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An efficient one-pot protocol for asymmetric bifunctionalization of 5,15-disubstituted porphyrins: direct access to *meso* activated alkenyl-substituted *meso*-formylporphyrins

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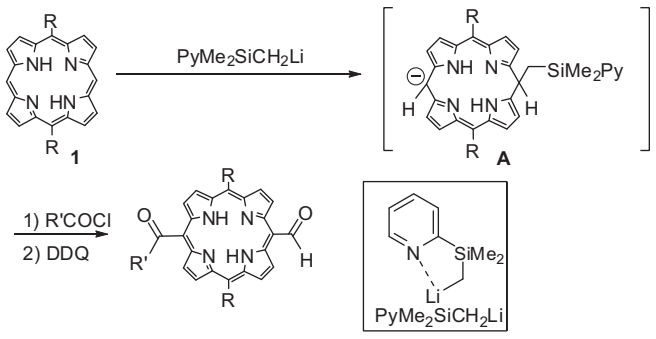
ABSTRACT

An efficient one-pot protocol for the direct conversion of free base 5,15-disubstituted porphyrins into the corresponding *meso* activated alkenyl-substituted *meso*-formylporphyrins has been developed using a sequential S_NAr reaction with $PyMe_2SiCH_2Li$, conjugate addition to enones or alkenoates in the presence of TMSCl, and oxidation with DDQ.

Interest in the chemistry of porphyrins and related tetrapyrrolic macrocycles has increased greatly in recent years, since these compounds have potentially important applications in many areas of chemistry, biology, and material sciences,[1] serving as, for example, homogeneous catalysts,[2] medicines for photodynamic therapy (PDT),[3] materials for nonlinear optics (NLO) and solar energy conversion systems,[4] and synthetic receptors for various organic and inorganic species.[5] Therefore, immense effort has been devoted to the development of novel and efficient synthetic strategies and intermediates for the preparation of porphyrin derivatives with a variety of peripheral substituents.[6,7] In this context, 'multifunctional porphyrins' that possess two or more different reactive functional groups, such as carbonyl, halogenic, alkenyl, and alkynyl groups, on the porphyrin core would be particularly attractive starting materials for further manipulation to construct more complex porphyrin derivatives, because each functional group, which is directly attached to the ring, can be individually replaced with other functionalities. Despite significant advances in the synthetic pathways and strategies in the field of porphyrin chemistry, only a limited number of general methods have been developed for the direct introduction to the porphyrin core of more than one reactive functional group, even with two functionalities, giving distinct reactivity.[8]

Recently, we reported an efficient one-pot procedure for the direct conversion of 5,15-disubstituted free base porphyrins into the corresponding *meso* acyl-substituted *meso*-formylporphyrins.[7a] As shown in Scheme 1, this one-pot asymmetric bifunctionalization of free base porphyrins involves a sequential nucleophilic substitution (S_NAr reaction)[9] of porphyrins **1** with (2-pyridyldimethylsilyl)methyllithium($PyMe_2SiCH_2Li$),[10] followed by trapping of the resulting anion **A** with acylchlorides (R′COCl) as an electrophile and oxidation with DDQ, where the $PyMe_2SiCH_2$ group works as a latent formyl functionality in the reaction.[7b] As a follow-up of our work, we chose α,β-unsaturated carbonyl compounds as an electrophile in the asymmetric bifunctionalization of porphyrins based on the S_NAr strategy with $PyMe_2SiCH_2Li$. Herein, we report the first example of an efficient direct



Scheme 1. Our previous work on one-pot preparation of *meso*-acyl-substituted *meso*-formylporphyrins.

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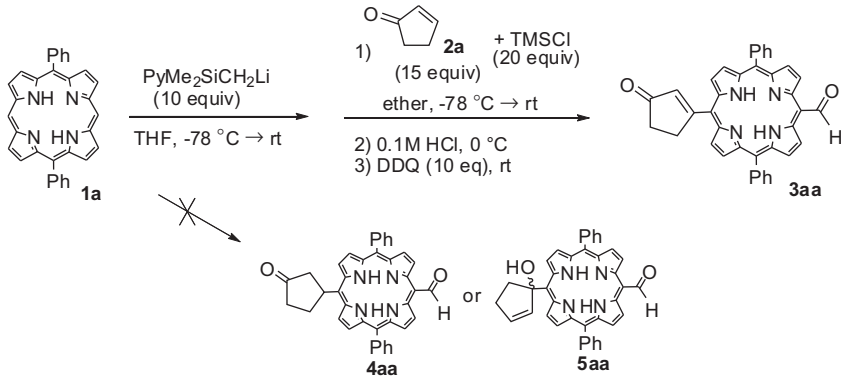
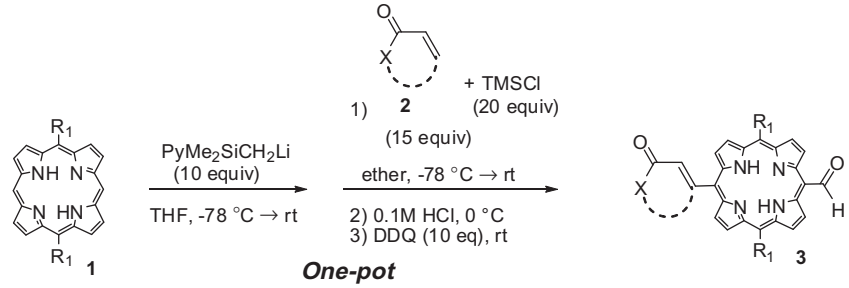
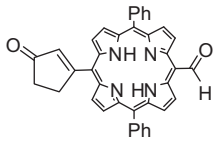
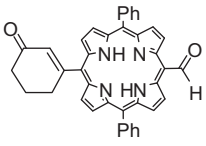


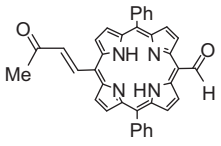
Scheme 2. One-pot direct conversion of 5,15-diphenylporphyrin **1a** to *meso* activated alkenyl-substituted *meso*-formylporphyrin **3aa** using cyclopentenone **2a** as an electrophile.

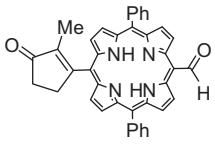
Table 1
Scope of 5,15-disubstituted porphyrins **1** and α,β-unsaturated carbonyl compounds **2** for the one-pot preparation of *meso* activated alkenyl-substituted *meso*-formylporphyrins **3**[a]

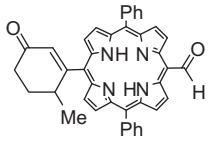


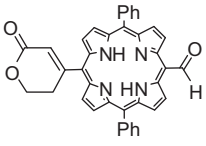

3aa (71%)

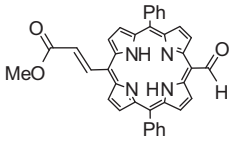

3ab (69%)

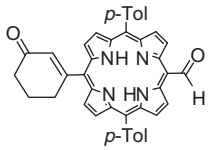

3ac (54%)[b]

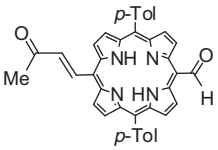

3ad (nd)

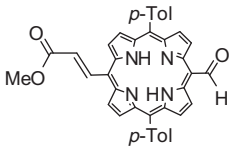

3ae (nd)

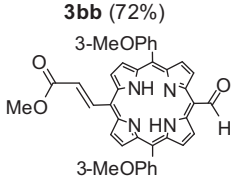

3af (43%)

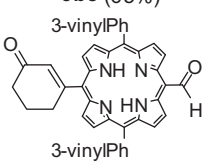

3ag (41%)[b,c]

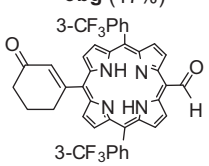

3bb (72%)

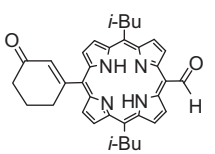

3bc (65%)[b]


3bg (47%)[b]

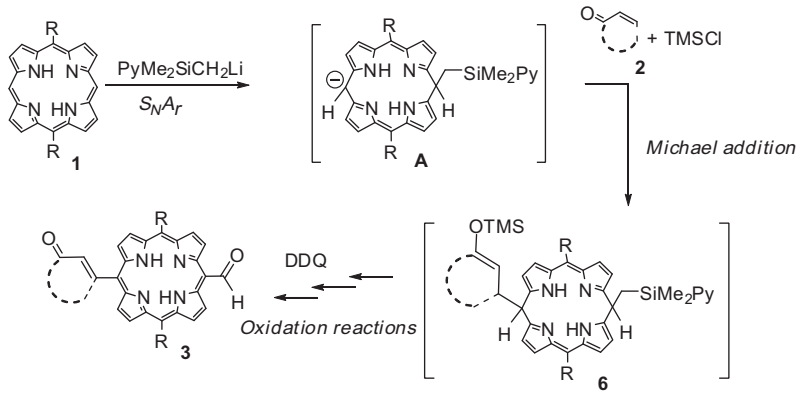

3cg (45%)[b]


3db (66%)


3eb (68%)


3fb (74%)[c]

[a] The numbers in the parentheses are isolated yields.
[b] *E*-isomer was isolated.
[c] Isolated yields after conversion of the crude products into the corresponding Ni(II) complexes (see, Ref. 14).



Scheme 3. Plausible reaction pathways for the one-pot direct conversion of 5,15-disubstituted porphyrins to the corresponding *meso* activated alkenyl-substituted *meso*-formylporphyrins.

introduction of a formyl group and an activated alkenyl substituent onto the porphyrin core at the *meso*-position in a simple one-pot procedure.

We began our studies by evaluating the asymmetric bifunctionalization of 5,15-diphenylporphyrin **1a** with $PyMe_2SiCH_2Li$ and 2-cyclopentene-1-one **2a** using similar reaction conditions to those previously reported for the one-pot synthesis of *meso* acyl-substituted *meso*-formylporphyrins.[7a] Thus, a solution of porphyrin **1a** in THF was treated in the following order: $PyMe_2SiCH_2Li$ (10 equiv) at −78 °C to rt, an ethereal solution of enone **2a** (15 equiv) and TMSCl (20 equiv) at −78 °C to rt, diluted aqueous HCl at 0 °C,[11] and then DDQ (10 equiv) at rt. As shown in Scheme 2, we unexpectedly did not obtain either the corresponding Michael type adduct **4aa** via 1,4-addition or the alcohol derivative **5aa** via 1,2-addition, but did obtain the enone moiety directly coupled adduct, *meso* activated alkenyl-substituted *meso*-formylporphyrin **3aa**, as the sole isolable product in 71% yield. In this reaction, TMSCl was found to be essential as the additive for the formation of **3aa**; any attempt without TMSCl gave only a trace amount of the Michael adduct **4aa** as an isolable product, along with an inseparable complex product mixture.[12] When TMSCl was replaced by other silylating agents, such as TESCl, TBSCl, and TMSOTf, significant deterioration in the yields of **3aa** (<30%) was observed.

Next, we investigated the scope of the above procedure using a range of 5,15-disubstituted porphyrins and α,β-unsaturated carbonyl compounds as substrates, and the representative results obtained are summarized in Table 1.[13–15] It was found that not only cyclic enones, **2a** and **2b**, but also an acyclic enone **2c** could readily participate in the asymmetric bifunctionalization of diphenylporphyrin **1a** to afford the corresponding *meso* activated alkenyl-substituted *meso*-formylporphyrins **3aa**, **3ab**, and **3ac** in good yields. However, sterically hindered enones appear to be a current limitation of our method, as 2-methylcyclopentenone **2d** and 4-methylcyclohexenone **2e** did not afford the desired products **3ad** and **3ae**, giving low yields (<20%) of *meso*-formylated diphenylporphyrin instead. This protocol is not limited to enones; both cyclic and acyclic alkenoates, **2f** and **2g**, were also compatible with the one-pot asymmetric bifunctionalization, furnishing the desired products **3af** and **3ag** in acceptable yields. Other porphyrins including 5,15-diarylporphyrins, **1b**–**1e**, of which the substituent on the phenyl ring is Me, MeO, CH_2=CH, and CF_3, and 5,15-dialkylporphyrin **1f** were evaluated next and also found to be good substrates for the present one-pot protocol; the corresponding *meso*-formylporphyrins substituted with enone and alkenoate moieties at the *meso*-position were obtained in good to moderate yields.

Mechanistically, we believe that the reaction proceeds via a porphodimethene derivative **6** bearing a $PyMe_2SiCH_2$ group and an enol silyl ether moiety on the sp^3 carbons of the ring (Scheme 3). Thus, anionic intermediate **A**, generated from the S_NAr reaction of porphyrin **1** with $PyMe_2SiCH_2Li$, undergoes conjugate addition to α,β-unsaturated carbonyl compound **2** in the presence of TMSCl to give the porphodimethene derivative **6**,[16] of which the silylmethyl group, enol silyl ether moiety, and porphodimethene ring are in turn oxidized with DDQ into the formyl group, the enone or alkenoate moiety, and the porphyrin core, respectively, leading to the final product **3**, although the precise order of these oxidation reactions is not yet clear.[17] This reaction process provides a satisfying explanation for the failure to obtain the desired activated alkenyl-substituted product **3** in the reaction performed without TMSCl (vide supra), which cannot create the porphodimethene intermediate **6** with an enol silyl ether substituent. Further experiments are currently underway to elucidate the reaction process in more detail.

In summary, direct introduction of an activated alkenyl substituent and a formyl group onto the *meso* carbons of free base 5,15-disubstituted porphyrins can now be realized using a simple one-pot procedure that involves a sequential S_NAr reaction with $PyMe_2SiCH_2Li$, conjugate addition to enones or alkenoates in the presence of TMSCl, and oxidation with DDQ. This one-pot protocol operates efficiently under mild conditions, can be applied to free base porphyrins, and is suitable for cyclic and acyclic alkenoates as well as enones. Most notably, unprecedented, formal direct couplings between enones or alkenoates and porphyrins at the *meso*-positions take place during the reaction to provide *meso* activated alkenyl-substituted *meso*-formylporphyrins, which has never been achieved by known porphyrin functionalization.[18] These asymmetrically bifunctionalized porphyrins, of which reactive functional groups at the *meso*-positions can be readily and individually replaced by a variety of other functionalities, will serve as versatile synthetic precursors in subsequent transformations for the construction of more complex porphyrin systems that could have potential applications. Further work to extend the porphyrin functionalization based on the S_NAr strategy with $PyMe_2SiCH_2Li$ is underway in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and characterization data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.025.

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11. Neutralization of the reaction mixture prior to the addition of DDQ is critical to obtain the desired product **3aa**: when the reaction was conducted without neutralization, significant amounts of oligomeric side products were noted.
12. NMR data were not available for **4aa** due to its poor solubility. Therefore, the structural differences between the enone moiety directly coupled adduct **3aa** and the Michael type adduct **4aa** were confirmed by the spectroscopic data of the corresponding Ni(II) complexes **Ni-3aa** and **Ni-4aa**. The procedure for the conversion of the free bases to the Ni(II) complexes is as follows: To a solution of a free base porphyrin (0.04 mmol) in DMF (3 mL) was added $Ni(OAc)_2{\cdot}4H_2O$ (50 mg, 0.2 mmol), and the mixture was stirred at 140 °C for 2 h. After completion of the reaction (monitored by TLC), the solution was poured into water (80 mL). The resulting precipitate was collected and washed with water and MeOH to give the Ni(II) complex in a nearly quantitative yield.
Complex **Ni-3aa**: ^{1}H NMR ($CDCl_3$) δ: 11.98 (1H, s, –C*H*O), 9.75 (2H, d, J = 5.1 Hz), 8.89 (2H, d, J = 5.1 Hz), 8.82 (2H, d, J = 5.1 Hz), 8.65 (2H, d, J = 5.1 Hz), 7.95–7.89 (4H, m), 7.71–7.69 (6H, m), 7.07 (1H, s, O=C–C*H*=C–), 3.50–3.44 (2H, m), 2.97–2.93 (2H, m); IR (KBr): 1705, 1674, 1605, 1566, 1439, 1358, 1277, 1161, 1076, 1007, 949, 791, 752, 702 cm^{-1}; UV/vis (CH_2Cl_2) λ_{max} (log ε): 423 (5.2), 549 (4.1), 596 (4.2) nm; HRMS (EI): calcd for $C_{38}H_{24}N_4NiO_2$: 626.1253; found: 626.1252.
Complex **Ni-4aa**: ^{1}H NMR ($CDCl_3$) δ: 11.88 (1H, s, –C*H*O), 9.68 (2H, d, J = 5.1 Hz), 9.09 (2H, d, J = 5.1 Hz), 8.71 (2H, d, J = 5.1 Hz), 8.57 (2H, d, J = 5.1 Hz), 7.92–7.86 (4H, m), 7.71–7.62 (6H, m), 5.31–5.20 (1H, m, O=C–CH_2–C*H*–Por), 3.56 (1H, dd, J = 19.5 and 11.5 Hz, O=C–C*H*H–CH–Por), 3.33 (1H, dd, J = 19.5 and 10.0 Hz, O=C–CH*H*–CH–Por), 3.30–3.26 (1H, m), 3.09–3.02 (1H, m), 2.97–2.90 (1H, m), 2.81–2.71 (1H, m); IR (KBr): 1742, 1673, 1541, 1441, 1354, 1236, 1162, 1077, 1009, 949, 793, 756, 704 cm^{-1}; UV/vis (CH_2Cl_2) λ_{max} (log ε): 426 (5.3), 556 (4.0), 602 (4.2) nm; HRMS (EI): calcd for $C_{38}H_{26}N_4NiO_2$: 628.1409; found: 628.1406.
13. General procedure for the one-pot preparation of *meso* activated alkenyl-substituted *meso*-formylporphyrins: An oven-dried 100 mL three-necked flask equipped with a magnetic stirring bar, a reflux condenser, and rubber septum was charged with a porphyrin **1** (0.2 mmol). The flask was evacuated and flushed with argon (three times), and then absolute THF (80 mL) was added. To the solution was added an ethereal solution of $PyMe_2SiCH_2Li$ (prepared by adding 1.3 mL of 1.58 M *t*BuLi in pentane to a solution of 2.4 mmol 2-pyridyltrimethylsilane in 3 mL of ether, followed by stirring at −78 °C for 2 h)[5] via a cannula at −78 °C. After being stirred at −78 °C for 5 min, the cooling bath was removed and the mixture was stirred at room temperature. The reaction was complete within 3 h, having been monitored by TLC. Upon completion of the reaction, the mixture was cooled to −78 °C, and then an ethereal solution of an enone or an alkenoate (3 mmol) and TMSCl (4 mmol, 0.51 mL) was added. After being stirred at −78 °C for 10 min, the mixture was warmed to room temperature, stirred for 3 h, and recooled to 0 °C. To the cooled mixture was added 10 mL of 0.1 M HCl. The resulting solution was stirred for 10 min at 0 °C, and then DDQ (2 mmol, 454 mg) was added. After being stirred at room temperature for 12 h, the mixture was concentrated under a reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (ca. 100 mL) and the solution was poured into brine. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, concentrated in vacuo, and subjected to chromatography on silica gel using 0–10% hexane/CH_2Cl_2 as an eluent. The eluate was evaporated and the resulting solid was purified by recrystallization from CH_2Cl_2/hexane to afford the *meso* activated alkenyl-substituted *meso*-formylporphyrin **3**.
14. In the cases of the preparation of **3ag** and **3fb**, impurities could not be removed from the crude products by recrystallization. These free bases, therefore, were further converted to their Ni(II) complexes, **Ni-3ag** and **Ni-3fb**, using a similar procedure for the preparation of **Ni-3aa** and **Ni-4aa**, see Ref. 12.
15. All the compounds reported herein showed spectral data consistent with the assigned structures, see Supplementary data.
16. All our attempts for isolating the porphodimethene intermediates **6** were unsuccessful probably because of their high susceptibility to moisture and oxygen in atmosphere.
17. It is known that DDQ can serve as an oxidant for the conversion of enol silyl ethers into enones, see: Bhattacharya, A.; DiMichele, L. M.; Dolling, U.-H.; Grabowski, E. J. J.; Grenda, V. J. *J. Org. Chem.* **1989**, *54*, 6118.
18. Preparation of *meso* activated alkenyl substituted porphyrins has been reported, see: (a) Yeung, M.; Ng, A. C. H.; Drew, M. G. B.; Vorpagel, E.; Breitung, E. M.; McMahon, R. J.; Ng, D. K. P. *J. Org. Chem.* **1998**, *63*, 7143; (b) Locos, O. B.; Arnold, D. P. *Org. Biomol. Chem.* **2006**, *4*, 902; (c) Horn, S.; Sergeeva, N. N.; Senge, M. O. *J. Org. Chem.* **2007**, *72*, 5414; (d) Sergeeva, N. N.; Bakar, M. B.; Senge, M. O. *J. Org. Chem.* **2009**, *74*, 1488.