ORGANIC LETTERS

2004
Vol. 6, No. 11
1837−1840

General Synthesis of *meso*-Amidoporphyrins via Palladium-Catalyzed Amidation

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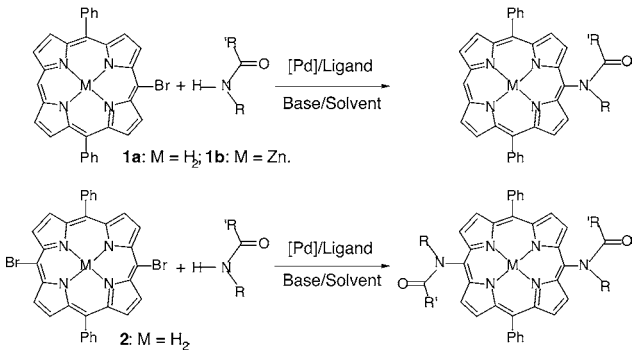
Received March 25, 2004

ABSTRACT



A series of *meso*-amidoporphyrins were facilely synthesized by direct reactions of *meso*-brominated porphyrins with amides via palladium-catalyzed amidation reaction. Using a combination of palladium precursor $Pd(OAc)_2$ or $Pd_2(dba)_3$ and phosphine ligand Xantphos, both 5-bromo-10,20-diphenylporphyrin and 5,15-dibromo-10,20-diphenylporphyrin, as well as their zinc complexes, can be effectively coupled with a wide variety of amides to give the corresponding mono- and bis-substituted *meso*-amidoporphyrins in high yields under mild conditions.

Porphyrins are a class of chemically and biologically important compounds that have found a broad spectrum of applications in different fields such as catalysis, medicine, and materials.[1] The strong dependence of the physical, chemical, and biological properties of porphyrins on their peripheral substituents has prompted great efforts in the synthesis of new porphyrins with different electronic, steric, and conformational enviroments.[1] The standard synthesis of porphyrins involves multiple condensations of pyrroles or dipyrromethanes with aldehydes under acidic conditions, followed by oxidation of resulting porphyrinogen intermediates.[2] Significant improvements of the synthesis have been achieved by Lindsey and co-workers with the introduction of new reaction conditions.[3] Recently, new synthetic methods based on the applications of metal-mediated carbon−carbon bond formation reactions such as Suzuki and Stille couplings to preformed halogenated porphyrins have received increasing attention.[4,5] This post-derivatization strategy allows efficient preparation of a large number of derivatives from a single halogenated porphyrin precursor.

In contrast with numerous applications of carbon−carbon couplings,[4,5] metal-catalyzed carbon−heteroatom bond formation reactions[6] have not been applied to the synthesis of heteroatom-functionalized porphyrins except for recent reports from us[7] and others.[8,9] By applying palladium-catalyzed amination to *meso*-brominated porphyrin precursors, we have recently developed a general and efficient method for the

(1) *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000−2003; Vols. 1−20.

(2) (a) Smith, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, p 1−43. (b) Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, p 45−118.

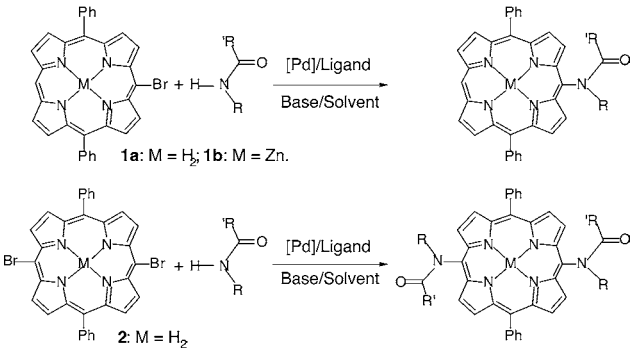
(3) (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969−4970. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827−836.

(4) For a review on this topic, see: Sharman, W. M.; Van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441−453.

10.1021/ol049440b CCC: $27.50
Published on Web 04/28/2004

synthesis of *meso*-arylamino- and -alkylamino-substituted porphyrins from reactions with amines.[7a] Similar methodology can also be effectively applied to brominated diphenylporphyrins and tetraphenylporphyrins, leading to versatile synthesis of porphyrin derivatives bearing multiple arylamino and alkylamino groups.[7b] Very recently, we described a convenient approach for the general synthesis of *meso*-aryloxy- and -alkoxy-substituted porphyrins from reactions with alcohols via palladium-catalyzed etheration.[7c] Expanding the synthetic strategy to palladium-catalyzed amidation,[10] we report herein a general method for the synthesis of *meso*-amidoporphyrins from corresponding bromoporphyrin precursors (Scheme 1). The synthesis can be carried out in high

Scheme 1. Palladium-Catalyzed Amidation Reactions of *meso*-Monobromo- and *meso*-Dibromoporphyrins



yields under mild conditions with a broad variety of amides, forming a series of novel porphyrins with an amido functionality directly attached at the *meso*-position with its nitrogen atom.[11]

The *meso*-brominated porphyrins 5-bromo-10,20-diphenylporphyrin (**1a**), its zinc complex (**1b**), and 5,15-dibromo-10,20-diphenylporphyrin (**2**) (Scheme 1), which were prepared via selective bromination,[5,7] were used as representative halogenated porphyrin precursors for palladium-catalyzed amidation. The reaction of monobromoporphyrin **1a** with benzamide was first evaluated under various conditions (Table 1). Among different ligands (Figure 1) screened in

Table 1. Palladium-Catalyzed Amidation of Bromoporphyrin **1a** with Benzamide under Various Conditons[a]

entry	ligand[b]	base	temp (C)	time (h)	yield (%)[c]
1	A	Cs_2CO_3	100	17	79
2	B	Cs_2CO_3	100	17	65
3	C	Cs_2CO_3	100	22	0
4	D	Cs_2CO_3	100	20	0
5	E	Cs_2CO_3	100	22	0
6	F	Cs_2CO_3	100	22	41
7	G	Cs_2CO_3	100	20	46
8	H	Cs_2CO_3	100	20	0
9	A	K_2CO_3	100	17	58
10	A	K_3PO_4	100	17	86
11	A	NaO*t*-Bu	100	17	65
12	A	NaO*t*-Bu	100	2	83
13[d]	A	NaO*t*-Bu	100	2	92
14[e]	A	Cs_2CO_3	100	17	79
15[f]	A	Cs_2CO_3	100	17	87
16[g]	A	Cs_2CO_3	100	19	88
17[h]	A	Cs_2CO_3	100	12	65
18[i]	A	Cs_2CO_3	100	22	72
19	A	Cs_2CO_3	100	28	72
20	A	Cs_2CO_3	100	8	83
21	A	Cs_2CO_3	80	17	81
22	A	Cs_2CO_3	68	17	88
23	A	Cs_2CO_3	23	19	83

[a] Carried out in THF under N_2 with 1.0 equiv of **1a**, 4.0 equiv of benzamide, 10 mol % $Pd(OAc)_2$, and 20 mol % ligand in the presence of 2.0 equiv of base. Concentration: 0.01 mmol bromoporphyrin/mL solvent. [b] See Figure 1. [c] Isolated yields. [d] 8.0 equiv of benzamide, 20 mol % $Pd(OAc)_2$, and 40 mol % ligand in the presence of 4.0 equiv of base. [e] In toluene. [f] 5 mol % $Pd_2(dba)_3$. [g] 5 mol % $Pd(OAc)_2$ and 10 mol % ligand. [h] 8.0 equiv of benzamide and 4.0 equiv of base. [i] 2.0 equiv of benzamide and 1.5 equiv of base.

combination with $Pd(OAc)_2$, the best result was obtained with Xantphos **A** (Table 1, entry 1).[10c] Although the *N*-heterocyclic carbene ligand **H** and biphenyl-based electron-rich bulky monophosphine ligands **C**, **D**, and **E** gave negative results (Table 1, entries 8 and 3−5), the desired *meso*-amidopor-

(5) For selective examples that applied Suzuki and Stille cross-coupling reactions for porphyrin synthesis, see: (a) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 2513. (b) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983. (c) Hyslop, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12676. (d) Liu, C.-J.; Yu, W.-Y.; Peng, S.-M.; Mak, T. C. W.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1998**, 1805. (e) Shi, X.; Amin, R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1650. (f) Shanmugathasan, S.; Johnson, C. K.; Edwards, C.; Matthews, E. K.; Dolphin, D.; Boyle, R. W. *J. Porphyrins Phthalocyanines* **2000**, *4*, 228. (g) Iovine, P. M.; Kellett, M. A.; Redmore, N. P.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 8717. (h) Deng, Y.; Chang, C. K.; Nocera, D. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1066. (i) Chng, L. L.; Chang, C. J.; Nocera, D. G. *J. Org. Chem.* **2003**, *68*, 4075.

(6) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (e) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (g) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (h) Hartwig, J. F. *Synlett* **1997**, 329.

(7) (a) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432. (b) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 6215. (c) Gao, G. Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261.

(8) Khan, M. M.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615. Note: no yields were reported in this paper.

(9) While this manuscript was being prepared, a paper utilizing a *meso*-brominated Ni(II) porphyrin precursor for the preparation of *meso*-amino- and *meso*-amidoporphyrins was reported: Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* **2003**, *44*, 7353.

(10) For recent examples of palladium-catalyzed amidation, see: (a) Browning, R. G.; Badarinarayana, V.; Mahmud, H.; Lovely, C. J. *Tetrahedron* **2004**, *60*, 359. (b) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207. (c) Yin, J.-J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.

(11) For examples of *meso*-amidoporphyrins, see: (a) Jayaraj, K.; Gold, A.; Ball, L. M.; While, P. S. *Inorg. Chem.* **2000**, *39*, 3652. (b) Johnson, C. K.; Dolphin, D. *Tetrahedron Lett.* **1998**, *39*, 4753. (c) Poignant, G.; Bourseul, A.; Geze, C.; Le Plouzennec, M.; Le Maux, P.; Bondon, A.; Simonneaux, G.; Moinet, C.; Vonarx, V.; Patrice, T. *Tetrahedron Lett.* **1996**, *37*, 7511. (d) Konishi, K.; Mori, Y.; Aida, T.; Inoue, S. *Inorg. Chem.* **1995**, *34*, 1292. (e) Konishi, K.; Miyazaki, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1990**, *112*, 5639. (f) Ichimura, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1444.

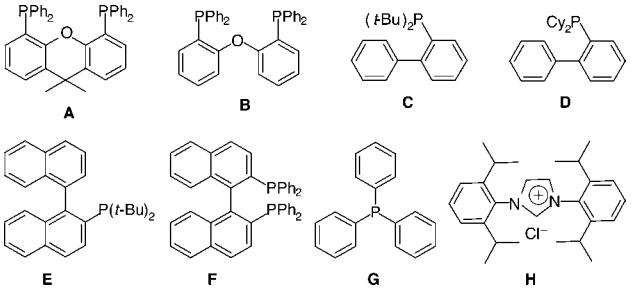


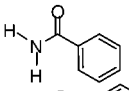
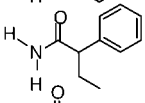
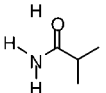
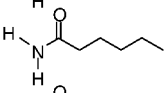
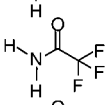
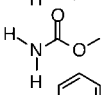
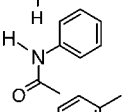
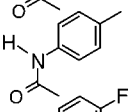
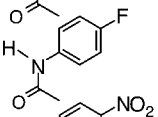
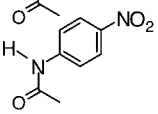
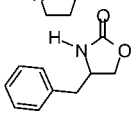
Figure 1. Structures of different supporting ligands.

phyrin was obtained in moderate yields with the use of other phenyl-substituted phosphine ligands such as DPEphos **B**, BINAP **F**, and even triphenylphosphine **G** (Table 1, entries 2, 6, and 7). In addition to Cs_2CO_3, the combination of Xantphos **A** with $Pd(OAc)_2$ could also catalyze the amidation in the presence of other bases. For example, a similar result was achieved with K_3PO_4, though the use of K_2CO_3 resulted in a lower yield (Table 1, entry 9). In the case of the strong base NaO*t*-Bu, reduction of time was needed for high-yielding reactions, as side products were observed after longer time (Table 1, entries 11−13). With Cs_2CO_3 as the base, the Xantphos **A**-based catalytic system could operate effectively for the amidation reaction under varied conditions, including another solvent (Table 1, entry 14), alternative palladium precursor (Table 1, entry 15), lower catalyst loading (Table 1, entry 16), different reaction times (Table 1, entries 19 and 20), and various reaction temperatures (Table 1, entries 21−23), although relatively lower yields were obtained when the amounts of benzamide and the base were altered (Table 1, entries 17 and 18).

Under similar conditions, the palladium-catalyzed amidation supported by Xantphos **A** could be effectively employed for the coupling of monobromoporphyrin **1a** with a wide variety of amides (Table 2). Besides benzamide (Table 2, entry 1), primary amides having various aliphatic chains, benzyl and trifluoromethyl groups could be well coupled (Table 2, entries 2−6). Carbamates such as methyl carbamate were also suitable substrates for the coupling reaction (Table 1, entry 7). Similarly, secondary amides such as acetanilide and its derivatives were successfully reacted with **1a** to afford the desired amidoporphyrins (Table 2, entries 8−11). The amidation system could also be applied to cyclic amides such as pyrrolidinone and oxazolidinone derivatives (Table 2, entries 12 and 13). It should be noted that the products existed as a mixture of two stereoisomers in the cases of primary amides containing aliphatic groups (Table 2, entries 2−5), presumably resulting from the restricted rotation around the amide bonds. No attempts were made to separate them.

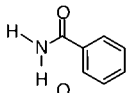
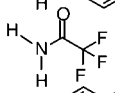
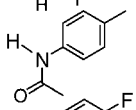
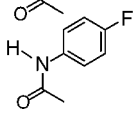
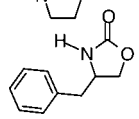
When dibromoporphyrin **2** was used, the Xantphos **A**-based system could catalyze double amidation reactions with different amides to afford the corresponding *meso*-diamidoporphyrins in a one-pot procedure. Representative examples that were examined include primary amides (Table 3, entries 1 and 2), secondary amides (Table 3, entries 3 and 4), and cyclic amides (Table 3, entries 5 and 6). In both cases of the secondary acyclic amides, the product existed as a mixture of two atropisomers (α,α- and α,β-isomers) in near equal amounts that were successfully separated (Table 3, entries 3 and 4), indicating a high rotation barrier around the bond between the porphyrin *meso*-carbon atom and the amide nitrogen atom. Although the same type of atropisomers were also detected in the product from reaction with the substituted oxazolidinone (Table 3, entry 6), only one set of resonances were observed in both ^1H and ^{13}C NMR spectra of products from reactions with the primary amides (Table

Table 2. Palladium-Catalyzed Amidation of Monobromoporphyrin **1a** with Different Amides[a]

entry	amide	temp (°C)	time (h)	yield (%)[b]
1		68	19	88
2[c]		68	21	71[h]
3[d]		100	22	69[i]
4[e]		80	10	70[j]
5		80	18	83[k]
6		80	18	89
7[f]		100	8	65
8		80	17	71
9		100	24	92
10		100	19	83
11[f]		100	23	53
12[c]		68	21	83
13[g]		80	19	60

[a] Carried out in THF under N_2 with 1.0 equiv of **1a**, 4.0 equiv of amide, 10 mol % $Pd(OAc)_2$, and 20 mol % ligand **A** in the presence of 2.0 equiv of Cs_2CO_3. Concentration: 0.01 mmol bromoporphyrin/mL THF. [b] Isolated yields. [c] 2.5 mol % $Pd_2(dba)_3$. [d] 2.0 equiv of amide and 1.5 equiv of base. [e] NaO*t*-Bu. [f] 8.0 equiv of amide. [g] 5 mol % $Pd_2(dba)_3$. [h] Existed as a 35:65 mixture of two stereoisomers. [i] Existed as a 38:62 mixture of two stereoisomers. [j] Existed as a 40:60 mixture of two stereoisomers. [k] Existed as a 50:50 mixture of two stereoisomers.

Table 3. Palladium-Catalyzed Double Amidation of Dibromoporphyrin **2** with Different Amides[a]

entry	amide	temp (°C)	time (h)	yield (%)[b]
1[c]		68	22	60
2[d]		100	2	73
3		80	19	66[f]
4		100	30	57[g]
5[e]		100	30	59
6[c]		68	22	62[h]

[a] Carried out in THF under N_2 with 1.0 equiv of **2**, 8.0 equiv of amide, 10 mol % $Pd(OAc)_2$, and 20 mol % ligand **A** in the presence of 4.0 equiv of Cs_2CO_3. Concentration: 0.01 mmol bromoporphyrin/mL THF. [b] Isolated yields. [c] 5 mol % $Pd_2(dba)_3$ and 20 mol % ligand **A**. [d] 20 mol % $Pd(OAc)_2$ and 40 mol % ligand **A**; NaO*t*-Bu as base. [e] 10 mol % $Pd_2(dba)_3$ and 40 mol % ligand **A**. [f] Existed as a 50:50 mixture of two atropisomers that were separated. [g] Existed as a 46:54 mixture of two atropisomers that were separated. [h] Existed as a 50:50 mixture of two atropisomers that were not separated.

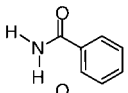
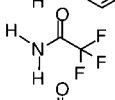
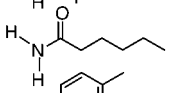
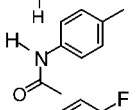
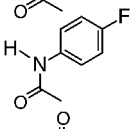
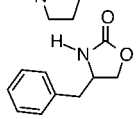
3, entries 1 and 2), as well as the unsubstituted pyrrolidinone (Table 3, entry 5), suggesting that there is a free rotation around the N−C bond at ambient temperature in these *meso*-diamidoporphyrins.

The fact that the free base porphyrins **1a** and **2** can be directly employed for the palladium-catalyzed amidation reactions without the use of a zinc ion or other metal ions as an "inorganic protective group" for the central NH units avoids extra synthetic steps associated with metalation and demetalation.[12,13] However, the zinc complex **1b** could also be coupled with different amides to afford the desired zinc *meso*-amidoporphyrins (Table 4), although the yields were consistently lower than the reactions of the free base **1a** (Table 2).

(12) Most reported examples that applied metal-mediated cross-coupling reactions for porphyrin synthesis employed zinc porphyrins or other metalloporphyrins as the precursors. See refs 4, 5, 8, and 9.

(13) We showed previously that free base porphyrins could also be directly used for palladium-catalyzed amination and etheration reactions. See ref 7.

Table 4. Palladium-Catalyzed Amidation of Zinc Complex of Monobromoporphyrin **1b** with Different Amides[a]

entry	amide	temp (°C)	time (h)	yield (%)[b]
1		80	17	68
2		80	19	75
3		80	16	60[c]
4		80	17	24
5		100	17	21
6		80	17	62
7		80	17	46

[a] Carried out in THF under N_2 with 1.0 equiv of **1b**, 4.0 equiv of amide, 10 mol % $Pd(OAc)_2$ and 20 mol % ligand **A** in the presence of 2.0 equiv of Cs_2CO_3. Concentration: 0.01 mmol bromoporphyrin/mL THF. [b] Isolated yields. [c] Existed as a 47:53 mixture of two stereoisomersq .

In summary, a new methodology has been developed for the synthesis of *meso*-amidoporphyrins from the brominated precursors via palladium-catalyzed amidation. The catalytic system operates efficiently under mild conditions, can be directly applied to free base porphyrins, and is suitable for a variety of amides. Considering the availability of large numbers of various amides, this methodology will allow the synthesis of a family of new porphyrins with *meso*-amido functionalities that could find potential applications.

Acknowledgment. We are grateful for financial support of this work from the UT Department of Chemistry, the UT Center of Excellence for Structural Biology (CESB), and the Hereditary Disease Foundation (HDF). We wish to acknowledge Dr. Al Tuinman for assistance with high-resolution mass spectroscopy and Chemetall Chemical Products, Inc. for providing cesium carbonate.

Supporting Information Available: Analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049440B