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Neutral-Eosin Y-Catalyzed Regioselective Hydroacylation of Aryl Alkenes under Visible-Light Irradiation

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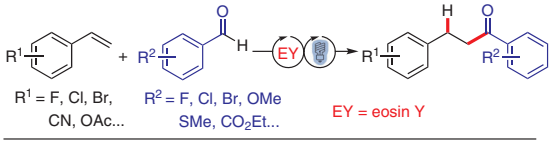

- Metal-free, additive-free
- Mild conditions
- Anti-Markovnikov selectivity
- Atom- and step-economy
- >20 examples, 19–75% yields

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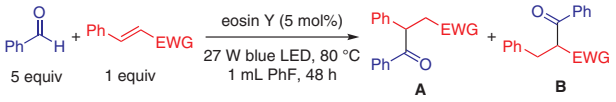
Abstract Styrene derivatives were hydroacylated with exclusive anti-Markovnikov selectivity by using neutral eosin Y as a direct hydrogen-atom-transfer (HAT) catalyst under visible-light irradiation. Aldehydes and styrenes with various substituents were tolerated (>20 examples), giving the corresponding products in moderate to high yields. The key acyl radical intermediate was generated from a direct HAT process induced by photoexcited eosin Y. Subsequent addition to styrenes and a reverse HAT process generated the ketone products.

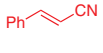
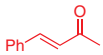
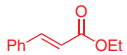
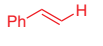
Key words hydroacylation, ketones, eosin Y, hydrogen atom transfer, acyl radicals, photocatalysis

Ketones are versatile and valuable building blocks in synthetic chemistry. They are also key motifs in many natural products and pharmaceuticals.[1] Developing efficient methods to access ketone compounds is highly desirable. Hydroacylation of alkenes by insertion of the C–H bond of an aldehyde is the most direct pathway for the synthesis of ketones, and has excellent atom- and step-economy. Transition-metal-mediated hydroacylation has become well established during the past few decades.[2] However, to avoid the side-reactions resulting from decarbonylation, a high pressure of CO and the use of aldehydes with coordinating groups are often required to deliver the final ketone products.[2b,3]

The emergency of photocatalysis has provided enormous opportunities for the synthetic community.[4] In this regard, hydroacylation through a radical mechanism under photoirradiation has been investigated. The key acyl radical intermediate can be generated from such precursors as aldehydes,[5] acyl silanes,[6] acyl chlorides,[7] α-keto acids,[8] carboxylic acids,[9] 4-acyl-1,4-dihydropyridines,[10] or acyl oximes[11] through either a single-electron-transfer (SET) or hydrogen-atom-transfer (HAT) process induced by photocatalysis.[12] Among these precursors, aldehydes are especially attractive because they permit the most atom-economical hydroacylation of alkenes. However, the generated acyl radicals are usually added to electron-deficient alkenes due to their nucleophilic property,[5,13] with only few exceptions.[10,14] Extending the scope of alkenes would provide direct access to a wider range of ketones. Photocatalysis has provided enormous opportunities for C–H functionaliza-

Table 1 Regioselectivity of Hydroacylation with Styrenes Possessing Various EWGs[a]



Entry	Michael acceptor	Conv. (%)	Yield[b] (%) of **A**	Yield[b] (%) of **B**
1		43	17	12
2		58	6	32
3		71	–	65
4		100	–	70

[a] Reaction conditions: PhCHO (1.0 mmol), Michael acceptor (0.2 mmol), eosin Y (5 mol%), PhF (1 mL), blue LEDs.
[b] Determined by ^{1}H NMR spectroscopy of the crude product with 1,3,5-trimethoxybenzene as an internal standard.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

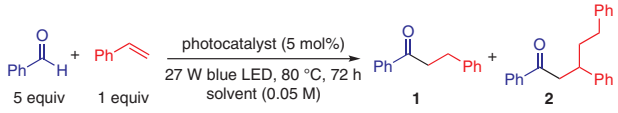
tion mediated by photopromoted HAT processes.[15,16] Our recent studies have shown that upon visible-light irradiation, neutral eosin Y can function as an excellent direct HAT photocatalyst in generating various carbon-centered radicals for further transformations.[17] Motivated by these discoveries, we surmised that hydroacylation of alkenes might be achieved by using this readily available and inexpensive organic dye as a photocatalyst.

We commenced our study by investigating hydroacylations of various Michael acceptors with eosin Y as a photocatalyst under 27 W blue LED (3 m strip) irradiation. When electron-withdrawing groups (EWGs) were present in a position β to the C=C bond of the styrene, acylation occurred at both its α- and β-positions. For instance, a mixture of ~17% α-addition products and 12% β-addition products was obtained when cinnamonitrile was used as the alkene partner (Table 1, entry 1). When less-electron-withdrawing substituents such as ketone or ester groups were present, the ratio of β-acylation products increased significantly (entries 2 and 3). Furthermore, changing the EWG to a hydrogen atom resulted in an exclusive β-acylation with 70% yield (entry 4). This selectivity is attributed to the formation of a benzylic radical intermediate that is stabilized by the phenyl substituent.

Next, the solvent for the hydroacylation of styrene were optimized (Table 2). Of the solvents tested, fluorobenzene was the most efficient, giving the hydroacylation product **1** in 70% yield, albeit accompanied by 10% of the alkylacylation byproduct **2** (Table 2, entry 1). This byproduct was formed by trapping of the benzyl radical adduct by a second molecule of styrene. Conducting the reaction in chlorobenzene, 1,2-dichloroethane, ethyl acetate, acetone, or acetonitrile all gave the required product but in low yields (entries 2–6). Other solvents (*t*-BuOH, DMSO, and DMF) were ineffective (entries 7–9).

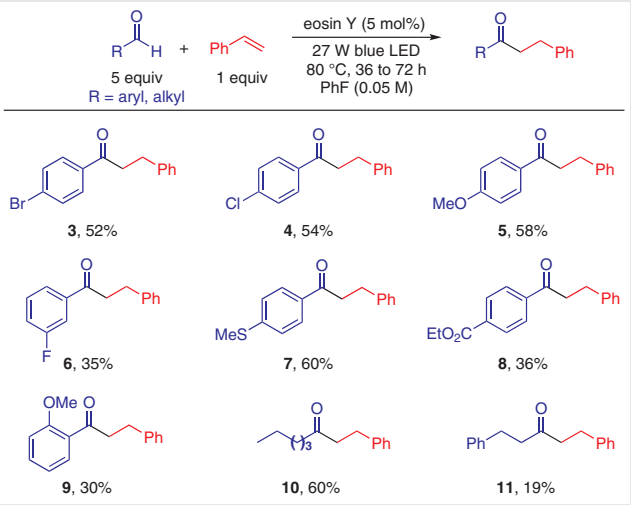
Other photocatalysts were subsequently evaluated. The common noble-metal-based photocatalysts $Ir(dFppy)_2(dtbpy)PF_6$ [dFppy = 2-(2,4-difluorophenyl)pyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] and $Ru(bpy)_3Cl_2·6H_2O$ were either much less effective or unreactive (entries 10 and 11). Although anthraquinone has been used as an effective direct HAT photocatalyst,[18] it gave no product under our reaction conditions (entry 12). In addition, the use of other organic dyes (erythrosin B, eosin B, or Acr-Mes-ClO_4) was also ineffective (entries 13–15). Finally, a control ex-

Table 2 Optimization of the Hydroacylation of Styrene[a]



Entry	Photocatalyst	Solvent	Conv. (%)	Yield[b] (%) of **1**	Yield[b] (%) of **2**
1	eosin Y	PhF	100	70	10
2	eosin Y	PhCl	100	37	12
3	eosin Y	EtOAc	70	34	9
4	eosin Y	DCE	60	19	6
5	eosin Y	acetone	40	14	5
6	eosin Y	MeCN	50	12	4
7	eosin Y	*t*-BuOH	20	–	–
8	eosin Y	DMSO	–	–	–
9	eosin Y	DMF	–	–	–
10	$Ir(dFppy)_2(dtbpy)PF_6$	PhF	35	11	5
11	$Ru(bpy)_3Cl_2·6H_2O$	PhF	–	–	–
12	anthraquinone	PhF	–	–	–
13	erythrosin B	PhF	–	–	–
14	eosin B	PhF	–	–	–
15	Acr-Mes-ClO_4[c]	PhF	–	–	–
16	–	PhF	–	–	–

[a] Reaction conditions: aldehyde (1.0 mmol), styrene (0.2 mmol), eosin Y (5 mol%), 4 mL solvent, blue LED light.
[b] By ^1H NMR spectroscopy of the crude product with 1,3,5-trimethoxybenzene as an internal standard.
[c] 9-Mesityl-10-methylacridinium perchlorate.



Scheme 1 Aldehyde scope for hydroacylation of styrene. *Reagents and conditions*: aldehyde (1.0 mmol), styrene (0.2 mmol), eosin Y (5 mol%), PhF (4 mL), blue LEDs. Isolated yields are reported. Alkylacylation byproducts were isolated in less than 10% yield in every case.

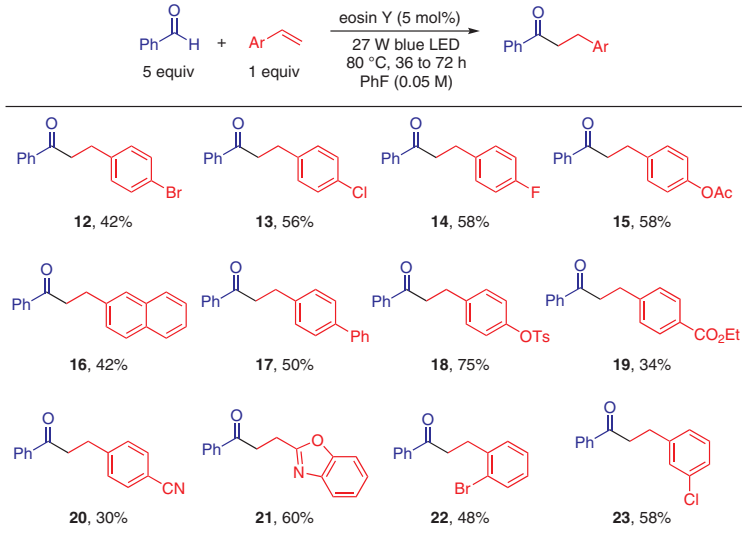
periment showed that the photocatalyst was essential to obtain the hydroacylation product (entry 16). These experiments indicated the unique effectiveness of neutral eosin Y for the present hydroacylation reaction.

With the optimized conditions in hand, we then investigated the acylation of various styrenes. As shown in Scheme 1, benzaldehydes with various functional groups on the phenyl ring, including halo groups (**3**, **4**, and **6**), ethers (**5**), sulfides (**7**), or esters (**8**), were well tolerated in the reaction.[19] Benzaldehydes possessing electron-donating (**5** or **7**) or electron-withdrawing (**3**, **4**, **6**, or **8**) substituents were all suitable substrates, affording the corresponding ketone products smoothly. A benzaldehyde bearing an *ortho*-substituent also delivered the corresponding hydroacylation product **9** smoothly, albeit in a lower yield. The acyl radical generated from hexanal was successfully incorporated into styrene with 60% yield (**10**). However, lower conversions were obtained from other aliphatic aldehydes, such as 3-phenylpropanal (**11**).

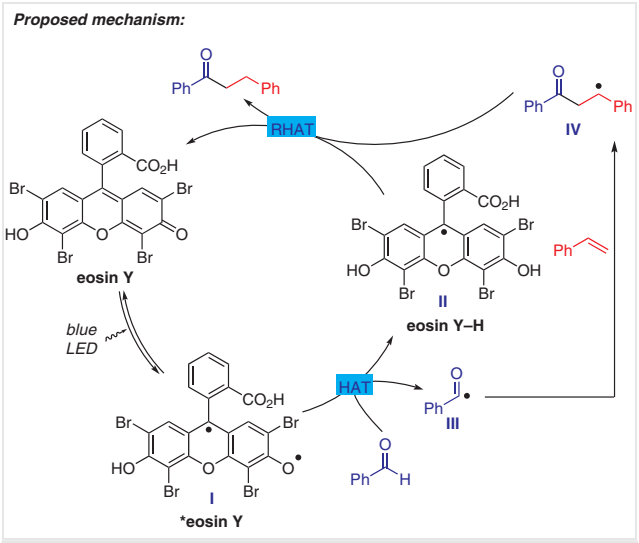
Various styrene derivatives with functional groups such as halo (**12**–**14**), acetate (**15**),[20] tosyl (**18**), ester (**19**), or cyanide (**20**) were also amenable to this transformation (Scheme 2). Styrenes with a halogen group in the *ortho*- (**22**) or *meta*-position (**23**) of the phenyl ring were also tolerated. Apart from the phenyl group, substrates bearing a naphthalene ring (**16**) or a benzoxazole ring (**21**) readily underwent the hydroacylation to afford the corresponding products in yields of 42 and 60%, respectively.

On the basis of our previous work on neutral eosin Y as a direct HAT photocatalyst,[17a] we propose the following mechanism for the hydroacylation of styrenes (Scheme 3). First, eosin Y is excited to *eosin Y (**I**) by the blue-light irradiation. The C(sp^2)–H atom of the aldehyde undergoes a HAT process mediated by **I**, delivering the key acyl radical species **III**, which is subsequently trapped by the styrene with anti-Markovnikov selectivity to form the more-stable benzylic radical **IV**. A reverse HAT between radical **IV** and eosin Y-H (**II**) finally turns over the catalytic cycle by regenerating the ground state eosin Y and releasing the required product. However, we cannot exclude the possibility of a SET process between intermediate **IV** and **II** at this stage.

In summary, we have developed a hydroacylation of styrene catalyzed by neutral eosin Y under photoirradiation conditions. This transformation accommodates a broad substrate scope with excellent anti-Markovnikov selectivity. Our protocol is distinguished by its operational simplici-



Scheme 2 Substrate scope for hydroacylation of various styrenes. *Reagents and conditions*: PhCHO (1.0 mmol), styrene (0.2 mmol), eosin Y (5 mol%), PhF (4 mL), blue LED light. Isolated yields are reported. Alkylacylation byproducts were isolated in less than 10% yield in every case.



Scheme 3 Proposed mechanism for hydroacylation of styrenes with neutral eosin Y as the photocatalyst

ty, green properties, and atom, step, and redox efficiency, and it represents an important addition to the methods available for synthesizing asymmetric ketones from abundant aldehydes and alkenes.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1319-6237.

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(19) **Ethyl 4-(3-Phenylpropanoyl)benzoate (8); Typical Procedure**

A 10 mL reaction tube equipped with a magnetic stirrer bar was charged with ethyl 4-formylbenzoate (1.0 mmol, 5.0 equiv), styrene (0.2 mmol, 1.0 equiv), eosin Y (0.01 mmol, 0.05 equiv), and PhF (4 mL). The tube was then sealed and degassed by using an argon balloon with a subsequent backfill with argon. The tube was then equipped with an argon balloon and placed under blue LEDs (3 m strip; 27 W) and irradiated for 72 h at 80 °C. The solvent was removed on a rotary evaporator under reduced pressure, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (15:1 to 1:1)] to give a colorless liquid; yield: 20.8 mg (36%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 0 8.08 (m, 2 H), 8.02–7.96 (m, 2 H), 7.34–7.27 (m, 2 H), 7.27–7.17 (m, 3 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 3.39–3.28 (m, 2 H), 3.08 (t, *J* = 7.6 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.77, 165.76, 141.00, 139.97, 134.25, 129.82, 128.59, 128.43, 127.91, 126.26, 61.46, 40.83, 30.01, 14.29. GC/MS: *m/z* = 282.1 [M$^+$].

(20) **4-(3-Oxo-3-phenylpropyl)phenyl Acetate (15)**

Prepared by the typical procedure from PhCHO (1.0 mmol, 5.0 equiv), 4-vinylphenyl acetate (0.2 mmol, 1.0 equiv), and eosin Y (0.01 mmol, 0.05 equiv) as a colorless liquid; yield: 31.1 mg (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.91 (m, 2 H), 7.63–7.53 (m, 1 H), 7.51–7.41 (m, 2 H), 7.30–7.20 (m, 2 H), 7.05–6.94 (m, 2 H), 3.34–3.20 (m, 2 H), 3.06 (t, *J* = 7.6 Hz, 2 H), 2.28 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.03, 169.65, 149.01, 138.89, 136.82, 133.13, 129.42, 128.65, 128.04, 121.56, 40.37, 29.46, 21.13. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{16}NaO_3$: 291.0992; found: 291.0995.