Communications
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Special Collection

Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions

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This paper is dedicated to Prof. Franco Cozzi on the occasion of his 70th birthday.

Organometallic allylic reagents are widely used in the construction of C–C bonds by Barbier-type reactions. In this communication, we have described a photoredox Barbier allylation of aldehydes mediated by bismuth, in absence of other metals as co-reductants. Mild reaction conditions, tolerance of oxygen, and use of aqueous solvent make this photoredox methodology attractive for green and sustainable synthesis of homoallylic alcohols.

In recent years, photoredox catalysis has been developed towards effective and practical new synthetic methodologies for C–C and C–X (X = O, N, S, P) bond-forming reactions.[1] Metalla photoredox catalysis, developed from the seminal work of Sanford,[2] Molander,[3] and MacMillan-Doyle,[4] has considerably expanded the repertoire of reactivity and scope, allowing the development of new, mild, and interesting transformations.[5] From the application of metalla photoredox catalysis in the context of cross-coupling reactions[6] the methodology has evolved to consider radical to polar crossover mechanism,[7] in which carbanion[8] or carbenium ion[9] are formed by the reaction of a metal with a radical generated under photoredox conditions. Recently, allylation reactions were described in Barbier conditions, with the involvement of nickel,[10] chromium,[11] titanium,[12] and cobalt.[13] Stereoselective allylation reactions with chromium[14] and nickel[15] were also developed, showing the possibilities offered by the use of photoredox conditions, in the presence of metals, for asymmetric reactions. Essentially, photoredox Barbier conditions avoid the need of a metal co-reductant (often Mn or Zn). In the examples reported with chromium, the photoredox cycle does not need a sacrificial reducing agent such as organic molecules, e.g. an amine (DIPEA or TEA) or Hantzsch's ester. In the case of nickel, cobalt, and titanium, the catalytic cycle is feasible with the use of an organic reducing agent. In both cases, the allylation reaction is performed in the presence of a photocatalyst (iridium complex or an organic dye), although recently Gansäuer pointed out[16] that titanium complexes themselves can act as photocatalysts under precise conditions (green light irradiation). The described methodologies are certainly innovative and can be further expanded towards other C–C bond-forming transformations. Barbier reactions with certain types of metals (zinc, indium, bismuth, gallium) were developed in aqueous solvents.[17] Tofurther extend the advantage of photoredox allylation reactions, and explore the use of green and sustainable conditions, we wondered if the mentioned metals could be employed in photoredox allylation reactions under aqueous Barbier conditions, and herein we report the successful endeavor of our investigations.

Bismuth is an inexpensive, safe, and environmentally-benign metal, that is commonly used in cosmetics, and as a component of oral gastrointestinal drugs.[18] Bismuth has been used in allylation reactions under various conditions,[19] and in the presence of stoichiometric metals as reductants, such as Al, Mg, Fe, and Zn.[20] Interestingly, also sodium borohydride was a suitable reductant for Barbier-typeallylation reaction with bismuth.[21] Based on these reports, we selected bismuth salts as metal catalysts for the catalytic photoredox allylation of aldehydes. Starting by employing 4-chlorobenzaldehyde as the model substrate, we have optimized the allylation reaction using allyl bromide and $Bi(OTf)_3$ (Table 1). We have avoided the employment of metal photocatalysts based on iridium and ruthenium, focusing our investigation on the class of thermally activated delayed fluorescence (TADF) organic dyes based on carbazoyl and diphenylamine substituted dicyanoarenes.[22] Among all the TADF dyes, 3CzClIPN[23] was the dye of choice. We also varied – in the model reaction – the solvent, finding that a 1:1 mixture of $EtOH/H_2O$ was convenient to satisfyingly perform the reaction (Table 1, entry 6). Furthermore, the reaction does not require strictly de-oxygenated solvents and can be conveniently settled without a freezing-pump thaw procedure to eliminate traces of oxygen (Table 1, entry 7). The reaction is not sensitive to the presence of radical scavengers like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, Table 1, entry 8). Different bismuth salts were also tested in the model reactions (see Table S3) and we found that $BiBr_3$ was also a compelling catalyst for the reaction (Table 1 entry 14). Due to

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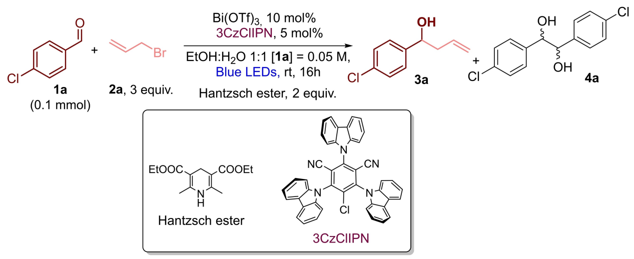
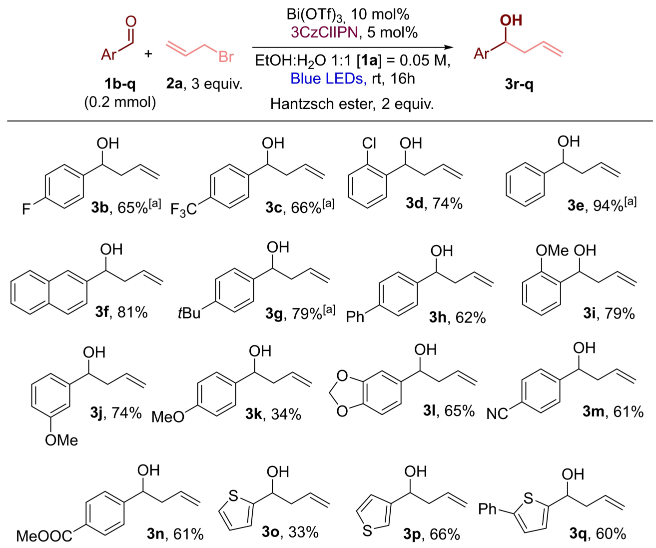
Table 1. Screening of reaction conditions for bismuth-mediated catalytic photoredox allylation of aldehydes.



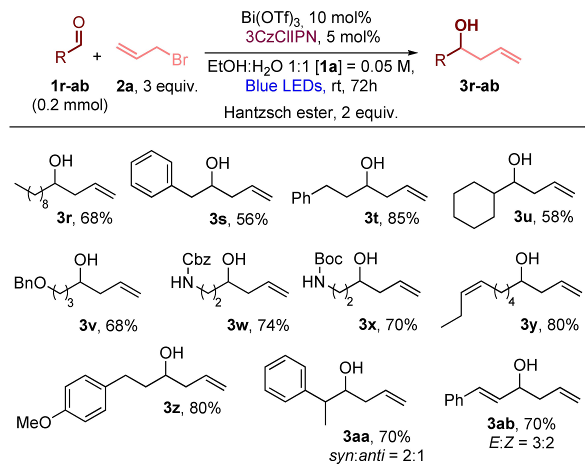
Entry[a]	Deviation from standard conditions	Conv. [%][b]	3a [%][c]	3a:4a [%][c]
1	Solvent THF:H_2O (1:1)	97	51	52:48
2	Solvent DMF:HO (1:1)	53	48	85:15
3	Solvent MeCN:H_2O (1:1)	81	45	56:44
4	Solvent MeOH:H_2O (1:1)	>99	79	79:21
5	Solvent DMSO:H_2O (1:1)	98	66	68:32
6	–	>99	83(74)	83:17
7	In air	90	70	79:21
8	In the presence of TEMPO (20 mol%)	>99	95	95:5
9	No $Bi(OTf)_3$	>99	16	16:84
10	No 3CzClIPN	59	59	>99:1
11	No $Bi(OTf)_3$; No 3CzClIPN	6	0	>1/99
12	No light	0	–	–
13	Allylchloride instead allylbromide	15	7	48:52
14	$BiBr_3$ instead $Bi(OTf)_3$	>99	87	87:13
15[e]	1 mmol scale	89	85(77)	95:5

[a] All the reactions were carried out under irradiation with Kessil® 40 W blue LED. [b] Conversions were measured by ^{1}H-NMR. Isolated yields after chromatographic purification are reported in parenthesis. [c] Yield% of the allylated product (**3a**) determined by ^{1}H-NMR. [d] Ratio% of allylated product (**3a**) and pinacol coupling (**4a**). The d.r. for (**4a**) is ca 1:1 for all the reactions. [e] The reaction was performed with 8 mol% of $Bi(OTf)_3$ and 3 mol% of 3CzClIPN.



[a] Reaction time 72h.

Scheme 1. Photoredox allylation of aromatic aldehydes mediated by bismuth.



Scheme 2. Photoredox allylation of aliphatic aldehydes mediated by bismuth.

the difficulty to manage this deliquescent salt, we decided to use $Bi(OTf)_3$, for further studies. Interestingly, in absence of the $Bi(OTf)_3$, but in the presence of 3CzClIPN, the pinacol coupling of the aldehyde is favored (Table 1, entry 9).[24] If the reaction is carried out without 3CzClIPN, under irradiation with blue LED (Table 1, entry 10), we have observed a clean allylation reaction, although in quite a minor conversion. This was probably due to the ability of bismuth to form a reactive allylating agent with the mediation of Hantzsch's ester under light irradiation. In fact, when bismuth is not introduced in the reaction mixture, and the photocatalyst 3CzClIPN is absent (Table 1 entry 11), the photoredox properties of the Hantzsch's ester favored the pinacol coupling.[25] The scale-up of the reaction is possible and on 1 mmol scale we have reduced to 8 mol% the percentage of bismuth catalyst (entry 15).

The optimal reaction conditions were explored with a large variety of aromatic and aliphatic aldehydes, and the salient results are reported in Scheme 1 and Scheme 2. In general, with aromatic aldehydes, the isolated yields were from moderate to good, with a variety of different functional groups compatible with the reaction conditions. Both electron-rich and -poor aromatic aldehydes are reactive and, in some cases, yields could be improved by an increase of the reaction time to 72 h. Sterical hindrance in *ortho* position does not hamper the reaction. Heteroaromatic aldehydes can be also employed, with some limitations. We found that electron-rich aldehydes bearing pyrrole or indole are unstable during chromatographic purifications due to their attitude to forming elimination products. Thiophene is a compatible group, but 2-thiophene carboxaldehyde **1o** was found poorly reactive, probably due to chelation of sulfur to the bismuth reagent. The reactivity is restored when 3-thiophene carboxaldehyde **1p** is employed. When long reaction times (72 h) were applied to the reactions of the aldehydes **1k**, **1o** and **1q**, byproducts were observed. We have detected (and isolated only for **1k**) the corresponding ethyl ether of the homoallylic alcohols (**3k,o,q**) formed by their reaction with ethanol (see Table S4). Although $Bi(OTf)_3$ is described as a catalyst for S_N1-type reaction of alcohols[26] the formation of ethers was determined by the Brønsted acidity of the oxidized Hantzsch's ester. This behavior was confirmed by dissolving the alcohol **3k** in EtOH in the presence of the pyridinium salt derived from the oxidation of Hantzsch's ester (see Table S5). The formation of these ether byproducts was observed only for alcohols bearing an electron-rich aromatic ring.

On the other hand, the reaction is useful with aliphatic aldehydes **1r**–**ab**. Several functional groups are tolerated in the reported conditions and the reaction is applicable to linear and branched aldehydes with a reaction time of 72 h. Interestingly, cinnamaldehyde (**1ab**) gave a mixture of *E* and *Z* isomer of the corresponding allylated product (**3ab**) probably due to photo-isomerization of cinnamaldehyde in presence of light and photocatalyst.[27]

Ketones showed a quite reduced reactivity in this reaction compared to aldehydes, and the corresponding products were detected only in traces (see Figure S1).

Substituted allyl bromides were tested in the reaction with poor conversions (see Table S6). Whereas prenyl and crotyl derivatives led to the exclusive formation of branched products, cinnamyl bromide gave a complex mixture of products.

In order to evaluate the mechanism of the reaction, we investigated the quenching of the photocatalyst's luminescence by each of the components of the reaction (see SI for details). As reported in our investigation on titanium photoredox allylation,[12] isophthalonitrile derivatives represent a class of remarkably visible emitters, which can show long emission lifetimes in specific experimental conditions because of their TADF behavior. Interestingly, 3CzClIPN displays double deactivation kinetics at $\lambda_{em} = 550$ nm even in air-equilibrated ethanol at r.t. most likely due to a TADF-active regime, featuring a delayed component with a lifetime around 150 ns (see SI for full details).

In the presence of increasing amounts of $Bi(OTf)_3$ or allyl bromide, no appreciable decrease in the emission intensities of 3CzClIPN was detected (see Figure S3 and Figure S4), thus showing that these two reactants are not involved in quenching mechanisms even at high concentrations. On the other hand, the addition of 4-chlorobenzaldehyde barely decreases the emission intensity of 3CzClIPN ($k_q = 6.2 \times 10^6\ M^{-1}\,s^{-1}$, see Figure S5), explaining the observed pinacol coupling in absence of $Bi(OTf)_3$. Similar behavior is observed when the Hantzsch's ester is introduced in solutions of 3CzClIPN, denoting a significantly more efficient quenching of the emission of the latter($k_q = 3.8 \times 10^8\ M^{-1}\,s^{-1}$, see Figure S6).

Based on the results of the photophysical investigation, and from studies reported in the literature,[20c] we can tentatively suggest that the reductive quenching of 3CzClIPN by HE induces the formation of $HE^{\bullet+}$ (Figure 1). The thermodynamic feasibility of the photoinduced electron transfer (PET) process relies on the reduction potential of the excited state of 3CzClIPN ($E^{1/2}_{3CzClIPN*/3CzClIPN^{\bullet-}} = 1.56$ V vs SCE)[23] and on the oxidation potential of the Hantzsch's ester ($E_{HE^{\bullet+}/HE} = +1.0$ vs SCE).[27] The reaction is thus producing $HE^{\bullet+}$ that can participate in further electron transfer events[27] and is a strong reductant. Furthermore, the reducing $3CzClIPN^{\bullet-}$ ($E^{1/2}_{3CzClIPN/3CzClIPN^{\bullet-}} = -1.16$ V vs SCE) species is formed. The high tolerance to oxygen and TEMPO is ruling out a radical mechanism and formation of allylic radicals. We have no direct evidence of the actually reduced bismuth species but, as suggested by the literature, the formation of Bi(0) could be considered. Multiple single electron transfer (SET) events could be responsible for the formation of Bi in low oxidations state from Bi(III) salt. Insertion of active bismuth to C–Br bond could forms allylbismuth(III), diallylbismuth(III), and triallylbismuth(III) as the organometallic intermediates, that react with aldehydes to give the corresponding homoallylic alkoxides.[20c] The protonated re-aromatized Hantzsch ester possesses a low pK_a and the aqueous conditions enable a facile protonation of the intermediate bismuth alkoxide, allowing the recycle of bismuth salts. We have demonstrated in previous studies that the pyridine, produced by the oxidation of the Hantzsch's ester, does not partecipate in quenching processes.

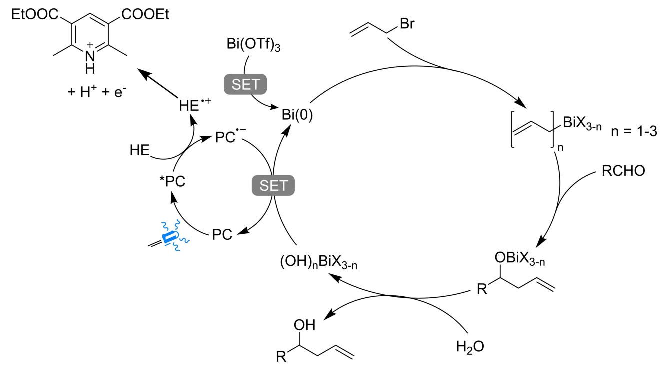


Figure 1. Proposed catalytic cycle for photoredox allylation of aldehydes mediated by bismuth.

To conclude, we have reported a photoredox Barbier allylation reaction that uses green solvents and conditions and employs a not toxic metal such as bismuth. The use of expensive transition metal-based photoredox catalysts and stoichiometric metals (e.g. Mn or Zn) is avoided. However, further mechanistic studies are needed to understand the reaction mechanism with the possibility to expand this chemistry to the use of other electrophiles.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Allylation · Aldehydes · Barbier reaction · Photoredox catalysis · Organic dyes

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