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Suzuki cross-coupling of *meso*-dibromoporphyrins for the synthesis of functionalized A₂B₂ porphyrins

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Abstract— C_2 -Symmetric *meso*-porphyrins have been prepared in high yields by a palladium-catalyzed cross-coupling reaction involving dibromoporphyrins and arylboronic acids. © 2001 Published by Elsevier Science Ltd.

Among the synthetic molecular architectures based on substituted (β - or *meso*-positions) porphyrins, the welldefined modular organization of the linear *meso*-porphyrins offers homogeneous structural motifs useful for the construction of supramolecular assemblies. Notable among them are porphyrin-based scaffolds of interest as organic-based materials, and as new catalysts for organometallic chemistry.¹ Recent applications of these systems include charge separation devices that mimic photosynthesis,² materials with nonlinear optical properties,³ chiral catalysts, synthetic receptors, potential sensitizers for photodynamic cancer therapy,⁴ liquid crystal and chiral sensors.⁵

The renaissance of porphyrin chemistry and its applications has been fuelled by the development of practical methods for the synthesis of porphyrin structures with the desired substitution pattern at the meso positions of the porphyrin core, mainly through the efforts of Lindsey and co-workers.⁶ Nevertheless, there are still some drawbacks on the synthesis of selected substitution patterns. In this regard, only two reliable syntheses of trans A_2B_2 phorphyrins have been developed, namely the condensation of a dipyrromethane and an aldehyde (the so-called MacDonald-type coupling^{6c,7}) and the self-condensation of a dipyrromethane monocarbinol, recently reported by Lindsey.8 The scrambling of the meso-substituents due to acid-catalyzed fragmentations and recombinations is the main limitation of the first approach, in particular for dipyrromethanes bearing a non-sterically demanding aryl substituent.^{6c} The greater reactivity of the dipyrromethane monocarbinol suppresses the scrambling, but the preparation of these building blocks involves the condensation of a dipyrromethane Grignard derivative with a pyridyl thioester.⁸

The construction of large porphyrin-based assemblies has also benefited in the last years from the concurrent development of transition metal-catalyzed coupling processes.9 Applications of the Sonogashira,¹⁰ Negishi,¹¹ Suzuki¹² and Stille^{11,13} cross-coupling reactions using β - or *meso*-substituted haloporphyrins have been published. The compatibility of the porphyrin core functionality with the organometallic component allowed the preparation of Zn(II)-porphyrinatomonoboronic acids,^{12b-c} which could be coupled to aryl iodides (and even bromoporphyrins) to afford the arylsubstituted^{12b} (or bis-porphyrin^{12c}) assembly. However, the coupling required 1.5-2.0 mol equiv. of valuable boronic acid to ensure high reaction rates under otherwise drastic reaction conditions [80°C; 6-24 h]. As an alternative approach, boronic acids have been coupled to monobromoporphyrins (β^{12a} or *meso*^{12b}) and octabromo- β -porphyrins^{12d} with unsatisfactory yields. The underlying reasons for this difference on coupling efficiency upon exchange of functionality has not been clarified. In contrast to this finding, we report herein a new high-yielding synthesis of *trans*-porphyrins (A_2B_2) based on Suzuki reactions involving commercially available boronic acids and dihalogenated porphyrin templates as reaction partners. As representative scaffolds, we selected the known meso-substituted Br₂A₂trans-porphyrins containing phenyl and mesityl groups. The dibrominated porphyrins were obtained in quantitative yields upon treating with N-bromosuccinimide,¹⁴ the corresponding meso-A2 porphyrins. These were prepared by MacDonald-type 2+2 reaction, i.e. the condensation of the corresponding dipyrromethanes with

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methylorthoformate in the presence of trichloroacetic acid, followed by oxidation with DDQ or chloranil, as illustrated in Scheme 1.¹⁵ The dipyrromethanes were

conveniently prepared on a multigram scale, following the refined Lindsey procedure, which involves the room temperature solvent-free acid-catalyzed condensation of



Scheme 1.

Table 1.



^a General reactions conditions: Pd(PPh₃)₄ (0.3 equiv), Na₂CO₃ 2M (8 equiv), R₂B(OH)₂ (5 equiv), DMF, 60 °C. ^b The yield refers to isolated porphyrin or Zn (II) porphyrinato, after chromatography. ^c Room temperature-interconverting atropisomers. ^d Separable atropisomers.

aldehydes and pyrrole.¹⁶ Excess pyrrole is required to maximize formation of dipyrromethane and to avoid appearance of higher oligomers and polymers. After completion, unreacted pyrrole is recovered by distillation and can be recycled.

For the coupling step, we explored different reaction conditions, changing the nature of the base, solvent and catalyst within the range of temperatures required for the coupling to take place. Although Therien reported the use of strongly basic conditions $[Pd(PPh_3)_4,$ $Ba(OH)_2 \cdot 8H_2O$, DME/H_2O , $80^{\circ}C$, 6–12 h] to couple Zn(II)-porphyrinato boronic acids,^{12b} a more polar solvent and a weaker base ensured good coupling rates when the porphyrin was functionalized as electrophile. Reaction conditions involving the use of $Pd(PPh_3)_4$ as catalyst, DMF as solvent, and solid Na₂CO₃ as base at 60°C proved optimal. Excess boronic acid was required to compensate for adventitious hydrolytic protiodeboronation. Rigorous exclusion of oxygen in the reaction flasks and solvents (through freeze-thaw cycles) was also required. Under those optimized conditions,¹⁷ the meso- A_2B_2 porphyrins were obtained in virtually quantitative yields. The results are collected in Table 1. The nature of selected arylboronic acids ranges from the phenyl to the 4-formyl derivative, as well as the formylthiophene isomers. Previously, it had been reported that boronic acids with electron-withdrawing groups at the *ortho* position of the aryl ring or boronic acids derived from strongly electron-deficient heterocycles, gave no coupling to octabromotetraarylporphyrins.¹⁸ However, 2-formylthiophene-3-boronic acid coupled to 3 and 4 in excellent yield, perhaps as a result of the activating effect of the formyl group. We could corroborate the lack of reactivity of 3-formyl-thiophene-2-boronic acid, even after heating to 90°C for 8 h, thus confirming the dependence of the Suzuki reaction to the electronic effects of the boronic acids. Due to the tedious separation of the excess boronic acid and free base A_2B_2 porphyrins containing formyl groups upon attempted purification by column chromatography, their isolation as the corresponding Zn(II)-porphyrinato complexes was more convenient, and these compounds released the free base upon treatment with TFA. It has been claimed that the use of free-base porphyrins should ensure milder reaction conditions when used as electrophiles in metal-catalyzed cross-coupling reactions, in metal-catalyzed cross-coupling reactions due to their reduced electron density compared to the electron-rich metalloporphyrins. However, the direct use of the more electron-rich dibromo-Zn(II)porphyrinato derived from 6 led to a faster Suzuki reaction, which was complete in only 1 h at 60°C (95%). For the orthoformylthiophene derivatives 12 and 9, two isomers were obtained, which differed in the orientations of the formyl group relative to the porphyrin ring. We could isolate and characterize both isomers of 12 $(\alpha, \alpha \text{ and } \alpha, \beta; 12a \text{ and } 12b)$, but all attempts at characterizing 9 after the separation of its components led to their rapid interconversion at room temperature.

In conclusion, the results reported here illustrate the utility of the Suzuki coupling reaction for the synthesis

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- 17. Representative procedure for Suzuki cross-coupling. A flask was charged with 5,15-dibromoporphyrin (1 equiv.), $Pd(PPh_3)_4$ (0.3 equiv.), arylboronic acid (5 equiv.), 2 M aqueous Na_2CO_3 (8 equiv.) and DMF. The purple suspension was degassed by the freeze-thaw method (three cycles) and was then heated to 60°C for 3 h under argon. The volatiles were removed under vacuum and the residue was purified by column chromatography, affording a purple solid.
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