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Access to axially chiral aryl 1,3-dienes by transient group directed asymmetric C–H alkenylations†

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We present a Pd-catalyzed atroposelective preparation of aryl 1,3-dienes from readily available styrenes and olefins through an aldehyde derived transient chiral auxiliary, proceeding by enantioselective olefinic C–H alkenylation of styrenes *via* seven-membered endo-cyclometallation. The generality of the protocol has been demonstrated by the smooth conversion of a wide range of 2-vinyl benzaldehyde derivatives to afford up to 99% yields and high to excellent enantioselectivities (up to >99% ee). The derived axially chiral carboxylic acid was demonstrated to be a more efficient ligand in the Cp*Co(III)-catalyzed asymmetric C(sp³)–H alkylation.

Introduction

Axially chiral aryl 1,3-dienes are quite useful in asymmetric synthesis as well as drug and natural product preparation, however, their enantioselective construction is quite challenging due to their relatively lower rotation barriers compared to biaryl compounds.¹ Pioneered in the work of Adams in the 1940s,^{2a} previous studies have been devoted to the asymmetric preparation of axially chiral styrenes using stoichiometric point-chiral molecules.² Recently, the asymmetric synthesis of axially chiral arylcyclohexenes was achieved by a palladium-catalyzed asymmetric cross-coupling^{3a,b} and cation-directed *O*-alkylation strategy,^{3c} as well as by the electrophilic carbothio-lation of alkynes.^{3d} However, the construction of more challenging chiral styrenes bearing an acyclic olefin moiety has been realized by the organocatalytic enantioselective addition of nucleophiles toward alkynes by Tan^{4a} and Yan.^{4b–d} Shi and co-workers reported a chiral CPA-catalyzed approach toward oxindole-based axially chiral styrenes by kinetic resolution.^{4e} Despite their remarkable progress, careful design and discovery of novel methods toward new types of axially chiral structures are still in high demand.

Asymmetric C–H functionalization has been demonstrated to be a powerful method for the preparation of axially chiral biaryl compounds by locking a preformed axis⁵ or creation of a biaryl axis *via* asymmetric cross-coupling.⁶ However, atroposelective C–H functionalization to afford axially chiral styrenes remains underdeveloped due to relatively higher reaction temperatures and lower rotation barriers.⁷ The Shi group developed an asymmetric aromatic C–H functionalization of styrenes bearing pyridine^{7a} and an aldehyde group^{7b} on the olefin moiety to efficiently afford their axially chiral derivatives. The Wang group demonstrated axially chiral preparations of styrene-type carboxylic acids by palladium-catalyzed enantioselective C–H alkenylation and arylation of cinnamic acids.^{7d} While enantioselective aromatic C–H functionalization has been explored,^{5–7} examples of asymmetric olefinic C–H functionalization to construct axial chirality remain scarce (Scheme 1a). The only example is the recent atroposelective thioether-directed alkenyl C–H olefination by the Shi group (Scheme 1b).⁸

In the past decade, chelation-assisted olefinic C–H functionalization has provided an atom- and step-economical atomic preparation of alkene derivatives in a regio- and stereoselective manner by cyclometallation events.^{9–11} However, the extension of this strategy to the selective functionalization of more complex styrene substrates is still underexplored. There has been a hydroxyl- or amino-directed olefinic activation/cyclization using 2-vinyl aniline/phenol substrates, proceeding by the formation of six-membered endo-metallo-cycles; however, the olefinic C–H functionalization by seven-membered metallo-cycles is still challenging and unexplored.^{12,13}

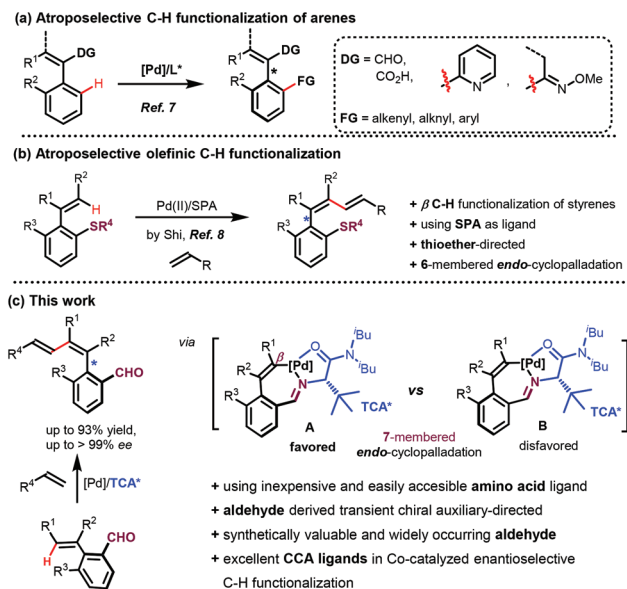
We recently published a regio-selective alkenyl C–H functionalization of styrenes under *N,N*-bidentate chelation assistance;¹⁴ herein, we focus on the asymmetric alkenyl C–H

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Scheme 1 Regioselective and asymmetric C–H functionalization of aryl alkenes.

functionalization of styrenes using specific transient chiral auxiliaries. It is proposed that asymmetric alkenyl C–H activation is preferred owing to the steric interaction to form enantio-enriched palladacycles **A** (Scheme 1c). Notably, this transformation proceeds by challenging 7-membered endo-palladacycles to realize the β -C–H functionalization. Compared to the recently published atroposelective thioether-directed β -C–H activation of styrenes,⁸ this work employed aldehyde derived transient directing groups and easily accessible amino acids as ligands instead of SPA (spiro phosphoric acid); the aldehyde is widely occurring and synthetically more valuable for further transformation.

Results and discussion

Inspired by the elegance of the transient directing group (TDG) strategy in C–H functionalization, which obviates the tedious steps for the installation/removal of directing groups,^{15,16} our study started with the C–H functionalization of challenging 2-vinyl benzaldehyde derivatives **1a**, which include competitive olefinic C–H bonds and aromatic C–H bonds. The reaction of aldehyde **1a** and acrylate **2a** by olefinic β -C–H functionalization was performed using 10 mol% Pd(OAc)₂, 30 mol% transient chiral auxiliary (TCA-1), 1.0 equivalent of Co(OAc)₂·4H₂O, 1.0 equivalent of BQ and 50 mol% of (BnO)₂PO₂H in HOAc/DMSO at 40 °C under an O₂ atmosphere, leading to the desired aryl 1,3-diene **3a** with 52% yield and 98% ee (Table 1, entry 1). A series of amino-acid derived TCAs were examined, and all of them led to decreased product yield and/or stereoselectivity (entries 2–5). Next, we turned to examine other co-oxidants such as MnO₂ instead. Although using 1.0 and 2.0 equivalents of MnO₂ led to 69% and 60%

Table 1 Optimization of catalytic conditions^a

TCAs:

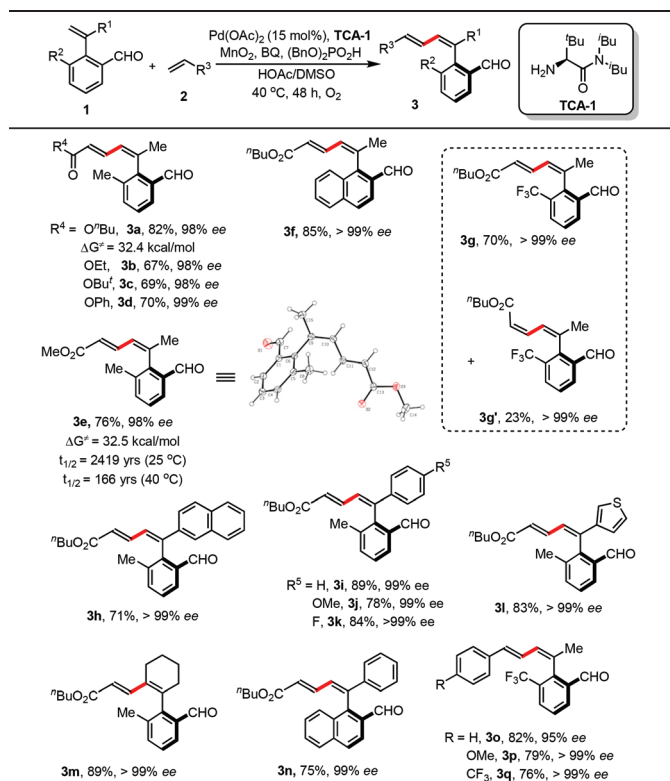
TCA	Yield (%)	ee (%)
TCA-1	52%	98%
TCA-2	16%	99%
TCA-3	19%	72%
TCA-4	16%	98%
TCA-5	0%	—

Entry	TCA	Oxidant	3a yield ^b (%)	ee ^b (%)
1	1	Co(OAc) ₂ ·4H ₂ O	52	98
2	2	Co(OAc) ₂ ·4H ₂ O	16	99
3	3	Co(OAc) ₂ ·4H ₂ O	19	72
4	4	Co(OAc) ₂ ·4H ₂ O	16	98
5	5	Co(OAc) ₂ ·4H ₂ O	0	—
6 ^c	1	MnO ₂	69	98
7 ^d	1	MnO ₂	60	98
8 ^e	1	MnO ₂	82	98
9 ^f	1	MnO ₂	45	98
10 ^g	1	MnO ₂	48	97

^a Reaction conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (4.0 equiv.), Pd(OAc)₂ (15 mol%), TCA (30 mol%), metal oxidant (1.0 equiv.), BQ (1.0 equiv.), (BnO)₂PO₂H (50 mol%), and HOAc/DMSO (10/1, v/v) as solvent at 40 °C for 48 h, under O₂ (1 atm). ^b Isolated yields; the ee value was determined by HPLC. ^c MnO₂ (1.0 equiv.) was added. ^d MnO₂ (2.0 equiv.) was added. ^e MnO₂ (1.5 equiv.) was added. ^f At 25 °C, MnO₂ (1.5 equiv.) was used. ^g Pd(OAc)₂ (5 mol%) with TCA-1 (15 mol%), MnO₂ (1.5 equiv.) was used.

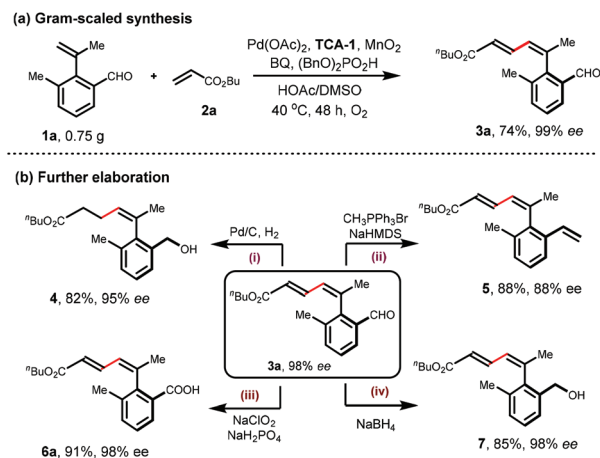
yields, respectively, adjusting the amount of MnO₂ to 1.5 equivalents further improved the yield to 82% with 98% ee (entries 6–8). This reaction even worked at room temperature, although the yield decreased to a moderate level without the erosion of the ee value (entry 9). Lower catalyst loading (5 mol% Pd) was also tested, and axially chiral product **3a** was obtained in 48% yield with 97% ee (entry 10). The aromatic C–H activation did not occur in this protocol, exhibiting its excellent regio-selectivity.

After that, we turned to investigate the generality of the atroposelective alkenyl C–H functionalization of styrenes (Table 2). Various acrylates are suitable with this reaction, affording the axially chiral products in 67–82% yields with excellent enantioselectivities (**3a–3e**, 98–99% ee). However, vinyl ketone, vinyl sulfone and acrylamide are unsuccessful. A naphthyl type substrate also showed excellent reactivity and enantioselectivity (**3f**, yield 85%, >99% ee). Interestingly, 3-CF₃ substituted styrene led to separable isomers **3g** and **3g'** in 70% and 23% yields, respectively, both of which were obtained with >99% ee. A wide range of substituents on alkenyl and phenyl moieties were examined, and we found that substrates bearing the naphthyl group (**3h** or **3n**), OMe (**3j**), fluoro (**3k**), or thienyl (**3l**) were all reacted smoothly to afford corresponding products in 71–89% yields with high enantioselectivities (≥99% ee). Notably, a cyclohexane imbedded substrate was also well converted to provide cyclic axially chiral product **3m** in 89% yield

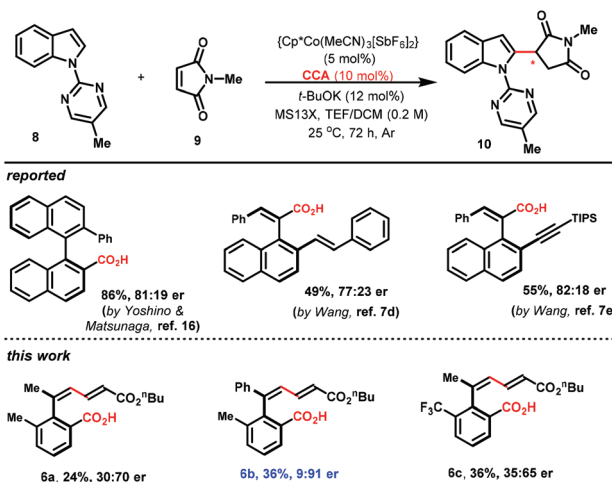
Table 2 Substrate scope of asymmetric C–H alkenylation^a

and >99% ee. Regio- and enantioselective cross-couplings between two styrenes were successful in this protocol, leading to **30–3q** in 76–82% yields and 95–>99% ee. All of the axially chiral products with *s-trans* conformation¹⁷ were assigned analogously to compound **3e**, whose absolute configuration was determined by X-ray crystallographic analysis (see the ESI†). DFT calculations of the rotation barrier for representative examples **3a** and **3e** exhibited their significant atropostability.¹⁸

To demonstrate the practicality of this method, we conducted a gram-scale preparation and product derivatization (Scheme 2). Cross-coupling between 2-vinyl-benzaldehyde **1a** and acrylate **2a** on a gram-scale occurred smoothly to afford **3a** in 74% yield and 99% ee (Scheme 2a). The obtained axially chiral product **3a** underwent a series of transformations (Scheme 2b). It is noteworthy that the axially chiral phenyl diene **3a** can be easily transferred into styrene **4** with 95% ee under hydrogenation (1 atm) with Pd/C (20 wt%). Benzaldehyde underwent the Wittig reaction to afford product **5** in 88% yield and 88% ee. Compound **3a** could also be oxidized to produce the corresponding axially chiral carboxylic acid **6a** without erosion of enantioselectivity. Reduction of the aldehyde with NaBH₄ efficiently afforded benzyl alcohol **7** without change of atroposelectivity.



Scheme 2 The gram-scale synthesis and further elaboration.



Scheme 3 Application of CCA ligands in Co-catalyzed enantioselective C–H functionalization.

The newly developed axially chiral carboxylic acids **6** were introduced as chiral ligands in asymmetric C–H functionalization (Scheme 3).^{7d,e,19} Alkenyl C–H alkenylation derived carboxylic acids **6a–c** were preliminarily investigated in Co(III)-catalyzed asymmetric 1,4-addition of indole **8** with maleimide **9**, exhibiting **6b** to be highly efficient with good enantioselectivity (9 : 91 er). The relatively higher er value obtained in the preliminary investigation demonstrated the obtained CCAs to be promising axially chiral ligands in asymmetric synthesis.

Conclusions

In conclusion, we have developed an *N,O*-bidentate-chelation assisted enantioselective β -C–H alkenylation of styrenes to afford various axially chiral aryl dienes, proceeded by seven-membered endo-cyclopalladation. This atroposelective olefinic C–H functionalization is enabled by the chiral transient

directing group derived from the *in situ* condensation between an aldehyde and a chiral amino acid. We expect that the regio- and enantioselective C–H functionalization of styrenes would streamline access to axially chiral aryl polyenes, which might be valuable synthons and promising axially chiral catalysts and ligands in asymmetric synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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