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Photocatalyst-free hydroacylations of electron-poor alkenes and enones under visible-light irradiation†

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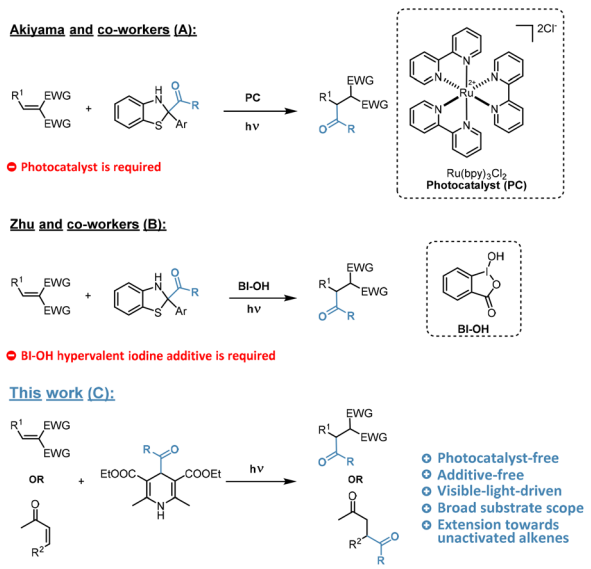
Herein we present a photocatalyst- and additive-free radical hydroacylation of electron-poor double bonds under mild reaction conditions. Using 4-acyl-Hantzsch ester radical reservoirs, various Michael acceptors, enones and *para*-quinone methide substrates could be used. The protocol enabled further derivatizations and it could also be extended to a few unactivated alkenes. Moreover, the nature of the radical process was also investigated.

Introduction

In the last few decades, the formation of C–C bonds has attracted significant attention within the field of synthetic organic chemistry. Apart from organocatalytic[1] and transition-metal-based approaches,[2,3] radical transfer reactions became of special interest for such transformations. Since the early examples from the 1980s,[4,5] the use of carbon-centered radicals became a crucial tool for forging new C–C bonds, thanks to their versatility and excellent functional group tolerance.[6,7] With most of these transformations relying either on (transition)metal-based[8–10] or metal-free photosensitizers[11–16] as well as on using radical initiators,[17,18] the development of photocatalyst-free strategies is particularly desired.

Hantzsch esters (HEs) are well-studied biomimetic reductants under thermal reaction conditions.[19] In the last decade, they have also been recognized as powerful photoreductants and proton sources for photocatalytic processes.[20] Moreover, 4-substituted Hantzsch esters can also serve as reservoirs for radical transfer reactions.[21] Relying on either transition-metal-based[22–24] or metal-free catalysts,[25] a broad range of such photocatalytic radical hydroalkylations emerged; furthermore, Hantzsch dihydropyridines could also be used in Ni/photoredox cross-coupling reactions.[26–28] However, it is worth mentioning that the use of Hantzsch esters for acyl transfer is much less explored. As one pioneer of this field, the Melchiorre group developed an elegant photo/organocatalytic method for the enantioselective hydroacylation of aromatic enals under deep-cooled conditions.[29] Moreover, Xia *et al.* investigated the acyl transfer to electron-rich alkenes, using Cs_2CO_3 as an additional base.[30]

Encouraged by the aforementioned advancements, we aimed for developing a photocatalyst- and additive-free hydroacylation protocol, which can be generally applicable for electron-poor alkenes and enones. As for the current state-of-the-art for such transformations, the Akiyama group reported a photoredox hydroacylation for Michael acceptors, relying on benzothiazolines as a radical source (Scheme 1A).[31] In the meantime, Zhu *et al.* developed another benzothiazoline-based process, in which a hypervalent iodine reagent was used



Scheme 1 Different concepts for the hydroacylation of electron-poor substrates.

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to generate a photoexcitable intermediate, facilitating the formation of acyl radicals (Scheme 1B).[32] In contrast to **A** and **B**, this work relies on the use of 4-acyl-substituted Hantzsch esters which can be directly photoexcited under simple visible light irradiation, and therefore requires neither a photocatalyst nor additives for effective hydroacylation (Scheme 1C).

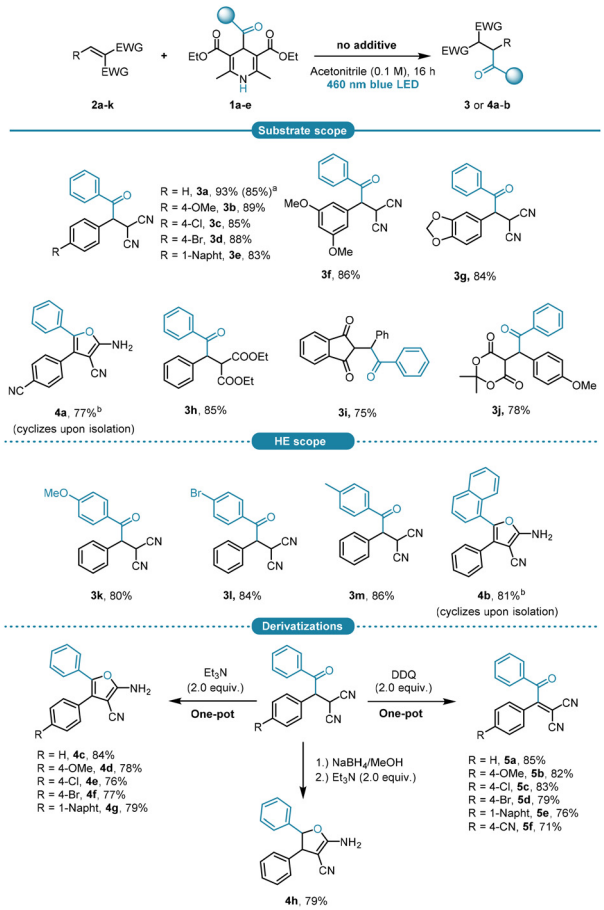
Results and discussion

Given its simple and one-pot synthesis, the Hantzsch dihydropyridine **1a** bearing a benzoyl moiety was chosen as a suitable radical reservoir for our initial studies. As a benchmark reaction, the hydroacylation of benzylidene malononitrile (**2a**) was first investigated under simple blue light irradiation (λ_{max} = 460 nm). Following a short parameter optimization and using only a slight excess of dihydropyridine **1a**, the hydroacylation product **3a** could be obtained in 93% isolated yield under photocatalyst- and additive-free conditions. While the use of either a transition-metal-based or metal-free photocatalyst indeed did not improve this result, working under an argon atmosphere was found to be an important aspect. Moreover, no conversion was observed without light irradiation, indicating the radical nature of the reaction. The optimization study can be found in the ESI (ESI, page S12†).

With the optimized reaction parameters in hand, we investigated the scope of acyl transfer for different Michael acceptors (Scheme 2, top).

The reaction showed good functional group tolerance: benzylidene malononitriles with different steric and electronic properties (**2a–g**) all provided the corresponding products in uniformly high 83–93% yields. Moreover, diester-, indandione- and meldrum-acid derivatives were also well tolerated (products **3h–3j**). However, it is worth mentioning that the hydroacylation products were unstable in two cases, and they readily cyclized to the corresponding tetrasubstituted furans (**4a and 4b**) upon column chromatographic purification, both on silica and neutral alumina stationary phases. Aiming for transferring acyl moieties with different steric and electronic properties, a small set of Hantzsch esters was also tested for the hydroacylation of **2a**, resulting in 80–86% yields (Scheme 2, middle). This protocol also enabled further derivatizations, providing straightforward access to furan and dihydrofuran heterocycles, and also to formal alkenylation products (Scheme 2, bottom). All derivatizations were carried out as a one-pot process, and – apart from **4h** – without changing the reaction media. As for the synthesis of furans and benzoylated alkenes, a small set of substrates was investigated, and the products **4c–g** and **5a–f** were all obtained in good yields, showing the general robustness of such derivatizations.

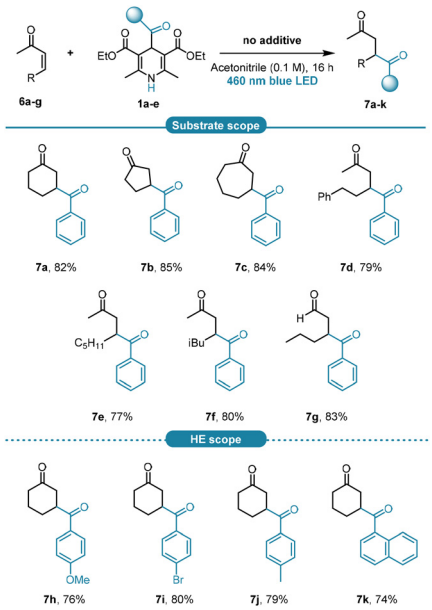
Given that 1,4-dicarbonyl compounds are versatile building units for the synthesis of pharmaceutical drugs,[33–36] we aimed for expanding our reaction scope towards the functionalization of enones as well. With the reaction conditions being identical to those in Scheme 2, we first investigated the acyl transfer using 2-cyclohexen-1-one (**6a**) as the radical acceptor, which provided the hydroacylation product **7a** in 82% yield



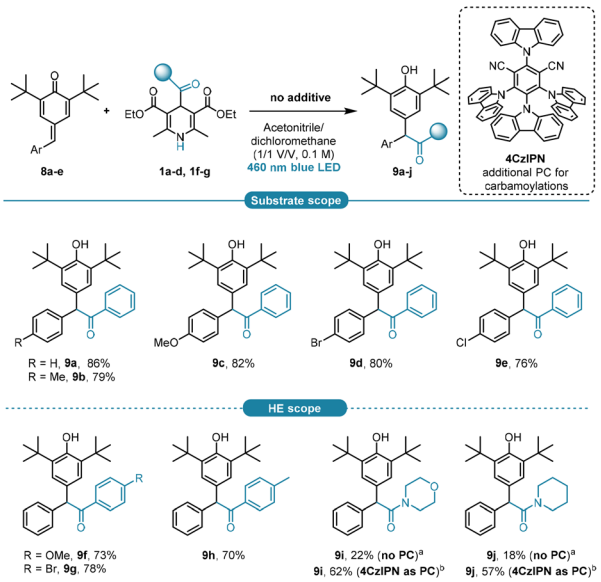
Scheme 2 Hydroacylation of Michael acceptors. Reaction conditions: **2a–k** (0.2 mmol, 1.0 equiv.), **1a–e** (0.24 mmol, 1.2 equiv.), 2.0 mL acetonitrile at 28 °C under 460 nm blue LED irradiation for 16 hours, unless otherwise noted. Yields refer to pure products after flash column chromatography, average yields of two parallel runs. [a]Performed on a 2.0 mmol scale. [b]The hydroacylation products were identified using crude NMR spectra.

(Scheme 3). To our delight, various cyclic and acyclic enones, as well as enal substrates could be used and the corresponding products (**7a–g**) were obtained in 77–85% yields. Moreover, the transfer of different acyl groups was also possible, affording **7h–k** in good yields of 74–80% (Scheme 3).

The functionalization of *para*-quinone methides (*p*-QMs) provides an important strategy for the synthesis of substituted phenol derivatives as crucial pharmaceutical drug intermediates.[37,38] Despite some recent advancements relying on classical photoredox approaches,[39,40] their synthesis is mostly limited to standard nucleophilic 1,6-additions.[41,42] In order to further broaden our reaction scope, we also investigated the photocatalyst-free hydroacylation of *p*-QM substrates (Scheme 4). Using a solvent mixture of acetonitrile and dichloromethane because of solubility reasons, a small set of *p*-QMs as well as different Hantzsch esters could be used, providing the substituted phenols **9a–h** in 70–89% yields. At this point, the possibility of carbamoyl transfer was also investigated. Even though only quite moderate results were obtained,



Scheme 3 Hydroacylation of α,β-unsaturated carbonyl substrates. Reaction conditions: **6a–g** (0.2 mmol, 1.0 equiv.), **1a–e** (0.24 mmol, 1.2 equiv.), 2.0 mL acetonitrile at 28 °C under 460 nm blue LED irradiation for 16 hours, unless otherwise noted. Yields refer to pure products after flash column chromatography, average yields of two parallel runs.

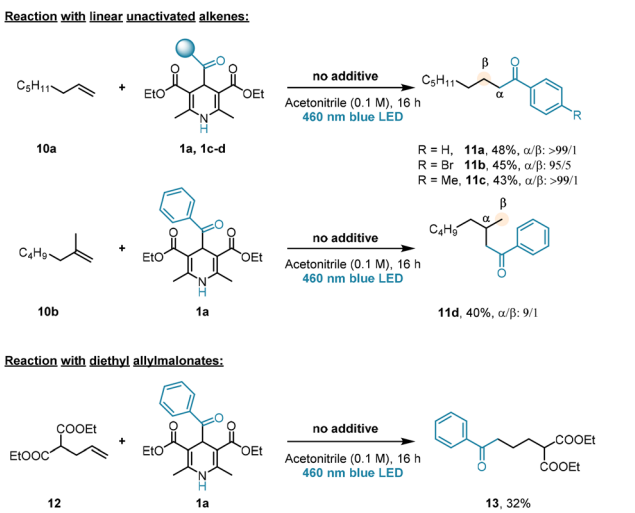


Scheme 4 Hydrofunctionalization of *para*-quinone methide substrates. Reaction conditions: **8a–e** (0.2 mmol, 1.0 equiv.), **1a–d, 1f and 1g** (0.24 mmol, 1.2 equiv.), 2.0 mL acetonitrile/dichloromethane (1/1 v/v) at 28 °C under 460 nm blue LED irradiation for 16 hours, unless otherwise noted. Yields refer to pure products after flash column chromatography. [a]GC-MS conversion, estimated from the ratio of **8a**, and **9i or 9j** (no side product was observed). [b]Isolated yields using 1 mol% of 4CzIPN as additional photocatalyst.

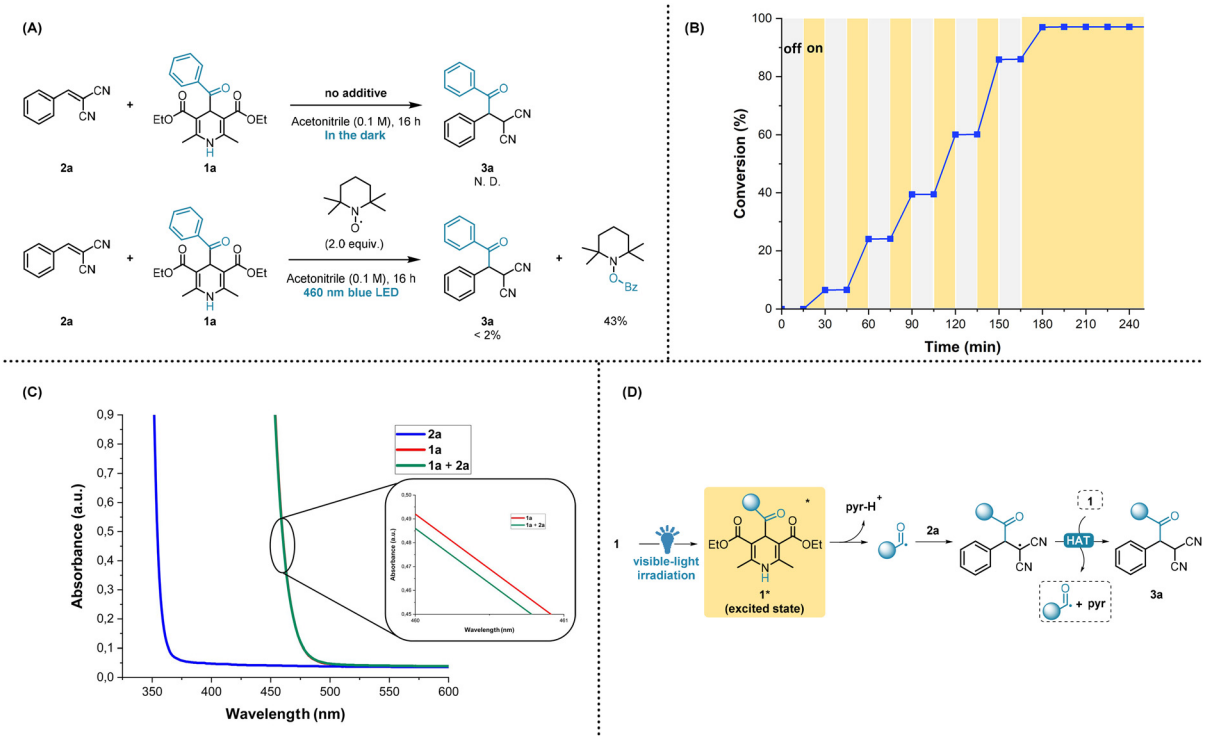
the reactivity could be significantly boosted when using the metal-free photocatalyst 4CzIPN as **9i and 9j** were isolated in 62% and 57% yields, respectively.

Eventually, we also investigated whether our photocatalyst- and additive-free protocol would be applicable for the hydroacylation of unactivated alkene species (Scheme 5). To our delight, we found that the reaction scope can also be expanded to aliphatic, non-activated alkenes, providing the products **11a–d** and **13** in moderate yields. Nevertheless, to the best of our knowledge, this is the first protocol for the hydroacylation of non-activated alkenes which requires neither a (photo)catalyst nor additives.

Aiming to gain mechanistic insights, control experiments and analytical studies for the hydroacylation of **2a** were carried out. When performing the reaction in the dark, no product formation was observed (Scheme 6A); meanwhile, the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical scavenger also readily inhibited the reaction, and the corresponding TEMPO adduct was detected by GC-MS analysis (Scheme 6A). The light on–off experiment confirmed that continuous light irradiation is indeed necessary, essentially excluding that long-lived radicals would contribute to product formation; moreover, it also showed excellent conversion after just 1.5 hours of net irradiation time (Scheme 6B). Comparing the UV/VIS spectra of **1a**, **2a** and their mixtures did not show any bathochromic shifts. In fact, the spectra of **2a** and the **1a** + **2a** mixture were basically identical (Scheme 6C), suggesting that the formation of an EDA complex does not take place. Furthermore, Stern–Volmer studies also showed strong quenching of the Hantzsch ester **1a** in the presence of **2a** (ESI, page S34†). In accordance with these results and based on the experimental findings of Melchiorre *et al.*,[27,29] the reaction most likely proceeds *via* direct photoexcitation. The visible-light excitation of the Hantzsch ester **1** affords the acyl radical, which undergoes a radical conjugate addition with **2a**, fol-



Scheme 5 Hydroacylation of unactivated alkenes. Reaction conditions: **10a and 10b**, or **12** (0.2 mmol, 1.0 equiv.), **1a**, **1c and 1d** (0.24 mmol, 1.2 equiv.), 2.0 mL acetonitrile at 28 °C under 460 nm blue LED irradiation for 16 hours, unless otherwise noted. Yields refer to pure products after flash column chromatography, average yields of two parallel runs. The orange circles for **11a–d** represent the formation of minor regioisomers.



Scheme 6 Mechanistic studies for the hydroacylation of **2a**. (A) Control experiments in the dark and by using TEMPO. (B) Light on–off kinetic experiment. (C) UV-VIS spectra of **1a**, **2a** and their equimolar mixtures, showing only a very marginal difference (zoomed-in picture). (D) The plausible reaction mechanism *via* direct photoexcitation.

lowed by hydrogen atom transfer (HAT) from the ground-state **1**, affording the hydroacylation product **3a** (Scheme 6D).

Conclusions

In summary, we have developed a visible-light-driven hydroacylation of electron-deficient alkenes and enones. By using Hantzsch esters as radical reservoirs, these transformations did not require a photocatalyst or additives for the efficient acyl transfer. Generally high yields were obtained for a broad range of electron-deficient substrates, also enabling different one-pot further derivatization strategies. This hydroacylation approach also showed moderate reactivity towards unactivated alkenes. The mechanistic studies basically excluded the possibility of EDA complex formation and strongly suggested that the reaction proceeds *via* direct photoexcitation.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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