Supporting Information of

HTE-enabled Discovery of Palladium-Catalysed (Hetero)Arylation of Barbituric Acid and Meldrum's Acid

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1. General Information

Experiments were conducted in a glovebox under an inert atmosphere as described in our publication on HTE OS: *Org. Proc. Res. Dev.* **2024**, *28*, 7, 2875–2884.

Reactions are conducted in 1 mL glass vials in 24- or 96-well aluminium reaction blocks. They are sealed using a PFA-film and rubber mats, held in place by a screw-top cover. Mixing is achieved by tumble-stirring. Solid-dosing and reaction execution happen in separate glove boxes to avoid contamination of the solids by solvent vapours. All solvents and chemicals are used without purification and stored under nitrogen. The potassium carbonate used is of 325 mesh particle size.

Liquids are added using an electronic pipette after solid dosing is finished. Sampling is performed by removing a representative sample using a multi-channel pipette and quenching it into MeCN/H_2O (4:1). Reaction mixtures contain an appropriate internal standard such as anthracene, biphenyl, 1,3,5-trimethoxybenzene or *o*-terphenyl.

Samples are analysed on a Waters UPLC MS using one of two standardised methods. Other analytical methods are only used if the separation on the standard methods is not adequate.

LC-MS were recorded on Waters UPLC-MS Systems equipped with Waters Acquity, a CTC PAL auto sampler and a Waters SQD single quadrupole mass spectrometer. The separation was achieved on a Zorbax Eclipse Plus C18 1,7 µm 2.1*30mm column at 50 °C; A = 0.1% formic acid in Water; B = acetonitrile with 0.07% formic acid at flow 1. gradient: 0 min 3%B, 0.2 min 3%B, 1.7 min 97%B, 2.0 min 97%B, 2.1 min 3%B. The injection volume was 1 µL. Ionization was done with polarity switching in ESI mode.

Hardware

Table S1. List of hardware including manufacturer and application.

Device name	Manufacturer	Application
LABMaster pro eco glovebox	MBraun	HTE: Solid dosing, liquid dosing
Junior Glove Box	LC Technologies	Reaction Execution
Chronect Quantos	Axel Semrau	HTE: Solid dosing
Unchained Labs Junior	Unchained Labs	Cooling, heating, tumble stirring, shaking
Paradox Parallel Synthesis Reaction Block	Analytical Sales	Reaction Plates
1 mL glass vials 8x30 mm	Analytical Sales or ZHEJIANG ALWSCI TECHNOLOGIES	Reaction Vessels
Multipette E3/E3x	Eppendorf	Liquid Dosing
Rainin	Mettler Toledo	Sampling
Label Printer	Brother	dosing head labels

Software

Table S2. List of software employed including manufacturer and application.

Software name	Manufacturer	Application
HTE OS - Workflow	*self-built*	
Google Sheets	Google	HTE Workflow
Apps Script	Google	Executing the Code driving the workflow
P-Touch Editor	Brother	Label printing
Dotmatics ELN	Dotmatics	ELN-Software

LEA Library Studio	Unchained Labs	Plate Design
LEA Automation Studio	Unchained Labs	Robot control and Workflow execution
CHRONOS® Software 5.3.2	Axel Semrau	Dosing sequence management software
HTE OS - Data Wrangling		
rpt-Parser	self-built	Google Cloud Function executed when new Waters rpt-files are uploaded
Chemical Translator	self-built	Fast API based on rdkit and isospec++ that interconverts molecule identifiers and generates drawings, running on Google Cloud Run.
Data Storage		
Google Drive	Google	Used to store the results from CSC software and the Solubility App
Google Sheets	Google	Used to store most of the chemical data.
MS SQL Server on Google Cloud	Microsoft	Used to store all analytical and some chemical data.
Data Visualization		
HTE OS - Data Analytics	self-built	
Spotfire 12.0 LTS	Cloud	Data Tagging, Analysis and Pipelining

Generic experimental procedure for HTE reactions

To start, register a new reaction in the Google Sheet tab Submit *Request*. This can be achieved either through importing the reactants or pasting their SMILES strings. After entering metadata such as project name, customer and reacting functional group, the request can be submitted. Upon submission, the reaction information is added to the different data tables and Google Slides are generated with information about the reaction and project.

Next, use the *PlateBuilder* tab to design the plate, either from scratch or using existing plate layouts for inspiration. Once the plate design is set, go to the *FileGenerator* tab and assign the plate design to the corresponding ELN-reaction. By selecting the correct ELN in the dropdown, the reaction information (information of the starting materials and Product) is being populated. If it is the first plate for the chosen reaction, the plate count will be 1. If not, the plate count will

adjust accordingly to the already existing plates in the database. Set the equivalents of the starting materials and all other substrates/solvents in the reaction. Most categories can be set globally, but you can always adjust each value (equivalents or, in case of solvents, volumes) separately in the “material table”. Add information about the plate's purpose and the experimental procedure to be followed. Saving the plate generates all input files for the robots, creates a *Cheat Sheet*, and adds the plate information to Google Slides. Now, everything is ready for execution in the laboratory.

In the laboratory, fill the solids into "dosing heads" and label them using the labels generated either automatically through *Submit Request* or *FileGenerator* or manually within the Registration Tab. When writing a new head, place it on the hotel, load the head-writing sequence, and add the substance name, batch, compound ID, filling weight, and hotel position. The RFID chip will be written with this information and updated with residual dosing amounts after each use. This information is also stored in the Google Platform, tracking solid amounts even when not on the hotel.

Place all required solids in the hotel and a plate (96-well or other) in the plate tray. In the *Hotelplanner* tab you can select the plate you want to dose, and it will show you all “missing heads” which are not yet available on the hotel. You can see which positions are used for the dosing, and which heads can be removed from the hotel. Once all solids are on the Hotel, load the input file in the Chronos software. This file includes all necessary information from the Google Sheet, such as batch ID, solid amounts, and vial sizes. Ensure you add the correct tray information to guarantee accurate dosing.

After dosing, go to the *Correction* tab in the Google Sheet, select the dosing log file, click "load". Filter the dosings by deviation boundary to select the dosings that need to be corrected. Create a correction file for the solid dosing robot if needed by clicking on the corresponding button.

The *Final Check* tab ensures all solids have been dosed within the selected boundaries, including corrections. Generate a final correction file if there are still vials with too low amounts or missing dosings.

After completing solid dosing, perform liquid dosing. In our case there are two gloveboxes, one dedicated to solid dosing and one for handling liquids. The liquid dosing is performed using Multipipette E3x from Eppendorf. The *Cheat Sheet* provides the order of liquid addition and indicates which liquids should be dosed into which vials. After adding the liquids, close the lid, and heat/stir the reaction. Sample manually by cooling the plate to room temperature before opening the lid and using the Multi Pipette LX12-10XLS+ from Mettler Toledo to transfer 3 uL aliquots to a sampling plate and dilute with 800 uL MeCN/H_2O (4:1).

We measure almost all samples with LCMS. The sequence file for LCMS, generated from the Google Sheet, includes information such as ELN ID, plate/sample number, molecular formulas for starting materials, products, and side products. The user amends the name with the reaction time and temperature.

In Spotfire, raw data from the LCMS (mass peaks, sampling information like time/ temperature, retention time etc.) as well as meta data from the Google Sheet (structural information, dosing weights, project information etc.) is being combined and visualised. For us, the auto integration from Masslynx is sufficient. In Spotfire, the peaks in the UV-visualization are being tagged according to the masses from LCMS. Therefore, in the Database the majority of the biggest UV-peaks contain structural information. Visualizations from Spotfire are used for interpretation and reporting in the gSlides.

2. Preliminary Screening / Malonate Arylation

These are the results of the initial screening request by the customer for an arylation of diisopropyl malonate. Several palladium catalysts effected the transformation, and all solvent/base combinations resulted in product formation.

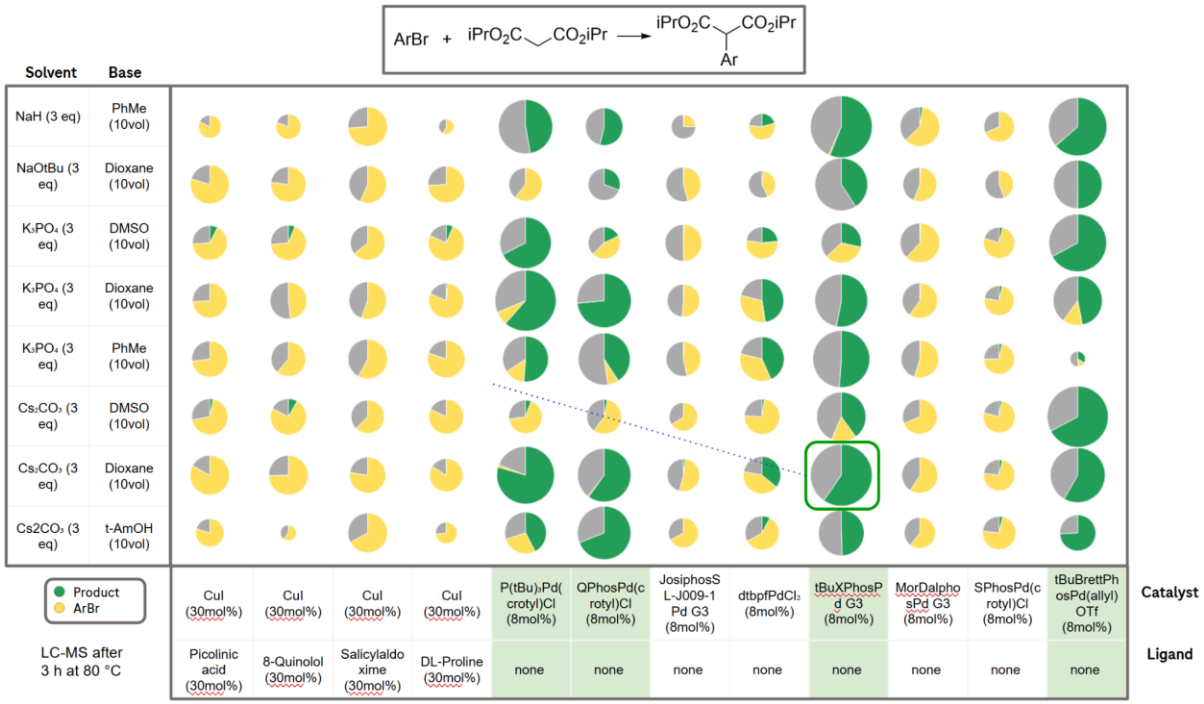


Figure S1. Results of plate 1, sample 1 taken after stirring at 3h, 80 °C.

3. Arylation of Barbituric Acid

This reaction was selected as a model reaction for fine-tuning the conditions found for the screening request by the customer. The design of the first plate is based on the results presented in Figure S1.

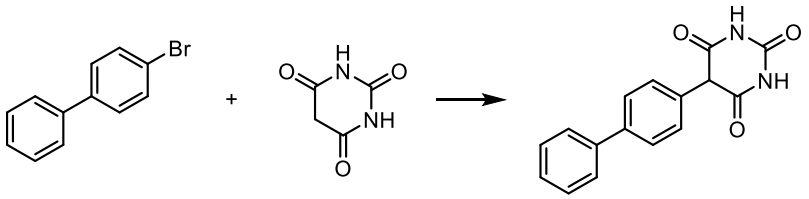


Plate 1: Initial screening on model substrate

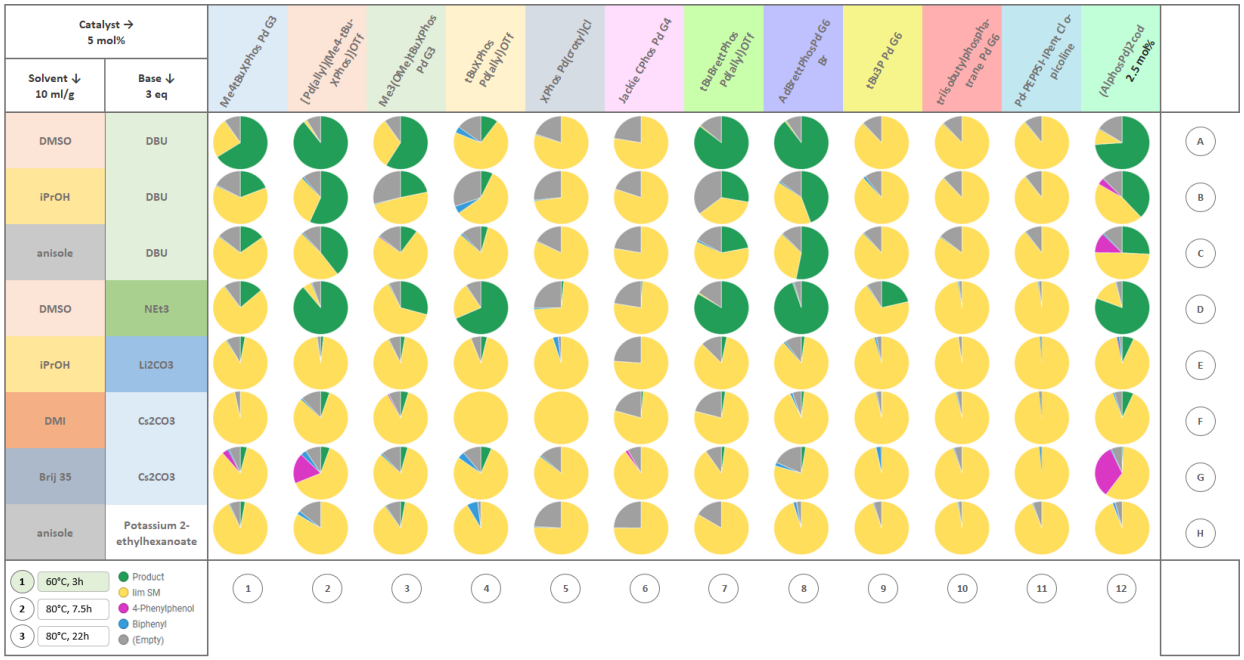


Figure S2. Results of plate 1, sample 1 taken after stirring at 3 h, 60 °C. (Empty) refers to an unassigned peak in the LCMS.

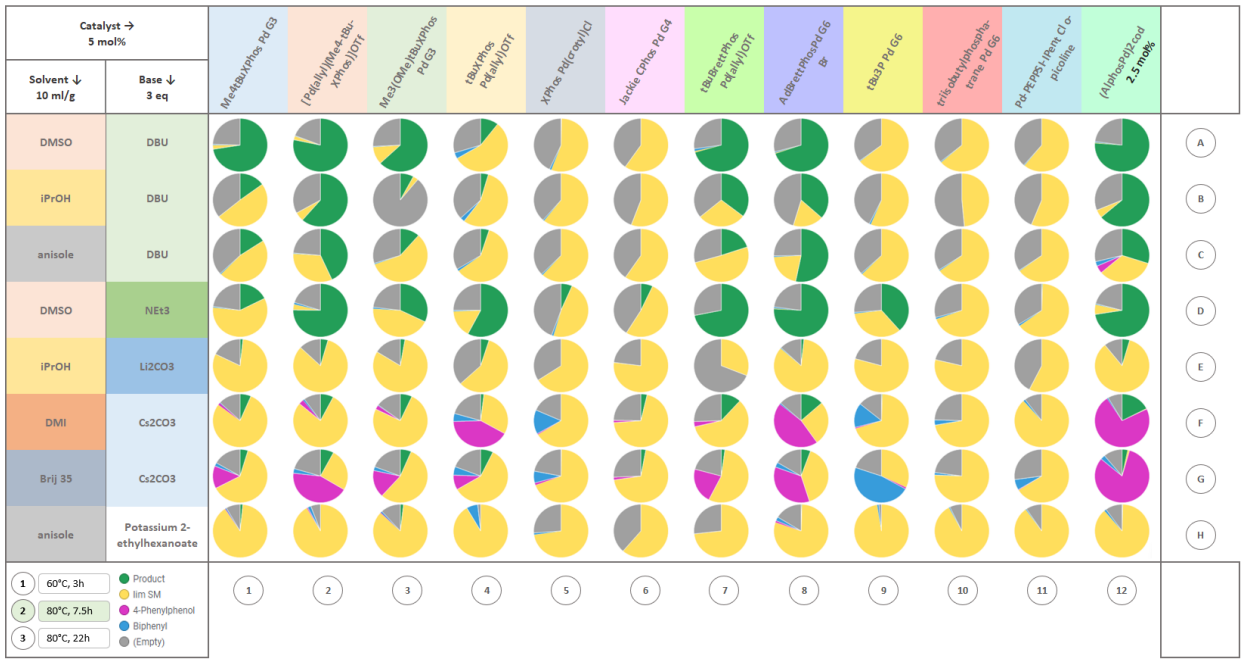


Figure S3. Results of plate 1, sample 2 taken after stirring at 7.5 h, 80 °C.

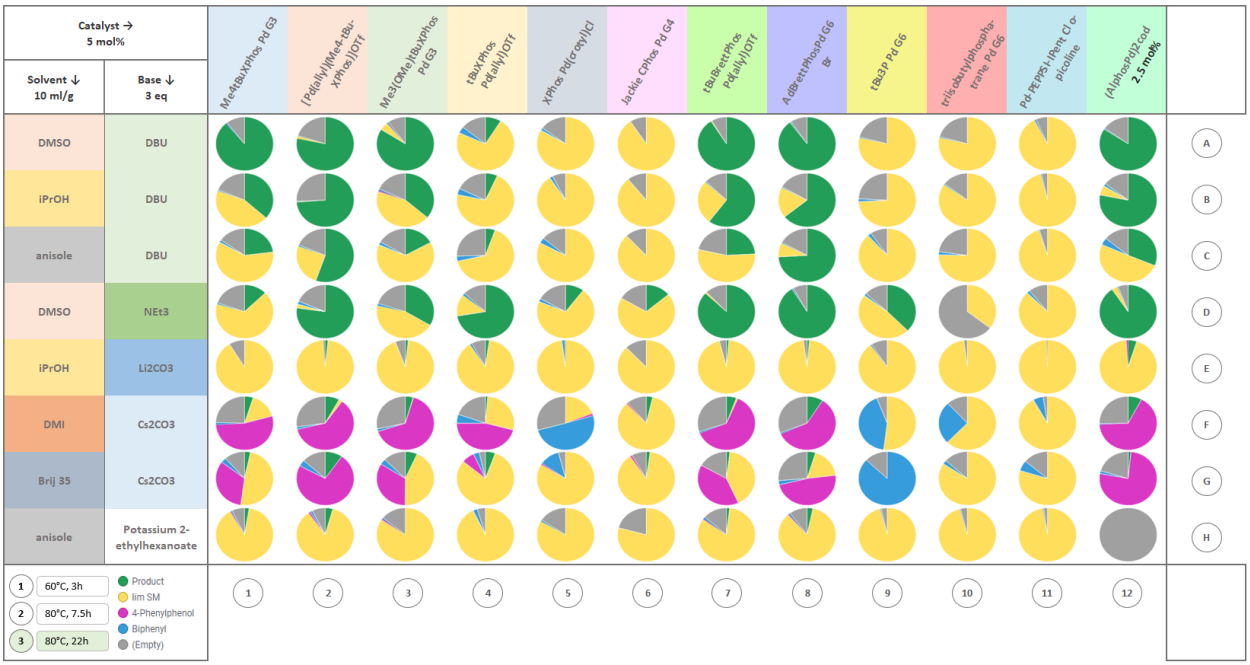


Figure S4. Results of plate 1, sample 3 taken after stirring at 22 h, 80 °C.

Plate 2: Refinement with respect to base, solvent and catalyst

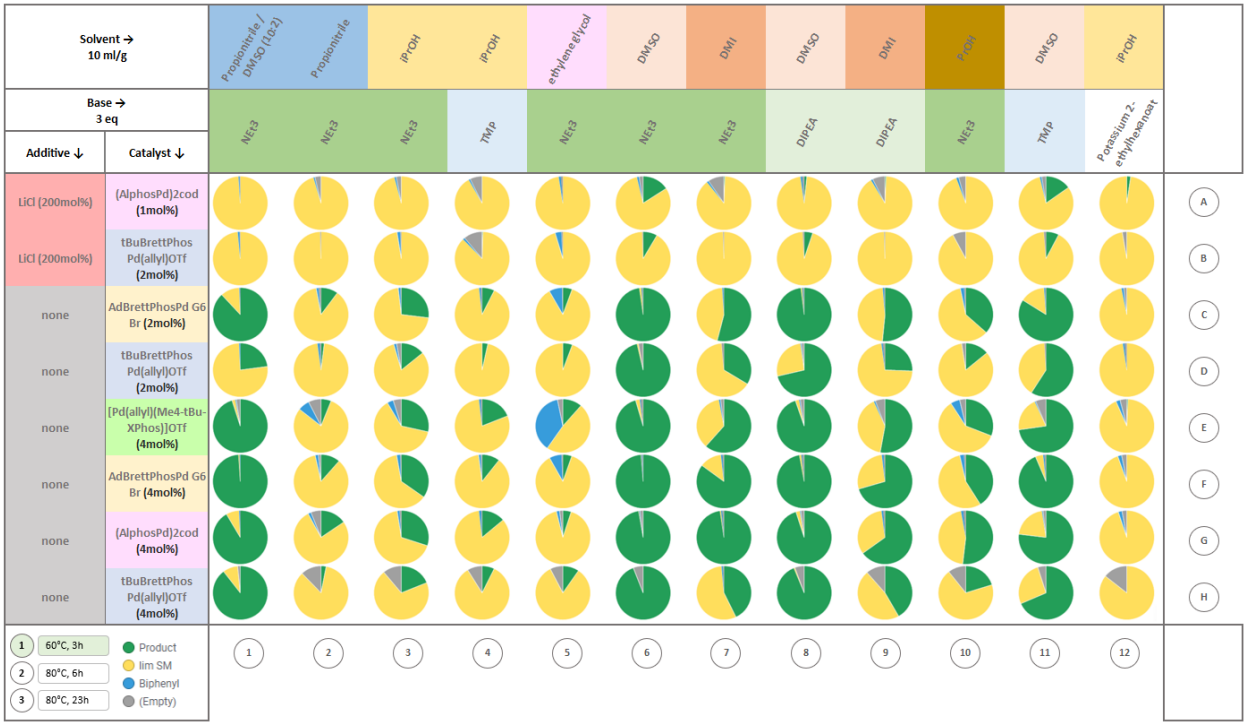


Figure S5. Results of plate 2, sample 1 taken after stirring at 3 h, 60 °C.

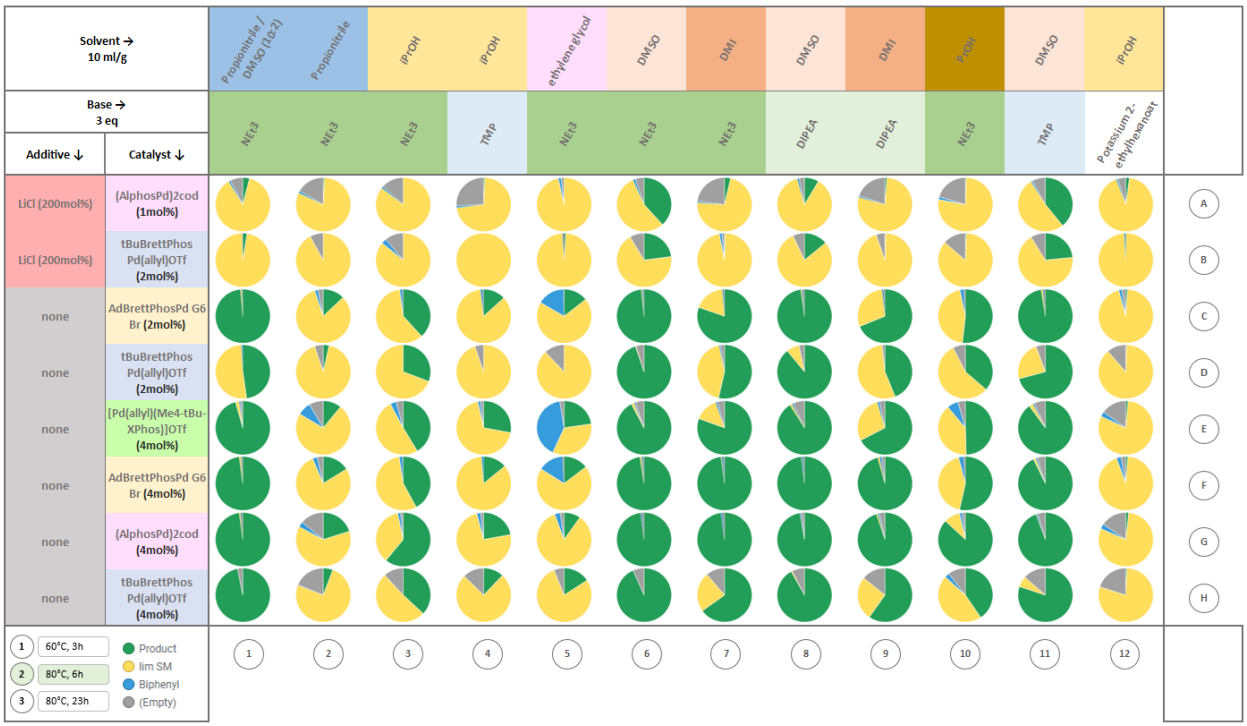


Figure S6. Results of plate 2, sample 2 taken after stirring at 6 h, 80 °C.

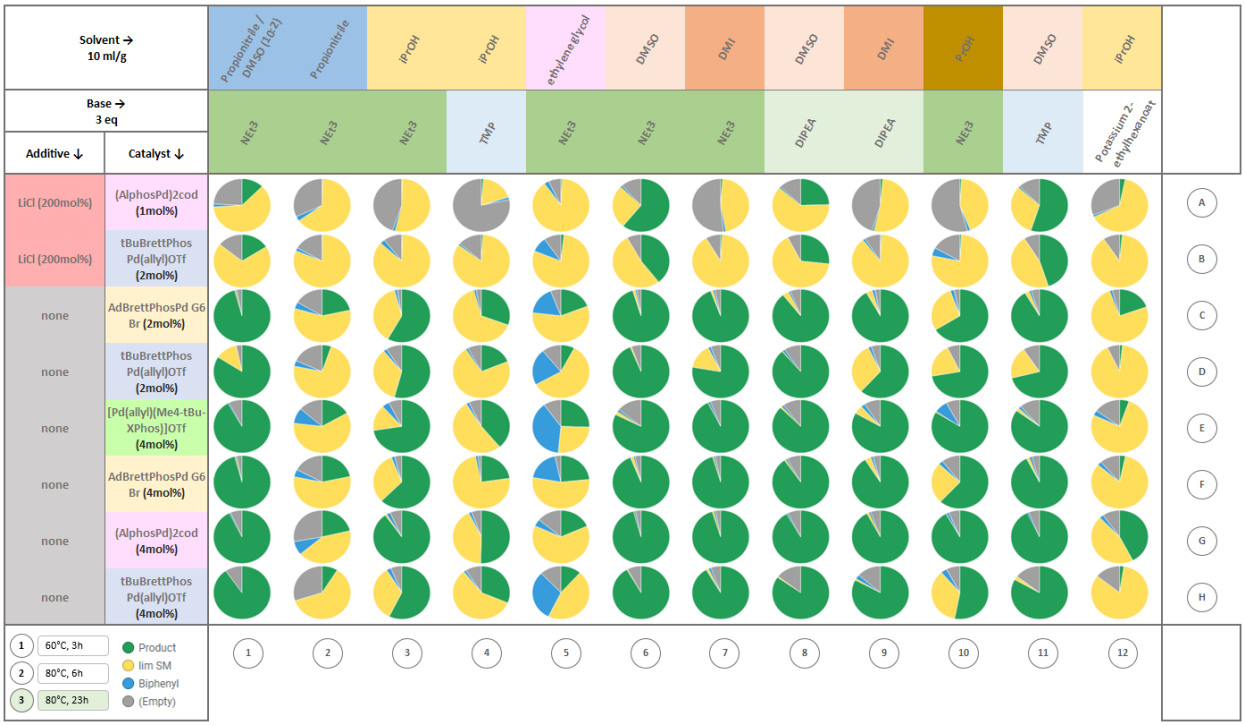


Figure S7. Results of plate 2, sample 3 taken after stirring at 23 h, 80 °C.

Plate 3: Solvent optimization

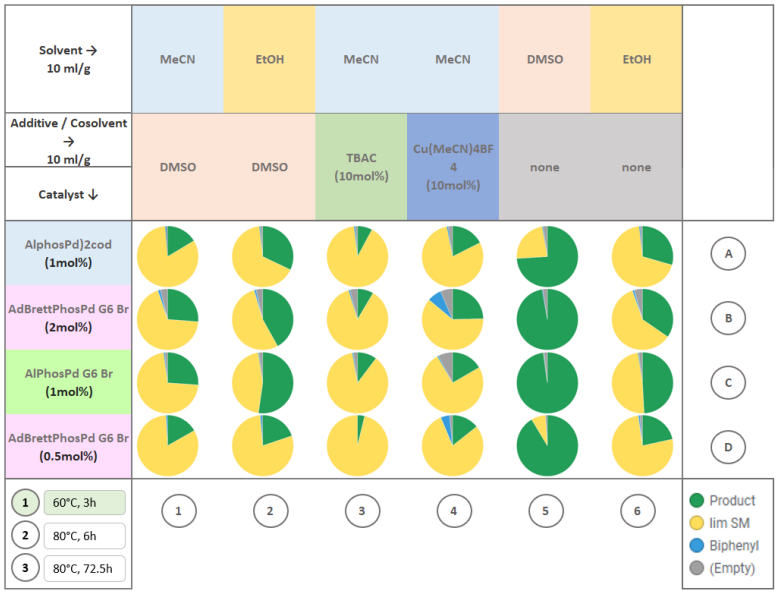


Figure S8. Results of plate 3, sample 1 taken after stirring at 3 h, 60 °C.

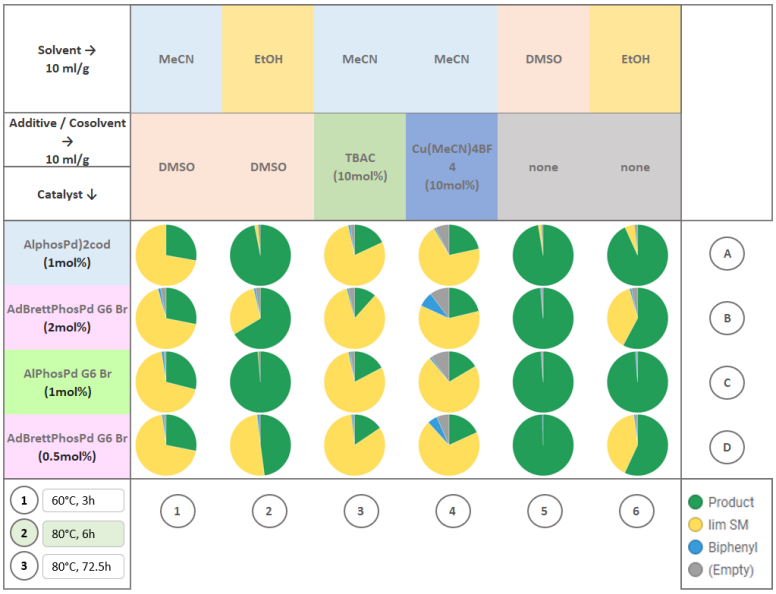


Figure S9. Results of plate 3, sample 2 taken after stirring at 6 h, 80 °C.

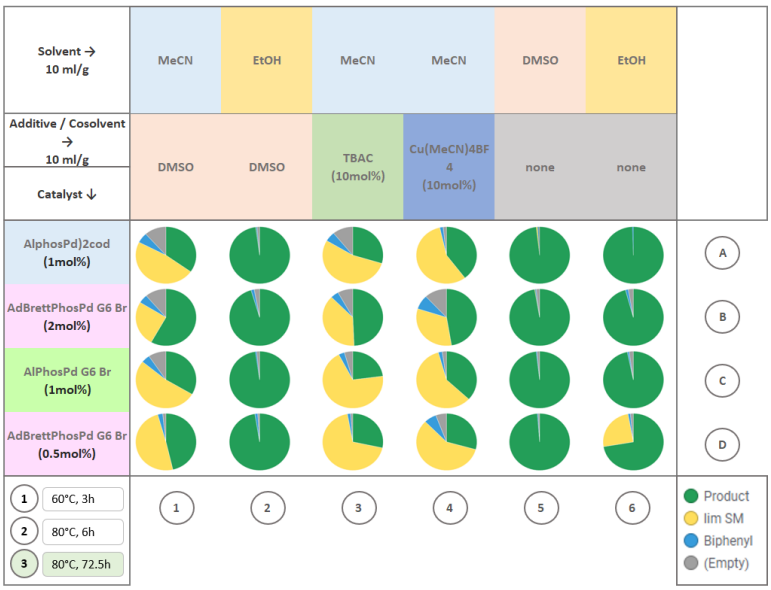


Figure S10. Results of plate 3, sample 3 taken after stirring at 72.5 h, 80 °C.

Plate 4: Scope Set 1

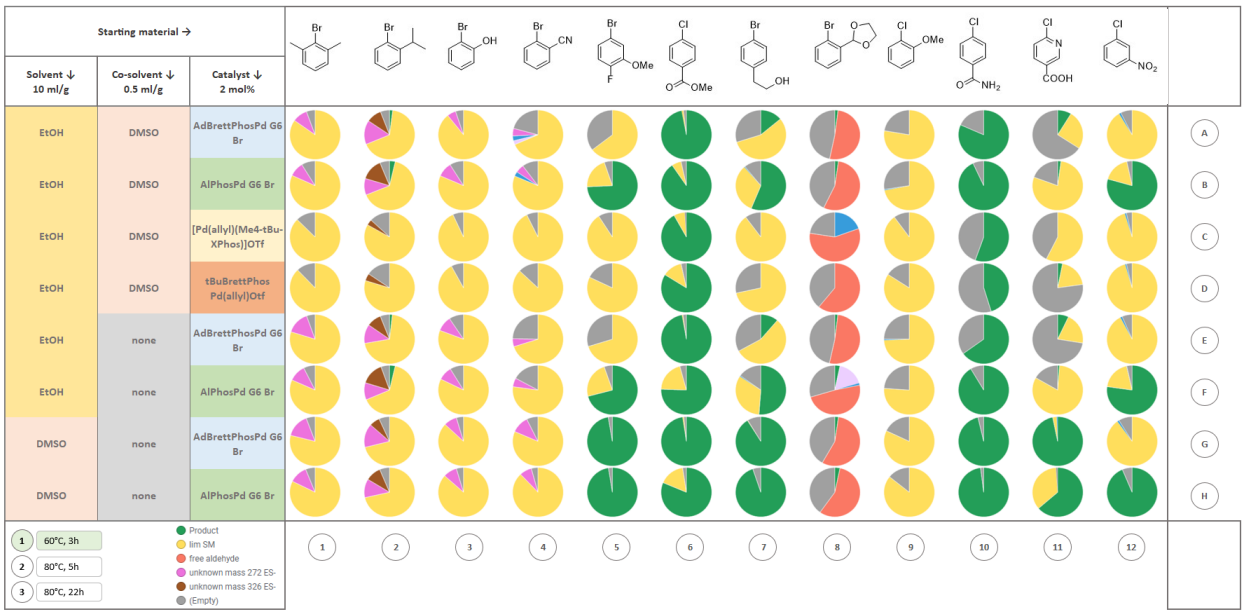


Figure S11. Results of plate 4, sample 1 taken after stirring at 3 h, 60 °C.

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

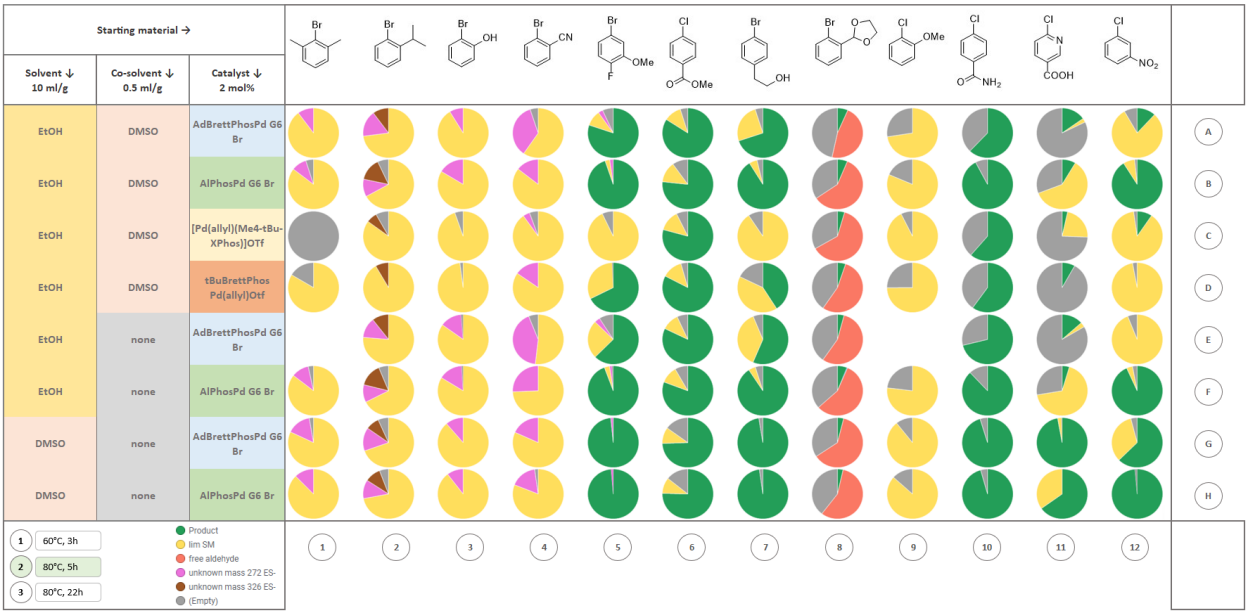


Figure S12. Results of plate 4, sample 2 taken after stirring at 5 h, 80 °C.

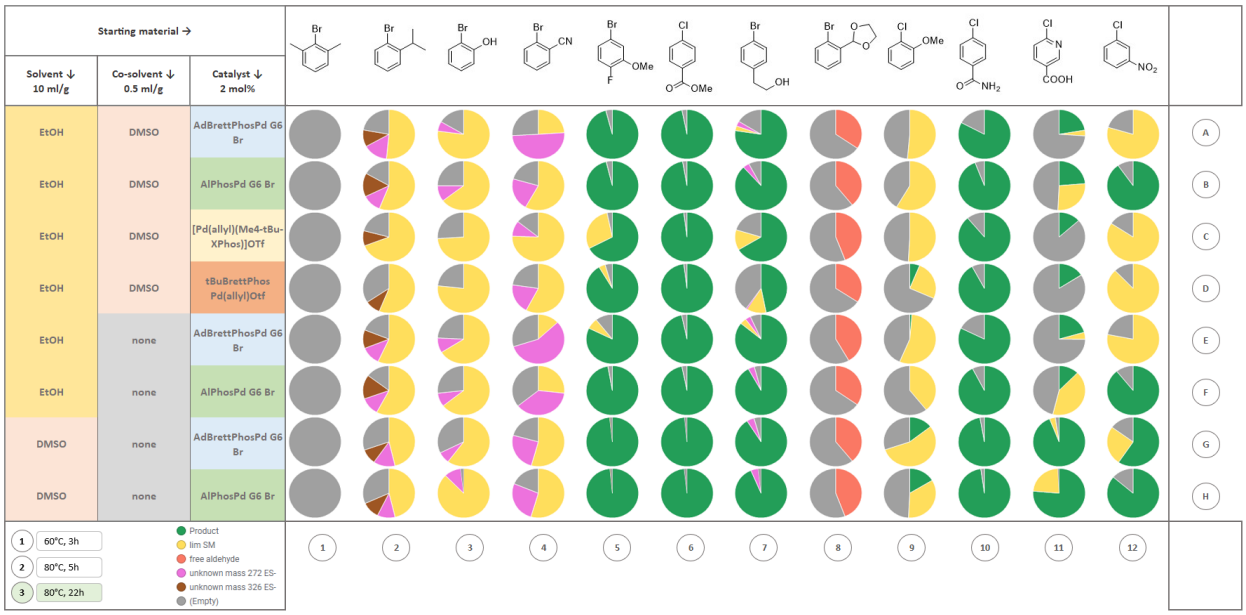


Figure S13. Results of plate 4, sample 3 taken after stirring at 22 h, 80 °C.

Plate 5: Scope Set 1, can we further optimize to tolerate *ortho*-substituents?

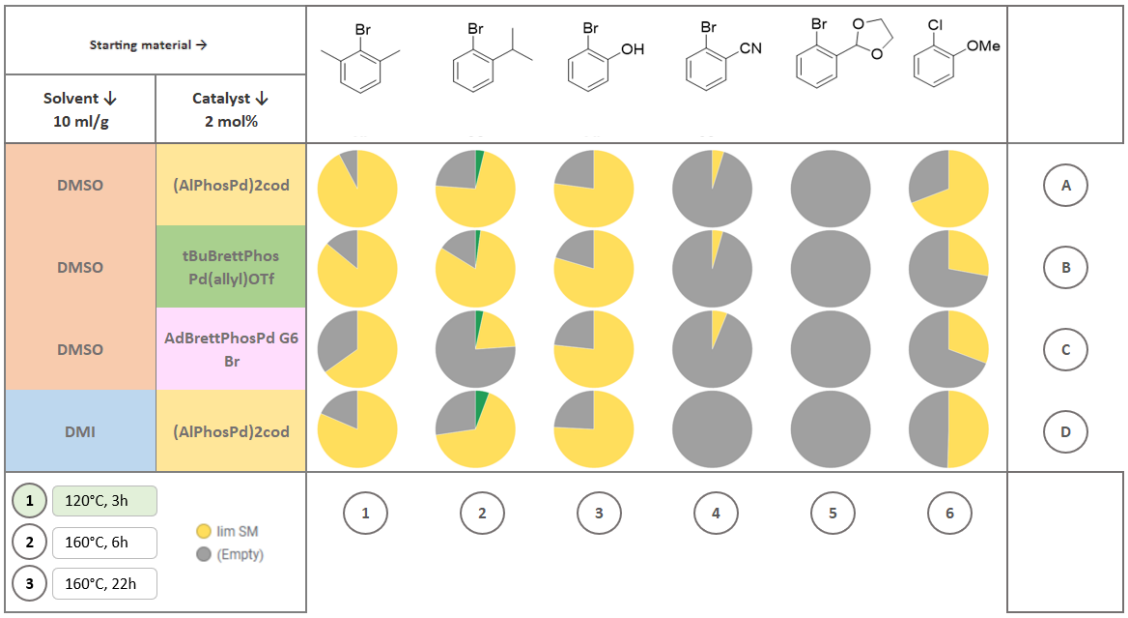


Figure S14. Results of plate 5, sample 1 taken after stirring at 3 h, 120 °C. 3 equiv of NEt_3 were present in the reaction as base.

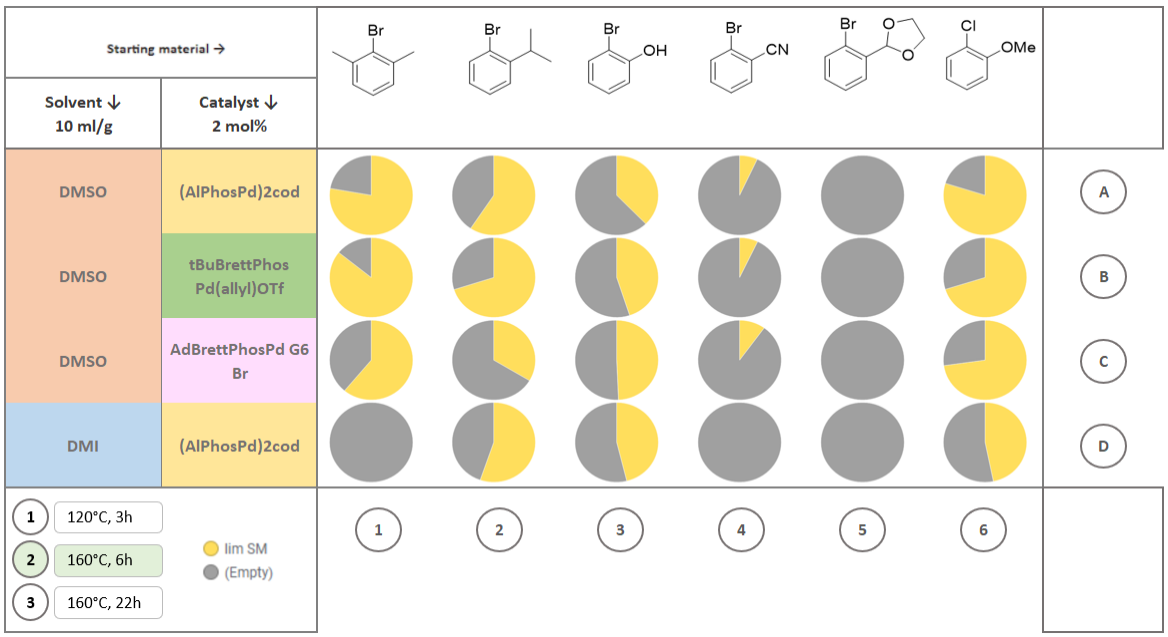


Figure S15. Results of plate 5, sample 1 taken after stirring at 6 h, 160 °C. 3 equiv of NEt_3 were present in the reaction as base.

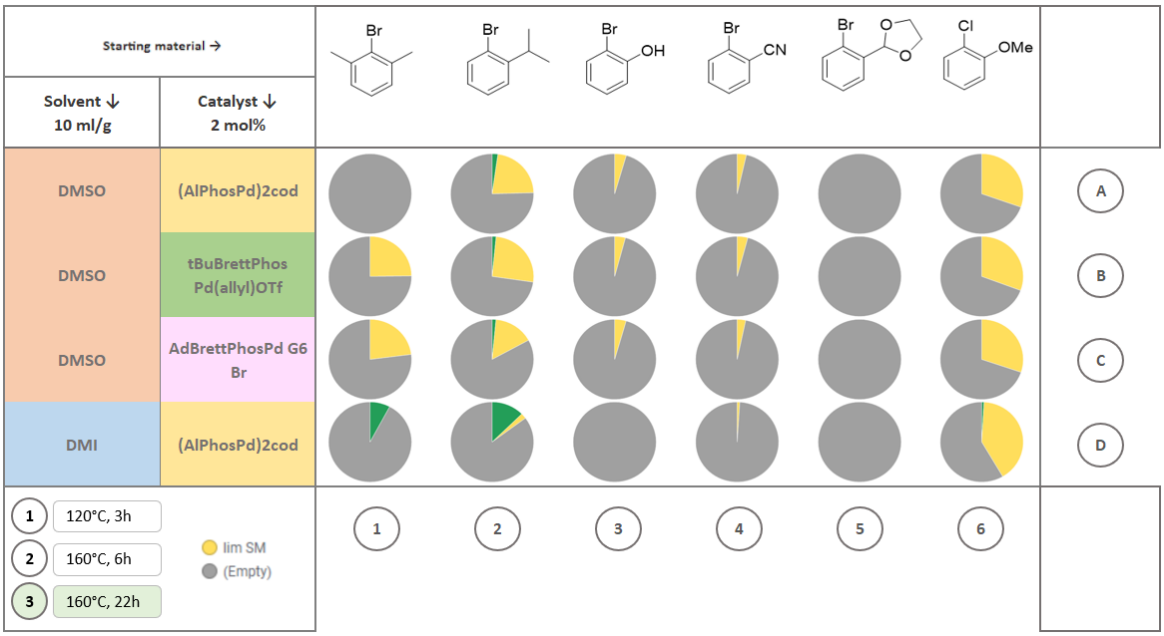


Figure S16. Results of plate 5, sample 3 taken after stirring at 22 h, 160 °C. 3 equiv of NEt_3 were present in the reaction as base.

Even under forcing conditions, we do not see significant conversion.

Plate 6: Scope Set 2

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

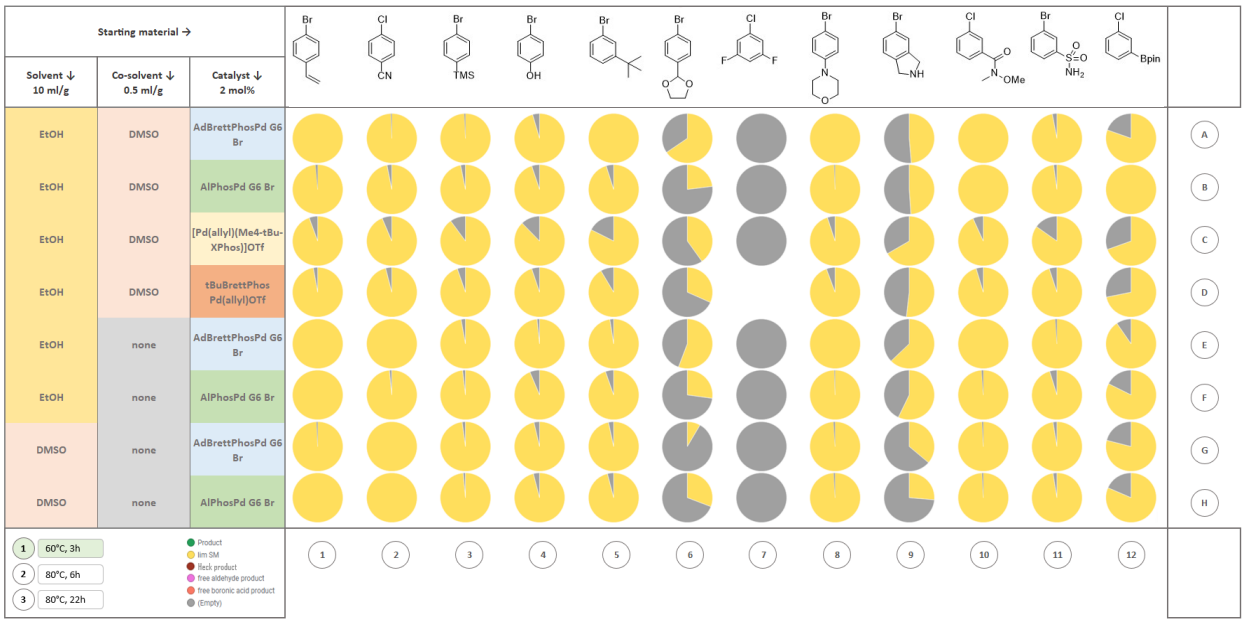


Figure S17. Results of plate 6, sample 1 taken after stirring at 3 h, 60 °C.

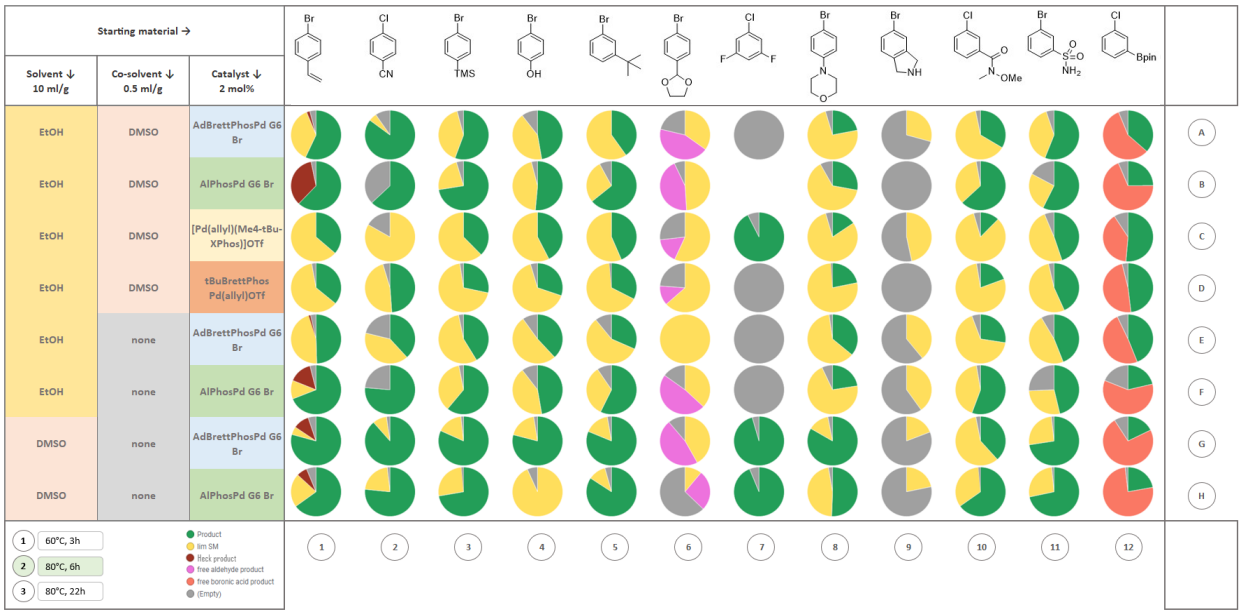


Figure S18. Results of plate 6, sample 1 taken after stirring at 6 h, 80 °C.

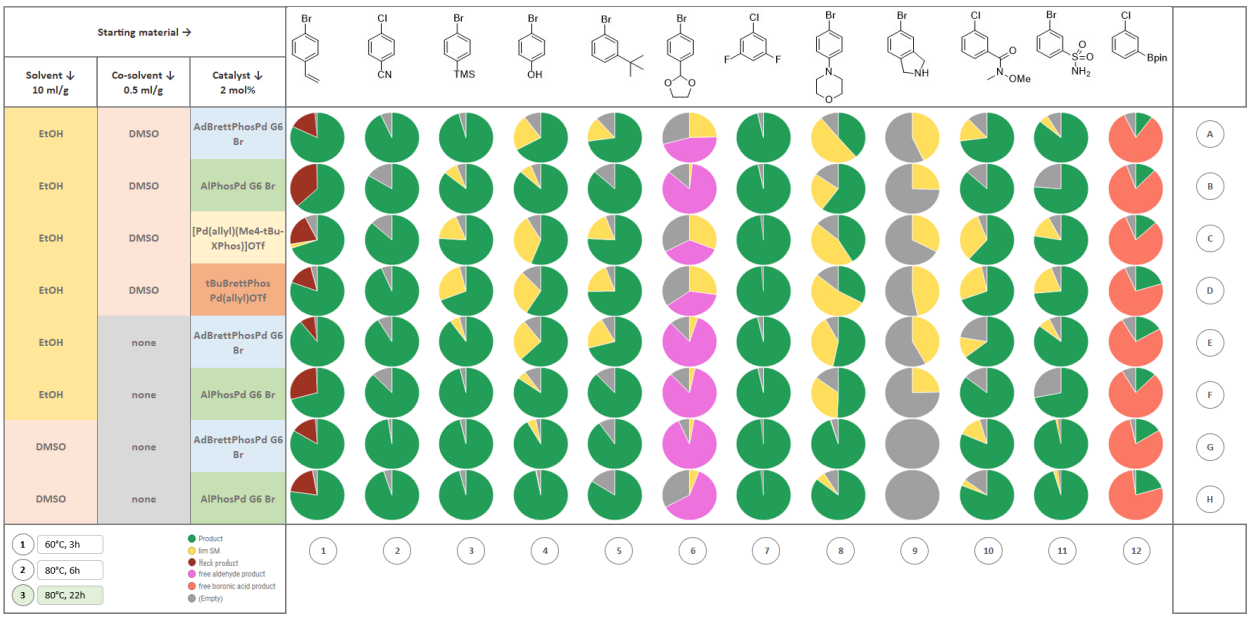


Figure S19. Results of plate 6, sample 1 taken after stirring at 22 h, 80 °C.

Plate 7: Scope Set 3

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

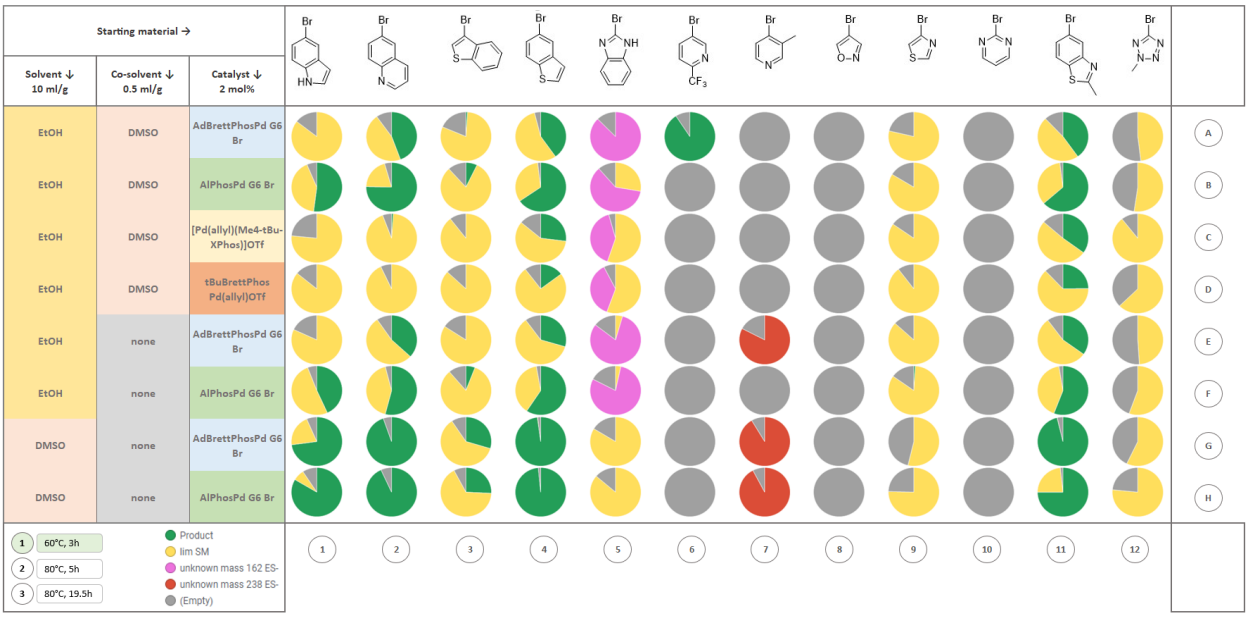


Figure S20. Results of plate 7, sample 1 taken after stirring at 3 h, 60 °C.

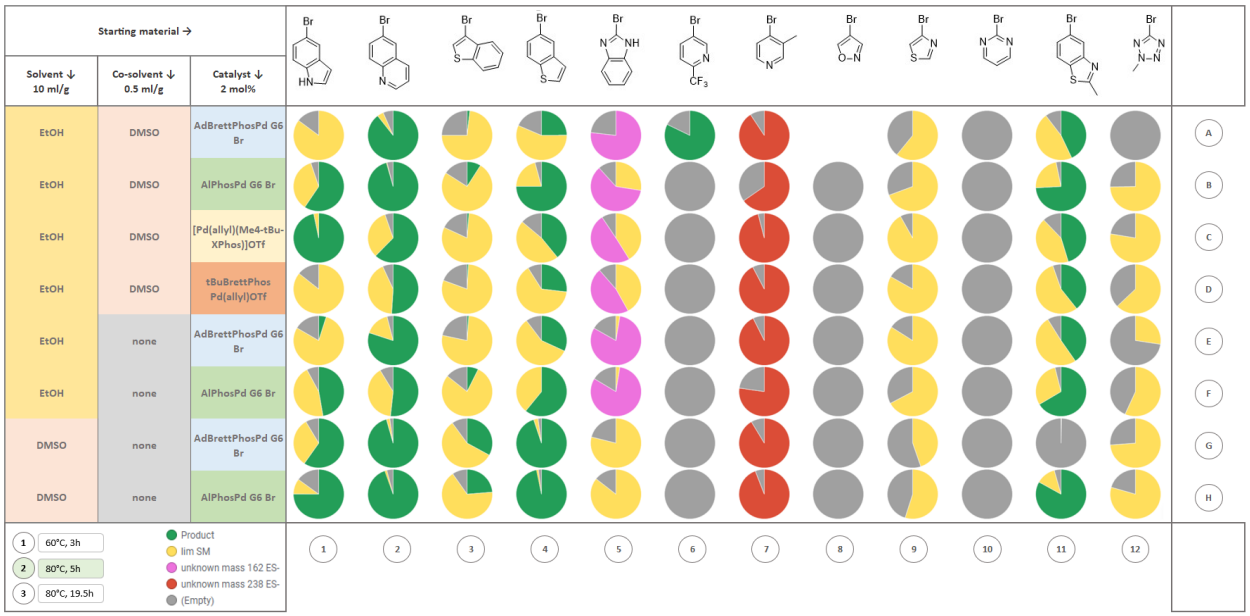


Figure S21. Results of plate 7, sample 2 taken after stirring at 5 h, 80 °C.

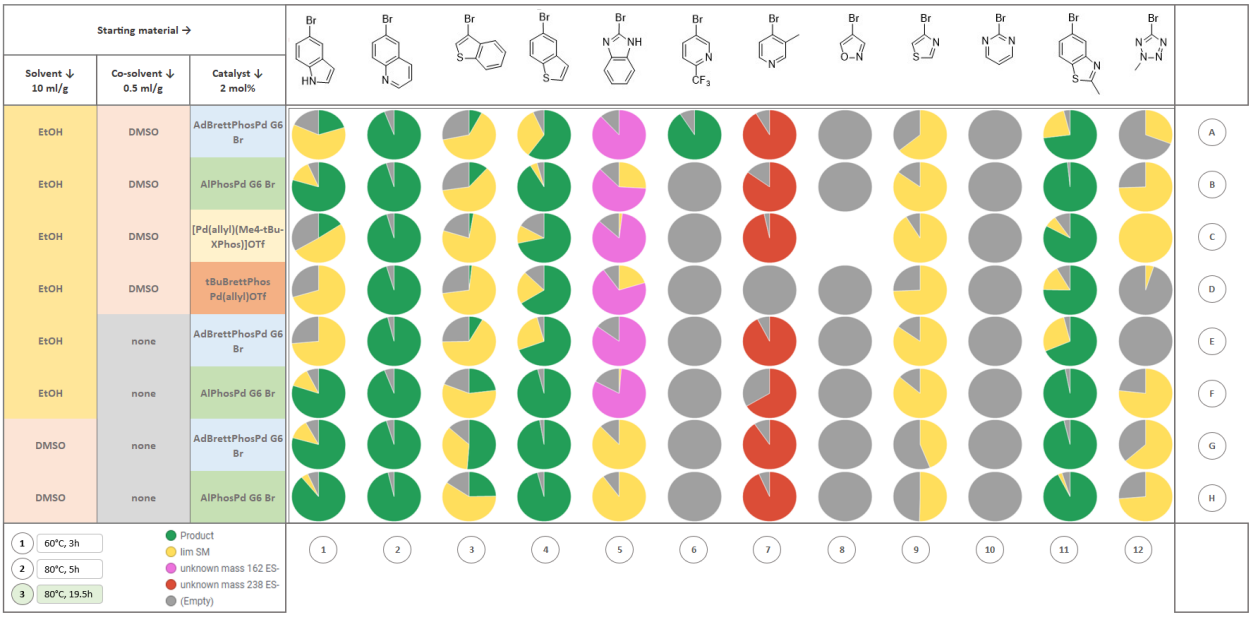


Figure S22. Results of plate 7, sample 3 taken after stirring at 19.5 h, 80 °C.

Plate 8: Scope Set 4

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

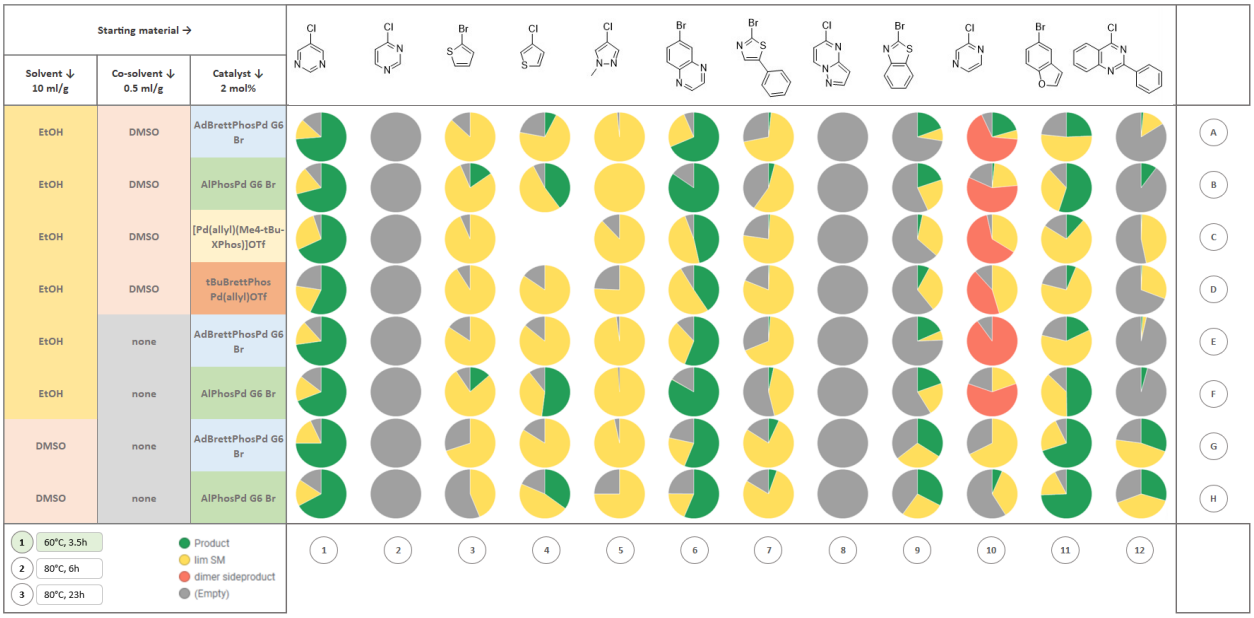


Figure S23. Results of plate 8, sample 1 taken after stirring at 3.5 h, 60 °C.

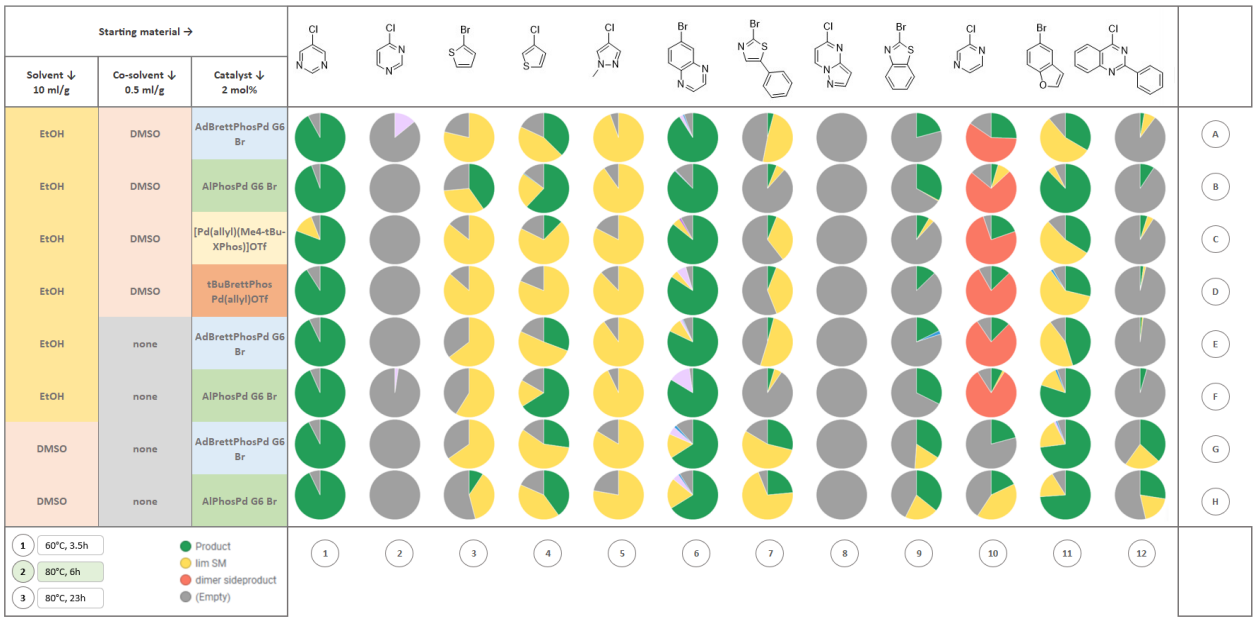


Figure S24. Results of plate 8, sample 2 taken after stirring at 6 h, 80 °C.

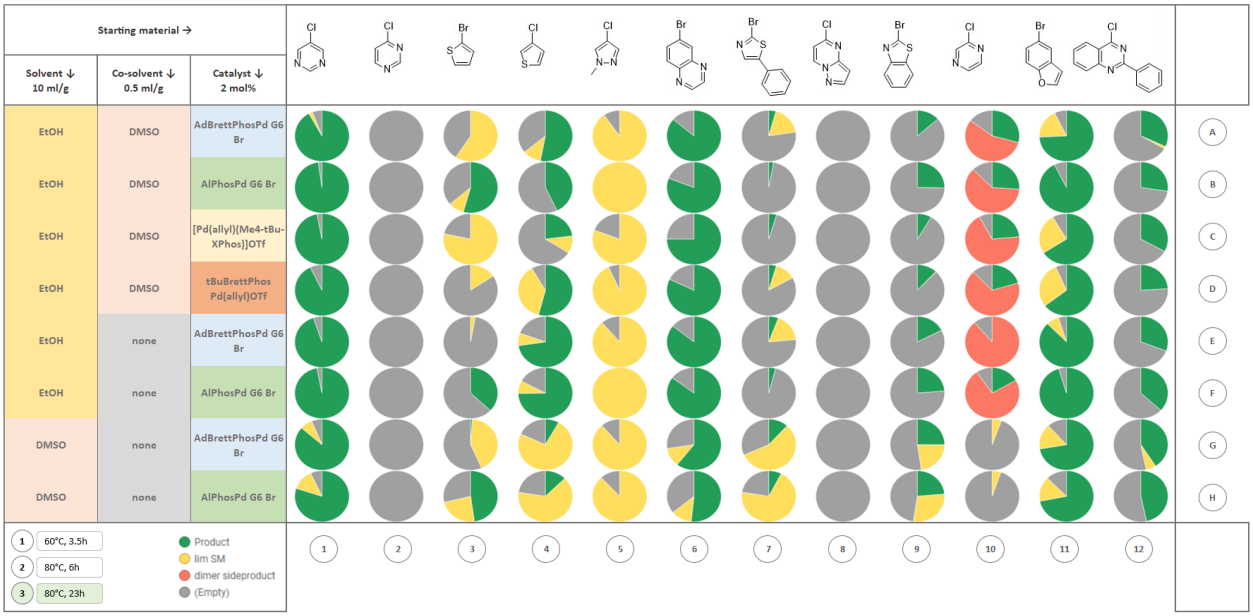


Figure S25. Results of plate 8, sample 3 taken after stirring at 23 h, 80 °C.

Plate 9: Scope Set of functional-group rich substrates

As column 4 contains a previously unpublished substrate, we omit the results here.

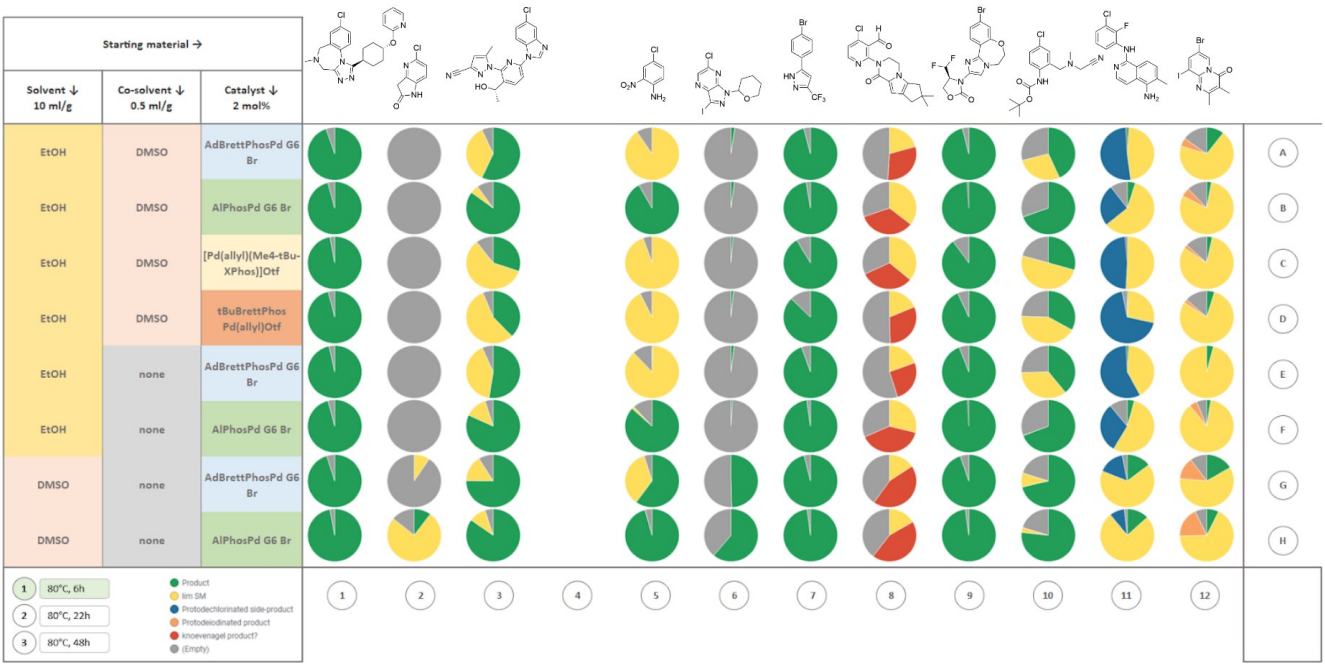


Figure S26. Results of plate 9, sample 1 taken after stirring at 6 h, 80 °C.

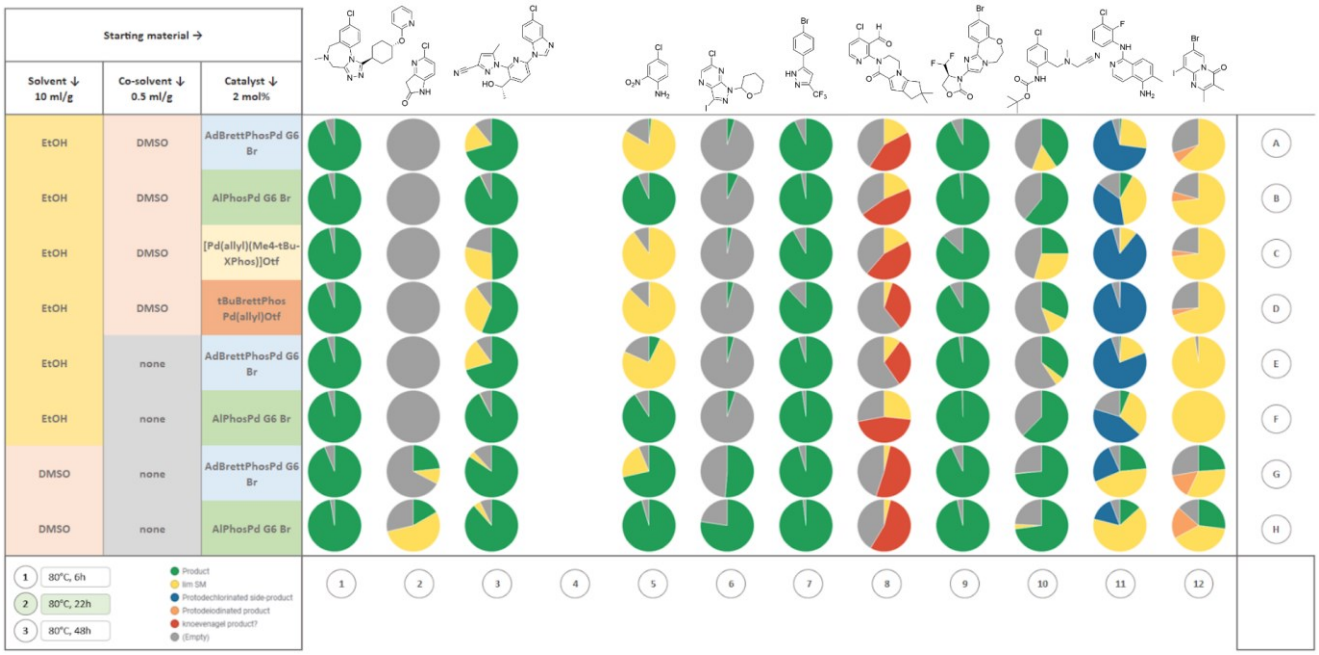


Figure S27. Results of plate 9, sample 2 taken after stirring at 22 h, 80 °C.

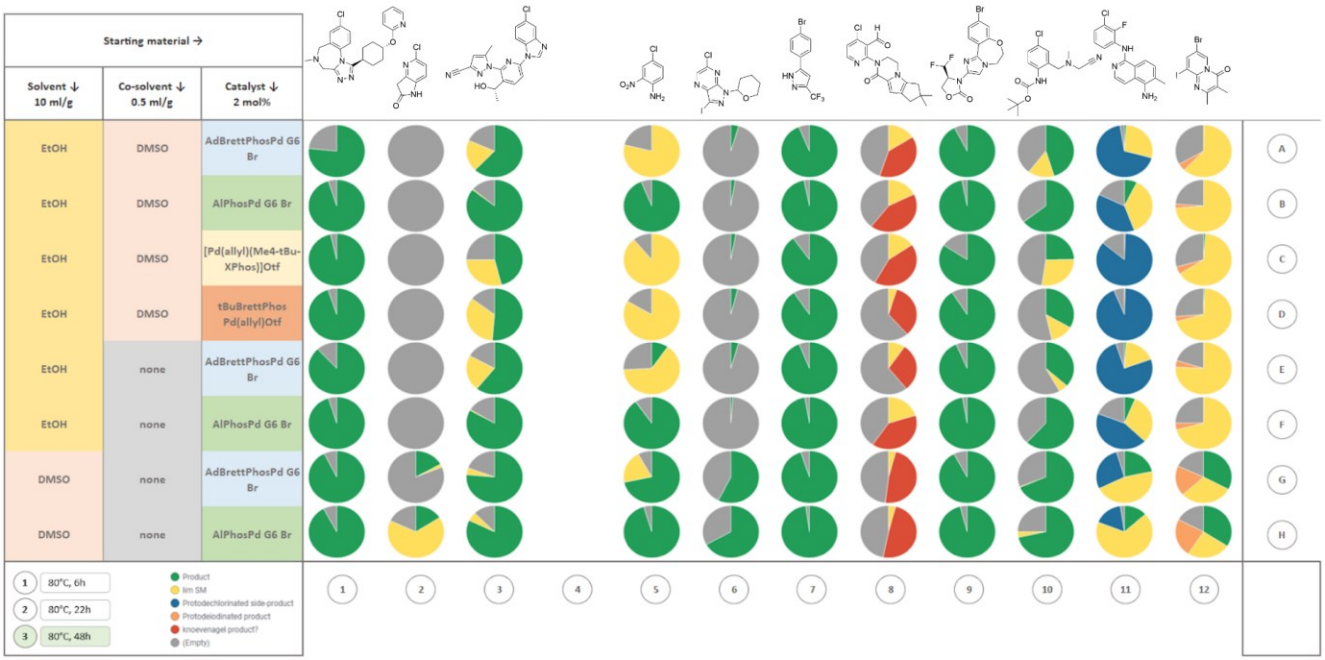


Figure S28. Results of plate 9, sample 3 taken after stirring at 48 h, 80 °C.

Plate 10: Condition Refinement

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

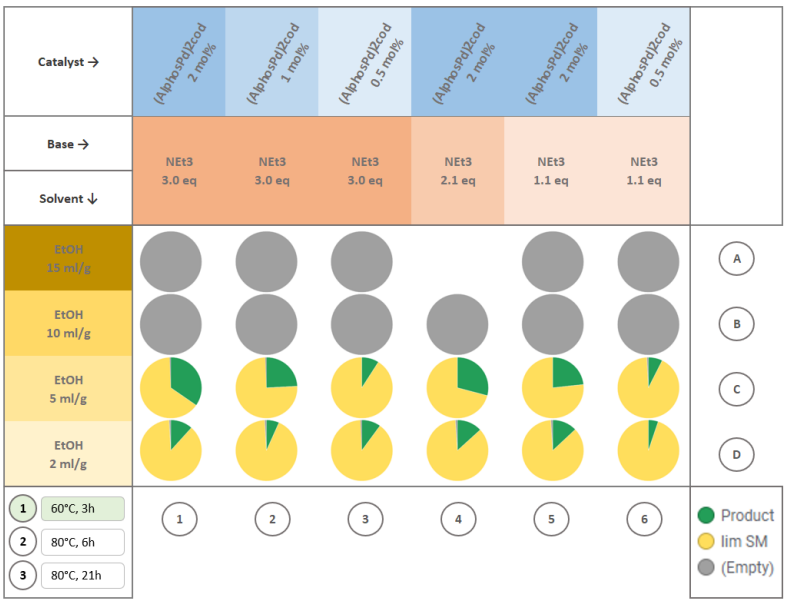


Figure S29. Results of plate 10, sample 1 taken after stirring at 3 h, 60 °C.

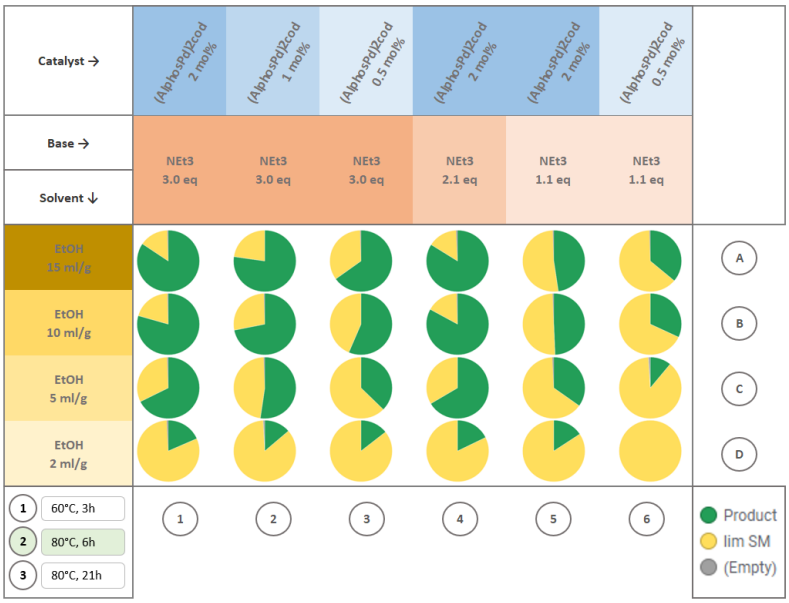


Figure S30. Results of plate 10, sample 2 taken after stirring at 6 h, 80 °C.

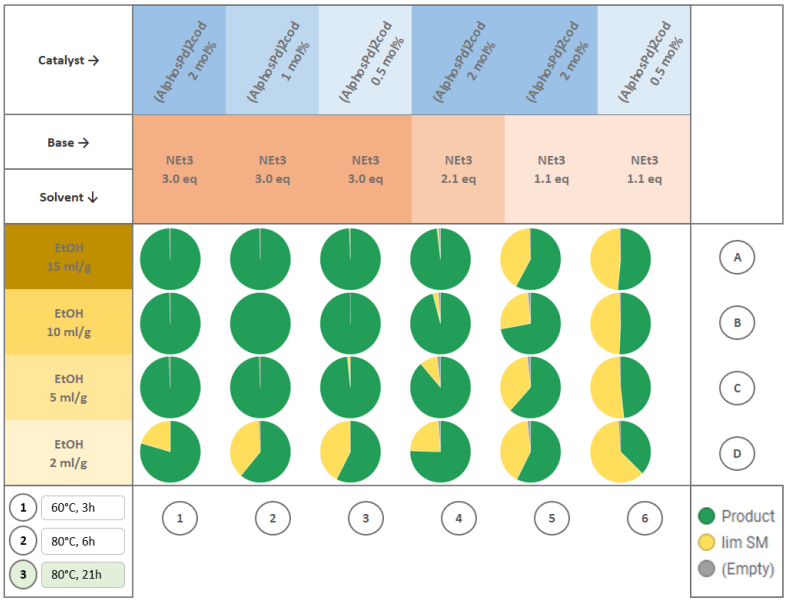


Figure S31. Results of plate 10, sample 3 taken after stirring at 21 h, 80 °C.

4. Arylation of Meldrum's Acid

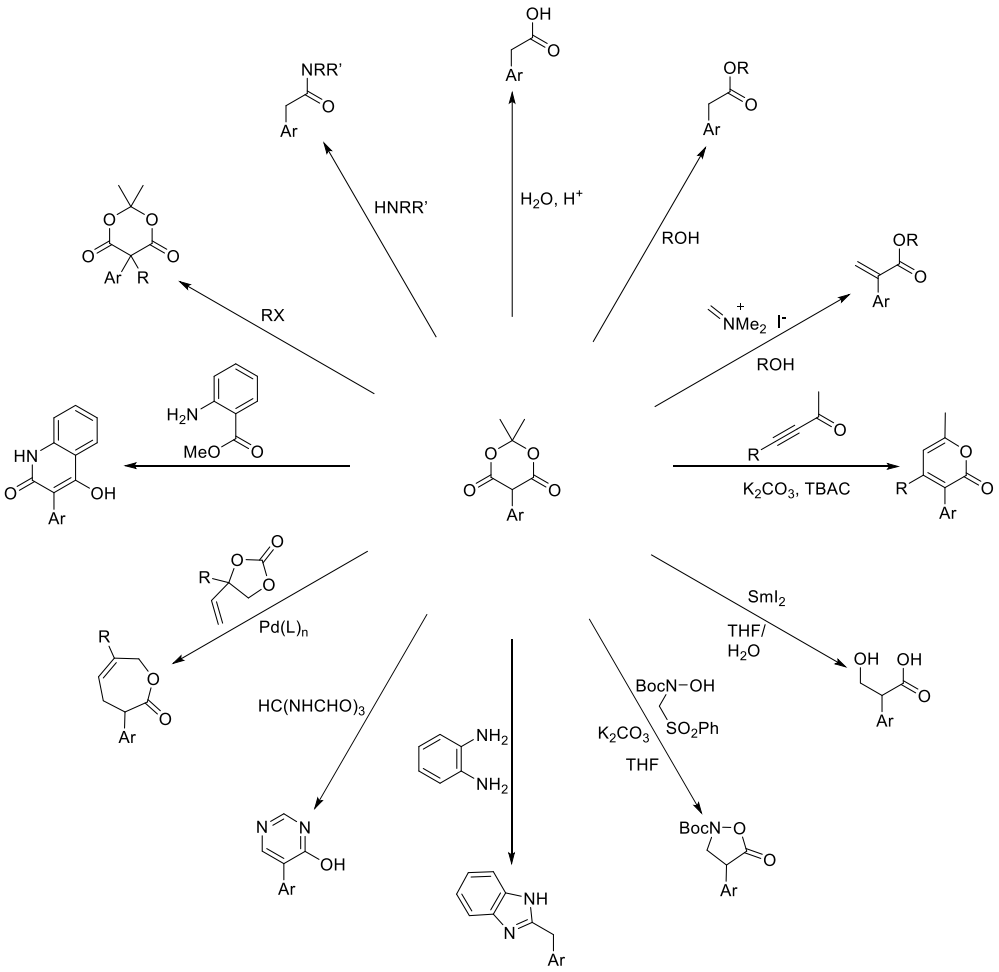


Figure S32. Structural motifs accessible from aryl Meldrum's acids.

This reaction was selected as the model reaction to study whether the conditions found for the arylation of barbituric acid are transferable to Meldrum's acid:

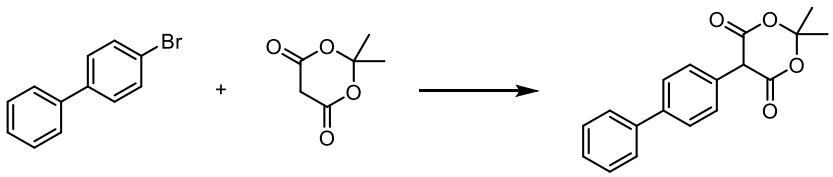


Plate 1: Branch out from what worked for Barbituric Acid

Figure S33. Results of plate 1, sample 1 taken after stirring at 3h, 60 °C

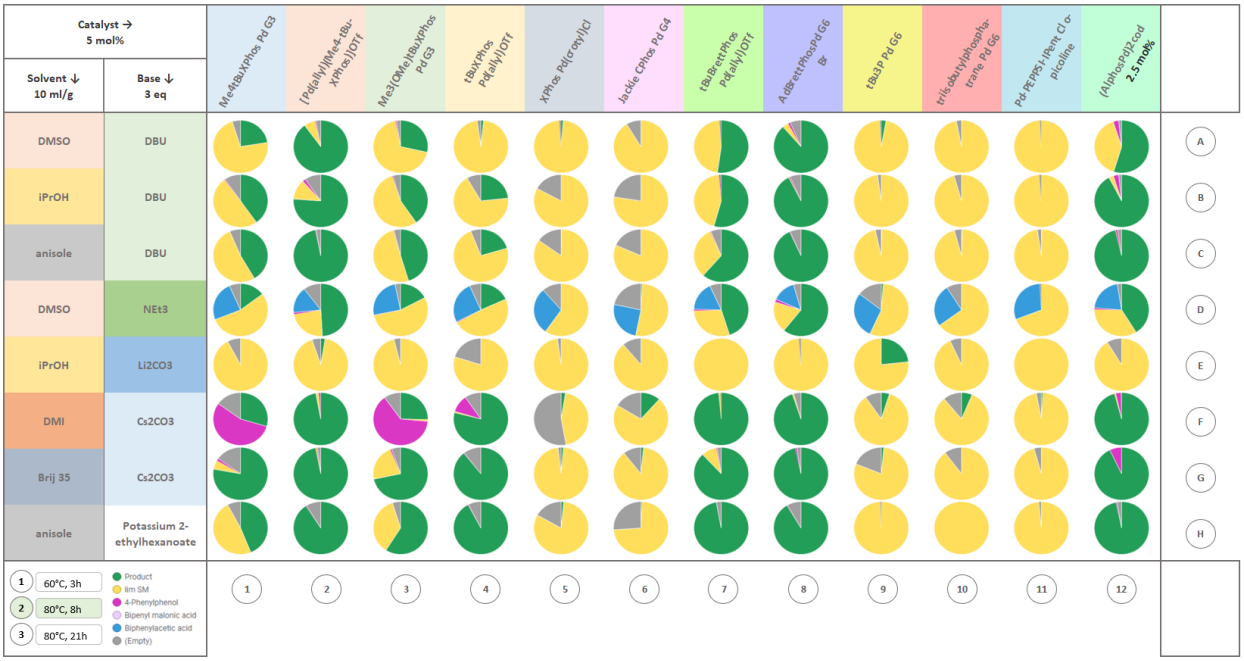


Figure S34. Results of plate 1, sample 2 taken after stirring at 8h, 80 °C

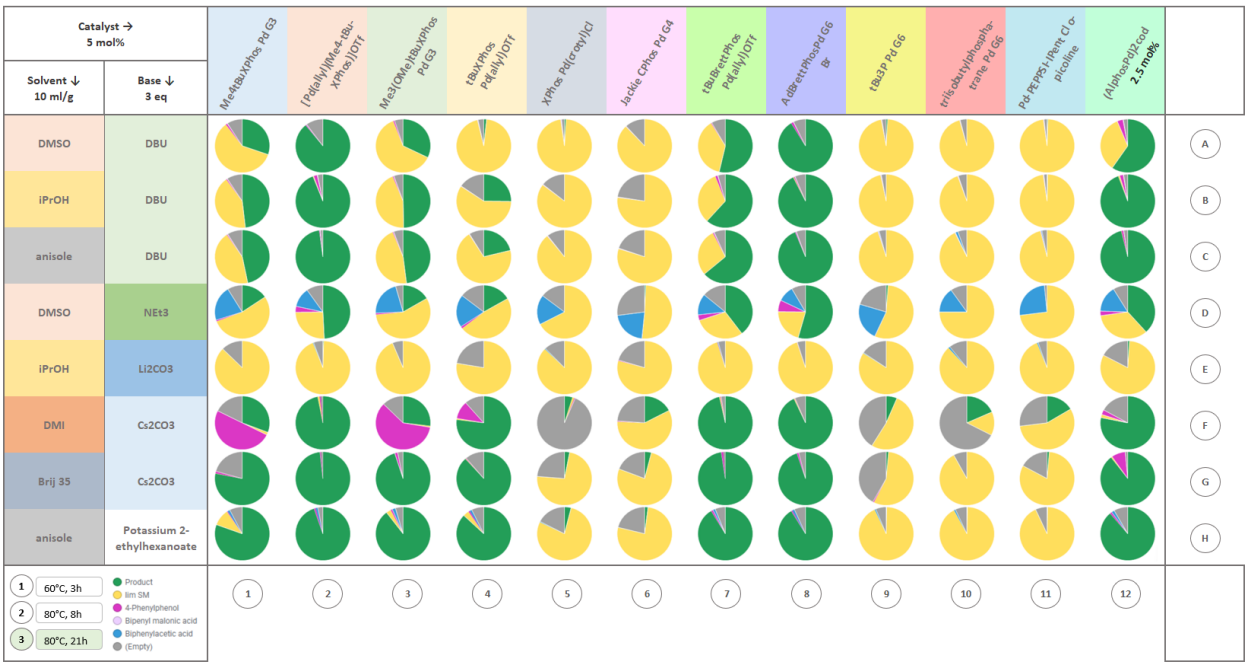


Figure S35. Results of plate 1, sample 3 taken after stirring at 21h, 80 °C

Plate 2: Refinement

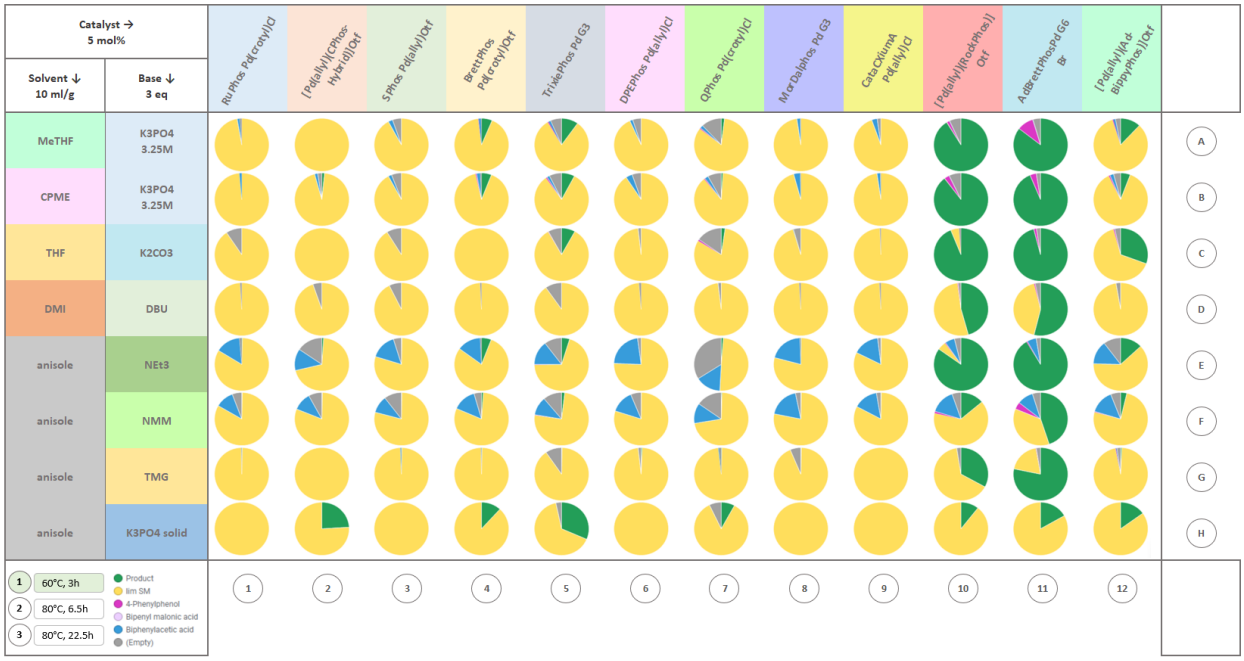


Figure S36. Results of plate 2, sample 1 taken after stirring at 3h, 60 °C

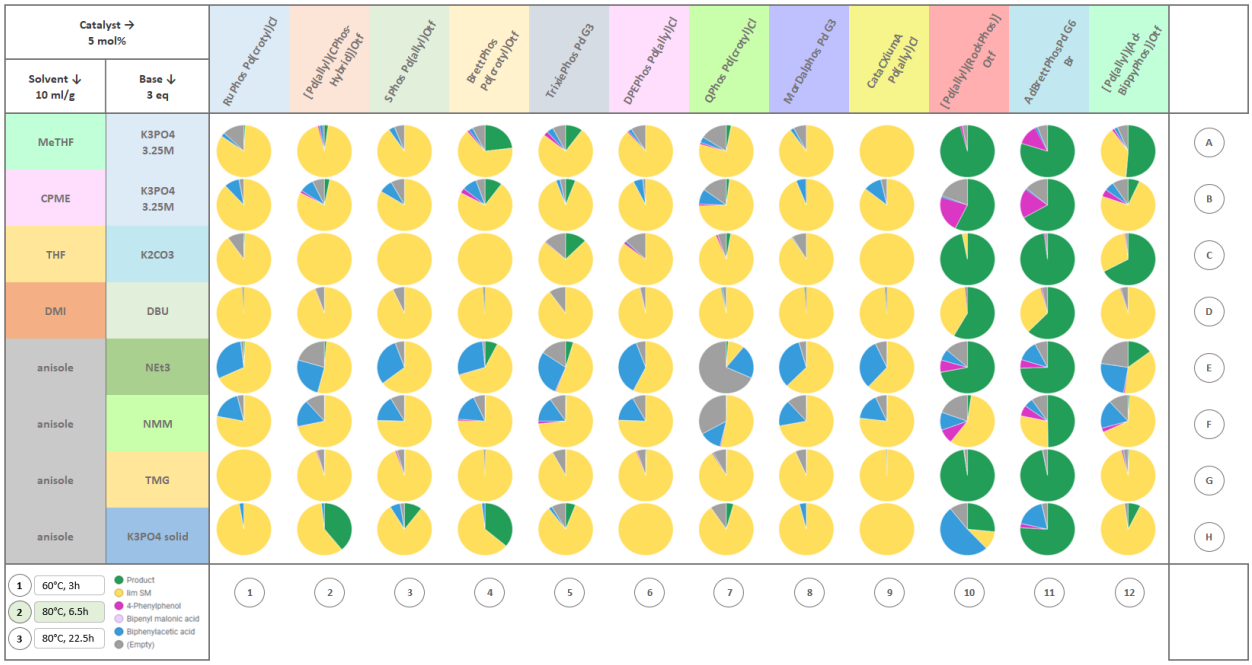


Figure S37. Results of plate 2, sample 2 taken after stirring at 6.5h, 80 °C

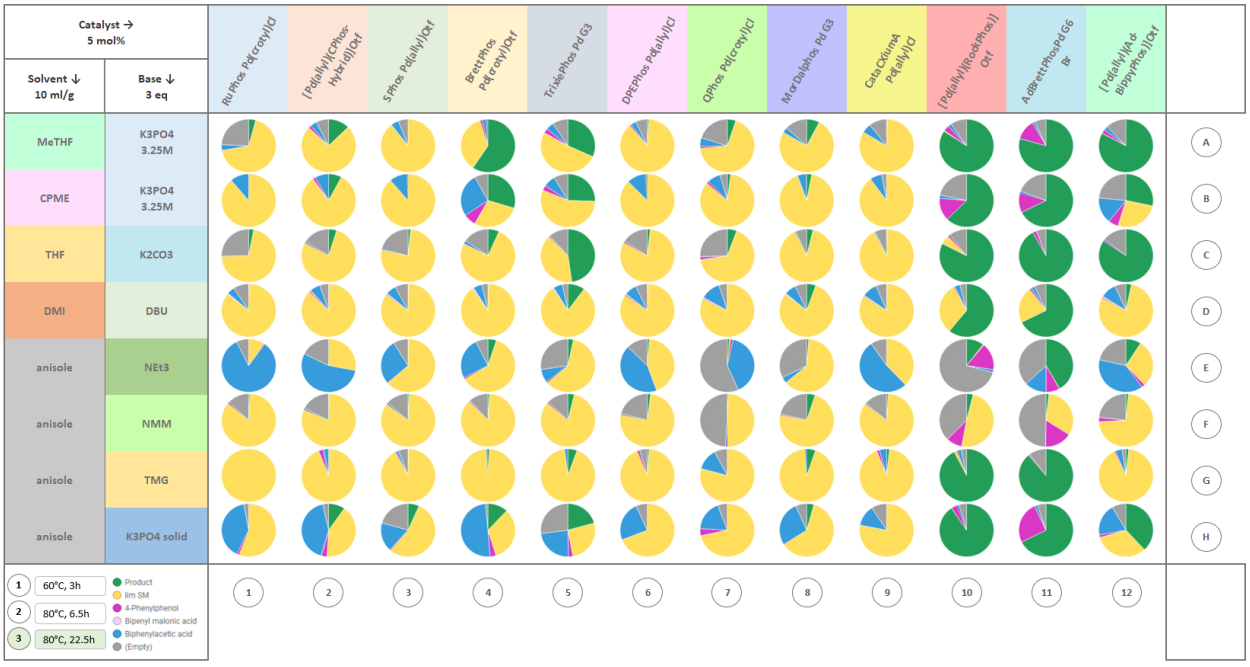


Figure S38. Results of plate 2, sample 3 taken after stirring at 22.5h, 80 °C

Plate 3: Exploration of catalyst space

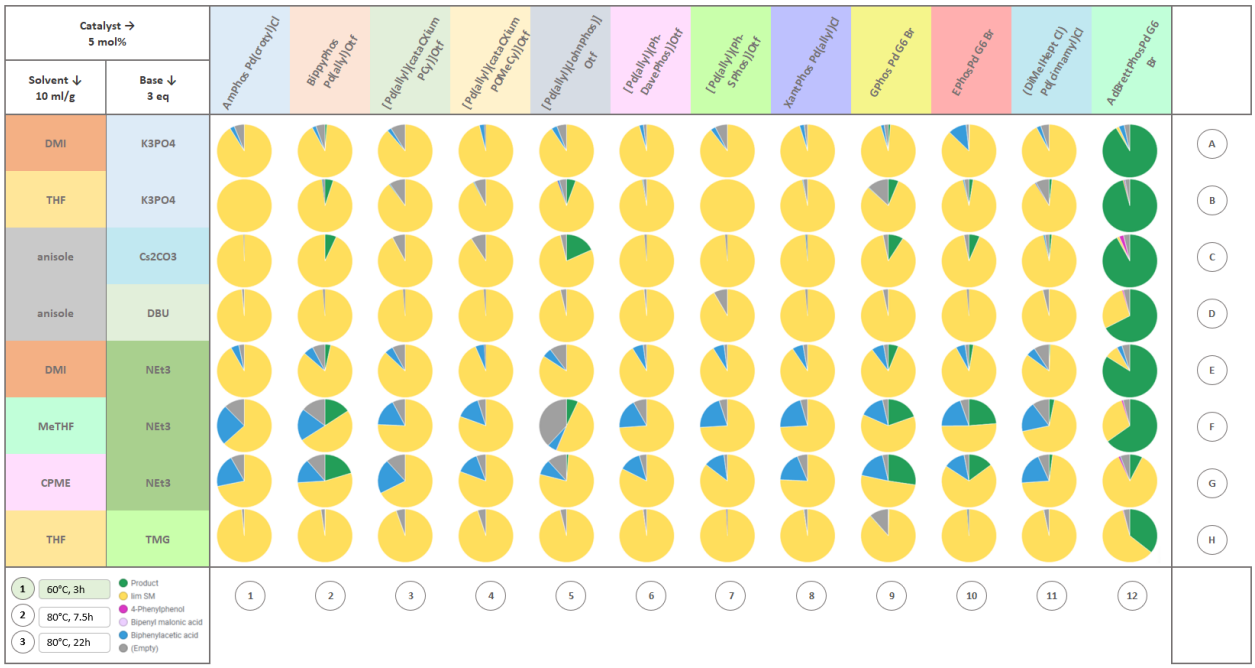


Figure S39. Results of plate 3, sample 1 taken after stirring at 3h, 60 °C

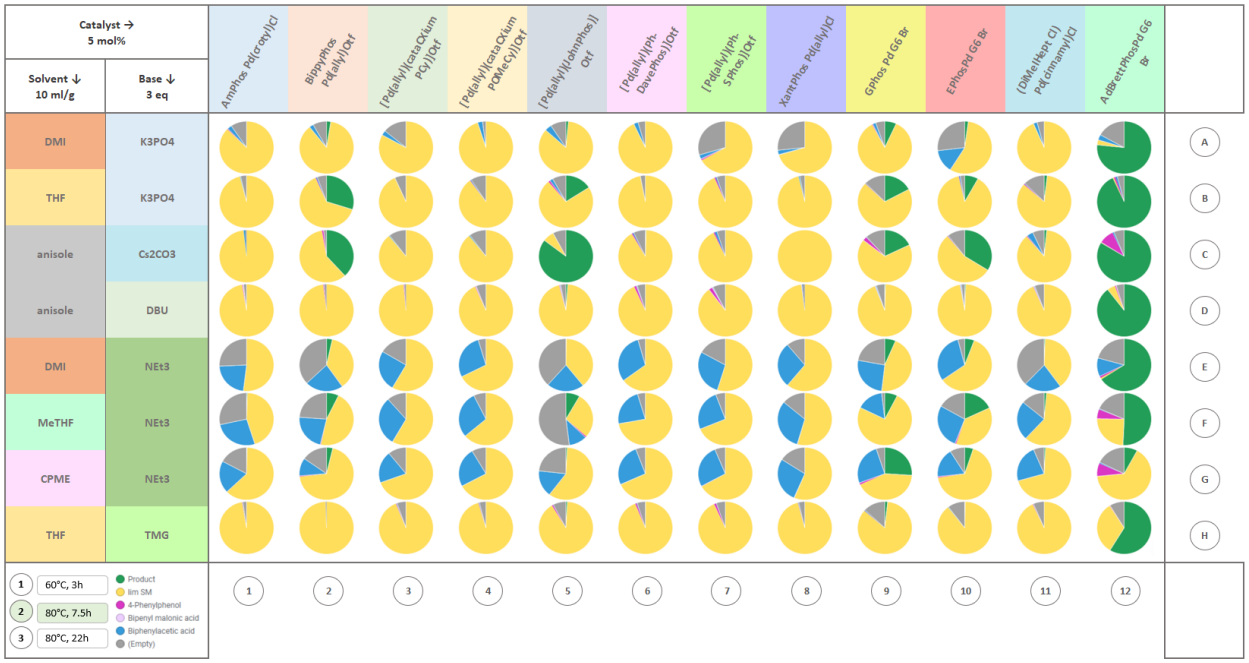


Figure S40. Results of plate 3, sample 2 taken after stirring at 7.5h, 80 °C

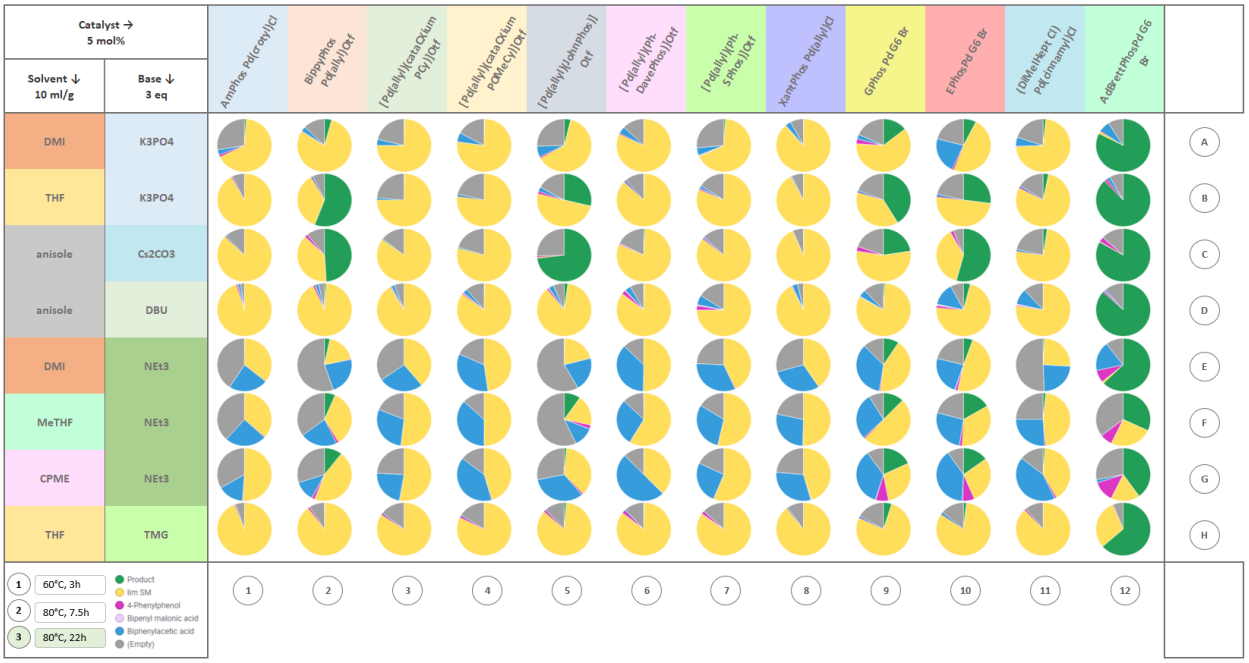


Figure S41. Results of plate 3, sample 3 taken after stirring at 22h, 80 °C

Plate 4: Scope Set 1

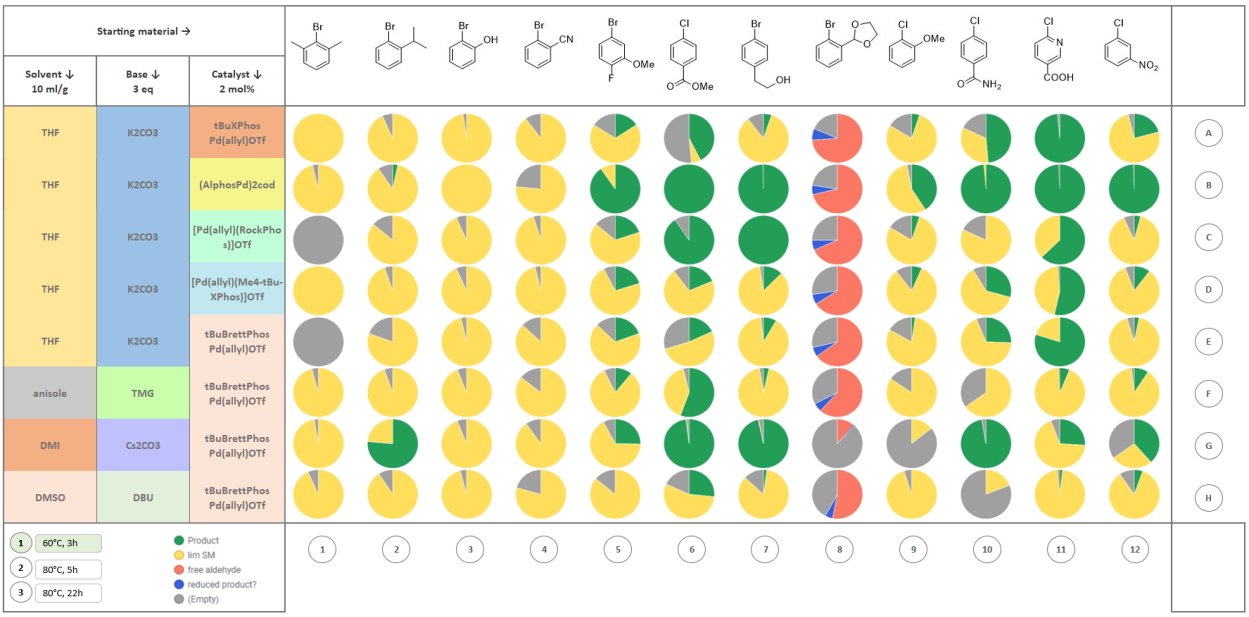


Figure S42. Results of plate 4, sample 1 taken after stirring at 3h, 60 °C

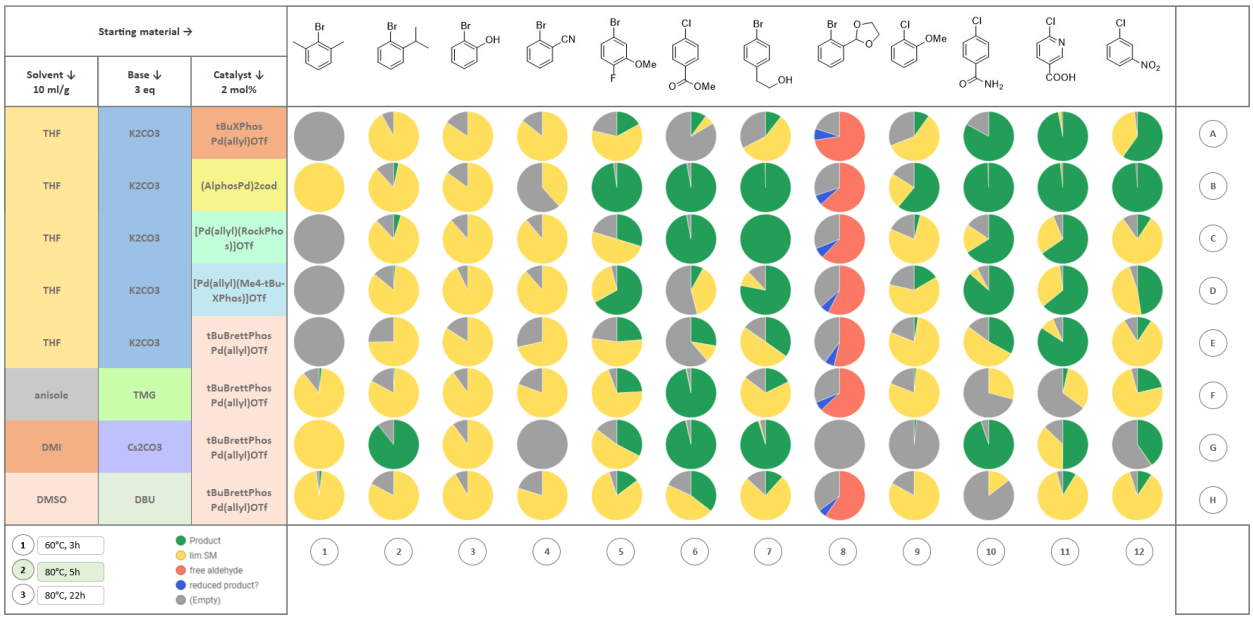


Figure S43. Results of plate 4, sample 2 taken after stirring at 5h, 80 °C

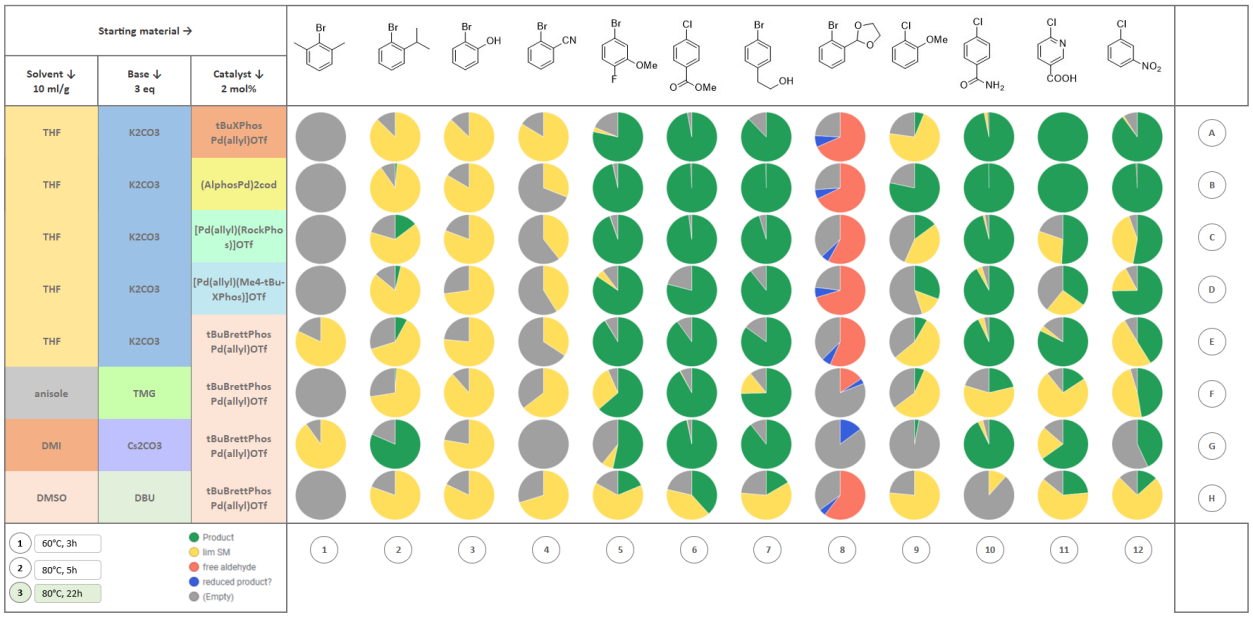


Figure S44. Results of plate 4, sample 3 taken after stirring at 22h, 80 °C

Plate 5: *Ortho* substituents

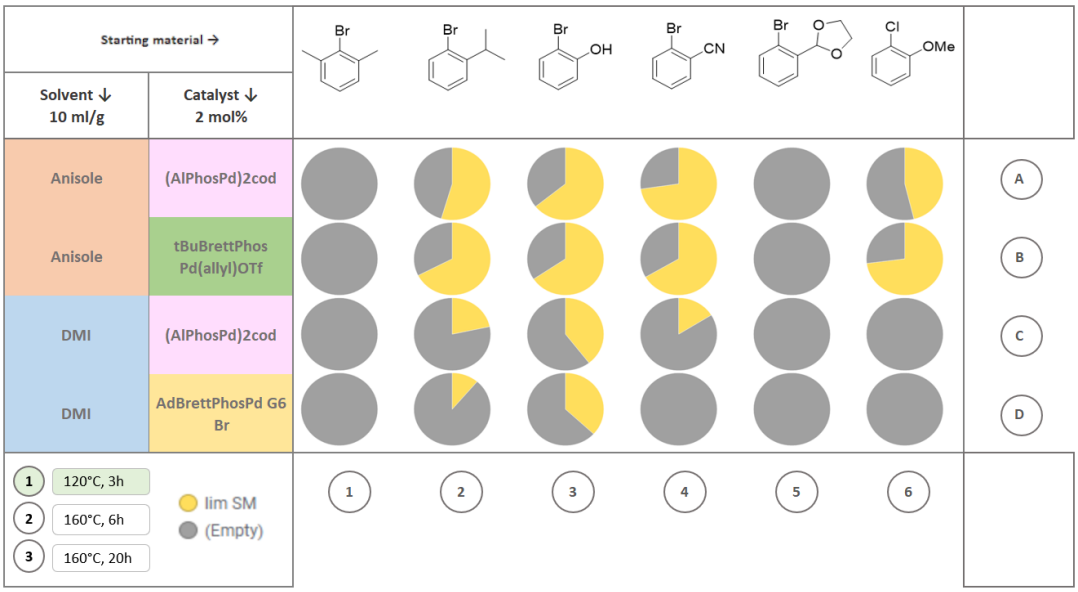


Figure S45. Results of plate 5, sample 1 taken after stirring at 3h, 120 °C. 3 equiv Cs_2CO_3 were used as base, present in all vials.

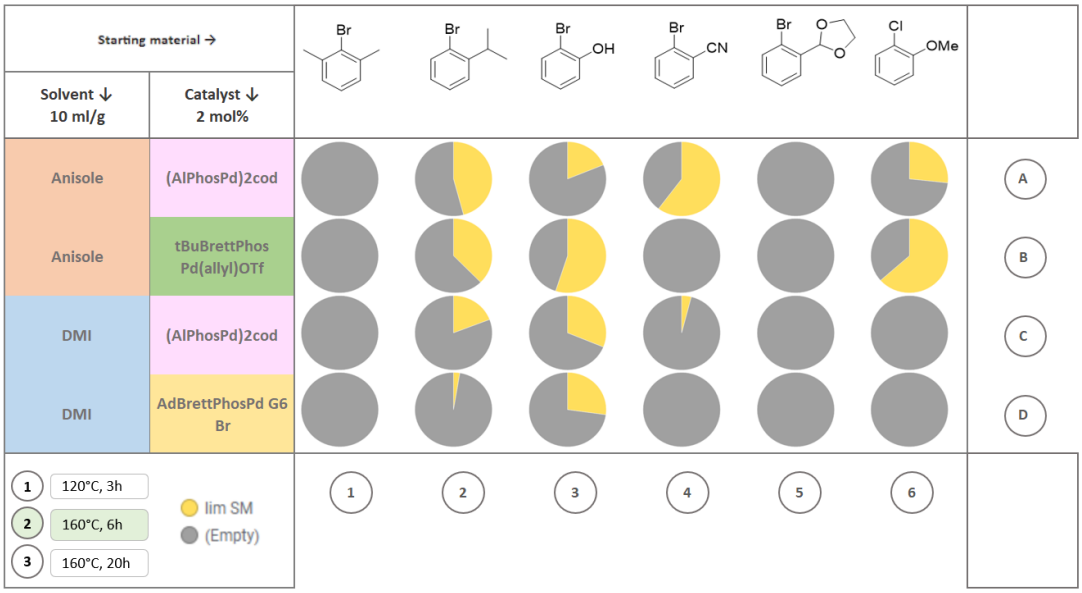


Figure S46. Results of plate 5, sample 2 taken after stirring at 6h, 160 °C

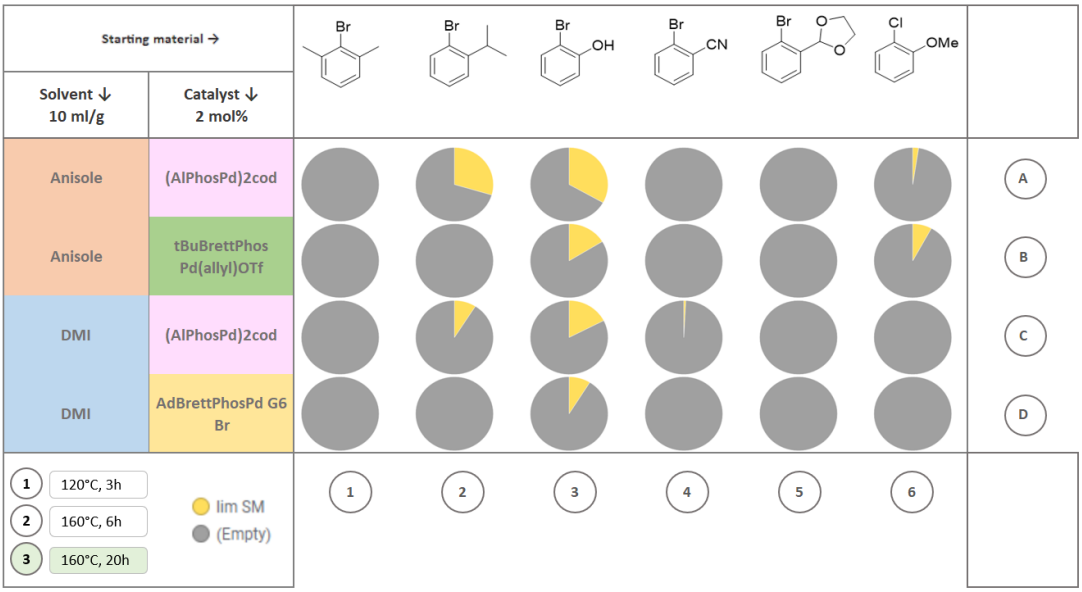


Figure S47. Results of plate 5, sample 3 taken after stirring at 20h, 160 °C. 3 equiv Cs_2CO_3 were used as base, present in all vials.

No conversion even under forcing conditions, instead decomposition was observed.

Plate 6: Scope Set 2

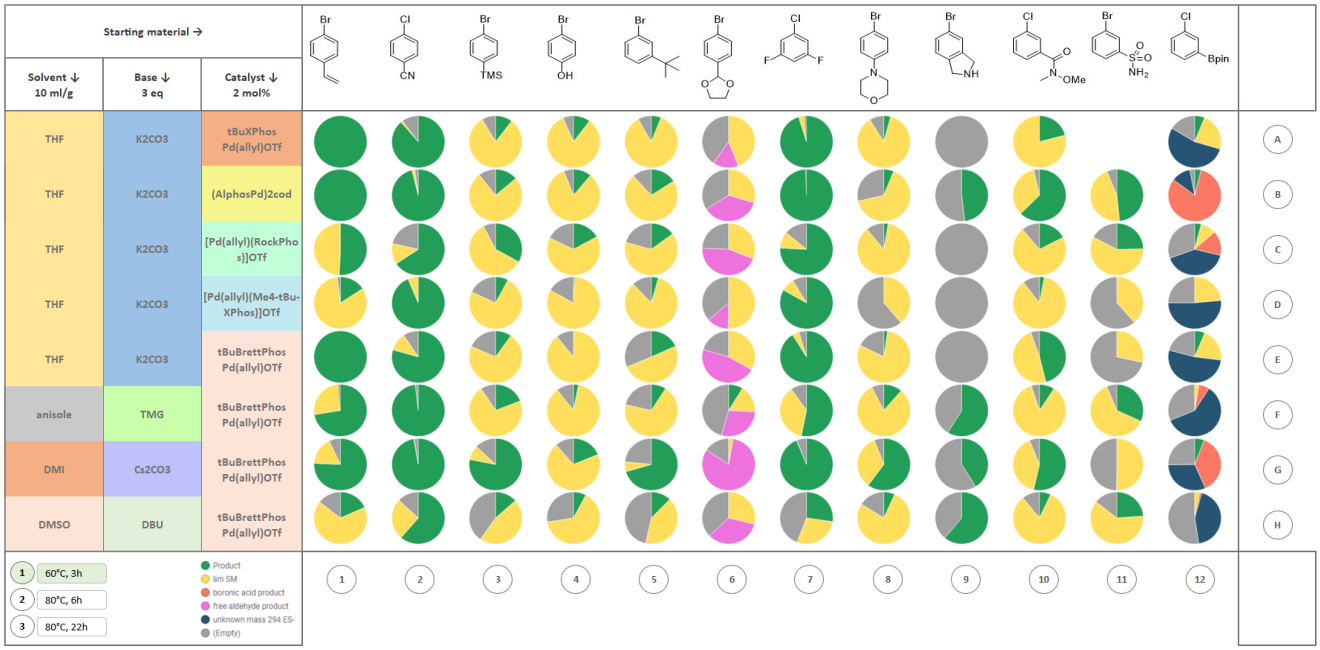


Figure S48. Results of plate 6, sample 1 taken after stirring at 3h, 60 °C

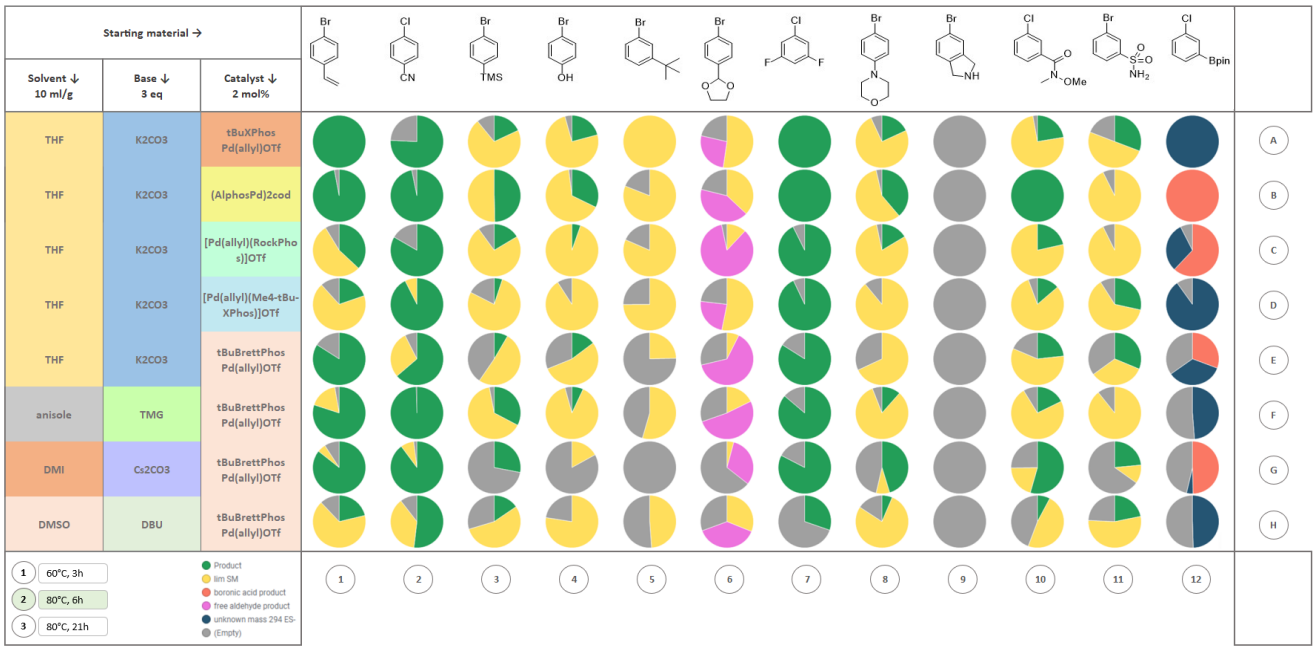


Figure S49. Results of plate 6, sample 2 taken after stirring at 6h, 80 °C

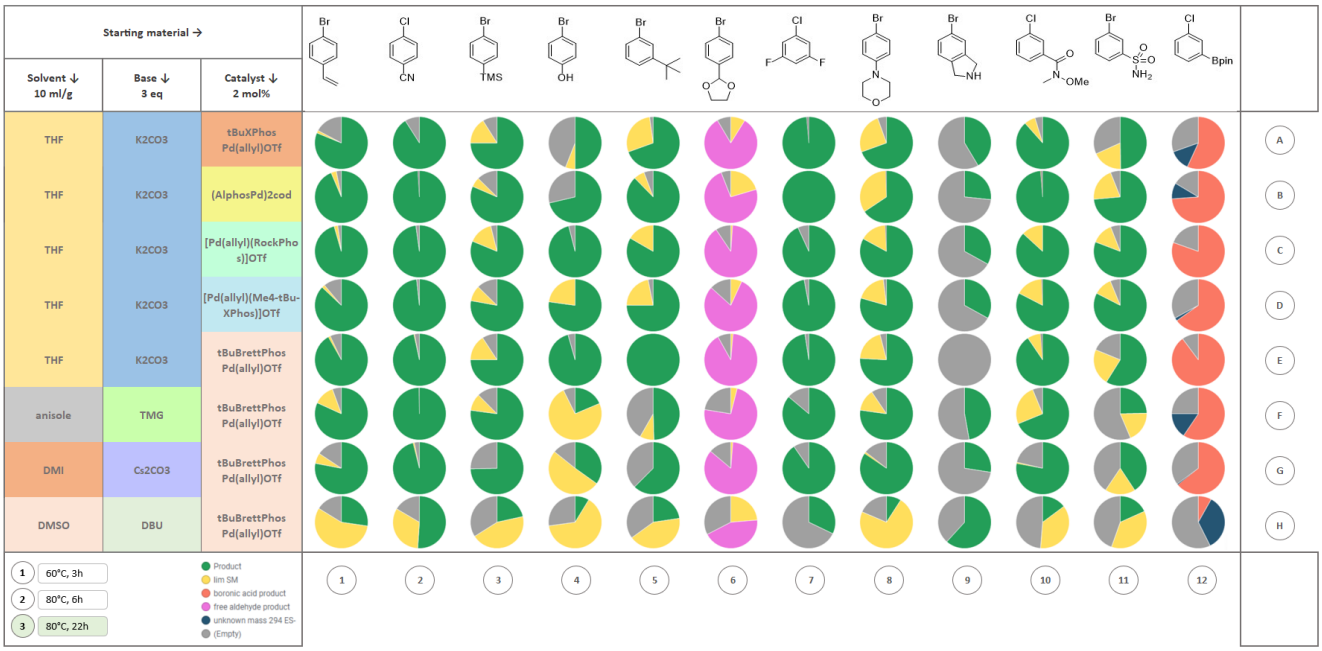


Figure S50. Results of plate 6, sample 3 taken after stirring at 22h, 80 °C

Plate 7: Scope Set 3

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

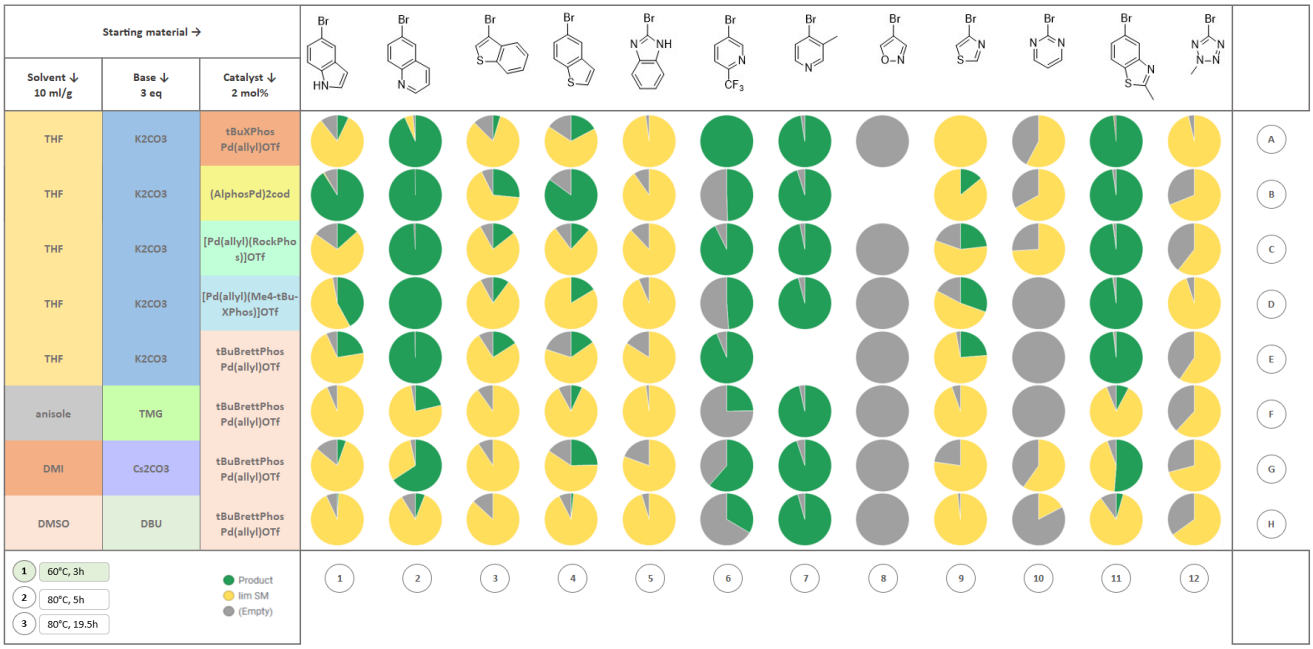


Figure S51. Results of plate 7, sample 1 taken after stirring at 3h, 60 °C

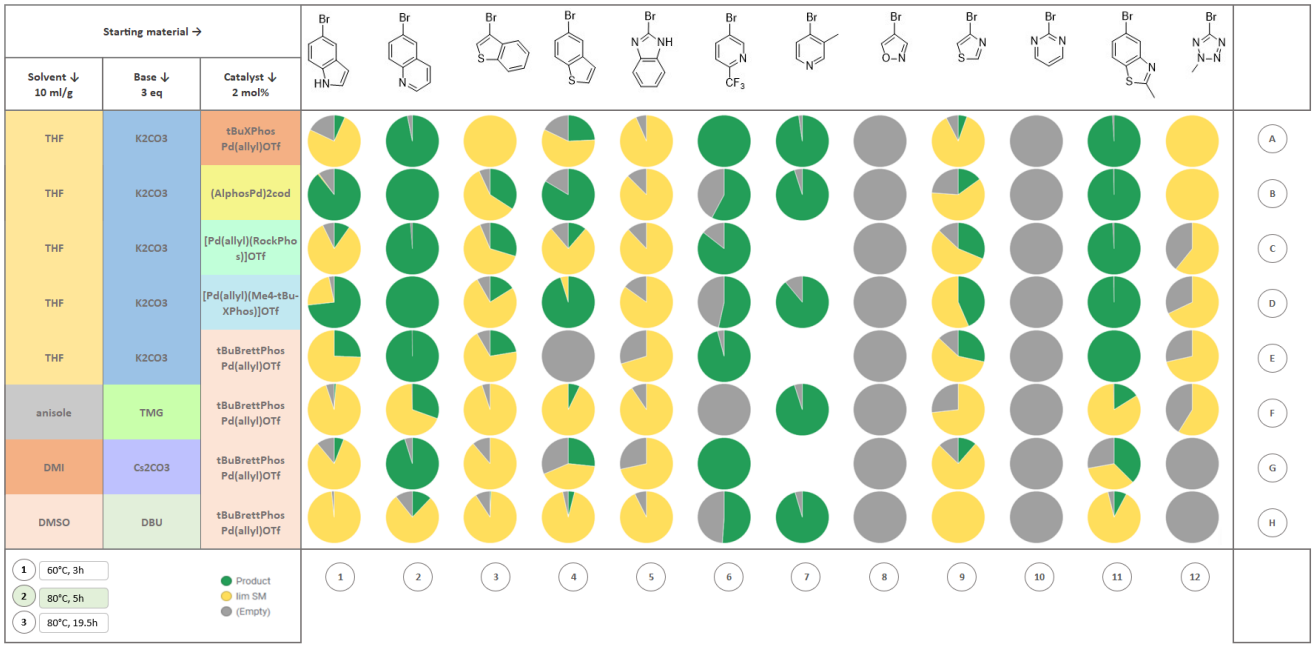


Figure S52. Results of plate 7, sample 2 taken after stirring at 5h, 80 °C

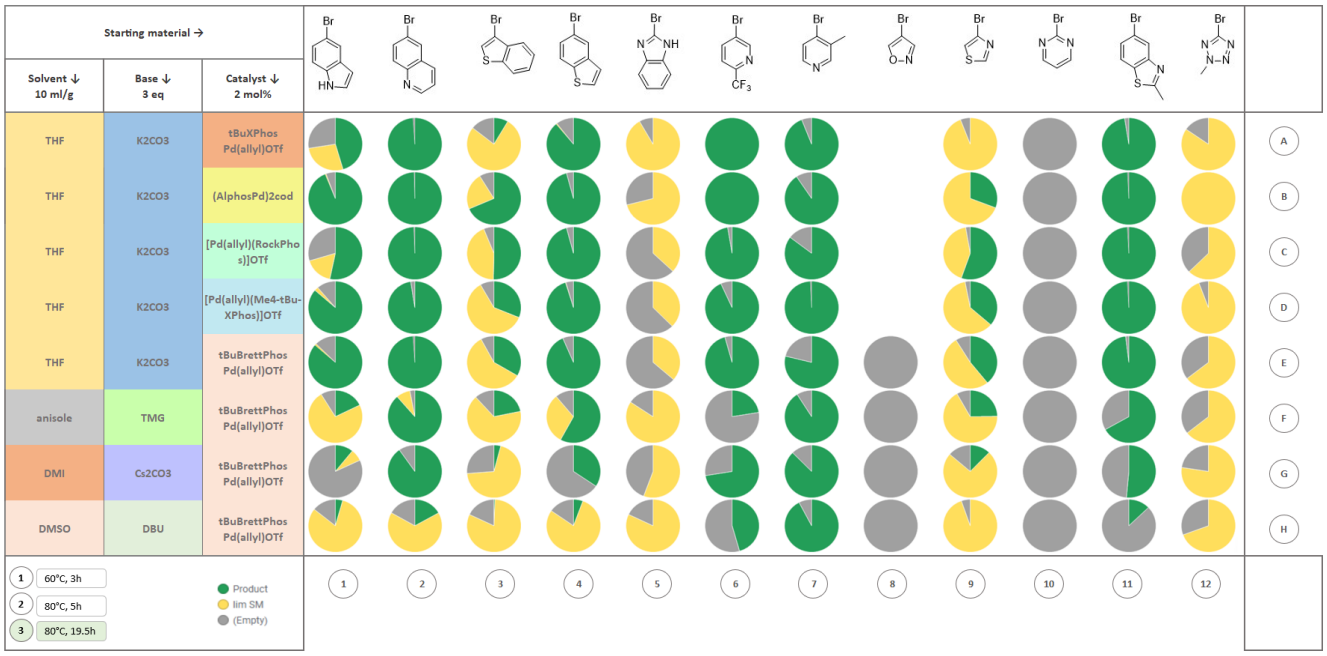


Figure S53. Results of plate 7, sample 3 taken after stirring at 19.5h, 80 °C

Plate 8: Scope Set 4

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

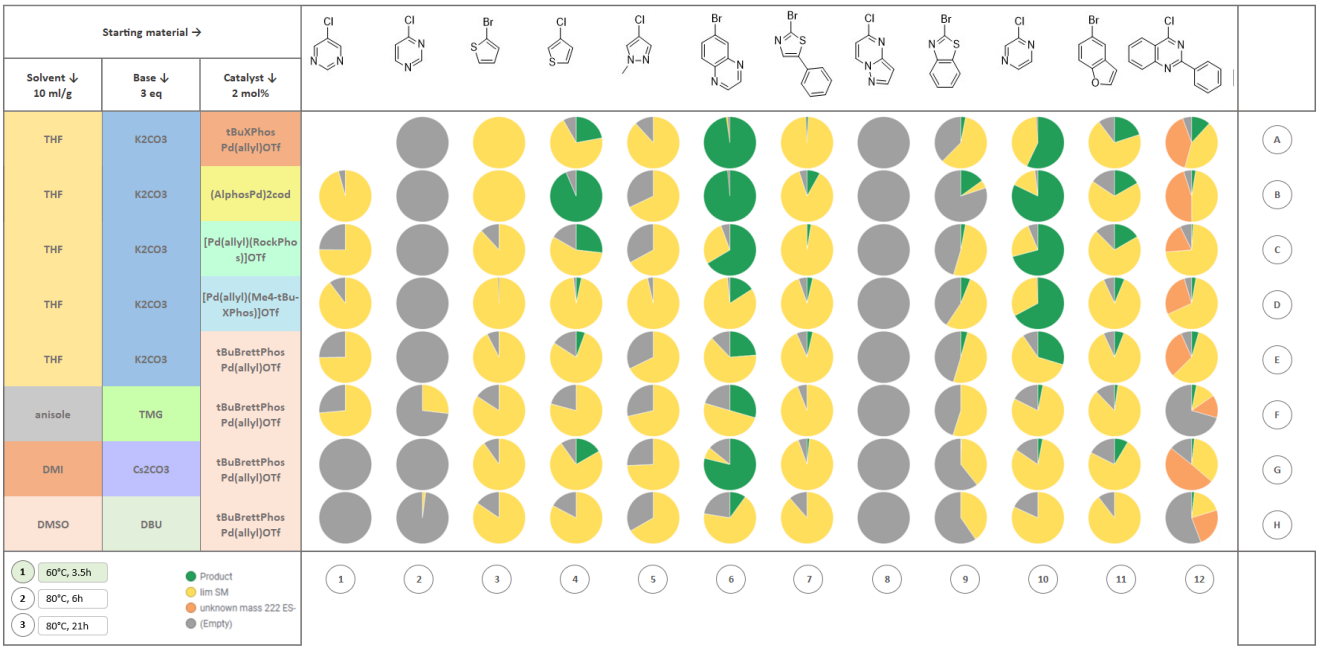


Figure S54. Results of plate 8, sample 3 taken after stirring at 3.5h, 60 °C

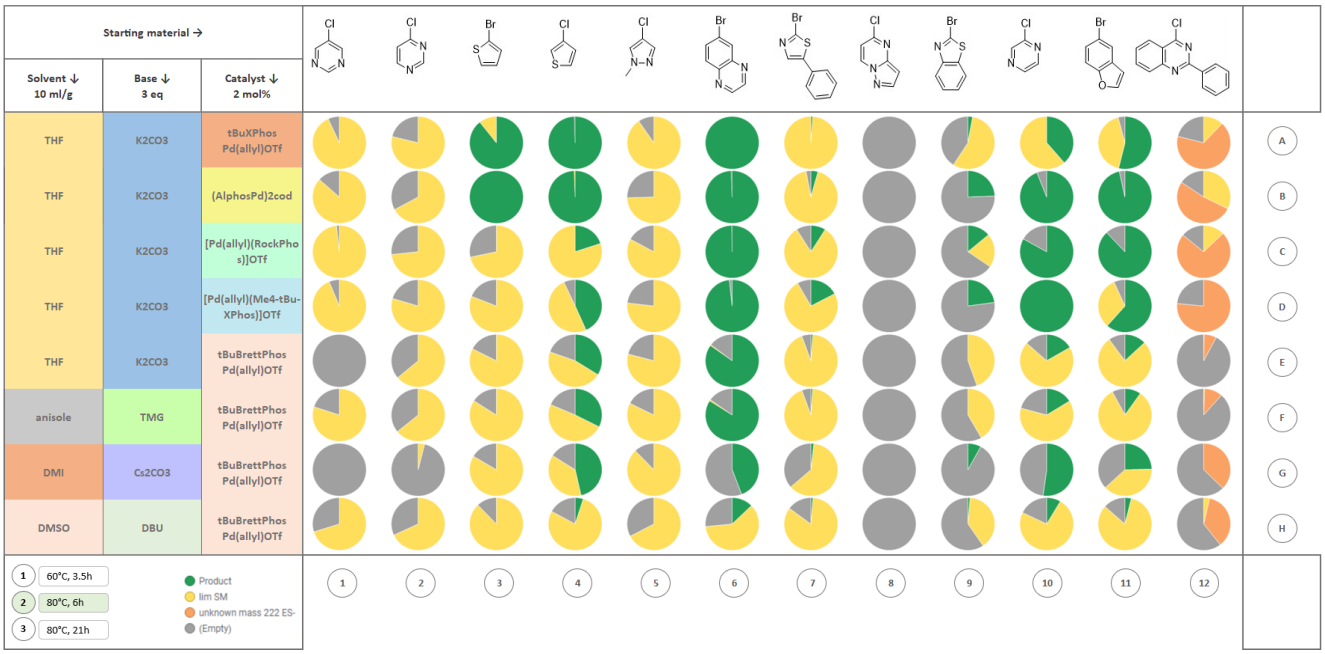


Figure S55. Results of plate 8, sample 2 taken after stirring at 6h, 80 °C

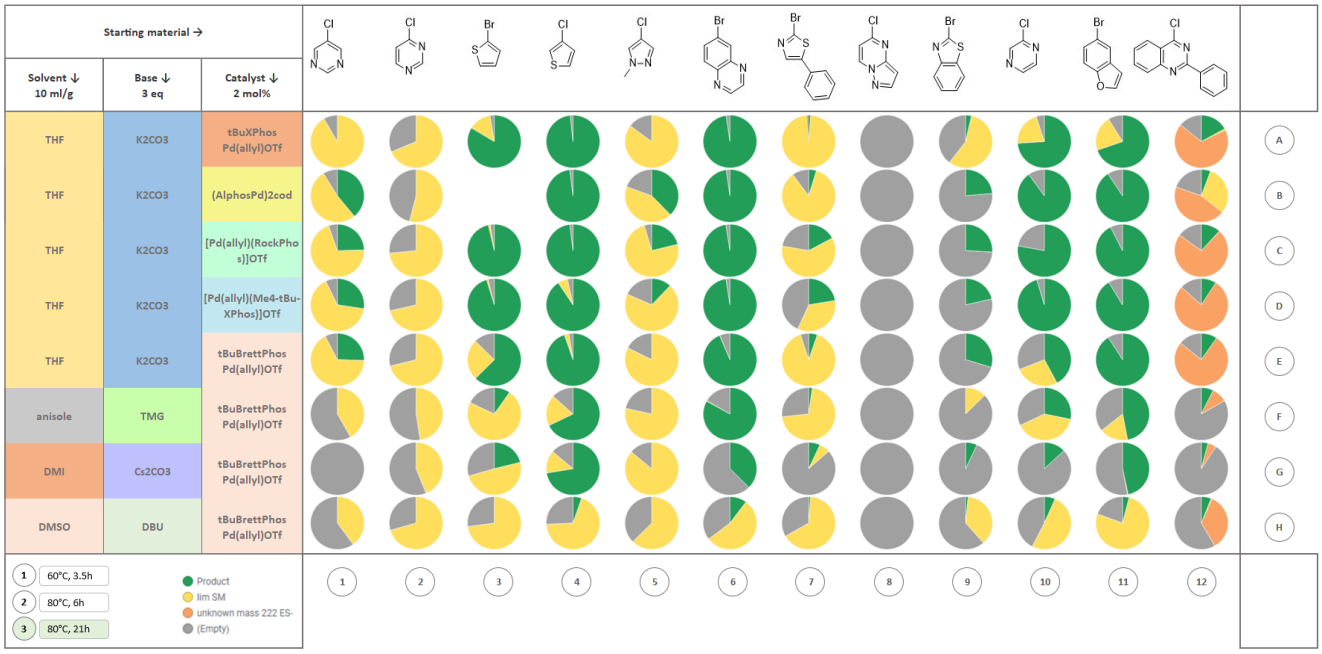


Figure S56. Results of plate 8, sample 3 taken after stirring at 21h, 80 °C

Plate 9: Scope Set more complex Molecules

As column 4 contains a previously unpublished substrate, we omitted the results here.

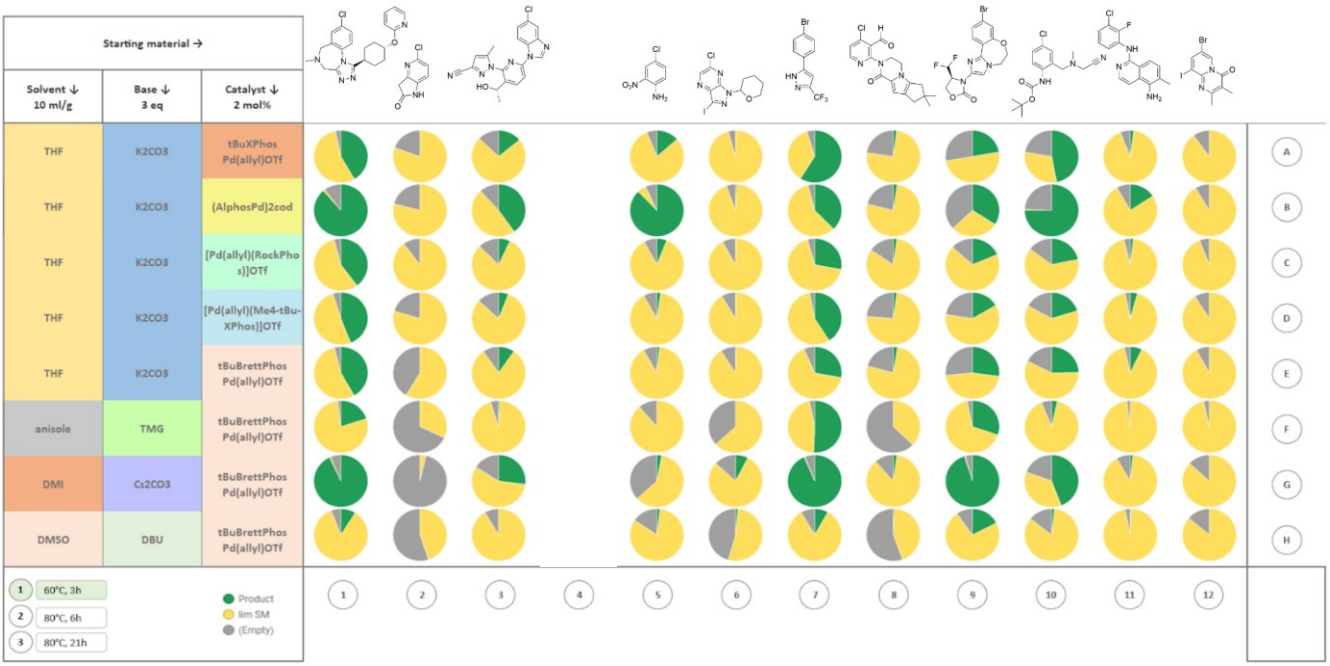


Figure S57. Results of plate 9, sample 1 taken after stirring at 3h, 60 °C

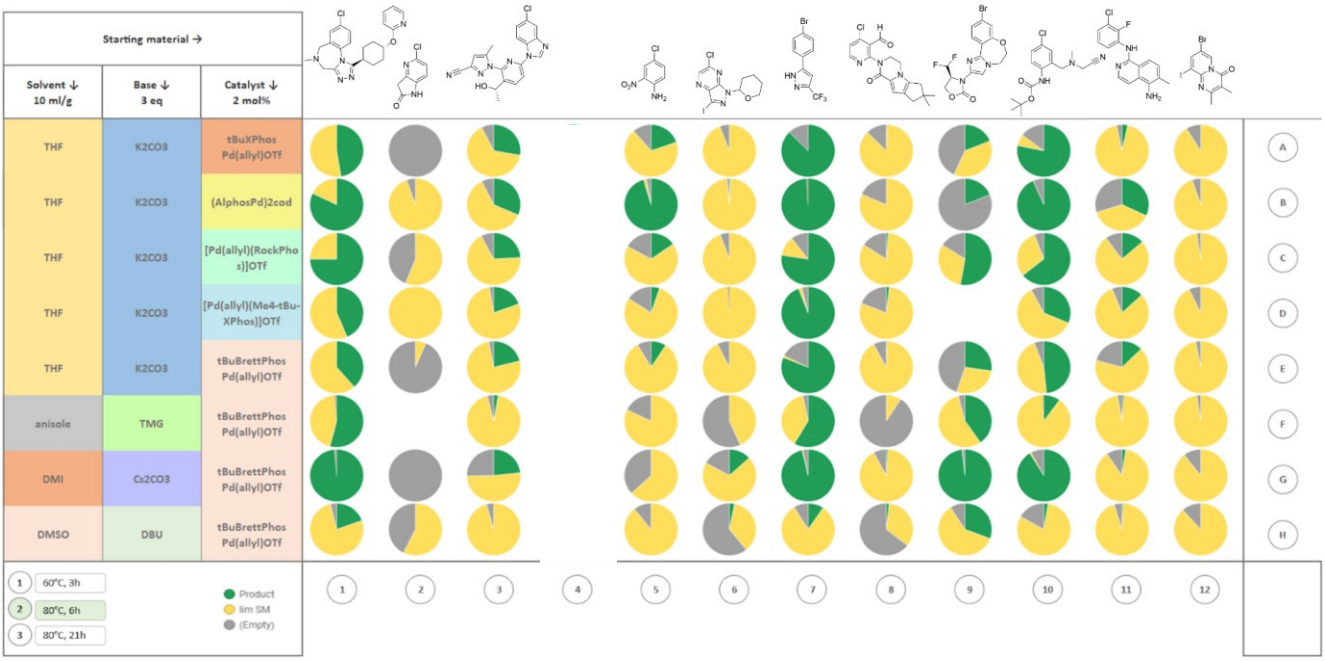


Figure S58. Results of plate 9, sample 2 taken after stirring at 6h, 80 °C

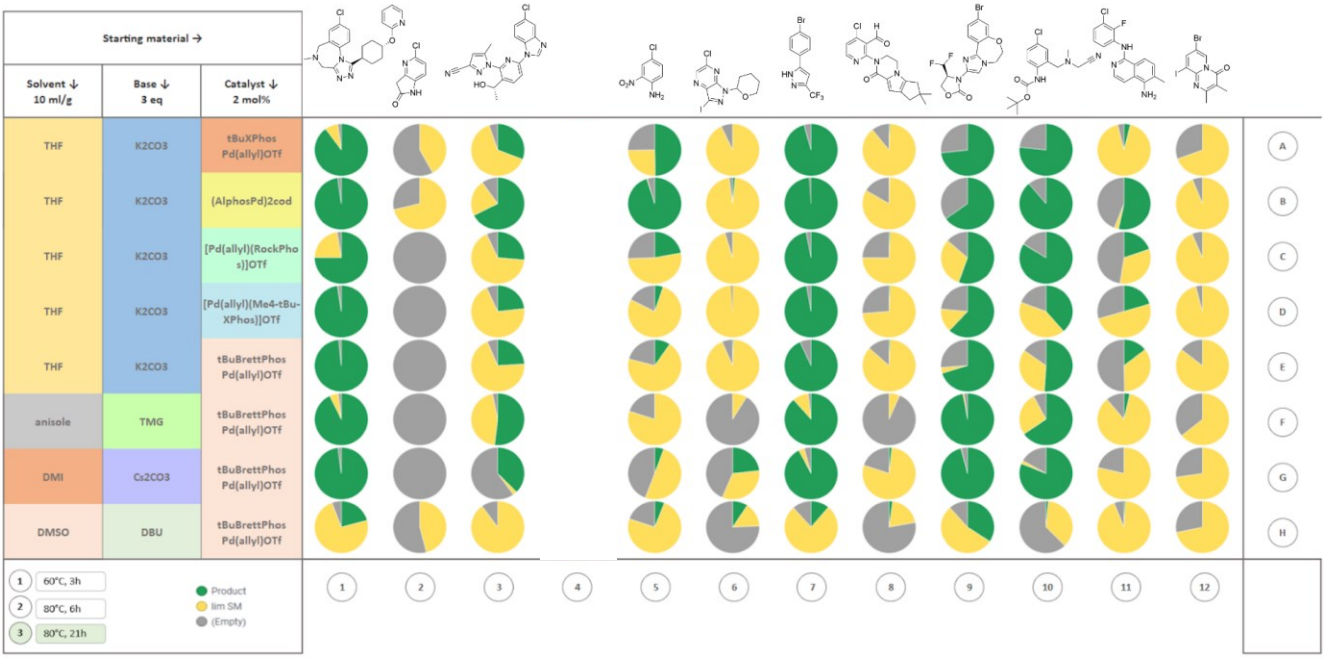


Figure S59. Results of plate 9, sample 3 taken after stirring at 22h, 80 °C

Plate 10: Condition Refinement

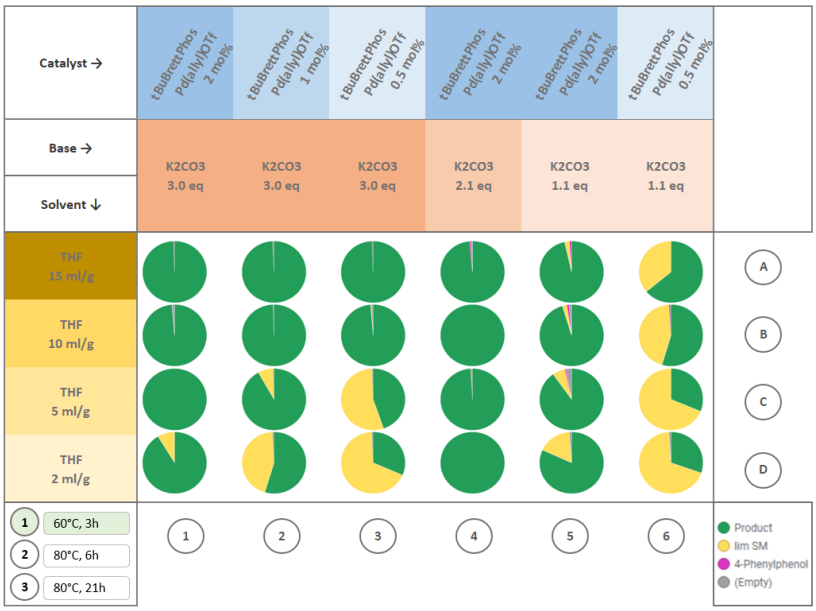


Figure S60. Results of plate 10, sample 1 taken after stirring at 3h, 60 °C

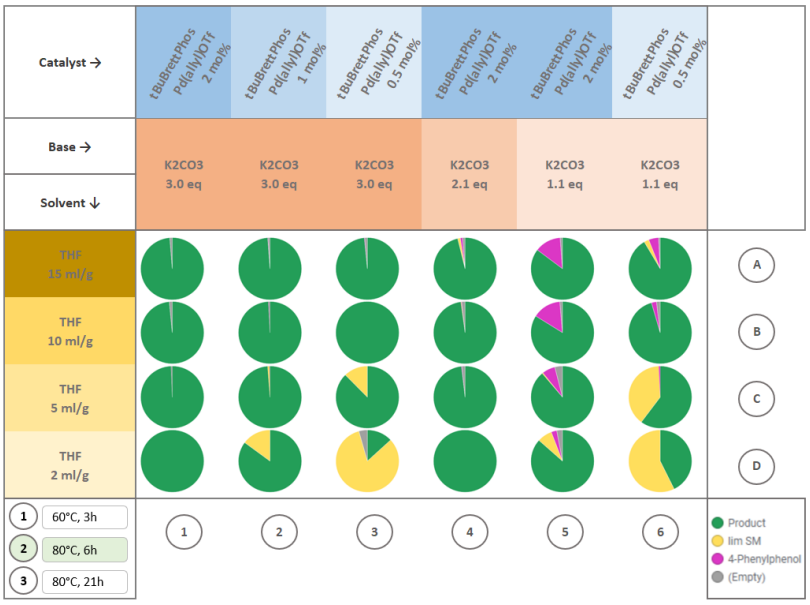


Figure S61. Results of plate 10, sample 2 taken after stirring at 6h, 80 °C

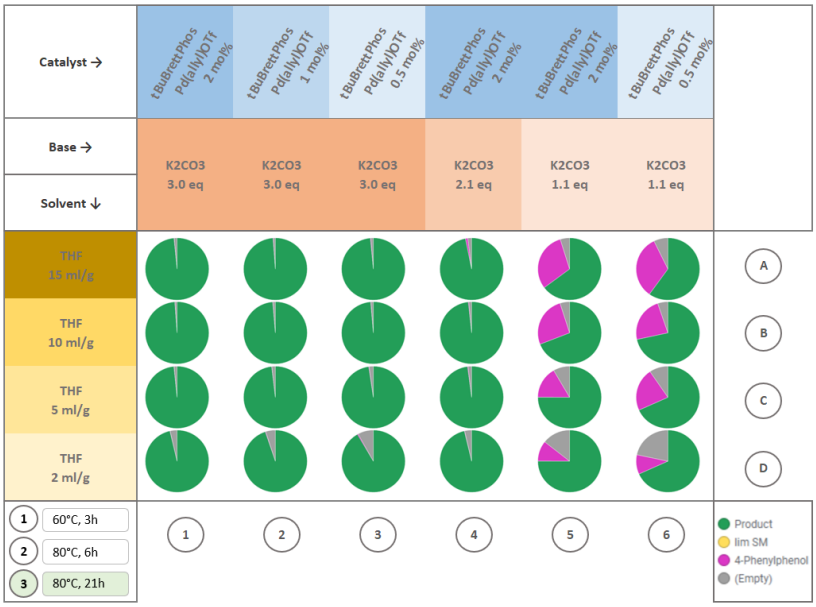


Figure S62. Results of plate 10, sample 3 taken after stirring at 21h, 80 °C

Scope Set Nucleophiles

Overview of other carbon-nucleophiles tested for the arylation reactions:

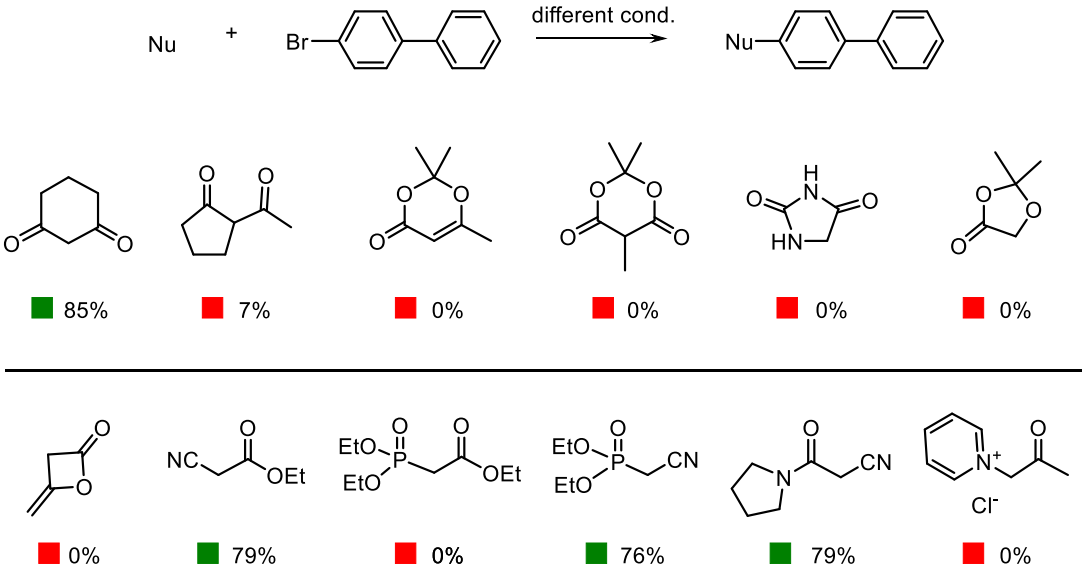


Figure S63. Nucleophile scope study

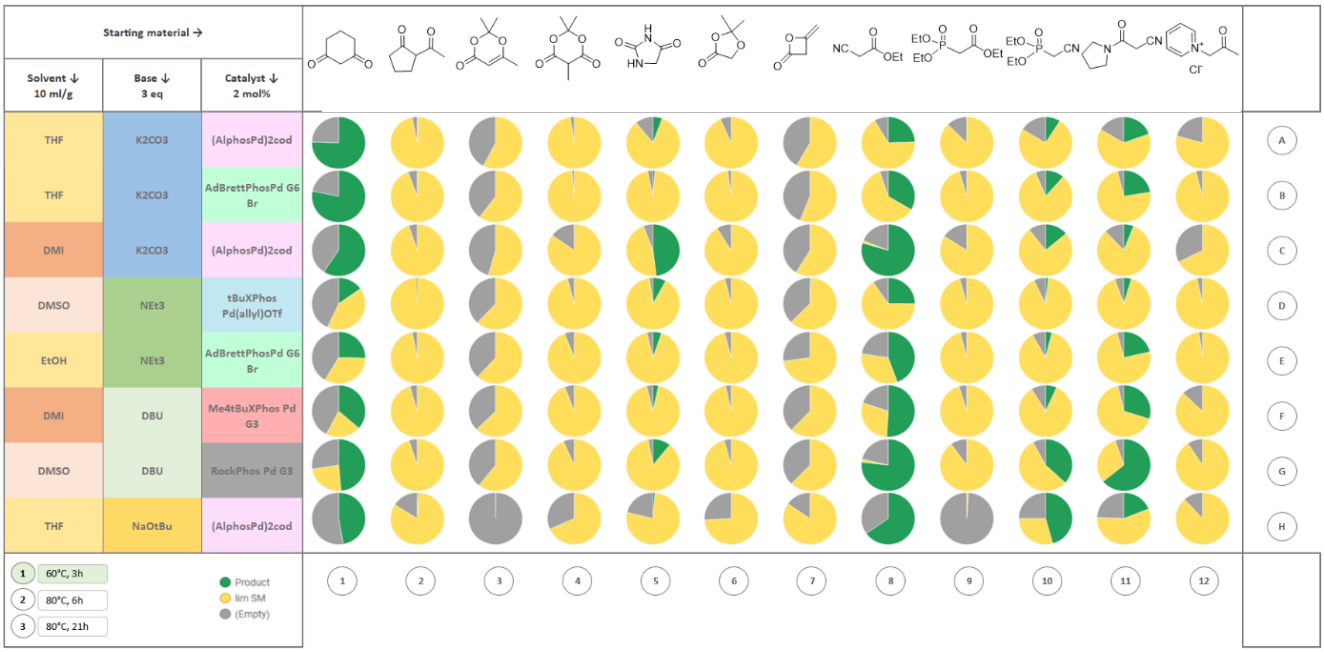


Figure S64. Nucleophile scope study, sample 1 taken after stirring at 3h, 60 °C.

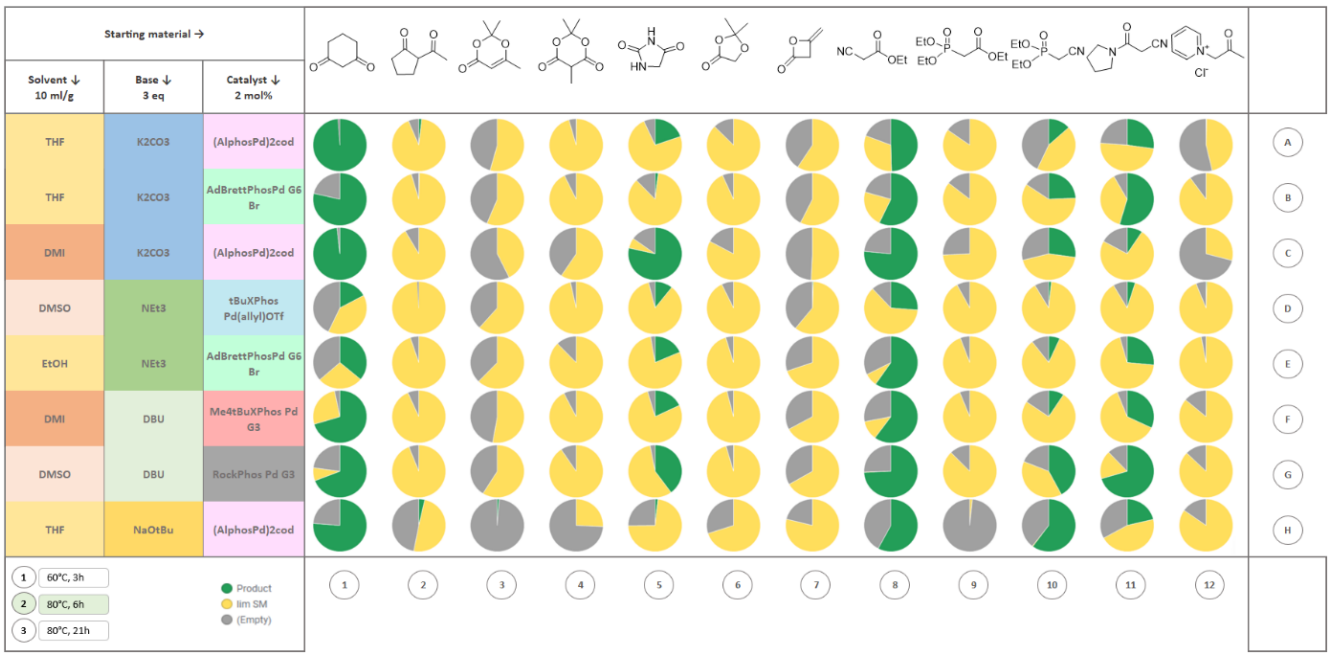


Figure S65. Nucleophile scope study, sample 2 taken after stirring at 6h, 80 °C.

Missing pies observed in this plate indicate problems during LCMS measurement that lead to data loss.

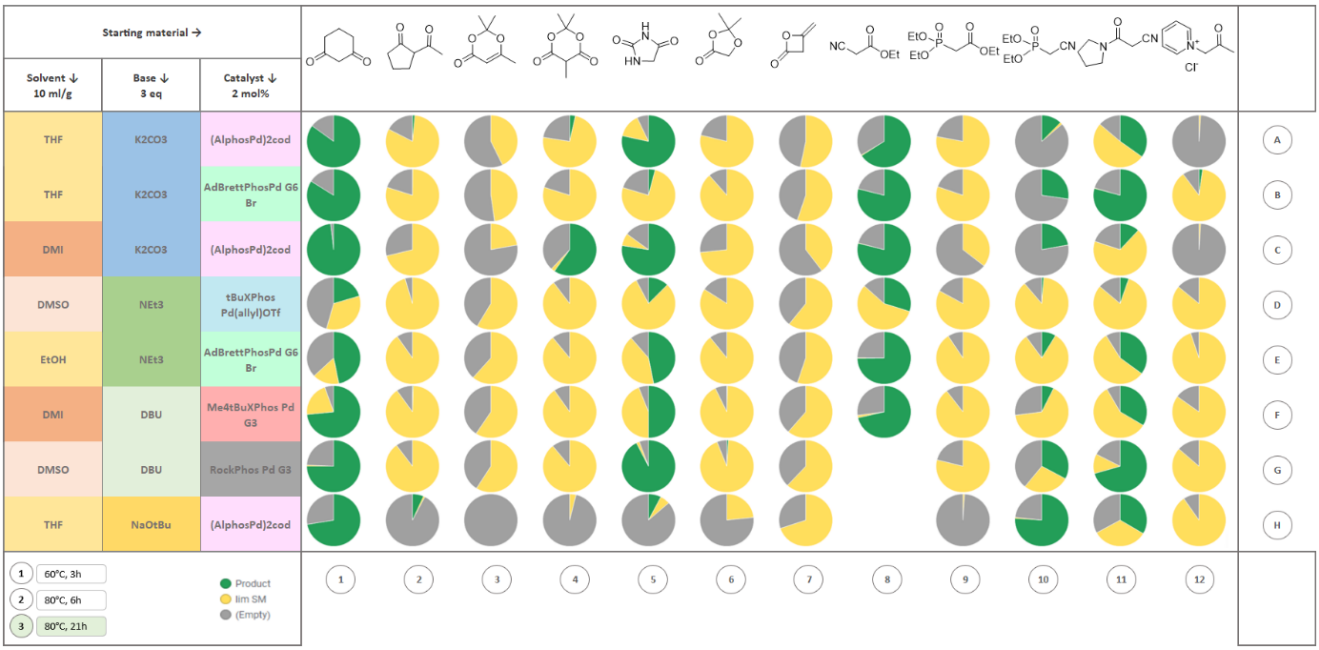


Figure S66. Nucleophile scope study, sample 3 taken after stirring at 21h, 80 °C.

Upon isolation, the product of the arylation of hydantoin was identified to be the 1-aryl-hydantoine. As N-arylation was not interesting to us and arylations of the other successful C-nucleophiles had already been described, we did not follow up with any of these.

5. Scale-up Experimental/Spectroscopic Data

General Procedure: Barbituric Acid Arylation

In a nitrogen-purged glovebox, the **aryl halide** (1.0 equiv), **barbituric acid** (1.1 equiv), and **AlPhos Pd G6 Br** (2 mol%) were dosed into a glass vial (8 or 20 mL) containing a stir bar and sealed (any liquid aryl halide was added outside the glovebox with the solvent). The vial was transferred to a fume hood, and argon-purged **EtOH** and **triethylamine** (2.1 equiv) were added via syringes under an inert atmosphere to achieve a reaction concentration of **0.2 mol/L** relative to the aryl bromide. The resulting suspension was transferred to a preheated aluminium block and stirred at **400 rpm** at **60 °C for 16 h (overnight)**. The reaction mixture was then transferred to a 100 mL round-bottom flask. Optionally, the mixture was basified with either **1 M aq. NaOH** solution or **10% w/w aq.** solution of **sodium carbonate** to a **pH of 11–12**. The **EtOH** was then evaporated under reduced pressure using a rotary evaporator. The reaction mixture was extracted with **TBME**, and the aqueous phase was filtered through a single-use membrane filter. The aqueous solution was then acidified to a **pH of 1–3** by the slow, dropwise addition of **2 M aq. phosphoric acid** solution, causing the product to crystallize out. The final product was isolated and washed by one of two options:

Option A (Centrifugation): The suspension was transferred to centrifugation vials, diluted with **distilled water**, and centrifuged at **9000 RPM** for **10 minutes**. The mother liquor was decanted, and the sediment was washed with **distilled water**, and dried directly in the vials in a **vacuum oven** at **60 °C** between **0.5 and 5 mbar** overnight.

Option B (Filtration): The product was isolated by filtration through a single-use membrane filter, washed with **distilled water**, and dried in a **vacuum oven** at **60 °C** between **0.5 and 5 mbar** overnight.

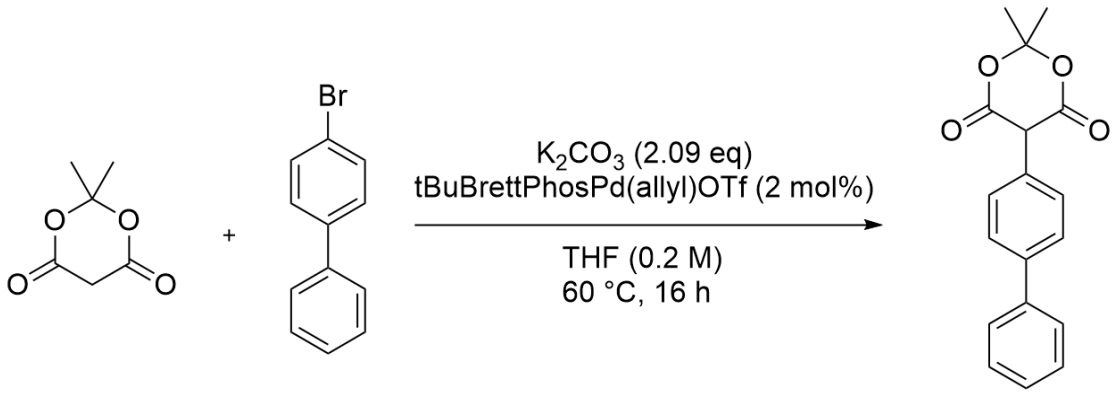
General Procedure: Meldrum's Acid Arylation

In a nitrogen-purged glovebox, **aryl halide** (1.0 equiv), **Meldrum's Acid** (1.1 equiv), the **potassium carbonate** (2.1 equiv), and **^{t}BuBrettPhosPd(allyl)OTf** (2 mol%) were charged into a glass vial (8 or 20 mL) containing a stir bar and sealed (any liquid aryl halide was added with the solvent outside the glovebox). The vial was transferred to a fume hood, and **THF** was added via syringe under an inert atmosphere (argon balloon) to achieve a reaction concentration of **0.2 mol/L** with respect to the aryl halide. The resulting suspension was transferred to a preheated aluminium block and stirred at **400 rpm** at **60 °C for 16 h (overnight)**. The reaction mixture was then transferred to a 100 mL round-bottom flask and basified with an **aq**. **10% w/w** solution of **sodium carbonate** under stirring until a **pH of 11–12** was reached. The **THF** was subsequently evaporated under reduced pressure using a rotary evaporator. The final product was isolated and washed by one of two options:

Option A (Filtration): The mixture was filtered through a single-use membrane filter.

Option B (Extraction): The mixture was extracted with **TBME** to remove neutral impurities (primarily unreacted aryl halide), and the aqueous phase was then filtered through a single-use membrane filter. The resulting aqueous solution was then acidified to a **pH of 1–3** by the slow, dropwise addition of **2 M aq. phosphoric acid** solution, which caused the product to crystallize out. The final product was isolated by filtration through a single-use membrane filter, washed with **distilled water**, and dried in a **vacuum oven** at **60 °C** between **0.5 and 5 mbar** overnight.

5-([1,1'-biphenyl]-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione



Option A of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (401 mg, 2.78 mmol, 1.1 equiv), 4-bromobiphenyl (587 mg, 2.52 mmol, 1.0 equiv), K_2CO_3 (729 mg, 5.27 mmol, 2.09 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (39 mg, 0.05 mmol, 0.02 equiv). After 16 h at 60 °C, LCMS indicated full conversion of the starting material. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) was used, acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (717.4 mg, 96% yield, 97% pure by LCMS) was obtained as a light-yellow powder.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.62 - 7.67 (m, 2 H), 7.56 - 7.60 (m, 2 H), 7.42 - 7.47 (m, 2 H), 7.33 - 7.40 (m, 3 H), 4.82 (s, 1 H), 1.90 (q, J=0.8 Hz, 3 H), 1.79 (q, J=0.8 Hz, 3 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.8, 141.9, 140.2, 129.6, 129.4, 128.9, 128.0, 127.7, 127.2, 105.8, 52.5, 28.6, 27.6 ppm

HRMS: $C_{18}H_{16}O_4$; calc. for ($M+H^+$) 296.1049, found: 296.1048.

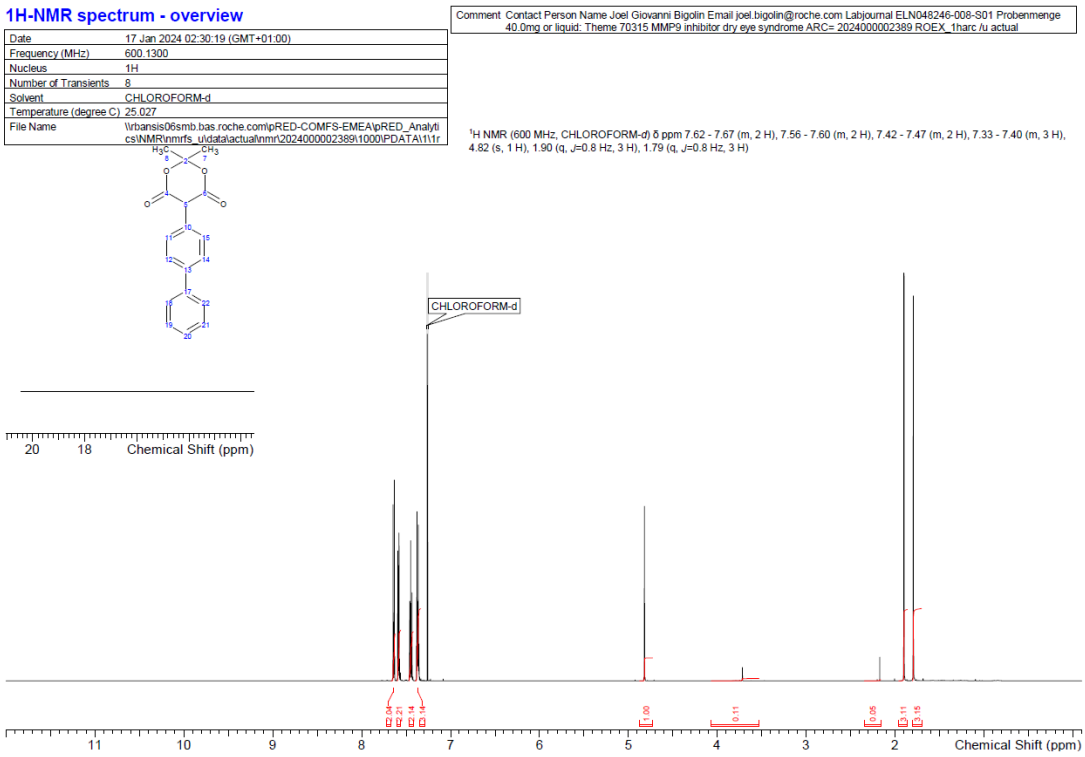


Figure S67. ^{1}H NMR (600 MHz, $CDCl_3$) of 5-([1,1'-biphenyl]-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

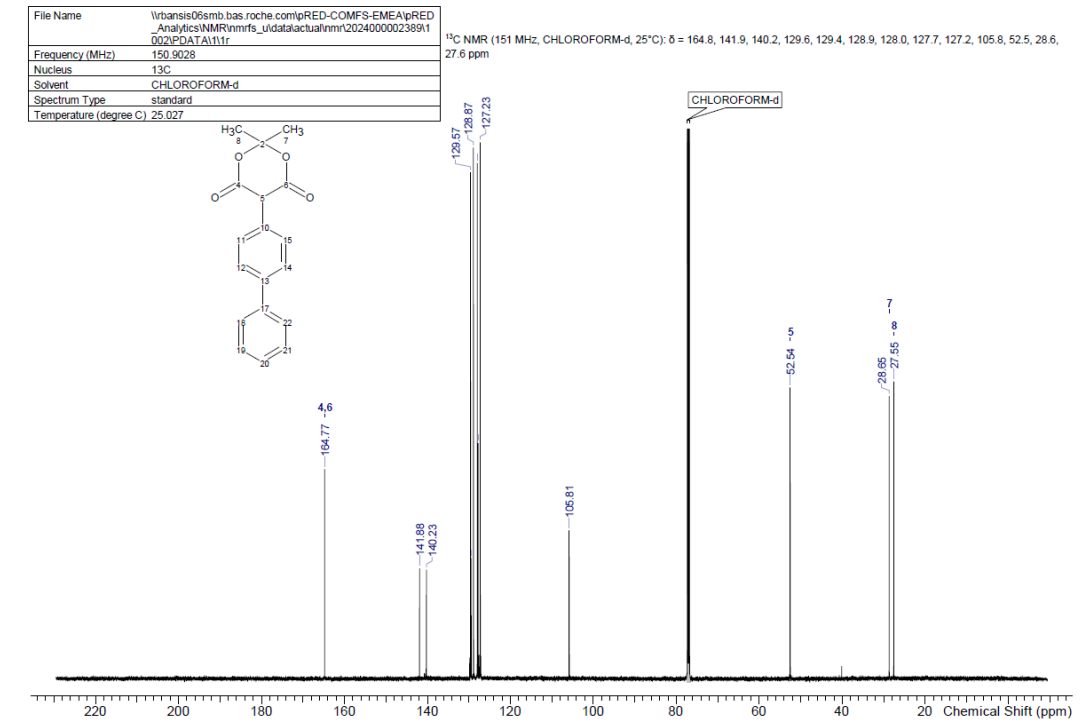


Figure S68. ^{13}C NMR (151 MHz, $CDCl_3$) of 5-([1,1'-biphenyl]-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

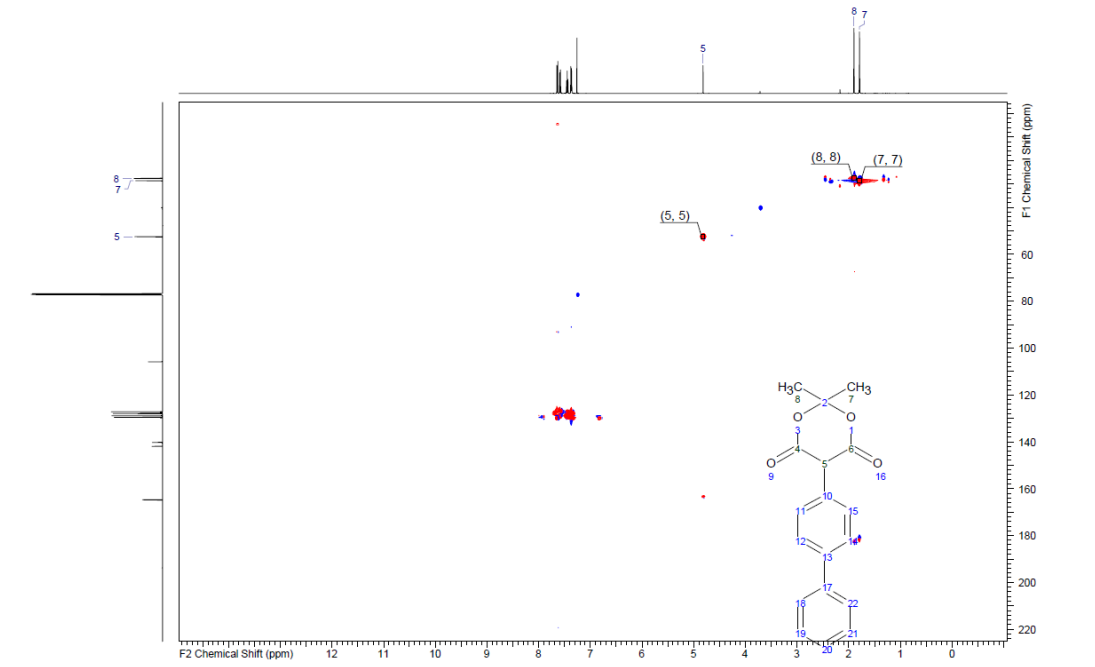


Figure S69. HSQC-DEPT of 5-([1,1'-biphenyl]-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

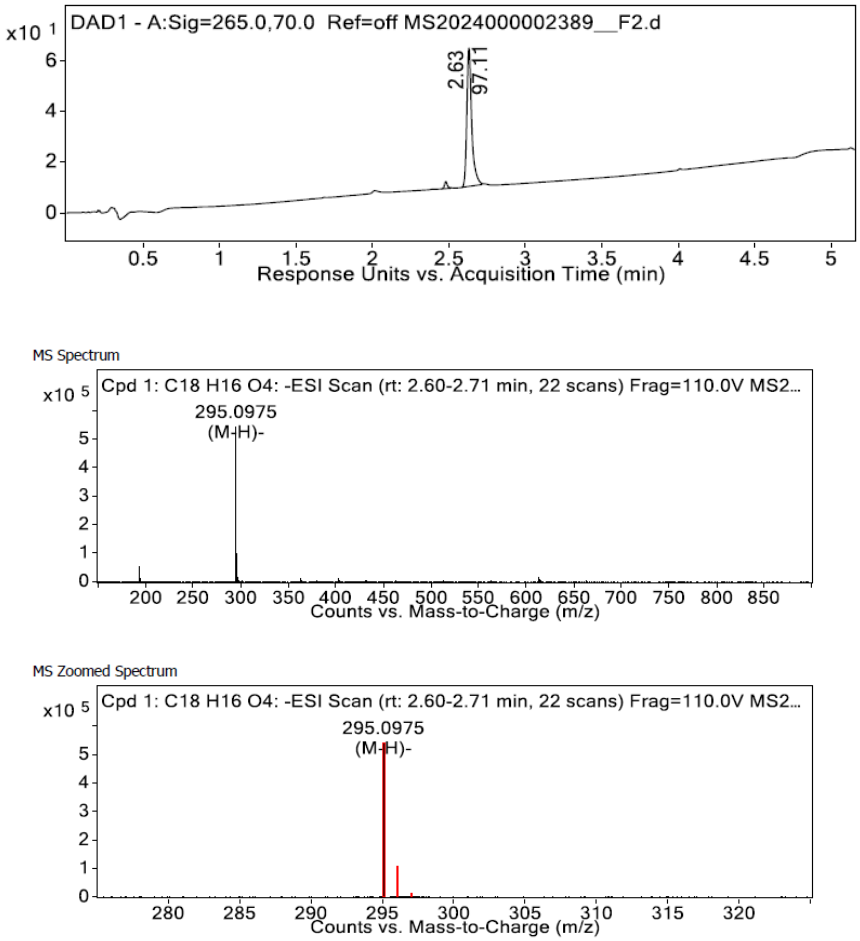
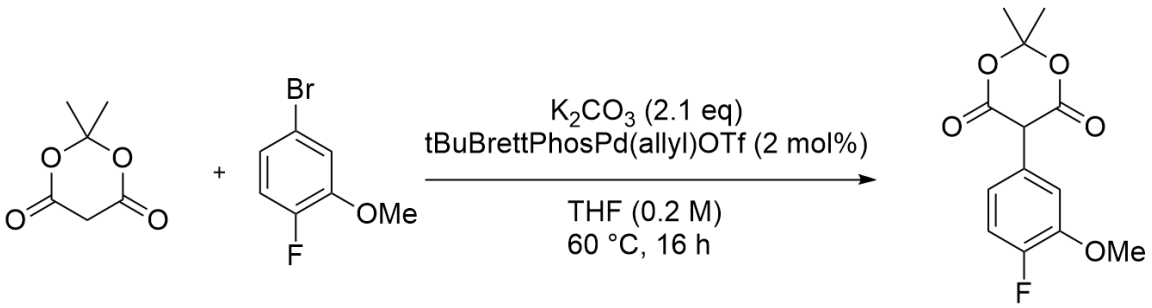


Figure S70. HRMS of 5-([1,1'-biphenyl]-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione



Option A of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (393 mg, 2.73 mmol, 1.1 equiv), 4-bromo-1-fluoro-2-methoxybenzene (0.34 mL, 2.49 mmol, 1.0 equiv), K_2CO_3 (723 mg, 5.23 mmol, 2.1 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (39.8 mg, 0.05 mmol, 0.02 equiv). After 16 h at 60 °C, LCMS indicated full conversion of the aryl bromide. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) was used with

additional H_2O (15 mL, due to high viscosity), acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (527.2 mg, 79% yield, 98% pure by LCMS) was obtained as an off-white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.11 (dd, J=10.9, 8.3 Hz, 1 H), 6.89 (dd, J=7.8, 2.3 Hz, 1 H), 6.81 (ddd, J=8.6, 4.0, 2.0 Hz, 1 H), 4.73 (s, 1 H), 3.89 (s, 3 H), 1.82 - 1.94 (m, 3 H), 1.77 (d, J=0.7 Hz, 3 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.5, 152.6, 148.2, 126.5, 121.8, 116.5, 114.4, 105.8, 56.3, 52.4, 28.6, 27.4 ppm

^{19}F NMR (565 MHz, $CDCl_3$) δ = -134.25 (ddd, J = 3.9, 7.5, 11.1 Hz)

HRMS: $C_{13}H_{13}FO_5$; calc. for ($M+H^+$) 268.0747, found: 268.0748.

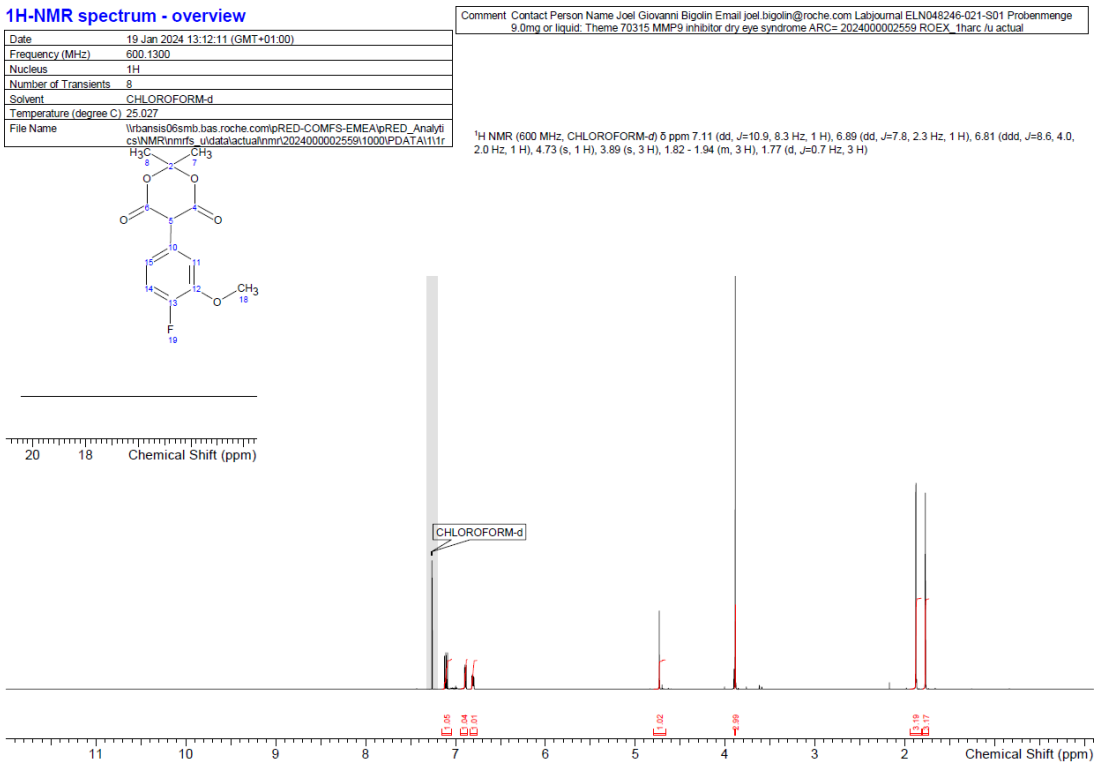


Figure S71. ^{1}H NMR (600 MHz, $CDCl_3$) of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

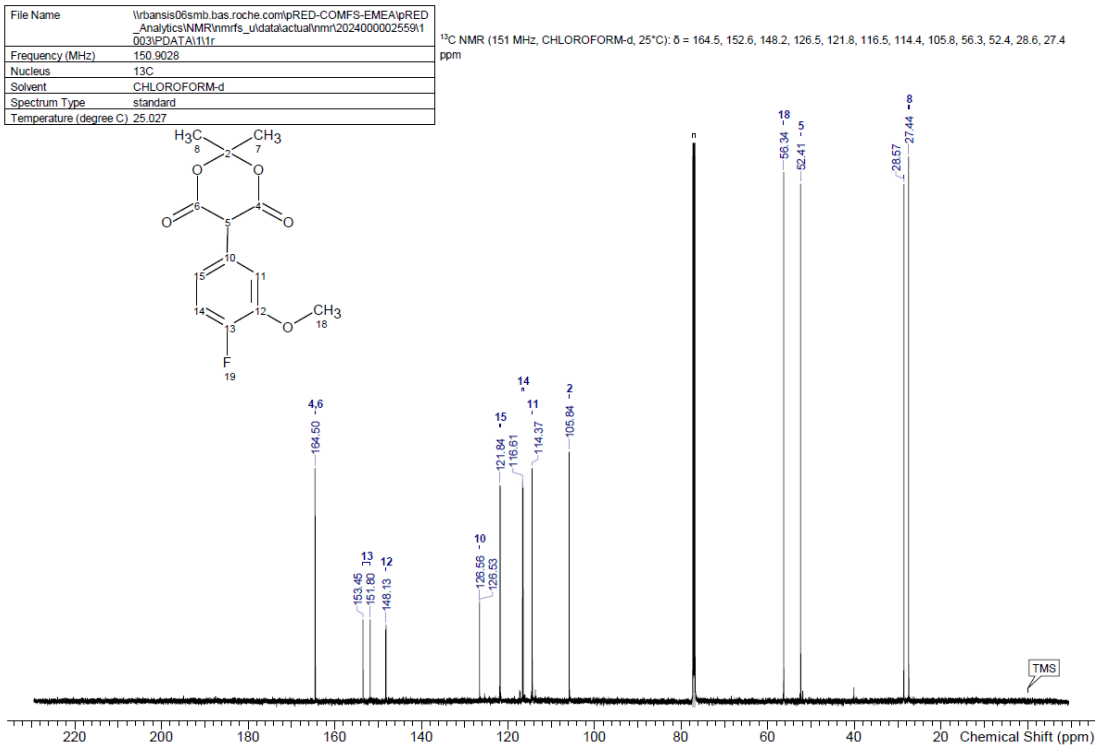


Figure S72. ^{13}C NMR (151 MHz, $CDCl_3$) of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

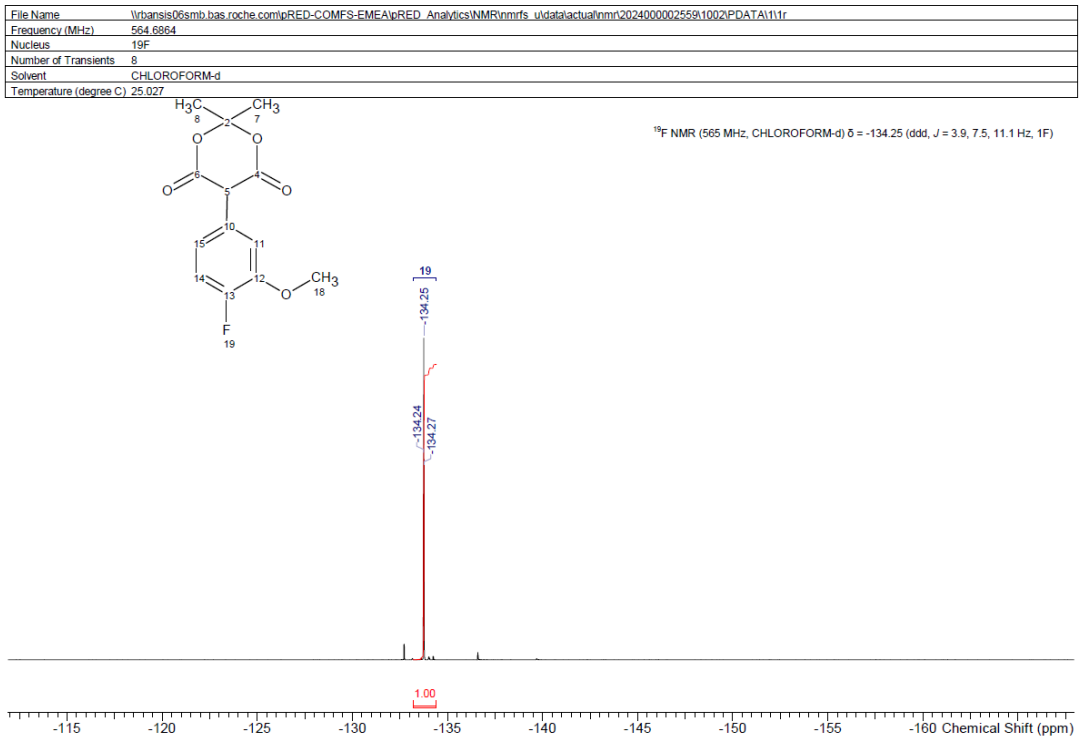


Figure S73. ^{19}F NMR (565 MHz, $CDCl_3$) of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

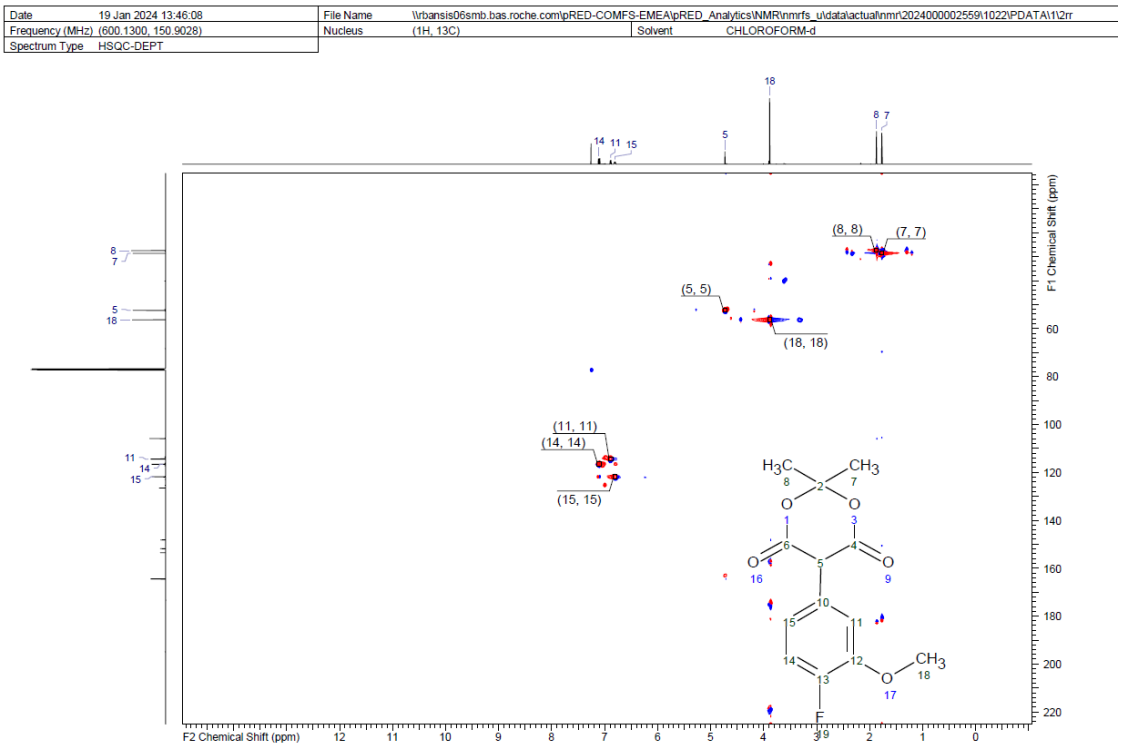


Figure S74. HSQC-DEPT of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

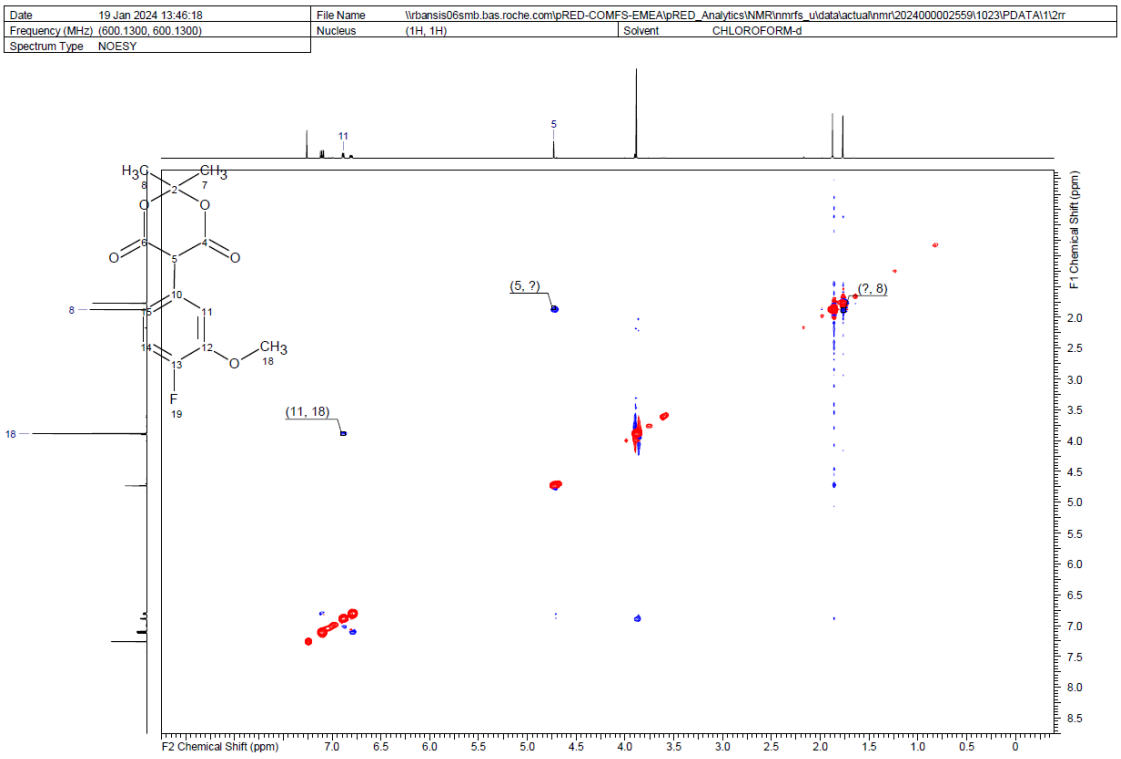


Figure S75. NOESY of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

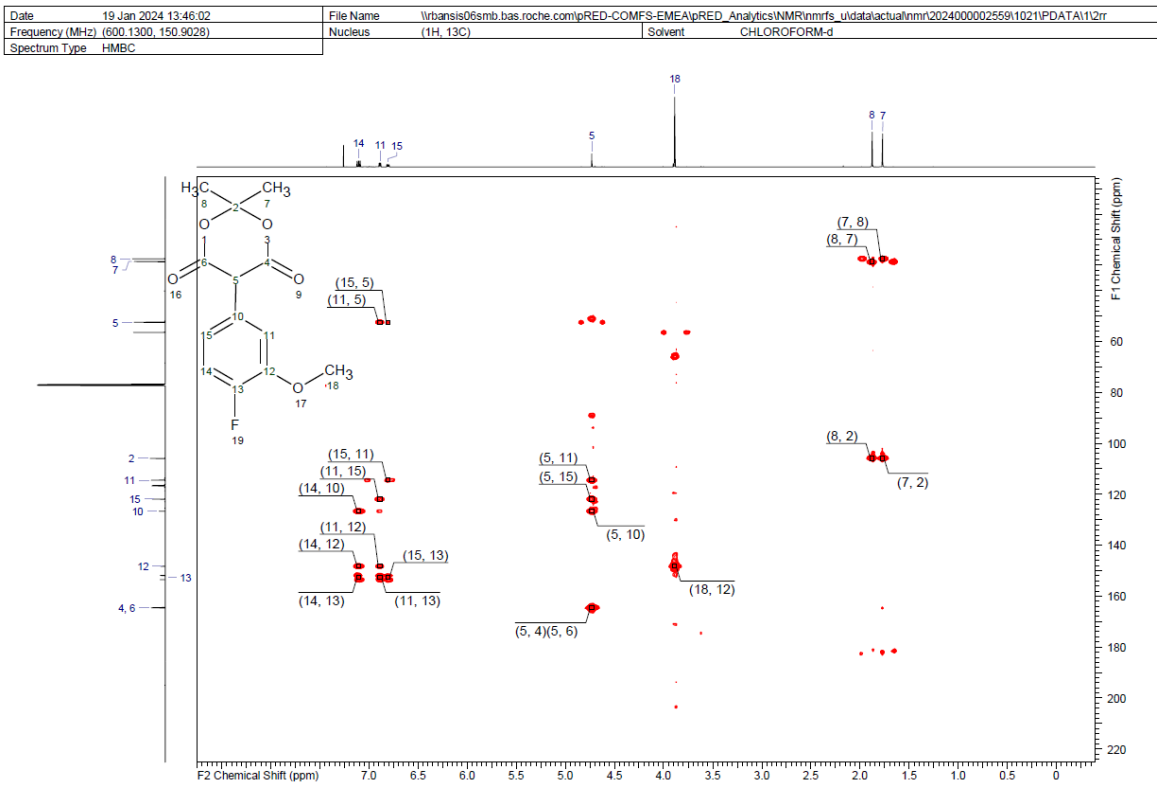


Figure S76. HMBC of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

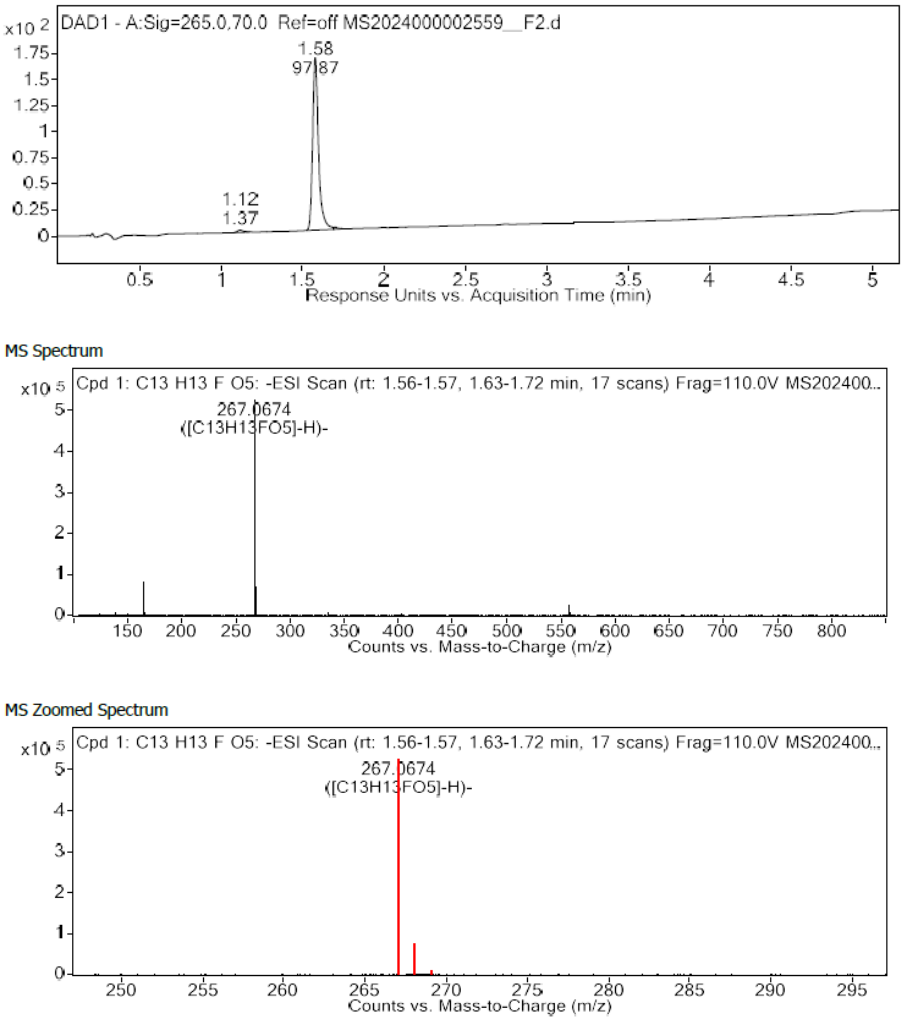
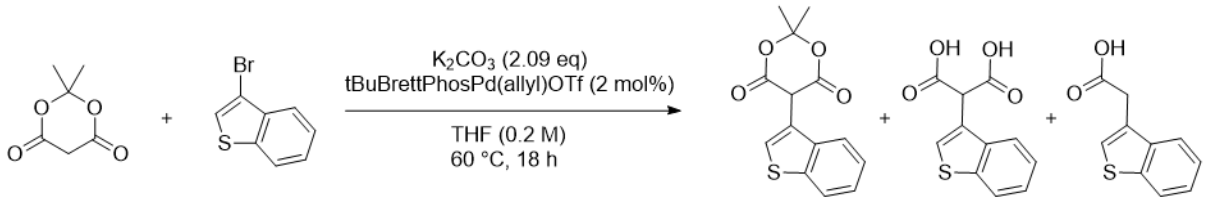


Figure S77. HRMS of 5-(4-fluoro-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6- dione

5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione



Option A of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (394 mg, 2.73 mmol, 1.08 equiv), 3-bromo-1-benzothiophene (0.33 mL, 2.52 mmol, 1.0 equiv), K_2CO_3 (730 mg, 5.28 mmol, 2.09 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (39.8 mg, 0.05 mmol, 0.02 equiv). After 18 h at 60 °C, LCMS indicated 19% conversion to the product. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) was used and acidified to pH 2.

As no product precipitated out and the aryl bromide was still present, the mixture was first acidified to pH 1 with a few drops of H_2SO_4 (still no product precipitated), basified to pH 10, extracted the aryl bromide with TBME (3 x 40 mL), acidified to pH 2 and again extracted the acidic products with TBME (3 x 40 mL). The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator. The product was dried in a vacuum oven at 60 °C and 0.5 – 5 mbar overnight. Instead of the title compound, the corresponding malonic acid and aryl acetic acid (69.1 mg) were obtained in a ratio of 6:4 as a brown solid.

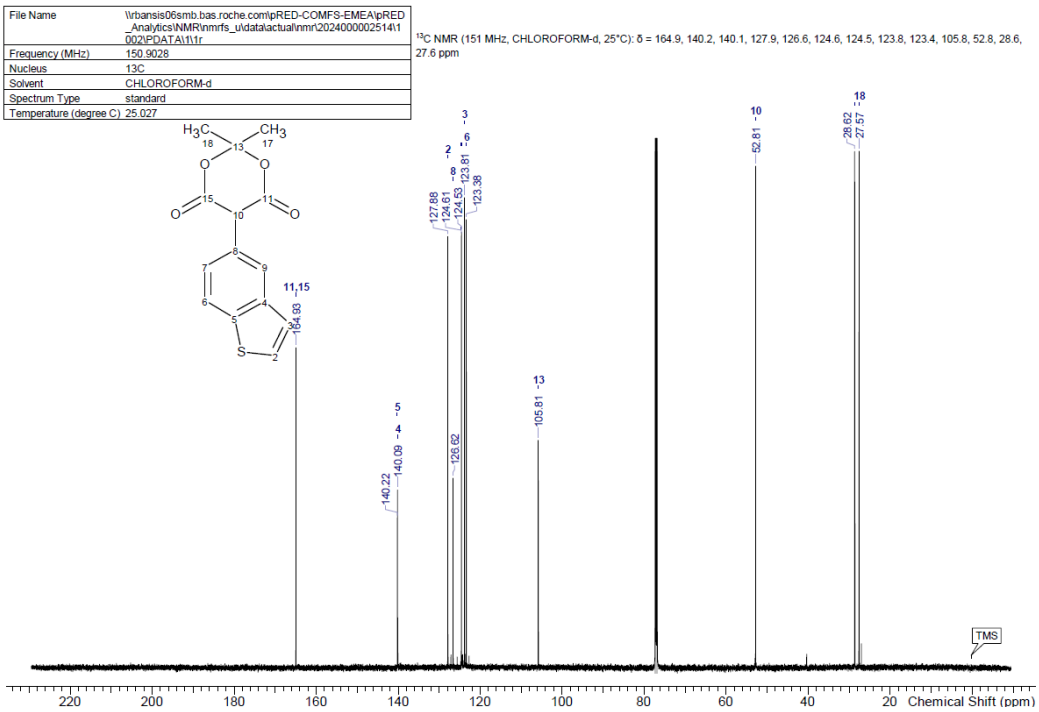


Figure S78. ^{13}C NMR (151 MHz, $CDCl_3$) of 5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

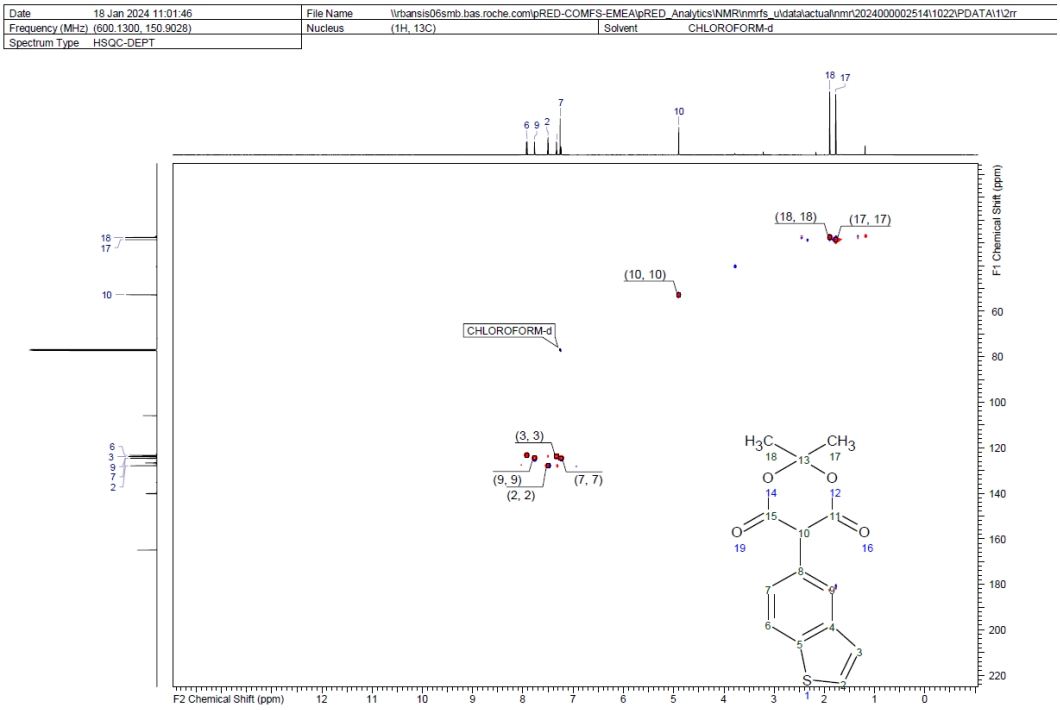


Figure S79. HSQC-DEPT of 5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

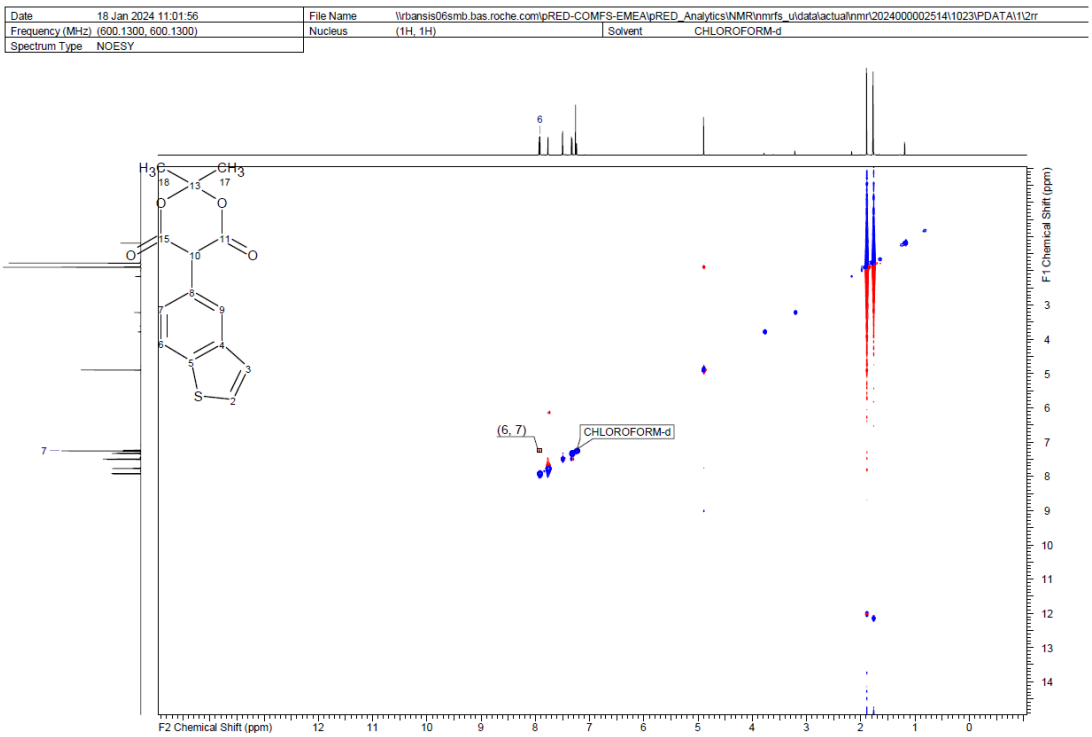


Figure S80. NOESY of 5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

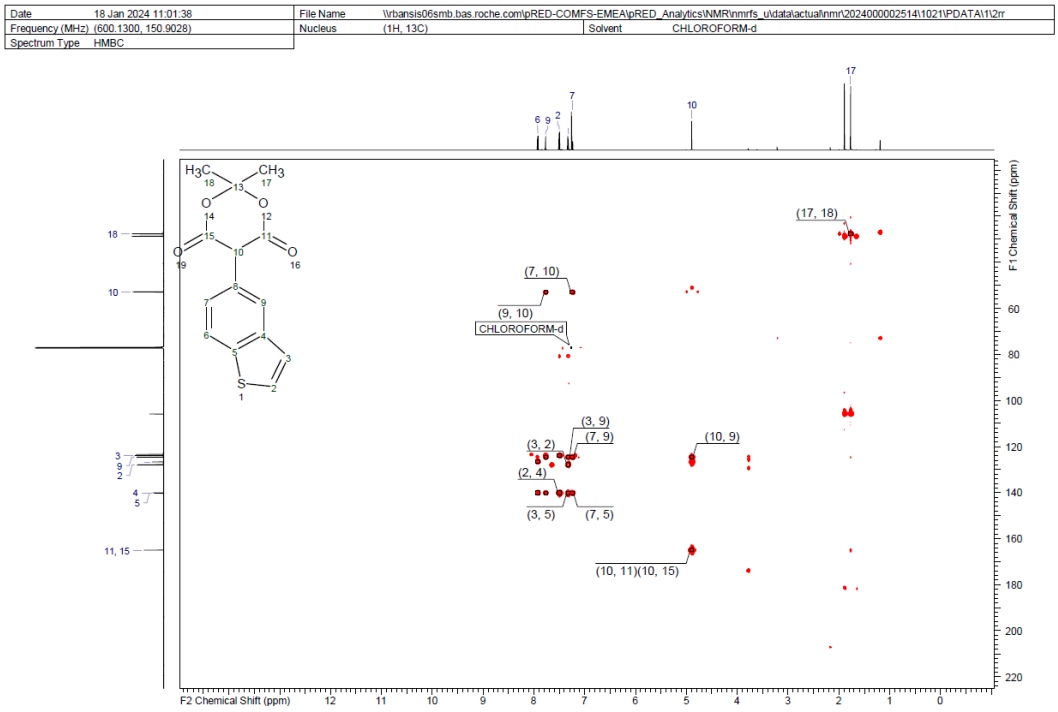


Figure S81. HMBC of 5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

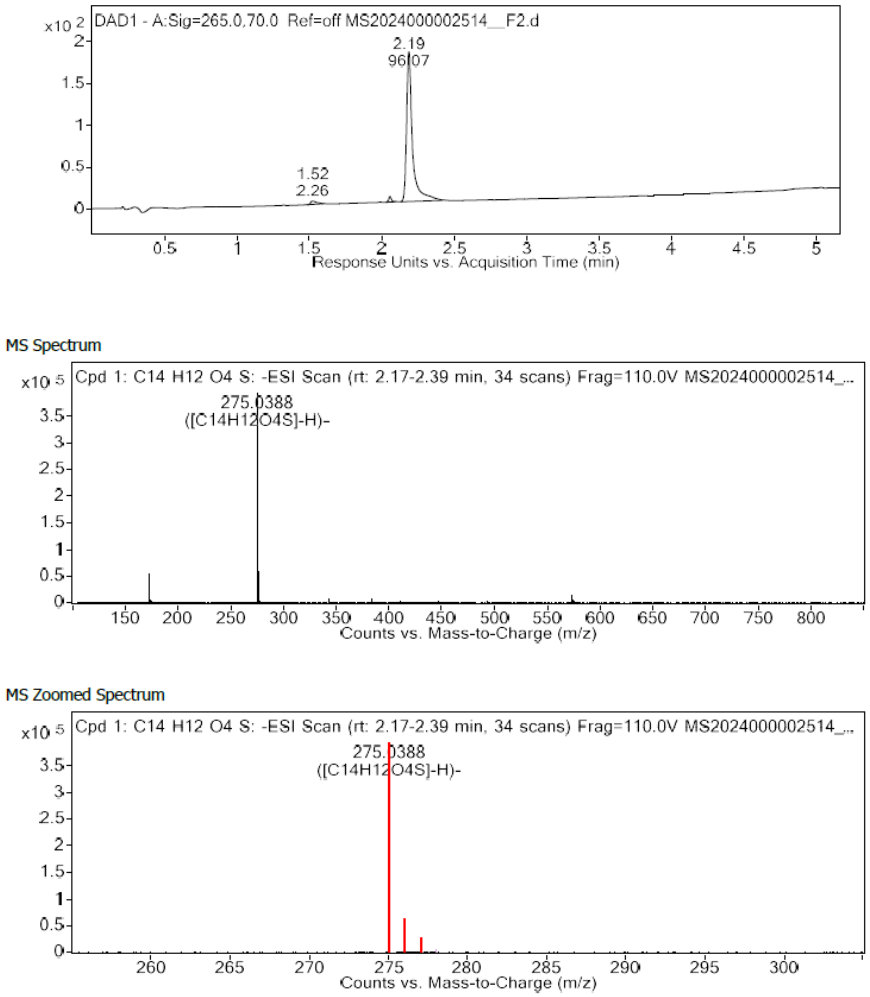
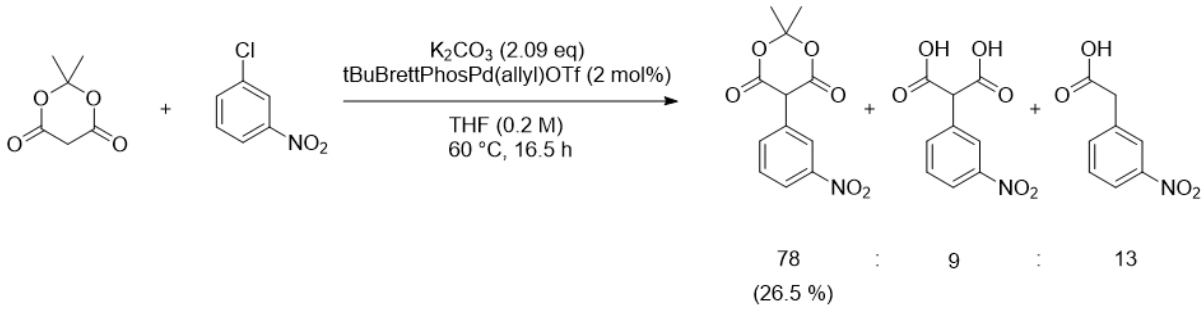


Figure S82. HRMS of 5-(1-benzothiophen-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione



Option B of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (396 mg, 2.75 mmol, 1.10 equiv), 1-chloro-3-nitrobenzene (392 mg, 2.49 mmol, 1.0 equiv), K_2CO_3 (719.5 mg, 5.21 mmol, 2.09 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (40.2 mg, 0.0515 mmol, 0.02 equiv). After 16.5 h at 60 °C, LCMS

indicated 37% conversion of the aryl bromide. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used and acidified to pH 2.

As no product precipitated out, the reaction mixture was extracted with TBME (4 x 40 mL). The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator. The product was dried in a vacuum oven at 60 °C and 0.5 – 5 mbar overnight. The title compound (243 mg, 27% yield, 73% pure by LCMS) was obtained as a brownish solid contaminated with the corresponding malonic acid and aryl acetic acid in a ratio of 78 : 9 : 13.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.27 - 8.30 (m, 1 H), 8.18 - 8.19 (m, 1 H), 7.63 (dt, J=5.0, 2.7 Hz, 1 H), 7.51 - 7.56 (m, 1 H), 4.88 - 4.89 (m, 1 H), 4.87 (s, 1 H), 1.95 (s, 3 H), 1.86 (d, J=0.7 Hz, 3 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.1, 163.6, 148.5, 135.8, 135.7, 135.5, 135.0, 132.4, 130.1, 129.9, 129.6, 125.2, 124.6, 124.5, 124.0, 123.9, 122.6, 106.1, 56.3, 52.6, 40.1, 28.6, 27.1 ppm

HRMS: $C_{12}H_{11}NO_6$; calc. for ($M+H^+$) 265.0586, found: 265.0587.

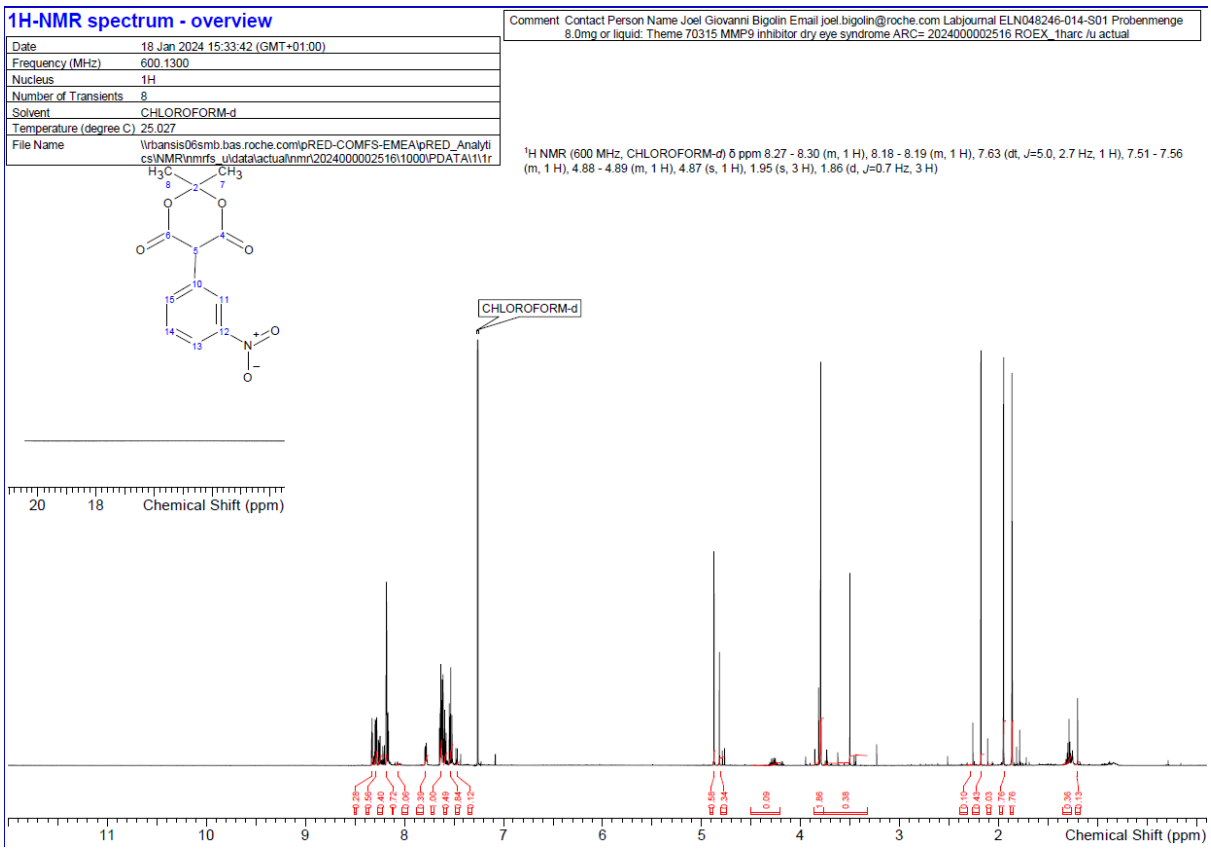


Figure S83. ^{1}H NMR (600 MHz, $CDCl_3$) of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

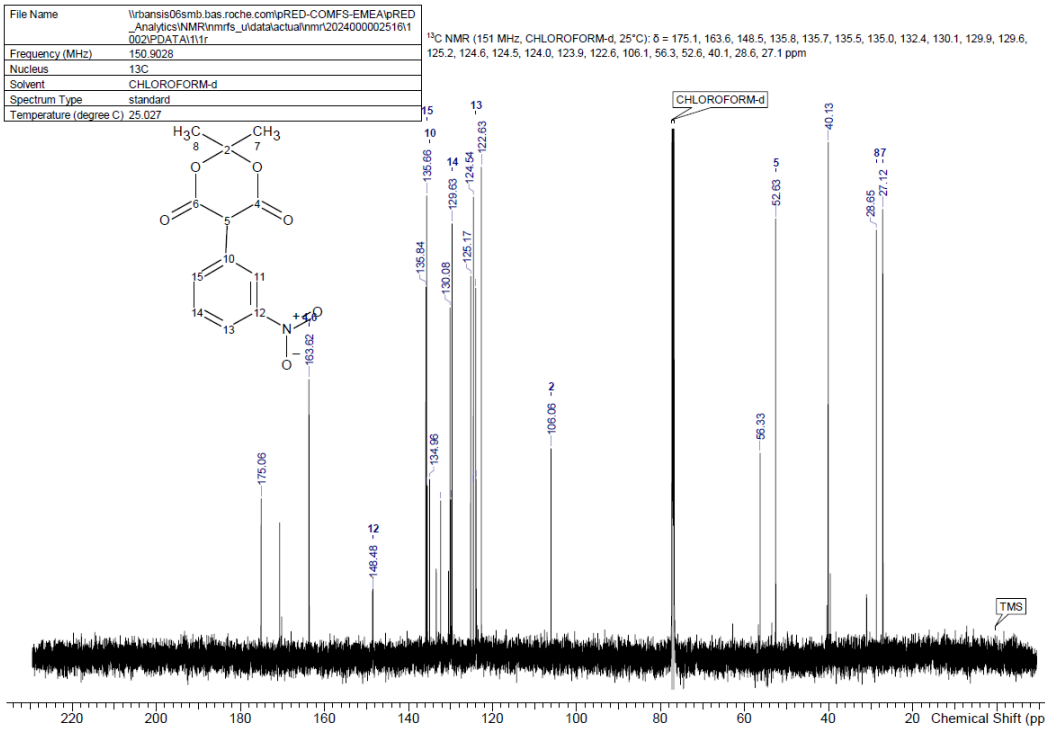


Figure S84. ^{13}C NMR (151 MHz, $CDCl_3$) of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

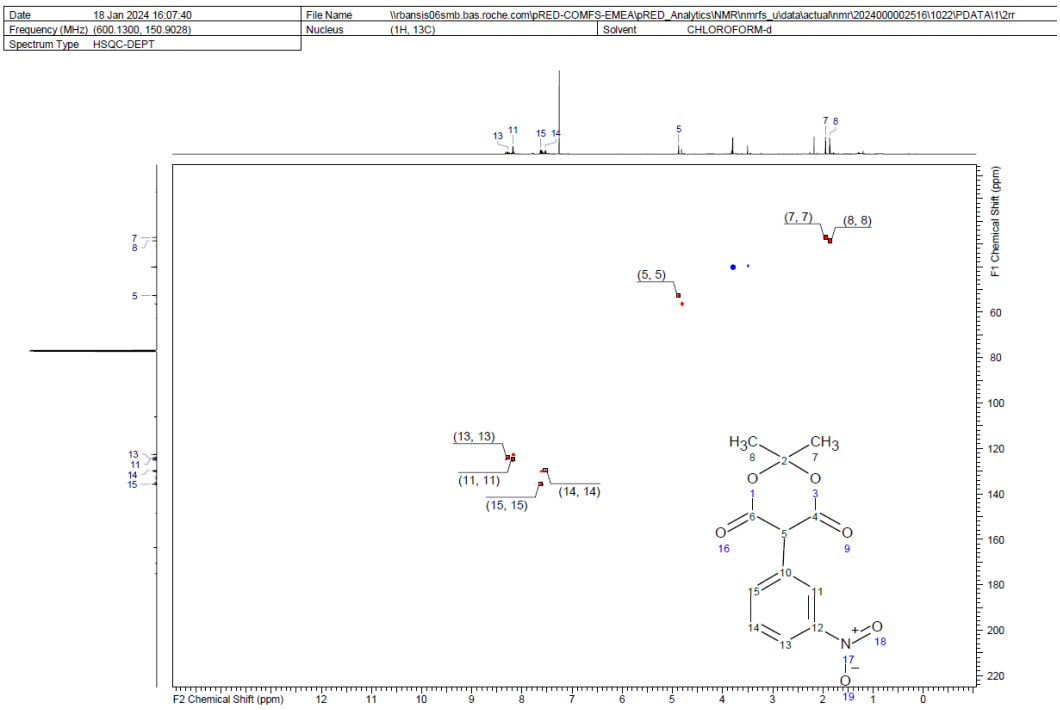


Figure S85. HSQC-DEPT of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

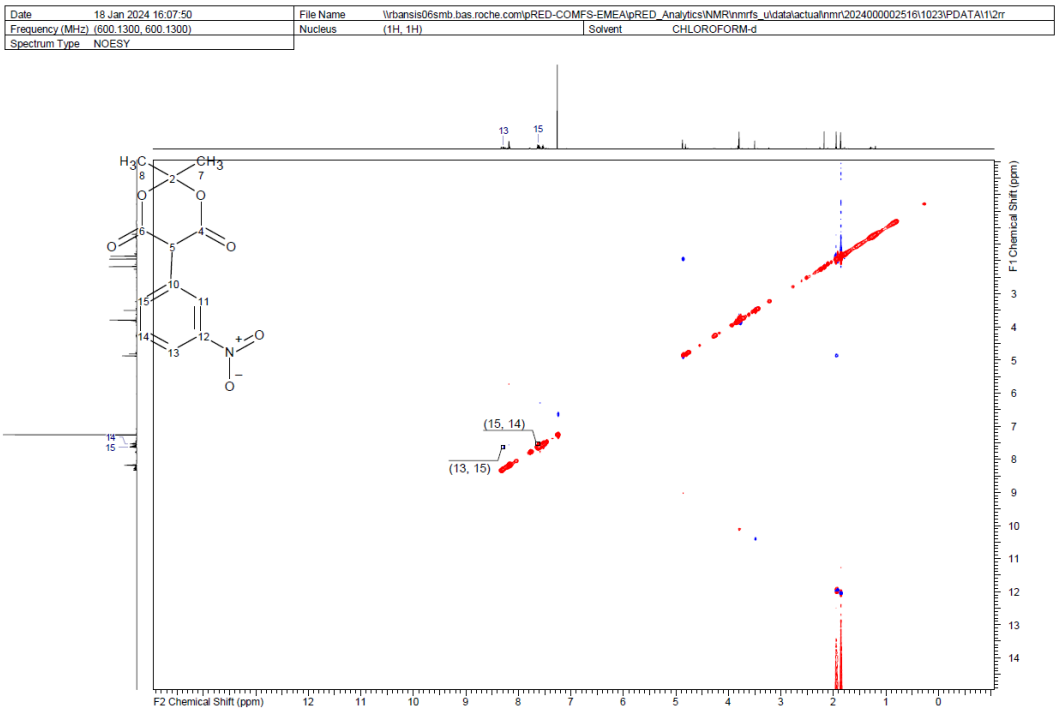


Figure S86. NOESY of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

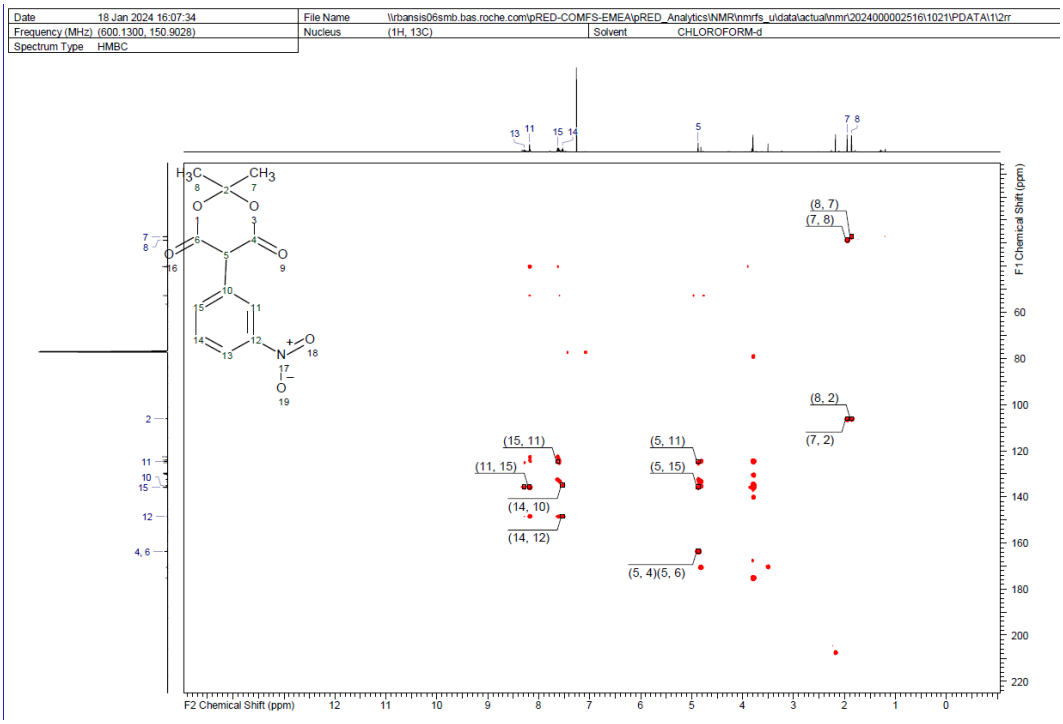


Figure S87. HMBC of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

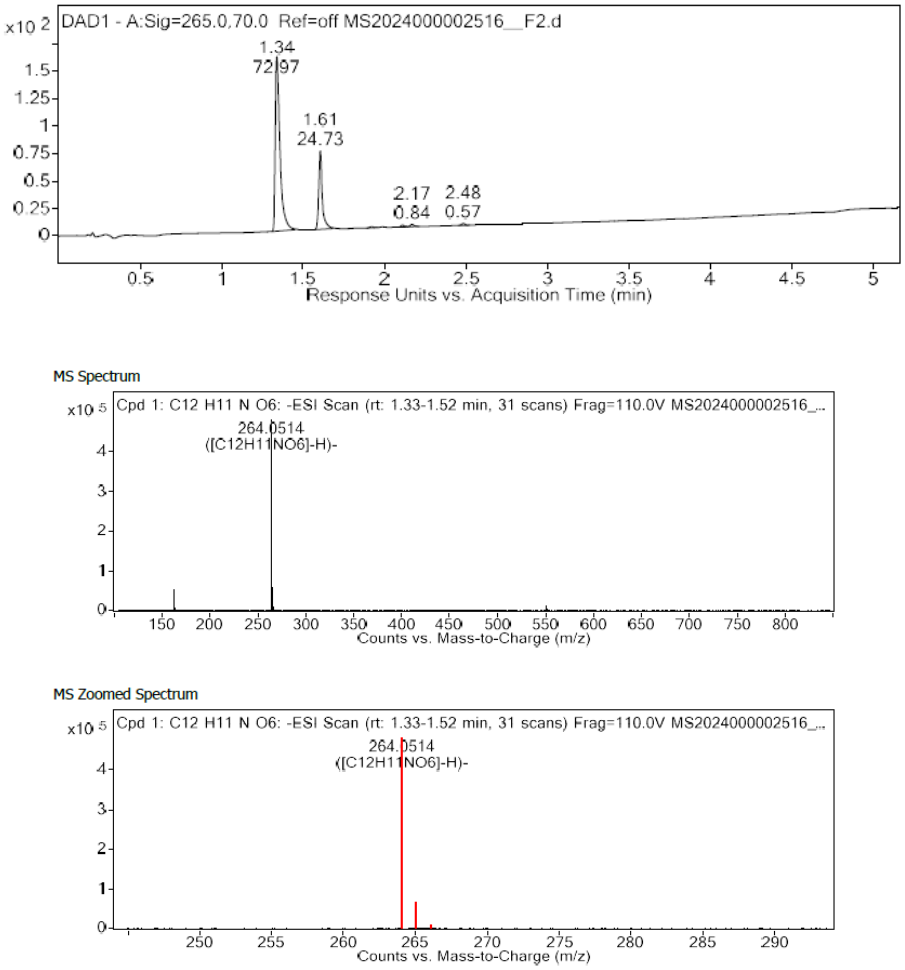
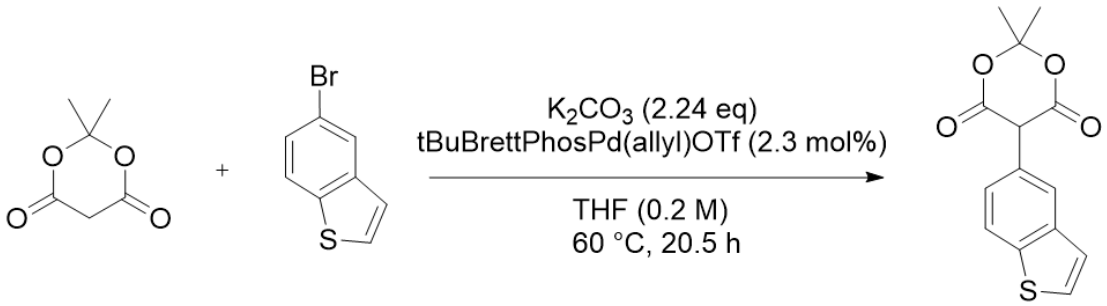


Figure S88. HRMS of 2,2-dimethyl-5-(3-nitrophenyl)-1,3-dioxane-4,6-dione

5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione



Option B of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (398 mg, 2.76 mmol, 1.18 equiv), 5-bromo-1-benzothiophene (499 mg, 2.34 mmol, 1.0 equiv), K_2CO_3 (725 mg, 5.25 mmol, 2.24 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (41.8 mg, 0.0525 mmol, 0.02 equiv). After 20.5 h at 60 °C, LCMS indicated 84% conversion of the aryl bromide. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used, acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (517 mg, 80% yield, 96% pure by LCMS) was obtained as an off-white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.92 (d, J=8.4 Hz, 1 H), 7.77 (d, J=1.9 Hz, 1 H), 7.50 (d, J=5.4 Hz, 1 H), 7.33 (dd, J=5.5, 0.8 Hz, 1 H), 7.25 (dd, J=8.4, 1.9 Hz, 1 H), 4.90 (s, 1 H), 1.89 (q, J=0.9 Hz, 3 H), 1.77 (q, J=0.8 Hz, 3 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.9, 140.2, 140.1, 127.9, 126.6, 124.6, 124.5, 123.8, 123.4, 105.8, 52.8, 28.6, 27.6 ppm

HRMS: $C_{14}H_{12}O_4S$; calc. for ($M+H^+$) 276.0456, found: 276.0461.

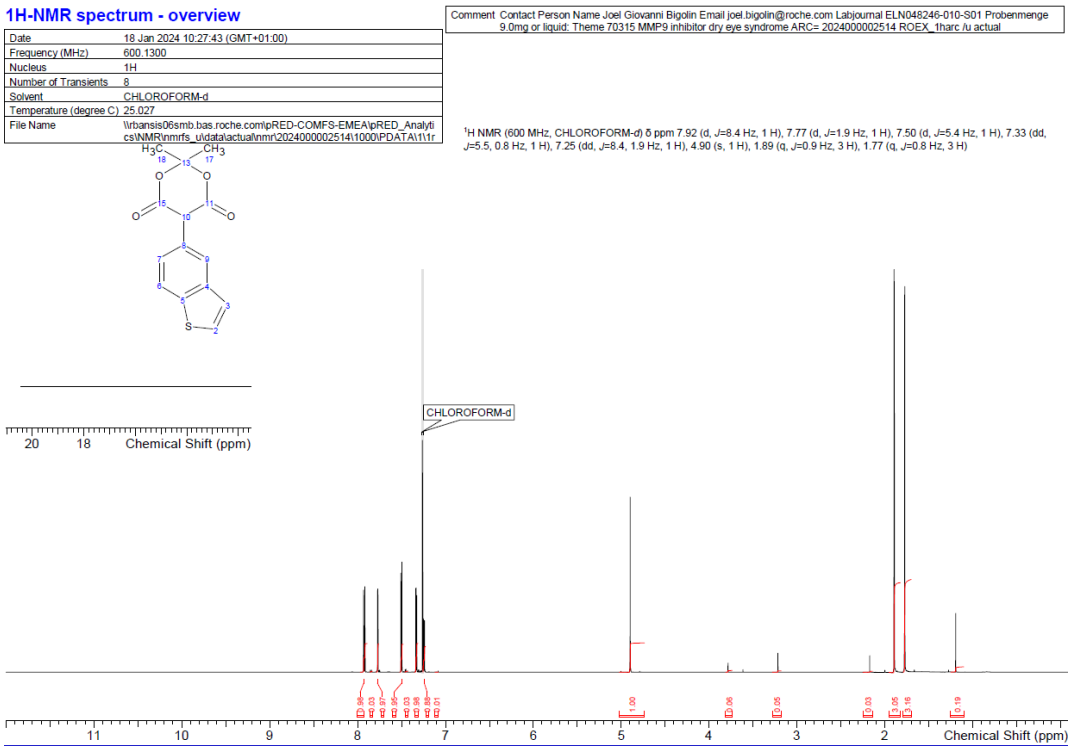


Figure S89. ^{1}H NMR (600 MHz, $CDCl_3$) of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

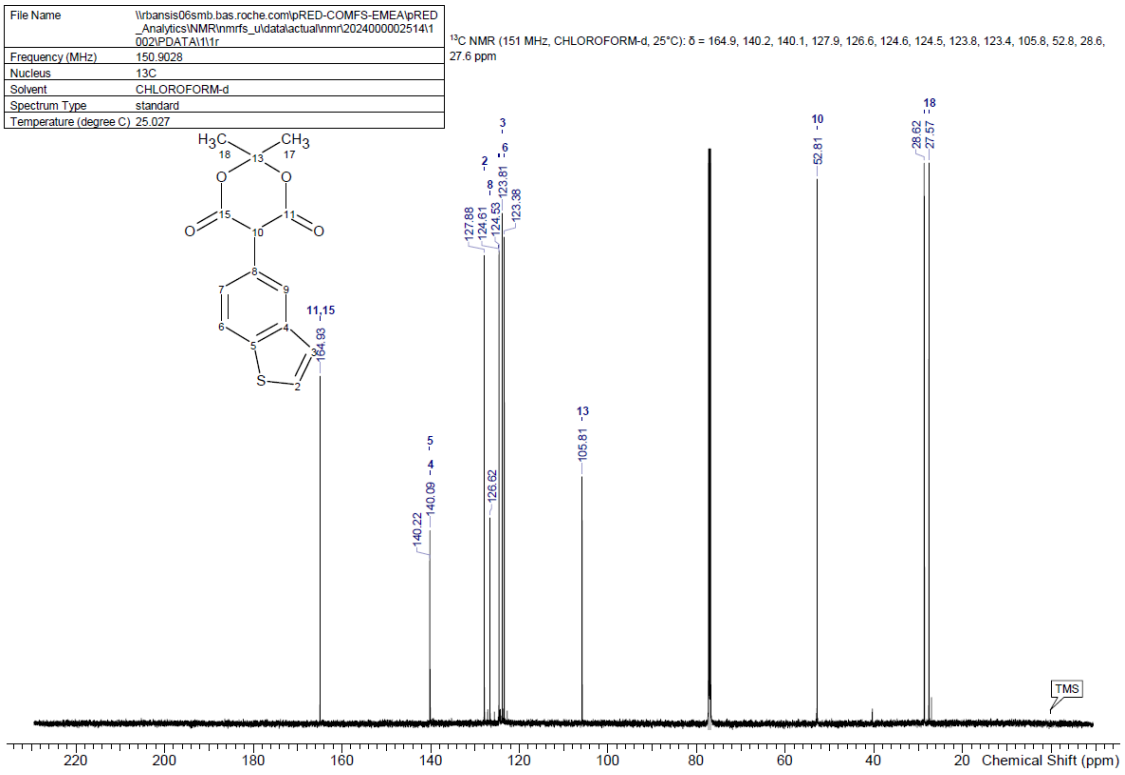


Figure S90. ^{13}C NMR (151 MHz, $CDCl_3$) of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

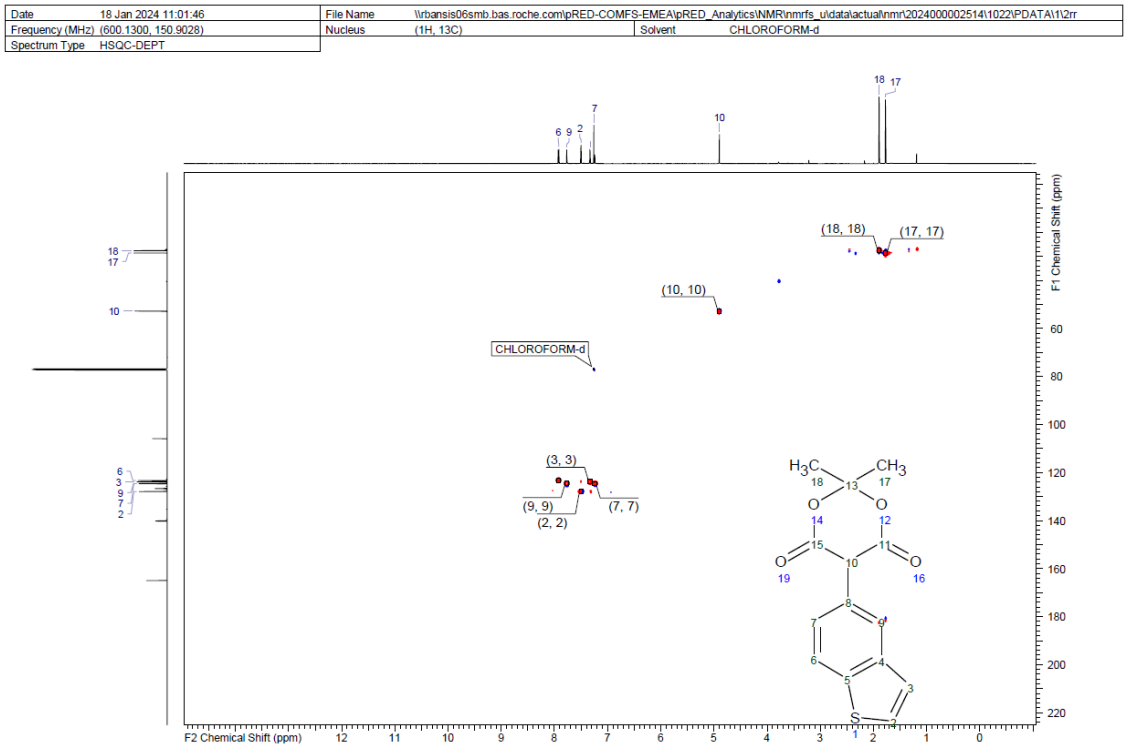


Figure S91. HSQC-DEPT of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

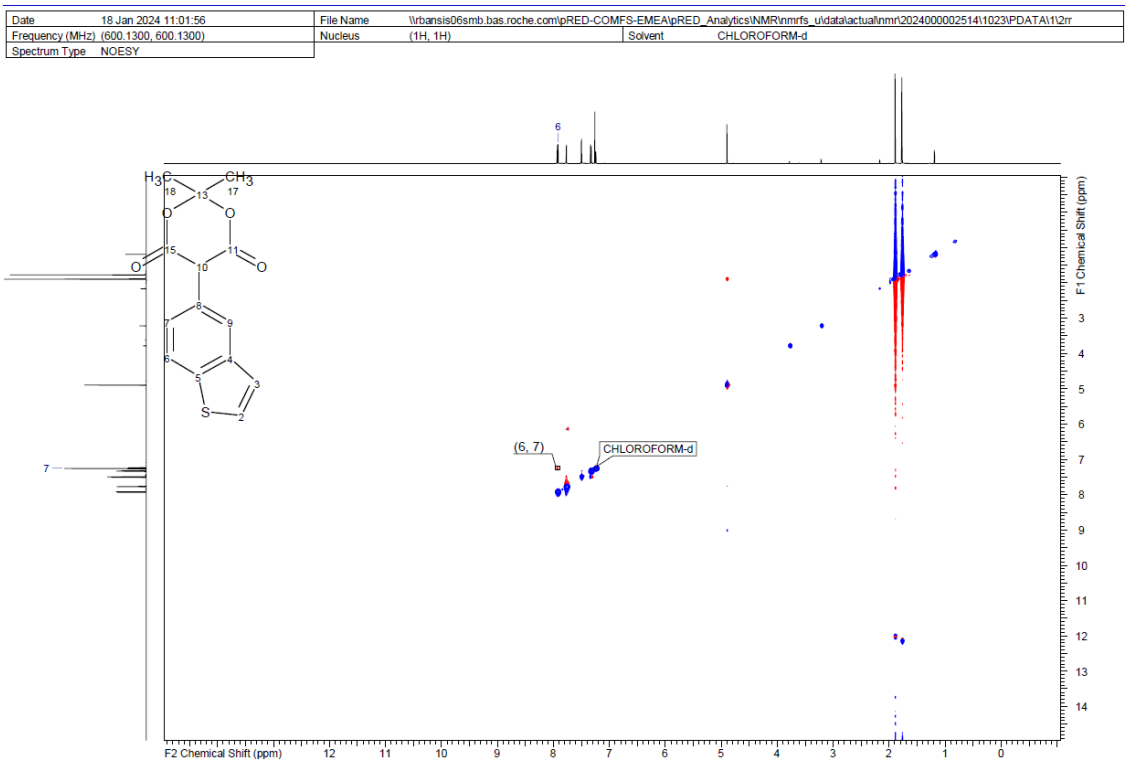


Figure S92. NOESY of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

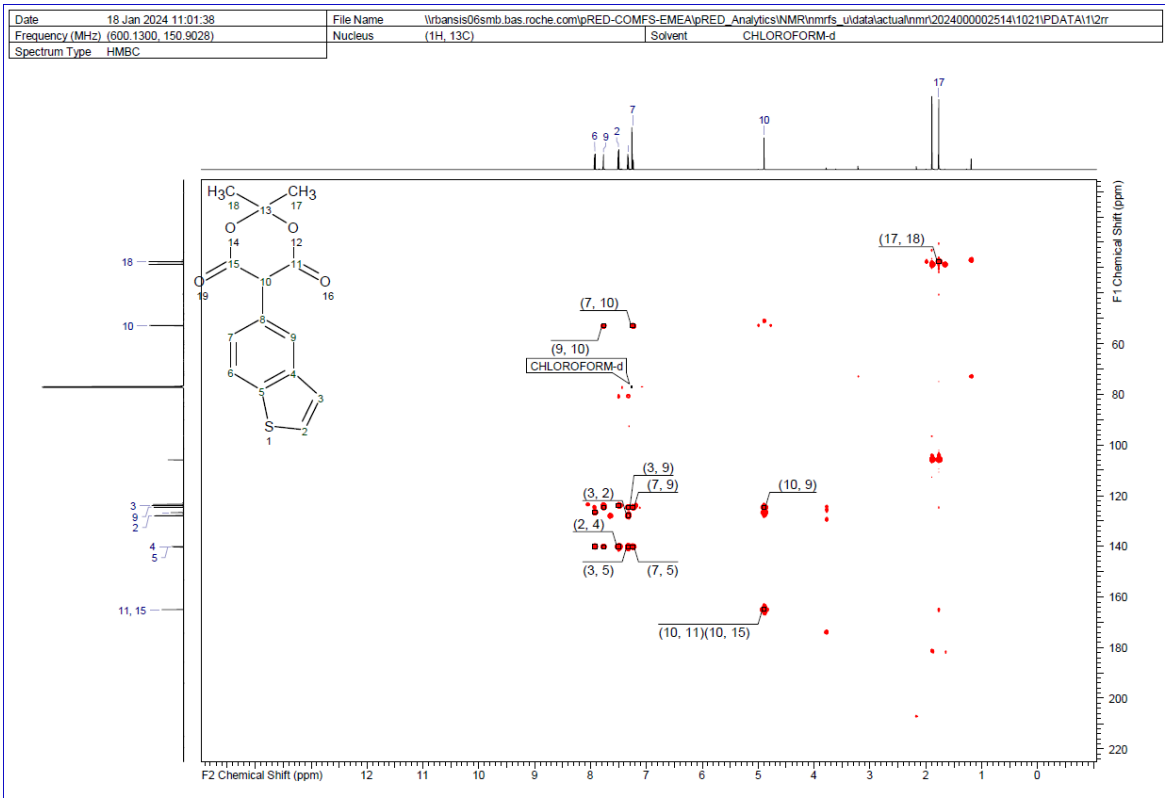


Figure S93. HMBC of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

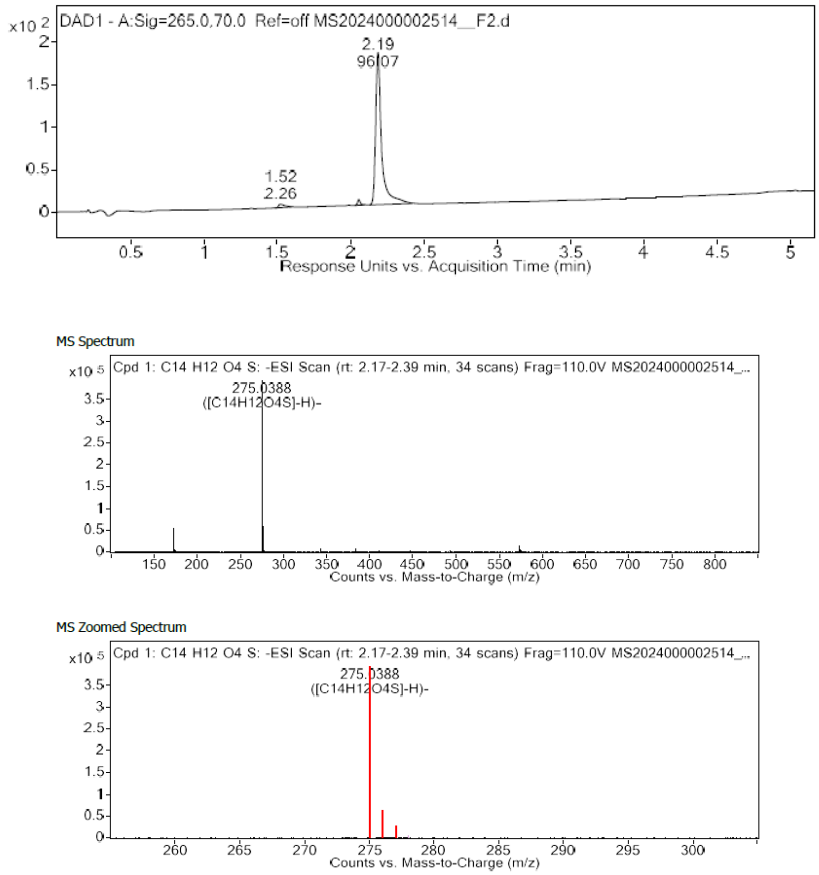
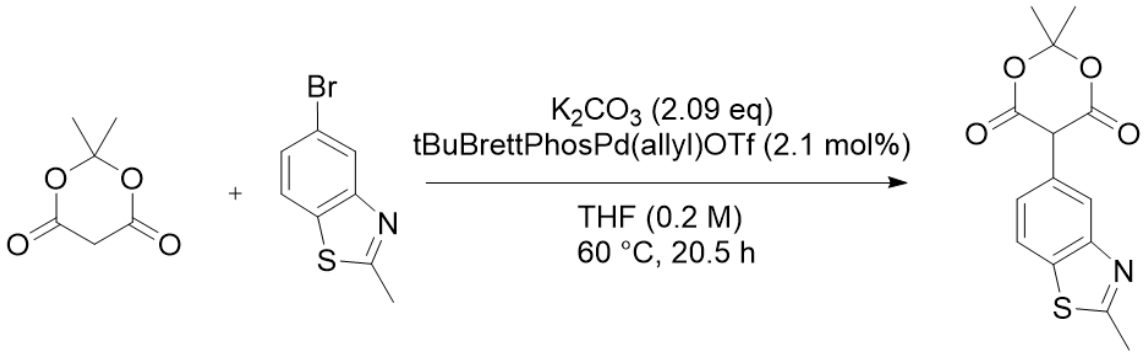


Figure S94. HRMS of 5-(1-benzothiophen-5-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione



Option B of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid (395 mg, 2.74 mmol, 1.09 equiv), 5-bromo-2-methyl-1,3-benzothiazole (572 mg, 2.51 mmol, 1.0 equiv), K_2CO_3 (726 mg, 5.25 mmol, 2.09 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (42 mg, 0.0538 mmol, 0.02 equiv). After 20.5 h at 60 °C, LCMS indicated full conversion of the aryl bromide. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used, acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (539.7 mg, 74% yield, 96% pure by LCMS) was obtained as a light yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.88 (d, J=1.9 Hz, 1 H), 7.87 (d, J=8.4 Hz, 1 H), 7.25 (dd, J=8.3, 2.0 Hz, 1 H), 4.89 (s, 1 H), 2.84 (s, 3 H), 1.91 (s, 3 H), 1.80 (d, J=0.6 Hz, 3 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.2, 164.4, 153.5, 136.0, 128.3, 125.1, 123.4, 121.9, 105.6, 52.6, 28.4, 27.2, 20.0 ppm

HRMS: $C_{14}H_{13}NO_4S$; calc. for ($M+H^+$) 291.0565, found: 291.0566.

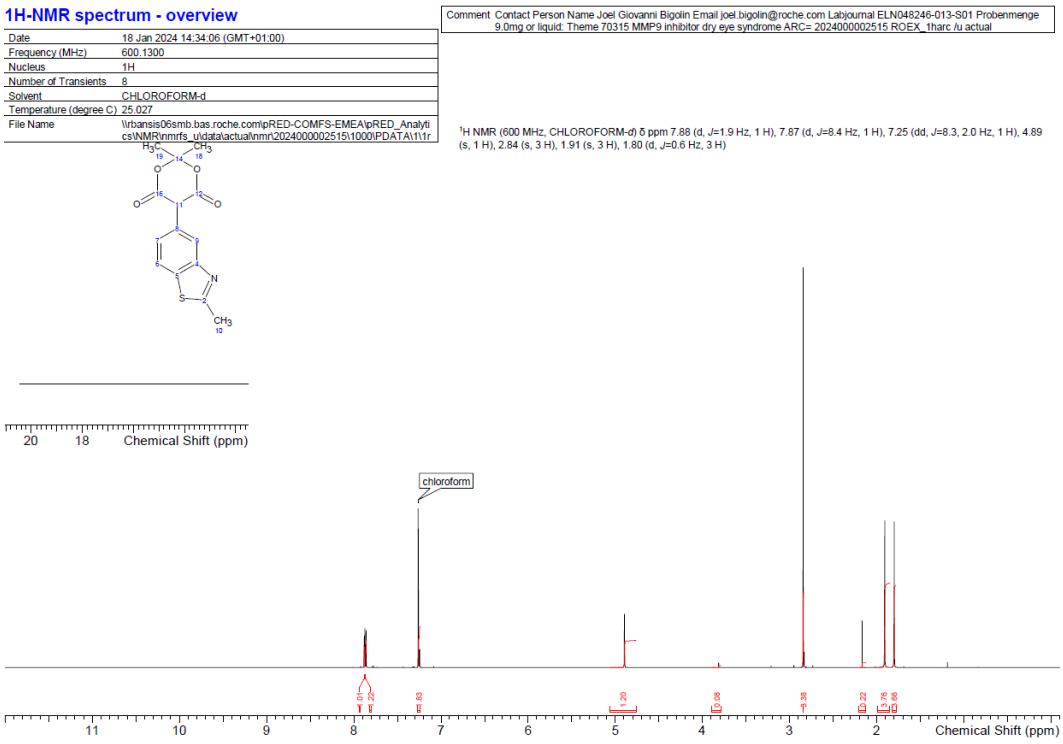


Figure S95. ^{1}H NMR (600 MHz, $CDCl_3$) of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

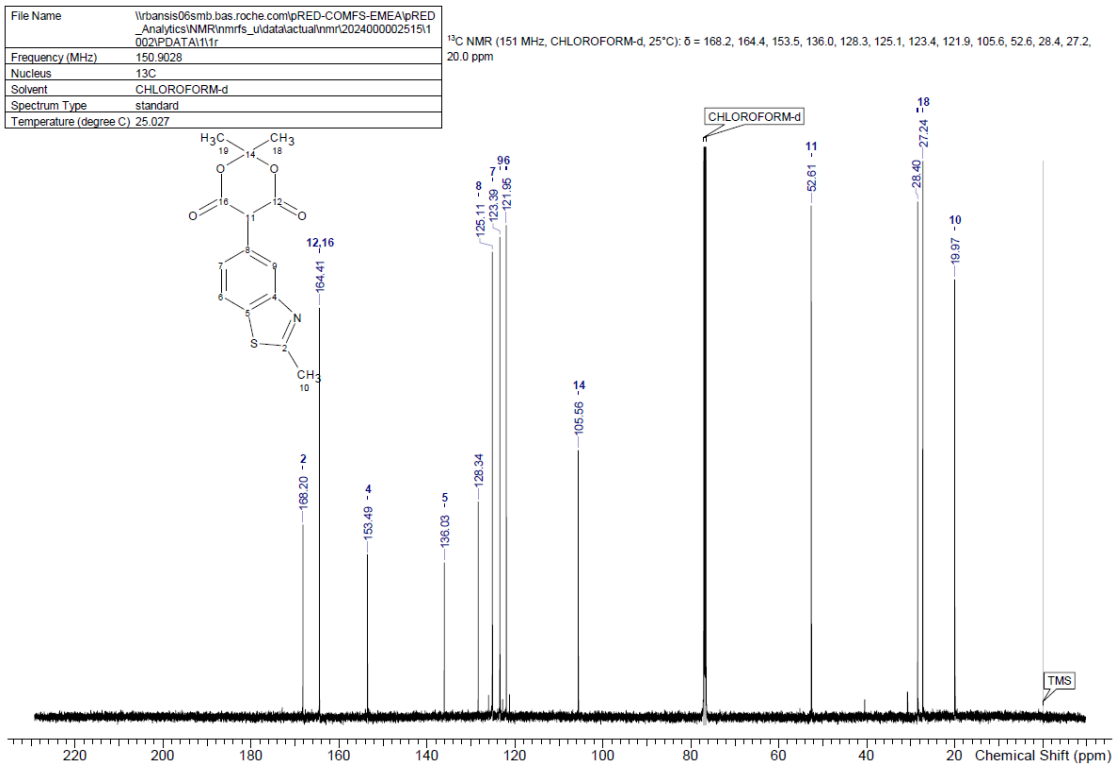


Figure S96. ^{13}C NMR (151 MHz, $CDCl_3$) of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

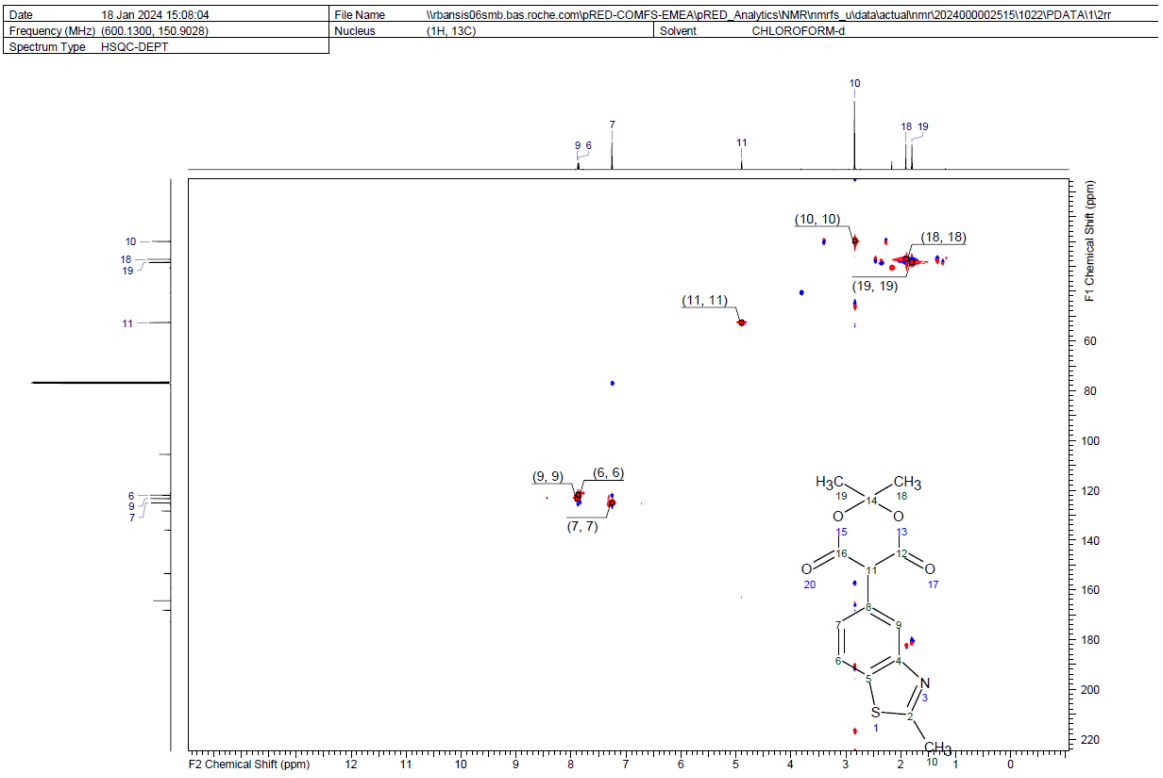


Figure S97. HSQC-DEPT of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

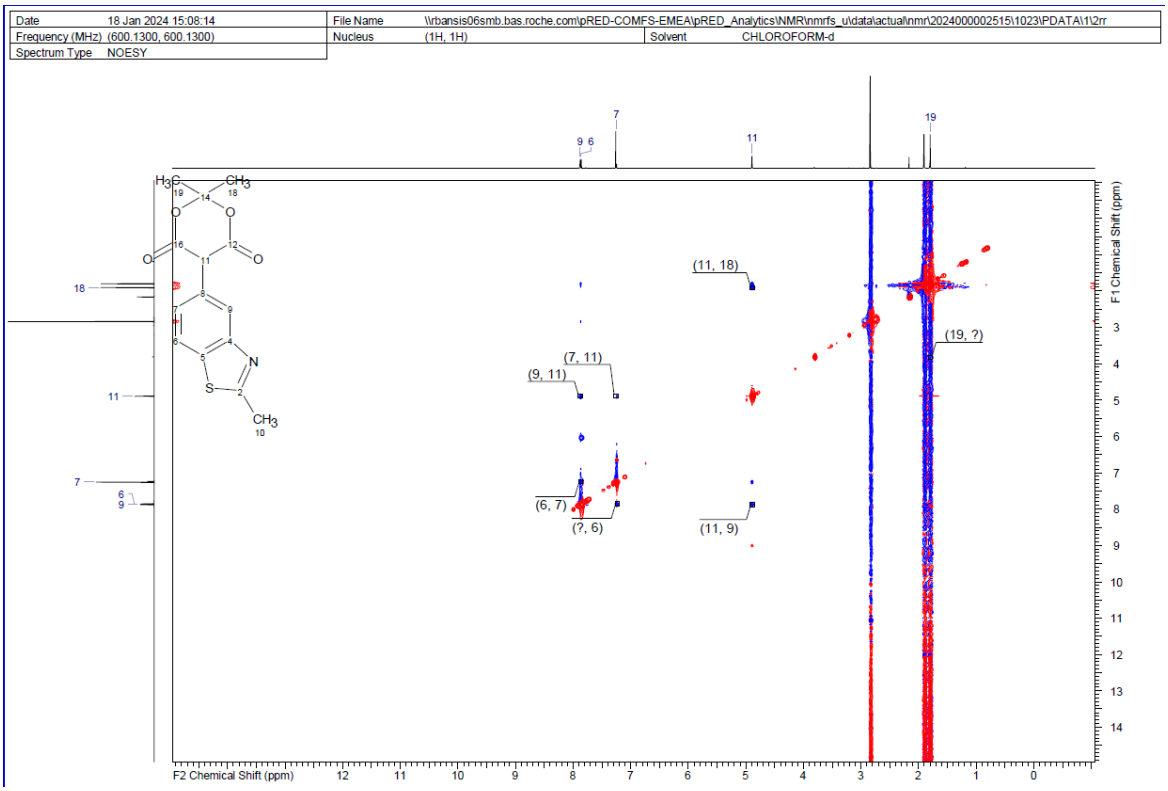


Figure S98. NOESY of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

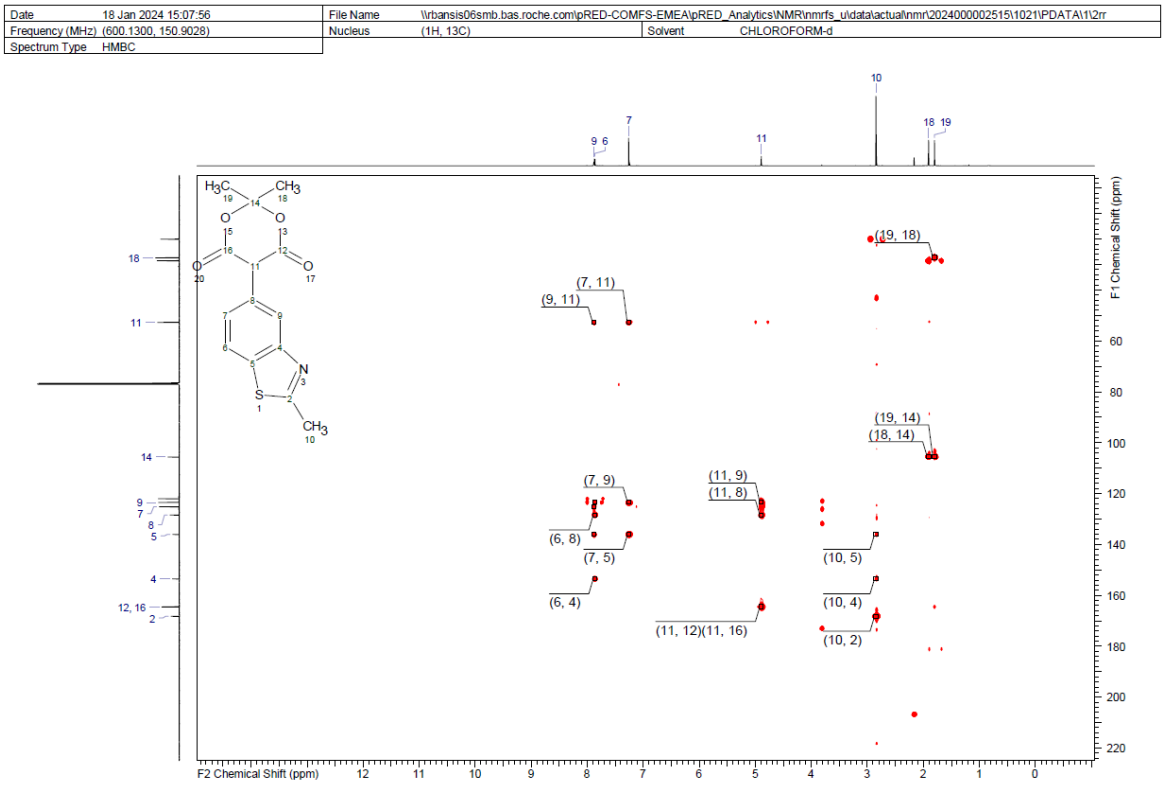


Figure S99. HMBC of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

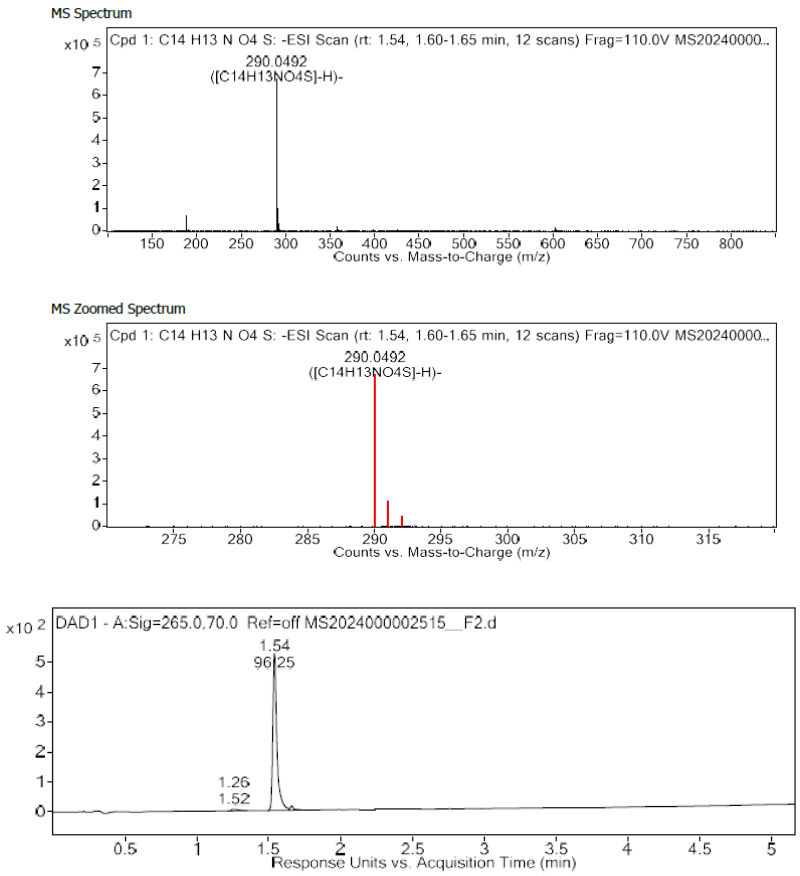
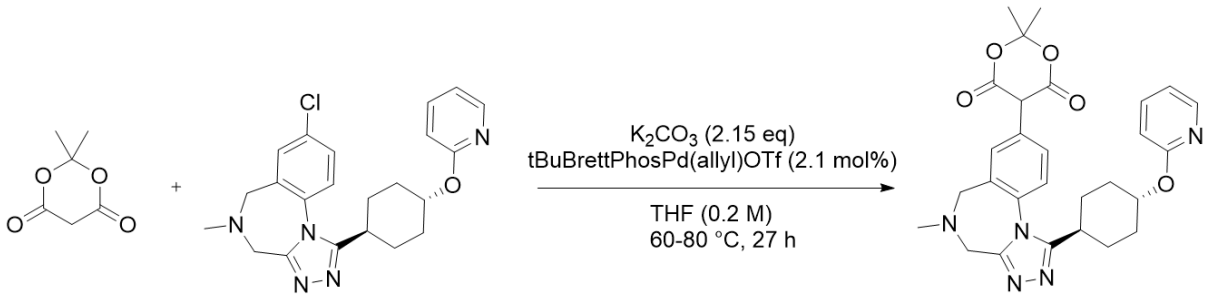


Figure S100. HRMS of 2,2-dimethyl-5-(2-methyl-1,3-benzothiazol-5-yl)-1,3-dioxane-4,6-dione

2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione



Option B of the Meldrum's Acid General Procedure was followed using a 20 mL vial, Meldrum's Acid **2** (396 mg, 2.75 mmol, 1.1 equiv), 8-chloro-5-methyl-1- [4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3a][1,4]benzodiazepine (1025 mg, 2.5 mmol, 1.0 equiv), K_2CO_3 (743 mg, 5.38 mmol, 2.2 equiv), THF (12.5 mL, 0.2M) and ^{t}BuBrettPhosPd(allyl)OTf (40.3 mg, 0.0516 mmol, 0.02 equiv). After 16 h at 60 °C, LCMS indicated 28% conversion of the aryl chloride. After 22h at 80 °C, LCMS indicated 60% conversion of the SM. After 27 h at 80 °C, LCMS indicated only 47% conversion of the aryl

chloride. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used and acidified to pH 2.

As no product precipitated out, the reaction mixture was extracted with TBME (3 x 40 mL). LCMS indicated no product in the organic phase and the pH was therefore elevated to 4 with Na_2CO_3 (10%, aq). After subsequent extractions with DCM (12 x 40 mL), the combined organic phases were dried over $MgSO_4$ and evaporated with a rotary evaporator. The product was then dried in a vacuum oven at 60 °C and 0.5 – 5 mbar overnight. The title product (419.3 mg, 28% yield, 88% pure by LCMS) was obtained as an off-white solid, mainly in the enol form.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.24 - 8.56 (m, 1 H), 8.07 - 8.18 (m, 1 H), 7.50 - 7.65 (m, 1 H), 7.47 - 7.77 (m, 1 H), 7.29 - 7.37 (m, 1 H), 6.80 - 6.87 (m, 1 H), 6.62 - 6.72 (m, 1 H), 5.05 - 5.25 (m, 1 H), 4.30 - 4.44 (m, 1 H), 4.13 - 4.29 (m, 2 H), 3.68 (s, 1 H), 3.30 - 3.38 (m, 1 H), 3.03 - 3.13 (m, 1 H), 2.68 - 3.04 (m, 3 H), 2.41 (br d, J=10.7 Hz, 1 H), 2.26 - 2.35 (m, 1 H), 2.18 - 2.26 (m, 2 H), 1.89 - 2.01 (m, 1 H), 1.80 - 1.86 (m, 1 H), 1.72 (s, 6 H), 1.58 - 1.67 (m, 1 H), 1.41 - 1.53 (m, 1 H) ppm

^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.5, 166.5, 163.2, 163.1, 159.3, 157.8, 146.9, 146.8, 138.7, 133.5, 133.1, 132.5, 132.2, 122.9, 122.2, 116.6, 116.6, 111.8, 111.5, 101.8, 101.7, 78.6, 78.6, 72.2, 72.1, 72.1, 56.2, 55.1, 46.6, 46.5, 42.8, 42.2, 41.5, 33.8, 33.5, 31.4, 31.4, 31.2, 31.2, 31.2, 31.0, 30.0, 29.7, 29.4, 27.7, 26.2 ppm

HRMS: $C_{28}H_{31}N_5O_5$; calc. for ($M+H^+$) 517.2325, found: 517.2333.

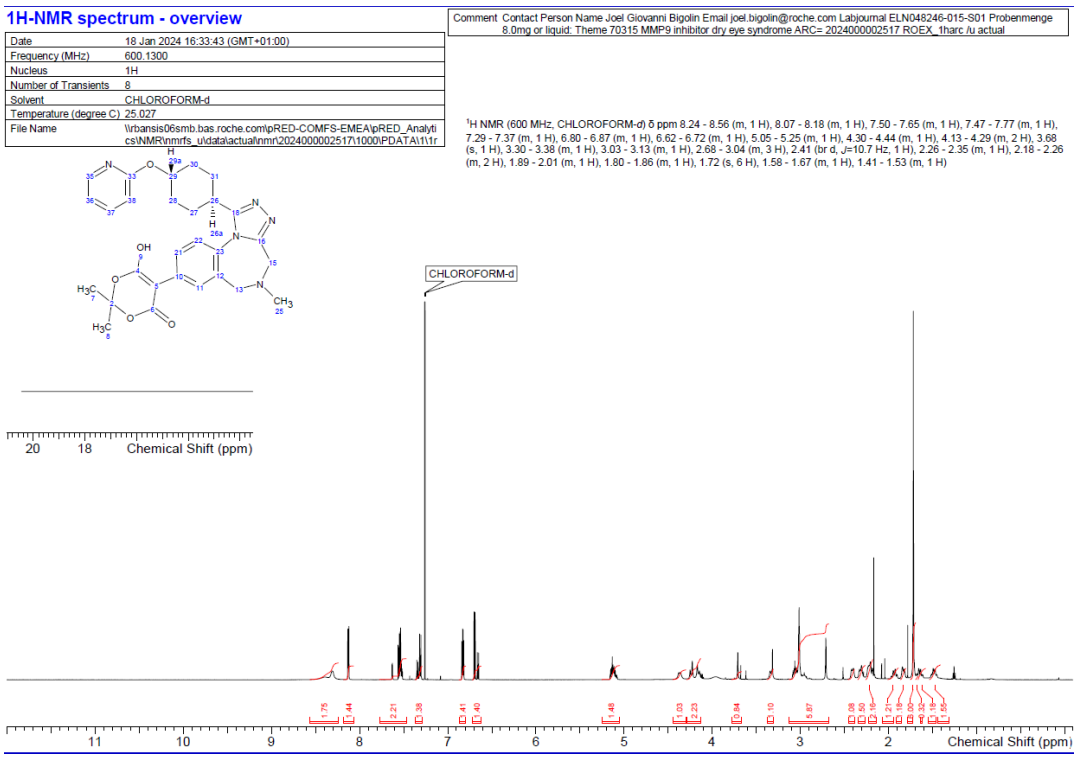


Figure S101. ^{1}H NMR (600 MHz, $CDCl_3$) of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

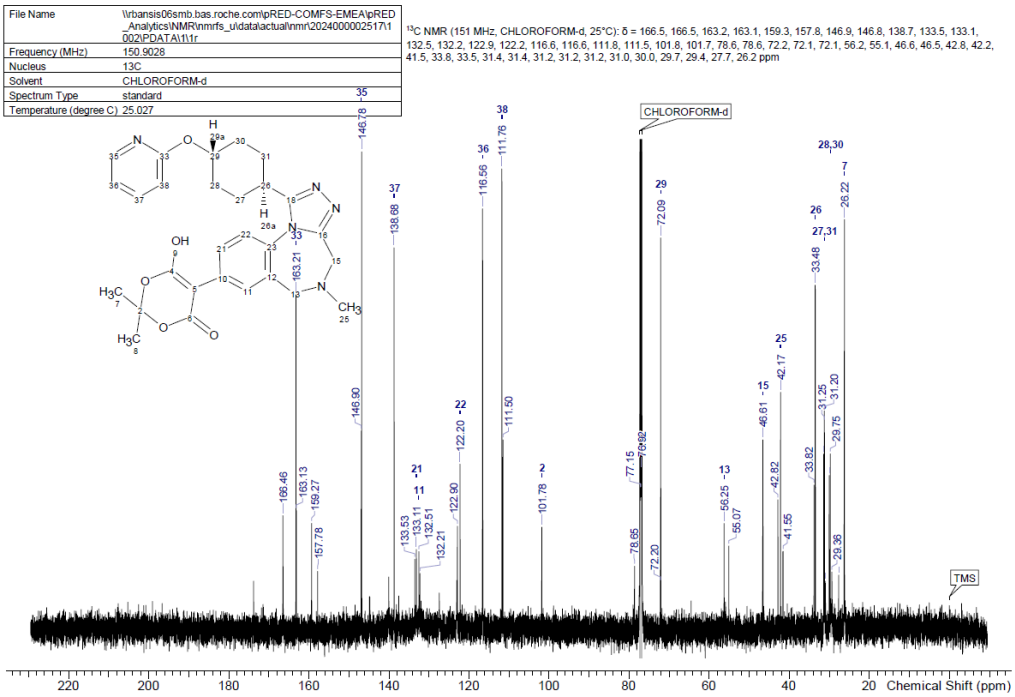


Figure S102. ^{13}C NMR (151 MHz, $CDCl_3$) of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

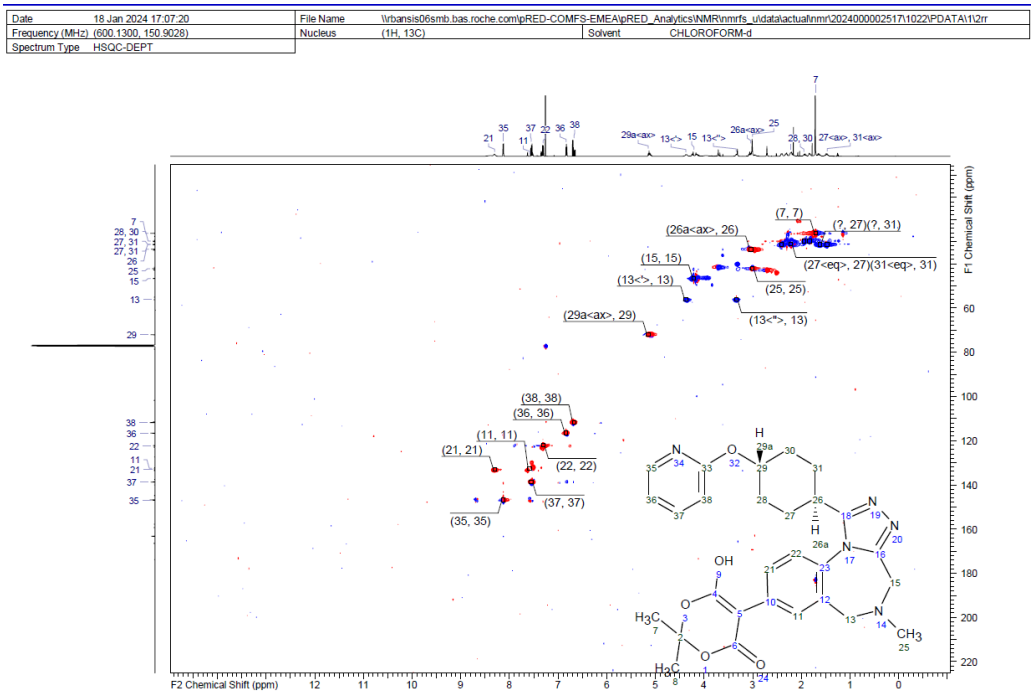


Figure S103. HSQC-DEPT of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

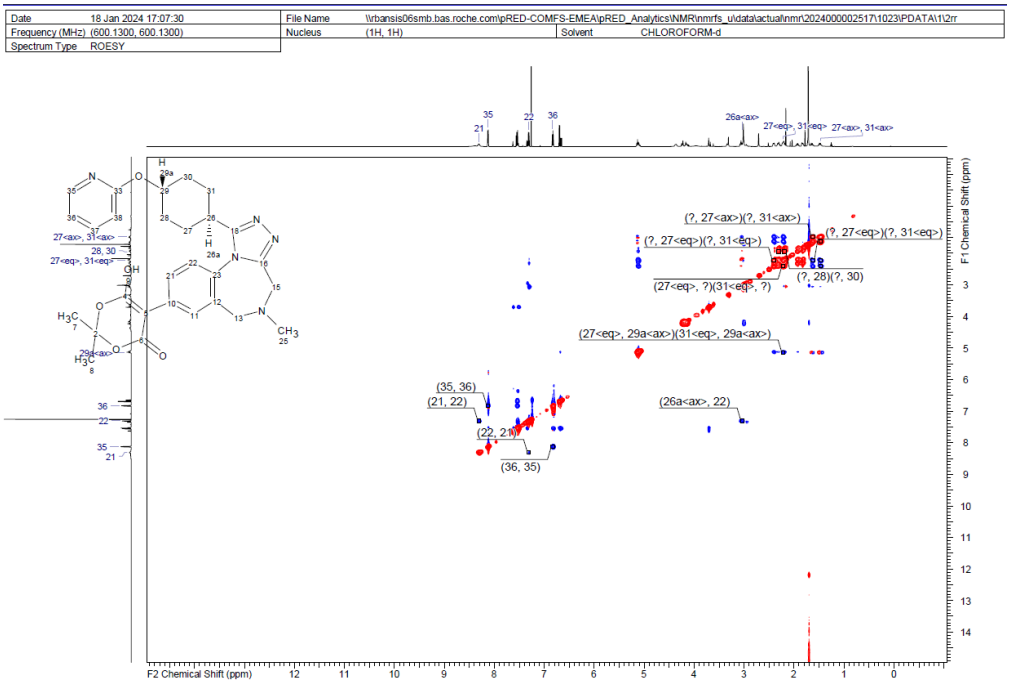


Figure S104. ROESY of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

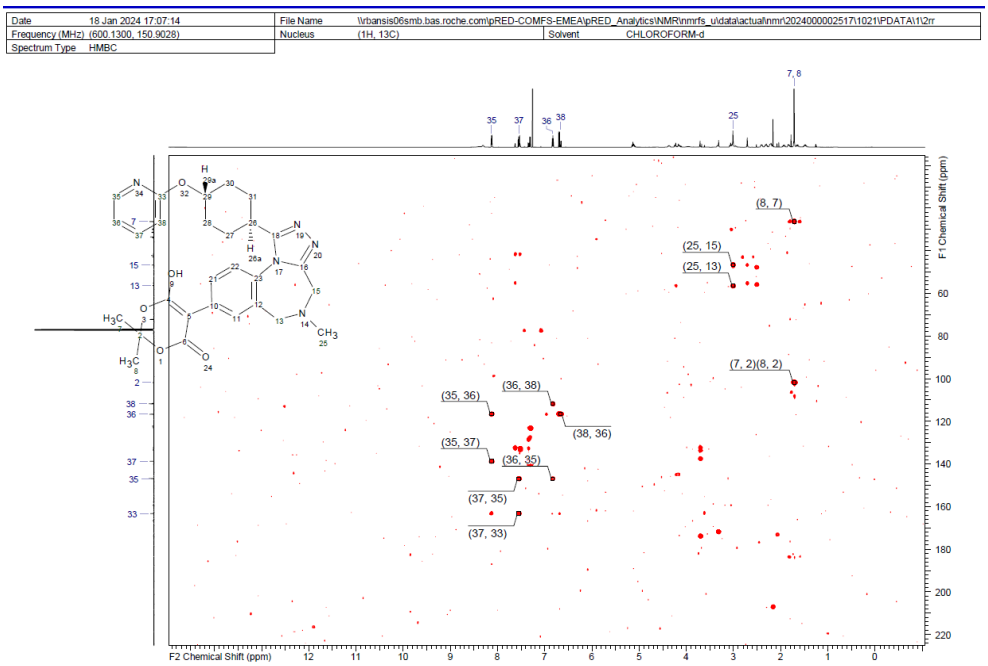


Figure S105. HMBC of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

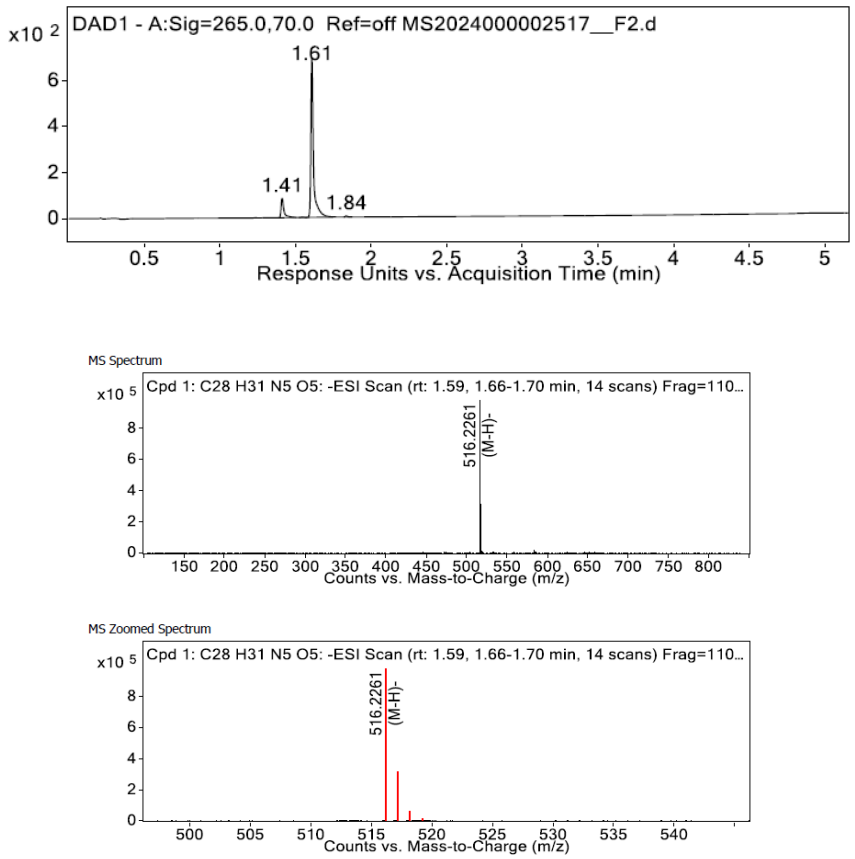
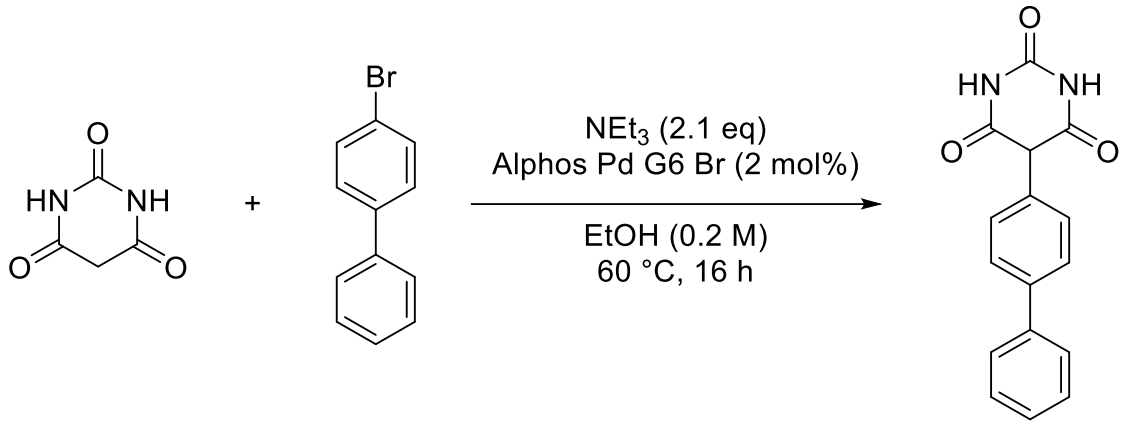


Figure S106. HRMS of 2,2-dimethyl-5-[5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-8-yl]-1,3-dioxane-4,6-dione

5-([1,1'-biphenyl]-4-yl)-1,3-diazinane-2,4,6-trione



Option A of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (359 mg, 2.80 mmol, 1.1 equiv), 4-bromobiphenyl (585 mg, 2.51 mmol, 1.0 equiv), triethylamine (730 uL, 5.24 mmol, 2.1 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (59.2 mg, 0.0516 mmol, 0.02 equiv). After 16 h at 60 °C, LCMS indicated full conversion of the aryl bromide. For the work-up, NaOH (12.5 mL, 1M, aq) was used. The washings were done with TBME (3 x 40 mL). Acidification to pH 2 and washed with H_2O (3 x 45 mL). The title compound (603.3 mg, 86% yield, >99% pure by LCMS) was obtained as a slightly pink solid (^{1}H-NMR and HRMS did indicate high purity) in a molar tautomeric ratio of 2:1 (keto / enol).

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.41 (br t, J=2.2 Hz, 1 H), 10.74 (br s, 1 H), 7.54 - 7.74 (m, 4 H), 7.44 - 7.51 (m, 2 H), 7.30 - 7.43 (m, 3 H), 4.91 (s, 1 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.6, 151.5, 150.3, 140.2, 140.1, 134.1, 132.1, 131.9, 130.4, 129.4, 128.1, 127.7, 127.7, 127.4, 127.2, 127.1, 127.0, 127.0, 126.4, 92.4, 55.2 ppm

HRMS: $C_{16}H_{12}N_2O_3$; calc. for ($M+H^+$) 280.0848, found: 280.0852.

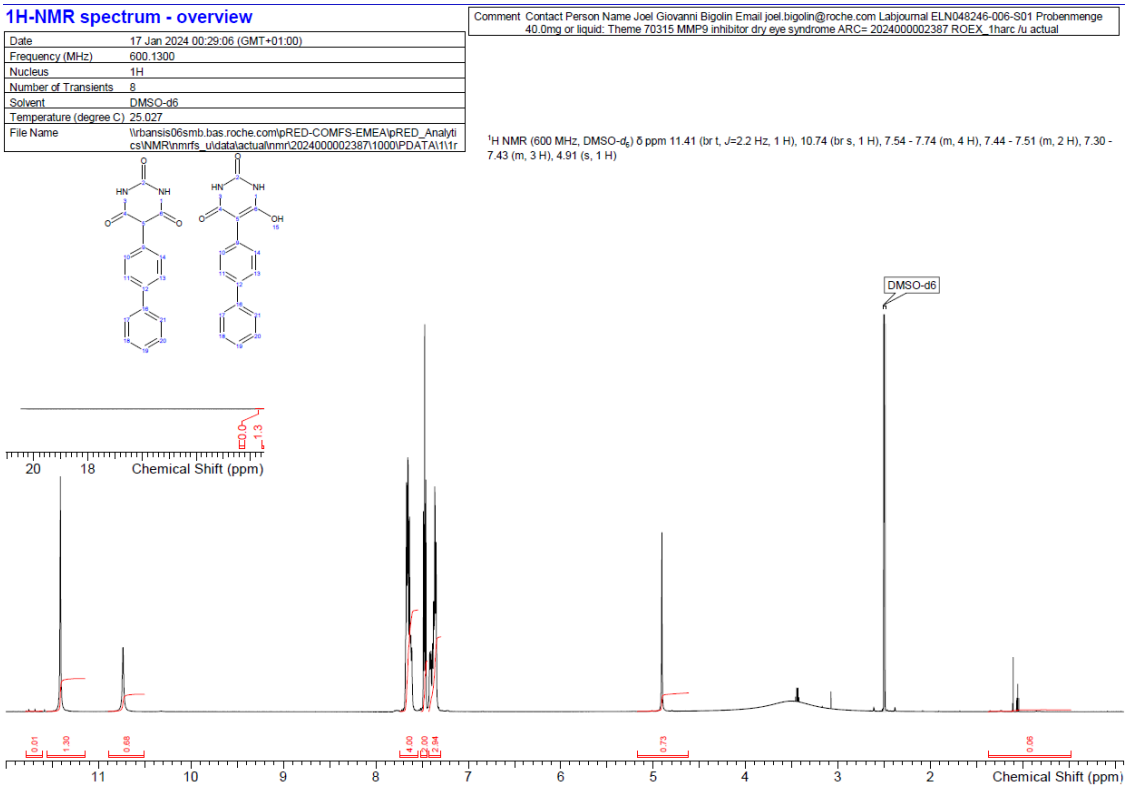


Figure S107. ^{1}H NMR (600 MHz, DMSO-d_6) of 5-([1,1'-biphenyl]-4-yl)-1,3-diazinane-2,4,6-trione

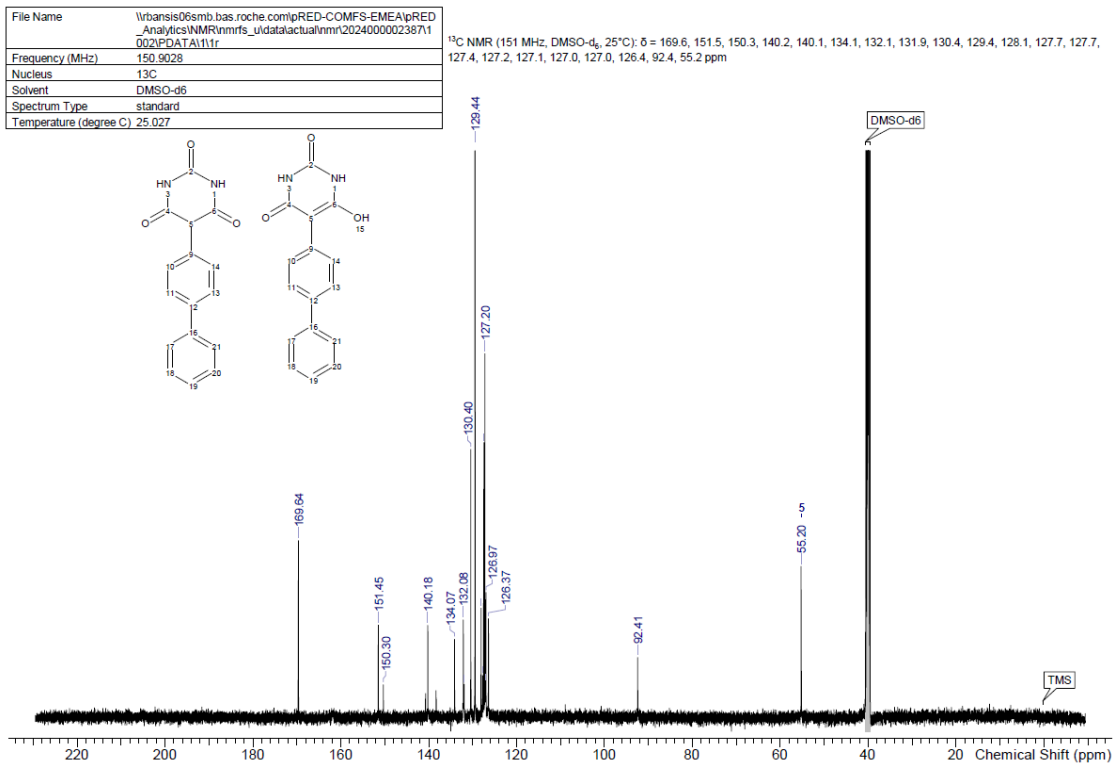


Figure S108. ^{13}C NMR (151 MHz, DMSO-d_6) of 5-([1,1'-biphenyl]-4-yl)-1,3-diazinane-2,4,6-trione

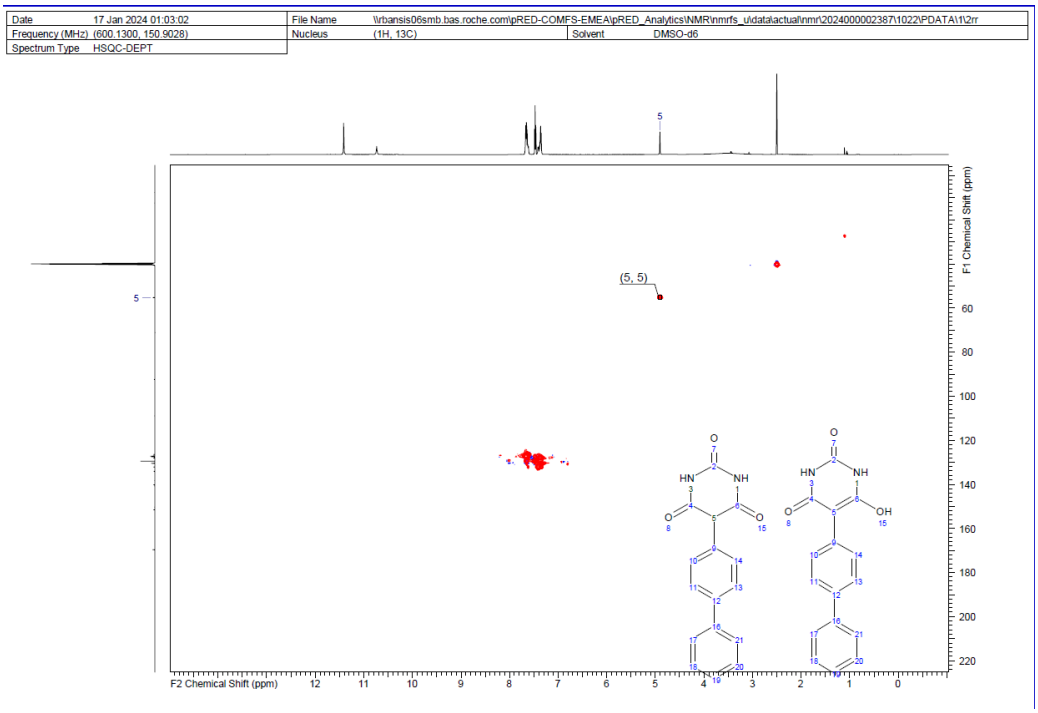


Figure S109. HSQC-DEPT of 5-([1,1'-biphenyl]-4-yl)-1,3-diazinane-2,4,6-trione

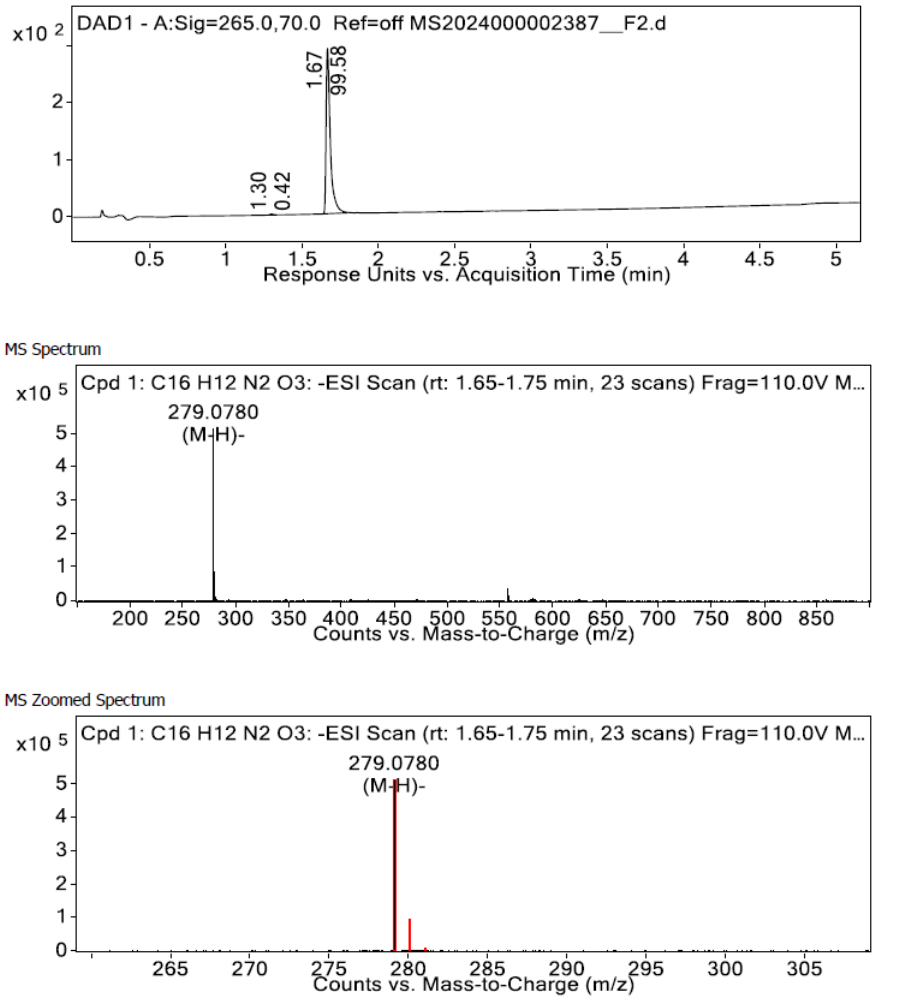
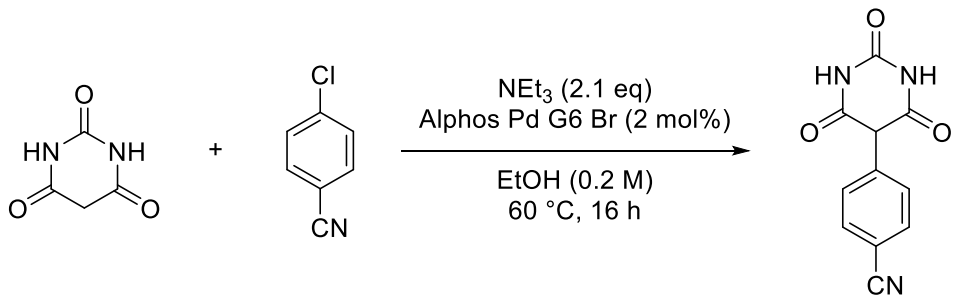


Figure S110. HRMS of 5-([1,1'-biphenyl]-4-yl)-1,3-diazinane-2,4,6-trione

4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile



Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (353 mg, 2.76 mmol, 1.1 equiv), 4-chlorobenzonitrile (345 mg, 2.51 mmol, 1.0 equiv), triethylamine (732 uL, 5.25 mmol, 2.09 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (57.1 mg, 0.0498 mmol, 0.02 equiv). After 16 h at 60 °C, LCMS indicated full conversion of the aryl chloride. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) was used. The washings were done with TBME (3 x 40 mL) and extracted back with H_2O (1 x 100 mL), due to a precipitate. Acidification

to pH 2 and washed with H_2O (3 x 45 mL). The title compound (497.6 mg, 87% yield, 99% pure by LCMS) was obtained as a white solid in a molar tautomeric ratio of 1:2 (keto / enol).

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.22 - 11.63 (m, 1 H), 10.37 - 10.80 (m, 1 H), 7.18 - 8.33 (m, 4 H), 5.18 - 5.35 (m, 1 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 168.8, 168.8, 162.2, 162.1, 162.1, 162.1, 162.1, 150.3, 139.3, 139.3, 139.3, 139.3, 132.7, 132.7, 132.7, 132.7, 131.8, 131.7, 131.5, 131.4, 119.9, 119.9, 107.8, 107.8, 91.3, 91.2, 55.6 ppm

HRMS: $C_{11}H_7N_3O_3$; calc. for ($M+H^+$) 229.0487, found: 229.0488.

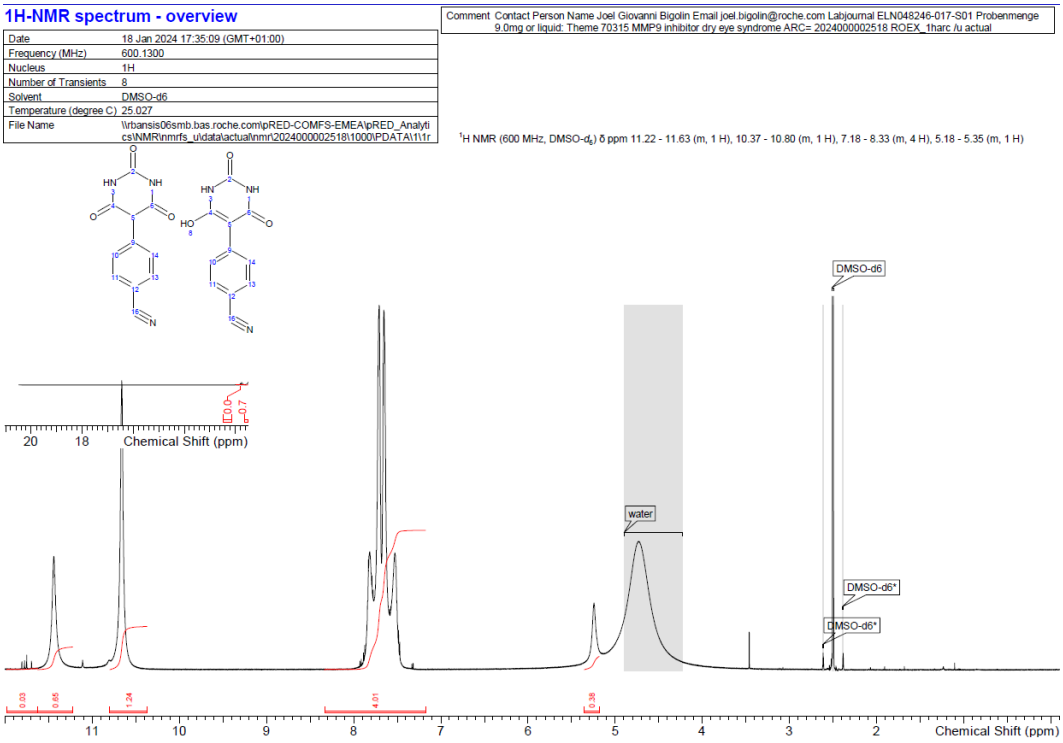


Figure S111. ^{1}H NMR (600 MHz, DMSO-d_6) of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

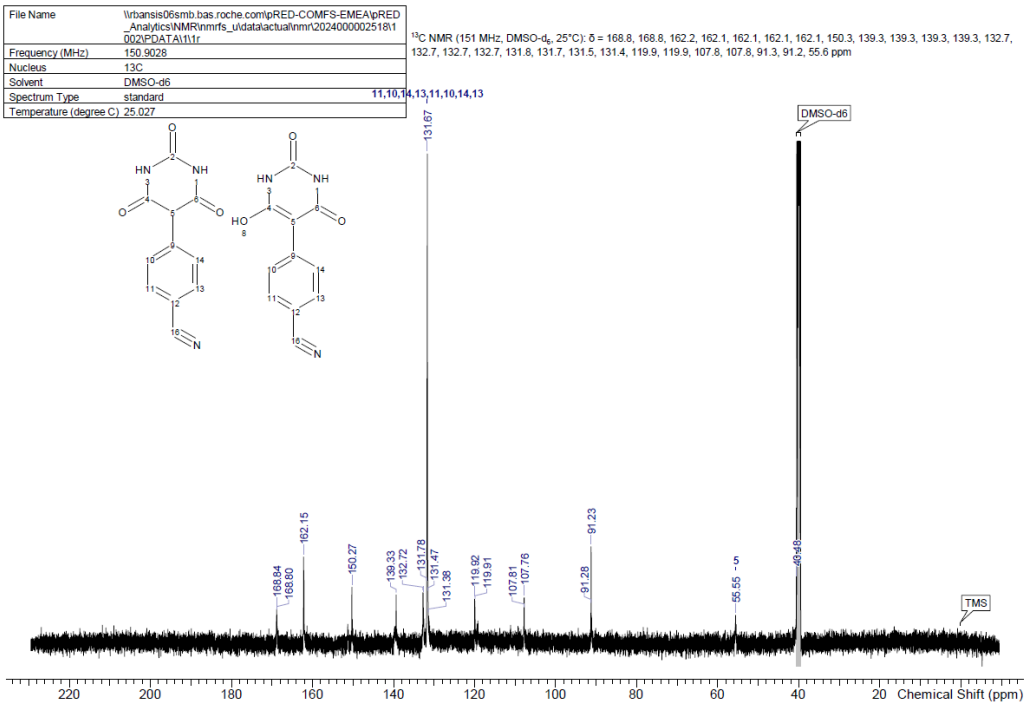


Figure S112. ^{13}C NMR (151 MHz, DMSO-d_6) of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

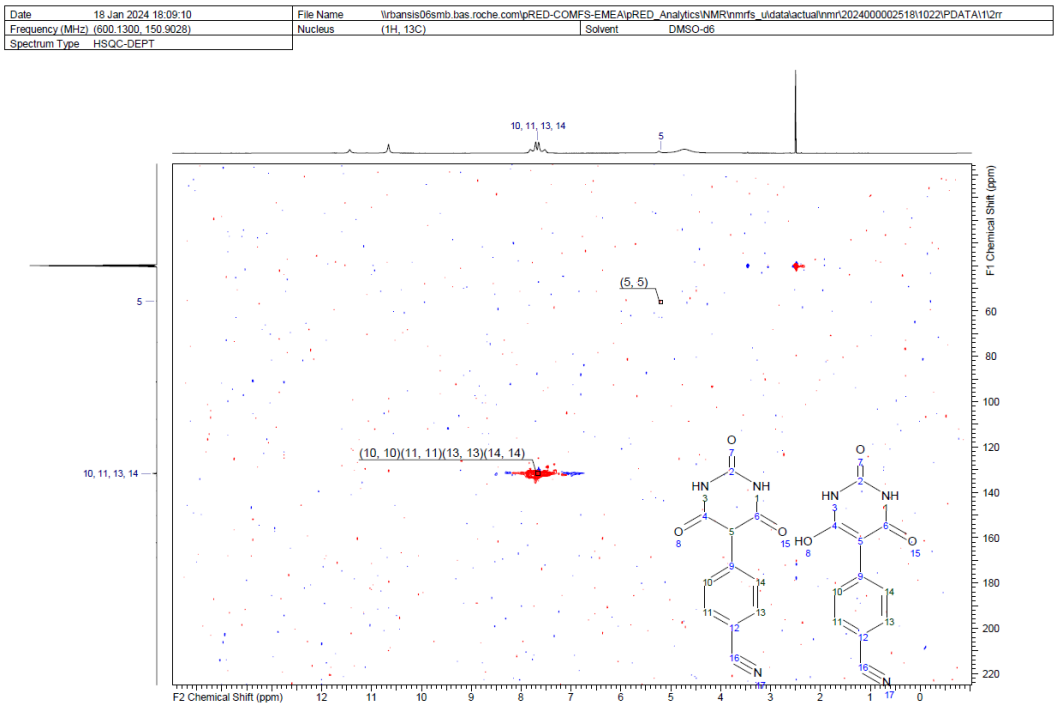


Figure S113. HSQC-DEPT of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

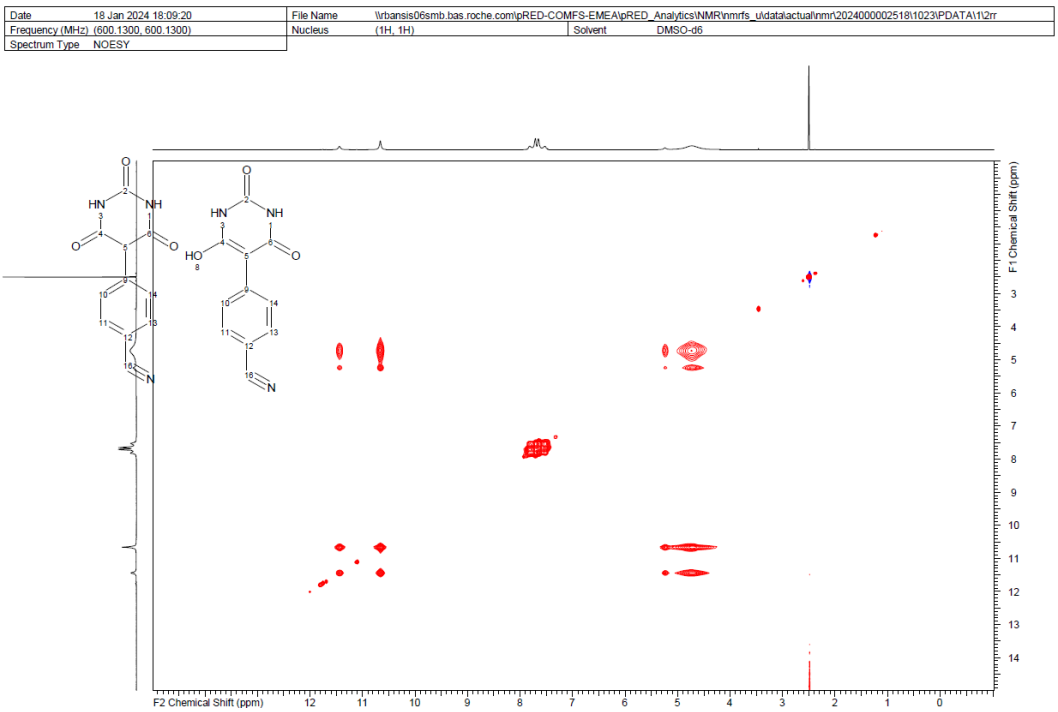


Figure S114. NOESY of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

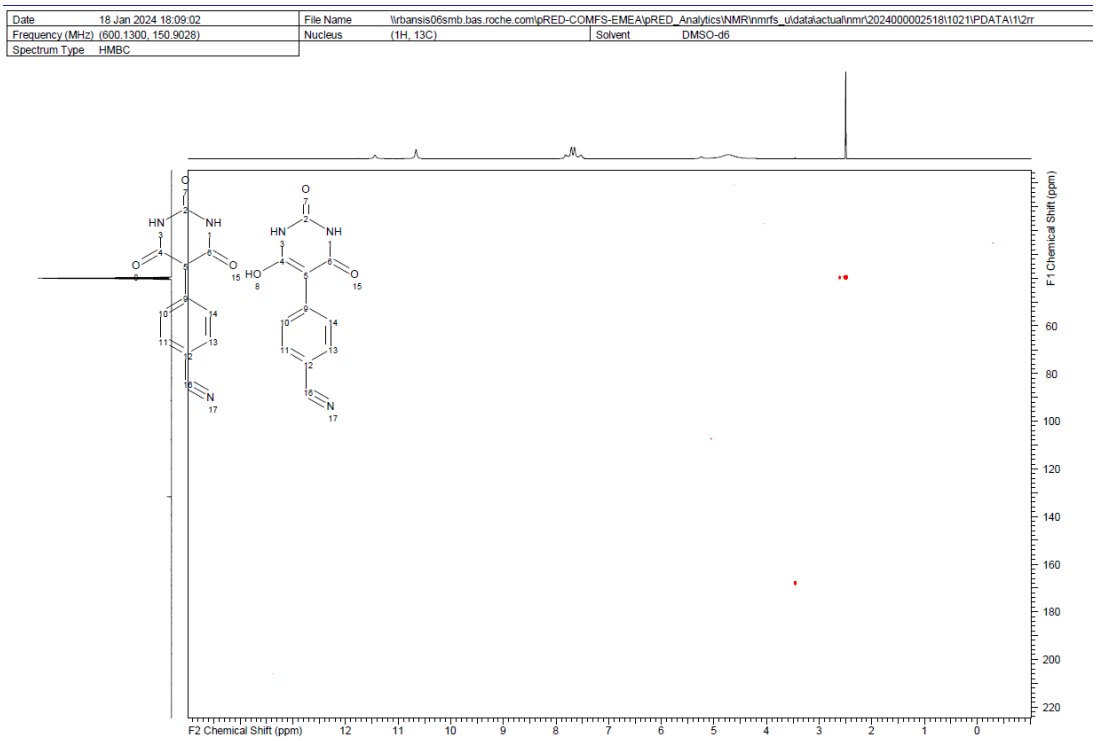


Figure S115. HMBC of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

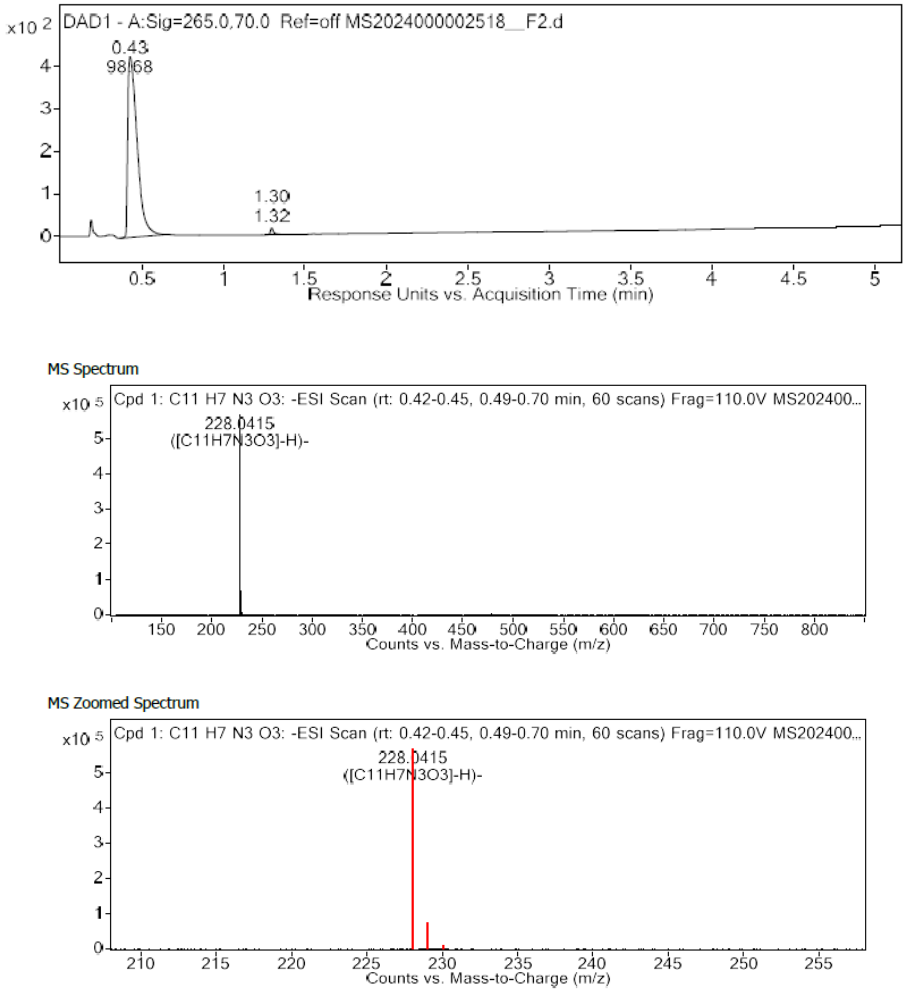
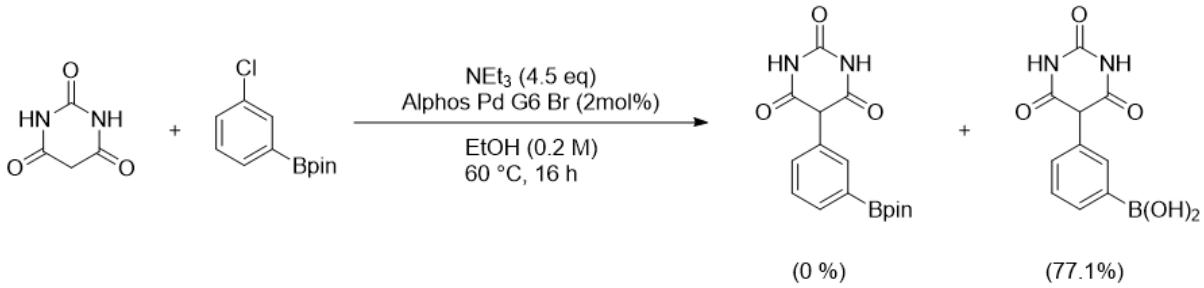


Figure S116. HRMS of 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzonitrile

[3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid



(0 %) (77.1%)

Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (354 mg, 2.76 mmol, 2.36 equiv), 2-(3-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (279 mg, 1.17 mmol, 1.0 equiv), triethylamine (732 uL, 5.25 mmol, 4.49 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (57.5 mg, 0.0502 mmol, 0.04 equiv). After 16 h at 60 °C, LCMS indicated full conversion of the starting material. For the work-up, NaOH (12.5 mL, 1N, aq) was used. The washings were done with TBME (3 x 20 mL). Acidification to pH 1 and washed with H_2O (3 x 45 mL). Instead of the title compound, the corresponding boronic acid (223.6 mg, 77% yield was obtained as a white solid in a molar tautomeric ratio of around 3.75:1 (keto / enol).

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.36 (br s, 1 H), 11.39 (s, 1 H), 10.73 (s, 1 H), 7.93 - 8.44 (m, 2 H), 7.56 - 7.88 (m, 2 H), 7.25 - 7.42 (m, 2 H), 4.70 (s, 1 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.8, 151.5, 150.3, 137.7, 134.8, 134.4, 134.0, 133.6, 131.5, 128.3, 127.3, 93.3, 55.5 ppm

HRMS: $C_{10}H_9BN_2O_5$; calc. for ($M+H^+$) 248.0605, found: 248.0609.

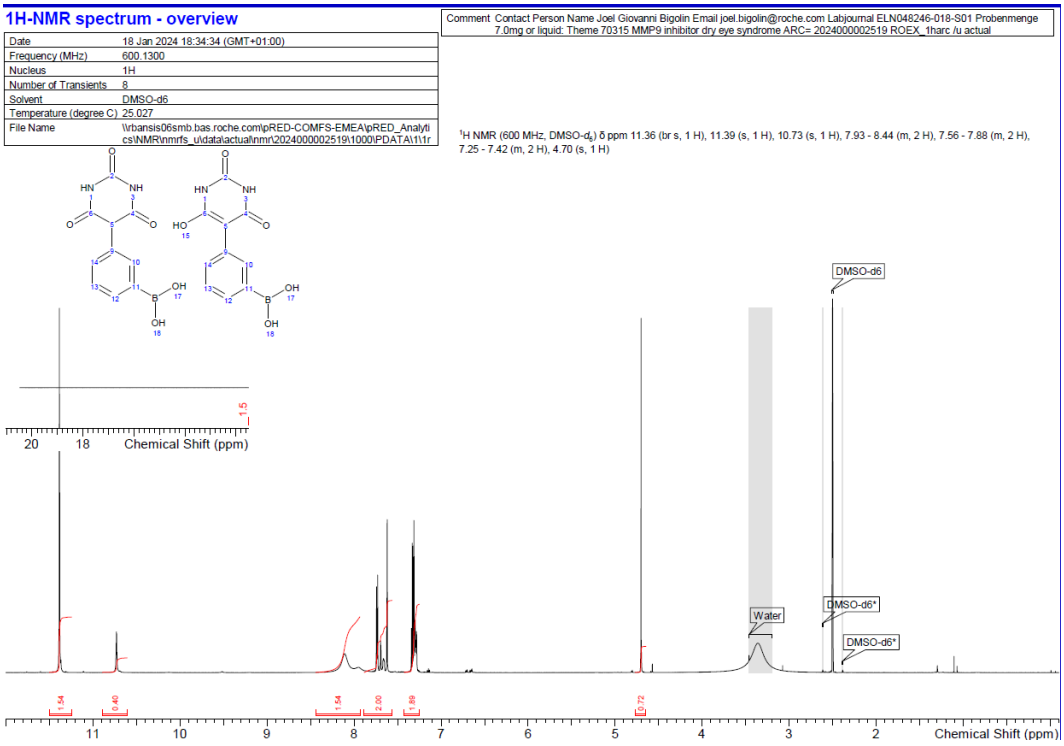


Figure S117. ^{1}H NMR (600 MHz, DMSO-d_6) of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

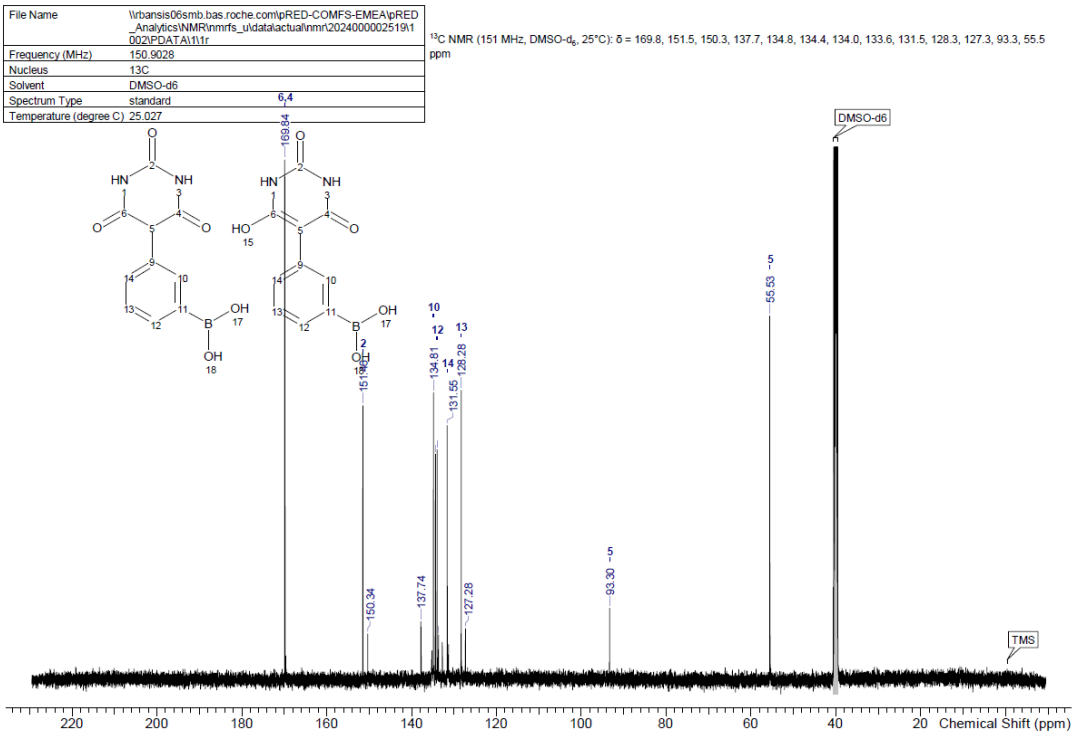


Figure S118. ^{13}C NMR (151 MHz, DMSO-d_6) of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

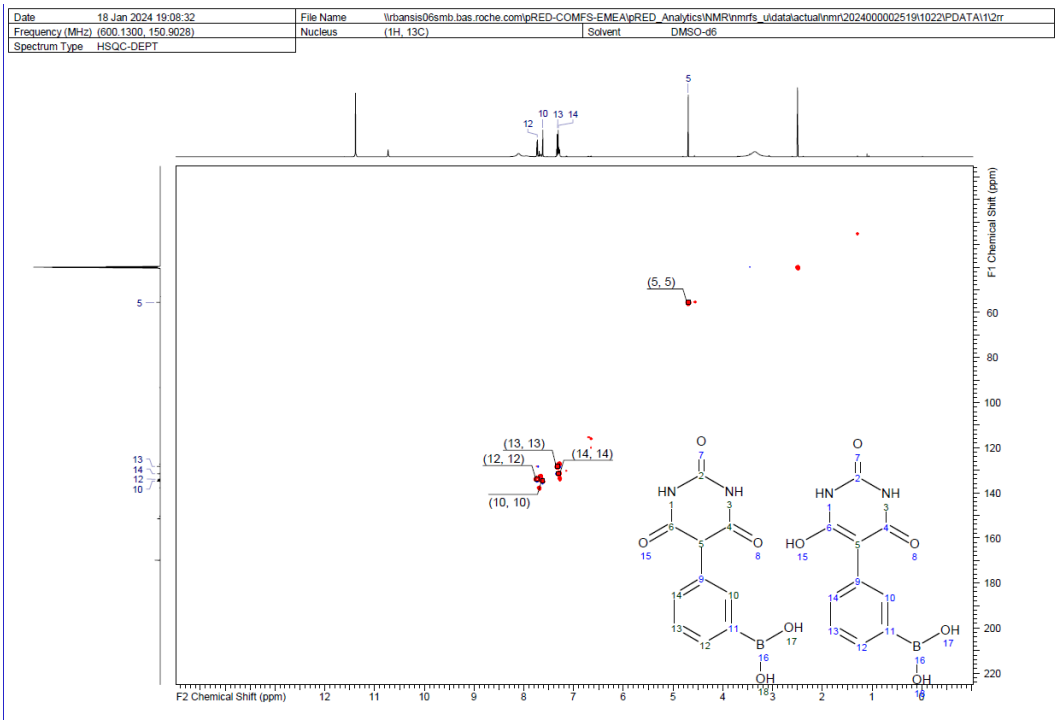


Figure S119. HSQC-DEPT of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

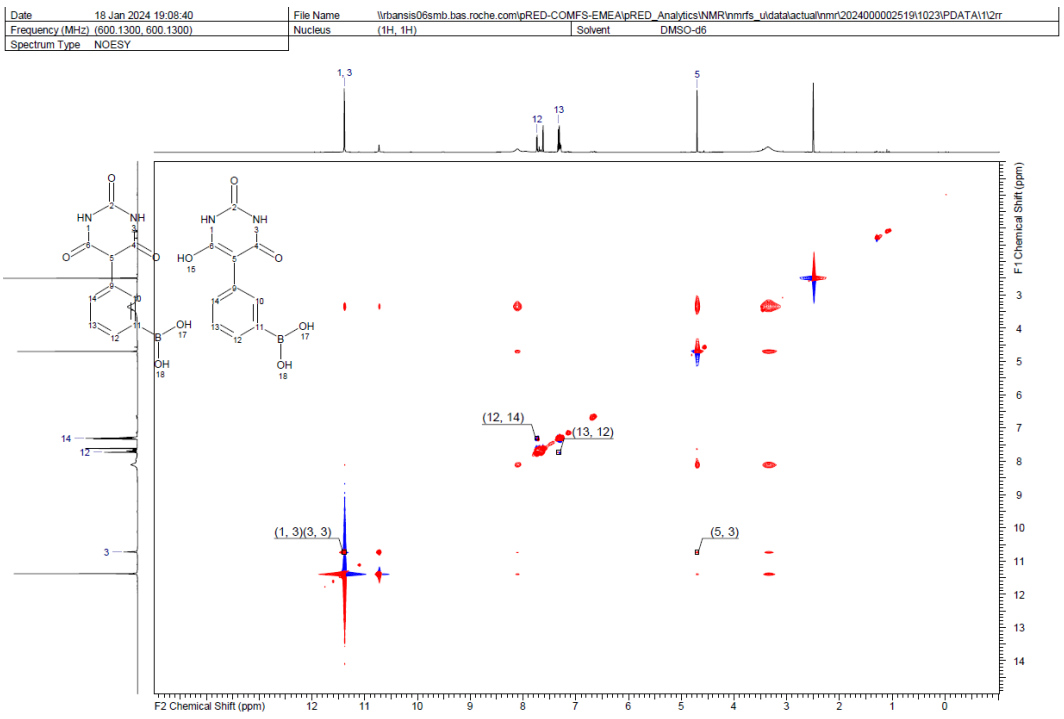


Figure S120. NOESY of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

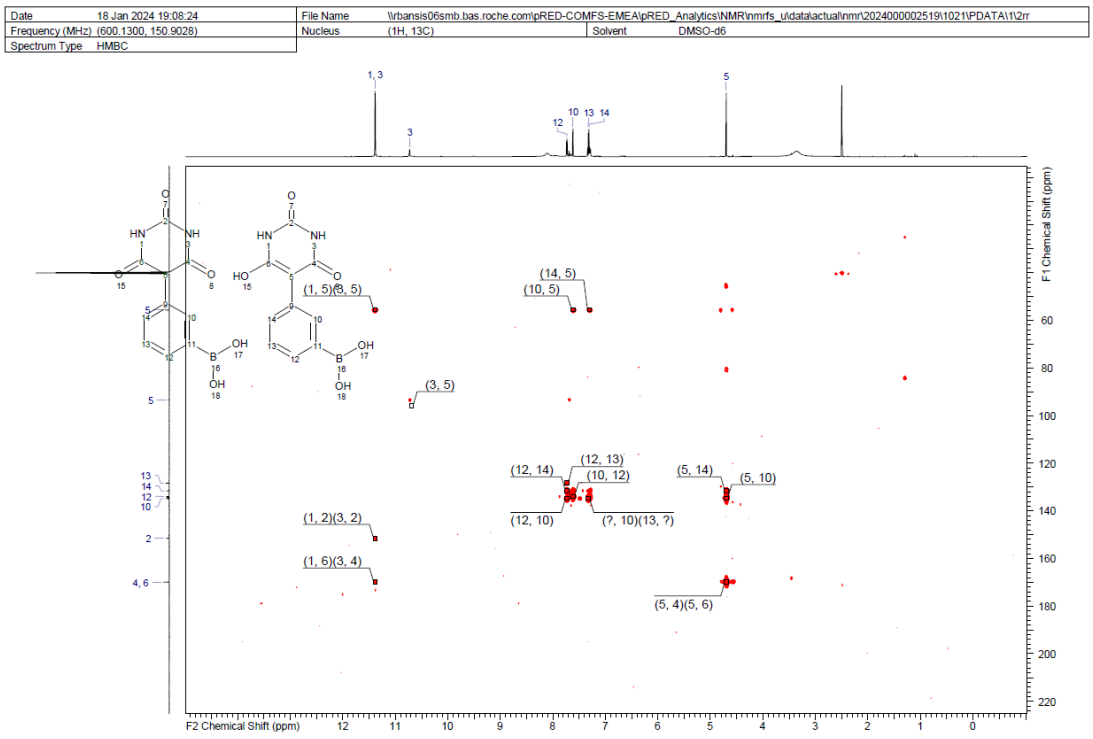


Figure S121. HMBC of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

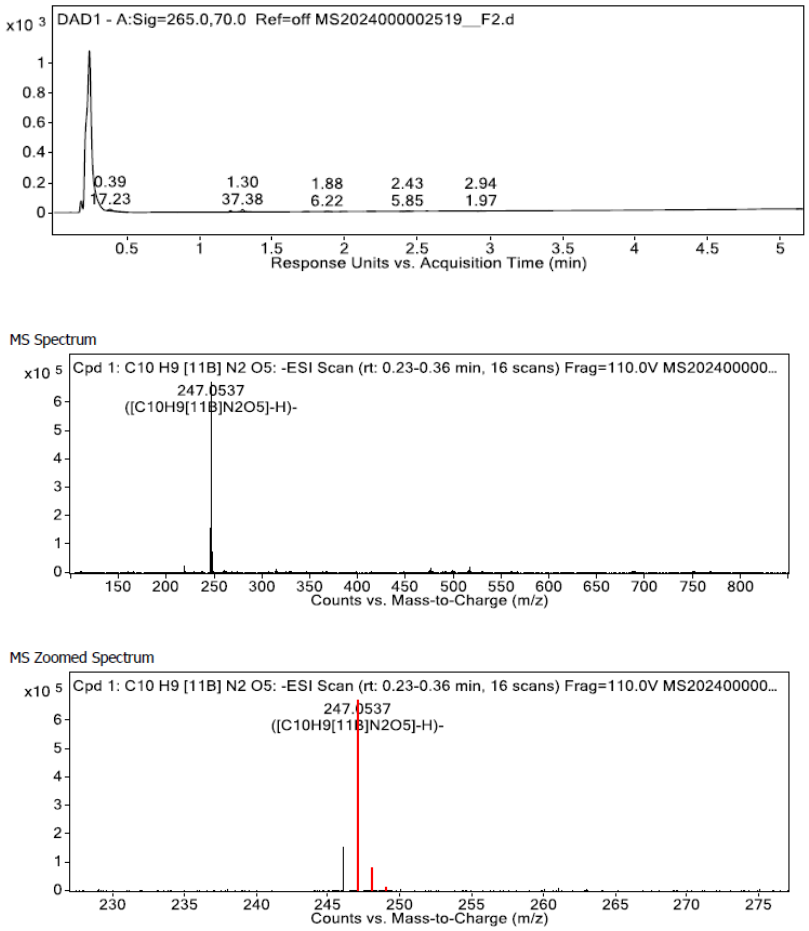
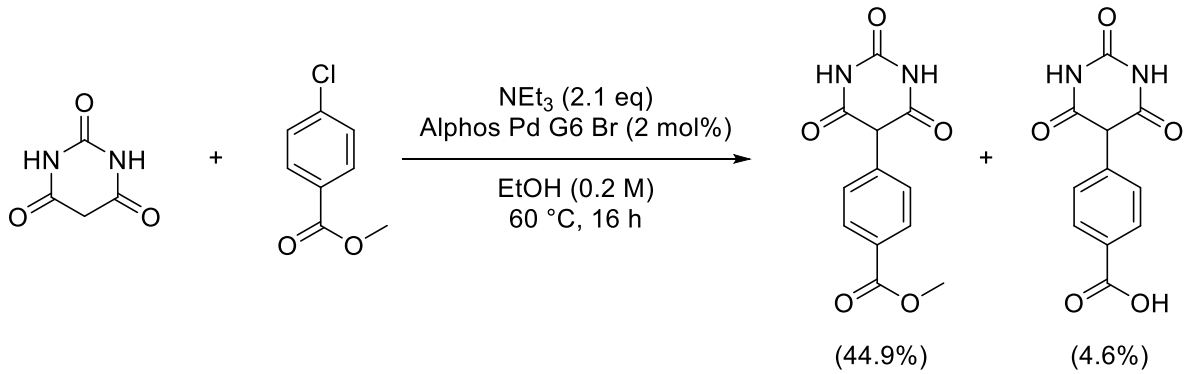


Figure S122. HRMS of [3-(2,4,6-trioxo-1,3-diazinan-5-yl)phenyl]boronic acid

Methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate



Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (353.6 mg, 2.76 mmol, 1.1 equiv), methyl 4-chlorobenzoate (427.6 mg, 2.51 mmol, 1.0 equiv), triethylamine (732 uL, 5.25 mmol, 2.1 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (57.5 mg, 0.05 mmol, 0.02 equiv). After 16.5 h at 60 °C, LCMS indicated full conversion of the

aryl chloride. For the work-up, Na_2CO_3 (12.5 mL, 1N, aq) and H_2O (30 mL) was used. The washings were done with TBME (3 x 20 mL). After acidification to pH 2, the organic layer was washed with H_2O (3 x 45 mL). The title compound (294.8 mg, 45% yield, 88% pure by LCMS) was obtained as an off-white solid in a molar tautomeric ratio of nearly 1:1 (keto / enol) containing the corresponding carboxylic acid (10 %area by LCMS) as a byproduct.

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.44 (br s, 1 H), 10.75 (br dd, J=2.2, 1.1 Hz, 1 H), 10.70 (br s, 1 H), 7.75 - 8.23 (m, 3 H), 7.39 - 7.59 (m, 3 H), 5.09 (br s, 1 H), 5.06 (br s, 1 H), 3.85 (s, 3 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.2, 169.1, 169.1, 166.8, 166.8, 166.5, 162.0, 162.0, 162.0, 162.0, 161.9, 151.4, 151.3, 150.2, 150.2, 139.9, 139.8, 138.7, 131.4, 131.3, 131.2, 130.8, 130.8, 130.8, 130.7, 130.7, 130.6, 130.4, 129.8, 129.7, 129.7, 129.5, 129.0, 128.8, 128.7, 127.0, 91.9, 91.8, 55.4, 52.7, 52.7, 52.7, 52.6, 52.5, 52.4, 40.5, 40.3 ppm

HRMS: $C_{12}H_{10}N_2O_5$; calc. for ($M+H^+$) 262.059, found: 262.0594.

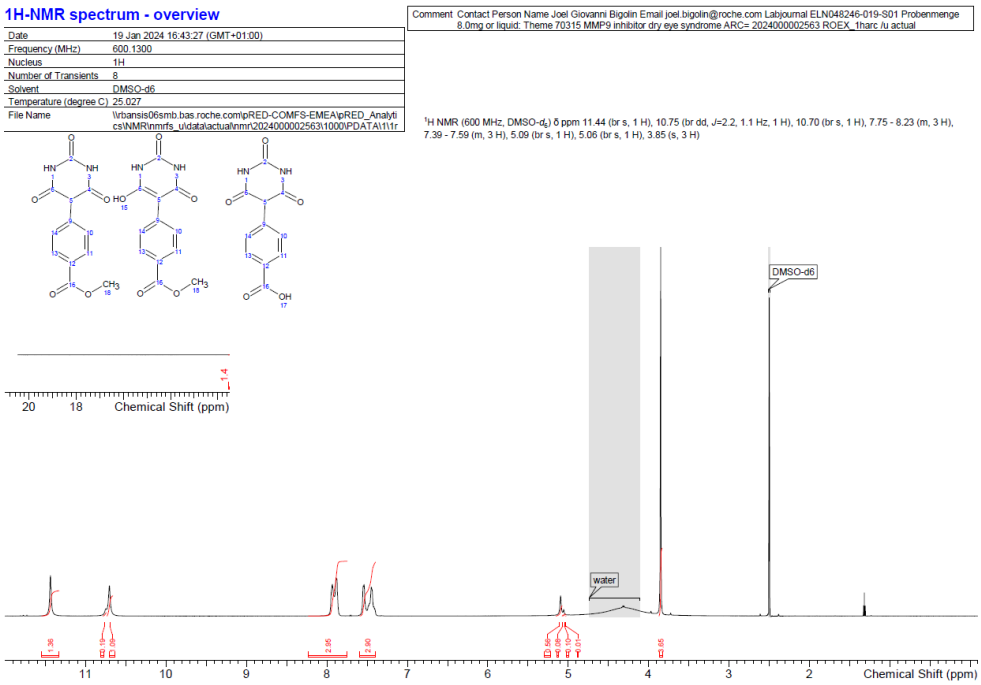


Figure S123. ^{1}H NMR (600 MHz, DMSO-d_6) of methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate

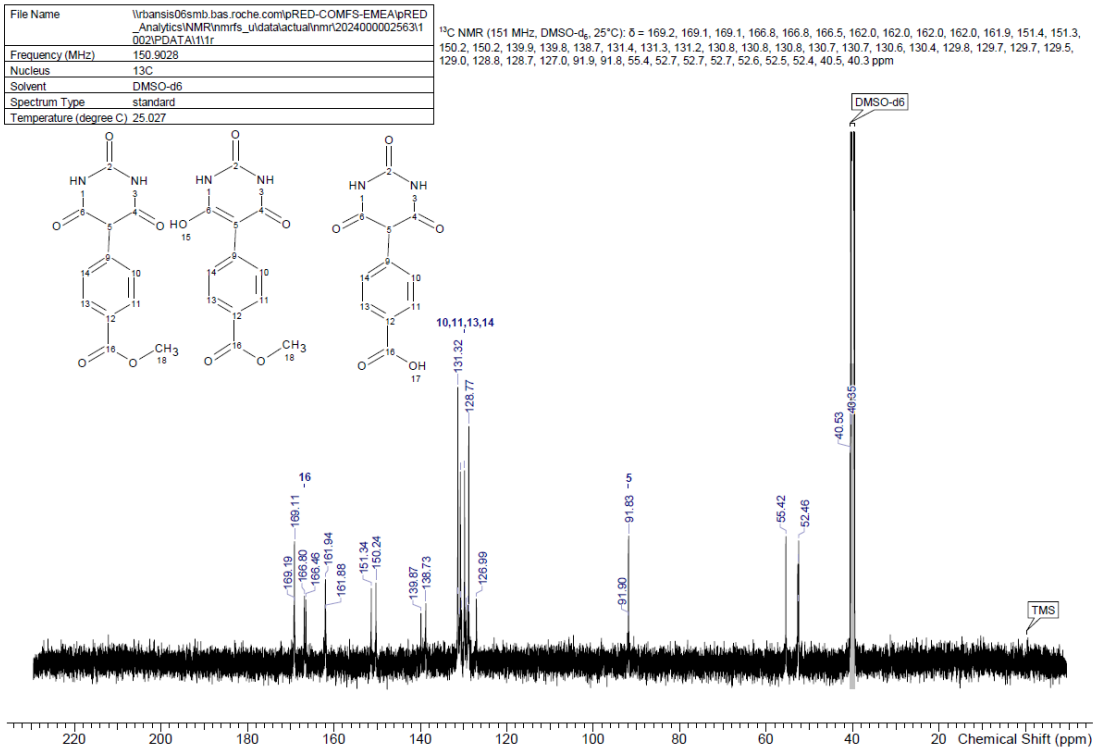


Figure S124. ^{13}C NMR (151 MHz, DMSO-d_6) of methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate

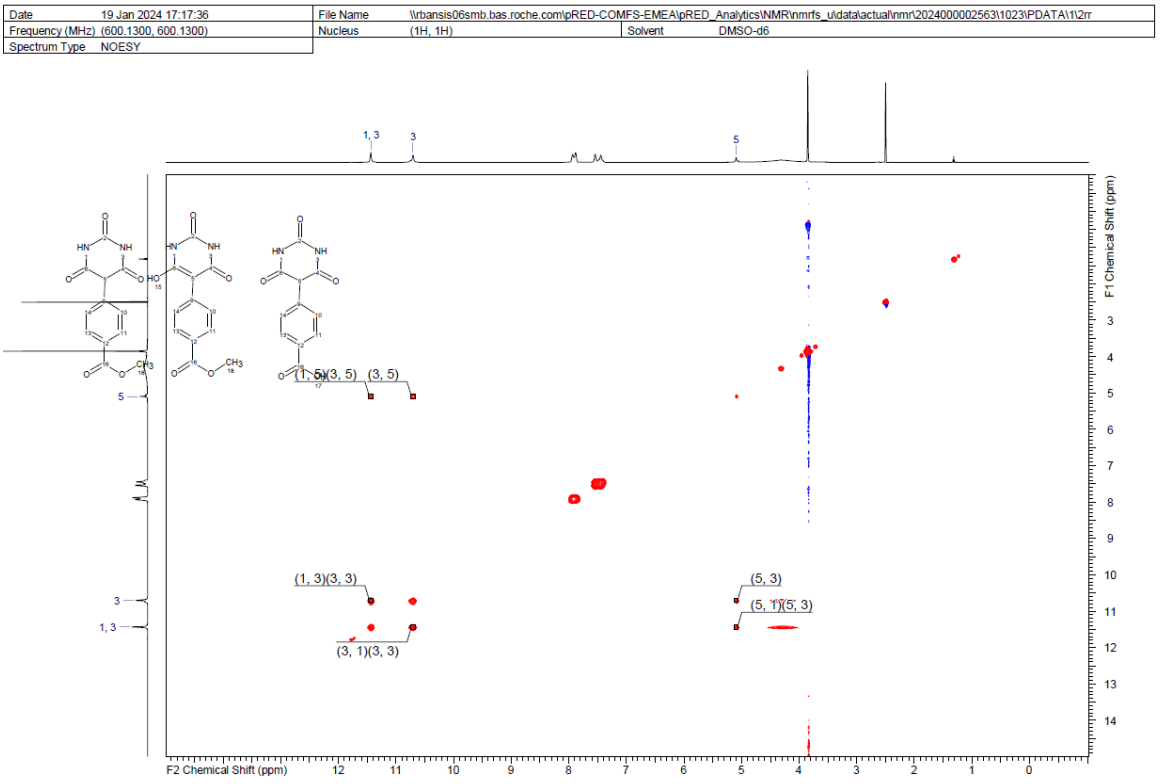


Figure S125. NOESY of methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate

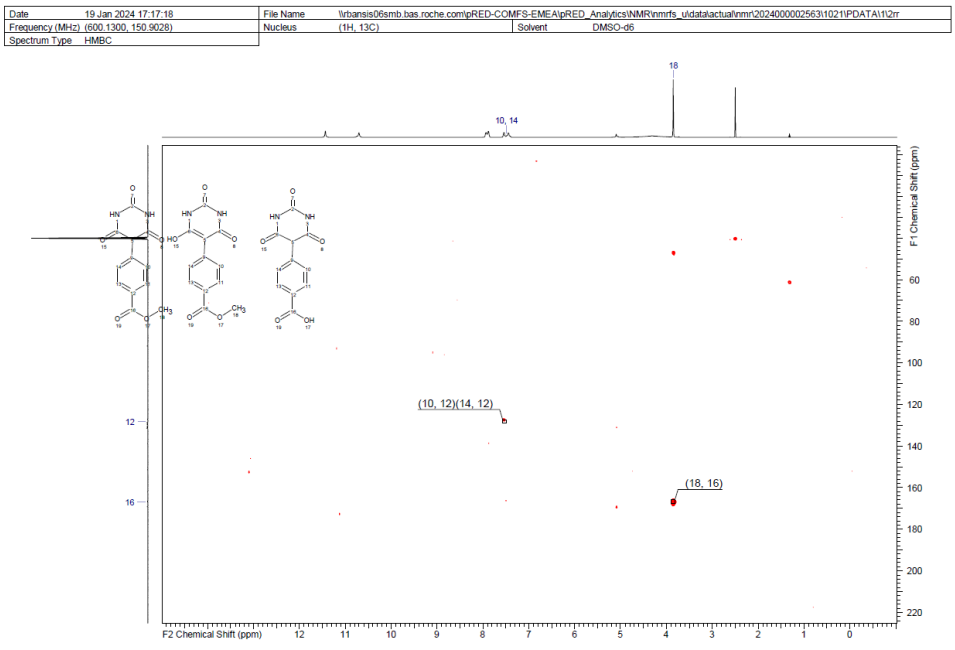


Figure S126. HMBC of methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate

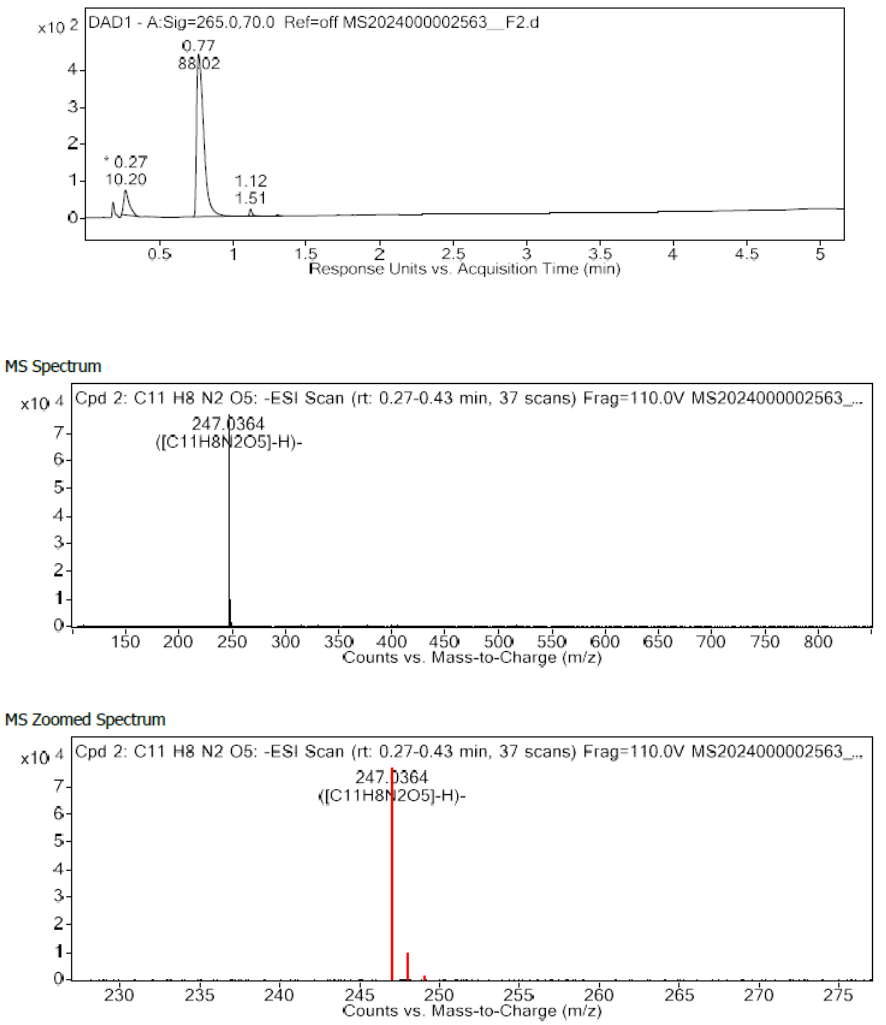
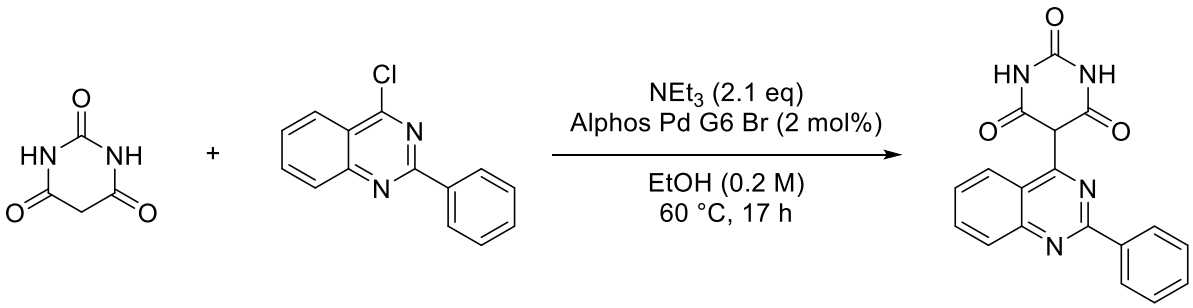


Figure S127. HRMS of methyl 4-(2,4,6-trioxo-1,3-diazinan-5-yl)benzoate

5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione



Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (352.8 mg, 2.75 mmol, 1.1 equiv), 4-chloro-2-phenylquinazoline (603.9 mg, 2.51 mmol, 1.0 equiv), triethylamine (732 uL, 5.25 mmol, 2.09 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (57.3 mg, 0.050 mmol, 0.02 equiv). After 17 h at 60 °C, LCMS indicated 22% conversion of the aryl chloride. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used,

acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (131.3 mg, 16% yield, 85% pure by LCMS) was obtained as reddish flakes as the enol form.

^{1}H NMR (600 MHz, DMSO-d_6) δ = 15.33 - 17.35 (m, 1 H), 10.26 - 11.81 (m, 2 H), 8.41 (br d, J=8.2 Hz, 1 H), 8.24 - 8.27 (m, 2H), 7.99 - 8.02 (m, 1 H), 7.92 - 7.95 (m, 1 H), 7.65 - 7.75 (m, 3 H), 7.58 (ddd, J=8.4, 7.0, 1.4 Hz, 1 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 165.9, 150.6, 150.6, 150.1, 136.7, 132.6, 131.7, 129.9, 128.3, 127.6, 126.4, 88.6 ppm

HRMS: $C_{18}H_{12}N_4O_3$; calc. for ($M+H^+$) 332.0909, found: 332.0912.

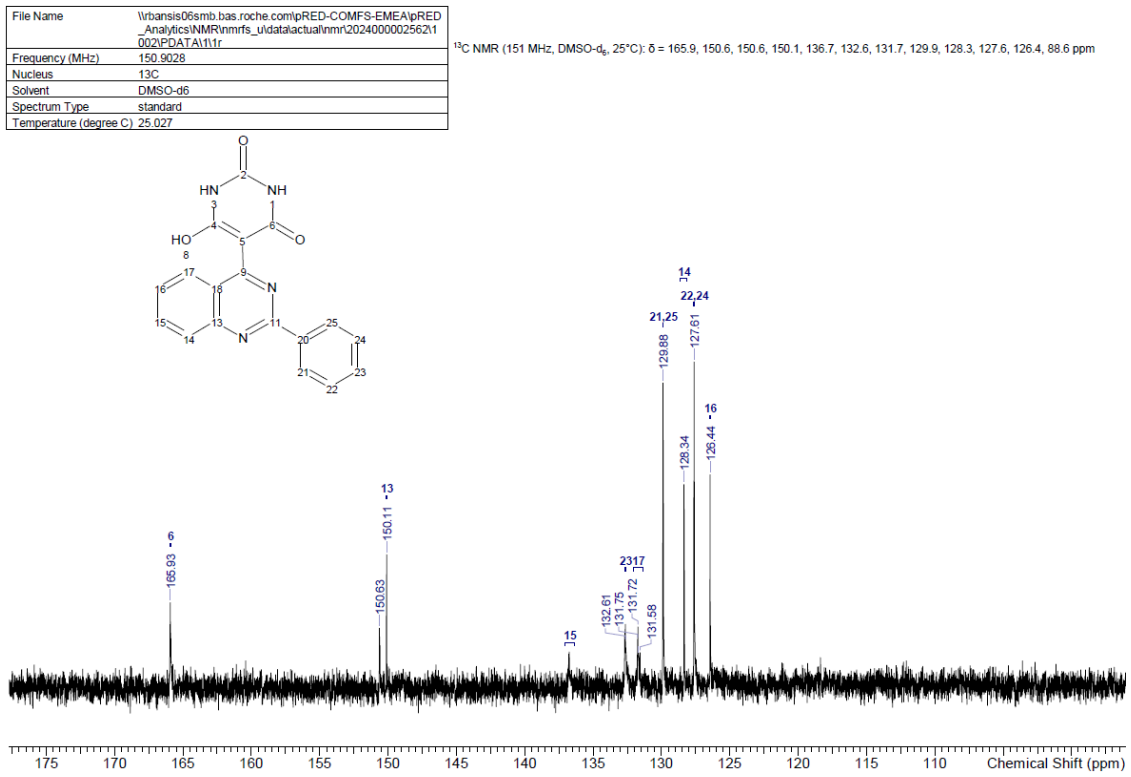


Figure S128. ^{13}C NMR (151 MHz, DMSO-d_6) of 5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione

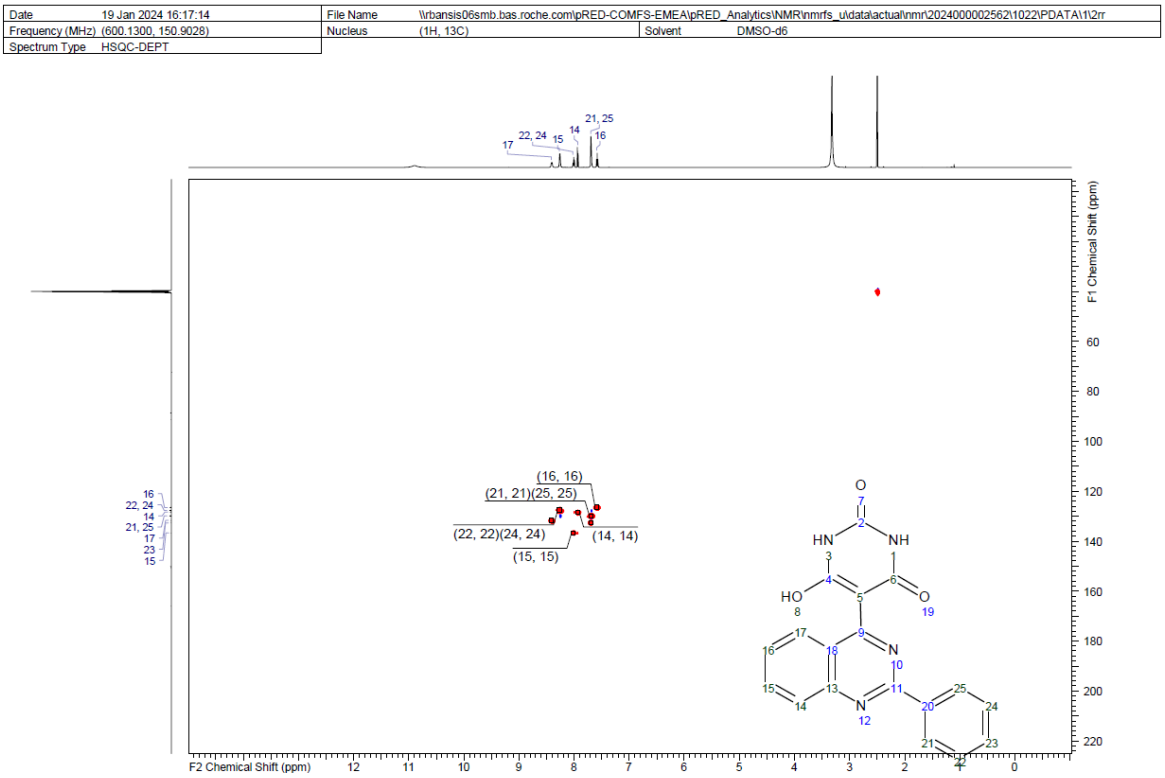


Figure S129. HSQC-DEPT of 5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione

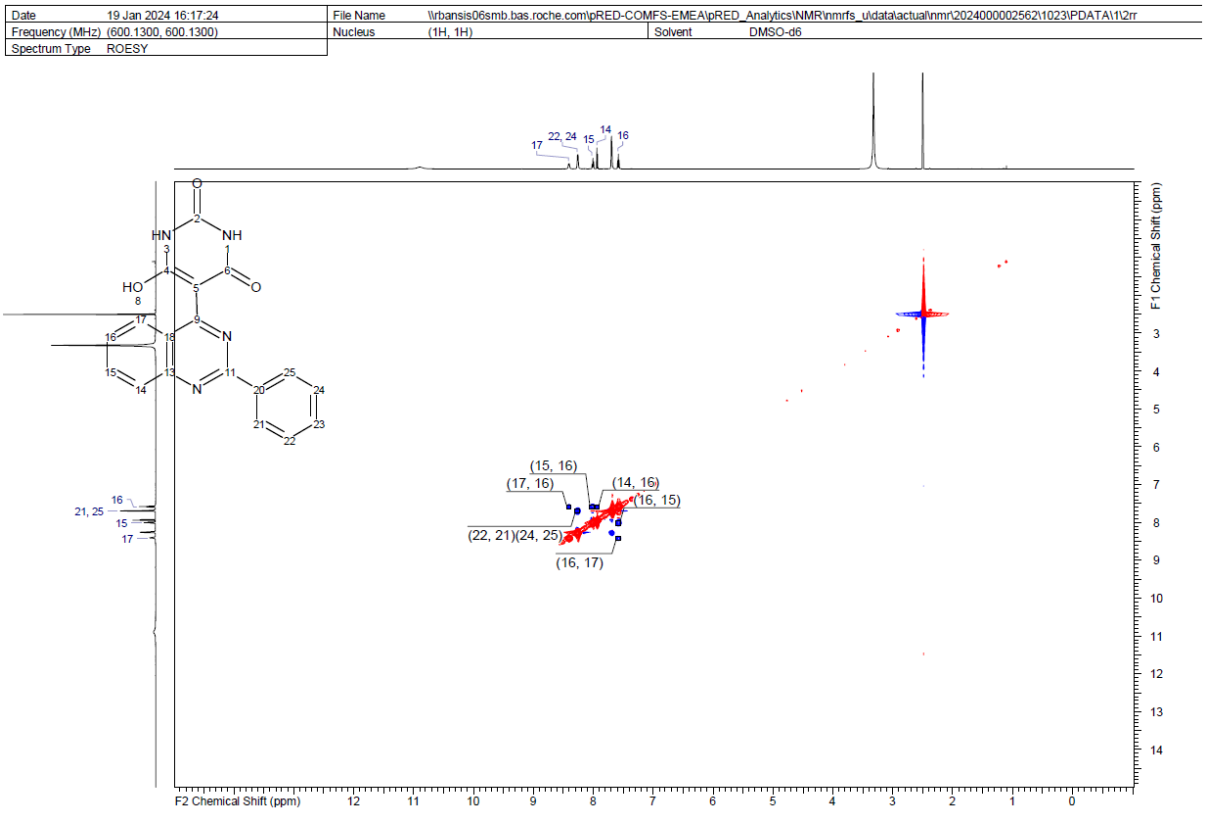


Figure S130. ROESY of 5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione

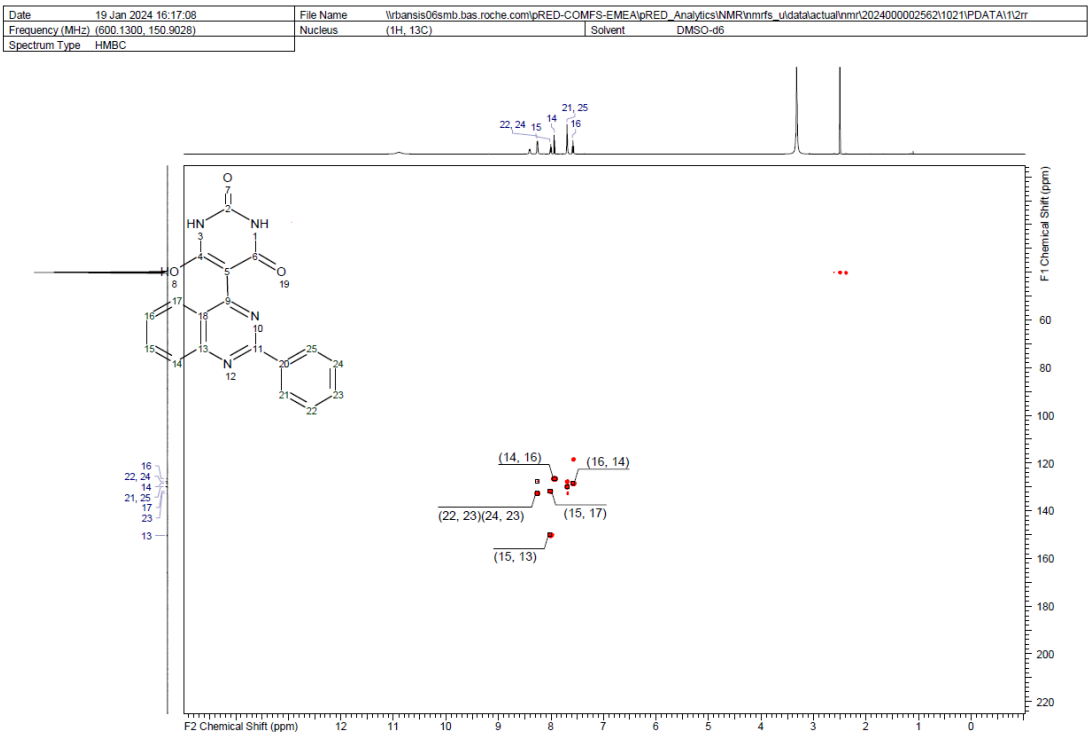


Figure S131. HMBC of 5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione

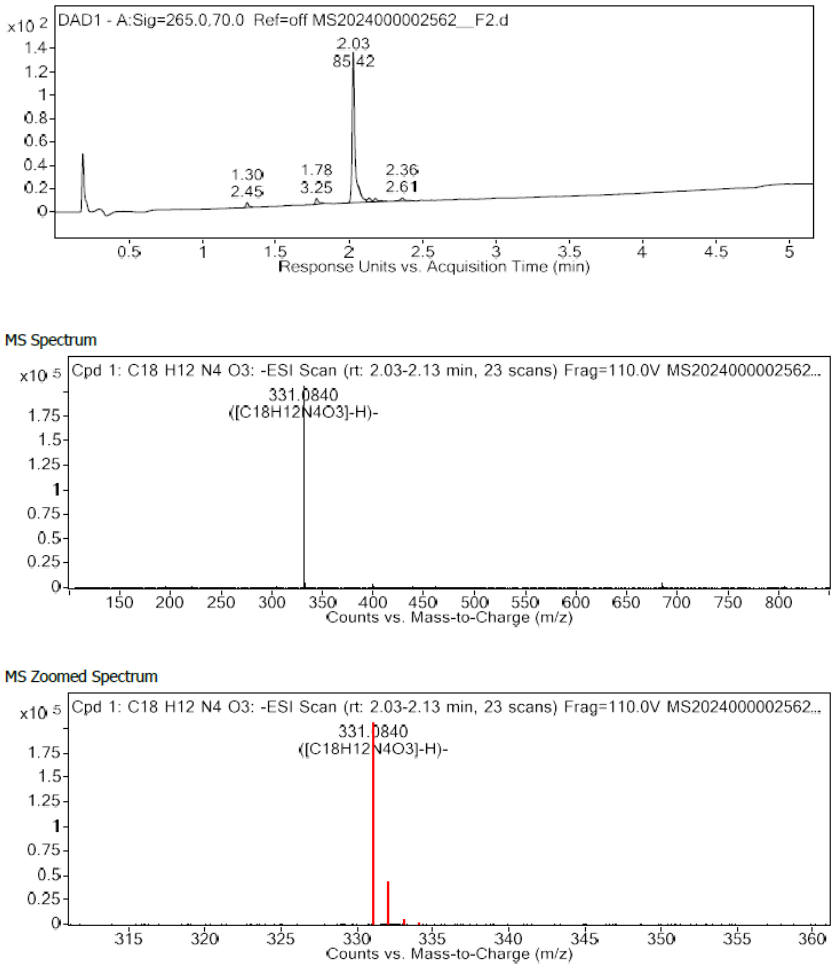
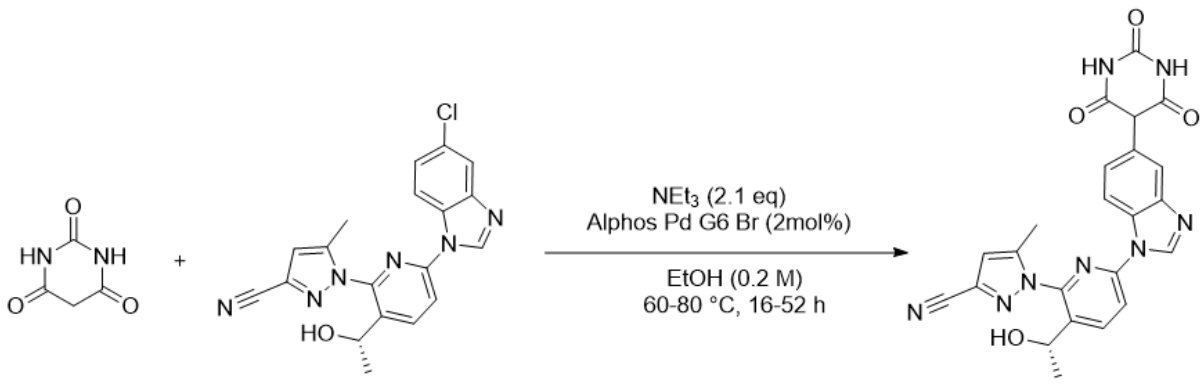


Figure S132. HRMS of 5-(2-phenylquinazolin-4-yl)-1,3-diazinane-2,4,6-trione

1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile



Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (356.7 mg, 2.78 mmol, 1.1 equiv), 1-[6-(5-chlorobenzimidazol-1-yl)-3 -[*rac*-(1S)-1-hydroxyethyl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile (948.6 mg, 2.5 mmol, 1.0 equiv), triethylamine (732 uL, 5.25 mmol, 2.1 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (57.3 mg, 0.050 mmol, 0.02 equiv). After 24 h at 60 °C, LCMS indicated 50% conversion of the aryl chloride. After 48 h at 60 °C, LCMS indicated 53% conversion of the SM. After 52 h at 80 °C, LCMS indicated 55% conversion of the SM. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 50 mL) were used, acidified to pH 2.5 and washed with H_2O (3 x 45 mL). The title compound (398.6 mg, 32% yield, 94% pure by LCMS) was obtained as a brown solid in a molar tautomeric ratio of 2 : 1 (keto / enol).

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.39 (s, 1 H), 10.69 (br s, 1 H), 9.08 (s, 1 H), 8.48 (d, J=8.5 Hz, 1 H), 8.25 - 8.34 (m, 1 H), 8.02 - 8.10 (m, 1 H), 7.62 - 7.82 (m, 1 H), 7.21 - 7.45 (m, 1 H), 7.09 (s, 1 H), 5.35 - 5.74 (m, 1 H), 5.00 (s, 1 H), 4.58 (q, J=6.5 Hz, 1H), 2.27 - 2.42 (m, 3 H), 1.19 - 1.38 (m, 3 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.8, 151.4, 147.8, 145.3, 144.7, 143.5, 143.3, 143.3, 143.3, 141.4, 137.6, 131.5, 130.2, 129.9, 128.5, 125.9, 125.0, 121.7, 116.9, 116.8, 114.7, 114.7, 114.2, 111.9, 63.2, 55.4, 25.0, 11.8 ppm

HRMS: $C_{23}H_{18}N_8O_4$; calc. for ($M+H^+$) 470.1456, found: 470.1451.

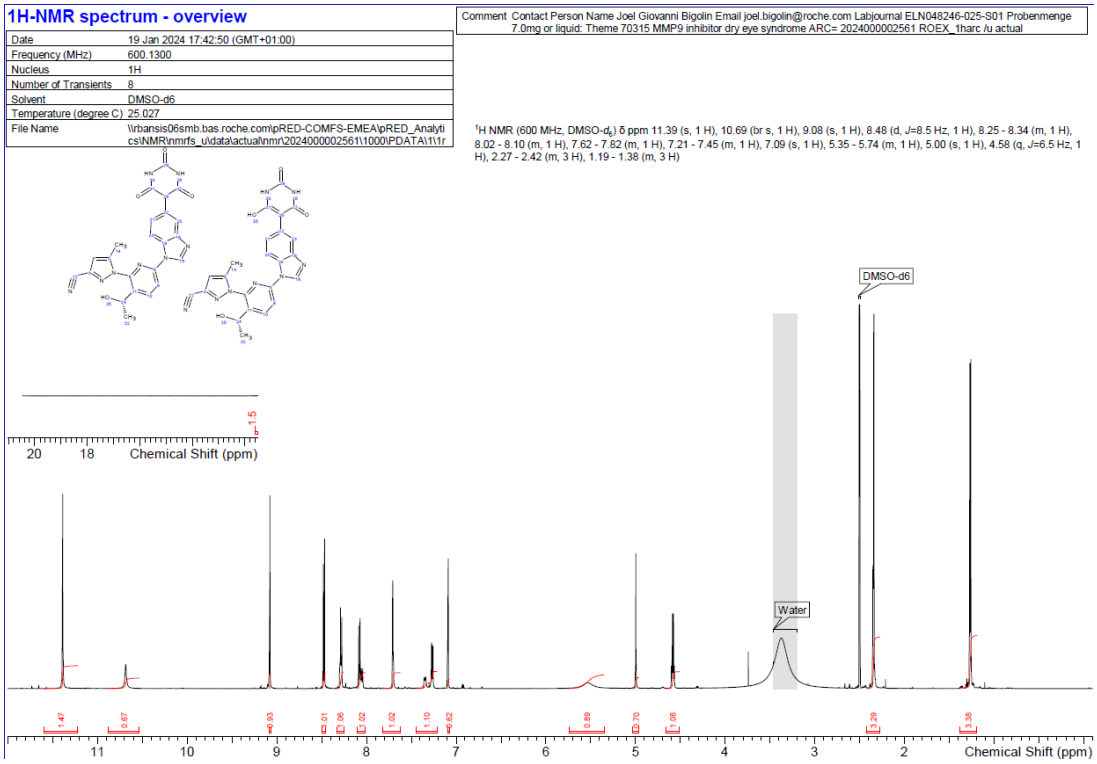


Figure S133. ^{1}H NMR (600 MHz, DMSO-d_6) of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

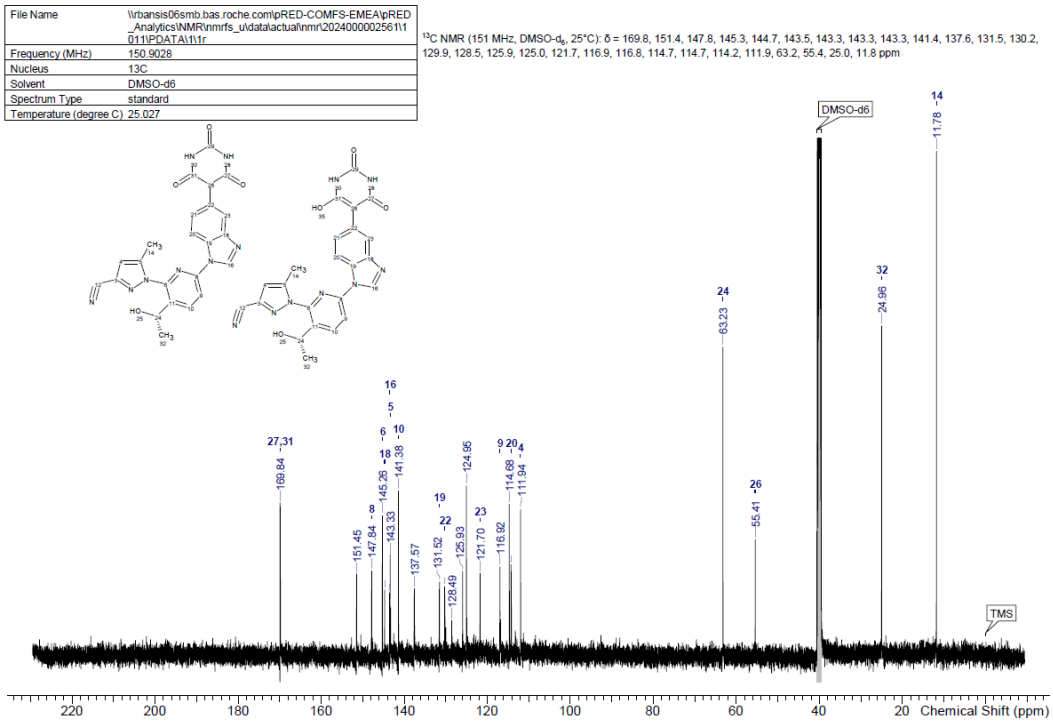


Figure S134. ^{13}C NMR (151 MHz, DMSO-d_6) of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

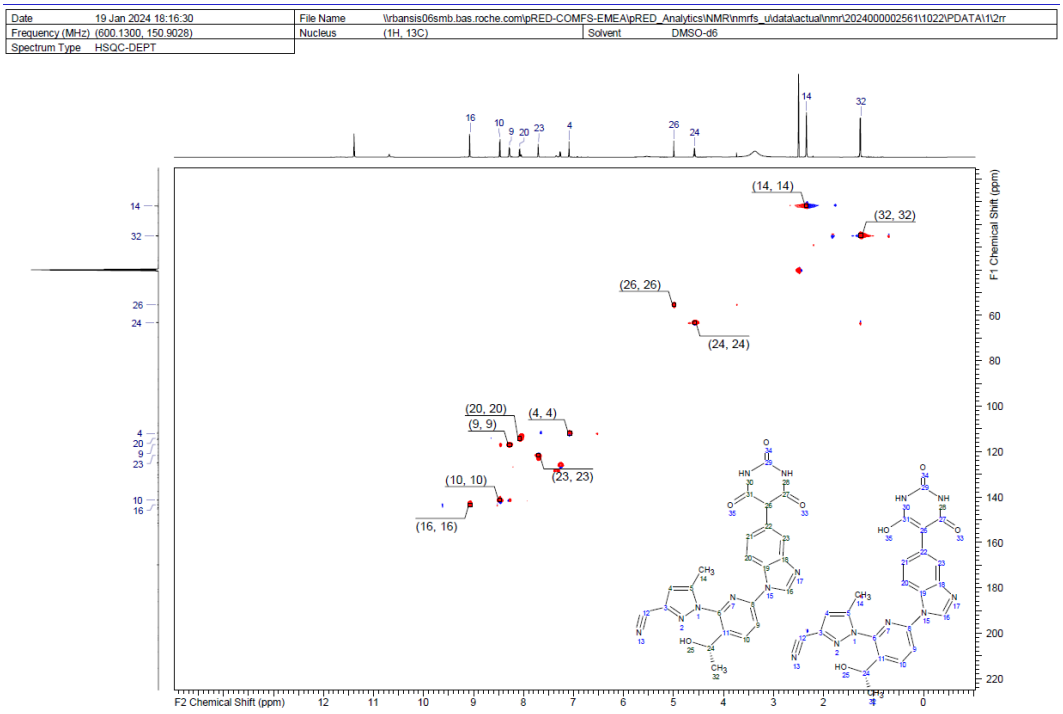


Figure S135. HSQC-DEPT of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

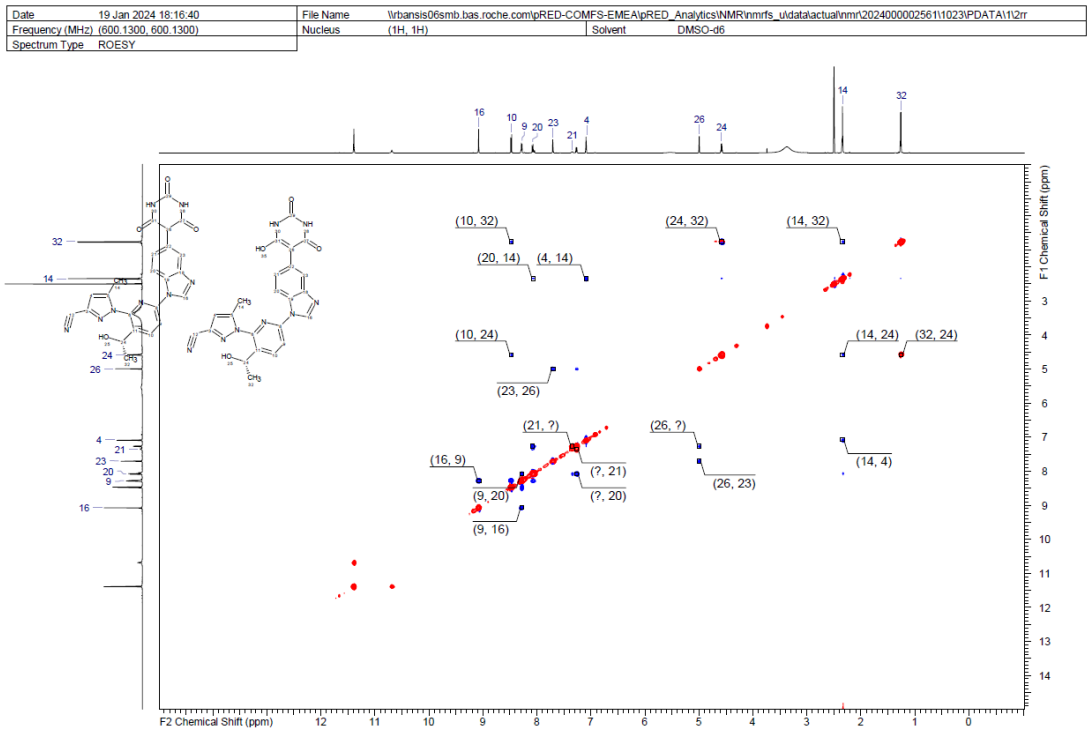


Figure S136. ROESY of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

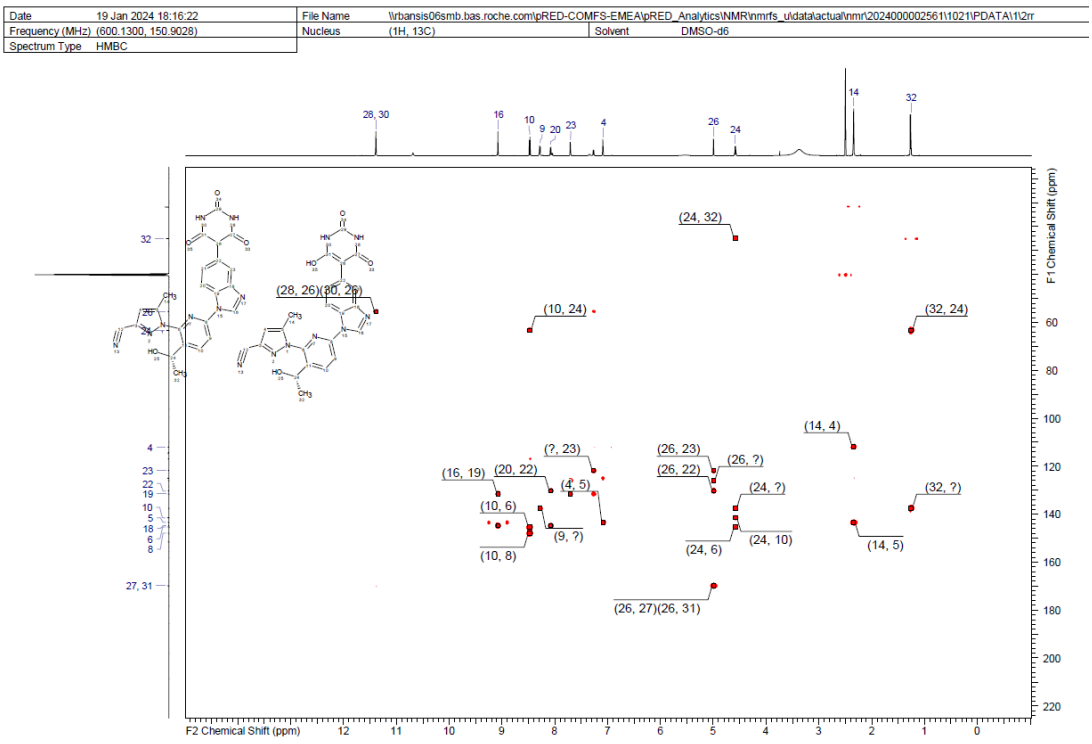


Figure S137. HMBC of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

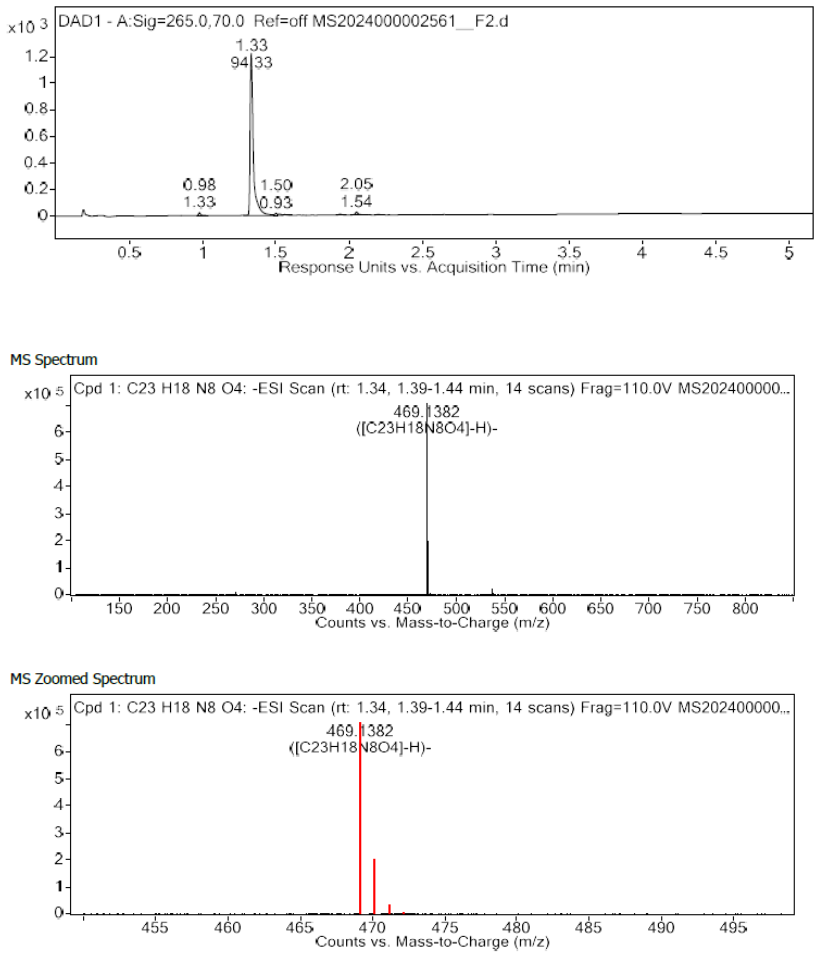
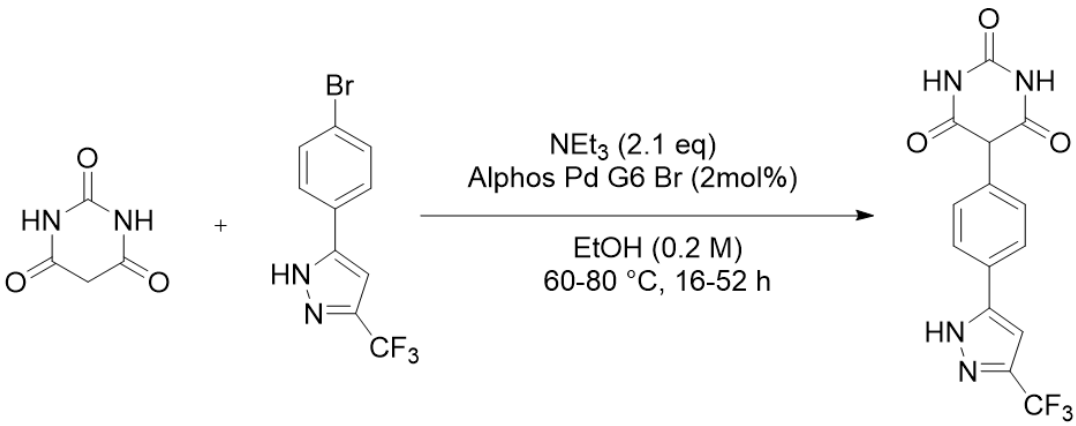


Figure S138. HRMS of 1-[3-[(1S)-1-hydroxyethyl]-6-[5-(1,3-diazinane-2,4,6-trione)benzimidazol-1-yl]-2-pyridyl]-5-methyl-pyrazole-3-carbonitrile

5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione



Option B of the Barbiturate General Procedure was followed using a 20 mL vial, barbituric acid (353 mg, 2.76 mmol, 1.1 equiv), 5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazole (732 mg, 2.51 mmol, 1.0 equiv), triethylamine (735 uL, 5.27 mmol, 2.1 equiv), EtOH (12.5 mL, 0.2M) and AlPhos Pd G6 Br (58.7 mg, 0.0512 mmol, 0.02 equiv). After 24 h at 60 °C, LCMS indicated

95% conversion of the aryl bromide. After 48 h at 60 °C, LCMS indicated 96% conversion of the SM. After 52 h at 80 °C, LCMS still indicated 96% conversion of the SM. For the work-up, Na_2CO_3 (12.5 mL, 10%, aq) and TBME (3 x 20 mL) were used, acidified to pH 2 and washed with H_2O (3 x 45 mL). The title compound (726.8 mg, 85% yield, 99% pure by LCMS) was obtained as an off-white solid in a molar tautomeric ratio of 1 : 1 (keto / enol).

^{1}H NMR (600 MHz, DMSO-d_6) δ = 13.76 - 14.26 (m, 1 H), 11.41 (br s, 1 H), 10.25 - 10.76 (m, 1 H), 7.67 - 7.84 (m, 2 H), 7.33 - 7.60 (m, 2 H), 7.09 - 7.25 (m, 1 H), 4.99 (br s, 1 H) ppm

^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.3, 151.3, 131.5, 130.8, 130.8, 126.1, 126.0, 124.9, 124.9, 124.9, 101.6, 100.8, 91.2, 72.4, 55.2, 55.1, 49.1 ppm

^{19}F NMR (565 MHz, DMSO-d_6) δ = -60.36 (br s), -60.40 (br s)

HRMS: $C_{14}H_9F_3N_4O_3$; calc. for ($M+H^+$) 338.0631, found: 338.0627.

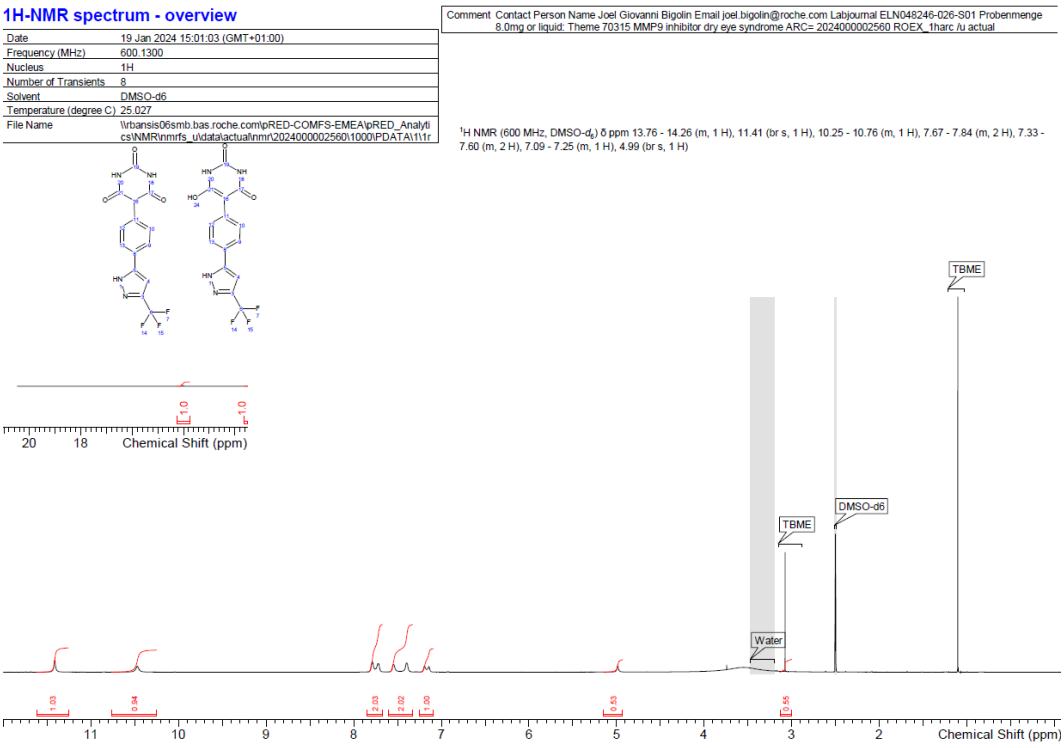


Figure S139. ^{1}H NMR (600 MHz, DMSO-d_6) of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione

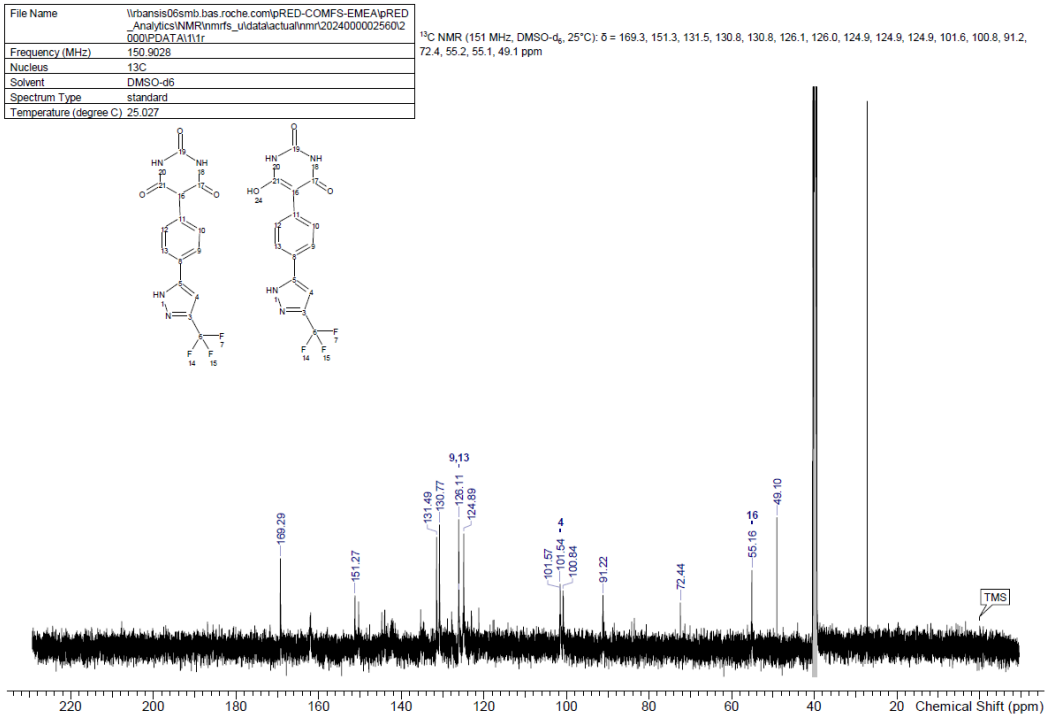


Figure S140. ^{13}C NMR (151 MHz, DMSO-d_6) of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione

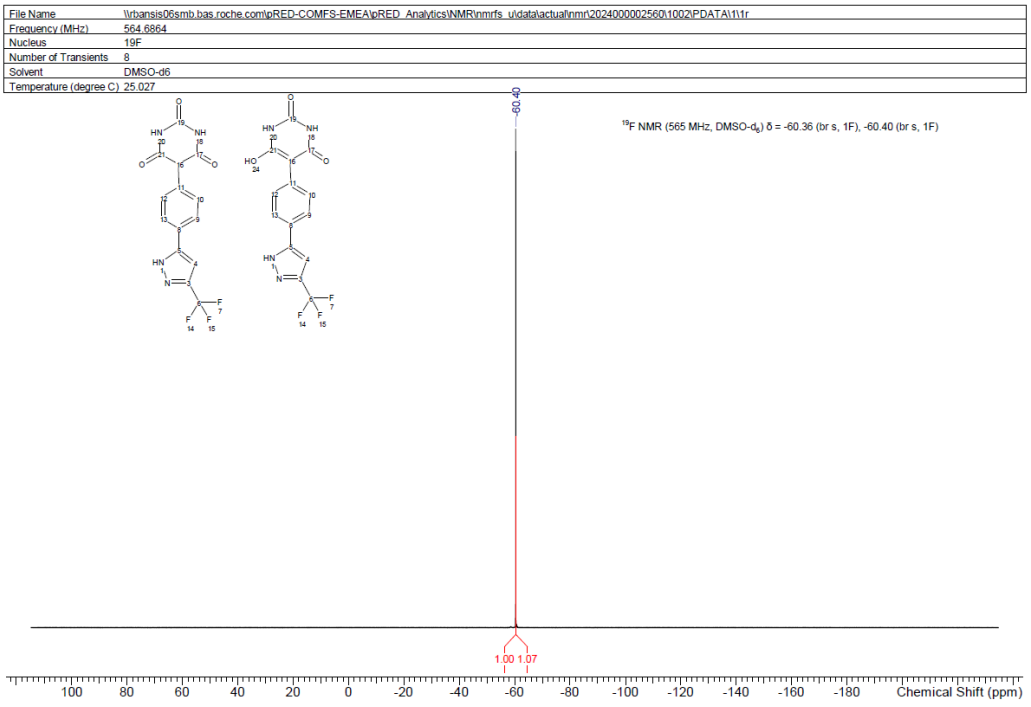


Figure S141. ^{19}F NMR (565 MHz, DMSO-d_6) of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione

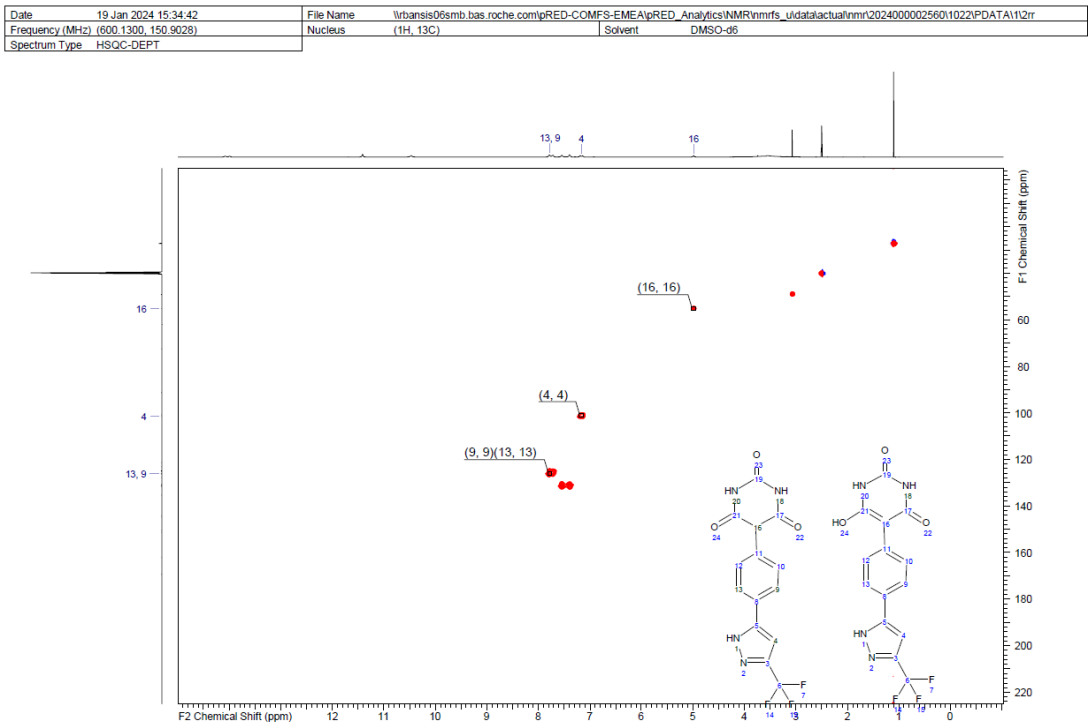


Figure S142. HSQC-DEPT of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione

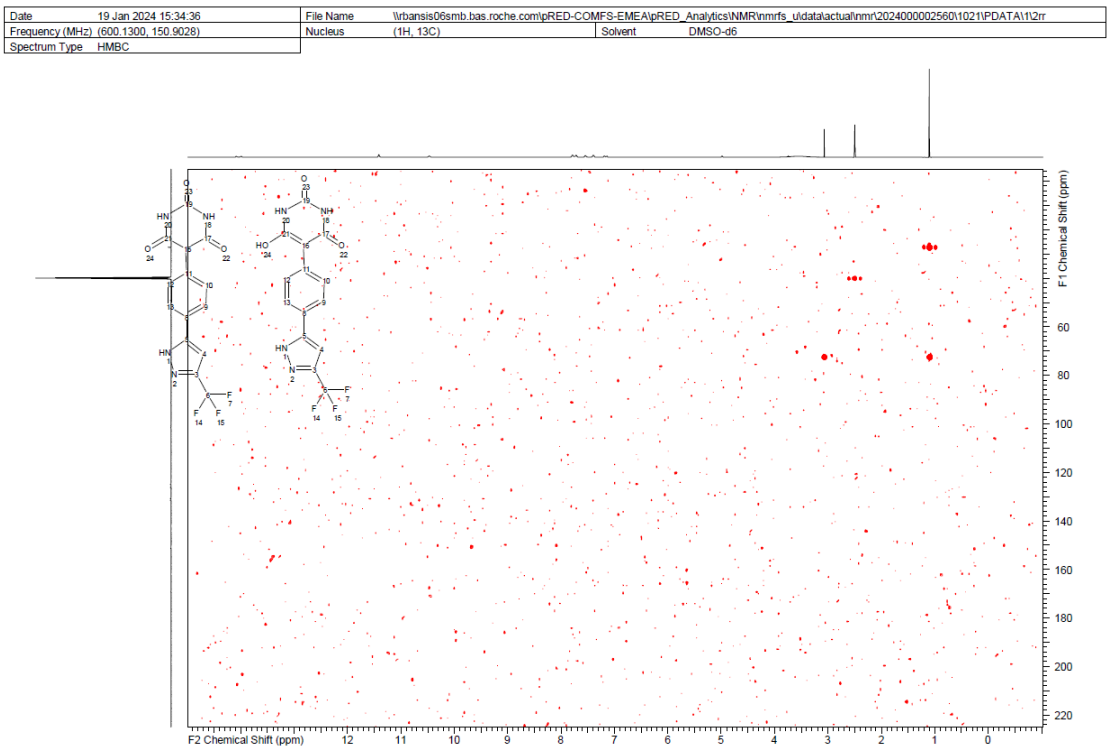


Figure S143. HMBC of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione

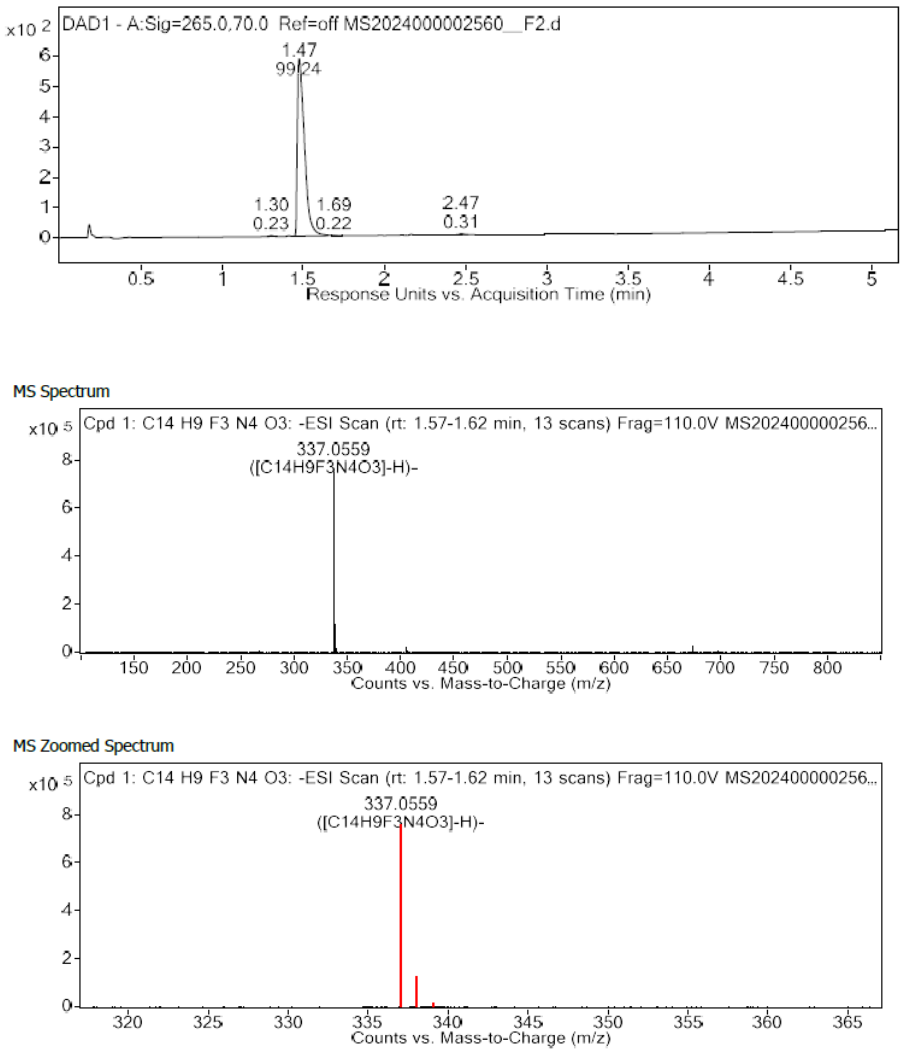


Figure S144. HRMS of 5-{4-[3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}-1,3-diazinane-2,4,6-trione