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Tandem Iridium Catalysis as a General Strategy for Atroposelective Construction of Axially Chiral Styrenes

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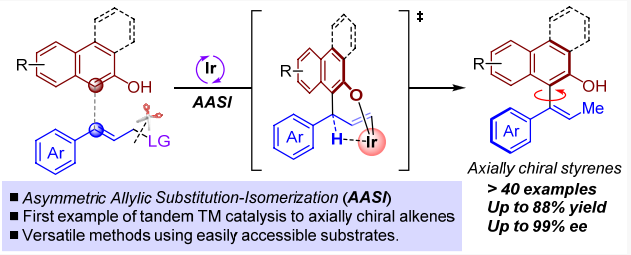
ABSTRACT: Axially chiral styrenes are of great interest since they may serve as a class of novel chiral ligands in asymmetric synthesis. However, only recently have strategies been developed for their enantioselective preparation. Thus, the development of novel and efficient methodologies is highly desirable. Herein, we reported the first tandem iridium catalysis as a general strategy for the synthesis of axially chiral styrenes enabled by *Asymmetric Allylic Substitution-Isomerization* (*AASI*) using cinnamyl carbonate analogues as electrophiles and naphthols as nucleophiles. In this approach, axially chiral styrenes were generated through two independent iridium-catalytic cycles: iridium-catalyzed asymmetric allylic substitution and *in situ* isomerization via stereospecific 1,3-hydride transfer catalyzed by the same iridium catalyst. Both experimental and computational studies demonstrated that the isomerization proceeded by iridium-catalyzed benzylic C−H bond oxidative addition, followed by terminal C−H reductive elimination. Amid the central-to-axial chirality transfer, the hydroxyl of naphthol plays a crucial role in ensuring the stereospecificity by coordinating with the Ir(I) center. The process accommodated broad functional group compatibility. The products were generated in excellent yields with excellent to high enantioselectivities, which could be transformed to various axially chiral molecules.



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1. INTRODUCTION

New strategies toward the construction of axially chiral compounds have been targeted in recent years due to their widespread appearance in natural products, biologically active compounds, and useful chiral ligands in asymmetric catalysis.[1] However, synthetic studies of axially chiral compounds beyond biaryl and heterobiaryl derivatives have been sparse. Axially chiral styrenes are one family of chiral compounds whose synthesis represents a major synthetic challenge due to their relatively low configurational stability.[2] In this context, the pioneering work of catalytic enantioselective construction of axially chiral arylcyclohexenes was reported by the Gu and Smith groups.[3] These kinds of styrene atropisomers have similar skeletons to biaryls, which enabled them high rotational barriers around the C−C axes.

However, the enantioselective preparation of axially chiral styrenes with an acyclic alkene is more challenging. Such synthetic methodologies have been realized very recently, and a significant process is achieved in this realm. One of the most widely used methods for preparing axially chiral styrenes is atroposelective organocatalysis. Key to this transformation was the generation of activated chiral allene intermediates, which are trapped by various nucleophiles, affording axially chiral styrenes (Scheme 1A, top).[4] The other reliable method is asymmetric C−H functionalization of pro-axially chiral styrenes by using palladium as catalysts and amino acid derivatives as ligands (Scheme 1A, middle).[5] A complementary approach to these methods is the stereoselective *N*-alkylation or acylation at sites proximal to the C−C axes (Scheme 1A, bottom).[6] While these methods have offered elegant and innovative routes to axially chiral styrenes, a vast majority of them require specialized substrates whose syntheses need multistep synthetic procedures, thus hampering the development of this important class of molecules. A versatile method for the catalytic synthesis of axially chiral styrenes still needs to be addressed.

Recently, our group developed an *asymmetric allylic substitution-isomerization* (*AASI*) strategy for the synthesis of axially chiral enamides (Scheme 1B).[7] In our mechanistic proposal, enantioenriched product **I** was formed via the iridium-catalyzed asymmetric allylic substitution,[8] followed by base-promoted *in situ* isomerization to axially chiral products **II** via central-to-axial chirality transfer (Scheme 1C, left).[9] In this context, 1,3-proton (H^+) transfer occurs via a stepwise deprotonation/reprotonation pathway through a chiral ion-pair intermediate. Meanwhile, the hydrogen-bonding interactions between the proton and enamide carbonyl played a significant role in promoting both the reactivity and the

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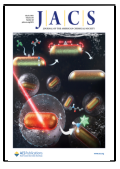

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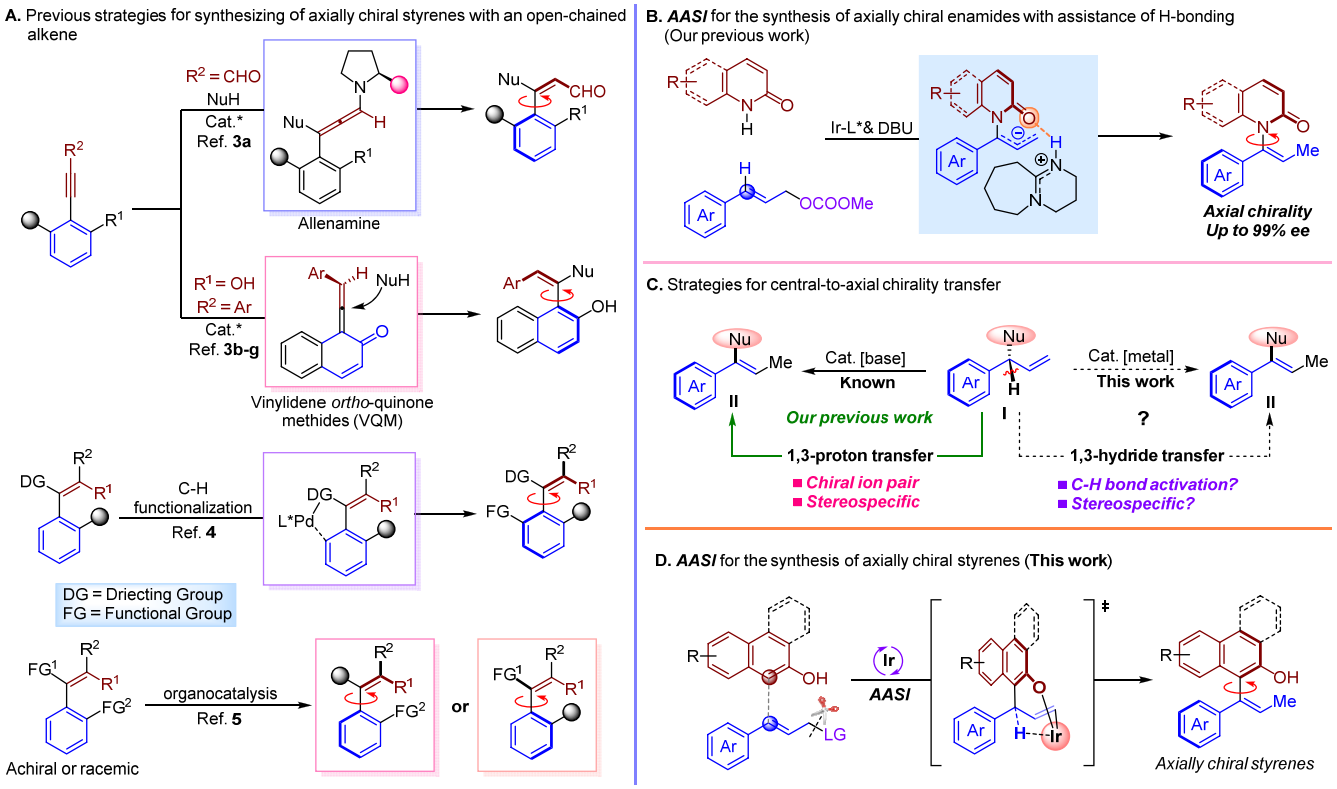
Scheme 1. Strategies for the Synthesis of Axially Chiral Styrenes with an Open-Chain Alkene



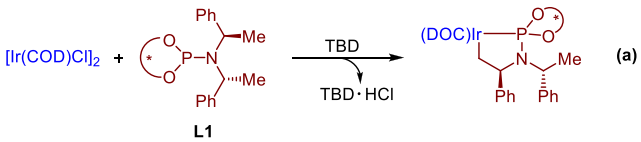
stereospecificity of the stepwise 1,3-proton transfer. Despite this achievement, this transformation would be challenging if the allylic compound **I** possesses a less acidic allylic C−H bond due to low reactivity in the base-promoted 1,3-proton transfer.

As an alternative strategy for the central-to-axial chirality transfer, transition-metal (TM)-catalyzed olefin isomerization is an exceptional technique for the construction of 1-propen-1-yl units.[10] However, TM-catalyzed C(sp3)−H bond oxidative cleavage for stereospecific 1,3-hydride (H^-) transfer remains largely unexplored so far. In our effort to develop the *AASI* strategy, we recognized that merging a transition-metal-catalyzed allylic substitution and catalytic olefin isomerization,[10d10m] might be an efficient approach for accessing axially chiral styrenes (Scheme 1C, right). Furthermore, it would be highly desirable that this cascade reaction process could be catalyzed by an identical TM complex in one pot. We hypothesized that this catalytic 1,3-hydride transfer can potentially give higher stereospecificity in the central-to-axial chirality transfer step.[11] If successful, it would represent a versatile method for the construction of axially chiral styrenes using easily accessible aryl allylic carbonates and naphthols. Although naphthols have been used as nucleophiles in asymmetric allylic substitution, they usually proceeded with dearomatization[12a−d] and allylic alkylation.[12e] The direct asymmetric vinylation of naphthols to atropisomers is yet to be explored. To this end, we herein demonstrate an iridium-catalyzed *Asymmetric Allylic Substitution-Isomerization (AASI)* as a general method for the synthesis of axially chiral styrenes (Scheme 1D).

2. RESULTS AND DISCUSSIONS

2.1. Reaction Development and Optimizations.

Catalyst Preparation. The iridacycle catalyst was *in situ* prepared by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) according to the literature.[13] The experiment was performed in an argon-filled glovebox. $[Ir(cod)Cl]_2$ (2.1 mg, 3 mol %), ligand (6 mol %), and TBD (2.1 mg, 15 mol %) were added to a vial equipped with a magnetic stirring bar. The vial was then charged with solvent (0.5 mL) and stirred at 25 °C for 30 min, generating an orange solution. The iridacycle catalyst containing the solvent was used directly for the catalysis system (taking **L1**, for example, see eq "a") (see the SI for details).



Optimization. We initially carried out the reaction of cinnamyl carbonates **1a** and 8-bromonaphthalen-2-ol **2a** in the presence of the *in situ* generated iridacycle catalyst (Table 1). In order to ensure the configurational stability of the products, introducing *p*-toluenesulfonyl chloride onto the naphthyl backbone was conducted in one pot after the *AASI* process. As expected, axially chiral styrenes **3a** was isolated in *Z*-selectivity with 92% ee in the presence of 3 mol % $[Ir(cod)Cl]_2$, 6 mol % **L1**, and 3.0 equiv of DBU in THF at 35 °C, albeit with a moderate yield of 61% (entry 1). The use of **L2**−**L5** gave us trace amounts of products (entries 2−5). The reaction with **L6** gave **3a** in 90% ee, but the yield was much lower (entry 6). Reactions conducted with other bases afforded **3a** in either lower yield or lower ee (entries 7−10). Examination of solvents revealed that reactions carried out in dioxane or toluene afforded **3a** in good yields and slightly

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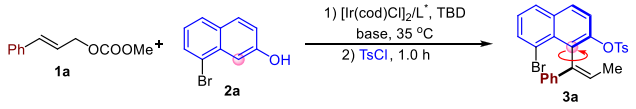
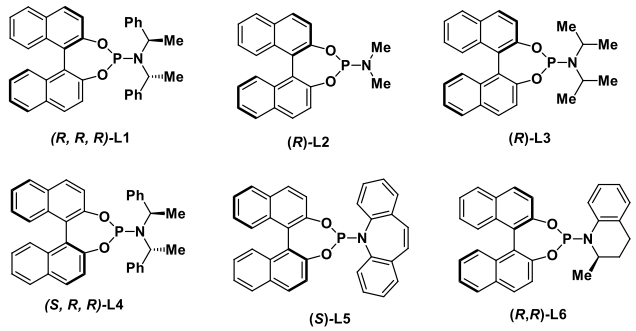
Table 1. Optimized Conditions[a]



Entry	Ligand	Base	Solvent	LG	yield(%)[b]	ee(%)[c]
1	L1	DBU	THF	OCOOMe	61	92
2	L2	DBU	THF	OCOOMe	-	-
3	L3	DBU	THF	OCOOMe	-	-
4	L4	DBU	THF	OCOOMe	-	-
5	L5	DBU	THF	OCOOMe	-	-
6	L6	DBU	THF	OCOOMe	35	90
7	L1	DABCO	THF	OCOOMe	72	88
8	L1	Et_3N	THF	OCOOMe	38	94
9	L1	TBD	THF	OCOOMe	34	82
10	L1	Cs_2CO_3	THF	OCOOMe	35	86
11	L1	DBU	Dioxane	OCOOMe	79	87
12	L1	DBU	Toluene	OCOOMe	84	87
13	L1	DBU	Toluene	OBoc	43	92
14	L1	DBU	Toluene	$OPO(OEt)_2$	-	-
15	L1	DBU	Toluene	Cl	-	-
16	L1	DBU	Toluene	OBz	58	92
17[d]	L1	DBU	Toluene	OCOOMe	84	95

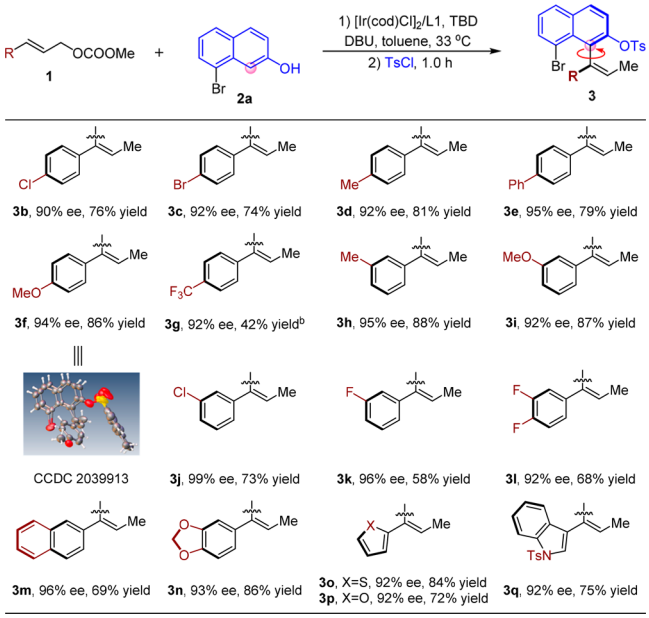


[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $[Ir(cod)Cl]_2$ (3 mol %), ligand (6 mol %), TBD (15 mol %), DBU (3.0 equiv), toluene (1.0 mL); then TsCl (3.0 equiv), 1.0 h. [b]Isolated yield. [c]ee determined by chiral HPLC. [d]Changing amount of **2a** from 0.1 to 0.15 mmol; reaction temperature from 35 to 33 °C.

lower ee (entries 11 and 12). Other leaving groups such as −Cl, −OBz, −OBoc, and $-OPO(OEt)_2$ had a detrimental impact on reactivity (entries 13−16). A final round of optimization enabled us to substantially increase the stoichiometry in **2a** and precisely control the temperature to 33 °C, gratefully, generating **3a** in 84% yield and 95% ee (entry 17).

Substrate Scope. With the optimized conditions in hand, we then studied the substrate scope of the reaction with respect to allylic carbonates (Table 2). Aryl allylic carbonates bearing both electron-rich and electron-poor groups at the *para* position were well tolerated, affording **3b**−**3g** in moderate to good yields (42−86%) with high enantioselectivities (90−95% ee). The absolute configuration of **3f** was determined by single-crystal X-ray crystallographic analysis, and others were assigned by analogy to **3f**. Substrates with *meta* substituents such as −Me, −MeO, −Cl, and −F all proceeded well, generating **3h**−**3k** in 58−88% yield and 92−99% ee.

Table 2. Substrate Scope of Allylic Carbonates[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $[Ir(cod)Cl]_2$ (3 mol %), L1 (6 mol %), TBD (15 mol %), DBU (3.0 equiv), toluene (1.0 mL); then TsCl (3.0 equiv), 1.0 h. Isolated yield. ee determined by chiral HPLC. Unless noted, products were obtained with more than 19:1 of *Z*/*E*. [b]**3g** was isolated without Ts protection.

Difunctionalized cinnamyl carbonate **1l** was compatible with the reaction, generating **3l** in 92% ee and 68% yield.

The fused rings of the R group in **1** were also accommodated, affording **3m** and **3n** in 96% and 93% ee, respectively. The examination of heteroarenes disclosed wide compatibility, for example, thienyl (**1o**), furyl (**1p**), and protected indolyl (**1q**) reacted smoothly, providing the corresponding products in 92% ee with 72−84% yields.

With respect to the *β*-naphthol scope, various substituted naphthols were investigated to showcase the generality of the reaction (Table 3). Replacement of −Br in **2** with other halo groups such as −Cl and −I resulted in both high enantioselectivities (94% ee) with 62% and 56% yield, respectively (**3r** and **3s**). Removal of the substituent at the 8-position was proved to have dramatic effects on the enantioselectivities of the reaction. Under optimized conditions, axially chiral styrenes **3t**−**3x** were effectively generated in 78−89% ee with 72−81% yield. The reaction of disubstituted *β*-naphthol provided the corresponding product **3y** in 85% ee and 72% yield. The slight lower ee's of **3t**−**3y** may be attributed to their racemization because of the lower conformational stability prior to the −tosyl protection. It is noteworthy that phenanthren-3-ol was also tolerated under the reaction conditions, affording **3z** in 92% ee, albeit with a moderate yield of 52%.

It is obvious that *β*-naphthols bearing 8-substituents are crucial for generating axially chiral styrenes with high enantioselectivities. After a slight adjustment of the reaction temperature, a broad range of 8-substituted *β*-naphthols proceeded smoothly with good results (Table 4). When 8-Me substituted *β*-naphthol was employed, **3a′** was afforded in a high ee of 95% with 76% yield. Notably, *N*-substituted *β*-naphthols at the 8-position were compatible with reaction conditions, giving the corresponding products in 93% and 90%

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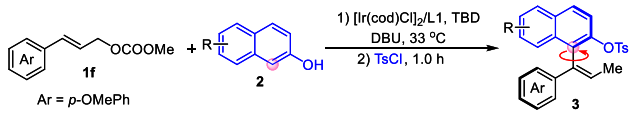
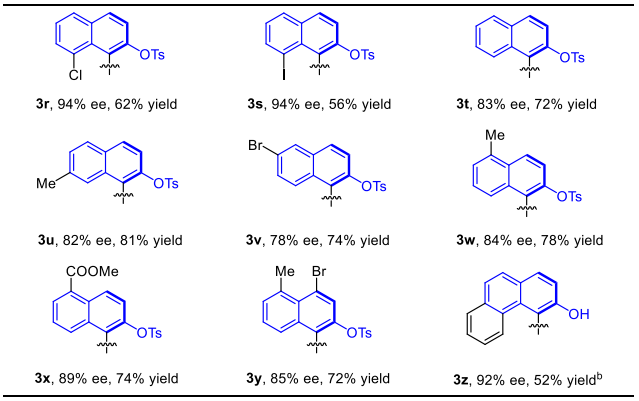
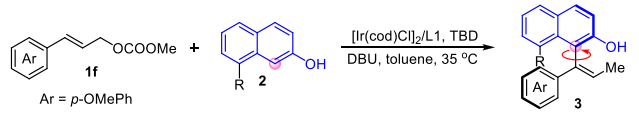
Table 3. Substrate Scope of β-Naphthols[a]

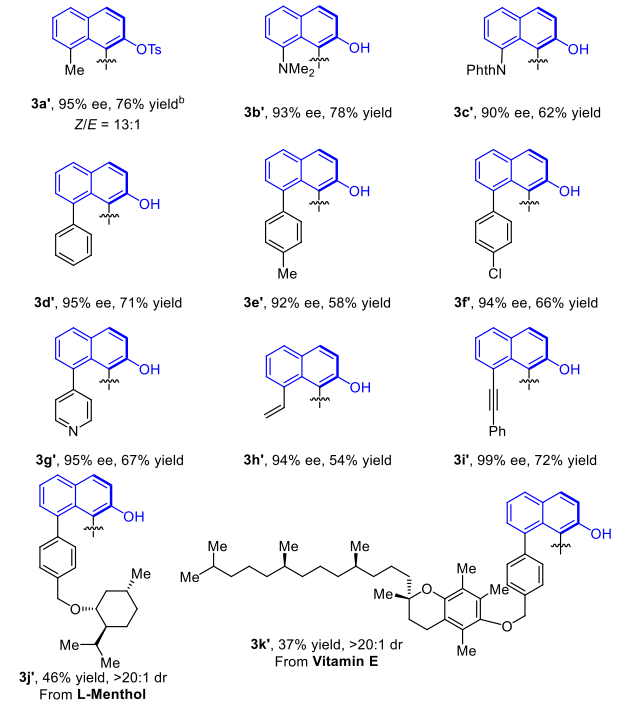




[a]Reaction conditions: **1f** (0.1 mmol), **2** (0.15 mmol), $[Ir(cod)Cl]_2$ (3 mol %), L1 (6 mol %), TBD (15 mol %), DBU (3.0 equiv), toluene (1.0 mL); then TsCl (3.0 equiv), 1.0 h. Isolated yield. ee determined by chiral HPLC. Unless noted, products were obtained with more than 19:1 of *Z*/*E*. [b]**3z** was isolated without Ts protection.

Table 4. Substrate Scope of 8-Substituted β-Naphthols[a]



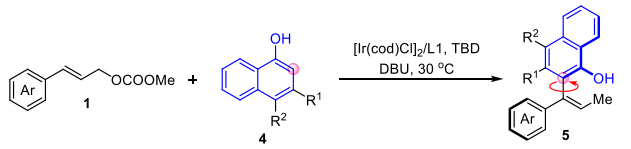


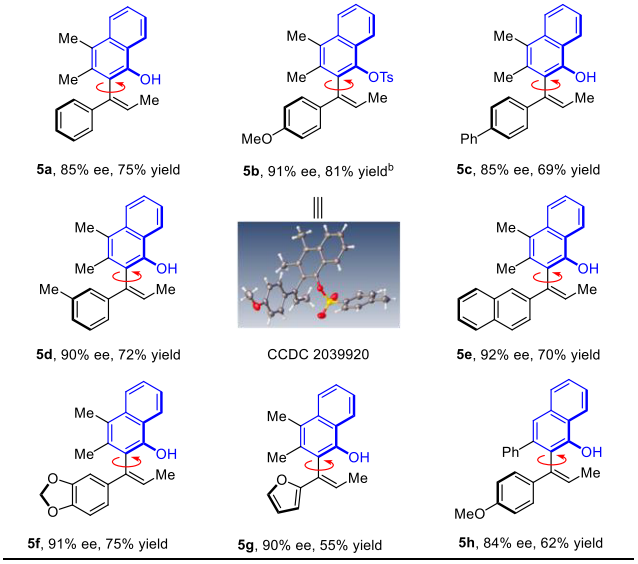
[a]Reaction conditions: **1f** (0.1 mmol), **2** (0.15 mmol), $[Ir(cod)Cl]_2$ (3 mol %), L1 (6 mol %), TBD (15 mol %), DBU (3.0 equiv), toluene (1.0 mL). Isolated yield. ee determined by chiral HPLC. Unless noted, products were obtained with more than 19:1 of *Z*/*E*. [b]**3a′** was isolated with Ts protection.

ee, respectively (**3b′** and **3c′**). The reaction was efficient regardless of the aromatic substitution explored, providing the products in 92−95% ee (**3d′**−**3g′**). Other functionalizable groups such as 8-alkene or 8-alkyne units underwent *AASI* efficiently, resulting in the desired products in 94% and 99% ee, respectively (**3h′** and **3i′**). It is worthwhile to mention that complex substrates derived from *L*-menthol and vitamin E could also be used in the reaction, yielding the products **3j′** and **3k′** in beyond 20/1 dr with 46% and 37% yield, respectively.

Having established the *AASI* of β-naphthols, we hypothesized that 3-substituted α-naphthols may also be suitable as nucleophiles for preparation of axially chiral styrenes. If the reaction works, it would represent a rare example for accessing axially chiral molecules by using α-naphthols as substrates (Table 5). To our delight, using cinnamyl carbonates **1a** and

Table 5. Substrate Scope of 3-Substituted α-Naphthols[a]





[a]Reaction conditions: **1** (0.1 mmol), **4** (0.15 mmol), $[Ir(cod)Cl]_2$ (3 mol %), L1 (6 mol %), TBD (15 mol %), DBU (3.0 equiv), toluene (1.0 mL). Isolated yield. ee determined by chiral HPLC. Unless noted, products were obtained with more than 19:1 of *Z*/*E*. [b]**5b** was isolated with Ts protection.

3,4-dimethylnaphthalen-1-ol **4a** as substrates, conditions similar to the optimized protocol, afforded **5a** in 85% ee with 75% yield. Several representative allylic carbonates were examined, generating products in 85−92% ee with 55−81% yield (**5b**−**5g**). The removal of the methyl group at the 4-position in α-naphthols was also tested. As a result, **5h** was obtained in 84% ee and 62% yield with high regioselectivity of vinylation in the 2-position rather than the 4-position.

2.2. Racemization Experiment. The configurational stability of axially chiral styrenes was one of the key factors for their utility. No diminished ee's of **3** were observed after storing in a freezer for a couple of months. Next, we selected representative examples and conducted the racemization

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experiments in toluene at 50 °C. As shown in Figure 1, comparison of the half-lives (**6** vs **7**) indicated that the non-8-

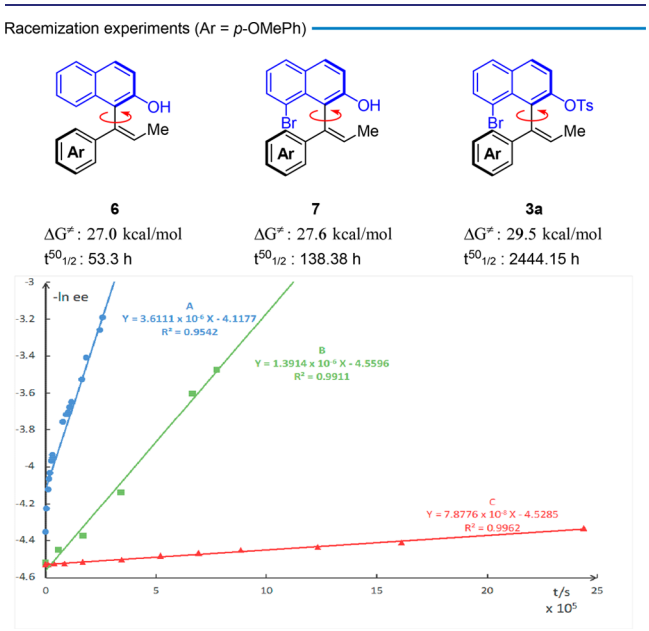


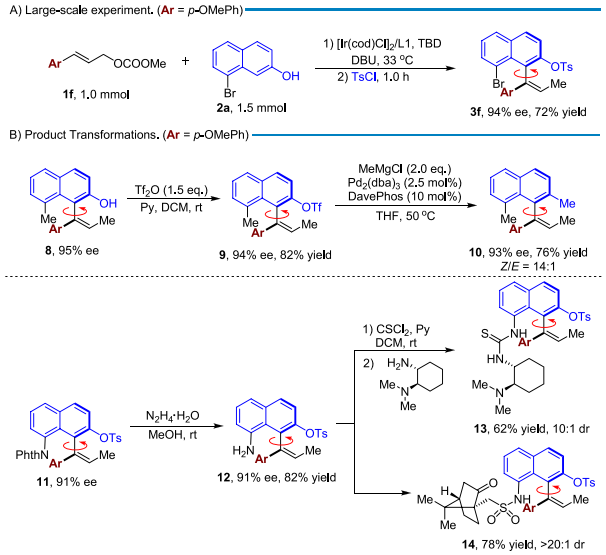
Figure 1. Racemization experiments. Measured at 50 °C in toluene; ee determined by chiral HPLC. See the Supporting Information (SI) for details.

substituted axially chiral styrene **6** has a lower configurational stability than the 8-substituted compound **7** (53.5 vs 138.38 h). This may be attributed to the fact that 8-substituted axially chiral styrene possesses a bigger steric hindrance that restricted the rotation about the C−C axes (red arrow in molecules). The importance of the steric hindrance on configurational stability was further demonstrated by comparing the half-lives of **7** and **3a**, in which the half-life of **3a** was 2444.15 h. These experiments suggested that the use of bulky naphthols as substrates was one of the essential criteria for the construction of high enantioselective axially chiral styrenes in *AASI*. When non-8-substituted *β*-naphthols were used for the reaction, the protection of the hydroxyl group is necessary to maintain the high enantioselectivities of axially chiral styrenes.

2.3. Derivatization of the Products. The synthetic utility of *AASI* was then demonstrated by conducting a series of derivatizations (Scheme 2). First, we performed the reaction in a 1.0 mmol scale, from which **3f** was obtained in 72% yield with 94% ee. According to the "standard conditions" in Table 4, compound **8** was readily isolated in 95% ee that can be easily transformed to **9** in 94% ee with 82% yield. Using **9** as a substrate, the cross-coupling with methyl Grignard reagent by palladium catalysis afforded **10** in 76% yield while maintaining the ee of 93%. In addition, deprotection of **11** (derived from **3b′**) delivered **12** in 82% yield with preservation of the initial ee of 91%. The free amino group in **12** could be further transformed to **13** via a two-step reaction in 62% yield with 10:1 dr. The sulfonamide **14** could also be efficiently generated in 78% yield with >20:1 dr. The facile synthesis of compounds **13** and **14** may provide a new type of axially chiral catalyst or ligand for asymmetric synthetic chemistry.

2.4. Mechanistic Studies. In order to explore the limitation to the strategy, a series of experiments were carried out. First, *β*-naphthols with protecting groups such as methyl,

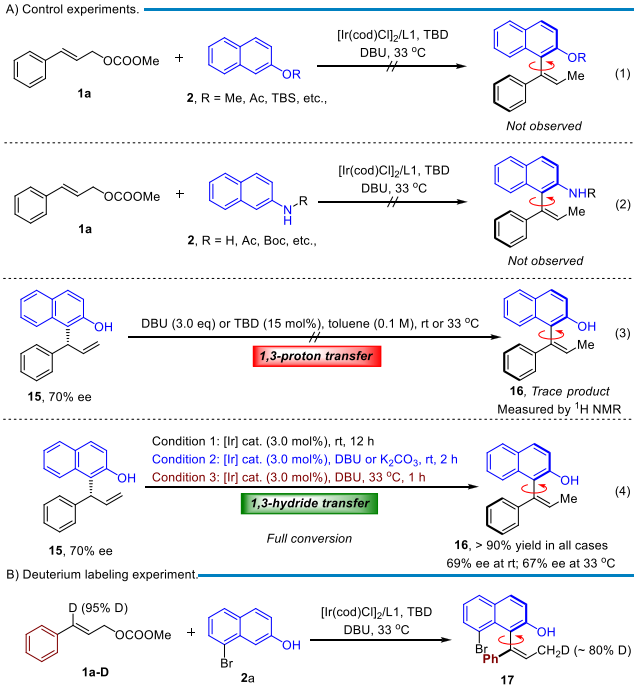
Scheme 2. Derivatization of the Products[a]



[a]See the Supporting Information for details. Py = pyridine.

acetyl, or TBS were used for the reaction, but no vinylation products were obtained and the starting materials recovered (Scheme 3A, eq 1). This result indicated that the −OH group

Scheme 3. Control Experiments and Deuterium Labeling Experiments



in **2** was crucial for the reaction. We next examined the reactivity of naphthalen-2-amine analogues for *AASI*. Still, there were no desired products obtained, and the allylic amination at the *N* site was observed in some cases (Scheme 3A, eq 2). To further understand the isomerization for the central-to-axial chirality transfer, several control experiments and deuterium labeling experiments were conducted. First, compound **15** was prepared in 70% ee via rhodium-catalyzed

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asymmetric allylic arylation.[12e] Surprisingly, by using DBU or TBD as the catalyst, only a trace amount of **16** was obtained for the isomerization of **15** in the absence of Ir catalyst (eq 3). This result indicated that the base-catalyzed 1,3-proton transfer is not involved in the isomerization process.

Interestingly, further control experiments showed that the isomerization proceeded smoothly under iridium catalysis which afforded axially chiral styrene **16** with full conversion (eq 4). The reaction was even faster if the iridium-catalyzed isomerization was performed under basic conditions (eq 4). More importantly, product **16** could be readily isolated beyond 90% yield in all cases with 67−69% ee (95−98% es).[14] These results indicated that the iridium-catalyzed stereospecific 1,3-hydride transfer may be involved for central-to-axial chirality transfer. In order to gain more mechanistic insights, a deuterium labeling experiment was then carried out. Using substrate **1a-D** labeling with deuterium next to the aryl ring led to product **17** with ∼80% D incorporation at the methyl group (Scheme 3, **B**). The incomplete D migration in the course of the transformation was attributed to H/D exchange of iridium hydride with solvent or water during the reaction process.[15] The high level central-to-axial chirality transfer maybe attributed to the coordination between allylic iridium hydride and the hydroxyl group which restricts the rotation of the reaction intermediate via chiral C−C axes during the chiral transfer process.

In order to gain more mechanistic insights into the central-to-axial chirality transfer process, density functional theory (DFT) calculations were performed to investigate whether the 1,3-H transfer process is catalyzed by the base (DBU) or the iridium catalyst. As shown in Figure 2, from the allylation product (*R*)-**18**, the DBU-catalyzed benzylic C−H deprotonation occurs through transition state **TS-1**. Although being assisted by the intramolecular hydrogen-bonding interaction[7] with the naphthol OH group, this process still requires a relatively high activation free energy of 24.0 kcal/mol. Subsequent protonation of the terminal allylic carbon in **19** takes place through **TS-2**, leading to the (*P*)-enantiomer of the axially chiral styrene product (*P*)-**20**. On the other hand, a more stable conformer of (*R*)-**18** could be located as **18a** through rotation around the C−C axes (via **TS-3**). The analogous 1,3-proton transfer from **18a** would lead to the (*M*)-product (*M*)-**20**. However, the deprotonation of **18a** via **TS-1a** requires a higher activation free energy than **TS-1** due to the steric repulsion between the bromine atom and the DBU. Computational results of the 1,3-proton transfer pathway show that the rate-determining step is the benzylic C−H deprotonation and the formation of (*P*)-**20** is more favorable from (*R*)-**18**. These results are consistent with the experimentally observed chirality of the product. Moreover, computational studies indicate that the racemization of (*P*)-**20** to form (*M*)-**20** is less likely because of a high energy barrier of 28.9 kcal/mol (via **TS-4**), which is consistent with the experimentally observed activation free energy of racemization of compound **7** (Figure 1).

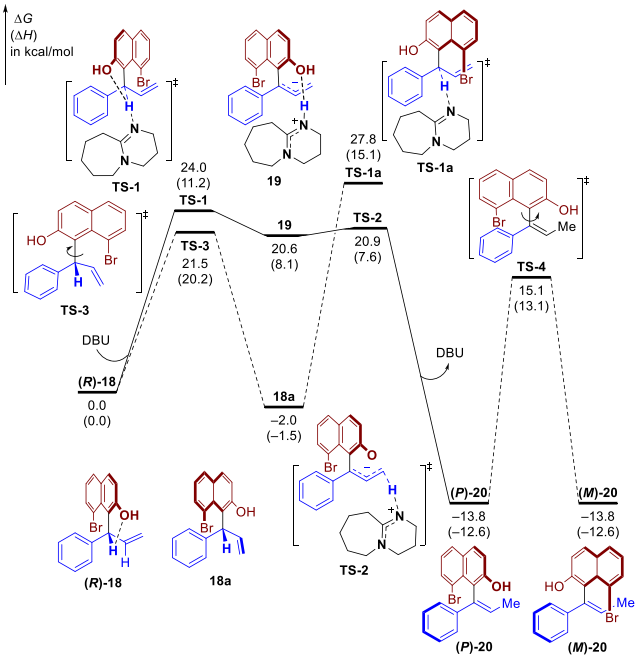

Figure 2. Free energy profile of the DBU-catalyzed 1,3-proton transfer pathway for central-to-axial chirality transfer. All energies were calculated at the M06-2X/6-311++G(d,p)/SMD(toluene)//M06-2X/6-31G(d) level of theory.

Next, we considered the iridium(I)-catalyzed stereospecific 1,3-hydride transfer pathway, which involves benzylic C−H oxidative addition to iridium(I) and C−H reductive elimination (Figure 3).[16] Because experimentally, the 1,3-H transfer was observed using either $[Ir(cod)Cl]_2$ catalyst or the iridacycle catalyst generated from $[Ir(cod)Cl]_2$, **L1**, and TBD (see Figure S6 of the Supporting Information for details), we used $[Ir(cod)Cl]_2$ in the DFT calculations for simplicity. First, complex **21** was generated through the coordination of the allylation product (*R*)-**18** to the iridium catalyst. From **21**, the iridium(I)-promoted deprotonation of naphthol with DBU leads to a naphthoxide iridium(I) intermediate **23**, which is 4.5 kcal/mol more stable than the naphthol complex **21**. The following benzylic C−H oxidative addition (via **TS-6**) and the C−H reductive elimination (via **TS-7**) then take place to accomplish the central-to-axial chirality transfer to form the

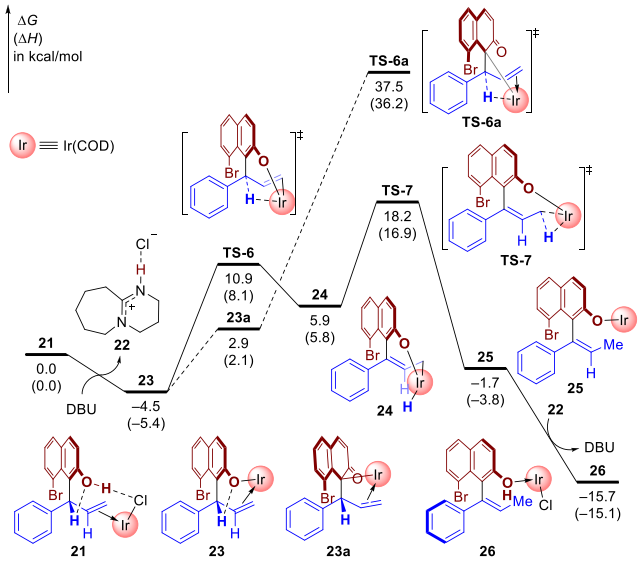

Figure 3. Free energy profile of the iridium(I)-catalyzed 1,3-hydride transfer pathway for central-to-axial chirality transfer. All energies were calculated at the M06-2X/6-311++G(d,p)−SDD/SMD-(toluene)//M06-2X/6-31G(d)−LANL2DZ level of theory.

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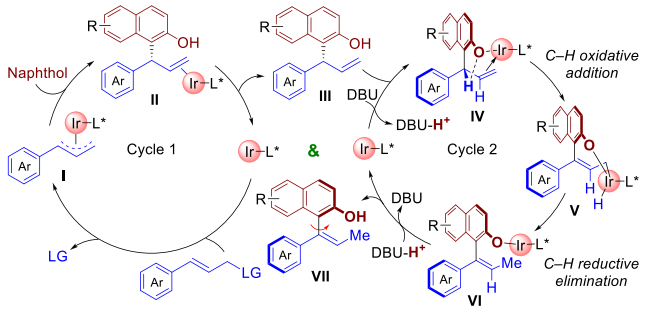
(*P*)-enantiomer of the styrene (**26**). The overall activation free energy of this pathway is 22.7 kcal/mol, which is 1.3 kcal/mol lower than that of the DBU-promoted 1,3-proton transfer pathway. Therefore, our computational results suggested that the central-to-axial chirality transfer is achieved through the iridium(I)-catalyzed 1,3-hydride transfer mechanism, instead of the 1,3-proton transfer mechanism. The benzylic C−H oxidative addition transition state (**TS-6a**) leading to the (*M*)-product [(*M*)-**20**] has a much higher activation free energy due to the lack of naphthoxide *O*-coordination to the Ir. The hydroxyl of naphthol plays a crucial role in ensuring the stereospecificity because the deprotonated naphthoxide can coordinate with the iridium(I) catalyst in the pathway leading to the favored (*P*)-product, which prevents the rotation around the C−C axes.

On the basis of the experimental and DFT results, a proposed mechanism for *AASI* is outlined which contained two independent iridium-catalytic cycles (Scheme 4). In catalytic

Scheme 4. Proposed Catalytic Cycle of the Ir-Catalyzed Asymmetric Allylic Substitution-Isomerization for the Formation of Axially Chiral Styrenes



cycle **1**, the classic iridium-catalyzed asymmetric allylic substitution occurs via intermediates **I** and **II**, generating compound **III** in high enantioselectivities. Catalytic cycle **2** then initiates through the coordination of naphthol of **III** to the iridium catalyst. A base-facilitated deprotonation of naphthol generates the chelating *O*-bound π-alkene iridium complex **IV**. The following benzylic C−H oxidative addition forms the iridium(III) hydride complex (**V**). Subsequently, the C−H reductive elimination and protonation of **VI** lead to the formation of product **VII** and regenerated the iridium catalyst.[9d] It should be noted that the origin of stereoselectivity of **VII** is attributed to the asymmetric allylic substitution step since $[Ir(cod)Cl]_2$ without ligand could also accomplish the stereospecific 1,3-hydride transfer (see the SI for details).

3. CONCLUSIONS

In summary, we have developed the first example of tandem iridium catalysis to control the enantioselectivity and stereospecificity of the chirality transfer step in an atroposelective synthesis of axially chiral styrenes. This transformation was facilitated by two independent iridium catalytic cycles of asymmetric allylic substitution-isomerization (*AASI*) using easily accessible allylic carbonates and naphthols as substrates. The reaction tolerated a broad substrate scope for both 1-naphthols and 2-naphthols, affording corresponding products in excellent yields and enantioselectivities. The racemization experiments exhibited the importance of the steric hindrance of naphthols for the preservation of enantiopurities. DFT studies of the isomerization process indicated that the stereospecific 1,3-hydride transfer takes place via iridium-catalyzed benzylic C−H oxidative addition and C−H reductive elimination. The hydroxyl of naphthol is critical for the stereospecificity during the central-to-axial chirality transfer because the coordination of the deprotonated hydroxyl with Ir(I) prevents rotation about the C−C axes. We expect that the *AASI* strategy by iridium catalysis would open a broader avenue for efficient access to various types of axially chiral molecules efficiently.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04400.

Materials and methods; experimental procedures; optimization studies; characterization data; ^{1}H, ^{13}C, and ^{19}F NMR; HPLC spectra; and mass spectrometry data of new compounds (PDF)

Accession Codes

CCDC 2039913 and 2039920 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. Total Synthesis of Chiral Biaryl Natural Products by Asymmetric Biaryl Coupling. *Chem. Soc. Rev.* **2009**, *38*, 3193. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563. (c) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent Advances and New Concepts for The Synthesis of Axially Stereoenriched Biaryls. *Chem. Soc. Rev.* **2015**, *44*, 3418. (d) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (e) Renzi, P. Organocatalytic Synthesis of Axially Chiral Atropisomers. *Org. Biomol. Chem.* **2017**, *15*, 4506. (f) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239. (g) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534.

(2) (a) Yoshimura, T.; Tomohara, K.; Kawabata, T. Asymmetric Induction via Short-Lived Chiral Enolates with a Chiral C−O Axis. *J. Am. Chem. Soc.* **2013**, *135*, 7102. (b) Mori, K.; Ohmori, K.; Suzuki, K. Hydrogen-Bond Control in Axially Chiral Styrenes: Selective Synthesis of Enantiomerically Pure C_2-Symmetric Paracyclophanes. *Angew. Chem., Int. Ed.* **2009**, *48*, 5638.

(3) (a) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls by a Cation-Directed O-Alkylation. *Nat. Chem.* **2017**, *9*, 558. (b) Feng, J.; Li, B.; He, Y.; Gu, Z. Enantioselective Synthesis of Atropisomeric Vinyl Arene Compounds by Palladium Catalysis: A Carbene Strategy. *Angew. Chem., Int. Ed.* **2016**, *55*, 2186. (c) For others, see: Liang, Y.; Ji, J.; Zhang, X.; Jiang, Q.; Luo, J.; Zhao, X. Enantioselective Construction of Axially Chiral Amino Sulfide Vinyl Arenes via Chiral Sulfide-Catalyzed Electrophilic Carbothiolation of Alkynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4959.

(4) (a) Zheng, S.-C.; Wu, S.; Zhou, Q.; Chung, L. W.; Ye, L.; Tan, B. Organocatalytic Atroposelective Synthesis of Axially Chiral Styrenes. *Nat. Commun.* **2017**, *8*, 15238. (b) Tan, Y.; Jia, S.; Hu, F.; Liu, Y.; Peng, L.; Li, D.; Yan, H. Enantioselective Construction of Vicinal Diaxial Styrenes and Multiaxis System via Organocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16893. (c) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. Organocatalytic Enantioselective Construction of Axially Chiral Sulfone-Containing Styrenes. *J. Am. Chem. Soc.* **2018**, *140*, 7056. (d) Huang, A.; Zhang, L.; Li, D.; Liu, Y.; Yan, H.; Li, W. Asymmetric One-Pot Construction of Three Stereogenic Elements: Chiral Carbon Center, Stereoisomeric Alkenes, and Chirality of Axial Styrenes. *Org. Lett.* **2019**, *21*, 95. (e) Li, S.; Xu, D.; Hu, F.; Li, D.; Qin, W.; Yan, H. Organocatalytic Asymmetric Atroposelective Construction of Axially Chiral 1,4-Distyrene 2,3-Naphthalene Diols. *Org. Lett.* **2018**, *20*, 7665. (f) Li, D.; Tan, Y.; Peng, L.; Li, S.; Zhang, N.; Liu, Y.; Yan, H. Asymmetric Mannich Reaction and Construction of Axially Chiral Sulfone-Containing Styrenes in One Pot from α-Amido Sulfones Based on the Waste-Reuse Strategy. *Org. Lett.* **2018**, *20*, 4959. (g) Wang, C.-S.; Li, T.-Z.; Liu, S.-J.; Zhang, Y.-C.; Deng, S.; Jiao, Y.; Shi, F. Axially Chiral Aryl-Alkene-Indole Framework: A Nascent Member of the Atropisomeric Family and Its Catalytic Asymmetric Construction. *Chin. J. Chem.* **2020**, *38*, 543.

(5) (a) Jin, L.; Yao, Q.-J.; Xie, P.-P.; Li, N.; Zhan, B.-B.; Han, Y.-Q.; Hong, X.; Shi, B.-F. Atroposelective Synthesis of Axially Chiral Styrenes via an Asymmetric C−H Functionalization Strategy. *Chem.* **2020**, *6*, 497. (b) Song, H.; Li, Y.; Yao, Q.-J.; Jin, L.; Liu, L.; Liu, Y.-H.; Shi, B.-F. Synthesis of Axially Chiral Styrenes via Pd-Catalyzed Asymmetric C-H Olefination Enabled by an Amino Amide Transient Directing Group. *Angew. Chem., Int. Ed.* **2020**, *59*, 6576. (c) Yang, C.; Wu, T.-R.; Li, Y.; Wu, B.-B.; Jin, R.-X.; Hu, D.-D.; Li, Y.-B.; Bian, K.-J.; Wang, X.-S. Facile Synthesis of Axially Chiral Styrene-Type Carboxylic Acids via Palladium-Catalyzed Asymmetric C−H Activation. *Chem. Sci.* **2021**, *12*, 3726.

(6) (a) Wang, Y.-B.; Wu, Q.-H.; Zhou, Z.-P.; Xiang, S.-H.; Cui, Y.; Yu, P.; Tan, B. Asymmetric Construction of Axially Chiral 2-Arylpyrroles by Chirality Transfer of Atropisomeric Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 13443. (b) Ma, C.; Sheng, F.-T.; Wang, H.-Q.; Deng, S.; Zhang, Y.-C.; Jiao, Y.-C.; Tan, W.; Shi, F. Atroposelective Access to Oxindole-Based Axially Chiral Styrenes via the Strategy of Catalytic Kinetic Resolution. *J. Am. Chem. Soc.* **2020**, *142*, 15686.

(7) Sun, C.; Qi, X.; Min, X.-L.; Bai, X.-D.; Liu, P.; He, Y. Asymmetric Allylic Substitution-Isomerization to Axially Chiral Enamides via Hydrogen-Bonding Assisted Central-to-Axial Chirality Transfer. *Chem. Sci.* **2020**, *11*, 10119.

(8) For selected reviews on iridium-catalyzed asymmetric allylic substitution, see: (a) Takeuchi, R.; Kezuka, S. Iridium-Catalyzed Formation of Carbon-Carbon and Carbon-Heteroatom Bonds. *Synthesis* **2006**, *2006*, 3349. (b) Hartwig, J. F.; Stanley, L. M. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461. (c) Tosatti, P.; Nelson, A.; Marsden, S. P. Recent Advances and Applications of Iridium-Catalysed Asymmetric Allylic Substitution. *Org. Biomol. Chem.* **2012**, *10*, 3147. (d) Liu, X.-J.; Zheng, C.; Yang, Y.-H.; Jin, S.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Aromatization Reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 10493. (e) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Iridium-Catalyzed Diastereo-, Enantio-, and Regioselective Allylic Alkylation with Prochiral Enolates. *ACS Catal.* **2016**, *6*, 6207. (f) Qu, J.; Helmchen, G. Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2539. (g) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855. (h) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite,Olefin) Ligands. *Acc. Chem. Res.* **2019**, *52*, 2657.

(9) (a) Molleti, N.; Martinez-Erro, S.; Cerdán, A. C.; Sanz-Marco, A.; Gomez-Bengoa, E.; Martín-Matute, B. Base-Catalyzed [1,n]-Proton Shifts in Conjugated Polyenyl Alcohols and Ethers. *ACS Catal.* **2019**, *9*, 9134. (b) Bai, X.-d.; Wang, J.; He, Y. Iridium-Catalyzed Propenylation Reactions for the Synthesis of 4-Pyridone Derivatives. *Adv. Synth. Catal.* **2019**, *361*, 496. (c) Huang, J.; Wang, W.; He, H.-Y.; Jian, L.; Fu, H.-Y.; Zheng, X.-L.; Chen, H.; Li, R.-X. An Approach to the Synthesis of 1-Propenylnaphthols and 3-Arylnaphtho[2,1-b]-furans. *J. Org. Chem.* **2017**, *82*, 2523. (d) Xu, Q.-L.; Dai, L.-X.; You, S.-L. Tandem Ir-Catalyzed Allylic Substitution Reaction of Allyl Sulfinates and Isomerization. *Org. Lett.* **2010**, *12*, 800. For selective reports on stereospecific [1,3]-H transfer, see: (e) Ascough, D. M. H.; Duarte, F.; Paton, R. S. Stereospecific 1,3-H Transfer of Indenols Proceeds via Persistent Ion-Pairs Anchored by NH···π Interactions. *J. Am. Chem. Soc.* **2018**, *140*, 16740. (f) Martinez-Erro, S.; Sanz-Marco, A.; Gómez, A. B.; Vázquez-Romero, A.; Ahlquist, M. S. G.; Martín-Matute, B. Base-Catalyzed Stereospecific Isomerization of Electron-Deficient Allylic Alcohols and Ethers through Ion-Pairing. *J. Am. Chem. Soc.* **2016**, *138*, 13408. (g) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. Combining NHC-Cu and Brønsted Base Catalysis: Enantioselective Allylic Substitution/Conjugate Additions with Alkynylaluminum Reagents and Stereospecific Isomerization of the Products to Trisubstituted Allenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694. (h) Bizet, V.; Pannecoucke, X.; Renaud, J.-L.; Cahard, D. Ruthenium-Catalyzed Redox Isomerization of Trifluoromethylated Allylic Alcohols: Mechanistic Evidence for an Enantiospecific Pathway. *Angew. Chem., Int. Ed.* **2012**, *51*, 6467. (i) Martinez-Erro,

https://doi.org/10.1021/jacs.1c04400
J. Am. Chem. Soc. 2021, 143, 10686−10694

S.; García-Vázquez, V.; Sanz-Marco, A.; Martín-Matute, B. Stereospecific Isomerization of Allylic Halides via Ion Pairs with Induced Noncovalent Chirality. *Org. Lett.* **2020**, *22*, 4123. (j) Golec, J. C.; Carter, E. M.; Ward, J. W.; Whittingham, W. G.; Simon, L.; Paton, R. S.; Dixon, D. J. BIMP-Catalyzed 1,3-Prototropic Shift for the Highly Enantioselective Synthesis of Conjugated Cyclohexenones. *Angew. Chem., Int. Ed* **2020**, *59*, 17417. (k) Saga, Y.; Motoki, R.; Makino, S.; Shimizu, Y.; Kanai, M.; Shibasaki, M. Catalytic Asymmetric Synthesis of R207910. *J. Am. Chem. Soc.* **2010**, *132*, 7905. (l) Wu, Y.; Singh, R. P.; Deng, L. Asymmetric Olefin Isomerization of Butenolides via Proton Transfer Catalysis by an Organic Molecule. *J. Am. Chem. Soc.* **2011**, *133*, 12458. (m) Wu, Y.; Deng, L. Asymmetric Synthesis of Trifluoromethylated Amines via Catalytic Enantioselective Isomerization of Imines. *J. Am. Chem. Soc.* **2012**, *134*, 14334. (n) Zhou, X.; Wu, Y.; Deng, L. Cinchonium Betaines as Efficient Catalysts for Asymmetric Proton Transfer Catalysis: The Development of a Practical Enantioselective Isomerization of Trifluoromethyl Imines. *J. Am. Chem. Soc.* **2016**, *138*, 12297. (o) Xue, X.-S.; Li, X.; Yu, A.; Yang, C.; Song, C.; Cheng, J.-P. Mechanism and Selectivity of Bioinspired Cinchona Alkaloid Derivatives Catalyzed Asymmetric Olefin Isomerization: A Computational Study. *J. Am. Chem. Soc.* **2013**, *135*, 7462.

(10) For selected transition-metal-catalyzed olefin isomerization, see: (a) Chen, C.; Dugan, T. R.; Brennesse, W. W.; Weix, D. J.; Holland, P. L. *Z*-Selective Alkene Isomerization by High-Spin Cobalt(II) Complexes. *J. Am. Chem. Soc.* **2014**, *136*, 945. (b) Trost, B. M.; Cregg, J. J.; Quach, N. Isomerization of *N*-Allyl Amides To Form Geometrically Defined Di-, Tri-, and Tetrasubstituted Enamides. *J. Am. Chem. Soc.* **2017**, *139*, 5133. (c) Larsen, C. R.; Grotjahn, D. B. Stereoselective Alkene Isomerization over One Position. *J. Am. Chem. Soc.* **2012**, *134*, 10357. (d) Biswas, S.; Huang, Z.; Choliy, Y.; Wang, D. Y.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S. Olefin Isomerization by Iridium Pincer Catalysts. Experimental Evidence for an η^3-Allyl Pathway and an Unconventional Mechanism Predicted by DFT Calculations. *J. Am. Chem. Soc.* **2012**, *134*, 13276. (e) Schmidt, A.; Nödling, A. R.; Hilt, G. An Alternative Mechanism for the Cobalt-Catalyzed Isomerization of Terminal Alkenes to (*Z*)-2-Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 801. (f) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. A Tandem Isomerization/Prins Strategy: Iridium(III)/Brønsted Acid Cooperative Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 12910. (g) Kita, M. R.; Miller, A. J. M. An Ion-Responsive Pincer-Crown Ether Catalyst System for Rapid and Switchable Olefin Isomerization. *Angew. Chem., Int. Ed.* **2017**, *56*, 5498. (h) Tian, Y.-C.; Jakoobi, M.; Boulatov, R.; Sergeev, A. Selective Cleavage of Unactivated Arene Ring C-C Bonds by Iridium: Key Roles of Benzylic C-H Activation and Metal-Metal Cooperativity. *Chem. Sci.* **2021**, *12*, 3568. For selected reviews, see: (i) Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo, W. A. L. Isomerization of Allylbenzenes. *Chem. Rev.* **2015**, *115*, 5462. (j) Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. Double Bond Migration in *N*-Allylic Systems Catalyzed by Transition Metal Complexes. *Coord. Chem. Rev.* **2008**, *252*, 1819. (k) Larionov, E.; Li, H.; Mazet, C. Well-Defined Transition Metal Hydrides in Catalytic Isomerizations. *Chem. Commun.* **2014**, *50*, 9816. (l) Li, M.; Sanz-Marco, A.; Martinez-Erro, S.; García-Vázquez, V.; Mai, B. K.; Fernández-Gallardo, J.; Himo, F.; Martín-Matute, B. Unraveling the Mechanism of the Ir^{III}-Catalyzed Regiospecific Synthesis of α-Chlorocarbonyl Compounds from Allylic Alcohols. *Chem.—Eur. J.* **2020**, *26*, 14978. (m) Hu, L.; Wu, Z.; Huang, G. Mechanism and Origins of Regio- and Stereoselectivities in Iridium-Catalyzed Isomerization of 1-Alkenes to *trans*-2-Alkenes. *Org. Lett.* **2018**, *20*, 5410.

(11) For selected early reports on central-to-axial chirality transfer, see: (a) Baker, R. W.; Hambley, T. W.; Turner, P.; Wallace, B. J. Central to Axial Chirality Transfer via Double Bond Migration: Asymmetric Synthesis and Determination of the Absolute Configuration of Axially Chiral 1-(3′-Indenyl)naphthalenes. *Chem. Commun.* **1996**, 2571. (b) Hattori, T.; Date, M.; Sakurai, K.; Morohashi, N.; Kosugi, H.; Miyano, S. Highly Stereospecific Conversion of C-centrochirality of a 3,4-Dihydro-2H-1,1'-binaphthalen-1-ol into Axial Chirality of a 3,4-Dihydro-1,1'-binaphthalene. *Tetrahedron Lett.* **2001**, *42*, 8035. (c) Mori, K.; Ohmori, K.; Suzuki, K. Stereochemical Relay via Axially Chiral Styrenes: Asymmetric Synthesis of the Antibiotic TAN-1085. *Angew. Chem., Int. Ed.* **2009**, *48*, 5633.

(12) For selected reports on TM-catalyzed asymmetric allylic dearomatization of naphthols, see: (a) Zhuo, C.-X.; You, S.-L. Palladium-Catalyzed Intermolecular Asymmetric Allylic Dearomatization Reaction of Naphthol Derivatives. *Angew. Chem., Int. Ed.* **2013**, *52*, 10056. (b) Tang, S.-B.; Tu, H.-F.; Zhang, X.; You, S.-L. Rhodium-Catalyzed Asymmetric Allylic Dearomatization of β-Naphthols: Enantioselective Control of Prochiral Nucleophiles. *Org. Lett.* **2019**, *21*, 6130. (c) Tu, H.-F.; Zheng, C.; Xu, R.-Q.; Liu, X.-J.; You, S.-L. Iridium-Catalyzed Intermolecular Asymmetric Dearomatization of β-Naphthols with Allyl Alcohols or Allyl Ethers. *Angew. Chem., Int. Ed.* **2017**, *56*, 3237. (d) Shen, D.; Chen, Q.; Yan, P.; Zeng, X.; Zhong, G. Enantioselective Dearomatization of Naphthol Derivatives with Allylic Alcohols by Cooperative Iridium and Brønsted Acid Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3242. For reports on TM-catalyzed asymmetric allylic alkylation of naphthols, see: (e) Li, C.; Breit, B. Rhodium-catalyzed Dynamic Kinetic Asymmetric Allylation of Phenols and 2-Hydroxypyridines. *Chem.—Eur. J.* **2016**, *22*, 14655.

(13) (a) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Brodner, K.; Helmchen, G. Ir-Catalyzed Asymmetric Allylic Substitutions with (Phosphoramidite)Ir Complexes—Resting States, Synthesis, and Characterization of Catalytically Active (π-Allyl)Ir Complexes. *Chem.—Eur. J.* **2009**, *15*, 11087. (b) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. Enantio-, Diastereo-, and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic β-Ketoesters. *J. Am. Chem. Soc.* **2013**, *135*, 17298. (c) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters via Ir-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation and Applications in Sequential Pd Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 10626. (d) Liu, W.-B.; Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement. *J. Am. Chem. Soc.* **2016**, *138*, 5234. (e) Bai, X.-D.; Zhang, Q.-F.; He, Y. Enantioselective Iridium Catalyzed α-Alkylation of Azlactones by a Tandem Asymmetric Allylic Alkylation/Aza-Cope Rearrangement. *Chem. Commun.* **2019**, *55*, 5547.

(14) See the SI for details. es = $ee_{prd}/ee_{sm}*100\%$.

(15) (a) Zhou, J.; Hartwig, J. F. Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization. *Angew. Chem., Int. Ed.* **2008**, *47*, 5783. (b) Klei, S. R.; Golden, J. T.; Tilley, T. D.; Bergman, R. G. Iridium-Catalyzed H/D Exchange into Organic Compounds in Water. *J. Am. Chem. Soc.* **2002**, *124*, 2092. (c) Iluc, V. M.; Fedorov, A.; Grubbs, R. H. H/D Exchange Processes Catalyzed by an Iridium-Pincer Complex. *Organometallics* **2012**, *31*, 39.

(16) For selective computational studies about Ir-catalyzed C−H oxdative addition and reductive elimination processes, see: (a) Xing, D.; Qi, X.; Marchant, D.; Liu, P.; Dong, G. Branched-Selective Direct alpha-Alkylation of Cyclic Ketones with Simple Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 4366. (b) Li, X.; Wu, H.; Lang, Y.; Huang, G. Mechanism, Selectivity, and Reactivity of Iridium- and Rhodium-Catalyzed Intermolecular Ketone α-Alkylation with Unactivated Olefins via an Enamide Directing Strategy. *Catal. Sci. Technol.* **2018**, *8*, 2417. (c) Huang, G.; Liu, P. Mechanism and Origins of Ligand-Controlled Linear Versus Branched Selectivity of Iridium-Catalyzed Hydroarylation of Alkenes. *ACS Catal.* **2016**, *6*, 809.

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