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Palladium-catalyzed reactions for the synthesis of chlorins and 5,10-porphodimethenes

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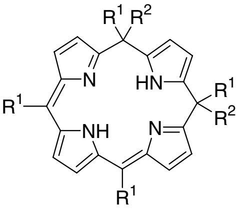
Abstract—The palladium-catalyzed reaction of RLi with various 5,10,15,20-tetrasubstituted porphyrins offers a convenient synthetic route to chlorins and porphodimethenes (calixphyrins). The reactions utilized various Pd catalysts and CuI and yielded either 2,3-substituted chlorins or 5,10-disubstituted porphodimethenes in yields ranging from 20–40%. The reaction of octaethylporphyrin with *t*-BuLi in the presence of a Pd-catalyst generated the corresponding 5,10-porphodimethene in 72% yield.

Recently, many studies have focused on the development of syntheses for hydroporphyrins, either related to natural pigments[1] or to calixpyrrole-type systems.[2] Being isomers, chlorins and porphodimethenes (also called calixphyrins) have a crucial structural difference and therefore differ in their physical and chemical properties. Chlorins play an important role in natural photosynthetic systems and have been utilized as photosensitizers in photodynamic therapy (PDT).[1] On the other hand, porphodimethenes contain sp^3-hybridized meso carbon atoms. This unique feature gives rise to specific conformations[3] and results in their remarkable anion-binding properties.[4]

The reaction of porphyrins with RLi (e.g., R = alkyl or aryl) is a powerful synthetic approach for the introduction of different residues into the meso position of unactivated porphyrins.[5–8] Furthermore, this method can also be applied to meso tetrasubstituted porphyrins with free β-positions. Earlier studies had shown that, depending on the free base porphyrin structure, phlorins (phlorins are cyclic tetrapyrrole systems with one sp^3 hybridized meso center and three NH-groups), chlorins (**2**,**3**) and/or porphodimethenes **1** can be formed in these reactions.[5,9–11] Further progress in using these reactions was hampered by very low yields (1–5%) and non-regioselectivity in the formation of chlorins and porphodimethenes. Alternative methods for the preparation of porphodimethenes including the classic reductive alkylation to yield 5,15-porphodimethenes,[12] used unselective condensations with low yields[13] or were used for the preparation of calix-type systems with non-hydrogen atom residues at the sp^3 hybridized meso centers.[2]



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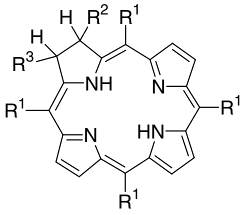

2 $R^3 = H$
3

Here we present results aimed at developing a method that can be used for the preparation of both types of hydroporphyrins by combining the use of lithium organic reagents with palladium-based catalysts. To the best of our knowledge, this type of Pd-catalysis has not been previously examined. In order to develop a suitable synthetic route to materials **1**–**3** we have systematically studied the influence of Pd-catalysts on the reactivity of both meso and β-substituted porphyrins with RLi. Initially, we chose the standard 5,10,15,20-tetraphenylporphyrin (TPP) as a model compound. It allows rapid characterization of the different products formed and a comparison of the results with previous works.

Keywords: Hydroporphyrins; Chlorins; Porphodimethenes; Palladium; Catalysis; Calixphyrins; Lithium.

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TPP smoothly reacted with *t*-BuLi in the presence of $Pd(PPh_3)_4$ and CuI to give the porphodimethene (PDM) **6** and chlorins **7** and **8** in 16%, 27% and 16% yields, respectively (Scheme 1). In contrast, Callot and Krattinger reported the isolation of only the porphodimethene **6** (5%) and the disubstituted chlorin **7** (1%) in a reaction without the catalyst.[11] A different reactivity was found for 5,10,15,20-tetra-(3-methoxyphenyl)porphyrin (TMeOPP) **5**. Here, treatment of the free base **5** under similar conditions with *t*-BuLi yielded only the mono- and disubstituted chlorins **11** (8%) and **12** (7%) in much lower yields compared to TPP. This is probably a result of the lower solubility and the slightly deactivating effect of the methoxyphenyl groups of the starting porphyrin.

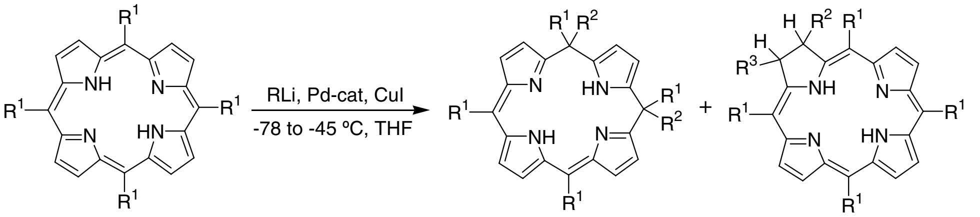
Using $Pd(PPh)_2Cl_2$ instead of $Pd(PPh_3)_4$ as a catalyst had no effect on the reaction of TPP and TMeOPP and gave the same products and yields (not shown). However, in the course of our studies on the influence of different catalysts, we discovered that, $Pd_3(dba)_2{\cdot}CHCl_3$ and CuI promoted the formation of monochlorin **8** (22%) and PDM **6** (21%) in the reaction of TPP. Similarly, the yields of compounds **11** and **12** increased significantly up to 26% each in the case of TMeOPP.

An interesting extension of this research concerned the use of sterically unhindered reagents for reaction with TPP. While *t*-BuLi in the absence of catalysts results in the formation of the respective phlorin and the monosubstituted chlorin[11] quite different reactivities were found in the presence of catalysts. Reaction of TPP with *n*-hexyllithium gave either the monosubstituted chlorin **10** (29%) or the respective di-alkyl substituted chlorin **9** (25%) as the sole product depending on the catalyst structure (Scheme 1).

Next, we turned our attention to the reactivity of meso tetraalkyl porphyrins (Scheme 2).[14] Initial studies on their reaction with *n*-BuLi in the presence of catalysts yielded complex mixtures. Likewise, experiments to react either 5,10,15,20-tetraisobutylporphyrin or tetrahexylporphyrin with 20 equiv of *t*-BuLi in the presence of $Pd(PPh_3)_4$ and CuI were unsuccessful, only traces of the target compounds were detected.

In contrast, reaction of **13** with only 5 equiv of *t*-BuLi and $Pd_3(dba)_2{\cdot}CHCl_3$ resulted in the formation of the PDM **16** and the 2-substituted chlorin **18** in 16% and 17% yields, respectively. In order to increase the yields we again tested other catalysts and found that $Pd_3(dba)_2$ allowed a preparation of **18** in 43% yield. This was accompanied by a slight reduction in the yield of the PDM **16** (12%). Other meso alkylporphyrins so far gave significantly lower yields of PDM (Scheme 2).

Thus, reaction of *t*-BuLi with the hexylporphyrin **14** in the presence of either $Pd_3(dba)_2{\cdot}CHCl_3$ or $Pd_3(dba)_2$ resulted in the formation of the porphodimethene **17** in 6–10% as the sole product; no chlorin was isolated under these conditions. These reactions were accompanied by the formation of many side products. On the other hand, the sterically more hindered 5,10,15,20-tetrakis-(1-ethylpropyl)porphyrin **15** gave only the monochlorin **19**, in 31% yield. No formation of the corresponding PDM was detected under these conditions.



4 R^1 = Ph
5 R^1 = 3-MeOC$_6$H$_4$

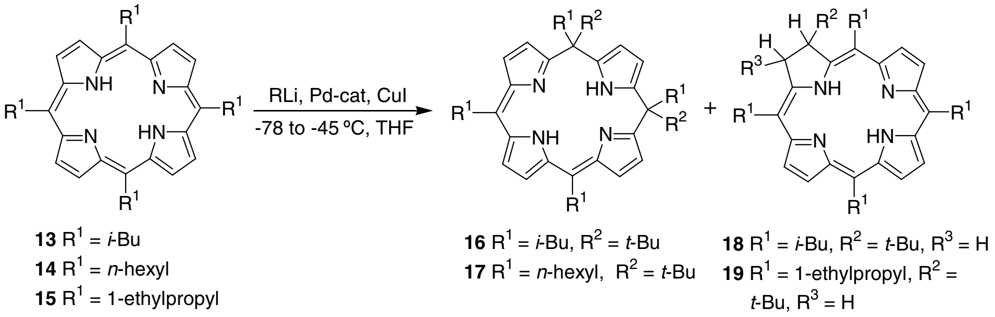
6 R^1 = Ph, R^2 = *t*-Bu

7 R^1 = Ph, R^2 = R^3 = *t*-Bu
8 R^1 = Ph, R^2 = *t*-Bu, R^3 = H
9 R^1 = Ph, R^2 = R^3 = *n*-hexyl
10 R^1 = Ph, R^2 = *n*-hexyl, R^3 = H
11 R^1 = 3-MeOC$_6$H$_4$, R^2 = R^3 = *t*-Bu
12 R^1 = 3-MeOC$_6$H$_4$, R^2 = R^3 = *t*-Bu

R^1	T, R^2Li	Catalyst	Porphodimethene, %	Chlorin, type **2**, %	Chlorin, type **3**, %
Ph	–78 °C, *t*-BuLi	$Pd(PPh_3)_4$	16 (**6**)	16 (**8**)	27 (**7**)
Ph	–60 °C, *t*-BuLi	$Pd_3(dba)_2{\cdot}CHCl_3$	21 (**6**)	22 (**8**)	20 (**7**)
Ph	–80 °C, *n*-hexylLi	$Pd(PPh_3)_4$	–	29 (**10**)	–
Ph	–60 °C, *n*-hexylLi	$Pd_3(dba)_2{\cdot}CHCl_3$	–	–	25 (**9**)
3-MeOC$_6$H$_4$	–45 °C, *t*-BuLi	$Pd(PPh_3)_4$	–	8 (**11**)	7 (**12**)
3-MeOC$_6$H$_4$	–55 °C, *t*-BuLi	$Pd_3(dba)_2{\cdot}CHCl_3$	–	26 (**11**)	26 (**12**)

Reaction conditions: porphyrin (1 eq), *t*-BuLi (20 eq), Pd-catalyst (0.1 eq), CuI (0.15 eq), THF.

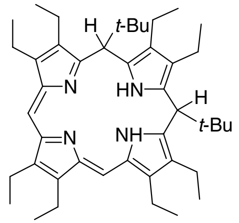
Scheme 1. The reaction of meso tetraarylporphyrins with RLi in the presence of Pd-catalyst.



R^1	T, t-BuLi (eq)	Catalyst	Porphodimethene, %	Chlorin, type **2**, %	Chlorin, type **3**, %
i-Bu	–60 °C, 5	$Pd_3(dba)_2·CHCl_3$	16 (**16**)	17 (**18**)	–
i-Bu	–60 °C, 10	$Pd_3(dba)_2$	12 (**16**)	43 (**18**)	–
n-Hexyl	–60 °C, 10	$Pd_3(dba)_2·CHCl_3$	6 (**17**)	–	–
n-Hexyl	–60 °C, 10	$Pd_3(dba)_2$	10 (**17**)	–	–
1-Ethylpropyl	–60 °C, 10	$Pd_3(dba)_2$	–	31 (**19**)	–

Scheme 2. The reaction of meso tetraalkylporphyrins with *t*-BuLi in the presence of Pd-catalyst.

Surprising results were obtained when 2,3,7,8,12,13,17,18-octaethylporphyrin was treated with *t*-BuLi in the presence of $Pd(PPh_3)_4$ and CuI. The reaction gave a single product in excellent yield (72%). Here, complete regioselectivity for the meso positions was achieved. Under standard conditions, without catalysts this porphyrin typically reacts with formation of 5,15-substituted oxidation resistant porphodimethenes[15] while a preference for the formation of 5,10-disubstituted porphyrins[6] was noted in many reactions. However, here the product was identified as the corresponding 5,10-porphodimethene **20**.[16] Attempts to oxidize the product with DDQ to the corresponding 5,10-disubstituted porphyrin were unsuccessful.



20

Thus, modification of the reaction conditions allows the selective preparation of PDMs and chlorins of types **1**, **2** or **3**. Compared to earlier studies, this Pd-catalyzed reaction of the meso tetrasubstituted porphyrins allows the preparation of either β-substituted chlorins (thermodynamic control, β-addition) in up to 43% yield or 5,10-PDM (kinetic control, meso-addition) in up to 20% yield. While copper is typically to be avoided in porphyrin building blocks to prevent (trans)metalation reactions,[17] we found the addition of CuI to be absolutely necessary to achieve full transformation. Reactions without CuI either gave only very low yields or increased the number of side-products formed. In particular, the synthesis of compound **20** can only be performed in the presence of CuI, without it only traces of the desired product were detected.

Acknowledgements

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