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Regio- and stereo-selective olefinic C–H functionalization of aryl alkenes in ethanol†

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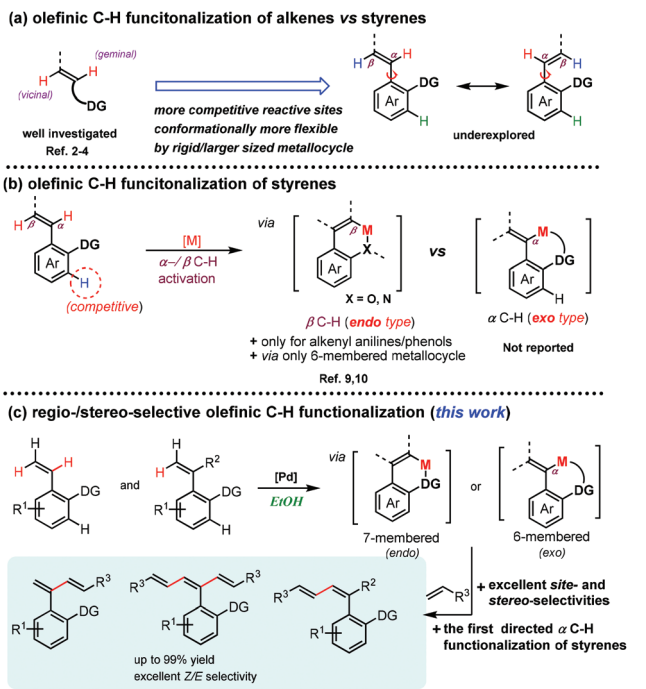
We report on *N*,*N*-bidentate-chelation-assisted α- and β-olefinic C–H alkenylation of aryl alkenes in ethanol to afford aryl dienes/trienes with excellent regio- and stereo-selectivities. The reaction of 2-alkenyl benzylamine and benzoic acid derived substrates proceeded through six-membered *exo*-cyclometallation and seven-membered *endo*-cyclometallation. The aerobic protocols feature wide functionality tolerance, high selectivities and yields, mild conditions and scalable preparation, and the directing group can be easily removed to afford Boc-protected amine by simple reduction.

Introduction

In the past decade, chelation-assisted olefinic C–H functionalization provided site- and stereo-selective preparation of alkene derivatives or (hetero) cycles that proceeds through five- or six-membered *endo*-/*exo*-metallocycles.[1] There are generally two kinds of functional group-directed olefinic C–H activation reactions. One is the vicinal group directed alkenyl C–H activation that proceeds through five-/six-membered *endo*-cyclometallation to afford *cis*-C–H functionalized alkene derivatives.[2] The other one is the geminal group-directed olefinic C–H functionalization by the formation of *exo*-metallocycle intermediates.[3] For example, the Engle group demonstrated a Pd-catalyzed olefinic C–H alkenylation of nonconjugated alkenyl amides to afford highly substituted 1,3-dienes under *N*,*N*-bidentate chelation assistance.[3a] Carreira and co-workers developed *N*,*N*-bidentate chelation-assisted alkenyl C–H iodination and alkynylation under palladium catalysis.[3b,c] The Dong group demonstrated an elegant Pd/NBE-catalyzed distal-selective olefinic C–H arylation assisted by an oxime ether based *exo*-directing group.[3i] Our group developed *O*-monodentate chelation-assisted alkenyl C–H alkenylation of simple alkenyl alcohols, amides and carbamates.[3d] Despite the efficacy of the chelation-assisted olefinic C–H activation of simple alkenes, extension of this strategy to the selective C–H functionalization of more complex and flexible olefinic systems, such as styrenes or polyenes, is still challenging and unexplored, owing to their reaction complexity and conformational flexibility (Scheme 1a).

Aryl alkenes such as styrenes occur widely in countless drugs and natural products, and are often utilized as valuable synthons and precursors for material preparation.[4] Many efforts have been devoted to the preparation of aryl alkenes;



Scheme 1 Regio- and stereo-selective olefinic C–H functionalization of aryl alkenes.

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however, the regio- and stereo-selective preparation of styrene derivatives with high atom economy remains highly sought after. Transition-metal-catalyzed cross-coupling reactions between arenes and alkenes or alkynes have been well investigated to afford di- and tri-substituted styrenes by aromatic C–H alkenylation or alkenyl C–H arylation.[5–8] In stark contrast, although simple styrenes occur widely and are easily accessible, direct C–H functionalization of simple styrenes to afford valuable styrene derivatives has attracted much less attention.[9,10] There has been hydroxyl- and amino-directed olefinic β-C–H activation/cyclization using 2-vinyl aniline/phenol substrates, proceeding through the formation of six-membered *endo*-metallocycles, in which directed aromatic C–H activation is impossible due to the disfavored formation of four-membered metallocycles. For example, Nachtsheim and co-workers demonstrated a rhodium-catalyzed hydroxyl-assisted alkenyl C–H alkynylation of 2-vinylphenol substrates using a hypervalent iodine reagent.[9a] The Mascareñas and Gulías group developed palladium- or rhodium-catalyzed annulation of *o*-vinylphenols or 2-alkenyl anilides with alkynes or allenes.[9a–f] To the best of our knowledge, while limited examples of group-directed β-C–H activation have been demonstrated, there is still no report on chelation-assisted α-C–H functionalization of styrenes presumably due to the difficult formation of aromatic *exo*-metallocycles with increased rigidity and strain under catalytic conditions (Scheme 1b).

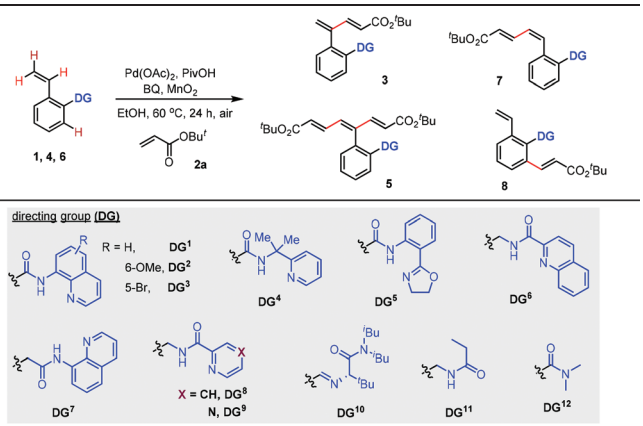
Polyenes, used as valuable synthons, are also key structures of many natural products and pharmaceutically relevant molecules. With our ongoing interest in olefinic C–H functionalization,[2i–o,3d,e] herein, we focus on selective α-/β-C–H functionalization of styrenes to afford aryl polyenes in a regio- and stereo-selective manner (Scheme 1c). However, compared to the well-defined directed alkenyl C–H functionalization, several new challenges can be envisaged for styrene substrates. First, more competitive C–H bonds exist in styrene substrates, including aromatic and alkenyl C–H bonds, which increase the reaction complexity. Second, the conformational complexity of the styrene substrate disfavors the desired C–H activation. Third, the judicious choice of a suitable directing group (DG) to modulate the reactivity and selectivity is extremely challenging (Scheme 1a and b).

Results and discussion

With these considerations in mind, our initial study started with C–H functionalization of challenging styrene substrates **1**, **4** or **6** derived from 2-vinyl benzyl amide/benzamide/benzaldehyde, which includes four competitive reaction sites: three olefinic C–H bonds and one aromatic C–H bond. In previous chelation-assisted alkenyl β-C–H functionalization of styrenes, the α-position of the substrate is generally blocked to obviate the reaction complexity, and aromatic (*ortho*) C–H activation is impossible due to the disfavored four-membered cyclometallation.[9,10] Notably, the only example using plain 2-vinyl phenol substrates still led to benzoxepine products *via* β-C–H activation under rhodium catalysis,[10c] and chelation-assisted α-C–H functionalization of styrenes remains a significant challenge. We initially examined a variety of Rh-, Ru-, Ir- and Pd-based catalytic conditions for mono *O*- or *N*-chelation-assisted alkenyl C–H functionalization,[1–3] using 2-vinyl benzyl amide/benzamide derivatives, but none of them led to the desired α-/β-functionalized products.

Inspired by the great success of the *N*,*N*-bidentate-chelation-assisted strategy in C–H activation,[11] we turned to examine substrates bearing Daugulis's 8-aminoquinoline (AQ) and picolinamide (PA) directing groups as well as their analogues.[12] Fortunately, the reaction between AQ-styrene (**DG^1**) and *tert*-butyl acrylate was successful, with the combination of a catalytic amount of $Pd(OAc)_2$/benzoquinone (BQ), a quantitative amount of the oxidant MnO_2 and the additive PivOH in ethanol, leading to the α-C–H olefination product **3a** in 69% yield with excellent selectivity (Table 1, entry 1). No product generated *via* β-olefinic or aromatic C–H activation was observed, exhibiting excellent regio-selectivity. Various solvents including alcohols such as MeOH, HFIP and CF_3CH_2OH were examined, but all of them led to decreased yields (see Table S1 in the ESI†). Electronically biased substituents such as OMe and Br on 8-aminoquinoline were examined, and both of them led to decreased product yields (entries 2 and 3). Other repre-

Table 1 Optimization of catalytic conditions using phthalimide[a]



Entry	DG	**3** yield (%)	**5** yield (%)	**7** yield (%)	**8** yield[b] (%)
1	**DG^1**	69	—	—	—
2	**DG^2**	61	—	—	—
3	**DG^3**	25	—	—	—
4	**DG^4**	30	—	—	—
5	**DG^5**	0	—	—	—
6	**DG^6**	<5	—	—	—
7	**DG^7**	<5	—	—	—
8	**DG^8**	23	—	—	—
9	**DG^9**	0	77	—	—
10[c]	**DG^9**	36	18	—	—
11	**DG^{10}**	23	—	—	—
12	**DG^{11,12}**	—	—	—	—

[a] Reaction conditions: **1**, **4** or **6** (0.15 mmol, 1.0 equiv.), **2a** (2.5 equiv.), $Pd(OAc)_2$ (15 mol%), PivOH (1.5 equiv.), BQ (10 mol%), MnO_2 (3 equiv.), and EtOH (1 mL) at 60 °C for 24 h, under air. [b] Isolated yields. [c] **2a** (1.25 equiv.) added.

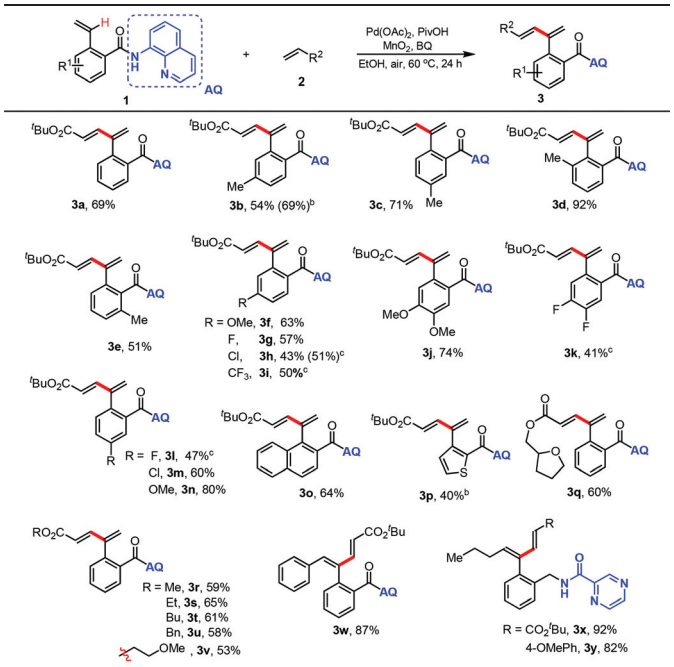
sentative *N*,*N*-bidentate-chelation directing groups (**DG**[4]–**DG**[7]) were investigated, but none of them led to satisfactory results (entries 4–7). Interestingly, although styrene bearing picolinamide **DG**[8] led to only α-C–H functionalization in 23% yield, 2-pyrazinamide **DG**[9] produced triene **5a** in 77% yield *via* α,β-bis C–H functionalization (entries 8 and 9). When the same reaction was performed using 1.25 equiv. of acrylate, a mixed mono-alkenylation and bis-alkenylation was obtained, exhibiting a sequential α- and β-C–H functionalization event in the formation of **5a** (entry 10). While aldehyde derived *N*,*O*-bidentate transient directing group **DG**[10] still led to 23% yield, simple amides (**DG**[11] and **DG**[12]) were ineffective (entries 10–12).

With the optimal conditions in hand, we turned to examine the generality of the olefinic C–H alkenylation of 2-vinylbenzamides **1**, bearing 8-aminoquinoline (AQ) as the directing group (Table 2). Various 3-, 4-, 5- and 6-methyl substituted 2-vinyl benzamides reacted well with *tert*-butyl acrylate to afford the corresponding phenyl dienes in 51–92% yields (**3b–3e**). Notably, 3- and 6-methyl substrates afforded 92% and 51% yields respectively, exhibiting good tolerance of sterically bulky substrates (**3d** and **3e**). Next, differently mono- and bis-substituted substrates bearing OMe, F, Cl and CF_3 were examined, and all of them were smoothly converted to afford the corresponding alkenylation products in 41–80% yields, showing a wide spectrum of functionality tolerance (**3f–3n**). Notably, the naphthyl substrate also reacted well, and even alkenyl thiophene led to a moderate yield at an elevated temperature (**3o** and **3p**). Moreover, a series of acrylates were also investigated, and all of them afforded satisfactory results (**3q–3v**, 53–65% yields). The *cis*-stilbene substrate bearing AQ reacted well with acrylate to afford **3w** in 87% yield. In addition, 2-pyrazinamide was an effective directing group in α-C(olefinic)–H alkenylation of *cis*-styrenes, using acrylate and 4-methoxystyrene as coupling partners (**3x** and **3y**).

Introduction of 8-aminoquinoline (AQ) led to only α-C–H alkenylation with plain 2-vinyl benzamides; however, α,β-bis C–H alkenylation products were smoothly obtained by employing 2-pyrazinamide (PC) as a directing group instead (Table 3). A series of acrylates coupled well with 2-vinylbenzylamine derived pyrazinamides **4** to provide phenyl trienes in 54–81% yields (**5a–5e**). However, ethyl acrylate led to the formation of a mixture of triene **5f** (71%) and diene **5f′** (21%). The protocol was successfully applied to various substrates bearing 2-Me, 5-Me, 4-OMe and 3-CF_3 substituents (**5g–5j**, 60–73% yields), under slightly modified optimal conditions.

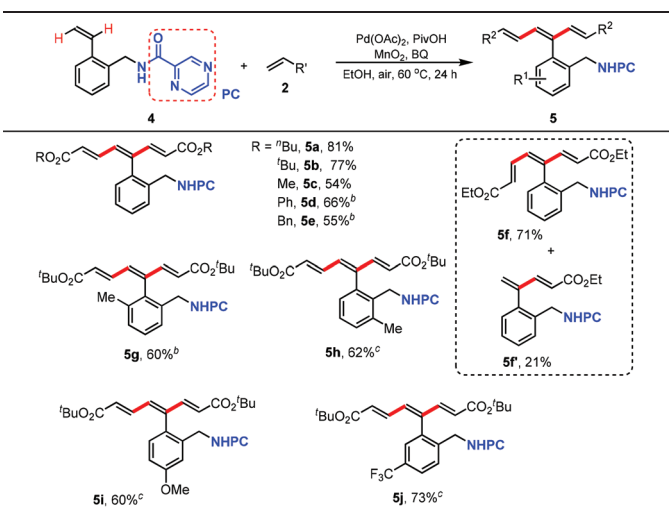
Next, we turned to examine the scope of β-C–H functionalization of 2-vinyl benzylamides bearing 2-pyrazinamide (PC) as the directing group (Table 4). A broad range of electron-deficient alkenes were suitable coupling partners, including alkyl/phenyl acrylates, acrylamide, vinyl ketone and vinyl phosphate, leading to 84%–99% yields with excellent *Z*/*E* selectivity (**7a–7h**). Substrates bearing functionalities such as Me, 3-F, 3-CF_3 and 4-OMe all afforded the desired products in excellent yields (**7i–7l**, 83–99% yields). Notably, both 3- and 6-methyl substituted styrenes reacted smoothly, indicating that steric hindrance had little influence on the reactivity, and styrene **7n** was obtained as a racemic mixture of axial chirality. Both α-ethyl and α-phenyl substituted styrenes reacted well with *tert*-butyl acrylate to afford the corresponding dienes **7o** and **7p** in

Table 2 Substrate scope of α-alkenylation[a]



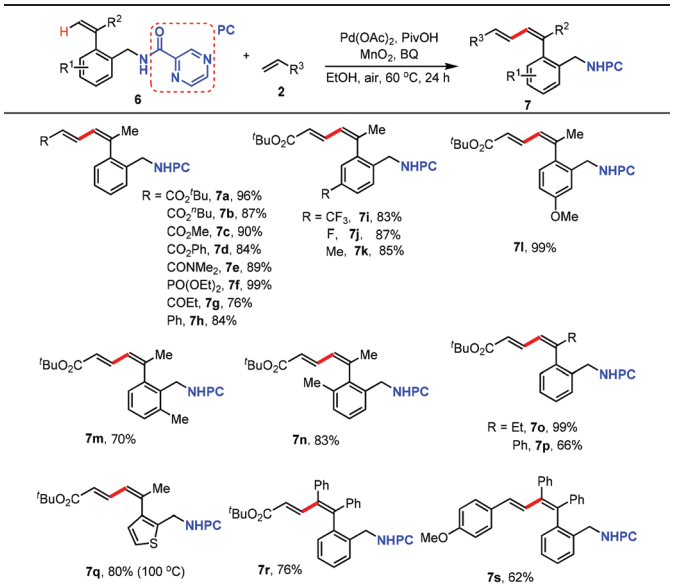
[a] Reaction conditions: **1** (0.15 mmol, 1.0 equiv.), **2** (2.5 equiv.), Pd(OAc)$_2$ (15 mol%), PivOH (1.5 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in EtOH (1 mL) at 60 °C for 24 h, under air; the yields are isolated yields. [b] At 80 °C. [c] 20 mol% Pd(OAc)$_2$ used.

Table 3 Substrate scope of α- and β-bis-alkenylation[a,b]



[a] Reaction conditions: **4** (0.15 mmol, 1.0 equiv.), **2** (2.5 equiv.), Pd(OAc)$_2$ (15 mol%), PivOH (1.5 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in EtOH (1 mL) at 60 °C for 24 h, under air; the yields are isolated yields. [b] 20 mol% Pd(OAc)$_2$ used. [c] 12 h.

Table 4 Substrate scope of β-alkenylation



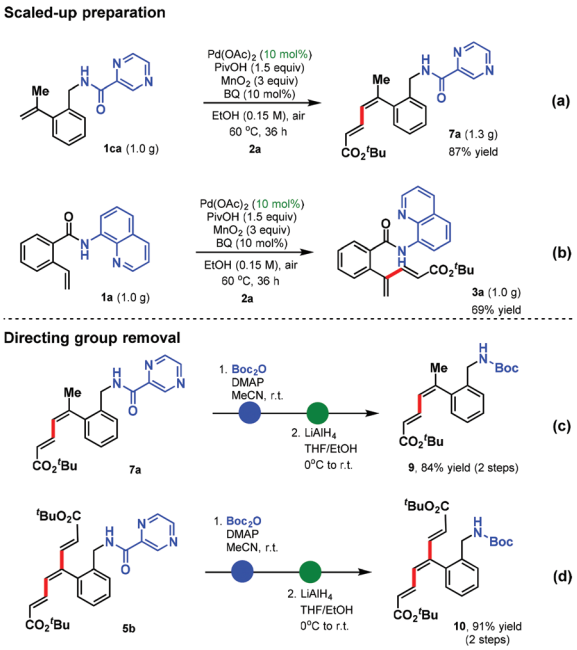
Reaction conditions: **6** (0.15 mmol, 1.0 equiv.), **2** (2.5 equiv.), $Pd(OAc)_2$ (15 mol%), PivOH (1.5 equiv.), MnO_2 (3.0 equiv.), BQ (10 mol%) in EtOH (1 mL) at 60 °C for 24 h, under air; the yields are isolated yields.

99% and 66% yields respectively. Interestingly, 3-vinyl thiophene also showed excellent reactivity at an elevated temperature (**7q**). All-carbon tetrasubstituted alkenes occur widely in natural products and pharmaceuticals, but their regio- and stereo-synthesis still faces significant challenges. Herein, triaryl substituted alkenes reacted well with *tert*-butyl acrylate and *p*-methoxystyrene to afford all-carbon tetrasubstituted alkenes **7r** and **7s** in 76% and 62% yields, respectively, with excellent stereo-selectivity.

On investigating the scalability, gram-scale β- and α-selective C–H alkenylations were both successful, leading to **7a** and **3a** in 87% and 69% yields respectively (Scheme 2a and b). Using a reported method on the deprotection of aminoquinoline,[13] the removal of the amide moiety in **7a** and **5b** was readily accomplished by carbamation and then reduction at room temperature to give Boc-protected amines **9** and **10** in 84% and 91% yields respectively (Scheme 2c).

Conclusions

In conclusion, we have presented Pd-catalyzed α- and β-olefinic C–H alkenylation of styrenes with excellent site- and stereo-selectivity using ethanol as the solvent, assisted by *N*,*N*-bidentate chelation. The protocol exhibits wide functionality tolerance and enables gram-scale preparation, demonstrating its practicality and versatility. Furthermore, the amide auxiliary could be smoothly removed to afford Boc-protected amine under mild reduction conditions. We anticipate that this C–H functionalization reaction will find broad applicability in multifarious synthetic endeavors.



Scheme 2 Synthetic applications.

Author contributions

J. Zhang conceived and designed this work. C. Shen, Y. Zhu, S. Jin, K. Xu, S. Luo and L. Xu performed the experiments and provided the results. G. Zhong and L. Zhong provided useful advice. C. Shen and Y. Zhu analyzed the data and wrote the manuscript. J. Zhang and G. Zhong checked and revised the manuscript. C. Shen and Y. Zhu contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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