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# Iridium(III)-catalyzed photoredox cross-coupling of alkyl bromides with trialkyl amines: access to $\alpha$ -alkylated aldehydes†

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**A C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross coupling approach based on an iridium-photocatalytic radical process has been developed enabling the synthesis of various  $\alpha$ -alkylated aldehydes from easily available/synthesized alkyl bromides and trialkyl amines under mild photocatalytic conditions. The synthesized aldehydes are also explored as a functional handle for various useful products such as carboxylic acid, alcohol and N-heterocycle synthesis.**

In the age of contemporary organic synthesis, cross coupling reactions enabling the formation of carbon-carbon bonds are some of the most crucial steps.<sup>1</sup> These reactions are highly significant synthetic tools for the synthesis of several medicines and naturally occurring compounds.<sup>2</sup> However, the majority of C-C bond forming cross-coupling methods involve the use of expensive metal complexes, strong oxidizing agents, high temperature and tedious work-up procedures.<sup>3</sup> Hence, alternative techniques that could overcome most of the existing glitches are highly needed. In this context, over the past two decades, photo-organic synthesis has seen a rebirth in comparison to the traditional approaches, and has become a potent tool for the cross-coupling C-C bond forming reactions.<sup>4</sup> Due to its unique capacity to produce extremely reactive radicals and radical ion intermediates by a direct single electron transfer (SET) event, photoredox methods have increased interest in recent years as a sustainable strategy for numerous syntheses.<sup>5</sup> Inspired by this, significant progress has been achieved in the creation of artificial photoredox reactions for the formation of C-C bonds.<sup>6</sup>

Functionalized aldehydes have been often employed as precursors towards the syntheses of numerous significant molecules such as carboxylic acids, amines, amides, alcohols, nitriles, and many other carbocyclic as well as heterocyclic systems.<sup>7</sup> They are also well-known vital constituents of many natural products and pharmaceutically important molecules.<sup>8</sup>

Functionalized aldehydes have also been utilized as new radical alkylating reagents,<sup>9</sup> as tools for a variety of synthetic, biological and in materials-based applications.<sup>10</sup> Over the past few years, most of the reported methods involve direct metal and chiral base-mediated arylation/alkylation of aldehydes under harsh reaction conditions.<sup>11</sup> Recently, a few photocatalytic methods for the direct functionalization of  $\alpha$ -CH of aliphatic aldehydes have been reported by some research groups.<sup>12</sup> Although all given methods successfully achieved the functionalized aliphatic aldehydes, the use of a co-catalytic system and direct use of aldehydes make these protocols a bit complex because of cost-ineffectiveness and formation of various side products by the oxidation of aldehydes under the given catalytic systems. Hence, an alternative method involving cost-effective low catalytic loading, which could possibly suppress the formation of oxidized side products, is highly needed. Herein, we report the cross-coupling reactions of phenacyl bromides with alkyl amines under Ir(III)-catalyzed photoredox conditions, which successfully provided the functionalized aliphatic aldehydes in good to excellent yields.

Keeping all the challenges in mind, optimization studies were conducted using the combination of 2-bromo-1-phenylethan-1-one (**1a**; 0.5 mmol, 1.0 equiv.) and TEA (**2a**; 2.0 mmol, 4.0 equiv.) in the presence of Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbpy)PF<sub>6</sub> (PC-1, 2.0 mol%) and TBAI (0.5 equiv.) in 1,4-dioxane (2.0 mL) under Kessil blue LED Light irradiation (blue; 40 W, 467 nm) at 30 °C for 5 h in an open atmosphere. The work-up of the reaction mixture provided the product **3a** in 76% isolated yield (characterized as 4-oxo-2-(2-oxo-2-phenylethyl)-4-phenyl butanal by NMR and HRMS studies, Table 1, entry 1). After the successful synthesis of **3a**, we moved to improve the reaction conditions for better outcomes. Using different transition metal photocatalysts such as PC-2 = Ir(ppy)<sub>2</sub>(dtbbpy)PF<sub>6</sub> and PC-3 = [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> could not provide better results, and **3a** was obtained in a lower yield than the initial reaction conditions (Table 1, entries 2 and 3). Next, to check the efficiency of the organic photocatalyst towards the model reaction, we used eosin Y (PC-4) instead of PC-1. Unfortunately, with PC-4 we did not get the desired product **3a** even in

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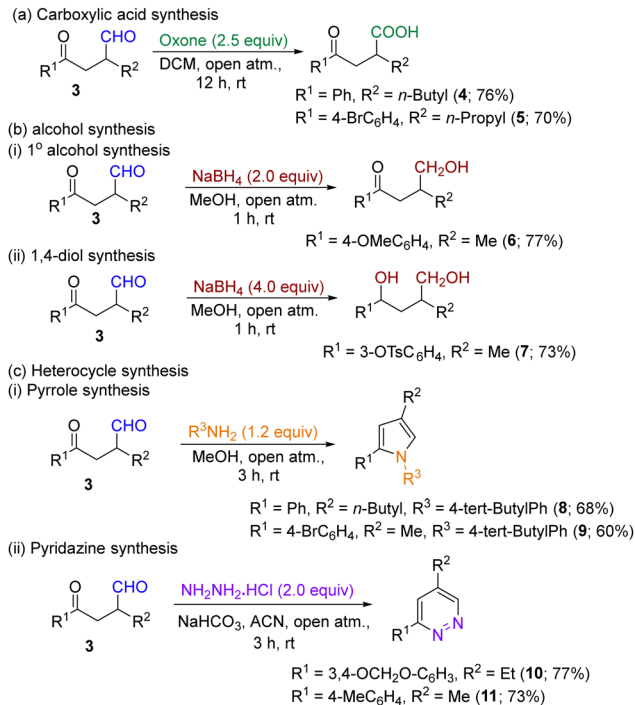
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optimized conditions, we employed *o*-CF<sub>3</sub> and *p*-CF<sub>3</sub> containing substrates (**1p** & **1q**). To our pleasure, both the substrates were converted to their corresponding aldehydes in excellent yields (**3p** & **3q**; 74% & 71%, respectively; Table 2). Furthermore, a 3,4-methylenedioxy containing substrate (**1r**) also furnished the desired product in a good yield (**3r**, 80%). A few extended aromatic substrates (**1s** & **1t**) were also tested under the optimized conditions, and provided the desired products in good yields (**3s** & **3t**; 68% & 70%, respectively, Table 2).

Next, we planned to explore some other trialkyl amines (**2b–2e**) for the synthesis of aldehydes under standard conditions. Using tri-propyl amine **2b**, surprisingly, yielded a new product **3u** (77%). Comprehensive NMR and HRMS studies of **3u** indicated that the product formation involved mono-functionalization of **2b**, unlike product **3a**, which involved bi-functionalization of **2a**. This unprecedented result might be attributed to the steric hindrance of the methyl group of **2b**, which inhibits the attack of the second molecule of **1a** to **3u**. With this unique result in hand, next, we explored the substrate scope of **1** with **2b**. A variety of differently substituted alkyl bromides were tolerated well under the optimized conditions furnishing the desired products **3u–3af** in excellent yields (Table 2). The substrates with electron-donating groups (Me, OMe, OTs and Et) as well as with electron-withdrawing groups (F, Cl and Br) at their respective positions (*ortho*, *meta*, *para*) were tolerated well with **2b** under the optimized photoredox conditions and furnished the desired  $\alpha$ -functionalized aldehydes in good to excellent yields (**3v–3ad**, 69–81%; Table 2). Moreover, 3,4-methylenedioxy and extended aromatic substituted substrates were also treated with **2b**, which provided the corresponding desired products in a good yield (**3ae** & **3af**, 85% & 80%, respectively Table 2). Next, to introduce a few long-chain aldehydes into the list, we performed our reaction with other trialkyl amines such as tri-butyl amine **2c**, tri-amyl amine **2d** and tri-hexyl amine **2e**. To our pleasure, all tested amines worked well under the optimized photoredox conditions and furnished their corresponding long chain  $\alpha$ -functionalized aldehydes in good to excellent yields (**3ag–3ar**, 71–83%; Table 2). However, the use of alkyl bromides such as bromoethane, 1-bromobutane and 1-bromopentane could not provide the desired product under the established protocols exhibiting the limitation of this protocol. The desired product could not be obtained even with secondary amines, and it afforded a simple nucleophilic substitution product.

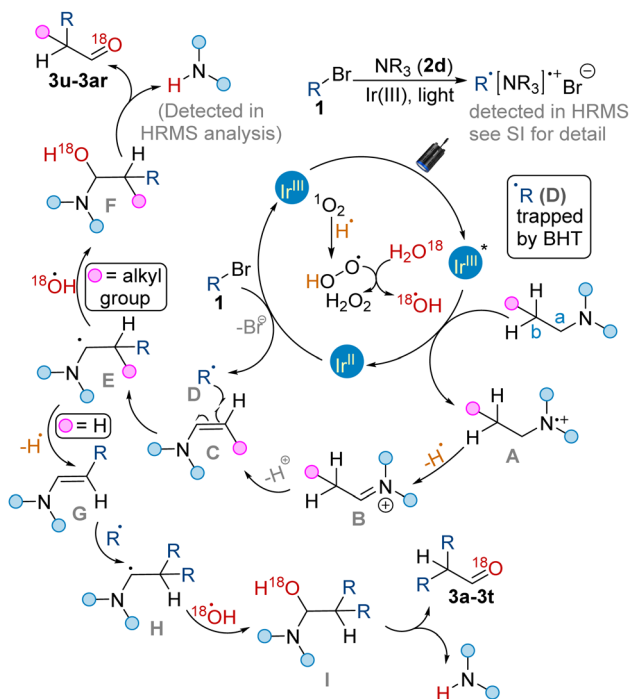
Following the successful photocatalytic synthesis of differentially substituted  $\alpha$ -functionalized aldehydes, our attention turned to converting these molecules to additional derivatives, including carboxylic acids, alcohols and N-heterocycles. Thus, when the aldehyde derivatives were subjected to oxidation in the presence of oxone under open atmospheric conditions, the corresponding acid derivatives were obtained in good yields (Scheme 1a). Additionally, under reductive conditions (NaBH<sub>4</sub> + MeOH), we successfully converted the products **3** to their corresponding primary alcohol derivative **6** and 1,4-diol derivative **7** in good yields (Scheme 1b). The synthesized aldehyde derivatives **3** have two carbonyl groups (one keto and one



Scheme 1 Synthetic applications of the aldehydes.

aldehyde), which could provide good reaction sites for the synthesis of heterocycles. Keeping this idea in mind, when we treated compound **3** with 4-*tert*-butylaniline in methanol at room temperature, the pyrrole derivatives (**8** & **9**) were obtained in good yields [Scheme 1c (i)]. Similarly, a few functionalized aldehydes effectively gave their respective pyridazine derivatives in high yields, when treated with hydrazine hydrochloride in the presence of NaHCO<sub>3</sub> in ACN at room temperature [Scheme 1c (ii)].

Based on previous reports,<sup>12,13</sup> and data collected from cyclic voltammetry and control experiments (see Scheme S3 in ESI† for details), we proposed a tentative mechanistic pathway for the formation of functionalized aldehydes by the cross-coupling of alkyl bromides **1** with alkyl amines **2** under Ir(III)-catalyzed photoredox conditions (Scheme 2). The first step of the reaction involved reductive quenching to generate *N*-centred radical cation **A** of alkyl amine **2** ( $E_{\text{ox}} = +0.98$  V for **2a**,  $E_{\text{ox}} = +1.02$  V for **2d** and  $E_{\text{ox}} = +0.91$  V for **2e**; see ESI† for detail CV experiments) by excited Ir(III)\* photocatalyst ( $E^{1/2 * \text{III}/\text{II}} = +1.21$  V vs. SCE).<sup>13</sup> This radical cation by the elimination of a hydrogen radical generated iminium intermediate **B**. Intermediate **B** on elimination of a proton generated suitable intermediate **C**. On the other hand, reductant Ir(II) carried out the reduction of alkyl bromide ( $E_{\text{red}} = -1.73$  V for **1a**) to generate alkyl radical **D** ( $\text{R} = \text{PhCO}$ ; trapped by BHT radical scavenger and detected in HRMS analysis; see ESI† for the detailed experiment), completing the iridium photoredox cycle. Next, the radical intermediate **D** reacted with **C** generating another radical intermediate **E**. The radical intermediate **E** upon reaction with hydroxyl radicals (which could possibly be generated by the reaction of singlet oxygen with hydrogen radicals



Scheme 2 Tentative mechanistic pathway.

followed by its reaction with  $\text{H}_2\text{O}$ ) produced intermediate **F**. Intermediate **F** on elimination of a secondary amine (detected in HRMS analysis; see ESI<sup>+</sup> for detail) provided aldehyde products (**3u–3ar**). In the case of TEA (**2a**), the radical intermediate **E** again undergoes hydrogen radical elimination to generate intermediate **G**. Intermediate **G** could follow the same mechanistic pathway (as followed by intermediate **C**) and produced the desired aldehyde products (**3a–3t**) upon elimination of a secondary amine.

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## Conflicts of interest

There are no conflicts to declare.

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