

Green Chemistry

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Visible-light induced oxidative Csp³-H activation of methyl aromatics to methyl esters

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Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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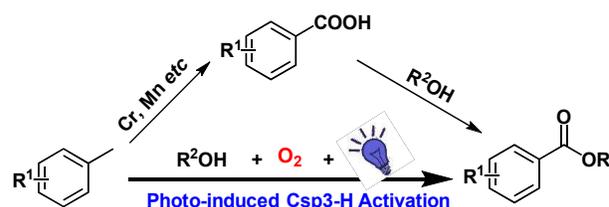
Directing functionalization of readily available hydrocarbons under mild conditions fulfills the requirements of green and sustainable chemistry. In this work, a mild and green catalytic oxidative Csp³-H activation of methyl aromatics mediated using O₂ via photocatalysis has been achieved. A lot of methyl aromatics can be tolerated, providing a green route for aromatic methyl carboxylates. In addition, this protocol can be scalable to gram scale.

Hydrocarbons are perhaps the most inexpensive and readily available materials, and utilization of such materials for the synthesis of essential chemicals is virtually and economically pragmatic. Toluene, the simplest and readily available alkylarene, has been used as a versatile building block.¹ Recently, the methylarene can serve as acyl source,² alkyl source³ and carboxylate source⁴. Although a lot of methodologies using methylarenes have been developed, the transition metal, strong oxidant or high temperature is always needed. Therefore, the development of mild and green conditions for methylarenes functionalization is highly desirable.

Aromatic alkyl carboxylates have attracted a great deal of interest in organic synthesis as versatile compounds or intermediates such as liquid crystal polymers, cosmetics, pharmaceuticals, agrochemicals, and food additives.⁵ Traditional methods to esterification is accomplished using activated carboxylic acids derivatives with alcohols. Recently, oxidative esterifications of an aldehydes⁶ and alcohols⁷ have also been developed. The ideal way to construct the ester is just from easy-available methylarenes and alcohols. During the past years, several methods has been achieved the aromatic esters synthesis from methyl aromatics. However, two steps involved in this process: oxidation of alkyl

aromatics to carboxylic acids with heavy metals such as Cr, Mn etc⁸ and then esterifications with alcohols⁹. The pursuit for direct oxidative esterification between methylarenes and alcohols is always on the way for organic chemist.¹⁰

The photoredox catalysis have been widely developed in organic synthesis since 2008, providing a mild condition for organic transformations.¹¹ Inputting energy by visible-light, the molecular can be activated and used in a lot of transformations. Due to redox property of the activated state photocatalyst, the benzylic Csp³-H bond can be activated via photocatalysis.¹² In 2015, our group successfully a photo-oxygenation of benzylic sp³ C-H reaction using O₂ mediated to the ketones.^{12h} Due to our continuous research interest for the methylarenes, seeking a mild and green way to functionalization of methylarenes is always under operation in our lab. Herein, we report a simple and green catalytic oxidative esterification approach that efficiently converts methyl aromatics to aromatic carboxylates mediated by visible-light using molecular oxygen as benign oxidant (Scheme 1). This condition tolerates a variety of methyl aromatics, providing a green route for aromatic methyl carboxylates. In addition, this protocol can also be scalable to gram scale.



Scheme 1. Visible light mediated efficient oxidative benzylic sp³ C-H activation to methyl esters from methyl aromatics.

Initially, we started our evaluation of the reaction parameters with *p*-xylene **1a** as the model substrate using Acr⁺-Mes ClO₄⁻ as the photocatalyst, which has a strong oxidative ability and already used in several oxidative reactions.^{12a, 12g, 13} The target methyl 4-methylbenzoate **2a** could be achieved in 38% yield in the presence of 3.0 mol% Acr⁺-Mes ClO₄⁻ using MeOH as the solvent in O₂ atmosphere under a 3W blue LEDs (Table 1, entry 1). In the control experiments, no desired product was observed with neither

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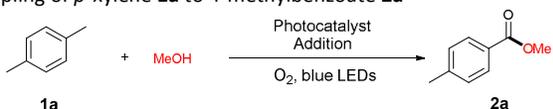
† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, and copies of ¹H, ¹³C NMR spectra. See DOI: 10.1039/c000000x/

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photoredox catalyst nor light indicating that the photoredox catalysis is essential to this process (Table 1, entries 2 and 3). The reaction did not happen without O₂ (Table 1, entry 4). Other data in Table 1 illustrates the impact of different conditions on the efficiency of this reaction. Other tested photocatalysts such as Ru(bpy)₃Cl₂, Eosin Y or Ir(ppy)₃ did not get desired product (Table 1, entries 5, 6 and 7). Among the screened acids (Table 1, entries 8–13), HCl as the additive provided a significant improvement in yield (entry 8, 65% yield). A further optimization of reaction parameters was subsequently conducted. The yield of **2a** decreased when shorten the time (entries 14 and 15), and increasing photocatalyst loadings also proved to be beneficial (entry 17, 74% yield). Further optimization using HCl as addition led us to reduce the amount of HCl to 0.2 equiv in 2.0 mL of MeOH (entry 18). Therefore, the best conditions for getting benzophenone product **2a** were using 7.0 mol% Acr⁺-Mes ClO₄⁻, 20 mol% HCl as the additive using MeOH as the solvent in O₂ atmosphere irradiated by 3W blue LEDs.

Table 1. The conditions screening of photo-induced oxidative coupling of *p*-xylene **1a** to 4-methylbenzoate **2a**^a



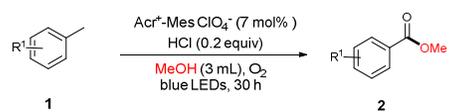
entry	Photo catalyst	Addition (equiv)	Time(h)	yield(%) ^b
1	Acr ⁺ -Mes	-	30	38
2 ^d	Acr ⁺ -Mes	-	30	n. d. ^c
3	-	-	30	n. d. ^c
4 ^e	Acr ⁺ -Mes	-	30	n. d. ^c
5	Ru(bpy) ₃ (PF ₆) ₂	-	30	n. d. ^c
6	Eosin Y	-	30	n. d. ^c
7	Ir(ppy) ₃	-	30	n. d. ^c
8	Acr ⁺ -Mes	HCl(0.3)	30	65
9	Acr ⁺ -Mes	HNO ₃ (0.3)	30	54
10	Acr ⁺ -Mes	HClO ₄ (0.3)	30	43
11	Acr ⁺ -Mes	HBr(0.3)	30	15
12	Acr ⁺ -Mes	HOAc(0.3)	30	50
13	Acr ⁺ -Mes	TFA(0.3)	30	40
14	Acr ⁺ -Mes	HCl(0.3)	12	39
15	Acr ⁺ -Mes	HCl(0.3)	24	50
16 ^f	Acr ⁺ -Mes	HCl(0.3)	30	23
17 ^g	Acr ⁺ -Mes	HCl(0.3)	30	74
18 ^g	Acr ⁺ -Mes	HCl(0.2)	30	76
19 ^g	Acr ⁺ -Mes	HCl(0.1)	30	71

^a Reaction conditions: **1a** (0.30 mmol), photocatalyst (3.0 mol%) and 0.2 eq. HCl in MeOH (2.0 mL) at rt in O₂ under 3W blue LEDs for 12 h. ^b Determined by GC using biphenyl as an internal standard. ^c n.d.= no desired product. ^d Without light. ^e Under N₂ atmosphere. ^f Acr⁺-Mes (1 mol%). ^g Acr⁺-Mes (7 mol%).

With the optimal conditions in hand, various methyl aromatics compounds were investigated and the results are summarized in Scheme 2. The methyl aromatics with an electron-donating group were good substrates that offer the corresponding methyl carboxylates in high yields. This oxidative reaction was compatible with aryl-Me, ^tBu, OMe and Ph groups (**2b** – **2h**). The C-Cl and C-Br group were well tolerated under this reaction conditions, providing the possibility for further functionalization (**2i** and **2j**). There were

no reaction when testing 4-nitrotoluene, 4-cyanotoluene and 2-picoline. When using 1- or 2-substituted methylnaphthalene as the starting materials under the standard conditions, the reagents were consumed completely while no desired ester products were generated.

Scheme 2. Visible light mediated efficient oxidative benzylic sp³ C–H to methyl esters^a



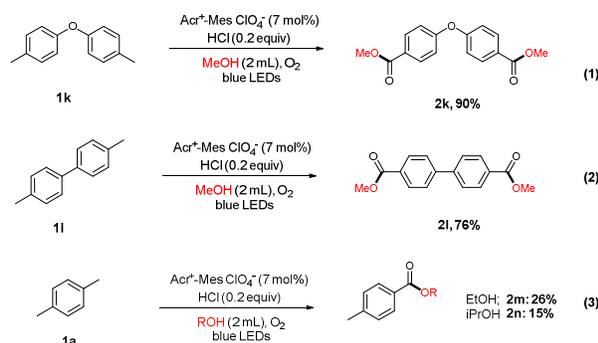
Entry	Substrate	Product	Yield ^b (%)
1			2a , 76% ^c
2			2b , 87% ^c
3			2c , 47% ^c
4			2d , 21% ^c
5			2e , 67%
6			2f , 77%
7			2g , 65%
8			2h , 63%
9			2i , 62%
10			2j , 50%

^a Reaction conditions: **1** (0.3 mmol), Acr⁺-Mer ClO₄⁻ (7.0 mol%) and HCl (0.2 equiv) in MeOH (3 mL) at room temperature in O₂ irradiated with 3 W Blue LEDs for 30 h. ^b Isolated yield. ^c GC yield.

Interestingly, 4,4'-dimethylbiphenyl (**1k**) and 4,4'-oxybis(methylbenzene) (**1l**) also afforded the corresponding dimethyl esters **2k** and **2l** in excellent yields (Scheme 3, eq 1 and eq 2), which are good intermediates for high-performance materials. In addition, we found that the EtOH and *i*-PrOH could be suitable for this transformation (**2m** and **2n**), while no desired product was formed when using *n*-PrOH. A variety of amines were also tried.

Unfortunately, there were no reaction when using common amines such as benzamide, pyrrolidine or piperidine.

Scheme 3. Direct aerobic photo-oxidative synthesis of methyl esters with alcohols



Furthermore, the gram-scale synthesis of methyl ester was also performed. In general, photoreaction is difficult at high concentration, fortunately, methyl ester **2f** was obtained in moderate yield even at 10 mmol scale (52%) (Scheme 4). This result provides a possibility for the usage of this method in industrial field.

Scheme 4. Gram-scale synthesis of methyl ester



As shown in Figure 1, the time profile of photocatalytic reaction 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 photo-catalytic transformation.

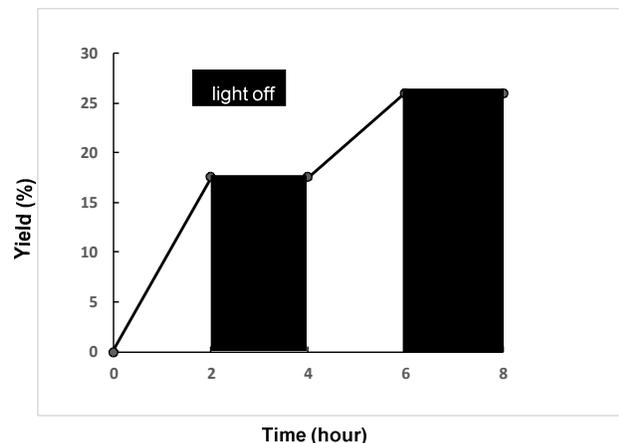
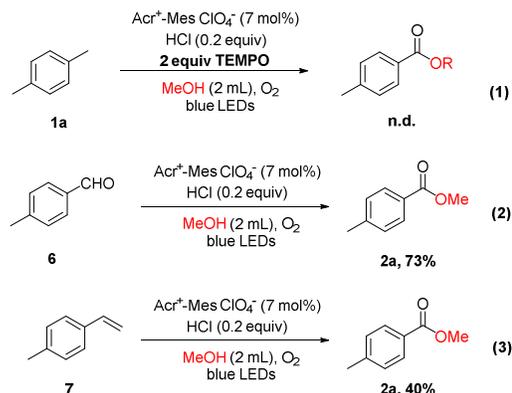


Figure 1. Time profile of photocatalytic reaction with and without visible light.

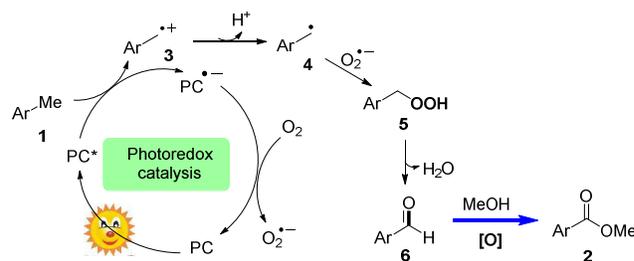
To gather more insights into this oxidative reaction, two equivalents 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was added to the model reaction and the reaction was totally inhibited, which

implied a radical mechanism was involved. When using *p*-toluylaldehyde **6** as the starting material under the standard conditions, 73% yield of the ester product **2a** was afforded. This result reveals that *p*-toluylaldehyde may serve as an intermediate in this transformation. We also tried 4-methylstyrene **7** in the reaction system (Scheme 5 Eq 3). To our surprise, the C=C bond was cleaved and the 4-methylbenzoate **2a** was afforded in 40% yield.

Scheme 5. Mechanistic studies



Based on the previous reports¹⁰ and experimental results, a plausible mechanism is proposed in Scheme 6. Firstly, the photocatalyst $\text{Acr}^+-\text{Mes ClO}_4^-$ is excited by visible light irradiation (3W blue LEDs) to generate the excited species $[\text{Acr}^+-\text{Mes ClO}_4^-]^*$, which then undergoes single electron transfer (SET) process with benzylic sp^3 C-H compound to generate radical cation **3**, and $[\text{Acr}^+-\text{Mes ClO}_4^-]$ radical anion. The $[\text{Acr}^+-\text{Mes ClO}_4^-]$ radical anion can be oxidized by O_2 to recycle the photocatalytic reaction. The generated radical cation **3** loses one proton to generate the radical **4**, followed by the reaction with O_2 or O_2 radical anion to generate the hydroperoxide intermediate **5**.^{10a,12h} The hydroperoxide intermediate **5** then loses one water to aldehyde **6**. The further oxidative coupling of aldehyde and MeOH to afford methyl ester **2** under photo-oxidative conditions.



Scheme 6. Proposed mechanism.

Conclusions

In conclusion, we have disclosed a simple and green catalytic oxidative esterification approach that efficiently converts methyl aromatics to aromatic carboxylates mediated by visible-light using molecular oxygen as benign oxidant. This condition tolerates a lot of

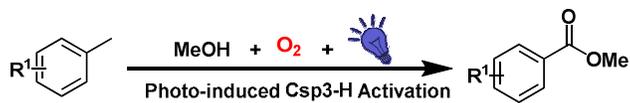
methyl aromatics, providing a green route for aromatic methyl carboxylates. In addition, this protocol can be scalable to gram scale. We believe photo-mediated this oxidative reaction will help chemists to design more and more interesting, useful, and sustainable reactions in the near future.

This work was supported by the 973 Program (2012CB725302), the National Natural Science Foundation of China (21390400, 21025206, 21272180, and 21302148), and the Research Fund for the Doctoral Program of Higher Education of China (20120141130002) and the Ministry of Science and Technology of China (2012YQ120060). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

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§ Lingling Zhang and Hong Yi contributed equally.

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