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Bromine–lithium exchange as a straightforward method to obtain *meso*-tetrakis(4-formylphenyl)porphyrin: a versatile intermediate

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ABSTRACT

A three step, one-pot reaction has been developed for the introduction of the formyl functional group to the *meso* position of porphyrins. Symmetric *meso*-tetrakis(4-formylphenyl)porphyrin ((**CHO)$_4$TPPH2**), an important cornerstone in porphyrin chemistry, was obtained selectively in good yields via bromine–lithium exchange and subsequent Bouveault reaction. The *meso*-tetrakis(4-formylphenyl)porphyrin was fully characterized by HR-ESI, UV–vis, NMR, and single crystal X-ray diffraction.

Porphyrins are the object of a broad spectrum of research in diverse areas including dyes,[1] solar cells,[2] sensors,[3] photodynamic therapy,[4] or the recently emerging field of Metal Organic Framework (MOF).[5] This is due to their relatively easy synthesis, robustness, high chemical versatility, relation to natural substances, and optical and electrochemical properties. Among these, the *meso*-tetraphenylporphyrins' subfamily are easy to prepare and are readily soluble in organic solvents. In addition, their structure can be efficiently tuned in simple ways by modifying the number, position, and nature of the functional groups introduced onto the (*meso*-)phenyl substituents.[6] In this regard, the formylation of *meso*-tetraphenylporphyrin is an important reaction as it opens the way for a plethora of further functionalization such as, condensation with primary amines to obtain Schiff base type molecules; Canizzaro disproportionation into the corresponding acid and alcohol; Wittig olefination, and nucleophilic addition by Grignard or organolithium reagents to give substituted alcohols. Moreover, aromatic aldehydes are precursors for the porphyrins themselves, as well as for the well-known fluorescent dye boron-dipyrromethene (Bodipy).[7] However, to date, there are few reported methods for the functionalization of porphyrins by formyl groups and in many cases they are not well described.

Direct formylation of the *meso*-tetraphenylporphyrin is commonly achieved by the Vilsmeier reaction (DMF/$POCl_3$ at 0 °C) which has an excellent yield but only allows mono-formylation at the β-pyrrolic positions to give 2-formyl-5,10,15,20-tetraphenylporphyrin.[8,9] Regioselective formylation of the *meso*-phenyl substituents cannot be directly achieved and requires multiple steps which lowers the total yield of the synthesis. Considering porphyrin synthetic methods based on the condensation of pyrrole and benzaldehyde, the incorporation of formyl groups may be achieved by introduction of a suitable group on benzaldehyde which can be removed afterward. One representative method for formylation at the *para*-position of the *meso*-phenyl substituent proceeding through an acetal-protected precursor utilizes 4-(4,4-dimethyl-2,6-dioxan-1-yl)benzaldehyde. Starting from 4-bromobenzaldehyde, the formyl group is protected as an acetal group which after treatment with *n*-BuLi followed by quenching with DMF[10] gives the condensation precursor. Following this so-called 'acetal group protecting route' the corresponding porphyrin is obtained in 21% yield using the Lindsey method (DDQ, CH_2Cl_2, TFA, RT)[11] to give an overall yield of 17%.

When the acetal protecting group is on the *meta*-position of the *meso*-phenyl substituent, the yield of the acetal protected route is even less (15%). Deprotection of the acetal group is completed in $CHCl_3$–H_2SO_4 with a 95% yield.[12] Therefore, the acetal group protecting route needs four time consuming steps, that require working at low-temperature (−78 °C), as well as usage of a Dean-Stark apparatus. Moreover, the synthesis of the acetal protected

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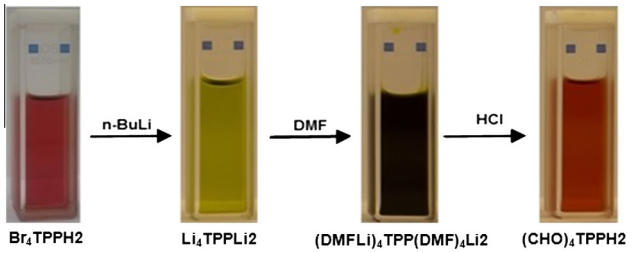


Figure 1. The color of the different reaction steps.

porphyrin is achieved in the presence of TFA as catalyst, a strong acid which may induce deprotection of acetal.[12] Consequently, the usage of this reaction process is tedious and requires great expertise.

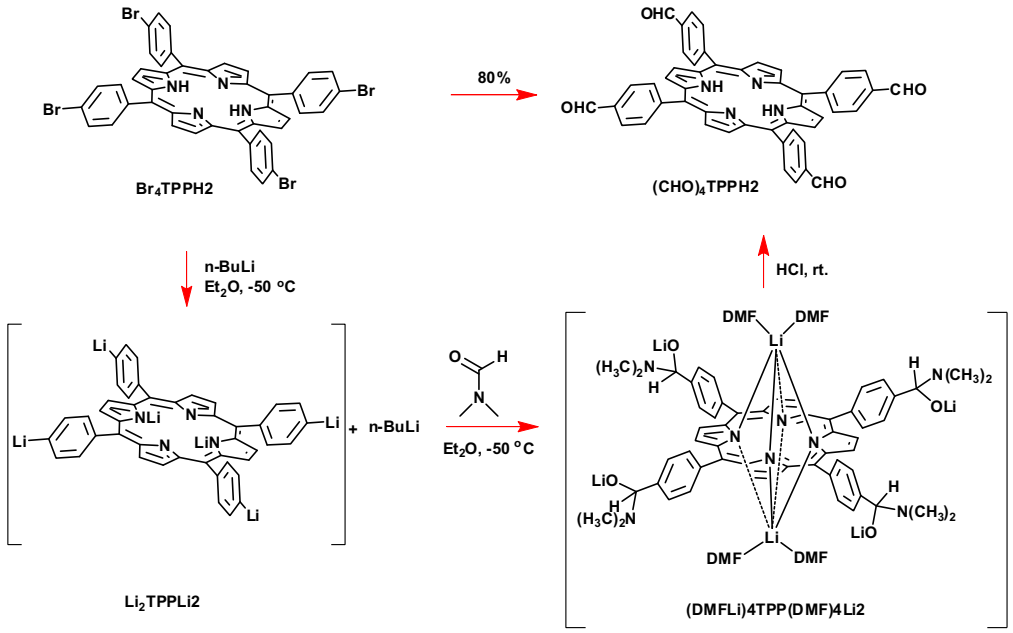
A second method proceeding through the reduction of a cyano group by sodium triethyoxyaluminohydride in THF, has been reported to give 5-(4-formylphenyl)-10,15,20-triphenylporphyrin, but without any synthetic description or yield mentioned.[13] In a third method, formylation on the *meso*-phenyl substituents is achieved by a regioselective bromine–lithium exchange mechanism known as the Bouveault aldehyde synthesis. However this has been reported only for mono- or di- formylation and with moderate yields.[14–16] Concerning the synthesis of *meso*-tetrakis(4-formylphenyl)porphyrin, it has been reported but without synthetic description.[17–19]

These examples show that there is still a need for straightforward formylation methods on the *meso*-phenyl substituents of *meso*-tetraphenylporphyrin. Herein, we report the controlled synthesis of *meso*-tetrakis(4-formylphenyl)porphyrin (**(CHO)$_4$TPPH2**). This was obtained in only two-steps using a regioselective and stoichiometric bromine–lithium exchange mechanism that avoids the formation of by products. The conditions have been optimized, and on the basis of reaction conditions and color changes involved, a reaction mechanism has been proposed involving the replacement of the bromines by the formyl groups proceeding through the formation of an O–Li complex. This compound has been characterized by UV–vis, NMR, HR-ESI-MS, and single-crystal X-ray diffraction methods.

First, *meso*-tetrakis(4-bromophenyl)porphyrin (**Br$_4$TPPH2**) was prepared by a slightly modified Adler procedure[20] from pyrrole and 4-bromobenzaldehyde in refluxing propionic acid in 25% yield. The formyl group was then introduced by the bromine–lithium exchange reaction. As the reactivity and selectivity of the bromine–lithium exchange is dependent on the chemical environment, the conditions and parameters of the reaction needed to be carefully chosen and controlled.[21,22] During the reaction, the temperature was kept low to prevent decomposition. As organometallic compounds are highly reactive, contaminants such as water, alcohols, and oxygen were carefully excluded and all solvents were carefully dried.

Tetrahydrofuran (THF) and diethylether (Et_2O) are the preferred solvents for organometallic reactions. The first attempts were performed in THF, due to the greater solubility of the starting compound (**Br$_4$TPPH2**) in this solvent, however this gave only an unidentified, green product. Fortunately, in Et_2O, porphyrins containing formyl groups were obtained as the only products. However, the solubility of **Br$_4$TPPH2** in Et_2O was low and decreased dramatically at the low temperature required to carry out the bromine–lithium exchange reaction. Therefore, this reaction was conducted under very dilute conditions. Variation of the equivalents of *n*-BuLi (from 6.25 equiv to 32 equiv) demonstrated that an excess of *n*-BuLi did not influence the reaction yield. The optimal conditions found were a solution of **Br$_4$TPPH2** ($8 \cdot 10^{-3}$ M) and 6.25 equiv. of *n*-BuLi in Et_2O at −50 °C. The *meso*-tetrakis(4-formylphenyl)porphyrin (**(CHO)$_4$TPPH2**) was obtained in 80% yield as a purple material after addition of 100 equiv. of DMF followed by treatment with acid (5% HCl) and purification by silica gel column chromatography. A small amount of the triformylated derivative *meso*-5,10,15-(4-formylphenyl)-20-phenylporphyrin (5%) was also observed.

To avoid the possible interaction of *n*-BuLi with the NH groups of the central core, the reaction was initially carried out using the zinc metallated *meso*-tetrakis(4-bromophenyl)porphyrin (**Br$_4$TPPZn**). However, this route was abandoned because treatment with acid led to partial demetallation of the formylated porphyrin as evidenced from the crystal structure. This increased the number of products obtained resulting in complicated purification by column chromatography as well as lowering the yield of the



Scheme 1. Putative bromine–lithium exchange reaction mechanism for *meso*-tetrakis(4-bromophenyl)porphyrin (**Br$_4$TPPH2**).

Table 1
UV–vis data of the porphyrins involved in the reaction

Compounds	λ (nm)	Solvent
Br_4TPPH2	418, 512, 547, 588, 644	DCM
Li_4TPPLi2	437, 459, 502, 577, 629	DMF
$(DMFLi)_4TPP(DMF)_4Li2$	439, 579, 625	DMF
$(CHO)_4$TPPH2	419, 523, 559, 600, 653	$CHCl_3$

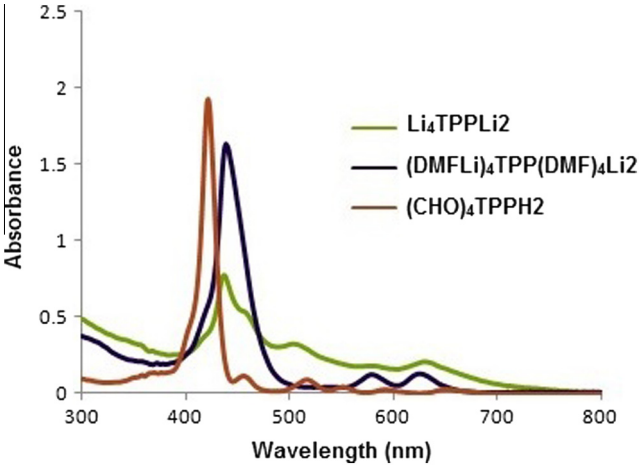


Figure 2. UV–vis absorption spectra.

reaction. Performing, the synthetic route with the free porphyrin proved to be the best for the formylation reaction and made the route more versatile for further functionalization and metallation.

We became interested in the mechanism of the reaction as the different steps were accompanied by significant color changes (Fig. 1).

At each step an aliquot of **Li_4TPPLi2** and **$(DMFLi)_4TPP(DMF)_4Li2$** was taken by syringe and diluted with DMF in a closed quartz UV cuvette. The UV spectra were recorded at this unknown concentration. Upon addition of *n*-BuLi, the deep red solution of the free porphyrin **Br_4TPPH2** immediately turned green. This was ascribed to the binding of two lithium ions to the nitrogens of the porphyrin core which is characteristic for dianionic porphyrins[23] in non-polar solvents such as Et_2O. The color slowly changed to dark blue-green after the addition of DMF and after hydrolysis with HCl returned to a red-brown solution revealing the presence of a free porphyrin which became red-purple after neutralization by NH_4OH and extraction with chloroform.

On the basis of UV–vis absorption spectrophotometry, presumptive structures for the intermediates were deduced (Scheme 1). The green intermediate, showed four bands in the visible spectrum consistent with the retention of the D_{2h} symmetry attributed to **Li_4TPPLi2**. In contrast, the well-defined spectrum of the dark blue-green intermediate reflected the higher D_{4h} symmetry of the molecule upon metallation, attributed to the symmetrically bounding of the lithium ion with the four porphyrin nitrogen atoms surrounded by symmetrical solvent molecules[23,24] corresponding to **$(DMFLi)_4TPP(DMF)_4Li2$**. The absorption spectra of the porphyrins are summarized in Table 1 and represented in Figure 2.

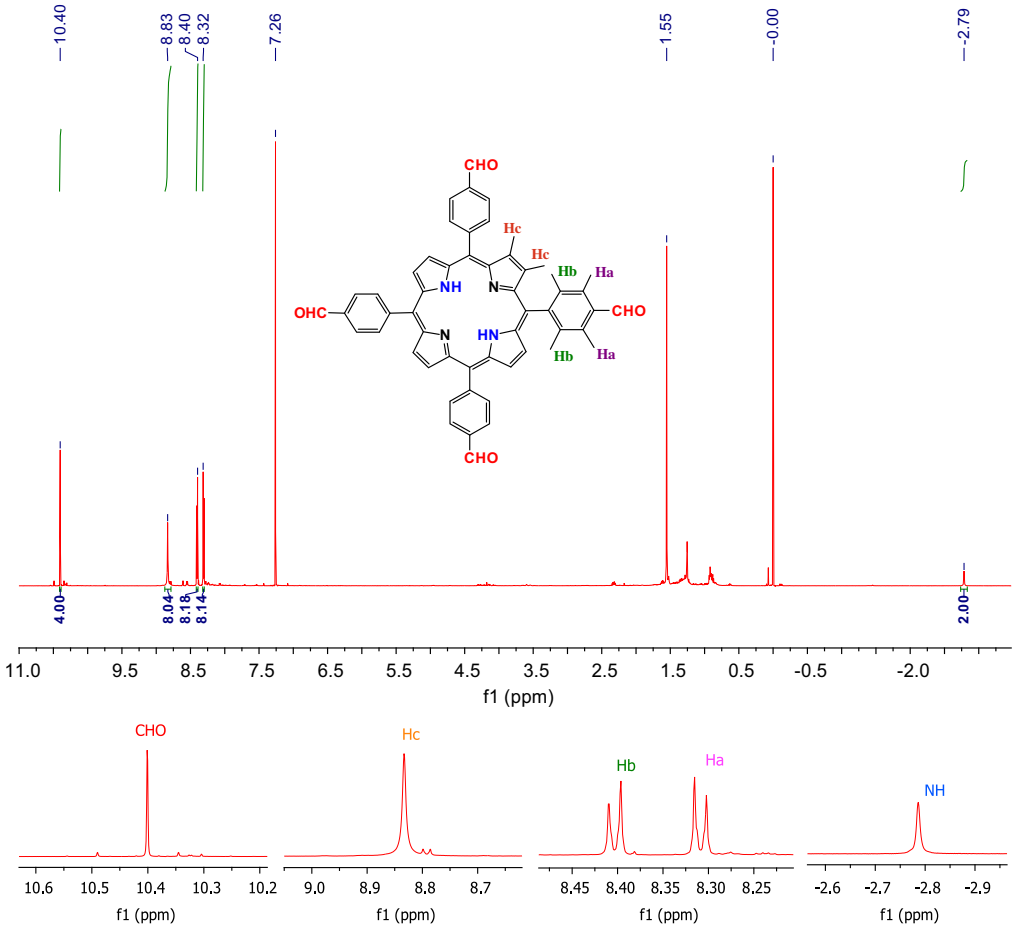


Figure 3. ^1H NMR spectrum of **$(CHO)_4$TPPH2** in $CDCl_3$.

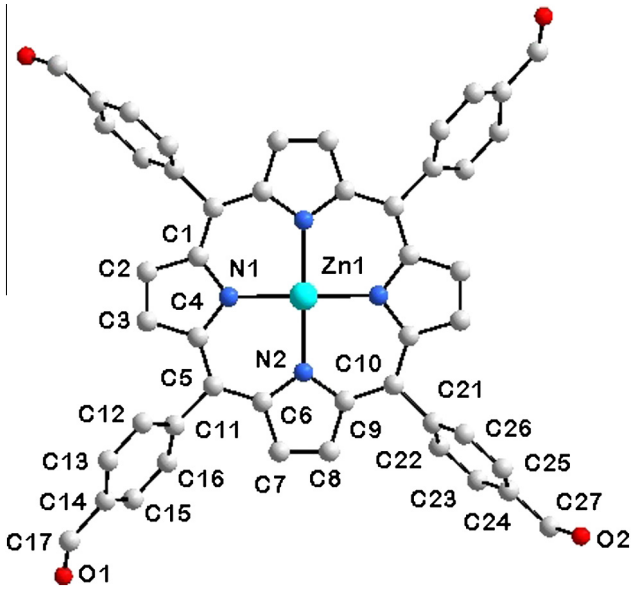


Figure 4. View of the molecular structure of the zinc(II) complex fraction (0.17) as determined X-ray diffraction of a single crystal of **{[(CHO)$_4$TPPZn]$_{0.17}$ [(CHO)$_4$TPPH2]$_{0.83}$} (C$_5$H$_{12}$)$_{0.5}$**. The hydrogen atoms and the disordered atoms found for one of the phenyl-CHO groups (O1) have been removed for clarity.

The structure of **(CHO)$_4$TPPH2** was unambiguously confirmed by HR-ESI Mass Spectroscopy, UV–vis, FT-IR, and single crystal X-ray diffraction. HR-ESI Mass spectroscopy displayed a parent molecular peak at m/z = 727.2348 (calculated for $C_{48}H_{30}N_4O_4$ m/z = 726.230) which corresponded to [M+H] (ESI Fig. S7). In the IR spectra, a sharp and intense peak at 1694 cm^{-1} which is characteristic of formyl vibration was observed (ESI Fig. S8).

The UV–vis spectrum of *meso*-tetrakis(4-formylphenyl)porphyrin (**(CHO)$_4$TPPH2**) measured in chloroform gave clear insights into the corresponding porphyrin (Fig. 2) exhibiting a strong and broad ill-defined Soret band around 420 nm and four weak Q-bands in the visible region between 500 and 650 nm due to a S0 → S1 transition.

The ^{1}H NMR spectrum of **(CHO)$_4$TPPH2** (Fig. 3) in $CDCl_3$ exhibited two doublets in the aromatic region at 8.32 and 8.40 ppm corresponding to the 8 protons of the ortho-CHAr (Hb) and the 8 protons of the meta-CHAr (Ha) on the *meso*-phenyl group. The β hydrogen atom of the pyrrole fragment was found as a singlet peak at 8.83 ppm and a characteristic singlet peak at 10.40 ppm corresponding to the proton of the formyl groups was observed. The shielded protons of the inner NH groups were observed at high field, −2.79 ppm in agreement with the literature.

The molecular structure (Fig. 4) was further proved using X-ray crystal structure determination from single crystals obtained during the formylation reaction on the zinc metallated porphyrin (vide infra).[25] Refinement of the structure showed an occupancy rate of 0.17 for the central zinc(II) ions. This indicated that the crystals were comprised of a mixture of free **CHO)$_4$TPPH2** (83%) and zinc metallated **CHO)$_4$TPPZn** (17%) which was in agreement with the previously discussed partial demetallation. This may also be viewed as a doping of the free porphyrin by zinc(II). As it can be expected, this was accompanied by disorder of one of the phenyl-CHO atoms, however the bond lengths and angle were normal. Tiny and twinned single crystals of the pure form of the free porphyrin **(CHO)$_4$TPPH2** were also obtained and were found to be isomorphs, however all attempts to refine the structure were unsuccessful. Irregardless, this un-ambiguously established that tetra-formylation had occurred on the *meso*-phenyl which was in agreement with other characterization methods.

In summary, we have demonstrated that the formyl functional group could be introduced in a straightforward manner by bromine–lithium exchange on the *para* position of the phenyl substituent present on the *meso* position of a porphyrin. This two-step, one-pot reaction regioselective proceeds through two successive lithium intermediates that give the *meso*-tetrakis (4-formylphenyl)porphyrin (**(CHO)$_4$TPPH2**) in an excellent yield of 80%. The overall yield of the **(CHO)$_4$TPPH2** synthetic pathway is higher than previous attempts and is a promising synthon for a vast variety of reactions which are currently being examined in our group.

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Supplementary data

Supplementary data (experimental section comprising information on materials, synthetic procedures, HR-ESI Mass, NMR and FT-IR spectroscopies and X-ray crystal structure determination of **{[(CHO)$_4$TPPZn]$_{0.17}$[(CHO)$_4$TPPH2]$_{0.83}$} (C$_5$H$_{12}$)$_{0.5}$**. CIF files for the crystal structure) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.021.

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