Supporting Information

Reaction Array Fingerprinting

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Table of Contents

1. **General Information.** Code to generate and visualize reaction array fingerprints was written in Python (version 3.9.10). Scikit-learn (version 1.0.1) was used to run TSNE and PCA dimensionality reduction algorithms. RDKit (version 2021.09.4) was used to convert reaction SMILES into fingerprints, umap-learn (version 0.5.3) was used to generate UMAPs, and sklearn-som (version 1.1.0) was used to run the SOM algorithm. Pandas (version 1.4.1) or SQLAlchemy (version 1.4.44) was used to load reaction data. Code for the webapp was written in Python (version 3.9.10) and ReactJS (version 18.2.0) with minimal dependencies. Python dependencies were limited to Flask (version 2.0.2), Numpy (version 1.22.2), Pandas (1.4.1), Matplotlib (version 3.5.1), and RDKit (version 2021.09.4), all installed via pip (version 22.0.3). JavaScript dependencies were limited to ReactJS (version 18.2.0) for the underlying user interface infrastructure and react-csv-reader (version 3.3.0). API endpoints were written in Flask and exposed via HTTPS.

   All datafiles used to make the figures in this manuscript alongside the entirety of the code needed to generate the figures are provided in a GitHub repository.

2. **Python Pseudocode for Reaction Array Fingerprint Generation**

```
reagentTypes = ["electrophile", "nucleophile", "catalyst_smiles", "base_smiles", "solvent"]
weights = {"electrophile":1, "nucleophile":3, "catalyst_smiles":1, "base_smiles":1, "solvent":1}
for i,k in data.iterrows():
    this_fp = np.zeros(2048)
    for rt in reagentTypes:
        mol = Chem.MolFromSmiles(k[rt])
        # generic fingerprint function, returned weighted fingerprint
        fp = getFP(mol, weights[rt])
        this_fp = this_fp + fp
    rfps.append(this_fp)

# use any embedding algorithm
X_TSNE_RFP = TSNE(n_components=2, n_jobs=-1, perplexity=15).fit_transform(np.array(rfps))
```

Figure S1. Basic template code in python to create the weighted reaction fingerprint.

3. Comparison of SOMs, TSNEs, PCAs, and UMAPs for Suzuki Reaction Dataset Reaction Array Fingerprints

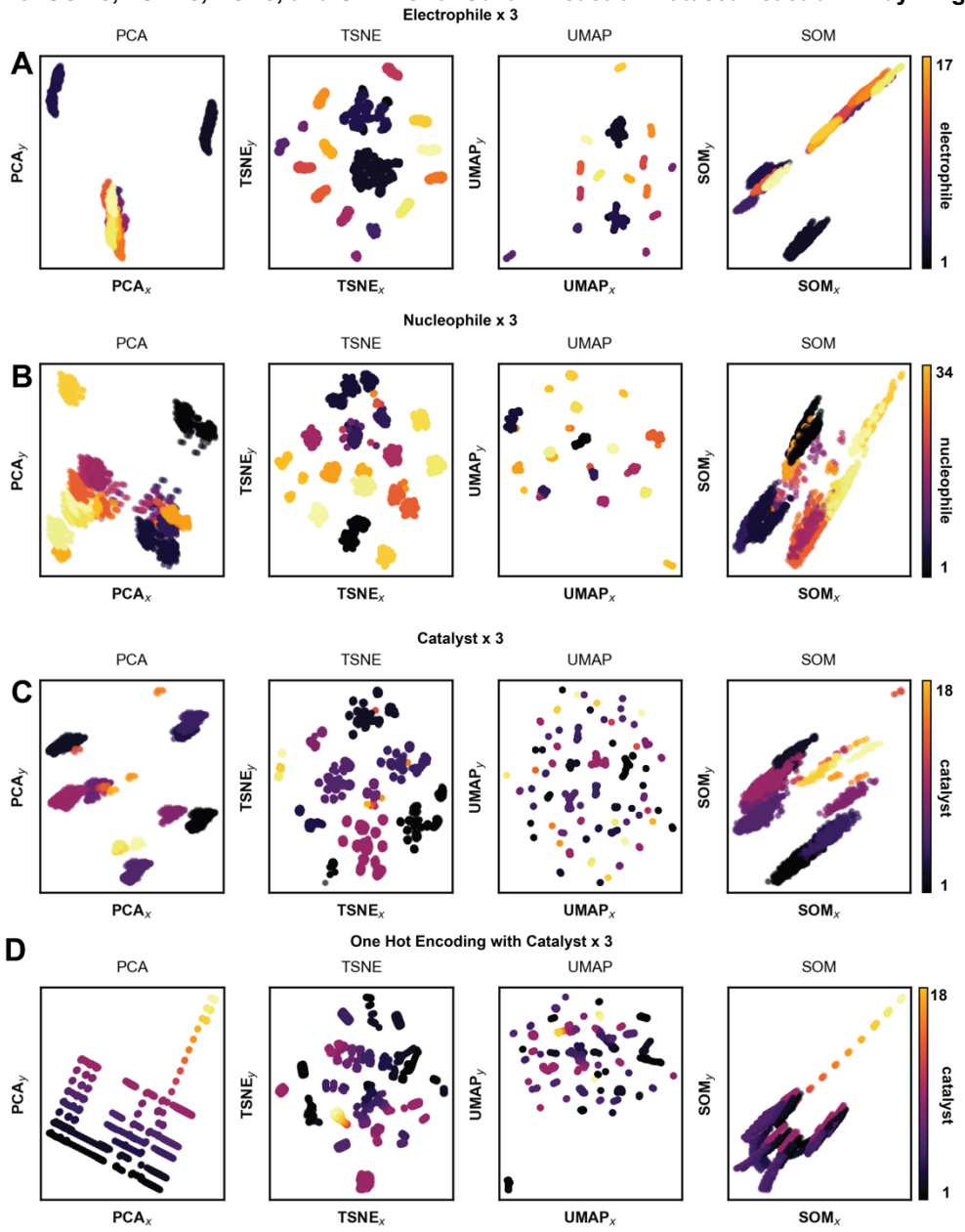


Figure S2. Different dimensionality reduction algorithms performed on the Suzuki dataset weighted reaction fingerprints. **A)** Electrophile fingerprints were multiplied by three. T-SNE and UMAP embeddings formulate distinct clusters. **B)** Nucleophile fingerprints were multiplied by three. **C)** Catalyst fingerprints were multiplied by three.

4. Perplexity Sweep Experiment

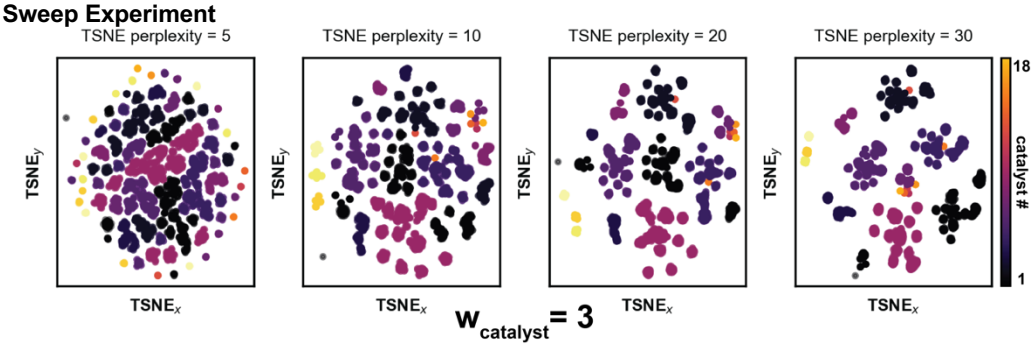


Figure S3. The perplexity value was changed for the Suzuki dataset where the weight of the catalyst was elevated to 3. The standard range for tSNE perplexity is 5-30.

5. Perplexity Sweep Experiment with MACCS fingerprints

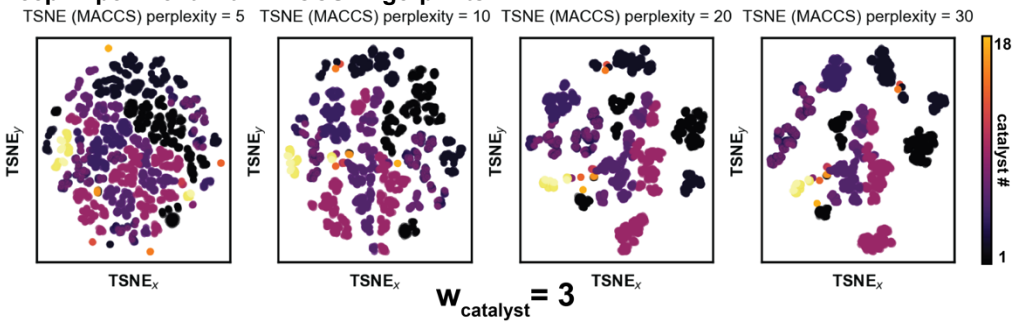


Figure S4. The perplexity value was changed for the Suzuki dataset where the weight of the catalyst was elevated to 3 when using MACCS as a fingerprint.

6. Unsupervised vs supervised UMAP Experiment

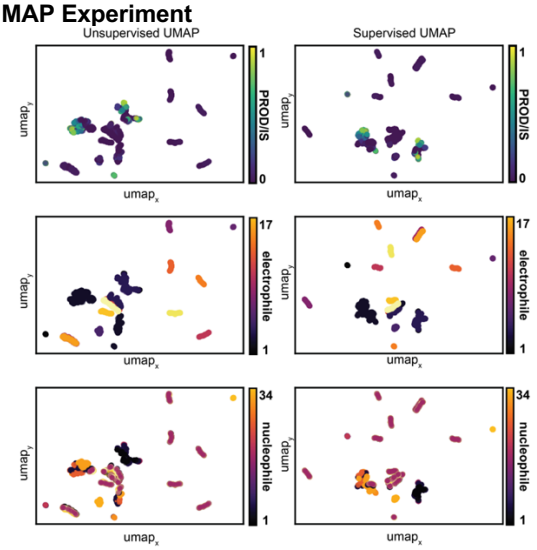


Figure S5. Unsupervised and supervised UMAP dimensionality reduction algorithms are compared. Little difference is indicated between the manifolds.

7. Weighted Reaction Fingerprints vs Concatenated Fingerprints vs Difference Fingerprints

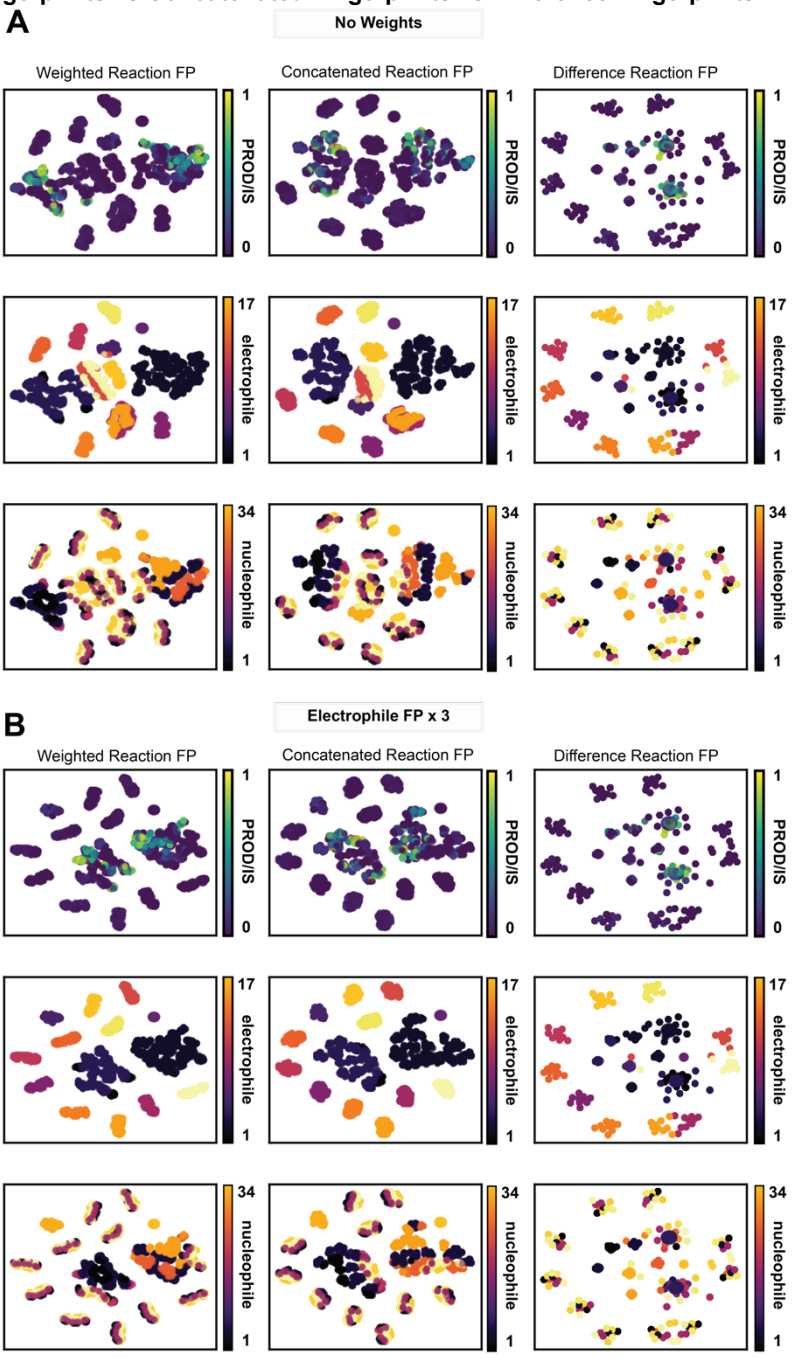


Figure S6. The introduced weighted reaction fingerprint is compared with the commonly used concatenated reaction fingerprints and difference reaction fingerprints found in the literature. **A)** The three fingerprint type manifolds without any feature weights compared side-by-side and colored by product/internal standard, electrophile, and nucleophile. **B)** The three fingerprint type manifolds where the electrophile fingerprints were given a weight of three. The change in the reaction embedding is noticed in the new weighted reaction fingerprint method and the concatenated reaction fingerprint (c.f. S6A).

8. Identifying reagents with generality

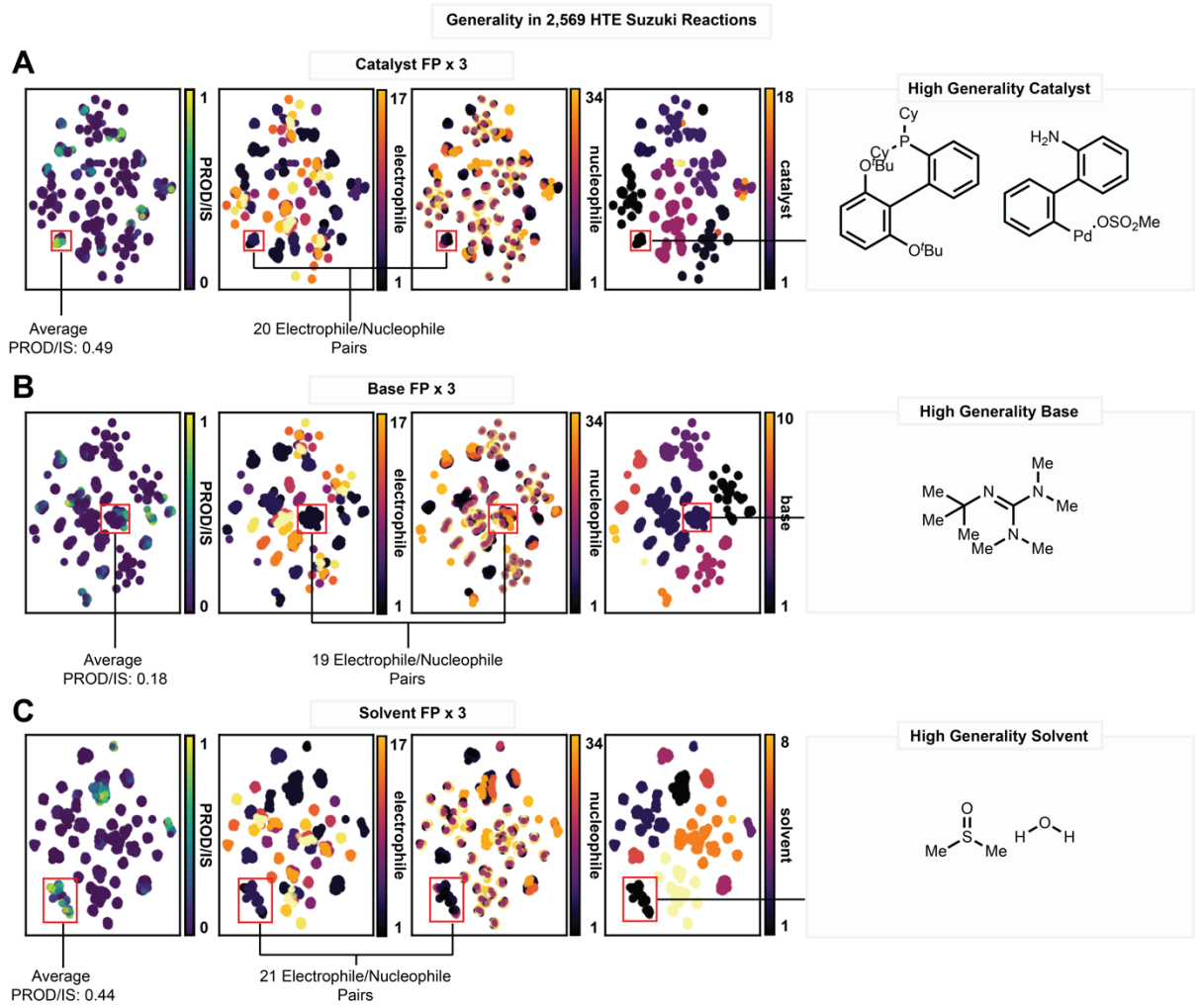


Figure S7. Condition generality demonstrated through the manipulation of weighted reaction fingerprint manifolds of the Suzuki dataset. **A)** When multiplying catalyst fingerprints by three, clusters containing many nucleophile and electrophile substrate pairs that work well with a specific catalyst can be identified. In this case RuPhos Pd G3 was found to produce an average of 49% product/internal standard integration for 20 substrate pairs. **B)** When weighing base fingerprints by three, the high generality base BTMG was found to product an average of 18% product/internal standard in 19 substrate pairs. **C)** A mixture of DMSO and water generated an average 44% product/internal standard integration in 21 substrate pairs.

9. Chi-squared validation of the reactivity cliff identified in figure 4.

high	med	low	zero	label
129	151	553	194	[w/ water]
0	8	827	707	[w/o water]

Figure S8. The contingency table of reactions in the Suzuki dataset split by those containing water as a co-solvent and those that do not. A chi-squared statistic is calculated to test the hypothesis of independence of the observed multivariate frequencies of the table. There are three degrees of freedom, and the chi-squared value is 522 with a p-value of 8.8e-113. This indicates that it is statistically likely that the difference between the observed distributions is not due to chance.

10. Box plots of solvent systems of data for figure 4

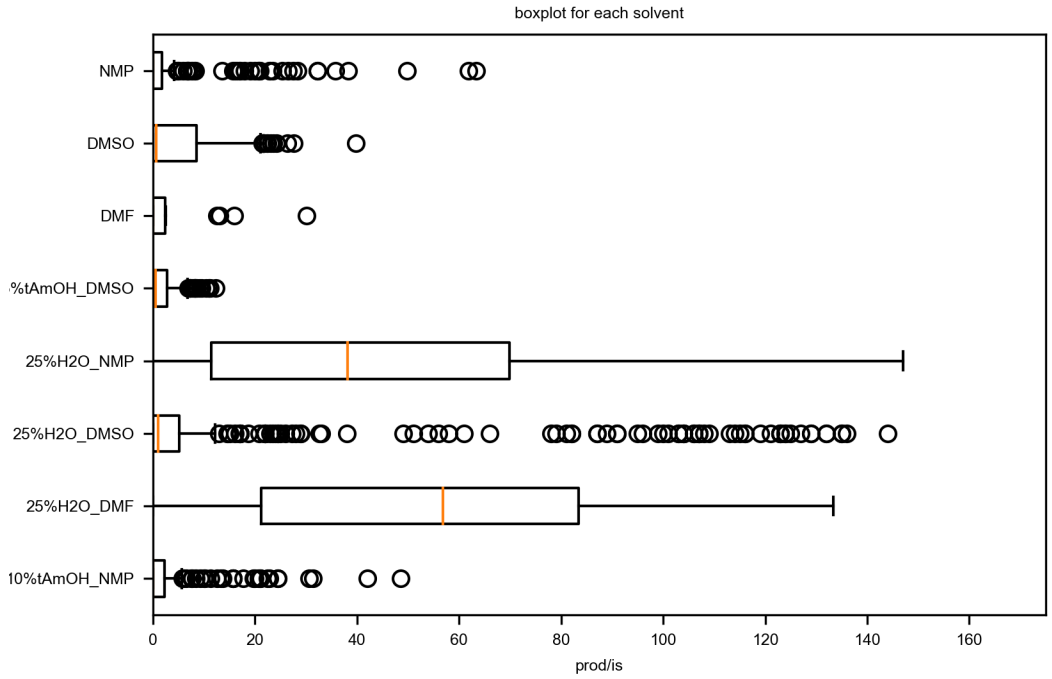


Figure S9. Boxplots grouped by solvent of reactions in the Suzuki dataset. While the best solvents are evident by average, the relation between solvent structure is lost.

11. Hyperparameters and weights used to generate figure 5 visualizations directly from phactor™ output data

Note that the t-SNE algorithm may produce variable results with the same data if a random state seed is not used. Clusters may be relocated or changed entirely. In this case the random state 1 was used in all experiments.

5A) ReductantOxidant Weight: 3, Perplexity: 25
5B) Electrophile Weight: 3, Perplexity: 20
5C) Ligand1 Weight: 3, Perplexity: 20
5D) Nucleophile Weight: 5, Perplexity: 20
5E) Nucleophile Weight: 5, Perplexity: 20

12. Pivot Table Heatmaps for D2B chemistry data of Figure 5E

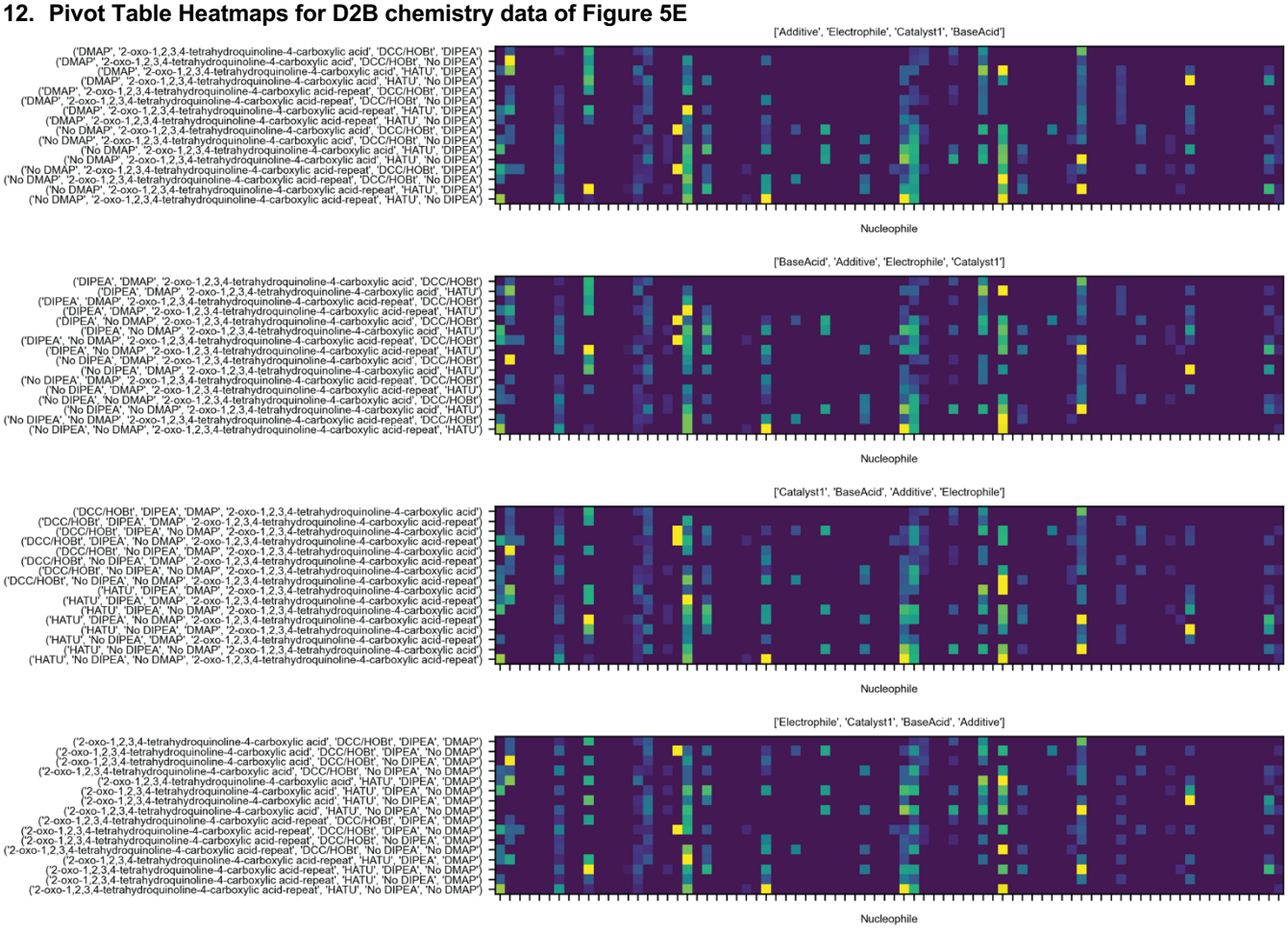


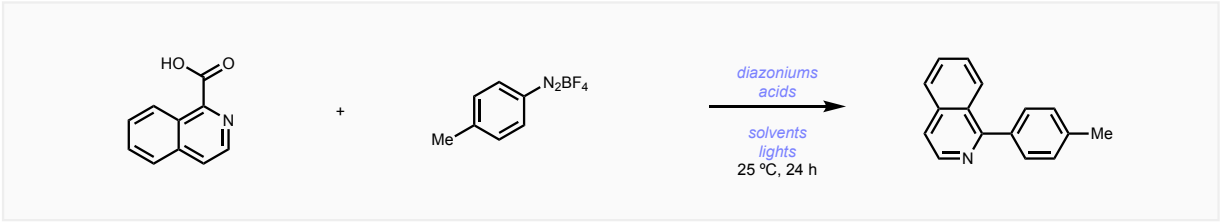
Figure S10. Pivot table heatmaps for the data of Figure 5E. Changing the hierarchy of row indices facilitates comparisons between datapoints.

13. Experimental

a. General Information

All chemical reactions were conducted in oven- or flame-dried glassware and set up in a fumehood exposed to air. All solvents and reagents were purchased from Sigma Aldrich, Alfa Aesar, Oakwood Chemical, or TCI Chemical and were used as received. Glass 2-dram vials (ChemGlass #CG-4912-02) were used as reaction vessels, fitted with a screw-cap with a Teflon-coated silicone septa (CG-4910-02), and magnetic stir bars (Fisher Scientific #14-513-93 or #14-513-65). Proton nuclear magnetic resonance spectra (1H NMR) were recorded on a Varian MR-500 MHz spectrometer and chemical shifts are reported in parts per million (ppm) using the solvent residual peak as an internal standard (DMSO6 at 2.54 ppm). Reaction analysis was typically performed by thin-layer chromatography on silica gel, or using a Waters I-class ACQUITY UPLC-MS (Waters Corporation, Milford, MA, USA) equipped with in-line photodiode array detector (PDA) and QDa mass detector (ESI positive ionization mode). 0.1 µL sample injections were taken from acetonitrile solutions of reaction mixtures or products (~1 mg/mL). A partial loop injection mode was used with the needle placement at 1.0 mm from bottom of the wells and a 0.2 µL air gap at pre-aspiration and post-aspiration. Column used: Waters Cortecs UPLC C18+ column, 2.1mm x 50 mm with (Waters #186007114) with Waters Cortecs UPLC C18+ VanGuard Pre-column 2.1mm x 5 mm (Waters #186007125), Mobile Phase A: 0.1% formic acid in Optima LC/MS-grade water, Mobile Phase B: 0.1% formic acid in Optima LC/MS-grade MeCN. Flow rate: 0.8 mL/min. Column temperature: 45 ºC. The PDA sampling rate was 20 points/sec. The QDa detector monitored m/z 150-750 with a scan time of 0.06 seconds and a cone voltage of 30 V. The PDA detector range was between 210 nm – 400 nm with a resolution of 1.2 nm. A 2-minute method was used. The method gradients are below: 0 min: 0.8 mL/min, 95% 0.1% formic acid in water/5% 0.1% formic acid in acetonitrile; 1.5 min : 0.8 mL/min, 0.1% 0.1% formic acid in water/99.9% 0.1% formic acid in acetonitrile; 1.91 min : 0.8 mL/min, 95% 0.1% formic acid in water/5% 0.1% formic acid in acetonitrile. Thin Layer Chromatography was performed on 25 µm TLC Silica gel 60 F254 glass plates purchased from Fisher Scientific (part number: S07876). Visualization was performed using ultraviolet light (254 nm).

b. Decarboxylative–deaminative sp^2–sp^2 carbon–carbon coupling



i. **General Screening Procedure.** Acids and diazonium salts were prepared as stock solutions as calculated by phactor™ in DMSO, methanol, or 1:1 DMSO:methanol solution. Diazonium stock solutions were kept in a freezer until dosage into the reaction plate was required. 50 microliters of each acid stock solution were added to corresponding wells, then diazonium solutions were sequentially removed from the freezer and 50 microliters of each was dosed into corresponding wells. The reactor block was then transferred to the LED reactor and allowed to stir for 10 minutes without irradiation. After 10 minutes, irradiation was turned on and the reaction was run for 18 hours. Reactions were quenched with 900 microliters of acetonitrile, and 100 microliter aliquots were transferred to an analytical plate containing equimolar caffeine and 900 microliters of acetonitrile in each well for UPLC-MS analysis. Product/Internal Standard values were calculated by taking the normalized ratio between the integrals of the total wavelength chromatogram peak corresponding to the product's ionized mass (M+1) and the peak corresponding to the caffeine internal standard.

Both acids and diazoniums are far more soluble in DMSO than methanol, and slurry loading or vigorous continued stirring may be required to dose suspensions when compound are poorly soluble.

Each of the following plates were run in tandem under two different light systems. For instance, bm20222101blue is the bm20221001 plate run under blue light, and bm20221001uv is the same plate instead run under UV light.

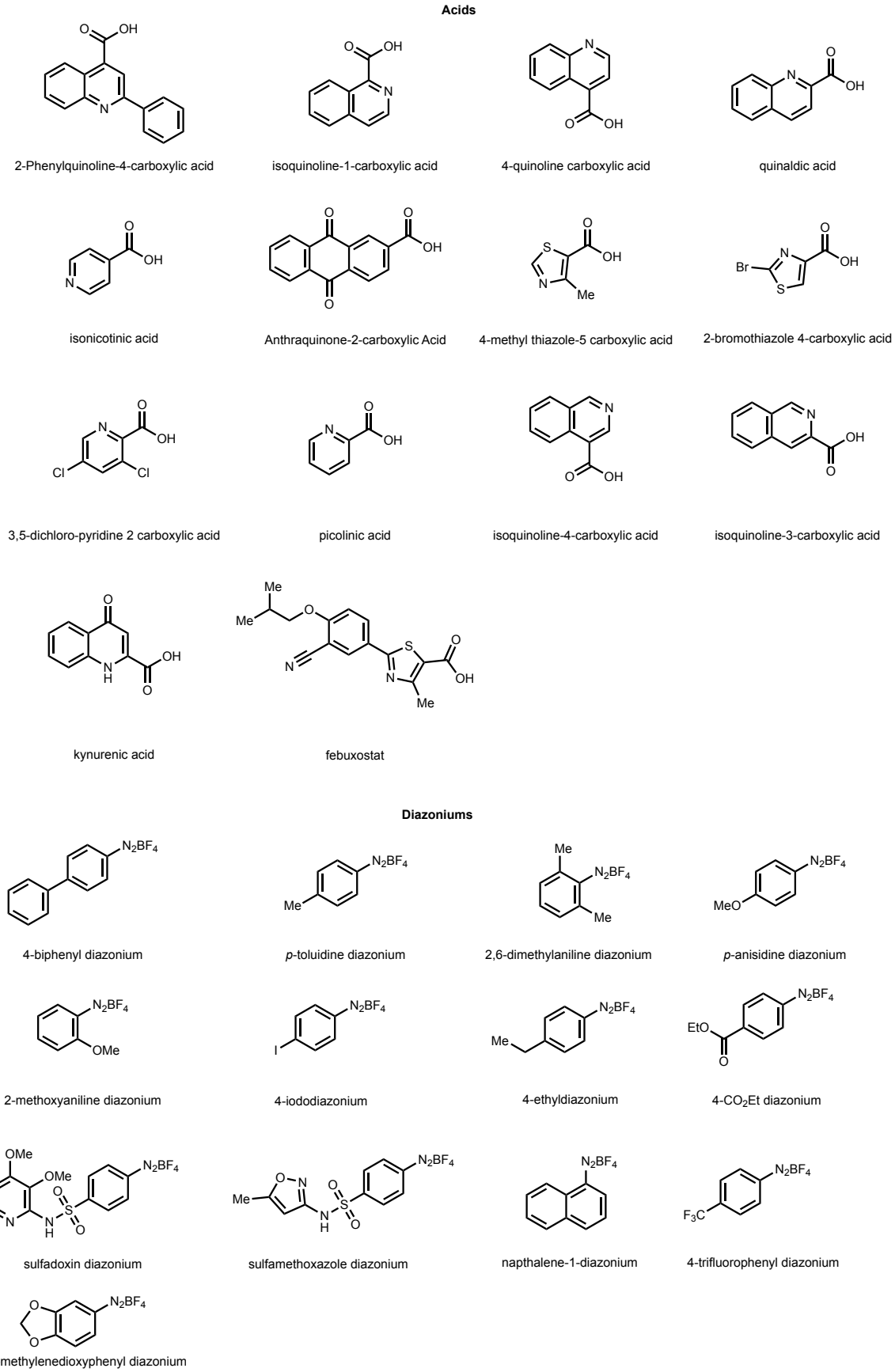


Figure S11. Acids and diazoniums used in catalyst-free sp^2–sp^2 deaminative decarboxylative C–C coupling reaction arrays

ii. bm20222101 – 12 diazonium salts, 8 acids, 2 lights. The general screening procedure was followed. Two reaction plates were dosed with 12 diazonium salts and eight heterocyclic sp^2 carboxylic acids. The solvent was pure methanol and the limiting reagent was the acid at a concentration of 0.1M. One plate was irradiated by blue light (top) while the other was irradiated by UV light (bottom). Two equivalents of diazonium were added.

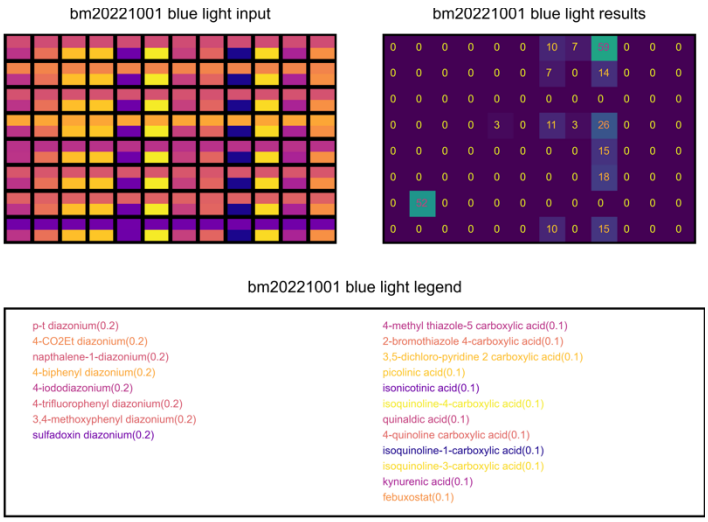


Figure S12. Input and outputs of 96-well array bm20221001blue.

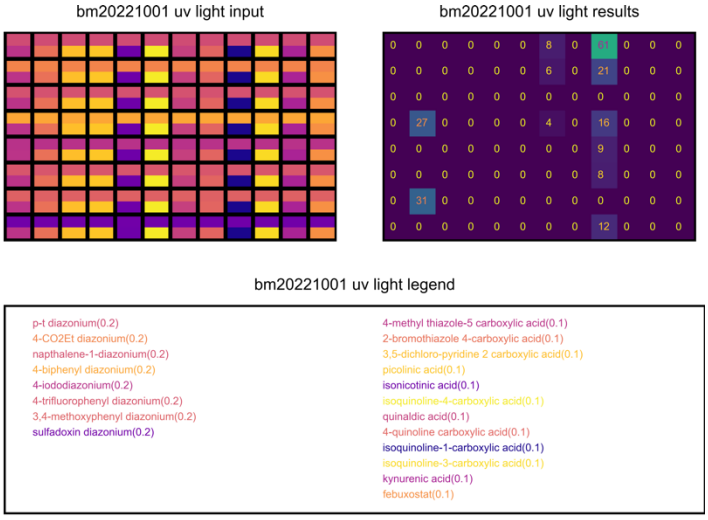


Figure S13. Input and outputs of 96-well array bm20221001uv.

iii. **bm20221014 – 4 diazonium salts, 6 acids, 2 lights.** The general screening procedure was followed. Two reaction plates were dosed with four diazonium salts and six acids. The solvent was 50:50 DMSO:methanol and the limiting reagent was the acid at a concentration of 0.1M. One plate was irradiated by blue light (top) while the other was irradiated by UV light (bottom). Two equivalents of diazonium were added.

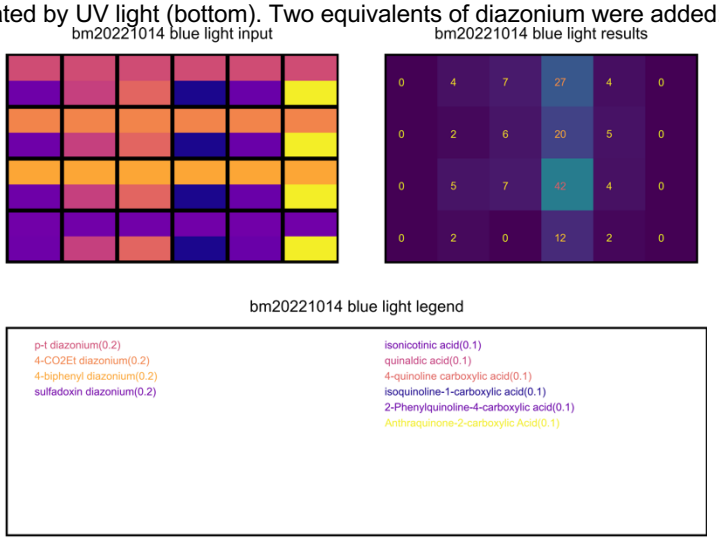


Figure S14. Input and outputs of 24-well array bm20221014blue.

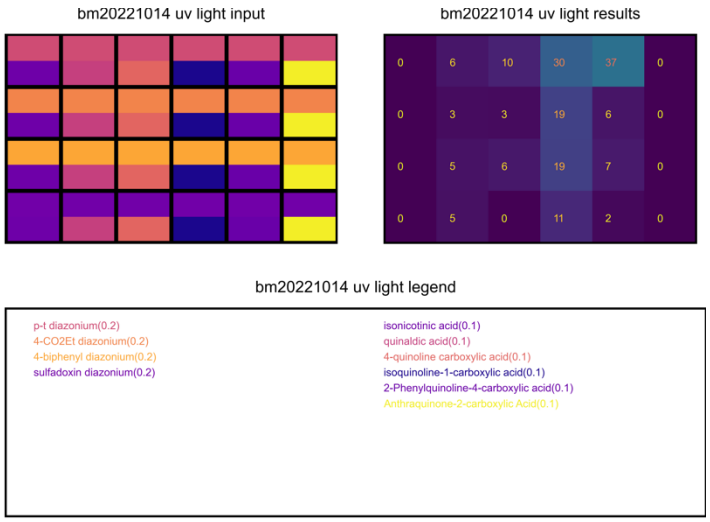


Figure S15. Input and outputs of 24-well array bm20221014uv.

iv. **bm20221019 – 6 diazonium salts, 4 acids, 2 lights.** The general screening procedure was followed. Two reaction plates were dosed with six diazonium salts and four acids. The solvent was 50:50 DMSO:methanol and the limiting reagent was the acid at a concentration of 0.1M. One plate was irradiated by blue light (top) while the other was irradiated by UV light (bottom). Two equivalents of diazonium were added.

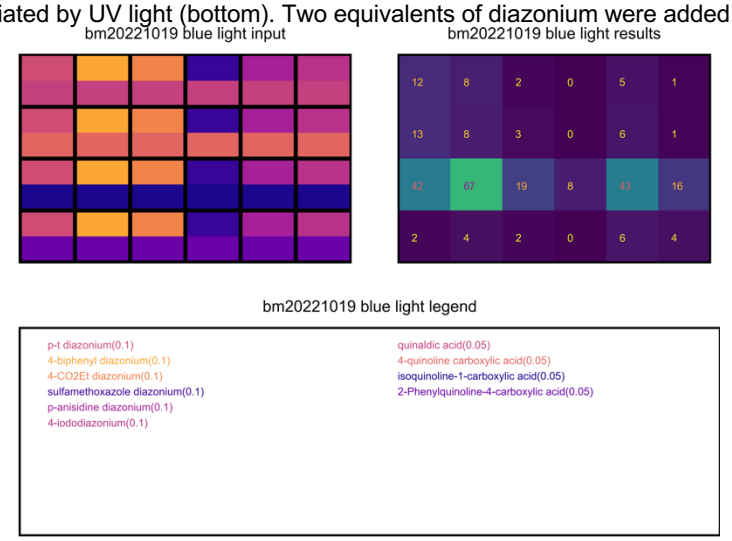


Figure S16. Input and outputs of 24-well array bm20221019blue.

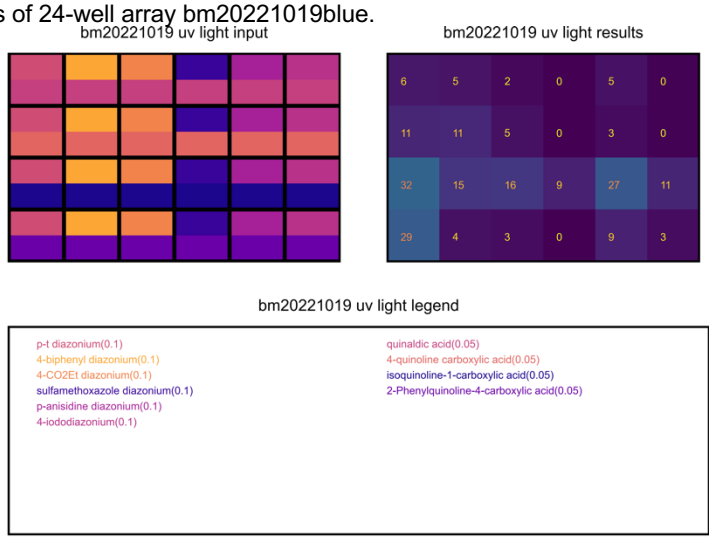


Figure S17. Input and outputs of 24-well array bm20221019uv.

v. **bm20221021 – 5 diazonium salts, 1 acids, 4 acid concentrations, 2 lights.** The general screening procedure was followed. Two reaction plates were dosed with five diazonium salts and 2-Phenylquinoline-4-carboxylic acid (**4**) at four different concentrations (0.05 M, 0.75 M, 0.1 M, 0.125 M). The solvent was pure DMSO. One plate was

irradiated by blue light (top) while the other was irradiated by UV light (bottom). One equivalent of diazonium was added.

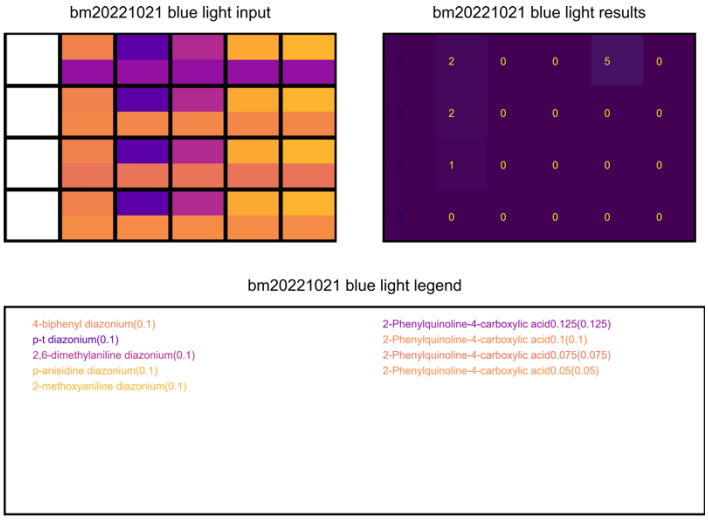


Figure S18. Input and outputs of 24-well array bm20221021blue.

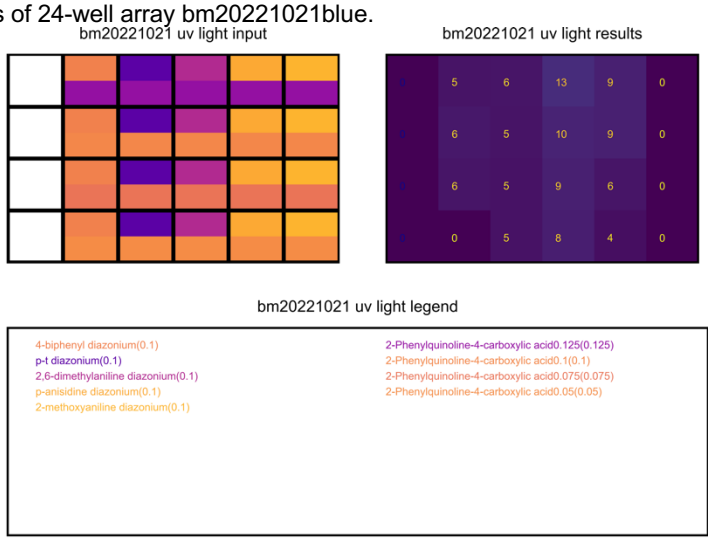


Figure S19. Input and outputs of 24-well array bm20221021uv.

vi. **bm20221024 – 6 diazonium salts, 4 acids, 2 lights.** The general screening procedure was followed. Two reaction plates were dosed with six diazonium salts and four acids. The solvent was pure DMSO in rows B and D and pure methanol in rows A and C. The limiting reagent was the acid at a concentration of 0.05M. One plate was irradiated by blue light (top) while the other was irradiated by UV light (bottom). One equivalent of diazonium was added.

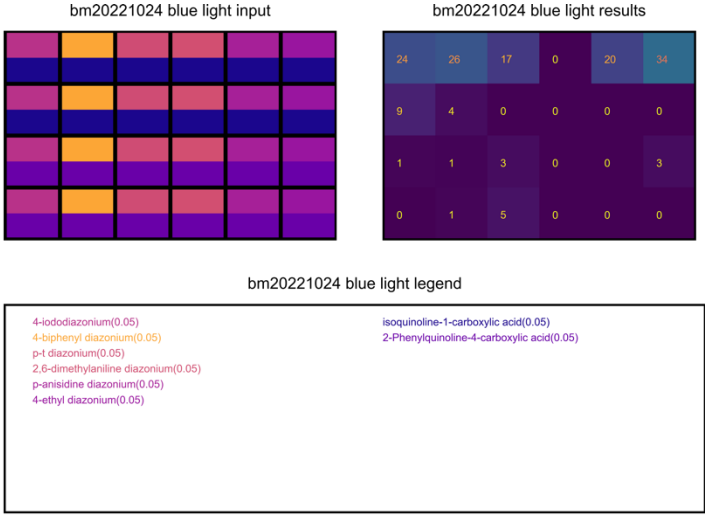


Figure S20. Input and outputs of 24-well array bm20221024blue.

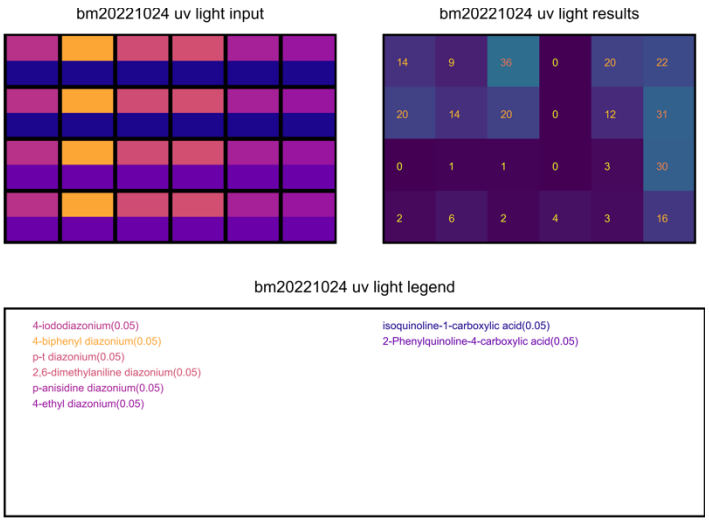


Figure S21. Input and outputs of 24-well array bm20221024uv.

vii. **bm20221026 – 6 diazonium salts, 4 acids, 2 lights.** The general screening procedure was followed. Two reaction plates were dosed with six diazonium salts and four acids. The solvent was pure methanol and the limiting reagent was the acid at a concentration of 0.05M. One plate was irradiated by white light (top) while the other was irradiated by UV light (bottom). Two equivalents of diazonium were added.

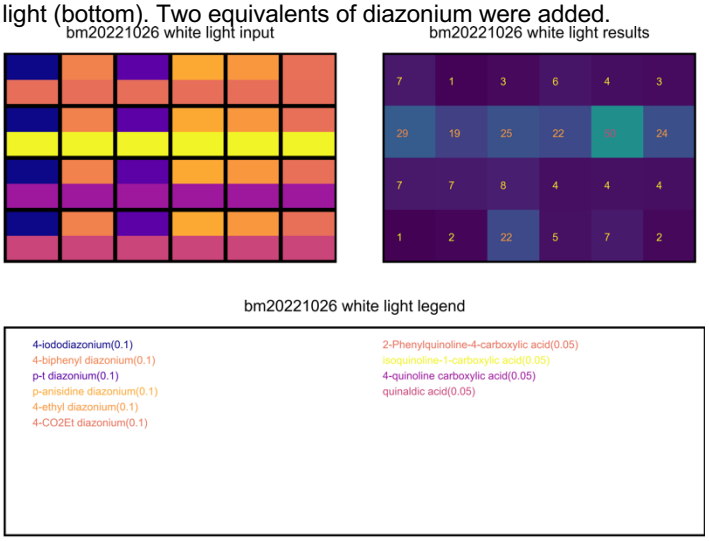


Figure S22. Input and outputs of 24-well array bm20221026white.

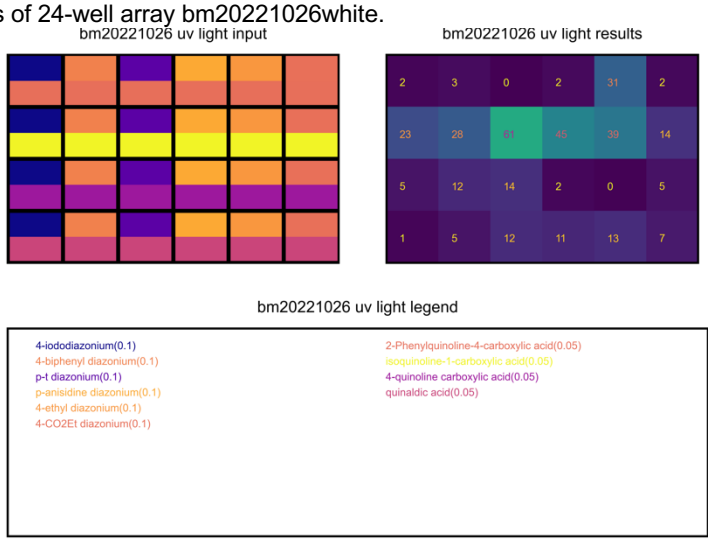


Figure S23. Input and outputs of 24-well array bm20221026uv.

viii. **Scale-up Procedure**

.1 mmol carboxylic acid and four equivalents of diazonium salt was added to a 2-dram vial with a stirbar. 1 mL of methanol was added, and the reaction was stirred without irradiation for 10 minutes. After 10 minutes, blue light was turned on and the reaction was run for 24 hours. Reactions were run at 0.1 M and at room

temperature. Reactions were quenched with bicarbonate and brine and the aqueous layer is washed with ethyl acetate twice. The organic layer is dried and solvent is removed. Crude mixture was then redissolved in dichloromethane and the product is isolated via flash chromatography.

ix. Scale up of 1-(*p*-tolyl)isoquinoline

The scale-up procedure was followed. 22 mg (97%) was isolated via column chromatograph using 20% EtOAC:Hexanes as eluent. Proton NMR for this compound is displayed in NMR section of the Supporting Information.

^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.61 – 8.63 (d, J = 5.8 Hz, 1H), 8.17 – 8.19 (dq, J = 8.6, 1.0 Hz, 1H), 7.91 – 7.93 (m, 1H), 7.73 – 7.76 (ddd, J = 8.2, 6.9, 1.2, Hz, 1H), 7.70 – 7.71 (d, J = 5.8 Hz, 1H), 7.62 – 7.65 (d, J = 8.1 Hz, 2H), 7.57 – 7.60 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.36 – 7.38 (d, J = 7.5 Hz, 2H), 2.47 (s, 3H)

The characterization data matched spectral values from literature.[1]

x. Scale up of 1-(4-ethylphenyl)isoquinoline

The scale-up procedure was followed. 21 mg (95%) was isolated via column chromatograph using 20% EtOAC:Hexanes as eluent. Proton NMR for this compound is displayed in NMR section of the Supporting Information.

^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.60 – 8.61 (d, J = 5.7 Hz, 1H), 8.16 – 8.18 (d, J = 8.5 Hz, 1H), 7.89 – 7.90 (d, J = 8.2 Hz, 1H), 7.69 – 7.72 (t, J = 7.5 Hz, 1H), 7.63 – 7.66 (m, 3H), 7.54 – 7.57 (t, J = 7.1 Hz, 1H), 7.37 – 7.38 (d, J = 8.0 Hz, 2H), 2.74 – 2.79 (q, J = 7.6 Hz, 2H), 1.30 – 1.33 (t, J = 7.6 Hz, 3H).

The characterization data matched spectral values from literature.[2]

xi. Scale up of 1-([1,1'-biphenyl]-4-yl)isoquinoline

The scale-up procedure was followed. 29 mg (72%) was isolated via column chromatograph using 20% EtOAC:Hexanes as eluent. Proton NMR for this compound is displayed in NMR section of the Supporting Information.

^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.66 (s, 1H), 8.23 – 8.25 (d, J = 8.6 Hz, 1H), 7.94 – 7.95 (d, J = 8.2 Hz, 1H), 7.82 – 7.84 (d, J = 8.2 Hz, 3H), 7.79 – 7.81 (d, J = 8.2 Hz, 3H), 7.69 – 7.71 (dd, J = 8.3, 1.3 Hz, 2H), 7.61 – 7.64 (t, J = 7.7 Hz, 1H), 7.48 – 7.51 (t, J = 7.7 Hz, 2H), 7.38 – 7.42 (m, 1H)

The characterization data matched spectral values from literature.[3]

1. 1-(*p*-tolyl)isoquinoline

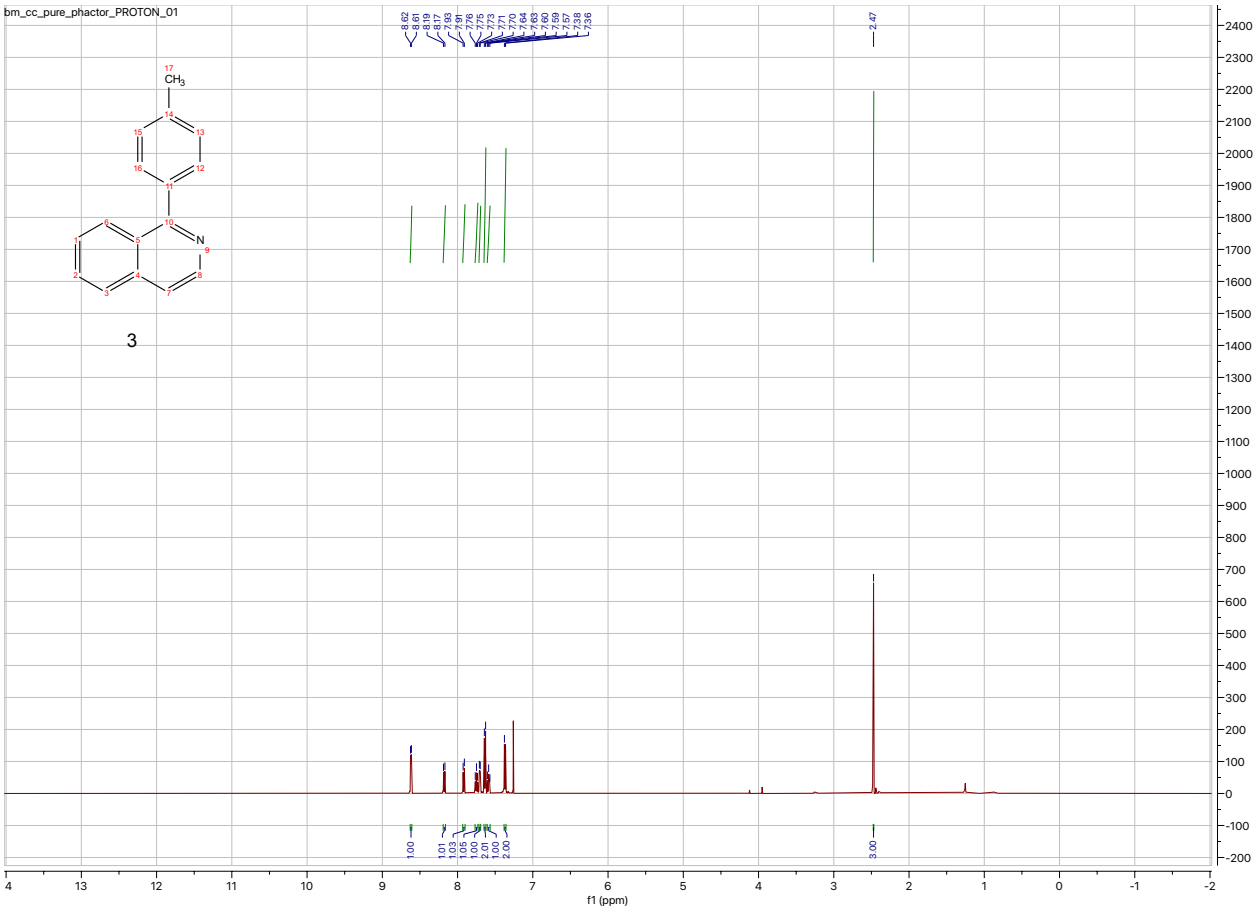


Figure S22. Proton NMR of 1-(*p*-tolyl)isoquinoline.

2. 1-(4-ethylphenyl)isoquinoline

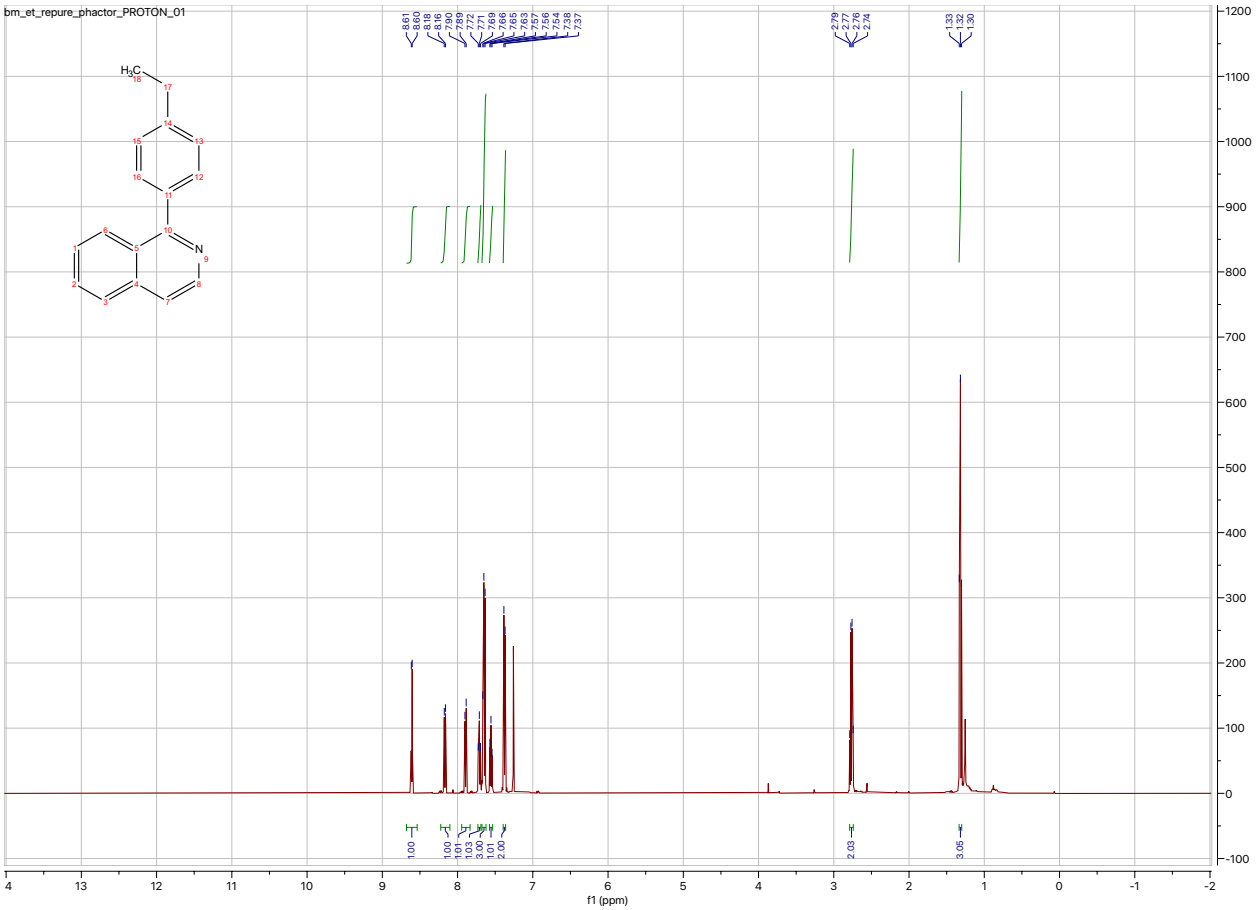


Figure S23. Proton NMR of 1-(4-ethylphenyl)isoquinoline.

3. 1-([1,1'-biphenyl]-4-yl)isoquinoline

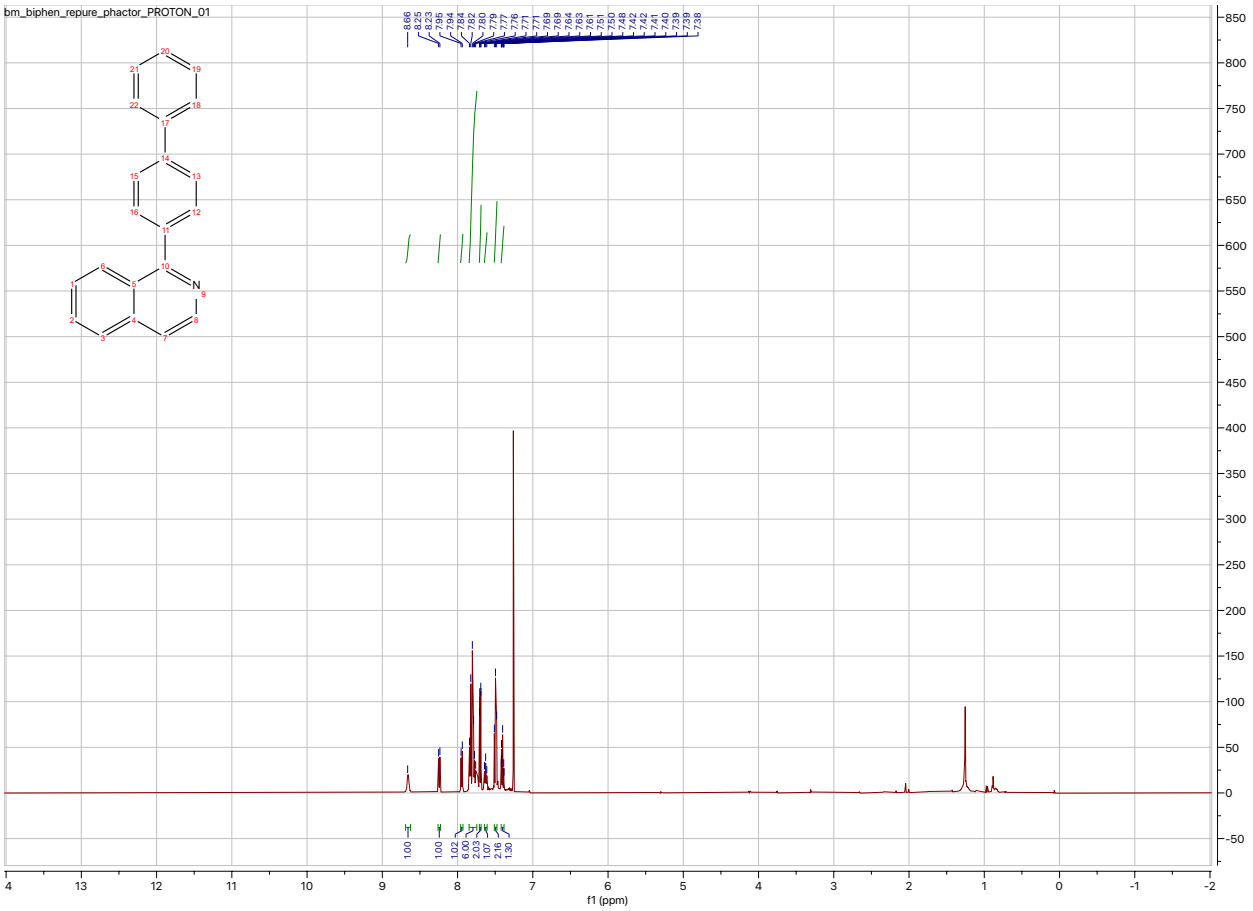


Figure S24. Proton NMR of 1-([1,1'-biphenyl]-4-yl)isoquinoline.