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Selective Oxidative Esterification from Two Different Alcohols via Photoredox Catalysis

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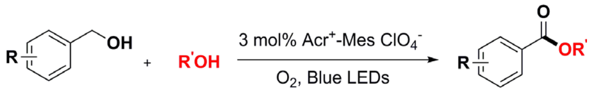
Esters functionalities are important building blocks that are extensively used in the chemical industry and academic laboratories. Direct oxidative esterification from easy-available alcohols to esters would be a much more appealing approach, especially using O_2 as terminal oxidant. Inputting external energy by photocatalysis for dioxygen activation, a mild and simple method for ester synthesis from two different alcohols has been achieved in this work. This reaction is performed under neutral conditions using O_2 as the terminal oxidant. A variety of primary alcohols, especially long chain alcohols and secondary alcohols are tolerated in this system.

Oxidation using dioxygen has been of long-standing interest and has fascinated chemists owing to its tremendous potential usage.[1] Although a variety of oxidation processes have been developed, direct oxidation of organic substrates using molecular oxygen under mild conditions still remains difficult.[2] Visible light, as a clean source of energy, has received increasing attention from the chemistry community.[3] The application of light-induced processes can avoid the need for further external energy supply, as the molecule takes up sufficient energy upon photochemical excitation for immediate product formation.[4] Over the years, various useful and unique organic reactions that are initiated by visible light irradiation have been well-developed.[5] The unique mode of "activating" molecule through photocatalysis carries great potential towards invention of novel chemical reactivity and mediating efficient transformation under mild and environmentally benign conditions. The molecular oxygen was also used as the oxidant in many visible-light mediated oxidative reactions.[6] On behalf of green and sustainable chemistry, using visible-light photoredox catalysis for dioxygen activation to synthesize useful compounds will be a challenging but highly desirable task.

Esters are important building blocks and widely found in natural products, bulk chemicals, and polymers.[7] Direct oxidative esterification from easy-available alcohols to esters would be a much more appealing approach. Although several reported methods with stoichiometric amounts of oxidants, such as metal salts, molecular iodine, and H_2O_2, can achieve this transformation,[8] large amounts of toxic waste are formed. In the search for a more sustainable chemical production, researchers have put considerable effort into the development of catalytic oxidations using air or molecular dioxygen as the stoichiometric oxidant. In 2012, Beller's group and our group independently realized the palladium-catalyzed direct oxidative esterification reactions between two different alcohols using molecular oxygen.[9] Later, other groups successfully realized direct oxidative esterification reactions from alcohols under homogeneous or heterogeneous conditions.[10] These methods provided general routes to a variety of esters through dioxygen activation. Despite notable recent efforts, transition metal catalysts, base, or special ligands are always needed and the alcohols are always limited to primary alcohols with short chains. Owing to the importance of the esters, seeking a mild and simple way to oxidative esterification from alcohols is always under operation in our lab. In this communication, we present a simple and efficient method for the direct esterification of alcohols through dioxygen activation promoted by visible light (Scheme 1). This protocol can tolerate a variety of primary and secondary alcohols, especially long chain alcohols.



Scheme 1. Oxidative esterification between two alcohols via photoredox catalysis.

We started our evaluation of oxidative esterification reaction parameters using benzylic alcohol and methanol as model substrates (Table 1). The desired ester product **3a** could be achieved in 76% yield in the presence of 3 mol% photocatalyst 9-mesityl-10-methylacridinium perchlorate (Acr^+-Mes ClO_4^-) using methanol (**2a**) as both the nucleophile and solvent under O_2 atmosphere. The data in Table 1 illustrates the impact of different conditions on the efficiency of this reaction. Other tested photocatalysts, such as tris(bipyridine)ruthenium(II) chloride $[Ru(bpy)_3Cl_2]$ or 2′,4′,5′,7′-tetrabromofluorescein (Eosin Y) did not promote this reaction and could not get desired

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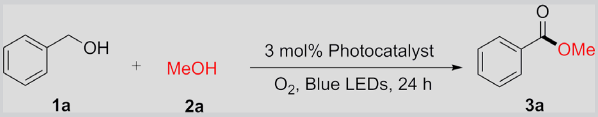
Table 1. Reaction optimization of visible light mediated aerobic oxidative direct esterification.[a]



Entry	Photocatalyst	Yield[b] [%]
1	Acr$^+$-Mes ClO_4	76
2	$Ru(bpy)_3(PF_6)_2$	n.d.
3[c]	Eosin Y	n.d.
4[d]	Acr$^+$-Mes ClO_4	29
5[e]	Acr$^+$-Mes ClO_4	n.d.
6[f]	Acr$^+$-Mes ClO_4	n.d.
7	none	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), photocatalyst (3.0 mol %) in CH_3OH (1.0 mL) at room temperature in O_2 using 3 W blue LEDs for 24 h. [b] Isolated product. n.d. = not detected. [c] Under 3 W green LEDs. [d] Under an air atmosphere. [e] Without light. [f] Under N_2 atmosphere.

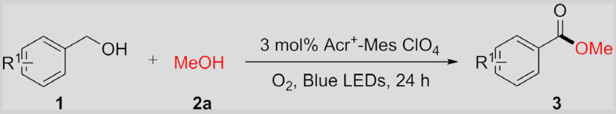
product (Table 1, entries 2 and 3). The desired ester product could be obtained in 29 % yield under air atmosphere (Table 1, entry 4). In the control experiments, no desired product was observed with neither photoredox catalyst nor light, indicating that the photoredox catalysis is essential to this oxidative process (Table 1, entries 5–7).

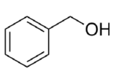
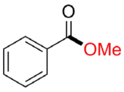
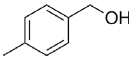
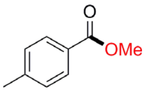
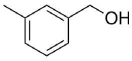
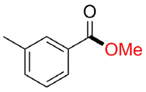
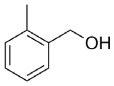
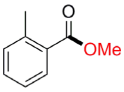
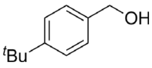
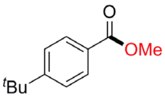
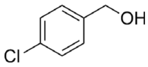
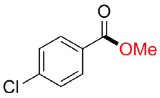
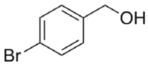
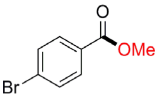
With the optimal conditions established, various substituted benzylic alcohols were employed in this aerobic oxidative esterification reaction (Table 2). The benzylic alcohols substituted with a methyl group in the *para*- and *meta*- positions could get the desired ester products in good yield (**3b** and **3c**). In addition, the sterically hindered benzylic alcohol substituted with methyl group in the *ortho*- position could also get 57 % yield of ester product (**3d**). An electron-donating group, such as a *tert*-butyl group, was well tolerated and afforded the desired product in 70 % yield (**3e**). Interestingly, the benzylic alcohols substituted with Cl and Br could also be smoothly converted into ester products in high yields, which can be used for further transformation (**3f** and **3g**). There was no reaction when testing benzylic alcohols substituted with other electron-withdrawing groups, such as CN and NO_2.

Next we applied the optimized reaction conditions to examine different alkyl alcohols using 4-bromobenzyl alcohol as the model substrate (Table 3). Reactions of **1g** with primary alcohols, such as EtOH, *n*-BuOH, and *iso*-BuOH (**3h**–**3j**) could afford the desired ester products in moderate yields. The long chain primary alcohols such as *n*-$C_6H_{13}OH$ and *n*-$C_{12}H_{25}OH$ were suitable for this reaction and could also obtained corresponding ester products (**3k** and **3l**). Especially, the secondary alcohol was also tested for this ester transformation. The isopropanol and heptan-2-ol could also be transformed into the ester products. However, the sterically hindered tertiary alcohol did not afford the product (**3o**).

Although the yield is not high, this provides a method for the synthesis of esters from two different alcohols using photoredox catalysis. We proposed this is because of low reactivity of the long-chain alcohols and secondary alcohols. Therefore, several Lewis acids have been screened to promote this oxida-

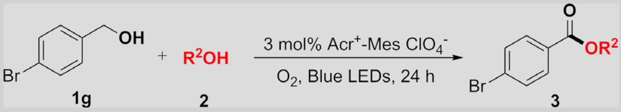
Table 2. Visible light mediated aerobic oxidative direct esterification between benzylic alcohol derivatives and methanol.[a]

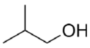
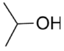
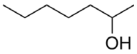
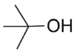


Entry	1	3	Yield
1			**3a**, 76 %
2			**3b**, 74 %
3			**3c**, 72 %
4			**3d**, 57 %
5			**3e**, 70 %
6			**3f**, 71 %
7			**3g**, 80 %

[a] Reaction conditions: **1** (0.5 mmol), Acr$^+$-Mer ClO_4 (3.0 mol %) in CH_3OH (1.0 mL) at room temperature in O_2 using 3 W Blue LEDs for 24 h. Isolated yield.

Table 3. Visible light mediated aerobic oxidative direct esterification between benzylic alcohol and alkyl alcohols.

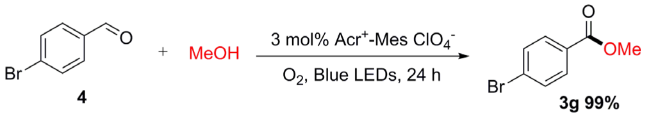


Entry	R^2OH	3	Yield[a] [%]	Yield[b] [%]
1	MeOH	**3g**	80	–
2	EtOH	**3h**	65	67
3	*n*BuOH	**3i**	50	70
4		**3j**	34	60
5	$CH_3(CH_2)_5OH$	**3k**	43	65
6	$CH_3(CH_2)_{11}OH$	**3l**	32	63
7		**3m**	30	59
8		**3n**	15	42
9		**3o**	n.d.	n.d.

[a] Reaction conditions: **1g** (0.5 mmol), Acr$^+$-Mer ClO_4 (3.0 mol %) in solvent (R^2OH/CH_3CN = 0.5 mL/1.0 mL) at room temperature in O_2 using 3 W blue LEDs for 24 h. Isolated yield. [b] Reaction conditions: **1g** (0.5 mmol), Acr$^+$-Mer ClO_4 (3.0 mol %), $Cu(OTf)_2$ (10 mol %) in solvent (R^2OH/CH_3CN = 0.5 mL/1.0 mL) at room temperature in O_2 under 3 W blue LEDs for 24 h. Isolated yield.

tive esterification reaction (see the Supporting Information for details). Using 4-bromobenzyl alcohol and isopropanol as model substrates, we found that 10 mol% copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] can promote the reaction and lead to the ester product up to 59% yield. Under the modified reaction conditions established using $Cu(OTf)_2$ as the additive, several primary and secondary alcohols, for which the yields are relatively low, were further tested. Reactions of **1g** with primary alcohols, such as EtOH, *n*-BuOH and *iso*-BuOH (**3h**–**3j**) can afford the desired ester product in good yields. The long chain primary alcohols, such as $C_6H_{13}OH$ and *n*-$C_{12}H_{25}OH$, could get the product in good yields (**3k** and **3l**). Isopropanol and heptan-2-ol can be transformed into the ester products in moderate yields under new reaction conditions (**3m** and **3n**). These results revealed the copper catalyst can promote this photo-induced oxidative esterification.

To gain some insights into this transformation, some mechanistic studies were demonstrated. Using the 4-bromobenzyl aldehyde **4** as the model substrate under photocatalytic conditions, almost quantitative yield of the ester product was formed, which reveals that benzyl aldehyde may be an intermediate in this oxidation esterification reaction (Scheme 2). The radical-inhibiting experiment indicated that a radical mechanism was involved in this transformation (Scheme 3).



Scheme 2. Oxidative esterification using benzyl aldehyde via photocatalysis.

Scheme 3. Radical inhibiting experiment using TEMPO.

The time profile of photocatalytic reaction shown in Figure 1 revealed that the reaction was totally inhibited in the absence of light. This result indicated that continuous irradiation of visible light is essential to this photocatalytic transformation. Furthermore, operando IR was also used to probe this oxidative reaction process. Figure 2 clearly shows an obvious decrease in the substrate (**1g**) and increase of product (**3g**). Based on this figure, an inductive period existed in this reaction for the forming of ester product.

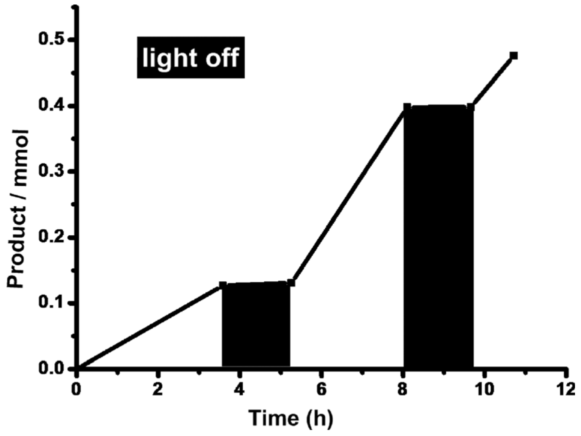


Figure 1. Time profile of photocatalytic reaction with and without visible light.

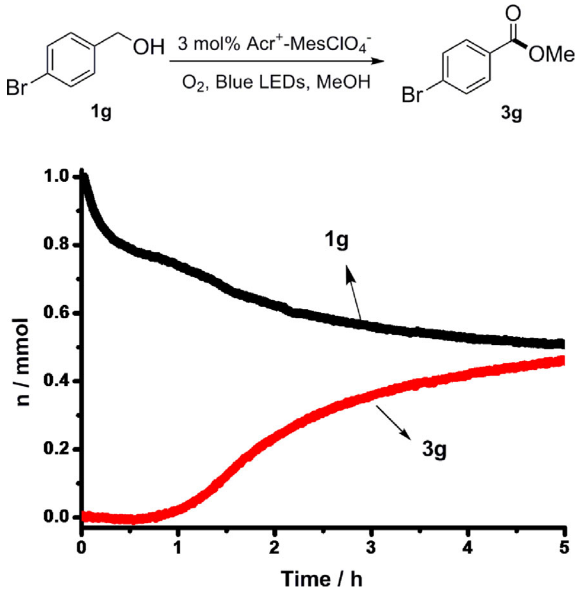
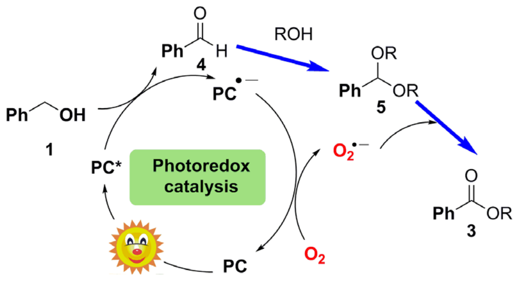


Figure 2. Kinetic studies using in situ IR. Oxidative esterification between (4-bromophenyl)methanol **1g** and MeOH.



Scheme 4. Proposed mechanism.

Based on the previous report[6f] and experimental results, a plausible mechanism is proposed in Scheme 4. Firstly, the photocatalyst Acr^+-Mes ClO_4^- is excited by visible-light irradiation (3 W blue LEDs) to generate the excited species [Acr^+-$MesClO_4^-$]*, which then undergoes a single electron transfer (SET) process with benzylic alcohol to generate benzyl aldehyde **4**, and [Acr^+-Mes ClO_4^-]$^{\bullet-}$. [Acr^+-Mes ClO_4^-]$^{\bullet-}$ can be oxidized by O_2 to recycle the photocatalytic reaction. The generated benzyl aldehyde can react with alcohol to form the hemiacetal intermediate **5**. This hemiacetal could be under further oxidation and transformed to ester **3**. The copper catalyst may have an impact on the hemiacetals formation for long-chain alcohols and secondary alcohols.

Overall, we have successfully developed a mild and simple method to esters from two different alcohols under visible-light conditions. This reaction is performed under neutral conditions using O_2 as terminal oxidant. A variety of primary alcohols, especially long chain alcohols and secondary alcohols are tolerated in this system. The protocol provides a mild route for dioxygen activation using photocatalysis, which will help chemists to design more interesting, useful, and sustainable reactions in the near future.

Acknowledgements

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Keywords: alcohol oxidation · dioxygen activation · esterfication · oxidative coupling · photoredox catalysis

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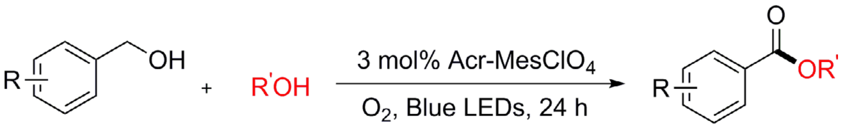

Photo for energy: Inputting energy by photocatalysis for dioxygen activation, a mild and simple method for ester synthesis from two different alcohols, is described. This reaction is performed under neutral conditions using O_2 as the terminal oxidant. A variety of primary alcohols, especially long chain alcohols and secondary alcohols are tolerated in this system.

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Selective Oxidative Esterification from Two Different Alcohols via Photoredox Catalysis