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A general approach to intermolecular olefin hydroacylation *via* light induced HAT initiation: an efficient synthesis of long chain aliphatic ketones and functionalized fatty acids

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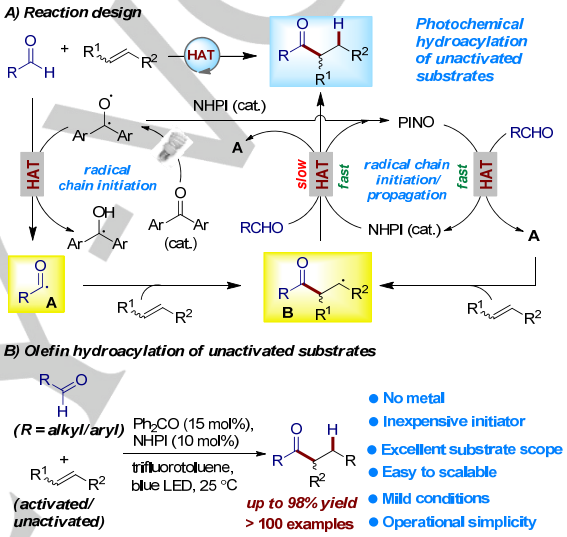
Abstract: Herein, an operationally simple, environmentally benign, and effective method for intermolecular radical hydroacylation of unactivated substrates employing photo-induced hydrogen atom transfer (HAT) initiation is described. The use of commercially available and inexpensive photoinitiators (Ph_2CO and NHPI) makes the process attractive. The olefin hydroacylation protocol applies to a wide array of substrates bearing numerous functional groups and many complex structural units. The reaction proves to be scalable (up to 5 g scale). Different functionalized fatty acids, petrochemicals and naturally occurring alkanes are synthesized with this protocol. A radical chain mechanism is implicated for the process.

Introduction

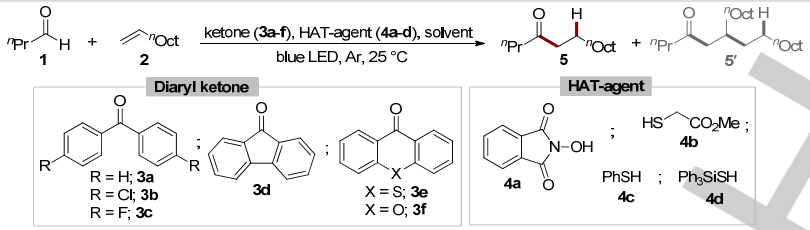
Ketones are privileged functional groups in chemistry.[1] Hence, numerous strategies for ketone synthesis have been developed. Among them, intermolecular olefin hydroacylation represents the most attractive technique. Consequently, various catalytic olefin hydroacylation including transition-metal catalysis[2] *via* chelation assisted activation of aldehydes[3],[4] and *N*-heterocyclic carbene (NHC) catalysis[5] have been reported, although significant limitation concerning substrate scope yet to address. In this connection, the radical olefin hydroacylation has also occupied an important place. Following the seminal work of Kharasch[6] on intermolecular olefin hydroacylation involving acyl radical, different protocols for the radical-chain olefin hydroacylation have been developed using acyl peroxide/UV light, different photoinitiators and aerobic oxidation of aldehydes.[7] However, these protocols are mainly applicable to electron-deficient olefins. Few reports on intermolecular radical hydroacylation of unactivated olefins are also existed.[8] Nevertheless, they have serious substrate scope limitation and require constant radical chain initiation with peroxides under thermal conditions. Hence the development of an efficient method for the radical olefin hydroacylation of unactivated substrates under mild conditions is in great demand.

Visible light-induced HAT catalysis emerges as an effective tool for selective generation of free-radical intermediates from neutral substrates under mild conditions.[9] Very recently, an interesting light mediated radical olefin hydroacylation employing phenylglyoxylic acid as radical initiator has been reported.[10] Using diaryl ketone as photocatalyst, we have reported radical C-H functionalization of abundant chemicals.[11] Inspired by this work, we note that the photo-excited triplet state of diaryl ketone could generate acyl radical **A** from aldehyde *via* HAT under mild conditions.[7l,12] Normally, the addition of the radical **A** to olefin would lead to a new carbon-centre radical **B**, which would provide the desired ketone along with the regeneration of acyl radical **A** *via* HAT from aldehyde. However, for unactivated olefin, the radical **B** is nucleophilic in nature. As a result, the prerequisite HAT from aldehyde to **B** is reported to be slow on account of unfavorable polar effect thus hampering the hydroacylation of unactivated olefin.[8d,8e] We envisage that this issue can be addressed using a catalytic amount of suitable hydrogen transfer agent like *N*-hydroxyphthalimide (NHPI), which could facilitate the slow HAT from aldehyde to **B** by replacing it with two consecutive fast HAT processes (Scheme 1A).[13] In the presence of NHPI, the reaction may also follow an alternative pathway, in which the photo-excited diaryl ketone could abstract hydrogen atom from NHPI resulting in the formation of phthalimidyl *N*-oxyl (PINO) radical. The electron deficient PINO is known to generate acyl radical upon HAT from aldehyde[8c],[14] thereby expecting to initiate the radical chain olefin hydroacylation in simultaneous cooperation with photo-excited diaryl ketone (Scheme 1A). Based on above analysis, herein, we describe an efficient method for the intermolecular radical hydroacylation of unactivated substrates under mild conditions *via* light-induced HAT initiation (Scheme 1B).



Scheme 1. Intermolecular radical olefin hydroacylation using light-induced HAT initiation: working principle and synthetic advantages

Table 1. Reaction optimization.



Entry[a]	Ketone (mol%)	HAT-agent (mol%)	Solvent	Conc. (M)	**1** (equiv)	Yield (%)	Ratio (**5** : **5'**)
1	**3a** (20)	**4a** (5)	benzene	2.5	6	70	94:6
2	**3b** (20)	**4a** (5)	benzene	2.5	6	54	95:5
3	**3c** (20)	**4a** (5)	benzene	2.5	6	67	95:5
4	**3d** (20)	**4a** (5)	benzene	2.5	6	16	94:6
5	**3e** (20)	**4a** (5)	benzene	2.5	6	27	94:6
6	**3f** (20)	**4a** (5)	benzene	2.5	6	10	94:6
7	**3a** (15)	**4a** (5)	benzene	2.5	6	72	94:6
8	**3a** (10)	**4a** (5)	benzene	2.5	6	64	95:5
9	**3a** (15)	**4a** (10)	benzene	2.5	6	75	96:4
10	**3a** (15)	**4a** (15)	benzene	2.5	6	69	96:4
11	**3a** (15)	**4b** (10)	benzene	2.5	6	46	97:3
12	**3a** (15)	**4c** (10)	benzene	2.5	6	12	94:6
13	**3a** (15)	**4d** (10)	benzene	2.5	6	55	92:8
14	**3a**(15)	**4a** (10)	trifluorotoluene	2.5	6	77	95:5
15	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	6	79	95:5
16	**3a** (15)	**4a** (10)	trifluorotoluene	1.0	6	68	95:5
17	**3a** (15)	**4a** (10)	trifluorotoluene	0.5	6	64	96:4
18	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	5	77	95:5
19	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	4	70	95:5
20	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	3	66	94:6
21	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	2	59	92:8
22	-	-	trifluorotoluene	2.0	5	N.R.	-
23	-	**4a** (10)	trifluorotoluene	2.0	5	N.R.	-
24	**3a** (15)	-	trifluorotoluene	2.0	5	42	90:10
25[b]	**3a** (15)	**4a** (10)	trifluorotoluene	2.0	5	N.R.	-

[a] Reaction conditions: 1-Decene (0.4 mmol, 1.0 equiv), *n*-butanal (6.0 equiv), diaryl ketone, HAT-agent, solvent, 24 h; overall isolated yields; the ratio of **5** & **5'** was determined by GC-analysis. [b] The reaction was performed in dark. N.R. = No reaction.

Results and Discussion

We began our study using *n*-butanal and 1-decene as model substrates under various reaction conditions with a catalytic amount of diaryl ketone and HAT-agent (Table 1). Following the initial optimization studies, the reaction between *n*-butanal (6 equiv) and 1-decene (1 equiv) in the presence of benzophenone (**3a**, 20 mol%), NHPI (5 mol%) and blue LED (Tuna Blue-Kessil

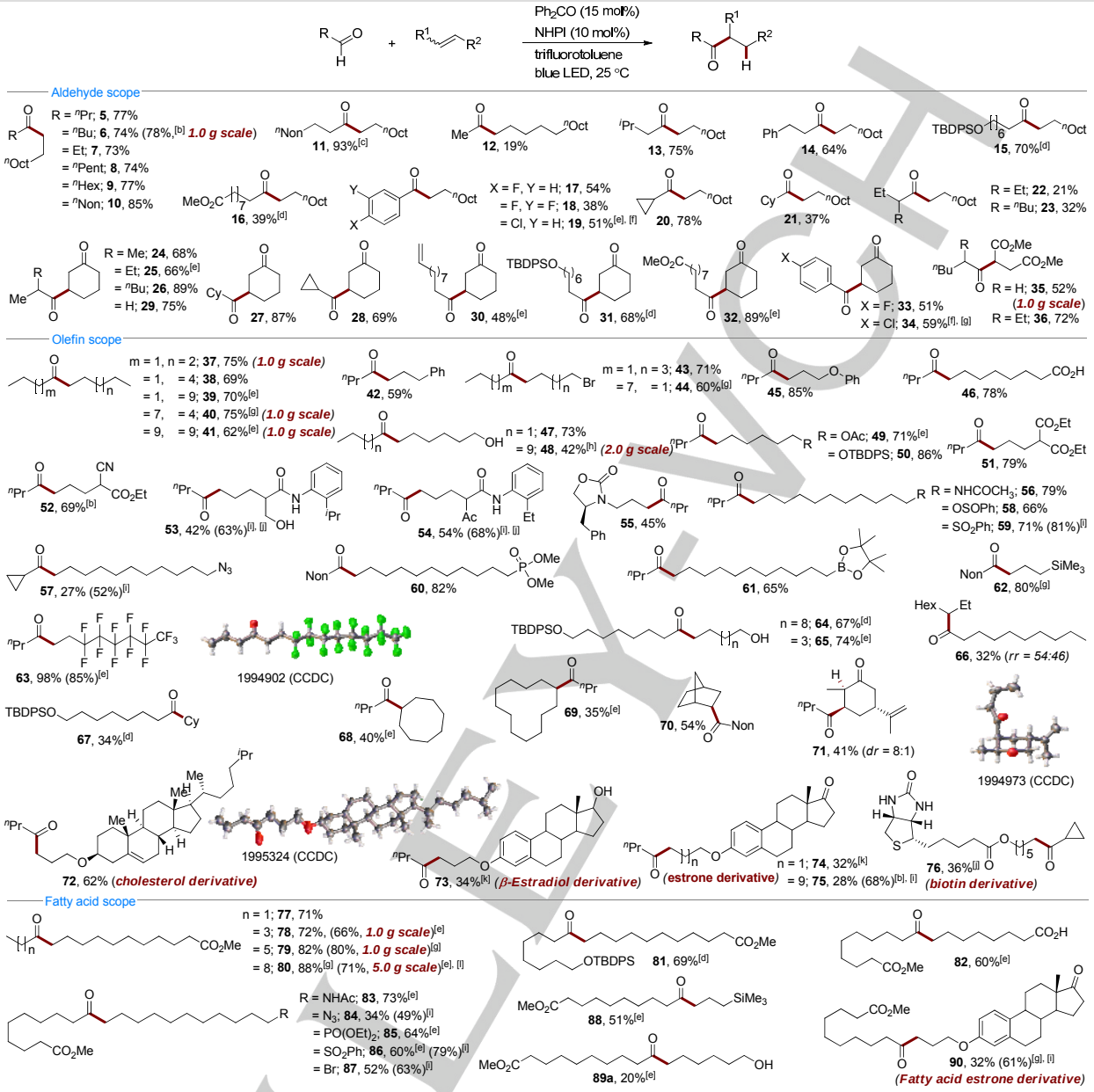
LED Lights)[15] afforded the product **5** in 70% yield along with the oligomeric product **5'** in a ratio of 94:6 under argon atmosphere in benzene (entry 1). We then evaluated five other commercially available aromatic ketones **3b-f** for the addition reaction between *n*-butanal and 1-decene (entries 2-6). Diarylketones **3a-c**, among the other tested ketones, effectively promoted the reaction. While the ketone **3b** gave a slightly low yield of the desired product, the ketones **3a** and **3c** found to be equally effective for the transformation. Fluorenone (**3d**), thioxanthone (**3e**) and xanthone (**3f**) furnished the desired product in low yield. These results prove that inexpensive benzophenone is the superior photo-initiator for the process. The reaction efficiency could be retained when the loading of benzophenone was reduced to 15 mol% (entry 7). Further reduction of benzophenone loading showed lowering of the yield of the product (entry 8). The optimal loading of NHPI set to be 10 mol% (entries 9, 10). Other commonly employed HAT-agents such as methyl thioglycolate, thiophenol and triphenylsilyl thiol were also tested in this transformation. However, none of them furnished the desired product in comparable yield (entries 11-13). The influences of solvent on the reaction were then examined by carrying out the transformation in different organic solvents and in water (see the SI for details). Based on these results, trifluorotoluene was identified as the most suited solvent for the process. A study on the reaction concentration for 1-decene established that 2.0 M olefin concentration was the optimal for the reaction (entries 14-17). A brief study on the variation of aldehyde amount showed that, using 5 equivalents of aldehyde, the reaction afforded the desired product in 77% isolated yield (entries 18-20). The reaction could also be performed with 2 equivalents of aldehyde, although a moderate yield of the desired product was obtained (entry 21). The reaction was completely inhibited in the absence of benzophenone and NHPI (entry 22). Also, NHPI alone could not promote the reaction (entry 23). In the absence of NHPI, the reaction gave low yield of desired product (entry 24). Furthermore, when the reaction was performed in dark no product formation was realized (entry 25).

With the optimized reaction conditions including aldehyde (5 equiv), olefin (1 equiv), **3a** (15 mol%), **4a** (10 mol%) and blue LED (Tuna Blue - Kessil LED Light) in trifluorotoluene (2.0 M) under an argon atmosphere, the hydroacylation reaction between *n*-butanal and 1-decene afforded the product **5** in 77% isolated yield (Chart 1). The substrate scope of the reaction was then studied with varying both aldehydes and olefins. At first, different unactivated aldehydes were allowed to react with 1-decene. As it is presented in Chart 1, the aliphatic aldehydes with varying chain length furnished the ketones **5**-**11** in good yields. The ketone **12** could be isolated with this protocol by the reaction of acetaldehyde with 1-tridecene. The reaction worked well with a *β*-branched aldehyde. Aliphatic aldehydes containing phenyl, OTBDPS and ester functional groups were included in the reaction rendering the products **14**-**16** in good to moderate yields. Aromatic aldehydes exhibited moderate reactivity with 1-decene under the optimized conditions. The addition of cyclopropanal to 1-decene worked well, delivering the ketone **20** in good yield. Importantly, the products **21-23** were isolated when *α*-branched aldehydes were allowed to react with 1-decene under this protocol in only moderate yields. High propensity for decarbonylation of the secondary acyl radical is likely the responsible for such observation.[7a,7d] A sharp improvement in the reactivity of *α*-branched aldehydes was observed with electron-deficient olefin. Accordingly, different acyclic as well as cyclic secondary aldehydes underwent the coupling reaction with cyclohexenone to afford the products **24**-**28** in good yields. The product **29** was obtained *via* the addition of *n*-butanal with cyclohexenone. The reaction of cyclohexenone with other linear aldehydes furnished products **30**-**32** in yields ranging from 48-89%. 4-Fluorobenzaldehyde exhibited moderate reactivity toward the addition reaction with cyclohexenone. Acyclic electron-deficient olefin worked equally well with both linear as well as *α*-branched aldehydes. Of note, the product **35** was prepared in 1 gram scale.

The reaction was then carried out by changing both the reaction partners (aldehydes and olefins). Linear ketones **37**-**41** varying chain lengths from C10-C25 were synthesized in good yields. Allyl benzene underwent the coupling reaction with *n*-butanal to afford the product **42**. Bromo substituted olefin reacted well (**43**, **44**); no product indicative of competing protodebromination was noticed. Unactivated olefins containing various useful functional groups were amenable to the reaction (products **45-50**). Notably, the product **48** was synthesized at 2 g scale with the recovery of unreacted starting materials, Ph_2CO and NHPI in good amount. Substrates having acid-sensitive *β*-diester, *β*-cyano ester, 1,3-amido alcohol and *β*-ketoamide were transformed to the corresponding products **51**-**54** in good yields with this protocol. The product **55** was obtained with complete retention of chirality. Amide substituted olefin could be hydroacylated with *n*-butanal in 79% yield. The sensitive azide group remained intact in this protocol, although the low yield of the product **57** was obtained. The unreacted olefin could be recovered in pure form. This simple hydroacylation protocol exhibited good reactivity with substrates having various synthetically useful functional groups like sulfinate (**58**), sulphonate (**59**), phosphonate (**60**), pinacolborate (**61**) and trimethylsilyl (**62**). Fluorine containing olefin gave the product in 98% yield. Mono-protected diol containing ketones **64**, **65** were synthesized in good yields by the coupling of TBDPS-protected hydroxy aldehyde with hydroxyl substituted olefin. They could be conveniently transformed to the corresponding aliphatic triols upon reduction of the carbonyl group. Different unactivated internal olefins underwent hydroacylation with aliphatic aldehydes, delivering the products **66**-**70** in moderate yields. However, they require a longer reaction time due to steric congestion. With this protocol, *n*-butanal reacted preferably at electron-deficient olefin of (*R*)-carvone, furnishing product **71** in 41% yield with 8:1 *syn* selectivity. The structure of **71** was proved by single-crystal X-ray analysis.

The synthetic potential of the radical hydroacylation process was further established by the preparation of keto-substituted cholesterol (**72**, X-ray) and *β*-estradiol (**73**). Furthermore, the reaction enabled diversification of estrone and biotin. Considering the complexity of the substrates, these results clearly demonstrate the synthetic power of the method despite the moderate yields of the products **74-76**. Notably, the unreacted substrates could be recovered and reused. Functionalized long-chain fatty-acids display significant biological applications.[16] In view of this, we decided to develop a flexible stagey for the synthesis of such materials applying the new olefin hydroacylation protocol with substrates possessing a carboxylic acid unit (Chart 1). Accordingly, the hydroacylation reactions between various aliphatic aldehydes and ester substituted olefins were carrying out, which afforded the

Chart 1. Substrate scope[a]



[a] Reaction conditions: Olefin (0.4 mmol, 1.0 equiv), aldehyde (5.0 equiv), **3a** (15 mol%), **4a** (10 mol%), trifluorotoluene (2.0 M), 24-64 h; overall isolated yields. [b] 6.0 equiv aldehyde. [c] 25.0 equiv acetaldehyde solution (35 wt.% in H_2O) was used. [d] 2.0 equiv aldehyde. [e] 3.0 equiv aldehyde. [f] Reaction was performed without **4a**. [g] 4.0 equiv aldehyde. [h] 2.25 equiv aldehyde. [i] Yield was calculated with respect to the amount of olefin reacted. [j] The reaction was performed at 1.0 M with respect to olefin. [k] 8.0 equiv aldehyde. [l]The reaction ran for 7 d.

corresponding keto-functionalized fatty acid esters **77-80** varying chain length from C14-C21 in good isolated yields. The fatty acid ester **81** was prepared in 69% yield by the reaction between a functionalized aldehyde and unsaturated ester. Direct synthesis of keto-functionalized fatty acid was also achieved using unsaturated aliphatic carboxylic acid as a radical acceptor. Keeping the ester group in aldehyde partner, the protocol enabled the synthesis of different fatty acid esters substituted with synthetically useful functional groups at the terminal. Accordingly, fatty acid esters having amide (**83**), azide (**84**), phosphonate (**85**), sulphonate (**86**), bromide (**87**), trimethylsilyl (**88**), hydroxyl (**89a**) groups were synthesized in good isolated yields. Furthermore, the reaction furnished estrone substituted fatty acid ester **90**.

The synthetic utility of the method was further demonstrated by the preparation of different valuable long-chain fatty acids (Fig. 1A). Upon ester hydrolysis, the products **77-79** were converted to the keto-functionalized fatty acids **91-93**. The $NaBH_4$ reduction of the ketones **79**, **80** and **93** resulted in the hydroxy fatty acid esters **95** and **96** and hydroxy fatty acid **94**.

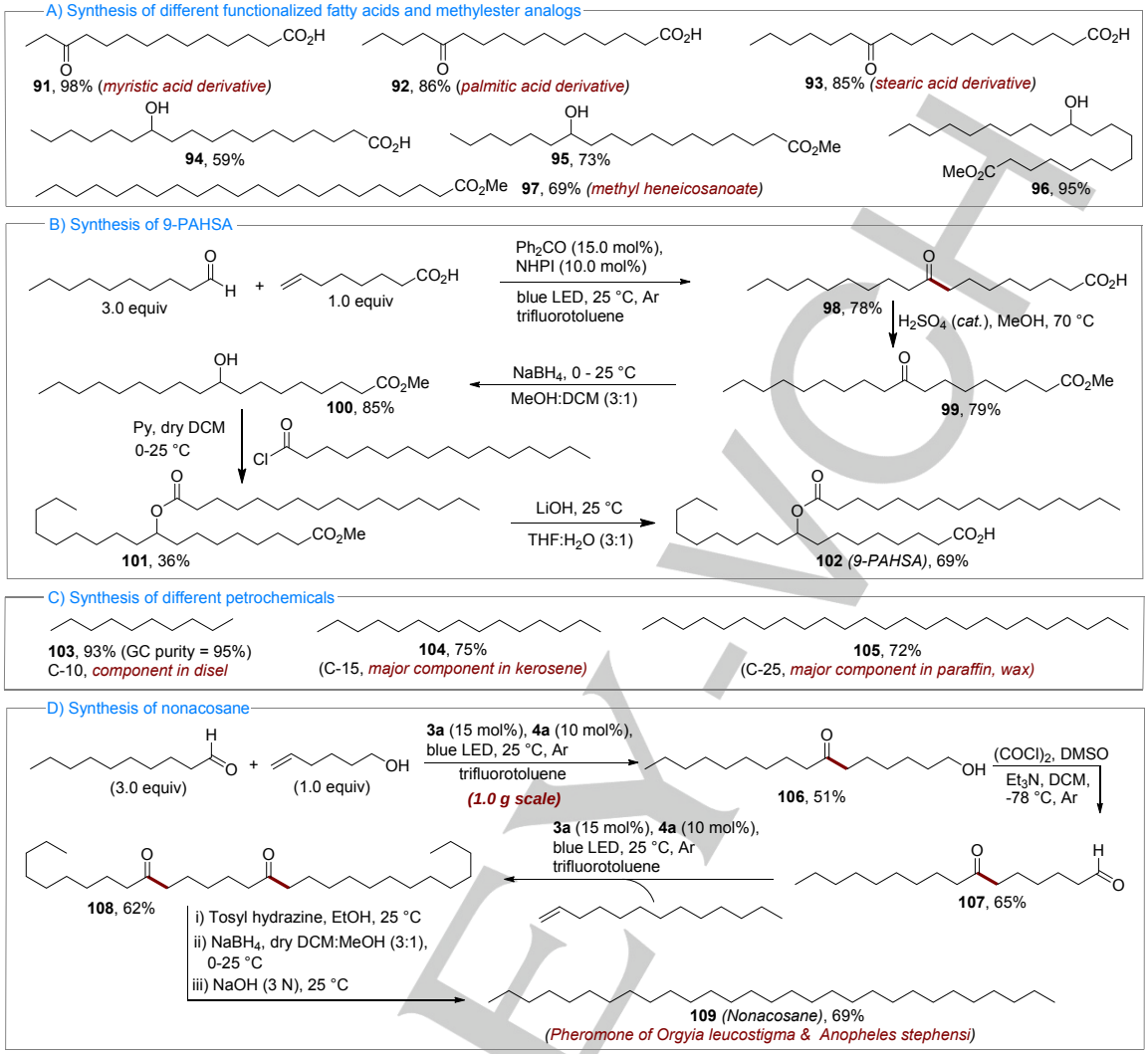


Figure 1. Synthetic applications.

Furthermore, the product **80** was conveniently transformed to methyl heneicosanoate, used as an internal standard for fatty acid quantification in dairy products[17] and in fish[18], *via* a one-pot reduction of the keto group.

Employing this hydroacylation reaction as key synthetic step, we developed a synthetic route to 9-PAHSA, a highly potent lipid exhibiting antidiabetic and anti-inflammatory activity.[19] The synthesis involved coupling of 1-decanal with 7-octenoic acid under the optimized reaction conditions delivering the acid **98**. Keeping free acid intact, the reduction of ketone **98** gave very low yield of the desired alcohol. Thus, the acid **98** was first transformed to the ester **99** prior to the reduction of keto group with $NaBH_4$ to obtain 9-hydroxy stearic acid ester **100**. Upon OH-acylation with palmitic acid chloride, the compound **100** was converted to the methyl ester analog of 9-PAHSA, which then finally transformed to the target compound **102** in good isolated yield *via* saponification of the ester with LiOH (Fig. 1B).

Additionally, the products **37**, **6**, and **41** were transformed to the alkanes **103**-**105** *via* simple chemical manipulation. The alkanes **103**-**104** are the major components of fuel[20] and **105** present in paraffin as well as in natural wax (Fig. 1C).[20a, 21]

We have then completed the total synthesis of nonacosane, a natural straight-chain hydrocarbon.[22] It plays a role in the chemical communication of several insects, including the female *Anopheles stephensi*.[21b,23] The synthesis began with the preparation of the hydroxy ketone **106** by carrying out the novel hydroacylation reaction between 1-decanal and 5-hexenol. The oxidation of primary alcohol of **106** gave the corresponding aldehyde **107** which was then allowed to react with 1-tridecene using this hydroacylation protocol to obtain diketone **108**. Finally, the reduction of both the keto-groups resulted in the target alkane **109** in good yield (Fig. 1D).

Several other studies were then carried out to provide experimental evidence to support the proposed radical pathway depicted in Scheme 1A. At first, we performed radical clock ring-opening experiment[24] using *n*-butanal and *β*-pinene under the optimized reaction conditions, which afforded the expected ketone **110** in 59% yield (Scheme 2). Likewise, the radical clock ring-closing experiment[24] rendered the cyclic ketone **111**

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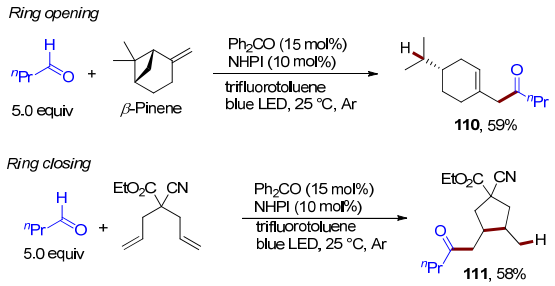
(Scheme 2). These results clearly prove that the reaction involves radical intermediate. This was further supported by radical quenching experiment with TEMPO. The reaction between *n*-decanal and 1-decene did not afford the desired product when performed in the presence of TEMPO. On the contrary, the formation of the TEMPO-adduct of the acyl radical derived from *n*-decanal was confirmed by GC-mass as well as HRMS analysis of the crude sample (see, SI).



Scheme 2. Radical clock experiments.

Furthermore, the reaction could be inhibited by turning light off. This result indicates that a constant photo-irradiation with blue LED is absolutely necessary for the success of the radical hydroacylation process. A very little progress of the reaction was observed in dark after 5 h photo-irradiation with blue LED (Fig. 2A). This may attribute a radical chain mechanism for the process. Following time dependent progress of the reactions that were carried out in the presence as well as the absence of NHPI *via* GC-analysis, it is confirmed that NHPI significantly impacts reactivity of the photo-induced radical hydroacylation reaction (Fig. 2B). In consequence, low yield of the desired product was obtained, when the reaction was performed in the absence of NHPI.

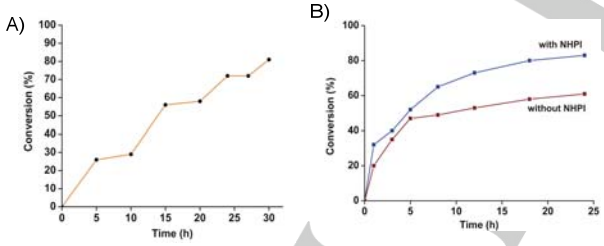


Figure 2. Light on-off experiments (A) and reaction kinetic (B).

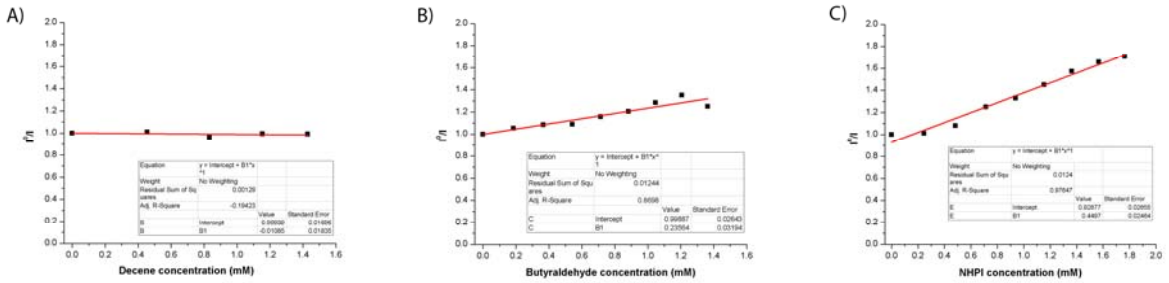


Figure 3. Stern-Volmer plot of fluorescence quenching experiments.

We then measured quantum yield of the radical process. Employing the standard ferrioxalate actinometry procedure reported by Yoon,[25] the quantum yield (Φ) of the reaction between *n*-butanal and 1-decene determined to be 4.7 under the optimized conditions, suggesting a radical chain mechanism for the reaction. Additionally, lower quantum yield (Φ = 3.2) of the reaction without using NHPI indicates role for NHPI as a radical chain carrier of the process (See SI). This is in agreement with the results obtained in the kinetic studies (Fig. 2B).

Fluorescence quenching studies for benzophenone **3a** were then performed with different quenchers including alkene, aldehyde and NHPI in CH_2Cl_2 (Fig. 3). The benzophenone (11.0 mM in CH_2Cl_2) was irradiated at 340 nm and its fluorescence was measured at 450 nm. The fluorescence of **3a** remained unaltered with an added amount of 1-decene (Fig. 3A). On the contrary, quenching of fluorescence of **3a** was observed with both *n*-butanal (**1**) and NHPI. These results may indicate that HAT from aldehyde as well as NHPI to the photo-exited **3a** is feasible (Fig. 3B & 3C). Consequently, the generation of acyl radical from aldehyde *via* photo-induced HAT process thereby the radical olefin hydroacylation could be achieved with/without using NHPI. This is in good agreement with the results obtained in reaction optimization studies. However, comparing the slopes between Stern-Volmer plots B and C, NHPI is identified as the primary quencher of the photo-excited **3a**. This observation may suggest that, in the presence of NHPI, HAT from NHPI to the photo-excited **3a** is favoured thereby leading to phthalimidyl *N*-oxyl (PINO) radical. The electrophilic PINO is known to facilitate the generation of an acyl radical from aldehyde *via* HAT thus far the initiation of the radical chain process is likely to have occurred.[8c],[14]

Conclusion

In summary, a general and effective method for intermolecular olefin hydroacylation of unactivated substrates (aldehydes and olefins) is demonstrated utilizing the photo-induced HAT process. The process is capable of promoting the coupling between aliphatic aldehydes and unactivated olefins, enabling the synthesis of a number of long-chain aliphatic ketones possessing numerous synthetically valuable functional groups. The method offers flexible synthesis of long-chain aliphatic ketones in the variation of chain length and the position of the carbonyl functional group. Notably, the hydroacylation reaction with substrates having ester as well as free-carboxylic acid unit

offers a great opportunity for the synthesis of various functionalized fatty acid derivatives with significant biological applications. Based on the results obtained in our mechanistic studies, a radical chain mechanism initiated by the photo-induced HAT is suggested for the reaction.

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Keywords: HAT • radical hydroacylation • unactivated olefin • fatty acid • light

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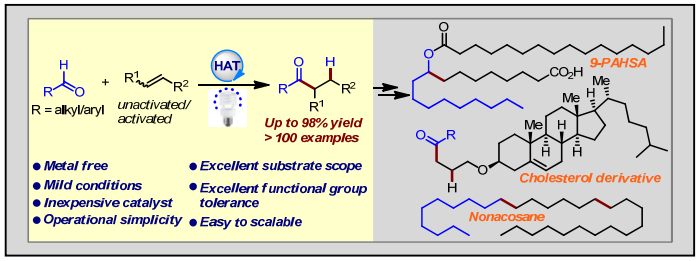

An efficient light-induced HAT process for the radical intermolecular hydroacylation of unactivated substrates is developed. The reaction allows synthesis of a large number of long-chain aliphatic ketones containing numerous synthetically valuable functional groups in good to excellent yields. The protocol is successfully applied toward the synthesis of various functionalized fatty acids, petrochemicals and naturally occurring alkanes. The results obtained in a series of studies indicate a radical chain mechanism for the hydroacylation process.