



Communication

Pd-Catalyzed enantioselective synthesis of 2-methyl-3-methyleneindoline

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ABSTRACT

A Pd-catalyzed enantioselective synthesis of 2-methyl-3-methyleneindoline in up to 89% yield and 84% *ee* from racemic vinyl benzoxazinones has been developed with the help of (*R,R*)-BenzP* ligand. Mechanism studies support the formation of palladacyclobutane as the key intermediate *via* C2 attack to π -allyl Pd complex. The β -hydride elimination provides a new reaction pathway for the palladacyclobutane.

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Palladium-catalyzed decarboxylative cycloaddition reaction has become an efficient method for the synthesis of *N*-heterocycles since Tunge firstly applied vinyl benzoxazinones as a powerful precursor [1]. A variety of [4 + 1] [2], [4 + 2] [3] and [4 + 3] [4] reactions have been developed to prepare 5-, 6- and 7-membered nitrogen-containing compounds diastereo- and enantioselectively *via* the zwitterionic intermediates after oxidative addition/decarboxylation with metal complexes. α,β -Unsaturated carbonyl compounds, sulfur-ylide, ketene and many other reagents were utilized to introduce the functional group complexity (Scheme 1, eq. 1). Nucleophilic addition to the more-substituted C1 carbon in the π -allyl/Pd intermediate was proposed. On the other hand, stoichiometric [5] and catalytic [6] cyclopropane formation reactions have been developed from allylic substrates by thenucleophilic attack to C2 carbon in the π -allyl/Pd complex *via* palladacyclobutane intermediate. However, reaction involving the palladacyclobutane intermediate from vinyl benzoxazinone precursor is still very rare. Zhai reported an elegant tetracyclic indoline synthesis, in which the migratory insertion of the palladacyclobutane to benzyne intermediate was proposed as the possible mechanism (Scheme 1, eq. 2) [7,8]. We assume that the palladacyclobutane species can undergo β -hydride elimination when R is methyl group and the stereocenter at C2 can be

controlled by chiral ligand in the C–N bond formation step. Herein, we report the Pd-catalyzed enantioselective synthesis of 2-methyl-3-methyleneindoline [9] in up to 89% yield and 84% *ee* with (*R,R*)-BenzP* as the chiral ligand.

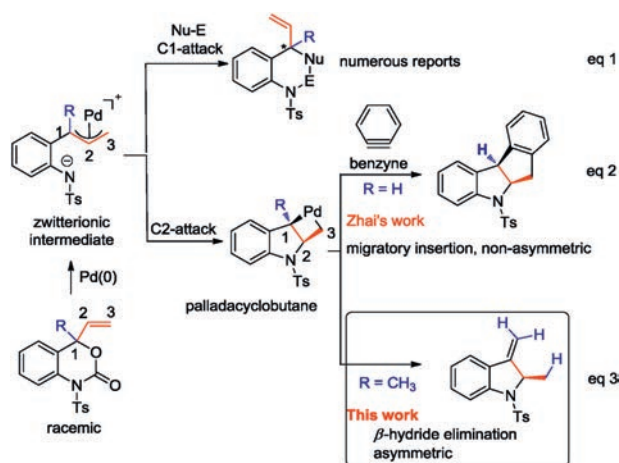
We started our study with methyl-substituted vinylbenzoxazinone **1a** as the model substrate (Table 1).

Different chiral ligands (Fig. 1) were examined using 5 mol% Pd(dba)₂ in THF at 80 °C. Reactions in the presence of chiral Phox ligands with different substitutions at the oxazoline ring (**L1–L4**) gave moderate to high yields of **2a**, while up to 60% *ee* could be observed (entries 1–4). The enantioselectivities with different chiral phosphoramidite ligands are also low (53% and 30%), although the yields of **2a** are high (entries 5 and 6). A variety of chiral diphosphine ligands were evaluated and higher chemical yields of **2a** could be obtained when **L5–L7** with two-carbon linker between the phosphine atoms are used. The highest enantioselectivity is 80% in case (*R,R*)-BenzP* was applied (entry 9). **2a** with 82% *ee* was synthesized when the reaction was conducted at 70 °C. Remarkable solvent effect was observed. Reactions in dioxane and DCE could not further improve the enantioselectivities (entries 11 and 12). Reaction in DMF affords **2a** with 86% *ee*, while the yield dropped to 30% (entry 13). Finally, reaction in toluene at 70 °C gave 89% of **2a** in 82% *ee*, which was selected as the optimized condition (entry 14).

With the optimized conditions in hand, we investigated the scope of the asymmetric synthesis of 2-methyl-3-methyleneindoline (Scheme 2). Chlorides at 6 or 7 position in the substrates have

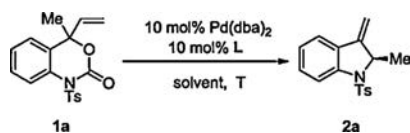
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Scheme 1. Reaction pathways for zwitterionic intermediate from vinyl benzoxazinone.

Table 1
Optimization of reaction conditions.^a



Entry	Solvent	T (°C)	Ligand	Yield (%) ^b	ee (%)
1	THF	80	L1	67	60
2	THF	80	L2	70	31
3	THF	80	L3	90	4
4	THF	80	L4	64	35
5	THF	80	L5	80	53
6	THF	80	L6	71	30
7	THF	80	L7	80	13
8	THF	80	L8	90	70
9	THF	80	L9	73	80
10	THF	70	L9	77	82
11	Dioxane	70	L9	79	81
12	DCE	70	L9	63	77
13	DMF	70	L9	30	86
14	Toluene	70	L9	89	82

^a Conditions: 0.1 mmol **1** in 1 mL of solvent were used as the standard condition.

^b Isolated yield.

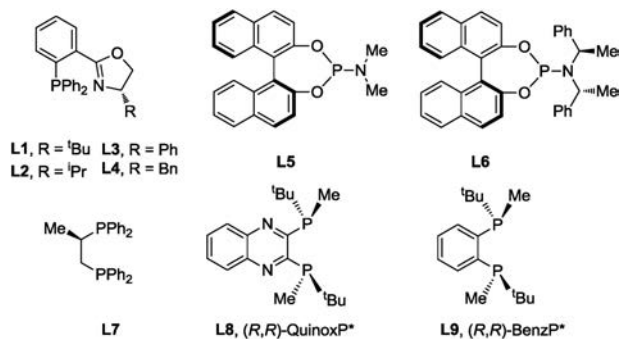
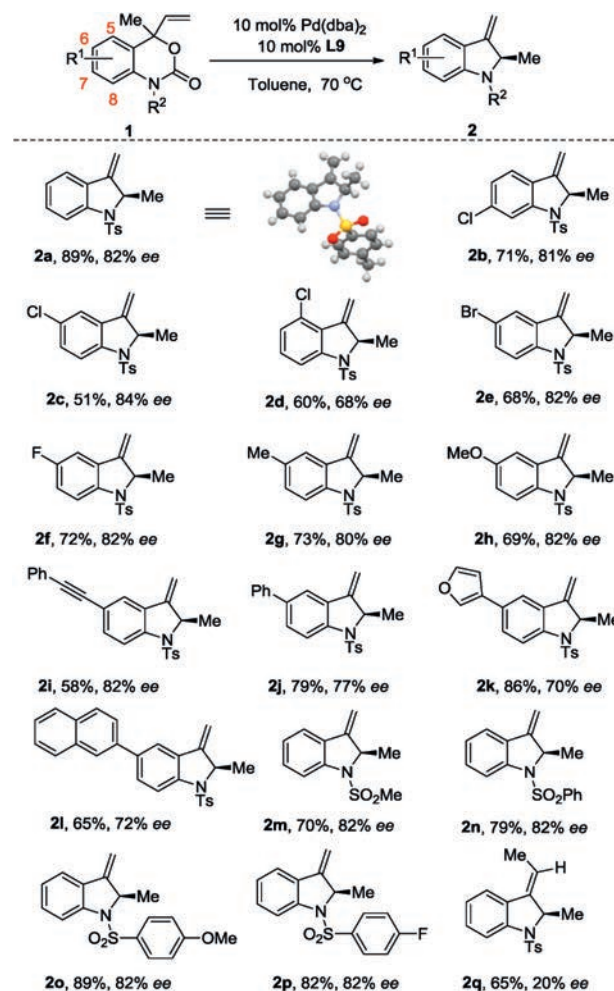


Fig. 1. Structures of chiral ligands.

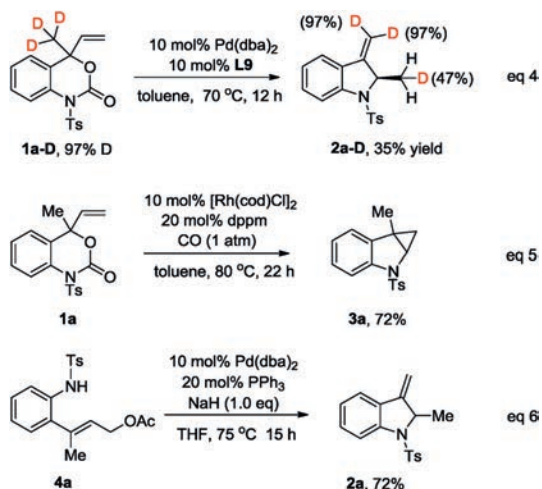
little effect to the selectivities (**2b** and **2c**). On the contrast, the reaction of **1d** with a chloride at 5 position is sluggish. **2d** could be isolated in 60% yield and the enantioselectivity dropped to 68% dramatically (**2d**). Electron-withdrawing bromide and fluoride



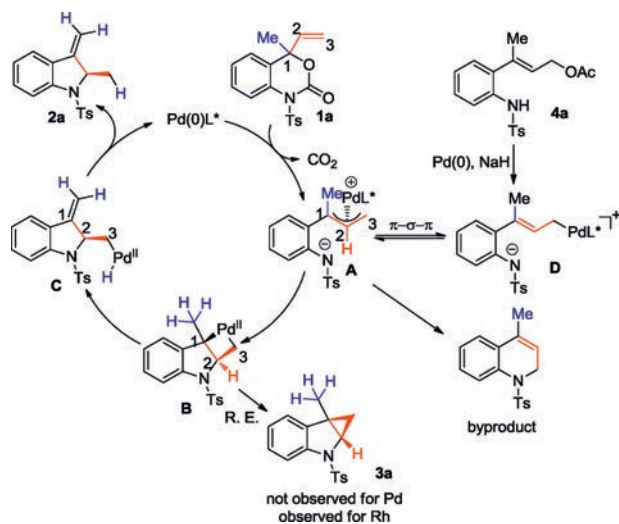
Scheme 2. The scope of the Pd-catalyzed 2-methyl-3-methyleneindoline synthesis.

(**2e** and **2f**) could be tolerated under the optimized condition as well as electron-donating methyl and methoxy groups (**2g** and **2h**). The presence of alkyne function in the substrate lead to lower conversion, while the enantioselectivity remains to be 82% (**2i**). Substrates with aromatic phenyl, 2-naphthyl, 3-furanyl groups at 6-position could also react smoothly to give the 2-methyl-3-methyleneindoline in high yields but relatively lower enantioselectivities (**2j**, **2k** and **2l**). Besides the substituents on the aromatic ring, the influence of the protecting groups on the nitrogen was also examined. The same level of enantioselectivities was obtained when simple methyl, phenyl, 4-MeOC₆H₄ or 4-FC₆H₄ sulfonyl groups were used (**2m** to **2p**). However, substrate with Ac groups leads to low conversion. When **1q** with an ethyl group was subjected to the same reaction condition, **2q** was isolated in 65% yield with *E* configuration, while only 20% ee was observed, probably due to the relatively slow interconversion of the racemic substrates. Substitutions on the vinyl group lead to complicated reaction mixture formation. The absolute configuration of **2a** was assigned to be *R* by single crystal X-ray diffraction analysis.

Several experiments were conducted to investigate whether the palladacyclobutane formation and β -hydride elimination mechanism is involved in the reaction (Scheme 3). Firstly, **1a-D** with deuterated methyl group could be transformed to **2a-D** in 35% yield under the identical condition, in which one of the hydrogen in the methyl group was deuterated in 43% (eq. 4). This reaction indicates that β -hydride elimination occurs in this transformation and it is likely a slow step in the catalytic cycle. Secondly, the reaction of **1a**



Scheme 3. Mechanism studies.

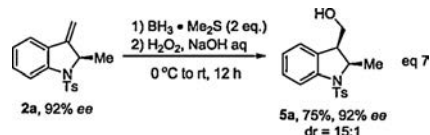


Scheme 4. The proposed reaction mechanism.

with Pd performed in the atmosphere of CO failed to give any cyclobutanone product as expected. However, **3a** with a cyclopropane skeleton was isolated in 72% yield when $[\text{Rh}(\text{cod})\text{Cl}]_2$ and dpmm were used as the catalyst (eq. 5). Thirdly, the dynamic kinetic asymmetric synthesis of **2a** from racemic **1a** suggest a fast π - σ - π equilibrium exists in the catalysis, which was supported by the fact that **4a** synthesized independently could be transformed into the same product **2a** with Pd under basic condition (eq. 6).

Based on the experiments above and literature reports, we proposed a plausible mechanism as shown in Scheme 4. **1a** undergoes oxidative addition with Pd complex and releases CO_2 to form zwitterionic intermediate **A**. **A** could have a fast equilibrium with σ -allyl Pd complex **D** to realize the interconversion of the diastereomeric intermediate. The linear substrate **4a** can be converted to the same complex **A** via **D**. From **A**, intramolecular attack of nitrogen to C3 leads to the formation of byproduct. While the attack to C2 generates the palladacyclobutane intermediate **B**, which is the stereo-determine step. Product **2a** could be obtained from **B** via β -hydride-elimination and reductive elimination sequence. The direct reductive elimination from **B** to give cyclopropane **3** is not observed for palladium. While **3** was isolated with Rh catalyst in the presence of CO atmosphere.

2a with 92% ee could be obtained by a simple recrystallization. A further hydroboration/oxidation sequence converts the double bond to the hydroxy group diastereoselectively to give **5a** in 75% yield and 15 : 1 dr (eq. 7).



In summary, we have reported an enantioselective Pd-catalyzed 2-methyl-3-methyleneindoline synthesis from racemic vinyl benzoxazinanes with the help of (R,R) -BenzP*. Mechanism studies support a C2 attack to π -allyl Pd complex and the formation of palladacyclobutane as the key intermediate. The β -hydride elimination provides a new reaction pathway besides migratory insertion to benzyne, which inspires us to explore further transformation for the palladacyclobutane structure.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2020.02.056>.

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