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Note

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Photoreductive removal of *O*-benzyl groups from oxyarene *N*-heterocycles assisted by *O*-pyridine – pyridone tautomerism

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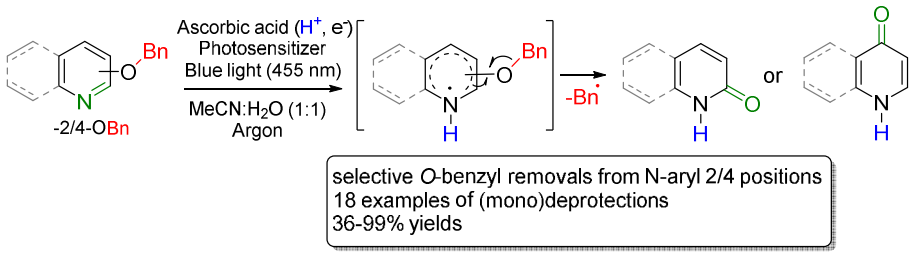


ABSTRACT: Facile photoreductive protocols have been developed to remove benzyl *O*-protective groups from oxyarene *N*-heterocycles at positions capable for 2-/4-*O*-pyridine – 2-/4-pyridone tautomerism. Blue light irradiation, a [Ru] or [Ir] photocatalyst and ascorbic acid in a water-acetonitrile solution debenzylates a variety of aryl *N*-heterocycles cleanly and selectively. Ascorbic acid has two functions in the reaction. On the one hand, it protonates the *N*-heterocycles that reduces their reduction potentials notably and on the other hand it acts as a sacrificial reductant. Reduction potentials and free energy barriers calculated at the CPCM-B3LYP/6-31+G** level can predict the reactivities of the studied substrates.

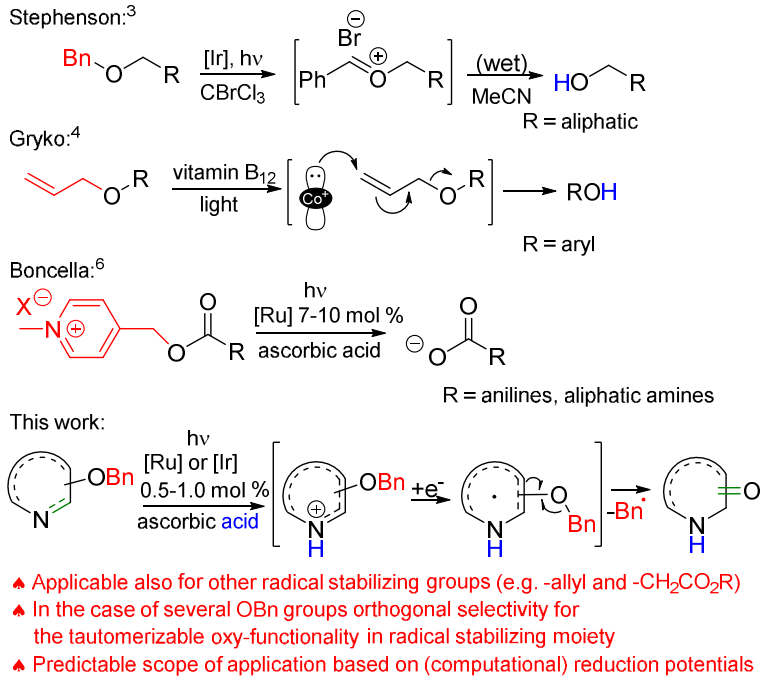
A variety of photoremovable protecting groups have been designed and developed for different functionalities to optionally allow traceless, orthogonal, and functional group tolerant protections, which are in some cases operable even in biological environments.[1] Typically, the protecting group chromophore absorbs an UV or a visible light photon that initiates the bond breaking processes and ultimately the deprotection. However, some of the deprotections carried out with high energy UV-light may, in addition to the desired bond cleavages, lead to unwanted side reactions and unclean deprotections.

The contemporary development of photoredox catalysis has conveyed a set of photocatalysts that utilize visible light to induce single electron transfers to accomplish organic bond cleavages and formations.[2] Accordingly, Stephenson and coworkers have developed a visible light-promoted catalytic method for deprotection of *O*-benzyl-protected aliphatic alcohols utilizing an [Ir]-catalyst and $CBrCl_3$ as a stoichiometric radical source that mediates the reaction (Scheme 1).[3] Gryko and

coworkers have recently shown that photoinduced deprotection of (allyloxy)arenes can be conducted *via* a nucleophilic vitamin B_{12}-catalysis.[4] Moreover, *N*-methyl-4-picolinium esters[5] and carbamates[6] have been practically photocleaved by reductive visible light [Ru] catalysis. Originally, Sundararajan and Falvey introduced the concept of reductive photocleavage of *N*-methyl-4-picolinium esters using *N*-methylcarbazole, laser dye or intramolecular electron donor photosensitizers.[7]

Conventionally, *O*-benzyl and -allyl groups are removed *via* a reductive hydrogenation with number of protocols.[8] Frequently-used methods include Pd/C or Ni catalyzed hydrogenations and stoichiometric reductions with $NaBH_4$, DIBAL or $LiAlH_4$. However, coordinative pyridine-type nitrogens tend to coordinate to catalytic metals inhibiting occasionally the catalytic reactions.[9] Since these are compounds of interest to us, *i.e.* aromatic hydroxyl functionalized *N*-heterocycles that have ability to hydroxy-oxo tautomerize,[10] we envisioned that the tautomerization could be utilized to promote the reductive protective group cleavage at the phenolic oxygen. Protonation of the pyridine-type nitrogen in the heterocycles would turn them into better electron acceptors that could be *in situ* photoreduced followed by a radical cleavage of the *O*-protective group *via* a tautomeric process.

Scheme 1



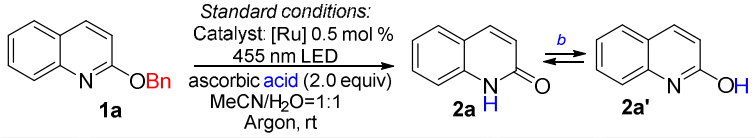
We initiated the study using 2-(benzyloxy)quinoline **1a** as a model compound for the reaction development (Table 1). Ascorbic acid was a rational choice for a sacrificial reductant as it can also protonate the

quinoline. For example, in the case of **1i**, protonation reduces its reduction potential by 1.13 V as measured by cyclic voltammetry (SI). Also with other substrates, reduction potentials[11] are reduced to appropriate values for the commonly used photocatalysts. The photocatalysts for the reaction screening were selected based on their adequate reduced state reduction potentials (RSRP) in MeCN.[2a]

Pleasingly, 2 equiv of ascorbic acid in MeCN:H_2O (1:1) mixture, 0.5 mol % of $Ru(bpy)_3Cl_2$ photocatalyst, with -1.33V (SCE)[2a] RSRP, removed the benzyl group cleanly after 1 h at rt under 455 nm irradiation (Table 1, entry 1); method **A**. In a similar fashion, $Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ catalyst with a slightly lower RSRP, -1.37 V (SCE),[2a] worked neatly with 1.0 mol% loading (entry 4); method **B**. Moreover, under the same conditions, the photocatalyst $[Ir(dtbbpy)(ppy)_2]PF_6$, with even lower RSRP (-1.51V, SCE),[2a] performed soundly giving clean conversion with 0.5 mol % loading in 1 h (entry 5); method **C**. Meanwhile, the catalyst *fac*-$Ir(ppy)_3$ with a substantially negative reported RSRP, -2.19 V (SCE),[2a] showed only modest reactivity (entry 6). Indicatively, a $[Ru(bpz)_3][PF_6]_2$ catalyst with higher RSRP -0.80 V (SCE)[2a] did not give any reactivity (entry 7). Apparently, the lack of reactivity relates to catalyst's modest RSRP value, while its reduced state formation should be smooth based on its high excited state via reduction potential, i.e. +1.45 V (SCE).[2a]

The catalysis with $Ru(bpy)_3Cl_2$ worked also moderately in MeOH; poorly in H_2O; and gave no conversion in MeCN or DMF (Table 1). The presence of the ascorbic acid was necessary for the reaction, while substoichiometric amounts of it provided incomplete conversion, while generally an excess, 2.0 equiv, was found to be beneficial for smooth reactions (*cf.* fluorescence quenching studies, SI). When a typical photocatalytic sacrificial base reductant DIPEA was used as an additive together with ascorbic acid, the reaction did not proceed. An inert atmosphere favored the progress of the reaction and, in the absence of light irradiation, no conversion was observed.

Table 1. Effects of the reaction parameters



entry	varied reaction parameters	time (h)	yield (%)[c]
	Catalyst and loading [mol %]		
1	$Ru(bpy)_3Cl_2*6H_2O$ [0.5]	1	>99
2	$Ru(bpy)_3Cl_2*6H_2O$ [0.1]	1	41
3	$Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ [0.5]	1	76
4	$Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ [1.0]	1	>99
5	$[Ir(dtbbpy)(ppy)_2]PF_6$ [0.5]	1	>99
6	*fac*-$Ir(ppy)_3$ [0.5]	1	32
7	$[Ru(bpz)_3][PF_6]_2$[0.5]	1	NR
8	no catalyst	24	NR
	Solvent		
9	MeCN	1	NR
10	H_2O	1	24
11	MeOH	1	79
12	DMF	1	NR

	other conditions		
13	no ascorbic acid	24	NR
14	0.5 equiv ascorbic acid	1	48
15	1.0 equiv ascorbic acid	1	>99
16	no light irradiation	24	NR
17	2.0 equiv DIPEA additive[d]	1	NR
18	ambient atmosphere	1	58

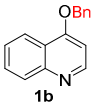
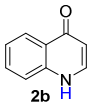
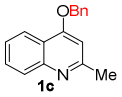
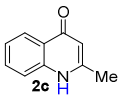
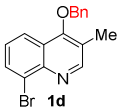
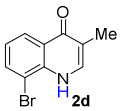
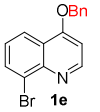
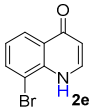
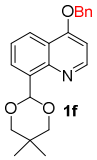
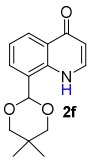
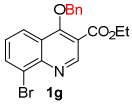
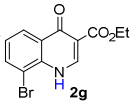
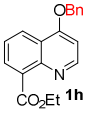
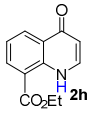
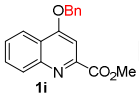
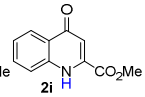
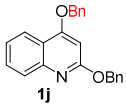
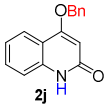
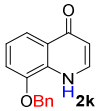
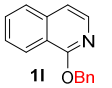
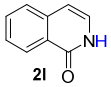
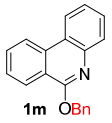
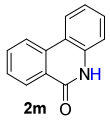
[a]reactions were performed at [0.2 M] in a 10 mL Schlenk tube irradiated with 455 nm LEDs (5*3W). [b]Tautomeric form is media dependent –polar and nonpolar media favours pyridone and pyridine isomers, respectively. [c]Isolated yield after SiO_2 chromatographic purification.[d] In the presence of ascorbic acid. NR = No reaction

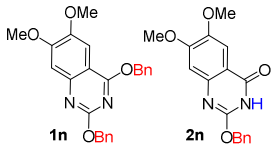
Computational methods allow the estimation of the redox potentials of organic compounds conveniently and we and others have used this approach previously.[12-14] With the CPCM-B3LYP/6-31+G** method, Nicewicz and coworkers have recently found a good correlation between a wide range of neutral organic redox potentials and experimentally measured potentials.[14] In our case, for the (*N*-protonated) quinolinium **1a**, the computational method gave a slightly lower value, -1.02V vs. the -0.86V experimental value (SCE). Since in this study, we were interested in reduction potentials of protonated compounds, a set of aromatic N-heterocycles were examined both experimentally and theoretically to justify the use of the method (SI). The analysis showed that there is a high linear correlation (R^2=0.97, SI) between calculated and experimental values,[15] but the latter were consistently -0.2 − -0.3V more negative (Figure S1, SI). The systematic deviation likely arises from the facts that the protonated *N*-aryls are calculated without counter ions and with implicit solvation model, conductor-like polarizable continuum model (CPCM), which is furthermore benchmarked to have the largest solvation energy errors for cations and anions.[16]

With this information in hand, the scope of the reaction was then studied with various mono- and bi- *O*-benzyl substituted quinoline type compounds (Table 2). Prior to catalytic tests, reduction potentials were calculated for all of the studied compounds to assess their reactivities. As expected, relying on the potentials, for most of the quinolines method **A** delivered smooth reactivity excluding three substrates **1j**, **1m** and **1n** (entries 9, 12 and 13) having slightly more negative reduction potentials. They were, however, catalyzed in a superior manner with method **B**; as clean conversions were obtained in 3 h. Evidently, the slightly more negative reduction potential of the Ir-catalyst was critical to provide the facile reactivity in these cases.

Significantly, in the case of dibenzyloxy substituted quinolines **1j**, **1k** and **1n** (entries 9, 10 and 13) a single benzyl group was cleaved regioselectively, using methods **A** and **B**. The calculation of the cleavage energy barriers for each benzyl group in the quinolinium radicals revealed that the removable benzyl exhibited correspondingly significantly lower energy barriers (Table S1, SI). From a methodologic perspective, the photoreduction catalysis provides a convenient access to pharma interest mono benzyloxy substituted quinolines such as 4-(benzyloxy)quinolin-2(1*H*)-one, **2j**.[17]

Table 2. Scope of the reaction with *O*-Bn protected quinolines[a]

entry	substrate	product	$E^{o}_{1/2}$[b] (V, SCE) SM + H^+	method	time (h)	yield (%)[c]
1	 **1b**	 **2b**	-1.11 (-0.98)[d]	**A**	1	>99
2	 **1c**	 **2c**	-1.18	**A**	1	>99
3	 **1d**	 **2d**	-0.85[e] (-0.56)[d]	**A**	1	93
4	 **1e**	 **2e**	-0.61[e]	**A**	2	>99
5	 **1f**	 **2f**	-1.14	**A**	0.5	90
6	 **1g**	 **2g**	-0.59[e]	**A**	1	>99
7	 **1h**	 **2h**	-0.89	**A**	2	36[f]
8	 **1i**	 **2i**	-0.55 (-0.36)[d]	**A,B**	24	NR
9	 **1j**	 **2j**	-1.32	**A** **B**	5 3	77 >99
10	 **1k**	 **2k**	-1.22	**A**	0.6	>99
11	 **1l**	 **2l**	-1.20	**A**	2	>99
12	 **1m**	 **2m**	-1.07 (-0.79)[d]	**A** **B**	4 3	74 >99

13		-1.24	**A** **B**	5.5 2	58 90

[a]Benzyl ether 0.2 mmol, ascorbic acid 0.4 mmol, MeCN/H_2O=1:1 10 mL. [b]Calculated with B3LYP/6-31+G** CPCM model for MeCN (details in SI). [c]Isolated yield after SiO_2 chromatographic purification. [d]experimental values determined in 0.1 M NBu_4PF_6 in MeCN using *p*-TSA to protonate the heterocycle. [e]Calculated with uwb97xd/def2-TZVP CPCM model for MeCN (details in SI). [f]In addition to unreacted SM unidentified side products were detected.

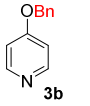
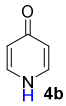
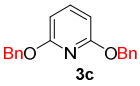
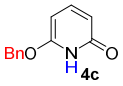
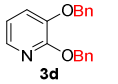
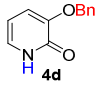
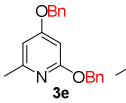
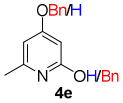
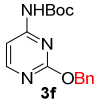
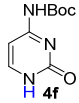
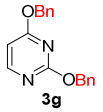
As exceptions in the quinoline series, compound **1h** (entry 7) having an ester functionality at the 8-position gave an unclean reaction with a modest conversion, while the quinoline **1i** (entry 8) failed to show any reactivity under any studied conditions even though it has a more positive reduction potential, which was rather baffling. Also, ester group substitution at the 3-position (**1g**, entry 6) did not inhibit the reactivity. However, DFT calculations of the quinolini-1-ums (neutral radicals of the protonated quinolines) showed two distinctive features for quinolin-1-ium **1i**+H$^{\bullet}$ (Figure S3, SI). At first, the comparison of the SOMOs morphologies of the **1g**, **1h** and **1i** radicals showed distinctively that for **1i** the density was the most localized on the ester group, which might be the reason for the observed inertness. Secondly, the free energy barrier for the benzyl group cleavage was higher for **1i** (16.8 kcal/mol) than for the two other quinoliniums (9.6 and 13.3 kcal/mol for **1g** and **1h**, respectively). We speculate that, due to a short lifetime of radical intermediates, low reaction barriers are needed for the cleavage reactions to compete with other decay pathways.

Related to the above, the quinoline **1f** having an electron donating acetal functionality at 8-position reacted cleanly, while corresponding 8-position aldehyde decomposed fully under the reaction conditions.[18] Whereas, in the case of Br-substituted BnO-quinolines, **1d**, **1e** and **1g**, the halogen substituent remained intact, and the photoreduction catalysis yielded clean chemoselective benzyl cleavages (entries 3, 4, and 6).

Next, we studied the scope of the reaction with mono- and bifunctionalized *O*-benzyl substituted pyridine and pyrimidine type compounds (Table 3). These compounds have inherently more negative reduction potentials than the quinolines. Consequently, method **A** failed to give any reactivity for these substrates, whereas method **B** delivered successful benzyl removal for the pyridines with the least negative reduction potentials (entry 1 and 4). For the bi *O*-benzyl substituted pyridine **3d**, the DFT calculations gave strikingly dissimilar energy barriers for the benzyl cleavages at the 2- and 3-positions (5.0 and 14.8 kcal/mol, respectively). The TS energies agree perfectly with the observed regioselectivity, as monoprotected 3-*O*-benzyl **4d** was received as

the only product. Alternatively, one could predict that the regioselectivity is simply based on the abilities of 2-hydroxyl compounds to participate in pyridine/-done tautomerism, which is excluded at the pyridine 3-oxo position.

Table 3. Scope of the reaction with mono and bi *O*-Bn protected pyridines and pyrimidines[a]

entry	substrate	product	$E^{o}_{½}$ [b] (V, SCE) SM + H^+	method	time (h)	yield (%)[c]
1	 3a	 4a	-1.31 (-1.06)[d]	**A** **B**	18 3	NR 95
2	 3b	 4b	-1.54 (-1.31)[d]	**A,B** **C**	24 21	NR >99
3	 3c	 4c	-1.51	**A-C**	24	NR
4	 3d	 4d	-1.33 (-1.20)[d]	**A** **B**	20 2	NR 95
5	 3e	 4e	-1.77 (-1.45)[d]	**A,B** **C**	24 23	NR 59[e]
6	 3f	 4f	-1.11	**A,B**	24	NR
7	 3g	 4g	-1.18	**B**	23	85

[a]Benzyl ether 0.2 mmol, ascorbic acid 0.4 mmol, MeCN/H_2O=1:1 10 mL. [b]Calculated with B3LYP/6-31+G** CPCM acetonitrile (details in SI). [c]Isolated yield after SiO_2 chromatographic purification. [d]experimental values determined in 0.1 M NBu_4PF_6 in MeCN using *p*-TSA to protonate the heterocycle. [e]mixture of mono deprotected regioisomers.

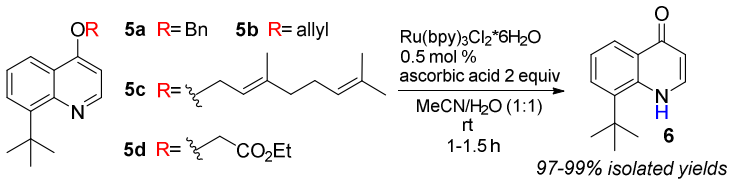
On the basis of the calculated reduction potential for 4-OBn-pyridine **3b** -1.54 V (SCE) it was anticipated that methods **A** and **B** would only show borderline catalytic activity, but method **C** should be effective. Indeed, the methods **A** and **B** did not yield any conversion after 24 h, while method **C** cleaved benzyl from **3b** quantitatively in 21 h. In contrast to this, for unknown reasons, pyridine **3c** did not show any reactivity under the studied conditions (entry 3) even though its estimated reduction potential is less negative than that of **3b**.[19] Nevertheless, method **C** was also able to cleave the benzyl from **3e** with a rather low reduction potential of -1.45/-1.77 V (SCE)

Exp./Cal. (entry 5). As a result, a mixture of monodeprotected compounds were obtained. This was also in agreement with the similar calculated energy barriers found for benzyl cleavages at the 2- and 4- positions, being 5.2 and 5.0 kcal/mol, respectively (Table S1, SI).

The pyrimidine compounds behaved somewhat unpredictably. On the one hand, *N*-Boc protected cytosine **3f** (entry 6) did not give any reactivity despite its high estimated reduction potential -1.11 V (SCE) and reasonably low energy barrier, 12.8 kcal/mol, for the benzyl cleavage. Pyridinium radicals are known to have other possible reactive pathways that may compete herein.[20] On the other hand, with *O*-dibenzyl protected uracil **3g** (entry 7), the catalysis with method **B** cleaved off both benzyls. The decrease of the amount of ascorbic acid resulted plainly in an incomplete conversion. The observed performance can be explained computationally as the reduction potential of the monodeprotected 2-OBn uracil (**3g-2,** SI) is similar to **3g**, while its radical has a negligible energy barrier for benzyl cleavage, being only 1.3 kcal/mol (Table S1, SI).

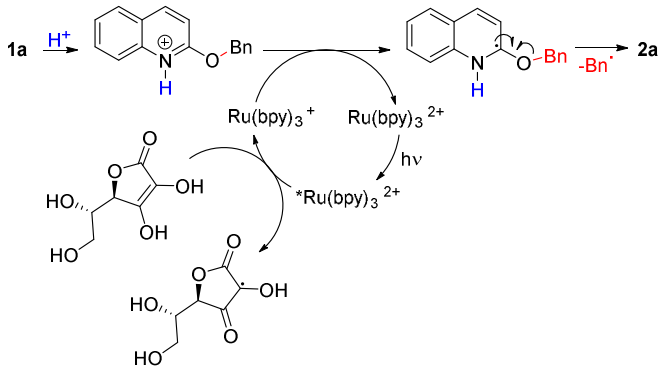
Finally, we were curious whether the benzyl, as removable group, could be replaced by some other radical stabilizing groups (Scheme 2). For this purpose, 8-*tert*-butyl-quinoline derivatives **5a** – **5d** were studied. Gratifyingly, with method **A**, allyl, substituted allyl (*O*-geranyl) and methylene ester could be cleaved off quantitatively in 1-1½ hour.

Scheme 2. Removal of other cleavable ethers



Our simplistic mechanistic proposal (Scheme 3) is similar to the one presented in a previous study involving analogous photocatalyst and ascorbic acid:[6] The cycle begins by ascorbic acid protonating the N-heterocycle and continues by reduction of the excited state of the photocatalyst with ascorbic acid. Thereafter, the reduced state catalyst donates electron for the substrate, which is fragmented into benzyl radical and neutral pyridone. This scenario is firmly supported by correlation of various substrate reduction potentials vs. several catalyst RSRPs. Additionally, Stern-Volmer plot indicate that ascorbic acid acts as a primary fluorescence quencher of [Ru] catalyst (SI).

Scheme 3. Plausible mechanism



In summary, we have discovered a mild, clean, regio- and chemoselective photoreductive methodology to remove selectively *O*-benzyl protections from oxyarene N-heterocycles, which have the ability to receive an electron from a photoreductant and are capable of 2-/4-*O*-pyridine – 2-/4-pyridone tautomerism. From a methodological perspective, it was shown that useful predictive information regarding the mode and scope of substrate reactivities could be straightforwardly obtained by relatively simple, low computational cost DFT methods.

EXPERIMENTAL SECTION

General information. All commercial chemicals were used as received. Photocatalysts were purchased from TCI Europe ($Ru(bpy)_3Cl_2*6H_2O$) and Sigma-Aldrich ($(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ and $[Ir(dtbbpy)(ppy)_2]PF_6$). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 27 °C using Varian Mercury 300 [299.95 MHz] or Varian Inova 500 [499.82 MHz] spectrometers. ^1H and $^{13}C\{^1H\}$ spectra were referenced to the residual solvent signals (in $CDCl_3$ 7.26 and 77.2 ppm, respectively; in DMSO-d_6 2.50 and 39.5 ppm, respectively). No special notation was used for equivalent carbons. IR spectra were measured with FTIR Bruker Alpha spectrometer. Cyclic voltammetry was performed with Gamry Interface 1000 potentiostat. Fluorescence spectra were measured with Horiba Jobin Yvon Fluoromax-4 spectrofluorometer. High resolution mass spectra were obtained with Bruker ESI microTOF$_{LC}$ instrument in positive ionisation mode. Supelco silica gel TLC-cards with fluorescent indicator (254 nm) were used for TLC chromatography and R_f-value determinations. The melting points were determined in capillary tubes with Büchi 510 melting point apparatus and are reported uncorrected. All photoreductive deprotections were performed in 10 mL Schlenk-tubes (ca. 110 x 10 mm) under an argon atmosphere. The distance from the light source was 5 cm. The 5 x 3W blue (455 nm) LEDs were positioned in a vertical row along the Schlenk-tube.

General procedures for photocatalytic benzyl deprotections:

Method **A** – using $Ru(bpy)_3Cl_2*6H_2O$ as photocatalyst. The corresponding benzyl ether (1 equiv) and ascorbic acid (2 equiv) were weighted in a Schlenk-tube equipped with a stir bar. A 10 mL of degassed MeCN/H_2O (1:1) solvent mixture and a $Ru(bpy)_3Cl_2*6H_2O$ catalyst (0.5 mol %) were added to the tube which was placed under a blue light irradiation (455 nm) on a magnetic stirrer plate for a reaction period at rt. The reaction was monitored with TLC. After completion, the reaction mixture was quenched with aq. NH_4OH and evaporated to dryness. The crude was purified with SiO_2 flash chromatography.

Method **B** – Using $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ as photocatalyst. Equivalent to Method **A** with an exception that 1.0 mol % catalyst loading was used.

Method **C** – Using $[Ir(dtbbpy)(ppy)_2]PF_6$ as photocatalyst. Equivalent to Method **A** with an exception that 1.0 mol % catalyst loading was used.

General procedure for the preparation of benzyl ethers:

Method A-Bn. A round-bottom flask equipped with a stirrer bar was charged with the corresponding phenol (1 equiv) and K_2CO_3 (2 equiv). 55 mL of toluene/DMF (50:5) solvent mixture was then added to the mixture followed by benzyl bromide (1.2 equiv). The reaction mixture was refluxed on a magnetic stirrer plate for the corresponding time. The progress of the reaction was monitored with TLC. After completion, the reaction mixture was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified with SiO_2 flash chromatography.

Method B-Bn. A round-bottom flask equipped with a stirrer bar was charged with NaH (2 equiv) and 20 mL DMF. Benzyl alcohol (1.5 equiv) was added dropwise to the reaction mixture which was stirred 30 min at rt on a magnetic stirrer plate. The corresponding chloro-derivate (1 equiv) was then added to the reaction mixture and it was further stirred at 80 °C for the corresponding time on a magnetic stirrer plate. The progress of the reaction was monitored with TLC. After completion, the reaction mixture was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified with SiO_2 flash chromatography. Tip: If there are difficulties with the purification of the product it can be salted out as the HCl salt. The salt can then be purified with SiO_2 flash chromatography eluting first with solvent that removes the impurities and then *in situ* neutralizing the salt by adding aq. NH_4OH to the eluent system of choice, thus providing pure and neutral product.

General procedure for the preparation of quinolones:

Method A-Qn – using biphenyl ether in the cyclization step**.** (Compounds **2e**, **2h**, **2k** and **6**) *Step 1:* preparation of intermediate. A round-bottom flask equipped with a stirrer bar was charged with Meldrum's acid (1.5 equiv) and trimethyl orthoformate (25 equiv). The reaction mixture was refluxed for 4 h on a magnetic stirrer plate after which the corresponding aniline (1 equiv) was added and the refluxing was continued for 20 h. After completion of the reaction, the excess of trimethyl orthoformate was evaporated and the solids were suspended in Et_2O. The solids were then filtrated off and washed with Et_2O. Tip: If needed, the crude intermediate can be purified, but usually it is sufficiently pure to be used without further purification. *Step 2:* cyclization**.** A round-bottom flask equipped with a stirrer bar was charged with the crude intermediate, which was dissolved in PhOPh (2 mL/mmol) and refluxed for the corresponding time in a heating mantle on magnetic stirrer plate. The progress of the reaction was monitored with TLC. After completion, the reaction mixture was cooled down and diluted with Et_2O. The precipitated solids were then filtrated off and washed with Et_2O. Tip: If the desired quinolone does not precipitate out of the reaction mixture, the whole reaction mixture can be purified with SiO_2 flash chromatography. First eluting with DCM or Et_2O to remove the PhOPh and then with the solvent of choice to eluate the desired quinolone.

Compound 2g. A round-bottom flask equipped with a stirrer bar was charged with 2-bromoaniline (1 equiv) and diethyl ethoxymethylenemalonate (1.1 equiv). The reaction mixture was stirred at 100 °C in neat conditions for 2½ h on a magnetic stirrer. The progress of the reaction was monitored with TLC. After the completion of the reaction, PhOPh (2 mL/mmol) was added to the mixture which was further refluxed for 4 h with the help of heating mantle. After cooling down, the reaction mixture was diluted with Et_2O. The precipitated solids were filtrated off and washed with Et_2O.

Compound 2d. *Step 1:* preparation of intermediate. A round-bottom flask equipped with a stirrer bar was charged with 2-bromoaniline (1 equiv) and diethyl oxalpropionate (1.1 equiv). Fifty milliliter of benzene was added to the reaction mixture followed by a catalytic amount of acetic acid. The reaction mixture was then refluxed for 96 h on a magnetic stirrer plate after which it was partitioned between Et_2O and 1 M HCl. The organic phase was washed with sat. K_2CO_3, dried over Na_2SO_4 and evaporated. The crude product was purified with flash chromatography (SiO_2) using *n*-hexane:EtOAc (5:1) as an eluent. *Step 2:* cyclization. A round-bottom flask equipped with a stirrer bar was charged with the purified intermediate, which was refluxed for 4h in PhOPh (2 mL/mmol) with the help of a heating mantle on a magnetic stirrer plate. After cooling down 50 mL 2 M NaOH was added to the reaction mixture, which was further refluxed for 2 h. Upon cooling and addition of water the crude product precipitated out. The precipitated solids were filtrated off and washed with water. The crude product was sufficiently pure to be used without further purifications. *Step 3:* decarboxylation**.** A round-bottom flask equipped with a stirrer bar was charged with the crude product, which was dissolved in PhOPh (2 mL/mmol) and refluxed for 3 h with the help of a heating mantle

on a magnetic stirrer plate. After completion of the reaction, the reaction mixture was cooled down and diluted with Et_2O. The precipitated solids were filtrated off and washed with

Method B-Qn – using polyphosphoric acid (PPA) in the cyclization step**.** A round-bottom flask fitted with a mechanical stirrer was charged with the corresponding aniline (1 equiv). Dimethyl acetylenedicarboxylate (1 equiv) was added dropwise to the reaction mixture which was stirred in neat conditions at room temperature for 1 h. The reaction was monitored with TLC. After the completion of the reaction, PPA was added and the reaction mixture was further stirred for 2 h at 140 °C. After completion of the reaction, the reaction mixture was quenched with water and extracted with DCM. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified with SiO_2 flash chromatography.

Synthesis of target compounds.

*2-(Benzyloxy)quinoline (**1a**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2-chloroquinoline – **7** (0.818 g, 5 mmol), benzyl alcohol (0.780 mL, 7.5 mmol) and sodium hydride 60% dispersion in mineral oil (0.336 g, 10 mmol). Reaction time 22 h. Yield 90% (1.060 g, 4.50 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (10:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[21] White solid; R_f=0.35 (*n*-hexane:EtOAc=20:1); mp. 46-47 °C; ^{1}H NMR (300MHz; $CDCl_3$) δ_h 8.01 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.0, 1.3 Hz, 1H), 7.65 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.46 – 7.34 (m, 4H), 6.98 (d, J = 8.8 Hz, 1H), 5.59 (s, 2H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 162.1, 146.8, 139.0, 137.6, 129.7, 128.7, 128.5, 128.1, 127.7, 127.5, 125.5, 124.3, 113.5, 67.9; FTIR(cm^{-1}) 2936(w), 2878(w).

*Quinolin-2-ol (**2a**)*. The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 2-(benzyloxy)quinoline – **1a** (0.0471 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield >99% (0.0290g, 0.2mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1) as eluent. Using Method **B**: Reaction time 1 h. Yield >99% (0.0290 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1) as eluent. Using Method **C**: Catalyst loading 0.5 mol %. Reaction time 1 h. Yield >99% (0.0290 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[22] White solid; R_f=0.35 (DCM:MeOH (20:1)); mp. 193-194 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.72 (s, 1H), 7.86 (d, J = 9.6 Hz, 1H), 7.62 (dd, J = 7.8, 1.1 Hz, 1H), 7.46 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H), 7.29 (dd, J = 8.3, 0.5 Hz, 1H), 7.13 (ddd, J = 7.8, 7.2, 1.1 Hz, 1H), 6.48 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz; DMSO) δ_c 162.6, 140.9, 139.6, 131.0, 128.5, 122.6, 122.4, 119.9, 115.8; FTIR(cm^{-1}) 2987(m), 2885(m).

*2-Chloroquinoline – (**7**).* A round-bottom flask equipped with a stirrer bar was charged with quinoline-2-ol (1.452 g, 10 mmol) dissolved in 100 mL of dry toluene. Phosphorous oxychloride (9.323 mL, 100 mmol) was then added and the reaction mixture was refluxed under argon for 21 h on a magnetic stirrer plate. After completion of the reaction, the mixture was carefully quenched with water (*NB! exothermic reaction*) and basified with aqueous NH_4OH. The reaction mixture was extracted with EtOAc, dried over Na_2SO_4 and evaporated to dryness. The crude was purified with SiO_2 flash chromatography. Yield 99.1% (1.621 g, 9.91 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. The characterization data of the obtained compound are in agreement with the literature values.[23] Light yellowish solid; R_f=0.25 (*n*-hexane:EtOAc (20:1)); mp**.** 36-37 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.07 (d, J = 8.6 Hz, 1H), 8.00 (ddt, J = 8.5, 1.3, 0.7 Hz, 1H), 7.79 (dd, J = 8.1, 1.3 Hz, 1H), 7.72 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.53 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 150.8, 148.1, 139.1, 130.8, 128.8, 127.8, 127.8, 127.0, 122.5; FTIR(cm^{-1}) 813(s), 777(s), 741(s).

*4-(Benzyloxy)quinoline (**1b**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from Quinolin-4-ol (0.581 g, 4 mmol), benzyl bromide (0.570 mL, 4.8 mmol) and potassium carbonate (1.106 g, 8 mmol). Reaction time 22 h. Yield 20.2% (0.190 g, 0.81 mmol). Purification: Flash chromatography (SiO_2) using DCM:EtOAc (2:1→1:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[24] White solid; R_f=0.20 (*n*-hexane:EtOAc (1:1)); mp. 75-76 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.74 (d, J = 5.2 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 11.1, 4.2 Hz, 1H), 7.55 – 7.37 (m, 5H), 6.79 (d, J = 5.2 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 161.5, 151.6, 149.6, 136.0, 130.0, 129.2, 129.0, 128.6, 127.7, 125.9, 122.2, 121.7, 101.4, 70.5; FTIR(cm^{-1}) 3003(w), 2957(w), 2933(w), 2873(w).

*Quinolin-4-ol – **(2b)**.* The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)quinoline – **1b** (0.0471 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield >99% (0.0290 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (10:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[25] White solid; R_f=0.31 (DCM:MeOH=10:1); mp. 198-199 °C; ^{1}H NMR (300MHz; DMSO) δ_h 11.77 (s, 1H), 8.08 (dd, J = 8.1, 1.5 Hz, 1H), 7.88 (dd, J = 7.2, 5.4 Hz, 1H), 7.61 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.28 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 6.03 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75MHz; DMSO) δ_c 177.6, 140.7, 140.1, 132.3, 126.5, 125.6, 123.7, 118.9, 109.4; FTIR(cm^{-1}) 3062(w), 2972(w), 2901(w).

*4-(Benzyloxy)-2-methylquinoline **(1c)**.* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from 2-methylquinolin-4-ol (0.796 g, 5 mmol), benzyl bromide (0.713 mL, 6 mmol) and potassium carbonate (1.382 g, 10 mmol). Reaction time 24 h. Yield 96% (1.197 g, 4.80 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (40:1) as eluent. Light yellowish solid; R_f=0.23 (DCM:MeOH (40:1)); mp**.** 105-106 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.20 (dd, J = 8.3, 0.9 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.65 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.54 – 7.34 (m, 6H), 6.68 (s, 1H), 5.24 (s, 2H), 2.68 (s, 3H); **^{13}C** NMR (75 MHz; $CDCl_3$) δ_c 161.5, 160.3, 149.2, 136.1, 130.0, 129.0, 128.6, 128.4, 127.7, 125.1, 122.0, 120.2, 101.8, 70.3, 26.2; FTIR(cm^{-1}) 3063(w), 3005(w), 2914(w), 2872(w); HRMS**:** calcd for $C_{17}H_{16}NO$ 250.1226 (M+H); found 250.1224 (Δ=0.99 ppm)

*2-Methylquinolin-4-ol **(2c)**.* The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)-2-methylquinoline – **1c** (0.0499 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1h. Yield 93.1% (0.0296 g, 0.19 mmol). Purification: Flash chromatography (SiO_2) using acetone as eluent. The characterization data of the obtained compound are in agreement with the literature values.[26] White solid; R_f=0.33 (DCM:MeOH (10:1)); mp. 229-230 °C; ^{1}H NMR (300MHz; DMSO) δ_h 11.58 (s, 1H), 8.05 (dd, J = 8.0, 1.3 Hz, 1H), 7.60 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.26 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 5.91 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75MHz; DMSO) δ_c 177.4, 150.3, 140.8, 132.1, 125.5, 125.2, 123.4, 118.4, 109.1, 20.1; FTIR(cm^{-1}) 3061(w), 2971(w), 2901(w), 2738(w), 2663(w).

*4-(Benzyloxy)-8-bromo-3-methylquinoline **(1d)**.* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from 8-bromo-3-methylquinolin-4-ol (0.238 g, 1 mmol), benzyl bromide (0.143 mL, 1.2 mmol) and potassium carbonate (0.276 g, 2 mmol). Reaction time 24 h. Yield 84.8% (0.278 g, 0.85 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (10:1) as eluent. Light yellowish solid; R_f=0.12 (*n*-hexane:EtOAc (10:1)); mp. 96-97 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.86 (s, 1H), 8.04 (dd, J = 8.4, 1.3 Hz, 1H), 7.97 (dd, J = 7.4, 1.3 Hz, 1H), 7.49 – 7.37 (m, 5H), 7.33 (dd, J = 8.4, 7.5 Hz, 1H), 5.10 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 160.2, 155.1, 146.1, 136.4, 132.7, 128.9, 128.7, 128.2, 126.8, 125.4, 124.9, 122.8, 121.9, 76.3, 14.0; FTIR(cm^{-1}) 3089(w), 3066(w), 3033(w), 2953(w), 2917(w), 766(s), 747(s), 694(s)); HRMS: calcd for $C_{17}H_{15}BrNO$ 328.0332 (M+H); found 328.0.327 (Δ=1.52 ppm)

*8-Bromo-3-methylquinolin-4-ol **(2d)**. By catalytic deprotection*: The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)-8-bromo-3-methylquinoline – **1d** (0.0656 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield 92.9% (0.0442 g, 0.19 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent.

By cyclization: The title compound was synthesized following the general procedure for preparation of quinolones *Method A-Qn* (compound **2d**). The intermediate **1** was obtained from 2-bromoaniline (5.161 g, 30 mmol) diethyl 2-methyl-3-oxosuccinate (6.224 mL, 33 mmol) and catalytic amount of acetic acid. Yield 56% (6.0 g, 16.84 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (5:1) as eluent. The intermediate **2** was obtained from intermediate **1** (6.0 g, 16.84 mmol), which was refluxed in PhOPh for 4 h. Then to the reaction mixture was added 50 mL 2 M NaOH and the reflux was continued for additional 2 h. Yield 15.3% (0.723 g, 2.56 mmol). The product was prepared from the intermediate **2** (0.600 g, 2.13 mmol), which was refluxed in PhOPh for 3 h. Yield 71.5% (0.326 g, 1.37 mmol). White solid; R_f=0.27 (DCM:MeOH (20:1)); mp. 224-225 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 10.99 (d, J = 4.6 Hz, 1H), 8.13 (dd, J = 8.1, 1.3 Hz, 1H), 7.92 (dd, J = 7.6, 1.4 Hz, 1H), 7.81 (dd, J = 6.0, 0.6 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 1.99 (s, J = 0.5 Hz, 3H); ^{13}C NMR (75 MHz; DMSO) δ_c 177.1, 138.1, 138.0, 135.3, 126.1, 125.7, 124.0, 118.1, 111.7, 14.1; FTIR(cm^{-1}) 3081(w), 2946(w), 2922(w), 2892(w), 746(s); HRMS: calcd for $C_{10}H_9BrNO$ 237.9862 (M+H); found 237.9858 (Δ=1.88 ppm)

*4-(benzyloxy)-8-bromoquinoline (**1e**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from 8-bromoquinolin-4-ol (2.241 g, 10 mmol), benzyl bromide (1.523 mL, 12 mmol) and potassium carbonate (2.764 g, 20 mmol). Reaction time 25 h. Yield 61.1% (1.921 g, 6.11 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (100:1→50:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[10a] light yellowish solid; R_f=0.30 (Hexane:EtOAc=2:1); mp. 125-126 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.86 (d, J = 5.2 Hz, 1H), 8.25 (dd, J = 8.4, 1.3 Hz, 1H), 8.03 (dd, J = 7.5, 1.3 Hz, 1H), 7.51 – 7.37 (m, 5H), 7.36 – 7.29 (m, 1H), 6.85 (d, J = 5.2 Hz, 1H), 5.28 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 161.7, 152.3, 146.6, 135.6, 133.8, 129.0, 128.8, 127.7, 126.2, 124.5, 123.1, 122.2, 102.1, 70.9; FTIR(cm^{-1}) 3059(w), 3032(w), 2942(w), 2881(w), 746(s), 699(s).

*8-Bromoquinolin-4-ol (**2e**). By catalytic deprotection*: The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)-8-bromoquinoline – **1e** (0.0628 g, 0.2 mmol), ascorbic acid (0.0704g, 0.4mmol) and [Ru] photocatalyst (0.00075g, 0.001mmol). Reaction time 2h. Yield >99% (0.0448g, 0.2mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1) using as eluent.

By cyclization: The title compound was synthesized following the general procedure for preparation of quinolones *Method A-Qn* (compounds **2e**, **2h**, **2k** and **6**). The intermediate was obtained from 2-bromoaniline (10.011 g, 58.2 mmol) Meldrum's acid (12.160 g, 84.4 mmol) and trimethyl orthoformate (159.027 mL, 1453.6 mmol). Yield 88.2% (16.739 g, 51.32 mmol). The product was prepared from the intermediate (6.0 g, 18.39 mmol), which was refluxed in PhOPh for 4 h. Yield 88.4% (3.642 g, 16.25 mmol). The characterization data of the obtained compound are in agreement with the literature values.[10a] White solid; $\boldsymbol{R_f}$=0.22 (DCM:MeOH (20:1)); mp. 164-165 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.09 (s, 1H), 8.10 (dd, J = 8.0, 1.0 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 6.10 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75MHz; DMSO) δ_c 177.2, 141.0, 138.3, 135.9, 127.9, 125.7, 124.6, 112.0, 110.1; FTIR(cm^{-1}) 3426 (br. w), 2988(w), 2901(w), 788(s), 742(s).

*4-(Benzyloxy)quinoline-8-carbaldehyde (**8**).* A Schlenk-flask equipped with a stirrer bar was charged with 4-(benzyloxy)-8-bromoquinoline – **2e** (0.730 g, 2.32 mmol) and 50 mL of dry THF under argon. The reaction mixture was cooled down to -78 °C and 2.5 M *n*-butyllithium (1.39 mL, 3.48 mmol) was added to it under magnetic stirring. The reaction mixture was then stirred at -78 °C for 30 min after which dry DMF (0.268 mL, 3.48 mmol) was added to it. The mixture was further stirred 3½ h at -78 °C. The reaction was quenched with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude was purified with SiO_2 flash chromatography. Yield 65.5% (0.400 g, 1.52 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. The characterization data of the obtained compound are in agreement with the literature values.[10a] Light yellowish solid; R_f=0.35 (Hexane:EtOAc=3:1); mp. 118-119 °C; ^{1}H NMR (300MHz; $CDCl_3$) δ_h 11.42 (s, 1H), 8.87 (d, J = 5.2 Hz, 1H), 8.56 (dd, J = 8.3, 1.6 Hz, 1H), 8.32 (dd, J = 7.2, 1.6 Hz, 1H), 7.63 (ddd, J = 8.1, 7.2, 0.7 Hz, 1H), 7.53 – 7.41 (m, 5H), 6.91 (d, J = 5.2 Hz, 1H), 5.33 (s, 2H); **^{13}C** NMR (75MHz; $CDCl_3$) δ_c 193.1, 161.7, 152.5, 149.1, 135.5, 131.5, 129.8, 129.1, 128.8, 128.8, 127.8, 125.4, 122.1, 102.1, 70.8; FTIR(cm^{-1}) 2988(w), 2968(w), 2923(w), 2877 (w), 1678(s).

*4-(Benzyloxy)-8-(5,5-dimethyl-1,3-dioxan-2-yl)quinoline – (**1f**).* A round-bottom flask equipped with a stirrer bar was charged with 4-(benzyloxy)quinoline-8-carbaldehyde – **8** (0.080 g, 0.3 mmol), 2,2-dimethylpropane-1,3-diol (0.156 g, 1.5 mmol) and 30 mL benzene. *p*-TSA (0.003 g, 0.015 mmol) was added to the mixture and it was refluxed in a Dean-Stark apparatus for 24 h on a magnetic stirrer plate. The reaction mixture was then quenched with 2N NaOH and extracted with EtOAc. Organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude was purified with SiO_2 flash chromatography. Yield 99% (0.104 g, 0.29 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (100:1→50:1) as eluent. White solid; R_f=0.17 (Hexane:EtOAc=2:1); mp. 202-203 °C; ^{1}H NMR (300MHz; $CDCl_3$) δ_h 8.77 (d, J = 5.2 Hz, 1H), 8.31 (dd, J = 8.4, 1.5 Hz, 1H), 8.15 (dd, J = 7.2, 1.5 Hz, 1H), 7.57 (dd, J = 8.3, 7.3 Hz, 1H), 7.52 – 7.34 (m, 5H), 6.80 (d, J = 5.2 Hz, 1H), 6.71 (s, 1H), 5.28 (s, 2H), 3.89 (d, J = 10.6 Hz, 2H), 3.82 (d, J = 10.9 Hz, 2H), 1.40 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 161.5, 151.2, 146.6, 135.9, 135.8, 129.0, 128.6, 128.0, 127.6, 125.8, 123.1, 121.5, 101.4, 97.8, 78.2, 70.4, 30.6, 23.5, 22.2; FTIR(cm^{-1}) 2989(w), 2858(w); HRMS: calcd for $C_{22}H_{24}NO_3$ 350.1751 (M+H); found 350.1749 (Δ=0.47 ppm)

*8-(5,5-Dimethyl-1,3-dioxan-2-yl)quinolin-4-ol – (**2f**).* The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)-8-(5,5-dimethyl-1,3-dioxan-2-yl)quinoline – **1f** (0.0349 g, 0.1 mmol), ascorbic acid (0.0352 g, 0.2 mmol) and [Ru] photocatalyst

(0.375 mg, 0.0005 mmol). Reaction time 40 min. Yield 90% (0.0232 g, 0.09 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1) as eluent. White solid; R_f=0.26 (DCM:MeOH (20:1)); mp**.** 69-70 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 10.36 (s, 1H), 8.39 (dd, J = 8.2, 1.5 Hz, 1H), 7.64 (ddd, J = 7.4, 3.9, 2.3 Hz, 2H), 7.31 (dd, J = 8.1, 7.4 Hz, 1H), 6.29 (d, J = 7.5 Hz, 1H), 5.71 (s, 1H), 3.85 (d, J = 11.4 Hz, 2H), 3.74 (d, J = 10.7 Hz, 2H), 1.33 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 178.9, 138.2, 138.1, 131.6, 127.6, 127.3, 125.1, 123.2, 110.2, 102.9, 78.2, 30.6, 23.6, 22.1; FTIR(cm^{-1}) 3259(br. w), 3083(w), 2956(w), 2865(w), 1787(w); HRMS**:** calcd for $C_{15}H_{18}NO_3$ 260.1281 (M+H); found 260.1285 (Δ=1.54 ppm)

*Ethyl 4-(benzyloxy)-8-bromoquinoline-3-carboxylate – **(1g)***. The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from ethyl 8-bromo-4-hydroxyquinoline-3-carboxylate (1.481 g, 5 mmol), benzyl bromide (0.761 mL, 6 mmol) and potassium carbonate (1.381 g, 10 mmol). Reaction time 24 h. Yield 50.5% (0.975 g, 2.52 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (100:1) as eluent. Light yellowish solid; R_f=0.16 (*n*-hexane:EtOAc (10:1)); mp**.** 89-90 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 9.34 (s, J = 3.4 Hz, 1H), 8.16 (dd, J = 8.4, 1.3 Hz, 1H), 8.08 (dd, J = 7.5, 1.3 Hz, 1H), 7.47 – 7.32 (m, 6H), 5.30 (s, 2H), 4.47 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 165.0, 164.2, 153.0, 148.1, 136.1, 135.5, 128.9, 128.5, 127.4, 125.5, 124.9, 123.7, 115.0, 78.4, 62.0, 14.5; FTIR(cm^{-1}) 3065(w), 3036(w), 2979(w), 2928(w), 2904(w), 1719(s), 779(s), 741(s), 690(s); HRMS: calcd for $C_{19}H_{17}BrNO_3$ 386.0386 (M+H); found 386.0397 (Δ=2.75 ppm)

*Ethyl 8-bromo-4-hydroxyquinoline-3-carboxylate **(2g)**. By catalytic deprotection*: The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from ethyl 4-(benzyloxy)-8-bromoquinoline-3-carboxylate – **1g** (0.0773 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield >99% (0.0592 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent.

By cyclization: The title compound was synthesized following the general procedure for preparation of quinolones *Method A-Qn* (compound **2g**). Starting from 2-bromoaniline (8.601 g, 50 mmol) and diethyl ethoxymethylenemalonate (11.115 mL, 55 mmol) Yield 93.2% (13.793 g, 46.56 mmol). The characterization data of the obtained compound are in agreement with the literature values.[27] White solid; R_f=0.32 (DCM:MeOH (20:1)); mp. 252-253 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.58 (s, 1H), 8.42 (s, 1H), 8.15 (dd, J = 8.1, 1.4 Hz, 1H), 7.99 (dd, J = 7.7, 1.4 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; DMSO) δ_c 173.5, 165.0, 146.2, 137.3, 136.6, 129.5, 126.3, 126.3, 112.4, 111.0, 60.5, 14.9; FTIR(cm^{-1}) 3149(w), 3081(w), 2975(w), 2925(w), 2901(w), 1710(m), 743(s).

*Ethyl 4-(benzyloxy)quinoline-8-carboxylate – **(1h)***. The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from ethyl 4-hydroxyquinoline-8-carboxylate (0.652 g, 3 mmol), benzyl bromide (0.428 mL, 3.6 mmol) and potassium carbonate (0.829 g, 6 mmol). Reaction time 28 h. Yield 80.7% (0.744 g, 2.42 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (1:1) as eluent. Yellowish solid; R_f=0.24 (Hexane:EtOAc (1:1)); mp. 99-100 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.86 (d, J = 5.2 Hz, 1H), 8.40 (dd, J = 8.4, 1.5 Hz, 1H), 7.98 (dd, J = 7.2, 1.5 Hz, 1H), 7.56 – 7.35 (m, 6H), 6.83 (d, J = 5.3 Hz, 1H), 5.28 (s, 2H), 4.52 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 168.1, 161.4, 152.6, 146.8, 135.7, 131.8, 130.6, 129.0, 128.7, 127.7, 125.5, 124.8, 122.1, 101.9, 70.6, 61.6, 14.6; FTIR(cm^{-1}) 3061(w), 2985(w), 2943(w), 2903(w), 1724(s); HRMS: calcd for $C_{19}H_{18}NO_3$ 308.1281 (M+H); found 308.1280 (Δ=0.47 ppm)

*Ethyl 4-hydroxyquinoline-8-carboxylate – **(2h)**. By catalytic deprotection*: The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from ethyl 4-(benzyloxy)quinoline-8-carboxylate – **1h** (0.0615 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 2 h. Yield 36.2% (0.0157 g, 0.07 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent.

By cyclization: The title compound was synthesized following the general procedure for preparation of quinolones *Method A-Qn* (compounds **2e**, **2h**, **2k** and **6**). The intermediate was obtained from ethyl 2-aminobenzoate (8.599 mL, 58.2 mmol) Meldrum's acid (12.160 g, 84.4 mmol) and trimethyl orthoformate (159.027 mL, 1453.6 mmol). Yield 86.8% (16.128 g, 50.51 mmol). The product was prepared from the intermediate (5.748 g, 18 mmol), which was refluxed in PhOPh for 3 h. Yield 73.7% (2.882 g, 13.27 mmol). Light yellowish solid; R_f=0.27 (DCM:MeOH (20:1)); mp. 151-152 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.72 (s, 1H), 8.40 (dd, J = 8.0, 1.4 Hz, 1H), 8.31 (dd, J = 7.6, 1.6 Hz, 1H), 7.98 (dd, J = 7.5, 6.3 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; DMSO) δ_c 177.1, 166.8, 141.2, 140.3, 135.4, 132.2, 127.3, 122.8, 116.7, 110.3, 62.1, 14.7; FTIR(cm^{-1})

3280(m), 2980(w), 2940(w), 2904(w), 1686(m); HRMS**:** calcd for $C_{12}H_{12}NO_3$ 218.0812 (M+H); found 218.0819 (Δ=3.12 ppm)

*Methyl 4-(benzyloxy)quinoline-2-carboxylate (**1i**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from methyl 4-hydroxyquinoline-2-carboxylate (0.610 g, 3 mmol), benzyl bromide (0.428 mL, 3.6 mmol) and potassium carbonate (0.829 g, 6 mmol). Reaction time 24 h. Yield 79% (0.693 g, 2.37 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (5:1→3:1) as eluent. White solid; R_f=0.19 (*n*-hexane:EtOAc (2:1)); mp. 128-129 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.29 (ddd, J = 8.4, 1.5, 0.6 Hz, 1H), 8.24 (ddd, J = 8.5, 1.1, 0.6 Hz, 1H), 7.76 (ddd, J = 8.5, 5.5, 1.5 Hz, 1H), 7.68 (s, 1H), 7.59 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.48 – 7.37 (m, 3H), 5.35 (s, 2H), 4.07 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 166.5, 162.6, 149.3, 148.8, 135.6, 130.7, 130.5, 129.0, 128.8, 127.9, 122.6, 122.2, 101.4, 70.9, 53.5; FTIR(cm^{-1}) 3109(w), 3074(w), 3035(w), 3009(w), 2954(w), 1744(m), 1721(m); HRMS: calcd for $C_{18}H_{16}NO_3$ 294.1125 (M+H); found 294.1115 (Δ=3.33 ppm)

*Methyl 4-hydroxyquinoline-2-carboxylate (**2i**)*. The title compound was synthesized following the general procedure for preparation of quinolones *Method B-Qn*. Starting from aniline (2.283 mL, 25 mmol) and dimethyl acetylenedicarboxylate (3.073 mL, 25 mmol). PPA was used as a solvent. Yield 58.2% (2.958 g, 14.56 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1→20:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[28] Light yellowish solid; R_f=0.27 (DCM:MeOH (20:1)); mp. 224-225 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 12.05 (s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 6.63 (s, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz; DMSO) δ_c 178.3, 163.3, 140.7, 138.3, 133.3, 126.6, 125.4, 124.7, 120.2, 110.9, 54.2; FTIR(cm^{-1}) 3072(w), 2954(w), 2875(w), 2761(w), 1738(m).

*2,4-Bis(benzyloxy)quinoline (**1j**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2,4-dichloroquinoline – **9** (0.990 g, 5 mmol), benzyl alcohol (1.560 mL, 15 mmol) and sodium hydride 60% dispersion in mineral oil (0.672 g, 20 mmol). Reaction time 18 h. Yield 86.4% (1.475 g, 4.32 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (10:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[29] White solid; R_f=0.27 (*n*-hexane:EtOAc=20:1); mp. 80-81 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.17 (dd, J = 8.2, 0.9 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.57 – 7.35 (m, 11H), 6.40 (s, 1H), 5.57 (s, 2H), 5.23 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 163.4, 163.2, 147.3, 137.7, 136.0, 130.3, 129.0, 128.7, 128.6, 128.1, 127.7, 127.2, 123.6, 122.3, 119.7, 92.2, 70.5, 68.0; FTIR(cm^{-1}) 3062(w), 3033(w), 2949(w), 2927(w), 2876(w).

*4-(Benzyloxy)quinolin-2-ol – (**2j**)*. The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 2,4-bis(benzyloxy)quinoline – **1j** (0.0683 g, 0.2 mmol), ascorbic acid (0.0704g, 0.4mmol) and [Ru] photocatalyst (0.0015g, 0.002mmol). Reaction time 5 h. Yield 76.5% (0.0385 g, 0.15 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (20:1) as eluent.

Using Method **B**: Reaction time 3 h. Yield 99% (0.0498 g, 0.19 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (20:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[17] White solid; R_f=0.31 (DCM:MeOH (20:1)); mp. 195-196 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 12.52 (s, 1H), 7.96 (dd, J = 8.1, 1.0 Hz, 1H), 7.54 – 7.36 (m, 7H), 7.18 (ddd, J = 8.2, 5.5, 1.4 Hz, 1H), 6.11 (s, 1H), 5.20 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 166.5, 164.1, 138.8, 135.5, 131.4, 129.0, 128.7, 127.8, 123.1, 122.3, 116.4, 115.8, 97.3, 70.8; FTIR(cm^{-1}) 3060(w), 2965(w), 2828(w), 2697(w).

*2,4-Dichloroquinoline (**9**)*. A round-bottom flask equipped with a stirrer bar was charged with quinoline-2,4-diol (1.612 g, 10 mmol) and 50 mL of dry toluene. Phosphorous oxychloride (9.323 mL, 100 mmol) was added to the reaction mixture which was then refluxed under argon for 21 h on a magnetic stirrer plate. After completion of the reaction, the reaction mixture was carefully quenched with water (*NB! exothermic reaction*) and basified with aqueous NH_4OH. The reaction mixture was then extracted with EtOAc, dried over Na_2SO_4 and evaporated to dryness. The crude was purified with SiO_2 flash chromatography. Yield 92.5% (1.833 g, 9.25 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. The characterization data of the obtained compound are in agreement with the literature values.[30] Light yellowish solid; R_f=0.30 (*n*-hexane:EtOAc (20:1)); mp. 64-65 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.17 (ddd, J = 8.4, 1.4, 0.5 Hz, 1H), 8.02 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.78 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.63

(ddd, J = 8.3, 5.8, 1.2 Hz, 1H), 7.49 (s, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 150.0, 148.3, 144.6, 131.7, 129.2, 128.1, 125.4, 124.4, 122.2; FTIR(cm^{-1}) 854(m), 842(s), 755(s), 708(s).

*4,8-Bis(benzyloxy)quinoline (**1k**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from 8-(benzyloxy)quinolin-4-ol (0.754 g, 3 mmol), benzyl bromide (0.428 mL, 3.6 mmol) and potassium carbonate (0.829 g, 6 mmol). Reaction time 16 h. Yield 31.4% (0.322 g, 0.94 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (1:1→EtOAc) as eluent. Light yellowish solid; R_f=0.34 (DCM:MeOH (40:1)); mp. 157-158 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.80 (d, J = 5.2 Hz, 1H), 7.83 (dd, J = 8.4, 1.1 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.45 – 7.28 (m, 7H), 7.03 (dd, J = 7.8, 1.0 Hz, 1H), 6.83 (d, J = 5.2 Hz, 1H), 5.44 (s, 2H), 5.27 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 161.4, 154.4, 150.5, 141.8, 137.3, 136.0, 129.0, 128.8, 128.6, 128.0, 127.6, 127.3, 125.8, 122.9, 114.2, 110.8, 102.0, 71.0, 70.5; FTIR(cm^{-1}) 3066(w), 3029(w), 2942(w), 2868(w); HRMS: calcd for $C_{23}H_{20}NO_2$ 342.1489 (M+H); found 342.1490 (Δ=0.36 ppm)

*8-(Benzyloxy)quinolin-4-ol (**2k**). By catalytic deprotection*: The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4,8-bis(benzyloxy)quinoline – **1k** (0.0683 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 40 min. Yield 98% (0.0490 g, 0.19 mmol). Purification: Solids were filtrated off and washed with water.

By cyclization: The title compound was synthesized following the general procedure for preparation of quinolones *Method A-Qn* (compounds **2e**, **2h**, **2k** and **6**). The intermediate was obtained from 2-benzyloxyaniline (3.985 g, 20 mmol) Meldrum's acid (4.324 g, 30 mmol) and trimethyl orthoformate (54.701 mL, 500 mmol). Yield 99% (6.996 g, 19.80 mmol). The product was prepared from the intermediate (3.534 g, 10 mmol), which was refluxed in PhOPh for 15 min. Yield 76.6% (1.925 g, 7.66 mmol). Light yellowish solid; R_f=0.22 (DCM:MeOH (20:1)); mp. 200-201 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.24 (d, J = 4.6 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.44 – 7.30 (m, 4H), 7.21 (t, J = 8.0 Hz, 1H), 6.07 (d, J = 7.4 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (75 MHz; DMSO) δ_c 177.4, 148.0, 139.7, 137.1, 131.7, 129.1, 128.7, 128.6, 127.4, 123.4, 117.2, 113.0, 109.9, 70.8; FTIR(cm^{-1}) 3162(w), 3122(w), 3087(w), 3032(w), 2940(w), 2876(w); HRMS: calcd for $C_{16}H_{14}NO_2$ 252.1019 (M+H); found 252.1015 (Δ=1.75 ppm)

*1-(Benzyloxy)isoquinoline (**1l**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 1-chloroisoquinoline (0.327 g, 2 mmol), benzyl alcohol (0.312 mL, 3 mmol) and sodium hydride 60% dispersion in mineral oil (0.134 g, 4 mmol). Reaction time 20 h. Yield 64.3% (0.326 g, 1.29 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. The characterization data of the obtained compound are in agreement with the literature values.[31] Yellowish liquid; R_f=0.27 (*n*-hexane:EtOAc (20:1)); ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.34 (ddt, J = 8.3, 1.4, 0.8 Hz, 1H), 8.04 (d, J = 5.9 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.67 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.46 – 7.33 (m, 3H), 7.25 (dd, J = 5.9, 0.8 Hz, 1H), 5.61 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 160.6, 139.9, 138.2, 137.7, 130.7, 128.7, 128.1, 126.9, 126.3, 124.5, 120.1, 115.4, 68.0; FTIR(cm^{-1}) 3055(w), 3032(w), 2944(w), 2886(w).

*Isoquinolin-1-ol (**2l**).* The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 1-(benzyloxy)isoquinoline – **1l** (0.0507 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0. 75 mg, 0.001 mmol). Reaction time 2 h. Yield >99% (0.0290 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[32] White solid; R_f=0.29 (DCM:MeOH (20:1)); mp. 201-202 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.20 (s, 1H), 8.17 (dd, J = 8.0, 0.6 Hz, 1H), 7.72 – 7.59 (m, 2H), 7.46 (ddd, J = 8.2, 6.7, 1.6 Hz, 1H), 7.15 (d, J = 6.8 Hz, 1H), 6.52 (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz; DMSO) δ_c 162.5, 138.6, 133.0, 129.6, 127.3, 127.0, 126.9, 126.8, 105.3; FTIR(cm^{-1}) 3159(w), 3003(w), 2982(w), 2914(w), 2887(w), 2852(w),.

*6-(Benzyloxy)phenanthridine (**1m**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 6-chlorophenanthridine – **10** (0.427 g, 2 mmol), benzyl alcohol (0.312 mL, 3 mmol) and sodium hydride 60% dispersion in mineral oil (0.134 g, 4 mmol). Reaction time 17 h. Yield 96.1% (0.549 g, 1.92 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (20:1) as eluent. White solid; R_f=0.38 (*n*-hexane:EtOAc (20:1)); mp. 75-76 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.51 (d, J = 8.3 Hz, 1H), 8.48 – 8.41 (m, 2H), 7.96 (ddd, J = 8.2, 1.3, 0.4 Hz, 1H), 7.81 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 7.72 – 7.59 (m, 4H), 7.55 – 7.34 (m, 4H), 5.76 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 158.8, 143.5, 137.8, 135.1, 131.1, 129.0, 128.8, 128.4, 128.2, 128.1, 127.5, 125.4,

124.7, 122.9, 122.4, 122.1, 120.3, 68.0; FTIR(cm^{-1}) 3066(w), 3035(w), 3020(w), 2930(w), 2876(w); HRMS: calcd for $C_{20}H_{16}NO$ 286.1226 (M+H); found 286.1235 (Δ=3.06 ppm)

*Phenanthridin-6-ol (**2m**)*. The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 6-(benzyloxy)phenanthridine – **1m** (0.0571 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.0015 g, 0.002 mmol). Reaction time 3 h. Yield >99% (0.0390 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (40:1) as eluent. Using Method **B**: Reaction time 3 h. Yield >99% (0.0390 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (40:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[33] Light yellowish solid; R_f=0.14 (DCM:MeOH (40:1)); mp**.** 286-287 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.66 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 8.38 – 8.29 (m, 2H), 7.88 – 7.78 (m, 1H), 7.66 – 7.58 (m, 1H), 7.46 (ddd, J = 8.2, 7.1, 1.3 Hz, 1H), 7.36 (dd, J = 8.2, 1.3 Hz, 1H), 7.23 (ddd, J = 8.2, 7.1, 1.4 Hz, 1H); ^{13}C NMR (75 MHz; DMSO) δ_c 161.5, 137.3, 134.9, 133.4, 130.2, 128.6, 128.1, 126.4, 123.9, 123.2, 122.9, 118.2, 116.8; FTIR(cm^{-1}) 3288(w), 3156(w), 3100(w), 2997(w), 2975(w), 2887(w).

*6-Chlorophenanthridine (**10**)*. A round-bottom flask equipped with a stirrer bar was charged with phenanthridin-6-ol (0.586 g, 3 mmol) and 30 mL of dry toluene. Phosphorous oxychloride (2.738 mL, 30 mmol) was added to the reaction mixture which was then refluxed under an argon for 19 h on a magnetic stirrer plate. After completion of the reaction, the reaction mixture was carefully quenched with water (*NB! exothermic reaction*) and basified with aqueous NH_4OH. The reaction mixture was then extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude was purified with SiO_2 flash chromatography. Yield 96.3% (0.617 g, 2.89 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. The characterization data of the obtained compound are in agreement with the literature values.[34] Light yellowish solid; R_f=0.20 (*n*-hexane:EtOAc (20:1)); mp**.** 111-112 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.55 – 8.49 (m, 1H), 8.49 – 8.38 (m, 2H), 8.10 – 8.01 (m, 1H), 7.84 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 7.75 – 7.59 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 151.6, 143.5, 134.7, 131.9, 129.5, 128.4, 127.9, 127.7, 125.1, 124.2, 122.4; FTIR(cm^{-1}) 754(s), 719(s).

*2,4-bis(benzyloxy)-6,7-dimethoxyquinazoline (**1n**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2,4-dichloro-6,7-dimethoxyquinazoline (0.518 g, 2 mmol), benzyl alcohol (0.624 mL, 6 mmol) and sodium hydride 60% dispersion in mineral oil (0.269 g, 8 mmol). Reaction was carried in THF at room temperature. Reaction time 22 h. Yield 88.6% (0.0713 g, 1.77 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (2:1) as eluent. White solid; R_f=0.34 (*n*-hexane:EtOAc (2:1)); mp. 137-138 °C; ^{1}H NMR (300MHz; $CDCl_3$) δ_h 7.56 – 7.48 (m, 4H), 7.44 – 7.33 (m, 6H), 7.31 (s, 1H), 7.11 (s, 1H), 5.61 (s, 2H), 5.52 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 167.6, 161.2, 156.0, 150.0, 147.9, 137.2, 136.5, 128.8, 128.6, 128.5, 128.1, 107.3, 106.0, 102.3, 69.1, 68.9, 56.4; FTIR(cm^{-1}) 3089(w), 3034(w), 3010(w), 2964(w), 2889(w); HRMS: calcd for $C_{24}H_{23}N_2O_4$ 403.1652 (M+H); found 403.1666 (Δ=3.34 ppm).

*2-(Benzyloxy)-6,7-dimethoxyquinazolin-4-ol (**2n**)*. The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 2,4-bis(benzyloxy)-6,7-dimethoxyquinazoline – **1n** (0.0805 g, 0.2 mmol), ascorbic acid (0.0704g, 0.4 mmol) and [Ru] photocatalyst (0.0015 g, 0.002 mmol). Reaction time 5½ h. Yield 57.6% (0.0360 g, 0.12 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (40:1) as eluent. Using Method **B**: Reaction time 2 h. Yield 89.8% (0.0561 g, 0.18 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent.

White solid; R_f=0.30 (*n*-hexane:EtOAc (1:1)); mp. 224-225 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 10.00 (s, 1H), 7.54 (s, 1H), 7.48 (dd, J = 7.8, 1.7 Hz, 2H), 7.43 – 7.34 (m, 3H), 6.97 (s, 1H), 5.49 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 163.0, 155.7, 151.9, 147.7, 145.3, 135.6, 128.8, 128.8, 128.6, 112.1, 107.1, 106.3, 69.4, 56.5; FTIR(cm^{-1}) 3004(w), 2962(w), 2872(w), 2831(w), 2745(w); HRMS: calcd for $C_{17}H_{17}N_2O_4$ 313.1183 (M+H); found 313.1182 (Δ=0.11 ppm).

*2-(Benzyloxy)pyridine (**3a**)*. The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2-bromopyridine (0.954 mL, 10 mmol), benzyl alcohol (1.560 mL, 15 mmol) and sodium hydride 60% dispersion in mineral oil (0.672 g, 20 mmol). Reaction was stirred at room temperature for 20 h. Yield 85.3% (1.580 g, 8.53 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane→ *n*-hexane:EtOAc (10:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[21] Colorless liquid; R_f=0.45 (*n*-hexane:EtOAc (10:1)); ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.17 (ddd, J = 5.1, 2.0, 0.8 Hz, 1H), 7.56 (ddd, J = 8.4, 7.1, 2.0 Hz, 1H), 7.46

(ddt, J = 3.7, 3.0, 1.5 Hz, 2H), 7.39 – 7.28 (m, 3H), 6.87 (ddd, J = 7.1, 5.1, 1.0 Hz, 1H), 6.80 (dt, J = 8.4, 0.9 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 163.8, 147.0, 138.7, 137.5, 128.6, 128.1, 127.9, 117.0, 111.5, 67.6; FTIR(cm^{-1}) 3064(w), 3032(w), 2944(w), 2884(w).

*Pyridin-2-ol – **(4a)**.* The title compound was synthesized following the general procedure for benzyl ether removal Method **B**. Starting from 2-(benzyloxy)pyridine – **3a** (0.0370 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ir] photocatalyst (0.0022 g, 0.002 mmol). Reaction time 3 h. Yield 95% (0.0180 g, 0.19 mmol). Purification: Flash chromatography (SiO_2) using acetone as eluent. The characterization data of the obtained compound are in agreement with the literature values. [35] Light brownish solid; R_f=0.42 (DCM:MeOH (10:1)); mp. 105-106 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 13.56 (s, 1H), 7.47 – 7.40 (m, 1H), 7.36 (ddd, J = 6.5, 2.1, 0.8 Hz, 1H), 6.59 – 6.51 (m, 1H), 6.25 (td, J = 6.6, 1.1 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 165.8, 141.9, 134.9, 120.4, 107.2; FTIR(cm^{-1}) 3092(w), 3066(w), 2981(w), 2875(w), 2789(w).

*4-(Benzyloxy)pyridine **(3b)**.* The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 4-chloropyridine hydrochloride (1.500 g, 10 mmol), benzyl alcohol (3.119 mL, 30 mmol) and sodium hydride 60% dispersion in mineral oil (1.344 g, 40 mmol). Reaction time 24 h. Yield 95% (1.760 g, 9.5 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (2:1→1:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[36] Yellowish solid; R_f=0.23 (DCM:MeOH (40:1)); mp. 51-52 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.43 (dd, J = 4.8, 1.6 Hz, 2H), 7.45 – 7.31 (m, 5H), 6.86 (dd, J = 4.8, 1.6 Hz, 2H), 5.09 (s, 2H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 164.9, 151.4, 135.9, 129.0, 128.6, 127.7, 110.8, 70.0; FTIR(cm^{-1}) 3064(w), 3036(w), 2938(w), 2875(w).

*Pyridin-4-ol – **(4b)**.* The title compound was synthesized following the general procedure for benzyl ether removal Method **C**. Starting from 4-(benzyloxy)pyridine – **3b** (0.0370 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ir] photocatalyst (0.0018 g, 0.002 mmol). Reaction time 21 h. Yield 98.9% (0.0188 g, 0.198 mmol). Purification: Flash chromatography (SiO_2) using $CHCl_3$:MeOH:NH_4OH (100:20:2) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[37] Light yellowish solid; R_f=0.14 ($CHCl_3$:MeOH:NH_4OH (100:20:2)); mp. 147-148 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 11.32 (br. s, 1H), 7.71 (d, J = 7.1 Hz, 2H), 6.18 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz; DMSO) δ_c 176.6, 140.4, 116.8.; FTIR(cm^{-1}) 3198(w), 3109(w), 3034(w), 2936(w), 2903(w), 2853(w), 2806(w).

*2,6-Bis(benzyloxy)pyridine – **(3c)**.* The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2,6-dichloropyridine (0.740 g, 5 mmol), benzyl alcohol (1.560 mL, 15 mmol) and sodium hydride 60% dispersion in mineral oil (0.672 g, 20 mmol). Reaction time 25 h. Yield 99% (1.442 g, 4.95 mmol). Purification: After the reaction was quenched with water, the precipitated solids were filtrated off and were washed with water. The characterization data of the obtained compound are in agreement with the literature values.[38] White solid; R_f=0.46 (Hexane:EtOAc (20:1)); mp. 73-74 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 7.52 (t, J = 7.9 Hz, 1H), 7.48 – 7.30 (m, 10H), 6.40 (d, J = 7.9 Hz, 2H), 5.37 (s, 4H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 162.5, 141.3, 137.8, 128.7, 128.0, 128.0, 102.2, 67.9; FTIR(cm^{-1}) 3062(w), 3037(w), 2942(w), 2885(w).

*2,3-bis(benzyloxy)pyridine **(3d)**.* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from pyridine-2,3-diol (0.556 g, 5 mmol), benzyl bromide (1.425 mL, 12 mmol) and potassium carbonate (2.764 g, 20 mmol). Reaction time 18 h. Yield 97% (1.414 g, 4.85 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (40:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[39] Light brown solid; R_f=0.31 (*n*-hexane:EtOAc (1:1)); mp. 104-105 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 7.43 (dq, J = 3.0, 2.0 Hz, 2H), 7.39 – 7.25 (m, 8H), 6.89 (dd, J = 6.9, 1.7 Hz, 1H), 6.62 (dd, J = 7.4, 1.7 Hz, 1H), 6.01 – 5.95 (m, 1H), 5.17 (s, 2H), 5.11 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 158.5, 149.3, 136.7, 136.6, 129.0, 128.8, 128.7, 128.5, 128.2, 127.6, 115.7, 105.1, 71.0, 52.2; FTIR(cm^{-1}) 3079(w), 3063(w), 2941(w), 2907(w), 2873(w).

*3-(Benzyloxy)pyridin-2-ol – **(4d)**.* The title compound was synthesized following the general procedure for benzyl ether removal Method **B**. Starting from 2,3-bis(benzyloxy)pyridine – **3d** (0.0583 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ir] photocatalyst (0.0022 g, 0.002 mmol). Reaction time 2 h. Yield 95% (0.0380 g, 0.18 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (40:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[40] Brownish solid; R_f=0.33 (DCM:MeOH (40:1)); mp. 127-128 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ_h 7.37 – 7.27 (m, 5H), 7.21 (s, 1H), 6.83 (dd, J = 7.0, 1.5 Hz, 1H), 6.80 (dd, J = 7.3, 1.4 Hz, 1H), 6.13 (t, J = 7.1 Hz, 1H),

5.19 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 159.0, 147.0, 136.1, 129.1, 128.4, 128.3, 126.9, 113.8, 107.2, 52.6; FTIR(cm^{-1}) 3211(w), 2988(w), 2902(w).

*2,4-Bis(benzyloxy)-6-methylpyridine (**3e**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method A-Bn*. Starting from 6-methylpyridine-2,4-diol (0.626 g, 5 mmol), benzyl bromide (1.425 mL, 12 mmol) and potassium carbonate (2.764 g, 20 mmol). Reaction time 18 h. Yield 36.2% (0.553 g, 1.81 mmol). Purification: Salted out as HCl salt and then flash chromatography (SiO_2) using DCM→DCM:NH_4OH (200:1) as eluent. Colorless liquid; R_f=0.44 (Hexane:EtOAc (10:1)); ^{1}H NMR (500 MHz; $CDCl_3$) δ_h 7.47 (d, J = 7.3 Hz, 2H), 7.42 – 7.29 (m, 8H), 6.44 (d, J = 1.7 Hz, 1H), 6.18 (d, J = 1.7 Hz, 1H), 5.37 (s, 2H), 5.05 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 167.6, 165.1, 157.2, 137.8, 136.3, 128.9, 128.6, 128.4, 128.3, 128.0, 127.9, 127.7, 105.7, 92.4, 70.0, 67.9, 24.5; FTIR(cm^{-1}) 3090(w), 3065(w), 3033(w), 2943(w), 2881(w); HRMS**:** calcd for $C_{20}H_{20}NO_2$ 306.1489 (M+H); found 306.1485 (Δ=1.25 ppm)

*2-(Benzyloxy)-6-methylpyridin-4-ol and 4-(benzyloxy)-6-methylpyridin-2-ol – (**4e** and **4e'**).* The title compounds were synthesized following the general procedure for benzyl ether preparation Method **C**. Starting from 2,4-bis(benzyloxy)-6-methylpyridine – **3e** (0.0611 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ir] photocatalyst (0.0018 g, 0.002 mmol). Reaction time 23 h. Yield **4e** 20.9% (0.0090 g, 0.04 mmol) and **4e'** 38.1% (0.0164 g, 0.08 mmol). Total yield 59% (0.0254 g, 0.12 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (5:1→1:1) → DCM:MeOH (20:1) as eluent.

*2-(Benzyloxy)-6-methylpyridin-4-ol (**4e**):* white solid; R_f=0.28 (*n*-hexane:EtOAc (1:1)); mp. 45-46 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h δ 7.41 – 7.26 (m, 5H), 6.23 (d, J = 1.8 Hz, 1H), 6.00 (d, J = 1.9 Hz, 1H), 5.12 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 173.5, 162.8, 152.4, 136.3, 128.7, 128.4, 128.1, 109.0, 93.9, 69.4, 22.1; FTIR(cm^{-1}) 3063(w), 3034(w), 2921(w), 2666(w), 2584(w); HRMS: calcd for $C_{13}H_{14}NO_2$ 216.1019 (M+H); found 216.1014 (Δ=2.54 ppm)

*4-(Benzyloxy)-6-methylpyridin-2-ol (**4e'**):* white solid; R_f=0.28 (DCM:MeOH=20:1); mp. 174-175 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 12.94 (s, 1H), 7.46 – 7.30 (m, 5H), 5.87 – 5.79 (m, 2H), 4.99 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 169.3, 167.8, 146.1, 135.7, 128.9, 128.6, 127.8, 100.4, 95.3, 70.2, 19.1; FTIR(cm^{-1}) 3118(w), 3025(w), 2915(w), 2842(w), 2727(w), 2688(w); HRMS: calcd for $C_{13}H_{14}NO_2$ 216.1019 (M+H); found 216.1013 (Δ=2.89 ppm)

*Tert-butyl (2-(benzyloxy)pyrimidin-4-yl)carbamate (**3f**).* The title compound was synthesized following the general procedure for benzyl ether preparation Method B-Bn. Starting from *tert*-butyl (2-chloropyrimidin-4-yl)carbamate – **11** (0.115 g, 0.5 mmol), benzyl alcohol (0.078 mL, 0.75 mmol) and sodium hydride 60% dispersion in mineral oil (0.024 g, 1 mmol). Reaction time 25 h. Yield 74.8% (0.113 g, 0.37 mmol). Purification: Flash chromatography (SiO_2) using DCM→DCM:MeOH (20:1) as eluent. White solid; R_f=0.12 (*n*-hexane:EtOAc (10:1)); mp. 95-96 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.35 (d, J = 5.7 Hz, 1H), 7.54 (d, J = 5.7 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.39 – 7.27 (m, 3H), 7.23 (s, 1H), 5.38 (s, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 164.7, 160.2, 159.9, 151.6, 136.8, 128.6, 128.1, 128.0, 102.6, 82.5, 69.0, 28.3; FTIR(cm^{-1}) 3226(br. w), 3074(w), 2976(w), 1725(m); HRMS: calcd for $C_{16}H_{20}N_3O_3$ 302.1499 (M+H); found 302.1502 (Δ=0.96 ppm).

*Tert-butyl (2-chloropyrimidin-4-yl)carbamate (**11**).* A round-bottom flask equipped with a stirrer bar was charged with 2-chloropyrimidin-4-amine (0.259 g, 2 mmol) and Boc-anhydride (0.524 g, 2.4 mmol). Then 20 mL of dry DCM was added followed by addition of DMAP (0.048 g, 0.4 mmol). The reaction mixture was then stirred 24 h on a magnetic stirrer plate. The crude product was purified with SiO_2 flash chromatography. Yield 30.7% (0.141 g, 0.61 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent.

White solid; R_f=0.37 (*n*-hexane:EtOAc (5:1)); mp. 145-146 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.41 (d, J = 5.8 Hz, 1H), 7.86 (d, J = 5.8 Hz, 1H), 7.59 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (75MHz; $CDCl_3$) δ_c 160.3, 160.2, 160.0, 151.3, 107.0, 83.2, 28.7; FTIR(cm^{-1}) 3188(w), 3122(w), 3049(w), 2978(w), 2929(w), 1738(s), 771(m); HRMS: calcd for $C_9H_{13}ClN_3O_2$ 230.0691 (M+H); found 230.0690 (Δ=0.38 ppm)

*2,4-Bis(benzyloxy)pyrimidine (**3g**).* The title compound was synthesized following the general procedure for benzyl ether preparation *Method B-Bn*. Starting from 2,4-dichloropyrimidine (0.745 g, 5 mmol), benzyl alcohol (1.560 mL, 15 mmol) and sodium hydride 60% dispersion in mineral oil (0.672 g, 20 mmol). THF was used as solvent and the reaction time was 4 h. Yield 86.6% (1.266 g, 4.33 mmol). Purification: Flash chromatography (SiO_2) using toluene:EtOAc (20:1) as eluent. The characterization data of the obtained compound are in agreement with the literature values.[41] Isolated as light yellowish liquid; R_f=0.30 (*n*-hexane:EtOAc (5:1)); ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.23 (d, J = 5.7 Hz, 1H), 7.52 – 7.46 (m,

2H), 7.45 – 7.32 (m, 8H), 6.43 (d, J = 5.7 Hz, 1H), 5.44 (s, 2H), 5.41 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 171.1, 165.1, 158.9, 136.8, 136.3, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 102.7, 69.3, 68.5; FTIR(cm^{-1}) 3090(w), 3064(w), 3033(w), 2953(w), 2893(w).

*Pyrimidine-2,4-diol (**4g**).* The title compound was synthesized following the general procedure for benzyl ether removal Method **B**. Starting from 2,4-bis(benzyloxy)pyrimidine – **3g** (0.0585 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ir] photocatalyst (0.0022 g, 0.002 mmol). Reaction time 18 h. Yield 84.8% (0.0190 g, 0.17 mmol). Purification: Flash chromatography (SiO_2) using EtOAc as eluent. The characterization data of the obtained compound are in agreement with the literature values.[42] White solid; R_f=0.11 (EtOAc); mp. >300 °C; ^{1}H NMR (300 MHz; DMSO) δ_h 10.88 (s, 2H), 7.38 (d, J = 7.6 Hz, 1H), 5.44 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75MHz; DMSO) δ_c 165.0, 152.2, 142.8, 100.9; FTIR(cm^{-1}) 3082(m), 2986(m), 2931(m), 2857(m), 2804(m), 2735(m).

*4-(Benzyloxy)-8-(tert-butyl)quinoline (**5a**).* The title compound was synthesized following the general procedure for benzyl ether preparation Method A-Bn. Starting from 8-(*tert*-butyl)quinolin-4-ol – **6** (1.006 g, 5 mmol), benzyl bromide (0.713 mL, 6 mmol) and potassium carbonate (1.382 g, 10 mmol). Reaction time 3 h. Yield 99% (1.442 g, 4.95 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (20:1) as eluent. Isolated as a colorless liquid; R_f=0.29 (*n*-hexane:EtOAc (20:1)); ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.76 (d, J = 5.1 Hz, 1H), 8.22 (dd, J = 8.3, 1.5 Hz, 1H), 7.68 (dd, J = 7.4, 1.5 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.48 – 7.34 (m, 3H), 6.77 (d, J = 5.1 Hz, 1H), 5.28 (s, 2H), 1.70 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 161.5, 148.7, 148.3, 147.8, 136.3, 128.9, 128.5, 127.6, 126.7, 125.3, 122.6, 120.6, 100.6, 70.3, 36.8, 31.3; FTIR(cm^{-1}) 3067(w), 3033(w), 3001(w), 2949(w), 2908(w), 2864(w); HRMS: calcd for $C_{20}H_{22}NO$ 292.1696 (M+H); found 292.1707 (Δ=3.88 ppm)

*4-(Allyloxy)-8-(tert-butyl)quinoline (**5b**).* A round-bottom flask equipped with a stirrer bar was charged with 8-(*tert*-butyl)quinolin-4-ol – **6** (1.006 g, 5 mmol) and potassium carbonate (1.382 g, 10 mmol). Then 55 mL of toluene:DMF (50:5) solvent mixture was added, followed by allyl bromide (0.508 mL, 6 mmol). The reaction mixture was then stirred at 90 °C for 3 h on a magnetic stirrer plate after which it was quenched with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4, evaporated to dryness and purified with SiO_2 flash chromatography. Yield 95.9% (1.158 g, 4.80 mmol). Purification: Flash chromatography (SiO_2) using DCM as eluent. Light yellowish solid; R_f=0.39 (*n*-hexane:EtOAc (20:1)); mp. 46-47 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.73 (d, J = 5.1 Hz, 1H), 8.16 (dd, J = 8.3, 1.5 Hz, 1H), 7.65 (dd, J = 7.4, 1.5 Hz, 1H), 7.40 (dd, J = 8.3, 7.4 Hz, 1H), 6.67 (d, J = 5.1 Hz, 1H), 6.12 (ddt, J = 17.3, 10.5, 5.2 Hz, 1H), 5.50 (ddd, J = 17.3, 3.1, 1.6 Hz, 1H), 5.35 (dq, J = 10.6, 1.4 Hz, 1H), 4.72 (dt, J = 5.2, 1.5 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 161.4, 148.7, 148.3, 147.8, 132.5, 126.5, 125.2, 122.6, 120.5, 118.3, 100.4, 69.0, 36.8, 31.3; FTIR(cm^{-1}) 3084(w), 3004(w), 2965(w), 2949(m), 2917(w), 2862(w); HRMS: calcd for $C_{16}H_{20}NO$ 242.1539 (M+H); found 241.1538 (Δ=0.67 ppm)

*(E)-8-(Tert-butyl)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)quinoline (**5c**).* A round bottom flask equipped with a stirrer bar was charged with 8-(*tert*-butyl)quinolin-4-ol – **6** (1.006 g, 5 mmol) and potassium carbonate (1.382 g, 10 mmol). Then 55 mL of toluene:DMF (50:5) solvent mixture was added, followed by (*E*)-1-bromo-3,7-dimethylocta-2,6-diene – **12** (1.303 g, 6 mmol). The reaction mixture was refluxed for 17 h on a magnetic stirrer plate after which it was quenched with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4, evaporated and purified with SiO_2 flash chromatography. Yield 87.7% (1.480 g, 4.39 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (20:1) as eluent. Yellowish liquid; R_f=0.50 (*n*-hexane:EtOAc (20:1)); ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.73 (d, J = 5.1 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.64 (dd, J = 7.4, 1.5 Hz, 1H), 7.38 (dd, J = 8.3, 7.4 Hz, 1H), 6.68 (d, J = 5.1 Hz, 1H), 5.62 – 5.51 (m, 1H), 5.17 – 5.04 (m, 1H), 4.73 (d, J = 6.4 Hz, 2H), 2.21 – 2.07 (m, 4H), 1.77 (s, 3H), 1.67 (s, 12H), 1.61 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 161.7, 148.6, 148.3, 147.7, 142.1, 132.1, 126.4, 125.1, 123.9, 122.8, 120.6, 119.1, 100.4, 65.4, 39.7, 36.8, 31.3, 26.5, 25.1, 18.0, 17.0; FTIR(cm^{-1}) 2947(m), 2913(m), 2860(w); HRMS: calcd for $C_{23}H_{32}NO$ 338.2478 (M+H); found 338.2465 (Δ=3.89 ppm).

*Ethyl 2-((8-(tert-butyl)quinolin-4-yl)oxy)acetate (**5d**).* A round-bottom flask equipped with a stirrer bar was charged with 8-(*tert*-butyl)quinolin-4-ol - **6** (1.006 g, 5 mmol) and potassium carbonate (1.382 g, 10 mmol). Then 55 mL of toluene:DMF (50:5) solvent mixture was added, followed by ethyl 2-chloroacetate (0.642 mL, 6 mmol). The reaction mixture was refluxed for 5 h on a magnetic stirrer plate after which it was quenched with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4, evaporated and purified with SiO_2 flash chromatography. Yield 97% (1.394 g, 4.85 mmol). Purification: Flash chromatography (SiO_2) using *n*-hexane:EtOAc (10:1→5:1) as eluent. Isolated as a white solid; R_f=0.16 (*n*-hexane:EtOAc (20:1)); mp. 82-83 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 8.74 (d, J = 5.1 Hz, 1H), 8.21 (dd, J =

8.3, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 7.4 Hz, 1H), 6.56 (d, *J* = 5.1 Hz, 1H), 4.81 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.67 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 168.2, 160.8, 148.7, 147.9, 147.8, 126.8, 125.6, 122.3, 120.5, 100.0, 65.4, 61.9, 36.8, 31.2, 14.4; FTIR(cm^{-1}) 3000(w), 2986(w), 2961(w), 2910(w), 2873(w), 1762(m); HRMS: calcd for $C_{17}H_{22}NO_3$ 288.1594 (M+H); found 288.1604 (Δ=3.46 ppm)

*8-(Tert-butyl)quinolin-4-ol (**6**). By catalytic deprotection*: From 4-(benzyloxy)-8-(*tert*-butyl)quinoline (**5a**). The title compound was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from 4-(benzyloxy)-8-(*tert*-butyl)quinoline – **5a** (0.0583 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield >99% (0.0403 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1→10:1) as eluent.

From 4-(allyloxy)-8-(*tert*-butyl)quinoline (**5b**). The title compound **6** was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from the quinoline **5b** (0.0483 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1 h. Yield >99% (0.0442 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1→10:1) as eluent.

From (*E*)-8-(*tert*-butyl)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)quinoline (**5c**). The title compound **6** was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from the quinoline **5c** (0.0675 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1½ h. Yield >99% (0.0403 g, 0.2 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1→10:1) as eluent.

From ethyl 2-((8-(*tert*-butyl)quinolin-4-yl)oxy)acetate (**5d**). The title compound **6** was synthesized following the general procedure for benzyl ether removal Method **A**. Starting from the compound **5d** (0.0574 g, 0.2 mmol), ascorbic acid (0.0704 g, 0.4 mmol) and [Ru] photocatalyst (0.75 mg, 0.001 mmol). Reaction time 1½ h. Yield 97% (0.0391 g, 0.19 mmol). Purification: Flash chromatography (SiO_2) using DCM:MeOH (20:1→10:1) as eluent.

By cyclization: The title compound was synthesized following the general procedure for the preparation of quinolones *Method A-Qn* (compounds **2e**, **2h**, **2k** and **6**). The intermediate was obtained from 2-(*tert*-butyl)aniline (4.678 mL, 30 mmol) Meldrum's acid (6.486 g, 45 mmol) and trimethyl orthoformate (82.052 mL, 750 mmol). Yield 99% (9.010 g, 29.7 mmol). The product was prepared from the intermediate (6.067 g, 20 mmol), which was refluxed in PhOPh for 2½ h. Yield 90.5% (3.641 g, 18.09 mmol). Purification: Flash chromatography (SiO_2) using DCM (until PhOPh out) → DCM:MeOH (40:1→20:1→10:1) as eluent. Off-white solid; R_f=0.44 (DCM:MeOH=10:1); mp. 210-211 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ_h 10.22 (s, 1H), 8.36 (dd, *J* = 8.1, 1.3 Hz, 1H), 8.08 – 7.98 (m, 1H), 7.65 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29 (dd, *J* = 9.8, 5.9 Hz, 1H), 6.34 (d, *J* = 7.4 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_c 179.8, 139.1, 138.4, 137.7, 129.3, 127.9, 124.8, 123.5, 109.1, 34.7, 30.8; FTIR(cm^{-1}) 3280(br. w), 3088(w), 2954(w), 2909(w), 2874(w); HRMS: calcd for $C_{13}H_{16}NO$ 202.1226 (M+H); found 202.1224 (Δ=1.36 ppm).

*(E)-1-bromo-3,7-dimethylocta-2,6-diene – (**12**).* A round-bottom flask equipped with a stirrer bar was charged with ice cold solution of (*E*)-3,7-dimethylocta-2,6-dien-1-ol (1.735 mL, 10 mmol) and 20 mL of dry THF. Then phosphorus tribromide (0.475 mL, 5 mmol) was added dropwise and the reaction mixture was stirred for 4 h at 0 °C on a magnetic stirrer plate. The reaction mixture was quenched with water and was extracted with Et_2O. Then the ethereal was dried over Na_2SO_4 and evaporated to dryness. The crude was used without further purification. Yield 99% (2.150 g, 9.90 mmol). The characterization data of the obtained compound are in agreement with the literature values.[43]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website
^{1}H, ^{13}C, NMR spectra, CV-data, Stern-Volmer plot, computational details, XYZ-parameters for TS geometries (PDF)

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Notes

The authors declare no competing financial interest.

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