JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Intramolecular β-Alkenylation of Cyclohexanones via Pd-Catalyzed Desaturation-Mediated $C(sp^3)-H$/Alkyne Coupling

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Cite This: *J. Am. Chem. Soc.* 2020, 142, 8962–8971
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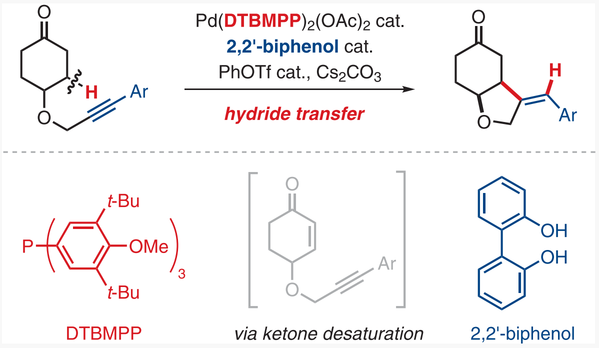
ABSTRACT: Site-selective C−C bond formation through the direct coupling of $C(sp^3)-H$ bonds with unsaturated hydrocarbons represents an atom-economical and redox-neutral way to functionalize chemically inert positions, such as those β to a carbonyl group. While most existing β-functionalization methods utilize a directing group (DG) strategy, here we report a Pd-catalyzed intramolecular β-alkenylation of ketones using alkynes as the coupling partner without the aid of DGs. Mediated by a ketone desaturation process, the reaction is redox-neutral and avoids using strong acids or bases. The resulting *cis*-5,6-fused bicycles can be diversely derivatized with excellent selectivity. Mechanistic studies imply an unusual "hydride-transfer" chain-like pathway, which involves the cyclometalation of an enyne intermediate and protonation of the resulting Pd enolate followed by an intermolecular hydride transfer through the desaturation of another substrate.



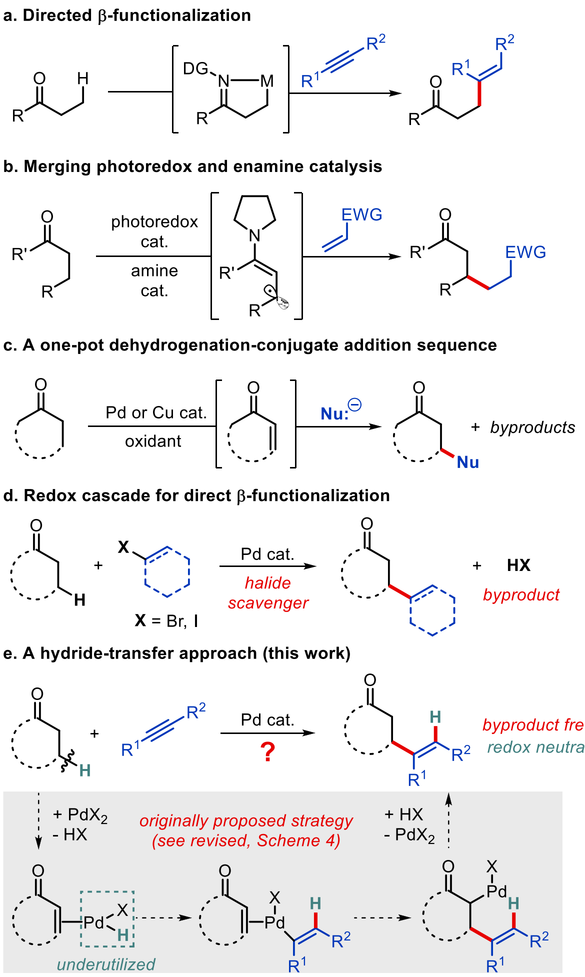
INTRODUCTION

Transformations and derivatizations of carbonyl compounds represent a cornerstone in organic synthesis.[1] While ipso and α-functionalization of carbonyl compounds capitalizing on the electrophilic C═O moiety and acidic α protons have been well studied over the past century, modern strategies that enable direct functionalization at the much less reactive β-position have emerged recently.[2] The majority of β-functionalization approaches utilize a directing group (DG) to enable reactivity and site-selectivity via a proximity effect (Scheme 1a).[3,4] While effective and versatile, the DG strategy is generally not suitable for cyclic carbonyl compounds. Alternatively, MacMillan and co-workers pioneered a unique photoredox-enamine catalysis strategy via generating β-radicals of ketones and aldehydes, which are then trapped by good radical acceptors, such as cyanoarenes, acrylates, arylketones, and imines (Scheme 1b).[5] In addition, a one-pot desaturation-conjugate addition sequence represents a practical and efficient means for β-functionalization, which involves the oxidation of saturated ketones to conjugated enones followed by the addition of a nucleophile (Scheme 1c).[6] As a complementary approach, our laboratory has been engaged in systematic development of a Pd-catalyzed redox-cascade strategy to realize the β-arylation,[7] alkylation,[8] and alkenylation[9] of ketones, in which organohalides have been employed as both oxidants and sources of the β-functional group. For example, we recently reported a direct β-alkenylation reaction using alkenyl bromides as the coupling partner (Scheme 1d).[9] While it is attractive to use readily available organohalides (RXs) as the functionalization reagents, the resulting HX byproducts are deleterious to the Pd-catalyzed ketone desaturation step; therefore, stoichiometric halide scavengers, such as silver salts, were required in these reactions.[7a,9] On the other hand, many alkyl and alkenyl halides are ultimately prepared from unsaturated hydrocarbons such as alkenes and alkynes.[10] Thus, it would be strategically appealing if unsaturated hydrocarbons could be directly coupled at the β position of ketones without the aid of DGs, which would be both atom-economical[11] and redox-neutral.[12,13] Herein, we describe our initial efforts toward the development of a hydride-transfer strategy for realizing the intramolecular β-alkenylation of ketones with alkynes (Scheme 1e).

While the Pd-catalyzed ketone desaturation has been well studied,[14,15] the "Pd−hydride" species generated via β-hydrogen elimination in this reaction, to the best of our knowledge, has not been utilized to allow for C−C couplings. Hence, our originally proposed strategy was to trap the Pd−hydride species with an unsaturated 2π unit (i.e., alkyne) and then add the resulting alkenyl−Pd species to the conjugated enone intermediate, which could install the β functional group and regenerate the Pd(II) catalyst (Scheme 1e). Such a hydride-transfer strategy is expected to furnish direct β-

Received: March 6, 2020
Published: April 19, 2020

Scheme 1. Catalytic β-Functionalization of Carbonyl Compounds



alkenylation of ketones via a formal C(sp^3)−H/alkyne coupling without DGs.

■ RESULTS AND DISCUSSION

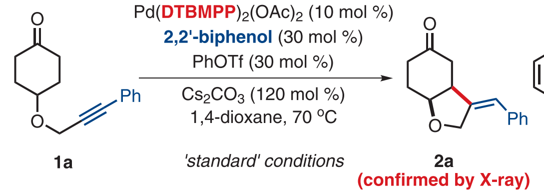
Reaction Discovery and Optimization. To test the feasibility of the proposed strategy, an alkyne-tethered ketone (**1a**) was selected as the model substrate (Table 1). Gratifyingly, using a precoordinated catalyst with Pd(OAc)$_2$ and tris(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (DTBMPP),[16] the overall β-alkenylation products were obtained in 64% yield (Table 1, entry 1). The desired direct C–H-coupling product (**2a**) was formed in 55% yield as a single diastereomer, and its structure was unambiguously determined by the X-ray crystallography of its hydrazone derivative (Supporting Information); the overoxidation products (**2aa** and **2ab**) were observed as minor products. Note that these β-alkenylation products can be unified using a one-pot reduction workup,[17] which eased the isolation of pure **2a**. In addition, alkyne reduction was observed as a side reaction of **1a**, which generated *cis*-alkene **1ar** in 5% yield under the optimized reaction conditions. A series of control experiments were then conducted to understand the role of each component. Both the palladium complex and the ligand were essential (entries 2 and 3). The separate addition of Pd(OAc)$_2$ and DTBMPP instead of the precoordinated complex gave comparable results (entry 4), and cationic Pd complexes such as Pd(MeCN)$_4$(OTf)$_2$ were also suitable catalysts (entry 5). Both the electron richness and bulkiness of the DTBMPP ligand were necessary for the success of this transformation, as similar ligands without methoxy (**L1**) or *tert*-butyl groups (**L2**) led to diminished yields (entries 6 and 7). In addition, triisopropylphosphine, a superior ligand for the previously developed β-functionalization reactions,[7−9] gave only a moderate yield (entry 8). Catalytic phenyl triflate was found to be a crucial additive for improved efficiency, likely serving as an initiator for this reaction (see the following section for a detailed discussion), though the reaction could still proceed without PhOTf (entry 9). A catalytic amount of bromobenzene or the use of chlorobenzene as a solvent also promoted the reaction (entries 10 and 11), though they gave either lower efficiency or selectivity. Interestingly, the reaction was benefited by adding a catalytic amount of 2,2′-biphenol (entry 12). For comparison, the use of simple phenol did not work; however, more acidic carboxylic acid additives were also effective, albeit with lower selectivity (entries 13−15). Though the exact role of 2,2′-biphenol is unclear at this stage, the observed higher reactivity, compared with the use of monophenol might be attributed to its enhanced acidity (pK_a = 8.0)[18] that could promote the protonation of the Pd-enolate intermediate. Finally, Cs$_2$CO$_3$ was found to be indispensable for this transformation, as substrate decomposition and various undesired side reactions (e.g., intramolecular ketone α-allylation)[16] occurred in the absence of Cs$_2$CO$_3$ (entry 16) or with weaker bases.

Mechanistic Studies. The unique transformation discovered here motivated us to gain more insight into the reaction mechanism. On the basis of the *Z*-olefin geometry of **2a** and the catalytic conditions employed, three plausible pathways could be proposed (Scheme 2). All pathways are expected to start with ketone desaturation by a Pd(II) species to deliver enyne intermediate **1ai** and a Pd−hydride (Pd−H) species. **Path a**, as the originally proposed strategy, involves an intramolecular Pd−H addition to the alkyne moiety, followed by conjugate addition to forge the β-C−C bond.[19] Alternatively, the Pd−H species could dissociate from the enyne intermediate and react with the alkyne moiety of another substrate (**path b**). Trost and co-workers demonstrated that X−Pd−H (e.g., X = OAc) could be a transient species, which is in equilibrium with Pd(0) and the acid (HX).[20] Thus, **path b** involves a proton-mediated Pd−H addition mechanism.[21] In addition, one can imagine that the β-C−C bond could be formed via cyclometalation between Pd(0) and the enyne intermediate (**path c**).[22−24] The resulting palladacycle could then undergo protonation at the enolate carbon and hydride transfer to the alkenyl position in the subsequent steps (vide infra).

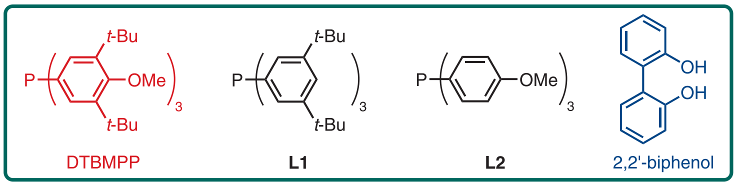
First, the kinetic profiles of the reaction were obtained with and without PhOTf (Figure 1). Under the standard conditions (with PhOTf additive), a 4 h induction period was observed before product **2a** started to form, during which period the fast accumulation of enyne intermediate **1ai** occurred. The product formation was accompanied by the consumption of enyne **1ai** in the next 24 h. Note that the alkyne reduction side product (**1ar**) appeared only after enyne **1ai** was mostly consumed (after 24 h). In contrast, in the absence of PhOTf, only a maximum of 2% enyne accumulation was observed during the induction period, which led to a low overall yield of **2a** and the early formation of alkyne-reduction product **1ar**. Considering the facts that **path a** involves an intramolecular Pd−H addition

https://dx.doi.org/10.1021/jacs.0c02654

Table 1. Selected Optimization of the Reaction Conditions[a]

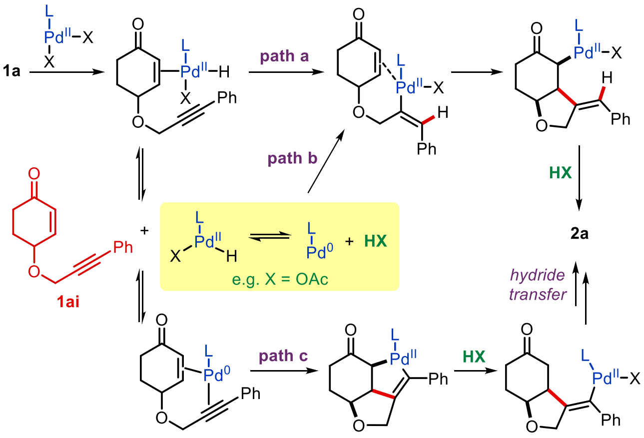


entry	variations from the 'standard' conditions	yield (%)[b] β-alkenylation	yield (%)[b] 2a/2aa/2ab	unreacted 1a (%)[b]
1	none	64 (**63**[c])	55/8/1	23
2	DTBMPP alone, without Pd(OAc)$_2$	n.d.		100
3	Pd(OAc)$_2$ alone, without DTBMPP	n.d.		78
4	Pd(OAc)$_2$ + DTBMPP as the catalyst	61	53/7/1	22
5	Pd(MeCN)$_4$(OTf)$_2$ + DTBMPP as the catalyst	59	51/6/2	26
6	Pd(OAc)$_2$ + **L1** as the catalyst	47	40/5/2	28
7	Pd(OAc)$_2$ + **L2** as the catalyst	21	20/1/0	56
8	Pd(OAc)$_2$ + P(*i*-Pr)$_3$ as the catalyst	45	32/5/8	29
9	without PhOTf	16	16/0/0	71
10	PhBr instead of PhOTf	54	48/5/1	25
11	PhCl instead of 1,4-dioxane, without PhOTf	59	43/8/8	28
12	without 2,2'-biphenol	42	39/3/0	34
13	phenol (60 mol %) instead of 2,2'-biphenol	18	17/1/0	47
14	phthalic acid (30 mol %) instead of 2,2'-biphenol	62	45/10/7	13
15	benzoic acid (60 mol %) instead of 2,2'-biphenol	56	41/9/6	24
16	without Cs$_2$CO$_3$	n.d.		n.d.



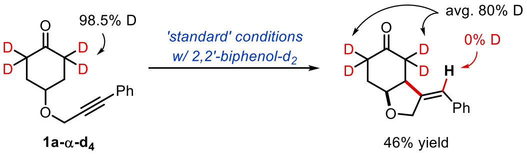
[a]Unless otherwise noted, all of the reactions were run with **1a** (0.1 mmol) in 1.0 mL solvent at 70 °C for 48 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]The yield in parentheses refers to the isolation yield after a one-pot reduction workup under the following conditions: Pd(PPh$_3$)$_4$ (0.002 mmol), ZnCl$_2$ (0.02 mmol), and Ph$_2$SiH$_2$ (0.05 mmol) at room temperature for 12 h. n.d. = not detected.

Scheme 2. Plausible Mechanisms



mechanism and the enyne intermediate was formed almost immediately, the unusually long induction period for **2a** formation is inconsistent with **path a**.

To understand the source of the alkenyl hydrogen in **2a**, a series of deuterium labeling experiments were conducted. Interestingly, the *α*-deuterated ketone substrate with 2,2′-biphenol-*d*$_2$ led to no deuterium incorporation at the alkenyl position (eq 1), while the *β*-deuterated substrate gave nearly complete deuterium transfer to the alkenyl position (eq 2). These results suggest that the alkenyl hydrogen does not arise from proton sources; instead, it should come from the ketone *β* position. In addition, a deuterium crossover experiment shows that the *β*-deuterium is equally distributed to both products (eq 3), which demonstrates that an intermolecular hydrogen-transfer mechanism is involved in the alkenyl C−H bond formation and further excludes **path a**. On the other hand, while the intermolecular Pd−H addition mechanism (**path b**) cannot be fully excluded, it is unlikely to represent the main reaction pathway. This is because when X is an electronegative ligand (e.g. OAc) the X−Pd−D species is known to undergo reversible reductive elimination to give DX that would have fast proton exchange with existing proton sources.[20] Thus, given the presence of various proton sources under the reaction conditions (e.g., 2,2′-biphenol and ketone *α*-protons) the lack of deuterium loss at the alkenyl position is not consistent with an intermolecular X−Pd−H addition mechanism (**path b**).



(1)

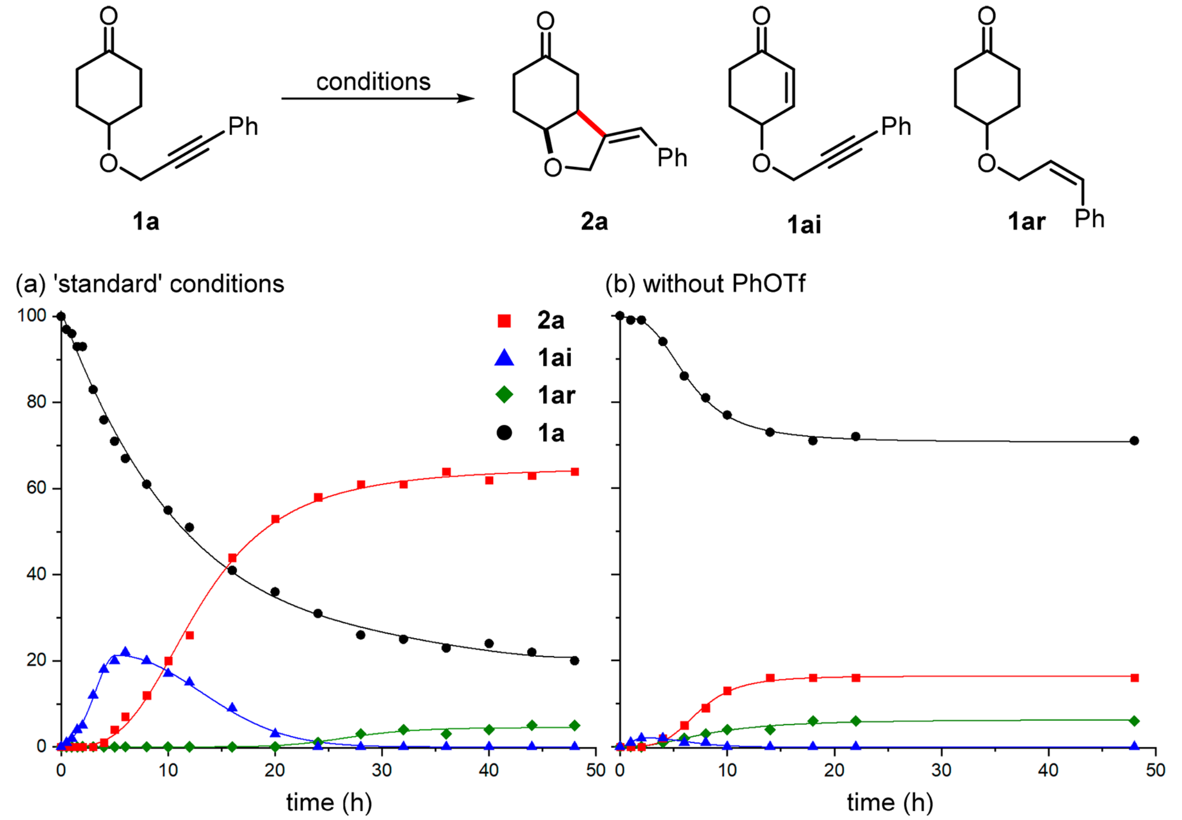
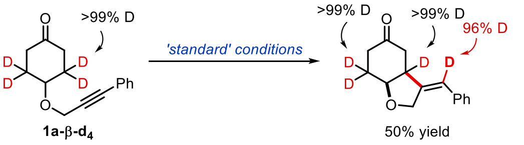
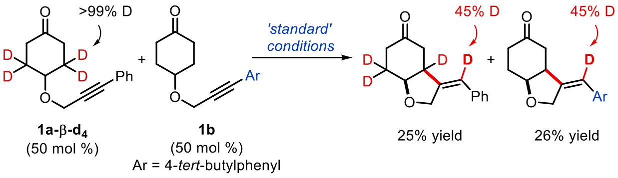


Figure 1. Kinetic profiles for the yields of various products (%) and remaining **1a** (%) over time: (a) under standard conditions and (b) under standard conditions but in the absence of PhOTf. The yield of **2a** refers to all β-alkenylation products.



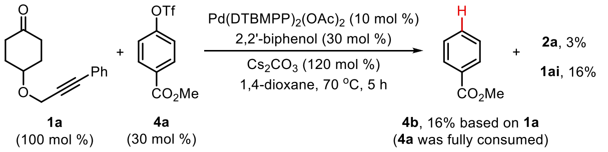
(2)



(3)

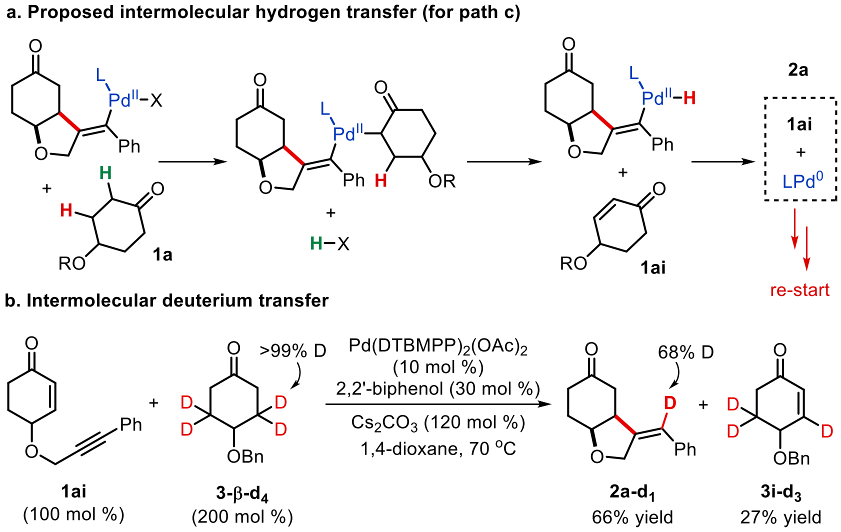
At this stage, the remaining questions are (1) whether **path c** could be a possible reaction pathway, (2) what the role of PhOTf is, and (3) how to explain the formation of the alkyne-reduction side product. To address the first question, one can imagine that, in **path c** after enyne cyclopalladation and protonation of the enolate, the resulting alkenyl Pd species could react with another ketone substrate as illustrated in Scheme 3a. The strong trans effect of the alkenyl group is expected to enhance the basicity of the X ligand on Pd;[25] after deprotonation of the ketone α-hydrogen, a sequence of β-hydrogen elimination and alkenyl C−H reductive elimination should furnish the desired product (**2a**) and reinitiate the catalytic cycle by giving Pd(0) and enyne **1ai** (a chain-like mechanism). This pathway is the most consistent with the deuterium labeling and crossover experiments (eqs 1−3). In addition, a reductive cyclization of enyne **1ai** using β-deuterated ketone **3-β-d$_4$** as the hydrogen source worked smoothly under similar conditions, which supports the intermediacy of the enyne species and an intermolecular hydrogen-transfer mechanism (Scheme 3b). The reduced deuterium incorporation in product **2a-d$_1$** was likely caused by some hydrogen transfer from substrate **1ai**.

To understand the role of PhOTf (see Table 1, entries 9−11 and Figure 1), 4-methoxycarbonylphenyl triflate (**4a**) was used as the additive instead for easy monitoring of the reaction. It was observed that **4a** was fully consumed in the first 5 h of the reaction, which corresponds to the initial enyne accumulation period (eq 4 and Supporting Information). The reduction product, methyl benzoate (**4b**), was detected, and its amount correlates with the amount of enyne **1ai** generated. The source of the hydrogen was further confirmed to be from the β-position of the ketone substrate (eq 5). These results indicate that in the initial stage the aryl triflate serves as the oxidant to initiate the reaction via a similar mechanism shown in Scheme 3a to generate the initial amount of enyne **1ai**. This could explain the existence of the induction period. One can imagine that Pd(0) would prefer to react with PhOTf (an irreversible oxidant) rather than enyne **1ai** during the induction period, which leads to the accumulation of the enyne intermediate. It also implies that (i) Pd(0) exists in the catalytic system and (ii) aryl triflates could be employed as an effective oxidant for ketone desaturation. These observations are consistent with the Pd(0)-initiated catalytic cycle (**path c**).



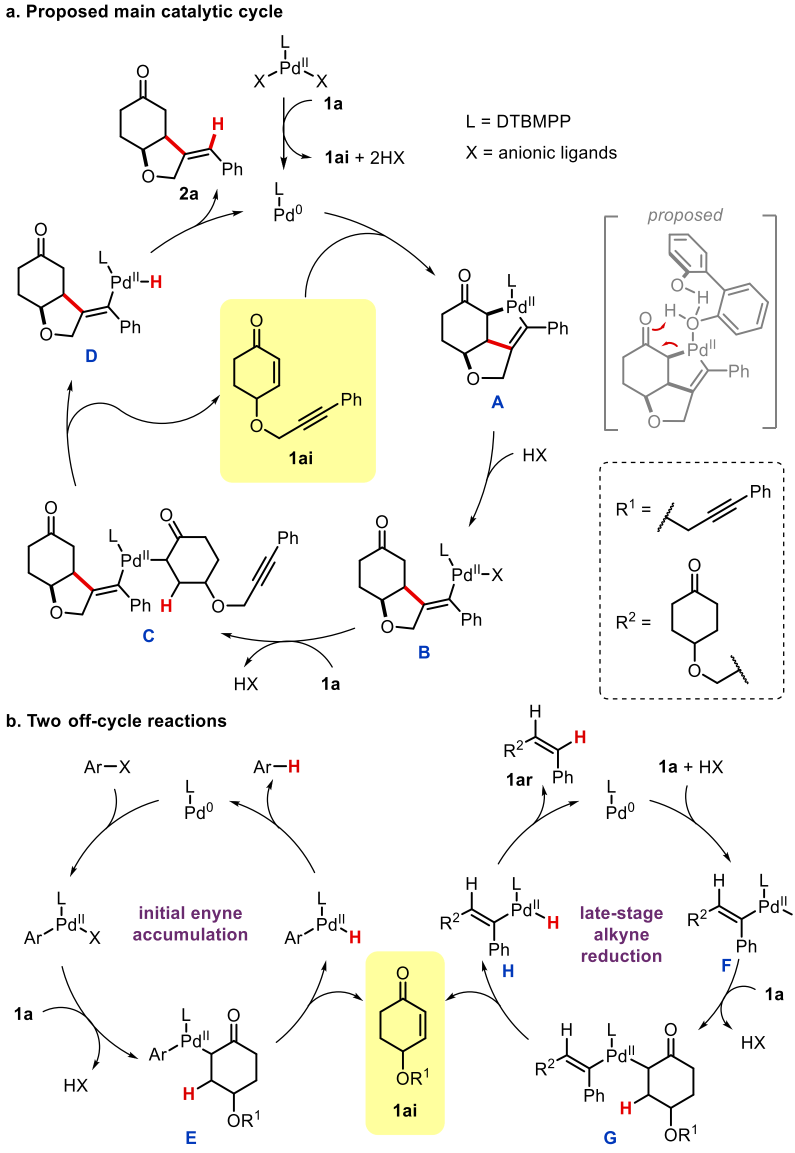
(4)

Scheme 3. Intermolecular Hydrogen Transfer

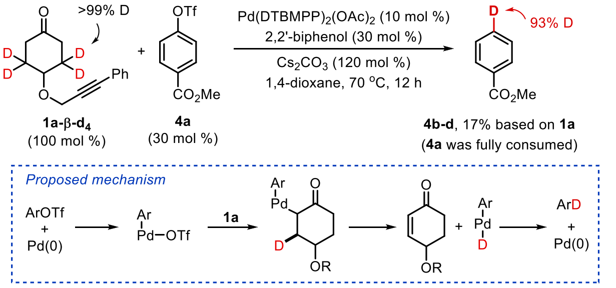

a. Proposed intermolecular hydrogen transfer (for path c)

b. Intermolecular deuterium transfer

Scheme 4. Summary of the Proposed Mechanism


a. Proposed main catalytic cycle

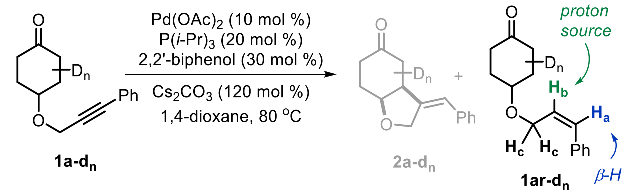
b. Two off-cycle reactions



(5)

Finally, one remaining question is to understand the formation of the alkyne reduction side product (**1ar**). Deuterium track experiments were conducted using a slightly different set of conditions that gave higher yields of **1ar** (Table 2, entry 1). Interestingly, $\mathbf{H_a}$ in the reduction product arose almost only from the β position of ketone (entry 2), while $\mathbf{H_b}$ clearly came from proton sources (entry 3). In addition, no deuterium was incorporated into the allylic position. According to the kinetic studies (Figure 1), **1ar** started to form when the enyne concentration was low, indicating a kinetic competition between enyne cyclometalation and alkyne reduction. Thus, we hypothesized that the alkyne reduction starts with the addition of a Pd−H species (in equilibrium with Pd(0) and a proton)[21] to the alkyne, and the resulting alkenylpalladium species then undergoes a similar β-hydrogen transfer process (as in Scheme 3a) to deliver the *cis*-alkene (vide infra, Scheme 4b). The observed regioselectivity is consistent with this hypothesis, where during the Pd−H addition step Pd stays at the more stable benzylic position.[26]

Table 2. Mechanistic Studies on the Alkyne Reduction



entry	substrate	yield of $\mathbf{2a\text{-}d_n}$ (%)	yield of $\mathbf{1ar\text{-}d_n}$ (%)	D incorporation ratio (%)		
				$\mathbf{H_a}$	$\mathbf{H_b}$	$\mathbf{H_c}$
1	**1a**	23	16	0	0	0
2	**1a-β-d$_4$**	19	10	88	0	0
3[a]	**1a-α-d$_4$**	10	5	0	58	0

[a] 2,2′-Biphenol-d_2 was used instead of 2,2′-biphenol.

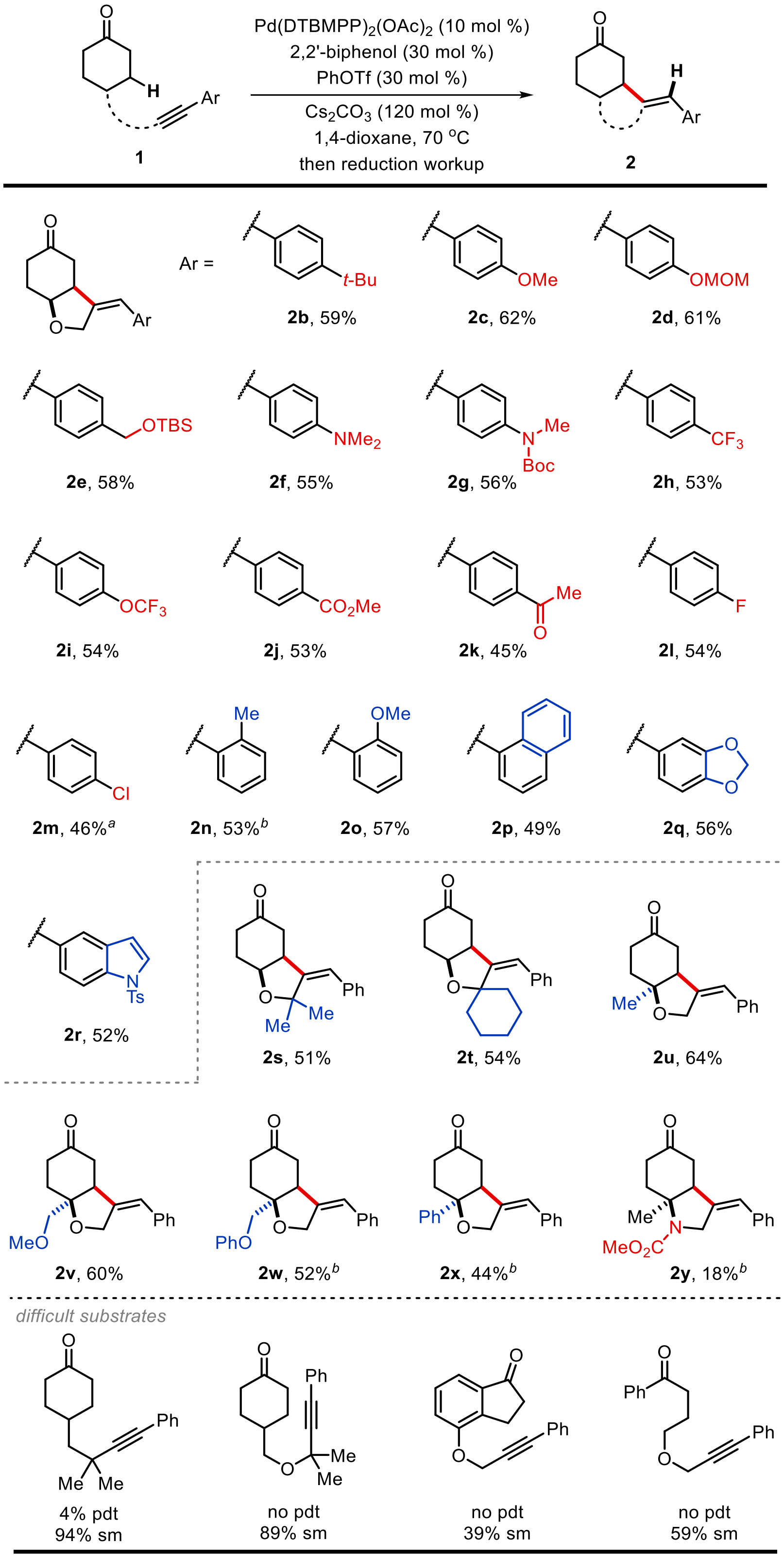
Proposed Catalytic Cycle. While some mechanistic details of this reaction remain unclear and are still topics of ongoing investigation, the data above allow us to propose a hypothesis for the main catalytic cycle (Scheme 4a). The reaction is initiated by the generation of active Pd(0) catalyst and enyne **1ai** via ketone desaturation. Cyclometalation followed by protonation of the enolate ligand gives alkenylpalladium species **B** that can deprotonate another ketone substrate (**1a**). The subsequent β-hydrogen elimination regenerates enyne **1ai** and forms alkenylpalladium hydride species **D**. Finally, C−H reductive elimination gives the β-alkenylation product and regenerates the Pd(0) catalyst that can re-enter the cycle with enyne **1ai** as a chain-like mechanism. The alkenyl hydrogen in **2a** is ultimately transferred from the β-hydrogen of ketone, consistent with the proposed hydride-transfer strategy. In addition, two off-cycle pathways are responsible for the initial enyne accumulation and alkyne reduction (Scheme 4b). During the induction period, Pd(0) would preferably undergo oxidative addition with aryl triflate (ArX) to give an arylpalladium species that effectively desaturates the ketone substrate. Subsequently, the normal catalytic cycle starts to convert enyne **1ai** and substrate **1a** to the β-alkenylation products. While in principle the enyne concentration should maintain constant, side reactions would reduce the enyne concentration during the reaction, such as overdesaturation of product **2a** to give **2aa** and **2ab** or the decomposition of **1ai** to phenol via elimination. When the enyne concentration becomes very low, the alkyne reduction pathway would be triggered due to the equilibrium between Pd(0)/HX and X−Pd−H. This involves the addition of Pd−H to the alkyne moiety, and resulting alkenylpalladium intermediate **F** can participate in another desaturation process. In this case, the alkyne moiety serves as a hydrogen acceptor or an oxidant, leading to more enyne (and eventually product **2a**) formation in the late stage (before the death of the catalyst). The role of 2,2′-biphenol is possibly to promote protonation from **A** to **B**. The role of the base (Cs_2CO_3) could be to neutralize HOTf generated in the reaction and to balance the reaction acidity.

Substrate Scope. The substrate scope of this transformation was then examined (Scheme 5). Substrates bearing either electron-rich (**2b**−**2g**) or electron-deficient (**2h**−**2m**) arenes are suitable for this reaction. Attributed to the relatively mild reaction conditions, a wide range of functional groups were tolerated, including methyl ether (**2c**), MOM (**2d**), TBS ether (**2e**), tertiary amine (**2f**), carbamate (**2g**), ester (**2j**), ketone (**2k**), and aryl halides (**2l** and **2m**). The reaction is not sensitive to steric hindrance on the arene, as both *ortho*-substituted phenyl (**2n**, **2o**) and 1-naphthyl (**2p**) groups delivered the β-alkenylation product in satisfactory yields. Heterocyclic moieties are also compatible, such as 1,3-benzodioxole (**2q**) and Ts-protected indole (**2r**). Interestingly, substituents on the propargylic position does not significantly influence the reactivity (**2s**, **2t**), which also excludes the involvement of alkyne to allene isomerization in the productive pathway.[16] Furthermore, 4-alkyl- and aryl-substituted cyclohexanones (**2u**−**2x**) were also suitable substrates. Besides oxygen linkers, a nitrogen-tethered substrate also delivered the desired bicyclic product, albeit in a lower yield (**2y**). Other types of linkers or ketone substrates exhibit low reactivity under the current reaction conditions likely due to the difficulties in the desaturation or enyne-cyclometalation step. (For more details on difficult substrates, see the Supporting Information.)

Synthetic Utility. Containing both the ketone and alkene moieties, the β-alkenylation product could undergo various transformations, leading to synthetically valuable products (Scheme 6). For example, the carbonyl group could be selectively converted to the corresponding alcohol (**5**) or *gem*-difluoro group (**6**). Notably, enolization took place selectively at the more sterically hindered site, likely due to the *cis*-5,6-fused bicyclic structure.[27] This led to the synthesis of an indole-derived tetracycle (**9**) and alkenyl triflate **7** with complete regioselectivity. Notably, alkenyl triflate **7** could be converted to an all-carbon tetrasubstituted olefin (**8**) in one step via our recently developed Pd/norbornene (NBE) catalysis.[28] Furthermore, the olefin could undergo ozonolysis to give diketone **10** or dihydroxylation to provide vicinal diol

https://dx.doi.org/10.1021/jacs.0c02654
J. Am. Chem. Soc. 2020, 142, 8962−8971

Scheme 5. Substrate Scope of the β-Alkenylation Reaction



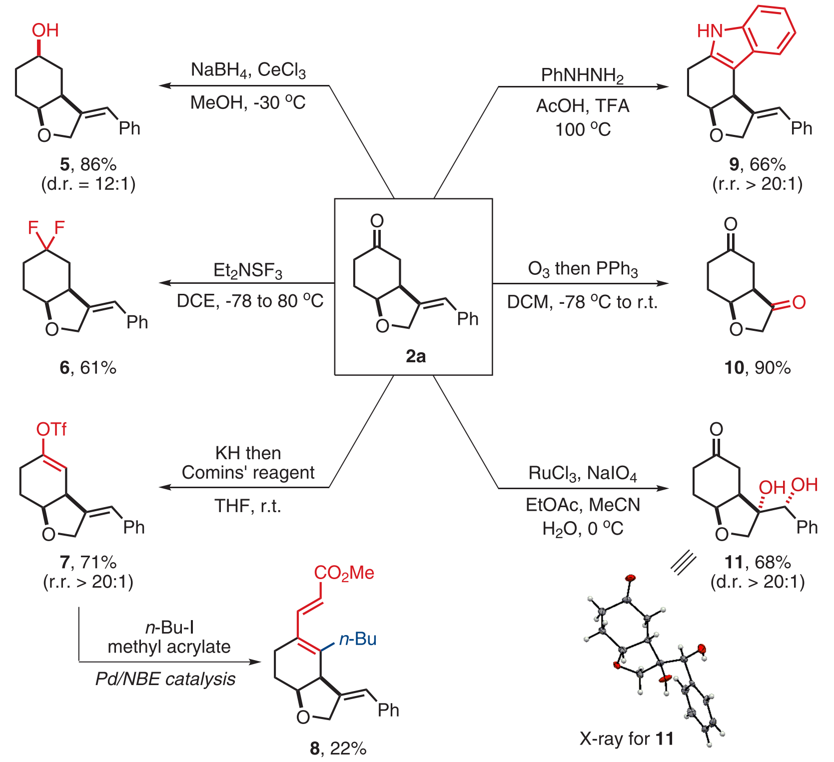
[a]Dechlorination product (**2a**) was observed in 5% yield. [b]Reactions were run for 60 h. pdt: β-alkenylation product; sm: starting material.

11 exclusively from the convex face, and the relative configuration of diol **11** has been elucidated by X-ray crystallography.

CONCLUSIONS

A new reaction mode for the direct β-alkenylation of ketones via a formal C(sp^3)−H/alkyne coupling has been discovered. The method capitalizes on a Pd-catalyzed hydride-transfer

Scheme 6. Transformations of Bicyclic Product 2a



strategy, which is distinct from other β-functionalization approaches. The reaction operates under relatively mild conditions and avoids the use of strong acids or bases; it is also overall redox-neutral without the need for stoichiometric oxidants or reductants, thus showing excellent functional group tolerance. Mechanistic studies reveal several interesting features of this reaction, which include (a) an ArOTf-mediated ketone desaturation during the induction period, (b) an enyne cyclization-promoted chain propagation, and (c) a *cis*-reduction of alkynes via transfer hydrogenation in the late stage. While the yields and scope of the reaction remain to be further improved, the concept of merging ketone desaturation with a constructive C−C-forming event using readily available 2π units should have broad implications. Efforts to examine other transition-metal catalyst systems to develop broadly useful and atom-economical β-functionalization methods are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c02654.

Experimental procedures and spectral data (PDF)
Crystallographic data for DMP-condensed **2a** (CIF)
Crystallographic data for **11** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Chicago and the NSF (CHE-1855556) for research support. P.Z. was supported by a CSC fellowship. Prof. Zhongxing Huang is acknowledged for initial attempts at this reaction. Dr. Ki-Young Yoon and Mr. Shusuke Ochi are thanked for X-ray crystallography.

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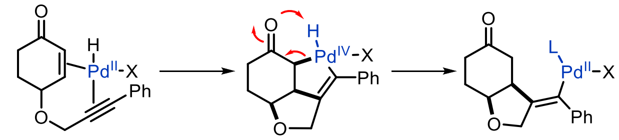

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