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Palladium-catalyzed *meso*-amination and amidation of porphyrins: marked acceleration with the Ni(II) central metal ion

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Abstract—The preparation of *meso*-amino and *meso*-amido substituted porphyrins was easily accomplished by palladium-mediated cross-coupling reactions of *meso*-brominated porphyrins with amines and amides. Ni(II) introduced as a central metal ion into the substrate porphyrin markedly accelerated the cross-coupling.

Porphyrins and metalloporphyrins play key roles in many biological processes, namely, oxygen activation and transfer, electron transfer, binding or transport of small molecules, light harvesting, and photosynthesis.[1] Although synthetic porphyrins have been extensively studied as models for these biological systems, regulation of steric events and electronic properties of porphyrins by their peripheral substituents still remains an important and fundamental issue in these studies. Amino groups are expected to greatly affect the electronic properties of the porphyrin core. Only a few methods, however, have been available for the introduction of amino groups to the porphyrin ring.[2–4] Very recently, a significant advance has been made by Zhang et al. on the preparation of *meso*-arylamino and *meso*-alkylamino substituted porphyrins via the palladium-catalyzed amination of the brominated precursors.[5] Unfortunately, their method can not be applied to the coupling reactions with aliphatic secondary amines, such as morphorin and piperidine. We report herein an efficient palladium-catalyzed coupling reaction of [5-bromo-10,20-diphenylporphyrino]Ni(II) (**1**) with a variety of amines and amides, the method being a new and more straightforward access to *meso*-amino and *meso*-amido substituted porphyrins.[6,7] The use of Ni(II) as a central metal ion of the substrate porphyrin is essential to promote the cross-coupling.

We initially investigated reaction conditions for the preparation of *meso*-amino substituted porphyrins with *meso*-brominated Ni(II) porphyrin **1** and *n*-hexylamine (**2a**) as model substrates.[8] Systematic variation of the Pd catalysts, ligands, bases, solvents and reaction temperatures revealed that a combination of Pd(OAc)$_2$, *rac*-BINAP, NaO^{t}Bu, 18-crown-6, and THF was the most effective catalyst system among the reaction conditions examined.[9–11] As shown in Table 1, the selection of the central metal ions of the starting porphyrins is particularly important in this cross-coupling reaction. The Ni(II) complex **1** was consumed efficiently within 0.5 h under the optimal conditions, providing the desired *N*-porphyrinylamino derivative (**3a**) as the sole isolable product in 85% yield (entry 1), whereas the reaction utilizing Zn(II) porphyrin (**6**) as a substrate was incomplete over 8 h under similar conditions, and gave the corresponding *meso*-hexylamino derivatives (**8**) in 55% yield along with the starting material **6** recovered in 12% yield (entry 2); free base porphyrin (**7**) gave an inseparable complex mixture in addition to the recovered starting material (entry 3).

We, then, examined the reactions of Ni(II) porphyrin **1** with various aliphatic and aryl amines under the optimal conditions determined.[12] As illustrated in Table 2, a wide variety of amines, such as alkyl amines (entries 1 and 2), cyclic amines (entry 3), primary and secondary aryl amines (entries 4 and 5), were easily applied to the coupling reactions, furnishing the *meso*-amino substituted Ni(II) porphyrins **3** in high yields. The reaction with *m*-phenylenediamine (**2f**) also proceeded smoothly without any protection of one of the amino groups of the substrate, affording the corresponding *meso*-amino substituted Ni(II) porphyrin (**3f**)

Keywords: porphyrin; [5-bromo-10,20-diphenylporphyrino]Ni(II); palladium-catalyzed amination; palladium-catalyzed amidation; *meso*-amino substituted porphyrin; *meso*-amido substituted porphyrin.

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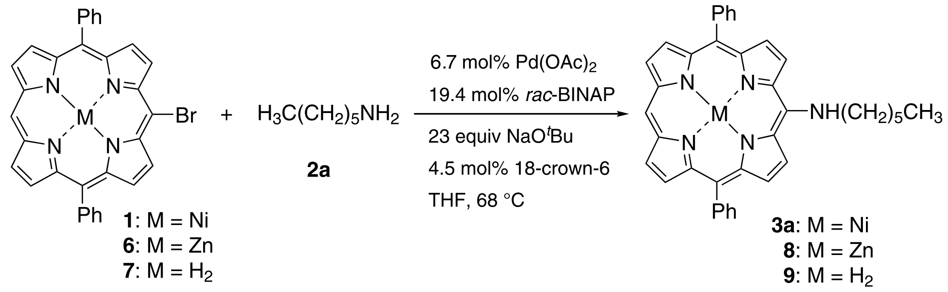
Table 1. Effects of central metal ions on the reactions of *meso*-brominated porphyrins with *n*-hexylamine[a]



Entry	Substrate (metal)	Time (h)	Product	Yield (%)[b]
1	**1** (Ni)	0.5	**3a**	85
2	**6** (Zn)	8	**8**	55[c]
3	**7** (H_2)	8		Complex mixture[d]

[a] 20 Equiv. **2a** was used.

[b] Isolated yields.

[c] Recovery of **6**: 12%.

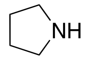
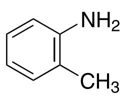
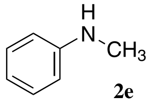
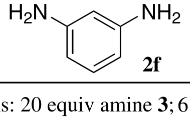
[d] Recovery of **7**: 70%.

in 96% yield under the same reaction conditions (entry 6).

We further expanded this cross-coupling reaction toward the synthesis of *meso*-amido substituted porphyrins. Table 3 summarizes representative results of the reactions of **1** with benzamide (**4a**) under several different conditions. Although the *meso*-amination conditions with $Pd(OAc)_2$/*rac*-BINAP/NaO^tBu/18-crown-6/THF were not applicable to the cross-coupling of **1** with **4a** (entry 1), switching the base from NaO^tBu to a weak base, Cs_2CO_3, led to the formation of the desired *meso*-amido substituted porphyrin (**5a**) in 98% isolated yield (entry 2). Dioxane was the most appropriate solvent investigated, and the reaction was dramatically accelerated in this solvent to give *meso*-amido substituted porphyrin **5a** in a quantitative yield (entry 3). In analogy with the *meso*-amination reactions described above, the use of Ni(II) as the central metal ion was crucial for the coupling. The use of the Zn(II) porphyrin **6** or free base porphyrin **7** as a substrate resulted in a low yield of the corresponding *meso*-amido substituted derivative or a complex mixture of products together with the recovery of the starting materials (entries 4 and 5). As shown in Table 4, the reactions of Ni(II) porphyrin **1** with a range of primary amides, including benzamide, formamide, acetamide and 2-pyrrolidinone, under the optimal conditions with a $Pd(OAc)_2$/*rac*-BINAP/Cs_2CO_3/dioxane catalyst system proceeded smoothly to give the corresponding *meso*-amido substituted porphyrins, **5a–d**, in good yields.[13]

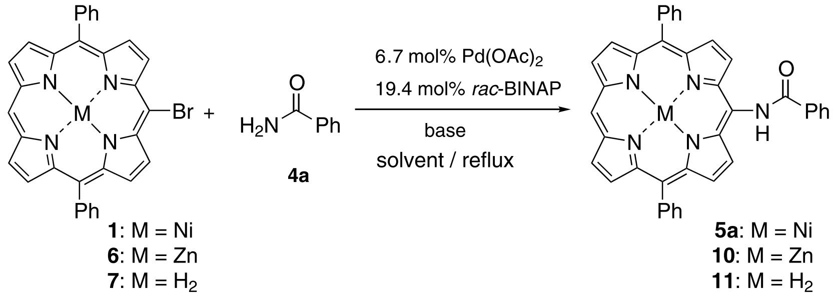
It is well known that the physicochemical properties of porphyrin compounds are precisely tunable not only by their peripheral substituents but also by the central metal ions. Therefore, the choice of appropriate metal ions is important for elaboration of the porphyrin-based new materials. Thus, we briefly examined demetalation of *meso*-amino and *meso*-amido substituted Ni(II) porphyrins to the corresponding free base porphyrins. Treatment of the *meso*-hexylamino Ni(II) porphyrin **3a** with H_2SO_4 gave the corresponding free base porphyrin (**9**) in a quantitative yield without any decomposition of its amino substituent.[14] Similarly, other Ni(II) porphyrins, such as *meso*-amino derivative **3c** and *meso*-amido derivative **5d** underwent demetala-

Table 2. Palladium-catalyzed amination of *meso*-bromo-substituted Ni(II) porphyrin **1** with amines **2**[a]

entry	amine	time (h)	product[b]	yield (%)[c]
1	$H_3C(CH_2)_5NH_2$ **2a**	0.5	**3a**	85
2	$^{i}PrNH_2$ **2b**	4	**3b**	80
3	 **2c**	2.5	**3c**	81
4	 **2d**	3	**3d**	quant
5	 **2e**	3	**3e**	quant
6	 **2f**	5	**3f**	96

[a] Conditions: 20 equiv amine **3**; 6.7 mol% $Pd(OAc)_2$; 19.4 mol% *rac*-BINAP; 23 equiv NaO^tBu; 4.5 mol% 18-crown-6; THF; 68 °C. [b] Structures of amino-porphyins **3b**-**3f** are shown in Figure 1. [c] Isolated yields.

Table 3. Reactions of *meso*-brominated porphyrins with benzamide **4a**[a]



Entry	Porphyrin (metal)	Base	Solvent	Time (h)	Product	Yield (%)[b]
1	**1** (Ni)	NaO^{t}Bu (12 equiv.)	THF	3	Complex mixture[c]	
2	**1** (Ni)	Cs_2CO_3 (12 equiv.)	THF	24	**5a**	98
3	**1** (Ni)	Cs_2CO_3 (2.4 equiv.)	Dioxane	5	**5a**	Quant
4	**6** (Zn)	Cs_2CO_3 (12 equiv.)	THF	24	**10**	32[d]
5	**7** (H_2)	Cs_2CO_3 (12 equiv.)	THF	24	Complex mixture[e]	

[a] 10 equiv. **4a** was used in entries 1, 2, 4 and 5; 2 equiv. **4a** was used in entry 3.

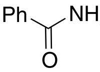
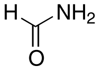
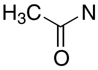
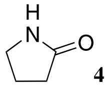
[b] Isolated yields.

[c] 4.5 mol% of 18-crown-6 was added.

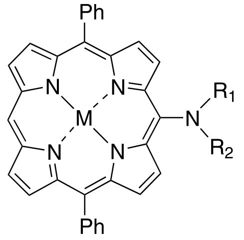
[d] Recovery of **6**: 77%.

[e] Recovery of **7**: 50%.

Table 4. Palladium-catalyzed amidation of *meso*-bromo-substituted Ni(II) porphyrin **1** with amides **4**[a]

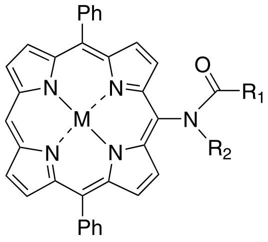
entry	amide	time (h)	product[b]	yield(%)[c]
1	 **4a**	5	**5a**	quant
3	 **4b**	2	**5b**	85
4	 **4c**	1	**5c**	83
7	 **4d**	5	**5d**	80

[a] Conditions: 2 equiv amide **4**; 6.7 mol% $Pd(OAc)_2$; 19.4 mol% *rac*-BINAP; 2.4 equiv Cs_2CO_3; dioxane; 100 °C. [b] Structures of amidoporphyrins **5b**-**5d** are given in Figure 2. [c] Isolated yields.



3b: M = Ni, R_1 = H, R_2 = ^{i}Pr
3c: M = Ni, R_1, R_2 = $-CH_2(CH_2)_2CH_2-$
3d: M = Ni, R_1 = H, R_2 =2-MePh
3e: M = Ni, R_1 = Me, R_2 = Ph
3f: M = Ni, R_1 = H, R_2 =3-NH_2Ph
12: M = H_2, R_1, R_2 = $-CH_2(CH_2)_2CH_2-$

Figure 1. Structures of *meso*-amino substituted porphyrins.



5b: M = Ni, R_1 = H, R_2 = H
5c: M = Ni, R_1 = Me, R_2 = H
5d: M = Ni, R_1, R_2 = $-CH_2CH_2CH_2-$
13: M = H_2, R_1, R_2 = $-CH_2CH_2CH_2-$

Figure 2. Structures of *meso*-amido substituted porphyrins.

tion to give free base porphyrins, **9** and **3**, in quantitative yields, respectively (Figs. 1 and 2).

In summary, we have developed a convenient and a highly reactive set of palladium catalyst systems for the introduction of amino and amido nitrogen onto the *meso*-carbon of porphyrins.[11] Efficiency of the reaction is notably influenced by the central metal ions of the substrate porphyrins, and Ni(II) was the most effective central metal ion among those examined. The method can be applied to a broad spectrum of amines and amides to provide *meso*-amino and *meso*-amido substituted porphyrins in good yields. Further studies of this and related functionalization reactions of the porphyrin core are in progress.

Acknowledgements

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5. Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432–4438.
6. Part of this work was presented at the 28th Symposium on Progress in Organic Reactions and Syntheses, Tama, Tokyo, Japan, November, 2002.
7. Zhang et al. made no comment on the amidation of porphyrins, see Ref. 5.
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12. General procedure for the preparation of *meso*-amino substituted Ni(II) porphyrins **3**: Ni(II) porphyrin **1** (40 mg, 0.067 mmol), NaO^{t}Bu (150 mg, 1.56 mmol), 18-crown-6 (0.9 mg, 0.003 mmol), $Pd(OAc)_2$ (1 mg, 0.0045 mmol), *rac*-BINAP (8.3 mg, 0.013 mmol) and amine **2** (if solid, 1.34 mmol) were added to a 50 ml Schlenk flask. The flask was then evacuated and backfilled with argon (three cycles). THF (10 ml) and amine **2** (if liquid, 1.34 mmol) were charged with a syringe at room temperature. The reaction mixture was stirred at 68°C for 0.5–8 h, and then allowed to reach room temperature. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (KANTO, Silica Gel 60/spherical) with a mixture of *n*-hexane and toluene as an eluate. All the products gave satisfactory NMR, IR and high-resolution mass spectra. For example, NMR and high-resolution mass spectral data of **3a** are as follows. **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.37 (t, $J=7.0$ Hz, 3H), 1.12–1.18 (m, 4H), 1.25–1.35 (m, 2H), 1.65 (q, $J=7.5$ Hz, 2H), 3.85 (t, $J=7.2$ Hz, 2H), 5.37 (s, 2H), 7.54–7.59 (m, 6H), 7.83–7.87 (m, 4H), 8.40 (d, $J=4.8$ Hz, 2H), 8.47 (d, $J=4.8$ Hz, 2H), 8.65 (d, $J=4.8$ Hz, 2H), 8.91 (d, $J=4.8$ Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.5, 26.60, 31.4, 31.5, 53.8, 100.5, 118.3, 125.9, 126.9, 127.5, 129.5, 131.1, 132.0, 133.0, 133.4, 135.3, 140.7, 140.8, 140.9, 144.6; HRMS-EI ([M$^+$]) calcd for $C_{38}H_{33}N_5Ni$ 617.2089, found: 617.2088.
13. The amidation reactions were carried out with Ni(II) porphyrin **1** (40 mg, 0.067 mmol), Cs_2CO_3 (52 mg, 0.16 mmol), $Pd(OAc)_2$ (1 mg, 0.045 mmol), *rac*-BINAP (8.3 mg, 0.013 mmol), amide (0.134 mmol) and dioxane (10 ml) at 100°C for 1–9 h. The procedure was essentially similar to that of the amination reaction, see Ref. 12. All

the products were characterized on the basis of NMR, IR and high-resolution mass spectrometry. For example, NMR and high-resolution mass spectra data of **5a** are as follows. **5a**: ^{1}H NMR (400 MHz, THF-d_8) δ 7.65–7.71 (m, 9H), 8.01–8.03 (m, 4H), 8.43–8.44 (m, 2H), 8.74 (d, $J=4.6$ Hz, 2H), 8.77 (d, $J=5.0$ Hz, 2H), 9.03 (d, $J=4.6$ Hz, 2H), 9.36 (d, $J=5.0$ Hz, 2H), 9.73 (s, 1H), 11.34 (s, 1H); ^{13}C NMR (100.4 MHz, THF-d_8) δ 96.1, 105.0, 108.7, 111.4, 114.1, 118.4, 126.6, 127.5, 127.9, 128.3, 129.3, 131.3, 131.8, 131.9, 132.0, 133.6, 135.3, 141.0, 142.8, 142.9; HRMS-EI ([M$^+$]) calcd for $C_{39}H_{25}N_5NiO$ 637.1413, found: 637.1414.

14. The demetalation reactions of Ni(II) porphyrins (30 mg) were performed with H_2SO_4 (2 ml) at room temperature according to the literature procedure: Paolesse, R.; Jaquinod, L.; Sala, F. D.; Nurco, D. J.; Prodi, L.; Montalti, M.; Natale, C. D.; D'Amico, A.; Carlo, A. D.; Lugli, P.; Smith, K. M. *J. Am. Chem. Soc.* **2000**, *122*, 11295–11302. All the products gave satisfactory NMR, IR and high-resolution mass spectra. For example, ^{1}H NMR data of **12** and **13** are as follows. **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ −2.17 (s, 2H), 2.43–2.48 (m, 4H), 4.42 (t, $J=6.5$ Hz, 4H), 7.66–7.69 (m, 6H), 8.10–8.13 (m, 4H), 8.63 (d, $J=4.6$ Hz, 2H), 8.75 (d, $J=4.6$ Hz, 2H), 9.03 (d, $J=4.6$ Hz, 2H), 9.24 (d, $J=4.6$ Hz, 2H), 9.74 (s, 1H). **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ −3.08 (s, 2H), 2.72–2.82 (m, 2H), 3.20 (t, $J=8.0$ Hz, 2H), 4.69 (t, $J=7.0$ Hz, 2H), 7.70–7.73 (m, 6H), 8.12–8.18 (m, 4H), 8.91 (d, $J=4.8$ Hz, 2H), 8.92 (d, $J=4.6$ Hz, 2H), 9.12 (d, $J=4.8$ Hz, 2H), 9.25 (d, $J=4.6$ Hz, 2H), 10.16 (s, 1H).