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Chelation-assisted multiple and relay C–H functionalization of unactivated aliphatic *E*-alkenes

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Olefinic C–H modification has been a highly sought-after objective to upgrade commodity molecules into densely functionalized compounds. Unactivated aliphatic *E*-alkenes of electronically and sterically unbiased properties are ubiquitous compounds, but they are challenging targets for alkenyl C–H functionalization due to low reactivity and selectivity issues. We report the first sequential and relay C–H functionalization of unactivated aliphatic *E*-alkenes using alkenes and alkynes to afford complex polyenes and polyeneynes. The dienes, obtained from olefinic C–H functionalization by alkyne hydroalkenylation, underwent upgrading and controllable C–H functionalization by a six- or seven-membered palladacycle. The method allows for a range of functionalizations such as oxidative alkenylation, hydroalkenylation and alkynylation, *via* five- to eight-membered cyclopalladation. The robustness of the protocols was demonstrated by the preparative scale, chemical derivation and intra-molecular reactions to produce 12- to 16-membered macrocycles. Mechanistic experiments combined with DFT calculations explained the reactivities and selectivities of various alkenyl C–H bonds.

Introduction

Configurated multi-substituted alkenes are one of the most widely used organic compounds,[1] and their stereo-selective synthesis remains a long-standing and challenging research topic. Alkenyl C–H functionalization affords atom- and step efficient synthesis of densely functionalized alkene compounds. One powerful method is non-directed alkenyl C–H functionalization such as the Heck type reaction[2] and radical reaction,[3] but they lead to extremely low reactivity and poor *E*/*Z* selectivity when applied to the reaction of internal alkenes. While chelation-assisted (directed) aromatic and aliphatic C–H functionalization have been well defined,[4] directed alkenyl C–H functionalization has been demonstrated to be a powerful method toward the synthesis of multi-substituted alkene derivatives in a regio- and stereo-selective manner,[4e,5] proceeding *via* a C–H cyclometallation event. However, previous reports generally employed disubstituted terminal alkenes[6] and disubstituted *Z*-alkenes[7] as substrates, reacted by the formation of *endo*- and *exo*-metallocycles respectively to give rise to tri-substituted alkenes, in which the competitive α- or β C–H positions were substituted (Scheme 1A(a and b)),[5–8] and the essential problem in achieving regio-selectivity remains unsolved. There have been examples of β-C–H functionalization of electronically biased (activated) alkenes such as *trans*-acrylic acids/amides by five-membered *endo*-metallocycles;[5a,6] however, α-C–H functionalization in these protocols is prevented due to difficulty in four-membered cyclometallation. Moreover, although there is a recent example of α-/β C–H functionalization of *trans*-styrenes (Scheme 1 A(d)),[8] C–H functionalization of more general unactivated aliphatic (*E*)-alkenes still remains unexplored (Scheme 1A(c)). Tetra-substituted alkenes are valuable targets and their *E*/*Z* preparation by olefinic C–H functionalization is quite challenging. There are only sporadic reports on this topic. Previously, sequential olefinic C–H arylation of simple alkenes by the Pd-catalyzed Heck reaction was disclosed by Itami and Yoshida[2d] and Studer.[2e] Recently, the Su group demonstrated a synthesis of triarylated all-carbon tetra-substituted olefins by a tandem remote-carbonyl-directed Heck arylation/isomerization/alkenyl C–H arylation of 1,1-disubstituted olefins.[6u] Directed sequential olefinic C–H functionalization of aliphatic *E*-alkenes without *E*/*Z* isomerization could also provide tetra-substituted alkenes which is unexplored.

Great efforts have been devoted to C–H functionalization of conjugated alkenes such as acrylic acids and their derivatives,[6a–j] enol[6k–n] or enamine derivatives[6o–q] and aryl alkenes.[6r–u,7j,k,8] In contrast, C–H functionalization of nonconjugated aliphatic alkenes is much less explored due to their steric and electronic unbias, inert properties of aliphatic C–C

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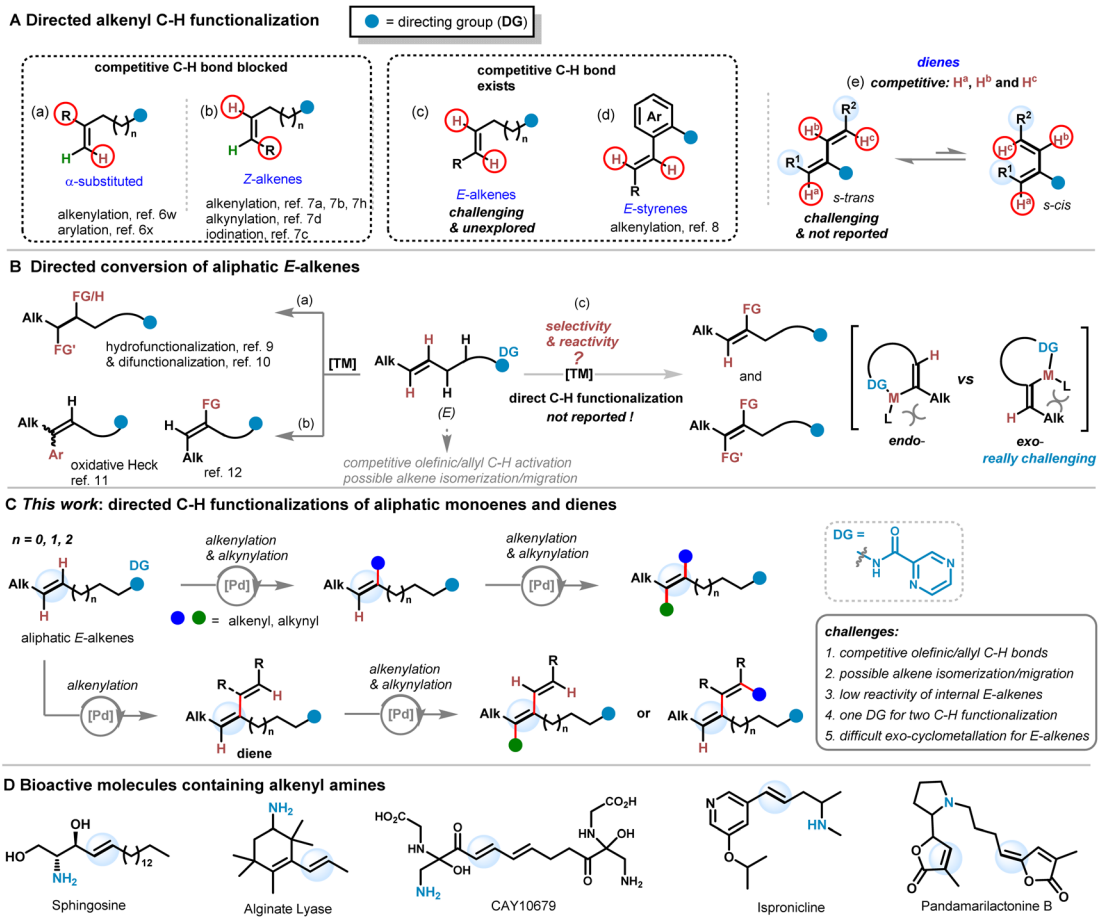

Scheme 1 (A) Challenges for C–H functionalization of unactivated aliphatic *E*-alkenes. (B) Group-directed olefinic C–H functionalization. (C) Multiple and relay C–H functionalization of unactivated aliphatic *E*-alkenes. (D) Bioactive molecules containing homoallyl and bishomoallyl amines.

double bonds, and the high degree of conformational flexibility for more challenging C–H cyclometallation.[7b,8] There have been limited examples of conversion of aliphatic alkenes.[6,7] Loh and Xu reported alkenyl C–H alkenylation of allyl and homoallyl alcohols.[6r] Engle[7a] and our group[7b] reported bidentate- and monodentate-chelation-assisted olefinic C–H alkenylation of *Z*-alkenes respectively. Carreira developed alkenyl C–H iodination[7c] and alkynylation[7d] of *Z*-alkenes. Also, there have been reports on C–H arylation[7e] of mono-substituted alkenes by *exo*-palladation. Unfortunately, these methods are restricted to aliphatic *Z*-alkenes, terminal alkenes and cyclic alkenes (Scheme 1A(a–d)). Furthermore, group-directed hydrofunctionalization and difunctionalization of aliphatic *E*-alkenes were well defined to afford complex alkanes (Scheme 1B(a)),[9,10] and there was also oxidative Heck arylation using aliphatic *E*-alkenes (Scheme 1B(b)).[11] However, chelation-assisted direct alkenyl C–H functionalization of aliphatic *E*-alkenes remains unexplored and elusive (Scheme 1B(c)).[12]

Polyenes such as dienes are occurring in countless natural products and drugs, and development of their selective alkenyl C–H functionalization could greatly expand the utility of the current strategy which also affords rapid construction of molecular libraries for new drug investigations. Unfortunately, selective C–H functionalization of polyenes such as 1,3-dienes bearing competitive olefinic C–H bonds has remained elusive and unexplored[2–8] presumably due to difficulties in selectivity control, reaction complexity (cyclization, decomposition, isomerization, *etc.*), conformational flexibility (s-*trans* *vs.* s-*cis*) and undesirable metal-coordination that may prevent the catalytic reaction (Scheme 1A(e)).

Multiple and sequential C–H functionalization enabled by one directing group greatly promotes the synthetic efficiency and practical usage by avoiding the tedious installation and removal process.[4,5] However, this research topic is really challenging due to problems rooted in both reactivity and selectivity. With our long-term interest in alkenyl C–H functionalization,[6g,7b,7j,8] we wondered whether we could develop selective and multiple alkenyl C–H functionalization of aliphatic *E*-alkenes of low reactivity. However, there are several challenges for such a transformation. The existence of competitive olefinic and allyl C–H bonds in aliphatic (*E*)-alkenes as well as possible alkene isomerization and migration may lead to poor selectivity and more side reactions under transition-metal-catalysis.[1b,6u,12] Additionally, group directed olefinic C–H

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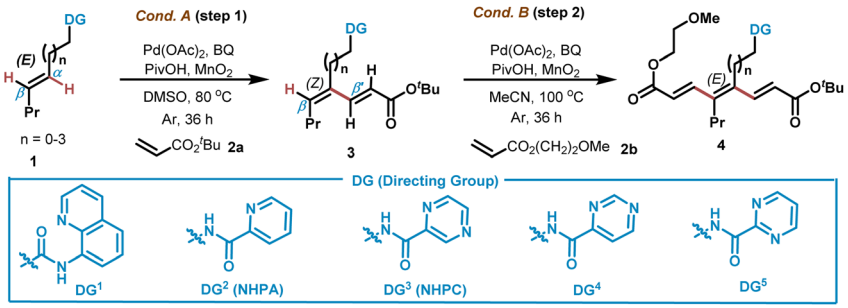
activation of *E*-alkenes by *exo*-cyclometallation is really challenging due to disfavored steric/electronic effects, and there is only one related example of α- and β-C–H activation of *trans*-styrenes (Scheme 1B).[8,12] Thirdly, selective C–H functionalization of conjugated polyenes is unexplored and elusive. Herein, we report the first selective and multiple alkenyl C–H functionalization of unactivated aliphatic *E*-alkenes, affording efficient synthesis of multi-substituted polyenes and polyeneynes with excellent regio- and *E*/*Z* ratio selectivity (Scheme 1C). Selective olefinic C–H functionalization of complex conjugated dienes is investigated for the first time.

Results and discussion

Alkenyl amines widely occur in countless natural products and drugs (Scheme 1D). At the beginning of our study, (*E*)-type allyl, homoallyl and bishomoallyl amine derivatives bearing two competitive olefinic C–H bonds were chosen as the substrates for C–H alkenylation using acrylate **2a**. The reported Pd, Ir, Ru, Rh and Co based catalytic conditions showed no catalytic activity for *E*-alkenyl amine derivatives bearing monodentate directing groups such as amide, sulfonamide, urea, *etc.*[4,5] We attributed the failure to the weak monodentate coordination and energetically unfavorable monocyclic C–H cyclometallation, also exhibiting the challenge of the C–H conversion of *E*-alkenes. In this regard, various bidentate directing groups were chosen in hope of promoting alkenyl C–H activation through the formation of more energetically favorable bicyclic metallocycles. We noticed that the reaction of bishomoallyl amide 1 bearing Daugulis's 8-aminoquinoline (DG^1) with acrylate **2a** led to desired product **3** in 26% yield with 85 : 15 *Z*/*E* ratio selectivity, using 10 mol% $Pd(OAc)_2$, 10 mol% *p*-benzoquinone (*p*-BQ), 1.5 equivalents of PivOH, and 3.0 equivalents of MnO_2 in DMSO at 80 °C (Cond. A) (Table 1, entry 1). Next, we turned to examine other *N*,*N*-bidentate-chelation-assisted directing groups such as pyridine-2-carboxamide (DG^2), 2-pyrazine carboxamide (DG^3), 4-pyrimidine carboxamide (DG^4) and pyrimidine-2-carboxamide (DG^5). While alkene bearing DG^2 afforded 73% yield, incorporation of DG^3 gave 81% yield with 93 : 7 *Z*/*E* ratio selectivity (entries 2–3). Notably, bishomoallyl amine bearing DG^4 and DG^5 also led to good results (85% and 73% yields respectively) (entries 4–5). Monodentate directing groups such as carboxylic acid failed to promote the reaction (entry 6). Decreasing $Pd(OAc)_2$ to 5 mol% still led to 64% yield (entry 3). Changing the chain length between DG^3 and the olefinic moiety remarkably influenced the reactivity of the

Table 1 Evaluation and optimization of reaction conditions



Entry	Step	DG	*n*	Conditions[a]	Yield[b] (%)	*E*/*Z*[c]	Metallacycle
1	1	DG^1	1	A	26	15 : 85	6-*Exo*
2	1	DG^2	2	A	73	7 : 93	6-*Exo*
3	1	DG^3	2	A	81(64)[d]	7 : 93	6-*Exo*
4	1	DG^4	2	A	85	7 : 93	6-*Exo*
5	1	DG^5	2	A	73	6 : 94	6-*Exo*
6	1	CO_2H	1, 0	A	0	—	6, 5-*Exo*
7	1	DG^3	1	A	56	20 : 80	5-*Exo*
8	1	DG^3	3	A	23	<1 : 99	7-*Exo*
9	1	DG^3	0	A	0	—	4-*Exo*
10[e]	1	DG^3	2	A	80	5 : 95	6-*Exo*
11	2	DG^2	2	B	35	>99 : 1	7-*Endo*
12	2	DG^3	2	B	60	>99 : 1	7-*Endo*
13	2	DG^4	2	B	48	>99 : 1	7-*Endo*
14	2	DG^5	2	B	52	>99 : 1	7-*Endo*
15	2	DG^3	1	B	55	>99 : 1	6-*Endo*
16[f]	2	DG^3	2	B	49	>99 : 1	7-*Endo*

[a] Conditions A: **1** (0.15 mmol, 1.0 equiv.), **2** (2.5 equiv.), $Pd(OAc)_2$ (10 mol%), PivOH (1.5 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in DMSO (0.15 M) at 80 °C for 36 h, under Ar. Conditions B: **3** (0.1 mmol, 1.0 equiv.), **2** (2.5 equiv.), $Pd(OAc)_2$ (10 mol%), AcOH (2.0 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%), in MeCN at 100 °C for 36 h, under Ar (1 atm). [b] Yields are isolated yields. [c] *E*/*Z* ratio was determined by ^1H NMR. [d] 5 mol% $Pd(OAc)_2$ was used. [e] **2b** was used instead of **2a**. [f] **2a** was used instead of **2b** for the second C–H alkenylation of diene **3** obtained in entry 10.

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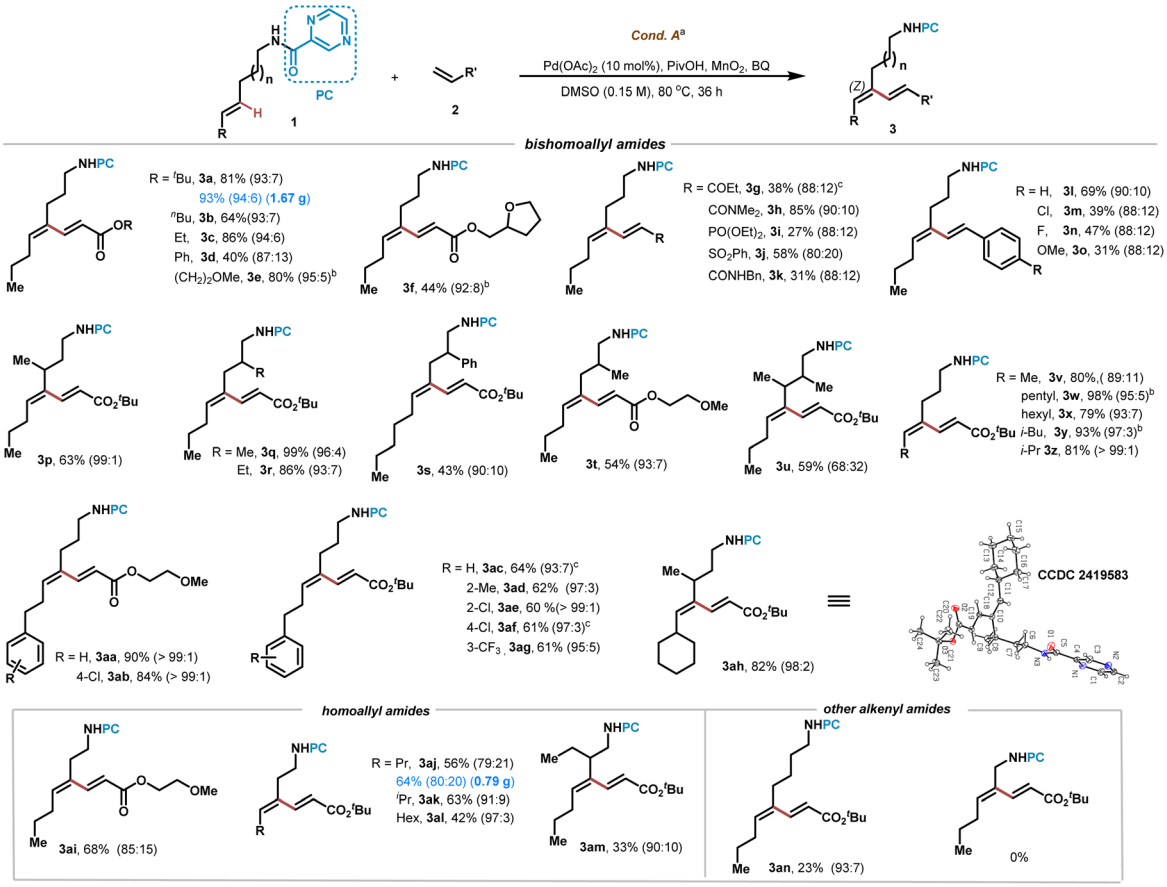

Scheme 2 Substrate scope of olefinic C–H alkenylation of aliphatic *E*-alkenes. (a) Reaction conditions: **1** (0.1 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (1.5 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in DMSO (0.15 M) at 80 °C for 36 h. (b) 48 h. (c) 100 °C. The yields are isolated yields based on **1**. *Z*/*E* ratios in parentheses were determined by ^{1}H NMR.

alkene substrates. For example, while the homoallyl amine substrate led to 56% yield with 80 : 20 *Z*/*E* ratio selectivity, the non-5-ene-1-amine derivative afforded an alkenylation product with only 23% yield, demonstrating the more favorable formation of five-membered *exo*-palladacycles over seven-membered *exo*-palladacycles under Cond. A (entries 7 and 8). No detection of other regio-isomers also shows the much more favorable formation of five- to seven-membered *exo*-palladacycles over six- to eight-membered *endo*-palladacycles.

However, the allyl amine derived substrate showed no reactivity (entry 9), presumably due to the difficulty in forming the strained metallocycle intermediate. The reaction also proceeded well by using acrylate **2b** instead (entry 10). Further C–H functionalization of the obtained diene **3** bearing three competitive olefinic C–H bonds was investigated. When diene **3** bearing DG[2] was subjected to 10 mol% $Pd(OAc)_2$, 10 mol% *p*-benzoquinone (*p*-BQ), 1.5 equivalents of PivOH, and 3.0 equivalents of MnO_2 in MeCN at 100 °C (Cond. B), C–H alkenylation occurred at the β-C–H bond and triene product **4** was obtained in 35% yield with > 99 : 1 *E*/*Z* ratio selectivity (entry 11). To our delight, the reaction of diene **3** bearing DG[3] led to the triene product in 60% yield with >99 : 1 *E*/*Z* ratio selectivity by the formation of a seven-membered *endo*-palladacycle, and no detection of other regio isomers exhibited the excellent site-selectivity of the protocol (entry 12). Other DGs such as DG[4] and DG[5] also performed well to provide triene products in 48% and 52% yields respectively with >99 : 1 *E*/*Z* ratio selectivity (entries 13 and 14). It is worth noting that the diene generated from homoallyl amine also underwent the second C–H alkenylation only at the β-position by a six-membered *endo*-palladacycle, and the triene **4** was successfully obtained with 55% yield and >99 : 1 *E*/*Z* ratio selectivity under Cond. B (entry 15). The second C–H alkenylation of diene **3** obtained in entry 10 also gave 49% yield using acrylate **2a** instead (entry 16).

Once we obtained the optimized conditions, we turned to examine the conversion of various *E*-configurated alkenyl amides **1** bearing DG[3] (Scheme 2). Oct-4-ene-amine derived amide reacted well with various acrylates to give dienes **3a–3f** in 40–81% yields with excellent *Z*/*E* ratio selectivity. Gram-scale preparation of **3a** (1.67 g) is successful (93% yield, 94 : 6 *Z*/*E* ratio) to demonstrate its robustness. Other electron-deficient alkenes such as vinyl ketone, acrylamide, vinyl phosphonate, vinyl sulphone and styrenes were all reacted well to give dienes **3g–3o** in 27–85% yields. Branched aliphatic *E*-alkenes bearing alkyl or aryl were suitable substrates to afford C–H alkenylation products **3p–3u** in 43–99% yields with up to 99 : 1 *Z*/*E* ratio

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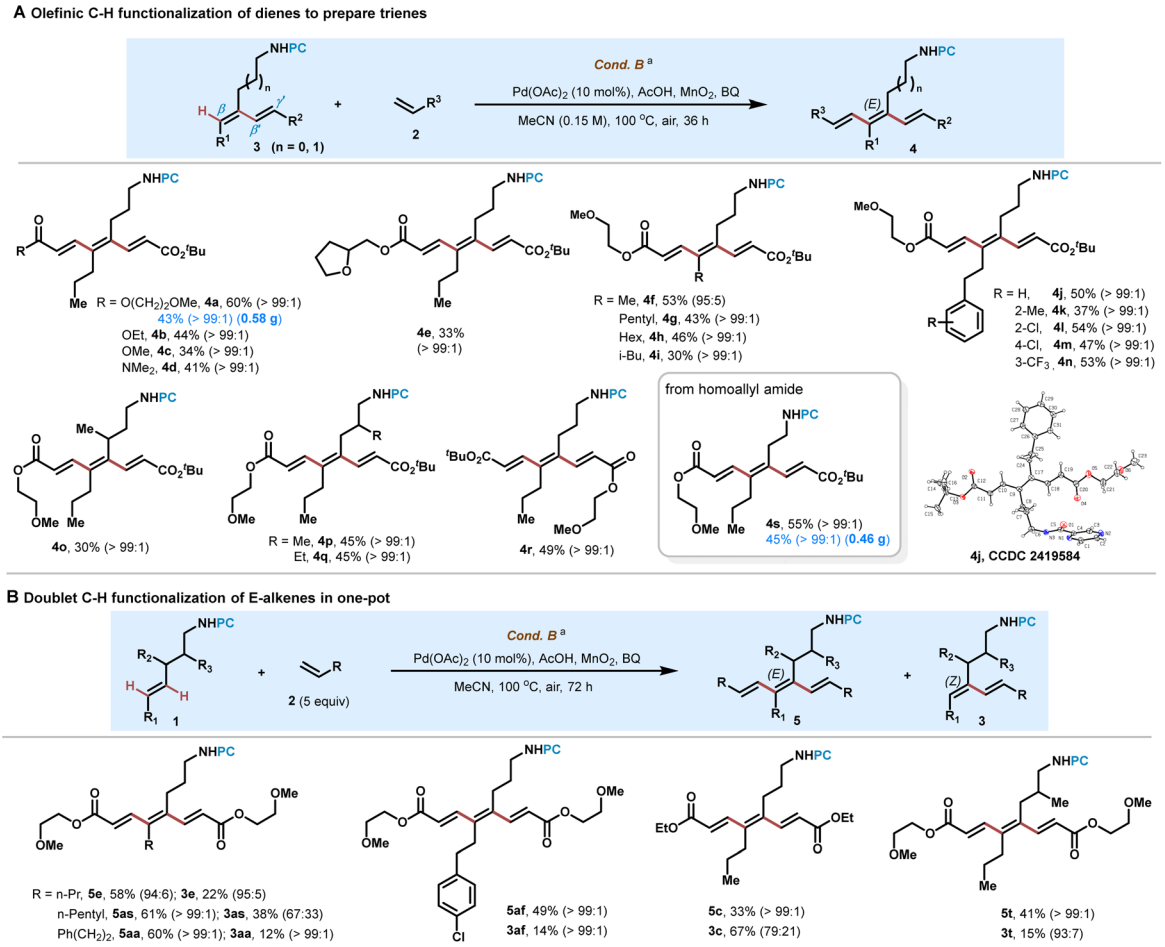

Scheme 3 Substrate scope of olefinic C–H alkenylation to prepare trienes. [a]Conditions B: **1** (0.1 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), AcOH (2.0 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in CH_3CN (0.15 M) at 100 °C for 36 h. The yields are isolated yields based on **1** or **3**. *E*/*Z* ratio in parentheses was determined by ^{1}H NMR.

selectivity. *E*-Alkenes bearing various groups such as methyl, pentyl, hexyl, isobutyl, isopropyl, arylethyl and cyclohexyl were examined, and all of them successfully led to desired products **3v–3ag** in 60–98% yields with up to >99/1 *Z*/*E* selectivity. Compound **3ah** was determined to be in (*Z*,*E*)-configuration and s-*trans* conformation (which is of lower energy) by X-ray crystallographic analysis (CCDC 2419583). Homoallyl amine derived substrates bearing *i*-Pr and *n*-Pr and *n*-hexyl were smoothly converted to give rise to **3ai–3al** in moderate to good yields. However, branched homoallyl amide led to **3am** in 33% yield with 90 : 10 *Z*/*E* ratio selectivity. While non-5-ene-1-amide afforded product **3an** in 23% yield, allyl amide showed no reactivity.

With the dienes **3** in hand, we then turned to examine their further C–H alkenylation by seven- and six-membered *endo*-cyclopalladation to prepare trienes **4** (Scheme 3A). Dienes **3** generated from alkenes **1** and acrylate **2a** reacted well with different acrylates and acrylamides, and C–H functionalization all occurred at the β-C–H bond far away from the ester to give corresponding trienes **4a–4e** in 33–60% yields with >99 : 1 *E*/*Z* ratio selectivity by the formation of seven-membered palladacycles. Other dienes bearing alkyl groups such as methyl, pentyl and hexyl were all converted smoothly to give **4f–4h** in moderate yields with 30–40% substrate recovery. Notably, even diene bearing a bulky *iso*-butyl was still able to give triene **4i** in 30% yield with >99 : 1 *E*/*Z* ratio selectivity. Incorporated phenyl ethyl bearing *ortho*, *meta*- or *para*-Me, Cl and CF_3 into alkene substrates reacted well with acrylate to provide trienes **4j–4n** in 37–54% yields with > 99 : 1 *E*/*Z* ratio selectivity. Dienes containing branched aliphatic chains also afforded alkenylation products **4o–4q** in moderate yields with > 99 : 1 *E*/*Z* ratio selectivity. (*E*,*E*,*E*)-Configuration and s-*trans* conformation of conjugated triene **4j** were determined by X-ray crystallographic analysis (CCDC 2419584), and all of the configurations and conformations of triene products **4** were assigned analogously to this compound. Diene **3e** also underwent C–H alkenylation with *tert*-butyl acrylate **2a** to produce **4r** in 49% yield. To our delight, diene **3aj** derived from homoallyl amine successfully led to triene **4s** in 55% yield with >99 : 1 *E*/*Z* ratio selectivity, by the formation of a six-membered palladacycle. Large scale preparation of **4a** (0.58 g) and **4s** (0.46 g) is also successful to show the robustness of the protocol.

Multiple C–H alkenylation of *E*-alkenes in "one-pot" fashion was also successful under Cond. B at 100 °C, using 5.0

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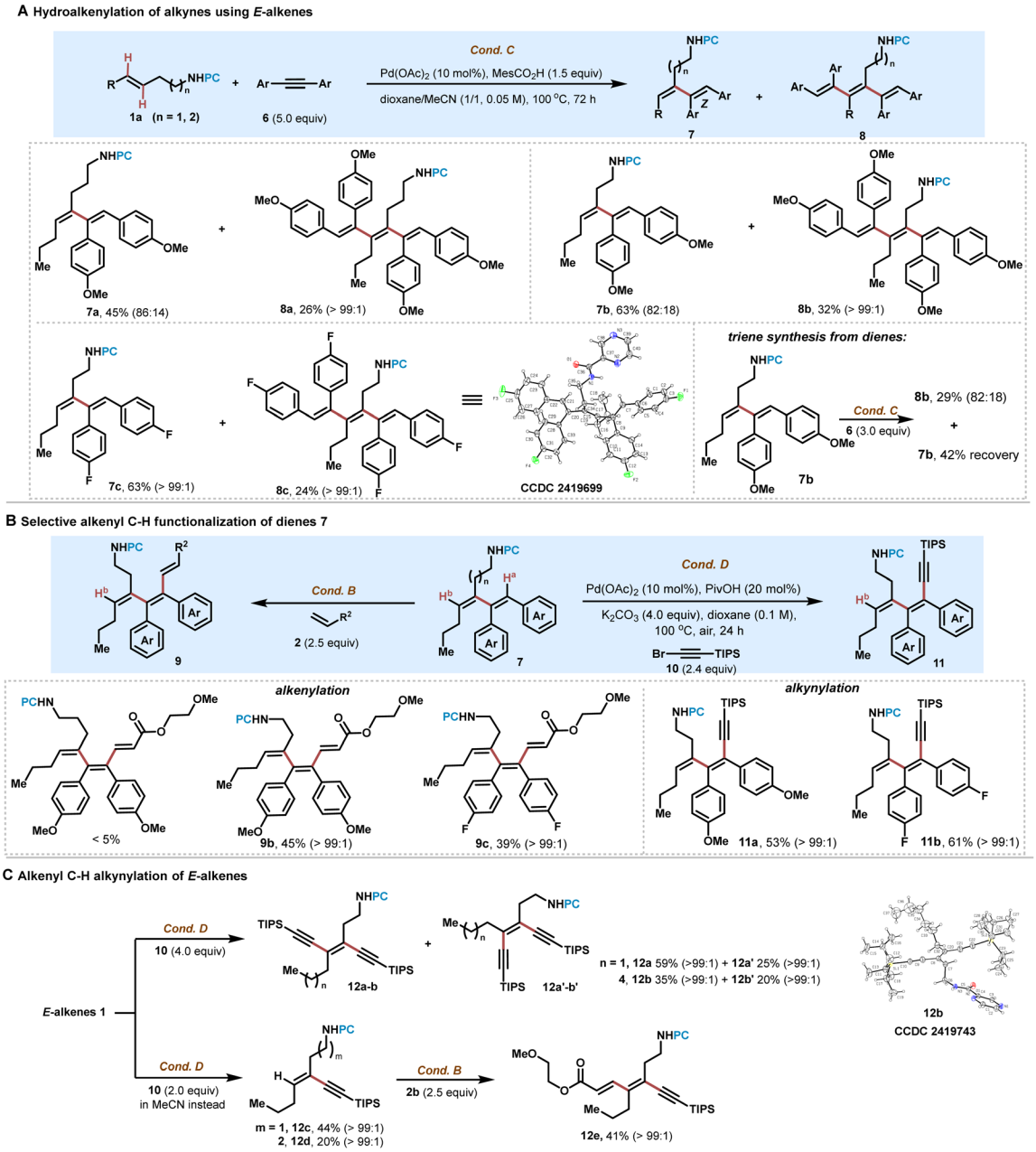

Scheme 4 Olefinic C–H functionalization to prepare polyenes and polyeneynes.

equivalents of electron-deficient alkenes (Scheme 3B). This protocol allowed an efficient approach toward the preparation of conjugated trienes **5** in 33–61% yields from simple *E*-monoenes, with the generation of diene **3** in 12–67% yields. Notably, all of these reactions afforded no regioisomeric products from β′- and γ′-C–H functionalization, exhibiting their excellent regio-selectivity.[14]

Other coupling partners were also investigated (Scheme 4). Internal alkynes **6** reacted with *E*-alkenes **1a** smoothly to produce mixed complex dienes **7a–7c** in 45–63% yield with the formation of trienes **8a–8c** in 24–32% yields with excellent *E*/*Z* ratio selectivity (up to >99 : 1), using 10 mol% $Pd(OAc)_2$ and 1.5 equivalents of $MesCO_2H$ in mixed dioxane/MeCN at 100 °C (Cond. C). (*Z*,*E*,*Z*)-Configuration of triene **8c** was determined by X-ray crystallographic analysis (CCDC 2419699). If **7b** was subjected to Cond. C, **8b** was obtained in 29% yield with 42% recovery. These results indicated a sequential α- and β C–H activation/*cis*-hydroalkenylation with alkynes **6**. Next, we turned to investigate other types of C–H functionalizations of dienes **7a–7c** bearing two competitive olefinic C–H bonds H^a and H^b. Diene **7a** from bishomoallyl amine exhibited no reactivity under either oxidative alkenylation (Cond. B) or alkynylation conditions (Cond. D). Interestingly, C–H alkenylation and alkynylation of dienes **7b** and **7c** underwent smoothly at the olefinic C–H bond H^a farther away from the directing group to afford trienes (**9b** and **9c**) and eneynes (**11a** and **11b**), with the alkenyl C–H

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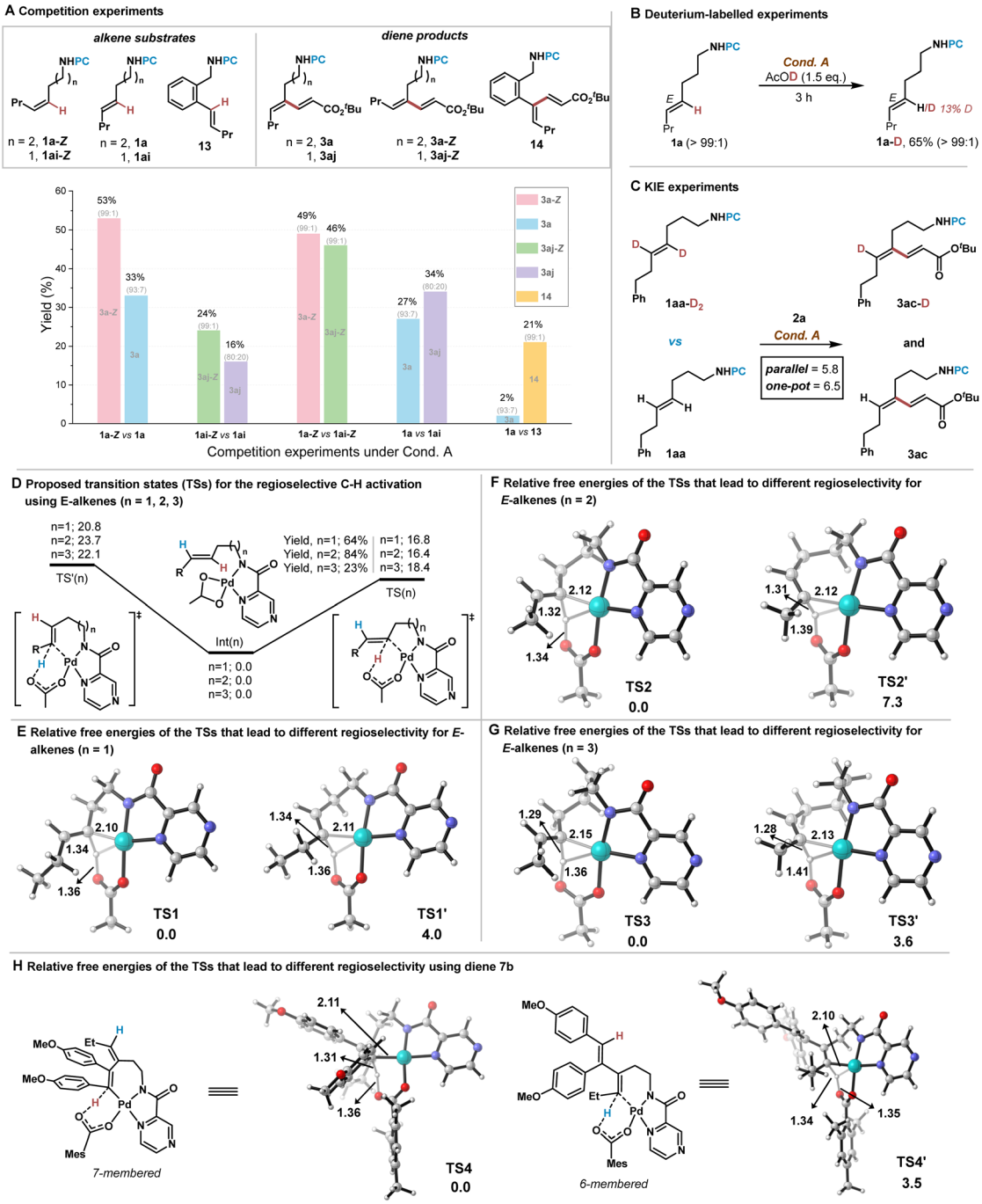

Scheme 5 Mechanistic experiments and DFT calculations. The relative free energies in DFT calculations are given in kcal mol^{-1}.

bond H^{b} closer to the directing group intact (Scheme 4B). Herein, functionalization of C–H bond H^{a} proceeding by a seven-membered C–H cyclopalladation was previously regarded to be energetically more disfavored than the activation of the C–H bond H^{b} by a six-membered palladacycle.[5–8] These results are different from the reactions of dienes **3** in Scheme 3 and dienes **7** in Scheme 4A.[15]

If aliphatic alkene **1** was subjected to alkynylation Cond. D, a *bis*-alkynylation reaction occurred to afford **12a** and **12b** in 59% and 35% yields, with the formation of *E*/*Z* isomers **12a′** and **12b′** in 25% and 20% yields respectively (Scheme 4C). (*E*)-Configuration of polyeneyne **12b** was confirmed by X-ray crystallographic analysis (CCDC 2419743). Interestingly, α-alkynylation products **12c** and **12d** were smoothly obtained in 44% and 20% yields respectively by using MeCN as a solvent instead. Notably, further alkenyl C–H alkenylation of **12c** was also successful under Cond. B, giving rise to **12d** in moderate yield with >99 : 1 *E*/*Z* ratio selectivity.

Competition experiments were performed to obtain additional mechanistic insight, using various *E*- and *Z*-configurated

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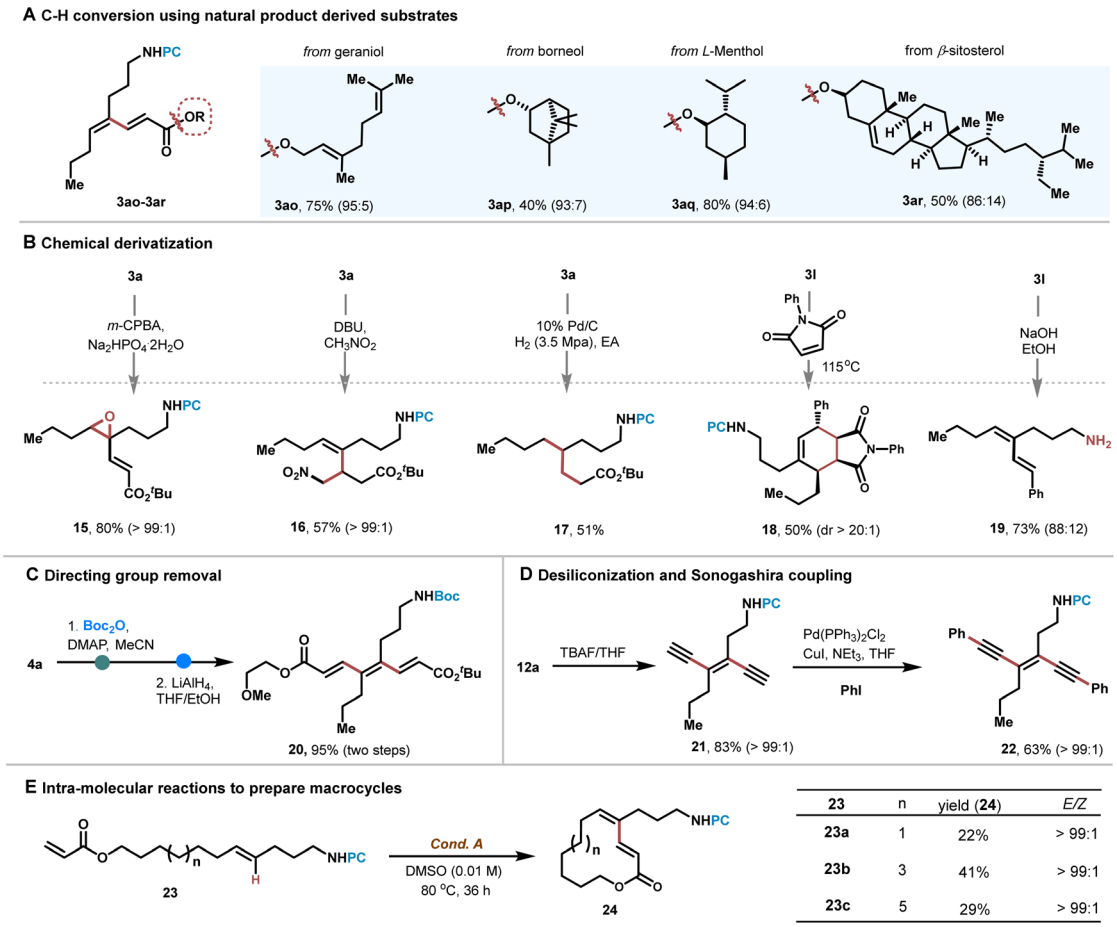

23	n	yield (24)	E/Z
23a	1	22%	> 99:1
23b	3	41%	> 99:1
23c	5	29%	> 99:1

Scheme 6 Synthetic demonstrations and chemical derivations.

alkenes under Cond. A (Scheme 5A). While both alkene **1a**-*Z* and **1a** were converted by six-membered C–H *exo*-cyclometallation, *Z*-type alkene **1a**-*Z* reacted much faster than the *E*-alkene **1a** (**3a**-*Z* 53%, **3a** 33%) due to decreased distortion energy which is consistent with our previous observations using aryl alkenes.[8] Competition experiments with alkene **1ai**-*Z* and **1ai** also demonstrated the *Z*-type alkene **1ai**-*Z* to be more reactive (**3aj**-*Z* 24% and **3aj** 16%) which were converted by five-membered C–H *exo*-cyclopalladation. If *Z*-type alkenes **1a**-*Z* and **1ai**-*Z* were subjected to Cond. A, they showed comparable reactivity toward acrylate (**3a**-*Z* 49% and **3aj**-*Z* 46%). Competition reactions using *E*-type alkenes **1a** and **1ai** were investigated. Product yield of **3aj** is higher than that of **3a** (**3a** 27% and **3aj** 34%), showing that the formation of the five-membered *exo*-palladacycle is more kinetically favored than that of the six-membered *exo*-palladacycle, which is different from the previous observations.[7b] Competition experiments using aliphatic alkene **1a** and styrene **13** showed that styrene **13** reacted much more quickly to outcompete the alkene **1a** (**3a** 2% and **14** 21%), also supporting the challenge of C–H cyclopalladation of aliphatic alkene substrates. Deuterium incorporation experiments using **1a** showed the six-membered C–H *exo*-cyclometallations to be reversible (13% D) with 65% recovery, and no *E*/*Z* isomerization was observed (Scheme 5B).[16] Kinetic isotope effect (KIE) experiments confirmed the olefinic C–H activation of **1a** by C–H *exo*-cyclopalladation to be the rate-determining step (Scheme 5C). These results exhibited the directed reversible C–H bond activation to originate the regioselectivity and exclude other possible pathways such as nucleometallation elimination and π-allyl Pd(II) mechanism.[13]

To further investigate the origin of the observed high/exclusive regioselectivity of the reaction, DFT calculations were performed on the key carboxylate-assisted Pd-catalyzed alkenyl C–H activation steps (Scheme 5D–H). We selected three substrates with various distances between the directing group and the alkene to calculate the relative free energies of key transition states leading to different regioisomeric products. It was found that for transition states TS(n) for *exo*-cyclopalladation, when $n = 2$, the reactivity is highest with an energy barrier of 16.4 kcal mol^{-1}. This can be attributed to the formation of a six-membered metallocycle with lower ring strain, and this speculation is further supported by comparing the activation energy barriers in the TS′(n) for *endo*-cyclopalladation, where the lowest energy barrier (20.8 kcal mol^{-1}) is observed when n is 1, in which a five-membered palladacycle is formed in the transition state **TS1′**. The computational results also indicate that for the olefin substrates 1 ($n = 1$, 2 and 3), the C(sp^2)–H bond closer to the directing group is more readily activated, which is consistent with the experimental results. Given that the two C(sp^2)–H bonds

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in the alkene of selected substrates have similar chemical environments, we speculate that the differential ring strain in these key transition states also dominates the regioselectivity. Interestingly, for diene substrates **7b** and **7c**, the transition state **TS4′** for the activation of the olefinic C(sp^2)–H bond by a six-membered palladacycle was 3.5 kcal mol^{-1} higher than the transition state **TS4** for the activation of the olefinic C(sp^2)–H bond far away from the directing group by a seven-membered palladacycle, which is in accordance with the experimental results in Scheme 4B.[17] The unique selectivity may be attributed to the significant difference in the chemical environment of the two C–H bonds, which are dominated by the C–H bond activation or the following insertion step (Scheme 5H).[15,17]

We also examined the compatibility of the protocols using natural products (Scheme 6A). Notably, acrylates bearing natural geraniol, menthol, borneol and β-sitosterol were all smoothly converted to afford corresponding dienes **3ao–3ar** in 40–80% yields with excellent *E*/*Z* ratio selectivity, showing the robustness of the protocol. Next, we turned to examine the chemical derivation of the obtained polyenes and eneynes. If diene **3a** was treated with *m*-CPBA (3-chloroperoxybenzoic acid), epoxidation occurred successfully to produce oxirane **15** in 80% yield, with the other olefinic moiety adjacent to the ester intact. Interestingly, diene **3a** reacted well with nitromethane by Michael addition to give olefin **16** in 57% yield. Hydrogenation of diene **3a** went well to produce alkane **17** in 51% yield. The Diels–Alder reaction using **3l** was successful in constructing bicyclic products **18**. Also, directing group PC was easily removed by subjecting **3l** to EtOH/NaOH to afford free amine **19** (Scheme 6B). The directing group in triene **4a** was also readily removed by Boc protection and reduction by $LiAlH_4$ to give Boc-NH amine **20** in quantitative yield (Scheme 6C). If eneyne **12** was treated with TBAF, desiliconization occurred smoothly to afford terminal alkyne **21** in 83% yield, which coupled with PhI to give **22** in 63% yield under palladium catalysis (Scheme 6D). Intramolecular cross-coupling reactions were also investigated. If alkenes **23a–c** were subjected to Cond. A in a low concentration (0.01 M in DMSO), 12-, 14- and 16-membered macrocycles **24a–c** were obtained in up to 41% yield with >99 : 1 *E*/*Z* ratio selectivity (Scheme 6E). We also examined the photophysical properties of products **8** and **11** with large conjugating structures. The fluorescence emission of compounds **8a–8c**, **11a** and **11b** was also investigated and the emission maxima altered from 387 to 468 nm, exhibiting good luminescent properties which may be potentially applied in optical materials (see the SI for details).

Conclusions

In summary, we report palladium-catalyzed multiple olefinic C–H functionalization of aliphatic monoenes and dienes to afford complex polyenes and eneynes. C–H functionalizations such as oxidative alkenylation, hydoalkenylation and alkynylation were all enabled by the *N*,*N*-bidentate directing group of 2-pyrazine carboxamide through the formation of five- to eight-membered *endo*- and *exo*-palladacycles. This protocol allowed olefinic C–H functionalization of a wide range of substrates including bishomoallyl amine, homoallyl amine and 5-ene-1-amine derived alkenyl amides which showed wide functionality tolerance. The synthetic applicability was demonstrated by the preparative scale, chemical derivation of the polyenes and eneynes, and primary success in intra-molecular reactions to produce 12–16 membered macrocycles. Selective C–H functionalization of dienes by a six- or seven-membered palladacycle is investigated for the first time which is controlled by both steric and electronic effects. Mechanistic experiments and DFT calculations were performed to explain the relative reactivities and selectivities of various *E*- and *Z*-alkenes.

Author contributions

Y. W., X. L., C. P., X. L. and Y. Z. performed all of the experiments. J. Z. conceived and supervised the project. J. Z. prepared this manuscript with the assistance of G. Z., Y. W. and X. L. P. Y. and Y. C. conducted DFT calculations. All of the authors participated in data analysis and discussions. Y. W. and X. L. contributed equally.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary information (SI). Supplementary information: materials and methods, experimental procedures, characterization data, and NMR spectra. See DOI: **https://doi.org/10.1039/d5sc07408h**.

CCDC 2419583 (**3ah**), 2419584 (**4j**), 2419699 (**8c**) and 2419743 (**12b**) contain the supplementary crystallographic data for this paper.[18a–d]

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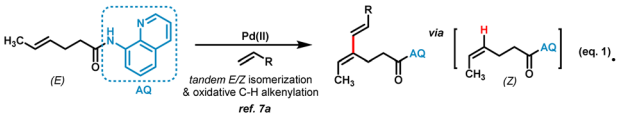

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14 It is proposed that electron-withdrawing groups such as ester on dienes 3 remarkably decrease the reactivity of the adjacent olefinic C–H bond, and the olefinic C–H bond farther away is electronically richer and easier to be C–H functionalized (Scheme 3). These results are in accordance with previous reports on conversion of aryl alkenes, also see ref. 8.

15 Herein, transition state **TS4′** of the olefinic C–H activation *via* a six-membered palladacycle was 3.5 kcal mol^{-1} higher than the transition state **TS4** of the olefinic C–H activation by a seven-membered palladacycle (Scheme 5H), and the C–H activation step may be rate-determining which dominates the selectivity in oxidative alkenylation and alkynylation reactions in Scheme 4B. In Scheme 4a, however, the C–H activation step should not be rate-determining and alkyne insertion of the palladacycle intermediate dominates the reaction selectivity to give **8b** and **8c** (alkyne insertion of a six-membered palladacycle is energetically more favorable than that of a seven-membered palladacycle).

16 For substrate **3a**, 13% deuterium incorporation was observed under Cond. B with *E*/*Z* isomerization (*Z*/*E* = 64:36) (98% recovery). For substrate **7b** (*Z*/*E* = 82:18), 32% deuterium incorporation occurred at the olefinic C–Ha bond and 9% deuterium incorporation occurred at the olefinic C–Hb bond with *E*/*Z* isomerization (*Z*/*E* = 79:21) (67% recovery) (see the SI for details).

17 These primary results exhibited electronic effects such as conjugation of the aromatic ring that may promote the olefinic C–H activation *via* larger-sized cyclopalladation (also see competition experiments in Scheme 5A, **1a** *vs.* **13**), and the detailed mechanistic studies will be discussed in a later report.

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