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Regioselective and Switchable *meso*-Aminations and Couplings of 5,15-Diarylchlorins

Qi Cheng,[†] Yu-Hao Qiu,[†] Sheng-Lin Luo,[‡] Li Shuai,[†] Yi Yuan,[†] Ying-Chun Chen,*[,†,§] and Qin Ouyang*[,†]

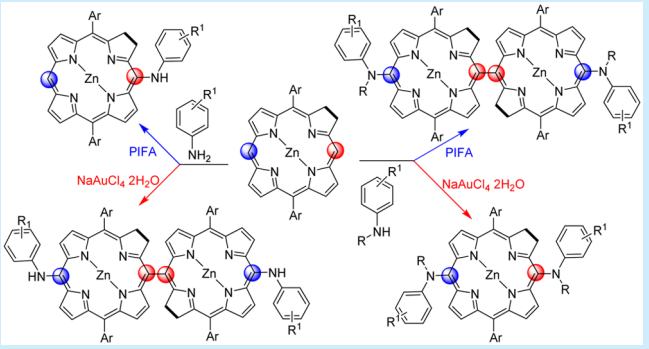
[†]College of Pharmacy, Third Military Medical University, Chongqing 400038, China

[‡]Institute of Combined Injury, State Key Laboratory of Trauma, Burns and Combined Injury, Department of Preventive Medicine, Third Military Medical University, Chongqing 400038, China

[§]Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

Supporting Information

ABSTRACT: Controllable chemo- and regiodivergent amination reactions of anilines and chlorins are accomplished by employing different oxidants and substrates, constructing aminated chlorin monomers and dimers with high structural diversity. Importantly, besides preferential 20-*meso*-position, the oxidative amination was also realized at the inactive 10-*meso*-position by using phenyliodine bis(trifluoroacetate) (PIFA) and gold(III)-based reagents.



Porphyrin and chlorin derivatives have attracted significant attention due to their numerous applications, such as artificial photosynthetic systems, sensors, and nonlinear optical (NLO) devices.[1] Chlorins, structurally more similar to photosynthetic pigments, are especially valuable as photosensitizers for photodynamic therapy (PDT) owing to their strong absorptions in red band (600−700 nm).[2] Several chlorin derivatives, such as Verteporfin,[3] Temoporfin,[4] and Talaporfin[5] (Figure 1), have been approved for clinical use to treat cancer, skin disease, and abnormal blood vessels, respectively.

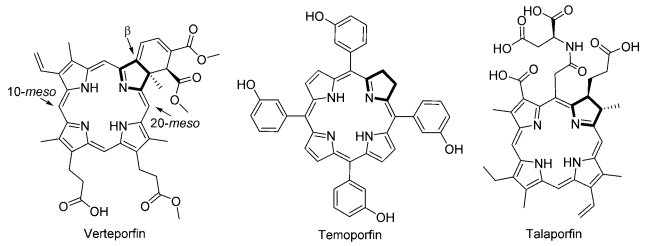


Figure 1. Chlorin photosensitizers approved for clinical use.

In addition to the natural extraction and derivation of chlorophyll, chemical synthesis has been proven as a powerful approach to produce new chlorin derivatives for photosensitizer discovery.[6] Beside modifying the pyrrole ring of porphyrins, introduction of substituted pyrroles before constructing chlorin rings was reported as a common synthetic strategy to generate multifarious *meso*- or *β*-substituted chlorin skeletons and derivatives.[7] Direct modifications at preferred 20-*meso*-position flanking the pyrroline ring of chlorins were rarely reported except bromination[7b,8] and direct coupling reactions.[9] The 10-*meso*-position of chlorins was considered as an inactive site in comparison with 7,8-*β*-positions for the bromination,[8c] though its functionalization might affect the physicochemical properties due to the short distance to the core of the ring. Developing a facile method to directly introduce *meso*-substituents, especially via amination reactions at inactive 10-position, would be extremely attractive, since amino groups are useful for dye-sensitized solar cell development as electron donating groups[10] and are favorable for drug discovery owing to their ubiquity in a variety of pharmaceuticals and natural products.

A variety of gold(III)-based catalysts have been reported to promote C−H aminations.[11] Specifically, an oxidative strategy by using phenyliodine diacetate (PIDA) and $NaAuCl_4{\cdot}2H_2O$ was presented to conduct the *meso*-amination of 5,10,20-trisubstituted porphyrins; however, for the amination of 5,15-diarylporphyrins, various porphyrin oligomers were generated.[12] Recently, as an environmentally friendly approach, hypervalent iodine(III) reagents have been successfully applied to synthesize *meso-meso* directly linked diporphyrins,[13] fused diporphyins,[14] and regioselective 20−20′ linked chlorin dimers.[9] Although numerous methods to construct C−N bonds for some kinds of special substrates have been reported using a metal-free oxidative strategy,[15] simplex hypervalent iodine(III) reagents failed to

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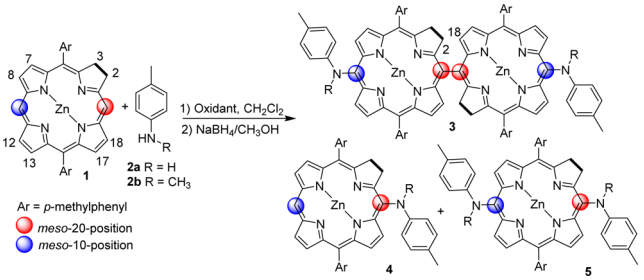
promote the amination of porphyrins.[12] Compared with porphyrins, chlorins are easier to be oxidized due to their lower first oxidation potential,[9] and have more diverse active sites to conduct amination, coupling, decomposition, or polymerization reactions. Thus, the reactions of chlorins and anilines by using oxidation strategies have more possibilities and challenges. Here we report our preliminary results by using hypervalent iodine(III) reagents or gold(III) salts for the preparation of chemo- and regioselective *meso*-aminated chlorin monomers and dimers. Importantly, besides preferential 20-*meso*-position, the amination was also conducted at the inactive 10-*meso*-position.

The initial reaction of chlorin **1** and *p*-toluidine **2a** proceeded rapidly at room temperature in the presence of PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:1). Unfortunately, few products were generated by using conventional saturated sodium thiosulfate solution to quench the reaction.[12] However, as previously reported,[14] $NaBH_4/CH_3OH$ were used to terminate the reaction, producing an unusual 10,10′-diaminated, 20,20′-linked chlorin dimer **3a** in 36% yield and 20-aminated chlorin **4a** in 20% yield (Table 1, entry 1). A higher yield of **3a** was obtained by increasing the amounts of $NaAuCl_4 \cdot 2H_2O$ (entry 2), and better selectivity with 68% yield of **3a** was observed by using $NaAuCl_4 \cdot 2H_2O$ independently (entry 3). No expected products were generated with PIDA (entry 4); however, phenyliodine bis(trifluoroacetate) (PIFA) promoted the reaction effectively, and interestingly, 20-aminated chlorin **4a** was produced in a moderate yield (entry 5). The yield of **4a** could be improved to 65% by employing 1.5 equiv of oxidants (entry 7). Further addition of oxidants produced a complex mixture probably because of decomposition (entry 8). Other oxidants, such as $AgSbF_6$, $FeCl_3$, O_2, 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), PIDA/$Cu(OAc)_2$ (1:0.2), and PIDA/$Sc(CF_3SO_3)_2$ (1:0.2), failed to promote this amination, while porphyrin was obtained as the major product in the reactions using $AgSbF_6$ or DDQ. Moreover, the amination could not be promoted in other solvents, such as THF, acetonitrile, and ethanol.

Table 1. Screening Studies of Oxidative Reactions of Chlorin 1 and Anilines 2[a]



entry	oxidant (equiv)	R	*t*	yield (%)[b]
1	PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:1)	H	1 min	**3a**, 36; **4a**, 20
2	PIDA/$NaAuCl_4 \cdot 2H_2O$ (1:4)	H	1 min	**3a**, 50; **4a**, 25
3	$NaAuCl_4 \cdot 2H_2O$ (1.5)	H	1 min	**3a**, 68; **4a**, < 5
4	PIDA (1)	H	12 h	trace[c]
5	PIFA (1)	H	1 min	**4a**, 40[d]
6	PIFA (0.25)	H	1 min	**4a**, 15[d]
7	PIFA (1.5)	H	1 min	**4a**, 65
8	PIFA (3)	H	1 min	decomposition
9	$NaAuCl_4 \cdot 2H_2O$ (1.5)	CH_3	1 min	**3b**, < 5; **5a**, 60
10	PIFA (1.5)	CH_3	1 min	**3b**, 61; **5a**,17

[a]Unless otherwise noted, reactions were performed with **1** (0.05 mmol), **2** (0.25 mmol), and oxidant in CH_2Cl_2 (30 mL) and quenched by $NaBH_4/CH_3OH$ (10 mg/2 mL). [b]Isolated yield. [c]53% of **1** was recovered. [d]Together with **1**.

Beside the oxidant-controlled reaction, the substrates also played an important role in regulating the chemoselectivity. The reaction of **1** and *N*-methyl *p*-toluidine **2b** produced 10,20-diaminated chlorin **5a** in a good yield with $NaAuCl_4 \cdot H_2O$, and trace amounts of chlorin dimer **3a** were isolated (entry 9). Surprisingly, by using PIFA, a 10,10′-diaminated and 20,20′-linked chlorin dimer **3b** was generated in a good yield, and minor diaminated chlorin **5a** was also isolated (Table 1, entry 10). Other possible products, such as 10,10′- or 10,20′-linked chlorin dimers were not observed and identified. The coupling reaction of 20-aminated chlorin **4a** could not be further promoted by adding PIFA or gold(III) salt. In addition, we also tried similar amination reactions for other metal chlorins. PIFA failed to promote the amination of Pd^{II} and Ni^{II} chlorin (**1**-Ni^{II}, and **1**-Pd^{II}, respectively), and self-coupling dimer also was not observed. In contrast, by using $NaAuCl_4 \cdot H_2O$ as the oxidant, the reaction of Ni^{II} chlorin and **2a** resulted in complex products, while **1**-Pd^{II} and **2a** produced a mixture of 10,20-diaminated Pd^{II} chlorin **5a**-Pd^{II} and diaminated Pd^{II} porphyrin [for more details, see the Supporting Information (SI)].

The structures of these chlorins were confirmed by their NMR data and mass spectrometry. A complete ^{1}H NMR assignment for the individual protons of **3a**, **4a**, and **5a** was achieved by 2D-NMR studies (for more details, see the SI). Compared with **1**, the signals of H-10 and H-20 of **3a** disappeared (Figure 2). Beside the upfield shifts of the proton signals near the 20-position (H-18 and H-2) due to the 20−20 connection, other *β*-Hs in **3a**, especially H-13 and H-7, showed obvious upfield shifts resulting from the introduction of *N*-substituent at the 10-position. Additionally, the interaction between H-2 and H-18 can be found in the ^{1}H-NOESY NMR spectra of **3a** and **3b** (see the SI), which further confirmed the linkage at 20-position. In the ^{1}H NMR spectrum of **4a**, the signal of H-20 disappeared and the signals of *β*-Hs-2,3,17,18 showed obvious upfield shifts due to the amination at 20-position. In contrast, beside the disappeared signals of H-10 and H-20, two signals of *N*-CH_3 and more upfield shifting signals of *β*-Hs in the ^{1}H NMR spectrum of **5a** proved that the chlorin ring was diaminated at 10,20-*meso*-positions.

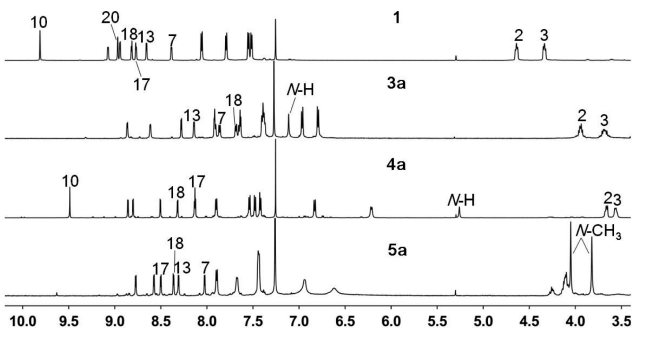


Figure 2. ^{1}H NMR spectra of **3a**, **4a**, **5a**, and **1** in $CDCl_3$.

In addition to PIFA-promoted self-coupling of chlorin,[9] we also found 20−20′-linked chlorin dimer **6** could be synthesized regioselectively from $NaAuCl_4 \cdot 2H_2O$ and **1** in CH_2Cl_2 within 1 min in 45% yield in the presence of K_2CO_3. Subsequently, chlorin dimer **6** reacted with **2a** or **2b** under the optimized oxidative conditions. PIFA promoted the formation of C−N bond with secondary amine **2b** in a good yield (Table 2, entry 1),

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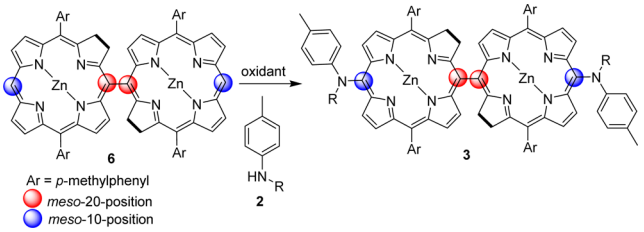
Table 2. Oxidative *meso*-Amination of Chlorin Dimer 6 and Anilines 2[a]



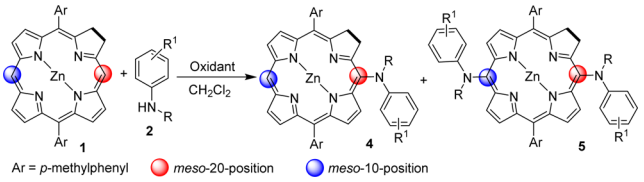
entry	oxidant (equiv)	R	*t*	yield (%)[b]
1	$NaAuCl_4{\cdot}2H_2O$ (1.5)	H	1 min	**3a**, 70
2	PIFA (1.5)	H	1 min	**3a**, 49
3	$NaAuCl_4{\cdot}2H_2O$ (1.5)	CH_3	1 min	**3b**, 67
4	PIFA (1.5)	CH_3	1 min	**3b**, 79

[a]Unless otherwise noted, reactions were performed with chlorin dimer **6** (0.05 mmol), aniline **2** (0.25 mmol), and oxidant (0.075 mmol) in CH_2Cl_2 (30 mL) and quenched by $NaBH_4/CH_3OH$ (10 mg/2 mL). [b]Isolated yield.

while the reaction of **6** and **2a** resulted in a low yield (entry 2). In contrast, gold(III) salt showed high activity for the amination reaction of **6** with either **2a** or **2b**, efficiently producing **3a** and **3b** in high yields (entries 3 and 4). These results suggested that the formation of aminated chlorin dimer might proceed through the self-coupling reaction at 20-*meso*-position and sequential C−N bond formation at 10-*meso*-position. As a result, a step by step strategy using PIFA and gold(III) salt could be considered as a general protocol for preparing the aminated chlorin dimers with different aniline substrates.

According to density functional theory (DFT) calculations[16] and experiments, we found that the reactivity of anilines, in a certain degree, depended on the energy of HOMO (ε_{HOMO}). For the reaction of *N*-unsubstituted anilines and chlorin by using PIFA, introducing an electron-donating methoxy group with higher ε_{HOMO} facilitated the reaction (Table 3, entry 2). In contrast, using substrate with an electron-withdrawing group resulted in a poorer yield due to its lower ε_{HOMO} (entry 3). Nevertheless, aniline with a 4-ester group failed to give the amination product, probably due to its low energy of HOMO (entry 4). The substituent position also affected the reaction, as using *o*-toluidine produced the aminated chlorin **4d** in a fair yield (entry 5). Additionally, $NaAuCl_4{\cdot}2H_2O$ was used to produce diaminated chlorins **5** in moderate yields (entries 6−11). It is worth noting that minor aminated chlorin **4e** was isolated along with **5c**, since 4-fluoro-*N*-methylaniline has a relatively lower ε_{HOMO} (−5.65 eV). It suggested that the oxidant might activate the *meso*-Hs at 10- and 20-positions sequentially. In addition to ε_{HOMO}, the steric hindrance also affected the reaction. Except that *N*-benzyl-*p*-toluidine could be used for the amination in a low yield (entry 11), other compounds with large steric hindrance or low ε_{HOMO} were not able to promote the amination, such as diphenylamine, carbazole, and *N*-(p-tolyl)acetamide. In addition to the literature reported single-electron transfer (SET) oxidation of chlorin,[12,17] the ε_{HOMO} depended results suggested that the possible reaction mechanism may also involve the oxidation of aniline to a radical.

Table 3. Substrate Scope and Limitations of the *meso*-Amination of Chlorin[a]



entry	R	R^1	ε_{HOMO} (eV)	oxidant	yield (%)[b]
1	H	4-Me	−5.36	PIFA	**4a**, 65
2	H	4-OMe	−5.10	PIFA	**4b**, 71
3	H	4-F	−5.63	PIFA	**4c**, 40
4	H	4-COOMe	−5.97	PIFA	mixture
5	H	2-Me	−5.48	PIFA	**4d**, 49
6	CH_3	4-Me	−5.21	$NaAuCl_4.2H_2O$	**5a**, 60
7	CH_3	4-OMe	−5.16	$NaAuCl_4.2H_2O$	**5b**, 45
8	CH_3	4-F	−5.65	$NaAuCl_4.2H_2O$	**5c**, 42; **4e**, 20
9	CH_3	4-COOMe	−5.86	$NaAuCl_4.2H_2O$	mixture[c]
10	Bn	4-Me	−5.45	$NaAuCl_4.2H_2O$	**5d**, 26

[a]Unless otherwise noted, reactions were performed with chlorin **1** (0.05 mmol), aniline **2** (0.25 mmol), and oxidant (0.075 mmol) in CH_2Cl_2 (30 mL) and quenched by $NaBH_4/CH_3OH$ (10 mg/2 mL). [b]Isolated yield. [c]40% of **1** was recovered.

The natural population analysis (NPA) charges were further calculated to understand the regioselectivity.[16] The *meso*-carbon at 20-position was evaluated to have higher electron density with a charge of −0.334, implying its activity for amination and self-coupling. In contrast, the *meso*-carbon at 10-position, selectively proceeding amination rather than self-coupling,[9] had a lower charge with a value of −0.184. Similarly, *meso*-carbon at 10-position of **6** and **4a** had similar charges (−0.176 and −0.170, respectively). However, the charges of 10-*meso*-carbons in these compounds were less negative than those of 7,8-*β*-carbons, which were consistent with the regioselectivity of bromination that involved a process of cation radical.[8c] Due to the unusual selectivity, we proposed the formation of a complex radical from chlorin radical and aniline anion, in which the N atom of aniline was coordinated with the Zn atom of chlorin. The shorter distance between *meso*-C atom and coordinated N atom may be the possible reason for the unusual selectivity at inactive 10-position (see the SI). As the amination could be conducted for 20- and 10-carbons sequentially, structural diversity may come from the competition between amination and self-coupling reaction at electron-rich 20-carbons.

As outlined in Figure 3, compared to **1**, the absorption spectrum of **3a** showed a broadened Soret band with a shoulder and a broadened Q bond ranging from 630−800 nm. Similar broadened and red-shift bonds were found in the spectrum of **4a**. These broad bonds may result from their self-assemble behavior,

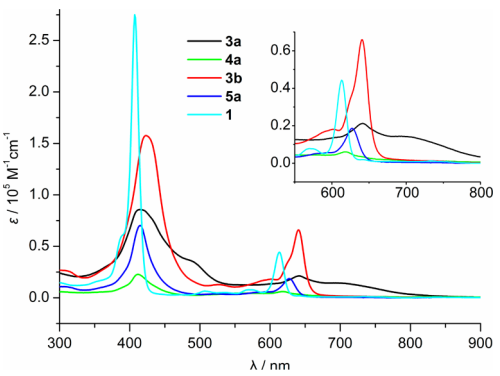


Figure 3. UV−vis spectra of **3a**, **3b**, **4a**, **5a**, and **1** in CH_2Cl_2.

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because they become sharper when adding a little DMSO into CH_2Cl_2 (see the SI). In contrast, sharper bonds were observed in the spectra of **3b** and **5a**, since the *N*-substituents might block the self-assembly by steric hindrance. Meanwhile, **3b** and **5a** showed obvious red-shift for both Soret and Q bands. The Q bands' maximum absorption wavelength of **3b** and **5a** were 641 and 627 nm, respectively, while that of **1** was 613 nm. Moreover, the DFT calculations showed that introducing *meso*-*N*-substituents would lead to lower energies of LUMO and LUMO−1, which might be the reason for the red-shifted Q bands.[16] Additionally, we also tested the relative fluorescence quantum yield and phototoxic activity of these synthesized chlorins, suggesting the amination of chlorin might be useful for developing potential new photosensitizers (see the SI).

In conclusion, we have investigated the reactions of anilines and chlorins by using different oxidants. Regioselective 20-aminated products are efficiently produced by using PIFA oxidation of *N*-unsubstitued anilines and chlorins. Diamination reactions between *N*-substituted anilines and chlorins at 10- and 20-positions are successfully finished by employing $NaAuCl_4 \cdot 2H_2O$. Interestingly, diaminated chlorin dimers have been obtained in the reactions of Zn^{II} chlorin monomers and *p*-toluidine with $NaAuCl_4 \cdot 2H_2O$ or *N*-methyl-*p*-toluidine with PIFA. It is worth mentioning that the amination could be conducted at the inactive 10-*meso*-position. These results should be helpful for producing more chlorin derivatives as structurally diverse *meso*-substituted photosensitizers. Additional results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01739.

Experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ycchen@scu.edu.cn
*E-mail: ouyangq@tmmu.edu.cn

ORCID

Ying-Chun Chen: 0000-0003-1902-0979
Qin Ouyang: 0000-0002-1161-5102

Notes

The authors declare no competing financial interest.

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