

# Transmetalation of Palladium Enolate and Its Application in Palladium-Catalyzed Homocoupling of Alkynes: A Room-Temperature, Highly Efficient Route To Make Diynes

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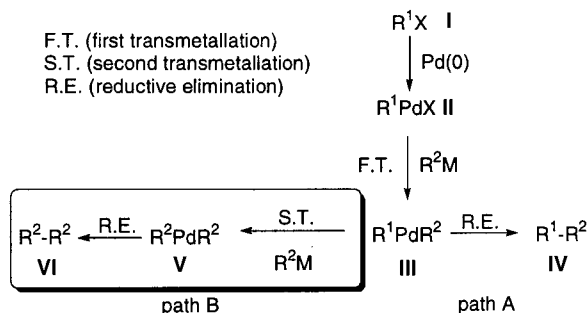
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**Abstract:** A novel pathway for the homocoupling reaction has been achieved using a similar protocol as the cross-coupling reaction. Ethyl bromoacetate is chosen to initiate the coupling reaction through oxidative addition to a Pd(0) species, and an PdBr(enolate) intermediate is formed. This intermediate can undergo double transmetalation with an alkynyl copper reagent, and reductive elimination produces a variety of diynes in high yields.

Over the past several decades, transition-metal-catalyzed carbon–carbon bond-forming reactions have been extensively studied and widely applied in organic synthesis.<sup>1</sup> The palladium-catalyzed coupling reaction has proved to be an extremely powerful tool to construct carbon–carbon or carbon–heteroatom bonds.<sup>2</sup> In a typical Pd-catalyzed process, oxidative addition of the palladium(0) species **I** and an aryl or vinyl halide or triflate occurs first. Transmetalation of **II** via a metal reagent to displace the halide or triflate anion on the palladium center followed by reductive elimination of **III** gives the

## Scheme 1. New Pathway in Pd-Catalyzed Homocoupling Reactions



coupling product **IV** (Scheme 1, path A). In this paper, we have explored an alternate pathway to form a homocoupling product **VI** (Scheme 1, path B). The intermediate **III** formed by the first transmetalation can undergo a second transmetalation with  $R^2M$  to generate the intermediate **V**. Subsequently, reductive elimination of **V** produces the coupling product **VI**. Although there are many reports of Pd-catalyzed coupling reactions using path A in Scheme 1, no systematic study of path B has been conducted. Research into path B is of significant interest in exploring the scope of palladium-catalyzed coupling reactions.

There are some major differences in the two different pathways depicted in Scheme 1. In path A, the product  $R^1R^2$  consists of two parts: one part comes from  $R^1X$  (**I**), and the other originates from  $R^2M$ . Due to the low activity of some  $R^1X$  species such as an aryl chloride or sterically hindered aryl halide, oxidative addition can be slow and the overall process to form  $R^1R^2$  may be inhibited.<sup>3</sup> In contrast, the homocoupling product  $R^2R^2$  in path B derives from a transmetalation reagent,  $R^2M$ . A reagent that readily undergoes oxidative addition,  $R^1X$ , can be selected. We propose that the key step in our desired homocoupling reaction is the second transmetalation of the intermediate **III** through displacement of  $R^1M$  to  $R^2M$ . In this paper, a new pathway has been utilized in the palladium-catalyzed homocoupling reaction of alkynes by choosing ethyl bromoacetate as an appropriate  $R^1X$  species and an alkynyl copper reagent as  $R^2M$ . We propose that a palladium enolate species is the key intermediate for the transmetalation step.

Palladium enolate chemistry has recently received considerable attention and enjoyed great progress.<sup>2a,f,4</sup> Reaction of Pd(0) complexes with  $\alpha$ -halo carbonyl compounds has been reported to produce halopalladium enolate complexes.<sup>5</sup> While it is well-known that the halide anion can serve as a good leaving group in a transmeta-

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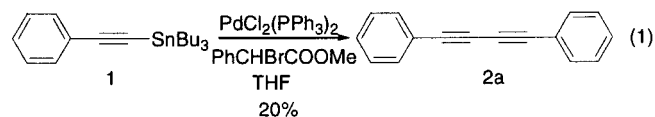
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lation step, an enolate anion as a leaving group to promote transmetalation is a relatively unexplored process. Herein, we report the first example of transmetalation of a palladium enolate anion with an alkynylcopper species. Double transmetalation of an alkynylcopper compound to replace both the halo and enolate anion groups on palladium produces a variety of diynes under mild conditions and in high yields. This new coupling reaction has certain advantages compared to Glaser and Sonogashira–Hagihara coupling reactions<sup>6</sup> for the formation of diynes: (1) the reaction can be carried out under an inert atmosphere to avoid side reactions of diynes associated with the Glaser coupling reaction, which uses O<sub>2</sub> as the oxidant; (2) formation of an alkynyl halide in the Sonogashira–Hagihara coupling reaction is avoided; (3) many terminal alkynes with alkyl groups can be effectively coupled in this reaction, wherein no activity and low yields are observed in the corresponding Glaser coupling reaction.

In our experiments, trimethyl(phenylacetylenyl)silane (1 mmol) was used as the substrate for the sp–sp homocoupling reaction. In the presence of 0.05 mmol of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and 1.0 mmol of methyl α-phenylbromoacetate in THF, no reaction was observed. When tetrabutylammonium fluoride was added to this mixture, a small amount of the desired homocoupling product was obtained (<10%). In another experiment, tributyl(phenylacetylenyl)tin (**1**; 0.5 mmol) in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol) and methyl α-phenylbromoacetate (1.0 mmol) at room temperature furnished the desired product, 1,4-diphenylbut-1,3-diyne (**2a**) in 20% yield after 3 days (eq 1). Although the reaction yield was low, the



feasibility of the reductive elimination between sp–sp carbon species at room temperature prompted us to explore a highly efficient sp–sp coupling reaction.

Inspired by the well-known Sonogashira–Hagihara coupling protocol,<sup>7</sup> an alkynylcopper reagent was chosen as a transmetalation reagent for the Pd-catalyzed sp–sp coupling reaction. Phenylacetylene (1 mmol) was coupled to form 1,4-diphenylbut-1,3-diyne in 99% yield in the presence of CuI (1.5 mmol), methyl α-phenylbromoacetate (1.2 mmol), diisopropylethylamine (1.5 mmol), and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol). When Pd(PPh<sub>3</sub>)<sub>4</sub>

**Table 1. Palladium-Catalyzed Homocoupling Reaction of Terminal Alkynes<sup>a</sup>**

$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow[\text{BrCH}_2\text{COOEt in THF, diisopropylethylamine}]{\text{PdCl}_2(\text{PPh}_3)_2 \text{ and CuI}} \text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}$			
Entry	Substrate	Product	Yield <sup>b</sup> (%)
1			99
2			99
3			99
4			98
5			81
6			66
7			47
8			62
9			99
10			94
11			83
12			99
13			99

<sup>a</sup> All reactions were performed using 60 mol % ethyl bromoacetate, 120 mol % diisopropylethylamine, 2 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, and 2 mol % CuI in 5 mL of THF. The reactions were done at room temperature for 2–24 h, and the progress of the reaction was monitored by TLC. <sup>b</sup> Isolated yields were reported.

was used as catalyst, only a 39% yield was obtained. Further optimization showed that only catalytic amounts of Cu(I) are required and an inexpensive α-halo carbonyl compound, ethyl bromoacetate, can be used to replace methyl α-phenylbromoacetate. For example, homocoupling of phenylacetylene proceeds in 98% yield in the presence of 0.05 mmol of CuI and no sp–sp<sup>3</sup> cross-coupling product was detected. We have also performed a number of control experiments: (1) in the absence of the palladium catalyst, no reaction occurred; (2) in the absence of CuI, the reaction proceeded slowly (3 days) in low yield (40%); (3) a low yield was observed when diisopropylethylamine was replaced by K<sub>2</sub>CO<sub>3</sub> (34% yield in THF); (4) in the absence of ethyl bromoacetate, the diyne was formed in 10% yield after 12 h.

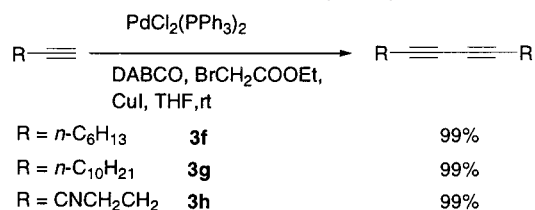
Under these optimized conditions, we have examined the substrate scope of this reaction. Our experiments indicate that a variety of functional groups can be tolerated in this reaction (Table 1). Alkenyl (entry 5), nitrile (entry 8), and hydroxyl (entries 9–13) are some functional groups on the terminal alkynes, which are not affected under the reaction conditions. Generally, terminal aliphatic alkynes are sluggish in undergoing Glaser dimerization due to the weaker acidity of the acetylenic proton.<sup>8</sup> Using our new protocol, the coupling reactions of **3f–h** were carried out to afford the corresponding coupling products in moderate yields (66%, 47%, and

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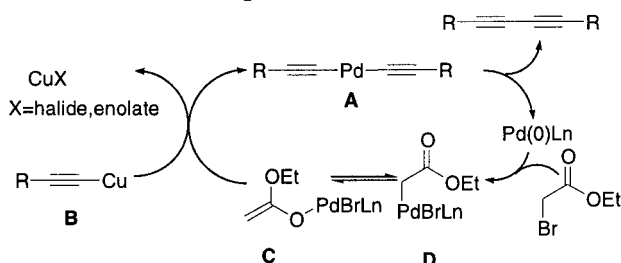
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### Scheme 2. Palladium-Catalyzed Homocoupling Reaction with Alkylalkynes



Scheme 2: Palladium-catalyzed homocoupling reaction with alkyl alkynes

### Scheme 3. Proposed Reaction Mechanism



62%, respectively). However, excellent yields (up to 99%) for coupling of **3f–h** were achieved when DABCO was chosen as a base (Scheme 2). These breakthrough results are critical for the polymerization of diynes with different linkers.

Scheme 3 illustrates our proposed mechanism for the *sp–sp* homocoupling of alkynes. The alkynylcopper intermediate **A** is formed from the reaction of a terminal alkyne and CuI in the presence of diisopropylethylamine, and it undergoes double transmetalation with a palladium bromide enolate.<sup>6c</sup> The transmetalation yields the dialkynylpalladium intermediate **B**, and then the reductive elimination from the dialkynylpalladium species leads to the *sp–sp* homocoupling product and Pd<sup>0</sup>Ln (Scheme 3). Oxidative addition of Pd<sup>0</sup>Ln and ethyl bromoacetate affords the intermediate **C**; isomerization of **C** generates the oxygen-bound palladium enolate bromide **D**. The formation of oxygen-bound palladium enolate bromide plays a crucial role in the *sp–sp* homocoupling reaction, by making the second transmetalation possible and providing the homocoupling product. The absence of *sp–sp*<sup>3</sup> cross-coupling product indicates that the process of the second transmetalation followed by

reductive elimination is faster than the reductive elimination of the intermediate formed after the first transmetalation.

In conclusion, we have successfully developed a novel pathway for the palladium-catalyzed homocoupling reaction, using ethyl bromoacetate to initiate the reaction. We propose that the double transmetalation of palladium enolate takes place with a suitable alkynylmetal reagent. High yields have been achieved in the palladium-catalyzed homocoupling of many alkynes. Further application of intramolecular cross-coupling of diynes and polymerization of alkynes using this methodology is ongoing and will be reported in due course.

### Experimental Section

**General Methods.** All reactions were carried out in an inert atmosphere using standard Schlenk techniques. Column chromatography was performed on EM silica gel 60 (200–400 mesh). <sup>1</sup>H NMR (360 MHz) and <sup>13</sup>C NMR (90 MHz) spectra were acquired in deuterated chloroform (CDCl<sub>3</sub>), methanol (CD<sub>3</sub>OD), and methylene chloride (CD<sub>2</sub>Cl<sub>2</sub>). THF was freshly distilled under nitrogen from sodium benzophenone ketyl. Alkynes were purchased from commercial sources (Aldrich, Lancaster, and Acros) and used without further purification.

**General Procedure for the Homocoupling of Alkynes Catalyzed by Palladium.** In a Schlenk tube, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (14.1 mg, 0.02 mmol), CuI (3.8 mg, 0.02 mmol), and base (1.2 mmol) were added and stirred under nitrogen. The tube was evacuated and refilled with nitrogen. THF (5 mL) and alkyne (1 mmol) were added under nitrogen to the above mixture. To this tube was added ethyl bromoacetate (100.2 mg, 0.6 mmol), and the reaction mixture was stirred at room temperature for 2–24 h. Progress of this reaction was monitored by TLC. After the reaction was complete, 5 mL of ethyl acetate and 2–3 g of silica gel was added and the solvent was removed under vacuum. The solid residue was then subjected to column chromatography.

**Deca-4,6-diyne Dinitrile (2h).** <sup>1</sup>H NMR: δ 2.64 (t, *J* = 6.4 Hz, 4H), 2.57 (t, *J* = 6.4 Hz, 4H). <sup>13</sup>C NMR δ 118.0, 74.3, 67.8, 17.5, 17.0. MS: *m/e* 156, 129, 116, 102, 89, 76, 63. HRMS: calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub> (M<sup>+</sup> + 1), 157.0766; found, 157.0752.

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**Supporting Information Available:** Text giving characterization data for the new compound **2h** (<sup>1</sup>H and <sup>13</sup>C NMR spectra) and details of the characterization of diynes **2a–m**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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