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Communication

Cobalt-Catalyzed Markovnikov-Selective Radical Hydroacylation of Unactivated Alkenes with Acylphosphonates

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ABSTRACT: Acylphosphonates having the 5,5-dimethyl-1,3,2-dioxophosphinanyl skeleton are developed as efficient intermolecular radical acylation reagents, which enable the cobalt-catalyzed Markovnikov hydroacylation of unactivated alkenes at room temperature under mild conditions. The protocol exhibits broad substrate scope and wide functional group compatibility, providing branched ketones in satisfactory yields. A mechanism involving the Co−H mediated hydrogen atom transfer and subsequent trapping of alkyl radicals by acylphosphonates is proposed.

Hydroacylation of alkenes represents a highly attractive protocol for ketone synthesis owing to the easy availability and low cost of alkenes. These processes can be catalyzed by a variety of transition metals such as rhodium, ruthenium, cobalt, nickel, and iridium complexes.[1−4] However, a serious limitation is that most intermolecular hydroacylation reactions exhibit anti-Markovnikov selectivity to form linear ketones. Markovnikov-selective hydroacylation to provide branched ketones is generally limited to activated alkenes (e.g., styrenes,[5−12] enones,[13,14] and 1,3-dienes[15,16]) or alkenes with a directing group[17−21] (e.g., allylic alcohols, homoallylic sulfides, and 1,5-dienes) and often suffers from undesired chain-walking side-reactions.[10,13,15] Meanwhile, acyl radical mediated intermolecular alkene hydroacylation also leads to the exclusive formation of anti-Markovnikov products.[22,23] In fact, there have been no reports to date of general methods for Markovnikov hydroacylation of unactivated alkenes.

On the other hand, metal hydride (MH, M = Co, Fe, Mn, etc.) catalyzed hydrogen atom transfer (HAT) processes[24−27] have enabled the successful implementation of a number of radical hydrofunctionalizations of alkenes with Markovnikov selectivity, as developed by the groups of Mukaiyama,[28] Carreira,[29−37] Boger,[38−40] Shigehisa,[41−45] Baran,[46−50] Herzon,[51,52] Shenvi,[53−60] and others.[61−66] In particular, the nickel−copper-catalyzed hydroacylation of vinylarenes with acyl fluorides and hydrosilanes was reported by Sawamura et al.[6] Inspired by these studies, we speculated that the Markovnikov hydroacylation of unactivated alkenes could also be realized in a similar manner. However, our initial attempts using in situ generated acyl-Ni^{II} intermediates[67−80] as acylating agents failed to give any hydroacylation products. Instead, the hydrogenation of alkenes prevailed along with the alkene isomerization (see Table S1 in the Supporting Information (SI) for details). Thus, it appears essential that the acylating agents suitable for MH-catalyzed hydroacylation should trap alkyl radicals faster than MH or a silane (as the H source) does. To our surprise, the long search for radical acylating reagents other than the above-mentioned unstable acyl-Ni^{II} species remains unsolved and a challenging task. Biacetyl has been reported as a radical acceptor, but its efficiency and generality are both far from satisfactory.[81,82] Acylphosphonates,[83−85] acylgermanes,[86] and thio- and seleno-esters[87] have been tested as radical acylating agents by the groups of Kim, Curran, and Zard. However, only intramolecular acylation reactions have been achieved, while analogous intermolecular acylation has proved unsuccessful.[83,88,89] As an alternative, sulfonyl oxime ethers have been used as surrogates for an indirect radical acylation approach, which requires acid hydrolysis in the last step.[88,89] It is therefore highly desirable to develop stable, highly reactive, and preferably nonmetallic reagents for direct, intermolecular radical acylation. Herein we report that, through structural modifications, a novel class of acylphosphonates are identified to exhibit a significantly enhanced reactivity toward alkyl radicals, thus enabling the cobalt-catalyzed intermolecular Markovnikov hydroacylation of unactivated alkenes to proceed with high efficiency (Figure 1).

We commenced our investigations by choosing 4-phenylbut-1-ene (**1a**) as the model substrate and the commonly used salen-cobalt complex **2** as the catalyst. After an extensive screening on the reaction parameters (Table 1; also see Tables S2 and S3 in SI for details), we were pleased to find that, with *p*-chlorobenzoylphosphonate **3a** as the acylating reagent,

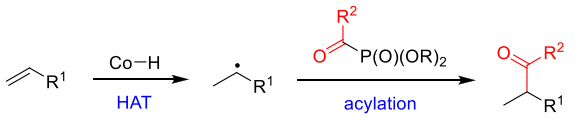

Figure 1. Working hypothesis.

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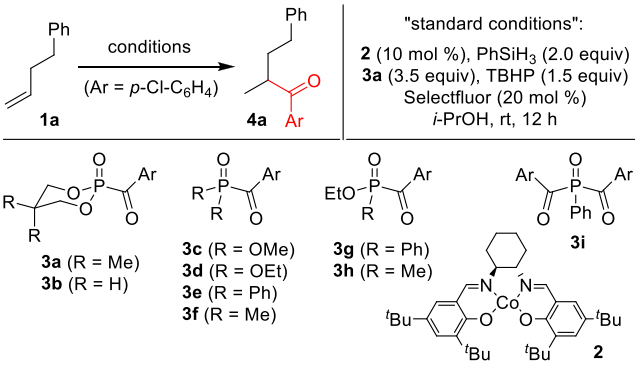
Table 1. Optimization of Reaction Conditions



entry[a]	variation from the "standard conditions"	yield (%)[a]
1	none	78
2	**3b** in place of **3a**	52
3	**3c** in place of **3a**	19
4	**3d** in place of **3a**	21
5	**3e** in place of **3a**	28
6	**3f** in place of **3a**	8
7	**3g** in place of **3a**	17
8	**3h** in place of **3a**	11
9	**3i** in place of **3a**	10
10	$(MeO)_3SiH$ in place of $PhSiH_3$	17
11	Et_3SiH in place of $PhSiH_3$	trace
12	without Selectfluor	60
13	without TBHP and Selectfluor	10
14	without **2**	0

[a]The reaction was carried out in 0.20 mmol scale in *i*-PrOH (6.0 mL). [b]Isolated yield based on **1a**.

phenylsilane as the hydrogen source, *tert*-butyl hydroperoxide (TBHP) as the oxidant, and 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor)[90,91] as the additive, the reaction of **1a** in isopropanol at room temperature (rt) delivered the desired ketone **4a** in 78% yield (entry 1, Table 1). No anti-Markovnikov hydroacylation product or chain-walking product[10] could be detected. Switching the acylating reagent from **3a** to its analog **3b** also provided ketone **4a** in 52% yield (entry 2, Table 1). In contrast, the use of dimethyl phosphonate **3c** or diethyl phosphonate **3d** in place of **3a** resulted in a very low (~20%) yield of **4a** (entries 3 and 4, Table 1). A poor result was also observed when **3a** was replaced by monoacylphosphine oxide **3e** or **3f** (entries 5 and 6, Table 1). Acylphosphinates **3g** and **3h** and diacylphosphine oxide **3i** proved to be incompetent acylating reagents (entries 7–9, Table 1). Phenylsilane exhibited much better performance than trimethoxysilane or triethylsilane (entries 10 and 11, Table 1). A catalytic amount of Selectfluor, an additive commonly used in cobalt-catalyzed hydrofunctionalization reactions, helped to increase the product yield (entry 12, Table 1). Other additives such as *N*-fluoropyridinium salts were less efficient than Selectfluor in promoting the transformation (see Table S2 in SI for details). TBHP proved to be an oxidant superior to other peroxides or hypervalent iodine reagents such as diacetoxyiodobenzene (also see Table S2). Interestingly, the reaction also took place in the absence of TBHP and Selectfluor, albeit in a low (10%) yield (entry 13, Table 1), presumably because of the contamination of trace O_2.[27] Finally, the control experiment demonstrated the role of cobalt as the catalyst (entry 14, Table 1).

The unexpected substituent effect on the reactivity of acylating reagents shown above (entries 1–9, Table 1) is remarkable. By simply changing the open-chain structures (as in **3c**–**3e**) to the 1,3,2-dioxophosphinanyl ring (as in **3a**), the reagent reactivity is drastically increased. Compared to the open-chain structures, the 1,3,2-dioxophosphinanyl ring might reduce the steric hindrance associated with the carbonyl group and thus facilitates the attack of alkyl radicals. The *gem*-dimethyl substitution in **3a** may help to stabilize the chair conformation of the heterocycle. This is evidenced by the X-ray crystal structures of **3a** and **3b** in that the six-membered heterocycle adopts a chair conformation in **3a** but a half-chair conformation in **3b**. The C═O and P═O groups in **3b** are almost coplanar with a dihedral angle of −176°, indicating that radical attack to the carbonyl from either face will encounter the same steric hindrance. In contrast, the C═O and P═O groups in **3a** have a dihedral angle of −128°, resulting in the blockade of one face of the carbonyl group but the clearance of the other. As a consequence, the reaction with **3a** exhibits higher efficiency than that with **3b**. These experiments are also the first examples of intermolecular acylation with acylphosphonates. It should also be noted that, in the literature reports,[67−80] the proposed species responsible for acylation of alkyl radicals are generally unstable organometallic intermediates such as acyl-Ni^{II} intermediates. As a comparison, acylphosphonates structurally similar to **3a** are stable crystalline solids that are easy to handle. Furthermore, they can be readily prepared by reaction of acyl chlorides with trialkyl phosphites in one step[83,92,93] or in two steps by dialkyl phosphite addition to aldehydes followed by Dess−Martin oxidation in excellent yields (see SI for details). These characteristics should encourage further applications of acylphosphonates as radical acylating agents.

With the optimized conditions in hand, we examined the scope of the method. As shown in Scheme 1, a variety of terminal alkenes underwent hydroacylation reaction smoothly leading to the synthesis of branched ketones **4b**–**4u** in satisfactory yields. Exclusive Markovnikov selectivity was observed in all cases. Chemoselective hydroacylation was observed in the case of **4u** in which the isopentenyl moiety remained intact. By lowering the catalyst loading to 5 mol % and slightly increasing the amounts of TBHP and **3a**, the protocol was also applicable to internal alkenes as exemplified by the synthesis of **4v**–**4x** from the corresponding cycloalkenes. Similarly, the reaction of methyl cyclopent-3-enecarboxylate furnished the expected product **4y** in 74% yield. The presence of a wide range of functional groups was well tolerated by the process. For example, alkyl (or aryl) halides, amides, sulfonamides, esters, sulfonates, ethers, silyl ethers, alkylphosphonates, nitriles, furans, and nitroalkanes all proved to be compatible with the reaction. This excellent functional group compatibility enabled the late stage modification of complex molecules or drug derivatives. For example, the reaction of alkene **1za** containing an *N*-Boc-protected dipeptide motif afforded product **4za** in 52% yield. Ketone **4zb** having the sensitive diacetonefructose skeleton was also achieved under the optimized conditions. Alkenes derived from ibuprofen, hymecromone, nortropine, and estrone produced the expected products **4zc**–**4zf** in good yields.

Encouraged by the above results, we went on to test the hydroacylation of alkene **1a** with a number of acylphospho-

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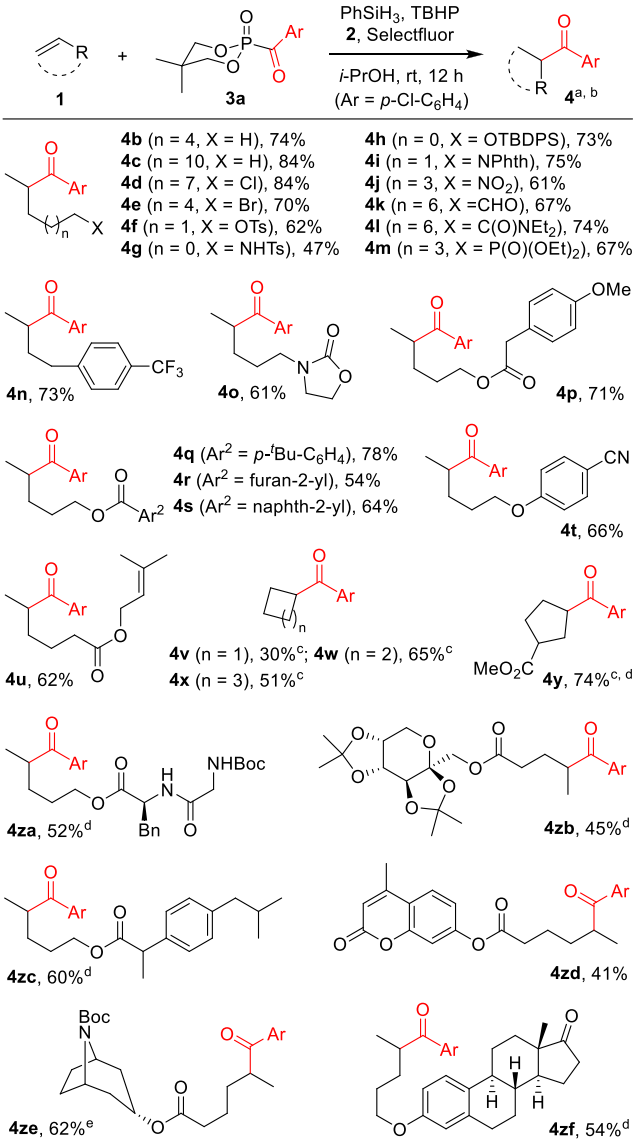
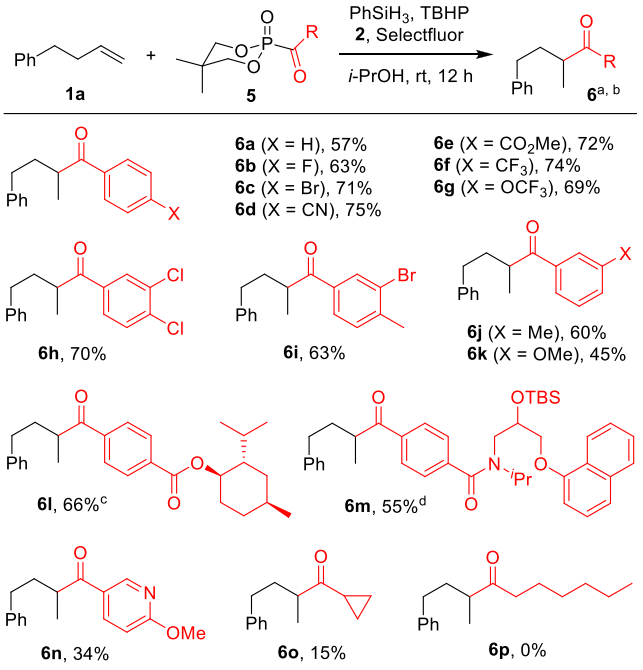
Scheme 1. Hydroacylation of Unactivated Alkenes with 3a



[a]Conditions: **1** (0.20 mmol), **2** (0.02 mmol), **3a** (0.70 mmol), $PhSiH_3$ (0.40 mmol), TBHP (0.30 mmol), Selectfluor (0.04 mmol), *i*-PrOH (6.0 mL), rt, 12 h. [b]Isolated yield based on **1**. [c]**2** (0.01 mmol), **3a** (0.80 mmol), and TBHP (0.40 mmol) were used. [d]d.r. = 50:50 determined by ^{1}H NMR (400 MHz). [e]d.r. = 50:50 determined by ^{13}C NMR (100 MHz).

nates other than **3a**. As shown in Scheme 2, benzoylphosphonates **5a**–**5k** bearing either electron-withdrawing or electron-donating substituents on the aromatic ring all participated in the reaction with **1a** to give the expected products **6a**–**6k** under the optimized conditions without further modification. Taking advantage of their easy availability, structurally complex benzoylphosphonates also served as ideal acylating reagents, as evidenced by the efficient synthesis of aromatic ketones **6l** containing a menthol group and **6m** having a propranolol motif. Pyridine-3-carbonylphosphonate **5n** also took part in the hydroacylation with **1a** to generate **6n** in a moderate yield. In another case, (cyclopropanecarbonyl)phosphonate **5o** led to the formation of cyclopropyl ketone **6o** in 15% yield. Nevertheless, further extension of the method to alkanoylphosphonates such as heptanoylphosphonate **5p** failed, which

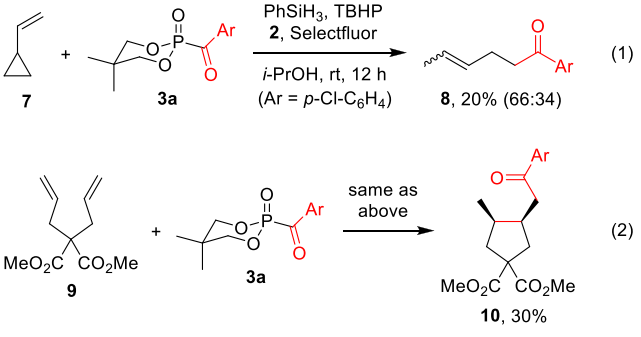
Scheme 2. Hydroacylation of 1a with Acylphosphonates



[a]Conditions: **1a** (0.20 mmol), **2** (0.02 mmol), **5** (0.70 mmol), $PhSiH_3$ (0.40 mmol), TBHP (0.30 mmol), Selectfluor (0.04 mmol), and *i*-PrOH (6.0 mL), rt, 12 h. [b]Isolated yield based on **1a**. [c]d.r. = 50:50 determined by ^{1}H NMR (400 MHz). [d]d.r. = 50:50 determined by ^{13}C NMR (100 MHz)

in turn indicated that alkanoylphosphonates were less reactive than benzoylphosphonates toward alkyl radicals.

The results in Schemes 1 and 2 clearly demonstrated the broad substrate scope and wide functional compatibility of the method. To gain further insight into the hydroacylation, the following radical clock experiments were designed. The reaction of vinylcyclopropane (**7**) with **3a** under the above optimized conditions afforded the ring-opening product **8** (eq 1). 1,6-Diene **9** underwent an addition–cyclization–acylation



sequence to provide cyclopentane **10** as a single diastereoisomer, whose configuration was unambiguously established by 2D NMR experiments (eq 2).

A tentative mechanism is thus proposed based on the above results and literature reports, as depicted in Figure 2. The oxidation of Co^{II} complex **2** by TBHP generates the $Co^{III}O_2{}^tBu$ species[43,94] that is then captured by phenylsilane to give the Co^{III}–H intermediate.[27,95] Selectfluor as a co-oxidant helps in the oxidation of Co^{II} to Co^{III}.[27] The cobalt hydride engages in the HAT with an alkene to produce radical

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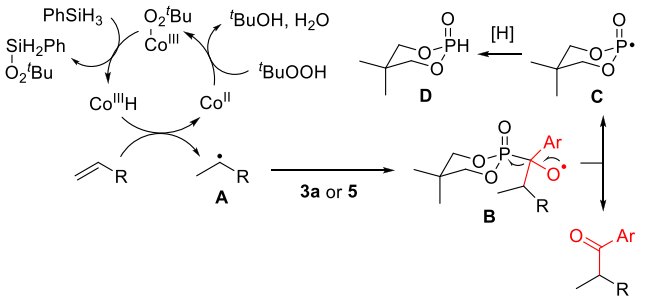

Figure 2. Proposed mechanism.

A and regenerates the Co^{II} catalyst. Next, the nucleophilic alkyl radical attacks the carbonyl group of an acylphosphonate to form alkoxyl radical **B**. Subsequent β-scission of radical **B** delivers the hydroacylation product and the phosphoryl radical **C**. The phosphoryl radical is then quenched by phenylsilane (or Co^{III}–H) via H-abstraction to offer dialkyl phosphite **D**. Indeed, the formation of **D** was clearly observed by the crude ^{31}P NMR. Note that the dialkyl phosphite **D** served as the starting material for the preparations of acylphosphonates (**3a** and **5**) and could be recycled in theory. Further investigations on the detailed mechanism are currently underway in our laboratory.

In conclusion, we have successfully accomplished the unprecedented cobalt-catalyzed intermolecular Markovnikov hydroacylation of unactivated alkenes with acylphosphonates as the acylating agents. As the procedure is mild, tolerant of sensitive functional groups, and broad in scope, the method should find applications in ketone synthesis. More importantly, our finding that the stable and readily available acylphosphonates consisting of the 5,5-dimethyl-1,3,2-dioxophosphinanyl skeleton are capable of intercepting alkyl radicals intermolecularly should inspire further development of new acylation reactions of important value.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02629.

Full experimental details, characterizations of new compounds, copies of ^{1}H, ^{13}C, ^{31}P, ^{19}F and 2D NMR spectra, and X-ray crystal structures of **3a** and **3b** (PDF)

Accession Codes

CCDC 2070525–2070526 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

[§]B.Z. and J.H contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Willis, M. C. Transition metal catalyzed alkene and alkyne hydroacylation. *Chem. Rev.* **2010**, *110*, 727–748.

(2) Leung, J. C.; Krische, M. J. Catalytic intermolecular hydroacylation of C-C π-bonds in the absence of chelation assistance. *Chem. Sci.* **2012**, *3*, 2202–2209.

(3) Willis, M. C. Hydroacylation of alkenes, alkynes, and allenes. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; Vol. 4, pp 961–994.

(4) Dong, V. M.; Kou, K. G. M.; Le, D. N. Transition-metal-catalyzed hydroacylation. *Org. React.* **2018**, *96*, 229–592.

(5) Yang, P.-F.; Shu, W. Direct synthesis of mono-α-arylated ketones from alcohols and olefins via Ni-catalyzed oxidative cross-coupling. *Org. Lett.* **2020**, *22*, 6203–6208.

(6) Ueda, Y.; Iwai, T.; Sawamura, M. Nickel-copper-catalyzed hydroacylation of vinylarenes with acyl fluorides and hydrosilanes. *Chem. - Eur. J.* **2019**, *25*, 9410–9414.

(7) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. Enantioselective CuH-catalyzed hydroacylation employing unsaturated carboxylic acids as aldehyde surrogates. *J. Am. Chem. Soc.* **2017**, *139*, 8126–8129.

(8) Bandar, J. S.; Ascic, E.; Buchwald, S. L. Enantioselective CuH-catalyzed reductive coupling of aryl alkenes and activated carboxylic acids. *J. Am. Chem. Soc.* **2016**, *138*, 5821–5824.

(9) Xiao, L.-J.; Fu, X.-N.; Zhou, M.-J.; Xie, J.-H.; Wang, L.-X.; Xu, X.-F.; Zhou, Q.-L. Nickel-catalyzed hydroacylation of styrenes with

simple aldehydes: reaction development and mechanistic insights. *J. Am. Chem. Soc.* **2016**, *138*, 2957−2960.
(10) Kim, J.; Yi, C. S. Intermolecular Markovnikov-selective hydroacylation of olefins catalyzed by a cationic ruthenium-hydride complex. *ACS Catal.* **2016**, *6*, 3336−3339.
(11) Murphy, S. K.; Bruch, A.; Dong, V. M. Substrate-directed hydroacylation: rhodium-catalyzed coupling of vinylphenols and nonchelating aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 2455−2459.
(12) Hong, Y.-T.; Barchuk, A.; Krische, M. J. Branch-selective intermolecular hydroacylation: hydrogen-mediated coupling of anhydrides to stryenes and activated olefins. *Angew. Chem., Int. Ed.* **2006**, *45*, 6885−6888.
(13) Fukuyama, T.; Doi, T.; Minamino, S.; Omura, S.; Ryu, I. Ruthenium hydride catalyzed regioselective addition of aldehydes to enones to give 1,3-diketones. *Angew. Chem., Int. Ed.* **2007**, *46*, 5559−5561.
(14) Murphy, S. K.; Zeng, M.; Herzon, S. B. Stereoselective multicomponent reactions using zincate nucleophiles: β-dicarbonyl synthesis and functionalization. *Org. Lett.* **2016**, *18*, 4880−4883.
(15) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. Ruthenium hydride-catalyzed addition of aldehydes to dienes leading to β,γ-unsaturated ketones. *J. Am. Chem. Soc.* **2008**, *130*, 14094−14095.
(16) Shibahara, F.; Bower, J. F.; Krische, M. J. Direct hydroacylation from the alcohol or aldehyde oxidation level via ruthenium-catalyzed C-C bond-forming transfer hydrogenation: synthesis of β,γ-unsaturated ketones. *J. Am. Chem. Soc.* **2008**, *130*, 14120−14122.
(17) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. Double-chelation-assisted Rh-catalyzed intermolecular hydroacylation. *Org. Lett.* **2003**, *5*, 1365−1367.
(18) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. Double-chelation-assisted Rh-catalyzed intermolecular hydroacylation between salicylaldehydes and 1,4-pneta- or 1,5-hexadienes. *J. Org. Chem.* **2004**, *69*, 1144−1150.
(19) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. Regio- and enantioselective intermolecular hydroacylation: substrate-directed addition of salicylaldehydes to homoallylic sulfides. *J. Am. Chem. Soc.* **2010**, *132*, 16330−16333.
(20) Murphy, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. Catalytic hydroacylation as an approach to homoaldol products. *Org. Lett.* **2011**, *13*, 6216−6219.
(21) Murphy, S. K.; Coulter, M. M.; Dong, V. M. β-Hydroxy ketones prepared by regioselective hydroacylation. *Chem. Sci.* **2012**, *3*, 355−358.
(22) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. Chemistry of acyl radicals. *Chem. Rev.* **1999**, *99*, 1991−2069.
(23) Banerjee, A.; Lei, Z.; Ngai, M.-Y. Acyl radical chemistry via visible-light photoredox catalysis. *Synthesis* **2019**, *51*, 303−333.
(24) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe- and Co-catalyzed radical hydrofunctionalization of olefins. *Chem. Rev.* **2016**, *116*, 8912−9000.
(25) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vasquez-Cespedes, S.; Shevick, S. L.; Shenvi, R. A. The high chemofidelity of metal-catalyzed hydrogen atom transfer. *Acc. Chem. Res.* **2018**, *51*, 2628−2640.
(26) Shenvi, R. A.; Matos, J. L. M.; Green, S. A. Hydrofunctionalization of alkenes by hydrogen-atom transfer. *Org. React.* **2019**, *100*, 383−470.
(27) Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A. Catalytic hydrogen atom transfer to alkenes: a roadmap for metal hydrides and radicals. *Chem. Sci.* **2020**, *11*, 12401−12422.
(28) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. Oxidation-reduction hydration of olefins with molecular oxygen and 2-propanol catalyzed by bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 449−452.
(29) Waser, J.; Carreira, E. M. Convenient synthesis of alkylhydrazides by the cobalt-catalyzed hydrohydrazination reaction of olefins and azodicarboxylates. *J. Am. Chem. Soc.* **2004**, *126*, 5676−5677.
(30) Waser, J.; Carreira, E. M. Catalytic hydrohydrazination of a wide range of alkenes with a simple Mn complex. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099−4102.
(31) Waser, J.; Nambu, H.; Carreira, E. M. Cobalt-catalyzed hydroazidation of olefins: convenient access to alkyl azides. *J. Am. Chem. Soc.* **2005**, *127*, 8294−8295.
(32) Waser, J.; Gonzalez-Gomez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. Cobalt-catalyzed hydrohydrazination of dienes and enynes: access to allylic and propargylic hydrazides. *Org. Lett.* **2005**, *7*, 4249−4252.
(33) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. Hydrazines and azides via the metal-catalyzed hydrohydrazination and hydroazidation of olefins. *J. Am. Chem. Soc.* **2006**, *128*, 11693−11712.
(34) Gaspar, B.; Waser, J.; Carreira, E. M. Cobalt-catalyzed synthesis of tertiary azides from α,α-disubstituted olefins under mild conditions using commercially available reagents. *Synthesis* **2007**, *2007*, 3839−3845.
(35) Gaspar, B.; Carreira, E. M. Mild cobalt-catalyzed hydrocyanation of olefins with tosyl cyanide. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519−4522.
(36) Gaspar, B.; Carreira, E. M. Catalytic hydrochlorination of unactivated oelfins with *para*-toluenesulfonyl chloride. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758−5760.
(37) Gaspar, B.; Carreira, E. M. Cobalt catalyzed functionalization of unactivated alkenes: regioselective reductive C-C bond forming reactions. *J. Am. Chem. Soc.* **2009**, *131*, 13214−13215.
(38) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. Total synthesis of vinblastine, vincristine, related natural products, and key structural analogues. *J. Am. Chem. Soc.* **2009**, *131*, 4904−4916.
(39) Barker, T. J.; Boger, D. L. Fe(III)/$NaBH_4$-mediated free radical hydrofluorination of unactivated alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 13588−13591.
(40) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. Iron(III)/$NaBH_4$-mediated additions to unactivated alkenes: synthesis of novel 20'-vinblastine analogs. *Org. Lett.* **2012**, *14*, 1428−1431.
(41) Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K. Hydroalkoxylation of unactivated olefins with carbon radical and carbocation species as key intermediates. *J. Am. Chem. Soc.* **2013**, *135*, 10306−10309.
(42) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K. Catalytic hydroamination of unactivated olefins using a Co catalyst for complex molecule synthesis. *J. Am. Chem. Soc.* **2014**, *136*, 13534−13537.
(43) Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K. Catalytic synthesis of saturated oxygen heterocycles by hydrofunctionalization of unactivated olefins: unprotected and protected strategies. *J. Am. Chem. Soc.* **2016**, *138*, 10597−10604.
(44) Date, S.; Hamasaki, K.; Sunagawa, K.; Koyama, H.; Sebe, C.; Hiroya, K.; Shigehisa, H. Catalytic direct cyclization of alkenyl thioester. *ACS Catal.* **2020**, *10*, 2039−2045.
(45) Ebisawa, K.; Izumi, K.; Ooka, Y.; Kato, H.; Kanazawa, S.; Komatsu, S.; Nishi, E.; Shigehisa, H. Catalyst- and silane-controlled enantioselective hydrofunctionalization of alkenes by cobalt-catalyzed hydrogen atom transfer and radical-polar crossover. *J. Am. Chem. Soc.* **2020**, *142*, 13481−13490.
(46) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. Functionalized olefin cross-coupling to construct carbon-carbon bonds. *Nature* **2014**, *516*, 343−348.
(47) Lo, J. C.; Yabe, Y.; Baran, P. S. A practical and catalytic reductive olefin coupling. *J. Am. Chem. Soc.* **2014**, *136*, 1304−1307.

https://doi.org/10.1021/jacs.1c02629
J. Am. Chem. Soc. 2021, 143, 4955−4961

(48) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. Hydromethylation of unactivated olefins. *J. Am. Chem. Soc.* **2015**, *137*, 8046−8049.
(49) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical olefin hydroamination with nitroarenes. *Science* **2015**, *348*, 886−891.
(50) Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. Fe-catalyzed C-C bond construction from olefins via radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2484−2503.
(51) King, S. M.; Ma, X.; Herzon, S. B. A method for the selective hydrogenation of alkenyl halides to alkyl halides. *J. Am. Chem. Soc.* **2014**, *136*, 6884−6887.
(52) Ma, X.; Herzon, S. B. Intermolecular hydropyridylation of unactivated alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 8718−9721.
(53) Crossley, S. W. M.; Barabe, F.; Shenvi, R. A. Simple, chemoselective, catalytic olefin isomerization. *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791.
(54) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. Simple, chemoselective hydrogenation with thermodynamic stereocontrol. *J. Am. Chem. Soc.* **2014**, *136*, 1300−1303.
(55) Obradors, C.; Martinez, R. M.; Shenvi, R. A. Ph(*i*-PrO)SiH_2: an exceptional reductant for metal-catalyzed hydrogen atom transfers. *J. Am. Chem. Soc.* **2016**, *138*, 4962−4971.
(56) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. Branch-selective hydroarylation: iodoarene-olefin cross-coupling. *J. Am. Chem. Soc.* **2016**, *138*, 12779−12782.
(57) Green, S. A.; Vasquez-Cespedes, S.; Shenvi, R. A. Iron-nickel dual-catalysis: a new engine for olefin functionalization and the formation of quaternary centers. *J. Am. Chem. Soc.* **2018**, *140*, 11317−11324.
(58) Shevick, S. L.; Obradors, C.; Shenvi, R. A. Mechanistic interrogation of Co/Ni-dual catalyzed hydroarylation. *J. Am. Chem. Soc.* **2018**, *140*, 12056−12068.
(59) Matos, J. L. M.; Vasquez-Cespedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. Branch-selective addition of unactivated olefins into imines and aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 16976−16981.
(60) Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. Hydroalkylation of olefins to form quaternary carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709−7714.
(61) Zheng, J.; Wang, D.; Cui, S. Fe-catalyzed reductive coupling of unactivated alkenes with *β*-nitroalkenes. *Org. Lett.* **2015**, *17*, 4572−4575.
(62) Wang, Y.-Y.; Bode, J. W. Olefin amine (OLA) reagents for the synthesis of bridged bicyclic and spirocyclic saturated N-heterocycles by catalytic hydrogen atom transfer (HAT) reactions. *J. Am. Chem. Soc.* **2019**, *141*, 9739−9745.
(63) Zhou, X.-L.; Yang, F.; Sun, H.-L.; Yin, Y.-N.; Ye, W.-T.; Zhu, R. Cobalt-catalyzed intermolecular hydrofunctionalization of alkenes: evidence for a bimetallic pathway. *J. Am. Chem. Soc.* **2019**, *141*, 7250−7255.
(64) Sun, H.-L.; Yang, F.; Ye, W.-T.; Wang, J.-J.; Zhu, R. Dual cobalt and photoredox catalysis enabled intermolecular oxidative hydrofunctionalization. *ACS Catal.* **2020**, *10*, 4983−4989.
(65) Song, L.; Fu, N.; Ernst, B. G.; Lee, W. H.; Frederick, M. O.; DiStasio, R. A. Jr.; Lin, S. Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes. *Nat. Chem.* **2020**, *12*, 747−754.
(66) Saladrigas, M.; Puig, J.; Bonjoch, J.; Bradshaw, B. Iron-catalyzed radical intermolecular addition of unbiased alkenes to aldehydes. *Org. Lett.* **2020**, *22*, 8111−8115.
(67) Wang, J.; Hoerrner, M. E.; Watson, M. P.; Weix, D. J. Nickel-catalyzed synthesis of dialkyl ketones from the coupling of N-alkyl pyridiniun salts with activated carboxylic acids. *Angew. Chem., Int. Ed.* **2020**, *59*, 13484−13489.
(68) Zheng, S.; Zhang, S.-Q.; Saeednia, B.; Zhou, J.; Anna, J. M.; Hong, X.; Molander, G. A. Diastereoselective olefin amidoacylation via photoredox PCET/nickel-dual catalysis: reaction scope and mechanistic insights. *Chem. Sci.* **2020**, *11*, 4131−4137.
(69) Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A radical approach to anionic chemistry: synthesis of ketones, alcohols, and amines. *J. Am. Chem. Soc.* **2019**, *141*, 6726−6739.
(70) Wang, J.; Cary, B. P.; Beyer, P. D.; Gellman, S. H.; Weix, D. J. Ketones from nickel-catalyzed decarboxylative, non-symmetric cross-electrophile coupling of carboxylic acid esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 12081−12085.
(71) Ackerman, L. K. G.; Alvarado, J. I. M.; Doyle, A. G. Direc C-C bond formation from alkanes using Ni-photoredox catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14059−14063.
(72) Amani, J.; Molander, G. A. Direct conversion of carboxylic acids to alkyl ketones. *Org. Lett.* **2017**, *19*, 3612−3615.
(73) Joe, C. L.; Doyle, A. G. Direct acylation of C(sp^3)-H bonds enabled by nickel and photoredox catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 4040−4043.
(74) Amani, J.; Sodagar, E.; Molander, G. A. Visible light photoredox cross-coupling of acyl chlorides with potassium alkoxymethyltrifluoroborates: synthesis of *α*-alkoxyketones. *Org. Lett.* **2016**, *18*, 732−735.
(75) Le, C. C.; MacMillan, D. W. C. Fragment couplings via CO_2 extrusion-recombination: expansion of a classic bond-forming strategy via metallaphotoredox. *J. Am. Chem. Soc.* **2015**, *137*, 11938−11941.
(76) Zhao, C.; Jia, X.; Wang, X.; Gong, H. Ni-catalyzed reductive coupling of alkyl acids with unactivated tertiary alkyl and glycosyl halides. *J. Am. Chem. Soc.* **2014**, *136*, 17645−17651.
(77) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Catalytic asymmetric reductive acyl cross-coupling: symthesis of enantioenriched acyclic *α*,*α*-disubstituted ketones. *J. Am. Chem. Soc.* **2013**, *135*, 7442−7445.
(78) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. Mild ketone formation via Ni-catalyzed coupling of unactivated alkyl halides with acid anhydrides. *Chem. Commun.* **2012**, *48*, 7034−7036.
(79) Wotal, A. C.; Weix, D. J. Synthesis of functionalized dialkyl ketones from carboxylic acid derivatives and alkyl halides. *Org. Lett.* **2012**, *14*, 1476−1479.
(80) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. A convenient method for the direct preparation of ketones from 2-(6-(2-methoxyethyl)-pyridyl) carboxylates and alkyl iodides by use of zinc dust and a catalytic amount of nickel dichloride. *Chem. Lett.* **1981**, *10*, 531−534.
(81) Bentrude, W. G.; Darnall, K. R. A free-radical acylation. *J. Am. Chem. Soc.* **1968**, *90*, 3588−3589.
(82) Kishi, A.; Kato, S.; Sakaguchi, S.; Ishii, Y. Catalytic radical acylation of adamantanes with biacetyl by a cobalt salt under atmospheric dioxygen. *Chem. Commun.* **1999**, 1421−1422.
(83) Kim, S.; Cho, C. H.; Lim, C. J. *β*-Elimination of a phosphonate group from an alkoxy radical: an intramolecular acylation approach using an acylphosphonate as a carbonyl group acceptor. *J. Am. Chem. Soc.* **2003**, *125*, 9574−9575.
(84) Cho, C. H.; Kim, S.; Yamane, M.; Miyauchi, H.; Narasaka, K. Radical cyclization of alkenyl acylphosphonate derivatives under thermal and photochemical condition. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1665−1672.
(85) Goh, K. K. K.; Kim, S.; Zard, S. Z. Free-radical variant for the synthesis of functionalized 1,5-diketones. *Org. Lett.* **2013**, *15*, 4818−4821.
(86) Curran, D. P.; Diederichsen, U.; Palovich, M. Radical cyclization of acylgermanes. New reagent equivalents of the carbonyl radical acceptor synthon. *J. Am. Chem. Soc.* **1997**, *119*, 4797−4804.
(87) Kim, S.; Jon, S. Y. Radical cyclization of thio- and seleno-esters - an intramolecular acylation approach. *Chem. Commun.* **1996**, 1335−1336.
(88) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. Novel radical reaction of phenylsulfonyl oxime ethers. A free radical acylation approach. *J. Am. Chem. Soc.* **1996**, *118*, 5138−5139.

https://doi.org/10.1021/jacs.1c02629
J. Am. Chem. Soc. 2021, 143, 4955−4961

(89) Kim, S. Free radical-mediated acylation and carboxylation reactions. *Adv. Synth. Catal.* **2004**, *346*, 19−32.
(90) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts: a novel family of electrophilic fluorinating agents. *J. Chem. Soc., Chem. Commun.* **1992**, 595−596.
(91) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. Selectfluor: mechanistic insight and applications. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212.
(92) Fang, Y.; Zhang, L.; Li, J.; Jin, X.; Yuan, M.; Li, R.; Wu, R.; Fang, J. Applications of α-phosphonovinyl tosylates in the synthesis of α-arylethenylphosphonates via Suzuki-Miyaura cross-coupling reactions. *Org. Lett.* **2015**, *17*, 798−801.
(93) Zhang, J.-Q.; Han, L.-B. Chlorosilane-catalyzed coupling of hydrogen phosphine oxides with acyl chlorides generating acylphosphine oxides. *Org. Lett.* **2020**, *22*, 4633−4637.
(94) Saussine, L.; Brazi, E.; Robine, A.; Mimoun, H.; Fischer, J.; Weiss, R. Cobalt(III) alkylperoxy complexes. Synthesis, X-ray structure, and role in the catalytic decomposition of alkyl hydroperoxides and in the hydroxylation of hydrocarbons. *J. Am. Chem. Soc.* **1985**, *107*, 3534−3540.
(95) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. Co(III)-alkyl complex- and Co(III)-alkylperoxo complex-catalyzed triethylsilylperoxidation of alkenes with molecular oxygen and triethylsilane. *Org. Lett.* **2002**, *4*, 3595−3598.

https://doi.org/10.1021/jacs.1c02629
J. Am. Chem. Soc. 2021, 143, 4955−4961