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Visible light-mediated synthesis of quinazolines from 1,2-dihydroquinazoline 3-oxides

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ABSTRACT

A series of quinazolines were synthesized in good to excellent yields by exposing 1,2-dihydroquinazoline 3-oxides to visible light in acetonitrile without the presence of any external sensitizers. The only exception was the 2-(*p*-nitrophenyl)-substituted substrate, which is insensitive to visible light. This compound could be first oxidized to quinazoline 3-oxide via ruthenium-catalyzed visible light photoredox catalysis, and followed by treating with PCl_3 to yield the corresponding quinazoline. The mechanisms of these visible light-mediated reactions were proposed.

1. Introduction

In pursuit of new reactions and chemoselective transformations under milder and more sustainable conditions is a continuing goal for synthetic organic chemists. Since 'light' is an abundant and renewable energy source for performing green chemical reactions, the photochemistry and photocatalysis have found broad utility in organic synthesis in the past century.[1] Unfortunately, the lack of visible light absorption by many organic molecules has limited the application of visible light-mediated reactions in organic synthesis. While this barrier can be overcome via utilizing visible light absorbing photocatalysts[2,3] to sensitize organic molecules and subsequently carry out required photochemical reactions, the development of new visible light-sensitive molecular scaffolds remains desirable, so the photochemical reactions can be performed under sensitizer-free conditions to fulfill the requirements of sustainable chemistry. In this respect, we recently reported that molecules bearing an *o*-nitrobenzylamino scaffold are susceptible to photoinduced intramolecular electron transfer from the electron donor amine to the electron acceptor *o*-nitrophenyl group to generate indazoles as the major products upon visible light irradiation.[4] In our continuing effort to explore new light-sensitive molecular scaffolds for visible light-mediated organic synthesis, here we describe another visible light-sensitive structure, that is, 1,2-dihydroquinazoline 3-oxide. Upon visible light irradiation, it can be converted to the quinazoline, which is a widely recognized moiety in organic syntheses[5] and medicinal applications.[6] While recent quinazoline synthetic strategies primarily involve either microwave irradiation[5b] or UV irradiation[5c] of the corresponding 2-aminoarylalkanone *O*-phenyl oximes, utilization of visible light irradiation of the 1,2-dihydroquinazoline 3-oxide precursors for the preparation of quinazoline derivatives has never been reported. In this paper, we investigate the scope and limitation of this visible light-mediated photochemical reaction. Further, a plausible mechanism for the formation of quinazolines is proposed.

2. Results and discussion

The starting material 1,2-dihydroquinazoline 3-oxides (**1**) were readily prepared in two steps as described in the literature (Scheme 1).[7] First, the 2′-aminoacetophenone (**2**) was converted to the corresponding oxime **3** by reacting with hydroxylamine hydrochloride under basic conditions in ethanol at 60 °C. Second, the condensation of the oxime **3** with various aryl aldehydes in the presence of a catalytic amount of *p*-TsOH in ethanol furnished 1,2-dihydroquinazoline 3-oxides (**1**). The molecular structures of **1** were verified by ^1H and ^{13}C NMR spectroscopy. In all proton NMR spectra, a characteristic singlet absorption peak appearing at chemical shift of 6.07–6.53 ppm was observed and assigned to the C-2 hydrogen of the dihydroquinazoline. The structure of **1d** (Ar=*p*-bromophenyl)[8] was further confirmed by single-crystal X-ray diffraction analysis as shown in Fig. 1, which clearly reveals a 1,2-dihydroquinazoline moiety along with an oxide group substituted at the *N*-3 position. This observation indicates that the

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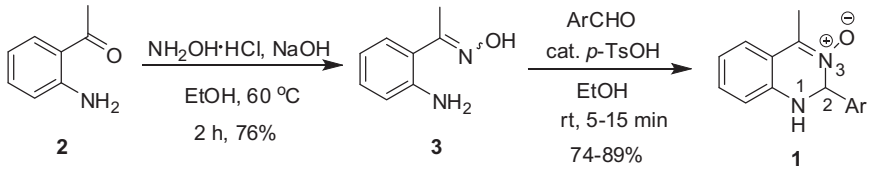


Scheme 1. Preparation of 1,2-dihydroquinazoline 3-oxides **1**.

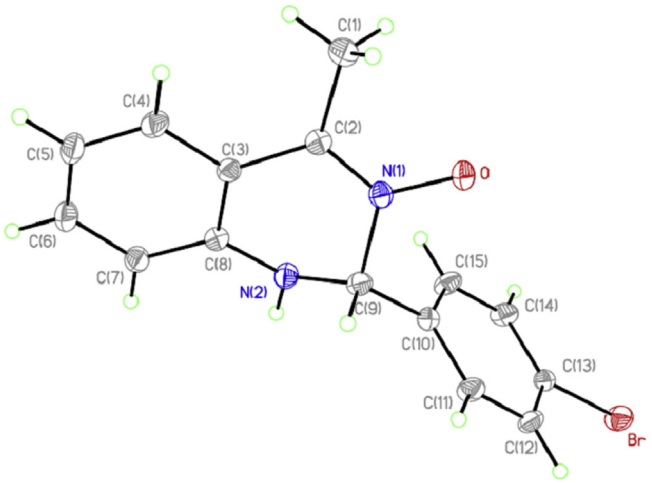


Fig. 1. X-ray crystal structure of **1d**.

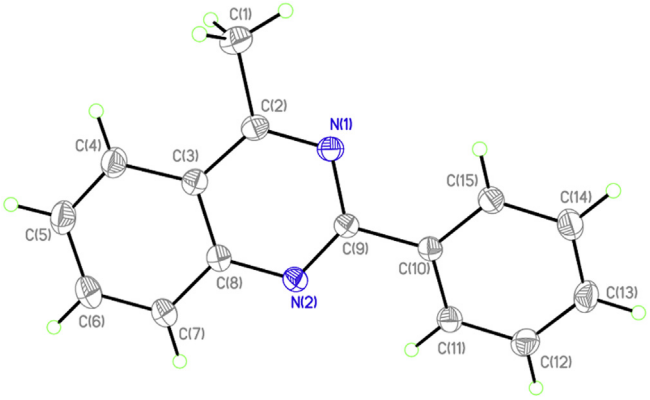


Fig. 2. X-ray crystal structure of **4a**.

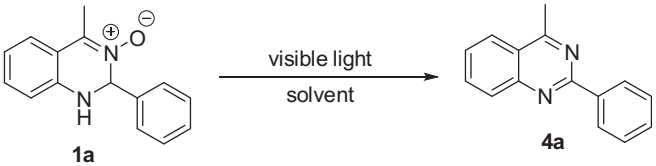
ring-closed iminium oxide **1** is thermodynamically more stable than the corresponding ring-opened oxime **6** (Scheme 2).

With the compounds **1** in hand, their photochemical properties were then investigated. The prepared 1,2-dihydroquinazoline 3-oxides (**1**) were found to be sensitive to visible light. For instance, when exposed to visible light irradiation (a 23 W fluorescence light bulb) in the absence of any external sensitizers under aerobic conditions, compound **1a** (Ar=phenyl) was converted to the corresponding quinazoline **4a**. The structure of **4a** was confirmed by single-crystal X-ray diffraction analysis as presented in Fig. 2.[8]

Table 1 summarizes the optimization of the photochemical reaction of **1a**. Among the various solvent systems tested, the irradiation of **1a** in acetonitrile (entry 10) appears to have the highest yield with irradiation time of approximate 16 h under the concentration of 5 mM. Thus, acetonitrile was employed subsequently as the solvent for further reactions.

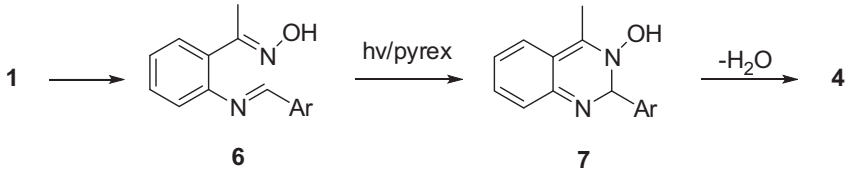
After the optimization of reaction conditions, we then focused our attention on the scope and the generality of the photochemical reaction as listed in Table 2. A series of reactions were examined with different substituents on either *ortho* or *para* position of the aromatic ring of **1**. When the substrates **1a**–**j** with either an electron-donating group, such as isopropyl and OMe or an electron-withdrawing group, such as F, CN, and CF_3 substituted at the C-2 position were exposed to visible light irradiation without any external sensitizers under aerobic conditions in dry CH_3CN, the photogenerated products were isolated and characterized to be the corresponding quinazolines **4a**–**j**, respectively, with the yields in the range of 76–94%. The only exception was the 2-(*p*-nitrophenyl)-substituted **1k**, which gave a negligible quantity of the product even after irradiation for 48 h.

Table 1
Optimization of photochemical reaction conditions



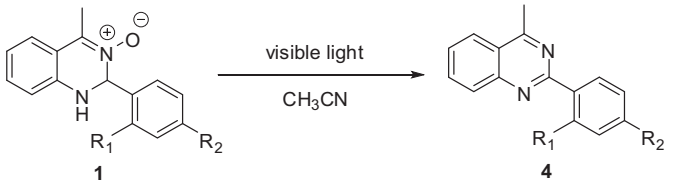
Entry	Solvent	Concentration (mM)	Time (h)	Yield (%)[a]
1	Benzene	10	28	85
2	Toluene	10	42	79
3	CH_2Cl_2	10	36	81
4	THF	10	26	89
5	Acetone	10	28	86
6	Ethanol	10	72	73
7	DMF	10	24	83
8	CH_3CN	10	24	89
9	CH_3CN	1	8	87
10[b]	**CH_3CN**	**5**	**16**	**90**
11	CH_3CN	20	48	89
12	CH_3CN	50	72	75

[a] Isolated yield.
[b] The best reaction conditions found.



Scheme 2. Proposed mechanism for the UV-mediated formation of quinazolines **4**.

Table 2
Scope of photochemical reaction of **1**



1 **4**

Compound	R_1	R_2	Time (h)	Product[a]	Yield (%)[b]
1a	H	H	16	**4a**	90
1b	H	$CH(CH_3)_2$	18	**4b**	92
1c	H	OCH_3	16	**4c**	94
1d	H	Br	18	**4d**	76
1e	Br	H	16	**4e**	83
1f	Cl	H	16	**4f**	89
1g	Cl	Cl	18	**4g**	85
1h	H	F	16	**4h**	86
1i	H	CN	18	**4i**	92
1j	H	CF_3	18	**4j**	90
1k	H	NO_2	48	**4k**	Trace

[a] Reactions were conducted with 5 mM (100 mL) reactant in a 250 mL flask.
[b] Isolated yield.

Previous studies have demonstrated that the quinazolines **4** can also be prepared by UV irradiation of the 1,2-dihydroquinazoline 3-oxides **1** through Pyrex glass with a 400 W medium pressure-mercury lamp.[5c] The reaction was proposed to proceed with the initial formation of the cyclic compound **7** from the ring-opened oxime **6** via a concerted six-electron electrocyclic ring closure mechanism, following by loss of water to give the quinazolines **4** (Scheme 2).

In our case, however, the intensity of visible light is not strong enough to initiate the electrocyclic reaction, and thus the dehydration reaction may probably undergo a different photochemical mechanism. Fig. 3 shows the UV–vis spectra of 1,2-dihydroquinazoline 3-oxide **1a** in acetonitrile. It has UV absorption at 241, 265, 300, and 359 nm (log ε=4.23, 3.99, 3.84, and 3.62) and does not have absorption in the visible light region. In light of the information that the amine is a well-known electron donor and the iminium oxide is a good electron acceptor, we speculate that this visible light-mediated photochemical reaction of 1,2-dihydroquinazoline 3-oxide may, similar to that of the *o*-nitrobenzylamino-containing compounds,[4] involve photoinduced electron transfer (PET) from the amine nitrogen atom to the nearby iminium oxide group.

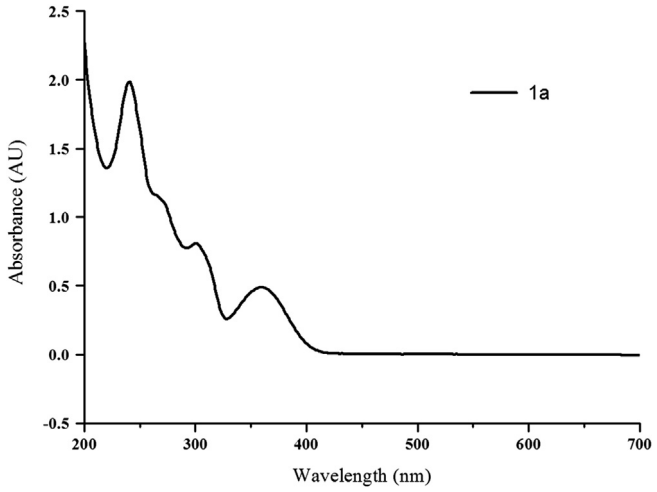


Fig. 3. UV–vis spectra of **1a** (1.18×10^{-4} M) in CH_3CN.

To gain more insights into the mechanism for this visible light-mediated dehydration, the 1,2-dihydroquinazoline 3-oxide **1a** was subjected to the EPR measurements. Fig. 4 depicts the EPR spectra of **1a** recorded in degassed CH_3CN solution at different irradiation times. After irradiation with visible light at room temperature for 20 min, strong splitting EPR signals were clearly observed at around 3460–3510 G. Prolonged irradiation increased the intensity of the signals but did not alter the absorption shape. To provide further mechanistic details, the photoreaction of **1a** was also performed in the presence of a radical scavenger ((2,2,6,6-tetramethylpiperidin-1-yl)oxy, TEMPO).[9] Fig. 5 shows the partial ^{1}H NMR spectra of **1a** in $CDCl_3$ after visible light irradiation for 1 h in the presence of (a) 0 (b) 0.1 (c) 0.5 (d) 1.0 equiv of TEMPO. Upon increasing the concentration of TEMPO, a progressive decrease in the product yields on the basis of the integration of the methyl hydrogens of **1a** was clearly observed. These results provide strong evidence to support that the photochemical reaction of **1a** involves, at least in part, a radical species as a transient intermediate.

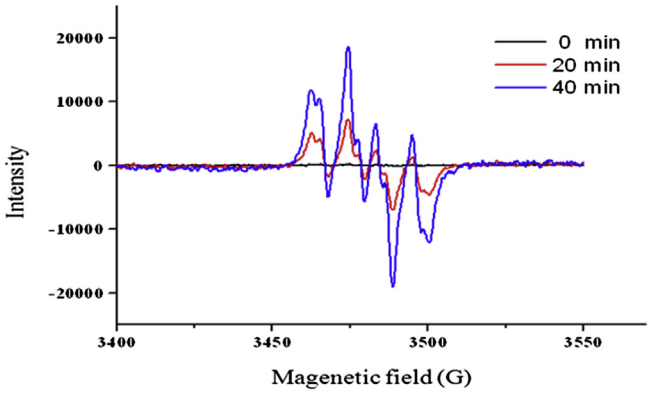


Fig. 4. EPR spectra of **1a** recorded in degassed CH_3CN solution at room temperature after being exposed to visible light, 0–40 min, in increments of 20 min.

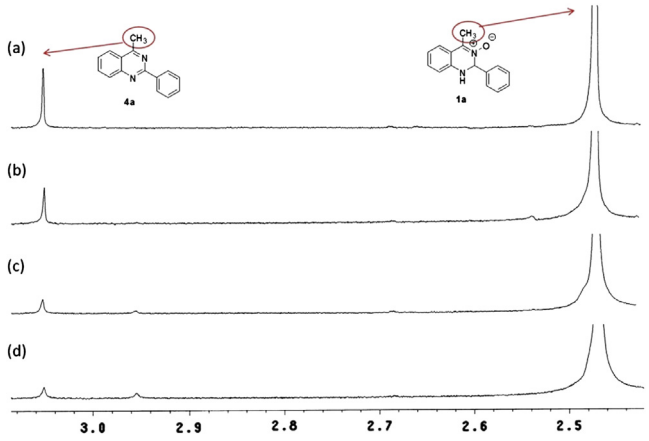
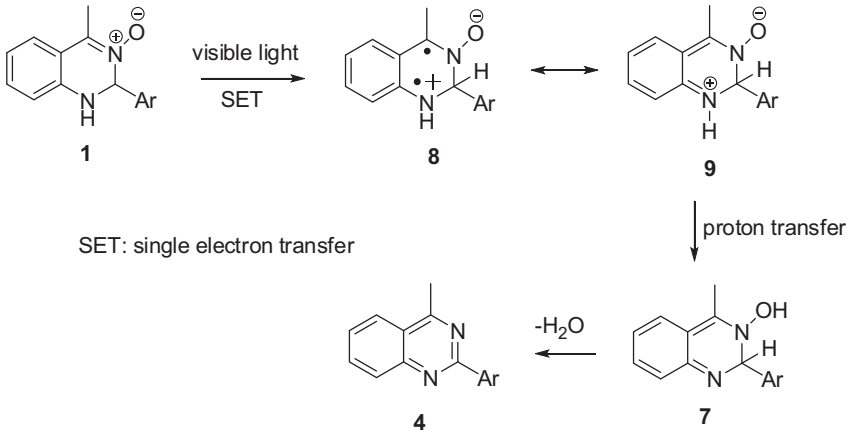


Fig. 5. Partial ^{1}H NMR spectra of **1a** (3.5×10^{-3} M in $CDCl_3$) after visible light irradiation for 1 h in the presence of (a) 0 (b) 0.1 (c) 0.5 (d) 1.0 equiv of TEMPO.

On the basis of the EPR and radical trapping experimental results, a plausible mechanism for the formation of the quinazolines **4** from **1** via visible light irradiation is proposed in Scheme 3. Presumably, the photoreaction involves a visible light-mediated single electron transfer (SET) from the amine nitrogen atom to the nearby iminium oxide group of **1** to generate the biradical species **8**, which is responsible for the observed EPR signals. The biradical **8** then undergoes electron recombination to give the charge separated



Scheme 3. Proposed mechanism for the visible light-mediated formation of quinazolines **4**.

transient species **9**. The subsequent proton transfer from the iminium hydrogen to nitrogen oxide generates the neutral hydroxylamine **7**. Final dehydration of **7** affords the aromatized quinazoline **4**. Essentially, the key step of this mechanism is the formation of the zwitterionic biradical species **8**, generated by photoinduced intramolecular electron transfer between the electron-donating amine and electron-accepting iminium oxide upon visible light irradiation.

As mentioned earlier, only a trace amount of product was obtained when the 2-(*p*-nitrophenyl)-substituted **1k** was exposed to visible light irradiation. We originally speculated that the light-insensitive properties of **1k** might result from the presence of the electron-withdrawing nitro group, which renders the amine nitrogen less susceptible to electron transfer upon irradiation. However, this speculation is soon abolished since it cannot account for the successful conversion of **1i** (Ar=cyanophenyl) and **1j** (Ar=trifluoromethylphenyl) to the corresponding **4i** and **4j** under the same reaction conditions. Although the reason why **1k** is insensitive to visible light merit further investigation, it can be oxidized to the corresponding quinazoline 3-oxide **5** in the presence of 0.5 mol % $Ru(bpy)_3Cl_2$ as a photocatalyst via visible light photoredox catalysis[3] in acetonitrile under aerobic conditions. Compound **5** can be further reduced to the quinazoline **4k** by reacting with phosphorus trichloride (PCl_3) in methylene chloride at room temperature (Scheme 4).[10] Fig. 6 shows the X-ray crystal structure of **5**,[8] in which an *N*-oxide moiety was clearly retained. Scheme 5 depicts the proposed visible light-mediated catalytic cycle catalyzed by the ruthenium complex for the formation of **5**. First, the $Ru(bpy)_3^{2+}$ is excited by visible light to its excited state. It then accepts one electron from the amine donor **1** to yield the $Ru(bpy)_3^{+}$ and the cation radical **10**. The subsequent electron transfer from $Ru(bpy)_3^{+}$ to the molecular oxygen yields the superoxide anion radical, along with the regenerated ground-state photocatalyst $Ru(bpy)_3^{2+}$.[11] Final proton and hydrogen transfers from the cation radical **10** to superoxide anion radical furnish the product quinazoline 3-oxide **5** and the by-product hydrogen peroxide. It is worth noting that no product was obtained when the photooxidation of

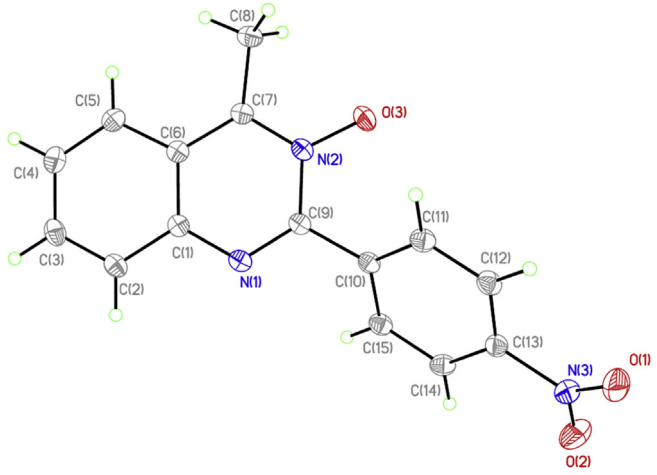
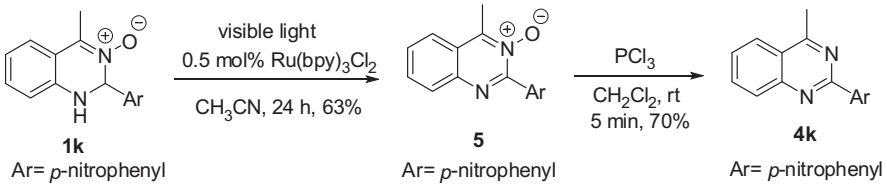


Fig. 6. X-ray crystal structure of **5**.

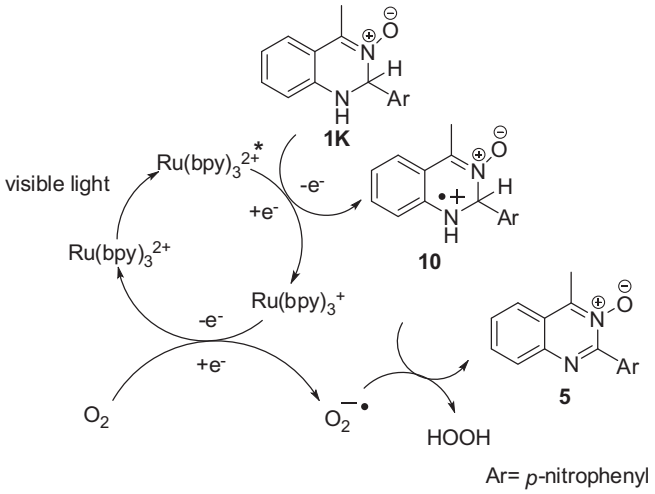
1k was performed under argon atmosphere. The result suggests that molecular oxygen is absolutely required and is indeed the oxidant for this photoreaction. Compared to the conventional oxidizing agents, such as lead tetraacetate,[7] this visible light-mediated oxidation of **1k** to **5** has the advantages of employing atom-economical and environmentally friendly molecular oxygen as the oxidant.

3. Conclusions

In summary, a series of 1,2-dihydroquinazoline 3-oxides were synthesized to investigate their photochemical properties. Our studies have demonstrated that the 1,2-dihydroquinazoline 3-oxides **1** (except for **1k**) are sensitive to light and are prone to undergo photoinduced intramolecular electron transfer from amine hydrogen to iminium oxide upon and subsequent



Scheme 4. Preparation of **5** and **4k**.



Scheme 5. Mechanism assumed for the formation of quinazoline 3-oxide **5**.

dehydration to the quinazolines upon visible light irradiation. As for the light-insensitive nitro-substituted **1k**, it can be converted to the quinazoline **4k** by first oxidation to the quinazoline 3-oxide **5** via visible light photoredox catalysis, and followed by PCl_3-mediated deoxygenation.

4. Experimental section

4.1. General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. MS were performed on JEOL JMS-SX/SX 102A spectrometer. IR spectra were obtained using a 1725XFT-IR spectrophotometer. Absorption spectra were acquired using an HP8453 spectrophotometer. Single-crystal structures were determined by a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. The EPR spectra were recorded on a Bruker EMX 10/12 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. The visible light irradiation reaction was performed with a 23 W household fluorescence lamp.

4.2. Preparation of 1-(2-aminophenyl)ethanone oxime (3)[12]

To a solution of 2′-aminoacetophenone (1.0 g, 7.40 mmol) in ethanol (25 mL) was added sodium hydroxide (2.4 g, 59.2 mmol) and hydroxylamine hydrochloride (1.6 g, 22.2 mmol) at room temperature. The resulting mixture was heated at 60 °C for 2 h. After cooled down to the room temperature, the solvent was concentrated in vacuo. The residual mixture was extracted with EtOAc and water. The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The product was recrystallized from CH_2Cl_2/hexane to give a white solid; yield 76%; R_f=0.4 (20% EtOAc/hexanes); mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1H), 7.35 (dd, J=8.1, 1.5 Hz, 1H), 7.12 (ddd, J=8.7, 7.2, 1.5 Hz, 1H), 6.75 (dd, J=7.8, 1.2 Hz, 1H), 6.70 (dd, J=7.8, 1.2 Hz, 1H), 5.37 (br s, 2H), 2.31 (s, 3H).

4.3. General procedure for the preparation of compounds 1a–k

To a solution compound **3** (300 mg, 1.99 mmol) in ethanol (30 mL) was added an aldehyde (1.99 mmol) and *p*-TsOH (19 mg, 0.1 mmol) at room temperature. The resulting mixture was stirred at room temperature for 5–15 min. After completion of the reaction, the solvent was concentrated in vacuo and the product was extracted with CH_2Cl_2/water. The combined organic layer was concentrated in vacuo and the product was recrystallized from CH_2Cl_2/hexane to give the pure compound.

*4.3.1. 4-Methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (**1a**).* Yellow solid; yield 85%; R_f=0.2 (70% EtOAc/hexanes); mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.48 (m, 2H), 7.33–7.31 (m, 3H), 7.25–7.15 (m, 2H), 6.90 (td, J=7.8, 1.2 Hz, 1H), 6.79 (ddd, J=7.8, 1.2, 0.6 Hz, 1H), 6.14 (d, J=3.0 Hz, 1H), 4.81 (br s, 1H), 2.45 (d, J=0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5, 139.3, 137.7, 130.2, 128.9, 128.4, 126.6, 124.5, 119.7, 117.4, 114.9, 79.3, 12.3; IR ν (KBr) 3257, 1608, 1485, 1315, 740 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{14}N_2O$ [M$^+$] 238.1106, found 238.1110.

*4.3.2. 2-(4-Isopropylphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1b**).* Yellow solid; yield 81%; R_f=0.2 (70% EtOAc/hexanes); mp 148–149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J=8.1 Hz, 2H), 7.24–7.20 (m, 2H), 7.16 (d, J=8.1 Hz, 2H), 6.88 (td, J=7.8, 1.2 Hz, 1H), 6.76 (dd, J=7.8, 1.2 Hz, 1H), 6.09 (d, J=2.7 Hz, 1H), 4.84 (s, 1H), 2.86 (septet, J=6.9 Hz, 1H), 2.44 (d, J=0.6 Hz, 3H), 1.22 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7, 140.3, 139.4, 135.2, 130.1, 126.7, 126.6, 124.5, 119.6, 117.4, 114.7, 79.3, 33.7, 23.8, 12.3; IR ν (KBr) 3258, 2958, 1483, 1311, 744 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{20}N_2O$ [M$^+$] 280.1576, found 280.1569.

*4.3.3. 2-(4-Methoxyphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1c**).* Yellow solid; yield 74%; R_f=0.2 (70% EtOAc/hexanes); mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (dd, J=7.2, 2.1 Hz, 2H), 7.24–7.15 (m, 2H), 6.89 (td, J=7.5, 1.2 Hz, 1H), 6.83 (dd, J=7.2, 2.1 Hz, 2H), 6.78 (dd, J=7.2, 1.2 Hz, 1H), 6.07 (d, J=2.7 Hz, 1H), 4.82 (br s, 1H), 3.76 (s, 3H), 2.43 (d, J=0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.0, 140.3, 139.5, 130.1, 129.8, 128.1, 124.5, 119.6, 117.3, 114.7, 113.7, 79.0, 55.1, 12.3; IR ν (KBr) 3273, 1605, 1516, 1248, 748 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{16}N_2O_2$ [M$^+$] 268.1212, found 268.1214.

*4.3.4. 2-(4-Bromophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1d**).* Light yellow solid; yield 82%; R_f=0.2 (70% EtOAc/hexanes); mp 192–193 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.37 (m, 4H), 7.23–7.17 (m, 2H), 6.91 (td, J=7.8, 1.2 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 6.09 (d, J=3.6 Hz, 1H), 5.00 (d, J=3.0 Hz, 1H), 2.42 (d, J=0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.2, 138.3, 136.4, 131.7, 130.3, 128.5, 124.7, 123.3, 120.9, 118.3, 115.5, 78.9, 12.4; IR ν (KBr) 3132, 1612, 1488, 1311, 746 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}BrN_2O$ [M$^+$] 316.0211, found 316.0207.

*4.3.5. 2-(2-Bromophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1e**).* Light yellow solid; yield 82%; R_f=0.2 (70% EtOAc/hexanes); mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (dd, J=7.8, 1.5 Hz, 1H), 7.29 (dd, J=7.8, 1.5 Hz, 1H), 7.22 (dd, J=7.2, 2.1 Hz, 1H), 7.19 (dd, J=7.2, 2.1 Hz, 1H), 7.15–7.05 (m, 2H), 6.87 (td, J=7.8, 1.2 Hz, 1H), 6.62 (ddd, J=7.8, 1.2, 0.3 Hz, 1H), 6.49 (d, J=2.4 Hz, 1H), 5.23 (s, 1H), 2.59 (d, J=0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 138.3, 135.4, 133.3, 130.4, 130.3, 127.8, 127.1, 124.3, 122.3, 119.9, 117.1, 114.5, 78.8,

12.2; IR ν (KBr) 1614, 1502, 1198, 1027, 747 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}BrN_2O$ [M^+] 316.0211, found 316.0205.

*4.3.6. 2-(2-Chlorophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1f**).* Yellow solid; yield 85%; R_f=0.2 (70% EtOAc/hexanes); mp 176–177 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (dd, J=7.8, 1.2 Hz, 1H), 7.29 (dd, J=7.8, 1.2 Hz, 1H), 7.24 (dd, J=7.8, 1.8 Hz, 1H), 7.18 (td, J=7.8, 1.2 Hz, 1H), 7.13 (dd, J=7.5, 1.2 Hz, 1H), 7.08 (dd, J=7.5, 1.8 Hz, 1H), 6.87 (td, J=7.8, 1.2 Hz, 1H), 6.62 (dd, J=7.8, 1.2 Hz, 1H), 6.53 (d, J=2.1 Hz, 1H), 5.15 (s, 1H), 2.59 (d, J=0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 138.6, 134.2, 132.7, 130.5, 130.3, 130.2, 127.4, 127.1, 124.5, 120.0, 117.2, 114.7, 77.6, 12.4; IR ν (KBr) 1614, 1502, 1197, 1035, 746 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}ClN_2O$ [M^+] 272.0716, found 272.0720.

*4.3.7. 2-(2,4-Dichlorophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1g**).* Light yellow solid; yield 82%; R_f=0.2 (70% EtOAc/hexanes); mp 167–168 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J=2.1 Hz, 1H), 7.29 (dd, J=7.8, 1.5 Hz, 1H), 7.16 (dd, J=8.4, 2.1 Hz, 1H), 7.13 (td, J=7.8, 1.5 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.89 (td, J=7.8, 1.5 Hz, 1H), 6.63 (dd, J=7.8, 1.5 Hz, 1H), 6.48 (d, J=2.4 Hz, 1H), 5.20 (s, 1H), 2.57 (d, J=0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 138.2, 135.5, 133.4, 132.7, 130.4, 129.9, 128.1, 127.5, 124.5, 120.3, 117.1, 114.6, 76.4, 12.3; IR ν (KBr) 3279, 1590, 1483, 1204, 752 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{12}Cl_2N_2O$ [M^+] 306.0327, found 306.0320.

*4.3.8. 2-(4-Fluorophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1h**).* Yellow solid; yield 76%; R_f=0.2 (70% EtOAc/hexanes); mp 177–178 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, J=8.4 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.23 (dd, J=7.8, 1.2 Hz, 1H), 7.18 (dd, J=7.8, 1.2 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 6.98 (td, J=8.7, 1.8 Hz, 1H), 6.91 (td, J=7.8, 1.2 Hz, 1H), 6.81 (d, J=7.8 Hz, 1H), 6.11 (d, J=3.3 Hz, 1H), 4.97 (br s, 1H), 2.43 (d, J=0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1 (d, $^1J_{C-F}$=246.8 Hz), 140.2, 138.7, 133.4 (d, $^4J_{C-F}$=2.9 Hz), 130.2, 128.7 (d, $^3J_{C-F}$=8.4 Hz), 124.7, 120.5, 117.9, 115.6, 115.3 (d, $^2J_{C-F}$=10.7 Hz), 78.8, 12.4; IR ν (KBr) 3284, 1602, 1505, 1203, 752 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}FN_2O$ [M^+] 256.1012, found 256.1015.

*4.3.9. 2-(4-Cyanophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**1i**).* Yellow solid; yield 87%; R_f=0.2 (70% EtOAc/hexanes); mp 174–175 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 7.25–7.20 (m, 2H), 6.96 (td, J=8.1, 1.2 Hz, 1H), 6.88 (dd, J=8.1, 1.2 Hz, 1H), 6.20 (d, J=3.9 Hz, 1H), 4.92 (br s, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.5, 141.0, 138.2, 132.2, 130.6, 127.4, 124.8, 120.9, 118.2, 117.9, 115.8, 112.6, 78.6, 12.4; IR ν (KBr) 3260, 2233, 1609, 1479, 747 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{13}N_3O$ [M^+] 263.1059, found 263.1052.

*4.3.10. 4-Methyl-2-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinazoline 3-oxide (**1j**).* Yellow solid; yield 89%; R_f=0.2 (70% EtOAc/hexanes); mp 212–213 °C; ^1H NMR (CD_3OD, 300 MHz) δ 7.65–7.59 (m, 4H), 7.36 (dd, J=8.1, 1.2 Hz, 1H), 7.23 (td, J=7.5, 1.2 Hz, 1H), 6.87–6.82 (m, 2H), 6.22 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 146.0, 143.4, 141.6, 133.0, 132.1 (q, $^2J_{C-F}$=32.5 Hz), 128.3, 126.7, 126.5 (q, $^3J_{C-F}$=3.9 Hz), 125.4 (q, $^1J_{C-F}$=269.7 Hz), 120.9, 117.6, 116.0, 79.6, 12.7; IR ν (KBr) 3273, 2425, 1329, 1122, 750 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{13}F_3N_2O$ [M^+] 306.0980, found 306.0985.

*4.3.11. 4-Methyl-2-(4-nitrophenyl)-1,2-dihydroquinazoline 3-oxide (**1k**).* Yellow solid; yield 77%; R_f=0.2 (70% EtOAc/hexanes); mp 166–167 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J=9.0 Hz, 2H), 7.75 (dd, J=9.0 Hz, 2H), 7.25–7.21 (m, 2H), 6.97 (td, J=8.1, 1.2 Hz, 1H), 6.91 (dd, J=8.1, 1.2 Hz, 1H), 6.25 (d, J=4.5 Hz, 1H), 4.90 (d, J=4.5 Hz, 1H), 2.46 (d, J=0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 144.3, 141.1, 138.0, 130.7, 127.8, 124.9, 123.6, 121.2, 118.2, 116.1, 78.5, 12.4; IR ν (KBr) 3238, 1610, 1535, 1354, 749 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}N_3O_3$ [M^+] 283.0957, found 283.0951.

4.4. General procedure for the preparation of compounds 4a–j

A dried 250 mL round bottom flask was charged with **1** (0.5 mmol) and CH_3CN (100 mL) at room temperature. The resulting mixture was placed at a distance of approximate 10 cm from a 23 W fluorescent lamp (Philips essential 57 lm/W, 6500 K) and was irradiated for 16–18 h. The solvent was then evaporated and the photogenerated product was purified by column chromatography (1:4 EtOAc/hexanes) to give the pure compound.

*4.4.1. 4-Methyl-2-phenylquinazoline (**4a**).* White solid; yield 90%; R_f=0.8 (20% EtOAc/hexanes); mp 90–91 °C (lit.[5c] 89–90 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.61 (dd, J=8.4, 1.8 Hz, 2H), 8.07 (dd, J=8.4, 1.8 Hz, 2H), 7.85 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.59–7.48 (m, 4H), 3.00 (s, 3H).

*4.4.2. 4-Methyl-2-(4-isopropylphenyl)quinazoline (**4b**).* Yellow liquid; yield 92%; R_f=0.7 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, J=8.4 Hz, 2H), 8.08 (d, J=7.5 Hz, 1H), 8.06 (d, J=8.4 Hz, 1H), 7.85 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.56 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 7.38 (d, J=8.1 Hz, 2H), 3.01 (s, 3H), 2.99 (septet, J=6.9 Hz, 1H), 1.31 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 160.2, 151.3, 150.3, 135.9, 133.3, 129.0, 128.5, 126.55, 126.46, 124.8, 122.7, 34.0, 23.8, 21.9; IR ν (KBr) 2960, 1609, 1493, 1179, 762 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}N_2$ [M^+] 262.1470, found 262.1469.

*4.4.3. 4-Methyl-2-(4-methoxyphenyl)quinazoline (**4c**).*[5j] Yellow solid; yield 94%; R_f=0.7 (20% EtOAc/hexanes); mp 102–103 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.58 (d, J=9.0 Hz, 2H), 8.03 (td, J=8.4, 0.6 Hz, 2H), 7.82 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.03 (d, J=9.0 Hz, 2H), 3.89 (s, 3H), 2.98 (s, 3H).

*4.4.4. 4-Methyl-2-(4-bromophenyl)quinazoline (**4d**).* White solid; yield 76%; R_f=0.6 (20% EtOAc/hexanes); mp 207–208 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J=8.4 Hz, 2H), 8.07 (d, J=8.1 Hz, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.85 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.53 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 159.1, 150.2, 137.1, 133.6, 131.6, 130.1, 129.1, 127.0, 125.1, 124.9, 122.9, 21.9; IR ν (KBr) 1572, 1547, 1341, 1005, 762 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{11}BrN_2$ [M^+] 298.0106, found 298.0109.

*4.4.5. 4-Methyl-2-(2-bromophenyl)quinazoline (**4e**).* Yellow solid; yield 83%; R_f=0.8 (20% EtOAc/hexanes); mp 103–104 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (ddd, J=8.4, 1.2, 0.6 Hz, 1H), 8.12 (ddd, J=8.4, 1.2, 0.6 Hz, 1H), 7.92 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.76 (dd, J=7.8, 1.8 Hz, 1H), 7.72 (dd, J=7.8, 1.2 Hz, 1H), 7.68 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.45 (td, J=7.5, 1.5 Hz, 1H), 7.30 (td, J=7.5, 1.5 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 161.9, 149.7, 140.3, 133.7, 133.5, 131.3, 130.1, 129.0, 127.6, 127.3, 124.9, 122.6, 121.8, 21.7; IR ν (KBr) 1548, 1434, 1342, 1022, 759 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{11}BrN_2$ [M^+] 298.0106, found 298.0109.

*4.4.6. 4-Methyl-2-(2-chlorophenyl)quinazoline (**4f**).* Yellow solid; yield 89%; R_f=0.8 (20% EtOAc/hexanes); mp 111–112 °C (lit.[5i] 110.3–111.6 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 8.11 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 7.92 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 7.80–7.77 (m, 1H), 7.68 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 7.54–7.51 (m, 1H), 7.43–7.36 (m, 2H), 3.04 (s, 3H).

*4.4.7. 4-Methyl-2-(2,4-dichlorophenyl)quinazoline (**4g**).* Yellow solid; yield 85%; R_f=0.8 (20% EtOAc/hexanes); mp 106–107 °C; ^1H

NMR ($CDCl_3$, 300 MHz) δ 8.15 (ddd, J=8.4, 1.2, 0.6 Hz, 1H), 8.09 (ddd, J=8.4, 1.2, 0.6 Hz, 1H), 7.92 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.68 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.39 (dd, J=8.4, 2.1 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 160.0, 149.7, 136.9, 135.3, 133.8, 133.7, 132.5, 130.2, 129.0, 127.7, 127.1, 124.9, 122.6, 21.8; IR ν (KBr) 1560, 1497, 1341, 1097, 767 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{10}Cl_2N_2$ [M^+] 288.0221, found 288.0227.

*4.4.8. 4-Methyl-2-(4-fluorophenyl)quinazoline (**4h**).* White solid; yield 86%; R_f=0.8 (20% EtOAc/hexanes); mp 124–125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66–8.60 (m, 2H), 8.09 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 8.05 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 7.87 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.59 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.22–7.17 (m, 2H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 164.5 (d, $^1J_{C-F}$=248.4 Hz), 159.1, 150.2, 134.4 (d, $^4J_{C-F}$=2.9 Hz), 133.5, 130.6 (d, $^3J_{C-F}$=8.4 Hz), 129.0, 126.8, 124.9, 122.8, 115.4 (d, $^2J_{C-F}$=21.8 Hz), 21.9; IR ν (KBr) 1575, 1553, 1344, 1214, 738 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{11}FN_2$ [M^+] 238.0906, found 238.0898.

*4.4.9. 4-Methyl-2-(4-cyanophenyl)quinazoline (**4i**).* White solid; yield 92%; R_f=0.7 (20% EtOAc/hexanes); mp 167–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, J=8.4 Hz, 2H), 8.13 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 8.09 (ddd, J=8.4, 1.5, 0.6 Hz, 1H), 7.91 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.81 (d, J=8.4 Hz, 2H), 7.65 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 158.1, 150.1, 142.3, 133.9, 132.2, 129.3, 128.9, 127.7, 125.0, 123.2, 118.9, 113.5, 22.0; IR ν (KBr) 2225, 1570, 1542, 1344, 760 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{11}N_3$ [M^+] 245.0953, found 245.0945.

*4.4.10. 4-Methyl-2-(4-trifluoromethylphenyl)quinazoline (**4j**).* White solid; yield 90%; R_f=0.7 (20% EtOAc/hexanes); mp 77–78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (d, J=8.4 Hz, 2H), 8.09–8.05 (m, 2H), 7.87 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 7.75 (d, J=8.4 Hz, 2H), 7.60 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 3.00 (d, J=1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 158.6, 150.2, 141.5, 133.7, 131.8 (q, $^2J_{C-F}$=32.0 Hz), 129.3, 128.7, 127.4, 126.0, 125.3 (q, $^3J_{C-F}$=4.0 Hz), 124.9, 124.2 (q, $^1J_{C-F}$=270.3 Hz), 21.9; IR ν (KBr) 1547, 1323, 1112, 1067, 751 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{11}F_3N_2$ [M^+] 288.0874, found 288.0871.

4.5. Preparation of compounds 5 and 4k

*4.5.1. 4-Methyl-2-(4-nitrophenyl)quinazoline 3-oxide (**5**).* To a solution of **1k** (200 mg, 0.71 mmol) in acetonitrile (100 mL) was added $Ru(bpy)_3Cl_2$ (1.0 mg, 0.5 mol %). The resulting mixture was placed at a distance of approximate 10 cm from a 23 W fluorescent lamp (Philips essential 57 lm/W, 6500 K) and was irradiated for 24 h. The solvent was then evaporated and the photogenerated product was purified by column chromatography (1:4 EtOAc/hexanes) to give a white solid; yield 63%; R_f=0.3 (50% EtOAc/hexanes); mp 167–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=9.0 Hz, 2H), 8.36 (d, J=9.0 Hz, 2H), 8.06 (ddd, J=8.1, 1.8, 0.9 Hz, 1H), 7.94 (ddd, J=8.1, 1.8, 0.9 Hz, 1H), 7.83–7.71 (m, 2H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 152.3, 148.8, 140.2, 138.6, 131.5, 131.4, 130.0, 129.5, 123.9, 123.3, 122.9, 13.3; IR ν (KBr): 1515, 1349, 1213, 854, 754 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{11}N_3O_3$ [M^+] 281.0800, found 281.0804.

*4.5.2. 4-Methyl-2-(4-nitrophenyl)quinazoline (**4k**).* To a solution of **5** (100 mg, 0.36 mmol) in methylene chloride (100 mL) was added phosphorus trichloride (0.2 mL) at room temperature. After completion of the reaction (within 5 min), the solvent was concentrated in vacuo and the product was extracted with CH_2Cl_2/water. The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (1:4 EtOAc/hexanes) to give a white solid; yield 70%; R_f=0.6 (20% EtOAc/hexanes); mp 167–168 °C (lit.[5b] 168–169 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, J=9.0 Hz, 2H), 8.37 (d, J=9.0 Hz, 2H), 8.16–8.10 (m, 2H), 7.93 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 7.67 (ddd, J=8.4, 6.9, 1.2 Hz, 1H), 3.05 (s, 3H).

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Supplementary data

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