

# Pd-Catalyzed Enantioselective Heck Reaction of Aryl Triflates and Alkynes

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**S** Supporting Information

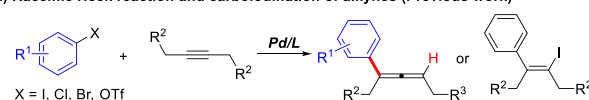
**ABSTRACT:** The first palladium-catalyzed asymmetric Heck reaction between aryl triflates and alkynes to give trisubstituted allenes with high er under mild reaction conditions is described. The key to the success is the discovery and fine-tuning of the different *N*-substituents of **Xu-Phos**, which ensure the enantioselectivity and reactivity. Synthetic transformation of the chiral allenes with high chirality transfer was also demonstrated.

Allene moieties with axial chirality are present in a variety of natural products with biological activities and pharmaceuticals.<sup>1</sup> In addition, as useful synthetic intermediates, the unique reactivity combined with the electronic and steric effects of substituents of allenes allow a wide range of synthetic applications through cycloaddition, nucleophilic addition, oxidation, cross-coupling, cycloisomerization, and so on.<sup>2</sup> Axial chirality could be transferred to central chirality to provide an irreplaceable entry to chiral molecules.<sup>3</sup> In view of the significance of chiral allenes in organic synthesis, the development of efficient methods in the formation of chiral allenes from readily available chemicals has received much attention.<sup>4</sup> Several strategies for synthesis of chiral trisubstituted allenes including kinetic resolution,<sup>5</sup> chirality transfer,<sup>6</sup> desymmetrization,<sup>7</sup> asymmetric diazo-coupling reaction,<sup>8</sup> isomerization,<sup>9</sup> asymmetric Wittig reaction,<sup>10</sup> conjugated enynes,<sup>11</sup> enantioselective carboxylation of propargyl derivatives,<sup>12</sup> asymmetric cycloaddition reaction,<sup>13</sup> and asymmetric transformations of cyclopropenone derivatives<sup>14</sup> have been developed.

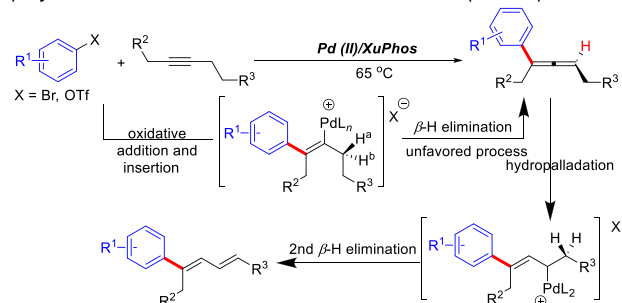
On the other hand, the Heck reaction of olefins is the most synthetically versatile method to construct a C–C bond in organic synthesis.<sup>15</sup> However, the Heck reaction of alkynes to form allene lags behind due to the energetically unfavored  $\beta$ -hydride elimination of vinyl palladium species.<sup>16</sup> In 1989, a trisubstituted allene was observed by Heck and co-workers for the first time as a side product with 4% yield from the reaction of 3-hexyne and methyl 2-iodobenzoate<sup>17</sup> (Scheme 1a). Based on this observation, Miura and co-workers achieved a more selective reaction with *ortho*-substituted aromatic bromides under related conditions, which might be ascribed to the increased steric repulsion between the *ortho*-substituted aryl group and the PdLn of the vinyl palladium species favors the energetically unfavored  $\beta$ -hydride elimination.<sup>18</sup> Hamblett has successfully developed an intramolecular Heck cyclization of

## Scheme 1. Palladium-Catalyzed Heck Reaction toward Trisubstituted Allenes

a) Racemic Heck reaction and carbodiodination of alkynes (Previous work)



b) Asymmetric Heck reaction to form chiral trisubstituted allenes (this work)



### Challenges:

- How to achieve high enantioselectivity and good yield?
- How to inhibit competing reactions, i.e. the formation of alkenes?
- How to avoid further isomerization to 1,3-dienes, and Heck reaction of allene?

an aryl chloride with an alkyne to selectively synthesize allenes or conjugated dienes via ligand switching.<sup>19</sup> In 2014, Larini, Jazzar and co-workers reported an intermolecular reaction between aryl bromides and alkynes to access allenes which proceeds via a base-assisted deprotonation rather than a Heck-type Pd-mediated  $\beta$ -hydride elimination and the key to successful is the use of a novel ligand (DFOTP).<sup>20</sup> In 2018, with the use of a new hybrid Pd(0)-catalyst incorporating a water-soluble dba ligand, Frantz and co-workers demonstrated an elegant Pd(0)-catalyzed Heck reaction between aryl triflates and alkynes to furnish trisubstituted allenes in 34–98% yield under mild conditions.<sup>21</sup> In 2019, Cheng reported the first regioselective carbopalladation of *ortho*-substituted aryl iodide with 1-aryl-1-alkynes that generates alkenyl palladium species with the Pd-center adjacent to the noncoordinative alkyl moiety, in which the *ortho*-substituent favors the  $\beta$ -hydride elimination.<sup>22</sup> In contrast, by the use of dAr<sup>F</sup>pe as ligand, Morandi found that an alternative carbodiodination reaction of alkynes rather than Heck reaction would take place to


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stereoselectively access functionalized tetrasubstituted alkenyl iodides.<sup>23</sup> So far, no example of a Pd-catalyzed enantioselective Heck-type reaction of aryl triflates and alkynes has been yet explored due to the lack of suitable chiral ligands to accelerate the unfavored  $\beta$ -hydride elimination as well as controlling the enantioselectivity.

Recently, Zhang group developed a series of new type of chiral phosphine ligands bearing a flexible sulfonamide moiety, so-called Sadphos(Sulfonamidophosphine),<sup>24</sup> which showed the good performance in asymmetric palladium-catalyzed cross-coupling reactions, reductive Heck reaction and related cascade reactions.<sup>25</sup> To further advance the applications of these new chiral ligands especially in difficult reactions, we became interested in whether these chiral ligands could be applied to the challenging asymmetric Heck reaction of aryl halides or triflates with alkynes. However, considerable challenges are associated with this hypothesis (Scheme 1). (1) How to control the product distribution (Heck reaction product vs carboiodination product. (2) The  $\beta$ -hydride elimination of vinyl palladium species to generate allenes is considered to be an energetically unfavored process;<sup>16</sup> thus, the exploration of a suitable chiral ligand to achieve good yields and high enantioselectivity would be very challenging. (3) Allene product might undergo subsequently isomerization to form the 1,3-diene product.<sup>26</sup> (4) Further Heck reaction of allene product with organic halides or triflates may take place.<sup>27</sup> Combined with the reported literature, we believed that ligand was the key to address these issues. Herein, we report the first example of palladium-catalyzed asymmetric Heck reaction between aryl triflates and alkynes to give enantioenriched trisubstituted allenes in good yield with good enantioselectivity.

The asymmetric Heck reaction of aryl triflate **1a** with alkyne **2a** was selected as a model reaction for screening reaction conditions (Table 1 and Figure 1). Many commercially available chiral ligands such as **L1** to **L6** are investigated but unfortunately failed to promote the reactions (see more ligands and details in Supporting Information). Inspired by the easy synthesis and modification of Sadphos and their good performance in asymmetric palladium catalysis, we next turned to screen a series of Sadphos. Ming-Phos, Xiang-Phos, Wei-Phos, and Xu-Phos with a free NH moiety could not give the product either. Inspired by Frantz's work, we envisaged that increasing the steric hindrance of the ligand may also promote the  $\beta$ -hydride elimination of vinyl palladium species. Indeed, the introduction of Me group at the sulfonamide moiety to the Xu-Phos, structured as Xu2 and Xu3, could catalyze this reaction in 30–38% yields with moderate enantioselectivity (Figure 1). Thus, some new Xu-Phos Xu4–Xu8 with different N-substituents were then prepared, and a simple summary of our optimization study with a selected set of these ligands is provided in Table 1. During this screening, we found that the protecting group on nitrogen in the molecular skeleton of Xu-Phos has a great influence on the enantioselectivity and reactivity, and the bigger one gave a better reactivity (Table 1, entries 1–3). We found that 70% yield of **3aa** with 92.5:7.5 er could be obtained under the optimal conditions with Pd<sub>2</sub>(dba)<sub>3</sub> as the precatalyst, Xu6 as the chiral ligand, and Na<sub>3</sub>PO<sub>4</sub> as the base in THF/H<sub>2</sub>O (v/v = 4/1) at 65 °C (Table 1, entry 3). When [Pd(allyl)Cl]<sub>2</sub> was used as a catalyst, 92% yield of **3aa** was delivered but with a relatively lower enantioselectivity (Table 1, entry 5). Pd1 could be used as a precatalyst to give **3aa** with 73% yield and 94:6 er (Table 1,

Table 1. Screening the Reaction Conditions<sup>a</sup>


entry	Pd source	Xuphos	yield <sup>b</sup> (%)	er <sup>c</sup> (%)
1	Pd <sub>2</sub> (dba) <sub>3</sub>	Xu4	35	85:15
2	Pd <sub>2</sub> (dba) <sub>3</sub>	Xu5	44	90.5:9.5
3	Pd <sub>2</sub> (dba) <sub>3</sub>	Xu6	70	92.5:7.5
4	Pd <sub>2</sub> (dba) <sub>3</sub>	Xu7	46	91.5:8.5
5	[Pd(allyl)Cl] <sub>2</sub>	Xu6	92	88.5:11.5
6	Pd(OAc) <sub>2</sub>	Xu6	<5	nr
7	Pd <sub>2</sub> (dba) <sub>3</sub> CHCl <sub>3</sub>	Xu6	42	90:10
8	Pd(TFA) <sub>2</sub>	Xu6	nr <sup>g</sup>	
9	Pd(NBD)Cl <sub>2</sub>	Xu6	nr	
10	Pd1 <sup>f</sup>	Xu6	75	94:6
11	Pd1	Xu8	77	94:6
12 <sup>d</sup>	Pd1	Xu8	76	94:6
13 <sup>d,e</sup>	Pd1	Xu8	76	94:6
14 <sup>d,e</sup>	Pd1	Xu8'	66	5.5:94.5

<sup>a</sup>Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), Pd (5 mol %), Xuphos (15 mol %), Na<sub>3</sub>PO<sub>4</sub> (0.105 mmol), THF (0.8 mL), deionized H<sub>2</sub>O (0.2 mL), 65 °C, 24 h. <sup>b</sup>Yield with CH<sub>2</sub>Br<sub>2</sub> as an internal standard was determined by <sup>1</sup>H NMR. <sup>c</sup>Determined by chiral high-performance liquid chromatography. <sup>d</sup>Pd1 (4 mol %), Xu6 (12 mol %). <sup>e</sup>2a (2 equiv.). <sup>f</sup>Pd1 = di- $\mu$ -chlorobis[2-[(dimethylamino)-methyl]phenyl-C,N]dipalladium(II). <sup>g</sup>nr = no reaction.

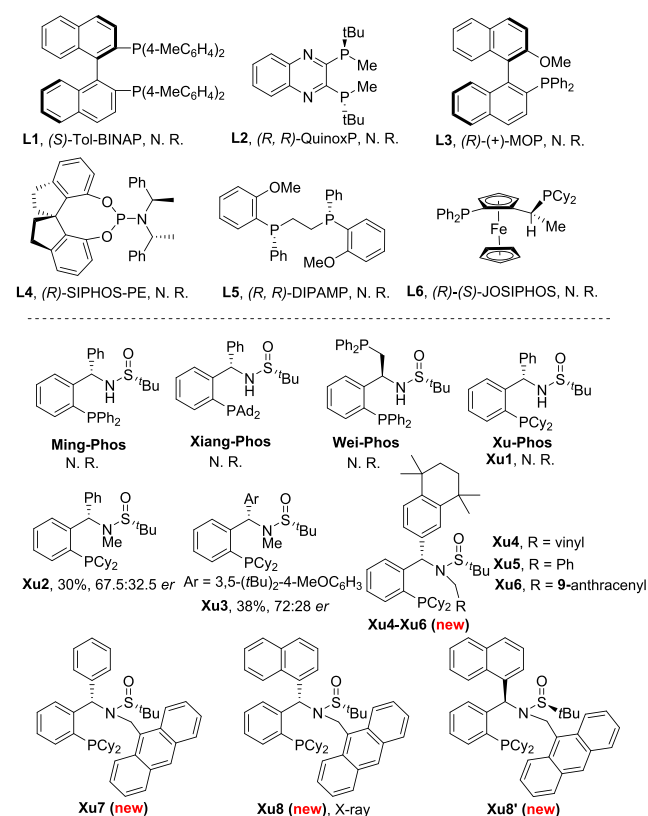


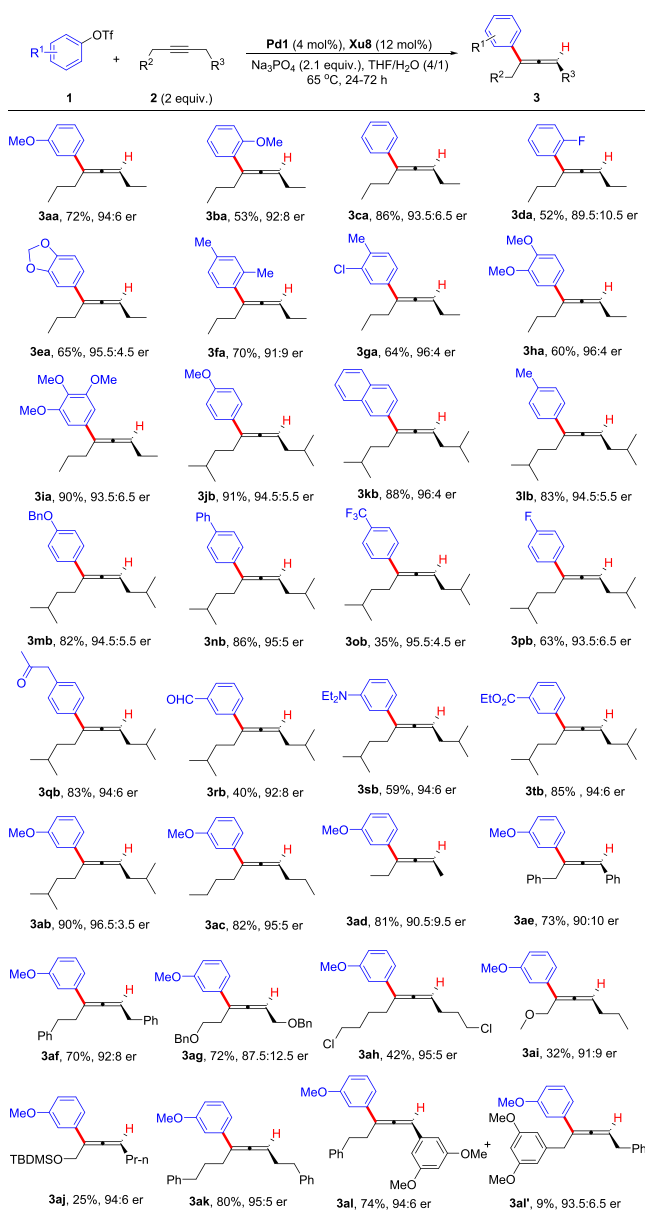
Figure 1. Selected examples of screened chiral ligands.

entry 10). Other palladium salts delivered lower ers and yields (Table 1, entries 7–9) and palladium(II) precursors seem better than palladium(0). Similar results were obtained with Xu8 (Table 1, entry 11). The same result was obtained when we reduced the amount of catalyst loading to 4 mol % (Table

1, entry 12). When reducing the amount of **2a** to 2 equiv, which could also give **3aa** in 74% yield and 94:6 er (Table 1, entry 13). We used the corresponding enantiomer **Xu8'** as a chiral ligand to give **3aa** with 5.5:94.5 er; that is the enantiomer of **3aa** is the major product (Table 1, entry 14). More screening parameters are summarized in the Supporting Information.

With optimal reaction conditions in hand, various aryl triflates and alkynes were then examined (Scheme 2). Aryl

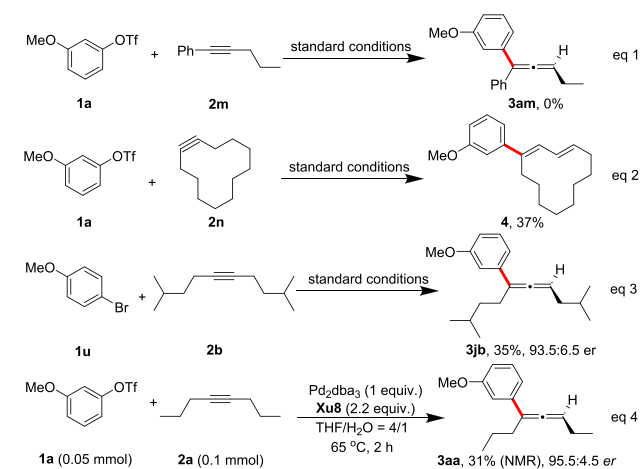
Scheme 2. Investigating the Reaction Scope



triflates with electron-withdrawing and electron-donating groups delivered the corresponding products with good enantioselectivity under the standard conditions, but lower reactivity was observed with those electron-deficient aryl triflates (Scheme 2, **3da**, **3ob**, **3pb**, **3rb**). Specifically, *meta*- and *para*-substituted aromatic triflates reacted similarly, but for *ortho*-substituted aromatic triflates, longer reaction time was required and delivered relatively lower enantioselectivity (**3ba**, **3da**, **3fa**) and **Xu6** showed better performance than **Xu8** (**3ba**,

**3fa**, **3ae**). The substrates containing functional groups such as ester (**3tb**), aldehyde (**3rb**), ketone (**3qb**), and protected amino group (**3sb**) were all tolerated under the reaction conditions, providing an opportunity for further elaborations. Lower enantioselectivity was obtained for alkynes with an ether functionality, probably because the oxygen atom coordinated with the metal center during the elimination process (**3ag**). On the other hand, nonsymmetrical alkynes afforded two products (**3al**, **3al'**) via different regioselective Heck reactions, but only one single product (**3ai**, **3aj**) was isolated in low yield via *anti*-regioselective Heck reaction due to the unstable allenyl ether. Finally, absolute configuration of the products was established to be *S* by comparing the specific optical rotation of allene **3ca** with the literature data.<sup>6e,l</sup>

Unfortunately, we explored the reaction of 1-aryl-1-alkylalkyne, but no desired allene product was delivered (eq 1). We also explored the reaction of cyclic alkyne **2n**; however,



cyclic conjugated diene **4** instead of allene was obtained, indicating that the cyclic allene product could indeed undergo further isomerization under the reaction conditions (eq 2). In addition, we also explored the use of aryl bromides and aryl iodides in the reaction, the reaction of aryl bromide **1u** with **2b** could give the desired allene product in 35% yield with 93.5:6.5 er (eq 3). To gain insight of the possible mechanism, the reaction of **1a** (0.05 mmol) and **2a** in the absence of  $\text{Na}_3\text{PO}_4$  with the use of a stoichiometric amount of catalyst was carried out, and **3aa** was obtained in 31% NMR yield after 2 h, which might rule out the possibility of that base-assisted asymmetric deprotonation pathway (eq 4).

In addition, a gram-scale reaction of **1a** and **2b** delivered 1.14 g of **4a** in 84% yield with 96:4 er (Scheme 3, a). Chiral trisubstituted allene **3aj** with a silyl ether group could be deprotected and then cyclized to give chiral 2,5-dihydrofuran **5** with 93:7 er under the catalysis of a gold catalyst<sup>28</sup> (Scheme 3, b). A Rh(III)-catalyzed *ortho* allylation of *N*-methoxybenzamide **6** with chiral trisubstituted allene **3ab** could deliver the desired product **7** with 95.5:4.5 er<sup>29</sup> (Scheme 3, c).

In light of the structure of the chiral ligand **Xu8** and binding mode of **Sadphos** with palladium and the absolute configuration of product *S*-**3aa**, a chirality induction model was proposed for the reaction (Figure 2).

In conclusion, we have developed a palladium-catalyzed asymmetric Heck reaction between aryl triflates and alkynes with the use of **Xu-Phos** bearing a fine-tuned relatively bulky *N*-substituent, which enables the energetically unfavored  $\beta$ -

## Scheme 3. Gram-Scale Synthesis and Axial to Central Chirality Transfer

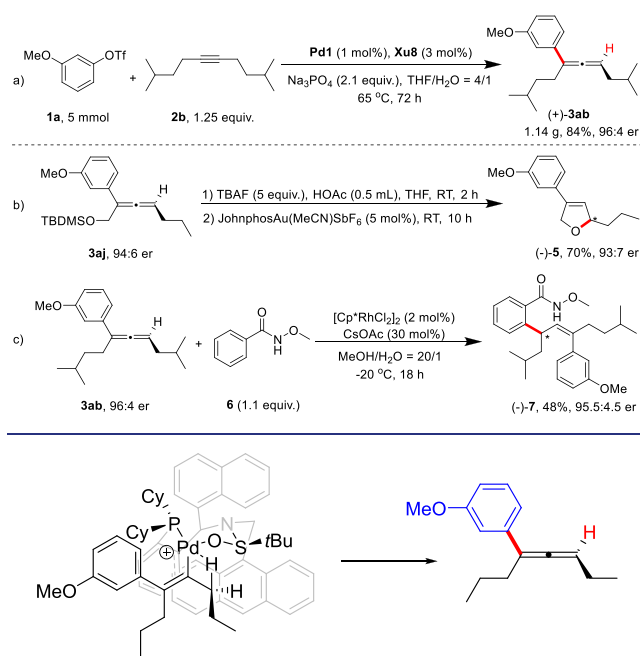


Figure 2. Proposed asymmetric induction model.

hydride elimination of vinyl palladium species. The reaction provides chiral trisubstituted allenes with various functional groups in moderate to high yields with up to 96.5:3.5 er under mild conditions. The axial chirality could be transferred to central chirality to provide an irreplaceable entry to chiral molecules.

## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.9b10883>.

Experimental procedure, optimization tables, and characterization data for all products (PDF)

X-ray data for Xu8 (CIF)

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## Notes

The authors declare no competing financial interest.

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