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Letter

Visible-Light-Promoted Photocatalyst-Free Hydroacylation and Diacylation of Alkenes Tuned by $NiCl_2$·DME

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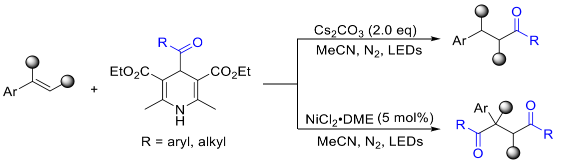

- wide substrate scope (55 examples)
- good to high yields, up to 99%
- excellent functional group tolerance
- scalable experiment
- latestage functionalization for drugs/medicinal intermediates/ natural products

ABSTRACT: Herein, we describe a visible light-promoted hydroacylation strategy that facilitates the preparation of ketones from alkenes and 4-acyl-1,4-dihydropyridines via an acyl radical addition and hydrogen atom transfer pathway under photocatalyst-free conditions. The efficiency was highlighted by wide substrate scope, good to high yields, successful scale-up experiments, and expedient preparation of highly functionalized ketone derivatives. In addition, this protocol allows for the synthesis of 1,4-dicarbonyl compounds through alkene diacylation in the presence of $NiCl_2$·DME.

The concept of modern organic synthesis consists of the development of economical, efficient, and environmentally friendly methods for construction of complex molecule architectures. As a result, currently photoredox catalysis has become one of the hottest topics in the synthetic chemistry domain and significant progress has been made over the past decade with the aid of different photosensitizers.[1] Typically, transition-metal-centered bipyridine complexes (Ru, Ir, Cu, etc.)[1b,c,2] and highly conjugated organic molecules (EosinY, Acr-Mes, Rose-bengal, etc.)[3] have long been proven to directly absorb visible light and efficiently initiate a redox cycle through single electron transfer (SET) with organic compounds. Recent progress has been made in photocatalytic synthesis toward the use of simple metal salts as promoters.[4] Moreover, catalyst-free manifolds have been established by the use of electron-donor−acceptor (EDA) complexes with visible-light irradiation.[5] In this context, from a practical perspective, seeking available, low-cost "media" or even catalyst-free conditions is of important significance for developing visible-light-induced synthetic strategies.

Ketones are among the most prevalent organic molecules found in natural products and biologically active compounds,[6] many of which commonly serve as valuable building blocks for the construction of molecular diversity and complexity. The addition of acyl group across unsaturated C−C multiple bonds has long been recognized as one of the most straightforward tools to access these structure motifs.[7] Generally, a transition-metal-catalyzed strategy using aldehydes as an acyl source might represent one of the most predominant approaches to achieve the hydroacylation transformation. This, however, often suffers from harsh conditions, poor functional group tolerance, decarbonylation, and regioselectivity issues.[7c,d,8] Recently, with the development of photoredox catalysis, methods for generating useful acyl radicals have been significantly improved. Types of functional groups (usually carbon−heteroatom bonds) such as aldehyde, carboxylic acids and their derivatives, carboxylic chloride, α-ketoacid, and oxime ester have been revealed to be good acyl radical precursors, thus providing a battery of useful strategies for the late-stage functionalization of delicate molecular scaffolds.[9] Taking advantage of the generated acyl radical to accomplish the radical alkene hydroacylations have been described by plentiful seminal works.[9b,10] Despite enormous advances, most of these synthetic strategies always strictly narrowed to electron-deficient alkenes.[5c,11] Therefore, developing a benign, general radical reaction protocol to access different types of carbonyl compounds is still in high demand.

1,4-Dihydropyridines (DHPs) have been extensively explored as well-known hydrogen and electron donors to readily produce alkyl radicals through the SET oxidation process with photocatalyst upon light irradiation.[12] Their synthetic potential in types of alkylations has been demonstrated by large numbers of research groups in the past decade. For instance, in 2016, Nishibayashi reported the first example of using benzyl-DHPs as alkyl radical reservoirs in the visible-light-induced aromatic substitution.[13] Thereafter, strategies that enabled the cross-couplings of DHP-derived alkyl radical with alkyl[14]/aryl[15] radical under photoredox conditions have been successively

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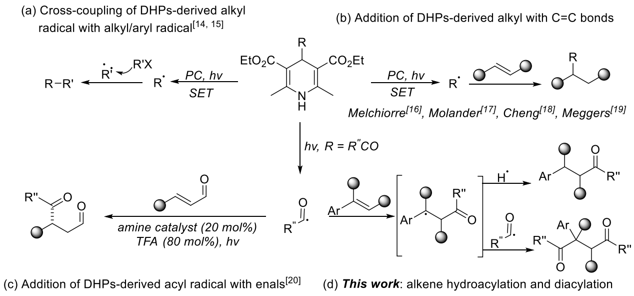
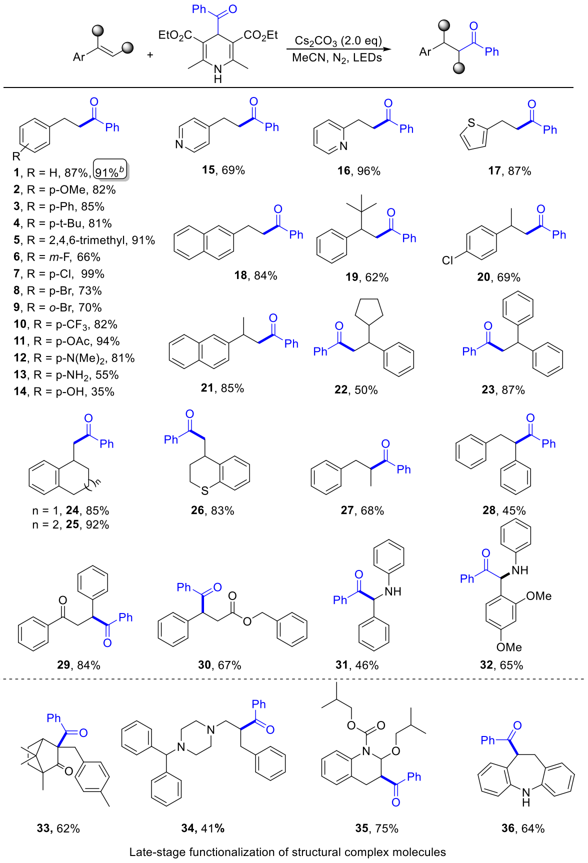
developed, thus providing a useful platform for constructing structural diversity (Scheme 1, a). In addition, Melchiorre,[16] Molander,[17] Cheng,[18] and Meggers,[19] respectively, documented the photocatalytic radical addition of alkyl-DHPs across C=C to form new $C_{sp3}-C_{sp2}$ bonds (Scheme 1, b). Nevertheless, in sharp contrast, such a mode to release acyl radicals had not been revealed until the Melchiorre group attributed it to the photo-/organocatalytic synthesis of 1,4-dicarbonyl compounds in strong acid conditions, in which an acyl radical could be easily obtained from the photoactivated acyl-DHPs and engaged in an enantioselectively conjugated addition to enals to afford the desired products (Scheme 1, c).[20] Motivated by the above research background, we wondered if the carbon radical intermediates generated from acyl radical addition to C=C bond might be quenched by a hydrogen atom absorption or radical interception process to achieve the functionalization of alkenes. Herein, we describe a visible-light-promoted strategy that facilitates the alkene hydroacylationin the absence of photocatalyst and a $NiCl_2\cdot DME$-mediated diacylation by using DHPs as acyl radical precursors (Scheme 1, d). Notably, the developed methodology was proved applicable to both electron-rich and electron-poor alkenes and featured broad substrate scope and good functional group tolerance. Its potential application was demonstrated by scalable experiment and expedient preparation of complex natural product/drug based ketones.

Scheme 1. Visible-Light-Promoted Synthetic Strategies Based on the Use of DHPs as Radical Precursors



The initial investigation was carried out by using styrene and 4-benzoyl-DHPs as model substrates under the irradiation of 36 W blue LEDs. In the presence of Eosin Y, we delightfully observed the formation of alkene hydroacylation product **1** with 17% isolation yield within 10 h under N_2 atmosphere in MeCN. Sets of photocatalysts with different natures were then evaluated,which displayed a similar effect on the reaction result. Next, we conducted the reaction without any photocatalyst and surprisingly found this protocol was still feasible, providing **1** in 26% yield. Subsequent extensive investigation on base disclosed 2.0 equiv of Cs_2CO_3 as a key and effective additive, dramatically improving the yield of **1** to 87%. After a series of screenings on solvents, MeCN was found to be the optimal medium. In addition, treatment of the reaction system under air atmosphere resulted in a sharp decrease in yield, which might be due to the radical quenching effect of oxygen molecules. Moreover, no reaction occurred in the absence of light irradiation, which strongly confirmed the visible-light-promoted property of this developed protocol. (For details of condition screening, see Table S1.)

Scheme 2. Investigation on the Alkene Scope of the Hydroacylation.[a]



[a] Standard conditions: alkene (0.2 mmol), DHPs (0.3 mmol), Cs_2CO_3 (0.4 mmol), MeCN (2 mL), N_2 atmosphere, blue LED irradiation for 10 h. [b] Reaction conducted on 15 mmol.

Having identified the optimal conditions, the reaction scope with respect to alkenes was next explored. As listed in Scheme2, the hydroacylation method was tested with different types of unsaturated C=C bond compounds. Styrene with either electron-withdrawing or electron-donating substituents on the phenyl ring reacted smoothly with 4-benzoyl-DHPs, providing the corresponding products in moderate to high yields (**1**−**14**). Various functional groups, such as alkoxyl (**2**), phenyl (**3**), alkyl (**4**, **5**) and halides (**6**−**10**), were well tolerated despite the substitution patterns. Notably, the practical potential of this developed method was corroborated by the scale-up experiment of styrene, which only required 48 h of irradiation to afford desired **1** in 91% isolation yield. In addition, many synthetically important and/or potentially reactive groups, like ester (**11**), amine (**12**, **13**), even the free alcohol (**14**), were well matched with the mild conditions. Hydroacylation products **15**−**18**, which, respectively, derived from heteroatom-containing and polycyclic aromatic alkenes, were obtained in good to excellent yields (69%, 96%, 87%, and 84%). Subsequently, the reaction scope was examined with various *gem*-disubstituted alkenes. Remarkably, alkenes with a chain/cyclic alkyl or phenyl on the *α*-position of C=C bonds were proved to be suitable substrates, affording the desired products in yields from 50% to 87% (**19**−**23**). Additionally, the transformations proceeded smoothly with benzo(heter)-cyclic derivatives to give the target hydroacylation products (**24**−**26**). In addition, nonterminal alkenes were compatible with this synthetic strategy with high regioselectivity (**27** and

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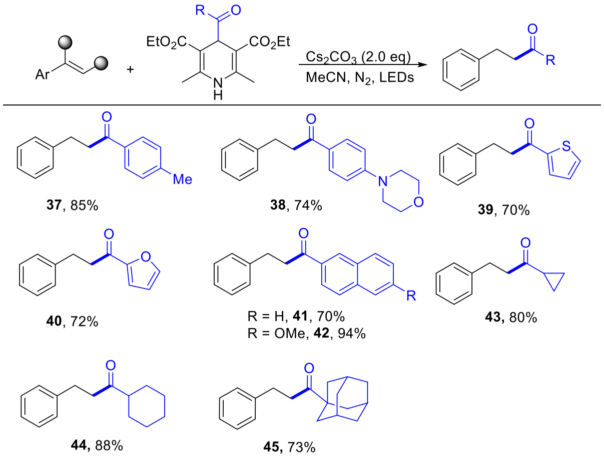
28). In the case of α, β-unsaturated alkene, likely due to the electronic effect, the hydroacylation occurred successfully via a Michel conjugate addition process to afford the irregular adducts (**29**, **30**). Notably, the substrate scope could be extended to C═N compounds. As exemplified by the reactions of benzophenone-derived imines with 4-benzoyl-DHPs, the carbonyl-contained secondary amines **31** and **32** were obtained in moderate yields. Moreover, this synthetic strategy was applied for late-stage functionalization of structural complex molecules. As seen in Scheme2, benzoyl was readily installed on natural product 3-(4′-methylbenzylidene)camphor (**33**),[21] drug cinnarizine (**34**),[22] and medical intermediates IIDQ (**35**)[23] and iminostilbene (**36**).[24] It is worth mentioning that active functional groups in these transformations remained unaffected, strongly highlighting the utility of this hydroacylation protocol.

To further explore the versatility of this established protocol, our attention was then shifted to investigate the reactivity of different acyl units on the C4-position of DHPs with styrene (Scheme 3). Functional groups on benzoyl have little influence on the photoreaction performance (**37**, **38**). Other types of acyl sources with a hetero/polyaromatic framework readily provided the corresponding radical species and took part in the following transformations with alkenes when exposed to the standard conditions (**39**−**42**). Importantly, DHPs with alkyl acyl groups also found to be adequate partners to furnish the hydroacylation products (**43**−**45**), thus making this protocol an amenable approach to access aliphatic ketone derivatives. In particular, compound **45** with a rigid adamantane structure could be efficiently prepared in a satisfactory yield of 73%.

Scheme 3. Investigation on the DHP Scope of the Hydroacylation[a]

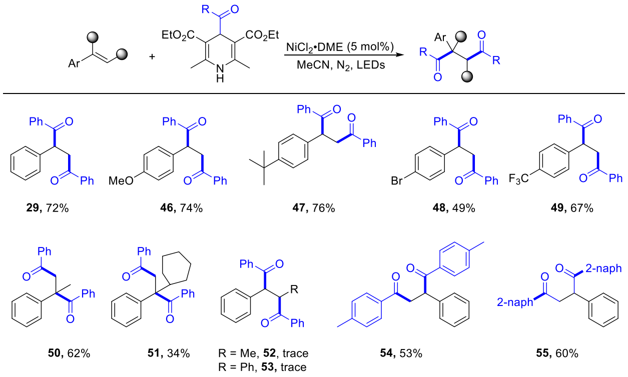


[a]Standard conditions: alkene (0.2 mmol), DHPs (0.3 mmol), Cs_2CO_3 (0.4 mmol), MeCN (2 mL), N_2 atmosphere, blue LEDs irradiation for 10 h.

Spurred by the above satisfactory results, we wonder whether the carbon radical intermediate generated by acyl radical addition to alkene might be trapped by another acyl radical to give 1,4-dicarbonyl compound. With this concept in mind, we continued to make a deep exploration on this visible-light-driven protocol. After extensive attempts, we were delighted to find that nickel salts could effectively promote such a transformation process in a one-pot reaction under visible light irradiation. The product yield could be improved to 72% by optimization of conditions when using 5 mol % $NiCl_2·DME$ as catalyst in MeCN (for details of condition screening, see Table S2).

A series of reactions were then performed to test the generality of the diacylation method (Scheme 4). By using 4-benzoyl-DHPs as representative acyl precursors, the bifunctionalization process proceeded smoothly with respect to electron-rich/poor substituted styrenes on phenyl ring, delivering corresponding products with moderate to high isolated yields (**29**, **46**−**49**). *Gem*-disubstituted alkenes were competent substrates, leading to the formation of **50** and **51** in yields of 62% and 34%, respectively. Unfortunately, trace amounts of the desired **52** and **53** were observed as for the reactions of nonterminal alkenes, and we believe the large steric effect might account for this photochemical behavior. In addition, we also attempted the diacylation with different 4-acyl-DHPs, which coupled effectively with styrenes in moderate yields (**54**, **55**).

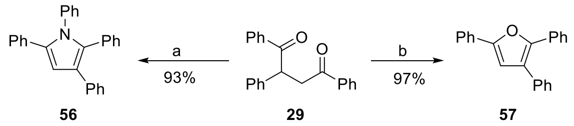
Scheme 4. Investigation on the Diacylation[a]



[a]Standard conditions: alkene (0.2 mmol), DHPs (0.1 mmol), $NiCl_2$.dme (5 mol %), MeCN (1 mL), N_2 atmosphere, blue LED irradiation for 48 h.

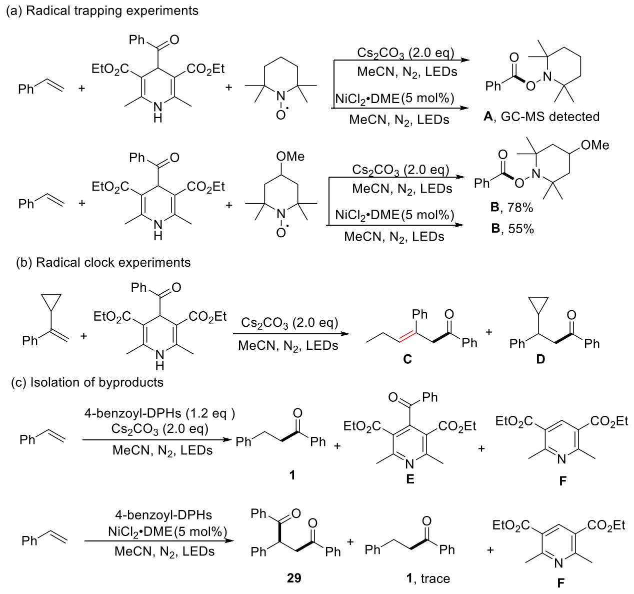
Considering the synthetic versatility of 1,4-dicarbonyl compounds as key intermediates in organic chemistry domain,[25] the obtained product **29** was employed for downstream transformations. As shown in Scheme 5, a and b, by means of the classical Paal−Knorr pyrrole and furan synthetic methods, **29** was respectively converted into the cyclic pyrrole and furan derivatives **56**, **57** with excellent yields via a condensation process (see the SI for reaction details). Both examples further demonstrated the synthetic application of the developed diacylation strategy in molecular assembly.

Scheme 5. Synthetic Applications of 1,4-Dicarbonyl Derivatives



Before the reaction mechanism was proposed, a range of control experiments were carried out by employing 4-benzoyl-DHPs as model acyl sources. As seen in in Scheme 6, the acylation process was completely suppressed in the presence of TEMPO and the formation of benzoyl-TEMPOA in both reaction systems was detected by GC−MS. Moreover, the

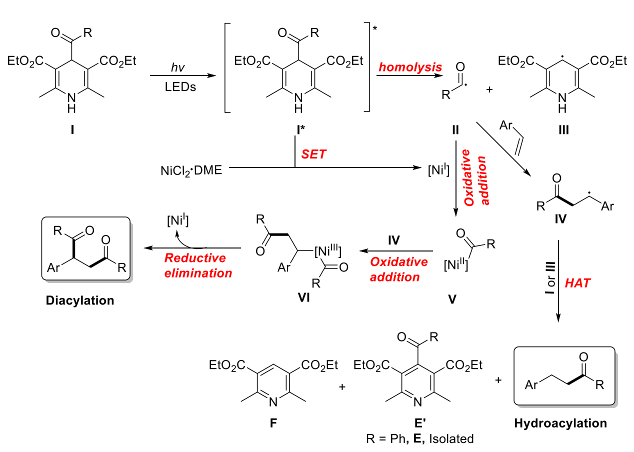
Scheme 6. Mechanistic Probe Experiments



isolated **B**, which derived from the reaction of TEMPO derivative with 4-benzoyl-DHPs, provided a persuasive evidence for an acyl radical-involved pathway (for hydroacylation and diacylation, 78% and 55% yields, respectively). In addition, a radical clock experiment had been conducted using (1-cyclopropylvinyl)benzene with 4-benzoyl-DHPs, which afforded a mixture of ring-open hydroacylation product **C** and **D** in 51% total yields. This result strongly suggested a radical addition of acyl to C═C bond in the photochemical process. Moreover, we separated few **E** and **F** as byproducts from the standard hydroacylation system, which implied the reaction might proceed through a HAT pathway. In addition, in the diacylation system, besides target **29**, we also detected the formation of hydroacylation product **1** and **F** adduct by GC−MS, indicating the acyl addition to alkene might be involved in the diacylation process.

On the basis of previous literature[18,20] as well the above results, tentative pathways for alkene hydroacylation and diacylation were outlined in Scheme 7. The visible-light irradiation of DHPs led to its excited stateI*, which was considered as a key initiator in the following acylation process. Subsequent homolytic cleavage of **I*** gave an acyl radical **II** and a dihydropyridine radical **III**. An addition of **II** to the *β*-position of the C═C bond of alkene yielded a relatively stable carbon radical intermediate **IV**, which, through a HAT procedure with **I** or **III**, furnished the final hydroacylation product, along with the formation of adducts **E′** and **F**. With respect to the diacylation process, a possible pathway was proposed as below. First, the NiCl$_2$·DME was reduced to a Ni(I) species though an SET event with the excited DHPs.[26] The generated acyl radical **II** was then added to the metal center of Ni(I) to form an oxidized species **V**, which underwent another oxidative addition of **IV** to produce the Ni(III) complex **VI**. A reductive elimination of **VI** took place to afford the desired diacylation product and regenerate the Ni(I) to the catalytic cycle.[27]

Scheme 7. Proposed Mechanism



In summary, we have disclosed a photocatalyst-free hydroacylation and diacylation of alkenes promoted by visible light. The mild reaction conditions were tolerated well with a wide range of functional groups, providing a highly effective, straightforward access to various valuable carbonyl and 1,4-dicarbonyl compounds. In addition, the potential application of the reaction protocol was highlighted by successful scale-up experiments, late-stage functionalization of complex pharmaceuticals, medicinal intermediates and natural products, as well downstream transformations. We anticipate that this green strategy will find more applications in medicinal chemistry and drug research in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04595.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for allthe referred compounds (PDF)

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Notes

The authors declare no competing financial interest.

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