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Synthesis of *meso*-substituted tetrabenzoporphyrin via selective *meso*-bromination of bicycloporphyrin

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ABSTRACT

Bicycloporphyrins (CPs) are important compounds as soluble precursors of tetrabenzoporphyrins (BPs). CPs can be converted to the corresponding BPs via selective bromination to *meso*-position, coupling reaction, and *retro* Diels–Alder reaction.

Highly π-conjugated porphyrins have interesting physical and chemical properties, and strong absorption of near-infrared light. Thus, these compounds have attracted much attention as organic semi-conductive materials,[1a] pigments, non-linear optical materials,[1b] and photosensitizers in photodynamic therapy.[1c] In particular, tetrabenzoporphyrins (BPs), which contain fused aromatic rings, have a similar skeleton to phthalocyanines and exhibit intriguing physical properties.[2] However, pure BP is difficult to obtain because its solubility in common solvents is extremely poor. In addition, isoindole, a building block of BP, is unstable at room temperature in air and under acidic conditions. We previously reported the preparation of BP from bicyclo[2.2.2] octadiene-fused porphyrin (CP; **1**) as a soluble precursor of BP by a *retro* Diels–Alder reaction (rDA) at 200 °C[3] (Fig. 1).

A bromine atom at the *meso*-position of porphyrins can be substituted with various functional groups by nucleophilic substitution or coupling reactions. However, only two methods for the *meso*-bromination of β-substituted porphyrins, such as octaethylporphyrin (OEP), have been reported. One method is extremely low yielding because a complicated reaction mixture is formed by bromination of the benzyl position. The other method is nitration of the *meso*-position of OEP using HNO_3 in combination with various other acids, followed by bromination by nucleophilic substitution at the *meso*-position. This method is ineffective. Thus, introducing a bromine atom to the *meso*-position of β-substituted porphyrins (OEP) is difficult. The steric hindrance of the bicyclic units of CP is smaller than that at the ethyl position of OEP, so we expected that a bromine atom could be introduced to CP efficiently.[4]

We have previously achieved the direct *meso*-halogenation (fluorination,[5] chlorination[6]) of CPs, and then converted the products to *meso*-halogenated BPs by the rDA reaction. We report here the synthesis of *meso*-brominated BPs (**3**) via *meso*-bromination of CPs (**2**) followed by the rDA reaction. We also describe the synthesis of various functionalized BPs by the Kumada, Suzuki, and Sonogashira coupling reactions using *meso*-bromo CPs (**2**) (Table 1).

Results and discussion

meso-Bromination of CPs (**2**) was carried out with various amounts of *N*-bromosuccinimide (NBS). When CP (**1**) was reacted with 1 equiv NBS, 5-bromo CP (**2a**) (40%) and 5,15-bromo CP (**2b**) (20%) were obtained. Next, 0.7 equiv NBS was reacted with **1**, and formation of **2b** was suppressed and **2a** was obtained in 54% yield. When a large amount of NBS (4 equiv) was used, complicated reaction mixtures arising from the introduction of the bromine atom into the double bond of the bicyclic units (**2c**) were obtained.[14] These results indicate that the porphyrin ring in **2b** was distorted by the steric hindrance of the bromine atom. When the reaction time was extended, byproducts of the rDA products (**1a**, **1b**) were obtained. The polarity of **2a** was similar to **1a** and **1b**, so isolating the compounds was difficult. Therefore, 3 h was the optimum reaction time. Heating **2a** and **2b** for 1 h at 200 °C

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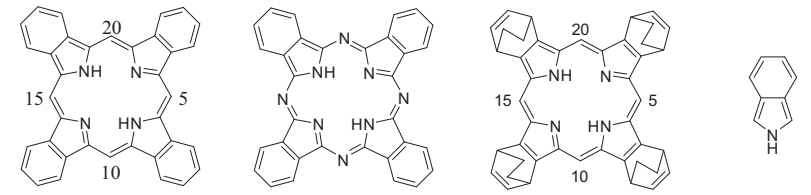


Figure 1. Structures of porphyrins and isoindole.

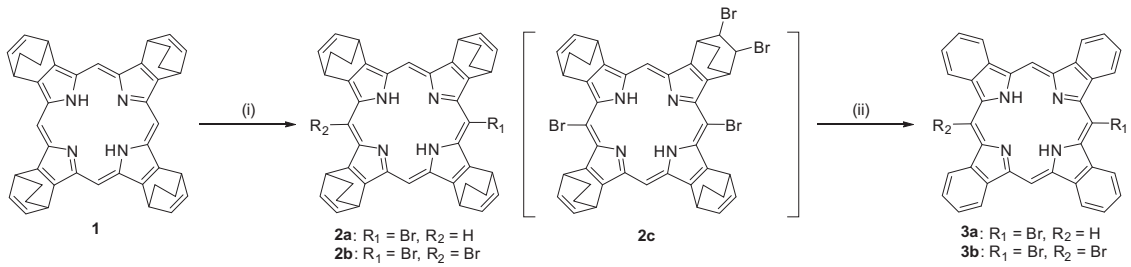
Table 1
Synthesis conditions of *meso*-bromo CP

Entry	NBS (equiv)	Yield (%)	
		2a	**2b**
1	0.5	29	Trace
2	0.7	54	Trace
3	1.0	40	20
4	2.0	20	60

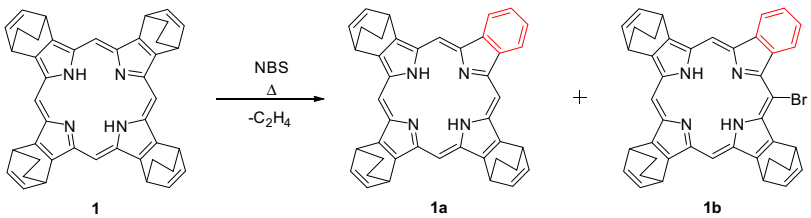
under vacuum (10 mm Hg) gave 5-bromo BP (**3a**) and 5,15-dibromo BP (**3b**) in 100% yields (Schemes 1–3).

Next, various coupling reactions of 5-bromo CP (**2a**) were performed. Porphyrin used in the coupling reaction was converted into a zinc complex (**2a-Zn**) to avoid deactivating the palladium catalyst.[15] First, we carried out a Kumada coupling reaction.[7] A solution of **2a**-**Zn** and catalytic quantity of $NiCl_2$(dppe) in THF was added to a Grignard reagent (PhMgBr or MeMgBr), and the reaction mixture was refluxed for 24 h. After comparing various conditions, the best yields of 5-PhCP (**4a**) (30%) and 5-MeCP (**4b**) (18%) were obtained when 10 equiv Grignard reagent was used. Unsubstituted CP zinc complexes were mainly formed by hydrolysis after transmetallation of **2a-Zn**with the Grignard reagent. Next, various substituents were introduced to the CPs with a Suzuki coupling reaction.[8] **2a-Zn** was dissolved in THF/H_2O (7:3), and the mixture was added to boronic acid, K_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$. The reaction mixture was refluxed for 24 h. The yield of the Suzuki coupling reaction was much higher than the yield of the Kumada coupling.[16] However, only small amounts of 5-EtCP and 5-*n*-BuCP were obtained. Instead of the desired product, an unsubstituted CP zinc complex was obtained due to elimination of the bromine atom. This resulted from the coordination of an empty Pd orbital to the β hydrogen after the transmetallation occurred and borate promoted β hydrogen elimination to eliminate the charge bias (Scheme 4). Therefore, introducing a hexyl group to CP by using the 1,1′-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex ($PdCl_2$(dppf)·CH_2Cl_2) ensured the vacant Pd orbital was capped by a ligand with trialkylborane to form a stable borate. *B*-*n*-Heptyl-9-BBN was obtained from 1-heptene and 9-borabicyclo[3.3.1]nonane by hydroboration.[9] A solution of **2a**-**Zn** in THF/H_2O (10:1) was added to K_2CO_3 and $PdCl_2$(dppf)·CH_2Cl_2. The reaction mixture was added to *B*-*n*-heptyl-9-BBN and refluxed for 24 h. However, the yield of the desired product was low under these conditions. An excess of the trialkylborane (20 equiv) produced 5-heptyl CP in 44% yield.[17] We introduced phenyl acetylene into CP (Sonogashira coupling).[10] Et_3N, $Pd(PPh_3)_4$ and ethynylbenzene were added to a THF solution of **2a**-**Zn** and CuI and the reaction mixture was stirred at room temperature for 12 h.[11] The NMR and MS results showed that a byproduct (**4f**) was formed when an excess of ethynylbenzene was used. **4f** was formed by the Heck reaction with the ethynylbenzene dimer and **2a**-**Zn**. The polarity of **4f** was close that of CP, and could not be isolated by column chromatography. Wu et al. reported that dimerization of acetylene was prevented at 25 °C in dimethylformamide.[12] We prevented the formation of **4f** by this method, and 5-phenylethynyl CP was obtained in 50% yield.[18]

We synthesized 5,15-substituted CP by Suzuki coupling by using a similar method to that for 5-substituted CP. When a large amount of the rDA product was obtained, the purification of pure coupling products (**4**, **6**) was difficult because the polarities of



Scheme 1. Reagents and conditions: (i) NBS, $CHCl_3$, reflux, 3 h; (ii) 200 °C, 1 h.



Scheme 2. rDA reaction of CP.