Scalable Synthesis of Acridinium Catalysts for Photoredox Deuterations

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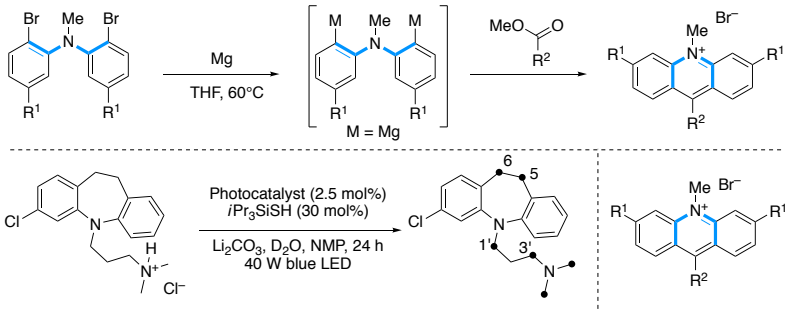
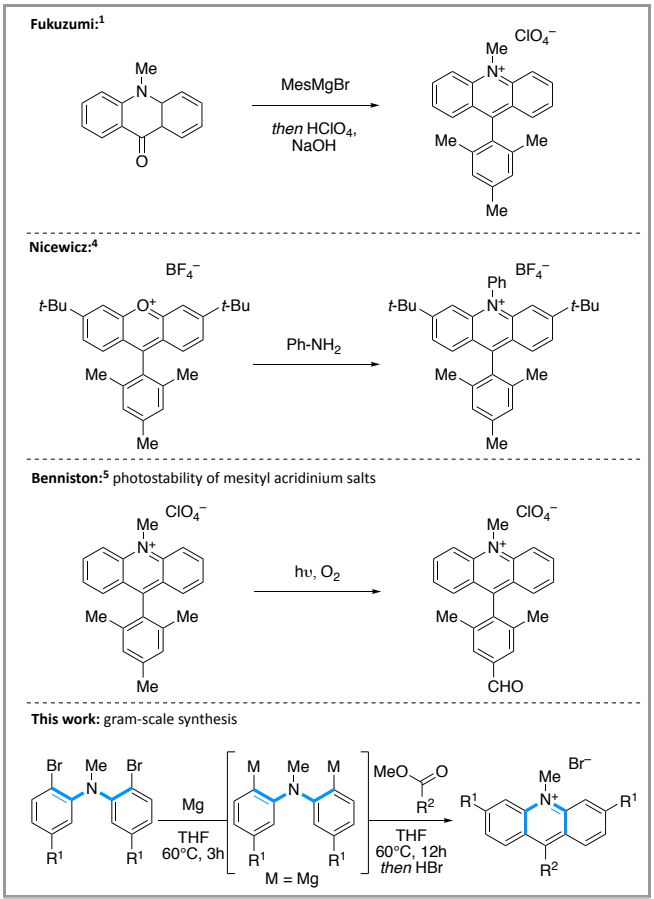


Abstract The continuous development of photocatalytic methods incentivizes the design of organic catalysts to complement the frequently used and precious polypyridyl transition metal systems. Herein, we describe a scalable synthesis of suitable acridinium dyes and their application in photoredox deuterations. The acridinium catalysts, prepared in multi-gram scale, allowed the deuteration of a pharmaceutically relevant scaffold in high yield and selectivity under mild conditions.

Key words acridinium salts, deuteration, Grignard reactions, photoredox catalysis, scalability

Acridinium salts, pioneered by Fukuzumi[1] and utilized for various innovative methodologies by Nicewicz,[2] are established as particularly valuable catalysts for photoredox chemistry (Scheme 1). As organocatalysts, efficient and scalable processes for their synthesis would render them potentially applicable for industrial applications. To further expand their accessibility, we thus developed a method for the preparation of acridinium salts by a twofold addition of a 1,5-bifunctional organometallic reagent to an ester[3] while Nicewicz and co-workers recently disclosed an alternative synthesis of acridinium salts based on late stage nucleophilic substitutions of xanthilium dyes.[4] Since the photostability of mesityl acridinium catalysts is impacted by the oxidation of the *para*-methyl group,[5] methods allowing variation of this moiety are particularly valuable. Owing to the expedient accessibility of 1,5-bifunctional organomagnesium reagents,[6] we anticipated that acridinium salts with different redox properties can be readily prepared on gram scale. Furthermore, our direct acridinium synthesis from esters allows to incorporate electron-donating groups such as amino functionalities, that impactfully modulate the properties of the organophotoredox catalysts. We hence set out to explore the synthesis of acridinium salts with and without amino groups, their scale-up and the performance in a photoredox deuteration as benchmark reaction.

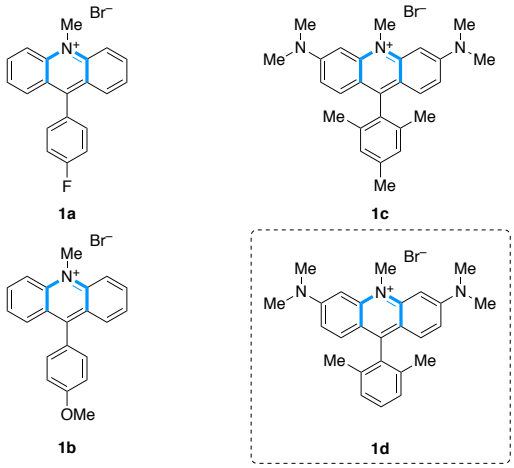


Scheme 1 Syntheses and photostability of acridinium photocatalysts

Our synthesis of the acridinium catalysts **1** started with the dibromophenyl-*N*-methylaniline precursor **2a**, which was obtained through a Buchwald–Hartwig amination followed by a methylation (Scheme 2).[7] The formation of the 1,5-bifunctional organometallic reagent, nucleophilic addition to ester substrates and dehydration using HBr,[3a] led to acridinium salts **1a** and **1b** in good yields (63% and 78%, Scheme 2). Encouraged by these results and the distinctive catalytic performance of organophotocatalyst **1c**,[3a] we next tackled the gram-scale synthesis of **1c** and **1d**. The former preparation of reagents **3** and **4** for the C-N cross coupling proved challenging during scale-up and led us to circumvent the Sandmeyer iodination from **3** to **4**.[8] Gratifyingly, an alternative route consisting of a reductive amination, a Finkelstein reaction and bromination[9] allowed us to access intermediate **4** in good to excellent yields without any column chromatography. A careful optimization of the nitration and reduction conditions delivered intermediate **3** in good yields, purified by recrystallisation.[10] With the two coupling partners in hand, a C-N cross-coupling, followed by a methylation were performed.[7] After recrystallisation, we received 35 g of the key intermediate **2b**. Similarly, the formation of the 1,5-bifunctional organometallic reagent was achieved on large scale, using elemental magnesium in refluxing THF. Addition of the different carboxylic acid esters to the reagents and HBr treatment provided 3.9 g of **1c** and **1d** in 83% and 84% yield, respectively.

Interestingly, catalyst **1a** exhibited a higher excited state reduction potential (Table 1, $E_{1/2}$ [P*/P$^-$] = +2.32 V vs SCE) compared to the Fukuzumi catalyst ($E_{1/2}$ [P*/P$^-$] = +2.18 V vs SCE).[1] On the other hand, **1b** displayed a similar excited state reduction potential ($E_{1/2}$ [P*/P$^-$] = +2.21 V vs SCE), indicating the influence of electron density at the phenyl moiety. The catalyst **1d** without the labile *para*-methyl group showed almost identical properties as compared to **1c** ($E_{1/2}$ [P*/P$^-$] = +1.25 V vs SCE) which makes it an ideal candidate for further investigations in photoredox catalysis.

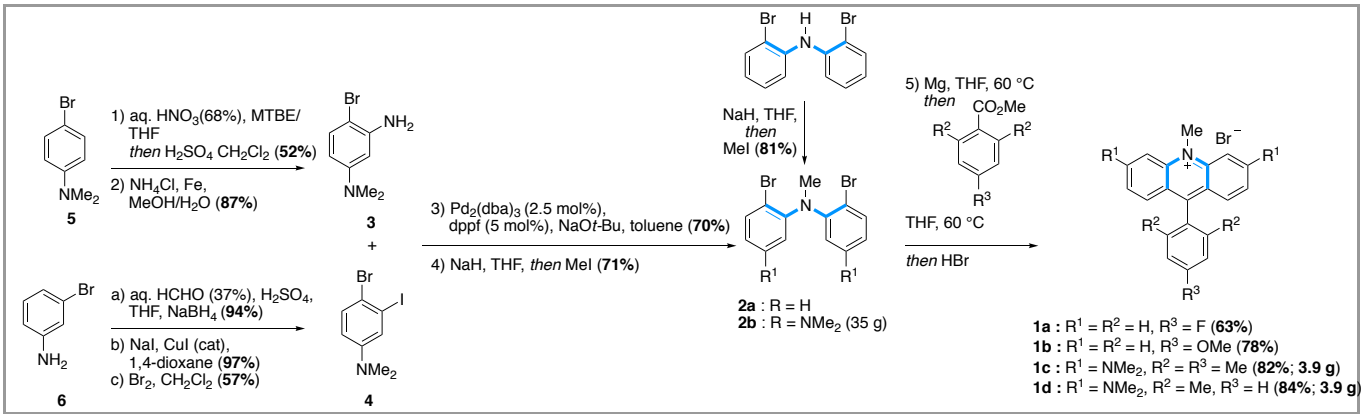
Table 1 Photophysical properties of the acridinium photocatalysts



Dye	λ_{abs} [nm][a]	λ_{em} [nm][a]	$E_{0,0}$ [eV][a]	$E_{1/2}$(P/P$^-$) [V][b]	$E_{1/2}$(P*/P$^-$) [V]
1a	426	512	2.83	–0.51	+2.32
1b	438	499	2.77	–0.56	+2.21
1c	503	530	2.40	–1.15	+1.25
1d	504	533	2.40	–1.15	+1.25

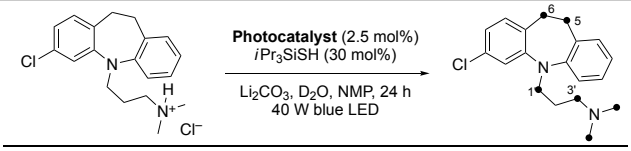
[a] Measured in MeCN (15 μmolL^{-1}).
[b] Measured in 0.1 molL^{-1} n-Bu$_4$N·PF$_6$ in dry, degassed MeCN against SCE.

To explore the catalytic performance of the acridinium catalysts, we studied the deuteration of clomipramine as benchmarking reaction.[11] An average isotopic incorporation of 7 deuterium atoms per molecule with a distribution between aliphatic and benzylic positions (C5, C6, C1', C3', NMe$_2$) has been reported by MacMillan and coworkers using 4CzIPN as photocatalyst. We thus tested several acridinium photocatalysts,[12] under identical reaction conditions (Table 2). Gratifyingly, a high selectivity for the aliphatic positions (C1' = 20%, C3'= 64%, NMe$_2$ = 39%), with an average of 4 deuterium atoms per molecule was observed when using **1c** with 1 mol% catalyst loading. A similar pattern was observed when employing **1d** with an even higher selectivity for the C3' position (70%) and an identical average incorporation of 4 deuterium atoms per molecule.

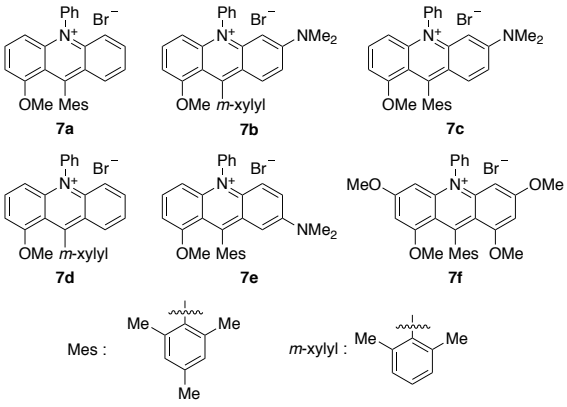


Scheme 2 Synthesis of acridinium salts **1a** and **1b** and gram scale preparation of **1c** and **1d**

Table 3 Photochemical deuteration of clomipramine



Photocat.[a]	Yield[c] (%)	Average ^{2}H/molecule	^{2}H Incorporation[d] (%)				
			C5	C6	C1′	C3′	NMe_2
4CzIPN	80	7.1	13	13	47	71	70
Fukuzumi	95	<1.0	-	-	-	11	4
1a[b]	86	1.0	-	-	-	25	9
1b[b]	88	<1.0	-	-	-	10	-
1c	92	**4.0**	-	-	20	64	39
1c[b]	92	**4.0**	-	-	20	64	39
1d[b]	**98**	**4.0**	-	-	15	**70**	39
7a	98	<1.0	-	-	3	15	7
7b	76	1.3	-	-	6	22	13
7c	88	3.0	-	-	12	49	30
7d	96	<1.0	-	-	3	19	5
7e	97	1.0	-	-	-	25	8
7f	97	2.2	-	-	4	43	21



[a] Reaction performed with clomipramine HCl (100 µmol), Li_2CO_3 (480 µmol), triisopropylsilanethiol (30 mol%), photocat. (2.5 mol%) unless stated otherwise, D_2O (5.00 mmol) in NMP (1.6 mL) at RT, 24h irradiation with Kessil A160WE tuna blue.
[b] Photocat. (1 mol%).
[c] Yield of isolated products.
[d] Determined by ^{1}H-NMR of the free base.

In conclusion, we describe an efficient synthesis to access acridinium salts with suitable photophysical properties. The direct transformation of esters into acridinium catalysts allowed the large-scale synthesis of amino-functionalized photocatalysts with attenuated photoredox properties. The utility of the catalysts was demonstrated by the deuteration of clomipramine, providing high selectivity for aliphatic positions using low catalyst loadings.

All reactions were carried out in dried glassware under an Ar atmosphere. THF (99.5%, Extra Dry, over Molecular Sieves, Stabilized, AcroSeal®, Code: 348455000) was purchased from Acros Organics. All starting materials and reaction solvents were purchased from commercial sources and used without further purification. Unless noted otherwise, all photoreactions were performed in a sealed Biotage® 2-5 mL microwave vial equipped with a 10 mm x 5 mm magnetic stir bar stirring at 1400 rpm. The vial was placed on a stirring plate laterally in 3 cm distance to a Kessil LED A160WE Tuna Blue, 40 W, adjusted to maximum intensity and white (λmax: 464 nm). A sideward fan was used to keep ambient temperature (~30 °C). All starting materials and reaction solvents were purchased from commercial sources and used without further purification. Solvents for extractions and chromatography were technical grade and distilled prior to use. Analytical thin layer chromatography (TLC) was performed on pre-coated *Merck* silica gel 60 F_{254} plates (0.25 mm) and visualised by UV. Flash column chromatography was carried out on *Silicycle* SiliaFlash P60 (230–400 mesh). Concentration *in vacuo* was performed by rotary evaporation to ~ 10 mbar at 40 °C unless stated otherwise. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Bruker Avance III* 500 MHz spectrometer at 298 K in $CDCl_3$ or MeOD supplied by *Cambridge Isotope Laboratories* (DLM-7TB-100S). Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (0.00 ppm). The multiplicities are reported in Hz as: s = singlet, br = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting points were measured on a *Büchi M-565* melting point apparatus and are uncorrected. IR spectra were measured on an ATR *Varian Scimitar 800* FT-IR spectrometer and reported in cm^{-1}. The intensities of the bands are reported as: w = weak, m = medium, s = strong. High-resolution mass spectrometry (HR-ESI) was performed by Dr. Michael Pfeffer of the University of Basel on a *Bruker maXis 4G* QTOF ESI mass spectrometer. Cyclic Voltammetry was performed in dry, degassed 0.1 $molL^{-1}$ tetra *n*butylammonium hexafluorophosphate in MeCN. Voltammograms were recorded with a Versastat3-200 potentiostat from Princeton Applied Research employing a glassy carbon disk working electrode, SCE reference electrode and a silver wire counter electrode and a potential sweep rate of 0.1 Vs^{-1}. The glassy carbon electrode and Ag wire were polished prior to measurement. UV/Vis spectroscopy was performed on a Shimadzu UV-1650 PC spectrometer in acetonitrile using Hellma fluorescence cells (111-QS, light path: 10 mm). Molar absorption coefficients (ε) were determined at the wavelength of maximum absorbance (labs) of a ~10 µ $molL^{-1}$ dye solution. Steady-state emission spectroscopy was carried out with a Fluorolog-3-22 instrument from Horiba Jobin-Yvon. Excitation occurred at the long-wavelength absorption band of the respective dye. All emission spectra were recorded in argon-saturated acetonitrile, and strongly diluted dye solutions (c < 15 µ mol L^{-1}) were used to avoid inner filter effects. All spectra so obtained were corrected for the wavelength dependent sensitivity of the spectrometer. Additional emission spectra of the pure solvent at all excitation and detection conditions were measured to ensure the absence of stray light or impurity signals.

*Synthesis of Acridinium Salts **1a** and **1b***

2-Bromo-*N*-(2-bromophenyl)-*N*-methylaniline

[CAS Reg. No.:87345-09-3]

Prepared according to a modified literature procedure.[7,13] Bis-(2-bromophenyl)amine (4.59 g, 14.0 mmol) in THF (70 mL) was treated with sodium hydride (60% dispersion in mineral oil, 700 mg, 17.5 mmol) at RT and refluxed for 30 min. Iodomethane (3.78 g, 1.66 mL, 26.6 mmol) was added and the mixture was refluxed for another two hours, cooled to RT and treated with H_2O (50 mL). The resulting mixture was extracted with Et_2O (3 x 65 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was washed with pentane and dried in vacuo to obtain a white solid (3.87 g, 81%, m.p. 106-108 °C).

IR (ATR, neat): 3434w, 3286w, 2959w, 2872w, 166w, 1544w, 1468m, 1341w, 1232w, 1141m, 1074m, 1017m, 990w, 866m, 755s, 625m.

^{1}H NMR (500 MHz, $CDCl_3$): δ =7.55 (dd, ^3J 7.9, ^4J 1.5, 2H, C3*H*), 7.24 (ddd, ^3J 8.0, 7.3, ^4J 1.5, 2H, C5*H*), 7.00 (dd, ^3J 8.0, ^4J 1.6, 2H, C6*H*), 6.94 (ddd, ^3J 7.9, 7.4, ^4J 1.6, 2H, C4*H*), 3.23 (s, 3H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.7 (*C*1), 134.4 (*C*3), 128.1 (*C*5), 124.8 (*C*4), 123.8 (*C*6), 120.3 (*C*2), 41.3 (*C*H_3).

HRMS (ESI): m/z calcd. for $C_{13}H_{11}Br_2N^+$ 339.9331 found 339.9334 [M+H$^+$].

1,5-Bifunctional Organomagnesium Reagent for the Ester to Acridinium Transformation

To a suspension of magnesium turnings (13.6 mg, 560 µmol) in anhydrous THF (0.20 mL) at 60 °C was added a solution of 2-bromo-*N*-(2 bromophenyl)-*N*-methylaniline (47.7 mg, 140 µmol) in anhydrous THF

(0.60 mL). The mixture was stirred at 60 °C for 3 h during which the reaction mixture turned yellow, leading to the 1,5-bifunctional organomagnesium reagent which was used directly in the next step.

General Procedure A

To a solution of the above reagent in THF (140 µmol) at 60 °C was added a solution of carboxylic acid ester (100 µmol) in anhydrous THF (1.00 mL) and the reaction mixture was stirred at the same temperature for 12 h. Aqueous HBr (1.00 mL, 8.8 molL^{-1}) was added and the solvent was removed in vacuo. The residue was dissolved in MeOH and filtered over a bed of Amberlyst A21 free base. The solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and 3.0 g of silica gel was added. The solvent was removed in vacuo and the residue purified by column chromatography with CH_2Cl_2 100% to CH_2Cl_2:MeOH 100:2 to 100:5 to 100:8 to yield acridinium salts **1a** and **1b**.

9-(4-Fluorophenyl)-10-methylacridinium bromide salt (1a)

Prepared according to general procedure A using methyl 4-fluorobenzoate (15.4 mg, 100 µmol) and the 1,5-bifunctional organomagnesium reagent to afford a yellow solid (22.8 mg, 63 %, m.p. 212–214 °C): R_f 0.10 (CH_2Cl_2:MeOH 10:1).

IR (ATR, neat): 3377w, 3059w, 2999w, 2923w, 2848w, 1601m, 1574m, 1544, 1504m, 1482w, 1446w, 1373m, 1272w, 1217m, 1156m, 1094m, 1023m, 926w, 866w, 816w, 767s, 722m, 666m, 614m.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.05 (d, ^3J 9.2, 2H, C4*H*, C5*H*), 8.41–8.44 (m, 2H, C3*H*, C6*H*), 7.97 (dd, ^3J 8.8, ^4J 1.2, 2H, C1*H*, C8*H*), 7.82 (dd, ^3J 8.7, 6.7, 2H, C2*H*, C7*H*), 7.47–7.50 (m, 2H, C2'*H*, C6'*H*), 7.42–7.45 (m, 2H, C3'*H*, C5'*H*), 5.34 (s, 3H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1 (d, $^1J_{CF}$ 253, *C*4'), 160.0 (*C*9), 141.8 (*C*4a, *C*10a), 139.4 (*C*3, *C*6), 132.0 (d, $^3J_{CF}$ 8.3, *C*2', *C*6'), 129.8 (*C*1, *C*8), 128.8 (d, $^4J_{CF}$ 3.7, *C*1') 128.3 (*C*2, *C*7), 126.3 (*C*8a, *C*9a), 120.0 (*C*4, *C*5), 116.7 (d, $^2J_{CF}$ 22, *C*3', *C*5'), 41.5 (N*C*H$_3$).

HRMS (ESI): m/z calcd. for $C_{20}H_{15}FN^+$ 288.1183 found 288.1185 [M$^+$].

Absorption spectroscopy (in MeCN): λ_{abs}: 426 nm; ε_{abs}: 8.4·10^2 Lcm^{-1}mol^{-1}; λ_{em}(exc 410): 512 nm; Stokes shift: 86 nm; $E_{0,0}$: 2.83 eV; Cyclic voltammetry (vs SCE): $E_{1/2}(P^*/P^-)$: +2.32 V, $E_{1/2}(P/P^-)$: –0.51 V.

9-(4-Methoxyphenyl)-10-methylacridinium bromide salt (1b)

Prepared according to general procedure A using 4-methoxybenzoate (16.6 mg, 100 µmol) and the 1,5-bifunctional organomagnesium reagent to afford an orange solid (29.6 mg, 78 %, decomp. at 185 °C): R_f 0.16 (CH_2Cl_2:MeOH 10:1).

IR (ATR, neat): 3336m, 3092w, 2931w, 1605s, 1547m, 1457m, 1376m, 1250s, 1176s, 1113w, 1022m, 922w, 932m, 761s, 725s, 666m, 617s.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.93 (d, ^3J 8.8 Hz, 2H, C4*H*, C5*H*), 8.34 (t, ^3J 7.5 Hz, 2H, C3*H*, C6*H*), 8.02 (d, ^3J 8.6, 2H, C1*H*, C8*H*), 7.73 (dd, ^3J 8.9, 6.6, 2H, C2*H*, C7*H*), 7.33–7.37 (m, 2H, C2'*H*, C6'*H*), 7.16–7.18 (m, 2H, C3'*H*, C5'*H*), 5.23 (s, 3H, NCH_3), 3.93 (3H, s, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4 (*C*4'), 161.4 (*C*9), 141.6 (*C*4a, *C*10a), 139.0 (*C*3, *C*6), 131.7 (*C*2', *C*6'), 130.2 (*C*1, *C*8), 127.8 (*C*2, *C*7), 126.2 (*C*8a, *C*9a), 124.8 (*C*1'), 119.7 (*C*4, *C*5), 114.6 (*C*3', *C*5'), 55.7 (O*C*H$_3$), 41.0 (N*C*H$_3$).

HRMS (ESI): m/z calcd. for $C_{21}H_{18}NO^+$ 300.1383 found 300.1384 [M$^+$].

Absorption spectroscopy (in MeCN): λ_{abs}: 438 nm; ε_{abs}: 3.2·10^2 Lcm^{-1}mol^{-1}; λ_{em}(exc 360): 499 nm; Stokes shift: 61 nm; $E_{0,0}$: 2.77 eV; Cyclic voltammetry (vs SCE): $E_{1/2}(P^*/P^-)$: +2.21 V, $E_{1/2}(P/P^-)$: –0.56 V.

*Gram-Scale Synthesis of Acridinium Salt **1c** and **1d***

4-Bromo-*N*^{1},*N*^{1}-dimethylbenzene-1,3-diamine (3)

[CAS Reg. No.: 90555-68-3]

Prepared according to a modified literature procedure.[10a] To a solution of 4-bromo-*N,N*-dimethylaniline (**5**, 50.0 g, 250 mmol) in TBME/THF (1 : 1, 340 mL) was added dropwise aq. nitric acid (68%, 16.5 mL). The mixture was stirred for 1 h at room temperature. The formed precipitate was filtered off and the residue was washed with TBME (2 x 30 mL) and dried under vacuum overnight.[14] The yellow salt (35.0 g, 133 mmol) was then dissolved in CH_2Cl_2 (210 mL) and the solution was added to conc. H_2SO_4 (58.0 mL) while maintaining the temperature below 5 °C. The mixture was allowed to warm up to room temperature and was stirred for 1 h. The mixture was then slowly added to cold water (210 mL) and aq. NH_4OH (28%) was added until the mixture reached pH 10. The aq. residue was extracted with DCM (2 x 500 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to obtain 4-bromo-*N,N*-dimethyl-3-nitroaniline as an orange solid (32.0 g, 52%, m.p. 90.4–91.9 °C). R_f 0.73 (CH_2Cl_2 100%).

IR (ATR, neat): 2920w, 1609m, 1530s, 1443w, 1369m, 1234w, 1190w, 1129w, 1069w, 881w, 679w.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, ^3J 9.0, 1H, C5*H*), 7.07 (d, ^4J 3.1, 1H, C2*H*), 6.69 (dd, ^3J 9.1, ^4J 3.1, 1H, C6*H*), 3.00 (s, 6H, N(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.4 (*C*3), 149.7 (*C*1), 134.9 (*C*5), 116.4 (*C*6), 108.3 (*C*2), 98.6 (*C*4), 40.3 (N(*C*H$_3$)$_2$).

HRMS (ESI): m/z calcd. for $C_8H_{10}BrN_2O_2^+$ 244.9920 found 244.9921 [M+H$^+$].

In agreement with literature data.[3a]

Prepared according to a modified literature procedure.[10b] To a solution of 4-bromo-*N,N*-dimethyl-3-nitroaniline (36.8 g, 150 mmol) in methanol/ water (1 : 1, 430 mL), was added ammonium chloride (64.2 g, 1.20 mol) and iron powder (41.9 g, 750 mmol). The reaction mixture was stirred for 1 h at 70 °C, filtered over celite and concentrated to remove methanol.[15] The aq. layer was treated with aq. HCl (10%) and washed with diethylether (2 x 500 mL). NH_4OH aq. (28%) was added until basic pH was reached. The aq. layer was extracted with CH_2Cl_2 (3 x 1 L). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to yield 4-bromo-*N*^{1},*N*^{1}-dimethylbenzene-1,3-diamine as a black solid (28.1 g, 87%, m.p. 57.1–58.7 °C). R_f 0.29 (CH_2Cl_2 100%).

IR (ATR, neat): 3460w, 3355w, 2956w, 2843w, 2794w, 1604s, 1568s, 1491m, 1350m, 1291m, 1153m, 1123m, 1057w, 972w, 893w, 817s, 778s, 710w.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, ^3J 8.8, 1H, C5*H*), 6.12 (d, ^4J 2.9, 1H, C2*H*), 6.08 (dd, ^3J 8.8, ^4J 2.9, 1H, C6*H*), 3.97 (br, 2H, NH_2), 2.88 (s, 6H, N(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0 (*C*1), 144.3 (*C*3), 132.5 (*C*5), 105.2 (*C*6), 99.7 (*C*2), 97.0 (*C*4), 40.6 (N(*C*H$_3$)$_2$).

HRMS (ESI): m/z calcd. for $C_8H_{12}BrN_2^+$ 215.0178 found 215.0181 [M+H$^+$].

In agreement with literature data.[3a]

4-Bromo-3-iodo-*N,N*-dimethylaniline (4)

[CAS Reg. No.: 1291063-32-5]

Prepared according to a modified literature procedure.[9a] To a suspension of NaI (39.0 g, 260 mmol), CuI (1.24 g, 6.50 mmol),*N,N'*-dimethylethylenediamine (1.40 mL, 13.0 mmol) in 1,4-dioxane (130 mL) at RT was added 3-bromo-*N,N*-dimethylaniline (18.6 mL, 130 mmol). The reaction mixture was stirred for 22 h at 110 °C and then cooled to RT, treated with aq. NH_4OH (28%, 650 mL) and H_2O (300 mL) and was extracted with CH_2Cl_2 (3 x 1.5 L). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 3-iodo-*N,N*-dimethylaniline as a brownish oil (31.3 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.01–7.03 (m, 2H, C4*H*, C6*H*), 6.91–6.94 (m, 1H, C5*H*), 6.65–6.67 (m, 1H, C2*H*), 2.92 (s, 6H, N(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.6 (*C1*), 130.4 (*C5*), 125.2 (*C4*), 121.1 (*C6*), 111.6 (*C2*), 95.5 (*C3*), 40.3 (N(CH_3)$_2$).

In agreement with literature data.[9b]

To a solution of 3-iodo-*N*,*N*-dimethylaniline (31.3 g, 127 mmol) in CH_2Cl_2 (200 mL) at 10 °C was added bromine (6.53 mL, 127 mmol). The reaction mixture was stirred 1 h at that temperature.[16] The suspension was treated with aq. sat. Na_2SO_3 (76.0 mL) and H_2O (170 mL) and was extracted with CH_2Cl_2 (3 x 350 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The red crude solid was recrystallized from hexane/EtOAc (50 mL; 4:1) to give 4-bromo-3-iodo-*N*,*N* -dimethylaniline as a beige solid (23.7 g, 57%).[17]

In agreement with literature data.[9c]

4-Bromo-*N*^{3}-(2-bromo-5-(dimethylamino)phenyl)-*N*^{1},*N*^{1},*N*^{3}-trimethylbenzene-1,3-diamine (2b)

To a degassed mixture of 4-bromo-3-iodo-*N*,*N*-dimethylaniline (55.4 g, 170 mmol), 4-bromo-*N*^{1},*N*^{1}-dimethylbenzene-1,3-diamine (36.6 g, 170 mmol) tris(dibenzylideneacetone)dipalladium (3.89 g, 4.25 mmol), 1,1'-bis(diphenylphosphino)ferrocene (4.71 g, 8.50 mmol) and sodium *t*-butoxide (24.5 g, 255.0 mmol) was added toluene (560 mL) at RT. The reaction mixture was stirred for 14 h at 105 °C. The solution was diluted with H_2O (800 mL) and extracted with CH_2Cl_2 (3 x 2 L). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography on silica gel (pentane/CH_2Cl_2 3:1 to 2:1 to 1:1) giving 4-bromo-*N*^{3}-(2-bromo-5-(dimethylamino)phenyl)-*N*^{1},*N*^{1}-dimethyl-benzene-1,3-diamine as a beige solid (48.9 g, 70%, m.p. 132.2–134.7 °C). R_f 0.53 CH_2Cl_2 (100%).

IR (ATR, neat): 3399w, 2895w, 2804w, 1590m, 1562s, 1496s, 1441m, 1354s, 1284s, 1230w, 1161m, 1065w, 989w, 921w, 814m, 770s, 737w, 682w.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, ^3J 8.7, 2H, C3*H*), 6.76 (d, ^4J 2.9, 2H, C6*H*), 6.32 (br, 1H, N*H*), 6.24 (dd, ^3J 8.7, ^4J 3.0, 2H, C4*H*) 2.89 (s, 12H, N(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.5 (*C*5), 140.3 (*C*1), 133.0 (*C*3), 107.3 (*C*4), 102.1 (*C*6), 100.8 (*C*2), 40.7 (N(CH_3)$_2$).

HRMS (ESI): m/z calcd. for $C_{16}H_{20}Br_2N_3^+$ 412.0018 found 412.0019 [M+H$^+$].

Prepared according to a modified literature procedure.[7] To a solution of of 4-bromo-*N*^{3}-(2-bromo-5-(dimethylamino)phenyl)-*N*,*N*^{1}-dimethyl-benzene-1,3-diamine (48.3 g, 117.0 mmol) in THF (334 mL) at RT was added sodium hydride (60% dispersion in mineral oil, 14.0 g, 351.0 mmol). The suspension was heated to 75 °C and stirred for 30 min at this temperature. Iodomethane (7.28 mL, 117.0 mmol) was added within 5 min at 75 °C and the reaction mixture was stirred for 2 h at this temperature. The suspension was treated with water (585 mL) and extracted with CH_2Cl_2 (3 x 1.5 L). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude solid was recrystallized from hexane/EtOAc (70 mL; 4:1) to give 4-bromo-*N*^{3}-(2-bromo-5-(dimethylamino)phenyl)-*N*^{1},*N*^{1},*N*^{3}-trimethylbenzene-1,3-diamine (**2b**) as a beige solid (35.6 g, 71%, m.p. 102.5–104.1°C): R_f 0.55 (CH_2Cl_2 100%).

IR (ATR, neat): 2883w, 2806w, 1588s, 1554s, 1492s, 1446m, 1358s, 1304m, 1233m, 1170s, 1133m, 1084m, 1022w, 987m, 909w, 801m, 735w.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, ^3J 8.8, 2H, C3*H*); 6.35 (d, ^4J 3.0, 2H, C6*H*), 6.31 (dd, ^3J 8.8, ^4J 3.0, 2H, C4*H*), 3.21 (s, 3H, NCH_3), 2.87 (s, 12H, 2 x N(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.7 (*C*5), 149.1 (*C*1), 134.0 (*C*3), 109.1 (*C*4), 108.3 (*C*6), 106.7 (*C*2), 41.3 (N*C*H$_3$), 40.6 (2 x N(*C*H$_3$)$_2$).

HRMS (ESI): m/z calcd. for $C_{17}H_{22}Br_2N_3^+$ 426.0175 found 426.0177 [M+H$^+$].

General Procedure B

To a suspension of magnesium turnings (1.36 g, 56.0 mmol) in anhydrous THF (20.0 mL) at 60 °C was added a solution of 4-bromo-*N*^{3}-(2-bromo-5-(dimethylamino)phenyl)-*N*^{1},*N*^{1},*N*^{3}-trimethylbenzene-1,3-diamine (**2b**, 5.98 g, 14.0 mmol) in anhydrous THF (60 mL) followed by 1,2-dibromoethane (0.319 mL, 4.20 mmol). The mixture was stirred at 60 °C for 3 h during which the reaction mixture turned yellow. To this solution at 60 °C was added a solution of carboxylic acid ester (10.0 mmol) in anhydrous THF (100 mL) and the reaction mixture was stirred at the same temperature for 12 h. Aqueous HBr (100 mL, 8.8 molL-1) was added and the aq. phase extracted with $CHCl_3$/*i*-PrOH (3 x 200 mL; 85:15). The solvent was removed in vacuo and the residue was recrystallized from water (10 mL) to yield acridinium salts **1c** and **1d**.

3,6-Bis(dimethylamino)-9-mesityl-10-methylacridinium bromide salt (1c)

Prepared according to general procedure B using methyl 2,4,6 trimethyl benzoate (1.78 g, 10 mmol) to afford an orange solid (3.9 g, 82%, decomp. at 192.9 °C): R_f 0.13 (CH_2Cl_2 : MeOH 10:1).

IR (ATR, neat): 3373w, 2918w, 2170w, 1591s, 1497s, 1435m, 1352s, 1210s, 1148s, 985w, 921s, 807m, 711s.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, ^3J 9.5, 2H, C1*H*, C8*H*), 7.06 (br, 2H, C3'*H*, C5'*H*), 6.95–6.96 (m, 2H, C4*H*, C5*H*), 6.94 (dd, ^3J 9.4, ^4J 2.1, 2H, C2*H* , C7*H*), 4.56 (s, 3H, NCH_3), 3.36 (s, 12H, 2 x N(CH_3)$_2$), 2.43 (s, 3H, CH_3) 1.80 (s, 6H, 2 x CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4 (*C*3, *C*6), 154.0 (*C*9), 143.9 (*C*4a, *C*10a), 139.0 (*C*4'), 136.0 (*C*2', *C*6'), 130.4 (*C*1, *C*8, *C*1'), 128.6 (*C*3', *C*5'), 116.1 (*C*8a, *C*9a), 114.3 (*C*2, *C*7), 94.3 (*C*4, *C*5), 41.1 (2 x N(*C*H$_3$)$_2$), 38.3 (N*C*H$_3$), 21.2 (*C*H$_3$), 19.8 (2 x *C*H$_3$).

HRMS (ESI): m/z calcd. For $C_{27}H_{32}N_3^+$ 398.2591 found 398.2594 [M+H$^+$].

In agreement with literature data. [3a]

3,6-Bis(dimethylamino)-9-(2,6-Dimethylphenyl)-10-methylacridinium bromide salt (1d)

Prepared according to general procedure B using methyl 2,4,6 trimethyl benzoate (1.78 g, 10 mmol) to afford an orange solid (3.9 g, 84%, decomp. at 238.6 °C): R_f 0.17 (CH_2Cl_2: MeOH 10:1).

IR (ATR, neat): 2917w, 2662w, 1595m, 1502m, 1439s, 1354m, 1259s, 1215m, 1147m, 1067s, 981s, 924m, 809m, 712s, 649s.

^{1}H NMR (500 MHz, MeOD): δ = 7.44 (t, ^3J 7.6, 1H, C4'*H*),7.31 (d, ^3J 7.6, 2H, C3'*H*, C5'*H*), 7.28 (d, ^3J 9.5, 2H, C1*H*, C8*H*), 7.18 (dd, ^3J 9.5, ^4J 2.2, 2H, C2*H* , C7*H*), 6.88 (d, ^4J 2.2, 2H, C4*H*, C5*H*), 4.30 (s, 3H, NCH_3), 3.34 (s, 12H, 2 x N(CH_3)$_2$), 1.85 (s, 6H, 2 x CH_3).

^{13}C NMR (125 MHz, MeOD): δ = 157.2 (*C*3, *C*6), 155.3 (*C*9), 145.4 (*C*4a, *C*10a), 137.3 (*C*2', *C*6'), 135.0 (*C*1'), 131.4 (*C*1, *C*8), 130.6 (*C*4'), 129.1 (*C*3', *C*5'), 117.3 (*C*8a, *C*9a), 116.1 (*C*2, *C*7), 94.5 (*C*4, *C*5), 40.8 (2 x N(*C*H$_3$)$_2$), 36.7 (N*C*H$_3$), 19.8 (2 x *C*H$_3$).

HRMS (ESI): m/z calcd. For $C_{26}H_{30}N_3^+$ 384.2434 found 384.2440 [M+H$^+$].

Absorption spectroscopy (in MeCN): λ_{abs}: 504 nm; ε_{abs}: 7.1·10^4 Lcm^{-1}mol^{-1}; λ_{em}(exc 450): 533 nm; Stokes shift: 29 nm; $E_{0,0}$: 2.4 eV; Cyclic voltammetry (vs SCE): $E_{1/2}(P^*/P^-)$: +1.25 V, $E_{1/2}(P/P^-)$: –1.15 V.

Photoredox Catalyzed Deuteration

General Procedure C

According to a modified literature procedure.[11] To a mixture of triisopropylsilanethiol (5.71 mg, 30 µmol), lithium carbonate (35.5 mg, 480 µmol), photocatalyst (1–2.5 mol%, see table 3) and deuterium oxide (90.0 µL, 5.00 mmol) in *N*-methylpyrrolidone (1.6 mL) was added clomipramine hydrochloride (33.7 mg, 100 µmol) and was degassed by a stream of argon for 20 min. The reaction was performed under an argon

atmosphere for 24 h with the light on. The reaction mixture was diluted in EtOAc (15 mL), washed with brine (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was concentrated in vacuo and the residue purified by column chromatography with *n*-hexane:acetone:Et_3N, 96:2:2 to afford clomipramine free base. R_f 0.34 (*n*-hexane:acetone:Et_3N, 8:1:1).

^{1}H NMR (500 MHz, MeOD): δ = 7.12–7.17 (m, 3H), 7.09–7.10 (m, 1H), 7.02–7.03 (m, 1H), 6.95–6.98 (m, 1H), 6.85–6.87 (m, 1H), 3.73–3.76 (m, 1.75H, 12% 2H, C1'*H*), 3.07–3.15 (m, 4H, C5*H*, C6*H*), 2.33–2.40 (m, 1.03H, 49% 2H, C3'*H*), 2.11–2.15 (m, 4.16H, 30% 2H, N(CH_3)$_2$), 1.70–1.74 (m, 2H, C2'*H*).

In agreement with literature.[11]

To afford the clomipramine HCl salt, the free base was dissolved in EtOAc, treated with HCl in dioxane (4 molL^{-1}, 250 µL), concentrated in vacuo, triturated from Et_2O and filtered.

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(14) The precipitate slowly formed after the addition of nitric acid and can be either grey or yellow (it will turn eventually yellow after drying under vacuum).

(15) The celite was washed with EtOAc.

(16) The reaction mixture turns beige immediately and the color remains until the end of the reaction.

(17) After heating up to 80°C, a hot filtration allowed to remove insoluble red solids, while the precipitate of product could be isolated at RT.