COMMUNICATION

Site-selective halogenation on *meso*-mesityl substituents of 10,20-dimesityl-5,15-diazaporphyrins with an AuX_3/AgOTf combination

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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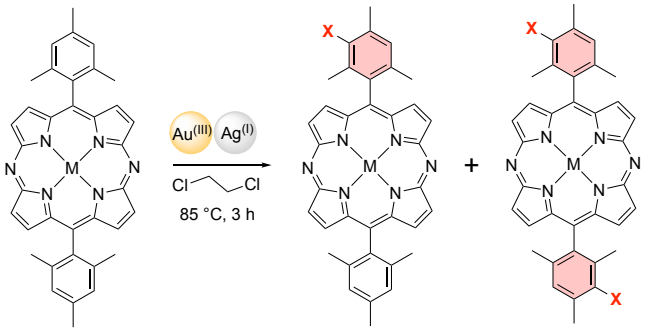
We have developed site-selective bromination on the mesityl substituents of 10,20-dimesityl-5,15-diazaporphyrins. Treatment of 10,20-dimesityl-5,15-diazaporphyrin and its nickel(II) complex with a combination of $AuBr_3$/AgOTf induced selective bromination on the mesityl groups. These brominated products can be employed for late-stage modification of the aryl substituents.

Introduction

Porphyrins and their analogues, porphyrinoids, often exhibit intriguing optical and electrochemical properties. These properties are often manipulated by the proper choice of the *meso*-substituents.[1] Furthermore, the *meso*-aryl substituents are of particular importance to control physical properties such as solubility and aggregation behaviour. However, selective late-stage modification of the *meso*-substituents is not trivial. The reactivity of the macrocyclic pyrrole subunits is generally higher than that of the *meso*-substituents.[2,3] Consequently, tailored *meso*-substituents should be introduced at the early stage of the synthesis as a functionalized aromatic aldehyde. Furthermore, the functionalized aldehyde is often commercially unavailable and requires a laborious synthesis.

Recently, 5,15-diazaporphyrins[4] have emerged as promising porphyrin analogues, which should be of particular interest as one- and two-photon photosensitizer in photodynamic therapy (PDT).[5] To modify 5,15-diazaporphyrins into more attractive photosensitizers, the fine-tuning of their photophysical properties have been extensively developed, especially by regioselective functionalization of their β-positions. These developments include regioselective halogenation,[4b] nitration,[6] nucleophilic addition,[7] and hydrogenation[5a,8] of the pyrrole C–C double bonds. The selective β-functionalization strategy offers attractive features such as NIR absorption and stable redox properties. In sharp contrast, the functionalization of the *meso*-substituents has been disregarded. However, the late-stage modification of the *meso*-substituents of 5,15-diazaporphyrins with polar functionalities such as sugars or amino acids should expand their applicability in the PDT field through balancing their hydrophilicity and hydrophobicity.

During our investigations on Au(III) metalation[9] of free-base 10,20-dimesityl-5,15-diazaporphyrin **1H**, we serendipitously found halogenation of the substrate rather than desired Au(III) metalation. Surprisingly, halogenation occurred selectively on the mesityl substituents leaving the macrocyclic π-system intact.[10] Such a selective functionalization of *meso*-aryl substituents has been rare and should be useful for the late-stage transformation of 5,15-diazaporphyrins.



1H: M = 2H
1Ni: M = Ni
X = Cl or Br
2H-X: M = 2H
2Ni-X: M = Ni
3H-X: M = 2H
3Ni-X: M = Ni

Scheme 1. Halogenation of 10,20-dimesityl-5,15-diazaporphyrins **1H** and **1Ni** with an AuX_3/AgOTf combination in 1,2-dichloroethane.

Results and discussion

We found that treatment of **1H** with a combination of $AuCl_3$ (3 equiv)/AgOTf (6 equiv) induced selective chlorination of the *meso*-mesityl groups to afford 10-(3-chloro-2,4,6-trimethylphenyl)-20-mesityl-5,15-diazaporphyrin **2H-Cl** and

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†Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

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10,20-di(3-chloro-2,4,6-trimethylphenyl)-5,15-diazaporphyrin **3H-Cl** in 12% and 26% yields, respectively (Scheme 1 and Table 1, entry 1). None of Au(III) 5,15-diazaporphyrin was detected in the reaction mixture. We found that the portionwise addition of $AuCl_3$ changed the ratio of **2H-Cl** to **3H-Cl** (entry 2) while the use of the increased amount of $AuCl_3$ improved the yield of the dichlorinated diazaporphyrin **3H-Cl** to 40% yield (entry 3). The use of sodium tetrachloroaurate also induced the same chlorination reaction but the yield of the dichlorinated products **3H-Cl** was lower (entry 4).

Table 1 Halogenation of 10,20-dimesityl-5,15-diazaporphyrins with an AuX_3/AgOTf combination in 1,2-dichloroethane.

entry	substrate	Au(III) (equiv)	Ag(I) (equiv)	products	yields (%)
1	**1H**	$AuCl_3$ (3)	AgOTf (6)	**2H-Cl/3H-Cl**	12/26
2	**1H**	$AuCl_3$ (1+1+1)	AgOTf (6)	**2H-Cl/3H-Cl**	25/7
3	**1H**	$AuCl_3$ (1+2+2)	AgOTf (6)	**2H-Cl/3H-Cl**	12/40
4	**1H**	$NaAuCl_4$ (1+2+2)	AgOTf (6)	**2H-Cl/3H-Cl**	26/20
5	**1H**	$AuBr_3$ (3)	AgOTf (6)	**2H-Br/3H-Br**	7/60
6	**1Ni**	$AuBr_3$ (3)	AgOTf (6)	**2Ni-Br/3Ni-Br**	–/62
7	**1H**	$AuBr_3$ (3)	$AgBF_4$ (6)	**2H-Br/3H-Br**	–/–
8	**1H**	$AuCl_3$ (3)	AgOTf (1)	**2H-Cl/3H-Cl**	<5/<5
9	**1H**	$AuCl_3$ (3)	–	**8/9**	32/25

Bromoarenes are better substrates than chloroarenes in palladium-catalysed cross-coupling reactions. We consequently shifted to the bromination reaction by the use of $AuBr_3$. The use of an $AuBr_3$ (3 equiv)/AgOTf (6 equiv) system provided monobrominated and dibrominated diazaporphyrins **2H-Br** and **3H-Br** in 7% and 60% yields, respectively (Table 1, entry 5). In this case, $AuBr_3$ was added to the reaction mixture at once. As compared with $AuCl_3$, the use of $AuBr_3$ improved the yields of the dihalogenated compounds. Ni(II) diazaporphyrin **1Ni** also underwent selective bromination of the *meso*-mesityl groups to furnish dibrominated product **3Ni-Br** in 62% yield (entry 6). The use of $AgBF_4$ instead of AgOTf resulted in the recovery of the starting material **1H** (entry 7). It should also be noted that decreasing the stoichiometry of the silver salt (less than 3 equiv) significantly reduced the yield of the products (<5%, entry 8). We also attempted the catalytic use of $AuCl_3$ (2 mol %) and AgOTf (4 mol %) combined with an excess amount of *N*-bromosuccinimide (2 equiv) but the reaction only yielded the core-brominated products, 3-bromo-5,15-diazaporphyrin **4**[7c] in 41% yield (Scheme 2).

The high-resolution atmospheric pressure chemical ionization time-of-flight (APCI-TOF) mass spectrum of **2H-Cl** showed a parent ion peak at *m/z* = 583.2387 (calcd for $C_{36}H_{32}{}^{35}ClN_6$, *m/z* = 583.2371 $[M+H]^+$), indicating that diazaporphyrin **1H** was mono-chlorinated. Moreover, the ^1H NMR spectrum of **2H-Cl** in $CDCl_3$ exhibits four sets of doublets at δ = 9.28, 9.27, 8.87 and 8.83 ppm. These signals were assignable as eight pyrrole β protons, thus revealing that no chlorination occurred on the macrocyclic core of **2H-Cl**. Furthermore, these four sets of doublet signals indicate a loss of molecular symmetry in **2H-Cl**. The signals due to the *meta*-hydrogens of mesityl groups appeared as two singlets at 7.39 (1H) and 7.31 (2H) ppm. Regarding the high-field region, five different benzylic methyl proton peaks were observed. Indeed, the methyl protons belonging to the mesityl moiety appeared at δ = 2.72 (3H) and 2.64 (3H) ppm for the *para* position and δ = 1.95 (3H), 1.85 (6H) and 1.80 (3H) ppm for the *ortho* position. These results support that the chlorination reaction selectively occurred on the aryl substituent and not on the macrocycle.

Further support for the selective chlorination on the aryl substituents was obtained from the X-ray diffraction analysis of dichlorinated diazaporphyrin **3H-Cl** (Fig. 1). Slow vapor diffusion of methanol into a chloroform solution of **3H-Cl** afforded suitable crystals for X-ray analysis. The analysis unambiguously elucidated that the chlorine atoms were introduced on the aromatic substituents. The macrocyclic skeleton of **3H-Cl** adopts a highly planar conformation with a mean plane deviation of 0.026 Å. The chlorin atom appeared disordered due to the presence of the rotational isomers.

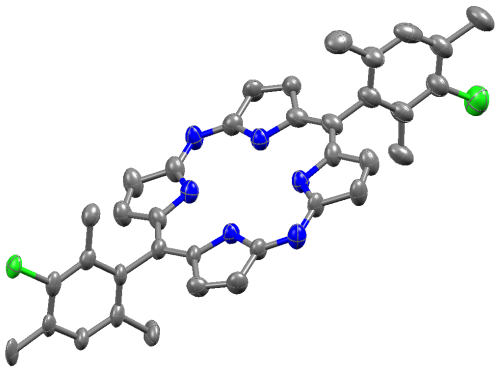
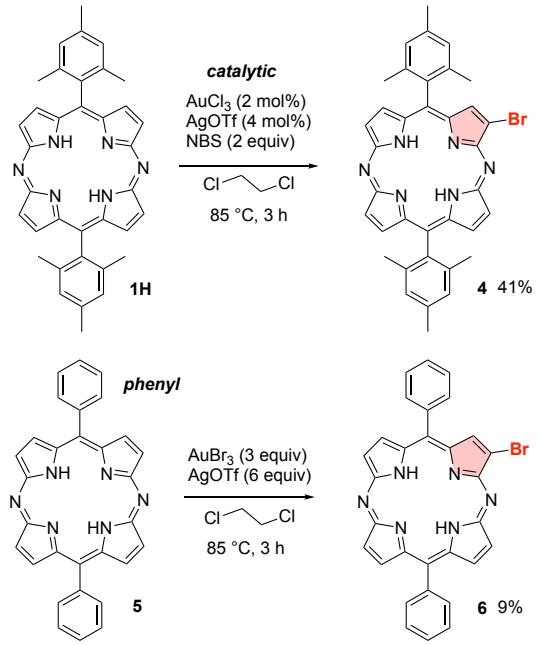


Fig. 1 Crystal structure of **3H-Cl**. One of the rotational isomers is shown. Thermal ellipsoids are shown at 50% probability and all hydrogen atoms are omitted for clarity.

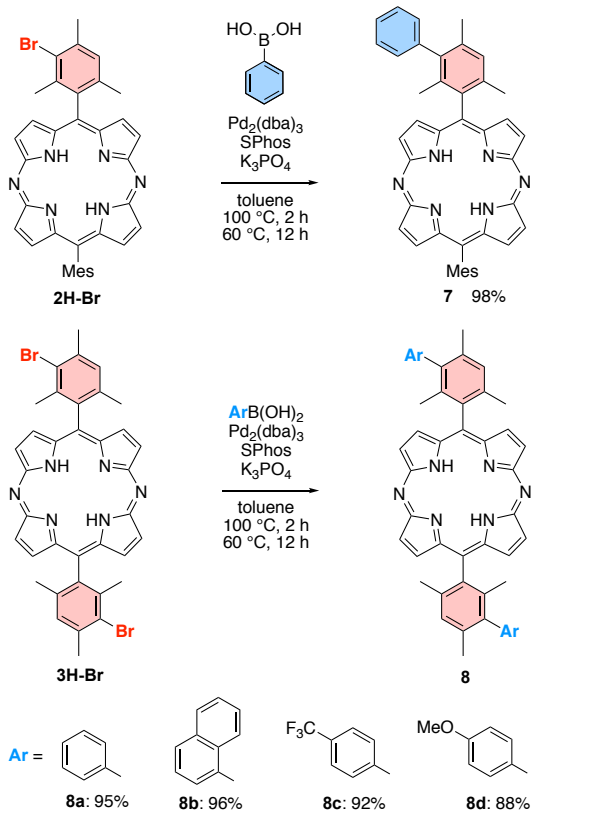
Unfortunately, selective halogenation of the aryl substituents seems to be specific to the mesityl group. The bromination reaction of free-base 10,20-diphenyl-5,15-diazaporphyrin **5** was performed under the same reaction conditions as entry 5 in Table 1. The product was 3-bromo-5,15-diazaporphyrin **6**, which was obtained in 9% yield (Scheme 2). (Bromophenyl)diazaporphyrin was not obtained. This result indicates that the subtle difference of the electronic and steric nature of the *meso*-aromatic substituents has a critical effect on the site-selectivity of the present gold-mediated halogenation reaction.



Scheme 2. Attempted bromination of free-base 5,15-diazaporphyrins **1H** and **5**.

We then decided to use the bromotrimethylphenyl-substituted diazaporphyrins **2H-Br** and **3H-Br** for further functionalization through palladium-catalysed Suzuki–Miyaura coupling with arylboronic acids (Scheme 3). Because of the steric congestion on the mesityl substituents, we employed SPhos as the phosphine ligand.[11] Brominated diazaporphyrin **2H-Br** was cross-coupled with phenylboronic acid to afford compound **7** in 98% yield (Scheme 3). The arylation reaction of dibromodiazaporphyrin **3H-Br** with several arylboronic acids also proceeded effectively to provide diarylated compounds **8a–8d** in excellent yields (88–96%). These compounds also exist as inseparable mixtures of the rotational isomers: The ^{1}H NMR spectrum of **8a** exhibited four singlet peaks at δ = 1.88, 1.85, 1.56 and 1.53 ppm for the *ortho*-methyl protons of the two isomers. The present efficient introduction of aryl groups is promising for the late state transformation of dibromodiazaporphyrins with functionalised aryl groups.

To clarify the electronic effect of the introduced substituents, the electrochemical property of arylated diazaporphyrins **7** and **8a–8d** were investigated by cyclic voltammetry. These biaryl-substituted diazaporphyrins exhibited two reversible reduction waves while their oxidation waves were irreversible (Supporting Information, Fig. S46). The reduction potentials of **7** and **8a–8d** varied slightly depending on the introduced aryl groups.



Scheme 3. Suzuki–Miyaura coupling reaction of brominated diazaporphyrins **2H-Br** and **3H-Br**.

Finally, we performed the reaction without the presence of silver salts (Table 1, entry 9). These conditions provided monogold and bisgold complexes **9** and **10** in 32% and 25% yields, respectively,[12] which were sufficiently stable to be separated by silica gel column chromatography. X-ray diffraction analysis of **9** and **10** clearly confirmed their structures, in which the Au(III) centres were bound to the *meso*-nitrogen atoms but not to the central cavity of the diazaporphyrin core (Figure 2). The Au(III) ion had a substantial impact on diazaporphyrins electronic properties. Both complexes exhibited bathochromic shifts of their Q bands (Fig. 3). The lower energy bands of **9** and **10** were shifted from 630 nm to 641 and 659 nm, respectively, indicating narrowed HOMO–LUMO gaps of these gold complexes induced by Au(III) metalation on the *meso*-nitrogen atoms. This situation is supported by the DFT calculations on **1**, **9** and **10** at the B3LYP/6-31G(d)+SDD level of theory (Supporting Information, Fig. S47). The MO energy levels of **9** and **10** were substantially lowered along with the reduction of their HOMO–LUMO gaps by the gold metalation. We speculate that the gold metalation on the *meso*-nitrogen atoms retards the electrophilic halogenation on the macrocyclic core leading to selective halogenation on the electron-rich mesityl substituents.

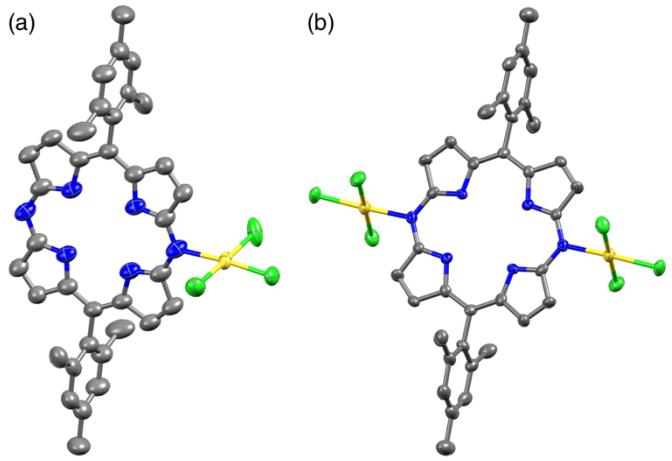


Fig. 2 Crystal structures of (a) **9** and (b) **10**. Thermal ellipsoids are shown at 50% probability and all hydrogen atoms are omitted for clarity.

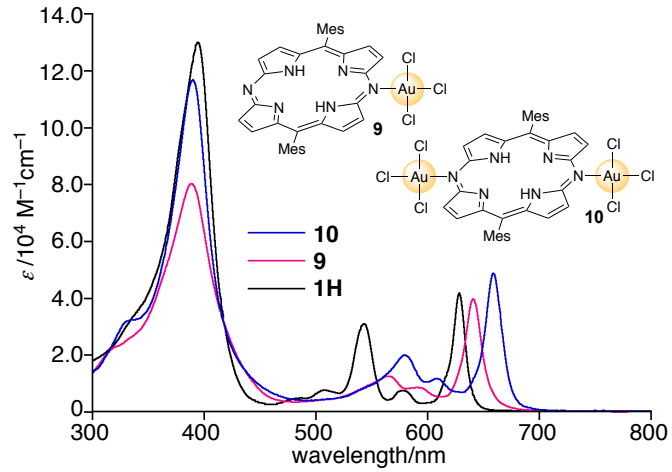


Fig. 3 UV-Vis absorption spectra of free base porphyrin **1H** as well as gold complexes **9** and **10** in CH_2Cl_2.

Conclusions

We have developed site-selective chlorination and bromination on the *meso*-mesityl substituents of 10,20-dimesityl-5,15-diazaporphyrin and its nickel(II) complex with an AuX_3/AgOTf combination. Interestingly, free-base 5,15-diazaporphyrin was halogenated without the formation of the corresponding gold and silver complexes. The resulting halogenated diazaporphyrins were employed as useful scaffolds to introduce aromatic substituents through the Suzuki–Miyaura coupling reaction. The present procedure would enable the late-stage functionalisation of 5,15-diazaporphyrins. The strategy to access functionalised photosensitizers for PDT applications is currently under investigation in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI grants JP17H01190 and JP19KK0138 from MEXT (Japan). J.F.L. expresses his gratitude for a JSPS Post-Doctoral Research Fellowship. H.S. gratefully acknowledges the Sumitomo Foundation for financial support.

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