

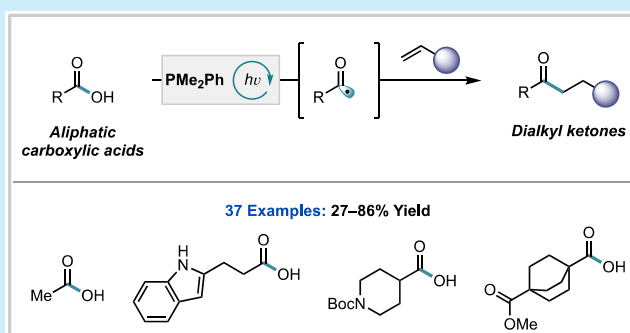
# Direct Use of Carboxylic Acids in the Photocatalytic Hydroacylation of Styrenes To Generate Dialkyl Ketones

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**S** Supporting Information

**ABSTRACT:** A general protocol for the hydroacylation of styrenes from aliphatic carboxylic acids is reported. These reactions proceed via  $\beta$ -scission of a phosphoranyl radical that is accessed by photoredox catalysis, followed by addition of the resulting acyl radical to the styrenyl olefin. We show that phosphine tunability is critical for efficient intermolecular coupling due to competitive quenching of the photocatalyst by the olefin. Primary, secondary, and structurally rigid tertiary carboxylic acids all generate valuable unsymmetrical dialkyl ketones.



Aliphatic ketones are versatile synthetic intermediates and common functional groups found in natural products and pharmaceuticals.<sup>1</sup> As a result, the development of mild and general methods for the construction of complex aliphatic ketones is important. Hydroacylation of olefins is one such strategy, as it affords ketones from abundant and structurally diverse feedstocks (Figure 1A). For example, transition metal-catalyzed hydroacylation of olefins with aldehydes has been extensively studied.<sup>2</sup> Nevertheless, the propensity of aliphatic aldehydes to undergo decarbonylation has limited the development of intermolecular hydroacylations. Successful examples are most often restricted to the use of aldehydes bearing coordinating functional groups or require the use of high pressures of carbon monoxide to ensure ketone formation.<sup>3</sup>

The addition of acyl radicals to a C–C double bond provides an alternative strategy for joining carbonyl and olefin substrates.<sup>4</sup> Hydrogen atom abstraction from aldehydes can furnish acyl radicals that undergo alkene addition. When an aldehyde possesses multiple weak C–H bonds and a highly reactive hydrogen atom abstractor is used, competitive abstractions may occur leading to complex reaction mixtures.<sup>4c,5</sup> Additionally, the propensity of aldehydes to undergo autoxidation limits their synthetic utility.<sup>6</sup> To overcome this issue, researchers have developed hydroacylation reactions with carbonyl substrates that access acyl radicals via alternative mechanisms, such as single-electron transfer or direct excitation (Figure 1B).<sup>4c–i</sup> For example, hydroacylations have recently been developed that couple olefins with acyl silanes<sup>4c</sup> or  $\alpha$ -keto acids,<sup>4d–f</sup> which undergo oxidative fragmentation to acyl radicals under photoredox catalysis. Activation of acyl derivatives via visible light fragmentation pathways have also been reported.<sup>4g–i</sup>

While the aforementioned methodologies enable the synthesis of ketones, the substrates for these reactions are often derived from carboxylic acids in multistep synthetic sequences. As a result, the functional group tolerance and step- and redox-economy of the hydroacylation reactions are compromised (Figure 1B).<sup>7</sup> Given the stability and wide availability of aliphatic carboxylic acids, their direct use for the generation of aliphatic ketones represents an attractive area for development. While the synthesis of ketones from carboxylic acids via cross-coupling has been reported,<sup>8</sup> these reactions use a prefunctionalized coupling partner. The hydroacylation of olefins directly with carboxylic acids has been far less developed, with seminal studies from Buchwald and Wang that are branch selective.<sup>9</sup>

With the Rovis group, we recently reported the C–OH activation of carboxylic acids using phosphines and photoredox catalysis (Figure 1C).<sup>10</sup> This work demonstrated that nucleophilic trapping of a phosphine radical cation could be leveraged to release acyl radicals via  $\beta$ -scission from a proposed phosphoranyl radical.<sup>11</sup> We showed that the acyl radical intermediate could be trapped with a hydrogen atom to afford aldehydes or trapped with a small subset of intramolecular  $\pi$ -systems to access cyclized products. Given the mild reaction conditions and the success of the intramolecular alkene trapping, we envisioned that translation of this strategy to an intermolecular hydroacylation would deliver a linear-selective synthesis of valuable unsymmetrical dialkyl ketones directly from carboxylic acids and olefin feedstocks. Recent work by Zhu and co-workers demonstrated the feasibility of this concept using triphenyl phosphine (PPh<sub>3</sub>) and aromatic

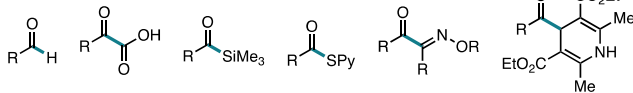
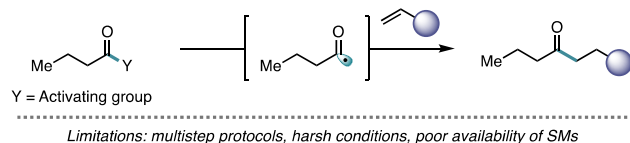
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## A. Hydroacylation of olefins



## B. Radical based approaches to hydroacylation of olefins



## C. Our approach: Intermolecular hydroacylation with phosphines and photoredox catalysis

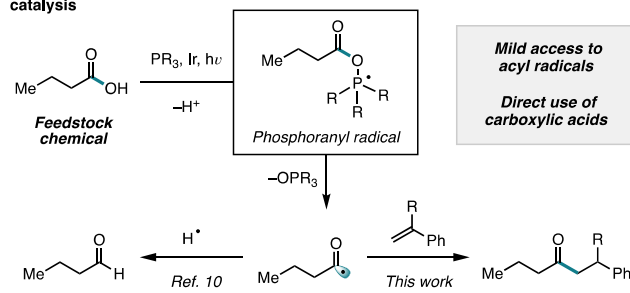


Figure 1. Hydroacylation of olefins with aliphatic carboxylic acids

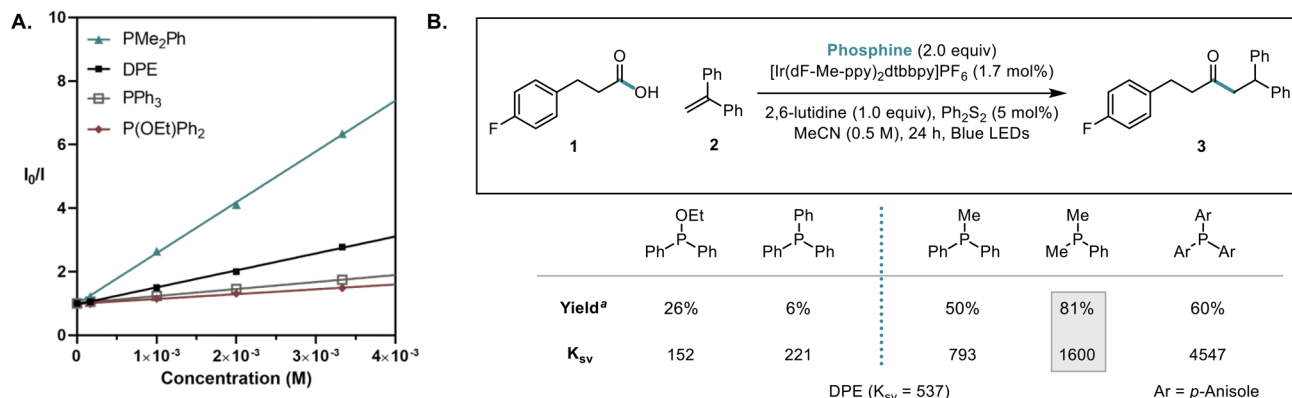
carboxylic acids.<sup>12</sup> However, no reactivity was observed with aliphatic carboxylic acids.

Our initial attempts to effect the intermolecular hydroacylation between hydrocinnamic acid **1** and 1,1-diphenyl ethylene **2** sought to use the same phosphines that we had previously reported for the reduction of acids to aldehydes.<sup>10</sup> However, both PPh<sub>3</sub> and ethyl diphenyl phosphinite (P(OEt)-Ph<sub>2</sub>) delivered less than 10% yield of product **3** under our previously optimized conditions, and optimization of standard reaction parameters failed to deliver significant improvements with these phosphines (see SI). Since the primary difference between our previous study and this work was the presence of alkene, we reasoned that electron or energy transfer to the

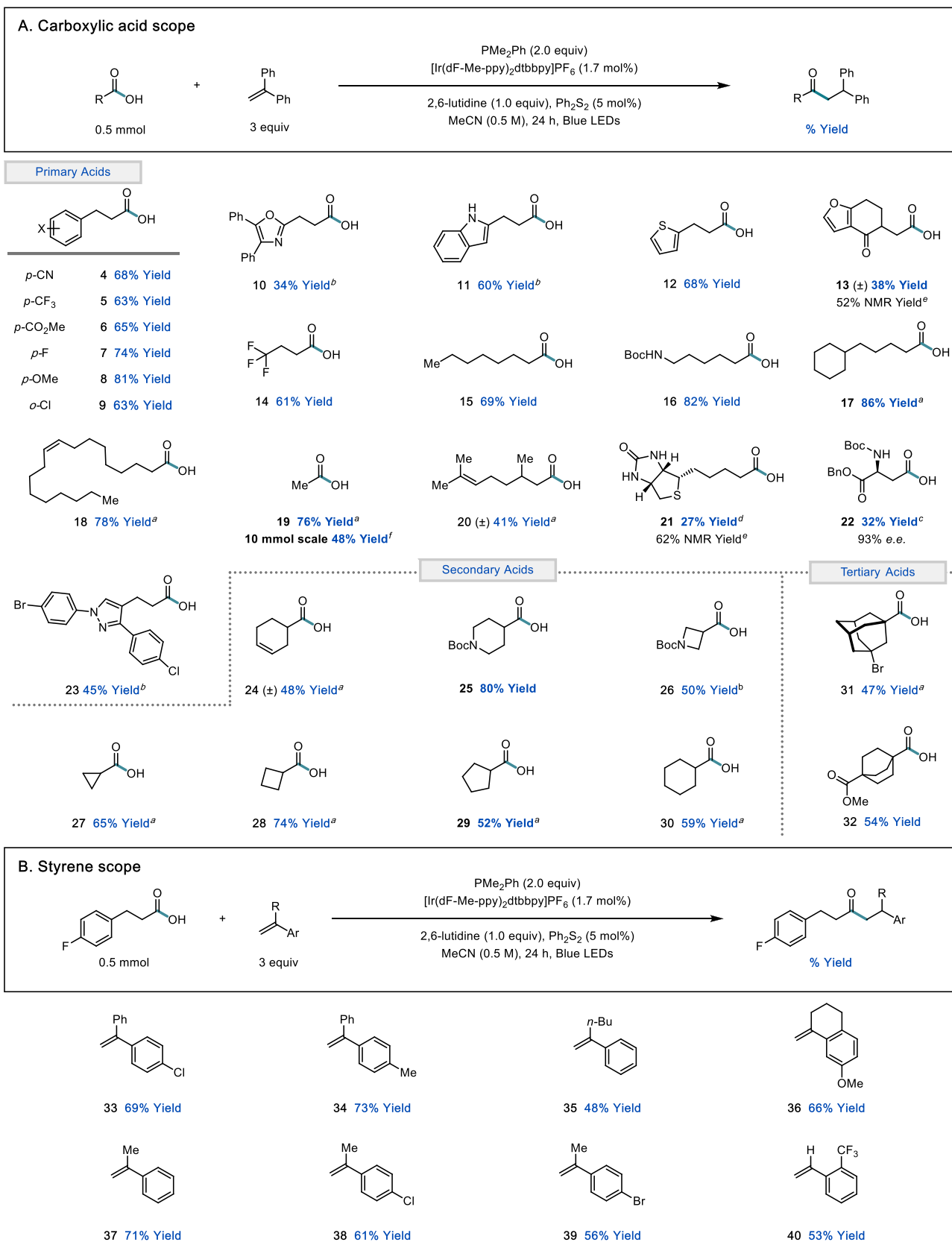
alkene was inhibiting formation of the phosphine radical cation, which was leading to poor reactivity.<sup>13</sup> Indeed, emission quenching experiments of the reaction components demonstrated that diphenyl ethylene quenched the excited state of the photocatalyst over two times faster than PPh<sub>3</sub> or P(OEt)Ph<sub>2</sub> (Figure 2A). Thus, we hypothesized that to achieve productive reactivity, we would need to use more electron-rich phosphines with lower oxidation potentials that could outcompete electron or energy transfer to the alkene (Figure S1).<sup>14</sup> A qualitative trend between yield and electron transfer rate for different phosphines was observed under optimized conditions, providing support for this proposal (Figure 2B).<sup>15</sup> Ultimately, commercially available dimethyl phenyl phosphine accomplished the intermolecular coupling in 81% <sup>1</sup>H NMR yield in 24 h.<sup>16</sup> Control studies confirmed that phosphine, light, and photocatalyst were all necessary reaction components for reactivity (Table S9).

With optimized reaction conditions,<sup>17</sup> the scope of this hydroacylation protocol was explored with commercially available carboxylic acids (Figure 3A). A variety of electron-deficient and electron-rich substituted hydrocinnamic acids were competent substrates (**4–9**). Of note are hydrocinnamic acids **4** and **6**, since traditional methods for ketone generation, such as the use of excess Grignard reagent, would afford poor chemoselectivity due to the pendant nitrile and ester.<sup>18</sup> Various heteroaromatic carboxylic acids were also tolerated. Oxazole **10**, indole **11**, thiophene **12**, and pyrazole **23** underwent hydroacylation in moderate to good yield. Acetic acid, which is produced annually on a multimillion-ton scale,<sup>19</sup> delivered the hydroacylated product in 76% yield. The hydroacylation with acetic acid was easily scaled to a 10 mmol scale, which afforded the ketone product in 48% yield under solvent-free conditions. Simple aliphatic carboxylic acids (**14–17**) showed high reactivity. Primary acids containing distal internal alkenes like oleic acid **18** and citronellic acid **20** were coupled in good yield.

Biotin **21** and an aspartic acid derivative **22** were tolerated in the reaction, highlighting the potential for the use of this methodology in late-stage functionalization or bioconjugation chemistry. Additionally, secondary carboxylic acids were also amenable to hydroacylation. Three- to six-membered ring carboxylic acids were coupled in good yield without suffering decarboxylation (**27–30**). However, depressed yields were



**Figure 2.** (A) Emission quenching plot of [Ir(dF-Me-ppy)<sub>2</sub>dtbbpy]PF<sub>6</sub> with diphenyl ethylene and phosphines. (dF-Me-ppy) = 2-(2,4-difluorophenyl)-5-methylpyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. DPE = diphenyl ethylene. (B) Reactivity studies with different phosphines. <sup>1</sup>H NMR yield determined using 1-fluoronaphthalene as external standard. K<sub>SV</sub> = K<sub>q</sub>τ<sub>0</sub>; K<sub>q</sub> = bimolecular quenching rate constant, τ<sub>0</sub> = excited state lifetime in the absence of quencher. See ref 16 for information on blue LEDs.



**Figure 3.** <sup>a</sup>Reactions run with 2.4 equiv of PMe<sub>2</sub>Ph and without Ph<sub>2</sub>S<sub>2</sub>. <sup>b</sup>Reactions run with 2.4 equiv of PMe<sub>2</sub>Ph and at 0.33 M in MeCN. <sup>c</sup>Reactions run at 0.25 M in MeCN. <sup>d</sup>Reactions run with 2.4 equiv of PMe<sub>2</sub>Ph, in 0.25 M DMA, on a 0.25 mmol scale with 6 equiv of alkene. <sup>e</sup><sup>1</sup>H NMR yield determined using 1-fluoronaphthalene as external standard. <sup>f</sup>The reaction was run neat.

observed with tertiary carboxylic acids (Figure S2), due to decarboxylation and competitive addition of the resulting alkyl

radical into diphenyl ethylene.<sup>20</sup> Nonetheless, structurally rigid tertiary carboxylic acids such as adamantane and norbornane

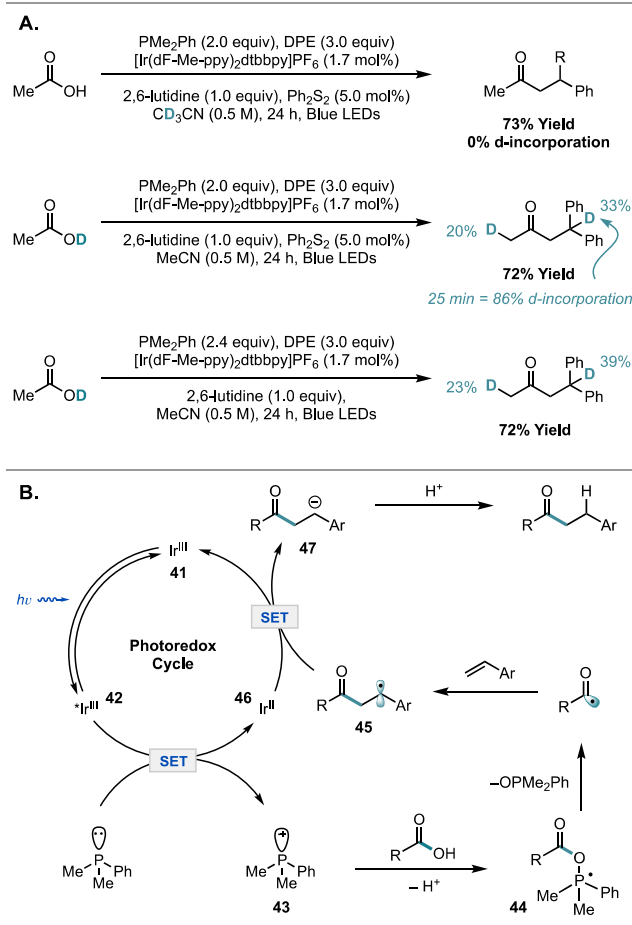
derivatives (**31** and **32**) provided the ketone product in good yield.

In addition to the carboxylic acid scope, various substituted styrene acceptors were explored (Figure 3B). Both electron-deficient and electron-rich diphenyl ethylene derivatives underwent hydroacylation efficiently (**33** and **34**). Comparable reactivity was observed using halogenated  $\alpha$ -methylstyrene derivatives (**38** and **39**), which provide a handle for further functionalization of the product. Although lower yielding, more sterically demanding alkene **35** was coupled in 48% yield. Reactivity was restored using the less sterically hindered cyclic alkene **36**, which furnished the ketone product in 66% yield. A current limitation is that electron-rich and neutral unsubstituted styrenes provide only moderate yield (30–40%) of the hydroacylation products under optimized reaction conditions (Figure S3).

Mechanistically, after acyl radical addition into the olefin, hydrogen atom transfer or a reduction-protonation sequence could result in the formation of the product. In our report on the reduction of carboxylic acids to aldehydes, we proposed that hydrogen atom transfer to the acyl radical furnished product. In Zhu and co-workers' aromatic acid hydroacylation, they suggest a reduction-protonation mechanism is operative. To probe these two pathways, we subjected acetic acid and 1,1-diphenyl ethylene to the standard reaction conditions in acetonitrile- $d_3$  (Figure 4A). No deuterium incorporation was observed, revealing that hydrogen atom transfer from solvent does not take place. The use of acetic acid- $d_1$  under the standard reaction conditions, on the other hand, showed 33% D-incorporation over 24 h. Deuterium incorporation into the enolizable C–H bonds of the product was also detected, indicating that isotope exchange by a polar mechanism likely decreases the efficiency of D incorporation at the methine site (see SI). Indeed, after 25 min, 86% D-incorporation at the methine position was observed. These findings are consistent with either a reduction-protonation sequence or hydrogen atom transfer from thiophenol. However, in the absence of diphenyl disulfide, deuterium incorporation was also observed at similar levels; taken together, these results suggest that a reduction-protonation sequence is most likely operative both in the presence and absence of diphenyl disulfide.<sup>21</sup>

These experiments and the emission quenching studies presented at the outset lend support for the mechanism proposed in Figure 4B. Initial visible light excitation of [Ir(dF-Me-ppy)<sub>2</sub>dtbppy]PF<sub>6</sub> (**41**) enables a long-lived excited state **42** that can serve as a one electron oxidant ( $E_{1/2}$  (III/II) = +0.97 V vs SCE in MeCN) for dimethyl phenyl phosphine ( $E_p$  = +0.89 V vs SCE in MeCN), generating phosphine radical cation **43**.<sup>22</sup> Nucleophilic trapping of the radical cation with the deprotonated carboxylic acid results in formation of a phosphoranyl radical **44**, followed by  $\beta$ -scission to generate an acyl radical. Addition into an alkene results in formation of aliphatic radical **45**, which is reduced to the anion with the reduced form of the photocatalyst (**46**).<sup>23</sup> Subsequent proton transfer from **47** results in product formation.<sup>12,24</sup>

In summary, a mild methodology for the hydroacylation of styrenyl olefins with carboxylic acids has been developed. Aliphatic acyl radicals are accessed from a phosphoranyl radical that is generated directly from a phosphine and a carboxylic acid. Key to the success of this reaction was tuning the phosphine for efficient electron transfer, which enabled hydroacylation with a diverse selection of aliphatic acids to afford valuable dialkyl ketone products.



**Figure 4.** (A) Deuterium labeling experiments. Deuterium incorporation was determined by quantitative <sup>13</sup>C NMR. Yield of product was determined using 1-fluoronaphthalene as external standard. (B) Proposed mechanism of the hydroacylation of aliphatic acids with alkenes using phosphines.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.9b03871>.

Experimental procedures, optimization data, characterization data, and mechanistic data (PDF)

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### Notes

The authors declare no competing financial interest.

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