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ARTICLE TYPE

# Palladium-Catalyzed Asymmetric [3+2] Cycloaddition to Construct 1,3-Indandione and Oxindole-Fused Spiropyrazolidine Scaffolds

**Bo Cao,[a] Liang-Yong Mei,[b] Xiao-Ge Li,[c] and Min Shi[a,b,*]**

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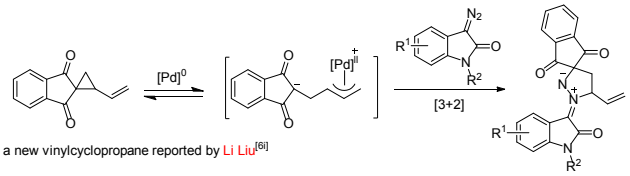
**Palladium-catalyzed asymmetric [3+2] cycloaddition of 3-diazooxindoles with 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione proceeded smoothly in the presence of chiral imidazoline-phosphine ligands to give the corresponding highly functionalized spiropyrazolidine derivatives in good to excellent yields (52-99%) along with good enantioselectivities (48-82% ee) under mild conditions.**

Pyrazolidine and its derivatives, consisting of a unique class of five-membered ring bearing a N-N bond, show various biological and pharmacological activities.[1] It has consequently captured great interest from synthetic and medicinal chemists to synthesize some new pyrazolidine derivatives from easily available starting materials under mild conditions. However, as for the enantioselective synthesis of pyrazolidines, very limited synthetic approaches have been reported thus far. Therefore, developing efficient methodologies for the synthesis of such compounds is highly desirable.

3-Diazooxindoles have been applied in a wide range of reactions, such as cyclopropanations,[2] X-H insertions,[3] ylide formations[4] and the other reactions.[5] However, 3-diazooxindoles serving as potential dipolarophiles for participation in annulations with an additional 1,3-dipole to construct C-N and N-N multiple bonds not only in just one step, but also in an atom-economical way have been rarely reported, except for one example reported by our group.[6h] In that paper, we reported a novel three-component one-pot tandem reaction of 3-diazooxindoles, vinylcyclopropanes and maleimides for the diastereo- and enantioselective construction of functionalized oxindole-fused spiropyrazolidine frameworks.

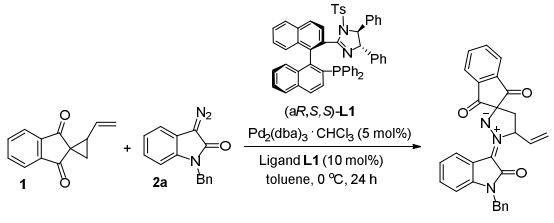
Recently, as a new family of "three-carbon-atom" precursors for asymmetric cycloadditions, vinylcyclopropanes bearing electron-withdrawing groups have attracted much attention.[7] Upon generating the corresponding 1,3-dipolar species in the presence of a Pd(0) catalyst and subsequent trapping with diverse dipolarophiles,[6] vinylcyclopropanes can provide direct approach to a variety of substituted five-membered rings. As part of our ongoing investigations on the Pd-catalyzed transformations[8] as well as our goal to construct heterocyclic compounds containing rigid spiropyrazolidine core, we used 3-diazooxindoles as the dipolarophiles to react with 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione, *a new vinylcyclopropane*, through a [3+2] cycloaddition to enantioselectively construct functionalized spiropyrazolidine derivatives in the presence of a Pd/chiral imidazoline-phosphine catalytic system (Scheme 1). Herein, we wish to report the detail of this context.

**Scheme 1**. Pd-Catalyzed [3+2] Cycloaddition for the Synthesis of Spiropyrazolidine




We began our investigation by exploring our previously developed catalytic system for palladium(0)-catalyzed asymmetric [3+2] cycloaddition of 3-diazooxindoles with vinylcyclopropane[6h] by employing $[Pd_2(dba)_3{\cdot}CHCl_3]$ (dba = dibenzylideneacetone) as the Pd(0) source and toluene as solvent at 0 °C. Therefore, we first examined the reaction between 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione **1** with 1-benzyl-3-diazoindolin-2-one **2a** in the presence of chiral imidazoline-phosphine ligand (a*R,S,S*)-**L1** (10 mol%) and $[Pd_2(dba)_3{\cdot}CHCl_3]$ (5 mol%) in toluene at 0 °C (Scheme 2). As expected, the [3+2] cycloaddition proceeded smoothly to afford the spiropyrazolidine derivative **3a** in 88% yield along with 48% ee.

**Scheme 2**. Initial Examination of Pd-Catalyzed Asymmetric [3+2] Cycloaddition.




[a] *Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Meilong Road No. 130, Shanghai, 200237 (China)*

[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 China. mshi@mail.sioc.ac.cn. Fax: 86-21-64166128*

[c] *Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. lixiaoge@sioc.ac.cn*

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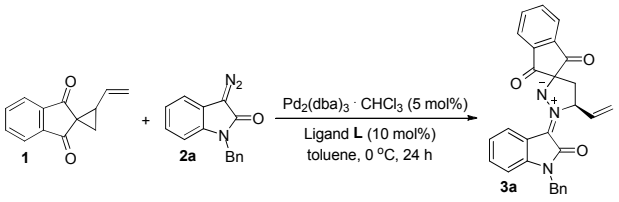
With this satisfying yield in hand, we next made our effort in improving the ee value of this reaction. On the basis of previous work, we realized that imidazoline-phosphine ligand played an important role in the formation of pyrazolidine derivative **3a**. Thus, we mainly examined the effects of ligands with different substituted groups. Four newly synthesized chiral imidazoline-phosphine ligands **L6**, **L7**, **L9** and **L10** along with previously reported ligands **L2-L5** and **L8** were used to screen the best ligand and optimal conditions for this reaction. By using **1** and **2a** as model substrates in toluene at 0 °C, we found that ligand (a*R,S,S*)-**L8** was the best one, furnishing the desired product **3a** in 95% yield and 78% ee (Table 1, entry 8). By comparison, chiral phosphine-oxazoline ligand (a*S,S*)-**L11** was also effective ligand for this reaction, but giving the desired product **3a** in a lower ee value (Table 1, entry 11). However, the ligand (a*R,S*)-**L12** and other ligands such as **L13-L15** with different chiral scaffolds produced **3a** in a trace amount. The entire results of these experiments are summarized in Table SI-1 in the Supporting Information.

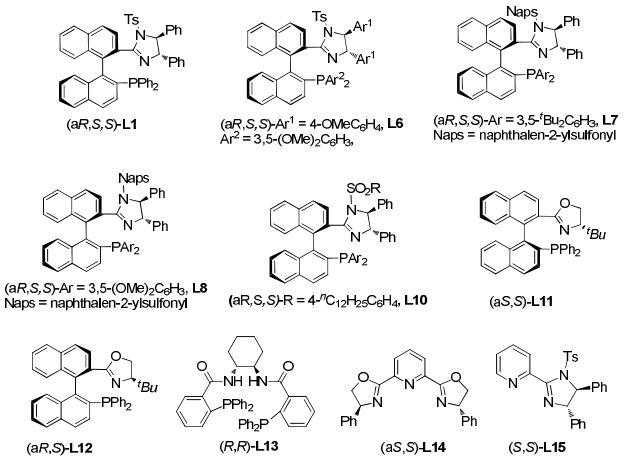
**Table 1**. Screening of Ligands for Pd-Catalyzed [3+2] Cycloaddition




| entry[a] | Ligand | yield [%][b] | ee [%][c] |
|---|---|---|---|
| 1 | **L1** | 88 | 48 |
| 2 | **L2** | 47 | 19 |
| 3 | **L3** | 97 | 70 |
| 4 | **L4** | 84 | 50 |
| 5 | **L5** | 92 | 60 |
| 6 | **L6** | 98 | 71 |
| 7 | **L7** | 96 | 61 |
| 8 | **L8** | 95 | 78 |
| 9 | **L9** | 96 | 67 |
| 10 | **L10** | 93 | 26 |
| 11 | **L11** | 88 | 15 |
| 12 | **L12** | trace | n. d. |
| 13 | **L13** | trace | n. d. |
| 14 | **L14** | trace | n. d. |
| 15 | **L15** | trace | n. d. |

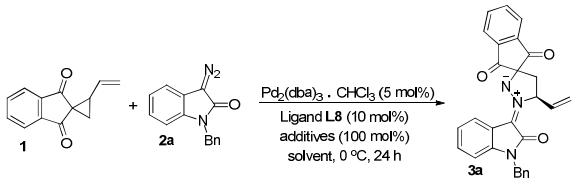
[a] The reaction was conducted with **1** (0.1 mmol) and **2a** (0.15 mmol) in toluene (0.75 mL). [b] Isolated yield. [c] The ee values were determined by chiral HPLC on Chiralcel IB-3.

**Figure 1**. Ligands for Pd-Catalyzed Asymmetric [3+2] Cycloaddition




On the basis of the above experiments, we chose **1** and **2a** as substrates, **L8** as the ligand, and $[Pd_2(dba)_3{\cdot}CHCl_3]$ as the Pd(0) source to screen the solvents and the additives to further improve the reaction outcome. The examination of solvent effects revealed that the reaction in toluene provided a better yield along with enantioselectivity than those in dichloromethane (DCM), tetrahydrofuran (THF), acetonitrile ($CH_3CN$), dichloroethane (DCE)(Table 2, entries 1-5). However, the alkali metal salt additives such as LiBr, NaBr, KBr, NaOAc, and $K_2CO_3$ as well as other additives including AgBr and $^nBu_4NOAc$ did not improve the yield or ee value of **3a** (Table 2).

**Table 2**. Screening of Additives for Pd-Catalyzed Asymmetric [3+2] Cycloaddition




| entry[a] | solvent | additive | yield [%][b] | ee [%][c] |
|---|---|---|---|---|
| 1 | DCM | - | 31 | 61 |
| 2 | THF | - | 100 | 74 |
| 3 | MeCN | - | 51 | 50 |
| 4 | DCE | - | 40 | 62 |
| 5 | toluene | - | 95 | 78 |
| 6 | toluene | LiBr | 92 | 30 |
| 7 | toluene | NaBr | 98 | 63 |
| 8 | toluene | KBr | 98 | 66 |
| 9 | toluene | AgBr | 100 | 64 |
| 10 | toluene | NaOAc | 100 | 75 |
| 11 | toluene | $^nBu_4NOAc$ | 76 | 52 |
| 12 | toluene | $K_2CO_3$ | 22 | -24 |

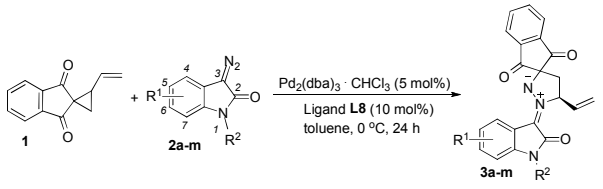
[a] The reaction was conducted with **1** (0.1 mmol) and **2a** (0.15 mmol) in solvent (0.75 mL) at 0 °C for 24 h. [b] Isolated yield. [c] The e alues were determined by chiral HPLC on Chiralcel IB-3.

With the optimized reaction conditions in hand, the substrate scope was explored and the results are shown in Table 3. At first, using **1** as the model substrate, the influence of substituents at different positions of the aromatic rings of 3-diazooxindoles was explored. We found that a diverse array of 3-diazooxindoles **2** with electronically different substituents at the C5 position gave the corresponding products **3b-3e** in 92%-99% yields and 64%-82% ee values (Table 3, entries 2-5). Moreover, introducing substituents at the C6 position of **2** such as substrates **2f**, **2g** and **2h**, the reaction also proceeded smoothly, giving the

corresponding adducts **3f**, **3g** and **3h** in 78-96% yields along with 59-77% ee values (Table 3, entries 6-8). Substrate with two methyl groups at C5 and C7 positions also provided the desired product **3j** in 80% yield but with 48% ee value (Table 3, entry 10). However, when electron-withdrawing substituent was introduced at C7 position, the corresponding products **3i** and **3k** were obtained in moderate yields along with 68% and 75% ee values, respectively (Table 3, entries 9 and 11). In this context, we also examined 3-diazooxindoles **2** bearing different N-protecting groups in this reaction, and found that the products **3l** and **3m** were obtained in 65% and 81% yields along with 77% and 84% ee values, respectively (Table 3, entries 12 and 13).

We have further explored the transformation of products **3** in order to illustrate their synthetic utility. As shown in Scheme 3, by serving as a 1,3-dipole, product **3a** could be easily converted into multi-spirooxindole compound **5** with multiple chiral centers in 76% yield and 74% ee value through a simple treatment with 1-benzyl-3-isothiocyanato-5-methylindolin-2-one **4** in DCE at room temperature (Scheme 3). The structure and the relative configuration of product **5** have been determined by X-ray crystallography (Figure 2),[9] and its absolute configuration has been assigned as the (*S,S,S*)-configuration by vibrational circular dichroism (VCD) spectroscopy (see Supporting Information for the details).

**Table 3**. Substrate Scope for Pd/**L8**-Catalyzed Asymmetric [3+2] Cycloaddition




| entry[a] | $R^1/R^2$ | yield [%][b] | ee [%][c] |
|---|---|---|---|
| 1 | H/Bn, **2a** | **3a**, 95 | 78 |
| 2 | 5-F/Bn, **2b** | **3b**, 99 | 64 |
| 3 | 5-Cl/Bn, **2c** | **3c**, 92 | 78 |
| 4 | 5-I/Bn, **2d** | **3d**, 98 | 69 |
| 5 | 5-Me/Bn, **2e** | **3e**, 99 | 82 |
| 6 | 6-Me/Bn, **2f** | **3f**, 78 | 59 |
| 7 | 6-MeO/Bn, **2g** | **3g**, 96 | 77 |
| 8 | 6-Cl/Bn, **2h** | **3h**, 96 | 65 |
| 9 | 7-$CF_3$/Bn, **2i** | **3i**, 52 | 68 |
| 10 | 5,7-$Me_2$/Bn, **2j** | **3j**, 80 | 48 |
| 11 | 5,7-$Cl_2$/Bn, **2k** | **3k**, 39 | 75 |
| 12 | H/MOM, **2l** | **3l**, 65 | 77 |
| 13 | H/Me, **2m** | **3m**, 81 | 84 |

[a] The reaction was conducted with 1 (0.1 mmol) and 2 (0.15 mmol) in toluene (0.75 mL) at 0 °C

**Scheme 3**. Transformation of Product **3a** in **5**

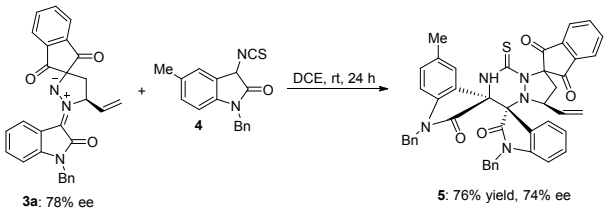
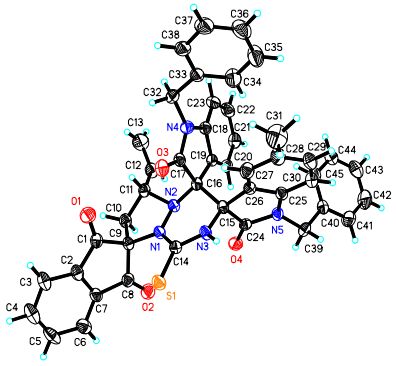
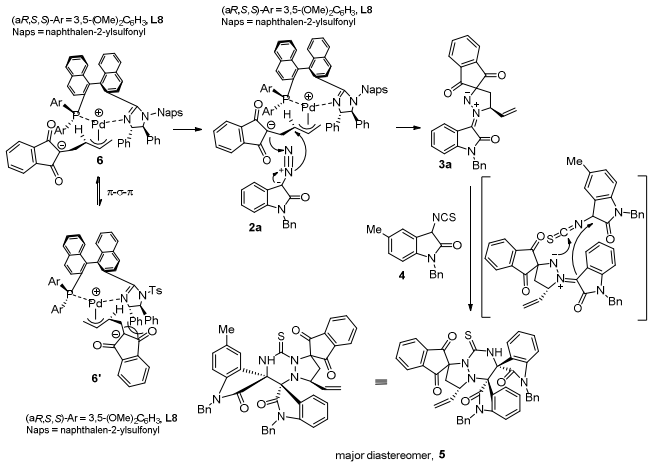



**Figure 2**. X-ray crystal structure of **5**



On the basis of our experimental results and previously reported mechanistic studies,[6a,d,h] we tentatively proposed a plausible reaction mechanism to explain the stereochemistry of this Pd/**L8**-catalyzed asymmetric reaction (Scheme 4). At first, the initial nucleophilic attack of palladium at the double bond of 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione **1** results in cyclopropyl ring opening to afford the active zwitterionic ($\pi$-allyl)) palladium intermediates **6** and **6'**. Intermediates **6** and **6'** can be interconverted with each other through $\pi$-$\sigma$-$\pi$ equilibration. Due to the more significant steric repulsion effect between phenyl group on imidazoline-phosphine ligand **L8** and diketohydrindene moiety in **1**, intermediate **6** is thermodynamically more favored. Next, the nucleophilic attack of the diketohydrindene anion onto the N-N triple bond in 3-diazooxindole **2a** and subsequent nucleophilic attack of another nitrogen atom onto the in situ generated ($\pi$-allyl)) palladium complex **6** gave the desired product **3a** along with the release of the Pd catalyst. Finally, the observed major diastereomer **5** was obtained through the [3+3] cycloaddition of **3** and 1-benzyl-3-isothiocyanato-5-methylindolin-2-one **4**.

**Scheme 4**. Proposed Reaction Mechanism




In conclusion, a facile and versatile palladium-catalyzed asymmetric [3+2] cycloaddition of 3-diazooxindoles with 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione to construct spiropyrazolidine derivatives has been developed, affording the corresponding adducts in excellent yields along with moderate to good enantioselectivities. Further transformation of the product has been explored. The chiral ligand (a*R,S,S*)-**L8** plays a crucial

role for achieving satisfactory enantioselectivities in this reaction. Further studies on expanding the scope of this reaction toward a range of other 1,3-dipoles as well as the applications of this protocol to natural product synthesis are in progress.

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9. The crystal data of **5** have been deposited in CCDC with number 1414548.

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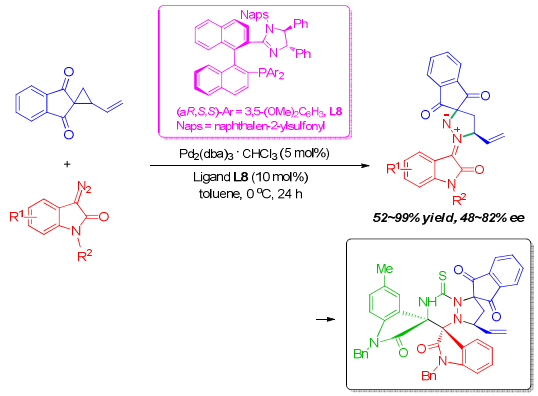


A facile and versatile palladium/**L8**-catalyzed asymmetric [3+2] cycloaddition of 3-diazooxindoles with 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione to construct spiropyrazolidine derivatives has been developed in excellent yields along with moderate to good enantioselectivities.

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