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Catalytic Asymmetric Spiroannulation to Access Polycyclic Spiro Enones via Transient Axial-to-Point Chirality Induction and Transfer

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Article

Keywords:

Posted Date: January 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8609924/v1

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Additional Declarations: There is **NO** Competing Interest.

Version of Record: A version of this preprint was published at Nature Communications on September 12th, 2026. See the published version at https://doi.org/10.1038/s41467-026-77436-w.

Abstract

Chiral spirocycles exhibit tremendous potential in drug discovery and asymmetric synthesis, owing to their unique three-dimensional rigid framework and superior stability. However, stereoselective construction of polycyclic spiro compounds through a single catalytic transformation remains significant and enduring challenge, owing to steric hindrance and electronic effects. Here we report a Pd/Sadphos-catalyzed dynamic kinetic asymmetric cascade Heck/Tsuji–Trost dearomative spiroannulation of racemic phenolic biaryls with 1,3-cyclohexadienes via transient axial-to-point chirality induction and transfer. A variety of valuable polycyclic spiro enones bearing three contiguous tertiary/quaternary stereocenters were afforded with excellent regio-, diastereo- and enantioselectivity. Moreover, in vitro experiments suggested that these multifunctional spiro enones have the potential to be lead compounds for anti-inflammatory drugs.

Introduction

Chiral spiro scaffolds are important privileged structures in natural products, bioactive molecules, and chiral catalysts.[1-7] They offer the advantage of unique (C)sp^3-rich three-dimensional rigid scaffolds and excellent chemical stability. Over the past two decades, owing to their profound importance, significant efforts have been devoted to developing catalytic asymmetric synthesis strategies.[8-14] However, one-step catalytic asymmetric construction of chiral polycyclic spiro compounds remains so far largely underdeveloped despite their high value (**Scheme 1A**). Probably due to the interactions between substituents at adjacent chiral centers through steric hindrance and electronic effects[15-17], it is challenging to simultaneously control multiple stereocenters and achieve polycyclic assembly in a single catalytic system. Consequently, the development of general and efficient strategies for the stereoselective synthesis of polycyclic spiro scaffolds bearing multiple contiguous stereocenters from readily available starting materials is highly attractive and challenging.[18-21]

Asymmetric transient axial chirality transfer strategy[22-23] offers an efficient and streamlined approach for accessing spiro quaternary carbon stereocenters.[16] In this catalytic process, racemic or prochiral arenes undergo a well-defined dynamic sequence of axial chirality formation, loss, and transfer (**Scheme 1B**). Since Luan[24] and You[25] independently reported back-to-back pivotal milestones in 2015, the asymmetric formal spiroannulation has emerged as an indispensable tool for stereoselective construction of chiral spirocycles via transient axial-to-point chirality transfer.[26-33] Specifically, Xu and colleagues demonstrated the first successful example of a catalytic chirality transfer strategy featuring transient axially chiral styrene intermediates.[34] Zhou and co-workers systematically established a palladium/chiral norbornene cooperative catalytic system, relying on transient axial-to-central chirality transfer through an intramolecular termination pathway.[35-37] We envision synergizing the dual capabilities of stereoinduction and chirality transfer from transient chiral intermediates to sequentially assemble multiple chiral centers in a single catalytic cycle. If successful, this strategy may open a new avenue for the asymmetric synthesis of multi-chiral-center spirocyclic compounds. As part of our long-

standing expertise in Sadphos-enabled asymmetric domino annulation reactions,[38-45] we herein disclose the dynamic kinetic asymmetric cascade dearomative Heck/Tsuji–Trost reaction of racemic biaryls **1** with cyclic dienes **2**, which stereospecifically furnishes enantioenriched polycyclic spiro enones[46,47] via transient axial-to-point chirality induction and transfer (**Scheme 1C**).

Several key challenges need to be addressed for this transformation: (1) precise control over enantio- and diastereoselectivity via traisient stereoinduction and chirality transfer; (2) suppression of unwanted 1,4-palladium migration in arylpalladium intermediates **Pd-1**, which can form from *o*-iodobiaryls via a Heck-type reaction;[48] (3) inhibition of unwanted *β*-hydride elimination to avoid the Heck byproduct.[49-51] We hypothesize that the chiral ligand is the key to overcoming these challenges.

Results

To validate this hypothesis, we initiated our investigation into the dynamic kinetic asymmetric dearomative Heck/Tsuji–Trost reaction of racemic phenolic biaryls **1a** with cyclic 1,3-diene **2a** by using $Pd_2(dba)_3$ as a precatalyst and K_2HPO_4 as the base in mesitylene at 60 ^oC. Full optimization of the reaction conditions is provided in the Supplementary information (SI), with key findings presented in **Table 1**. A series of commercially available privileged ligands (representative chiral C_2-symmetric bisphosphine ligand **L1**, DACH-Ph Trost ligand **L2**, N,N-bidentate bisoxazoline ligand **L3**, and monodentate chiral phosphoramidite ligands **L4**–**L5**), which have also shown good performance in *π*-allylpalladium chemistry, were first investigated. Unfortunately, none of them delivered **3aa** in satisfactory yields, and only very poor enantiocontrol was achieved in each case (**Table 1** and SI, **Fig. S1** for details). Furthermore, this domino *Si*-face-selective spiroannulation occurs chemo-, regio-, and enantioselectively at the less-hindered olefin of dienes **2**, and no other possible regioisomers were detected by ^1H NMR analysis. Additionally, unconsumed **1a** was consistently recovered as a racemic mixture when the reaction of **1a** and **2a** was conducted. To our delight, chiral sulfinamide phosphine ligands Sadphos family (**PC-Phos, PC1**-**PC5**), developed by our group and characterized by non-*C2* symmetry, tunable structure, easy availability, and adaptive coordination, turned out to be superior in terms of both efficiency and selectivity for this transformation. Inspired by previous findings that tuning the electronic nature of the backbone could affect the catalytic activity and enantioselectivity,[40] we synthesized a new ligand **PC4** bearing an electron-donating group on the xanthene backbone and subjected it to the reaction, the enantioselectivity increased from 92% to 96% ee. Subsequently, the best-performing ligand **PC4** was further optimized with respect to other reaction parameters, including catalyst precursor, solvent, catalyst loading, and control experiments. Nevertheless, this optimization did not yield performance superior to that under the standard conditions. (see **Table 1B,** entries 1–14 and **SI, Fig. S2**).

With the optimal reaction conditions in hand, we investigated the substrate scope using various racemic phenolic biaryls **1** and conjugated dienes **2** (**Table 2**). A variety of phenol-based biaryl substrates **1** reacted smoothly under the spiroannulation conditions, affording spirocyclic molecules **3** and **4** in

moderate to high yields with excellent enantioselectivities. Notably, the electron-donating (methoxyl, trifluoromethoxy, methyl), electron-withdrawing (trifluoromethyl, methoxycarbonyl), and halide (fluoro, chloro) groups substituted at various positions of the phenyl ring were compatible, delivering products **3aa**–**3an** in good to high yields with 81–98% *ee*. Moreover, cyclic 1,3-diene **2** can be easily synthesized through the 1,4-dehydration of allylic alcohols. The applicability of this protocol to a wide range of substituents and functional groups on dienes **2** was explored, providing the corresponding products **3ba**–**3by** in comparable efficiency and selectivity. For example, substituents including fluoro, chloro, methyl, phenyl, methoxyl, methylthio, trimethylsilyl, trifluoromethoxy, and trifluoromethyl on the aryl moiety of 1-aryl-cyclohexadienes **2** are well-tolerated, affording the desired spirocyclic products **3ba**–**3bo** in 60–85% yields with 84–99% ee. The configuration of product **3bh** has been established as (*R,R,S*) by X-ray crystallographic analysis (CCDC 2422360). It's supposed that the Pd/Sadphos catalyst system can preferentially undergo oxidative addition with (*Sa*)-**1**, following a domino *Si*-face-selective spiroannulation.[24] Moreover, 2-naphthyl, dioxaphthyl, 6-benzofuryl, 6-benzothienyl, 3-thienyl, benzyl, *n*-butyl, and cyclohexyl derived cyclohexadienes **2** and cyclohexadiene could also produce **3bp**–**3bx** in good yields with 91–97% *ee* as single regioisomer and diastereomer. Additionally, acyclic 1,3-dienes with a phenyl substituent at the terminal position, which exhibit relatively lower reactivity compared to cyclic dienes, can also undergo the dynamic kinetic cascade reaction. This reaction yields compound **3by** in 52% yield with 32% *ee*, suggesting that new ligands should be screened. With the pharmaceutical derivatives (*L*-Menthol, *L*-Borneol, and *L*-Perillyl alcohol) as dienes, the desired products **4a**–**4c** could be obtained in moderate yields with excellent diastereoselectivity.

To demonstrate the practical utility of our protocol, a gram-scale reaction was carried out under standard reaction conditions, furnishing 1.2 g of **3aa** in 63% yield with 96% ee (**Table 3A**). The presence of unsaturations in the spirocyclic scaffold provides a handle for further divergent manipulations (**Table 3B**). For instance, the selective Luche reduction of **3aa** in the presence of $NaBH_4$ afforded the alcohol **5** in 52% yield with 96% ee and was followed by treatment with *p*-toluenesulfonic acid (TsOH), delivering the rearranged product **6** in 47% yield with 93% ee. The selective epoxidation of the two olefin moieties of **3aa** with *m*-CPBA delivered the target epoxide **7** in 55% yield with 96% ee. In light of the structures of the chiral Pd/Sadphos catalyst[52] and the (*R,R,S*)-spiro enones **3**, a possible catalytic chirality induction model was proposed for the reaction (**Table 3C**). The atroposelective O.A. of rapidly racemizing biaryls **1** with the Pd/Sadphos catalytic complex proceeds.[53] This stereocontrol is achieved by **PC4**, which bears a 4-(trifluoromethyl)phenyl group and effectively discriminates the enantiotopic faces of **1**'s phenolic ring, thus differentiating the formation rates of axially chiral intermediates (*Sa*)-**Pd-1** and (*Ra*)-**Pd-1**. Consequently, *syn*-migratory insertion of dienes **2** into the C–Pd bond and subsequent intramolecular nucleophilic attack occur exclusively at the *Si*-face of the alkene moiety, driven by the transient axial-to-point chirality induction and transfer, thus affording the *cis*-configured spiroannulated product **3** with high diastereo- and enantioselectivity. On the other hand, natural products and small molecules containing conjugated cycloenone skeletons have demonstrated broad anti-inflammatory activity,[54,55] yet the anti-inflammatory effects of these newly synthesized spiro enones derivatives **3** (**Scheme 2**) remain underexplored. Notably, the increased pro-inflammatory cytokine production in RAW 264.7 cells

has been implicated as the key mediators in the inflammation response.[56] To evaluate the anti-inflammatory effects of the spiro enones **3** in vitro, enzyme-linked immunosorbent assay (ELISA) kits were employed to investigate their effects on the lipopolysaccharide (LPS)–induced pro-inflammatory cytokine production in RAW 264.7 cells. Following treatment of RAW 264.7 cells with spiro enones **3** (20 and 50 μM) and stimulated by LPS, the levels of two main pro-inflammation cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), were reduced. Collectively, these results indicate that the five derivatives (**3ac**, **3ah**, **3am, 3ao**, and **3bb**) of spiro enones **3** may serve as promising novel inflammatory inhibitors.

Discussion

In summary, we have developed a Pd/Sadphos-catalyzed dynamic kinetic asymmetric cascade dearomative Heck/Tsuji–Trost reaction of racemic phenolic biaryls with 1,3-cyclohexadienes via the transient axial-to-point chirality induction and transfer, which provides a promising tool for the modular synthesis of enantioenriched spiro enones with three contiguous tertiary/quaternary stereocenters and intrinsic anti-inflammatory activity. The chiral sulfinamide phosphine (Sadphos) ligand plays a pivotal role in regulating the selectivity and catalytic activity of this domino *Si*-face-selective spiroannulation. Further studies include expanding the application of Sadphos in asymmetric metal catalysis, especially in more challenging asymmetric cascade reactions, via the synergistic effect of stereoinduction and chirality transfer.

Methods

General procedure for the synthesis of 3 and 4

Under argon atmosphere, to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar were added $Pd_2(dba)_3$ (5 mol%, *Energy Chemical*), Sadphos (20 mol%, **PC4**), K_2HPO_4 (2.0 equiv), and mesitylene (1.5 mL). The catalyst, ligand and base in solution were stirred for 1 h at room temperature. After 1 h, racemic biaryl **1** (0.3 mmol, 1.0 equiv) and 1,3-dienes **2** (3.0 equiv) were added sequentially. The resulting mixture was then stirred vigorously (550 rpm) at 60 ^{o}C in oil bath for about 96–108 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated to dryness and the residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford the desired product **3** and **4**.

Declarations

Data availability

All data supporting the findings of this study are available within the article and its Supplementary Information. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 2422360 (**3bh**). Copies of the

data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures. Data relating to the characterization data of materials and products, general methods, optimization studies, experimental procedures,mechanistic studies, and NMR spectra are available in the Supplementary information. All data are also available from the corresponding author upon request.

Acknowledgements

We gratefully acknowledge the funding support of National Key R&D Program of China (Grant 2021YFF0701600) to J.Z., the National Natural Science Foundation of China (Grants 22401293, 22371019, 22031004 and 21921003) to P.-C.Z., Y.L. and J.Z., the Shanghai Municipal Education Commission (Grant 20212308) to J.Z., and the School Youth Initiation Foundation (Grant 2023QN024) to P.-C.Z.. We greatly appreciate Yanfei Niu and Prof. Xiaoli Zhao at East China Normal University for their kind help with X-ray single-crystal structural analysis.

Author contributions

P.-C.Z., J.Z., and Y.L. conceived the project, analyzed the data, and wrote the paper. Q.W. and P.-C.Z., performed most of experiments. M.-H.H. and W.-W.Z. helped with the synthesis of substrates. All authors discussed the results and commented on the paper.

Competing interests

The authors declare no competing interests.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Schemes

Schemes 1 and 2 are available in the Supplementary Files section.

Supplementary Files

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