

# An efficient two-step synthesis of metal-free phthalocyanines using a Zn(II) template†

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A new family of cationic phthalocyanines containing four guanidinium groups was synthesized in pyridine–HCl at 120 °C; under these conditions zinc was removed from both the starting materials and products to reveal a new synthetic route to metal-free phthalocyanines.

Initially observed as unexpected byproducts,<sup>1,2</sup> an astonishing  $5 \times 10^{10}$  g of phthalocyanines (Pcs) and metallophthalocyanines are now synthesized per year.<sup>3</sup> Their remarkable photophysical properties and extreme chemical, thermal, and photostability make Pcs ideal dyestuffs and useful components of synthetic catalysts, photovoltaic devices, chemical sensors and data storage devices.<sup>4–6</sup> Pcs also have interesting *in vivo* applications as tattoo inks and sensitizers for photodynamic therapy.<sup>7</sup>

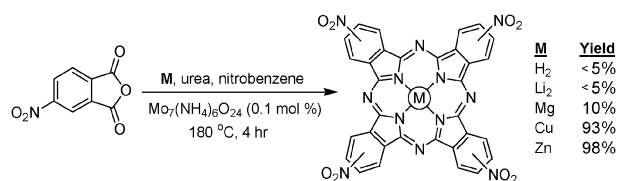
Phthalocyanines are prepared by high-temperature cyclotetramerization of phthalic acid or dicyano derivatives.<sup>4–12</sup> Metal ion templates can dramatically enhance the yields of these reactions.<sup>4,6,8–10</sup> To illustrate this effect, the cyclotetramerization of 4-nitrophthalic anhydride was conducted in the presence or absence of Li(I), Mg(II), Cu(II), or Zn(II) using a modified Wyler procedure.<sup>9</sup> Poor yields were obtained in the presence of LiCl and MgCl<sub>2</sub>, or in the absence of template, while near-quantitative yields were obtained in the presence of Cu(II) and Zn(II) (Scheme 1).† It is well known that strongly coordinating ions like Mn(II), Fe(II), Co(II), Cu(II), Ni(II), Cu(II), and Zn(II) can dramatically improve the yields of such reactions, but their subsequent removal is thought to be difficult or even impossible without destruction of the Pc itself.<sup>8,10a</sup> Indeed, previous attempts to remove Zn(II) using strong acids resulted in Pc decomposition, and no examples of Zn(II) demetallation are found in the literature.<sup>11</sup>

Metal-free phthalocyanines are normally prepared by heating dicyano or diiminoisindoline precursors in a high-boiling solvent and strong base. While these reactions can, in some cases, furnish metal-free products in good to moderate yields,<sup>12</sup> isolated yields ranging from 10 to 30% are also very common.<sup>13</sup> Recently, inexpensive phthalic anhydride and phthalimide precursors have been utilized for metal-free Pc syntheses in yields ranging from 20 to 60% by heating a mixture of hexamethyldisilazane, DMF, *p*-toluenesulfonic acid, and water at 150 °C.<sup>14</sup> During our synthesis of guanidinium-

containing phthalocyanines we discovered a new demetallation reaction that, together with the effective templating effects of Zn(II), provides a new high-yielding route to metal-free phthalocyanines.

As part of our program aimed at developing new high-affinity G-quadruplex ligands, we became interested in the synthesis of cationic phthalocyanines containing guanidinium groups. This design was motivated by the impressive translocation properties of oligo- and poly-guanidino peptides,<sup>15</sup> and by the improved cellular uptake and enhanced RNA affinity of guanidinium-containing small molecules as compared to analogous ammonium-containing compounds.<sup>16</sup> Guanidino phthalocyanines (GPcs) were synthesized by reacting a known tetraamino-zinc-phthalocyanine (**2**)<sup>17</sup> with various carbodiimides in a pyridine–HCl ionic liquid (4 : 1 molar ratio) at 120 °C (Scheme 2).† Under these relatively mild and neutral reaction conditions, Zn(II) was removed to furnish the metal-free GPcs **3–5** in isolated yields of 70–83%. The metal-free products **3–5** were characterized by UV-vis spectroscopy, RP HPLC, high resolution ESI MS, and <sup>1</sup>H NMR. All analytical data were consistent with the complete removal of zinc during these reactions.† At first glance, we suspected that the combined electron-withdrawing effects of four guanidinium groups might facilitate Zn(II) removal, but under these conditions, demetallation was independent of the substituents on the Pcs.

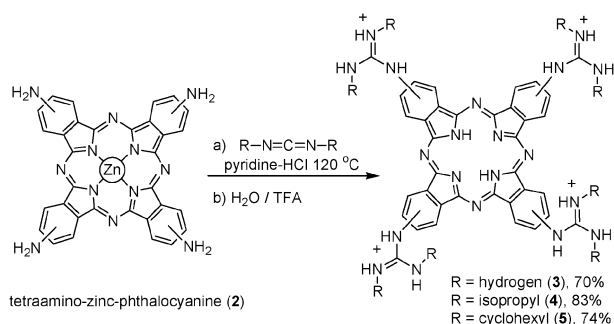
To gauge the scope of this new demetallation reaction, a variety of electron rich, electron poor, and unsubstituted phthalocyanines were heated in pyridine–HCl (4 : 1 molar ratio, lacking any carbodiimide) at 120 °C.† For all substrates tested, Zn(II) demetallation generated the metal-free phthalocyanines in high yield (Schemes 3 and 4). Other strongly coordinated metal ions including Cu(II), Co(II), Ni(II), and Pd(II) were not removed under these conditions even when electron deficient GPcs were used (Scheme 3).<sup>18</sup> The Zn(II) selectivity of these reactions might be explained by the formation of a ternary pyridine–Pc–Zn complex with square pyramidal zinc coordination and a non-planar, dome-shaped macrocycle prior to demetallation.<sup>19</sup>



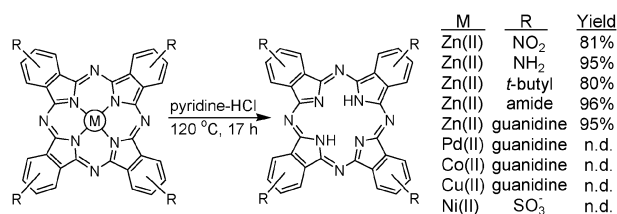
**Scheme 1** Isolated yields for phthalocyanines formed in the presence or absence of LiCl, MgCl<sub>2</sub>, CuCl<sub>2</sub>, or ZnCl<sub>2</sub>. Yields are for the sum of all possible regioisomers.

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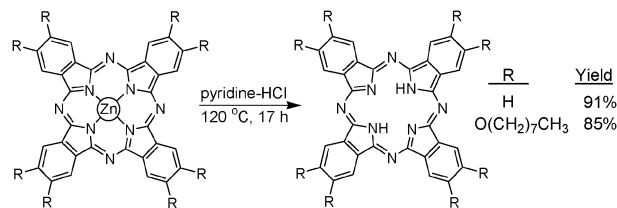
† Electronic supplementary information (ESI) available: Details regarding the synthesis and characterization of all new compounds are available. See DOI: 10.1039/b822985f



**Scheme 2** Synthesis of guanidino phthalocyanines (GPs). Counter ions for 3–5 are trifluoroacetate.



**Scheme 3** Demetallation of tetrasubstituted metallophthalocyanines and isolated yields ("n.d." = no product detected).<sup>18</sup>



**Scheme 4** Demetallation of C<sub>4</sub> symmetric zinc phthalocyanines and isolated yields.

It is well known that strongly chelating metal ion templates can dramatically improve the yields of cyclotetramerization under a wide variety of conditions using readily available starting materials (Scheme 1).<sup>4,6,8,10</sup> The main problem with this approach has been the lack of reported conditions for the subsequent removal of such ions to generate metal-free phthalocyanines.<sup>8,10a,11</sup> During our synthesis of guanidinium-containing phthalocyanines we discovered a new demetallation reaction that, to the best of our knowledge, provided the first examples of Zn(II) removal without destroying the phthalocyanine itself. This demetallation reaction appears to be general as it works for electron rich, electron poor, alkyl-, ether-, and even unsubstituted zinc phthalocyanines. Zn(II)-templated cyclotetramerization, followed by Zn(II) removal, therefore provides a new high-yielding route to diverse, metal-free phthalocyanines. These products are, in turn, important starting materials for making Pcs and GPs with variable metal centers. Given the industrial and academic importance of these compounds, it is expected that this new demetallation reaction will find numerous applications.

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## Notes and references

‡ Under these reaction conditions weakly bound metal ions like Sn(II) and Hg(II) were also removed from GPs, and Zn(II) was quantitatively removed from porphyrins.

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- 18 Where "guanidine" = diisopropylguanidinium, and "amide" = NHC(O)CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H.
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