



# Alkene migration to the end-terminal carbon bearing a phenyl group over a chiral siloxy carbon center in Heck reaction



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On the celebration of Tetrahedron Prize 2014, this paper is dedicated to Professor Jiro Tsuji for his great contribution on Pd-chemistry

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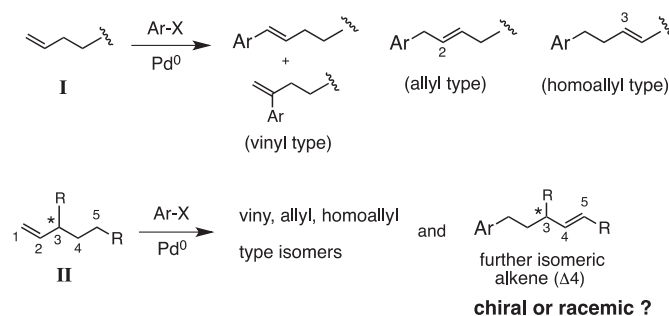
## ABSTRACT

The Heck reaction of aryl bromide with a terminal alkene substrate having a chiral center at the allylic position and a phenyl substituent at another terminal carbon is reported. An alkene migration to the phenyl-substituted end carbon is observed, along with the typical Heck reaction. This zipper-type migration occurs through multiple internal carbon bonds, and the stereochemistry of the internal chiral center is completely retained during this process.

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## 1. Introduction

The Heck reaction is an important coupling reaction for the formation of carbon–carbon bonds.<sup>1</sup> The reaction involves the addition of ArPdX to an alkene, followed by  $\beta$ -hydride elimination to give an aryl substitution alkene.<sup>2</sup> Typically, electronically biased alkenes with no hydrogen atom at their allylic position are used.<sup>3</sup> Otherwise, the reaction becomes sluggish and gives complex regioisomeric mixtures.<sup>4</sup> The Heck arylation of a terminal alkene, such as **I**, affords two regioisomeric vinyl-type alkenes<sup>5</sup> also allyl- and homoallyl-type alkenes (Scheme 1). However, the stereochemistry of the internal chiral center in the substrate, such as in **II**, in the Heck reaction has not been investigated, most likely because minimal 4-alkenyl bond migration occurs.<sup>6</sup> The formation of the isomeric alkene decreases in the order of vinyl, allyl( $\Delta 2$ ), homoallyl( $\Delta 3$ ) and further isomeric( $\Delta 4$ ) types of alkenes. However, we are interested in the stereochemistry of the isomeric alkene( $\Delta 4$ ) product in the Heck reaction in which a chiral center exists at the allylic position of the terminal alkene, such as in the case of **II**.



Scheme 1. Heck reaction of terminal alkene with ArX.

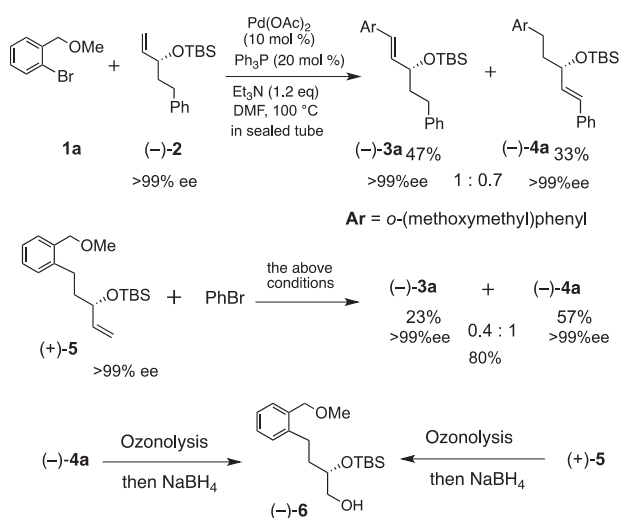
For this purpose, the installation of an alkene-stabilizing substituent (R), e.g., a phenyl or ester group, may be required at the C-5 position of the substrate to increase its formation. Either racemization or retention of the chiral carbon center will provide details of the alkene migration process in the Heck reaction. In this study, we have found the following results: (i) the migration of an alkene through three to five bonds to give the terminal styrenyl product in 30–40% yield when a phenyl group is installed at the terminal

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carbon and (ii) the retention of the stereochemistry without racemization of the siloxy or methoxy chiral carbon center during the migration process.

## 2. Results and discussion

We first examined the Heck reaction of chiral alkene (–)-**2** having an (*R*)-TBSOxy group at the C-3 carbon with aryl bromide **1a**. The reaction was conducted in DMF at 100 °C with Pd(OAc)<sub>2</sub> and Ph<sub>3</sub>P as the catalyst in the presence of Et<sub>3</sub>N to give (–)-**3a** in 47% yield, along with its alkene regioisomer (–)-**4a** in 33% yield. No enol silyl ether product was detected in the reaction mixture. Surprisingly, product **4a** was optically pure, with greater than 99% ee, as determined by chiral HPLC.<sup>7</sup> The reaction of the reverse combination of terminal alkene (+)-**5** and bromobenzene gave the same products (–)-**3a** and (–)-**4a** in a ratio of 0.4:1 under the same reaction conditions. In both cases, the alkenyl bond migrated to the end-terminal position by chain walking of σ-Pd complex, which resembles a zipper reaction in the alkyne migration process (Scheme 2).<sup>8</sup>



Scheme 2. Heck reaction of aryl bromide and alkene.

We examined this Pd-catalyzed migration process for other terminal alkenes (–)-**2** and (+)-**7–11** with aryl bromides **1a–d** (Fig. 1); the results are shown in Table 1.

The reaction of (–)-**2** with *o*-(hydroxymethyl)bromobenzene **1b** gave (–)-**3b** and (–)-**4b** in 70% yield with a ratio of 1:0.5 (entry 2). Similarly, the reaction of (–)-**2** with *o*- and *p*-bromotoluenes **1c** and **1d** afforded a mixture of **3c** and **4c** in 82% yield with a 1:0.6 ratio and **3d** and **4d** in 81% yield with a 1:0.7 ratio (entries 3 and 4, respectively). Methyl ether (+)-**7** afforded compounds (–)-**3e** and (+)-**4e** in 51% and 30% yields with 99% ee, respectively (entry 5). A small amount of exomethylene isomer **3e'** was also isolated in this

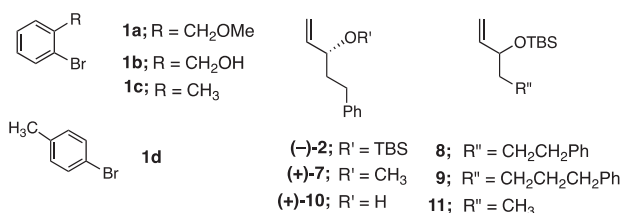
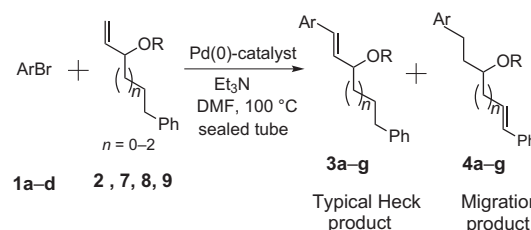


Fig. 1. Structures of ArBr and terminal alkenes.

Table 1  
Heck reactions of ArBr and terminal alkenes



Entry	Compound	Alkene	Time (h)	Product <b>3+4</b>	Yield <sup>a</sup> (%)	Ratio <sup>b</sup> ( <b>3:4</b> )
1	<b>1a</b>	(–)- <b>2</b>	24	<b>3a+4a<sup>c</sup></b>	80	1:0.7
2	<b>1b</b>	(–)- <b>2</b>	20	<b>3b+4b<sup>c</sup></b>	70	1:0.5
3	<b>1c</b>	(–)- <b>2</b>	27	<b>3c+4c<sup>d</sup></b>	82	1:0.6
4	<b>1d</b>	(–)- <b>2</b>	19	<b>3d+4d<sup>d</sup></b>	81	1:0.7
5	<b>1b</b>	(+)- <b>7</b>	24	<b>3e+4e<sup>e</sup></b>	81	1:0.6
6	<b>1b</b>	<b>8</b>	24	<b>3f+4f<sup>c</sup></b>	66	1:0.4
7	<b>1a</b>	<b>9</b>	14	<b>3g+4g<sup>c</sup></b>	88	1:0.5

<sup>a</sup> Combined yield.

<sup>b</sup> Ratio was determined by <sup>1</sup>H NMR.

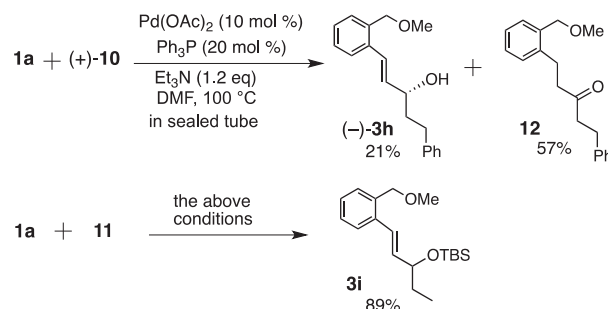
<sup>c</sup> Compounds are separable by HPLC.

<sup>d</sup> Compounds are inseparable by HPLC.

<sup>e</sup> Exomethylene isomer was produced in less than 5% yield.

case. These results indicated that starting terminal α,β-unsaturated alkene (*n*=0) gave δ,ε-unsaturated product in Heck arylation reaction. The reaction of **8**, which is a one-carbon-extended substrate (*n*=1) between the siloxy carbon center and the terminal phenyl group, with **1b** gave compounds **3f** in 47% yield and **4f** in 19% yield with a ratio of 1:0.4 (entry 6). The alkene migration proceeded again to the terminal end to form ε,ζ-unsaturated product **4f**. The reaction of the two-carbon-extended alkene **9** (*n*=2) with **1b** also gave the typical Heck product **3g** with ζ,η-unsaturated product **4g** in 88% yield with a ratio of 1:0.5 (entry 7). All of the isomers **4a–g** were obtained as side products in which the alkenyl bond isomerized to the conjugated position with the terminal phenyl group. Surprisingly, in the case of **9**, σ-Pd complex moved over four carbon bonds by chain walking to reach 1,5-transposition and furnished styrenyl product.<sup>9</sup> It is noteworthy that the internal chiral center completely retain the stereochemistry during the process in all the cases. While, the internal alkenes produced in the migration process were poorly detected in the products.

When terminal alkene (+)-**10** bearing a hydroxy group instead of a siloxy or methoxy group was used with **1a**, the typical Heck product (–)-**3h** formed as an optically pure form in 21% yield and no zipper product was produced. Instead, the migration process terminated at the enol intermediate to afford ketone **12** in 57% yield.<sup>6,9</sup> The reaction of a simple 3-silyloxy-pentene **11** with **1a** exclusively gave the typical Heck product **3i** in 89% yield (Scheme 3).



Scheme 3. Heck Reaction of **1a** with (+)-**10** and **11**.

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