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Graphical Abstract

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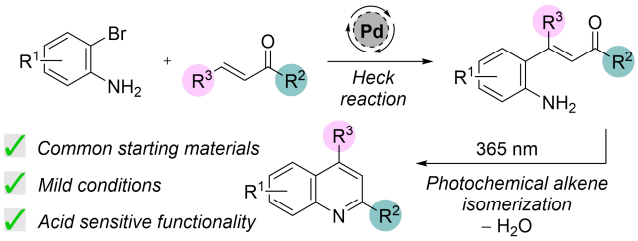

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Dedicated to Professor Richard Taylor.

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ABSTRACT

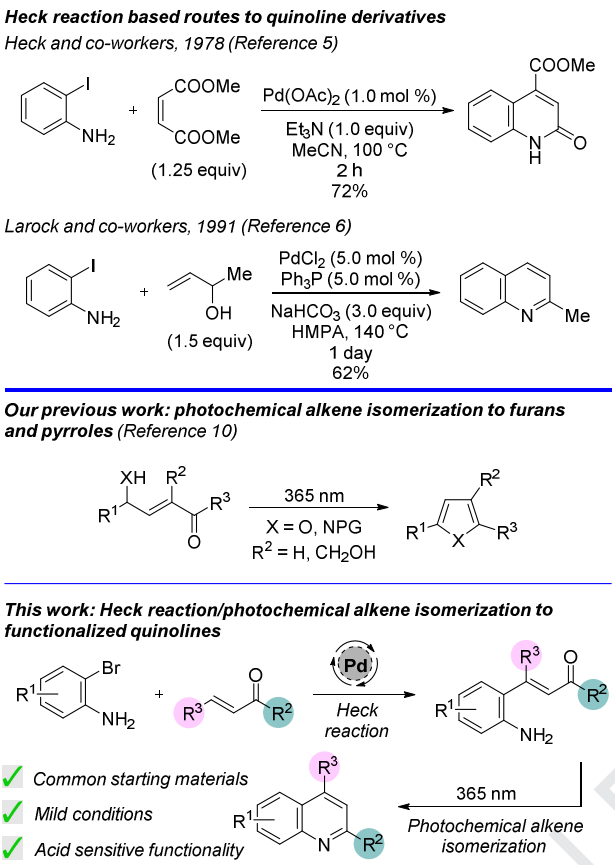
A route to prepare functionalized quinolines based on a Heck reaction/UV-induced alkene isomerization sequence is described. The method allows for the preparation of quinolines under mild and neutral conditions and has broad functional group tolerance. Acid-sensitive functional groups that would not be tolerated under previous approaches can be included and a one-pot quinoline forming procedure is also reported.

1. Introduction

Quinolines are key motifs found within a variety of natural products[1] and bioactive compounds,[2] and are generally valuable intermediates in organic synthesis. Traditional routes to quinolines include the venerable Skraup, Combes, Doebner–Miller and Friedlander syntheses.[3] However, each of these methods has their limitations, namely poor functional group tolerance arising from the harsh reaction conditions, poor selectivity, or low yields.[3] This situation has led to an extensive search for new approaches to prepare quinolines, with many ingenious disconnections now available.[4] One strategy reported by Heck and co-workers used a palladium-catalyzed coupling reaction between an *ortho*-iodoaniline and dimethyl maleate to arrive at the corresponding quinolone derivative (Scheme 1, top).[5] Later, Larock and co-workers disclosed a related approach using allyl alcohols as the Heck reaction partner,[6] which proceeded first via the β-aryl ketone to provide a cyclized dihydroquinoline, and then exploited their *in-situ* Pd(0)-catalyzed dehydrogenation to form the desired quinolines in moderate yields. These reports were the starting point for a series of innovative approaches to quinoline synthesis based around the disconnection provided by the Heck reaction.[7] Alternative methods of accessing similar β-aryl ketone-type intermediates have also been reported in the context of quinoline synthesis.[8]

Our group has a longstanding interest in the application of catalytic transformations for the de-novo synthesis of aromatic heterocycles.[9] We recently reported an alkene metathesis/photochemical isomerization approach for the rapid synthesis of functionalized furans and pyrroles (Scheme 1, bottom).[10] A number of acid-sensitive functionalities could be incorporated into the target using the mild photochemical conditions and we wondered whether a similar strategy could also be applied to quinoline synthesis.[11]

Our plan was to perform a Heck reaction[12] between readily available *ortho*-bromoanilines (in contrast to the less common *ortho*-iodoanilines which are conventionally used) and enones to access β-aryl-α,β-unsaturated ketones. These would then be subjected to our previous photochemical alkene isomerization conditions to allow formation of the desired quinolines.[13–16] The direct use of enone derivatives in the Heck reaction would circumvent the need for an oxidation step, and the mild photochemical isomerization conditions would hopefully allow for the incorporation of a variety of functionality, overcoming the issues of limited substrate scope and harsh conditions of previous methods. However, it should be noted that the Heck reaction between *ortho*-haloanilines and enones is rare. During the course of our investigation, a report by Wang, Zhai and co-workers reported the isomerization of similar β-aryl-α,β-unsaturated ketone intermediates to quinolines using blue LEDs.[17] No general access to these key intermediates was reported, although some were prepared via Heck reaction with *ortho*-iodoanilines. Herein, we report our results to complement their publication.



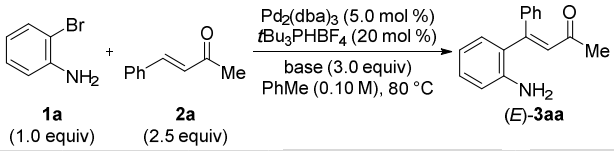
Scheme 1. Approaches to functionalized quinolines. HMPA = hexamethylphosphoramide, PG = protecting group.

2. Results and discussion

2.1. Heck reaction optimization

We began by studying the reaction between *ortho*-bromoaniline (**1a**) and benzylideneacetone (**2a**). Using Heck reaction conditions based on those reported by Fu and co-workers, aniline (*E*)-**3aa** could be isolated in 41% yield (Table 1, entry 1).[18] Reversing the stoichiometry to make *ortho*-bromoaniline (**1a**) the limiting reagent led to an improved yield of 72% (entry 2). However, raising the temperature of the reaction resulted in a large reduction in yield (entry 3). Switching to *i*Pr_2NEt as base provided aniline **3aa** in 91% isolated yield (entry 4). Neither reducing the excess of enone **2a** nor switching to 2-chloroaniline as the limiting reagent led to any further improvement (entries 5 and 6). Note that the (*E*)-geometry of enone **3aa** was verified by nOe enhancements (see Supporting Information). Compound (*Z*)-**3aa** was not observed in the ^{1}H NMRs of the crude reaction mixtures, although trace quantities of the cyclized quinoline (<5%) were occasionally found. We presume that if compound (*Z*)-**3aa** did form during the course of the reaction it is likely that cyclization to the corresponding quinoline would occur spontaneously.

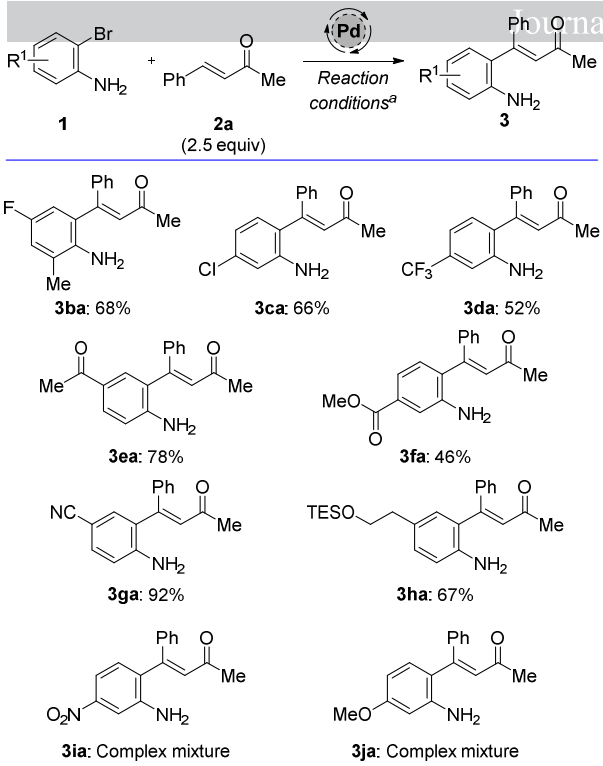
Table 1. Optimization of the Heck reaction. [a] Yield of isolated material



entry	base	time	modification to reaction conditions	yield **3aa** (%)[a]
1	Cy_2NMe	5 h	2.5 equiv **1a**, 1.0 equiv **2a**	41
2	Cy_2NMe	5 h	–	72
3	Cy_2NMe	5 h	100 °C	33
4	***i*Pr$_2$NEt**	**20 h**	–	**91**
5	*i*Pr_2NEt	20 h	1.5 equiv **2a**	64
6	*i*Pr_2NEt	20 h	2-chloroaniline	31

2.2. Heck Reaction Substrate Scope

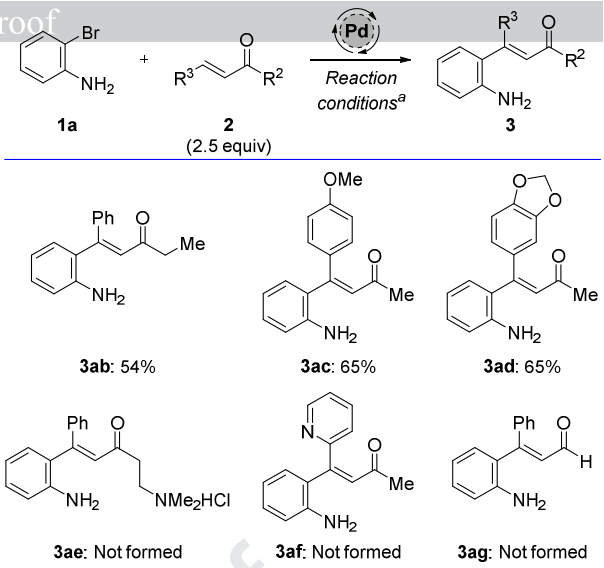
With optimized conditions in hand, we proceeded to investigate the scope of the Heck reaction. In some cases, trace quantities (<5%) of the cyclized quinoline were also detected in the ^{1}H NMRs of the crude reaction mixtures, but these were not isolated. Pleasingly, a range of substituted *ortho*-bromoanilines were tolerated in moderate to excellent yields (Scheme 2). *ortho*-Bromoanilines incorporating additional halogen substituents including fluorine (to give **3ba**) and chlorine (to give **3ca**) provided the corresponding quinolines in 68% and 66% yield respectively. A substrate containing the electron-withdrawing trifluoromethyl group gave compound **3da** in 52% yield. Carbonyl-based functional groups were also well tolerated, with ketone-containing **3ea** formed in 78% yield and methyl ester-containing **3fa** isolated in 46% yield.



Scheme 2. Scope of Heck reaction: variation of *ortho*-bromoaniline **1**. (a) reaction conditions: $Pd_2(dba)_3$ (5.0 mol %), *t*Bu_3PHBF_4 (20 mol %), *i*Pr_2NEt (3.0 equiv), PhMe (0.10 M), 80 ºC, 20 h. The (*E*) geometry of compounds **3ba**-**3ha** was assigned by analogy to **3aa**.

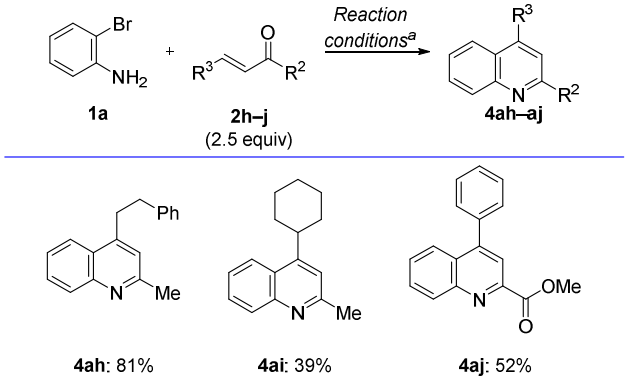
Some acid-sensitive functional groups including nitriles and silyl ethers could also be incorporated to produce **3ga** and **3ha** in 92% and 67% yield respectively. These functional groups would likely be troublesome under the harsher reactions conditions typical of quinoline synthesis. Unfortunately, reactions with nitro and methoxy-substituted *ortho*-bromanilines failed, providing only complex reaction mixtures.

Variation of the enone component was also investigated (Scheme 3). Increased substitution at the α-position of the carbonyl was possible giving **3ab** in 54% yield. Alternatively, electron-rich substituents could be incorporated on the β-aryl ring; **3ac** and **3ad** were each formed in 65% yield. Unfortunately, substrates containing basic functionality such as amines (as in **2e**) or pyridines (as in **2f**) were not amenable to the reaction, with no reactivity observed. Presumably these relatively unhindered basic species coordinated to the palladium catalyst, shutting down the reaction. Aldehyde species were also not compatible; no reaction was observed with cinnamaldehyde (**2g**).



Scheme 3. Scope of Heck reaction: variation of the enone **2**. (a) reaction conditions: $Pd_2(dba)_3$ (5.0 mol %), *t*Bu_3PHBF_4 (20 mol %), *i*Pr_2NEt (3.0 equiv), PhMe (0.10 M), 80 ºC, 20 h.

Interestingly, on a number of occasions, we were surprised to find that the quinoline was in fact the sole product from the Heck reaction; none of the expected enone was observed (Scheme 4). Enones **2h-i** bearing aliphatic substituents at the β-position (R^3 = aliphatic) reacted to afford quinolines **4ah** and **4ai** in 81% and 39% yield. Enone **2j**, with an ester group (R^2) adjacent to the carbonyl also led directly to quinoline **4aj**, which was isolated in 52% yield. The substrates in these particular cases were all electronically distinct from those previously discussed in that the alkene lacked a conjugating aryl group at R^3 (**4ah**, **4ai**) or possessed an activating R^2 group (**4aj**). We suggest that these factors may activate the initial Heck alkene product towards reversible addition reactions and thus lead to isomerisation, and cyclisation, during the Heck reaction itself.[19]

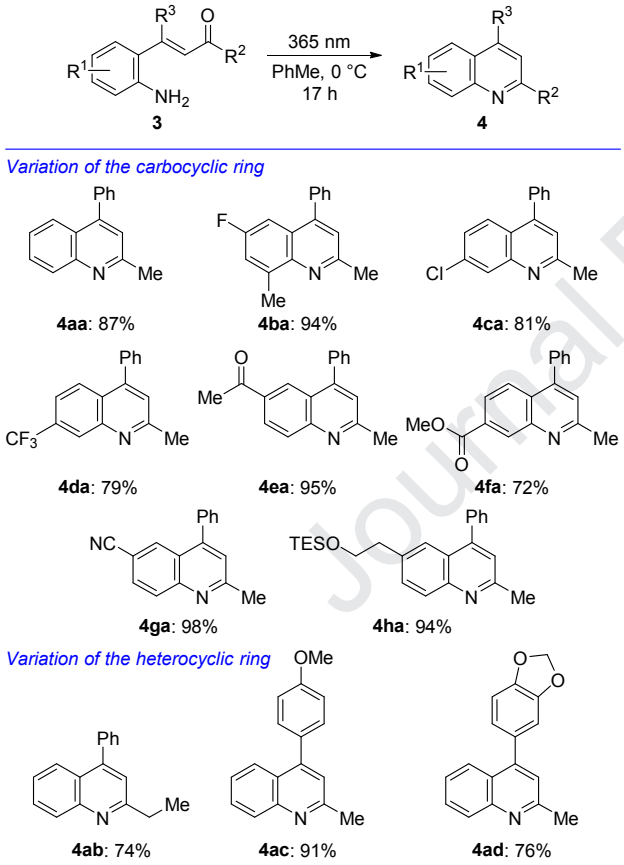


Scheme 4. Scope of Heck reaction: direct formation of quinolines. (a) reaction conditions: $Pd_2(dba)_3$ (5.0 mol %), *t*Bu_3PHBF_4 (20 mol %), *i*Pr_2NEt (3.0 equiv), PhMe (0.10 M), 80 ºC, 20 h.

2.3. Photochemical alkene isomerization

We then turned to the isomerization of the Heck reaction products, which we hoped would furnish the target quinolines. The UV-Vis absorption spectra of **3aa** demonstrated that, as before,[10] the enone intermediates absorbed in the 300–400 nm range and should be able to absorb at the wavelength provided by

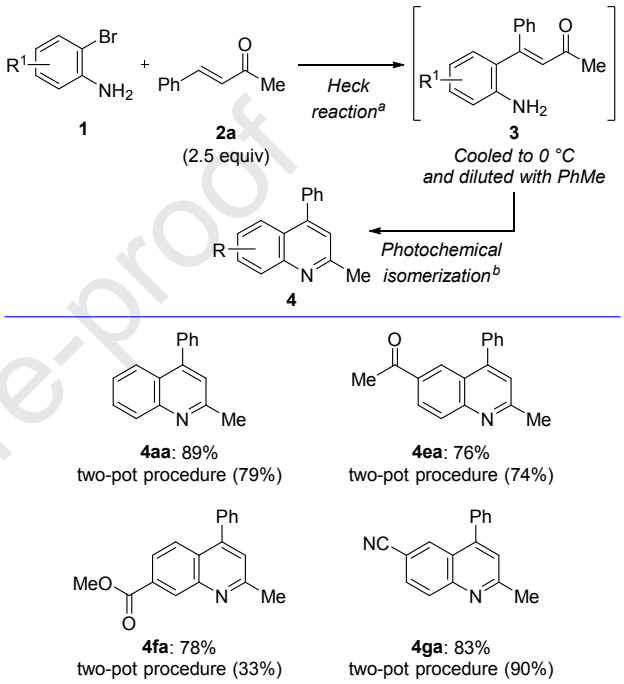
a commercially available 365 nm Pen-Ray source (see Supporting Information for UV-Vis spectra).[20] We were delighted to find that all of the Heck reaction products could indeed be isomerized and cyclized to the corresponding quinolines in high yields at 0 °C (Scheme 5). None of the enones we had prepared failed to react. Model enone **3aa** was converted to quinoline **4aa** in 87% yield. Halogen substituted enones **3ba** and **3ca** gave quinolines **4ba** and **4ca** in 94% and 81% yields respectively. Trifluoromethyl-substituted quinoline **4da** could be accessed in 79% yield. Quinolines incorporating carbonyl groups (**4ea**, **4fa**) were also prepared in 95% and 72% yields. The acid-sensitive nitrile and silyl ether functional groups were tolerated extremely well under the mild photochemical conditions to afford quinolines **4ga** and **4ha** in 98% and 94% yield respectively. Quinolines with differently functionalized heterocyclic rings were also formed, with quinoline **4ab** isolated in 74% yield and aryl ether substituted quinolines **4ac** and **4ad** in 91% and 76% yield respectively.



Scheme 5. Scope of the photochemical alkene isomerization.

2.4. One-pot Heck reaction/photochemical alkene isomerization sequence

Finally, we wondered whether we might be able to develop a one-pot procedure for the sequence, thus obviating the need to isolate the intermediate Heck product. As both Heck and photochemical isomerization reactions had been run in toluene, we hoped that simple irradiation of the crude Heck reaction mixture would allow for formation of the final quinoline products. After some optimization we established that this was the case, and both reactions could be performed in the same Schlenk tube without an intermediate work-up. The only manipulation required was the addition of extra toluene to allow for efficient irradiation. The crude Heck reaction mixture was thus cooled to 0 °C, once the reaction was complete, and then diluted with more toluene before being irradiated at 365 nm to afford the corresponding quinolines (Scheme 6). The one-pot procedure generally compares favourably to the previous two-pot approach. Quinoline **4aa** was isolated in 89% yield compared to 79% previously. Using the one-pot method, quinolines **4ea** and **4fa** were also isolated in higher yields than before. Only nitrile-containing quinoline **4ga** was isolated in a slightly lower 83% yield (90% previously).



Scheme 6. One-pot Heck reaction/photochemical alkene isomerization to quinolines. (a) Heck reaction conditions: $Pd_2(dba)_3$ (5.0 mol %), tBu$_3$PHBF$_4$ (20 mol %), iPr$_2$NEt (3.0 equiv), PhMe (0.10 M), 80 °C, 20 h. (b) Photochemical alkene isomerization reaction conditions: 365 nm, PhMe (10 µM), 0 °C, 20 h.

3. Conclusion

In summary, we have developed a route to functionalized quinolines based on a Heck reaction/photochemical alkene isomerization sequence. Compared with previous reports, the advantages of this approach include the direct use of enones in the Heck reaction, removing the need for an oxidation step, and the use of the more available *ortho*-bromoanilines as reaction partners. Photochemical alkene isomerization provides a means of converting the Heck intermediates into quinolines under mild conditions, allowing for the inclusion of acid-sensitive functionality (such as nitriles and silyl ethers) that would likely not be tolerated by the more typical, harsh reaction conditions used to access quinoline derivatives. A one-pot procedure, eliminating the need to isolate the intermediate Heck products, was also developed.

4. Experimental section

4.1. General experimental

All solvents and reagents were obtained from Acros, Alfa Aesar, Fischer Scientific, Fluorochem, Sigma-Aldrich, Strem or Tokyo Chemical Industry (TCI). All reagents were used as received or were purified using standard laboratory techniques. CH_2Cl_2, tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene (PhMe) were dried over activated 3□ molecular sieves for 2 days and then filtered through an activated alumina purification column prior to use. Brine refers to a saturated solution of NaCl in de-ionised H_2O. All glassware was flame-dried under vacuum and reactions performed in an argon atmosphere unless otherwise stated. All stated temperatures refer to external bath temperatures. Flash column chromatography was performed with Merck Kieselgel 60 (0.040–0.063 mm) except where explicitly stated otherwise. All solvents used for chromatographic purification were HPLC grade or equivalent and supplied by Sigma-Aldrich or Fischer Scientific. TLC analyses were performed on Merck Kieselgel 60 F_{254} precoated aluminium-backed plates with layer thickness between 175 and 225 µm. Product spots were visualised under UV light (λ_{max} = 254 nm) and/or by staining with a potassium permanganate, vanillin or phosphomolybdic acid solution. All NMR spectra were recorded on a Bruker AVIII HD 400 or Bruker AVIII HD 500 instrument with the deuterated solvent acting as internal deuterium lock. ^{1}H NMR spectra were recorded at 400 or 500 MHz, ^{13}C NMR spectra at 101 or 125 MHz with broadband proton decoupling and ^{19}F NMR spectra at 377 MHz without proton decoupling as stated. The residual protic solvent signal acted as an internal reference for ^{1}H NMR and the deuterated solvent carbon signal acted as an internal reference for ^{13}C NMR ($CDCl_3$: ^{1}H NMR = 7.26 ppm, ^{13}C NMR = 77.16 ppm). ^{19}F NMR spectra were not externally referenced. Chemical shifts are reported to 0.01 ppm for ^{1}H NMR spectra except in cases where two distinguishable peaks are within 0.01 ppm, in which case the shifts are reported to 0.001 ppm. Chemical shifts are reported to 0.1 ppm for ^{13}C NMR spectra except in cases where two distinguishable peaks are within 0.1 ppm, in which case the shifts are reported to 0.01 ppm. Coupling constants are quoted to the nearest 0.1 Hz for ^{1}H NMR. The multiplicity of a signal is reported as such: s–singlet, d–doublet, t–triplet, q–quartet, quint.–quintet, sext.–sextet, sept.–septet, oct.–octet, non.–nonet, m–multiplet, br.–broad, app.–apparent, or combinations thereof. Structural assignments were made with the aid of DEPT135, COSY, HSQC, HMBC, 1-D nOe and 2-D NOESY experiments. Fourier-transform infrared (FTIR) spectra were recorded from evaporated films or neat samples on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Selected absorption maxima are given in wavenumbers (cm^{-1}). Electrospray ionisation (ESI) high resolution mass spectrometry (HMRS) spectra were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass. The error is calculated with reference to the values given. UV-visible spectroscopy spectra were recorded on a PG instruments T60 UV/VIS spectrophotometer. All emission spectra were recorded at room temperature and in steady state mode unless otherwise stated. Melting points (M.P.) were obtained using a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and are uncorrected. The solvent systems used for recrystallisation are quoted in parentheses. Photochemical alkene isomerizations were performed in a 10 mL irradiation vessel made by Terri Adams at the University of Oxford. The outer compartment was made of pyrex glass and fitted with inlet and outlet side-arms. The removable inner glass compartment was made of fused quartz. A silicone ring placed at the connection of the two compartments served as a seal and a ring screw cap held the assembly together, allowing the UV lamp to be held within the inner compartment. Reactions on were performed with 7–8 mL of solvent to ensure efficient irradiation of the reaction mixture by the Pen-Ray. Before carrying out photochemical reactions, the irradiation setup was purged with argon for 30 min. The argon outlet was then disconnected while maintaining a moderate argon stream and the reaction solution was added through the argon outlet with a syringe. The argon outlet was reattached and the headspace was purged with argon for another 10 min. During photochemical reactions at reduced temperatures, the vessel was immersed into an ice or cryogenic bath. One-pot Heck/photochemical alkene isomerizations were performed in a 100 mL Schlenk tube fitted with a 24/40 joint adapter that was custom-made by Terri Adams at the Department of Chemistry, University of Oxford. A Teflon ring inside the adapter head tightly fitted an adjustable-depth pyrex glass inner compartment, into which the Pen-Ray was placed, providing an airtight seal and allowing light transmission. The isomerizations in the one-pot sequence were performed with 45 mL of solvent to ensure efficient irradiation of the reaction mixture by the Pen-Ray. The Pen-Ray mercury lamp was purchased from Ultra-Violet Products, Cambridge, UK (365 nm using a Pen-Ray Light Source 11SC-2.25PB (P/N 90-0019-01)) with a PS-1 power supply.

4.2. General procedure for Heck reactions (GP1)

Pd_2dba_3 (22.9 mg, 25.0 µmol, 5.00 mol%) and tBu$_3$PHBF$_4$ (29.1 mg, 0.100 mmol, 20.0 mol%) were added to a microwave vial. The vial was flushed with argon and sealed with a crimped cap. Argon sparged toluene (2.5 mL) and iPr$_2$NEt (0.27 mL, 1.5 mmol, 3.0 equiv) were added and the solution was stirred for 5 min at room temperature. The appropriate bromoaniline **1** (0.5 mmol, 1 equiv) and enone **2** (1.25 mmol, 2.50 equiv) were dissolved in argon sparged toluene (2.5 mL) and added to the reaction. The reaction was placed in a pre-heated oil bath at 80 ºC and stirred for 20 h. The reaction was cooled to room temperature and filtered through Celite® eluting with EtOAc. The filtrate was concentrated *in vacuo* before being purified by flash column chromatography (SiO_2) to afford the title compound.

4.3. General procedure for photochemical alkene isomerization (GP2)

In a 10 mL custom-made irradiation vessel, fitted with an argon inlet and an outlet to a silicon oil filled bubbler, the appropriate enone **3** was dissolved in argon-sparged toluene (8 mL) under argon atmosphere and the reaction cooled to 0 °C. The resulting colourless solution was irradiated at 365 nm for 17 h. The reaction was warmed to room temperature and directly concentrated *in vacuo* before being purified by flash column chromatography (SiO_2) to afford the title compound.

4.4. General procedure for one-pot Heck reaction/photochemical alkene isomerization (GP3)

A 100 mL Schlenk tube was fitted with the custom-made irradiation adapter, with the inner glass compartment adjusted to the top position. Under a slight positive pressure of argon *via* the side-tap, the vessel was sequentially charged with Pd_2dba_3 (22.9

mg, 25.0 μmol, 5.00 mol%), *t*Bu_3PHBF_4 (29.1 mg, 0.100 mmol, 20.0 mol%), the appropriate aryl bromide **1** (0.5 mmol, 1 equiv), the appropriate enone **2** (1.25 mmol, 2.50 equiv), argon-sparged toluene (5 mL) and *i*Pr_2NEt (0.27 mL, 1.5 mmol, 3.0 equiv). The vessel was flushed with argon while stirring at room temperature for 5 min and all joints were sealed with parafilm. The argon tap was then closed and the reaction stirred at 100 ºC for 20 h. The reaction was allowed to cool to room temperature and further argon-sparged toluene (45 mL) was added, the solution was cooled to 0 ºC and the inner glass custom-made irradiation adapter was lowered into the solution. The Pen-Ray mercury lamp was inserted into the inner adapter and the solution was then irradiated at 365 nm for 20 h. The reaction mixture was filtered through a plug of Celite® eluting with EtOAc. and concentrated *in vacuo*. The filtrate was concentrated *in vacuo* before being purified by flash column chromatography (SiO_2) to afford the title compound.

4.5. Experimental procedures: synthesis of starting materials

*4.5.1 2-Bromo-4-(2-((triethylsilyl)oxy)ethyl)aniline (**1h**).* Chlorotrimethylsilane (0.44 mL, 2.6 mmol, 1.3 equiv) in CH_2Cl_2 (4 mL) was added to a solution of 2-(4-amino-3-bromophenyl)ethan-1-ol[21] (0.43 g, 2.0 mmol, 1.0 equiv) and Et_3N (0.56 mL, 4.0 mmol, 2.0 equiv) in CH_2Cl_2 (16 mL) at –20 °C. The reaction was stirred for 1 h before being warmed to room temperature. The reaction was diluted with CH_2Cl_2 and washed sequentially with $NaHCO_3$ (sat., aq.) and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 37:3) to afford the title compound as a colourless liquid (0.59 g, 89%). R_f: 0.26 (pentane:EtOAc, 37:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1H), 6.94 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.9 Hz, 9H) and 0.56 ppm (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.4, 133.0, 130.6, 129.2, 115.8, 109.4, 64.3, 38.5, 6.9 (3C) and 4.5 ppm (3C). FTIR (thin film) ν_{max}: 3468, 3361, 2953, 2910, 2875, 1620, 1503, 1090, 1036, 1006, 813, 726 and 671 cm^{-1}.

*4.5.2 (E)-1-Phenylpent-1-en-3-one (**2b**).* Cinnamaldehyde (1.70 mL, 13.5 mmol, 1.00 equiv) was added dropwise over 1 h to a solution of ethylmagnesium bromide (1.0 M in THF, 14.9 mL, 14.9 mmol, 1.10 equiv) in THF (50 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 12 h before being quenched by dropwise addition of NH_4Cl (sat. aq.). The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was the dissolved in CH_2Cl_2 (54 mL) and cooled to 0 °C. Dess–Martin Periodinane (6.30 g, 14.9 mmol, 1.10 equiv) was added and the reaction was stirred at 0 °C for 1 h before being warmed to room temperature and stirred for a further 1 h. The reaction was diluted with $NaHCO_3$ (sat. aq.) and $Na_2S_2O_3$ (sat. aq.) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 19:1) to afford the title compound as a yellow solid (0.99 g, 45%). Data were consistent with those previously reported.[22] M.P.: 33–36 ºC ($CHCl_3$). R_f: 0.22 (pentane:EtOAc, 19:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 16.1 Hz, 1H), 7.56–7.51 (m, 2H), 7.42–7.36 (m, 3H), 6.74 (d, *J* = 16.2 Hz, 1H), 2.69 (q, *J* = 7.3 Hz, 2H) and 1.17 ppm (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.0, 142.3, 134.7, 130.5, 129.0 (2C), 128.3 (2C), 126.1, 34.1 and 8.3 ppm.

*4.5.3 (E)-4-(4-Methoxyphenyl)but-3-en-2-one (**2c**).* NaOH (10% aq., 5.0 mL) was added dropwise over 30 min to a solution of 4-methoxybenzaldehyde (1.22 mL, 10.0 mmol) in acetone (7.35 mL, 100 mmol, 10.0 equiv) and H_2O (2 mL) at 0 °C. The reaction was stirred at room temperature for 24 h. HCl (1.0 M, aq.) was added until pH = 7. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concetrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a white solid (0.476 g, 27%). Data were consistent with those previously reported.[23] M.P.: 72–73 ºC ($CHCl_3$). R_f: 0.18 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 16.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 16.2 Hz, 1H), 3.84 (s, 3H) and 2.36 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.6, 161.7, 143.4, 130.1 (2C), 127.2, 125.1, 114.6 (2C), 55.5 and 27.6 ppm.

*4.5.4 (E)-4-(Benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (**2d**).* NaOH (10% aq., 0.29 mL) was added to a solution of piperonal (1.50 g, 10.0 mmol) in acetone (2.90 mL, 39.4 mmol, 3.94 equiv) and H_2O (0.14 mL) at room temperature. The reaction was stirred at room temperature for 24 h. HCl (1.0 M, aq.) was added until pH = 2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a white solid (0.81 g, 42%). Data were consistent with those previously reported. [23] M.P.: 107–110 ºC ($CHCl_3$). R_f: 0.19 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 16.1 Hz, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 16.2 Hz, 1H), 6.02 (s, 2H) and 2.35 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.5, 149.9, 148.6, 143.4, 128.9, 125.4, 125.0, 108.8, 106.6, 101.8 and 27.7 ppm.

*4.5.5 (E)-6-Phenylhex-3-en-2-one (**2h**).* 1-(Triphenylphosphoranylidene)-2-propanone (1.91 g, 6.00 mmol, 1.20 equiv) was added to a solution of 3-phenylproponal (0.66 mL, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred until consumption of starting material. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 19:1) to afford the title compound as a colourless oil (413 mg, 47%). Data were consistent with those previously reported.[24] R_f: 0.12 (pentane:EtOAc, 19:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2H), 7.25–7.14 (m, 3H), 6.82 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.09 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.83–2.76 (m, 2H), 2.60–2.51 (m, 2H) and 2.23 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.8, 147.3, 140.8, 131.8, 128.7 (2C), 128.5 (2C), 126.4, 34.5, 34.3 and 27.1 ppm.

*4.5.6 (E)-4-Cyclohexylbut-3-en-2-one (**2i**).* NaOH (10% aq., 15 mL) was added dropwise over 30 min to a solution of cyclohexanecarbaldehyde (1.82 mL, 15.0 mmol) in acetone (11.0 mL, 150 mmol, 10.0 equiv) and H_2O (3 mL) at 0 °C. The reaction was stirred at room temperature for 24 h. HCl (1.0 M, aq.) was added until pH = 7. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* before being purified by flash column

chromatography (SiO_2, pentane:EtOAc, 9:1) to afford the title compound as a colourless oil (0.94 g, 41%). Data were consistent with those previously reported.[25] R_f: 0.18 (pentane:EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (dd, *J* = 16.1, 8.1 Hz, 1H), 6.01 (dd, *J* = 16.2, 1.2 Hz, 1H), 2.23 (s, 3H), 2.19–2.09 (m, 1H), 1.81–1.71 (m, 4H), 1.71–1.64 (m, 1H), 1.36–1.23 (m, 2H) and 1.23–1.09 ppm (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.4, 153.6, 128.9, 40.8, 31.9 (2C), 27.0, 26.0 and 25.8 ppm (2C).

*4.5.7 Methyl (E)-2-oxo-4-phenylbut-3-enoate (**2j**).* A solution of KOH (842 mg, 15.0 mmol, 1.50 equiv) in MeOH (3 mL) was added dropwise over 30 min to a solution of pyruvic acid (0.695 mL, 10.0 mmol, 1.00 equiv) and benzaldehyde (1.02 mL, 10.0 mmol, 1.00 equiv) in MeOH (0.8 mL) at 0 °C. The reaction was then stirred at 40 °C for 1 h before being cooled to 0 °C and stirred overnight. The resulting precipitate was filtered, washed with MeOH (×2) and Et_2O, and dried *in vacuo*. This solid (1.29 g) was then added to a solution of acetyl chloride (4.94 mL, 69.5 mmol, 11.5 equiv) in MeOH (34.5 mL) at 0 °C and the reaction stirred for 30 min before being warmed to room temperature and stirred for a further 2 h. The reaction was then stirred at reflux overnight. The reaction was cooled to room temperature and directly concentrated *in vacuo*. The residue was dissolved in water and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (sat., aq.), H_2O and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2, pentane:EtOAc, 9:1) to afford the title compound as a yellow solid (435 mg, 22%). Data were consistent with those previously reported.[26] M.P.: 66–69 ºC ($CHCl_3$). R_f: 0.21 (pentane:EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 16.1 Hz, 1H), 7.68–7.60 (m, 2H), 7.49–7.40 (m, 3H), 7.37 (d, *J* = 16.1 Hz, 1H) and 3.94 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.5, 162.7, 148.8, 134.1, 131.8, 129.2 (2C), 129.2 (2C), 120.6 and 53.2 ppm.

4.6. Experimental procedures: Synthesis of enones 3

*4.6.1 (E)-4-(2-Aminophenyl)-4-phenylbut-3-en-2-one (**3aa**).* 2-Bromoaniline (86.0 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow solid (108 mg, 91%). Data were consistent with those previously reported.[27] M.P.: 84–85 ºC ($CHCl_3$). R_f: 0.12 (pentane:EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 3H), 7.31–7.25 (m, 2H), 7.16 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.6, 1H), 6.75 (td, *J* = 7.5, 1.2, 1H), 6.65 (dd, *J* = 8.1, 1.2, 1H), 6.41 (s, 1H), 3.65 (bs, NH_2, 2H) and 2.03 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.9, 152.5, 144.6, 138.8, 131.2, 130.2, 129.9, 129.5, 129.4 (2C), 128.8 (2C), 127.0, 118.4, 116.5 and 30.9 ppm.

*4.6.2 (E)-4-(2-Amino-5-fluoro-3-methylphenyl)-4-phenylbut-3-en-2-one (**3ba**).* 2-Bromo-4-fluoro-6-methylaniline (102 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as a yellow solid (92.6 mg, 68%). M.P.: 111–113 ºC ($CHCl_3$). R_f: 0.17 (pentane:EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 3H), 7.31–7.24 (m, 2H), 6.82 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.67 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.38 (s, 1H), 3.50 (bs, NH_2, 2H), 2.13 (s, 3H) and 2.04 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8, 155.3 (d, *J* = 236.1 Hz), 151.4 (d, *J* = 1.7 Hz), 138.7, 138.3, 130.5, 129.6, 129.3 (2C), 128.8 (2C), 127.5 (d, *J* = 7.5 Hz), 124.9 (d, *J* = 7.6Hz), 117.8 (d, *J* = 22.2 Hz), 114.7 (d, *J* = 22.4 Hz), 30.9 and 18.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –127.7 ppm. FTIR (thin film) ν_{max}: 3467, 3375, 3056, 2918, 1687, 1657, 1624, 1591, 1475, 1445, 1353, 865 and 707 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 270.1290; $C_{17}H_{16}FNO$ requires 270.1289, Δ = 0.37 ppm.

*4.6.3 (E)-4-(2-Amino-4-chlorophenyl)-4-phenylbut-3-en-2-one (**3ca**).* 2-Bromo-5-chloroaniline (103 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow oil (89.9 mg, 66%). R_f: 0.11 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.33 (m, 3H), 7.30–7.23 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.70 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 6.37 (s, 1H), 3.71 (bs, NH_2, 2H) and 2.02 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8, 151.3, 145.7, 138.3, 135.8, 132.3, 130.1, 129.7, 129.4 (2C), 128.9 (2C), 125.3, 118.4, 116.0 and 30.8 ppm. FTIR (thin film) ν_{max}: 3478, 3369, 2980, 2980, 1684, 1656, 1619, 1592, 1569, 1488, 1419 and 701 cm^{-1}. HRMS (ESI^+): Found $[M+Na]^+$ = 294.0657; $C_{16}H_{14}ClNO$ requires 294.0656, Δ = 0.34 ppm.

*4.6.4 (E)-4-(2-Amino-4-(trifluoromethyl)phenyl)-4-phenylbut-3-en-2-one (**3da**).* 2-Bromo-5-(trifluoromethyl)-aniline (120 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow oil (80.2 mg, 52%). R_f: 0.17 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 3H), 7.30–7.24 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.38 (s, 1H), 3.84 (bs, NH_2, 2H) and 2.05 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 150.6, 144.8, 137.8, 132.0 (q, *J* = 32.3 Hz), 131.4, 130.6, 129.8, 129.7, 129.2 (2C), 128.9 (2C), 125.4 (q, *J* = 273.7 Hz), 114.6 (q, *J* = 3.8 Hz), 112.8 (q, *J* = 3.9 Hz) and 30.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.0 ppm. FTIR (thin film) ν_{max}: 3480, 3371, 1687, 1662, 1626, 1591, 1436, 1337, 1246, 1168, 1122 and 701 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 306.1101; $C_{17}H_{14}F_3NO$ requires 306.1100, Δ = 0.33 ppm.

*4.6.5 (E)-4-(5-Acetyl-2-aminophenyl)-4-phenylbut-3-en-2-one (**3ea**).* 1-(4-Amino-3-bromophenyl)ethan-1-one (107 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:Et_2O, 1:4) to afford the title compound as an orange solid (110 mg, 78%). M.P.: 123–126 ºC ($CHCl_3$). R_f: 0.24 (pentane:Et_2O, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.45–7.35 (m, 3H), 7.31–7.27 (m, 2H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.39 (s, 1H), 4.06 (bs, NH_2, 2H), 2.51 (s, 3H) and 2.05 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.9, 196.4, 150.9, 149.1, 137.8, 132.1, 131.1, 130.6, 129.8, 129.2 (2C), 129.0 (2C), 127.6, 125.7, 115.3, 30.8 and 26.2 ppm. FTIR (thin film) ν_{max}: 3480, 3358, 3233, 1662, 1622, 1586, 1357, 1286, 1257, 1235 and 700 cm^{-1}. HRMS (ESI^+): Found $[M+Na]^+$ = 302.1150; $C_{18}H_{17}NO_2$ requires 302.1152, Δ = 0.66 ppm.

*4.6.6 Methyl (E)-3-amino-4-(3-oxo-1-phenylbut-1-en-1-yl)benzoate (**3fa**).* Methyl 3-amino-4-bromobenzoate (115 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as a yellow oil (68.5 mg, 46%). R_f: 0.21 (pentane:EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5H), 7.22–7.16 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.32 (s, 1H), 3.80 (s, 3H), 3.71 (bs, NH_2, 2H) and 1.97 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 167.0, 151.0, 144.6, 137.9, 131.5, 131.1, 131.0, 130.5, 129.7, 129.3 (2C), 128.9 (2C), 119.2, 117.3, 52.3 and 30.9 ppm. FTIR (thin film) ν_{max}: 3474, 3372, 1718, 1688, 1661, 1623, 1591, 1569, 1438,

1297, 1237, 765 and 702 cm^{-1}. HRMS (ESI^+): Found $[M+Na]^+$ = 318.1096; $C_{18}H_{17}NO_3$ requires 318.1101, Δ = 1.57 ppm.

*4.6.7 (E)-4-Amino-3-(3-oxo-1-phenylbut-1-en-1-yl)benzonitrile (**3ga**)*. 4-Amino-3-bromobenzonitrile (98.5 mg, 0.500 mmol) and (*E*)-4-phenybut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 13:7) to afford the title compound as a yellow oil (121 mg, 92%). R_f: 0.17 (pentane:EtOAc, 13:7). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.37 (m, 4H), 7.36 (dd, *J* = 2.0, 0.4 Hz, 1H), 7.28–7.24 (m, 2H), 6.63 (dd, *J* = 8.4, 0.4 Hz, 1H), 6.37 (s, 1H), 4.14 (bs, NH_2, 2H), and 2.05 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.6, 149.4, 148.3, 137.4, 135.2, 133.8, 130.9, 130.1, 129.20 (2C), 129.15 (2C), 126.6, 119.7, 116.1, 100.6 and 30.9 ppm. FTIR (thin film) ν_{max}: 3480, 3364, 3229, 2217, 1625, 1603 and 1501 cm^{-1}. HRMS (ESI^+): Found $[M-H]^-$ = 261.1028; $C_{17}H_{14}NO_2$ requires 261.1033, Δ = 1.91 ppm.

*4.6.8 (E)-4-(2-Amino-5-(2-((triethylsilyl)oxy)ethyl)phenyl)-4-phenylbut-3-en-2-one (**3ha**)*. 2-Bromo-4-(2-((triethylsilyl)oxy)ethyl)aniline (165 mg, 0.500 mmol and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a red oil (133 mg, 67%). R_f: 0.18 (pentane:EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.33 (m, 3H), 7.31–7.25 (m, 2H), 7.01 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.38 (s, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 3.52 (bs, NH_2, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.02 (s, 3H), 0.92 (t, *J* = 7.9 Hz, 9H) and 0.56 ppm (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.2, 152.9, 143.0, 139.0, 131.8, 131.1, 130.0, 129.7, 129.6 (2C), 129.3, 128.9 (2C), 127.2, 116.8, 64.7, 38.9, 31.0, 7.1 (3C) and 4.7 ppm (3C). FTIR (thin film) ν_{max}: 3466, 3368, 2953, 2912, 2875, 1656, 1621, 1589, 1500, 1238, 1094, 1014, 742, 726 and 700 cm^{-1}. HRMS (ESI^+): Found $[M+Na]^+$ = 418.2176; $C_{24}H_{33}NO_2Si$ requires 418.2173, Δ = 0.72 ppm.

*4.6.9 (E)-1-(2-Aminophenyl)-1-phenylpent-1-en-3-one (**3ab**)*. 2-Bromoaniline (86.0 mg, 0.500 mmol) and (*E*)-1-phenylpent-1-en-3-one (200 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow oil (68.1 mg, 54%). R_f: 0.16 (pentane:EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.31 (m, 3H), 7.31–7.23 (m, 2H), 7.15 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.75 (td, *J* = 7.5, 1.2 Hz, 1H), 6.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.42 (s, 1H), 3.63 (s, NH_2, 2H), 2.38 (q, *J* = 7.3 Hz, 2H) and 1.03 ppm (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.8, 151.8, 144.8, 138.9, 131.2, 130.2, 129.4 (2C), 129.4, 129.0, 128.8 (2C), 127.4, 118.5, 116.6, 37.0 and 8.7 ppm. FTIR (thin film) ν_{max}: 3370, 2965, 2934, 1686, 1617, 1491, 1452, 1306, 1118, 750 and 700 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 252.1383; $C_{17}H_{17}NO$ requires 252.1383, Δ = 0.00 ppm.

*4.6.10 (E)-4-(2-Aminophenyl)-4-(4-methoxyphenyl)but-3-en-2-one (**3ac**)*. 2-Bromoaniline (86.0 mg, 0.500 mmol) and (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (220 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:Et_2O, 1:1) to afford the title compound as a yellow oil (87.6 mg, 65%). R_f: 0.11 (pentane:Et_2O, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.7 Hz, 2H), 7.16 (td, *J* = 7.7, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.75 (td, *J* = 7.5, 1.2 Hz, 1H), 6.64 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.31 (s, 1H), 3.83 (s, 3H), 3.61 (bs, NH_2, 2H) and 2.05 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.1, 160.8, 152.4, 144.7, 131.2, 131.2 (2C), 130.7, 130.2, 128.8, 127.3, 118.4, 116.4, 114.1 (2C), 55.5 and 30.9 ppm. FTIR (thin film) ν_{max}: 3468, 3364, 2360, 2342, 1655, 1605, 1509, 1490, 1453, 1353, 1294, 1250, 1179, 1149, 1029, 840 and 752 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 268.1339; $C_{17}H_{17}NO_2$ requires 268.1338, Δ = 0.37 ppm.

*4.6.11 (E)-4-(2-Aminophenyl)-4-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (**3ad**)*. (*E*)- 4-phenylbut-3-en-2-one (86.0 mg, 0.500 mmol) and (*E*)-4-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (238 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as a yellow oil (92.1 mg, 65%). R_f: 0.20 (pentane:EtOAc, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.85–6.77 (m, 2H), 6.77–6.71 (m, 2H), 6.64 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.31 (s, 1H), 5.99 (s, 2H), 3.66 (bs, NH_2, 2H) and 2.08 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.9, 152.0, 148.9, 148.1, 144.7, 132.5, 131.1, 130.2, 129.3, 127.0, 124.0, 118.4, 116.4, 109.6, 108.5, 101.6 and 30.8 ppm. FTIR (thin film) ν_{max}: 3469, 3366, 2897, 1656, 1619, 1579, 1487, 1452, 1439, 1356, 1328, 1038, 932 and 753 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 282.1126; $C_{17}H_{15}NO_3$ requires 282.1125, Δ = 0.33 ppm.

4.7. Experimental procedures: Synthesis of quinolines 4

*4.7.1 2-Methyl-4-phenylquinoline (**4aa**)*. **From enone 3aa**: (*E*)-4-(2-Aminophenyl)-4-phenylbut-3-en-2-one (35.5 mg, 0.150 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow oil (28.7 mg, 87%). **One-pot procedure**: 2-Bromoaniline (86.0 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP3**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 5:1) to afford the title compound as a yellow oil (97.6 mg, 89%). Data were consistent with those previously reported.[28] R_f: 0.28 (pentane:EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 7.86 (ddd, *J* = 8.5, 1.5, 0.6 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.55–7.46 (m, 5H), 7.43 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.24 (s, 1H) and 2.78 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 148.6, 148.5, 138.3, 129.6 (2C), 129.4, 129.1, 128.6 (2C), 128.4, 125.8, 125.8, 125.2, 122.4 and 25.5 ppm.

*4.7.2 6-Fluoro-2,8-dimethyl-4-phenylquinoline (**4ba**)*. (*E*)-4-(2-Amino-5-fluoro-3-methylphenyl)-4-phenylbut-3-en-2-one (40.4 mg, 0.150 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 97:3) to afford the title compound as a white solid (35.7 mg, 94%). M.P.: 58–61 ºC ($CHCl_3$). R_f: 0.21 (pentane:EtOAc, 97:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.44 (m, 5H), 7.34–7.27 (m, 2H), 7.24 (s, 1H), 2.85 (s, 3H) and 2.77 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 244.8 Hz), 156.5, 148.2 (d, *J* = 5.6 Hz), 144.7, 140.2 (d, *J* = 9.1 Hz), 138.4, 129.5 (2C), 128.7 (2C), 128.5, 125.8 (d, *J* = 9.6 Hz), 122.7, 119.3 (d, *J* = 25.4 Hz), 106.8 (d, *J* = 22.5 Hz), 25.6 and 18.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –115.0 ppm. FTIR (thin film) ν_{max}: 3058, 2924, 2854, 1763, 1622, 1569, 1487, 1124, 863, 764 and 702 cm^{-1}. HRMS (ESI^+): Found $[M+H]^+$ = 252.1183; $C_{17}H_{14}FN$ requires 252.1183, Δ = 0.00 ppm.

*4.7.3 7-Chloro-2-methyl-4-phenylquinoline (**4ca**)*. (*E*)-4-(2-Amino-4-chlorophenyl)-4-phenylbut-3-en-2one (46.6 mg, 0.170

mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 17:3) to afford the title compound as a yellow solid (35.1 mg, 81%). M.P.: 70–71 ºC ($CHCl_3$). R_f: 0.18 (pentane:EtOAc, 17:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 2.1 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.55–7.43 (m, 5H), 7.36 (dd, J = 8.9, 2.2 Hz, 1H), 7.22 (s, 1H) and 2.76 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 149.0, 148.6, 137.7, 135.3, 129.5 (2C), 128.8 (2C), 128.7, 128.1, 127.2, 126.7, 123.6, 122.4 and 25.5 ppm. FTIR (thin film) ν_{max}: 3057, 2920, 1593, 1488, 1403, 1180, 1072, 930, 881, 824, 774 and 701 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 254.0733; $C_{16}H_{12}ClN$ requires 254.0731, Δ = 0.79 ppm.

*4.7.4 2-Methyl-4-phenyl-7-(trifluoromethyl)quinoline (**4da**).* (*E*)-4-(2-Amino-4-(trifluoromethyl)phenyl)-4-phenylbut-3-en-2-one (38.9 mg, 0.127 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:Et_2O, 4:1) to afford the title compound as a yellow oil (29.1 mg, 79%). R_f: 0.18 (pentane:Et_2O, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42–8.38 (m, 1H), 7.98 (dt, *J* = 8.8, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.57– 7.45 (m, 5H), 7.34 (s, 1H) and 2.80 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.3, 148.7, 147.6, 137.5, 131.2 (q, *J* = 32.5 Hz), 129.6 (2C), 128.9 (3C), 127.1, 127.0 (q, *J* = 4.4 Hz), 126.9, 124.2 (q, *J* = 272.5 Hz), 124.0, 121.4 (q, *J* = 3.2 Hz) and 25.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7 ppm. FTIR (thin film) ν_{max}: 1595, 1373, 1340, 1298, 1185, 1156, 1126, 1065 and 702 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 288.0993; $C_{17}H_{12}F_3N$ requires 288.0995, Δ = 0.69 ppm.

*4.7.5 1-(2-Methyl-4-phenylquinolin-6-yl)ethan-1-one (**4ea**).* **From enone 3ea**: (*E*)-4-(5-Acetyl-2-aminophenyl)-4-phenylbut-3-en-2-one (41.2 mg, 0.147 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as a white solid (36.7 mg, 95%). **One-pot procedure**: 1-(4-Amino-3-bromophenyl)ethan-1-one (107 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP3**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 5:1) to afford the title compound as a white solid (100 mg, 76%). M.P.: 133–136 ºC ($CHCl_3$). R_f: 0.17 (pentane:EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 1.9 Hz, 1H), 8.23 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.58–7.48 (m, 5H), 7.30 (s, 1H), 2.80 (s, 3H) and 2.59 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 161.3, 150.5, 150.1, 137.5, 134.3, 129.7, 129.6, 129.0 (2C), 128.9 (2C), 128.0, 127.8, 124.4, 123.2, 26.8 and 25.7 ppm. FTIR (thin film) ν_{max}: 2359, 2342, 1681, 1608, 1592, 1257, 842, 762 and 703 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 262.1226; $C_{18}H_{15}NO$ requires 262.1226, Δ = 0.00 ppm.

*4.7.6 Methyl 2-methyl-4-phenylquinoline-7-carboxylate (**4fa**).* **From enone 3fa**: Methyl (*E*)-3-amino-4-(3-oxo-1-phenylbut-1-en-1-yl)benzoate (54.6 mg, 0.184 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 3:1) to afford the title compound as a yellow oil (36.9 mg, 72%). **One-pot procedure**: Methyl 3-amino-4-bromobenzoate (115 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP3**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 5:1) to afford the title compound as a yellow oil (109 mg, 78%). R_f: 0.19 (pentane:EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 1.7 Hz, 1H), 8.00 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.56–7.44 (m, 5H), 7.30 (s, 1H), 3.97 (s, 3H) and 2.78 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0, 159.7, 148.4, 147.9, 137.6, 131.7, 130.7, 129.5 (2C), 128.8 (2C), 128.7, 127.7, 126.1, 125.3, 124.0, 52.5 and 25.5 ppm. FTIR (thin film) ν_{max}: 2951, 1720, 1593, 1413, 1270, 1235, 1093, 759, 745 and 701 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 278.1175; $C_{18}H_{15}NO_2$ requires 278.1176, Δ = 0.36 ppm.

*4.7.7 2-Methyl-4-phenylquinoline-6-carbonitrile (**4ga**).* **From enone 4ga**: (*E*)-4-Amino-3-(3-oxo-1-phenylbut-1-en-1-yl)benzonitrile (39.3 mg, 0.150 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as a white solid (36.1 mg, 98%). **One-pot procedure**: 4-Amino-3-bromobenzonitrile (98.5 mg, 0.500 mmol) and (*E*)-4-phenylbut-3-en-2-one (183 mg, 1.25 mmol, 2.50 equiv) were subjected to **GP3**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 5:1) to afford the title compound as a white solid (102 mg, 83%). M.P.: 154–157 ºC ($CHCl_3$). R_f: 0.29 (pentane:EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 1.8 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.83 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.60–7.50 (m, 3H), 7.49–7.43 (m, 2H), 7.36 (s, 1H) and 2.82 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2, 149.6, 149.1, 136.7, 132.5, 130.6, 130.2, 129.5 (2C), 129.2, 129.1 (2C), 124.9, 123.8, 119.1, 109.5 and 25.8 ppm. FTIR (thin film) ν_{max}: 2921, 2851, 2227, 1726, 1592, 839, 763 and 703 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 245.1073; $C_{17}H_{12}N_2$ requires 245.1073, Δ = 0.00 ppm.

*4.7.8 2-Methyl-4-phenyl-6-(2-((triethylsilyl)oxy)ethyl)quinoline (**4ha**).* (*E*)-4-(2-Amino-5-(2-((triethylsilyl)oxy)ethyl)phenyl)-4-phenylbut-3-en-2-one (54.0 mg, 0.150 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 17:3) to afford the title compound as an orange oil (53.7 mg, 94%). R_f: 0.20 (pentane:EtOAc, 17:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.54–7.45 (m, 5H), 7.19 (s, 1H), 3.82 (t, *J* = 6.9 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.75 (s, 3H), 0.86 (t, *J* = 7.9 Hz, 9H) and 0.50 ppm (t, *J* = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 148.2, 147.4, 138.4, 137.0, 131.3, 129.6 (2C), 128.8, 128.6 (2C), 128.3, 125.2, 125.0, 122.4, 64.0, 39.7, 25.4, 6.8 (3C) and 4.4 ppm (3C). FTIR (thin film) ν_{max}: 2953, 2875, 1592, 1098, 1015, 834, 745 and 702 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 378.2245; $C_{24}H_{31}NOSi$ requires 378.2248, Δ = 0.79 ppm.

*4.7.9 2-Ethyl-4-phenylquinoline (**4ab**).* (*E*)-1-(2-Aminophenyl)-1-phenylpent-1-en-3-one (33.4 mg, 0.132 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 9:1) to afford the title compound as a yellow oil (22.9 mg, 74%). R_f: 0.22 (pentane:EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.87 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 8.6, 1.4 Hz, 1H), 7.55–7.46 (m, 5H), 7.43 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.26 (s, 1H), 3.05 (q, *J* = 7.6 Hz, 2H) and 1.44 ppm (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.6, 148.8, 148.5, 138.5, 129.7 (2C), 129.3 (2C), 128.6 (2C), 128.4, 125.8, 125.8, 125.4, 121.2, 32.5 and 14.2 ppm. FTIR (thin film) ν_{max}: 3059, 3033, 2967, 2931, 2872, 1593, 1557, 1490, 833, 763 and 701 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 234.1277; $C_{17}H_{15}N$ requires 234.1277, Δ = 0.00 ppm.

*4.7.10 4-(4-Methoxyphenyl)-2-methylquinoline (**4ac**).* (*E*)-4-(2-Aminophenyl)-4-(4-methoxyphenyl)but-3-en-2-one (41.4 mg, 0.154 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 4:1) to afford the title compound as a yellow oil (35.3 mg, 91%). Data were consistent with those previously reported.[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 8.5, 1.2, 0.6 Hz, 1H), 7.90 (ddd, *J* = 8.4, 1.5, 0.7 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.46–7.39 (m, 3H), 7.20 (s, 1H), 7.07–7.01 (m, 2H), 3.88 (s, 3H) and 2.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8, 158.6, 148.5, 148.3, 130.8 (2C), 130.5, 129.3, 129.0, 125.8, 125.7, 125.3, 122.3, 114.1 (2C), 55.5 and 25.4 ppm.

*4.7.11 4-(Benzo[d][1,3]dioxol-5-yl)-2-methylquinoline (**4ad**).* (*E*)-4-(2-Aminophenyl)-4-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (56.9 mg, 0.202 mmol) was subjected to **GP2**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 7:3) to afford the title compound as an off-white solid (40.9 mg, 76%). M.P.: 94–97 ºC ($CHCl_3$). R_f: 0.21 (pentane:EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.20 (s, 1H), 7.00–6.93 (m, 3H), 6.06 (s, 2H), 2.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.61, 148.57, 148.2, 147.9 (2C), 132.1, 129.4, 129.2, 125.8, 125.7, 125.3, 123.4, 122.3, 110.1, 108.6, 101.5 and 25.5 ppm. FTIR (thin film) ν_{max}: 1593, 1501, 1485, 1439, 1409, 1242, 1225, 1037, 932, 878, 806 and 765 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 264.1019; $C_{17}H_{13}NO_2$ requires 264.1019, Δ = 0.00 ppm.

*4.7.12 2-Methyl-4-phenethylquinoline (**4ah**).* 2-Bromoaniline (86.0 mg, 0.500 mmol) and (*E*)-6-phenylhex-3-en-2-one (220 mg, 1.26 mmol, 2.53 equiv) were subjected to **GP1**. The reaction was purified by flash column chromatography (SiO_2, pentane:EtOAc, 9:1→7:3) and preperative thin layer chromatography (SiO_2, glass plate, 2000 µm, 20 × 20 cm, cyclohexane:EtOAc, 8:2) to afford the title compound as a yellow oil (100 mg, 81%). R_f: 0.14 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.99 (m, 2H), 7.68 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.38–7.28 (m, 2H), 7.28–7.20 (m, 3H), 7.09 (s, 1H), 3.38–3.29 (m, 2H), 3.12–3.01 (m, 2H) and 2.69 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 148.3, 147.4, 141.3, 129.6, 129.2, 128.7 (2C), 128.5 (2C), 126.5, 125.8, 125.7, 123.3, 121.9, 36.4, 34.3 and 25.5 ppm. FTIR (thin film) ν_{max}: 3026, 2924, 2361, 1601, 749 and 699 cm^{-1}. HRMS (ESI$^+$): Found $[M+H]^+$ = 248.1435; $C_{18}H_{17}N$ requires 248.1434, Δ = 0.40 ppm.

*4.7.13 4-Cyclohexyl-2-methylquinoline (**4ai**).* 2-Bromoaniline (85.2 mg, 0.495 mmol) and (*E*)-4-Cyclohexyl-3-buten-2-one (190 mg, 1.25 mmol, 2.53 equiv) were subjected to **GP1** with a modified work up. The crude reaction mixture was diluted in Et_2O and washed with HCl (1.0 M, aq.). K_2CO_3 was added to the aqueous phase until pH = 9 and the aqueous phase was then extracted with CH_2Cl_2 (×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2 15–40 µm, pentane:EtOAc, 19:1→4:1) to afford the title compound as an orange oil (43.4 mg, 39%). Data were consistent with those previously reported.[30] R_f: 0.23 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 9.0 Hz, 2H), 7.67–7.61 (m, 1H), 7.51–7.45 (m, 1H), 7.16 (s, 1H), 3.37–3.20 (m, 1H), 2.72 (s, 3H), 2.06–1.78 (m, 5H), 1.62–1.43 (m, 4H) and 1.42–1.26 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.9, 153.5, 148.3, 129.7, 128.9, 125.4, 125.3, 123.0, 118.4, 38.9, 33.7 (2C), 27.1 (2C), 26.5 and 25.6 ppm.

*4.7.14 Methyl 4-phenylquinoline-2-carboxylate (**4aj**).* 2-Bromoaniline (86.5 mg, 0.503 mmol) and methyl (*E*)-2-oxo-4-phenylbut-3-enoate (239 mg, 1.26 mmol, 2.50 equiv) were subjected to **GP1** with a modified work up. The crude reaction mixture was diluted in Et_2O and washed with HCl (1.0 M, aq., ×3). The organic layer was dried over K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* before being purified by flash column chromatography (SiO_2 15–40 µm, pentane:EtOAc, 4:1) to afford the title compound as a pale crystalline solid (68.4 mg, 52%). Data were consistent with those previously reported.[31] M.P.: 92–99 °C (CH_2Cl_2). R_f: 0.20 (pentane:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.16 (s, 1H), 7.98 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.79 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.58–7.48 (m, 5H) and 4.09 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2, 150.1, 148.3, 147.6, 137.6, 131.2, 130.2, 129.7 (2C), 128.9, 128.81 (2C), 128.79, 128.0, 125.9, 121.4 and 53.4 ppm.

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Supplementary Material

Supplementary data to this article can be found online at (please insert link here).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: