Porphyrinoids

International Edition: DOI: 10.1002/anie.201800471
German Edition: DOI: 10.1002/ange.201800471

Direct and Regioselective Amination of β-Unsubstituted 5,15-Diazaporphyrins with Amines: A Convenient Route to Near-Infrared-Responsive Diazaporphyrin Sensitizers

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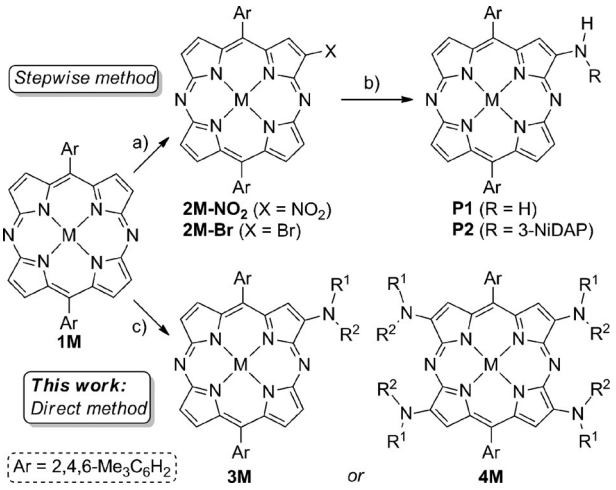
Abstract: *We have established a convenient method for the base-promoted direct amination of β-unsubstituted 5,15-diazaporphyrins (DAPs) with secondary and primary amines to produce 3,7,13,17-tetraamino- and 3-amino-DAPs, respectively, regioselectively. The amino groups attached at the periphery cause significant red shifts of the absorption bands as a result of their perturbation of the HOMO and/or LUMO in the DAP π-system. The palladium complex of a 3,7,13,17-tetrakis(diphenylamino)-DAP generated singlet oxygen in high yield under irradiation with near-infrared light.*

Recently, considerable attention has been paid to porphyrin-based photosensitizers that are capable of harvesting near-infrared (NIR) light. These properties are important in materials science, for example, for photodynamic therapy and organic solar cells. The introduction of an amino group on a porphyrin ring is a reliable strategy for achieving high light-harvesting ability in the long-wavelength region.[1] For example, electrodonating *meso*-diarylamino porphyrins are effective photosensitizers for dye-sensitized solar cells.[2] Recently, we reported **P1** and **P2** as the first examples of 5,15-diazaporphyrins (DAPs) bearing an amino group at the periphery (Scheme 1).[3] Notably, **P1** (M = Ni, Cu) and **P2** (M = Ni) have large charge-transfer (CT) character, reflecting the high-lying highest occupied molecular orbital (HOMO) of the peripheral amino group and the low-lying lowest unoccupied molecular orbital (LUMO) of the DAP ring.[4] As a result, **P1** and **P2** exhibit considerably red shifted CT absorption bands, at 700 and 760 nm, respectively.[3] We envisioned that the further amination of DAP would afford a promising scaffold for constructing new NIR-light-responsive photosensitizers.



Scheme 1. Synthesis of amino-DAPs. a) Nitration (to **2M-NO$_2$**) or bromination (to **2M-Br**); b) reduction (from **2M-NO$_2$** to **P1**) or N–C cross-coupling (from **2M-Br** to **P2**); 3-NiDAP = 10,20-dimesityl-5,15-diaza(nickel)porphyrin-3-yl. c) Base-promoted direct substitution with amines (this study).

In general, *meso*- and β-aminoporphyrins have been prepared by cross-coupling of the corresponding haloporphyrins with amines,[5] the nucleophilic substitution of nitroporphyrins with amines,[6] the reduction of nitroporphyrins,[7] or the direct amination of porphyrins via porphyrin radical cations.[8] The 3-amino-DAPs **P1** and **P2** were also prepared by the reduction of **2M-NO$_2$** and the N–C cross-coupling reaction of **2M-Br** with **P1**, respectively (Scheme 1).[3] However, these reactions require prefunctionalization (nitration and halogenation) of porphyrin/DAP rings or a stoichiometric amount of an oxidant, such as a hypervalent iodine compound or an amyl radical, to generate the precursors. Furthermore, synthetic difficulties concerning amination at multiple peripheral positions precludes straightforward access to multiaminated porphyrin/DAP derivatives.[9] Therefore, the development of a more convenient method for introducing one or more amino groups onto a DAP ring is an important challenge in both organic synthesis and materials science.

Herein, we report direct and regioselective amination reactions of metal(II) complexes and the free base of DAP (MDAP; M = Ni, Cu, Pd, H_2) by the use of primary and secondary amines under basic conditions to afford 3-amino- and 3,7,13,17-tetraamino-DAPs, respectively (Scheme 1c). The lowest-energy absorption bands of 3,7,13,17-tetrakis(di-

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201800471.

phenylamino)-MDAPs were found to be significantly red shifted into the NIR region. The photosensitized singlet oxygen ($^1O_2$)-generation properties of the palladium complex are also reported.

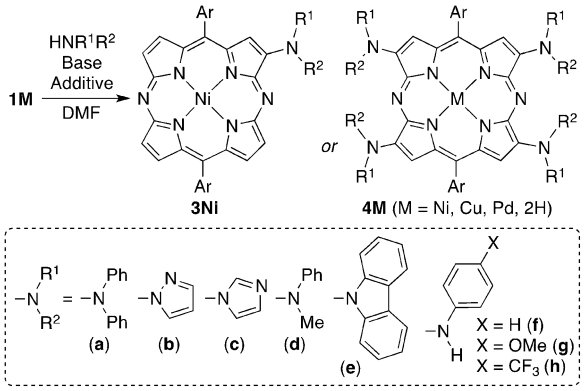
Initially, we had planned to use N–C cross-coupling reactions of 3-bromo-NiDAP **2Ni-Br** with amines to prepare 3-amino-NiDAPs **3Ni** (see Scheme S1 in the Supporting Information). The reaction of **2Ni-Br** with diphenylamine ($HNPh_2$) in the presence of NaO^{t}Bu and the catalyst PEPPSI-IPr ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride) in THF afforded 3-Ph_2N-NiDAP **3Ni-a**, as expected. However, to our surprise, the reaction of **2Ni-Br** with pyrazole in the presence of Cs_2CO_3 and CuI (20 mol%) in DMF afforded 3,7,13,17-tetrakis(1-pyrazolyl)-NiDAP **4Ni-b** as the sole isolable product. The unexpected formation of **4Ni-b** indicated that direct substitution with pyrazole occurred at the multiple pyrrolic β-carbon atoms.[10] Indeed, β-unsubstituted NiDAP **1Ni** reacted with 4 equivalents of pyrazole in the presence of Cs_2CO_3 to give **4Ni-b** in both the presence and absence of CuI (Table 1, entries 1 and 2). The direct multiamination of **1Ni** with imidazole also proceeded to afford 3,7,13,17-tetrakis(1-imidazolyl)-NiDAP (**4Ni-c**; entry 3).

Encouraged by these results, we screened reaction conditions for the direct amination of **1Ni** with $HNPh_2$. No reaction took place in the absence of a base. The treatment of **1Ni** with an excess of $HNPh_2$ in the presence of NaOH in DMF for 24 h at room temperature afforded 3,7,13,17-tetrakis(diphenylamino)-NiDAP **4Ni-a** in 55% yield (as determined by NMR spectroscopy). The addition of 3 Å molecular sieves (MS3A) accelerated the reaction and dramatically increased the yield of **4Ni-a** (Table 1, entry 4). In contrast, the addition of water completely suppressed the formation of **4Ni-a**. These results suggested that the amount of water had a significant impact on amination in the present reaction, in which a diphenylamide ion was probably generated as the active nucleophile (see below). Besides NaOH, KOH and Me_4NOH were effective bases (entries 5 and 6), whereas Cs_2CO_3 was not.

Having established optimal reaction conditions (NaOH and MS3A), we examined the direct amination of **1M** with several secondary and primary amines in DMF at room temperature. Substitution with pyrazole proceeded more rapidly than that with $HNPh_2$ (Table 1, entries 7 and 4). Multiamination of **1Ni** with *N*-methylaniline and carbazole gave the corresponding 3,7,13,17-tetraamino-NiDAPs **4Ni-d** and **4Ni-e**, respectively (entries 8 and 9). In contrast, the reaction of **1Ni** with aniline and *para*-substituted anilines afforded only 3-amino-NiDAPs **3Ni-f–h** in 64–78% yield (entries 10–12). β-Unsubstituted CuDAP **1Cu**, PdDAP **1Pd**, and H_2DAP **1H$_2$** also underwent the direct amination with $HNPh_2$ (for **1Cu**, **1Pd**; method B) or pyrazole (for **1H$_2$**; method A) to yield the corresponding tetraamino-MDAPs (entries 13–15).[11] No reaction took place between **1Ni** and aliphatic amines (diisopropylamine and *tert*-butylamine) under the NaOH/MS3A/DMF conditions. However, when **1Ni** was treated with lithium diisopropylamide in THF at room temperature, direct amination occurred to afford 3,17-bis(diisopropylamino)-NiDAP **5Ni** in low yield as an isolable product (see Scheme S2). Notably, 5,15-dimesitylporphyrinatonickel(II), the porphyrin analogue of **1Ni**, did not react with $HNPh_2$ under the same conditions. Therefore, the observed reactivity was unique to MDAP.

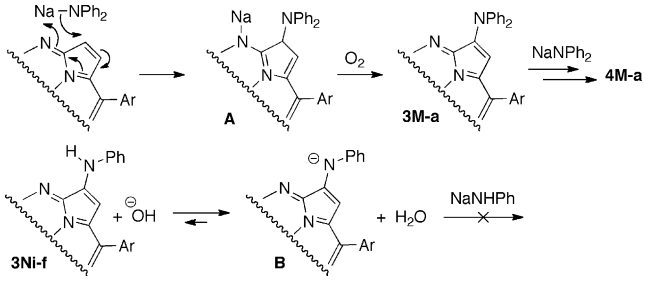
All aforementioned reactions were conducted under N_2 flow or in a capped flask under atmospheric pressure. When the same reaction of **1Ni** with $HNPh_2$/NaOH/MS3A was conducted under strictly deaerated conditions, only **3Ni-a** was obtained in low to moderate yield with recovery of the remaining **1Ni** (see Figure S1 in the Supporting Information). This result implied that an adequate amount of molecular oxygen was necessary to promote multiamination. We propose the following reaction mechanism for this amination (Scheme 2): Sodium diphenylamide is initially generated by deprotonation of $HNPh_2$ by NaOH in the presence of MS3A[12] and then undergoes nucleophilic addition to the pyrrolic β-carbon atom of **1Ni**, which has a relatively large orbital coefficient in the LUMO.[13] Oxidative aromatization of the resulting intermediate **A** by atmospheric dioxygen generates **3Ni-a** as the initial product. Further amination–oxidation reactions of **3Ni-a** occur in a stepwise manner to

Table 1: Amination reactions of **1M**.[a]



Entry	MDAP	Amine (HNR^1R^2)	Base	Method	Product (yield [%])
1	**1Ni**	pyrazole	Cs_2CO_3	A	**4Ni-b** (87)
2	**1Ni**	pyrazole[b]	Cs_2CO_3	A	**4Ni-b** (67)[c]
3	**1Ni**	imidazole	Cs_2CO_3	A	**4Ni-c** (54)
4	**1Ni**	$HNPh_2$	NaOH	B	**4Ni-a** (99)[c,d]
5	**1Ni**	$HNPh_2$	KOH	B	**4Ni-a** (98)[c]
6	**1Ni**	$HNPh_2$	Me_4NOH	B	**4Ni-a** (76)[c]
7	**1Ni**	pyrazole[e]	NaOH	B	**4Ni-b** (77)[c]
8	**1Ni**	HNMePh	NaOH	B	**4Ni-d** (52)
9	**1Ni**	carbazole	NaOH	B	**4Ni-e** (73)
10	**1Ni**	H_2NPh	NaOH	B	**3Ni-f** (64)
11	**1Ni**	$H_2NC_6H_4$-*p*-OMe	NaOH	B	**3Ni-g** (73)
12	**1Ni**	$H_2NC_6H_4$-*p*-CF_3[e]	NaOH	B	**3Ni-h** (78)
13	**1Cu**	$HNPh_2$	NaOH	B	**4Cu-a** (73)
14	**1Pd**	$HNPh_2$	NaOH	B	**4Pd-a** (55)
15	**1H$_2$**	pyrazole[b,f]	Cs_2CO_3	A	**4H$_2$-b** (40)

[a] Method A: amine (4 equiv), base (6 equiv), CuI (40 mol%), 120°C, 2.5 h. Method B: amine (50 equiv), base (40–50 equiv), MS3A, room temperature, 24–26 h. Yields are for the isolated product, unless otherwise noted. [b] The reaction was carried out without CuI. [c] The yield was determined by NMR spectroscopy. [d] The product was isolated in 70% yield. [e] Reaction time: 3 h. [f] Reaction time: 2 h. DMF = *N*,*N*-dimethylformamide.



Scheme 2. Plausible reaction mechanisms.

afford **4Ni-a** as the final product. In the reaction with aniline, the N–H group of product **3Ni-f** is deprotonated under the reaction conditions to generate amide **B**, which is unlikely to undergo subsequent nucleophilic attack owing to its anionic character. This proposed mechanism explains the selective formation of the singly substituted product **3Ni-f**. The generation of **B** was further confirmed by a trapping experiment with iodomethane (see Scheme S3). As mentioned above, the present amination probably involves the generation of an amide ion in a pre-equilibrium step. However, in the reaction of **1Ni** with diisopropylamine ($pK_a = 36$ in THF),[14] an effective amide concentration was not achieved by treatment with NaOH in DMF.

Figure 1 shows the X-ray crystal structures of **4Ni-a** and **4H$_2$-b**. In **4Ni-a**, the DAP ring was slightly ruffled owing to steric repulsion between the β-diphenylamino groups. This steric effect was also reflected in the relatively large torsion angles at the peripheral C(β)–N(amino) bonds (see Table S1 in the Supporting Information). The average C(β)–N(amino) bond length (1.395 Å) was shorter than the average C(Ph)–N(amino) bond length (1.419 Å), thus suggesting that the lone pair of the amino nitrogen atom could conjugate with the DAP π-electron system. In **4H$_2$-b**, the four pyrazole rings were almost coplanar with the DAP ring with dihedral angles of 11.5–25.9°. The average C(β)–N(amino) bond length (1.396 Å) was very close to that of **4Ni-a**.

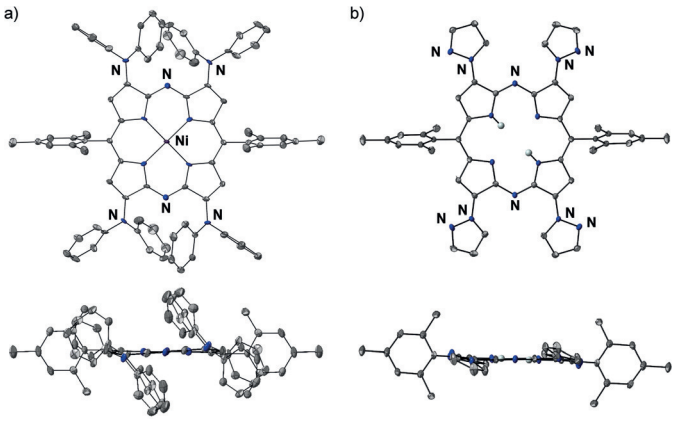


Figure 1. ORTEP diagrams (50% probability ellipsoids) of a) **4Ni-a** (CCDC 1813299) and b) **4H$_2$-b** (CCDC 1813302). Hydrogen atoms, except in NH groups (for **4H$_2$-b**), are omitted for clarity.

We measured the UV/Vis absorption spectra of **1M**, **3M**, and **4M** in CH_2Cl_2 (Figure 2; see also Figure S4 and a summary of their absorption maxima (λ_{max}) in Table S2). The pyrazolyl-substituted derivative **4Ni-b** showed a Q band at $\lambda_{max} =$

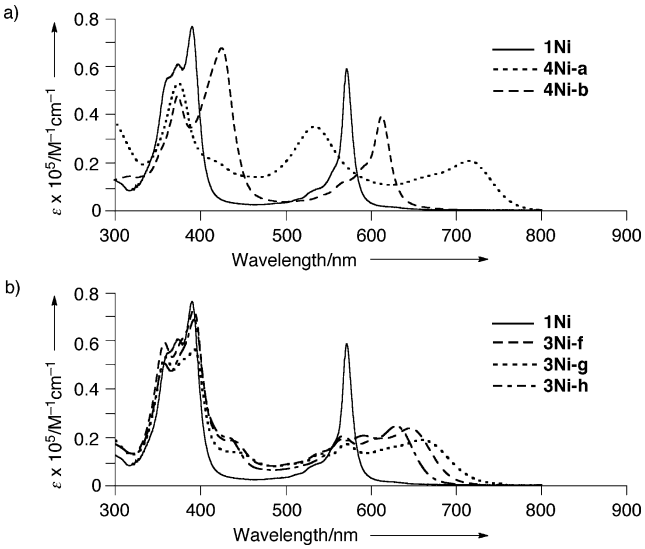


Figure 2. UV/Vis absorption spectra of a) **1Ni**, **4Ni-a**, and **4Ni-b** and b) **1Ni**, **3Ni-f**, **3Ni-g**, and **3Ni-h** in CH_2Cl_2.

615 nm, which was red-shifted as compared to that of **1Ni** ($\lambda_{max} = 571$ nm), whereas the Ph_2N-substituted derivative **4Ni-a** displayed two absorption bands at $\lambda_{max} = 537$ and 718 nm, with the longer-wavelength band extending into the NIR region. The *para* substituents on the *N*-phenyl group of **3Ni** had a major impact on the λ_{max} values, with electron-donating groups causing a red shift of the Q band.

To understand the effect of β substituents on the HOMO and LUMO energy levels of the DAP π-electron system, we measured the redox potentials of **3M** and **4M** and performed density functional theory (DFT) calculations on two models, **4Ni-am** and **4Ni-bm** (see Figures S5–S9 and Tables S3 and S4). Substitution with four 1-pyrazolyl groups caused a moderate positive shift in the first reduction potential ($\Delta E_{ox} = +0.06$ V, $\Delta E_{red} = +0.26$ V, **4Ni-b** vs. **1Ni**), whereas substitution with four NPh_2 groups caused a significant negative shift in the first oxidation potential ($\Delta E_{ox} = -0.72$ V, $\Delta E_{red} = -0.17$ V; **4Ni-a** vs. **1Ni**); the LUMO of **4Ni-b** was largely stabilized, whereas the HOMO of **4Ni-a** was largely destabilized as compared to the corresponding orbitals of **1Ni**. These properties were supported by the DFT calculations for **4Ni-am** and **4Ni-bm**. The different substituent effects on the LUMO were also reflected in the different amination reaction times of 24 h for $HNPh_2$ and 3 h for pyrazole (Table 1, entries 4 and 7, respectively). Therefore, the electrophilicity of the DAP π-system was gradually enhanced as the number of electron-withdrawing 1-pyrazolyl groups at the periphery increased. The failure of the porphyrin counterpart to undergo direct amination was rationalized by considering its relatively high LUMO level ($E_{red} = -1.77$ V vs. Fc/Fc^+),[15] which reflected its low electrophilicity. In the series of 3-amino-NiDAPs **3Ni**, *para*-substituent effects mainly emerged

in the HOMO levels. On the basis of time-dependent (TD) DFT calculations for **4Ni-am**, the two absorption bands at $\lambda_{max} = 718$ and 537 nm observed for **4Ni-a** were attributed to HOMO-to-LUMO and HOMO−1-to-LUMO electronic transitions, respectively. The HOMO of **4Ni-am** was somewhat localized on the NPh_2 groups (see Figure S8). Therefore, the lowest excitation seemed to have CT character from the amine center (donor) to the DAP ring (acceptor), as observed for related amino-DAP derivatives **P1**.

Finally, we examined the $^1O_2$-generation ability of palladium(II) complex **4Pd-a**. Irradiation of a toluene solution containing **4Pd-a** and 1,3-diphenylisobenzofuran (DPBF; a $^1O_2$ quencher) using a xenon lamp through a band-path filter ($\lambda_{ex} = 540$ and 720 nm) caused a decrease in the amount of DPBF, which was monitored by UV/vis absorption spectroscopy (for details, see the Supporting Information and Table S5).[16] The chemically determined quantum yields for $^1O_2$ generation (Φ) were 96–99%, which were higher than those reported for 3,7,13,17-tetramethyl-2,8,12,18-tetrahexyl-ZnDAP ($\Phi = 94\%$).[17]

In summary, we have established a convenient method for the direct amination of DAPs with primary and secondary amines under mild conditions. Our method requires only NaOH, MS3A, DMF, and an adequate amount of dioxygen to ensure complete regioselectively at the 3- or 3,7,13,17-positions of the DAP ring, and affords the corresponding amino-DAPs in good yields. This unprecedented reactivity of DAPs can be primarily attributed to their low-lying LUMO. The observed results strongly support the proposed mechanism of nucleophilic addition of the amide ion to the β-carbon atom and subsequent oxidative rearomatization to the 18π DAP ring. 3,7,13,17-Tetrakis(diphenylamino)-DAP exhibited high light absorptivity, and its palladium(II) complex generated $^1O_2$ under irradiation with long-wavelength visible or NIR light. The present study provides not only valuable information about the molecular design of NIR-responsive DAP-based dyes, but also a new synthetic protocol for direct C–N bond-forming reactions of electron-deficient aromatic compounds with various amines.

Acknowledgements

This research was supported by JSPS KAKENHI (15K13762 to Y.M., 15K05392 to H.N.), a Research Fellowship (16J07131 to S.O.) from MEXT, Japan, and the Program for the Strategic Research Foundation at Private Universities (S1311027 to M.M.) of MEXT.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amination · C–H activation · diazaporphyrins · dyes/pigments · porphyrinoids

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 3797–3800
Angew. Chem. **2018**, *130*, 3859–3862

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Manuscript received: January 12, 2018
Accepted manuscript online: February 2, 2018
Version of record online: March 1, 2018

