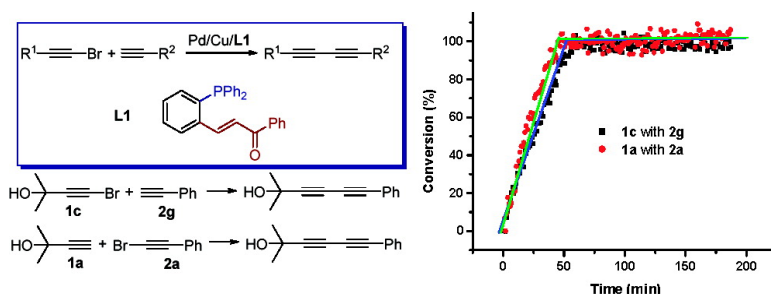


Investigation of an Efficient Palladium-Catalyzed C(sp)³C(sp)³ Cross-Coupling Reaction Using Phosphine#Olefin Ligand: Application and Mechanistic Aspects

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J. Am. Chem. Soc., **2008**, 130 (44), 14713-14720 • DOI: 10.1021/ja8049436 • Publication Date (Web): 11 October 2008

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Investigation of an Efficient Palladium-Catalyzed C(sp)–C(sp) Cross-Coupling Reaction Using Phosphine–Olefin Ligand: Application and Mechanistic Aspects

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Abstract: A π -acceptor phosphine–electron-deficient olefin ligand was found effective in promoting Pd-catalyzed C(sp)–C(sp) cross-coupling reactions. The new protocol realized the cross-coupling of a broad scope of terminal alkynes and haloalkynes in good to excellent yields with high selectivities. Electron-rich alkynes, which are normally difficult substrates in Glaser couplings, could be employed as either nucleophiles or electrophiles. Alkynes bearing similar substituents, such as n -C₅H₁₁CCBr and n -C₄H₉CCH, which usually suffer from homocoupling side reactions under Cadiot–Chodkiewicz conditions, were successfully cross-coupled in the system. Preliminary kinetic studies revealed that the reaction rate was zero-order in the concentrations of both haloalkynes and terminal alkynes and first order in the loading of Pd(dba)₂ and exhibited no obvious dependence on the loading of the copper salt. Control experiments with other phosphines such as PPh₃ and DPPF as the ligand were carried out. All the kinetic evidence indicated that the phosphine–olefin ligand facilitated the reductive elimination in the catalytic cycle.

Introduction

Diyne and polyynes are important building blocks in organic synthesis,^{1–8} and in this family, 1,3-conjugated diynes occur widely in a variety of natural products with antibacterial, anticancer, or anti-HIV biological activities, etc.^{9–15} For example, (+)-diptyne A (Figure 1) and its derivatives, isolated from the Philippines sponge *Diplastrella*, show anti-HIV activity.¹³ Both the (+)- and (–)-isomers of falcarinol (Figure

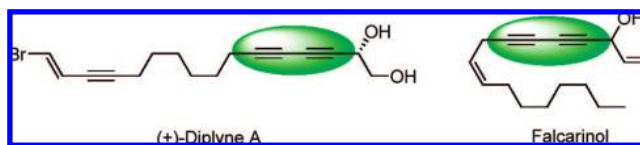


Figure 1. Conjugated diynes in natural products.

1), isolated from *Panax ginseng*, exhibit selective cytotoxicity toward several cancer cell lines.^{16,17} Furthermore, conjugated diynes play an important role in the properties of many functional materials, such as nonlinear optical materials, electrical conductive plastics, fibers with high density and strength, and liquid crystals.^{2,4,5,18–21} Therefore, artificial synthesis of conjugated diynes, especially unsymmetrical diynes, has attracted great attention for a long time.^{1,5,8,21–38}

Glaser coupling and Cadiot–Chodkiewicz coupling have been the major methods to prepare conjugate diynes for over 50

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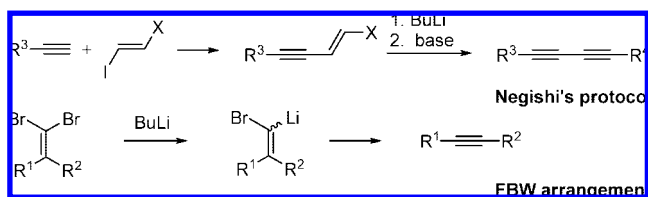
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years.^{5,23,39} The Glaser reaction, first reported in 1869, involves Cu salts as reagents or catalysts and oxidatively homocouples two terminal alkynes to construct symmetric diynes.^{15,24,31,33,40–43} Cadiot–Chodkiewicz coupling, developed over four decades ago, utilizes a 1-haloalkyne as the electrophile and a terminal alkyne as the nucleophile to construct unsymmetrical diynes.^{28,29,32,44–48} Though powerful in many cases, Cadiot–Chodkiewicz coupling often suffers from poor selectivity and results in a considerable amount of homocoupled byproducts, especially when the electronic properties of the substituents attached to the haloalkynes and the terminal alkynes are similar.^{8,23,39,49} To inhibit the homocoupling of the haloalkynes, excessive terminal alkynes are usually required.²³ Also, the Cadiot–Chodkiewicz coupling system is usually complicated, requiring specific amines as the solvent and reductive reagents such as hydroxylamine hydrochloride to keep the Cu salts in a low oxidation state.^{23,28,32,48} In addition, few mechanistic studies have been conducted on the process of triple-triple bond formation of the above two reactions.^{8,39,50,51}

During the past three decades, several Pd-catalyzed conjugate diyne formation methods have been reported. Negishi et al. developed an efficient tandem protocol by combining Pd-catalyzed coupling of terminal alkynes and ICH=CHCl with subsequent base-induced elimination to afford the conjugate diynes.^{39,52–55} Tykwinski et al. utilized alkyldiene carbenoid

Scheme 1. Palladium-Catalyzed Syntheses of Conjugated Diynes



rearrangement (FBW rearrangement) to furnish unsymmetrical diynes and polyynes (Scheme 1).^{4,56–58} Nye,³⁶ Wityak,⁵⁹ and Alami⁴⁹ et al. introduced Pd into the C(sp)–C(sp) cross-coupling reactions for the synthesis of unsymmetrical diynes and improved the yield and selectivity in some cases.

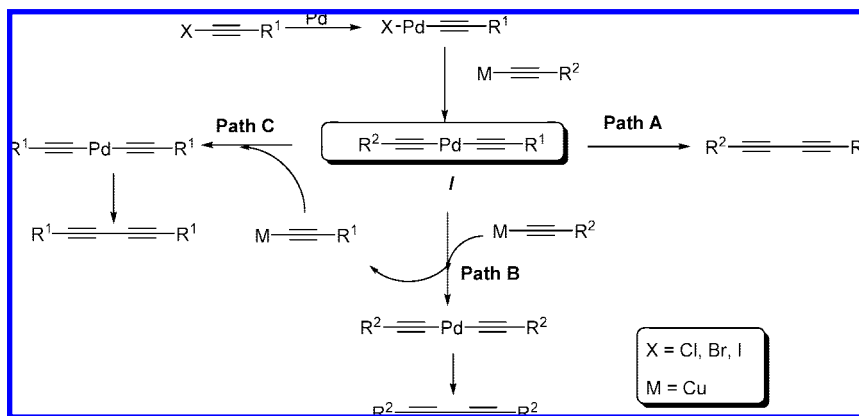
However, Pd-catalyzed C(sp)–C(sp) cross-coupling reactions are not well established yet. The major problem is still the competitive formation of the two homocoupled products.³⁹ A speculated mechanism of the Pd-catalyzed C(sp)–C(sp) coupling is outlined in Scheme 2. After oxidative addition of the 1-haloalkyne to the Pd catalyst and transmetalation with the alkenylmetal reagent generated from the terminal alkyne, key intermediate **I** was gained. **I** could undergo direct reductive elimination to furnish the desired unsymmetrical diynes (path A) or further transmetalate with the alkenylmetal reagents in the reaction system and release homocoupled side products (paths B and C). Accordingly, one reasonable way to improve the selectivity for path A is to facilitate the reductive elimination of intermediate **I**.

Steric ligands^{54,60–62} and π -acid ligands or additives^{63–75} are known to facilitate reductive elimination process. Based upon this concept, our group has developed a new phosphine–electron-deficient olefin ligand **L1** (Figure 2), which effectively promotes the Negishi cross-coupling of aryl iodides and alkylzinc reagents with β -H.⁷⁶ The efficiency of the reaction was proposed to arise

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Scheme 2. Proposed Pathways of Palladium-Catalyzed C(sp)–C(sp) Coupling



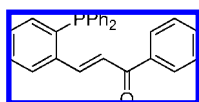
from the π -acid olefin part of the ligand, which could facilitate the reductive elimination of C(sp²)–Pd–C(sp³) species. Recently, we have explored the effect of ligand **L1** in a palladium-catalyzed C(sp)–C(sp) cross-coupling reaction, aiming at accelerating the reductive elimination of species **I** (Scheme 2), and herein we report the results of our synthetic application and preliminary kinetic investigation of the reaction.

Results and Discussions

1. Optimization of the Catalytic Conditions. The reaction of bromoethynylbenzene (**1a**) and 2-methylbut-3-yn-2-ol (**2a**) was chosen as the model reaction, and the initial screening results concerning the palladium precursors and ligands are listed in Table 1. Palladium was essential under the tested conditions, and only 8% of the cross-coupled product **3a** was generated after 9 h without any palladium catalyst (Table 1, entry 1). PdCl₂(PPh₃)₂ afforded 42% **3a** in 9 h together with 21% 1,4-diphenylbutadiyne (Table 1, entry 2). Pd(dba)₂ improved the yield of **3a** to 69% (Table 1, entry 3). When 2 mol % of Pd(dba)₂ together with 2 mol % of phosphine–olefin ligand **L1** was utilized, **3a** was obtained in 90% yield in 9 h, along with only 9% homocoupled 1,4-diphenylbutadiyne product (Table 1, entry 4).

Further optimization revealed that CuI was essential in this reaction as well. Without CuI, only 32% **3a** was produced, and the selectivity dropped to 76:24 (Table 2, entry 1). The ratio of Pd(dba)₂/**L1** to CuI was crucial. When Pd(dba)₂:**L1**:CuI was 1:1:1, 90% **3a** was obtained and the selectivity was 91:9 (Table 2, entry 2). Enhancing the loading of CuI to 4 or 10 mol % reduced the yield and selectivity (Table 2, entries 3 and 4). At the same CuI loading (2 mol %), higher yield was obtained with higher Pd(dba)₂/**L1** loading (Table 2, entries 2, 5, and 6).

2. Scope of Substrates. The substrate generality of Cu-mediated Cadiot–Chodkiewicz reactions or the current Pd-catalyzed alkyne–alkyne cross-coupling reactions is usually limited, and 2 equiv or more of alkynes is usually needed to get the desired cross-coupled products in good yields.^{5,8,39,49} However, our system required only 1.2 equiv of the terminal alkynes (vide supra), offering a greener and more economical

Figure 2. P-olefin ligand **L1**.Table 1. Screening of Palladium Catalysts and Ligands^a

entry	Pd (2 mol %)	ligand	yield (%) ^b	selectivity ^c
1	none	none	8	–
2	PdCl ₂ (PPh ₃) ₂	none	42	69:31
3	Pd(dba) ₂	none	69	83:17
4	Pd(dba) ₂	L1	90	91:9

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), NEt₃ (2 equiv), CuI (2 mol %) in 1 mL of DMF at room temperature. Other additives are given in the table. ^b Determined by gas chromatography with biphenyl as the internal standard. ^c Molar ratio of **3a** to 1,4-diphenylbutadiyne.

Table 2. Effects of Catalyst Loadings^a

entry	Pd(dba) ₂ / L1 (mol %)	CuI (mol %)	yield of 3a (%) ^b	selectivity ^c
1	2	0	32	76:24
2	2	2	90	91:9
3	2	4	78	85:15
4	2	10	62	77:23
5	1	2	89	90:10
6	4	2	92 (82 ^d)	92:8

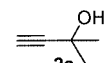
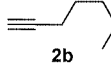
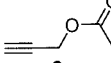
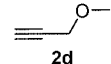
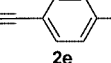
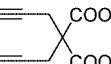
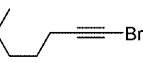
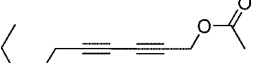
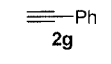
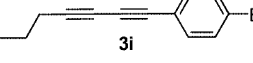
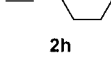
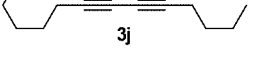
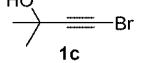
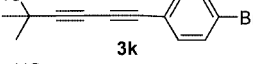
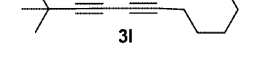
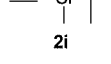
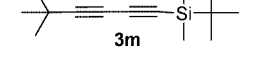
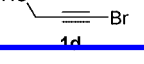
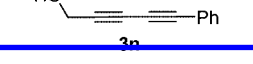
^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), NEt₃ (2 equiv) in 1 mL of DMF at room temperature. Other additives are given in the table. ^b Determined by gas chromatography with biphenyl as the internal standard. ^c Molar ratio of **3a** to 1,4-diphenylbutadiyne. ^d Isolated yield.

alternative. To evaluate the substrate scope, we examined the protocol employing various 1-bromoalkynes and terminal alkynes, and the results are listed in Table 3.

When 1-bromoalkyne **1a** was the electrophile, the reactions with terminal alkynes bearing either an aliphatic *n*-pentyl group or an electron-donating methoxy group gave good yields (Table 3, entries 2 and 4). The reaction between **1a** and propargyl acetate **2c** afforded the desired product in 82% isolated yield, and the reactive acetate group was well preserved (Table 3, entry 3). It was noteworthy that the protocol displayed excellent tolerance toward a bromophenyl group, and the reaction of **1a** with 1-bromo-4-ethynylbenzene (**2e**) provided the desired cross-coupled diyne **3e** in 96% isolated yield (Table 3, entry 5). For diethyl 2,2-di(prop-2-ynyl)malonate (**2f**), possessing two symmetric terminal alkynyl groups, selective formation of mono-cross-coupled product **3f** was achieved in 77% yield when the ratio of **1a** to **2f** was 1:1.1 (Table 3, entry 6), while di-cross-

Table 3. Substrate Scope Exploration^a

$$\text{R}^1\text{-C}\equiv\text{C-Br} + \text{C}\equiv\text{C-R}^2 \xrightarrow[\text{DMF, r.t., 2-9h}]{\text{Pd(dba)}_2/\text{L1, NEt}_3, \text{CuI}} \text{R}^1\text{-C}\equiv\text{C-C}\equiv\text{C-R}^2$$

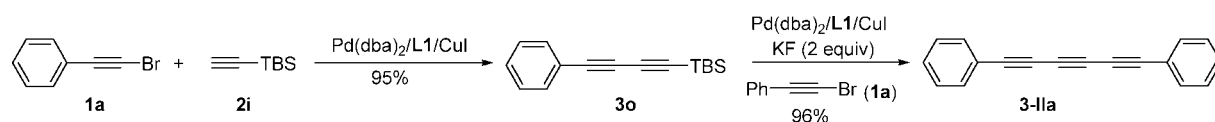
entry	1	2	3	yield ^b
1	Ph-C≡C-Br 1a	 2a	Ph-C≡C-C≡C-C(CH ₃) ₂ -OH 3a	82%
2	1a	 2b	Ph-C≡C-C≡C-CH ₂ (CH ₂) ₄ -CH ₃ 3b	82%
3	1a	 2c	Ph-C≡C-C≡C-CH ₂ -O-CO-CH ₃ 3c	82%
4	1a	 2d	Ph-C≡C-C≡C-CH ₂ -O-CH ₃ 3d	88%
5 ^c	1a	 2e	Ph-C≡C-C≡C-C ₆ H ₄ -Br 3e	96%
6 ^d	1a	 2f	Ph-C≡C-C≡C-C(CH ₃) ₂ (COOEt) ₂ 3f	77%
7 ^e	1a	2f	Ph-C≡C-C≡C-C(CH ₃) ₂ (COOEt) ₂ 3g	78%
8	 1b	2c	 3h	87%
9	1b	 2g	3b	92%
10 ^f	1b	2e	 3i	87%
11	1b	 2h	 3j	82%
12	 1c	2g	3a	99%
13	1c	2e	 3k	94%
14	1c	2b	 3l	83%
15	1c	 2i	 3m	91%
16	 1d	2g	 3n	77%

^a Reactions conditions: **1** (0.5 mmol), **2** (0.6 mmol), Pd(dba)₂ (4 mol %), **L1** (4 mol %), CuI (2 mol %), NEt₃ (2 equiv), DMF (1 mL). ^b Isolated yields. ^c DMF (2 mL) was used. ^d **2** (0.55 mmol) was used. ^e **1** (1.2 mmol) and **2** (0.5 mmol) were used. ^f DMF (2 mL) was used.

coupled product **3g** was isolated in 78% when the ratio of **1a** to **2f** was 2.4:1 (Table 3, entry 7). Bromo alkynes bearing either aliphatic (**1b**) or hydroxyl groups (**1c,d**) were all suitable substrates in the reactions with different terminal alkynes (Table 3, entries 8–17). Importantly, the coupling of 1-bromohept-1-yne (**1b**) with 1-hexyne (**2h**) provided the cross-coupled product trideca-5,7-diyne **3j** in 82% yield with less than 10% of byproducts (Table 3, entry 11). To the best of our knowledge,

this is the first example in which an electrophile and a nucleophile with similar electronic properties were successfully cross-coupled in a highly selective manner.^{5,39} Both Cadiot–Chodkiewicz reactions and other Pd-catalyzed processes typically gave low yields of cross-coupled products along with homocoupled side products.

Furthermore, it should be noted that the products of the reactions of **1a** with **2b** (Table 3, entry 2) and **1b** with **2g** (Table

Scheme 3. Stepwise Synthesis of Triyne **3-IIa**Table 4. One-Pot Synthesis of Triynes^a

$$\text{R}^1\text{—C}\equiv\text{C—Br} + \text{C}\equiv\text{C—TBS} \xrightarrow[\text{NEt}_3, \text{DMF}]{\text{Pd(dba)}_2/\text{L1}, \text{CuI}} \text{R}^1\text{—C}\equiv\text{C—C}\equiv\text{C—TBS} \xrightarrow[\text{one-pot synthesis}]{\text{KF, R}^2\text{—C}\equiv\text{C—Br (1-II)}} \text{R}^1\text{—C}\equiv\text{C—C}\equiv\text{C—R}^2$$

R ¹ —C≡C—Br	R ² —C≡C—Br	product	Overall yield ^b
1a	1a	Ph—C≡C—C≡C—Ph 3-IIa	84%
1a	1b	Ph—C≡C—C≡C—(CH ₂) ₄ —CH ₃ 3-IIb	60%
1a	1c	Ph—C≡C—C≡C—C(OH)(Me) ₂ 3-IIc	63%
1b	1b	(CH ₂) ₄ —CH ₂ —C≡C—C≡C—(CH ₂) ₄ —CH ₂ 3-IIId	84%
1c	1c	HO—C(OH)(Me) ₂ —C≡C—C≡C—C(OH)(Me) ₂ 3-IIe	81%

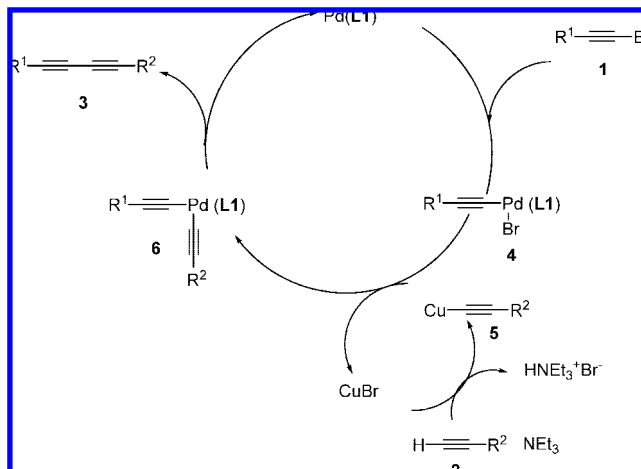
^a Reactions conditions: step 1, **1-I** (0.5 mmol), **2i** (0.6 mmol), Pd(dba)₂ (4 mol %), **L1** (4 mol %), CuI (2 mol %), NEt₃ (2 equiv), DMF (1 mL); step 2, KF (2 equiv) and **1-II** (0.5 mmol) were added under N₂. ^b Isolated yields.

3, entry 9) were the same, and the yields of both reactions were similarly good. This comparison indicated that our system was not sensitive to the choices of the electrophile and the nucleophile regarding their electronic properties, which is usually necessary to be considered in Cadiot–Chodkiewicz reactions.³⁹ The supposition was further supported by the comparison between the reactions of **1a** with **2a** (Table 3, entry 1) and **1c** with **2g** (Table 3, entry 12).

The synthesis of triynes has attracted much less attention compared to that of conjugated diynes, though triynes are useful building blocks as well.^{2,5} Tykwinski et al. employed the FBW rearrangement to obtain triynes or polyynes.^{4,57,58} Negishi et al. developed the iterated Pd-catalyzed alkynyl–alkenyl coupling and got polyynes as well.⁷⁷ Kim et al. also achieved the same goal based on the classic Cadiot–Chodkiewicz coupling reaction.²⁷ We were delighted to observe that our protocol cross-coupled TBS-protected terminal alkynes with 1-bromoalkynes in high yields (Table 3, entry 15, and Scheme 3). The resulting TBS-protected diyne **3o** further reacted with phenylacetylene bromide in the presence of KF and produced triyne **3-IIa** in 96% yield (Scheme 3).

The success of the above stepwise synthesis of **3-IIa** inspired us to move on to one-pot synthesis of triynes, and the results are summarized in Table 4. Different alkynyl bromides **1** were treated with **2i** to produce TBS-protected alkynes **3** following the procedure in Table 3. Upon complete conversion of **1**, 2.0 equiv of KF and 1 equiv of another alkynyl bromide were added to the batch, and triynes **3-II** were obtained in good yields without obvious side products. This simple method provided a convenient option for the synthesis of symmetric and unsymmetrical triynes.

Scheme 4. Proposed Catalytic Cycle of the Palladium-Catalyzed Alkyne–Alkyne Cross-Coupling Reaction



3. Kinetic Analysis. The mechanism of palladium-catalyzed alkyne–alkyne cross-coupling reactions is not well established yet.³⁹ Based upon the general comprehension of palladium-mediated coupling reactions,^{22,54,62,78,79} we proposed a catalytic cycle for the Pd(dba)₂/L1 promoted alkyne–alkyne cross-coupling reaction as shown in Scheme 4. First, bromoalkyne **1** undergoes oxidative addition to Pd(0) species to form intermediate **4**. Transmetalation between **4** and alkynecopper **5** then affords **6**. Finally, reductive elimination of **6** furnishes the desired cross-coupled diyne **3** and regenerates the Pd(0) species. Alkynecopper **5** is generated from the Cu(I) salt and terminal alkynes with the assistance of NEt₃. As proposed in Scheme 2,

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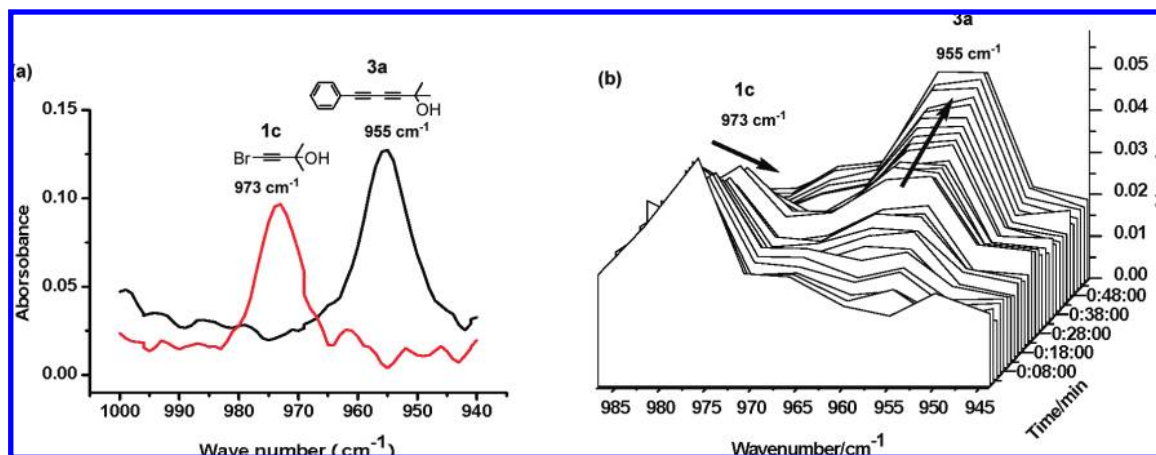


Figure 3. (a) Standard IR spectra of **1c** and **3a** recorded by in situ IR in MeCN. (b) Depletion of **1c** and formation of **3a** tracked by the changes of the peaks at 973 and 955 cm^{-1} by in situ IR in MeCN.

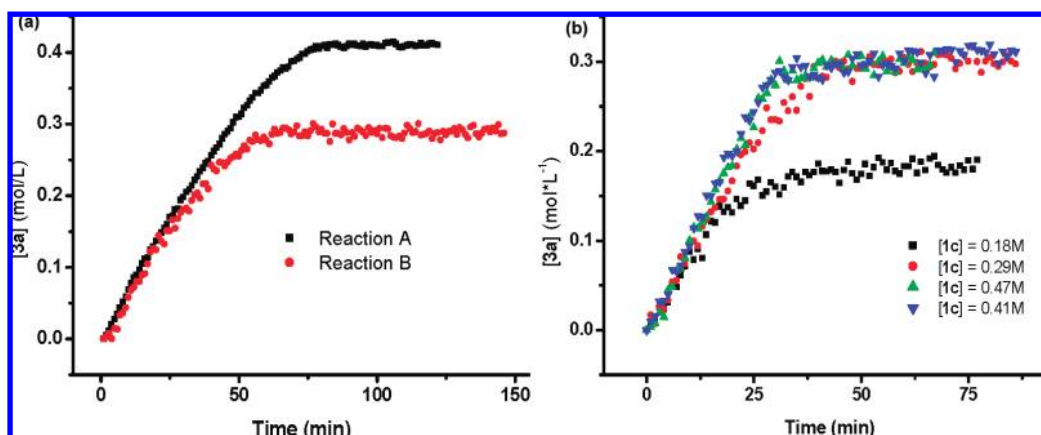


Figure 4. (a) Different initial concentrations of starting materials: reaction A, $[\mathbf{1c}] = 0.41 \text{ M}$, $[\mathbf{2g}] = 0.43 \text{ M}$; reaction B, $[\mathbf{1c}] = 0.29 \text{ M}$, $[\mathbf{2g}] = 0.31 \text{ M}$. Other conditions were the same: $[\text{Pd}(\text{dba})_2] = 0.006 \text{ M}$, $[\text{CuI}] = 0.003 \text{ M}$, carried out in 1.5 mL of MeCN at room temperature. $[\mathbf{3a}]$ was determined by in situ IR and GC. (b) Reaction profiles of different initial concentrations of **1c**. Reaction conditions: $[\mathbf{2g}] = 0.29 \text{ M}$, $[\text{Pd}/\text{L1}] = 0.006 \text{ M}$, $[\text{CuI}] = 0.003 \text{ M}$, room temperature. $[\mathbf{3a}]$ was determined by in situ IR and GC.

homocoupled diynes, common side products in alkyne–alkyne cross-coupling reactions, are formed from the reaction of intermediate **I** (i.e., **6** in Scheme 4) with another alkynylcopper (i.e., **5** in Scheme 4) when the reductive elimination of **I** is slow. However, in our system, highly efficient and selective couplings between terminal alkynes and bromoalkynes were achieved (see sections 1 and 2). Therefore, we speculated that **L1** played an important role in facilitating the reductive elimination of intermediate **6** (Scheme 4), and preliminary kinetic studies of this reaction were conducted to explore the possibility of this hypothesis.

3.1. Observed Kinetics of the Reaction between **1c** and **2g**.

The coupling of **1c** (0.29 M) and **2g** (0.31 M) at 15 °C in MeCN was clean, reproducible, and efficient (see Supporting Information), and the characteristic peaks of the reactant **1c** and product **3a** were easy to follow by IR (Figure 3a). Therefore, this reaction was chosen as the model for kinetic analysis, and the progress was monitored by in situ IR. The depletion of **1c** and formation of **3a** were tracked by the changes of the peaks at 973 and 955 cm^{-1} , respectively (Figure 3b).

Overlay was observed in “same excess experiments” as shown in Figure 4a, indicating that no catalyst poisoning or deactivation occurred during the reaction process.^{78–80} Furthermore, the concentration of the product **3a** increased linearly with time in most of the reaction, and the slopes (i.e., rates) overlapped

regardless of the initial concentrations of **1c** and **2g** (Figure 4b). These data indicate that the reaction rate is zero-order in both $[\mathbf{1c}]$ and $[\mathbf{2g}]$. According to the proposed catalytic cycle in Scheme 4, the independence of the reaction rate on $[\mathbf{1c}]$ and $[\mathbf{2g}]$ could be rationalized by either of the following possibilities: (1) The rate-determining step was the transmetalation of alkynylcopper **5** with alkynylpalladium bromide **4**, when both $[\mathbf{5}]$ and $[\mathbf{4}]$ were constant. (2) The rate-determining step was the reductive elimination of complex **6**.

3.2. Reaction Rate Dependence on Metal Loading. To observe the reaction rate dependence on $[\text{Pd}(\text{dba})_2/\text{L1}]$, kinetic measurements were conducted at different loadings of catalysts ($[\text{Pd}(\text{dba})_2/\text{L1}] = 3\text{--}30 \text{ mM}$) with $[\mathbf{1c}] = 0.29 \text{ M}$ and $[\mathbf{2g}] = 0.31 \text{ M}$ in MeCN at 15 °C. The reaction rate was first-order in $[\text{Pd}(\text{dba})_2/\text{L1}]$ under the tested conditions (Figure 5), which is consistent with either of the possibilities described in section 3.1.

Further kinetic studies revealed that the reaction rate was scarcely influenced by CuI loading from 0.003 to 0.03 mol/L with $[\mathbf{1c}] = 0.29 \text{ M}$, $[\mathbf{2g}] = 0.31 \text{ M}$, and $[\text{Pd}(\text{dba})_2/\text{L1}] = 12 \text{ mM}$ at 15 °C (Figure 6). It was found that the solubility of phenylacetylene copper in MeCN was less than $6 \times 10^{-6} \text{ mol/L}$

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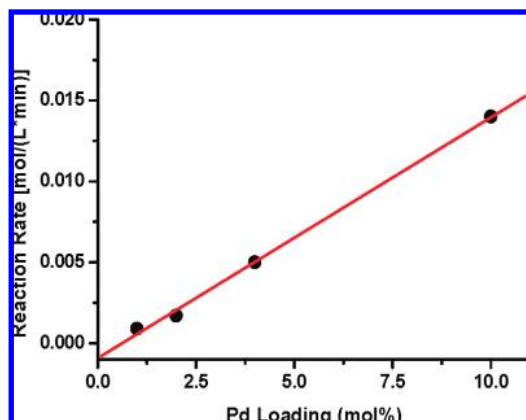


Figure 5. Reaction profiles of different $\text{Pd}(\text{dba})_2$ loadings with $[\text{CuI}] = 0.006 \text{ M}$, $[\mathbf{1c}] = 0.29 \text{ M}$, and $[\mathbf{2g}] = 0.31 \text{ M}$. Reaction rates were calculated by in situ IR and GC.

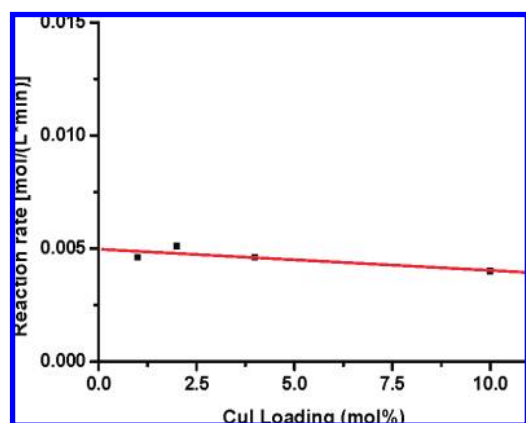


Figure 6. Reaction profiles at different CuI loadings with $[\text{Pd/L1}] = 0.012 \text{ M}$, $[\mathbf{1c}] = 0.29 \text{ M}$, and $[\mathbf{2g}] = 0.31 \text{ M}$. Reaction rate was calculated by in situ IR and GC.

(0.006 mM). Therefore, phenylacetylene copper **5** (i.e., **5** in Scheme 4) was envisioned to remain saturated in the reaction system, and variation of CuI loading would not influence the concentration of **5** or the reaction rate.

3.3. Deduction of the Rate-Determining Step. To deduce which step described in section 3.1 was rate-determining, we chose the reaction of **1a** and **2a** to compare with the reaction of **1c** and **2g**. For the two reactions, the transmetalation reactants were different, while the reductive elimination precursors were the same. So if transmetalation was the rate-determining step, the rates of the two reactions should be different. On the other hand, if the reductive elimination was the slow step, the rates should be the same. It turned out that the rates of the two reactions were comparable under parallel conditions (Figure 7, $0.0050 \text{ mol L}^{-1} \text{ min}^{-1}$ for the reaction of **1c** and **2g** and $0.0053 \text{ mol L}^{-1} \text{ min}^{-1}$ for the reaction of **1a** and **2a**), supporting that reductive elimination was the rate-determining step.

3.4. Comparison of L1 with Other Phosphine Ligands. To gain some understanding of the effects of ligand **L1** in this reaction, we investigated the processes of the model reaction using 1,2-bis(diphenylphosphino)benzene (**L2**), DPPF (Figure 8), and PPh_3 as the ligand separately for comparison (Figures 9 and 10).

The rate of the reaction with 1 equiv of DPPF (vs Pd) as the ligand was slower than that with 1 equiv of **L1** (vs Pd, see Figure 9). The reaction plot was not linear, and the selectivity was poor, with 40% homocoupled side product 1,4-diphenylbutadiyne generated (Figure 10). One equivalent of **L2** completely inhibited the reaction. The **1c** consumption rate of the reaction with 1 equiv of PPh_3 as the ligand was just slightly slower than that with **L1** (Figure 9), but the former reaction produced only 56% (determined by GC, see Figure 10) of the desired cross-coupled diyne **3a** together with 44% of homocoupled side product 1,4-diphenylbutadiyne. Either 2 or 5 equiv of either PPh_3 or **L1** completely shut down the reaction, probably due to the low reactivity of *trans*-dialkynylpalladium species **7**, which were reported to be prepared and isolated as rather stable complexes (Scheme 5a).⁸¹

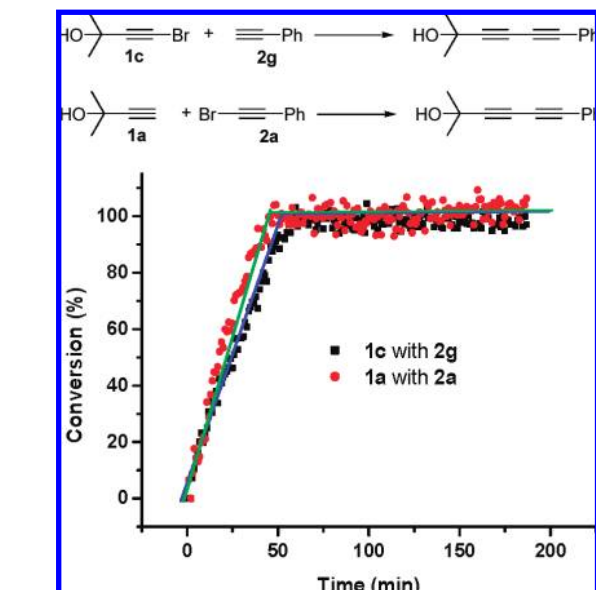


Figure 7. Reaction conditions: $[\text{CuI}] = 0.006 \text{ M}$, $[\text{Pd/L1}] = 0.012 \text{ M}$, $[\mathbf{1c}] = [\mathbf{2g}] = [\mathbf{1a}] = [\mathbf{2a}] = 0.29 \text{ M}$. Reaction rate was calculated by in situ IR and GC.

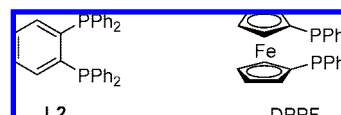


Figure 8. Bidentate phosphine ligands utilized for comparison.

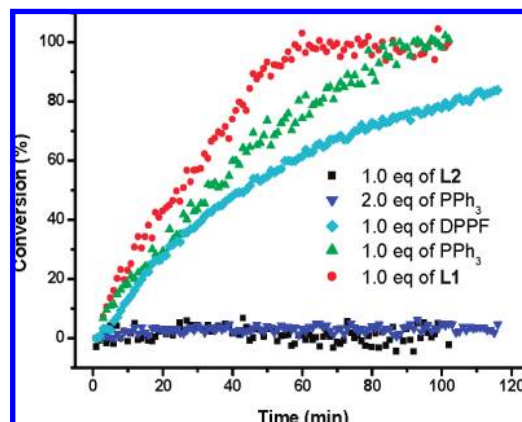


Figure 9. Comparison of **L1** with other ligands. Reaction conditions: $[\text{CuI}] = 0.006 \text{ M}$, $[\text{Pd}(\text{dba})_2] = 0.012 \text{ M}$, $[\mathbf{1c}] = 0.29 \text{ M}$, $[\mathbf{2g}] = 0.31 \text{ M}$. Reaction rates were calculated by in situ IR and GC.

On the basis of the above results, we speculated that, in the reaction system with 1 equiv of **L1** as the ligand, two species

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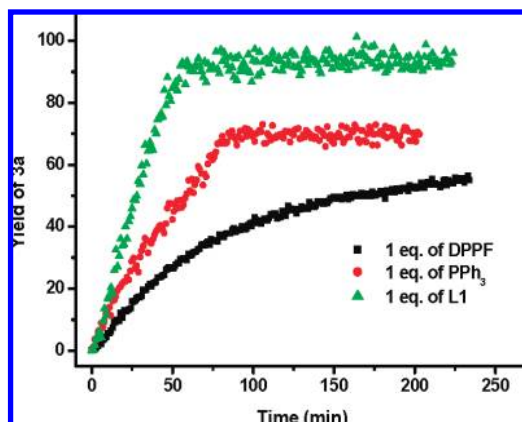
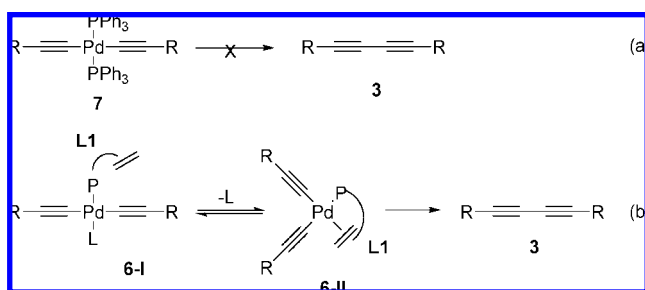


Figure 10. Comparison of **L1** with other ligands. Reaction conditions: $[\text{CuI}] = 0.006 \text{ M}$, $[\text{Pd}(\text{dba})_2] = 0.012 \text{ M}$, $[\text{1c}] = 0.29 \text{ M}$, $[\text{2g}] = 0.31 \text{ M}$. Reaction rates were calculated by in situ IR and GC.

Scheme 5. Speculated Processes of Reductive Elimination: (a) Stable *trans*-Dialkynylpalladium Species and (b) When 1 Equiv of **L1** as the Ligand (L Could Be dba or Solvent in the Reaction System)



6I and **6II** existed in equilibrium after transmetalation. The bidentate feature of **L1** would facilitate the shift from **6I** to **6II**, and the π -acceptor ability of the olefin part of **L1** would accelerate the reductive elimination of **6II** to produce the cross-coupled diynes (Scheme 5b).⁸²

Conclusions

A clean, highly efficient, and versatile method to synthesize unsymmetrical 1,3-diynes promoted by $\text{Pd}(\text{dba})_2$ and a phosphine–olefin ligand was developed. The reaction yields were good, with little or no dependence on substrates in most cases, even when both the electrophile and the nucleophile were substituted with electronically similar aliphatic groups. One-pot synthesis of symmetric and unsymmetrical triynes was also achieved employing the protocol. The convenience of the methodology promised good potential for application in synthesizing a broad range of conjugate diynes or triynes in bioactive natural products or other specific organic materials. Preliminary mechanistic analysis indicated that the phosphine–olefin ligand facilitated the reductive elimination step in the catalytic cycle.

(82) Recently, evidence has revealed that tri-coordinated Pd complexes were the active species for reductive elimination.^{83–85} However, the reaction catalyzed by 1 equiv of PPh_3 (vs Pd) and Pd was slower than that catalyzed by **L1**/Pd (see Figure 10). So the olefin part of **L1** should have played a role in accelerating the reaction. Thus, we speculated that, in our system, **6-II** as the reductive elimination precursor was more possible than an active tri-coordinated Pd complex.

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Experimental Procedures

General Experimental Procedure and Reagent Availability.

All manipulations were carried out under an inert atmosphere using an argon-filled glovebox or standard Schlenk techniques. All glassware was oven-dried at 120 °C for more than 1 h prior to use. Triethylamine and dimethylformamide (DMF) were obtained from commercial sources and dried with molecular sieves (4 Å). Acetone nitrate was distilled from P_2O_5 and degassed by purging with nitrogen for more than 45 min. $\text{Pd}(\text{dba})_2$ and other palladium complexes were prepared according to the literature. **L1** ligand was prepared as reported previously. CuI was obtained from commercial sources (Acros) and used without further purification. All new compounds were characterized by ^1H NMR, ^{13}C NMR, GC-MS, and HRMS. The known compounds were characterized by ^1H NMR, ^{13}C NMR, and GC-MS. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz NMR spectrometer. GC-MS spectra were recorded on a Varian GC-MS 3900-2100T spectrometer. All ^1H NMR data are reported in parts per million (ppm) downfield of TMS. All ^{13}C NMR data are reported in ppm and were obtained with ^1H decoupling. Gas chromatographic analyses were performed on a Varian GC 2000 gas chromatography instrument with a flame ionization detector, and biphenyl was added as internal standard. IR spectra were recorded on a Mettler Toledo React IR 4000 spectrometer using a Si–C comb.

General Procedures for the Coupling Reactions. To an oven-dried Schlenk tube with a magnetic stir bar were added $\text{Pd}(\text{dba})_2$ (11.5 mg, 0.02 mmol), **L1** ligand (7.9 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol). DMF (1 mL) was added via a syringe. The system was vacuumed with an oil pump at 0 °C and filled with nitrogen, and this was repeated five times. After the mixture was stirred under nitrogen for about 10 min, alkyne (0.6 mmol) was added via a microliter and stirred for another 5 min. 1-Bromoalkyne was added last via a microliter syringe. The system was stirred at room temperature for 10 h. Upon completion, 4 mL of brine was added, and the mixture was extracted by ethyl acetate (3 mL \times 3). The product was obtained by flash column chromatography.

General Procedure for the Kinetic Experiments (4 mol % of Pd and 2 mol % of Cu). To an oven-dried three-neck reactor with a magnetic stir bar were added $\text{Pd}(\text{dba})_2$ (11.5 mg, 0.02 mmol), **L1** ligand (7.9 mg, 0.02 mmol), CuI (1.9 mg, 0.01 mmol), and biphenyl (20.0 mg). The reactor was purged with nitrogen for 10 min. MeCN (1.5 mL) was added via a syringe. The mixture was stirred for 5 min until ligand **L1** was dissolved. Triethylamine (0.17 mL, 1.2 mmol) and phenylacetylene (58 μL , 0.53 mmol) were then added, and the spectropic data collection by in situ IR was started. 4-Bromo-2-methylbut-3-yn-2-ol (60 μL , 0.50 mmol) was added to initiate the reaction. The system was stirred at 15 °C for 4 h, and the data collection was continued throughout the reaction process.

Preparation of (Phenylethynyl)copper. CuI (2.02 g, 10.5 mmol) was dissolved in ammonium hydroxide to form a blue solution. While stirring, this solution was added dropwise to the solution of phenylacetylene (1.07 g, 10.5 mmol) in 50 mL of ethanol. The system was allowed to stand for 15 min to form a yellow precipitate. The precipitate was filtered out and washed with water, ethanol, and diethyl ether, three times each. The solid was vacuum-dried, and 1.3 g (yield 75%) of a bright yellow solid was obtained.

Acknowledgment. Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday. This work was supported by National Natural Science Foundation of China (20772093, 20502020), the Excellent Youth Foundation of Hubei Scientific Committee, Specialized Research Fund for the Doctoral Program of Higher Education (20060486005), and a startup fund from Wuhan University.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA8049436