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- Title: The Combination of Benzaldehyde and Nickel-Catalyzed Photoredox sp3-C-H Alkylation/Arylation
- Authors: Lumin Zhang, Xiaojia Si, Yangyang Yang, Marc Zimmer, Sina Witzel, Kohei Sekine, Matthias Rudolph, and A. Stephen K. Hashmi

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# The Combination of Benzaldehyde and Nickel-Catalyzed Photoredox *sp*<sup>3</sup>-C-H Alkylation/Arylation

Lumin Zhang,<sup>[a]</sup> Xiaojia Si,<sup>[a]</sup> Yangyang Yang,<sup>[a]</sup> Marc Zimmer,<sup>[a]</sup> Sina Witzel,<sup>[a]</sup> Kohei Sekine,<sup>[a]</sup>Matthias Rudolph,<sup>[a]</sup> A. Stephen K. Hashmi<sup>[a,b],\*</sup>

[a] M.Sc. L. M. Zhang, M.Sc. X. J. Si, M.Sc. Y. Y. Yang, M.Sc. M. Zimmer, M.Sc. S.

Witzel, Dr. K. Sekine, Dr. M. Rudolph, Prof. Dr. A. S. K. Hashmi

Organisch-Chemisches Institut

Heidelberg University

Im Neuenheimer Feld 270

69120 Heidelberg

Germany

[b] Prof. Dr. A. S. K. Hashmi

**Chemistry Department** 

Faculty of Science

King Abdulaziz University (KAU)

Jeddah 21589

Saudi Arabia

**ABSTRACT**: Herein we report a highly selective photoredox  $sp^3$ -C-H alkylation/arylation of ethers via the combination of a photo-organocatalyst (benzaldehyde) and a transition metal catalyst (nickel). This methodology provides simple and general strategy for  $sp^3$ -C-H alkylation/arylation of ethers, a selective late-stage modification of (-)-Ambroxide has also been conducted to demonstrate the applicability.

In modern organic chemistry, a selective functionalization of C-H bonds is one of the most challenging transformations, traditional approaches often require pre-activation of substrates, directing groups, stoichiometric additives or oxidants, to name just a few drawbacks.<sup>[1]</sup> Along with the emergingXX of photocatalysis over the past decades, which allows to achieve previously inaccessible transformations under mild conditions, more recently, the strategy of combining photoredox (metal complex-based) with transition-metal catalysis, namely metalla-photoredox, has emerged to be a breakthrough for constructing C-C and C-heteroatom bonds in organic synthesis and even allows late-stage functionalization of pharmaceutical compounds.<sup>[2]</sup> Although numerous marvelous strategies concerning C-H functionalization have been reported, to the best of our knowledge, the direct  $sp^3$ -C-H alkylation by normal alkyl halides has only been reported by MacMillan's group, the strategy of polarity-match by combining photoredox of an iridium complex Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> (110 USD/ 100 mg from Sigma Aldrich) with a nickel catalyst and a hydrogen-atom transfer catalyst (quinuclidine) (Figure 1A).<sup>[3]</sup> With this in mind, the requirement for exploring new and alternative methodologies for the direct  $sp^3$ -C-H alkylation with alkyl halides is desirable. Compared with relatively expensive metal-catalysts such as iridium, ruthenium and dimeric gold used in photoredox, it is well known that the inexpensive photo-organocatalysts can also absorb photons, and then activate substrates through single electron transfer (SET), energy transfer or direct hydrogen atom transfer (DHAT) processes. The process of DHAT, which can selectively cleave a C-H bond by forming

a carbon radical without the limitation of redox potentials, would open up enormous opportunities for  $sp^3$ -C-H alkylation and arylation.

#### Ni/photoredox *sp*<sup>3</sup> C-H alkylation (*previous study*)



**Figure 1**. Previous study about photoredox  $sp^3$ -C-H alkylation catalyzed by nickel, photochemistry of benzaldehyde and our hypothesis.

Benzaldehyde (51.8 USD/ 100 ml from Sigma Aldrich), same as other commonly used carbonyl compounds such as benzophenones, acetophenones and quinones, which are effective and productive photosensitizers and hydrogen abstractors for a variety of hydrogen-donating solvents due to their low-lying and thermally accessible triplet  $n,\pi^*$ -states.<sup>[4]</sup> The photochemistry of benzaldehyde has been widely investigated (Figure 1), ground state benzaldehyde going to singlet state by irradiation with UV light, transferring to more reactive triplet state by ISC (inter-system crossing), then benzene and CO are produced by going through Norrish I type reaction (Figure 1, path B). Besides, this photoexcited benzaldehyde can undergoes HAT process either from

ground state benzaldehyde resulting in benzaldehyde and benzoin (Figure 1, path A) or from hydrogen-donating solvent resulting  $\alpha$ -hydroxybenzyl radicals and solvent radicals. This  $\alpha$ -hydroxybenzyl radicals would further abstract a hydrogen from solvent to form benzyl alcohol or led to homocoupling products (Figure 1, path C). Given the powerful hydrogen abstract performance of excited benzaldehyde, the  $\alpha$ -hydroxybenzyl radicals intermediate and THF radical formed after HAT process, we are wondering whether this more general and simple photo-organocatalyst can merge with transition metal catalysis for constructing C-C and C-heteroatom bonds or not? Herein, we designed a novel combination of a nickel catalyst and a photo-organocatalyst (benzaldehyde), which might act both as photosensitizer and HAT catalyst in challenging  $sp^3$ -C-H alkylation reactions.

0 1a	UVA + Br - Ph - Ph - Ph - Ph - NiBr <sub>2</sub> .glyme (10 mol%) - dtbbpy (10 mol%) - K <sub>2</sub> HPO <sub>4</sub> (2.0 eq)	O Ph 3aa
entry	conditions	yield <sup>b</sup>
1	no variation	92%
2	without UVA	0%
3	without PhCHO	0%
4	without NiBr <sub>2</sub> .glyme	0%
5	without dtbbpy	0%
6	without $K_2HPO_4$	trace
7 <sup>c</sup>	acetone	83%
8 <sup>d</sup>	acetophenone	12%
9 <sup>d</sup>	benzophenone	37%
10 <sup>d</sup>	<i>p</i> -OMe-PhCHO	27%
11 <sup>d</sup>	<i>p</i> -F-PhCHO	75%
12 <sup>e</sup>	<i>p</i> -OMe-PhCHO	0%

Table 1.	Select	ontimizati	ion results	and o	control	studies <sup>a</sup>
Table 1.	Scient	opumzau	ion results	and	control	studies

<sup>*a*</sup> 0.2 mmol scale in THF (1.0 ml), N<sub>2</sub>, 72 h; <sup>*b*</sup> Using 1,3,5-trimethoxybenzene as the internal standard; <sup>*c*</sup> THF (1.0 mmol, 10.0 equiv) in acetone (1.0 ml), 96h; <sup>*d*</sup> Replace benzaldehyde with other relevant photosensitizers. <sup>*e*</sup> Benzaldehyde replaced by *p*-OMe-PHO and irradiated by CFL light source.

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On the basis of our mechanistic assumption, this novel photoredox coupling between (3-bromopropyl)benzene and THF has been initiated by using NiBr2•glyme and 4,4'-di*tert*-butyl-2,2'-bipyridyl (dtbbpy) as nickel catalyst, benzaldehyde as both photosensitizer and hydrogen abstractor, in combination with K<sub>2</sub>HPO<sub>4</sub> as base and under irradiation with UVA light. To our delight, the desired  $sp^3$ - $sp^3$ -coupling product could be isolated in 92% yield after reaction optimization (see supporting information). Furthermore, a series of control experiments were conducted to confirm the necessity of each component. As the experimental results in Table 1 indicate, UVA light, benzaldehyde, precatalyst NiBr2•glyme, the ligand dtbbpy and the base K2HPO4 are all critical for the reaction (entries 1-6). Only a trace of the desired product can be detected in the absence of  $K_2$ HPO<sub>4</sub>, which would be consistent with our hypothesis of electron transfer between the ketyl anion radical and the nickel catalyst (entry 6). That other known photosensitizers with ketyl structure weren't efficient in this reaction could result from steric bulk compared with benzaldehyde (entries 8 and 9). Benzaldehydes with different substituents are less efficient than benzaldehyde (entries 10 and 11). No reaction was detected when using p-OMe-PCHO as photosensitizer with CFL as light source in our reactions (entry 12)<sup>[4h]</sup>. Our reaction can also proceed well using 10.0 equivalents of THF with acetone as solvent, 83% yield were obtained after extending the reaction time (entry 7).

**Table 2.** Scope with respect to the alkyl and aryl bromide<sup>a</sup>



<sup>a</sup>Isolated yields. 0.2 mmol scale. 72-96 h.

With optimized conditions in hand, we next sought to determine the generality with respect to the bromide components in this photoredox  $sp^3$ -C-H alkylation/arylation reaction. As shown in Table 2, functional groups such as aryl, heteroaryl, esters, ethers, OTBS, boronic esters, acetals, amides (**3aa-3af**, **3ah**, **3ak-3al**) were all compatible. We also found that the coupling occurred selectively at the bromide-bearing carbon when 1-bromo-3-chloropropane was subjected to the same reaction condition, yielding **3ag** 

in 83% yield. Cyclic substrates with sterically demanding also gave the coupling product (**3ai**, 36% yield). Secondary-secondary C-C coupling can also be achieved with high levels of efficiency, which has been a challenge for a long time in the area of cross-coupling (**3aj**). Further exploration of the scope demonstrated that these reaction conditions tolerated a variety of aryl and heteroaryl bromides. For aryl bromide containing either an electron-withdrawing substituent (trifluoromethyl) or electron-donating substituent (methoxy) the corresponding  $sp^3$  C-H coupling products were isolated in high yields (**3am-3ao**). Notably, even medically relevant heteroaromatic coupling partners, which are notoriously problematic in many photoredox coupling technologies, performed well under our reaction conditions including thiazoles, benzothiazoles, furans, pyridines, quinolones, pyrimidines (**3ap-3au**, 74-82% yield).





<sup>a</sup>Isolated yields. 0.2 mmol scale. 72 and 96 h.

We next evaluated ether coupling partners in this  $sp^3$ - $sp^3$ -cross-coupling reaction. As shown in Table 3, along with THF, both commonly used cyclic and acyclic ether all

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performed well under identical conditions, providing primary, secondary coupling products. For symmetric cyclic ethers, such as cyclobutane (**3ba**), tetrahydropyran (**3ca**), dioxane (**3da**), it is appreciable that the reaction only occurred at the position adjacent to the oxygen-atom. The diminished reactivity of cyclobutane and tetrahydropyran compare with THF would be influenced by both ring strain and stereoelectronic factors as well. In the case of the diether 1,4–dioxane, although it have comparable steric demands, the second oxygen atom in this molecule wouldn't favor radical formation by either stereoelectronic or direct mesomeric interactions.<sup>[5]</sup> Symmetric acyclic ether also compatible to this  $sp^3-sp^3$ -photoredox coupling condition with moderate yield for **3ea** and **3fa**. For substrate **3fa**, a selectivity between methyl and methylene group is occurred, giving the linear product preferentially (1.4:1, branched: linear) in a combined 48% yield. Furthermore, in the case of unsymmetric substrates, both cyclic **3ga** and acyclic **3ha** ethers are all preformed in good yields, 82% and 80%, respectively.



Figure 3. Results with other substrates.

While having succeed in the reaction of photoredox  $sp^3$  C-H alkylation by the combination of benzaldehyde and a nickel catalyst, extensive future work has to be conducted in order to gain detailed insight into the mechanism. Other substrates, such as benzyl and vinyl bromides, do not efficiently couple under our reaction conditions (Figure 3).



**Figure 4**. Selective late-stage modification of the natural product (-)-Ambroxide by  $sp^3$ -C-H alkylation and arylation.

In conclusion, a simple photoredox sp<sup>3</sup>-C-H alkylation/arylation was achieved by the combination of a quite inexpensive photo-organocatalyst benzaldehyde, the transition metal nickel and UVA light. The applications clearly suggest that our strategy is a promising synthetic method and late-stage modification tool for natural products. Detailed studies of the mechanism and other new combinations of photo-organocatalysts and transition metals are currently ongoing.

Keywords: benzaldehyde, nickel catalysis, sp<sup>3</sup> C-H alkylation/arylation, photoredox

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#### **TOC graphic**

н Br**−**R

UVA PhCHO (0.5 eq) NiBr<sub>2</sub>.glyme (10 mol%) dtbbpy (10 mol%) K<sub>2</sub>HPO<sub>4</sub> (2.0 eq)

R

29 examples 36-XX98 % yield