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C(alkenyl)–H Activation via Six-Membered Palladacycles: Catalytic 1,3-Diene Synthesis

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Supporting Information Placeholder

ABSTRACT: A catalytic method to prepare highly substituted 1,3-dienes from two different alkenes is described using a directed, palladium(II)-mediated C(alkenyl)–H activation strategy. The transformation exhibits broad scope across three synthetically useful substrate classes masked with suitable bidentate auxiliaries (4-pentenoic acids, allylic alcohols, and bishomoallylic amines) and tolerates internal non-conjugated alkenes, which have traditionally been a challenging class of substrates in this type of chemistry. Catalytic turnover is enabled by either MnO_2 as the stoichiometric oxidant or by co-catalytic $Co(OAc)_2$ and O_2 (1 atm). Experimental and computational studies were performed to elucidate the preference for C(alkenyl)–H activation over other potential pathways. As part of this effort, a structurally unique alkenylpalladium(II) dimer was isolated and characterized.

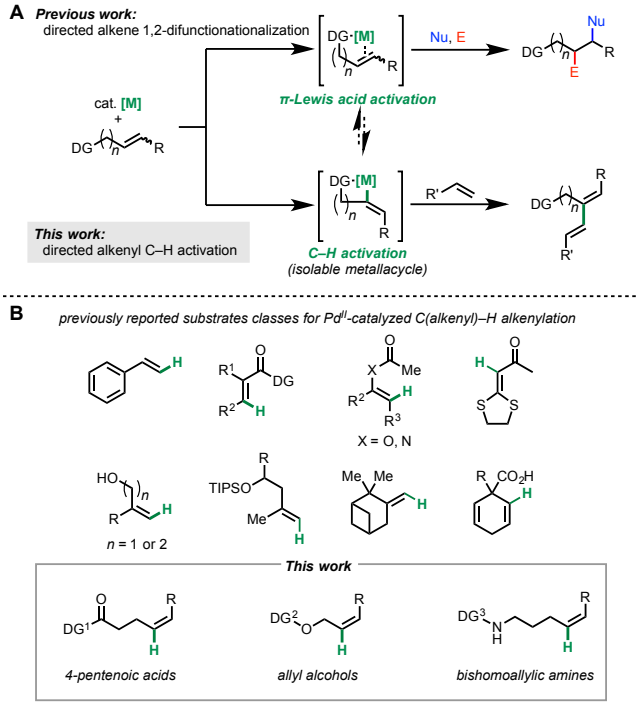
Introduction

The selective synthesis and functionalization of alkenes is a central theme in organic chemistry. Our laboratory has recently developed a series of substrate-directed palladium(II)-catalyzed alkene hydrofunctionalization and 1,2-difunctionalization reactions (Scheme 1A).[1] These reactions employ removable bidentate directing groups to facilitate π-Lewis acid activation of the proximal alkene for nucleopalladation. Given that this family of directing groups also promotes C(sp^2)–H and C(sp^3)–H activation,[2,3] we questioned whether it would be possible to achieve selective C(alkenyl)–H functionalization within these synthetically versatile alkene substrate classes (Scheme 1B). In terms of synthetic strategy, the proposed mode of reactivity would offer expedient access to highly substituted alkene products and would complement directed alkene 1,2-difunctionalization chemistry.

Compared to C(alkyl)–H and C(aryl)–H activation, C(alkenyl)–H activation has been less thoroughly explored.[4] C(alkenyl)–H functionalization reactions are complicated by competitive reactivity of the alkene moiety, which can make chemoselectivity a significant challenge. Additionally, site selectivity can be difficult to control due to the presence of alternative C–H cleavage sites (e.g. C(allylic)–H activation). Such issues are particularly problematic in C–H activation of internal di- or tri-alkyl substituted alkenes.

Oxidative coupling of C(alkenyl)–H bonds with alkenes represents an attractive approach to access 1,3-dienes and polyene motifs, which are important synthetic targets due to their presence in natural products, their utility in [4+2] cycloaddition reactions, and their unique materials properties. At present, the most common methods for accessing these targets include the Wittig/Horner–Wadsworth–Emmons reactions[5] or transition-metal-catalyzed cross-coupling reactions.[6] While robust, these routes possess disadvantages in that they require prefunctionalized starting materials, generate stoichiometric byproducts, and in some cases deliver *E*/*Z* product mixtures. Several previous reports have described palladium(II)-catalyzed C(alkenyl)–H alkenylation, with the vast majority of examples employing conjugated alkenes, such as styrenes[7]

Scheme 1. Approaches to directed alkene functionalization



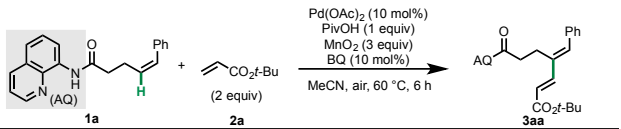
acrylates/acrylamides,[8] enamides,[9] and enol esters/ethers[10]. Despite the synthetic utility of expanding this reactivity toward non-conjugated alkenes, reports of such a transformation are rare. Notably, the Gusevskaya group developed a camphene dimerization reaction[11] and Loh and coworkers employed an alcohol or silyl ether directing group to achieve C(alkenyl)–H activation of 1,1-disubstituted non-conjugated terminal alkenes.[12] During the preparation of this manuscript, Chou and co-workers reported a carboxylate-directed C(alkenyl)–H alkenylation of 1,4-cyclohexadiene compounds, which

undergo decarboxylative rearomatization in situ.[13] In the present study, we report a method for preparing 1,3-dienes starting from a directing-group-containing alkene (4-pentenoic acid, allyl alcohol, or 4-pentenamine derivative) and an electron-poor alkene coupling partners. The reaction involves a directed C(alkenyl)–H activation step[4] which is highly selective for the C(alkenyl)–H bond via a six-membered palladacycle intermediate.

Results and Discussion

1. Reaction optimization. We commenced this investigation by surveying reaction conditions using (*Z*)-5-phenyl-4-pentenamide **1a** bearing Daugulis's 8-aminoquinoline (AQ) directing group[2,3] as the model substrate and *tert*-butylacrylate **2a** as the coupling partner (Table 1).[14] We found that in the presence of $Pd(OAc)_2$ γ-C(alkenyl)–H activation via a six-membered palladacycle took place selectively; the other potential products from β-C(allylic)–H activation via a five-membered palladacycle/π-allyl intermediate or δ-C(alkenyl)–H activation via a seven-membered palladacycle were not observed (*vide infra*). Extensive optimization revealed that a carboxylic acid promoter was beneficial, and among those tested, pivalic acid was found to be optimal. Achieving efficient reoxidation in this catalytic cycle proved to be highly challenging. Ultimately, we identified two effective oxidation systems. First, it was found that a combination of a catalytic amount of benzoquinone (BQ) and 3 equiv MnO_2 gave both high conversion and good material balance.[15] Control experiments confirmed that palladium is required (Table 1, entries 16–18). Second, by substituting MnO_2 with 10 mol% $Co(OAc)_2$ and running the reaction under an O_2 atmosphere (1 atm), equivalently high yield was also observed (Table 1, entries 19 and 20). We envisioned that both conditions could be useful to end-users depending on the setting, so both were explored further (*vide infra*). Although the reaction occurred at room temperature (90% isolated yield after 6 d using MnO_2), we elected to conduct the substrate scope on 60 °C and 6 h because of the convenient reaction temperature and time

Table 1. Optimization of conditions



1a 2a 3aa

Entry	Variation from Standard Conditions	Yield[a]	Entry	Variation from Standard Conditions	Yield[a]
1	**none**	**(97%)**	11	DMA	29%
2	HOAc	65%	12	HFIP	16%
3	benzoic acid	41%	13	MnO_2 (1 equiv)[b]	57%
4	1-AdaCO_2H	46%	14	MnO_2 (2 equiv)[b]	76%
5	squaric acid	44%	15	no BQ[b]	39%
6	$PdCl_2$	10%	16	no $Pd(OAc)_2$	0%
7	$PdBr_2$	11%	17	$Mn(OAc)_2$ (1 equiv) instead of [Pd]	0%
8	$Pd(OTFA)_2$	38%	18	$Mn(OAc)_3$•H_2O (1 equiv) instead of [Pd]	0%
9	toluene	8%	19	$Co(OAc)_2$ (10 mol%) + O_2, 6 h	78%
10	THF	47%	**20**	**$Co(OAc)_2$ (10 mol%) + O_2, 10 h**	**(97%)**

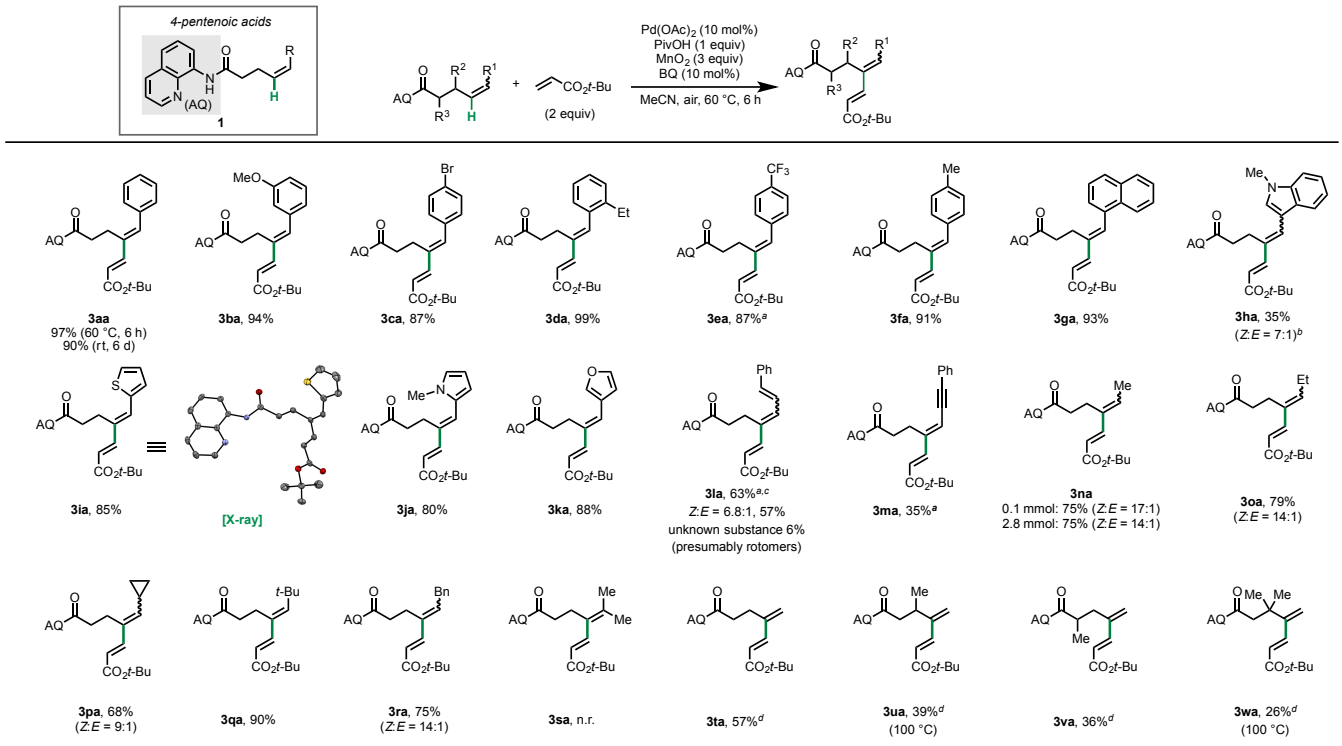
[a] ^1H NMR yield using CH_2Br_2 as internal standard. Isolated yields in parentheses. [b] 1:1 MeCN:toluene.

Table 2. Substrate scope (4-pentenoic acids)

2. Substrate scope. We examined the substrate scope with respect to 4-pentenoic acid structure, first using MnO_2 as the oxidant (Table 2).[16] Different substituents on the aryl ring were examined, and a variety of electron-donating and -withdrawing groups were found to be well tolerated (**3aa**–**3ka**). Additionally, steric bulk at the *ortho* position (**3da**) did not hamper the reaction. Electron-rich heterocycles were tolerated in the reaction (**3ha**–**3ka**). Furthermore, 1,3-diene and 1,3-enyne substrates reacted with exquisite site selectivity, offering expedient access to highly conjugated products **3la** and **3ma**. The reaction was highly sensitive to the *E*/*Z*-configuration of the alkene starting material as the corresponding *E*-phenyl substrate was unreactive, presumably due to steric repulsion in the C–H activation step (see SI). In addition to aryl groups on the alkene, *Z*-alkyl groups, such as methyl, ethyl, cyclopropyl, *tert*-butyl, and benzyl, provided moderate to high yields (**3na**–**3ra**). In some case *E*/*Z* isomerization was observed (**3na**–**3pa** and **3ra**) (*vide infra*).[17] A large-scale reaction was performed with 2.8 mmol of *Z*-methyl substrate **1n**, and the yield of **3na** was essentially identical to that of the small-scale trial, illustrating the preparative utility of this method. Introducing substituents on either of the methylene carbon atoms between the alkene and the carbonyl group led to attenuated reactivity, and these substrates required harsher conditions (**3ua**–**3wa**). Groups α to the carbonyl (**3va**) had a more significant effect in suppressing product formation compared to groups β to the carbonyl group (**3ua**).

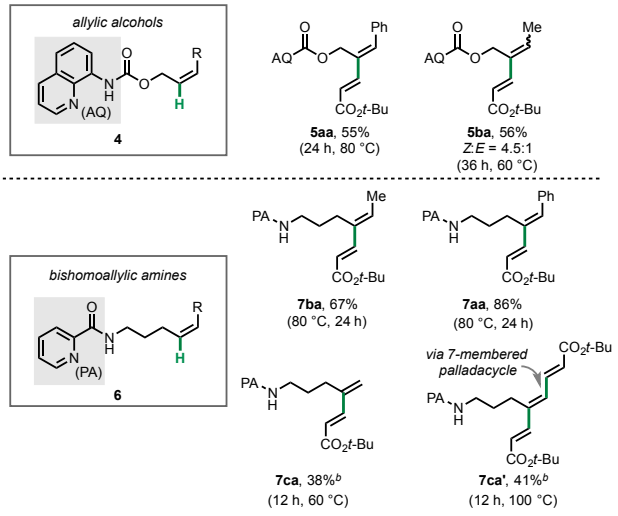
Apart from 4-pentenamide substrates, other substrate classes were also compatible with this reaction using different directing groups (Table 3). Allylic alcohols masked as their AQ-carbamates could be functionalized with this method (**5aa** and **5ba**). With bishomoallylic amine substrates (*i.e.*, 4-pentenamines), we found that Daugulis's picolinamide directing group[2,3] facilitated analogous C(alkenyl)–H olefination in moderate to good yields (**7aa**–**7ca**). Interestingly, the *endo* alkenyl C–H bond was activated at 60 °C (**7ca**) while the *exo* C–H bond (**7ca'**) could be subsequently activated at elevated temperature via a seven-membered palladacycle.

Next, we proceeded to test the scope of alkene coupling partners using **1a** as the model reactant (Table 4). Several different electron-deficient alkenes reacted in moderate to good yields (**3ab**–**3ah**). In particular, vinylsulfonylfluoride (**3ac**), which to our knowledge has not previously been used in C–H alkenylation, was successfully incorporated with high yield.[18] In the case of acrylonitrile (**2h**), the minor *Z*



[a] 12 h. [b] Z:E = 1:1 before purification and 7:1 after purification. [c] 6% of an unknown impurity. [d] 12 h, 20 mol% $Pd(OAc)_2$, MeCN:toluene 1:1

Table 3. Substrate scope (allylic alcohols bishomoallylic amines)[a]

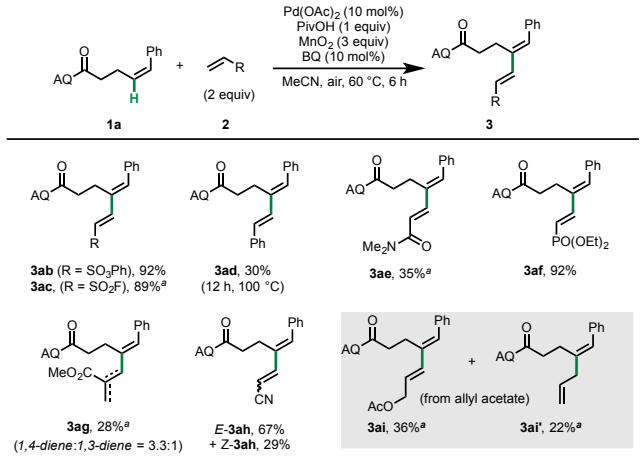


[a] Reaction conditions were as in Table1, entry 1 unless otherwise statated. [b] 20 mol% $Pd(OAc)_2$

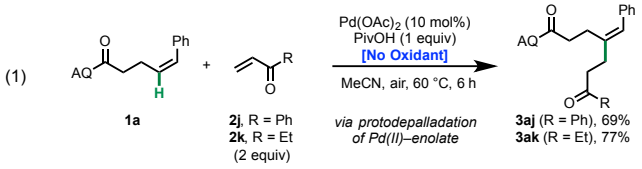
alkene isomer (*Z*-**3ai**) was also formed. When methyl methacrylate (**2g**) was employed in the reaction, the regioselectivity of β-hydride elimination was found to differ from the other examples, giving the non-conjugated 1,4-diene as the major product. Non-conjugated alkenes were generally ineffective; however, allyl acetate was an exception. Interestingly, in this case, β-H elimination (**3ai**) was found to be competitive with β-OAc elimination, which leads to allylation product (**3ai'**).

With vinyl ketones (**2j** and **2k**), a different reaction outcome was observed (eq. 1). In this case, a formal Michael-type 1,4-conjugate addition[19] took place (**3aj** and **3ak**), and the reactions did not require exogenous oxidant, consistent with being redox-neutral. We speculate that in this case the more strongly electron-withdrawing ketone leads to an *O*-bound palladium enolate, which is prone to protodepalladation under the reaction conditions (eq. 1).

Table 4. Coupling partner scope



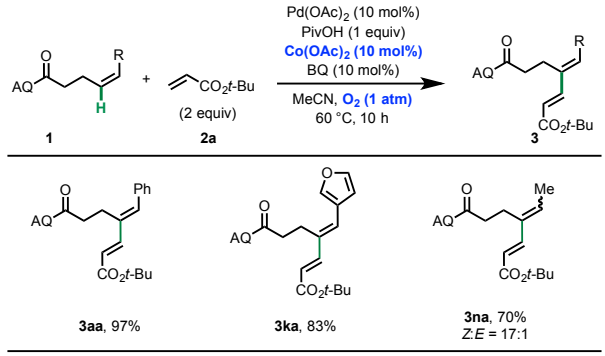
[a] 12 h



3. Aerobic redoxidation. The method above using stoichiometric MnO_2 as oxidant is straightforward and operationally convenient, as it does not require use of a compressed gas, special safety considerations, or dedicated equipment. Nevertheless, it has the disadvantage of generating stoichiometric manganese waste. Thus, in line with goals of sustainable synthesis, we also sought to probe the scope of the alternative reaction conditions using catalytic $Co(OAc)_2$ as an electron

transfer mediator under O_2 atmosphere (Scheme 2).[20] Three representative substrates (**1a, 1k** and **1n**) were tested and delivered the desired products in essentially identical yields to the stoichiometric MnO_2 conditions. In this case, the only stoichiometric waste generated during the course of the reaction is H_2O. These results demonstrate that either method can be used depending on the goals of the end-user.

Scheme 2. Aerobic reoxidation system



4. Tandem *E*/*Z* isomerization/C(alkenyl)–H alkenylation. As mentioned above, alkyl-substituted internal alkenes underwent isomerization under the reaction conditions prior to reacting (see SI). Though a detailed investigation of the mechanism of *E*/*Z*-isomerization in this case is outside of the scope of the present work, three possibilities based on previous studies[21–24] of this general phenomenon include (1) π-allylpalladium(II) formation, (2) nucleometalation/β-X elimination, and (3) π-Lewis acid activation to form a secondary carbocation that is susceptible to isomerization. Irrespective of the mechanism, we reasoned that this process could be harnessed to accomplish a productive reaction.[24] Because *E*-substituted alkenes are far less reactive, we considered whether we could potentially carry out an *in situ* *E*/*Z*-isomerization and selectively react the *Z*-isomer via C–H alkenylation (Scheme 3). This strategy would offer the possibility of carrying out dynamic kinetic resolution of *E*/*Z*-alkene mixtures. This reaction system requires that the palladium(II) catalyst perform two distinct tasks, *E*/*Z* isomerization and C(alkenyl)–H alkenylation with appropriate rates. Hence, we surmised that judicious selection of reaction conditions would be required. To test this idea, we selected *E*-**1n** as the model substrate and optimized reaction conditions (Table 5) to maximize yield and *Z*/*E* ratio. Different palladium catalysts were screened,[25] and $Pd(OAc)_2$ performed the best (entries 5–8). Temperature was found to influence the yield and stereoselectivity of this reaction (entries 2–4); the best selectivity was observed at room temperature, while the highest yield was obtained at 50 °C. The choice of carboxylic acid was also found to play an important role in controlling yield and selectivity. In contrast to aliphatic acids, certain aromatic carboxylic acids were more successful in promoting this isomerization. Neither electron-rich nor electron-poor aromatic carboxylic acids were compatible; however, naphthoic acid was found to be optimal. Under optimal conditions, **3na'** was obtained in 64% yield with 6.4 *Z*/*E* selectivity from pure *E*-**1n**. Control experiments (see SI) confirmed the presence of the *Z*-isomer of the starting material (*Z*-**1n**) under the reaction conditions and ruled out the alternative pathway whereby *E*-**1n** is first C–H functionalized to *E*-**3na'**, which is then selectively isomerized to *Z*-**3na** (which in this mechanism would be assumed to be the thermodynamically favored product).

Scheme 3. Proposed tandem E/Z/isomerization/C–H activation

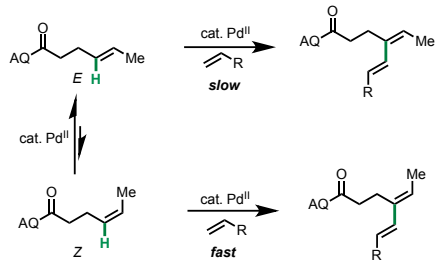
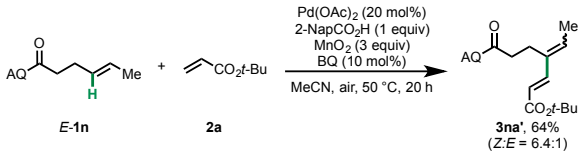
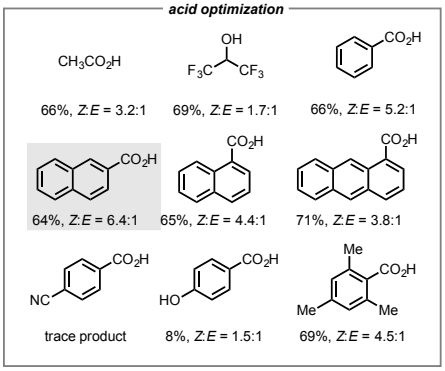


Table 5. Optimization of tandem *E*/*Z* isomerization/C(alkenyl)–H alkenylation

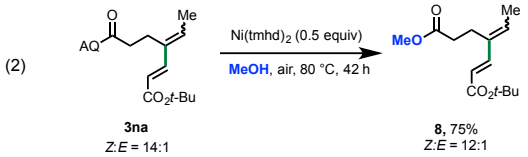


Entry	Variation from Standard Conditions	Yield[a]	*Z*:*E*[a]
1	**none**	**(64%)**	**6.4:1**
2[b]	room temperature	25%	4.5:1
3[b]	40 °C	59%	4.1:1
4[b]	50 °C	63%	4.0:1
5[c]	$PdCl_2$	9%	3.3:1
6[c]	$Pd(OTFA)_2$ (10 mol%)	20%	2.9:1
7[c]	$Pd(acac)_2$ (10 mol%)	30%	3.7:1
8[c]	White catalyst (10 mol%)	20%	2.0:1
9[d]	$Pd(OAc)_2$ (10 mol%)	51%	3.3:1



[a] ^1H NMR yield using CH_2Br_2 as internal standard. Isolated yields in parentheses. [b] PivOH, 16 h. [c] PivOH, 60 °C, 19 h. [d] PivOH, 60 °C, 6 h.

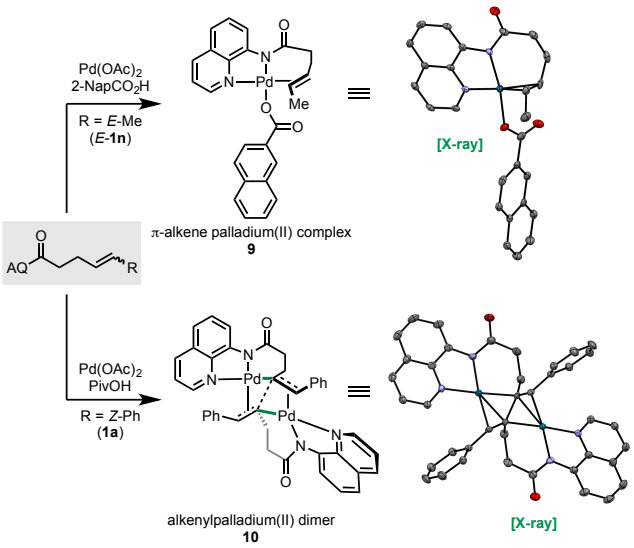
5. Directing group removal. The directing group could be conveniently removed under Ohshima's recently reported nickel-catalyzed methanolysis conditions,[26] providing 75% yield with only slight erosion of *Z*/*E* stereochemistry (eq. 2). This result further establishes the utility of this method in preparative synthetic chemistry.

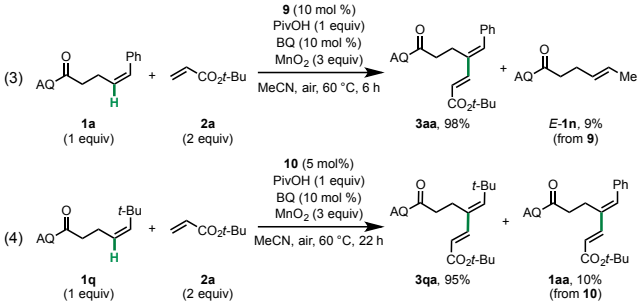


6. Mechanistic studies. The high levels of site selectivity for the γ-C(alkenyl)–H bond prompted us to investigate the reaction mechanism using a combination of different techniques. First, we prepared two organopalladium intermediates relevant to the catalytic cycle, π-alkene complex **9** and alkenylpalladium(II) dimer **10**, by combining stoichiometric quantities of $Pd(OAc)_2$ with two different alkenes and carboxylic acid additives. Complex **9** is a ring-expanded analog of previously reported structures.[1a,b] Complex **10** is a six-membered palladacycle as anticipated; however the dimeric structure is notable, as alkenylpalladium(II) dimer motif has not been

previously reported to the best of our knowledge.[27] Interestingly, the distance between the two alkenyl carbons of each monomers is only 1.55 Å, which is in the range of that of a typical C–C bond. Both **9** and **10** were found to be catalytically competent in the reaction (Scheme 4).

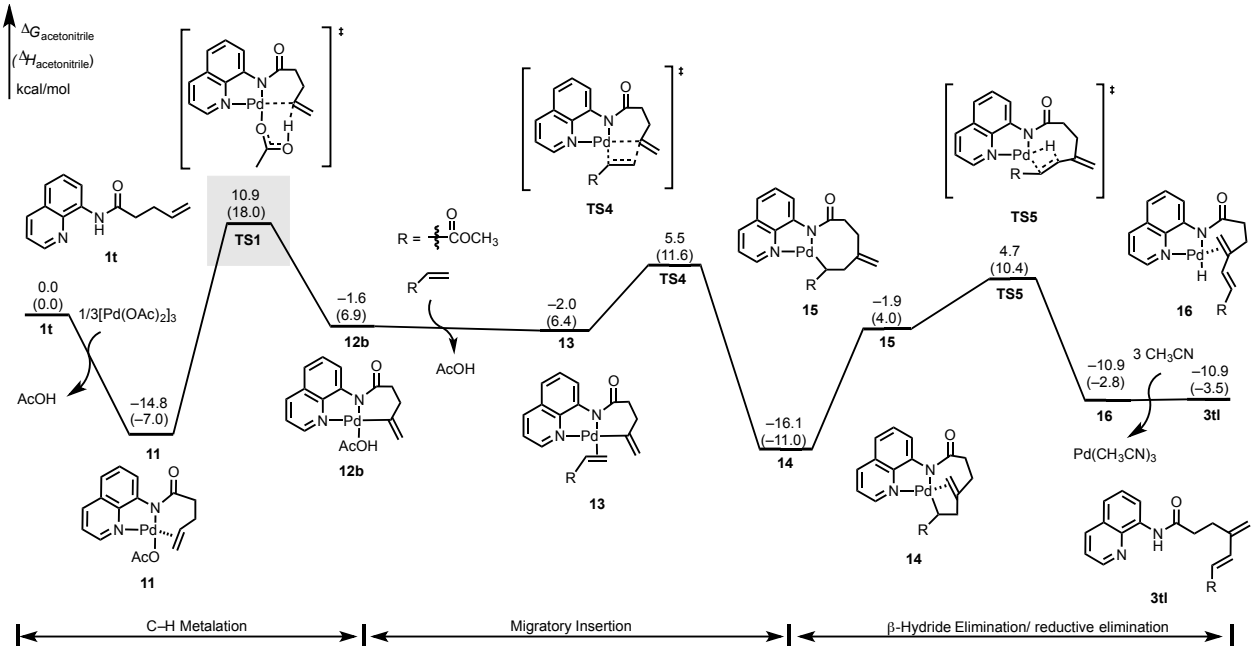
Scheme 4. Synthesis of organopalladium complexes 9 and 10.



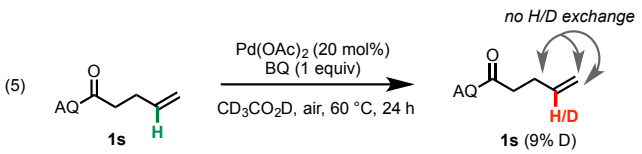


Complex **9** promotes the reaction with similar reactivity to that of $Pd(OAc)_2$ (eq. 3), suggesting rapid dissociation of alkene *E*-**1n** under the reaction conditions. Interestingly, in this case, isomerization of *E*-**1n** was not detected under the reaction conditions. Complex **10** was less reactive than $Pd(OAc)_2$ (eq. 4), requiring 22 h to reach completion, which suggests that **10** may not typically be formed under catalytic conditions where palladium(II) concentration is relatively low. Presumably, complex **10** first disaggregates, then the monomeric palladacycles react with the electron-poor alkene coupling partner to initiate the reaction, as both **1aa** and **3qa** were isolated from the crude reaction mixture.

Figure 1. Computed energy profile for the formation of 1,3-diene via the γ-C(alkenyl)–H activation of 4-pentenamide substrate



Next, to interrogate whether C–H activation was possible at other reaction sites, we performed an H/D exchange experiment (eq. 5). Terminal alkene substrate **1t** was subjected to the reaction conditions in the absence of the electron-poor alkene coupling partner using acetic acid-d_4. In the experiment, 9% deuterium substitution was observed at the γ-C(alkenyl)–H bond.

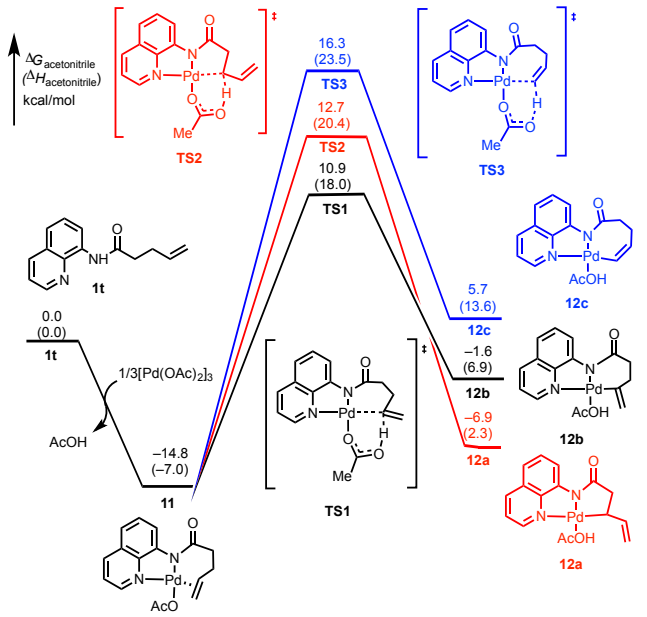


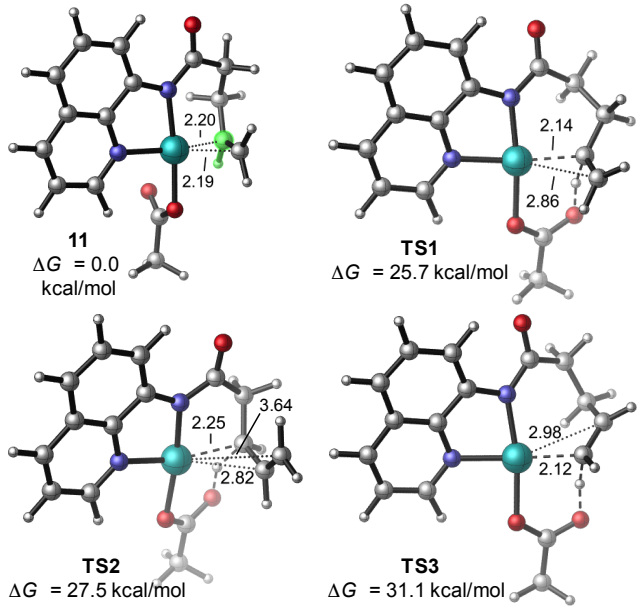
Deuterium incorporation could not be detected at the other positions. This result rules out a scenario in which other C–H activation pathways, such as five-membered C(allylic)–H cleavage to form the corresponding π-allyl,[28] are operative under the reaction conditions but lead to intermediates that are not competent in downstream steps.

7. Computational studies. Lastly, we performed density functional theory (DFT) calculations to further probe the reaction coordinate using **1t** as the model substrate (Figure 1). First, three possible C–H metalation pathways from π-alkene complex **11** were examined to reveal the origin of site-selectivity (Figure 2, see SI for details). The carboxylate-assisted concerted metalation-deprotonation (CMD)

Figure 2. Computed (A) energy profiles and (B) transition states for 5-, 6-, and 7-membered pathways for C–H metalation

A **B**



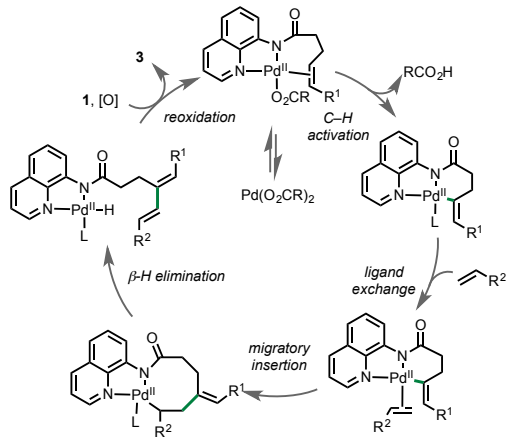


of the γ-C(alkenyl)–H (**TS1**) has an activation free energy of 25.7 kcal/mol, with respect to the π-alkene complex **11,** lower than those of the β-C(allylic) –H (**TS2**) and δ-C(alkenyl)–H (**TS3**) metalation pathways (27.5 and 31.1 kcal/mol, respectively[29]). This indicates the formation of the six-membered palladacycle is kinetically favored, consistent with the experimental selectivity for the γ-C(alkenyl)–H bond. The γ-C(alkenyl)–H metalation is promoted by the pre-organization of the π-alkene complex (**11**), which orients the highlighted γ-C(alkenyl)–H bond co-planar with the acetate and therefore decreases the distortion of the C–H bond in the CMD transition state (**TS1**).[30] In addition, **TS1** is stabilized by the stronger alkene coordination that maximizes the favorable d → π* interactions in the metalation transition state.[31]

The coordination of the electron-deficient alkene to the six-membered palladacycle followed by 2,1-migratory insertion and β-hydride elimination was modeled next using methyl acrylate (**2l**) as the coupling partner. The activation energies for the migratory insertion (**TS4**) and β-hydride elimination (**TS5**) steps are lower than that of **TS1**, indicating γ-C(alkenyl)–H metalation is the rate- and selectivity-determining step of the reaction.

A plausible catalytic cycle for this reaction is shown in Scheme 5. Following substrate coordination to give a π-alkene palladium complex (as in **11**), γ-C(alkenyl)–H activation takes

Scheme 5. Proposed catalytic cycle



place to generate the six-membered palladacycle (as in dimer **10**). Coordination of the electron-deficient alkene, followed by 2,1-migratory insertion, β-H elimination, and reoxidation of the catalyst then closes the cycle.

Conclusion

In conclusion, we have developed a catalytic method to synthesize 1,3-dienes via directed site-selective C(alkenyl)–H activation. A broad array of substrates and coupling partners are tolerated in this reaction. In order to meet the needs and preferences of potential end-users, two separate conditions for reoxidation of the palladium(II) catalyst have been demonstrated, using stoichiometric oxidant (MnO_2) or O_2 and catalytic $Co(OAc)_2$. At present, a drawback of the chemistry is the need for relatively high loading (10 mol%) of $Pd(OAc)_2$ that is needed to ensure high yield. Nevertheless, the transformation can be performed on gram scale, and the amide auxiliary can be conveniently removed. Through mechanistic studies, we have characterized key intermediates in the catalytic cycle and elucidated factors relevant to the key C(alkenyl)–H activation step. We anticipate that this method and the underlying mechanistic insights will stimulate interest in developing synthetically enabling C(alkenyl)–H activation methods to expand the alkene synthesis toolkit.

ASSOCIATED CONTENT

Supporting Information

Experiment details, spectral data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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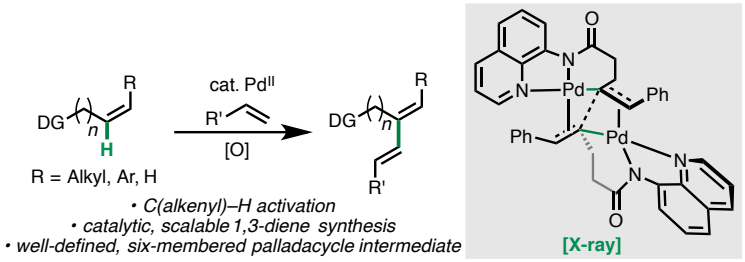
R
DG
n
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R = Alkyl, Ar, H
cat. Pd^II
R'
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DG
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R
R'
• C(alkenyl)–H activation
• catalytic, scalable 1,3-diene synthesis
• well-defined, six-membered palladacycle intermediate
O
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