The enones as new alkenyl reagents via ligand promoted C–C bonds activation

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Complementary to C–H bond activation, C–C bond activation has emerged over the past few years as an increasingly powerful tool to access and modify complex molecules. Ketones, owing to their versatility and availability, provide a significant platform for C–C bond activating reactions. Herein, we reported a β-carbon elimination strategy for alkene(sp2)–C(O) bonds to realize the olefination of unstrained enones via a vinyl palladium species, which delivers a series of conjugated polyene compounds. The protocol features broad substrate scope, excellent functional group tolerance and can be extended to dba (dibenzylideneacetone) substrates for olefination, alkynylation, arylation and amination, which demonstrates the generality of the approach and affords two valuable products in one pot. Furthermore, the late-stage functionalization of natural products (β-ionone and acetyl cedrene) and synthesis of natural products (piperine, lignarenone, novenone) highlight the potential utility of the reaction.

Ketones, as an important structural motif, are abundant in drug molecules and functional materials, especially natural products in which both ketones (15.9%) and enones (6.0%) are found.[1] In recent years, transition-metal-catalyzed C–C bond activation, in addition to C–H bond activation, has received growing attention from chemists, and has become a powerful tool for the modification and construction of various molecules.[2] As one of the most privileged and versatile functional groups, ketones also provide an alternative platform for C–C bond activation to transform functional units and construct complex compounds.[3] With regard to the C–C bond activation of ketones, two strategies, including ring-strain release[4] and chelation assistance,[3] account for the vast majority of reactions in this area. Unstrained C–C bond activation of ketones however remains relatively undeveloped. Successful examples principally focus on the cleavage of alkyne(*sp*)–C(O),[5] alkane(sp^3)–C(O)[6] and arene(sp^2)–C(O)[7] bonds with the aid of directing group. Metal-catalyzed activation of alkene(sp^2)–C(O) bond, namely enones, has been reported few so far (Scheme 1a). Owing to their wide

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range of sources and easy accessibility, enones via C–C bond activation serving as alternative alkenyl source will provide an appealing practical avenue for the synthesis of alkene compounds.

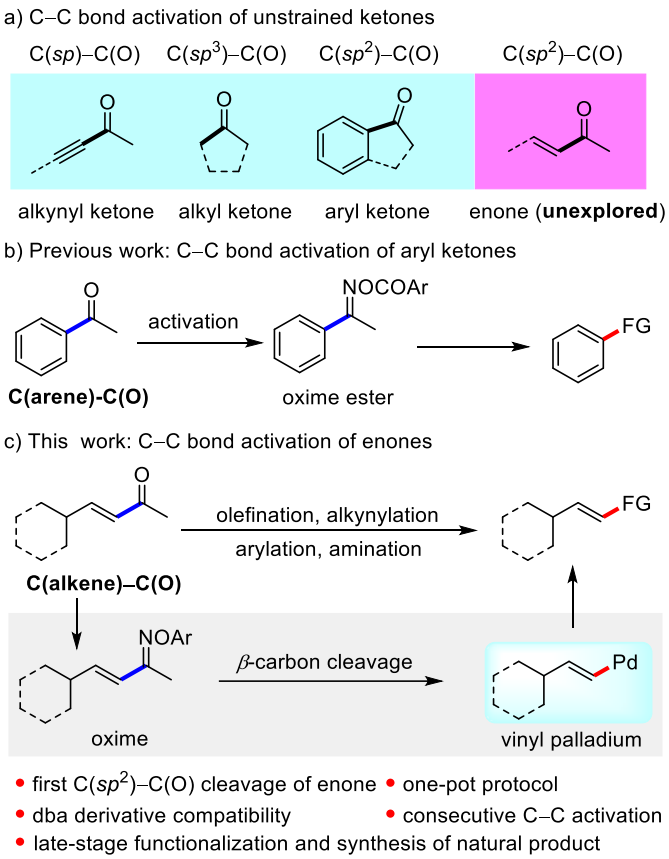
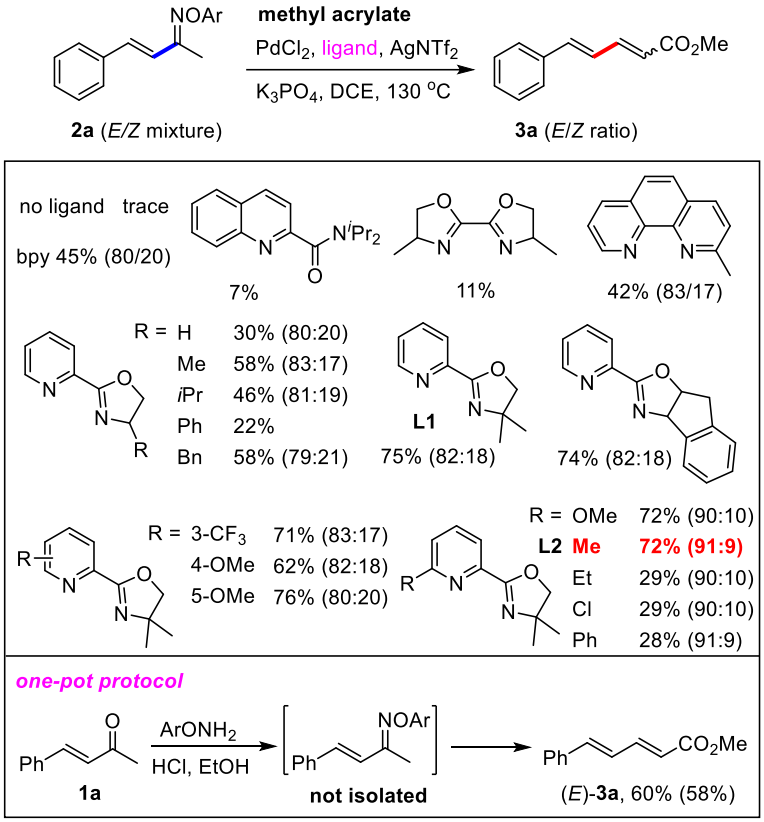


Fig. 1 | C–C bond activation of unstrained ketones. a, C–C bond activation of unstrained ketones. **b**, Previous research in the C–C bond activation of aryl ketones to access diverse transformation. **c**, Present work: C–C bond activation of unstrained enones.

Conjugated alkenes are versatile organic synthetic building blocks[8] and are found in a wealth of bioactive molecules and natural products.[9] In addition to the conventional synthetic methods of carbonyl olefination[10] and cross-coupling reactions,[11] C–H bond activation[12] has gained significant interest in recent years. The olefination of enones via C–C bond activation will also provide a new approach for the synthesis of 1,3-dienes. Pioneered by Narasaka's early work,[13a,13b] oximes have been studied widely as nitrogen electrophiles via metal oxidative addition into N–O bonds.[13] In the previous research, we realized C–C bond cleavage of oxime esters derived from common unstrained aryl ketones through the same initial step followed by *β*-carbon elimination to generate aryl palladium species (Fig. 1b).[14] As our enduring interest and effort on C–C activation of ketones, we have developed the cleavage of alkene(sp^2)–C(O) bonds. Herein, we report the deacetylative olefination of enones via a vinyl palladium intermediate produced by the *β*-carbon

elimination of oximes, delivering a series of conjugated polyene compounds. The potential applications of this methodology for the late-stage functionalization and synthesis of natural products have been demonstrated (Fig. 1c).

Table 1. | Screening of ligands



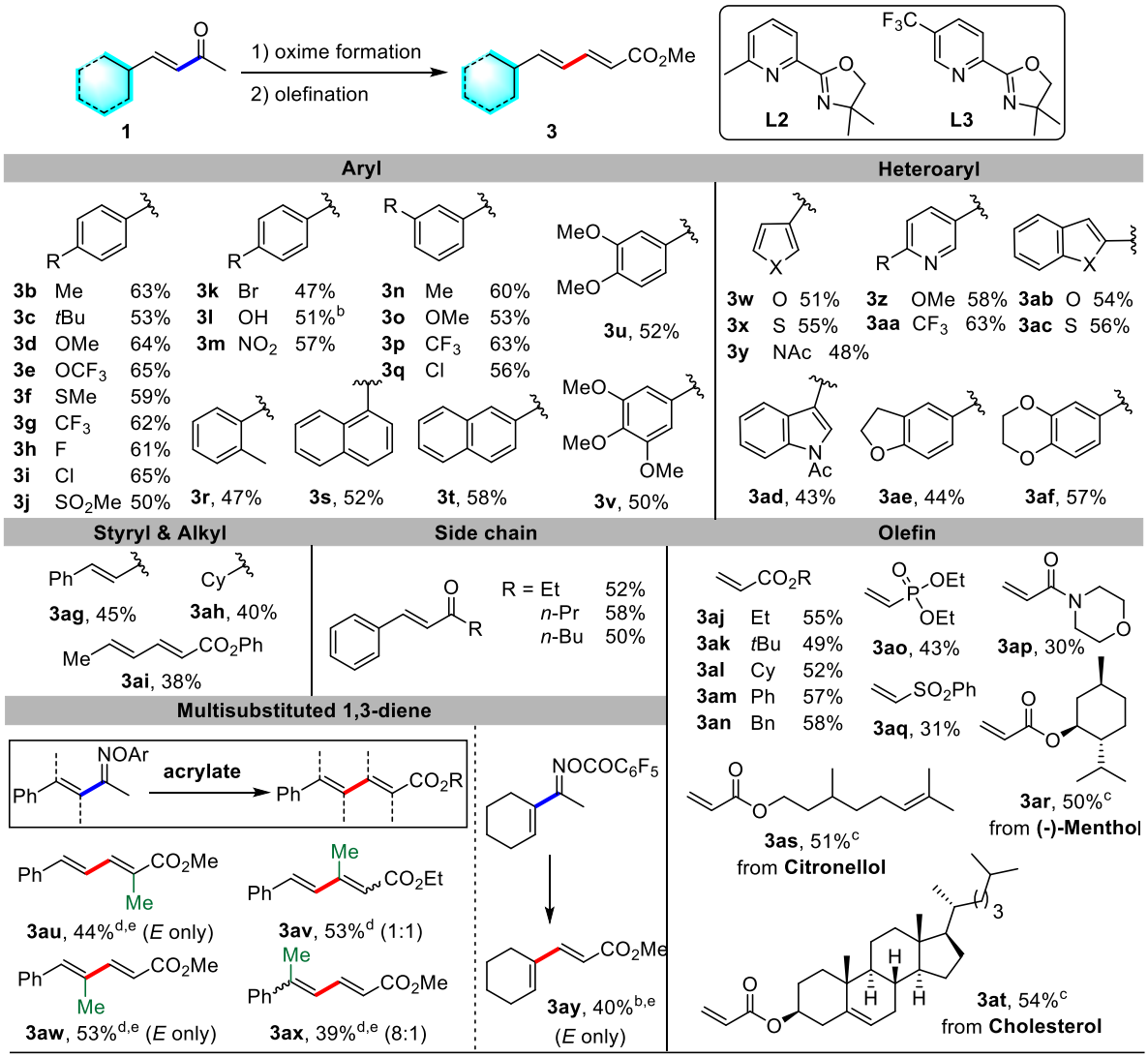
Conditions: **2a** (0.1 mmol), methyl acrylate (0.2 mmol), 10 mol% $PdCl_2$, 20 mol% ligand, 20 mol% $AgNTf_2$, K_3PO_4 (0.1 mmol), DCE (3 mL), 130 °C, N_2, 12 h. ^1H NMR yields of *Z/E* isomers. Isolated yield of (*E*)-**3a** in the parentheses. Ar = 2,4-di-NO_2-C_6H_3. bpy, 2,2'-bipyridine.

Results and discussion

Initial investigations were carried out using **2a** and methyl acrylate as model substrates in the presence of 10 mol% $PdCl_2$, 20 mol% ligand, 20 mol% $AgNTf_2$, 1.0 equivalent K_3PO_4, in 3 mL DCE, and conducting the reaction at 130 °C. Based on our previous research,[14] reaction optimization was focused on the screening of the N, N-bidentate ligands (Table 1). As expected, pyridine-oxazoline outperformed bipyridine, pyridine-amide, bioxazoline and phenanthroline ligands in the reaction. The use of ligand **L1** bearing a di-Me substituted oxazoline gave the desired product in 75% yield and 82:18 *E*/*Z* selectivity. In order to optimize reaction stereoselectivity, we investigated the influence of the substituents effect on the pyridine ring. We were pleased to find that 6-substituted ligands provide good *E*/*Z* selectivity, with 6-Me substituted pyridine-oxazoline **L2** affording the best result (72% yield, 91:9 *E*/*Z* ratio). To further improve

the practicality of the reaction, a one-pot reaction was conducted using the enone as a direct starting material; the desired product was obtained in good yield (58% isolated yield for *E*-**3a**).

Table 2. | Olefination scope[a]



[a]Standard conditions: 1) **1** (0.1 mmol), $ArONH_2$ (0.1 mmol), catalytic amount of HCl in 2 mL EtOH, stirred for a special time, then solvent removed; 2) olefin (0.2 mmol), 10 mol% $PdCl_2$, 20 mol% **L2**, 20 mol% $AgNTf_2$, K_3PO_4 (0.1 mmol), DCE (3 mL), 130 °C, N_2, 12 h. Isolated yields. In all case, *E/Z* ratios were around 91:9. Ar = 2,4-di-NO_2-C_6H_3. [b]Performed with $Pd(TFA)_2$. [c]1.2 equiv acrylate. [d]Performed with 15 mol% $Pd(TFA)_2$. [e]Performed with **L3**.

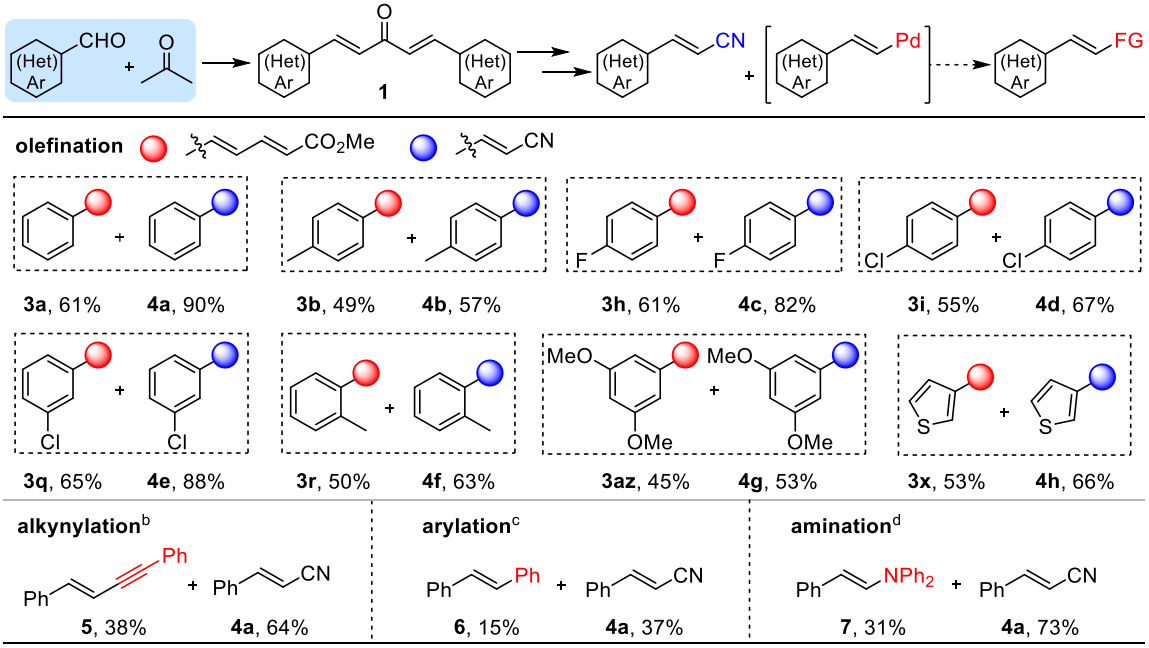
With the optimal condition in hand, we next evaluated olefination scope. As shown in Table 2, the reaction featured broad substrate scope and excellent functional group tolerance. A series of *para*-substituted aryl substrates containing electron-donating or electron-withdrawing groups proceeded smoothly to give corresponding products in good yields(**3b-3j**). Even sensitive substituents, such as Br, OH and NO_2 were compatible with the reaction system and

afforded products with moderate yields (**3k-3m**). Substrates bearing a *meta*-substituted group also worked well (**3n-3q**), and so did *ortho*-substituted enones (**3r**). Aryl substrates with naphthalene, disubstituent, trisubstituent can be converted to the corresponding dienes in good yields (**3s-3v**). A variety of heteroaryl substrates incorporating oxygen, nitrogen, sulfur atom, such as furan, thiophene, pyrrole, pyridine, benzofuran, benzothiophene, indole, dihydrobenzofuran and benzodioxane were also tolerated and gave satisfactory yields (**3w-3af**). A conjugated styryl compound was lengthened successfully to deliver the triene product by using styryl substrate with 45% yield (**3ag**). In addition to (Het)aryl, alkyl substrates including Cy and Me were also amenable to the reaction and gave their corresponding product in 40% and 38% yields, respectively (**3ah**, **3ai**). Different side chains on the enones, such as Et, *n*-Pr and *n*-Bu had a negligible effect on the reactivity. Furthermore, we continued to test the scope of active olefins. Various acrylates with Et, *t*-Bu, Cy, Ph and Bn worked well and provided good yields (**3aj**-**3an**). Other olefins bearing amide, phosphate and sulfone groups were all amenable to the reaction, though the diverse array of products were obtained in lower yields (**3ao**-**3aq**). Using acrylate derived from (-)-menthol, citronellol and cholesterol, we can conveniently modify natural products with satisfactory yields (**3ar**-**3at**). We next explored more challenging substrates bearing multisubstituent in olefinic bond, it turned out the reaction went beyond the synthesis of normal disubstituted 1,3-dienes, and can be extended to trisubstituted products. Utilizing an α-Me substituted acrylate, the product can be obtained in 44% yield (**3au**). Use of an internal acrylate possessing β-Me resulted in lower stereoselectivity and furnished the desired product in 53% yield with a 1:1 *Z*/*E* ratio (**3av**). A γ-Me diene was prepared in 53% yield using an α-Me substituted enone (**3aw**). A β-Me substituted enone could also react albeit with diminished yield (**3ax**), likely due to the steric hindrance of the Me group hindering β-carbon elimination. An oxime ester substrate with a cyclic olefinic bond was also tolerated and gave the product **3ay** in 40% yield.

With the hypothesis that use of a dienone substrate obtained from the condensation of an aldehyde and acetone could capture a byproduct-nitrile and deliver two value-added products in one pot, we explored the reaction of an oxime from dba and successfully obtained both diene and cinnamonitrile products, versatile intermediates in the synthesis of various fine chemicals[39] (Table 3). Aryl substrates with Me, halogen, OMe, and heteroaryl groups were all tolerated and

gave the desired dienes and nitriles in good yields. In addition to olefination, alkynylation, arylation and amination were also achieved via transformation of vinyl palladium intermediate to deliver corresponding products albeit low yields, which demonstrated the generality of our protocol. The fact that nitriles are obtained in higher yields compared with functionalized products indicates that *β*-carbon elimination can occur smoothly and that partial decomposition of the subsequent vinyl palladium intermediate leads to low conversion. It is noteworthy that stereospecific (*E*)-cinnamonitrile derivatives are obtained and no (*Z*)-isomers are detected in the reaction.

Table 3. | Functionalization of dba derivatives[a]



[a]Standard conditions: oxime (0.1 mmol), methyl acrylate (0.2 mmol), 10 mol% $PdCl_2$, 20 mol% **L2**, 20 mol% $AgNTf_2$, K_3PO_4 (0.1 mmol), DCE (3 mL), 130 °C, N_2, 12 h. In all case, *E/Z* ratios of **3** were around 91:9. [b]Oxime, trimethyl(phenylethynyl)silane, $PdCl_2(MeCN)_2$, ligand, $NaBAr_F$, K_2CO_3, DCE/butyronitrile, 140 °C, N_2. [c]Potassium phenyltrifluoroborate, $Pd(OTf)_2(MeCN)_4$, ligand, $AgNTf_2$, K_3PO_4, DCE, 100 °C, N_2. [d]Ph_2NH, $Pd(OTf)_2(MeCN)_4$, ligand, $AgNTf_2$, K_2CO_3, DCE, 130 °C, N_2. Isolated yields for final step. See supporting information for detailed experiments.

In the mechanistic investigation, a radical pathway was excluded because the addition of butylated hydroxytoluene (BHT) had no effect on the reaction and the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) only resulted in a drop in yield, which may be because the TEMPO with strong oxidation competed with substrate oximes[16] (Fig. 2a). The double bond geometry of oxime **2a** was also investigated, showing that (*Z*/*E*)-isomers had the same stereoselectivity, but the latter outperformed the former with regards to reactivity. This can be explained by the stronger coordination of

the double bond of the (*Z*)-isomer with the palladium, hindering the initial oxidative addition of the oxime to the palladium (Scheme 2b). We further examined an oxime substrate derived from chalcone which incorporates both alkenyl(sp^2)–C(O) and Ar(sp^2)–C(O) groups, and obtained four products with some selectivity at the same time (Fig. 2c). It turns out the C–C bond cleavage of enone (site a) is prior to aryl ketone (site b), perhaps owing to bulkier steric hindrance of the Ph group. The use of ligand **L2** with a 6-substituent on the pyridine ring can partly improve the regioselectivity and stereoselectivity, and favor C–C bond activation of the alkene(sp^2)–C(O) group. A gram-scale experiment proceeded smoothly to produce **3a** in 54% yield, showing the practicality of our protocol (Fig. 2d).

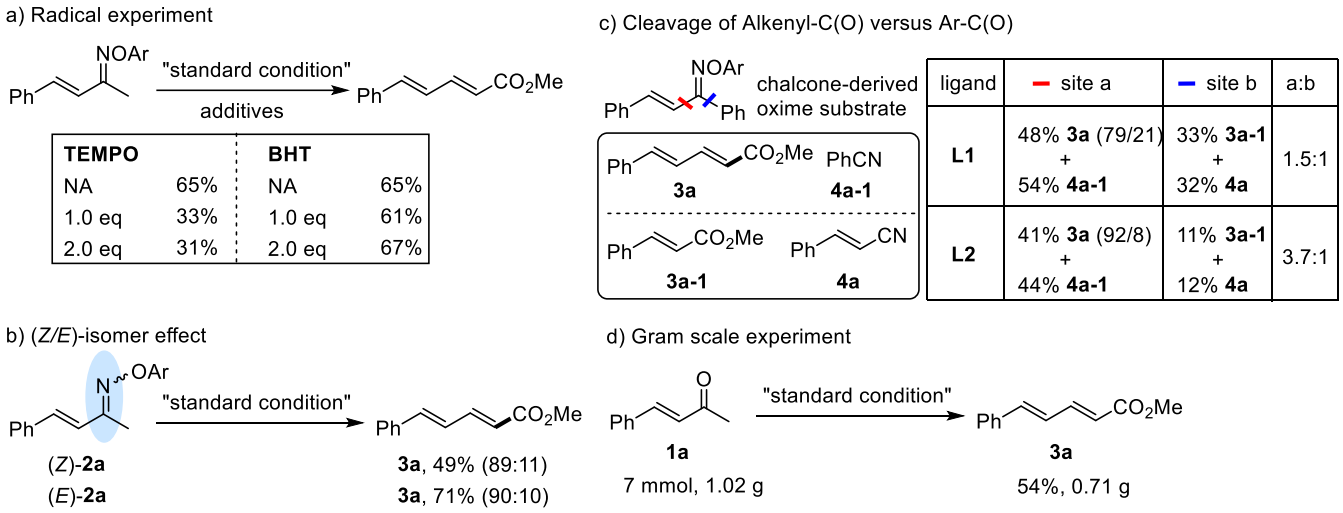


Fig. 2 | Mechanistic investigation and gram scale experiment. a, Radical experiment to exclude proposed radical pathway. **b**, Stereostructure of substrate has considerable effect on reactivity. **c**, Investigation on the priority of cleavage of enone and aryl ketone. **d**, Gram scale synthesis for **3a**.

To highlight the synthetic utility of our approach, we employed it in the rapid late-stage modification and synthesis of a number of natural products (Fig. 3). Terpenes bearing a carbonyl motif, such as *β*-ionone and acetyl cedrene can undergo easy olefination to give the corresponding 1,3-diene derivatives. Piperine, an alkaloid with diverse bioactivities,[17] was obtained via Witting reaction[18] followed by olefination from commercially available aldehyde **8** in 34% overall yield for two steps. Using acrolein as an active olefin, phenyl-containing dienal **10** was synthesized in 40% yield; a subsequent Witting reaction[19] afforded lignarenone B,[20] an alarm pheromone isolated from Mediterranean mollusk *Scaphander lignarius*. Successive deacetylative olefinations were also achieved successfully by using methyl

vinyl ketone (MVK) in the reaction, furnishing navenone B,[21] which possesses a tetraenone moiety and is another alarm pheromone found in opisthobranch *Navanax inermis*. The yields are acceptable at every step. These examples clearly demonstrate the potential of our methodology for diversification and synthesis of natural products.

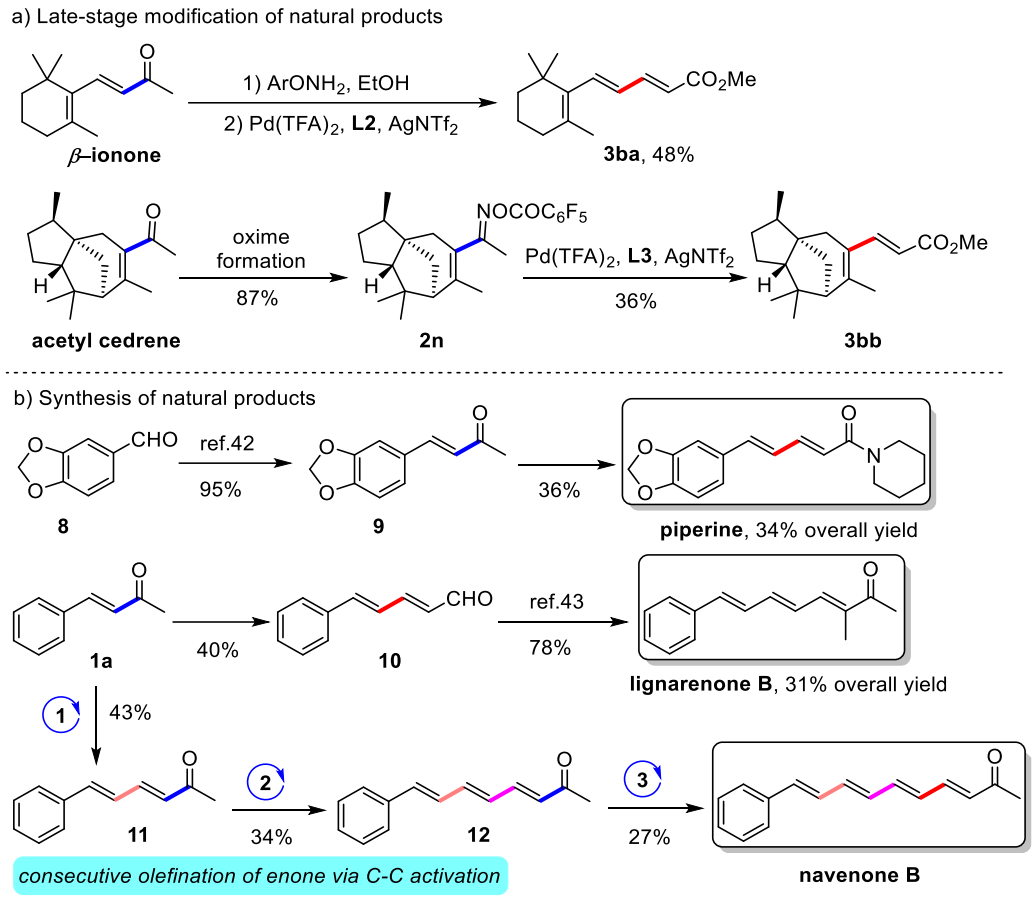


Fig. 3 | Synthetic application. a, Late-stage modification of *β*-ionone and acetyl cedrene. **b**, Synthesis of piperine, lignarenone B and navenone B. See supporting information for detailed experiments.

Conclusion

In summary, we have developed an unstrained C–C bond activation strategy of alkenyl(sp^2)–C(O) bonds for olefination of enones via a vinyl palladium species generated from the ligand-promoted *β*-carbon elimination of oxime. The methodology is suitable for a broad range of substrates, shows excellent functional group compatibility and can be conducted one-pot operation. The reaction delivers a series of conjugated polyene compounds and can be extended to dba substrates for olefination, alkynylation, arylation and amination allowing for the generation of two value-added

products in one-pot procedure. The late-stage modification and concise synthesis of a number of natural products further highlights potential application of the methodology.

Methods

General Procedure for Olefination. Enone **1** (0.1 mmol), *O*-(2,4-dinitrophenyl)hydroxylamine (0.1 mmol), hydrochloric acid in EtOH (2 mL) were added to a 15 mL sealed vials and stirred for 12 h at room temperature. After completion, solvent was removed to give oxime. To the oxime were added olefin (0.2 mmol), $PdCl_2$ (1.8 mg, 10 mol%), **L2** (3.8 mg, 20 mol%), $AgNTf_2$ (7.8 mg, 20 mol%), K_3PO_4 (21.2 mg, 1.0 eq), DCE (3 mL), and the mixture was stirred at 130 ºC for 12 h. The mixture was filtered through Celite, and evaporated to remove solvent under reduced pressure. The residue was subjected to column chromatography for isolation (gradient eluent: hexane/ethyl acetate) to give product **3**. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information Files.

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Competing interests The authors declare no competing interests.

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