



## **Red-Light Methylene Blue/Iodide Photocatalysis for the Aerobic Construction of Imidazo[1,2-*a*]pyridines: Statistical Optimisation, Mechanistic Profiling and Continuous-Flow Scale-Up**

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### **ABSTRACT**

Imidazo[1,2-*a*]pyridines sit in many marketed drugs, yet most routes to them still rely on stoichiometric halogenating agents, copper salts or heat. We report a metal-free alternative in which methylene blue (MB) and potassium iodide (KI) assemble 2-arylimidazo[1,2-*a*]pyridines from 2-aminopyridines and aryl methyl ketones under 660 nm light, in ethanol, with air as the terminal oxidant. A matched-photon-flux screen of seven organic photocatalysts placed MB first ( $82.0 \pm 1.0\%$  qNMR yield), ahead of rose bengal (73.0%) and eosin Y (68.0%). A resolution-V fractional factorial design (16 combinations, 48 responses;  $R^2 = 0.9941$ ) reduced five factors to three, and a central composite design located a provisional optimum at 2.20 mol% MB, 23.5 mol% KI and 8.5 h (predicted 87.87%; validated 88.22%). Under rounded practical conditions the model product 2-phenylimidazo[1,2-*a*]pyridine (IP01) formed in  $88.00 \pm 0.61\%$  qNMR and  $85.0 \pm 0.8\%$  isolated yield. Thirty substrates gave products in 48–88% isolated yield (mean 73.9%), and eight failures are reported with their causes. Low-conversion competition experiments gave a Hammett  $\rho$  of  $-0.653$  ( $R^2 = 0.9991$ ). Light on/off cycling, an initial quantum yield of  $0.0983 \pm 0.0027$ , Stern–Volmer quenching led by iodide ( $K_{sv} = 220 \text{ M}^{-1}$ ), a parallel kinetic isotope effect of 1.41 and an 81% dark yield from a preformed  $\alpha$ -iodoketone together point to light-driven ketone iodination followed by thermal ring closure. A 10 mL gas–liquid PFA coil reactor delivered 5.07 g of IP01 over 30 h at 87% isolated yield (space–time yield  $16.9 \text{ g L}^{-1} \text{ h}^{-1}$ ), lowering process mass intensity from 94 in batch to 61 in flow.

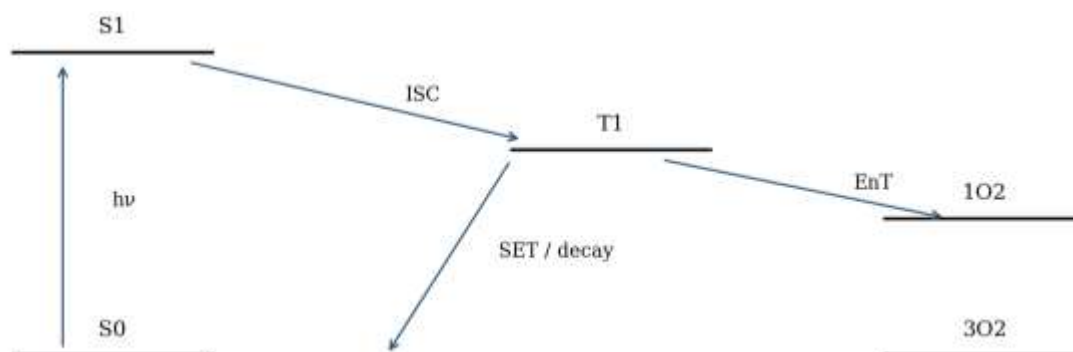
**Keywords:** organophotocatalysis; methylene blue; imidazo[1,2-*a*]pyridine; aerobic oxidation; design of experiments; continuous flow; quantum yield

### **1. INTRODUCTION**

Nitrogen heterocycles dominate small-molecule medicine; roughly six in seven drugs approved by the US Food and Drug Administration contain at least one such ring (Vitaku et al., 2014). The imidazo[1,2-*a*]pyridine core, found in zolpidem, alpidem and olprinone, is one of the more valuable of these because its C3 position remains open for further substitution after the ring is built. Its standard synthesis condenses a 2-aminopyridine with an  $\alpha$ -haloketone. Over the past decade many variants have replaced the preformed haloketone with an in situ oxidant, but most of them still rely on copper, stoichiometric iodine or elevated temperature (Bagdi et al., 2015).

Visible-light photoredox catalysis offers a gentler way to activate the ketone. An excited photocatalyst is both a stronger oxidant and a stronger reductant than its ground state, and it can move single electrons to or from substrates at room temperature (Prier et al., 2013). Organic dyes now cover a redox window at least as wide as the ruthenium and iridium complexes that founded the field, at a small fraction of their cost (Fukuzumi & Ohkubo, 2014; Romero & Nicewicz, 2016). Methylene blue is especially attractive: it absorbs strongly in the red, where most organic substrates are transparent, and its excited state readily passes energy or charge to molecular oxygen (Figure 1).

Two problems make published photochemical heterocycle syntheses hard to compare and hard to scale. First, irradiation is rarely reported as a measured quantity, so a better yield under one lamp may simply reflect more photons. Second, optimisation is usually done one variable at a time, which hides interactions between catalyst loading, additive loading and reaction time. Marzo et al. (2018) raised the broader question of when visible light genuinely improves on a thermal route, and that question can only be answered when photon delivery and material use are counted. This study therefore treats light as a measured reagent, optimises by statistical design, tests the mechanism with several independent probes, and carries the reaction into continuous flow.

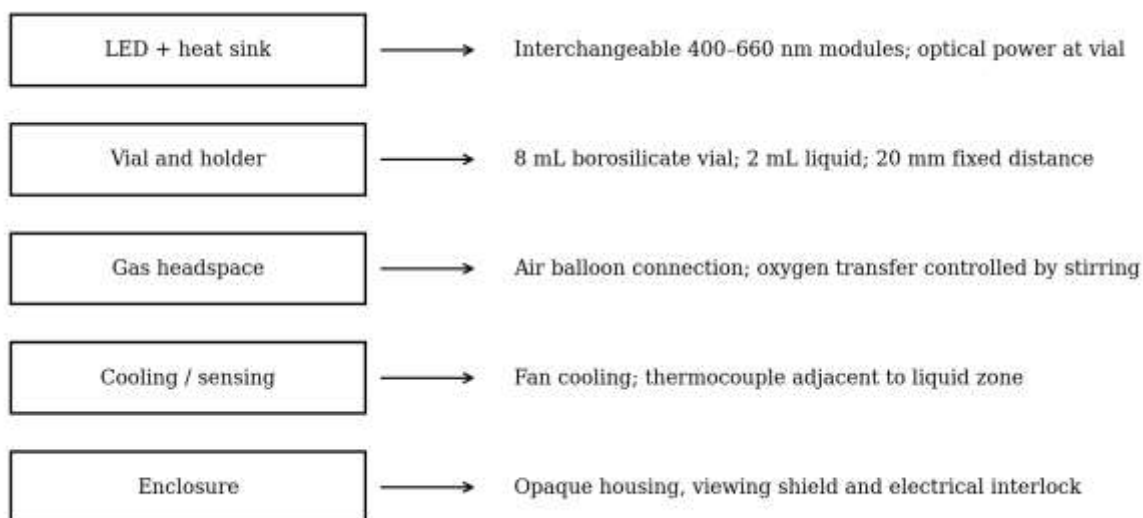


**Figure 1.** Photophysical events available to the excited dye: absorption, intersystem crossing and energy transfer to molecular oxygen.

## 2. EXPERIMENTAL

### 2.1 Photoreactor and light measurement

Batch reactions were run in 8 mL borosilicate vials containing 2.0 mL of solution, held in a machined block with the liquid zone 20 mm from the LED face (Figure 2). Fan cooling held the liquid at  $25 \pm 2$  °C; a thermocouple beside the liquid zone logged temperature throughout, and direct liquid measurements were taken during commissioning. Aerobic runs used an unpressurised air balloon. Light shields excluded stray light during dark controls.



**Figure 2.** Batch photoreactor arrangement showing the fixed vial holder, LED module, cooling and temperature measurement positions.

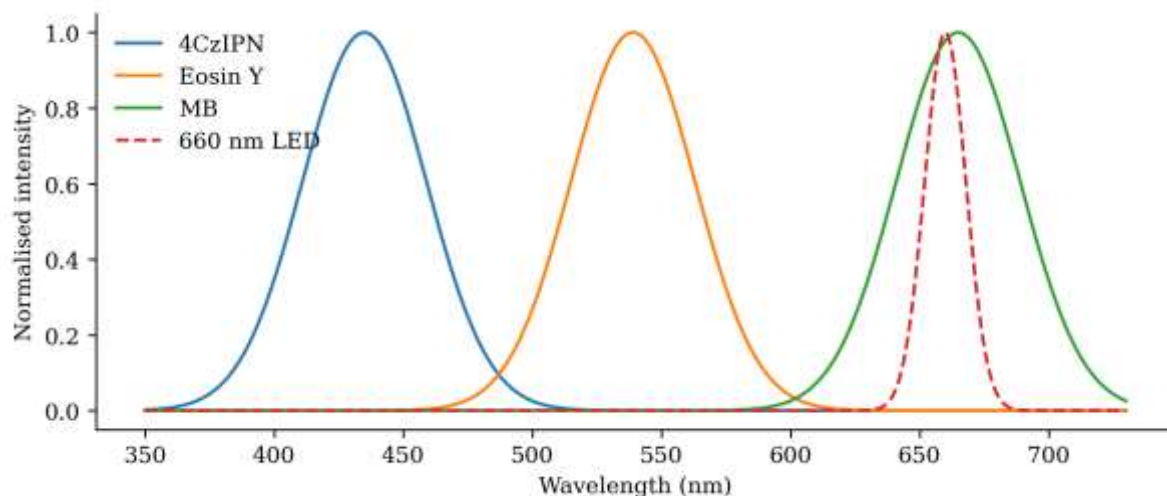
Five LED modules were characterised at the vial position (Table 1). Optical power was converted to molar photon flux with  $q = P\lambda/(hcN_A)$ . Flux was confirmed by chemical actinometry following IUPAC (Kuhn et al., 2004); because ferrioxalate calibration does not extend reliably to 660 nm, the red module was checked by calibrated radiometry. For the catalyst and wavelength screens, the incident flux of each module was set to  $1.15 \times 10^{-7} \text{ mol s}^{-1}$ .

**Table 1**

*LED characterisation at the vial position*

| LED (nm) | FWHM (nm) | Power (mW) | Photon flux ( $\text{mol s}^{-1}$ ) |
|----------|-----------|------------|-------------------------------------|
| 400      | 16        | 45.0       | $1.505 \times 10^{-7}$              |
| 427      | 18        | 47.0       | $1.678 \times 10^{-7}$              |
| 456      | 20        | 49.0       | $1.868 \times 10^{-7}$              |
| 525      | 24        | 50.0       | $2.194 \times 10^{-7}$              |
| 660      | 19        | 43.0       | $2.372 \times 10^{-7}$              |

*Note.* Flux calculated from optical power at the sample position using the monochromatic approximation.



**Figure 3.** Normalised absorption of the candidate photocatalysts and emission profile of the 660 nm LED.

The initial product quantum yield was calculated as  $\Phi = \Delta n_{\text{product}} / (q_{\text{incident}} \times f_{\text{abs}} \times \Delta t)$ , with  $f_{\text{abs}} = 1 - 10^{-A^*}$ . Three independent low-conversion intervals of 600 s were used (Table 2), following the intermittent-illumination and actinometry approach of Pitre et al. (2015).

**Table 2**

*Photon and product balance for the initial quantum yield*

| Quantity                              | Run 1                 | Run 2                 | Run 3                 |
|---------------------------------------|-----------------------|-----------------------|-----------------------|
| Incident flux ( $\text{mol s}^{-1}$ ) | $1.15 \times 10^{-7}$ | $1.15 \times 10^{-7}$ | $1.15 \times 10^{-7}$ |
| Absorbed fraction                     | 0.85                  | 0.85                  | 0.85                  |
| Exposure (s)                          | 600                   | 600                   | 600                   |
| Product ( $\mu\text{mol}$ )           | 5.60                  | 5.78                  | 5.91                  |
| Absorbed photons ( $\mu\text{mol}$ )  | 58.65                 | 58.65                 | 58.65                 |
| Product quantum yield                 | 0.0955                | 0.0986                | 0.1008                |

## 2.2 Analytical conventions

Yields were determined by quantitative  $^1\text{H}$  NMR against 1,3,5-trimethoxybenzene (0.100 mmol), comparing its three aromatic protons with the single C3–H singlet of IP01:  $n_{\text{P}} = (I_{\text{P}}/N_{\text{P}})/(I_{\text{S}}/N_{\text{S}}) \times n_{\text{S}}$ . The relaxation delay was at least five times the longest measured  $T_1$ . Integrals were corrected for aliquot volume to whole-reaction equivalents. Three independently prepared reactions define  $n = 3$ , and values are given as mean  $\pm$  sample standard deviation. Isolated yields after chromatography are recorded separately (Table 3).

**Table 3**

*qNMR calculation and reproducibility for IP01 (limiting substrate 0.200 mmol)*

| Run  | Product integral (1H) | Standard integral (3H) | qNMR yield (%) | Isolated yield (%) |
|------|-----------------------|------------------------|----------------|--------------------|
| 1    | 0.583                 | 1.000                  | 87.45          | 84.2               |
| 2    | 0.591                 | 1.000                  | 88.65          | 85.0               |
| 3    | 0.586                 | 1.000                  | 87.90          | 85.8               |
| Mean | —                     | —                      | 88.00          | 85.00              |
| SD   | —                     | —                      | 0.61           | 0.80               |

### 2.3 General procedure for imidazo[1,2-*a*]pyridine synthesis (GP-A)

A vial was charged with the 2-aminopyridine (0.20 mmol), the ketone (0.30 mmol, 1.5 equiv), methylene blue (2 mol%) and KI (20 mol%) in ethanol (2.0 mL, 0.10 M). The vial was fitted with an air balloon and irradiated at 660 nm and 25 °C for 8 h with stirring. An aliquot was analysed by qNMR, after which the mixture was worked up by a common extraction and purified by flash chromatography on silica gel. Supplier, purity, batch and chemical form (salt, hydrate or neutral) were recorded for each dye and reagent.

### 2.4 Mechanistic and spectroscopic methods

Emission quenching used optically dilute MB solutions titrated with one component at a time, with inner-filter correction and a blank dilution series (Lakowicz, 2006). Cyclic voltammetry used a three-electrode cell with supporting electrolyte and an internal redox reference converted to SCE; irreversible processes are reported as peak potentials (Elgrishi et al., 2018). EPR spin trapping used DMPO (50 mM) at X-band (nominal 9.5 GHz) across a 330–346 mT window, with microwave power and modulation amplitude matched across controls. Kinetic isotope effects were measured by parallel low-conversion runs with acetophenone and acetophenone-*d*<sub>3</sub>, with label retention checked before and after exposure to ethanol and water.

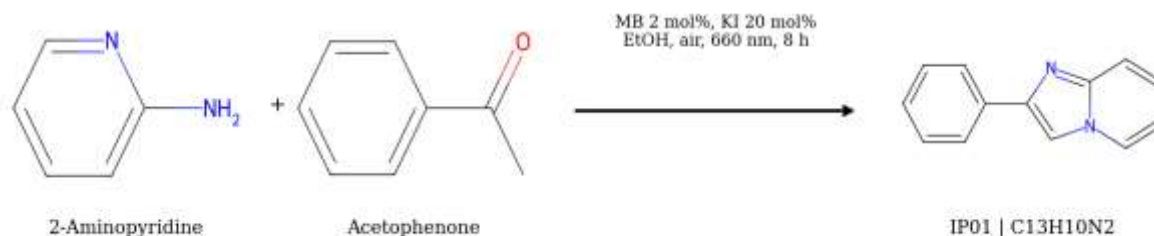
### 2.5 Continuous-flow procedure (GP-G)

A 0.10 M feed was pumped together with air into a PFA coil of 10.0 mL liquid holdup wound around a 660 nm LED array, through a back-pressure regulator and a gas–liquid separator (Figure 20). At least three holdup volumes were discarded before collection, and product was collected only while outlet composition was steady. Liquid residence time was defined as  $V_{\text{liquid}}/Q_{\text{liquid}}$ .

## 3. RESULTS AND DISCUSSION

### 3.1 Model reaction and catalyst selection

The model reaction couples 2-aminopyridine with acetophenone to give IP01 (Scheme 1). The ring nitrogen and the exocyclic amine supply the two nitrogen atoms of the new five-membered ring, and the ketone supplies the remaining two carbons and the C2 phenyl group. The idealised balance is aminopyridine + acetophenone +  $\frac{1}{2}\text{O}_2 \rightarrow \text{IP01} + 2\text{H}_2\text{O}$ .



**Scheme 1.** Model aerobic construction of 2-phenylimidazo[1,2-*a*]pyridine (IP01).

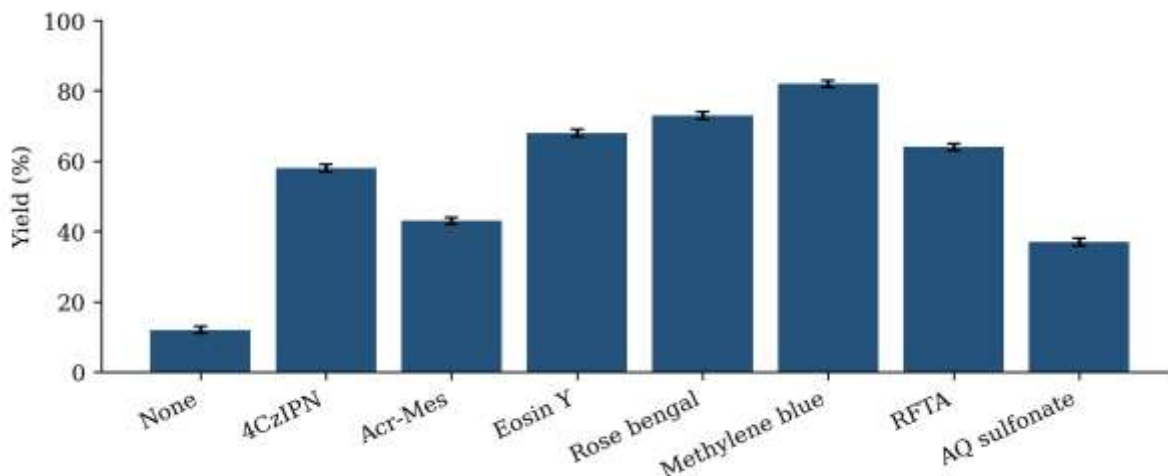
Seven organic photocatalysts covering the cyanoarene, acridinium, xanthene, thiazine, flavin and quinone classes were compared at 2 mol% with 20 mol% KI, each irradiated near its absorption band at the same incident flux (Table 4, Figure 4). Methylene blue gave the highest yield (82.0%), followed by rose bengal (73.0%) and eosin Y (68.0%). The strongly oxidising acridinium salt performed poorly (43.0%), which shows that excited-state oxidising power alone does not predict success here (Romero & Nicewicz, 2016). Without any dye the reaction still reached 12.0%, so a background pathway exists and the no-dye control has to be kept in every comparison.

**Table 4**

*Photocatalyst screen at matched incident photon flux ( $1.15 \times 10^{-7} \text{ mol s}^{-1}$ )*

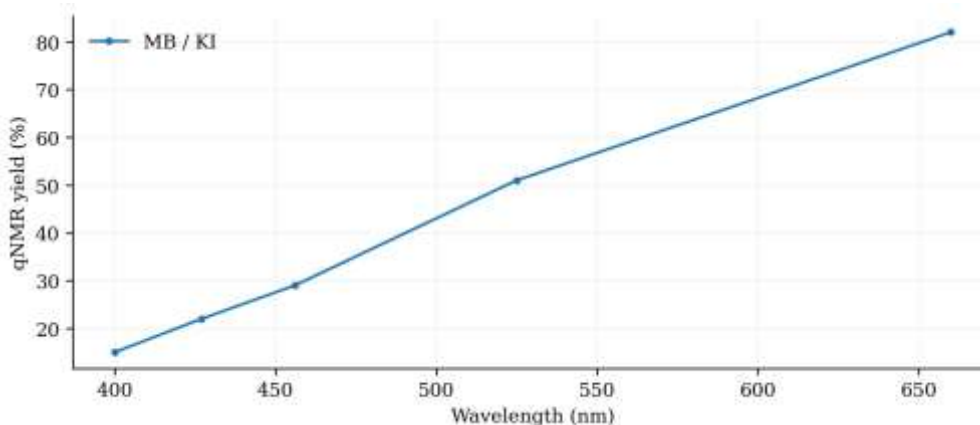
| Catalyst              | LED (nm) | Run 1 | Run 2 | Run 3 | Mean $\pm$ SD (%) |
|-----------------------|----------|-------|-------|-------|-------------------|
| None                  | 660      | 10.9  | 12.2  | 12.9  | 12.0 $\pm$ 1.0    |
| 4CzIPN                | 427      | 56.9  | 58.2  | 58.9  | 58.0 $\pm$ 1.0    |
| Acr <sup>+</sup> -Mes | 427      | 41.9  | 43.2  | 43.9  | 43.0 $\pm$ 1.0    |
| Eosin Y               | 525      | 66.9  | 68.2  | 68.9  | 68.0 $\pm$ 1.0    |
| Rose bengal           | 525      | 71.9  | 73.2  | 73.9  | 73.0 $\pm$ 1.0    |
| Methylene blue        | 660      | 80.9  | 82.2  | 82.9  | 82.0 $\pm$ 1.0    |
| RFTA                  | 456      | 62.9  | 64.2  | 64.9  | 64.0 $\pm$ 1.0    |
| AQ sulfonate          | 400      | 35.9  | 37.2  | 37.9  | 37.0 $\pm$ 1.0    |

*Note.* qNMR yields; 0.20 mmol scale, 2 mol% catalyst, 20 mol% KI, EtOH, air, 8 h.



**Figure 4.** Photocatalyst screening response; error bars show sample standard deviations ( $n = 3$ ).

MB was then run under all five LED modules at the same incident flux (Figure 5). Yield rose towards the red absorption band of the dye. Because this is an end-point comparison rather than a true action spectrum, the trend supports choosing 660 nm without proving a wavelength-specific mechanism; lower dye bleaching or a shorter induction period could produce the same pattern. Red light does have one clear advantage: almost none of the colourless substrates absorb at 660 nm, so direct substrate excitation is largely excluded.



**Figure 5.** End-point wavelength response for MB/KI at matched incident photon flux (0.20 mmol, EtOH, air, 8 h,  $25 \pm 2$  °C).

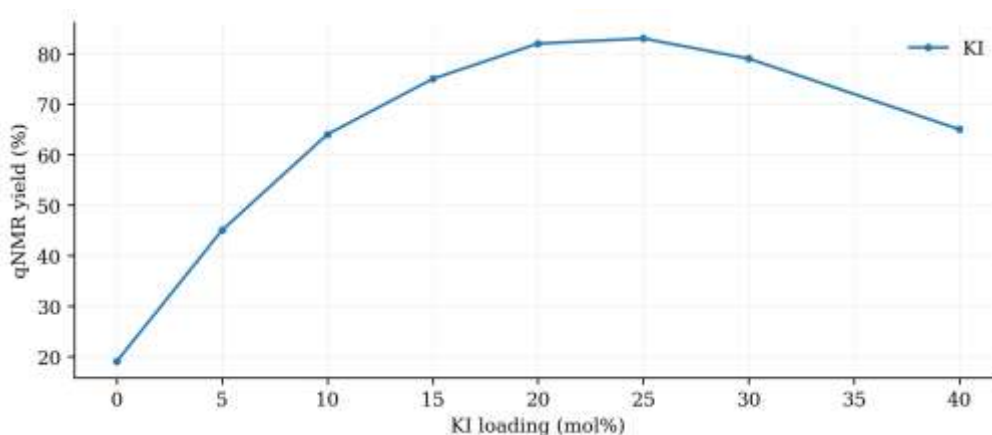
### 3.2 Additive, solvent, atmosphere and temperature

The iodide source mattered more than its counter-ion (Table 5). KI, NH<sub>4</sub>I and NaI performed similarly (82, 79 and 77%), whereas bromide and chloride gave little more than the iodide-free background. Molecular iodine (70%) produced more side material than iodide. The KI loading curve had a broad maximum at 20–25 mol% and fell at 40 mol% (Figure 6), possibly because excess iodide quenches the excited dye unproductively or holds iodine in an inactive form. We kept 20 mol% for screening, since a 1-point gain at 25 mol% lies within replicate scatter.

**Table 5**

*Iodide and related additive screen*

| Additive          | Loading (mol%) | qNMR (%) | Observation        |
|-------------------|----------------|----------|--------------------|
| None              | —              | 19       | Slow background    |
| KI                | 20             | 82       | Reference          |
| NaI               | 20             | 77       | Slightly lower     |
| NH <sub>4</sub> I | 20             | 79       | Competitive        |
| TBAI              | 20             | 74       | No improvement     |
| I <sub>2</sub>    | 20             | 70       | More side material |
| KBr               | 20             | 31       | Weak response      |
| KCl               | 20             | 20       | Weak response      |



**Figure 6.** Dependence of IP01 yield on KI loading.

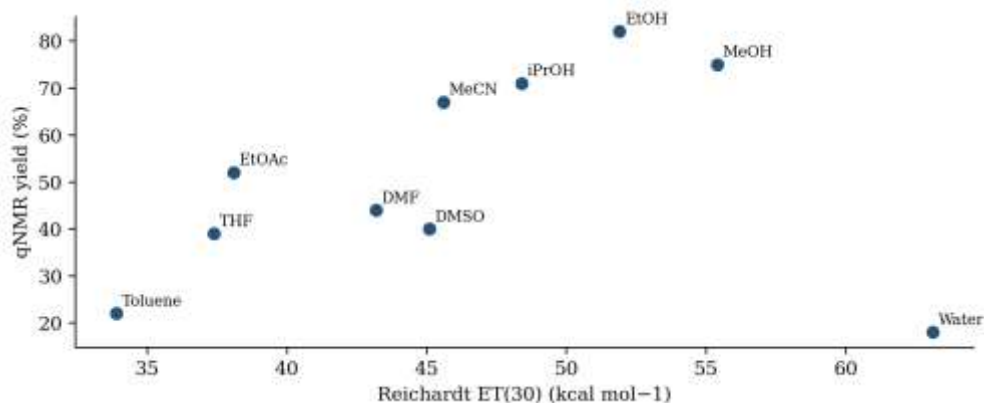
Among ten solvents, ethanol gave the best result (82%), followed by methanol (75%) and isopropanol (71%); toluene (22%) and water (18%) were poor (Table 6). Plotting yield against the Reichardt  $E_T(30)$  parameter gave no single trend (Figure 7). Water, the most polar medium, was among the worst, so polarity alone cannot explain the results (Reichardt, 1994). Dye aggregation, iodide solubility, oxygen transport and the dehydrative condensation step all change with solvent at the same time. Ethanol is also a convenient green solvent.

**Table 6**

*Solvent screen and polarity descriptor*

| Solvent | $E_T(30)$ (kcal mol <sup>-1</sup> ) | qNMR (%) |
|---------|-------------------------------------|----------|
| MeCN    | 45.6                                | 67       |
| EtOH    | 51.9                                | 82       |
| MeOH    | 55.4                                | 75       |

| Solvent       | $E_T(30)$ (kcal mol <sup>-1</sup> ) | qNMR (%) |
|---------------|-------------------------------------|----------|
| <i>i</i> PrOH | 48.4                                | 71       |
| DMSO          | 45.1                                | 40       |
| DMF           | 43.2                                | 44       |
| THF           | 37.4                                | 39       |
| EtOAc         | 38.1                                | 52       |
| Toluene       | 33.9                                | 22       |
| Water         | 63.1                                | 18       |



**Figure 7.** Solvent yield plotted against  $E_T(30)$ .

Under argon the yield fell to 23%; air restored it to 82%, and an oxygen balloon gave a modest further gain to 85% (Table 7). Yield peaked between 25 and 35 °C. At 50 °C it dropped to 70%, with selectivity falling to 83%. Dark controls held at the measured illuminated temperature gave 4% at 25 °C and 13% at 50 °C, so lamp heating does not explain the photochemical result. Raising concentration from 0.10 to 0.20 M lowered the yield to 69%, which is consistent with stronger light attenuation in the more concentrated, more strongly coloured solution.

**Table 7**

*Atmosphere, temperature and concentration variations*

| Variable    | Setting                | qNMR (%) | Selectivity (%) |
|-------------|------------------------|----------|-----------------|
| Atmosphere  | Argon                  | 23       | 71              |
| Atmosphere  | Air                    | 82       | 94              |
| Atmosphere  | O <sub>2</sub> balloon | 85       | 94              |
| Temperature | 15 °C                  | 65       | 96              |
| Temperature | 25 °C                  | 82       | 94              |



| Variable      | Setting | qNMR (%) | Selectivity (%) |
|---------------|---------|----------|-----------------|
| Temperature   | 35 °C   | 84       | 92              |
| Temperature   | 50 °C   | 70       | 83              |
| Concentration | 0.05 M  | 80       | 95              |
| Concentration | 0.10 M  | 82       | 94              |
| Concentration | 0.20 M  | 69       | 89              |
| Dark control  | 25 °C   | 4        | 61              |
| Dark control  | 50 °C   | 13       | 66              |

### 3.3 Fractional factorial screening

Five factors were screened in a  $2^{5-1}$  half-fraction of resolution V, generated by E = ABCD (defining relation I = ABCDE), so main effects are aliased only with four-factor interactions (Montgomery, 2017). Each of the 16 combinations was prepared three times in randomised order, giving 48 responses (Tables 8 and 9).

**Table 8**

*Fractional factorial factors and coded levels*

| Code | Factor           | −1  | +1  |
|------|------------------|-----|-----|
| A    | MB (mol%)        | 1   | 3   |
| B    | KI (mol%)        | 10  | 30  |
| C    | Time (h)         | 4   | 10  |
| D    | Temperature (°C) | 20  | 35  |
| E    | Ketone (equiv)   | 1.2 | 2.0 |

*Note.* Coding:  $x = (\text{actual} - \text{midpoint})/(\text{half-range})$ .

**Table 9**

*Resolution-V design matrix and independent qNMR responses (%)*

| Run | A  | B  | C  | D  | E  | Y1   | Y2   | Y3   |
|-----|----|----|----|----|----|------|------|------|
| 1   | −1 | −1 | −1 | −1 | +1 | 40.5 | 40.9 | 38.5 |
| 2   | −1 | −1 | −1 | +1 | −1 | 44.6 | 48.4 | 49.3 |
| 3   | −1 | −1 | +1 | −1 | −1 | 42.4 | 44.2 | 44.0 |
| 4   | −1 | −1 | +1 | +1 | +1 | 45.5 | 45.3 | 44.1 |
| 5   | −1 | +1 | −1 | −1 | −1 | 51.0 | 50.4 | 49.5 |
| 6   | −1 | +1 | −1 | +1 | +1 | 53.9 | 54.6 | 53.7 |

| Run | A  | B  | C  | D  | E  | Y1   | Y2   | Y3   |
|-----|----|----|----|----|----|------|------|------|
| 7   | -1 | +1 | +1 | -1 | +1 | 58.0 | 59.1 | 57.2 |
| 8   | -1 | +1 | +1 | +1 | -1 | 64.6 | 66.2 | 63.1 |
| 9   | +1 | -1 | -1 | -1 | -1 | 45.5 | 47.2 | 45.6 |
| 10  | +1 | -1 | -1 | +1 | +1 | 49.0 | 49.9 | 48.3 |
| 11  | +1 | -1 | +1 | -1 | +1 | 57.1 | 58.1 | 57.4 |
| 12  | +1 | -1 | +1 | +1 | -1 | 64.2 | 65.7 | 65.5 |
| 13  | +1 | +1 | -1 | -1 | +1 | 60.2 | 58.6 | 58.4 |
| 14  | +1 | +1 | -1 | +1 | -1 | 65.4 | 64.6 | 66.1 |
| 15  | +1 | +1 | +1 | -1 | -1 | 81.8 | 81.1 | 83.4 |
| 16  | +1 | +1 | +1 | +1 | +1 | 84.6 | 84.1 | 84.9 |

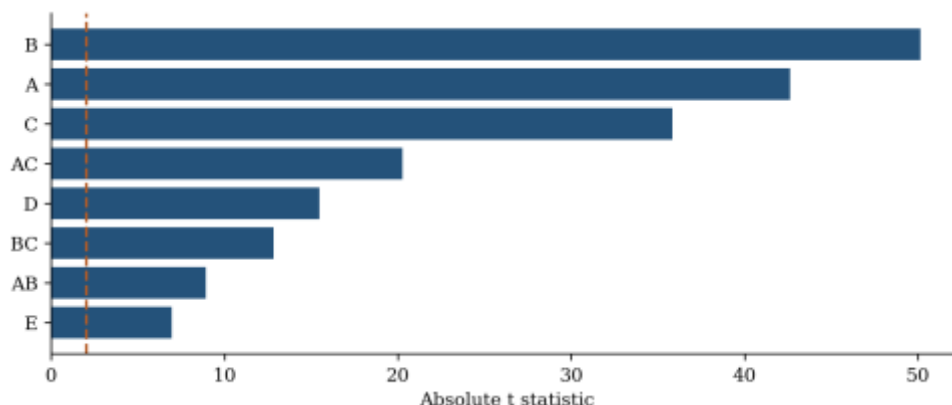
The retained model (five main effects plus the AB, AC and BC interactions) explained 99.41% of the variance (adjusted  $R^2 = 0.9929$ ; residual SD 1.07 points; Table 10). In coded units, KI loading had the largest coefficient ( $B = 7.779$ ), followed by MB loading ( $A = 6.615$ ) and time ( $C = 5.562$ ). Temperature had a smaller effect ( $D = 2.402$ ), and ketone equivalents a slightly negative one ( $E = -1.078$ ). All three two-factor interactions were positive ( $AC = 3.143$ ,  $BC = 1.993$ ,  $AB = 1.385$ ): raising catalyst and time together helps more than the sum of the separate changes. The Pareto and half-normal plots (Figure 8) single out A, B and C, so temperature and ketone equivalents were fixed at 25 °C and 1.5 equiv for the response-surface study.

**Table 10**

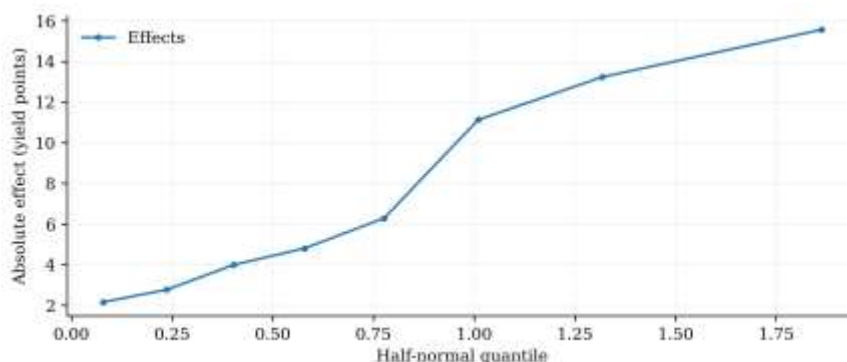
*ANOVA for the fractional factorial response model*

| Source   | df | SS      | MS     | <i>F</i> | <i>p</i> |
|----------|----|---------|--------|----------|----------|
| Model    | 8  | 7579.59 | 947.45 | 819.87   | < 0.0001 |
| Residual | 39 | 45.07   | 1.16   | —        | —        |
| Total    | 47 | 7624.66 | —      | —        | —        |

*Note.* Coded coefficients: intercept 56.990; A 6.615; B 7.779; C 5.562; D 2.402; E -1.078; AC 3.143; AB 1.385; BC 1.993.



**Figure 8a.** Pareto ranking of retained terms by absolute  $t$  statistic; the dashed line marks the two-sided 5% reference.



**Figure 8b.** Half-normal plot of absolute screening effects.

### 3.4 Central composite optimisation

A three-factor central composite design (8 factorial, 6 axial and 6 centre points;  $\alpha = 8^{1/4} = 1.682$ ) was centred on 2 mol% MB, 20 mol% KI and 8 h (Tables 11 and 12). The six centre runs (86.35–87.33%) all exceeded every factorial corner, which already points to an interior maximum.

**Table 11**

*Central composite design: physical factor levels*

| Factor    | $-\alpha$ | -1    | 0     | +1    | $+\alpha$ |
|-----------|-----------|-------|-------|-------|-----------|
| MB (mol%) | 0.65      | 1.20  | 2.00  | 2.80  | 3.35      |
| KI (mol%) | 3.18      | 10.00 | 20.00 | 30.00 | 36.82     |
| Time (h)  | 4.64      | 6.00  | 8.00  | 10.00 | 11.36     |

**Table 12**

*Central composite design matrix and qNMR response*

| Run | MB (mol%) | KI (mol%) | Time (h) | qNMR (%) |
|-----|-----------|-----------|----------|----------|
| 1   | 1.20      | 10.00     | 6.00     | 66.13    |



| Run | MB (mol%) | KI (mol%) | Time (h) | qNMR (%) |
|-----|-----------|-----------|----------|----------|
| 2   | 1.20      | 10.00     | 10.00    | 67.26    |
| 3   | 1.20      | 30.00     | 6.00     | 68.54    |
| 4   | 1.20      | 30.00     | 10.00    | 71.30    |
| 5   | 2.80      | 10.00     | 6.00     | 68.65    |
| 6   | 2.80      | 10.00     | 10.00    | 70.45    |
| 7   | 2.80      | 30.00     | 6.00     | 73.81    |
| 8   | 2.80      | 30.00     | 10.00    | 82.15    |
| 9   | 3.35      | 20.00     | 8.00     | 72.49    |
| 10  | 2.00      | 36.82     | 8.00     | 77.51    |
| 11  | 2.00      | 20.00     | 11.36    | 77.13    |
| 12  | 0.65      | 20.00     | 8.00     | 65.21    |
| 13  | 2.00      | 3.18      | 8.00     | 66.24    |
| 14  | 2.00      | 20.00     | 4.64     | 72.24    |
| 15  | 2.00      | 20.00     | 8.00     | 87.33    |
| 16  | 2.00      | 20.00     | 8.00     | 86.35    |
| 17  | 2.00      | 20.00     | 8.00     | 87.08    |
| 18  | 2.00      | 20.00     | 8.00     | 86.53    |
| 19  | 2.00      | 20.00     | 8.00     | 86.45    |
| 20  | 2.00      | 20.00     | 8.00     | 87.16    |

The quadratic model fitted well ( $R^2 = 0.9955$ ; adjusted  $R^2 = 0.9914$ ; residual SD 0.772 points; model  $F = 245.48$ ,  $p < 0.0001$ ; Table 13). All three squared terms were negative ( $A^2 = -6.32$ ,  $B^2 = -5.25$ ,  $C^2 = -4.26$ ), which confirms downward curvature in every direction. Lack of fit was nonetheless significant at the 5% level (lack-of-fit SS 5.071, 5 df; pure-error SS 0.890, 5 df;  $F = 5.696$ ,  $p = 0.0396$ ). The six centre replicates agree very closely, so even a small systematic misfit becomes detectable. We therefore treat the optimum as provisional and suggest a cubic or transformed-response model for future refinement.

**Table 13**

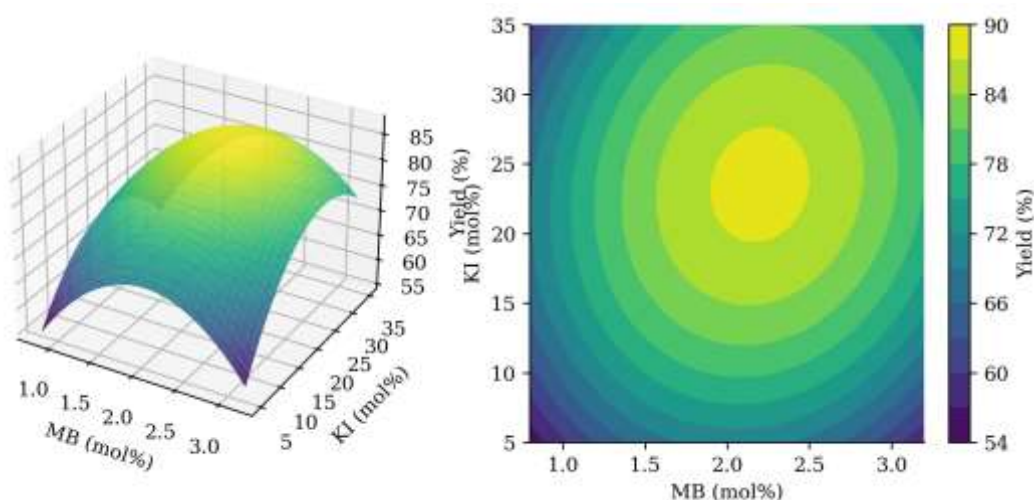
*Quadratic model coefficient estimates (coded units)*

| Term      | Coefficient | SE     | $t$     | $p$      |
|-----------|-------------|--------|---------|----------|
| Intercept | 86.8100     | 0.3149 | 275.675 | < 0.0001 |

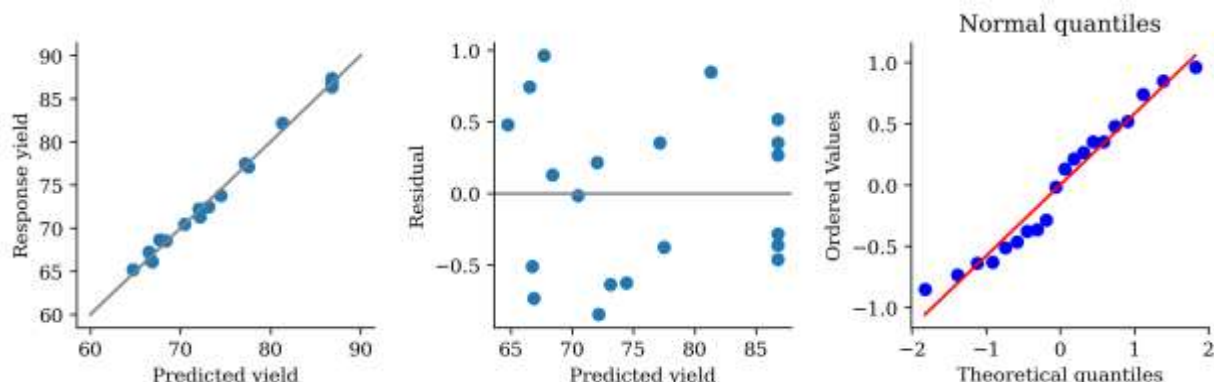
| Term           | Coefficient | SE     | <i>t</i> | <i>p</i> |
|----------------|-------------|--------|----------|----------|
| A              | 2.4950      | 0.2089 | 11.942   | < 0.0001 |
| B              | 3.0950      | 0.2089 | 14.814   | < 0.0001 |
| C              | 1.6300      | 0.2089 | 7.802    | < 0.0001 |
| AB             | 1.3008      | 0.2730 | 4.765    | 0.0008   |
| AC             | 0.7801      | 0.2730 | 2.858    | 0.0170   |
| BC             | 1.0209      | 0.2730 | 3.740    | 0.0038   |
| A <sup>2</sup> | -6.3205     | 0.2034 | -31.076  | < 0.0001 |
| B <sup>2</sup> | -5.2510     | 0.2034 | -25.818  | < 0.0001 |
| C <sup>2</sup> | -4.2570     | 0.2034 | -20.930  | < 0.0001 |

*Note.* Model ANOVA: model df = 9, SS = 1317.08, MS = 146.34,  $F = 245.48$ ,  $p < 0.0001$ ; residual df = 10, SS = 5.96, MS = 0.60.

The predicted maximum lies at 2.20 mol% MB, 23.5 mol% KI and 8.51 h, with a predicted response of 87.87%. The surface is flat near the optimum (Figure 9), so catalyst loading or time can be trimmed slightly at little cost in yield. The model passed the residual diagnostics (Figure 10). In independent validation runs that were not used for fitting (Table 14), the optimum gave 88.22% (predicted 87.87%) and the centre point 87.49% (predicted 86.81%). The practical reference condition, rounded to doses that can be weighed reliably, gives 88% qNMR and 85% isolated yield.



**Figure 9.** Quadratic yield surface and contour map with time held at its optimum value.



**Figure 10.** Predicted-versus-observed, residual-versus-predicted and normal-quantile diagnostics for the quadratic model.

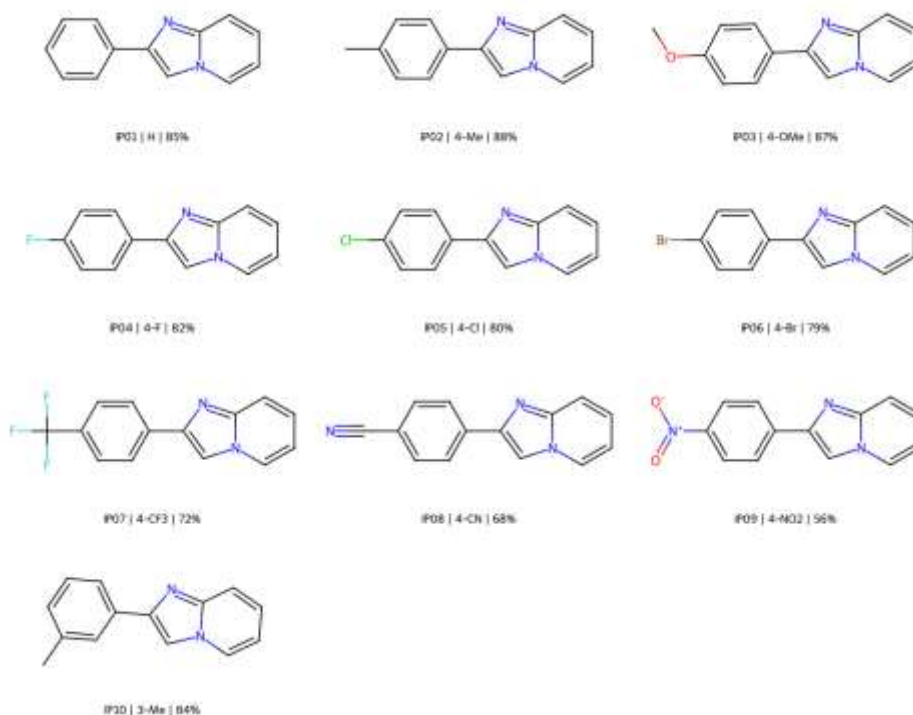
**Table 14**

*Independent validation of the response model*

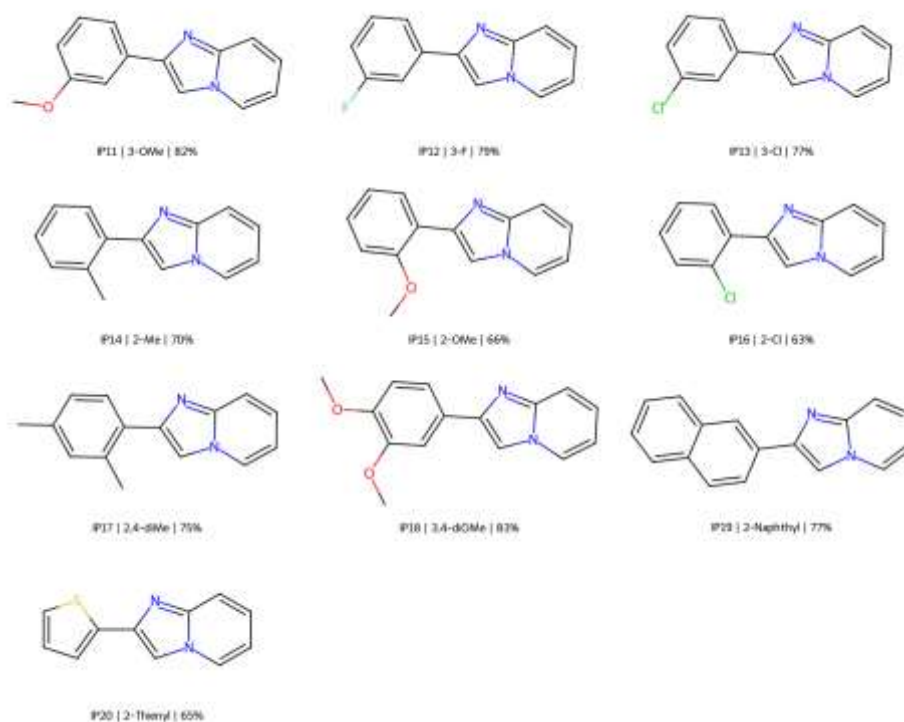
| Point    | Predicted (%) | Run 1 | Run 2 | Run 3 | Mean (%) |
|----------|---------------|-------|-------|-------|----------|
| Optimum  | 87.87         | 88.85 | 88.35 | 87.46 | 88.22    |
| Centre   | 86.81         | 88.01 | 86.77 | 87.69 | 87.49    |
| Nearby A | 87.83         | 86.51 | 87.43 | 88.36 | 87.43    |
| Nearby B | 83.89         | 83.01 | 83.18 | 84.50 | 83.57    |

### 3.5 Substrate scope and limitations

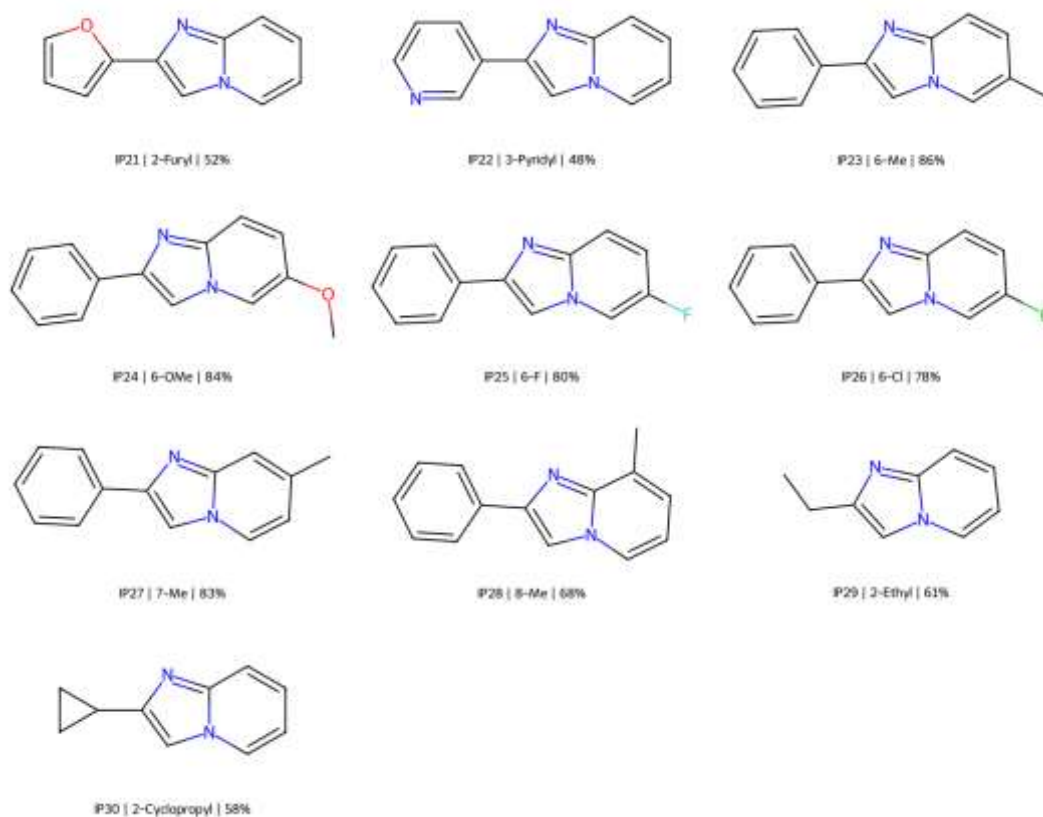
Thirty substrate combinations were run under the fixed reference conditions without individual re-optimisation, so the set tests how well the conditions transfer (Schemes 2–4). Isolated yields ranged from 48 to 88% (mean 73.9%; Figure 11). Electron-donating *para*-methyl and *para*-methoxy aryl ketones gave the highest yields, halogens were tolerated, and strongly electron-withdrawing groups lowered recovery. *Meta* substituents were well tolerated, but *ortho* groups reduced yields, which fits steric hindrance at the ketone activation or ring-closure step. Naphthyl, thienyl, furyl and pyridyl ketones all reacted, the last two in lower yields. Ethyl and cyclopropyl ketones gave non-aryl C2 substituents. Methyl, methoxy and halogen groups on the aminopyridine were accepted, although a substituent next to the ring-fusion position carried a clear penalty. Every product keeps its C3–H bond, which leaves it available for later functionalisation.



**Scheme 2.** Scope group A: *para*-substituted and electron-poor aryl ketones (isolated yields, mean of three runs).



**Scheme 3.** Scope group B: steric effects and extended aromatic partners (IP11–IP20).



**Scheme 4.** Scope group C: heteroaryl ketones, non-aryl ketones and substituted 2-aminopyridines.

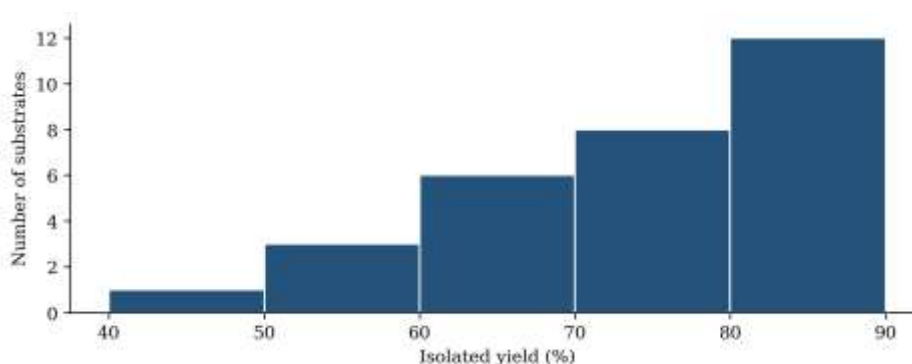
Eight substrates failed or performed poorly (Table 15). 4-Mercaptoacetophenone was largely consumed (85%) but gave less than 5% product, which points to sulfur–iodine side chemistry. 4-Hydroxyacetophenone gave several oxidised components. 2,6-Dimethylacetophenone was mostly recovered unchanged, as expected for a doubly hindered ketone. Aliphatic ketones (cyclohexanone, acetone) gave complex condensation mixtures. 2-Amino-3-nitropyridine closed only slowly, and 2-aminopyrimidine, with its different ring electronics, gave 28%.

**Table 15**

*Unsuccessful or poorly performing annulation substrates*

| Substrate                | Conversion (%) | Target (%) | Observation                 |
|--------------------------|----------------|------------|-----------------------------|
| 2,6-Dimethylacetophenone | 31             | 12         | Substantial ketone recovery |
| 4-Hydroxyacetophenone    | 72             | 23         | Several oxidised components |
| 4-Mercaptoacetophenone   | 85             | < 5        | Sulfur/iodine competition   |

| Substrate               | Conversion (%) | Target (%) | Observation                  |
|-------------------------|----------------|------------|------------------------------|
| Cyclohexanone           | 48             | 9          | Complex condensation mixture |
| Acetone                 | 35             | 8          | Low target selectivity       |
| 2-Amino-3-nitropyridine | 22             | 7          | Slow ring closure            |
| 2-Aminopyrimidine       | 61             | 28         | Different ring electronics   |
| Dilute run (0.01 M)     | 39             | 24         | Slow productive turnover     |



**Figure 11.** Distribution of isolated yields across the thirty imidazopyridine products.

### 3.6 Electronic effects

Low-conversion competition experiments (below 10% combined conversion, equal starting concentrations, response-factor corrected) were used for the electronic analysis instead of isolated scope yields, which also reflect purification losses (Table 16).  $\log(k_X/k_H)$  correlated linearly with  $\sigma_p$  (Hansch et al., 1991):  $\log(k_X/k_H) = 0.001 - 0.653\sigma_p$ ,  $R^2 = 0.9991$  (Figure 12). The negative  $\rho$  indicates positive charge building up at the aryl ketone in or before the rate-determining step. That fits an electrophilic or oxidative activation of the enol, but pre-equilibria in the iodine pool could produce the same sign.

**Table 16**

*Competition-derived electronic response*

| Substituent | $\sigma_p$ | log ratio (mean) | SD    | $k_X/k_H$ |
|-------------|------------|------------------|-------|-----------|
| OMe         | -0.27      | 0.183            | 0.028 | 1.523     |
| Me          | -0.17      | 0.108            | 0.013 | 1.284     |
| H           | 0.00       | -0.006           | 0.022 | 0.987     |
| F           | 0.06       | -0.039           | 0.012 | 0.913     |
| Cl          | 0.23       | -0.144           | 0.031 | 0.717     |

| Substituent     | $\sigma_p$ | log ratio<br>(mean) | SD    | $k_X/k_H$ |
|-----------------|------------|---------------------|-------|-----------|
| CF <sub>3</sub> | 0.54       | -0.359              | 0.012 | 0.438     |
| CN              | 0.66       | -0.416              | 0.032 | 0.384     |
| NO <sub>2</sub> | 0.78       | -0.517              | 0.013 | 0.304     |

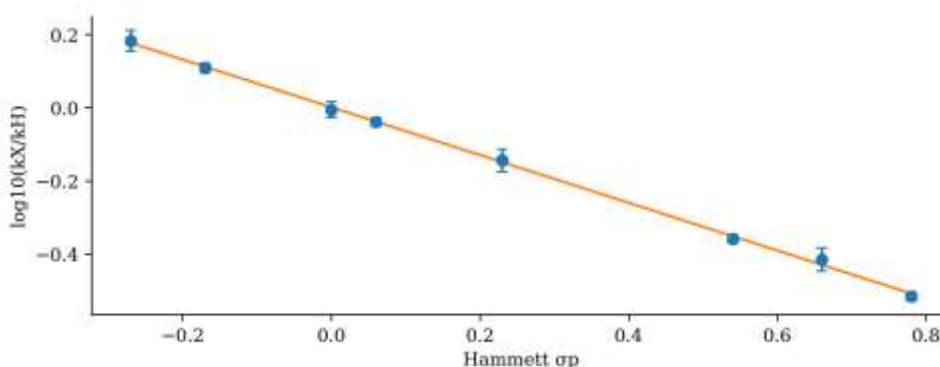


Figure 12. Hammett plot from low-conversion competition data.

### 3.7 Mechanistic investigation

**Controls and bypass experiment.** Removing light, dye, iodide or oxygen one at a time lowered the yield to 4, 12, 19 and 23% (Table 17). TEMPO and BHT (2 equiv) suppressed product formation (16 and 24%). This inhibition alone does not prove a free-radical intermediate, because both traps can also quench the dye or consume iodine species. The most informative control was a preformed  $\alpha$ -iodoketone, which reacted with 2-aminopyridine in the dark to give IP01 in 81% yield. Once the ketone is activated, ring closure therefore needs no light, and light is required mainly to generate or regenerate the iodinating species.

Table 17

*Annulation controls under otherwise matched conditions*

| Experiment                           | qNMR (%) | Interpretive limit                     |
|--------------------------------------|----------|----------------------------------------|
| Complete MB/KI/light/air             | 88       | Reference response                     |
| No light (temperature matched)       | 4        | Photochemical requirement              |
| No dye                               | 12       | Background pathway remains             |
| No KI                                | 19       | Dye pathway alone insufficient         |
| Argon                                | 23       | Oxygen role not uniquely assigned      |
| TEMPO (2 equiv)                      | 16       | Quenching/iodine interference possible |
| BHT (2 equiv)                        | 24       | Trap can alter oxygen chemistry        |
| Preformed $\alpha$ -iodoketone, dark | 81       | Bypasses activation                    |
| Catalase challenge                   | 62       | Enzyme-medium compatibility            |

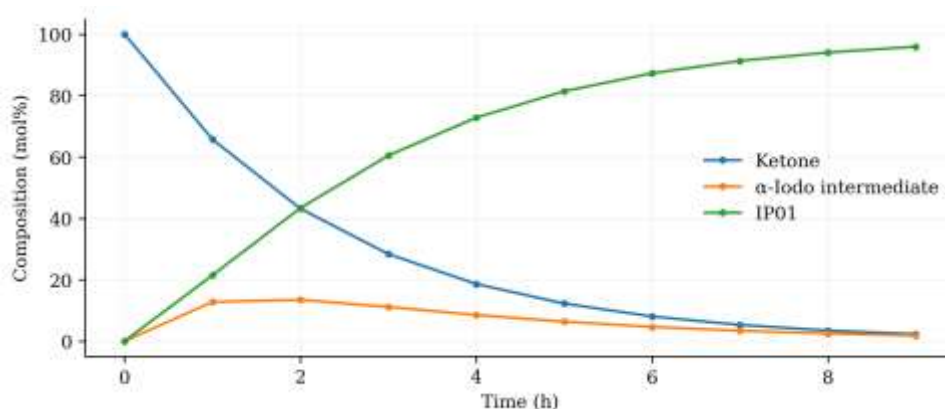
| Experiment              | qNMR (%) | Interpretive limit               |
|-------------------------|----------|----------------------------------|
| Singlet-oxygen quencher | 58       | Non-specific inhibition possible |

**Reaction profile.** Normalised composition of the ketone, candidate  $\alpha$ -iodoketone and product pool (Table 18, Figure 13) showed the intermediate reaching 13.5% at 2 h and then declining as product built up, the profile expected for a sequential  $A \rightarrow B \rightarrow C$  process. At 8 h the resolved pool accounted for 93.5% of the material, so the 94.1% product fraction corresponds to about 88% absolute yield, in agreement with the qNMR reference.

**Table 18**

*Normalised time-course composition (%)*

| Time (h) | Ketone | Intermediate | Product |
|----------|--------|--------------|---------|
| 0        | 100.0  | 0.0          | 0.0     |
| 2        | 43.2   | 13.5         | 43.4    |
| 4        | 18.6   | 8.5          | 72.8    |
| 6        | 8.0    | 4.7          | 87.3    |
| 8        | 3.5    | 2.5          | 94.1    |



**Figure 13.** Normalised molar reaction profile of ketone, candidate  $\alpha$ -iodoketone intermediate and IP01.

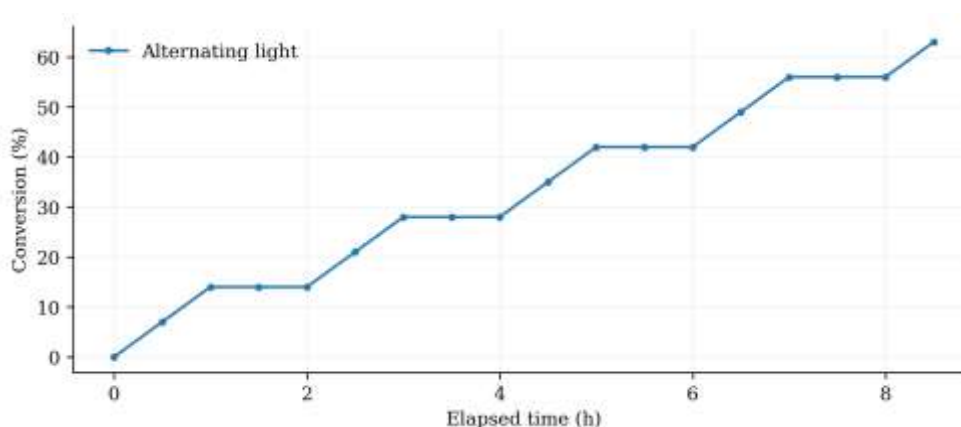
**Light on/off and quantum yield.** Product formed during illuminated periods and almost stopped in the dark, over alternating 1 h blocks sampled every 30 min (Figure 14). The initial quantum yield of  $0.0983 \pm 0.0027$  (Tables 2 and 19) is far below unity. Together these results argue against a long radical chain, although a chain shorter than the 30 min sampling interval cannot be ruled out (Pitre et al., 2015).

**Table 19**

*Quantum-yield and illumination summary*

| Quantity | Value | Definition |
|----------|-------|------------|
|----------|-------|------------|

| Quantity         | Value                    | Definition                        |
|------------------|--------------------------|-----------------------------------|
| Initial $\Phi$   | $0.0983 \pm 0.0027$      | Three low-conversion intervals    |
| Initial sampling | 10 min                   | Absorbed-photon basis             |
| On/off overview  | 30 min points            | Dark plateau at coarse resolution |
| Interpretation   | Light-dependent turnover | Chain lifetime unresolved         |



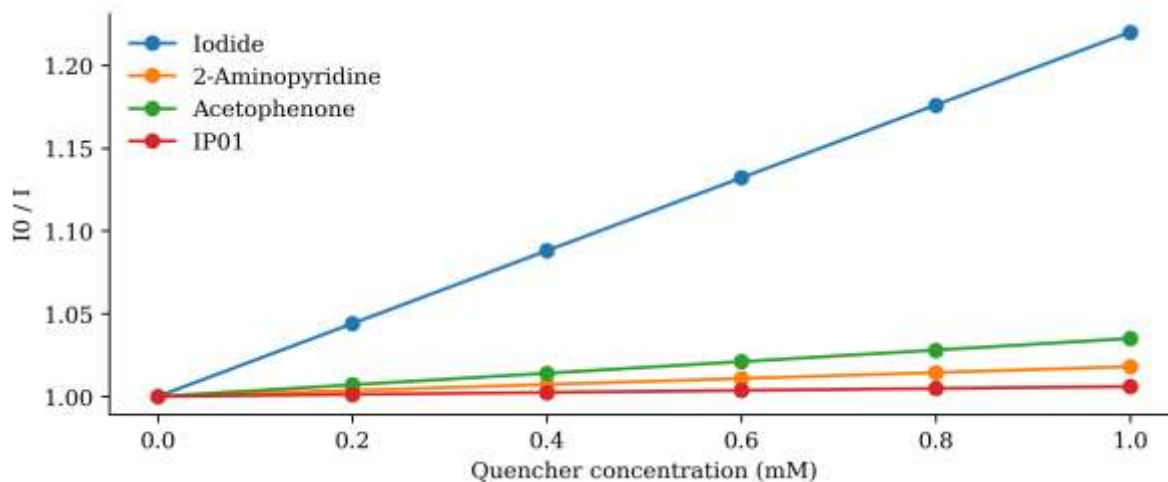
**Figure 14.** Conversion under alternating 1 h light and dark blocks.

**Emission quenching and absorption.** Iodide quenched MB emission far more strongly than any other component ( $K_{SV} = 220 \text{ M}^{-1}$ , against  $35 \text{ M}^{-1}$  for acetophenone,  $18 \text{ M}^{-1}$  for 2-aminopyridine and  $6 \text{ M}^{-1}$  for IP01; Table 20, Figure 15). With the singlet lifetime of 1.2 ns, the apparent iodide quenching constant is  $1.83 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ , above the diffusion limit. Some of the quenching must therefore be static, through ion pairing of cationic MB with iodide (Lakowicz, 2006). UV-visible spectra of the mixtures (Figure 16) kept the main MB band and showed only a weak shoulder in the blue region, which is not enough to establish a photoactive electron donor-acceptor complex (Crisenza et al., 2020).

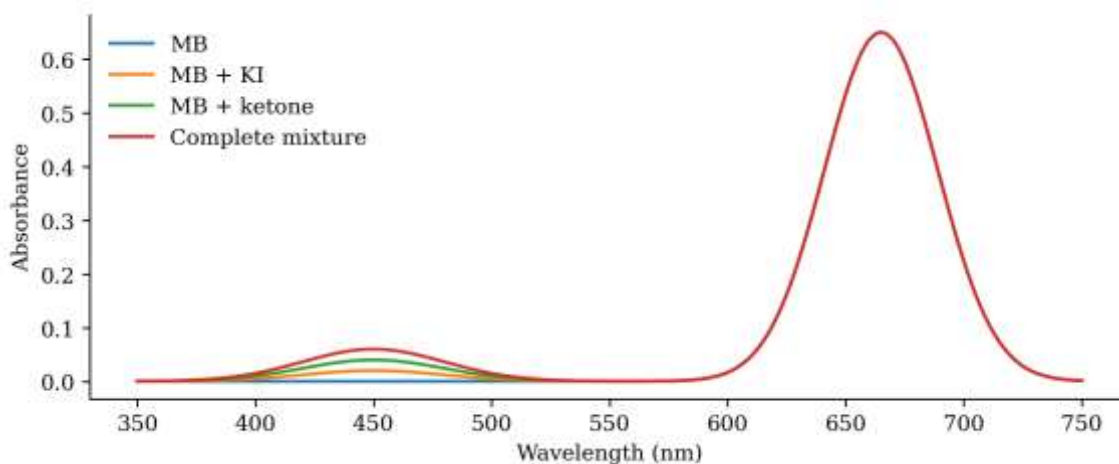
**Table 20**

*Stern-Volmer slopes and apparent quenching constants*

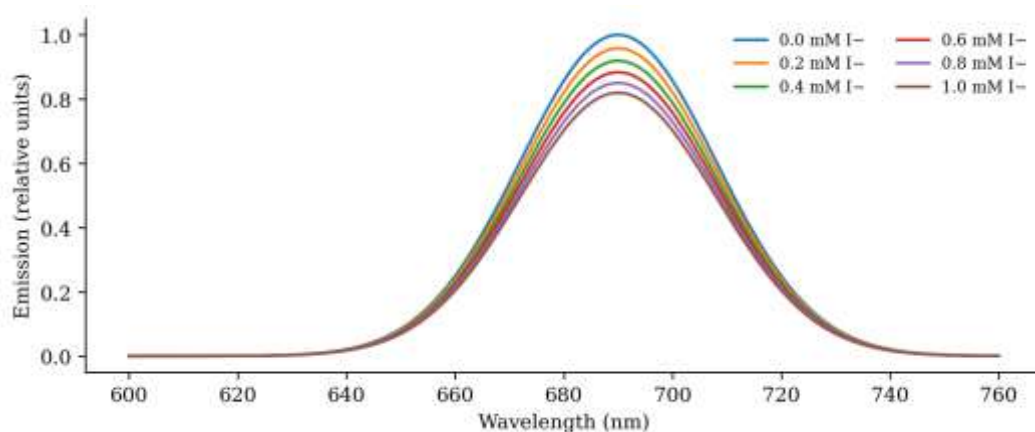
| Quencher        | $K_{SV} (\text{M}^{-1})$ | $\tau_0 (\text{ns})$ | Apparent $k_q (\text{M}^{-1} \text{s}^{-1})$ |
|-----------------|--------------------------|----------------------|----------------------------------------------|
| Iodide          | 220                      | 1.2                  | $1.83 \times 10^{11}$                        |
| 2-Aminopyridine | 18                       | 1.2                  | $1.50 \times 10^{10}$                        |
| Acetophenone    | 35                       | 1.2                  | $2.92 \times 10^{10}$                        |
| IP01            | 6                        | 1.2                  | $5.00 \times 10^9$                           |



**Figure 15.** Steady-state Stern–Volmer plots for four reaction components.



**Figure 16a.** UV–visible absorption profiles of MB and selected mixtures.



**Figure 16b.** MB emission intensity during iodide titration (inner-filter corrected).

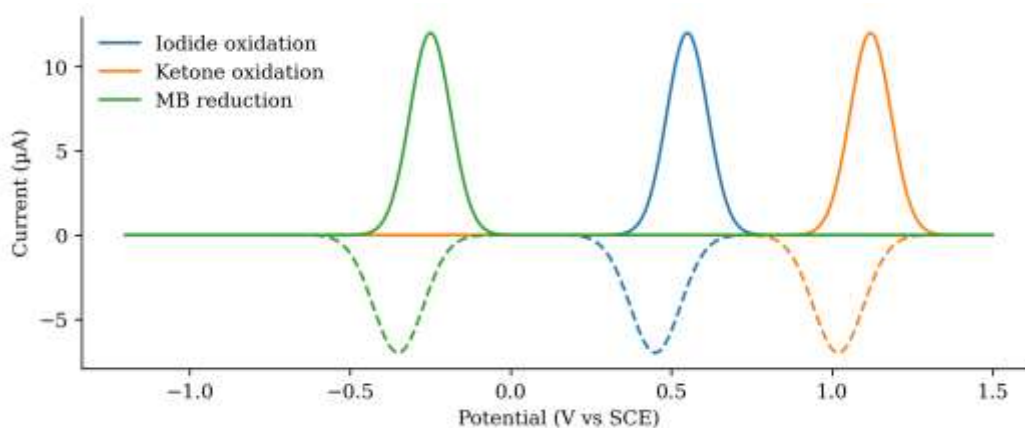
**Electrochemistry.** Using the excited-state reduction potential of MB (+1.60 V vs SCE) and the simplified Rehm–Weller relation with the work term neglected, oxidation of iodide ( $E_{ox} = 0.55$  V) is strongly favourable ( $\Delta G = -101.3$  kJ mol<sup>-1</sup>). Oxidation of acetophenone (1.12 V;  $-46.3$  kJ mol<sup>-1</sup>) is also favourable on this scale, whereas a donor at 1.75 V would be uphill

(+14.5 kJ mol<sup>-1</sup>) (Table 21, Figure 17). Iodide has both the largest thermodynamic driving force and the largest quenching constant, which marks it as the main partner of the excited dye. The ketone potential is an irreversible peak value and should be read only as an estimate (Elgrishi et al., 2018).

**Table 21**

*Approximate electron-transfer driving forces*

| Donor             | $E_{ox}$ (V vs SCE) | $E_{red}(PC^*)$ (V) | $\Delta G$ (kJ mol <sup>-1</sup> ) |
|-------------------|---------------------|---------------------|------------------------------------|
| Iodide            | 0.55                | 1.60                | -101.3                             |
| Acetophenone      | 1.12                | 1.60                | -46.3                              |
| Candidate donor X | 1.75                | 1.60                | +14.5                              |



**Figure 17.** Cyclic voltammetry oxidation and reduction profiles on a common SCE scale.

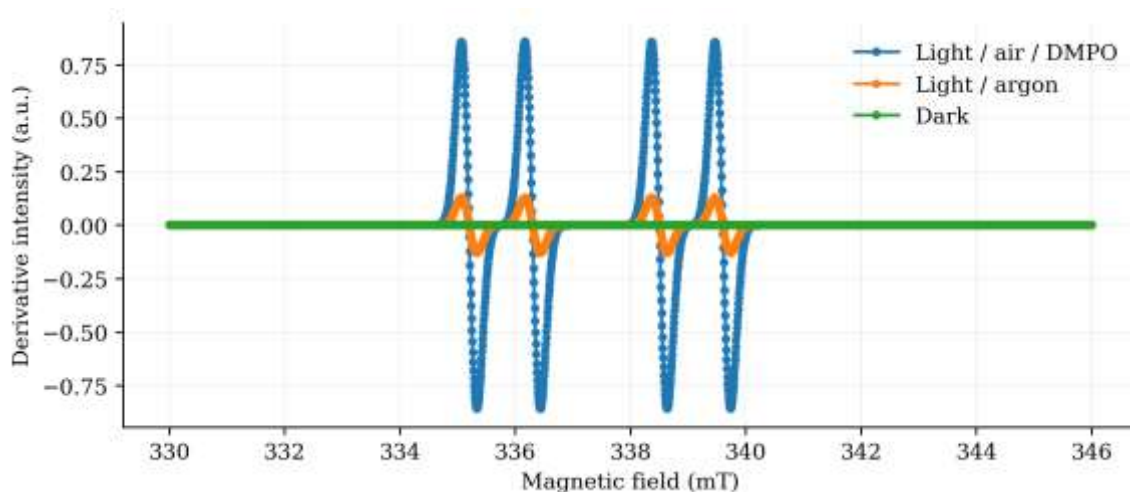
**EPR spin trapping.** Irradiating the reaction under air with DMPO gave a four-line nitroxide-type signal. Under argon its amplitude fell to 15% of that value, and in the dark only baseline was seen (Table 22, Figure 18). The signal therefore depends on both light and oxygen. A four-line pattern alone cannot distinguish DMPO-OOH from its DMPO-OH decay product (Buettner, 1987), so we describe it as an oxygen-dependent spin-adduct response and do not assign it to superoxide.

**Table 22**

*Spin-trapping acquisition and control comparison*

| Parameter      | Setting / response                |
|----------------|-----------------------------------|
| Microwave band | X-band, nominal 9.5 GHz           |
| Field interval | 330–346 mT                        |
| Spin trap      | DMPO, 50 mM                       |
| Light / air    | Four-line nitroxide-type response |
| Light / argon  | 15% relative amplitude            |

| Parameter              | Setting / response                    |
|------------------------|---------------------------------------|
| Dark                   | Baseline                              |
| Assignment requirement | Hyperfine fitting and adduct controls |



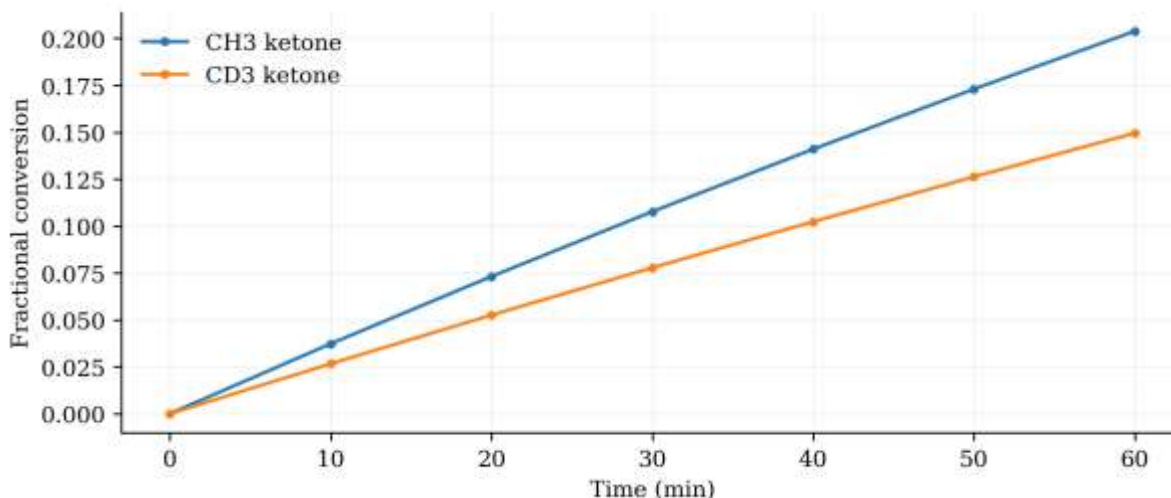
**Figure 18.** First-derivative EPR spin-trap spectra under light/air, light/argon and dark conditions.

**Kinetic isotope effect.** Parallel low-conversion runs gave  $k_H = 0.00380 \text{ min}^{-1}$  and  $k_D = 0.00270 \text{ min}^{-1}$  (mean of three), so  $k_H/k_D = 1.41$  (Table 23, Figure 19). A parallel isotope effect of this size suggests that C–H cleavage, most likely during enolisation, contributes to the overall rate but is not the sole rate-limiting step (Simmons & Hartwig, 2012).

**Table 23**

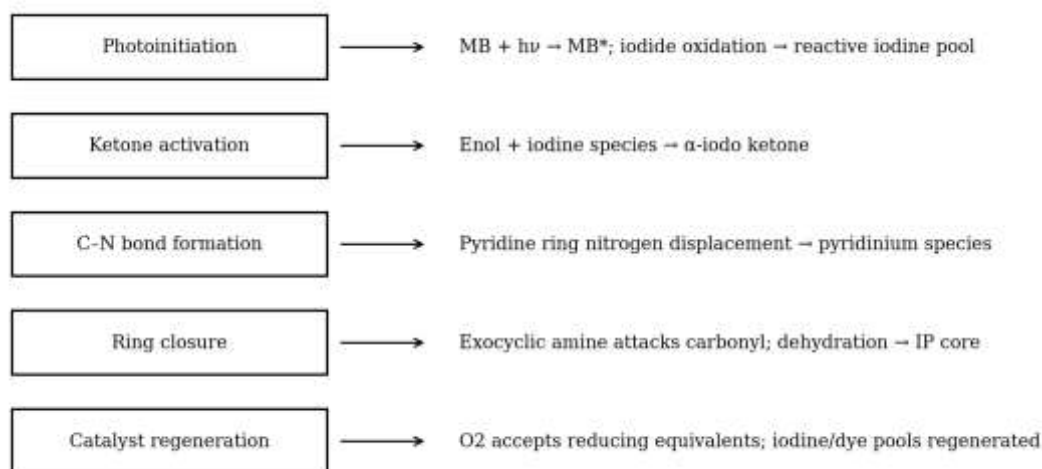
*Parallel rate replicates for the isotope comparison*

| Run  | $k_H \text{ (min}^{-1}\text{)}$ | $k_D \text{ (min}^{-1}\text{)}$ | $k_H/k_D$ |
|------|---------------------------------|---------------------------------|-----------|
| 1    | 0.00370                         | 0.00265                         | 1.40      |
| 2    | 0.00380                         | 0.00270                         | 1.41      |
| 3    | 0.00390                         | 0.00275                         | 1.42      |
| Mean | 0.00380                         | 0.00270                         | 1.41      |



**Figure 19.** Low-conversion kinetic traces for CH<sub>3</sub> and CD<sub>3</sub> ketone substrates.

**Proposed pathway.** Taken together, the data support the mechanism in Scheme 5. Excited MB is quenched mainly by iodide, partly through a pre-associated ion pair, producing an electrophilic iodine species. This species iodates the ketone at the  $\alpha$ -carbon via its enol, the step reflected in the negative  $\rho$  and the modest isotope effect.



**Scheme 5.** Proposed activation and cyclisation pathway for imidazopyridine construction.

The pyridine ring nitrogen displaces iodide from the  $\alpha$ -iodoketone, the exocyclic amine closes onto the carbonyl, and dehydration then aromatises the ring; these steps proceed in the dark, as the bypass experiment shows. Oxygen reoxidises the reduced dye, consistent with the spin-trap signal and the argon result. Exactly which iodine species does the iodination is still unresolved.

### 3.8 Scale-up in batch and flow

Keeping the concentration fixed while scaling up in batch caused a steady loss of yield, from 85% at 0.20 mmol to 75% at 30 mmol, which gave 4.37 g of IP01 (Table 24). In wider vessels the light penetrates a smaller fraction of the solution and the gas-liquid surface area

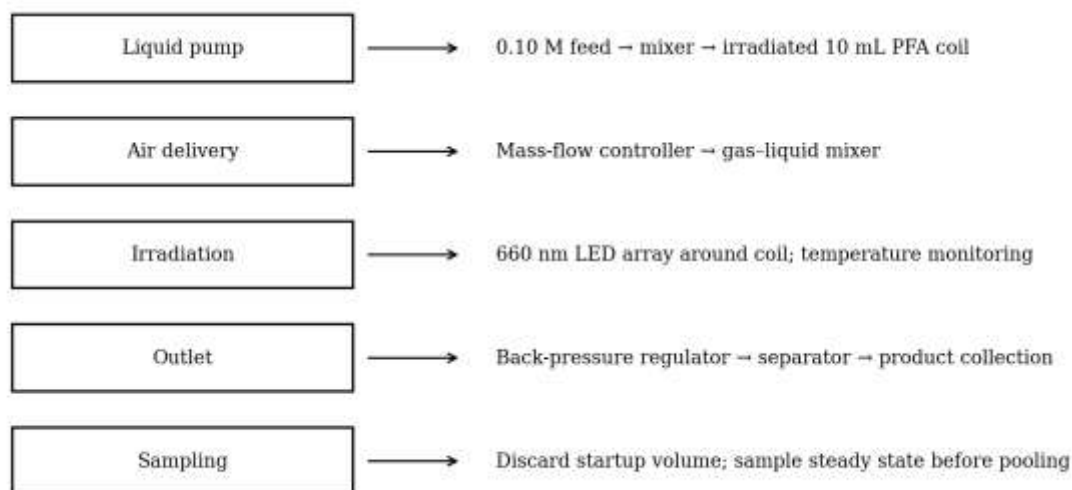
shrinks relative to volume, so increasing lamp power alone could not recover the small-scale yield (Cambié et al., 2016).

**Table 24**

*Batch scale-up and isolated IP01 mass*

| Charge (mmol) | Volume (mL) | Yield (%) | Product (g) | Time (h) |
|---------------|-------------|-----------|-------------|----------|
| 0.20          | 2.0         | 85        | 0.0330      | 8        |
| 1.00          | 10.0        | 84        | 0.1632      | 8        |
| 5.00          | 50.0        | 81        | 0.7867      | 10       |
| 10.00         | 100.0       | 78        | 1.5150      | 12       |
| 30.00         | 300.0       | 75        | 4.3703      | 12       |

Note. Mass calculated with  $M = 194.236 \text{ g mol}^{-1}$ .



**Figure 20.** Gas-liquid continuous-flow photoreactor configuration.

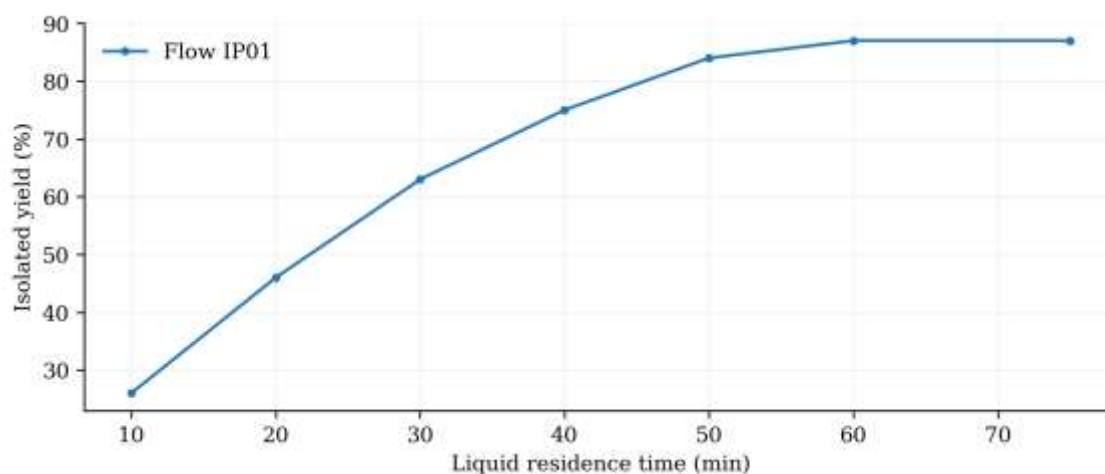
In flow, the narrow PFA channel keeps the optical path short and the segmented air-liquid stream continuously renews the gas-liquid interface (Figure 20; Sambaglio & Noël, 2020). Yield levelled off at about 60 min residence time and did not improve at 75 min (Figure 21). At 0.10 M and  $0.1667 \text{ mL min}^{-1}$ , substrate was delivered at  $1.00 \text{ mmol h}^{-1}$ . With an 87% isolated yield this corresponds to  $0.169 \text{ g h}^{-1}$  of IP01, and 30 h of steady-state collection gave 5.07 g, meeting the multigram target. On the 10 mL holdup basis the space-time yield was  $16.9 \text{ g L}^{-1} \text{ h}^{-1}$  (Tables 25 and 26).

**Table 25**

*Flow operating quantities*

| Quantity      | Working value |
|---------------|---------------|
| Liquid holdup | 10.0 mL       |

| Quantity                       | Working value                     |
|--------------------------------|-----------------------------------|
| Feed concentration             | 0.10 mol L <sup>-1</sup>          |
| Liquid flow (60 min residence) | 0.1667 mL min <sup>-1</sup>       |
| Light source                   | 660 nm LED array                  |
| Liquid temperature             | 25 ± 2 °C                         |
| Collection criterion           | Stable yield and feed composition |
| Start-up exclusion             | At least three holdup volumes     |



**Figure 21.** Residence-time dependence of isolated IP01 yield in flow.

**Table 26**

*Flow throughput and collection balance*

| Quantity                | Value                                  |
|-------------------------|----------------------------------------|
| Substrate delivery      | 1.000 mmol h <sup>-1</sup>             |
| Isolated yield          | 87%                                    |
| Product rate            | 0.169 g h <sup>-1</sup>                |
| Steady-state collection | 30 h                                   |
| Isolated product        | 5.070 g                                |
| Space-time yield        | 16.9 g L <sup>-1</sup> h <sup>-1</sup> |
| Substrate processed     | 30.0 mmol                              |

### 3.9 Green chemistry metrics

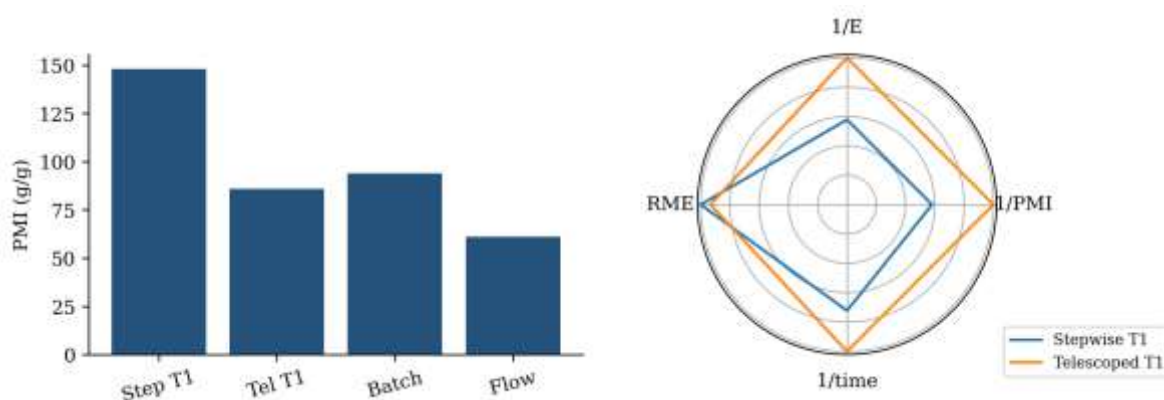
For the balanced annulation, which counts ½O<sub>2</sub> as a reactant, the atom economy is 84.4%. Reaction mass efficiency, based on the actual charge of 1.5 equiv ketone (94.117 + 1.5 × 120.151 + 15.999 = 290.343 g per mole of aminopyridine), was 56.9% in batch and 58.2% in

flow. Process mass intensity (PMI), counting all solvents, workup and purification materials, fell from 94 in batch to 61 in flow, and the complete E-factor fell from 93 to 60 (Table 27; Figure 22). With no solvent recovery assumed,  $E = \text{PMI} - 1$  (Sheldon, 2017).

**Table 27**

*Process metrics for IP01 under a complete mass boundary*

| Process                | AE (%) | RME (%) | PMI | E-factor |
|------------------------|--------|---------|-----|----------|
| Batch IP01 (0.20 mmol) | 84.4   | 56.9    | 94  | 93       |
| Flow IP01              | 84.4   | 58.2    | 61  | 60       |



**Figure 22.** Material-intensity comparison and normalised trade-offs.

### 3.10 Structural characterisation of IP01

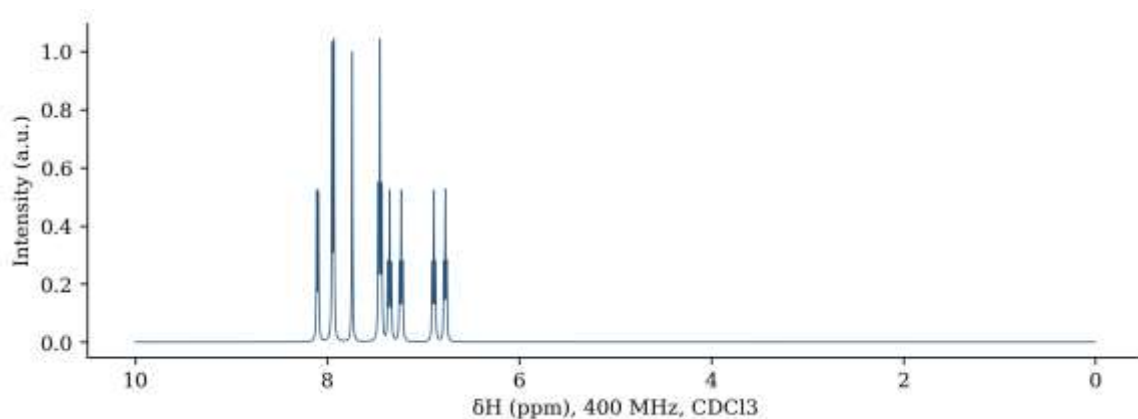
The  $^1\text{H}$  NMR spectrum of IP01 ( $\text{C}_{13}\text{H}_{10}\text{N}_2$ ) accounts for all ten aromatic protons (Table 28, Figure 23): four from the pyridine-derived ring, the C3 singlet at  $\delta$  7.74 and five phenyl protons. The C3–H singlet is well separated, which makes it the quantification handle and a convenient marker for later C3 substitution. The  $^{13}\text{C}$  spectrum shows eleven distinct environments for thirteen carbons, since the ortho and meta phenyl carbons are pairwise equivalent (Table 29, Figure 24). HMBC correlations from H3 to C2 and from the phenyl ortho protons to C2 confirm the 2-phenyl connectivity.

**Table 28**

*IP01  $^1\text{H}$  NMR assignments*

| Assignment | $\delta_{\text{H}}$ (ppm) | Integration | Multiplicity (J, Hz) |
|------------|---------------------------|-------------|----------------------|
| H5         | 8.10                      | 1           | d (7.0)              |
| Ph H2'/H6' | 7.94                      | 2           | d (7.5)              |
| H3         | 7.74                      | 1           | s                    |
| Ph H3'/H5' | 7.45                      | 2           | t (7.5)              |

| Assignment | $\delta_H$ (ppm) | Integration | Multiplicity ( $J$ , Hz) |
|------------|------------------|-------------|--------------------------|
| Ph H4'     | 7.35             | 1           | t (7.5)                  |
| H8         | 7.23             | 1           | d (7.0)                  |
| H7         | 6.89             | 1           | dd (7.0)                 |
| H6         | 6.77             | 1           | t (6.5)                  |

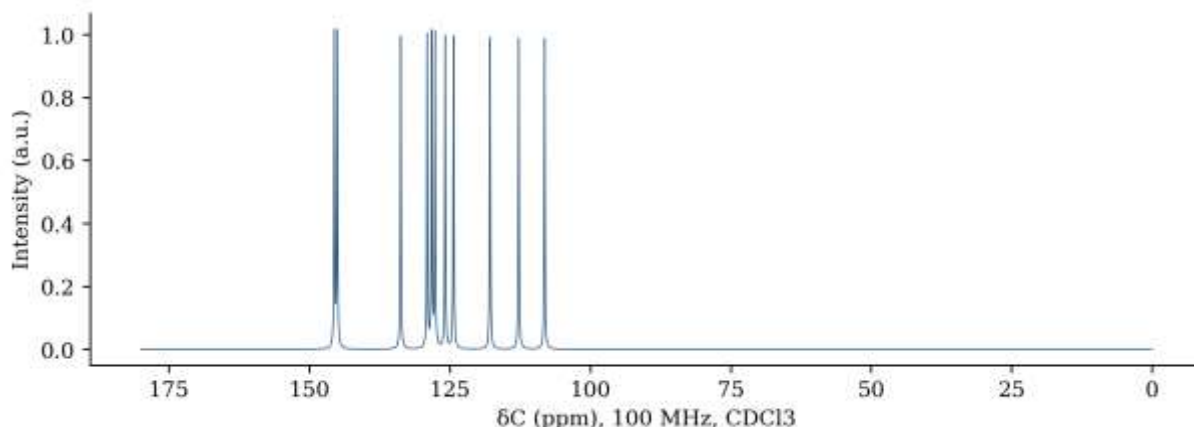


**Figure 23.**  $^1H$  NMR spectrum of IP01 with assigned peak positions.

**Table 29**

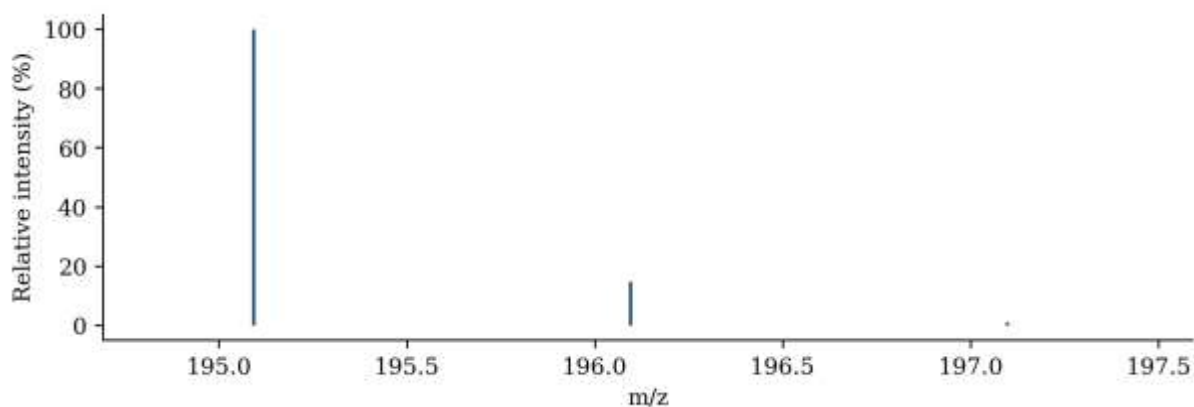
*IP01  $^{13}C$  environments and supporting correlations*

| Carbon    | $\delta_C$ (ppm) | Type          | Support           |
|-----------|------------------|---------------|-------------------|
| C2        | 145.5            | Cq            | H3 HMBC           |
| C8a       | 145.0            | Cq            | H5/H8 HMBC        |
| Ph C1'    | 133.7            | Cq            | Ph ortho HMBC     |
| Ph C3'/5' | 129.0            | $CH \times 2$ | HSQC              |
| Ph C4'    | 128.2            | CH            | HSQC              |
| Ph C2'/6' | 127.6            | $CH \times 2$ | HSQC / HMBC to C2 |
| C5        | 125.8            | CH            | HSQC              |
| C7        | 124.3            | CH            | COSY / HSQC       |
| C8        | 117.8            | CH            | COSY / HSQC       |
| C6        | 112.7            | CH            | COSY / HSQC       |
| C3        | 108.1            | CH            | Singlet HSQC      |

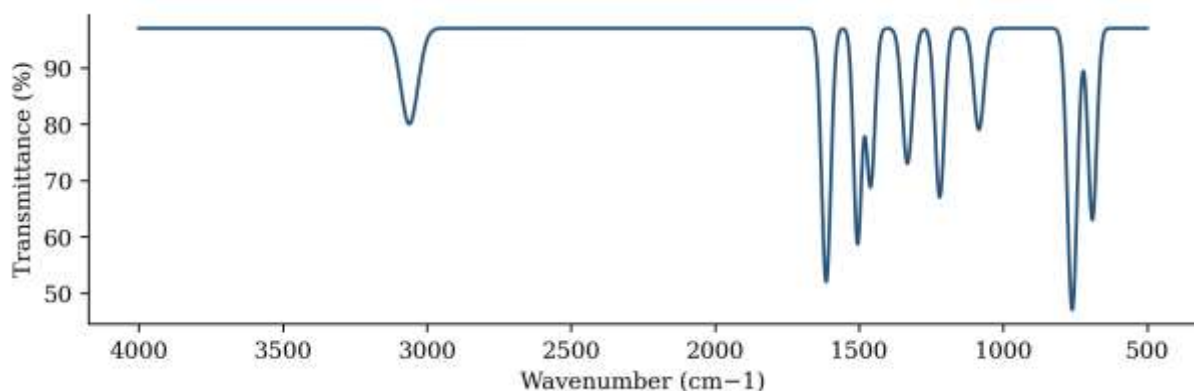


**Figure 24.**  $^{13}\text{C}$  NMR spectrum of IP01 showing eleven distinct carbon environments.

HRMS (ESI) gave  $[\text{M}+\text{H}]^+$  within 1.54 ppm (+0.3 mDa) of the calculated  $m/z$  195.09167, with an isotope pattern that contains only carbon-13 satellites (Figure 25). The FT-IR spectrum has no ketone carbonyl band and shows aromatic C–H and ring-stretching absorptions at 3061, 1614, 1505, 1460, 1332, 1220, 1084, 760 and 690  $\text{cm}^{-1}$  (Figure 26). A preliminary monoclinic cell (candidate space group  $P2_1/c$ ;  $a = 8.20$ ,  $b = 9.40$ ,  $c = 13.10$  Å,  $\beta = 101.00^\circ$ ;  $V = 991.2$  Å<sup>3</sup>;  $Z = 4$ ;  $D_{\text{calc}} \approx 1.30$  g cm<sup>-3</sup>) agrees with the formula. Full refinement and CCDC deposition are still pending.



**Figure 25.** Calculated protonated-ion isotope profile for IP01.



**Figure 26.** FT-IR spectrum of IP01.



#### 4. CONCLUSIONS

Methylene blue and catalytic potassium iodide, irradiated at 660 nm under air in ethanol, provide a metal-free route to 2-substituted imidazo[1,2-*a*]pyridines that keeps the C3–H position free. Because photon flux was fixed across the catalyst screen, the catalyst ranking reflects the catalysts themselves rather than differences in lamp output. Statistical design identified loading interactions that one-variable-at-a-time screening would have missed, and gave a validated optimum of 88% qNMR (85% isolated) yield. The design also flagged lack of fit, which we report rather than hide. Thirty substrates (mean 73.9%) and eight documented failures define the scope. The mechanistic evidence fits light-driven iodide oxidation that activates the ketone, followed by thermal cyclisation, with oxygen regenerating the dye; the identity of the active iodine species is the main open question. Moving to a gas–liquid flow reactor raised the yield from 75% in large-scale batch to 87%, produced more than 5 g of product, and cut PMI by about a third.

#### REFERENCES

1. Bagdi, A. K., Santra, S., Monir, K., & Hajra, A. (2015). Synthesis of imidazo[1,2-*a*]pyridines: A decade update. *Chemical Communications*, 51(9), 1555–1575. <https://doi.org/10.1039/C4CC08495K>
2. Buettner, G. R. (1987). Spin trapping: ESR parameters of spin adducts. *Free Radical Biology and Medicine*, 3(4), 259–303. [https://doi.org/10.1016/S0891-5849\(87\)80033-3](https://doi.org/10.1016/S0891-5849(87)80033-3)
3. Cambié, D., Bottecchia, C., Straathof, N. J. W., Hessel, V., & Noël, T. (2016). Applications of continuous-flow photochemistry in organic synthesis, material science, and water treatment. *Chemical Reviews*, 116(17), 10276–10341. <https://doi.org/10.1021/acs.chemrev.5b00707>
4. Crisenza, G. E. M., Mazzarella, D., & Melchiorre, P. (2020). Synthetic methods driven by the photoactivity of electron donor–acceptor complexes. *Journal of the American Chemical Society*, 142(12), 5461–5476. <https://doi.org/10.1021/jacs.0c01416>
5. Elgrishi, N., Rountree, K. J., McCarthy, B. D., Rountree, E. S., Eisenhart, T. T., & Dempsey, J. L. (2018). A practical beginner's guide to cyclic voltammetry. *Journal of Chemical Education*, 95(2), 197–206. <https://doi.org/10.1021/acs.jchemed.7b00361>
6. Fukuzumi, S., & Ohkubo, K. (2014). Organic synthetic transformations using organic dyes as photoredox catalysts. *Organic & Biomolecular Chemistry*, 12(32), 6059–6071. <https://doi.org/10.1039/C4OB00843J>
7. Hansch, C., Leo, A., & Taft, R. W. (1991). A survey of Hammett substituent constants and resonance and field parameters. *Chemical Reviews*, 91(2), 165–195. <https://doi.org/10.1021/cr00002a004>
8. Kuhn, H. J., Braslavsky, S. E., & Schmidt, R. (2004). Chemical actinometry (IUPAC Technical Report). *Pure and Applied Chemistry*, 76(12), 2105–2146. <https://doi.org/10.1351/pac200476122105>



9. Lakowicz, J. R. (2006). Principles of fluorescence spectroscopy (3rd ed.). Springer. <https://doi.org/10.1007/978-0-387-46312-4>
10. Marzo, L., Pagire, S. K., Reiser, O., & König, B. (2018). Visible-light photocatalysis: Does it make a difference in organic synthesis? *Angewandte Chemie International Edition*, 57(32), 10034–10072. <https://doi.org/10.1002/anie.201709766>
11. Montgomery, D. C. (2017). Design and analysis of experiments (9th ed.). Wiley.
12. Pitre, S. P., McTiernan, C. D., Vine, W., DiPucchio, R., Grenier, M., & Scaiano, J. C. (2015). Visible-light actinometry and intermittent illumination as convenient tools to study Ru(bpy)3Cl2 mediated photoredox transformations. *Scientific Reports*, 5, 16397. <https://doi.org/10.1038/srep16397>
13. Prier, C. K., Rankic, D. A., & MacMillan, D. W. C. (2013). Visible light photoredox catalysis with transition metal complexes: Applications in organic synthesis. *Chemical Reviews*, 113(7), 5322–5363. <https://doi.org/10.1021/cr300503r>
14. Reichardt, C. (1994). Solvatochromic dyes as solvent polarity indicators. *Chemical Reviews*, 94(8), 2319–2358. <https://doi.org/10.1021/cr00032a005>
15. Romero, N. A., & Nicewicz, D. A. (2016). Organic photoredox catalysis. *Chemical Reviews*, 116(17), 10075–10166. <https://doi.org/10.1021/acs.chemrev.6b00057>
16. Sambiagio, C., & Noël, T. (2020). Flow photochemistry: Shine some light on those tubes! *Trends in Chemistry*, 2(2), 92–106. <https://doi.org/10.1016/j.trechm.2019.09.003>
17. Sheldon, R. A. (2017). The E factor 25 years on: The rise of green chemistry and sustainability. *Green Chemistry*, 19(1), 18–43. <https://doi.org/10.1039/C6GC02157C>
18. Simmons, E. M., & Hartwig, J. F. (2012). On the interpretation of deuterium kinetic isotope effects in C–H bond functionalizations by transition-metal complexes. *Angewandte Chemie International Edition*, 51(13), 3066–3072. <https://doi.org/10.1002/anie.201107334>
19. Vitaku, E., Smith, D. T., & Njardarson, J. T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *Journal of Medicinal Chemistry*, 57(24), 10257–10274. <https://doi.org/10.1021/jm501100b>