[14] Although a decrease in the concentration of amine additive was observed, we have not quantified the extent of its conversion into a silylamine.

[15] If this mechanism is operative, it would require that the product amine be liberated from the silicon polymer by exchange with primary amine.

[16] Certain mechanistic similarities exist between this process and asymmetric dihydroxylation of olefins: J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125.

Facile *meso* Functionalization of Porphyrins by Nucleophilic Substitution with Organolithium Reagents**

Werner W. Kalisch and Mathias O. Senge*

Dedicated to Professor Emanuel Vogel
on the occasion of his 70th birthday

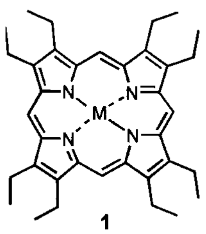
It is generally accepted that the *meso* positions of porphyrins are the most reactive both for electrophilic and nucleophilic substitutions.[1] While several examples have been described for S_E reactions on porphyrins[1, 2] only scattered attempts have been made to use S_N reactions for the modification of porphyrins. Published examples of the latter all utilized some form of activated porphyrin, for example π-radical cations or dications,[3] high-valent metal derivatives,[4] or activated porphyrins with electron-withdrawing substituents.[5] Some of these reactions are suitable only for the preparation of 5,5′-disubstituted dihydroporphyrins (phlorins).[4b, 6] At best two substituents could be introduced with electrophilic or nucleophilic reagents, and the methods were limited with regard to the starting porphyrin or the introduction of different substituents.[7] To date, no general method exists for the direct *meso* substitution of unactivated porphyrins with alkyl or aryl residues or for the introduction of more than two substituents.

During a systematic study on the use of organometallic reagents for C–C coupling reactions, we found that octaethylporphyrin (H_2(oep); oep = dianion of octaethylporphyrin) undergoes facile substitution reactions with organolithium reagents; this allows the synthesis of a variety of porphyrins with alkyl or aryl substituents at the *meso* positions. Treatment of [Ni(oep)] (**1a**) with butyllithium (3–4 equiv) between −80 and −100 °C in THF followed by hydrolysis of the intermediate (a Meisenheimer-type complex) provided the corresponding 5-butyl-15-hydroporphodimethene. Subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the *meso*-butylporphyrin **2a** in quantitative yield. The reaction sequence formally proceeds as shown in Equation (a).

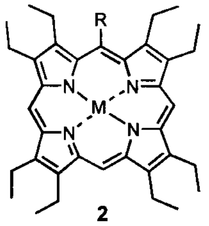
$$[\mathrm{M(oep)}]\xrightarrow{\mathrm{LiR}}[\mathrm{M(oepLiR)}]\xrightarrow{\mathrm{H_2O}}[\mathrm{M(oepHR)}]\xrightarrow[-\mathrm{H_2}]{\mathrm{DDQ}}[\mathrm{M(oepR)}] \qquad (a)$$

The reaction is easily extended to a variety of different alkyl and aryl reagents, including those that allow further chemical modifications and coupling reactions. For example, reaction of **1a** with 2-(1,3-dioxane-2-yl)ethyllithium gave **2e** in 70% yield. The reaction is not limited to alkyllithium reagents, but can also be used for the convenient introduction of aryl groups. Reaction of phenyllithium with **1a** gave **2f** in 65% yield. Again, aryl substituents could be introduced which will allow further chemical transformations. Compound **2h**, whose 4-bromophenyl group is useful for other organometallic coupling reactions, could be prepared from **1a** with *p*-bromophenyllithium in 40% yield. Introduction of the 2,5-dimethoxyphenyl group in **2i**, which proceeded in 65% yield, is an example of the synthesis of donor–acceptor systems (by formation of the benzoquinone). The free base porphyrins substituted in the 5-position are available by demetalation of the nickel(II) complexes. For example, treatment of **2a** with concentrated sulfuric acid gave **2b** in 75% yield.

Next, we turned out attention to the reactivity of different metals in the same porphyrin. Treatment of **1b** with butyllithium under standard conditions gave the respective free base **2b** in 40% yield, while **1c** and **1d** could be converted into the monobutylmetalloporphyrins **2c** and **2d** in 75 and 40% yield, respectively. Even more surprising was the result that free base porphyrins such as **1e** could be treated directly with butyllithium to give **2b** in 50% yield or with phenyllithium to give **2g** in 90% yield. Presumably, this reaction proceeds by initial formation of a dilithioporphyrin [Li_2(oep)] of the type

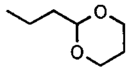
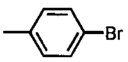
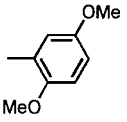


1



2

	M
1a	Ni
1b	Zn
1c	Cu
1d	Co
1e	2H

	M	R
2a	Ni	Bu
2b	2H	Bu
2c	Cu	Bu
2d	Co	Bu
2e	Ni	
2f	Ni	Ph
2g	2H	Ph
2h	Ni	
2i	Ni	

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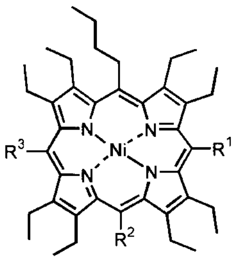
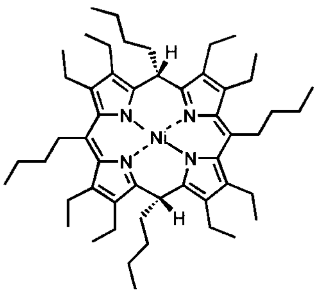
described by Arnold.[8] With the exception of the reaction of free base porphyrins with phenyllithium, nickel complexes gave higher yields and were used for most reactions.

The reaction is not limited to the introduction of one *meso* substituent. With butyllithium as reagent, **2a** (λ_{max} (CH_2Cl_2) = 410, 572 nm) could be converted into a dialkylated product, which was present as a regioisomeric mixture (**3a**, 70%, λ_{max} = 427, 595 nm; **3b**, 15%, λ_{max} = 423, 595 nm). The regioisomers could be separated by chromatography and again be used for another substitution/oxidation cycle with butyllithium to yield 5,10,15-tributylporphyrin (**3c**) quantitatively (λ_{max} = 441, 613 nm). A further reaction sequence starting with butyllithium resulted in the conversion of **3c** into **3d** (50%, λ_{max} = 459, 634 nm); porphyrin **4** was formed as a side product (40%, λ_{max} = 451, 551 nm).



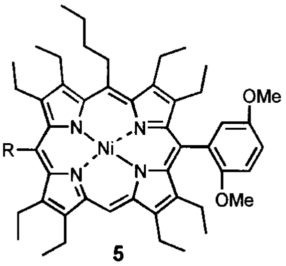
3

3a, R^1 = Bu, R^2 = R^3 = H
3b, R^1 = R^3 = H, R^2 = Bu
3c, R^1 = R^2 = Bu, R^3 = H
3d, R^1 = R^2 = R^3 = Bu



4

Highly substituted porphyrins such as **3a**–**d** are of principal interest with regard to studies on the conformational flexibility of porphyrins.[9] Sterically encumbered dodecaalkylporphyrins such as **3d** cannot be obtained by conventional porphyrin syntheses (acid-catalyzed condensation of pyrroles and aldehydes followed by oxidation); instead, an unoxidizable porphodimethene of unknown configuration is formed.[9a] The structure of **3c**, one of the highly substituted alkylporphyrins we prepared, is shown in Figure 1.[10] The macrocycle adopts a ruffled conformation, and the *meso* positions are significantly displaced out of the plane (average displacement of the *meso*-carbon atoms 0.93 Å). Despite the presence of only three *meso*-butyl groups in **3c** the conformation is already more nonplanar than that in (pyridine)[5,10,15,20-tetra(*tert*-butyl)porphyrinato]zinc(II) (average displacement of the *meso*-carbon atoms 0.9 Å), the most nonplanar porphyrin with a ruffled conformation described so far.[9b] Therefore, **3d** will be even more nonplanar. The synthetic methodology presented here should allow the facile preparation of a wide variety of novel nonplanar porphyrins with tailor-made distortion modes. As examples of porphyrins with mixed substitution patterns, **5a** was prepared from **2a** in 50% yield and **5b** from **3a** in 50% yield with use of 2,5-dimethoxyphenyllithium.



5

5a, R = H
5b, R = Bu

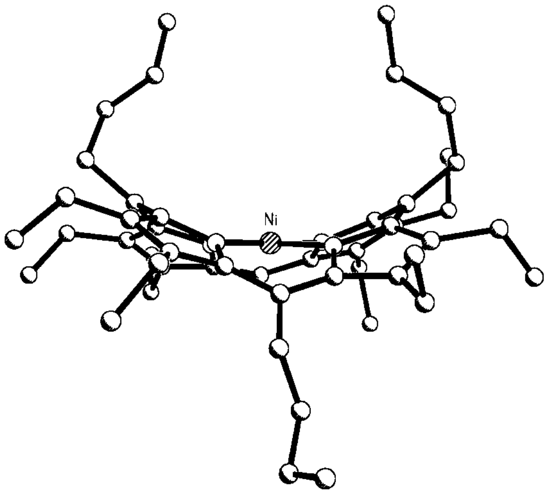


Figure 1. Side view of the molecular structure of **3c** in the crystal. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å]: Ni–N21 1.882(3), Ni–N22 1.873(3), Ni–N23 1.883(3), Ni–N24 1.880(3); the average deviation of the 24 macrocycle atoms from their least-squares plane is 0.45 Å; the average deviation of the *meso*-carbon atoms from the N-N-N-N plane is 0.93 Å; individual displacements of *meso*-carbon atoms [Å]: C5 0.94, C10 1.04, C15 0.94, C20 0.80.

While working with the more sterically encumbered porphyrins **3a**–**d**, we obtained brown side products in high yield when the reaction temperature was allowed to rise above −80 °C. These products were identified as 5,15-dialkylporphodimethenes with *syn*-axial orientation of the *meso*-alkyl substitutents. The molecular structure of the side product **4** formed during the synthesis of **3d** is shown in Figure 2.[10, 11] These porphodimethenes could not be oxidized to porphyrins with either DDQ or Br_2. The exact structure of the porphodimethene intermediates in our porphyrin synthesis is still unknown. We assume that it might be different

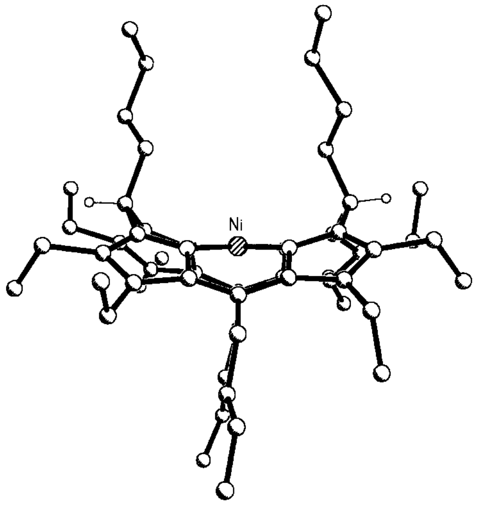
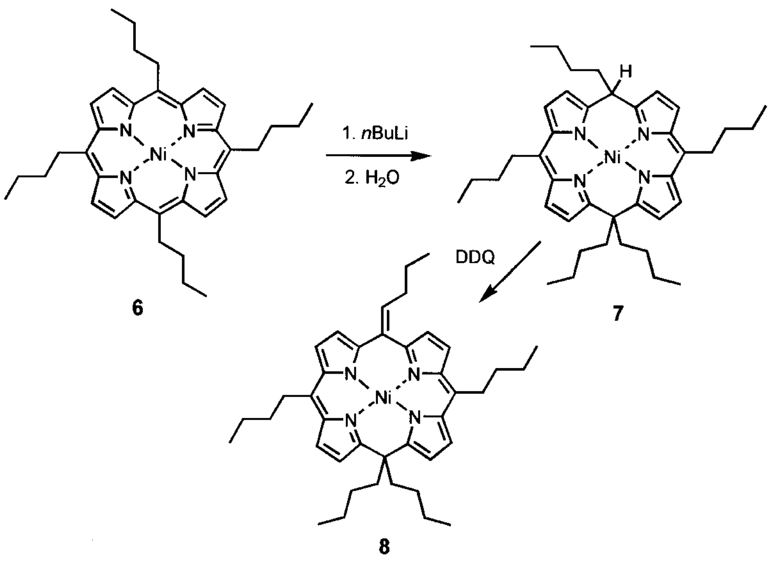


Figure 2. Side view of the molecular structure of **4** in the crystal. Only the *meso*-hydrogen atoms are shown for clarity.



Scheme 1. Synthesis of **8**.

from the *syn*-axial structure of **4** and that the configuration of the porphodimethene intermediates formed during the synthesis of sterically encumbered porphyrins is of crucial importance for the potential oxidation to the desired porphyrin.

To study the reaction in more detail we utilized tetra-*meso*-alkylporphyrins such as **6** as starting materials (Scheme 1). Krattinger and Callot[6] showed that tetraphenylporphyrin reacts with butyllithium under formation of a phlorin and chlorin. Treatment of **6** with butyllithium at −100 °C followed by addition of water gave **7** in 90 % yield ($\lambda_{max} = 432, 525$ nm). Owing to the dialkylated *meso* position the porphodimethene **7** cannot be converted into a porphyrin. Nevertheless, treatment of **7** with DDQ gave **8** in 80 % yield ($\lambda_{max} = 434, 541$ nm); here a *meso*- and an *ipso*-carbon atom were oxidized, leading to a novel porphodimethene with an exocyclic double bond. We are currently expanding the scope of this reaction towards the synthesis of asymmetric porphyrins with mixed substituent types and towards biomimetic systems, and are studying the reaction mechanism in more detail.

Experimental Section

[Ni(oep)] (**1a**) (100 mg, 0.17 mmol) was dissolved in dried THF (60 mL) and cooled to −70 °C. Within 10 min butyllithium (0.6 mmol, 0.3 mL of a 2 M solution in cyclohexane) was added dropwise. The cold bath was removed, and water (1 mL) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 10 min, DDQ (10 mL of a 0.06 M solution in dichloromethane) added, and the mixture stirred for another 20 min. Finally, the reaction mixture was filtered through neutral alumina (Brockmann grade I) and subjected to column chromatography on neutral alumina (grade III) with hexane/CH_2Cl_2 (4/1) as eluant. Preparation of higher alkylated porphyrins **3a–d** required lower temperatures (−80 to −100 °C) and less solvent.

UV/Vis and ^{1}H NMR data for **2a** and **3a–d**: UV/Vis (CH_2Cl_2): λ_{max}(**2a**) (lg ε) = 410 nm (5.23), 535 (4.02), 572 (4.10); λ_{max}(**3a**) (lg ε) = 427 nm (5.19), 555 (4.09), 595 (3.99); λ_{max}(**3b**) (lg ε) = 423 nm (5.20), 552 (4.00), 595 (3.82); λ_{max}(**3c**) (lg ε) = 441 nm (5.08), 570 (3.91), 613 sh (3.20); λ_{max}(**3d**) (lg ε) = 459 nm (4.93), 5.91 (3.92), 634 (3.56). ^{1}H NMR (500 MHz, $CDCl_3$): δ(**2a**) = 0.51 (t, J = 7.5 Hz, 3 H, butyl-CH_3), 0.85 (m, 4 H, butyl-CH_2), 1.68, 1.74, 1.75, 1.85 (each t, J = 7.5 Hz, 24 H, ethyl-CH_3), 3.79 (br s, 16 H, ethyl-CH_2), 4.42 (t, J = 7.5 Hz, 2 H, 5-C$H_2$$CH_2CH_2CH_3$), 9.32 (s, 1 H, 15-*H*), 9.33 (s, 2 H, 10,20-*H*); δ(**3a**) = 0.60 (t, J = 7.5 Hz, 6 H, butyl-CH_3), 0.77 (br s, 4 H, butyl-CH_2), 1.05 (m, 4 H, butyl-CH_2), 1.69, 1.75, 1.85 (each t, J = 7.5 Hz, 24 H, ethyl-CH_3), 3.73 (br s, 16 H, ethyl-CH_2), 4.27 (t, J = 7.5 Hz, 4 H, 5,10-C$H_2$$CH_2CH_2CH_3$), 9.05 (s, 2 H, 15,20-*H*); δ(**3b**) = 0.53 (t, J = 7.5 Hz, 6 H, butyl-CH_3), 0.85 (m, 6 H, butyl-CH_2), 0.93 (m, 4 H, butyl-CH_2), 1.65, 1.79 (each t, J = 7.5 Hz, 24 H, ethyl-CH_3), 3.69 (br s, 16 H, ethyl-CH_2), 4.29 (t, J = 7.5 Hz, 4 H, 10,20-C$H_2$$CH_2CH_2CH_3$), 9.05 (s, 2 H, 10-20-*H*); δ(**3c**) = 0.58 (t, J = 7.5 Hz, 6 H, butyl-CH_3), 0.65 (br s, 2 H, butyl-CH_2), 0.97 (br s, 4 H, butyl-CH_2), 1.04 (br s, 6 H, butyl-CH_2), 1.65, 1.75, 1.78, 1.79 (each t, J = 7.5 Hz, 24 H, ethyl-CH_3), 3.44–3.52 (m, 16 H, ethyl-CH_2), 4.03–4.18 (m, 6 H, C$H_2$$CH_2CH_2CH_3$), 8.77 (s, 1 H, 20-*H*); δ(**3d**) = 0.59 (t, J = 7.5 Hz, 12 H, butyl-CH_3), 0.73, 1.06 (each m, 6 H, CH_2CH_2C$H_2$$CH_3$), 1.74 (t, J = 7.5 Hz, 24 H, ethyl-CH_3), 3.48, 3.58 (each br s, 16 H, ethyl-CH_2), 4.03 (m, 6 H, C$H_2$$CH_2CH_2CH_3$).

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[10] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100789. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] The formation of different configuration isomers for 5,5′,15,15′-substituted decaalkylporphyrins has been described by Buchler in his elegant studies on the reductive alkylation of [Zn(oep)].[7] Crystal structures of his stable porphodimethenes showed the same *syn*-axial orientation of the *meso*-alkyl groups as described here for **4**. See ref. [7 b–d] and references therein.

1433-7851/98/3708-1109 $ 17.50+.50/0