An efficient one-pot procedure for asymmetric bifunctionalization of 5,15-disubstituted porphyrins: a simple preparation of *meso* acyl-, alkoxycarbonyl-, and carbamoyl-substituted *meso*-formylporphyrins†

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An efficient one-pot procedure which converts 5,15-disubstituted porphyrins into their corresponding *meso* acyl-, alkoxycarbonyl-, and carbamoyl-substituted *meso*-formylporphyrins has been developed, where the procedure involves a sequential S_NAr reaction of porphyrins with $PyMe_2SiCH_2Li$, followed by acylation or related reactions and oxidation.

There has been continuous interest in the synthesis of porphyrins and their derivatives due to their ubiquitous nature and broad spectrum of applications in different fields such as catalysis, medicine, molecular recognition/sensing, and materials science.[1,2] It is also well documented that the physical, chemical and biological properties of porphyrins can be precisely controlled through the introduction of peripheral substituents with diverse electronic and steric environments.[1] As a consequence, intensive efforts have been dedicated to the discovery of new synthetic intermediates and strategies for preparing porphyrin derivatives with a variety of peripheral substituents.[3–5] Asymmetric porphyrins bearing two distinct reactive carbonyl groups at the *meso* positions (their generalized structure is illustrated in Fig. 1) are regarded as valuable building blocks for more complex porphyrin systems, as each of these carbonyl groups directly attached on the porphyrin core can be individually replaced with other functionalities. However, to our knowledge, there are as yet no reports on the preparation of such asymmetric porphyrins that bear two carbonyl groups with distinct chemical reactivities.[6]

Herein, we report our studies on the development of an efficient, general one-pot procedure for the direct conversion of the 5,15-disubstituted porphyrin **1** into the *meso*-acyl-, *meso*-alkoxycarbonyl-, and *meso*-carbamoyl-substituted *meso*-formylporphyrins **3**, **5**, and **7**, respectively. The process involves a sequential nucleophilic substitution (S_NAr reaction)[7] with (2-pyridyldimethylsilyl)methyllithium ($PyMe_2SiCH_2Li$)[8] followed by acylation or related reactions and oxidation. This simple one-pot procedure can be carried out under mild conditions with a wide range of 5,15-diaryl- and 5,15-dialkyl-substituted porphyrins, allowing direct access to a variety of asymmetric porphyrins with formyl groups and other chemically reactive functionalities directly attached at the *meso* positions in good yields.

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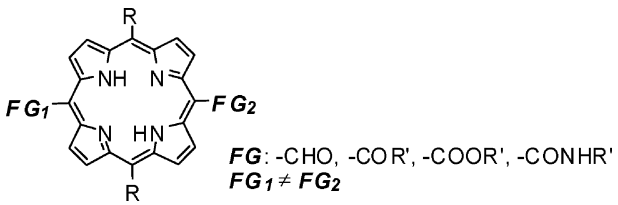
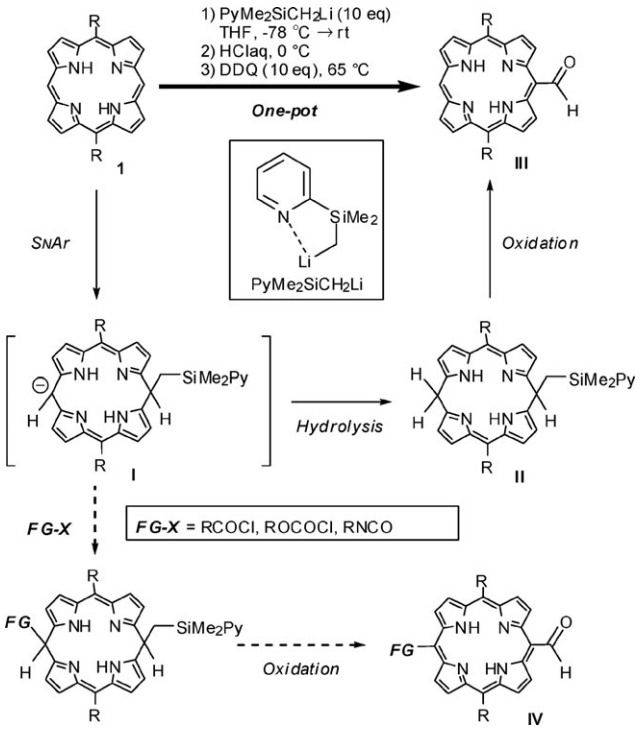


Fig. 1 Asymmetric bifunctionalized porphyrins bearing two different carbonyl groups at the *meso*-positions.

Recently, our research group disclosed a novel direct *meso* formylation of the 5,15-disubstituted porphyrins **1** based on a one-pot three-step procedure *via* the S_NAr reaction of porphyrins with $PyMe_2SiCH_2Li$ followed by hydrolysis and oxidation with DDQ, where the $PyMe_2SiCH_2$ group works as a latent formyl functionality in the reaction.[5c] As shown in Scheme 1, the reaction proceeds through the anionic intermediate **I** generated from the S_NAr reaction of porphyrins with $PyMe_2SiCH_2Li$, which is subsequently hydrolyzed to form the dihydroporphyrin **II** and that in turn is oxidized to



Scheme 1 Reaction pathway for one-pot formylation of 5,15-disubstituted porphyrins using S_NAr reaction with $PyMe_2SiCH_2Li$, and our hypothesis for their direct asymmetric bifunctionalization.

the *meso*-formylporphyrin **III**. Thus, we envisaged that the anionic intermediate **I** would be trapped by electrophiles (FG-X) such as acyl chlorides to form the asymmetric porphyrin **IV** with a formyl group and other chemically reactive functionalities.

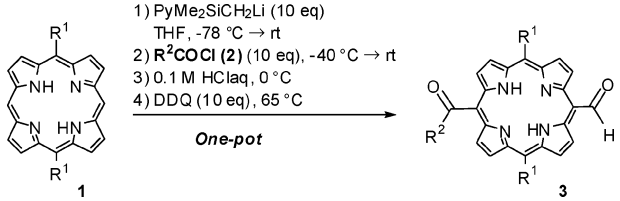
In order to confirm our hypothesis, we initially examined the asymmetric bifunctionalization of 5,15-diphenylporphyrin **1a** by using a one-pot procedure involving a S_NAr reaction with $PyMe_2SiCH_2Li$ followed by the trapping of the resulting anion with benzoylchloride **2a** as an electrophile and oxidation. Thus, a solution of **1a** in THF was treated in the following order with: 10 equiv. of $PyMe_2SiCH_2Li$ at −78 °C to room temperature, 10 equiv. of **2a** at −40 °C to room temperature, aqueous HCl at 0 °C, and then 10 equiv. of DDQ at 65 °C. The one-pot sequential reaction proceeded smoothly, enabling the direct conversion of **1a** into the desired asymmetric bifunctionalized product 5-benzoyl-15-formyl-10,20-diphenylporphyrin **3aa** in 85% yield (Table 1, entry 1).

To determine the scope of the above procedure, different 5,15-substituted free-base porphyrins **1a–e** and acylchlorides **2a–e** were employed as substrates (Table 1). The benzoylchloride derivatives **2b** and **2c** with methoxy and trifluoromethyl substituents on their aromatic ring are compatible with the asymmetric bifunctionalization of **1a** to afford the corresponding *meso* acyl-substituted formylporphyrins **3ab** and **3ac** in good yields (entries 2 and 3). Both the primary and the secondary aliphatic acylchlorides could also participate as substrates in the transformation (entries 4 and 5). With regard to 5,15-diarylporphyrins, substrates with electron-rich, electron-neutral, and electron-poor aromatic moieties on the porphyrin core are all compatible with the asymmetric bifunctionalization conditions (entries 6–8). The 5,15-dialkyl-substituted porphyrin **1e** also yielded a favorable reaction (entry 9).

With the use of the chloroformate **4** as an electrophile, the *meso*-alkoxycarbonyl-substituted formylporphyrins **5** can also be prepared similarly (Table 2). For example, the sequential treatment of **1a** with $PyMe_2SiCH_2Li$ (10 equiv.) followed by **4a** (10 equiv.), aqueous HCl, and DDQ (10 equiv.) led to the formation of 5-formyl-15-methoxycarbonyl-10,20-diphenylporphyrin **5aa** in 76% yield (entry 1). Likewise, other porphyrins **1b–e** and chloroformates including isopropylchloroformate **4b** and benzylchloroformate **4c** readily participated in the transformation as substrates, furnishing the corresponding *meso*-alkoxycarbonyl-substituted formylporpyrins in good to moderate yields (entries 2–7).

The one-pot procedure can also be applied to the synthesis of the *meso*-carbamoyl-substituted formylporphyrins **7** by using isocyanates **6** as an electrophile (Table 3). For example, subjecting the diphenylporphyrin **1a** and phenylisocyanates **6a–c** substituted with electron-rich, electron-neutral, and electron-poor arenes to the asymmetric bifunctionalization conditions led to the desired *meso*-carbamoyl-substituted formylporphyrins in 73–60% yields (entries 1–3). The process is not limited to arylisocyanates. Nonbranched, branched, and cyclic alkylisocyanates were all compatible with the

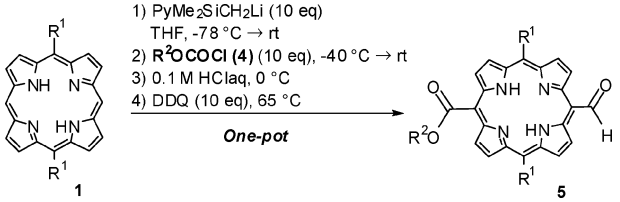
Table 1 One-pot preparation of *meso*-acyl-substituted formylporphyrins **3** using acylchloride **2** as an electrophile



Entry	Porphyrin	Acylchloride	Product	Yield[a] (%)
1	**1a** (R^1 = Ph)	**2a** (R^2 = Ph)	**3aa**	85
2	**1a** (R^1 = Ph)	**2b** (R^2 = 4-MeOPh)	**3ab**	70
3	**1a** (R^1 = Ph)	**2c** (R^2 = 4-CF_3Ph)	**3ac**	77
4	**1a** (R^1 = Ph)	**2d** (R^2 = Me)	**3ad**	68
5	**1a** (R^1 = Ph)	**2e** (R^2 = *i*Pr)	**3ae**	61
6	**1b** (R^1 = *p*-Tol)	**2a** (R^2 = Ph)	**3ba**	70
7	**1c** (R^1 = 3-MeOPh)	**2a** (R^2 = Ph)	**3ca**	74
8	**1d** (R^1 = 3-CF_3Ph)	**2a** (R^2 = Ph)	**3da**	72
9	**1e** (R^1 = *i*Bu)	**2a** (R^2 = Ph)	**3ea**	71

[a] Isolated yield.

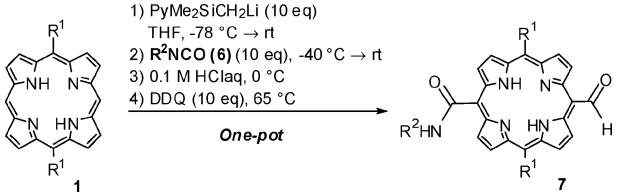
Table 2 One-pot preparation of *meso*-alkoxycarbonyl-substituted formylporphyrins **5** using chloroformates **4** as an electrophile



Entry	Porphyrin	Acylchloride	Product	Yield[a] (%)
1	**1a** (R^1 = Ph)	**4a** (R^2 = Me)	**5aa**	76
2	**1a** (R^1 = Ph)	**4b** (R^2 = *i*Pr)	**5ab**	70
3	**1a** (R^1 = Ph)	**4c** (R^2 = CH_2Ph)	**5ac**	46
4	**1b** (R^1 = *p*-Tol)	**4a** (R^2 = Me)	**5ba**	65
5	**1c** (R^1 = 3-MeOPh)	**4a** (R^2 = Me)	**5ca**	62
6	**1d** (R^1 = 3-CF_3Ph)	**4a** (R^2 = Me)	**5da**	60
7	**1e** (R^1 = *i*Bu)	**4a** (R^2 = Me)	**5ea**	60

[a] Isolated yield.

Table 3 One-pot preparation of *meso*-carbamoyl-substituted formylporphyrins **7** using isocyanates **6** as an electrophile



Entry	Porphyrin	Isocyanate	Product	Yield[a] (%)
1	**1a** (R^1 = Ph)	**6a** (R^2 = Ph)	**7aa**	73
2	**1a** (R^1 = Ph)	**6b** (R^2 = 4-MeOPh)	**7ab**	65
3	**1a** (R^1 = Ph)	**6c** (R^2 = 4-BrPh)	**7ac**	60
4	**1a** (R^1 = Ph)	**6d** (R^2 = Et)	**7ad**	85
5	**1a** (R^1 = Ph)	**6e** (R^2 = *i*Pr)	**7ae**	74
6	**1a** (R^1 = Ph)	**6f** (R^2 = *c*-C_6H_{11})	**7af**	71
7	**1c** (R^1 = 3-MeOPh)	**6d** (R^2 = Et)	**7cd**	66
8	**1d** (R^1 = 3-CF_3Ph)	**6d** (R^2 = Et)	**7dd**	68
9	**1e** (R^1 = *i*Bu)	**6d** (R^2 = Et)	**7ed**	67

[a] Isolated yield.

asymmetric bifunctionalization conditions, and gave the corresponding asymmetric porphyrins in good yields (entries 4–6). As expected, the reactions of other porphyrins **1c–e** with ethylisocyanate **6e** proceeded smoothly to furnish the corresponding *meso*-carbamoyl-substituted formylporphyrins **7cd**, **7dd**, and **7ed** in 68–66% yields (entry 7–9).

Although most of the reactions described above were performed on a 0.1 mmol scale (see ESI†), they can easily be scaled up if needed. For example, the reaction employing the porphyrin **1a** and the ethylisocyanate **6e** as substrates can be carried out on a 1 mmol scale under similar reaction conditions, furnishing the desired porphyrin **7ae** at 515 mg and in 92% yield, which is virtually the same yield as that on a 0.1 mmol scale (*cf.* Table 3, entry 4).

In summary, we have developed a novel and facile one-pot procedure for the direct asymmetric bifunctionalization of 5,15-disubstituted free base porphyrins *via* a sequential S_NAr reaction with $PyMe_2SiCH_2Li$ followed by acylation or related reactions and oxidation. This simple one-pot procedure provides an efficient approach to the synthesis of a variety of asymmetric free base porphyrins which bear a formyl group and other chemically reactive functional groups, such as acyl, alkoxycarbonyl, and carbamoyl functionalities, at the *meso* positions in good yields. The operational simplicity as well as the mild reaction conditions and the broad substrate scope render this method attractive for the synthesis of more complicated porphyrin derivatives, which could find potential applications in areas such as catalysis, medicine, and molecular recognition/sensing. Such studies are currently under way in our laboratory, the results from which will be reported in due course.

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