

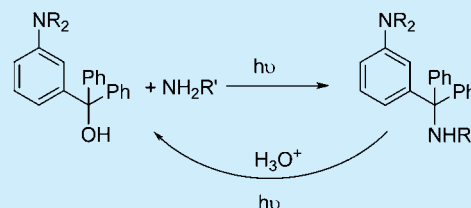
# Photochemical Formation and Cleavage of C–N Bond

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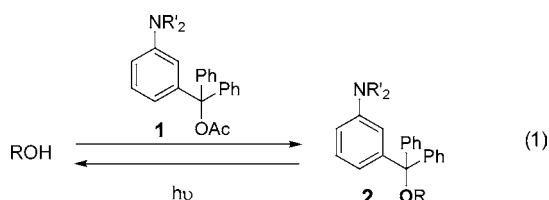
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**S** Supporting Information

**ABSTRACT:** A new photochemical method of C–N bond formation has been developed. A properly substituted trityl alcohol can cleave the benzylic C–O bond and replace it with a C–N bond which is stable under the irradiation conditions. The C–N bond can then be photochemically cleaved with the same light source when the nitrogen is protonated.



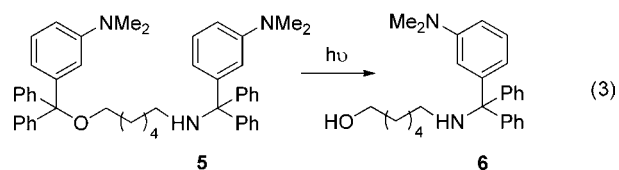
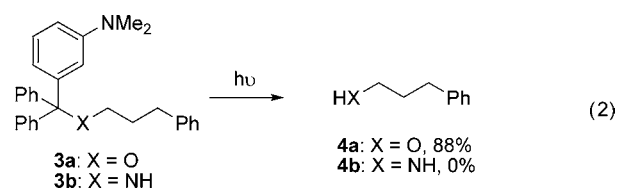
Light-promoted covalent bond formation and cleavage is appealing to many different research areas in that photoreactions can typically take place under mild conditions without using any chemical reagents and can be precisely controlled with a high spatial and temporal resolution. For instance, photochemical bond cleavage reactions have been utilized in developing various photolabile protecting groups (PPGs). PPGs are crucial to a broad spectrum of applications ranging from organic synthesis and dynamic studies in biology to polymer science, surface patterning, and photolithographic preparation of high density biochips.<sup>1–7</sup> On the basis of the excited state meta effect,<sup>8–11</sup> we have recently developed a series of salicyl alcohol-based carbonyl PPGs<sup>12–17</sup> and trityl alcohol-based hydroxyl PPGs (as in 2, eq 1).<sup>18–20</sup> For example,



we have demonstrated that 3-dimethylaminotriyl group (DMATr) protects both primary and secondary alcohols and photochemically releases alcohols in high yields with high photoefficiency.

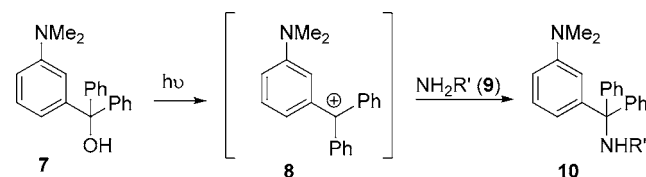
To expand the scope of structurally simple hydroxyl PPG DMATr, we examined its application in the protection of amino groups. First, we compared the photoreactions of 3a and 3b (eq 2). Under the same conditions, 3-phenyl-1-propanol (4a) was released in 88% yield from 3a (5.0 mM in CD<sub>3</sub>OD) after 8 min of irradiation while 3b was stable.<sup>21</sup> Irradiation of the compound 5 (3.0 mM in CH<sub>3</sub>OH) for 8 min resulted in removal of the DMATr group on the hydroxyl group to release the alcohol 6 in 73% of yield based on <sup>1</sup>H NMR analysis, consistent with the 72% isolated yield (eq 3).

These results suggest that the DMATr PPG on amino groups is photochemically inactive under the irradiation conditions for releasing alcohols. Thus, we hypothesize that irradiation of 7 would cleave the C–O bond, and the resulting tritylium



intermediate 8 could trap an amine (9) to form a photochemically inert covalent C–N bond in 10 (Scheme 1).

## Scheme 1. Photochemical C–N Bond Formation



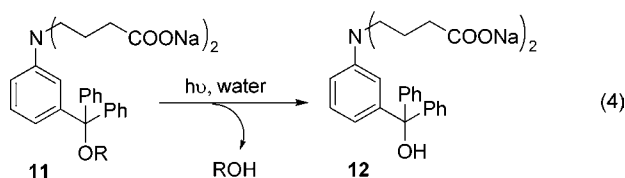
To assess this idea, we first examined the irradiation of 7 in the presence of *n*-butyl amine (9a).<sup>21</sup> The reaction of 7 (6.0 mM) produced the best results in methanol.<sup>22</sup> With 2 equiv of *n*-butyl amine in methanol, the yields of 10a (R' = *n*-butyl) increased from 24% for 15 min irradiation to 37% for 60 min irradiation. By increasing the amine to 13 equiv, 15 min irradiation led to a 65% yield of 10a. However, the reaction became less clean with increased irradiation time.

Encouraged by these results, we turned our attention to photochemical C–N bond construction in aqueous solution. It is known that release of ROH from protection of the water-soluble analog of DMATr, *i.e.*, release of ROH from 11, is clean

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and fast in aqueous solution (eq 4).<sup>20</sup> Recent Laser Flash Photolysis (LFP) studies by Wan et al. indicate that



photocleavage of the benzylic C–O bond of **11** occurs within a laser pulse of 29.6 ns;<sup>23</sup> we anticipated that cleavage of the C–O of **12** and the subsequent C–N bond formation will also be clean and fast in aqueous media.

We first irradiated **12** (10.0 mM in D<sub>2</sub>O) alone for 40 min without the presence of an amine, and no perceptible change in the <sup>1</sup>H NMR spectrum could be detected. However, in the presence of 2 equiv of *n*-butylamine (**9a**), irradiation for 20, 40, and 70 min led to **13a** in 59%, 53%, and 45% yield, respectively (Table 1, entry 1). By changing the ratio of **12/9a** to 2:1 ([**12**]

**Table 1. Photochemical C–N Bond Formation in Water**

entry	RNH <sub>2</sub>	[ <b>12</b> ]/mM	<b>12/9</b>	<b>13<sup>a,b</sup></b> 20 min	<b>13<sup>a,b</sup></b> 40 min	<b>13<sup>a,b</sup></b> 70 min
1	<b>9a</b>	10.0	1:2	59%	53%	45%
2	<b>9a</b>	10.0	2:1	45%	45%	40%
3	<b>9a</b>	20.0	1:2	62%	81%	75%
4	<b>9a</b>	20.0	2:1	67%	78%	72%
5	<b>9a</b>	20.0	5:1	60%	67%	59%
6	<b>9b</b>	20.0	1:2	–	68%	–
7	<b>9b</b>	20.0	2:1	–	81%	–
8	<b>9c</b>	20.0	1:2	–	63%	–
9	<b>9c</b>	20.0	2:1	–	74%	–

<sup>a</sup>Irradiation with a 450 W medium pressure mercury lamp without deaeration. <sup>b</sup>Yield determined by <sup>1</sup>H NMR analysis with an internal standard.

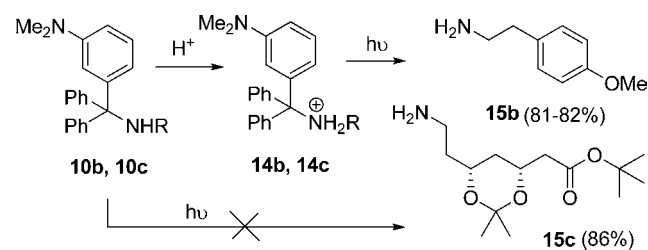
= 10.0 mM), the yield of **13a** formation after 20, 40, and 70 min of irradiation changed to 45%, 45%, and 40%, respectively (Table 1, entry 2). When a large excess of **9a** was used (*i.e.*, **12/9a** = 1:20), 20 min irradiation led to a 56% yield of **13a**, similar to the yield obtained with only 2 equiv of **9a**. A longer irradiation time did not improve the yield. By increasing the concentration of **12** to 20.0 mM, the yields of **13a** increased (Table 1, entries 3–5). It appeared that irradiation for 40 min produced the best results. Extension of the irradiation time after 40 min (Table 1, entries 1–5) or increasing the **12/9a** ratio to 5:1 ([**12**] = 20.0 mM) could not further improve the yield of **13a** (Table 1, entry 5). We then irradiated **12** (20.0 mM) for 40 min in the presence of sodium glycinate (**9b**) and Ac-L-Lys-NHMe (**9c**) (Table 1, entries 6–9). With the **12/9** ratio at 2:1, the corresponding **13b** and **13c** were obtained in 81% and 74%

yields, respectively (Table 1, entries 7 and 9), better than when using an excess of amine (Table 1, entries 6 and 8).

The photochemically stable benzylic C–N bond in **13** can actually be converted to a photolabile bond and cleaved photochemically with the same light source. For example, irradiation of **13a** (1.0 mM in D<sub>2</sub>O/CD<sub>3</sub>OD 4:1 or 5.0 mM in CD<sub>3</sub>OD) in the presence of 3 equiv of HCl cleanly cleaved the C–N bond and released **9a**. In control experiments, without irradiation, the acidified solution of **13a** remained unchanged at 40 °C even after 60 min.

Photocleavage of C–N was further confirmed with DMATr-protected amines (**10b** and **10c**, Scheme 2). Thus,

**Scheme 2. Photochemical Cleavage of C–N Bond<sup>21</sup>**



preirradiation treatment of **10b** with 1 equiv of TFA or HCl led to **14b** as clearly evidenced by <sup>1</sup>H NMR analysis. In the ammonium salt **14**, the C–N bond is thermally stable. Control experiments showed that the C–N bond in **10a** remained stable with an excess amount of HCl (5–160 equiv in methanol) at 40–55 °C without irradiation. Irradiation of **14b** for only 6 min resulted in release of the amine **15b** in 81% (with HCl) and 82% (with TFA) yield, respectively.<sup>24,25</sup>

In control experiments, irradiation of **10b** (5.0 mM in CD<sub>3</sub>OD) in the absence of any acids for 10 min did not show any perceptible release of 4-methoxyphenethylamine **15b**, in agreement with observations from the photoreactions of **3b** and **6** (eqs 2 and 3). In the presence of 1 equiv of HCl, the amine **15c** was released from **10c** in 86% yield and 6-amino-1-hexanol from **6** in 77% yield. Since only a stoichiometric amount of proton is needed to facilitate the C–N cleavage, the acidic conditions are mild enough to be compatible with the acid-sensitive protecting groups in **15c**.

In summary, we have developed a new photochemical C–N bond formation reaction. The new chemistry should be potentially useful in many research areas such as protein labeling and macromolecule cross-linking. Moreover, the photochemically formed C–N bond can be converted to a photolabile bond through protonation of the nitrogen and cleaved photochemically with the same light source.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full characterization, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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- (21) Irradiation with a 450 W medium pressure mercury lamp with a Pyrex filter sleeve in a Honovia photoreaction box without deaeration. The yield was determined by <sup>1</sup>H NMR spectroscopy analysis unless indicated otherwise.
- (22) A complex mixture was obtained when the same reaction was carried out in DMF, MeCN, THF, diethyl ether, or acetone. The reaction of **7** in pure 1-butylamine led to <10% conversion. In methanol, the reaction of **3a** with amine showed similar reactivity.
- (23) Wang, Y.-H.; Wan, P. Unpublished results.
- (24) With 1.2 equiv of acetic acid, the conversion of **10b** in the photoreaction was only 40%.
- (25) Without using HCl, irradiation of **10** (5 mM in CD<sub>3</sub>OD) with 0.5% of CHCl<sub>3</sub> (v/v) for 10 min also resulted in effective cleavage of the C–N bond. Presumably, HCl was generated in situ from methanol and chloroform upon irradiation. We examined several acid-promoted reactions by using light-generated acid from CHCl<sub>3</sub>/MeOH. For example, irradiation of 3,4-dihydro-2H-pyran (DHP) in methanol showed no sign of reaction; however, in the presence of chloroform, under the same irradiation conditions, DHP was converted to the corresponding THP-OMe. If irradiation was stopped before complete conversion of DHP and the reaction mixture was kept in the dark, the remaining DHP slowly converted to the THP-OMe product. Irradiation of CHCl<sub>3</sub>/MeOH first and then mixing with DHP in the dark also led to clean production of THP-OMe. In another example, the light-generated acid removed MMT<sup>r</sup> to release alcohol in excellent yields.