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# Pd-Catalyzed Heck-Type Reaction: Synthesizing Highly Diastereoselective and Multiple Aryl-Substituted P-Ligands

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**(5)** Supporting Information

**ABSTRACT:** In this work, an efficient palladium-catalyzed Heck-type reaction was successfully used to synthesize a wide range of monoaryl- or diaryl-substituted P-ligands with excellent yields and diastereoselectivity (up to 98% yield, dr >20:1). The preliminary mechanistic studies demonstrated that it possibly underwent a cationic Heck reaction that was assisted by silver salt, and it revealed the significant role of  $P(O)Ar_2$  for excellent yields and diastereoselectivity.

**D** hosphine ligands bearing a biaryl scaffold have played an important role in transition metal catalysis.<sup>1</sup> Consequently, a series of efficient methods have been developed to modify biarylphosphines. In the beginning, a coupling reaction acts as a unique strategy for C-C bond formation, which was used to synthesize different aryl-substituted phosphine ligands. In general, phosphine-containing aryl halide substrates are coupled with an aryl reagent to build aryl-substituted phosphine ligands through oxidative addition (Scheme 1a).<sup>2</sup> With environmental concerns in mind, C–H bond activation has been an emerging area in organic synthesis.<sup>3</sup> As a significant advance, a process of  $R_2(O)P$ -directed palladium-catalyzed C-H arylation via a rare seven-membered cyclopalladium intermediate was reported by our group in 2014 (Scheme 1b).<sup>4</sup> Shi's group also accomplished the work of rhodium(I)-catalyzed PR<sub>2</sub>-directed C-H arylation in 2017.<sup>5</sup> There is little doubt that the strategy has a high atomic economy in the modification of phosphine ligands, which was compared with other research results (Scheme 1c).

When it comes to C–C bond formation, the Mizoroki–Heck reaction (Heck reaction) is the most momentous transformation.<sup>6</sup> During the past few decades, significant progress has been made by the groups of Hayashi,<sup>7</sup> Jung,<sup>8</sup> Sigman,<sup>6a,d,e</sup> and Zhou,<sup>6b,c,f</sup> etc. On the basis of a large amount of experimental data, the cyclic olefins are common substrates for the Heck reaction. These existing methods have advantages in many aspects; however, obtaining a good aryl site selectivity is always an ultimate challenge.<sup>9</sup> Significantly, our group has been committed to exploring new methodologies for the synthesis of novel phosphine ligands. The P(O)Ar<sub>2</sub> group shows an excellent performance in selectivity.<sup>10</sup> Herein, we achieved a series of highly diastereoselective and good aryl-site-selective phosphine-containing products via the Heck reaction (Scheme 1d).

We selected (1-(cyclohex-1-en-1-yl)naphthalen-2-yl)diphenylphosphine oxide (1a), a modified cyclic olefin, as a model substrate for reaction discovery (for details, see Table S1



Previous routes for synthesizing phosphine ligands.



in the Supporting Information). One of the typical Heck reaction conditions was investigated with iodobenzene (2a) in the presence of  $Pd(OAc)_2$  and  $K_2CO_3$  in 1,2-dichloroethane. Unfortunately, no desired product was detected. Surprisingly, we could obtain the monoarylation (3aa) and diarylation (4aa) products in 71% yield, with a ratio of 6:1 when  $Ag_2CO_3$  took the



place of  $K_2CO_3$  (Table S1, entry 2). Subsequently, different solvents, Ag salts, Pd species, and additives were screened, and the optimal reaction condition of monosubstituted product (**3aa**) was obtained using Pd(OAc)<sub>2</sub> (1.0 mol %) as catalyst, AgTFA (1.5 equiv) in 2 mL of DCM for 0.3 mmol **1a**, and 0.2 mmol **2a** at 80 °C under an argon atmosphere (Table S1, entry 18). At the same time, the reaction could exclusively afford **4aa** with excellent yield and dr (Table S1, entry 26, 92% yield, dr >20:1) using Pd(OAc)<sub>2</sub> (5.0 mol %) as catalyst, Ag<sub>2</sub>CO<sub>3</sub> (1.5 equiv), and TfOH (50 mol %) in 2 mL of DCM at 80 °C for 0.2 mmol **1a** and 0.6 mmol **2a** at 80 °C under an argon atmosphere.

With two optimal procedures in hand, the monosubstituted products were first investigated using different substituted aryl iodide compounds in Scheme 2 under conditions A. Good yields



<sup>*a*</sup>Reaction conditions A: 1 (0.3 mmol), 2 (0.2 mmol),  $Pd(OAc)_2$  (1 mol %), and AgTFA (1.5 equiv) in 2 mL of DCM at 80 °C for 15 h. <sup>*b*</sup>Isolated yields based on 2. <sup>*c*</sup>The dr value was determined using <sup>31</sup>P NMR. <sup>*d*</sup>n.r. = no reaction.

and moderate dr were obtained for substrates bearing halogen groups (F, Cl, Br) (3ab-3ad, 76-81%, 6.2:1-7.9:1 dr). The aryl iodide compounds that were substituted at the para position with an electron-donating or electron-withdrawing group could obviously impact the results. For example, Me, OMe, and <sup>t</sup>Bu were advantageous for the reaction, which gave the desired product in excellent yields and moderate dr value (3ae-3ag, 77-81%, 8.6:1-10.7:1 dr). On the other hand, aryl iodide derivatives bearing Ph also afforded the desired product in good yield (3ah, 84%, 7.1:1 dr). However, the reaction would be terminated by strong electron-withdrawing substituents, such as CN or NO<sub>2</sub> (3ai, 3aj). As we expected, the selectivity of the product was somewhat affected by the steric effect. A higher dr value was observed by stronger sterically hindered aryl iodide compounds that carry a meta-Me or ortho-Me group (3ak, 12.5:1 dr; 3al, 16.8:1 dr). What disappointed us most was that 5iodo-1-methylindole and other heterocyclic compounds could not be reacted smoothly under these conditions (3am).

Moreover, the reactions with different substituted diarylphosphine oxides proceeded successfully with good yields and acceptable dr. For example, diarylphosphine oxides bearing *para*-Me, *para*-OMe, and *meta*-Me produced the desired products with excellent yields and good dr (**3ba**, 82%, 10.1:1 dr; **3ea**, 79%, 9.7:1 dr; **3ca**, 67%, 10.8:1 dr). In addition, diarylphosphine oxide bearing a bulky substitute (**1d**) successfully afforded **3da** (79%, 10.4:1 dr). Likewise, an electron-withdrawing substituent at the *para* position on the diarylphosphine gave moderate yield (**3fa**, 55%, 7.4:1 dr).

Based upon the importance of disubstituted phosphine ligands that bear a biaryl scaffold, we explored this new strategy with a variety of aryl iodide compounds. As expected, excellent diastereoselectivity was obtained with dr up to >20:1. The parasubstituents bearing different substituents such as halogen, Me, OMe, <sup>t</sup>Bu, and Ph on the aromatic rings could offer desired products with good to excellent yields (4ab-4ah, 71-94%, dr >20:1). The structure of 4ae was confirmed by X-ray crystallography. It is noteworthy that the desired products could be obtained with aromatic rings bearing CN and NO<sub>2</sub> in 39 and 32% yields, respectively (4ai, 4aj). Similarly, 2n and 20 could give 4an and 4ao in good yields (68 and 79%) under conditions B. However, when the aryl iodide compound was used, an ortho-Me group monoarylation production 3al was obtained exclusively (not shown in Scheme 3). 2m also could not give the desired product under conditions B. 4ap was obtained in 67% yield in the presence of 2-iodonaphthalene (2p). Furthermore, different substituted diarylphosphine oxides were scoped. Diarylphosphine oxides containing electrondonating groups, such as Me and OMe at *meta* or *para* positions, provided desired products with decent yields and excellent dr

Scheme 3. Scope of the Diarylation Products $^{a,b}$ 



<sup>*a*</sup>Reaction conditions B: 1 (0.2 mmol), 2 (0.6 mmol),  $Pd(OAc)_2$  (5 mol %),  $Ag_2CO_3$  (1.5 equiv), and TfOH (50 mol %) in 2 mL of DCM at 80 °C for 15 h. <sup>*b*</sup>Isolated yields based on 1. <sup>*c*</sup>The dr value was determined using <sup>31</sup>P NMR. <sup>*d*</sup>n.r. = no reaction.

(4ba-4ea, 68–89%, dr >20:1). Notably, 4f bearing  $CF_3$  could also give 46% yield with excellent dr (4fa, dr >20:1).

To our knowledge, there are few reports of different arylation reactions under the same conditions. Most of them must have other additives or increase the temperature because of the lower reactivity or bulky steric hindrance of the monoarylation products which were produced by the first step.<sup>5,11</sup> Taking the reaction applications into account, we further explored this reaction with **3aa** (Scheme 4). Interestingly, **3aa** led to higher



<sup>*a*</sup>Reaction conditions A: 1 (0.2 mmol), 2 (0.3 mmol),  $Pd(OAc)_2$  (5 mol %), AgTFA (1.5 equiv) in 2 mL of DCM at 80 °C for 15 h. Reaction conditions B: 1 (0.2 mmol), 2 (0.3 mmol),  $Pd(OAc)_2$  (5 mol %), Ag<sub>2</sub>CO<sub>3</sub> (1.5 equiv), and TfOH (50 mol %) in 2 mL of DCM at 80 °C for 15 h. <sup>*b*</sup>Isolated yields based on 3aa. <sup>*c*</sup>The dr value was determined using <sup>31</sup>P NMR. <sup>*d*</sup>Twenty hours. <sup>*e*</sup>n.r. = no reaction.

reactivity, and 4aa was obtained with excellent yields and excellent dr (A: 95%; B: 98%, dr up to >20:1). To confirm the position of the double bond and provide evidence for the direction of  $\beta$ -hydrogen elimination, the structure of **5aae** was confirmed using X-ray crystallography. In addition, a range of aryl iodide compounds with various electronic properties are compatible with this method. Different groups at the para position of aryl iodides, such as halogens, Me, OMe, Ph, and CO<sub>2</sub>Et, provided good yields (5aab-5aah, 67-92%, dr >20:1). Satisfactory results were also obtained when substituents were at different positions, for instance, para-Me (Saae, A: 89%; B: 82%, dr >20:1), meta-Me (Saak, A: 76%; B: 71%, dr >20:1), and ortho-Me (5aal, A: 83%; B: 75%, dr >20:1). Although strong electron-withdrawing aryl compounds have been challenging substrates for the above results, they delivered desired products with excellent yield and dr under conditions A/B (**5aai**, A: 84%; B: 75%, dr >20:1; **5aaj**, A: 73%; B: 83%, dr >20:1). Inspired by the high activity of 3aa, we obtained estrone-derived aryl iodide compound 2q under this reaction in 47% yield. These

conditions provided an alternative method for modifying such complex natural products.

To test the tolerance of the reaction further, some other types of olefin derivatives were tested under conditions A/B in Scheme 5. Moderate yields were obtained with cyclopentene

### Scheme 5. Scope of the Olefins<sup>a</sup>



<sup>*a*</sup>Conditions A: **6** (0.2 mmol), PhI (0.3 mmol), Pd(OAc)<sub>2</sub> (5 mol %), and AgTFA (1.5 equiv) in 2 mL DCM at 80 °C for 15 h. Conditions **B**: **6** (0.2 mmol), PhI (0.3 mmol), Pd(OAc)<sub>2</sub> (5 mol %), Ag<sub>2</sub>CO<sub>3</sub> (1.5 equiv), and TfOH (50 mol %) in 2 mL DCM at 80 °C for 15 h. Isolated yields. <sup>*b*</sup>**6** (0.3 mmol), PhI (0.2 mmol). <sup>*c*</sup>**6** (0.2 mmol), PhI (0.6 mmol). <sup>*d*</sup>The dr value was determined using <sup>31</sup>P NMR. <sup>*e*</sup>48 h. <sup>*f*</sup>n.r. = no reaction.

derivatives. However, **7aa'** was isolated with a low dr value (1.5:1 dr). In addition, **6b** could produce the same product **7ba** in good yield and excellent dr value under conditions A/B (**7ba**, A: 72%; B: 78%, dr >20:1). However, **7ca** was only obtained in a very low yield of 6% after 15 h under conditions A, whereas prolonging the reaction time can increase the yield to 38%. It may be due to the disadvantage of  $\beta$ -hydrogen elimination. Incidentally, the 1,2-diphenylethylene derivative affords tetraar-yl-substituted ethylene in good yields (**7da**, A: 54%; B: 79%).

The potential practicality of these methods was assessed in Scheme 6. We explored the model substrate 1a. It can be scaled

### Scheme 6. Gram-Scale Experiment and Derivatization



up to gram scale in good yields under both conditions A and B (**3aa**, 1.05 g, 69%; **4af**, 1.35 g, 77%). Furthermore, we demonstrated the diverse and practical derivatization, which could be readily converted to a series of P-ligands. Although P-ligand **8a** was obtained with a low dr value, a new type of diaryl-substituted vinyl arene P-ligand **8b** was obtained with excellent

dr (**8b**, 74%; dr >20:1) when product **4af** was reduced.<sup>12</sup> Finally, in the presence of DDQ, monoarylation or diarylation of the P-ligands' precursors bearing a biaryl scaffold was obtained easily (**9a**, 90%; **9b**, 85%).

To clarify the  $P(O)Ar_2$  group's participation, we switched **1a** to 1-(cyclohex-1-en-1-yl) naphthalene **10** under conditions A/B and only observed a mixture of products. The desired products were hard to separate (Scheme 7a, conditions A: totally 12%,





**10a**/**10b** = 2.4:1; conditions B: totally 10%, **10a**/**10b** = 1:1.2). To formulate a mechanistic model, we carried out a mass spectrometry experiment to gain more insight into intermediates (Scheme 7b).<sup>13</sup> First, a set of signal peaks in the ESI/MS at m/z 925.2327 and m/z 1077.2957 were detected, which correspond to  $[A + H]^+$  and  $[A' + H]^+$ . It might show that both substrates and products could be used as ligands that coordinate with the Pd<sup>0</sup> species. Another set of signal peaks at m/z 1001.2643 and m/z 1153.3268 was detected, which probably were generated from PhI via oxidative addition and then migratory insertion of B or B'. Subsequently, we measured the changes in pH under conditions A (before reaction, pH = 1.83, after reaction, pH = 1.32). This phenomenon indicated that there may be acid that was produced during the reaction.

Based on these results and those reported in the literature,  ${}^{6h,13,14}$  a possible mechanism was proposed (Scheme 8). Take conditions A as an example: Pd<sup>0</sup> was formed by an in situ reduction of Pd(OAc)<sub>2</sub>. Complex A was formed through coordination to both P=O and the double bond. Then, PhI was converted to Pd<sup>II</sup> complex B through oxidative addition by Pd<sup>0</sup> in the presence of AgTFA.<sup>15</sup> This was followed by diastereoselective 1,2-migratory insertion. After that,  $\beta$ -hydride

### Scheme 8. Possible Reaction Mechanism



elimination of intermediate C afforded the desired product I. Finally, hydridopalladium reductive elimination releases acid and regenerates the  $Pd^0$  species (cycle A). When AgTFA was replaced with Ag<sub>2</sub>CO<sub>3</sub>, product I also would be produced first. In addition, the catalytic cycle still operates effectively, and product II would be obtained after another catalytic cycle because TfOH promoted hydridopalladium reductive elimination to release acid and regenerate the  $Pd^0$  species (cycle B).

In conclusion, we have developed a new strategy to synthesize a wide range of monoaryl- or diaryl-substituted P-ligand precursors with excellent yields and diastereoselectivity (up to 98% yield, dr >20:1). The monoarylation products have high reactivity, and they could be obtained as asymmetrical diarylsubstituted products under different conditions. It provides an effective and valuable tool for P-ligand modification.

### ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02697.

Detailed experimental procedures, spectra data for all compounds, copies of <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P, and <sup>19</sup>F NMR spectra (PDF)

### **Accession Codes**

CCDC 1889906 and 1889964 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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