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# A New Tool in the Quest for Biocompatible Phthalocyanines: Palladium Catalyzed Aminocarbonylation for Amide Substituted Phthalonitriles and Illustrative Phthalocyanines Thereof

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**Abstract:** The amide peptide bond type linkage is one of the most natural conjugations available, present in many biological synthons and pharmaceutical drugs. Hence, aiming the direct conjugation of potentially biologically active compounds to phthalocyanines, herein we disclose a new strategy for direct modulation of phthalonitriles, inspired by an attractive synthetic strategy for the preparation of carboxamides based on palladium-catalyzed aminocarbonylation of aryl halides in the presence of carbon monoxide (CO) which, to our knowledge, has never been used to prepare amide-substituted phthalonitriles, the natural precursors for the synthesis of phthalocyanines. Some examples of phthalocyanines prepared thereof are also reported, along with their full spectroscopic characterization and photophysical properties initial assessment.

**Keywords:** peptide bond; phthalonitriles; phthalocyanines; aminocarbonylation; palladium catalysts

## 1. Introduction

Molecules of the tetrapyrrole family (e.g., porphyrin and phthalocyanine derivatives) are probably the most appealing chromophores for a vast array of photoactivated processes, such as phototherapy [1–3], photodiagnosis [4–6], photocatalysis [7,8], solar energy conversion [9,10], and also as photomaterials [11–13]. In particular, phthalocyanines largely fulfil a crucial optical requisite, necessary for photomedicinal applications, which is a strong absorption in near-infrared (NIR) spectral region (600–900 nm), as light in this region affords the deepest penetration in soft tissue. These highly stable compounds, possessing high molar absorptivity, high quantum yields of fluorescence and structural versatility [4,13,14], can be conveniently modified to grant suitable biological solubility [15–18], by introduction of hydrophilic moieties in the structure. The majority of the moieties used so far are negatively charged, such as sulfonates or carboxylates [15,19] or positively charged, like quaternized amines [15,20]. These ionic features present some important drawbacks like low cellular uptake and/or cellular internalization, due to the negatively-charged character of the cell plasma membranes, in the case of anionic phthalocyanines [21], or exaggerated phospholipid affinity, leading to phospholipidosis, in the case of cationic phthalocyanines [22]. Thus, in the search for biocompatibility, the amide peptide bond type linkage is one of the most natural conjugations available, present in many biological synthons, such as peptides, proteins, or amino acids [23], as well in

pharmaceutical drugs [24,25]. Nevertheless, amide-substituted phthalocyanines are rare [26–35], when compared with other functionalities, including a few reports of phthalocyanines conjugated with amino acids [27–30] and peptides [31–35]. The main reason for the scarcity in phthalocyanine-amino acid conjugates arises from the difficult synthetic manipulation, which relies in troublesome transformations and purification procedures using highly polluting chemicals [25,27–30,36,37].

Apparently, phthalocyanine post-synthetic modulation would not be a very straightforward option, due to the chemical stability owned by phthalocyanines, which are quite stable against this type of structural variation. On the other hand, modification of precursory phthalonitriles bearing carboxylic acids is also demanding, given the sensitiveness of nitrile functions. It is worth mentioning that we have tested the strategies ourselves, to explain our points, and results were as described in the text. Whether in case of post-synthetic phthalocyanine modification or phthalonitrile modulation, no reproducible results could be obtained, always leading to cumbersome work-up approaches.

Palladium-catalyzed carbonylation reactions were first described by Heck almost 40 years ago [38]. Since then, many developments have been reported [6,39–46] and nowadays carbonylation has become an indispensable alternative to the classic organic synthesis of carbonyl compounds, including carboxylic acid derivatives (e.g., amides, esters) with valuable application in both industrial and fine chemistry. Among these reactions, aminocarbonylation [47–50], carried out using Ar–X substrates (X = I, Br, Cl, OTf, OTs, etc.), in the presence of *N*-nucleophiles, emerges as a sustainable, one-step synthetic approach, for the efficient, selective and mild synthesis of amides.

Herein we disclose a new strategy for direct modulation of phthalonitriles, inspired by an attractive synthetic strategy for the preparation of carboxamides based on optimized palladium-catalyzed aminocarbonylation of aryl halides in the presence of carbon monoxide (CO) [38,51] which, to our knowledge, has never been used to prepare amide-substituted phthalonitriles, the natural precursors for the synthesis of phthalocyanines. Furthermore, transformation thereof to the desired phthalocyanines is also described.

## 2. Results and Discussion

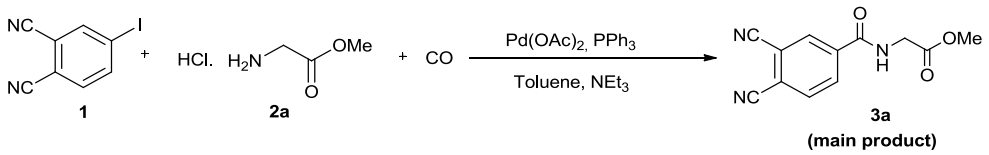
Modification of phthalonitriles is usually the chosen methodology when attempting to introduce significant changes at the phthalocyanine periphery, instead of phthalocyanine post-synthetic modulation [52], due to the known chemical stability owned by phthalocyanines. A conceivable example would be, for instance, to synthesize a phthalocyanine bearing peripheral four carboxylic acid groups, followed by acyl chloride formation, using a hazardous chlorinating agent, and then functionalization with an amine. The main issue regarding this strategy would be the proneness to form mixtures of mono-, di-, tri-, and tetra-amide substituted phthalocyanines requiring the use of excessive amounts of nucleophile, giving raise to cumbersome purification and low yields.

Our herein envisaged strategy uses 4-iodophthalonitrile (**1**) [53] as substrate and a range of amines as nucleophiles, in presence of a palladium catalyst formed in situ by addition of palladium(II) acetate to triphenylphosphine (in 1:2 molar ratio), together with $Et_3N$ as base and carbon monoxide as reagent (Table 1) [54,55]. Our studies began with the aminocarbonylation of 4-iodophthalonitrile (**1**) using glycine methyl ester hydrochloride (**2a**) as model nucleophile, to optimize reaction conditions (temperature, pressure of CO and time reaction parameters) in the palladium-catalyzed aminocarbonylation reaction (Table 1).

The first reaction conditions employed ($P_{CO}$ = 10 bar and T = 65 °C) (Table 1, entry 1) afforded only 25% substrate conversion, after 24 h. Then, we investigated the effect of increasing temperature, keeping the CO pressure at 10 bar, and it was found that, at 85 °C, the reaction proceeded faster, and full conversion of substrate **1** within 24 h was obtained (Table 1, entry 2). Keeping CO pressure at 10 bar and temperature at 85 °C, the reaction was not complete when reaction time was decreased to 12 h, reaching only 70% conversion of **1** (Table 1, entry 3). Conversely, when the reaction temperature was increased to 100 °C, keeping the pressure at 10 bar and reaction time at 12 h, substrate **1** was totally transformed into the desired amide (Table 1, entry 4). In addition, when the CO pressure was

reduced to 5 bar, keeping the temperature at 100 °C, after 12 h, the conversion of substrate **1** was >97% (Table 1, entry 5). However, keeping CO pressure at 5 bar and reducing the temperature to 65 °C, it required 70 h until full conversion of substrate **1** was observed (Table 1, entry 6). Thus, this indicates that the temperature plays the most important role on the activity of the catalyst. To evaluate the effect of solvent, an additional experiment was performed using DMF instead of toluene and, regardless of the high conversion obtained using the same conditions, this reaction yielded a complex mixture of products (Table 1, entry 7), as checked and compared using thin layer chromatography-TLC, which may be attributed to decomposition of DMF. Summing, it was found that a temperature of 100 °C, a CO pressure of 5 bar and a reaction time of 12 h were the optimal reaction parameters selected to extend the scope of 4-iodophthalonitrile functionalization.

**Table 1.** Optimization of reaction conditions [a].



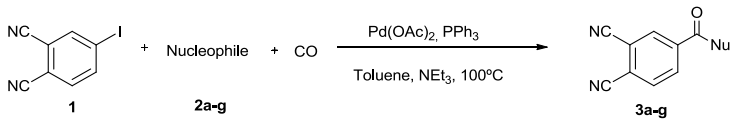

| Entry | Solvent | CO Pressure (bar) | Temperature (°C) | Time (h) | Conversion (%) [b] |
|---|---|---|---|---|---|
| **1** | toluene | 10 | 65 | 24 | 25 |
| **2** | toluene | 10 | 85 | 24 | >98 |
| **3** | toluene | 10 | 85 | 12 | 70 |
| **4** | toluene | 10 | 100 | 12 | >98 |
| **5** | toluene | 5 | 100 | 12 | >98 |
| **6** | toluene | 5 | 65 | 70 | >97 |
| **7** [c] | DMF | 5 | 100 | 12 | >98 |

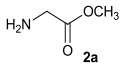
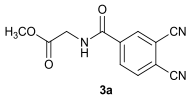
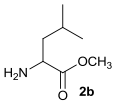
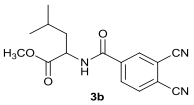
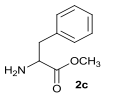
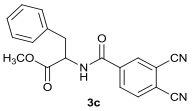
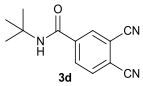
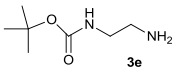
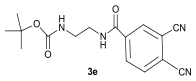
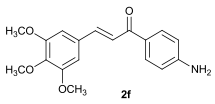
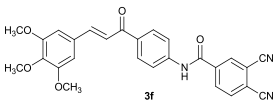
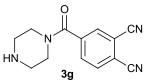
[a] General reaction conditions: 2.5 mol % $Pd(OAc)_2$, 5 mol % $PPh_3$, 8 equiv. $Et_3N$, 1.1 equiv. **2a**. [b] Substrate conversion determined by $^1$H-NMR on the reaction mixture obtained after evaporation of the solvent; [c] gave a complex mixture of products.

Hence, our next step was to promote the catalytic aminocarbonylation reaction between 4-iodophthalonitrile (**1**) with a wide range of amines as nucleophiles (**2a**–**2g**) to obtain the corresponding carboxamides (Table 2). Several structurally different amines as *N*-nucleophiles were used: three amino acid methyl esters (methyl glycinate (**2a**), methyl leucinate (**2b**) and methyl phenylalaninate (**2c**)), *tert*-butylamine (**2d**), *N*-BOC-ethylenediamine (**2e**), chalcone (*E*)-1-(4-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**2f**) [56], and piperazine (**2g**) (Table 2). Each reaction's progress was followed by TLC of aliquots taken from the reactor via *cannula*. After complete conversion of **1** to the corresponding carboxamides, the reaction mixture was then subjected to work-up and chromatographic purification procedures (See SI), yielding amide substituted phthalonitriles **3a**–**3g**, in good isolated yields (54–80%) at optimized reaction conditions (Table 2) (see also Figures S1–S21, SI).

When aminoesters were used as nucleophiles (**2a**–**2c**), 12 h were necessary for the complete conversion of the substrate, leading to carboxamides **3a**, **3b** and **3c** in 65%, 54%, and 59% isolated yields, respectively (Table 2, entries 1–3). It is worth mentioning that the yields obtained were higher than the ones reported for the model substrate iodobenzene using similar aminoesters as nucleophiles [57,58]. This may be attributed to the presence of cyano electron-withdrawing groups in 4-iodophthalonitrile, which enables an easier oxidative addition step in the catalytic cycle (A in Figure 1).

**Table 2.** Palladium catalyzed aminocarbonylation of 4-iodophthalonitrile using several amines as nucleophiles [a].




| Entry | Nucleophile (NuH) | Amine/(1) Ratio (equiv.) | Time (h) | Product | Yield (%) [b] |
|---|---|---|---|---|---|
| **1** |  **2a** | 1.1 | 12 |  **3a** | 65 |
| **2** |  **2b** | 1.1 | 12 |  **3b** | 54 |
| **3** |  **2c** | 1.1 | 12 |  **3c** | 59 |
| **4** |  **2d** | 3.3 | 4 |  **3d** | 74 |
| **5** |  **3e** | 1.2 | 3 |  **3e** | 80 |
| **6** |  **2f** | 1.2 | 25 |  **3f** | 70 |
| **7** |  **2g** | 6 | 7 |  **3g** | 77 |

[a] General reaction conditions: 5 bar (CO), 2.5 mol % $Pd(OAc)_2$, 5 mol % $PPh_3$, 8 equiv. $Et_3N$. Reactions were carried out in toluene (0.1 M, concerning substrate **1**). [b] Isolated yield.

Simpler aliphatic amines such as *tert*-butylamine (**2d**) were also used as nucleophiles. In this case, using 3.3 equivalents of **2d**, the aminocarbonylation reaction of **1** proceeded in the presence of palladium catalyst formed in situ by addition of palladium(II) acetate to triphenylphosphine (in 1:2 molar ratio), using toluene as solvent, under a CO pressure of 5 bar. Complete conversion of **1** was obtained in just 4 h, yielding carboxamide **3d** in 74% isolated yield (Table 2, entry 4).

Moreover, an *N*-mono-protected-ethylenediamine (**2e**) was also used. We had to prepare the mono-protected amine since, under the same reaction conditions, when unprotected ethylenediamine as nucleophile was used, a complex mixture of *N*-mono and *N,N'*-bis-substituted ethylenediamine, along with degradation products was formed, according to $^1$H-NMR analysis. To overcome this problem, we then prepared **2e**, using *tert*-butyloxycarbonyl protecting group (BOC group) following a literature procedure [59]. Next, we promoted the aminocarbonylation reaction of **1** with nucleophile *N*-BOC-ethylenediamine (**2e**), yielding **3e** in 80% isolated yield after just 3 h (Table 2, entry 5). Next, the aminocarbonylation of **1** with chalcone **2f**, which is a potential anti-microbial agent [60], yielded carboxamide **3f** in 70% isolated yield, under standard reaction conditions, after 25 h (Table 2, entry 6). Since the chalcone is an aromatic amine, it is expected to be less nucleophilic and, consequently

a prolonged period of time was necessary for the complete conversion of the substrate **1** into the corresponding carboxamide.

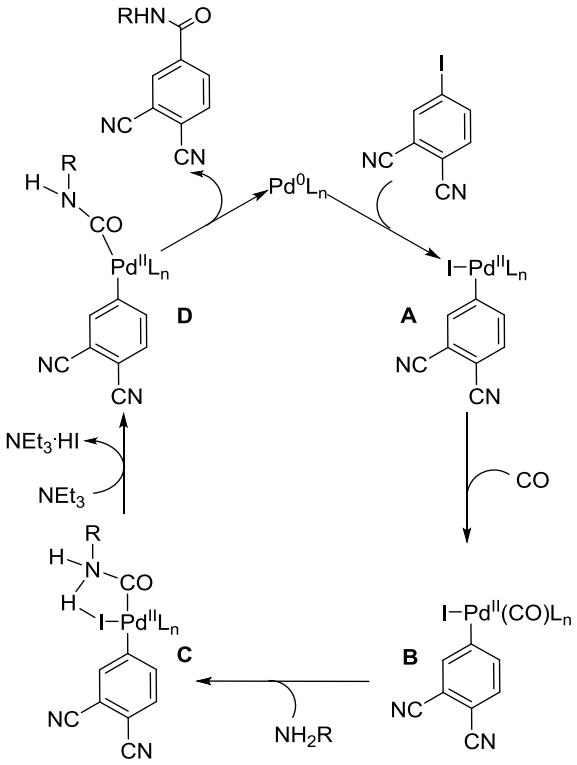



**Figure 1.** Simplified catalytic cycle describing the formation of 4-amide substituted phthalonitriles. L = $PPh_3$.

Using similar conditions, we also investigated the use of cyclic diamines in the palladium catalyzed aminocarbonylation reaction for the synthesis of *N*-mono-substituted diamines. Unprotected diamine piperazine (**2g**) is quite useful and interesting because the presence of two amine groups could enable the conjugation with bioactive molecules or functionalization with other relevant chemical groups. In order to attain the desired *N*-mono-substituted diamine we have selected an excess of 6 equiv. of the diamine **2g**. In the presence of palladium catalyst formed in situ by addition of palladium(II) acetate to triphenylphosphine (in 1:2 molar ratio), together with $Et_3N$ as base in toluene solvent, under a CO pressure of 5 bar, complete conversion of **1** was obtained, after 7 h, yielding carboxamide **3g** after work-up and purification in 77% isolated yield (Table 2, entry 7).

According to previously described [49,51,61–64], a simplified mechanism for the formation of 4-amide substituted phthalonitrile is proposed in Figure 1. The catalytic cycle begins with the oxidative addition of the in situ formed Pd(0)$L_n$ active species to the 4-iodophthalonitrile, resulting in an arylpalladium(II) intermediate **A**, which is able to coordinate to carbon monoxide, leading to intermediate **B**. Then, this complex undergoes a nucleophilic attack by the desired amine (*N*-nucleophile), affording **C**. Through HI elimination with the aid of $Et_3N$, intermediate **D** is formed, yielding the desired 4-amide substituted phthalonitrile, upon reductive elimination.

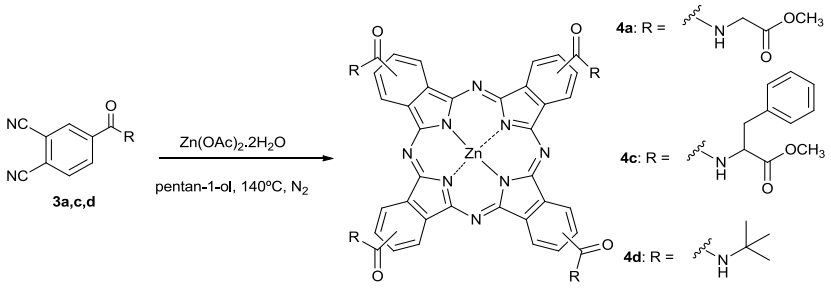
All carboxamide substituted phthalonitriles were characterized by $^1H$, $^{13}C$-NMR and mass spectrometry and their structures confirmed. It is worth mentioning that, under the reaction conditions employed (100 °C and 5 bar), 100% chemoselectivity toward the mono-carboxamide products was obtained, since no double carbon monoxide insertion product was observed, using these amines as nucleophiles [55,65].

Having established a methodology for the synthesis of several carboxamide-containing phthalonitriles **3a**–**3g**, we have then prepared, as selected examples, phthalocyanines **4a**, **4c**, and **4d**,

starting from the corresponding phthalonitriles **3a**, **3c**, and **3d** (Table 3) (see also Figures S22–S27, SI). We have used an approach where the tetramerization of the phthalonitriles was carried out in pentan-1-ol at 140 °C, in the presence of zinc(II) acetate, for 20 h, with all reactions progress being followed by TLC and UV–VIS spectroscopy. Phthalocyanines **4a**, **4c** and **4d** were obtained, after purification and isolation by column chromatography on silica gel, in 58, 65 and 68% yields, respectively.

We have observed that the purification procedure for phthalocyanines **4a** and **4c** was considerably more demanding than for phthalocyanine **4d**. We have found that, even after repeated recrystallization from methanol/diethyl ether, pentan-1-ol remained coordinated with the waxy phthalocyanine molecules **4a** and **4c**, as observable on their corresponding $^1$H-NMR spectra. On the other hand, solid phthalocyanine **4d**, bearing *tert*-butyl carboxamide groups, was easily recrystallized from methanol. We assume this occurrence to the nature of the carboxamide substituent, as amino acid derivatives are more prone to establish interactions with alcohol molecules, in our case pentan-1-ol [66,67]. This was also corroborated by the elemental analysis of **4a** and **4c**, which agreed with the presence of two molecules of pentan-1-ol per molecule of phthalocyanine. All the other typical metallophthalocyanine characteristics in terms of $^1$H-NMR, mass spectrometry and UV–VIS spectroscopy were met, in agreement with the structures.

**Table 3.** Synthesis of zinc (II) metallophthalocyanines **4a**, **4c**, and **4d** and their spectral fundamental/excited state properties, studied in THF.




| Compound | Isolated Yield (%) | $\lambda_{max}$ (nm) (log ε) | Stokes Shift $\Delta_{stokes}$ (nm) | Emission $\lambda_{max}$ (nm) | $\Phi_F$ [a] |
|---|---|---|---|---|---|
| **4a** | 58 | 350 (4.52); 611 (4.22); 676 (4.87) | 9 | 685 | 0.26 |
| **4c** | 65 | 350 (4.14); 610 (3.81); 675 (4.48) | 11 | 686 | 0.31 |
| **4d** | 68 | 351 (4.41); 610 (4.49); 676 (5.10) | 9 | 685 | 0.38 |

[a] Relative to unsubstituted ZnPc in DMSO (ΦF = 0.18) [68].

Initial photophysical assessment was carried out for the synthesized metallophthalocyanines. Absorption, emission and fluorescence quantum yields for the phthalocyanines **4a**, **4c**, and **4d** were recorded, using THF as solvent and the results are presented in Table 3.

The electronic absorption spectra of **4a**, **4c**, and **4d**, whose values of molar absorptivity coefficients (ε) are in the typical of range for zinc(II) metallophthalocyanines (Table 3), showed monomeric behavior evidenced by a single and sharp Q band, typical of non-aggregated metallated phthalocyanine complexes, with a maximum at respectively 676, 675 and 676 nm in THF, and a Soret band (the B-band) being observed at around 350 nm, as shown in Table 3 and Figure 2a. The B-bands are broad due to the superimposition of the $B_1$ and $B_2$ bands in the 350 nm region. Moreover, the absorption spectra, Figure 2a, shows that the introduction of the different substituents at the periphery of the phthalocyanine, does not disturb the UV–VIS spectrum, since the absorption bands maximum are similar.

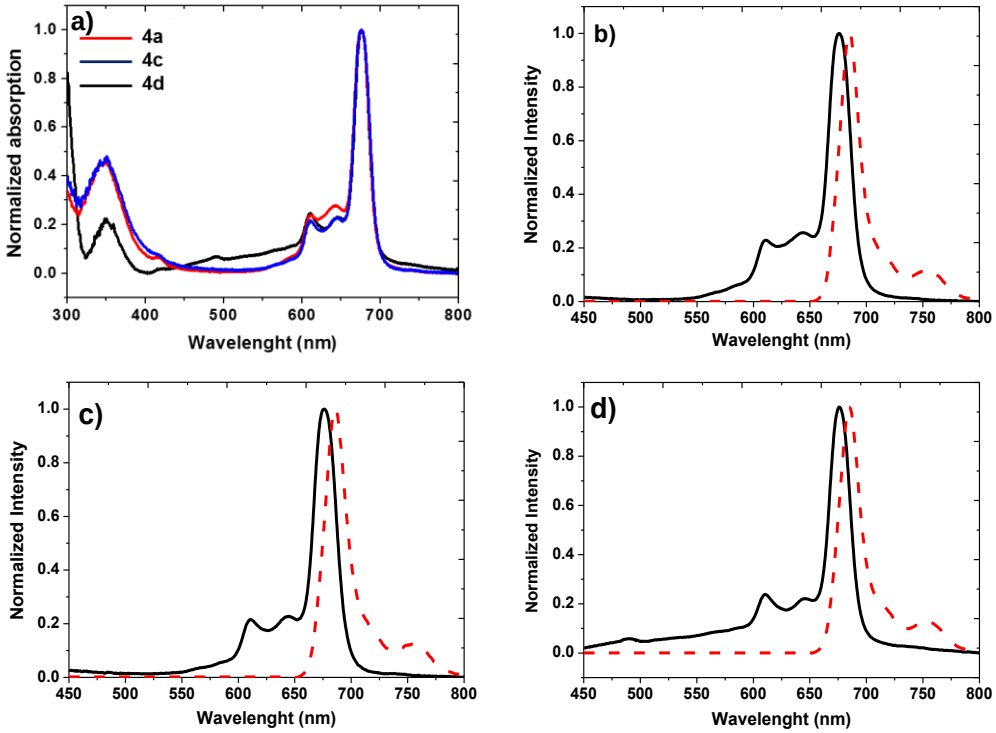



**Figure 2.** UV–VIS spectra of metallophthalocyanines **4a, 4c**, and **4d** in THF (**a**); normalized UV–Vis of studied phthalocyanines with absorption (black solid line) and emission spectra (red dashed line) in THF of: Zn(II)-**4a** (**b**); Zn(II)-**4c** (**c**); Zn(II)-**4d** (**d**). Fluorescence quantum yields ($\Phi_F$) of the zinc phthalocyanines **4a** and **4c–d,** are presented in Table 3, were determined by the comparative method (Equation (1)) using the unsubstituted Zn phthalocyanine in DMSO as standard ($\Phi_F$ = 0.18) [68], and both the samples and the standard were excited at the same wavelength (640 nm). The $\Phi_F$ were calculated as 0.26, 0.31 and 0.38 for **4a**, **4c** and **4d**, respectively. The $\Phi_F$ value of zinc phthalocyanine complexes functionalized with the amino acid esters **4a** and **4c** have the same order of magnitude ($\Phi_F$ = 0.26–0.31) and are lower than non-biocompatible zinc phthalocyanine **4d** ($\Phi_F$ = 0.38).

The steady-state fluorescence emission spectra of the compounds in THF are shown in Figure 2 and the related data were listed with Stokes shifts in Table 3. Upon excitation at 640 nm, **4a**, **4c**, and **4d** showed fluorescence emission at 685, 686, and 685 nm, respectively. Again, and as expected, the fluorescence emission spectra of all phthalocyanines were similar, as all zinc metal complexes have maximum emission at the same wavelength ($\lambda_{max}$ = 685–686 nm). It should be noted that the absorption spectra of all phthalocyanines were mirror images of the fluorescent spectra in THF, and that the emission is observed in the region of NIR, a pre-requisite for applications in fluorescence imaging within the important therapeutic window (λ = 650–900 nm) [2,5,69]. The observed Stokes shifts, were within the region ≈9–11 nm are typical of β-substituted phthalocyanines, which is a consequence of the rigidity of the macrocyclic ligand [70].

## 3. Experimental

### *3.1. Materials and Methods*

Commercially available reagents were purchased from Aldrich (Lisbon, Portugal) and Fluorochem (Derbyshire, UK) and used as received. All solvents were pre-dried according to standard laboratory techniques. UV–VIS absorption spectra were recorded on *a Hitachi U-2010* (Hitachi Corporation, Tokyo, Japan) using quartz cells. The molar absorption coefficients were determined using THF as solvent. The fluorescence spectra for the determination of fluorescence quantum yields were acquired on a Spex Fluorolog 3 spectrofluorimeter (Horiba Instruments Incorporated, Edison, NJ, USA). $^{1}$H and $^{13}$C-NMR

spectra were recorded on a *Bruker Advance III* spectrometer (Bruker, Karlsruhe, Germany) (400.13 for $^{1}$H, and 100.61 MHz for $^{13}$C). Chemical shifts for $^{1}$H and $^{13}$C are expressed in ppm, relatively to an internal pattern of TMS. The MALDI-TOF mass spectra were acquired using a Bruker Daltonics Flex Analysis apparatus (Bruker, Madrid, Spain). High-resolution mass spectrometry analysis was carried out with a Bruker Microtof apparatus (Bruker, Madrid, Spain), equipped with selective ESI detector. Elemental analyses were acquired using a FISONS model EA 1108 (Thermo Scientific, Waltham, MA, USA). Column chromatography was performed with silica gel grade 60, 70–230 mesh. 4-Iodophthalonitrile (**1**) was prepared according to the literature procedure [53] starting from 4-nitrophthalonitrile. The nucleophiles (*E*)-1-(4-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**2f**) [56] and *N*-BOC-ethylenediamine (**2e**) [59] were prepared as described in the literature.

Fluorescence quantum yields ($\Phi_F$) were determined in DMSO using a comparative method with the Equation (1), using unsubstituted zinc(II) phthalocyanine (ZnPc) in DMSO ($\Phi$ = 0.18)[68] as standard:

$$\Phi_F = \Phi_F{}^{Std} \frac{F\ A_{Std}\ \eta^2}{F_{Std}\ A\ \eta_{Std}{}^2} \quad (1)$$

where F and $F_{Std}$ are the areas under the fluorescence curves of the samples and the standard, respectively; A and $A_{Std}$ are the corresponding absorbances of the samples and standard at the excitation wavelengths, respectively; $\eta^2$ and $\eta^2_{Std}$ are the refractive indices of solvents used for the sample and standard, respectively. The absorbance of the solutions at the excitation wavelength was around 0.1.

### *3.2. General Procedure for Synthesis of CARBOXAMIDE Substituted Phthalonitriles* **3a–g**

In a typical aminocarbonylation reaction, the catalyst precursor $Pd(OAc)_2$, triphenylphosphine ($PPh_3$) ligand, substrate 4-iodophthalonitrile and the nucleophile were directly introduced in a high pressure reactor having a magnetic stirrer inside. The reactor was sealed and three vacuum/CO gas cycles were performed. Under vacuum, the reaction solvent was then added (toluene) via cannula, followed by triethylamine as base. The reactor was then pressurized using 5 bar CO and the reaction mixture maintained at 100 °C for the required period of time. After this period, the reactor was cooled to room temperature and depressurized. Palladium particles were filtered, the solvent rotary evaporated, and the crude product was then purified according to the corresponding procedure. All new compounds were characterized by means of $^{1}$H-, $^{13}$C-NMR, and mass spectrometry and presented in ESI.

Methyl 2-(3,4-dicyanobenzamido)acetate (glycine substituted phthalonitrile) (**3a**). Following the above described procedure, 6.75 mg (0.030 mmol) of $Pd(OAc)_2$, 15.74 mg (0.060 mmol) of $PPh_3$, 300 mg (1.18 mmol) of 4-iodophthalonitrile, 163.4 mg (1.30 mmol) glycine methyl ester hydrochloride (**2a**), and 1.1 mL $Et_3N$ were dissolved in 10 mL of toluene. The reaction was pressurized and maintained at 100 °C for 12 h. The residue was dissolved in dichloromethane (20 mL), washed with brine (3 × 20 mL) and water (3 × 20 mL). The organic phase was dried with sodium sulfate and the solvent evaporated. The product was purified by recrystallization with ethyl acetate/*n*-hexane yielding **3a** in 65% yield (158 mg). $^{1}$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 8.26 (s, 1H), 8.15 (d, $J$ = 8.1 Hz, 1H), 7.93 (d, $J$ = 8.1 Hz, 1H), 6.77 (s, 1H), 4.27 (d, $J$ = 4.9 Hz, 2H), 3.84 (s, 9H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 170.0, 163.7, 138.4, 134.1, 132.4, 131.6, 118.6, 116.9, 114.8, 114.7, 53.0, 42.1. HRMS (ESI-TOF) $m/z$ calcd for $[M + Na]^+$: $C_{12}H_9N_3NaO_3$ 266.0536; found 266.0532.

(S)-Methyl 2-(3,4-dicyanobenzamido)-4-methylpentanoate (leucine substituted phthalonitrile) (**3b**). Following the above described procedure, 6.75 mg (0.030 mmol) of $Pd(OAc)_2$, 15.74 mg (0.06 mmol) of $PPh_3$, 300 mg (1.18 mmol) of 4-iodophthalonitrile, 236.6 mg (1.30 mmol) leucine methyl ester hydrochloride (**2b**) and 1.1 mL $Et_3N$ were dissolved in 10 mL toluene. The reaction was pressurized and maintained at 100 °C for 12 h. The residue was dissolved in dichloromethane (20 mL), washed with brine (3 × 20 mL) and water (3 × 20 mL).The organic phase was dried with sodium sulfate and the solvent evaporated. The product (**3b**) was purified by column chromatography on

silica gel (stationary phase) first using chloroform and then a mixture of chloroform/ethyl acetate (20/1) and obtained in 54% yield (120 mg), after being washed with *n*-hexane. $^{1}$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 8.24 (d, $J$ = 8.1 Hz, 1H), 8.14 (dd, $J$ = 1.7 Hz, $J$ = 8.1 Hz, 1H), 7.91 (d, $J$ = 8.1 Hz, 1H), 6.77 (br s, 1H), 4.86–4.80 (m, 1H), 3.79 (s, 3H), 1.80–1.66 (2 m, 3H), 1.00–0.97 (m, 6H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 173.4, 163.5, 138.6, 134.1, 132.4, 131.9, 118.3, 116.6, 114.9, 52.9, 51.8, 41.6, 25.1, 22.9, 22.0. HRMS (ESI-TOF) $m/z$ calcd for $[M + Na]^+$: $C_{16}H_{17}N_3NaO_3$ 322.1162; found 322.1153.

(S)-Methyl 2-(3,4-dicyanobenzamido)-3-phenylpropanoate (phenyl alanine substituted phthalonitrile) (**3c**). Following the above described procedure, 6.75 mg (0.030 mmol) of $Pd(OAc)_2$, 15.74 mg (0.06 mmol) of $PPh_3$, 300 mg (1.18 mmol) of 4-iodophthalonitrile, 280.4 mg (1.30 mmol) phenyl alanine methyl ester hydrochloride (**2c**) and 1.1 mL $Et_3N$ were dissolved in 10 mL toluene. The reaction was pressurized and maintained at 100 °C for 12 h. The residue was dissolved in dichloromethane (20 mL), washed with brine (3 × 20 mL) and water (3 × 20 mL). The organic phase was dried with sodium sulfate and the solvent evaporated. The product (**3c**) was purified by column chromatography on silica gel (stationary phase) first using chloroform and then a mixture of chloroform/ethyl acetate (10/1) and obtained in 59.0% yield (192 mg), after being washed with *n*-hexane. $^{1}$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J$ = 1.7 Hz, 1H), 8.00 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.88 (d, $J$ = 8.1 Hz, 1H), 7.30–7.29 (m, 3H), 7.10–7.08 (m, 2H), 6.64 (br s, 1H), 5.09–5.04 (m, 1H), 3.82 (s, 3H), 3.34–3.21 (m, 2H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 171.7, 163.3, 138.6, 135.4, 134.1, 132.4, 131.6, 129.3, 128.9, 127.6, 118.4, 116.6, 114.8, 114.8, 54.0, 52.9, 37.7. HRMS (ESI-TOF) $m/z$ calcd for $[M + Na]^+$: $C_{19}H_{15}N_3NaO_3$ 356.1003; found 356.1006.

N-Tert-butyl-3,4-dicyanobenzamide (**3d**). Following the above described procedure, 4.4 mg (0.020 mmol) of $Pd(OAc)_2$, 10.5 mg (0.040 mmol) of $PPh_3$, 200 mg (0.79 mmol) of 4-iodophthalonitrile, 0.28 mL (2.6 mmol) of *tert*-butyl amine (**2d**) and 0.8 mL $Et_3N$ were dissolved in 6 mL of toluene. The reaction was pressurized and maintained at 100 °C for 4 h. The residue was dissolved in dichloromethane (20 mL), washed with brine (3 × 20 mL) and water (3 × 20 mL). The organic phase was dried with sodium sulfate and the solvent evaporated. The product (**3d**) was purified by column chromatography on silica gel (stationary phase) using a mixture of dichloromethane/ethyl acetate (20/1) and obtained in 74% yield (132.9 mg). $^{1}$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 8.14 (bs, 1H), 8.06 (d, $J$ = 8.1 Hz, 1H), 7.88 (d, $J$ = 8.1 Hz, 1H), 5.94 (br s, 1H), 1.49 (s, 9H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 163.1, 140.6, 134.0, 132.1, 131.6, 117.8, 116.4, 115.0, 53.0, 28.8. HRMS (EI) $m/z$ calcd for $[M]^+$: $C_{13}H_{13}N_3O$ 227.1059; found: 227.1060.

N-BOC-Ethylenediamine-3,4-dicyanobenzamide (**3e**). Following the above described procedure, 4.4 mg (0.020 mmol) of $Pd(OAc)_2$, 10.5 mg (0.040 mmol) of $PPh_3$, 200 mg (0.79 mmol) of 4-iodophthalonitrile, 151 mg (0.94 mmol) of *N*-BOC-ethylenediamine (**2e**) and 0.8 mL $Et_3N$ were dissolved in 6 mL toluene. The reaction was pressurized and maintained at 100 °C for 3 h. The product (**3e**) precipitated in the middle of the reaction and then was washed with *n*-hexane and obtained in 80% yield (198.5 mg). $^{1}$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 8.31 (sl, 1H), 8.21 (dd, $J$ = 8.1, 1.1 Hz, 1H), 8.17 (br s, 1H), 7.89 (d, $J$ = 8.1 Hz, 1H), 5.18 (br s, 1H), 3.56–3.53 (m, 2H), 3.43–3.41 (m, 2H), 1.43 (s, 9H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 163.6, 158.7, 138.9, 133.9, 132.4, 131.7, 117.9, 116.4, 115.0, 114.9, 80.9, 43.6, 39.7, 28.4. HRMS (ESI-TOF) $m/z$ calcd for $[M + H]^+$: $C_{16}H_{18}N_4NaO_3$ 337.1271; found 337.1271.

(E)-3,4-Dicyano-N-(4-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl)benzamide (**3f**). Following the above described procedure, 4.4 mg (0.020 mmol) of $Pd(OAc)_2$, 10.5 mg (0.040 mmol) of $PPh_3$, 200 mg (0.79 mmol) of 4-iodophthalonitrile, 296 mg (0.94 mmol) of (*E*)-1-(4-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**2f**), and 0.8 mL $Et_3N$ were dissolved in 6 mL toluene. The reaction was pressurized and maintained at 100 °C for 25 h. The product (**3f**) precipitated in the middle of reaction and was washed with methanol and cyclohexane and obtained in 70% yield (256 mg). $^{1}$H-NMR (400.13 MHz, acetone-$d_6$) $\delta$ 10.23 (s, 1H), 8.64 (d, $J$ = 1.5 Hz, 1H), 8.51 (dd, $J$ = 8.2, 1.6 Hz, 1H), 8.26 (d, $J$ = 8.2 Hz, 1H), 8.18 (d, $J$ = 8.7 Hz, 2H), 8.01 (d, $J$ = 8.7 Hz, 2H), 7.84 (d, $J$ = 15.5 Hz, 1H), 7.73 (d, $J$ = 15.5 Hz, 1H), 7.19 (s, 2H), 3.91 (s, 6H), 3.79 (s, 3H). $^{13}$C-NMR (100.61 MHz, acetone-$d_6$) $\delta$188.7, 163.9,

154.9, 145.3, 143.8, 141.8, 140.6, 135.4, 133.9, 133.8, 131.8, 130.7, 122.1, 120.8, 120.7, 118.9, 117.0, 116.3, 107.4, 60.9, 56.8. HRMS (ESI-TOF) $m/z$ calcd for $[M]^+$: $C_{27}H_{21}N_3O_5$ 468.1554; found 468.1555.

N-Piperazine-3,4-dicyanobenzamide (**3g**). Following the above described procedure, 4.4 mg (0.020 mmol) of $Pd(OAc)_2$, 10.5 mg (0.040 mmol) of $PPh_3$, 200 mg (0.79 mmol) of 4-iodophthalonitrile, 407 mg (4.72 mmol) piperazine (**2g**), and 0.8 mL $Et_3N$ were dissolved in 6 mL toluene. The reaction was pressurized and maintained at 100 °C for 7 h. The product (**3g**) was purified by column chromatography on silica gel (stationary phase) using ethanol as eluent and obtained in 77% yield (146 mg). $^1$H-NMR (400.13 MHz, $CDCl_3$) $\delta$ 7.87 (d, $J$ = 8.0 Hz, 1H), 7.83 (d, $J$ = 1.3 Hz, 1H), 7.75 (dd, $J$ = 8.0, 1.3 Hz, 1H), 3.75 (s, 2H), 3.32 (s, 2H), 2.90 (d, $J$ = 49.8 Hz, 4H). $^{13}$C-NMR (100.61 MHz, $CDCl_3$) $\delta$ 166.1, 141.1, 134.0, 132.2, 131.7, 116.8, 116.7, 114.9, 114.8, 49.01, 46.6, 45.9, 43.6. HRMS (ESI-TOF) $m/z$ calcd for $[M + H]^+$: $C_{13}H_{13}N_4O$ 241.1084; found 241.1081.

### *3.3. General Procedure for Synthesis of Carboxamide Substituted Phthalocyanines*

In a typical experiment, the desired phthalonitrile and $Zn(OAc)_2{\cdot}2H_2O$ were dissolved in high boiling solvent pentan-1-ol and the mixture heated to reflux temperature for the required time for total consumption of the substrate (checked by TLC) under nitrogen atmosphere. After distilling off most of the solvent, the mixture was cooled to room temperature, and *n*-hexane was added to precipitate the crude compound. The solid was filtered, washed with water and purified according to the corresponding procedure. All new compounds were characterized by means of $^1$H-NMR, UV–VIS, fluorescence and mass spectrometry and presented in ESI.

2(3)-Tetra-(keto-N-glycinyl) phthalocyaninato zinc(II) (**4a**). Following the procedure described above, 100 mg of phthalonitrile **3a** (0.41 mmol) and 29.7 mg $Zn(OAc)_2{\cdot}2H_2O$ (0.14 mmol) were dissolved in 1 mL of pentan-1-ol. The mixture was heated to 140 °C and stirred for 20 h. After workup procedure, the zinc(II) phthalocyanine complex **4a** was purified by column chromatography on silica gel first using dichloromethane/ethyl acetate (1/1) and then a mixture of dichloromethane/ethanol (20/1) as eluent to obtain 62 mg of **4a** (58% yield), as a waxy dark blue solid. UV–VIS (THF) $\lambda_{max}$ (log $\varepsilon$) 350 (4.52), 611 (4.22), 676 (4.87). $^1$H-NMR (400.13 MHz, acetone-$d_6$, 30 °C) $\delta$ 8.46 (br s, 4H), 8.34 (d, $J$ = 7.7 Hz, 4H), 8.29 (s, 4H), 7.94 (d, $J$ = 7.7 Hz, 4H), 4.04–3.94 (m, 8H), 2.76 (s, 12H). MS (MALDI-TOF-INFUSION) $m/z$ calcd for $[M + Li]^+$: $C_{48}H_{36}N_{12}O_{12}LiZn$ 1043.2023; found 1043.2050. EA calcd for $C_{48}H_{36}N_{12}O_{12}Zn{\cdot}2C_5H_{12}O{\cdot}2H_2O$ C, 55.70; H, 5.16; N, 13.44; found C, 55.55; H, 5.35; N, 13.50.

(*S*,*S*,*S*,*S*)-2(3)-Tetra-(keto-*N*-phenyl alaninyl) phthalocyaninato zinc(II) (**4c**). Following the procedure described above, 45 mg of phthalonitrile **3c** (0.14 mmol) and 11 mg $Zn(OAc)_2{\cdot}2H_2O$ (0.05 mmol) were dissolved in 0.5 mL of pentan-1-ol. The mixture was heated to 140 °C and stirred for 20 h. After workup procedure, the zinc(II) phthalocyanine complex **4c** was purified by column chromatography on silica gel first using dichloromethane/ethyl acetate (5/1) and then a mixture of dichloromethane/ethanol (20/1) as eluent to obtain 32 mg of **4c** (65% yield), as a waxy dark blue solid. UV–VIS (THF) $\lambda_{max}$ (log $\varepsilon$) 350 (4.14), 610 (3.81), 675 (4.48). $^1$H-NMR (400.13 MHz, acetone-$d_6$) $\delta$ 8.34 (br s, 4H), 8.24 (d, $J$ = 7.8 Hz 4H), 8.20 (s, 4H), 7.89 (d, $J$ = 7.7 Hz, 4H), 7.27 (2m, 20H), 4.93 (m, 4H), 3.31 (m, 4H), 3.19 (m, 4H), 2.86 (s, 12H). MS (ESI-TOF-INFUSION) $m/z$ calcd for $[M]^+$: $C_{76}H_{60}N_{12}O_{12}Zn$ 1396.3745; found 1396.3754. EA calcd for $C_{76}H_{60}N_{12}O_{12}Zn{\cdot}2C_5H_{12}O{\cdot}H_2O$ C, 64.84; H, 5.44; N, 10.55; found C, 64.59; H, 5.75; N, 10.83.

2(3)-Tetra-(tert-butyl-carboxamidyl) phthalocyaninato zinc(II) (**4d**). Following the procedure described above, 100 mg of phthalonitrile **3d** (0.44 mmol) and 32.9 mg $Zn(OAc)_2{\cdot}2H_2O$ (0.15 mmol) were dissolved in 0.5 mL of pentan-1-ol. The mixture was heated to 140 °C and stirred for 20 h. After workup procedure, the zinc(II) phthalocyanine complex (**4d**) was purified by column chromatography on silica gel using a mixture dichloromethane/methanol (20/1) as eluent to obtain 74 mg of (**4d**) (68% yield) as a dark blue solid, after recrystallization from methanol. UV–VIS (THF) $\lambda_{max}$ (log $\varepsilon$) 351 (4.41), 610 (4.49), 676 (5.10). $^1$H-NMR (400.13 MHz, acetone-$d_6$) $\delta$ 8.26–8.20 (br s, 8H), 7.88–7.86 (br s, 4H), 7.58 (s, 4H), 1.48 (sl, 36H). MS (MALDI-TOF) $m/z$ calcd for $[M]^+$: $C_{52}H_{52}N_{12}O_4Zn$ 972.3; found 972.3;

$[M + Na]^+$, $m/z$: 995.3. EA calcd for $C_{52}H_{52}N_{12}O_4Zn{\cdot}2H_2O$ C, 61.81; H, 5.59; N, 16.63; found C, 62.06; H, 5.50; N, 16.43.

## 4. Conclusions

In conclusion, we have established a straightforward methodology to prepare carboxamide substituted phthalonitriles, using the well-known palladium-catalyzed aminocarbonylation of aryl halides in the presence of carbon monoxide (CO) to our advantage. In virtue of this direct modification of phthalonitriles, a more accessible preparation of biocompatible phthalocyanines is, hence, achieved. Current efforts are being devoted to extending the methodology to other phthalonitriles and phthalocyanines thereof. Initial assessment of the photophysical properties led us to conclude that this type of phthalocyanines may be usable in medicinal applications, namely optical fluorescence imaging, given the high fluorescence quantum yields ($\Phi_F$ = 0.31 for biocompatible amino acid ester substituted phthalocyanine **4c**) and acceptable Stokes shifts.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-4344/8/10/480/s1, 1. Experimental procedures for the synthesis of phthalonitriles **3a–g** and copies of 1H, 13C NMR and Mass Spectra, 2. Experimental procedures for the synthesis of phthalocyanines and copies of 1H NMR and Mass Spectra.

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