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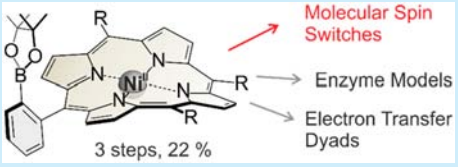
Modular Synthetic Route to Monofunctionalized Porphyrin Architectures

Gernot Heitmann, Marcel Dommaschk, Roland Löw, and Rainer Herges*

Otto Diels-Institute for Organic Chemistry, University of Kiel, Otto-Hahn-Platz 4, Kiel D-24119, Germany

Supporting Information

ABSTRACT: The synthesis of a borylated Ni^{2+} porphyrin and its application as a versatile precursor for building up functional *ortho*-substituted tetraaryl porphyrin architectures is reported. This precursor porphyrin provides the basis for efficient modular syntheses of porphyrin compounds with covalently attached axial ligands which are important as enzyme model complexes, electron transfer dyads, and many other applications. In the present study, the precursor porphyrin was used for the synthesis of molecular spin switches which previously showed high potential as photoresponsive contrast agents for magnetic resonance imaging.



Porphyrins and metalloporphyrins are an important class of macrocyclic compounds and are extensively studied. These tetrapyrrolic macrocycles exhibit a high stability, a rigid structure, interesting photophysical properties, a rich coordination chemistry, and redox activity. They are ubiquitous in biological systems and have found technical applications in a large number of fields, e.g., catalysis,[1] solar energy harvesting,[2] sensors, tracers,[3] and triplet sensitizers in photodynamic therapy.[4−6] *meso*-Tetraarylporphyrins are the predominant molecular structures in synthetic porphyrin chemistry. A number of functionalized tetraaryl-substituted porphyrins are commercially available. Furthermore, they are relatively easy to synthesize, highly stable, and allow the introduction of a variety of functionalities by the proper choice of starting components or by postsynthetic derivatization of the *meso*-aryl substituents.[7,8] In particular, the *ortho* position of the *meso*-aryl groups is of great interest for the tethering of functional elements because it provides the closest connecting point with respect to the metal ion in the porphyrin center. Asymmetric tetraaryl porphyrins with only a single functional substituent connected in the *ortho*-position at one of the *meso*-aryl groups (see Figure 1) have been applied, e.g., for intramolecular axial coordination,[9,10] photoinduced electron transfer in porphyrin−fullerene dyads,[11,12] or enzyme model complexes.[13,14] We used this porphyrin architecture for the intramolecular light-driven coordination-induced spin-state switching (LD-CISSS)[15] of Ni^{2+} porphyrins.[16−21]

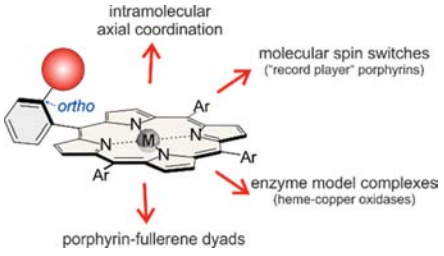


Figure 1. Asymmetric tetraaryl porphyrins with a functional substituent in the *ortho*-position at one of the aromatic *meso*-substituents are of interest for a number of applications.

The covalently bound functional substituent in this case is an azopyridine[16−19] or azoimidazole[20,21] that is reversibly coordinated to the Ni^{2+} porphyrin upon *cis*/*trans* isomerization of the azo function. The coordination and decoordination of the axial ligand gives rise to a spin transition between a diamagnetic ($S = 0$) state and a paramagnetic ($S = 1$) state. We coined the above-mentioned porphyrins "record player" molecules because the light-induced coordination of the switchable azo unit ("tone arm") to the metal center resembles the movement of a needle that is put down on a vinyl record. Light-driven spin transition in solution is highly promising for a number of applications such as light-controlled magnetic levitation,[22−25] photoactivatable paramagnetic relaxation enhancement,[26] and particularly responsive contrast agents for magnetic resonance imaging (MRI).[17,20,27−30] However, to date, the low-yielding, multistep syntheses of the spin switches (up to 14 individual steps)[20] are the major bottlenecks toward practical applications. Three key steps have to be performed during the synthesis of every derivative (see Figure 2): the formation of the switchable azo unit (yellow), the tethering of the switching unit to the porphyrin's *meso* substituent (blue), and the porphyrin synthesis including the Ni^{2+} insertion (red). Within the well-established linear approach (Figure 2a), these key steps are performed consecutively.[17−21] This route suffers from the disadvantage that even slight variations in the switching unit require each synthesis to be performed from scratch. Moreover, the "mixed aldehyde" porphyrin synthesis, though using cheap components, is known to give notoriously low yields and many side products. Therefore, it should preferentially be performed as the first step of the synthesis. In our previous procedure, the porphyrin synthesis in the final

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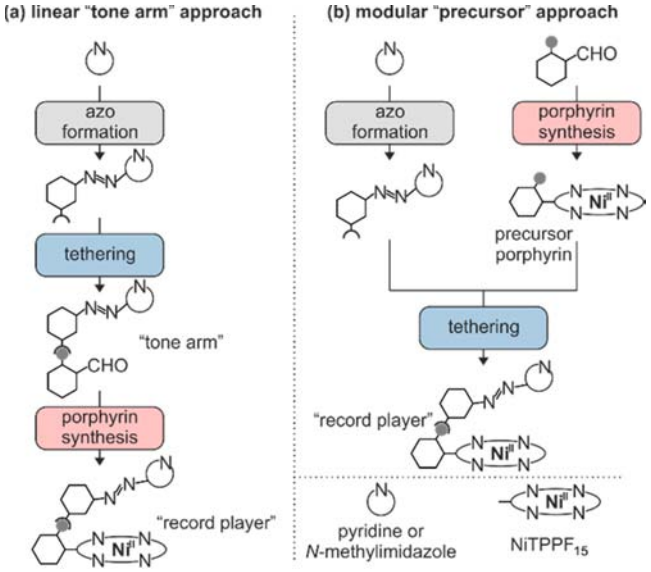
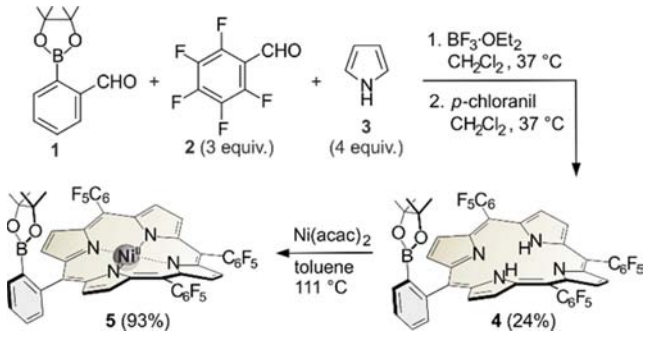


Figure 2. Schematic depiction of possible synthetic routes toward "record player" molecules. Key steps are the formation of the switchable azo unit (gray), tethering the switching unit to the porphyrin's *meso* substituent (blue), and the synthesis of the Ni^{2+} porphyrin (red). The key steps might be carried out (a) in a linear fashion via the well-established "tone arm" approach or (b) in a convergent fashion via a modular approach which requires the synthesis of a suitable precursor porphyrin.

step gives rise to a significant loss of the valuable azo compound. A modular approach with an appropriate precursor porphyrin (Figure 2b) would certainly be much more efficient.

We previously reported a monoiodinated derivative of the widely used Ni^{2+} porphyrin Ni–$TPPF_{20}$ as a precursor porphyrin. The porphyrin was obtained in nine synthetic steps (five pots) and was coupled with borylated azopyridine to give the perfluorinated "record player" derivative.[16] To provide an even more straightforward access to the porphyrin key intermediate, we use the commercially available 2-formylphenylboronic acid pinacol ester (**1**) pentafluorobenzaldehyde (**2**), and pyrrole (**3**) for the porphyrin synthesis via the Lindsey method (see Scheme 1).[31,32] The monoborylated metal-free

Scheme 1. Synthesis of Precursor 5



porphyrin **4** was obtained in a fairly high yield, and the following metalation with nickel(II) acetylacetonate gave almost quantitative yields of the desired precursor porphyrin **5**. The synthesis of a similar Zn(II)porphyrin has been described previously.[33] However, this porphyrin did not contain the *meso*-pentafluorophenyl substituents that are required for efficient spin switching, and it was obtained in only very poor yields. Porphyrin **5** is easily accessible in high purity, exhibits a high thermal stability, and can be stored at ambient conditions for several months without any sign of degradation. Therefore, it meets all requirements for an efficient precursor for monosubstituted porphyrins.

With the key intermediate **5** in hand, we set out to evaluate its scope in Suzuki cross-coupling reactions,[34,35] particularly with photoisomerizable azo compounds (see Scheme 2). For this purpose, we synthesized the iodinated azobenzenes **6**[36] with the azo substituent in the *ortho* (**6a**), *meta* (**6b**), and *para* (**6c**) position with regard to the iodo substituent (for details, see the Supporting Information). The azobenzenes **6** were reacted with precursor **5** by applying a standard Suzuki cross-coupling protocol we already used for the former linear approach.[17,19] By using tetrakis(triphenylphosphine)-palladium(0) as catalyst, potassium carbonate as the base, and a toluene–ethanol–water solvent mixture, all azobenzenes **6** were coupled to precursor **5**, giving the respective azo-functionalized Ni^{2+} porphyrins **7** in excellent isolated yields (**7a**, 94%; **7b**, 97%; **7c**, 93%, see Scheme 2, middle). Cross coupling of **5** is also feasible with (3′-bromophenylazo)-pyridines **8** and (3′-bromophenylazo)-*N*-methylimidazoles **9**, which provide a photoresponsive coordinating unit and therefore are suitable ligands for molecular spin switches. The azo heterocycles **8** and **9** were synthesized according to convenient synthetic routes (for details, see the SI).[37−39] The Suzuki cross-coupling reactions of **5** with azopyridines **8** were performed by applying the same synthetic protocol we used for azobenzenes **6**. The respective azopyridine-functionalized porphyrins **10** were obtained in very high yields (**10a**, >99%; **10b**, 95%; **10c**, 90%; see Scheme 2, right). For the coupling reactions with azoimidazoles **9**, we had to adjust the synthetic protocol and used [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) as catalyst, cesium carbonate as base, and a 1,4-dioxane–water solvent mixture, giving the derivatives **11** in satisfying yields as well (**11a**, 90%; **11b**, 82%; **11c**, 93%; **11d**, 66%; see Scheme 2, left).

Table 1 compares the yields of spin switches **10a**,[19] **10b**,[17] and **11a**[20] obtained from both the linear and the convergent synthesis. The formation and derivatization of the azo unit (Figure 2, gray) is identical for both synthetic approaches. Therefore, we only considered the respective linear sequence which includes the Ni^{2+} porphyrin synthesis (Figure 2, red) and the tethering of the switching unit to the porphyrin's *meso*-substituent (Figure 2, blue). The yields for the tethering step via Suzuki cross-coupling reactions are almost identical (90% or higher). However, the synthesis of the Ni^{2+} porphyrin is much more efficient for the convergent route. Precursor porphyrin **5** was obtained in 22% yield, whereas the linear approach provided only 2–5% yield for the porphyrin synthesis and metalation. Consequently, the modular (convergent) route improves the overall yields strikingly by a factor of 4–11. Furthermore, porphyrin **5** is accessible from commercially available starting materials. In the linear route, more than 95% of the compounds synthesized in previous steps are lost because the last step (porphyrin synthesis) proceeds only in 2–5% yield.

In summary, we present the synthesis of the boronic acid pinacol ester functionalized Ni^{2+}porphyrin **5** and its applications as a building block for the convergent syntheses of functionalized porphyrins. The Ni^{2+}porphyrin **5** is accessible in pure form from commercially available compounds in only

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Scheme 2. Suzuki Cross-Coupling Reactions of Precursor 5 with Azobenzenes 6, Azopyridines 8, and Azoimidazoles 9

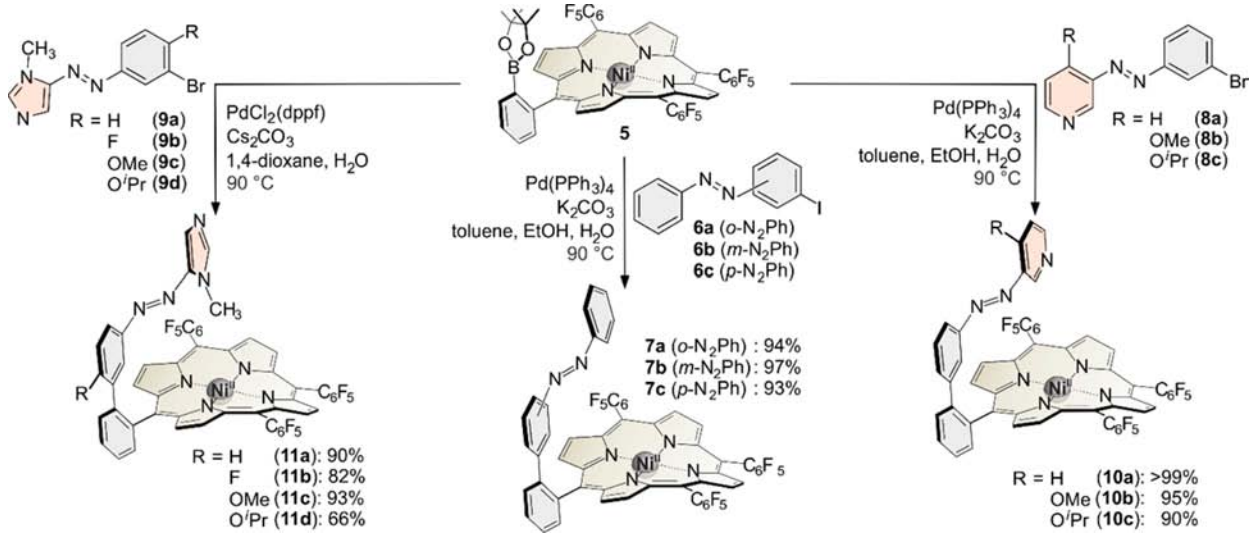

Table 1. Yields (Suzuki Coupling and Porphyrin Synthesis) for Spin Switches 10a, 10b, and 11a via the Linear Approach and the New Modular Approach

	overall yield (%)	
derivative	linear approach	modular approach
10a	5.0[19]	22
10b	1.9[17]	21
11a	3.3[20]	20

three synthetic steps (two pots) and can be stored for several months at ambient conditions without degradation. Subsequent Suzuki cross-coupling reactions of **5** were successfully demonstrated. Porphyrin **5** was coupled with 10 different halogenated azo compounds in high isolated yields. The reaction with photoswitchable azopyridines or azoimidazoles provides efficient access to molecular spin switches that exhibit intramolecular light-driven coordination-induced spin-state switching (LD-CISSS). The modular synthetic approach via the novel precursor porphyrin **5** is a considerable improvement to previously applied routes. Our new synthetic concept certainly will help us to further develop and optimize our spin switches toward applications as smart MRI contrast agents. The new precursor porphyrin should also be a versatile key intermediate for other functional porphyrins. *Ortho*-substitution in asymmetric tetraaryl porphyrins is a recurring structural element and is found in many studies regarding different applications. The pentafluorophenyl substituents at the porphyrin's *meso*-positions further increase the possibilities for functionalization since they are highly reactive in nucleophilic aromatic substitution reactions[40−42] and allow, for example, the introduction of solubilizing substituents.[43]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02507.

Syntheses of azo compounds **6**, **8**, and **9**, experimental procedures, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rherges@oc.uni-kiel.de.

Notes

The authors declare no competing financial interest.

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