Photochemical α-Aminonitrile Synthesis using Zn-Phthalocyanines as Near-Infrared Photocatalysts

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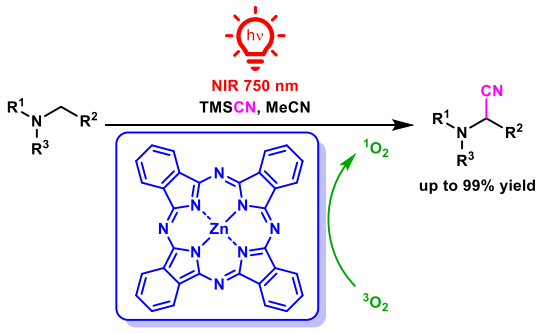
Table of Contents/Abstract Graphics



Abstract

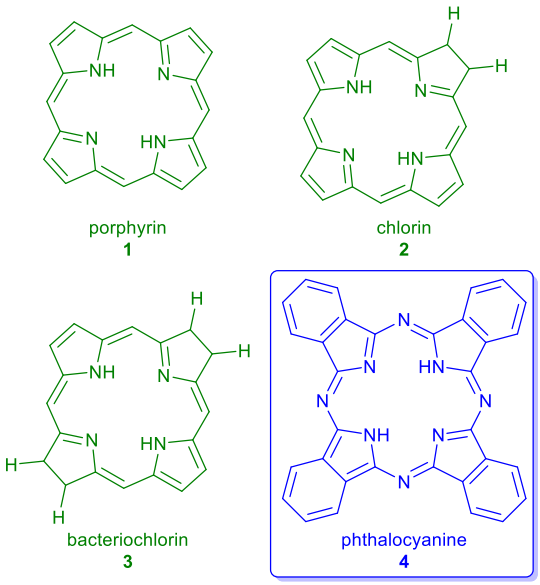
While photochemical transformations with sunlight almost exclusively utilize the UV-Vis part of the solar spectrum, the majority of the photons emitted by the sun have frequencies in the near-infrared region. Phthalocyanines show high structural similarity to the naturally occurring light-harvesting porphyrins, chlorins and mainly bacteriochlorins, and are also known for being efficient and affordable near-infrared light absorbers as well as triplet sensitizers for the production of singlet oxygen. Although having been neglected for a long time in synthetic organic chemistry due to their low solubility and high tendency towards aggregation, their unique photophysical properties and chemical robustness make phthalocyanines attractive

photocatalysts for the application in near-infrared light-driven synthesis strategies. Herein, we report a cheap, simple and efficient photocatalytic protocol, which is easily scalable under continuous flow conditions. Various phthalocyanines were studied as near-infrared photosensitizers in oxidative cyanations of tertiary amines to generate α-aminonitriles, a synthetically versatile compound class.

Introduction

The first phthalocyanine was incidentally discovered in the early 20th century and the first synthetic procedures for these compounds were established soon afterwards.[1-3] Nevertheless, it was not before the 1930s when Linstead and Robertson successfully elucidated a defined structure[4] and focused on the preparation of a general synthetic methodology for phthalocyanine derivatives.[5-7]

In contrast to their naturally occurring analogs, the porphyrins, chlorins and bacteriochlorins, phthalocyanines do not exist in nature but show high structural similarity to the former natural product classes (see Scheme 1).[8] Although being known as robust organic dyes for a long time,[8-9] their additional features such as the interesting photophysical properties have long been disregarded because of limited solubility and their tendency towards aggregation.[10] Nevertheless, various syntheses of phthalocyanine derivatives have been developed during the past decades, which allow for the modulation of chemical as well as photophysical properties and have led to wide application of phthalocyanines. These include the areas of catalysis,[11-15] materials science (e.g. solar cells,[16-19] gas sensors[20]), opto- and thermoelectronic devices[18] or medicinal applications[21] such as photodynamic therapy (PDT).[22-24]



Scheme 1: Porphyrinoid and phthalocyanine chemical structures.

Furthermore, phthalocyanines show promising absorption properties in the near-infrared region of the solar spectrum, and are known to be efficient triplet sensitizers for the production of singlet oxygen.[25-28] As the maximum of the solar photon emission is centered around 880 nm,[29] increasing interest was devoted to applying this relatively low-energy radiation in chemical reactions,[30-31] which led to various chemical modifications of phthalocyanine derivatives for reaching even more efficient photophysical properties especially in the infrared region.[10, 28, 32-33] After having explored the harvesting of infrared photons by surface-modified TiO_2 nanoparticles for the oxidative α-cyanation of tertiary amines,[34] we became interested in using direct infrared photochemistry in homogeneous solution for the same purpose. The products, α-aminonitriles, show a unique reactivity pattern[35-36] and are synthetically useful compounds[35-37] (*e.g.* in syntheses of natural products,[37] peptide bond formation,[38] or as building blocks for various heterocycles[39]). During the past decades, plenty of photocatalyzed approaches towards α-aminonitriles have been reported,[34, 40-44] but to the best of our knowledge, only very few of them make direct use of near-infrared light as the driving force, or suffer from time-consuming catalyst preparation.[34, 45] Parallel to our work, the Furuyama group very recently reported the application of different sulfur-substituted phthalocyanine

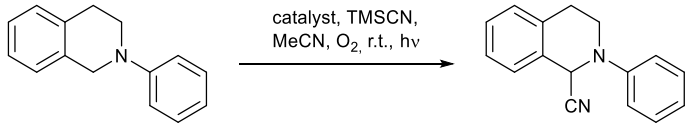
catalysts in the context of various NIR-driven cross dehydrogenative coupling (CDC) reactions in methanol/pyridine mixtures.[46] Herein, we report a protocol using unsubstituted zinc phthalocyanine (ZnPc) as an inexpensive commercial organic photosensitizer in acetonitrile as an environmentally benign solvent, for the efficient and scalable near-infrared photocatalyzed formation of α-aminonitriles.

Results and discussion

Optimization

As a starting point, the photooxidation of *N*-phenyltetrahydroisoquinoline (NPTHIC, **5**) as an easily oxidizable amine reagent was investigated by applying zinc-phthalocyanine (ZnPc, **6**) and its perfluorinated derivative (F-ZnPc, **7**) as photosensitizers together with TMSCN as the cyanide source in the presence of molecular oxygen.

Table 1: Initial screening of reaction conditions.



5 **5a**

Light Source / Catalyst	LED NIR (750 nm), yields in %	LED NIR (772 nm), yields in %
ZnPc	**76;** 17[d]; 51[e]; 27[f]; **71**[g]	56
F-ZnPc	48	46
No catalyst	3; 18[a]; 11[b]; 15[c]	2

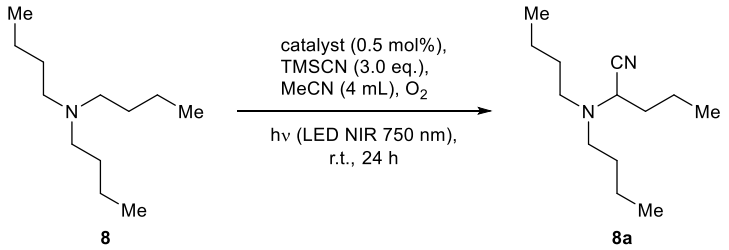
Conditions unless stated otherwise: reaction time 24 h; TMSCN 3.0 eq.; phthalocyanines 2 mol%.; MeCN volume 4 mL; yields determined via ^{1}H-NMR (internal standard dimethylsulfone).
[a] reaction time 48 h. [b] reaction time 72 h. [c] reaction time 96 h. [d] inert gas atmosphere, Zn-phthalocyanine 0.5 mol% [e] with water cooling instead of fan. [f] 29H,31H-phthalocyanine 0.5 mol%. [g] ZnPc 0.5 mol%.

The benchmark reaction using **5** was examined by applying different NIR light sources with either λ_{max} = 750 nm or λ_{max} = 772 nm. The background reaction without additional catalyst or under the exclusion of light did not lead to significant product formation, yet warming the

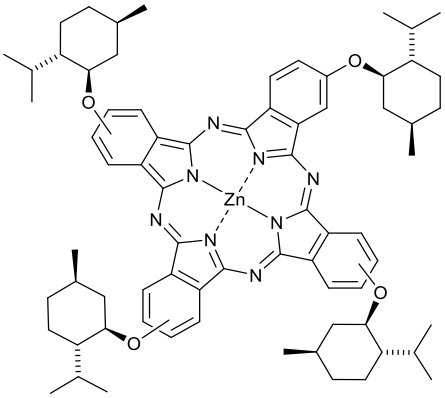
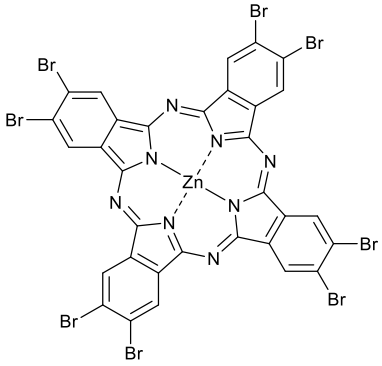
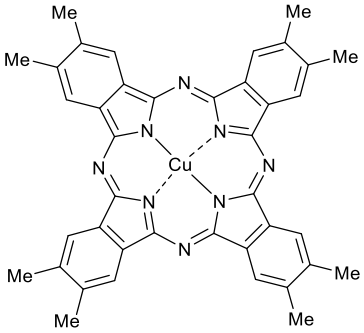
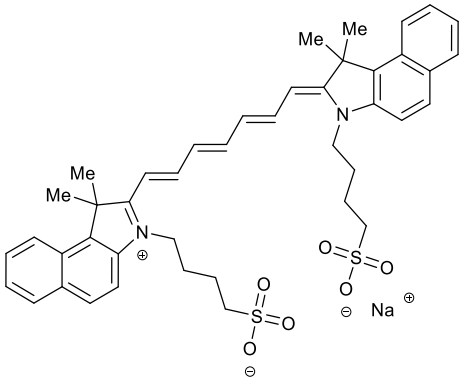
reaction mixture to 50 °C did lead to a significant background reaction (see Table TS1 in the SI). Undesired warming of the reaction medium by the light source was therefore prevented by air cooling. The reaction was also tested in the absence of oxygen, which indeed did not lead to any product formation (for further initial screening conditions, see the supporting information). As can be seen from Table 1, aminonitrile **5a** could be obtained in 76% NMR-yield at λ = 750 nm by applying commercially available ZnPc (2 mol%) as the catalyst, whereas more electron-deficient perfluorinated zinc-phthalocyanine (F-ZnPc) afforded **5a** in only 48% yield. Thus, all further optimization was performed using ZnPc. Next, the catalyst loading was investigated. It was found that the amount of ZnPc can be decreased to just 0.5 mol% without a significant decrease in yield (71% ^{1}H-NMR yield, see Table 1), whereas a higher catalyst loading in contrast did not lead to a convincing increase in product formation (see Table TS2 in the SI). Therefore, it was decided to continue with 0.5 mol% catalyst loading. Subsequently, the cyanide loading was investigated. By varying the amount of TMSCN, the initial application of 3.0 eq. turned out to be optimal. Lowering or increasing the reactant concentration resulted in lower product formation, which was also seen in changing the solvents to ethyl acetate, isopropanol, DCM, benzene or MTBE, probably related to the change in the solubility of oxygen in the respective solvents[47] (for more details please see Table TS3-TS5 in the SI). Kinetic studies revealed that the product yield increases in approximately linear fashion during the first 24 hours, but under further irradiation (up to 48 h), the yield remained almost constant (Table TS6 in SI). The optimized reaction conditions for the near-infrared-catalyzed cyanation of **5** are depicted in Scheme 2.

Scheme 2: Optimized reaction conditions of the benchmark reaction.As *N*-aryltetrahydroisoquinolines can be oxidized very easily (hence also the significant background reaction under thermal conditions), tributylamine (**8**) as a more challenging substrate was also subjected to the previously optimized reaction conditions. Furthermore, autoxidation of the substrate which is sometimes seen in *N*-aryltetrahydroisoquinolines can be excluded for **8** and the reaction should occur exclusively through photoexcitation. This experiment afforded the corresponding 2-(*N*,*N*-dibutylamino)pentanenitrile **8a** in 71% isolated yield, indicating the ZnPc photosensitizer to transform also the more challenging non-benzylic aliphatic amines. In this context, three additional phthalocyanine derivatives **9-11** together with indocyanine green **12** were applied as alternative infrared photosensitizers using tributylamine as the reagent, with results ranging from inactivity to slightly higher yields than the ZnPc standard (see Table 2). The slightly more efficient but environmentally problematic octabrominated derivative Br-ZnPc **10** (Table 2, Entry 2) was neglected due to the excellent commercial availability of the environmentally benign ZnPc.

Table 2: Additionally applied photosensitizers in NIR tributylamine cyanation.



8 **8a**

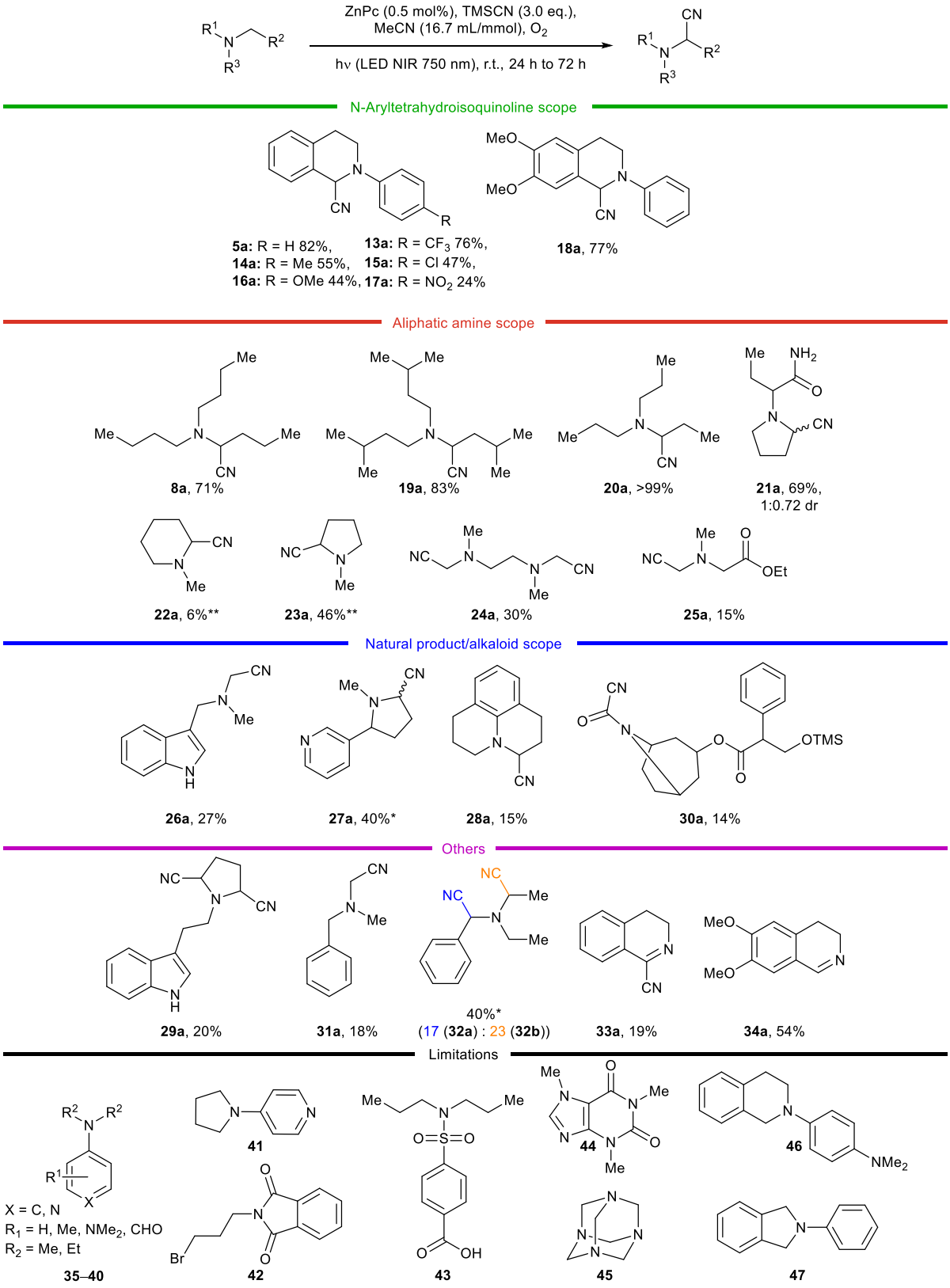
Entry	Catalyst	Yield[a)]
1	 *Menthol-ZnPc* **9**	64%
2	 *Br-ZnPc* **10**	89%
3	 *Me-CuPc* **11**	0%
4	 *Indocyanine green* **12**	0%

[a)] Yields determined via ^{1}H-NMR (internal standard dimethylsulfone).

With the optimized reaction conditions in hand, the substrate scope was investigated, starting with various *N*-aryltetrahydroisoquinoline derivatives **5** and **13-17** with isolated yields from 24% to 82%. As shown in Scheme 3, the unsubstituted *N*-phenyltetrahydroisoquinoline **5a** could be obtained in the highest of all isolated yields in this context (82%), but also *para*-substitution with a CF_3 unit on the phenyl ring (**13**) affords the corresponding aminonitrile **13a** in good yield (76%). The methyl-substituted substrate **14** gives 55% yield of **14a** which is almost in line with the *para*-chloro and p*ara*-methoxy- substituted derivatives **15** and **16** furnishing the respective products **15a** and **16a** in 47% (Cl) and 44% (OMe) yields, respectively. An electron-withdrawing group such as NO_2 reduced the yield of the corresponding product **17a** to 24%, which would be expected as electron-poor systems are less susceptible to oxidation. Substitution with two methoxy groups on the tetrahydroisoquinoline scaffold affords the respective aminonitrile **18a** in 77% yield. Aliphatic amines such as triisopentylamine (**19** to **19a**, 83%), tributylamine (**8** to **8a**, 71%) and tri-*n*-propylamine (**20** to **20a**, >99%) were successfully cyanated, and also the aliphatic acetamide **21** could be reacted in a yield of 69%, furnishing a diastereomeric product mixture of the corresponding aminonitriles **21a+b**. Cyclic aliphatic amines were also tested as substates and afforded the cyanated products in 6% yield for *N*-methylpiperidine **22a** and 46% yield for *N*-methylpyrrolidine **23a** (both determined by quantitative ^{1}H-NMR). To elucidate any possible yield loss due to work-up or volatility of the products, the reactions were performed in deuterated acetonitrile CD_3CN for direct investigation by ^{1}H-NMR. The conversion for the piperidine derivative **22** nevertheless was very low. TMEDA (**24**) as a substrate with two dimethylamino groups afforded the corresponding doubly cyanated product **24a** in 30% isolated yield with cyanation occurring symmetrically on the methyl groups. Side reactions (single cyanation or C−C-bond cleavage) might be a possible explanation for the rather low yield. *N,N*-

Dimethylglycine ethyl ester (**25**) furnished the respective aminonitrile **25a** in 15% yield with cyanation occurring on one of the methyl groups. Furthermore, diverse natural products and alkaloids such as gramine (**26**), (–)-nicotine (**27**) and julolidine (**28**) could be converted to the corresponding aminonitriles **26a**-**28a** in yields between 15% and 40%; the indole bearing scaffold **29** was cyanated even twice giving the aminonitrile **29a** in 20% isolated yield.

Another example that was tested in the context of naturally occurring alkaloids was atropine (**30**), leading to the respective carbamoyl cyanide **30a** instead of the expected aminonitrile in 14% isolated yield. Dimethylbenzylamine (**31**) was cyanated one of the methyl groups instead of the benzylic position to **31a** in 18% yield. Diethylbenzylamine (**32**) cyanation resulted in nucleophilic attack of CN^- either in the benzylic position (**32a**, 17%) or at one of the ethyl substituents (**32b**, 23%) giving an inseparable product mixture. Possible over-oxidation of tetrahydroisoquinoline **33** afforded the respective dihydroisoquinoline 1-carbonitrile **33a** in 19% yield, which may result from decomposition during chromatographic purification. When subjecting 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**34**) to the reaction conditions, only the corresponding imine **34a** could be isolated in 54% yield instead of the desired aminonitrile. Aromatic amines such as DMAP (**35**), *N,N*-dimethyl- or *N,N*-diethylaniline derivatives and others (**35-41**) could not be converted into their corresponding aminonitriles (Scheme 3, bottom). The same applies for electron-deficient structures such as phthalimide **42** or (sulfon-) amides (**43**, **44**). Compounds in which the intermediate iminium ion would violate Bredt's rule (**45**) cannot be cyanated as well.[48-49] Furthermore, *para*-dimethylamino-substituted *N*-phenyltetrahydroisoquinoline **46** and *N*-phenylisoindoline **47** could not be converted to the desired products. For both, exclusively imine and lactam formation or no conversion of the starting material could be observed by LC-MS.

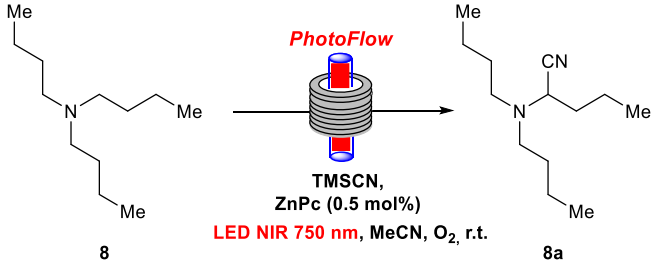


Scheme 3: Substrate scope and limitations of the developed procedure. All yields are those of the isolated compounds after chromatographic purification, unless stated otherwise. * Yields

determined via ^{1}H-NMR with internal standard dimethylsulfone. ** Reaction performed in CD_3CN, yield determined via ^{1}H-NMR with internal standard phenanthrene.

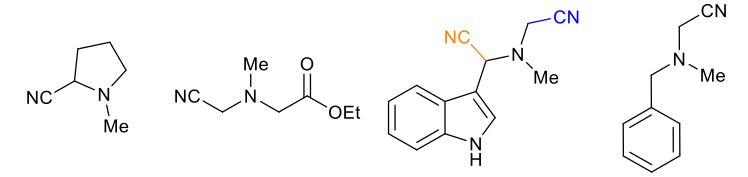
Aiming at a scale-up of this protocol, the cyanation of tributylamine **8** was investigated under continuous-flow conditions (details of the experimental setup can be found in the supporting information). The same optimized reaction conditions (Scheme 2) were used and the amount of processed starting material was also maintained up to the optimization of the flow conditions (Table 3, entries 1-6). Using a flow rate of 100 μL.min^{-1} and only a pre-saturation of the solvent with oxygen, the aminonitrile **8a** was obtained in 13% yield (determined by quantitative ^{1}H NMR) (Table 3, Entry 1). The adoption of a tube-in-tube reactor for maximum oxygen saturation increased the yield to 40% (Table 3, Entry 2). The dilution of the reaction mixture further increased the yield of **8a** up to 51% (Table 3, Entry 3). Aminonitrile **8a** was obtained in 57% yield when the flow rate was set to 50 μL.min^{-1}, and up to 73% yield at 25 μL.min^{-1}, the latter value corresponding to a residence time of 80 min (t_R, see Table 3, Entries 4 and 5, respectively). In a 24 h continuous production run, tributylamine **8** (2.25 mmol) was converted to **8a** in 58% isolated yield (Table 3, Entry 6).

Table 3: Conditions screening for NIR tributylamine cyanation in continuous-flow conditions with irradiation at λ = 750 nm. t_R is the residence time.



Entry	Compound 8 processed [mmol]	Concentration (8) [mmolL^{-1}]	Flow rate [µL.min^{-1}]	t_R (min)	Yield (%)[a]
1[b]	0.25	62.5	100	20	13
2	0.25	62.5	100	20	40
3	0.25	31.2	100	20	51
4	0.25	62.5	50	40	57
5	0.25	62.5	25	80	**73**
6	2.25	62.5	25	80	**58**[c]

Continuous Flow Amine Scope[d]



23a, 15% (46%)[e] | **25a**, 25% (15%) | 49% (43 (**26a**) : 6 (**26b**)) 27% (27 (**26a**) : 0 (**26b**)) | **31a**, 45% (18%)

[a] Determined by NMR spectroscopy using dimethylsulfone as internal standard. [b] Without tube-in-tube system. [c] Isolated yield in a 24 h continuous experiment. [d] Reactions performed at room temperature under continuous flow conditions using 1 mmol of amine, 3 eq. of TMSCN, 0.5 mol% of ZnPc in 16 mL of MeCN and irradiated with LED (750 nm) for 80 minutes (residence time). Yields were determined after column chromatography. For comparison, in parenthesis are the yields obtained in batch conditions. [e] Reaction performed in CD_3CN, yield determined via ^{1}H-NMR with phenanthrene as an internal standard.

In general, the continuous flow conditions furnished aminonitriles in higher yields in a shorter reaction time than batch conditions and permit easy scale-up of the reaction up to 2.25 mmol

scale. The compound **25a** was obtained in 25% isolated yield which is slightly better compared to batch (15%). Compound **31a** was isolated in 45% yield under continuous flow conditions, which is more than twice the yield under batch conditions (18%). The cyanation of gramine under batch conditions afforded the corresponding aminonitrile **26a** in 27% isolated yield, whereas under continuous flow conditions it was possible to obtain the compounds **26a+b** in 43% and 6% yield as mixture of two regioisomers (see Table 3, bottom).

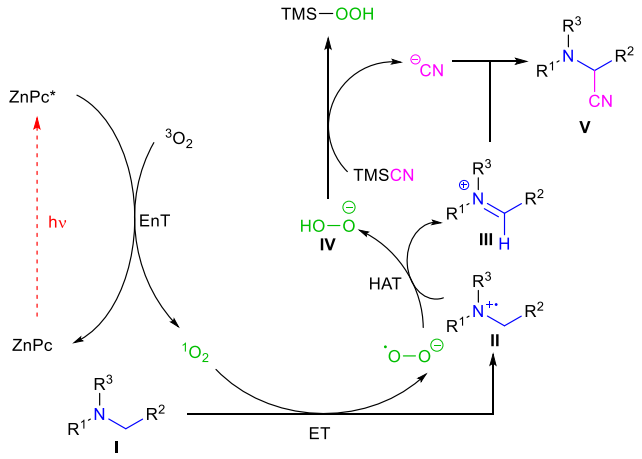
Additionally, a follow-up hydrolysis reaction of aminonitrile **5a** to its corresponding carboxamide **48** was performed (see Scheme SS2 in the Supporting Information).

Mechanistic investigations

The proposed mechanism for the conversion of amines to α-aminonitriles using ZnPc, TMSCN, O_2 and NIR light can be found in Scheme 4. Upon irradiation in the Q-band of ZnPc with near-infrared light (λ = 750 nm) and intersystem crossing,[50] the photosensitizer is obtained in a $^3(\pi$-$\pi^*)$ state ZnPc*, which is known to convert $^3O_2$ to singlet oxygen $^1O_2$ through Dexterenergy transfer.[51] Electron transfer from the amine substrate **I** to singlet oxygen generates an aminium radical cation **II** and superoxide, which then abstracts a hydrogen atom from the α-position of **II** to generate the respective iminium ion **III** and a hydroperoxide anion **IV**. Alternatively, the iminium ion **III** and hydroperoxide anion **IV** could be formed directly via a concerted pericyclic reaction.[41] Upon cyanide release from TMSCN through the generated hydroperoxide anion, CN^- might be able to attack the iminium ion to furnish the desired α-aminonitrile product **V** (see Scheme 4). Various resulting TMS-peroxo-species could be detected via ^{29}Si-NMR (see TS7, FS4-6 in the Supporting Information).

The luminescence lifetime of the triplet state of ZnPc was determined via time-correlated single photon counting (TCSPC) in deaerated MeCN as τ_{ZnPc*} = 4.0 ns (see Supporting Information, Figure FS14), which perfectly matches literature values ranging from τ = 2.89 ns to τ = 5.06 ns

depending on the solvent.[52] Singlet oxygen production was detected through trapping experiments with α-terpinene followed via LC- or GCMS for *N*-phenyltetrahydroisoquinoline and tributylamine as the amine reactants (see Figures FS7-FS10 in the SI). Additionally, $^1O_2$ was detected directly via its phosphorescence at 1274 nm upon excitation of ZnPc in CD_3CN at 665 nm. The lifetime of the $^1O_2$ emission was determined as 437 µs. For further details, see Figures FS13-FS15 in the supporting information.



Scheme 4: Mechanistic proposal.

Conclusion

A simple and efficient near-infrared photocatalysis protocol has been developed that uses only 0.5 mol% of zinc-phthalocyanine as an inexpensive, commercially available and eco-friendly photocatalyst for efficient singlet oxygen production. Various α-aminonitriles were synthesized in a standard batch reaction setup, including aliphatic and aromatic amines, with high functional group tolerance. Additionally, a continuous-flow reaction setup was developed, which requires significantly shorter irradiation times and permits easy scale-up (demonstrated up to 2.25 mmol scale), being the first example of a homogeneous NIR photoreaction under continuous flow conditions. To the best of our knowledge, this is also the first report of a direct homogeneous near-infrared initiated photocatalyzed reaction which does not require extensive catalyst design,

multistep catalyst preparation or any sort of additives to furnish various α-aminonitriles by simply starting from readily available amines, TMSCN and the photosensitizer ZnPc under an oxygen-saturated atmosphere.

Experimental Section

Unless stated otherwise, all commercially available solvents and reagents were used as provided without further purification. The eluents used for column chromatography (cyclohexane and ethyl acetate) were purchased in technical grade and distilled prior to use. Deuterated solvents were purchased from a local commercial supplier. Solvents were evaporated under reduced pressure at 40 °C.

Flash column chromatography was performed on 35-70 μm silica gel. Automatic flash column chromatography was performed using an UV-diode array detector, together with silica cartridges (10 g or 25 g) as solid phases. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{245} visualized by irradiation with UV light (λ = 254 nm and λ = 365 nm). R_f-values are referred to the corresponding eluents.

All photoreactions in a standard batch setup were performed at room temperature using a 750 nm Infrared IR High Power LED Light with P = 55 W and λ = 720-740 nm ($\lambda_{max,stated}$ = 730 nm, $\lambda_{max,measured}$ = 750 nm). The reaction vessel (10 mL vial) was purged with oxygen for approximately 30 seconds and equipped with an oxygen filled balloon (on top of a vial sealed with a rubber septum) and was placed approximately 15 cm from the light source within a ventilated fume hood. A small fan was used to keep the reaction mixture cooled to room temperature (checked by internal thermometer). *Fehler! Verweisquelle konnte nicht gefunden werden.* in the Supporting Information shows the experimental setup.

For continuous-flow experiments, the photoreactor (2 mL) was assembled with a radially wound PFA tube (ID: 1/16 in) and was placed approximately 5 cm from both, light source (LED 750 nm) and a fan. The reaction mixture was pumped through a tube-in-tube system with a

molecular oxygen pressure at 6 bar (87 psi). All system was pressured with a backpressure regulator at 100 psi (see **Fehler! Verweisquelle konnte nicht gefunden werden.** in the Supporting Information). For more details concerning the light sources used for all photochemical reactions please see the Supporting Information.

UV-Vis spectra were recorded on an Evolution 201 UV-Visible Spectrophotometer.

Fluorescence spectra were recorded in a quartz cuvette on an FP-8300 spectrofluorometer using a septum screw cap. The reaction solution in the cuvette was flushed with argon before the sample was injected, followed by argon purging for 30 seconds.

Emission and excitation spectra of ZnPc were recorded using an spectrofluorometer using a xenon lamp (Xe_2) as excitation source. Luminescence lifetime measurements on ns-timescale were determined with a time-correlated single-photon counting system (TCSPC, FLS1000) in reverse mode using a picosecond-pulsed laser (NKT-FIU-6 SuperK Fianium FIU-6) as excitation source. Luminescence lifetimes on µs-timescale were determined with a multichannel scaling (MCS, FLS1000) system with a microsecond xenon flashlamp as excitation source (µF2). All measurements were performed under stirring at 20.0°C in a Peltier-cooled holder. Luminescence decays were fitted using the software Fluoracle. The photomultipliers N-G11 PMT-980 (250–980 nm) and liquid nitrogen cooled N-G09 PMT-1700 (500–1700 nm) were used for detection (as well as for the emission spectra of the applied LED light sources). Samples for measurements in absence of oxygen were prepared in a glovebox using degassed solvents and measured in airtight cuvettes.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 300, 400 or 600 MHz spectrometer using standard pulse sequences. Chemical shifts were referred to the corresponding deuterated solvents ($CDCl_3$: $\delta = 7.26$ ppm and DMSO-d_6: $\delta = 2.50$ ppm for ^{1}H-NMR; $CDCl_3$: $\delta = 77.16$ ppm and DMSO-d_6: $\delta = 39.52$ ppm for $^{13}C\{^{1}H\}$ NMR) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS: $\delta = 0.00$ ppm).[53] Coupling constants (J) were reported in Hz and the following abbreviations for NMR signal multiplicities were used:

s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and combinations of these. Structural assignments were made with additional information from gCOSY, gHSQC and gHMBC experiments.

Electron spray ionization (ESI) masses were recorded by LC-MS using a binary pump system and an integrated diode array detector coupled to a LC/MSD Ion Trap mass spectrometer. Ionization was achieved by an electron spray ionization source (ESI). High resolution masses were recorded on an QTOF instrument with a *LockSpray* interface and a suitable external calibrant.

Gas chromatographic measurements were performed using a GC system coupled to a GC/MS detector using Helium as carrier gas with a flowrate of 1.2 ml/min. The injection temperature was 250 °C, the transfer line-temperature was 250 °C, the MS-source temperature was 230 °C and the MS-quadrupole temperature was 150 °C. The column stove temperature was adjusted to 40 °C for 2 minutes followed by a temperature gradient of 50 °C/min over 5.6 minutes to 320 °C. This temperature was kept for 7.4 minutes.

Melting points were measured in open capillary tubes and are uncorrected.

Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit and are reported in terms of frequency of absorption ($\tilde{\nu}$, cm^{-1}).

General synthesis of α-aminonitriles.

Zn-phthalocyanine **6** (0.691 mg, 0.001 mmol, 0.005 eq.) and the respective amine (0.239 mmol, 1.0 eq.) were dissolved in MeCN (4.0 mL). The vial was purged with oxygen for about 1 min and an oxygen-filled balloon was placed with a needle through the septum onto the vial, then TMSCN (0.09 mL, 0.72 mmol, 3.0 eq.) was added. The reaction mixture was irradiated with the respective light source. After 24 h, the reaction mixture was poured into 10 mL of a saturated $NaHCO_3$ solution and extracted with dichloromethane (3x15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced

pressure. The crude aminonitrile product was purified by flash column chromatography on silica gel.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (5a). According to the general procedure, ZnPc **6** (0.691 mg, 0.001 mmol, 0.005 eq.) and *N*-phenyltetrahydroisoquinoline **5** (50.00 mg, 0.239 mmol, 1.0 eq.) were dissolved in MeCN (4.0 mL). The vial was purged with oxygen for about 1 min and an oxygen-filled balloon was placed with a needle to the rubber-sealed vial, then TMSCN (0.09 mL, 0.717 mmol, 3.0 eq.) was added. The reaction mixture was irradiated with the respective light source. After 24 h, the reaction mixture was poured into 10 mL of saturated $NaHCO_3$ solution and extracted with dichloromethane (3x15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) yielding the title compound (46.0 mg, 0.196 mmol, 82%) as a colorless oil. R_f = 0.51 (5:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2925, 1598, 1503, 1378, 1287, 1222, 938, 754, 742, 693. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.42 – 7.34 (m, 2H), 7.37 – 7.20 (m, 4H), 7.14 – 7.07 (m, 2H), 7.07 – 7.00 (m, 1H), 5.53 (s, 1H), 3.79 (dddd, *J* = 12.4, 6.0, 3.1, 1.2 Hz, 1H), 3.50 (ddd, *J* = 12.4, 10.6, 4.1 Hz, 1H), 3.18 (dddd, *J* = 16.5, 10.6, 6.0, 0.9 Hz, 1H), 3.04 – 2.93 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 148.5, 134.7, 129.7, 129.5, 128.9, 127.2, 127.0, 122.0, 117.7, 117.6, 53.4, 44.3, 28.7. MS (ESI): *m/z* = 235.1 [M($C_{16}H_{14}N_2$)+H]$^+$. The spectroscopic data match to those reported in the literature.[54-56]

2-(*N*,*N*-Dibutylamino)pentannitrile (8a). Following the general procedure, tributylamine **8** (0.06 mL, 0.24 mmol, 1.0 eq.) was applied and the reaction mixture was irradiated for 24 h. The crude product was purified by column chromatography (SiO_2, eluent: 2:1 cyclohexane/ethyl acetate) furnishing the title compound (35.5 mg, 0.17 mmol, 71%) as a colorless oil. R_f = 0.86 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2958, 2878, 1466, 1379, 1170, 1117, 1090, 878, 741. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.58 (t, *J* = 7.7 Hz, 1H), 2.57 (dt, *J* = 13.1, 7.7 Hz, 2H),

2.33 (ddd, J = 12.9, 7.7, 5.1 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.55 – 1.44 (m, 2H), 1.39 (dddd, J = 14.4, 7.1, 4.4, 1.7 Hz, 4H), 1.35 – 1.22 (m, 4H), 0.93 (dt, J = 10.2, 7.1 Hz, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 118.6, 54.3, 51.4, 33.9, 30.2, 20.4, 19.3, 14.0, 13.5. MS (ESI): *m/z* = 211.2 $[M(C_{13}H_{26}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[34]

2-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (13a). Following the general procedure, 2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline **13** (66.2 mg, 0.24 mmol, 1.0 eq.) was applied as the amine reactant. The reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (54.8 mg, 0.18 mmol, 76%) as a colorless oil. R_f = 0.79 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 1616, 1524, 1382, 1325, 1225, 1202, 1108, 1071, 937, 820, 753, 736, 593. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.61 (d, J = 8.6 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.34 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.09 (d, J = 8.5 Hz, 2H), 5.59 (s, 1H), 3.86 (dddd, J = 12.4, 5.5, 4.3, 1.0 Hz, 1H), 3.57 (ddd, J = 12.4, 9.6, 4.4 Hz, 1H), 3.22 – 3.13 (m, 1H), 3.05 (dt, J = 16.2, 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): 150.3, 134.6, 129.2, 129.1, 129.0, 127.2, 127.0, 127.0 (q, J = 3.7 Hz), 123.3 (q, J = 271.3 Hz), 122.5 (q, J = 32.9 Hz), 120.4, 117.5, 115.3, 51.2, 43.9, 28.3. ^{19}F NMR ($CDCl_3$, 376 MHz): -61.6 (s). MS (ESI): *m/z* = 303.1 $[M(C_{17}H_{13}F_3N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[57]

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (14a). Following the general procedure, 2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline **14** (53.3 mg, 0.24 mmol, 1.0 eq.) was used and the reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (32.9 mg, 0.13 mmol, 55%) as a colorless oil. R_f = 0.92 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 3029, 2921, 2832, 1615, 1515, 1378, 1200, 938, 810, 773, 754 735, 520. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.35 – 7.30 (m, 1H), 7.30 – 7.27 (m, 2H), 7.26 – 7.23 (m, 1H), 7.19 (m, 2H), 7.06 – 6.99 (m, 2H), 5.48 (s, 1H), 3.72 (dddd,

J = 12.4, 6.1, 2.6, 1.3 Hz, 1H), 3.46 (ddd, *J* = 12.4, 11.0, 4.0 Hz, 1H), 3.17 (ddd, *J* = 16.8, 11.0, 6.1 Hz, 1H), 2.96 (ddd, *J* = 16.4, 3.6, 2.4 Hz, 1H), 2.34 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): 146.3, 134.5, 131.8, 130.1, 129.4, 128.7, 127.1, 126.8, 118.3, 117.7, 54.1, 44.4, 28.6, 20.6. MS (ESI): *m/z* = 249.1 $[M(C_{17}H_{16}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[54]

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (15a). Following the general procedure, 2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline **15** (58.1 mg, 0.24 mmol, 1.0 eq.) was used and the reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (29.9 mg, 0.11 mmol, 47%) as a colorless solid. R_f = 0.58 (4:1 cyclohexane/ethyl acetate). Mp: 150.5-152.8 °C (cyclohexane/ethyl acetate) lit.[54] mp: 152-153 °C. IR/cm^{-1} (ATR): 3674, 1596, 1496, 1380, 1225, 1203, 1050, 938, 815, 745. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.34 – 7.30 (m, 2H), 7.38 – 7.26 (m, 3H), 7.24 (s, 1H), 7.05 – 6.99 (m, 2H), 5.46 (s, 1H), 3.72 (dddd, *J* = 12.4, 6.0, 3.2, 1.2 Hz, 1H), 3.47 (ddd, *J* = 12.3, 10.6, 4.1 Hz, 1H), 3.16 (ddd, *J* = 16.5, 10.6, 5.9 Hz, 1H), 2.98 (dt, *J* = 16.8, 3.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): 147.0, 134.4, 129.5, 129.4, 129.2, 128.9, 127.0, 127.0, 118.9, 117.4, 53.2, 44.3, 28.4. MS (ESI): *m/z* = 269.0 $[M(C_{16}H_{13}ClN_2)+H]^+$. The spectroscopic data match to those reported in the literature.[54]

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (16a). Following the general procedure, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **16** (57.1 mg, 0.24 mmol, 1.0 eq.) was used as the amine reactant and the reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (27.6 mg, 0.10 mmol, 44%) as a colorless oil. R_f = 0.60 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2834, 1510, 1463, 1245, 1204, 1184, 1034, 937, 826, 756, 734. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.31 (ddd, *J* = 7.3, 5.0, 3.8 Hz, 1H), 7.28 – 7.26 (m, 2H), 7.23 (dt, *J* = 7.3, 1.1 Hz, 1H),

7.12 – 7.06 (m, 1H), 6.95 – 6.89 (m, 1H), 5.37 (s, 1H), 3.81 (s, 3H), 3.59 (dddd, *J* = 12.2, 6.4, 2.2, 1.3 Hz, 1H), 3.44 (ddd, *J* = 12.2, 11.2, 4.0 Hz, 1H), 3.23 – 3.11 (m, 1H), 2.94 (dddd, *J* = 16.4, 4.0, 2.2, 0.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): 155.7, 142.6, 134.4, 129.7, 129.5, 128.7, 127.1, 126.7, 121.0, 117.6, 114.8, 55.6, 55.5, 44.9, 28.7. MS (ESI): *m/z* = 265.1 $[M(C_{17}H_{16}N_2O)+H]^+$; 238.1 $[M(C_{16}H_{16}NO)]^+$ imine. The spectroscopic data match to those reported in the literature.[54]

2-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (17a). Following the general procedure, 2-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **17** (60.7 mg, 0.24 mmol, 1.0 eq.) was used. The reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (16.3 mg, 0.06 mmol, 24%) as a bright yellow oil. R_f = 0.36 (1:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2926, 1595, 1504, 1430, 1382, 1325, 1231, 1203, 1114, 937, 828, 751, 692. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.28 – 8.20 (m, 2H), 7.41 – 7.34 (m, 3H), 7.34 – 7.28 (m, 1H), 7.04 – 6.96 (m, 2H), 5.64 (s, 1H), 3.89 (dt, *J* = 11.7, 5.6 Hz, 1H), 3.76 – 3.63 (m, 1H), 3.20 – 3.12 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): 152.1, 140.2, 134.7, 129.5, 129.1, 128.6, 127.5, 127.0, 126.1, 117.2, 113.4, 49.9, 44.1, 28.2. MS (ESI): *m/z* = 280.1 $[M(C_{16}H_{13}N_3O_2)+H]^+$, 253.1 $[M(C_{15}H_{13}N_2O_2)]^+$ imine. The spectroscopic data match to those reported in the literature.[58]

6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (18a). Following the general procedure, 6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline **18** (64.3 mg, 0.24 mmol, 1.0 eq.) was used as the amine. The reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (53.9 mg, 0.18 mmol, 77%) as a colorless oil. R_f = 0.42 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2835, 1599, 1519, 1504, 1463, 1268, 1247, 1215, 1118, 1027, 731, 694. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.36 (dd, *J* = 8.7, 7.5 Hz, 2H), 7.08 (dd, *J* = 8.7, 7.5 Hz, 2H), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.76 (s,

1H), 6.68 (s, 1H), 5.46 (s, 1H), 3.88 (d, *J* = 1.1 Hz, 6H), 3.77 (dddd, *J* = 12.5, 6.0, 2.7, 1.2 Hz, 1H), 3.44 (ddd, *J* = 12.5, 11.1, 4.0 Hz, 1H), 3.14 – 3.02 (m, 1H), 2.85 (ddd, *J* = 16.1, 3.9, 2.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): 149.4, 148.5, 148.1, 129.6, 126.9, 121.9, 121.1, 117.9, 117.7, 111.6, 109.4, 56.1, 56.0, 53.1, 44.2, 28.1. MS (ESI): *m/z* = 295.1 $[M(C_{18}H_{18}N_2O_2)+H]^+$, 268.1 $[M(C_{17}H_{18}NO_2)]^+$ (imine). The spectroscopic data match to those reported in the literature.[54]

2-(Diisopentylamino)-4-methylpentanenitrile (19a). Following the general procedure, triisopentylamine **19** (54.3 mg, 0.24 mmol, 1.0 eq.) was used and the reaction mixture was irradiated for 24 h. The crude product was purified by column chromatography (SiO_2, eluent: 4:1 cyclohexane/ethyl acetate) affording the title compound (49.8 mg, 0.20 mmol, 83%) as a colorless oil. R_f = 0.79 (4:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2956, 2929, 2870, 1469, 1385, 1368, 1169, 1133, 1089, 735. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.66 (t, *J* = 7.7 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.38 – 2.26 (m, 2H), 1.83 (sept, *J* = 6.7 Hz, 1H), 1.69 – 1.52 (m, 4H), 1.38 – 1.28 (m, 4H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.90 (dd, *J* = 6.6, 3.1 Hz, 12H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): 118.7, 52.7, 49.9, 40.6, 37.0, 26.0, 24.6, 23.0, 22.4, 22.3, 22.1. MS (ESI): *m/z* = 253.2 $[M(C_{16}H_{32}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[44]

2-(*N*,*N*-Dipropylamino)butannitrile (20a). Following the general procedure, tripropylamine **20** (0.09 mL, 0.48 mmol, 1.0 eq.) was applied together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN for 24 h of irradiation. The crude product was purified by column chromatography (SiO_2, eluent: 4:1 cyclohexane/ethyl acetate) furnishing the title compound (89.2mg, 0.53 mmol, >99%) as a colorless oil. R_f = 0.71 (4:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2963, 2875, 2821, 1463, 1383, 1260, 1191, 1178, 1068, 1025, 862, 803. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.45 (t, *J* = 7.9 Hz, 1H), 2.49 (ddd, *J* = 13.0, 8.3, 6.2 Hz, 2H), 2.34 (ddd, *J* = 13.0, 8.3, 6.2 Hz, 2H), 1.84 – 1.64 (m, 2H), 1.55 – 1.33 (m, 4H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR

($CDCl_3$, 101 MHz): 118.6, 56.5, 53.7, 25.4, 21.2, 11.7, 10.8. MS (ESI): *m/z* = 169.2 $[M(C_{10}H_{20}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[44, 59]

2-(2-Cyanopyrrolidin-1-yl)butanamide (21a). Following the general procedure, 2-(pyrrolidin-1-yl)butanamide **21** (74.6 mg, 0.48 mmol, 1.0 eq.) was used together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN for 24 h of irradiation. The crude product was purified by flash column chromatography (SiO_2, eluent: 2:1 cyclohexane/ethyl acetate) affording the title compound (59.7 mg, 0.33 mmol, 69%) as a colorless oil in a diastereomeric mixture. R_f = 0.07 (2:1 cyclohexane/ethyl acetate). Mp: 102.5—104.2 °C (cyclohexane/ethyl acetate). There is no melting point given in the literature. IR/cm^{-1} (ATR): 3327, 3200, 2971, 2880, 2831, 1671, 1461, 1326, 1141, 1089, 585. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.32 – 6.11 (m, 2H), 4.04 (dd, *J* = 6.1, 3.1 Hz, 1H), 3.17 – 2.87 (m, 2H), 2.58 (dtd, *J* = 33.7, 9.0, 7.4 Hz, 1H), 2.25 – 2.12 (m, 2H), 2.04 – 1.81 (m, 1H), 1.79 – 1.58 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C{1H} NMR ($CDCl_3$, 75 MHz): 174.6, 117.8, 67.3, 50.7, 50.3, 29.5, 24.8, 21.9, 10.0. MS (ESI): *m/z* = 182.1 $[M(C_9H_{15}N_3O)+H]^+$. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_9H_{16}N_3O$ 182.1288; Found 182.1291. There is no spectroscopic data reported in the literature.

1-Methylpiperidine-2-carbonitrile (22a). Following the general procedure, 1-methylpiperidine **22** (23.7 mg, 0.24 mmol, 1.0 eq.) was used as the amine in deuterated acetonitrile. The reaction mixture was irradiated for 24 h. The crude product yield (0.01 mmol, 6%) was determined by ^{1}H-NMR using phenanthrene as the internal standard due to high volatility. R_f = 0.45 (1:1 cyclohexane/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 3.81 (t, *J* = 3.6 Hz, 1H). MS (ESI): *m/z* = 125.1 $[M(C_7H_{12}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[60]

1-Methylpyrrolidine-2-carbonitrile (23a). Following the general procedure, 1-methylpyrrolidine **23** (20.3 mg, 0.24 mmol, 1.0 eq.) was used as the amine in deuterated acetonitrile. The reaction mixture was irradiated for 24 h. The crude product yield (0.02 mmol,

46%) was determined by ^{1}H-NMR using phenanthrene as the internal standard due to high volatility. R_f = 0.85 (1:1 cyclohexane/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 3.34 (m, 1H). MS (ESI): *m/z* = 111.2 $[M(C_6H_{10}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[60]

2,2'-(Ethane-1,2-diylbis(methylazanediyl))diacetonitrile (24a). Following the general procedure, *N,N,N,N*-tetramethylethylenediamine **24** (55.5 mg, 0.48 mmol, 1.0 eq.) was used together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN and the reaction mixture was irradiated for 48 h. The crude product was purified by column chromatography (SiO_2, eluent: 10:1 dichloromethane/methanol) affording the title compound (23.5 mg, 0.14 mmol, 30%) as a cyan oil. R_f = 0.39 (10:1 dichloromethane/methanol). IR/cm^{-1} (ATR): 2952, 2801, 1680, 1460, 1323, 1118, 1080, 1041, 925, 860. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.61 (s, 4H), 2.61 (s, 4H), 2.39 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 114.5, 52.8, 45.2, 42.3. MS (ESI): *m/z* = 167.1 $[M(C_8H_{14}N_4)+H]^+$. The spectroscopic data match to those reported in the literature.[61]

Ethyl-*N*-(cyanomethyl)-*N*-methylglycinate (25a). Following the general procedure, *N,N*-dimethylglycine ethyl ester **25** (62.7 mg, 0.48 mmol, 1.0 eq.) was used together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN and the reaction mixture was irradiated for 52 h. The product yield (0.07 mmol, 15%) was determined using ^{1}H-NMR and phenanthrene as the internal standard due to decomposition during work-up and purification. R_f = 0.28 (1:1 diethyl ether/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 3.72 (s, 2H). MS (ESI): *m/z* = 157.1 $[M(C_7H_{12}N_2O_2)+H]^+$. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_7H_{13}N_2O_2$ 157.0972; Found 157.0969. There is no spectroscopic data reported in the literature.

2-(((1*H*-Indol-3-yl)methyl)(methyl)amino)acetonitrile (26a). Following the general procedure, gramine **26** (41.6 mg, 0.24 mmol, 1.0 eq.) was applied as the amine reactant and the reaction mixture was irradiated for 24 h. The crude product was purified by flash column

chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (12.8 mg, 0.06 mmol, 27%) as a slightly brown oil. R_f = 0.23 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 3409, 1651, 1619, 1456, 1426, 1339, 1240, 980, 745, 419. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.16 (bs, 1H), 7.76 – 7.71 (m, 1H), 7.39 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.18 (m, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 3.82 (s, 2H), 3.46 (s, 2H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ [ppm] = 136.5, 127.2, 124.1, 122.5, 119.9, 119.5, 114.8, 111.7, 111.2, 51.2, 43.6, 42.4. MS (ESI): *m/z* = 173.1 [M($C_{11}H_{13}N_2$)$^+$] imine. The spectroscopic data match to those reported in the literature.[44]

1-Methyl-5-(pyridin-3-yl)pyrrolidine-2-carbonitrile (27a). Following the general procedure, nicotine **27** (77.5 mg, 0.48 mmol, 1.0 eq.) was used together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN and the reaction mixture was irradiated for 24 h. The crude product was purified by column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (0.19 mmol, 40%) as a colorless oil. The yield was determined via ^{1}H-NMR using phenanthrene as the internal standard due to decomposition during work-up and purification. R_f = 0.25 (1:1 cyclohexane/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 4.12 (m, 1H). MS (ESI): *m/z* = 188.1 [M($C_{11}H_{13}N_3$)+H]$^+$. The spectroscopic data match to those reported in the literature.[34]

Julolidine-α-carbonitrile (28a). Following the general procedure, julolidine **28** (82.8 mg, 0.48 mmol, 1.0 eq.) was used together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.14 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN and the reaction mixture was irradiated for 72 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) affording the title compound (13.9 mg, 0.07 mmol, 15%) as a colorless oil. R_f = 0.58 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2934, 2844, 1666, 1597, 1506, 1478, 1336, 1305, 1200, 1112, 765, 732, 419. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.84 (d, *J* = 7.4 Hz, 2H), 6.71 – 6.59 (m, 1H), 4.18 (td,

J = 3.8, 1.4 Hz, 1H), 3.37 (ddd, *J* = 10.8, 8.4, 5.2 Hz, 1H), 3.25 – 3.04 (m, 2H), 2.79 (tdd, *J* = 21.1, 16.4, 6.6 Hz, 3H), 2.37 – 2.17 (m, 2H), 2.13 – 1.89 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): 138.2, 127.7, 127.1, 123.2, 120.7, 118.5, 118.2, 50.8, 49.2, 27.3, 25.1, 24.1, 21.8. MS (ESI): *m/z* = 199.1 $[M(C_{13}H_{14}N_2)+H]^+$. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2$ 199.123; Found 199.1233. The spectroscopic data match to those reported in the literature.[57, 62]

1-(2-(1*H*-Indol-3-yl)ethyl)pyrrolidine-2,5-carbodinitrile (29a). Following the general procedure, 3-(2-(pyrrolidine-1-yl)ethyl)-1*H*-indole **29** (51.6 mg, 0.24 mmol, 1.0 eq.) was used as the amine and the reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (12.7 mg, 0.05 mmol, 20%) as a light yellow oil. R_f = 0.63 (1:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 3414, 2949, 2836, 1458, 1340, 1230, 1095, 746. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.04 (bs, 1H), 7.68 – 7.61 (m, 1H), 7.38 (d, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 3.89 – 3.78 (m, 2H), 3.43 – 3.25 (m, 1H), 3.16 – 2.99 (m, 3H), 2.50 – 2.17 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): 136.1, 127.2, 122.2, 121.9, 119.6, 118.6, 117.9, 112.6, 111.2, 52.3, 51.2, 28.6, 24.3. MS (ESI): *m/z* = 265.1 $[M(C_{16}H_{16}N_4)+H]^+$, 238.1 $[M(C_{15}H_{16}N_3)]^+$ imine. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}N_4$ 265.1448; Found 265.1444. There is no spectroscopic data reported in the literature.

8-(Cyanocarbonyl)-8-azabicyclo[3.2.1]octan-3-yl-2-phenyl-3-((trimethylsilyl)oxy) propanoate (30a). Atropine base **30** was isolated using 200.0 mg of atropine sulfate monohydrate, which was dissolved in H_2O (4 mL). After pH adjustment to pH = 14 using 2M NaOH, the precipitating white solid was extracted with ethyl acetate (3x15 mL), the combined

organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Following the general procedure, the resulting atropine base **30** (58.6 mg, 0.20 mmol, 1.0 eq.) was used and the reaction mixture was irradiated for 45 h. The crude product was purified by column chromatography (SiO_2, eluent 2:1 cyclohexane/ethyl acetate) affording the title compound (11.3 mg, 0.03 mmol, 14%) as a yellow oil in a diastereomeric mixture. R_f = 0.68 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2957, 1732, 1676, 1423, 1252, 1198, 1163, 1103, 1079, 1035, 842. ^{1}H NMR ($CDCl_3$, 600 MHz,): 7.34 (tt, *J* = 6.8, 1.2 Hz, 2H), 7.32 – 7.29 (m, 3H), 5.17 – 5.10 (m, 1H), 4.49 (ddd, *J* = 13.6, 6.9, 3.2 Hz, 1H), 4.62 – 4.36 (m, 1H), 4.21 – 4.12 (m, 1H), 3.77 (q, *J* = 5.2 Hz, 2H), 2.19 – 2.12 (m, 2H), 2.12 – 1.99 (m, 2H), 1.98 – 1.84 (m, 2H), 1.83 – 1.69 (m, 2H), 0.09 (d, *J* = 3.1 Hz, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz,): 171.6, 139.3, 135.3, 128.9, 128.0, 127.9, 110.6, 67.0, 64.6, 56.0, 54.8, 51.5, 37.9, 35.8, 27.3, 26.9, -0.6. MS (ESI): *m/z* = 327.1 [M($C_{18}H_{19}N_2O_4$)]$^-$. HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{29}N_2O_4Si$) 401.1891; Found 401.1882. There is no spectroscopic data reported in the literature.

(*N*-Benzyl-*N*-methyl)aminoacetonitrile (31a). Following the general procedure, *N*,*N*-dimethylbenzylamine **31** (32.3 mg, 0.24 mmol, 1.0 eq.) was used as the amine reactant under irradiation for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (6.7 mg, 0.04 mmol, 18%) as a light blue oil. R_f = 0.57 (20:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2801, 1667, 1454, 1371, 1126, 1038, 1027, 862, 741, 670. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.37 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 3.63 (s, 2H), 3.46 (s, 2H), 2.45 (s, 3H). ^{13}C{1H} NMR ($CDCl_3$, 75 MHz): 136.7, 129.1, 128.7, 127.9, 114.4, 60.1, 44.1, 42.3. MS (ESI): *m/z* = 161.1 [M($C_{10}H_{12}N_2$)+H]$^+$. The spectroscopic data match to those reported in the literature.[63-64]

2-(Diethylamino)-2-phenylacetonitrile (32a). Following the general procedure, *N*,*N*-diethylbenzylamine **32** (78.0 mg, 0.48 mmol, 1.0 eq.) was used as the amine reactant with

the photocatalyst (1.4 mg, 0.002 mmol, 0.005 eq.) and TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) in 8 mL MeCN. The reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (0.08 mmol, 17%) as a colorless oil. The yield was determined using ^{1}H-NMR and phenanthrene as the internal standard due to an inseparable product mixture together with **32b**. R_f = 0.88 (2:1 cyclohexane/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 5.04 (s, 1H). MS (ESI): *m/z* = 189.1 $[M(C_{12}H_{16}N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[64]

2-(Benzyl(ethyl)amino)propanenitrile (32b). Following the general procedure, *N*,*N*-diethylbenzylamine **32** (78.0 mg, 0.48 mmol, 1.0 eq.) was used as the amine reactant with the photocatalyst (1.4 mg, 0.002 mmol, 0.005 eq.) and TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) in 8 mL MeCN. The reaction mixture was irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) furnishing the title compound (0.11 mmol, 23%) as a colorless oil. The yield was determined using ^{1}H-NMR and phenanthrene as the internal standard due to an inseparable product mixture together with **32a**. R_f = 0.88 (2:1 cyclohexane/ethyl acetate). Characteristic ^{1}H NMR signal ($CDCl_3$, 300 MHz): 1.44 (d, 3H). MS (ESI): *m/z* = 189.1 $[M(C_{12}H_{16}N_2)+H]^+$. There is no spectroscopic data reported in the literature.

3,4-Dihydroisoquinoline-1-carbonitrile (33a). Following the general procedure, 1,2,3,4-tetrahydroisoquinoline **33** (63.6 mg, 0.48 mmol, 1.0 eq.) was applied together with TMSCN (0.18 mL, 1.43 mmol, 3.0 eq.) and the photocatalyst (1.4 mg, 0.002 mmol, 0.005 eq.) in 8 mL of MeCN and the reaction mixture was irradiated for 48 h. The crude product was purified by flash column chromatography (SiO_2, eluent: cyclohexane/ethyl acetate, gradient 0% - 80% ethyl acetate) yielding the title compound (8.3 mg, 0.09 mmol, 19%) instead of the desired aminonitrile as light blue oil. R_f = 0.63 (2:1 cyclohexane/ethyl acetate). IR/cm^{-1} (ATR): 2955, 1671, 1608, 1568, 1455, 1276, 1016, 744, 738, 709, 659. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.68

(dd, *J* = 7.5, 1.4 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.22 (dt, *J* = 7.5, 0.9 Hz, 1H), 4.03 – 3.94 (m, 2H), 2.83 (t, *J* = 8.8, 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 146.7, 143.3, 135.8, 133.1, 127.8, 126.3, 114.4, 48.7, 24.3. MS (ESI): *m/z* = 157.1 $[M(C_{10}H_8N_2)+H]^+$. The spectroscopic data match to those reported in the literature.[65]

6,7-Dimethoxy-3,4-dihydroisoquinoline (34a). Following the general procedure, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **34** (46.1 mg, 0.24 mmol, 1.0 eq.) was applied and irradiated for 24 h. The crude product was purified by flash column chromatography (SiO_2, eluent: dichloromethane/methanol, gradient 0% - 10% methanol) yielding the title compound (28.2 mg, 0.13 mmol, 54%) instead of the desired aminonitrile as a cyan oil. R_f = 0.21 (20:1 dichloromethane/methanol). IR/cm^{-1} (ATR): 2938, 1573, 1516, 1463, 1323, 1278, 1117, 1015, 988, 777. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.22 (t, *J* = 2.2 Hz, 1H), 6.80 (s, 1H), 6.65 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.71 (ddd, *J* = 10.1, 6.4, 2.2 Hz, 2H), 2.67 (dd, *J* = 8.9, 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 159.8, 151.4, 147.9, 130.0, 121.4, 110.5, 110.4, 56.2, 56.1, 47.2, 24.8. MS (ESI): *m/z* = 192.1 $[M(C_{11}H_{13}NO_2)+H]^+$. The spectroscopic data match to those reported in the literature.[66]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (48). According to a modified procedure of *F. Tiemann and K. Piest*.[67] In a 10 mL reaction vessel, 2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **5a** (50.0 mg, 0.21 mmol, 1.0 eq.) was dissolved in 0.1 mL of concentrated H_2SO_4 and stirred at room temperature for 24 h. The reaction mixture was then diluted with H_2O (0.7 mL) and neutralized dropwise with concentrated $NH_4OH_{(aq.)}$ solution. An orange solid precipitated which was crystallized from water (1.0 mL) to afford the title compound (38.7 mg, 0.15 mmol, 72%) as a beige-brown solid. R_f = 0.76 (10:1 dichloromethane/methanol). Mp: 137.8–139.7 °C (water). There is no melting point given in the literature. IR/cm^{-1} (ATR): 3451, 2840, 1674, 1598, 1503, 1455, 1380, 1343, 1227, 1037, 909, 750, 731, 692. ^{1}H NMR (methanol-d_4, 300 MHz): 7.49 – 7.42 (m, 1H), 7.24 (dd, *J* = 7.0, 1.9 Hz, 2H), 7.22 – 7.14 (m, 3H), 6.87 (dt, *J* = 7.9, 1.0 Hz, 2H), 6.77 (tt, *J* = 7.3, 1.0 Hz, 1H),

4.95 (s, 1H), 3.94 – 3.83 (m, 1H), 3.24 – 3.12 (m, 2H), 3.00 – 2.82 (m, 1H). $^{13}C\{^{1}H\}$ NMR (methanol-d_4, 75 MHz): 176.6, 148.5, 134.8, 132.1, 128.0, 127.2, 126.6, 126.5, 125.3, 117.4, 112.8, 63.7, 43.3, 27.7. MS (ESI): *m/z* = 253.1 $[M(C_{16}H_{16}N_2O)+H]^+$. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O$ 253.1336; Found 253.1336. There is no spectroscopic data reported in the literature.

Supporting Information

Additional General Experimental Information, General Synthesis Procedure, Optimization of Reaction Conditions, Mechanistic Studies, Follow-up Hydrolysis Reaction, References, ^{1}H- and ^{13}C-NMR Spectra of Compounds.

Acknowledgements

We thank Jan Brauer for helpful discussions, Leander Geske for help with structure elucidation, Dr. Johannes C. Liermann for NMR spectroscopy, and Dr. Christopher J. Kampf for mass spectrometry (all JGU Mainz).

Financial support by the São Paulo Research Foundation - FAPESP - (grant numbers: 2019/27176-8, 2020/06874-6; R.C.S fellowship 2018/00879-6), the Conselho Nacional de Pesquisa - CNPq (Grant 407990/2018-6 and K.T.O. research fellowship 303890/2019-3), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Financial Code 001, and the Fonds of the Chemical Industry (Kekulé fellowship for W.R.K.) are gratefully acknowledged. We thank the German Research Foundation (DFG) through grant INST 247/1018-1 FUGG to K.H. and T.O.

Associated Content

The Supporting Information is available free of charge.

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