

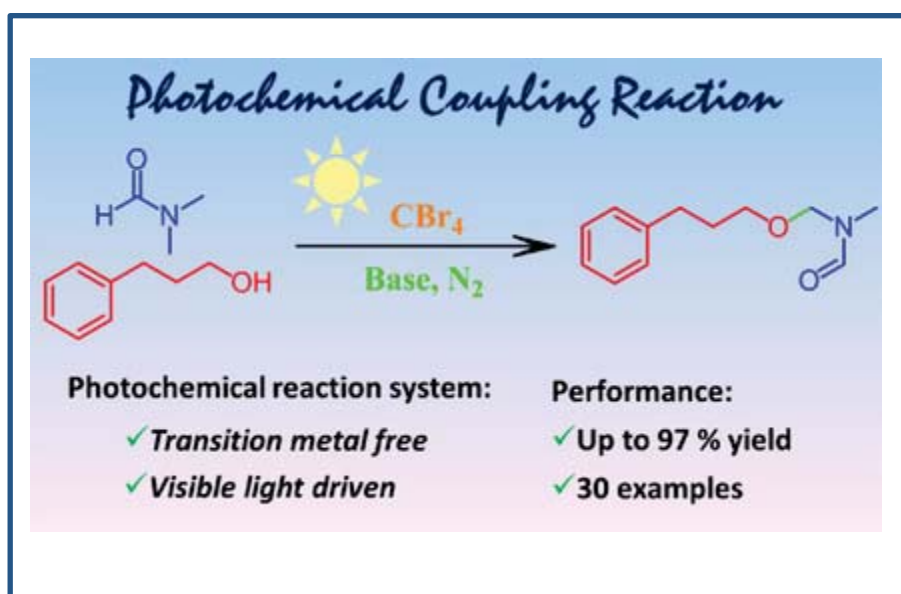


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## Visible-light-Driven Photochemical Activation of $sp^3$ C-H Bond for Hemiaminal Formation

Lina Li, Guigang Zhang, Aleksandr Savateev, Bogdan Kurpil, Markus Antonietti and Yubao Zhao



**A metal-free photochemical system** with carbon tetrabromide is developed for the synthesis of hemiaminal compounds. This photochemical conversion system shows high yield and broad substrate scope. The  $sp^3$  C-H bond of the N-alkyl group in the amide is photochemically activated, producing an ionic iminium species. The hemiaminal compounds are produced by nucleophilic attack of the iminium ion by alcohol in the presence of a base.

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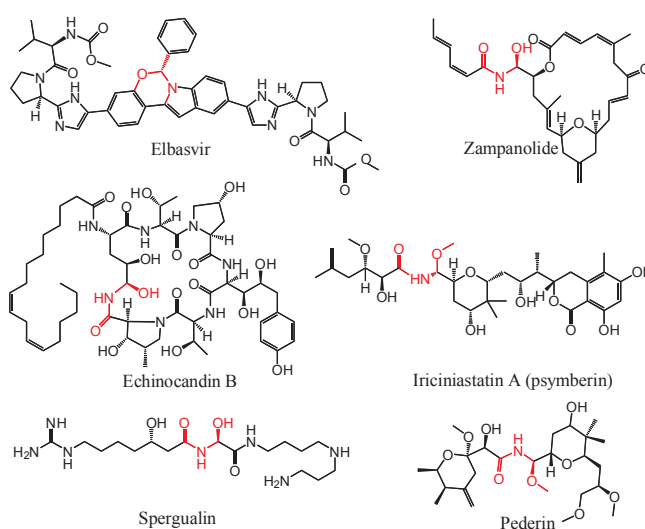
Lina Li, Guigang Zhang, Aleksandr Savateev, Bogdan Kurpil, Markus Antonietti, Yubao Zhao\*

**Abstract:** Photochemical synthesis of organic chemicals has attracted a massive revitalized research interest. A metal-free photochemical system with carbon tetrabromide ( $CBr_4$ ) is here developed for the synthesis of hemiaminal compounds. In this reaction system, the  $sp^3$  C-H bond of the N-alkyl group in the amide is photochemically activated, producing an ionic iminium species. The hemiaminal compounds are produced by nucleophilic attack of the iminium ion by alcohol in the presence of base. This photochemical conversion system shows high yield and broad substrate scope.

Solar irradiation is the most sustainable energy source, as it is clean, abundant, and inexhaustible. Employing solar light to drive chemical reactions is resurgent in the recent decades, due to the significance of converting solar energy into more valuable chemical potential.<sup>[1]</sup> Visible light accounts for 44% of the solar spectrum, the conversion and storage of the visible light is essential to improve the solar light utilization efficiency. However, there is only limited number of small organic building blocks that can be excited by the visible light. Therefore, the visible light photocatalysts/sensitizer, either heterogeneous or homogeneous, are prevailing in recently developed photo-redox catalytic organic conversion systems. Despite of the versatility of these photo-redox systems, the visible light driven photochemical conversion systems are still attractive and favourable, due to their intrinsically advantageous elimination of the additional photocatalysts/sensitizers, which contributes to lower cost, and simplified product purification process.<sup>[2]</sup>

In synthetic organic chemistry, direct functionalization of the  $sp^3$  C-H bond under mild and efficient condition is a long-standing goal.<sup>[3]</sup> The activation of the  $sp^3$  C-H bond adjacent to an amino group is a powerful tool for constructing nitrogen contained compounds.<sup>[4]</sup> Hemiaminals, also named as carbinolamines, N,O-aminals, N,O-hemiaminals, or N,O-acetals, are a class of organic molecules with a (sterogenic) carbon center germinally substituted by an amino group and an alkoxy (or hydroxyl) group. The hemiaminal unit is an important structural motif in various natural products and pharmaceutical intermediates, such as elbasvir, irciniastatin A (psymberin), spergualin, tallysomyins, zampanolide, echinocandin B, pederin, and many more (Figure 1).<sup>[5]</sup> It is also employed as a versatile building block in organic synthesis.<sup>[6]</sup> There are various reaction systems reported for the synthesis of hemiaminals, such as dicyclohexylboron chloride-

triethylamine system for coupling of amide and aldehyde, polyvalent iodine reagent oxidation systems, phosphoric acid catalysed addition of alcohol to N-acyl imines, the Pd-catalysed C-N coupling reaction, titanium ethoxide catalyzed coupling of amide and aldehyde, et al.<sup>[5b, 7]</sup> Among those methodologies, nucleophilic addition of alkoxy group to the imine is one of the typical methods for the synthesis of hemiaminals.<sup>[5c, 7c, 7d, 8]</sup>



**Figure 1.** Examples of the pharmaceuticals containing hemiaminal motif.

Under visible light irradiation, the metal-free  $CBr_4$  produces radicals by homolytic cleavage of the C-Br bond; and these active radicals could initiate a couple of oxidation or bromination reactions.<sup>[9-11]</sup> It is reasonable to expect the activation of the  $sp^3$  C-H bond adjacent to an amino group by oxidation, which could be thereafter coupled with alcohol in the nucleophilic addition reaction to form hemiaminal functional motif. Herein, we report the visible light driven coupling of amide and alcohol with  $CBr_4$  as the photochemical radical initiator, affording hemiaminal compounds with broad substrate scope and good yields.

Our experiments to run the described coupling reaction commenced with dimethylformamide and 3-phenyl-propanol as a couple in the presence of  $CBr_4$ . The base additive is essential in this photo-driven system. The reaction presents a low yield of 35 % without base additive (Table 1, entry 1). The addition of the 2,6-lutidine and  $NaH_2PO_4$  in the reaction system shows no enhancement of coupling reaction (Table 1, entries 2 and 3). When a series of carbonate salts are employed as base additives, the yields significantly increase. The photo-driven reactions with  $NaHCO_3$  and  $Li_2CO_3$  show remarkable yields of 91 % and 93%, respectively. The coupling reaction of DMF and 3-phenyl propanol

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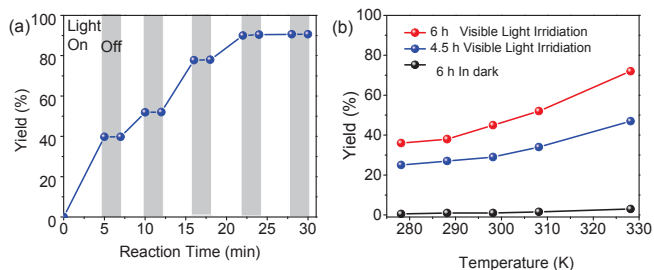
with  $\text{NaHCO}_3$  as the base additive is chosen as the model reaction for investigating the details of this photochemical reaction system. Control reactions show that light irradiation and the presence of  $\text{CBr}_4$  are both indispensable to the conversion.

**Table 1.** Effect of the base additives on the performance of photo-driven coupling reaction between DMF and 3-phenyl propanol under the otherwise standard reaction conditions.

Entry	Base additives	Yield (%)
1	No base	35
2	$\text{NaHPO}_4$	32
3	2,6-Lutidine	30
4	$\text{CaCO}_3$	87
5	$\text{Li}_2\text{CO}_3$	93
6	$\text{K}_2\text{CO}_3$	84
7	$\text{Cs}_2\text{CO}_3$	87
8	$\text{NaHCO}_3$	91

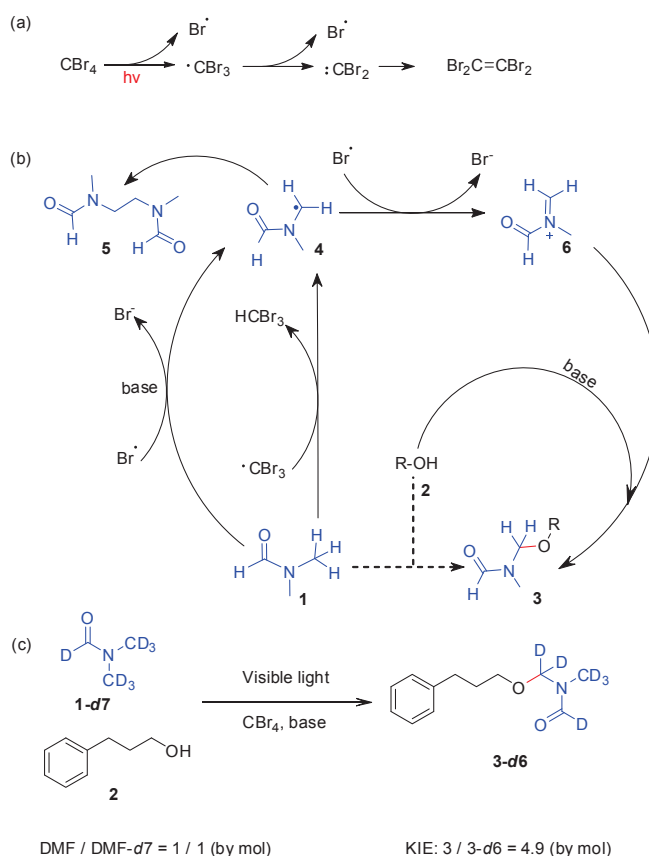
Reaction conditions: 400 mg (1.2 mmol)  $\text{CBr}_4$ , 1.2 mmol base additive, 0.3 mmol phenyl propanol, and 5 mL anhydrous amides were added into a 6 mL glass vial. The glass vial was capped and flushed with  $\text{N}_2$  flow for 15 minutes before being irradiated by visible light (100 W White LED,  $\lambda > 400$  nm) under room temperature for 20 h. The yield was determined by GC-FID with internal standard.

In order to study the effect of light irradiation to the reaction performance, the photo-driven reaction is run under alternating light and dark phases. As shown in Figure 2a, the first 5 hours irradiation affords 40 % yield, and there is no reaction in the following 2 hours in dark. The reaction starts again and shows 52 % yield after additional 3 hours visible light irradiation, and the reaction stopped immediately when the light irradiation is blocked. This demonstrates that the reaction needs a flow of photons for driving the coupling reaction to the end.



**Figure 2.** (a) The reaction performance of the coupling reaction between DMF and 3-phenyl-propanol with alternating light irradiation and dark phases. (b) The impact of the reaction temperature on the reaction system performance. The experiments for studying the temperature-dependence of the reaction were conducted in a jacketed photo-reactor connected with a temperature controlled water circulation system. The reaction mixture was sampled during the reaction and the yield was determined by GC-FID with internal standard.

The temperature dependence of the photo-driven reaction performance of this system is also studied. As shown in Figure 2b, with the increase of the reaction temperature from 278 K to 328 K, the yield of compound **3** after 6 hour's visible light irradiation increases from 36 % to 72 %. However, in dark, only trace amounts of product are detected at 328 K. This repeatedly indicates that this coupling reaction is photo-initiated, and the rate-determine step is temperature sensitive.



**Scheme 1.** (a, b) Proposed reaction mechanism for the visible light driven coupling of dimethylformamide and alcohol. (c) Isotope labelling and kinetic isotope effect (KIE) studies of the coupling reaction. Reaction conditions for the kinetic isotope effect measurement: 5 ml mixture of DMF and DMF- $d_7$  with molar ratio of 1/1 was charged in a glass vial, 400 mg (1.2 mmol)  $\text{CBr}_4$ , 100mg (1.2 mmol)  $\text{NaHCO}_3$ , 0.3 mmol alcohol were added into the reactor, followed by nitrogen degassing and visible light irradiation for 5 hours. The reaction mixture was then sampled and analysed by GC-MS. The KIE value was determined by molar ratio of **3** and **3-d6**.

Based on the experimental facts, a tentative reaction mechanism is proposed. As shown in Scheme 1a,  $\text{CBr}_4$  has weak visible light absorbance,<sup>[9]</sup> and under visible light irradiation,  $\text{CBr}_4$  generates bromine radical and tribromomethyl radical by homolytic cleavage. The tribromomethyl radical could further release one more bromine radical and dibromocarbene, which is evidenced by the carbene coupling product (tetrabromoethylene).

In the presence of base additive, the  $\text{sp}^3$  C-H bond is activated by bromine radicals via oxidative dehydrogenation reaction, and radical **4** is produced, which can be confirmed by the detection of radical coupling product **5** in small amount by GC-MS (Scheme 1b). In the meantime, the bromine radical is changed to bromide ion in the presence of base.  $\text{CBr}_3$  radical is also able to oxidize

DMF, affording  $\text{HCBBr}_3$  and radical **4**. The second oxidation step converts radical **4** into the iminium ion **6**. With the assistance of base additive, the following nucleophilic attack of the iminium ion by alcohol affords the final coupling product **3**.

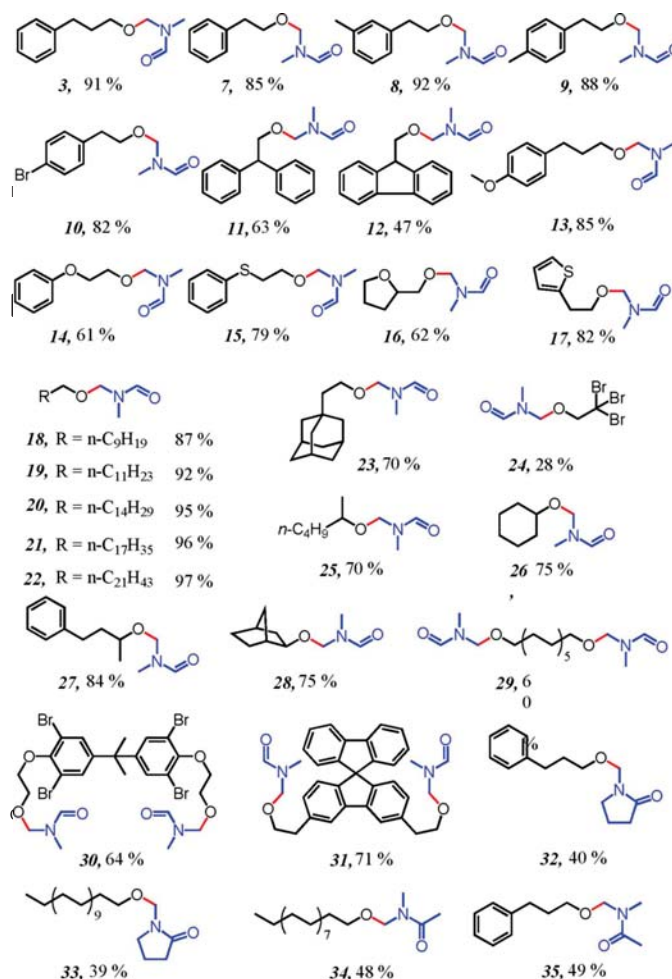
Moreover, the addition of the radical scavenger butylated hydroxytoluene (BHT) causes a significantly decreased reaction rate. Under standard reaction conditions, 8 hours visible light irradiation generates the coupling product **3** with a yield of 52 %; while this value decreases to 20 % in the presence of 0.09 mmol BHT (30 % of the molar amount of alcohol) in the reaction mixture. Consistent with the proposed reaction mechanism, these probe reactions describe the nature of radical reaction in this system.

To further understand the reaction mechanism, the kinetic isotope effect (KIE) in this system is studied by measuring the isotope competition during the coupling reaction. DMF and  $\text{DMF-}d_7$  are mixed in equal molar amounts and employed as the reactant, and a KIE value of 4.9 was determined by mass spectrometry of the product (Scheme 1c). In the proposed reaction mechanism, the first step is the activation of DMF which bears the C-H bond to be cleaved, and the C-H cleavage step not likely involves in the product determine step, which is a nucleophilic addition step. Moreover, this reaction is photo-initiated and the rate-determine step is temperature sensitive. We thus speculate that the oxidation of DMF molecule via single electron transfer occurs first; and then C-H bond cleavage follows and involves in the rate-determining step.

With the optimized reaction condition in hand, the compatibility of the reaction system is further investigated (Figure 3). Various aromatic primary alcohols have been tested in this photo-driven coupling reaction system, affording the coupling products **7** – **13** with good yields. Phenyl ether and phenyl thio ether are also suitable substrates, and the coupling reactions with DMF produce **14** and **15** with yields of 61% and 79%, respectively. The coupling reactions between DMF and the alcohols with heterocyclic motif afford **16** and **17** with good yields. Aliphatic primary alcohols are smoothly coupled with DMF in this photochemical reaction system, affording hemiaminals **18** – **22** with excellent yield of 87 % – 97%. As compared to the aliphatic primary alcohols, the coupling reaction of 1-adamantaneethanol with DMF gives a hemiaminal **23** with a slightly lower yield of 70%. Tribromoethanol is also able to be coupled with DMF to produce **24**, but with low yield of 28% after 20 h of photoreaction, which could be due to the low nucleophilicity and the steric hindrance effect of the tribromoethyl group.

This reaction system is also capable of coupling the secondary alcohol with amide, giving the coupling product (**25** – **28**) with still acceptable yields of 70 % – 84 %. Similarly, diols are also smoothly coupled with DMF, affording the hemiaminals **29** – **31** with yields around 60 % – 70%. *N*-methyl-2-pyrrolidone (NMP) and *N,N*-dimethylacetamide (DMAc) were employed in this coupling reaction as well, but both of them show lower reactivity as compared to DMF. In this reaction system, the C-H bond on *N*-methyl group is more favourable for activation and coupling reaction. NMP is coupled with 3-phenyl-propanol and 1-docosanol, giving coupling product **32** and **33** with around 40 % yield. Diethylformamide is not capable of coupling with alcohol to give an acceptable yield. The coupling reactions of DMAc with 1-octadecanol and 3-phenyl-propanol afford hemiaminals **34** and **35** with yields of 48% and 49%, respectively. The benzylic alcohols

and tertiary alcohols failed to couple with DMF, which could be due to the poor nucleophilicity and steric hindrance of the nucleophiles in the coupling reaction.



**Figure 3.** Substrate scope of the photo-driven coupling reaction between amides and alcohols. Standard reaction conditions: 400 mg (1.2 mmol)  $\text{CBr}_4$ , 100mg (1.2 mmol)  $\text{NaHCO}_3$ , 0.3 mmol alcohol and 5 mL anhydrous amides were added into a 6 mL glass vial. The glass vial was capped and flushed with  $\text{N}_2$  flow for 15 minutes before being irradiated by visible light (100 W White LED,  $\lambda > 400$  nm) under room temperature for 20 h. After the visible light irradiation, the crude mixture with internal standard was concentrated and dissolved in  $\text{CDCl}_3$ , and the yield of the reaction was determined by  $^1\text{H}$  NMR with 1,3,5-tribromobenzene as the internal standard.

In summary, a novel visible-light-driven reaction system for hemiaminals production by coupling of amides and alcohols is presented. In this photochemical reaction system, the  $\text{sp}^3$  C-H besides the amidic nitrogen is selectively activated in the presence of base, producing iminium ions for the coupling with the alcohol. This reaction system shows broad substrate scope and good functional group tolerance, and 30 hemiaminal compounds are presented in this work.



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**Keywords:** Photochemical Reaction • C-H activation • Solar Conversion • Reaction Mechanism • Hemiaminal

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