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Facile and Efficient Hypervalent Iodine(III)-Mediated *meso*-Functionalization of Porphyrins

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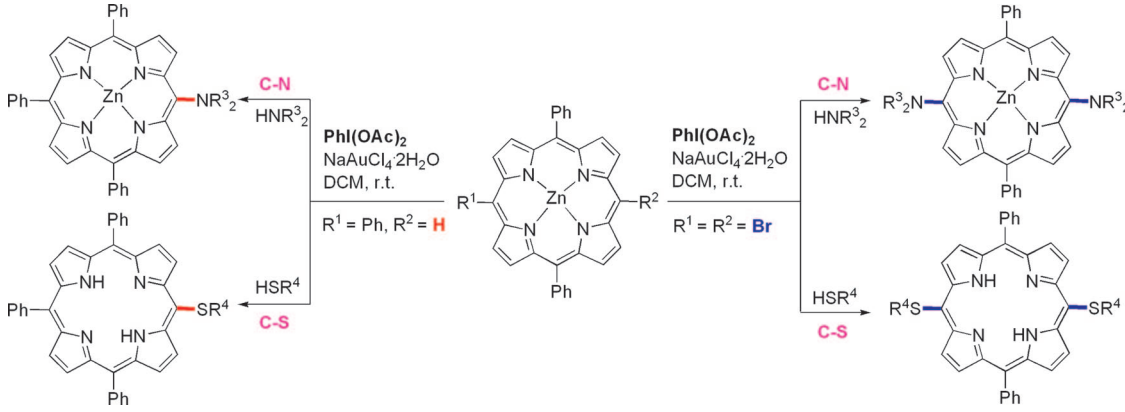

Highly facile and efficient synthesis of a variety of *meso*-functionalized porphyrins was accomplished by $PhI(OAc)_2$-$NaAuCl_4$ mediated direct nucleophilic substitution reactions of [5,10,15-triphenylporphyrinato]zinc(II) (**Zn1**) with different amines and thiophenols. When [5,15-dibromo-10,20-diphenylporphyrinato]zinc(II) (**Zn12**) was used as the starting porphyrin under similar conditions, the double nucleophilic substitution products were obtained in good yields.

Introduction

Functionalization of porphyrins has always attracted much interest because it is the main foundation of modulating various properties of the porphyrin macrocycle and further constructing new and valuable porphyrins. To address this issue, a large number of methods have been developed.[1] Among them, transition metal-catalyzed reactions of halogenated porphyrins represent recent considerable progress and enable convenient and quick installation of a variety of potentially useful porphyrins, despite the need for prefunctionalization of the porphyrin macrocycle.[2−4] To the best of our knowledge, no reports on direct synthesis of the above porphyrins have appeared so far.

π-Radical cations of metalloporphyrins are readily generated by their reactions with various oxidants. They are relatively stable due to the delocalization of the unpaired electron over the π-electron system of the macrocycle. But under appropriate conditions they do undergo oxidative coupling reactions affording various interesting and useful directly fused porphyrin arrays[5,6] or react with some nucleophiles providing the corresponding β- and *meso*-substituted porphyrins.[7] With these in mind, we developed a facile and efficient hypervalent iodine(III)-mediated nucleophilic substitution reaction for direct and convenient synthesis of a wide range of *meso*-amino or *meso*-arylsulfanyl-substituted porphyrins. Herein the results are presented.

Results and Discussion

Hypervalent iodine(III) reagents, such as phenyliodine diacetate (**PIDA**) and phenyliodine di(trifluoroacetate) (**PIFA**), have

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

(2) For relevant reviews, see:(a) Senge, M. O.; Richter, J. *J. Porphyrins Phthalocyanines* **2004**, *8*, 934. (b) Sharman, W. M.; Van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441.

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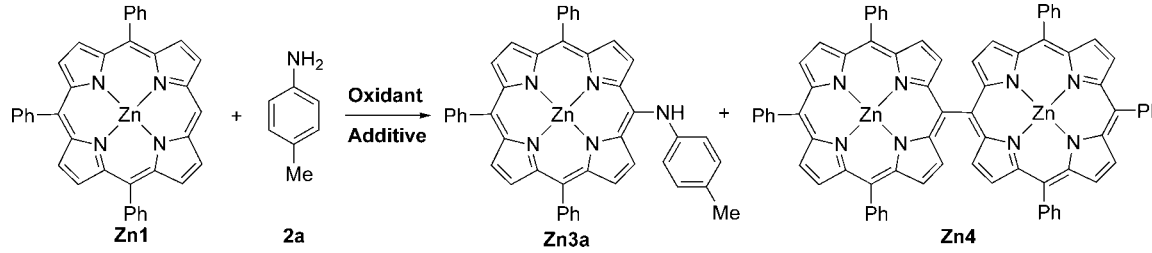
TABLE 1. Nucleophilic Substitution Reactions of Zn1 with 2a under Various Conditions[a]



entry	oxidant/additive (equiv)	base	solvent	*T* (°C)	*t* (h)	yield (%)[b] Zn3a	yield (%)[b] Zn4
1	PIFA (1)	Cs_2CO_3	CH_2Cl_2	25	2	10[c]	0
2	PIFA (3)	Cs_2CO_3	CH_2Cl_2	25	2	5[d]	30
3	PIDA (1)	Cs_2CO_3	CH_2Cl_2	25	2	25[c]	0
4	PIDA (3)	Cs_2CO_3	CH_2Cl_2	25	2	25[c]	0
5	PIDA (1)	KOH	CH_2Cl_2	25	2	25[c]	0
6	PIDA (1)	K_2CO_3	CH_2Cl_2	25	2	25[c]	0
7	PIDA (1)	Et_3N	CH_2Cl_2	25	2	25[c]	0
8	PIDA (1)	–[e]	CH_2Cl_2	25	2	25[c]	0
9	PIDA (1)	–[e]	CH_2Cl_2	40	2	25[c]	0
10	PIDA (1)	–[e]	CH_2Cl_2	25	48	40[f]	0
11	DDQ (1)	–[e]	CH_2Cl_2	25	2	0[g]	0
12	DDQ (10)	–[e]	CH_2Cl_2	25	0.5	0[d]	0
13	$AgPF_6$ (1)	–[e]	CH_2Cl_2	25	0.5	0	85
14	$NaAuCl_4 \cdot 2H_2O$ (1)	–[e]	CH_2Cl_2	25	0.5	0	93
15	PIDA (1)	–[e]	$ClCH_2CH_2Cl$	84	2	25[c]	0
16	PIDA (1)	–[e]	toluene	110	2	25[c]	0
17	PIDA (1)	–[e]	THF	25	2	0[g]	0
18	PIDA/$FeCl_3 \cdot 6H_2O$ (1:1)	–[e]	CH_2Cl_2	25	2	55	40
19	PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:1)	–[e]	CH_2Cl_2	25	0.5	65	25
20	PIDA/$NaAuCl_4 \cdot 2H_2O$ (1.5:1)	–[e]	CH_2Cl_2	25	0.5	55	40
21	**PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:1.5)**	–[e]	**CH_2Cl_2**	**25**	**0.5**	**92**	**5**
22	PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:2)	–[e]	CH_2Cl_2	25	0.5	92	5

[a] Reactions were carried out in solvent (10 mL) with **Zn1** (30 mg, 1.0 equiv), **2a** (5.0 equiv), and base (5.0 equiv) in air in the presence of an oxidant. [b] Isolated yields. [c] Recovery of **Zn1**: 70−85%. [d] Serious degradation of porphyrin was observed. [e] No base was used. [f] Recovery of **Zn1**: ~55%. [g] No reaction occurred. Recovery of **Zn1**: ~95%.

been extensively employed in organic synthesis as popular and useful oxidants due to their unique and beneficial properties.[8]

Our group recently reported efficient synthesis of various directly fused porphyrin arrays promoted by them via porphyrin cation radical intermediates.[5] In connection with these investigations, we attempted to conduct the direct nucleophilic substitution reaction of [5,10,15-triphenylporphyrinato]zinc(II) (**Zn1**) with 4-methylaniline (**2a**) in the presence of different hypervalent iodine(III) reagents. The detailed results are listed in Table 1. We were delighted to find that the reaction utilizing PIDA or

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(6) For some examples of the leading reports, see:(a) Osuka, A.; Shimidzu, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 135. (b) Ogawa, T.; Nishimoto, Y.; Yoshida, N.; Ono, N.; Osuka, A. *Chem. Commun.* **1998**, 337. (c) Tsuda, A.; Osuka, A. *Science* **2001**, *293*, 79. (d) Sahoo, A. K.; Nakamura, Y.; Aratani, N.; Kim, K. S.; Noh, S. B.; Shinokubo, H.; Kim, D.; Osuka, A. *Org. Lett.* **2006**, *8*, 4141. (e) Nakamura, Y.; Aratani, N.; Shinokubo, H.; Takagi, A.; Kawai, T.; Matsumoto, T.; Yoon, Z. S.; Kim, D. Y.; Ahn, T. K.; Kim, D.; Muranaka, A.; Koayashi, N.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 4119, and references cited therein. (f) Shi, X.; Amin, S. R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1665.

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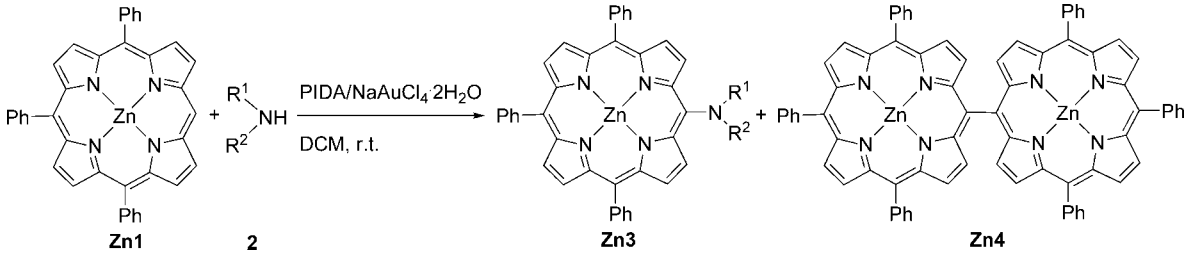
(8) For selective leading reviews, see:(a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, Germany, 2003.

TABLE 2. Nucleophilic Substitution Reactions of Zn1 with Various Amine 2[a]



entry	R^1, R^2NH	product	yield (%)[b] Zn3	yield (%)[b] Zn4	entry	R^1, R^2NH	product	yield (%)[b] Zn3	yield (%)[b] Zn4
1	Me-C$_6$H$_4$-NH$_2$ **2a**	**Zn3a**	92	5	7	MeO-C$_6$H$_4$-NH$_2$ **2g**	**Zn3g**	58[c]	0
2	C$_6$H$_5$-NH$_2$ **2b**	**Zn3b**	86	8	8	C$_6$H$_5$-NH-CH$_3$ **2h**	**Zn3h**	82	10
3	Cl-C$_6$H$_4$-NH$_2$ **2c**	**Zn3c**	76	12	9	C$_6$H$_{10}$NH **2i**	**Zn3i**	53[d]	0
4	2-Cl-C$_6$H$_4$-NH$_2$ **2d**	**Zn3d**	76	12	10	Et_2NH **2j**	**Zn3j**	50[d]	0
5	O_2N-C$_6$H$_4$-NH$_2$ **2e**	**Zn3e**	60	20	11	$(CH_3CH_2CH_2)_2NH$ **2k**	**Zn3k**	50[d]	0
6	2-OCF_3-C$_6$H$_4$-NH$_2$ **2f**	**Zn3f**	45	30	12	$(CH_2{=}CHCH_2)_2NH$ **2l**	**Zn3l**	32[d]	0

[a] Reactions were carried out in CH_2Cl_2 (10 mL) with **Zn1** (30 mg, 1.0 equiv) and **2** (5.0 equiv) in air at room temperature for 30 min in the presence of PIDA-$NaAuCl_4\cdot 2H_2O$ (1:1.5 equiv). [b] Isolated yields. [c] Recovery of **Zn1**: ~25%. [d] Recovery of **Zn1**: 40−50%.

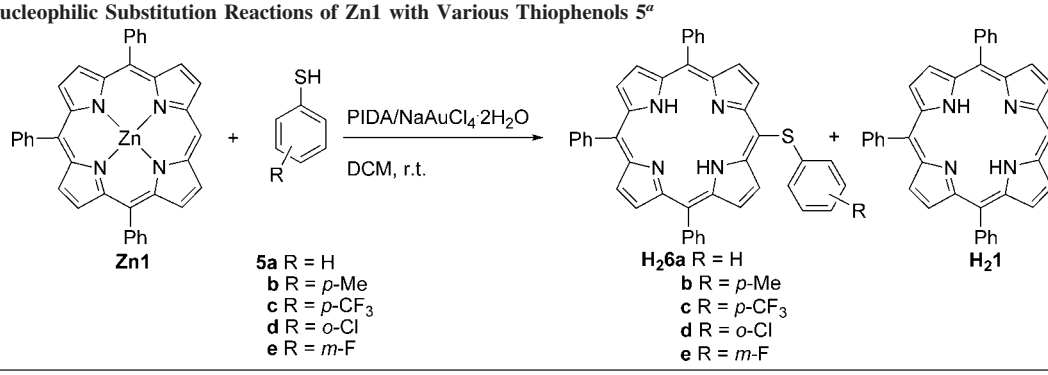
PIFA as an oxidant in dichloromethane successfully resulted in the desired nucleophilic substitution product **Zn3a** without notable formation of the oxidative coupling product **Zn4**, although the yields were low (Table 1, entries 1−4). The use of base and an elevated temperature proved unnecessary for the reaction because similar results were obtained in its absence or at higher temperature (Table 1, entries 1−9). Extended reaction time facilitated the reaction since the conversion obviously increased after 48 h (Table 1, entry 10). When using other oxidants instead of PIDA or PIFA, such as DDQ, $AgPF_6$, and $NaAuCl_4\cdot 2H_2O$, no desired nucleophilic substitution product **Zn3a** was formed under analogous conditions (Table 1, entries 11−14). Additionally, a significant solvent effect on the reaction was also observed. Noncoordinating solvents 1,2-dichloromethane or toluene led to similar results, whereas no reaction occurred with the use of THF, which is in line with the literature (Table 1, entries 15−17).[6f]

Encouraged by these preliminary results, we decided to further optimize the reaction conditions by adding some additives because it was reported that additives, especially Lewis acids, exercised a great influence on the activity of hypervalent iodine(III) reagents and the reaction course.[8,9] The influences of additives, such as $BF_3\cdot Et_2O$, $AlCl_3$, $Cu(OAc)_2\cdot H_2O$, $AgPF_6$, I_2, $Ce(SO_4)_2\cdot 4H_2O$, $Na_2S_2O_8$, $NaIO_4$, and PIFA, on the nucleophilic substitution reaction were very slight (see the Supporting Information). When $FeCl_3\cdot 6H_2O$ was used as an additive, noticeable improvement in the conversion and yield was observed, though a considerable amount of the oxidative coupling product **Zn4** was formed (Table 1, entry 18). Finally, $NaAuCl_4\cdot 2H_2O$ was proven a superior additive, giving good yield of the desired nucleophilic substitution product **Zn3a** and a small amount of **Zn4** in shorter reaction time (30 min) (Table 1, entry 19). Further investigations indicated that excellent yield of **Zn3a** and a trace of **Zn4** were obtained by controlling the equivalents of PIDA and $NaAuCl_4\cdot 2H_2O$ (Table 1, entry 20−22). On the basis of these results, the nucleophilic substitution reactions were successfully conducted in dichloromethane at room temperature in the presence of PIDA-$NaAuCl_4\cdot 2H_2O$ (1:1.5 equiv). Moreover, there is no need for dried solvent and nitrogen protection.

With the optimal conditions in hand, we carried out the reactions of **Zn1** with various aryl and aliphatic amines. Representative results are summarized in Table 2. A number of primary anilines with different substituents were efficiently applied to the direct nucleophilic substitution reactions, generally furnishing the desired necleophilic substitution products in good yields with small amounts of the oxidative coupling product **Zn4** (Table 2, entries 1−7). The secondary *N*-methylaniline was also a suitable coupling partner for the reaction, providing similar good yield of the desired product (Table 2, entry 8).

(9) (a) Dohi, T.; Ito, M.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301. (b) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (c) Dohi, T.; Morimoto, K.; Kiyono, Y.; Maruyama, A.; Tohma, H.; Kita, Y. *Chem. Commun.* **2005**, 2930. (d) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386.

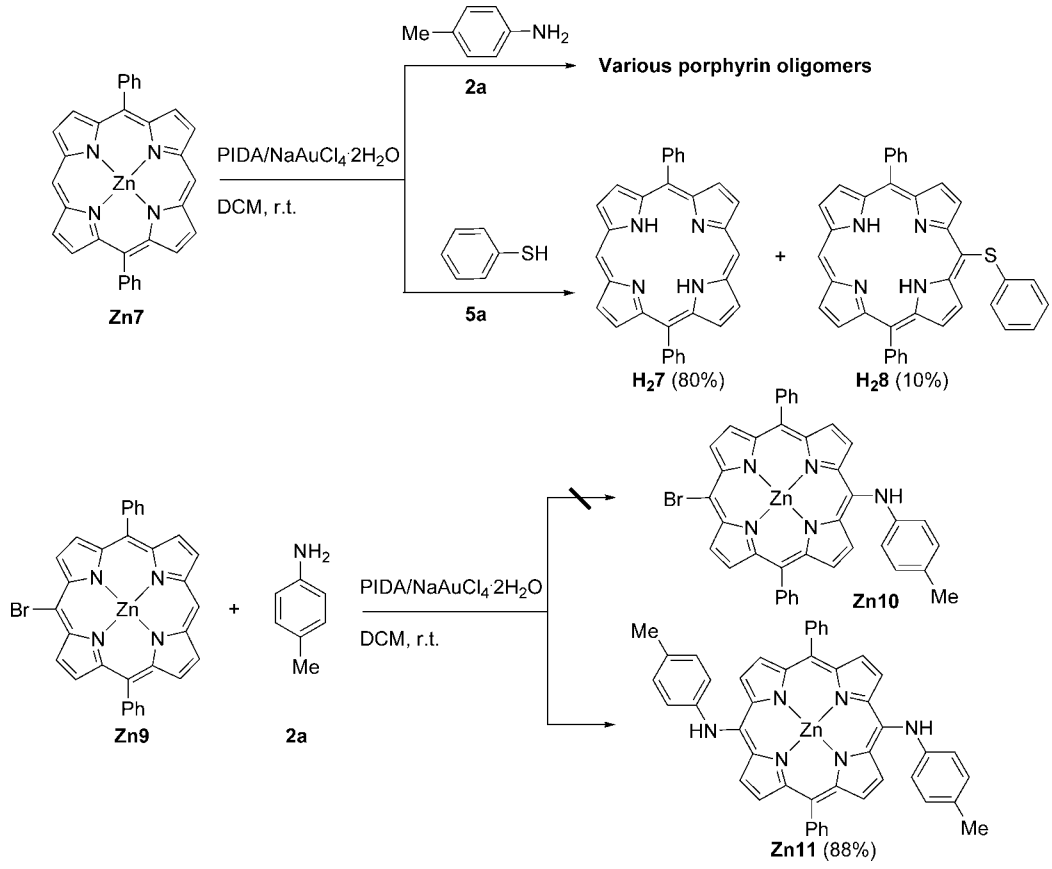
TABLE 3. Nucleophilic Substitution Reactions of Zn1 with Various Thiophenols 5[a]



entry	reactant	*t* (h)	product	yield[b](%) H_26	yield[b](%) H_21
1	**5a**	2	H_26**a**	65	15
2	**5b**	2	H_26**b**	70	15
3	**5c**	4	H_26**c**	50	35
4	**5d**	4	H_26**d**	60	25
5	**5e**	4	H_26**e**	40	40

[a] Reactions were carried out in CH_2Cl_2 (10 mL) with **Zn1** (30 mg, 1.0 equiv) and **5** (5.0 equiv) in air at room temperature in the presence of PIDA-$NaAuCl_4 \cdot 2H_2O$ (1:1.5 equiv). [b] Isolated yields.

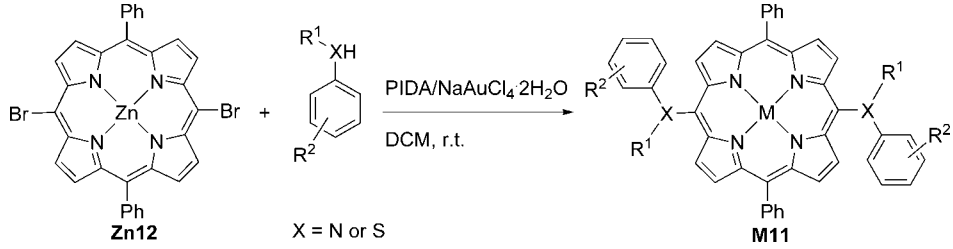
SCHEME 1

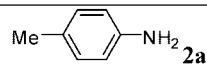
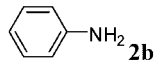
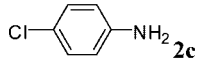
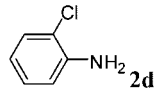
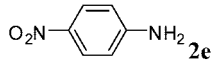
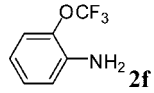
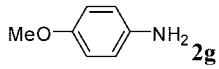
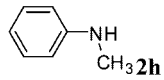
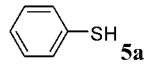
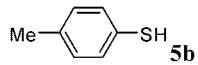
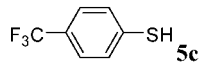
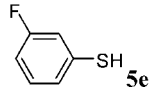


The uses of secondary aliphatic amines only led to the nucleophilic substitution products besides the recovered starting porphyrin and no oxidative coupling product **Zn4** was observed (Table 2, entries 9−12).

We then tried to expand the scope of the nucleophilic substitution reaction by subjecting a variety of thiophenols to the reaction. As demonstrated in Table 3, thiophenols with both electron-donating and electron-withdrawing substituents were easily reacted with **Zn1**, resulting in acceptable yields of the desired nucleophilic substitution products without formation of the oxidative coupling product, though a small amount of the demetalated starting porphyrin H_21 was obtained. It should be mentioned that central zinc ions in the nucleophilic substitution products left during the reaction probably due to the presence of excess amounts of thiophenols and acids in the reaction system, which is consistent with the previous reports.[10] The relatively lower yields might be attributed to the demetalation

TABLE 4. Double Nucleophilic Substitution Reactions of *meso*-Dibromoporphyrin Zn12 with Various Amines and Thiophenols[a]



entry	reactant	*t* (h)	M	product	yield[b] (%)
1	 **2a**	0.5	Zn	**Zn11a**	91
2	 **2b**	0.5	Zn	**Zn11b**	90
3	 **2c**	0.5	Zn	**Zn11c**	85
4	 **2d**	0.5	Zn	**Zn11d**	72
5	 **2e**	0.5	Zn	**Zn11e**	65
6	 **2f**	0.5	Zn	**Zn11f**	63
7	 **2g**	0.5	Zn	**Zn11g**	50
8	 **2h**	0.5	Zn	**Zn11h**	88
9	 **5a**	2	2H	**H$_2$11i**	75
10	 **5b**	2	2H	**H$_2$11j**	65
11	 **5c**	4	2H	**H$_2$11k**	70
12	 **5e**	4	2H	**H$_2$11l**	50

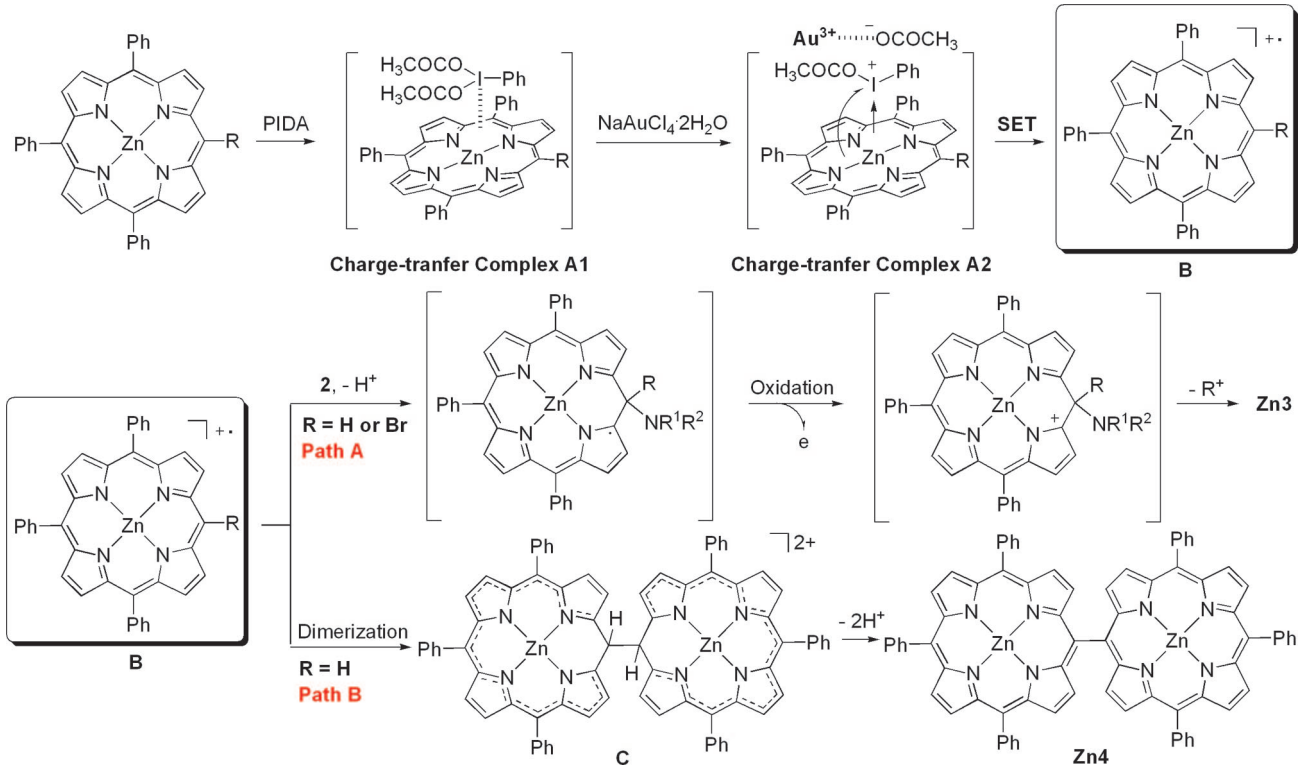
[a] Reactions were carried out in CH_2Cl_2 (10 mL) with **Zn12** (30 mg, 1.0 equiv) and **2** or **5** (5.0 equiv) in air in the presence of PIDA-$NaAuCl_4 \cdot 2H_2O$ (1:1.5 equiv). [b] Isolated yields.

of the starting porphyrin, which results in higher oxidation potential. This was further supported by the fact that no reaction occurred when utilizing free-base porphyrin **H$_2$1** as the starting porphyrin under similar conditions.

Next, we examined the nucleophilic substitution reaction of [5,15-diphenylporphyrinato]zinc(II) (**Zn7**)[3c] with 4-methylaniline (**2a**) and thiophenol **5a** under the similar conditions, expecting to obtain the double nucleophilic substitution products. However, the reaction with **2a** resulted in a complex mixture including various porphyrin oligomers (Scheme 1). In the case of **5a**, the demetalated starting porphyrin **H$_2$7** was observed in addition to a trace of demetalated mononucleophilic substitution product **H$_2$8** (Scheme 1). In view of the important role of bromoporphyrins as building

(10) (a) Battersby, A. R.; Jones, K.; Snow, R. J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 734. (b) Lewis, N. J.; Pfaltz, A.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 735.

SCHEME 2. Proposed Reaction Mechanism for the PIDA-$NaAuCl_4$-Mediated Nucleophilic Substitution Reactions



blocks for easy construction of various novel and useful porphyrins,[2−4] we decided to use [5-bromo-10,20-diphenylporphyrinato]zinc(II) (**Zn9**) as an alternative starting porphyrin. Surprisingly, its reaction with **2a** did not lead to the expected mononucleophilic substitution product **Zn10**, but the double nucleophilic substitution product **Zn11** in high yield, indicating that the *meso*-bromine atom cannot be retained in the reaction (Scheme 1). Considering the relatively ready availability of *meso*-dibromoporphyrin, [5,15-dibromo-10,20-diphenylporphyrinato]zinc(II) (**Zn12**) was used for the following double nucleophilic substitution reactions. As illustrated in Table 4, various aromatic amines and thiols could be well transformed, affording good yields of the double nucleophilic substitution products.

On the basis of the above results and the literature,[5,6,9] a possible reaction mechanism for the PIDA-$NaAuCl_4$-mediated nucleophilic substitution reaction was outlined in Scheme 2. The combination of PIDA and the porphyrin macrocycle generates the charge-transfer complex **A1**, which further forms the charge-transfer complex **A2** by coordination of gold(III) cation with the acetate anion in **A1**. The key intermediate porphyrin radical cation **B** is subsequently produced via the single-electron transfer (SET) oxidation. In situ trapping of radical cation **B** by nucleophiles followed by further oxidation and deprotonation/debromination results in the formation of nucleophilic substitution products (path A). At the same time, the porphyrin cation radical **B** might dimerize to form the intermediate **C**, which leads to the oxidative coupling product **Zn4** after deprotonation (path B).

Conclusions

In summary, we have developed a facile and efficient synthesis of various *meso*-functionalized porphyrins directly from [5,10,15-triphenylporphyrinato]zinc(II) (**Zn1**) with a single free *meso* position by PIDA-$NaAuCl_4$-mediated nucleophilic substitution reactions, which allows quick and easy access to a wide range of *meso*-amino or *meso*-arylsulfanyl-substituted porphyrins. The use of noncoordinating solvents and $NaAuCl_4 \cdot 2H_2O$ as an additive are critical for the reaction. This protocol can also be applied to *meso*-dibromoporphyrin, providing the corresponding double nucleophilic substitution products in good yields.

Experimental Section

General Procedure for $PhI(OAc)_2$-$NaAuCl_4$-Mediated Nucleophilic Substitution Reactions of Zn1 with Various Amines 2 or Thiophenols 5. Porphyrin **Zn1** (30 mg, 0.05 mmol, 1.0 equiv), amine **2** or thiophenol **5** (5.0 equiv), PIDA (16 mg, 1.0 equiv), and $NaAuCl_4 \cdot 2H_2O$ (30 mg, 1.5 equiv) were added to a round-bottomed bottle and CH_2Cl_2 (10 mL) was charged. The reaction mixture was stirred in air at room temperature for 30−240 min. Then a saturated solution of $Na_2S_2O_3$ (10 mL) was added. After being stirred for 10 min, the reaction mixture was washed with water three times. The organic layer was collected, filtered through dry silica gel, and evaporated to dryness. The resulting solid was purified by flash chromatography to give the desired nucleophilic substitution products in good yields.

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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.

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