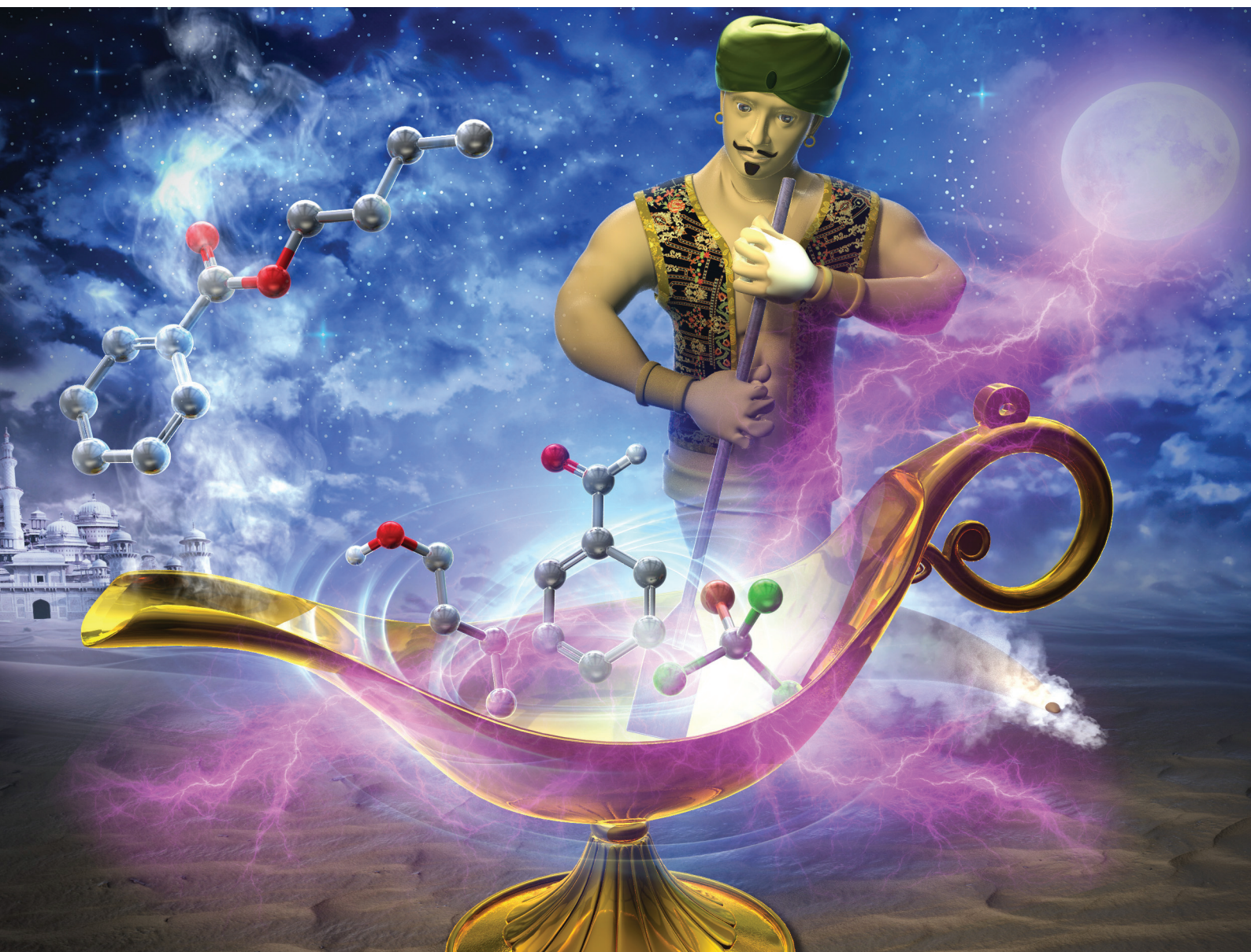


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A direct oxidative esterification of aldehydes with alcohols mediated by photochemical C–H bromination†

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The photochemical direct esterification of aldehydes with alcohols via *in situ*-generated acyl-bromides presented in this report is an attractive complementary addition to hitherto reported methods, as these are usually carried out in a two-step, one-pot procedure in order to avoid side reactions such as the oxidation of alcohols by halogen sources.

Esterification is a practical method in organic chemistry for the synthesis of various bioactive compounds and functional materials. Over the past decades, the esterification of carboxylic acids with alcohols has typically been performed using various condensation reagents.¹ Alternatively, the direct oxidative esterification of aldehydes with alcohols has emerged as a complementary method. The classical oxidative esterification of aldehydes proceeds *via* the oxidation of a hemiacetal intermediate using stoichiometric oxidants (Scheme 1(a)).² Although these reactions are useful to synthesize esters, the development of a more efficient approach for the esterification of aldehydes with alcohols would be highly desirable in the pursuit of sustainable organic synthesis.

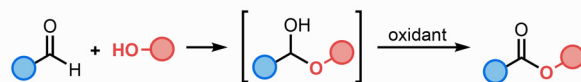
Oxidative esterifications *via* acyl halides represent a highly useful method in organic chemistry to generate functionalized esters (Scheme 1(b)). Recently, Kim and coworkers have reported an oxidative esterification with dibromoisocyanuric acid (DBI) *via* acyl bromides.³ Furthermore, photochemical esterifications with halogen sources such as *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) have also been developed.⁴ Despite these advances, these reactions

are usually carried out in a two-step, one-pot procedure in order to avoid side reactions such as the oxidation of alcohols by halogen sources.⁵ Thus, the development of more efficient methods, such as direct esterifications, still remains desirable.

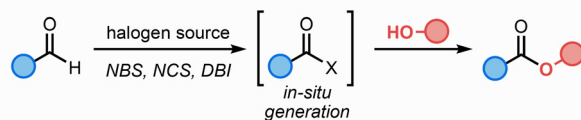
Our group has developed various visible-light-induced photochemical reactions.⁶ During our investigations, we have discovered an unexpected photochemical esterification of an aldehyde with an alcohol, which prompted us to investigate the direct photochemical esterification of aldehydes. Here, we report the esterification of aldehydes with alcohols mediated by a photochemical C–H bromination.

We initially investigated the optimization of the reaction conditions for the photochemical esterification of benz-

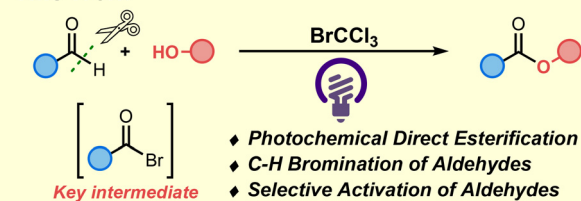
a) Classical Esterification of Aldehydes with Alcohols



b) A Two Step, One-pot Esterification of Aldehydes with Alcohols



This Work



Scheme 1 Examples of oxidative esterifications of aldehydes with alcohols.

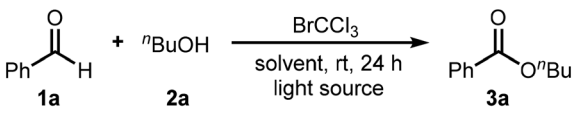
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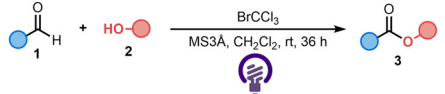
Table 1 Photochemical esterification of benzaldehyde with 1-butanol^a

			
Entry	Light source (nm)	Solvent	Yield (%)
1	425	CH ₂ Cl ₂	10
2	380	CH ₂ Cl ₂	75
3	365	CH ₂ Cl ₂	74
4	380	Toluene	18
5	380	CH ₃ CN	15
6	380	Hexane	66
7 ^b	380	CH ₂ Cl ₂	64
8 ^c	380	CH ₂ Cl ₂	Trace
9 ^d	380	CH ₂ Cl ₂	40
10 ^e	380	CH ₂ Cl ₂	86
11 ^f	380	CH ₂ Cl ₂	0
12	—	CH ₂ Cl ₂	Trace

^a All reactions were carried out using benzaldehyde (**1a**; 0.2 mmol), 1-butanol (**2a**; 0.26 mmol), and BrCCl₃ (0.6 mmol) in the specified solvent (2.0 mL) at room temperature under an argon atmosphere and photoirradiation. ^b CBr₄ was used instead of BrCCl₃. ^c CCl₄ was used instead of BrCCl₃. ^d BrCCl₃ (1.0 equiv.) was used. ^e MS3A (50 mg) was added to the reaction at 36 h. ^f Without BrCCl₃.

aldehyde (**1a**) with 1-butanol (**2a**) (Table 1). When the reaction was carried out under irradiation from blue LEDs ($\lambda_{\text{ex}} = 425$ nm), the desired ester (**3a**) was obtained in low yield (Table 1, entry 1). In contrast, under irradiation from purple LEDs ($\lambda_{\text{ex}} = 380$ nm), the product yield was increased to 75% (Table 1, entry 2), suggesting that the Br–C bond of BrCCl₃ is efficiently cleaved under these conditions. Ultraviolet light ($\lambda_{\text{ex}} = 365$ nm) can also be used for this reaction (Table 1, entry 3). Typical solvents such as toluene, CH₃CN, and hexane furnished the product in low to moderate yields (Table 1, entries 4–6). Although CBr₄ can be used instead of BrCCl₃, CCl₄ is not suitable, suggesting that the presence of a bromo group is important for the reaction to proceed (Table 1, entries 7 and 8). Reducing the amount of BrCCl₃ used resulted in a lower product yield (Table 1, entry 9). When the reaction was carried out for 36 h in the presence of MS3 Å, the desired product was obtained in high yield due to the reduced formation of benzoic acid (Table 1, entry 10). Control experiments, wherein BrCCl₃ or the light source were omitted, did not proceed, and it can therefore be concluded that both elements are crucial for the reaction to proceed (Table 1, entries 11 and 12).

Table 2 Scope of the photochemical esterification of aldehydes with alcohols^a

	
3b 87%	
3c 72%	
3d 82% ^b	
3e 49%	
3f 58%	
3g 61%	
3h 31%	
3i 70% ^c	
3j 70% ^b	
3k 96%	
3l 54% ^c	
3m 80%	
3n 82%	
3o 97%	
3p 63% ^d	
3q 42% ^d	
3r 54% ^e	
3a 86%	
3s 97%	
3t 72%	
3u 21%	
3v 36%	
3w 24% ^f	
3x 82%	
3y 58%	

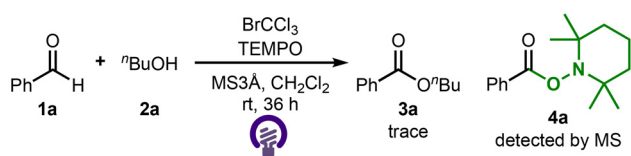
^a All reactions were carried out using aldehyde (**1**; 0.2 mmol), alcohol (**2**; 0.26 mmol), BrCCl₃ (0.6 mmol), and MS3 Å (50 mg) in CH₂Cl₂ (2.0 mL) at room temperature under an argon atmosphere and irradiation from purple LEDs ($\lambda_{\text{ex}} = 380$ nm). ^b CBr₄ was used under irradiation with ultraviolet light ($\lambda_{\text{ex}} = 365$ nm) for 72 h. ^c NaHCO₃ (1.4 mmol) was added to the reaction. ^d Alcohol (**2**; 1.2 mmol) and CBr₄ (1.2 mmol) were used under irradiation with ultraviolet light ($\lambda_{\text{ex}} = 365$ nm) for 72 h. ^e Alcohol (**2**; 1.8 mmol) and CBr₄ (1.8 mmol) were used under irradiation with ultraviolet light ($\lambda_{\text{ex}} = 365$ nm) for 72 h. ^f Alcohol (**2**; 0.52 mmol) was used.



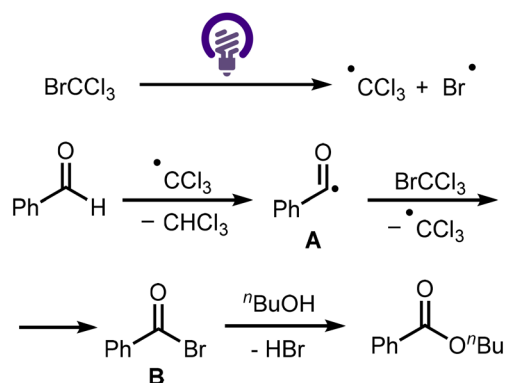
With the optimal conditions in hand, we subsequently screened the photochemical esterification using various alcohols and aldehydes (Table 2). Both electron-rich and -deficient aromatic systems are compatible with the applied reaction conditions (**3b–g**), and heteroaromatic aldehydes (**1h–1i**) are also tolerated. Cinnamaldehyde (**1j**) is a good substrate for this reaction. Furthermore, aliphatic aldehydes (**1k–1o**) are well tolerated, in particular those with more sterically congested groups, such as an adamantyl group (**1o**), which furnished the desired ester (**3o**) in excellent yield. Although aliphatic aldehydes have higher acyl-C–H bond dissociation energies relative to arylaldehydes, these reactions smoothly proceed to give the corresponding esters in good yields.⁷ Moreover, the reaction could be applied to multi-substituted aldehydes to give the corresponding esters (**3p–3r**) in moderate yields. Since these multi-substituted esters are found in functional materials,⁸ the present reaction constitutes a promising tool for the synthesis of these useful compounds. Notably, the current reaction allows for the synthesis of trisubstituted esters such as **3r**,⁹ for which there are so far only a few examples.¹⁰ A variety of aliphatic alcohols, including primary and secondary alcohols, furnished the desired esters (**3a–3y**) in moderate to high yields. While direct esterification reactions mediated by other halogen sources such as NBS are difficult due to side reactions between the halogen sources and the alcohols,^{3–5} the present reaction with BrCCl₃ can be effectively applied to alcohols **1a–1y**. In fact, when the reactions of **1t** or **1x** were carried out with NBS, the desired products were not obtained.¹¹

To examine the reaction mechanism, we used a radical scavenger in the reaction (Scheme 2). When the reaction was performed with TEMPO, the product yield decreased effectively. In addition, an acyl radical was trapped by TEMPO and detected as **4a** using mass spectrometry. Thus, the reaction may produce an acyl radical *via* a radical reaction.

A feasible reaction mechanism is proposed in Scheme 3. Homolytic cleavage of BrCCl₃ under irradiation from purple LEDs affords a trichloromethyl radical and a bromo radical.¹² The bromo group is important for the reaction to proceed, as evident from the result obtained when using CCl₄ (Table 1, entry 8). According to Scheme 2, the trichloromethyl radical can dissociate the C–H bond of benzaldehyde to form acyl radical **A**, which reacts with BrCCl₃ to form acyl bromide **B**.^{3,4,13} This hypothesis is supported by the detection of benzoyl bromide using ¹H and ¹³C NMR spectroscopy.¹⁴



Scheme 2 Mechanistic study of the photochemical esterification. The reaction was carried out using benzaldehyde (**1a**; 0.2 mmol), 1-butanol (**2a**; 0.26 mmol), BrCCl₃ (0.6 mmol), TEMPO (0.6 mmol), and MS3 A (50 mg) in CH₂Cl₂ (2.0 mL) at room temperature under an argon atmosphere and irradiation from purple LEDs (λ_{ex} = 380 nm).



Scheme 3 Proposed reaction mechanism.

Finally, the alcohol can react with acyl bromide **B** to furnish the desired ester.

Conclusions

In summary, we have developed a direct photochemical esterification of aldehydes with alcohols under irradiation from purple LEDs. A variety of alcohols that are difficult to use in hitherto reported two-step, one-pot methods using halogen sources such as NBS are also suitable for this reaction. Various aromatic and aliphatic aldehydes are selectively activated by BrCCl₃ and thus suitable for this reaction. Notably, the reaction can be applied to multi-substituted aldehydes, resulting in the corresponding esters, which are found in functional materials. According to a mechanistic study using TEMPO, an acyl-radical intermediate is generated during the reaction. The present reaction provides access to a variety of functionalized esters and therefore constitutes a promising tool for the synthesis of bioactive compounds and functional materials.

Data availability

The data underlying this study are available in this article and its ESI.†

The data that support the findings of this study are available from the corresponding author, Kenta Tanaka, upon reasonable request.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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