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Introduction

Enantiopure carboxylic acids, especially natural amino acids, have been widely used as readily available chiral substances for facile syntheses of complex chiral compounds, known as the strategy of 'chiral pool synthesis'.1 Meanwhile, chiral carboxylic acids serve not only as an important class of organocatalysts for various enantioselective transformations,² but also as chiral ligands for transition-metal-catalyzed asymmetric chemical processes ranging from academic to industrial settings.3,4 With the enormous progress made in the past several decades in enantioselective C-H functionalization,5 chiral carboxylic acids (CCAs) have recently emerged as powerful ligands for this stepand atom-economic transformation. For instance, chiral aminoacid or cyclopropane-derived dirhodium tetracarboxylates enabled a plethora of asymmetric intra- and inter-molecular C-H functionalizations via a stereo-controlled insertion of Rhcarbene into C-H bonds.³ Although Cp^*M^{III} (M = Co, Rh, Ir) has recently been developed as an efficient catalyst for C-H functionalization,⁶ the lack of extra coordination sites for extrinsic chiral ligands presented distinct difficulties for catalytic stereo-control of such transformations.7 To address this issue, CCAs have been used as chiral ligands to enable enantioselective C-H activation without the use of a synthetically difficult chiral Cp*M^{III} catalyst.^{4,7} Apart from central^{4b-df,k-n} and

Facile synthesis of axially chiral styrene-type carboxylic acids *via* palladium-catalyzed asymmetric C–H activation†

Chi Yang, Tian-Rui Wu, Yan Li, Bing-Bing Wu, Ruo-Xing Jin, Duo-Duo Hu, Yuan-Bo Li, Kang-Jie Bian and Xi-Sheng Wang *

A novel method by a one-step introduction of axial chirality and sterically hindered group has been developed for facile synthesis of axially chiral styrene-type carboxylic acids. With the palladium-catalyzed C-H arylation and olefination of readily available cinnamic acid established, this transformation demonstrated excellent yield, excellent stereocontrol (up to 99% yield and 99% ee), and broad substrate scope under mild conditions. The axially chiral styrene-type carboxylic acids produced have been successfully applied to Cp*Co^{III}-catalyzed asymmetric C-H activation reactions, indicating their potential as chiral ligands or catalysts in asymmetric synthesis.

planar CCAs,^{4g} highly sterically demanding axial CCAs have been designed and used for efficient recognition of the prochiral C–H bonds. While a sterically hindered aryl group adjacent to the carboxyl group is required to control the enantioselectivity of C–H activation, a multiple-step synthesis to modify the binaphthyl backbone remains still a tedious task and definitely hampers their application in organic synthesis.^{4e,h-j}

Although various synthetic methods have been well established for the synthesis of such biaryl atropisomers,⁸ their "diphenyl analogs", axially chiral styrenes with the chiral axis between a substituted alkene and an aromatic ring, have long been neglected⁹ despite their potential in total synthesis and asymmetric synthesis as chiral catalysts or ligands.^{10,11a,b} Besides the "central to axial chirality transfer" strategy which required the use of stoichiometric chiral intermediates,11 transition-metal or organo-catalyzed asymmetric reactions have recently been developed as efficient approaches for the construction of axially chiral styrenes.12-15 To mimic the rigidity of biaryls, alkene skeletons with the C=C double bond trapped within six-membered-rings have been used to synthesize chiral arylcyclohexenes.12 Meanwhile, a structure with the chiral axis between an open-chain alkene and an aromatic ring, which exhibited lower rotation energy, was first constructed by Tan13 and Yan14 by incorporation of sterically hindered groups into the alkynes using an organocatalytic addition strategy. Very recently, Pd-catalyzed asymmetric olefination of C-H bonds has been developed by Shi and co-workers to make axially chiral styrenes, although this protocol required the use of strongly coordinating pyridyl or other transient directing groups (TDGs).15 As part of our continuous efforts in enantioselective C-H functionalizations,¹⁶ we conceived a method in which the readily



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Hefei National Laboratory for Physical Sciences at the Microscale, Department of Chemistry, Center for Excellence in Molecular Synthesis of CAS, University of Science and Technology of China, Hefei, Anhui 230026, China. E-mail: xswang77@ ustc.edu.cn

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Scheme 1 Chiral carboxylic acids as ligands for asymmetric C–H functionalization.

available racemic cinnamic acid derivative could be used as an efficient precursor to make axially chiral styrene-type ligands *via* asymmetric C–H functionalization, which thus provides an efficient and rapid way to furnish novel axially chiral acid ligands by a simple modification of racemic acids (Scheme 1).

Herein, we describe a novel strategy for the facile synthesis of axially chiral styrene-type carboxylic acids by modification of cinnamic acid derivatives *via* palladium(II)-catalyzed C–H arylation or olefination.¹⁷ The carboxyl group, which serves as a key motif in the resulting chiral ligands, plays an important role as a weakly coordinating group in the one-step introduction of axial chirality and sterically hindered group in this catalytic method.¹⁸ This new transformation demonstrated excellent stereocontrol, broad scope under mild conditions, and the produced axially chiral styrene-type carboxylic acids have been successfully applied to Cp*Co^{III}-catalyzed asymmetric C–H activation reactions.

Results and discussion

Our study commenced with the investigation of the Pd(II)-catalyzed C-H arylation of the cinnamic acid derivative rac-1a with 4-(methoxycarbonyl)benzeneboronic acid pinacol ester 2a used as the coupling partner. After extensive examination of the reaction conditions, the desired product 3aa was obtained in 74% yield and 97% ee in the presence of 10 mol% of $Pd(OAc)_2$, 1.5 equiv. of Ag₂CO₃, 0.5 equiv. of BQ, 2.0 equiv. of KHCO₃, 0.2 equiv. of Boc-1-tert-leucine, and 20.0 equiv. of H2O in tAmylOH at 40 °C for 72 hours in an air atmosphere (Table 1, entry 1). A series of control experiments were then conducted, which indicated that no arylation product was detected in the absence of the palladium catalyst or base (entries 2 and 3). Meanwhile, removing the N-protecting group from Boc-L-tert-leucine completely quenched the reaction (entry 4). Furthermore, screening of oxidants showed that the combination of Ag₂CO₃ and BQ was crucial for this transformation, and the replacement of Ag₂CO₃ with Ag₂O or omitting the addition of BQ resulted in a sharp decrease of yields (entries 5 and 6). Interestingly, H₂O played a key role in improving both yield and enantioselectivity in this reaction system (entry 7). A careful examination of bases and solvents clearly showed that KHCO3 and tAmylOH were the optimal choices for this asymmetric C-H arylation (see the ESI[†] for details), while the use of KH₂PO₄ as the base gave 3aa in only 49% yield (entry 8) and the employment of iPrOH as the solvent decreased the yield dramatically to 34%, albeit still with excellent enantioselectivity (entry 9). Meanwhile, the replacement of Boc-L-tert-leucine with other Nprotected amino acids (MPAAs) as ligands furnished only lower enantioselectivity to some extent. Not surprisingly, raising the reaction temperature to 60 °C led to a better yield but poor enantioselectivity (entry 11).

 Table 1
 Optimization of reaction conditions^a



Entry	Change from standard conditions	$\operatorname{Yield}^{b}(\%)$	$\operatorname{Ee}^{c}(\%)$
1	None	74	97
2	No $Pd(OAc)_2$	0	
3	No KHCO ₃	0	_
4	<i>tert</i> -Leucine instead of Boc- <i>L</i> - <i>tert</i> -leucine	0	_
5	Ag ₂ O instead of Ag ₂ CO ₃	51	97
6	No BQ	51	90
7	No H ₂ O	41	67
8	KH_2PO_4 instead of $KHCO_3$	49	94
9	<i>i</i> PrOH as the solvent	34	96
10	Fmoc-L-tert-leucine instead of Boc-L-tert-leucine	60	92
11	Raising the temperature to 60 $^{\circ}C$	86	70

^{*a*} Standard conditions: *rac*-**1a** (0.2 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (0.1 equiv.), Boc-L-*tert*-leucine (0.2 equiv.), BQ (0.5 equiv.), Ag₂CO₃ (1.5 equiv.), KHCO₃ (2.0 equiv.), H₂O (20.0 equiv.) in *t*AmylOH 1.0 mL in air at 40 °C for 72 h, the crude mixture was methylated using MeI. ^{*b*} Isolated yields. ^{*c*} The evalue was determined by HPLC.

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With the optimized conditions in hand, the scope and functional group tolerance of the aryl-aryl coupling were next investigated (Table 2). Firstly, the examination of various *ortho*substituted phenylacetic acids indicated that sterically bulky substituents were required for high enantioselective control, and larger alkyl groups (**3ba-3da**) gave excellent

Table 2 Substrate scope of Pd catalyzed enantioselective C-H arylation a,b,c

scope of cinnamic acids

Pd(OAc)₂/Boc-L-tert-leucine then Mel, K₂CO₃

Ph

3

DMF, r.t. 2 h

ArBpin (2)

Ag₂CO₃, BQ, KHCO₃, H₂O

tAmyIOH, 40 °C, 72 h, air

COOMe COOMe COOM COOM COOMe OOMe Ph Me Ft 3ab 3da 302 57%, 94% ee 65% 98% ee 81%, 98% ee COOMe COOMe COON COOM COOM COOME Ph CI F₃C 3fa 3ga 22%, 98% ee 52%, 98% ee 61%, 90% ee COOMe COOMe COOM COOMe COOMe COOMe Ph Me ÓМе 312 3ja Me 3ka 62%, 95% ee 65%, 98% ee 72%, 91% ee COOMe COOME COOMe COOMe COOMe 31a 3ma 53%, 97% ee 41%, 97% ee 3ab scope of aryl-boronic acid pinacol esters 81%, 94% ee .OMe COOM OOMe COOMe 1 3ad 3ac 53%, 96% ee 66 %, 97% ee 66% 89% ee COOMe NO COOMe COOME 3af 3ah 3ag 56%, 91% ee 79%, 95% ee 79 %, 96% ee COOME COOM OOMe OM COOMe 3ai 3ak 3ai 60%, 96% ee 73%, 96% ee 74%, 94% ee tBu CF₃ COOMe COOMe -tBu CF 3al 3am 3an 57%, 95% ee 41% 97% ee 49% 94%

^{*a*} Rac-1 (0.2 mmol), 2 (2.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.), Boc-t-tert-leucine (0.2 equiv.), BQ (0.5 equiv.), Ag_2CO_3 (1.5 equiv.), $KHCO_3$ (2.0 equiv.), H_2O (20.0 equiv.) in *t*AmylOH 1.0 mL in air at 40 °C for 72 h, the crude mixture was methylated using MeI. ^{*b*} Isolated yields. ^{*c*} The ee value was determined by HPLC.

enantioselectivities (94-98% ee) due to the higher rotational barriers. While the steric hindrance apparently affected the enantioselectivities, they had no influence on the reactivity, and these transformations exhibited moderate to good yield. Unsurprisingly, a strong electron-withdrawing group $(-CF_3)$ on the phenyl ring significantly reduced the reactivity and afforded the desired product in a much lower yield (22%) but still with high enantioselectivity (1f, 98% ee). At the same time, Cl- and Ph-substituents were well tolerated to afford 3ea (61%, 90% ee) and 3ga (52%, 98% ee) smoothly. Multisubstituted cinnamic acid derivatives 1i and 1j were also successfully arylated in good yields and excellent enantioselectivities (3ia, 65%, 98% ee; and 3ja 72%, 91% ee). The substituent effect on naphthalene was also investigated, which showed that methyl and phenyl were quite compatible in this transformation (3ka, 62%, 95% ee; 3la, 53%, 97% ee). Notably, a pyrene group connected to the styrene was also tolerated to provide the desired arylation product (3ma) in 41% yield and with 97% ee. The scope of different arylboronic acid pinacol esters has also been demonstrated in this C-H arylation system. Electron-withdrawing groups at the paraposition such as cyano, trifluoromethyl, nitro, and phenyl gave the desired chiral styrenes (3ad-3ag) in moderate to good yields and with excellent enantioselectivities. The coupling of 1a with electron-rich aryl-boronic acid pinacol ester 2c afforded 3ac in a yield of 66% with slightly lower enantioselectivity (89% ee). To our delight, halogen substituents were also well tolerated in this reaction, affording 3ah and 3ai in 96% and 94% ee, respectively. Such halogenated chiral styrenes could be further transformed into various functional groups through late-stage crosscoupling reactions. Meta-substituted aryl-boronic acid pinacol esters 2j and 2k were also well compatible with the reaction conditions, furnishing the corresponding products 3aj and 3ak both in 96% ee. Multi-substituted substrates afforded the desired products (3al-3an) in slightly lower yields with similar enantioselectivities.

To further expand the diversity of such axially chiral styrenetype CCAs, Pd-catalyzed C-H olefination reactions were then explored with 1a and methyl acrylate 4a as model substrates (see the ESI† for detailed optimizations). The desired olefination product 5aa was obtained in 97% yield and 97% ee with 10 mol% Pd(OAc)₂ used as the catalyst and 30 mol% Boc-L-tertleucine used as the ligand, and 2.0 equiv. of KOH as the base under 1 atm O2 in iPrOH at 30 °C for 72 h. The absolute configuration of 5aa was determined to be R by single crystal Xray diffraction,19, which is in contrast to that of the product furnished by the TDG strategy in spite of using ligands derived from the same amino acid. To rationalize the origin of the stereoselectivity, according to previous studies, stereo-models of the transition states of two different catalysis systems are proposed in Scheme 2. In TS-1, palladium is coordinated with the MPAA ligand and the substrate in a square-planar coordination. The bulky side-chain of the amino acid points upward, which pushes the alkenyl group away from the palladium coordination plane to avoid steric repulsion.17h,20 However, in TS-2, palladium fused with cinnamaldehyde imine presents a square-planar coordination. The upward side-chain extrudes



Scheme 2 Transient states of two catalysed models.

the alkenyl group downward, which leads to contrary absolute configurations.^{15b,21}

With the optimized conditions in hand, we sought to test the olefination scope under the standard conditions (Table 3). To our delight, these transformations exhibited high efficiency, and moderate to good yields and excellent enantioselectivities were achieved in most cases. Alkyl groups (1b-1c) and chloro-(1d) on the cinnamic acid were well-tolerated, giving high enantiocontrol (5aa-5da, 90-99% ee). As expected, when a trifluoromethyl substituent was tested, inferior yield was obtained, albeit with a high enantioselectivity (5fa, 47%, 99% ee). In addition, phenyl- and MeOCH₂- at the ortho position were well compatible with this transformation, and furnished the corresponding products 5ga and 5ha with high ee in moderate yield. The olefinated product 5ia was obtained in 87% yield with 98% ee when multisubstituted cinnamic acid derivative 1i was employed. Notably, substituted naphthalenes (1k, 1l) also served as suitable coupling partners with good stereocontrol as well as high yields (5ka, 79%, 89% ee; and 5la, 77%, 93% ee). To our delight, substrate 1m bearing a pyrene group gave the desired olefination product smoothly, in a yield of 54% with 99% ee. Various other acrylates were compatible with this reaction, affording corresponding products (5ab-5ah) in good yields and excellent enantioselectivities. Most remarkably, 4methoxystyrene and 4-trifluoromethylstyrene were also suitable partners for this transformation, producing 5ai and 5aj in yields of 59% and 60%, respectively, with excellent enantioselectivities of 98% ee and 96% ee.

To gain insights into the utility of the reaction, gram-scale synthesis and transformations were conducted (Scheme 3). First, the reaction of *rac*-**1a** and **2b** on a 5 mmol scale was performed, and the desired **CCA 1** was isolated with retentive enantioselectivity (77%, 94% ee, 1.34 g). The 5 mmol scale reaction of *rac*-**1a** and **4a** gave **5aa** in a yield of 95% and 95% ee. Subsequently, **CCA 1** was reduced to form alcohol **6** under mild conditions with a mild loss in enantioselectivity. The olefination product **5aa** could undergo a van Leusen reaction and afford the hetero-aryl compound **7** in 77% yield and 93% ee.

In order to demonstrate the application prospect of our methodology, both olefinated and arylated axially chiral styrene-type carboxylic acids (CCA 1–CCA 6) were treated as chiral ligands in a Co^{III}-catalyzed asymmetric synthesis, as shown in Scheme 4. In 2019, Matsunaga and co-workers demonstrated that the combination of an achiral Co^{III}

Table 3 Substrate scope of Pd catalyzed enantioselective C–H $olefination^{a,b,c}$



^{*a*} Rac-1 (0.2 mmol), 4 (3.0 equiv.), Pd(OAc)₂ (0.1 equiv.), Boc-L-tertleucine (0.3 equiv.), KOH (2.0 equiv.), H₂O (10.0 equiv.) in *i*PrOH 2.0 mL in 1 atm O₂ at 30 °C for 72 h, the crude mixture was methylated using MeI. ^{*b*} Isolated yields. ^{*c*} The ee value was determined by HPLC. ^{*d*} 84 h. ^{*e*} 108 h. ^{*f*} 132 h.

complex and CCA promotes asymmetric $C(sp^3)$ -H amidation reactions of thioamides **8** with dioxazolones **9**.^{4/s} A series of newly developed axially chiral styrene-type CCAs were employed (Scheme 4a), and the desired product **10** was obtained in moderate to good yields. When **CCA 6** was employed, a better enantioselectivity (17 : 83 er) was obtained. Meanwhile, enantioselective **1**,4-addition reaction of indole **11** with maleimide **12** which proceeds *via* a C2-selective C–H activation was also conducted.⁴⁴ The product **13** was obtained in 49% yield with



Scheme 3 Gram scale reactions and transformations of CCA 1 and 5aa.



Scheme 4 Application of axially chiral styrene-type carboxylic acids as ligands in Co^{III}-catalyzed enantioselective C–H activation reactions.

77 : 23 er, when **CCA 4** was employed (Scheme 4b). Although the enantioselectivity of the aforementioned transformations needs to be improved, these results demonstrate that the chiral styrene-type CCA skeleton is promising in developing a new class of chiral ligands and may find more applications in catalytic asymmetric transformations.

Conclusions

In conclusion, we have developed palladium-catalyzed C-H arylation or olefination of cinnamic acid derivatives for facile

synthesis of axially chiral styrene-type carboxylic acids through a one-step incorporation of axial chirality and sterically hindered group. This method demonstrated broad scope, good yields, excellent enantioselective control, and mild conditions. The axially chiral styrene-type carboxylic acids produced have been successfully applied to Cp*Co^{III}-catalyzed asymmetric C–H activation reactions as potential chiral ligands. This strategy offered a valuable solution for rapid and efficient construction of novel axially chiral styrenes, which may serve as a class of novel chiral ligands or catalysts in asymmetric synthesis. Further exploration of asymmetric C–H activation to enable axially chiral motifs is underway in our laboratory.

Conflicts of interest

The authors declare no conflict of interest.

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