JOC Article

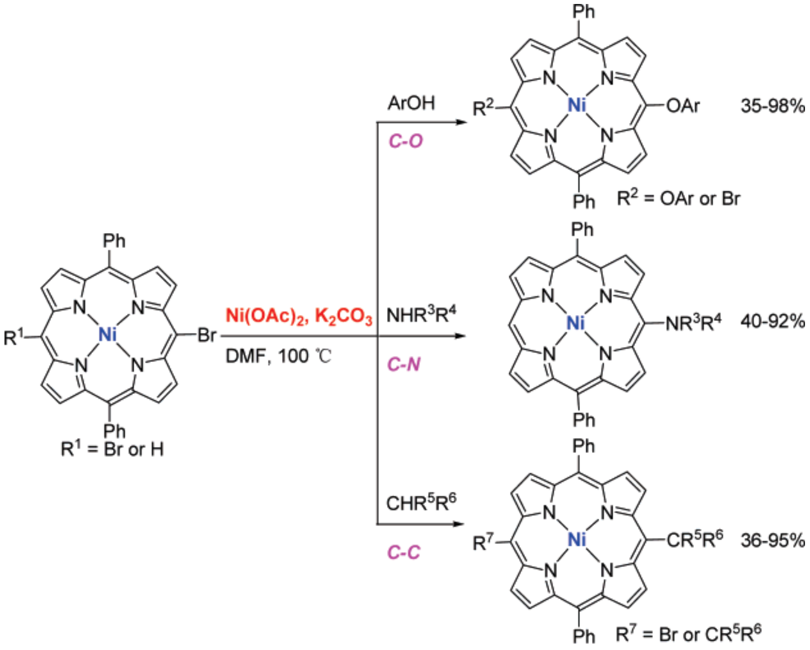
Practical and Efficient Synthesis of Various *meso*-Functionalized Porphyrins via Simple Ligand-Free Nickel-Catalyzed C−O, C−N, and C−C Cross-Coupling Reactions

Chao Liu, Dong-Mei Shen, and Qing-Yun Chen*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

chenqy@mail.sioc.ac.cn

Received September 11, 2006



Various *meso*-functionalized porphyrins were conveniently synthesized by direct reactions of *meso*-bromoporphyrins with oxygen-, nitrogen-, and carbon-based nucleophiles in moderate to high yields via practical, efficient, and ligand-free nickel-catalyzed C−O, C−N, and C−C bond-forming reactions. The central metal ions of the substrate porphyrin have much effect on the reactions. Introduction of Ni(II) as a central metal ion into the substrate porphyrin markedly accelerated the cross-coupling.

Introduction

Functionalization of the porphyrin macrocycle has always received much attention, and considerable progress has been made over the past decades.[1] The introduction of different functionality into the porphyrin periphery can offer the means by which properties of the porphyrin macrocycle can be modulated and also provide access to various new potentially useful porphyrins by affording a reaction site for further transformations. With the development of transition-metal-catalyzed cross-coupling reactions,[2] a large amount of novel porphyrins have been constructed by applying these cross-coupling reactions to performed halogenated porphyrin precursors.[3] For example, Zhang and co-workers[3e−i] have recently

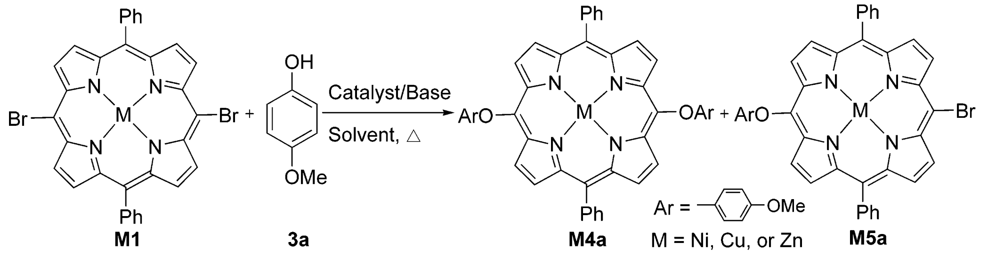
---

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

[2] For selective and recent reviews on transition-metal-catalyzed cross-coupling reactions, see: (a) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley: Weinheim, 2004. (b) Montgomery, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908. (c) Li, Z.; Fu, Y.; Liu, L.; Guo, Q.-X. *Chin. J. Org. Chem.* **2005**, *25*, 1508−1529. (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041−2075.

10.1021/jo0618728 CCC: $37.00

TABLE 1. Nickel-Catalyzed C−O Cross-Coupling of *meso*-Dibromoporphyrin M1 (M = Ni, Cu, Zn, or 2H) with 4-Methoxylphenol (3a) under Various Conditions[a]



entry	BrPor	catalyst	base	solvent	T (°C)	t (h)	yield[c] (%) Ni4a	yield[c] (%) Ni5a
1	**Ni1**	NiCl$_2$(PPh$_3$)$_2$[b]	NaO^{t}Bu	PhMe	100	12	*d*	*d*
2	**Ni1**	NiCl$_2$(PPh$_3$)$_2$[b]	Cs$_2$CO$_3$	THF	80	12	*d*	*d*
3	**Ni1**	NiCl$_2$(PPh$_3$)$_2$[b]	NaO^{t}Bu	PhMe	100	12	*d*	*d*
4	**Ni1**	NiCl$_2$(PPh$_3$)$_2$[b]	Cs$_2$CO$_3$	THF	80	12	*d*	*d*
5	**Ni1**	NiCl$_2$(PPh$_3$)$_2$[b]	K$_2$CO$_3$	DMF	100	1	98	0
6	**Ni1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	100	1	98	0
7	**Ni1**	Ni(acac)$_2$	K$_2$CO$_3$	DMF	100	1	25	65
8[e]	**Ni1**	NiCl$_2$	K$_2$CO$_3$	DMF	100	1	<5	15
9	**Ni1**	*f*	K$_2$CO$_3$	DMF	100	1	*d*	*d*
10	**Ni1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	60	1	<5	85
11[g]	**Cu1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	100	1	70	25
12[h]	**Zn1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	100	1	0	15
13	**H$_2$1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	100	1	*i*	*i*
14[j]	**Ni1**	Ni(OAc)$_2$	K$_2$CO$_3$	DMF	100	1	<5	85

[a] Reactions were carried out in solvent (6 mL) under N$_2$ with **M1** (30 mg, 1.0 equiv, M = Ni, Cu, Zn, or 2H), **3a** (4.0 equiv), and base (4.0 equiv) in the presence of catalyst (10 mol %). [b] Zn and PPh$_3$ were used as cocatalysts. NiCl$_2$(PPh$_3$)$_2$/Zn/PPh$_3$ = 0.1:2.0:0.2. [c] Isolated yields. [d] Complete recovery of **Ni1**. [e] Recovery of **Ni1**: 75%. [f] No catalyst was used. [g] The products are **Cu4a** and **Cu5a**. [h] Recovery of **Zn1**: 80% and the products are **Zn4a** and **Zn5a**. [i] Only formation of a small amount of **Ni1** was observed and no desired coupling products was obtained. [j] **3a** (1.1 equiv) was used.

developed several general and efficient methods for the synthesis of a variety of heteroatom-substituted porphyrins including amino, amido, sulfo, and oxo by palladium-catalyzed cross-coupling reactions. However, these methods generally use relatively expensive palladium and special ligands, limiting their application at least in large-scale preparation. On the other hand, compared with the well-established palladium catalysts in synthesis of various porphyrins,[3] the inexpensive and practical nickel-based catalysts have never been utilized in similar syntheses thus far. Our aim at pursuing an inexpensive and mild procedure for the convenient synthesis of various functionalized porphyrins prompts us to explore the feasibility of employing nickel-based catalysts. Herein, we describe our results on the practical and efficient synthesis of various *meso*-functionalized porphyrins from the corresponding readily available bromoporphyrin precursors via simple ligand-free nickel-catalyzed C−O, C−N, and C−C bond-forming reactions.

Results and Discussion

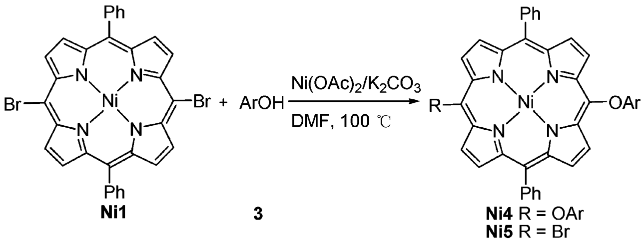
5,15-Dibromo-10,20-diphenylporphyrins **M1 (**M = 2H, Ni, Cu, Zn) and [5-bromo-10, 20-diphenylporphyrinato]nickel(II)-(**Ni2**) were used as ideal building blocks in this work because of their ease of preparation.[4] Our initial attempts were conducted with the reaction of *meso*-dibromoporphyrin **Ni1** with 4-methoxylphenol (**3a**) under a variety of different catalytic conditions. The results are listed in Table 1. A combination of NiCl$_2$(PPh$_3$)$_2$/Zn/PPh$_3$ as catalyst, NaO^{t}Bu or Cs$_2$CO$_3$ as base, and THF or PhMe as solvent proved invalid for the reaction, resulting in the complete recovery of the starting bromoporphyrin (Table 1, entries 1−4). However, we were delighted to find that an excellent yield of the desired dietheration product **Ni4a** was obtained when the polar solvent DMF and common weaker base K$_2$CO$_3$ were utilized under similar conditions (Table 1, entry 5). Further investigation on the catalyst revealed that Ni(OAc)$_2$ was the most suitable one, although the reaction proceeded smoothly using other nickel-based catalysts (Table 1, entries 5−8). It is worth noting that no expensive and special ligand was required for the reaction. In contrast, no reaction occurred when no catalyst was used for the reaction under similar conditions (Table 1, entry 9). Elevated reaction temperatures facilitated the formation of the dietheration product because the reaction mainly afforded monoetheration

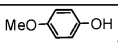
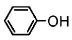
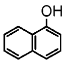
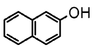
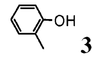
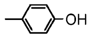
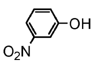
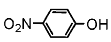
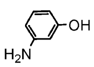
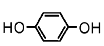
---

(3) For recent and selective reports on porphyrin functionalization by transition-metal-catalyzed cross-coupling reactions of bromoporphyrins, see: (a) Shen, D. M.; Liu, C.; Chen, Q. Y. *J. Org. Chem.* **2006**, *71*, 6508. (b) Liu, C.; Shen, D. M.; Chen, Q. Y. *Eur. J. Org. Chem.* **2006**, 2703. (c) Liu, C.; Chen, Q. Y. *Synlett* **2005**, *8*, 1306. (d) Liu, C.; Chen, Q. Y. *Eur. J. Org. Chem.* **2005**, 3680. (e) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 8886. (f) Gao, G. Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2004**, *6*, 1837. (g) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261. (h) Gao, G. Y.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 6215. (i) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432. (j) Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* **2003**, *44*, 7353. (k) Khan, M. M.; Ali, H.; Van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615. (l) Cheng, L. L.; Chang, C. J.; Nocera, D. G. *J. Org. Chem.* **2003**, *68*, 4075. (m) Vas, B.; Alvarez, R.; Nieto, M.; Paniello, A. I.; de Lera, A. R. *Tetrahedron Lett.* **2001**, *42*, 7409. (n) Deng, Y.; Chang, C. K.; Nocera, D. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1066. (o) Iovine, P. M.; Kellett, M. A.; Redmore, N. P.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 8717. (p) Shanmugathasan, S.; Johnson, C. K.; Edwards, C.; Matthews, E. K.; Dolphin, D.; Boyle, R. W. *J. Porphyrins Phthalocyanines* **2000**, *4*, 228. (q) Shi, X.; Amin, R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1650. (r) Sharman, W. M.; Van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441 and references cited therein.

(4) (a) Liu, C.; Shen, D. M.; Chen, Q. Y. *Chem. Commun.* **2006**, 770. (b) Shen, D. M.; Liu, C.; Chen, Q. Y. *Chem. Commun.* **2005**, 4982.

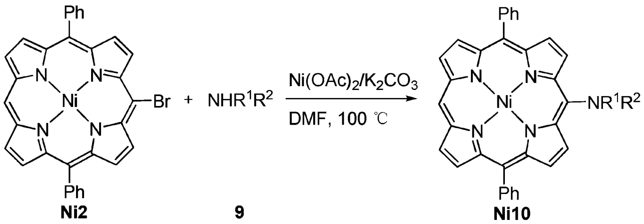
TABLE 2. Nickel-Catalyzed Dietheration Reaction of *meso*-Dibromoporphyrin Ni1 with Various Phenol Derivatives[a]

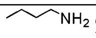
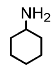
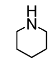
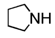
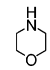


entry[b]	ArOH	t (min)	product	yield (%)[c]
1	 **3a**	60	**Ni4a**	98
1’		20	**Ni5a**	90
2	 **3b**	60	**Ni4b**	98
2’		20	**Ni5b**	91
3	 **3c**	60	**Ni4c**	95
3’		20	**Ni5c**	80
4	 **3d**	60	**Ni4d**	90
4’		20	**Ni5d**	85
5	 **3e**	60	**Ni4e**	98
5’		20	**Ni5e**	85
6	 **3f**	60	**Ni4f**	95
6’		20	**Ni5f**	92
7	 **3g**	120	**Ni4g**	80
7’		20	**Ni5g**	70
8	 **3h**	1200	**Ni4h**	60[d]
8’		120	**Ni5h**	65[d]
9	 **3i**	150	**Ni4i**	48[e]
9’		20	**Ni5i**	60[e]
10	 **3j**	120	**Ni4j**	35[e]
10’		40	**Ni5j**	50[e]

[a] Reactions were carried out in DMF (10 mL) under N_2 at 100 °C with **Ni1** (50 mg, 1.0 equiv), **3** (1.1 or 4.0 equiv), and K_2CO_3 (1.1 or 4.0 equiv) in the presence of $Ni(OAc)_2$ (10 mol %). [b] Entries 1−10: dietheration reactions, **3** (4.0 equiv), and K_2CO_3 (4.0 equiv) were used. Entries 1′−10′: monoetheration reactions, **3** (1.1 equiv), and K_2CO_3 (1.1 equiv) were used. [c] Isolated yields. [d] Serious degradation of porphyrin was observed. [e] Lower yield might be due to side reactions arising from the existence of active functional groups in **3**.

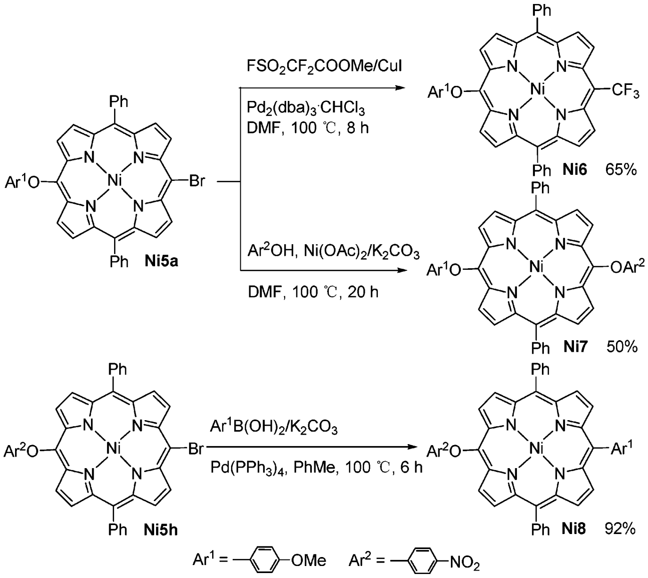
TABLE 3. Nickel-Catalyzed C−N Cross-Coupling of *meso*-Monobromoporphyrin Ni2 with Various Aliphatic Amines[a]



entry	amine	product	t (h)	yield (%)[b]
1	 **9a**	**Ni10a**	6	56[c]
2	 **9b**	**Ni 10b**	12	45[c]
3	 **9c**	**Ni 10c**	1	92
4	 **9d**	**Ni 10d**	1	75
5	 **9e**	**Ni 10e**	12	40[c]

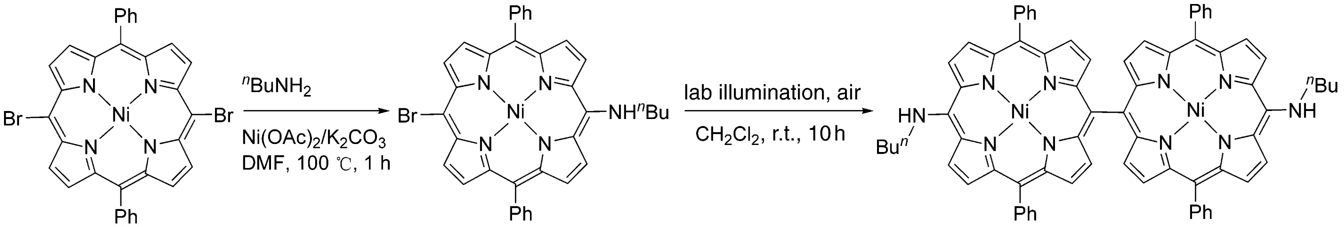
[a] Reactions were carried out in DMF (10 mL) under N_2 at 100 °C with **Ni2** (50 mg, 1.0 equiv), **9** (4.0 equiv), and K_2CO_3 (4.0 equiv) in the presence of $Ni(OAc)_2$ (10 mol %). [b] Isolated yields. [c] Serious degradation of porphyrins was observed.

SCHEME 1. Transformations of the Monoetheration Porphyrins



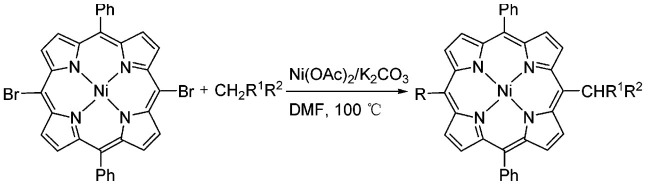
product in addition to a small amount of dietheration product when the reaction temperature was decreased to 60 °C (Table 1, entry 10). These systematic variations of the nickel catalysts, bases, solvents, and reaction temperatures revealed that a combination of $Ni(OAc)_2$, K_2CO_3, DMF, and 100 °C was the most efficient catalyst system among the reaction conditions examined. The selection of central metal ions of the starting bromoporphyrins was particularly important in the reaction.[3c,j] The Ni(II) porphyrin **Ni1** was consumed efficiently within 1 h under the optimal conditions, providing the dietheration product

SCHEME 2. Nickel-Catalyzed Monoamination Reaction of *meso*-Dibromoporphyrin Ni1 with *n*-Butylamine and Dimerization Reaction of the Monoamination Product

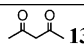
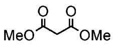
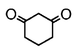
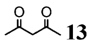
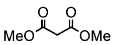


Ni1 **Ni11** 91% **Ni12** 95%

TABLE 4. Nickel-Catalyzed C−C Cross-Coupling of *meso*-Dibromoporphyrin Ni1 with Various Carbon-Based Nucleophiles[a]

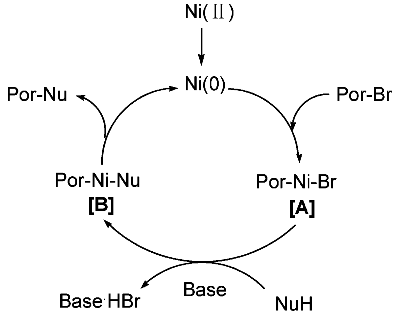


Ni1 **13** **Ni14** R = Br **Ni15** R = CHR^1R^2

entry	$CH_2R^1R^2$	product	*t* (h)	yield (%)[b]
1	 **13a**	**Ni14a**	1	85
2	 **13b**	**Ni14b**	2	75
3	 **13c**	**Ni14c**	3	76
4	$NCCH_2COOEt$ **13d**	**Ni14d**	3	48[c]
5[d]	 **13a**	**Ni15a**	4	95
6[d]	 **13b**	**Ni15b**	20	36[c]

[a] Unless otherwise noted, reactions were carried out in DMF (10 mL) under N_2 at 100 °C with **Ni1** (50 mg, 1.0 equiv), **13** (2.0 equiv), and K_2CO_3 (2.0 equiv) in the presence of $Ni(OAc)_2$ (10 mol %). [b] Isolated yields. [c] Serious degradation of porphyrins was observed. [d] **13** (4.0 equiv) and K_2CO_3 (4.0 equiv) were used, and dicoupled product was obtained.

SCHEME 3. Possible Mechanism for the Nickel-Catalyzed C−O, C−N, and C−C Cross-Coupling of *meso*-Bromoporphyrins with Various Nucleophiles



Por = *meso*-bromoporphyrin macrocycle
NuH = nucleophile reagent

as the sole product in excellent yield (Table 1, entry 6), whereas the reaction utilizing Cu(II) porphyrin **Cu1** as a substrate gave a 70% yield of dietheration product and 25% yield of the monoetheration product (Table 1, entry 11). Zn(II) porphyrin **Zn1** was incompletely consumed, furnishing only 15% yield of monoetheration product in addition to 80% recovery of the starting porphyrin (Table 1, entry 12). It should be pointed out that no transmetallated products were observed in the reactions, which was in contrast with the previous report.[3c,d] The reaction of free base porphyrin **H$_2$1** under similar conditions resulted in no formation of desired coupling products but a small amount of **Ni1** and recovery of the starting free base porphyrin **H$_2$1** (Table 1, entry 13). In addition, the monoetheration product could be selectively obtained in good yields by controlling the amount of phenol derivatives **3** used, indicating the diversity and efficiency of the reaction (Table 1, entry 14).

With the optimal conditions, a variety of representative phenol derivatives were examined in this reaction (Table 2). In most cases, the cross-coupling reactions proceeded smoothly, providing good yields of dietheration or monoetheration product by controlling the amount of phenol derivatives used. For electron-rich or neutral phenol derivatives such as 4-methylphenol, phenol, 1-naphthol, 2-naphthol, as well as two cresol isomers, the reactions successfully afforded the desired dietheration products in excellent yields (Table 2, entries 1−6). By contrast, electron-poor phenol derivatives such as 3-nitro- and 4-nitophenol could also be smoothly subjected to the reaction, leading to relatively lower yields of the desired dietheration products (Table 2, entries 7 and 8). In the case of hydroquinone and 3-aminophenol, lower yields of the dietheration products were obtained (Table 2, entries 9 and 10). Unexpectedly, no reaction occurred with the use of alcohols such as butanol, benzyl alcohol, or 2,2,2-trifluoroethanol as substrates under similar conditions. The use of stronger base such as NaO^{t}Bu or NaH instead of K_2CO_3 resulted in an inseparable complex mixture. On the other hand, various monoetheration products were obtained in good yields in addition to a trace of dietheration products by controlling the amount of phenol derivatives used under similar conditions (Table 2, entries 1′−10′). Bromine atoms remaining in monoetheration products made them very useful precursors for synthesizing various regional-functional-porphyrin derivatives and new kinds of push−pull chromophores. For example, as outlined in Scheme 1, making use of the improved trifluoromethylation reaction conditions,[3d] treatment of **Ni5a** with FSO_2CF_2COOMe/CuI (10:5 equiv) in DMF at 100 °C in the presence of $Pd_2(dba)_3$·$CHCl_3$ (10 mol %) for 8 h smoothly produced the corresponding trifluoromethylation product **Ni6** in 65% yield. Meanwhile, **Ni5a** could be further subjected to the ligand-free nickel-catalyzed etheration reaction with 4-nitrophenol (**3h**) to finish new asymmetrical cross-coupling push−pull chromophore **Ni7** in 50% yield.

Following standard Suzuki reaction conditions,[5] treating **Ni5a** with 4-methoxylbenzylboronic acid ($(p\text{-MeO})PhB(OH)_2$) (2.0 equiv) in the presence of $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (4.0 equiv) in toluene at 100 °C for 6 h effectively afforded **Ni8** in 92% yield.

Under similar conditions, the ligand-free nickel-catalyzed system could be successfully extended to amination of *meso*-monobromoporphyrin **Ni2** with various aliphatic amines. As summarized in Table 3, primary amines such as *n*-butylamine and cyclic hexylamine were efficiently coupled with **Ni2** to yield the *meso*-amination porphyrins in acceptable yields (Table 3, entries 1 and 2). Cyclic secondary amines such as piperidine and pyrrolidine were also suitable partners with **Ni2** to give good yields of the desired *meso*-amination porphyrins (Table 3, entries 3 and 4), though morpholine gave a relatively lower yield of the product (Table 3, entry 5). However, the use of aromatic amines such as aniline resulted in complete recovery of the starting porphyrin under similar conditions. To our surprise, the reaction of *n*-butylamine with *meso*-dibromoporphyrin **Ni1** for 1 h led to a high yield of monoamination porphyrin **Ni11**, which was unstable in CH_2Cl_2 under laboratory illumination and air at room temperature and coupled each other to provide dimeric product **Ni12** in 95% yield (Scheme 2). Extended reaction times resulted in serious degradation of porphyrins and no formation of *meso*-diamination porphyrin. Involvement of radical species in the dimerization reaction was proposed because addition of electron-transfer scavenger, i.e., *p*-dinitrobenzene (*p*-DNB) (20 mol %), or free-radical inhibitor, i.e., hydroquinone (HQ) (20 mol %), to CH_2Cl_2 solution of **Ni11** completely suppressed the reaction under similar conditions.

We further expanded the scope of this method by subjecting a variety of carbon-based nucleophiles to the reaction. As seen in Table 4, ketones and malonate-type nucleophiles could be coupled with **Ni1** to produce *meso*-monocoupled porphyrin in acceptable yields. Although **13a** and **13b** could be successfully reacted with **Ni1** to furnish *meso*-dicoupled porphyrins when the amounts of nucleophiles were increased to 4.0 equiv, **13c** and **13d** resulted in serious degradation of the porphyrins and no formation of *meso*-dicoupled porphyrin was observed under similar conditions.

Based on known organometallic chemistry, we speculate that the plausible mechanism of this reaction should follow the catalytic cycle in the nickel-catalyzed cross-coupling of simple aromatic halides.[2] As shown in Scheme 3, oxidative addition of Ni(0) active species generated under reaction conditions to a C−Br bond of the *meso*-bromoporphyrin provides the Ni(II) complex **A**. The resulting organometallic species **A** undergoes a transmetalation with a nucleophile to afford the key Ni(II) intermediate **B**, which after reductive elimination produces the desired *meso*-functionalized porphyrin and Ni(0) active species for continuing the catalytic cycle. However, it is puzzling that alcohols and aromatic amines are not suitable substrates for the reaction. We sugguest that the difficulty might lie in the transmetalation/reductive elimination steps. Detailed mechanistic explanations call for further investigations.

Conclusions

In summary, we have developed a practical, efficient, and ligand-free nickel-catalyzed method for facile synthesis of a variety of *meso*-functionalized porphyrins via C−O, C−N, and C−C bond-forming reactions of readily available *meso*-bromoporphyrins. Because the catalytic system operates simply and effectively under mild conditions, it may allow convenient preparation of various potentially useful *meso*-functionalized porphyrins on a large scale. Further studies on application of the catalytic system and *meso*-functionalized porphyrins are now in progress.

Experimental Section

General Procedure for the Nickel-Catalyzed Etheration Reaction of *meso*-Dibromoporphyrin Ni1 with Various Phenol Derivatives. *meso*-Dibromoporphyrin **Ni1** (50 mg, 1.0 equiv), $Ni(OAc)_2$ (10 mol %), phenol derivative **3** (1.1 or 4.0 equiv), and K_2CO_3 (1.1 or 4.0 equiv) were added to a Schlenk flask. The flask was then evacuated and backfilled with N_2 (three cycles). DMF (10 mL) was charged with a syringe at room temperature. The reaction mixture was stirred at 100 °C. After completion of the reaction, the mixture was allowed to reach room temperature, diluted with CH_2Cl_2, and filtered through Celite. The resulting solvent was washed three times with water. The organic layer was passed through dry silica gel and evaporated to dryness. The resulting solid was purified by flash chromatography (CH_2Cl_2/PE as eluent) to provide the desired monoetheration or dietheration products in good yields.

Acknowledgment. We thank the Natural Science Foundation of China (Nos. 20272026, D20032010, and 20532040) for supporting this work.

Note Added after Publication. There was an error in the experimental data for compound **Ni10c** in the Supporting Information published ASAP March 10, 2007; the revised version was published ASAP March 30, 2007.

Supporting Information Available: Experimental details, characterization data, and copies of ^1H and ^{19}F NMR spectra of all new porphyrins. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0618728

---

[5] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, p 11. (d) Kotha, S.; Lahiri, K. Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (e) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (f) Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679.