

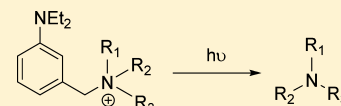
Photochemical Cleavage of Benzylic C–N Bond To Release Amines

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S Supporting Information

ABSTRACT: The 3-(diethylamino)benzyl (DEABn) group has been studied for releasing primary, secondary, and tertiary amines by direct photochemical breaking of the benzylic C–N bond. While photochemical release of primary and secondary amines provides high yields in methanol, release of tertiary amines in MeCN/water can improve yields and reduce the undesired dealkylation side reaction.



INTRODUCTION

Photochemical removal of protecting groups utilizes light as a traceless reagent in the chemical process. This approach is attractive to a wide range of research areas due to the unique advantages it offers.^{1–11} Growing interest in using photolabile protecting groups (PPG) in basic and applied research has generated an increasing demand for more PPGs to complement existing ones. The past several decades have witnessed tremendous efforts in developing new PPGs and creative applications of PPGs. Despite the progress, efficient, fast, and direct release of amines remains challenging.¹ There are only a few examples of directly releasing amines photochemically, for instance, from phenacyl anilinium salts,^{12–14} or in the photochemical reaction of generating *o*-quinone methides.^{15,16}

We have recently demonstrated that the 3-(dimethylamino)-trityl (DMATr) aminium salts release simple primary amines in both organic and aqueous solutions.¹⁷ Most recently, Literak, Klan, and co-workers have conducted detailed studies on release of various primary, secondary, and tertiary amines from their corresponding 4-hydroxyphenacyl (pHP) aminium salts in aqueous solutions.¹⁸ The pH of irradiated solutions plays a pivotal role in the amine-release process from pHP. While the pHP group is effective for elementary primary and secondary aliphatic amines at or below physiological pH, release of tertiary amines seems to be problematic.

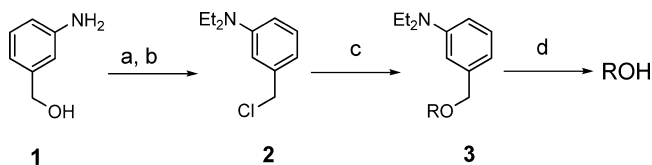
We have recently reported that the 3-(diethylamino)benzyl group (DEABn),¹⁹ which was designed on the basis of the excited state meta effect,^{20–23} released various alcohols (including primary, secondary, and tertiary alcohols) efficiently in high chemical yields (Scheme 1). Thus, starting with commercially available 3-aminobenzyl alcohol **1**, it takes two

steps to synthesize the PPG reagent **2** (DEABn-Cl). Its reaction with alcohol ROH results in the corresponding ether **3** ($\epsilon_{308 \text{ nm}}(\text{MeCN}) = 2900 \text{ M}^{-1} \text{ cm}^{-1}$) in high yields. UV irradiation can release primary, secondary, and tertiary alcohols from DEABn protection in high chemical and photochemical efficiencies. The DEABn PPG differs from the known 3,5-dimethoxybenzyl (DMBn) PPG, which was also based on the meta effect.²⁴ The latter is known for only releasing good leaving groups such as carboxylate, carbonate, and carbamate. Herein, we demonstrate a new photochemical reaction of DEABn that can release amines (including primary, secondary, and tertiary amines) effectively.

RESULTS AND DISCUSSION

With the PPG reagent (diethylamino)benzyl chloride (DEABn-Cl, **2**), the PPG was installed onto the primary and secondary amines (**4a–e**) under mild conditions to provide the caged amine **5a–e** (Table 1). For primary and secondary amines, the release of amines can take place in methanol. For example, irradiation of **5a** in CD₃OD for 8 min led to **4a** being released in 30% yield along with 56% unreacted **5a**.²⁵ Irradiation for 15 min resulted in a complex mixture; the amine **4a** was released in a lower yield along with some unidentified byproducts in spite of the increased conversion of **5a** to 73%. The photoreaction of **5a** in other solvents (such as acetonitrile, acetonitrile/water, and DMSO) did not produce better results than in methanol. However, we noticed that there was a difference in the reaction efficiency in deuterium solvent and in protium solvent. While the conversion of **5a** in CD₃OD was 73%, it increased to 90% in CH₃OH under the same irradiation conditions. This solvent isotope effect suggests that photochemical cleavage of the C–N bond is probably facilitated by stabilizing the partially negative charge developed at the nitrogen atom through hydrogen bonding with solvent molecules in the transition state. Based on this hypothesis, we infer that addition of a protonic acid should facilitate photocleavage of the C–N bond by converting the poor amide leaving group into a better amine leaving group through protonation.

Scheme 1. New Bn-Type PPG-Releasing Alcohols^a

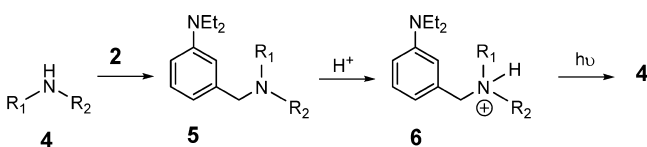


^aReagents and conditions: (a) Na₂HPO₄, EtI, 69%; (b) SOCl₂, 98%; (c) NaH, Bu₄NI, ROH, 86–98%; (d) *hν*, 81–98%.

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Table 1. Photochemical Cleavage of C–N Bond To Release Primary and Secondary Amines

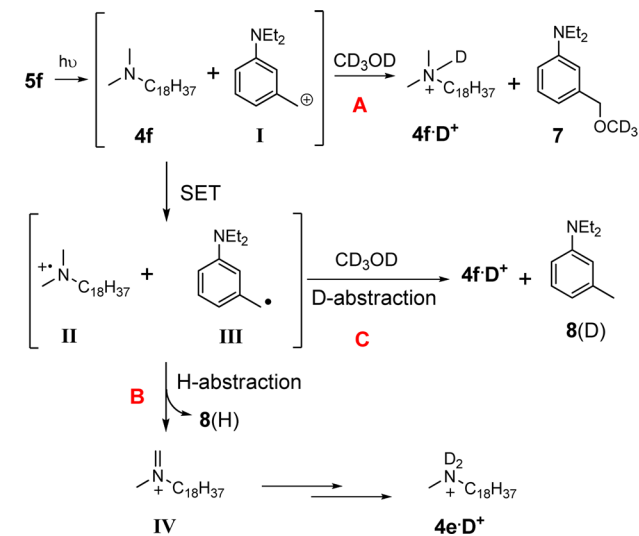
entry	Amine (4)	yield of 5 (%) ^a	yield of released 4 (%) ^c
1	NH ₂ (CH ₂) ₁₈ H (4a)	62 ^b	81 ^d
2	(4b)	66	98 ^d 94 ^{e,f}
3	(4c)	95	90 ^d 96 ^e
4	C ₈ H ₁₇ -N(C ₈ H ₁₇) (4d)	88	75 ^d (70 ^g)
5	(4e)	92	72 ^d

^aThe amine **4**, PPG reagent **2**, NaI, and K₂CO₃ in acetone at 40–50 °C. ^bThe amine **4a**, PPG reagent **2**, and Bu₄Ni in DCM/DMF at 35 °C. ^cA 5.0 mM solution in the presence of AcOH (6.0 equiv) in a specified solvent in 5 mm NMR tubes was irradiated for 15 min with a 450 W medium pressure mercury lamp equipped with a Pyrex filter sleeve ($\lambda > 300$ nm) without deaeration. The yields were determined by proton NMR with an internal standard, and isolated yields are in parentheses. ^dIn CD₃OD. ^eIn D₂O. ^f10.0 mM solution. ^gIn CH₃OH.

We examined photoreaction of **5a** (pK_a of the protonated amine ~ 10) in the presence of acetic acid ($pK_a = 4.76$).²⁵ With the amount of acetic acid increased from 1 to 6 equiv, complete conversion of **5a** was achieved in 15 min, and the yield of the released amine product increased from 66% to 81%. A further increase of the amount of acetic acid up to 30 equiv did not significantly change the yield of the released amine (i.e., 83%). With stronger acids such as trifluoroacetic acid (TFA, $pK_a = -0.25$), acid-enhanced amine releases were also observed with 1–10 equiv of TFA. However, with 30 equiv of TFA or 6 equiv of HCl ($pK_a = -8.0$), the amine-releasing process was significantly diminished, leading to the yield of the corresponding aminium of **4a** in only 42% and 8%, respectively. Presumably, protonation at the diethylamino group ($pK_a \sim 5$) suppresses the photocleavage of the benzylic C–N bond. In ¹H NMR analysis of the preirradiation reaction solution of **5**, downfield shifting of the benzylic methylene signal and the aromatic hydrogens is indicative of protonation at the respective aliphatic and aromatic amino group.

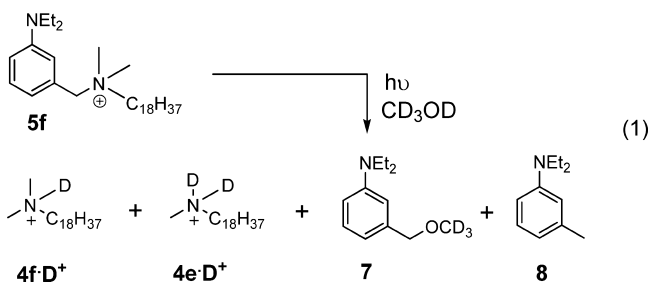
Similar acid-enhanced release of amines was confirmed with other protected primary and secondary amines (Table 1, entries 2–5). For example, **5b** ($\epsilon_{310\text{ nm(MeOH)}} = 2800\text{ M}^{-1}\text{ cm}^{-1}$), in the presence of acetic acid (6 equiv) released the aminium salt of 1-adamantanamine cleanly in 98% yield in CD₃OD ($\Phi = 0.14$) (Table 1, entry 2). The aminium salts of secondary amines **4c–e** were also released in good yields under the same acidic conditions (Table 1, entries 3–5). For example, **5d** ($\epsilon_{310\text{ nm(MeOH)}} = 2400\text{ M}^{-1}\text{ cm}^{-1}$) released the salt of di-*n*-octylamine (**4d**) in 75% yield in CD₃OD ($\Phi = 0.09$). In a run in the presence of acetic acid (6 equiv) in CH₃OH, the

secondary amine **4d** was isolated in 70% yield (after derivatizing with FmocCl to facilitate separation). The relatively higher yield of **4b** (compared with other amines) can probably be attributed to the lack of a geminal hydrogen at C-1, which might prevent potential SET-originated side reactions of amines under the irradiation conditions (for the mechanism, see Scheme 2, pathway B). It is noteworthy that the yield of

Scheme 2. Mechanism of Photolysis of 5f

releasing amines can be further improved in deaerated solutions, especially for the reactions carried out in the absence of protonic acid. However, control experiments showed that oxygen did not play a role in influencing the yield of releasing alcohols and acids from their DEABn protection, which suggests that oxygen probably enhances undesired photo-oxidation of amines. Photochemical release of protonated amines **5** from their 3-(diethylamino)benzyl aminium salts can also take place in a water solution. For example, the aminium salt **6b**, prepared from **5b** and 1 equiv of DCl dissolved in D₂O (10.0 mM) and irradiated for 30 min, led to the corresponding deuterated aminium salt of **4b** in 94% yield.²⁵ The aminium salt **6c** (5.0 mM in D₂O), prepared in the same manner, led to the corresponding deuterated aminium salt of **4c** in 96% yield upon 30 min of irradiation.²⁵

For the tertiary amines, the same method was used to install the DEABn group, and high yields were obtained, i.e., 88% from *N,N*-dimethyloctadecylamine (**4f**) to **5f** and 93% from triethylamine (**4g**) to its aminium salt **5g**. The photoreaction conditions are different from releasing primary and secondary amines. Thus, without using a protonic acid, irradiation of **5f** ($\epsilon_{320\text{ nm(MeOH)}} = 1600\text{ M}^{-1}\text{ cm}^{-1}$) in CD₃OD for 8 min released **4f·D⁺** in 67% yield along with the demethylated byproduct **4e·D⁺** in 26% yield (eq 1 and Table 2, entry 1). The PPG part was converted mainly into the ether **7** (29%) and the reduced product **8** (40%). With 15 min of irradiation in CD₃OD, the yields of **4f·D⁺** and **4e·D⁺** changed to 62% and 33%, respectively (Table 2, entry 2). Switching solvents to CH₃OH did not affect product distribution significantly. Irradiation of **5f** in CH₃OH for 15 min released **4f·H⁺** and **4e·H⁺** in 62% and 30% yield, respectively (Table 2, entry 3). The yields were confirmed by the isolated yields of **4f** and **4e** (as its Fmoc derivative) in 63% and 30%, respectively (Table 2,

Table 2. Photoreaction of **5f** in Methanol

salt	solvent	irradiation time ^a (min)	yield of 4f ^b (%)	yield of 4e ^b (%)	
1	5f	CD ₃ OD	8	67	26
2	5f	CD ₃ OD	15	62	33
3	5f	CH ₃ OH	15	62 (63) ^c	30 (30) ^d

^a5.0 mM irradiated in 5 mm NMR tubes with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve without deaeration. The yields were determined by proton NMR with an internal standard, and isolated yields are in parentheses. ^bReleased as the corresponding aminium. ^cIsolated as **4f**. ^dIsolated as the Fmoc derivative.

entry 3). The structure of **8** was confirmed by comparison with the authentic sample (see the [Experimental Section](#)).

Contrary to the high yields obtained with primary and secondary amines in water solution, irradiation of **5f** and **5g** (5 mM in D₂O) was less efficient (Table 3). For example,

Table 3. Photochemistry of **5g** in Water

	9	4g·D⁺	10	11	12	
	5g (%)	9 (%)	4g·D⁺ (%)	10 (%)	11 (%)	12 (%)
10 min	55	24	32	12	7	4
20 min	21	35	56	20	11	9
30 min	8	39	67	23	14	10

irradiation of **5g** for 10, 20, and 30 min led to **4g·D⁺** in 32%, 56%, and 67% yield, respectively, along with the aminium salt of diethylamine (**10**) in 12%, 20%, and 23%, respectively (Table 3). Acetaldehyde (**11**) was also observed in 7% yield at 10 min increasing to 14% yield at 30 min, along with its hydrate (**12**) increasing from 4% at 10 min to 10% at 30 min. In this reaction, the compound **8** was observed along with other unrecognized products originating from the PPG moiety.

For the photoreaction of the caged tertiary amines (exemplified with **5f**), we postulated that the initial step would lead to the C–N bond cleavage and formation of the desired tertiary amine **4f** and the PPG benzylic cation **I** (Scheme 2). There could be multiple possible photochemical and thermal reaction pathways starting from the pair of **4f** and **I** under the reaction conditions. For example, quenching of **I**

with methanol would result in the ether **7**. The released deuteron would deuteronate **4f** to provide the salt **4f·D⁺** (pathway A). A competing process would likely involve electron transfer between **4f** and the benzylic cation **I** to produce the radical cation **II** and the benzyl free radical **III**. The intermediate **II** could also be formed through SET between **4f** and molecular oxygen under the irradiation reaction conditions. Starting from here, the reaction pathway could be further diverted into two directions (i.e., pathway B and C), depending the reaction conditions such as the solvent. Pathway B would involve hydrogen abstraction of **III** from **II**, leading to formation of the reduced product **8** and the iminium intermediate **IV**. Solvolysis of **IV** would eventually generate the dealkylated product **4e·D⁺**. Pathway C would involve deuterium abstraction from the solvent by both **II** and **III** separately, leading to **4f·D⁺** and **8**, respectively.

Formation of an iminium intermediate and thus converting a tertiary amine to the corresponding secondary amine is known in the literature.^{26–33} A recent example is the observation of diethylamine and acetaldehyde formation in the release of triethylamine from its 4-hydroxyphenylacetaminium salt in aqueous solutions.¹⁸ A mechanism involving UV-initiated SET from the tertiary amine to the PPG moiety followed by a subsequent reaction sequence similar to the pathway B postulated in Scheme 2 might also operate.

Based on this working mechanism, we inferred that by using a solvent with better hydrogen-donating ability than methanol pathway C would be enhanced, improving release of the tertiary amine and minimizing production of the secondary amine byproduct. Thus, we anticipated that switching solvent from methanol (DE_{C–H} = 92 kcal/mol) to acetonitrile (DE_{C–H} = 86 kcal/mol)³⁴ would improve the ratio of product to byproduct. Indeed, the photoreaction of **5f** in MeCN/water became more chemically efficient with fewer byproducts. Irradiation of **5f** in CD₃CN/D₂O (9:1) for 15 min led to **4f·D⁺** in 83% yield (Φ = 0.18) along with the reduced production of **4e·D⁺** in 12% yield (Table 4, entry 1). In a larger scale run, irradiation of **5f** under

Table 4. Photoreaction of **5f** and **5g** in Different Solvents

salt	solvent	irradiation time ^a (min)	yield of 3° amine ^b (%)	yield of 2° amine ^b (%)
1	5f CD ₃ CN/D ₂ O (9:1)	15	83	12
2	5f CH ₃ CN/H ₂ O (9:1)	15	85 ^c	ND ^d
3	5f CD ₃ CN	15	80	0
4	5g CD ₃ CN/D ₂ O (9:1)	15	91	ND ^d

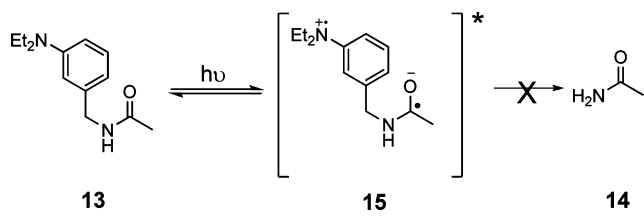
^a5.0 mM irradiated in 5 mm NMR tubes with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve without deaeration. The yields were determined by proton NMR with an internal standard, and isolated yields are in parentheses. ^bReleased as the corresponding aminium. ^cIsolated as **4f**. ^dND = not determined.

the same conditions in CH₃CN/H₂O (9:1) led to **4f** in 85% isolated yield (Table 4, entry 2).³⁵ In pure acetonitrile, the yield of **4f·D⁺** was 80%, while the formation of the **4e·D⁺** was completely eliminated (Table 4, entry 3); the main product derived from the PPG portion was the *N*-[(3-(diethylamino)phenyl)methyl]acetamide in 30% yield. The high yield of tertiary amine product in MeCN/water was then confirmed with the reaction of **5g** CD₃CN/D₂O (9:1); the triethylamine salt was released in 91% yield (Table 4, entry 4). As expected,

the solvent isotope effect was not significant, and the presence of 6 equiv of acetic acid in the solution of **5f** did not change the reaction yields. These results suggest that addition of acid to **5a–e** probably facilitates photocleavage of the C–N by converting the amino group into a good leaving group instead of preventing the SET-related side reactions of the released amine.

It is also worth noting that the PPG-incorporated acetamide **13** is photochemically stable under the irradiation conditions. Despite the fact that the acetamide **14** is a better leaving group than amine, there was no perceptible reaction detected by ¹H NMR analysis in the reaction solution of pure **13** irradiated in methanol or MeCN/water with or without the presence of acetic acid (1–30 equiv) (Scheme 3). Presumably, with the

Scheme 3. Photochemical Inertness of Acetamide



carbonyl group's presence, a SET process between the aromatic amino group and the carbonyl and the subsequent decay of the intermediate **15** back to **13** serves as an effective internal filtering process (Scheme 3). This hypothesis is in agreement with our previous observations that release of an acid from DEABn protection is less efficient than release of an alcohol. In releasing acid, a similar SET process might also be operative.^{36,37}

In summary, we demonstrated that the DEABn PPG can effectively release primary, secondary, and tertiary amines by direct breaking of C–N bond photochemically. While photochemical release of primary and secondary amines provide high yields in methanol, release of tertiary amines in MeCN/water can improve yields and reduce the undesired dealkylation side reaction.

EXPERIMENTAL SECTION

General Methods. Organic solutions were concentrated by rotary evaporation at ca. 12 Torr. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using glass plates precoated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Infrared (IR) data are presented as frequency of absorption (cm⁻¹). Proton and carbon-13 nuclear magnetic resonance (¹H NMR or ¹³C NMR) spectra were recorded on 300, 400, and 700 MHz NMR spectrometers; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl₃; δ 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constants in hertz (Hz), integration. HRMS was conducted with an ESI ionization method and with a TOF mass analyzer.

Materials. Anhydrous solvents tetrahydrofuran (THF), dimethylformamide (DMF), and dichloromethane (DCM) were used without distillation. Solvents for workup and column chromatography, such as petroleum ether (PE), ethyl acetate (EA), methanol (MeOH), and triethylamine (TEA), and other chemicals were obtained from commercial vendors and used without further purification.

N,N-Diethyl-3-((octadecylamino)methyl)aniline (5a). To the solution of 3-(N,N-diethylamino)benzyl chloride **2** (0.1 g, 0.507 mmol) and octadecan-1-amine **4a** (0.82 g, 3.04 mmol) in DCM/DMF (2 mL:0.5 mL) was added tetrabutylammonium iodide (56 mg, 0.151 mmol). The mixture was stirred at 35 °C for 4 days. The reaction mixture was then concentrated, and the residue was purified with flash column chromatography (from DCM/EtOAc 1:1 to EtOAc) to provide **5a** (136 mg, 62%) as a yellow oil: *R*_f 0.4 (DCM/MeOH/Et₃N 1:1:0.01); ¹H NMR (300 MHz, CDCl₃) δ 7.16 (t, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 6.60–6.55 (m, 2H), 3.72 (s, 2H), 3.34 (q, *J* = 7.0 Hz, 4H), 2.63 (t, *J* = 7.2 Hz, 2H), 1.55–1.45 (m, 1H), 1.25 (m, 32H), 1.15 (t, *J* = 7.0 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.1, 141.8, 129.3, 115.4, 111.7, 110.6, 54.8, 49.7, 44.4, 32.0, 30.3, 29.8, 29.7, 29.5, 27.5, 22.8, 14.2, 12.7; IR (neat) 2921, 2851, 1601, 1580, 1496, 1456, 1394, 1374, 1355, 1270, 1199, 1176, 1145, 1118, 1094, 1076, 1024, 989, 909, 849, 768, 732, 693, 434; HRMS (ESI) *m/z* calcd for C₂₉H₅₃N₂ (M + H) 431.4365, found 431.4367.

N-(3-Aminobenzyl)adamantan-1-amine (5b). To the solution of **2** (0.5 g, 2.5 mmol) and 1-adamantanamine **4b** (0.383 g, 2.5 mmol) in acetone were added NaI (95 mg, 0.63 mmol) and potassium carbonate (0.42 g, 3.04 mmol). The mixture was stirred at 45 °C for 24 h and was then concentrated. The residue was purified with flash column chromatography (PE/EA 7:3 to EA) to provide **5b** (0.52 g, 66%) as a colorless liquid: *R*_f = 0.45 (DCM/MeOH/Et₃N 1:1:0.01); ¹H NMR (300 MHz, CDCl₃) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.65–6.53 (m, 3H), 3.70 (s, 2H), 3.33 (q, *J* = 7.0 Hz, 4H), 2.08 (m, 3H), 1.72–1.602 (m, 13H), 1.14 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 147.9, 142.4, 129.3, 115.4, 111.9, 110.4, 50.9, 45.7, 44.2, 42.7, 36.7, 29.6, 12.6; IR (neat) 2967, 2902, 2846, 1601, 1579; HRMS (ESI) *m/z* calcd for C₂₁H₃₃N₂ (M + H) 313.2644, found 313.2640.

3-((4-Benzylpiperidin-1-yl)methyl)-N,N-diethylaniline (5c). To the solution of **2** (0.3 g, 1.52 mmol) and 4-benzylpiperidine **4c** (0.266 g, 1.52 mmol) in acetone were added NaI (57 mg, 0.38 mmol) and potassium carbonate (0.210 g, 1.52 mmol). The reaction mixture was stirred at 40 °C for 24 h and then concentrated. The residue was purified by flash column chromatography (PE/EA 8:1 to 1:1) to provide **5c** as a colorless liquid (0.487 g, 95%): *R*_f = 0.5 (DCM/MeOH/Et₃N 1:1:0.01); ¹H NMR (300 MHz, CDCl₃) δ 7.28–7.24 (m, 2H), 7.19–7.10 (m, 4H), 6.62–6.54 (m, 3H), 3.42 (s, 2H), 3.32 (q, *J* = 7.0 Hz, 4H), 2.90–2.86 (m, 2H), 2.51 (d, *J* = 6.8 Hz, 2H), 1.88 (td, *J* = 2.2, 11.6 Hz, 2H), 1.62–1.60 (m, 2H), 1.60–1.45 (m, 1H), 1.35–1.28 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 147.7, 140.8, 139.4, 129.0, 128.8, 128.0, 125.6, 116.4, 112.6, 110.4, 63.9, 53.7, 44.3, 43.2, 37.2, 32.2, 12.5; IR (neat) 3025, 2967, 2920, 2846, 2795, 2750, 1600, 1579, 1494; HRMS (ESI) *m/z* calcd for C₂₃H₃₃N₂ (M + H) 337.2644, found 337.2642.

3-(Diocylamino)methyl)-N,N-diethylaniline (5d). To the solution of **2** (0.4 g, 2.03 mmol) and di-*n*-octylamine **4d** (0.4 g, 1.65 mmol) in acetone were added NaI (62 mg, 0.41 mmol) and potassium carbonate (0.229 g, 1.65 mmol). The mixture was stirred at 40 °C for 12 h and was then concentrated. The residue was purified with flash column chromatography (PE/EA 8:2) to provide **5d** (0.581 g, 88%) as a colorless liquid: *R*_f = 0.3; ¹H NMR (300 MHz, CDCl₃) δ 7.12 (t, *J* = 7.9 Hz, 1H), 6.71 (s, 1H), 6.59–6.53 (m, 2H), 3.49 (s, 2H), 3.33 (q, *J* = 7.0 Hz, 4H), 2.39 (t, *J* = 7.5 Hz, 4H), 1.45 (m, 4H), 1.25 (m, 20H), 1.15 (t, *J* = 6.9 Hz, 6H), 0.87 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 147.9, 141.4, 128.9, 116.3, 112.5, 110.5, 59.2, 54.0, 44.5, 32.0, 29.8, 29.5, 27.7, 27.3, 22.8, 14.2, 12.8; IR (neat) 2955, 2923, 2853, 2794, 1601, 1580, 1495; HRMS (ESI) *m/z* calcd for C₂₇H₅₁N₂ (M + H) 403.4052, found 403.4049.

N,N-Diethyl-3-((methyl(octadecyl)amino)methyl)aniline (5e). To the solution of **2** (0.25 g, 1.27 mmol) and *N*-methyl(octadecyl)amine **4e** (0.360 g, 1.27 mmol) in acetone were added NaI (47 mg, 0.317 mmol) and potassium carbonate (0.21 g, 1.52 mmol). The mixture was stirred at 50 °C for 24 h and was then concentrated. The residue was purified with flash column chromatography (PE/EA 7:3 to EA) to provide **5e** (0.514 g) as a colorless liquid: yield 92%; *R*_f = 0.56 (DCM/MeOH 9:1); ¹H NMR (300 MHz, CDCl₃) δ 7.14 (t, *J* = 7.9 Hz, 1H), 6.65–6.56 (m, 3H), 3.42 (s, 2H), 3.33 (q, *J* = 7.0 Hz, 4H), 2.34 (t, *J* =

7.6 Hz, 2H), 2.20 (s, 3H), 1.50 (m, 2H), 1.25 (m, 30H), 1.15 (t, $J = 7.0$ Hz, 6H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.8, 140.2, 128.9, 116.3, 112.5, 110.4, 62.9, 57.4, 44.2, 42.4, 31.9, 29.6, 29.3, 27.5, 22.6, 14.1, 12.6; IR (neat) 2921, 2851, 2784, 1601, 1580, 1495; HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{57}\text{N}_2$ ($\text{M} + \text{H}$) 445.4522, found 445.4517.

***N*-(3-(Diethylamino)benzyl)-*N,N*-dimethyloctadecan-1-aminium Chloride (5f).** To the solution of **2** (0.400 g, 2.0 mmol) and *N,N*-dimethyl-*n*-octadecylamine **4f** (0.725 g, 2.4 mmol) in acetone was added NaI (15 mg, 0.10 mmol). The mixture was stirred at 40 °C for 15 h and was then concentrated. The residue was purified with flash column chromatography (DCM/MeOH 9:1) to provide **5f** (0.910 g, 88%) as a colorless liquid: $R_f = 0.4$; ^1H NMR (300 MHz, CDCl_3) δ 7.22 (t, $J = 7.4$ Hz, 1H), 6.88 (s, 1H), 6.74–6.69 (m, 2H), 4.79 (s, 2H), 3.54–3.48 (m, 2H), 3.36 (q, $J = 7.0$ Hz, 4H), 3.33 (s, 6H), 1.80 (br, 2H), 1.34–1.25 (m, 30H), 1.16 (t, $J = 7.0$ Hz, 6H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.4, 130.1, 128.2, 119.2, 116.1, 113.6, 68.6, 63.9, 50.3, 44.5, 32.1, 29.82, 29.76, 29.70, 29.6, 29.5, 29.4, 26.5, 23.2, 22.8, 14.2; IR (neat) 3384, 3045, 3015, 2962, 2914, 2847, 1602, 1578, 1500; HRMS (ESI) m/z calcd for $\text{C}_{31}\text{H}_{59}\text{N}_2$ ($\text{M} - \text{Cl}$) 459.4678, found 459.4682.

***N*-(3-(diethylamino)benzyl)-*N,N*-diethylethanaminium chloride (5g).** To the solution of **2** (0.4 g, 2.03 mmol) and triethyl amine **4g** (1.69 mL, 12.1 mmol) in acetone was added NaI (15 mg, 0.10 mmol). The mixture was stirred at 50 °C for 4 days and was then concentrated. The residue was purified with flash column chromatography (PE/EA 7:3 to EA) to provide **5g** (0.567 g, 93%) as a colorless liquid: $R_f = 0.4$ (DCM/MeOH 9:1); ^1H NMR (300 MHz, CDCl_3) δ 7.20 (t, $J = 7.2$ Hz, 1H), 6.73–6.70 (m, 2H), 6.60 (d, $J = 7.6$ Hz, 1H), 4.52 (s, 2H), 3.44 (q, $J = 7.0$ Hz, 6H), 3.33 (q, $J = 7.1$ Hz, 4H), 1.46 (t, $J = 7.1$ Hz, 9H), 1.14 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.8, 129.8, 127.4, 117.9, 114.6, 113.1, 61.5, 52.4, 44.0, 12.1, 8.1; IR (neat) 3375, 2972, 1600, 1577, 1502, 1481; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{31}\text{N}_2$ (M^+) 263.2487, found 263.2486.

General Procedure for Photoreaction. Photoreaction in 5 mm NMR Tube in Deuterated Solvent. To a 5 mm NMR tubes was added 0.5 mL of the stock solution of **5** (5.0 mM) with a microsyringe. The proper amount of acid was then added. One NMR tube containing the solution was kept in the dark as a control. Another NMR tube was then bound to the immersion well condenser of the photoreactor. A 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve ($\lambda > 300$ nm) was used as the light source. After irradiation, an equal amount of the internal standard solution (such as mesitylene) was added to both the control tube and the reaction tube. The conversion and yields of the photoreaction were then determined by ^1H NMR analysis of the photoreaction samples and the control sample with the internal standard. For photoreactions under inert atmosphere, the reaction tube was bubbled argon for ~2 min through a long needle to exclude air.

Photoreaction in Nondeuterated Solvent. To a 5 mm NMR tube was added 0.5 mL of the stock solution of 3-((diethylamino)methyl)-*N,N*-diethylaniline (**5d**) (5.0 mM) with a microsyringe. The proper amount of acid was then added. One NMR tube containing the solution was kept in the dark as a control. Another NMR tube was then bound to the immersion well condenser of the photoreactor. A 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve ($\lambda > 300$ nm) was used as the light source. After UV irradiation, the reaction solution and the control were transferred separately to respective vials, and the solvent was removed under reduced pressure. The residue was redissolved in CDCl_3 and an equal amount of the internal standard solution (such as mesitylene) was added to both the reaction mixture and the control. The conversion and yields were calculated based on integration of mesitylene and the products.

Photolysis of 3-((Diethylamino)methyl)-*N,N*-diethylaniline (5d) in Methanol. The solution of **5d** (40 mg, 0.1 mmol) with acetic acid (34 μL , 0.6 mmol) in 20 mL of methanol was divided equally into 13 5 mm NMR tubes. The tubes were bound to the immersion well condenser of the photoreactor and irradiated for 15 min. After irradiation, the reaction solutions were combined and concentrated. The residue was then subject to the standard procedure in

acetonitrile/water (3:1) with Fmoc-Cl and sodium carbonate to provide the Fmoc-protected amine **5l** (32.8 mg, 70%) as a colorless oil after flash column (PE/EA 20:1) purification: ^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 7.5$ Hz, 2H), 7.57 (d, $J = 7.5$ Hz, 2H), 7.40–7.24 (m, 4H), 4.48 (d, $J = 6.3$ Hz, 2H), 4.22 (t, $J = 6.3$ Hz, 1H), 3.18 (t, $J = 7.5$ Hz, 2H), 3.02 (t, $J = 7.5$ Hz, 2H), 1.48 (m, 2H), 1.26–1.11 (m, 22H), 0.89–0.87 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.2, 144.4, 141.5, 127.6, 127.1, 124.9, 120.0, 66.7, 47.6, 47.3, 31.9, 29.5, 29.4, 28.8, 28.3, 27.0, 22.8, 14.2; IR (neat) 2954, 2923, 2854, 1697, 1464; HRMS (ESI) m/z calcd for $\text{C}_{31}\text{H}_{46}\text{NO}_2$ ($\text{M} + \text{H}$) 464.3529, found 464.3524.

Photolysis of *N*-(3-(Diethylamino)benzyl)-*N,N*-dimethyloctadecan-1-aminium Chloride (5f) in Methanol. The solution of **5f** (74 mg, 0.15 mmol) in 30 mL of methanol was divided equally into 20 5 mm NMR tubes. The tubes were bound to the immersion well condenser of the photoreactor and irradiated for 15 min. After irradiation, the reaction solutions were combined and concentrated. The residue was then subject to the standard procedure in acetonitrile/water (3:1) with Fmoc-Cl and sodium carbonate to convert the secondary amine **4e** to (9*H*-fluoren-9-yl)methyl methyl-(octadecyl)carbamate **52**. The reaction solution was then concentrated and purified with flash column (PE/EA 20:1) to provide **4f** (28.2 mg, 63%) and **52** (23.2 mg, 30%). For **52**: ^1H NMR (300 MHz, CDCl_3) δ 7.77 (d, $J = 7.4$ Hz, 2H), 7.62 (m, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.28 (t, $J = 7.3$ Hz, 2H), 4.48 (d, $J = 5.6$ Hz, 1H), 4.42 (d, $J = 6.7$ Hz, 1H), 4.25 (m, 1H), 3.30 (m, 1H), 3.12 (t, $J = 7.0$ Hz, 1H), 2.90 (d, $J = 10.7$ Hz, 3H), 1.06–1.63 (m), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.2, 144.2, 141.3, 127.5, 126.9, 125.0, 124.8, 119.9, 66.9, 48.9, 47.4, 34.5, 31.9, 29.7, 29.6, 29.4, 29.3, 27.8, 27.5, 26.7, 22.6, 14.1; IR (neat) 2922, 2852, 1704, 1478; HRMS (ESI) m/z calcd for $\text{C}_{34}\text{H}_{52}\text{NO}_2$ ($\text{M} + \text{H}$) 506.3998, found 506.3994. For *N,N*-diethyl-3-(methoxymethyl)aniline (**7**): ^1H NMR (300 MHz, CDCl_3) δ 7.18 (t, $J = 7.5$ Hz, 1H), 6.65–6.59 (m, 3H), 4.40 (s, 2H), 3.39–3.32 (m, 7H), 1.15 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.2, 139.3, 129.4, 115.0, 111.4, 111.2, 75.4, 58.1, 44.4, 12.7; IR (cm^{-1}) 2969, 2926, 2870, 2818, 1601, 1580, 1496; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{20}\text{NO}$ ($\text{M} + \text{H}$) 194.1545, found 194.1544.

***N,N*-Diethyl-3-methylaniline (8).** To the ice–water bath cooled solution of LiAlH_4 (19 mg, 0.5 mmol) in 1.8 mL of dry THF was added **2** (40 mg, 0.2 mmol) in 0.2 mL of THF. The mixture was allowed to warm to room temperature and stir overnight and was then quenched with 19 μL of water, 38 μL of 10% NaOH (aq), and 57 μL of water. The crude product was concentrated and purified with flash column chromatography (PE/EA 25:1) to provide **8** (16 mg, 49%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.12 (t, $J = 7.1$ Hz, 1H), 6.53–6.47 (m, 3H), 3.35 (q, $J = 7.2$ Hz, 4H), 2.32 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.1, 139.0, 129.3, 116.5, 112.8, 109.3, 44.4, 22.1, 12.8; IR (neat) 3044, 2967, 2927, 2870, 1599, 1579, 1496, 1467; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{N}$ ($\text{M} + \text{H}$) 164.1439, found 164.1436.

Photolysis of *N*-(3-(Diethylamino)benzyl)-*N,N*-dimethyloctadecan-1-aminium Chloride (5f) in MeCN/H₂O. (A) The solution of **5f** (74 mg, 0.15 mmol) in 30 mL of MeCN/H₂O (9:1) was divided equally into 20 5 mm NMR tubes. The tubes were bound to the immersion well condenser of the photoreactor and irradiated for 15 min. After irradiation, the reaction solutions were combined, concentrated, and purified with flash column (PE/EA 20:1) to provide **4f** (38 mg, 85%). (B) The solution of **5f** (500 mg, 1.0 mmol) was dissolved in 250 mL of MeCN/H₂O (9:1) in a 250 mL photoreactor vessel. The reaction solution was irradiated for 60 min with stirring. After irradiation, the reaction solution was concentrated. To the residue were added MeCN/H₂O (90 mL, 3:1), Fmoc Cl (0.39 g, 1.5 mmol), and Na_2CO_3 (0.21 g, 2.0 mmol), and the reaction solution was stirred at room temperature for 19 h. The reaction mixture was then concentrated and purified with flash column chromatography (PE/EA 9:1 to DCM/MeOH 9:1) to provide **4f** (0.21 g, 70%).

Quantum Yield Determination. A 5.0 mM solution of phenylglyoxylic acid ($\text{CD}_3\text{CN}/\text{D}_2\text{O}$ 3:1) and a 5.0 mM solution of **5** in NMR tube were placed behind a standard 1 cm quartz UV cuvette containing the filter solution.³⁸ Filtered light centered at 312 nm was obtained by

passing light from the 450 W medium-pressure mercury lamp through a solution of 2.0 mM K_2CrO_4 in a 5% K_2CO_3 aqueous solution.^{39,40} The yields of photoreactions were determined by 1H NMR for every 15 min of irradiation.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00508.

1H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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performed. The yield was determined by 1H NMR spectroscopy analysis unless indicated otherwise.

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