Chirality Transfer

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Palladium-Catalyzed Transient Chirality Transfer and Atroposelective C-H Functionalization to Access Quaternary Stereocenters

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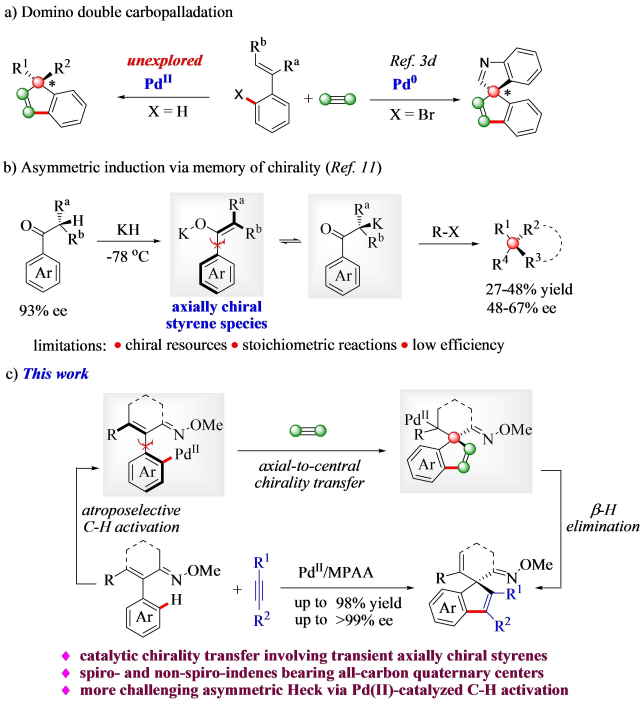
Dedicated to Professor Masakatsu Shibasaki on the occasion of his 75th birthday

Abstract: Although palladium-catalyzed asymmetric C–H functionalization and Heck reactions represents one of the most important synthetic strategies for the construction of quaternary stereocenters, developing the enantioselective version of Pd^{II}-catalyzed carbopalladation-initiated cascade reactions still remains a formidable challenge. Herein, an unprecedent enantioselective [3+2] annulation of oxime ethers and alkynes has been developed, providing both spiro and nonspiro indenes bearing all-carbon quaternary stereocenters in good yields (up to 98 %) with excellent enantioselectivities (up to >99 % ee). This annulation is accomplished by merging the Pd^{II}-catalyzed atroposelective C–H activation/double carbopalladation and the transient axial-to-central chirality transfer process, constituting the first successful example of catalytic chirality transfer strategy involving axially chiral styrene intermediate.



Scheme 1. The literature methods and our new strategy for generation of quaternary carbon stereocenters.

Indenes bearing quaternary stereocenters are an important class of core structures that are widespread in bioactive and material molecules.[1] Due to their potential significance, divergent asymmetric synthetic methods have been developed,[2] among which the asymmetric [3+2] annulative reactions of arenes with alkynes represents a more straightforward approach to them.[3] Althouth the asymmetric Heck reaction involving carbopalladation of double bonds of alkenes and (hetero)arenes has proved to be an efficient strategy for construction of quaternary stereocenters,[4] a vast majority of the reported enantioselective transformations are restricted to the use of prefunctionalized substrates.[5] For example, bromoarenes underwent smooth annulation with internal alkynes via domino intermolecular alkyne insertion/intramolecular alkene insertion, producing all-carbon quaternary stereocenters in high enantioselectivity (Scheme 1a, right).[3d] Undoubtedly, using the inert C–H activation as starting point would be much more appealing from the practical utility points of view (Scheme 1a, left).[6] However, during cascade carbopalladation of triple and double bonds, protodemetallation or direct olefination after C–H activation could occur, rendering this strategy extremely challenging.[7] On the other hand, either the dearomatization or the carbocyanation method was only suitable to access one single structure of indenes.[3] Therefore, a general and efficient approach for the synthesis of spiro and nonspiro indenes is still in a high demand.

Recently, we and other groups have developed an atropisomeric C–H activation strategy for the synthesis of axially chiral styrenes relying on the in situ formed axially chiral palladium species.[8] Inspired by the well-known "Memory of Chirality" (MOC) concept,[9] we envision that a transient axial-to-central chirality transfer process,[10] based on the catalytic atroposelective C–H activation and aryl-Pd-initiated annulation, might be an efficient strategy to

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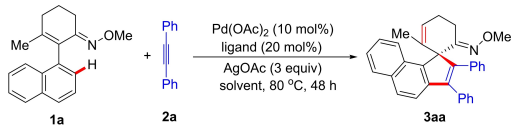
produce a quaternary carbon stereocenter. If successful, it would provide a versatile method for the construction of indenes, featuring high atom-economy and overcoming the limitations of MOC (Scheme 1b).[11] However, several challenges would be expected: 1) In contrast to the diverse routes to axially chiral biaryls, the catalytic atroposelective synthesis of axially chiral styrenes is exceedingly difficult and has been realized till recently, due to their relatively low configurational stability. So far, only sparse cases of transient axial-to-central chirality transfer strategies have emerged for the rigid biaryl atropisomers.[3a,d,12] 2) Compared to a plethora of Pd^0-catalyzed intramolecular asymmetric Heck reactions, developing the Pd^{II}-catalyzed intermolecular variant, not to mention cascade reactions, still remains a formidable task and less explored, largely due to the competitive side reactions of highly active C-palladium intermediates (e.g., direct C–H functionalization, regioselective migratory insertion of π-bonds, various double C–H activation etc.). (3) How to ensure efficient axial-to-central chirality transfer represents the essential challenge. The previously reported chirality transfer process that involved transient axially chiral styrene-typed short-lived species was stoichiometric reactions and necessarily carried out at much lower temperature to maintain their conformational stability. However, the C–H bonds are so strong chemical bonds that the harsh reaction conditions required for the C–H activation might inhibit the enantioselectivity. As our continuous effort to develop the new methods toward the construction of quaternary carbon stereocenters,[13] herein, we report a novel transient axial-to-central chirality transfer strategy for the highly enantioselective synthesis of indenes with a chiral all-carbon quaternary center by Pd^{II}-catalyzed tandem C–H olefination/Heck reactions (Scheme 1c). This is the first successful example of transition metal-catalyzed transient axial-to-central chirality transfer strategy employing axially chiral styrene intermediate. Considering the rich transformation chemistry of organopalladium, this strategy not only opens up a facile and straightforward route to access chiral indenes with both spiro and nonspiro scaffold via a highly atom economical approach, but also can be applied to other chirality transfer and induction processes.

At the outset, we chose 3-methyl-2-naphthylcyclohex-2-enone oxime ether **1a** and diphenylacetylene **2a** as model substrates to examine the feasibility of tandem C–H olefination/Heck coupling sequence (Table 1). To our delight, using **2a** in place of ethyl acrylate led to the desired spirocycle product **3aa** in 30% yield and 96% *ee* under otherwise identical conditions to our previously reported olefination conditions (Table S1 in Supporting Information).[8a]

Encouraged by this initial result, we systematically investigated the influence of reaction parameters to enhance the reactivity and enantioselectivity. Increasing the temperature to 80 °C resulted in 62% yield without erosion of the enantioselectivity (Entry 1 of Table 1). Further optimization focused on different solvents with higher boiling points. Compared to MeOH, *t*-AmOH could remarkably improve the yield to 87%, while the enantioselectivity was decreased slightly (Entry 2). The solvents dioxane and 1,2-dichloroethane (DCE) gave inferior results in terms of yields and enantioselectivities (Entries 3 and 4). Finally, the best yield (89%) and *ee* value (97%) was obtained in tetrahydrofuran (THF). Notably, attempts to further improve the yield and/or enantioselectivity by tuning the reaction temperature, changing the oxidants, and varying the substituents of chiral amino acids failed. The following optimum conditions were identified: $Pd(OAc)_2$ (10 mol%), Ac-L-Ala-OH (20 mol%) as a chiral ligand, and AgOAc (3 equiv) as an oxidant, in THF and at 80 °C under an air atmosphere. It should be noted that the competing twofold C–H annulation product with a C–C chiral axe was not observed even in the presence of up to 3 equivalents of internal alkynes.[14]

Table 1: Optimization of the enantioselective annulation.[a]

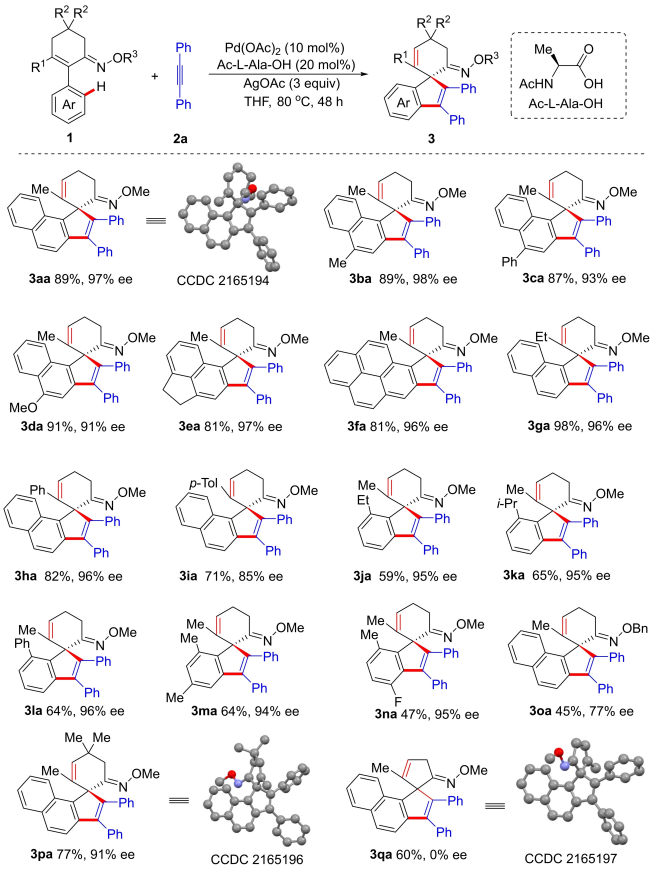


1a 2a 3aa

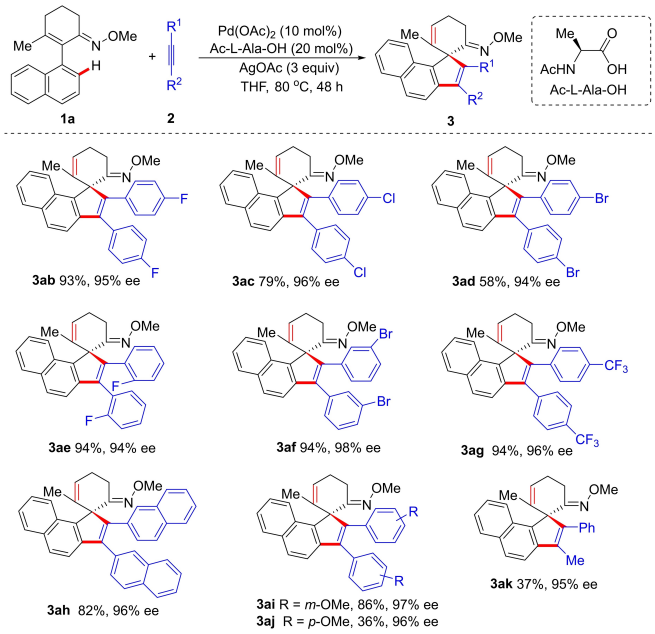
Entry	Ligand	Solvent	Yield [%][b]	ee [%][c]
1	Ac-L-Ala-OH	MeOH	62	96
2	Ac-L-Ala-OH	*t*-AmOH	87	94
3	Ac-L-Ala-OH	dioxane	77	93
4	Ac-L-Ala-OH	DCE	87	85
5	Ac-L-Ala-OH	THF	89	97
6	Boc-L-Val-OH	THF	68	89
7	Boc-L-Leu-OH	THF	64	77
8	Ac-L-Leu-OH	THF	76	89

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), AgOAc (3 equiv), solvent (2 mL), 80 °C for 48 h under air atmosphere. [b] Isolated yield. [c] The *ee* values were determined by HPLC using chiral columns.

Having the optimal conditions in hand, we turned our attention to evaluate the scope of this tandem C–H olefination/Heck coupling sequence. First, we tested the generality of the intermolecular spiroannulation reaction for a variety of 2-arylcyclohex-2-enone oxime ethers **1** with **2a** as a coupling partner. As depicted in Scheme 2, all the substrates containing electron-deficient and electron-rich groups at the various positions of aromatic ring and cyclohexene ring proved to be amenable to this transformation and the corresponding spiro indene products were produced in moderate to excellent yields (45–98%) and good to excellent enantioselectivities (77–98% *ee*), except for **3q** displaying no central chirality, which could be rationalized by considering the lower rotation energy of the corresponding axially chiral aryl-Pd species relative to those of other substrates.[8a] Specifically, the Me, Ph, and OMe substituents (**1b–d**) at 4-position of the naphthalenyl ring were well tolerated under the optimal reaction conditions, giving the corresponding spiro indene products in 81–89% yield with 93–98% *ee*. In addition, substrates with polycyclic skeletons such as **1e** and **1f** proceeded smoothly to furnish the desired products in fairly good yields with 96–97% *ee*. It was noteworthy that changing the substituent from methyl to ethyl group on the upper cyclohexene led to the full conversion of starting material within 48 hours, thus affording the desired product **3ga** in almost quantitative yield



Scheme 2. Reaction scope of 2-arylcyclohex-2-enone oxime ethers in palladium-catalyzed annulation with diphenylacetylene **2a**.

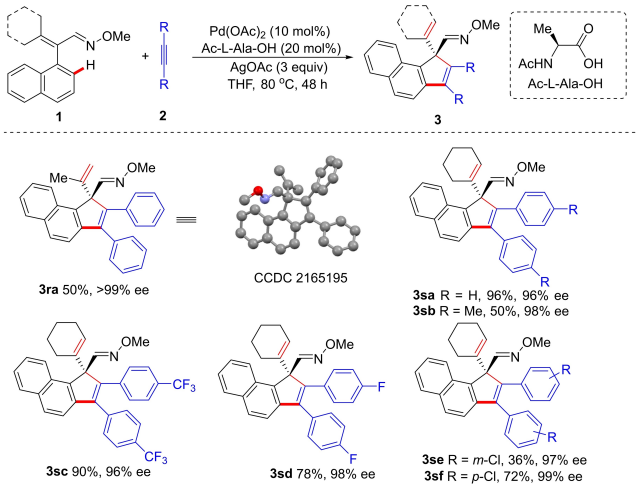


Scheme 3. Reaction scope of the internal alkynes in palladium-catalyzed annulation with 3-methyl-2-naphthylcyclohex-2-enone oxime ether **1a**.

(98 %) with 96 % *ee*. Meanwhile, we found that the slight modification of aryl groups on the cyclohexene have major effect on reactivity and enantioselectivity as illustrated by the reactions of substrates **1h** and **1i**. Generally speaking, mono- and disubstituted 2-phenylcyclohex-2-enone oxime ether substrates **1j–n** underwent annulation in inferior yields (81–89 %) and comparable enantioselectivities (94–96 % *ee*) to 2-naphthalenylcyclohex-2-enone oxime ethers. It was demonstrated that the substituent at the nitrogen atom of the oxime directing group had dramatic influence on the results of annulation reactions and *O*-methyl oxime outperformed the *O*-benzyl oxime since the latter decreased the yield and enantioselectivity largely (for example of **3oa**, 45 % yield and 77 % *ee*). The isophorone-derived substrate **1p** with two methyl groups at 5-position of the cyclohexene was well tolerated, providing **3pa** in satisfactory yield and enantioselectivity. The absolute configuration of (*S*)-**3aa** and (*S*)-**3pa** was unambiguously determined by single crystal X-ray diffraction analysis.[15]

Subsequently, we carried out the spiroannulation of 2-naphthalenylcyclohex-2-enone oxime ether **1a** with various internal alkynes to investigate their scope (Scheme 3). As to the symmetrical alkynes containing two substituted aromatic rings, both electron-withdrawing groups (F, Cl, Br, and CF_3) and electron-donating group (OMe) on the phenyl ring were well tolerated, delivering the targeted products **3ab–aj** in up to 98 % yield with 94–98 % *ee*. Although the steric hindrance generally exhibited a negative effect on the annulation reaction, changing the substitution position of F atom on the phenyl ring from *para* to *ortho* position had negligible influence on reaction results (**3ab** vs. **3ae**). Furthermore, the yields of **3af** and **3ai** increased significantly while maintaining excellent enantioselectivities in comparison to **3ad** and **3aj**, respectively. Besides phenyl substituted internal alkynes, 1,2-di(naphthalen-2-yl)ethyne was also compatible with the reaction conditions, leading to **3ah** in 82 % yield and 96 % *ee*. Notably, when a nonsymmetrical aryl alkyl alkyne was subjected to asymmetric spiroannulation, a single isomer (**3ak**) was produced in synthetically useful yield and excellent enantioselectivity.

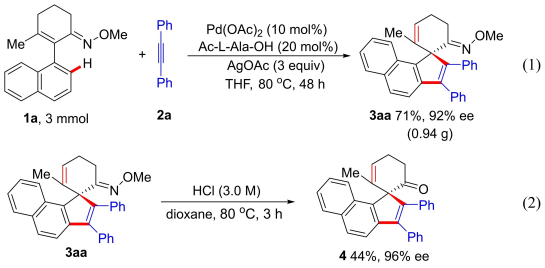
Encouraged by the above results, we then turned our attention to investigate the annulation reaction of acyclic oxime ethers with internal alkynes (Scheme 4). If successful, it would provide an alternative method for the construction of nonspiro indenes, which cannot be synthesized by the asymmetric [3+2] annulative dearomatization strategy. Delightedly, the reaction of 2-naphthalenylacrylaldehyde oxime ether **1r** with **2a** gave the annulated product **3ra** in 50 % yield with >99 % *ee* under the same reaction conditions. It was worth mentioning that the absolute configuration of **3ra** was assigned to be (*R*) by X-ray analysis, opposite to those of spiro indenes.[15] Replacement of dimethyl with cyclohexyl in the alkene terminus resulted in considerable enhancement of reactivity with excellent enantioselectivity (96 % *ee*), probably due to that **3sa** formed a more stable cyclohexene structure than the terminal alkene in **3ra** after β-H elimination. In addition to simple diphenylethyne, Me (**3sb**), CF_3 (**3sc**), F (**3sd**), and Cl (**3se** and **3sf**) groups at the aromatic substituents of the alkynes were all compatible, affording the corresponding chiral nonspiro indene products



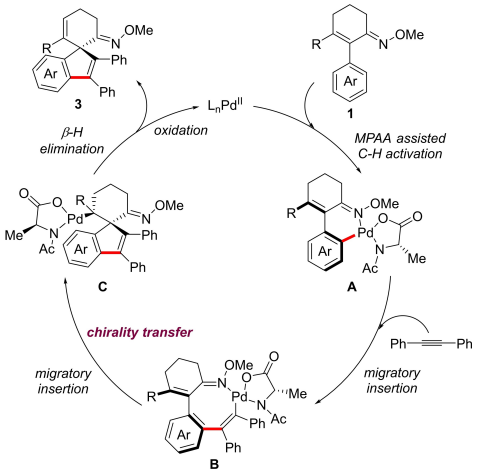
Scheme 4. Enantioselective synthesis of nonspiro-indenes by palladium-catalyzed annulation of acyclic oxime ethers with internal alkynes.

in moderate to excellent yields (36–90 %) and excellent enantioselectivities (96–99 % *ee*).

To demonstrate the practicality and efficiency of our strategy, scale-up synthesis and transformations were conducted (Scheme 5). It was observed that this asymmetric annulation reaction of **1a** and **2a** could be performed on a 3 mmol scale and the desired product **3aa** was isolated with



Scheme 5. Scale- up synthesis and derivatization.



Scheme 6. Proposed mechanism.

slightly diminished reactivity and chiral induction (71 %, 92 % *ee*, 0.94 g) [Scheme 5, Eq. (1)]. In addition, the oxime ether directing group was removed readily to release the parent ketone **4** [Scheme 5, Eq. (2)].

On the basis of the aforementioned experimental results and previous reports,[16] a plausible catalytic cycle for this reaction was proposed in Scheme 6. As outlined in Scheme 6, the oxime-directed and MPAA-assisted atroposelective C–H activation of **1** may occur to generate axially chiral palladium intermediate **A**. Subsequent alkyne coordination and migratory insertion gives an eight-membered palladacycle **B**. Then **B** undergoes intramolecular migratory insertion to produce alkylpalladium species **C**, accompanied by transient axial-to-central chirality transfer. Finally, β-H elimination of **C** affords the desired product **3** with the regeneration of the Pd^{II} species after oxidation to finish the catalytic cycle.

In summary, we have developed a novel chirality transfer strategy for the highly enantioselective construction of all-carbon quaternary stereogenic centers, allowing efficient and atom-economical synthesis of both spiro and nonspiro indenes with excellent enantioselectivities. This asymmetric [3+2] annulation of oxime ethers and alkynes relies on the elegant combination of the Pd^{II}-catalyzed tandem C–H olefination/Heck coupling process with the transient axial-to-central chirality transfer. To the best of our knowledge, this is the first successful example of catalytic chirality transfer strategy employing axially chiral styrene intermediate. Further extension of the current method to other domino reactions via C–H bond activation is underway in our lab.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Activation · Chiral Indenes · Chirality Transfer · Palladium Catalysis · Quaternary Stereocenter

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Communications

Chirality Transfer

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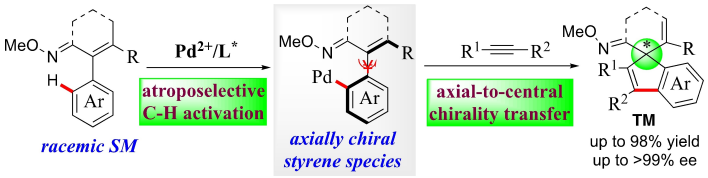
Palladium-Catalyzed Transient Chirality Transfer and Atroposelective C-H Functionalization to Access Quaternary Stereocenters



An enantioselective [3+2] annulation of oxime ethers and alkynes has been developed via catalytic transient axial-to-central chirality transfer strategy. More importantly, this annulation represents a rare example of construction of all-carbon quaternary centers through tandem Pd^{II}-catalyzed atroposelective C–H activation/double carbopalladation process.