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COMMUNICATION

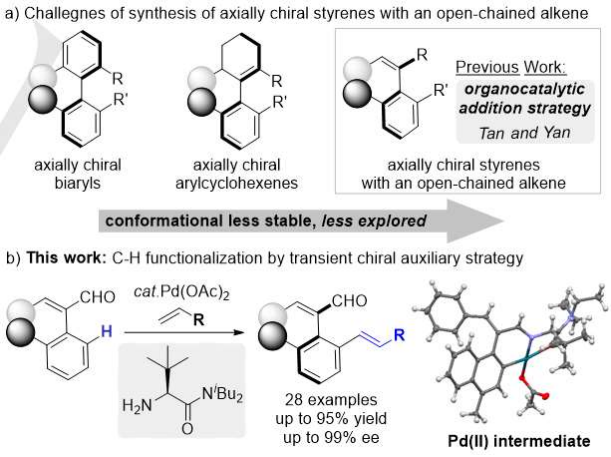
Synthesis of Axially Chiral Styrenes via Pd-Catalyzed Asymmetric C-H Olefination Enabled by an Amino Amide Transient Directing Group

Hong Song, Ya Li, Qi-Jun Yao, Liang Jin, Lei Liu, Yan-Hua Liu and Bing-Feng Shi*

Abstract: The atroposelective synthesis of axially chiral styrenes remains a formidable challenge, due to their relatively lower rotational barriers compared to the biaryl atropoisomers. Herein, we describe the construction of axially chiral styrenes by Pd(II)-catalyzed atroposelective C–H olefination, using a bulky amino amide as transient chiral auxiliary. Various axially chiral styrenes were produced with good yields and high enantioselectivities (up to 95% yield and 99% ee). The resulting axially chiral styrenes derivatized chiral carboxylic acids showed superior enantiocontrol over the biaryl counterparts in Co(III)-catalyzed enantioselective C(sp^3)-H amidation of thioamide. Mechanistic studies suggest that C-H cleavage is the enantioselectivity-determining step.

Axially chiral styrenes, a class of atropoisomers arising from the sterically hindered rotation along a single bond between a substituted alkene and an aromatic ring, was first studied by Adams and co-workers in the 1940s.[1] This novel type of atropoisomers have been overlooked for a long time and received attentions only recently. These atropoisomers have been used as versatile synthons in total synthesis[2] and as chiral ligands in asymmetric catalysis.[3] Consequently, the development of novel strategies for the atroposelective synthesis of these skeletons has been a central topic in organic synthesis. However, in sharp contrast to the well-established approaches for the asymmetric synthesis of axially chiral biaryls,[4] methods to the enantioselective synthesis of axially chiral styrenes remains rare (Scheme 1a).[5] Early studies focused on the use of stoichiometric chiral compounds with point chirality via point-to-axial chirality transfer strategy.[2,6] Catalytic asymmetric synthesis is more attractive but also more challenging. Gu[7] and Smith[8] reported the highly enantioselective construction of axially chiral arylcyclohexenes, a kind of styrene atropoisomers with the alkene unit trapped within a rigid hexacycle to maintain a comparable stability with that of biaryls. Due to the flexible structure and relatively lower conformational stability, the asymmetric synthesis of chiral styrene with an acyclic alkene is more challenging. To date, the only strategy for its efficient synthesis is asymmetric organocatalytic addition developed by the Tan and Yan groups recently.[9] The mild reaction conditions generally used in organocatalytic synthesis (at or below room temperature) ensure the high enantiocontrol in the transition state and the maintenance of the chirality of the resulting styrene atropoisomers.

Recently, asymmetric C-H functionalization has emerged as a powerful synthetic approach for the rapid access of axially chiral biaryls.[4f,h,10] Inspired by the pioneering work by Yu on the construction of central chirality through transient chiral auxiliary (TCA) enabled C-H functionalization strategy,[11] we recently reported the highly atroposelective construction of biaryl atropoisomers using *tert*-leucine (Tle) as TCA.[12] As part of our ongoing efforts in asymmetric C−H functionalization,[12,13] we had great interests in constructing axially chiral styrenes via TCA strategy. We assumed that the enantiocontrolled introduction of a large substituent at the *ortho*-position of properly designed 2-arylacrylaledhydes to lock the preformed axis through TCA enabled C-H activation would be an attractive synthetic approach. Although this strategy sounds promising, the adoption of atroposelective C-H functionalization to styrene atropoisomers is not straightforward, due to the following daunting challenges: (1) unlike organocatalytic synthesis that generally conducted at room temperature or below, C-H activation usually occurs at relatively high temperature, which might lead to poor enantiocontrol and significantly loss of chirality due to the low atropo-stability of styrene atropoisomers. (2) acrylaldehydes contain multiple reactive sites and are prone to undergo several undesired reactions, such as oxidation, Michael addition, and/or isomerization. We now describe our efforts that overcome those challenges and prepare axially chiral styrenes with an open-chained alkene through a Pd-catalyzed atroposelective C−H olefination using a bulky amino amide as transient auxiliary (Scheme 1b).



Scheme 1. Challenges of synthesis of axially chiral styrenes, previous approaches and our strategy.

To verify the feasibility of our assumption, we initiated our investigations by investigating the reaction of *rac*-**1a** and butyl acrylate (**2a**). The desired product **3aa** was obtained in 91% yield and 95% ee when using 10 mol% $Pd(OAc)_2$, 1.0 equivalent of BQ, 1.0 equivalent of $Co(OAc)_2{\cdot}4H_2O$, 0.5 equivalent of $(BnO)_2PO_2H$ and 0.3 equivalent of **TCA-1** in HOAc/DMSO at 40 °C for 48 hours under O_2 atmosphere (Table 1, entry 1, standard conditions). Control experiments showed that no olefination product was observed in the absence of the palladium catalyst (entry 2). The use of *tert*-leucine

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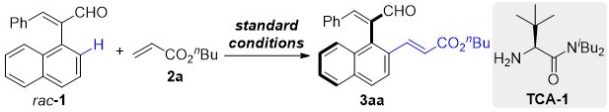
(**TCA-8**) instead of **TCA-1** led to reduced yield and enantioselectivity (entry 3, 39%, 80% ee). In 2018, Yu and co-workers developed a bulky amino amide transient auxiliary to control the stereochemistry of the C(sp^3)-H activation.[11b] Inspired by this pionnering work, a number of α-amino acids derived amides were screened (Tables S3 and S7) and we were delighted to find that *tert*-leucine-derived amino amide **TCA-1** was the optimal one. Control experiments on the effect of other additives were tested (entries 4-12). The choices of oxidants and solvents were crucial for this reaction. The removal of BQ resulted in significantly reduced yield (entry 4). Only trace product was observed in the absence of DMSO (entry 6), which might act as ligand to stabilize the palladium catalyst. $(BnO)_2PO_2H$ was also an important additive to better tune the acidity of the reaction system. $Co(OAc)_2{\cdot}4H_2O$ was found to promote the reaction (entry 8), probably acting as a co-oxidant. The reaction proceeded more effectively under O_2 atmosphere (entry 9).

Table 1. Optimization of reaction conditions.[a]

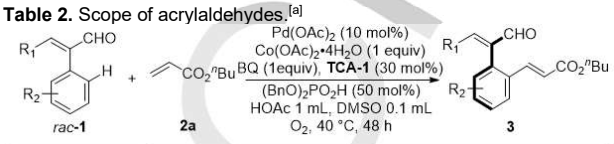


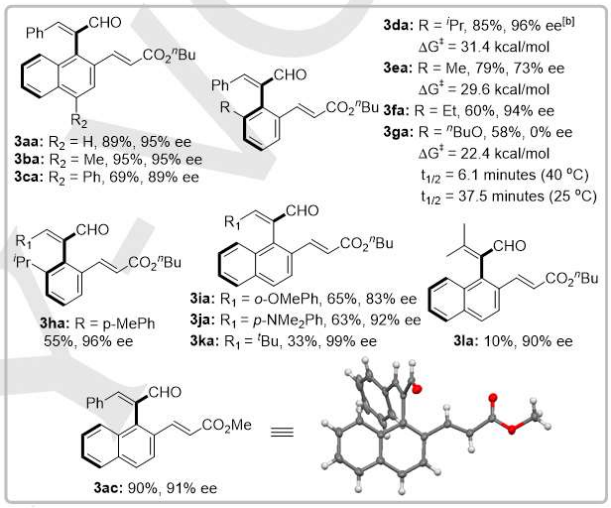
Entry	Deviation from standard conditions	Yield(%)[b]	ee(%)[c]
1	none	91	95
2	no $Pd(OAc)_2$	0	-
3	*tert*-leucine instead of **TCA-1**	39	80
4	no BQ	58	90
5	add BQ (30 mol%)	51	85
6	no DMSO	trace	82
7	no $(BnO)_2PO_2H$	89	87
8	no $Co(OAc)_2{\cdot}4H_2O$	64	82
9	air instead of O_2	85	89
10	HOAc:MeOH:DMSO (7:3:1) instead of HOAc:DMSO (10:1)	41	92

[a] Standard conditions: *rac*-**1a** (0.1 mmol), **2a** (4.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **TCA-1** (0.3 equiv), BQ (1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 equiv), $(BnO)_2PO_2H$ (0.5 equiv) in HOAc/DMSO (10:1, v/v,1.1 mL) under O_2 for 48 h. [b] Determined by ^{1}H NMR spectroscopy using tetrachloroethane as the internal standard. [c] The ee value was determined by HPLC. DMSO = dimethyl sulfoxide, TCA=transient chiral auxiliary

With the optimal reaction conditions in hand, we explored the generality of the atroposelective C-H olefination. The scope of acrylaldehydes was first examined (Table 2). Generally, sterically bulkyl substituents positioned *ortho* to the chiral axis were necessary to ensure enantioselectivity (**3da**, R = iPr, 96% ee; **3ea**, R = Me, 73% ee). Cinnamaldehyde **1g** bearing *ortho*-butoxyl group led to **3ga** with no axial chirality. To explain these results, density functional theory (DFT) calculations were performed to investigate the atropostability of several representative products. There appeared a noteworthy trend that the cinnamaldehyde derivatives bearing relatively larger substituent have significantly higher rotational barriers compared with the smaller substituent (**3da**, R = *i*Pr, $\Delta G^{\ddagger}$ = 31.4 kcal/mol; **3ea**, R = Me, $\Delta G^{\ddagger}$ = 29.6 kcal/mol; **3ga**, R = ^{n}BuO, $\Delta G^{\ddagger}$ = 22.4 kcal/mol).[14] This effect is an interesting addition to the general consensus that the steric bulkiness of the ortho-substituents of styrenes compounds is the leading factor that controls the rotational barrier. These results also proved that the formation of **3ga** as racemate is due to the lack of atropostability under the reaction conditions or even at temperature ($t_{1/2}$= 6.1 minutes at 40 °C; $t_{1/2}$ = 37.5 minutes at 25 °C, see SI for details). Cinnamaldehyde derivatives with electron-donating groups on the phenyl ring also gave good to excellent enantioselectivity (**3ha**, *p*-Me; **3ia**, *o*-OMe; **3ja**, R = *p*-NMe_2). acrylaldehydes with alkyl substituents were compatible with the protocol, albeit with relatively lower yield, and sterically bulky substituents gave higher enantioselectivity as expected (**3ka**, ^{t}Bu, 33%, 99% ee; **3la**, Me, 10%, 92% ee). (**3ka**, up to 99% ee). The absolute configuration of product **3ac** was determined by the X-ray analysis and those of the other products were assigned by analogy.[15]

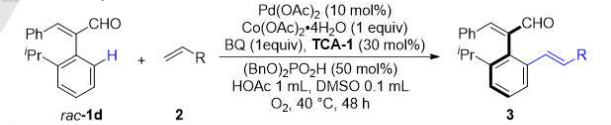
Table 2. Scope of acrylaldehydes.[a]

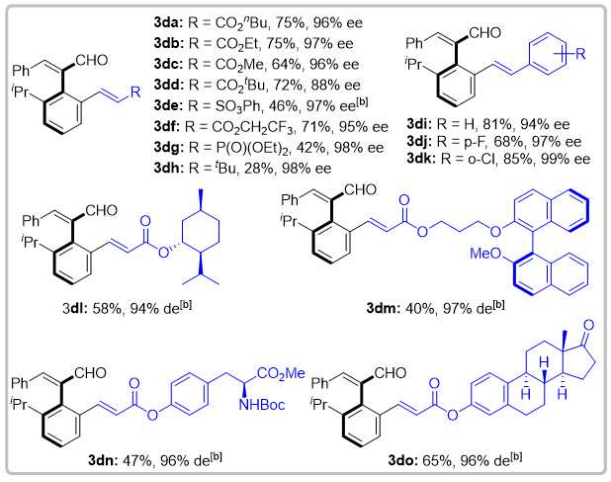




[a] *rac*-**1** (0.1 mmol), **2a** (4.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **TCA-1** (0.3 equiv), BQ (1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 equiv), $(BnO)_2PO_2H$ (0.5 equiv) in HOAc/DMSO (10:1, v/v,1.1 mL) under O_2 for 48 h, isolated yield. [b] 96 h.

Table 3. Scope of Olefins.[a]

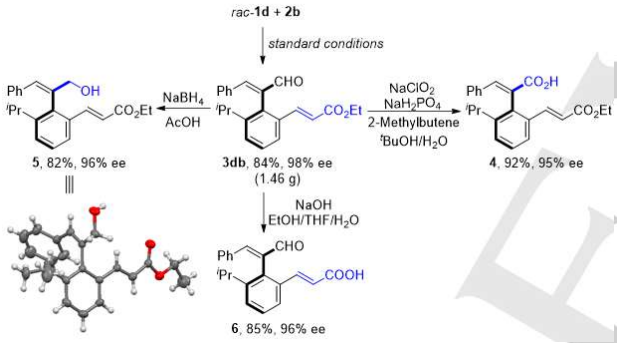




[a] *rac*-**1d** (0.1 mmol), **2** (4.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **TCA-1** (0.3 equiv),BQ (1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 equiv), $(BnO)_2PO_2H$ (0.5 equiv) in HOAc/DMSO (10:1, v/v,1.1 mL) under O_2 for 48 h, isolated yield. [b] **2** (2.0 equiv).

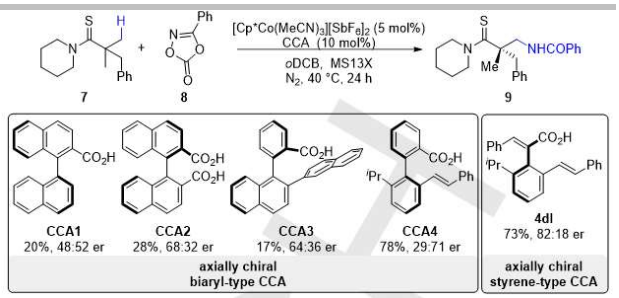
Next, cinnamaldehyde derivative (*rac*-**1d**) bearing relatively larger substituent (*i*Pr) was used to test the generality of olefins (Table 3). To our delight, various olefins, such acrylates, alkenylphosphate, phenylsulphate, and styrenes, were compatible with our optimal conditions and the corresponding axially chiral products were obtained in excellent atroposelectivities (94-99% ee). Moreover, aliphatic olefin **2h** was also compatible, giving **3dh** with high enantioselectivity, albeit with lower isolated yield (28%, 98% ee). Moreover, natural product-derived acrylates were also efficient coupling partners (**3dl-3do**), which might found potential application in pharmaceuticals. Styrenes with electron-withdrawing substituents, such as fluoro and chloro, could also give good yields and excellent atroposelectivities (**3dj** and **3dk**).

To demonstrate the practicality of our strategy, gram-scale synthesis and transformations have been conducted (Scheme 2). First, the reaction of *rac*-**1d** and **2b** on a 5 mmol scale was performed, and the desired product **3db** was isolated with retentive enantioselectivity (84%, 98% ee, 1.46 g). Subsequently, a series of transformations of axially chiral styrene **3db** were demonstrated. **3db** could be oxidized to carboxylic acid **4** and selectively reduced to form alcohol **5** under mild conditions without the loss of enantioselectivity. Ester hydrolysis also gave carboxylic acid **6** without significant change of atroposelectivity.



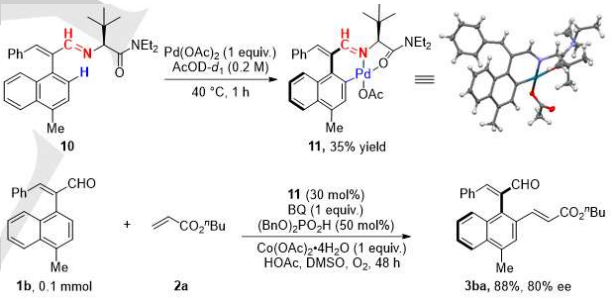
Scheme 2. Gram-scale synthesis and transformation of **3db.**

To demonstrate the significance of the axially chiral atropoisomers, the use as chiral ligands in asymmetric synthesis was shown Scheme 3. Recently, the Matsunaga group reported the enantioselective C(sp^3)–H amidation of thioamides catalysed by a Co(III)/chiral carboxylic acid (CCA) hybrid system.[16] They have elegantly demonstrated that both bulky α-amino acid bearing a central chirality[16a] and 2-aryl ferrocene carboxylic acids with planar chirality[16b] are suitable chiral ligands for this reaction. the target product **9** was obtained in good yield and moderate enantioselectivity (73%, 82:18 er). To expanding the scope of CCA-enabled enantioselective C-H activation reactions,[13d,17,18] we aimed to further develop proper CCAs with axial chirality. Although axially chiral biaryl-type CCAs **(L1-L4)** gave poor enantiocontrol (48:52 to 29:71 er), the newly developed axially chiral styrene-type CCA **4dl** gave better enantioselectivity (82:18 er), indicating that the novel styrene atropisomers might open up a new door in asymmetric synthesis.



Scheme 3. Application as chiral ligand in Co(III)-catalyzed enantioselective C(sp^3)-H amidation of thioamide.

To shed light on the reaction mechanism, stoichiometric reaction of the pre-formed imine **10** and $Pd(OAc)_2$ was performed in AcOD-d_1 at 40 °C and palladacycle intermediate **11** was isolated after chromatography.[11b] The structure of **11** was confirmed by single-crystal X-ray diffraction, which has the same stereochemistry as **3ba**.[15] The reaction of **1b** and **2a** using intermediate **11** as catalyst led to **3ba** in good yield and slightly reduced enantioselectivity (Scheme 4). Furthermore, a KIE value of 2.3 was observed (see SI for details). These results suggested that C-H cleavage is both the enantioselectivity- and rate-determining step. The reaction of ***rac*-1d** in AcOD-d_1 with omission of butyl acrylate for 24 h led to 25% deuteration of the recovered starting material, indicating the C-H activation step is reversible.



Scheme 4. Mechanistic studies.

In summary, we have developed an efficient and practical method to construct a new class of axially chiral styrenes by Pd-catalyzed atroposelective C-H olefination. This method employs a bulky amino amide as transient chiral auxiliary. We hope that strategy would provide new chance to construct axially chiral styrene skeletons, which might be a class of promising axially chiral ligands/catalysts in asymmetric synthesis.

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Keywords: C-H olefination • palladium • transient directing group • axially chiral styrenes • atroposelectivity •

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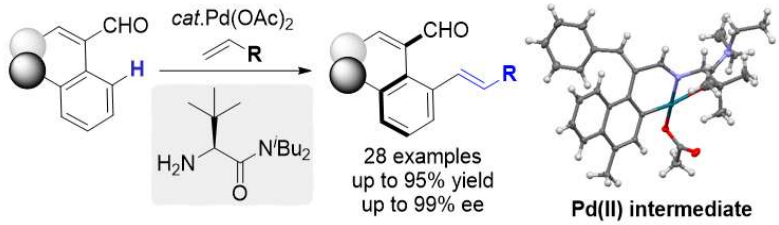

The atroposelective synthesis of axially chiral styrenes remains a formidable challenge, due to their relatively lower rotational barriers compared to the biaryl atropoisomers. Herein, we describe the construction of axially chiral styrenes by Pd(II)-catalyzed atroposelective C–H olefination, using a bulky amino amide as transient chiral auxiliary. Various axially chiral styrenes were produced with good yields and high enantioselectivities (up to 95% yield and 99% ee). The resulting axially chiral styrenes derivatized chiral carboxylic acids showed superior enantiocontrol over the biaryl counterparts in Co(III)-catalyzed enantioselective C(sp^3)-H amidation of ferrocenes. Mechanistic studies suggest that C-H cleavage is the enantioselectivity-determining step.

*Hong Song, Ya Li, Qi-Jun Yao, Liang Jin, Lei Liu, Yan-Hua Liu and Bing-Feng Shi**

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Synthesis of Axially Chiral Styrenes via Pd-Catalyzed Asymmetric C-H Olefination Enabled by an Amino Amide Transient Directing Group