Palladium-catalysed $\alpha$ and $\beta$ C−H allylation of aryl alkenes†

Yilei Liao,†a Xiandie Zhang,†a Xiaoli Li, a Xiuying Liu, a Jiakai Chen, a Chao Shen, *b Rui He, d Guofu Zhong †a, c and Jian Zhang †a, c

Remarkable progress has been made on chelation-assisted $\alpha$ and $\beta$ C−H functionalization of aryl alkenes; however, there is no report on C−H allylation reactions. This work focuses on the first $\alpha$ and $\beta$ C−H allylation of aryl alkenes using allyl carbonates to produce linear and branched 1,4-dienes enabled by chelation-assistance of pyridine-2-carboxamide, simply performed with Pd(OAc)$_2$/AcOH in ethanol. This operationally simple protocol exhibited wide functionality tolerance and broad substrate scope and enabled successful gram-scaled preparation.

Introduction

Chelation-assisted C−H functionalization represents a powerful strategy toward structural complexity from simple raw feedstocks. Among them, olefinic C−H functionalization has attracted remarkable attentions, which provide regio- and stereo-selective synthesis of olefinic derivatives such as 1,3-dienes, 1,4-dienes, and eneynes.$^{1−3}$ These chelation-assisted alkenyl C−H functionalizations proceed by endo- or exo-metallocycle intermediates, generally using 1,1-disubstituted alkenes$^2$ and disubstituted Z-alkenes$^3$ as the substrates, with the other possible reaction sites blocked (Scheme 1a). To the best of our knowledge, although C−H functionalization of Z-alkenes by exo-metallocycle has shown remarkable progress,$^3$ chelation-assisted $\alpha$ C−H functionalization of $E$-alkenes (including $E$-styrenes) bearing two competitive C−H bonds through exo-cyclometallation remains unexplored.

Aryl alkenes are widely occurring and show extensive applications in material and pharmaceutical science.$^4$ Significant progress has been made on chelation-assisted olefinic C−H functionalization of aryl alkenes.$^{5−13}$ The well-defined one is the $\beta$ C−H functionalization of aryl alkenes by endo-metalloycles, including C−H allynylation, alkenylation, cyanation and amino-carbonylation (Scheme 1a).$^{6−13}$ However, $\alpha$ C−H functionalization of aryl alkenes has attracted very limited attention, and the reported methods not only restricted to C−H alkenylation reactions but also employed only ($Z$)-configured aryl alkenes$^{14}$ or plain styrenes (Scheme 1b).$^{1,2}$ For example, Engle$^{14a}$ and our group$^{14b}$ simultaneously reported on (asymmetric) $\alpha$ C−H alkenylation of aryl alkenes, affording (axially chiral) aryl dienes. In stark contrast, $\alpha$ C−H functionalization of $E$-aryl alkenes is rarely reported due to the more difficult

---

†These authors contributed equally to this work.

---

*College of Material, Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Hangzhou Normal University, Hangzhou, 311121 Zhejiang, China. E-mail: zhangjian@hznu.edu.cn
†Key Laboratory of Pollution Exposure and Health Intervention of Zhejiang Province, College of Biology and Environmental Engineering, Zhejiang Shuren University, Hangzhou 310015, P. R. China. E-mail: shenchao@zjsru.edu.cn
‡Department of Chemistry, Eastern Institute of Technology, Ningbo 315200, Zhejiang, China. E-mail: ghong@eitech.edu.cn
§Department of Stomatology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou Normal University, Hangzhou310015, Zhejiang, China
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. See DOI: https://doi.org/10.1039/d4qo00188e

---

Scheme 1  Chelation-assisted $\alpha$ and $\beta$ C−H allylation of aryl alkenes.
exocyclometallation and the existence of two competitive C–H bonds. Moreover, although remarkable progress has been made on olefinic C–H alkylation of simple alkenes, there is no report on α or β C–H alkylation of aryl alkenes (Scheme 1a–c).

Development of α C–H alkylation of (E)- and (Z) configurated styrenes is highly desirable not only for the synthetic diversity to giving skipped diene products with complementary E/Z selectivity but also for providing in-depth mechanistic insight into C–H cyclometallation. With our ongoing interest in olefinic C–H functionalization, herein, we report on the first chelation-assisted α and β C–H alkylation of various styrenes, affording linear and branched skipped dienes and even triene in excellent E/Z ratio selectivity (Scheme 1d).

Results and discussion

Based on our previous reports, we herein turned to examine the C–H alkylation of trans-styrene bearing a N,N-bidentate-chelation directing group (DG1)17 led to no reaction with allyl carbonate (Table 1, entry 1), the substrate bearing pyridine-2-carboxamide (DG2)18 afforded α C–H alkylation product 3a in 77% yield, simply in the presence of 10 mol% Pd(OAc)2 and 2.0 equivalent AcOH in EtOH at 80 °C (entry 2). Aryl alkenes bearing pyrimidine-4-carboxamide (DG3) led to comparable results (entry 3). Other nitrogen heterocycle carbamates such as pyrimidine-2-carboxamide (DG4), pyrazinamide (DG5) and isoquinoline-3-carboxamide (DG6) were also examined, demonstrating that DG2 was the best one (entries 4–6). Using PivOH instead of AcOH led to a 63% yield (entry 7). The reaction without carboxylic acid only afforded a trace product, exhibiting a carboxylate-assisted C–H activation event (entry 8). Therefore, the reaction was unsuccessful using H2O as a solvent, however, H2O/MeOH still led to a 53% yield to demonstrate its robustness (entries 9 and 10). Some other alkylation reagents (AR) were also examined in such C–H alkylation reactions. While allyl iodide 2b and allyl alcohol 2e afforded no reaction, allyl carboxylates 2c and 2d gave moderate yields (entries 11–14).

With the optimized conditions in hand, C–H alkylation between various trans-styrenes 1 and allyl carbonates 2 were examined (Table 2). meta- and para-Substitutes such as F, OMe, CF3, and Me were all well tolerated, affording aryl 1,4-dienes in 49–77% yields (3a–3h). Styrene bearing longer aliphatic chains such as pentyl afforded 3i in 59% yield. However, changing propyl to methyl and phenyl groups decreased the product yield to 33% (3j) and 23% (3k), respectively. Substrates bearing dimethoxy phenyl and naphthyl also gave 3l and 3m in good yields. Secondary amine-derived amide still converted well to give 3n in 66% yield. Unfortunately, neither aniline nor phenylethylamine derivatives showed reactivity, exhibiting the difficult formation of five- and seven-membered palladacycle. Notably, branched allyl carbonate 2f also reacted well to give rise to 3o in 70% yield with 65 : 35 E/Z ratio selectivity. However, other allyl carbonates from 2-phenyl prop-2- en-1-ol (2g) and cinnamyl alcohol (2h) exhibited no reactivity.

After that, we turned to examine the β C–H alkylation of aryl alkenes 4 also bearing pyridine-2-carboxamide (DG2) (Table 3). Under the optimal conditions, styrenes bearing F, CF3 and OMe were converted smoothly to afford 1,4-dienes 5a–5d in 51–76% yields. Notably, branched allyl carbonate 2f reacted well to give diene product 5e in 83% yield. Aryl alkenes bearing phenyl or ethyl at the α position reacted successfully to afford 5f and 5g in 74% and 65% yields, respectively, with excellent E/Z ratio selectivity.

Next, we investigated the reaction of Z-configurated aryl alkenes 6 and plain styrene 8 under optimal conditions. While Z-styrene gave rise to α C–H alkylation product 7 in 66% yield with 93 : 7 E/Z ratio selectivity (Scheme 2a), plain styrene afforded triene product 9 in 51% yield with >99 : 1 E/Z ratio selectivity (Scheme 2b).
To explore the mechanism of this C–H allylation of styrenes, controlled reactions were performed as described in Scheme 3. If E-styrene 1a was subjected to the optimal conditions with EtOD (0.1 M), 97% deuterium incorporation was observed with 81% recovery, exhibiting the α C–H activation to be facile and reversible (Scheme 3a). If the same reaction was conducted in the presence of allyl carbonate 2a, 38% product yield and 50% recovery of 1a without deuterium incorporation were observed, which demonstrated a much faster olefin insertion to outcompete the C–H activation step (Scheme 3b).

Allylation product 3a was obtained in 38% yield with 0% deuterium incorporation, exhibiting a direct 2a insertion followed by liberation of CO₂ and MeOH. An intermolecular competition experiment between 6 and 1a was conducted to give the product 7 in 40% yield and 3a in trace amount, exhibiting a much higher reactivity of Z-styrene to outcompete E-styrene, also exhibiting a more difficult formation of exo-metallocycle with E-alkenes (Scheme 3c). Aliphatic E-alkene 10 was also examined, and only a trace product was detected under optimal conditions (Scheme 3d). Benzyl amide 11 led to no aromatic C–H allylation, exhibiting the difficult formation of five-membered palladacycle (Scheme 3e).

Gram-scaled preparation of 3a was successful using 5 mol% Pd(OAc)₂ to demonstrate the robustness and practicality of this method (Scheme 4a). The directing group was readily removed by N-Boc protection followed by reduction with LiAlH₄, providing NHBoc benzylamine 11 in 78% yield (Scheme 4b). Terminal alkene of 1,4-diene 3a was selectively reduced to give alkene 12 in 76% yield by using 10% Pd/C under hydrogen (1 atm) (Scheme 4c). Notably, two olefin moieties in 3o were completely reduced to a fork branched alkane 13 in 45% yield (Scheme 4d).

Based on previous reports and experiment results, a plausible catalytic cycle is proposed in Scheme 5. Coordination between the substrate and metal occurred to give a π-olefin palladacycle 1, which then formed a six-membered palladacycle.
ladacycle II by a reversible α-C–H activation. Ligand exchange by allyl carbonate coordination and alkene insertion took place to afford an eight-membered palladacycle IV. Finally, β-oxygen elimination occurred to produce aryl 1,4-diene 3.

**Conclusions**

In conclusion, we have developed N,N-bidentate-chelation assisted α and β C–H allylation of E- and Z-configurated aryl alkenes, as well as α-substituted styrenes and plain styrenes, producing linear and branched 1,4-dienes and 1,4,7-triene with excellent Z/E ratio selectivity. The operationally simple protocol showed a broad substrate scope and enabled gram-scaled preparation. This method is anticipated to exhibit wide applications in multifarious organic synthesis.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (No. 22278103, 21502037, 21672048 and 81570989), Natural Science Foundation of Zhejiang Province (ZJNSF) (LY19B020006), Major Project of Hangzhou Health Science and Technology Plan (Z20200046), and Key Subject of Stomatology in Hangzhou for financial support.

**References**

1 (a) X.-J. Shang and Z.-Q. Liu, Transition metal-catalyzed C\textsubscript{vinyl}–C\textsubscript{vinyl} bond formation via double C\textsubscript{vinyl}–H bond activation, *Chem. Soc. Rev.*, 2013, **42**, 3253–3260; (b) K. Wang, F.-D. Hu, Y. Zhang and J.-B. Wang, Directing group-assisted transition-metal-catalyzed vinylic C–H bond functionali-
This journal is © the Partner Organisations 2024.


Research Article


14 (a) M.-Y. Liu, J.-T. Sun, T. G. Erbay, H.-Q. Ni, R. Martín-Montero, P. Liu and K. M. Engle, Pd(ni)-Catalyzed C(alkenyl)–H Activation Facilitated by a Transient Directing


19 1,4-Diene was not obtained herein, and this is because 1,4-diene from allylation of 8 is more reactive than 8 to undergo the second allylation to give triene.

20 All of the substrates in Tables 2 and 3 and Scheme 2 afforded no aromatic C–H allylation, exhibiting excellent regio selectivity.