ChemPlusChem 84.6 (2019): 673-679

DOI: https://doi.org/10.1002/cplu.201800631

WILEY-VCH

Crosswise Phthalocyanines with Collinear Functionalization: New Paradigmatic Derivatives for Efficient Singlet Oxygen Photosensitization

Miguel A. Revuelta-Maza,[a] Cormac Hally,[d] Santi Nonell,[d] Gema de la Torre*[a],[b] Tomás Torres*[a],[b],[c]

Dedication ((optional))

Abstract: We describe here the preparation of a number of *trans*-ABAB Zn(II) phthalocyanines (ZnPcs) **1a-g**, which combine several interesting features. First, these compounds present high solubility and hindered aggregation, due to the functionalization of two facing isoindole constituents (B) of the ZnPc with bis(trifluoromethylphenyl) units. Second, the other two isoindoles (A) hold extra-annulated phthalimide units containing different substituents in the nitrogen positions, this feature resulting in a collinear arrangement of a variety of functional groups. Some of these collinearly functionalized ZnPcs are interesting building blocks for constructing either homo- or heteroarrays containing ZnPc units. On the other hand, the amphiphilic nature of some members of the series renders them interesting candidates for photosensitization of singlet oxygen. Photophysical studies on ZnPc **1c**, selected as model compound of the series, have proven these molecules efficient singlet oxygen photosensitizers in both polar and apolar media, with $^1O_2$ quantum yields (ϕ_Δ) as high as 0.74.

Introduction

Phthalocyanines (Pcs) are focus of research because of their exceptional electronic properties and their stability under a wide range of environmental conditions.[1] These chromophores are appealing targets for many different applications, as a result of their strong absorption in the visible/near infrared ranges of the electromagnetic spectrum, and their extraordinary robustness. Moreover, Pcs can form complexes with a large variety of metal atoms, and can be endowed with a range of substituents at axial and/or peripheral positions. This structural versatility has a strong impact on their electronic properties, such as molar absorption coefficients, redox potentials and excited-state lifetimes, among others. All these interesting features have driven their use in two broad scientific areas: i) biological applications,[2] namely, for therapeutic treatments as anticancer and antimicrobial agents, taking advantage of the ability of some Pc derivatives to sensitize singlet oxygen ($^1O_2$) due to their long-lived triplet excited states; and ii) as functional materials, for instance, as catalytic systems[3] or dyes for energy conversion schemes.[4] For most of these applications, the formation of well-defined nanoassemblies offers a route to improve the function of the Pc molecules. In this regard, the presence of certain functional groups on the periphery of the Pcs provides a tool for the engineering of outstanding supramolecular arrays. For instance, the incorporation of Pcs in 2D or 3D ensembles of different shapes and sizes relies on the preparation of macrocycles with highly directional binding motifs. Particularly, an angular orientation of the binding sites of 180º permits to create complex linear arrangements, such as Pc-containing polymers,[5] or to use Pcs as subcomponents for the self-assembly of metalloorganic cavities for host-guest interactions.[6] On the other hand, appropriate functionalization of the Pcs with collinear lipophilic/hydrophilic substituents may lead to nanovesicles in water media, which can be envisioned as delivery systems for photodynamic and photothermal therapies (PDT).[7],[8],[9] In this regard, we have recently described the preparation of *trans*-A_2B_2 Pcs[10] containing: i) two crosswise isoindoles functionalized with bulky bis(trifluoromethyl)phenyl groups at the non-peripheral positions, which provide solubility and hinder the aggregation between macrocyles; and ii) two croswise isoindoles endowed with iodine atoms.[10b,c] Importantly, the presence of opposite iodine atoms has allowed us to prepare amino-containing, ditopic Pc ligands able to self-assemble into supramolecular cages by metal-ligand coordination with iron(II) salts.[6] However, the fact that each of the iodine atoms in the starting Pc is offset with respect to one of the central N-N axes by a 30° angle results in the presence of two positional isomers (i.e syn and anti) with the same ratio. Therefore, to obtain Pc ligands with well-defined coordination geometries,[6] it was necessary to separate the corresponding isomers.

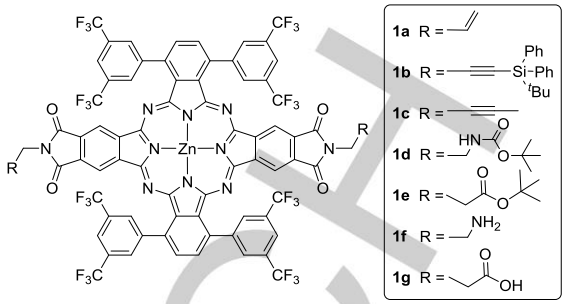
In the previous context, it is indeed challenging to achieve a truly linear arrangement of the functional groups at the Pc core. However, this task is not trivial because of the limitations imposed by the geometry of Pcs and the methodology for their synthesis. An approach to prepare Pc derivatives holding substituents that are collinear with the N-N axes of the macrocycles is to use phthalonitrile derivatives endowed with fused five membered rings, which give rise to extra-annulated Pc derivatives. Several examples of Pc derivatives endowed with one or more fused imidazole and/or thiophene units have been reported.[11],[12] A relevant work was reported by Youngblood, who prepared *trans*-ABAB bis(benzimidazole)phthalocyanines holding alkyl, phenyl

[a] Miguel A. Revuelta-Maza, Dr. Gema de la Torre, Prof. Tomás Torres
Universidad Autónoma de Madrid, c/Francisco Tomás y Valiente 7, 28049 Madrid, Spain
E-mail: tomas.torres@uam.es
[b] Dr. Gema de la Torre, Prof. Tomás Torres
Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain
[c] Prof. Tomás Torres
Instituto Madrileño de Estudios Avanzados (IMDEA)-Nanociencia, c/ Faraday 9, Cantoblanco, 28049 Madrid, Spain
[d] C. Hally, Dr. S. Nonell
Institut Químic de Sarrià
Universitat Ramon Llull
08017 Barcelona (Spain)

Supporting information for this article is given via a link at the end of the document

or ethynylphenyl moieties linked to the 2-position of the benzimidazole unit, resulting in compounds with a linear arrangement of the substituents.[13] However, *N*-alkylation at the imidazole ring was necessary, rendering a mixture of two positional isomers with different orientations of the *N*-alkyl chains. On the other hand, extra-annulation with phthalimide units containing substituents in the *N* position has been also described as a route to obtain highly symmetrical, isomerically pure, D_{4h} tetrafunctionalized Pcs.[14] This type of phthalimide derivatives have been synthesized either from the tetraanhydrides of 2,3,9,10,16,17,23,24-octacarboxyPcs and the corresponding amines,[14a,c] or by cyclotetramerization of imide-phthalonitriles.[14b] However, to the best of our knowledge, ABAB Pcs with a collinear arrangement of *N*-functionalized phthalimide outer rings have not been described yet.

Herein, we report a unique family of ABAB ZnPcs (**1a-g**) with a collinear arrangement of binding moieties located at the *N* position of facing phthalimide outer rings, (Scheme 1). The synthesis of this series of *trans*-ABAB ZnPcs relies on the use of bulky 2,5-bis(trifluoromethyl)phenylphthalonitrile to direct the reaction towards the cross-condensation product, as previously described by us.[10a] The extraannulation with the phthalimide rings was attempted by the formation of a tetracarboxy-ZnPc, which could be further reacted with different amines to form the targeted compounds, and also by cross-condensation of differently functionalized imido-phthalonitriles with the bulky phthalonitrile. The prepared ZnPc derivatives can be considered as motifs for bulding either linear or macrocyclic assemblies of Pcs, through efficient click thiol-ene (**1a**), Pd-catalyzed Sonogashira coupling (**1b**) or alkyne-methathesis (**1c**) reactions. On the other hand, the amphiphlic nature of some members of the series (**1f,g**),[15] combined with hindered aggregation due to the presence of the trifluoromethylphenyl units, renders them interesting for photosensitization of singlet oxygen. Importantly, the presence of trifluoromethylphenyl units at the alfa position of the outer benzene rings of the Pc is expected to enhance the photostability and lipophilicity.[16] This substitution pattern has been never explored in ZnPcs as a means to obtain non-aggregated ZnPcs. In fact, these ABAB-type ZnPcs constitute a new paradigm for PDT photosensitizers.[17] Moreover, the geometry of these derivatives and the presence of amino, carboxylic acid, vinyl or ethynyl moieties permits to build third-generation photosensitizers, where the ZnPc can be covalently conjugated to two site-specific delivery agents affording solubility in physiological media and selective accumulation within the targeted tissue.[2b] Therefore, it appears of interest to establish the singlet oxygen generation capabilities of this family of compounds. To this end, photophysical studies have been realized on ZnPc **1c** as model compound.



Scheme 1. Structure of ZnPcs **1a-g**.

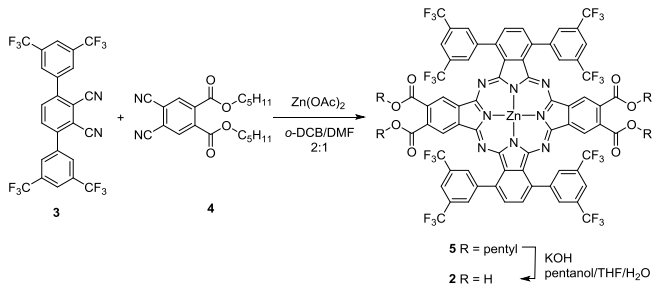
Results and Discussion

The preparation of ZnPcs **1a-g** was undertaken by two different approaches. First, a most convergent route was attempted, which consisted in the preparation of a tetracarboxy-ZnPc **2,** (Scheme 2), as a synthon for the preparation of the targeted *N*-functionalized phthalimide-ZnPcs. For the sake of obtaining a soluble precursor of **2** that could be easily purified by column chromatography, we performed a cross-condensation reaction between the bulky 2,5-bis(trifluoromethyl)phenylphthalonitrile (**3**) (B unit),[10] and 4,5-bis(pentyloxycarbonyl)phthalonitrile (**4**) (A unit)[18] to obtain ZnPc **5**, which could be hydrolized in a second step to the tetracarboxy-derivative. As previously established in the group,[10] yields in the cross-condensation towards ABAB ZnPcs are maximized when a mixture of dry *o*-dichlorobenzene (*o*-DCB) and DMF is used as solvent, and $Zn(OAc)_2$ as source of metal. Moreover, in this particular case, avoiding the use of alcoholic solvents is crucial to circumvent subtitutions of the alkoxy moieties at the ester functions. Yet, the reaction yielded ZnPc **3** in only 5%, probably due to the strong tendency of phthalonitriles functionalized with electron-withdrawing groups to give self-condensation instead of the crossed condensation with the bulky phthalonitrile. In fact, **5**-A_3B and **5**-A_4 ZnPcs were isolated in 9 and 10% yield, respectively.

The next step was to carry out the hydrolysis of the ester function. Although several conditions were tested, most of them failed to yield the tetracarboxy-ZnPc **2**. When using KOH in a pentanol/THF/water mixture (see Supporting Information), only traces of **2** were obtained. These results compelled us to direct our synthetic efforts towards the preparation of appropriately functionalized phthalimide-derived phhalonitriles, for the straightforward cross-condensation with bulky phthalonitrile **3**.

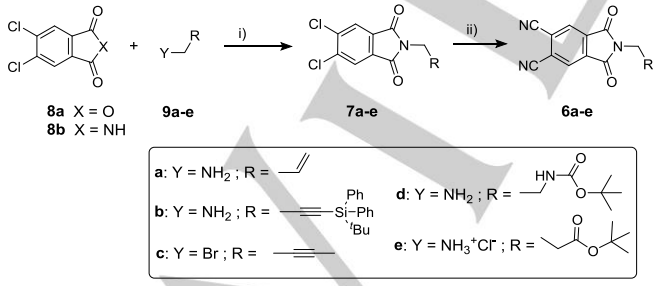
As mentioned in the Introduction section, one of the aims of the work is to establish a synthetic approach that allows to prepare differently substituted ABAB ZnPc, all of them with a linear arrangement of functional groups at the Pc core. These geometrically well-defined disposition of the functional groups can be exploited for the preparation of Pc assemblies, and also to impart a marked amphiphilic character to the Pc molecule, when it is functionalized with facing lipophilic and hydrophilic substituents in the same Pc ring. To this end, different *N*-substituted 5,6-dichloroisoindoline-1,3-diones (Scheme 3) were

envisioned, endowed either with reactive vinyl/acetylene moieties that can further give rise to efficient chemical transformations (**6a-c**), or with protected amino or carboxy moieties (**6d,e**) that can be deprotected (**6f**,**g**) towards the final preparation of a novel archetype of amphiphilic photosensitizers for PDT.



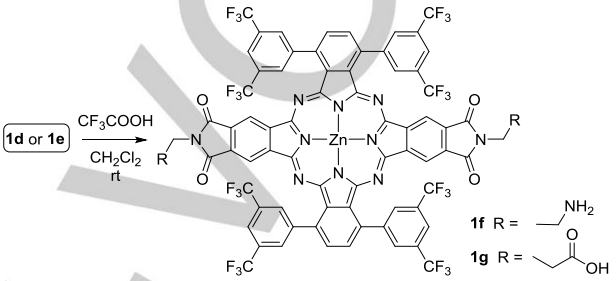
Scheme 2. Synthesis of tetracarboxy-ZnPc **2**.

The synthesis of 5,6-dicyano-1,3-dioxoisoindoline derivatives **6a-g** was accomplished by the initial preparation of *N*-substituted-5,6-dichlorophthalimides (**7a-e**) followed by Pd-catalyzed cyanation reactions. Two general methods were applied for the synthesis of **7a-e** depending on the availability of the reactants, namely, the condensation reaction between 5,6-dichlorophthalic anhydride (**8a**) and the corresponding alkylamine (**9a,b,d**) or alkylamine hydrochloride (**9e**), and the *N*-alkylation of 5,6-dichlorophthalimide (**8b**) with the bromopropargyl derivative **9c** (Scheme 3). The reaction of 5,6-dichlorophthalic anhydride and the corresponding alkylamine or alkylamine hydrochloride was performed either by thermal (reaction with **9d,e**) or microwave (reaction with **9a,b**) activation. All these reactions proceeded in good yields, ranging from 68 to 91%. However, the corresponding cyanations rendered phthalonitriles **6a-e** in moderate yields (31-53%), with the exception of phthalonitrile **6a** that was isolated in a poor 5% yield. It is worth mentioning that, although we envisioned the preparation of 5,6-dicyano-1,3-dioxoisoindoline derivatives with aromatic *N*-substituents, this type of precursors proved very unstable and could not be utilized to prepare ABAB ZnPcs.



Scheme 3. Reagents and conditions. i) for **7a** (83%) and **7b** (68%): **8a**, **9a** or **9b**, acetic acid, MW, 150°C, 2h; for **7c** (70%): **8b**, **9c**, *N,N*-diisopropylethylamine, acetonitrile, Ar, rt. ii) $Pd_2(dba)_3$, dppf, Zn powder, $Zn(CN)_2$, *N,N*-dimethylacetamide, Ar, 120°C, 2-4h; for **7d** (84%): **8a**, **9d**, acetic acid, 100°C, 1.5 h; for **7e** (91%): **8a**, **9e**, *N,N*-diisopropylethylamine, anhydrous toluene, Dean-Stark trap.

Next, we undertook the synthesis of the target ABAB ZnPcs, which was carried by cross condensation between equimolecular amounts of bulky phthalonitrile **3** (B) and 5,6-dicyano-1,3-dioxoisoindoline derivatives **6a-e** (A). In all the reactions, *trans*-ABAB ZnPcs were formed, together with the related A_3B and A_4 ZnPcs, but with no traces of Pcs holding two adjacent B units. Nevertheless, the target compounds were isolated in low yields. Additionally, the carbamate and ester functions of compounds **1d** and **1e**, respectively, were easily removed using trifluoroacetic acid, yielding the diamino (**1f**) and dicarboxylic acid (**1g**) amphiphilic ZnPcs in good yields (Scheme 4).



Scheme 4. Synthesis of amphiphilic ZnPcs **1f** and **1g.**

All the ZnPcs have in common good solubility features and hindered aggregation in solution imparted by the bis(trifluoromethyl)phenyl moieties. These facts, together with the high symmetry exhibited by all the derivatives, result in extremely well-resolved ^{1}H- and ^{13}C-NMR spectra, which is infrequent for ZnPcs. As an example, the ^{1}H-NMR spectrum of compound **1e** is shown in Figure 1.

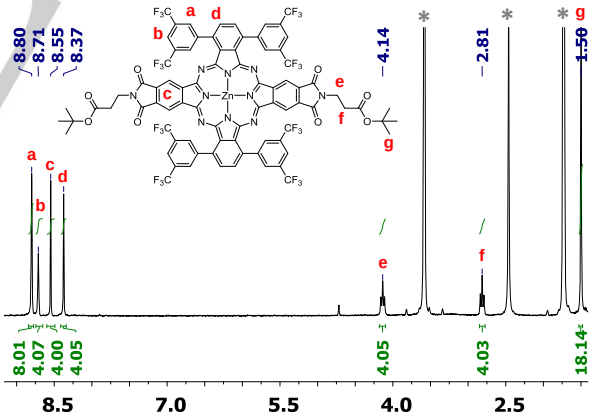


Figure 1. ^{1}H-NMR spectrum of ZnPc **1e**. *: Solvent residual peaks.

The UV-Vis spectra of ABAB ZnPcs **1a-g** show symmetric, split Q bands, as generally observed in MPcs with D_{2h}-symmetry.[19] Indeed, the absorption spectra of these compounds in solvents such as non-coordinating toluene or coordinating THF do not show any evidence of aggregation, as otherwise expected for these compounds due to the presence of rather bulky substituents at the non-peripheral positions of the Pc core. Further confirmation of the lack of aggregation of these ZnPcs result from

the absorption studies performed at a range of concentrations. These studies were performed on compound **1c**, which was selected as a model to study the photophysical properties (Table 1) of this novel family of ABAB ZnPcs. Absorption spectra of **1c** were registered in a range of concentrations (between $1.56 \cdot 10^{-6}$ M and $7.71 \cdot 10^{-6}$ M) (Figure 2) For the verification of the Lambert-Beer law, an analysis of linear regression between the intensity of the Q-band and the concentration of **1c** was performed, with R^2 values of ~0.999.

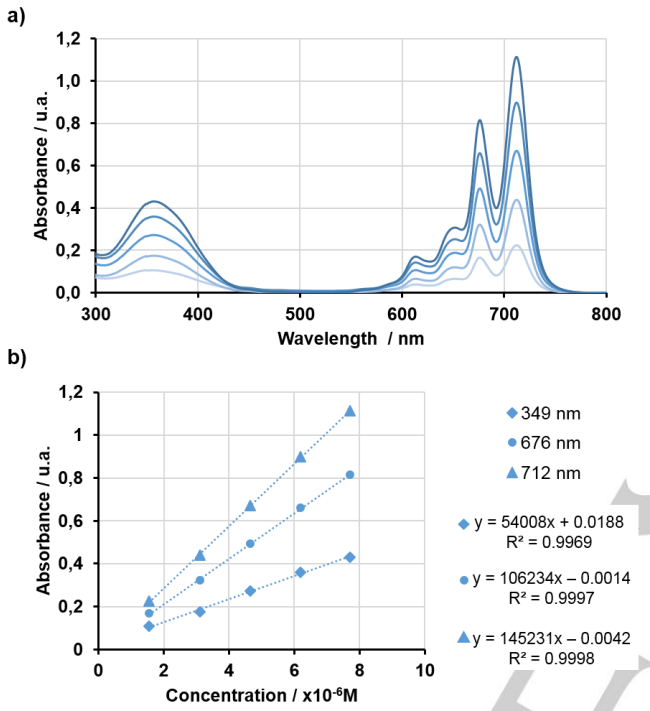


Figure 2. a) UV-Vis spectra of **1c** in THF at different concentrations ($1.56 \cdot 10^{-6}$ M – $7.71 \cdot 10^{-6}$ M); b) linear regression between the intensity of the Q-band and the concentration of **1c** in THF.

Fluorescence studies on **1c** have been also performed in toluene and THF (Figures S29 and S30 in the Supporting Information). The results (Table 1) are consistent with those of non-aggregated ZnPcs, and show a modest solvent dependence. The monoexponential fluorescence decay kinetics confirm that **1c** is in monomeric form in solution. The singlet excited-state lifetime is similar between the two solvents, although the fluorescence quantum yield is almost double in toluene than in THF. The quantification of the $^1O_2$ quantum yield (ϕ_Δ) was performed by direct observation of the $^1O_2$ phosphorescence at 1275 nm (Figures S31 and S32 in the Supporting Information) exciting at 355 nm, both in toluene and THF solutions. Comparing with fluorescence results, the $^1O_2$ quantum yields, ϕ_Δ, change concomitantly in the opposite direction. This indicates that THF, a coordinating solvent, perturbs both the radiative and non-radiative singlet excited-state decay processes of **1c**. The measured ϕ_Δ values are moderately higher than that of the unsubstituted ZnPc (ϕ_Δ = 0.52 in ethanol)[20] and other substituted ZnPcs reported in the literature,[21] which suggests that the substitution pattern of this family of compounds improves the photoproperties of the ZnPc core, rendering them adequate for phototherapeutic applications.

Table 1. Photophysical properties of **1c**.

Solvent	logε (λ)	λ_f/nm	ϕ_f	τ_S/ns	τ_T/μs[a]	ϕ_Δ
THF	4.73 (349) 5.03 (676) 5.16 (712)[b]	717	0.13	2.1	0.13	0.74
Toluene	4.81 (359) 5.11 (682) 5.28 (707)[b]	711	0.24	2.3	0.22	0.65

[a] in air-saturated solutions; [b] Q-band maximum.

It is worth mentioning that preliminary $^1O_2$ generation studies had been previously performed on compounds **1c**, **1d** and **1e** by measuring the photoinduced decomposition of 1,3-diphenylisobenzofuran (DPBF) in DMSO solutions, under the irradiation of the corresponding ZnPcs (see Supporting Information for experimental details). Although the indirect method is quantitatively less accurate, it can be useful for comparative purposes. In fact, we can conclude that the three compounds gave similar ϕ_Δ values, which are consistent with their similar substitution nearby the ZnPc core, with only slight changes in the *N*-functionalization of the extra-annulated phthalimide. Also for the sake of comparison, ϕ_Δ was also determined for **1c** in DMSO by the straightforward measurement of the $^1O_2$ phosphorescence, giving a similar value (0.67) than those reported in THF and toluene.

Conclusions

We describe here the preparation of a series of trans-ABAB ZnPcs **1a-g** featuring high solubility, hindered aggregation and a collinear arrangement of a variety of functional groups. These compounds constitute a paradigmatic type of ZnPcs that can be exploited for the construction of multi-phthalocyanine arrays. Importantly, this substitution pattern permits to obtain amphiphilic ZnPcs with inherent non-aggregating features that are independent of the solvent employed. This is an outstanding characteristic, not easy to achieve in ZnPcs, and that is fundamental for using them as photosensitizers for the production of singlet oxygen in therapeutic applications. For this reason, photophysical studies have been realized to establish the singlet oxygen generation capabilities of this family of compounds, using ZnPc **1c** as model. The ϕ_Δ found in different solvents are higher than the average values reported in the literature for other functionalized ZnPcs. This result encourages us to prepare novel ABAB ZnPc derivatives with balanced hydrophilicity and lipophilicity, in the search of non-aggregated chromophores, soluble in water media, which can find application in photodynamic therapies.

Experimental Section

General. Chemicals were purchased from commercial suppliers and used without further purification unless stated otherwise. 3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':4',1''-terphenyl]-2',3'-dicarbonitrile (**3**)[10a] dipentyl 4,5-dicyanophthalate (**4**),[22] 5,6-dichloroisoindoline-1,3-dione (**8b**),[23] 4,5-dichlorophthalic anhydride (**8a**), and 3-(*tert*-butyl(diphenyl)silyl)prop-2-yn-1-amine (**9b**),[24] have been prepared according to published procedures. The monitoring of the reactions has been carried out by thin layer chromatography (TLC), employing aluminum sheets coated with silica gel type 60 F254 (0.2 mm thick, E. Merck). Purification and separation of the synthesized products was performed by column chromatography, using silica gel (230-400 mesh, 0.040-0.063 mm, Merck). Eluents and relative proportions of the solvents are indicated for each particular case. Size exclusion chromatography was performed using Bio-Beads S-X1 (200-400 mesh, Bio-Rad). Microwave-activated reactions were performed in a Biotage Initiator+ 4.1.2 equipment, all reactions were performed in capped glass vials (Biotage Microwave vials 2-5 mL) under argon atmosphere. Infrared (IR) spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrophotometer, employing in all cases solid samples (diamond ATR). Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) spectra were recorded employing Electronic Impact (EI), Fast Atom Bombardment (FAB-MS), ESI Positive TOF_MS-500-4000.m, APCI or Matrix Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF), using a VG-AutoSpec spectrometer for EI and FAB-MS and a Bruker Reflex III spectrometer, with a nitrogen laser operating at 337 nm, for MALDI-TOF. The different matrixes employed are indicated for each spectrum. Mass spectrometry data are expressed in *m/z* units. NMR spectra (^{1}H-NMR, ^{13}C-NMR) were recorded on a Bruker AC-300 (300 MHz) instrument or a Bruker XRD-500 (500 MHz). UV-Vis spectra were recorded on a JASCO-V660 UV-Vis spectrophotometer using spectroscopic grade solvents.

Synthesis of 5. 3 (0.27 mmol, 150 mg), **4** (0.27 mmol) and anhydrous $Zn(AcO)_2$ (0.27 mmol, 50 mg) were placed in a 5 mL high pressure resistant flask equipped with a magnetic stirrer, and then 2.7 mL ([**3**]=0.1 M) of dry *o*-dichlorobenzene/DMF (dried over 4Å molecular sieves) 2:1 was added. The mixture was heated to 150-160°C overnight under an argon atmosphere. After cooling the solvent was removed under vacuum. The product was purified by column chromatography on SiO_2 (THF/heptane in gradient from 1:4 to 1:1) where the first fraction to elute containing the desired product **5-ABAB**, followed by compounds **5-A_3B**, and **5-A_4**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with MeOH. Yield: 13.5 mg, (5%). IR(ATR) v^{-1} (cm^{-1}): 1716 (C=O st), 1380 (pyrrole ring), 1277, 1217 (C-F st), 1176 (C-F st), 1134 (C-F st), 1092 (C-O st); ^{1}H NMR (500 MHz, THF-d_8): δ 8.79 (s, 8H, Ar); 8.57 (s, 4H, Ar); 8.52 (s, 4H, Ar); 8.31 (s, 4H, Ar); 4.56 (t, 8H, *J* = 6.99 Hz, CH_2); 1.92-1.98 (m, 8H, CH_2); 1.46-1.58 (m, 16H, CH_2), 1.02 (t, 12H, J = 7.04 Hz, CH_3); ^{13}C NMR (125 MHz, THF-d_8): δ 14.4 (CH_3), 23.4(CH_2), 29.2(CH_2), 29.5(CH_2), 66.7 (COOC*H_2), 124.3 (C Ar), 125.0 (q, *J* = 272.7 Hz, CF_3), 131.9 (br s, C*CF_3), 132.6 (C Ar), 132.7 (C Ar),134.6 (C Ar), 136.7 (CH Ar), 138.2 (CH Ar), 140.0 (CH Ar), 143.9 (CH Ar), 153.5 (C=N), 154.5 (C=N), 167.9 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2100): First fraction, **5-ABAB**, *m/z* 1903.3676 $[M+Na]^+$ (calculated: 1903.3648); MS (MALDI, matrix DCTB): Second fraction, **5-A_3B**, *m/z* 1684.4 (calculated: 1684.5); third fraction: **5-A_4**, *m/z*, 1488.6 (calculated: 1488.6); UV-Vis (THF), λ_{max} (log ε): 686 (5.12),619 (sh), 349 (4.56) nm.

General procedure for the synthesis of *N*-substituted 5,6-dichloroisoindoline-1,3-diones (7a-e).

Method A. MW assisted reaction: To a microwave test tube were added **8a** (300 mg, 1.38 mmol), acetic acid (2 mL), and alkyl amine (**9a** or **9b**) (1.52 mmol). The reaction was stirred in a microwave reactor, at 150°C for 2 h. After that time, the crude reaction mixture was diluted with EtOAc (50 mL), poured carefully in aqueous solution of $NaHCO_3$ (sat) (50 mL) to neutralize the acetic acid. The organic phase was washed with the $NaHCO_3$ (sat) (50 mL) solution, and with H_2O (2x20 mL). The organic phase was separated and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the corresponding product. **Thermal reaction: 9d** (369 mg, 2.30 mmol) was added to a solution of **8a** (500 mg, 2.30 mmol) in 11 mL acetic acid. The mixture was stirred for 1.5 h at 100°C and after being cooled to rt, it was treated with H_2O (20 mL). The solid was filtered and washed several times with H_2O (20 mL), $NaHCO_3$ (sat) (2x20 mL) and H_2O (20 mL).

Method B: 8b (500 mg, 2.31 mmol), *N,N*-diisopropylethylamine (605 µL, 3.47 mmol), alkyl bromide (**9c**) (230 µL, 2.55 mmol) and acetonitrile (5 mL) were placed in a round bottom flask and stirred at rt under argon atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was filtered, the solid was washed with H_2O (10 mL) and dried in a vacuum oven overnight.

Method C: Alkyl amine hydrochloride (**9e**) (1.38 mmol), *N,N*-diisopropylethylamine (503 µL, 2.89 mmol), **8a** (300 mg, 1.38 mmol), and anhydrous toluene (150 mL) were added. The apparatus was equipped with a Dean−Stark trap, and the mixture was refluxed overnight. Finally, toluene was removed under reduced pressure.

Synthetic details and spectroscopic data for each compound are described in the Supporting Information.

General procedure for the synthesis of *N*-substituted 1,3-dioxoisoindoline-5,6-dicarbonitriles (6a-e).

N-Substituted 1,3-dioxoisoindoline-5,6-dicarbonitriles were prepared from *N*-substituted 5,6-dichloroisoindoline-1,3-diones **6a-e** via Pd-catalyzed cyanation reactions.[22] All of them were performed in oven-dry glassware under dry argon atmosphere. Dry *N,N*-dimethylacetamide was kept over 4Å molecular sieves. 5,6-Dichloroisoindoline-1,3-dione **6a-e** (0.70 mmol), $Pd_2(dba)_3$ (27 mg, 0.03 mmol), dppf (22 mg, 0.04 mmol), Zn powder (9 mg, 0.14 mmol), and $Zn(CN)_2$ (99 mg, 0.84 mmol) were placed in a dry flask flushed with argon. *N,N*-Dimethylacetamide (3.6 mL) was added via syringe. The resulting mixture was heated at 120°C

for 2-4h (monitorized by TLC), then cooled to rt, and diluted with EtOAc (50 mL). The resulting mixture was filtered and mixed with H_2O (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with H_2O (50 mL), dried over $MgSO_4$, and concentrated in vacuum.

Synthetic details and spectroscopic data for each compound are described in the Supporting Information.

General procedure for the synthesis of ABAB ZnPcs 1a-e.

7 (0.27 mmol, 150 mg), phthalonitrile **6a-e** (0.27 mmol) and anhydrous $Zn(AcO)_2$ (0.27 mmol, 50 mg) were placed in a 5 mL high pressure resistant flask equipped with a magnetic stirrer, and then 2.7 mL ([**7**]=0.1 M) of dry *o*-diclorobenzene/DMF (dried over 4Å molecular sieves) 2:1 was added. The mixture was heated to 150-160°C overnight under an argon atmosphere. After cooling the solvent was removed under vacuum.

Synthesis of 1a. Compound **1a-ABAB** was synthesized from **6a**. The product was purified by column chromatography on SiO_2 (dioxane/heptane in gradient from 4:1 to 1:0) where the first fraction to elute containing the desired product **1a-ABAB**, followed by compounds **1a-A$_3$B**, and **1a-A$_4$**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with heptane. Yield: 6 mg, (3%). IR(ATR) v^{-1} (cm^{-1}): 3085 (=CH_2 st), 3044 (=CH st), 1768 (C=O st), 1700 (C=O st), 1618 (C=C st), 1382 (pyrrole ring), 1274, 1179 (C-F st), 1128 (C-F st); ^{1}H NMR (300 MHz, THF-d_8): δ 8.81 (s, 8H, Ar), 8.72 (s, 4H, Ar), 8.55 (s, 4H, Ar), 8.37 (s, 4H, Ar), 6.18-6.02 (m, 2H, HC=C), 5.40 (d, 2H, *J* = 17.12 Hz, C=CH_2), 5.26 (d, 2H, *J* = 10.27 Hz, C=CH_2), 4.50 (d, 4H, *J* = 5.27 Hz, CH_2); ^{13}C NMR (75 MHz, THF-d_8): 41.3 (CH_2), 117.8 (C Ar), 118.2 (CH=C*H_2), 125.0 (q, *J*= 274.3 Hz, CF_3), 132.0 (br s, C*CF_3), 132.5 (C Ar), 132.9 (C Ar), 133.0 (C Ar), 133.4 (C*H=CH_2), 134.1 (C Ar), 136.8 (CH Ar), 138.4 (CH Ar), 142.7 (CH Ar), 143.8 (CH Ar), 153.7 (C=N), 155.0 (C=N), 167.5 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2000): First fraction, **1a-ABAB**, *m/z* 1642.1380 [M^+] (calculated: 1642.1354); MS (MALDI, matrix DCTB): Second fraction, **1a-A$_3$B**, *m/z* 1327.1 (calculated: 1327.1); third fraction: **1a-A$_4$**, *m/z*, 1012.2 (calculated: 1012.1); UV-Vis (THF), λ_{max} (log ε): 710 (4.90), 676 (4.79), 649 (sh), 613 (sh), 356 (4.44) nm.

Synthesis of 1b. Compound **1b-ABAB** was synthesized from **7b**. The product was purified by column chromatography on SiO_2 (THF/heptane 1:1) where the first fraction to elute contained the desired product **1b-ABAB**, followed by compounds **1b-A$_3$B**, and **1b-A$_4$**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with heptane. Yield: 8.6 mg, 3%. IR(ATR) v^{-1} (cm^{-1}): 2920 (ar C-H st), 2851 (ar C-H st), 2184 (C≡C st), 1772 (C=O st), 1720 (C=O st), 1276, 1381 (C-F st), 1136 (C-F st); ^{1}H NMR (500 MHz, THF-d_8): δ 1.12 (s, 18H, CH_3), 4.88-4.90 (s, 4H, CH_2), 7.35-7.41 (m, 12H, Ar), 7.86-7.92 (m, 8H, Ar), 8.37 (s, 4H, Ar), 8.60 (s, 4H, Ar), 8.75 (s, 4H, Ar), 8.81 (s, 8H, Ar); ^{13}C NMR (125 MHz, THF-d_8): 19.2 (C*(CH_3)$_3$), 27.5 (C(C*H_3)$_3$), 29.1 (CH_2), 84.0 (C≡C), 105.3 (C≡C), 118.5 (C Ar), 125.0 (q, *J* = 273.5 Hz, CF_3), 130.4 (CH Ar-TBDPS), 132.0 (br s, C*CF_3), 132.6 (C Ar), 132.9 (C Ar), 133.0 (C Ar), 134.0 (C Ar), 136.6 (CH Ar-TBDPS), 136.8 (CH Ar),138.4 (CH Ar), 142.7 (CH Ar), 143.8 (CH Ar), 153.6 (C=N), 155.1 (C=N), 166.8 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2000): First fraction, **1b-ABAB**, *m/z* 2114.3486 [M^+] (calculated: 2114.3397), 2137.3334 [M+Na]$^+$ (calculated: 2137.3294); MS (MALDI, matrix DCTB + NaI): Second fraction, **1b-A$_3$B**, *m/z* 2058.5 [M+Na]$^+$ (calculated: 2058.4); MS (MALDI, matrix ditranol): Third fraction: **1b-A$_4$**, *m/z*, 1960.6 (calculated: 1960.6); UV-Vis (THF), λmax (log ε): 713 (3.97), 676 (3.84), 653 (sh), 613 (sh), 357 (3.49) nm.

Synthesis of 1c. Compound **1c-ABAB** was synthesized from **7c**. The product was purified by column chromatography on SiO_2 (THF/heptane in gradient from 2:1 to 1:1) where the first fraction to elute containing the desired product **1c-ABAB**, followed by compounds **1c-A$_3$B**, and **1c-A$_4$**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with heptane. Yield: 5.6 mg, (2%). IR(ATR) v^{-1} (cm^{-1}): 2359 (C≡C st), 1771 (C=O st), 1708 (C=O st), 1384 (CH_3 δ sim), 1384 (pyrrole ring), 1277, 1178 (C-F st), 1136 (C-F st); ^{1}H NMR (300 MHz, THF-d_8): δ 8.81 (s, 8H, Ar), 8.73 (s, 4H, Ar), 8.56 (s, 4H, Ar), 8.38 (s, 4H, Ar), 4.49 (s, 4H, CH_2), 1.84 (s, 6H, CH_3); ^{13}C NMR (75 MHz, THF-d_8): δ 3.2 (CH_2), 28.2 (CH_3), 74.1 (C≡C), 79.2 (C≡C), 118.3 (C Ar), 125.0 (q, *J* = 270. 8 Hz, CF_3), 131. (br s, C*CF_3), 132.5 (C Ar), 133.0 (C Ar), 133.0 (C Ar), 134.0 (C Ar), 136.8 (CH Ar), 138.4 (CH Ar), 142.7 (CH Ar), 143.8 (CH Ar), 153.6 (C=N), 155.1 (C=N), 166.8 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2000): First fraction, **1c-ABAB**, *m/z* 1666.1343 [M^+] (calculated: 1666.1354); second fraction, **1c-A$_3$B**, *m/z* 1363.1356 (calculated: 1363.1397); UV-Vis (THF), λ_{max} (log ε): 712 (5.15), 676 (5.05), 652 (sh), 613 (sh), 355 (4.74) nm.

Synthesis of 1d. Compound **1d-ABAB** was synthesized from **6d**. The product was purified by column chromatography on SiO_2 (THF/heptane in gradient from 1:2 to 3:1) where the first fraction to elute containing the desired product **1d-ABAB**, followed by compounds **1d-A$_3$B**, and **1d-A$_4$**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with heptane. Yield: 6.3 mg, (3%). IR(ATR) v^{-1} (cm^{-1}): 1770 (C=O st), 1717 (C=O st), 1384 (pyrrole ring), 1276, 1180 (C-F st), 1133 (C-F st); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 18H, CH3), 3.42-3.53 (m, 4H, CH_2), 3.99 (t, 4H, *J* = 5.24 Hz, CH_2), 6.40 (br s, 2H, NH), 8.37 (s, 4H, Ar), 8.54 (s, 4H, Ar), 8.71 (s, 4H, Ar), 8.80 (s, 8H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): 28.7 (CH_3), 39.3 (CH_2), 39.9 (CH_2), 78.6 (C*(CH_3)$_3$), 117.9 (C Ar), 125.0 (q, *J* = 277.2 Hz, CF_3), 131.9 (br s, C*CF_3), 132.5 (C Ar), 132.8 (C Ar), 132.9 (C Ar), 134.2 (C Ar), 136.8 (CH Ar), 138.3 (CH Ar), 142.6 (CH Ar), 143.9 (CH Ar), 153.8 (C=N), 155.0 (C=O), 156.9 (C=N), 168.1 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2000): First fraction, **1d-ABAB**, *m/z* 1848.2635 [M^+] (calculated: 1848.2621); second fraction, **1d-A$_3$B**, *m/z* 1636.3289 (calculated: 1636.3296); UV-Vis (THF), λ_{max} (log ε): 709 (4.75), 676 (4.66), 648 (sh), 614 (sh), 355 (4.29) nm.

Synthesis of 1e. Compound **1e-ABAB** was synthesized from **6e**. The product was purified by column chromatography on SiO_2

(dioxane/heptane in gradient from 1:1 to 1:0) where the first fraction to elute containing the desired product **1e-ABAB**, followed by compounds **1e-A_3B**, and **1e-A_4**. The product was further purified by an additional column chromatography on Bio-Beads using $CHCl_3$ as eluent. After evaporation of the solvent a blue solid was obtained, which was washed with heptane. Yield: 5.2 mg, (2%). IR(ATR) v^{-1} (cm^{-1}): 1766 (C=O st), 1714 (C=O st), 1386 (pyrrole ring), 1277, 1178 (C-F st), 1128 (C-F st), 1094 (C-O st), 1040 (C-O st); ^{1}H NMR (300 MHz, THF-d_8): δ 8.80 (s, 8H, Ar), 8.71 (s, 4H, Ar), 8.54 (s, 4H, Ar), 8.37 (s, 4H, Ar), 4.13 (t, 4H, *J* = 7.53 Hz, CH_2), 2.81 (t, 4H, *J* = 7.53 Hz, CH_2), 1.50 (s, 18H, CH_3); ^{13}C NMR (75 MHz, THF-d_8): δ 28.3 (CH_3), 34.9 (CH_2), 35.3 (CH_2), 81.0 (C*(CH_3)$_3$), 118.2 (C Ar), 125.0 (q, *J* = 272.7 Hz, CF_3), 131.9 (br s, C*CF_3), 132.5 (C Ar), 133.0 (C Ar), 134.1 (C Ar), 136.8 (CH Ar), 138.4 (CH Ar), 142.6 (CH Ar), 143.8 (CH Ar), 153.7 (C=N), 155.0 (C=N), 167.7 (C=O), 170.5 (C=O); HR-MS (MALDI, matrix DCTB + PPGNa 2000): First fraction, **1e-ABAB**, *m/z* 1818.2439 [M^+] (calculated: 1818.2403), 1840.2975 [M+Na^+]; MS (MALDI, matrix DCTB): Second fraction, **1e-A_3B**, *m/z* 1591.2 (calculated: 1591.3); third fraction: **1e-A_4**, *m/z*, 1364.3 (calculated: 1364.4); UV-Vis (THF), λ_{max} (log ε): 711 (5.09), 676 (4.99), 650 (sh), 613 (sh), 356 (4.67) nm.

Synthesis of 1f from 1d. A mixture of **1d-ABAB** (4 mg, 0.0022 mmol) and trifluoroacetic acid (4 x 19 µL, every 30 minutes) in dry CH_2Cl_2 (1 mL) was stirred at rt in an argon atmosphere and monitored by TLC. After the reaction was completed the volatiles were removed under reduced pressure, then the residue was dissolved in CH_2Cl_2 (15 mL), washed with H_2O (3x15 mL) and concentrated in vacuum. Yield: 3.1 mg, (87%). IR(ATR) v^{-1} (cm^{-1}): 3283 (NH_2 st), 1770 (C=O st), 1716 (C=O st), 1690 (NH_2 δ), 1386 (pyrrole ring), 1278, 1182 (C-F st), 1133 (C-F st); ^{1}H NMR (300 MHz, THF-d_8): δ 8.81 (s, 8H, Ar), 8.60 (s, 4H, Ar), 8.53 (s, 4H, Ar), 8.26 (s, 4H, Ar), 4.22 (br s, 4H, CH_2), 3.52 (br s, 4H, CH_2); HR-MS (ESI Positive TOF_MS-500-4000.m): 1649.1644 [M+H]$^+$ (calculated: 1649.1650); UV-Vis (THF), λ_{max} (log ε): 709 (4.48), 676 (4.39), 649 (sh), 614 (sh), 357 (4.09) nm.

Synthesis of 1g from 1e. A mixture of **1e-ABAB** (3 mg, 0.0016 mmol) and trifluoroacetic acid (0.14 mL) in dry CH_2Cl_2 (0.40 mL) was stirred at rt for 30 minutes in an argon atmosphere. The volatiles were removed under reduced pressure, then the residue was dissolved in CH_2Cl_2 (15 mL), washed with H_2O (15 mL x3) and concentrated in vacuum. Yield: 2.5 mg, (90%).IR(ATR) v^{-1} (cm^{-1}): 3281 (O-H st), 2919 (O-H st), 2851 (O-H st), 1690 (C=O st); ^{1}H NMR (300 MHz, THF-d_8): δ 8.80 (s, 8H, Ar), 8.72 (s, 4H, Ar), 8.54 (s, 4H, Ar), 8.36 (s, 4H, Ar), 4.14 (t, 4H, *J* = 7.45 Hz, CH_2), 2.86 (t, 4H, *J* = 7.45 Hz, CH_2); HR-MS (MALDI, matrix DCTB + PEGNa 1500): *m/z* 1706.1114 [M^+] (calculated: 1706.1151), 1729.9667 [M+Na^+]; UV-Vis (THF), λmax (log ε): 710 (4.23), 676 (4.14), 650 (sh), 613 (sh), 357 (3.79) nm.

Acknowledgements

This work has been supported by Comunidad de Madrid, Spain (S2013/MIT-2841, FOTOCARBON), MINECO, Spain (CTQ2017-85393-P and CTQ2016-78454-C2-1-R), and the "Solar Energy goes Hybrid" Initiative of the Bavarian Ministry for Science, Culture and Education (SolTech). C. H. thanks the European Social Funds and the SUR del DEC de la Generalitat de Catalunya for his predoctoral fellowships (Grant No. 2017 FI_B 00617 and 2018 FI_B1 00174).

Keywords: collinear functionalization • fluorescence • photophysics • phthalocyanine • singlet oxygen

[1] N. B. McKeown in *Phthalocyanine Materials Synthesis, Structure and Function*, Cambridge University Press, Cambridge, **1998**

[2] a) S. Singh, A. Aggarwal, N. V. S. D. K. Bhupathiraju, G. Arianna, K. Tiwari, C. M. Drain, *Chem. Rev.* **2015**, *115*, 10261-10306; b) V. Almeida-Marrero, E. van de Winckel, E. Anaya-Plaza, T. Torres, A. de la Escosura, *Chem. Soc. Rev*. **2018**, *47*, 7369-7400.

[3] A. B. Sorokin, *Chem. Rev*. **2013**, *113*, 8152–8191.

[4] a) M. V. Martinez-Diaz, G. de la Torre, T. Torres, *Chem. Commun*. **2010**, *46*, 7090–7108; b) H. Imahori, T Umeyama, K. Kurotobi, Y. Takano, *Chem. Commun*. **2012**, *48*, 4032–4045; c) G. de la Torre, G. Bottari, T. Torres, *Adv. Energy Mater*. **2016**, 1601700.

[5] R. P. Kingsborough, T. M. Swager, *Angew. Chem., Int. Ed*. **2000**, *39*, 2897-2900.

[6] E. Fazio, C. J. E. Haynes, G. de la Torre, J. R. Nitschke, T. Torres, *Chem. Commun*. **2018**, *54*, 2651–2654.

[7] a) S. S. Lucky, K. C. Soo, Y. Zhan, *Chem. Rev*. **2015**, *115*, 1990−2042; b) X. Li, S. Lee, J. Yoon, *Chem. Soc. Rev*. **2018**, *47*, 1174-1188.

[8] a) J. F. Lovell, C. S. Jin, E. Huynh, H. Jin, C. Kim, J. L. Rubinstein, W. C. W. Chan, W. Cao, L. V. Wang, G. Zheng, *Nature Mater.* **2011**, *10*, 324-332; b Q. Zou, M. Abbas, L. Zhao, S. Li, G. Shen, X. Yan, *J. Am. Chem. Soc.* **2017**, *139*, 1921−1927.

[9] X. Li, D. Lee, J.-Dong Huang, J. Yoon, *Angew. Chem. Int. Ed.* **2018**, *57*, 9885–9890.

[10] a) N. Kobayashi, T. Ashida, T. Osa, *Chem. Lett*. **1992**, 2031-2034. b) E. Fazio, J. Jaramillo-García, G. de la Torre, T. Torres, *Org. Lett*. **2014**, *16*, 4706-4709. c) E. Fazio, J. Jaramillo-García, M. Medel, M. Urbani, M. Grätzel, M. K. Nazeerudin, G. de la Torre, T. Torres, *ChemistryOpen* **2017**, *6*, 121-127.

[11] P. A. Stuzhin, C. Ercolani in *The Porphyrin Handbook*, Eds.: K. M. Kadish, K. M. Smith, R. Guilard, Academic Press: San Diego, 2003; vol. 15, pp 263-364.

[12] a) J. V. Bakboord, M. J. Cook, E. Hamuryudan, *J. Porphyrins Phthalocyanines,* **2000**, *4*, 510-517; b) D. M. Knawby, T. M. Swage, *Chem. Mater.* **1997**, *9*, 535-538; c) C. Pardo, M. Yuste, J. Elguero, *J. Porphyrins Phthalocyanines,* **2000**, *4*, 505-509.

[13] W. J. Youngblood, *J. Org. Chem*. **2006**, *71*, 3345-3356.

[14] a) N. Kobayashi, T. Ohya, M. Sato, S. Nakajima, *Inorg. Chem*. **1993**, *32*, 1803-1808; b) M. Gonidec, D. B. Amabilino, J. Veciana, *Dalton Trans.* **2012**, *41*, 13632-13639; c) X. Li, L. E. Sinks, B. Rybtchinski, M. R. Wasielewski, *J. Am. Chem. Soc.* **2004**, *126*, 10810-10811; d) G. Mezei, A. R. Venter, J. W. Kreft, A. A. Urech, N. R. Mouch, *RSC Adv*. **2012**, *2*, 10466–10469.

[15] I. J. MacDonald, T. J. Dougherty, *J. Porphyrins Phthalocyanines*, **2001**, *5*, 105-129.

[16] N. V. S. D. K. Bhupathiraju, W. Rizvi, J. D. Batteasb, C. M. Drain, *Org. Biomol. Chem*. **2016**, *14*, 389–408.

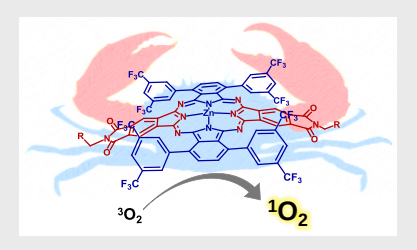
[17] Although other *trans*-ABAB porphyrazine derivatives had been previously established as efficient singlet oxygen generators, (see for example K. Ishii, H. Itoya, H. Miwa, M. Fujitsuka, O. Ito, N. Kobayashi, *J. Phys. Chem. A* **2005**, *109*, 5781-5787) this is, to the best of our knowledge, the first study on the photosensitization abilities of isomerically pure ABAB-phtalocyanines.

[18] D. M. Opris, F. Nüesch, C. Löwe, M. Molberg, M. Nagel, *Chem. Mater.* **2008**, *20*, 6889–6896.
[19] N. Kobayashi, H. Miwa, V. N. Nemykin, *J. Am. Chem. Soc*. **2002**, *124*, 8007-8020.
[20] G. Valduga, S. Nonell, E. Reddi, G. Jori, S. E. Braslavsky, *Photochem. Photobiol*. **1988**, *48*, 1-5.
[21] K. Ishii*, Coord. Chem. Rev*. **2012**, *256*, 556–1568.
[22] B. Tylleman, R. Gómez-Aspe, G. Gbabode, Y. H. Geerts, S. Sergeyev, *Tetrahedron* **2008**, *64*, 4155-4161.
[23] D. Wöhrle, M. Eskes, K. Shigehara, A. Yamada, *Synthesis,* **1993**, 194-196.
[24] I. E. Valverde, A. F. Delmas, V. Aucagne, *Tetrahedron*, **2009**, *65*, 7597-7602.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

Phthalocyanines are facing new challenges. A unique family of *trans*-ABAB ZnPcs with hindered aggregation and a collinear arrangement of functional groups located at the *N* position of facing phthalimide outer rings is described. The excellent singlet oxygen generation abilities of some members of the series proves them excellent candidates for photodynamic therapies.



Miguel A. Revuelta-Maza, Cormac Hally, Santi Nonell, Gema de la Torre, Tomás Torres**

Page No. – Page No.
Crosswise Phthalocyanines with Collinear Functionalization: New Paradigmatic Derivatives for Efficient Singlet Oxygen Photosensitization