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Stereoselective Synthesis of Complex Polyenes through Sequential α-/β-C−H Functionalization of *trans*-Styrenes

Yuhang Zhu,[†][a] Yini Wang,[†][a] Wenzhou Shen,[†][a] Xiaoyu Chen,[a,b] Qiuhua Liu,[c] Limin Yang,[a]* Guofu Zhong,[a,b]* and Jian Zhang[a,d]*

Abstract: Sequential C−H functionalization of molecules containing multiple C−H bonds can efficiently lead to structural diversity. Herein we present the first chelation-assisted sequential α-/β-C−H functionalization of *E*-styrenes with simple alkenes and alkynes in excellent *regio*- and *stereo*-selectivity. The process involves α C−H functionalization by six-membered *exo*-cyclopalladation to result in tri- and tetrasubstituted 1,3-dienes and β C−H functionalization through seven-membered *endo*-cyclopalladation to produce tetra- and pentasubstituted 1,3,5-trienes in up to 97% yield with up to > 99/1 *E/Z* selectivity, both enabled by the chelation assistance of pyrazinamide. The protocol is demonstrated to be widely applicable, tolerant to a wide range of functional groups and bioactive fragments, and suitable for gram-scale synthesis as well as one-pot and two step preparation of trienes. Mechanistic experiments and density functional theory (DFT) calculations were performed to elucidate the selectivity and reactivity.

Chelation-assisted alkenyl C−H functionalization by cyclometallation is a highly effective method for producing alkene derivatives with exceptional site- and *Z/E* selectivity. This versatile technique encompasses a range of transformations, including alkenylation, allylation, arylation, and alkynylation, which enable the synthesis of a variety of alkenyl compounds, such as 1,3-dienes, 1,4-dienes, styrenes, enynes, and more.[1-5] As we know, directing group shed great influence on reaction activity, and the installation and removal of the directing group for each C−H functionalization step is tedious and limit the practical application. So, it would be more desirable if a directing group could promote multiple C−H functionalization in a single alkene substrate by a sequential manner to afford structural diversity. Unfortunately, extensively explored substrates like 1,1-disubstituted alkenes and disubstituted *Z*-alkenes are limited to giving only *tri*-substituted alkenes and further directed olefinic C−H functionalization to afford *tetra*-substituted alkenes is prohibited by proximity-driven reactivity (Figure 1A). Actually, *tetra*-substituted alkenes are widely occurring and utilized, but their *E/Z* selective preparation by C−H functionalization still remains a formidable challenge.[6-9]

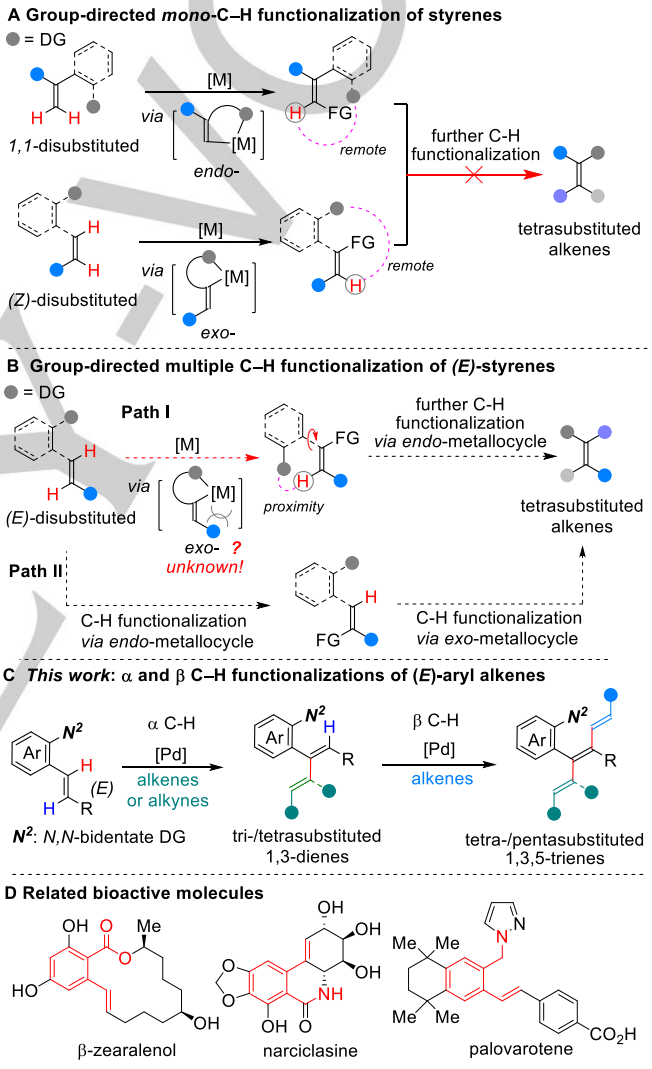

Figure 1. Vicinal- and geminal group-directed olefinic C−H functionalization.

Group directed alkenyl C−H functionalization by *endo*-cyclometallation has been well-studied using alkenes that bear a directing group *cis* to the target olefinic C−H bond.[2] In stark contrast, there are very limited olefinic C−H functionalization *via exo*-cyclometallation, reported by Engle,[3a] Carreira,[3b-d] Chen,[3g] Dong,[3j] and us,[3e] and the substrate scope is only restricted to disubstituted *Z*-alkenes that bear a directing group geminal to the target C−H bond. However, the α or β positions are "blocked" in

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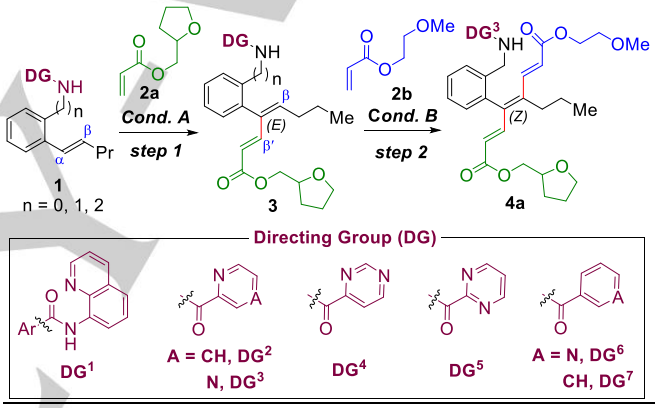
these β and α C−H functionalization of disubstituted alkenes by *exo*- and *endo*-metallocycles, so the essential problem in the selectivity between α and β C−H activation still remains to be solved (Figure 1A). To date, achieving alkenyl α C−H functionalization of *E*-disubstituted alkenes (including *E*-styrenes) by *exo*-cyclometallation continues to pose a significant challenge presumably due to the additional steric hindrance, and the exact mechanism behind this phenomenon remains unclear (Figure 1B).[4-5] Recently, the Engle group[4a] and our group[4b] almost simultaneously reported Pd-catalyzed (asymmetric) α C−H alkenylation of (*Z*)-2-vinyl benzaldehydes using a transient directing group (TDG), and *E*-configurated substrate showed significantly low reactivity. Sequential C−H functionalization of molecules containing multiple C−H bonds can lead to efficient approaches for achieving structural diversity.[7-8] However, controlling the positional selectivity and sequence of C−H cleavage is a significant challenge, and very limited examples have been reported on sequential olefinic C−H functionalization.[9] Itami and Yoshida reported a sequential olefinic C−H arylation by Pd-catalyzed Mizoroki-Heck reaction to afford α,β,β triarylated vinyl sulfides.[9a] The Studer group demonstrated a Pd-catalyzed Heck arylation for the synthesis of triarylated alkenes.[9b] Unfortunately, these protocols are restricted to Heck-type C−H arylation reactions and suffered from regio-/stereo-selectivity erosion due to insertion/elimination mechanisms.

In our proposal, disubstituted *E*-alkene would be a promising substrate for multiple olefinic C−H functionalization, which involves proposed C−H *exo*-cyclometallation followed by C−H *endo*-cyclometallation or vice versa (Figure 1B). In this regard, realizing unexplored α C−H functionalization of disubstituted *E*-alkenes through *exo*-cyclometallation is highly demanding,[1-5] which not only expands the reaction type but also provides in-depth mechanistic insight into the C−H cyclometallation event. Moreover, the judicious choice of a suitable directing group (DG) to modulate the reactivity and selectivity is also extremely challenging. With our ongoing interest in olefinic C−H functionalization,[2i-o,3e-f,4b] herein, we focused on the first example on chelation-assisted sequential α-/β-C−H alkenylation of disubstituted *E*-alkenes to selectively prepare tri-/tetrasubstituted 1,3-dienes and tetra-/pentasubstituted 1,3,5-trienes which are challenging to access using traditional methods (Figure 1C).[10]

E-Styrenes are widely occurring in countless bioactive molecules (Figure 1D). After extensive condition screening with various *E*-styrenes, it is noticed that *E*-alkenyl benzamide **1** bearing Daugulis's 8-aminoquinoline (**DG^1**) [11] reacted with tetrahydro-2-furanylmethyl acrylate **2a** to give α C−H alkenylation product in 41% yield with excellent *E*/*Z* selectivity (*E*/*Z* > 99/1), using 5 mol% $Pd(OAc)_2$, 10 mol% *p*-benzoquinone (*p*-BQ), 1.5 equivalent of PivOH, 3.0 equivalent of MnO_2 in EtOH at 40 °C under an argon atmosphere (Table 1, entry 1). However, incorporation of 2-picolinamide (**DG^2**) led to 36% yield with 65/35 *E*/*Z* ratio selectivity (entry 2). To our satisfactory, styrene substrate bearing an uncommon 2-pyrazinamide (**PC**) (**DG^3**) afforded **3a** in 95% yield with 95/5 *E*/*Z* ratio selectivity (entry 3). While 4-pyrimidine (**DG^4**) led to 51% yield with 93/7 *E*/*Z* ratio selectivity, 2-pyrimidine (**DG^5**) afforded 39% yield with 90/10 *E*/*Z* ratio selectivity (entries 4 and 5). Both 3-picolinamide (**DG^6**) and benzamide (**DG^7**) failed to react (entries 6 and 7). All of the results suggested the key role of *N,N*-bidentate chelation assistance in such α C−H functionalization by *exo*-cyclopalladation. While aniline derivative showed no reactivity, phenylethyl amine derivative delivered alkenylation product in only 9% yield (entries 8 and 9), exhibiting the difficult formation of five- and seven-membered *exo*-palladacycles under the catalytic conditions. The other potential products from aromatic- or β C−H activation *via* a five- or seven-membered palladacycle were not observed, showing the excellent *regio*-selectivity of the protocol. Next, β C−H functionalization of obtained *tri*-substituted diene **3a** was examined (step 2). Although Cond. A were inefficient at this stage, using mixed dioxane/AcOH (10/1, *v*/*v*) as a solvent instead remarkably improved the β C−H alkenylation, affording triene **4a** in 77% yield with 97/3 *Z*/*E* ratio selectivity (entries 10 and 11). Notably, β′ C−H alkenylation was not observed presumably due to the difficult formation of seven-membered *exo*-palladacycle. Styrene bearing **DG^1** was subjected to Cond. B, affording only α

Table 1. Evaluation and optimization of the reaction conditions.[a]



Entry	Step	DG	n	Conditions	Yield [%][a]	*E*/*Z* (or *Z*/*E*)[b]
1	1	DG^1	1	**A**	41	>99:1
2	1	DG^2	1	**A**	36	65:35
3	1	DG^3	1	**A**	95 (**3a**)	95:5
4	1	DG^4	1	**A**	51	93:7
5	1	DG^5	1	**A**	39	90:10
6	1	DG^6	1	**A**	0	-
7	1	DG^7	1	**A**	0	-
8	1	DG^3	0	**A**	0	-
9	1	DG^3	2	**A**	9	91:9
10	2	DG^3	1	**A**	< 5	-
11	2	DG^3	1	**B**	77 (**4a**)	97:3
12	1	DG^1	1	**B**	30	75:25
13	1, 2	DG^3	1	**B**	80 (**4a**)	97:3

[a] Conditions A: **1** (0.15 mmol, 1.0 equiv), **2** (2.5 equiv), $Pd(OAc)_2$ (5 mol%), PivOH (1.5 equiv), MnO_2 (3.0 equiv), BQ (10 mol%) in EtOH (0.15 M) at 40 ℃ for 48 h, under Ar. The yields are isolated yields; the *E*/*Z* ratio was determined by ^{1}H NMR. Conditions B: **3** (0.1 mmol, 1.0 equiv), **2** (2.5 equiv), $Pd(OAc)_2$ (5 mol%), PivOH (1.5 equiv), MnO_2 (3.0 equiv), BQ (10 mol%), in dioxane/AcOH (10/1, v/v) at 80 ℃ for 24 h, under Ar (1 atm); the yields are isolated yields. [b] The *E*/*Z* or *Z*/*E* ratio was determined by ^{1}H NMR.

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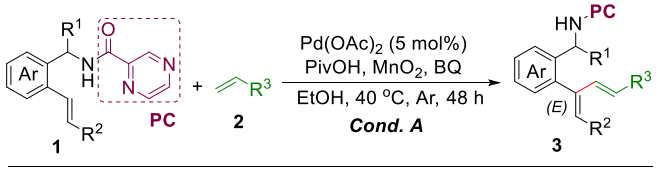
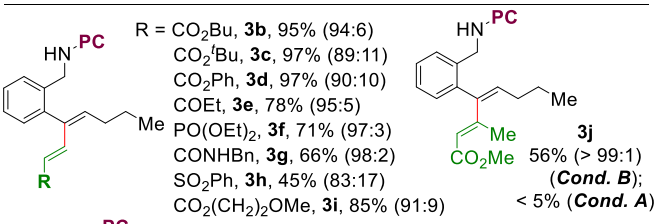
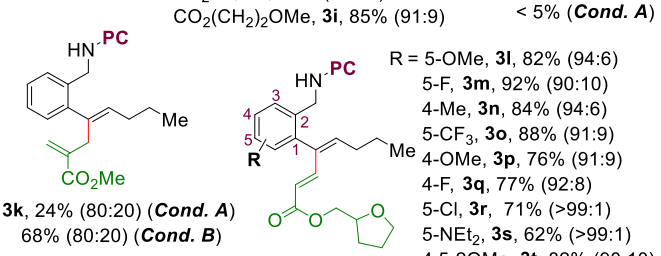
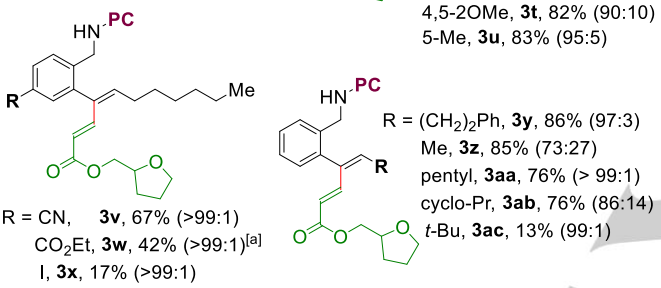
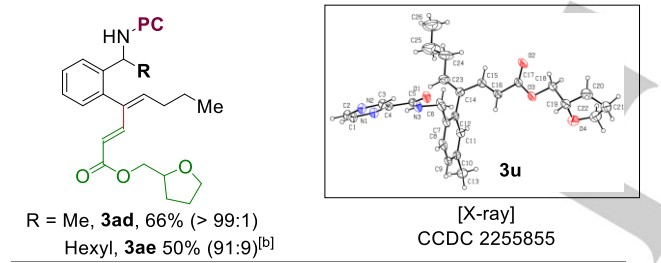
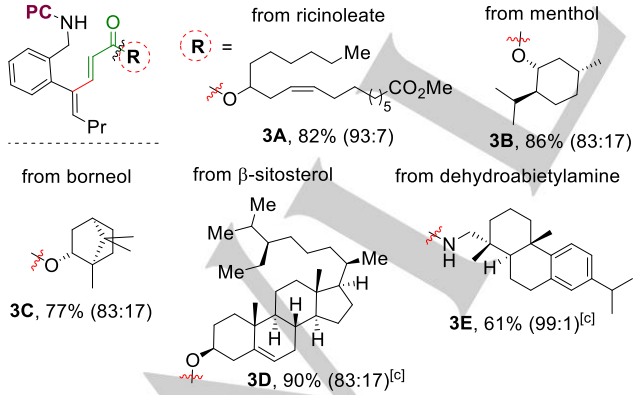




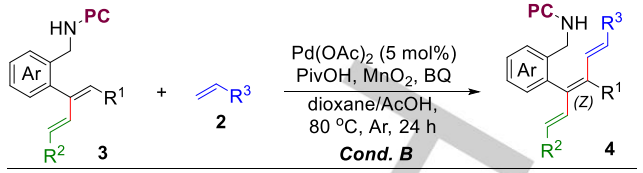


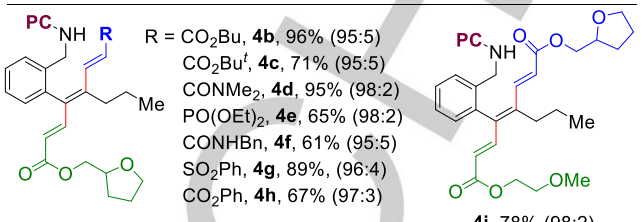


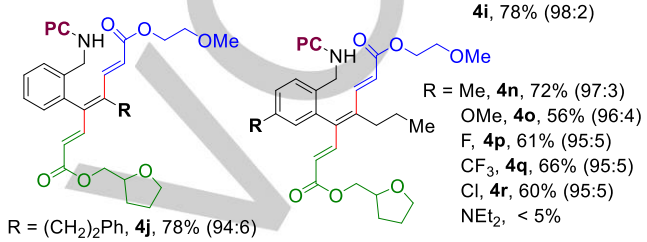


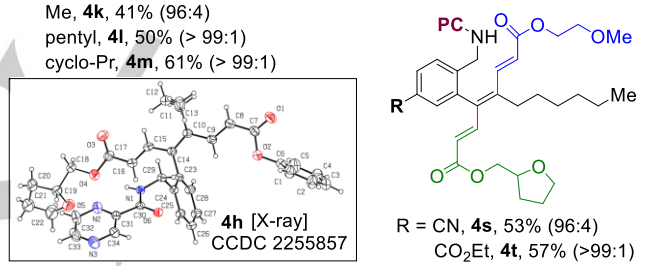


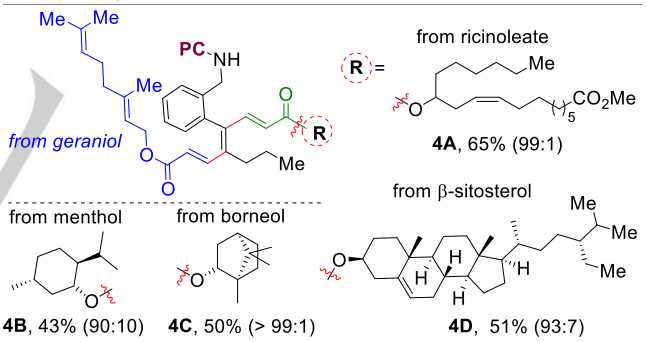
Scheme 1. Scopes of α C−H alkenylation of *E*-alkenes **1**. Reaction conditions A: **1** (0.15 mmol, 1.0 equiv), **2** (2.5 equiv), $Pd(OAc)_2$ (5 mol%), PivOH (1.5 equiv), MnO_2 (3.0 equiv), BQ (10 mol%) in EtOH (0.15 M) at 40 ℃ for 48 h, under Ar. The yields are isolated yields; the *E*/*Z* ratio was determined by ^1H NMR. [a] at 60 ℃. [b] at 70 ℃. [c] at 80 ℃.











Scheme 2. Scope of β C−H alkenylation of dienes **3**. Conditions B: **3** (0.1 mmol, 1.0 equiv), **2** (2.5 equiv), $Pd(OAc)_2$ (5 mol%), PivOH (1.5 equiv), MnO_2 (3.0 equiv), BQ (10 mol%), in dioxane/AcOH (10/1, *v*/*v*) at 80 ℃ for 24 h, under Ar (1 atm); the yields are isolated yields; the *Z*/*E* ratio was determined by ^1H NMR.

C−H alkenylation product in 30% yield with 75/25 *E*/*Z* ratio selectivity (entry 12). To our delight, triene **4a** was successfully obtained in "*one-pot*" reaction using styrene **1** by sequential addition of acrylates **2a** and **2b** under Cond. B (entry 13).

With the optimized conditions in hand, the reactions between *E*-styrenes **1** and various alkenes **2** such as acrylates, vinyl ketone, vinyl phosphonate, vinyl sulfone and acrylamide were examined, and all of them reacted smoothly to afford corresponding dienes in moderate to excellent yields (Scheme 1, 45-97% yields, **3b-3i**). The reaction of α and β substituted acrylates were also examined. While *trans*-methyl crotonate gave

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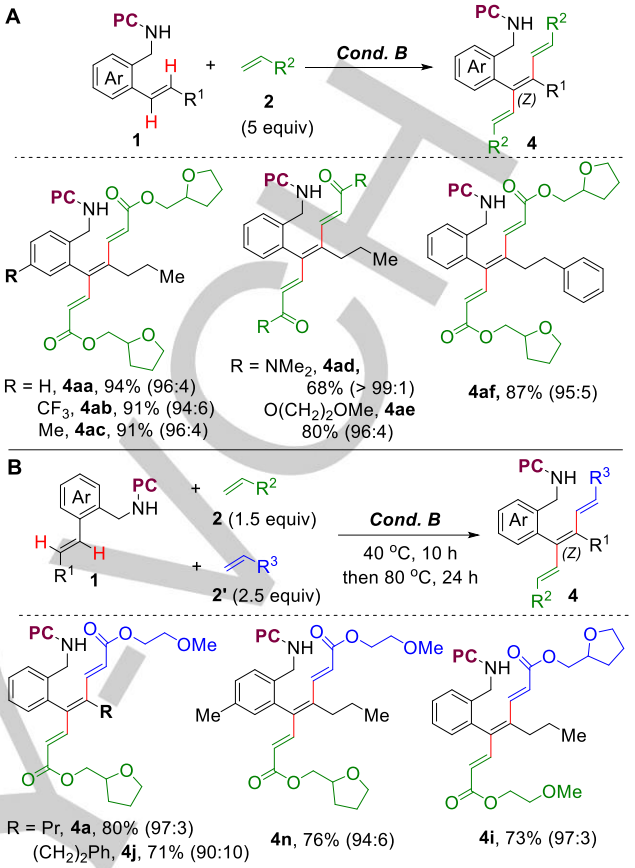
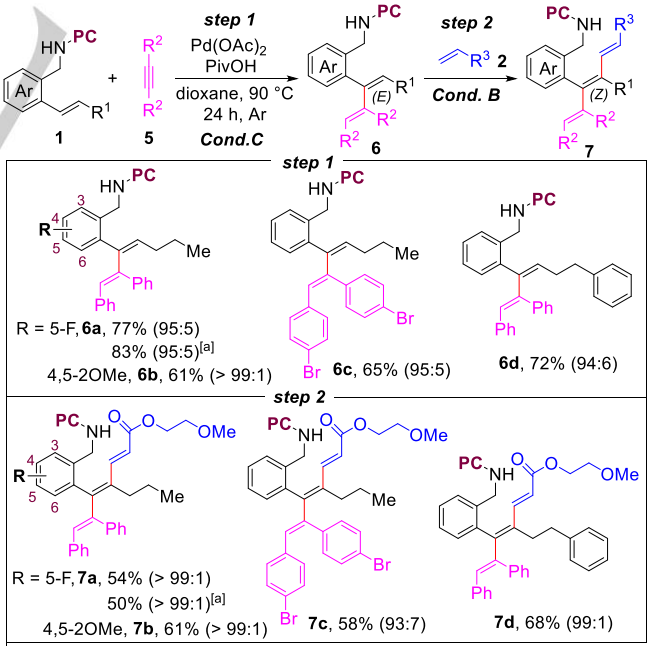
tetra-substituted 1,3-diene **3j** in 56% yield with > 99/1 *E/Z* ratio selectivity, methacrylate afforded skipped diene **3k** in 68% yield with 80/20 *E/Z* ratio selectivity (under Cond. B). Aromatic ring bearing 2, 3, 4 or 5-substituted Me, F, CF_3, OMe, Cl, NEt_2, CO_2Et, and even CN were all well tolerated to give rise to 1,3-dienes **3l-3w** in 42-92% yields with excellent *E/Z* ratio selectivity (up to > 99/1). However, iodo substrate only led to **3x** in 17% yield. (*E,E*)-Configuration and *s-trans* conformation of **3u** was determined by X-ray crystallographic analysis.[12] Installation of other substituents such as methyl, phenyl ethyl, pentyl or even cyclopropyl on olefin were all converted smoothly (76-86% yields, **3y-3ab**). However, styrene bearing tert-butyl group led to **3ac** in only 13% yield. Introduction of methyl and hexyl group to benzyl position still produced diene **3ad** in 66% yield (*E/Z* > 99/1) and **3ae** in 50% yield (*E/Z* = 91/9) respectively. Notably, substrate bearing natural (+)-dehydroabietylamine, β-sitosterol, ricinoleate, menthol and borneol were all well reacted (**3A-3E**).

After that, we turned to investigate β C−H functionalization of *tri*-substituted dienes **3** to prepare various *tetra*-substituted trienes (Scheme 2). Various alkenes such as acrylates, acrylamides, vinylphosphonate and vinyl sulfone are suitable for this β C−H alkenylation, affording the all-carbon *tetra*-substituted trienes **4b-4i** in 61-96% yields with excellent *Z/E* ratio selectivity. (*E,Z,E*)-Configuration and *s-trans* conformation of conjugated triene **4h** were determined by X- ray crystallographic analysis, and all of the conformations of triene products were assigned analogously to compound **4h**.[12] *Tri*-substituted diene bearing phenylethyl was also converted well to afford **4j** in 78% yield with *Z/E* ratio selectivity of 94/6. However, methyl substituted substrate led to **4k** in moderate yield, and the *Z/E* selectivity is still excellent (*Z/E* = 96/4). Dienes bearing pentyl and cyclopropyl were converted smoothly to give **4l** and **4m** in 50% and 61% yields respectively. Phenyl ring bearing various substituents such as Me, OMe, F, CF_3, Cl, CN and CO_2Et were all well tolerated (**4n-4t**, 53-72%). Unfortunately, introduction of amino such as NEt_2 failed to give product. The synthetic application of this method was further highlighted by the successful conversion of alkenes bearing natural (+)-dehydroabietylamine, β-sitosterol, ricinoleate, menthol and borneol as well as geraniol (**4A-4D**). Notably, sensitive geraniol moiety is unsuitable for previous alkenylation conditions with silver salt, highlighting the robustness of this protocol.[3e]

One-pot preparation of *tetra*-substituted trienes **4aa-4af** by α and β *bis*-C−H alkenylation of *E*-styrenes **1** was also successful under Cond. B to demonstrate the robustness of the protocol, by simple increasing the amount of coupling partners (Scheme 3A). By sequential addition of two different alkene coupling-partners, α and β *bis*-C−H alkenylation of *E*-styrenes was still successful in one-pot fashion, performed under Cond. B (Scheme 4B). *E*-styrenes **1** reacted well with (tetrahydrofuran-2-yl) methyl acrylate **2a** and then 2-methoxyethyl acrylate **2b** to give corresponding trienes **4a**, **4j** and **4n** in good yields (71-80% yield) with excellent *Z/E* ratio selectivity (up to 97/3). By a reverse addition of two acrylates **2b** and **2a**, triene **4i** was obtained in 73% yield with *Z/E* ratio selectivity of 97/3. The successful one-pot preparation not only shows the robustness of the protocol, but also highlights a significantly efficient synthesis of 1,3,5-trienes which obviates tedious separation procedure.



Scheme 3. Scope of "one-pot" preparation.



Scheme 4. Scopes of α-/β-C−H alkenylation of aryl alkenes **1** using alkynes **5** and alkenes **2**. Conditions C: **1** (0.1 mmol, 1.0 equiv), alkyne **5** (2.5 equiv), $Pd(OAc)_2$ (10 mol%), PivOH (1.5 equiv) in dioxane (0.15 M) at 90 ℃ for 24 h, under Ar; the yields are isolated yields; the *E/Z* or *Z/E* ratio in parenthesis was determined by ^1H NMR. [a] Gram-scaled synthesis: **6a** (1.19 g, 83%), **7a** (0.75 g, 50%).

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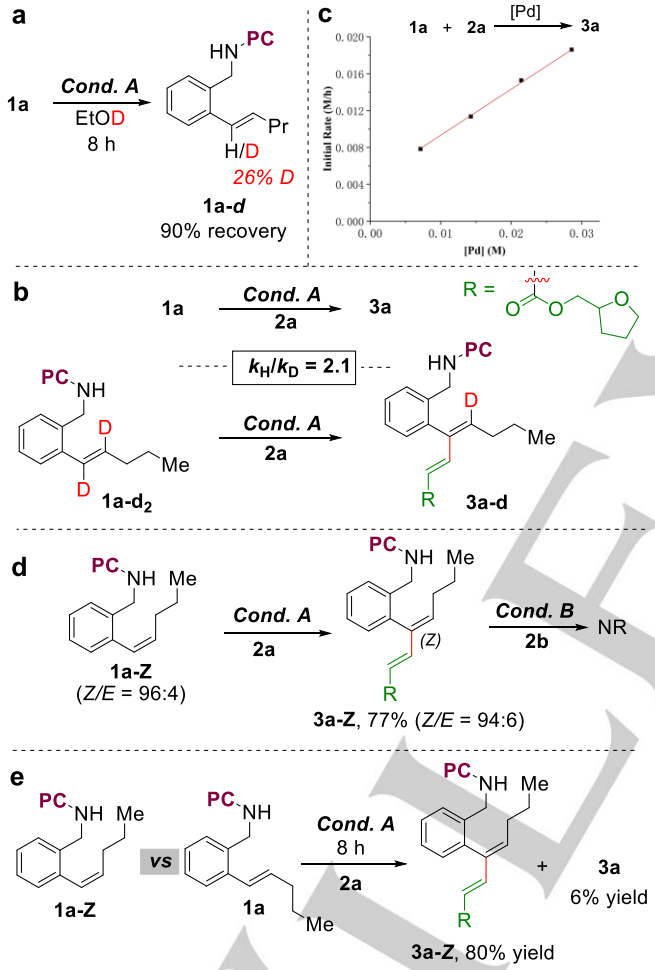
Other coupling partner such as alkynes was also investigated (Scheme 4). Olefinic C−H alkenylation using alkynes was successful in the presence of $Pd(OAc)_2$ (10 mol%) and PivOH (1.5 equiv) in dioxane (Cond. C), affording *tetra*-substituted 1,3-dienes **6a-6d** with 100% atom efficiency in 61-77% yields with excellent *E/Z* selectivity (*E/Z* up to > 99/1). The *Z*-configuration of the product was determined by a NOESY NMR spectrum study, suggesting a *cis* hydro-alkenylation of internal alkynes. To our satisfactory, the subsequent alkenyl β C−H alkenylation using alkenes underwent smoothly under Cond. B to give *penta*-substituted 1,3,5-trienes **7a-7d** in good yields (54-68% yields) with excellent *Z/E* selectivity (*Z/E* up to > 99/1). Moreover, the gram-scaled preparation of **6a** and **7a** was also successful.



Scheme 5. Mechanistic experiments.

Next, mechanistic experiments were performed (Scheme 5). If styrene **1a** was subjected to Cond. A with EtOD, 26% deuterium incorporation at α C−H bond was observed, thereby exhibiting a reversible C−H *exo*-cyclopalladation event. *E/Z* isomerization was not observed in the recovered substrate (Scheme 5a). Kinetic isotope effect (KIE) values determined *via* parallel experiments using non-deuterated and deuterated styrenes **1a** and **1a-d$_2$** suggested alkenyl C−H cleavage to be the rate-determining step (Scheme 5b).[13] Next, dependence of initial rates of the α C−H alkenylations on the amount of $Pd(OAc)_2$ were examined, using substrates **1a** and acrylate **2a**. Initial reaction rates dependence on [Pd] were first-order, confirming the olefinic C−H cleavage to be the rate-determining step (Scheme 5c, see the details in the Supporting Information). To obtain further mechanistic insight for the origin of the reactivity and selectivity, some representative controlled experiments were performed (Scheme 5d-e). If *cis*-styrene **1a-*Z*** was subjected to conditions A, α C−H functionalization by *exo*-cyclopalladation proceeded quite well to afford **3a-*Z*** in 77% yield with 94/6 *Z/E* ratio selectivity, which failed to react further under Cond. B, and the starting material was totally recovered (Scheme 5d).[14] Competitive experiments between *cis*-styrene **1a-*Z*** and *trans*-styrene **1a** revealed the **1a-*Z*** to be much more reactive (Scheme 5e). These results also suggested the much more difficult formation of *exo*-palladacycle intermediate with *E*-alkene, which is consistent with the previous reports.[1-5]

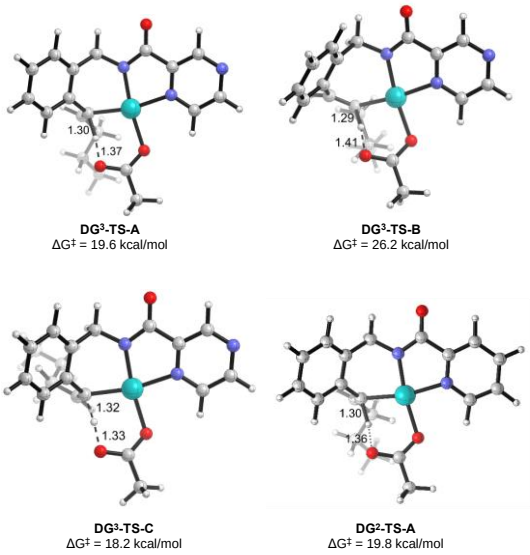


Figure 2. The DFT-optimized transition state structures for C−H activation at different positions and relative free energies with respect to the corresponding alkene complexes. **DG^3-TS-A**: TS for *E*-styrene at α-position (bearing **DG^3**); **DG^3-TS-B**: TS for *E*-styrene at β-position (bearing **DG^3**); **DG^3-TS-C**: TS for *Z*-styrene at α-position (bearing **DG^3**). **DG^2-TS-A**: TS for *E*-styrene at α-position (bearing **DG^2**).

Based on the mechanistic experimental results, we focused on the rate-determining step of carboxylate-assisted concerted metalation deprotonation (CMD) and performed DFT calculations to investigate the origin of selectivity (Figure 2). Firstly, to further interrogate whether C−H activation was possible at other reaction sites, two possible transition state structures were located to reveal the origin of site-selectivity. **DG^3-TS-A**, the transition state for α C(alkenyl)−H activation of *E*-styrene, was located in a free energy barrier of 19.6 kcal/mol with respect to the corresponding *E*-alkene complex, lower than **DG^3-TS-B**, the transition state for β C(alkenyl)−H activation of *E*-styrene, by 6.6 kcal/mol. It indicates that the formation of six-membered *exo*-palladacycle is kinetically more favored than seven-membered *endo*-palladacycle,

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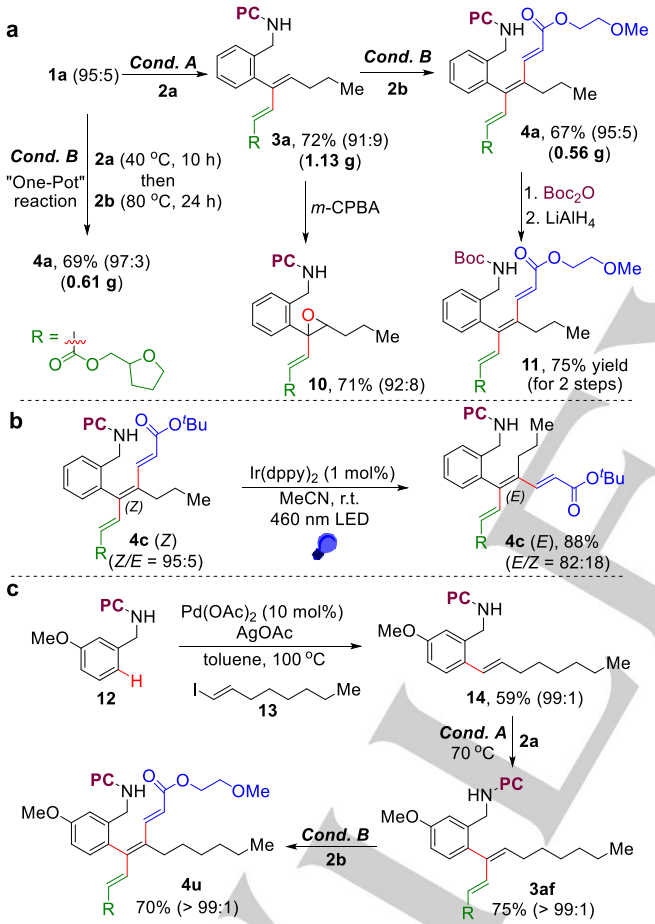
consistent with the experimental site-selectivity. Next, **DG^3-TS-C**, the transition state for α C(alkenyl)−H activation of aromatic *Z*-alkene, was located in an activation free energy of 18.2 kcal/mol with respect to the corresponding *Z*-alkene complex, lower than **DG^3-TS-A** by 1.4 kcal/mol due to the distortion energy of the substrate.[15] Thus, the reactivity of aromatic *Z*-alkene is higher than aromatic *E*-alkene, in accordance with experimental observation (**3a-*Z*/3a** = 13.3/1 in calculation *vs* 80%:6% yield in Scheme 5e). To obtain further computational insights into the directing group, the transition state **DG^2-TS-A** of *E*-styrene at α-position was located with 2-picolinamide (**DG^2**). It is shown that **DG^3** exhibits a significantly better performance than **DG^2** with even **DG^3-TS-A** energetically favored than **DG^2-TS-A** by 0.2 kcal/mol on account of a more effective electronic effect of pyrazine compared to pyridine ring.



Scheme 6. Synthetic application.

To demonstrate the practicality of this method, we conducted gram-scaled preparation and product derivations (Scheme 6a). α C−H alkenylation using styrene **1a** and (tetrahydrofuran-2-yl) methyl acrylate **2a** on a gram-scale occurred smoothly to afford 1.13 g **3a** in 72% yield with 91/9 *E/Z* ratio selectivity. The subsequent β C−H alkenylation afforded 0.56 g **4a** in 67% yield with *Z/E* ratio selectivity of 95/5. The one-pot and two-step synthesis was quite successful to give **4a** in satisfactory results (0.61 g, 69% yield). If *tri*-substituted **3a** was treated with *m*-CPBA, epoxidation occurred smoothly to give phenyl oxirane **10** in 71% yield. The 2-pyrazinamide was readily removed by *N*-Boc-protection and reduction to deliver *N*-Boc benzyl amine **11** in 75% yield (for 2 steps). Recently, visible-light-mediated *E/Z* isomerization of mono-olefins has attracted remarkable attentions,[16] and there are very limited reports on the site-selective *E/Z* conversion of polyenes such as trienes. In an initial study, conjugated triene **4c** undergoes a regioselective *Z/E* isomerization at internal alkene moiety with 1 mol% Ir(dppy)$_2$ in MeCN using a 460 nm LED, providing **4c**-(*E*) in 88% yield with *E/Z* ratio selectivity of 82/18 (Scheme 6b). This remarkable example provides a complementary protocol to our *E/Z* selective 1,3,5-triene synthesis. Using simple benzyl amide **12** as a substrate, we also envisioned a novel and efficient construction of aryl dienes and trienes by multiple C−H alkenylation enabled by pyrazinamide functionality. Palladium-catalyzed aromatic C−H alkenylation of benzyl amide **12** with alkenyl iodide **13** is successful to give styrene **14** in good yield, which underwent subsequent α C−H alkenylation to produce diene **3af** in 75% yield and β C−H alkenylation to afford triene **4u** in 70% yield with excellent *Z/E* selectivity (> 99/1) (Scheme 6c).

In summary, we have successfully developed a sequential α-/β-C−H alkenylations of *E*-styrenes to afford various complex 1,3-dienes and 1,3,5-trienes. This method utilizes *N,N*-bidentate-chelation assistance of pyrazinamide to achieve excellent site- and *E/Z* selectivity via six-membered *exo*-cyclopalladation and seven-membered *endo*-cyclopalladation. The protocol is tolerated a wide range of functionalities such as (+)-dehydroabietylamine, β-sitosterol, ricinoleate, menthol and borneol as well as geraniol and capable of producing a variety of *multi*-substituted 1,3-dienes and 1,3,5-trienes on a gram scale. Complex 1,3,5-trienes were successfully prepared in a one-pot and two-step synthesis. Selectivity and reactivity of the C−H functionalization were elucidated based on mechanistic experiments and DFT calculations. We anticipate that this innovative C−H functionalization strategy will greatly simplify the synthesis of *tetra*-substituted alkenes that feature a range of diverse substituents, including alkenyl, alkyl, aryl, silyl, boryl, and alkynyl. These compounds are highly desirable synthons and are expected to have significant applications in organic synthesis.

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Keywords: C−H bond activation • palladium • alkenylation • alkenes • trienes

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[12] Deposition numbers 2255855 (for **3u**) and 2255857 (for **4h**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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[14] Aliphatic *E*-alkenes led to α C−H functionalization product in only 13% yield with 78/22 *Z/E* ratio selectivity under Cond. A, exhibiting that the embedded phenyl played a key role in such α C−H activation, presumably due to more favorable entropy reduction than flexible aliphatic substrate and conjugated effect to promote C−H cyclopalladation event. Although plain styrene led to trace product under Cond. A, it afforded conjugated triene in 79% yield under Cond. B (see details in the Supplementary Information).

[15] The distortion/interaction analysis shows that the origin of the energy difference between **DG³-TS-A** and **DG³-TS-C** mainly lies into the distortion energy of pent-1-en-1-yl benzene fragment in the substrate. The distortion energy of substrate in **DG³-TS-C** is 22.4 kcal/mol, less than that in **DG³-TS-A** by 3.1 kcal/mol (see details in the Supplementary Information).

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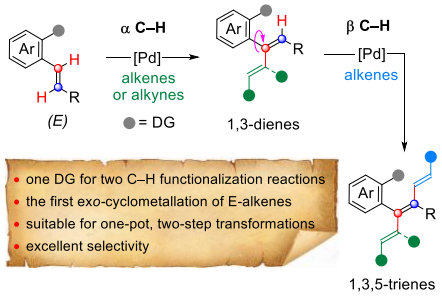

The α-/β-C−H functionalization of E styrenes with simple alkenes and alkynes is presented. The process involves α C−H functionalization via a six-membered exo-palladacycle to afford tri- and tetrasubstituted 1,3-dienes and β C−H functionalization via a seven-membered endo-palladacycle to produce tetra- and pentasubstituted 1,3,5-trienes, both enabled by the chelation assistance of pyrazinamide.