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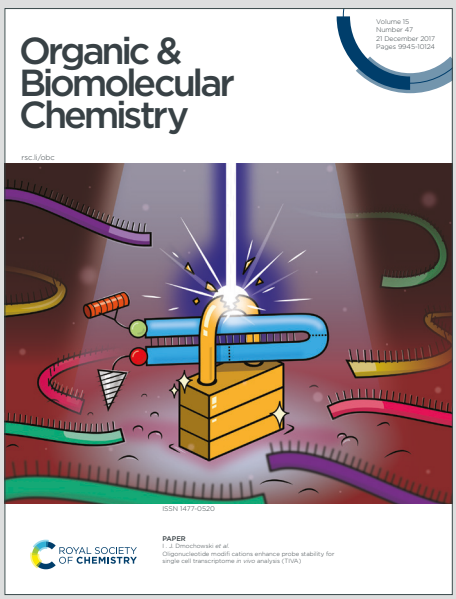

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COMMUNICATION

Central zinc metal-controlled regioselective *meso*-bromination of *zincated* β-silylporphyrins—rapid access to *meso*,β-dual-functionalized porphyrins

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A convenient method for the preparation of *meso*,β-dual-functionalized porphyrin was developed. The bromination of *zincated* β-silylporphyrin with NBS selectively yielded *meso*-bromo-β-silylporphyrin, whereas, the bromination of *free-base* β-silylporphyrin selectively yielded β-bromoporphyrin via an *ipso*-substitution of the silyl group. These *meso*,β-dual-functionalized porphyrins could be used as multipurpose synthons for fabricating various porphyrin derivatives.

Because of their widespread applicability in the fields of catalysis,[1,2] material science,[3] chemical sensing,[4,5] and medicinal chemistry,[6] interest in the synthesis of porphyrin derivatives has been steadily increasing in recent years. The function and properties of these artificial porphyrins can be tuned both by the diverse steric and electric effects of their peripheral substituents and their central metal ions.[7] Consequently, great efforts have been committed to the discovery of new synthetic intermediates and strategies for preparing various porphyrin derivatives using a variety of substituents at the desired *meso* and β positions.[8,9] Porphyrins bearing two distinct reactive substituents (FG_1 and FG_2) at the *meso* and β positions (Fig. 1 illustrates their generalized structure) are regarded as the versatile synthetic precursors of more complex porphyrin systems. This is because each of these functional groups, when directly attached to a porphyrin core, can be individually modified to enable alternate functionalities. However, to our knowledge, there is a very limited number of reports[10] on the preparation of such porphyrins that bear two functional groups with distinct chemical reactivities.

This study outlines an unprecedented *meso*-selective bromination of β-silyl zinc porphyrins providing dual-functionalized porphyrins, *i.e.*, *meso*-bromo-β-silyl-substituted zinc porphyrins via the simple bromination of *meso*-unsubstituted-β-silylporphyrins with NBS. In this case, the zinc ion of a porphyrin core plays an essential role in the regioselectivity of the bromination occurring at the *meso* position of the *zincated* β-silylporphyrins, leaving the β-silyl-group untouched. Furthermore, bromo-desilylation occurred at the β position of the *free-base* β-silylporphyrins.

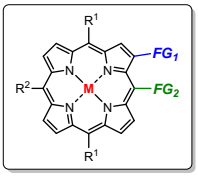
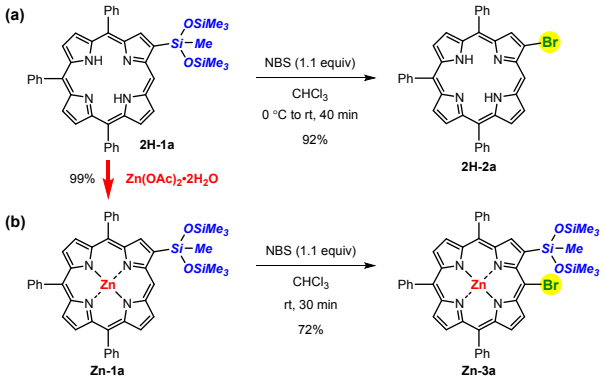


Fig. 1 *Meso*,β-dual-functionalized porphyrin bearing two distinct reactive substituents.

Recently, we reported on the efficient preparation of *meso*-unsubstituted *free-base* β-silylporphyrins **2H-1a**[11] with the Ir-catalyzed activation of C–H using $HSiMe(OSiMe_3)_2$ as the source of Si.[12] This β-selective silylation of porphyrin demonstrated broad substrate compatibility, and the bulky silyloxysilyl group was able to be subjected to a series of transformations such as halogenation, oxidation, and Hiyama cross-coupling reactions.[11,13] As expected, the β-silyl group on the *free-base* **2H-1a** was readily converted to a β-bromo group in high yield via a bromo-desilylation at the *ipso*-position with NBS, resulting in **2H-2a** (Scheme 1a). In exploring this bromination with other substrates, we were surprised to find



Scheme 1 Conventional (a) and unprecedented (b) regioselectivity in the bromination of **2H-1a** and **Zn-1a** with NBS.

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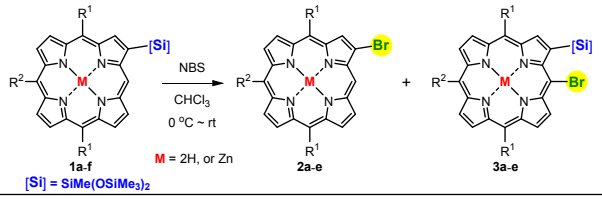
Table 1 Regioselective preparation of β-bromoporphyrin and *meso*-bromo-β-silylporphyrin[a]

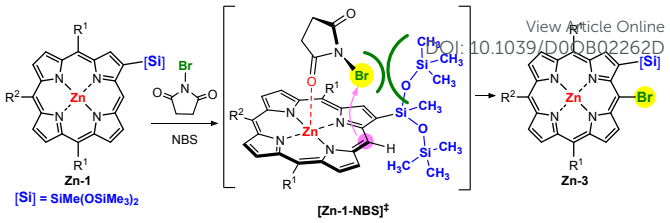


Entry	1	M	R¹, R²	Product	Yield 2 (%)	Yield 3 (%)
1	**2H-1a**	2H	Ph, Ph	**2H-2a**	92	0
2	**2H-1b**	2H	*n*-Bu, Ph	**2H-2b**	94	0
3	**2H-1c**	2H	*n*-Bu, CH_2CO_2Et	**2H-2c**	41	0
4	**2H-1d**	2H	*n*-Bu, Br	**2H-2d**	71	0
5	**2H-1e**	2H	Ph, Br	**2H-2e**	74	0
6	**Zn-1a**	Zn	Ph, Ph	**Zn-3a**	0	72
7	**Zn-1b**	Zn	*n*-Bu, Ph	**Zn-3b**	0	70
8[b]	**Zn-1c**	Zn	*n*-Bu, CH_2CO_2Et	**Zn-3c**	0	47
9	**Zn-1d**	Zn	*n*-Bu, Br	**Zn-3d**	0	66
10[c]	**Zn-1e**	Zn	Ph, Br	**Zn-3e**	0	54

[a] Reaction conditions, **1** (0.1 mmol), NBS (0.11 mmol), $CHCl_3$ (10 mL); yields are based on isolated product. [b] Pyridine (1 equiv) was added. [c] Succinimide (1 equiv) was added.

that the bromination of *zincated* β-silylporphyrin **Zn-1a** resulted in *meso*-bromoporphyrin **Zn-3a**,[14] but it did not yield any *ipso*-brominated porphyrins (Scheme 1b). The presence of a Zn(II) central metal ion in the porphyrin core completely altered the course of the bromination reaction.

Thereafter, we explored the regioselectivity of the bromination for other *free-base* and *zincated* β-silylporphyrins bearing aryl, alkyl, ester, and bromo groups (**2H-1b-e** and **Zn-1b-e**) using NBS (1.1 equivalents) in $CHCl_3$ at 0 °C to room temperature. Table 1 clearly shows that the presence of the Zn(II) central metal ion in the porphyrin core completely altered the reaction course of the bromination. Hence, the brominations of *free-base* β-silylporphyrins **2H-1a-e** occurred readily, yielding bromodesilylated β-bromoporphyrins (Entries 1–5). By sharp contrast, *zincated* β-silylporphyrins **Zn-1a-e** reacted with NBS at the *meso* position, yielding *zincated meso*-bromo-β-silylporphyrin **Zn-3a-e** without the substitution of the β-silyl group (Entries 6–10). These reactions tolerated aromatic and alkyl substituents, resulting in excellent-to-good yields of the *ipso*-substituted products **2H-2a**-**e** and *meso*-substituted products **Zn-3a**-**e**; no bromination of the phenyl rings or benzylic position of the alkyl group was observed (Entries 1–5 and 6–10). The bromination of ester-substituted porphyrins **2H-1c** and **Zn-1c** resulted in moderate yields of the desired products **2H-2c** and **Zn-3c**[15,16] (Entries 3 and 8). The *meso*-β-asymmetrically brominated porphyrins **2H-2d** and **2H-2e** were selectively obtained via the *ipso*-bromination of the β-silyl group from *meso*-bromo-β-silylporphyrins **2H-1d** and **2H-1e** (Entries 4 and 5). Contrastingly, the bromination of *zincated meso*-bromo-β-silylporphyrin yielded highly functionalized *zincated meso*,*meso*-dibromo-β-silyl-porphyrin **Zn-3d** and **Zn-3e**[17] (Entries 9 and 10). These results indicate that the bromination of *zincated* β-silylporphyrin **Zn-1** is a useful method for synthesizing a variety of *meso*,β-dual-functionalized porphyrins regioselectively.

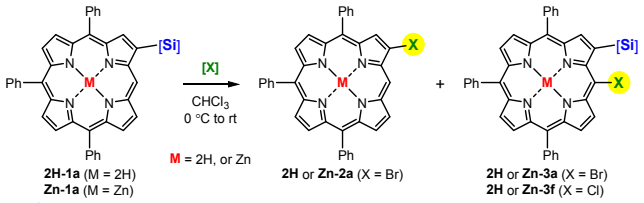


Scheme 2 Proposed coordination model for the regioselective *meso*-bromination of *zincated* β-silylporphyrin.

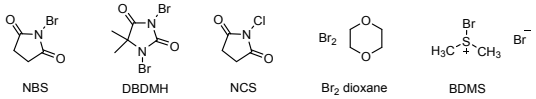
The bromination of *free-base* **2H-1** with NBS, which works as an electrophile, occurred at the *ipso*-position because of the stabilization effect offered to an adjacent carbonium ion by the carbon–silicon bond, which is known as the β-cation stabilization effect.[12,18] However, the bromination of *zincated* β-silylporphyrin **Zn-1** yielded *meso*-brominated porphyrin **Zn-3** without the *ipso*-substitution of the silyl group. Thus, the *meso*-bromination of *zincated* porphyrin **Zn-1** appears to have proceeded along a different reaction pathway from that of *free-base* **2H-1** porphyrin. We postulated that the *meso*-bromination of **Zn-1** may be assisted intramolecularly by the coordination of the NBS's carbonyl group to the porphyrin's zinc ion (Scheme 2). The tethered NBS may undergo electrophilic bromination at *the meso* position via **[Zn-1-NBS]‡** governed by the steric repulsion from the bulky silyl group to yield *zincated meso*-bromo-β-silylporphyrin **Zn-3**.

To evaluate the coordination effects of the brominating agents to the zinc ion of the porphyrin core on the regioselectivity of the *meso*-bromination, *N*-haloamide-based reagents bearing coordinative carbonyl groups, such as NBS, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), *N*-chloro-

Table 2 Examination of brominating agents [a].



Entry	M	[X] reagent	X	Yield 2a (%)	Yield 3a (%)
1	**2H**	**NBS**	**Br**	**92**	**0**
2	**2H**	**DBDMH**	**Br**	**83**	**0**
3	2H	Br_2	Br	65	0
4	2H	Br_2 dioxane	Br	38	0
5	2H	BDMS	Br	38	0
6	**Zn**	**NBS**	**Br**	**0**	**72**
7	**Zn**	**DBDMH**	**Br**	**0**	**66**
8	Zn	Br_2	Br	41	15
9	Zn	Br_2 dioxane	Br	36	11
10	Zn	BDMS	Br	34	8
11	**Zn**	**NCS**	**Cl**	**0**	**70**



[a] Reaction conditions **1** (0.1 mmol), Br reagent (0.11 mmol), $CHCl_3$ (10 mL); yields are based on isolated product.

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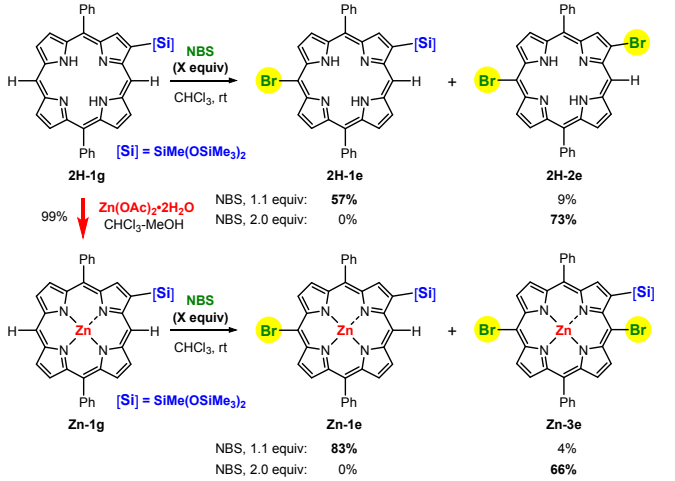
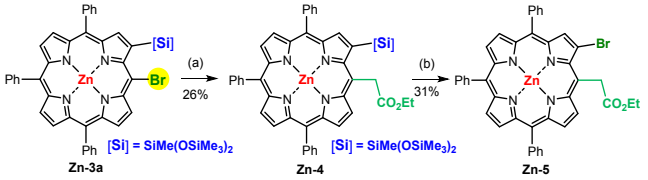
succinimide (NCS), and Br_2-based reagents lacking in the coordinative group, such as Br_2, Br_2-dioxane, and bromodimethyl-sulfonium bromide, were examined with *free-base* **2H-1a** and *zincated* **Zn-1a** (Table 2). In the bromination of *free-base* **2H-1a**, the predominant occurrence was the *ipso* displacement of the β-silyl group, regardless of the presence of the coordinative groups on the brominating agents (Entries 1–2 vs. 3–5). However, bromination with NBS and DBDMH selectively yielded *meso*-brominated β-silylporphyrin **Zn-3a** and the observed regioselectivity for *zincated* porphyrin **Zn-1a** was completely controlled by the presence of a coordinative carbonyl group on the brominating agents (Entries 6–7 vs. 8–10). Chlorination was also examined using NCS. Although the reaction of *free-base* **2H-1a** with NCS in $CHCl_3$ at 0 °C to room temperature did not occur at all,[19] *zincated* **Zn-1a** readily reacted, resulting in a 70% yield of *zincated meso*-chloro-β-silylporphyrin **Zn-3f**. These results indicated that the central zinc ion of the porphyrin core activated the NCS via the coordination of the carbonyl group, and this coordinated NCS selectively yielded the *meso*-chlorinated product. Therefore, we concluded that the *meso*-regioselectivity of the bromination of *zincated* β-silylporphyrin by NBS was controlled by the coordination of the NBS's carbonyl group to the zinc ion.

This simple bromination procedure can be applied to the synthesis of various substitution types of dual- and triple-functionalized porphyrins using *meso*,*meso*-unsubstituted-β-silylporphyrin **2H-1g** and **Zn-1g** (Scheme 3). In the bromination of *free-base* **2H-1g**, a reaction with NBS (1.1 equiv) occurred at the less-crowded *meso* position, resulting in a 57% yield of *meso*-bromo-β-silylporphyrin **2H-1e**, whereas, the use of NBS (2 equiv) resulted in a 73% yield of asymmetric *meso*,β-dibromoporphyrin **2H-2e**. Zincated **Zn-1g** was readily synthesized from *free-base* **2H-1g** with $Zn(OAc)_2$ in a 99% yield. With the use of NBS (1.1 equiv), *meso*,*meso*-unsubstituted **Zn-1g** also reacted regioselectively at the *meso* position far from the bulky silyl group, resulting in an 83% yield of mono-brominated **Zn-1e**. The bromination of NBS (2 equiv) occurred at the two vacant *meso* positions without replacing the β-silyl group, resulting in a 66% yield of highly functionalized *zincated* *meso*,*meso*-dibromo-β-silylporphyrin **Zn-3e**.



Scheme 3 Regioselective bromination of *free-base* and *zincated meso*-unsubstituted-β-silylporphyrin **2H-1g** and **Zn-1g** with NBS (1.1 and 2 equiv).



Scheme 4 Regioselective *meso*,β-functionalization of **Zn-3a**—the yields reported are for isolated materials. Reaction conditions—(a) $BrZnCH_2CO_2Et$ (50 equiv), $Pd(OAc)_2$ (10 mol%), Cy_3P (20 mol%), THF, 60 °C, 2 d; (b) NBS (1.5 equiv), $CHCl_3$, rt, and 1 h.

Further functionalization of the *meso* and β positions was conducted to demonstrate the synthetic utility of *meso*,β-dual-functionalized porphyrin **Zn-3a** (Scheme 4). The regioselective introduction of the ethoxycarbonylmethyl group to the *meso* position was achieved via palladium-catalyzed Negishi cross-coupling with a bromozinc reagent,[20] yielding ester-functionalized **Zn-4**. The bromination of the β-silyl group on **Zn-4** occurred readily with NBS, yielding **Zn-5**. Although the reaction conditions were not fully optimized, it was established that both *meso*-bromo and β-silyl groups can be independently transformed into various functional groups.

To conclude, we have developed an efficient method for synthesizing *meso*,β-dual-functionalized porphyrins. The reaction of *zincated* β-silylporphyrin with NBS gave *meso*-bromo-β-silyl-porphyrin in good yield with high regioselectivity under mild reaction conditions, whereas, the bromination of *free-base* β-silylporphyrin yielded β-bromoporphyrin via the *ipso*-substitution of the β-silyl group. These β- and *meso*-bromination events demonstrated favorable substrate compatibility. A close study of the relationship between the bromination's regioselectivity and the brominating agent's structure suggested that the coordination of NBS's carbonyl group to the zinc ion of the porphyrin core is an essential factor contributing to the *meso*-selectivity of the bromination. The exploration of further synthetic applications of *meso*,β-dual-functionalized porphyrins with a silyl group and halogen is currently underway in our research group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 The structure of **Zn-3c** was confirmed by X-ray crystallography (CCDC 2035888). See supporting information.

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