Quinoline-Derived Two-Photon Sensitive Quadrupolar Probes

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Quinoline-Derived Two-Photon Sensitive Quadrupolar Probes

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The first quadrupolar 8-dimethylaminoquinoline-derived 6-(8-DMAQ-OAc)$_2$ **1** and 5-(8-DMAQ-OAc)$_2$ **2** photosensitive probes underwent photolysis under UV (365 nm), and NIR (730 nm two-photon (TP)) irradiation conditions showing Q_u = 6.6% and 9.3 % quantum yields and δ_u = 0.40 GM and 0.07 GM uncaging cross-sections, respectively.

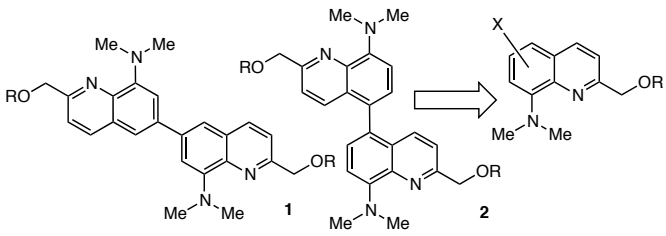
Introduction

Photosensitive protecting groups ('caging' groups) combined with one or two photon microscopy are valuable tools in research in cell biology, developmental biology and neuroscience. They can achieve spatiotemporal resolution on a msec and micron scale, a spatiotemporal scale similar to most biological processes. However, they require further development to improve photolytic efficiency and thereby reduce phototoxicity, particularly for two-photon excitation deep within complex tissues such as the brain or embryos.

Although considerable effort has been made to develop TP-optimized probes, limitations arise from the restricted wavelength range of comercial pulsed lasers, relatively inefficient two photon cross-sections of small molecule cages, and the poor aqueous solubility of reagents with large TP cross-sections. Although the structure activity relationship (SAR) is well understood in large highly π-conjugated compounds used in material sciences, the translation of photophysical SAR to small hydrophilic cages like heteroaromatic compounds poorly understood. Previous attempts to increase uncaging cross sections concentrated on the modification of the substitution pattern of chromophores and resulted in only small improvement of TP efficiency. Further improvements can be expected from the better understanding of symmetry on the TP efficiency, similar to TP fluorophores.[1] In their seminal analysis Albota *et* al. showed that variation of the conjugation lengths and donor and acceptor strengths leads to exceptionally large TP cross-sections in quadrupolar dyes.[2] Further, they showed that in C_2 centrosymmetric quadrupolar molecules the first excited electronic state is TP-forbidden, whereas there is a higher excited electronic state which is one-photon-forbidden but two-photon-allowed. While the incorporation of symmetry elements was fruitful in TPA dye design, much less is known on the effect of symmetry on the TP photolysis of quadrupolar 'caged' compounds. Specht *et* al. showed important improvement in the TP uncaging cross-section of the planar non-centrosymmetric nitrobenzyl-derived quadrupolar BNSF-Glu$_2$ system, built around a fluorene core and monomeric NPE-Glu.[3] Picard *et* al. showed 10-fold improvement in the photolysis cross-section in the nitroindoline (NI) – fluorene tandem non-centrosymmetric triad system.[4] Here, the effects of the C_2 centrosymmetric constructs in TP-sensitive 'cage' design are compared in the 8-dimethylaminoquinoline caging groups investigated in our earlier work.

Results and discussion

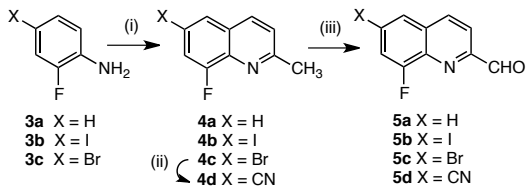
As part of a larger program[5] we were interested to examine the effect of the molecular symmetry on the photophysical proprieties of quinoline-derived[6] quadrupolar probes, and in particular to prepare and test **1** and **2** as representative analogues of C_2 symmetric photoprotecting groups, composed from two covalently grafted 8-DMAQ units (Scheme 1). The parent monomer 8-DMAQ acetate and glutamate derivatives showed excellent photofragmentation proprieties under UV, and also by femtosecond-pulsed two-photon (TP) irradiation conditions.[5]



Scheme 1. Retrosynthetic disconnection of C_2 symmetric 6-(8-DMAQ)$_2$ (**1**) and 5-(8-DMAQ)$_2$ (**2**) quadrupolar probes.

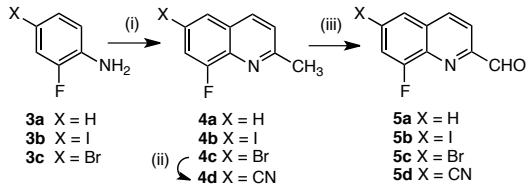
A straightforward synthesis of **1** and **2** appeared by the assembly of conveniently substituted dimethylaminoquinolines by Suzuki-Miyaura-type coupling (Scheme 1). The synthesis of the common halo-dimethylaminoquinoline precursors revealed, however, unexpectedly delicate. In particular the introduction of the dimethylamine into the appropriately functionalized dihalo-quinaldine revealed difficult.[7]

For the preparation of the C(6)-halo-aminoquinoline intermediate a simple path via S_NAr reaction from the corresponding fluoro-aryl appeared attractive, while this reaction had no direct precedent in the litterature.[8] Synthetically useful nucleophile substitution of halogens on aryls are typically associated to highly electron-deficient fluorobenzene derivatives having additional electron-withdrawing groups, such as nitro, carbonyl, sulfonyl, nitrile, or fluorine, located in *ortho*, or, *para* positions to the fluorine.[9,10] Fluoroaryls having EWG activating groups in the *meta* position are usually considered as poor substrates in S_NAr reactions.[11] Also, less activated fluoroaryls afford usually slower conversions and lower chemical yields while the substitution of unactivated fluorobenzenes,[12] or, of 2- and 4-fluoronitrophenols[13] have been also reported. Reactions can be accelerated by the judicious choice of the base and solvent, or by the formation of the intermediate Meisenheimer sigma complex.[10] Nevertheless the transformation requires usually harsh conditions such as high temperature and extended reaction time. The same tendency can be established for the substitution of haloquinolines with *N*-nucleophiles.[14] Singh *et al.* recently reported aminations of 2-chloroquinoline-3-carbonitriles in water.[15] Also, as 7-fluoroquinoline did not show sufficient reactivity, van den Berg *et al.* exploited the substitution of 7-fluoro-1-methylquinolinium iodide.[16]



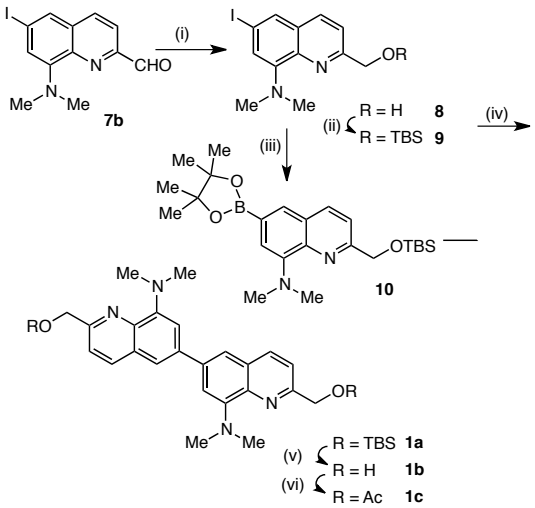
Scheme 2: Reagents and conditions: (i) crotonaldehyde (2 equiv), HCl (6 N), 120 °C, 3 h; (ii) CuCN, DMF, 170 °C, 12 h; (iii) SeO_2 (1.3 equiv), dioxane, 80 °C, 3 h.

We speculated, that the dimethylamination reaction can eventually be accelerated be the presence of a distal iminium group, formed under the reaction conditions in the presence of the secondary amine reagent. In order to probe the iminium approach, substrates **4a-c** were prepared from corresponding fluoroanilines **3a-c** via Doebner-Miller-type reaction followed by SeO_2 oxidation of the C(2) methyl group (Scheme 2). The 6-cyano derivative **4d** was prepared from 6-bromo-8-fluoroquinaldine **4c** by using CuCN in DMF (87%, Scheme 2) followed by SeO_2 oxidation. Amination reactions were realized using excess (20 equiv) of dimethylamine (~5.6 M in ethanol) at 80 °C. S_NAr reactions of 6-iodo-, 6-bromo- and 6-cyano-8-fluoroquinoline-2-carbaldehydes **5b-d** were efficient and afforded the desired products in 70%, 65%, and 85% yield, respectively (Scheme 3). Also, the substitution of 8-fluoro-quinoline-2-carbaldehyde **5a** without halogen group at ring B resulted no reaction, and the starting material was integrally recovered after 24 h (Scheme 3).



Scheme 2: Reagents and conditions: (i) crotonaldehyde (2 equiv), HCl (6 N), 120 °C, 3 h; (ii) CuCN, DMF, 170 °C, 12 h; (iii) SeO_2 (1.3 equiv), dioxane, 80 °C, 3 h.

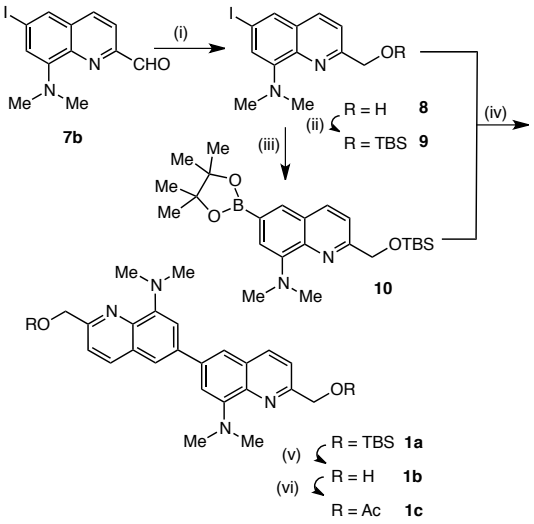
The reaction was compatible with a variety of cyclic and acyclic secondary amine nucleophiles, **6b-e** although the transformation required usually longer reaction time (Scheme 4). While pyrrolidine afforded product after 24 h in 70%, the completion of the reaction using piperidine and morpholine required 72 h and afforded products in 85% and 68% yields, respectively (Scheme 4). Noteworthy, when *n*-propylamine was used as *N*-nucleophile low conversion was observed even after 72 h of reaction (35%, Scheme 4) suggesting the importance of the formation of iminium for decent reaction rate.



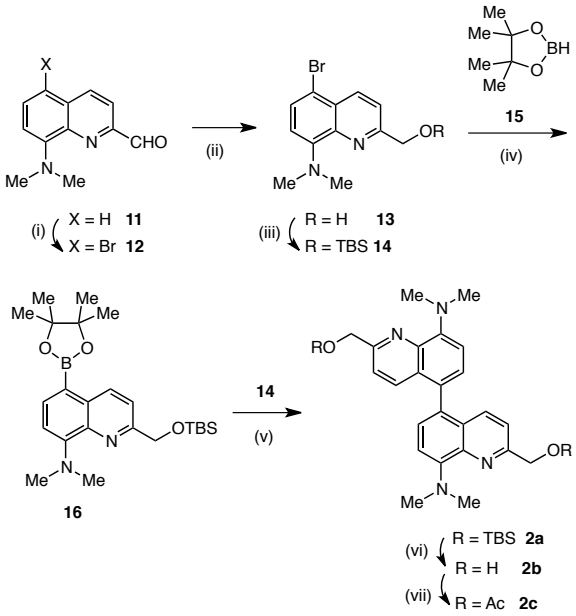
Scheme 4: Reagents and conditions: (i) Amine reagent **6** (20 equiv), EtOH, 80 °C, 72 h; [a] 24 h.

The completion of the synthesis of the quadrupolar "cage" compound **1c** is depicted in Scheme 5. The iodo-aldehyde **7b** was transformed to the protected alcohol **9** using $NaBH_4$ followed by silylation under standard conditions. The boronate **10** was prepared from **9** using bis(pinacolato)diboron in the presence of $Pd(dppf)Cl_2$, (10 mol%) catalyst at 80 °C (55%).

The Suzuki-Miyaura coupling of **9** and **10** afforded the dimeric quinoline **1a** that was converted to the diacetate by deprotection/acylation (52%, two steps).



Scheme 5: Reagents and conditions: (i) $NaBH_4$, EtOH, RT, 30 min (98%); (ii) TBS-Cl, imidazole, DMF, RT, 16 h (87%); (iii) Bis(pinacolato)diboron, KOAc, $Pd(dppf)Cl_2$, DMSO, 80 °C, 16 h (55%); (iv) $Pd(PPh_3)_4$, Na_2CO_3 aq. (2 M), DME, 80 °C, 16 h, (67%); (v) HF/pyridine, CH_3CN, RT, 2 h (98%); (vi) Ac_2O, DMAP, Et_3N, DCM, RT, 2 h (53%).



Scheme 6: Reagents and conditions: (i) NBS, $CHCl_3$, RT, 3 h (90%); (ii); $NaBH_4$, EtOH, RT, 1 h (61%); (iii) TBS-Cl, imidazole, DMF, RT, 16 h (96%); (iv) $Pd(PPh_3)_4$, NEt_3, THF, 100 °C, 16 h (89%); (v) $Pd(PPh_3)_4$, Na_2CO_3 aq. (2 M), DME, 80 °C, 48 h (40%); (vi) HF/pyridine, CH_3CN, RT, 1 h (94%); (vii) Ac_2O, DMAP, Et_3N, DCM, RT, 1 h (quant).

The C(5)-dimer **2c** was prepared from the known intermediate **11** (Scheme 6).[4] Selective bromination at C(5) followed by reduction and protection of the formed alcohol as TBS ether afforded the key intermediate **14**. Part of the bromoquinoline **14** was converted to the pinacol-boronate **16** then coupled with **14** under Suzuki-Miyaura conditions. The dimeric quinoline **2a** was converted to the diacetate **2c** by deprotection/acylation (94%, two steps).

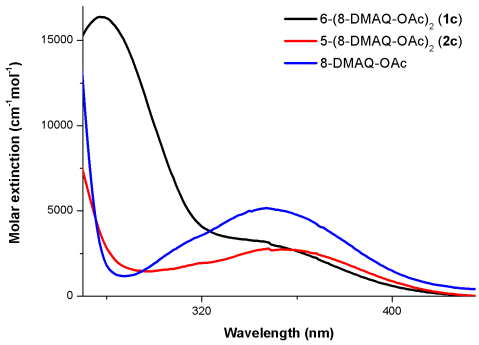
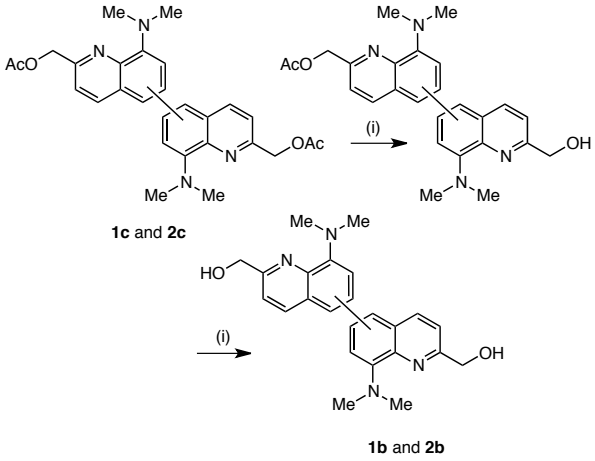


Figure 1. Absorption spectra of (*N,N*-dimethylamino)-2-acetoxymethyl quinoline dimers 6-(8-DMAQ-OAc)$_2$ (**1c**) and 5-(8-DMAQ-OAc)$_2$ (**2c**) and 8-DMAQ acetate in acetonitrile/TRIS buffer (20 mM) 1/1 at 293 K.



Scheme 7: Photolysis of **1c** and **2c.** Reagents and conditions: (i) *h*ν (366 nm), acetonitrile/TRIS buffer (20 mM) 1/1 at 293 K, pH 7.4.

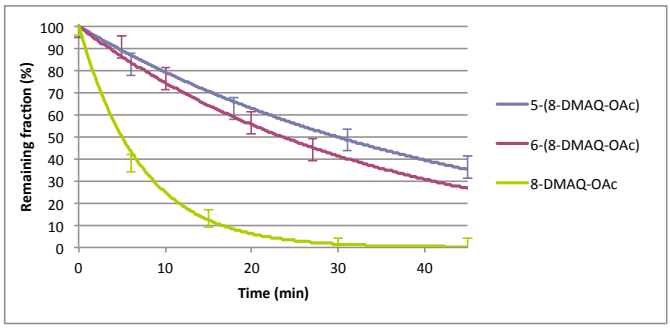


Figure 2. The photolysis of 6-(8-DMAQ-OAc)$_2$ (**1c**), and 5-(8-DMAQ OAc)$_2$ (**2c**) at 366 nm *vs* the reference 8-DMAQ-OAc with the calculated time course of the photolyses determined by HPLC.

Absorption spectra of **1c** and **2c** were recorded in acetonitrile/TRIS (20 mM) (1/1) solution (Figure 1). Compounds **1c** and **2c** have qualitatively similar absorption spectra that show also close similarity to the parent 8-DMAQ acetate. The first absorption maxima of compound **1c** is located at 341 nm having molar extinction at the absorption maxima ε_{max} 3280 $M^{-1}cm^{-1}$ close to the parent 8-DMAQ acetate (λ_{max} = 347 nm and ε_{max} = 4800 $M^{-1}.cm^{-1}$) (Table 1). As compared to 5-(8-DMAQ)$_2$ acetate **2c** which absorb at 353 nm, 6-(8-DMAQ)$_2$ acetate **1c** is slightly blue-shifted (by more than 10 nm). The relatively small differences compared to the parent monomer indicates low electronic coupling between the branches of the dimers.

Before irradiation it was ascertained that acetates 1c and 2c are hydrolytically stables at rt and at pH 7.4 and the background hydrolysis in the dark is less than 1% per hour. Samples of compounds **1c** and **2c** were photolyzed in a mixture of acetonitrile/ TRIS (20 mM) (1/1) solution by 366 nm irradiation. The photofragmentation was monitored by HPLC. Photoproducts were analysed by HPLC-MS and structures were also ascertained by comparison with authentic samples. Although the simultaneous release of two acetates can be envisaged from this quadrupolar system, the sequential release of acetates was observed, as depicted in Scheme 7. Kinetic plots show the first fragmentation (Figure 2). No quantitative analysis of the liberated acetic acid was made. 6-(8-DMAQ)$_2$ acetate **1c** samples were photolysed more quickly by UV (366 nm) than that of 5-(8-DMAQ)$_2$ acetates, **2c**, while the photolysis was more than 3 times less efficient than that of the parent 8-DMAQ acetate monomer.

Two-photon uncaging cross section ($\delta_u = \sigma_2 Q_u$) values were measured directly from the fractional conversion of acetates **1c** and **2c** to the free monocarbinols. A 45 µl volume was irradiated in a 3 mm pathlength quartz cuvette by the beam of a TiS mode-locked laser (MaiTai BB; SpectraPhysics) at 730 nm wavelength with 100 fs pulses at 86 MHz. The expanded beam was focused with a 50 mm fl lens so that the whole of the excitation volume was contained in the cuvette. Samples were irradiated for 4 hours at 100 mW average power. The loss of the cage was measured by HPLC and the photolysis cross-sections calculated from the rate of reduction of the fractional cage concentration at the laser beam parameters given above. Under these conditions **1c** had a photolysis cross-section of 0.07 GM (10^{-50} cm^4s/photon) and **2c** δ_u was 0.40 GM. Photophysical results are collected in Table 1.

Table 1: Photophysical properties of chromophores **1c** and **2c.**

	λ_{max} (nm)	ε_{max} ($M^{-1}.cm^{-1}$)	ε_{366} ($M^{-1}.cm^{-1}$)	Q_u (%)	εQ_u ($M^{-1}.cm^{-1}$)	$\delta_{u,730}$ (GM)
1c	341	3280	2340	9.3	217	0.07
2c	353	2750	2550	6.6	167	0.40

The fact that both isomer **1c** and **2c** undergo photolysis by near IR (730 nm) irradiation was surprising, as the S_0-$^2S_1$ transition of centrosymmetric chromophores is predicted TP-forbidden. The single-photon vs two-photon photolysis efficiency shows opposite tendency for **1c** and **2c**. While the "elbow"-assembled **1c** shows roughly one order of magnitude lower ($\delta_{u,730}$ = 0.06 GM) TP uncaging cross section than the parent 8-DMAQ acetate[5] the linear D-D system **2c** was photolysed with a decent 0.40 GM TP uncaging cross section. As the MM3 conformational analysis suggests (Figure 3), the relatively high TP response of these symmetric chromophores can be atributed to the conformation mobility of **1c** and **2c** in which the C_2-symmetric structure is weakly present: similar to related binaphtyl systems, there is a large isoenergetic hypersurface without conformational energy minima within a large dihedral angle, resulting broken C_2-symmetry. The "out of plan" conformation results also weak electronic couplings between branches (NB: UV spectra of **1c, 2c** and the parent 8-DMAQ acetates are qualitatively similar), due to the weak overlapping of the twisted diaryl system. The observed photophysics is thus much more the consequence of a substituent effect of the heteroaryl groups than to a quadrupolar coupling.

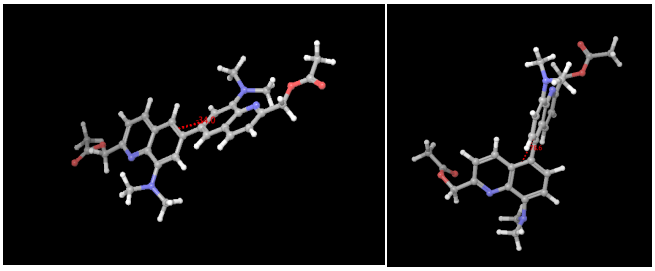


Figure 3. MM3 minimized conformations in the gas phase of **1c** (a) and **2c** (b).

Conclusions

In summary, the first C_2 symmetric quadrupolar 8-dimethylaminoquinoline-derived photosensitive protecting groups **1** and **2** were prepared. The key dimethylamino C(6)-haloquinoline intermediate of the synthesis was prepared by an expeditious S_NAr amination reaction that is believed to be accelerated by the presence of the distal iminium group formed under the reaction conditions. The amination reaction may be considered thus as a non-asymmetric organocatalytic reaction in which the secondary amine reagent promotes also the aromatic substitution.[16] The acetate derivatives of the quadrupolar probes, **1c** and **2c** undergo photolysis either under UV (single-photon) at 365 nm and under NIR (two-photon) femtosecond-pulsed photolysis conditions at 730 nm showing Q_u = 9.3 % and 6.6 % quantum yield, and a δ_u = 0.07 GM and 0.40 GM uncaging cross-section, respectively. As the first excited electronic transition of C_2 symmetric chromophores is forbidden in TP-photolysis the relatively high uncaging TP cross-section of **1c** and **2c** is surprising The high TP uncaging cross section can be ascribed to the conformational mobility of

the dimers in which the C_2 symmetrc structure is broken, or, contributes weakly (if any) to the averaged electronic distribution, and also to the fact, that the low electronic coupling between branches isolates them and makes behaving rather like covalently linked two monomer than a dimer. In this context the drain on the quantum efficiency compared to the 8-DMAQ-OAc is probably a result of the substitution at the C(5)- and C(6)-positions by the heteroaryl groups.

Materials and methods

Chromatography: Thin layer chromatography was performed on aluminium-backed Merck Kieselgel 60 F 254 pre-coated plates.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 250 spectrometer (250 MHz and 63 MHz) and on a Bruker AV-500 spectrometer (500 MHz and 125 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent ($CDCl_3$: δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet), coupling constants in Hertz (Hz), integration. All solvents and inorganic reagents were from commercial sources and used without purification unless otherwise noted. Methods for HPLC analysis : the HPLC analyses were carried out on Waters device 515 with a normal inverse phase column X-Terra® MS C18 (length : 75 mm, diameter: 4.6 mm, stationary phase: 2.5 µm) using a Waters 2487 Dual Absorbance Detector (260-360 nm) and an isocratic system of elution (MeOH-MeCN-H_2O 7-2-1 / H_2O-$AcONH_4$ 10 mM pH 4.6). The volume of injection was 50 µL. The Mass analyser was an Agilent from Thermo-Fisher. The capillary tension was 3.5 kV. The cone tension was 24 V. The temperature of the source was 130 °C and the temperature of desolvatation was 350 °C. Data were treated on ThermoQuest.

The UV and NIR irradiation experiences were realized by irradiation for 1-4 hours of solution in 0.1 mM concentration in an acetonitrile/TRIS buffer 1/1 solvent mixture (pH 7.4). For the UV irradiation, an aliquot (1 mL) of this solution was irradiated at approximately 366 nm by using 8W Carl Roth lamp. One-photon quantum yields were determined by using Eq 1:[18]

$$Q_u = [\varepsilon(\lambda_{exc})I_0(\lambda_{exc})t_{90\%}]^{-1} \quad \text{(Eq 1)}$$

where $\varepsilon(\lambda_{exc})$ is the molar extinction coefficient of the compound at the excitation wavelength in $mol^{-1}.\ cm^{-1}$ (10^3 times smaller than the usual extinction coefficient in $M^{-1}.cm^{-1}$), $t_{90\%}$ is the time at which 90% of the product was converted, as determined by HPLC, and $I_0(\lambda_{exc})$ is the light intensity at the excitation wavelength and is measured in Einstein $\cdot\ cm^2 \cdot s^{-1}$. Between each durations, a small aliquot (20 µL) of the solution was removed for analysis by reverse-phase HPLC using dual absorbance detection at 260 and 360 nm. Optical densities at 366 nm were kept around 0.1 so that inner-filtering of the irradiation and spatial gradients of concentrations could be neglected, and the progress curves were simple decaying exponentials. Dark hydrolysis rates were measured similarly except without illumination.

Uncaging two photon cross-sections (δ_u) were calculated from the fractional conversion of the cage with exposures of approx. 4 hours in a 45 microlitres cuvette of 3 mm pathlength. The expanded output of a MaiTai BB (Spectra-Physics) pulsed laser was focused with a 50 mm focal length lens into the cuvette. The two-photon excitation volume was entirely contained within the cuvette volume to obviate the need to measure the beam waist. Beam parameters were 720 or 730 nm with 100 fs pulse width at 80 MHz and 100 mW average power after the cuvette. Samples were centrifuged if necessary to remove particles if apparent in the transmitted beam. For reference the two-photon uncaging cross-section for acetate release from the widely used MNI-caged glutamate determined in this way was 0.05 GM (10^{-50} cm^4.s/photon). The conversion of the product was assayed by HPLC by monitoring the remaining caged compound. The two-photon uncaging cross section δ_u was calculated as follows:

$$C/C_0 = 0.5\ \delta_u\ (P\ \lambda/\ hc\ /\ F)^2\ /\ T\ (\pi\ n\ /4\lambda/V)\ t\ F \quad \text{(Eq 2)}$$

where C/C_0 = fractional conversion; δ_u = TP uncaging cross-section (cm^4.s/photon); P = average power (W); λ = wavelength (cm); h = Planck constant (J. sec); c = velocity of light (cm/s); F = pulse frequency (Hz); T = pulse width (s); n = refractive index; V = sample volume (cm^3); t = exposure time (s).

General procedure for Doebner-Miller reaction

The aniline (5.00 mmol, 1.0 equiv) was dissolved in a solution of HCl (6M, 20 mL), after addition of crotonaldehyde (0.83 mL, 10.00 mmol, 2.0 equiv) the mixture was stirred 1 h at room temperature. Then toluene (5 mL) was added and the reaction was heated at reflux temperature for 3 h. After cooling down to room temperature, the organic layer was removed. The aqueous layer was neutralized by adding NaOH, the solution was extracted with CH_2Cl_2 and the organic layer was washed twice with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

8-Fluoro-2-methylquinoline (4a)[19]

Column chromatography: cyclohexane:EtOAc 4:1. Pale yellow oil (61%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.5, 1.6 Hz, 1H), 7.18 (dd, J = 5.9, 5.0 Hz, 1H), 7.08-7.01 (m, 2H), 6.95 (d, J = 8.5 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.8 (d, J = 1.5 Hz), 156.9 (d, J = 255.2 Hz), 137.3 (d, J = 11.4 Hz), 135.2 (d, J = 3.1 Hz), 127.6 (d, J = 2.6 Hz), 124.7 (d,

J = 8.0 Hz), 122.6 (d, *J* = 4.6 Hz), 122.4, 112.9 (d, *J* = 19.1 Hz), 24.9. GCMS (m/z$^+$): 161.

8-Fluoro-6-iodo-2-methylquinoline (4b)

Beige crystals (40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 1H), 7.73 (s, 1H), 7.50 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 2.77 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.1 (d, *J* = 1.6 Hz),, 157.4 (d, *J* = 260.8 Hz), 137.0 (d, *J* = 11.3 Hz), 134.9 (d, *J* = 3.1 Hz), 128.9 (d, *J* = 3.0 Hz), 125.5 (d, *J* = 4.8 Hz), 124.1, 117.9 (d, *J* = 9.5 Hz), 117.7 (d, *J* = 22.7 Hz), 25.6. MS (APCI): *m/z* = 288.0 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_7FIN+H]^+$ 287.9696, found 287.9697.

6-Bromo-8-fluoro-2-methylquinoline (4c)[20]

Column chromatography: CH_2Cl_2:cyclohexane 2:1. Yellow crystals (53%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.67–7.40 (m, 1H), 7.45 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.9, 157.2 (d, *J* = 261.0 Hz), 136.8 (d, *J* = 11.5 Hz), 134.8 (d, *J* = 3.2 Hz), 128.7 (d, *J* = 2.9 Hz), 125.4 (d, *J* = 4.7 Hz), 124.0, 117.8 (d, *J* = 9.4 Hz), 117.5 (d, *J* = 22.7 Hz), 25.5. MS (ESI): *m/z* = 239, 241 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_7BrFN+H]^+$ 239.9700 and 241.9700, found 239.9817 and 241.9795.

8-Fluoro-2-methylquinoline-6-carbonitrile (4d)

6-bromo-8-fluoro-2-methylquinoline, **4c** (480 mg, 2.0 mmol, 1.0 eq) and CuCN (313 mg, 3.5 mmol, 1.7 eq) were dissolved in DMF (1.4 mL). The mixture was heated at 170°C for 12h. After cooling down to room temperature, the crude product was poured on a solution of ice and water. The solid was solubilized in ethylene diamine and extracted with toluene. The organic phase was washed twice with 10% KCN, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The quinaldine **4d** was obtained as a brown solid (324 mg, 87%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.95-7.90 (m, 1H), 7.47 (dd, *J* = 9.8, 1.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 2.78 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.2, 157.5 (d, *J* = 260.3 Hz), 139.7 (d, *J* = 10.7 Hz), 136.2 (d, *J* = 2.5 Hz), 129.6 (d, *J* = 4.8 Hz), 127.7 (d, *J* = 3.0 Hz), 124.8, 117.6 (d, *J* = 9.3 Hz) , 114.6 (d, *J* = 23.0 Hz), 108.9 (d, *J* = 9.8 Hz), 25.8. MS (ESI): *m/z* = 187.1 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{11}H_7FN_2+H]^+$ 187.0600, found 187.0671.

General procedure for selenium dioxide oxidation

A mixture of selenium dioxide (144 mg, 1.30 mmol, 1.3 equiv) in dioxane (5 mL) was heated at 80°C for 30 min, then the quinaldine (1.00 mmol, 1.0 equiv) was introduced and the mixture was stirred 3 h at 80°C. After cooling down to room temperature, the mixture was filtered through celite, eluted with CH_2Cl_2. The crude product was purified by column chromatography on silica gel.

8-Fluoroquinoline-2-carbaldehyde (5a)

Column chromatography: cyclohexane:EtOAc 4:1. Beige crystals (90%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.14 (d, *J* = 0.9 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.62– 7.54 (m, 1H), 7.51 (dd, *J* = 8.5, 4.8 Hz, 1H), 7.39 (ddd, *J* = 10.8, 7.0, 2.0 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.1, 158.3 (d, *J* = 259.9 Hz), 152.3 (d, *J* = 1.7 Hz), 138.1 (d, *J* = 12.2 Hz), 137.2 (d, *J* = 3.0 Hz), 131.3, 129.2 (d, *J* = 8.2 Hz), 123.5 (d, *J* = 4.8 Hz), 118.1, 114.5 (d, *J* = 18.8 Hz). GCMS (m/z$^+$): 175. HRMS (ESI): *m/z* calcd for $[C_{10}H_6FNO+H]^+$ 176.0506, found 176.0507.

8-Fluoro-6-iodoquinoline-2-carbaldehyde (5b)

Column chromatography: cyclohexane:EtOAc 7:1. Beige crystals (77%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.24 (d, *J* = 0.8 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.14–8.11 (m, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 9.5, 1.8 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.0, 157.6 (d, *J* = 266.1 Hz), 152.7 (d, *J* = 1.8 Hz), 137.7 (d, *J* = 12.2 Hz), 136.0 (d, *J* = 3.0 Hz), 132.8 (d, *J* = 5.0 Hz), 132.5 (d, *J* = 1.8 Hz), 124.0 (d, *J* = 21.3 Hz), 119.2 (d, *J* = 1.0 Hz), 93.7 (d, *J* = 8.0 Hz). MS (APCI): *m/z* = 301.9 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{10}H_5FINO+H]^+$ 301.9473, found 301.9476.

6-Bromo-8-fluoroquinoline-2-carbaldehyde (5c)

Column chromatography: cyclohexane:EtOAc 9:1. Beige crystals (90%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.85 (s, 1H), 7.60 (dd, *J* = 9.5, 1.8 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 192.8, 158.1 (d, *J* = 265.9 Hz), 152.6, 137.2 (d, *J* = 12.3 Hz), 136.3 (d, *J* = 3.0 Hz), 131.9, 126.0 (d, *J* = 4.9 Hz), 122.6 (d, *J* = 9.4 Hz), 119.3, 118.9 (d, *J* = 22.0 Hz). GCMS (m/z$^+$): 254, 256. HRMS (ESI): *m/z* calcd for $[C_{10}H_5BrFNO+H]^+$ 253.9611 and 255.9596 found 253.9614 and 255.9593.

8-Fluoro-2-formylquinoline-6-carbonitrile (5d)

Column chromatography: cyclohexane:EtOAc 2:1. Yellow crystals (quant). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.45 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.18-8.15 (m, 1H), 7.69 (dd, *J* = 9.5, 1.3 Hz, 1H). ^{13}C NMR (63 MHz): δ 192.5, 158.7 (d, *J* = 265.1 Hz), 154.6, 138.1, 131.0, 129.9 (d, *J* = 5.6 Hz), 120.0, 117.2, 115.7 (d, *J* = 22.9 Hz), 112.9 (d, *J* = 9.8 Hz). MS (ESI): *m/z* = 201.1 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{11}H_5FN_2O+H]^+$ 201.0464, found 201.0463.

General procedure for the S_NAr substitution

A mixture of the fluoro derivative (0.25 mmol, 1.0 equiv) and the amine (5.00 mmol, 20.0 equiv) in EtOH (95%, 0.75 mL) was heated at 80°C in a sealed tube. After completion of the reaction, the mixture was evaporated under vacuum. The

residue was taken up in CH_2Cl_2 and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel.

8-(Dimethylamino)-6-iodoquinoline-2-carbaldehyde (7b)

Column chromatography: cyclohexane:EtOAc 4:1. Orange crystals (70%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 1.6 Hz, 1H), 3.23 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 151.6, 150.0, 141.0, 136.4, 133.0, 128.1, 124.5, 118.0, 97.2, 44.5. MS (APCI): *m/z* = 326.9 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{11}IN_2O+H]^+$ 326.9994, found 326.9989.

6-Bromo-8-(dimethylamino)quinoline-2-carbaldehyde (7c)

Column chromatography: cyclohexane:EtOAc 4:1. Orange crystals (65%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 3.25 (s, 6H).^{13}C NMR (63 MHz, $CDCl_3$) δ 193.1, 151.8, 149.6, 140.4, 136.6, 132.5, 124.5, 120.9, 118.7, 117.9, 67.2, 44.3. MS (ESI): *m/z* = 279.2, 281.1. HRMS (ESI): *m/z* calcd for $[C_{12}H_{11}BrN_2O+H]^+$ 279.0100 and 281.0100, found 279.0131 and 281.0101.

8-(Dimethylamino)-2-formylquinoline-6-carbonitrile (7d)

Column chromatography: CH_2Cl_2. Orange crystals (85%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 3.29 (s, 6H). ^{13}C NMR (125 MHz) δ 192.9, 151.5, 151.4, 142.8, 138.5, 131.4, 123.9, 118.9, 118.5, 115.4, 113.4, 44.4. MS (ESI): *m/z* = 226.1 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{13}H_{11}N_3O+H]^+$ 226.0900, found 226.0982.

6-Iodo-8-(pyrrolidin-1-yl)quinoline-2-carbaldehyde (7e)

Column chromatography: CH_2Cl_2:cyclohexane 2:1. Orange crystals (72%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.06 (d, *J* = 0.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 6.98 (d, *J* = 1.5 Hz, 1H), 3.88-3.80 (m, 4H), 2.08–2.01 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.1, 148.8, 147.8, 139.3, 135.4, 133.1, 123.1, 119.1, 117.7, 98.3, 52.4, 25.9. GCMS (m/z$^+$): 352. HRMS (ESI): *m/z* calcd for $[C_{14}H_{13}IN_2O+H]^+$ 353.0145, found 353.0147.

6-Iodo-8-(piperidin-1-yl)quinoline-2-carbaldehyde (7f)

Column chromatography: cyclohexane:EtOAc 4:1. Yellow crystals (85%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.14 (d, *J* = 0.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 3.44–3.36 (m, 4H), 1.95–1.85 (m, 4H), 1.75-1.63 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.6, 152.2, 150.2, 141.5, 136.6, 132.9, 129.2, 126.0, 117.9, 97.3, 53.7, 26.2, 24.6. GCMS (m/z$^+$): 366. HRMS (ESI): *m/z* calcd for $[C_{15}H_{15}IN_2O+H]^+$ 367.0302, found 367.0302.

6-Iodo-8-morpholinoquinoline-2-carbaldehyde (7g)

Column chromatography: cyclohexane:EtOAc 9:1. Yellow crystals (68%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.13 (d, *J* = 0.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 4.08-4.00 (m, 4H), 3.54-3.46 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.2, 150.7, 150.4, 141.2, 136.8, 132.9, 130.1, 125.8, 118.1, 96.9, 67.0, 52.5. GCMS (m/z$^+$): 369. HRMS (ESI): *m/z* calcd for $[C_{14}H_{13}IN_2O_2+H]^+$ 369.0095, found 369.0098.

6-Iodo-8-(propylamino)quinoline-2-carbaldehyde (7h)

Column chromatography: CH_2Cl_2:cyclohexane 2:1. Yellow crystals (35%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.12 (d, *J* = 0.8 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.33 (br s, 1H), 3.28 (q, *J* = 7.3 Hz, 2H), 1.83 (sext, *J* = 7.3 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.1, 149.3, 146.4, 136.6, 135.7, 132.0, 121.9, 118.6, 114.0, 99.1, 45.0, 22.4, 11.9. GCMS (m/z$^+$): 340. HRMS (ESI): *m/z* calcd for $[C_{13}H_{13}IN_2O+H]^+$ 341.0145, found 341.0144.

(8-(Dimethylamino)-6-iodoquinolin-2-yl)methanol (8)

To a mixture of the carbaldehyde, **7b** (855 mg, 2.62 mmol, 1.0 equiv) and EtOH (10 mL), $NaBH_4$ (109 mg, 2.88 mmol, 1.1 equiv) was added at 0 °C. The mixture was stirred at room temperature for 30 min before being quenched with 1M HCl. The EtOH was evaporated, the residue was taken up in CH_2Cl_2 and the organic layer was washed with water (2×) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:MeOH 95:5). Yellow solid (845 mg, 98%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 1.8 Hz, 1H), 4.88 (s, 2H), 3.06 (s, 6H). ^{13}C NMR (63 MHz): δ 157.2, 150.4, 140.0, 136.0, 130.2, 128.9, 124.6, 118.8, 92.3, 64.7, 44.3. MS (ESI): *m/z* = 328.9 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}IN_2O+H]^+$ 329.0151, found 329.0154.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-iodo-*N*,*N*-dimethylquinolin-8-amine (9)

A solution of alcohol, **8** (388 mg, 1.16 mmol, 1.0 equiv), TBSCl (192 mg, 1.28 mmol, 1.1 equiv) and imidazole (87 mg, 1.28 mmol, 1.1 equiv) in DMF (5 mL) was stirred at rt overnight, then the solvent was removed under reduced pressure. CH_2Cl_2 was added and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was

purified by column chromatography on silica gel (cyclohexane:EtOAc 9:1) to afford 439 mg (87 %) of the corresponding protected alcohol as a pale yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 5.00 (s, 2H), 3.05 (s, 6H), 0.96 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.6, 150.8, 140.6, 135.7, 130.1, 129.0, 124.2, 118.8, 91.9, 67.0, 44.4, 26.0, 18.4, -5.2. MS (ESI): *m/z* = 443.0 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{18}H_{27}IN_2OSi+H]^+$ 443.1010, found 443.1018.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-8-amine (10)

A mixture of the iodo derivative, **9** (100 mg, 0.23 mmol, 1.0 equiv), $PdCl_2$(dppf) (18 mg, 0.02 mmol, 0.08 equiv), KOAc (27 mg, 0.28 mmol, 1.2 equiv), and bis(pinacolato)diboron (64 mg, 0.25 mmol, 1.1 equiv) in anhydrous DMSO (3 mL) was heated to 80°C overnight. The reaction mixture was poored into 15 mL water and extracted with EtOAc (4x15 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 2:1). Yellow oil (56 mg, 55%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 1.0 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 1.0 Hz, 1H), 5.05 (s, 2H), 3.09 (s, 6H), 1.39 (s, 12H), 0.98 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.7, 149.2, 143.3, 137.8, 129.5, 129.5, 128.2, 120.0, 118.2, 84.1, 67.3, 44.8, 26.1, 25.1, 18.5, -5.2. MS (ESI): *m/z* = 443.3 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{24}H_{39}BN_2O_3Si+H]^+$ 443.2896, found 443.2908.

2,2'-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*^{8},*N*^{8},*N*$^{8'}$,*N*$^{8'}$-tetramethyl-[6,6'-biquinoline]-8,8'-diamine (1a)

A mixture of the iodo derivative, **9** (53 mg, 0.12 mmol, 1.2 equiv), the boronate **10** (46 mg, 0.10 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (6 mg, 0.05 mmol, 0.05 equiv), 2M Na_2CO_3 (100 µL) and DME (500 µL) were heated to 80°C overnight under argon. The mixture was taken up in 15 mL EtOAc and the organic phase was washed with water and brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 9:1). Yellow oil (42 mg, 67%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 1.5 Hz, 2H), 7.42 (d, *J* = 1.5 Hz, 2H), 5.08 (s, 4H), 3.18 (s, 12H), 1.00 (s, 18H), 0.16 (s, 12H). ^{13}C (250 MHz, $CDCl_3$) δ 159.6, 150.4, 141.2, 139.0, 137.4, 129.0, 119.0, 118.8, 115.6, 67.3, 44.8, 26.1, 18.6, -5.1. MS (ESI): *m/z* = 631.3 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{36}H_{54}N_4O_2Si_2+H]^+$ 631.3858, found 631.3862.

(8,8'-bis(Dimethylamino)-[6,6'-biquinoline]-2,2'-diyl)dimethanol (1b)

To the TBS protected alcohol **1a** (33 mg, 0.05 mmol, 1.0 equiv) in CH_3CN (500 µL) HF-pyridine (15 µL, 0.25 mmol, 5.0 equiv) was added at 0°C and the mixture was stirred at rt for 2 h in the dark. After completion of the reaction, saturated $NaHCO_3$ solution was added and the mixture was concentrated under reduced pressure. The residue was taken up in a 1:1 mixture of CH_2Cl_2 and water (30 mL), the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 2:1) to afford the product as a yellow oil (20 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 1.5 Hz, 2H), 7.44 (d, *J* = 1.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.96 (s, 4H), 3.22 (s, 12H). ^{13}C (125 MHz, $CDCl_3$) δ 156.8, 150.1, 140.5, 139.4, 137.9, 129.4, 118.9, 118.7, 116.0, 64.7, 44.6. MS (ESI): *m/z* = 403.2 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{24}H_{26}N_4O_2+H]^+$ 403.2129, found 403.2138.

(8,8'-Bis(dimethylamino)-[6,6'-biquinoline]-2,2'-diyl)bis(methylene) diacetate (1c)

To a solution of the alcohol, **1b** (20 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (500 µL) was added triethylamine (7 µL, 0.08 mmol, 1.5 equiv), acetic anhydride (7 µL, 0.08 mmol, 1.5 equiv) and a catalytic amount of DMAP. The mixture was stirred in the dark at room temperature for 2h. The crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 2:1) to afford the product as a yellow oil (13 mg, 53%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 2.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 2.0 Hz, 2H), 5.47 (s, 4H), 3.21 (s, 12H), 2.21 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.8, 153.6, 150.5, 141.4, 139.6, 137.7, 129.2, 119.5, 118.6, 115.6, 67.9, 44.6, 21.1. MS (ESI): *m/z* = 487.2 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{28}H_{30}N_4O_4+H]^+$ 487.2340, found 487.2349.

5-Bromo-8-(dimethylamino)quinoline-2-carbaldehyde (12)

To a solution of 8-(dimethylamino)quinoline-2-carbaldehyde[4] **11** (800 mg, 4.0 mmol, 1.0 equiv) in $CHCl_3$ (20 mL), was added recrystallized *N*-bromosuccinimide (570 mg, 3.2 mmol, 0.8 equiv), and the mixture was stirred at room temperature for 3 h. The mixture was then washed with a solution of $Na_2S_2O_3$ and extracted with DCM. The organic layer was washed twice with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The compound was obtained as a yellow solid and was used without further purification (1.0 g, 90%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.18 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 192.9, 150.8, 149.7, 142.3, 137.2, 133.1, 130.3, 117.9, 115.8, 111.5, 44.4. MS (ESI): *m/z* = 279.1, 281.1 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{11}BrN_2O+H]^+$ 279.0100 and 281.0100, found 279.0135 and 281.0114.

(6-Bromo-8-(dimethylamino)quinolin-2-yl)methanol (13)

To a mixture of the carbaldehyde, **12** (2.5 g, 8.80 mmol, 1.0 equiv) and EtOH (100 mL), $NaBH_4$ (400 mg, 10.50 mmol, 1.2 equiv) was added at 0 °C. The mixture was stirred at room temperature for 1 h before being quenched with 1M HCl. The EtOH was evaporated and to the residue water was added. The solution was extracted with CH_2Cl_2 and the organic layer was washed with water (2×) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:MeOH 9:1). Yellow solid (1.40 g, 61%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.92 (s, 2H), 3.00 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.8, 149.3, 141.5, 136.4, 129.7, 127.4, 119.1, 116.1, 112.9, 64.7, 44.3. MS (ESI): *m/z* = 281.0 and 283.0 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}BrN_2O+H]^+$ 281.0200 and 283.0200, found 281.0288 and 283.0268.

5-Bromo-2-(((tert-butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethylquinolin-8-amine (14)

A solution of the alcohol, **13** (630 mg, 2.20 mmol, 1.0 equiv), TBDMSCl (675 mg, 4.50 mmol, 2.0 equiv) and imidazole (305 mg, 4.50 mmol, 2.0 equiv) in DMF (5 mL) was stirred at rt overnight, then the solvent was removed under reduced pressure. CH_2Cl_2 was added and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The compound was obtained as a brown oil (851 mg, 96%) and was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.04 (s, 2H), 3.00 (s, 6H), 0.94 (s, 9H), 0.11 (6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.7, 149.6, 142.1, 136.3, 129.4, 127.3, 119.1, 115.6, 112.9, 66.6, 44.3, 25.8, 18.2, -5.4. MS (ESI): *m/z* = 395, 397 $[M+2H]^+$. HRMS (ESI): *m/z* calcd for $[C_{18}H_{27}BrN_2OSi+H]^+$ 395.1149 and 397.1149, found 395.1142 and 397.1120.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-8-amine (16)

To a solution of the bromo derivative, **14** (200 mg, 0.50 mmol, 1.0 equiv) in dry Et_3N (510 µL) and dry THF (2.55 mL), $Pd(PPh_3)_4$ (18 mg, 0.02 mmol, 0.03 equiv) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82 µL, 0.60 mmol, 1.1 equiv) were added. The mixture was heated at 100°C overnight in a sealed tube under argon, and then was filtered through silica gel and concentrated under reduced pressure. The product was obtained as a yellow oil (200 mg, 89%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.97 (s, 2H), 3.06 (s, 6H), 1.32 (s, 12H), 0.92 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.2, 152.8, 141.1, 137.7, 136.5, 132.7, 128.5, 118.4, 114.7, 83.4, 67.1, 44.4, 26.0, 25.0, 18.4, -5.2. MS (ESI): *m/z* = 444 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{24}H_{39}BN_2O_3Si+H]^+$ 443.2896, found 443.2885.

2,2'-bis(((*tert*-Butyldimethylsilyl)oxy)methyl)-N^8,N^8,$N^{8'}$,$N^{8'}$-tetramethyl-[5,5'-biquinoline]-8,8'-diamine (2a)

A mixture of the bromo derivative **14** (25 mg, 0.06 mmol, 1.1 equiv), the boronate **16** (28 mg, 0.06 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (4 mg, 0.003 mmol, 0.05 equiv), 2M Na_2CO_3 (63 µL) and DME (500 µL) were heated to 80°C for 48 h under argon. The mixture was taken up in 15 mL EtOAc and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 9:1). Yellow oil (10 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.05 (s, 4H), 3.16 (s, 12H), 0.94 (s, 18H), 0.11 (s, 12H). ^{13}C (125 MHz, $CDCl_3$) δ 159.3, 149.8, 141.6, 135.9, 130.5, 128.6, 128.2, 118.2, 115.1, 67.2, 44.9, 26.1, 18.5, -5.2. MS (ESI): *m/z* = 632 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{36}H_{54}N_4O_2Si_2+H]^+$ 631.3858, found 631.3841.

(8,8'-bis(Dimethylamino)-[5,5'-biquinoline]-2,2'-diyl)dimethanol (2b)

To the TBS protected alcohol, **2a** (10 mg, 0.01 mmol, 1.0 equiv) in CH_3CN (150 µL) HF-pyridine (1 drop) was added at 0°C and the mixture was stirred at rt for 1 h in the dark. After completion of the reaction, EtOAc was added and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The diol was obtained as a yellow oil (6 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.92 (s, 4H), 3.20 (s, 12H). ^{13}C (125 MHz, $CDCl_3$) δ 156.5, 149.4, 140.8, 136.1, 130.0, 128.9, 128.8, 118.2, 115.6, 64.6, 44.6. MS (ESI): *m/z* = 403 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{24}H_{26}N_4O_2+H]^+$ 403.2129, found 403.2119.

(8,8'-bis(Dimethylamino)-[5,5'-biquinoline]-2,2'-diyl)bis(methylene) diacetate (2c)

To a solution of the alcohol, **2b** (6 mg, 0.02 mmol, 1.0 equiv) in CH_2Cl_2 (75 µL) was added triethylamine (3 µL, 0.02 mmol, 1.5 equiv), acetic anhydride (2 µL, 0.02 mmol, 1.5 equiv) and a catalytic amount of DMAP. The mixture was stirred in the dark at room temperature for 1h. After completion of the reaction, CH_2Cl_2 was added and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained as a yellow oil (7 mg, 96%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.44 (s, 4H), 3.20 (s, 12H), 2.17 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.8, 153.4, 149.9, 141.7, 136.1,

129.8, 129.0, 128.8, 119.0, 115.3, 67.8, 44.8, 21.1. MS (ESI): *m/z* = 487 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[C_{28}H_{30}N_4O_4+H]^+$ 487.2340, found 487.2329.

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Notes and references

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