Pd-Catalyzed Regioselective C–H Alkenylation and Alkynylation of Allylic Alcohols with the Assistance of a Bidentate Phenanthroline Auxiliary

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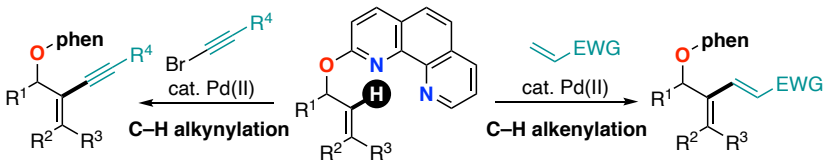
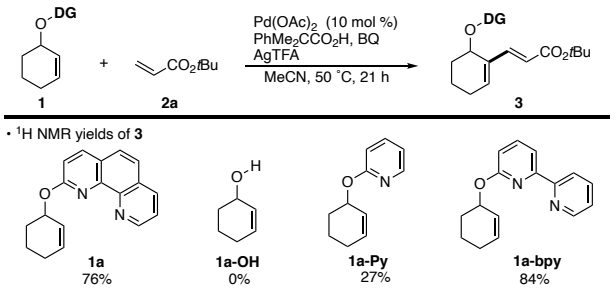
Supporting Information Placeholder



ABSTRACT: A Pd-catalyzed regioselective C–H alkenylation of allylic alcohols with electron-deficient alkenes has been developed. The key to success is the introduction of bidentately coordinating phenanthroline directing group, which enables the otherwise challenging and regioselective C–H activation at the proximal alkenyl C–H bonds over the conceivably competitive allylic C–O bond activation. The same Pd/phenanthroline system is efficient for the C–H alkynylation of allylic alcohols with alkynyl bromides.

Allylic alcohols are important building blocks in organic synthesis and also frequently used as the site of fragment coupling in the synthesis of complex natural products.[1] Accordingly, synthetic chemists have developed numerous methodologies for the preparation of allylic alcohols, particularly multisubstituted derivatives, such as reductive coupling reactions of alkynes with carbonyls[2] and Cr/Ni-mediated Nozaki-Hiyama-Kishi-Takai-type reactions.[3] On the other hand, a decoration of relatively simple allylic alcohols via metal-mediated alkenyl C–H functionalizations[4] is considered to be a good alternative. In particular, the Pd-catalyzed regioselective C–H alkenylation is an attractive strategy to deliver the conjugated dienyl alcohols. However, due to their potential lability and capability of formation of π-allyl metal species via allylic C–O bond activation,[5] there are a few successful examples in the literature. Xu and Loh reported the Pd-catalyzed OH-directed C–H alkenylation of alkenyl alcohols, but only one allylic alcohol was employed and limited to the 1,1-disubstituted Ph-conjugated substrate.[6] Engle also developed the 8-aminoquinoline-directed,[7] Pd-catalyzed regioselective C–H alkenylation but with just two examples of allylic alcohols.[8] Very recently, Zhang and Zhong disclosed the more general C–H alkenylation strategy by using the carbamate directing group.[9] However, all reported procedures are still restricted in scope: only terminal or *cis*-allylic alcohols could be employed. Herein, we report a phenanthroline-directed,[10] Pd-catalyzed regioselective C–H alkenylation of allylic alcohols: a bidentate chelating nature of phenanthroline auxiliary enables the C–H activation selectively at the proximal position over the conceivable allylic C–O activation. The Pd catalysis accommodates *cis*-, *trans*-, and even more challenging trisubstituted substrates. The conjugated dienyl alcohol derivatives obtained are also readily converted to the dienyl amines and ethers as well as free OH alcohols. We also describe a related C–H alkynylation of allylic alcohols, which is unprecedented in the literature, to the best of our knowledge.

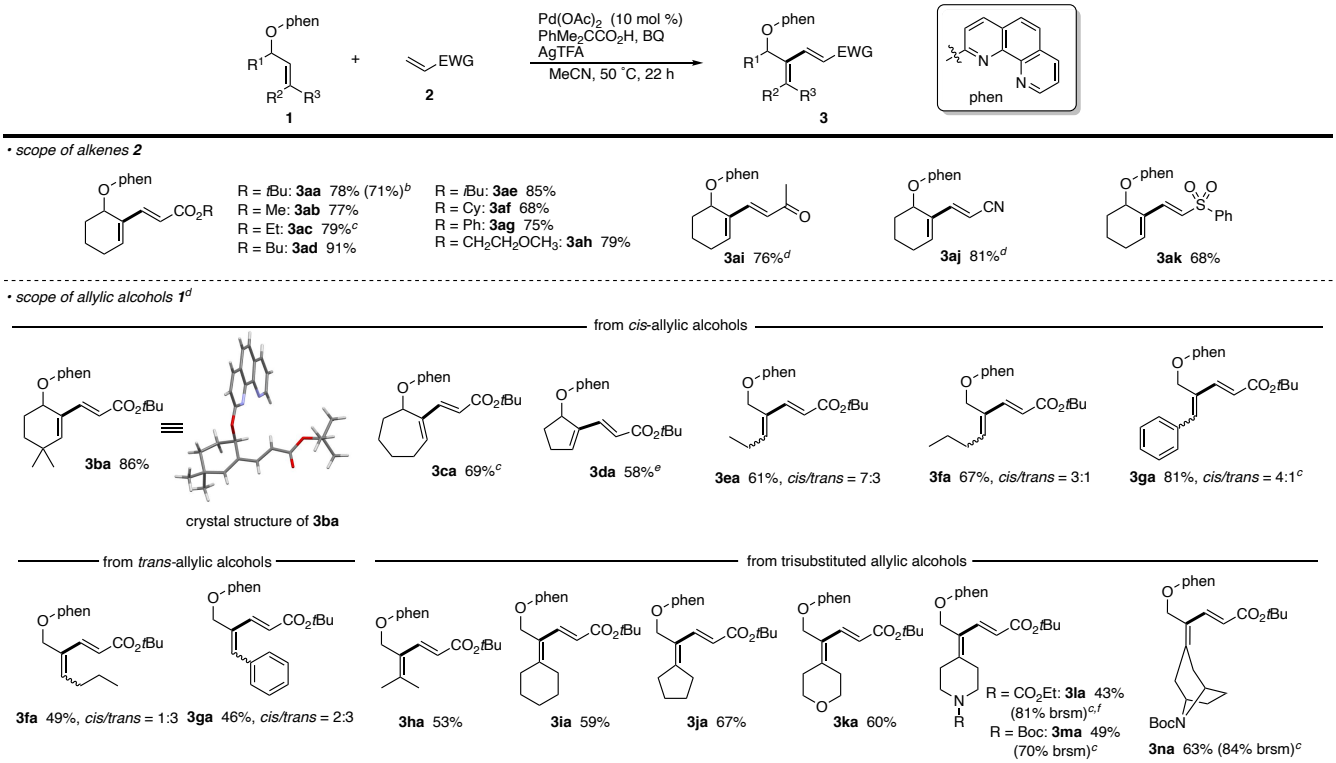
Scheme 1. Effects of Directing Groups in Pd-Catalyzed Regioselective C–H Alkenylation of Cyclohexenols 1 with 2a[a]



[a]Conditions: **1** (0.10 mmol), **2a** (0.20 mmol), $Pd(OAc)_2$ (0.010 mmol), $PhMe_2CCO_2H$ (0.10 mmol), BQ (0.010 mmol), AgTFA (0.20 mmol), MeCN (1.0 mL), 50 ˚C, 21 h.

We selected the 2-cyclohexenol derivative **1a** and *tert*-butyl acrylate (**2a**; 2.0 equiv) as model substrates and started optimization studies (Scheme 1). After extensive screening of various reaction parameters, we pleasingly found that the reaction proceeded in the presence of $Pd(OAc)_2$ catalyst, AgTFA oxidant (2.0 equiv), and 2-phenylisobutyric acid/benzoquinone (BQ) additives (100 and 10 mol %, respectively) in heated MeCN (50 ˚C) to form the corresponding dienyl alcohol **3aa** in 76% ^{1}H NMR yield as the single regio- and stereoisomer.[11] The acid and BQ additives were not indispensable but improved the reaction efficiency. On the other hand, the choice of directing group was critical: the free alcohol (**1a-OH**) and monodentate pyridine-directed substrate (**1a-Py**) resulted in no and much less formation of alkenylated products, respectively. Only a similarly bidentately coordinating **1a-bpy** showed a comparable reactivity. However, given the more ready availability of phenanthroline-based directing group (easily prepared on a decagram scale from commercially available simple phenanthroline),[10,12] subsequent studies were performed with **1a**.

Scheme 2. Products of Phenanthroline-Directed, Pd-Catalyzed Regioselective C–H Alkenylation of Allylic Alcohols 1 with Electron-Deficient Alkenes 2[a]



[a]Conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (0.020 mmol), $PhMe_2CCO_2H$ (0.050 mmol), BQ (0.040 mmol), AgTFA (0.40 mmol), MeCN (1.0 mL), 50 ˚C, 22 h. Isolated yields are shown. [b] On a 2.0 mmol scale. [c] With $PhMe_2CCO_2H$ (0.10 mmol). [d] At 65 ˚C. [e] With **2a** (0.60 mmol) and AgTFA (0.30 mmol) at 50 ˚C. [f] 36 h.

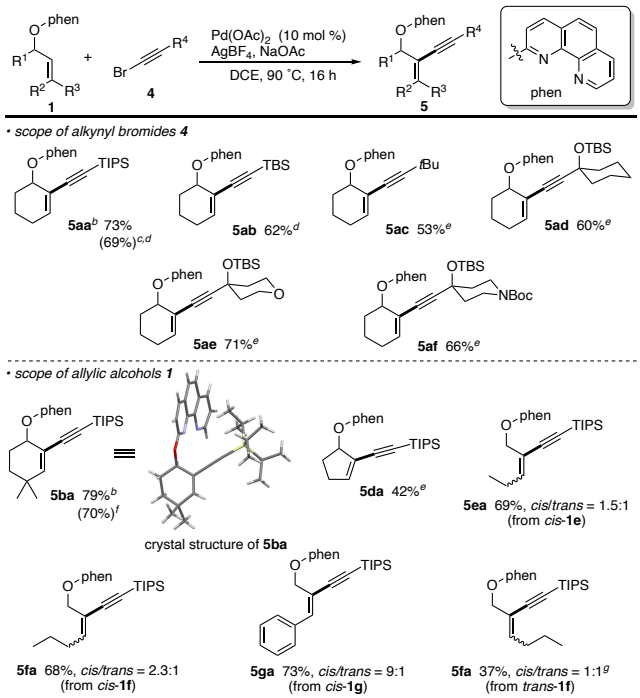
Additional fine tunings finally revealed that the desired **3aa** was isolated in 78% yield with 10 mol % $Pd(OAc)_2$, 25 mol % acid, and 20 mol % BQ (0.20 mmol scale; Scheme 2). Under the optimal conditions, the generality of reaction was investigated. The α,β-unsaturated esters were good coupling partners toward **1a**, and primary (**2b**–**e**) and secondary alkyl (**2f**) acrylates provided the corresponding conjugated 1,3-dienes **3ab**–**af** in good to high yields. The somewhat labile phenyl and ethylene glycol esters **2g** and **2h** also underwent the reaction smoothly (**3ag** and **3ah**). Additionally, the unsaturated ketone, nitrile, and sulfone were amenable to the reaction, giving the functionalized dienols **3ai**–**ak** in 68–81% yields.

The salient feature of Pd catalysis with the phenanthroline bidentate auxiliary is that the scope of allylic alcohols was broader than that of reported procedures.[6,8,9] The reaction was compatible with the 4,4-dimethylcyclohexenol **1b** as well as larger seven-membered and smaller five-membered allylic alcohols **1c** and **1d** (**3ba**–**da**). The structure of **3ba** was unambiguously confirmed by X-ray crystallography (CCDC 1990132). The linear *cis*-allylic alcohols **2e**–**g** also afforded the C–H alkenylated products **3ea**–**ga** albeit with some erosion of stereochemistry of allyl moiety.[13] It is noteworthy that the more sterically demanding *trans*-allylic alcohols also reacted with **1a** to furnish **3fa** and **3ga** in favor of *trans* geometry. Particularly notable is the successful transformation of the sterically hindered trisubstituted substrates: the prenyl alcohol **2h** was converted to the multisubstituted 1,3-diene **3ha** in a synthetically useful yield. The cyclic substructure on the alkene terminus was also accommodated to form the cyclohexylidene- and cyclopentylidene-containing systems **3ia** and **3ja**. Moreover, the *O*- and *N*-heterocycles were also tolerated under reaction conditions: tetrahydropyran (**3ka**), piperidine (**3la** and **3ma**), and bicyclic tropinone derivatives (**3na**) were obtained in good yields.

The reaction could be set up without any special precautions to exclude air and moisture and thus easily performed on a 10-fold larger scale (**3aa**).[14]

The Pd/phenanthroline system was also applicable to the regioselective alkenyl C–H alkynylation of allylic alcohols, which is unprecedented and one of the limited successful examples of the Pd-catalyzed directed C–H alkynylation of unconjugated internal alkenes.[15] Namely, a treatment of **1a** with TIPS-substituted alkynyl bromide **4a** in the presence of $Pd(OAc)_2$ catalyst and $AgBF_4$/NaOAc additives in heated 1,2-dichloroethane (DCE; 90 ˚C) afforded the conjugated enyne **5aa** in 73% isolated yield (Scheme 3). Both additives were critical: $AgBF_4$ could abstract Br derived from **4a** to enable the catalytic turnover of Pd, whereas NaOAc greatly improved the mass balance of the reaction. As seen in the alkenylation, the phenanthroline bidentate auxiliary was necessary for the acceptable conversion.[11] Several other bulky alkynyl bromides **4** were successfully coupled with **1a**. For example, the reaction with TBS- and *tert*-butyl-substituted alkynyl bromides **4b** and **4c** provided **5ab** and **5ac**, respectively, in good yields. The Pd catalysis was also tolerated with the protected propargylic alcohol derivatives that bear the cyclohexyl as well as the heterocyclic pyran and piperidine rings (**5ad**–**af**). At higher reaction temperature (110 ˚C), the corresponding alkynyl chloride was also available for use (**5aa**). As a general trend, $AgPF_6$ showed better performance than $AgBF_4$ when the alkyl-substituted alkynyl bromides were employed. The scope of allylic alcohols **1** was also evaluated. The 4,4-dimethylcyclohexenol **1b** smoothly reacted with **4a** to form the corresponding conjugated enyne **5ba** in 79% yield; the structure of which was determined by the single X-ray crystallographic analysis (CCDC 2022024). The reaction was scalable and easily conducted on a 2.0 mmol scale. The reactivity of cyclopentenol derivative was somewhat lower, but the targeted **5da** was isolated in a synthetically useful yield. The linear *cis*-allylic alcohols were also amenable, and the corresponding C–H alkynylated products **5ea**-**ga** were obtained albeit with variable stereospecificity (*cis*/*trans* = 1.5:1–9:1). Moreover, the conceivably more challenging *trans*-allylic alcohol formed the desired product **5fa**.[16]

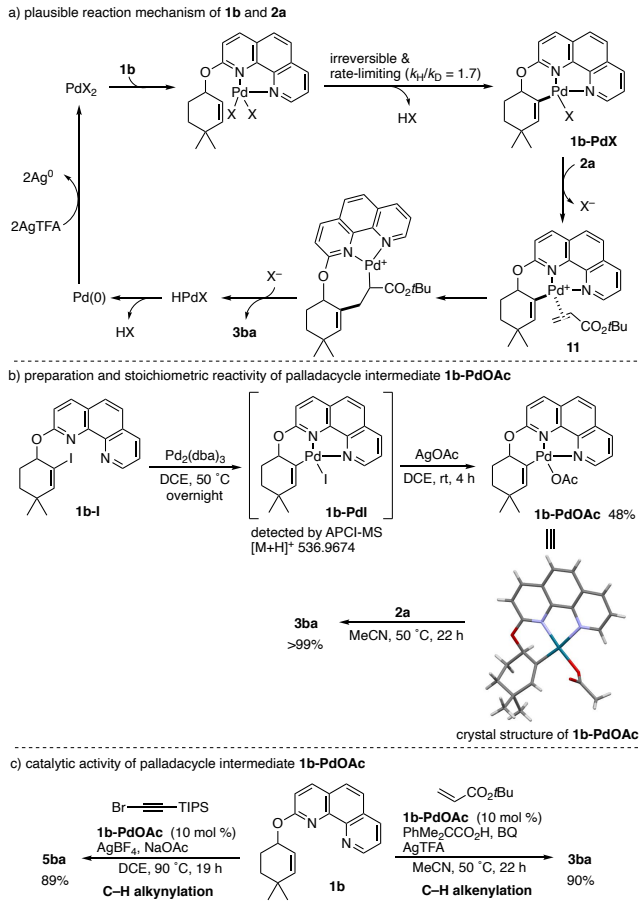
Scheme 3. Products of Phenanthroline-Directed, Pd-Catalyzed Regioselective C–H Alkynylation of Allylic Alcohols 1 with Alkynyl Bromides 4[a]



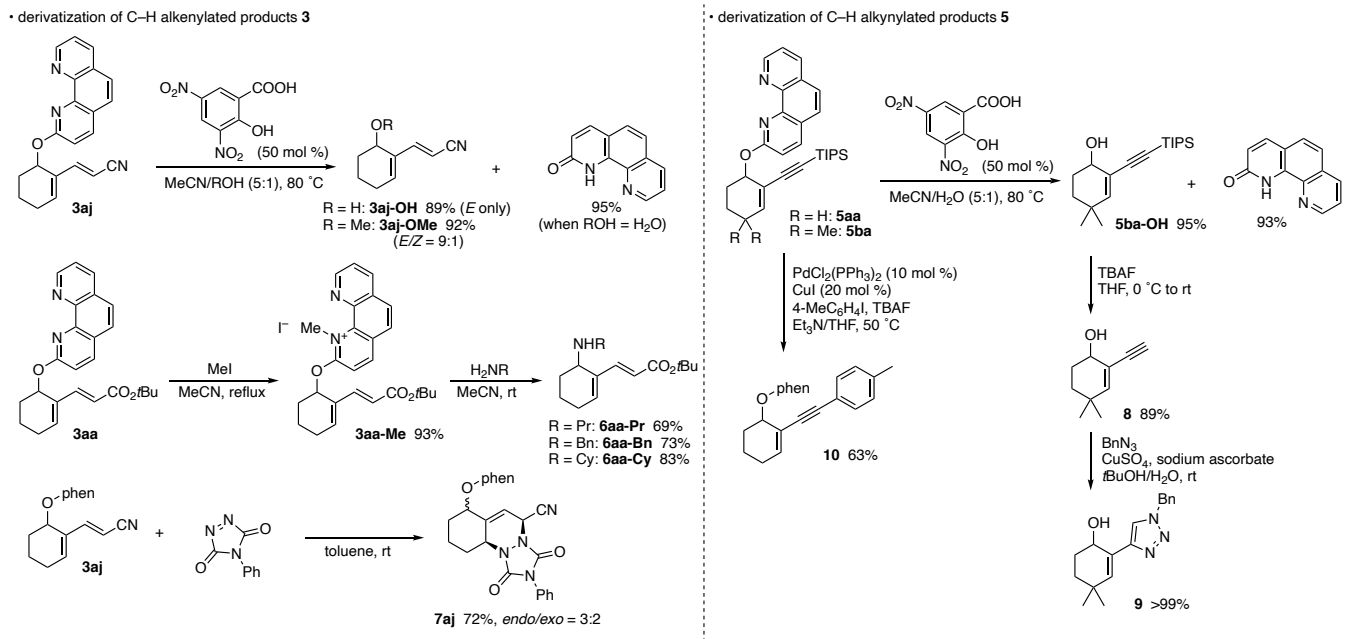
[a]Conditions: **1** (0.20 mmol), **4** (0.40 mmol), $Pd(OAc)_2$ (0.020 mmol), $AgBF_4$ (0.20 mmol), NaOAc (0.20 mmol), DCE (2.0 mL), 90 ˚C, 16 h. [b] On a 0.10 mmol scale. [c] With the corresponding alkynyl chloride instead of **4a**. [d] At 110 ˚C. [e] With $AgPF_6$ instead of $AgBF_4$. [f] On a 2.0 mmol scale. [g] At 100 ˚C.

The phenanthroline auxiliary in the products could be easily removed and manipulated (Scheme 4). The Brønsted acid catalyzed[17] substitution of **3aj** with H_2O proceeded smoothly to deliver the corresponding free dienyl alcohol **3aj-OH** and 2-phenanthrolinone in 89 and 95% yields, respectively.[18] The latter was easily recycled via conversion back into the directing group precursor.[10a] The etherification with the alcohol nucleophile was also feasible (**3aj-OMe**). Moreover, the dienylamines **6aa-Pr**–**Cy** were obtained by the quaternary-driven nucleophilic amination with primary amines. On the other hand, the formed 1,3-diene moiety was a reactive enophile, and Diels-Alder reaction with the triazoledione was possible to afford the cycloadduct **7aj** in a good yield. The C–H alkynylated product **5ba** was also readily and regioselectively converted to the free alcohol **5ba-OH** along with phenanthrolinone under the aforementioned acid-mediated conditions. The cleavage of the TIPS moiety with TBAF (**5ba-OH** to **8**) was followed by the Cu-catalyzed azide-alkyne cycloaddition to afford the functionalized triazole **9** in a good overall yield. Additionally, the direct desilylative Sonogashira coupling of **5aa** could also be performed to form the aryl-conjugated enyne **10**, which overcomes the limitation of alkynyl bromides in the C–H alkynylation.[16]

Scheme 5. (a) Plausible Reaction Mechanism of 1b and 2a; (b) Preparation and Stoichiometric Reactivity of 6-Membered Palladacycle; (c) Catalytic Activity of 6-Membered Palladacycle



Scheme 4. Derivatization of C–H Alkenylated and Alkynylated Products 3 and 5



formed by successive insertion and β-H elimination. The liberation of HX and reoxidation with AgTFA regenerate the starting PdX_2 to complete the catalytic cycle. The deuterium incorporation experiments and KIE studies with the deuterated **1b** suggest the irreversible and rate-limiting C–H cleavage.[19] Given the better reactivity of **1a** and **1a-bpy** than **1a-Py** observed in Scheme 1 and our previous Cu-catalyzed phenanthroline-directed C–H amination of phenols,[10a] the chelating nature of phenanthroline (and bipyridine) moiety accelerates the otherwise challenging C–H cleavage step. Additionally, the positive effects of acid additive can support the operation of acetate-ligand-promoted concerted metalation-deprotonation mechanism.[20] The exact role of BQ is not

Our proposed reaction mechanism for the phenanthroline-directed Pd-catalyzed alkenylation of **1b** with **2a** is shown in Scheme 5a. The initial coordination of phenanthroline moiety of **1b** to PdX_2 (X = OAc, $OCOCMe_2Ph$, or TFA) is followed by C–H cleavage to form the 6-membered palladacycle intermediate **1b-PdX**. Subsequent ligand exchange on Pd between the alkene **2a** and X^- occurs to afford an alkene-coordinated cationic Pd species **11**. The C–H alkenylated product **3ba** is

clear at this stage, but it can coordinate to Pd(0) to avoid the formation of catalytically inactive Pd black.[21]

All attempts to detect and isolate the key palladacycle intermediate **1b-PdX** from **1b** and $Pd(OAc)_2$ remained unsuccessful, but we were pleased to prepare the corresponding acetate complex **1b-PdOAc** from the alkenyl iodide **1b-I** and $Pd_2(dba)_3$ (Scheme 5b). Oxidative addition of **1b-I** to the Pd proceeded smoothly in DCE at 50 °C, and complete consumption of **1b-I** and formation of **1b-PdI** were assigned by APCI-HRMS. Subsequent addition of AgOAc at room temperature promoted I/OAc ligand exchange to give the targeted **1b-PdOAc** as a bench-stable white solid in 48% overall yield. The structure was confirmed by $^1H/^{13}C$ NMR, ESI-HRMS, and X-ray crystallography (CCDC 2022025); **1b-PdOAc** has a typical tetracoordinated planar structure with 360.05° sum of bond angle around Pd. The stoichiometric reaction of **1b-PdOAc** with **2a** in the absence of any external additives formed the alkenylated product **3ba** in a quantitative yield. Additionally, **1b-PdOAc** worked well as the catalyst to couple **1b** and **2a** with comparable efficiency to that under standard conditions in Scheme 2 (Scheme 5c). Similarly high catalytic activity of **1b-PdOAc** was also observed in the reaction of **1b** with the alkynyl bromide **4a**. Thus, a related palladacycle intermediate would be involved in the catalytic cycle of both C–H alkenylation and alkynylation.[22]

In conclusion, we have developed a phenanthroline-directed Pd-catalyzed C–H alkenylation of allylic alcohols with electron-deficient alkenes. The bidentate coordinating nature of phenanthroline enables the otherwise challenging and regioselective C–H activation at the proximal alkenyl C–H bond over the competitive allylic C–O bond activation (conventional π-allyl Pd chemistry). The same phenanthroline/Pd system is applicable to the C–H alkynylation of allylic alcohols, which is unprecedented, to the best of our knowledge. Some mechanistic studies with the independently prepared 6-membered palladacycle intermediate suggest that the regioselective, directed C–H palladation is the key step in the C–H alkenylation and alkynylation. More detailed investigation of reaction mechanism and further development of Pd/phenanthroline system for the more challenging C–H activation of oxygenated molecules are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

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

^1H and $^{13}C\{^1H\}$ NMR spectra, detailed optimization studies, experimental procedures, *trans/cis* isomerization test, and isotope-labeling experiments (PDF)

Accession Codes

CCDC 1990132, 2022024, and 2022025 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) See the Supporting Information for more detailed optimization studies.

(12) The corresponding 6-chloro-2,2'-bipyridine directing group seems to be prepared by the almost same protocol as the 2-chlorophenanthroline directing group. However, in the chlorination step, the desired C6- and undesired C4-chlorination competitively occurred. Additionally, the efficiency in its attachment and detachment steps was much lower than that of 2-chlorophenanthroline. See: Moran, D. B.; Morton, G. O.; Albright, J. D. Synthesis of (Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines, *J. Heteocycl. Chem.* **1986**, *23*, 1071.

(13) We checked the *trans/cis* isomerization of both starting substrate and product. While the starting substrate gradually underwent the isomerization, the stereochemistry of initially formed product remained under the optimal conditions. See the Supporting Information for more details. A similar isomerization was observed also in the literature. See refs 8 and 15c and references cited therein.

(14) We also prepared the bipyridine-derived trisubstituted allylic alcohol substrates **1h-bpy** and **1i-bpy** and investigated their reactivity. However, we found no significant improvement, and almost the same isolated yields of the corresponding alkenylated products were obtained. See the Supporting Information for details.

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(19) See the Supporting Information for more details.

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