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Intramolecular β-Alkenylation of Cyclohexanones via Pd-Catalyzed Desaturation-Mediated C(sp^3)−H/Alkyne Coupling

Chengpeng Wang, Nevin A. Naren, Pengfei Zheng,* and Guangbin Dong*

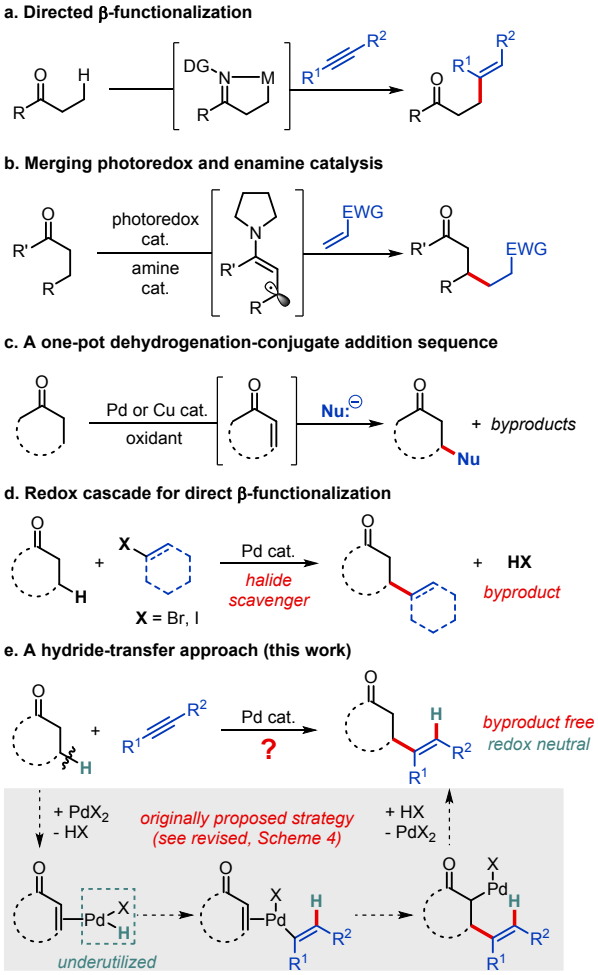
ABSTRACT: Site-selective C−C bond formation through direct coupling of C(sp^3)−H bonds with unsaturated hydrocarbons represents an atom-economical and redox-neutral way for functionalizing chemically inert positions, such as those β to a carbonyl group. While most existing β-functionalization methods utilize a directing group (DG) strategy, here we report a Pd-catalyzed intramolecular β-alkenylation of ketones using alkynes as the coupling partner without 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 cyclometallation of an enyne intermediate and protonation of the resulting Pd enolate followed by an intermolecular hydride transfer through 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 proximity effect (Scheme 1a).[3,4] While effective and versatile, the DG strategy is generally not suitable for cyclic carbonyl compounds. Alternatively, MacMillan and coworkers pioneered a unique photoredox-enamine catalysis strategy via generating β-radicals of ketones and aldehydes, which are then trapped by good radical accepters, 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 oxidation of saturated ketones to conjugated enones followed by 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 β-arylation[7], alkylation[8] and alkenylation[9] of ketones, in which organohalides have been employed as both oxidant and source 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, and, 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 aid of DGs, which would be both atom economical[11] and redox neutral.[12,13] Herein, we describe our initial efforts towards the development of a hydride-transfer strategy for realizing an intramolecular β-alkenylation of ketones with alkynes (Scheme 1e).

Scheme 1. Catalytic β-Functionalization of Carbonyl Compounds.



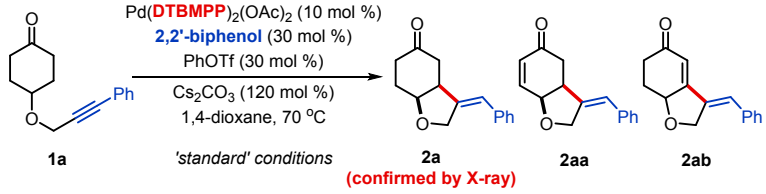
While the Pd-catalyzed ketone desaturation has been well studied,[14,15] the "Pd−hydride" species generated via β-hydrogen elimination in this reaction, to the best of our knowledge, has not been utilized to allow for C−C couplings. Hence, our originally proposed strategy was to trap the "Pd−hydride" 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-alkenylation of ketones via a formal C(sp^3)−H/alkyne coupling without DGs.

RESULTS AND DISCUSSION

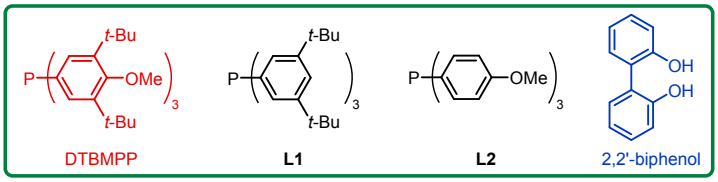
Reaction discovery and optimization. To test the feasibility of the proposed strategy, an alkyne-tethered ketone **1a** was selected as the model substrate (Table 1). Gratifyingly, using a precoordinated catalyst with $Pd(OAc)_2$ and tris(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (DTBMPP),[16] the 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 X-ray crystallography of its hydrazone derivative (see 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). 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] only gave a moderate yield (entry 8). Catalytic phenyl triflate was found to be a crucial additive for the improved efficiency, likely serving as an initiator for this

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



entry	variations from the 'standard' conditions	yield (%)[b] β-alkenylation	**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	$Pd(MeCN)_4(OAc)_2$ + 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_2CO_3	n.d.		n.d.



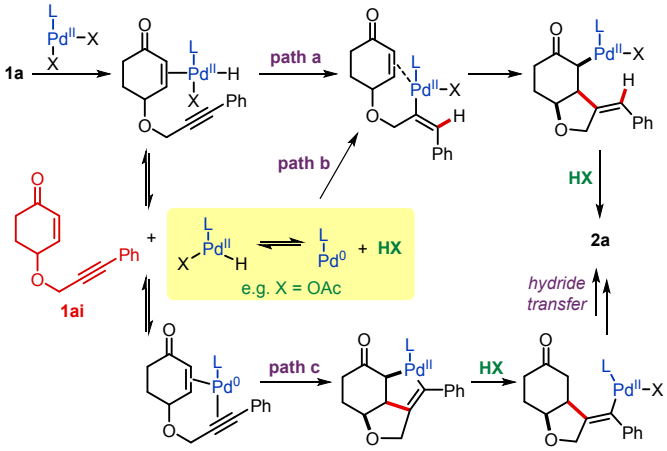
[a]Unless otherwise noted, all the reactions were run with **1a** (0.1 mmol) in 1.0 mL solvent at 70 °C for 48 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]Yield in the parenthesis refers to the isolation yield after a one-pot reduction workup with the following conditions: $Pd(PPh_3)_4$ (0.002 mmol), $ZnCl_2$ (0.02 mmol) and Ph_2SiH_2 (0.05 mmol) at room

temperature for 12 h. n.d. = not detected.

reaction (see the following section for detailed discussion), though the reaction could still proceed without PhOTf (entry 9). A catalytic amount of bromobenzene or use of chlorobenzene as 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 mono phenol, might be attributed to its enhanced acidity (pK_a = 8.0)[18] that could promote protonation of the Pd-enolate intermediate. Finally, Cs_2CO_3 was found 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_2CO_3 (entry 16) or with weaker bases.

Mechanistic studies. The unique transformation discovered here motivated us to gain more insights into the reaction mechanism. Based on 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 coworkers 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 cyclometallation 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*).

Scheme 2. Plausible Mechanisms



First, the kinetic profiles of the reaction were obtained with and without PhOTf (Fig. 1). Under the standard conditions (with PhOTf additive), a 4-hour induction period was observed before product **2a** started to form, during which period fast accumulation of enyne intermediate **1ai** occurred. The product formation was accompanied with consumption of enyne **1ai** in the next 24 hours. Note that

the alkyne reduction side product (**1ar**) only appeared 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 early formation of alkyne-reduction product **1ar**. Considering the facts that **path a** involves an intramolecular Pd−H addition mechanism and the enyne intermediate was formed almost immediately, the unusually long induction period for **2a** formation is inconsistent with **path a**.

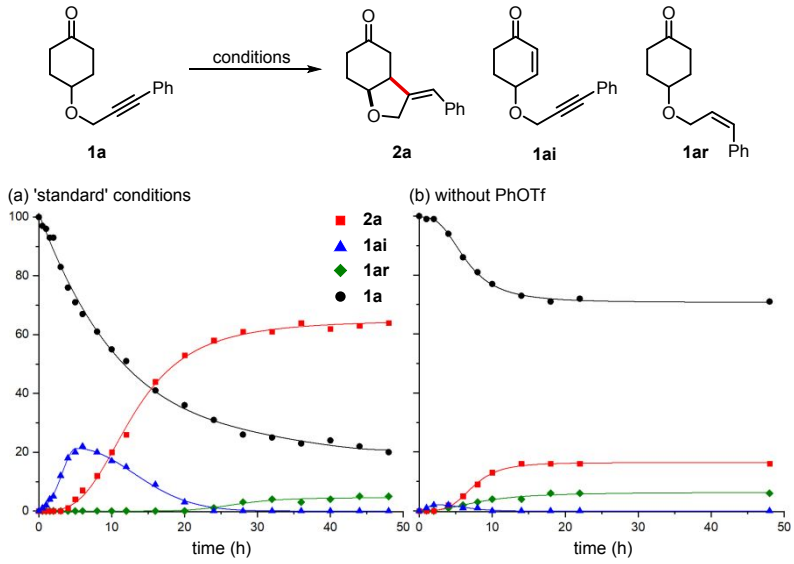
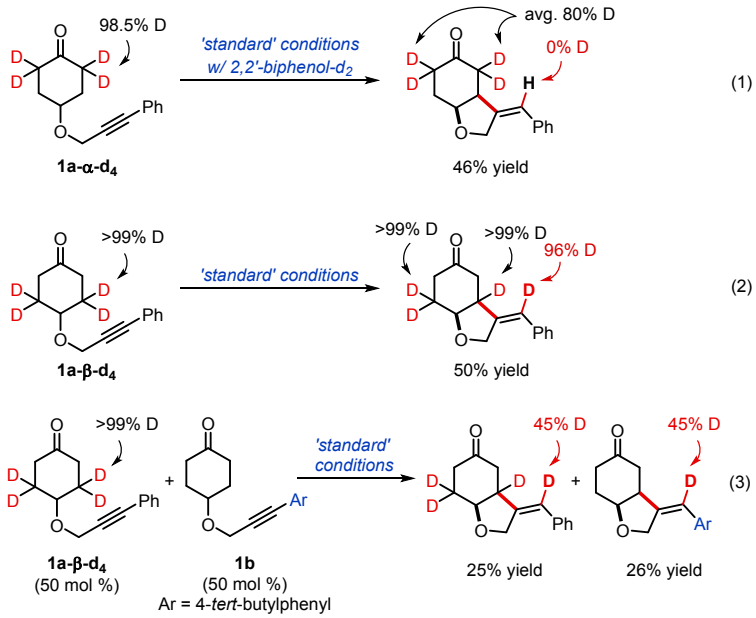


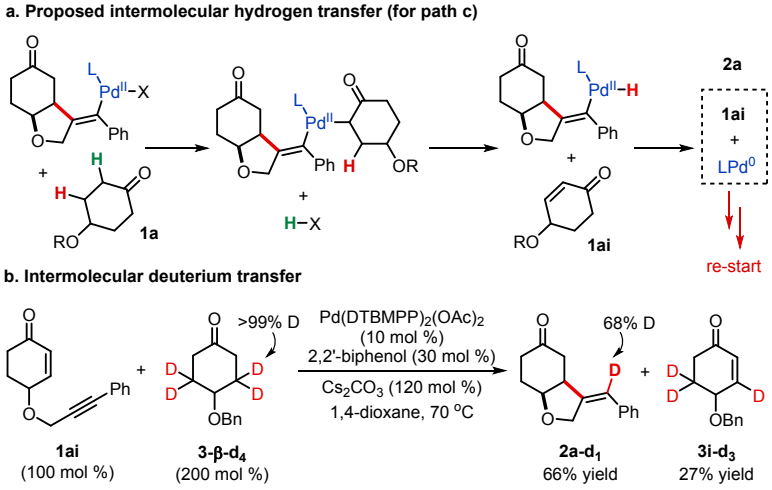
Figure 1. Kinetic profiles for the yields of various products (%) and remaining **1a** (%) over time: (a) under the 'standard' conditions; (b) under the 'standard' conditions but in the absence of PhOTf. The yield of **2a** refers to all β-alkenylation products.

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 cross-over experiment shows that the β-deuterium equally distributes 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 in 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**).



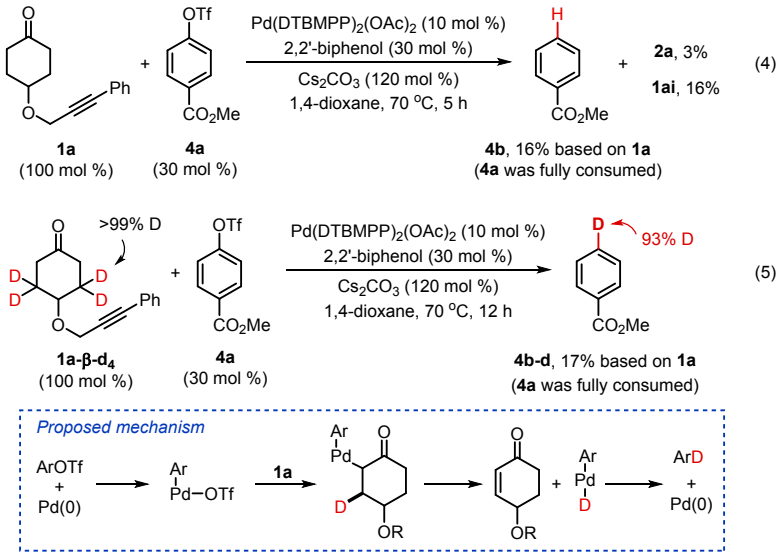
At this stage, the remaining questions are: 1) whether **path c** could be a possible reaction pathway; 2) what the role of PhOTf is and 3) how to explain the formation of the alkyne-reduction side product. To address the first question, one can imagine that, in **path c** after enyne cyclopalladation 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**.

Scheme 3. Intermolecular Hydrogen Transfer



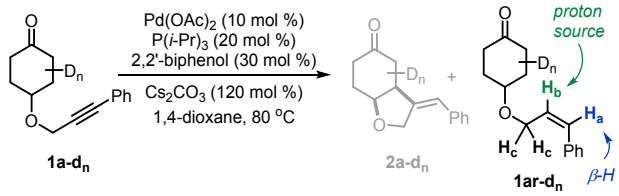
To understand the role of PhOTf (See Table 1, entries 9−11 and Fig. 1), 4-methoxycarbonylphenyl triflate (**4a**) was used as the additive instead for easy monitoring of the reaction. It was observed

that **4a** was fully consumed in the first 5 hours 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 at 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 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**).



Lastly, 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 found incorporated into the allylic position. According to the kinetic studies (Fig. 1), **1ar** started to form when the enyne concentration was low, indicating a kinetic competition between enyne cyclometallation and alkyne reduction. Thus, we hypothesized that the alkyne reduction starts with 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]

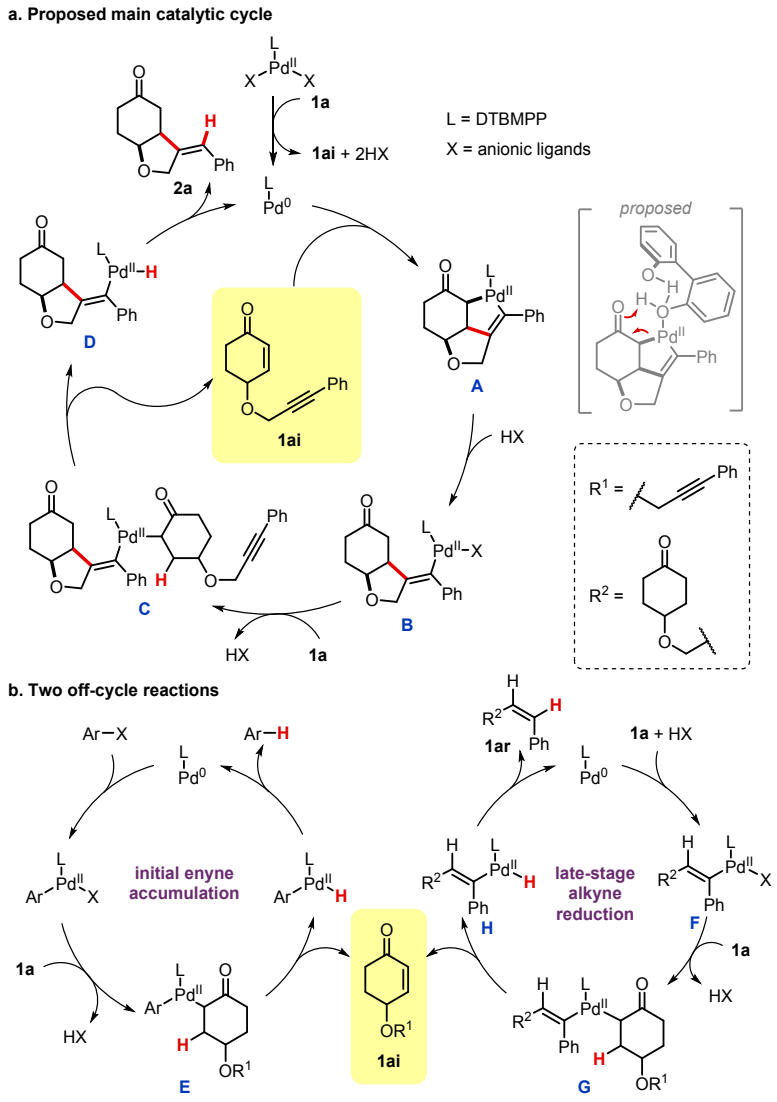
Table 2. Mechanistic Studies on the Alkyne Reduction



entry	substrate	yield of **2a-d$_n$** (%)	yield of **1ar-d$_n$** (%)	D incorporation ratio (%) H_a	H_b	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.

Scheme 4. A Summary of the Proposed Mechanism

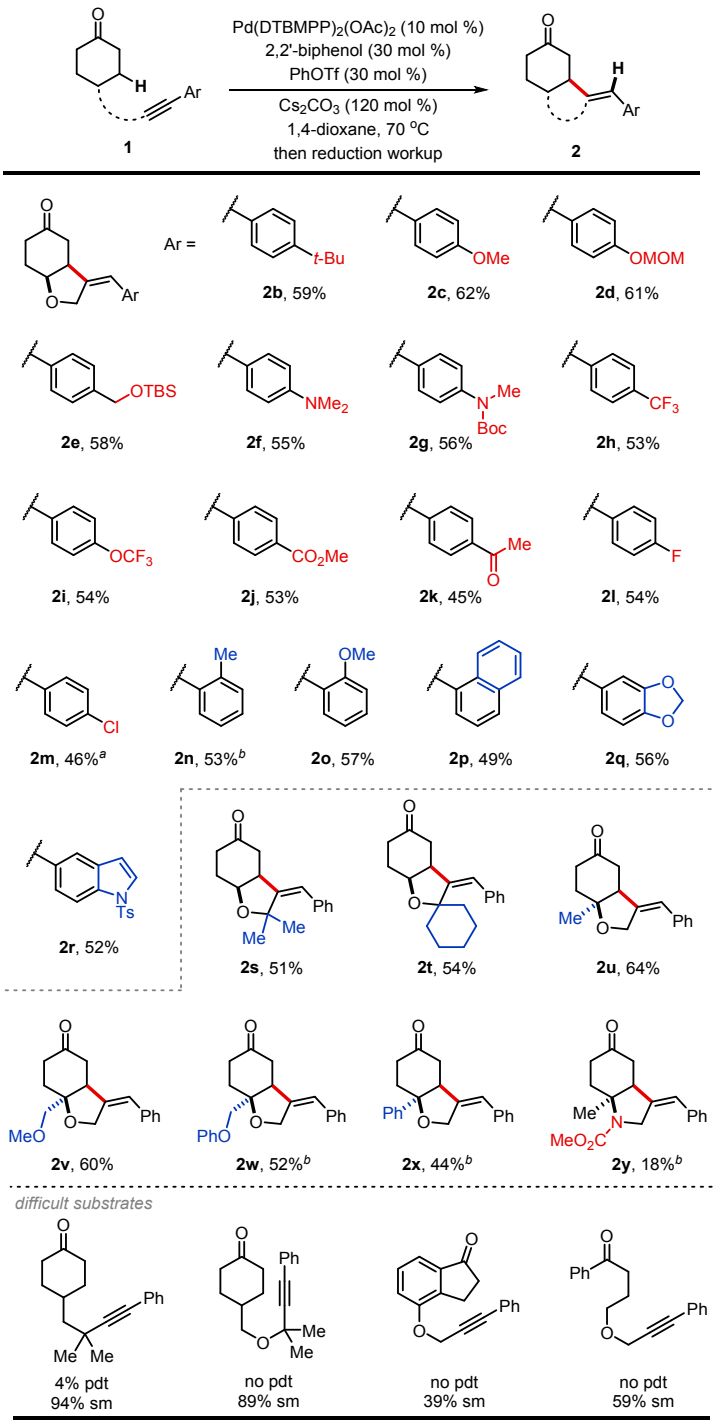


Proposed catalytic cycle. While some mechanistic details of this reaction remain unclear and are still topics of ongoing investigation, the data above allow us to propose a hypothesis for the main catalytic cycle (Scheme 4a). The reaction is initiated by generation of active Pd(0) catalyst and enyne **1ai** via ketone desaturation. Cyclometallation followed by protonation of the enolate ligand gives an alkenylpalladium species **B** that can deprotonate another ketone substrate (**1a**). The

subsequent β-hydrogen elimination regenerates enyne **1ai** and forms an alkenylpalladium hydride species **D**. Finally, C−H reductive elimination gave 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, such as over desaturation of product **2a** to give **2aa** and **2ab** or decomposition of **1ai** to phenol via elimination, would reduce the enyne concentration during the reaction. 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 addition of Pd−H to the alkyne moiety and the 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 at 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**, **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 of the desaturation or enyne-cyclometallation step (for more details of the difficult substrates, see Supporting Information).

Scheme 5. The Substrate Scope of the β-Alkenylation Reaction

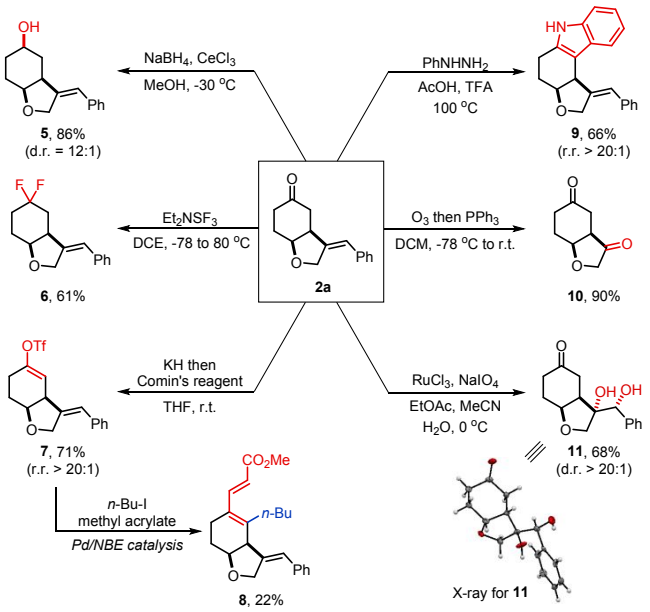


[a]Dechlorination product (**2a**) was observed in 5% yield. [b]Reactions were run for 60 h. pdt: β-alkenylation product; sm: starting material.

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

Scheme 6. Transformations of Bicyclic Product 2a



CONCLUSION

In summary, a new reaction mode for direct β-alkenylation of ketones via a formal C(sp^3)−H/alkyne coupling has been discovered. The method is capitalized on a Pd-catalyzed hydride-transfer strategy, which is distinct from other β-functionalization approaches. The reaction operates at relatively mild conditions and avoids use of strong acids or bases; it is also overall redox neutral without need of 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 on examining other transition-metal catalyst systems for developing broadly useful and atom-economical β-functionalization methods are ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data

Crystallographic data for DMP-condensed **2a** (CIF)

Crystallographic data for **11** (CIF)

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Notes
The authors declare no competing financial interest.

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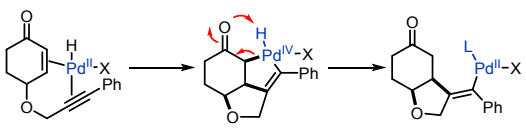

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