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Access to Chiral Tetrahydrofluorenes through Palladium-Catalyzed Enantioselective Tandem Intramolecular Heck/Tsuji–Trost Reaction

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Ying Zhang,[‡]^a Hong-Cheng Shen,[‡]^a Yang-Yang Li,^a Yong-Shuang Huang,^b Zhi-Yong Han,^a and Xiang Wu^{*b}

Α palladium-catalyzed enantioselective coupling of 2.5cyclohexadienyl-substituted aryl iodides and carbon or heteroatom nucleophiles is described. The reaction proceeded via a tandem asymmetric Heck insertion and Tsuji-Trost allylation, enabling the rapid construction of valuable chiral tetrahydrofluorenes by using а chiral H₈-BINOL-based phosphoramidite ligand.

The demand for the development of new methodologies to achieve complex and valuable optically active compounds has increased steadily in synthetic organic chemistry.¹ A tandem asymmetric Heck²/Tsuji-Trost³ reaction, the nucleophilic substitution of π -allyl Pd intermediates formed by a Heck carbopalladation, is a typical solution for efficiently building up complex chiral molecules from simple and easily available substrates.⁴ Recently, palladium-catalyzed cascade asymmetric difunctionalization of 1,3-dienes proceeding through a Heck/Tsuji-Trost process has received increasing attention for the synthesis of structurally diverse and densely functionalized chiral molecules, characterized by the generation of π -allyl palladium intermediate.⁵ However, in contrast to 1,3-dienes, only few nonconjugated 1,4-dienes have been successfully employed in this type of reaction, but all giving racemic products.⁶ In 1991, Larock and co-workers described a nonenantioselective three-component coupling of iodobenzene, 1,4-cyclohexadiene and diethyl malonate through a palladiumcatalyzed tandem Heck/Tsuji-Trost reaction to furnish a transproduct 1 (Fig. 1A).^{6a} Then, Larock further identified that 1,4cyclohexadiene-tethered 2-iodobenzene could undergo palladium-catalyzed intramolecular Heck reaction and subsequent Tsuji-Trost reaction with diethyl malonate to provide tetrahydrofluorene 2 (Fig. 1B).6e Functionalized

tetrahydrofluorenes are ubiquitous core structures found in a variety of biologically active natural products such as the asterogynins⁷ and taiwaniaquinoids⁸ as well as lead pharmaceutical compounds⁹ and represent key structural elements in materials science¹⁰. Thus, efficient synthetic methods to access optically pure tetrahydrofluorenes are still in great demand. However, asymmetric palladium-catalyzed tandem intramolecular Heck¹¹/Tsuji–Trost reaction for the construction of enantioenriched tetrahydrofluorenes has not yet been accomplished. Herein, we will report the first enantioselective coupling of 2,5-cyclohexadienyl-substituted aryl iodides and carbon or heteroatom nucleophiles catalyzed by chiral Pd complexes for the synthesis of optically active tetrahydrofluorenes (Fig. 1C).



80% yield

This work: enantioselective tandem intramolecular Heck/Tsuji-Trost reaction (C) Coupling of 2-iodobenzene-tethered 1,4-cyclohexadiene with nucleophiles for the synthesis of chiral tetrahydrofluorenes



Fig. 1 Tandem Heck/Tsuji-Trost Reaction.

As shown in Fig. 1C, a Pd(II) intermediate II is generated from the oxidative addition of a Pd(0) complex to an aryl iodine and subsequent desymmetrizing Heck insertion

^{a.} Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China

^{b.} Anhui Province Key Laboratory of Advanced Catalytic Materials and Reaction Engineering, School of Chemistry and Chemical Engineering, Hefei University of Technology, 193 Tunxi Road, Hefei 230009, China. E-mail: <u>wuxiang@hfut.edu.cn</u>

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[‡] These authors contributed equally to this work.

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reaction.^{11a-c, 11e} Migration of palladium of **II** along the carbon chain on the same face of the ring results in the formation of a π -allylpalladium species **III**. The intermediate **III** undergoes backside intermolecular nucleophilic attack to afford corresponding products **3-5**. In the whole reaction process, the chiral ligand tunes the reactivity of metal catalyst and efficiently controls the stereoselectivity of the Heck reaction and Tsuji–Trost allylation respectively. Therefore, the identification of an ideal ligand turns out to be the key to realize the asymmetric version of this reaction.

As a consequence, the chiral ligands were firstly investigated for the Pd-catalyzed tandem reaction of methyl 1-(2iodobenzyl)cyclohexa-2,5-diene-1-carboxylate 6a with dibenzyl malonate 7a (Table 1). As chiral phosphoramidite ligands were beneficial for the palladium-catalyzed asymmetric allylic substitutions,12 BINOL-derived phosphoramidites L1-L4 bearing substituents at the 3,3'-positions of the binaphthyl backbone were examined. Delightedly, in the presence of $Pd(dba)_2$ in CH₃CN at 80 °C using K₂CO₃ as a base, these ligands perform well to afford the product 3aa as a single diastereoisomer with moderate enantioselectivities and in high yields (entries 1-4). Particularly, the presence of electronically deficient 3,5ditrifluoromethylphenyl substituents at 3,3'-positions of the binaphthyl moiety, as shown in L4, enabled the reaction to deliver higher level of asymmetric induction (76% ee, entry 4). A little higher ee value (79% ee) and quantitative yield were

Table 1 Optimization of the reaction conditions^a

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| | CO ₂ Me | + CH ₂ (CO ₂ 7a | Bn) ₂ Bn) ₂ bas solve | 1(dba) ₂ (10 mol%) L (11 mol%) base (2.5 equiv) Jovent. temp. 12 h | | | |
|--------------------------|----------------------|---|--|--|-------------------------|---------|--|
| 6 | a | F | | Saa CH(CO ₂ Bn) ₂ | | | |
| (| | | | $ \begin{array}{c} F \\ F \\ F \\ C \\ C \\ R \end{array} $ | | | |
| | L2 R = 4 L3 R = 4 | -FC ₆ H ₄ -NO ₂ C ₆ H ₄ | | | | | |
| | L4 R = 3 | ,5 ⁻ (CF ₃) ₂ C ₆ H ₃ | | | ,5-(CF3)2C6H3 | (0/)d | |
| entry | ligand | base | solvent | temp (°C) | yield(%) ^{5,e} | ee (%)" | |
| 1 | L1 | K ₂ CO ₃ | CH₃CN | 80 | 96 | 28 | |
| 2 | L2 | K_2CO_3 | CH₃CN | 80 | 96 | 54 | |
| 3 | L3 | K_2CO_3 | CH₃CN | 80 | 66 | 65 | |
| 4 | L4 | K ₂ CO ₃ | CH₃CN | 80 | 83 | 76 | |
| 5 | L5 | K_2CO_3 | CH₃CN | 80 | 99 | 79 | |
| 6 | L5 | K_2CO_3 | CH₃CN | 40 | 95 | 91 | |
| 7 | L5 | Na_2CO_3 | CH₃CN | 40 | - | - | |
| 8 | L5 | Ag_2CO_3 | CH₃CN | 40 | 23 | 65 | |
| 9 | L5 | КОН | CH₃CN | 40 | 72 | 89 | |
| 10 | L5 | Et₃N | CH₃CN | 40 | - | - | |
| 11 | L5 | K ₂ CO ₃ | DMSO | 40 | 42 | 38 | |
| 12 | L5 | K ₂ CO ₃ | DMF | 40 | 98 | 80 | |
| 13 | L5 | K ₂ CO ₃ | toluene | 40 | - | - | |
| 14 | L5 | K ₂ CO ₃ | DCE | 40 | - | - | |
| 15 | L5 | K ₂ CO ₃ | CH₃CN | 25 | 44 | 96 | |
| 16 ^{<i>e,f</i>} | L5 | K ₂ CO ₃ | CH_3CN | 25 | 90 (89) | 93 | |

 a Unless indicated otherwise, reactions of **6a** (0.10 mmol), **7a** (0.2 mmol), Pd(dba)₂ (0.01 mmol), **L** (0.011 mmol) and base (0.25 mmol) were carried out in solvent (1 mL) at temperature for 12 h. b The yields were determined by ¹H-NMR analysis of the crude products based on internal standard. c Isolated yields indicated in parentheses. d Determined by HPLC analysis. e The reaction

was carried out for 48 h. $^{/}$ Pd(dba)_2 (0.005 mmol), L5 (0.01 mmol) view Article Online

provided by H₈-BINOL-based phosphoramidite¹⁰¹³ (entry ³). Interestingly, the enantioselectivity could be improved to 91% ee remarkably by conducting the reaction at 40 °C (entry 6). The screening of bases revealed that K_2CO_3 was preferred for the reaction (entries 6-10). The evaluation of solvents showed that CH₃CN was the most suitable medium for the present reaction (entries 6, 11-14). When the temperature decreased further to 25 °C, the highest enantioselectivity was obtained albeit in a moderate conversion (entry 15). Importantly, by prolonging the reaction time to 48 h and tuning the amounts of Pd(dba)₂ and **L5**, a higher yield of 90% was obtained with a maintained enantioselectivity of 93% ee (entry 15 vs 14).

Under the optimized reaction conditions, a range of 2,5cyclohexadienyl-substituted aryl iodides 6 and malonate esters 7 were investigated (Table 2). In most cases, electron-donating and electron-withdrawing substituents at the phenyl ring of 6 were generally well-tolerated, affording 3ba-ka as single diastereoisomers in good yields and with excellent enantioselectivities (entries 1-10). Probably due to steric hindrance, 3- and 6-substituent of the substrate 6b and 6e resulted in considerably lower enantioselectivity (entries 1 and 4). Electron-donating groups (Me or MeO) or a strong electron-withdrawing group (CF₃) at the 5-position of the substrate degraded the conversion, affording the product in only moderate yield but with excellent ee respectively (entries 3, 8 and 10). Ethyl and t-butyl ester derivatives 6l and 6m could also work efficiently in the reaction (entries 11 and 12). Moreover, the variation of ester substituents of malonates 7b**d** was also amenable to the reaction, providing corresponding products 3ab-ad in good yields (84%-88%) and with high ee's (93%-94%) (entries13-15).

Table 2 Scope of 2,5-cyclohexadienyl-substituted aryl iodides 6and malonate esters 7^a

| $R^{1}_{4} = \frac{1}{2} + CH_{2}(CO_{2}R^{2}) + CH_{2}(CO_{2}F) + CH$ | | | | O ₂ R ³) ₂ = Bn | Pd(dba) ₂ L5 (10 K ₂ CO ₃ (2 CH ₃ CN, 2 | (5 mol%) mol%) 2.5 equiv) 25 °C, 48 h | $\mathbf{R}^{1} \overset{\mathbf{H}}{\overset{\mathcal{H}}{H$ | |
|--|-------|--|----------|--|---|--|--|---------------------|
| 6a-6m | | 70 R ² = Me 7c R ³ = Et 7d R ³ = <i>i</i> -Pr | | - | | CH(CO ₂ R ³) ₂ | | |
| | entry | 6 | R^1 | R ² | 7 | 3 | yield (%) ^b | ee (%) ^c |
| | 1 | 6b | 3-Me | Me | 7a | 3ba | 71 | 83 |
| | 2 | 6c | 4-Me | Me | 7a | 3ca | 86 | 95 |
| | 3 | 6d | 5-Me | Me | 7a | 3da | 56 | 94 |
| | 4 | 6e | 6-Me | Me | 7a | 3ea | 75 ^d | 86 ^d |
| | 5 | 6f | 4-F | Me | 7a | 3fa | 96 | 94 |
| | 6 | 6g | 4-Cl | Me | 7a | 3ga | 94 | 96 |
| | 7 | 6h | 4-Br | Me | 7a | 3ha | 72 | 97 |
| | 8 | 6i | 4-OMe | Me | 7a | 3ia | 51 | 97 |
| | 9 | 6j | 5-Cl | Me | 7a | 3ja | 99 | 95 |
| | 10 | 6k | $5-CF_3$ | Me | 7a | 3ka | 49 | 94 |
| | 11 | 61 | н | Et | 7a | 3la | 80 | 92 |
| | 12 | 6m | Н | <i>t-</i> Bu | 7a | 3ma | 84 | 90 |
| | 13 | 6a | Н | Н | 7b | 3ab | 84 | 93 |
| | 14 | 6a | Н | Н | 7c | 3ac | 88 | 94 |
| | 15 | 62 | Ц | Ц | 74 | 2-4 | 97 | 02 |

carried at 40 °C.

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Instead of malonate esters 7, aromatic phenols 8 could also work as oxygen nucleophiles in the reaction under the same conditions. Upon the reaction with aryl iodide 6a, chiral tetrahydrofluorenes 4 including an allylic aryl ether functional group could be obtained with high enantioselectivities and good yields (Scheme 1). Regardless of the electronic character of the substituents at the phenols 8, reactions proceeded smoothly under the optimal conditions, furnishing chiral tetrahydrofluorenes 4aa-ae as single diastereoisomers in moderate yields (78-87%) with high enantioselectivities (90-92% ee). Moreover, some aromatic phenols such as β -napthol and 6-hydroxyindole performed well and led to the products with high stereochemical outcomes (4af and 4ag). Notably, enantiopure chiral estrone could also smoothly undergo the reaction with 6a to deliver the corresponding product 4ah with moderate efficiency and outstanding diastereomeric excess. The structure and absolute configuration of product 4ah was assigned by X-ray analysis.13 The absolute configurations of all other compounds were assigned by analogy. Alternatively, electron-rich aniline 9a as nitrogen nucleophile was also applicable for the reaction, providing product 5aa with 81% yield and 89% ee (eq 1).14



Scheme 1 Scope of oxygen nucleophiles. ^{*a*} Reactions of **6a** (0.10 mmol), **8a-h** (0.2 mmol), Pd(dba)₂ (0.005 mmol), **L5** (0.01 mmol) and K_2CO_3 (0.25 mmol) were carried out in CH₃CN (1 mL) at 25 °C for 48 h.



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To gain more insight into the reaction mechanism_{rt} isotope labeling experiments were conducted (Scheme 2). The reaction of [D5]-**6a** and **7a** under the standard conditions gave [D]-**3aa** with 50% deuterium at the 3-position and 4-position on the cylcohexene ring respectively. These results clearly demonstrated that the key steps of β -hydride elimination and reinsertion had indeed occurred to give π -allyl Pd-species **E** from homoallylic Pd-intermediate **B** which furnished the final product by backside intermolecular nucleophilic attack (Scheme 2).



Scheme 2 Isotope labeling experiments and proposed reaction mechanism.

To demonstrate the practicability, we carried out a gramscale synthesis and derivative studies (Scheme 3). Under the optimized reaction conditions, a reaction of **6h** with **7b** on 3.5 mmol scale was performed, giving **3hb** in high yield (82%, 1.25 g), with excellent enantioselectivity (97% ee). Pleasingly, the product **3hb** could be transformed into various derivatives



Scheme 3 Scale-up experiment and transformation of the product. Reaction conditions: a) *m*-CPBA, CH₂Cl₂; b) Pd/C, H₂, CH₃OH; c) (i) NaOH, THF/H₂O=1:1; (ii) Pyridine, H₂O, 80 °C; (iii) 4-BrC₆H₄NH₂, EDCI, CH₂Cl₂; d) 4-OMeC₆H₄B(OH)₂, Pd(P^tBu₃)₂, K₂CO₃, dioxane/H₂O= 3:1, 95 °C.

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under different conditions. mCPBA-mediated epoxidation of 3hb proceeded to give the product 10 in a diastereospecific manner. The hydrogenation of **3hb** under the catalysis of Pd/C in MeOH resulted in the saturation of the alkene and reductive removal of bromine atom at the same time, affording the product 11 in high yield. Hydrolysis of the esters with NaOH in THF and H₂O, subsequent decarboxylation of malonic acid assisted by pyridine at 80 °C and followed by the condensation with 4-bromideaniline in the presence of EDCI, provided the diamide 12 in 57% yield in three steps.¹⁵ The Suzuki-Miyaura coupling of **3hb** with 4-methoxyphenylboronic acid under the catalysis of Pd(P^tBu₃)₂ proceeded cleanly to furnish the aryl substituted tetrahydrofluorene 13.

In summary, we demonstrate a chiral Pd complex-catalyzed asymmetric coupling of 2,5-cyclohexadienyl-substituted aryl iodides with carbon or heteroatom nucleophiles, furnishing the optically active tetrahydrofluorenes containing three chiral centers as single diastereoisomers in moderate to high yields (49-99%) with excellent enantioselectivities (83-97% ee) from readily available starting materials. The reaction proceeds via a Pd-catalyzed tandem intramolecular desymmetrizing Heck insertion and allylic alkylation, oxygenation or amination, capable of tolerating a broad scope of substrates. In the reaction, the choice of a H₈-BINOL-derived phosphoramidite ligand bearing electron-withdrawing substituents is crucial for successful catalysis, which not only enhances the catalytic activity but also provides an appropriate chiral environment for asymmetric induction. Moreover, the reaction could be conducted in gram-scale, and the products of the reaction could be readily converted to various useful derivatives.

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Conflicts of interest

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There are no conflicts to declare.

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A palladium-catalyzed enantioselective tandem reaction of 2,5-cyclohexadienyl-substituted aryl iodides and carbon or heteroatom nucleophiles has been successfully established by using a chiral H₈-BINOL-based phosphoramidite ligand.