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Dehydrative Allylation of Alkenyl sp^2 C−H Bonds

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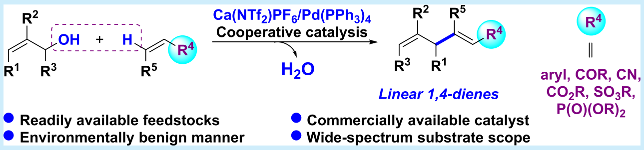
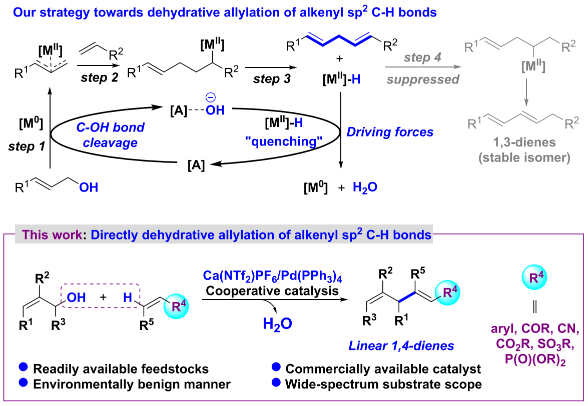
ABSTRACT: We designed a cooperative catalytic system by combining commercially available Ca(NTf$_2$)PF$_6$ and Pd(PPh$_3$)$_4$ to address the dehydrative allylation of alkenyl sp^2 C−H bonds in an environmentally benign manner. A novel C−OH bond cleavage method was found to be crucial for this practical protocol. A variety of alkenes and allylic alcohols equipped with wide-spectrum functional groups can be successfully incorporated into the desired cross-coupling, affording 1,4-dienes with moderate to excellent yields and high stereo- and regioselectivity.



Alkenyl sp^2 C−H bond functionalization with concomitant carbon−carbon bond formation is in great demand in the organic synthesis and pharmaceutical industry.[1] Particularly important achievements are palladium-catalyzed arylation/alkenylation of alkenes via Heck-reaction[2] or sp^2 C−H bond activation,[3] which has been extensively applied to synthetic communities.[2,3] In sharp contrast, the allylation of alkenes by delivering 1,4-dienes lags behind, although this structural motif has seen amplified interest from medicine as a result of its prevalence in biologically and pharmaceutically active molecules, such as ripostatin, piericidin, jerangolid, etc.[4] The present complications ascribed to olefins are unreactive nucleophile equivalents in the presence of allylic palladium intermediates but facilitate competitive di-/polymerization.[5] In the rarely successful case, alkenes have to be selected as the solvent.[6] Therefore, highly active allylic compounds and alkenylmetals[7] rather than alkenes have been considered the only suitable precursors for accessing 1,4-dienes. Although few carefully tailored Rh[8]/Ni[9]/Ir[10] catalytic systems, with the assistance of stoichiometric additives,[9] have been developed concerning styrene[8,10] or alkylalkenes,[9] the incorporation of functionalized alkenes, such as acrylates, into 1,4-dienes remains elusive. To circumvent formidable challenges, other impressive strategies, such as hydroalkenylation of 1,3-dienes[11] and hydroallylation of alkynes[1c],[12] have been documented for the construction of 1,4-dienes from alkenes or alkynes.

Taking sustainability and waste minimization into account, the direct dehydrative cross-coupling[13] of generally available alcohols with olefins is highly sought after and represents a much greener, atom- and step-economical approach for alkenyl sp^2 C−H bond functionalization. However, it is challenging to break the inherently strong C−O[14] and alkenyl sp^2 C−H bond.[3] In 2011, the elegant catalyst [(C$_6$H$_6$)(PCy$_3$)(CO)RuH]BF$_4$ was developed by Yi and co-workers for the coupling of simple alkenes with various alcohols.[15] However, 1,4-dienes are typically inaccessible in this catalytic circumstance. With the {Ir(cod)Cl}$_2$ catalyst, Carreira realized the impressive coupling of allylic alcohols with disubstituted alkenes to afford 1,5-dienes.[16] Reek and Bruin realized pioneering allylstyrene coupling to obtain (1,5-di)aryl-substituted 1,4-dienes[17] in moderate yield and selectivity. These investigations revealed that C−OH bond activation and selectivity (chemo-/stereoselectivity) alternation are significant challenges.[15−17] With our continuing interest in green chemistry,[18] we envisioned that the nature of the cocatalyst used to activate the C−OH bond is the key factor. The version which enables C−OH bond cleavage with the generation of allylic metals and hydroxide ions (rather than water) is crucial (Scheme 1, top, step 1). Theoretically, the alkene insertion (Scheme 1, top, step 2) and

Scheme 1. 1,4-Diene Skeletons and Dehydrative Allylation of Alkenyl sp^2 C−H Bond Strategy



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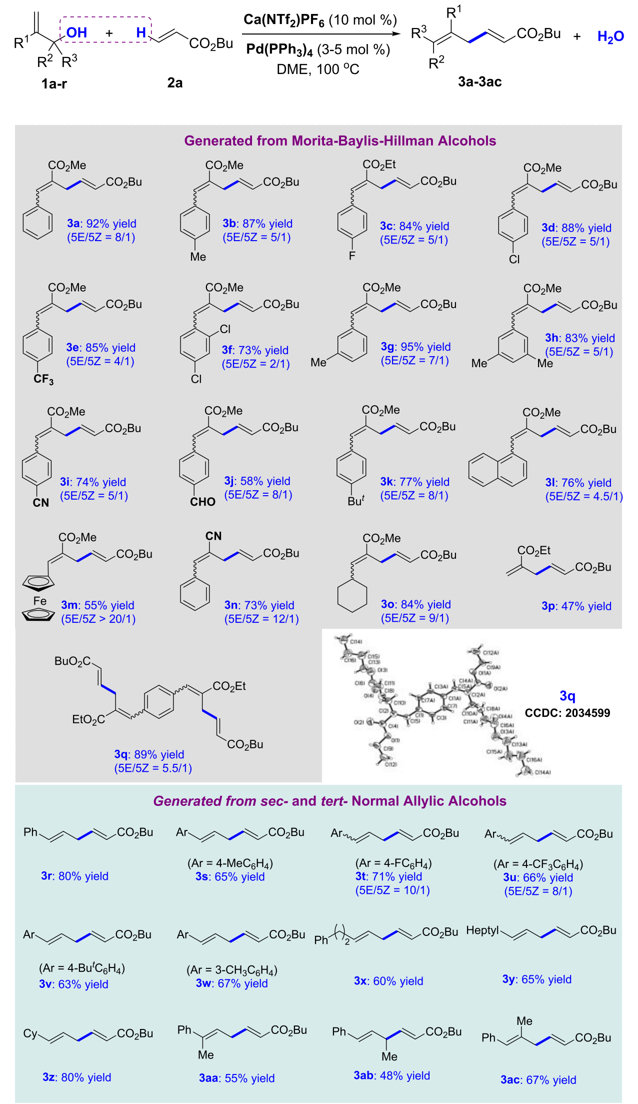
β-hydride elimination process (Scheme 1, top, step 3) will be favored by "quenching" the metal hydride with hydroxide ions. Meanwhile, the transition-metal-migration process (Scheme 1, top, step 4) can also be suppressed, thus enabling the delivery of 1,4-dienes as a major product (Scheme 1, top). Herein, we developed a $Ca(NTf_2)PF_6/Pd(PPh_3)_4$ cooperative catalytic system to efficiently address the obstacles for dehydrative allylation of alkenyl sp^2 C−H bonds (Scheme 1, bottom).

At the outset of our work, we began by evaluating the challenging dehydrative allyl−alkene coupling reaction of allylic alcohol **1a** (methyl 2-(hydroxy(phenyl)methyl)acrylate) with butyl acrylate **2a** under a palladium catalytic system. Notably, acrylates are the largest volume feedstock (over 2 million tons annual production)[11b] but have scarcely been incorporated into 1,4-dienes due to their homodimerization and thermodynamically favored isomerization process from 1,4-dienes to 1,3-dienes.[19] The utility of this reaction will be vastly enhanced if functionalized alkene acrylates can be used as suitable coupling partners. We have demonstrated that abundant alkaline-earth metals can affect the activation of C−OH bond.[20] Extensive investigations of reaction parameters indicated that the nature of alkaline-earth metals and their combination with palladium was crucial for this protocol (Supporting Information (SI) Table 1, entries 1−8). In this respect, the strong oxophilicity and Lewis acidity of $Ca(NTf_2)PF_6$ were identified as the best partners for palladium (SI Table 1, entries 3, 9−11). In all of the tested cases, $Pd(PPh_3)_4$ showed the best performance (SI Table 1, entries 3, 12−16), while Pd^{II} was ineffective for this transformation (SI Table 1, entries 13−16). For the solvent, DME (1,2-dimethoxyethane) gave a much more positive result than others, such as THF, 1,4-dioxane, CH_3CN, and DMF (SI Table 1, entries 17−23). Notably, neither palladium nor alkaline-earth metals themselves can promote ideal dehydrative cross-coupling (SI Table 1, entries 24−27). By combining $Pd(PPh_3)_4$ (3 mol %) with $Ca(NTf_2)PF_6$ (10 mol %) and DME (1,2-dimethoxyethane), the desired 1,4-diene **3a** was isolated in 92% yield (SI Table 1, entry 3). The reaction was sensitive to the temperature; decreasing the temperature resulting in a diminished yield (SI Table 1, entries 28 and 29). Upon decreasing the catalyst loading to $Pd(PPh_3)_4$ (1 mol %)/$Ca(NTf_2)PF_6$ (5 mol %), **3a** can also be obtained in 65% yield (SI Table 1, entries 30−32), which further proves the high efficiency of the catalyst system for this process.

Subsequently, the general reaction involving a variety of allylic alcohols was explored under the optimized conditions. As depicted in Scheme 2, *pri-*, *sec-*, and *tert*-allylic alcohols can be successfully incorporated into cross-coupling with butyl acrylate **2a**, affording the corresponding 1,4-dienes with linear selectivity. In the attempt to access multifunctionalized 1,4-dienes, Morita−Baylis−Hillman (MBH) alcohols were first selected to investigate the generality of this protocol. As expected, the electronic properties and position of the substituents on the phenyl ring have limited effects on the yield (**3a**−**3h**). To some extent, the stereoselectivity was sensitive to the electronic properties, and a phenyl ring bearing an electron-withdrawing group resulted in the desired product with lower *E*/*Z* selectivity (**3e**, **3f**). Multisubstituted aromatic allylic alcohols were also suitable substances for this reaction (**3f**, **3h**). It should be noted that the functional groups CN (**3i**) and CHO (**3j**) on the phenyl ring were well tolerated, albeit giving the corresponding 1,4-dienes in a slightly lower yield. Sterically demanding (**3k**) and fused aromatic allylic alcohols (**3l**) can also be successfully incorporated into this transformation. Ferrocenyl-substituted allylic alcohols were amendable to this protocol and afforded the corresponding **3m** in moderate yield. In addition to the MBH alcohols equipped with ester groups, the CN-substituted version was also tolerated for this reaction (**3n**). In addition, alkyl-substituted MBH alcohols can also serve as powerful substrates for this reaction (**3o**). 1-Butyl 6-methyl (*E*)-5-methylenehex-2-enedioate (**3p**) was also isolated in moderate yield when the MBH alcohols generated from ethyl acrylate and formaldehyde were employed. The double-dehydrative allyl−alkene coupling reaction was performed well by using ethyl 3-(4-(2-(ethoxycarbonyl)-1-hydroxyallyl)phenyl)-2-hydroxybut-3-enoate (**3q**). Moreover, the configuration of 1,4-diene **3q** was determined by X-ray analysis (for details, see the SI). In addition to the MBH alcohols, other α-substituted *sec-* and *tert-*

Scheme 2. Dehydrative Cross-Coupling between Allylic Alcohols and Butyl Acrylate[a]

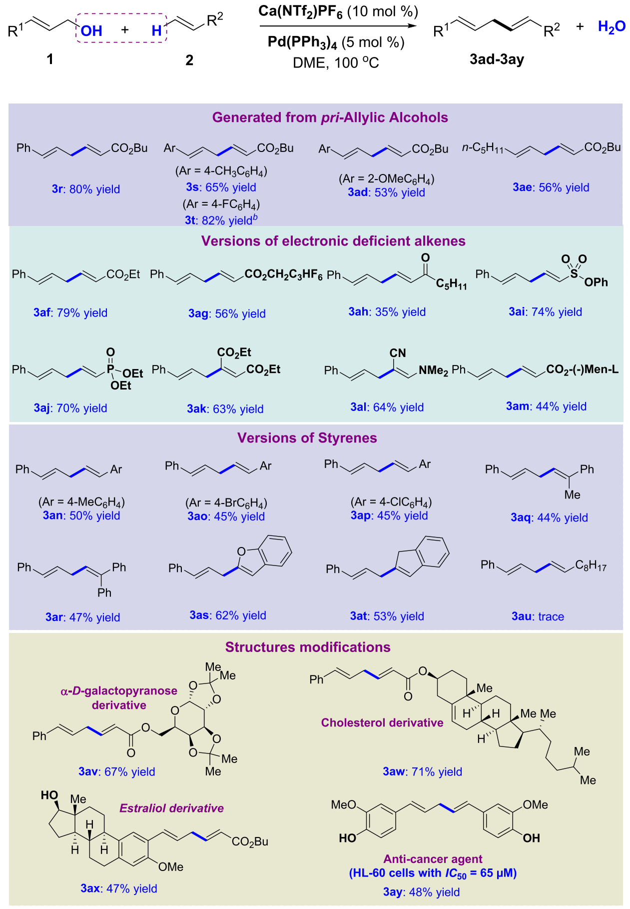


[a] Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), and catalyst $Pd(PPh_3)_4$ (3−5 mol %), $Ca(NTf_2)_2$ (10 mol %), KPF_6 (10 mol %) in 4.0 mL of solvent (DME) in argon atmosphere at 100 °C for 12 h. Isolated total yield. The ratio of (2*E*,5*E*)/(2*E*,5*Z*) isomer was determined by crude ^1H NMR. For **3a**−**3q**, $Pd(PPh_3)_4$ (3 mol %); for **3r**−**3ac**, $Pd(PPh_3)_4$ (5 mol %).

allylic alcohols were screened (**3r**−**3ac**). As expected, a variety of α-aromatic substituted allylic alcohols were found to be suitable coupling partners regardless of the electron-withdrawing or -donating group on the phenyl ring (**3s**−**3w**). Remarkably, either acyclic (**3x**, **3y**) or cyclic (**3z**) alkyl-substituted allylic alcohols were well tolerated, affording the corresponding 1,4-dienes in moderate to high yields. Even the *tert*-allylic alcohol 2-phenylbut-3-en-2-ol, which favored the competitive self-dehydration process with the generation of conjugated 1,3-dienes, can be successfully incorporated into the desired cross-coupling with butyl acrylate, efficiently producing **3aa**. With the attempt to access 3-substituted 1,4-diene skeletons, (*E*)-4-phenylbut-3-en-2-ol was then selected as the starting material. To our delight, the corresponding **3ab** was also successfully generated in moderate yield. Remarkably, the β-blocked allylic alcohol 2-methyl-1-phenylprop-2-en-1-ol was identified as a powerful precursor, affording **3ac** in 67% yield.

pri-Allylic alcohols were then explored under identical conditions. As shown in Schemes 2 and 3, only the linear selective products (**3r**−**3t**) were obtained with either 1-aryl-2-en-1-ol (Scheme 2) or cinnamyl alcohol derivatives (Scheme 3) when reacted with butyl acrylate. These results reveal that the same π-allylpalladium intermediates can be generated from these two kinds of isomeric allylic alcohols (**3r**−**3t**). In addition, sterically demanding cinnamyl alcohol derivatives can be successfully incorporated into this transformation, albeit affording **3ad** in a slightly lower yield. (*E*)-Oct-2-en-1-ol was also proven to be an amenable substrate for this protocol (**3ae**). As presented in Scheme 3, a variety of alkenes readily participate as coupling partners in this reaction with cinnamyl alcohol. In addition to the standard butyl acrylate **2a**, volatile ethyl acrylate (**3af**) and multifluoro-substituted butyl acrylate (**3ag**) also provided the respective corresponding products effectively. Even the highly active ketone carbonyl groups could be introduced into the corresponding 1,4-dienes when oct-1-en-3-one was selected as the initial substance (**3ah**). To our satisfaction, other electron-deficient alkenes, such as phenyl ethenesulfonate (**3ai**) and diethyl vinylphosphonate (**3aj**), were proven to be viable coupling partners for this reaction. In addition to terminal olefins, diethyl maleate (**3ak**) and (*E*)-3-(dimethylamino)acrylonitrile (**3al**) can also react with cinnamyl alcohol well, affording the corresponding 1,4-dienes in moderate to high yields. The L-(−)-methenyl group can be incorporated into multifunctionalized 1,4-dienes (**3am**). This newly developed catalytic protocol is not only suitable for electron-deficient alkenes but is also applicable to styrene derivatives (**3an**−**3ap**), regardless of the electron-withdrawing or electron-donating groups on the phenyl ring. α-Alkyl- (**3aq**) or aryl-substituted (**3ar**) styrenes smoothly completed the desired cross-coupling process. Pleasingly, benzofuran (**3as**) and 1*H*-indene (**3at**) were identified as practical substances involved in this dehydrative cross-coupling. Unfortunately, only a trace amount of the desired product was detected when simple olefins such as dec-1-ene (**3au**) were used as the coupling partner. Remarkably, the reaction also can perform well on gram scale affording **3r** in 1.43 g (73% yield), which has been proven as a powerful synthetic intermediate for multifunctionalized pyrrolidines.[21]

Scheme 3. Dehydrative Cross-Coupling between Primary Allylic Alcohols and Various Alkenes[a]

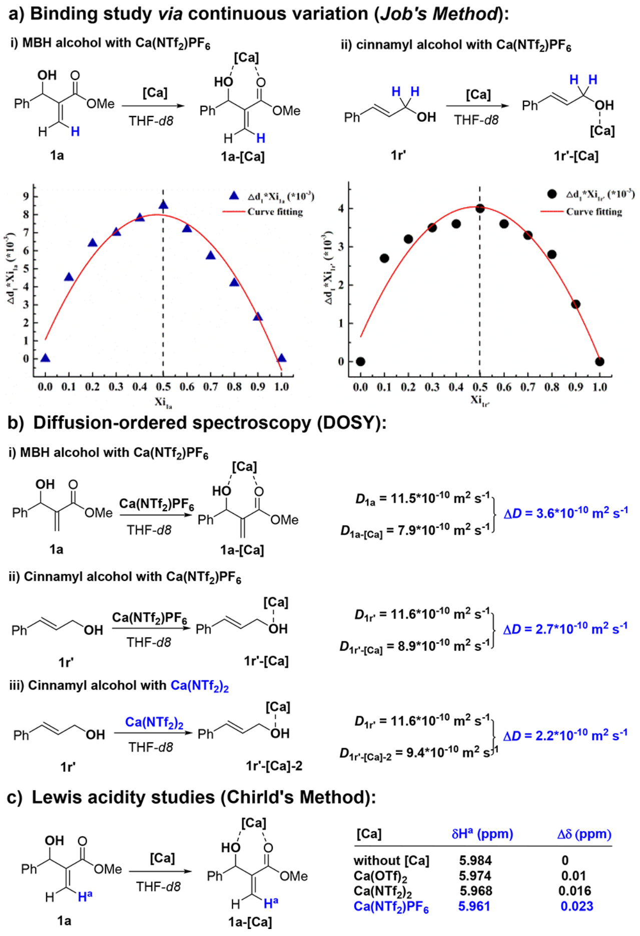


[a]Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), and Pd(PPh$_3$)$_4$ (5 mol %), Ca(NTf$_2$)$_2$ (10 mol %), KPF$_6$ (10 mol %) in 4.0 mL of solvent (DME) in argon atmosphere at 100 °C for 12 h. Isolated total yield. Only one isomer was detected. [b]Two isomers were detected (5*E*/5*Z* = 10/1).

Next, we examined the allyl−alkene coupling concerning several biologically active skeletons. The acrylates, bearing the motifs of α-D-galactopyranose or cholesterol, can be consumed smoothly, affording the corresponding **3av** and **3aw** in high yields. Even an estraliol moiety with an active hydroxyl group was also well tolerated (**3ax**). These results further highlight the utility of this method in pharmaceutical-related studies. Recently, 4,4′-((1*E*,4*E*)-penta-1,4-diene-1,5-diyl)bis(2-methoxyphenol) (**3ay**) was recently found to be highly potent against cancer and human promyelocytic leukemia (HL-60 cells with an IC$_{50}$ of 65 μM).[22] With our developed method, the desired **3ay** can be conveniently obtained in moderate yield, which is much better than the reported method (less than 10% yield[22]).

Having demonstrated the versatility of the resultant products, we attempted to gain insight into the key step of C−OH bond activation. We preliminarily studied the binding of allylic alcohols and Ca(NTf$_2$)PF$_6$ by using the method of continuous variation (Job's method), which revealed that a 1/1 stoichiometry for the Ca(NTf$_2$)PF$_6$/C−OH complex was formed, regardless of cinnamyl alcohol or MBH versions (Scheme 4a). Moreover, diffusion-ordered spectroscopy (DOSY) can also account for the formation of the aforementioned complex (Scheme 4b). For cinnamyl alcohol (D_a = 11.6 * 10^{-10} m^2 s^{-1}), the translational diffusion coefficient significantly decreased to D_a = 8.9 * 10^{-10} m^2 s^{-1}

Scheme 4. Investigations Concerning Calcium-Promoted C−OH Bond Cleavage



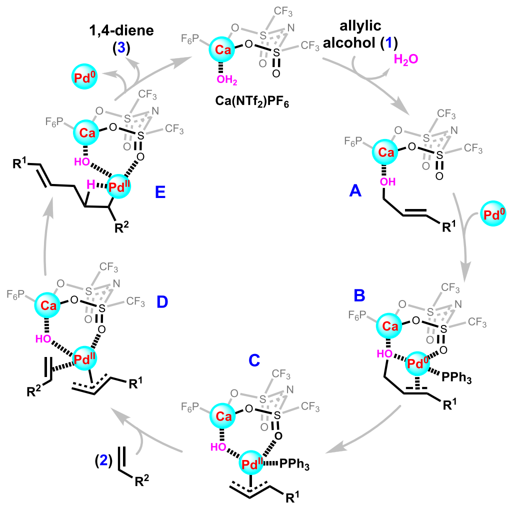
[Ca]	δH^a (ppm)	$\Delta\delta$ (ppm)
without [Ca]	5.984	0
$Ca(OTf)_2$	5.974	0.01
$Ca(NTf_2)_2$	5.968	0.016
$Ca(NTf_2)PF_6$	5.961	0.023

when stoichiometric amounts of $Ca(NTf_2)PF_6$ were introduced. Remarkably, $D_a = 9.4 * 10^{-10}$ m^2 s^{-1} was observed when $Ca(NTf_2)PF_6$ was replaced by $Ca(NTf_2)_2$. This result, to some extent, indicated the stronger coordinating effect of C-OH to $Ca(NTf_2)PF_6$ than $Ca(NTf_2)_2$, which is in line with the catalytic activity for C−OH bond activation (Scheme 4c). In the presence of $Ca(NTf_2)PF_6$, a sharper decrease in the translational diffusion coefficient was detected (from 11.5×10^{-10} m^2 s^{-1} to 7.9×10^{-10} m^2 s^{-1}) for MBH alcohol, probably because it contains other ester binding sites.

Control experiments were then conducted. No reaction occurred when $Ca(NTf_2)PF_6$ was replaced by traditional Bronsted acids ($HNTf_2$, TsOH, $PhCO_2H$, CPA), which further proved that calcium salts with suitable Lewis acidity are crucial for this transformation (SI, Scheme 1a). Upon treatment of butyl acrylate **2a** with isotopically labeled experiments, no H/D exchange was detected in the absence of allylic alcohols. Moreover, an intermolecular KIE for this allyl−alkene cross coupling was determined to be $k_H/k_D = 0.7$, which indicated that alkenyl sp^2 C−H bond cleavage was not involved in the rate-determining step for this cross-coupling protocol (SI, Scheme 1b). This result combined with the results (**3an**−**3au**) can be used to safely lead to the conclusion that this reaction was initiated with the generation of allylic palladium intermediates followed by Heck-like alkene insertion and β-hydride elimination processes.

Based upon this investigation, a reaction mechanism was proposed and is shown in Scheme 5. Initially, the interaction between calcium and hydroxyl groups realized C−OH bond activation (**A**), which was followed by the oxidative addition of palladium (**A**−**B**−**C**) to afford intermediate **C**. In this key step, the elimination of OH was from the face of palladium (**B**) through a neighborhood-participation-like process. This can be attributed to the coordination effect of electron-rich oxygen atoms (NTf_2) to palladium as well as the interaction between OH and palladium. The following oxidative addition of palladium to the C−OH bond was facilitated by $Ca(NTf_2)PF_6$ owing to the Ca−OH bond formation. Subsequently, the combination of intermediate **C** with alkenes through the interaction between palladium and double bonds delivered intermediate **D**. Then the Heck-like double-bond insertion process (**D**−**E**) and subsequent β-elimination process (**E**-**3**) afforded the desired 1,4-dienes with regeneration of the palladium catalyst and calcium salt.

Scheme 5. Proposed Allyl−Alkene Coupling Mechanism



In conclusion, we have developed an efficient $Ca(NTf_2)PF_6$/$Pd(PPh_3)_4$ catalytic system to address the allylation of alkenyl sp^2 C−H bonds with the largest volume of feedstock allylic alcohols and alkenes. This investigation revealed that $Ca(NTf_2)PF_6$ used to activate the C−OH bond is crucial for this protocol. With all commercially available and economical catalysts, dehydrative allyl−alkene coupling proceeded smoothly with water as the only byproduct. This reaction tolerated a broad range of alkenes and allylic alcohols, providing a conceptually new and practical protocol to give 1,4-dienes in moderate to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01309.

> Experimental procedures, screening reaction conditions, analytical data for all new compounds (**3a**−**3ay**), and NMR spectra for the products (PDF)

Accession Codes

CCDC 2034599 contains 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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