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PALLADIUM-CATALYZED TETRAARYLATION OF 5,15-DIALKYLPORPHYRINS WITH ARYL BROMIDES

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Abstract – Nickel complexes of 5,15-dialkylporphyrins are subjected to palladium-catalyzed direct arylation under the modified Fagnou conditions. The arylation takes place still exclusively at the four less hindered *β* positions although the *meso*-nonyl, hexyl, and propyl groups are considered to impose less steric hindrance than the *meso*-3,5-di-*tert*-butylphenyl group in the previous report.

INTRODUCTION

Due to the important roles that porphyrins adopt in a variety of pivotal biological processes, chemists have devoted much time to the design and synthesis of new artificial porphyrins that can be utilized in advanced functional materials.[1] Peripheral functionalizations of a porphyrin core is an effective strategy that allows for the systematic construction of porphyrin-based architechtures.[2] Palladium-catalyzed cross-coupling reactions[3] can be used to successfully introduce a direct carbon–carbon bond at the periphery of a porphyrin.[1,2,4] However, these reactions generally take place in moderate yield. Unlike benzene-based building blocks, which are cheap and readily available, prefunctionalized porphyrins such as bromoporphyrins and borylporphyrins are far more precious. It is therefore essential that extensive efforts be made to develop much more efficient, scalable, and reliable synthetic methodologies for achieving these highly desirable molecules.

A recent dramatic growth in reports of transition-metal-catalyzed direct C–H arylations has changed the landscape of biaryl synthesis.[5] Direct arylation does not require either an aryl metal reagent or an aryl halide and therefore represents the ideal arylation. We have been interested in the modification of functional aromatics by direct arylation[6,7] and we have recently developed conditions for palladium-

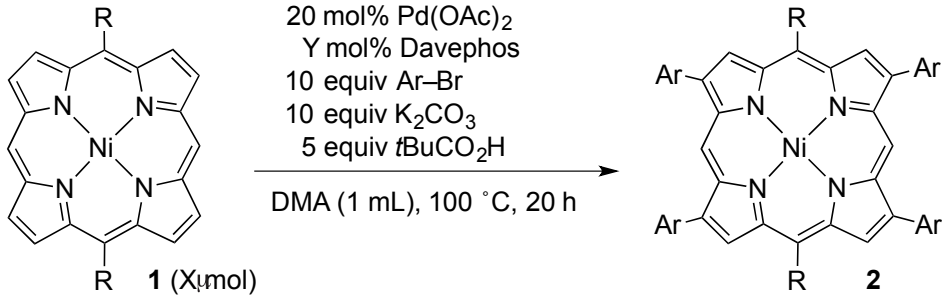
This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

catalyzed *β*-selective direct arylation of porphyrins[8,9] based on procedures originally reported by Fagnou.[10,11] Our direct *β*-arylation has proved to be applicable to nickel complexes of 5,10,15-triarylporphyrin, 5,15-diarylporphyrin, and 5,10,15-triaryl-20-formylporphyrins bearing bulky 3,5-di-*tert*-butylphenyl groups as the aryl groups at their *meso* positions. Since the regioselective outcome of porphyrin arylation is heavily governed by sterics, the size of the group that is present at the *meso* position is a critical factor. To test this hypothesis, we have synthesized a small series of porphyrins bearing alkyl chains of various sizes at the *meso* positions. The regioselective outcome of direct arylation reactions of this small series of porphyrins is reported.

RESULTS AND DISCUSSION

Three dialkylporphyrins, **1a** (R = C_9H_{19}), **1b** (R = C_6H_{13}), and **1c** (R = C_3H_7), were prepared and subjected to the palladium-catalyzed tetraarylation[8] (Table 1). Tetraarylation proceeded very smoothly to afford the corresponding tetraarylated products **2** as the sole isolated products with exclusive regioselectivity. Considering the reaction involves the simultaneous formation of four C–C bonds, the yields are extremely high.[12] The presence of Davephos (2-dicyclohexylphosphino-2'-dimethylaminobiphenyl) led to slightly better yields of **2** (Entries 1, 3, 5, 7 vs. 2, 4, 6, 8). Arylation with bulky 2-bromotoluene also proceeded

Table 1. Direct arylation of 5,15-dialkylporphyrin nickel complexes **1**



Entry	R	X	Y	Ar	**2**	Yield /%
1	C_9H_{19}	50	40	3,5-dimethylphenyl	**2a**	97
2	C_9H_{19}	50	0	3,5-dimethylphenyl	**2a**	85
3	C_9H_{19}	50	40	2-methylphenyl	**2a'**	98
4	C_9H_{19}	50	0	2-methylphenyl	**2a'**	83
5	C_6H_{13}	25	40	3,5-dimethylphenyl	**2b**	96
6	C_6H_{13}	25	0	3,5-dimethylphenyl	**2b**	78
7	C_3H_7	25	40	3,5-dimethylphenyl	**2c**	77
8	C_3H_7	25	0	3,5-dimethylphenyl	**2c**	76

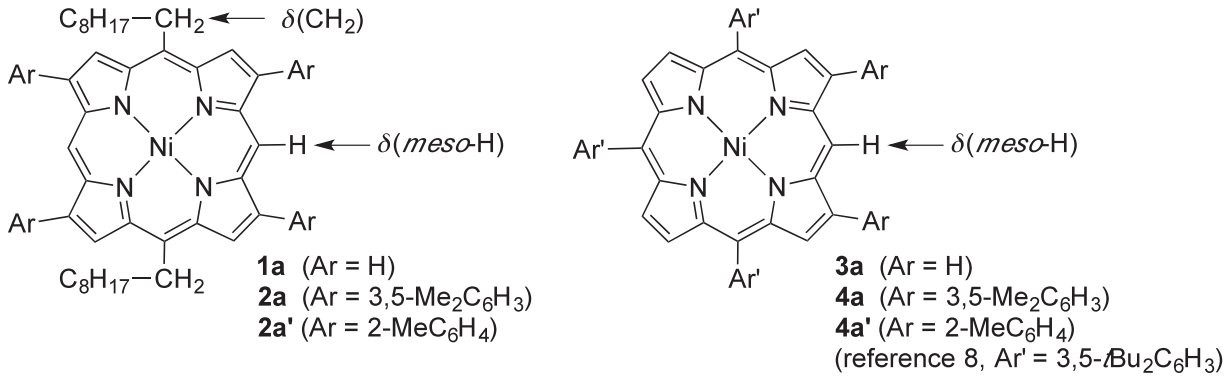
favorably (Entries 3, 4). The reactivities of **1a** and **1b** are comparable to those of *meso*-diarylporphyrins. On the other hand, the yields of **2c** were slightly lower (Entries 7, 8). We speculate this is because **1c** is equipped with short propyl groups that exhibit poor solubility in *N*,*N*-dimethylacetamide (DMA).

Unfortunately, we could not obtain crystals of **2** suitable for X-ray crystallographic analysis. Nevertheless, we can safely assume that the four aryl groups are located at the less hindered β positions (2, 8, 12, 18 positions), as indicated. It is improbable for the four aryl groups to be introduced at the more crowded β positions (3, 7, 13, 17 positions) adjacent to the alkyl groups since Fagnou's direct arylation has been established to follow steric control.[10] The anticipated regioselectivity is additionally confirmed by ^{1}H NMR spectroscopy (Table 2). The *meso*-H signal of porphyrin **2a** bearing four 3,5-dimethylphenyl groups appear at 9.83 ppm and is shifted downfield by 0.13 ppm compared to that of starting material **1a** (9.70 ppm). In contrast, porphyrin **2a'** bearing four 2-methylphenyl groups shows its *meso*-H signal at 9.15 ppm, significantly shifted upfield by 0.55 ppm. This dramatic upfield shift most likely originates from the diatropic ring current of the β-benzene rings, which would be nearly perpendicular to the porphyrinic plane due to the steric crash with the *ortho* methyl group and would thus cover the *meso* protons. Notably, the arylation of **1a** did not induce drastic changes in the chemical shifts of the signals corresponding to the methylene protons that are in closest proximity to the porphyrin core, as illustrated by limited upfield shifts, 0.14 ppm in **2a** and 0.07 ppm in **2a'**. The significant changes in the chemical shifts for the *meso* protons and the small changes for the methylene protons are strong evidence that the aryl groups introduced are located at the less hindered β positions next to the unsubstituted *meso* positions. Furthermore, similar changes in the chemical shifts for *meso* protons were observed in the previous β-diarylation of 5,10,15-triarylporphyrin at the 2 and 18 positions,[8] where the introduction of 3,5-dimethylphenyl groups and of 2-methylphenyl groups gave rise to a downfield shift (0.25 ppm) and an upfield shift (0.47 ppm), respectively.

The UV-visible absorption spectra of **1a**, **2a**, and **2a'** are illustrated in Figure 1. The introductions of the aryl groups in **2a** and **2a'** obviously resulted in red-shifted absorptions. Notably, **2a** bearing 3,5-dimethylphenyl groups shows more red-shifted absorption than **2a'** bearing 2-methylphenyl groups. The difference in the absorption exhibits that **2a'** has less effective conjugation than **2a** and implies that the 2-methylphenyl groups in **2a'** would be more tilted to the porphyrin plane than the 3,5-dimethylphenyl groups in **2a**. This implication is consistent with the significant upfield shift of the *meso* protons in the ^{1}H NMR analysis of **2a'**.

In conclusion, 5,15-dialkylporphyrin nickel complexes undergo palladium-catalyzed direct tetraarylation under modified Fagnou conditions using pivalic acid as a mediator. The arylation is high-yielding and takes place exclusively at the four less hindered β positions as observed in the arylation of *meso*-3,5-di-*tert*-butylphenyl-substituted porphyrins.

Table 2. Chemical shifts of notable protons



Porphyrin	δ(*meso*-H) /ppm	δ(CH_2) /ppm	$\Delta\delta$(*meso*-H)[a] /ppm	$\Delta\delta$(CH_2)[a] /ppm
1a	9.70	4.67	–	–
2a	9.83	4.53	+0.13	–0.14
2a'	9.15	4.60	−0.55	−0.07
3a	9.83	–	–	–
4a	10.08	–	+0.25	–
4a'	9.36	–	−0.47	–

[a] Difference of chemical shifts between the arylated product (**2** or **4**) and the parent porphyrin (**1** or **3**).

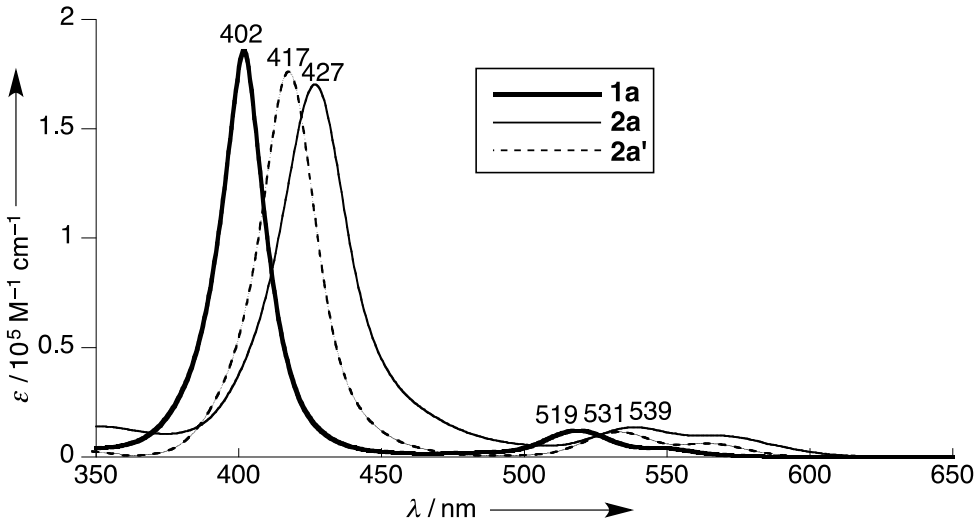


Figure 1. UV-visible absorption spectra of **1a**, **2a**, and **2a'**

EXPERIMENTAL

^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra were taken on a JEOL ECA-600 spectrometer. Chemical shifts are reported on a delta scale in ppm relative to residual $CHCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and to $CDCl_3$ (δ = 77.16 ppm) for ^{13}C NMR. Spectroscopic grade solvents were used for all

spectroscopic studies without further purification. UV-Visible absorption spectra were recorded on a Shimadzu UV-2550 and Shimadzu UV-3600PC spectrometer. ESI-TOF-MS spectra were recorded on a Bruker Daltonics micrOTOF II instrument using a positive-ion mode. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Preparative separations were performed by silica-gel column chromatography (Wako gel C-200, C-300, or C-400).

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. DMA was distilled from barium oxide and kept over Molecular Sieves 4Å under argon. Palladium acetate, nickel acetylacetonate, and Davephos were purchased from Wako Pure Chemicals, nacalai tesque, and Aldrich, respectively.

Starting Materials. Free base 5,15-dialkylporphyrins were prepared according to the literature.[13] Subsequent nickelation proceeded quantitatively by treatment of the free base porphyrins with an excess amount of nickel acetylacetonate in boiling toluene overnight.

(5,15-Dinonylporphyrinato)nickel (1a): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.70 (s, 2H, *meso*), 9.43 (d, 4H, J = 4.8 Hz, β), 9.17 (d, 4H, J = 4.8 Hz, β), 4.67 (t, 4H, J = 8.3 Hz, nonyl), 2.36 (m, 4H, nonyl), 1.65 (m, 4H, nonyl), 1.46 (m, 4H, nonyl), 1.35–1.21 (m, 16H, nonyl), 0.86 (t, 6H, J = 6.9 Hz, nonyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.68, 141.55, 132.27, 129.56, 117.45, 104.27, 37.80, 34.38, 32.04, 30.62, 29.76 (overlap), 29.50, 22.81, 14.25 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 402 (190000), 519 nm (12000); MS (ESI, positive): m/z = 619.3279. Calcd for $C_{38}H_{49}N_4Ni$: 619.3305 [M+H]$^+$.

(5,15-Dihexylporphyrinato)nickel (1b): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.71 (s, 2H, *meso*), 9.45 (d, 4H, J = 4.6 Hz, β), 9.18 (d, 4H, J = 4.6 Hz, β), 4.68 (t, 4H, J = 8.3 Hz, hexyl), 2.37 (m, 4H, hexyl), 1.66 (m, 4H, hexyl), 1.45 (m, 4H, hexyl), 1.35 (m, 4H, hexyl), 0.91 (t, 6H, J = 7.8 Hz, hexyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.65, 141.52, 132.23, 129.50, 117.40, 104.01, 37.77, 34.36, 31.96, 30.29, 22.85, 14.29 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 402 (210000), 518 (13000), 550 nm (4000); MS (ESI, positive): m/z = 535.2345. Calcd for $C_{32}H_{37}N_4Ni$: 535.2366 [M+H]$^+$.

(5,15-Dipropylporphyrinato)nickel (1c): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.70 (s, 2H, *meso*), 9.44 (d, 4H, J = 4.8 Hz, β), 9.17 (d, 4H, J = 4.8 Hz, β), 4.66 (t, 4H, J = 7.8 Hz, propyl), 2.40 (m, 4H, propyl), 1.21 (t, 6H, J = 7.3 Hz, propyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.81, 141.62, 132.35, 129.71, 117.22, 104.08, 36.34, 30.69, 15.03 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 401 (210000), 518 (14000), 550 nm (5000); MS (ESI, positive): m/z = 451.1419. Calcd for $C_{26}H_{25}N_4Ni$: 451.1427 [M+H]$^+$.

Direct Arylation of 5,15-Dinonylporphyrin: 5,15-Dinonylporphyrin **1a** (0.050 mmol, 31.1 mg), $Pd(OAc)_2$ (0.010 mmol, 2.2 mg), Davephos (0.020 mmol, 7.9 mg), K_2CO_3 (0.50 mmol, 69.1 mg), and tBuCO$_2$H (0.25 mmol, 25.6 mg) were added to a reaction flask. The reaction flask was purged with argon, and DMA (1.0 mL) and aryl bromide (0.50 mmol, 70 μL for 1-bromo-3,5-dimethylbenzene or 60 μL for 2-bromotoluene) were added. The reaction mixture was then stirred at 100 ˚C for 20 h. The

resulting mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, and passed through a pad of Celite with copious washings with CH_2Cl_2. After evaporation of the solvent, the product was separated by silica-gel column chromatography (CH_2Cl_2/hexane). Further purification by recrystallization from CH_2Cl_2/MeOH yielded the corresponding product (**2a**, 50.2 mg, 0.0484 mmol, 97%; **2a'**, 48.0 mg, 0.0490 mmol, 98%).

Direct Arylation of 5,15-Dihexyl- or 5,15-Dipropylporphyrin: 5,15-Dihexylporphyrin **1b** (0.025 mmol, 13.4 mg) or 5,15-dipropylporphyrin **1c** (0.025 mmol, 11.3 mg), $Pd(OAc)_2$ (0.005 mmol, 1.1 mg), Davephos (0.010 mmol, 3.9 mg), K_2CO_3 (0.25 mmol, 34.5 mg), and *t*$BuCO_2H$ (0.125 mmol, 12.8 mg) were placed in a reaction flask under argon. DMA (1.0 mL) and 1-bromo-3,5-dimethylbenzene (0.25 mmol, 35 μL) were added, and the whole mixture was heated at 100 ˚C for 20 h. The resulting mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2, and filtered through a pad of Celite with copious washings with CH_2Cl_2. The filtrate was concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/hexane) followed by recrystallization from CH_2Cl_2/MeOH afforded **2b** (22.8 mg, 0.0240 mmol, 96%) or **2c** (16.6 mg, 0.0191 mmol, 77%).

[**2,8,12,18-Tetrakis(3,5-dimethylphenyl)-5,15-dinonylporphyrinato]nickel (2a):** ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.83 (s, 2H, *meso*), 9.27 (s, 4H, β), 7.68 (s, 8H, Ar-*o*), 7.20 (s, 4H, Ar-*p*), 4.53 (t, 4H, J = 8.7 Hz, nonyl), 2.53 (s, 24H, Ar–Me), 2.34 (m, 4H, nonyl), 1.60 (m, 4H, nonyl), 1.42 (m, 4H, nonyl), 1.32–1.18 (m, 16H, nonyl), 0.84 (t, 6H, J = 6.9 Hz, nonyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 146.29, 140.93, 139.73, 138.51, 136.42, 129.24, 128.74, 127.30, 116.55, 103.95, 37.35, 34.05, 32.02, 30.54, 29.76, 29.71, 29.51, 22.79, 21.73, 14.23 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 427 (170000), 539 (15000), 565 nm (10000); MS (ESI-MS, positive): *m/z* = 1057.5657. Calcd for $C_{70}H_{80}N_4NiNa$: 1057.5629 [M+Na]$^+$.

[2,8,12,18-Tetrakis(2-methylphenyl)-5,15-dinonylporphyrinato]nickel (2a'): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.30 (s, 4H, β), 9.15 (s, 2H, *meso*), 7.76 (d, 4H, J = 5.8 Hz, Ar-*o*), 7.49–7.41 (m, 12H, Ar-*m* Ar-*p*), 4.60 (t, 4H, J = 8.0 Hz, nonyl), 2.43 (s, 12H, Ar–Me), 2.38 (m, 4H, nonyl), 1.60 (m, 4H, nonyl), 1.42 (m, 4H, nonyl), 1.30–1.18 (m, 16H, nonyl), 0.83 (t, 6H, J = 7.1 Hz, nonyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 145.87, 141.38, 140.97, 137.56, 135.77, 132.52, 130.61, 129.00, 128.16, 125.70, 117.27, 103.18, 37.76, 34.32, 32.02, 30.60, 29.76, 29.47, 22.78, 21.37, 20.89, 14.23 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 417 (180000), 531 (11000), 561 nm (6000); MS (ESI-MS, positive): *m/z* = 979.5140. Calcd for $C_{66}H_{73}N_4Ni$: 979.5183 [M+H]$^+$.

[**2,8,12,18-Tetrakis(3,5-dimethylphenyl)-5,15-dihexylporphyrinato]nickel (2b):** ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.83 (s, 2H, *meso*), 9.28 (s, 4H, β), 7.68 (s, 8H, Ar-*o*), 7.20 (s, 4H, Ar-*p*), 4.53 (t, 4H, J = 8.0 Hz, hexyl), 2.53 (s, 24H, Ar–Me), 2.34 (m, 4H, hexyl), 1.61 (m, 4H, hexyl), 1.41 (m, 4H, hexyl), 1.33 (m, 4H, hexyl), 0.89 (t, 6H, J = 7.3 Hz, hexyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 146.38, 140.98, 139.80,

138.54, 136.44, 129.28, 128.77, 127.35, 116.63, 103.96, 37.45, 34.16, 31.96, 30.30, 22.88, 21.74, 14.30 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 426 (160000), 538 (12000), 568 nm (8000); MS (ESI-MS, positive): *m/z* = 951.4823. Calcd for $C_{64}H_{69}N_4Ni$: 951.4870 $[M+H]^+$.

[**2,8,12,18-Tetrakis(3,5-dimethylphenyl)-5,15-dipropylporphyrinato]nickel (2c):** ^1H NMR (600 MHz, $CDCl_3$) δ = 9.87 (s, 2H, *meso*), 9.32 (s, 4H, β), 7.70 (s, 8H, Ar-*o*), 7.20 (s, 4H, Ar-*p*), 4.56 (t, 4H, *J* = 8.0 Hz, propyl), 2.54 (s, 24H, Ar–Me), 2.39 (m, 4H, propyl), 1.20 (t, 6H, *J* = 7.4 Hz, propyl) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 146.38, 140.01, 139.80, 138.52, 136.40, 129.27, 128.75, 127.38, 116.37, 104.00, 36.13, 34.16, 30.42, 21.73, 15.08 ppm; UV-vis (CH_2Cl_2): λ_{max} (ε [$M^{-1}cm^{-1}$]) = 426 (190000), 537 (15000), 568 nm (10000); MS (ESI-MS, positive): *m/z* = 867.3888. Calcd for $C_{58}H_{57}N_4Ni$: 867.3931 $[M+H]^+$.

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