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Palladium catalyzed coupling reactions of cationic porphyrins with organoboranes (Suzuki) and alkenes (Heck)

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Abstract—The carbon–carbon coupling reaction in aqueous medium between 5,10,15-tri-(4-*N*-methylpyridyl)-20-(4-bromophenyl)-porphyrin and a variety of organoboranes, fluoroorganoboranes and alkenes using palladium catalyst (Suzuki and Heck) is explored.

The unique physical–chemical and spectral properties of porphyrin derivatives make them one of the most highly studied macrocyclic and coordination compounds.[1] They have found many applications as catalysts, model compounds for enzymic transformations and as photosensitizers for the photodynamic therapy (PDT) of various medical conditions.[1,2] Positively charged water-soluble porphyrins are of particular interest for PDT due to their preferential uptake by mitochondria and high binding affinity for DNA.[3] More recently, cationic porphyrins were also shown to inhibit telomerase activity due to their favorable properties for interacting with the guanine tetrads of DNA.[4] Their efficacy as photosensitizer is directly related to their biodistribution and pharmacokinetics, which in turn can be modulated by the nature of substituents.[5] Conventional methods to prepare cationic porphyrins proceed under reflux in organic acid, that is, conditions incompatible with the use of labile substituents. We recently developed an alternative method to prepare libraries of porphyrins for QSAR studies using the palladium catalyzed (Sonogashira) carbon–carbon coupling reaction between 5,10,15-tri-(pyridyl)-20-(4-bromophenyl)-porphyrin and various terminal alkynyls in aqueous medium.[6] Some of these compounds exhibit strong photodynamic properties (unpublished results), which led us to further explore other reactions to enlarge our library. Both Suzuki[7] and Heck[8] reactions have been reported to proceed in aqueous media. Here we investigated the use of these processes for the modification of cationic porphyrins under green chemistry conditions. The use of water instead of organic solvents has several advantages such as reduced toxicity and unusual reactivity as well as ease of catalyst recovery.[9]

The precursors for the coupling reactions, the 5,10,15-tri-(pyridyl)-20-(4-bromophenyl)-porphyrin (**1**) and the 5,10-di-(pyridyl)-15,20-di-(4-bromophenyl)-porphyrin, were prepared by modifying a known procedure.[10] The stoichiometric condensation of 4-pyridine-carboxaldehyde, 4-bromo-benzaldehyde and pyrrole in refluxing propionic acid followed by purification over silica gel using THF and CH_2Cl_2 as eluants gave the mono- through tetra-bromo cationic porphyrins in low yield. Two different routes were investigated for the preparation of the water-soluble substituted porphyrins. The first procedure involves a palladium catalyzed reaction in aqueous media between the methylated compound **3** and organoboranes or alkenes to yield the final products **4** or **6** (green chemistry conditions). The second route involves initial coupling of the bromo compound **1** with organoboranes or alkenes in organic solvent, followed by methylation with iodomethane to yield the final products **4** and **6**.

Recently we showed that the coupling of the methylated, water-soluble cationic porphyrin **3** to terminal alkynyls

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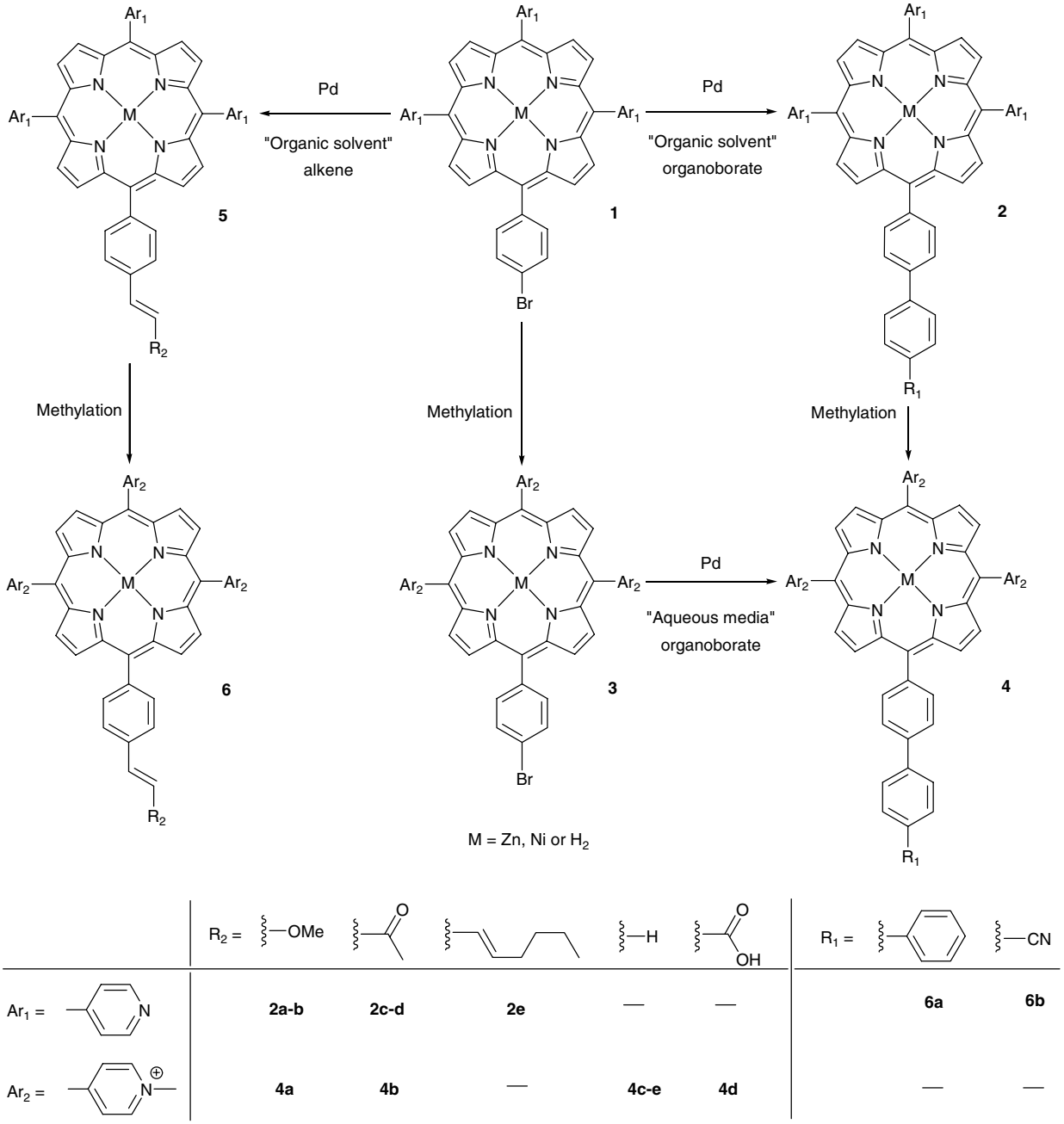
(Sonagashira) smoothly proceeds under aqueous conditions. In contrast, coupling of the non-methylated porphyrin **1** in organic medium required a stronger catalyst, such as $Pd_2(dba)_3/P(t\text{-}Bu)_3$.[6]

The monobromo cationic porphyrin **3** reacted smoothly with phenylboronic acid in aqueous medium (H_2O/CH_3CN) using $Pd(OAc)_2$/TPPTS catalyst/ligand to yield the coupling product **4a** in moderate yield. Other substituted phenylboronic acids also reacted under these conditions (Table 1). Changing the central Zn ion for Ni reduced the reactivity, requiring longer reaction times (24 h vs 5 h). No coupling product was obtained with non-metalated porphyrin. Organofluoroboranes are more stable and more reactive as compared to boronic acids, and also give superior yields in Pd-catalyzed coupling reactions.[11] Thus, we attempted the Suzuki coupling reaction in aqueous medium using potassium trifluoroborane derivatives. Yields were higher as with the boronic acids but required longer reaction times (Table 2).



	R_2 = —OMe	O		—H	O OH	R_1 =	—CN
Ar_1 = N	**2a-b**	**2c-d**	**2e**	—	—	**6a**	**6b**
Ar_2 = $N^{\oplus}$—	**4a**	**4b**	—	**4c-e**	**4d**	—	—

We also performed the Suzuki coupling reaction of the known porphyrin **1** with organoboranes in organic medium. As previously reported,[6] this reaction also required the strong $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst. However, the Et_3N base needed to be replaced by Cs_2CO_3 in order to obtain the desired compounds **2** in moderate yields (Table 3). The latter were methylated to give the

Table 1. Suzuki reaction of porphyrin **3** and organoborane to yield **4** in aqueous media

Compd	Metal	Alkyne	Time (h)	Yield (%)[a]
4a	Zn	Phenylboronic acid	5	56
4b	Zn	4-Acetylphenylboronic acid	5	66
4c	Zn	4-Methoxyphenylboronic acid	6	56
4d	Zn	4-Carboxyphenylboronic acid	8	34
4e	Ni	Phenylboronic acid	24	45
4f	H_2	Phenylboronic acid	24	0

Reaction conditions: $Pd(Oac)_2$/TPPTS in H_2O/CH_3CN (1:1, v/v) and K_2CO_3 at 60–70 °C.
[a] Isolated yield.

Table 2. Suzuki reaction of zinc porphyrin **3** and fluoroorganoborane to yield **4** in aqueous media

Compd	Organoborane	Time (h)	Yield (%)[a]
2f	Potassium 4-*tert*-butylphenyl-trifluoroborane	12	67
2g	Potassium vinyltrifluoroborane	12	56
2h	Potassium 3-hydroxyphenyl-trifluoroborane	12	72

Reaction conditions: $Pd(OAc)_2$/TPPTS in H_2O/CH_3CN (1:1, v/v) and K_2CO_3 at 60–70 °C.
[a] Isolated yield.

Table 3. Suzuki coupling reaction of porphyrin **1** and organoborane to yield **2** in organic solvent

Compd	Metal	Organoborane	Time (h)	Yield (%)[a]
2a	Zn	4-Methoxyphenylboronic acid	6	65
2b	Ni	4-Methoxyphenylboronic acid	24	58
2c	Zn	4-Acetylphenylboronic acid	5	75
2d	Ni	4-Acetylphenylboronic acid	24	71
2e	Zn	*trans*-1-Hexen-1-ylboronic acid	6	76

Reaction conditions: $Pd_2dba_3/P(t\text{-}Bu)_3$ in DMF and Cs_2CO_3 at 90 °C.
[a] Isolated yield.

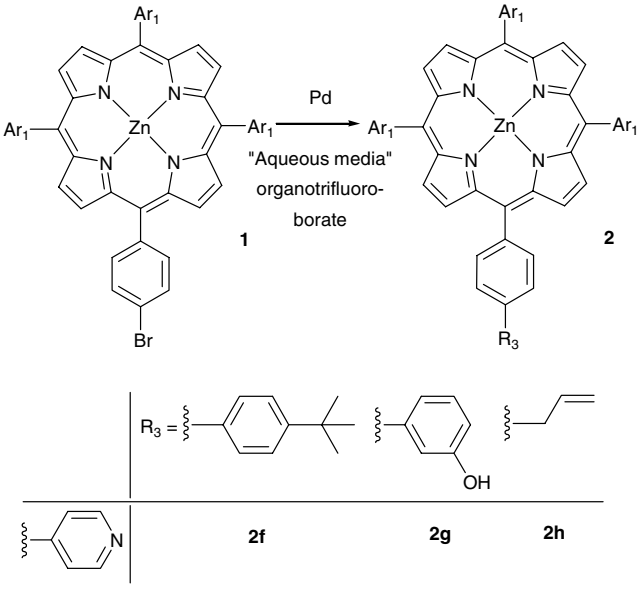
Table 4. Heck reaction of zinc porphyrin **3** and organoborane to yield **4** in organic solvent

Entry	Alkene	Time (h)	Yield (%)[a]
6a	Styrene	12	32
6b	Acrylonitrile	12	47

Reaction conditions: $Pd_2dba_3/P(t\text{-}Bu)_3$ in DMF and Et_3N at 90 °C.
[a] Isolated yield.

water-soluble porphyrin **4**, which is the same compound as that obtained via the Suzuki coupling of **3** in aqueous medium.

The Heck procedure is also known to proceed under aqueous conditions. However, all attempts to obtain Pd-catalyzed coupling products in aqueous media failed. This reaction can be achieved in organic solvent (DMF and Et_3N base) using the non-methylated porphyrin **1** to yield coupling product **5** (Table 4), which upon methylation gives the water-soluble product **6**. In the case of the Heck[6] reaction, we were not able to isolate the nickel porphyrin coupling products. Interestingly, when the reaction was performed with the dipyridine dibromo analog of **1** a much weaker catalyst such as $Pd[P(Ph)_3]_4$ could be used to accomplish the above reactions (unpublished results).



We also studied the Pd-catalyzed coupling between cationic porphyrins and other substrates such as amines,[12] thiols[13] and phosphines.[14] In the case of the amines and phosphines, using either organic solvent or aqueous conditions, HPLC analysis did not reveal any coupling products. The coupling reaction with thiol likewise did not proceed in organic solvent. However, in aqueous medium the bromo compound **3** reacted with 2-mercaptoethanol to yield a complex reaction mixture that did not contain any expected coupling product.

All products obtained from the reactions conducted in aqueous medium were purified on a reversed-phase polymer-based column using aqueous buffer and acetonitrile.[15] While most of the products could be recovered by this method, some impurities including some of the desired product, remained on the column and could only be eluted with 100% DMSO. This may explain the somewhat lower yield obtained with the aqueous-based coupling reaction as compared to the reaction performed in organic solvent (Tables 1 and 3). All the new products were characterized using 1H NMR, UV–vis and mass spectroscopic analyses.[16]

In summary, we have shown that cationic porphyrins can be modified under various Pd-catalyzed reaction conditions using aqueous as well as organic media. However, the reactivity and yield vary extensively depending on the nature of the reactants, solvent, central metal ion as well as the number of pyridine rings attached to the porphyrin core.

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15. PRP reversed-phase column, 10 mM TFA/TEA pH 2.5 buffer in CH_3CN.
16. Compound **1** (M = Zn): ^{1}H NMR δ 8.98 (d, 6H, $J = 5.6$ Hz), 8.84–8.79 (m, 8H), 8.19 (d, 6H, $J = 5.6$ Hz), 8.05 (dd, 4H, $J_1 = 8.3$ Hz, $J_2 = 37.9$ Hz); MS m/z (M+H) for $C_{41}H_{24}BrN_7Zn$ calcd: 757.0568. Found: 757.0683. Compound **1** (M = Ni): MS m/z (M+H) for $C_{41}H_{24}BrN_7Ni$ calcd: 751.0630. Found: 751.6521. Compound **1** ($M = H_2$): MS m/z (M+H) for $C_{41}H_{26}BrN_7$ calcd: 695.1433. Found: 695.7193. Compound **2a**: ^{1}H NMR δ 9.00 (d, 8H, $J = 5.3$ Hz), 8.92 (d, 3H, $J = 4.7$ Hz), 8.84–8.80 (m, 3H), 8.23–8.21 (m, 8H), 8.12–8.04 (m, 4H), 8.00–7.94 (m, 4H), 7.17 (d, 2H, $J = 8.6$ Hz), 3.87 (s, 3H); MS m/z (M+H) for $C_{48}H_{31}N_7OZn$ calcd: 785.1882. Found: 788.6107. Compound **2b**: MS m/z (M+H) for $C_{48}H_{31}N_7NiO$ calcd: 779.1944. Found: 780.5341. Compound **2c**: ^{1}H NMR δ 9.02 (d, 8H, $J = 4.6$ Hz), 8.93–8.91 (m, 2H), 8.83 (s, 6H), 8.82–8.19 (m, 16H), 2.10 (s, 3H); MS m/z (M+H) for $C_{49}H_{31}N_7OZn$ calcd: 797.1882. Found: 798.5821. Compound **2d**: MS m/z (M+H) for $C_{49}H_{31}N_7NiO$ calcd: 791.1944. Found: 792.2315. Compound **2e**: ^{1}H NMR δ 8.96 (d, 6H, $J = 4.5$ Hz), 8.79–8.68 (m, 8H), 8.25 (dd, 4H, $J_1 = 7.8$ Hz, $J_2 = 14.8$ Hz), 8.15 (d, 6H, $J = 5.4$ Hz), 7.85 (m, 2H), 1.83–1.2 (m, 9H); MS m/z (M+H) for $C_{47}H_{35}N_7Zn$ calcd: 761.2245. Found: 762.0783. Compound **2f**: MS m/z (M+H) for $C_{51}H_{37}N_7Zn$ calcd: 811.2402. Found: 812.4326. Compound **2g**: MS m/z (M+H) for $C_{44}H_{29}N_7Zn$ calcd: 719.1776. Found: 720.7396. Compound **2h**: MS m/z (M+H) for $C_{47}H_{29}N_7OZn$ calcd: 771.1725. Found: 772.5837. Compound **4a**: MS m/z (M+H) for $C_{51}H_{40}N_7OZn$ calcd: 830.2586. Found: 830.1345. Compound **4b**: MS m/z (M+H) for $C_{52}H_{40}N_7OZn$ calcd: 842.2586. Found: 842.4365. Compound **4c**: MS m/z (M+H) for $C_{50}H_{38}N_7Zn$ calcd: 800.2480. Found: 800.3146. Compound **4d**: MS m/z (M+H) for $C_{51}H_{38}N_7O_2Zn$ calcd: 844.2378. Found: 844.2365. Compound **4e**: MS m/z (M+H) for $C_{50}H_{38}N_7Ni$ calcd: 794.2542. Found: 894.2521. Compound **6a**: MS m/z (M+H) for $C_{49}H_{31}N_7Zn$ calcd: 781.1932. Found: 782.2941. Compound **6b**: ^{1}H NMR δ 9.00 (d, 6H, $J = 4.3$ Hz), 8.82–8.77 (m, 8H), 8.32 (dd, 4H, $J_1 = 8.0$ Hz, $J_2 = 15.7$ Hz), 8.19 (d, 6H, $J = 5.5$ Hz), 7.93 (s, 2H). MS m/z (M+H) for $C_{44}H_{26}N_8Zn$ calcd: 730.1572. Found: 731.5576.