (AD-Hoc)[23], C–N Cross-couplings, a set of substrates known to be especially challenging in common Buchwald-Hartwig couplings was subjected to a total of four reaction conditions.

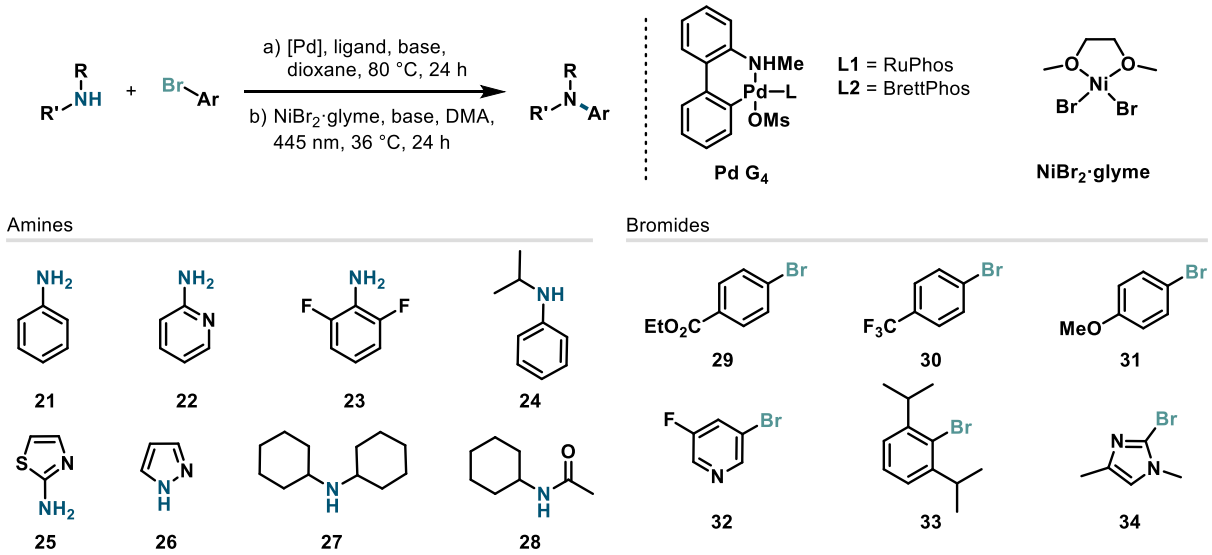


Figure S17. Evaluated scope for C–N cross-couplings under Buchwald-Hartwig and adaptive dynamic homogeneous catalysis (AD-HoC) conditions.

S4.1. Palladium-catalyzed C–N Cross-couplings

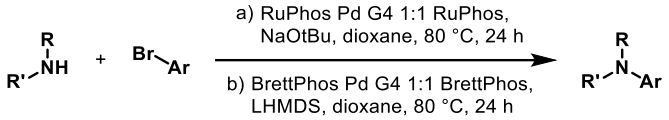


Figure S18. General reaction scheme for palladium-catalyzed C–N cross-couplings.

The *N*-nucleophiles **21**-**28**, bromides **29**-**34**, precatalysts RuPhos Pd G4 and BrettPhos Pd G4 and ligands RuPhos and BrettPhos were weighted into 4 mL scintillation vials under air. RuPhos was weighted into a a 4 mL scintillation vial in a glovebox under an argon atmosphere with oxygen levels at around 2 ppm. All scintillation vials were flooded with argon before dry and degassed solvent 1,4-dioxane was added to each vial as specified in Table S7, and the solutions were degassed by bubbling argon through a needle pinched through the vials rubber septum for 15 minutes. The design of the 96-reaction array was divided into two parts: The left side, from well A1 up to and including well H6, was set up for condition C (RuPhos Pd G4 (7.5 mol%), RuPhos ligand (7.5 mol%) and base sodium *tert*-butoxide (NaOtBu, 2.4 equiv)). The right side, from well A7 up to and including well H12, was set up for condition D (BrettPhos Pd G4 (7.5 mol%), BrettPhos ligand (7.5 mol%) and base lithium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide (LiHMDS, 2.4 equiv)). The solid bases NaOtBu and LiHMDS were added to the 96-reaction wells using polypropylene transfer scoops in a glovebox under an argon atmosphere with oxygen levels at around 2 ppm. All stock solutions, the 96-Well Block Assemblies equipped with 96 stirring bars and the solid bases, custom-made polytetrafluorethylene (PTFE) reservoirs, 8- and 12-channel piston pipettes and a screwdriver were then transferred into a glove box under a positive pressure of argon with oxygen levels at around 100 ppm. According to the design of the 96-reaction array, the corresponding precatalyst and ligand stock solutions were used for each half of the array, and the plate was set up as follows. 60 µL of the corresponding bromide (0.02 mmol, 1 equiv) were dispensed into two columns (one column each for conditions C and D) of the reaction array. Next, 60 µL of the corresponding *N*-nucleophile (0.024 mmol, 1.2 equiv) were dispensed into each row of the reaction array. 80 µL of the combined RuPhos Pd G4 and RuPhos ligand stock solutions (1.5 µmol, 7.5 mol%) were dispensed into the left half of the array, while 80 µL of the combined BrettPhos Pd G4 and BrettPhos ligand stock solutions (1.5 µmol, 7.5 mol%) were dispensed into the right half of the array. This resulted in a total volume of 200 µL per well. The 96-well plate was then sealed and screwed tight, removed from the screening box, placed on a magnetic stirrer at 800 rpm, and heated to 80 °C for 24 hours. The stock solution of the standard dodecane was prepared in a 20 mL volumetric flask. After 24 hours, the plate was unscrewed and opened to add 100 µL of the dodecane stock solution (0.02 mmol, 1 equiv) to each well. Then, the workup was conducted according to section S1.3, and the GC analysis was conducted according to section S1.4. All samples were measured in split mode with an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min (GC method file can be found on zenodo at 10.5281/zenodo.10407762). Reaction yields are shown in Figure S19.

GC-PA-FID method:

All samples were measured in split mode (split ratio: 5:1, split flow 7.5 mL/min) with an injection volume of 1 µL at an inlet temperature of 280 °C and a septum purge flow of 3 mL/min. The column flow was set to 1.5 mL/min. The temperature program started at an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min. The FID was operated at 320 °C with an air flow of 400 mL/min, a hydrogen flow of 2 mL/min and a makeup flow (N_2) of 25 mL/min (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

GC-MS method:

All samples were measured in split mode (split ratio: 50:1, split flow 50 mL/min) with an injection volume of 2 µL at an inlet temperature of 300 °C and a septum purge flow of 3 mL/min. The column flow was set to 1 mL/min. The temperature program started at an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min. The MS detector was operated with a solvent delay of 1.75 min. (GC method file can be found on zenodo at 10.5281/zenodo.10407762).

Table S7. Weighings and solvent volumes for stock solutions.

IUPAC Name	CAS Number	MW [g/mol]	*m* [mg]	*V* [µL]
Anilinen (**21**)	62-53-3	93.13	40.2	1080
Pyridin-2-amin (**22**)	504-29-0	94.12	40.7	1080
2,6-Difluoroaniline (**23**)	5509-65-9	129.11	55.8	1080
N-(Isopropyl)aniline (**24**)	768-52-5	135.21	58.4	1080
1,3-Thiazol-2-amine (**25**)	96-50-4	100.14	43.3	1080
1*H*-Pyrazole (**26**)	288-13-1	68.08	29.4	1080
N-Cyclohexylcyclohexanamine (**27**)	101-83-7	181.32	78.3	1080
N-Isopropylacetamide (**28**)	1118-69-0	101.15	43.7	1080
Ethyl 4-bromobenzoate (**29**)	5798-75-4	229.07	110.0	1440
1-Bromo-4-(trifluoromethyl)benzene (**30**)	402-43-7	225.01	108.0	1440
1-Bromo-4-methoxybenzene (**31**)	104-92-7	187.04	89.8	1440
3-Bromo-5-fluoropyridine (**32**)	407-20-5	175.99	84.5	1440
2-Bromo-1,3-bis(isopropyl)benzene (**33**)	57190-17-7	241.17	115.8	1440
2-Bromo-1,4-dimethyl-1*H*-imidazol (**34**)	235426-30-9	175.03	84.0	1440
RuPhos Pd G4	1599466-85-9	850.39	79.1	2480
RuPhos	787618-22-8	466.64	43.4	2480
Sodium *tert*-butoxide	865-48-5	96.10	286.0	-
BrettPhos Pd G4	1599466-83-7	920.53	85.6	2480
BrettPhos	1070663-78-3	536.77	49.9	2480
Lithium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide	4039-32-1	167.33	498.0	-
Dodecane	112-40-3	170.34	681.4	20000

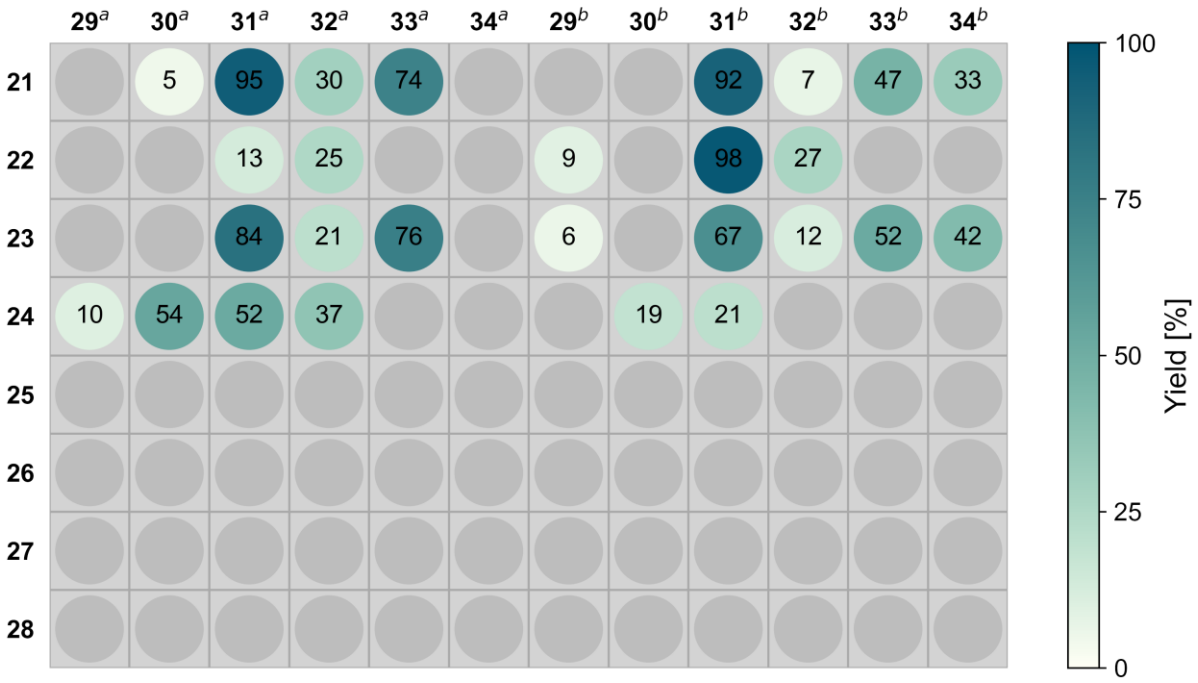


Figure S19. Heatmap illustrating the reaction yields of C-N cross-couplings under palladium-catalyzed conditions.

S4.2. Adaptive Dynamic Homogeneous Catalysis (AD-Hoc) C–N Cross-couplings

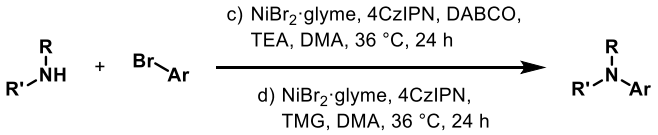


Figure S20. General reaction scheme for nickel-catalyzed C-N cross-couplings.

The *N*-nucleophiles **21**-**28**, bromides **29**-**34** and bases *N*,*N*,*N*′,*N*′-Tetramethylguanidine (TMG), 1,4-diazabicyclo[2.2.2]octane (DABCO) and Triethylamine (TEA) were weighted into 4 mL scintillation vials under air (Table S8). (1,2-Dimethoxyethane)nickel dibromide ($NiBr_2$·glyme) and photocatalyst 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) were weighted into 8 mL scintillation vials under air (Table S8). All vials were flooded with argon before dry and degassed solvent DMA was added to each vial as specified in Table S8, and the solutions were degassed by bubbling argon through a needle pinched through the vial's rubber septum for 15 minutes. All stock solutions, a 96-Well Block Assemblies equipped with 96 stirring bars, custom-made polytetrafluorethylene (PTFE) reservoirs, 8- and 12-channel piston pipettes and a screwdriver were then transferred into a glove box under a positive pressure of argon with oxygen levels at around 100 ppm. The design of the 96-reaction array was divided into two parts: The left side, from well A1 up to and including well H6, was set up for conditions A (DABCO (1.8 equiv) and TEA (0.25 equiv)). The right side, from well A7 up to and including well H12, was set up for conditions B (TMG (1.2 equiv)). Accordingly, the corresponding base stock solutions were used for each half of the array, and the plate was set up as follows. 50 µL of the corresponding bromide (0.040 mmol, 1.0 equiv) were dispensed into two columns (one column each for conditions c and d) of the reaction array. Next, 50 µL of the corresponding *N*-nucleophile (0.080 mmol, 2 equiv) were dispensed into each row of the reaction array. 30 µL DABCO stock solution (0.072 mmol, 1.8 equiv) and 30 µL TEA (0.010 mmol, 0.25 equiv) stock solution were dispensed into the left half of the array, while 60 µL TMG (0.048 mmol, 1.2 equiv) were dispensed into the right half of the array. Lastly, 20 µL of $NiBr_2$·glyme stock solution (2 µmol, 5 mol%) and 20 µL of 4CzIPN (0.2 µmol, 0.5 mol%) stock solution were dispensed into all 96 wells. This resulted in a total volume of 200 µL per well. The 96-well plate was then sealed and screwed tight, removed from the screening box, and placed on the Lumidox® II 96-well LED arrays at 445 nm with custom water cooling and cooling fan for 24 hours under irradiation at 36 °C while shaking at 500 rpm (details in section S1.1). The stock solution of the standard dodecane was prepared in a 25 mL volumetric flask. After 24 hours, the plate was unscrewed and opened to add 100 µL of the dodecane stock solution (0.040 mmol, 1.0 equiv) to each well. Then, the workup was conducted according to section S1.3, and the GC analysis was conducted according to section S1.4. All samples were measured in split mode with an initial oven temperature of 80 °C followed by a 20 °C/min ramp until 310 °C. The final temperature was held for 1 min (GC method file can be found on zenodo at 10.5281/zenodo.10407762). Reaction yields are shown in Figure S21.

Table S8. Weighings and solvent volumes for stock solutions.

IUPAC Name	CAS Number	MW [g/mol]	*m* [mg]	*V* [µL]
Aniline (**21**)	62-53-3	93.13	119.2	800
Pyridin-2-amin (**22**)	504-29-0	94.12	120.5	800
2,6-Difluoroaniline (**23**)	5509-65-9	129.11	165.3	800
N-(Isopropyl)aniline (**24**)	768-52-5	135.21	173.1	800
1,3-Thiazol-2-amine (**25**)	96-50-4	100.14	128.2	800
1*H*-Pyrazole (**26**)	288-13-1	68.08	87.1	800
N-Cyclohexylcyclohexanamine (**27**)	101-83-7	181.32	232.1	800
N-Isopropylacetamide (**28**)	1118-69-0	101.15	129.5	800
Ethyl 4-bromobenzoate (**29**)	5798-75-4	229.07	210.7	1150
1-Bromo-4-(trifluoromethyl)benzene (**30**)	402-43-7	225.01	207.0	1150
1-Bromo-4-methoxybenzene (**31**)	104-92-7	187.04	172.1	1150
3-Bromo-5-fluoropyridine (**32**)	407-20-5	175.99	161.9	1150
2-Bromo-1,3-bis(isopropyl)benzene (**33**)	57190-17-7	241.17	221.9	1150
2-Bromo-1,4-dimethyl-1*H*-imidazol (**34**)	235426-30-9	175.03	161.0	1150
(1,2-Dimethoxyethane)nickel dibromide	28923-39-9	308.62	77.2	2500
2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile	1416881-52-1	788.91	19.7	2500
1,4-Diazabicyclo[2.2.2]octane	280-57-9	112.18	500.8	1860
N,*N*-Diethylethanamine	121-44-8	101.19	62.7	1860
N,*N*,*N*′,*N*′-Tetramethylguanidine	80-70-6	115.18	342.8	3720
Dodecane	112-40-3	170.34	1703.4	25000

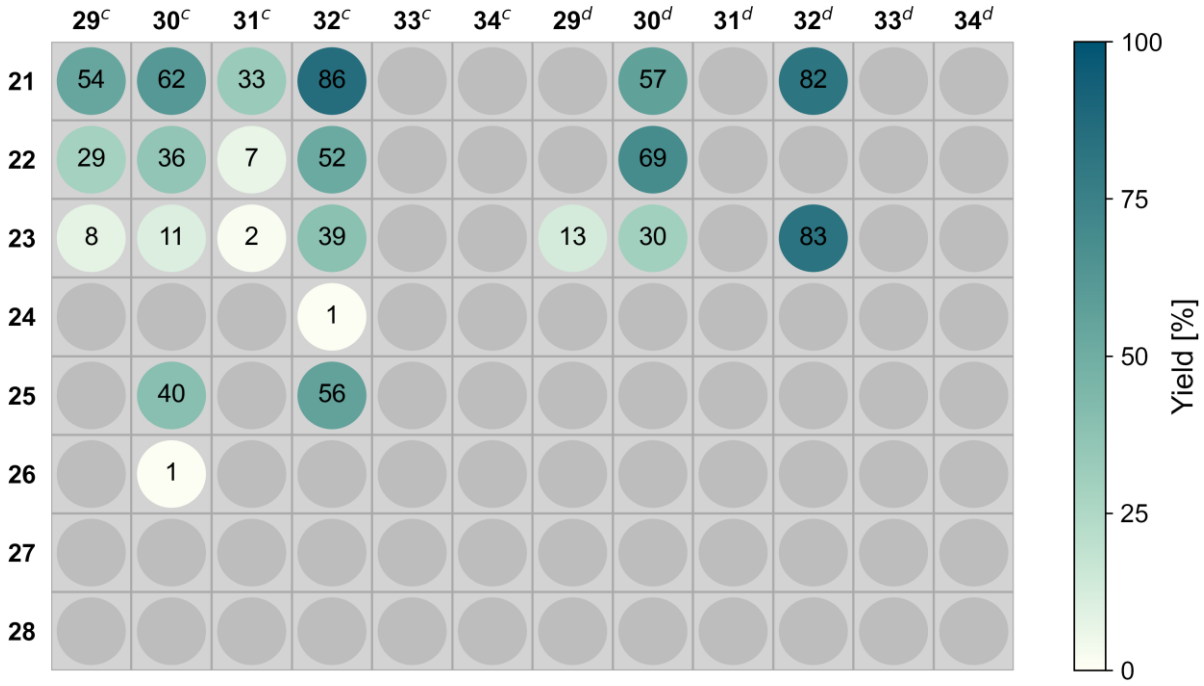
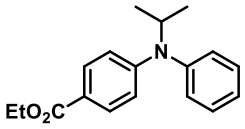


Figure S21. Heatmap illustrating the reaction yields of C-N cross-couplings under nickel AD-Hoc conditions.

S4.3. Spectral Matching

Synthesis of Ethyl 4-(isopropyl(phenyl)amino)benzoate (24a)



$Pd_2(dba)_3$ (5.5 mg, 0.0060 mmol, 2.0 mol%), RuPhos (7.0 mg, 0.015 mmol, 5.0 mol%) and potassium phosphate (95.5 mg, 0.450 mmol, 1.5 equiv) were added to an oven-dried Schlenk tube inside an argon-filled glovebox. Afterward, toluene (2.0 mL), ethyl 4-bromobenzoate (68.7 mg, 0.300 mmol, 1.0 equiv) and *N*-isopropylaniline were added outside the glovebox and the suspension was stirred for 18 h at 100 °C. The crude mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc two times before the combined organic phases were dried over magnesium sulfate. Volatile components were removed under reduced pressure. The crude was purified by flash column chromatography with 3% EtOAc in pentane, yielding the product ethyl 4-(isopropyl(phenyl)amino)benzoate (**24a**) (69.1 mg, 0.243 mmol, 81%) as a light yellow oil.

R_f (3% EtOAc in pentane) = 0.30.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 – 7.79 (m, 2H), 7.48 – 7.41 (m, 2H), 7.39 – 7.32 (m, 1H), 7.13 – 7.09 (m, 2H), 6.54 – 6.48 (m, 2H), 4.39 (p, $J_{H\text{-}H}$ = 6.6 Hz, 1H), 4.30 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H), 1.34 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H), 1.17 ppm (d, $J_{H\text{-}H}$ = 6.6 Hz, 6H).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 167.00, 152.70, 141.87, 131.21, 131.15, 129.83, 127.28, 118.29, 112.99, 60.24, 48.39, 21.12, 14.60 ppm.

HR-MS (ESI): *m/z* calculated for $[M+Na]^+$: 306.14645, measured: 306.14591.

An example illustrating the spectral matching and peak identification capabilities of pyGecko can be found at https://github.com/FelixKatz77/pyGecko/tree/main/examples. In this script, a GC-MS measurement of a pure sample of product **24a** is used to identify it in well **24**/**29**^{a} of the palladium-catalyzed C–N Cross-coupling array. By comparing the spectrum of the pure sample with all peak spectra in the reaction chromatogram, the product peak is identified with a cosine similarity of 0.999.

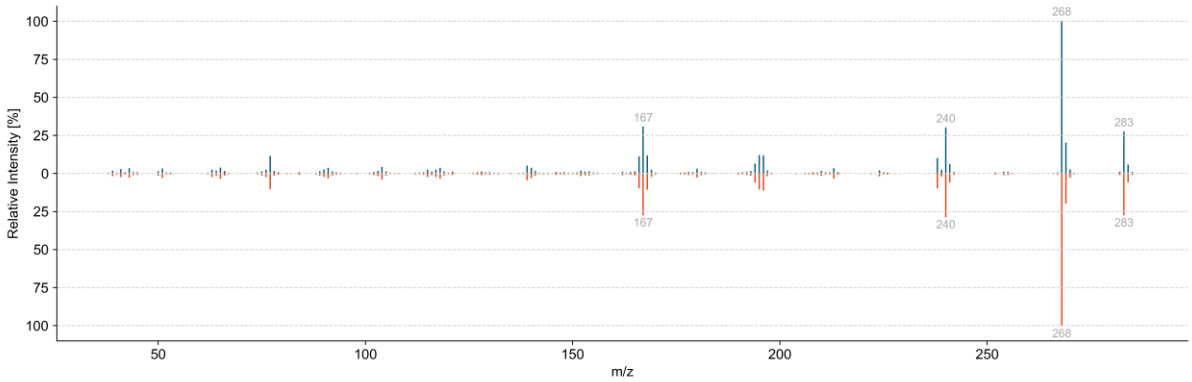


Figure S22. Comparison of MS spectra of a pure sample of product **24a** and the corresponding peak identified in the MS chromatogram of well **24**/**29a** of the palladium-catalyzed C–N Cross-coupling array by spectral matching.

S5. Crystal Structure

X-ray diffraction:

The data set for compound **6b** was collected with a Bruker D8 Venture Photon III Diffractometer. Programs used: data collection: *APEX4* Version 2021.4-0;[24] cell refinement: *SAINT* Version 8.40B;[24] data reduction: *SAINT* Version 8.40B;[24] absorption correction, *SADABS* Version 2016/2;[24] structure solution *SHELXT*-Version 2018-3;[25] structure refinement *SHELXL*-Version 2018-3[26] and graphics, *XP*.[27] *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

X-ray crystal structure analysis of 6b (glo10522):

A colorless, plate-like specimen of $C_{15}H_{11}NS_2$, approximate dimensions 0.048 mm x 0.146 mm x 0.250 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a single crystal diffractometer Bruker D8 Venture Photon III system equipped with a micro focus tube Cu ImS (CuKα, λ = 1.54178 Å) and a MX mirror monochromator.

A total of 1072 frames were collected. The total exposure time was 7.95 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 6319 reflections to a maximum θ angle of 66.50° (0.84 Å resolution), of which 2139 were independent (average redundancy 2.954, completeness = 98.9%, R_{int} = 4.68%, R_{sig} = 5.16%) and 1997 (93.36%) were greater than $2\sigma(F^2)$. The final cell constants of a = 5.7105(4) Å, b = 7.5196(5) Å, c = 14.8153(10) Å, β = 94.132(4)°, volume = 634.53(7) $Å^3$, are based upon the refinement of the XYZ-centroids of 5058 reflections above 20 σ(I) with 5.981° < 2θ < 133.0°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.760. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4650 and 0.8460.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21 1, with Z = 2 for the formula unit, $C_{15}H_{11}NS_2$. The final anisotropic full-matrix least-squares refinement on F^2 with 163 variables converged at R1 = 3.43%, for the observed data and wR2 = 9.00% for all data. The goodness-of-fit was 1.063. The largest peak in the final difference electron density synthesis was 0.200 $e^-/Å^3$ and the largest hole was -0.313 $e^-/Å^3$ with an RMS deviation of 0.054 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.410 g/cm^3 and F(000), 280 e^-. CCDC Nr.: 2327437.

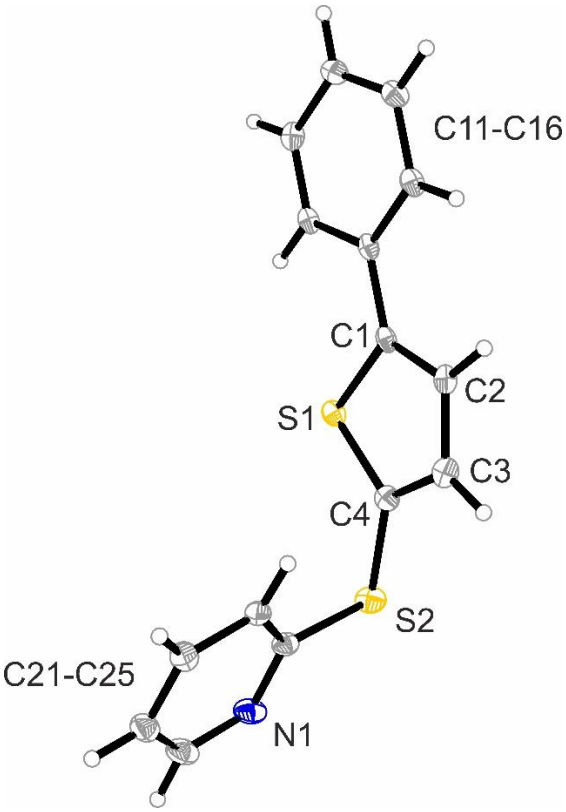


Figure S23. Crystal structure of compound **6b**. Thermal ellipsoids are shown at 30% probability.

S6. References

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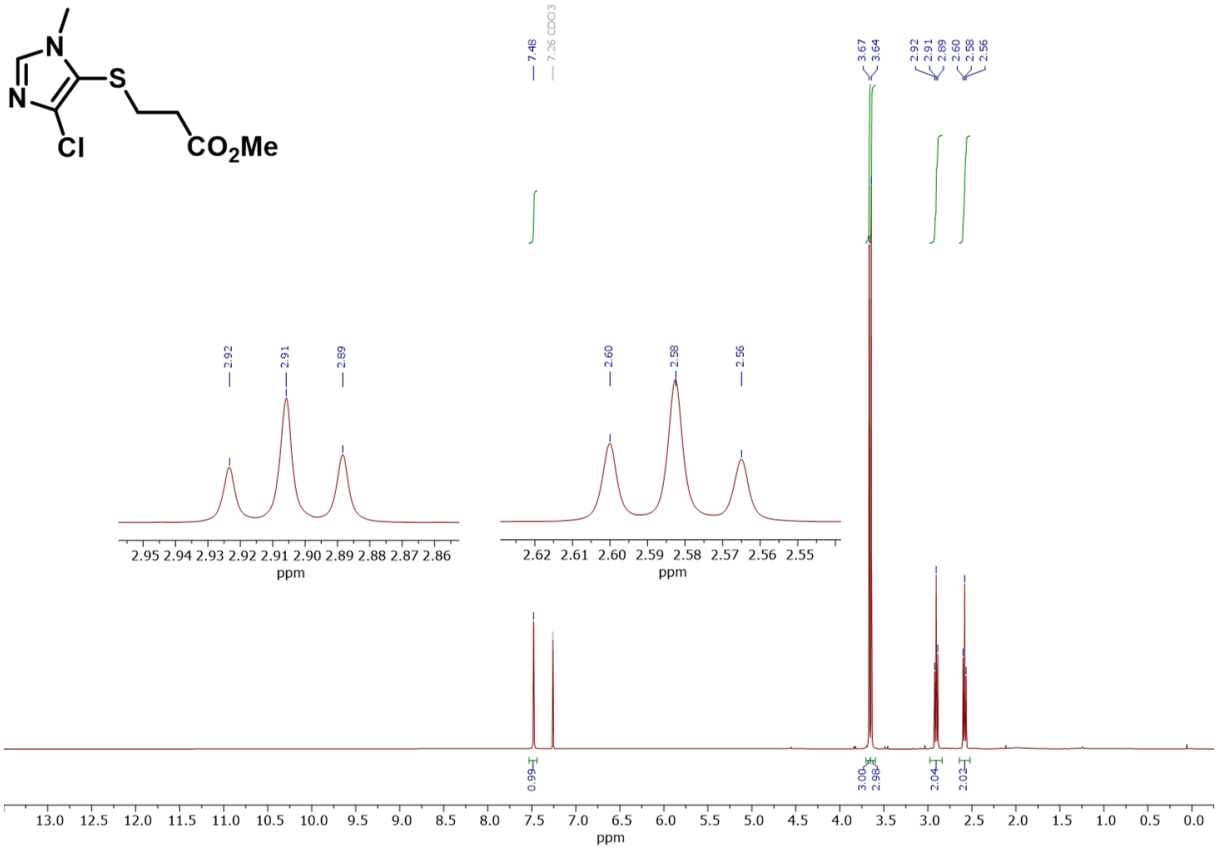
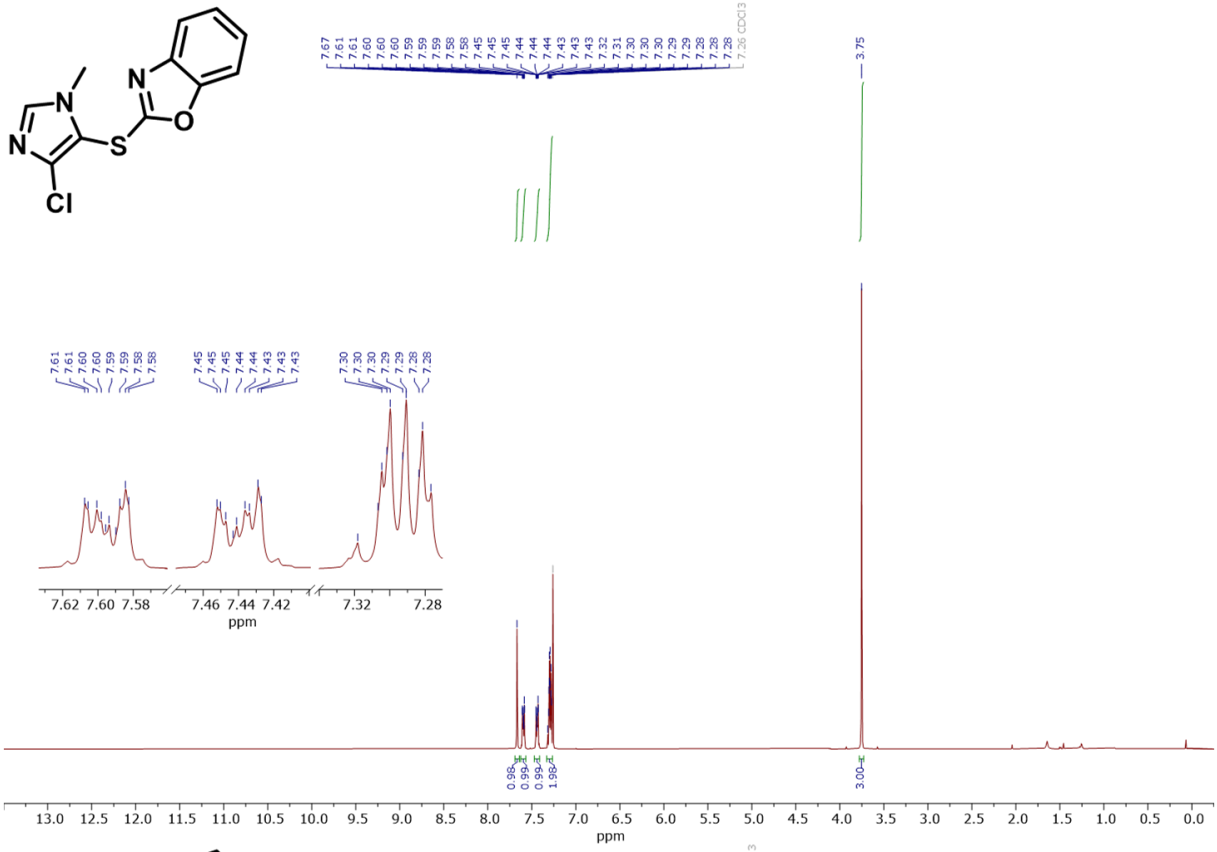
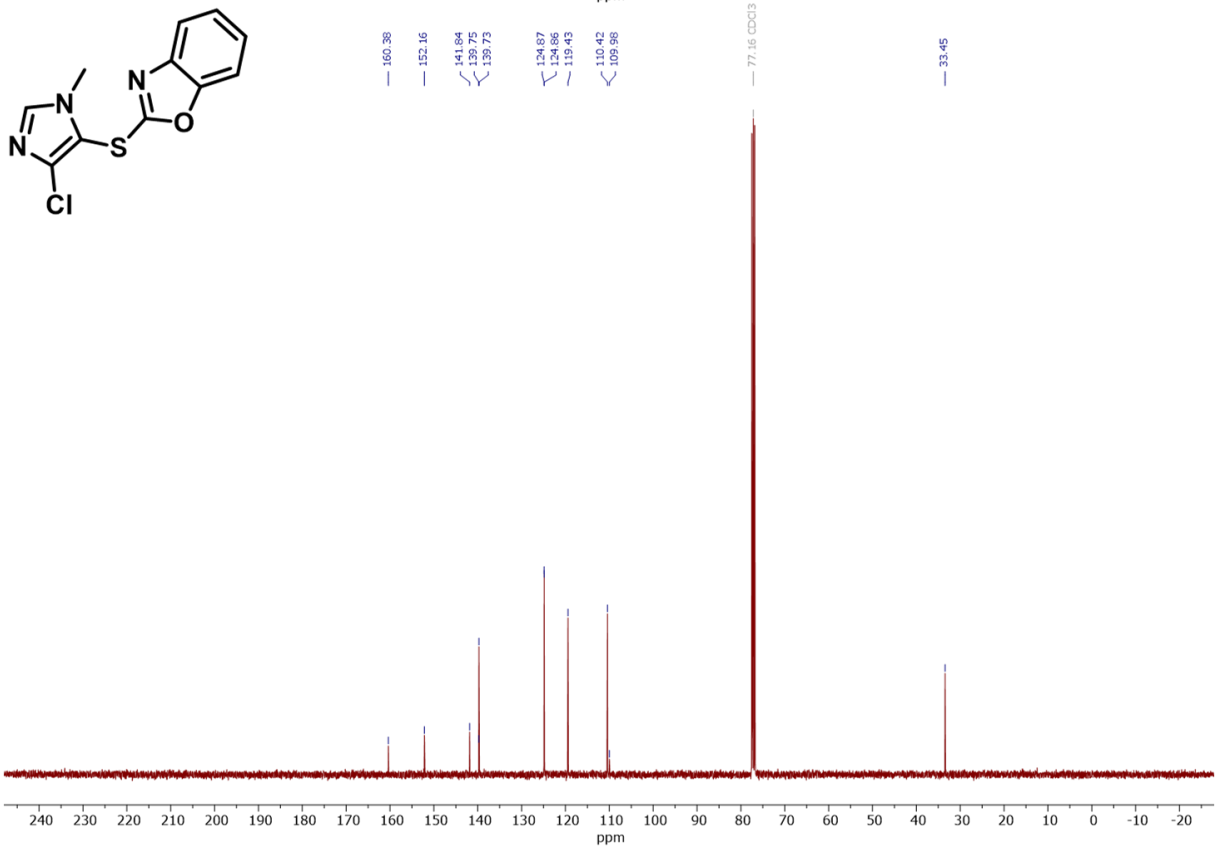
S7. NMR Spectra

Methyl 3-((4-chloro-1-methyl-1H-imidazol-5-yl)thio)propanoate (1a)

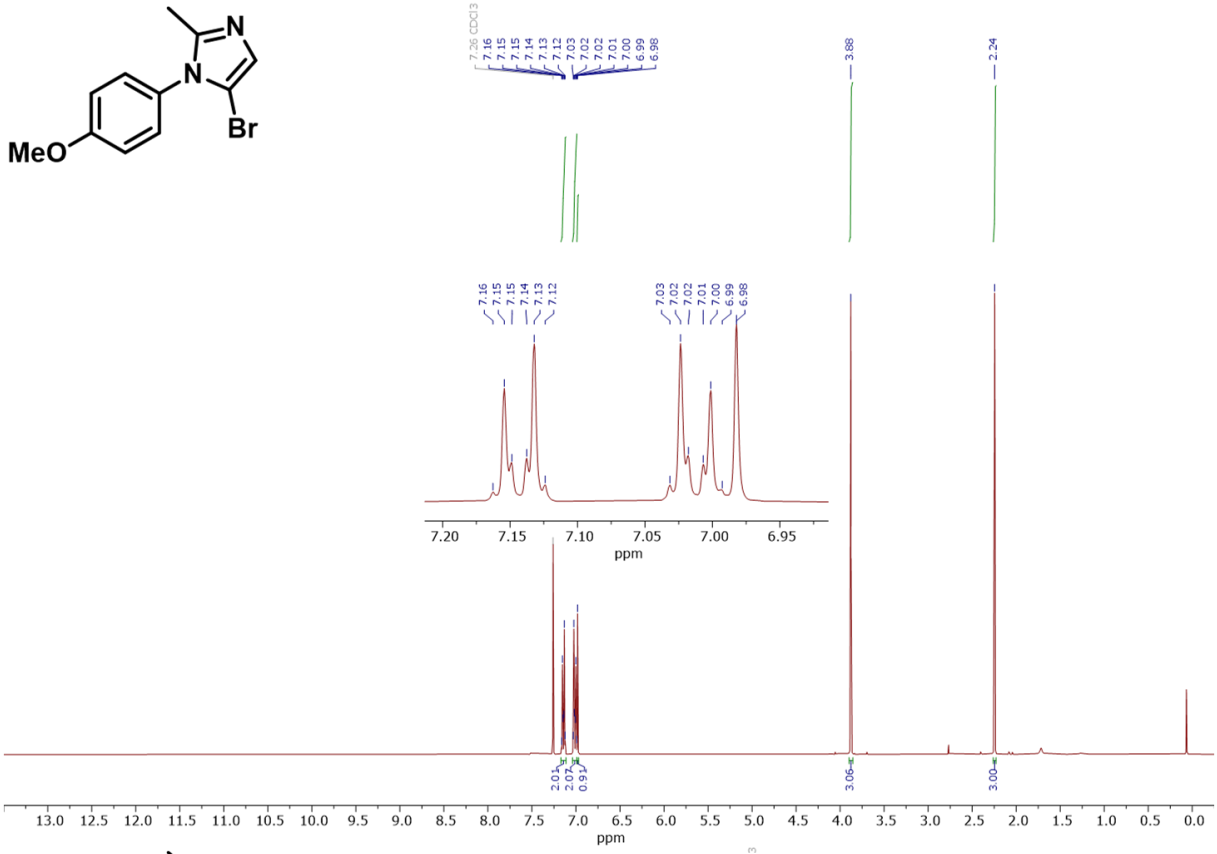


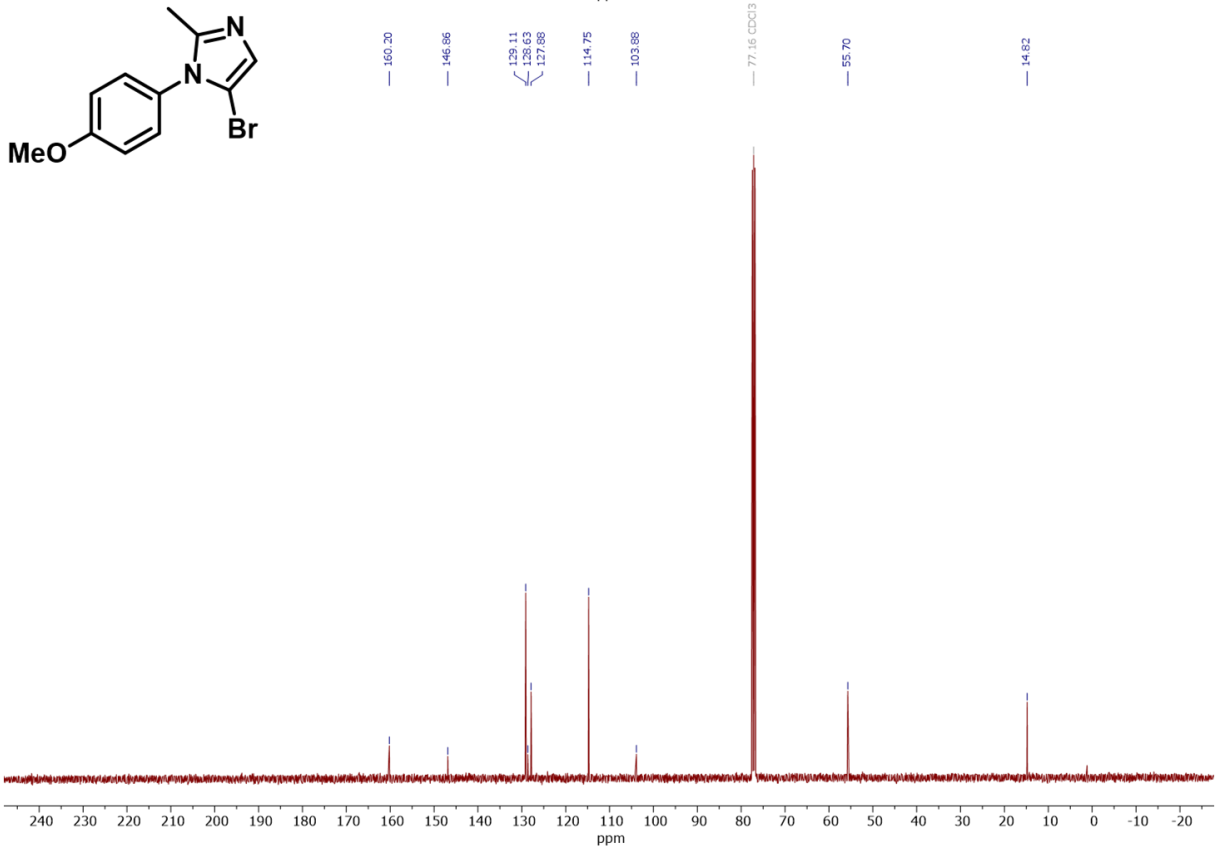
2-((4-Chloro-1-methyl-1H-imidazol-5-yl)thio)benzo[*d*]oxazole (1b)



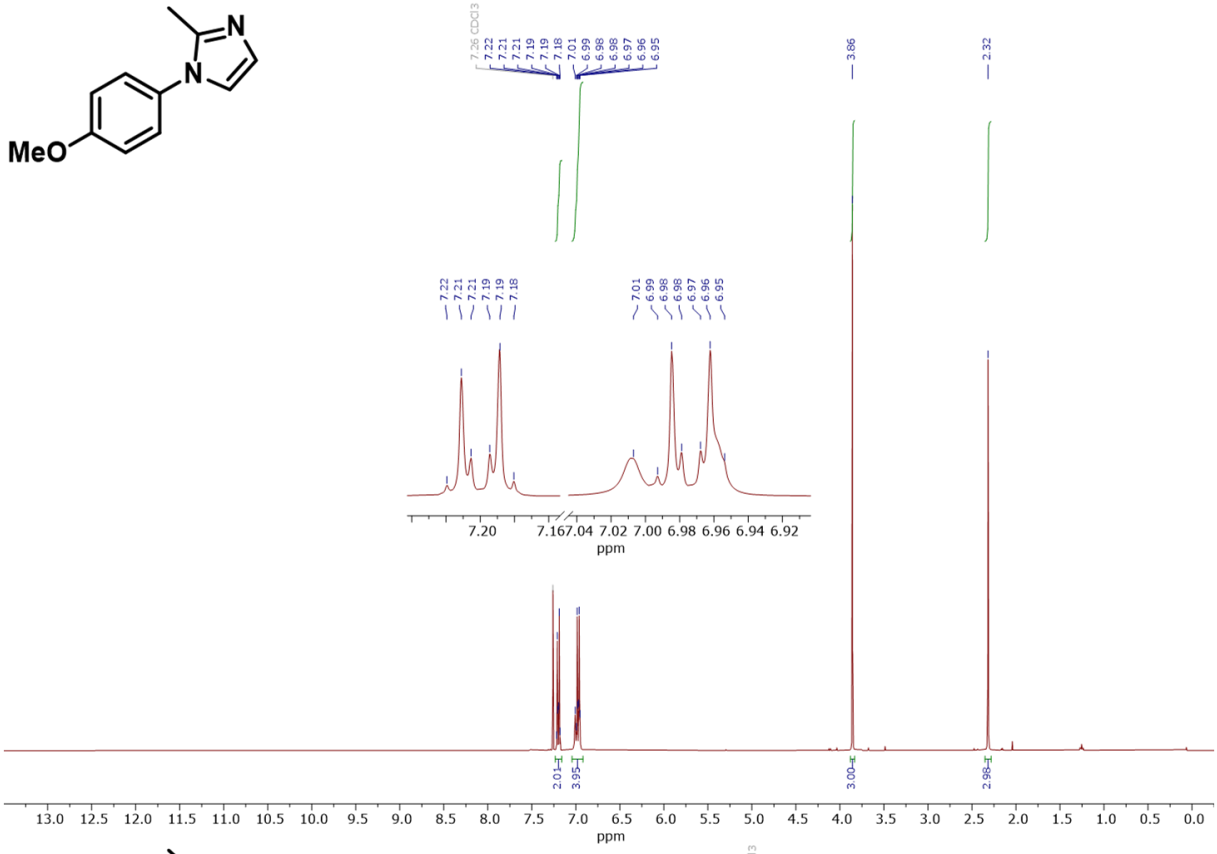


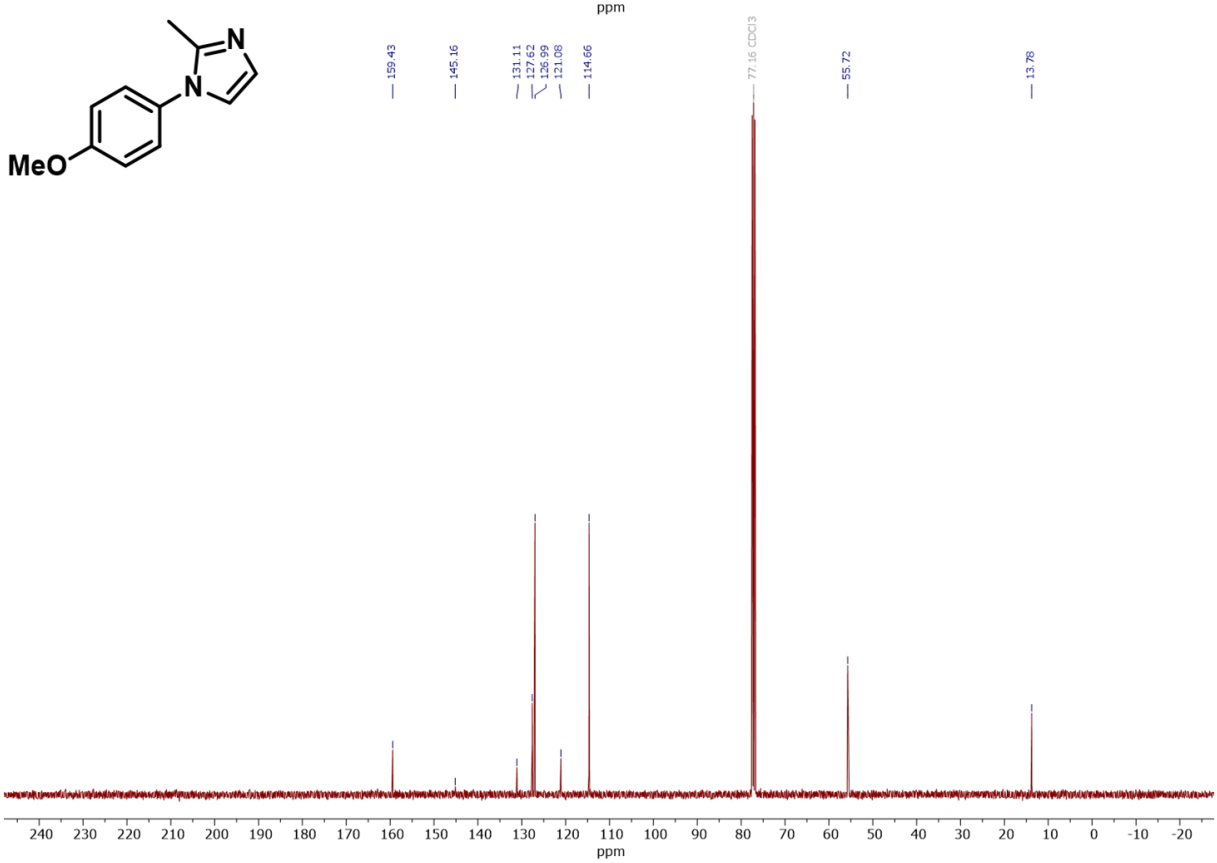
5-Bromo-1-(4-methoxyphenyl)-2-methyl-1H-imidazole (3)



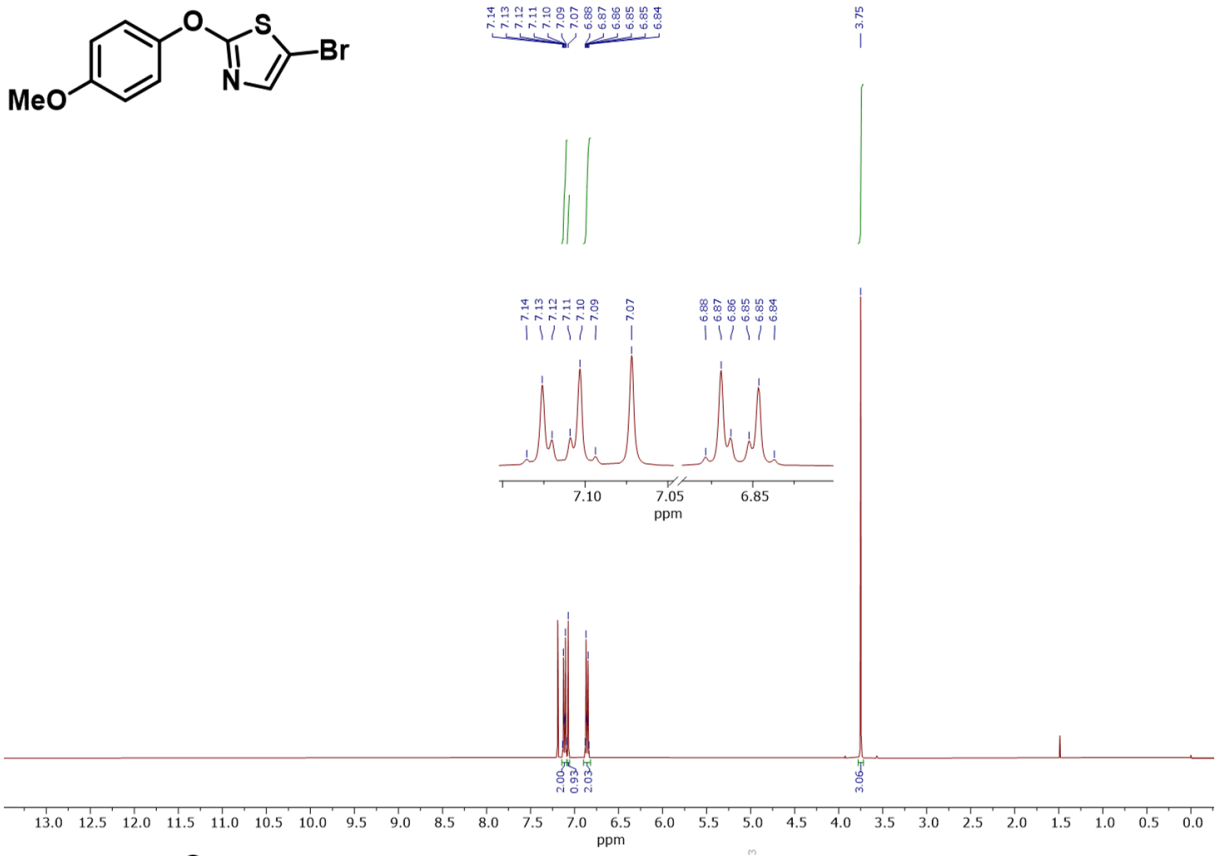


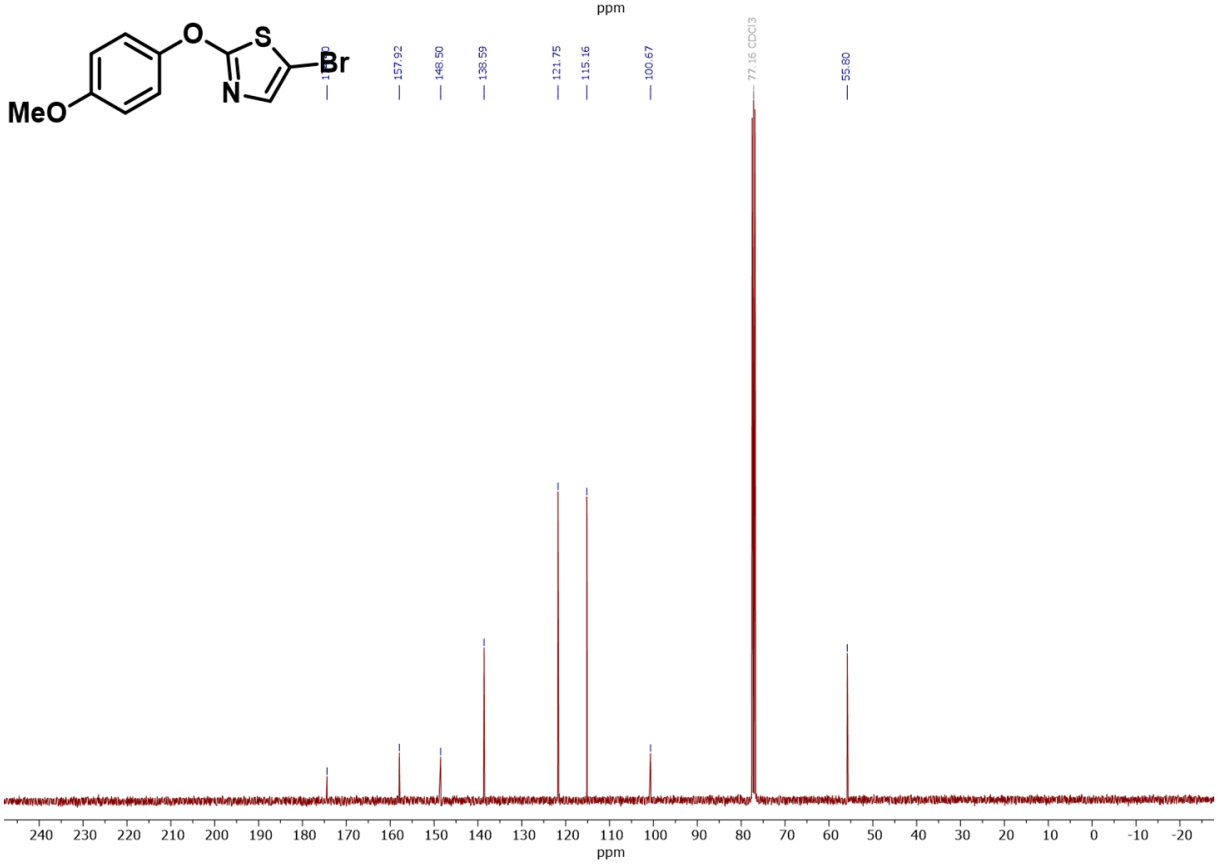
1-(4-Methoxyphenyl)-2-methyl-1*H*-imidazole (3')



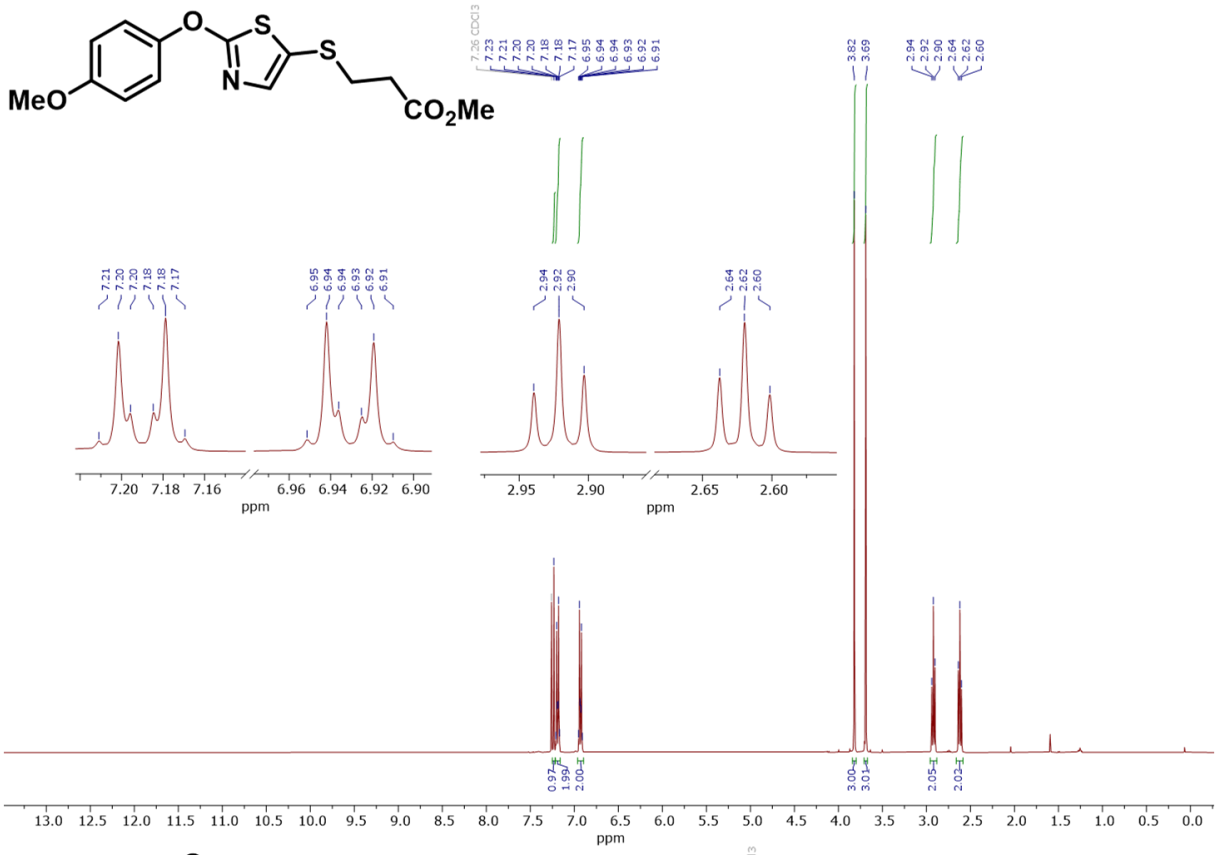


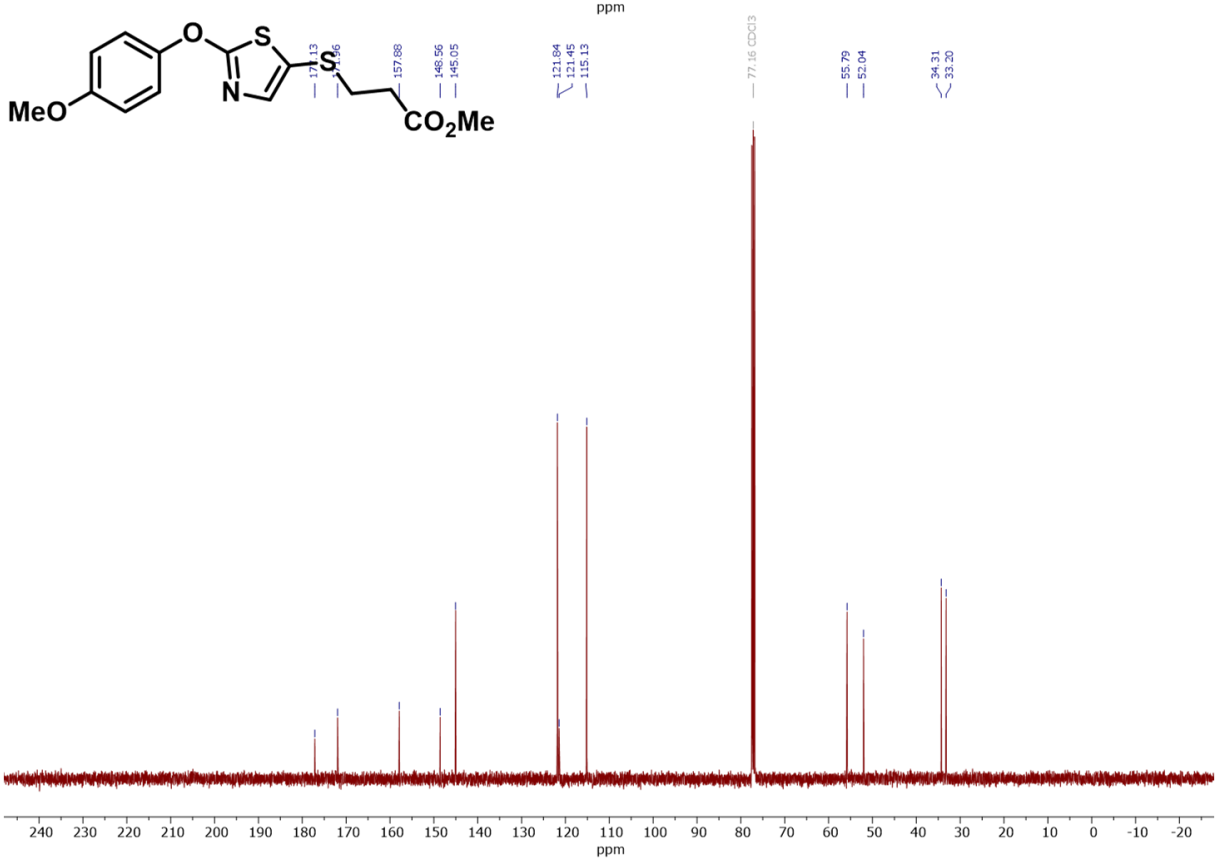
5-Bromo-2-(4-methoxyphenoxy)thiazole (4)



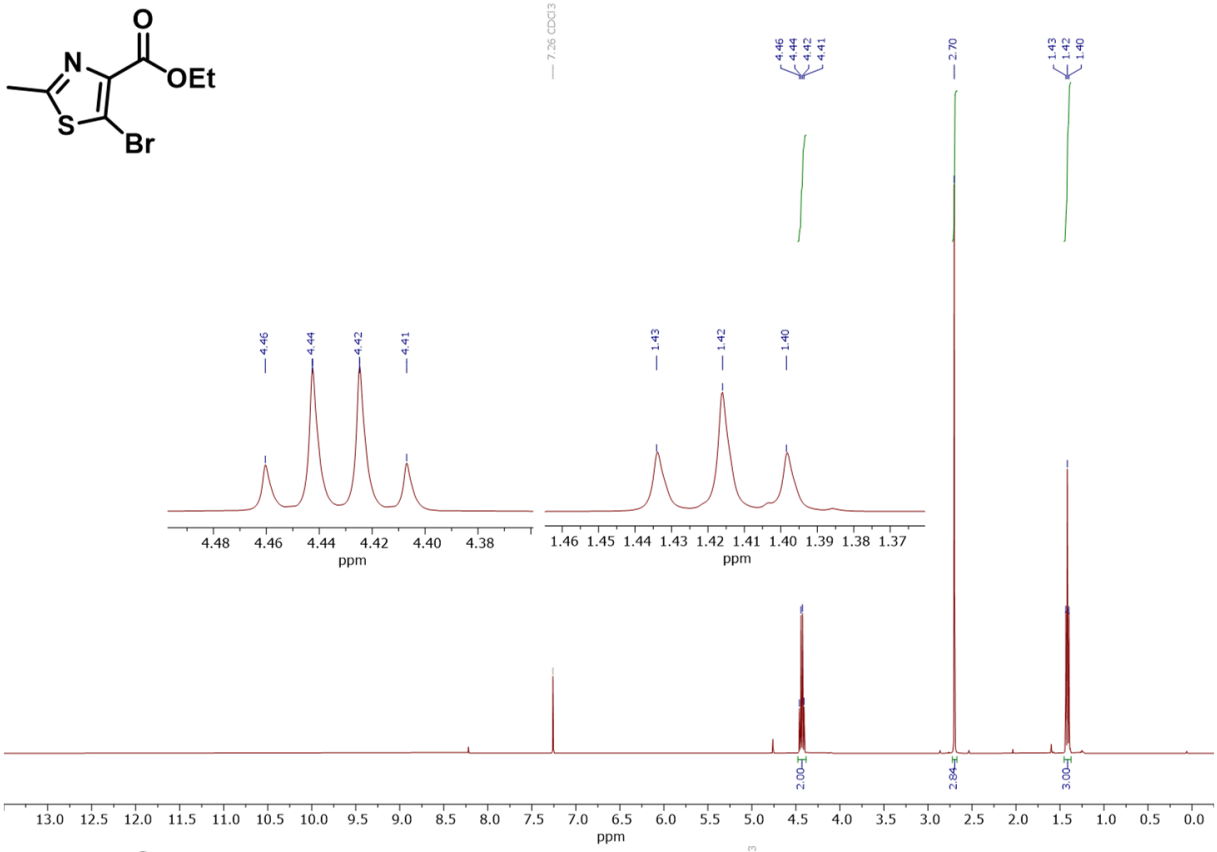


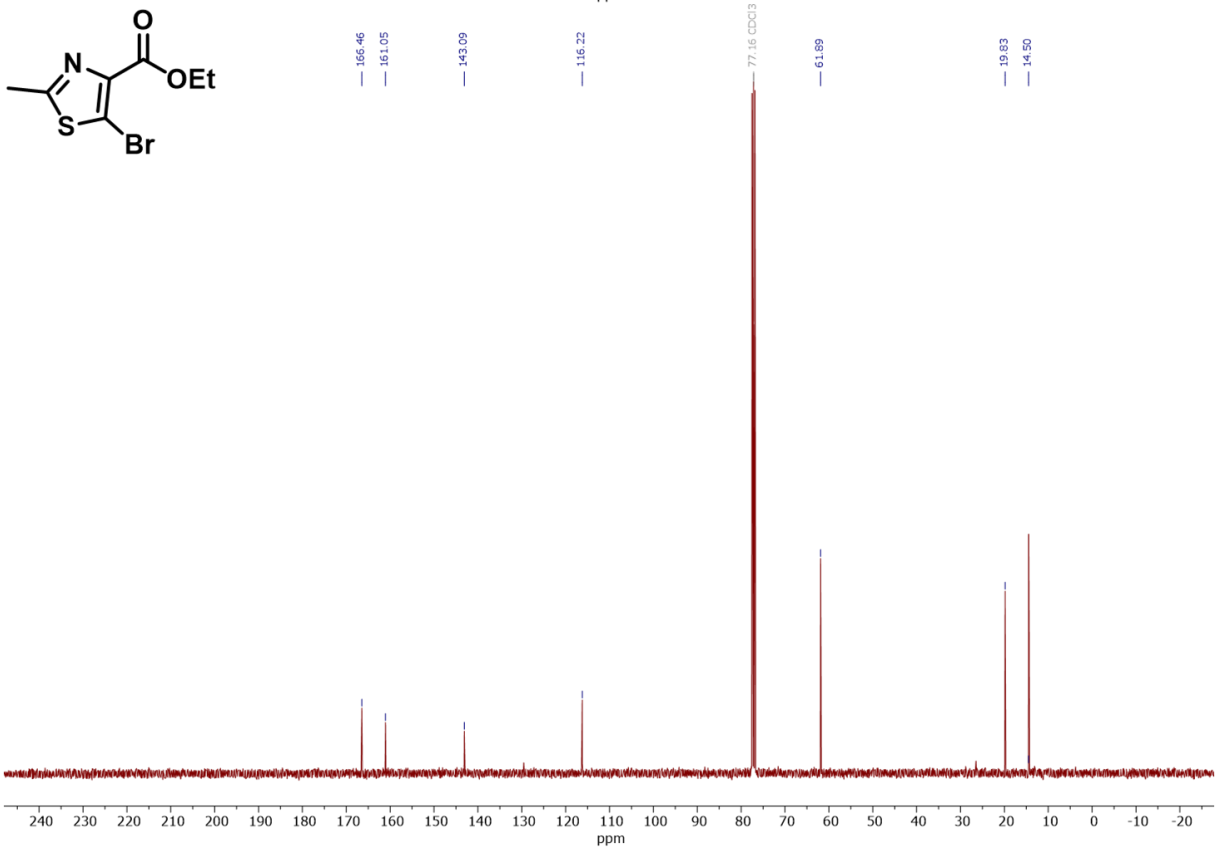
Methyl 3-((2-(4-methoxyphenoxy)thiazol-5-yl)thio)propanoate (4a)



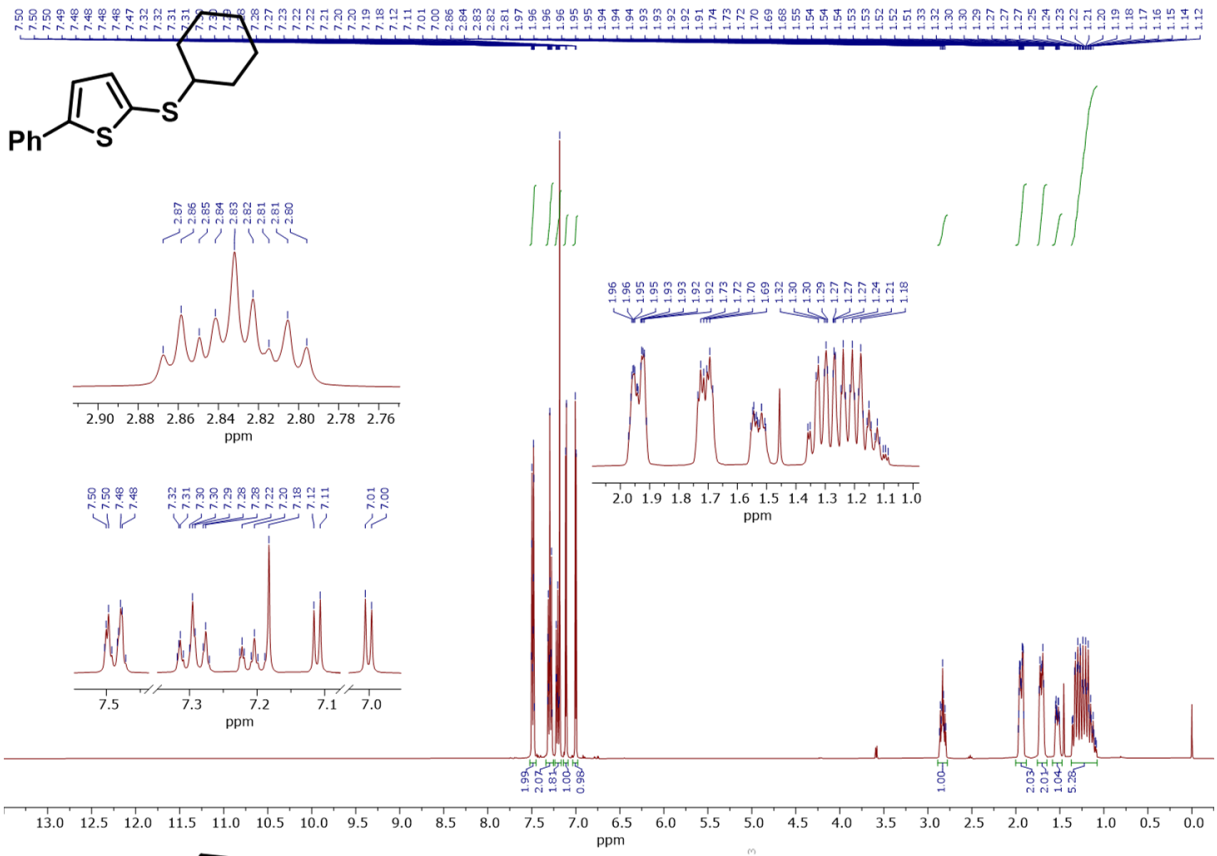


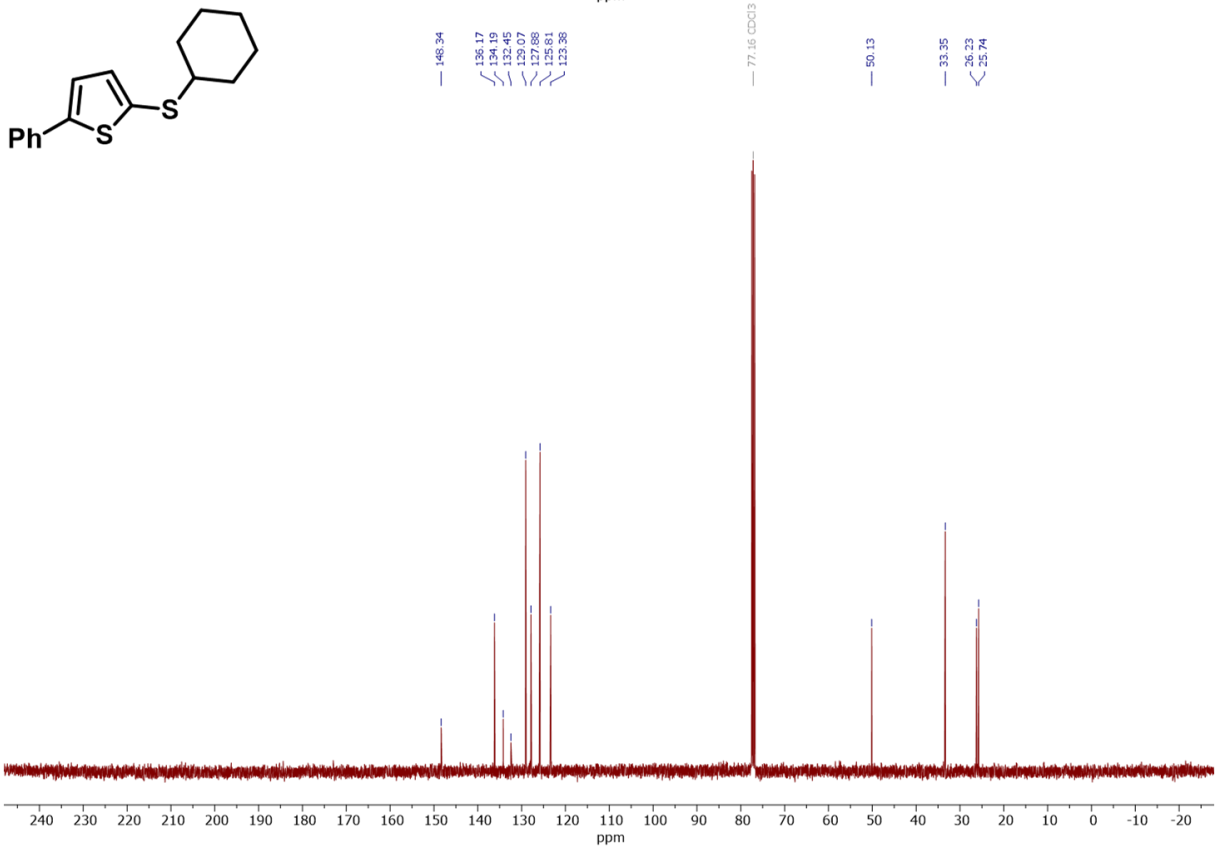
Ethyl 5-bromo-2-methylthiazole-4-carboxylate (5)



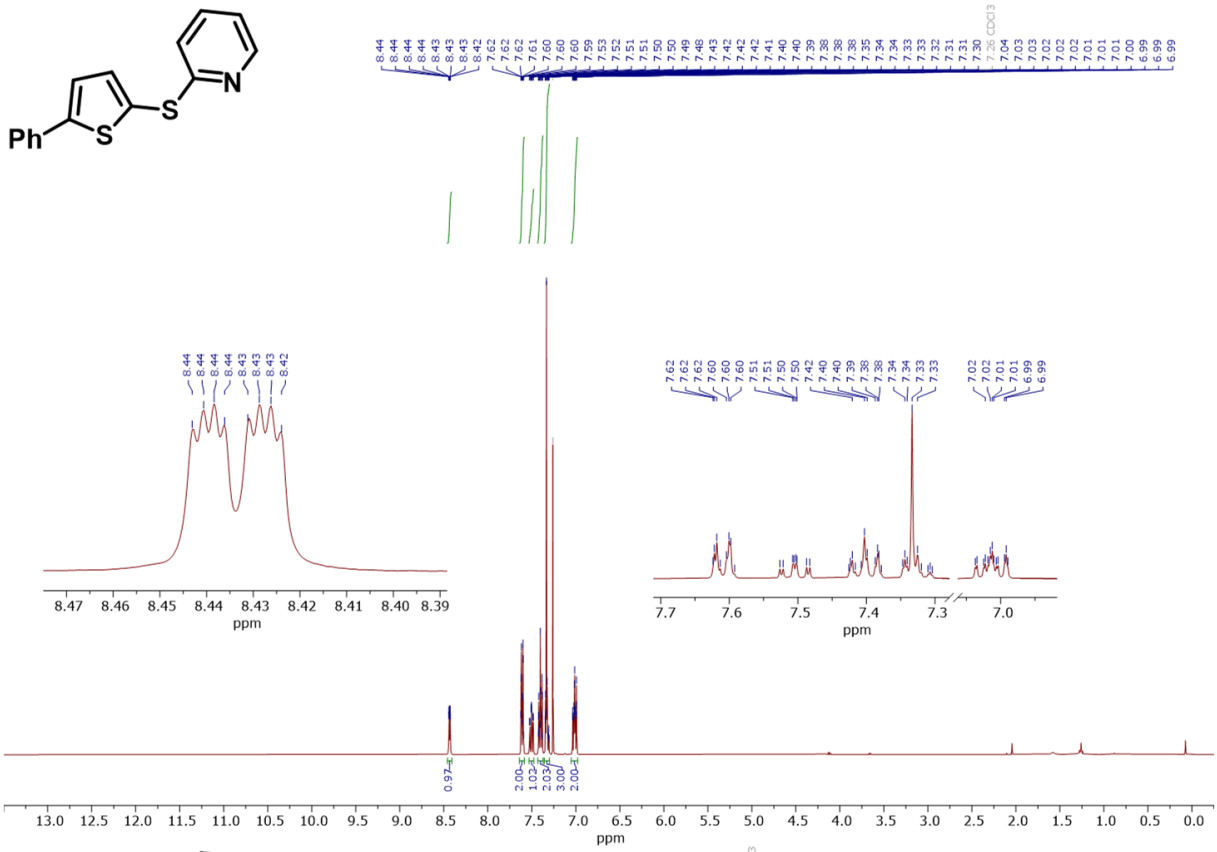


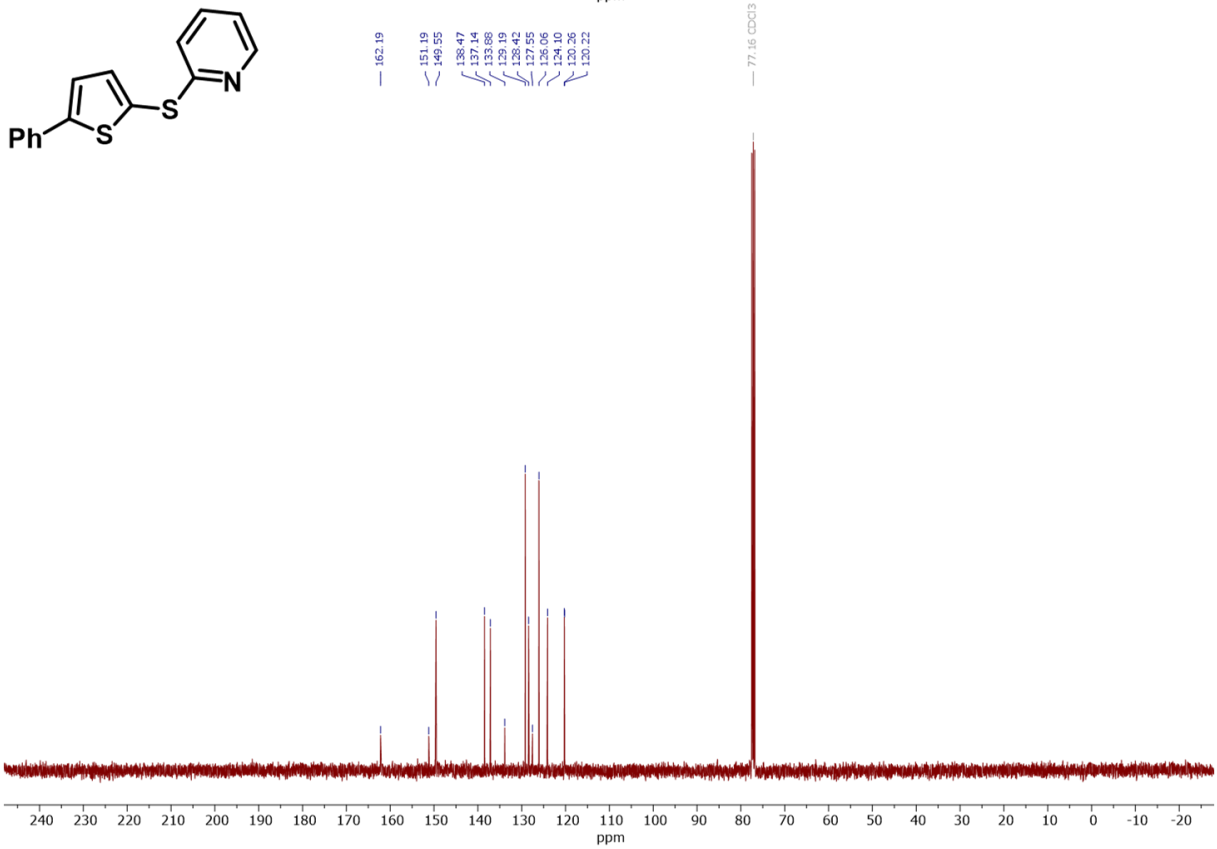
2-(Cyclohexylthio)-5-phenylthiophene (6a)



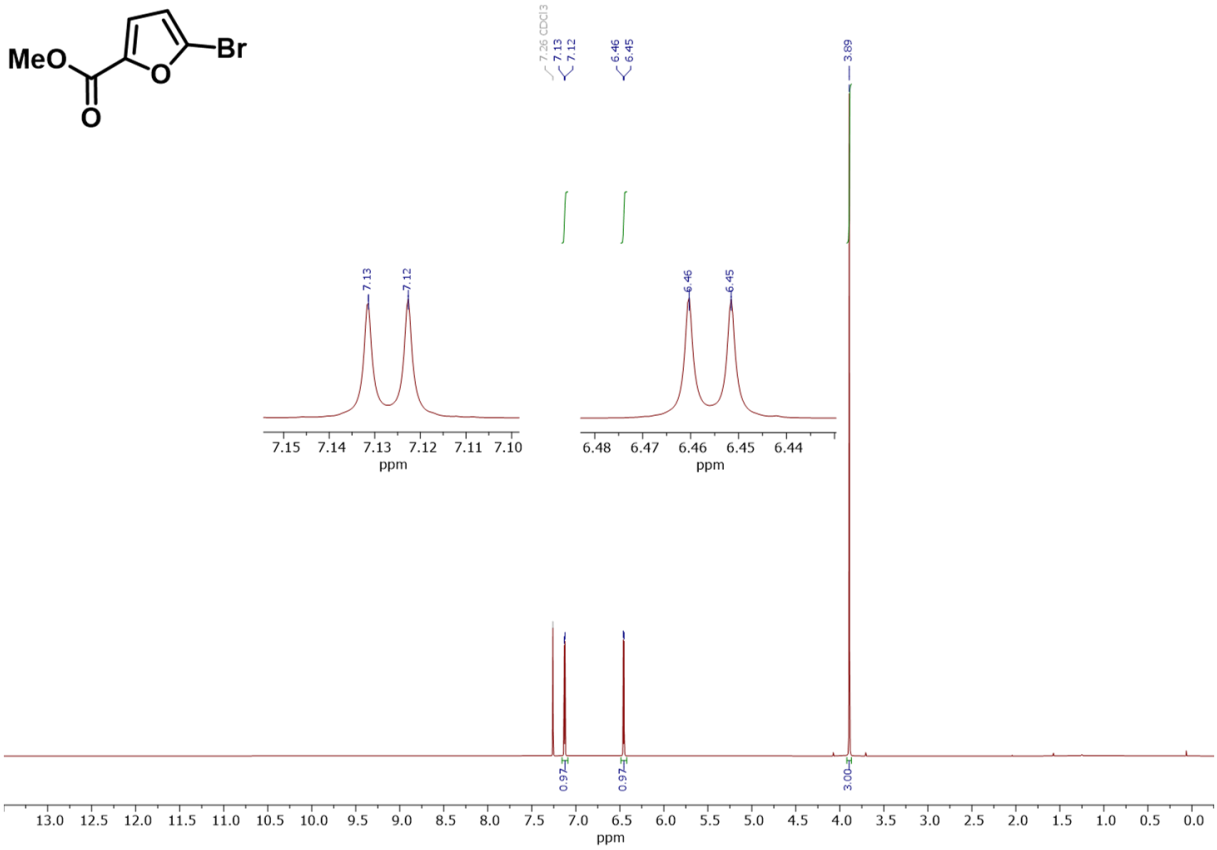


2-((5-Phenylthiophen-2-yl)thio)pyridine (6b)

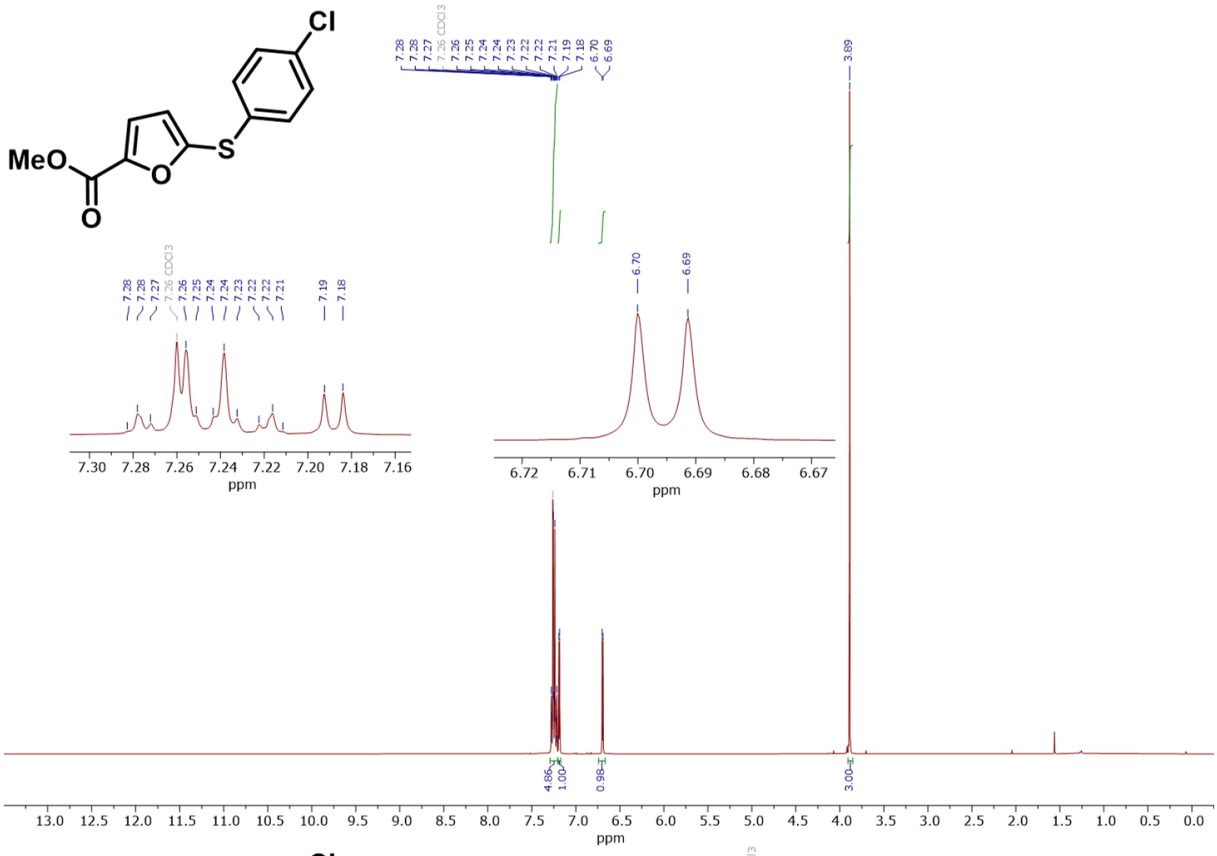


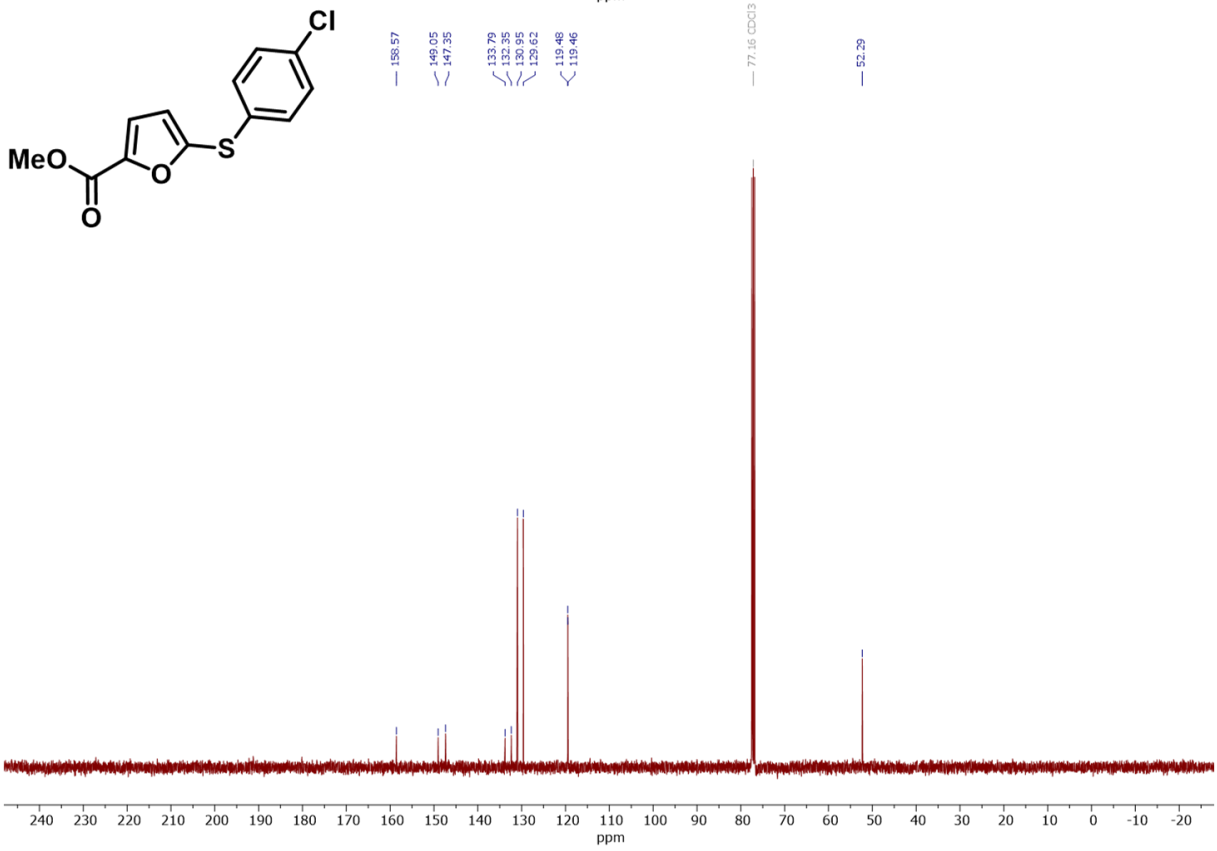


Methyl 5-bromofuran-2-carboxylate (8)

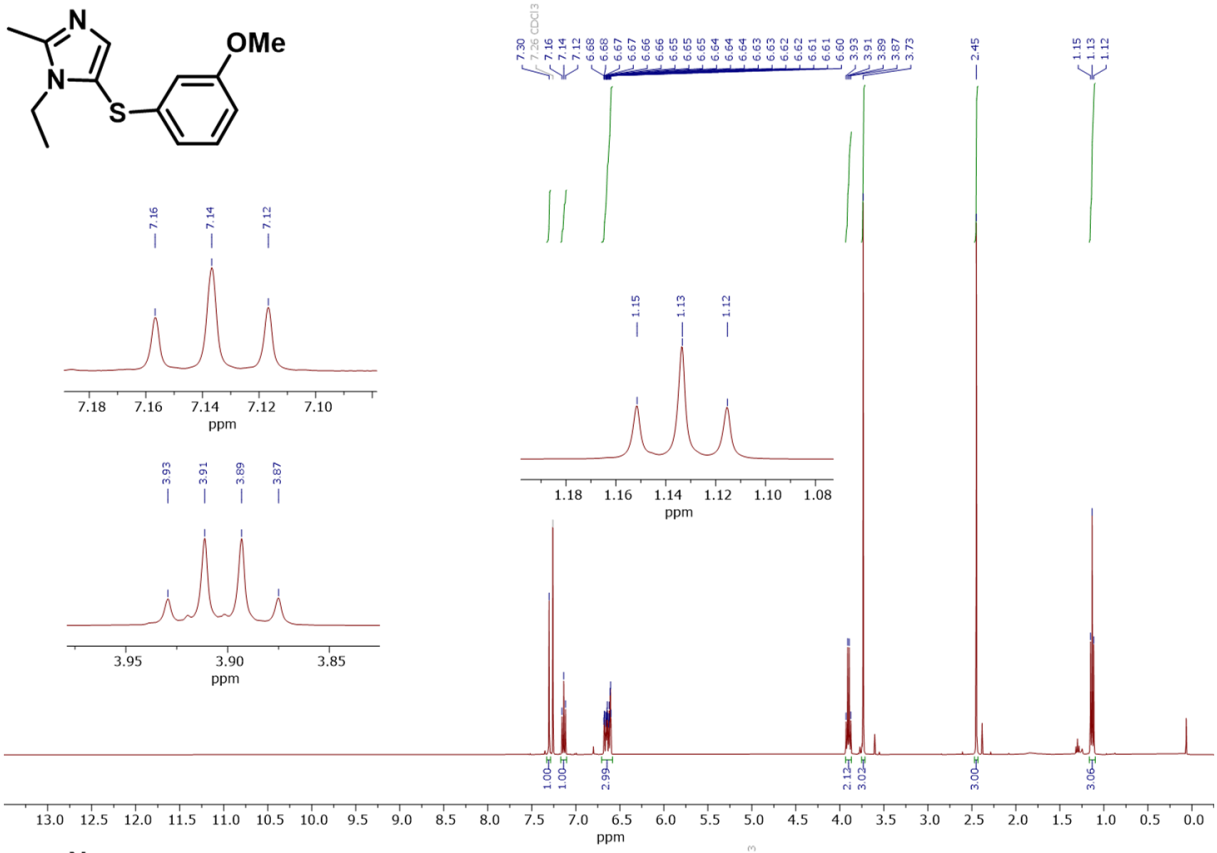


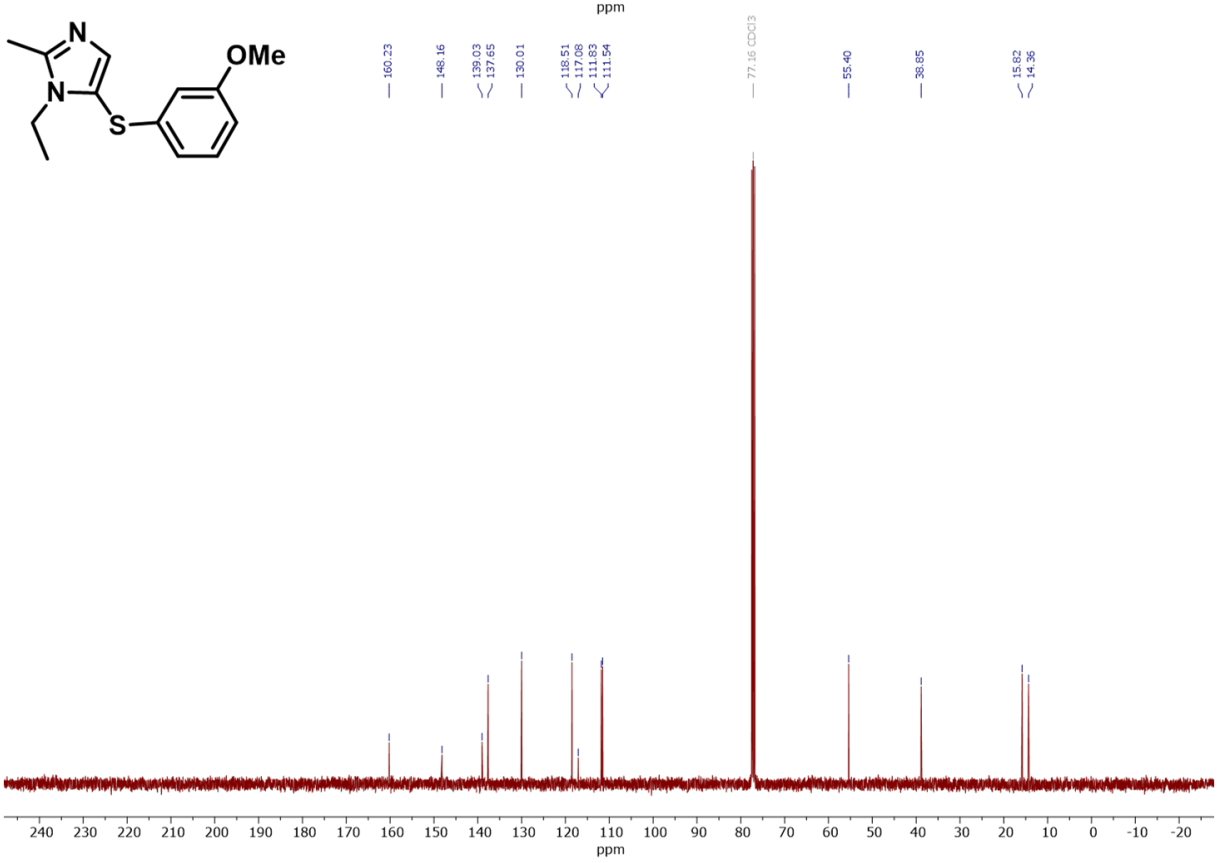
Methyl 5-((4-chlorophenyl)thio)furan-2-carboxylate (8a)





1-Ethyl-5-((3-methoxyphenyl)thio)-2-methyl-1H-imidazole (14a)





Ethyl 4-(isopropyl(phenyl)amino)benzoate (24a)