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Synthesis of Diporphyrins via Palladium-Catalyzed C−O Bond Formation: Effective Access to Chiral Diporphyrins

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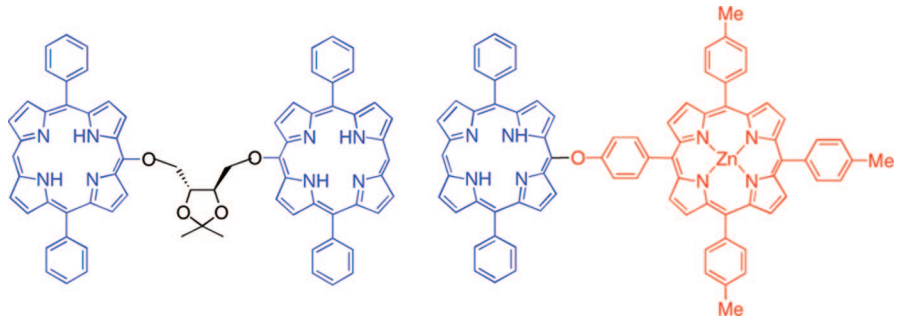

Diporphyrins can be efficiently synthesized from bromoporphyrin precursors via palladium-catalyzed C−O bond formation. The synthetic methodology is general and can be applied to various diols, forming a series of homo-diporphyrins containing different types of spacers in high to excellent yields. Chiral diporphyrins can be readily constructed through the use of optically active diols. A similar strategy allows access to hetero-diporphyrins and triporphyrins, including free-base and metalloporphyrin hetero dimers.

Introduction

Much effort has been devoted to the synthesis of chiral porphyrins because of their many important applications.[1] For example, chiral porphyrins have been employed as catalysts in asymmetric synthesis, as sensors for chiral recognition, and as mimics for enzymatic processes.[2] Several approaches have been applied for chiral porphyrin synthesis.[1] Of these, post-construction employing chiral building blocks fastened to a preformed porphyrin synthon bearing peripheral functional groups is regarded as the most practical method, considering the inherent low yield of porphyrin ring formation and higher cost of optically active compounds.[1,2] Accordingly, several useful synthons have been developed, including *meso*-tetrakis(2-aminophenyl)porphyrin,[3] *meso*-tetrakis(2,6-diaminophenyl) porphyrin,[4] *meso*-tetrakis(2,6-dihydroxyphenyl)porphyrin,[5] and *meso*-tetrakis(2,6-dicarboxyphenyl)porphyrin.[6] They have been successfully utilized to attach chiral acids, amines, and alcohols through multiple amide or ester bond formations.[1,2] Despite these achievements, the development of new synthons that permit effective construction of chiral porphyrins with improved generality and practicality is warranted to further their applications.[1,2]

Recently, a powerful strategy, founded on metal-mediated carbon−heteroatom bond formation,[7] has emerged for the general and efficient synthesis of heteroatom-substituted porphyrins through systematic studies by us[8] and others.[9] It involves

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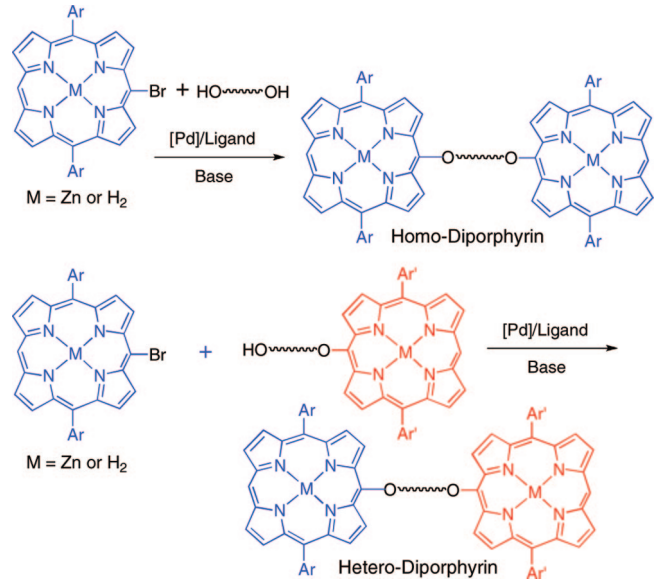
catalytic reactions of halogenated porphyrins, especially bromoporphyrins, with a broad array of soft, non-organometallic nucleophiles such as amines, amides, alcohols, thiols, selenols, and phosphines.[8,9] Generally, these catalytic processes proceed effectively under mild conditions to furnish a diverse family of functionalized porphyrins in high yields. Given that a variety of chiral amines, amides, and alcohols are readily accessible, the success of this synthetic strategy prompted us to consider the development of halogenated porphyrins, especially bromoporphyrins, as a new class of synthons for the construction of chiral porphyrins. As a result, we demonstrated that 5,10-bis(2′,6′-dibromophenyl) porphyrins,[8f] *meso*-dibromoporphyrins,[8g] and β-bromo porphyrins[8h] are versatile synthons for the modular preparation of *ortho*-, *meso*-, and β-chiral porphyrins, respectively, via Pd-catalyzed amidation/etheration with chiral amides/alcohols. The catalytic carbon−heteroatom bond formation reactions could be accomplished with various chiral building blocks under mild conditions, constructing a family of new chiral porphyrins in high yields.[8f–h]

SCHEME 1. General Synthesis of Homo- and Hetero-Diporphyrins via Palladium-Catalyzed C−O Coupling Reactions



Results and Discussion

In our ongoing efforts to develop practical metalloporphyrin-based processes for catalytic carbene[8f,g,10] and nitrene[11] transfer reactions, some of these chiral porphyrins have been demonstrated as effective ligands to support cobalt-catalyzed asymmetric cyclopropanation with excellent diastereo- and enantioselectivity.[8f,10h,i] To broaden these efforts, we initiated a project to synthesize chiral diporphyrins with hopes of exploring their potential applications in supporting dinuclear complexes as bifunctional catalysts for challenging asymmetric processes.[12,13] To this end, we decided to apply the Pd-mediated etheration strategy[8c,g,h] for the preparation of dimeric porphyrins. We report herein that a series of homo- and hetero-diporphyrins as well as triporphyrins were efficiently synthesized from reactions of bromoporphyrin synthons with various diols via Pd-catalyzed C−O bond formation (Scheme 1). With this synthetic methodology, chiral diporphyrins could be readily constructed by using widely available optically active diols.

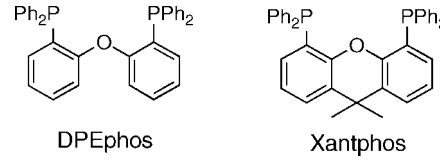


FIGURE 1. Structures of bidentate phosphine ligands.

On the basis of results from our previous work,[8c] DPEphos and Xantphos (Figure 1) in combination with $Pd_2(dba)_3$ were examined as catalysts for the double etheration reaction of representative synthon **1** with various diols **2** for the synthesis of homo-diporphyrins (Scheme 2). It was found that the combination of DPEphos and $Pd_2(dba)_3$ could effectively catalyze the double C−O bond formations of flexible diols such as ethylene glycol and 1,6-hexanediol, resulting in diporphyrin **3a** and **3b** in 53% and 96% yields, respectively.[14] Using the

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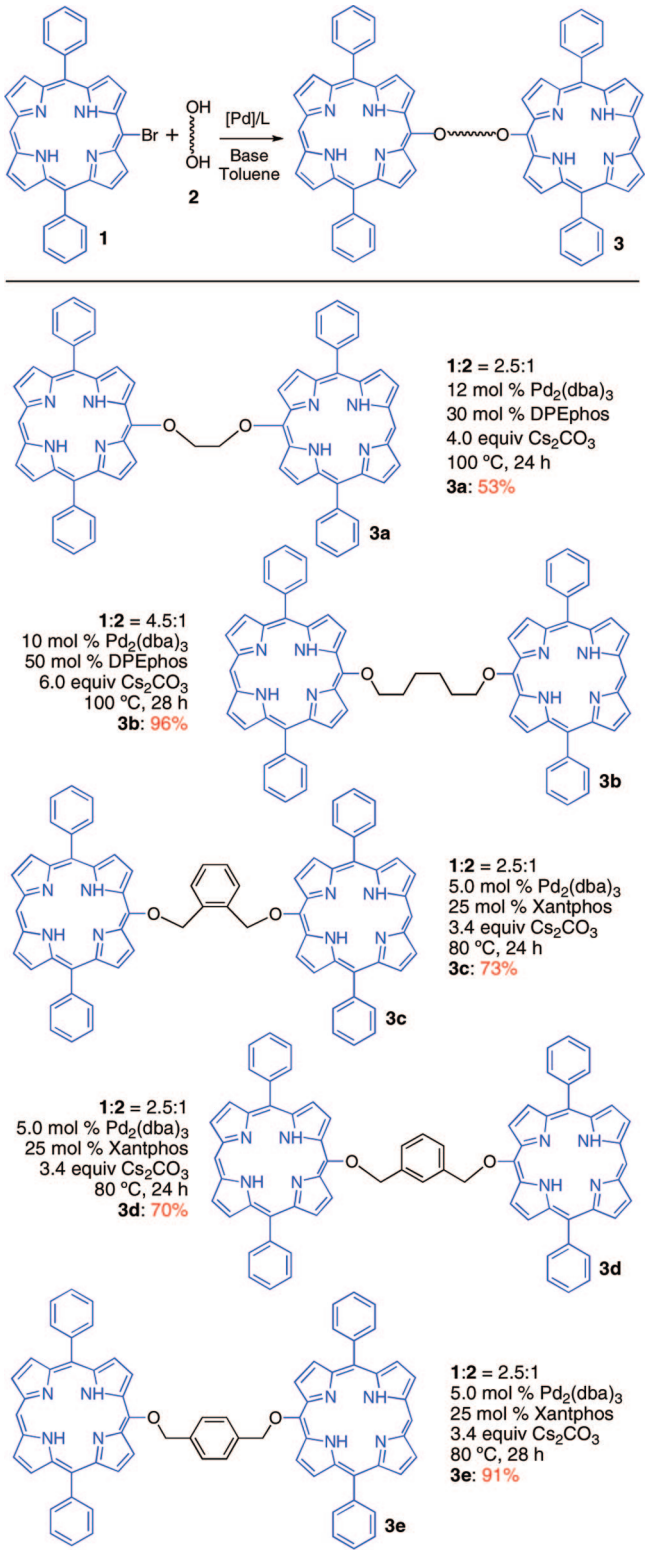
(14) For low-yielding reactions, mono-coupling products along with some starting bromoporphyrins could be isolated. In many cases, a trace amount of debromination products could be also observed.

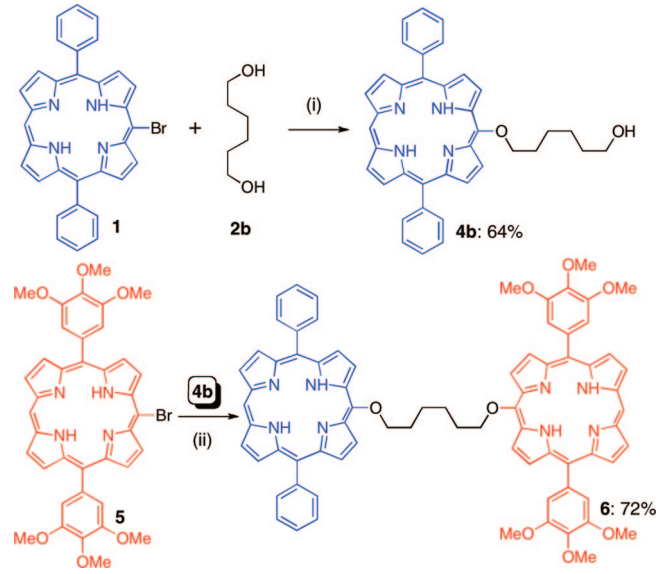
SCHEME 2. Synthesis of Homo-Diporphyrins



combination of Xantphos and $Pd_2(dba)_3$ as the catalyst, the relatively more rigid diols such as *o*-, *m*-, and *p*-xylene-α,α′-diols were successfully coupled with **1** to form the corresponding diporphyrins **3c**, **3d**, and **3e** in good to high yields (Scheme 2).

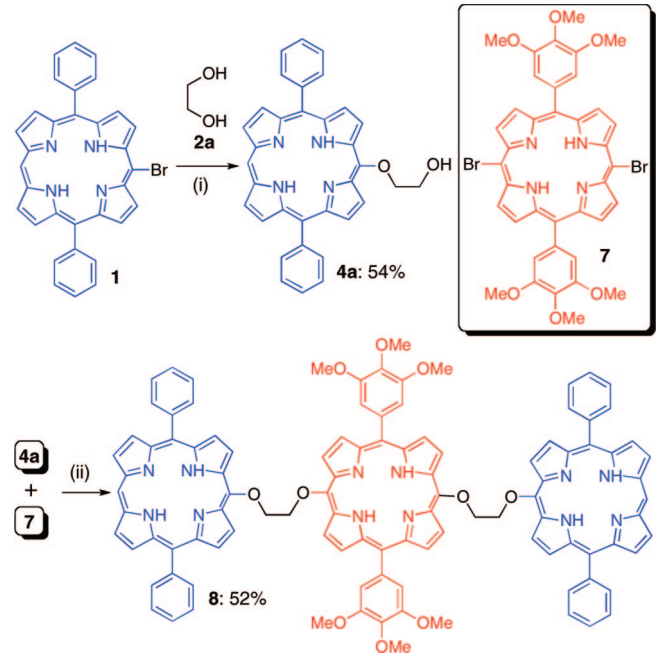
Through the use of excess diols, the Pd-catalyzed etherations could be controlled toward the selective formation of mono-coupled products, as demonstrated with the reaction of 1,6-hexanediol **2b** with **1** resulting in the formation of **4b** (Scheme 3). This stepwise approach allowed the synthesis of hetero-diporphyrins. For example, **4b**, which bears a pendant hydroxyl group, was effectively coupled with a different synthon **5**, forming hetero-diporphyrin **6** in 72% yield (Scheme 3).

SCHEME 3. Synthesis of Hetero-Diporphyrin[a]



[a] Reaction conditions: (i) **1**:**2b** = 1:2.5; 5 mol % $Pd_2(dba)_3$; 25 mol % DPEphos; 2.0 equiv of Cs_2CO_3; toluene; 80 °C; 24 h. (ii) **4b**:**5** = 1.5:1; 5 mol % $Pd_2(dba)_3$; 25 mol % DPEphos; 3.4 equiv of Cs_2CO_3; toluene; 100 °C; 24 h.

SCHEME 4. Synthesis of Hetero-Triporphyrins[a]

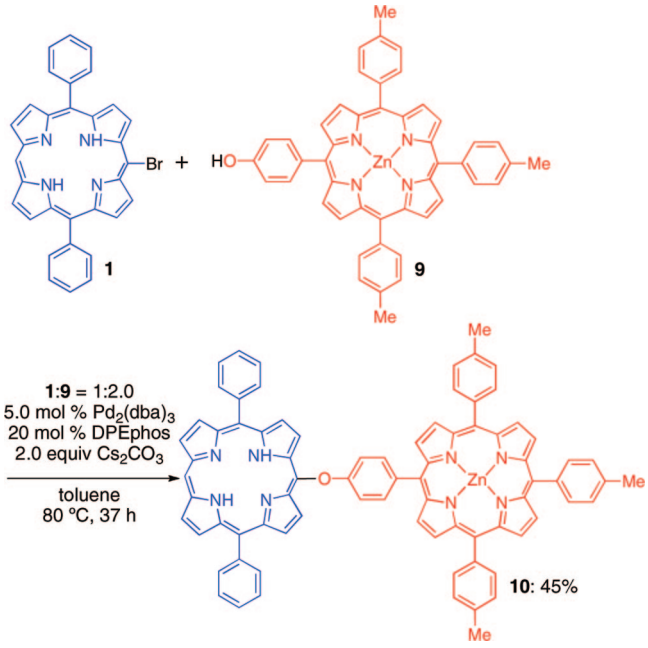


[a] Reaction conditions: (i) **1**:**2a** = 1:10; 5 mol % $Pd_2(dba)_3$; 25 mol % DPEphos; 4.0 equiv of Cs_2CO_3; toluene; 100 °C; 24 h. (ii) **4a**:**7** = 2:1; 10 mol % $Pd_2(dba)_3$; 40 mol % DPEphos; 4.0 equiv of Cs_2CO_3; toluene; 80 °C; 42 h.

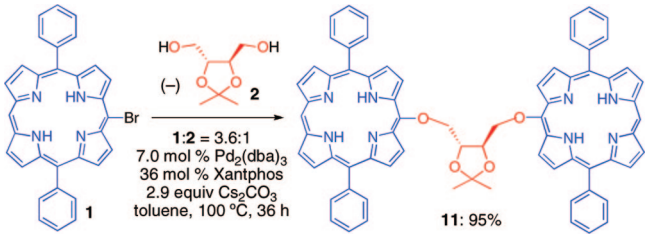
The same stepwise approach also provided a straightforward way to synthesize either homo- or hetero-triporphyrins. For example, the monocoupling product **4a**, resulted from controlled reaction of **1** and **2a**, was successfully coupled with dibromoporphyrin **7** to furnish hetero-triporphyrin **8** in 52% yield (Scheme 4).

In addition to free-base diporphyrins and triporphyrins (Schemes 1, 2, 3, and 4), hetero-dimers consisting of free-base and metal-

SCHEME 5. Synthesis of Free-Base/Metalloporphyrin Heterodimer



SCHEME 6. Synthesis of Chiral Diporphyrin



loporphyrins could also be made via Pd-catalyzed C−O bond formation. As illustrated in Scheme 5, under the catalytic action of the combination of DPEphos and $Pd_2(dba)_3$, coupling of free-base **1** with preformed Zn complex **9** containing a hydroxyl group offered the free-base/zinc hetero-diporphyrin **10** in 45% yield.

Considering the ready availability of a wide range of optically pure chiral diols, these demonstrated synthetic schemes suggested a convenient approach for the construction of various chiral diporphyrins. As a demonstration of the utility of this new approach, the commercially available (−)-2,3,-*O*-isopropylidene-D-threitol was coupled with bromoporphyrin **1** using the combination of Xantphos and $Pd_2(dba)_3$ as the catalyst, producing chiral diporphyrin **11** in 95% isolated yield (Scheme 6). The high effectiveness of the coupling reaction was notable, especially in view of the nature of double etheration (the 95% overall yield represents an average yield of over 97% per C−O coupling).

Conclusions

In summary, we have developed an efficient methodology for the preparation of homo- and hetero-diporphyrins as well as triporphyrins from bromoporphyrin synthons via Pd-catalyzed C−O bond formation. The synthetic approach is general and a wide range of diols can be employed as spacers. Through the use of this approach with readily available optically active diols, effective access to chiral diporphyrins may be realized and implemented in a myriad of potential applications, including their use as bifunctional catalysts for asymmetric processes.

Experimental Section

General Procedures for Synthesis of Porphyrin Dimer. An oven-dried Schlenk tube equipped with a stirring bar was degassed on a vacuum line and purged with nitrogen. The tube was then charged with palladium precursor, phosphine ligand, bromoporphyrin, alcohol, and base. The tube was capped with a Teflon screwcap, evacuated, and backfilled with nitrogen. After the Teflon screwcap was replaced with a rubber septum, solvent (4−6 mL) was added via syringe. The tube was purged with nitrogen (1−2 min), and the septum was then replaced with the Teflon screwcap and sealed. The reaction mixture was heated in an oil bath with stirring and monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with ethyl acetate, washed with water (×3) and concentrated to dryness. The solid residue was purified by flash chromatography.

{5-[(10′,20′-Diphenyl-porphyrin-15′-yloxy)]phenyl-10,15,20-tritolyl-porphyrinato} Zinc (10). The general procedure was used to couple 5-bromo-10,20-diphenylporphyrin (27.1 mg, 0.05 mmol) with [5-(4-hydroxyphenyl)-10,15,20-tritolyl-porphyrinato] zinc (69.4 mg, 0.1 mmol), using $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and DPEphos (5.4 mg, 0.01 mmol) in the presence of Cs_2CO_3 (37.6 mg, 0.1 mmol). The reaction was conducted in toluene at 80 °C for 37 h. The title compound was isolated by flash chromatography [silica gel, methylene chloride/hexanes (v/v) = 6:4] as a purple-red solid (26.0 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 9.66 (d, J = 4.2 Hz, 2H), 9.25 (d, J = 4.2 Hz, 2H), 8.96 (m, 12H), 8.29 (d, J = 5.4 Hz, 4H), 8.00−8.08 (m, 8H), 7.82 (m, 6H), 7.54 (m, 6H), 7.30 (d, J = 7.5 Hz, 2H), 2.70 (s, 6H), 2.69 (s, 3H), −2.67 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 150.3, 141.3, 139.8, 137.0, 136.2, 135.5, 134.7, 134.4, 131.6, 131.9, 131.8, 131.6, 131.1, 128.0, 127.8, 127.2, 127.0, 121.1, 119.8, 114.7, 104.7, 21.5. UV−vis ($CHCl_3$), λ_{max} nm (log ϵ): 413(5.63), 425(5.72), 510(4.33), 549(4.42), 587(4.05), 641(3.60). Fluorescence emission (λ_{ex} = 423 nm, CH_2Cl_2) λ_{max} (nm): 599, 647, 713. HRMS-MALDI ([M − Zn + 2H + 1]$^+$): calcd for $C_{79}H_{57}N_8O$, 1133.4655; found, 1133.4627.

Chiral Diporphyrin 11. The general procedure was used to couple 5-bromo-10,20-diphenylporphyrin (180.5 mg, 0.25 mmol) with (−)-2,3-*O*-Isopropylidene-D-threitol (11.3 mg, 0.07 mmol), using $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and DPEphos (13.6 mg, 0.025 mmol) in the presence of Cs_2CO_3 (65.2 mg, 0.2 mmol). The reaction was conducted in toluene at 100 °C for 36 h. The title compound was isolated by flash chromatography [silica gel, methylene chloride/hexanes (v/v) = 8:2] as a purple solid (72.0 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 2H), 9.78 (d, J = 4.8 Hz, 4H), 9.23 (d, J = 4.8 Hz, 4H), 8.96 (d, J = 4.8 Hz, 4H), 8.87 (d, J = 4.8 Hz, 4H), 8.18 (m, 8H), 7.74 (m, 12H), 5.44 (m, 4H), 5.41 (m, 2H), 2.00 (s, 6H), −2.80 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 141.3, 137.7, 134.6, 131.5, 131.3, 130.6, 127.7, 127.1, 126.8, 119.5, 110.9, 104.0, 83.9, 27.5. UV−vis ($CHCl_3$), λ_{max} nm (log ϵ): 412(5.61), 478(3.75), 509(4.37), 544(4.07), 585(3.89), 641(3.87). Fluorescence emission (λ_{ex} = 411 nm, CH_2Cl_2) λ_{max} (nm): 646, 712; HRMS-ESI ([M + H]$^+$): calcd for $C_{71}H_{55}N_8O_4$, 1083.4341; found, 1083.4348.

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Supporting Information Available: General experimental methods, complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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