OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

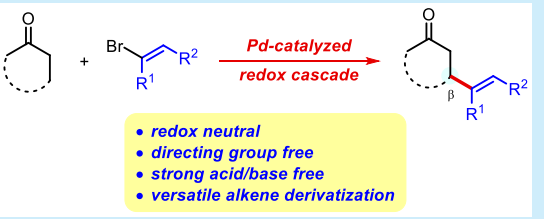
Direct β-Alkenylation of Ketones via Pd-Catalyzed Redox Cascade

Chengpeng Wang, Alexander J. Rago, and Guangbin Dong*

Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

Supporting Information

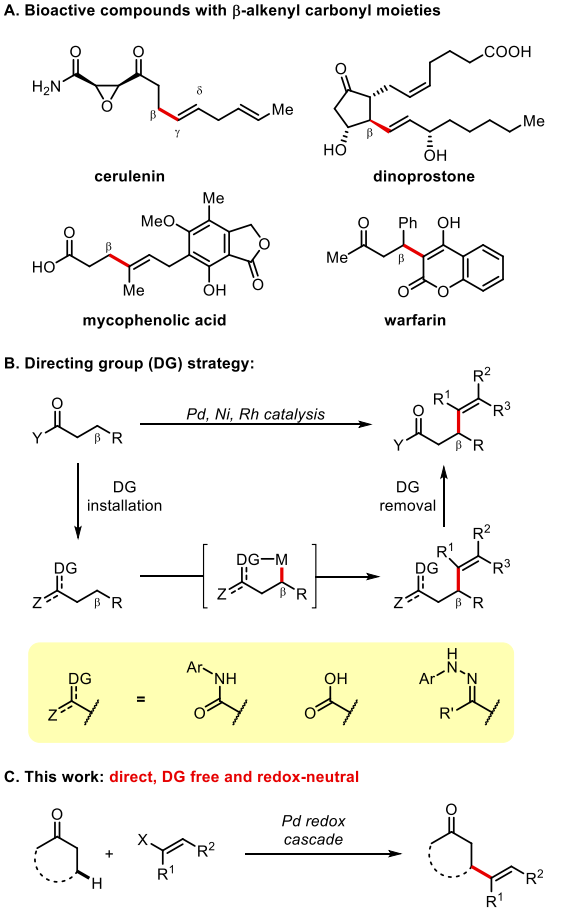
ABSTRACT: A direct β-alkenylation of simple ketones with alkenyl bromides is reported via a Pd-catalyzed redox cascade strategy. The reaction is redox neutral and directing-group-free, in the absence of strong acids or bases. Both cyclic and linear ketones are suitable substrates, and various alkenyl bromides can be coupled. The resulting β-alkenyl ketones are readily derivatized through diverse alkene functionalization.



Preparation and derivatization of carbonyl compounds are cornerstones in organic synthesis.[1] While classical methods mainly focus on functionalizing the electrophilic carbonyl carbon and the acidic α-C−H bond, direct C−C bond forming reactions at the more inert β-positions have been substantially developed over the past decade.[2] Among these transformations, β-alkenylation of carbonyl compounds is of particular interest,[3−7] not only because γ,δ-unsaturated carbonyl structures are commonly found in pharmaceuticals and natural products (Scheme 1A) but also due to the fact that olefin moieties can serve as a versatile precursor to access various other functional groups.[8] In the past decade, the directing group (DG)-based strategy has emerged as a powerful approach to achieve the direct β-alkenylation of carbonyl compounds (Scheme 1B). Amides and carboxylic acids have been extensively used as DGs in the Pd-catalyzed C−H alkenylation,[3,4] in which both vinyl halides and Michael acceptors can serve as the alkenylation reagents. In addition, the Ni-catalyzed alkenylation using alkynes as the coupling partner has also been demonstrated.[5] In contrast, the direct β-alkenylation of simple ketones remains challenging. We recently reported that through a hydrazone intermediate a Rh-catalyzed β-alkenylation of ketones with alkynes could be realized.[6] Newhouse and co-workers disclosed an efficient one-pot β-alkenylation strategy through a Pd-catalyzed ketone dehydrogenation with allyl oxidants followed by subsequent conjugate addition with organocuprates.[7] To the best of our knowledge, a direct, DG-free, and redox-neutral β-alkenylation of ketones has not been reported yet. Herein, we describe our development of such a transformation through direct coupling between simple ketones and vinyl bromides via Pd-catalyzed redox cascade (Scheme 1C).

Our laboratory has been engaged in systematic development of a Pd-catalyzed redox-cascade strategy for direct β-functionalization of carbonyl compounds.[9] As described in the proposed catalytic cycle (Scheme 2), the approach starts with a Pd(II)-mediated carbonyl desaturation to deliver an α,β-unsaturated carbonyl intermediate.[10] The generated Pd(0) then undergoes oxidative addition with an organohalide to form an organopalladium(II) species, which subsequently constructs the β-C−C bond through conjugate addition. Finally, protonation of the resulting Pd(II) enolate provides the product and regenerates the Pd(II) catalyst.[11] The

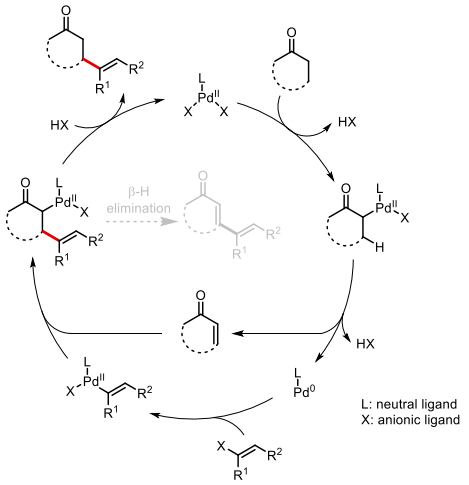
Scheme 1. β-Alkenylation of Carbonyl Compounds



Received: March 29, 2019

DOI: 10.1021/acs.orglett.9b01116
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Proposed Strategy

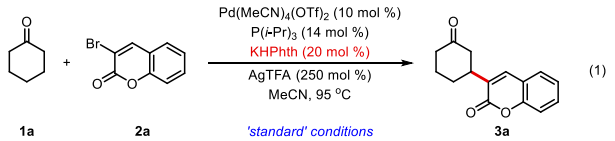


organohalide serves as both the oxidant for the carbonyl desaturation and the carbon source for the β-C−C forming event. Distinct from the DG strategy, the Pd redox cascade avoids additional operations for DG installation and removal and enables the functionalization at the β-positions of cyclic ketones that are hard to reach through the DG approach.

However, extension of the electrophile scope to vinyl halides in the Pd-catalyzed redox cascade would introduce two new challenges: (1) compared to aryl halides, alkenyl halides are generally less stable, e.g. to a base or a strong oxidant; and (2) the alkenyl moiety could possibly undergo further Pd-catalyzed reactions under the reaction conditions. Thus, the key would be to balance the reaction rates among ketone desaturation, alkenyl conjugate addition, and protonation of the alkenylated Pd(II) enolate. In addition, we anticipated that a weakly acidic environment could be crucial for both minimizing the alkenyl halide decomposition and promoting the final protonation step.

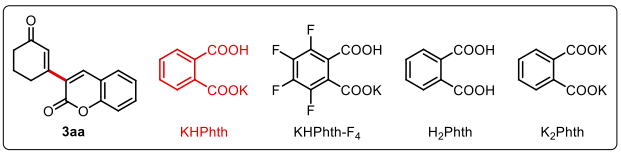
To explore this proposal, cyclohexanone (**1a**) and 3-bromocoumarin (**2a**) were chosen as the model substrates. After systematic optimization of the reaction conditions, the desired β-alkenylation product (**3a**) was ultimately obtained in 73% yield (Table 1, entry 1) using $Pd(MeCN)_4(OTf)_2$/P(*i*-Pr)$_3$ as the metal/ligand combination. The alkenylation exhibited complete β-selectivity. The overoxidation side product (**3aa**), generated from the undesired β-H elimination of the alkenylated Pd(II) enolate (instead of protonation), was only formed in 5% yield. Other side reactions of **2a**, i.e. reductive debromination and dimerization, were observed in 2% and 4% yields, respectively. In order to understand the role of each component in the reaction, a series of control experiments were conducted (Table 1). No reaction occurred in the absence of the Pd precatalyst (entry 2). $Pd(TFA)_2$ was also a viable precatalyst though the yield was inferior compared to the case of cationic $Pd(MeCN)_4(OTf)_2$ (entry 3). The P(*i*-Pr)$_3$ ligand was indispensable for this transformation (entry 4). A 1.4:1 P(*i*-Pr)$_3$ to Pd ratio was found to be optimal: the 2:1 ratio gave a lower conversion, while the 1:1 ratio gave more overoxidation products (entries 5 and 6). Replacing P(*i*-Pr)$_3$ with PPh_3 gave a worse catalytic performance and more overoxidation (entry 7). Using DMSO as the ligand almost shut down the reaction (entry 8). Interestingly, potassium hydrogen phthalate (KHPhth) was found to be an effective additive to promote the reaction conversion (entry 9). While a

Table 1. Selected Optimization of Reaction Conditions[a]



1a **2a** *'standard' conditions* **3a**

entry	variations from the 'standard' conditions	yield of **3a** (%)[b]	yield of **3aa** (%)[b]	unreacted **2a** (%)[b]
1	none	73	5	11
2	without $Pd(MeCN)_4(OTf)_2$	0	0	99
3	$Pd(TFA)_2$ instead of $Pd(MeCN)_4(OTf)_2$	58	4	30
4	without P(*i*-Pr)$_3$	1	2	96
5	P(*i*-Pr)$_3$ 20 mol % instead of 14 mol %	67	3	23
6	P(*i*-Pr)$_3$ 10 mol % instead of 14 mol %	72	7	6
7	PPh_3 instead of P(*i*-Pr)$_3$	23	13	44
8	DMSO instead of P(*i*-Pr)$_3$	2	4	92
9	without KHPhth	58	3	32
10	PhCOOH + PhCOOK instead of KHPhth	72	5	15
11	KHPhth-F_4 instead of KHPhth	58	6	23
12	H_2Phth instead of KHPhth	69	5	13
13	K_2Phth instead of KHPhth	67	8	12
14	CsTFA instead of AgTFA	1	0	85
15	$Cu(TFA)_2$ instead of AgTFA	16	2	48
16	**1a** 150 mol % instead of 250 mol %	58	6	25



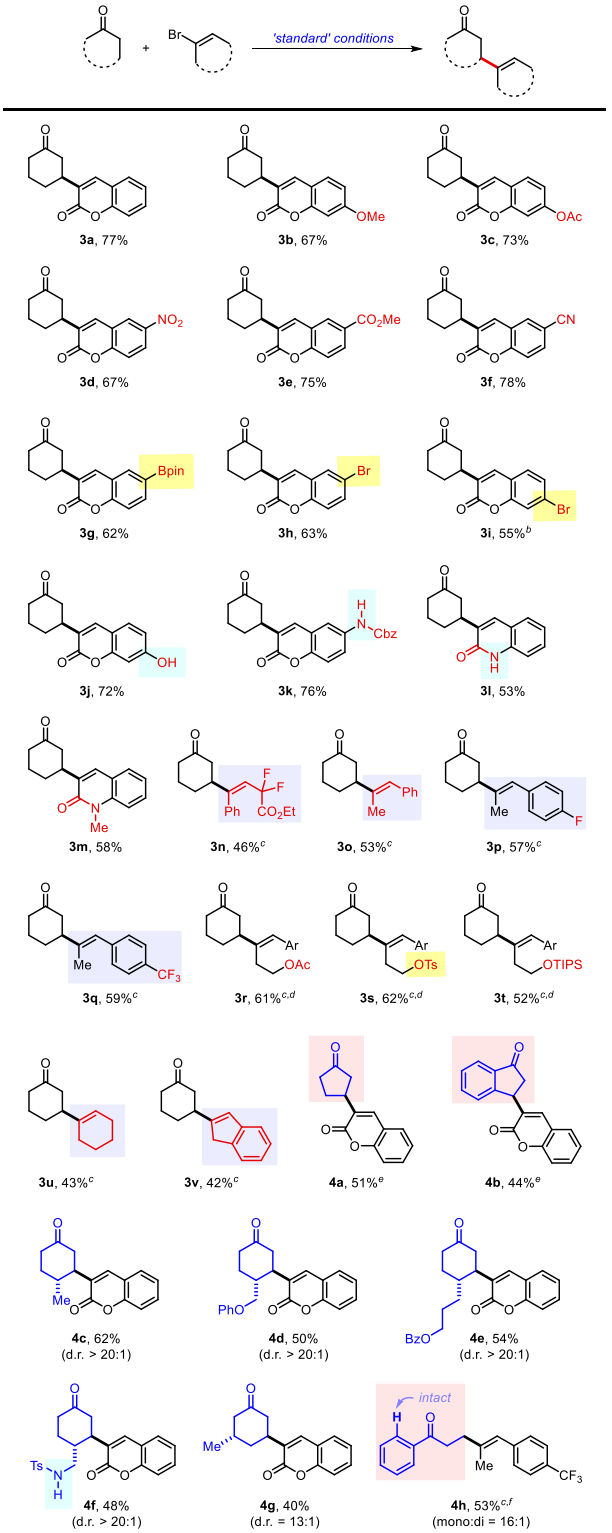
[a]Unless otherwise noted, all the reactions were run with **1a** (0.25 mmol) and **2a** (0.1 mmol) in 0.4 mL of MeCN for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard.

combination of benzoic acid and potassium benzoate gave a comparable result to KHPhth, more acidic potassium hydrogen tetrafluorophthalate (KHPhth-F_4) or phthalic acid (H_2Phth) led to diminished yields (entries 10−12) and the more basic potassium phthalate (K_2Phth) caused slightly more over-oxidation (entry 13). While the exact role of KHPhth is unclear at this stage, we postulated that the carboxylate moiety in this additive can serve as an X ligand to promote ketone desaturation,[12] and such a buffered system may also facilitate the protonation of the Pd(II) enolate. MeCN was the optimal solvent, as it could help stabilize the Pd catalyst and dissolve the inorganic salts. CsTFA and $Cu(TFA)_2$ were not as effective as AgTFA (entries 14 and 15). Finally, decreasing the amount of ketone **1a** to 1.5 equiv still afforded the desired product in 58% yield (entry 16).

The substrate scope of the alkenyl bromides was first investigated (Scheme 3).[13] Considering that coumarin moieties are often found in biologically important compounds,[14] a number of substituted 3-bromocoumarins were first tested and found to proceed smoothly in good yields (**3a**−**3k**). 2-Quinolone-derived alkenyl bromides were also viable substrates (**3l**, **3m**). In addition, a range of linear and cyclic alkenyl bromides *without* conjugated carbonyls can be used for this transformation under slightly modified conditions (**3n**−**3v**). While the yields were moderate due to lower conversions of these substrates, it nevertheless showed that the alkenyl bromide scope could be generalized.[15] Moreover, a large variety of functional groups were tolerated, including methoxy (**3b**), acetoxy (**3c**), nitro (**3d**), methoxycarbonyl (**3e**), cyano (**3f**), fluoro (**3p**), and trifluoromethyl (**3q**) groups, as well as acetyl (**3r**), benzoyl (**4e**), and silyl-protected alcohols (**3t**). The tolerance of acidic hydrogens, such as free phenols (**3j**), carbamates (**3k**), lactams (**3l**), and sulfonamides (**4f**), makes

DOI: 10.1021/acs.orglett.9b01116
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope[a]



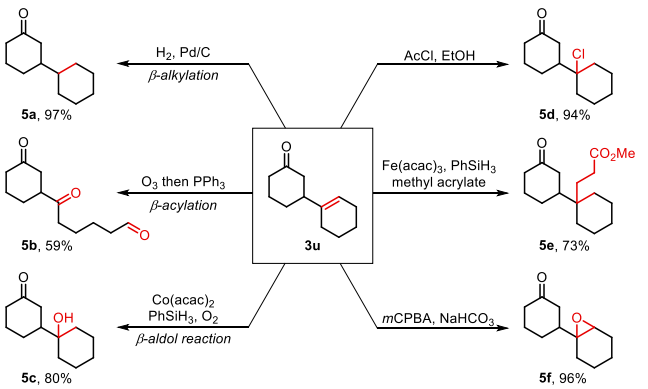
[a]Unless otherwise noted, all the reactions were run with 0.5 mmol of ketone and 0.2 mmol of alkenyl bromide in 0.8 mL of MeCN at 95 °C for 18 h. [b]The β-arylation side product was obtained in 11% yield. [c]The reactions were run in 1,4-dioxane at 90 °C. [d]Ar = p-$CF_3C_6H_4$. [e]15 mol % $Pd(MeCN)_4(OTf)_2$ and 21 mol % P(i-Pr)$_3$ were used. [f]5 equiv of ketone and 20 mol % P(i-Pr)$_3$ were used; the overoxidation product was converted to **4h** via reduction with $HSiCl_3$/HMPA.

this method complementary to the conventional 1,4-addition approach, which often uses alkenyl organometallic species. Encouragingly, aryl boronic esters (**3g**), aryl bromides (**3h**, **3i**), and alkyl tosylates (**3s**), which are typically reactive functional groups in the Pd-catalyzed reactions, largely remained intact. This allows for further transformations of these functional groups, which would increase molecular complexity.

Regarding the ketone scope, besides cyclohexanone, cyclopentanones and 1-indanones (**4a** and **4b**) could be successfully alkenylated at their β positions. Cyclohexanones with substitutions at the C4-position exhibited satisfactory reactivity, and the products obtained (**4c**–**4f**) were single diastereomers, tentatively assigned as the *trans* configuration based on our prior study.[9a] Moreover, 3-methylcyclohexanone also predominantly delivered the *trans*-alkenylation product in a moderate yield (**4g**). Linear ketones, e.g. propiophenone, were competent substrates, though more overoxidation occurred due to a faster β-H elimination pathway. However, a selective 1,4-reduction can be employed subsequently to obtain the pure β-alkenylation product (**4h**).[16] It is noteworthy that, distinct from the DG approach,[17] the *ortho* C(sp^2)–H bond on the phenyl ring was untouched during the reaction.

Finally, derivatizations of the β-alkenylation product are illustrated using **3u** as the representative substrate (Scheme 4).

Scheme 4. Derivatization of the Alkenylation Product



Since alkenes are highly versatile functional groups that can readily undergo diverse transformations,[8] this direct β-alkenylation method opens the door to access various other β-functionalized products. For example, formal β-alkylation, acylation, and aldol products can be afforded through hydrogenation, ozonolysis, and Mukaiyama hydration[18] of the alkene moiety, respectively (**5a**–**5c**). In addition, an electrophilic hydrochlorination (**5d**)[19] and an iron-mediated quaternary carbon-center formation (**5e**)[20] were successfully demonstrated in high efficiency. Moreover, difunctionalization of the alkene was also possible through epoxidation (**5f**).

In summary, a direct method for β-alkenylation of simple ketones has been developed using the Pd-catalyzed redox cascade strategy. Different from the existing β-alkenylation methods, this approach avoids the use of DGs, tolerates both cyclic and acyclic ketones, and is redox neutral. The high functional group compatibility could make this method attractive for preparing complex molecules. Efforts on further enhancing the reaction efficiency and developing enantioselective reactions are ongoing.

DOI: 10.1021/acs.orglett.9b01116
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01116.

Experimental procedures; spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gbdong@uchicago.edu.

ORCID

Chengpeng Wang: 0000-0002-9196-2613
Guangbin Dong: 0000-0003-1331-6015

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank University of Chicago for the research support. Dr. Xiaoyang Chen from the University of Chicago is thanked for checking the experiments.

■ REFERENCES

(1) *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.

(2) For recent reviews, see: (a) Huang, Z.; Dong, G. Catalytic C−C Bond Forming Transformations via Direct β-C−H Functionalization of Carbonyl Compounds. *Tetrahedron Lett.* **2014**, *55*, 5869−5889. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition Metal-Catalyzed Ketone-Directed or Mediated C−H Functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786.

(3) For selected examples of amide-directed β-C−H alkenylation reactions, see: (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. Pd(II)-Catalyzed Olefination of sp^3 C−H Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 3680−3681. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C−H Activation of Cyclopropanes. *J. Am. Chem. Soc.* **2011**, *133*, 19598−19601. (c) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. Sequential $C_{sp}3$−H Arylation and Olefination: Total Synthesis of the Proposed Structure of Pipercyclobutanamide A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507−7510. (d) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. Ligand-Controlled C(sp^3)−H Arylation and Olefination in Synthesis of Unnatural Chiral α-Amino Acids. *Science* **2014**, *343*, 1216−1220. (e) Wang, B.; Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. Palladium-Catalyzed Stereoretentive Olefination of Unactivated C(sp3)−H Bonds with Vinyl Iodides at Room Temperature: Synthesis of β-Vinyl α-Amino Acids. *Org. Lett.* **2014**, *16*, 6260−6263. (f) Shan, G.; Huang, G.; Rao, Y. Palladium-Catalyzed Unactivated β-Methylene C(sp^3)−H Bond Alkenylation of Aliphatic Amides and Its Application in a Sequential C(sp^3)−H/C(sp^2)−H Bond Alkenylation. *Org. Biomol. Chem.* **2015**, *13*, 697−701. (g) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. Enantioselective Total Synthesis of (+)-Psiguadial B. *J. Am. Chem. Soc.* **2016**, *138*, 9803−9806. (h) Wu, Q.-F.; Wang, X.-B.; Shen, P.-X.; Yu, J.-Q. Enantioselective C−H Arylation and Vinylation of Cyclobutyl Carboxylic Amides. *ACS Catal.* **2018**, *8*, 2577−2581.

(4) For selected examples of β-C−H alkenylation of carboxylic acids, see: (a) Zhuang, Z.; Yu, C.-B.; Chen, G.; Wu, Q.-F.; Hsiao, Y.; Joe, C. L.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. Ligand-Enabled β-C(sp^3)−H Olefination of Free Carboxylic Acids. *J. Am. Chem. Soc.* **2018**, *140*, 10363−10367. (b) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective C(sp^3)−H Activation/Cross-Coupling Reactions of Free Carboxylic Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 2134−2138.

(5) For selected examples of Ni-catalyzed β-C−H alkenylation of amides with alkynes, see: (a) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. Nickel-Catalyzed Addition-Type Alkenylation of Unactivated, Aliphatic C−H Bonds with Alkynes: A Concise Route to Polysubstituted γ-Butyrolactones. *Org. Lett.* **2015**, *17*, 2546−2549. (b) Maity, S.; Agasti, S.; Earsad, A. M.; Hazra, A.; Maiti, D. Nickel-Catalyzed Insertion of Alkynes and Electron-Deficient Olefins into Unactivated sp^3 C−H Bonds. *Chem. - Eur. J.* **2015**, *21*, 11320−11324. (c) Lin, C.; Chen, Z.; Liu, Z.; Zhang, Y. Nickel-Catalyzed Stereoselective Alkenylation of C(sp^3)−H Bonds with Terminal Alkynes. *Org. Lett.* **2017**, *19*, 850−853.

(6) Xu, Y.; Young, M. C.; Dong, G. Catalytic Coupling between Unactivated Aliphatic C−H Bonds and Alkynes via a Metal−Hydride Pathway. *J. Am. Chem. Soc.* **2017**, *139*, 5716−5719.

(7) Chen, Y.; Huang, D.; Zhao, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed Ketone Dehydrogenation Enables Telescoping with Enone α,β-Vicinal Difunctionalization. *Angew. Chem., Int. Ed.* **2017**, *56*, 8258−8262.

(8) For selected reviews on alkene functionalization, see: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981−3019. (c) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912−9000.

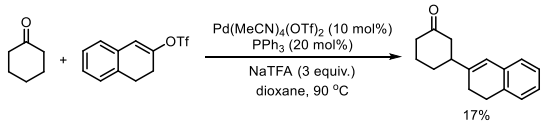
(9) (a) Huang, Z.; Dong, G. Catalytic Direct β-Arylation of Simple Ketones with Aryl Iodides. *J. Am. Chem. Soc.* **2013**, *135*, 17747−17750. (b) Huang, Z.; Sam, Q. P.; Dong, G. Palladium-Catalyzed Direct β-Arylation of Ketones with Diaryliodonium Salts: a Stoichiometric Heavy Metal-Free and User-Friendly Approach. *Chem. Sci.* **2015**, *6*, 5491−5498. (c) Chen, M.; Liu, F.; Dong, G. Direct Palladium-Catalyzed β-Arylation of Lactams. *Angew. Chem., Int. Ed.* **2018**, *57*, 3815−3819. (d) Huang, Z.; Dong, G. Palladium-Catalyzed Redox Cascade for Direct β-Arylation of Ketones. *Tetrahedron* **2018**, *74*, 3253−3265. (e) Wang, C.; Dong, G. Direct β-Alkylation of Ketones and Aldehydes via Pd-Catalyzed Redox Cascade. *J. Am. Chem. Soc.* **2018**, *140*, 6057−6061.

(10) For recent examples of Pd-catalyzed direct dehydrogenation of ketones, see: (a) Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566−14569. (b) Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. General Palladium-Catalyzed Aerobic Dehydrogenation to Generate Double Bonds. *Chem. Sci.* **2012**, *3*, 883−886. (c) Diao, T.; Wadzinski, T. J.; Stahl, S. S. Direct Aerobic α,β-Dehydrogenation of Aldehydes and Ketones with a $Pd(TFA)_2$/4,5-Diazafluorenone Catalyst. *Chem. Sci.* **2012**, *3*, 887−891. (d) Diao, T.; Pun, D.; Stahl, S. S. Aerobic Dehydrogenation of Cyclohexanone to Cyclohexenone Catalyzed by $Pd(DMSO)_2(TFA)_2$: Evidence for Ligand-Controlled Chemoselectivity. *J. Am. Chem. Soc.* **2013**, *135*, 8205−8212.

(11) O'Duill, M. L.; Engle, K. M. Protodepalladation as a Strategic Elementary Step in Catalysis. *Synthesis* **2018**, *50*, 4699−4714.

(12) The basic carboxylate ligand could be helpful to promote the Pd(II) enolate formation by accelerating α-C−H cleavage. For a related mechanistic study, see ref 10d.

(13) Alkenyl triflates could also be coupled, but they were found to be less stable, thereby giving a poor mass balance. The following alkenyl triflate delivered the β-alkenylation product in 17% yield in the absence of any silver salt.



DOI: 10.1021/acs.orglett.9b01116
Org. Lett. XXXX, XXX, XXX−XXX

(14) Venugopala, K. N.; Rashmi, V.; Odhav, B. Review on Natural Coumarin Lead Compounds for Their Pharmacological Activity. *BioMed Res. Int.* **2013**, *2013*, 963248.
(15) Less substituted alkenyl bromides, such as β-bromostyrene, also worked for this transformation albeit in a lower yield (21%); dimerization of the alkenyl group became the major competing pathway.
(16) Sugiura, M.; Sato, N.; Kotani, S.; Nakajima, M. Lewis Base-Catalyzed Conjugate Reduction and Reductive Aldol Reaction of α,β-Unsaturated Ketones Using Trichlorosilane. *Chem. Commun.* **2008**, 4309−4311.
(17) For an example of ketone-directed Pd-catalyzed C(sp^2)−H activation with aryl iodides, see: Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. Synthesis of Phenanthrone Derivatives from *sec*-Alkyl Aryl Ketones and Aryl Halides via a Palladium-Catalyzed Dual C−H Bond Activation and Enolate Cyclization. *J. Am. Chem. Soc.* **2010**, *132*, 8569−8571.
(18) Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 1071−1074.
(19) Yadav, V. K.; Babu, K. G. A Remarkably Efficient Markovnikov Hydrochlorination of Olefins and Transformation of Nitriles into Imidates by Use of AcCl and an Alcohol. *Eur. J. Org. Chem.* **2005**, *2005*, 452−456.
(20) Lo, J. C.; Yabe, Y.; Baran, P. S. A Practical and Catalytic Reductive Olefin Coupling. *J. Am. Chem. Soc.* **2014**, *136*, 1304−1307.

DOI: 10.1021/acs.orglett.9b01116
Org. Lett. XXXX, XXX, XXX−XXX