

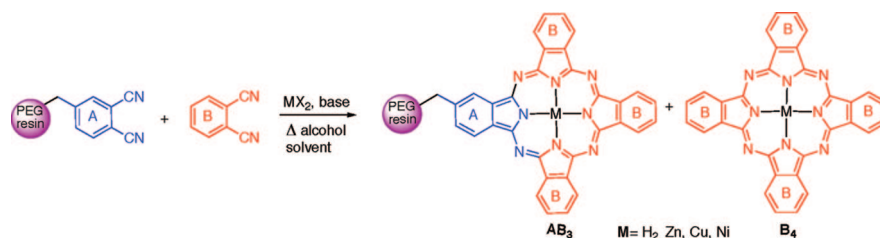
## Solid-Phase Synthesis of Asymmetrically Substituted “AB<sub>3</sub>-Type” Phthalocyanines

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Synthesis of phthalocyanines with asymmetrical substitution on the periphery is often difficult due to the problems in purification of the phthalocyanine mixtures obtained. Using a poly(ethylene glycol) (PEG)-based support with a Wang-type linker, we have developed the synthesis of monohydroxylated, oligoethylene glycol substituted phthalocyanines utilizing an amidine-base-promoted phthalonitrile tetramerization reaction. The use of a hydrophilic support allows symmetrical phthalocyanine product formed in solution to be readily and completely removed by washing while leaving the “AB<sub>3</sub>” product on the support. Acid cleavage with 10% trifluoroacetic acid provides the pure unsymmetrically substituted Pc. This method was applied to several metallo Pcs. Additionally, methods to avoid premature reactions on-resin that give A<sub>2</sub>B<sub>2</sub> products are provided.

### Introduction

Phthalocyanines (Pcs) absorb and emit light in the far-red and near-infrared, which make them important as dyes for photographic and printing applications and as materials for light harvesting in photovoltaic devices.<sup>1</sup> Pcs, derivatives of the aromatic tetra-azaporphyrins, have large extinction coefficients, are generally chemically and photochemically robust, and thus are useful for a variety of applications in materials and biology.<sup>2</sup> For a number of uses, Pcs with two or more different substituents on the exterior of the ring system would be advantageous. For example, asymmetrically substituted Pcs with one group for use in covalent labeling, while the other peripheral groups improve the solubility in aqueous solution and would be useful dyes for near-infrared fluorescent tagging of biomolecules.<sup>3–7</sup> An advantage of Pcs over other common dye classes is that their photophysical properties are readily altered by changing the substitution pattern or the metal guest of the Pc. For example, Zn, Si, and Al metallo-Pcs are strongly fluorescent, while Ru(II)Pcs are phosphorescent,<sup>8</sup> and Cu(II)–Pcs do not have significant luminescence.<sup>2</sup> Thus, water-soluble,

labeling Pcs may also be useful in a number of bioanalytical detection strategies utilizing time-resolved or resonance energy transfer techniques.<sup>9–11</sup>

Synthesis of Pcs with asymmetrical substitution on the periphery is most commonly performed by a statistical condensation of two different phthalonitriles, diiminoisoindoles, or related derivatives, which theoretically yields a mixture of six

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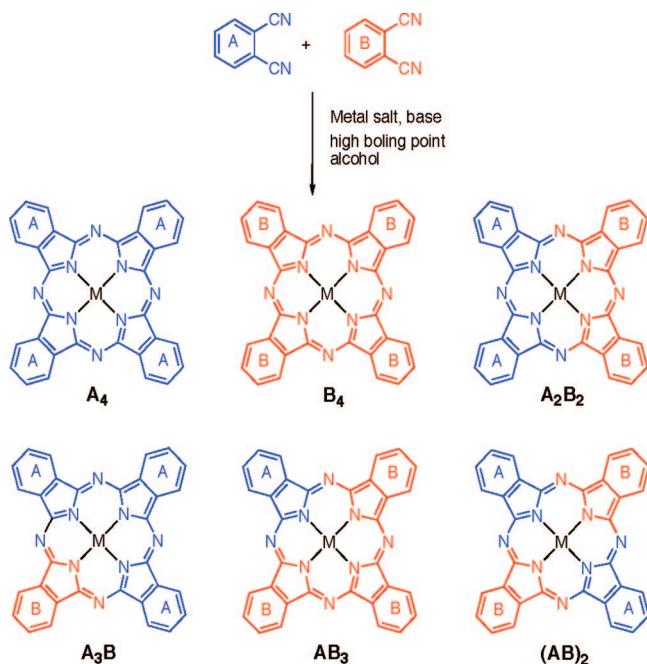
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## SCHEME 1. Statistical Condensation Method

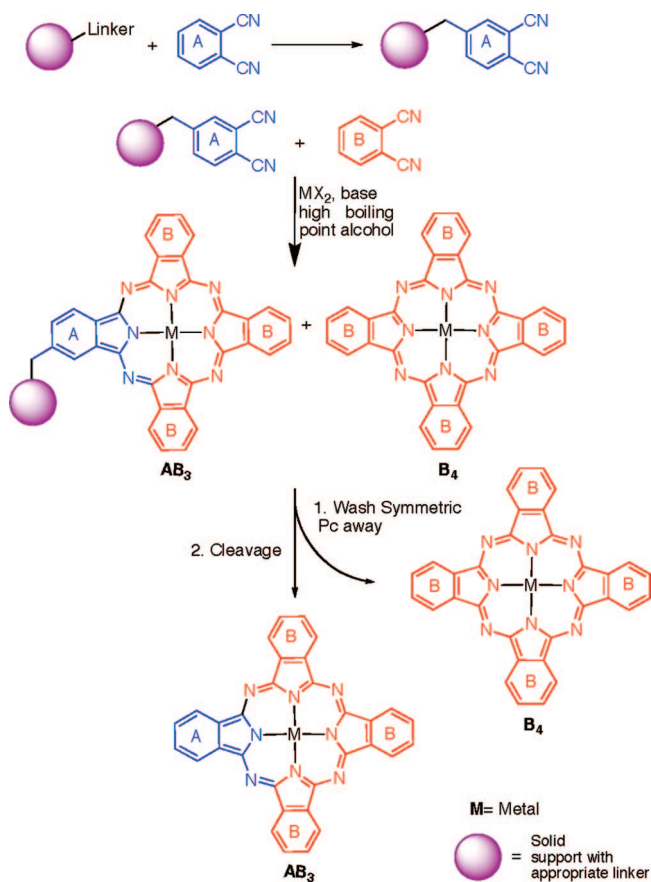


Pc congeners (Scheme 1).<sup>12</sup> Isolation of the desired “3 + 1” Pc product, here referred to as  $AB_3$  (or  $A_3B$ ), is often laborious due to difficulty in separating chemically similar species out of the Pc mixtures obtained.

To date, several chemoselective techniques for asymmetric Pc synthesis have been described in the literature including the subphthalocyanine (subPc) route<sup>13</sup> and solid-phase synthesis.<sup>14–16</sup> The subPc route is a well-known method for the synthesis of  $AB_3$  type of Pcs, though it is only applicable to certain phthalonitrile precursors. For example, the condensation of a diiminoisoindoline having electron-donating groups and an unsubstituted subPc or one with electron-withdrawing groups promotes the selective synthesis of  $AB_3$ -type Pcs. Contrastingly, the presence of electron-donating substituents on the subPc leads to a mixture of Pcs through a scrambling process that results from disassembly of the subPc under the reaction conditions to form the Pc.<sup>17–19</sup>

Solid-phase synthesis of  $AB_3$ -type asymmetric Pcs is as yet an underutilized method. Leznoff and co-workers' solid-phase synthesis of  $AB_3$ -type asymmetrically substituted Pcs using a polystyrene resin support is touted as the first synthesis of pure asymmetric Pcs.<sup>14,15</sup> Solid-phase synthesis of Pcs starts with one of the phthalonitrile precursors (Scheme 2) attached to the support via a cleavable linker. Reaction of the solid-supported phthalonitrile with an excess of phthalonitrile B in solution produces the  $AB_3$ -type, asymmetrically substituted Pc on the solid support while the  $B_4$ -type symmetrical Pc forms in

## SCHEME 2. Solid-Phase Synthesis Method



solution. Symmetrical Pc is removed by washing and subsequent cleavage of the linkage of “A” from the resin yields the pure  $AB_3$ -type Pc (Scheme 2). Such a strategy has also been utilized in the polymer-supported synthesis of monofunctionalized meso-tetraarylporphyrins as developed by Borhan and co-workers.<sup>20</sup>

One of the challenges of the method of Leznoff is the requirement for extensive washing via Soxhlet extraction to remove symmetrical  $B_4$  Pc from the hydrophobic polystyrene resin. Additionally, Soxhlet extraction is required to fully remove the cleaved asymmetrical  $AB_3$  Pc from the polymer support. For example, Leznoff reports<sup>15</sup> that 4–5 days of Soxhlet extraction are required to isolate pure asymmetrical Pc. The challenge of removing the symmetrical Pc product was demonstrated in a later paper by Leznoff<sup>16</sup> that reported the failure of even extensive Soxhlet extraction to completely remove the symmetrical Pc from the resin. This resulted in a contaminated “ $AB_3$ ” product after cleavage from the support that required additional chromatographic purification to obtain pure asymmetrically substituted Pc.

Here we describe the solid-phase synthesis of  $AB_3$  type asymmetrically substituted Pcs utilizing a poly(ethylene glycol) (PEG)-based support. In a desire to provide a scalable and rapid synthesis of asymmetrically substituted Pcs, we hypothesized that a more hydrophilic resin would reduce nonspecific adsorption of Pc products on the solid support. Thus, we utilized a hydrophilic, poly(ethylene glycol) (PEG) resin in place of the more traditional polystyrene support. Using a Wang-type linker, we have developed the synthesis of monohydroxylated, oligo-

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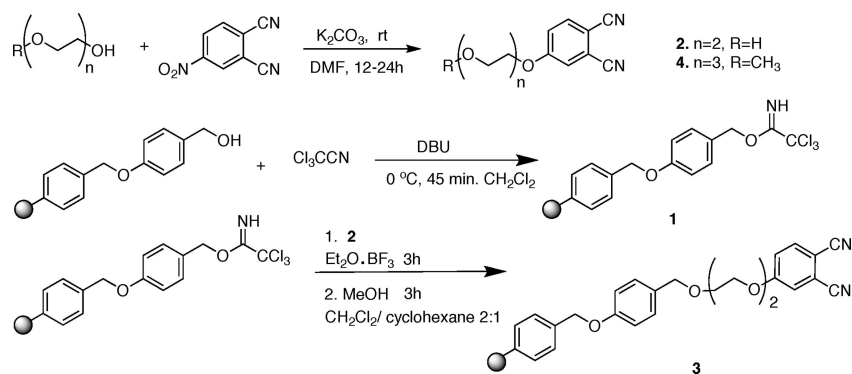
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## SCHEME 3. Activation of Wang Resin for Attachment of Phthalonitrile via an Ether Linkage



ethylene glycol substituted Pcs utilizing an amidine-base promoted, solid-supported phthalonitrile tetramerization reaction. The use of the hydrophilic support allows symmetrical Pc product formed in solution to be readily and completely removed by washing, while retaining the AB<sub>3</sub> product on the support.

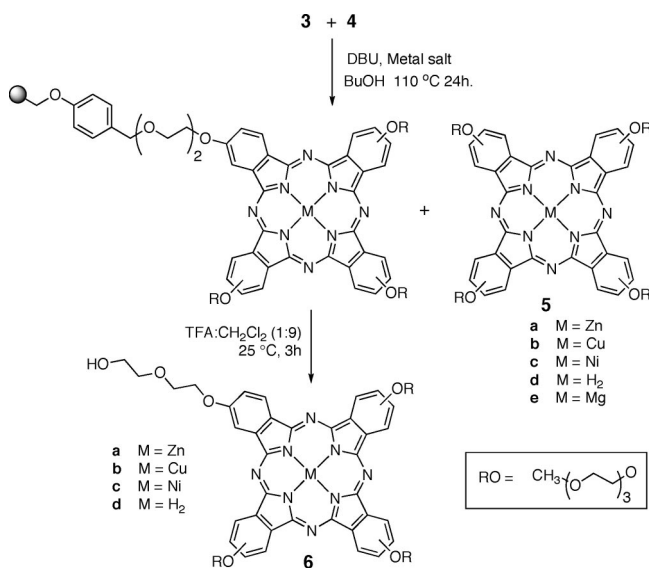
## Results and Discussion

Wang–ChemMatrix resin was chosen as the point of attachment for a hydroxy-functionalized phthalonitrile to the solid support since the benzyl ether linkage would be stable to the basic reaction conditions for Pc formation. We chose this system of almost symmetrical oligo(ethylene glycol)-substituted Pcs as a demonstration of the method as it would be nearly impossible to separate mixtures of congeners of such similar Pcs by chromatographic or other methods. The Wang linker was activated by trichloroacetonitrile, and the resulting trichloroacetimidate resin<sup>21</sup> **1** was treated with an excess of hydroxy-functionalized phthalonitrile **2**, synthesized from commercially available 4-nitrophthalonitrile and diethylene glycol,<sup>12</sup> to give resin-bound phthalonitrile **3** in high yield with a loading capacity of 0.54 mmol/g (90% yield based on starting loading capacity of the Wang resin, 0.6 mmol/g) (Scheme 3). As further evidence for the integrity of the reaction, FT-IR shows the disappearance of the acetimidate NH band at 3055 cm<sup>-1</sup> of resin **1** and the appearance of a C≡N band at 2229 cm<sup>-1</sup> of polymer-bound phthalonitrile **3**.

Phthalonitrile **4** was synthesized from commercially available 4-nitrophthalonitrile and triethylene glycol monomethyl ether in 74% yield.<sup>12</sup> Condensation of resin-bound phthalonitrile **3** with phthalonitrile **4** in solution in the presence of Zn(OAc)<sub>2</sub> and DBU in refluxing BuOH for 24 h produced a mixture of resin-bound AB<sub>3</sub> Pc and the corresponding symmetrically substituted Pc **5** in solution (Scheme 4). The resin was washed with hot BuOH and CH<sub>2</sub>Cl<sub>2</sub> until a colorless filtrate was collected. The absorbance spectrum of each successive wash solution showed decreasing absorbance. Dramatic decrease of the absorbance was observed after the first two washes indicating the most of the Pc **5** was washed away by the first BuOH and CH<sub>2</sub>Cl<sub>2</sub> washes (typical washing times, 3–5 h).

Polymer-bound *p*-alkoxybenzyl ethers can be cleaved in 1–10% TFA in CH<sub>2</sub>Cl<sub>2</sub> solution.<sup>21</sup> High concentrations of TFA (>70%) resulted in decomposition of Pc as well as removal of the metal from the Pc core. Cleavage conditions were optimized by monitoring the absorbance of the cleavage cocktail at 1%, 5%, and 10% TFA in CH<sub>2</sub>Cl<sub>2</sub>. 10% TFA in CH<sub>2</sub>Cl<sub>2</sub> resulted in

## SCHEME 4. Solid-Phase Synthesis of Oligo(ethylene glycol)-Substituted Pcs



the highest cleavage yield (as judged by absorbance of the washes) without loss of the metal from the Pc core and thus was selected as the standard cleavage cocktail.<sup>22</sup>

Analysis of the crude cleavage solution showed that none of the symmetrical B<sub>4</sub> product was present, but that the desired AB<sub>3</sub> Pc was accompanied by a significant amount (~20%, MALDI-MS) of the A<sub>2</sub>B<sub>2</sub> Pc. This may have been due to increased rate of intraresin reactions<sup>23,24</sup> due to the relatively high loading of the resin (0.54 mmol/g). That is, reactions between phthalonitrile active sites on the resin **3** are similar in rate to reactions between activated phthalonitrile species in solution and resin-bound phthalonitriles, thus producing the undesired A<sub>2</sub>B<sub>2</sub> Pc. In order to overcome this problem, we reduced the loading of the resin (Scheme 3) by reaction of trichloroacetimidate resin (**1**) with only 1.2 equiv of hydroxy-phthalonitrile **2** followed by capping of the remaining amidate sites with an excess of MeOH to give a phthalonitrile resin **3** at a loading of 0.28 mmol/g. Resin-bound phthalonitrile **3** was reacted as before with an excess of **4** in the presence of Zn(OAc)<sub>2</sub>. Following the removal of symmetrical **5a** by washing, the desired Pc was cleaved from the polymer support.

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TABLE 1. Oligoethylene Glycol Substituted Pc

	compd no. <sup>a</sup>	metal salt	Pc	yield <sup>b</sup> (%)	solvent	$\lambda_{\max}$ (abs) (nm)	$\log \epsilon$ (cm <sup>-1</sup> M <sup>-1</sup> )	$\lambda_{\max}$ (em) (nm) <sup>c</sup>	$\phi_f^c$
ssymmetric Pcs (AB <sub>3</sub> )	<b>6a</b>	Zn(OAc) <sub>2</sub>	ZnPc	12	DMSO	680	4.9	690	0.15
	<b>6b</b>	CuBr <sub>2</sub>	CuPc	13	DMSO	681	4.8	n.d.	n.d.
	<b>6c</b>	NiCl <sub>2</sub>	NiPc	11	THF	671	4.3	678	0.0003
	<b>6d</b>	MgCl <sub>2</sub>	H <sub>2</sub> Pc	16	DMSO	646, 676, 706	3.4, 3.5, 3.4	709	0.08
symmetric Pcs (B <sub>4</sub> )	<b>5a</b>	Zn(OAc) <sub>2</sub>	ZnPc	21	DMSO	681	5.5	691	0.15
	<b>5b</b>	CuBr <sub>2</sub>	CuPc	15	DMSO	681	5.1	n.d.	n.d.
	<b>5c</b>	NiCl <sub>2</sub>	NiPc	17	THF	671	5.1	678	0.0038
	<b>5d</b>		H <sub>2</sub> Pc	18	DMSO	676, 706	3.5, 3.5	709	0.06
	<b>5e</b>	MgCl <sub>2</sub>	MgPc	20	DMSO	682	5.5	691	0.31

<sup>a</sup> Asymmetrical Pcs **6** were purified by filtration through silica gel, except for **6b** and **6d** which were purified by Sephadex LH-20 chromatography.

<sup>b</sup> Yields of asymmetrically substituted Pcs were calculated based on the loading of the phthalonitrile on the support. <sup>c</sup> Fluorescence spectra and quantum yield determinations were done using 605 nm excitation wavelength for **6a**, **6c**, **6d**, **5a**, 607 nm for **5c** and **5e**, and 615 nm for **5d**. CuPcs **5b** and **6b** did not show any detectable fluorescence, which is noted in the table as "n.d.". Fluorescence quantum yield measurements for all Pcs were done using methylene blue as a standard at absorbance 0.04 - 0.05 for both Pc and standard solutions to avoid any error due to inner-filter effect.<sup>26</sup>

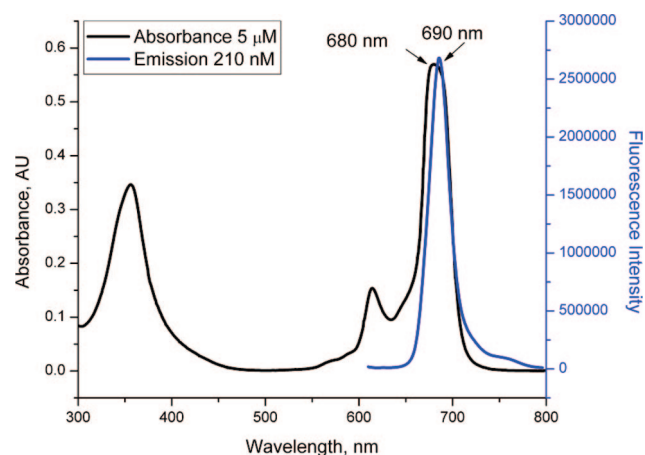


FIGURE 1. Absorbance and emission spectra of **6a**.

The crude mixture was filtered through a silica gel column to remove low molecular weight impurities to give Zn–Pc **6a** in 12% yield (based on 0.28 mmol/g loading capacity) without contamination from the A<sub>2</sub>B<sub>2</sub> Pc product (Scheme 4). Reducing the loading capacity resulted in the pure AB<sub>3</sub> type Pc, but the overall yield, based on the initial loading of the phthalonitrile, was not reduced. All the symmetric Pc products **5** were recovered and purified by precipitation of a MeOH solution into ether. Asymmetrical Pcs **6** were purified by filtration through silica gel column, except for **6b** and **6d** which were purified by Sephadex LH-20 chromatography. We have found that LH-20 is the preferred method of purification as there is less nonspecific adsorption of Pcs to the LH-20 matrix and results in improved Pc recovery.

The same synthetic route to **6a** was applied to synthesize Cu, Ni, and metal-free Pcs. Condensation of **4** with **3** in the presence of CuBr<sub>2</sub> and DBU in refluxing BuOH for 24 h gave a dark blue solution and resin (Scheme 4). Following purification, **6b** was obtained in 13% yield (Table 1). In the case of Ni Pcs (**5c**, **6c**) NiCl<sub>2</sub> was employed as a metal source. Due to the low solubility of NiCl<sub>2</sub> in BuOH, the reaction was carried out at higher temperature and Ni–Pc **6c** was purified by filtration through a silica gel column in 11% yield (Table 1). All Pcs prepared in this work were characterized by absorbance and fluorescence spectroscopy, HPLC, and mass spectrometry. Figure one shows example spectra of ZnPc **6a** that had a sharp Q-band at 680 nm in the absorbance spectrum and band at 690 nm (Figure 1), which are typical for these kinds of chromophores. Fluorescence quantum yield of **6a** was calculated as

0.15, which is in the range of the reported quantum yields of tetrasubstituted ZnPcs.<sup>25</sup>

To synthesize the metal-free Pc (**5d**, **6d**), the same strategy was employed except without any metal ion. But in this case, cleavage of metal-free Pc resin yielded two products, the AB<sub>3</sub> metal-free Pc (**6d**) and an A<sub>2</sub>B<sub>2</sub> H<sub>2</sub>Pc in 3:2 molar ratio. As an alternative route to the asymmetrical H<sub>2</sub>Pc, Mg<sup>2+</sup> ion was utilized to template the tetramerization, as it is known that the acidity of the cleavage cocktail is sufficient for the removal of Mg from the Pc core to yield metal free Pc. Thus, condensation of **3** with **4** in the presence of MgCl<sub>2</sub> (Scheme 4) gave, following the cleavage, AB<sub>3</sub> H<sub>2</sub>Pc **6d** without any contamination by the A<sub>2</sub>B<sub>2</sub> product in 17% yield.

From the results of the synthesis of the metal-free Pc **6d**, it is clear that the metal ion plays a crucial role in the tetramerization process. Adding divalent metal ion improves the site-isolation of the reactive groups in the resin matrix. As argued by Jayalekshmy and Mazur, this improved "pseudodilution"<sup>24</sup> of sites is a kinetic phenomena since we know that phthalonitrile cyclotetramerization is faster in the presence of metal ion. We propose a pathway that accounts for this pseudodilution in the presence of metal ion, which follows from the proposed mechanism of DBU-promoted phthalonitrile tetramerization in alcohol.<sup>27</sup> That is, metal chelated isoindolines (or other similar phthalonitrile derived precursors) present in solution react faster with resin-bound phthalonitriles than the resin-bound phthalonitriles can react with themselves, resulting in only AB<sub>3</sub> products. In the absence of metal, the reaction of resin-bound phthalonitriles with solution intermediates is slowed so that resin-bound intermediates have a longer time to find a proximate resin-bound phthalonitrile with which to react, thus giving rise to a significant fraction of A<sub>2</sub>B<sub>2</sub> H<sub>2</sub>Pc products (Scheme 5).

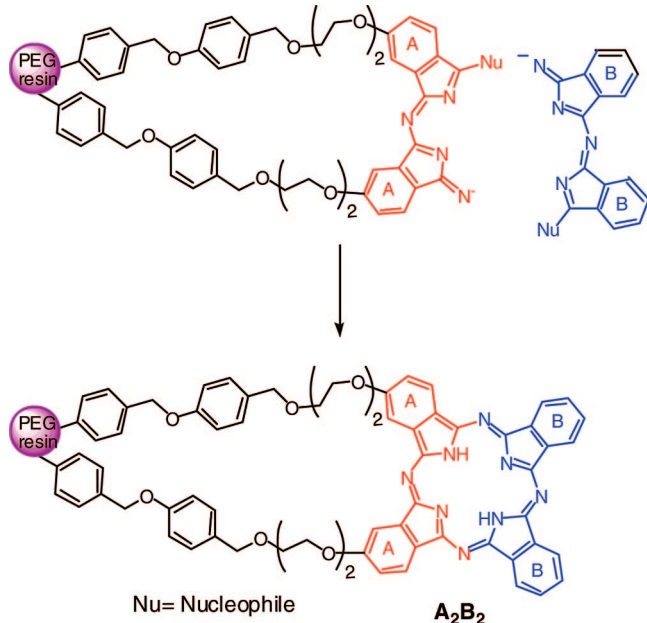
Solid-phase synthesis is a fundamental methodology in organic synthesis, and it has been utilized for preparation of myriad different molecular classes and cyclization reaction types. Since the development of solid-phase synthesis<sup>28</sup> related phenomena such as intrasite interaction and site isolation have been extensively studied. It has been shown that the outcome of a reaction on solid support is significantly influenced from intrasite reactions, which can be diminished by altering the loading or the cross-linked density of the polymer, changing

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SCHEME 5. Formation of A<sub>2</sub>B<sub>2</sub> Pcs in Solid Support

the structure of the linker, increasing the concentration of incoming reagent, or changing the solvent and reaction temperature.<sup>29</sup> While intrasite interaction generally leads to undesired products, it can be utilized for selective synthesis of dimeric cross-linked molecules. Schreiber et al. showed the synthesis of homodimeric molecules via intrasite olefin cross-metathesis on solid support using highly loaded (1–2 mmol/g) and lightly cross-linked (1% DVB) polystyrene resin with the goal of split-pool synthesis of homodimer libraries.<sup>30</sup> Thus, it may be possible through optimization of resin, solvent, and other reaction conditions to prepare “2 + 2” (A<sub>2</sub>B<sub>2</sub>) Pc products as the predominant or only product, which may have unique applications as well.

### Conclusion

The advantage of the solid-phase method described here is the ability to synthesize a variety of asymmetrical phthalocyanines quickly and easily without the need for extensive purification steps to get homogeneous Pc products. The method is a significant advancement of previous solid-phase synthesis of Pcs and applicable to Pcs with wide variety of substituents. The use of hydrophilic PEG-based resin is key for the success of this method to allow easy removal of symmetrical Pc

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coproducts by washing of the resin as well as to prevent noncovalent adsorption of the desired AB<sub>3</sub> Pc to the support. Site-isolation on the PEG-based resin can be accomplished using slightly lower loadings and by inclusion of a divalent metal ion in alkoxide-promoted phthalonitrile tetramerization.

The method described here provides *pure* asymmetrical substituted Pcs is very efficient, taking <3 days to complete including loading, Pc formation, washings, cleavage, and simple chromatography. Using alternative solid-support linking strategies and Pc synthesis conditions, this time-effective method is now being applied to the synthesis of functionalized asymmetrical substituted Pcs with a variety of physical and spectral properties.

### Experimental Section

**General Procedure for Synthesis of Pc (5 and 6).** Resin **3** (0.6 g) was swelled in anhydrous BuOH (15 mL) overnight. A 9-fold molar excess of phthalonitrile **4** (3.24 mmol, 0.94 g) and metal salt (0.9 mmol) were dissolved in anhydrous BuOH (7 mL) and added to well swelled resin under Ar. Concentration of phthalonitrile in the reaction mixture was kept around 0.16 M. The mixture was heated up to 90 °C and DBU (1.8 mmol, 0.27 mL) was added to mixture. The reaction was carried out at 110 °C for 24 h. The resin was washed until a colorless filtrate was obtained, first with hot BuOH (10 × 25 mL), CH<sub>2</sub>Cl<sub>2</sub> (5 × 25 mL), and then BuOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1) (3 × 25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 × 25 mL).

**General Procedure for Cleavage of the AB-Type Pc (6).** The resin was suspended into a solution of TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:9) (50 mL) and shaken for 3 h at room temperature. The filtrate was evaporated to dryness, and the crude mixture was purified by filtration through a silica gel or LH-20 column.

**General Procedure for Purification of Symmetrical Pcs (5).** Filtrate solutions were combined and evaporated to dryness. A portion (100 mg) of the crude mixture was dissolved in ~3 mL of CH<sub>3</sub>OH, and 50 mL of diethyl ether was added to solution. Solution was left at –20 °C overnight, and the suspension was centrifuged to give Pc **5** as a blue-green solid.

**Determination of the Loading Capacity of Resin **3**.** Resin **3** (0.5 g) was suspended into a solution of TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:9) (50 mL) and left in the shaker for 3 h. at room temperature. Filtrate was evaporated to dryness and the product was filtered through a pad of silica gel with EtOAc as the eluent.

**Acknowledgment.** We thank the National Science Foundation (CHE-0304833, EPS-0346411) and the National Institutes of Health (EB006639 and HG01499) for financial support and Ms. Brooke Delhomme for technical assistance.

**Supporting Information Available:** Experimental procedures, spectroscopic data, and HPLC for **1–6e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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