Great efforts have been made in the activation of a C(alkenyl)-H bond vicinal to the directing group to proceed via five- or six-membered endo-metalloccycles. In stark contrast, functionalization of a C(alkenyl)-H bond geminal to the directing group via exo-metalloccycle pathway continued to be elusive. Here we report the selective transformation of an olefinic C-H bond that is geminal to the directing group bearing valuable hydroxyl, carbamate or amide into a C-C bond, which proceeds through four- to eight-membered exo-palladacycles. Compared to the reported mechanisms proceeding only through six-membered exo-palladacycles via N,N-bidentate chelation, our weak and O-monodentate chelation-assisted C (alkenyl)-H activations tolerate longer or shorter distances between the olefinic C-H bonds and the coordinating groups, allowing for the functionalizations of many olefinic C-H bonds in alkenyl alcohols, carbamates and amides. The synthetic applicability has been demonstrated by the preparative scale and late-stage C-H functionalization of steroid and ricinoleate derivatives.
Active C-H functionalizations prepared via cyclometallations and ortho olefination through radical addition to alkenes and following single-electron transfer (SET) oxidation/elimination. However, the site- and stereo-selectivity of C(alkenyl)-H activations due to the addition-elimination mechanisms. Actually, controlling the site- and stereo-selectivity of C(alkenyl)-H cleavage still remains a formidable challenge due to very subtle differences in terms of bond strength and electronic properties.

Pioneered Murai’s work on Ru-catalyzed carbonyl-directed ortho-C-H activation, broadly defined directing groups (DGs) have served as highly effective tools for converting C–H bond activations via cyclometallations. Most of the directed aromatic and aliphatic C–H activations proceeded through a normal five- or six-membered cyclometallated intermediate, however, there are very limited reports on protocols by distinct cyclometallations. The Yu group previously disclosed a Pd(II)-catalyzed aromatic C–H functionalizations directed by distal weakly coordinating functional groups via six- or seven-membered cyclopalladation. The same group also reported a nitrile-based template directed meta-selective C–H alkenylation, proceeding by a macrocyclic pre-transition state. Functionalization of para C–H bonds was addressed as well using the similar template-based strategy by the Mori group. Chelation-assisted strategy was also widely used in aliphatic C–H activations. The Gaunt group reported a palladium-catalyzed C–H bond activation through a four-membered cyclopalladation pathway, leading to the selective synthesis of heterocycles. Sanford and coworkers described a nitrogen-directed transannular C(alkyl)-H activation of aliphatic amines. Very recently, the Yu group disclosed an aliphatic γ-C–H arylation protocol to be proceeded by conventionally disfavored six-membered cyclopalladation, using a strained directing group derived from pyruvic acid. Considering the number of novel reactions that have arisen from metalacycle intermediates, identification of distinct cyclometallation pathways would lead to novel C–H bond transformations.

Remarkable efforts have been made in the vicinal group-directed olefinic C–H bond functionalization such as alkenylation, alkynylation, alkylation, and others. However, their applicability can be severely curtailed by vicinal selectivity displayed through the only 5- or 6-membered endo-metallocycles, and by the biased electronic and steric properties of the alkene substrates (Fig. 1a). Moreover, the cyclometallation
A concept has been remarkably expanded to positional selective C-H bond activation in arenes and alkanes, but its utilization in site-selective C(alkenyl)-H bond functionalization still remains elusive. Formation of exo-metallocycle is rare in catalytic reactions and is often less competitive when forming an endo-metallocycle, presumably due to added conformational degrees of freedom and increased energy. Dong and co-workers demonstrated an exo-directing-group-enabled functionalization of sp3 C-H bonds via five-membered exo-palladacycles to provide 1,2-diols. Recently, Engle's group reported a carboxylic acid-enabled C(alkenyl)-H functionalization via a characterized six-membered palladacycle, using strong N,N-bidentate auxiliary which was removable under nickel-catalyzed methanolysis conditions. Carreira and co-workers also demonstrated an alkenyl C-H iodination via six-membered alkenyl palladacycle intermediate, using picolinamide as the bidentate-chelation directing group (Fig. 1c). However, the major limitation is that the exquisite selectivity is strictly restricted to the cleavage of the C(alkenyl)-H bond that will result in six-membered exo-cyclopalladation. Moreover, the installation and removal of strongly coordinating directing group may impede the widespread application of these transformations.

Hydroxyl, carbamate and amide are valuable and widely occurring functionalities which have been used in C-H functionalization, and we envisioned that these weak and monodentate directing group could also enable the distal geminal C(alkenyl)-H activation by monodentate-chelation protocol. Comparing to thermodynamically more stable and bicyclic palladacycles by N,N-bidentate chelation, monodentate-chelation protocol may functionalize widespread geminal carbon centers that are one or more bonds further away from functional groups.

### Table 1 Development of gem-group-directed olefinic C-H alkenylation

| entry | FG | R1 | R2 | n | conditions | yield (%) | metallocycle |
|-------|----|----|----|---|------------|-----------|-------------|
| 1     | FG^1 | Pr | H  | 0 | A          | 30 (3va)  | 4           |
| 2     | FG^1 | Et | H  | 1 | A          | 69 (3aa)  | 5           |
| 3     | FG^1 | pentyl | H | 2 | A          | 15 (3za)  | 6           |
| 4     | FG^1 | Et | H  | 3 | A          | <5        | 7           |
| 5     | FG^1 | Me | Me | 1 | A          | <5        | 5           |
| 6     | FG^1 | H  | Et | 1 | A          | 5         | 5           |
| 7     | FG^1 | H  | H  | 1 | A          | <5        | 5           |
| 8     | FG^2 | Pr | H  | 0 | B          | 56 (5aa)  | 6           |
| 9     | FG^2 | Et | H  | 1 | B          | <5        | 7           |
| 10    | FG^2 | Me | Me | 0 | B          | 0         | 6           |
| 11    | FG^2 | H  | H  | 0 | B          | 0         | 6           |
| 12    | FG^2 | Pr | H  | 0 | B          | 0         | 6           |
| 13    | FG^3 | pentyl | H | 1 | C          | 74 (7aa)  | 6           |
| 14    | FG^4 | pentyl | H | 1 | C          | 60 (7ha)  | 6           |
| 15    | FG^4 | pentyl | H | 0 | C          | 40 (7qa)  | 5           |
| 16    | FG^4 | Et | H  | 2 | C          | 37 (7ra)  | 7           |
| 17    | FG^4 | Et | H  | 3 | C          | 18 (7ta)  | 8           |
| 18    | FG^4 | Me | Me | 1 | C          | 0         | 6           |
| 19    | FG^4 | H  | H  | 1 | C          | 0         | 6           |
| 20    | FG^4 | H  | Me | 1 | C          | 0         | 6           |
| 21    | FG^5 | Et | H  | 0.1 | A,B,C | 0         | 0           |
| 22    | FG^6 | Et | H  | 0.1 | A,B,C | <5        | 5           |
| 23    | FG^7 | Pr | H  | 0.1 | A,B,C | 0         | 0           |
| 24    | FG^8 | Pr | H  | 0.1 | A,B,C | 0         | 0           |
| 25    | FG^9 | pentyl | H | 0.1 | A,B,C | 0         | 0           |
| 26    | FG^10 | pentyl | H | 0.1 | A,B,C | 0         | 0           |

*The yields are isolated yields

The sizes of exo-metallocycles
by the formation of small- to medium-sized \textit{mono}-cyclic metalloccycle intermediate, which are transient but less strained. While the formation of four-membered metalloccycle is highly challenging, seven- and eight-membered cyclometallation are also much less favored in general as the aliphatic carbon between the alkenyl motif and the coordinating group rotates freely and increases the entropic barrier significantly.\textsuperscript{9,14} In line with our ongoing interest in olefinic C–H activation\textsuperscript{19,34}, herein, we focus on \textit{gem}-olefinic C–H activation via four- to eight-membered \textit{exo}-cyclometallation, and the utility is characterized by the C–H functionalization of a wide range of functionalized alkenes, including synthetically valuable homoallyl-, bishomoallyl- and allyl alcohols/carbamates/amides that constitute integral structural motifs in natural products and drug design (Fig. 1d, e).

**Results**

**Development of \textit{gem}-group-directed alkenyl C–H alkenylation.**

As the alcohol can be naturally incorporated into the product without installation and removal steps in C–H functionalization, we started investigation by employing previously reported Ru-, Rh- or Pd-catalyzed systems for hydroxyl-chelation-assisted C–H alkenylation reactions.\textsuperscript{42–44} Unfortunately, (\textit{E})-3-hexen-1-ol with acrylate led to trace alkenylated/alkylation product and/or poor regioselectivity under a variety of catalytic conditions. In this context, we envisioned that (\textit{Z})-alkenyl alcohol could be suitable due to the following two inherent effects. First, incorporation of R^1 group would make target olefinic C–H bond more reactive (Fig. 1b) due to increased nucleophilicity toward transition metal and block or obviate competitive vicinal C–H activation sites. Second, absence of R^2 group would avoid steric repulsion and facilitate subsequent insertion step. Although various of ligands were inefficient, \textit{mono}-N-protected amino acid (MPAA) combined with palladium was found to promote the alkenylation reaction,\textsuperscript{45,46} with Ac-Phe-OH emerging as the best one (see Supplementary Table 1). Fine-tuning the chain length between the hydroxyl and olefinic carbon greatly influenced such C–H functionalization. While the reactions of (\textit{Z})-3-hexen-1-ol (1a) (5-\textit{exo}) reacted smoothly with acrylate to provide diene 3 in 69% and the utility is characterized by the C–H functionalization of a wide range of functionalized alkenes, including synthetically valuable homoallyl-, bishomoallyl- and allyl alcohols/carbamates/amides that constitute integral structural motifs in natural products and drug design (Fig. 1d, e).

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yield, cis-2-hexen-1-ol (4-exo) and cis-4-decen-1-ol (6-exo) led to desired products in only 30% and 15% yields respectively (Table 1, entries 1–3). However, cis-5-octen-1-ol (7-exo) failed to react (Table 1, entry 4). Reactions of differently substituted alkenyl alcohols were performed to investigate the steric and electronic influences on geminal C-H activation. Unfortunately, (E)-3-hexen-1-ol and 4-methyl-3-penten-1-ol led to trace product due to the difficulty in formation of exo-palladacycle and/or alkenylation by steric repulsion (Table 1, entries 5 and 6). Meanwhile, terminal alkenyl alcohol showed very limited reactivity presumably due to the decreased nucleophilicity of C-H bond toward transition metal (Table 1, entry 7). Carbamate derived from (Z)-allylic alcohol also led to satisfactory results with the help of Ac-Ile-OH ligand instead via 6-membered exo-palladacycle (Table 1, entry 8). However, homoallyl carbamate did not react (7-exo) (Table 1, entry 9). Similarly, other differently substituted alkenyl carbamate exhibited no reactivity toward acrylate due to disfavored steric and/or electronic influences (Table 1, entries 10–12). Although acrylamides were commonly used in alkenyl C-H functionalization, there is still no report on C_{sp2}-H transformation of nonconjugated alkenyl amides. Herein, amide was successfully demonstrated to be effective in geminal C-H functionalization. Both secondary and tertiary amides provided corresponding geminal products in good yields, which proceeded by 6-membered palladacycles (Table 1, entries 13 and 14). Notably, this protocol also allowed palladium catalyst to functionalize alkenes bearing longer or shorter chain lengths between the amide and olefinic carbon, which proceeded by 5- and even 7-membered palladacycles, albeit with moderate yields (Table 1, entries 15 and 16). Interestingly, a weak coordinating of amide to form 8-membered palladacycle was also observed, albeit with most of the amide substrate recovered (Table 1, entry 17). Moreover, steric and electronic influences on geminal C-H activation were consistent with the reactions of alcohols and carbamates (Table 1, entries 18–20). All of these results showed a precise recognition of distance and geometry in these alkyl C-H functionalizations. Other alcohol-derived functional groups (FGs), such as ester (FG5), ether (FG8), urea (FG7), acetonitrile oxide (FG6) and amides with acidic N-H bonds (FG9 and FG10), were also tested, but none of them could furnish desired C-H functionalization (Table 1, entries 21–26).

**Substrate scope.** With the optimized reaction conditions in hand, we firstly examined the scope and limitation of alkenes 2 by employing alcohol 1a as the substrate (Table 2). It was found that a wide variety of acrylates 2 could provide the alkenylated products in 39–81% yields (3aa–3ai). Remarkably, vinyl ketones were also suitable coupling partners (3aj and 3ak). Moreover, both vinyl phosphonate and styrene were reacted smoothly, affording products 3al and 3am in 75% and 54% yields, respectively. Even acrylamides reacted well, though amides are usually prone to coordination (3an and 3ao). Thereafter, we turned our attention to expand the scope of the reaction to other representative homoallylic alcohols 1. Alcohols bearing longer alkylic chain also reacted well (3ba and 3ca). Introducing of alkylic group at the allylic position showed moderate yield (3da). The versatile catalytic system was not limited to primary alcohols. Indeed, we were pleased to identify easily oxidized secondary alcohols as viable substrates in this protocol likewise. Incorporation of alkyl, aryl and even alkenyl groups at the carbon adjacent to hydroxyl group showed good results (3ea–3sa). In particular, aryl ring bearing substituents such as F and Cl can be well tolerated in this protocol (3na and 3oa), which is synthetically useful for further elaborations of the products. Unfortunately, alkenyl alcohol bearing sensitive para-Br led to decreased yield due to undesired side reactions (3qa). Interestingly, easily decomposed tertiary alcohol also reacted, but leading to cyclization products 3A (33%) and 3A′ (17%) due to restricted conformational freedom and bond angle compression. Herein, the Z-configuration of product 3A′ implied the involvement of the anti-alkoxypalladation process in the cyclization. Moreover, 4-phenyl-3-buten-1-ol converted well (3ua). Cyclic alcohol such as 2-cyclohexene-1-methanol also reacted, albeit with reduced efficiency (3ta).

Notably, simple allylic alcohols, widely used as alkylation reagent, are seldom C-H functionalized due to competitive...
Moreover, reduced efficacy of the help of Ac-Gly-OH ligand instead (Table 3). Various acrylates could be served as coupling partners (5aa-5ah). Different dialkyl carbamates were examined to optimize the C–H activation, and installation of bulky isopropyl group led to alkenylated product in 62% yield (5da-5fa). Carbamate derived from secondary alcohol also converted without any decrease in efficiency (5ga).

C–H cleavage sites and easy decomposition under catalytic conditions. Meanwhile, four-membered metallocycle is very rare in catalytic reactions14, whose utilization in olefinic C–H activation has not been reported17–33. To our satisfaction, (Z)-allyl alcohols could be alkenylated in moderate yields, using N-acetyl-L-isoleucine (Ac-Ile-OH) as the ligand (3va,3ya). Moreover, cis-4-decen-1-ol was proved to be reactive, albeit with reduced efficiency (3za). The synthetic flexibility afforded by allyl- and bishomoallyl alcohols greatly expands the range of core structures that can subsequently be accessed.

The carbamate was usually employed as both a DG and an alcohol surrogate in C–H activation. Herein, allylic alcohol masked as its carbamate could be well C–H functionalized with the help of Ac-Gly-OH ligand instead (Table 3). Various acrylates

**Table 4 Olefinic C–H alkenylation of alkenyl amides**

| n = 0, 1, 2, 3 | R1 | R2 | R3 | R4 | R5 |
|---------------|----|----|----|----|----|
| 6-membered exo-palladacycle | R = Bu, 7aa, 74% | R = Me, 7ab, 70% | R = Et, 7ac, 64% | R = tBu, 7ad, 72% | R = Ph, 7ae, 61% |
| 5-membered exo-palladacycle | R = Bu, 7ba, 67% | R = Me, 7bb, 60% | R = Et, 7bc, 58% | R = tBu, 7bd, 63% |
| 7-membered exo-palladacycle | R = Bu, 7ca, 64% | R = Me, 7cb, 62% | R = Et, 7cc, 49% | R = tBu, 7cd, 51% | R = Ph, 7ce, 40% |
| 8-membered exo-palladacycle | R = Bu, 7da, 41% | R = Me, 7db, 51% | R = Et, 7dc, 43% | R = tBu, 7dd, 63% |

*a The yields are isolated yields based on amide 6.*
Next, we focused on substrate scope of alkyl amide directed geminal C(alkenyl)-H functionalization by 5- to 8-membered palladacycles (Table 4). The C-H alkenylation proceeded smoothly with various olefinic coupling partners such as acrylates, vinyl ketone and even styrene, providing 43–74% yields (7aa-7ah). Differently N-substituted secondary amides also reacted well with acrylates (7ba-7ea). Although primary amide led to trace product, tertiary amides led to good yields (7fa and 7ia). Incorporation of alkyl and benzyl groups at the carbon adjacent to amide group showed good results (7ja, 7ka and 7la). Differently N-substituted alkenyl amides 6m-6q also led to moderate yields proceeded by 5-membered exo-palladacycles. Notably, although alkenyl 6r exhibited decreased reactivity due to the difficulty in the formation of 7-membered exo-palladacycle, incorporation of methyl group greatly facilitate the C-H alkenylation (7sa, 60% yield). Interestingly, amide 6t bearing longer alkyl chain still showed limited reactivity toward acrylate (7ta).

**Competition experiments and mechanistic considerations.**

Next, competition experiments were performed for acrylate 2a and alcohols 1 or amides 6 under optimal conditions to rank the relative reactivities, thus demonstrating the preferential formation of the related alkyl metallocycle intermediates (see Fig. 2 and Supplementary Tables 4-5).

On the basis of the data compiled from intermolecular competition experiments, the relative reactivities of alcohols 1a, 1v, 8 and 1z’ were ranked to be 1a > 8 > 1v > 1z’ (Fig. 2a, trend under Cond. A). These results exhibited that alkyl C-H activation by 5-membered exo-palladacycle (1a) occurred preferentially over 4-membered exo-palladacycle (1v), and the C-H activation by 6-membered exo-palladacycle (1z’) was the most disfavored because the added freely rotating sp² carbon center significantly increases the entropic barrier for assembling the desired transition state, thus consistent with our observation in substrate scoping (Table 2). Notably, vicinal C=C=H functionalization by 5-membered endo-palladacycle (8) was also efficient under Cond. A. However, formation of 5-endo-metallacycle was found to be more competitive than the formation of 5-exo-metallacycle (1a > 8). An alcohol 9 bearing two alkenyl moieties was synthesized and reacted under Cond. A, and the C-H alkenylation only occurred on Z-alkenyl moiety to provide product 9a (Fig. 2b). Both of the inter- and intra-molecular competition experiments showed the preferential formation of 5-exo-palladacycle over 5-endo-palladacycle, being inconsistent with previous reports. Similarly, while 4-methyl-4-pentenamide exhibited limited reactivity (14% yield) and poor selectivity under conditions C, 7ra was obtained in 37% yield, suggesting the preferential formation of exo-palladacycle. Also, competition studies were performed for acrylate 2a with amide 6h, 6q, 6r or 6t under conditions C, and the relative reactivities of amides were ranked to be 6h > 6q > 6r > 6t. These results were generally consistent with prior substrate scoping (Table 4) and the kinetically and thermodynamically favored exo-cyclopalladation dominating the geminal C=C=H activation (Fig. 2a, trend under Cond. C). Notably, both substrates 1z’ and 6h converted by the formation of 6-membered exo-palladacycles, but alkenyl amide 6h reacted efficiently because the carbonyl group reduced conformational degrees of freedom. Moreover, while amide 6r did react via 7-exo-cyclopalladation, homoallyl carbamate did not convert even at elevated temperatures (Table 1, entry 9), exhibiting the great influence of coordinating effect. All of these primary results exhibited that the exo- and endo-cyclopalladations were governed by coordination strength and conformation effects on the C-H activation step, and the detailed mechanistic studies will be discussed in a later report. Deuterium incorporation experiments supported the irreversibility of the C-H activation steps, and no Z/E isomerization excluded other possible mechanistic pathway such as π-allylpalladium(II) formation or nucleometalation/β-X elimination. These results combined with kinetic isotope effect (KIE) experiments exhibited that the irreversible C-H bond cleavage step originated the site selectivity, thus possible mechanisms based on exo-palladacycles are proposed (see Supplementary Figs. 1–4).51

**Preparative scale synthesis and coordinating group removal.**

To establish scalability, the conversion of 1a was run at a gram scale to give 3aa in 71% yield (Fig. 3a). Olefinic C-H alkenylation of 4j at a preparative scale was also successful. The removal of the carbamate in 5ja was readily accomplished by reduction at room temperature to give diol 11 in 73% yield (Fig. 3b). Moreover, geminal C-H olefination of alkenyl amides reacted smoothly at gram-scale, providing 7aa and 7ha in good yields. Notably, amide
Fig. 3 Gram-scale synthesis and directing group removal. a Gram-scale synthesis of compound 3aa. b Gram-scale synthesis of compound 5ja and carbamate removal. c Gram-scale synthesis of compound 7aa/7ha and amide removal.

Fig. 4 Late-stage C–H functionalization of natural and pharmaceutical compounds. a Olefinic C–H modifications including natural products and drug derivatives. b Olefinic C–H alkenylation of methyl 1-testosterone derivative. c Selective conversion of inseparable Z/E alkenyl amides.
removal was realized by simple hydrolysis, yielding dienoic acid 12 in good yield (Fig. 3c).

**Late-stage C-H functionalization.** To further demonstrate the utility of our methods, we attempted late-stage C-H functionalization of natural and medicinal compounds (Fig. 4). Gratifyingly, these protocols were characterized by high chemoselectivity, highlighting the successful conversion of sensitive geraniol and (±)-dehydroabietylamine as well as the cholesteryl derivatives (3ap, 3aq, 3ar and 5pj). Ricinoleate derivatives were smoothly reacted, delivering the targets in good to excellent yields (10aa–10bl, 59–82% yields) (Fig. 4a). Methyl-1-testosterone is an anabolic steroid derivative to treat male testosterone deficiency. Herein, using steroid-derived carbamate 13a as a representative drug molecule for diversification, three different alkenylation analogs were readily accessed (13aa–13aq, 55–76% yields, Fig. 4b).

Given that many therapeutic agents contain alkenyl alcohol moieties, we expect our methodology to provide valuable opportunities for streamlining analog generation and thereby accelerating structure-activity relationship studies in drug discovery. Finally, if an inseparable mixture of Z- and E-alkenyl amides 6h was subjected to Cond. C, Z-alkene reacted smoothly to provide diene 7ha in 75% yield, with the unreacted E-isomer successfully recovered (Fig. 4c).

**Discussion**

In summary, we have presented a chelation-assisted geminal C(alkenyl)-H functionalization of alkenyl alcohols, carbanates and amides by palladium catalysis. Such olefinic C-H functionalization proceeds via unconventional four- to eight-membered exo-palladacycles and allows the alkenylation of (Z)-configured and cyclic homoallyl-, bishomoallyl-, and allyl alcohols/carbanates/amides, which are particularly important features of numerous natural products and pharmaceutical agents. The protocols tolerate a wide variety of distances between the olefinic C-H bonds and the coordinating groups, enable the gram-scale preparation and modification of ricinoleate and even steroid derivatives, demonstrating the practicality and versatility. Furthermore, the carbanate and amide auxiliary are smoothly removed under mild reduction or hydrolysis conditions. This work greatly expands the utility of current C(alkenyl)-H activation reactions that are based on five- and six-membered endo-/exo-cyclometallation, and we anticipate that this method will find broad applicability in multifarious synthetic endeavors.

**Methods**

**General procedure for C-H alkenylation of alcohols.** An oven-dried vial was charged with Pd(OAc)₂ (10 mol%, 0.03 mmol), Ac-Phe-OH (50 mol%, 0.15 mmol), Ag₂CO₃ (1.5 equiv, 0.45 mmol), Cs₂CO₃ (30 mol%, 0.09 mmol), CF₃CH₂OH (10 equiv, 3.0 mmol) and 1,4-dioxane (0.6 mL). Then, alcohol 1 (1.0 equiv, 0.3 mmol) and alkene 2 (2.0 equiv, 0.6 mmol) were added into the solution in sequence. The vial was sealed under argon and heated to 70 °C with stirring for 16–24 h. After cooling down, the mixture was concentrated to give the crude product which was directly applied to a flash column chromatography for separation (EtOAc/petroleum ether mixtures).

**General procedure for C-H alkenylation of carbanates.** An oven-dried vial was charged with Pd(OAc)₂ (10 mol%, 0.02 mmol), Ac-Phe-OH (50 mol%, 0.1 mmol), Ag₂CO₃ (1.5 equiv, 0.3 mmol), LiOH (30 mol%, 0.06 mmol), CF₃CH₂OH (5.0 equiv, 1.0 mmol) and MeCN (0.1 mL). Then, amide 6 (1.0 equiv, 0.20 mmol) and alkene 2 (2.0 equiv, 0.4 mmol) were added into the solution in sequence. The vial was sealed under argon and heated to 70 °C with stirring for 16 h. After cooling down, the mixture was concentrated to give the crude product which was directly applied to a flash column chromatography for separation (EtOAc/petroleum ether mixtures).

**General procedure for C-H alkenylation of amides.** An oven-dried vial was charged with Pd(OAc)₂ (10 mol%, 0.02 mmol), Ac-Phe-OH (50 mol%, 0.1 mmol), Ag₂CO₃ (1.5 equiv, 0.3 mmol), LiOH (30 mol%, 0.06 mmol), CF₃CH₂OH (5.0 equiv, 1.0 mmol) and MeCN (0.1 mL). Then, amide 6 (1.0 equiv, 0.20 mmol) and alkene 2 (2.0 equiv, 0.4 mmol) were added into the solution in sequence. The vial was sealed under argon and heated to 70 °C with stirring for 16–24 h. After cooling down, the mixture was filtered and concentrated to give the crude product which was directly applied to a flash column chromatography for separation (EtOAc/petroleum ether mixtures).

**Data availability**

The authors declare that all data supporting the findings of this study are available within the article and its Supplementary Information files. All data are also available from the corresponding authors upon reasonable request.

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Author contributions

J.Z. and G.Z. supervised and J.Z. conceived the project. K.M., T.L., C.S. performed all of the experiments, and K.M., T.L., and C.Y. contributed equally. J.Z. prepared this manuscript with the assistance of G.Z., K.M., and T.L. All of the authors participated in data analysis and discussions.

Competing interests

The authors declare no competing interests.

Additional information

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