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A Mild and Efficient Procedure for Ring-Opening Reactions of Piperidine and Pyrrolidine Derivatives by Single Electron Transfer Photooxidation

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Abstract—Various *N*-arylamino-1-pyrrolidines and *N*-arylamino-1-piperidines are selectively converted into the corresponding acyclic aminoaldehydes or amino-dialkylacetals under mild photooxidation conditions.

Introduction

During the course of our work on the reactivity of heterocyclic nitrogen compounds to photooxidation by single electron transfer, we have already reported the high regio- and stereoselectivity observed during such oxidations.[1–4] For example, we recently described the photooxidation of *N*-arylamino-1-pyrrolidines and *N*-arylamino-1-piperidines.[5]

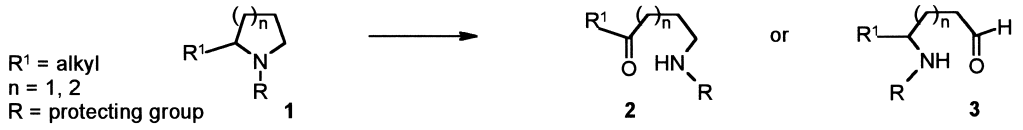
We then decided to investigate the ring-opening reactions of some piperidine and pyrrolidine systems in order to demonstrate the selectivity in such an approach to acyclic functionalised nitrogen compounds.

Thus, we required a procedure for mild and efficient nitrogen ring-opening reactions. In the case of unsymmetrical compounds **1** ($R^1 \neq H$), the regioselectivity should be controlled, thereby leading either to ketonic compound **2** or aldehydic product **3** (Scheme 1).

The classical approach involves the oxidation of a lactam intermediate which is then followed by hydrolysis on heating.[6] This sequence (oxidation, ring-opening) leads regioselectively to cleavage on the less substituted side but requires drastic conditions. Stanforth and co-workers[7–9] have described a one-step ring-opening reaction of *N*-aryl-1,2,3,4-tetrahydroisoquinoline and 2,3,4,5-tetrahydro-1*H*-2-benzazepine derivatives when heated (100°C) in presence of DMSO and O_2 or NBS. Weinreb and others[10–12] have developed a process involving a cuprous ion-promoted oxidation of *o*-aminobenzamides into α-methoxybenzamides via *N*-acyliminium ion intermediates. It has been shown that treatment of various *o*-aminobenzamides with sodium nitrite and dry HCl in methanol containing 5% cuprous chloride leads to oxidation products in good yields. In the case of pyrrolidine-derived systems, ring-opening of α-methoxybenzamide tends to occur only if extended reaction times are used. However, mixtures of oxidation products have been obtained and further studies are needed in order to fully understand the mechanistic origin of the selectivity observed.

We believe that photooxidation of cyclic amines by single electron transfer followed by ring-opening has potential as a convenient method for the synthesis. We therefore set out to find reaction conditions for the process which satisfy the following criteria:

- the oxidative cleavage must be mild and regioselective;
- the choice of the R substituent should provide access to



Scheme 1.

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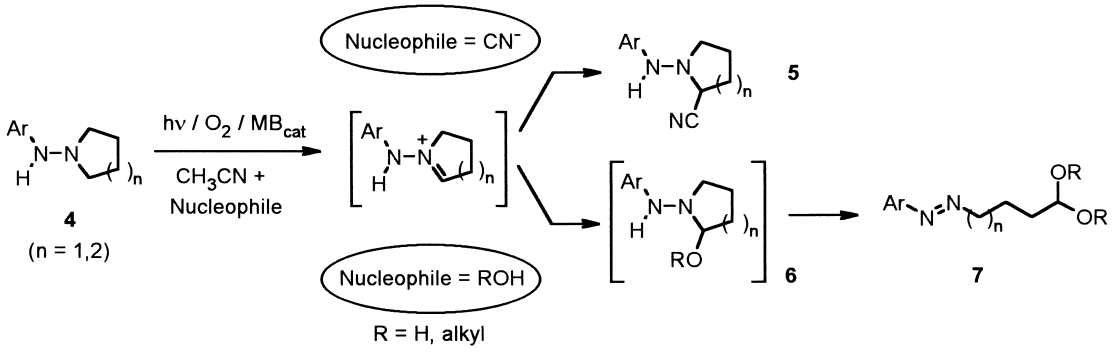


Scheme 2.

the open forms **2** or **3**, without any equilibration between open and cyclised forms;

- the strategy would use an *N*-substituent, which is easily removed under mild conditions (protecting group) and in high yields.

Results and Discussion

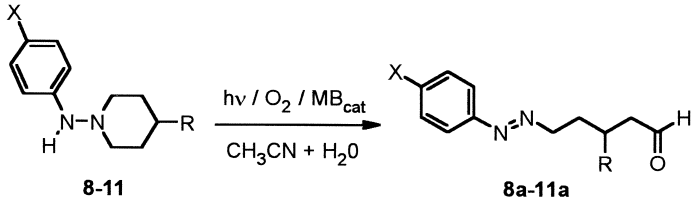
We decided to investigate further the oxidation of *N*-arylamino-1-piperidines and *N*-arylamino-1-pyrrolidines. The substrates **4** used in our previous study[5] were irradiated by visible light ($\lambda > 630$ nm), with a catalytic amount of methylene blue (MB) and trimethylsilylcyanide (TMSCN) as a source of cyanide ion, and were converted into α-hydrazinonitrile derivatives **5** (Scheme 2). Application of this amine oxidation procedure in the presence of alcohol or water as nucleophile (ROH instead of cyanide ions), yields α-hydrazinoalkoxy derivatives **6** (not isolated), and ultimately, after ring-opening the corresponding acetals or aldehydes **7** are obtained in good yields.

Symmetrical piperidine or pyrrolidine ring-opening photochemical reactions

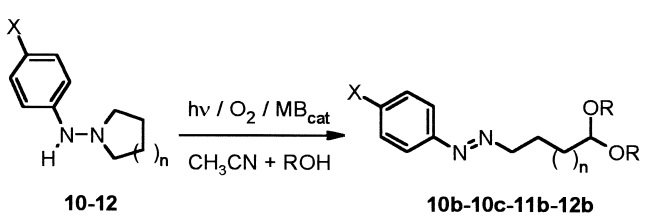
As can be seen from Scheme 3, ring-opening of piperidine compounds **8**–**11** was effected in high yields (75–97%) in presence of water as nucleophile. In all these ring-opening reactions, only aldehyde products (**8a**–**11a**) were observed by ^{1}H NMR spectroscopy and none of the corresponding hemiaminal could be detected. Overall, the procedure for such a transformation involves mild and selective oxidative conditions compatible with the reactivity of the resulting aldehyde group.

Using alcoholic solvent as nucleophile allows us to obtain the corresponding acetals **10b**, **10c**, **11b** and **12b**. However, the purity of those products was substantially reduced, and after purification by column chromatography, overall product yields were disappointingly low.

In the case of the pyrrolidine system **12**, the ring was easily opened in a mixture of acetonitrile and water (9:1). We observed the formation of the intermediate aldehyde **12c**

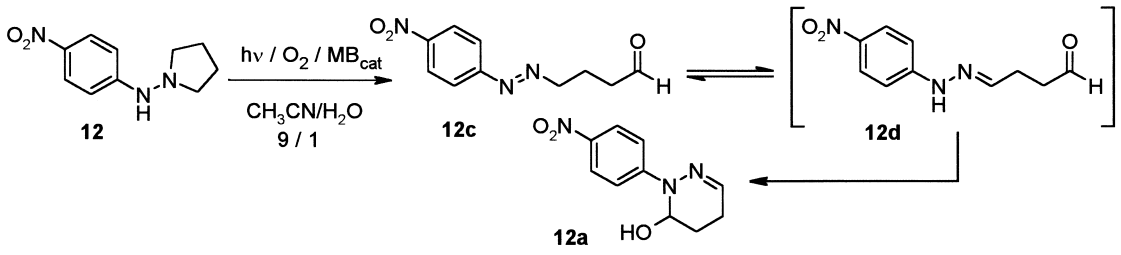


Substrate[(i)]			Product[(ii)]	
	X	R	yield (%)[(v)]	
8	H	H	**8a**	75
9	H	CH_3	**9a**	84
10	NO_2	H	**10a**	97
11	CO_2Et	H	**11a**	81



Substrate[(i)]				Product[(ii)(iii)]	
	n	X	R	yield (%)[(iv)]	
10	2	NO_2	CH_3	**10b**	52
10	2	NO_2	C_2H_5	**10c**	48
11	2	CO_2Et	CH_3	**11b**	45
12	1	NO_2	CH_3	**12b**	46

Scheme 3. (i) Synthesis of products **8**–**12** are detailed in the Experimental; (ii) the structures of the products were fully determined by spectroscopic analyses; (iii) besides the desired product, a by-product was also formed (25%) and separated by column chromatography; (iv) yield after purification by flash chromatography on aluminium oxide; (v) these products were pure enough for further reactions.



Scheme 4.

(isolated and characterised), which spontaneously cyclised to give the corresponding tetrahydropyridazine **12a** (yield: 49% after purification by flash chromatography). A possible mechanism which involves the formation of the azoaldehyde **12c** from compound **12** followed by cyclisation of a hydrazone intermediate **12d** is shown in Scheme 4.

These one-pot ring-opening reactions proceed by three steps as shown in Scheme 5:

- Preliminary step: as previously described,[5] the oxidation occurs on the carbon atom α to the nitrogen ring atom to give an hydrazinium alkylidene cation. The nucleophilic attack of ROH leads to the oxidised hemiaminal **6**.
- Second and third steps: the proposed reaction sequence involves an initial cleavage of the nitrogen carbon bond of the hemiaminal leading to the arylhydrazine **13** which is subsequently photooxidised in situ. However, the sequence of those two steps is not determined.

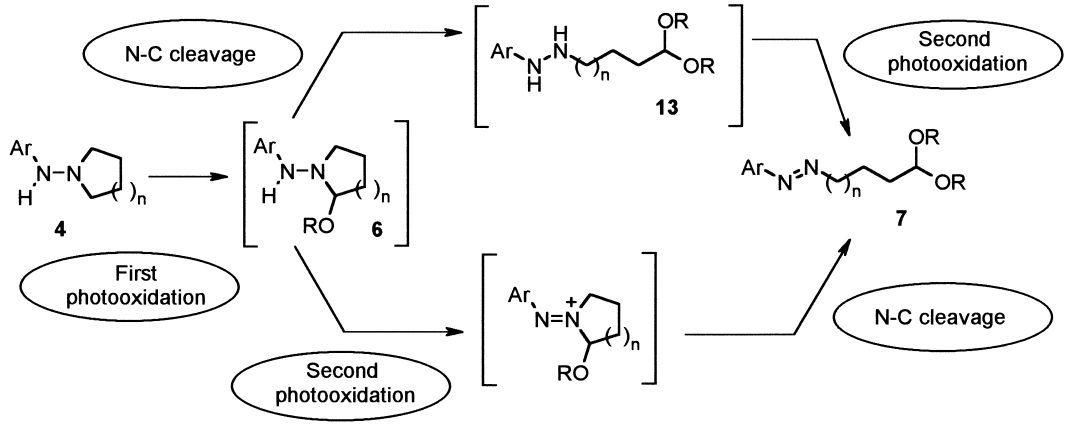
It should be noted that such nitrogen–carbon bond cleavage leading to ring-opening of piperidine derivatives does not work under the conditions used in this methodology when tertiary amines are involved. Thus, irradiation by visible light of *N*-cyclohexylpiperidine in a mixture of CH_3CN/H_2O (9:1) in presence of catalytic amount of methylene blue and with oxygen bubbling affords the unchanged starting material.

Regioselectivity of piperidine ring-opening photochemical reactions with unsymmetrical systems

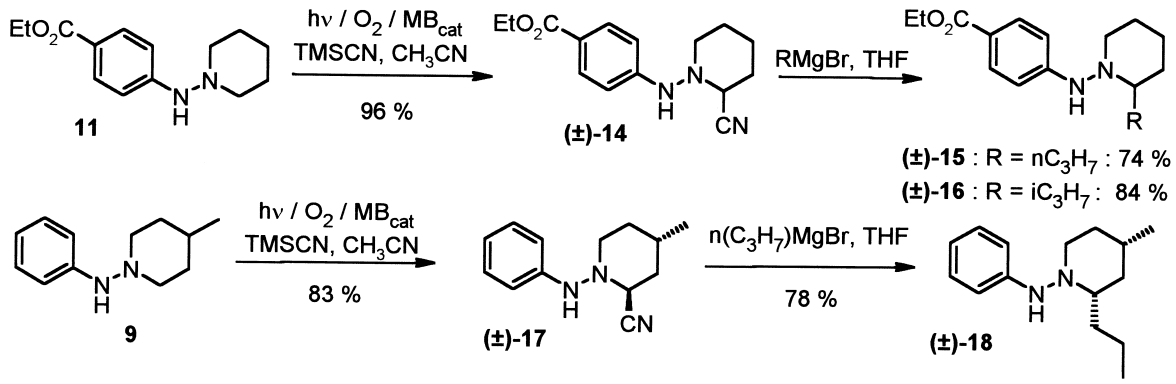
Since the scope of this new methodology would be greatly expanded if the procedure showed good regioselectivity with unsymmetrical systems we decided to examine photooxidation in a series of 2-alkyl-*N*-aminopiperidine derivatives. Synthesis of these unsymmetrical compounds are described in Scheme 6. The photocyanation[5] of *N*-aminopiperidine **11** gives the α-hydrazinonitrile (±)-**14** in an excellent yield of 96%. Thus treatment of **14** with an excess of Grignard reagent in refluxing tetrahydrofuran under argon atmosphere affords good yields of alkylated piperidines (±)-**15**, (±)-**16**. With the same methodology irradiation of 4-methyl-*N*-phenylamino-1-piperidine **9** in presence of trimethylsilylcyanide as nucleophile source leads stereospecifically to the corresponding *trans*-(±)-2-cyano-4-methyl-*N*-phenylamino-1-piperidine **17** with 83% yield (d.e.>99%).[5] Further alkylation of this compound by propylmagnesium bromide gives only one dialkylated product (±)-**18** (d.e.>99% determined by HPLC) bearing a *cis* relationship between the methyl and propyl chains (78% yield).

Finally, the 2-methyl-*N*-arylamino-1-piperidine (±)-**19** is produced by consecutive reductive amination steps of the two carbonyl groups of 5-oxohexanal with 4-nitrophenylhydrazine by using sodium cyanoborohydride in methanol.

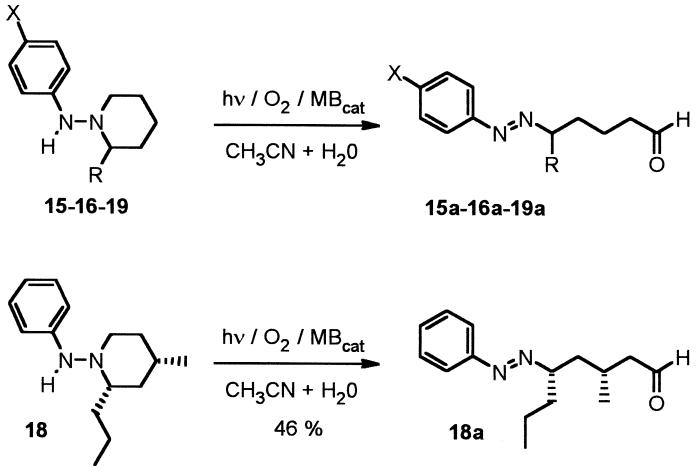
As can be seen from Scheme 7, the ring-opening of cyclic compounds **15**, **16**, **18**, **19** by irradiation in visible light leads with satisfactory to good yields (46–98%) to the selective bond cleavage between the nitrogen atom and the less substituted carbon atom. No ketonic product has been detected. The reaction proceeds smoothly and regiospecifically, and the resulting acyclic compounds conserve the high diastereomerical purity of the starting substrates (e.g. the photochemical ring-opening reaction of compound **18** affords the acyclic azoaldehyde (±)-**18a**, conserving the



Scheme 5.



Scheme 6.



Substrate			Product[(i)]	
	X	R	yield (%)	
(±)-**15**	CO_2Et	$n(C_3H_7)$	(±)-**15a**	78
(±)-**16**	CO_2Et	$i(C_3H_7)$	(±)-**16a**	98
(±)-**19**	NO_2	CH_3	(±)-**19a**	81

Scheme 7. (i) The structures of the products were fully determined by complete spectroscopic analyses and they were pure enough for further reactions.

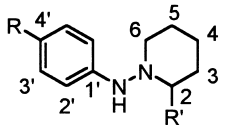
relative stereochemistry of the initial ring substituents). Further example illustrating such relative stereocontrol will be reported in due course.

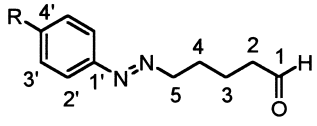
In summary, our results illustrate a new application of photosensitization of *N*-arylamino-1-piperidine and *N*-arylamino-1-pyrrolidines. We have developed experimental conditions for converting the prepared cyclic hydrazium alkylidene cation intermediates into linear aldehydes with excellent yields and a total regioselectivity. The reactions described herein allow a practical method for the preparation of azoaldehydes. These compounds would give aminoaldehydes which are versatile tools in organic chemistry.[13–16]

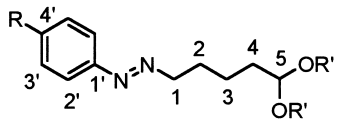
Experimental

All materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from benzophenone/sodium prior to use. IR spectra (cm^{-1} with polystyrene calibration, in $CHCl_3$ unless otherwise noted) were recorded on a Perkin–Elmer 457 spectrophotometer or on Philips PU9716 spectrophotometer. ^1H NMR (400 or 300 MHz, in $CDCl_3$, reference: TMS, δ_H=0.0 ppm) and ^{13}C NMR (100.6 or 75.4 MHz, in $CDCl_3$, reference: $CDCl_3$, δ_C=77.0 ppm) spectra were recorded on a Bruker AM400 spectrometer or a Bruker AC300P spectrometer. Chemical shift data are reported in parts per million downfield from TMS, and coupling constants (*J*) are reported in hertz (Hz). GC–MS spectra (EI and CI) were performed on a HP G1019A (70 ev, *m/z*) spectrometer. Elemental analyses were performed by the SIAR (Service Régional de Microanalyse de l'Université Paris VI). HRMS spectra were performed by the Laboratory of the ENS (Ecole Normale Supérieure de Paris). Flash column and thin-layer chromatography were done by using Aluminium oxide 90 (Merck, act. II-III) or Silica gel 60 (230–400 Mesh).

For a better homogeneity of the attribution of the NMR signals, the structures have the following numbering systems which are different from the IUPAC one:







***N*-Phenylamino-1-piperidine (8).** To a −78°C solution of 1.144 g (10.5 mmol) of *N*-phenyl hydroxylamine, 1.46 mL (10.5 mmol) of triethylamine and 80 mL of CH_2Cl_2 was added dropwise a solution of 2.00 mL (10.5 mmol) of diphenylphosphinyl chloride in 20 mL of CH_2Cl_2. The white suspension which was quickly formed was stirred at −30°C for 30 min. The mixture was then cooled to −78°C and a solution of 1.56 mL (15.75 mmol) of piperidine, 1.46 mL (10.5 mmol) of triethylamine and 40 mL of CH_2Cl_2 was added dropwise over 10 min. The resulting solution was allowed to warm to rt overnight. After removal of the solvent in vacuo, the residue was purified by flash chromatography (Al_2O_3, 20% CH_2Cl_2/cyclohexane) to give 540 mg (3.07 mmol, 29%) of *N*-phenylamino-1-piperidine (**8**) as an orange oil: spectral data are in agreement with Katritzky's results.[17]

4-Methyl-*N*-phenylamino-1-piperidine (9). This compound was prepared from 1.144 g (10.5 mmol) of *N*-phenylhydroxylamine and 1.86 mL (15.75 mmol) of 4-methylpiperidine by the procedure used to synthesise product **8**. The desired piperidine **9** was obtained as a yellow oil (618 mg, 3.25 mmol, 31%): IR (neat) 2940, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (2H, dd, J^3=8.4, 7.4 Hz, H-3′), 6.88 (2H, d, J^3=8.4 Hz, H-2′), 6.76 (1H, tt, J^3=7.4, 1.1 Hz, H-4′), 4.30 (H, s, N–H), 3.14 (2H, d, J^2=11.0 Hz, H-2_{eq}), 2.18 (2H, dd, J^2=10.8 Hz, J^3=10.8 Hz, H-2_{ax}), 1.67 (2H, d, J^2=9.2 Hz, H-3_{eq}), 1.45–1.30 (3H, m, H-4_{ax}, H-3_{ax}), 0.95 (3H, d, J^3=5.9 Hz, 4-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 147.8 (C-1′), 129.1 (C-3′), 119.1 (C-4′), 113.6 (C-2′), 56.6 (C-2), 34.3 (C-3), 30.2 (C-4), 21.5 (4-CH_3); MS (EI) *m/z* (rel. intensity): 191 (14), 190 ($M^{+\cdot}$, 100), 133 (14), 98 (16), 93 (38), 92 (36), 77 (22), 65 (17). HR-MS (EI):calcd for $C_{11}H_{14}N_2O$: ($M^{+\cdot}$) *m/z* 190.1470, obsd 190.1463.

***N*-(4-Nitrophenyl)amino-1-piperidine (10).** To a −15°C solution of 3.25 g (21.2 mmol) of 4-nitrophenylhydrazine and 1.00 mL of acetic acid (17.5 mmol) in 100 mL of methanol was added dropwise a solution of 2.30 g (23.0 mmol) of glutaric dialdehyde in 50 mL of methanol, followed by the addition of 1.34 g (21.2 mmol) of $NaBH_3CN$. The resulting solution was allowed to warm to room temperature and was stirred for 20 h and monitored by TLC. The mixture was cooled to 0°C and quenched with 0.5 M HCl solution (30 mL). The volatiles were removed under reduced pressure and aqueous Na_2CO_3 (50 mL, 10%) was added, followed by 60 mL of CH_2Cl_2. The organic solution was separated and the aqueous solution was extracted with CH_2Cl_2 (2×60 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Al_2O_3, 30% cyclohexane/CH_2Cl_2) to give as a yellow crystalline solid, the *N*-(4-nitrophenyl)amino-1-piperidine (**10**) (2.00 g, 9.0 mmol, 43%): mp 121–122°C; IR (KBr) 3280, 2940, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (2H, d, J^3=8.5 Hz, H-3′), 6.84 (2H, d, J^3=8.5 Hz, H-2′), 5.17 (1H, s, N–H), 2.69 (4H, s, H-2), 1.73 (4H, tt, J^3=5.7, 5.7 Hz, H-3), 1.46 (2H, s, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.8 (C-1′), 139.1 (C-4′), 126.3 (C-3′), 111.1 (C-2′), 57.2 (C-2), 25.8 (C-3), 23.3 (C-4); MS (EI) *m/z* (rel. intensity): 222 (13), 221 ($M^{+\cdot}$, 100), 220 (16), 138 (9), 122 (19), 99 (8), 91 (10), 90 (10), 84 (16), 83 (10), 65 (9), 64 (10), 55 (18); Anal. Calcd for $C_{11}H_{15}N_3O_2$: C 59.71; H 6.83; N 18.99. Found: C 59.68; H 6.89; N 19.09.

4-[(Piperidin-1-yl)amino]ethylbenzoate (11). To a 0°C solution of 3.0 g (19.7 mmol) of 4-hydrazinobenzoic acid in 100 mL of ethanol was added dropwise 2.7 g (22.3 mmol) of thionyl chloride. The resulting solution was allowed to warm to room temperature and was stirred for 15 min. The mixture was then refluxed for 15 h. After cooling at room temperature, 90 mL of Et_2O was added and the resulting solution was filtered. The solid was washed with Et_2O (2×30 mL) and dried in vacuo to give 3.48 g (16.1 mmol, 82%) of (4-hydrazino)ethylbenzoate hydrochloride as a glossy solid, which was identical in all respects to the literature data.[18] This product was stirred for 15 min at room temperature in a mixture of 50 mL of an aqueous Na_2CO_3 solution (10%) and 50 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with an aqueous solution of Na_2CO_3 (10%), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 100 mL of methanol and 1 mL (17.5 mmol) of acetic acid, and the solution was cooled to −15°C. A solution of 1.89 g (18.9 mmol) of glutaric dialdehyde in 50 mL of methanol was added dropwise, followed by the addition of 1.02 g (16.2 mmol) of $NaBH_3CN$. The resulting solution was allowed to warm to room temperature and was stirred for 20 h and monitored by TLC. The mixture was cooled to 0°C and quenched with 0.5 M HCl solution (30 mL). The volatiles were removed under reduced pressure and aqueous Na_2CO_3 (50 mL, 10%) was added, followed by 60 mL of CH_2Cl_2. The organic solution was separated and the aqueous solution was extracted with CH_2Cl_2 (2×60 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Al_2O_3, 40% CH_2Cl_2/cyclohexane) to give 2.20 g (8.9 mmol, 55%) of 4-[(piperidin-1-yl)amino]ethylbenzoate (**11**) as a white crystalline solid: mp 125–126°C; IR (KBr) 3040, 1700, 1600, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (2H, d, J^3=8.8 Hz, H-3′), 6.84 (2H, d, J^3=8.7 Hz, H-2′), 4.77 (1H, s, N–H), 4.30 (2H, q, J^3=7.1 Hz, O–CH_2), 2.70–2.60 (4H, m, H-2), 1.70 (4H, tt, J^3=5.6, 5.6 Hz, H-3), 1.48–1.39 (2H, m, H-4), 1.37 (3H, t, J^3=7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.8 (C=O), 151.5 (C-1′), 131.3 (C-3′), 120.3 (C-4′), 111.8 (C-2′), 60.2 (O–CH_2), 57.3 (C-2), 25.9 (C-3), 23.5 (C-4), 14.5 (CH_3); MS (EI) *m/z* (rel. intensity): 248 ($M^{+\cdot}$, 100), 203 (16), 149 (21), 119 (16), 108 (16), 92 (14), 84 (27), 65 (15); Anal. Calcd for $C_{11}H_{15}N_3O_2$: C 67.71; H 8.12; N 11.28. Found: C 67.89; H 8.16; N 11.32.

***N*-(4-Nitrophenyl)amino-1-pyrrolidine (12).** To a 0°C suspension of $LiAlH_4$ (1.14 g, 29.9 mmol) in 75 mL of dry

THF was added dropwise a solution of 2.34 g (10.0 mmol) of 1-[(4-nitrophenyl)amino]-1*H*-pyrrole-2,5-dione (synthesised as previously described[19]) in 25 mL of dry THF. The red mixture was stirred at room temperature for 3 h, monitored by TLC and then was cooled to 0°C. 125 μL of water, 1.21 mL of aqueous NaOH (15%) and 7.8 mL of water were successively added and the resulting mixture was stirred at room temperature for 1 h, and then filtered, dried over $MgSO_4$ and concentrated under reduced pressure to give as an orange solid the *N*-(4-nitrophenyl)amino-1-pyrrolidine (**12**) (1.00 g, 4.83 mmol, 49%). It was identical in all respects to the literature compound:[20] Anal. Calcd for $C_{10}H_{13}N_3O_2$: C 57.96; H 6.32; N 20.28. Found: C 57.97; H 6.29; N 20.35.

Ring-opening reactions by SET photooxidation of symmetrical compounds

The ring-opening reactions were realised according to a general procedure. The preparation of **8a** outlined below represents a typical experiment.

5-(Phenylazo)pentanal (8a). A solution of *N*-phenylamino-1-piperidine (**8**) (200 mg, 1.14 mmol) in acetonitrile (18 mL) and water (2 mL) to which was added a catalytic amount of MB (4 mg, 0.01 mmol) was irradiated under oxygen bubbling for 4 h with a 1800 W Xenon lamp through a UV cut-off glass filter ($\lambda>630$ nm) at 20°C. After reaction, monitored by TLC, the resulting reaction mixture was concentrated under reduced pressure to give a blue oil. The crude product was dissolved in 50 mL of water, followed by 50 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure to give as a yellow oil the 5-(phenylazo)pentanal (**8a**) (162 mg, 0.85 mmol, 75%): IR (neat) 2940, 1740, 1720, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.79 (1H, t, J^3=1.8 Hz, H-1), 7.69–7.63 (2H, m, H-3′), 7.51–7.39 (3H, m, H-2′, H-4′), 4.07 (2H, t, J^3=7.0 Hz, H-5), 2.53 (2H, dt, J^3=7.4, 1.8 Hz, H-2), 2.04–1.74 (4H, m, H-3, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 202.2 (C-1), 152.0 (C-4′), 130.5 (C-1′), 129.0 (C-3′), 122.2 (C-2′), 68.9 (C-5), 43.6 (C-2), 27.3 (C-3), 20.0 (C-4); MS (EI) *m/z* (rel. intensity): 190 ($M^{+\cdot}$, 9), 106 (3), 105 (38), 94 (3), 91 (2), 85 (2), 78 (9), 77 (100), 65 (2), 51 (9); HR-MS (EI): calcd for $C_{11}H_{14}N_2O$: ($M^{+\cdot}$) *m/z* 190.1106, obsd 190.1104.

3-Methyl-5-(phenylazo)pentanal (9a). According to the typical procedure, **9a** (180 mg, 0.88 mmol, 84%) was prepared by irradiation of the 4-methyl-*N*-phenylamino-1-piperidine (**9**) (200 mg, 1.05 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 4 h and was obtained as a yellow oil: IR (neat) 2940, 1740, 1720, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.77 (1H, dd, J^3=2.2, 1.9 Hz, H-1), 7.69–7.63 (2H, m, H-3′), 7.56–7.39 (3H, m, H-2′, H-4′), 4.10 (2H, dd, J^3=7.0, 7.0 Hz, H-5), 2.55 (1H, ddd, J^2=16.2 Hz, J^3=7.0, 1.9 HZ, H-2_a), 2.34 (1H, ddd, J^2=16.2 Hz, J^3=7.7, 1.9 Hz, H-2_b), 2.32–2.20 (1H, m, H-3), 1.98 (1H, m, H-4_a), 1.87 (1H, m, H-4_b), 1.07 (3H, d, J^3=6.6 Hz, 3-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 202.4 (C-1), 152.0 (C-4′), 130.5 (C-1′), 128.8 (C-3′), 122.1 (C-2′), 67.1 (C-5), 50.8 (C-2), 34.6 (C-3), 26.4 (C-4), 19.9 (3-CH_3); MS (EI) *m/z* (rel. intensity): 204 ($M^{+\cdot}$, 9), 120 (6), 105 (35), 78 (8), 77 (100), 55 (5), 51(8); HR-MS (EI): calcd for $C_{12}H_{16}N_2O$: ($M^{+\cdot}$) *m/z* 204.1263, obsd 204.1263.

5-[(4-Nitrophenyl)azo]pentanal (10a). According to the typical procedure, **10a** (237 mg, 1.01 mmol, 97%) was prepared by irradiation of the *N*-(4-nitrophenyl)amino-1-piperidine (**10**) (230 mg, 1.04 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 3.5 h and was obtained as a yellow oil: IR (neat) 2940, 1750, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (1H, t, J^3=1.5 Hz, H-1), 8.33 (2H, d, J^3=9.0 Hz, H-3′), 7.77 (2H, d, J^3=9.0 Hz, H-2′), 4.16 (2H, t, J^3=7.0 Hz, H-5), 2.55 (2H, td, J^3=7.3 Hz, 1.5, H-2), 2.02 (2H, tt, J^3=7.3, 7.3 Hz, H-3), 1.81 (2H, tt, J^3=7.7, 7.7 Hz, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 201.9 (C-1), 155.1 (C-1′), 148.6 (C-4′), 124.7 (C-3′), 122.8 (C-2′), 69.8 (C-5), 43.5 (C-2), 27.2 (C-3), 19.9 (C-4); MS (CI/NH_3) *m/z* (rel. intensity): 253 (M^++18, 20), 237 (37), 236 (M^++1, 100), 220 (10); HR-MS (CI/CH_4): calcd for $C_{11}H_{14}N_3O_3$: (M^++1) *m/z* 236.1035, obsd 236.1032.

1-(5,5-Dimethoxypentyl)-2-(4-nitrophenyl)diazene (10b). According to the typical procedure, **10b** (99 mg, 0.35 mmol, 52%) was prepared by irradiation of the *N*-(4-nitrophenyl)amino-1-piperidine (**10**) (150 mg, 0.68 mmol) in a solution of acetonitrile (18 mL) and dry methanol (2 mL) for 7 h followed by flash chromatography (Al_2O_3, 30% cyclohexane/(CH_2Cl_2): and was obtained as a yellow oil: IR (neat) 2920, 1600, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, J^3=9.0 Hz, H-3′), 7.77 (2H, d, J^3=9.0 Hz, H-2′), 4.40 (1H, t, J^3=5.7 Hz, H-5), 4.14 (2H, t, J^3=7.0 Hz, H-1), 3.33 (6H, s, O–CH_3), 1.99 (2H, tt, J^3=7.4 Hz, H-3), 1.75–1.66 (2H, m, H-2), 1.58–1.46 (2H, m, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.2 (C-1′), 148.6 (C-4′), 124.7 (C-3′), 122.9 (C-2′), 104.3 (C-5), 70.2 (C-1), 52.8 (O–CH_3), 32.3 (C-4), 27.6 (C-3), 22.6 (C-2); MS (CI) *m/z* (rel. intensity): 292 (M^++18, 4), 282 (M^++1, 19), 251 (20), 250 (100); HR-MS (CI/CH_4): calcd for $C_{13}H_{20}N_3O_4$: (M^++1) *m/z* 282.1454, obsd 282.1459.

1-(5,5-Diethoxypentyl)-2-(4-nitrophenyl)diazene (10c). According to the typical procedure, **10c** (101 mg, 0.33 mmol, 48%) was prepared by irradiation of the *N*-(4-nitrophenyl)amino-1-piperidine (**10**) (150 mg, 0.68 mmol) in a solution of acetonitrile (18 mL) and anhydrous ethanol (2 mL) for 8 h followed by flash chromatography (Al_2O_3, 30% cyclohexane/CH_2Cl_2) and was obtained as a yellow oil: IR (neat) 2920, 1600, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, J^3=9.2 Hz, H-3′), 7.77 (2H, d, J^3=9.2 Hz, H-2′), 4.51 (1H, t, J^3=5.6 Hz, H-5), 4.15 (2H, t, J^3=7.0 Hz, H-1), 3.65 (2H, dq, J^2=9.2 Hz, J^3=7.0 Hz, O–CH_a), 3.50 (2H, dq, J^2=9.2 Hz, J^3=7.0 Hz, O–CH_b), 1.98 (2H, tt, tt, J^3=7.3 Hz, H-3), 1.76–1.67 (2H, m, H-2); 1.59–1.47 (2H, m, H-4); 1.20 (6H, dd, J^3=7.0 Hz, CH_3), ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.2 (C-1′), 148.6 (C-4′), 124.7 (C-3′), 122.9 (C-2′), 102.7 (C-5), 70.2 (C-1), 61.1 (O–CH_2), 33.4 (C-4), 27.7 (C-3), 22.7 (C-2), 15.4 (CH_3); MS (CI) *m/z* (rel. intensity): 310 (M^++1, 8), 265 (22), 264 (100), 239 (13), 222 (8); HR-MS (CI/NH_3): calcd for $C_{15}H_{24}N_3O_4$: (M^++1) *m/z* 310.1767, obsd 310.1764.

4-[(5-Oxopentyl)diazenyl]ethylbenzoate (11a). According to the typical procedure, **11a** (184 mg, 0.74 mmol, 83%) was prepared by irradiation of the 4-[(piperidin-1-yl)amino]-ethylbenzoate (**11**) (234 mg, 0.90 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 4 h and was obtained as a brown oil: IR (neat) 3300, 3000, 1700, 1580, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (1H, t, J^3=1.5 Hz, H-1), 8.13 (2H, d, J^3=8.6 Hz, H-3′), 7.68 (2H, d, J^3=8.5 Hz, H-2′), 4.39 (2H, q, J^3=7.1 Hz, O–CH_2), 4.11 (2H, t, J^3=7.0 Hz, H-5), 2.56 (2H, td, J^3=7.3, 1.5 Hz, H-2), 2.00 (2H, tt, J^3=7.3, 7.3 Hz, H-3), 1.80 (2H, tt, J^3=7.6, 7.6 Hz, H-4), 1.42 (3H, t, J^3=7.2, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 201.9 (C-1), 165.9 (C=O), 154.4 (C-1′), 130.5 (C-3′), 122.8 (C-4′), 121.9 (C-2′), 69.4 (C-5), 61.2 (O–CH_2), 43.6 (C-2), 27.3 (C-3), 20.0 (C-4), 14.3 (CH_3); MS (CI) *m/z* (rel. intensity): 280 (M^++18, 25), 263 (M^++1, 100); HR-MS (CI/CH_4): calcd for $C_{14}H_{19}N_2O_3$: (M^++1) *m/z* 263.1396, obsd 263.1399.

4-[(5,5-Dimethoxypentyl)diazenyl]ethylbenzoate (11b). According to the typical procedure, **11b** (112 mg, 0.36 mmol, 45%) was prepared by irradiation of the 4-[(piperidin-1-yl)amino]-ethylbenzoate (**11**) (200 mg, 0.81 mmol) in a solution of acetonitrile (18 mL) and anhydrous methanol (2 mL) for 4 h followed by flash chromatography (Al_2O_3, 30% cyclohexane/CH_2Cl_2) and was obtained as a brown oil: IR (neat) 3300, 3000, 1700, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.13 (2H, d, J^3=8.6 Hz, H-3′), 7.68 (2H, d, J^3=8.5 Hz, H-2′), 4.43–4.35 (3H, m, H-5, O–CH_2), 4.11 (2H, t, J^3=7.1 Hz, H-1), 3.31 (6H, s, O–CH_3), 1.99 (2H, tt, J^3=7.4 Hz, H-3), 1.75–1.66 (2H, m, H-2), 1.58–1.46 (2H, m, H-4), 1.41 (3H, t, J^3=7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.0 (C=O), 154.5 (C-1′), 130.4 (C-3′), 122.8 (C-4′), 121.9 (C-2′), 104.3 (C-5), 69.8 (C-1), 61.2 (O–CH_2), 52.8 (O–CH_3), 32.3 (C-4), 27.6 (C-3), 22.6 (C-2), 14.3 (CH_3); MS (CI) *m/z* (rel. intensity): 326 (M^++18, 7), 309 (M^++1, 22); 277 (100); HR-MS (CI/CH_4): calcd for $C_{16}H_{24}N_2O_4$: ($M^{+\cdot}$) *m/z* 308.1736, obsd 308.1731.

2-(4-Nitrophenyl)-2,3,4,5-tetrahydropyridazin-3-ol (12a). According to the typical procedure, **12a** (108 mg, 0.49 mmol, 49%) was prepared by irradiation of the *N*-(4-nitrophenyl)amino-1-pyrrolidine (**12**) (207 mg, 1.00 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 3 h, followed by flash chromatography (Al_2O_3, 1% methanol/CH_2Cl_2) and was obtained as a green amorphous solid: IR (KBr) 3420, 1580, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (2H, d, J^3=9.6 Hz, H-3′), 7.29 (2H, d, J^3=9.6 Hz, H-2′), 7.09 (1H, m, H-2), 5.65 (1H, m, H-5), 3.42 (1H, s, O–H), 2.44 (1H, dddd, J^2=20.2 Hz, J^3=14.0, 6.6, 1.5 Hz, H-3_{ax}), 2.29–2.09 (2H, m, H-3_{eq}, H-4_{eq}), 1.84 (1H, dddd, J^2=13.7 Hz, J^3=13.7, 5.9, 2.7 Hz, H-4_{ax}); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.7 (C-1′), 142.0 (C-2), 140.3 (C-4′), 125.6 (C-3′), 112.8 (C-2′), 73.7 (C-5), 23.8 (C-4), 17.4 (C-3); HR-MS (CI/CH_4): calcd for $C_{10}H_{11}N_3O_3$: ($M^{+\cdot}$) *m/z* 221.0800, obsd 221.0802. The by-product **4-[(4-nitrophenyl)azo]butanol (12c)** isolated as a yellow oil (15 mg, 0.07 mmol, 7%) during the flash chromatography was fully characterised: IR (neat) 2940, 1750, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.84 (1H, t, J^3=1.1 Hz, H-1), 8.34 (2H, d, J^3=9.0 Hz, H-3′), 7.78 (2H, d, J^3=9.0 Hz, H-2′), 4.17 (2H, t, J^3=7.0 Hz, H-4), 2.68 (2H, td, J^3=7.3, 1.1 Hz, H-2), 2.31 (2H, tt, J^3=7.0, 7.0 Hz, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 201.2 (C-1), 154.9 (C-1′), 148.7 (C-4′), 124.7 (C-3′), 122.9 (C-2′), 68.9 (C-4), 41.5 (C-2), 20.3 (C-3); MS (CI) *m/z* (rel. intensity): 239 (M^++18, 23), 223 (30), 222 (M^++1, 100), 206 (12).

1-(5,5-Dimethoxybutyl)-2-(4-nitrophenyl)diazene (12b). According to the typical procedure, **12b** (104 mg, 0.39 mmol, 46%) was prepared by irradiation of the *N*-(4-nitrophenyl)amino-1-piperidine (**12**) (175 mg, 0.85 mmol) in a solution of acetonitrile (18 mL) and anhydrous methanol (2 mL) for 5 h followed by flash chromatography (Al_2O_3, 30% cyclohexane/CH_2Cl_2) and was obtained as a yellow oil: IR (neat) 2940, 1600 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, J^3=9.0 Hz, H-3′), 7.77 (2H, d, J^3=9.0 Hz, H-2′), 4.46 (1H, t, J^3=5.7 Hz, H-4), 4.16 (2H, t, J^3=7.3 Hz, H-1), 3.34 (6H, s, O–CH_3), 2.03 (2H, tt, J^3=7.3, 7.3 Hz, H-2), 1.82–1.72 (2H, m, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.1 (C-1′), 148.6 (C-4′), 124.7 (C-3′), 122.9 (C-2′), 104.1 (C-4), 69.8 (C-1), 52.8 (O–CH_3), 30.3 (C-3), 22.9 (C-2); MS (EI) *m/z* (rel. intensity): 235 ($M^{+\cdot}$−32, 33), 150 (26), 122 (94), 117 (19), 85 (100), 71 (59), 58 (19); HR-MS (CI/CH_4): calcd for $C_{12}H_{18}N_3O_4$: (M^++1) *m/z* 268.1297, obsd 268.1295.

Synthesis of unsymmetrical compounds

The cyanations were realised according to a general procedure. The preparation of **14** outlined below represents a typical experiment.

4-[2′-Cyanopiperidin-1-yl)amino]ethylbenzoate (14). A solution of 4-[(piperidin-1-yl)amino]-ethylbenzoate (**11**) (200 mg, 0.81 mmol) in acetonitrile (20 mL) to which was added a catalytic amount of MB (4 mg, 0.01 mmol) and 300 μL of TMSCN (2.24 mmol) was irradiated under oxygen bubbling for 5 h with a 1800 W Xenon lamp through a UV cut-off glass filter (λ>630 nm) at about 20°C. After reaction, monitored by TLC, the resulting reaction mixture was concentrated under reduced pressure to give a blue oil. The crude product was dissolved in 50 mL of aqueous Na_2CO_3 (10%), followed by 50 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with an aqueous solution of Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure to give as a brown oil the 4-[(2′-cyanopiperidin-1-yl)-amino]ethylbenzoate (**14**) (211 mg, 0.77 mmol, 96%): IR (neat) 3250, 2920, 2220, 1675, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, J^3=8.8 Hz, H-3′), 6.85 (2H, d, J^3=8.8 Hz, H-2′), 5.22 (1H, s, N–H), 4.31 (2H, q, J^3=7.2 Hz, O–CH_2), 4.10 (1H, m, H-2_{eq}), 3.02 (1H, d, J^2=10.8 Hz, H-6_{eq}), 2.66 (1H, ddd, J^2=10.1 Hz, J^3=10.1, 2.7 Hz, H-6_{ax}), 2.07–1.92 (2H, m, H-3), 1.60–1.82 (4H, m, H-4, H-5), 1.36 (3H, q, J^3=7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.5 (C=O), 150.1 (C-1′), 131.4 (C-3′), 121.8 (C-4′), 116.5 (CN), 112.2 (C-2′), 60.4 (O–CH_2), 56.1 (C-2), 52.2 (C-6), 28.7 (C-3), 25.1 (C-5), 19.6 (C-4), 14.4 (CH_3); Anal. Calcd for $C_{15}H_{19}N_3O_2$: C 65.93; H 6.96; N 15.38. Found: C 65.89; H 7.01; N 15.42; HR-MS (EI): calcd for $C_{15}H_{19}N_3O_2$: (M^++1) *m/z* 274.1556, obsd 274.1558.

(2*R, 4*R**)-4-Methyl-1-(phenylamino)piperidin-2-carbonitrile (17).** According to the typical procedure, **17** (187 mg, 0.87 mmol, 83%) was prepared by irradiation of 4-methyl-*N*-phenylamino-1-piperidine (**9**) (200 mg, 1.05 mmol) with TMSCN (300 μL, 2.24 mmol) in a solution of acetonitrile (20 mL) for 6 h and was obtained as an orange oil: IR (neat) 3260, 2930, 2220, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (2H, dd, J^3=8.8, 7.4 Hz, H-3′), 6.90–6.80 (3H, m, H-2′, H-4′), 4.80 (1H, s, N–H), 4.17 (1H, m, H-2_{eq}), 3.10 (1H, dddd, J^2=11.4 Hz, J^3=4.4, 2.4, 1.1 Hz, H-6_{eq}), 2.63 (1H, ddd, J^2=11.4 Hz, J^3=11.4, 2.5 Hz, H-6_{ax}), 1.96 (1H, ddd, J^2=12.9 Hz, J^3=5.5, 2.6 Hz, H-3_{eq}), 1.84–1.58 (3H, m, H-3_{ax}, H-5), 1.39 (1H, m, H-4_{ax}), 1.00 (3H, d, J^3=6.2 Hz, 4-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 146.2 (C-1′), 129.2 (C-3′), 120.3 (C-4′), 116.8 (CN), 113.7 (C-2′), 55.7 (C-2), 51.5 (C-6), 36.4 (C-3), 33.6 (C-5), 26.5 (C-4), 21.0 (4-CH_3); MS (EI) *m*/*z* (rel. intensity): 215 ($M^{+\cdot}$; 100), 188 (15), 133 (48), 120 (16), 119 (21), 107 (20), 106 (19), 93 (65), 92 (59), 77 (39), 65 (30); HR-MS (EI): calcd for $C_{13}H_{17}N_3$: ($M^{+\cdot}$) *m*/*z* 215.1422, obsd 215.1417.

The alkylations were realised according to a general procedure. The preparation of **15** outlined below represents a typical experiment.

4-[(2′-Propylpiperidin-1-yl)amino]ethylbenzoate (15). To a 0°C solution of 211 mg (0.77 mmol) of 4-[(2′-cyanopiperidin-1-yl)amino]ethylbenzoate (**14**) in dry THF (20 mL) was added dropwise a solution of propylmagnesium bromide (prepared by classical procedure with 55 mg (2.31 mmol) of magnesium turnings and 196 μL of propyl bromide (2.16 mmol)) in 10 mL of dry THF. The mixture was stirred for 2 h at room temperature and the reaction was monitored by TLC. The resulting mixture was cooled to 0°C and 10 mL of aqueous NH_4Cl were added, followed by 10 mL of aqueous Na_2CO_3 (10%). The organic solution was separated and the aqueous solution was extracted with Et_2O (2×30 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Al_2O_3, 30% CH_2Cl_2/cyclohexane) to give as a yellow oil the 4-[(2′-propylpiperidin-1-yl)amino]ethylbenzoate (**15**) (166 mg, 0.57 mmol, 74%): IR (neat) 3040, 1700, 1600, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (2H, d, J^3=8.9 Hz, H-3′), 6.81 (2H, d, J^3=8.7 Hz, H-2′), 4.61 (1H, s, N-H), 4.31 (2H, q, J^3=7.1 Hz, O–CH_2), 3.10 (1H, d, J^2=10.6, H-6_{eq}), 2.28 (2H, m, H-6_{ax}, H-2_{ax}), 1.84–1.57 (6H, m, H-3, H-4, H-5), 1.35 (3H, t, J^3=7.1 Hz, O–CH_2–CH_3), 1.43–1.10 (4H, m, 2-CH_2–CH_2), 0.81 (3H, t, J^3=7.1 Hz, 2-$(CH_2)_2$–CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.8 (C═O), 152.6 (C-1′), 131.3 (C-3′), 119.7 (C-4′), 111.3 (C-2′), 65.5 (C-2), 60.4 (O–CH_2), 57.6 (C-6), 35.1 (C-3), 26.9 (2-CH_2), 25.7 (C-5), 24.0 (C-4), 18.8 (2-CH_2–CH_2), 14.5 (2-(CH2)$_2$–CH_3), 14.5 (O–CH_2–CH_3); MS (EI) *m*/*z* (rel. intensity): 290 ($M^{+\cdot}$; 34), 248 (16), 247 (100), 245 (11), 217 (22), 174 (11), 173 (25), 164 (13), 108 (10), 84 (11); HR-MS (EI): calcd for $C_{17}H_{26}N_2O_2$: ($M^{+\cdot}$) *m*/*z* 290.1994, obsd 290.1989.

4-[(2′-Isopropylpiperidin-1-yl)amino]ethylbenzoate (16). According to the typical procedure, **16** (189 mg, 0.65 mmol, 84%) was prepared from 211 mg (0.77 mmol) of 4-[(2′-cyanopiperidin-1-yl)amino]-ethylbenzoate (**14**) and isopropylmagnesium bromide (prepared by classical procedure with 55 mg (2.31 mmol) of magnesium turnings and 203 μL of propyl bromide (2.16 mmol)) and was obtained as a yellow oil: IR (neat) 3040, 1700, 1600, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, J^3=8.9 Hz, H-3′), 6.82 (2H, d, J^3=8.6 Hz, H-2′), 4.49 (1H, s, N–H), 4.31 (2H, q, J^3=7.1 Hz, O–CH_2), 3.17 (1H, d, J^2=11.6 Hz, H-6_{eq}), 2.27 (1H, m, H-2_{ax}), 2.18 (1H, ddd, J^2=11.2 Hz, J^3=11.2, 4.0 Hz, H-6_{ax}), 2.09 (1H, d, J^2=10.8 Hz, H-3_{eq} or H-5_{eq}), 1.77 (1H, d, J^2=12.4 Hz, H-5_{eq} or H-3_{eq}), 1.70–1.50 (4H, m, H-3_{ax}, H-5_{ax}, H-4), 1.34 (3H, t, J^3=7.1, O–CH_2–CH_3), 1.30–1.16 (1H, m, 2-CH), 0.84 (3H, d, J^3=7.1 Hz, CH_3), 0.80 (3H, d, J^3=6.8 Hz, CH_3′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.7 (C═O), 152.2 (C-1′), 131.3 (C-3′), 119.7 (C-4′), 111.3 (C-2′), 70.4 (C-2), 60.1 (O–CH_2), 58.1 (C-6), 27.8 (2-CH), 26.9 (C-3), 24.2, 24.1 (C-5, C-4), 19.6 (2-CH–CH_3), 16.5 (2-CH–CH_3′), 14.5 (O–CH_2–CH_3); MS (EI) *m*/*z* (rel. intensity): 290 ($M^{+\cdot}$; 19), 248 (17), 247 (100), 217 (24), 174 (11), 173 (26), 164 (13), 108 (10), 84 (10); HR-MS (EI): calcd for $C_{17}H_{26}N_2O_2$: ($M^{+\cdot}$) *m*/*z* 290.1994, obsd 290.1994.

(2*R, 4*R**)-2-Propyl-4-methyl-*N*-phenylamino-1-piperidine (18).** According to the typical procedure, **18** (168 mg, 0.73 mmol, 78%) was prepared from 200 mg (0.93 mmol) of (2*R**, 4*R**)-4-methyl-1-(phenylamino)piperidin-2-carbonitrile (**17**) and propylmagnesium bromide (prepared by classical procedure with 67 mg (2.79 mmol) of magnesium turnings and 228 μL of propyl bromide (2.51 mmol) and was obtained as a yellow oil: IR (neat) 3260, 2930, 1710, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (2H, dd, J^3=8.4, 7.14 Hz, H-3′), 6.88 (2H, d, J^3=8.5 Hz, H-2′), 6.74 (1H, dd, J^3=7.5, 7.5 Hz, H-4′), 4.62 (1H, s, N–H), 2.84 (1H, ddd, J^2=11.7 Hz, J^3=8.0, 3.7 Hz, H-2_{ax}), 2.72 (1H, m, H-6_{aq}), 2.61 (1H, ddd, J^2=11.1 Hz, J^3=7.1, 3.7 Hz, H-6_{ax}), 1.87–1.17 (9H, m, H-4_{ax}, H-3, H-5, 2-CH_2–CH_2), 0.95 (3H, d, J^3=6.7 Hz, 4-CH_3), 0.88 (3H, t, J^3=7.2 Hz, 2-$(CH_2)_2$–CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 148.4 (C-1′), 128.6 (C-3′), 118.4 (C-4′), 113.0 (C-2′), 59.0 (C-2), 49.7 (C-6), 35.8 (C-3), 31.8 (C-4), 26.7 (2-CH_2), 24.7 (C-5), 19.8 (4-CH_3), 19.4 (2-CH_2–CH_2), 16.1 (2-$(CH_2)_2$–CH_3); MS (EI) *m*/*z* (rel. intensity): 232 ($M^{+\cdot}$; 33), 190 (13), 189 (100), 187 (21), 98 (12), 93 (9), 92 (29), 69 (10), 65 (9); HR-MS (EI): calcd for $C_{15}H_{24}N_2$: ($M^{+\cdot}$) *m*/*z* 232.1939, obsd 232.1949.

2-Methyl-*N*-(4-nitrophenyl)amino-1-piperidine (19). To a −15°C solution of 450 mg (2.94 mmol) of 4-nitrophenylhydrazine and 0.25 mL of acetic acid (4.5 mmol) in 20 mL of methanol was added dropwise a solution of 370 mg (3.2 mmol) of 5-oxohexanal in 5 mL of methanol, followed by the addition of 190 mg (3.0 mmol) of $NaBH_3CN$. The resulting solution was allowed to warm to rt and was stirred for 20 h and monitored by TLC. The mixture was cooled to 0°C and quenched with a solution 0.5 M HCl (10 mL). The volatiles were removed under reduced pressure and aqueous Na_2CO_3 (20 mL, 10%) was added, followed by 30 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with aqueous Na_2CO_3 (10 mL, 10%), dried over $MgSO_4$ and concentrated

under reduced pressure. The residue was purified by flash chromatography (Al_2O_3, 30% cyclohexane/CH_2Cl_2) to give as a yellow crystalline solid the 2-methyl-*N*-(4-nitrophenyl)-amino-1-piperidine **19** (420 mg, 1.8 mmol, 61%: mp 134–135°C; IR (KBr) 3240, 2960, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (2H, d, J^3=9.0 Hz, H-3′), 6.83 (2H, d, J^3=9.0 Hz, H-2′), 5.14 (1H, s, N–H), 3.07 (1H, m, H-6_{eq}), 2.45–2.26 (2H, m, H-2_{eq}, H-6_{ax}), 1.81–1.60 (4H, m, H-3, H-5), 1.48–1.20 (2H, m, H-4), 1.05 (3H, d, J^3=6.2 Hz, 2-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 154.0 (C-1′), 138.4 (C-4′), 126.2 (C-3′), 110.5 (C-2′), 61.3 (C-2), 57.4 (C-6), 33.9 (C-3), 25.9 (C-5), 23.8 (C-4), 19.6 (2-CH_3); MS (EI) *m/z* (rel. intensity): 235 ($M^{+\cdot}$; 46), 221 (14), 220 (100), 186 (12), 118 (12), 84 (31), 69 (11), 64 (12), 56 (14), 55 (19); HR-MS (EI): calcd for $C_{12}H_{17}N_3O_2$: ($M^{+\cdot}$) *m/z* 235.1321, obsd 235.1328.

Ring-opening reactions by SET photooxidation of unsymmetrical compounds

The ring-opening reactions were realised according to the general procedure previously described for the ring-opening reactions of symmetrical compounds.

4-[(2-Propyl-5-oxopentyl)diazenyl]ethylbenzoate (15a). According to the typical procedure, **15a** (105 mg, 0.35 mmol, 78%) was prepared by irradiation of 4-[(2′-propylpiperidin-1-yl)amino]ethylbenzoate (**15**) (129 mg, 0.44 mmol) in a solution of acetonitrile (9 mL) and water (1 mL) for 4 h and was obtained as a brown oil: IR (neat) 3300, 3000, 1700, 1580, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (1H, t, J^3=1.6 Hz, H-1), 8.12 (2H, d, J^3=8.7 Hz, H-3′), 7.66 (2H, d, J^3=8.7 Hz, H-2′), 4.39 (2H, q, J^3=7.1 Hz, O–CH_2), 3.63 (1H, qt, J^3=4.3 Hz, H-5), 2.44 (2H, t, J^3=7.2 Hz, H-2), 2.05–1.85 (2H, m, H-3), 1.85–1.65 (2H, m, H-4), 1.65–1.48 (2H, m, 5-CH_2), 1.41 (3H, t, J^3=7.1 Hz, O–CH_2–CH_3); 1.25 (2H, td, J^3=7.5 Hz, 5-CH_2–CH_2), 0.89 (3H, t, J^3=7.3 Hz, 5-$(CH_2)_2$–CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 202.0)C-1), 165.9 (C=O), 154.4 (C-1′), 130.5 (C-3′), 122.8 (C-4′), 121.9 (C-2′), 77.9 (C-5), 61.2 (O–CH_2), 43.6 (C-2), 35.7 (C-3), 32.9 (5-CH_2), 19.3 (C-4), 18.7 (5-CH_2–CH_2), 14.3 (O–CH_2–CH_3), 13.9 (5-$(CH_2)_2$–CH_3); MS (CI) *m/z* (rel. intensity): 322 (M^++18, 20), 305 (M^++1, 100); HR-MS (CI/CH_4): calcd for $C_{17}H_{25}N_2O_3$: (M^++1) *m/z* 305.1865, obsd 305.1865.

4-[(2-Isopropyl-5-oxopentyl)diazenyl]ethylbenzoate (16a). According to the typical procedure, **16a** (164 mg, 0.54 mmol, 98%) was prepared by irradiation of 4-[(2′-isopropylpiperidin-1-yl)amino]ethylbenzoate (**16**) (160 mg, 0.55 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 4 h and was obtained as a brown oil: IR (neat) 3300, 3000, 1700, 1580, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (1H, t, J^3=1.6 Hz, H-1), 8.12 (2H, d, J^3=8.7 Hz, H-3′), 7.66 (2H, d, J^3=8.7 Hz, H-2′), 4.38 (2H, q, J^3=7.1 Hz, O–CH_2), 3.35 (1H, ddd, J^3=9.6, 6.25, 3.37 Hz, H-5), 2.41 (2H, m, H-2), 2.17 (1H, m, 5-CH), 2.04 (1H, m, H-4), 1.80 (1H, m, H-4′), 1.49 (2H, tt, J^3=7.4, 7.4 Hz, H-3), 1.39 (3H, t, J^3=7.1 Hz, O–CH_2–CH_3), 0.98 (3H, d, J^3=6.8 Hz, CH_3), 0.93 (3H, d, J^3=6.8 Hz, CH_3′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 202.1 (C-1), 166.0 (C=O), 154.4 (C-1′), 130.5 (C-3′), 122.3 (C-4′), 122.0 (C-2′), 83.6 (C-5), 61.2 (O–CH_2), 43.6 (C-2), 31.9 (5-CH), 29.9 (C-4), 19.4 (CH_3), 19.1 (CH_3′), 18.8 (C-3), 14.3 (O–CH_2–CH_3); MS (CI) *m/z* (rel. intensity): 322 (M^++18, 24), 305 (M^++1, 100); HR-MS (Cl/CH_4): calcd for $C_{17}H_{25}N_2O_3$: (M^++1) *m/z* 305.1865, obsd 305.1863.

(3*S, 5*R**)-3-Methyl-5-(phenylazo)octanal (18a).** According to the typical procedure, **18a** (180 mg, 0.88 mmol, 46%) was prepared by irradiation of the 2-propyl-4-methyl-*N*-phenylamino-1-piperidine (**18**) (200 mg, 1.05 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 4 h and was obtained as a yellow oil: IR (neat) 2940, 1740, 1720, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.77 (1H, dd, J^3=2.2 Hz, 1.9, H-1), 7.69–7.63 (2H, m, H-3′), 7.56–7.39 (3H, m, H-2′, H-4′), 3.65 (1H, m, H-5), 2.50 (1H, m, H-2), 2.20–1.45 (6H, m, H-2, H-3, H-4, 5-CH_2), 1.40–1.00 (2H, m, 5-CH_2–CH_2) 1.00–0.64 (6H, m, 5-$(CH_2)_2$–CH_3, 3-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 202.3 (C-1), 152.0 (C-4′), 130.1 (C-1′), 128.8 (C-3′), 121.9 (C-2′), 75.4 (C-5), 49.8 (C-2), 40.2 (C-3), 35.7 (5-CH_2), 29.5 (C-4), 20.4 (3-CH_3), 19.1 (5-CH_2–CH_2), 13.8 (5-$(CH_2)_2$–CH_3); MS (EI) *m/z* (rel. intensity): 247 (17), 246 ($M^{+\cdot}$; 100), 203 (19), 161 (22), 108 (54) 93 (65), 92 (52), 77 (27), 69 (31), 65 (24); HR-MS (EI): calcd for $C_{15}H_{22}N_2O$: ($M^{+\cdot}$) *m/z* 246.1732, obsd 246.1726.

5-[(4-Nitrophenyl)azo]hexanal (19a). According to the typical procedure, **19a** (172 mg, 0.69 mmol, 81%) was prepared by irradiation of the 2-methyl-*N*-(4-nitrophenyl)-amino-1-piperidine (**19**) (200 mg, 0.85 mmol) in a solution of acetonitrile (18 mL) and water (2 mL) for 6 h and was obtained as a yellow oil: IR (neat) 2940, 1750, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 9.78 (1H, t, J^3=1.5 Hz, H-1), 8.33 (2H, d, J^3=9.2 Hz, H-3′), 7.77 (2H, d, J^3=8.8 Hz, H-2′), 3.86 (1H, qt, J^3=7.3, 6.7 Hz, H-5), 2.49 (2H, td, J^3=7.3 Hz, 1.5, H-2), 2.10–1.58 (4H, m, H-3, H-4), 1.38 (3H, d, J^3=6.6 Hz, 5-CH_3), ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 201.7 (C-1), 154.9 (C-1′), 148.4 (C-4′), 124.5 (C-3′), 122.8 (C-2′), 73.5 (C-5), 43.5 (C-2), 34.3 (C-3), 18.6 (5-CH_3), 18.6 (C-4); MS (EI) *m/z* (rel. intensity): 249 ($M^{+\cdot}$; 1), 150 (25), 122 (60), 99 (41), 92 (13), 81 (100), 76 (28), 75 (23), 57 (21), 55 (100); HR-MS (CI/CH_4): calcd for $C_{12}H_{15}N_3O_3$: (M^++1) *m/z* 250.1192, obsd 250.1190.

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