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First example of a palladium catalyzed coupling reaction between cationic porphyrins and alkynyls in aqueous medium

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Abstract—The first example of the palladium catalyzed (Sonogashira) carbon–carbon coupling reaction in aqueous medium between 5,10,15-tri-(4-*N*-methylpyridyl)-20-(4-bromophenyl)-porphyrin and a variety of terminal alkynyls is reported.

Porphyrin derivatives have received much attention over the past decades for applications in material sciences, optics and catalysis and as photosensitizers for the photodynamic therapy (PDT) of various medical conditions.[1] Positively-charged water-soluble porphyrins exhibit preferential uptake by mitochondria and high binding affinity for DNA, rendering them of particular interest for photodynamic applications. The extent of their cytotoxicity is directly related to their intracellular distribution pattern, which in turn can be modulated by the nature of moieties attached to the chromophore core structure.[2]

Conventional methods to prepare cationic porphyrins involve the use of aldehyde and pyrrole in organic acid at reflux.[3] However the extreme reaction conditions to form the porphyrin macrocycle are often incompatible with the stability of sensitive substituents. The Lindsey method,[4] which proceeds under relative mild conditions, failed to afford pyridyl porphyrins probably due to the poor solubility of the heterocyclic aldehyde precursor.[5] Modification of the porphyrin periphery after condensation is an attractive alternative approach to overcome such problems. In particular, the use of palladium catalyzed carbon–carbon bond formation permits the preparation of a large variety of substituted porphyrins. Furthermore, the latter method can be rendered compatible with green chemistry conditions.[6] In addition to being non-toxic, the use of water as a reaction medium has the advantages to facilitate the separation of products and the recovery of catalyst. The use of water has the disadvantage that either substrate or catalyst may be insoluble under the reaction conditions. This problem can be solved through the use of water soluble ligands, phase-transfer catalysts or new heterogeneous catalyst systems.[7] To our knowledge the modification of cationic porphyrins in aqueous medium has not been reported previously. Here we explore various procedures to prepare water soluble, positively-charged *meso*-phenyl porphyrins, based on the Sonogashira cross-coupling reaction both in organic solvent and aqueous medium.

The 5,10,15-tri-(pyridyl)-20-(4-bromophenyl)-porphyrin (**1**), that is, the precursor for the palladium catalyzed carbon–carbon cross-coupling reaction, was prepared in 3–5% yield by a modified, published procedures[3] involving the stoichiometric condensation of 4-pyridinecarboxaldehyde, 4-bromobenzaldehyde and pyrrole in refluxing propionic acid, followed by purification over silica gel. In view of the low yield obtained for the preparation of such porphyrins, efficient, high yield procedures are required for further modifications. We explored two different routes to synthesize the water soluble tri-cationic porphyrin **4** (Scheme 1). The first procedure involves the palladium-catalyzed coupling reaction of **1** in organic solvent to yield **2**, followed by alkylation of the *meso*-pyridyl nitrogens to give **4**. In the second procedure alkylation of **1** to give **2** is done prior to the coupling step to yield **4**, which is accomplished in aqueous medium. Both methods have their advantages and

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Keywords: Palladium catalyst; Cationic porphyrins; Green chemistry.

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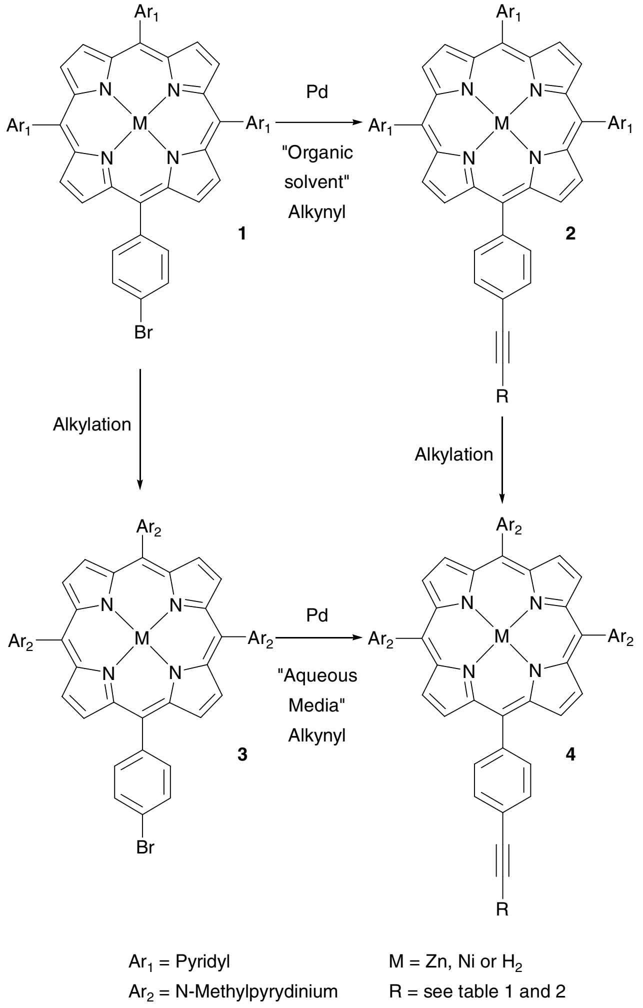

Scheme 1.

disadvantages. For example, the latter procedure avoids possible decomposition of the organic moieties during alkylation, while the conventional, organic solvent procedure yields products that can be readily purified by silica gel chromatography.

We previously reported the coupling of 5-(4-iodophenyl)-10,15,20-triphenylporphyrin zinc with phenylacetylene and 3-butyn-1-ol using $Cl_2(TPP)_2Pd/CuI$ in DMF containing Et_3N (2–4 h, room temperature).[8] Using the same conditions 5,10,15-tri-(pyridyl)-20-(4-bromophenyl)-porphyrin nickel (**1**) failed to yield any product, even at elevated temperature (100 °C). We then investigated the reactivity of several established and new palladium catalyst systems[9] in DMF/Et_3N at different temperatures. Most of them, including $Pd(PPh_3)_4/CuI$, $[PdCl(allyl)]_2/CuI$, $PdCl_2(dppf)$, $Cl_2(PPh_3)_2Pd/CuI$, $Pd(PPh_3)_4/Ag$ and $Pd_2(dba)_3/AsPh_3$, failed to provide any or very little coupling products. At higher temperature, the desired compounds were detectable by HPLC but yields were low (<5%). Evidently stronger catalysts and high temperatures (90 °C) are required for this reaction to proceed. Recently palladium catalyst with electron rich, bulky tri-*t*-Bu phosphine ligand was shown to exhibit unusual high reactivity at room temperature.[9,10] Using $Pd_2(dba)_3/P(t\text{-}Bu)_3$, we were able to couple porphyrin **1** with a number of alkynes to give **2a**–**h** in 40–60% yield after silica gel column chromatography in THF/CH_2Cl_2 (Table 1). Reaction progress and purity (>95%) of the final products were confirmed by HPLC after alkylation of products with CH_3I (PRP reversed-phase, 10 mM TFA/TEA buffer in CH_3CN).

Changing the central metal ion from nickel to zinc substantially affect the reactivity of the porphyrin and consequently the yield of the coupling reaction (Table 1). The choice of co-catalyst was also critical since certain metal ions, such as copper, readily insert in the core of non-metallated porphyrins. Indeed our optimized condition does not require any co-catalyst. Using identical conditions, the reaction with the zinc porphyrin is faster, cleaner and provides better yields as compared to the nickel porphyrin. Metal free porphyrin was also studied and shown to exhibit a slightly lower reactivity than the zinc porphyrin, likely due to its low solubility (Table 1).

Next we turned our attention to the use of palladium catalyst in homogenous aqueous media (Table 2). In addition to the advantages associated with the use of an environmentally-friendly solvent, the mild reaction conditions permit the use of a wider selection of organic and bioactive moieties to couple to the porphyrin core and the use of less sensitive catalysts. In a 1:1 mixture of H_2O/CH_3CN with K_2CO_3 using the TPPTS/$Pd(OAc)_2$ catalyst system,[11] the reaction between the 5,10,15-tri-(4-*N*-methylpyridyl)-20-(4-bromophenyl)-porphyrins (**3**) and phenylacetylene afforded the desired coupling compounds **4a**–**e** in good yield (Table 2). Products **4a**–**e** were purified >95% by reversed phase column chromatography (Sepra SDB-L, 255 Å, Phenomenex)

Table 1. Sonogashira coupling reaction of porphyrin **1** and alkyne to yield **2** in organic solvent

Compound	M	Alkyne	Time (h)	Yield (%)[a]
2a	Zn	Phenylacetylene	4	74
2b	Ni	Phenylacetylene	24	60
2c	H_2	Phenylacetylene	6	48
2d	Zn	1-Hexadecyne	5	63
2e	Ni	1-Hexadecyne	24	40
2f	Zn	3-Butyn-1-ol	5	58
2g	Zn	Ethynylferrocene	5	83
2h	Zn	10-Undecynoic acid	5	67

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

Table 2. Sonogashira reaction of porphyrin **3** and phenylacetylene to yield **4** in aqueous media

Compound	Metal	Alkyne	Time (h)	Yield (%)[a]
4a	Ni	Phenylacetylene	24	45
4b	Ni	3-Butyn-1-ol	24	52
4c	Zn	Phenylacetylene	3	62
4d	Zn	3-Butyn-1-ol	3	68
4e	H_2	Phenylacetylene	5	55

Reaction conditions: $Pd(OAc)_2$/TPPTS in H_2O/CH_3CN (1:1, v/v) and Na_2CO_3 at 60–70 °C.
[a] Isolated yield.

and their homogeneity was confirmed by HPLC as described above. In an effort to further improve the yield, various other ligands were evaluated including TPPTS to TPPDS, TXPTS and 1,2-bis(di-4-sulfonatophenylphosphino) benzene tetrasodium salt.[12] In all cases this resulted in loss of the catalytic activity. Interestingly, the effect of the central metal ion on the reactivity of the methylated (water soluble) and non-methylated porphyrins was found to be similar ($Zn \sim H_2 > Ni$) (Tables 1 and 2). Assigned structures of all new compounds were confirmed by ^1H NMR (300 MHz) in DMSO-d_6 and HRMS (MALDI-TOF).[13]

In summary, our results confirm the versatility of the Sonogashira cross-coupling reaction for the preparation of cationic porphyrins with terminal alkyne groups. We also demonstrate for the first time that such cationic porphyrins can be modified in good yield using the same coupling reaction in aqueous medium. These milder, aqueous reaction conditions provide for an interesting alternative approach to prepare libraries of cationic porphyrins with a wide range of biological applications, particularly for PDT.

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References and notes

1. Ali, H.; van Lier, J. E. *Chem. Rev.* **1999**, *99*, 2379–2450.
2. Woodburn, K. W.; Vardaxis, N. J.; Hill, J. S.; Kaye, A. H.; Phillips, D. R. *Photochem. Photobiol.* **1991**, *54*, 725–732; Georgiou, G. N.; Ahmet, M. T.; Houlton, A.; Silver, J. R.; Cherry, J. *Photochem. Photobiol.* **1994**, *60*, 419–422; Wall, R. K.; Shelton, A. H.; Bonaccorsi, L. C.; Bejune, S. A.; Dubé, D.; McMillin, D. R. *J. Am. Chem. Soc.* **2001**, *123*, 11480–11481; Nyarko, E.; Tabata, M. *J. Porphyrins Phthalocyanines* **2001**, *5*, 873–880; He, H.; Tian, T.; Wang, P.; Wu, L.; Xu, J.; Zhou, X.; Zhang, X.; Cao, X.; Wu, X. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3013–3016; Detty, M. R.; Gibson, S. L.; Wagner, S. J. *J. Med. Chem.* **2004**, *47*, 3897–3915; Cauchon, N.; Tian, H.; Langlois, R.; La Madeleine, C.; Martin, S.; Ali, H.; Hunting, D.; van Lier, J. E. *Bioconjugate Chem.* **2005**, *16*, 80–89.
3. Ding, L.; Cascas, G.; Etemad-Moghadam, G.; Meunier, B. *New J. Chem.* **1990**, *14*, 421–431.
4. Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y.-Y. *J. Org. Chem.* **1994**, *59*, 579–589.
5. Gryko, D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 2249–2252.
6. http://www.epa.gov/greenchemistry/principles.html.
7. Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559–1563; Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080–4086; Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892, See also Refs. 9–11.
8. Ali, H.; van Lier, J. E. *Tetrahedron* **1994**, *50*, 11933–11944.
9. For recent reviews and examples of palladium-catalyzed akynylation: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017; Sharman, W. M.; van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441–453; Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935–2937; Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191–4194; Schouteenen, S.; Tranchier, J.-P.; Rose-Much, F.; Rose, E.; Auffrant, A. *Organometallics* **2004**, *23*, 4308–4316; Mito, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikawa, T. L.; Hull, L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199–3202.
10. Böhm, V. P.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679–3681; Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.
11. Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330; Depuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savigniac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.
12. Western, E. C.; Daft, J. R.; Johnson, E. M.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767–6774; Moore, L. R.; Shaughnessy, K. H. *Org. Lett.* **2004**, *6*, 225–228; Hessler, A.; Stelzer, O. *J. Org. Chem.* **1997**, *62*, 2362–2369.
13. Compound **1** ($M = Zn$): ^1H 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 $C_{43}H_{26}BrN_7$ calcd: 695.1433. Found: 695.7193. Compound **2a**: ^1H NMR δ 8.94 (d, 6H, $J = 5.5$ Hz), 8.86–8.81 (m, 7H), 8.21–8.17 (m, 8H), 7.95 (d, 2H, $J = 6.3$ Hz), 7.73–7.68 (m, 2H), 7.50–7.48 (m, 4H); MS *m*/*z* (M+H) for $C_{49}H_{29}N_7Zn$ calcd: 779.1776. Found: 779.2013. Compound **2b**: MS *m*/*z* (M+H) for $C_{49}H_{29}N_7Ni$ calcd: 773.1838. Found: 772.9463. Compound **2c**: MS *m*/*z* (M+H) for $C_{49}H_{31}N_7$ calcd: 717.2641. Found: 717.3547. Compound **2d**: ^1H NMR δ 8.98 (d, 6H, $J = 4.8$ Hz), 8.83–8.76 (m, 8H), 8.19 (d, 6H, $J = 5.6$ Hz), 8.12 (d, 2H, $J = 8.0$ Hz), 7.78 (d, 2H, $J = 8.1$), 2.55 (t, 2H, $J_1 = 6.5$ Hz, $J_2 = 6.7$ Hz), 1.70–1.14 (m, 23H), 0.81–0.77 (m, 4H); MS *m*/*z* (M+H) for $C_{57}H_{53}N_7Zn$ calcd: 899.3654. Found: 899.3762. Compound **2e**: MS *m*/*z* (M+H) for $C_{57}H_{53}N_7Ni$ calcd: 893.3716. Found: 893.6541. Compound **2f**: ^1H NMR δ 9.02 (d, 6H, $J = 5.6$ Hz), 8.90–8.84 (m, 8H), 8.23 (d, 6H, $J = 5.6$ Hz), 8.11 (d, 2H, $J_1 = 8.3$ Hz), 7.89 (d, 2H, $J = 8.2$ Hz), 3.68 (t, 2H, $J_1 = 5.8$ Hz, $J_2 = 6.2$ Hz), 2.25 (t, 2H, $J_1 = 5.7$ Hz, $J_2 = 5.9$ Hz); MS *m*/*z* (M+H) for $C_{45}H_{29}N_7OZn$ calcd: 747.1725. Found: 747.1326. Compound **2g**: ^1H NMR δ 8.97 (s, 6H), 8.86 (s, 2H), 8.81 (s, 6H), 8.19 (s, 8H), 7.93–7.85 (m, 2H), 4.70 (s, 4H), 4.41 (s, 5H), 4.37 (s, 9H); MS *m*/*z* (M+H) for $C_{53}H_{33}FeN_7Zn$ calcd: 887.1438. Found: 887.2003. Compound **2h**: ^1H NMR δ 9.09 (s, 6H), 8.86 (d, 8H, $J = 5.6$ Hz), 8.37 (s, 6H), 8.14 (d, 2H, $J = 8.0$ Hz), 7.82 (d, 2H, $J = 6.1$ Hz), 2.64–2.59 (m, 2H), 1.92–1.87 (m, 2H), 1.26–1.17 (m, 2H); MS *m*/*z* (M+H) for $C_{47}H_{31}N_7O_2Zn$ calcd: 789.1831. Found: 789.1947. Compound **3** ($M = Zn$): ^1H NMR δ 9.35 (d, 6H, $J = 6.1$ Hz), 9.05 (s, 4H), 8.95 (dd, 4H, $J_1 = 4.6$ Hz, $J_2 = 16.2$ Hz), 8.88 (d, 6H, $J = 5.6$ Hz), 8.07 (dd, 4H, $J_1 = 8.0$ Hz, $J_2 = 26.7$ Hz), 4.68 (s, 9H), MS *m*/*z* (M+H) for $C_{44}H_{33}BrN_7Zn$ calcd: 802.1272. Found: 802.1574. Compound **3** ($M = Ni$): MS *m*/*z* (M+H) for $C_{44}H_{33}BrN_7Ni$ calcd: 796.1334. Found: 796.5641. Compound **3** ($M = H_2$): MS *m*/*z* (M+H) for $C_{44}H_{35}BrN_7$ calcd: 740.2137. Found: 740.6571. Compound **4a**: MS *m*/*z* (M+H) for $C_{52}H_{38}N_7Ni$ calcd: 818.2542. Found: 817.9564. Compound **4b**: MS *m*/*z* (M+H) for $C_{48}H_{38}N_7NiO$ calcd: 786.2491. Found: 786.3246. Compound **4c**: MS *m*/*z* (M+H) for $C_{52}H_{38}N_7Zn$ calcd: 824.2480. Found: 824.2623. Compound **4d**: MS *m*/*z*

(M+H) for $C_{48}H_{38}N_7OZn$ calcd: 792.2429. Found: 792.6874. Compound **4e**: MS *m/z* (M+H) for $C_{52}H_{40}N_7$ calcd: 762.3245. Found: 762.2168. ^{1}H NMR spectra of compounds **4** were similar to those of the corresponding non-methylated compounds **2**, except for the characteristic singlet of the CH_3 protons around δ 4.68 (s, 9H).