



Build, Then Functionalise in the Same Pot: Organic-Dye Photocatalytic Construction of Quinoline, Quinoxaline and Imidazopyridine Cores Telescoped with C3 Chalcogenation, Alkylation and Amination

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Abstract

Photocatalytic ring construction and photocatalytic C–H functionalisation are usually developed separately, even though the same dyes, solvents and light sources serve both. We asked whether a heterocycle can be built aerobically and then functionalised in the same vessel, and what such telescoping costs or saves. Three dye-catalysed annulations were first established on a common 0.20 mmol basis. 2-Aminopyridine and acetophenone gave the imidazo[1,2-a]pyridine IP01 (MB/KI, 660 nm; 85% isolated). Aniline, ethyl glyoxylate and styrene gave the quinoline-2-carboxylate QN01 (eosin Y with 10 mol% acid, 525 nm; 74%), and o-phenylenediamine and phenacyl alcohol gave 2-phenylquinoxaline QX01 (eosin Y, 525 nm; 86%). Before any reaction mixtures were combined, a robustness screen measured how much each likely carryover component (ethanol, water, iodide, acid, residual amine, oxygen) suppressed each second stage. Acid (21–45% yield retention) and the wrong atmosphere (48–65%) were the most damaging. On that basis three staged sequences were developed: C3 phenylthiolation of IP01 (T1, 72% overall), Minisci-type C3 cyclohexylation of QX01 after an air-to-argon switch (T2, 65%), and C3 amination of N-methylquinoxalin-2(1H)-one with morpholine (T3, 70%). Adding the second reagent at the start lowered yields to 38% (T1) and 29% (T3). Against matched stepwise routes, telescoping cost 2.8–5.5 percentage points of overall yield but reduced process mass intensity by 38–42% (148 → 86, 182 → 112, 136 → 79).

Keywords: telescoped synthesis; one-pot; organophotocatalysis; quinoxaline; imidazo[1,2-a]pyridine; Minisci reaction; process mass intensity; robustness screen

1. Introduction

Nitrogen heterocycles appear in most small-molecule drugs (Vitaku et al., 2014), and three fused families recur in this chemistry: the imidazo[1,2-a]pyridine of zolpidem, the quinoline of chloroquine and the quinoxaline of brimonidine (Figure 1). These drugs only illustrate the scaffolds; none of them is made by the routes described here. What the three families share is a C3 position that can still be functionalised after the ring is built, provided the construction step leaves that C–H bond in place.

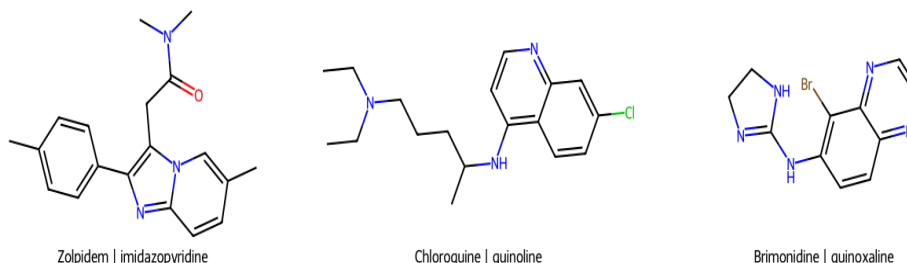


Figure 1. Representative drugs containing the three core families studied.

Visible-light catalysis with organic dyes now handles both halves of this problem. Eosin Y, rose bengal, methylene blue and the cyanoarene 4CzIPN cover a wide redox window without precious metals (Hari & König, 2014; Luo & Zhang, 2016; Romero & Nicewicz, 2016). Aerobic photochemical annulations build quinolines and related cores from simple precursors (Dong et al., 2016). Radical additions to heteroarenes, Minisci reactions in particular, install alkyl groups directly at C–H positions (Proctor & Phipps, 2019; Ravelli et al., 2016), and visible-light cross-dehydrogenative coupling forms C3–N bonds on quinoxalinones (Ke et al., 2019; Wei et al., 2018). The two halves, however, are almost always developed separately. Each step is optimised, the intermediate is isolated and purified, and only then is the next step run. Isolating every intermediate costs solvent, silica, time and product. Telescoping avoids those losses only if whatever the first step leaves in the flask (acid, iodide, water, unreacted amine, dissolved oxygen) does not poison the second. A telescoped route may also need its own operations, such as staged reagent addition, a solvent adjustment or a gas exchange (Figure 2), and these must be counted. This study therefore tests compatibility before combining conditions, using a robustness screen of the kind introduced by Collins and Glorius (2013), and compares telescoped and stepwise routes on yield and process mass intensity measured within the same boundaries.

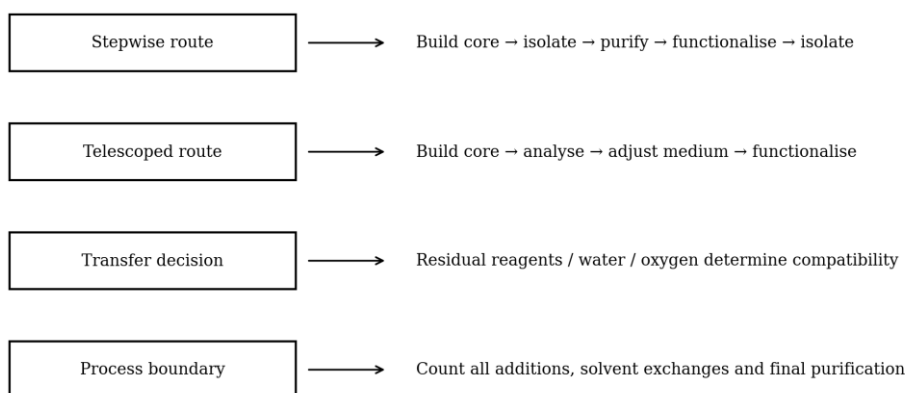


Figure 2. Stepwise and telescoped process concepts. The telescoped route may still require staged addition, solvent adjustment or gas exchange.



Oxygen plays a dual role in these sequences. In the annulations it is the terminal oxidant, reoxidising the reduced dye or accepting triplet energy to form singlet oxygen (Strieth-Kalthoff et al., 2018). In a radical addition step, however, it competes for the carbon-centred radical (Shaw et al., 2016). Switching the atmosphere between the two stages is therefore a deliberate process operation, not a minor detail.

2. Experimental

2.1 General information

Reactions were run in 8 mL borosilicate vials (2.0 mL working volume) held at a fixed 20 mm distance from calibrated LED modules (456, 525 or 660 nm), with fan cooling to 25 ± 2 °C. Yields were measured by quantitative ^1H NMR against 1,3,5-trimethoxybenzene and, separately, as isolated yields after a common chromatographic endpoint. Every value is the mean of three independently prepared reactions. Supplier, purity, batch and chemical form were recorded for each dye and reagent. All yields refer to the limiting starting material of the first stage.

2.2 General procedures

GP-A (imidazopyridine IP01). 2-Aminopyridine (0.20 mmol), acetophenone (0.30 mmol), methylene blue (2 mol%) and KI (20 mol%) in ethanol (2.0 mL), air balloon, 660 nm, 25 °C, 8 h.

GP-B (quinoline QN01). Aniline (0.20 mmol), ethyl glyoxylate (0.24 mmol) and styrene (0.30 mmol) with eosin Y (2 mol%) and a Brønsted acid (10 mol%) in ethanol under air, 525 nm, 10 h. Aromatic product and partially aromatised components were quantified separately.

GP-C (quinoxaline QX01). o-Phenylenediamine (0.20 mmol) and phenacyl alcohol (0.24 mmol) with eosin Y (2 mol%) in ethanol (2.0 mL), air, 525 nm, 6 h. Residual diamine was quantified before any T2 transfer.

GP-D (T1, telescoped chalcogenation). GP-A was run until core conversion reached at least 95%. Diphenyl disulfide (0.75 equiv relative to the initial aminopyridine) was then added without isolating IP01, and irradiation was continued under the same aerobic ethanol conditions.

GP-E (T2, telescoped alkylation). After GP-C, the core was quantified by qNMR, the medium was adjusted and the atmosphere was exchanged for argon. The cyclohexanecarboxylic acid redox-active ester (1.5 equiv), 4CzIPN (2 mol%) and acid (0.5 equiv relative to the core) were added, and the mixture was irradiated at 456 nm. Preparation of the activated ester and the solvent exchange were included in the material balance.

GP-F (T3, lactam assembly and amination). N-Methylquinoxalin-2(1H)-one QO01 was assembled from N-methyl-o-phenylenediamine and an ethyl glyoxylate source. Once the lactam endpoint was confirmed, morpholine (2 equiv) and eosin Y (2 mol%) were added and the mixture was irradiated at 525 nm under air. A sample of purified QO01 served as the clean stage-2 reference.

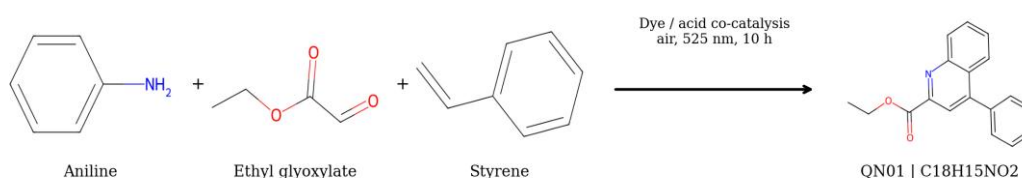
2.3 Robustness screen and process metrics

Each independently optimised second stage was challenged with one representative carryover component at a time (Collins & Glorius, 2013). Yield retention was defined as $100 \times (\text{challenged yield})/(\text{clean reference yield})$. Process mass intensity was calculated as total input mass divided by product mass, including reaction solvents, workup, chromatography and, for T2, preparation of the redox-active ester (Jiménez-González et al., 2011). With no solvent recovery, the complete E-factor equals PMI – 1. Atom economy follows Trost (1991), and reaction mass efficiency follows Constable et al. (2002).

3. Results and Discussion

3.1 Three aerobic annulations

Quinolines. Condensing aniline with ethyl glyoxylate gives an imine, which undergoes acid-assisted Povarov-type addition of styrene and cyclisation; oxidative aromatisation then gives ethyl 4-phenylquinoline-2-carboxylate QN01 (Scheme 1). The ideal balance consumes one equivalent of O₂ and releases three molecules of water. Eosin Y with 10 mol% acid under air gave 74% (Table 1). Without acid the yield fell to 31%, and under argon to 26%. Methylene blue (57%) and rose bengal (65%) were weaker than eosin Y. This system was designed for the present work; the aerobic photochemical Povarov chemistry reported for quinoline-fused lactones provides reaction-class precedent rather than the exact conditions (Dong et al., 2016).



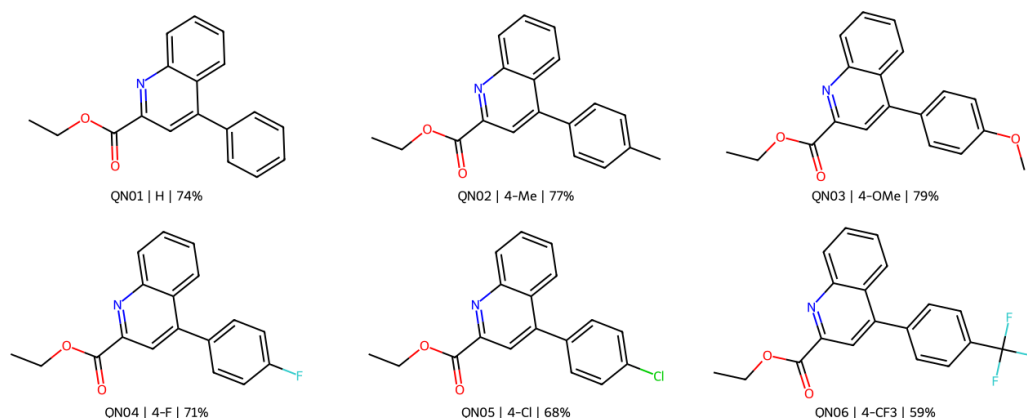
Scheme 1. Three-component aerobic construction of quinoline QN01.

Table 1

QN01 condition comparison

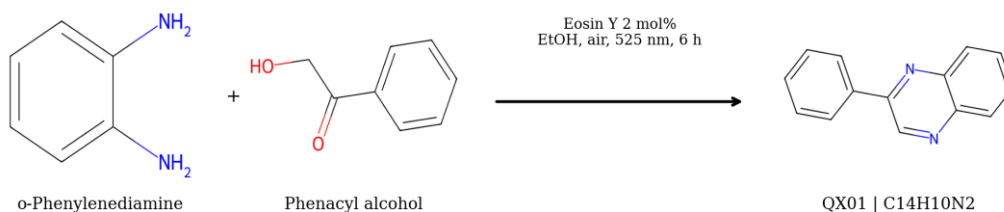
Dye / additive	Atmosphere	Time (h)	Isolated (%)
Eosin Y / acid 10 mol%	Air	10	74
Eosin Y / no acid	Air	10	31
MB / acid 10 mol%	Air	10	57
Rose bengal / acid	Air	10	65
No dye / acid	Air	10	18
Eosin Y / acid	Argon	10	26

Varying the styrene aryl group (Scheme 2) showed that electron-rich styrenes give higher isolated yields than the strongly electron-withdrawing example. The C2 ester comes from the glyoxylate and the C4 aryl group from the styrene. HMBC correlations from H3 to both the ester-bearing and the aryl-bearing ring carbons support this regiochemistry, a point HRMS alone cannot settle. Because aromatisation erases any stereochemistry set in the cycloaddition, the products are achiral.



Scheme 2. Quinoline scope (isolated yields).

Quinoxalines. In this system the dye oxidises phenacyl alcohol to a phenylglyoxal equivalent, which condenses with o-phenylenediamine to give 2-phenylquinoxaline QX01 (Scheme 3; ideal balance diamine + hydroxyketone + $\frac{1}{2}\text{O}_2 \rightarrow \text{QX01} + 3\text{H}_2\text{O}$). Eosin Y in ethanol under air gave 86% in 6 h (Table 2). With preformed phenylglyoxal the condensation reached 81% in the dark without any dye, which shows that light is needed only for the alcohol oxidation, not for ring formation. Monosubstituted products were chosen deliberately: a 2,3-diaryl quinoxaline has no C3–H left for the T2 alkylation.



Scheme 3. Aerobic construction of monosubstituted quinoxaline QX01.

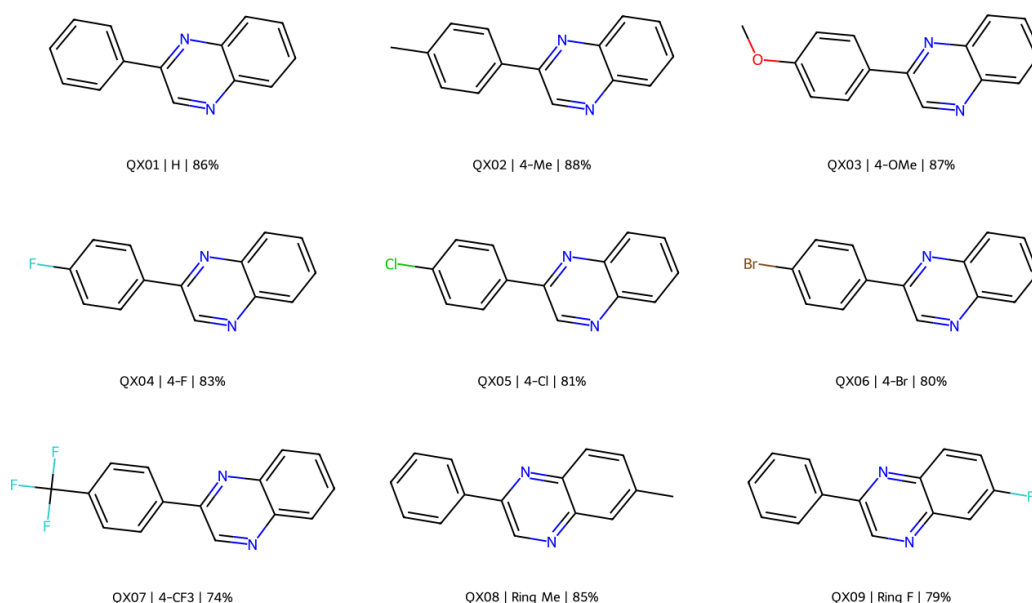
Table 2

QX01 optimisation and bypass control

Entry	Condition	Isolated (%)
1	Eosin Y, EtOH, air, 6 h	86

Entry	Condition	Isolated (%)
2	Rose bengal, EtOH, air	79
3	MB, EtOH, air	70
4	Eosin Y, MeCN, air	73
5	Eosin Y, EtOH, argon	24
6	No dye, hydroxyketone, air	17
7	Preformed glyoxal, no dye, dark	81

The nine-member quinoxaline scope (Scheme 4) covered aryl substituent changes and substituted diamines, and every product kept its C3–H bond. With unsymmetrical diamines two positional isomers are possible, so each displayed connectivity needs two-dimensional NMR support. Residual diamine was tracked closely because, if carried forward, it can act as a competing quencher or electron donor in a subsequent photoredox step.



Scheme 4. Quinoxaline scope; all products retain C3–H for later functionalisation.

Comparison. Table 3 sets the three annulations side by side. QX01 gave the highest yield in the shortest time. QN01 needs the most components and gave the lowest yield, so it was the least promising starting point for telescoping. IP01 (85% isolated, from MB/KI at 660 nm) has the most thoroughly optimised conditions and a well-defined C3 site for chalcogenation. All three cores keep a C3–H bond.



Table 3

Comparison of the annulation reference formulations (0.20 mmol basis)

Property	IP01	QN01	QX01
Core	Imidazopyridine	Quinoline	Quinoxaline
Dye	MB	Eosin Y	Eosin Y
Light (nm)	660	525	525
Exposure (h)	8	10	6
Isolated yield (%)	85	74	86
qNMR yield (%)	88	79	90
Key additive	KI	Brønsted acid	None
Ideal O ₂ (equiv)	0.5	1.0	0.5
Ideal water (equiv)	2	3	3
Next target site	C3–H	C3–H	C3–H

3.2 Compatibility mapping before telescoping

Table 4 and Figure 3 summarise how each second stage tolerated the components a first-stage mixture would leave behind. Ethanol (20 vol%) and water (5 vol%) were well tolerated, with 81–94% retention. A full equivalent of p-TsOH was the most damaging challenge (39, 21 and 45% retention for T1, T2 and T3), and T2 was also strongly affected by the wrong atmosphere (48% under air instead of argon). T2 lost the most in every category, which is expected for a radical step in which the alkyl radical can be intercepted by oxygen and acid changes both heteroarene protonation and reduction of the redox-active ester (Proctor & Phipps, 2019). Residual KI reduced T2 to 54% retention, possibly because iodide competes as a quencher for the excited 4CzIPN.

Table 4

Robustness challenges: second-stage yield retention (%)

Challenge	Addition basis	T1	T2	T3
EtOH	20 vol% in stage 2	94	84	90
Water	5 vol%	92	88	81
KI	20 mol% vs core	72	54	74
Acid	1 equiv p-TsOH	39	21	45
Residual amine	0.10 equiv	83	66	87
Oxygen	O ₂ vs air (T1/T3); air vs Ar (T2)	65	48	62

Note. Retention = $100 \times \text{challenged yield} / \text{clean reference yield}$. Values are not absolute yields.

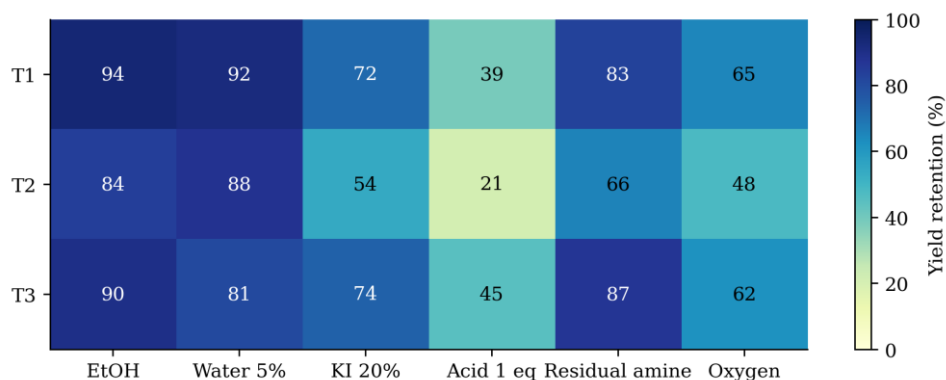


Figure 3. Heat map of yield retention under defined carryover challenges.

The screen translated into a specific transfer operation for each sequence (Table 5). For T1, the ethanol medium is kept and the disulfide added only after the core has formed. For T2, the solvent is adjusted, air is exchanged for argon and residual diamine must be no more than 0.10 equiv. For T3, the lactam must be fully assembled before the amine is added. In every sequence the core was quantified by qNMR before the second reagent went in, so the second stage started from a measured endpoint rather than after a fixed time.

Table 5

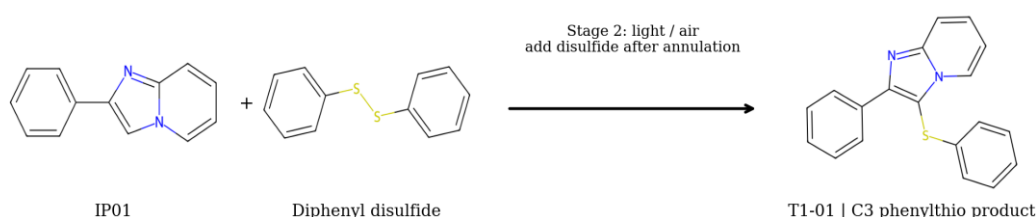
Transfer operations selected from compatibility screening

Sequence	Operation	Required endpoint
T1	Retain EtOH; staged disulfide addition	Core $\geq$ 95% conversion
T2	Adjust solvent; exchange air for argon	Residual diamine $\leq$ 0.10 equiv
T3	Complete lactam assembly before amine addition	Residual glyoxylate controlled
All	Sample before adding stage-2 reagent	Core amount recorded by qNMR

3.3 Sequence T1: imidazopyridine construction and C3 thiolation

T1 builds IP01 and then replaces its C3–H with a phenylthio group (Scheme 5). Adding diphenyl disulfide at the start gave only 68% core conversion and 38% overall yield (Table 6), presumably because the donor competes with the ketone for iodine species or the excited dye. Staged addition after core formation raised the overall yield to 64% with 0.50 equiv, 72% with 0.75 equiv and 70% with 1.00 equiv of donor. Since each disulfide carries two transferable sulfur groups, 0.75 equiv corresponds to 1.5 sulfur equivalents. The second stage still required

light (25% in the dark) and air (43% under argon), which fits an iodine-mediated, light-sustained thiolation of the electron-rich C3 position similar to the I₂-catalysed chalcogenations of Rafique et al. (2016).



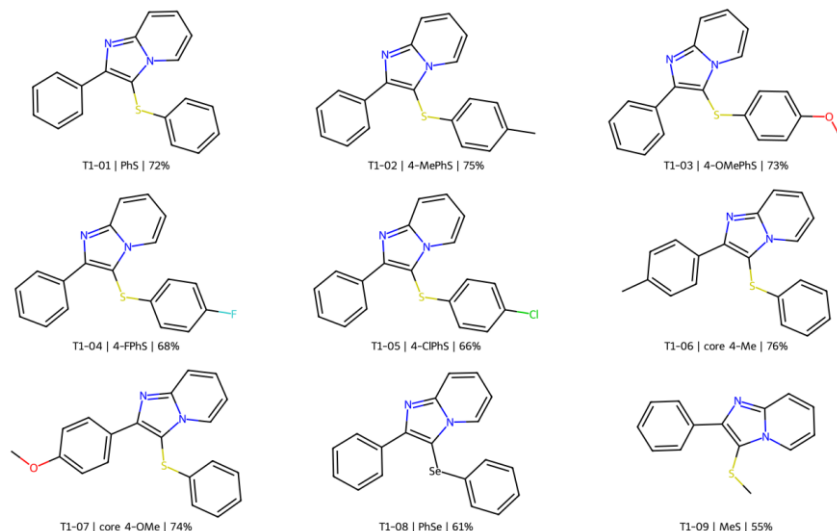
Scheme 5. Sequence T1: IP construction followed by C3 phenylthiolation in the same vessel.

Table 6

T1 second-stage optimisation

Condition	Core conversion (%)	Overall isolated (%)
Disulfide added at t = 0	68	38
Staged, 0.50 equiv donor	95	64
Staged, 0.75 equiv donor	98	72
Staged, 1.00 equiv donor	99	70
Staged, dark second step	41	25
Staged, argon second step	61	43

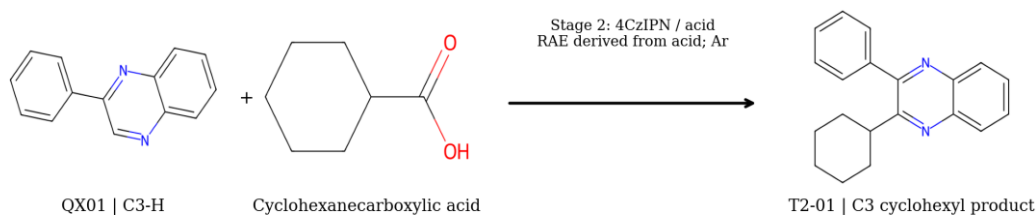
Aryl disulfides gave useful overall yields, the methylthio donor was less efficient, and a diselenide example extended the method to selenium (Scheme 6). C3 substitution, rather than N-functionalisation or oxidation to sulfoxide, was confirmed by the disappearance of the H3 singlet (δ 7.74 in IP01), the appearance of donor-derived signals with long-range correlations to C3, and sulfur or selenium isotope patterns in the HRMS.



Scheme 6. T1 chalcogenation scope; percentages are overall isolated yields from the aminopyridine.

3.4 Sequence T2: quinoxaline construction and Minisci C3 alkylation

After aerobic construction of QX01, the medium was adjusted and the headspace exchanged for argon. The cyclohexanecarboxylic acid N-hydroxyphthalimide ester was then added with 4CzIPN and acid (Scheme 7). Single-electron reduction of the ester releases CO₂ and the phthalimide anion, and the cyclohexyl radical adds to the protonated quinoxaline at C3 (Garza-Sanchez et al., 2017; Proctor & Phipps, 2019). The best conditions (4CzIPN, 0.5 equiv acid, argon) gave 65% overall with 12% residual QX01 (Table 7). Without acid, much of the core was left unreacted (49%) and the yield fell to 28%. With 1.5 equiv of acid it dropped to 49%. Running the step under air reduced the yield to 31%, and eosin Y (42%) was less effective than 4CzIPN, whose reducing excited state better matches redox-active esters (Luo & Zhang, 2016). The acid optimum reflects two competing needs: enough protonation to activate the heteroarene, as in enantioselective Minisci chemistry (Proctor et al., 2018), but not so much acid that it disrupts radical generation.



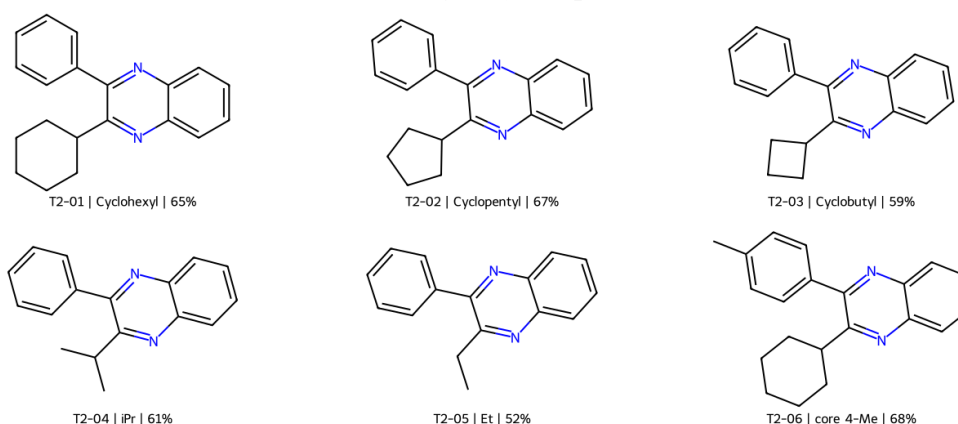
Scheme 7. Sequence T2: radical-source lineage and C3 alkylation of QX01.

Table 7

T2 second-stage condition comparison

Condition	Overall isolated (%)	Residual QX01 (%)
4CzIPN, acid 0.5 equiv, Ar	65	12
4CzIPN, no acid, Ar	28	49
4CzIPN, acid 1.5 equiv, Ar	49	21
4CzIPN, acid 0.5 equiv, air	31	37
Eosin Y, acid 0.5 equiv, Ar	42	29
No dye, acid 0.5 equiv, Ar	9	67

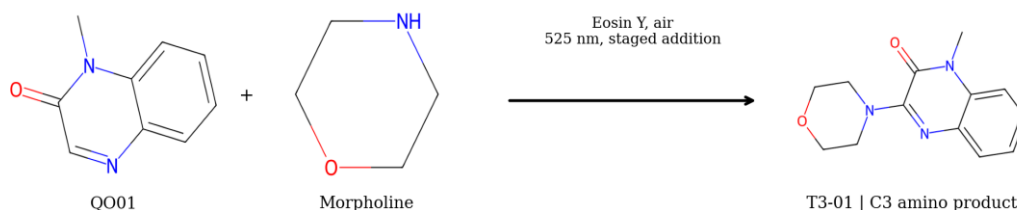
Cyclic secondary radicals performed better than the primary ethyl radical under the common conditions (Scheme 8). This ranking combines ester fragmentation, radical addition and rearomatisation, so it should not be read as a ranking of radical stability. Because C2 already carries the phenyl group, the alkyl group can only enter at C3; HMBC correlations from the new alkyl CH to the ring carbons confirm this. The activated esters are counted as separate reagents in the material balance, since listing only the parent acid would understate waste.



Scheme 8. T2 C3 alkylation scope; overall isolated yields from the diamine.

3.5 Sequence T3: quinoxalinone assembly and C3 amination

T3 first condenses N-methyl-o-phenylenediamine with a glyoxylate source to give N-methylquinoxalin-2(1H)-one QO01 (92% assembly), then couples morpholine at C3 under eosin Y and air (Scheme 9). This extends the visible-light cross-dehydrogenative C–N coupling of Wei et al. (2018) to a staged one-pot sequence. Waiting for the assembly endpoint before adding the amine was essential: adding morpholine at the start lowered assembly to 65% and the overall yield to 29%, against 70% for the staged route (Table 8). Without light the second step gave 11%, and under argon 27%, showing that light and oxygen are both required for the amination. With purified QO01 the amination step alone gave 82%.



Scheme 9. Sequence T3: QO01 assembly followed by C3 amination with morpholine.

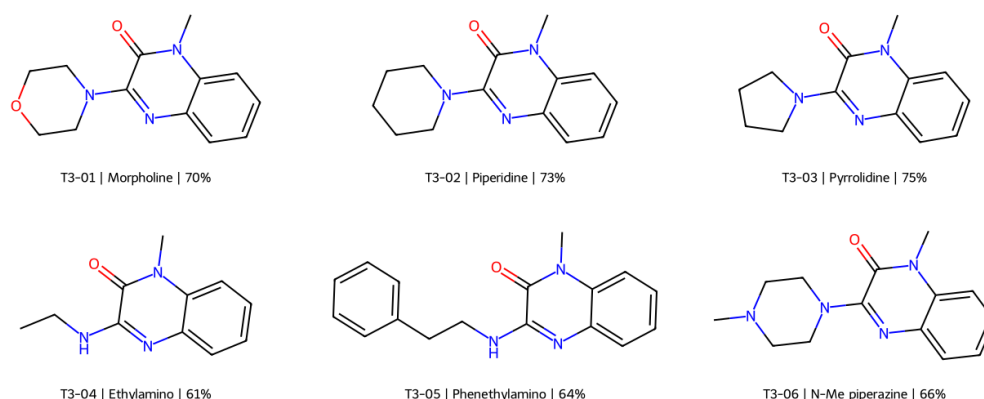
Table 8

T3 staging and second-stage response

Entry	Assembly (%)	Overall target (%)
Amine added initially	65	29
Assembly endpoint, then morpholine	92	70
Pre-isolated QO01 reference	—	82 ^a
Second step without light	92	11
Second step under argon	92	27

Note. ^aIsolated second-stage yield from purified QO01, not an overall route yield.

Pyrrolidine and piperidine gave higher overall yields than the primary aliphatic amines (Scheme 10). Morpholine was kept as the model because its ether oxygen tests chemoselectivity. Amine oxidation can generate an aminium radical cation, an N-centred radical or an iminium ion, and α -C–H functionalisation is a possible side reaction (Ke et al., 2019). HMBC from the morpholine NCH₂ protons to C3 showed that the new bond is C3–N and not C3–C.



Scheme 10. T3 amination scope; overall isolated yields.



3.6 Working mechanisms of the staged steps

Figure 4 summarises the working pathways. In T1, the sulfur donor may be activated either by radicals or by an electrophilic iodine species, and inhibition by radical traps alone cannot tell these apart. In T2, the reduced 4CzIPN radical anion transfers an electron to the ester, which fragments to the alkyl radical. The radical adds to the protonated quinoxaline, and oxidation followed by deprotonation restores aromaticity. In T3, the excited eosin Y oxidises the amine, a C3–N bond forms, and oxidative rearomatisation, with oxygen as the terminal acceptor, completes the cycle. Telescoping combines the process operations in one vessel, but each stage keeps its own mechanism (Shaw et al., 2016).

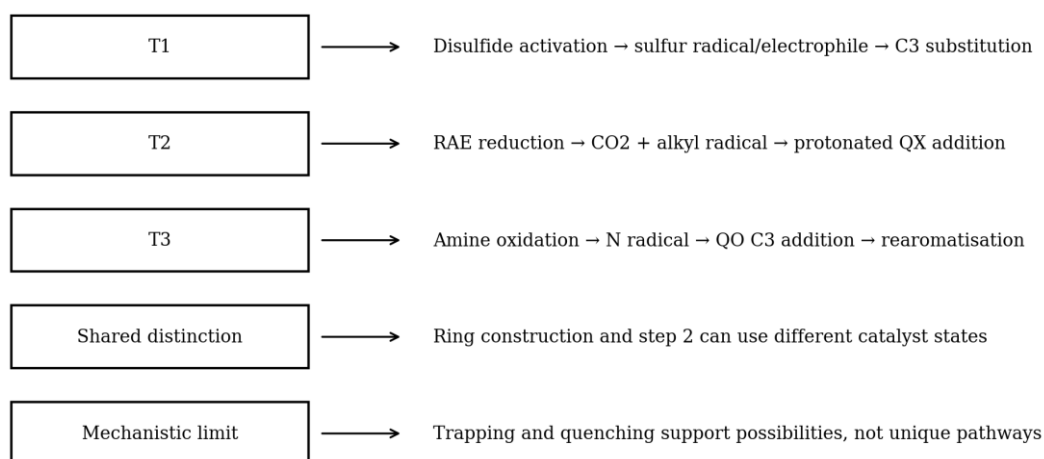


Figure 4. Working pathways for the three staged functionalisation sequences.

3.7 Telescoped versus stepwise: yield and material intensity

The stepwise overall yield is the product of the two isolated stage yields. For T1 it is $0.85 \times 0.88 = 74.8\%$, against 72.0% telescoped; for T2, 70.5% against 65.0%; and for T3, 75.4% against 70.0% (Table 9, Figure 5). Telescoping therefore did not improve yield. The gap is small for T1 (2.8 points) and larger for T2 and T3 (5.4–5.5 points). The material saving is much larger: PMI fell by 42% for T1 (148 → 86), 38% for T2 (182 → 112) and 42% for T3 (136 → 79). Almost all of this saving comes from avoiding the intermediate workup and chromatography, which dominate the input mass in small-scale synthesis (Jiménez-González et al., 2011). T2 has the highest PMI in both formats because of the solvent exchange and the separately prepared redox-active ester.

Table 9

Matched comparison of stepwise and telescoped routes

Route	Stepwise yield (%)	Telescoped yield (%)	PMI stepwise	PMI telescoped
T1	74.8	72.0	148	86



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Route	Stepwise yield (%)	Telescoped yield (%)	PMI stepwise	PMI telescoped
T2	70.5	65.0	182	112
T3	75.4	70.0	136	79

Note. Same starting-material basis, target compound and purification endpoint. PMI counts all charged materials per gram of isolated final product.

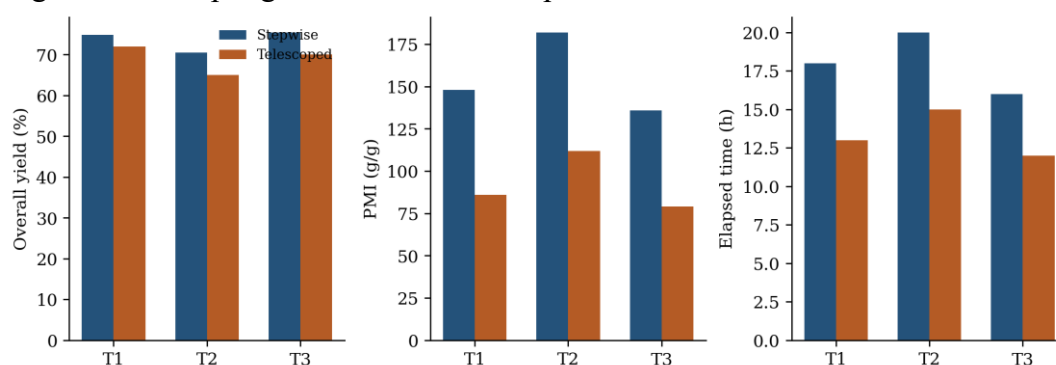


Figure 5. Overall yield, material intensity and elapsed time for stepwise and telescoped routes.

The complete mass balance for T1 (Table 10) shows the same trade-off. Reaction mass efficiency is slightly lower when telescoped (48.6% against 52.1%), because the yield is lower and the reagent charge is the same. The E-factor, however, falls from 147 to 85 (Figure 6). Atom economy is fixed by the balanced reactions and does not change with the process format. Telescoping is worthwhile when solvent, silica and operator time outweigh a few points of yield, as is usually the case in analogue synthesis (Constable et al., 2002). These metrics should still be read alongside the yield loss, and they do not include energy use or solvent hazard.

Table 10

T1 process metrics under a complete mass boundary

Process	AE	RME (%)	PMI	E-factor
Stepwise T1	Route-specific	52.1	148	147
Telescoped T1	Same stoichiometry	48.6	86	85

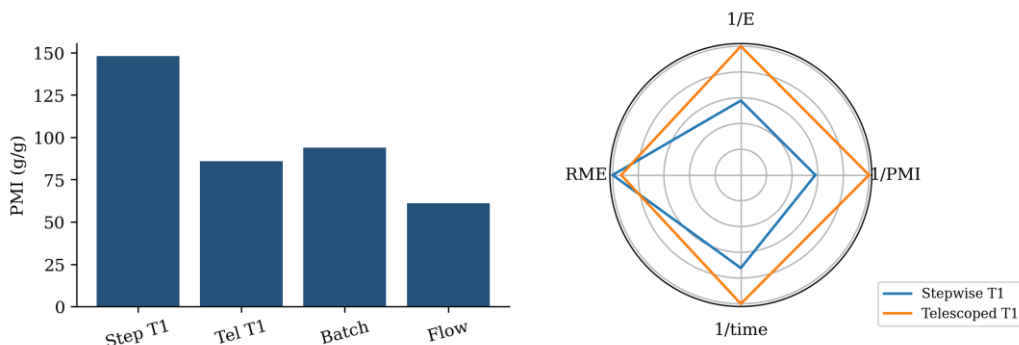


Figure 6. Material-intensity comparison and normalised T1 trade-offs (inverse PMI, inverse E-factor, inverse time).

3.8 Characterisation of model and sequence products

Table 11 lists the formula, calculated $[M+H]^+$ and diagnostic NMR regions for each model and sequence product. Loss of the C3–H signal identifies each functionalised product: the δ 7.74 singlet of IP01 is absent in T1-01, the δ 9.28 singlet of QX01 is replaced by cyclohexyl signals at δ 3.45–1.20 in T2-01, and the δ 8.20 singlet of QO01 gives way to morpholine signals at δ 3.84–3.25 in T3-01. For the sulfur-containing T1-01, the HRMS isotope pattern shows the expected ^{34}S contribution.

Table 11

Characterisation data for model and sequence products

Code	Formula	$[M+H]^+$ calc.	Yield (%)	^1H regions (ppm)	^{13}C regions (ppm)
IP01	$\text{C}_{13}\text{H}_{10}\text{N}_2$	195.09167	85	8.10, 7.94, 7.74, 7.45–6.77	145.5–108.1
QN01	$\text{C}_{18}\text{H}_{15}\text{NO}_2$	278.11756	74	8.24–7.30; 4.42 q; 1.42 t	166.2; 154–121; 61.7; 14.3
QX01	$\text{C}_{14}\text{H}_{10}\text{N}_2$	207.09167	86	9.28 s; 8.24–7.46	151.5–128.0
QO01	$\text{C}_9\text{H}_8\text{N}_2\text{O}$	161.07094	92	8.20 s; 7.75–7.12; 3.66 s	154.6; 137–114; 29.2
T1-01	$\text{C}_{19}\text{H}_{14}\text{N}_2\text{S}$	303.09505	72	8.22–6.93; no H3 singlet	148.1–111.8
T2-01	$\text{C}_{20}\text{H}_{20}\text{N}_2$	289.16993	65	8.19–7.34; 3.45– 1.20	156.2–127.5; 43.1–26.2
T3-01	$\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2$	246.12370	70	7.72–7.04; 3.84– 3.25	153.1–113.1; 66.7; 48.3; 29.5



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4. Conclusions

Organic dyes under air built three heterocyclic cores, imidazopyridine (85%), quinoline (74%) and quinoxaline (86%), each with its C3–H bond intact, and the same flask could then be used for a C3 functionalisation. Measuring carryover tolerance before combining steps identified acid and atmosphere as the two variables that most often break a telescoped sequence, and showed that the radical alkylation (T2) is the most sensitive. Staged addition, an air-to-argon switch and an endpoint check before the second reagent was added turned these findings into working procedures, with 72, 65 and 70% overall yields for C3 thiolation, alkylation and amination. Telescoping cost 3–6 points of yield relative to the matched stepwise routes and reduced process mass intensity by about 40%. We think this is an honest picture of telescoped photochemistry: its value lies in material efficiency rather than higher yield. Further work should address the identity of the active sulfur-transfer species in T1 and the scale-up of T2 in flow, where shorter optical paths and better gas handling should help (Buglioni et al., 2022).

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