

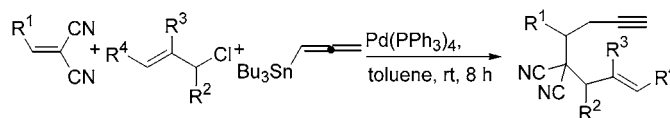
# Highly Regio- and Chemoselective Palladium-Catalyzed Three-Component Assembly of Arylethylidene Malononitriles, Allylic Chlorides, and Allenylstannanes: A Novel Route to 1,7-Enyne Derivatives

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Received January 9, 2003

## ABSTRACT



An efficient method for the synthesis of 1,7-enyne derivatives via a palladium-catalyzed three-component assembly of arylethylidene malononitriles, allylic chlorides, and allenylstannanes is described.

The metal-catalyzed addition of an electrophile and a nucleophile to an unsaturated carbon–carbon bond is a powerful method for constructing complex organic molecules.<sup>1</sup> Recently, Yamamoto reported a new type of palladium-catalyzed three-component coupling process of allyl chloride and allylstannane with activated olefins<sup>2</sup> or benzyne<sup>3</sup> to form the corresponding bis-allylation products. The catalytic reaction involves an amphiphilic bis-allyl palladium intermediate generated from allyl chloride and allylstannane. In the bis-allyl palladium intermediate, the  $\sigma$ -allyl acts as a nucleophile and the  $\pi$ -allyl group as an electrophile. The substrates used in the study were limited only to allyl chloride and allylstannane. Subsequently, Szabó et al. reported a similar type of palladium-catalyzed reactions of substituted allylic chlorides and allylstannanes with activated olefins<sup>4</sup>

or isocyanates.<sup>5</sup> Although, the two allyl groups come from two different reagents, it is extremely difficult to control the regiochemistry of this reaction due to the fact that this bis-allyl palladium intermediate readily undergoes  $\sigma$ – $\pi$  exchange leading to interchange of the nucleophilicity and electrophilicity (eq 1). Thus, a challenging problem of this chemistry is whether it is possible to use new nucleophiles for the three-component reaction and control the regiochemistry of the reaction.

We have contributed considerable work on palladium-catalyzed three-component coupling reactions of allenes leading to the formation of two carbon–carbon bonds.<sup>6</sup> Our continuing interest in metal-mediated allene chemistry<sup>7</sup> prompted us to investigate the possibility of using allenylstannanes as nucleophiles for the palladium-catalyzed three-component assembly reaction involving arylethylidene malononitriles and allylic chlorides. Herein, we report a highly regio- and chemoselective palladium–phosphine-mediated

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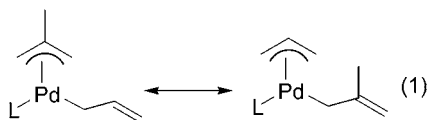
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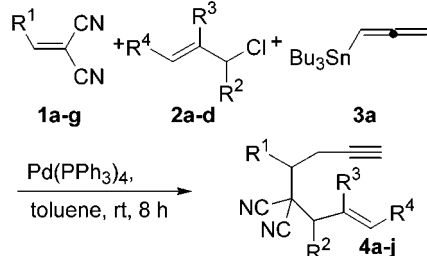
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three-component assembly of arylethylidene malononitriles, allylic chlorides, and allenylstannanes leading to the formation of 1,7-enyne derivatives in good to excellent yields. The catalytic reaction likely involves an unprecedented amphiphilic  $\sigma$ -allenyl  $\pi$ -allyl palladium species, reacting with activated alkene as a nucleophile and an electrophile.



Treatment of phenylethylidene malononitrile (**1a**) with allyl chloride (**2a**) and *n*-tributylallenylstannane (**3a**) in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %) in toluene at room temperature for 8 h led to a three-component assembly product **4a** in 86% yield (Scheme 1). The catalytic reaction

Scheme 1



- 1a:** R<sup>1</sup> = Ph  
**1b:** R<sup>1</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>  
**1c:** R<sup>1</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>  
**1d:** R<sup>1</sup> = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>  
**1e:** R<sup>1</sup> = 1-naphthyl  
**1f:** R<sup>1</sup> = 2-furyl  
**1g:** R<sup>1</sup> = 2-thienyl
- 2a:** R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
**2b:** R<sup>2</sup> = R<sup>4</sup> = H, R<sup>3</sup> = Me  
**2c:** R<sup>2</sup> = R<sup>4</sup> = Me, R<sup>3</sup> = H  
**2d:** R<sup>2</sup> = R<sup>3</sup> = H, R<sup>4</sup> = Ph

is highly regioselective, with the propargyl group from allenylstannane adding to the carbon connected to the phenyl group and the allyl group from allyl chloride adding to the carbon bonded to the cyano groups of **1a**. Product **4a** was fully characterized by its spectral data. The regiochemistry was established on the basis of the results of the proton decoupling NMR experiments. Control experiments revealed that in the absence of palladium catalyst, no reaction occurred. To the best of our knowledge, this is the first palladium-catalyzed three-component assembly of arylethylidene malononitrile, allylic chloride, and allenylstannane.

To understand the effect of the ligand on the present palladium-catalyzed reaction, the reaction of **1a** with **2a** and **3a** was carried out in toluene using different palladium complexes. Phosphine-free palladium complexes Pd(dba)<sub>2</sub>, Pd(OAc)<sub>2</sub>, and PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> were totally ineffective for the reaction. Palladium–phosphine complexes such as PdCl<sub>2</sub>(PCy)<sub>2</sub> and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyzed the reaction, but **4a** was obtained in lower yields of 42 and 46%, respectively. Pd-

**Table 1.** Results of Palladium-Catalyzed Three-Component Assembly of Malononitriles **1a–g**, Allylic Chlorides **2a–d**, and Allenylstannane **3a**

entry	1	2	product	yield (%) <sup>a</sup>
1	<b>1a</b>	<b>2a</b>		<b>4a</b> 78 (86)
2	<b>1a</b>	<b>2b</b>		<b>4b</b> 80
3	<b>1a</b>	<b>2c</b>		<b>4c</b> 76
4	<b>1a</b>	<b>2d</b>		<b>4d</b> 74
5	<b>1b</b>	<b>2b</b>		<b>4e</b> 77
6	<b>1c</b>	<b>2b</b>		<b>4f</b> 78
7	<b>1d</b>	<b>2b</b>		<b>4g</b> 76
8	<b>1e</b>	<b>2b</b>		<b>4h</b> 75
9	<b>1f</b>	<b>2b</b>		<b>4i</b> 76
10	<b>1g</b>	<b>2b</b>		<b>4j</b> 79

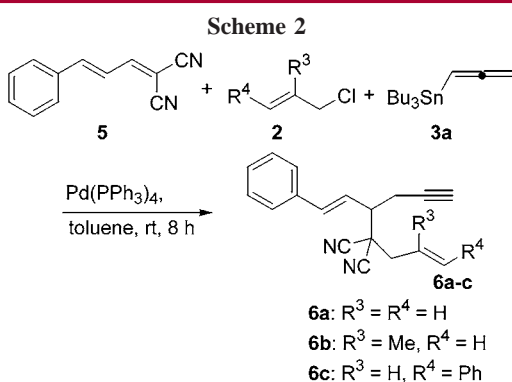
<sup>a</sup> Isolated yields; yield in parentheses was determined by the <sup>1</sup>H NMR integration method using mesitylene as an internal standard.

(PPh<sub>3</sub>)<sub>4</sub> shows the highest catalytic activity, giving **4a** in 86% yield. A brief examination of the effect of solvent using Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst on the yield of **4a** revealed that toluene was the solvent of choice. In addition to toluene, THF was also effective, affording **4a** in 71% yield. Other solvents such as EA, CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, and DMF were less suitable, furnishing **4a** in much lower yields. The nature of the leaving group on the allylic substrate shows great influence on the yield of the product. Allyl chloride gave the highest yield, while allyl bromide, iodide, acetate, and alcohol were less effective, affording **4a** in 45, 15, 10, and 5% yields, respectively.

Several substituted allylic chlorides, including methallyl chloride (**2b**), 4-chloro-pent-2-ene (**2c**), and cinnamyl chloride (**2d**), also undergo three-component assembly smoothly with **1a** and **3a** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> to afford the corresponding 1,7-enyne derivatives **4b–d** in 80, 76, and 74% yields, respectively (Table 1, entries 2–4). In addition

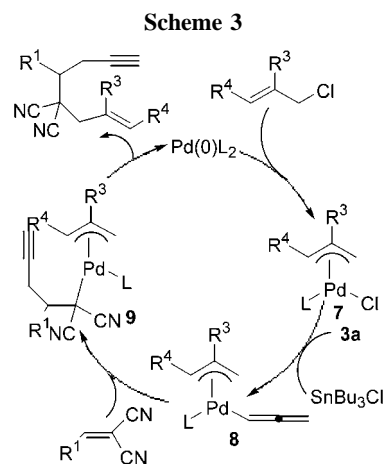
to **1a**, various substituted arylolefinylidene malononitriles **1b–e** react with **2b** and **3a** to furnish the corresponding three-component assembling products **4e–h** in good yields (entries 5–8). The results show that the catalytic reaction is compatible with a variety of substituents on the aromatic ring of **1**. The catalytic reaction can be successfully extended to heterocyclic alkenes. Thus, reactions of furylolefinylidene malononitrile (**1f**) and thiophenylethylidene malononitrile (**1g**) with **2b** and **3a** afforded **4i** and **4j** in 76 and 79% yields, respectively (entries 9 and 10). It is noteworthy that the 1,7-enyne derivatives<sup>8</sup> find versatile applications in various reactions, including Pauson–Khand reaction,<sup>9</sup> metal-catalyzed cycloisomerization,<sup>10</sup> and cycloreduction reaction.<sup>11</sup>

To further understand the regioselectivity of this catalytic reaction, the reaction of conjugated alkene **5** with **2a** and **3a** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> was investigated (Scheme 2).



The reaction is highly regio- and chemoselective, affording 1,2-addition product **6a** in 79% yield. No other regioisomer or 1,4-addition product was detected in the <sup>1</sup>H NMR spectroscopy. The regio- and stereochemistry of **6a** was established by <sup>1</sup>H NMR NOE experiments. Under similar reaction conditions, the three-component assembly reactions of **5** and **3a** with **2b** as well as **2d** also proceeded effectively in completely regio- and chemoselective fashion to give **6b** and **6c** in 75 and 71% yields.

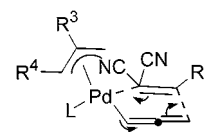
On the basis of the known palladium-catalyzed three-component coupling reactions,<sup>2–5</sup> a mechanism is proposed to account for the present catalytic reaction (Scheme 3). The first step involves the oxidative addition of allylic chloride to Pd(0) to give  $\pi$ -allyl palladium complex **7**. Transmetalation of allenylstannane **3a** with **7** gives  $\sigma$ -allenyl  $\pi$ -allyl



palladium intermediate **8** and Bu<sub>3</sub>SnCl.<sup>12</sup> Reaction of activated olefin **1** with **8** gives **9**. Subsequent reductive elimination of **9** affords the final product and regenerates the Pd(0) catalyst.

Transmetalation of allenylstannane with palladium(II) complex to give  $\eta^1$ -allenyl palladium intermediate was evidenced by the palladium-catalyzed coupling of aryl iodides or aryl triflates with allenylstannane to afford aryllallene.<sup>13</sup> The accompanying formation of Bu<sub>3</sub>SnCl was supported by the observation of the Bu<sub>3</sub>SnCl signals in the <sup>1</sup>H NMR spectra of the crude reaction mixtures of the reaction of **1** with **2** and **3a**. While the exact reason for the high product yield obtained for the allyl chloride compared to other allylic substrates is not known, a possible driving force is the great stability of the Sn–Cl bond and the facile formation of Bu<sub>3</sub>SnCl in the transmetalation step.

The formation of intermediate **9** likely occurs via an S<sub>E</sub>2' pathway that involves the attack of  $\gamma$ -carbon of the allenyl group of **8** at activated olefin **1**. A six-membered cyclic transition state (Figure 1) formed by alkene **1**, palladium



**Figure 1.**

metal, and the allenyl group in **8** can account for the facile transformation of **8** to **9**. Such a six-membered transition state has been used to explain the propargylation of aldehydes by allenylstannanes.<sup>14</sup> The results of the following deuterium study give strong support for the six-membered cyclic transition state. The reaction of D-allenylstannane **3b** with **1a** and **2a** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> in toluene at room

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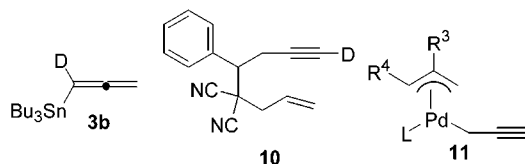
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temperature for 8 h gave **10** in 78% yield. The deuterium is incorporated in the terminal carbon of the propargyl group of **10** with 79% deuterium purity. No deuterium label was observed in the methylene carbon of the propargyl group. The above deuterium result clearly indicates that the  $\gamma$ -carbon of the allenyl group undergoes propargylation with the electrophilic carbon of activated olefins.



Another possible mechanism involves a  $\sigma$ -propargyl  $\pi$ -allyl palladium intermediate **11** from the reaction of **7** with the  $\gamma$ -carbon of the allenyl group in **3a**.<sup>12</sup> Migratory insertion of alkene **1** to the propargyl–Pd bond in **11** gives **9** (see Scheme 3). This pathway cannot be totally ruled out, but it is less likely on the basis of the following observation. The reaction of alkene **1a** with propargyl chloride and allylstannane under our standard conditions did not afford the expected three-component assembly product **4a**.<sup>15</sup>

The high regioselectivity of the present catalytic reaction can be attributed to the ready formation of a  $\sigma$ -allenyl  $\pi$ -allyl palladium complex **8** and the absence of  $\sigma$ – $\pi$  exchange of this intermediate. This intermediate regioselectively transfers the  $\sigma$ -allenyl group to the  $\beta$ -carbon and the  $\pi$ -allyl group to the  $\alpha$ -carbon of the activated alkenes to give the final product. It is to be noted that in the bisallylation reaction reported by Szabó, a mixture of regioisomers was observed for the three-component reaction of methallyl chloride, allylstannane, and activated alkene due to  $\sigma$ – $\pi$  exchange of the allyl groups in the resulting palladium intermediate.<sup>4,5</sup> However, in the present three-component reaction of methallyl chloride, **1**, and **3a**, only a single regioisomer was obtained (Table 1, entries 2, 5–10).

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(15) We thank the reviewer who suggested that we carry out this reaction.

There is no direct coupling product of allenylstannane with allylic chlorides detected under our standard conditions, although both allyl and allenyl groups are on palladium intermediate **8**. A palladium-catalyzed coupling of allenylstannanes with allylic acetates to give the corresponding allylic propargylation product has been reported by Keinan and Peretz.<sup>12</sup> In the present case, the  $\sigma$ -allenyl  $\pi$ -allyl palladium intermediate seems to react with the activated olefins faster than the coupling of the allenyl and the allyl group.

Attempts to use *trans*-styryl(tributyl)stannane or tributyl-(2-phenyl-1-ethynyl)stannane as the nucleophile to replace allenylstannane **3a** in the three-component assembly reaction failed probably due to the fact that no six-membered cyclic transition state can be formed. On the basis of the results of Yamamoto's bis-allylation and our present catalytic reaction, it appears that an allyl or allenyl group with  $\gamma$ -addition ability is necessary to act as the nucleophile in this type of catalytic three-component reaction.

In conclusion, we have developed a new palladium-catalyzed three-component assembly reaction of arylolefinylidene malononitriles with allylic chlorides and allenylstannanes. This method allows an efficient synthesis of various 1,7-enyne derivatives in good to excellent yields. The remarkable regioselectivity of this reaction is likely due to the unfavorable  $\sigma$ – $\pi$  exchange in the  $\sigma$ -allenyl  $\pi$ -allyl palladium intermediate. Further applications of the methodology in organic synthesis and detailed mechanistic studies of the catalytic reaction are in progress.

**Acknowledgment.** We thank the National Science Council of the Republic of China (NSC 91-2113-M-007-053) for support of this research.

**Supporting Information Available:** General experimental procedures, spectral data for all compounds, decoupling data for **4a,b**, NOE data for **6a,b**, and <sup>1</sup>H NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL034039V