

## Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201600696  
Internationale Ausgabe: DOI: 10.1002/anie.201600696Palladium-Catalyzed Oxidative Synthesis of  $\alpha$ -Acetoxyated Enones from Alkynes

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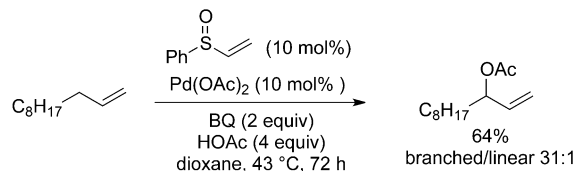
**Abstract:** We report a palladium-catalyzed oxidative functionalization of alkynes to generate  $\alpha$ -acetoxyated enones in one step. A range of functional groups are well-tolerated in this reaction. Mechanistic studies, including the use of  $^{18}\text{O}$ -labeled DMSO, revealed that the ketone oxygen atom in the product originates from DMSO.

Reactions involving C–H functionalization have been widely recognized as highly demanding methodologies for the direct introduction of new functional groups into molecules. For several decades, these reactions have been comprehensively studied in the realm of late-transition-metal catalysis, most recently with the assistance of some directing groups.<sup>[1,2]</sup> In the absence of directing groups, the reaction outcome is mainly determined by its intrinsic reactivity and/or selectivity. In the palladium-catalyzed allylic C(sp<sup>3</sup>)–H acetoxylation reaction, early studies on cyclic alkenes by the Åkermark<sup>[3]</sup> and our group<sup>[4]</sup> showed that in acetic acid, the reaction proceeds via a  $\pi$ -allylpalladium(II) intermediate. White and co-workers later found that in the reaction of acyclic terminal olefins, the addition of sulfoxide ligands significantly promoted the allylic C–H oxidation and also allowed the amount of acetic acid to be lowered to 4 equivalents (Scheme 1 a).<sup>[5]</sup>

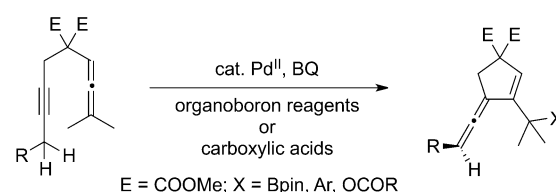
Following our long-term interest in palladium-catalyzed oxidation chemistry, we have actively engaged in the development of various oxidative carbocyclization reactions.<sup>[6,7]</sup> In our recent studies of the cyclization of allenynes, we observed an unconventional propargylic C–H activation pathway, and the vinylallene products could be formed selectively (Scheme 1 b).<sup>[8]</sup> An interesting question is whether a similar propargylic C–H functionalization can also take place with simple alkynes, via either an allenyl- or a propargylpalladium intermediate, which could then undergo a suitable functionalization step, for example, acetoxylation (Scheme 1 c).<sup>[9,10]</sup> In our evaluation of various acetate sources in the presence of sulfoxides and 1,4-benzoquinone (BQ), no desired allenyl/

## Previous work

a) Sulfoxide-promoted allylic C–H acetoxylation

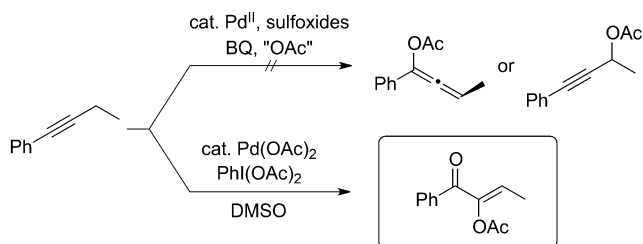


b) Unusual allene formation through propargylic C–H activation



## This work

c) Sulfoxide-promoted oxidative functionalization of alkynes



**Scheme 1.** Palladium-catalyzed allylic and propargylic C–H functionalization. DMSO = dimethyl sulfoxide.

propargyl acetates were observed. However, we found that the treatment of alkynes with catalytic amounts of Pd(OAc)<sub>2</sub> and (diacetoxyiodo)benzene (PIDA) in DMSO afforded (Z)- $\alpha$ -acetoxyated enones with high selectivity (Scheme 1 c).<sup>[11]</sup> To the best of our knowledge,  $\alpha$ -acetoxyated enones were previously only accessible from prefunctionalized starting materials, for example, through the isomerization of propargylic acetates<sup>[12]</sup> or acylation of 1,2-diketone compounds.<sup>[13]</sup> The use of simple alkynes to directly generate such functionality-rich structures is unprecedented.<sup>[14]</sup> Herein, we report a palladium-catalyzed one-step oxidative protocol for the conversion of alkynes into  $\alpha$ -acetoxyated enones.

We initiated the investigation by using 1-phenyl-1-butyne (**1a**) as the model substrate. When alkyne **1a** was treated with Pd(OAc)<sub>2</sub> (5 mol%) and PIDA (1.5 equiv) in [D<sub>6</sub>]DMSO at 50 °C for 18 h, the  $\alpha$ -acetoxyated enone **2a** was formed in 46% yield, and the vicinal diketone **3a** was also observed as a side product (7% yield; Table 1, entry 1).<sup>[15]</sup> No reaction

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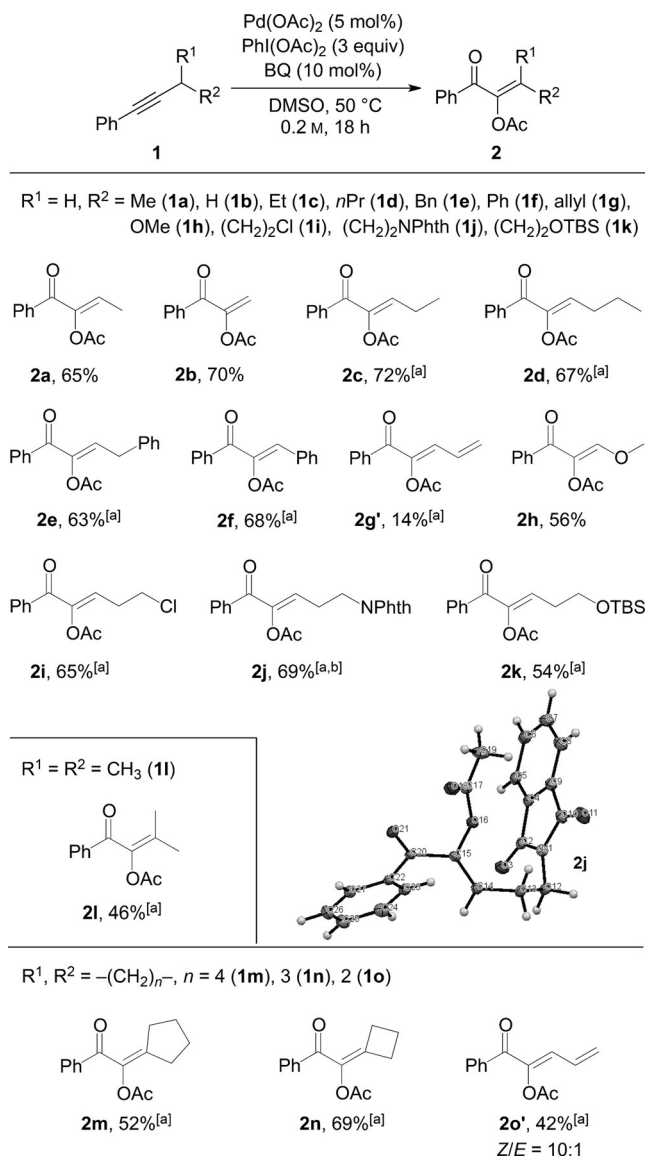
**Table 1:** Optimization of the reaction conditions.<sup>[a]</sup>

Entry	PIDA (x equiv)	"BQ"	Yield of	
			2a [%] <sup>[b]</sup>	3a [%] <sup>[b]</sup>
1	1.5	— <sup>[c]</sup>	46	7
2	2.5	— <sup>[c]</sup>	62	9
3	3	— <sup>[c]</sup>	64	11
4	3	BQ	69	11
5	3	2,6-Me <sub>2</sub> -BQ	66	13
6	3	2,6- <i>t</i> Bu <sub>2</sub> -BQ	64	12
7	3	2,6-(MeO) <sub>2</sub> -BQ	65	12
8	3	2-Cl-BQ	65	15
9	3	F <sub>4</sub> -BQ	62	16
10	3	maleic anhydride	64	14
11 <sup>[d]</sup>	3	BQ	67 (65) <sup>[e]</sup>	13 <sup>[e]</sup>

[a] Reaction conditions: **1a** (0.1 mmol), Pd(OAc)<sub>2</sub> (5 mol %), PIDA (x equiv), "BQ" (10 mol %), [D<sub>6</sub>]DMSO (0.5 mL), 50 °C, 18 h. [b] The yield was determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with anisole as the internal standard. [c] No quinone or quinone analogue was added. [d] The reaction was carried out on a 0.3 mmol scale in DMSO. [e] Yield of the crude product after workup. The yield of isolated **2a** is given in parenthesis.

occurred in the absence of either Pd(OAc)<sub>2</sub> or PIDA.<sup>[16]</sup> Acetonitrile, chloroform, and toluene could be used as cosolvents, but no increase in yield was observed under these conditions.<sup>[17]</sup> Increased amounts of PIDA improved the reaction outcome, and with 3 equivalents of PIDA, **2a** was generated in 64% yield (Table 1, entry 3). The addition of ligands, such as 2,2'-bipyridine and 1,10-phenanthroline (5 mol %), completely shut down the reaction. Among all the tested additives,<sup>[18]</sup> we found that BQ enhanced the reaction: With 10 mol % of BQ, the yield of **2a** was elevated to 69% (Table 1, entry 4). The evaluation of quinone analogues, including maleic anhydride, showed that non-substituted BQ was optimal (Table 1, entries 5–10). When the reaction was carried out on a 0.3 mmol scale in DMSO, the α-acetoxyated enone **2a** was obtained in 65% yield (Table 1, entry 11).

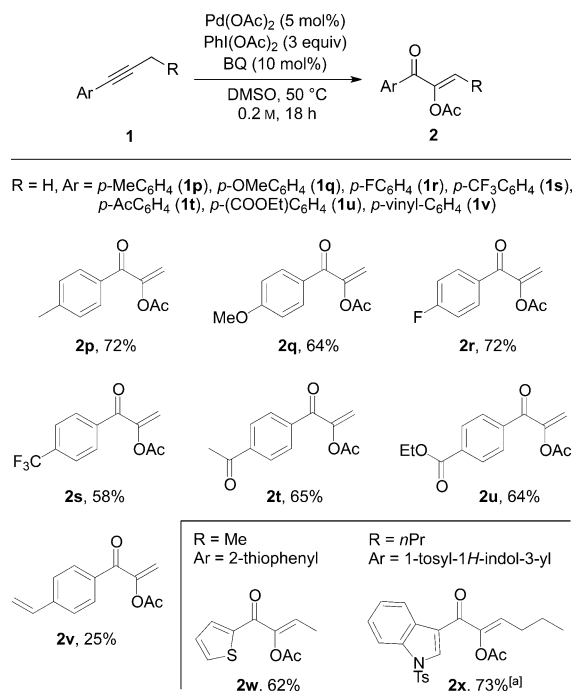
Having optimized the reaction conditions, we continued to explore the scope of the reaction, first by examining different substituents at the propargylic position of the substrate (Scheme 2). Variation of the length of the alkyl chain at the propargylic position had a minor influence on the yield of the corresponding α-acetoxyated enone **2b–e**. Alkyne **1f** containing a benzyl substituent underwent the reaction smoothly to deliver **2f** in 68% yield. In sharp contrast, substrate **1g** bearing an allyl group on the alkyne was converted into the desired product **2g'** in only 14% yield, which implies poor compatibility of the reaction with olefins. We were delighted to find that the propargyl ether **1h** was well-tolerated, as well as a number of other functional groups, including alkyl halides (substrate **1i**) and protected heteroatoms, such as phthalimides (substrate **1j**) and silyl ethers (substrate **1k**). Notably, the products **2a** and **2c–k** were detected as only the *Z* isomers.<sup>[19]</sup> As for propargylic disub-



**Scheme 2.** Acetoxylation of substrates with different propargylic substituents. Reactions were carried out on a 0.3 mmol scale. Yields are for the isolated product. [a] Reaction time: 24 h. [b] For the detailed X-ray crystal structure of **2j**, see the Supporting Information. Bn = benzyl, NPhth = phthalimido, TBS = *tert*-butyldimethylsilyl.

stituted alkynes, the isopropyl alkyne **1l** gave the tetrasubstituted olefin **2l** in a diminished yield of 46%. More importantly, we noticed that substrates incorporating a cycloalkyl group differed significantly in their reactivity. The cyclopentyl- and cyclobutyl-substituted alkynes **1m** and **1n** were converted into the corresponding cycloalkylidene products **2m** and **2n** in good yields. However, in the case of the cyclopropyl alkyne **1o**, the expected cyclopropylidene product was not formed. The reaction was dominated by a ring-opening pathway and provided the α-acetoxyated dienone **2o'** in 42% yield (*Z/E* = 10:1).

Following these encouraging results for different propargylic substituted alkynes, we investigated the scope of the reaction with respect to the arene unit (Scheme 3). Both



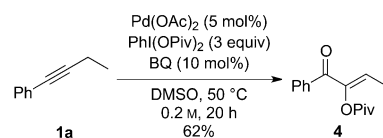
**Scheme 3.** Acetoxylation of substrates with different aryl substituents. Reactions were carried out on a 0.3 mmol scale. Yields are for the isolated product. [a] Reaction time: 40 h.

electron-donating and electron-withdrawing groups, such as alkyl groups, alkoxy groups, and halides, were compatible with the reaction conditions. Moreover, the ketone- and ester-containing substrates **1t** and **1u** reacted smoothly, and these carbonyl groups are valuable handles for subsequent transformations. Alkyne **1v** with an olefin moiety underwent the reaction poorly to give the desired  $\alpha$ -acetoxyenone **2v** only in 25% yield. For synthetically attractive heteroarenes, we were delighted to find that an electron-rich thiophene group (substrate **1w**) was well-tolerated, and no side products arising from potential arene C–H oxidation were detected. Similarly, indole moieties could also be incorporated; the  $\alpha$ -acetoxyenone **2x** could be utilized as a precursor in the synthesis of indole-type natural products.

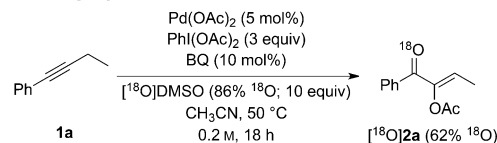
We carried out additional experiments to gain a deeper understanding of the reaction. When  $\text{PhI}(\text{OAc})_2$  was replaced with  $\text{PhI}(\text{OPiv})_2$ , a pivalate group could be installed at the  $\alpha$  position of enone **4** in good yield, thus revealing that the carboxylate functionality can be varied by the use of different iodine(III) reagents (Scheme 4a). When the reaction of alkyne **1a** was carried out with [<sup>18</sup>O]DMSO (86% <sup>18</sup>O), we observed the incorporation of <sup>18</sup>O into the product [<sup>18</sup>O]**2a** (62% <sup>18</sup>O), as determined by ESI-MS analysis (Scheme 4b; see also the Supporting Information).<sup>[20]</sup> This result shows that the ketone oxygen atom originates from the sulfoxide.

As the propargylic C–H bond is broken in the reaction, we performed some kinetic isotope effect (KIE) studies with the deuterium-labeled substrate [D<sub>3</sub>]**1b**. In an intermolecular competition experiment, an equimolar amount of **1b** and [D<sub>3</sub>]**1b** gave **2b** and [D<sub>2</sub>]**2b** in a nearly 1:1 ratio ( $k_{\text{H}}/k_{\text{D}} = 1.05$ ; Scheme 5a). This observation shows that the cleavage of propargylic C–H and C–D bonds occurs after the first

a) Use of  $\text{PhI}(\text{OPiv})_2$  as the iodine(III) reagent

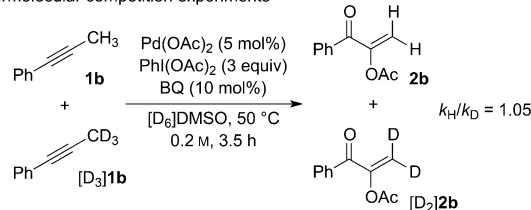


b) Reaction with [<sup>18</sup>O]DMSO

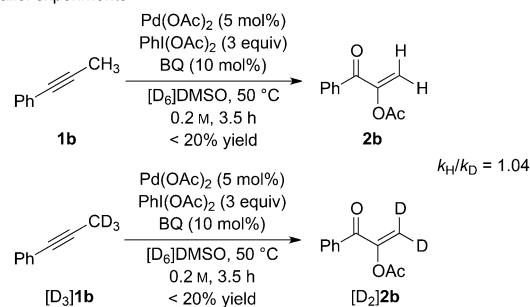


**Scheme 4.** Reactions of **1a** with  $\text{PhI}(\text{OPiv})_2$  or [<sup>18</sup>O]DMSO.

a) Intermolecular competition experiments



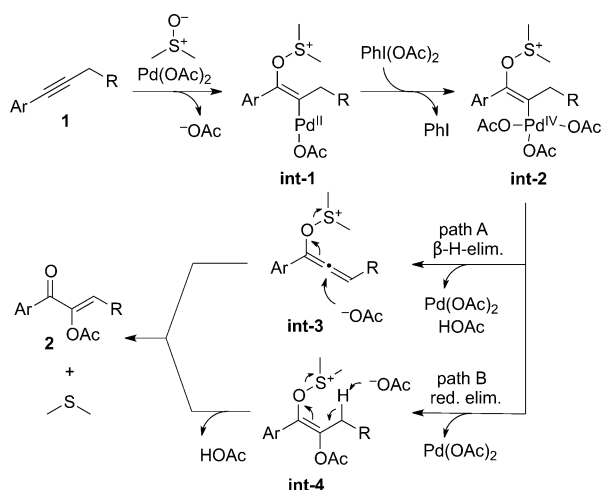
b) Parallel experiments



**Scheme 5.** Isotope-labeling experiments.

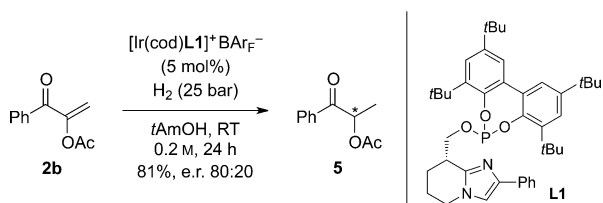
irreversible step of the catalytic cycle. When alkyne **1b** and [D<sub>3</sub>]**1b** reacted separately, a KIE value ( $k_{\text{H}}/k_{\text{D}}$  from the initial rates) of 1.04 was observed (Scheme 5b).<sup>[21]</sup> Such a negligible isotope effect clearly indicates that propargylic C–H bond cleavage is not involved in the rate-determining step.<sup>[22]</sup>

On the basis of the experimental results, we propose a plausible mechanism for this oxidative alkyne functionalization reaction (Scheme 6). Initially, a Wacker-type nucleophilic attack<sup>[23]</sup> by DMSO on the palladium(II)-activated alkyne provides a vinylpalladium(II) intermediate **int-1**.<sup>[24–26]</sup> This palladium(II) species is oxidized by PIDA to a vinylpalladium(IV) intermediate **int-2**,<sup>[27]</sup> which can undergo  $\beta$ -hydride elimination (path A) or reductive elimination (path B)<sup>[28]</sup> to generate **int-3** or **int-4**, respectively. Nucleophilic attack by acetate on **int-3** (path A) would give the desired product **2**; alternatively, the cleavage of an allylic C–H bond, followed by double-bond migration (path B), would also deliver product **2**. Dimethyl sulfide is expelled as the by-product and was detected by GC–MS analysis of the crude mixture.<sup>[29,30]</sup> Although it is known that BQ can promote different catalytic steps in palladium-catalyzed oxidation reactions,<sup>[31]</sup> the exact role of BQ in this reaction remains unclear.



Scheme 6. Proposed reaction mechanism.

To demonstrate the synthetic utility of the products, we performed an iridium-catalyzed asymmetric hydrogenation reaction of the  $\alpha$ -acetoxy enone **2b** by using a chiral N,P ligand.<sup>[32]</sup> Upon selective reduction of the olefin moiety, the enantiomerically enriched  $\alpha$ -acetoxy ketone **5**, a valuable building block, was obtained in 81% yield with e.r. 80:20 (Scheme 7).<sup>[33]</sup>



Scheme 7. Asymmetric hydrogenation of  $\alpha$ -acetoxy enones.  $t\text{AmOH}$  = 2-methyl-2-butanol,  $\text{cod}$  = 1,5-cyclooctadiene.

In conclusion, we have developed a palladium-catalyzed oxidative protocol for the synthesis of  $\alpha$ -acetoxy enones from readily available alkynes. This reaction shows good tolerance of a range of functional groups. Mechanistic studies revealed that DMSO acts as an oxygen nucleophile and propargylic C–H cleavage occurs at a later stage of the reaction, as evidenced by KIE studies. We are currently pursuing further studies on propargylic C–H oxidative functionalization.

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- [15] Control experiments showed that **2a** was not converted into **3a** under the reaction conditions and vice versa.
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- [17] For detailed results of the optimization study, see the Supporting Information.
- [18] Acidic additives such as HOAc and Ac<sub>2</sub>O diminished the yield of **2a**. Basic additives, including various sodium and potassium salts, DIPEA, TMP and 2,6-lutidine, hindered the reaction.
- [19] The configuration of olefins was assigned according to Ref. [12d] and by analogy with the X-ray crystal structure of **2j**.
- [20] The loss of <sup>18</sup>O from 86 % in DMSO to 62 % in the product is most likely due to exchange of the ketone with traces of water.
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